Development and Developmental Disorders of the Forebrain

9

Hans J. ten Donkelaar, Martin Lammens,
Johannes R.M. Cruysberg, Karin Kamphuis-van Ulzen,
Akira Hori, and Kohei Shiota

Contents

H.J. ten Donkelaar, M.D., Ph.D. (✉)
935 Departments of Neurology,
Radboud University Nijmegen Medical Centre,
9101, 6500 HB Nijmegen, The Netherlands
e-mail: hans.tendonkelaar@radboudumc.nl,
hjtendonkelaar@gmail.com

M. Lammens, M.D., Ph.D.
Department of Pathology,
University Hospital Antwerpen,
Wilrijkstraat 10, B-2650 Edegem, Belgium

J.R.M. Cruysberg, M.D., Ph.D.
Department of Ophthalmology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

K. Kamphuis-van Ulzen, M.D.,
766 Department of Radiology, Radboud University Nijmegen MC,
9101, 6500 HB Nijmegen, The Netherlands

A. Hori, M.D., Ph.D.
Institute of Pathology, Medizinische Hochschule,
Hannover, Germany

Research Institute for Longevity Medicine, Fukushimura Hospital,
Noyori-Yamanaka 19-14, Toyohashi 441-8124, Japan

K. Shiota, M.D., Ph.D.
Congenital Anomaly Research Center,
Kyoto University Gradute School of Medicine, Kyoto 606-8501, Japan

Shiga University of Medical Sciences, Otsu, Shiga 520-2192,
Japan

H.J. ten Donkelaar et al., *Clinical Neuroembryology*,
DOI 10.1007/978-3-642-54687-7_9, © Springer-Verlag Berlin Heidelberg 2014

9.1 Introduction

The forebrain comprises those structures that are derived from the most rostral part of the neural plate, i.e. the **primary prosencephalon**. The primary prosencephalon divides into two major components, the (epichordal) caudal diencephalon and the rostral secondary prosencephalon. The **secondary prosencephalon** is the entire prechordal part of the neural tube, and includes the rostral diencephalon or hypothalamus, the optic vesicles, the preoptic region and the telencephalon. The derivatives of the forebrain are shown in MR images of human embryos (Fig. 9.1). The two major telencephalic subdivisions are the pallium (the roof) and the subpallium (the base). The pallium gives rise to the cerebral cortex, whereas the basal ganglia and most cortical interneurons derive from the subpallium. The amygdala has pallial as well as subpallial origins. Like the rest of the neural tube, the embryonic forebrain appears to be organized into transverse (prosomeres) and longitudinal subdivisions (alar and basal plates; Fig. 9.2). The caudal diencephalon arises from the prosomeres 1–3, whereas the rostral diencephalon was suggested to arise from the prosomeres 4–6 (Bergquist and Källén 1954; Puelles 1995; Rubinstein et al. 1998; Puelles et al. 2000). The relationship of these postulated segments to telencephalic subdivisions, however, remained controversial. More recently Puelles and Rubinstein (2003), revised their prosomeric subdivision of the forebrain by advocating a single, complex protosegment for the secondary prosencephalon, not further subdividable into prosomeres 4–6, but later again they distinguished two hypothalamic prosomeres and the acroterminal region as the most rostral part of the forebrain (Sect. 9.2). The theoretical framework of the prosomeric model has been extensively discussed by Puelles et al. (2012a).

Patterning of the forebrain involves the two general sets of mechanisms common to the neural plate, one along the

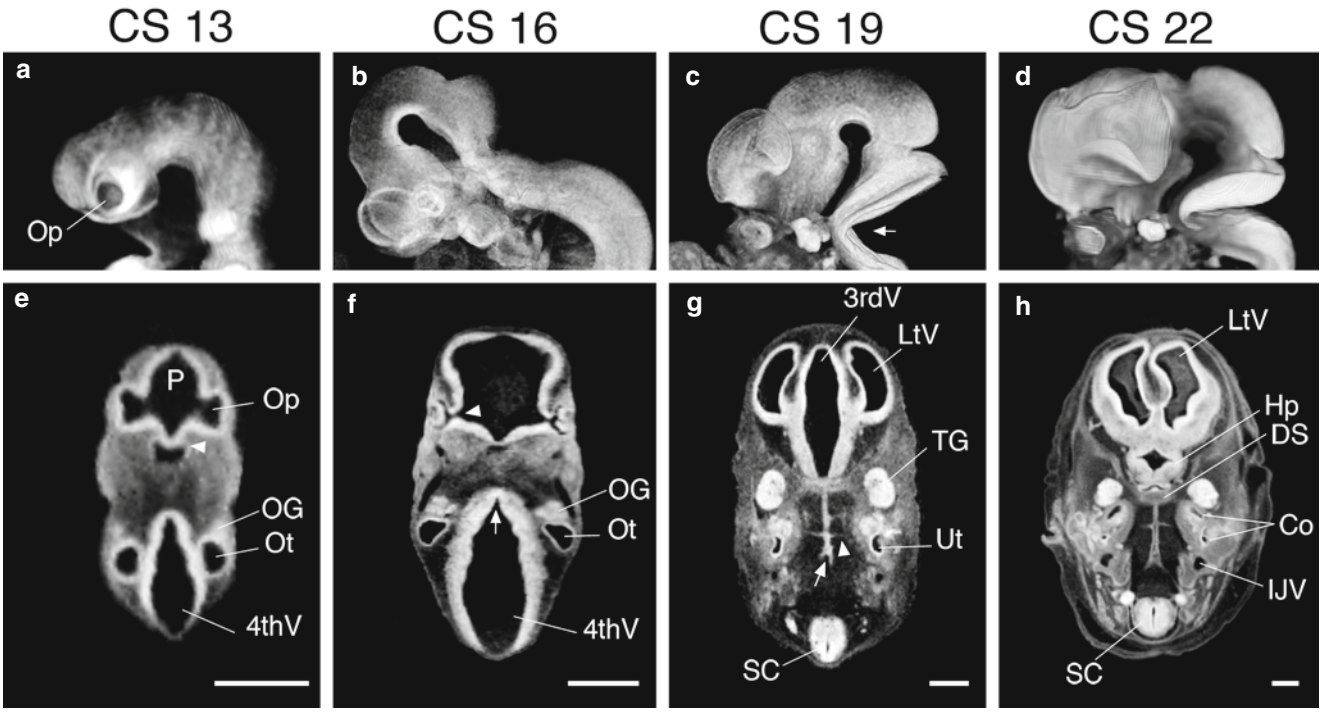

Fig. 9.1 Derivatives of the forebrain in human embryos of Carnegie stages (CS) 13–22. MR images are shown as 3D volumes (**a**–**d**) and 2D transverse sections (**e**–**h**) to illustrate development of the forebrain. At CS 13 (**a**), the optic cup (*Op*) is seen as a prominent evagination from the prosencephalon (*P*). A transverse section (**e**) shows the optic cup and the otic vesicle (*Ot*), the craniopharyngeal pouch (*arrowhead* in **e**) is in contact with the floor of the forebrain. At CS16 (**b**, **f**), the optic stalk (*arrow*) is shown. At CS 19 (**c**, **g**), the cerebral hemispheres enlarge and the pontine flexure (*arrow*) is prominent. In the 2D view (**g**), the lateral ventricle (*LtV*) and the third ventricle (*3rdV*) can be seen. The cochlea (*Co*) is developing posterior to the trigeminal ganglion (*TG*). By CS 22 (**d**, **h**), the cerebral hemispheres have greatly enlarged and elongated posteriorly (**d**). In the 2D section (**h**), the cerebral cortex around the lateral ventricles (*LtV*) has thickened and below the lateral ventricles, the medial and lateral ganglionic eminences can be distinguished. The adenohypophysis can be observed with the dorsum sellae (*DS*) just below the hypothalamus (*Hp*). Other abbreviation: *IJV* internal jugular vein, *OG* otic ganglion, *SC* spinal cord, *Ut* utriculus, 4thV fourth ventricle (From Yamada et al. 2010; with permission and courtesy Shigehito Yamada, Kyoto)

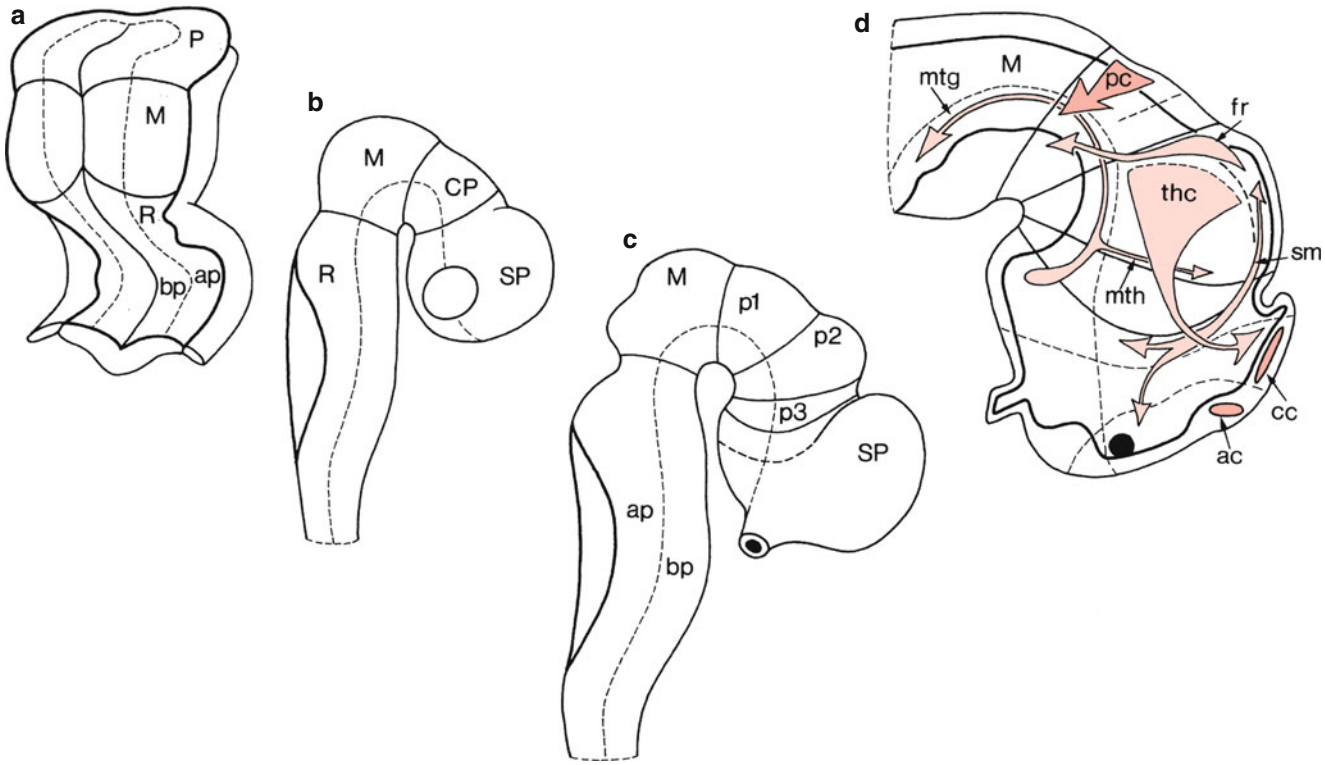

Fig. 9.2 (**a**–**c**) Prosomeric segmentation of the murine brain at E8.5 (**a**), E9.5 (**b**) and E10.5 (**c**) and **d** segmental organization of the murine diencephalon. *ac* anterior commissure, *ap* alar plate, *bp* basal plate, *cc* corpus callosum, *CP* caudal prosencephalon, *fr* fasciculus retroflexus, *M* mesencephalon, *mtg* mammillotegmental tract, *mth* mammillothalamic tract, *P* prosencephalon, *pc* posterior commissure, *p1-p3* prosomeres, *R* rhombencephalon, *sm* stria medullaris, *SP* secondary prosencephalon, *thc* thalamocortical projection (After Martínez and Puelles 2000)

anteroposterior axis and the other along the mediolateral axis (Chap. 2). An additional dorsal-ventral patterning mechanism is important for subdividing the telencephalon into dorsal, pallial and ventral, subpallial structures (Marín and Rubinstein 2002; Campbell 2003; Zaki et al. 2003; Sousa and Fishell 2010; Medina and Abellán 2012). Genetic engineering has produced a great variety of knockout mice and zebrafish, the study of which has greatly improved our knowledge of these patterning mechanisms (Schier 2001; Marín and Rubinstein 2002; Rallu et al. 2002b; Zaki et al. 2003; Tvrdik and Capecchi 2012). Defects in mediolateral patterning lead to the ***prosencephalies***, a group of complex malformations of the forebrain, involving the hypothalamus, the eyes and the basal telencephalon. ***Holoprosencephaly*** (***HPE***) is the most common developmental malformation of the forebrain, ranging from 1 in 16,000 in live births to 1 in 250 in therapeutic abortions (Matsunaga and Shiota 1977; Shiota 1993; Muenke and Beachy 2001; Cohen and Shiota 2002; Shiota and Yamada 2010). Several developmental pathways such as those operating the Sonic hedgehog (SHH) and Nodal signalling factors are involved in the pathogenesis of HPE and laterality defects (Roessler and Muenke 2001, 2010; Cohen 2010; Sect. 9.7.2). In this chapter the development of the various derivatives of the embryonic forebrain and disorders that may appear during this development, HPE in particular, will be discussed. The further development of the cerebral cortex and its disorders will be discussed in Chap. 10.

9.2 Prosomeres and Pattern Formation of the Forebrain

Already during neurulation, the prosencephalon becomes subdivided into two transverse **proneuromeric regions**, known as the caudal, epichordal, proneuromere, giving rise to the caudal diencephalon, and the rostral, prechordal, proneuromere forming the secondary prosencephalon (Fig. 9.2). The secondary prosencephalon gives rise to the telencephalon, the eye vesicles and the hypothalamus or

rostral diencephalon (Puelles 1995; Shimamura et al. 1995; Rubinstein et al. 1998; Puelles and Rubinstein 2003; Puelles et al. 2008, 2012a). The prosencephalic proneuromeres were subsequently subdivided into smaller transverse domains known as **prosomeres** (Puelles et al. 1987; Bulfone et al. 1993; Puelles 1995; Rubinstein et al. 1998; Puelles et al. 2000, 2008, 2013), which are composed of alar and basal components. Prosomeres P1–P3 form the diencephalon proper or **caudal diencephalon**: P1 is known as the synencephalon, P2 as the caudal parencephalon and P3 as the rostral parencephalon. The alar component of the synencephalon forms the pretectum, that of the caudal parencephalon the epithalamus and dorsal thalamus, and that of the rostral parencephalon the ventral thalamus or prethalamus. The basal components form the rostral part of the dopaminergic substantia nigra-ventral tegmental area of Tsai (VTA) complex and the interstitial nucleus of Cajal, some related nuclei and the fields of Forel, collectively the diencephalic or prerubral tegmentum. Molecular marker expression data in chicken and mouse embryos suggest the **zona limitans intrathalamica** (**ZLI**) or mid-diencephalic organizer as a bona fide compartment with local signalling function (Scholpp and Lumsden 2010; Kiecker and Lumsden 2012. The **protosegment**, previously described as the prosomeres P4–P6 gives rise to the secondary prosencephalon. From this prechordal part of the prosencephalon the hypothalamus or **rostral diencephalon**, the optic vesicles and the telencephalon arise (Puelles and Rubinstein 2003; Puelles et al. 2012a, 2013). Two hypothalamic prosomeres can be distinguished, a rostral (terminal) and a caudal (peduncular) one. The basal plate of the secondary prosencephalon gives rise to various subdivisions of the hypothalamus, as originally defined for human embryos by His (1893; Keyser 1972, 1979), and the subthalamic nucleus, whereas from the alar part the anterior hypothalamus, the supraoptic nucleus (SON) and paraventricular nucleus (PVN) and the entire telencephalon arise. From the most rostral part of the secondary prosencephalon, known as the **acroterminal region**, the commissural plate, the eye vesicles, the most rostral parts of the hypothalamus and the neurohypophysis arise (Fig. 9.3).

Fate mapping experiments suggest that the telencephalon derives from the anterolateral neural plate and the anterior neural ridge (Chap. 2). Ventral parts of the forebrain such as the hypothalamus and the eye vesicles arise from the medial part of the prosencephalic part of the neural plate. Pallial and subpallial parts of the telencephalon arise from the lateral parts of the prosencephalic neural plate. The lateral border of this part of the neural plate forms the dorsal, septal part of the telencephalon, whereas its rostral, median part gives rise to the commissural plate from which the anterior commissure, the corpus callosum and the hippocampal commissure arise. During the formation of the neural plate, **anteroposterior patterning** within the forebrain appears to be controlled by

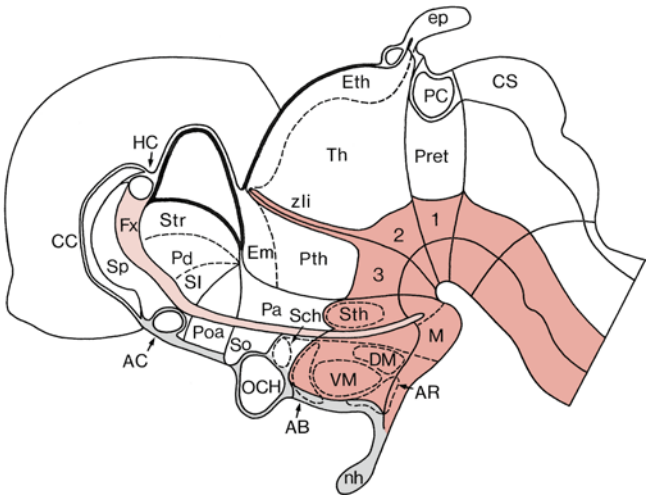

Fig. 9.3 Prosomeric model of the human brain. The basal part of the mesencephalon and the prosencephalon are indicated in *medium red*, the fornix (*Fx*) in *light red* and the acroterminal region, the most rostral part of the prosencephalon, in *light grey*. *AB* anterobasal hypothalamic nucleus, *AC* anterior commissure, *AR* arcuate nucleus, *CC* corpus callosum, *CS* corpus superior, *DM* dorsomedial hypothalamic nucleus, *Em* eminentia prethalamica, *ep* epiphysis, *Eth* epithalamus, *HC* hippocampal commissure, *M* mammillary nucleus, *nh* neurohypophysis, *OCH* optic chiasm, *Pa* paraventricular nucleus, *PC* posterior commissure, *Pd* pallidum, *Poa* preoptic area, *Pret* pretectum, *Pth* prethalamus, *Sch* suprachiasmatic nucleus, *SI* substantia innominata, *So* supraoptic nucleus, *Sp* septum pellucidum, *Sth* subthalamic nucleus, *Str* striatum, *Th* thalamus, *VM* ventromedial hypothalamic nucleus, *zli* zona limitans intrathalamica, *1–3* tegmental part of prosomeres 1–3 (After Puelles et al. 2008)

the **anterior neural ridge** at the rostral end of the neural plate (Shimamura and Rubinstein 1997; Houart et al. 1998, 2002; Marín and Rubinstein 2002; Rallu et al. 2002b). Its patterning properties may be mediated by FGF8. FGF8 signalling regulates the expression of *Foxg1* (earlier known as *brain factor 1* or *BF1*), a transcription factor that is required for normal telencephalic and cortical morphogenesis (Shimamura et al. 1995; Shimamura and Rubinstein 1997; Monuki and Walsh 2001). In all vertebrates studied, the forkhead transcription factor Foxg1, previously named BF-1, is one of the first transcription factors expressed in the neural plate telencephalic territory (Danesin and Houart 2012). It has been shown to be essential to many aspects of telencephalic development. Loss and gain of function mutations in the *FOXG1* gene have been found to cause severe intellectual disability such as Rett syndrome, epilepsy and microcephaly (Chap. 10). In zebrafish and mice, *Foxg1* orchestrates dorsoventral patterning of the telencephalon by integrating several signalling centres (Danesin et al. 2009): Foxg1-depleted telencephalic cells fail to adopt a ventral identity and transform into more dorsal fates. Early Wnt signalling appears to be required in formation of the pallium. Activation of the pathway is done by Wnt8b, secreted by the telencephalic dorsal signalling centre. Partition of the telencephalon in *subpallial*

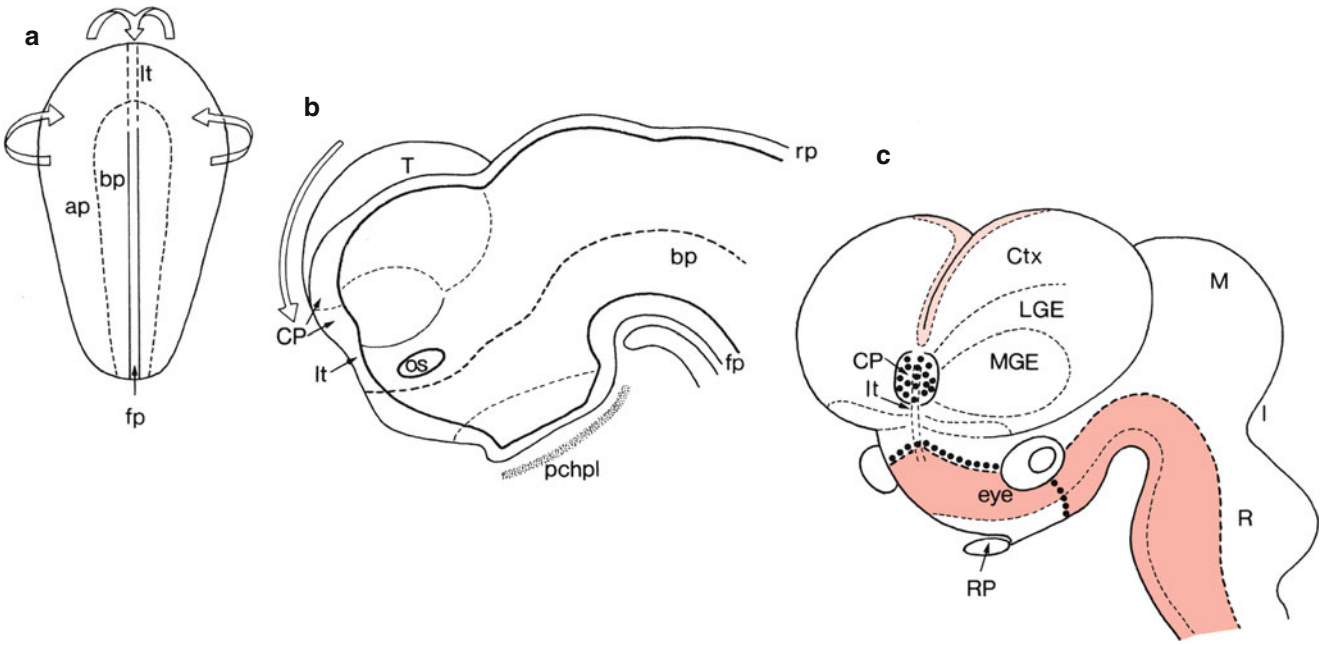

Fig. 9.4 The longitudinal organization and signalling centres of the developing murine prosencephalon: (**a**) model of the longitudinal domains of the neural plate; (**b**) medial view of the neural tube; (**c**) signalling centres in the prosencephalon. The expression of FGF8 is indicated by *dots*, that of BMP4 and WNT3a in *light red* and that of SHH in *red. ap* alar plate, *bp* basal plate, *CP* commissural plate, *Ctx* cortex, *fp* floor plate, *I* isthmus, *LGE* lateral ganglionic eminence, *lt* lamina terminalis, *M* mesencephalon, *MGE* medial ganglionic eminence, *os* optic stalk, *pchpl* prechordal plate, *R* rhombencephalon, *RP* Rathke's pouch, *rp* roof plate, *T* telencephalon (After Shimamura et al. 1995; Marín and Rubinstein 2002)

and *pallial* halves therefore depends upon Hh (secreted by the telencephalic floor) and Wnt (secreted by the roof plate) signalling. Foxg1 acts as an integrator of these two signalling activities in telencephalic progenitors.

Coordinate regulation and synergistic actions of BMP4, SHH and FGF8 in the rostral prosencephalon regulate morphogenesis of the telencephalic and optic vesicles (Hébert et al. 2002; Ohkubo et al. 2002). In mice, reduction in FGF8 expression in the anterior neural ridge leads to rostral midline defects in the forebrain (Shanmugalingam et al. 2000), similar to that described in mice lacking the *Foxg1* gene (Xuan et al. 1995; Dou et al. 1999). Fibroblast growth factor (FGF) signalling is also required for olfactory bulb morphogenesis (Hébert et al. 2003). The olfactory bulb may be particularly susceptible to FGF signalling as observed in mouse embryos carrying a hypomorphic allele of *Fgf8* (Meyers et al. 1998): they lack olfactory bulbs. Hébert et al. (2003) showed that the FGF receptor gene *Fgfr1* is essential for the formation of the olfactory bulb. In *Fgfr1* mutant mice, only small bulb-like protrusions are formed. Anteroposterior patterning of the rest of the telencephalon appears to be largely normal in *Fgfr1* mutants.

Whereas anteroposterior patterning of the forebrain generates transverse subdivisions, i.e. the prosomeres, mediolateral patterning generates longitudinal subdivision of the neural plate into alar and basal plates (Fig. 9.4). **Mediolateral patterning** of the forebrain involves signals from the axial mesendoderm (the prechordal plate) and non-neural ectoderm (Rubinstein and Beachy 1998; Lee and Jessell 1999). **Medial** or **ventral patterning** of the prosencephalic part of the neural plate is primarily regulated by the prechordal plate through SHH signalling, whereas its **lateral** or **dorsal patterning** is mediated by members of the transforming growth factor β (TGFβ) superfamily such as bone morphogenetic proteins (BMPs) and growth differentiating factors, largely derived from the neural ridge and non-neural ectoderm flanking the anterior neural plate. Mouse embryos that lack SHH fail to form normal ventral brain structures and show markedly reduced expression of ventral markers (Chiang et al. 1996; Litingtung and Chiang 2000; Rallu et al. 2002a, b). In *Drosophila*, all hedgehog signalling is mediated through the *cubitus interruptus* (*ci*) gene (Aza-Blanc and Kornberg 1999). The mammalian homologues of *ci*, the *Gli* genes, have a similar function. *Gli1* and *Gli2* act as activators and *Gli3* mainly as a repressor (Matise and Joyner 1999). In *Gli3* mutant mice, ventral telencephalic markers expand dorsally into the cortex (Grove et al. 1998; Theil et al. 1999; Rallu et al. 2002a, b). The balance between *Shh* and *Gli3* gene function appears to be crucial for the establishment of dorsoventral patterning within the telencephalon (Rallu et al. 2002b; Sousa and Fishell 2010). The SHH-GLI pathway may be deregulated in brain tumours (Dahmane et al. 2001; Biesecker 2008; Chap. 8).

9.3 Development of the Diencephalon

The diencephalon in its classic, columnar view (Herrick 1910; Droogleever Fortuyn 1912) was divided into four dorsoventrally arranged columns separated by ventricular sulci, i.e. the epithalamus, the dorsal thalamus, the ventral thalamus or subthalamus, and the hypothalamus (Fig. 9.5). Extensive embryological studies by the Swedish school of neuroembryologists (Bergquist and Källén 1954; Chap. 2) and a more recent Spanish school initiated by Luis Puelles made it clear that the thalamic 'columns' are derived from transversely oriented zones, the prosomeres. Currently, the diencephalon is subdivided into three segmental units (Puelles et al. 2008, 2012a, b, 2013; Figs. 9.3 and 9.6) which, from caudal to rostral, contain in their alar domains the pretectum (prosomere 1 or P1), the epithalamus and the thalamus (P2), and the prethalamus and the eminentia thalami (P3). The diencephalic basal plate contains the substantia nigra-VTA complex, the interstitial nucleus of Cajal and related nuclei and the fields of Forel, collectively the prerubral tegmentum (Fig. 9.6). The entire hypothalamus arises from the alar and basal components of the secondary prosencephalic protomere. The neurohypophysis appears to arise very rostrally from the acroterminal region (included in P6). Several genes show a diencephalic prosomere-related pattern, including *Gbx2* (Bulfone et al. 1993; Miyashita-Lin et al. 1999), *Otx1*/*Otx2* (Simeone et al. 1992, 1993; Larsen et al. 2001; Zeltser et al. 2001), *Pax6* (Stoykova et al. 1996; Grindley et al. 1997), *Dlx2* (Larsen et al. 2001; Zeltser et al. 2001), and *Dlx5* and *Math4a* (González et al. 2002; Fig. 9.29). For more recent data, see the Allen Developing Mouse Brain Atlas (http://developingmouse.brain-map.org). *Emx2* cooperates with *Otx2* at the onset of its expression to generate the territory of the future diencephalon (Suda et al. 2001). The ZLI is established by the interaction between *Fez* and *Otx* genes (Scholpp and Lumsden 2010). The first step in generating neuronal diversity in the thalamus is the formation of spatial diversity of thalamic progenitor cells, which is

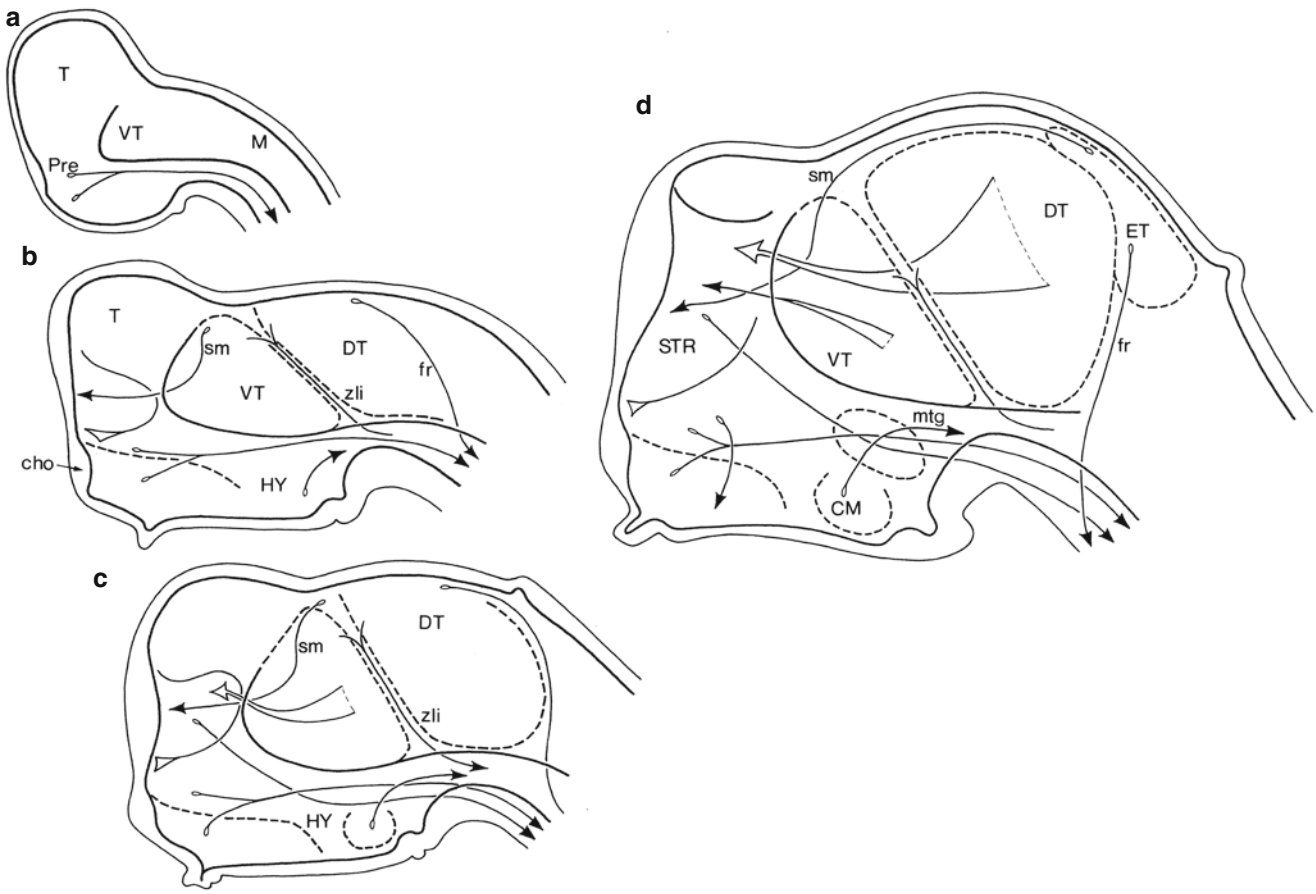

Fig. 9.5 Classic subdivision of the human diencephalon and early phases in the development of fibre connections of the forebrain, (**a**) 6-mm crown-rump length (*CRL*); (**b**) 9.5-mm CRL; (**c**) 11-mm CRL; (**d**) 18-mm CRL. Note that this figures precludes the prosomeric subdivision of the prosencephalon. Dorsal thalamic, ventral thalamic and hypothalamic domains are found in a caudorostral position to each other, not dorsoventral. *cho* chiasma opticum, *CM* corpus mammillare, *DT* dorsal thalamus, *ET* epithalamus, *fr* fasciculus retroflexus, *HY* hypothalamus, *M* mesencephalon, *mtg* mammillotegmental tract, *Pre* preoptic area, *sm* stria medullaris, *STR* striatum, *T* telencephalon, *VT* ventral thalamus, *zli* zona limitans intrathalamica (After Gilbert 1935)

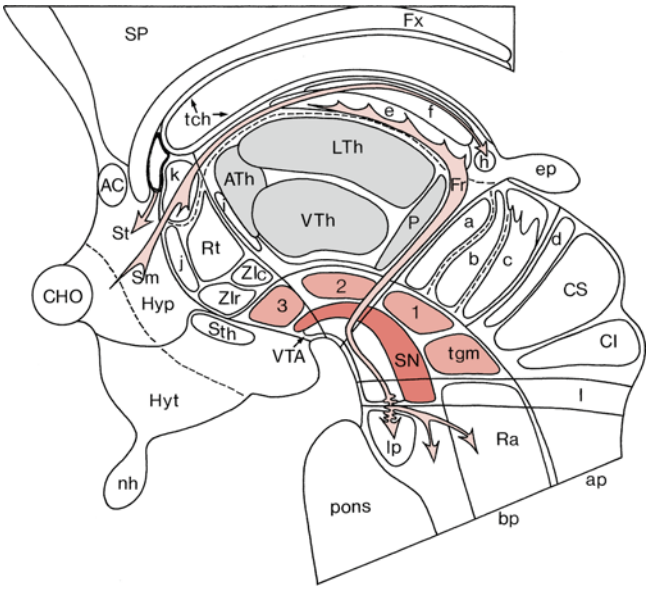

Fig. 9.6 Subdivision of the human diencephalon based on the prosomeric approach. The thalamic nuclear groups are indicated in *light grey*, some fibre bundles in *light red*, the tegmental parts of the diencephalon and mesencephalon in *medium red* and the substantia nigra (*SN*) in *red*. *a* precommissural tectal region, *AC* anterior commissure, *ap* alar plate, *Ath* anterior thalamic nuclei, *b* juxtacommissural pretectal nuclei, *bp* basal plate, *c* commissural pretectal nucleus, *CHO* chiasma opticum, *CI* colliculus inferior, *CS* colliculus superior, *d* tectal grey, *e* lateral habenular nucleus, *ep* epiphysis, *f* medial habenular nucleus, *Fr* fasciculus retroflexus, *Fx* fornix, *h* habenular commissure, *Hyp* peduncular hypothalamus, *Hyt* terminal hypothalamus, *I* isthmus, *i* intergeniculate leaflet, *Ip* interpeduncular nucleus, *j* perireticular nucleus, *k* interstitial nucleus of stria medullaris, *Lth* lateral thalamic nuclei, *nh* neurohypophysis, *P* posterior thalamic nuclei, *Ra* raphe nucleus, *Rt* reticular thalamic nucleus, *Sm* stria medullaris, *SP* septum pellucidum, *St* stria terminalis, *Sth* subthalamic nucleus, *tch* tela choroidea, *tgm* tegmentum mesencephali, *VTA* ventral tegmental area, *Vth* ventral thalamic nuclei, *Zlc*, *Zlr* caudal and rostral parts of zona incerta, *1–3* tegmental parts of prosomeres 1–3 (After Puelles et al. 2008)

controlled by locally expressed signalling molecules such as Shh, Wnt proteins and Fgf8 (Nakagawa and Shimogori 2012).

9.3.1 Development of the Thalamus

The development of the human thalamus has been rather extensively studied with classic staining techniques (Schwalbe 1880; Gilbert 1935; Cooper 1950; Dekaban 1954; Kuhlenbeck 1954; Yamadori 1965; Yakovlev 1969; Kostović 1990; Mojsilović and Zečević 1991). The thalamus is involved in central processing of sensory, motor and limbic functions. Early in development, the human diencephalon is thin-walled, but later the anlage of the thalamus expands enormously. Due to this expansion, the telencephalic-diencephalic boundary plane enlarges and changes its orientation from more or less transverse to almost rostrocaudal. Moreover, the lateral geniculate body becomes laterocaudally displaced.

The **dorsal thalamus** or, more appropriately, the **thalamus** is largely composed of nuclei, relaying sensory, motor and limbic information to the cerebral cortex and subpallial structures. The following groups are usually distinguished (Jones 1985; Hirai and Jones 1989; Armstrong 1990; Onye 1990; Morel et al. 1997; Voogd et al. 1998; Percheron 2004), partly separated by the internal medullary lamina (Fig. 9.7a):

1. A **lateral group**, involved in somatosensory relay (*nucleus ventralis posterior complex*) and motor control (*nuclei ventralis lateralis* and *ventralis anterior*).
2. A **medial group**, formed by the *mediodorsal nucleus* with extensive projections to the prefrontal cortex, and *midline* and *intralaminar nuclei* with projections to the striatum and to that part of the cerebral cortex that innervates the same part of the striatum.
3. An **anterior group**, relaying information from the mammillary nuclei to the limbic cortex, the cingulate cortex in particular. The more posteriorly situated *laterodorsal nucleus* is often associated with the anterior group for its connections with the cingulate gyrus.
4. A large **posterior group** is composed of the *posterior complex*, involved in pain transmission, the *nucleus lateralis posterior* and the *pulvinar*, involved in visual orientation, eye movements and accommodation, and the *medial* and *lateral geniculate nuclei* which relay auditory and visual information, respectively.

The thalamocortical and corticothalamic projections pass via the internal capsule (Chap. 10). The maturation of thalamic radiations between 34 and 41 weeks of gestation has been studied with DTI (Aeby et al. 2009). The cortical projection areas of the main thalamic nuclei in the adult human brain are shown in Fig. 9.7b, c.

The **ventral thalamus** is usually said to be composed of the ventral lateral geniculate or pregeniculate nucleus, the thalamic reticular nucleus and the zona incerta. Puelles and Rubinstein (2003) advocated the term **prethalamus** as an alternative. The **thalamic reticular nucleus** is a shell-like structure along the lateral border of the thalamus, and is situated between the external medullary lamina and the internal capsule (Fig. 9.7a). The human fetal reticular nucleus consists of four subdivisions, clearly visible in the sixth/seventh gestational month (Ulfig et al. 1998; Ulfig 2002b). The main portion and the perireticular nucleus are prominent structures. Both parts are dramatically reduced in size during further development. The *perireticular nucleus* is not even visible in the adult brain (Ulfig et al. 1998). In rats, the perireticular nucleus also disappears almost completely (Mitrofanis and Baker 1993; Earle and Mitrofanis 1996). These transient features can be correlated with the role of the reticular nucleus in guiding outgrowing thalamocortical axons and as an intermediate target for corticofugal fibres

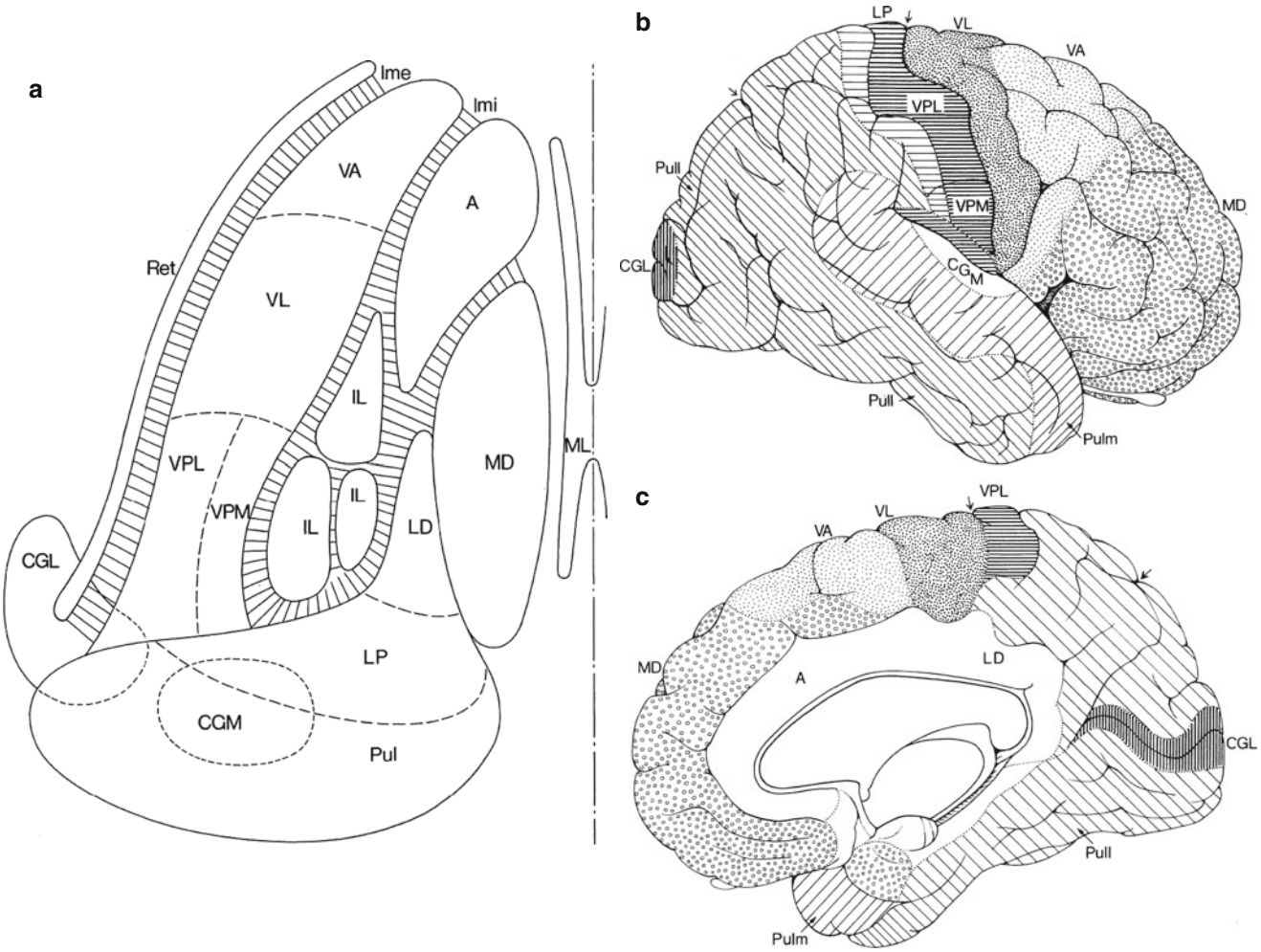

Fig. 9.7 (**a**) Principal cell masses in the human thalamus shown in a horizontal section; (**b**, **c**) thalamocortical projection areas shown in lateral (**b**) and medial views (**c**) of the human cerebrum. *Arrows* indicate the central and parieto-occipital sulci. *A* anterior nucleus, *CGL* corpus geniculatum laterale, *CGM* corpus geniculatum mediale, *IL* intralaminar nuclei, *LD* laterodorsal nucleus, *lme* external medullary lamina, *lmi* internal medullary lamina, *LP* nucleus lateralis posterior, *MD* mediodorsal nucleus, *ML* midline nuclei, *Pul* pulvinar, *Pull* lateral part of pulvinar, *Pulm* medial part of pulvinar, *Ret* nucleus reticularis thalami, *VA* nucleus ventralis anterior, *VL* nucleus ventralis lateralis, *VPL* nucleus ventralis posterolateralis, *VPM* nucleus ventralis posteromedialis

(Mitrofanis 1992; Mitrofanis and Baker 1993; Earle and Mitrofanis 1996).

The **subthalamic nucleus** is usually included in the basal ganglia, but is a dorsally migrated *hypothalamic* cell mass, which originated from the retromammillary area (Keyser 1972; Marchand et al. 1986; Skidmore et al. 2008). This migration can be easily verified in the Allen Atlas using the gene markers *Pitx2* and *Foxp1* (Puelles et al. 2012a). Therefore, the subthalamic nucleus must be classified as a hypothalamic nucleus.

In rodents, the **birthdays** of the thalamic nuclei have been extensively analysed in [^{3}H]thymidine studies (Angevine 1970, 1978; Keyser 1972; McAllister and Das 1977; Altman and Bayer 1979a, b, c; Bayer and Altman 1995a, b). Most thalamic nuclei are born between E13 and E19 (Table 9.1). Spatiotemporal gradients were found in the time of origin of thalamic nuclei (Fig. 9.8), in general, caudorostrally, ventrodorsally and outside-in oriented. Cells of posterior thalamic nuclei are born before those of anterior nuclei. Ventral thalamic nuclei such as the reticular nucleus are generated slightly earlier than dorsal thalamic nuclei. Lateral nuclei are born before medial nuclei such as the mediodorsal nucleus. Bayer et al. (1995) estimated that in human embryos the reticular nucleus and the medial and lateral geniculate nuclei are generated from late in week 5 to week 6 of development, ventrobasal complex neurons from late in week 5 up to the middle of week 7 of development, and the anterior complex from weeks 7–11 (Table 9.1). Two thalamic nuclei in particular received much attention, the **lateral geniculate nucleus** (**LGN**) and the pulvinar.

Table 9.1 Time of neuron origin data of diencephalic nuclei in Chinese hamsters, rats and estimated data for the human brain

Diencephalic nuclei	Time of neuron origin data in Chinese hamsters in embryonic days (gestation time: 20–21 days)	Time of neuron origin data in rats in embryonic days (gestation time: 21–22 days)	Estimated data human brain (developmental weeks)	Estimated data human brain (developmental weeks)
			Time of neuron origin	Migration and settling
Dorsal thalamus				
Anterior nuclei	?	E15–16(17)	6–8	7–11
Ventrobasal complex	?	E(14)15–E16	Late 5–middle 7	7–9
Lateral geniculate nucleus	E14	E14–E15	Late 5–6	7–9
Medial geniculate nucleus	E13	E14(15)	Late 5 to late in 6	End of 6–8
Ventral thalamus				
Reticular nucleus	E14	E(13)14–E15	Late 5–7	Late 7–11
Hypothalamus				
Supraoptic and paraventricular nuclei	E13	E13–E15	Early 5 to beginning of 7	Middle 7
Suprachiasmatic nucleus	E14–E16	E14-E17	5–6	Late 5–7
Lateral hypothalamus	?	E(12)13–E14(15)	Early 5 to beginning of 7	Late 5–7
Mammillary body				
Lateral	E13	E13–E14(15)	4–6	5–7
Medial	E14	E(14)15–E16	5–8	7–14
Preoptic regions				
Median	E15?	E13–E15(17)	4–10	5–7
Medial	E13	E(14)15–E17(19)	4–8	5–7
Lateral	E12	E12–E14(15)	4–7	5–7
Sexually dimorphic nucleus	?	E(15)16–E19(20)	End of 6–11	?

Sources: After Keyser (1972), Altman and Bayer (1978a, b, 1979a, b, c) and Bayer et al. (1995)

The development of the LGN or **corpus geniculatum laterale** (**CGL**) has been extensively studied in rat (Brückner et al. 1976; Lund and Mustari 1977), cat (Shatz et al. 1990), ferret (Sur and Leamey 2001), rhesus monkey (Rakic 1977a, b) and human (Gilbert 1935; Cooper 1945, Dekaban 1954; Hitchcock and Hickey 1980; Hevner 2000) embryonic and fetal material. In the rhesus monkey, LGN neurons are generated during 8–9 days at the end of the first quarter of the 165-day gestational period. The first neurons are generated at E36, approximately 6 days after the first retinal ganglion cells are being born (Rakic 1977a, b). Several generations of neurons produced in a restricted area of the ventricular zone appear to migrate along a single cellular fascicle and accumulate in a column-shaped aggregate. Neurons are generated along an outside-in gradient (Fig. 9.9). Initially, the axis of this gradient is oriented lateromedially but later becomes oriented ventrodorsally, so that in the mature monkey, early generated neurons lie in the ventral magnocellular layers, whereas neurons generated later become part of the dorsal parvocellular layers. In the human brain, the CGL develops its characteristic six-layered structure from the 22nd until the 25th gestational week (Cooper 1945; Dekaban 1954; Hitchcock and Hickey 1980). Its cell layers are initially oriented parallel to the dorsoventral axis but, owing to rotation

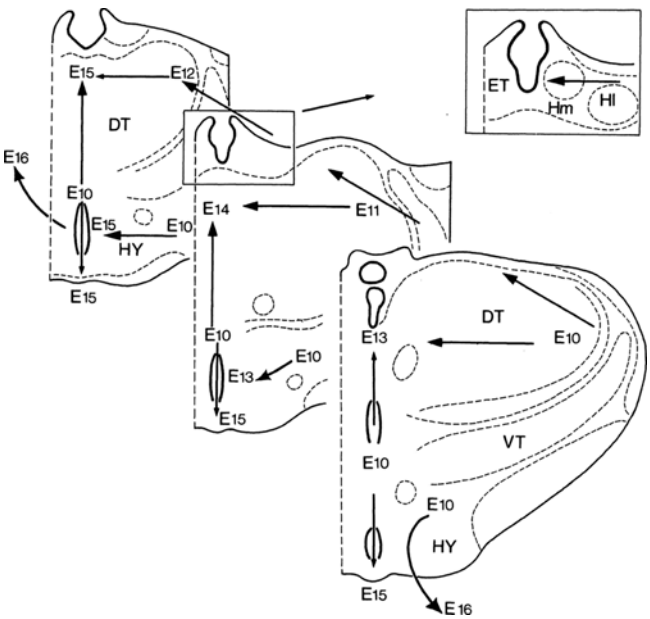

Fig. 9.8 Summary of rodent [^{3}H]thymidine data diencephalon. The various caudorostral, ventrodorsal, dorsoventral and lateromedial gradients are indicated with *arrows*. *DT* dorsal thalamus, *ET* epithalamus, *Hl* lateral habenular nucleus, *Hm* medial habenular nucleus, *HY* hypothalamus, *VT* ventral thalamus (After Angevine 1970)

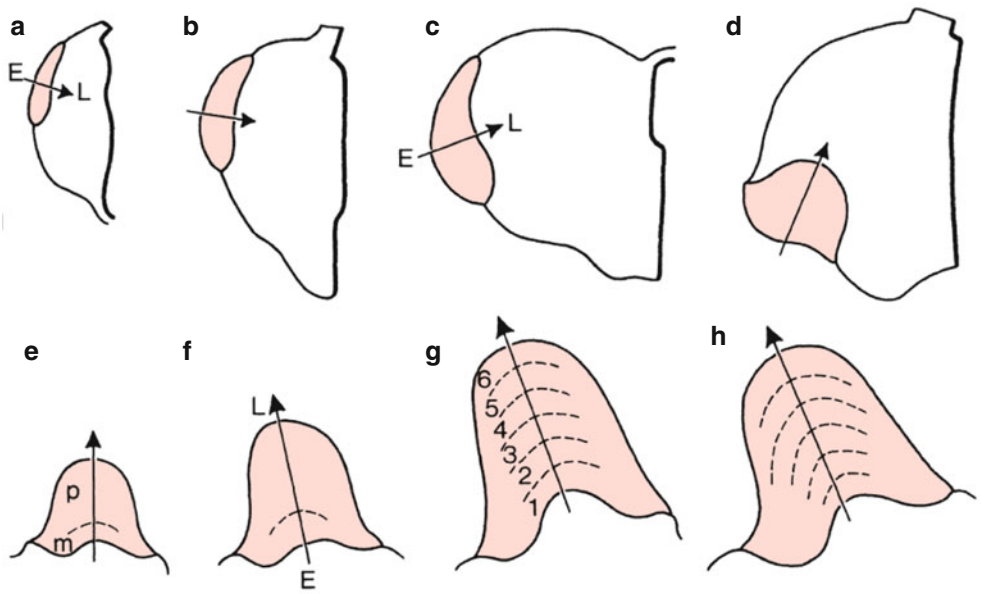

Fig. 9.9 Development of the monkey lateral geniculate nucleus in coronal sections of the diencephalon at E48 (**a**), E58 (**b**), E77 (**c**), E84 (**d**), E91 (**e**), E97 (**f**), E112 (**g**) and P60 (**h**). The *E-L* axis indicates the early-to-late gradient of generated neurons. *m* magnocellular part, *p* parvocellular part, *1–6* layers emerging between E90 and E105 (After Rakic 1977b)

and differential growth of the thalamus, become oriented almost parallel to the mediolateral axis by the time of birth (Hevner 2000).

The **pulvinar**, the most prominent thalamic nucleus in the human brain, is not only generated in the diencephalic ventricular zone but, moreover, receives neurons from the ganglionic eminence of the telencephalon (Fig. 9.10). Rakić and Sidman (1969) showed that between the 16th and 34th week of gestation, cells pass from the medial ganglionic eminence into the lateral and posterior parts of the thalamus. Most of these neurons appear to migrate along a transient fetal structure, the **gangliothalamic body**. In a subsequent study of the fetal monkey brain, Ogren and Rakic (1981) were unable to demonstrate the presence of a gangliothalamic body, and suggested that this migration pathway is a unique feature of the developing human brain. Letinić and Kostović (1997) found the gangliothalamic body between 15 and 34 gestational weeks along the entire rostrocaudal thalamus, particularly at the level of the anterior nuclear complex, the mediodorsal nucleus, the pulvinar and the CGL, and suggested that, apart from the pulvinar, also the mediodorsal and anterior nuclei and the CGL are recipients of telencephalic neurons. Letinić and Rakic (2001) showed that these neurons are GABAergic and express *Dlx1*/*Dlx2*. A similar migratory pathway has not been found in non-human primates and rodents (Anderson et al. 1997a, 1999; Lavdas et al. 1999; Wichterle et al. 1999, 2001), supporting the idea that it may be a special feature of human thalamic development. GABAergic neurons are absent in many thalamic nuclei, except for the CGL (Harris and Hendrickson 1978; Ottersen and Storm-Mathisen 1984), but in the primate brain GABAergic cells form approximately 30 % of the neurons in every thalamic nucleus (Montero and Zempel 1986).

Thalamocortical projections arise rather early in development. Yamadori (1965) studied the development of thalamocortical projections in 5–130-mm-long human embryos. The first fibres were already recognized in the thalamus of a 5-mm embryo (approximately 3 weeks of development). Developing thalamocortical axons leave the thalamus ventrally and turn dorsolaterally at the telencephalic-diencephalic boundary. They advance below the ganglionic eminences and pause at the corticostriatal junction before entering the developing cerebral cortex. The earliest corticofugal projections, most of which originate from preplate neurons as shown in rodents, pause within the corticostriatal junction. In rodents, the **corticostriatal junction** has been characterized by lack of both *Emx1* and *Dlx1* gene expression and the presence of *Pax6* expression (Smith-Fernández et al. 1998; Puelles et al. 2000; Zaki et al. 2003; Fig. 9.29, Table 9.2). Experiments in rodents indicate that the ganglionic eminence may be an intermediate target for corticofugal and thalamocortical axons (Métin and Godement 1996; Garel et al. 2002), and that the corticostriatal junction plays an active role in the further development of these connections (Molnár et al. 1998, 2012; Auladell et al. 2000; Molnár and Hannan 2000; Molnár and Butler 2002). It has become increasingly clear that several mechanisms are involved at different stages of thalamocortical development, and each

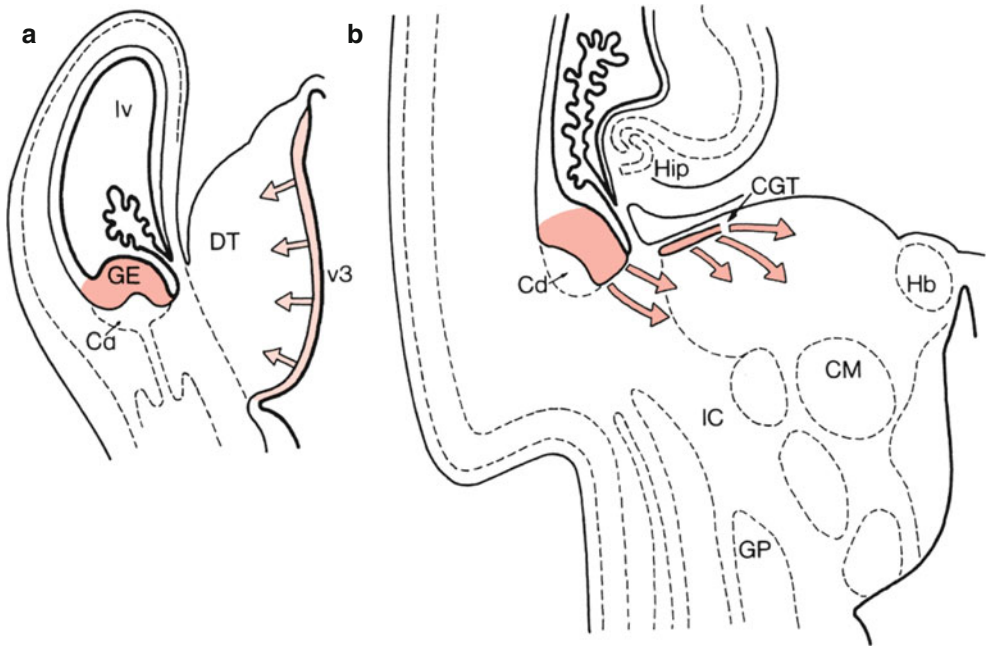

Fig. 9.10 The role of the ganglionic eminence in the development of the human thalamus. Dorsal thalamic neurons are not only generated in the neuroepithelium lining the third ventricle (*v3*, *light red*), but also in the ganglionic eminence (*GE*, *red*). These GABAergic neurons migrate along the corpus gangliothalamicum (*CGT*) and parallel routes to the dorsal thalamus. *Cd* caudate nucleus, *CM* centrum medianum, *GP* globus pallidus, *Hb* habenula, *Hip* hippocampus, *IC* internal capsule, *lv* lateral ventricle (After Rakić and Sidman 1969)

Table 9.2 Summary of mutant mice with altered early thalamocortical development

Emx2	Targeted KO	Primary defect in cortical development; disturbed thalamocortical growth at diencephalotelencephalic boundary	Not known	Mallamacci et al. (2000)
Tbr1	Targeted KO	Thalamocortical and corticothalamic axon elongation defect	Not known	Hevner et al. (2001)
Gbx2	Targeted KO	Thalamocortical and corticothalamic axon elongation disrupted at internal capsule (IC)	Not known	Hevner et al. (2002)
Mash1	Targeted KO	No thalamic fibre outgrowth beyond IC	Not known; IC cells with thalamic projections missing	Tuttle et al. (1999)
Pax6$^{Sey/Sey}$	Spontaneous mutation (*Small eye*)	Thalamocortical and corticofugal axon elongation disrupted at IC	Not known	Kawano et al. (1999), Hevner et al. (2002)
Pax6LacZ	Targeted KO	Disturbed thalamocortical and corticothalamic axon elongation at the corticostriatal junction	Not known	Stoykova et al. (2000), Jones et al. (2002)
L1	Targeted KO	Thalamocortical axon fasciculation defects in IC and at the corticostriatal junction	Selective fasciculation defect mediated by L1	Cohen et al. (1997), Dahme et al. (1997)

Source: After Molnár and Hannan (2000); López-Bendito and Molnár (2003)

contributes substantially to the eventual outcome (Molnár et al. 2012; Chap. 2). Subsequent to their interaction with cells at the corticostriatal junction, thalamocortical and corticofugal fibres proceed, intimately associated with each other, to their targets. They become 'captured' for a **waiting period** in the subplate before entering the cortical plate (Shatz et al. 1990).

Thalamocortical projections display **two levels** of **topographic organization** (Molnár 1998; López-Bendito and Molnár 2003; Marín 2003). First, specific thalamic nuclei, relaying distinct modalities of sensory (visual, somatosensory, auditory) or motor information, project to specific neocortical areas (**interareal topography**). In rodents, these thalamic nuclei are arranged following a more or less caudolateral to rostromedial gradient, whereas their corresponding cortical targets are found in caudorostral progression in the cortex. This interareal topography arises early in development and appears to be largely independent of functional activity within the thalamocortical radiation. The second level of topographic organization concerns the **topic representation** of different parts of the body, retina or inner ear in projections of thalamic nuclei to their cortical

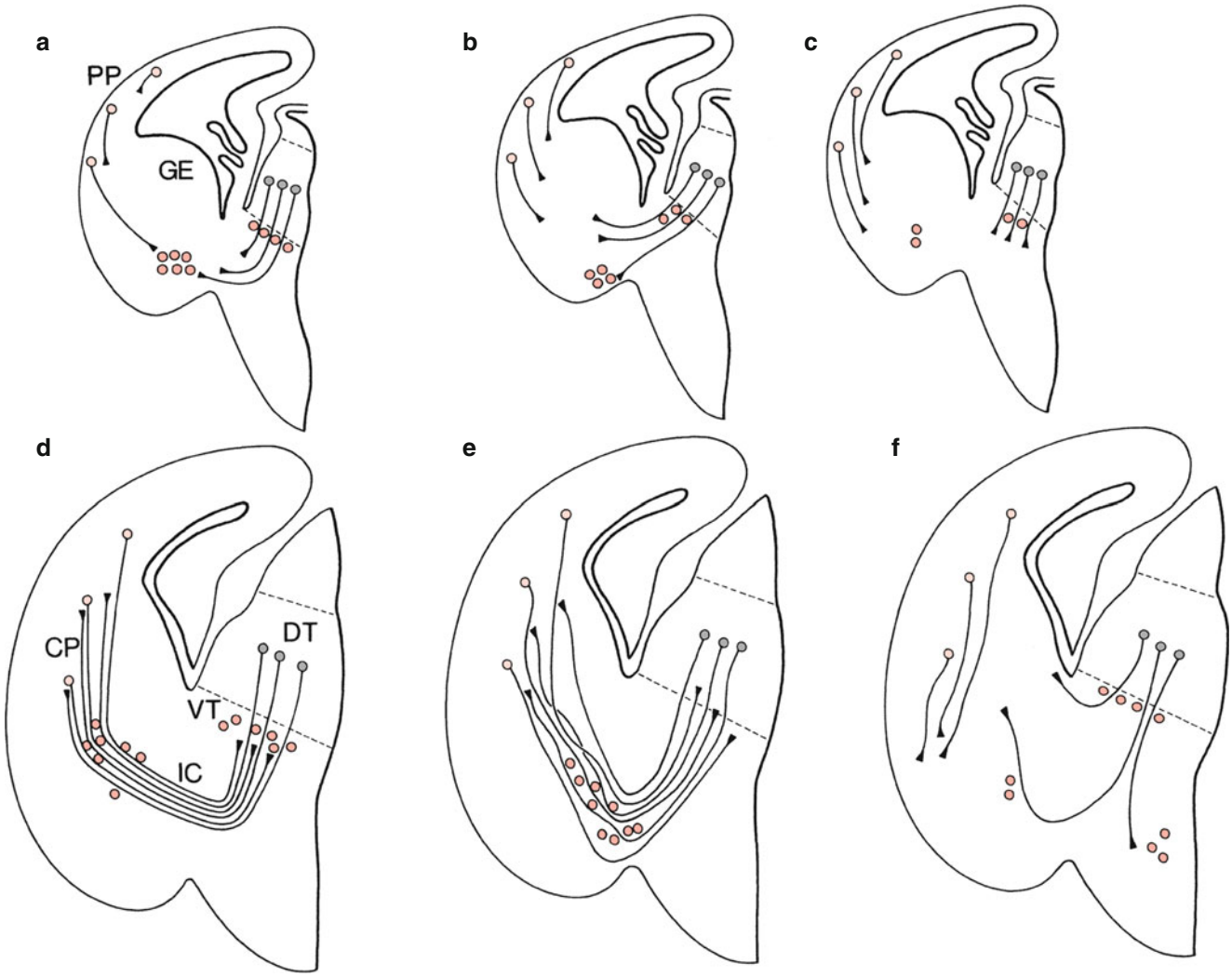

Fig. 9.11 Thalamocortical projections: data in the developing rat brain/mouse mutants : (**a**, **d**) Normal rat E13.5 and E18.5 embryos, illustrating the 'handshake' hypothesis (Fig. 2.30). (**b**, **e**) Comparable data in an *Emx2−/−* mutant. (**c**, **f**) Comparable data in a *Pax6/LacZ−/−* mutant (see text for explanation). 'Guidepost' cells in the ventral thalamus (*VT*), the basal forebrain and the internal capsule (*IC*) are indicated in *red*, thalamocortical projection neurons in *grey* and corticofugal neurons in *light red*. *CP* cortical plate, *DT* dorsal thalamus, *GE* ganglionic eminence, *PP* preplate (After López-Bendito and Molnár 2003)

targets, resulting in somatotopic, retinotopic and tonotopic maps, respectively. This second level of topographic mapping appears later in development than interareal topography. It is redefined during the first postnatal weeks, partly through activity-dependent mechanisms (López-Bendito and Molnár 2003). Interareal topography may be explained by the expression of localized cues within the cortex, controlling the targeting of thalamic axons, or by the '**handshake hypothesis**' (Blakemore and Molnár 1990; Molnár and Blakemore 1995; Molnár 1998; Fig. 9.11; Chap. 2). In this hypothesis it has been proposed that axons from the thalamus and from the early-born cortical preplate cells meet and intermingle in the basal telencephalon, so that thalamic axons grow over the scaffold of preplate axons. In mouse mutants (Table 9.2), often the disruption of thalamocortical and corticothalamic fibres is correlated (Cohen et al. 1997; Dahme et al. 1997; Kawano et al. 1999; Tuttle et al. 1999; Braisted et al. 2000; Mallamacci et al. 2000; Stoykova et al. 2000; Hevner et al. 2001, 2002; Jones et al. 2002; Molnár and Butler 2002; Molnár et al. 2012). Garel et al. (2002) showed that the establishment of topographic thalamocortical projections is not strictly determined by cortical cues, but instead is influenced by the relative position of thalamic axons inside the ventral telencephalon (Vanderhaeghen and Polleux 2004). It seems likely that the topographic organization that thalamic axons adopt in the cortex is already set upon their entry into the telencephalon, and that any alteration of their topography in this intermediate target results in a parallel perturbation of their topography in the cortex. Therefore, the develop-

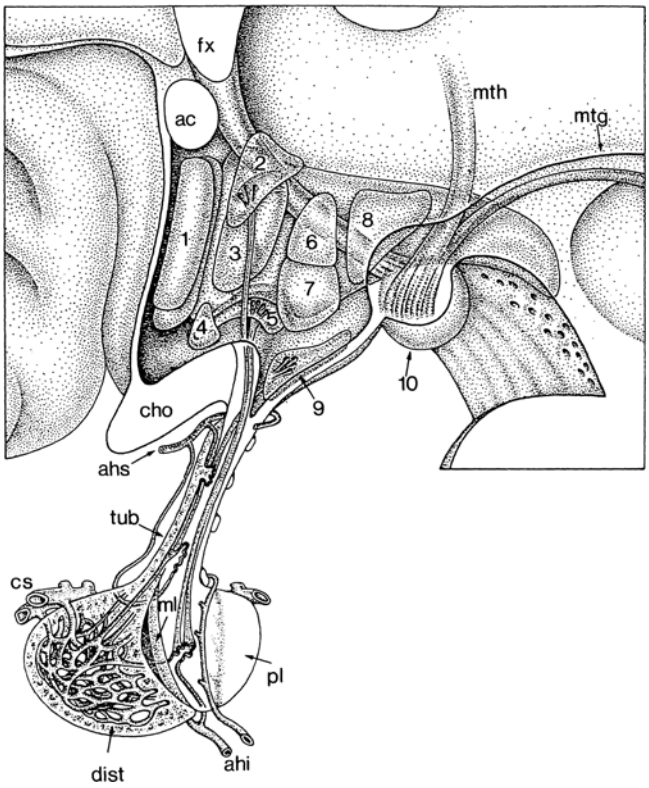

Fig. 9.12 Organization of the human hypothalamus and hypothalamo-hypophysial relations. *ac* anterior commissure, *ahi* inferior hypophysial artery, *ahs* superior hypophysial artery, *cho* chiasma opticum, *cs* sinus cavernosus, *dist* distal part of anterior pituitary lobe, *fx* fornix, *ml* middle pituitary lobe, *mtg* mammillotegmental tract, *mth* mammillothalamic tract, *pl* posterior pituitary lobe, *tub* tuberal part of anterior pituitary lobe, *1* preoptic nucleus, *2* paraventricular nucleus, *3* anterior nucleus, *4* suprachiasmatic nucleus, *5* supraoptic nucleus, *6* dorsomedial nucleus, *7* ventromedial nucleus, *8* posterior nucleus, *9* arcuate nucleus, *10* corpus mammillare (After Nauta and Haymaker 1969)

ment of interareal topography within the thalamocortical system occurs through the sorting out of thalamocortical axons in the ventral telencephalon. This sorting out is controlled by ephrins (Dufour et al. 2003; Seibt et al. 2003; Vanderhaeghen and Polleux 2004).

9.3.2 Development of the Hypothalamus

The hypothalamus is involved in a wide variety of functions in the brain. Alterations in hypothalamic nuclei are found in various endocrine diseases such as diabetes insipidus, Wolfram and Prader-Willi syndromes, and in various neurodegenerative diseases such as Alzheimer, Parkinson and Huntington diseases (reviewed in Swaab 1997, 2004). The hypothalamus is usually subdivided into four regions (Fig. 9.12), from caudal to rostral: (1) the mammillary region; (2) the tuberal region; (3) the anterior complex; and (4) the preoptic region (Braak and Braak 1987, 1992; Swaab et al. 1993; Swaab 1997, 2003; Voogd et al. 1998; Saper 2004), although the preoptic region is of subpallial origin. From a developmental point of view, however, three longitudinal subdivisions of the hypothalamus can be distinguished (Angevine 1970; Altman and Bayer 1986; Mai and Ashwell 2004) as originally proposed by Crosby and Woodburne (1940; Nauta and Haymaker 1969): a periventricular zone, an intermediate zone, and a lateral zone. The hypothalamus is now thought to arise from that part of the secondary prosencephalon that is known as the rostral diencephalon (Puelles and Rubinstein 2003).

The prosomeric approach to the development of the hypothalamus (Puelles et al. 2008, 2012a) revealed **rostral** (terminal) and **caudal** (peduncular) parts of the hypothalamus, earlier known as hypothalamic domains 2 and 1 and roughly comparable to Herrick's ventral and dorsal hypothalamus, respectively (Figs. 9.3 and 9.6). The most rostral part, the **acroterminal territory**, is characterized by *Six6* and *Foxb1* gene expression (Conte et al. 2005; Zhao et al. 2008). Shimogori et al. (2010) identified over 1,000 genes expressed dynamically over the course of hypothalamic development. Only a handful of them have been analysed functionally in any detail. The scaffold of molecularly delimited major **progenitor domains** detected in the hypothalamus is formed by two alar and three basal domains in each of the two hypothalamic parts. The addition of the corresponding acroterminal areas makes a total of at least 15 distinct major histogenetic territories, some of which may be further subdivided (Puelles et al. 2012a). This emphasizes that the hypothalamus must be considered more complex than previously assumed.

Early steps in the development of the hypothalamus include the induction of hypothalamic identity and the migration of hypothalamic precursors. The prechordal plate provides the SHH protein necessary for the formation of the hypothalamus. In mice lacking the *Shh* gene, hypothalamic tissue is absent, whereas overexpression of SHH leads to ectopic expression of hypothalamic markers (Mathieu et al. 2002). Disturbance of the development of hypothalamic nuclei may be due to disruption of genes involved in neurogenesis (*Otp*), cell migration (*Otp*, *SF-1*), cell death (*Brn2*, *Sim1*, *Arnt2*) and differentiation (*Nkx2.1*). *Brn4* knockout mice show a loss of the SON and PVN, and in mice with mutations in the gene encoding for the nuclear receptor SF-1 the ventromedial hypothalamic nucleus is absent (Martin and Camper 2001). These data suggest that similar defects may exist in human disease (Swaab 2003).

In rodents, in autoradiographic studies the hypothalamic nuclei were found to be generated mainly from E13 until E16, and preoptic nuclei over an even more protracted period, extending from E12 until E19 (Angevine 1970, 1978; Keyser 1972; Altman and Bayer 1978a, b; 1986; Bayer and Altman 1987a; Fig. 9.8, Table 9.1). The sexually dimorphic nucleus (SDN; Gorski et al. 1978) originates exceptionally

late (E15-E19). Extrapolated to the human brain, hypothalamic nuclei would be generated between the fifth and the eighth week of development, and those from the preoptic region from weeks 4 to 11 of development (Bayer et al. 1995; Table 9.1). In the fetal human hypothalamus, Koutcherov et al. (2002); see also Mai and Ashwell 2004 found three waves of neurogenesis and migration as in the rodent brain (Altman and Bayer 1986). The first neurons generated migrate into the future lateral longitudinal zone of the hypothalamus where they form the lateral hypothalamic area, the posterior hypothalamus, the lateral tuberal nucleus and the perifornical nucleus. The second wave of postmitotic neurons form the nuclei of an intermediate longitudinal zone, including the medial preoptic nucleus, the anterior hypothalamic nucleus, the ventromedial and the dorsomedial nuclei, and the mammillary body. The last neurons to be generated differentiate in close proximity to the periventricular zone, and form the suprachiasmatic nucleus, the arcuate nucleus, the PVN and the SON. All nuclei are apparent early fetally.

In humans, the **sexually dimorphic nucleus** (**SDN**) is located between the SON and the PVN. In young adult males, this nucleus is twice as large as in adult women (Swaab and Fliers 1985; Swaab et al. 1993; Swaab 1997, 2003). At birth, only about 20 % of the SDN neurons are present and sexual dimorphism is not found in the human brain. From birth up to the age of 4 years, cell numbers increase equally rapid in both sexes. About the fourth year postnatally, the number of cells starts to decrease in girls (Swaab and Hofman 1988). The large neurosecretory cells of the **supraoptic nucleus** (**SON**) and **paraventricular** (**PVN**) **nucleus** produce the neuropeptides vasopressin and oxytocin, and innervate the neurohypophysis (Dierickx and Vandesande 1977). Vasopressin acts as antidiuretic hormone in the kidney and, in women, oxytocin is involved in labour and lactation. The **infundibular nucleus** contains, among many other neuropeptides and transmitters, gonadotropin-releasing hormone (GnRH) neurons, earlier known as luteinizing hormone-releasing hormone (LHRH) neurons (Muske 1993; Swaab 1997, 2003). GnRH neurons are found in the human fetal hypothalamus from the 9th week of development. The GnRH neurons are generated in the epithelium of the medial olfactory pit and migrate from the nose into the forebrain along branches of the terminal and vomeronasal nerves rich in the neural cell adhesion molecule NCAM (Schwanzel-Fukuda and Pfaff 1989; Schwanzel-Fukuda et al. 1989). No GnRH neurons were seen in the brain until a bridge of the terminal and vomeronasal nerves was formed between the nose and the forebrain. Observations in Kallmann syndrome (Sect. 9.7.4) suggested that GnRH neurons fail to migrate from the olfactory placode into the developing brain (Schwanzel-Fukuda et al. 1989). In human embryos, GnRH-immunoreactivity was first detected in the olfactory epithelium and in cells associated with the terminal and vomeronasal nerves at 42 days of gestation (Schwanzel-Fukuda et al. 1996). GnRH neurons appear to have multiple embryonic origins (Muske 1993; Northcutt and Muske 1994), however: the olfactory placode giving rise to the septo-preoptic system, and a second, non-placodal structure giving rise to the posterior GnRH neurons.

9.3.3 Development of the Pituitary Gland

The development of the human **hypophysis cerebri** or **pituitary gland** has been extensively studied (Atwell 1926; Conklin 1968; Andersen et al. 1971; Ikeda et al. 1988; O'Rahilly and Müller 2001). It consists of two main parts, the adenohypophysis and the neurohypophysis that form the sellar pituitary. The two components are in close contact from the beginning (Figs. 9.13, 9.14, and 9.15). The area of contact between Rathke's pouch (Rathke 1838) and the forebrain gradually moves from rostral to caudal and, after 13 weeks of development, has a position similar to that found in the newborn (Ikeda et al. 1988).

The **adenohypophysial primordium** is induced by the adjacent floor of the rostral forebrain, from which the neurohypophysis develops (Sheng and Westphal 1999). In amphibian and avian embryos, the adenohypophysis originates from the anterior neural ridge (Eagleson et al. 1986; Couly and Le Douarin 1987; Chap. 2). In rats, it arises from a small area just anterior to the rostral end of the neural plate (Kouki et al. 2001). The neurohypophysis arises from the most rostral part of the secondary prosencephalon, the acroterminal region (Puelles and Rubinstein 2003; Puelles et al. 2012a). At the time Rathke's pouch forms, the oral ectoderm is in direct contact with the neuroectoderm of the ventral forebrain (Fig. 9.13), without intervening mesoderm (Schwind 1928). In in vitro tissue recombination assays a dramatic effect of neuroectoderm on the growth and differentiation of Rathke's pouch has been demonstrated (Daikoku et al. 1982; Watanabe 1982). The homeobox gene *Nkx2.1*, expressed in the ventral forebrain but not in the oral ectoderm or Rathke's pouch (Lazzaro et al. 1991), may provide the inductive signal. In *Nkx2.1* mutants, apart from severe defects in the development of the forebrain, the pituitary gland is ablated (Kimura et al. 1996). A **two-step induction** of Rathke's pouch is required (Watkins-Chow and Camper 1998; Sheng and Westphal 1999; Dattani and Robinson 2000; Zhu and Rosenfeld 2004). Both a BMP4 signal and FGF8 activity from the ventral forebrain are required for the development of a definitive pouch. Initially, at E8.5, BMP4 induces the oral ectoderm to form a pouch placode. Formation of the definitive pouch requires the activation of two LIM homeobox factors (*Lhx3* and *Lhx4*) in the rudiment. FGF8, expressed in the ventral forebrain at E9.25, provides the signal that initiates and maintains *Lhx* gene expression in the pouch (Sheng et al. 1997; Sheng and Westphal 1999; Zhu and Rosenfeld 2004). Hedgehog

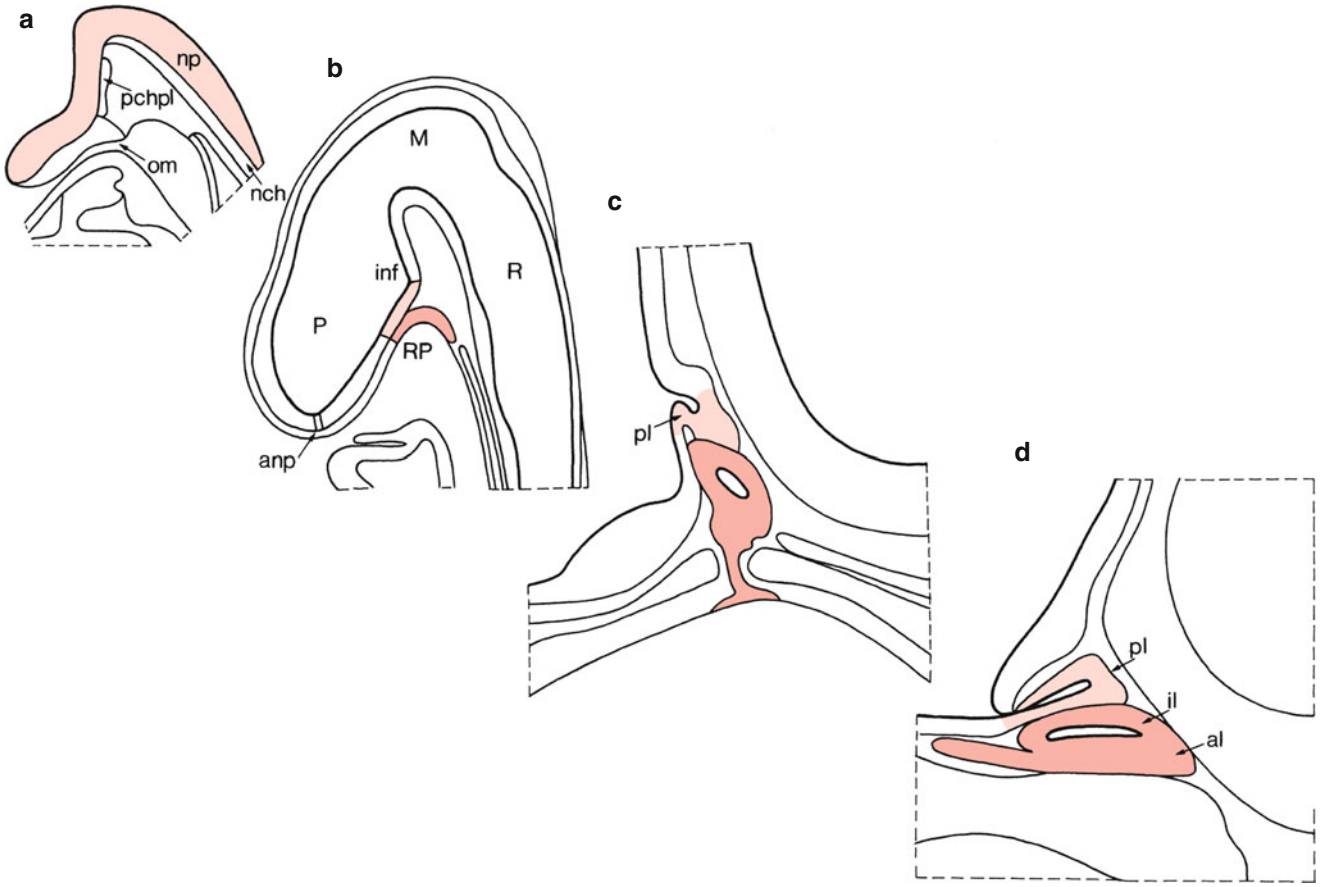

Fig. 9.13 Rodent pituitary development: (**a**) growth of the preinfundibular part of the neural plate and establishment of the presumptive Rathke's pouch area (rat: E8.5; mouse: E8.0-E8.5) (**b**) formation of a rudimentary pouch (rat: E11; mouse: E9.5); (**c**) formation of the definitive pouch (rat: E14.5; mouse: E12); (**d**) developing pituitary gland (rat: E19.5; mouse: E17). The neural plate (*np*) and the neurohypophysis are indicated in *light red* and the developing adenohypophysis in *red*. *al* anterior lobe, *anp* anterior neuropore, *il* intermediate lobe, *inf* infundibulum, *M* mesencephalon, *nch* notochord, *om* oral membrane, *P* prosencephalon, *pchpl* prechordal plate, *pl* posterior lobe, *R* rhombencephalon, *RP* Rathke's pouch. (After Schwindt 1928; Sheng and Westphal 1999, with permission)

signalling is also required for pituitary gland development (Treier et al. 2001). In rats, by E12.5 pituitary-specific cell types are formed (Camper et al. 2002). *Pitx1* and *Pitx2* regulate precursor and cell-type specific proliferation (Szeto et al. 1999; Suh et al. 2002). Targeted disruption of the *Pitx1* gene results in minor defects in later phases of pituitary development and defects in hindlimb and craniofacial morphogenesis (Kioussi et al. 2002), whereas *Pitx2*–/– mice display multiple developmental defects, including failure of body-wall closure, cardiac outflow tract abnormalities and defects in pituitary, eye and tooth development (Gage et al. 1999; Kitamura et al. 1999; Lin et al. 1999). Invagination of Rathke's pouch and direct contact with the neuroepithelium occur normally, but the pituitary is developmentally arrested by E10.5. *Hesx1* regulates pituitary proliferation indirectly through the interaction with *Tle* genes (Dasen et al. 2001). Deletion of *Hesx1* results in either a complete lack of the pituitary gland (5 %) or multiple oral ectoderm invagination and/or cellular overproliferation of all pituitary cell types (Dattani et al. 1998; Martinez-Barbera et al. 2000; Dasen et al. 2001). Members of the *Six* homeodomain gene family (*Six1*, *Six3*, *Six6*) are required for tissue-specific precursor proliferation (Zhu and Rosenfeld 2004). *Six1* and *Eya* modulate precursor cell proliferation in many organs, including the eyes, the pituitary, the auditory system, the kidneys and somites (Li et al. 2003).

In human embryos, the primordium of the adenohypophysis is situated immediately rostral to the oropharyngeal membrane at stage 11, and forms the **adenohypophysial pouch**. Between stages 14 and 17, the floor of the forebrain forms the **neurohypophysial evagination**, and by stages 20 and 21, the pouch loses its contact with the roof of the mouth (Figs. 9.14 and 9.15). The portion of the pouch that is in contact with the neurohypophysial evagination forms the **pars intermedia** of the hypophysis. Other parts of the adenohypophysis that surround the stalk of the neurohypophysis form the **pars tuberalis**, and the remaining part the **pars distalis**. The oropharyngeal part remains as the **pharyngeal hypophysis** throughout life (Boyd 1956). Rathke's pouch migrates

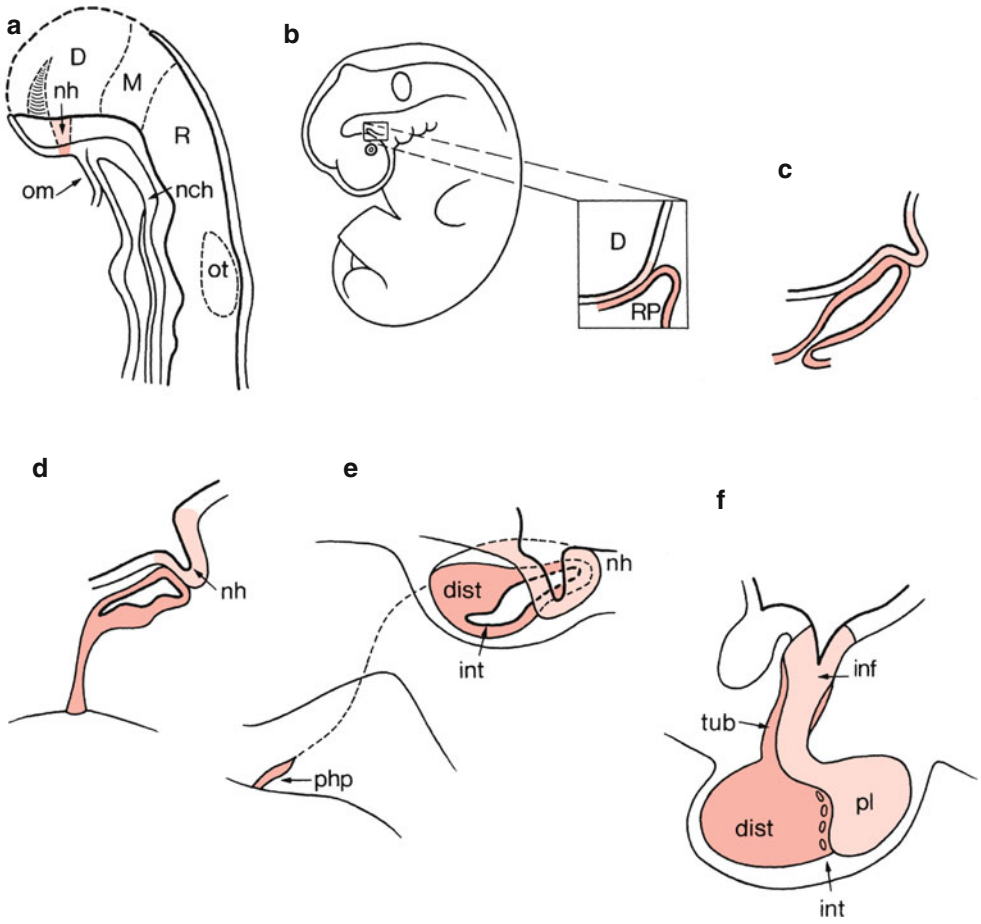

Fig. 9.14 Development of the human pituitary gland: (**a**) median section at 4.5 weeks of development (Carnegie stage 11); (**b**) embryo of 4.5 weeks of development (stage 14), showing Rathke's pouch; (**c**) at 6 weeks (stage 17); (**d**) at stage 19; (**e**) at the end of the embryonic period (stage 23); (**f**) fetal pituitary. The developing neural hypophysis (*nh*) is indicated in light red and the adenohypophysis in red. *D* diencephalon, *dist* distal part, *inf* infundibulum, *int* intermediate part, *M* mesencephalon, *nch* notochord, *om* oral membrane, *ot* otocyst, *php* pharyngeal pituitary, *pl* posterior lobe, *R* rhombencephalon, *RP* Rathke's pouch, *tub* tuberal part (After O'Rahilly and Müller 2001)

together with the pituitary cells, and remnants may be found in the sellar pituitary (Kjaer and Fischer-Hansen 1995; Hori et al. 1999b). Pituitary hormones are produced at the end of the embryonic period. In immunohistochemical studies of human embryonic and fetal pituitaries, adrenocorticotropic hormone and somatotropic hormone were demonstrated at gestational week 8, whereas thyrotropic hormone, follicle-stimulating hormone, luteinizing hormone and prolactin-releasing hormone were found at week 12 (Asa et al. 1986, 1988; Ikeda et al. 1988).

9.3.4 Developmental Disorders of the Hypothalamus and the Pituitary Gland

Developmental disorders of the ***hypothalamus*** are common in anencephaly and in HPE and related disorders. In ***anencephaly*** and in fetuses with HPE, adenohypophysial tissue was found not only in the sella turcica but also in the open craniopharyngeal canal (Nakano 1973; Kjaer and Fischer-Hansen 1995; Hori et al. 1999a, b). The intermediate part of the pituitary and the neurohypohysis are absent in most of the anencephalic cases studied (Nakano 1973; Visser and Swaab 1979). The adrenocorticotropic deficiency of the distal part of the pituitary is evident from the fact that the adrenal glands in anencephalics are invariably hypoplastic (Nakano 1973; Visser and Swaab 1979; Mazzitelli et al. 2002). At 17–18 weeks of gestation, the number and size of adrenocorticotropic hormone cells in the anencephalic pituitary gland are normal, but after 32 weeks their number and size are reduced (Pilavdzic et al. 1997). The involvement of the hypothalamus in HPE is discussed in Sect. 9.7.2.

Panhypopituitarism may also occur in ***transsphenoidal encephaloceles*** (Chong and Newton 1993; Brodsky et al. 1995; Morioka et al. 1995). These sporadic and rare anomalies are often associated with other midline anomalies such as cleft palate, hypertelorism, colobomata and agenesis of the corpus callosum. A 50 % reduction in the number of oxytocinergic PVN neurons was found in patients with ***Prader-Willi syndrome*** (Gabreëls et al. 1994, 1998; Gabreëls 1998), which is characterized by gross obesity and insatiable hunger. This syndrome is further characterized by diminished fetal motility, severe infantile hypotonia, intellectual disability, hypogonadism and hypogenitalism (Prader et al. 1956). ***Diabetes insipidus*** may have different hypothalamic causes. Apart from trauma, haemorrhage, inflammation and surgical manipulations, familial hypothalamic diabetes insipidus is found, owing to point mutations in the vasopressin-neurophysin-glycopeptide gene

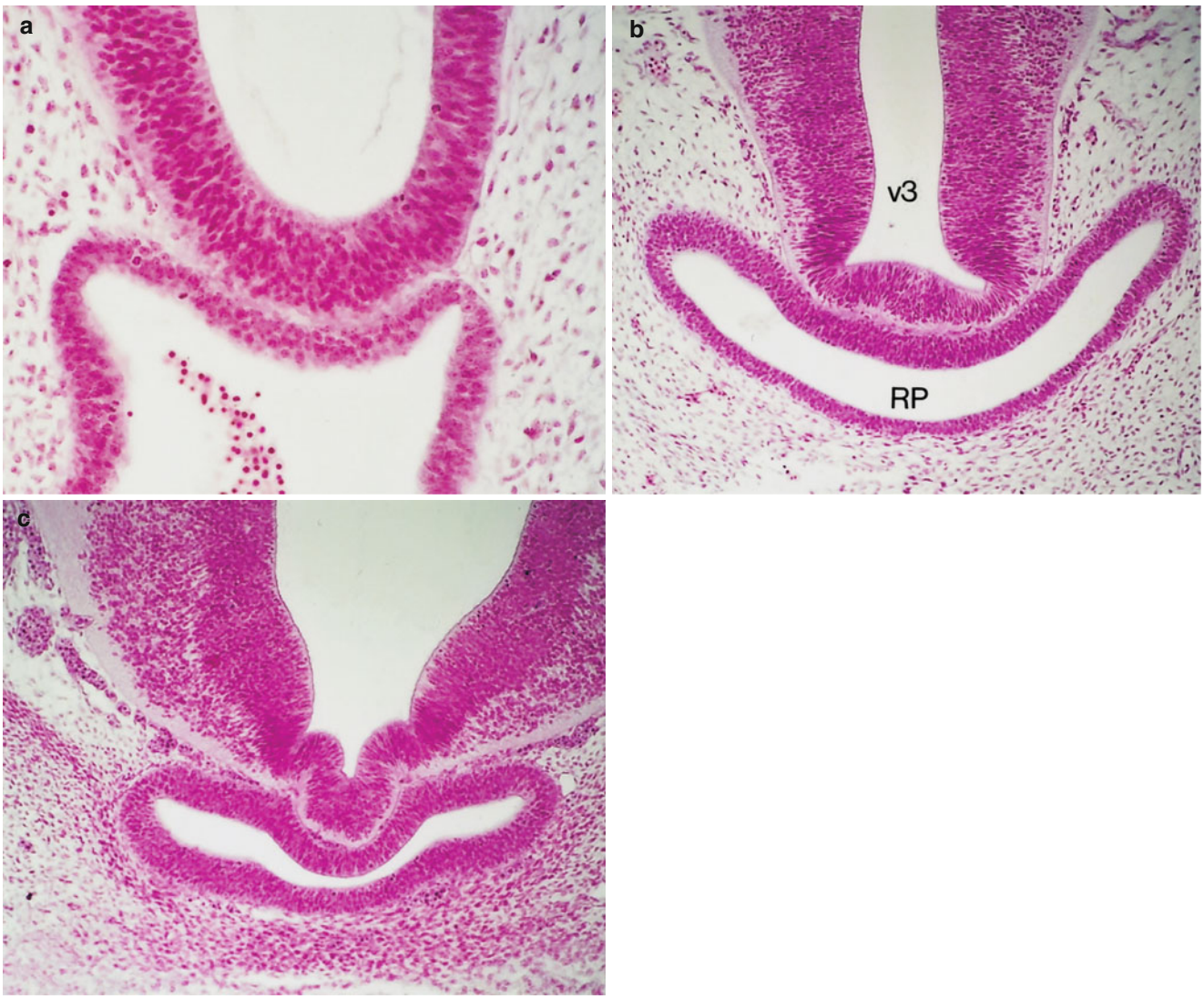

Fig. 9.15 Series of photomicrographs showing the development of the human pituitary gland at Carnegie stages 14 (**a**), 16 (**b**) and 18 (**c**); haematoxylin-eosin staining. *RP* Rathke's pouch, *v3* third ventricle (From the Kyoto Collection of Human Embryos)

(Ito et al. 1991; Bahnsen et al. 1992; Nagasaki et al. 1995; Rittig et al. 1996). Available postmortem data suggest severe neuronal death in the SON and PVN in cases of familial hypothalamic diabetes insipidus associated with a loss of innervation of the posterior pituitary (Braverman et al. 1965; Nagai et al. 1984; Bergeron et al. 1991). Diabetes insipidus is also observed as part of midline developmental anomalies such as HPE and septo-optic dysplasia. The SON and PVN are also affected in ***Wolfram syndrome***, an autosomal recessive disorder involving diabetes insipidus, diabetes mellitus, slowly progressive atrophy of the optic nerve and deafness (Wolfram 1938; Carson et al. 1977; Cremers et al. 1977). The PVN contains vasopressin neurons that cannot produce vasopressin by a precursor-processing deficiency.

Pituitary malformations include agenesis of the anterior pituitary gland (Brewer 1957; Larroche 1981), partial agenesis of anterior pituitary components (Miyai et al. 1971; Sato et al. 1975), a hidden pituitary gland (Paroder et al. 2013), duplication of the entire pituitary (Hori 1983; Hori et al. 1999b; Clinical Case 9.1) and ectopias (Decker 1985; Colohan et al. 1987; Ikeda et al. 1987). ***Developmental anomalies*** of the ***anterior pituitary*** include non-separation of the primary pituitary gland into sellar and pharyngeal components, a ***pharyngosellar pituitary*** (Hori et al. 1995; Clinical Case 9.2), and ectopic migration into the subarachnoid space. Invasion of basophil cells into the posterior lobe, the frequency and intensity of which increase in accordance with aging, is rather a physiological phenomenon (Hori et al. 1999a, b; Swaab 2004). Novel mutations in the homeobox gene *Hesx1/HESX1* may play a role in ***undescended*** or ***ectopic posterior pituitary*** (Brickman et al. 2001). ***Pallister-Hall syndrome***, a highly variable autosomal dominant disorder is due to mutations in the *GLI3* gene (Kang et al. 1997; Biesecker 2008; Clinical Case 9.3).

Clinical Case 9.1 Duplication of the Pituitary Gland

Duplication of parts of the CNS has been observed occasionally. In a 26-day-old female baby, Hori (1983) described a brain with two complete pituitary glands, associated with malformations of ventral midline structures of the CNS and cranium (see Case Report). This rare condition of double hypophysis should be classified among the median cleft face syndrome (DeMyer 1967; Gorlin et al. 1977) in contrast to reported cases of double hypophysis in partial twinning (Ahlfeld 1880; Morton 1957; Warkany 1971). In the present case, the pituitary anlage, both of neurohypophysis and adenohypophysis, may have been divided during early development due to a median cleft. Subsequent histogenesis of each separate anlage may have caused duplication of the hypophysis.

Case Report. The child was born at term after an uncomplicated pregnancy and delivery, apart from an umbilical hernia operation on the 23-year-old mother early in her pregnancy. Apgar scores were 6/7/9 and asphyxia was evident, so the baby received assisted respiration for several days until her discharge. She was readmitted at the age of 26 days because of feeding difficulties. General examination revealed a V-shaped frontal hair line, hypertelorism, cleft palate, low-set ears, retrognathia, a wide prominent nasal root and a split on the top of the nose. Neurological and laboratory (chromosomal, amino acid and blood analyses) findings were normal. On X-ray examination no clear contour of the sella turcica was seen. The baby was in no distress at the time of admission. Shortly after feeding, she was found dead in bed the same evening. Hereditary diseases or malformations were not apparent in the family.

At autopsy, body weight was 2,750 g and length 54 cm. The head was not enlarged and the fontanelles were of normal size. After removal of the brain, the 'sella' appeared shallow and empty. Instead, two sellae were found situated on either side of the regular one, posterior to both optic canals (Fig. 9.16a). Both sellae contained a pituitary gland beneath the sellar diaphragm. Histologically, both hypophyses were completely normal. The distance between the optic canals was 2.3 cm (normal about 1.1 cm), and that between the cribriform plates 2 cm (normal about 0.8 cm). The very short clivus had a round midline defect, through which a stalk of connective tissue, extending from the leptomeninx of the pontine base, protruded into the nasal cavity. Histologically, the connective tissue consisted of collagen fibres and striated tissue with a small penetrating artery. The posterior fossa was of normal size. At the base of the brain (Fig. 9.16b), the olfactory bulbs and tracts were set widely apart, and the optic chiasm had a wide angle. A mass of hyperplastic tissue displaced the mammillary bodies laterally. The circle of Willis was abnormal with a very short basilar artery and elongated posterior communicating arteries. Between these communicating arteries and the vertebral arteries, two ectopic masses were found, measuring 2.5 mm × 4 mm and 3 mm × 5 mm, respectively. These contained neurons and myelinated fibres. In the forebrain, the corpus callosum, the anterior commissure and the posterior cingulate gyri were absent. The pineal gland had its normal position. Between the laterally displaced mammillary bodies, a mass of hypothalamic tissue formed the base of the third ventricle. This tissue contained magnocellular and medium-sized neurons without glial proliferation of any importance. Posterior to the chiasm, two hypophyseal stalks were present. Heterotopia were found in the tegmental raphe ventral to the aqueduct, in a slit-like deep floor of the rhomboid fossa of the medulla oblongata and in the dentate nuclei. The spinal cord showed a duplicated anterior median fissure at the cervico-thoracic level. In between, hyperplastic grey matter with myelinated fibers protruded from the central spinal grey matter. Posterior roots entered the cord not only medial but also lateral to the posterior horn. Immunohistochemical staining for anterior pituitary hormones, performed recently, revealed no abnormalities in the distribution of the hormone-producing cells in both of the pituitary glands. Since hedgehog signalling is required for both pituitary development (Sect. 9.3.3) and for the development of the ventral part of the spinal cord (Chap. 6), the presence of duplication of the pituitary gland and of part of the ventral spinal cord may be related to SHH signalling.

References

Ahlfeld F (1880) Die Mißbildungen des Menschen. Grunow, Leipzig

DeMyer W (1967) The median cleft face syndrome. Differential diagnosis of cranium bifidum occultum, hypertelorism, and median cleft nose, lip and palate. Neurology 17:961–971

Gorlin RJ, Červenka J, Cohen MM Jr (1977) "Newer" facial clefting syndromes. Birth defects, original article series 13:1–9

Hori A (1983) A brain with two hypophyses in median cleft face syndrome. Acta Neuropathol (Berl) 59:150–154

Morton WRM (1957) Duplication of the pituitary and stomatodaeal structures in a 38-week male infant. Arch Dis Child 32: 135–141

Warkany J (1971) Congenital malformations. Year Book Med Publ, Chicago, p 419

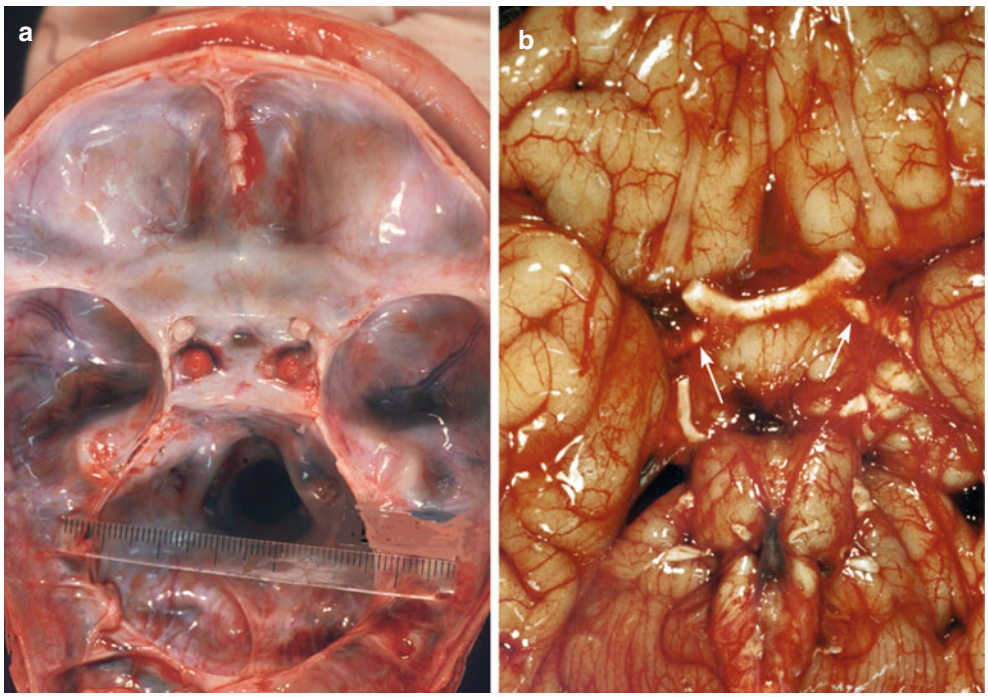

Fig. 9.16 Duplication of the pituitary gland: (**a**) skull base with two hypophyses, in between is an empty sella; note the wide distance between the cribriform laminae and optic canals; (**b**) basal view of the brain showing duplicated pituitary glands (*arrows*) behind the optic nerves (From Hori 1983, with permission)

Clinical Case 9.2 Pharyngosellar Pituitary

In ***pharyngosellar pituitary***, the anterior part of the gland is continuous from the pharyngeal roof to the sella turcica. Hori et al. (1995) described this rare malformation in a 17-gestational-week-old male fetus with an encephalocele and amnion rupture sequence (see Case Report). The first description of this anomaly was made by Müller (1958). Later, this anomaly was found in several cases of trisomy 18 (Kjaer et al. 1998).

Case Report. The pregnancy of a 27-year-old mother was unremarkable until at gestational week 17 the amnion was ruptured and the fetus was aborted spontaneously. The male fetus had a crown-heel length of 19 cm, a head circumference of 10 cm and weighed 190 g. Morphological examination of the fetus revealed a slight double cleft lip, left cleft palate, adhesive strangs at the nose, forehead and right hand, and short eye fissures with slight hypertelorism. A large encephalocele covered with skin was observed in the vertex of the microcephalic head, and an additional smaller encephalocele was found on the left forehead. After removing the covering of the head, a large round skull defect was found through which the larger encephalocele herniated. The skull base was hypoplastic: the anterior cranial fossa was narrow in transverse diameter, the middle fossa was shallow and the posterior fossa was normal in size. Anterior and posterior protuberances of the sella were absent. The pituitary gland was found in the ordinary position when observed from the cranial base. The encephalocele consisted of telencephalic tissue with molecular and neuronal cortical cell layers, white matter as well as basal ganglia-like structures. Part of the skull base, including the sella turcica, clivus and pharyngeal roof, was removed and divided through the midline (Fig. 9.17a); both blocks were embedded in paraffin without decalcification and sliced serially. Sections were stained by haematoxylin and eosin, periodic acid-Schiff (PAS) stain, and Gomori's reticulin staining. Immunostaining for pituitary hormones was also performed.

The pituitary gland was found in the persistent craniopharyngeal canal as an elongated structure expanding from the pharyngeal roof to the sella turcica (Fig. 9.17b), forming a pharyngosellar pituitary. Reconstruction of the pharyngosellar pituitary from the histological sections revealed that the pituitary was composed of sellar and pharyngeal parts. The pituitary tissue was covered with a poorly ciliated epithelial layer at its pharyngeal end. The majority of the cell constituents of the pituitary gland were histologically chromophobic. The pituitary stalk and the posterior lobe were histologically normal.

Immunohistochemical examination for anterior pituitary hormones showed that the distribution of hormone-producing cells in the malformed pituitary tissue was irregular: thyrotropic hormone (TSH) producing, follicle stimulating hormone (FSH) producing and luteinizing hormone (LH) producing cells were nearly absent in the sellar and middle sections of the pituitary but were found in small numbers mainly in the pharyngeal part of the pituitary. Somatotropic hormone (STH) producing, prolactin releasing hormone (PRL) producing, and adrenocorticotropic hormone (ACTH) producing cells were distributed diffusely. ACTH-producing cells were abundant in the pharyngeal part. Only few TSH-, FSH- and LH-producing cells were found in the sellar and middle sections. They were mostly found in the pharyngeal section.

References

Hori A, Schmidt D, Feyerabend B (1995) Pharyngosellar pituitary: a rare developmental anomaly of the pituitary gland. Acta Neuropathol (Berl) 89:459–463

Kjaer I, Kreeling JW, Reintoft I, Hjalgrim H, Nolting D, Hansen BF (1998) Pituitary gland and sella turcica in human trisomy 18 fetuses. Am J Med Genet 76:87–92

Müller W (1958) On the pharyngeal hypophysis. In: Currie AR (ed) Endocrine aspects of breast cancer. Proceedings of a conference held at the University of Glasgow, 8–10 July 1957. Livingstone, Edinburgh, pp 106–110

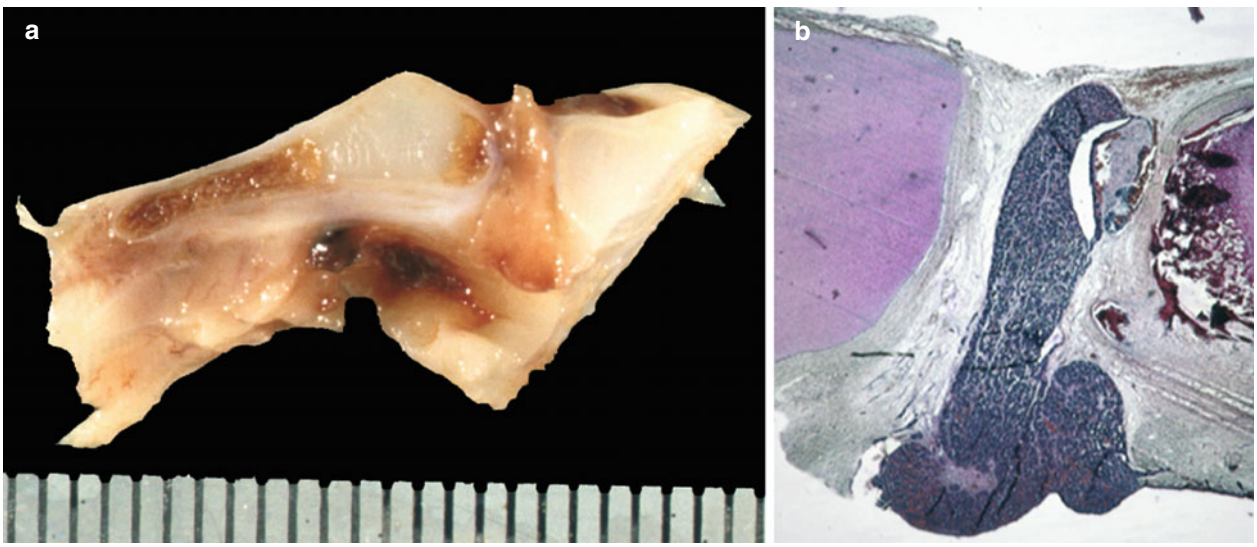

Fig. 9.17 Pharyngosellar pituitary: (**a**) gross appearance of the pituitary gland in the craniopharyngeal canal; (**b**) Gomori-stained section, showing the pharyngeal pituitary attached to the posterior lobe (From Hori et al. 1995; with permission)

Clinical Case 9.3 Pallister-Hall Syndrome

Pallister-Hall syndrome is a developmental disorder consisting of hypothalamic hamartoma, pituitary dysfunction, polydactyly and visceral malformations. This syndrome was first reported in infants (Clarren et al. 1980; Hall et al. 1980). It consists of hamartoblastomas of the hypothalamus with primitive, undifferentiated neurons. The disorder is inherited as an autosomal dominant trait with incomplete penetration, variable expressivity or gonadal or somatic mosaicism (Penman Splitt et al. 1994) and has been mapped to chromosome 7p13. Most cases are sporadic (Kuo et al. 1999). Hamartoblastomas probably arise in the fifth week of pregnancy and seem to be part of a complex pleitrophic congenital syndrome that includes absence of the pituitary, craniofacial abnormalities, cleft palate, malformations of the epiglottis or the larynx, congenital heart defects, hypopituitarism, short-limb dwarfism with postaxial polydactyly, anorectal atresia, renal anomalies and abnormal lung lobulation and hypogenitalism (see Case Report).

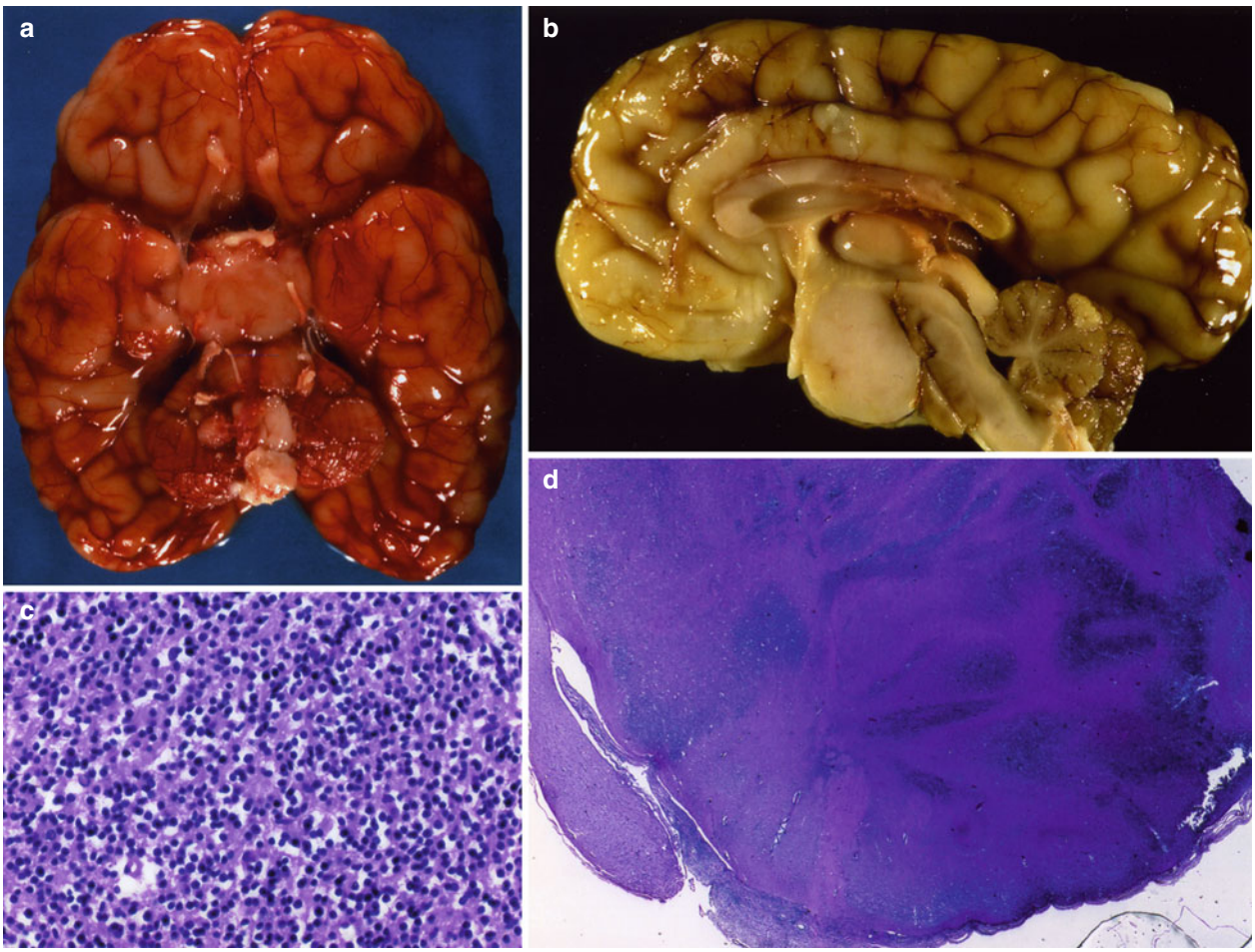

Fig. 9.18 Basal view (**a**) and median section (**b**) of a fetal brain with Pallister-Hall syndrome. The hamartoma of the hypothalamus (**d**) showed 'matrix cell' aggregation (**c**; Courtesy Akira Hori, Toyohashi; from ten Donkelaar and Hori 2011)

Case report: Twins, born at the 35th week of gestation, both died shortly after birth. The first died on the second postnatal day with multiple malformations as the second child, but no autopsy was performed. The second child presented with multiple malformations such as facial dysmorphism, heptasyndactyly of the hands, hexadactyly of the feet and imperforate anus and died six days later due to anuria. At autopsy, other urogenital malformations were found including renal hypoplasia, ureter atresia and genital hypoplasia. Neuropathological examination revealed a large hamartoma of the hypothalamus and complete agenesis of the pituitary gland (Fig. 9.18). A diagnosis of ***Pallister-Hall syndrome*** was made. Histological examination showed 'matrix cell' aggregation and a few ganglion-like cells.

References

Clarren SK, Alvord EC Jr, Hall JC (1980) Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and post-axial polydactyly – a new syndrome? Part 2: Neuropathologic considerations. Am J Med Genet 7:75–83

Hall JG, Pallister PD, Clarren SK, Beckwith JB, Wigglesworth FW, Fraser FC (1980) Ibid. Part 1: clinical, causal, and pathogenetic considerations. Am J Med Genet 7:47–74

Kuo J, Casey SO, Thompson L, Truwit CL (1999) Pallister-Hall syndrome: clinical and MR features. AJNR Am J Neuroradiol 20:1839–1841

Penman Splitt M, Wright C, Perry R, Burn J (1994) Autosomal dominant transmission of Pallister-Hall syndrome. Clin Dysmorphol 3:301–308

9.4 Development of the Visual System

9.4.1 Development of the Eye

The optic primordia are present very early in development (Mann 1928; O'Rahilly 1966; Hinrichsen 1990; Barishak 2001; O'Rahilly and Müller 2001; Sundin 2012). Presumably, a single eye field exists at the rostral end of the neural plate, the median part of which is suppressed under the influence of the prechordal plate, resulting in bilateral optic primordia (Li et al. 1997). In pioneering studies in *Ambystoma*, Adelmann (1929a, b, 1930, 1936a, b) showed that the vertebrate eye first develops as a single developmental field. Factors supplied by the prechordal plate are then required for its separation into two distinct eye structures. Any perturbation of this process may lead to ***cyclopia*** (Sect. 9.7.2). The lens arises from the surface ectoderm. In human embryos, the **optic primordium** becomes first visible as the **optic sulcus** appears in each neural fold at stage 10, i.e. at about 4 weeks of development. The right and left primordia are connected by a ridge that will become the optic chiasm. The optic sulcus deepens and forms an evagination at stage 11, leading to the formation of the **optic vesicle** at stage 12 (Figs. 9.19 and 9.20). By 4.5 weeks, the optic vesicle and the

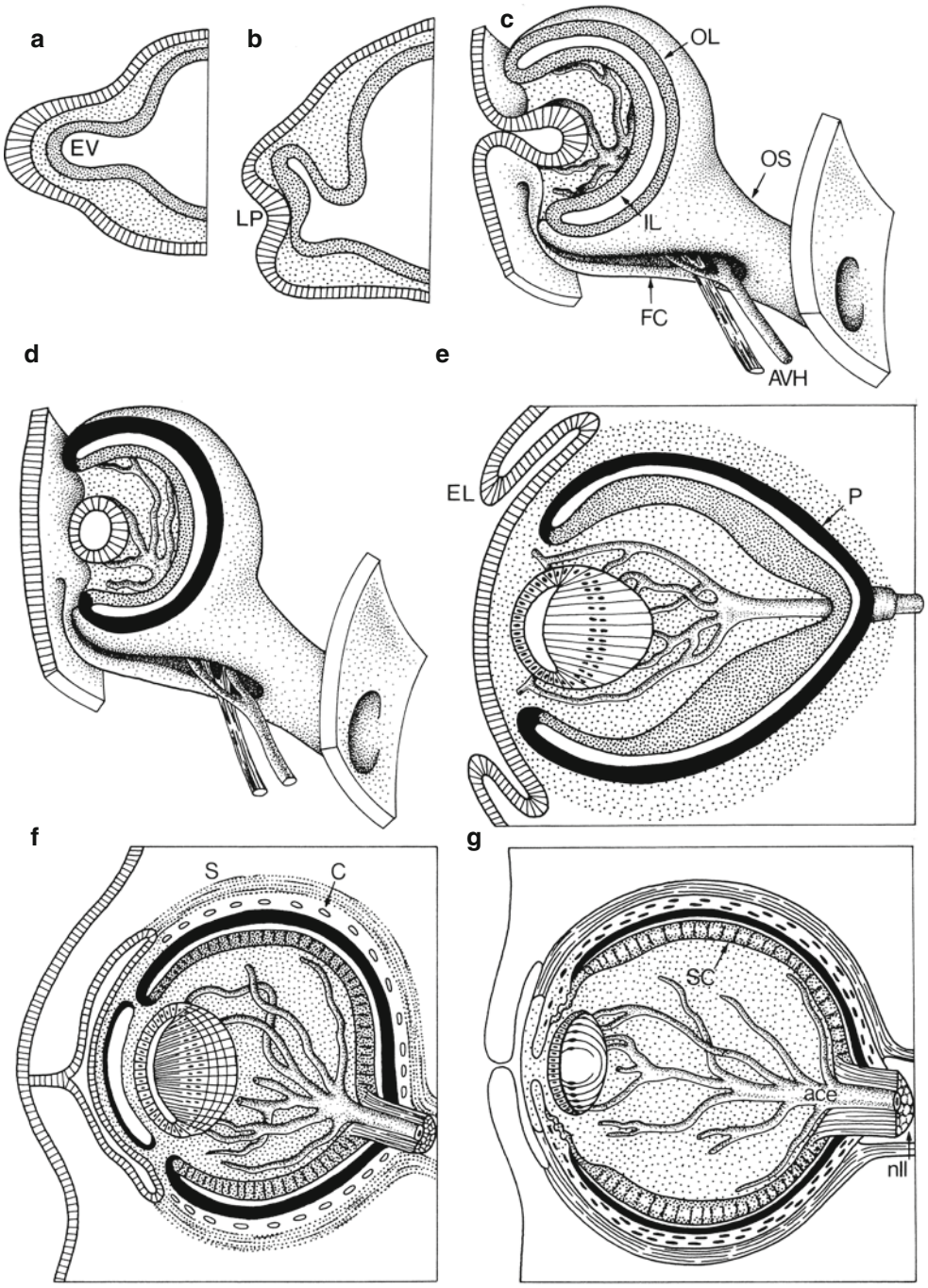

Fig. 9.19 Development of the human eye in the fourth (**a**), fifth (**b**), sixth (**c**), seventh (**d**), eighth (**e**) and ninth week (**f**) and in the seventh month (**g**) of development. *ace* a. centralis retinae, *AVH* hyaloid artery and vein, *C* choroid, *EL* eyelid, *EV* eye vesicle, *FC* fissura choroidea, *IL* inner layer of eye cup, *LP* lens placode, *nII* optic nerve, *OL* outer layer of eye cup, *OS* optic stalk, *P* pigment layer of retina, *S* sclera, *SC* stratum cerebrale of retina (After Hamilton and Mossman 1972, based on reconstructions by Mann 1928)

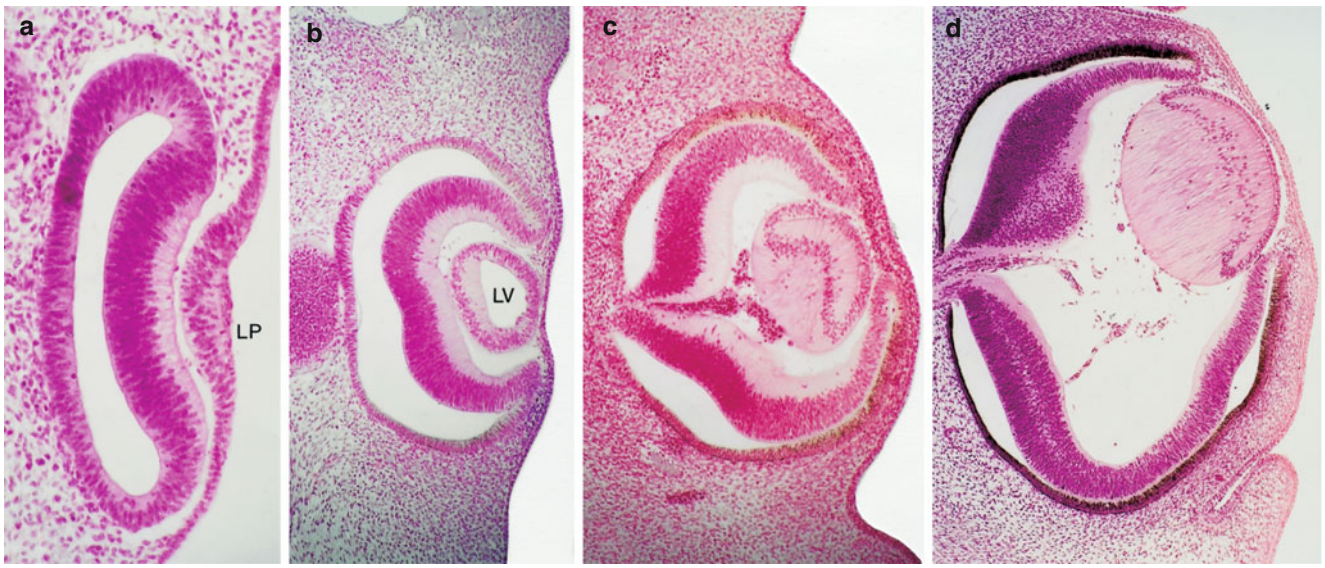

Fig. 9.20 Series of photomicrographs showing the development of the human eye at Carnegie stages 14 (**a**), 16 (**b**), 18 (**c**) and 20 (**d**); haematoxylin-eosin staining. *LP* lens placode, *LV* lens vesicle (From the Kyoto Collection of Human embryos)

adjacent surface ectoderm thicken and form at stage 13 the **retinal disc** and the **lens disc**, respectively. The retinal disc becomes invaginated, resulting in a double-layered **optic cup**. This invagination extends partly onto the stalk of the optic cup to form the transient **retinal fissure**. A disturbance in the closure of the retinal fissure may lead to a ***coloboma*** (Fig. 9.21). The inverted layer of the optic cup is readily comparable to the wall of the developing forebrain. The walls of the optic cup form the optic part of the retina and the epithelium of the ciliary body and the iris. The lens disc becomes indented to form the **lens pit** at stage 14 which closes at stage 15 to form the **lens vesicle**. At the same time, retinal pigment appears in the external layer of the optic cup. The cells of the deep wall of the lens vesicle become elongated and form the primary lens fibres. Anterior cells of the lens form a simple epithelium from which the secondary lens fibres arise that form the bulk of the mature lens. Moreover, the **primary vitreous body** and the **hyaloid artery** develop. The hyaloid artery enters the vitreous cavity through the retinal fissure and supplies the thickened inner layer, the lens vesicle and the intervening mesenchyme. Later, the hyaloid artery disappears within the eye. Its stem forms the central retinal artery. The optic cup is anchored to the forebrain by the **optic stalk** that will form the optic nerve. Axons of retinal ganglion cells grow via the optic stalk to the brain. The lumen of the optic stalk is gradually obliterated as axons of ganglion cells accumulate in the inner layer of the optic stalk, resulting in the formation of the optic nerve between the sixth and eighth weeks of development. The optic vesicle becomes enveloped by a sheath of neural-crest-derived mesenchyme. This sheath forms the two coverings of the eye: the thin inner **choroid** and the fibrous outer **sclera**.

The development of the **retina** is shown in Fig. 9.22. The thinner outer layer of the optic cup becomes the **pigmented layer** of the retina. The inner layer can soon be divided into a thicker nine-layered posterior part, the **pars optica retinae**, which develops into the visual receptive part of the retina, and a thinner, one-layered part, the **pars caeca retinae**. The pars caeca does not develop photoreceptive cells and becomes subdivided into a posterior part, the **pars ciliaris retinae**, and an anterior part firmly fused with the outer pigmented layer to form the **pars iridis retinae**. The cavity of the optic vesicle is soon occluded by the apposition of its inner layer to the pigmented layer. The **intraretinal space**, separating the two layers, is obliterated as the retina develops, but the two layers never fuse firmly. The differentiation of the neural retina takes place between the sixth week and the eighth month (Mann 1928; Hinrichsen 1990; O'Rahilly and Müller 2001). By the fifth week the first of a series of shifts in nuclear arrangement occurs, resulting in the formation of an inner layer devoid of cells, and an outer nuclear layer. About the middle of the sixth week cells of

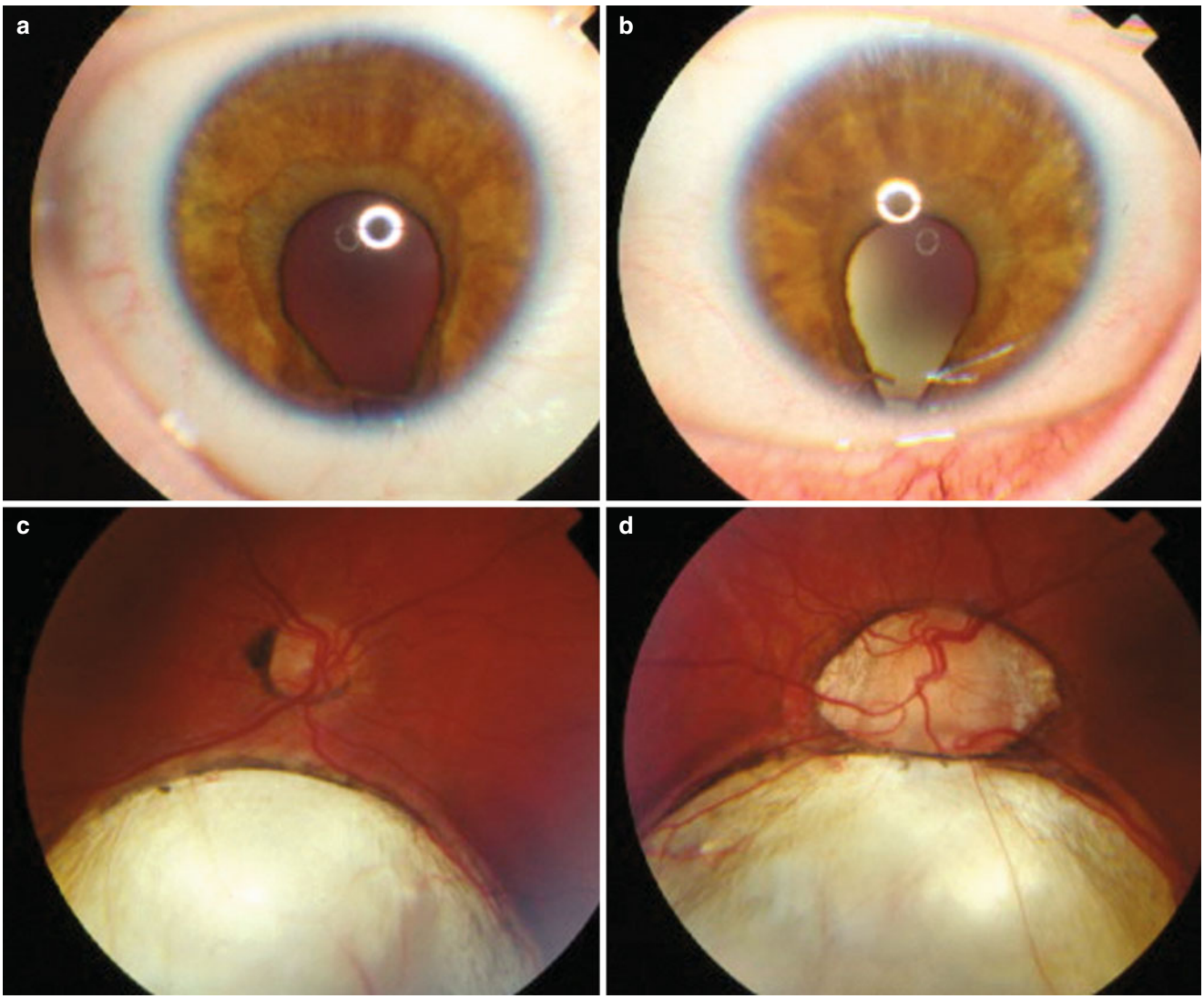

Fig. 9.21 Colobomas present in one patient: (**a**, **b**) iris colobomas of right and left eye, respectively; (**c**, **d**) retinal colobomas of both eyes and optic disk coloboma of the left eye (**d**; Courtesy Johannes Cruysberg, Nijmegen)

the outer nuclear layer migrate centrally and form an inner cellular zone. Between the two layers the transient layer of Chievitz appears. In the third month the ganglion cells arise from the inner neuroblastic layer. As additional cells migrate from the outer neuroblastic layer to the inner zone, the layer of Chievitz disappears. Now, three nuclear zones can be distinguished separated by fibrous layers. From within outwards, these nuclear zones are the ganglion cell layer, the inner nuclear layer and the outer nuclear layer. The majority of the cells of the inner nuclear layer give rise to the bipolar neurons which relay impulses from the rods and cones to the ganglion cells. The cells in the outer layer form the rods and cones. **Vascularization** of the retina begins at about 15 weeks of development (Ashton 1970). **Retinal cell diversity** is achieved by the sequential production of cell types in a defined histogenetic order (Provis et al. 1985a; Young

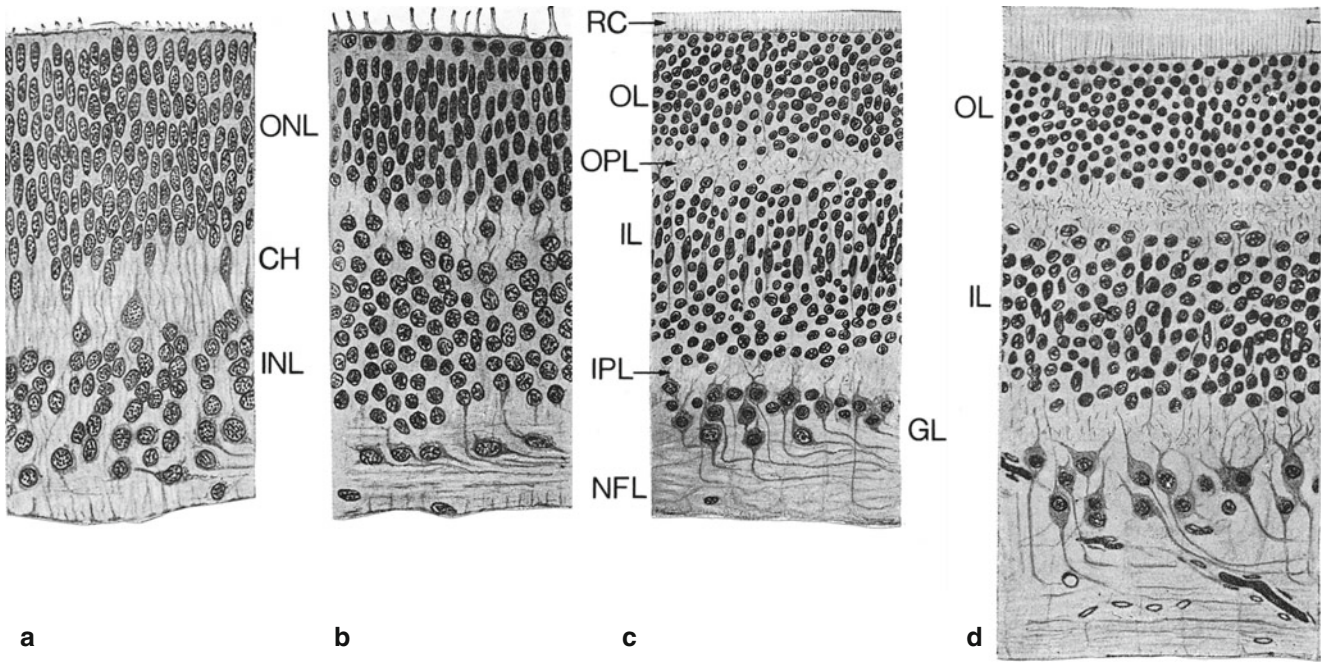

Fig. 9.22 Development of the human retina in an embryo of 7 weeks (**a**), and fetuses of about 11 (**b**), 19 (**c**) and 27 (**d**) weeks of development. *CH* transient fibre layer of Chievitz, *ELM* external limiting membrane, *GL* ganglion cell layer, *IL* inner nuclear layer (bipolar cells), *INL* inner neuroblast layer, *IPL* inner plexiform layer, *NFL* nerve fibre layer, *OL* outer nuclear layer (nuclei of rods and cones), *ONL* outer neuroblast layer, *OPL* outer plexiform layer, *RC* layer of rods and cones (After Mann 1928)

1985; Dowling 1987; Fuhrmann et al. 2000; Marquardt and Gruss 2002). Retinal ganglion cells and horizontal cells differentiate first, followed in overlapping phases by cone photoreceptors, amacrine cells, rod photoreceptors, bipolar cells and, finally, Müller glia cells.

9.4.2 Congenital Malformations of the Eye

Genetic control of **eye development** has been extensively studied in the embryonic mouse brain (Macdonald and Wilson 1996; Graw 2000, 2003; Hirsch and Grainger 2000; Wawersik et al. 2000; Horsford et al. 2001; Pichaud and Desplan 2002; Sundin 2012). Mutations in at least ten human transcription factor genes have been shown to disrupt eye development. A large number of additional mouse transcription factor genes are also associated with developmental abnormalities of the eye (Hirsch and Grainger 2000; Graw 2000, 2003; Kerryson and Newman 2007; Sundin 2012). Human eye phenotypes can involve one or more ocular structures. Developmental anomalies that affect many parts of the eye are known as panocular defects, whereas other abnormalities may be restricted to the anterior segment, the posterior segment or the differentiation or maintenance of photoreceptors. Examples of such anomalies are shown in Clinical Cases 9.4 and 9.5. For a summary of prenatal imaging of the eye see Broaddus et al. (2012).

Panocular defects are broad phenotypes (Table 9.3) that arise by at least two different general mechanisms (Horsford et al. 2001; Graw 2003; Sachdeva and Traboulsi 2012). The first mechanism, shown for heterozygous mutations in the paired box gene *PAX6*, reflects the fact that the gene is expressed in and required for the normal development of all regions of the developing eye. The second mechanism by which panocular defects arise is due to mutations in genes such as *CHX10* that are expressed in one region of the developing eye but, via secondary physiological processes, are essential for the normal development of other ocular structures. *Pax6* is one of the nine members of the *Pax* gene family unified by the presence of a paired domain. The paired

Table 9.3 Inherited eye diseases in man and mice due to mutations in transcription factor genes: panocular defects

Gene	Function or required for	Disease	Inheritance and genetic mechanisms	Phenotypes
PAX6	Lens induction and all subsequent development of retina, iris and cornea; development of forebrain, cerebellum, nasal structures and pancreas	Aniridia	AD; haploinsuffiency in most cases	Human: aniridia, accompanied by foveal or optic nerve hypoplasia, cataract, glaucoma and corneal dystrophy Mouse (heterozygotes): small eye, cataract and iris hypoplasia Mouse (homozygotes): neonatally lethal with anophthalmia, rudimentary nasal structures and forebrain and cerebellar anomalies; pancreas anomalies
CHX10	Involved in the retina and in optic nerve development	Microphthalmia	AR; loss of function alleles	Human: microphthalmia, cataracts, iris colobom, and blindness Mouse (homozygotes): microphthalmia, optic nerve aplasia and cataracts

After Macdonald and Wilson (1996), Graw (2000, 2003), Horsford et al. (2001), Sachdeva and Traboulsi (2012)
AD autosomal dominant, *AR* autosomal recessive

domain is a 128 aminoacid DNA-binding domain named after the prototypical *Drosophila* segment polarity gene *paired*. Haploinsufficiency for *PAX6* function in humans leads to ***aniridia*** (Clinical Case 9.4), a heritable panocular disorder characterized by iris and foveal hypoplasia which can be accompanied by cataracts, corneal opacification, and progressive glaucoma (Glaser et al. 1995; Horsford et al. 2001; Sachdeva and Traboulsi 2012). Mutations in *PAX6* have also been found in patients with Peters anomaly, congenital cataract, autosomal dominant keratopathy and isolated foveal hypoplasia (Prosser and van Heyningen 1998; van Heyningen and Williamson 2002, 2008; Sachdeva and Traboulsi 2012).

In mice, a naturally occurring mutation, *Small eye* (*Sey*), results from mutations in the *Pax6* gene (Hill et al. 1991). Like human aniridia, *Sey* is inherited in a semidominant fashion, with *Sey*/+ heterozygotes showing corneal and lenticular abnormalities and *Sey*/*Sey* homozygotes lacking eyes entirely (Hogan et al. 1986). In *Sey*/*Sey* embryos, the lens and nasal placodes fail to develop, the optic vesicle fails to constrict and subsequently degenerates, and mesenchymal cells become interposed between the surface ectoderm and the optic vesicle (Hogan et al. 1988). Moreover, in *Sey* homozygotes, the anterior commissure, the corpus callosum and the olfactory bulbs are absent (Schmahl et al. 1993; Stoykova et al. 1996). In mice, the optic vesicle forms at E8.5 and comes into contact with the head and ectoderm at E9.0. Signals from the optic vesicle induce the lens placode to form by E9.5. At E10.0, the lens placode invaginates to form a lens pit, while the optic vesicle infolds and becomes the optic cup. The invagination of the lens pit is complete at E10.5, at which time the vesicle begins to separate from the overlying ectoderm. Normally, *Pax6* is expressed in both the head ectoderm and the optic vesicle at E8.5, prior to lens induction (Walther and Gruss 1991; Grindley et al. 1995). At E9.5, prior to thickening of the head ectoderm to form the lens placode, the expression of *Pax6* becomes restricted to the presumptive placodal region. In later stages, *Pax6* is expressed in the optic cup as well as in the invaginated lens placode. The close similarities in phenotype and mode of inheritance between aniridia and *Sey* suggest that *Pax6* functions in a similar way in human and mouse eye development (van Heyningen and Williamson 2002, 2008). Mild extraocular phenotypes are found in *Sey*, including olfactory bulb hypoplasia, axon guidance defects, cortical plate hypocellularity and decreased basal ganglia volume (Schmahl et al. 1993; Stoykova et al. 1996; Mastick et al. 1997). Using MRI and smell testing, Sisodiya et al. (2001) showed absence or hypoplasia of the anterior commissure and reduced olfaction in a large proportion of aniridia cases. Moreover, Ellison-Wright et al. (2004) found that individuals with aniridia have structural abnormalities of grey matter in the anterior cingulate cortex, the cerebellum and the medial temporal lobe as well as white matter deficits in the corpus callosum. Functional MRI demonstrated reduced activation of fronto-striato-thalamic systems during performance of, for instance, overt verbal fluency (Ellison-Wright et al. 2004). Therefore, *PAX6* haploinsufficiency appears to cause more widespread malformations than previously thought.

CHX10, a paired-like homeodomain protein, regulates neuronal development, particularly the proliferation of interneurons. Homozygous putative null mutations of the *CHX10*

Table 9.4 Inherited eye diseases in man and mice due to mutations in transcription factor genes: anterior segment defects

Gene	Function or required for	Disease	Inheritance and genetic mechanisms	Phenotypes
MITF	Regulates genes in melanin synthesis pathway; in mice, required for normal eye growth and prevention of overproliferation of the retinal pigment epithelium	Waardenburg syndrome type 2	AD; haploinsufficiency	Human: iris pigment defects, hearing loss, white forelock Mouse (heterozygotes): minor eye and skin pigment defects Mouse (homozygotes): small eye, with hyperproliferation of RPE, defects in various other pigment cell types
FOXC1/*FOXF2*/*FOXQ1* forkhead cluster	Development cornea and iris; murine homozygotes die perinatally with haemorrhagic hydrocephalus and skeletal defects	Axenfeld-Rieger anomaly	AD; haploinsufficiency	Human: minor: glaucoma, iris hypoplasia Major: iridogoniodysgenesis, posterior embryotoxon Mouse (heterozygotes): anterior segment defects Mouse (homozygotes): iris hypoplasia, corneal defects, unfused eyelids
PITX2	Development of ocular mesenchyme, maxillary and mandibular epithelia, umbilicus, pituitary and laterality	Rieger syndrome, iridogonial dysgenesis syndrome	AD; haploinsufficiency	Human: Rieger anomaly and dental hypoplasia, facial dysmorphism and umbilical abnormalities Mouse (heterozygotes): corectopia and iris abnormalities Mouse (homozygotes): optic nerve coloboma and absence of ocular muscles
PITX3	Developing lens placode and maturing lens	Anterior segment mesenchymal dysgenesis; congenital cataract	AD; haploinsufficiency	Human: defects in all tissues of anterior eye chamber Mouse: aphakia in homozygotes

After Macdonald and Wilson (1996), Graw 2000, 2003, Horsford et al. 2001, Smith and Traboulsi 2012)

homeobox gene affect only the eye, resulting in blindness with microphthalmia and cataracts (Horsford et al. 2001). Its mouse equivalent, known as *ocular retardation* (*or*), is a recessive mutant with abnormal eye development. Homozygous *or* mice are blind with obvious microphthalmia, cataract, a poorly differentiated, thin retina, and no optic nerve (Truslove 1962; Theiler et al. 1976; Silver and Robb 1979). Burmeister et al. (1996) showed that the allele or^{1} has a premature stop codon in the homeobox of the *Chx10* gene.

Anterior segment defects primarily affect the anterior chamber, iris, lens, cornea and trabecular network, and are phenotypically varied (Table 9.4). They result from mutations in a number of different transcription factor genes: the forkhead cluster *FOXC1*/*FOXF2*/*FOXQ1*, the paired-like/bicoid-like homeodomain genes *PITX2* and *PITX3*, and the leucine zipper transcription factor *MITF* (Table 9.3). Similar phenotypes result from mutations at different loci, and there is a phenotypic overlap with some *PAX6* missense mutations (Horsford et al. 2001; Smith and Traboulsi 2012). Genetic manipulations in murine embryos suggest that *Pax6* regulates responsiveness of the head ectoderm to the inductive effect of the optic vesicle and *Prox1* probably regulates signal reception from the retina in promoting lens fibre development. *Sox2*/*Sox3* and *Maf* encoded proteins are probably the key factors of lens cell differentiation. *Pax6* inhibits expression of genes for fibre characteristics in the epithelial cells, whereas *Sox1* and *c-Maf*/*L-Maf* support fibre differentiation (Kondoh 1999; Hirsch and Grainger 2000; Smith and Traboulsi 2012). Autosomal dominant Waardenburg syndrome type 2A is associated with mutations in *MITF* (Tassabehji et al. 1994). *MITF* is expressed predominantly in developing pigment cells and neural crest cells. The mouse *microphthalmia* (*mi*) mutation, first described by Hertwig (1942), includes at least 17 mutant alleles at chromosome 6 (Steingrimsson et al. 1994). The affected gene encodes *Mitf* (microphthalmia-associated transcription factors).

Table 9.5 Inherited eye diseases in man and mice due to mutations in transcription factor genes: posterior segment defects

Gene	Function or required for	Disease	Inheritance and genetic mechanisms	Phenotypes
PAX2	Developing optic cup narrowed to just optic stalk, particularly retinal fissure; also expressed in kidney and otic vesicle	Papillorenal syndrome	AD; haploinsufficiency	Human: optic disk dysplasia, renal hypoplasia, vesicoureteral reflux and occasional deafness Mouse (heterozygotes): optic nerve coloboma Mouse (homozygotes): globe colobomata, optic nerve defects, absence of optic chiasm
HESX1	Forebrain, optic vesicle, nasal placode and pituitary development	Septo-optic dysplasia	AR; one allele known, with a severe loss of function	Human: optic disc hypoplasia, midline brain abnormalities, pituitary hormone defects and septum pellucidum absence Mouse: see Dattani et al. (1998)

After Macdonald and Wilson (1996), Graw (2000, 2003), Horsford et al. (2001)

Table 9.6 Inherited eye diseases in man and mice due to mutations in transcription factor genes: abnormal photoreceptor differentiation/maintenance

Gene	Function or required for	Disease	Inheritance and genetic mechanisms	Phenotypes
CRX	Morphogenesis and maintenance of photoreceptor outer segment; transactivation of expression of rhodopsin and other outer-segment proteins	Cone-rod dystrophy	AD; haploinsufficiency	Human: degeneration of cone, then rod, photoreceptors Mouse (homozygotes): lack of photoreceptor outer segments and circadian rhythm abnormalities
CRX	As above	Leber congenital amaurosis	AD; haploinsufficiency or dominant negative alleles;	Human: congenital absence of functional photoreceptors, or early photoreceptor degeneration;
			AR; loss-of-function alleles	Mutations in at least six other genes known
NRL	Cotransactivator, with *CRX*, of rhodopsin expression	Retinitis pigmentosa	AD; one mutant allele known: gain-of-function allele, increasing transactivation of rhodopsin	Human: rod photoreceptor degeneration

After Macdonald and Wilson (1996), Graw (2000, 2003); Horsford et al. (2001), Santos and Traboulsi (2012)

Congenital aphakia (absence of the lens) in man occurs in primary and secondary forms (Vermeij-Keers 1975). Primary absence of the lens is characterized by the total absence of the lens or lens primordium, the iris and the anterior chamber, whereas secondary forms result from disturbances during lens development at a later stage by rubella infection and other factors affecting normal lens development. Several mouse mutants are known (Graw 2000).

Posterior segment defects, affecting only the retina and optic nerve, include optic nerve defects due to mutations in *PAX2* and *HESX1*, and abnormalities in photoreceptor differentiation or maintenance due to mutations in *CRX* and *NRL* (Santos and Traboulsi 2012; Table 9.5). In 2012, more than 170 genes were known to cause retinal diseases (Retnet: http://www.sph.uth.tmc.edu/Retnet). In mouse embryos, *Pax2* is expressed during the morphogenesis of the optic cup and stalk, and in the period of axogenesis (Nornes et al. 1990). In *Pax2* null mutants (Torres et al. 1996) and in the $Pax2^{Neu}$ mutation (Favor et al. 1996), the pigmented retina extends into the optic stalk, the optic fissure fails to close, leading to coloboma, no optic chiasm is formed, and some malformations of the inner ear are found. The mouse $Pax2^{Neu}$ mutation is identical to a human *PAX2* mutation in a family with renal-coloboma syndrome and results in developing defects of the brain, eye, ear and kidney (Favor et al. 1996). 'Renal coloboma syndrome' is more appropriately called ***papillorenal syndrome***, because the dysplastic disks in papillorenal syndrome show no absence of ocular tissue owing to incomplete closure of the embryonic optic fissure, and consequently no characteristics of coloboma (Parsa et al. 2002). The paired-like homeobox gene *HESX1* is mutated in cases of septo-optic dysplasia (Dattani et al. 1998, 1999; Brickman et al. 2001).

Mutations in two genes, *CRX* and *NRL*, result in ***abnormalities*** of ***photoreceptor differentiation*** or ***maintenance*** (Table 9.6). ***Leber congenital amaurosis*** is characterized by generalized rod and cone dystrophy and presents at birth or early in infancy (Aicardi 1998; Graw 2003; Koenekoop et al. 2012). It is responsible for 10–18 % of cases of congenital blindness. The disease may present only with ophthalmological

features, but in some cases it is associated with intellectual disability, encephaloceles (Vaizey et al. 1977) and, especially, anomalies of the cerebellar vermis. Apart from *CRX*, various other genes contribute to this disorder (Fazzi et al. 2003; Graw 2003; Koenekoop et al. 2012). In the genetic subtype caused by mutations in *RPE65*, genetic replacement therapy has been found to be successful (Bainbridge et al. 2008; Maguire et al. 2008).

Retinitis pigmentosa is characterized by progressive visual field loss, night blindness and pigmentary deposition in the retina (Clinical Case 9.5). It is aetiologically very heterogeneous (Wang et al. 2001; Ferreyra and Heckenlively 2012). Mutations in at least 49 different identified genes can lead to non-syndromic forms. Retinitis pigmentosa is inherited through any of the known monogenic inheritance patterns (autosomal dominant, autosomal recessive and X-linked). Most forms of retinitis pigmentosa and related retinal degenerations affect only the eye, but in a minority of cases the retinal degeneration belongs to a syndrome that includes other systemic abnormalities such as deafness in Usher syndrome (Chap. 7).

In summary, mutations that lead to clinically relevant phenotypes highlight important steps in eye development (Graw 2003). Some affect genes that function at the top of the regulatory hierarchy and therefore at the initial stages of eye development. Mutations in such genes (*PAX6*, *SOX2*) lead to anophthalmia, microphthalmia and aniridia. Other genes (*FKHL7*, *PITX3* and *MAF*) function downstream or later during development. Some mutants define genes that are important for only one particular tissue such as the crystalline-encoding genes in the development of the lens and *PAX2* in the optic nerve.

Clinical Case 9.4 Aniridia

Aniridia is a bilateral congenital ocular disorder with absent or rudimentary iris. The disorder can be autosomal dominant or sporadic, and is caused by a defect in the *PAX6* gene. Sporadic aniridia is associated with Wilms tumour (nephroblastoma) in one third of the cases.

Case Report. A newborn female was referred to the Ophthalmology Clinic because of congenital absence of the iris in both eyes. Ocular examination showed bilateral aniridia, microcornea (7–8 mm; normal 9–10 mm), mild posterior polar cataract, and small grey optic discs (Fig. 9.23). Systemic examination disclosed microcephaly (less than P3) and multiple ventricular septal defects (VSDs) with pulmonary hypertension. The patient was suspected to suffer from 11p-syndrome WAGR (Wilms tumour, aniridia, genitourinary malformations). The child died from pulmonary oedema and respiratory insufficiency at the age of 3 months. Postmortem examination confirmed the congenital heart defect, but no renal tumour or genitourinary abnormalities were found. Rao et al. (1992) described a 2-year-old female child with bilateral Wilms tumour along with multiple congenital anomalies like bilateral aniridia with congenital cataracts and nystagmus, microcephaly, mental retardation and ventricular septal defect. Karyotype analysis revealed 46 XX, del 11p13-14.1. Association of a VSD with the classic features of 'Aniridia-Wilms tumour association' is an unusual feature.

Reference

Rao SR, Athale UH, Kadam PR, Gladstone B, Nair CN, Pai SK, Kurkure PA, Advani SH (1992) Aniridia-Wilms' tumour association: a case with 11p 13–14.1 deletion and ventricular septal defect. Indian J Cancer 29:117–121

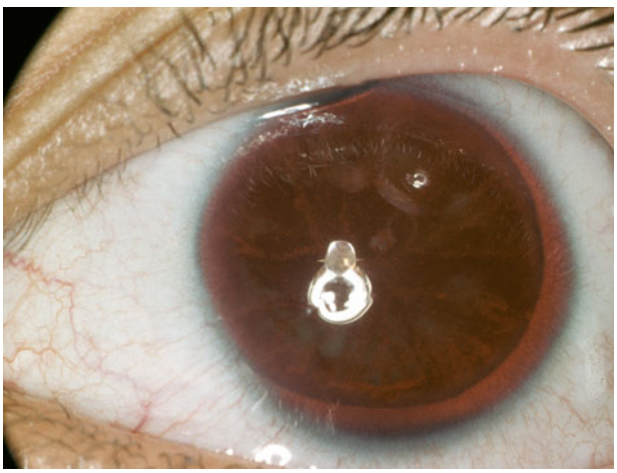

Fig. 9.23 Aniridia in a female newborn (Courtesy Johannes Cruysberg, Nijmegen)

Clinical Case 9.5 Retinitis Pigmentosa with CNS Malformations

Congenital disorders of glycosylation (CDGs) form a new group of autosomal recessive multisystem disorders characterized by defective glycoprotein biosynthesis. Disorders of nearly all organs and systems have been described (Jaeken and Carchon 2004; Chap. 3). Cerebral and ocular manifestations are common in the various biochemical CDG subtypes.

Case Report. A 12-year-old girl was referred to the Ophthalmology Clinic with a history of early childhood strabismus and encephalopathy of unknown aetiology. Signs of general hypotonia and psychomotor retardation were established in the first year of life. Microcephaly, short stature and inverted nipples were apparent in infancy, followed by ataxia, dyspraxia, dysmetria and progressive polyneuropathy in the first decade. Neuroimaging showed severe cerebellar vermis hypoplasia. The eyes showed convergent strabismus with slight limitation of abduction. The ocular media were clear. Ophthalmoscopy showed retinitis pigmentosa of both eyes, with typical bony spicules in the retinal periphery and an indication of bull's eye pattern maculopathy (Fig. 9.24). The electroretinogram was extinguished. At that time (1984) no systemic diagnosis could be made. At 18 years of age, the patient showed general signs of glycoprotein dysfunction, such as gonadal dysfunction and hypothyroidism. The diagnosis CDG syndrome type 1a was established by finding abnormal transferrin fractions with isoelectric focussing of serum. This type is the most common form in the group of CDGs. In the third decade, the retinitis pigmentosa was progressive and posterior subcapsular cataracts developed in both eyes.

Reference

Jaeken J, Carchon H (2004) Congenital disorders of glycosylation: a booming chapter of pediatrics. Curr Opin Pediatr 16:434–439

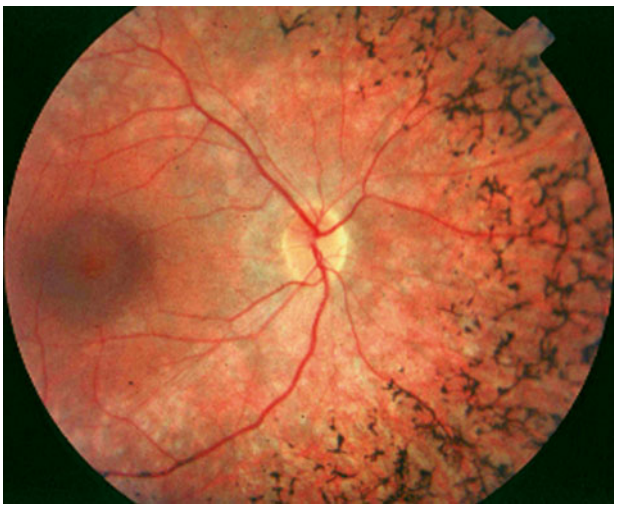

Fig. 9.24 Retinitis pigmentosa case in a 12-year-old girl (Courtesy Johannes Cruysberg, Nijmegen)

9.4.3 Development of the Visual Projections

The optic nerves of the two eyes converge to form the optic chiasm. Here the fibres from the nasal half of each retina cross to the opposite side and pass via the optic tract to the LGN (Fig. 9.25). Fibres from the temporal half of each retina pass to the LGN without crossing. LGN neurons relay the visual input via the optic radiation to the primary visual cortex. Each optic tract as well as the LGN and geniculocalcarine tract contain information from the contralateral visual hemifield. Axons from the two eyes terminate in different layers of the six-layered LGN (Hubel and Wiesel 1977; Hubel et al. 1977). Originally, two types visual pathways were distinguished: axons of M-type ganglion cells terminate in the two ventrally located magnocellular layers of the LGN, whereas axons of the smaller P cells terminate in the four dorsal parvocellular layers. This segregation continues in the optic radiation into the striate cortex and even beyond in the extrastriate visual areas (Livingstone and Hubel 1988; Merigan 1989; Gulyas et al. 1993; Zeki 1993). More recently, three retinal ganglion cell types have been linked with parallel pathways that remain segregated through the LGN and into the input layers and compartments of V1 (Dacey 2000; Hendry and Reid 2000; Kaplan 2004; Field and Chichilnisky 2007; Nassi and Callaway 2009).

Midget, parasol and bistratified ganglion cells form approximately 90 % of all ganglion cells found in the primate retina (Fig. 9.26). The **midget ganglion cells** (or **P cells**) give rise to the **parvocellular pathway** to the parvocellular layers of the LGN and form some 70 % of the total population of cells that project to the LGN (Dacey 2000). **Parasol ganglion cells** (or **M cells**) are the origin of the **magnocellular pathway** and project to the magnocellular layers of the LGN. They form some 10 % of the cells that innervate the LGN (Dacey 2000). Small and large **bistratified ganglion cells** make up at least part of the **koniocellular pathway** and together form some 8 % of the total population of cells that project to the LGN, which in turn projects to the

cytochrome oxidase (CO) blobs of layers 2/3 in V1 (Hendry and Reid 2000). Lesion studies in primates have shown that **magnocellular lesions** result in a large decrease in luminance contrast sensitivity or motion discrimination (Merigan et al. 1991a, b). **Parvocellular lesions** cause an almost complete loss of colour vision (Dacey 2000; Kaplan 2004). ***Developmental dyslexia*** may be due to abnormalities of the magnocellular component of the visual system (Stein and Walsh 1997; Demb et al. 1998; Chap. 10).

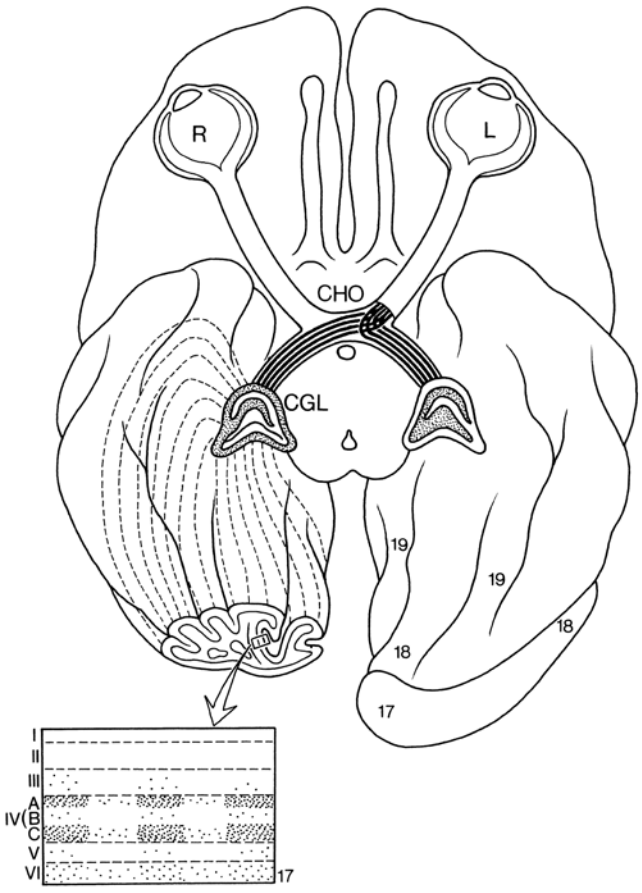

Fig. 9.25 Major visual pathways in the rhesus monkey. *CHO* chiasma opticum, *CGL* corpus geniculatum laterale, *L* left eye, *R* right eye, *I-VI* cortical layers (area 17), *17–19* visual cortical areas (After Rakic 1977a)

The development of visual projections has been extensively studied in rat (Brückner et al. 1976; Lund and Mustari 1977; Blakemore and Molnár 1990), ferret (Sur and Leamey 2001), cat (Shatz 1983; Shatz and Luskin 1986; Shatz et al. 1990) and rhesus monkey (Rakic 1974, 1975, 1977a, b) embryonic and fetal brains, and more recently also in human fetuses (Hevner 2000). In the developing rat brain, neurons of the LGN are born between E12 and E14 (Brückner et al. 1976; Lund and Mustari 1977). Outgrowth of geniculocortical axons begins around E14-E15. By E16-E17, geniculocortical axons have reached the internal capsule and some already accumulate in the subplate below the primary visual cortex (Lund and Mustari 1977; Blakemore and Molnár 1990). In cats, Shatz and co-workers studied the development of retinogeniculate (Shatz 1983) and geniculocortical (Shatz and Luskin 1986; Shatz et al. 1990; Ghosh and Shatz 1992) projections. Axons from the LGN have entered the internal capsule by E30 (duration of gestation in cats 65 days). Axons reach the developing visual cortex by E36, and accumulate in the subplate over the following 3 weeks. Between E46 and E55, geniculocortical axons invade the marginal zone (layer 1), but an appreciable number of terminals in the cortical plate does not appear before E55. By birth, most axons have left the subplate and have established branches within layer 4 (Shatz and Luskin 1986; Shatz et al. 1990).

In rhesus monkeys for which the gestation period lasts about 165 days, Rakic (1977a) showed with the [^{3}H]thymidine birthday labelling technique that the first retinal ganglion cells are generated about the 30th day of gestation (E30), whereas those for the LGN start to be born around E36 (Rakic 1977b). Neurogenesis of neurons of the primary visual cortex takes place between about E43 and E102 (Rakic 1974, 1975). Geniculocortical axons fan up towards the

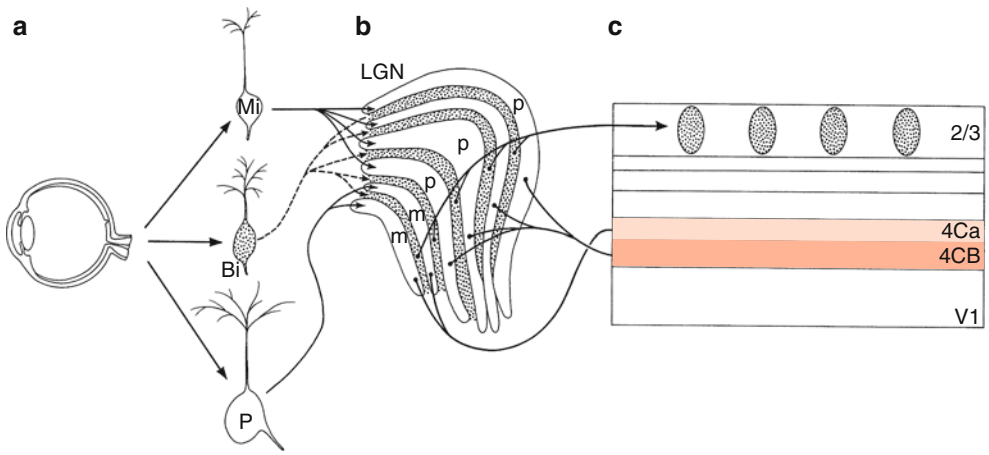

Fig. 9.26 Parallel streams from **a** the retina to **b** the lateral geniculate nucleus and **c** the primary visual cortex (After Nassi and Callaway 2009, from ten Donkelaar and Cruysberg 2011)

cortex in the optic radiation as early as midgestation (Rakic 1976, 1977a). They gather in the subplate below the occipital cortical plate and only penetrate the plate itself after a long waiting period (Smart et al. 2002). LGN axons are visible throughout the lower layers of the primary visual cortex 3 weeks before birth, and terminals are beginning to concentrate in the lower part of layer 4. Efferent connections from the visual cortex to the LGN, the pulvinar and the superior colliculus are established in a 1-month period, E63-E97 (Shatz and Rakic 1981), roughly in synchrony with the genesis of geniculocortical projections. Geniculocalcarine fibres segregate into columns postnatally according to ocular dominance (Hubel and Wiesel 1977; Hubel et al. 1977).

In the developing human brain, optic tract fibres reach the CGL by about seven gestational weeks (Gilbert 1935; Cooper 1945), and synapses between optic fibres and CGL neurons are formed by about 13–14 gestational weeks (Khan et al. 1993, 1994). The homogeneous CGL anlage becomes separated into its characteristic six layers at about 22 weeks of gestation (Cooper 1945; Dekaban 1954; Hitchcock and Hickey 1980). Each cellular layer receives retinal fibres from only one eye. Geniculocortical axons have reached the subplate below the visual cortex as early as 8.5 weeks of gestation (Kostović and Rakic 1990). After a long waiting period, geniculocortical synapses in the cortical plate are formed around 23–25 weeks of gestation (Kostović and Rakic 1990). In a 1,1′-dioctadecyl- 3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI) tracing study in fixed brains of human fetuses of 20–22 gestational weeks, Hevner (2000) showed that retinogeniculate projections were already segregated into eye-specific layers by 20 gestational weeks, preceding the cellular lamination of the CGL. Thalamocortical axons densely innervated the subplate, but hardly the cortical plate, consistent with observations on a waiting period in the human brain (Kostović and Rakic 1990). The human visual cortex attains its six-layered organization early during the third trimester (for data on the human visual cortices see Clarke and Miklossy 1990). The fetal human optic nerve shows **overproduction** and subsequent elimination of retinal ganglion cell axons. Provis et al. (1985b) found 1.9 million axons by about 10 weeks of development, 3.7 million at about 16 weeks, but only 1.1 million axons at about 27 weeks. The period of cell loss from the retinal ganglionic cell layer occurs after 30 weeks (Provis et al. 1985a), suggesting that many cells of the fetal ganglionic cell layer do not contribute axons to the optic nerve during the process between 20 and 30 weeks of development. **Myelination** of the optic nerve does not begin until about 32 weeks, and is largely complete by 7 months after birth (Magoon and Robb 1981). Myelination of the optic radiation begins at the CGL. For a DTI study of the optic radiation in premature neonates ranging from 29 to 41 weeks of gestational age, see Berman et al. (2009).

In ***albinism***, retinofugal axons are misrouted in the optic chiasm so that some of the axons from the temporal retina, which normally stay ipsilaterally, cross to the other side. Abnormalities in the CGL of a human albino have been noted (Guillery et al. 1975). The opposite is found in ***isolated absence*** of the ***optic chiasm*** or ***non-decussating retinofugal fibre syndrome*** as first described by Apkarian et al. (1993, 1995) in two unrelated children, presenting with oculomotor instabilities. Comparable cases were described by Jansonius et al. (2001; Clinical Case 9.6) and Korff et al. (2003). In such cases, nasal retinal fibres project ipsilaterally, resulting in retinothalamic and thalamocortical misprojections and aberrant retinotopic cortical mapping. ***Optic nerve hypoplasia***, a developmental defect in the number of optic nerve fibres, may be unilateral or bilateral (Aicardi 1998; Brooks and Traboulsi 2012). It may occur as an isolated defect or be associated with other CNS defects such as absence of the septum pellucidum in ***septo-optic dysplasia*** (Sect. 9.7.3). Zeki et al. (1992) found that optic nerve hypoplasia can be associated with partial or complete absence of the septum pellucidum (in 52 % of their cases), hydrocephalus (in 38 %), porencephaly (in 24 %), dilatation of the suprasellar and chiasmatic cisterns (in 19 %), partial or complete absence of the corpus callosum (in 14 %), or an intracranial cyst. ***Colobomas*** of the ***optic nerve*** may extend to involve the retina, the iris, the ciliary body and the choroid. Colobomas of the optic disc may be isolated, appearing as deep excavations with abnormal emergence of retinal vessels. They may be unilateral or bilateral and are often associated with agenesis of the corpus callosum, in isolation or as a component of the Aicardi syndrome (Chevrie and Aicardi 1986; Aicardi et al. 1987; Brooks and Traboulsi 2012).

Clinical Case 9.6 Isolated Absence of the Optic Chiasm

Isolated absence of the optic chiasm or non-decussating retinofugal syndrome is very rare (Apkarian et al. 1993, 1995; Jansonius et al. 2001; Korff et al. 2003). The four patients described so far presented with oculomotor instabilities (see Case Report). In this condition, nasal retinal fibres erroneously project ipsilaterally, resulting in aberrant retinothalamocortical mapping.

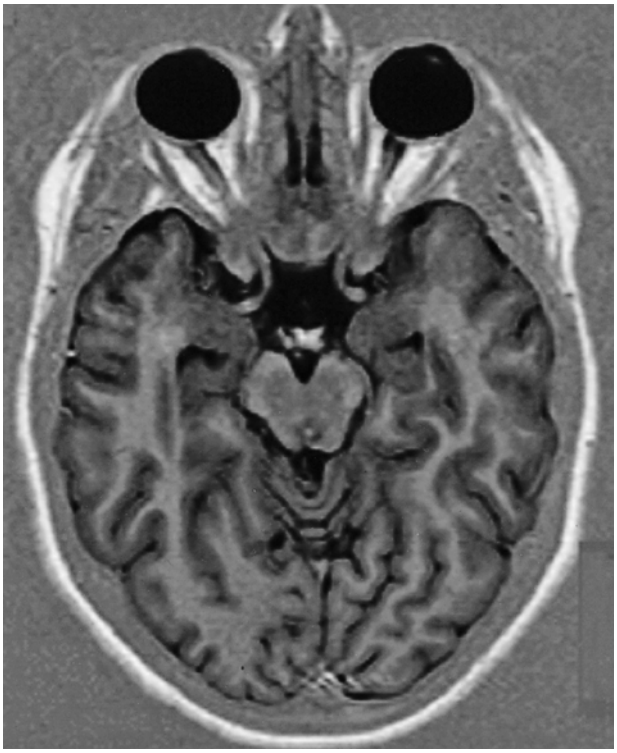

Fig. 9.27 Axial MRI, showing that both optic nerves curve to the lateral side of the suprasellar cistern without crossing over as would have been the case in the presence of a chiasm (Courtesy Ton van der Vliet, Nijmegen)

Case Report. An otherwise healthy 15-year-old girl with a congenital nystagmus was evaluated at a University Department of Ophthalmology using visual evoked potential recording and subsequent MRI examination. She appeared to have the unique inborn absence of the optic chiasm (Fig. 9.27). Unlike the cases described by Apkarian et al. (1993, 1995) she did not seem to display a seesaw nystagmus (Jansonius et al. 2001).

This case was kindly provided by Nomdo M. Jansonius (Department of Ophthalmology, Groningen University Medical Centre) and Ton van der Vliet (Groningen).

References

Apkarian P, Bour L, Barth PG (1993) A unique achiasmatic anomaly detected in non-albinos with misrouted retinal-fugal projections. Eur J Neurosci 6:501–507

Apkarian P, Bour L, Barth PG, Wenniger-Prick L, Verbeeten B Jr (1995) Non-decussating retinal-fugal fibre syndrome: an inborn achiasmatic malformation associated with visuotopic misrouting, visual evoked potential ipsilateral asymmetry and nystagmus. Brain 118:1195–1216

Jansonius NM, van der Vliet AM, Cornelissen FW, Pott JWR, Kooijman AC (2001) A girl without a chiasm: electrophysiologic and MRI evidence for the absence of crossing optic nerve fibers in a girl with a congenital nystagmus. J Neuro-Ophthalmol 21:26–29

Korff CM, Apkarian P, Bour LJ, Meuli R, Verrey J-D, Roulet Perez E (2003) Isolated absence of optic chiasm revealed by congenital nystagmus, MRI and VEPs. Neuropediatrics 34: 219–221

9.5 Overview of the Development of the Telencephalon

Each developing cerebral hemisphere consists of a thick basal part, the subpallium, giving rise to the basal ganglia, the diagonal band and the preoptic area, and a thin part, the pallium that becomes the future cerebral cortex. The **telencephalon medium** or **impar** forms the non-evaginated part of the telencephalon. It surrounds the rostral part of the third ventricle and consists of the lamina terminalis and the preoptic region. The dorsal part of the lamina terminalis transforms into the commissural plate, from which the anterior commissure, the corpus callosum and the hippocampal commissure arise (Chap. 10). Dorsal and ventral domains of the developing telencephalon are distinguished by different patterns of gene expression, reflecting the initial acquisition of regional identity by progenitor populations (Puelles et al. 2000; Schuurmans and Guillemot 2002; Campbell 2003; Zaki et al. 2003; Sousa and Fishell 2012; Medina and Abellán 2012). The **subpallium** appears as medial and lateral elevations, known as the **ganglionic** (*Ganglionhügel* of His 1889) or **ventricular eminences** (Figs. 9.28 and 9.29). The derivatives of the ganglionic eminences are summarized in Table 9.7. The caudal part of the ventricular eminences or **caudal ganglionic eminence** (**CGE**) primarily gives rise to the subpallial parts of the amygdala. The **medial ganglionic eminence** (**MGE**) is involved in the formation of the globus pallidus and the basal nucleus of Meynert, the source of

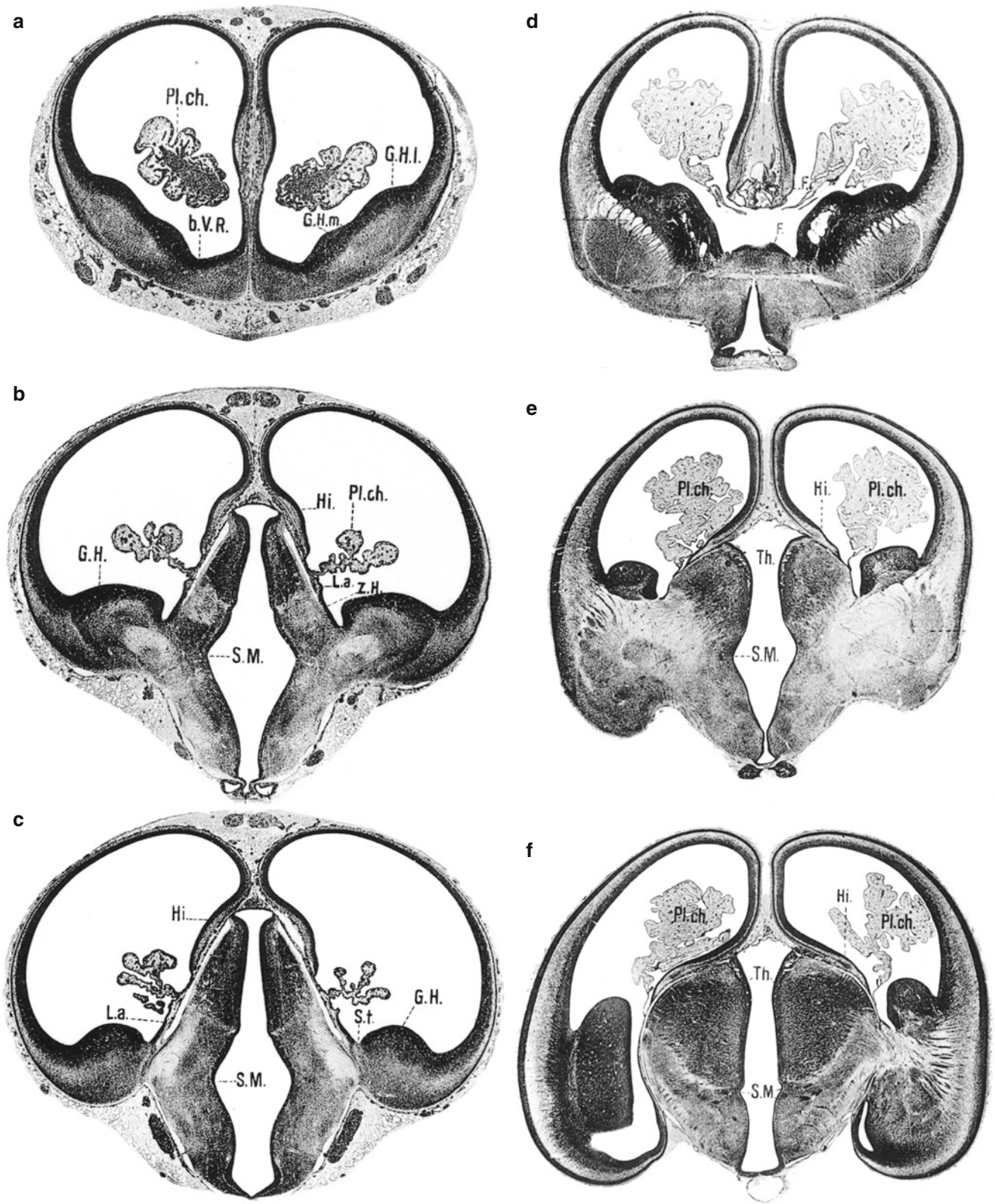

Fig. 9.28 Series of photomicrographs of the developing human forebrain: (**a**–**c**) a 25-mm embryo (late embryonic period); (**d**–**f**) early fetal period (46.5-mm CRL). *F* fornix, *GH* ganglionic eminence, *GHl* lateral ganglionic eminence, *GHm* medial ganglionic eminence, *Hi* Hippocampus, *Plch* choroid plexus, *SM* medial sulcus, *Th* thalamus (From Hochstetter 1919)

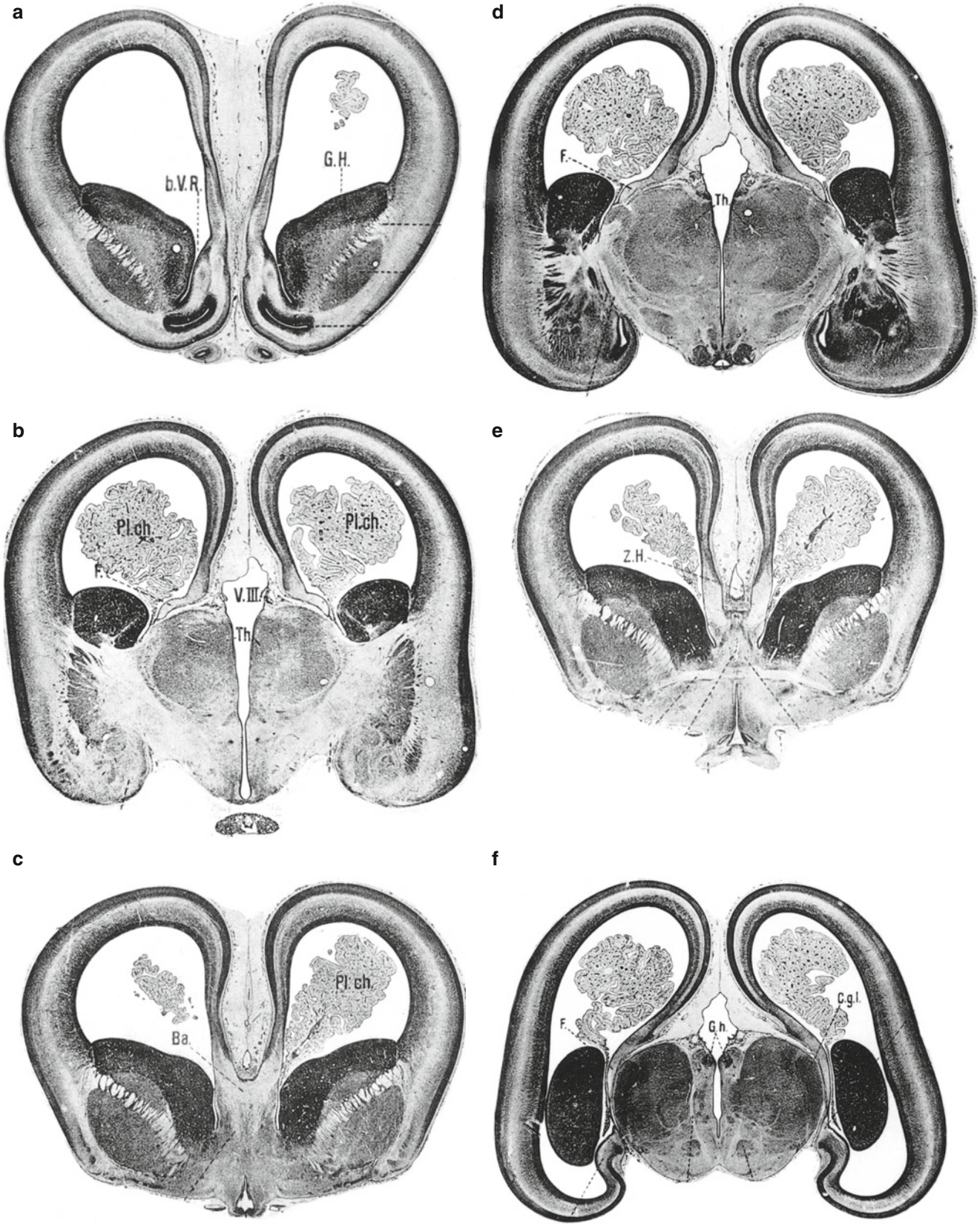

Fig. 9.29 Series of photomicrographs of the developing human forebrain in a 87-mm-CRL fetus. *Cgl* corpus geniculatum laterale, *F* fornix, *GH* ganglionic eminence, *Gh* ganglion habenulae (epithalamus), *Plch* choroid plexus, *Th* Thalamus, *VIII* third ventricle (From Hochstetter 1919)

Table 9.7 Derivatives of the ganglionic eminences

Ganglionic eminence	'Specific' gene expression	Derivatives
Lateral ganglionic eminence	*Dlx1*, *Dlx2*,*Dlx 5*, *Dlx6*	Projection neurons for caudate, putamen, accumbens and olfactory tubercle Late component neocortical interneurons Granule and periglomerular cells olfactory bulb (SVZ) Glial cells (SVZ)
Medial ganglionic eminence	*Dlx1*, *Dlx2*, *Dlx5*, *Dlx6*; *Lhx6*	Projection neurons for globus pallidus and ventral pallidum Basal nucleus of Meynert Most striatal interneurons Most neocortical and hippocampal interneurons GABAergic neurons for some thalamic nuclei Glial cells (SVZ)
Caudal ganglionic eminence	*Dlx2*; cellular retinol binding protein 1	Amygdaloid nuclei Contribution to interneuron population cortex and hippocampus

After Marín and Rubinstein (2002), Nery et al. (2002), Brazel et al. (2003)
SVZ subventricular zone

cholinergic input to the cerebral cortex. The **lateral ganglionic eminence** (**LGE**) gives rise to the caudate nucleus and the putamen. Both the LGE and the MGE are also involved in the formation of the cerebral cortex. The pyramidal cells of the cerebral cortex arise from the pallial ventricular zone, but its GABAergic interneurons arise from both ganglionic eminences, the medial eminence in particular (Anderson et al. 1997a, 2001; Parnavelas 2000; Marín and Rubinstein 2001, 2002; Chédotal and Rijli 2009). The caudal part of the human ganglionic eminence also gives rise to a contingent of GABAergic neurons for thalamic association nuclei such as the pulvinar through a transient fetal structure, the ganglio-thalamic body (Rakić and Sidman 1969; Letinić and Kostović 1997; Letinić and Rakic 2001). The ganglionic eminence of the human fetal brain plays an important role in prematurely born infants (Ulfig 2002a) and it is the most common site of intracranial haemorrhage, a frequent CNS complication in prematurely born infants (Chap. 3).

The **pallium** is usually divided into a medial pallium or archipallium, a dorsal pallium or neopallium, and a lateral pallium or paleopallium (Fig. 9.30). In mice, gene-expression studies led to redefining of the pallial-subpallial boundary and to a fourth component of the pallium, the ventral pallium (Puelles et al. 2000; Marín and Rubinstein 2002; Molnár and Butler 2002; Schuurmans and Guillemot 2002; Campbell 2003; Stenman et al. 2003). The **medial pallium** or **archipallium** forms the hippocampal cortex, the three-layered allocortex. Parts of the surrounding transitional cingulate and entorhinal cortex, the four-to-five-layered mesocortex, may have the same origin. The **dorsal pallium** or **neopallium** forms the six-layered isocortex or neocortex. The **lateral pallium** forms the olfactory cortex and the **ventral pallium** the claustro-amygdaloid complex. The development of the medial and the dorsal pallium and their malformations will be discussed in Chap. 10. The midline and paramedian areas of the telencephalon (the '**cortical hem**') form specialized

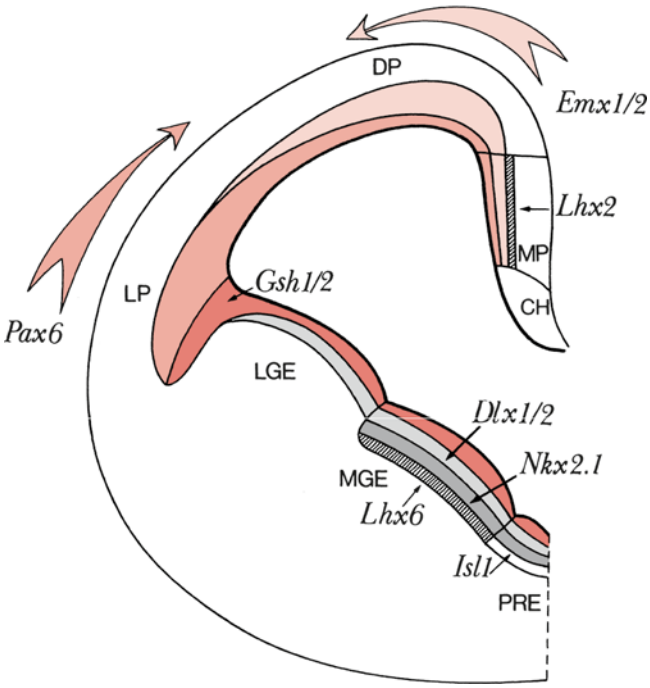

Fig. 9.30 Subdivision of the mouse forebrain and the expression of genes regulating its regionalization (see text for explanation). *DP* dorsal pallium, *LP* lateral pallium, *MP* medial pallium, *LGE* lateral ganglionic eminence, *MGE* medial ganglionic eminence, *PRE* anterior preoptic region (After Zaki et al. 2003)

structures, and give rise to the commissural plate and the choroid plexus, respectively (Chap. 10).

The **subpallium** consists of three primary regions, the LGE, the MGE and the preoptic area. Among other structures such as cortical contributions the LGE gives rise to the striatum and the MGE to pallidal structures. The preoptic area is located close to the pallidal domain, and contains the preoptic area and the major fibre bundles to and from the telencephalon.

After induction of anterior neural character and specification of telencephalic character (Chap. 2), **dorsoventral regionalization** of the telencephalon occurs. **Genetic analyses** in mice have revealed that regionally restricted genes participate in the specification of the identity of the telencephalic territory in which they are expressed (Rubinstein et al. 1998; Smith-Fernández et al. 1998; Puelles et al. 2000; Marín and Rubinstein 2002; Zaki et al. 2003; Table 9.8). *Emx1* and *Emx2*, and *Dlx1* and *Dlx2* are among the earliest expressed pallial and subpallial markers, respectively. Their expression delineates three main telencephalic subdivisions in vertebrates (Figs. 9.30 and 9.31): the pallial, intermediate or ventral pallial, and subpallial neuroepithelial domains. The **ventral pallium** uniquely expresses the homeobox gene *Dbx1* (Yun et al. 2001) and is *Emx1*-negative (Puelles et al. 2000). The specific **boundaries** of the other **pallial domains** are less easily marked by discrete gene expression. Here, graded gene expression is more common. *Emx1*, *Emx2* and *Lhx2* all show high expression in the medial pallium with a progressive reduction in expression in more lateral regions (Gulisano et al. 1996; Pellegrini et al. 1996; Yoshida et al. 1997; Tole et al. 2000a; Mallamacci et al. 2000; Yun et al. 2001), whereas *Pax6* and *Tbr1* show an opposite profile with highest expression in the lateral and ventral pallium (Puelles et al. 2000; Toresson et al. 2000; Yun et al. 2001). *Emx2* and *Pax6* are involved in many aspects of cortical morphogenesis (Chap. 10). Nevertheless, in the absence of either *Emx2* or *Pax6*, cerebral cortex does form. In *Emx2*−/−; *Pax6*$^{Sey/Sey}$ double mutant mice, however, conversion of the cerebral cortex into basal ganglia occurs (Muzio et al. 2002). It seems likely that at least one fully functional allele of either *Emx2* or *Pax6* is necessary and sufficient for activating corticogenesis and to suppress competing subpallial morphogenetic programs.

In the **subpallium**, many genes are expressed, more in particular the *Dlx1*, *Dlx2*, *Dlx5* and *Dlx6* genes (Eisenstat et al. 1999; Long et al. 2009a, b) as well as *Gsh1* and *Gsh2* (Toresson et al. 2000; Toresson and Campbell 2001; Yun et al. 2001) and *Mash1* (Long et al. 2009a, b; Medina and Abellán 2012). The ventromedial telencephalon, including the MGE and the preoptic area, expresses *Nkx2.1* (Shimamura et al. 1995; Sussel et al. 1999; Sousa and Fishell 2010). The preoptic area also expresses *Isl1* (Marín and Rubinstein 2001). The CGE shares some molecular markers with both the LGE and the MGE (Xu et al. 2004; Flames et al. 2007; García-López et al. 2008). The CGE expresses *Dlx2* and *Ascl1* (formerly known as *Mash1*) at levels equivalent to those in the other ganglionic eminences. In contrast, *Lhx6* is highly expressed in the MGE (Lavdas et al. 1999), hardly in the LGE and in only low levels in the CGE. The CGE is further characterized by a high level of cellular retinol binding protein 1 (Nery et al. 2002). The LGE can be subdivided into two major portions each with two domains (Flames et al. 2007). The dorsal LGE, characterized by *Pax6* expression, appears to produce the GABAergic and dopaminergic interneurons of the olfactory bulb rostrally and caudally the lateral part of the central amygdala. The dorsal LGE also contributes cells to the caudate-putamen, the olfactory tubercle, the accumbens and the central extended amygdala. The ventral LGE, characterized by *Isl1* expression, is the major source of projection neurons of the caudate-putamen and the accumbens and at caudal levels of the medial part of the central amygdala. The globus pallidus, the ventral pallidum and the extended amygdala are derived from the MGE (Xu et al. 2008; Long et al. 2009a, b). Most of the cortical GABAergic interneurons appear to arise in the MGE domain (Xu et al. 2008; Long et al. 2009a, b), which may contain five distinct progenitor domains (Flames et al. 2007). The embryonic preoptic area also contributes to the production of cortical interneurons (Gelman et al. 2009).

The **pallial-subpallial** or **corticostriatal boundary** does not lie at the boundary between the ventral pallial and LGE progenitor zones but is slightly more ventral in the dorsalmost part of the LGE. The early expression of the *Pax6* and *Gsh2* homeobox transcription factors overlaps in the dorsal part of the LGE. In *Gsh2* mutants, the dorsal part of the LGE is respecified into a ventral pallium-like structure, whereas in *Pax6* mutants the ventral pallium is respecified into a dorsal LGE-like structure (Stoykova et al. 1996, 2000; Toresson et al. 2000; Yun et al. 2001). Patterning defects caused by loss of Pax6 function result in multiple morphological abnormalities in the brain of *Sey* mutants such as dysgenesis of the piriform, insular and lateral cortices, and of the claustrum, failure in the differentiation of a subpopulation of cortical precursors, and absence of the olfactory bulbs. *Tlx* and *Pax6* cooperate in the establishment of the pallial-subpallial boundary in the embryonic mouse telencephalon (Stenman et al. 2003). *Tlx* homozygous mutants show alterations in the development of this boundary similar, but less severe than those seen in *Sey*/*Pax6* mutants. Malformations occur in the lateral and basolateral amygdala, both of which are derived from the ventral pallium. In human embryos, *PAX6* is expressed early in the neural tube, just after its closure (Gérard et al. 1995). *PAX6* haploinsufficiency causes cerebral malformation and olfactory dysfunction in humans (Sisodiya et al. 2001).

Like in the spinal cord, the roof plate (Fig. 9.4) may play an essential role in **dorsal telencephalic** or **pallial patterning** through BMP signalling. Explant studies support a role for BMPs in dorsal telencephalic development (Furuta et al. 1997) and in the expression of *Lhx2* (Monuki et al. 2001). Receptor blocking studies, however, suggest that loss of BMP signalling in the dorsal telencephalon leads to a normal dorsal-ventral pattern but maldevelopment of the choroid plexus, suggesting only a local role for BMPs in the dorsal telencephalic midline (Hébert et al. 2002). Genetic ablation

Table 9.8 Some gene expression patterns during the development of the murine forebrain

Transcription factor gene or extracellular signalling molecule	Beginning of expression	Site of expression	Mouse mutant	Phenotype of mouse mutant	Human homologue and phenotype
Induction of anterior neural character					
Otx2	E6.5	Prosencephalon, mesencephalon	*Otx2−/−*	Absence of forebrain and large part of brain stem; lethal in embryonic period	
Otx1	E8	Dorsal part telencephalon, mesencephalon	*Otx1−/−*	Cell reduction in cerebral cortex, epilepsy	
Specification of telencephalic character					
Foxg1 (BF1)	E8	Dorsal telencephalon	*Foxg1−/−*	Early postnatal lethality; severe hypoplasia telencephalon with absence of subpallium	
Dorsoventral patterning telencephalon					
Gli3			*Gli3−/−* *Extra toes*	Early postnatal lethality; ventral markers expand into the cortex	*GLI3* mutations lead to Greig syndrome
Shh	E8	Medial part neural plate	*Shh−/−*	Malformations basal telencephalon, cyclopia	*SHH* mutations lead to HPE
Proneural genes					
Ngn1			*Ngn1−/−*	Neonatal lethal; decrease in number of neurons in preplate	
Ngn2			*Ngn2−/−*	Perinatal lethal; ventral markers upregulated; cortical ectopia	
Regionalization					
Pallium					
Emx2	E8	Pallium	*Emx2−/−*	Loss of dentate gyrus	*EMX2* mutations may lead to schizencephaly
Pax6	E8	Pallium and eye primordia	$Pax6^{Sey/Sey}$	Heterozygotes: small eye, iris hypoplasia	*PAX6* mutations result in aniridia
				Homozygotes: absence of eyes	
Emx1	E9.5	Pallium	*Emx1−/−*	Absence of corpus callosum	
Tbr1	E10	Pallium	*Tbr1−/−*	Loss of certain neuron types in cortex	
Lhx2		Medial pallium	*Lhx2−/−*	Agenesis of hippocampal anlage; hypoplasia cortical plate and basal ganglia	
Subpallium					
Nkx2.1	E8	Medial ganglionic eminence, preoptic area	*Nkx2.1−/−*	Absence pallidum and severe loss of cortical interneurons	
Ascl1 (*Mash1*)		Subpallium, olfactory bulb and epithelium	*Mash1−/−*	Widespread defects in primary olfactory pathway	
Dlx1/2	E9.5	Subpallium		Single mutants only mild phenotype	
Dlx5		Subpallium, olfactory bulb and epithelium	*Dlx5−/−*	Lack of innervation of olfactory bulb with other secondary defects	
Lhx6		Medial ganglionic eminence			
Gsh1/2		Lateral ganglionic eminence	*Gsh2−/−*	Lateral ganglinoic eminence reduced in size; medial ganglionic eminence relatively normal	
			Gsh1/2−/−	Lateral ganglionic eminence more affected than in *Gsh2−/−*; medial ganglionic eminence relatively normal	
Isl1		Preoptic area			

After Rubinstein et al. (1998), Marín and Rubinstein (2002), Zaki et al. 2003)

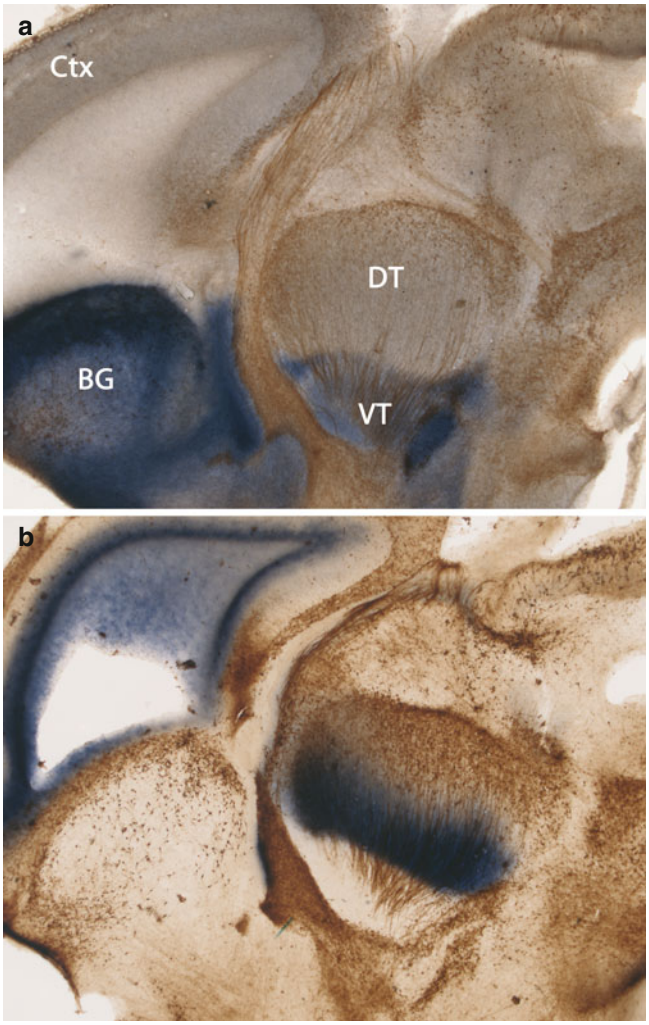

Fig. 9.31 Photomicrographs of *Dlx5* (**a**) and *Math4a* (**b**) labelling in the E14.5 mouse forebrain. *BG* basal ganglia, *Ctx* cortex, *DT* dorsal thalamus, *VT* ventral thalamus (Courtesy Luis Puelles, Murcia, and Loreta Medina, Lleda)

of the telencephalic roof plate leads to a severely reduced expression of *Lhx2* and a severe reduction in cortical size (Monuki et al. 2001). Another transcription factor that is crucial in dorsal patterning is the zinc-finger gene *Gli3* (Rallu et al. 2002b; Campbell 2003). *Gli3* is required to antagonize the ventralizing signal SHH in the dorsal telencephalon (Rallu et al. 2002a). Loss of *Gli3* function in *Extra-toes* mutants results in a loss of *Emx* gene expression as well as in the ectopic expression of certain genes characteristic of ventral telencephalic progenitors such as *Gsh2* (Theil et al. 1999; Tole et al. 2000b; Rallu et al. 2002a). *Extra-toes* mutant mice also lack the telencephalic choroid plexus and olfactory bulbs (Franz 1994). *Gli3* mutations are also responsible for the abnormalities in the arhinencephalic *Pdn*/*Pdn* (homozygote of *Polydactyly Nagoya* mouse, *Pdn*) mice (Naruse and Keino 1995). In man, *GLI3* mutations lead to Greig's (Greig 1926) cephalopolysyndactyly syndrome (Vortkamp et al. 1992), characterized by the presence of hypertelorism and polysyndactyly, and Pallister-Hall syndrome (Kang et al. 1997).

The secreted glycoprotein SHH is required for **ventral telencephalic** or **subpallial patterning** as shown in *Shh*-null mice (Chiang et al. 1996; Litingtung and Chiang 2000). Although these mutants lack any sign of MGE development such as expression of the *Nkx2.1* homeodomain protein, many of them express genes normally found in both the MGE and the LGE such as *Gsh2* and *Dlx2* (Rallu et al. 2002a, b); therefore, SHH is required for ventromedial telencephalic development. A mutation in *Nkx2.1* results in the acquisition of striatal-like properties by the presumptive pallidum, suggesting that *Nkx2.1* both specifies an MGE fate and inhibits LGE phenotypes (Sussel et al. 1999; Butt et al. 2008; Flandin et al. 2010). Nodal signalling is also required for induction of *Nkx2.1* expression as shown in zebrafish (Rohr et al. 2001). In *Pax6* (*Sey*) mutants, MGE markers expand into the LGE, leading to an overall reduction in size of the striatum and expression of MGE-derived structures (Stoykova et al. 2000); therefore, *Pax6* and *Nkx2.1* both operate at the LGE-MGE border, maintaining LGE and MGE identity, respectively. *Gsh1* and *Gsh2* also encode homeodomain proteins and are important for ventral telencephalic specification. In *Gsh2* single and *Gsh1*/*Gsh2* double mutants, dorsal markers cross the LGE-pallial boundary into the LGE and ventral markers are suppressed (Corbin et al. 2000; Toresson et al. 2000; Toresson and Campbell 2001). Probably, *Gsh2* maintains dorsal LGE identity without directly regulating ventral marker expression (Toresson et al. 2000), whereas expression of ventral genes in the ventral part of the LGE involves a more direct role of *Gsh1* and/or *Gsh2* (Toresson and Campbell 2001; Yun et al. 2001; Waclaw et al. 2009). Sousa and Fishell (2010) suggested that ventral telencephalic patterning is largely mediated by two sequential periods of competence, designated as C1 and C2. The SHH-mediated induction of *Nkx2.1* expression provides the hallmark of the initiation of MGE development and correspondingly the C1 period. This is followed by the C2 competence period, during which SHH signalling induces the LGE/CGE. Both structures induced during C1 (MGE) and C2 (LGE/CGE) are characterized by early production of projection neurons from their ventral aspects and late production of interneurons from their dorsal domains. In the human brain, cortical interneurons are also produced in the dorsal subventricular zone (Chap. 10).

Dlx1, *Dlx2*, *Dlx5* and *Dlx6* are expressed in overlapping sets of cells in the developing forebrain and single mutants have mild phenotypes, suggesting redundancy of function (Bulfone et al. 1993; Anderson et al. 1997b; Liu et al. 1997; Eisenstat et al. 1999; Panganiban and Rubinstein 2002). *Dlx2* is expressed before *Dlx1*, which is expressed before *Dlx5* and *Dlx6*. In the basal forebrain, the *Dlx*-positive cells differentiate into striatal and pallidal projection neurons as well as into interneurons for the cerebral cortex and olfactory

bulb. *Dlx2* mutants have reduced numbers of dopaminergic neurons in the olfactory bulb (Acampora et al. 1999; Eisenstat et al. 1999). In *Dlx1*/*Dlx2* double mutants, neurogenesis in the subpallium is disturbed, in particular the subventricular zone fails to mature (Anderson et al. 1997b; Marín et al. 2000). Cortical interneuron development appears to be dependent on *Dlx* dosage: one wild type *Dlx2* allele in a *Dlx1* null background is sufficient to rescue tangential migration to the cortex, though not subsequent radial migration into the cortical plate (Cobos et al. 2007). *Dlx* function is tightly labelled to the development of neurons derived from the basal telencephalon that produce GABA, acetylcholine and dopamine (Marín and Rubinstein 2002; Panganiban and Rubinstein 2002). Ectopic expression of *Dlx2* and *Dlx5* genes induces the expression of glutamic decarboxylase (GAD), the enzyme that synthesizes GABA (Stühmer et al. 2002). Moreover, *Dlx5* regulates the development of peripheral and central components of the olfactory system (Long et al. 2003). *Ascl1*, formerly known as *Mash1*, a basic helix-loop-helix transcription factor, regulates neurogenesis in the ventral telencephalon (Casarosa et al. 1999). *Mash1* mutant mice show severe loss of progenitors, particularly of neuronal precursors in the subventricular zone of the MGE. Discrete neuronal populations of the basal ganglia and cerebral cortex are subsequently missing. Loss of *Mash1* function also causes widespread defects in the primary olfactory pathway (Murray et al. 2003). Cells that migrate tangentially from the subpallium to the pallium express *Dlx1*/*Dlx2*, *Arx* and/or *Lhx6*. Lack of both *Dlx1* and *Dlx2*, or *Arx*, or *Lhx6* in mice is correlated with a dramatic decline in the number of GABAergic interneurons in the cerebral cortex (Anderson et al. 1997b, 2001; Cobos et al. 2005a, b, 2007). The decline of specific subtypes of GABAergic interneurons in the cerebral cortex due to mutations in *Dlx1* or *Arx* has been correlated with epileptic activity in mice and with epilepsy, lissencephaly and intellectual disability in humans (Kitamura et al. 2002; Colombo et al. 2004, 2007; Cobos et al. 2005b; Kato and Dobyns 2005; Marsh et al. 2009; Price et al. 2009; Chap. 10).

In the forebrain two main modes of **migration** can be recognized: radial and tangential (Fig. 9.32). The coexistence of these two different methods of cell migration has been well established for the developing cerebral cortex (Chap. 10). Lineage analysis studies showed that radially and tangentially migrating cells in the developing cortex arise from different progenitors (Mione et al. 1997; Tan et al. 1998). Moreover, the presence of *Dlx2*-positive neurons in the developing cortex suggested that cells of subpallial origin might have migrated tangentially into the pallium (Porteus et al. 1994). It is now clear that most cortical GABAergic neurons are born in the subpallium as already suggested by van Eden et al. (1989), and reach the developing cortex in several tangentially migrating streams (de Carlos et al. 1996; Anderson et al. 1997a; Tamamaki et al. 1997).

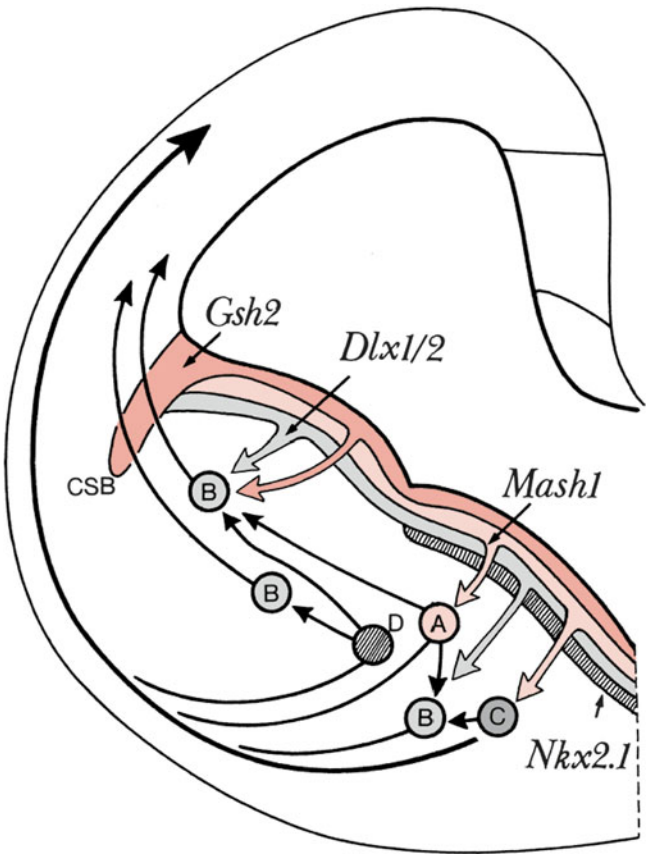

Fig. 9.32 Genes involved in specification and/or migration of tangentially migrating interneuron populations in the ventral forebrain (see text for explanation). Neurons indicated *A-D* express the following genes: A, *Mash1*; B, *Dlx1*/*2*; C, *Lhx6* and D, *Nkx2.1*. *CSB* corticostriatal boundary (After Zaki et al. 2003)

After these first studies on the origin of GABAergic neurons from the subpallium, a variety of experimental studies showed that GABAergic neurons for the entire cerebral cortex, including the neocortex, the piriform cortex and the hippocampus arise subpallially (Lavdas et al. 1999; Wichterle et al. 1999, 2001; Corbin et al. 2001; Marín and Rubinstein 2001; Nery et al. 2002; Brazel et al. 2003; Kriegstein and Noctor 2004). The three ganglionic eminences contribute different types of cells to different brain structures, and a similar pattern is likely to be present in man. The MGE appeared to be the main source of cortical interneurons (Lavdas et al. 1999; Wichterle et al. 1999, 2001). These cells express the LIM homeobox gene *Lhx6* and reach to the cerebral cortex via **dorsal** and **lateral cortical streams** (Fig. 9.33). The MGE also contributes cells to the globus pallidus and the cholinergic basal nucleus of Meynert. LGE cells migrate ventrally and anteriorly, and give rise to the GABAergic medium spiny neurons in the striatum, nucleus accumbens and olfactory tubercle, and to granule and periglomerular cells of the olfactory bulb. The striatal and olfactory bulb cells arise from two distinct progenitor populations in the LGE (Stenman et al. 2003). Progenitor

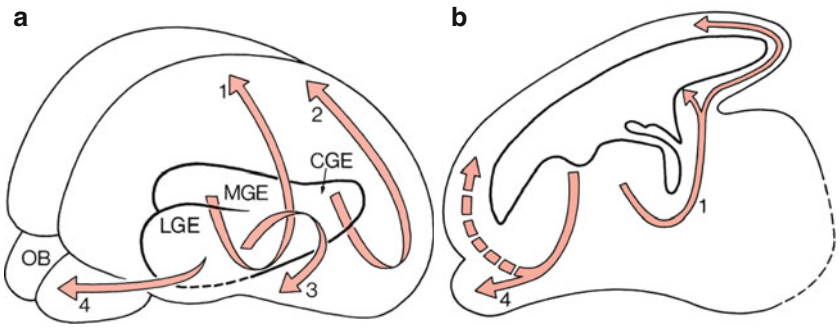

Fig. 9.33 Major routes of tangential migration in the murine forebrain: *1* dorsal migratory stream, *2* caudal migratory stream, *3* lateral cortical stream, *4* rostral migratory stream. *CGE* caudal ganglionic eminence, *LGE* lateral ganglionic eminence, *MGE* medial ganglionic eminence, *OB* olfactory bulb (After Corbin et al. 2001; Wichterle et al. 2001)

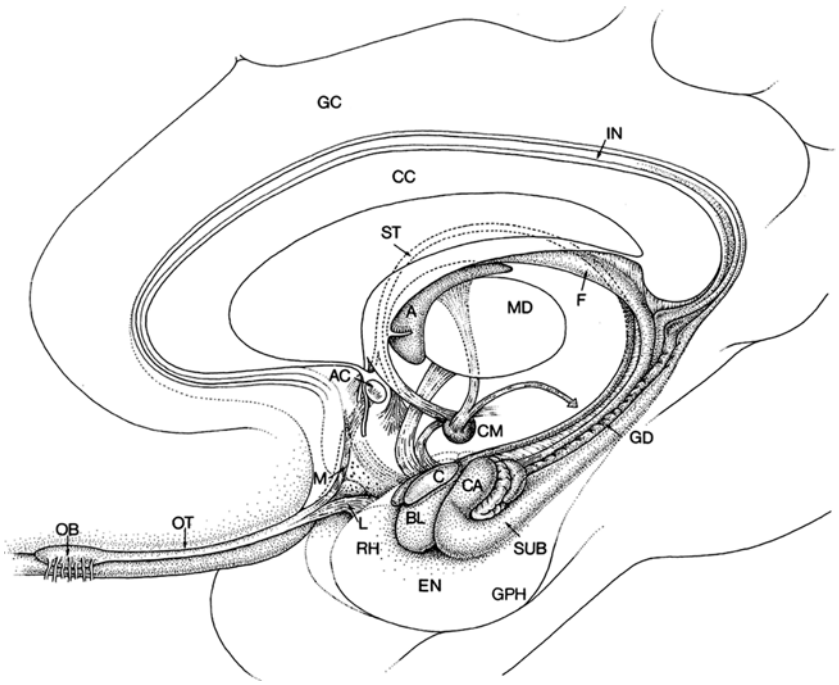

Fig. 9.34 Overview of the human rhinencephalon. *A* anterior nucleus, *AC* anterior commissure, *BL* basolateral amygdala, *C* cortical amygdala, *CA* cornu Ammonis, *CC* corpus callosum, *CM* corpus mammillare, *EN* entorhinal cortex, *F* fornix, *GC* gyrus cinguli, *GD* gyrus dentatus, *GPH* gyrus parahippocampalis, *IN* indudium griseum, *L* lateral olfactory stria, *M* medial olfactory stria, *MD* mediodorsal nucleus, *OB* olfactory bulb, *OT* olfactory tract, *ST* stria terminalis, *SUB* subiculum

cells in the subventricular zone of the LGE generate granule and periglomerular cells for the olfactory bulb (Hinds 1968a, b; Altman 1969; Bayer 1983; Kishi 1987). In neonatal and adult rodents and primates, these cells reach their final position via a **rostral migratory stream** (Luskin 1993; Lois and Alvarez-Buylla 1994; Kornack and Rakic 2001). The CGE contributes to the posterior neocortex, the hippocampus, the amygdala and posterior parts of the striatum and globus pallidus (Nery et al. 2002).

9.6 Development of the Rhinencephalon

The mammalian **rhinencephalon**, i.e. the part of the telencephalon involved in the processing of chemosensory information, is composed of the main olfactory system, the accessory olfactory or vomeronasal system and the terminal nerve (Stephan 1975; Voogd et al. 1998). Olfactory fibres originate in the olfactory epithelium and pass as **fila olfactoria** through the cribriform plate of the ethmoid to contact the olfactory bulb. The central part of the **main olfactory system** comprises the olfactory bulb and the targets of its projections within the telencephalon, i.e. the retrobulbar region or anterior olfactory nucleus, the olfactory tubercle, the prepiriform, periamygdaloid and entorhinal cortices, and the cortical and medial nuclei of the amygdaloid complex (Lohman and Lammers 1967; Price 1990; Shipley et al. 1995; Fig. 9.34). The **accessory olfactory system**, also known as the **vomeronasal system**, comprises the vomeronasal organ of Jacobson, the accessory olfactory bulb and some nuclei of the amygdaloid complex (Halpern 1987; Shipley et al. 1995). The accessory olfactory system is primarily involved in the regulation of reproductive behaviour, elicited by pheromones, chemical messengers

from other members of the same species (Dulac and Torello 2003). In humans, the vomeronasal system is established during embryonic development and regresses in the fetal period (Ortmann 1989; Kjaer and Fischer-Hansen 1996), although as many as 850 cells may be present by 4 months after birth (Oelschläger et al. 1987). The human **vomeronasal organ** of **Jacobson**, a pocket lying in the nasal septum, opens into the vomeronasal pit, about 1 cm dorsal to the columella and 1–2 mm above the floor of the nose. In some 40 % of adults, this opening can be seen macroscopically (Moran et al. 1991), and even in 73 % of the population using endoscopy (Trottier et al. 2000).

The **olfactory bulb** arises as an evagination of the rostral telencephalon (Fig. 9.35) and receives primary olfactory afferent fibres from neurons in the olfactory epithelium. The primary olfactory fibres synapse on the dendrites of glutaminergic projection neurons (the *mitral* and *tufted cells*) found in specialized structures called **glomeruli**, forming the glomerular layer. Many thousands of olfactory receptor cells synapse with the dendritic branches of one or only a few mitral cells within a glomerulus, resulting in a high degree of convergence of olfactory receptors onto mitral cells (Shepherd and Greer 1990). A large number of inhibitory, GABAergic interneurons are present in the olfactory bulb, the most common of which are the *granule* and *periglomerular cells*. Most of the periglomerular cells are GABAergic as well as dopaminergic. The following layers can be recognized in the olfactory bulb: (1) the *outer fibre layer*, consisting of the incoming olfactory fibres; (2) the *glomerular layer*, consisting of several rows of glomeruli surrounded by periglomerular cells; (3) the *external plexiform layer*, containing the dendritic branches of mitral cells and granule cells; (4) the *mitral cell layer*, not well-defined in man; (5) an ill-defined *internal plexiform layer*, largely composed of axons of mitral and tufted cells; (6) the *granular layer*, with the granule cells; and (7) a *periventricular layer*, composed of the *subventricular zone*, a reservoir of progenitor cells that produces new granule and periglomerular cells in the adult brain, and *ependymal cells*, remnants of the epithelial layer of the olfactory ventricle.

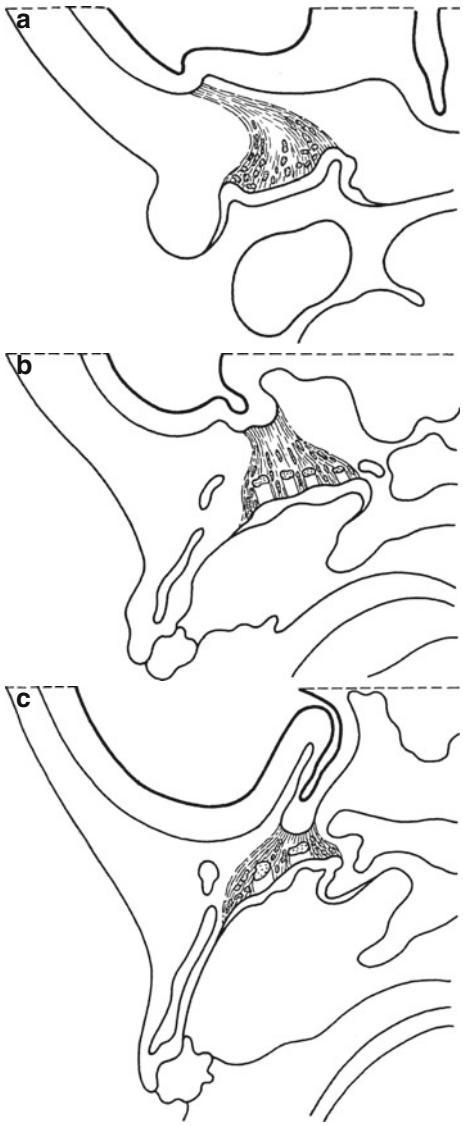

Fig. 9.35 Development of the human olfactory bulb: (**a**) a stage 18 embryo (about 42 days of development); (**b**) a 3.2-mm fetus; (**c**) a 4.9-mm fetus (After Pearson 1941b; Hinrichsen 1990)

Development of the **olfactory bulb** begins with its induction and evagination from the rostral telencephalon. FGF signalling through FGFR1 is required for olfactory bulb morphogenesis (Hébert et al. 2003). Signalling from the olfactory placode may contribute to patterning the anlage of the olfactory bulb (Graziadei and Monti-Graziadei 1992; de Carlos et al. 1995; LaMantia et al. 2000). The mitral and tufted neurons have a pallial origin and are regulated by cortical transcription factors such as *Tbr1* (Bulfone et al. 1998), whereas the granule and periglomerular cells have a subpallial origin and are regulated by subpallial transcription factors such as *Dlx1* and *Dlx2* (Qiu et al. 1995; Bulfone et al. 1998). The *Dlx* family of homeobox genes is expressed in the olfactory bulb as well as in the olfactory epithelium (Acampora et al. 1999; Depew et al. 1999; Long et al. 2003). In particular, *Dlx5* is expressed in the olfactory placode, the

olfactory epithelium and local circuit neurons of the olfactory bulb. In *Dlx5–/–* mutants, the size of the olfactory epithelium is reduced and the few olfactory neurons formed fail to generate axons that innervate the olfactory bulb (Long et al. 2003). Despite this lack of innervation, the olfactory bulb forms, and neurogenesis of projection and local circuit neurons proceeds. Widespread defects in the primary olfactory pathway are caused by loss of *Ascl1* (formerly *Mash1*) function (Murray et al. 2003). This homologue of the *Drosophila* proneural genes *achaete* and *scute* is normally expressed by neuronal progenitors in the developing peripheral nervous system and CNS, including the olfactory epithelium and the olfactory bulb and ganglionic eminences (Guillemot et al. 1993; Cau et al. 2002). *Neurogenin 1*, related to the *Drosophila* proneural gene *atonal*, is necessary for the differentiation of olfactory sensory neuron progenitors (Cau et al. 2002). In human cases of arhinencephaly as found in HPE and in Kallmann syndrome, both olfactory receptor cells and olfactory nerves are present (Braddock et al. 1995), also suggesting that the initial development of the olfactory nerves is independent of the formation of the olfactory bulb. Bilaterally enlarged olfactory bulbs with abnormal laminar structures were described as ***olfactory bulb dysplasia*** in a case of Pena-Shokeir phenotype (Yamanouchi et al. 1999). Loss of smell (***anosmia***) is rather common and the frequency increases with age. A much smaller group have no memory of ever being able to smell and are classified as having ***isolated congenital anosmia*** (Karstensen and Tommerup 2012). Families are rare and tend to present in a dominant inheritance pattern. Anosmia is part of the clinical spectrum in various diseases such as Kallmann syndrome, various ciliopathies and congenital insensitivity to pain.

Pearson (1941b, 1942) described the **development** of the **human olfactory bulb** (Fig. 9.35). At the end of the first gestational month (stage 13), the olfactory placodes can be distinguished as epithelial thickenings on either side of the head. Subsequently, the olfactory placodes are overgrown by the nasal folds, resulting in the formation of the olfactory pits (Chap. 5). The first bipolar cells appear in the olfactory placode at stage 14. At stage 16, olfactory fibres enter the wall of the telencephalon when still no olfactory bulb can be identified (Lemire et al. 1975; Bossy 1980; Pyatkina 1982; Müller and O'Rahilly 1989a, 2004). Soon afterwards, the olfactory bulb begins as a slight bulge (stage 17), and by stage 20 it consists of a slight protrusion. By stage 22 all layers of the olfactory bulb are represented (Humphrey 1967; Lemire et al. 1975; Bossy 1980; Müller and O'Rahilly 1989b, 2004). Occasionally, a remnant olfactory ventricle may be observed (Clinical Case 9.7).

The **vomeronasal organ** of **Jacobson** first appears as a groove in the nasal septum at stage 18 (Humphrey 1940). Nerve fibres from this region may be traced into the vomeronasal and terminal nerves. The **vomeronasal nerve** arises from cells found in the medial border of the olfactory placode and is difficult to separate from the terminal nerve which arises in the same area at the same time (Pearson 1941a, 1942; Fig. 9.36). Vomeronasal fibres pass dorsomedially along the developing olfactory bulb to enter the accessory olfactory bulb around stage 18 (Humphrey 1940). The **accessory olfactory bulb** moves from its original dorsomedial position to a dorsolateral position. It begins to regress at the beginning of the third gestational month and is vestigial by the end of the third gestational month (Humphrey 1940; Lemire et al. 1975; Meisami and Bhatnagar 1998; Meredith 2001; Savic et al. 2001). The development of the vomeronasal nerve and accessory olfactory bulb parallels the development and regression of the vomeronasal organ in the human embryo. The **terminal nerve** is characterized by ganglion cells along its course and has been described in adults (Crosby and Humphrey 1941). At stages 16 and 17, the terminal nerve arises from cells in the medial part of the olfactory placode and is closely associated with the vomeronasal nerve (Pearson 1941a). GnRH neurons migrate along the vomeronasal and terminal nerves to the forebrain (Schwanzel-Fukuda and Pfaff 1989; Schwanzel-Fukuda et al. 1989; Boehm et al. 1994; Berliner et al. 1996). GnRH neurons can be detected in the olfactory epithelium as early as 5.5 weeks of development (Fig. 9.55a, b). These cells migrate along the developing vomeronasal and terminal nerves shortly afterwards (Verney et al. 1996).

The development of human primary and secondary olfactory areas is shown in basal views of the brain (Fig. 9.37). At first olfactory regions of the brain occupy a large part of the basal aspect of the brain. Later in development, the olfactory regions become restricted to a small part of the basal frontal lobe and the rostromedial part of the temporal lobe (Macchi 1951; Gastaut and Lammers 1961; Kahle 1969; Stephan 1975).

Extensive **birthdating studies** on the **olfactory system** have been carried out in rodents. Data are available for the olfactory bulb (Hinds 1968a, b; Bayer 1983, 1986a, b), the olfactory tubercle (ten Donkelaar and Dederen 1979; Bayer 1985a; Bayer and Altman 1987b) and the primary olfactory cortex (Bayer 1985b; Bayer and Altman 1987b). In rats,

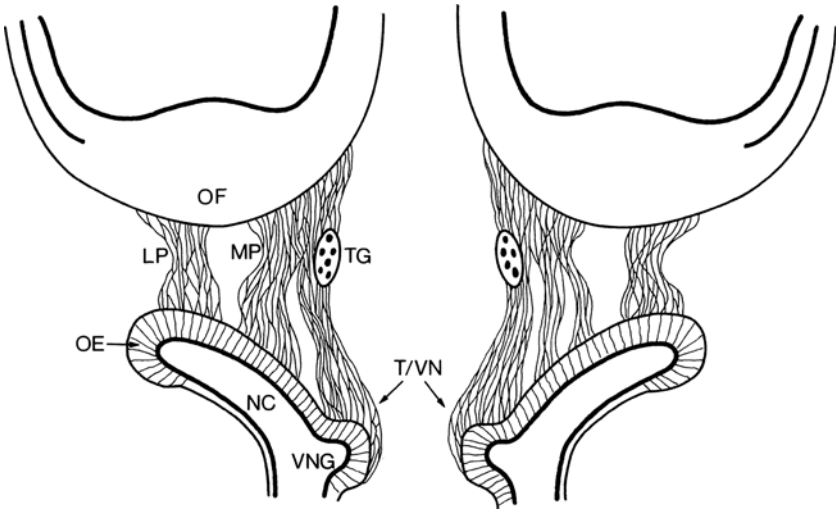

Fig. 9.36 Development of the human vomeronasal and terminal nerves at stage 18. *LP* lateral olfactory plexus, *MP* medial olfactory plexus, *NC* nasal cavity, *OE* olfactory epithelium, *OF* olfactory field, *TG* terminal ganglion, *T/VN*, terminal and vomeronasal nerves, *VNG* vomeronasal groove (After Ashwell and Waite 2004)

mitral cells in the olfactory bulb are born on E14-E16, and granule cells from E20 onwards, continuing in the adult brain. Several neurogenetic gradients in all structures receiving olfactory input were found. Bayer (1986b) suggested a relationship between these gradients in the olfactory target structures and their connections with the olfactory bulb. Bayer et al. (1995) estimated the time of neuron origin of human mitral cells between 5 and 8 weeks of development. Human granule cells are formed from the 19th week of development onwards.

The **development** of **olfactory bulb projections** has been studied in rats (Schwob and Price 1984; López-Mascaraque et al. 1996; Hongo et al. 2000). Using the fluorescent carbocyanine tracer DiI, the first olfactory projections can already be detected at E13 (López-Mascaraque et al. 1996). Pioneering fibres begin to grow through the ventral part of the telencephalon. At E14 and E15, these fibres have reached distant parts in the basal and lateral parts of the telencephalic vesicle, and establish the first contacts with the future amygdaloid area and the primary olfactory cortex. At E16, fibres from the olfactory bulb run caudally in a fan-like fashion, the lateral olfactory tract increases considerably and some fibres course along the anterior commissure. At E17, the major fibre systems appear already established, providing the substrate of the adult pattern. The further development of axonal connections in the central olfactory system has been studied by Schwob and Price (1984). In genetic arhinencephaly mouse embryos (*Pdn*/*Pdn*), the olfactory bulb is not formed, and olfactory fibers do not enter the CNS. They form a tangled mass under the cerebral hemisphere at E16 (Hongo et al. 2000). *Pdn*/*Pdn* mice exhibit preaxial polydactyly in both the forelimbs and hindlimbs (Naruse and Keino 1995). Newborns do not suckle milk and die within 1 day after birth. They also exhibit various brain malformations, including absence of the olfactory bulbs and corpus callosum. Apoptosis of precursor mitral cells in the anlage of the olfactory bulb may be induced by non-innervation of olfactory neurons, and sequential apoptosis of precursor neurons in the pyriform cortex may be induced by non-innervation due to death of mitral cells (Naruse and Keino 1995).

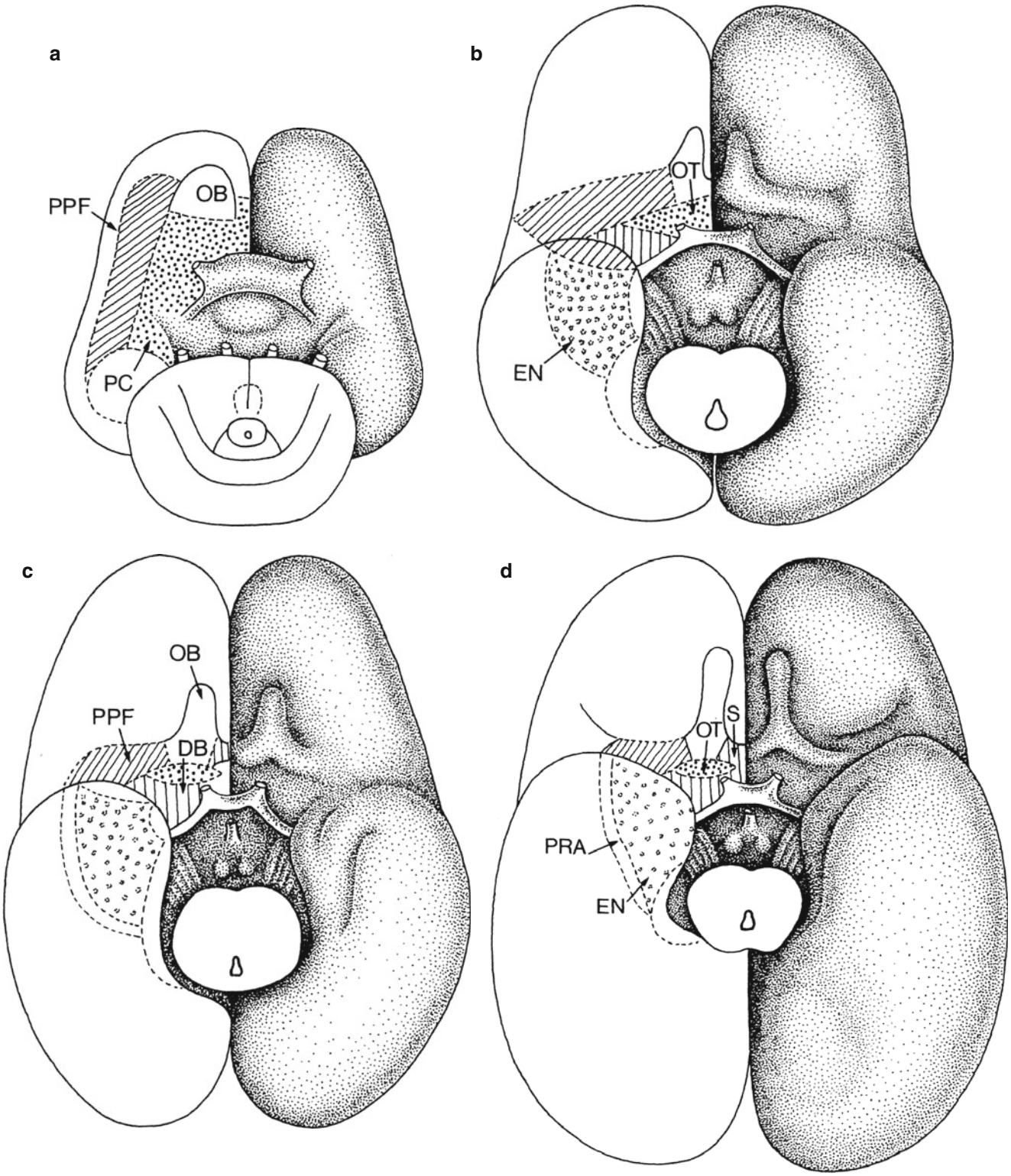

Fig. 9.37 Basal views of the human brain in the second (**a**), third (**b**), fourth (**c**) and sixth (**d**) months of development. *DB* diagonal band of Broca, *EN* entorhinal cortex, *OB* olfactory bulb, *OT* olfactory tubercle, *PC* paleocortex, *PPF* prepiriform cortex, *PRA* perirhinal cortex, *S* septum (After Macchi 1951; Gastaut and Lammers 1961; Kahle 1969; Stephan and Andy 1977)

Clinical Case 9.7 A Remnant Olfactory Ventricle

An olfactory ventricle is an embryonic structure which appears in connection with the development of the olfactory nerve. It regresses after the formation of the olfactory bulb, but in certain pathological conditions, a ***remnant olfactory ventricle*** persists (see Case Report).

Case Report. A newborn male baby without any familial history died of a connatal infection shortly after birth. No gross malformations were observed. At autopsy, only agenesis of the olfactory nerves was observed (Fig. 9.38a). On the right side of the brain, there was a small protrusion, suggesting a rudimentary olfactory structure in which histologically a remnant olfactory ventricle was found (Fig. 9.38b). An olfactory ventricle is seen in embryonic stages (Fig. 9.38c). The persistence of such an embryonic structure may indicate a developmental disturbance.

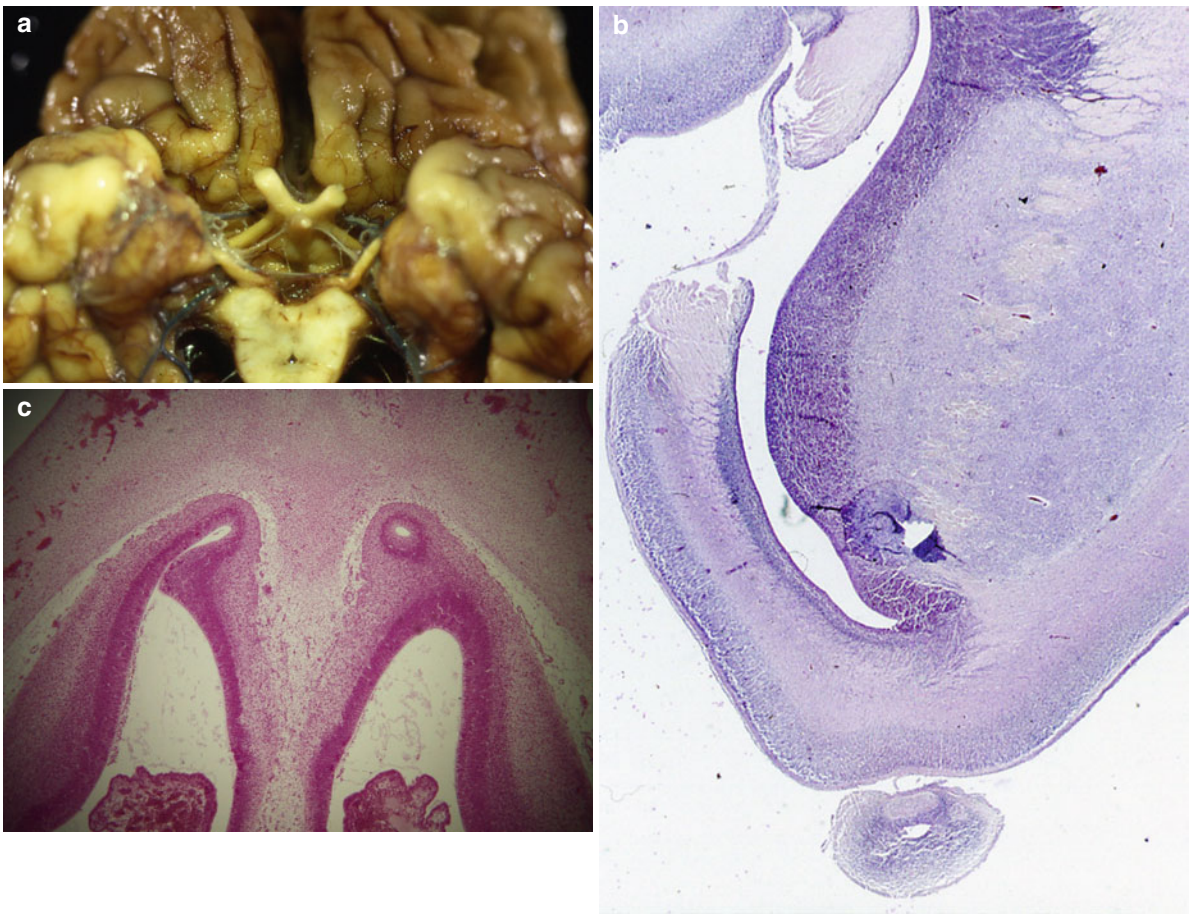

Fig. 9.38 A remnant olfactory ventricle: (**a**) the base of the cerebrum, showing agenesis of the olfactory nerves; on the right side a rudimentary olfactory protrusion is present; (**b**) horizontal section of the embryonic cerebral hemispheres at Carnegie stage 21, showing the olfactory ventricles (Courtesy Kohei Shiota, Kyoto); (**c**) frontal section of the present case, showing the olfactory ventricle at the bottom (Courtesy Akira Hori, Toyohashi)

9.7 The Prosencephalies

Prosencephalic malformations may be the result of defects in mediolateral patterning of the rostral part of the embryonic neural plate. Since this anlage gives rise to the forebrain with the eye vesicles and the hypothalamus/neurohypophysis, prosencephalic defects are usually accompanied by anomalies of the eyes and the pituitary gland. These disorders are sometimes described as ***midline field defects*** (Opitz 1993; Opitz et al. 1997; Roessler and Muenke 2001) but from an embryological point of view they are quite heterogeneous and a real midline field does not exist (O'Rahilly and Müller 2001). The general term ***prosencephalies*** (Probst 1979) includes a scala of malformations, ranging from aprosencephaly to partial or lobar HPE (Sergi and Schmitt 2000; Kakita et al. 2001; Table 9.9). The most severe forms of developmental malformations of the forebrain are complete absence of the forebrain (aprosencephaly) or of the telencephalon (atelencephaly). The most frequent prosencephalies are the various forms of HPE. Related disorders are septo-optic dysplasia (de Morsier syndrome) and isolated arhinencephaly as found in disorders such as Kallmann syndrome.

Table 9.9 Subdivision of the prosencephalies

Subdivision	Further subdivision	Remarks
Aprosencephaly		
Atelencephaly		
Prosencephaly		
	Complete sac category (pseudo-aprosencephaly)	
	Dorsal sac category (holosphere with dorsal sac)	Phenotypes: Cyclopia; Ethmocephaly; Cebocephaly; Median (or bilateral cleft) lip/palate; Minor dysplasias or without facial defects
	Intermediate category	
	Pseudohemispheric category (holosphere without sac)	
	Partial prosencephaly (anterior part of holosphere divided, posterior part continuous)	
	Middle interhemispheric variant	

After Probst (1979), Sergi and Schmitt (2000)

9.7.1 Aprosencephaly

Aprosencephaly and ***atelencephaly*** are extremely rare CNS defects. Several cases were studied neuropathologically (Garcia and Duncan 1977; Siebert et al. 1986, 1987; Lurie et al. 1979, 1980; Towfighi et al. 1987; Kim et al. 1990; Harris et al. 1994; Ippel et al. 1998; Sergi and Schmitt 2000; Kakita et al. 2001; Clinical Case 9.8). In ***aprosencephaly***, the forebrain structures derived from the telencephalon (the cerebral cortex, the basal ganglia and the hypothalamus) and the diencephalon (the eyes and the thalamus) are absent or rudimentary. In ***atelencephaly***, the thalami are developed and some residual hemispheres may be found. The aetiology of aprosencephaly and atelencephaly remains controversial. Some cases may be due to a destructive, encephaloclastic process (Norman et al. 1995), but could also be primary malformations (Leech and Shuman 1986; Sergi and Schmitt 2000). Sergi and Schmitt (2000) described two cases of a vesicular forebrain (***pseudo-aprosencephaly***), a possible missing link in the teratogenic spectrum of defective forebrain anlage (Table 9.9). Which genes are involved is unknown, but *OTX2* is apparently not involved (Florell et al. 1996). The case of aprosencephaly described by Kakita et al. (2001) did not show evidence of destruction. In their case, a male fetus of 20 weeks of gestation, the prosencephalon was extremely small and was replaced by a solid, cylindrical mass without hemispheric cleavage or a ventricle. The most rostral part of the CNS penetrated through a midsagittal ectopic canal in the sphenoid bone, comparable to a case of cyclopia (Kakita et al. 1997).

Clinical Case 9.8 Aprosencephaly

Aprosencephaly is an extremely rare fetal CNS defect in which the forebrain structures derived from both the telencephalon and the diencephalon are absent or rudimentary (Kakita et al. 2001; see Case Reports). Sergi and Schmitt (2000) reported a case in which the forebrain was missing but remnants of a forebrain bleb were observed (***pseudo-aprosencephaly***).

Case Reports. In the first case, on ultrasound examination of the fourth pregnancy of a 32-year-old mother with severe diabetes mellitus type 1, the fetus was suspected for anencephaly; therefore, delivery was induced at 20 gestational weeks. The immature female fetus showed multiple congenital malformations (Fig. 9.39a–c), including: (1) ***aprosencephaly***, characterized by the absence of the diencephalon and the telencephalon with absence of the olfactory bulbs and a malformed optic

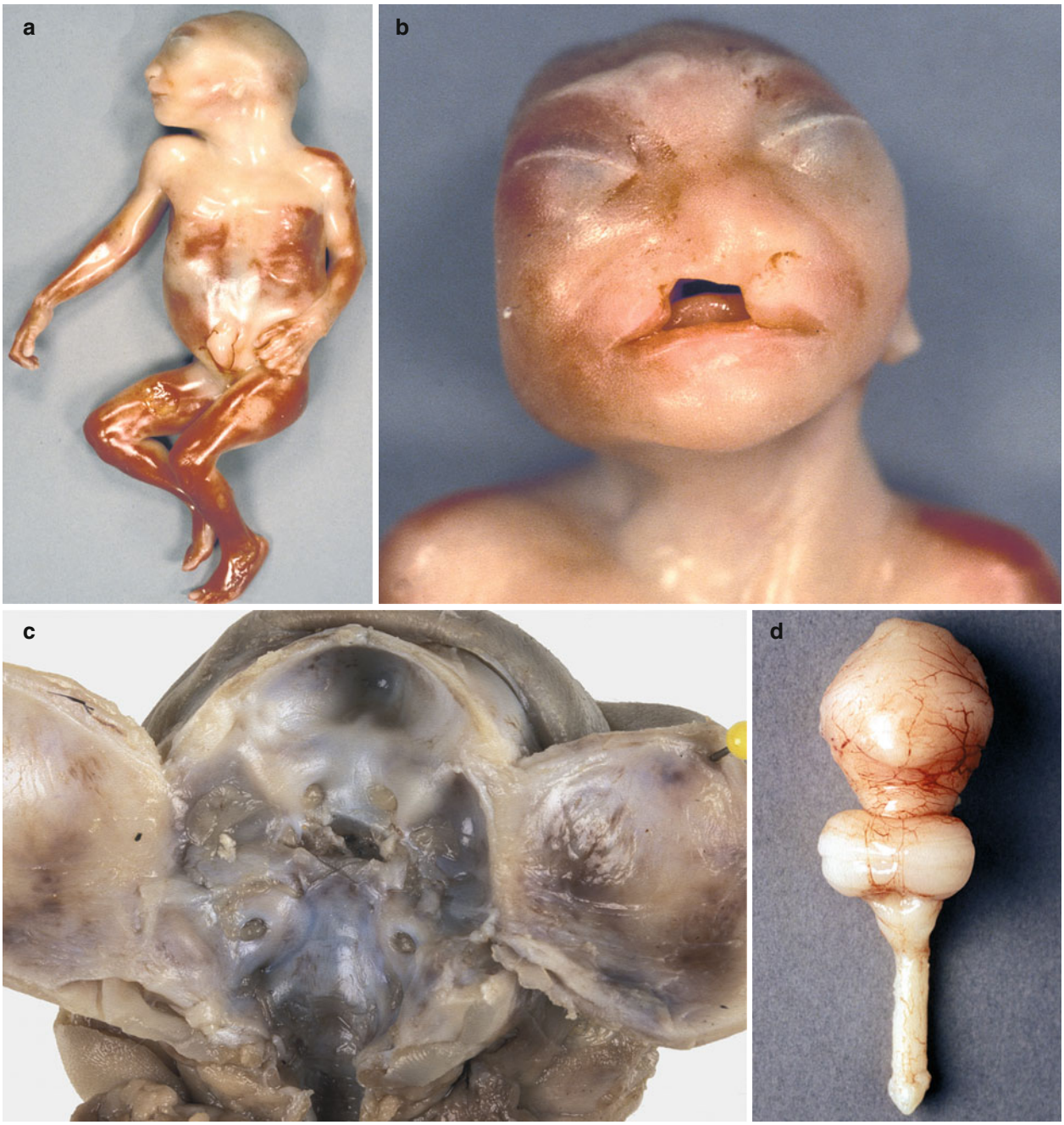

Fig. 9.39 Aprosencephaly found in a 20-week-old fetus: (**a**) overview of fetus; (**b**) craniofacial malformations; (**c**) malformed skull base with absent crista galli and only one frontal bone; (**d**) dorsal view of the CNS. The rostral end of the mesencephalon is nodular and rounded (Courtesy Gerard van Noort, Enschede)

chiasm; (2) low brain weight (6.8 g instead of the 40 g normal for 20 gestational weeks); (3) skull malformations with a strongly flattened skull cap, a malformed skull base with absence of the crista galli and one frontal bone, and absence of fonticuli; (4) lateral cheilognathopalataschisis on the right; (5) low-positioned, malformed ears; (6) short neck with slight webbing; (7) skeletal malformations (immature skeleton, fusion of some ribs, open spine at the Th11 level. Chromosomal analysis showed a normal 46XX karyotype. The rostral end of the mesencepha-

lon was nodular and rounded (Fig. 9.39d). Microscopically, disorganized neuronal tissue was present without recognizable structures.

In the second case, amniotic band constriction of the fetus was diagnosed in a primigravida during routine examination at the 16th week of gestation. Abortion was induced and at autopsy no amniotic strang was found but a dysmorphic face with asymmetrical eyes and a hare lip extending through the nose to the forehead (Fig. 9.40a). The small head was partially covered by membranous tissue in the frontal area with a defective calvarium. The prosencephalon was absent when the cranial vault was opened but the cerebellum was grossly identified and the pituitary gland existed. The anterior cranial fossa was narrow and the roof of the orbita elevated (Fig. 9.40b). A small tissue fragment from the cranial base appeared as leptomeninx and was histologically shown hypervascularized, suggesting an area cerebrovasculosa (Fig. 9.40c). The desmocranium showed ossification and a heterotopic subcutaneous cartilaginous fragment (Fig. 9.40d). The structure of the cerebellum and pons was histoloically normal (Fig. 9.40e). This case of aprosencephaly may be caused by a destructive process given the area cerebrovasculosa-like tissue fragments and the clinical diagnosis of amniotic band constriction.

The first case was kindly provided by Gerard van Noort (Laboratory for Pathology East-Netherlands, Enschede, The Netherlands) and the second case by Akira Hori (Toyohashi).

References

Kakita A, Hayashi S, Arakawa M, Takahashi H (2001) Aprosencephaly: histopathologic features of the rudimentary forebrain and retina. Acta Neuropathol (Berl) 102:110–116

Sergi C, Schmitt HP (2000) The vesicular forebrain (pseudo-aprosencephaly): a missing link in the teratogenic spectrum of the defective brain anlage and its discrimination from aprosencephaly. Acta Neuropathol (Berl) 99:277–284

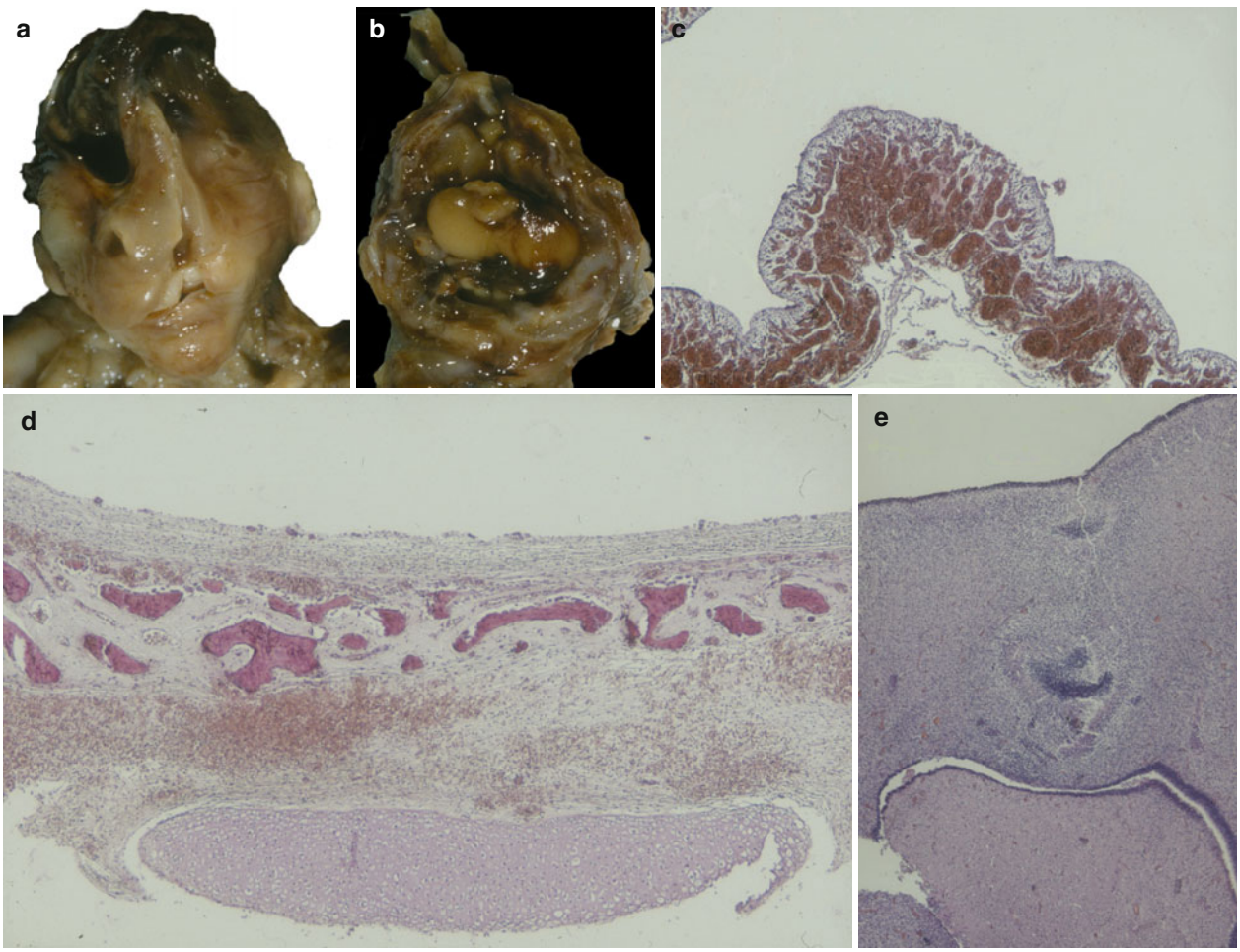

Fig. 9.40 Aprosencephaly found in a 16-week-old fetus: (**a**) facial dysmorphism; (**b**) details of the aprosencephaly and frontal cranial base; (**c**) tissue fragments from the frontotemporal cranial area, showing an area cerebrovasculosa; (**d**) desmocranium with ossification and heterotopic cartilage fragment below; (**e**) cerebellum with vermis and pons seems well-developed (Courtesy Akira Hori, Toyohashi)

9.7.2 Holoprosencephaly

Holoprosencephaly (***HPE***) is usually described as a developmental field defect of impaired midline cleavage of the embryonic forebrain (DeMyer and Zeman 1963; Probst 1979; DeMyer 1987; Cohen 1989a, b; Siebert et al. 1990; Cohen and Sulik 1992; Norman et al. 1995; Golden 1998; Muenke and Beachy 2000, 2001; Roessler and Muenke 2001; Sarnat and Flores-Sarnat 2001; Cohen and Shiota 2002). HPE is frequently associated with specific craniofacial anomalies, including midline facial defects, cyclopia and nasal malformations (Chap. 5), and a broad range of ophthalmological anomalies (Pineda-Alvarez et al. 2011. Its incidence in live-born children with normal chromosomes has been estimated to be 0.48–0.88 per 10,000. In contrast, the rate among therapeutic abortuses was estimated at 40 per 10,000, indicating a very high rate of embryonic and fetal loss (Matsunaga and Shiota 1977; Shiota 1993; Shiota and Yamada 2010). In a large epidemiologic study in a Californian population, Croen et al. (1996) observed an overall prevalence of 1.2 per 10,000 live births and fetal deaths, whereas the prevalence for live births was 0.88 per 10,000.

HPE is aetiologically very heterogeneous. It can be associated with chromosomal abnormalities, single gene mutations, polygenic mechanisms, and environmental factors such as diabetes mellitus and alcohol (Warkany 1971; Cohen 1989a; Cohen and Sulik 1992; Norman et al. 1995; Kelley et al. 1996; Muenke and Beachy 2001; Cohen and Shiota 2002; Edison and Muenke 2003). Cytogenetic studies of HPE patients suggest at least 13 different autosomal dominant loci (Roessler and Muenke 1998, 2010; Nanni et al. 2000; Bendavid et al. 2010; Cohen 2010; Table 9.10), giving rise to about 15–20 % of all cases of HPE (Cohen and Shiota 2002). Several HPE genes have been identified: *SHH* (also known as HPE3: Belloni et al. 1996; Roessler et al. 1996; Nanni et al. 1999), *SIX3* (HPE2: Wallis et al. 1999; Domené et al. 2008), *ZIC2* (HPE5: Brown et al. 1998; Roessler et al. 2009), *TGIF* (HPE4: Gripp et al. 1998; El-Jaick et al. 2007), *Patched*/*PTCH* (Ming and Muenke 1998; Ming et al. 2002), *GLI2* (HPE9: Roessler et al. 2003) and *NODAL* (Roessler et al. 2008). Their possible interactions with normal signalling pathways and cholesterol biosynthesis is shown in Fig. 9.41. *SHH* mutations account for about 17 % of familial cases, and 3.7 % of all HPE cases (Cohen and Shiota 2002). Clinical manifestations of HPE are quite variable among patients and even among family members who carry a defined type of gene mutation (Ming and Muenke 2002; Edison and Muenke 2003).

HPE is a developmental malformation sequence in which impaired midline cleavage of the forebrain up to no cleavage (a *holosphere*) is the basic feature. The more severe forms can be diagnosed prenatally by ultrasound (Blaas et al. 2002; Pooh 2009; Volpe et al. 2009; Clinical Case 9.9).

In a majority of cases, this non-cleavage involves the basal ganglia, thalamus and hypothalamus. ***Diabetes insipidus*** occurs in about 67 % of children with HPE (Sarnat and Flores-Sarnat 2001), but other endocrine disorders involving the anterior pituitary occur less common and usually in addition to diabetes insipidus. The hypothalamus shows the highest incidence of non-cleavage of subcortical structures in HPE (Simon et al. 2000). The involvement of the basal ganglia may lead to generalized chorea (Louis et al. 1995). The most severe, complete or alobar type, and the incomplete forms, including the semilobar type and the least severe lobar type, represent degrees of severity rather than clearly distinguishable forms of this disorder. Together with the associated craniofacial malformations they constitute the HPE sequence (Cohen and Sulik 1992). The craniofacial malformations also vary in extent from the most severe being cyclopia with a single proboscis located above the midline eye to mild facial abnormalities. In general, the "face predicts the brain" (DeMyer et al. 1964; Fig. 9.42). It should be emphasized, however, that in 10–20 % of the holoprosencephalies no or only minor craniofacial abnormalities are present (Chap. 5), and that severe HPE may be present in the absence of obvious facial anomalies. The severity of the malformations has an anterior-to-posterior gradient, with the anterior portions being the least well formed (Cohen 1989b; Norman et al. 1995; Golden 1998; Simon et al. 2000). The **gyral pattern** of the posterior cerebrum more closely resembles the normal gyral pattern than that of the anterior cerebrum (Barkovich et al. 2002). Most HPE patients have normal cortical thickness (Barkovich et al. 2002). Sylvian fissures were displaced further rostrally

Table 9.10 Causative genes of human holoprosencephaly

Human locus	Chromosome	Gene	Function
HPE1	21q22.3	?	
HPE2	2p21	*SIX3*	Homeoprotein important for development of eye and forebrain
HPE3	7q36	*SHH*	Ventral CNS patterning
HPE4	18p11.3	*TGIF*	Homeoprotein interacting with Smad2
HPE5	13q32	*ZIC2*	Zinc finger transcription factor important for axis formation and dorsal brain development
HPE6	2q17.1-q37.3	?	
HPE7	9q22.3	*PTCH1*	Receptor for hedgehog ligands
HPE8	14q13	?	
HPE9	2q14	*GLI2*	Transcription factor mediating hedgehog signalling
HPE10		?	
–	1q42	*DISP1*	Release of hedgehog ligands
–	10q	*NODAL*	TGFβ-like ligand involved in midline and laterality establishment
–	8q	*FOXH1*	Transcription factor for NODAL signalling

After Roessler and Muenke (2010)

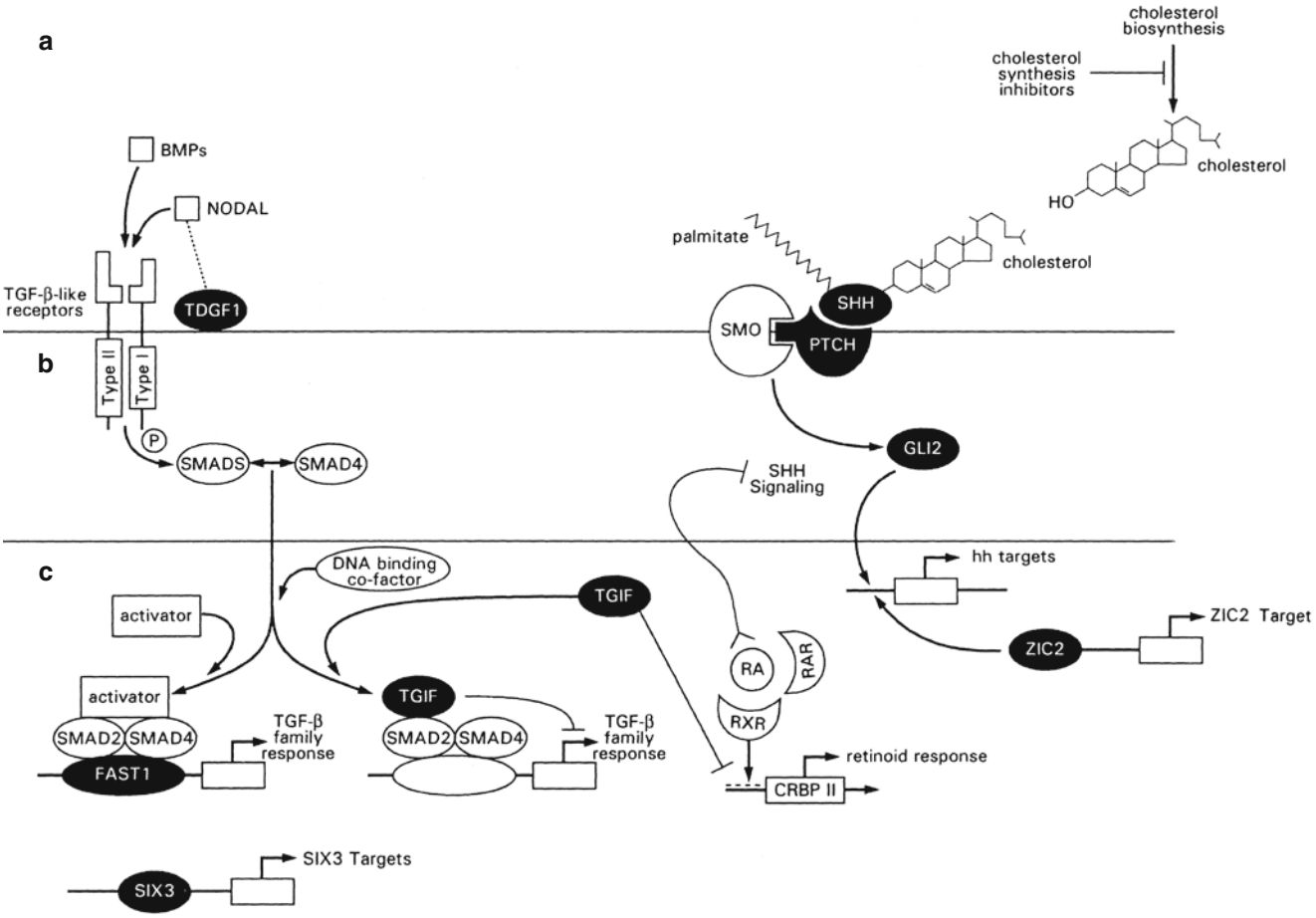

Fig. 9.41 Association of holoprosencephaly with abnormal function of signalling pathways, cholesterol biosynthesis, and various transcription factors in (**a**) extracellular space, (**b**) cytoplasm and (**c**) nucleus (After Edison and Muenke 2003)

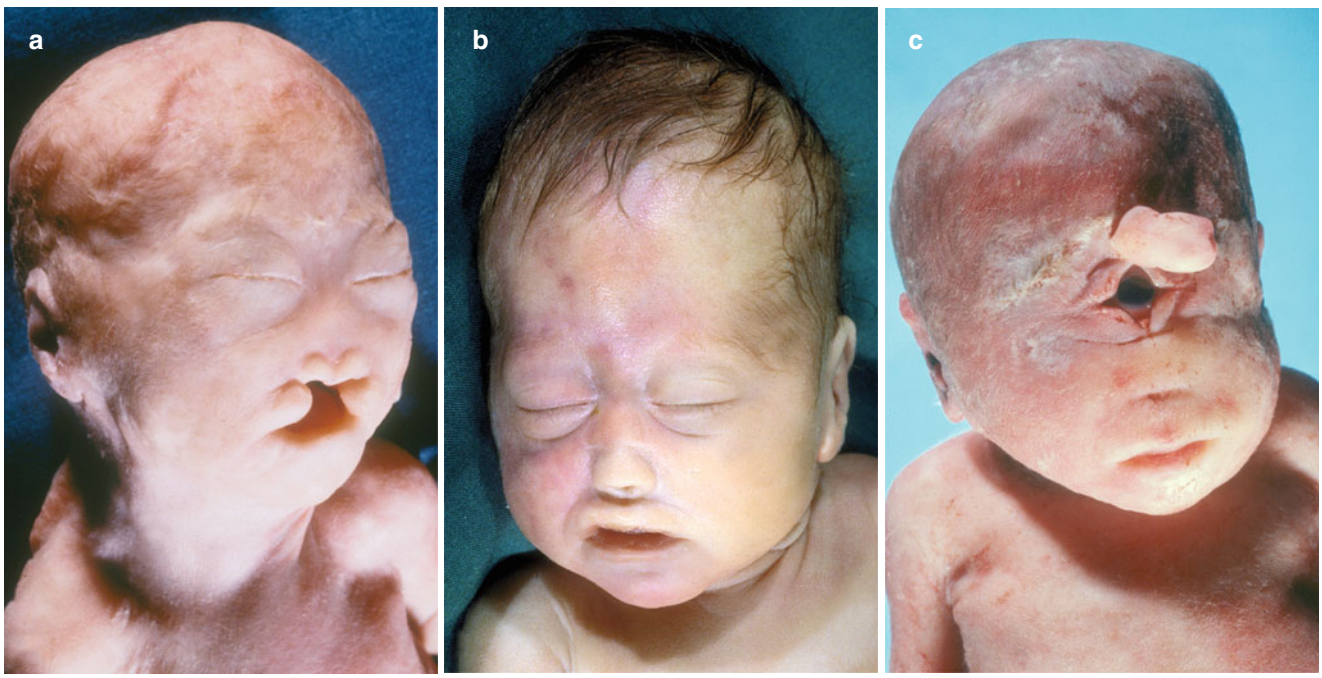

Fig. 9.42 Craniofacial malformations in cases of holoprosencephaly: (**a**) a female fetus of 26 weeks of gestation; (**b**) a female born at 34 weeks of gestation, showing a single nasal opening and choanal atresia; (**c**) a male fetus of 24 weeks of gestation with cyclopia and a proboscis; (**d**) a fetus with cyclopia and a proboscis; (**e**) a female fetus, 39 weeks of gestation, showing a single nasal opening; (**f**) a fetus of approximately 30 weeks of gestation. Examples of their brain malformations are shown in Fig. 9.43 (From the Department of Neuropathology, Medizinische Hochschule Hannover; courtesy Akira Hori)

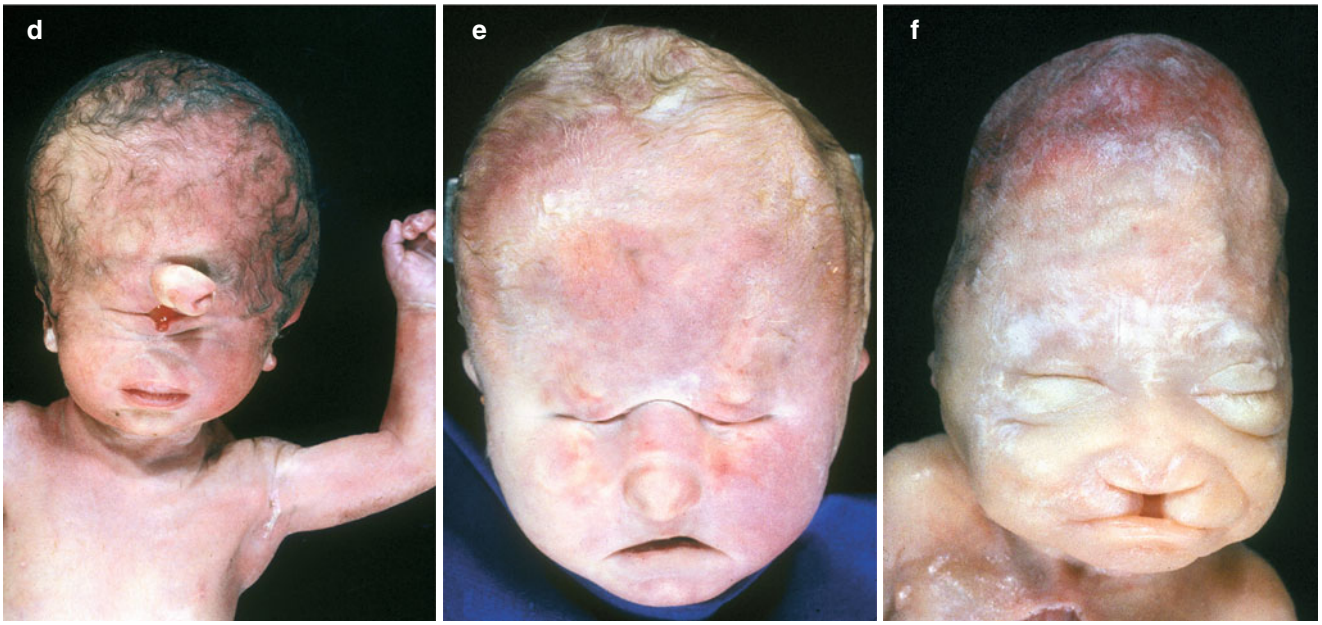

Fig. 9.42 (continued)

and medially as HPE became more severe, until in the most severe cases, no Sylvian fissures could be identified at all. These data corroborate Yakovlev's (1959) cytoarchitectonic analysis of the cerebral cortex of alobar and semilobar cases of HPE. The typical motor cortex was found in the cortex of the anterior midline. The **arterial pattern** in HPE brains varies (van Overbeeke 1991; van Overbeeke et al. 1994). The rostral part of the circle of Willis is usually absent. In two cases with incomplete HPE, both internal carotid arteries contributed to the vascularization of the cerebral cortex. In six other specimens with incomplete and complete forms of HPE, one of the internal carotids supplied the largest part of the brain.

Cyclopia has been known since ancient times through the figure of the cyclopean shepherd Polyphemos in Homer's *Odyssey* (around 800 BC). Modern knowledge of cyclopia and prosencephalies originates from the three-volume treatise on teratology by Geoffroy Saint-Hilaire (1832–1837) who introduced the terms ethmocephaly and cebocephaly. Kundrat (1882) extended these observations and distinguished six types of forebrain malformations as arhinencephaly. Much of our present knowledge on HPE dates back to the work of DeMyer and Zeman (DeMyer and Zeman 1963; DeMyer et al. 1964; DeMyer 1987), whose practical subdivision into alobar, semilobar and lobar types is commonly used. In the ***alobar form***, only one single ventricle (a holosphere) of variable size is present without interhemispheric diversion. Posteriorly, a membrane usually closes the holosphere. This membrane is actually the posterior roof of the single ventricle (Golden 1998) and may bulge dorsally to form a fluid-filled 'dorsal sac' or cyst (Fig. 9.43a). The dorsal cyst may originate as a dilatated suprapineal recess of the third ventricle (Sarnat and Flores-Sarnat 2001; Simon et al. 2001; Marcorelles and Laquerrière 2010). Probst (1979) based his subdivision of prosencephalies on the presence and extent of the dorsal sac (Table 9.9). Siebert et al. (1990) proposed a simpler subdivision of the holoprosencephalies into ***complete*** and ***incomplete forms***. The thalami and corpora striata are undivided. The olfactory bulbs and tracts and the corpus callosum are always absent. In the ***semilobar type***, rudimentary cerebral lobes with an interhemispheric posterior fissure and a rudimentary corpus callosum may be present. The olfactory bulbs and tracts are absent or hypoplastic. In the least severe, ***lobar type***, a distinct interhemispheric fissure is present with some midline continuity. The olfactory bulbs and tracts may vary from normal to absent. Midline separation of the thalami and corpora striata may be incomplete. Fertuzinhos et al. (2009) showed selective depletion of molecularly defined cortical interneurons in human holoprosencephaly with severe striatal hypoplasia (Chap. 10). More recently, five types of HPE are distinguished (Hahn and Barnes 2010; Solomon et al. 2010; Table 9.11). Some examples of MR imaging of HPE are shown in Figs. 9.44 and 9.45. Two rare HPE cases, one with hypertrophic olfactory nerves, the other with a unique traversed coronal sulcus, are shown in Clinical Cases 9.10 and 9.11, respectively.

An additional form is known as the ***middle interhemispheric variant*** or ***syntelencephaly*** (Barkovich and Quint 1993; Lewis et al. 2002; Simon et al. 2002; Pulitzer et al. 2004; Marcorelles and Laquerrière 2010; Clinical Case 9.12). In this variant, the posterior and anterior portions of

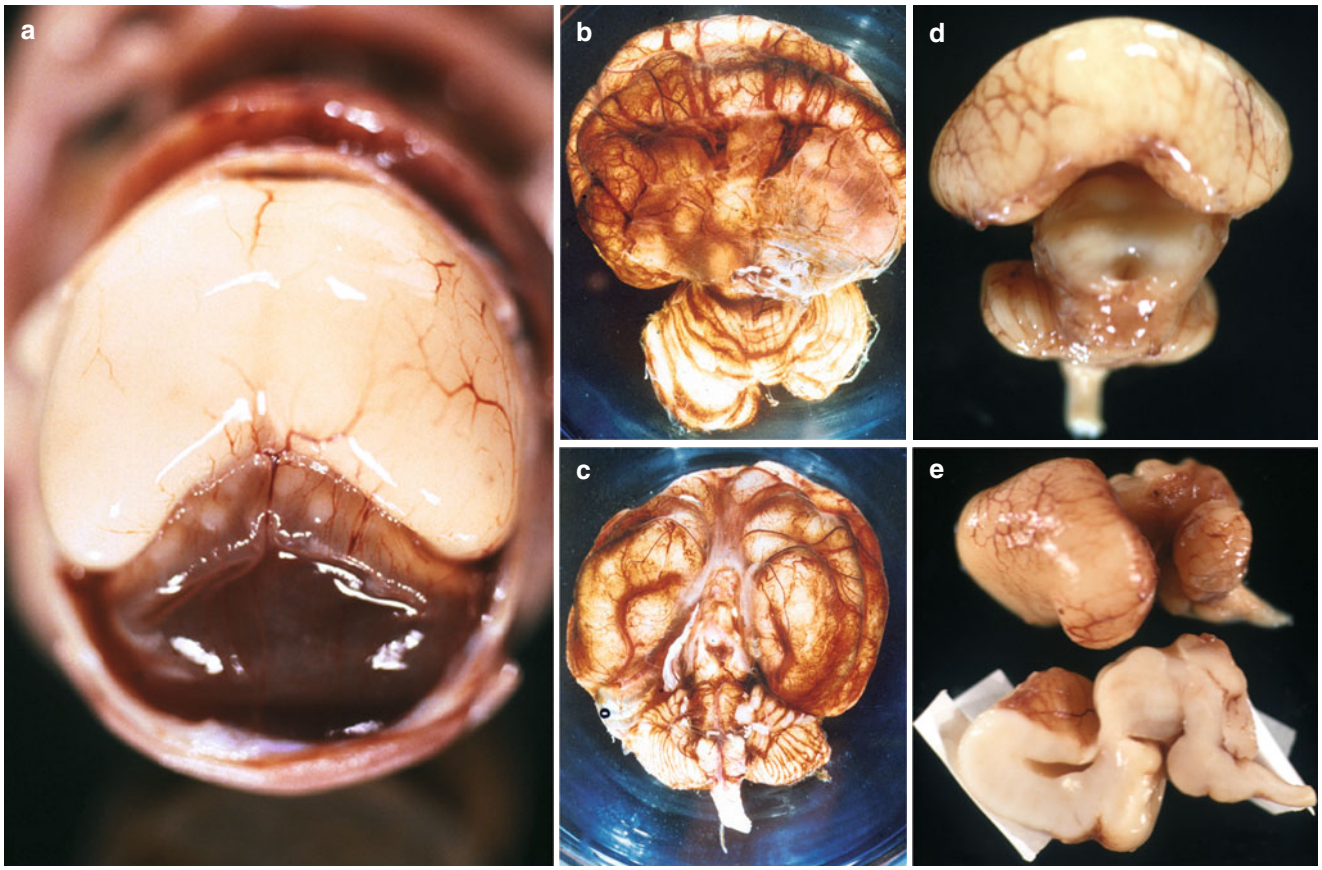

Fig. 9.43 Selection of neuropathological data in fetuses with holoprosencephaly: (**a**) large dorsal sac in situ, which is collapsed artificially at autopsy; (**b**, **c**) dorsal and basal views of the brain in the case shown in Fig. 9.42b; (**d**, **e**) dorsal (**d**) and lateral (**e**; *top*) views, and a median section (**e**; *bottom*) of the case shown in Fig. 9.42c (From the Department of Neuropathology, Medizinische Hochschule Hannover; courtesy Akira Hori)

Table 9.11 Types of holoprosencephaly

Alobar	Semilobar	Lobar	MIHV	Microform
Complete or near-complete lack of interhemispheric separation	No anterior interhemispheric separation; some posterior separation	Non-separation of only the most rostal/ventral frontal neocortex	Failure of separation of posterior frontal and parietal lobes	Absence of interhemispheric fusion
Single midline forebrain ventricle	Absent frontal horns of lateral ventricle, septum pellucidum and anterior corpus callosum	Absent corpus callosum in affected region	Absent body of corpus callosum	May have other subtle midline defects such as agenesis of corpus callosum
Absent interhemispheric fissure, falx cerebri, olfactory bulbs and corpus callosum	Absent or hypoplastic olfactory bulbs	Hypoplastic falx cerebri, olfactory bulbs and interhemispheric fissure, usually containing azygous anterior cerebral artery	Grey matter heterotopia or cortical dysplasia	
			Azygous anterior cerebral artery	
Non-separation of deep grey nuclei	Incomplete separation of deep grey nuclei		Frequent incomplete separation of thalami and caudate nuclei	
	May have dorsal cysts			Presence of milder craniofacial anomalies such as microcephaly, single central incisor or hypotelorism

After Solomon et al. (2010)

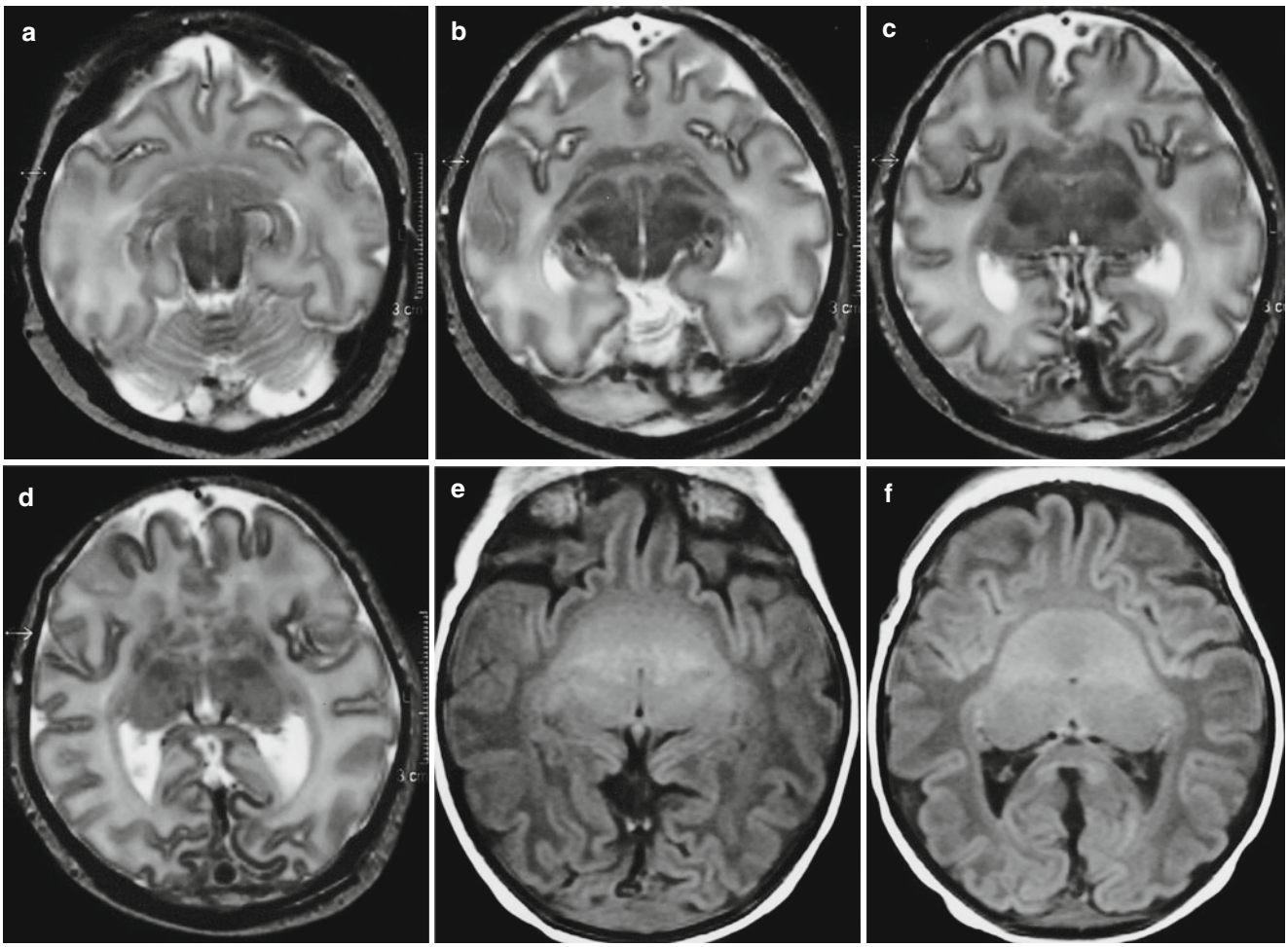

Fig. 9.44 Axial T2-weighted images of microcephalic newborns with holoprosencephaly. (**a**–**c**) Lobar holoprosencephaly; note incomplete formation of interhemispheric fissure and cerebral falx and lack of sulci in the frontal lobes; the thalami are separated by a normal third ventricle; in **a**, at the *top* an unpaired anterior cerebral artery can be seen; (**d**–**f**) Fluid attenuated inversion recovery images of a semilobar holoprosencephaly case, in which the incomplete separation of the cerebral hemispheres is more severe. Rostrally, midline structures are absent, and basal ganglia and thalami are not separated. Posteriorly, the callosal splenium is present (**f**) (Courtesy Berit Verbist, Leiden)

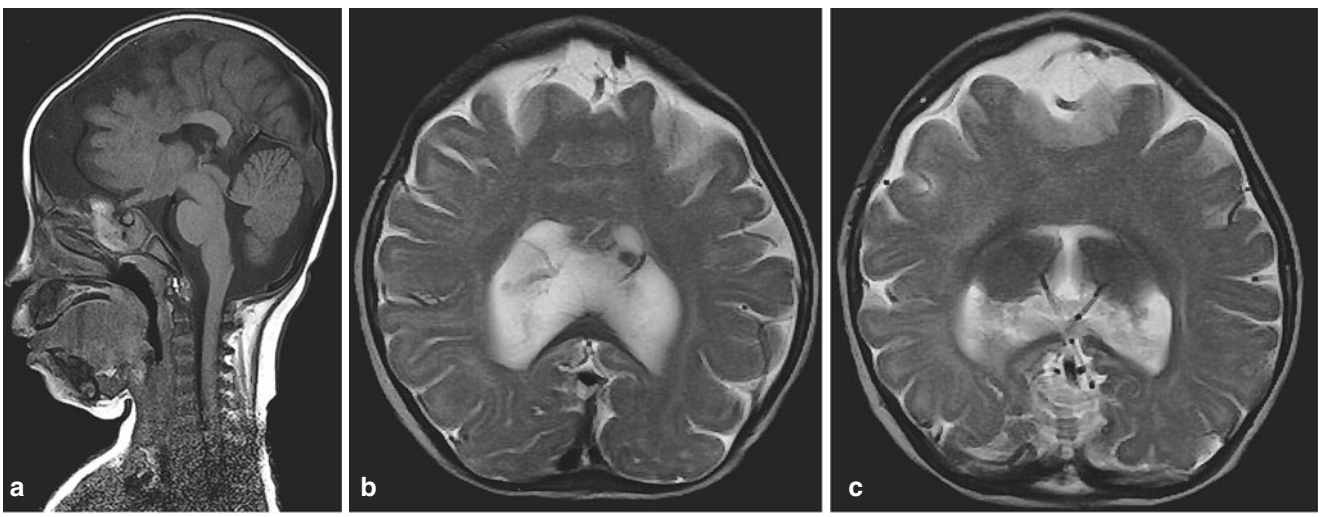

Fig. 9.45 A case of semilobar holoprosencephaly in a neonate: (**a**) sagittal section; (**b**–**f**) series of axial sections showing the incomplete separation of the brain from above (**b**) to below (**f**) (Courtesy Karin Kamphuis-van Ulzen, Nijmegen)

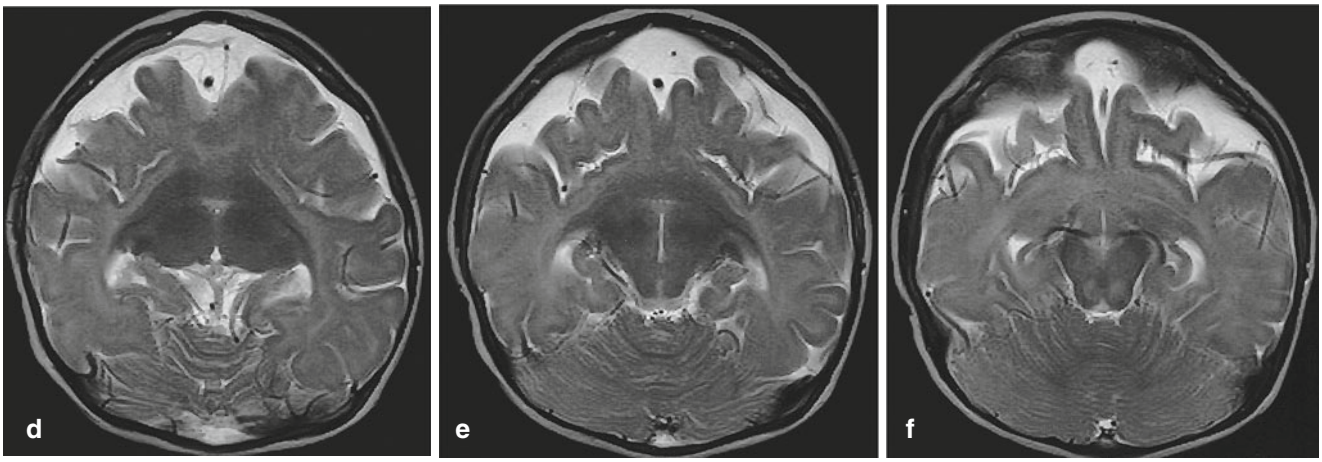

Fig. 9.45 (continued)

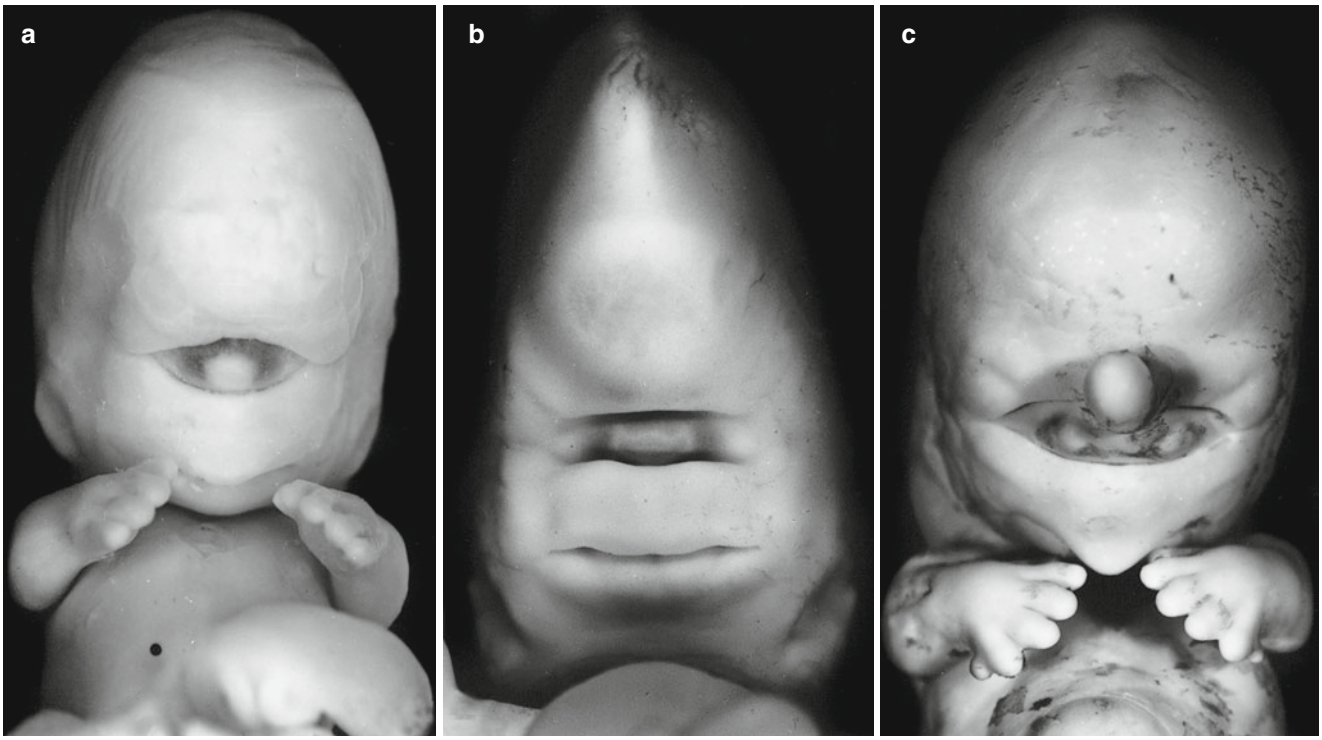

Fig. 9.46 Holoprosencephaly in human embryos: (**a**, **b**) complete, true cyclopia in 7-week-old (**a**) and 6-week-old (**b**) embryos; (**c**) synophthalmia (partially fused eyes in a single eye fissure) in a 7-week-old embryo (From Yamada et al. 2004, with permission; courtesy Shigehito Yamada, Kyoto)

the falx cerebri are present, but its midportion is absent near the frontoparietal convexity. Here, the cerebral hemispheres 'fuse' in the midline, mainly in the posterior frontal lobes. The middle part of the corpus callosum may be misformed, the septum pellucidum is absent and the olfactory bulbs and tracts may show variable deficiency. This anomaly may best be explained by a focal paucity of the primitive dorsal meninx leading to failure of induction within this small area (Barkovich 2000). Recently, a mild subtype of HPE, ***septopreoptic HPE*** has been distinguished (Hahn et al. 2010), in which midline fusion is restricted to the septal region or preoptic region of the telencephalon.

Part of the phenotypic variability in human HPE as found in the Kyoto Embryological Collection is illustrated in Fig. 9.46 (Yamada et al. 2004). Other embryological cases were described by Mall (1917), Vermeij-Keers (1987; Chap. 5) and Müller and O'Rahilly (1989c). Embryos after Carnegie stage 18 were classified into complete (true) cyclopia (Fig. 9.47), synophthalmia (partially fused eyes in a single eye fissure), closely apposed eyes (possible forerunners

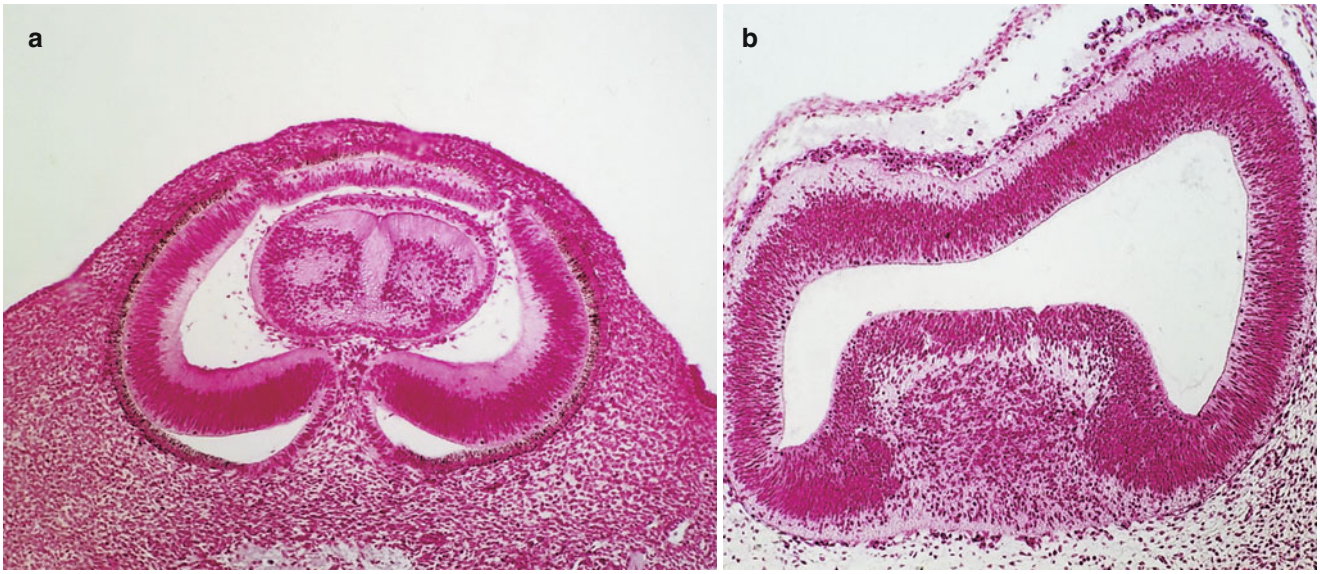

Fig. 9.47 Cyclopia (**a**) and non-separated thalami (**b**) in the embryo with holoprosencephaly shown in Fig. 9.46a (From Yamada et al. 2004, with permission; courtesy Shigehito Yamada, Kyoto)

of ethmocephaly and cebocephaly) and milder forms of HPE with median cleft lip (premaxillary agenesis). At Carnegie stages 13–17, when facial morphogenesis is not completed, HPE embryos showed some facial characteristics which are specific to these stages and different from those in older HPE embryos. The midline structures of the brain, including the pituitary gland, were lacking or seriously hypoplastic. Complete cyclopia was found in two cases after CS18 but none at earlier stages.

The **eye field** begins as a single structure that spans the midline (Adelmann 1936a, b; Li et al. 1997; Chap. 5). Under the influence of signals from the prechordal plate, the vertebrate eye field splits into discrete left and right eyes (Marlow et al. 1998; Varga et al. 1999). In zebrafish, this process has been directly studied under time-lapse photography (England et al. 2006). The division of the eye fields is an active process involving directed cellular movements and the critical orientation of the midline prechordal plate signalling centre beneath the telencephalon. If these developmental stages are not completed correctly the default result is ***cyclopia*** (Roessler and Muenke 2010). For example, when the prechordal plate is surgically removed, such animals consistently develop cyclopia (Shih and Fraser 1996; Feldman et al. 1998). Hedgehog signalling is also required: reduced hedgehog signalling results in hypotelorism, whereas no hedgehog leads to cyclopia (Cordero et al. 2004).

Clinical Case 9.9 Prenatal Diagnosis of Holoprosencephaly

The ***holoprosencephalies*** are usually classified into three variations: (1) the ***alobar type***, a single-sphered cerebral structure with a single common ventricle, a posterior large cyst of the third ventricle (a dorsal sac), absence of the olfactory bulbs and tracts and a single optic nerve; (2) the ***semilobar type*** with formation of a posterior portion of the interhemispheric fissure; and (3) the ***lobar type*** with formation of the interhemispheric fissure anteriorly and posteriorly but not in the midhemispheric region; fusion of the fornices is seen. Associated anomalies include: (1) facial abnormalities such as cyclopia, ethmocephaly, cebocephaly, a flat nose, a cleft lip and palate are invariably associated with HPE; (2) extracerebral abnormalities are also invariably associated and include: renal cysts/dysplasia, omphalocele, cardiac disease or myelomeningocele. HPE can be diagnosed prenatally (Pooh 2009). Two cases are shown in Figs. 9.48 and 9.49.

Data for this case were kindly provided by Ritsuko Pooh (Osaka, Japan).

Reference

Pooh R (2009) Neuroscan of congenital brain abnormality. In: Pooh R, Kurjak A (eds) Fetal neurology. Jaypee, St Louis, pp 59–139

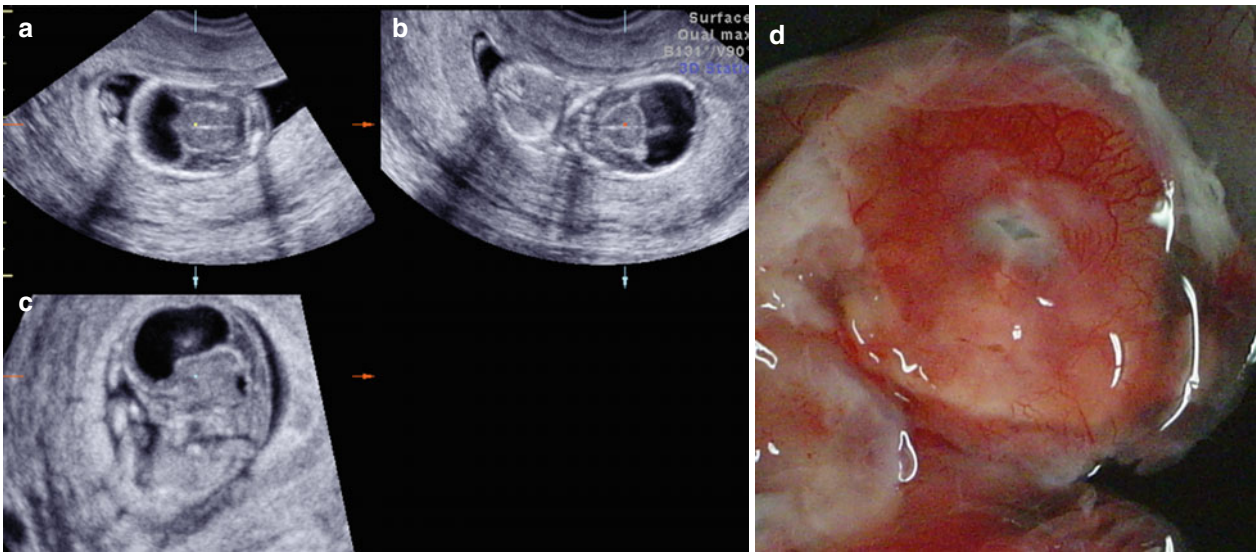

Fig. 9.48 Prenatal diagnosis of a case of alobar holoprosencephaly at 13 weeks of gestation: (**a**–**c**) three orthogonal views demonstrating the holoprosencephaly; crown-rump-length was compatible with 10 weeks of gestation; (**d**) face of aborted fetus with cyclopia, arhinia and small mouth. Chromosome examination showed 69, XXX, triploidy (From Pooh 2009; images and photograph kindly provided by Ritsuko Pooh, Osaka)

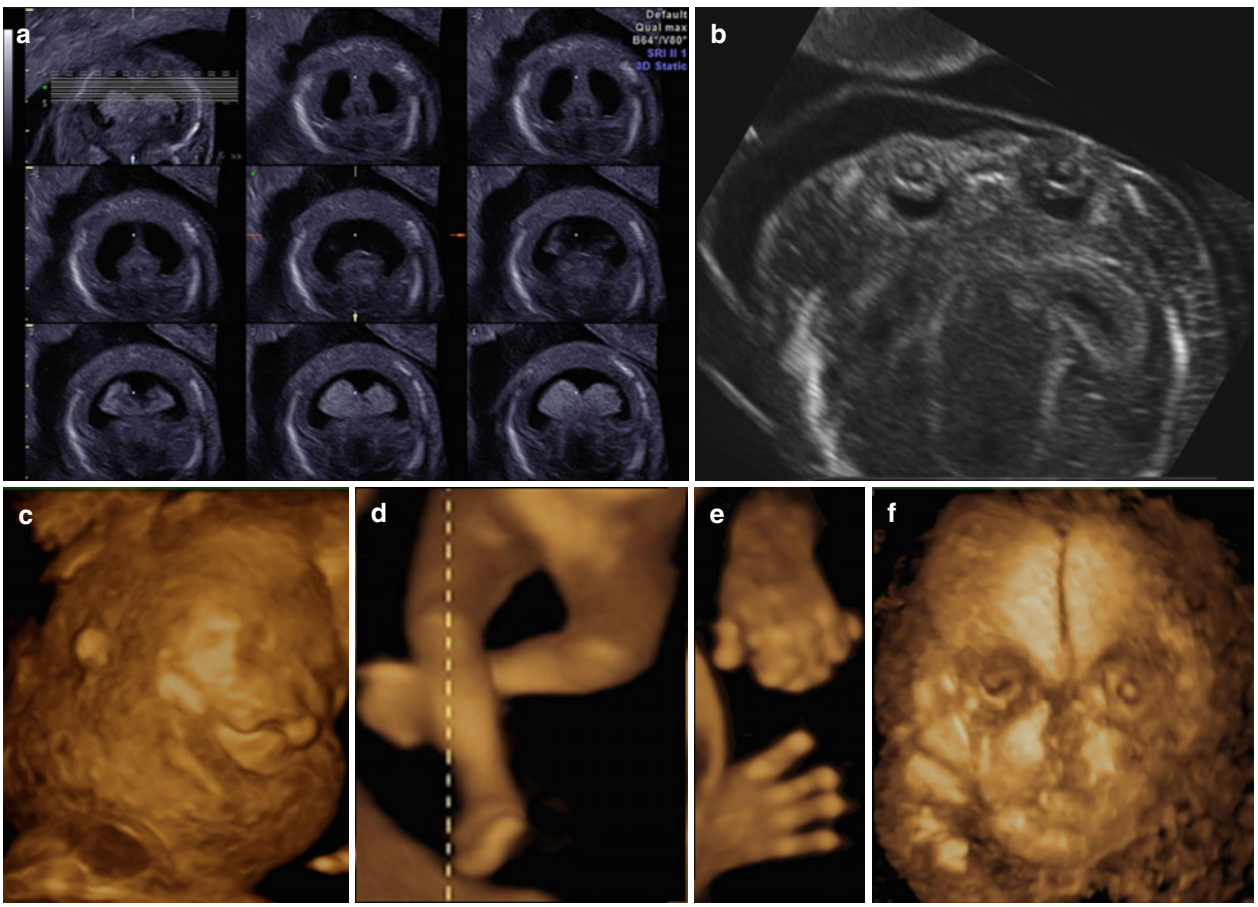

Fig. 9.49 Prenatal diagnosis of a case of semilobar holoprosencephaly: (**a**) series of tomographic coronal ultrasound images, showing semilobar holoprosencephaly; (**b**) 2D ultrasound image of echogenic eye lenses indicating congenital cataract; (**c**–**e**) 3D surface imaging of fetal face and limbs, showing cleft lip (**c**), mild clubfoot (**d**) and polydactyly and syndactyly of the left hand (**f**); **g** 3D ultrasound image of the fetal face (From Pooh 2009; images kindly provided by Ritsuko Pooh, Osaka)

Clinical Case 9.10 Holoprosencephaly with Hypertrophic Olfactory Nerves

Holoprosencephaly (***HPE***) has a wide spectrum of morphological features, ranging from alobar through semilobar to lobar types. The term ***arhinencephaly*** was once used as a synonym for HPE, although in fact it is a misnomer since not all rhinencephalic structures are lacking in HPE. Agenesis of the olfactory nerves does not define arhinencephaly. In his series of HPE cases, Akira Hori found olfactory nerves in 24 % of the cases and two fetal HPE cases with hypertrophic olfactory nerves (see Case Report).

Case Report. Following spontaneous abortion at the 22nd gestational week, a male fetus came to autopsy with a body length of 30.3 cm and body weight of 525 g. General pathology revealed open ductus venosus Arantii, foramen ovale and dusctus arteriosus Botalli. Neuropathological examination revealed a plain cranial base without laminae cribrosae. No longitudinal interhemispheric fissure was formed and the cerebral surface was lissencephalic. The olfactory nerves protruded from a hypertrophic grey substance in the middle part of the frontal lobe base (Fig. 9.50a). In the infratentorial structures no malformations were observed. Macroscopically, the atypical cut surface of the hypertrophic substance with protrusion showed grey substance corresponding to the olfactory nerve (Fig. 9.50b). Histologically, a mass of matrix cells were recognized in the hypertrophic grey matter including primitive neuroblasts (Fig. 9.50c). Apoptotic rates were extremely low (TUNEL method; Fig. 9.50d) and apoptosis inhibition was demonstrated by Bcl-2 immunohistochemistry (Fig. 9.50e). In conclusion, in this case HPE with hypertrophic olfactory nerves was found, a rare morphological variation of HPE.

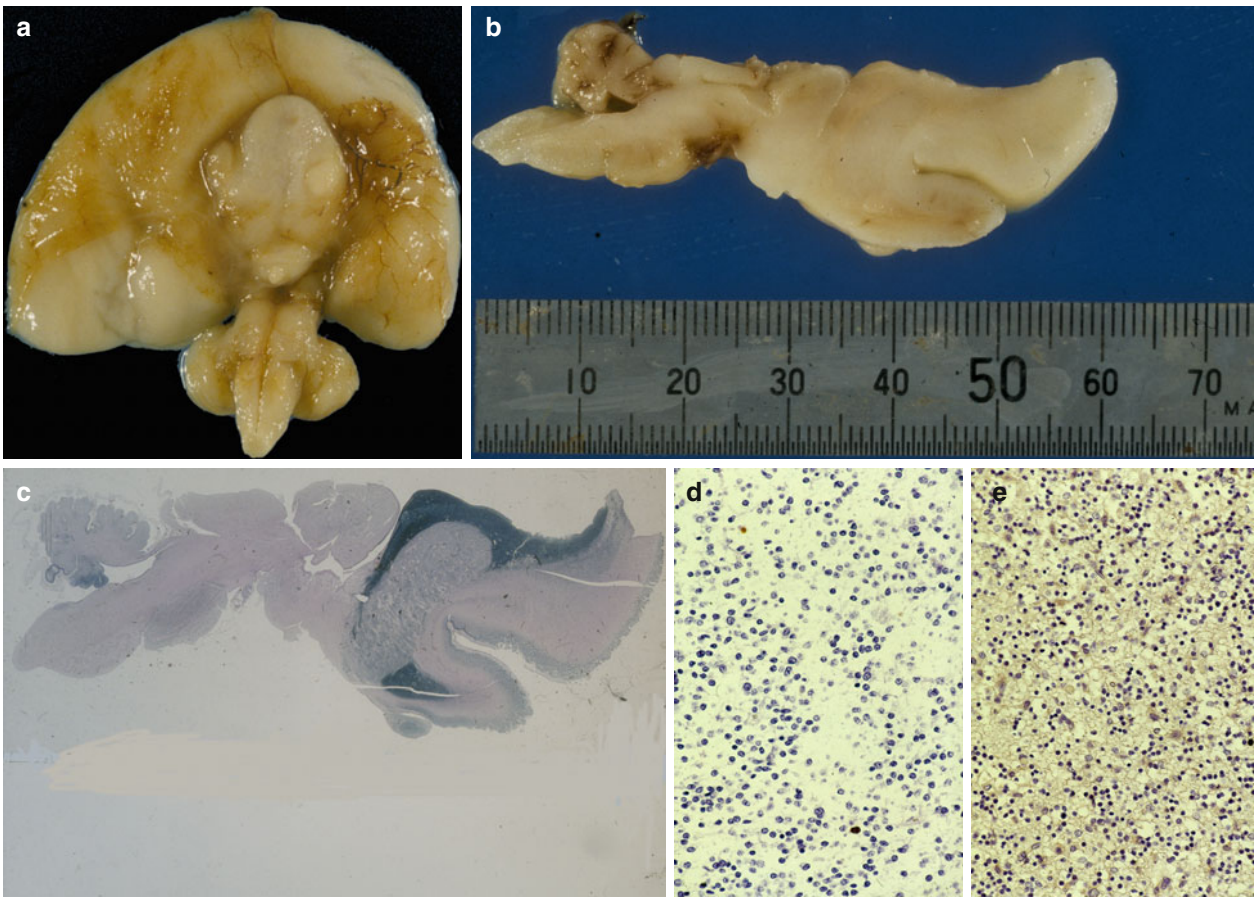

Fig. 9.50 A case of HPE with hypertrophic olfactory nerves in a 22-week-old fetus: (**a**) basal aspect of the holoprosencephalic brain with olfactory nerves which protrude from the hypertrophic midline; (**b**) section through the left olfactory nerve and hypertrophic grey substance at the right and the brain stem and cerebellum to the left; (**c**) corresponding histological section; (**d**) only two TUNEL-positive cells (at the top and below) are present indicating extremely low rate of apoptosis; (**e**) Bcl-2 immunopositive, brown neuroblasts are present, suggesting blocked apoptosis (Courtesy Akira Hori, Toyohashi)

Clinical Case 9.11 Semilobar Holoprosencephaly with a Unique Traversed Coronal Sulcus

Holoprosencephaly (***HPE***) is a developmental disorder in which the forebrain fails to divide into two separate hemispheres. Although at least 13 different chromosomal loci contributing to HPE have been reported, mutations of the four most common genes (*SHH*, *ZIC2*, *SIX3* and *TGIF*) have been identified in HPE patients (Roessler and Muenke 2010; Solomon et al. 2010a, b). With regard to genotype-phenotype correlation, structural brain anomalies were most commonly observed in individuals with the *ZIC2* mutation. Itoh et al. (2011) presented an HPE case with a *ZIC2* deletion, showing a unique coronal sulcus which divided the brain into rostral and caudal parts (see Case Report).

Case Report. Fetal ultrasonography at the 18th week of gestation showed HPE with a normal facial appearance in a male fetus (Fig. 9.51a–c). A normal karyotype 46XY was demonstrated by G-band chromosome analysis and no increased number of the chromosome 13 was discerned by conventional FISH analysis of amniotic fluid. The fetus was stillborn at the 20th week of gestation. His face appeared normal and no external anomalies were found (Fig. 9.51d, e). At autopsy, the external appearance of the cerebral hemispheres was unique in that a deep coronal sulcus traversed from one side to the other across the midline when viewed dorsally, and it was partially separated by the interhemispheric fissure at the fronto-orbital and occipital areas (Fig. 9.51f). Knotted olfactory bulbs, extending medially and then rostrally, appearing immature for the gestational age, but other structures, such as the optic chiasm, infundibulum and pituitary gland, were formed normally. The brain stem appeared normal but the posterior part of the cerebellum was not well developed. The cut surface of the brain showed a single ventricle with a partial separation in the orbital and occipital areas by the interhemispheric wall (Fig. 9.51g). The separated fronto-orbital ventricles were fused in the dorsal part and communicated with a large single ventricle by a narrow canal. The caudal ventricle was separated again by the interhemispheric wall. The fornix and the corpus callosum were not identifiable. The basal ganglia, the thalamus and the hypothalamus were separated into right and left parts with a normally formed third ventricle in between.

Comparative genomic hybridization microarray revealed a copy number loss at the regio spanning chromosome 13q32.3 to 13q33.3, including the *ZIC2* gene, which indicated a deletion of *ZIC2*. Solomon et al. (2010b) reviewed 16 cases with a *ZIC2* deletion, including 5 with alobar HPE, 3 with semilobar HPE and 1 with lobar HPE. It is tempting to speculate that the semilobar type of HPE with a traversed coronal sulcus, may be one of the distinct phenotypes of HPE, accompanied by the loss of function due to a *ZIC2* deletion (Roessler et al. 2009).

References

Itoh K, Ogi H, Yaoi T, Yoshifugi K, Pooh R, Yamasaki M, Fushiki S (2011) Semilobar holoprosencephaly with a unique traversed sylvian sulcus. Neuropathol Appl Neurobiol 37:685–688

Roessler E, Lacbawan F, Dubourg C, Paulussen A, Herbergs J, Hehr U et al (2009) The full spectrum of holoprosencephaly-associated mutations within the *ZIC2* gene in humans predicts loss-of-function as the predominant disease mechanism. Hum Mut 39:E541-E554

Roessler E, Muenke M (2010) The molecular genetics of holoprosencephaly. Am J Med Genet Part C 154C:52–61

Solomon BD, Mercier S, Vélez JI, Pineda-Alvarez DE, Wyllie A, Zhou N et al (2010a) Analysis of genotype-phenotype correlations in human prosencephaly. Am J Med Genet Part C 154C:133–141

Solomon BD, Lacbawan F, Mercier S, Clegg NJ, Delgado MR, Rosenbaum K et al (2010b) Mutations in ZIC2 in human prosencephaly: description of a novel *ZIC2* specific phenotype and comprehensive analysis of 157 individuals. J Med Genet 47:513–524

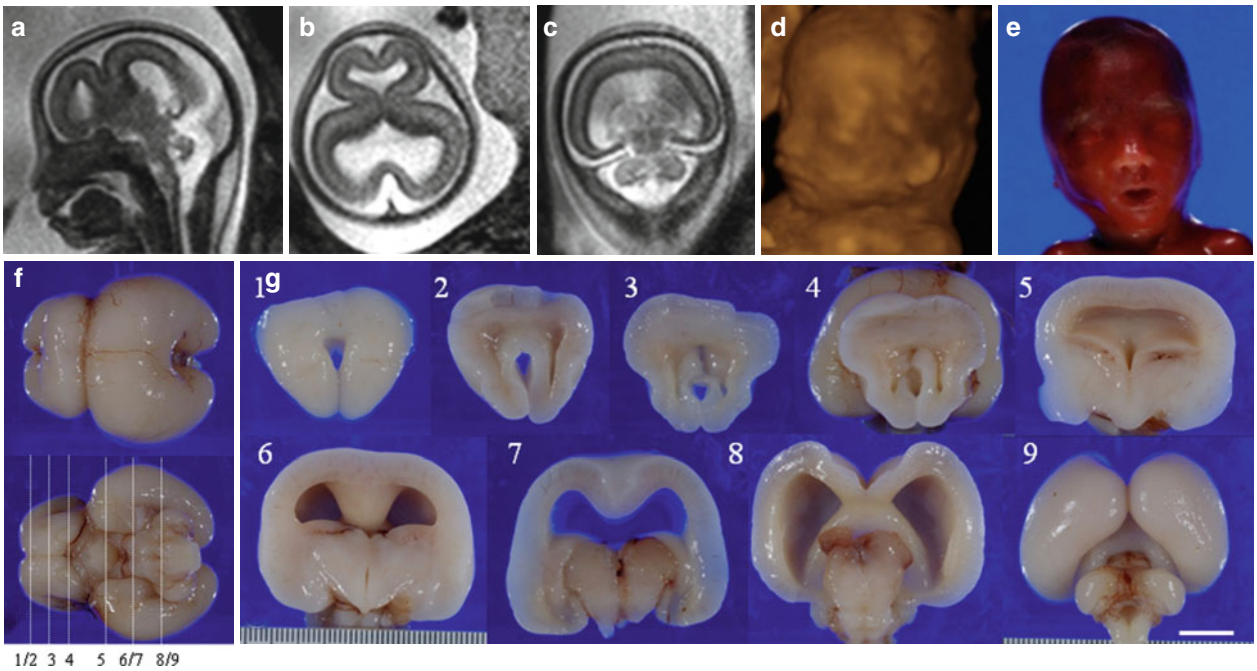

Fig. 9.51 A case of semilobar holoprosencephaly with a unique traversed coronal sulcus: (**a**–**c**) MRIs of the fetal brain at 19 weeks of gestation; (**d**) 3D ultrasonography of the fetal face at 19 weeks of gestation; (**e**) face of the fetus at 20 weeks of gestation; (**f**) dorsal and ventral views of the brain; (**g**) coronal sections of the brain (numbers refer to the levels indicated in (**f**)) (Courtesy Kyoko Itoh, Kyoto)

Clinical Case 9.12 Middle Interhemispheric Variant of Holoprosencephaly

The middle interhemispheric variant of holoprosencephaly (MIH) is a rare malformation in which the cerebral hemispheres fail to divide in the posterior frontal and parietal regions (Barkovich and Quint 1993; Simon et al. 2002). Autopsy was done in only a few cases (Pulitzer et al. 2004; see Case Report).

Case Report. The patient was born at 42 weeks of gestation as the fourth child of a 36-year-old healthy mother, who had already three healthy children. There were no previous obstetrical problems. Some intrauterine growth retardation was apparent. Birth was normal with Apgar scores of 9/10. Birth weight was 3,345 g and crown-heel length 49 cm. There were microcephaly, a midface hypoplasia, bilateral cheilognathopalatoschisis (Fig. 9.52a) and panhypopituitarism. Colobomas were found in both eyes. Ultrasound examination of the head suggested holoprosencephaly. A falx was only apparent in the frontal part of the head. MRI could not be performed anymore due to the rapid deterioration of the child. The child died at day 8 owing to necrotizing enterocolitis with sepsis.

At autopsy, the necrotizing enterocolitis and a complicating acute respiratory distress syndrome were found. Brain weight was 300 g (normal range: 420 ± 33 g). The brain showed a gyral pattern that was somewhat less-developed than normal with underdeveloped frontal lobes. From above, the presence of two hemispheres separated over their whole length was suggested (Fig. 9.52b). The olfactory bulbs and the pituitary gland were absent. The optic nerves were smaller than normal. In frontal sections (Fig. 9.52c–e), there was no subdivision of the cerebrum into two hemispheres in the rostral half of the brain. A gyrus in the depth of a midsagittal sulcus crossing from left to right gave the false impression of two hemispheres rostrally. Two hemispheres were evident from the level of the globus pallidus caudalwards. At that level a corpus callosum could be seen as well as a small third ventricle. In the posterior half of the brain the two hemispheres looked quite normal. There were no structural abnormalities in the brain stem and cerebellum, except for some hypoplasia of the pyramids.

References

Barkovich AJ, Quint DJ (1993) Middle interhemispheric fusion: an unusual variant of holoprosencephaly. AJNR Am J Neuroradiol 14:431–440

Pulitzer SB, Simon EM, Crombleholme TM, Golden JA (2004) Prenatal MR findings of the middle interhemispheric variant of holoprosencephaly. AJNR Am J Neuroradiol 25:1034–1036

Simon EM, Hevner RF, Pinter JD, Clegg NJ, Delgado M, Kinsman SL et al (2002) The middle interhemispheric variant of holoprosencephaly. AJNR Am J Neuroradiol 23:151–155.

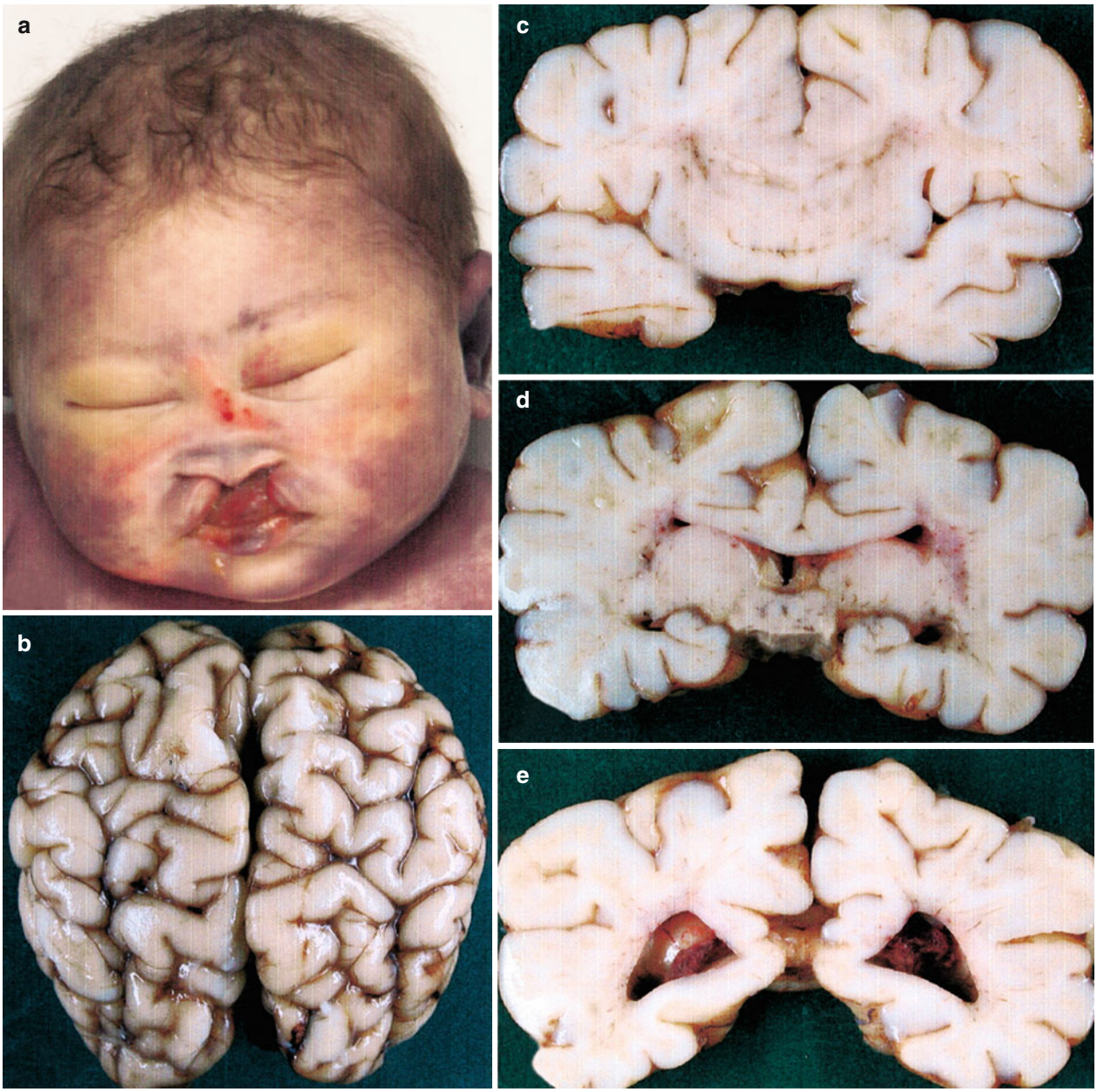

Fig. 9.52 Midline, interhemispheric variant of holoprosencephaly: (**a**) craniofacial malformations; (**b**) dorsal view of the brain; (**c**–**e**) three frontal slices through the brain, showing non-separation of forebrain structures rostrally, and fully separated hemispheres caudally (Courtesy Martin Lammens, Nijmegen)

9.7.3 Septo-optic Dysplasia

Primary absence of the ***septum pellucidum*** is rarely an isolated finding (Fig. 9.53) and frequently associated with other malformations such as HPE, agenesis of the corpus callosum and septo-optic dysplasia (Bruyn 1977; Friede 1989). It may be secondary to head trauma (Corsellis et al. 1973). De Morsier (1956) emphasized the combination of optic atrophy and defects of the septum pellucidum. The cases described as ***septo-optic dysplasia*** (***de Morsier syndrome***) form a rather heterogeneous group of disorders (Roessmann et al. 1987; Barkovich and Norman 1989; Barkovich et al. 1989; Friede 1989; Norman et al. 1995; Clinical Case 9.13). The clinical manifestations include a characteristic triad (Morishima and Aranoff 1986; Willnow et al. 1996; Hellström et al. 2000; Miller et al. 2000): (1) hypopituitarism, ranging from panhypopituitarism to insufficiency of isolated hormones; (2) aplasia of the optic disks that present with amblyopia or hemianopia; and (3) absence of the septum pellucidum. Aetiological factors may be viral infections, gestational diabetes, vascular disruption, drug toxicity and fetal alcohol syndrome (Hellström et al. 2000; Miller et al. 2000). The homeobox gene *HESX1* is implicated in a familial form of septo-optic dysplasia (Dattani et al. 1998, 1999; Brickman et al. 2001; Thomas et al. 2001).

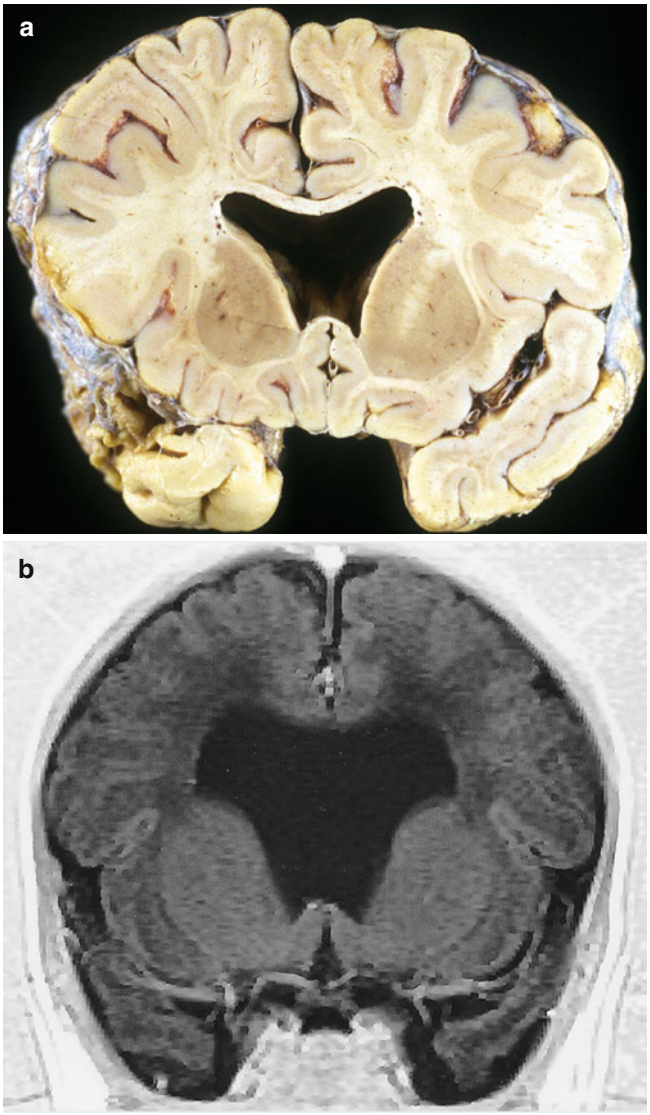

Fig. 9.53 (**a**) Isolated absence of the septum pellucidum in a 42-year-old man with brain contusion and internal hydrocephalus; note the fornices on the ventricular floor; (**b**) comparable MRI in a neonate ((**a**) Courtesy Akira Hori, Hannover/Toyohashi; (**b**) courtesy Karin Kamphuis-van Ulzen, Nijmegen)

Clinical Case 9.13 Septo-optic Dysplasia

Septo-optic dysplasia is a developmental disorder of midline structures characterized by uni- or bilateral hypoplasia of the optic nerves, tracts and chiasm, and by the absence of the septum pellucidum, first described by de Morsier (1956). The syndrome is not rare and highly variable (Morishima and Aranoff 1986; Roessmann et al. 1987; Miller et al. 2000; see Case Report).

Case Report. The infant was born after an uncomplicated pregnancy of her 33-year-old mother. Multiple malformations were noted at birth, including bilateral cleft lips and palate, ulnar deviation of the hands, polydactyly and frontal synostosis. The infant was septic from the second day of life. She died at the age of 1 week. The cause of death appeared to be peritonitis due to perforated colonic ulcers and bilateral bronchopneumonia. The fixed brain weighed 287 g. The olfactory nerves were absent. The right eye and optic nerve were smaller than the left eye and optic nerve and both optic tracts were hypoplastic. The cerebellum was small. Coronal sections revealed an abnormal mass in the region of the genu of the corpus callosum that extended down to the third ventricle (Fig. 9.54). The walls of the third ventricle were fused at the base. Microscopic examination revealed marked retinal dysplasia. The lateral geniculate nuclei were reduced in size and showed no lamination. The tumour-like mass in the place of the corpus callosum consisted of a mixture of immature grey and white matter. Bundles of fibres, likely fornix fibers, was seen dorsal and ventral to the corpus callosum. Pronounced glial heterotopia were present at the base of the brain. The medullary pyramids were small, the pyramidal crossing was incomplete, and corticospinal fibres in the spinal cord were found predominantly in the anterior column.

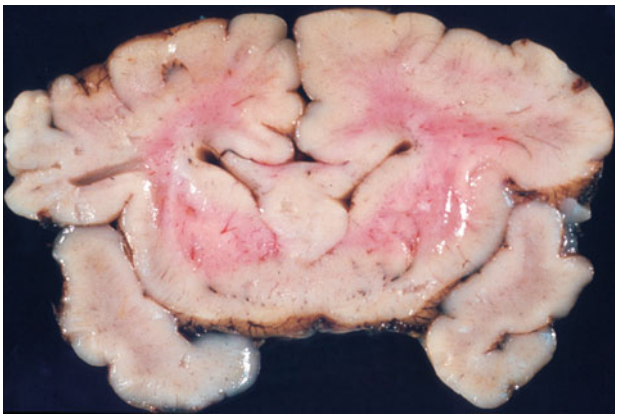

Fig. 9.54 Septo-optic dysplasia (From Roessmann et al. 1987, with permission; courtesy Akira Hori, Toyohashi)

References

de Morsier G (1956) Etudes sur les dysraphies crânio-encéphaliques. III. Agénésie du septum pellucidum avec malformation du tractus optique. La dysplasie septo-optique. Schweiz Arch Neurol Psychiatr 77:267–292

Miller SP, Shevell MI, Patenaude Y, Poulin C, O'Gorman AM (2000) Septo-optic dysplasia plus: a spectrum of malformations of cortical development. Neurology 54:1701–1703

Morishima A, Aranoff GS (1986) Syndrome of septo-optic dysplasia: the clinical spectrum. Brain Dev 8:233–239

Roesmann U, Velasco ME, Small EJ, Hori A (1987) Neuropathology of "septo-optic dysplasia" (de Morsier syndrome) with immunohistochemical studies of the hypothalamus and pituitary gland. J Neuropathol Exp Neurol 46:597–608

9.7.4 Isolated Arhinencephaly

Olfactory hypoplasia and ***isolated absence*** of the ***olfactory bulbs*** may occur without other cerebral malformations as an accidental finding at autopsy (Norman et al. 1995). In 1856, Maestre de San Juan first observed the association of hypogonadism with olfactory system abnormalities. Isolated absence of the olfactory bulb and tract can be transmitted as a single gene defect, especially in Kallmann syndrome. ***Kallmann syndrome*** (hypogonadotropic hypogonadism; Kallmann et al. 1944) is inherited in various ways, as an autosomal dominant trait (KAL2) with variable penetrance, and less commonly as an autosomal recessive (KAL3) or X-linked (KAL1) disorder (Cohen 1989a; Ballabio and Rugarli 2001; Oliveira et al. 2001). So far, six causative genes (*KAL1*, *FGFR1*, *FGF8*, *CHD7*, *PROK2* and *PROKR2*) have been documented in Kallmann syndrome, explaining about 305 of all cases (Dodé et al. 2006; Hardelin and Dodé 2008; Karstensen and Tommerup 2012). It is the most common form of isolated gonadotropin deficiency due to a migration disorder. Olfactory cells (Fig. 9.55) and GnRH-producing cells in the hypothalamus fail to migrate along their normal pathway from the developing olfactory placode (Schwanzel-Fukuda and Pfaff 1989; Schwanzel-Fukuda et al. 1989, 1996; Wray et al. 1989a, b). The gene responsible for the X-linked form (*KAL1*) encodes an extracellular matrix protein (anosmin-1) that is expressed in the olfactory bulb (Franco et al. 1991; Legouis et al. 1991; Rugarli et al. 1993; Izumi et al. 1999, 2001). It has been suggested that anosmin-1 is involved in terminal stages of olfactory axon guidance to the bulb and that olfactory bulb hypoplasia or aplasia in Kallmann syndrome is secondary to lack of innervation (Hardelin et al. 1999; Rugarli 1999; Ballabio and Rugarli 2001; Hardelin 2001; Hardelin and Dodé 2008). The most pertinent findings in Kallmann syndrome are abnormalities of the olfactory system such as hypoplasia or aplasia of the olfactory bulbs, and hypoplasia of the anterior aspect of the

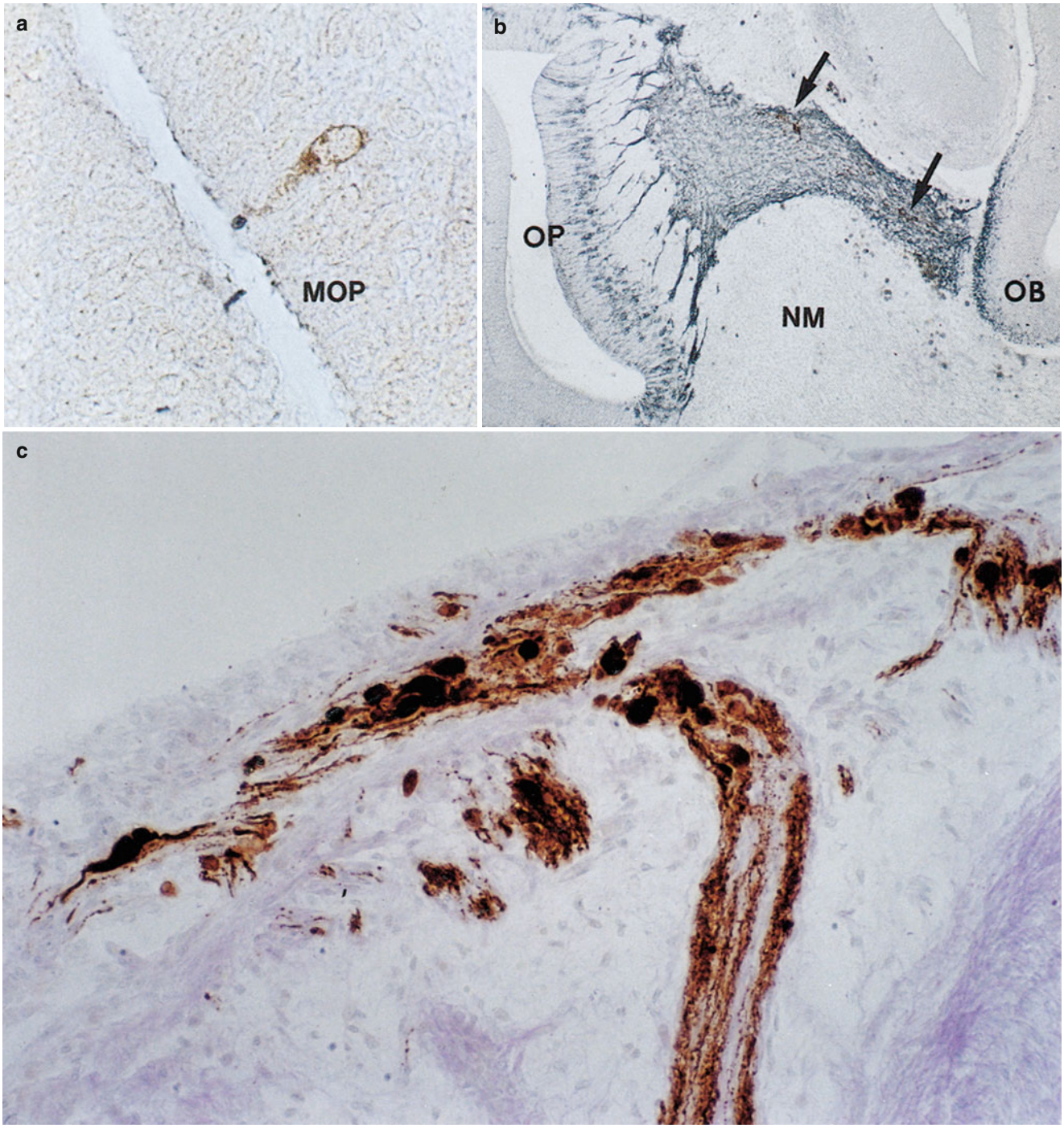

Fig. 9.55 Migration of human gonadotropin-releasing hormone (*GnRH*) expressing neurons: (**a**) a GnRH-immunoreactive cell in the epithelium of the medial olfactory pit (*MOP*); (**b**) a few GnRH-immunoreactive cells (*arrows*) along the broad path of NCAM-immunoreactive cell bodies and neurites, extending from the epithelium of the olfactory pit (*OP*) and forming an aggregate in the nasal mesenchyme (*NM*) below the forebrain and the developing olfactory bulb (*OB*); (**c**) 19-week-old fetus with Kallmann syndrome. A large GnRH-immunoreactive branch of the terminal nerve is seen coursing upwards through a perforation of the cribriform plate. Clusters of GnRH-expressing neurons can be seen on the dorsal surface of the cribriform plate, where they remain ((**a**, **b**) Reproduced with permission from Schwanzel-Fukuda et al. 1996; copyright 1996, Wiley-Liss Inc., a subsidiary of John Wiley & Sons, Inc.; (**c**) courtesy Marlene Schwanzel-Fukuda, New York)

olfactory sulci (Truwit et al. 1993; Quinton et al. 1996). More recently, the *KAL2* gene was identified (Dodé et al. 2003). Mutations in the *FGFR1* gene appear to be responsible for the autosomal dominant trait of Kallmann syndrome. The *CHD7* gene is frequently found mutated in patients with ***CHARGE syndrome*** (Kim et al. 2008). CHARGE patients have aplasia or hypoplasia of the olfactory bulb and hypogonadotroph hypogonadism (Pinto et al.

2005; Asakura et al. 2008). *CBD7* is expressed during development of the olfactory bulb and the olfactory epithelium, consistent with the associated anosmia (Sanlaville et al. 2006).

9.8 Development and Developmental Disorders of the Basal Ganglia and the Amygdala

9.8.1 Development of the Basal Ganglia

The **basal ganglia** are a group of closely connected cell masses, forming a continuum, extending from the telencephalon to the midbrain tegmentum. This complex comprises the striatum (the nucleus caudatus and the putamen, largely separated by the internal capsule), the globus pallidus, the subthalamic nucleus and the substantia nigra. The output of the basal ganglia is aimed at the ventral anterior and ventral lateral thalamic nuclei (parts of the motor thalamus), the centromedian thalamic nucleus, the habenula, the pedunculopontine tegmental nucleus and the superior colliculus (ten Donkelaar et al. 2011). In most non-primate mammals, the nucleus caudatus and the putamen are not clearly separated by an internal capsule and are known as the caudate-putamen complex. In primates, the globus pallidus consists of external or lateral and internal or medial parts. In other mammals, the homologue of the internal segment is formed by the entopeduncular nucleus. The caudate nucleus, the putamen and the globus pallidus form the **dorsal part** of the **striatal complex**. Heimer and co-workers (Heimer 1976; Heimer et al. 1982, 1991, 1997; Alheid et al. 1990) introduced the terms **ventral striatum** and **ventral pallidum** to include the limbic system into the basal ganglia. The nucleus accumbens, both cytoarchitectonically and histochemically closely resembling the caudate nucleus and the putamen, and the greater part of the olfactory tubercle form the ventral striatum (Fig. 9.56). The rostral part of the substantia innominata forms a ventral extension of the globus pallidus. The substantia innominata also contains the widely spread cholinergic basal nucleus of Meynert, the main source of cholinergic input to the cerebral cortex. The globus pallidus, the ventral pallidum and the substantia nigra are iron-rich areas of the brain as shown with Perl's diaminobenzidine method (Switzer et al. 1982; Hill and Switzer 1984) and high-resolution MRI (Drayer et al. 1986).

The cerebral cortex, including its sensory and motor fields, has extensive connections with the striatum that, via the globus pallidus and ventral thalamic nuclei, projects to the motor, premotor and prefrontal areas of the cortex. This **cortico-striato-pallido-thalamocortical circuit** is known as the principal striatal circuit or loop and is involved in initiating motor activities stemming from cognitive activities (Figs. 9.57, 9.65a). The ventral striatum and pallidum are included in a limbic striatal loop, involving the allocortex, the nucleus accumbens, the ventral pallidum, the mediodorsal thalamic nucleus, and prefrontal and limbic cortices. The ventral striatopallidum is involved in initiating movements in response to emotionally or motivationally powerful stimuli (Heimer et al. 1991, 1997; Nieuwenhuys 1996). Nearly all cortical areas in primates participate in a strip-like patterned corticostriatal projection (Kemp and Powell 1970). Input from the somatosensory and motor cortices is extensive, whereas that from the visual cortex is minimal. In the rhesus monkey, Künzle (1975) showed that the motor cortex projects almost exclusively, organized in patches and in a somatotopical pattern, to the putamen. A comparable pattern of termination was found for the primate somatosensory cortex (Künzle 1977). In contrast, associative areas of the prefrontal, temporal, parietal and anterior cingulate cortices appear to project almost exclusively to the monkey caudate nucleus (Kemp and Powell 1970; Goldman and Nauta 1977; Künzle 1978; Van Hoesen et al. 1981). The various areas of the association cortex in monkeys project to longitudinal territories that occupy restricted mediolateral domains of the striatum (Selemon and Goldman-Rakic 1985). Limbic regions, particularly the basolateral part of the amygdala, and allocortical (entorhinal, piriform and hippocampal) structures, project to the striosomes of the ventromedial part of the caudate nucleus and to the ventral striatum (Graybiel 1986; McGeorge and Faull 1989). These findings suggest that the caudate nucleus in primates is more closely related to complex and associative types of behaviour, whereas the putamen appears more directly involved in sensorimotor control. The segregation of influences from the association and sensorimotor cortices that exist in the caudate nucleus and the putamen, respectively, is not only preserved at pallidal levels, but is also maintained at nigral and thalamic levels (DeLong and Georgopoulos 1981; Alexander et al. 1986; Gerfen and Wilson 1996). The current model of basal ganglia circuitry, introduced by Albin et al. (1989) and elaborated by DeLong and collaborators (Alexander and Crutcher 1990; DeLong 1990), involves two major striatal efferent pathways, known as the **direct** and **indirect pathways**, the first to facilitate or induce movements and the second to 'brake' movements. Although challenged by the increasing complexity brought about by anatomical, physiological and clinical observations (see ten Donkelaar et al. 2011 for review), this model still serves as a basis to explain pathophysiological mechanisms underlying motor disorders (Sect. 9.8.2). Psychic disorders such as ***obsessive-compulsive behaviour*** are observed in patients with lesions affecting various parts of the basal ganglia circuitry (Graybiel and Rauch 2000; Heimer 2000). This may also be true for mood disorders (Price and Drevets 2011). The ventral parts of the basal ganglia are intimately related to the basal nucleus of Meynert and the extended amygdala. These interdigitating and partly overlapping anatomical systems are involved in

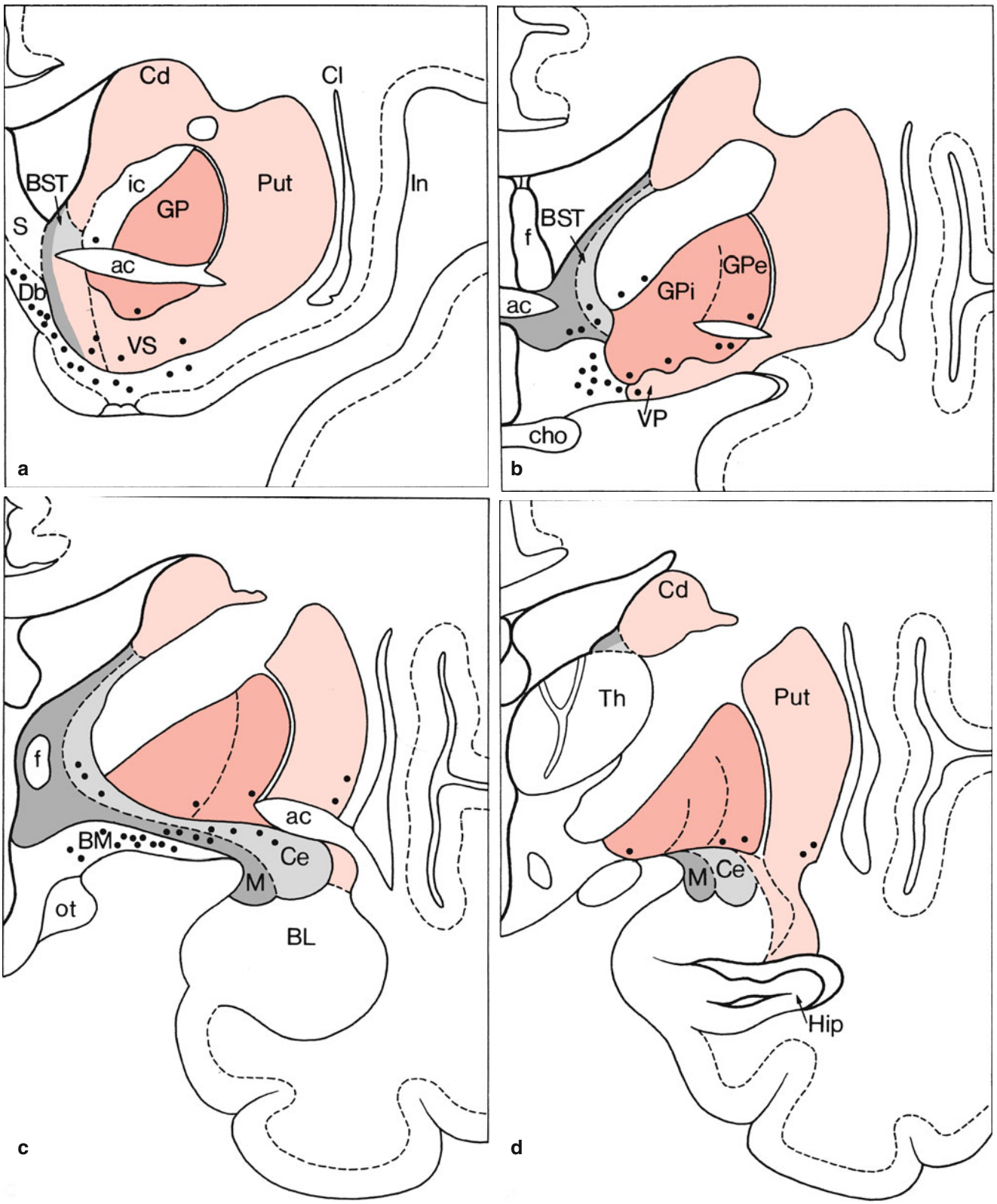

Fig. 9.56 Human basal forebrain showing the current subdivision of the basal ganglia and amygdala. Comparable structures are indicated in *various colours. Transition areas* are indicated as parts of the striatum, but do show some amygdaloid features. The *large dots* indicate the large, cholinergic cells of the basal nucleus of Meynert (*BM*). *ac* anterior commissure, *BL* basolateral amygdala, *BST* bed nucleus of the stria terminalis, *Cd* caudate nucleus, *Ce* central amygdala, *cho* chiasma opticum, *Cl* claustrum, *Db* diagonal band of Broca, *f* fornix, *GP* globus pallidus, *GPe* external part of globus pallidus, *Gpi* internal part of globus pallidus, *Hip* hippocampus, *In* insula, *M* medial amygdala, *ot* optic tract, *Put* putamen, *S* septum, *Th* thalamus, *VP* ventral pallidum, *VS* ventral striatum (After Heimer et al. 1991)

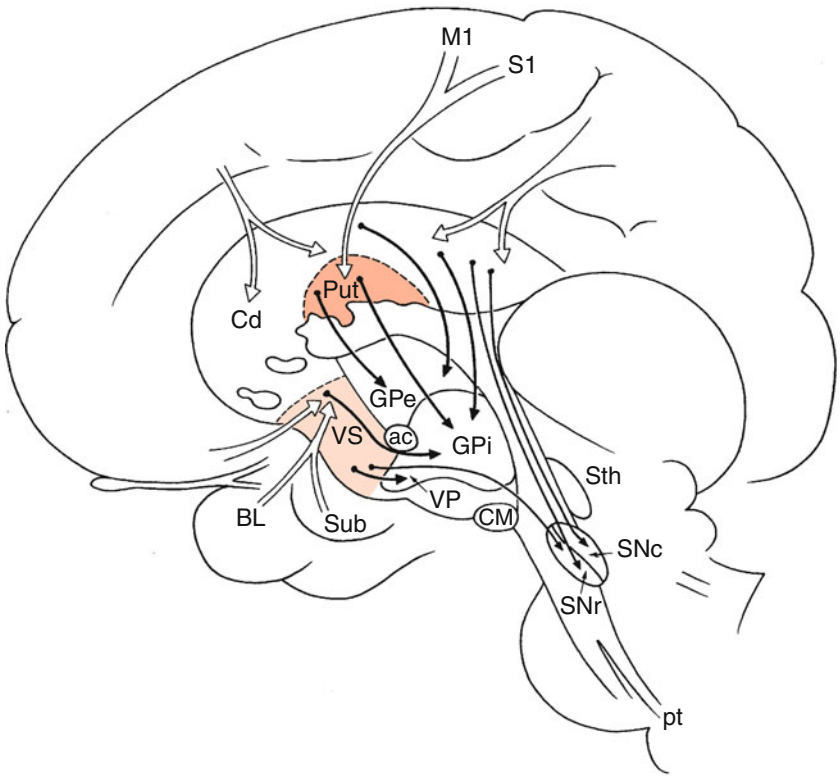

Fig. 9.57 Overview of the fibre connections of the basal ganglia. The primary motor cortex (*M1*) and the primary somatosensory cortex (*S1*) innervate the putamen (*Put*), whereas the prefrontal cortex innervates the caudate nucleus (*Cd*), and the basolateral amygdala (*BL*) and the subiculum (*Sub*) innervate the ventral striatum (*VS*). These input stations of the basal ganglia innervate the external (*GPe*) and internal (*GPi*) parts of the globus pallidus (the dorsal pallidum), the ventral pallidum (*VP*) and the substantia nigra pars reticulata (*SNr*) as well as the pars compacta of the substantia nigra (*SNc*). *ac* anterior commissure, *CM* corpus mammillare, *pt* pyramidal tract, *Sth* subthalamic nucleus (After Alheid et al. 1990; from ten Donkelaar et al. 2011)

some of the most devastating neuropsychiatric disorders such as schizophrenia and Alzheimer disease (Alheid and Heimer 1988; Heimer et al. 1991, 1997; Heimer 2000).

Compartmental organization of the mammalian striatum has been demonstrated with histochemistry (acetylcholinesterase staining) and immunohistochemistry (staining for tyrosine hydroxylase, an enzyme necessary for dopamine biosynthesis, dopamine, enkephalins and other neuropeptides). Clustering of striatal neurons is obvious particularly in the developing mammalian striatum (Goldman-Rakic 1981, 1982; Graybiel 1984). The dopaminergic innervation of the striatum of young animals is organized in patches ('dopamine islands') as first shown with formaldehyde-induced catecholamine fluorescence (Olson et al. 1972; Tennyson et al. 1972), spatially corresponding with acetylcholinesterase-rich patches (Graybiel et al. 1981). In adult animals, the distribution of tyrosine hydroxylase or dopamine immunoreactivity does not show such prominent local inhomogeneities except in the ventral striatum – accumbens region (Graybiel et al. 1981; Graybiel 1984). With acetylcholinesterase staining, Graybiel and Ragsdale (1978) showed that within the otherwise acetylcholinesterase-rich striatal tissue (the **striatal matrix**) a mosaic of small zones of low acetylcholinesterase activity was present and called them '**striosomes**' (Fig. 9.58). In cats, during development the dopamine islands first correspond with acetylcholinesterase-rich patches of the immature striatum, but later in development with the acetylcholinesterase-poor striosomes (Graybiel 1984). A similar patchy arrangement of the striatum was shown in the developing human brain (Kostović 1986; Holt et al. 1997). Letinić and Kostović (1996) showed that patches rich in calbindin-immunoreactive neuropil correspond to acetylcholinesterase-rich patches of prenatal brains. Ulfig et al. (2001) showed that the expression of AKAP79, a kinase-anchoring protein enriched in postsynaptic densities, in the striatal compartments of the fetal human brain correlates with the dopaminergic innervation of the striatum (Fig. 9.59). These data provided the basis for heterogeneity in the arrangement of striatal fibre connections (Graybiel 1990; Parent and Hazrati 1995; Parent et al. 1995; Gerfen and Wilson 1996; Haber and Gdowski 2004).

The basal ganglia and the amygdala arise from the **ganglionic eminences** (Fig. 9.60) as already suggested in early studies on the developing human forebrain (His 1889; Hochstetter 1919; Macchi 1951; Hewitt 1958, 1961; Humphrey 1968, 1972; for data in rhesus monkey see Gribnau and Geysberts 1985). The olfactory tubercle and the nucleus accumbens arise from the rostral part of the LGE, the nucleus caudatus and putamen from its intermediate part, and the subpallial part of the amygdala from the caudal eminence

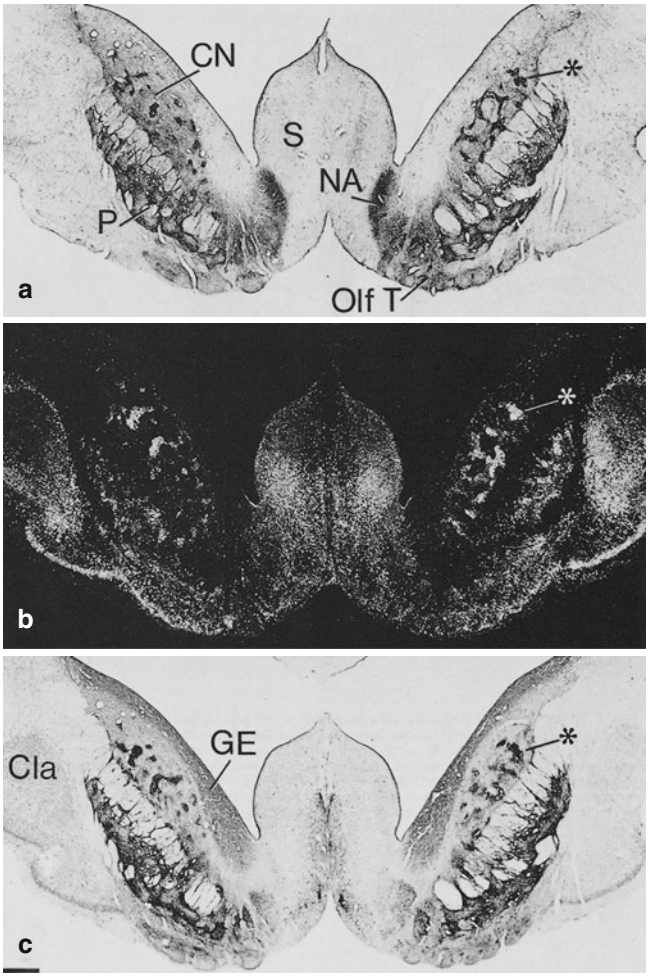

Fig. 9.58 Striosomes. Three adjacent sections from the brain of an E50-E52 kitten showing the precise match between tyrosine hydroxylase positive patches (**a**), clusters of [^{3}H]thymidine-labelled neurons (**b**) and acetylcholinesterase-positive patches (**c**) in the caudate nucleus and putamen. *Asterisks* mark one such match for a dorsal patch in the caudate nucleus. *Cla* claustrum, *CN* caudate nucleus, *GE* ganglionic eminence, *NA* nucleus accumbens, *Olf T* olfactory tubercle, *P* putamen, *S* septum (Reproduced with permission from Graybiel 1984; copyright 1984, Elsevier)

(Table 9.7). The MGE gives rise to the globus pallidus, the basal nucleus of Meynert and the bed nucleus of the stria terminalis. The **nucleus basalis complex** develops the earliest acetylcholinesterase activity in the human telencephalon (Kostović 1986) and sends widely distributed fibres to the anlage of the neocortex and limbic cortex by the end of the second trimester of gestation (Fig. 9.61). The development of the cortical layer innervation coincides with the appearance of an 'adult' pattern of topographic relationships. The LIM homeobox gene *L3*/*Lhx8* is necessary for proper development of basal forebrain cholinergic neurons (Mori et al. 2004).

In rodents, the **time** of **neuron origin** has been determined in the **basal ganglia** and related basal forebrain (ten Donkelaar and Dederen 1979; Fentress et al. 1981; Bayer 1984; Marchand and Lajoie 1986; Marchand et al. 1986; Bayer and Altman 1987b; Van der Kooy et al. 1987). Large-celled structures such as the globus pallidus, the nucleus of the horizontal limb of the diagonal band of Broca as well as large cells in the rostral part of the substantia innominata, the caudate-putamen-complex and the olfactory tubercle arise early, whereas medium-sized and small cells in the basal forebrain have a persistent origin over a much longer period. Neuron formation in the basal forebrain persists decrementally until P4. A clear caudorostral spatiotemporal gradient as well as a distinct 'outside-in' gradient have been found in the caudate-putamen complex. The time span for neurogenesis in the nucleus accumbens is essentially the same as for the medial part of the caudate-putamen complex. Medium-sized neurons in the neostriatum and the nucleus accumbens, generated simultaneously, are usually arranged in scattered clusters. The neurons of the two striatal compartments are generated during largely non-overlapping developmental periods (Marchand et al. 1986; Van der Kooy et al. 1987). Most of the earliest-born neurons form the patch compartment, and later-born cells make up the matrix compartment. Cell counts indicate that in rats there may be as many as 2,000,000 neurons in the striatum on each side at P4, but that that number is reduced by apoptosis to the adult figure of approximately 690,000 at P8 (Fentress et al. 1981), suggesting extensive programmed cell death in the striatum. About 97 % are medium-sized neurons and about 3 % are large cells. Itoh et al. (2001) studied the presence of programmed cell death in the human striatum and globus pallidus of fetuses and newborns (gestational age ranging from 12 to 40 weeks) with the transferase-mediated dUTP-biotin nick end-labelling (TUNEL) technique. In the caudate and putamen, TUNEL-labelled cells were observed from the 12th week of gestation onwards. The numerical density of the total number of neurons was significantly decreased, whereas the labelling index of apoptotic cells was significantly increased with advancing gestational age. In the globus pallidus, comparable data were obtained.

The GABAergic **striatal projection neurons** are derived from the LGE (Deacon et al. 1994; Olsson et al. 1995, 1998; Anderson et al. 1997b; Flames et al. 2007; Sect. 9.5) and *Dlx1*,*2*,*5*,*6*, *Gsh2* and *Mash1* are involved in their specification and differentiation (Porteus et al. 1994; Anderson et al. 1997b; Casarosa et al. 1999; Eisenstat et al. 1999; Toresson and Campbell 2001). Most **striatal interneurons** appear to migrate tangentially from the MGE or the adjacent preoptic/anterior entopeduncular area, and express the NKX2.1 homeodomain protein (Marín et al. 2000). *Nkx2.1* mutants are defective in striatal interneurons (Sussel et al. 1999), whereas the number of striatal interneurons is reduced in *Mash1* and *Dlx1*/*Dlx2* mutants (Casarosa et al. 1999; Eisenstat et al. 1999). *Mash1* mutants primarily have a reduction of early-born striatal interneurons, whereas *Dlx1*/*Dlx2*

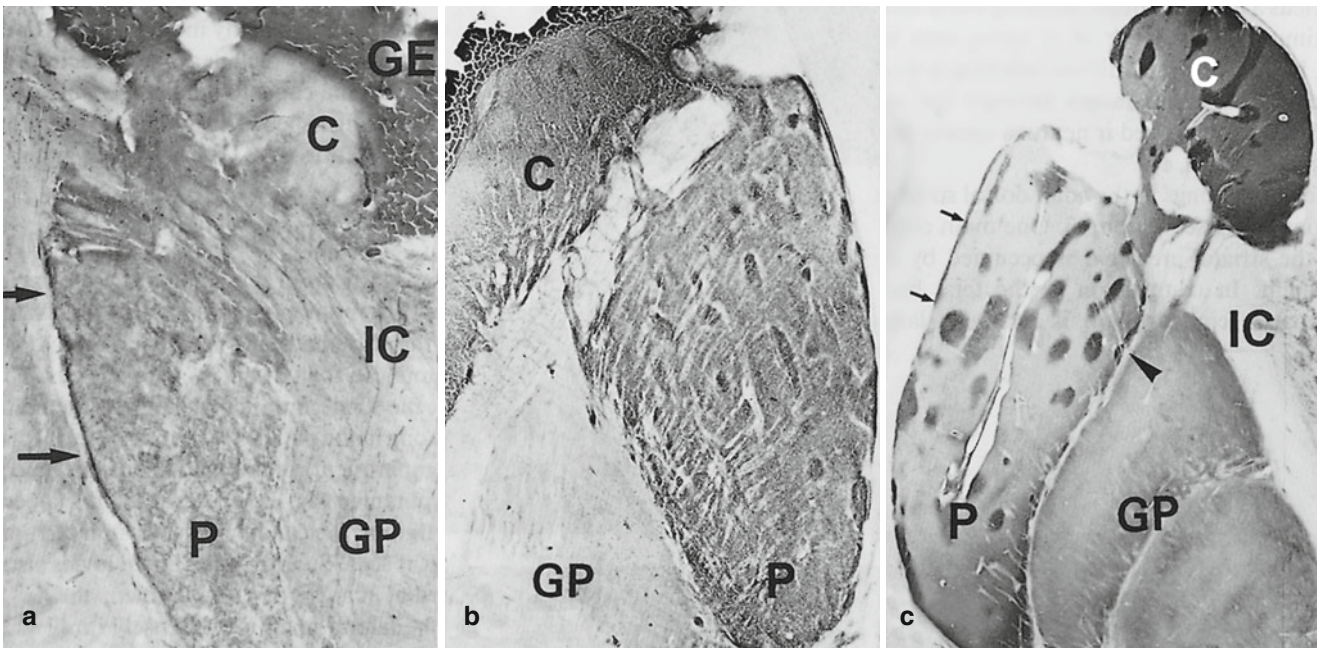

Fig. 9.59 Striosome labelling in the human basal ganglia in 16-week-old (**a**) and 22-week-old (**b**) fetuses, and in the first postnatal week (**c**); AKAP79-staining. *C* caudate nucleus, *GE* ganglionic eminence, *GP* globus pallidus, *IC* internal capsule, *P* putamen (Reproduced with permission from Ulfig et al. 2001; copyright 2001, S. Karger, AG)

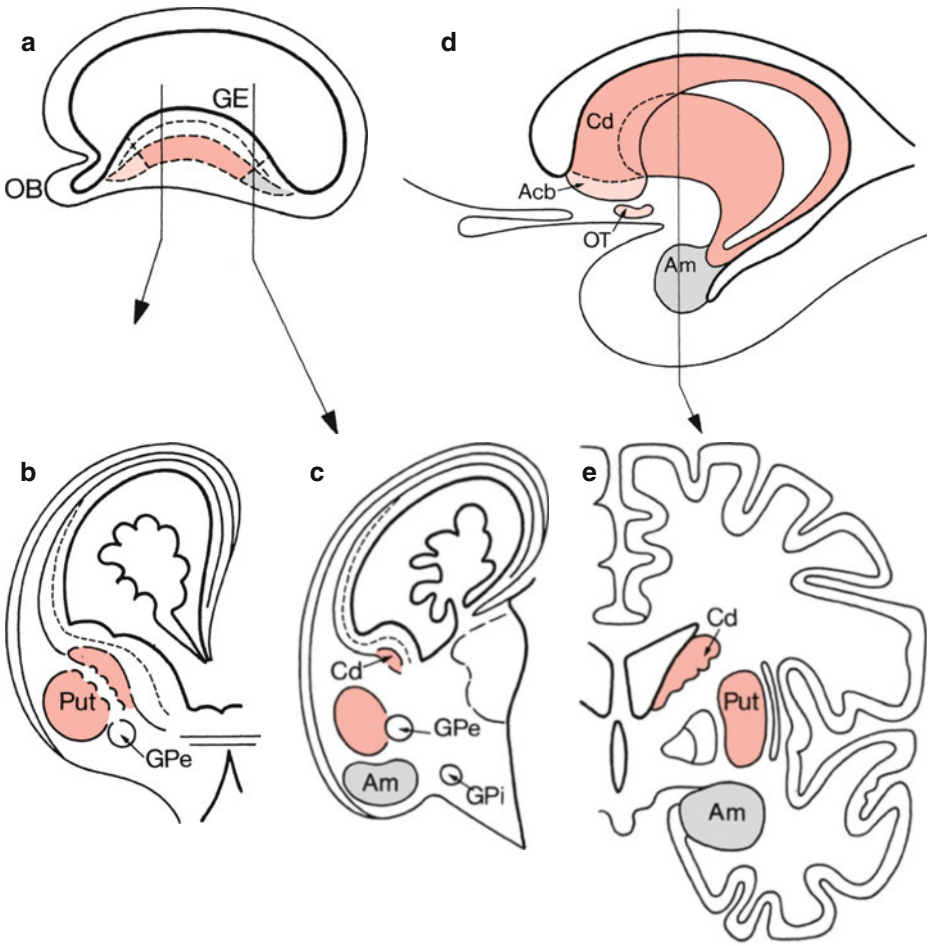

Fig. 9.60 Overview of the development of the human basal ganglia and amygdala: (**a**–**c**) sagittal and frontal sections of a 9-week-old fetus; (**d**–**e**) adult situation. The rostral part (*light red*) of the ganglionic eminence (*GE*) gives rise to the nucleus accumbens and the olfactory tubercle, the large intermediate part (*red*) to the caudate nucleus (*Cd*) and the putamen (*Put*), and the caudal part (*grey*) to the amygdala (*Am*). *Acb* nucleus accumbens, *GPe* external part of globus pallidus, *GPi* internal part of globus pallidus, *OB* olfactory bulb, *OT* olfactory tract (Based on Nieuwenhuys 1977)

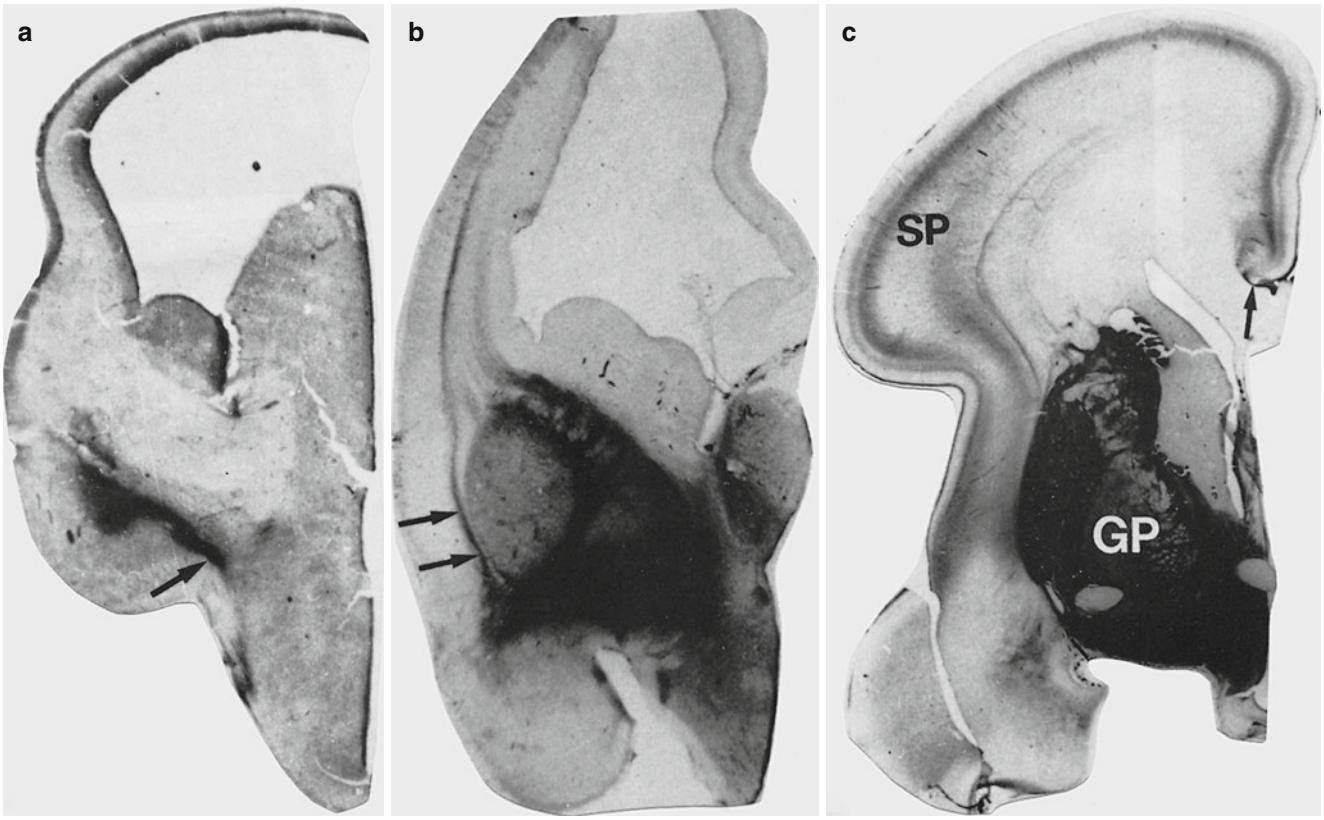

Fig. 9.61 Photomicrographs of acetylcholinesterase-stained sections of the developing forebrain in human fetuses of 9.5 (**a**), 10.5 (**b**) and 24 (**c**) weeks of age. The *arrows* in (**b**) indicate cholinergic fibres to the cerebral cortex. *GP* globus pallidus, *SP* subplate (Reproduced with permission from Kostović 1986; copyright 1986, Elsevier)

mutants primarily have reduced numbers of late-born striatal interneurons.

SHH and FGF8 are essential for the formation of the **dopaminergic neurons** of the **substantia nigra** and the **ventral tegmental area** (VTA; Ye et al. 1998; Wurst and Bally-Cuif 2001; Holzschuh et al. 2003; Chap. 7). Several early ventral midbrain markers contribute to their specification, including *En1*/*En2*, *Lmx1b*, *Pax2*/*Pax5* and *Wnt1* (Hynes and Rosenthal 1999; Smidt et al. 2000), before expression of dopamine-specific markers. In mice, TH is present at E11.5, shortly after expression of the orphan nuclear receptor Nurr1 (Zetterstrom et al. 1996, 1997) and the homeobox gene *Pitx3* (Smidt et al. 1997; van den Munckhof et al. 2003). *Nurr1* mutants fail to induce TH in the mesencephalic dopaminergic progenitor neurons and die soon after birth (Zetterstrom et al. 1997). *Pitx3* expression is maintained throughout life in both mice and men (Smidt et al. 1997). *Pitx3* is also expressed in the developing lens (Semina et al. 1997). *PITX3* mutations were found in two families with inherited forms of cataract and anterior segment dysgenesis (Semina et al. 1998). Abnormal lens development is also found in a naturally occurring mouse mutant, the *aphakia* mouse, which has two deletions in the *Pitx3* gene (Rieger et al. 2001). Van den Munckhof et al. (2003) showed that *Pitx3* is expressed only in the ventral tier of the substantia nigra pars compacta and in about half of the VTA neurons. In *aphakia* mice, *Pitx3* was not detectable, and selective degeneration of dopaminergic neurons was found, leading to a more than 90 % decrease in striatal dopamine levels and marked reduction in spontaneous locomotor activity.

Most of the neurons of the substantia nigra are generated between E13 and E15, according to a gradient from rostral/dorsolateral to caudal/ventromedial (Hanaway et al. 1971; Altman and Bayer 1981; Marchand and Poirier 1983). This gradient extends to the VTA: neurons of the VTA are born later (E14-E16) than those of the substantia nigra (Altman and Bayer 1981; Marchand and Poirier 1983). It should be emphasized that the classic unitary SN/VTA is in fact a plurisegmental series of very similar units from the floor plate and the contiguous basal plate found across prosomeres 1–3, mesomeres 1 and 2 and the isthmic rhombomere (Puelles and Verney 1998; Verney et al. 2001a; Fig. 9.62).

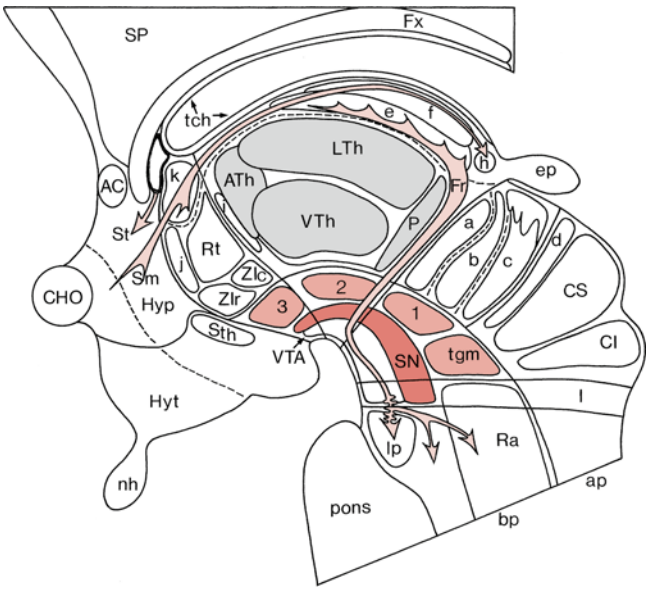

Fig. 9.62 Subdivision of the human diencephalon and mesencephalon based on the prosomeric approach. The substantia nigra is indicated in *red. CI* colliculus inferior, *CS* colliculus superior, *I* isthmus, *tgm* tegmentum of mesencephalon, *VTA* ventral tegmental area (for other abbreviations see Fig. 9.6) (After Puelles et al. 2008)

The neurogenetic gradients in both the substantia nigra (Altman and Bayer 1981) and the caudate-putamen complex (ten Donkelaar and Dederen 1979; Fentress et al. 1981; Bayer 1984) in rodents can be correlated with the topographic principles in the nigrostriatal projections. The axonal projections are arranged so that the oldest nigral neurons are located in the dorsolateral part (generated before E15), whereas the younger neurons (born after E15) are located in the ventromedial part. In the rhesus monkey, substantia nigra neurons are generated between E36 and E43 with a peak around E38-E40 and without an appreciable spatiotemporal gradient (Levitt and Rakic 1982). All neurons in the caudate nucleus and putamen are generated within the first half of gestation (Brand and Rakic 1979). Dopaminergic axons are present in the putamen around E60 (Brand and Rakic 1984). The first morphologically defined synapses appear in the putamen at E60 and in the head of the caudate at E65 (Brand and Rakic 1984). During this period the neostriatum receives its first corticostriatal input (Goldman-Rakic 1981), preceding its cytoarchitectonic differentiation into separate island and matrix cellular components (Goldman-Rakic 1982). A similar putamen-to-caudate gradient of synaptogenesis has been observed in the developing human neostriatum (Zečević and Kostović 1980).

Data on the **development** of the **human substantia nigra** are limited. Cooper (1946) first delineated the substantia nigra at the end of the embryonic period (stages 20–21), but (by extrapolating rhesus monkey data) its cells are presumably generated between stages 18 and 21. Ontogeny of human mesencephalic dopaminergic cells was studied with histofluorescence (Nobin and Björklund 1973; Olson et al. 1973) and TH immunohistochemistry (Pearson et al. 1980; Pickel et al. 1980; Freeman et al. 1991; Verney et al. 1991, 2001a, b; Zecevic and Verney 1995; Almqvist et al. 1996; Puelles and Verney 1998). Evidence of TH-immunoreactive substantia nigra neurons as found as early as stages 15–16, i.e. at 4.5 weeks of development (Puelles and Verney 1998; Verney et al. 2001a). DiI labelling suggests that dopaminergic neurons innervate the striatum as early as week 10 of fetal life (Sailaja and Gopinath 1994). Binding studies for dopaminergic markers suggest that dopaminoceptive neurons in the striatum expressing the dopamine receptors D1R or D2R are present in the human fetal striatum at least from week 16 of life (Brana et al. 1995, 1996) and from week 12 in the substantia nigra and VTA (Aubert et al. 1997).

The **development** of the **striatal dopaminergic innervation** in rats has been studied with histofluorescence techniques (Olson and Seiger 1972; Seiger and Olson 1973) and immunohistochemical techniques using antibodies against TH (Specht et al. 1981a, b) and dopamine (Voorn et al. 1988). At E14, the first dopaminergic, nigrostriatal fibres reach the striatal anlage. This projection rapidly increases in size. The developmental pattern of the dopaminergic innervation of the striatum and the nucleus accumbens and the pattern of their neurogenesis are closely related. The first dopaminergic fibres arrive in the two striatal subdivisions well before their peaks in neurogenesis. In the immature caudate-putamen complex the dopaminergic innervation is organized as a system of patches called ‘dopamine islands’ (Olson et al. 1972). These islands express high TH-like immunoreactivity and are also rich in acetylcholinesterase activity. In rats, at E19 the first signs of this inhomogeneous distribution of dopaminergic fibres can be observed in the dorsolateral part of the striatum. In the following prenatal and postnatal days these dopaminergic patches, i.e. the first sign of structural compartments in the developing striatum, also appear more medially. By the third postnatal week, however, most of the patches are no longer detectable and only the most dorsolaterally located (the first arising) remain visible through the adult stage (Voorn et al. 1988). Data on the development of the human nigrostriatal projection indicate that already in the early fetal period the neostriatum receives dopaminergic terminals. The putamen becomes innervated somewhat earlier than the caudate nucleus (Olson et al. 1973). Nobin and Björklund (1973) studied 3–4-month-old fetuses (10–15-cm crown-rump length). At this stage of development, catecholaminergic cell groups and nigrostriatal pathways are already richly developed and innervate abundantly the basal ganglia and olfactory region (Fig. 9.63). TH studies in 9–10-week-old fetuses (about 50-mm crown-

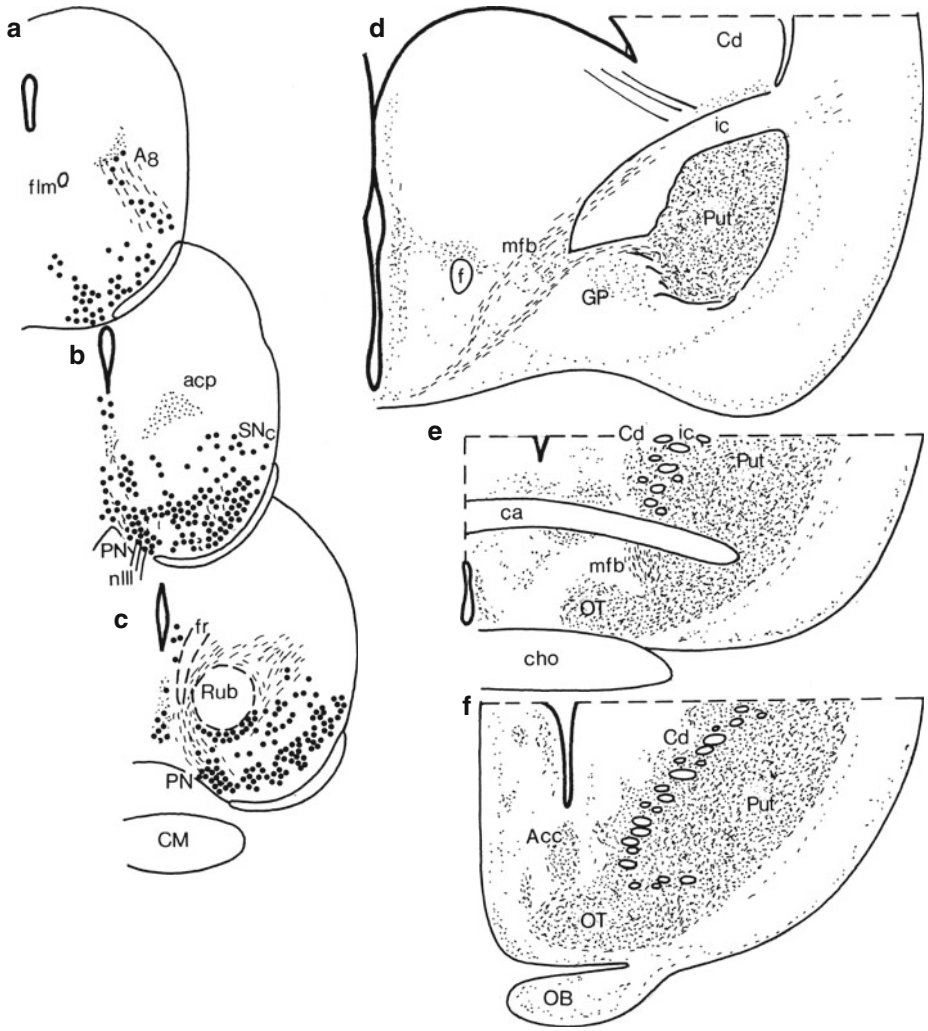

Fig. 9.63 Development of the striatal dopaminergic innervation in 3-4-month-old human fetuses: **a**-**c** catecholaminergic cell groups; **d**-**f** nigrostriatal innervation of the basal ganglia. *Acc* nucleus accumbens, *acp* ascending catecholaminergic pathway, *A8* medullary catecholaminergic cell group, *C* caudate nucleus, *ca* commissura anterior, *cho* chiasma opticum, *CM* corpus mammillare, *flm* fasciculus longitudinalis medialis, *GP* globus pallidus, *ic* internal capsule, *mfb* medial forebrain bundle, *nIII* oculomotor nerve, *OB* olfactory bulb, *OT* olfactory tubercle, *PN* nucleus paranigralis, *Put* putamen, *Rub* nucleus ruber, *SNc* substantia nigra pars compacta (After Nobin and Björklund 1973)

rump length) show that loose clusters of TH-immunoreactive neurons are present in the pars compacta of the substantia nigra and the VTA. In these early fetal stages, the TH-immunoreactive neurons in the substantia nigra already have well-established processes which are richly distributed in the pars reticulata and in the basal ganglia. These data strongly suggest that also in primates including man the generation of neurons in the substantia nigra and the VTA as well as the ingrowth of nigrostriatal fibres takes place in the last part of the embryonic period, i.e. between stages 17 and 23, comparable to E14-E17 in rat (Table 9.12). In rat and human embryos, the penetration of dopaminergic fibres in the cerebral cortex occurs at similar developmental stages in each species (Verney et al. 1982, 1993, 2001b; Kalsbeek et al. 1988; Zecevic and Verney 1995).

9.8.2 Congenital and Acquired Disorders of the Basal Ganglia

Developmental malformations of the ***basal ganglia*** are rare, and are usually associated with malformations of other areas of the CNS (Lemire et al. 1975; Friede 1989). Sarnat (2000) reported a case of congenital absence of the basal ganglia (Fig. 9.64). ***Acquired disorders*** of the ***basal ganglia*** are much more common, especially in the perinatal period. From a clinical point of view disorders of movement due to abnormal functioning of the basal ganglia can be divided into two broad groups (Fig. 9.65): (1) the hypokinetic-rigid syndromes, the fundamental disturbances of which consist of hypokinesia and/or bradykinesia, i.e. difficulty and/or slowness in initiating and completing

Table 9.12 Development of dopaminergic cell groups in the mesencephalon and their innervation of the basal ganglia and prefrontal cortex in rats, rhesus monkeys, and man

Species	Time of neuron origin SN/VTA	First appearance DA-immunoreactivity	First ingrowth DAergic fibres	Neurogenesis neostriatum and prefrontal cortex	Start of fetal period	Gestation time (in days)
Rat	SN: E13–15[1, 8, 11] VTA: E14-E16[1, 11]	SN: E13[13, 19, 20, 23]	Neostriatum: E14[13, 19, 20, 23] Prefrontal cortex: E17[9]	Neostriatum: E13-P2[2] Prefrontal cortex: E13-E18[9]	E17[21]	21–22[21]
Rhesus monkey	SN: E36-E43[10] (stages 18–21) VTA: E38-E43[10] (stages 19–21)	? ?	Neostriatum: before E60[5] ?	Neostriatum: E36–E80[4] (peak: E43-E50, i.e. stages 21–23) Prefrontal cortex: E40-E90[10]	E46–50[7]	160–170[7]
Man	SN: stages 19 and 20[3, 6, 15, 22] (early 5th to middle 7th week) VTA: Late 5th to 7th week [3, 22]	SN: between 5.5 and 9 week[12, 16, 17, 18, 22] ?	Neostriatum: before 9th week[14, 16, 17, 18, 22, 24] Prefrontal cortex: by about 12weeks [12, 14, 22, 25]	Early week 7 to 18[3] Prefrontal cortex?	E56–60[15]	260–280[15]

After van Domburg and ten Donkelaar (1990), Zecevic and Verney (1995), Puelles and Verney (1998), Verney et al. (2001a, b)
SN substantia nigra, *VTA* ventral tegmental area of Tsai
References: [1]Altman and Bayer (1981), [2]Bayer (1984), [3]Bayer et al. (1995), [4]Brand and Rakic (1979), [5]Brand and Rakic (1984), [6]Cooper (1946), [7]Gribnau and Geysberts (1981), [8]Hanaway et al. (1971), [9]Kalsbeek et al. (1988), [10]Levitt and Rakic (1982), [11]Marchand and Poirier (1983), [12]Nobin and Björklund (1973), [13]Olson and Seiger (1972), [14]Olson et al. (1973), [15]O'Rahilly et al. (1988), [16]Pearson et al. (1980), [17]Pickel et al. (1980), [18]Puelles and Verney (1998), [19]Seiger and Olson (1973), [20]Specht et al. (1981a), [21]Theiler (1972), [22]Verney et al. (2001a, b), [23]Voorn et al. (1988), [24]Zečević and Kostović (1980), [25]Zecevic and Verney (1995)

movements, generally associated with rigidity; and (2) the dyskinesias, including tremor, chorea and ballismus, dystonia and athetosis, tics, and myoclonus (Fernández-Alvarez and Aicardi 2001; Hoon et al. 2003; Sanger 2003). Disorders with a **hypokinetic-rigid syndrome** in childhood include early-onset Parkinson disease, juvenile Huntington disease, Wilson disease, juvenile GM2 gangliosidosis, multiple-system atrophies, Hallervorden-Spatz disease and many other rare disorders (Fernández-Alvarez and Aicardi 2001; Clinical Case 9.14; Table 9.13). Many patients with Hallervorden-Spatz disease have mutations in the gene encoding pantothenate kinase 2 (PANK2), resulting in pantothenate kinase associated neurodegeneration (Hayflick et al. 2003). The 'eye-of-the-tiger sign' is typical on MRI examination. The medial part of the globus pallidus appears to be especially sensitive to deficiency of PANK2.

A **selective vulnerability** of the basal ganglia is found in many acquired lesions such as subependymal haemorrhages affecting the ganglionic eminence, status marmoratus, subacute necrotizing encephalopathy (Leigh syndrome; Clinical Case 9.16 and kernicterus. The basal ganglia are susceptible to injury because they are metabolically very active in the immature brain (Chugani and Phelps 1986) and possess a high concentration of excitatory receptors (Mitchell et al. 1999). ***Subependymal*** or ***germinal matrix haemorrhages*** are very common in premature infants (see Norman et al. 1995; Squier 2002). ***Status marmoratus*** (marbled state or *état marbré*) is characterized by the presence of myelinated fibres in aggregations of a density abnormal for a given site (Norman 1947). Typically, such aggregations are associated with abnormal collections of glial fibres. Status marmoratus is usually restricted to the striatum, but may involve the globus pallidus, red nucleus and cerebral cortex. It is usually associated with the athetoid form of cerebral palsy (Malamud 1950). Severe intellectual disability, spasticity and epileptic seizures are common. ***Kernicterus*** may result as a complication of infantile hyperbilirubinaemia from any cause, and may lead to necrosis of selective brain stem, basal ganglia and cerebellar neurons (Kinney and Armstrong 1997). In the term infant, the common sites of the gross lesions with a bright yellow colour are the globus pallidus, subthalamus and Ammon's horn. Kernicterus is now rare in regions where hyperbilirubinaemia can be anticipated, treated or prevented.

Chorea is a relatively infrequent movement disorder in children but at least 150 causes of chorea have been described (Padberg and Bruyn 1986). Primary (idiopathic) and secondary

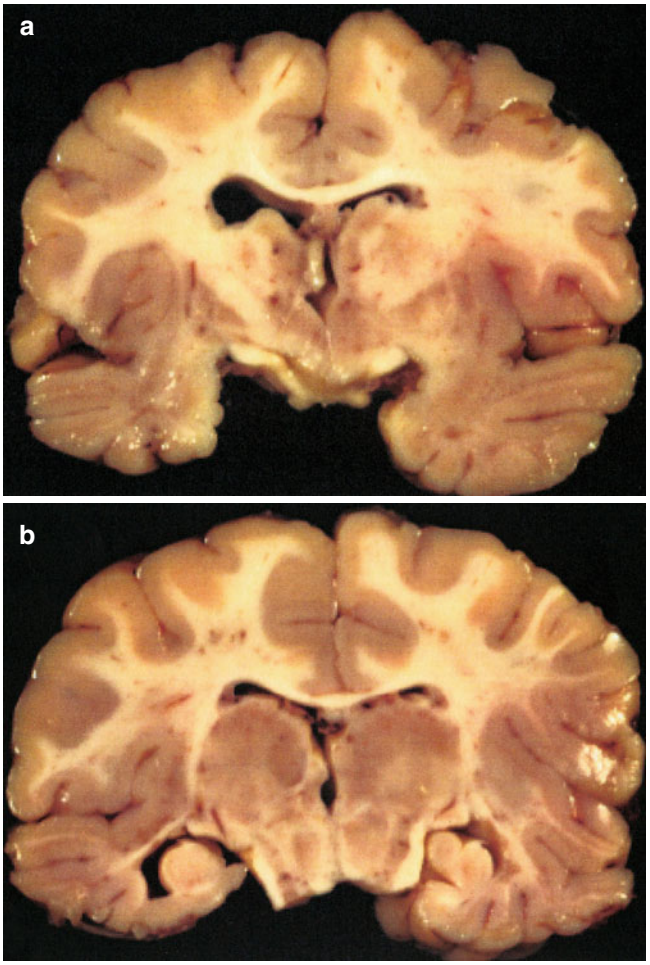

Fig. 9.64 Two frontal sections of the forebrain at the level of the amygdala (**a**) and of the hippocampus (**b**) in a case of bilateral congenital absence of the deep cerebral nuclei in a 14-month-old male infant (kindly provided by Ellsworth Alvord, Seattle)

forms of dystonia are found. ***Secondary dystonias*** can be classified into structural, metabolic, degenerative and miscellaneous disorders. Dystonia is a frequent symptom in the course of many inborn errors of metabolism such as ***glutaric aciduria type 1***, an autosomal recessive metabolic disorder, which is characterized by severe reduction or total absence of glutaryl-coenzyme A dehydrogenase (GCDH) activity (Goodman et al. 1977; Goodman and Frerman 2001). Its prevalence has been estimated to be 1 in 30,000 (Kyllerman and Steen 1980). At least 100 disease-causing mutations have been described (Goodman et al. 1998; Zschocke et al. 2000). GCDH deficiency leads to an accumulation of the marker metabolites 3-hydroxyglutaric acid, glutaric acid and glutaryl carnitine. If untreated, the disease is complicated by acute encephalopathic crises, resulting in neurodegeneration of vulnerable brain regions, especially the putamen. 3-Hydroxyglutaric acid is the major neurotoxin in this disease (Kölker et al. 2003). Clinical manifestations generally appear between 5 and 14 months of age, but mild symptoms such as slight motor delay and hypotonia can be observed earlier (Hoffmann et al. 1996; Fernández-Alvarez and Aicardi 2001). Macrocephaly at birth or somewhat later in infancy is present in about 70 % of cases (Hoffmann et al. 1996). In about two thirds of cases, the disease starts abruptly, on average at 12 months of age, with focal seizures or generalized convulsions and vomiting, usually following an infectious disease. Psychomotor regression and dystonic or choreoathetotic movements then appear (Fernández-Alvarez and Aicardi 2001). Autopsy studies have shown rather minimal changes in severely affected patients who died at 1 year of age but changes much more marked in patients who died at more than 2 years of age (Goodman et al. 1977; Leibel et al. 1980; Chow et al. 1988; Soffer et al. 1992; Kimura et al. 1994; Clinical Case 9.15). These findings are remarkably similar to those in 'familial holotopistic striatal necrosis' (Miyoshi et al. 1969) or 'familial striatal degeneration' (Roessmann and Schwarz 1973). These cases may have been unrecognized forms of glutaric aciduria.

In s***ubacute necrotizing encephalopathy*** or ***Leigh syndrome*** (Leigh 1951), movement disorders of any type, including hypokinetic-rigid syndrome, chorea, myoclonus or dystonia, may be the most obvious clinical features. Leigh syndrome is characterized by multifocal, bilateral areas of subtotal necrosis in the basal ganglia, the brain stem tegmentum, the cerebellum and to some extent the spinal cord. The lesions may involve the white matter, especially the posterior columns, the corticospinal tracts, the optic nerves and the superior cerebellar peduncles (Lemire et al. 1975). This syndrome usually presents in infancy with feeding difficulties, psychomotor retardation, ophthalmoplegia, ataxia and weakness. Leigh syndrome is a heterogeneous mitochondrial disorder among children that may be associated with deficiency of pyruvate dehydrogenase and of enzymes of the respiratory chain, especially complex I and complex IV (Zeviani et al. 1996; Darin et al. 2001; Tulinius et al. 2003; Clinical Case 9.16).

MRI studies have shown ***bilateral lesions*** of the ***thalamus*** and the ***basal ganglia*** in children with severe birth asphyxia, leading to dyskinetic and spastic types of cerebral palsy (Yokochi et al. 1991; Rutherford et al. 1992; Krägeloh-Mann et al. 1995; Rademakers et al. 1995; Rutherford 2002). In addition to hyperintensity (T2-weighed images) in the ventrolateral thalamus and the posterior part of the nucleus lentiformis, lesions of the perirolandic region and of the hippocampus were found in some patients. Bilateral lesions

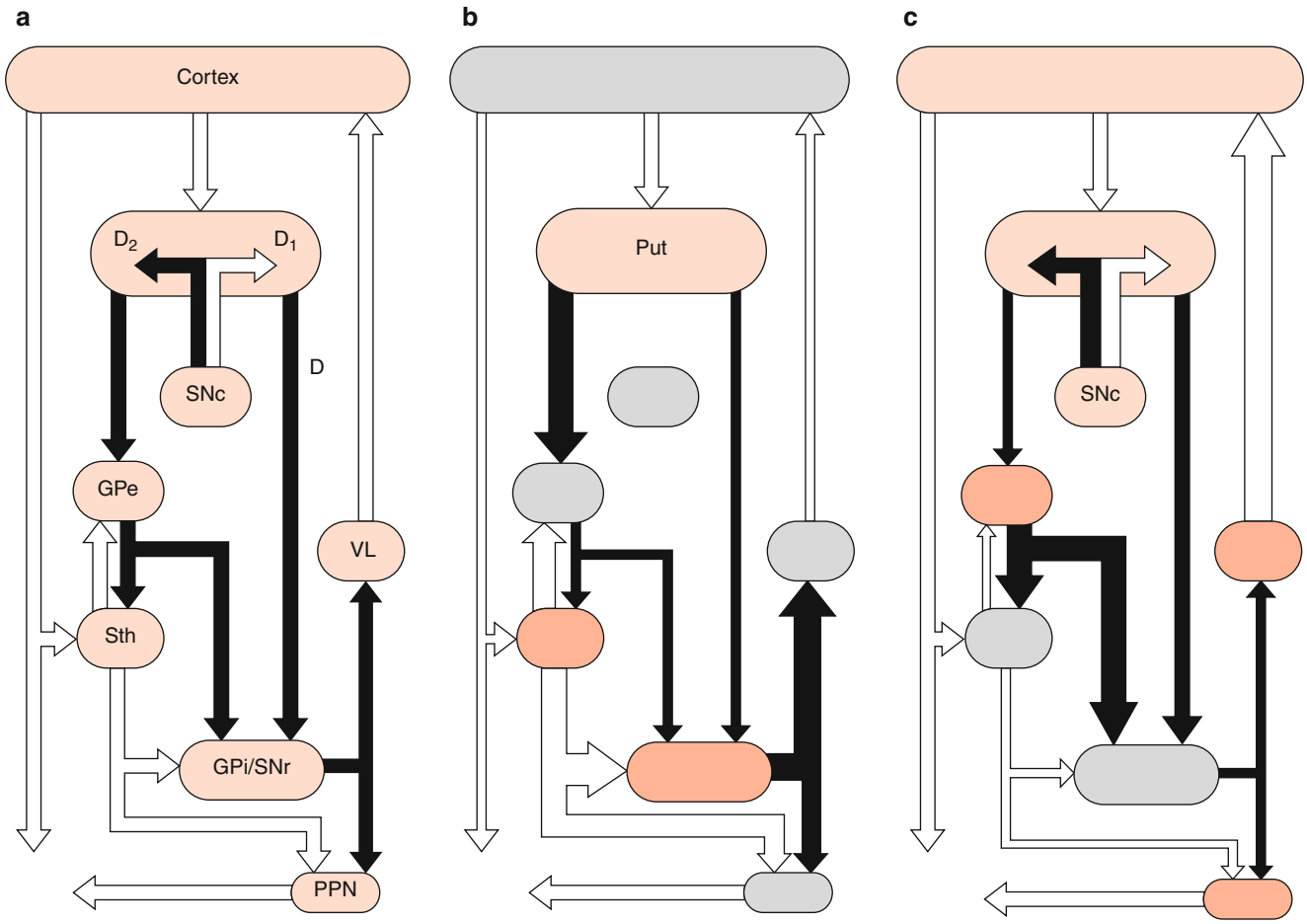

Fig. 9.65 The motor basal ganglia-thalamocortical circuit in the normal situation (**a**), in parkinsonian conditions (**b**) and in hyperkinetic disorders (**c**). Normal cell activity is indicated in *light red*, upregulation in *red* and downregulation in *grey*. Inhibitory pathways are shown as *black arrows* and excitatory pathways as *open arrows*. The size of the arrows indicates the changes occurring. Parkinsonism leads to differential changes in the two striatopallidal projections, and the inhibitory basal ganglia output to the thalamus in increased. In Huntington disease (**c**), degeneration of the striato-GPe pathway results in increased inhibition of the subthalamic nucleus and of GPi, leading to reduced basal ganglia output to the thalamus. *D* direct pathway, *D1*, *D2* dopamine receptors, *GPe* external part of globus pallidus, *GPi* internal part of globus pallidus, *I* indirect pathway, *PPN* pedunculopontine tegmental nucleus, *SNc* compact part of substantia nigra, *SNr* reticular part of substantia nigra, *Sth* subthalamic nucleus, *VL* ventrolateral thalamic nucleus (After Wichmann et al. 2000; from ten Donkelaar et al. 2011)

of the thalamus and the basal ganglia have also been found in term neonates as a consequence of severe birth asphyxia (Voit et al. 1987; Pasternak et al. 1991; Baenziger et al. 1993; Rutherford et al. 1995; Sie et al. 2000; Rutherford 2002). Krägeloh-Mann et al. (2002) defined three different patterns of MRI lesions in children with bilateral lesions of the thalamus and basal ganglia due to birth asphyxia, neonatal shock or late prenatal compromise: (1) a mild pattern with involvement of the lentiform nucleus and ventrolateral thalamus only; (2) an intermediate pattern with involvement of the lentiform nucleus, the ventrolateral thalamus and pericentral regions; and (3) a severe pattern with additional involvement of the entire thalamus and of the hippocampus. This grading of MRI findings corresponded rather well with the severity of cognitive and motor impairment and the type of cerebral palsy. Normal cognitive development and mild motor delay was only seen with the mild pattern. All children developed cerebral palsy: purely dyskinetic cerebral palsy was only found with the mild pattern, the dyskinetic-spastic or spastic forms were found in all three groups, with dyskinetic-spastic cerebral palsy more related to the moderate pattern, and purely spastic cerebral palsy more related to the severe pattern.

Table 9.13 Involvement of the basal ganglia in some childhood motor impairment syndromes

Disorder	Inheritance/gene defect	Involvement of basal ganglia	Selected references
Bilateral striatal necrosis	Autosomal recessive; maps to chromosome 19q	Caudate, putamen, globus pallidus	Friede (1989) Basel-Vanagaite et al. (2004)
Dentatorubro-pallidoluysian atrophy	Autosomal dominant	External globus pallidus, subthalamic nucleus; (dentate and red nuclei)	Takahashi et al. (1988) Warner et al. (1994, 1995)
Glutaric aciduria type I	Autosomal recessive; deficiency in glutaryl-CoA-dehydrogenase	Caudate, putamen; see Clinical Case 9.15	Chow et al. (1988) Kimura et al. (1994) Goodman and Frerman (2001)
Hypoxic-ischaemic encephalopathy: Bilateral lesions thalamus/basal ganglia		Putamen, thalamus, perirolandic areas	Krägeloh-Mann et al. (1995, 2002) Rutherford (2002)
Juvenile Huntington disease		Caudate, putamen	Ho et al. (1995)
Kernicterus		Globus pallidus	Johnston and Hoon (2000) Yilmaz et al. (2001)
Leigh syndrome	Mitochondrial disorder; deficiency complexes I or IV	Caudate, putamen, brain stem, white matter; see Clinical Case 9.16	Leigh (1951)
Pantothenate kinase-associated neurodegeneration (Hallervorden-Spatz disease)	Autosomal recessive disorder; many patients with *PANK2* mutations	Globus pallidus, subthalamic nucleus	Hayflick et al. (2003)
Pyruvate dehydrogenase deficiency		Globus pallidus, caudate, putamen	Brown et al. (1989) Robinson (2001)
Wilson disease	Autosomal recessive disorder with abnormal deposition of copper in liver, brain, cornea, and other tissues	Putamen, globus pallidus, caudate	Brewer et al. (1999)

After Fernández-Alvarez and Aicardi (2001), Hoon et al. (2003)

Clinical Case 9.14 Selective Vulnerability of the Basal Ganglia

A **selective vulnerability** of the basal ganglia is found in many acquired lesions such as subependymal haemorrhages affecting the ganglionic eminence, status marmoratus, subacute necrotizing encephalopathy (Leigh syndrome; see ***Clinical case*** 9.16) and kernicterus. The basal ganglia are susceptible to injury because they are metabolically very active in the immature brain and possess a high concentration of excitatory receptors (Mitchell et al. 1999). Moreover, many disorders of movement due to abnormal functioning of the basal ganglia occur (Fernández-Alvarez and Aicardi 2001). Some examples are shown as Case Reports.

Case Report 1: In ***methyl-malonic acidemia*** (***MMA***), a severe, classic organic aciduria, the globus pallidus is selectively involved. In a seven-year-old girl with MMA, an MRI showed bilateral destruction of the globus pallidus (Fig. 9.66a, b). She presented in the first week of life with an acute encephalopathy with coma and seizures. Laboratory investigation revealed a severe metabolic acidosis and hypoglycaemia. Despite appropriate treatment in the acute phase and interventions during follow-up, such as a special diet and prevention of a catabolic state during intercurrent illnesses, she became severely disabled with profound mental retardation, spasticity and dystonia.

Case Report 2: In ***infantile bilateral striatal necrosis***, patients present with progressive motor disturbances. A previously healthy boy with a so far normal development presented with such symptoms at the age of five years. Neurological examination showed generalized, symmetrical dystonia and chorea. An MRI resembled the images as reported in infantile bilateral striatal necrosis

(Fig. 9.66c). Laboratory investigations did not show any arguments in favour of an underlying mitochondrial or other metabolic disorder, poststreptococcal chorea or other causative disease processes. Molecular analysis of the only gene known to be responsible for infantile bilateral striatal necrosis (*nup62*) was negative.

Case Report 3: In ***kernicterus***, hyperbilirubinaemia leads to bilateral damage of the globus pallidus (Fig. 9.66d–g). In a female neonate, postnatal development was complicated by hyperbilirubinaemia, despite phototherapy and transfusions. At the age of one week, MR images showed bilateral signal abnormalities in the globus pallidus, prominent on T1-weighted images but hardly visible on T2. At the age of three months, the T1-weighted images have become almost fully normal, including the globus pallidus. On these T1-weighted images, the stripes with increased signal intensity reflect the normal pattern of myelination of the posterior limb of the internal capsule at this age; these areas show normal low signals on T2-weighted images. Three months later, however, on T2-weighted images, strong signal intensities of the globus pallidus are now clearly visible. These images illustrate the transition of signal changes depending on the stage (acute versus chronic) of the disorder and the selective vulnerability of the globus pallidus in bilirubin encephalopathy.

References

Fernández-Alvarez E, Aicardi J (2001) Movement disorders in children. MacKeith, London

Mitchell IJ, Cooper AJ, Griffiths MR (1999) The selective vulnerability of striatopallidal neurons. Prog Neurobiol 59:691–719

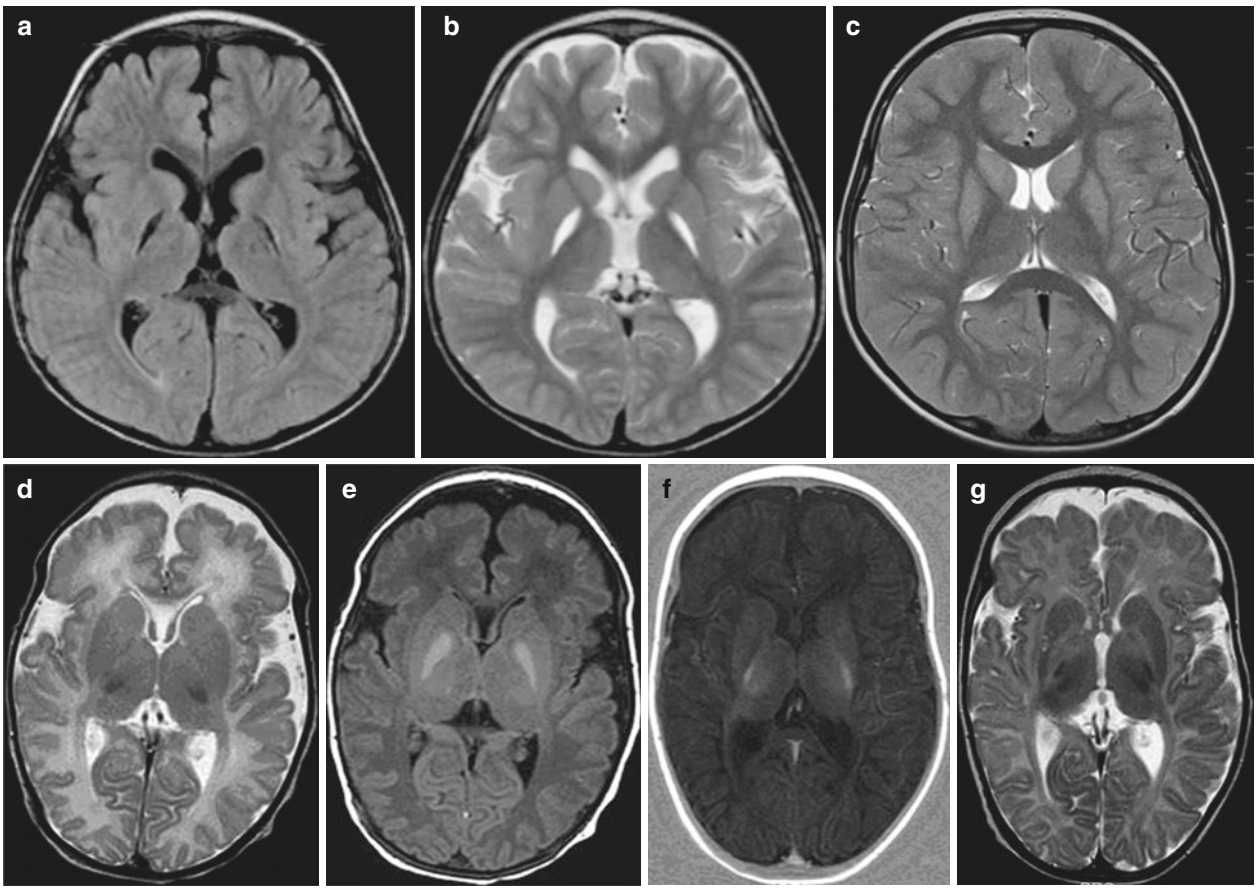

Fig. 9.66 MRIs of cases of methylmalonic acidemia (**a**, **b**), infantile bilateral necrosis (**c**) and kernicterus (**d**–**g**; see text for further explanation; From ten Donkelaar et al. 2011; courtesy Michèl Willemsen, Nijmegen)

Clinical Case 9.15 Familial Striatal Degeneration (Glutaric Aciduria Type 1)

Glutaric aciduria type 1 (***GA-1***) is an autosomal recessive metabolic disorder which is characterized by severe reduction or total absence of glutarylcoenzyme A dehydrogenase (GCDH) activity (Goodman et al. 1977; Kimura et al. 1994; Hoffmann et al. 1996). The neuropathological findings in a 15-year-old Turkish male adolescent will be discussed as the Case Report.

Case Report. Rapidly progressive neurological symptoms were evident from birth in this 15-year-old male adolescent whose parents were consanguineous to the third degree. Hypertonia began at the left side, became generalized later and ended with episodes of generalized epilepsy. His monozygous twin brother and two sisters were neurologically and developmentally normal, but a younger brother also had GA-1. They both displayed the so-far unreported mutation M801 (240 G→C) in exon 3 of the GCDH gene.

His first episode occurred at 7 months of age when, 2 weeks after gastroenteric dehydration, he had paroxysmal hypertonia of the left arm which progressed to status epilepticus with subcoma. The idiopathic relapsing fever was labelled as acute encephalopathy without any obvious metabolic cause. The second episode occurred 11 months later, again in the form of gastroenteric dehydration and encephalopathy. A peak of urinary glutaric acid (GA) and the presence of 3-OH-GA suggested the diagnosis of glutaric aciduria type 1. Blood tests were normal, but the patient's CSF revealed a raised acetic acid level. The finding of normal GCDH activity in hepatocytes and fibroblasts, however, led to the erroneous dismissal of the GA-1 diagnosis. Constant episodes of laryngeal dyspnoea when he was 4 years old led to retesting of organic acid levels. They were found to be normal and so GA-1 was completely dismissed. The patient had now severe psychomotor retardation. He suffered from dyskinetic dystonia with compulsive nuchal torsion dystonia to the right side. Additional manifestations included hip adduction hypertonia, hyperextension and torsion of the spine. Although no fixed contractures were found, there was total loss of voluntary movements, except for visual expression and eye motility. The patient had hypotonia alternating with periods of opisthotonus and an overall dystrophic expression of the body until he died at the age of 15 years from bronchopneumonia. The diagnosis of GA-1 could only be confirmed after postmortem gene analysis.

At autopsy, the spleen and liver were found to be normal, making the diagnosis of a storage disease unlikely. The brain weighed 1,275 g. Macroscopically, there were widened lateral ventricles and loss of gyral convolutions. Frontal atrophy and a small caudate nucleus and putamen were also evident (Fig. 9.67a). The white matter appeared grossly normal. Microscopically, the striatum showed

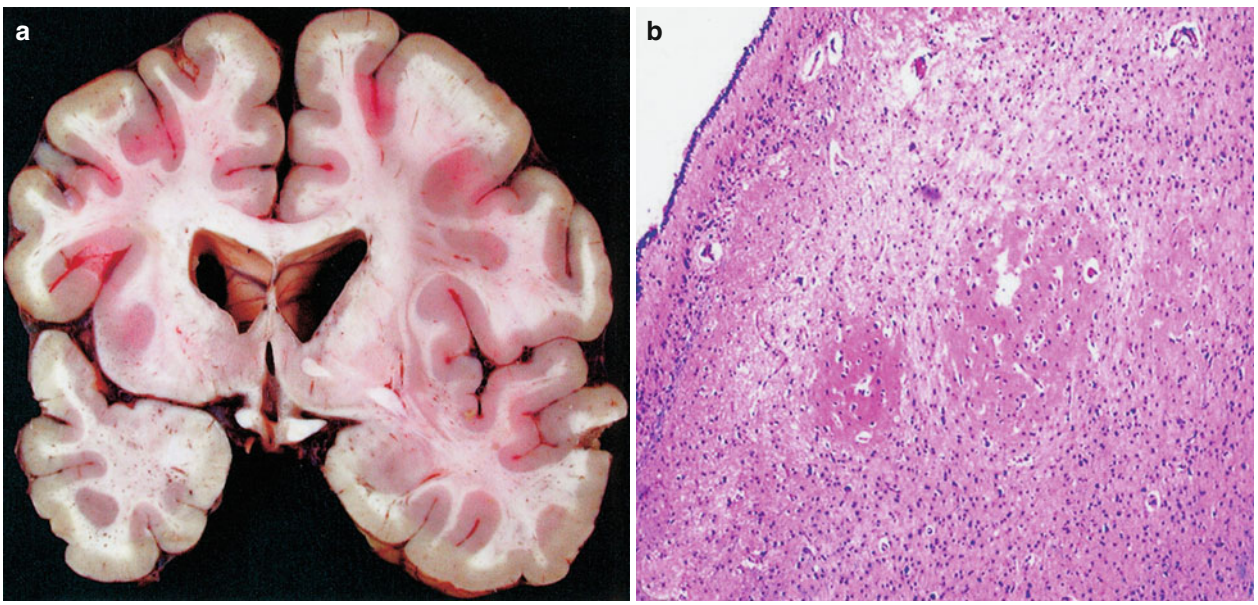

Fig. 9.67 Familial striatal degeneration: (**a**) frontal section through the brain demonstrating very atrophic caudate nuclei; (**b**) histological section through the caudate nucleus with severe gliosis (*lower* and *right* parts of the picture); centrally, two round structures (striosomes) are somewhat spared from the gliosis (Courtesy Martin Lammens, Nijmegen)

obvious neuron loss, with small neurons being more affected than large cells (Fig. 9.67b). This was marked in the putamen, moderate in the caudate nucleus and only mild in the globus pallidus. This neuronal loss was associated with marked astrocytic gliosis. Interestingly, on close examination of the striatum we noted that the neuronal loss and astrogliosis were non-continuous in nature. In fact, such changes were confined to areas within the sections which bore great resemblance to the patch-matrix compartments of the striatum.

References

Goodman SI, Norenberg MD, Shikes RH, Brelick DJ, Moe PG (1977) Glutaric aciduria: biochemical and morphological considerations. J Pediatr 90:746–750

Hoffmann GF, Athanassopoulos S, Burlina AB, Duran M, de Klerck JBC, Lehnert W et al (1996) Clinical course, early diagnosis, treatment and prevention of disease in glutaryl-CoA dehydrogenase deficiency. Neuropediatrics 27:115–123

Kimura S, Hara M, Nezu A, Osaka H. Yamazaki S (1994) Two cases of glutaric aciduria type 1: clinical and neuropathological findings. J Neurol Sci 123:38–43

Clinical Case 9.16 Leigh Syndrome

Leigh syndrome (Leigh 1951) or ***subacute necrotizing encephalomyopathy*** is a progressive subcortical disorder, characterized by multifocal, bilateral areas of subtotal necrosis in the basal ganglia, the brain stem tegmentum, the cerebellum, and to some extent the spinal cord (see Case Report). It is the prototype of a large group of mitochondrial encephalomyopathies, currently known as defects of oxidative phosphorylation (OXPHOS defects; Chap. 3).

Case Report. A boy was born after an uncomplicated pregnancy as the second child of non-consanguineous parents. His mother and grandmother were known with retinitis pigmentosa. As a baby, head balance was poor and the boy was very quiet. Marked developmental delay and subsequently progressive loss of motor and social skills became evident at the age of 8 months. Cerebral MRI showed marked cerebral atrophy and abnormal signs in the basal ganglia (Fig. 9.68), suggesting Leigh syndrome. Blood lactate levels were between 1.8 and 9.4 mmol/l (normally below 2.0 mmol/l), and CSF lactate was also elevated to 4.8 mmol/l (normally 1.2–2.0 mmol/l). At the age of 11 months, respiratory failure due to pneumonia necessitated artificial ventilation. At that time a muscle biopsy was taken. Histological

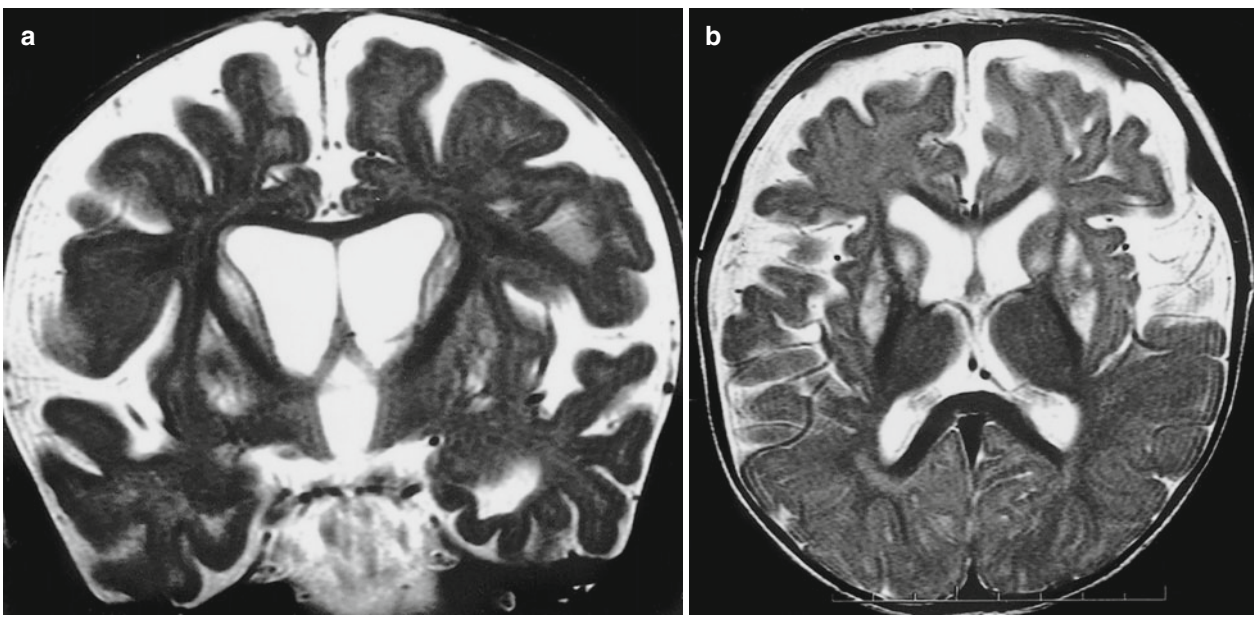

Fig. 9.68 Coronal (**a**) and axial (**b**) MRI of Leigh syndrome. Note the zones of hyperintensity in the caudate nucleus and the putamen bilaterally (Courtesy Michèl Willemsen, Nijmegen)

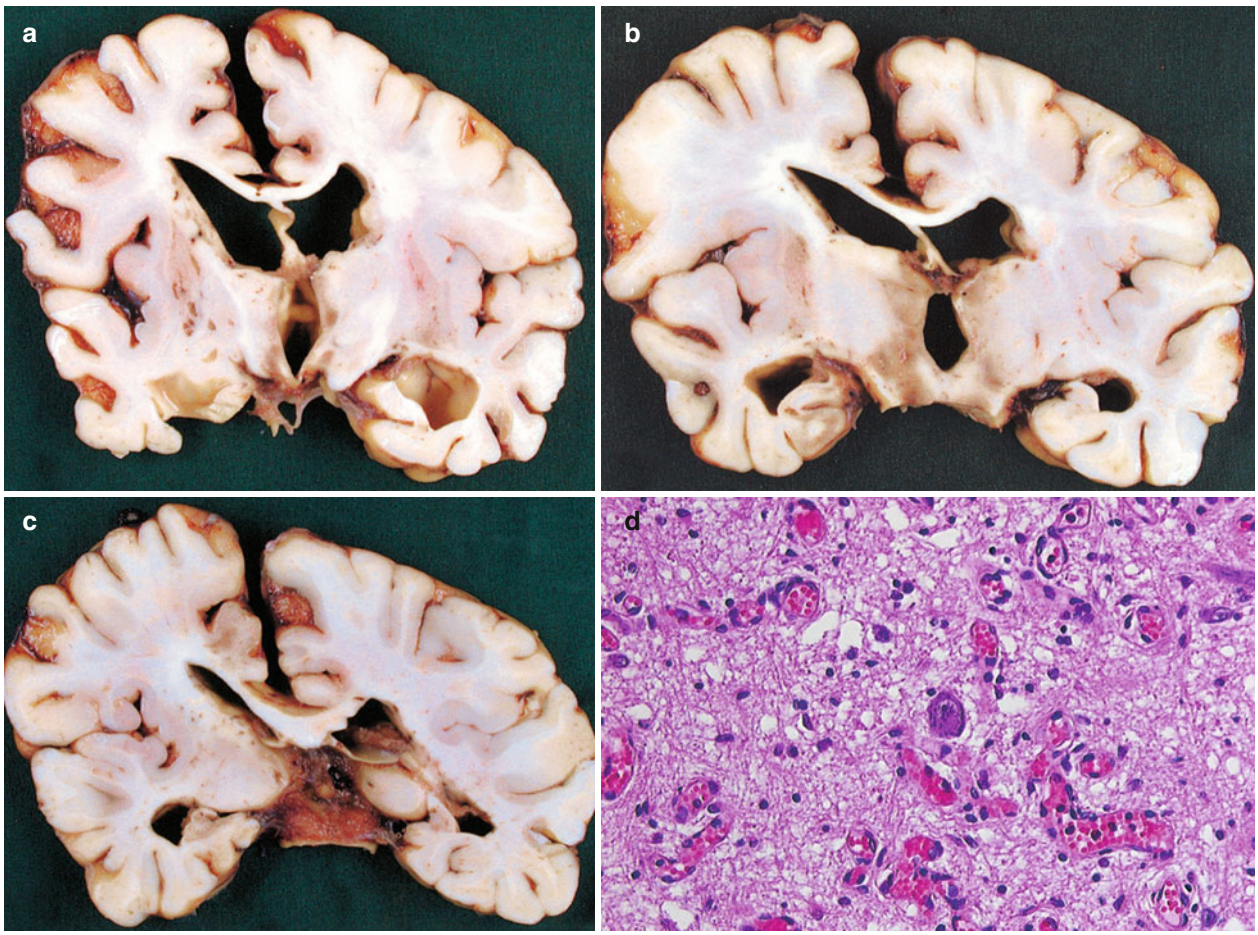

Fig. 9.69 Leigh syndrome: (**a**) frontal section at the level of the mammillary bodies showing atrophy of the basal ganglia and thalamus, dilatated lateral ventricles, brown discolorated regions in the right thalamus, and atrophic cerebral cortex; (**b**) frontal section at the level of the substantia nigra; especially the regions around the left substantia nigra and both subthalamic nuclei are damaged with brown discoloration; (**c**) frontal section showing a cystin the left pulvinar; (**d**) haematoxylin-eosin-stained section of a lesion in the left subthalamic nucleus: spongiosis, slight gliosis and capillary proliferation are present, and centrally the cell body of an intact large neuron is visible (Courtesy Martin Lammens, Nijmegen)

examination of the tissue showed no structural abnormalities of the muscle fibres. Biochemical analysis demonstrated defective respiratory chain functions. Mutation analysis finally confirmed the diagnosis Leigh syndrome by demonstration of the 8993 T>G mutation in mitochondrial DNA. Although he initially recovered, the boy died at the age of 14 months due to aspiration and subsequent respiratory failure.

At autopsy, brain weight was 830 g. Macroscopical inspection revealed bilateral slightly asymmetric, dark grey to light brown lesions in the thalamus, hypothalamus, mesencephalic tegmentum, periaqueductal grey matter and hindbrain nuclei (Fig. 9.69a–c). The putamen and the pulvinar were bilaterally pseudocystically degenerated. All these lesions were characterized by spongiosis of the neuropil, reactive astrocytes and important capillary proliferation and endothelial swelling (Fig. 9.69d). In the less severe lesions such as in the periaqueductal grey matter, neurons were still well recognizable. In the more severely affected regions such as the putamen, almost all

neurons had disappeared, leading to pseudocystic lesions. These are the classic signs found in Leigh syndrome. Large parts of the cerebral cortex, including frontal, insular and temporobasal cortex, were atrophic, and showed gliosis in the molecular layer and spongiosis and neuronal loss in layer II. Such lesions are reminiscent of Alpers disease. Moreover, in the occipital cortex an ischaemic lesion at the borderzone between the territories of the anterior and middle cerebral arteries was found with pseudolaminar necrosis of the complete cortex. There was also important cell loss and spongiosis in areas CA1 and CA3 of the hippocampus. Probably, these lesions resulted from generalized circulatory failure.

Reference

Leigh D (1951) Subacute necrotizing encephalomyopathy in an infant. J Neuro Neurosurg Psychiatr 14:216–221

9.8.3 Development of the Amygdala

The **amygdala** is composed of pallial and subpallial parts (Lammers 1972; Stephan and Andy 1977; Amaral 1987; de Olmos 1990, 2004; Heimer et al. 1991). The basolateral parts and the associated cortical amygdala form the pallial part, whereas the central and medial amygdaloid nuclei form the subpallial part (Fig. 9.70). The centromedial amygdala forms a continuum with the bed nucleus of the stria terminalis, known as the extended amygdala (Alheid and Heimer 1988; Alheid et al. 1995; Heimer et al. 1997; de Olmos 2004). **Time** of **neuron origin** data in rodents indicate a rostrocaudal gradient within the amygdaloid complex (ten Donkelaar et al. 1979; Bayer 1980; McConnell and Angevine 1983) and strongly support a subdivision of the amygdala into two groups: a group of early-arising (E13-E15/E17) structures (central, medial and anterior cortical nuclei) and a group of later-born (E14/E15-E16/E17) nuclei (lateral, basolateral, basomedial and posterior cortical nuclei). This distinction between two groups of nuclei in the amygdaloid complex is comparable with the subdivision of Stephan and Andy (1977). Molecular genetic data have been reviewed by Medina and Abellán (2012). In rhesus monkeys, neurogenesis in the amygdaloid nuclear complex starts at E33, peaks between E38 and E48 and ceases between E50 and E56 (Kordower et al. 1992).

Developmental studies on the **human amygdala** are few (Macchi 1951; Humphrey 1968, 1972; Kahle 1969; Ulfig 2002b; Ulfig et al. 2003a, b; Müller and O'Rahilly 2006). The primordial amygdala is recognized as a thickening in the ventrocaudal wall of the interventricular foramen as soon as the cerebral hemisphere has evaginated (stages 14–16). Apparently, slightly later, the medial nucleus develops first, followed by the basolateral complex later at stage 20. Most of the amygdaloid nuclei arise from the medial ganglionic eminence (Müller and O'Rahilly 2006). All amygdaloid nuclei are present by stages 21–22. Kahle (1969) and Ulfig and co-workers (Ulfig 2002b; Ulfig et al. 2003a, b) studied the fetal development of the human amygdala (Fig. 9.71). In the fifth and six gestational month, the inferior part of the amygdala reveals cell-dense columns merging with the caudal part of the ganglionic eminence. These columns contain

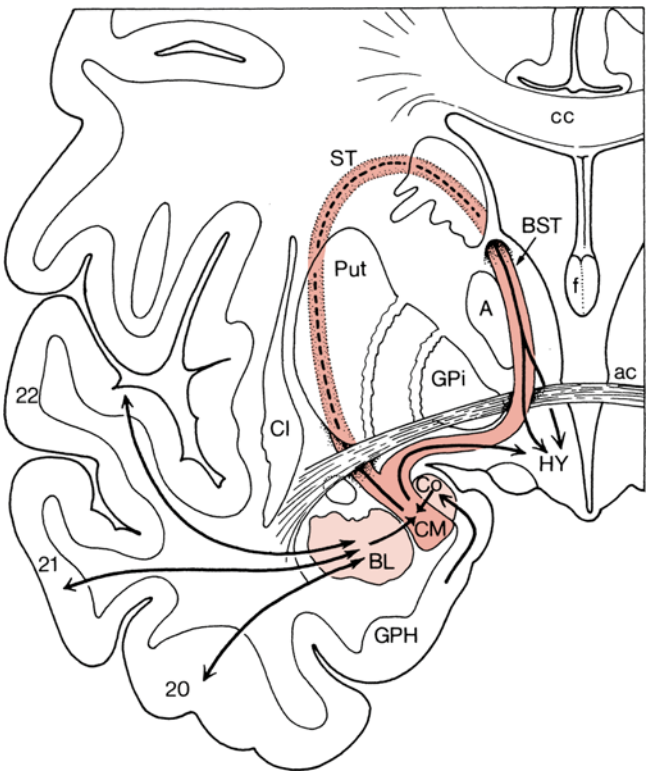

Fig. 9.70 Overview of the amygdala and extended amygdala. The centromedial nuclei and the extended amygdala are indicated in *red*, the basolateral amygdala (*BL*) and cortical amygdala (*Co*) in *light red*. *A* anterior nucleus, *ac* anterior commissure, *BST* bed nucleus of stria terminalis, *cc* corpus callosum, *Cl* claustrum, *CM* centromedial amygdala, *f* fornix, *GPH* gyrus parahippocampalis, *GPi* internal globus pallidus, *HY* hypothalamus, *Put* putamen, *ST* stria terminalis, *20–22* temporal cortical areas

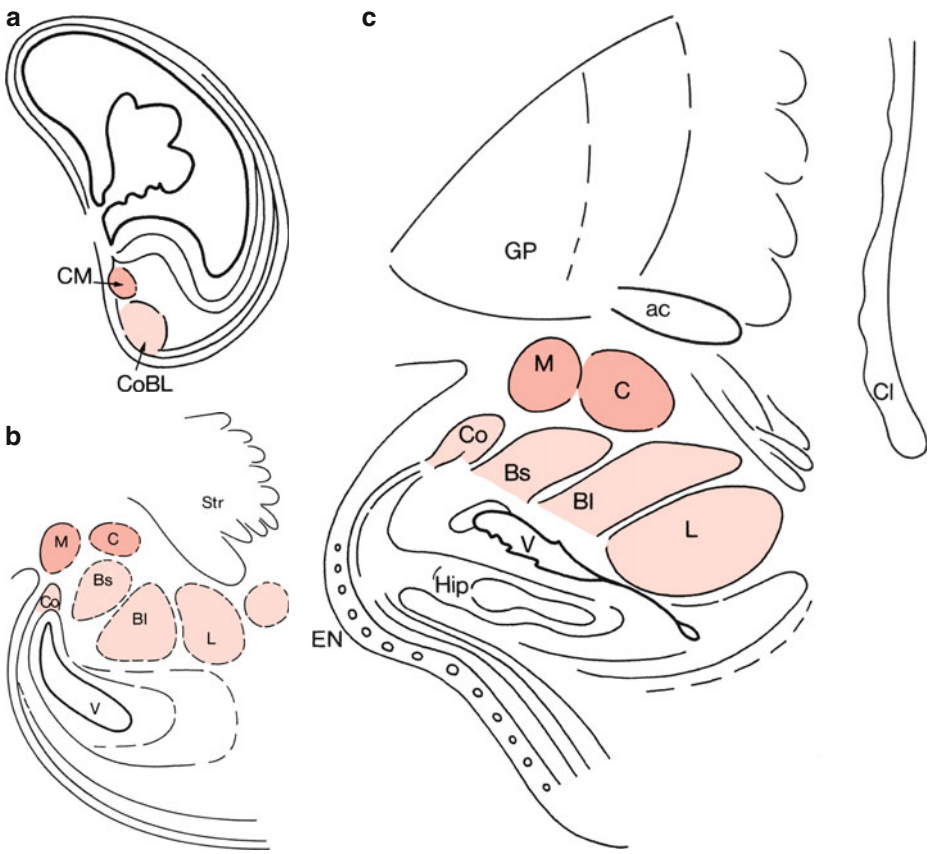

Fig. 9.71 Development of the human amygdala: (**a**) frontal section through the forebrain of a 35-mm-CRL embryo; (**b**, **c**) the amygdala complex in a 4-month-old fetus and an 8-month-old fetus, respectively. The centromedial cell group (*CM*) and its derivatives are indicated in *red* and the corticobasolateral cell group (*CoBL*) and its derivatives in *light red*. *ac* anterior commissure, *Bl* large-celled part of basal nucleus, *Bs* small-celled part of basal nucleus, *C* central nucleus, *Cl* claustrum, *Co* cortical nucleus, *EN* entorhinal cortex (with cell nests), *GP* globus pallidus, *Hip* hippocampus, L lateral nucleus, *M* medial nucleus, *Str* striatum ((**a**) After Stephan 1975; (**b**) after Kahle 1969)

vimentin-positive glial fibres which provide a scaffold for migrating neurons. In the seventh and eighth month, distinct reorganization of the cytoarchitecture of the amygdala occurs, accompanied by a rearrangement and disappearance of vimentin-positive fibres, leading to a high degree of maturity in the eighth month.

The amygdala may be involved in Ammon's horn sclerosis and in schizophrenia and other neurobehavioural disorders such as the ***autism spectrum disorder*** (Chap. 10). Postmortem and MRI studies have highlighted the frontal lobes, the amygdala and the cerebellum as pathological in autism (Amaral et al. 2008; Chap. 10). The amygdala in boys with autism appears to undergo an abnormal developmental time course that includes a period of precocious enlargement that persists through late childhood (Sparks et al. 2002; Schumann et al. 2004). Sparks et al. (2002) found a 13–16 % abnormal enlargement of the amygdala in young children with autism (36–56 months of age). Amygdala enlargement may be associated with severe anxiety (Juranek et al. 2006) and worse social and communication skills (Munson et al. 2006). Schumann et al. (2004) found that the amygdala was enlarged by 15 % in 8- to 12-year-old boys with autism relative to typically developing controls, but did not differ in 13- to 18-year-old boys. Kemper and Baumann (1993) were the first to report abnormalities in the microscopic organization of the amygdala. Quantitative observations in six postmortem cases of autism between 9 and 29 years of age (five with intellectual disability, four with seizures) indicated that neurons in certain nuclei of the amygdala in autism cases appeared unusually small and more densely-packed than in age-matched controls. Schumann and Amaral (2006) compared nine autism cases 10–44 years of age without seizures with ten typically developing age-matched male controls. The autism group had significantly fewer neurons in the total amygdala and in the lateral nucleus than the controls. The amygdala is selectively involved in ***Urbach-Wiethe disease***, a rare autosomal recessive neurocutaneous disorder (Clinical Case 9.17).

Clinical Case 9.17 Urbach-Wiethe Disease

Urbach-Wiethe disease, also known as ***lipoid proteinosis***, is a rare autosomal recessive neurocutaneous disorder caused by mutations in the extracellular matrix protein 1 gene (*ECM1*; Hamada et al. 2003). ECM1 is thought to contribute to protein binding of collagens and glycosaminoglycans. Hoarseness, due to laryngeal deposition of hyaline material, is generally the first manifestation of the disease. The CNS gradually becomes affected with characteristic calcifications of the amygdala leading to temporal lobe epilepsy and neuropsychiatric manifestations. Histologically, the skin disorder is characterized by periodic acid-Schiff (PAS)-positive basement membrane thickening and accumulation of hyaline material. Based on the clinical observations of three patients, Adolphs et al. (1995, 1999) suggested that the amygdala is involved in a broad spectrum of social attributions.

Case report. A 15-year-old girl was referred to the Department of Pediatric Neurology after she was diagnosed with Urbach-Wiethe disease due to a homozygous nonsense mutation in the *ECM1* gene by a dermatologist. From infancy onwards, the girl was known with remarkable hoarseness and typical skin abnormalities. Her motor and language development were fully normal and her school performance was excellent. From the age of 11 years onwards, she had suffered from unexplained paroxysms with strange abdominal sensations, followed by a short period with confusion but without motor signs. Neurological examination and routine electroencephalography were completely normal. Cerebral CT showed bilateral calcifications of the globus pallidus and amygdala (Fig. 9.72). The paroxyms were considered partial epileptic seizures, caused by cerebral involvement in Urbach-Wiethe disease. During follow-up, her epilepsy appeared drug-resistant and she developed memory problems as well as a panic disorder.

This case was kindly provided by Michèl Willemsen (Department of Pediatric Neurology, Radboud University Nijmegen Medical Centre, Nijmegen).

References

Adolphs RD, Tranel D, Damasio H, Damasio AR (1995) Fear and the human amygdala. J Neurosci 15:5879–5891

Adolphs RD, Tranel D, Hamann S, Young AW, Calder AJ, Phelphs EA et al (1999) Recognition of facial emotion in nine subjects with bilateral amygdala damage. Neuropsychologia 37:1111–1117

Hamada T, Wessagowit V, South AP, Ashton GH, Chan I, Oyama N et al (2003) Extracellular matrix protein 1 gene (ECM1) mutations in lipoid proteinosis and genotype-phenotype correlation. J Invest Dermatol 120:345–350

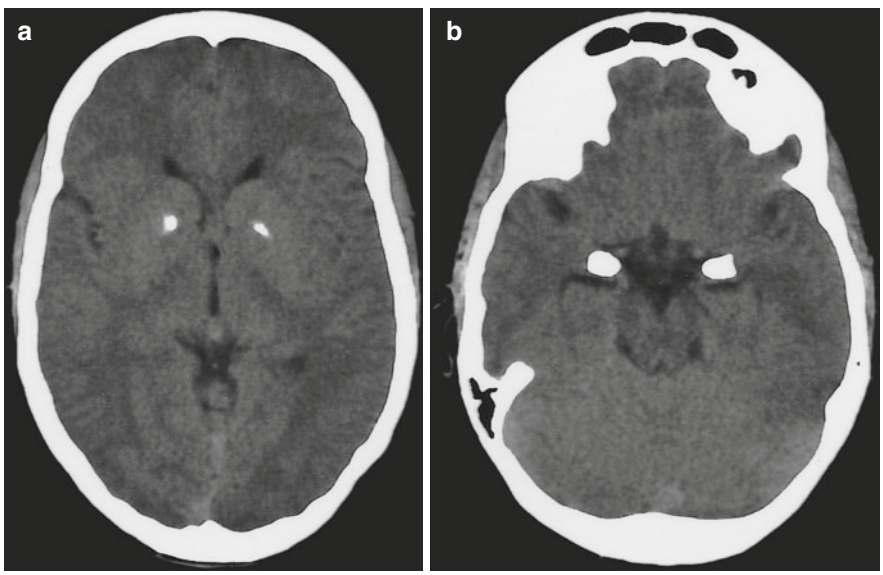

Fig. 9.72 CTs of a 15-year-old girl with Urbach-Wiethe disease demonstrating bilateral calcifications of the globus pallidus (**a**) and of the amygdalar (**b**) in the medial temporal lobe (Courtesy Michèl Willemsen, Nijmegen)

References

Acampora D, Merlo GR, Paleari L, Zerega B, Postiglione MP et al (1999) Craniofacial, vestibular and bone defects in mice lacking the *Distal-less*-related gene *Dlx5*. Development 126:3795–3809

Adelmann HB (1929a) Experimental studies on the development of the eye. I. The effect of the removal of median and lateral areas of the anterior end of the urodelan neural plate on the development of the eyes (*Triton teniatus* and *Amblystoma punctatum*). J Exp Zool 54:249–290

Adelmann HB (1929b) Experimental studies on the development of the eye. II. The eye-forming potencies of the median portions of the urodelan neural plate (*Triton teniatus* and *Amblystoma punctatum*). J Exp Zool 54:291–317

Adelmann HB (1930) Experimental studies on the development of the eye. III. The effect of the substrate ('Unterlagerung') on the heterotopic development of median and lateral strips of the anterior end of the neural plate of *Amblystoma*. J Exp Zool 57:223–281

Adelmann HB (1936a) The problem of cyclopia, part I. Q Rev Biol 11:116–182

Adelmann HB (1936b) The problem of cyclopia, part II. Q Rev Biol 11:284–364

Aeby A, Liu Y, De Tiège X, Denolin Y, David P, Balériaux D et al (2009) Maturation of thalamic radiations between 34 and 41 weeks' gestation: a combined voxel-based study and probabilistic tractography with diffusion tensor imaging. AJNR Am J Neuroradiol 30:1780–1786

Aicardi J (1998) Disorders of visual perception. In: Aicardi J (ed) Diseases of the nervous system in childhood, 2nd edn. Mac Keith, London, pp 675–688

Aicardi J, Chevrie JJ, Baraton J (1987) Agenesis of the corpus callosum. Handb Clin Neurol 50:149–173

Albin RL, Young AR, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci 12:366–375

Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 13:266–271

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381

Alheid GF, Heimer L (1988) New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. Neuroscience 27:1–39

Alheid GF, Heimer L, Switzer RC (1990) Basal ganglia. In: Paxinos G (ed) The human nervous system. Academic, San Diego, pp 483–582

Alheid GF, de Olmos JS, Beltramino CA (1995) Amygdala and extended amygdala. In: Paxinos G (ed) The rat nervous system, 2nd edn. Academic, San Diego, pp 495–578

Almqvist PM, Akesson E, Wahlberg LU, Pschera H, Seiger Å, Sundström E (1996) First trimester development of the human nigrostriatal dopamine system. Exp Neurol 139:227–237

Altman J (1969) Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. J Comp Neurol 137:433–457

Altman J, Bayer SA (1978a) Development of the diencephalon in the rat. I. Autoradiographic study of the time of origin and settling patterns of neurons of the hypothalamus. J Comp Neurol 182:945–972

Altman J, Bayer SA (1978b) Development of the diencephalon in the rat. II. Correlation of the embryonic development of the hypothalamus with the time of origin of its neurons. J Comp Neurol 192:973–994

Altman J, Bayer SA (1979a) Development of the diencephalon in the rat. IV. Quantitative study of the time of origin of neurons and the internuclear chronological gradients in the thalamus. J Comp Neurol 188:455–472

Altman J, Bayer SA (1979b) Development of the diencephalon in the rat. V. Thymidine-radiographic observations on internuclear and intranuclear gradients in the thalamus. J Comp Neurol 188:473–500

Altman J, Bayer SA (1979c) Development of the diencephalon in the rat. VI. Re-evaluation of the embryonic development of the thalamus on the basis of thymidine-radiographic datings. J Comp Neurol 188:501–524

Altman J, Bayer SA (1981) Development of the brain stem in the rat. V. Thymidine-radiographic study of the time of origin of neurons in the midbrain tegmentum. J Comp Neurol 198:677–716

Altman J, Bayer SA (1986) The development of the rat hypothalamus. Adv Anat Embryol Cell Biol 100:1–178

Amaral DG (1987) Memory: anatomical organization of candidate brain regions. In: Mountcastle VB, Plum F, Geiger SR (eds) Handbook of physiology, sect I: the nervous system, part 1, vol 5. American Physiological Society, Bethesda, pp 211–294

Amaral DG, Schumann CM, Nordahl CW (2008) Neuroanatomy of autism. Trends Neurosci 31:137–145

Andersen H, von Bülow FA, Mollgård K (1971) The early development of the pars distalis of the human foetal pituitary gland. Z Anat Entwicklungsgesch 135:117–138

Anderson SA, Eisenstat DD, Shi L, Rubinstein JLR (1997a) Interneuron migration from basal forebrain to neocortex: dependence on Dlx genes. Science 278:474–476

Anderson SA, Qiu M, Bulfone A, Eisenstat DD, Meneses JJ, Pedersen RA, Rubinstein JLR (1997b) Mutations of the homeobox genes *Dlx-1* and *Dlx-2* disrupt the striatal subventricular zone and differentiation of late born striatal neurons. Neuron 19:27–37

Anderson SA, Mione M, Yun K, Rubinstein JLR (1999) Differential origins of neocortical projection and local circuit neurons: role of Dlx genes in neocortical interneurogenesis. Cereb Cortex 9:646–654

Anderson SA, Marín O, Horn C, Jennings K, Rubinstein JLR (2001) Distinct cortical migrations from the medial and lateral ganglionic eminences. Development 128:353–363

Angevine JB Jr (1970) Time of neuron origin in the diencephalon of the mouse. An autoradiographic study. J Comp Neurol 139:129–188

Angevine JB Jr (1978) Embryogenesis and phylogenesis in the limbic system. In: Livingston KE, Hornykiewicz O (eds) Limbic mechanisms. The continuing evolution of the limbic system concept. Plenum, New York, pp 23–46

Apkarian P, Bour L, Barth PG (1993) A unique achiasmatic anomaly detected in non-albinos with misrouted retinal-fugal projections. Eur J Neurosci 6:501–507

Apkarian P, Bour L, Barth PG, Wenniger-Prick L, Verbeeten B (1995) Non-decussating retinal-fugal fibre syndrome. An inborn achiasmatic malformation with visuotopic misrouting, visual evoked potential ipsilateral asymmetry and nystagmus. Brain 118:1195–1216

Armstrong E (1990) Limbic thalamus: Anterior and mediodorsal nuclei. In: Paxinos G (ed) The Human Nervous System. Academic, San Diego, CA, pp 469–481

Asa SL, Kovacs K, Laszlo FA, Domokos I, Ezrin C (1986) Human fetal adenohypophysis. Histologic and immunocytochemical analysis. Neuroendocrinology 43:308–316

Asa SL, Kovacs K, Horvath E, Losinski NE, Laszlo FA, Domokos I, Halliday WC (1988) Human fetal adenohypophysis. Electron microscopic and ultrastructural immunocytochemical analysis. Neuroendocrinology 48:423–431

Asakura Y, Toyota Y, Muroya K, Kurosawa K, Aida N, Kawane H et al (2008) Endocrine and radiological studies in patients with molecularly confirmed CHARGE syndrome. J Clin Endocrinol Metab 93:920–924

Ashton W (1970) Retinal angiogenesis in the human embryo. Br Med Bull 26:103–106

Ashwell KWS, Waite PME (2004) Development of the peripheral nervous system. In: Paxinos G, Mai JK (eds) The Human Nervous System, 2nd edn. Elsevier, Amsterdam, pp 95–110

Atwell WJ (1926) The development of the hypophysis cerebri in man, with special reference to the pars tuberalis. Am J Anat 37:159–193

Aubert I, Brana C, Pellevoisin C, Giros B, Caillé I, Carles D et al (1997) Molecular anatomy of the development of the human substantia nigra. J Comp Neurol 379:72–87

Auladell C, Pérez-Sust P, Supèr H, Soriano E (2000) The early development of thalamocortical and corticothalamic projections in the mouse. Anat Embryol (Berl) 201:169–179

Aza-Blanc P, Kornberg TB (1999) *Ci*: A complex transducer of the hedgehog signal. Trends Genet 15:458–462

Baenziger O, Martin E, Steinlin M, Good M, Largo R, Burger R et al (1993) Early pattern recognition in severe perinatal asphyxia: a prospective MRI study. Neuroradiology 35:437–442

Bahnsen U, Oosting P, Swaab DF, Nahke P, Richter D, Schmale H (1992) A missense mutation in the vasopressin-neurophysin precursor gene cosegregates with human autosomal dominant neurohypophyseal diabetes insipidus. EMBO J 11:19–23

Bainbridge JW, Smith AJ, Barker SS, Robbie S, Henderson R, Balaggan K et al (2008) Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med 358:2231–2239

Ballabio A, Rugarli EI (2001) Kallmann syndrome. In: Scriver CR, Beaudet al, Sly WS, Valle D (eds) The Metabolic & Molecular Bases of Inherited Disease, 8th edn. McGraw-Hill, New York, pp 5729–5740

Barishak YR (2001) Embryology of the Eye and Its Adnexa, 2nd edn. Karger, Basel

Barkovich AJ (2000) Pediatric Neuroimaging, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, PA

Barkovich AJ, Norman D (1989) Absence of the septum pellucidum: a useful sign in the diagnosis of congenital brain malformations. Am J Radiol 152:353–360

Barkovich AJ, Quint DJ (1993) Middle interhemispheric fusion: an unusual variant of holoprosencephaly. AJNR Am J Neuroradiol 14:431–440

Barkovich AJ, Fram EK, Norman D (1989) Septo-optic dysplasia: MR imaging. Radiology 171:189–192

Barkovich AJ, Simon EM, Clegg NJ, Kinsman SL, Hahn JS (2002) Analysis of the cerebral cortex in holoprosencephaly with attention to the sylvian fissures. AJNR Am J Neuroradiol 23:143–150

Basel-Vanagaite L, Straussberg R, Ovadia H, Kaplan A, Magal N, Shorer Z et al (2004) Infantile bilateral striatal necrosis maps to chromosome 19q. Neurology 62:87–90

Bayer SA (1980) Quantitative radiographic analysis of neurogenesis in the rat amygdala. J Comp Neurol 194:845–875

Bayer SA (1983) [^{3}H]Thymidine-radiographic studies of neurogenesis in the rat olfactory bulb. Exp Brain Res 50:329–340

Bayer SA (1984) Neurogenesis in the rat neostriatum. Int J Dev Neurosci 2:163–175

Bayer SA (1985a) Neurogenesis in the olfactory tubercle and islands of Calleja in the rat. Int J Dev Neurosci 3:135–147

Bayer SA (1985b) Neurogenesis in the magnocellular basal telencephalic nuclei in the rat. Int J Dev Neurosci 3:229–243

Bayer SA (1986a) Neurogenesis in the anterior olfactory nucleus and its associated transition areas in the rat brain. Int J Dev Neurosci 4:225–249

Bayer SA (1986b) Neurogenesis in the rat primary olfactory cortex. Int J Dev Neurosci 4:251–271

Bayer SA, Altman J (1987a) Development of the preoptic area: time and site of origin, migratory routes, and settling of its neurons. J Comp Neurol 265:65–95

Bayer SA, Altman J (1987b) Directions in neurogenetic gradients and patterns of anatomical connections in the telencephalon. Prog Neurobiol 29:57–106

Bayer SA, Altman J (1995a) Neurogenesis and migration. In: Paxinos G (ed) The Rat Nervous System, 2nd edn. Academic, San Diego, CA, pp 1041–1078

Bayer SA, Altman J (1995b) Principles of neurogenesis, neuronal migration, and neural circuit formation. In: Paxinos G (ed) The Rat Nervous System, 2nd edn. Academic, San Diego, CA, pp 1079–1098

Bayer SA, Altman J, Russo RJ, Zhang X (1995) Embryology. In: Duckett S (ed) Pediatric Neuropathology. Williams & Wilkins, Baltimore, MD, pp 54–107

Belloni E, Muenke M, Roessler E, Traverso G, Siegel-Bartelt J, Frumkin A et al (1996) Identification of Sonic hedgehog as a candidate gene responsible for holoprosencephaly. Nat Genet 14:353–356

Bendavid C, Dupé V, Rochard L, Gicquel I, Dubourg C, David V (2010) Holoprosencephaly: An update on cytogenetic abnormalities. Am J Med Genet C Semin Med Genet 154C:86–92

Bergeron C, Kovacs K, Ezrin C, Mizzen C (1991) Hereditary diabetes insipidus: An immunohistochemical study of the hypothalamus and pituitary gland. Acta Neuropathol (Berl) 81:345–348

Bergquist H, Källén B (1954) Notes on the early histogenesis and morphogenesis of the central nervous system in vertebrates. J Comp Neurol 100:627–659

Berliner DL, Monti-Bloch L, Jennings-White C, Diaz-Sanchez V (1996) The functionality of the human vomeronasal organ (VNO): evidence for steroid receptors. J Steroid Biochem Mol Biol 58:259–265

Berman JI, Glass HC, Miller SP, Mukherjee P, Ferreiro DM, Barkovich AJ et al (2009) Quantitative fiber tracking analysis of the optic radiation correlates with visual performance in premature newborns. AJNR Am J Neuroradiol 30:120–124

Biesecker LG (2008) *GLI3* and the Pallister-Hall and Greig cephalopolysyndactyly syndromes. In: Epstein CJ, Erickson RP, Wynshaw-Boris A (eds) Inborn Errors of Development, 2nd edn. Oxford University Press, Oxford, pp 313–321

Blaas H-GK, Eriksson AG, Salvesen KÅ, Isaksen CV, Christensen B, Møllerløkken G, Eik-Nes SH (2002) Brains and faces in holoprosencephaly: pre- and postnatal description of 30 cases. Ultrasound Obstet Gynecol 19:24–38

Blakemore C, Molnár Z (1990) Factors involved in the establishment of specific interconnections between thalamus and cerebral cortex. Cold Spring Harb Symp Quant Biol 55:491–504

Boehm N, Roos J, Gasser B (1994) Luteinizing hormone-releasing hormone (LHRH)-expressing cells in the nasal septum of human fetuses. Brain Res Dev Brain Res 82:175–180

Bossy J (1980) Development of olfactory and related structures in staged human embryos. Anat Embryol (Berl) 161:225–236

Boyd JD (1956) Observations on the human pharyngeal hypophysis. J Endocrinol 14:66–77

Braak H, Braak E (1987) The hypothalamus of the human adult: chiasmatic region. Anat Embryol (Berl) 176:315–330

Braak H, Braak E (1992) Anatomy of the human hypothalamus (chiasmatic and tuberal regions). Prog Brain Res 93:3–16

Braddock SR, Grafe MR, Jones KL (1995) Development of the olfactory nerve: its relationship to the craniofacies. Teratology 51:252–256

Braisted JE, Catalano SM, Stimac R, Kennedy TE, Tessier-Lavigne M, Shatz CJ, O'Leary DDM (2000) Netrin-1 promotes thalamic axon growth and is required for proper development of the thalamocortical projection. J Neurosci 20:5792–5801

Brana C, Charron G, Aubert I, Carles D, Martin-Negrier ML, Trouette H et al (1995) Ontogeny of the striatal neurons expressing neuropeptide genes in the human fetus and neonate. J Comp Neurol 360:488–505

Brana C, Caillé I, Pellevoisin C, Charron G, Aubert I, Caron MG et al (1996) Ontogeny of the striatal neurons expressing the D_1 dopamine receptors in humans. J Comp Neurol 370:23–34

Brand S, Rakic P (1979) Genesis of the primate neostriatum: [^{3}H] Thymidine autoradiographic analysis of the time of neuron origin in the rhesus monkey. Neuroscience 4:767–778

Brand S, Rakic P (1984) Cytodifferentiation and synaptogenesis in the neostriatum of fetal and neonatal rhesus monkeys. Anat Embryol (Berl) 169:21–34

Braverman LE, Mancini JP, McGoldrick DM (1965) Hereditary idiopathic diabetes insipidus. Ann Intern Med 63:563–568

Brazel CY, Romanko MJ, Rothstein RP, Levison SW (2003) Roles of the mammalian subventricular zone in brain development. Prog Neurobiol 69:49–69

Brewer DB (1957) Congenital absence of the pituitary gland and its consequences. J Pathol Bacteriol 73:59–67

Brewer GJ, Fink JK, Hedera P (1999) Diagnosis and treatment of Wilson's disease. Semin Neurol 19:261–270

Brickman JM, Clements M, Tyrell R, McNay D, Woods K, Warner J et al (2001) Molecular effects of novel mutations in *Hesx1/HESX1* associated with human pituitary disorders. Development 128:5189–5199

Broaddus E, Patno D, Reid J, Chapa J, Traboulsi EI, Singh AD (2012) Prenatal imaging of the eye and ocular adnexae. In: Traboulsi EI (ed) Genetic diseases of the eye, 2nd edn. Oxford University Press, Oxford, pp 163–173

Brodsky MC, Hoyt WF, Hoyt CS, Miller NR, Lam BL (1995) Atypical retinochoroidal coloboma in patients with dysplastic optic discs and transsphenoidal encephaloceles. Arch Ophthalmol 113:624–628

Brooks BP, Traboulsi EI (2012) Congenital anomalies of the optic nerve. In: Traboulsi EI (ed) Genetic diseases of the eye, 2nd edn. Oxford University Press, Oxford, pp 124–149

Brown GK, Brown RM, Scholem RD, Kirby DM, Dahl H-HM (1989) The clinical and biochemical spectrum of human pyruvate dehydrogenase complex deficiency. Ann NY Acad Sci 573:360–368

Brown SA, Warburton D, Brown LY, Yu C, Roeder ER, Stengel-Rutkowski S et al (1998) Holoprosencephaly due to mutations in *ZIC2*, a homologue of *Drosophila odd-paired*. Nat Genet 20:180–183

Brückner G, Mares V, Biesold D (1976) Neurogenesis in the visual system of the rat: an autoradiographic investigation. J Comp Neurol 166:245–256

Bruyn GW (1977) Agenesis septi pellucidi, cavum septi pellucidi, cavum Vergae, and cavum veli interpositi. Handb Clin Neurol 30:299–316

Bulfone A, Puelles L, Porteus MH, Frohman MA, Martin GR, Rubinstein JLR (1993) Spatially restricted expression of *Dlx-1*, *Dlx-2*, (*Tes-1*), *Gbx-2*, and *Wnt-3* in the embryonic day 12.5 mouse forebrain defines potential transverse and longitudinal boundaries. J Neurosci 13:3155–3172

Bulfone A, Wang F, Hevner RF, Anderson SA, Cutforth T, Chen S et al (1998) An olfactory sensory map develops in the absence of normal projection neurons or GABAergic interneurons. Neuron 21: 1273–1282

Burmeister M, Novak J, Liang MY, Basu S, Ploder L, Hawes NL et al (1996) Ocular retardation mouse caused by *Chx10* homeobox null allele: impaired retinal progenitor proliferation and bipolar cell differentiation. Nat Genet 12:376–384

Butt SJ, Sousa VH, Fuccillo MV, Hjerling-Leffler J, Miyoshi G, Kimra S, Fishell G (2008) The requirement of Nkx2-1 in the temporal specification of cortical interneuron subtypes. Neuron 59:722–732

Campbell K (2003) Dorsal-ventral patterning in the mammalian telencephalon. Curr Opin Neurobiol 13:50–56

Camper S, Suh H, Raetzman L, Douglas K, Cushman L, Nasonkin I et al (2002) Pituitary gland development. In: Rossant J, Tam PPL (eds) Mouse development – patterning, morphogenesis, and organogenesis. Academic, San Diego, pp 499–518

Carson MJ, Slager UT, Steinberg RM (1977) Simultaneous occurrence of diabetes mellitus, diabetes insipidus, and optic atrophy in a brother and sister. Am J Dis Child 131:1382

Casarosa S, Fode C, Guillemot F (1999) *Mash1* regulates neurogenesis in the ventral telencephalon. Development 126:525–534

Cau E, Casarosa S, Guillemot F (2002) *Mash1* and *Ngn1* control distinct steps of determination and differentiation in the olfactory sensory neuron lineage. Development 129:1871–1880

Chédotal A, Rijli FM (2009) Transcriptional regulation of tangential neuronal migration in the developing forebrain. Curr Opin Neurobiol 193:139–145

Chevrie JJ, Aicardi J (1986) Aicardi syndrome. In: Pedley TA, Meldrum BS (eds) Recent advances in epilepsy, vol 3. Churchill Livingstone, Edinburgh, pp 189–210

Chiang C, Litingtung Y, Lee E, Young KE, Corden JL, Westphal H, Beachy PA (1996) Cyclopia and defective axial patterning in mice lacking *Sonic hedgehog* gene function. Nature 383:407–413

Chong BW, Newton TH (1993) Hypothalamic and pituitary pathology. Radiol Clin North Am 31:1147–1183

Chow CW, Haan EA, Goodman SI, Anderson RMD, Evans WA, Kleinschmidt-DeMasters BK et al (1988) Neuropathology in glutaric acidaemia type 1. Acta Neuropathol (Berl) 76:590–594

Chugani HT, Phelps ME (1986) Maturational changes in cerebral function in infants determined by 18 FDG positron emission tomography. Science 231:840–843

Clarke S, Miklossy J (1990) Occipital cortex in man: organization of callosal connections, related myelo- and cytoarchitecture, and putative boundaries of functional visual areas. J Comp Neurol 298:188–214

Cobos I, Broccoli V, Rubinstein JLR (2005a) The vertebrate ortholog of aristaless is regulated by Dlx genes in the developing forebrain. J Comp Neurol 483:292–303

Cobos I, Calcagnotto ME, Vilaythong AJ, Thwin MT, Noebels JL, Baraban SC, Rubinstein JLR (2005b) Mice lacking Dlx1 show subtype-specific loss of interneurons, reduced inhibition and epilepsy. Nat Neurosci 8:1059–1068

Cobos I, Borello U, Rubinstein JLR (2007) Dlx transcription factors promote migration through repression of axon and dendrite growth. Neuron 54:873–888

Cohen MM Jr (1989a) Perspectives on holoprosencephaly: part I. Epidemiology, genetics, and syndromology. Teratology 40:211–235

Cohen MM Jr (1989b) Perspectives on holoprosencephaly: Part III. Spectra, distinctions, continuities, and discontinuities. Am J Med Genet 34:271–288

Cohen MM Jr (2010) Hedgehog signaling update. Am J Med Genet A 152A:1875–1914

Cohen MM Jr, Shiota K (2002) Teratogenesis of holoprosencephaly. Am J Med Genet 109:1–15

Cohen MM Jr, Sulik KK (1992) Perspectives on holoprosencephaly: part II. Central nervous system, craniofacial anatomy, syndrome commentary, diagnostic approach, and experimental studies. J Craniofac Genet Dev Biol 12:196–244

Cohen NR, Taylor CJSH, Scott LB, Guillery RW, Soriano P, Furley AJW (1997) Errors in corticospinal axon guidance in mice lacking the neural cell adhesion molecule L1. Curr Biol 8:26–33

Colohan ART, Grady MS, Bonnin JM, Thorner MO, Kovacs K, Jane JA (1987) Ectopic pituitary gland simulating a suprasellar tumor. Neurosurgery 20:43–48

Colombo E, Galli R, Cossu G, Gécz J, Broccoli V (2004) Mouse orthologue of ARX, a gene mutated in several X-linked forms of mental retardation and epilepsy, is a marker of adult stem cells and forebrain GABAergic neurons. Dev Dyn 231:631–639

Colombo E, Collombat P, Colasante G, Bianchi M, Long J, Mansouri A, Rubinstein JLR (2007) Inactivation of Arx, the murine ortholog of the X-linked lissencephaly with ambiguous genitalia gene, leads to severe disorganization of the ventral telencephalon with impaired neuronal migration and differentiation. J Neurosci 27:4786–4798

Conklin JL (1968) The development of the human fetal adenohypophysis. Anat Rec 160:79–91

Conte I, Morcillo J, Bovolenta P (2005) Comparative analysis of *Six3* and *Six6* distribution in the developing and adult mouse brain. Dev Dyn 234:718–725

Cooper ERA (1945) The development of the human lateral geniculate body. Brain 68:222–239

Cooper ERA (1946) The development of the human substantia nigra. Brain 69:22–33
Cooper ERA (1950) The development of the thalamus. Acta Anat (Basel) 9:201–226
Corbin JG, Gaiano N, Machold RP, Langston A, Fishell G (2000) The *Gsh2* homeodomain gene controls multiple aspects of telecephalic development. Development 127:5007–5020
Corbin JG, Nery S, Fishell G (2001) Telencephalic cells take a tangent: non-radial migration in the mammalian forebrain. Nat Neurosci 4(Suppl):1177–1182
Cordero D, Marcucio R, Hu D, Gaffield W, Tapadia M, Helms JA (2004) Temporal perturbations in sonic hedgehog signaling elicit the spectrum of holoprosencephaly phenotypes. J Clin Invest 114:485–494
Corsellis JAN, Bruton CJ, Freeman-Browne D (1973) The aftermath of boxing. Psychol Med 3:270–303
Couly GF, Le Douarin NM (1987) Mapping of the early neural primordium in quail-chick chimeras. II. The prosencephalic neural plate and neural folds: implications for the genesis of cephalic congenital abnormalities. Dev Biol 120:198–214
Cremers CWRJ, Wijdeveld PGAB, Pinckers AJLG (1977) Juvenile diabetes mellitus, optic atrophy, hearing loss, diabetes insipidus, atonia of the urinary tract and bladder, and other abnormalities (Wolfram's syndrome): A review of 88 cases from the literature with personal observations on 3 new patients. Adv Paed Scand (Suppl) 264:3–16
Croen LA, Shaw GM, Lammer EJ (1996) Holoprosencephaly: Epidemiologic and clinical characteristics of a California population. Am J Med Genet 64:465–472
Crosby EC, Humphrey T (1941) Studies of the vertebrate telencephalon. II. The nuclear pattern of the anterior olfactory nucleus, tuberculum olfactorium and the amygdaloid complex in adult man. J Comp Neurol 74:309–352
Crosby EC, Woodburne RT (1940) The comparative anatomy of the preoptic area and the hypothalamus. Proc Assoc Res Nerv Ment Dis 20:52–169
Dacey DM (2000) Parallel pathways for spectral coding in primate retina. Annu Rev Neurosci 23:743–775
Dahmane N, Sánchez P, Gitton Y, Palma V, Sun T, Beyna M et al (2001) The sonic hedgehog-Gli pathway regulates dorsal brain growth and tumorigenesis. Development 128:5201–5212
Dahme M, Bartsch U, Martini R, Anliker B, Schachner M, Mantei N (1997) Disruption of the mouse L1 gene leads to malformations of the nervous system. Nat Genet 17:346–349
Daikoku S, Chikamori M, Adachi T, Maki Y (1982) Effect of basal diencephalon on the development of Rathke's pouch in rats: a study in combined organ culture. Dev Biol 90:198–202
Danesin C, Houart C (2012) A Fox stops the Wnt: implications for forebrain development and diseases. Curr Opin Genet Dev 22: 323–330
Danesin C, Peres JN, Johansson M, Snowden V, Cording A, Papalopulu N, Houart C (2009) Integration of telencephalic Wnt and hedgehog signaling center activities by Foxg1. Dev Biol 16:576–587
Darin N, Oldfors A, Moslemi A-R, Tulinius M (2001) The incidence of mitochondrial encephalomyopathies in childhood: Clinical features and morphological, biochemical, and DNA abnormalities. Ann Neurol 49:377–383
Dasen JS, Barbera JP, Herman TS, Connell SO, Olsen L, Ju B et al (2001) Temporal regulation of a paired-like homeodomain repressor/TLE corepressor complex and a related activator is required for pituitary organogenesis. Genes Dev 15:3193–3207
Dattani MT, Robinson JC (2000) The molecular basis for developmental disorders of the pituitary gland in man. Clin Genet 57: 337–346
Dattani MT, Martinez-Barbera JP, Thomas PQ, Brickman JM, Gupta R, Mårtensson IL et al (1998) Mutations in the homeobox gene *HESX1*/*Hesx1* associated with septo-optic dysplasia in human and mouse. Nat Genet 19:125–133
Dattani MT, Martinez-Barbera JP, Thomas PQ, Brickman JM, Gupta R, Wales JKH et al (1999) HESX1: a novel gene implicated in a familial form of septo-optic dysplasia. Acta Paediatr Suppl 88:49–54
de Carlos JA, López-Mascaraque L, Valverde F (1995) The telencephalic vesicles are innervated by olfactory placode-derived cells: a possible mechanism to induce neocortical development. Neuroscience 68:1167–1178
de Carlos JA, López-Mascaraque L, Valverde F (1996) Dynamics of cell migration from the lateral ganglionic eminence in the rat. J Neurosci 16:6146–6156
de Morsier G (1956) Etudes sur les dysraphies crânio-encéphaliques. III. Agénésie du septum lucidum avec malformation du tractus optique. La dysplasie septo-optique. Schweiz Arch Neurol Psychiatr 77:267–292
de Olmos J (1990) Amygdaloid nuclear gray complex. In: Paxinos G (ed) The human nervous system. Academic, San Diego, pp 583–710
de Olmos J (2004) Amygdala. In: Paxinos G, Mai JK (eds) The human nervous system, 2nd edn. Elsevier, Amsterdam, pp 739–868
de San M, Juan A (1856) Teratologia: falta total de los nervios olfactorios con anosmian en un individuo en quien existia un atrofia congenita de los testiculos y membro viril. El Siglo Med 3:211 (Quoted from Ballabio and Rugarli 2001)
Deacon TW, Pakzaban P, Isacson O (1994) The lateral ganglionic eminence is the origin of cells committed to striatal phenotypes: Neural transplantation and developmental evidence. Brain Res 668:211–219
Decker RE (1985) The ectopic pituitary gland in cases of craniopharyngiomas. Report of two cases. J Neurosurg 62:291–292
Dekaban A (1954) Human thalamus: an anatomical, developmental, and pathological study. II. Development of the human thalamic nuclei. J Comp Neurol 100:63–97
DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13:281–285
DeLong MR, Georgopoulos AP (1981) Motor functions of the basal ganglia. In: Brooks VB (ed) Handbook of physiology, sect 1: the nervous system, vol 2, Motor control. American Physiological Society, Bethesda, pp 1017–1061
Demb JB, Boynton GM, Heeger DJ (1998) Functional magnetic resonance imaging of early visual pathways in dyslexia. J Neurosci 18:6939–6951
DeMyer WE (1987) Holoprosencephaly (cyclopia-arhinencephaly). Handb Clin Neurol 50:225–244
DeMyer WE, Zeman W (1963) Alobar holoprosencephaly (arhinencephaly) with median cleft lip and palate: clinical, nosologic and electroencephalographic considerations. Confin Neurol 23:1–36
DeMyer WE, Zeman W, Palmer C (1964) The face predicts the brain: diagnostic significance of median anomalies for holoprosencephaly (arhinencephaly). Pediatrics 34:256–263
Depew MJ, Liu JK, Long JE, Presley R, Meneses JJ, Pedersen RA, Rubinstein JLR (1999) Dlx5 regulates regional development of the branchial arches and sensory capsules. Development 126:3831–3846
Dierickx K, Vandesande F (1977) Immunocytochemical localization of the vasopressinergic and ocytocinergic neurons in the human hypothalamus. Cell Tissue Res 184:15–27
Dodé C, Levilliers J, Dupont JM, de Paepe A, le Du N, Soussi-Yanicostas N et al (2003) Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome. Nat Genet 33:463–465
Dodé C, Teixeira L, Levelliers J et al (2006) Kallmann syndrome: mutations in genes encoding prokineticin-2 and prokineticin receptor-2. PLOS Genet 2:e175
Domené S, Roessler E, El-Jaick KB, Snir M, Brown JL, Vélez JI et al (2008) Mutations in the human SIX3 gene in holoprosencephaly are loss of function. Hum Mol Genet 17:3919–3928
Dou CL, Li S, Lai E (1999) Dual role of brain factor-1 in regulating growth and patterning of the cerebral hemispheres. Cereb Cortex 9:543–550

Dowling JE (1987) The retina: an approachable part of the brain. Belknap, Cambridge, MA

Drayer B, Burger P, Darwin R, Riederer S, Herfkens R, Johnson GA (1986) Magnetic resonance imaging of brain iron. Am J Neuroradiol 7:373–380

Droogleever Fortuyn AB (1912) Die Ontogenie der Kerne des Zwischenhirns beim Kaninchen. Arch Anat Physiol Anat Abt 36:303–352

Dufour A, Seibt J, Passante L, Depaepe V, Ciossek T, Frisén J et al (2003) Area specificity and topography of thalamocortical projections are controlled by ephrin/Eph genes. Neuron 391:453–465

Dulac C, Torello AT (2003) Molecular detection of pheromone signals in mammals: from genes to behaviour. Nat Rev Neurosci 4:551–562

Eagleson GW, Jenks BL, van Overbeeke AP (1986) The pituitary adrenocorticotropes originates from neural ridge tissue in *Xenopus laevis*. J Embryol Exp Morphol 95:1–14

Earle KL, Mitrofanis J (1996) Genesis and fate of the perireticular thalamic nucleus during early development. J Comp Neurol 367:246–263

Edison R, Muenke M (2003) The interplay of genetic and environmental factors in craniofacial morphogenesis: holoprosencephaly and the role of cholesterol. Congenit Anom (Kyoto) 43:1–21

Eisenstat DD, Liu JK, Mione M, Zhong W, Yu G, Anderson SA et al (1999) DLX-1, DLX-2, and DLX-5 expression define distinct stages of basal forebrain differentiation. J Comp Neurol 414:217–237

El-Jaick KB, Powers SE, Bartholin L, Myers KR, Hahn J, Orioli IM et al (2007) Functional analysis of mutations in TGIF associated with holoprosencephaly. Mol Genet Metab 90:97–111

Ellison-Wright Z, Heyman I, Frampton I, Rubia K, Chitnis X, Ellison-Wright I et al (2004) Heterozygous PAX6 mutation, adult brain structure and fronto-striato-thalamic function in a human family. Eur J Neurosci 19:1505–1512

England SJ, Blanchard GB, Mahadevan L, Adams RJ (2006) A dynamic fate map of the forebrain shows how vertebrate eyes form and explains two causes of cyclopia. Development 133:4613–4617

Favor J, Sandulache R, Neuhäuser-Klaus A, Pretsch W, Chatterjee B, Senft E et al (1996) The mouse *Pax2*^{1Neu} mutation is identical to a human *PAX2* mutation in a family with renal-coloboma syndrome and results in developmental defects of the brain, ear, eye, and kidney. Proc Natl Acad Sci U S A 93:13870–13875

Fazzi E, Signonni SG, Scelsa B, Bova SM, Lanzi G (2003) Leber's congenital amaurosis: an update. Eur J Pediatr Neurol 7:13–22

Feldman B, Gates MA, Egan ES, Dougan ST, Rennebeck G, Sirotkin HI et al (1998) Zebrafish organizer development and germ-layer formation require nodal-related signals. Nature 395:181–185

Fentress JC, Stanfield BB, Cowan WM (1981) Observations on the development of the striatum in mice and rats. Anat Embryol (Berl) 163:275–298

Fernández-Alvarez E, Aicardi J (2001) Movement disorders in children. Mac Keith, London

Ferreyra HA, Heckenlively JR (2012) Retinitis pigmentosa. In: Traboulsi EI (ed) Genetic diseases of the eye, 2nd edn. Oxford University Press, Oxford, pp 381–392

Fertuzinhos S, Krsnik Z, Imamura Kawasawa Y, Rašin M-R, Kwan KY, Chen J-G et al (2009) Selective depletion of molecularly defined cortical interneurons in human holoprosencephaly with severe striatal hypoplasia. J Neurosci 19:2196–2207

Field GD, Chichilnisky EJ (2007) Information processing in the primate retina: circuitry and coding. Annu Rev Neurosci 30:1–30

Flames N, Pla R, Gelman DM, Rubinstein JLR, Puelles L, Marín O (2007) Delineation of multiple subpallial progenitor domains by the combinatorial expression of transcriptional codes. J Neurosci 27:9682–9695

Flandin P, Kimura S, Rubinstein JLR (2010) The progenitor zone of the ventral medial ganglionic eminence requires Nkx2-1 to generate most of the globus pallidus but few neocortical interneurons. J Neurosci 30:2812–2823

Florell SR, Townsend JJ, Klatt EC, Pysher TJ, Coffin CM, Wittwer CT, Viskochil DH (1996) Aprosencephaly and cerebellar dysgenesis in sibs. Am J Med Genet 63:542–548

Franco B, Guiolo S, Pragliola A, Incerti B, Bardoni B, Tonlorenzi R et al (1991) A gene deleted in Kallmannn's syndrome shares homology with neural cell adhesion and axonal pathfinding molecules. Nature 353:529–536

Franz T (1994) Extra-toes (Xt) homozygous mutant mice demonstrate a role for the Gli-3 gene in the development of the forebrain. Acta Anat (Basel) 150:38–44

Freeman TB, Spence MS, Boss BD, Spector DH, Strecker RE, Ola CW, Kordower JH (1991) Development of dopaminergic neurons in the human substantia nigra. Exp Neurol 113:344–353

Friede R (1989) Developmental neuropathology, 2nd edn. Springer, Berlin/Heidelberg/New York

Fuhrmann S, Chow L, Reh TA (2000) Molecular control of cell diversification in the vertebrate retina. In: Fini ME (ed) Vertebrate eye development. Springer, Berlin/Heidelberg/New York, pp 69–91

Furuta Y, Piston DW, Hogan BLM (1997) Bone morphogenetic proteins (BMPs) as regulators of dorsal forebrain development. Development 124:2203–2212

Gabreëls BATF (1998) Vasopressin secretion disorders in diabetes insipidus, Prader-Willi syndrome and Wolfram syndrome. University of Amsterdam, Thesis

Gabreëls BATF, Swaab DF, Seidah NG, van Duijnhoven HLP, Martens GJM, van Leeuwen FW (1994) Differential expression of the neuroendocrine polypeptide 7B2 in hypothalami of Prader-(Labhart)-Willi syndrome patients. Brain Res 657:281–293

Gabreëls BATF, Swaab DF, de Kleijn DPV, Seidah NG, van de Loo J-W, van de Ven WJM et al (1998) Attenuation of the polypeptide 7B2, prohormone convertase PC2 and vasopressin in the hypothalamus of some Prader-Willi patients: Indications for a processing defect. J Clin Endocrinol Metab 83:591–599

Gage PJ, Suh H, Camper SA (1999) Dosage requirement of Pitx2 for development of multiple organs. Development 126:4643–4651

Garcia CA, Duncan C (1977) Atelencephalic microcephaly. Dev Med Child Neurol 19:227–232

García-López M, Abellán A, Legaz I, Rubinstein JLR, Puelles L, Medina L (2008) Histogenetic compartments of the mouse centromedial and extended amygdala based on gene expressio patterns during development. J Comp Neurol 506:46–74

Garel S, Yun K, Grosschedl R, Rubinstein JLR (2002) The early topography of thalamocortical projections shifted in *Ebf1* and *Dlx1/2* mutant mice. Development 129:5621–5634

Gastaut H, Lammers HJ (1961) Anatomie du rhinencéphale. Masson, Paris

Gelman DM, Martini FJ, Nóbrega-Pereira S, Pierani A, Kessaris M, Marín O (2009) The embryonic preoptic area is a novel source of cortical GABAergic interneurons. J Neurosci 29:9380–9389

Geoffroy Saint-Hilaire I (1832–1837) Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux (Traité de Tératologie). Baillière, Paris

Gérard M, Abitbol M, Delezoide A-L, Dufier J-L, Mallet J, Vekemans M (1995) PAX-genes expression during human embryonic development, a preliminary report. C R Acad Sci Paris 318:57–66

Gerfen CR, Wilson CJ (1996) The basal ganglia. In: Swanson LW, Björklund A, Hökfelt T (eds) Handbook of chemical neuroanatomy, vol 12, Integrated systems of the CNS, part III. Elsevier, Amsterdam, pp 371–468

Ghosh A, Shatz CJ (1992) Pathfinding and target selection by developing geniculocortical axons. J Neurosci 12:39–55

Gilbert M (1935) The early development of the human diencephalon. J Comp Neurol 62:81–115

Glaser T, Cai J, Epstein J, Walton DS, Jepeal L, Maas RL (1995) *PAX6* mutations in aniridia. In: Wiggs JR (ed) Molecular genetics of eye diseases. Wiley, New York, pp 51–82

Golden JA (1998) Holoprosencephaly: a defect in brain patterning. J Neuropathol Exp Neurol 57:991–999

Goldman PS, Nauta WJH (1977) An intricately patterned prefrontocaudate projection in the rhesus monkey. J Comp Neurol 171:369–386

Goldman-Rakic PS (1981) Prenatal formation of cortical input and development of cytoarchitectonic compartments in the neostriatum of the rhesus monkey. J Neurosci 1:721–735

Goldman-Rakic PS (1982) Cytoarchitectonic heterogeneity of the primate neostriatum: subdivision into *island* and *matrix* cellular compartments. J Comp Neurol 205:398–413

González G, Puelles L, Medina L (2002) Organization of the mouse dorsal thalamus based on topology, calretinin immunostaining, and gene expression. Brain Res Bull 57:439–442

Goodman SI, Frerman FE (2001) Organic acidemia due to defects in lysine oxidation: 2-Ketoadipic acidemia and glutaric acidemia. In: Scriver CR, Beaudet al, Sly WS, Valle D (eds) The metabolic & molecular bases of inherited disease, 8th edn. McGraw-Hill, New York, pp 2195–2206

Goodman SI, Norenberg MD, Shikes RH, Breslick DJ, Moe PG (1977) Glutaric aciduria: biochemical and morphological considerations. J Pediatr 90:746–750

Goodman SI, Stein DE, Schlesinger S, Christensen E, Schwartz M, Greenberg CR, Elpeleg ON (1998) Glutaryl-CoA dehydrogenase mutations in glutaric acidemia (type 1): review and report of thirty novel mutations. Hum Mutat 12:141–144

Gorski RA, Gordon JH, Shryne JE, Southam AM (1978) Evidence for a morphological sex difference within the medial preoptic area of the rat brain. Brain Res 148:333–346

Graw J (2000) Mouse mutants for eye development. In: Fini ME (ed) Vertebrate eye development. Springer, Berlin/Heidelberg/New York, pp 219–256

Graw J (2003) The genetic and molecular basis of congenital eye defects. Nat Rev Genet 4:876–888

Graybiel AM (1984) Correspondence between the dopamine islands and striosomes of the mammalian striatum. Neuroscience 13:1157–1187

Graybiel AM (1986) Neuropeptides in the basal ganglia. In: Martin JD, Barchas JD (eds) Neuropeptides in neurologic and psychiatric disease. Raven, New York, pp 135–161

Graybiel AM (1990) Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci 13:244–254

Graybiel AM, Ragsdale CW Jr (1978) Histochemically distinct compartments in the striatum of human, monkey and cat demonstrated by acetylcholinesterase staining. Proc Natl Acad Sci U S A 75:5723–5726

Graybiel AM, Rauch SL (2000) Toward a neurobiology of obsessive-compulsive disorder. Neuron 28:343–347

Graybiel AM, Pickel VM, Joh TH, Reis DJ, Ragsdale CW Jr (1981) Direct demonstration of correspondence between the dopamine islands and acetylcholinesterase patches in the developing striatum. Proc Natl Acad Sci U S A 78:5871–5875

Graziadei PP, Monti-Graziadei AG (1992) The influence of the olfactory placode on the development of the telencephalon in *Xenopus laevis*. Neuroscience 46:617–629

Greig DM (1926) Oxycephaly. Edinburgh Med J 33:189–218

Gribnau AAM, Geysberts LGM (1981) Developmental stages in the rhesus monkey (Macaca mulatta). Adv Anat Embryol Cell Biol 68:1–84

Gribnau AAM, Geysberts LGM (1985) Morphogenesis of the brain in staged rhesus monkey embryos. Adv Anat Embryol Cell Biol 91:1–69

Grindley JC, Davidson DR, Hill RE (1995) The role of *Pax-6* in eye and nasal development. Development 121:1433–1442

Grindley JC, Hargett LK, Hill RE, Ross A, Hogan BL (1997) Disruption of PAX6 function in mice homozygous for the *Pax6/Sey-1/Neu* mutation produces abnormalities in the early development and regionalization of the diencephalon. Mech Dev 64:111–126

Gripp KW, Edwards MC, Mowat D, Meinecke P, Richieri-Costa A, Zackai EH et al (1998) Mutations in the transcription factor TGIF in holoprosencephaly. Am J Hum Genet 63:A32

Grove EA, Tole S, Limon J, Yip L, Ragsdale CW (1998) The hem of the embryonic cerebral cortex is defined by the expression of multiple *Wnt* genes and is compromised in *Gli3*-deficient mice. Development 125:2315–2325

Guillemot F, Lo LC, Johnson JE, Auerbach A, Anderson DJ, Joyner AL (1993) Mammalian achaete-scute homolog 1 is required for the early development of olfactory and autonomic neurons. Cell 75:463–476

Guillery RW, Okoro AN, Witkop CJ (1975) Abnormal visual pathways in the brain of the human albino. Brain Res 96:373–377

Gulisano M, Broccoli V, Pardini C, Boncinelli E (1996) Emx1 and Emx2 show different patterns of expression during proliferation and differentiation of the developing cerebral cortex in the mouse. Eur J Neurosci 8:1037–1050

Gulyas B, Ottoson D, Roland PE (1993) Functional organization of the human visual cortex. Pergamon, Oxford

Haber SN, Gdowski MJ (2004) The basal ganglia. In: Paxinos G, Mai JK (eds) The human nervous system, 2nd edn. Elsevier, Amsterdam, pp 676–738

Hahn JS, Barnes PD (2010) Neuroimaging advances in holoprosencephaly: refining the spectrum of the midline malformation. Am J Med Genet C Semin Med Genet 154C:120–132

Hahn JS, Barnes PD, Clegg NJ, Stashinko EE (2010) Septopreoptic holoprosencephaly: a mild subtype associated with midline craniofacial anomalies. AJNR Am J Neuroradiol 31:1596–1601

Halpern M (1987) The organization and function of the vomeronasal system. Annu Rev Neurosci 10:325–362

Hamilton WJ, Mossman HW (1972) Hamilton, Boyd and Mossman's human embryology, 4th edn. Heffer, Cambridge

Hanaway J, McConnell JA, Netsky MG (1971) Histogenesis of the substantia nigra, ventral tegmental area of Tsai and interpeduncular nucleus: an autoradiographic study of the mesencephalon in the rat. J Comp Neurol 142:59–74

Hardelin J-P (2001) Kallmann syndrome: towards molecular pathogenesis. Mol Cell Endocrinol 179:75–81

Hardelin J-P, Dodé C (2008) *KAL1*, *FGFR1*, *PROKR2*, *PORK2* and Kallmann syndrome. In: Epstein CJ, Erickson RP, Wynshaw-Boris A (eds) Inborn errors of development, 2nd edn. Oxford University Press, Oxford, pp 482–490

Hardelin J-P, Julliard AK, Moniot B, Soussi-Yanicostas N, Verney C, Schwanzel-Fukuda M et al (1999) Anosmin-1 is a regionally restricted component of basement membranes and interstitial matrices during organogenesis: implications for the developmental anomalies of X chromosome-linked Kallmann syndrome. Dev Dyn 215:26–44

Harris RM, Hendrickson AE (1978) Local circuit neurons in the rat ventrobasal complex – a GABA immunocytochemical study. Neuroscience 21:229–236

Harris CP, Townsend JJ, Norman MG, White VA, Viskochil DH, Pysher TJ, Klatt EC (1994) Atelencephalic aprosencephaly. J Child Neurol 9:412–416

Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KHL, Gitschier J (2003) Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. N Engl J Med 348:33–40

Hébert JM, Mishina Y, McConnell SK (2002) BMP signaling is required locally to pattern the dorsal telencephalic midline. Neuron 35:1029

Hébert JM, Lin M, Partanen J, Rossant J, McConnell SK (2003) FGF signaling through FGFR1 is required for olfactory bulb morphogenesis. Development 130:1101–1111

Heimer L (1976) The olfactory cortex and the ventral striatum. In: Livingston KE, Hornykiewicz O (eds) Limbic mechanisms: the

continuing evolution of the limbic system concept. Plenum, New York, pp 95–187
Heimer L (2000) Basal forebrain in the context of schizophrenia. Brain Res Rev 31:205–235
Heimer L, Switzer RD, Van Hoesen GW (1982) Ventral striatum and ventral pallidum. Components of the motor system? Trends Neurosci 5:83–87
Heimer L, de Olmos J, Alheid GF, Záborsky L (1991) "Perestroika" in the basal forebrain: opening the border between neurology and psychiatry. Prog Brain Res 87:109–165
Heimer L, Harlan RE, Alheid GF, Garcia MM, de Olmos J (1997) Substantia innominata: a notion which impedes clinical-anatomical correlations in neuropsychiatric disorders. Neuroscience 76:957–1006
Hellström A, Aronsson M, Axelson C, Kyllerman M, Kopp S, Steffenberg S et al (2000) Children with septo-optic dysplasia – how to improve and sharpen the diagnosis. Horm Res 53(Suppl 1):19–25
Hendry SH, Reid RC (2000) The koniocellular pathway in primate vision. Annu Rev Neurosci 23:127–153
Herrick CJ (1910) The morphology of the forebrain in Amphibia and Reptilia. J Comp Neurol 20:413–545
Hertwig P (1942) Neue Mutationen und Koppelungsgruppen bei der Hausmaus. Z Indukt Abstammungs-Vererbungsl 80:220–246
Hevner RF (2000) Development of connections in the human visual system during fetal midgestation: a DiI-tracing study. J Neuropathol Exp Neurol 59:385–392
Hevner RF, Shi L, Justice N, Hsueh Y, Sheng M, Smiga S et al (2001) *Tbr1* regulates differentiation of the preplate and layer 6. Neuron 29:353–366
Hevner RF, Miyashita E, Rubinstein JLR (2002) Cortical and thalamic axon pathfinding defects in Tbr1, Gbx2, and Pax6 mutant mice: evidence that cortical and thalamic axons interact and guide each other. J Comp Neurol 447:8–17
Hewitt W (1958) The development of the human caudate and amygdaloid nucleus. J Anat (Lond) 92:377–382
Hewitt W (1961) The development of the human internal capsule and lenticular nucleus. J Anat (Lond) 55:191–199
Hill JM, Switzer RC (1984) The regional distribution and cellular localization of iron in the rat brain. Neuroscience 11:595–603
Hill RE, Favor J, Hogan BLM, Ton CCT, Saunders GF, Hanson IM et al (1991) Mouse *Small eye* results from mutations in a paired-like homeobox-containing gene. Nature 354:522–525
Hinds JW (1968a) Autoradiographic study of histogenesis in the mouse olfactory bulb. I. Time of origin of neurons and neuroglia. J Comp Neurol 134:287–304
Hinds JW (1968b) Autoradiographic study of the histogenesis in the mouse olfactory bulb. II. Cell proliferation and migration. J Comp Neurol 134:305–322
Hinrichsen KV (1990) Augenentwicklung. In: Hinrichsen KV (ed) Humanembryologie. Lehrbuch und Atlas der vorgeburtlichen Entwicklung des Menschen. Springer, Berlin/Heidelberg/New York, pp 477–500
Hirai T, Jones EG (1989) A new parcellation of the human thalamus on the basis of histochemical staining. Brain Res Rev 14:1–34
Hirsch N, Grainger RM (2000) Induction of the lens. In: Fini ME (ed) Vertebrate eye development. Springer, Berlin/Heidelberg/New York, pp 51–68
His W (1889) Die Formentwickelung des menschlichen Vorderhirns vom Ende des ersten bis zum Beginn des dritten Monats. Abh Kön Sächs Ges Wiss Math Phys Kl 15:675–735
His W (1893) Vorschläge zur Eintheilung des Gehirns. Arch Anat Physiol Anat Abt 17:172–179
Hitchcock PF, Hickey TL (1980) Prenatal development of the human lateral geniculate nucleus. J Comp Neurol 194:395–411
Ho VB, Chuang HS, Rovira MJ, Koo B (1995) Juvenile Huntington disease: CT and MR features. AJNR Am J Neuroradiol 16: 1405–1412
Hochstetter F (1919) Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns. I. Teil, Deuticke
Hoffmann GF, Athanassopoulos S, Burlina AB, Duran M, de Klerck JBC, Lehnert W et al (1996) Clinical course, early diagnosis, treatment and prevention of disease in glutaryl-CoA dehydrogenase deficiency. Neuropediatrics 27:115–123
Hogan BL, Horsburgh G, Cohen J, Hetherington CM, Fisher G, Lyon MF (1986) *Small eye* (*Sey*): a homozygous lethal mutation on chromosome 2 which affects the differentiation of both lens and nasal placodes in the mouse. J Embryol Exp Neurol 97:95–110
Hogan BL, Hirst EM, Horsburgh G, Hetherington CM (1988) *Small eye* (*Sey*): a mouse model for the genetic analysis of craniofacial abnormalities. Development 103:115–119
Holt DJ, Graybiel AM, Saper CB (1997) Neurochemical architecture of the human striatum. J Comp Neurol 384:1–25
Holzschuh J, Hauptmann G, Driever W (2003) Genetic analysis of the roles of Hh, FGF8, and nodal signaling during catecholaminergic system development in the zebrafish brain. J Neurosci 23:5507–5519
Hongo T, Hakuba A, Shiota K, Naruse I (2000) Suckling dysfunction caused by defects in the olfactory system in genetic arhinencephalic mice. Biol Neonate 78:293–299
Hoon AH Jr, Belcito KM, Nagae-Poetscher LM (2003) Neuroimaging in spasticity and movement disorders. J Child Neurol 18:S25–S39
Hori A (1983) A brain with two hypophyses in median cleft face syndrome. Acta Neuropathol (Berl) 59:150–154
Hori A, Schmidt D, Feyerabend B (1995) Pharyngosellar pituitary: a rare developmental anomaly of the pituitary gland. Acta Neuropathol (Berl) 89:459–463
Hori A, Schmidt D, Rickels E (1999a) Pharyngeal pituitary: development, malformation, and tumorigenesis. Acta Neuropathol (Berl) 98:262–272
Hori A, Schmidt D, Kuebber S (1999b) Immunohistochemical survey of migration of human anterior pituitary cells in developmental, pathological, and clinical aspects: a review. Micr Res Technol 46:59–68
Horsford DJ, Hanson I, Freund C, McInnes RR, van Heyningen V (2001) Transcription factors in eye disease and ocular development. In: Scriver CR, Beaudet al, Sly WS, Valle D (eds) The metabolic & molecular bases of inherited disease. McGraw-Hill, New York, pp 5987–6032
Houart C, Westerfield M, Wilson SW (1998) A small population of anterior cells patterns the forebrain during zebrafish gastrulation. Nature 391:788–792
Houart C, Caneparo L, Heisenberg C-P, Take-Uchi M, Wilson SW (2002) Establishment of the telencephalon during gastrulation by local antagonism of Wnt signaling. Neuron 35:255–265
Hubel DH, Wiesel TN (1977) Functional architecture of macaque monkey visual cortex. Proc R Soc Lond B 198:1–59
Hubel DH, Wiesel TN, LeVay S (1977) Plasticity of ocular dominance columns in monkey striate cortex. Philos Trans R Soc Lond B 278:377–409
Humphrey T (1940) The development of the olfactory and the accessory olfactory formations in human embryos and fetuses. J Comp Neurol 73:431–468
Humphrey T (1967) The development of the human tuberculum olfactorium during the first three months of life. J Hirnforsch 9:437–469
Humphrey T (1968) The development of the human amygdala during early embryonic life. J Comp Neurol 132:135–166
Humphrey T (1972) The development of the amygdaloid complex. In: Eleftheriou BE (ed) The neurobiology of the amygdala. Plenum, New York, pp 21–77
Hynes M, Rosenthal A (1999) Specification of dopaminergic and serotonergic neurons in the vertebrate CNS. Curr Opin Neurol 9:26–36
Ikeda H, Niizuma H, Suzuki J, Takabayashi T, Ozawa N (1987) A case of cebocephaly-holoprosencephaly with aberrant adenohypophysis. Childs Nerv Syst 3:251–254

Ikeda H, Suzuki J, Sasano N, Niizumi H (1988) The development of morphogenesis of the human pituitary gland. Anat Embryol (Berl) 178:327–336

Ippel PF, Breslau-Siderius EJ, Hack WWM, van der Blij HF, Bouve S, Bijlsma JB (1998) Atelencephalic microcephaly: a case report and review of the literature. Eur J Pediatr 157:493–497

Ito M, Mori Y, Oiso Y, Saito H (1991) A single base substitution in the coding region for neurophysin II associated with familial central diabetes insipidus. J Clin Invest 87:725–728

Itoh K, Suzuki K, Bise K, Itoh H, Mehraein P, Weis S (2001) Apoptosis in the basal ganglia of the developing human nervous system. Acta Neuropathol (Berl) 101:92–100

Izumi Y, Tatsumi K, Okamoto S, Hosokawa A, Ueno S, Fukui H, Amino N (1999) A novel mutation of the *KAL1* gene in Kallmann syndrome. Endocrinol J 46:651–658

Izumi Y, Tatsumi K, Okamoto S, Ogawa T, Hosokawa A, Matsuo T et al (2001) Analysis of the *KAL1* gene in 19 Japanese patients with Kallmann syndrome. Endocrinol J 48:143–149

Jansonius NM, van der Vliet AM, Cornelissen FW, Pott JWR, Kooijman AC (2001) A girl without a chiasm: electrophysiologic and MRI evidence for the absence of crossing optic nerve fibers in a girl with a congenital nystagmus. J Neuroophthalmol 21: 26–29

Johnston MV, Hoon AH (2000) Possible mechanisms in infants for selective basal ganglia damage from asphyxia, kernicterus, or mitochondrial encephalopathies. J Child Neurol 15:588–591

Jones EG (1985) The thalamus. Plenum, New York

Jones L, López-Bendito G, Gruss P, Stoykova A, Molnár Z (2002) *Pax6* is required for the normal development of the forebrain axonal connections. Development 129:5041–5052

Juranek J, Filipek PA, Berenji GR, Modahl C, Osana K, Spence MA (2006) Association between amygdala volume and anxiety level: magnetic resonance imaging (MRI) study in autistic children. J Child Neurol 21:1051–1058

Kahle W (1969) Die Entwicklung der menschlichen Großhirnhemisphäre. Springer, Berlin/Heidelberg/New York

Kakita A, Wakabayashi K, Sekizuka N, Takahashi H (1997) Cyclopia: histogenesis of the single optic nerve. Acta Neuropathol (Berl) 94: 509–513

Kakita A, Hayashi S, Arakawa M, Takahashi H (2001) Aprosencephaly: histopathological features of the rudimentary forebrain and retina. Acta Neuropathol (Berl) 102:110–116

Kallmann FJ, Schoenfeld WA, Barrera SE (1944) The genetic aspects of primary eunuchoidism. Am J Ment Defic 48:203–236

Kalsbeek A, Voorn P, Buys RM, Pool CW, Uylings HBM (1988) Development of the dopaminergic innervation in the prefrontal cortex of the rat. J Comp Neurol 269:58–72

Kang S, Graham JM Jr, Olney AH, Biesecker LG (1997) GLI3 frameshift mutations cause autosomal dominant Pallister-Hall syndrome. Nat Genet 15:266–268

Kaplan E (2004) The M, P, and K pathways of the primate visual system. In: Chalupa LM, Werner JS (eds) The visual neurosciences. MIT, Cambridge, MA, pp 481–493

Karstensen HG, Tommerup N (2012) Isolated and syndromic forms of congenital anosmis. Clin Genet 81:210–215

Kato M, Dobyns WB (2005) X-linked lissencephaly with abnormal genitalia as a tangential migration disorder causing intractable epilepsy: proposal for a new term, 'interneuronopathy'. J Child Neurol 20:392–397

Kawano H, Fukuda T, Kubo K, Horie M, Uyemura K, Takeuchi K et al (1999) Pax-6 is required for thalamocortical pathway formation in fetal rats. J Comp Neurol 408:147–160

Kelley RI, Roessler E, Hennekam RCM, Feldman GL, Kosaki K, Jones MC et al (1996) Holoprosencephaly in RSH/Smith-Lemli-Opitz syndrome: does abnormal cholesterol metabolism affect the function of *Sonic Hedgehog*? Am J Med Genet 66:478–484

Kemp JM, Powell TPS (1970) The cortico-striate projection in the monkey. Brain 93:525–546

Kemper TL, Bauman ML (1993) The contribution of neuropathologic studies to the understanding of autism. Neurol Clin 11:175–187

Kerryson JB, Newman NJ (2007) Genetic causes of blindness. In: Schapira AHV (ed) Neurology and clinical neuroscience. Mosby Elsevier, Philadelphia, pp 274–284

Keyser AJM (1972) The development of the diencephalon of the Chinese hamster. Acta Anat (Basel) 83(Suppl 59):1–178

Keyser AJM (1979) Development of the hypothalamus in mammals. An investigation into its morphological position during ontogenesis. In: Morgane PJ, Panksepp J (eds) Handbook of the hypothalamus, ol 1: anatomy of the hypothalamus. Dekker, New York, pp 65–136

Khan AA, Wadhwa S, Pandey RM, Bijlani V (1993) Prenatal human lateral geniculate nucleus: a quantitative light microscopic study. Dev Neurosci 15:403–409

Khan AA, Wadhwa S, Bijlani V (1994) Development of the human lateral geniculate nucleus: an electron microscopic study. Int J Dev Neurosci 7:661–672

Kiecker C, Lumsden A (2012) The role of organizers in patterning the nervous system. Annu Rev Neurosci 35:347–367

Kim TS, Cho S, Dickson DW (1990) Aprosencephaly: review of the literature and report of a case with cerebellar hypoplasia, pigmented epithelial cyst and Rathke's cleft cyst. Acta Neuropathol (Berl) 79:424–431

Kim HG, Kurth I, Lan F, Meliciani I, Wenzel W, Eom SH et al (2008) Mutations in CHD7, encoding a chromatin-remodeling protein, cause idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. Am J Hum Genet 83:511–519

Kimura S, Hara M, Nezu A, Osaka H, Yamazaki S, Saitoh U (1994) Two cases of glutaric aciduria type 1: clinical and neuropathological findings. J Neurol Sci 123:38–43

Kimura S, Hara Y, Pineau T, Fernandez-Salguero P, Fox CH, Ward JM, Gonzalez FJ (1996) The *Tlebp* null mouse: thyroid-specific enhancer-binding protein is essential for the organogenesis of the thyroid, lung, ventral forebrain, and pituitary. Genes Dev 10:60–69

Kinney HC, Armstrong DD (1997) Perinatal neuropathology. In: Graham DI, Lantos PL (eds) Greenfield's neuropathology, 6th edn. Arnold, London, pp 536–599

Kioussi C, Briata P, Baek SH, Rose DW, Hamblet NS, Herman T et al (2002) Identification of a Wnt/Dvl/beta-Catenin – Pitx2 pathway mediating cell-type-specific proliferation during development. Cell 111:673–685

Kishi K (1987) Golgi studies on the development of granule cells of the rat olfactory bulb with reference to migration in the subependymal layer. J Comp Neurol 258:112–124

Kitamura K, Miura H, Miyagawa-Tomita S, Yanazawa M, Katoh-Fukui Y, Suzuki R et al (1999) Mouse Pitx2 deficiency leads to anomalies of the ventral body wall, heart, extra- and periocular mesoderm and right pulmonary isomerism. Development 126:5749–5758

Kitamura K, Yanazawa M, Sugiyama N, Miura H, Iizuka-Kogo A, Kusaka M et al (2002) Mutation of ARX cause abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. Nat Genet 32:359–369

Kjaer I, Fischer-Hansen B (1995) Human fetal pituitary gland in holoprosencephaly and anencephaly. J Craniofac Genet Dev Biol 15: 222–229

Kjaer I, Fischer-Hansen B (1996) The human vomeronasal organ: prenatal developmental stage, and distribution of luteinizing hormone-releasing hormone. Eur J Oral Sci 104:34–40

Koenekoop RK, Cremers FPM, Lopez I, den Hollander AI (2012) Leber congenital amaurosis: clinical, genetic and therapeutic perspectives. In: Traboulsi EI (ed) Genetic diseases of the eye, 2nd edn. Oxford University Press, Oxford, pp 491–503

Kölker S, Hoffmann GF, Schor DSM, Feyh P, Wagner L, Jeffrey I et al (2003) Glutaryl-CoA dehydrogenase deficiency: region-specific

analysis of organic acids and acylcarnitines in postmortem brain predicts vulnerability of the putamen. Neuropediatrics 34: 253–260
Kondoh H (1999) Transcription factors for lens development assessed *in vivo*. Curr Opin Genet Dev 9:301–318
Kordower JH, Piecinski P, Rakic P (1992) Neurogenesis of the amygdaloid nuclear complex in the rhesus monkey. Brain Res Dev Brain Res 68:9–15
Korff CM, Apkarian P, Bour LJ, Meuli R, Verrey J-D, Roulet-Perez E (2003) Isolated absence of optic chiasm revealed by congenital nystagmus, MRI and VEPs. Neuropediatrics 34:219–223
Kornack DR, Rakic P (2001) The generation, migration, and differentiation of olfactory neurons in the adult primate brain. Proc Natl Acad Sci U S A 98:4752–4757
Kostović I (1986) Prenatal development of the nucleus basalis complex and related fiber systems in man: a histochemical study. Neuroscience 17:1047–1077
Kostović I (1990) Zentralnervensystem. In: Hinrichsen KV (ed) Humanembryologie. Lehrbuch und Atlas der vorgeburtlichen Entwicklung des Menschen. Springer, Berlin/Heidelberg/New York, pp 381–448
Kostović I, Rakic P (1990) Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. J Comp Neurol 297:441–470
Kouki T, Imai H, Aoto K, Eto K, Shioda S, Kawamura K, Kikuyama S (2001) Developmental origin of the rat adenohypophysis prior to the formation of Rathke's pouch. Development 128: 959–963
Koutcherov Y, Mai JK, Ashwell KWS, Paxinos G (2002) Organization of human hypothalamus in fetal development. J Comp Neurol 446:301–324
Krägeloh-Mann I, Petersen D, Hagberg G, Vollmer B, Hagberg B, Michaelis R (1995) Bilateral spastic cerebral palsy – MRI pathology and origin. Analysis from a representative series of 56 cases. Dev Med Child Neurol 38:379–397
Krägeloh-Mann I, Helber A, Mader I, Staudt M, Wolff M, Groenendaal F, de Vries L (2002) Bilateral lesions of thalamus and basal ganglia: origin and outcome. Dev Med Child Neurol 44:477–484
Kriegstein AR, Noctor SC (2004) Patterns of neuronal migration in the embryonic cortex. Trends Neurosci 27:392–399
Kuhlenbeck H (1954) The human diencephalon. A summary of development, structure, function and pathology. Confin Neurol 14(Suppl):1–230
Kundrat H (1882) Arhinencephalie als typische Art von Missbildung. Von Leuschner und Lubensky, Graz
Künzle H (1975) Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis*. Brain Res 88:195–209
Künzle H (1977) Projections from the primary somatosensory cortex to the basal ganglia and thalamus in the monkey. Exp Brain Res 30:481–492
Künzle H (1978) An autoradiographic analysis of the efferent connections from premotor and adjacent prefrontal regions (areas 6 and 9) in *Macaca fascicularis*. Brain Behav Evol 15:185–234
Kyllerman M, Steen G (1980) Glutaric aciduria: a "common" metabolic disorder? Arch Fr Pediatr 37:279
LaMantia AS, Bhasin N, Rhodes K, Heemskerk J (2000) Mesenchymal-epithelial induction mediates olfactory pathway formation. Neuron 28:411–425
Lammers HJ (1972) The neural connections of the amygdaloid complex in mammals. In: Eleftheriou BE (ed) The neurobiology of the amygdala. Plenum, New York, pp 123–144
Larroche JC (1981) Agenesis of the pituitary gland. Handb Clin Neurol 42:11
Larsen CW, Zeltser LM, Lumsden A (2001) Boundary formation and compartition in the avian diencephalon. J Neurosci 21:4699–4711
Lavdas AA, Grigoriou M, Pachnis V, Parnavelas JG (1999) The medial ganglionic eminence gives rise to a population of early neurons in the developing cerebral cortex. J Neurosci 19:7881–7888
Lazzaro D, Price M, De Felice M, Di Lauro R (1991) The transcription factor TTF1 is expressed at the onset of thyroid and lung morphogenesis and in restricted regions of the foetal brain. Development 113:1093–1104
Lee KJ, Jessell TM (1999) The specification of dorsal fates in the vertebrate central nervous system. Annu Rev Neurosci 22:261–294
Leech RW, Shuman RM (1986) Holoprosencephaly and related midline cerebral anomalies: a review. J Child Neurol 1:3–18
Legouis R, Hardelin J-P, Levilliers J, Claverie J-M, Compain S, Wunderle V et al (1991) The candidate gene for X-linked Kallmann syndrome encodes a protein related to adhesion molecules. Cell 67:423–435
Leibel RL, Shih VE, Goodman SI, Bauman ML, McCabe ERB, Zwerdling RG, Bergman I, Costello C (1980) Glutaric acidemia: a metabolic disorder causing progressive choreoathetosis. Neurology 30:1163–1168
Leigh D (1951) Subacute necrotizing encephalomyelopathy in an infant. J Neurol Neurosurg Psychiatr 14:216–221
Lemire RJ, Loeser JD, Leech RW, Alvord EC Jr (1975) Normal and abnormal development of the human nervous system. Harper & Row, Hagerstown
Letinić K, Kostović I (1996) Transient patterns of calbindin-D28K expression in the developing striatum of man. Neurosci Lett 220:211–214
Letinić K, Kostović I (1997) Transient fetal structure, the gangliothalamic body, connects telencephalic germinal zone with all thalamic regions in the developing human brain. J Comp Neurol 384: 373–395
Letinić K, Rakic P (2001) Telencephalic origin of human thalamic GABAergic neurons. Nat Neurosci 9:931–936
Levitt P, Rakic P (1982) The time of genesis, embryonic origin and differentiation of the brainstem monoamine neurons in the rhesus monkey. Brain Res 4:35–57
Lewis AJ, Simon EM, Barkovich AJ, Clegg NJ, Delgado MR, Levey E, Hahn JS (2002) Middle interhemispheric variant of holoprosencephaly. A distinct cliniconeuroradiologic subtype. Neurology 59: 1860–1865
Li H, Tierney C, Wen L, Wu JY, Rao Y (1997) A single morphogenetic field gives rise to two retina primordia under the influence of the prechordal plate. Development 124:603–615
Li X, Oghi KA, Zhang J, Krones A, Bush KT, Glass CK et al (2003) Eya protein phosphatase activity regulates Six1-Dach-Eya transcriptional effects in mammalian organogenesis. Nature 426: 247–254
Lin CR, Kioussi C, O'Connell S, Briata P, Szeto D, Liu F et al (1999) Pitx2 regulates lung asymmetry, cardiac positioning and pituitary and tooth morhogenesis. Nature 401:279–282
Litingtung Y, Chiang C (2000) Control of Shh activity and signaling in the neural tube. Dev Dyn 219:143–154
Liu JK, Ghattas I, Liu S, Chen S, Rubinstein JLR (1997) Dlx genes encode DNA-binding proteins that are expressed in an overlapping and sequential pattern during basal ganglia differentiation. Dev Dyn 210:498–512
Livingstone M, Hubel D (1988) Segregation of form, color, movement, and depth: anatomy, physiology, and perception. Science 240:740–749
Lohman AJM, Lammers HJ (1967) On the structure and fibre connections of the olfactory system in mammals. Prog Brain Res 23: 65–82
Lois C, Alvarez-Buylla A (1994) Long-distance neuronal migration in the adult mammalian brain. Science 264:1145–1148
Long JE, Garel S, Depew MJ, Tobet S, Rubinstein JLR (2003) DLX5 regulates development of peripheral and central components in the olfactory system. J Neurosci 23:568–578

Long JE, Swan C, Liang WS, Cobos I, Potter GB, Rubinstein JLR (2009a) Dlx1&2 and Mash1 transcription factors control striatal patterning and differentiation through parallel and overlapping pathways. J Comp Neurol 512:556–572

Long JE, Cobos I, Potter GB, Rubinstein JLR (2009b) Dlx1&2 and Mash1 transcription factors control MGE and CGE patterning and differentiation through parallel and overlapping pathways. Cereb Cortex 19(Suppl 1):i96–i106

López-Bendito G, Molnár Z (2003) Thalamocortical development: how are we going to get there? Nat Rev Neurosci 4:276–289

López-Mascaraque L, de Carlos JA, Valverde F (1996) Early onset of the rat olfactory bulb projections. Neuroscience 70:255–266

Louis ED, Lynch T, Cargan AL, Fahn S (1995) Generalized chorea in an infant with semilobar holoprosencephaly. Pediatr Neurol 13: 355–357

Lund RD, Mustari MJ (1977) Development of the geniculocortical pathway in rats. J Comp Neurol 173:289–305

Lurie IW, Nedzved MK, Lazjuk GI, Kirillova IA, Cherstvoy ED (1979) Aprosencephaly-atelencephaly and the aprosencephaly (XK) syndrome. Am J Med Genet 3:303–309

Lurie IW, Nedzved MK, Lazjuk GI, Kirillova IA, Cherstvoy ED, Ostrovskaja TI, Shved IA (1980) The XK-aprosencephaly syndrome. Am J Med Genet 7:231–234

Luskin MB (1993) Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. Neuron 11:173–189

Macchi G (1951) The ontogenetic development of the olfactory telencephalon in man. J Comp Neurol 95:245–305

Macdonald R, Wilson SW (1996) Pax proteins and eye development. Curr Opin Neurobiol 6:49–56

Magoon EH, Robb RM (1981) Development of myelin in human optic nerve and tract. A light and electron microscopic study. Arch Ophthalmol 99:655–670

Maguire AM, Simonelli F, Pierce EA, Pugh EN, Mingozzi F, Bennicelli J et al (2008) Safety and efficacy of gene transfer to Leber's congenital amaurosis. N Engl J Med 358:2240–2248

Mai JK, Ashwell KWS (2004) Fetal development of the central nervous system. In: Paxinos G, Mai JK (eds) The human nervous system, 2nd edn. Elsevier, Amsterdam, pp 49–94

Malamud N (1950) Status marmoratus: a form of cerebral palsy following either birth injury or inflammation of the central nervous system. J Pediatr 37:610–619

Mall FP (1917) Cyclopia in the human embryo. Contrib Embryol Carnegie Instn 6:5–33

Mallamacci A, Muzio L, Chan CH, Parnavelas J, Boncinelli E (2000) Area identity shifts in the early cerebral cortex of *Emx2*−/− mutant mice. Nat Neurosci 3:679–686

Mann IC (1928) The development of the human eye. Cambridge University Press, London

Marchand R, Lajoie L (1986) Histogenesis of the striatopallidal system in the rat. Neurogenesis of its neurons. Neuroscience 17:573–590

Marchand R, Poirier LJ (1983) Isthmic origin of neurons of the rat substantia nigra. Neuroscience 9:373–381

Marchand R, Lajoie L, Blanchet C (1986) Histogenesis at the level of the basal forebrain: the entopeduncular nucleus. Neuroscience 17: 591–607

Marcorelles P, Laquerrière A (2010) Neuropathology of holoprosencephaly. Am J Med Genet C Semin Med Genet 154C:109–119

Marín O (2003) Thalamocortical topography reloaded: it's not where you go, but how you get there. Neuron 39:388–391

Marín O, Rubinstein JLR (2001) A long, remarkable journey: tangential migration in the telencephalon. Nat Rev Neurosci 2:780–790

Marín O, Rubinstein JLR (2002) Patterning, regionalization, and cell differentiation in the forebrain. In: Rossant J, Tam PPL (eds) Mouse development – patterning, morphogenesis, and organogenesis. Academic, San Diego, pp 75–106

Marín O, Anderson SA, Rubinstein JLR (2000) Origin and molecular specification of striatal interneurons. J Neurosci 20:6063–6076

Marlow F, Zwartkruis F, Malicki J, Neuhaus SC, Abbas L, Weaver M et al (1998) Functional interactions of genes mediating convergent extension, knypek and trilobite, during the partitioning of the eye primordium in zebrafish. Dev Biol 203:382–399

Marquardt T, Gruss P (2002) Generating neuronal diversity in the retina: one for nearly all. Trends Neurosci 25:32–38

Marsh E, Fulp C, Gomex E, Nasrallah I, Minarszik J, Sudi J et al (2009) Targeted loss of Arx results in a developmental epilepsy mouse model and recapitulates the human phenotype in heterozygous females. Brain 132:1563–1576

Martin D, Camper SA (2001) Genetic regulation of forebrain and pituitary development. In: Rappaport R, Anselem S (eds) Hypothalamic-pituitary development. Genetic and clinical aspects. Karger, Basel, pp 1–12

Martínez S, Puelles L (2000) Neurogenetic compartments of the mouse diencephalon and some characteristic gene expression patterns. In: Goffinet AM, Rakic P (eds) Mouse brain development. Springer, Berlin/Heidelberg/New York, pp 91–104

Martinez-Barbera JP, Rodriguez TA, Beddington RS (2000) The homeobox gene Hesx1 is required in the anterior neural ectoderm for normal forebrain formation. Dev Biol 223:422–430

Mastick GS, Davis NM, Andrew GL, Easter SS Jr (1997) *Pax-6* functions in boundary formation and axon guidance in the embryonic mouse forebrain. Development 124:1985–1997

Mathieu J, Barth A, Rosa FM, Wilson SW, Peyriéras N (2002) Distinct and cooperative roles for Nodal and Hedgehog signals during hypothalamic development. Development 129:3055–3065

Matise MP, Joyner AL (1999) Gli genes in development and cancer. Oncogene 18:7852–7859

Matsunaga E, Shiota K (1977) Holoprosencephaly in human embryos: epidemiologic studies of 150 cases. Teratologia 16:261–272

Mazzitelli N, Vauthay L, Grandi C, Fuksman R, Rittler M (2002) Reviewing old concepts at the scent of a new millennium: growth restriction, adrenal hypoplasia, and thymomegaly in human anencephaly. Teratology 66:105–114

McAllister JP, Das GD (1977) Neurogenesis in the epithalamus, dorsal thalamus and ventral thalamus of the rat: an autoradiographic and cytological study. J Comp Neurol 172:647–686

McConnell J, Angevine JB Jr (1983) Time of origin in the amygdaloid complex of the mouse. Brain Res 272:150–156

McGeorge AJ, Faull RLM (1989) The organization of the projection from the cerebral cortex to the striatum in the rat. Neuroscience 29:503–537

Medina L, Abellán A (2012) Subpallial structures. In: Watson C, Paxinos G, Puelles L (eds) The mouse nervous system. Elsevier, Amsterdam, pp 173–220

Meisami E, Bhatnagar KP (1998) Structure and diversity in mammalian accessory olfactory bulb. Microsc Res Tech 43:476–499

Meredith M (2001) Human vomeronasal organ function: a critical review of best and worse cases. Chem Senses 26:433–445

Merigan WH (1989) Chromatic and achromatic vision of macaques: role of the P pathway. J Neurosci 9:776–783

Merigan WH, Katz LM, Maunsell JH (1991a) The effects of parvocellular lateral geniculate lesions on the acuity and contrast sensitivity of macaque monkeys. J Neurosci 11:994–1001

Merigan WH, Byrne CE, Maunsell JH (1991b) Does primate motion perception depend on the magnocellular pathway? J Neurosci 11:3422–3429

Métin C, Godement P (1996) The ganglionic eminence may be an intermediate target for corticofugal and thalamocortical axons. J Neurosci 16:3219–3235

Meyers EN, Lewandowski M, Martin GR (1998) An Fgf8 mutant allelic series generated by Cre- and Flp-mediated recombination. Nat Genet 18:136–141

Miller SP, Shevell MI, Patenaude Y, Poulin C, O'Gorman AM (2000) Septo-optic dysplasia plus: a spectrum of malformations of cortical development. Neurology 54:1701–1703

Ming JE, Muenke M (1998) Holoprosencephaly: from Homer to hedgehog. Clin Genet 53:155–163

Ming JE, Muenke M (2002) Multiple hits during early embryonic development: digenic diseases and holoprosencephaly. Am J Hum Genet 71:1017–1032

Ming JE, Kaupas ME, Roessler E, Brunner HG, Golabi M, Tekin M et al (2002) Mutations in PATCHED-1, the receptor for SONIC HEDGEHOG, are associated with holoprosencephaly. Hum Genet 110:297–301

Mione MC, Cavanagh JFR, Harris B, Parnavelas JG (1997) Cell fate specification and symmetrical/asymmetrical divisions in the developing cerebral cortex. J Neurosci 17:2018–2029

Mitchell IJ, Cooper AJ, Griffiths MR (1999) The selective vulnerability of striatopallidal neurons. Prog Neurobiol 59:691–719

Mitrofanis J (1992) Patterns of antigenic expression in the thalamic reticular nucleus of developing rats. J Comp Neurol 320:161–181

Mitrofanis J, Baker GE (1993) Development of the thalamic reticular and perireticular nuclei in rats and their relationship to the course of growing corticofugal and corticopetal axons. J Comp Neurol 338:575–587

Miyai K, Azukizawa M, Kumahara Y (1971) Familial isolated thyrotrophin deficiency with cretinism. N Engl J Med 285:1043–1048

Miyashita-Lin EM, Hevner R, Wassarman KM, Martínez S, Martin GR, Rubinstein JLR (1999) Neocortical regionalization is preserved in the absence of thalamic innervation in newborn *Gbx-2* mutant mice. Science 285:906–909

Miyoshi K, Matsuoka T, Mizushima S (1969) Familial holotopistic striatal necrosis. Acta Neuropathol (Berl) 13:240–249

Mojsilović J, Zečević N (1991) Early development of the human thalamus: Golgi and Nissl study. Early Hum Dev 27:119–144

Molnár Z (1998) Development of thalamocortical connections. Springer/Landes, Berlin, Heidelberg, New York/Georgetown

Molnár Z, Blakemore C (1995) How do thalamic axons find their way to the cortex? Trends Neurosci 18:389–397

Molnár Z, Butler AB (2002) The corticostriatal junction: a crucial region for forebrain development and evolution. Bioessays 24:530–541

Molnár Z, Hannan AJ (2000) Development of thalamocortical projections in normal and mutant mice. In: Goffinet AM, Rakic P (eds) Mouse brain development. Springer, Berlin/Heidelberg/New York, pp 293–332

Molnár Z, Adams R, Blakemore C (1998) Mechanisms underlying the early establishment of thalamocortical connections in the rat. J Neurosci 18:5723–5745

Molnár Z, Garel S, López-Bendito G, Maness P, Price DJ (2012) Mechanisms controlling the guidance of thalamocortical axons through the embryonic forebrain. Eur J Neurosci 35:1573–1585

Montero VM, Zempel J (1986) The proportion and size of GABA-immunoreactive neurons in the magnocellular and parvocellular layers of the lateral geniculate nucleus of the rhesus monkey. Exp Brain Res 62:215–223

Monuki ES, Walsh CA (2001) Mechanisms of cerebral cortical patterning in mice and human. Nat Neurosci 4:1199–1206

Monuki ES, Porter FD, Walsh CA (2001) Patterning of the dorsal telencephalon and cerebral cortex by a roof plate-Lhx2 pathway. Neuron 32:591–604

Moran DT, Jafek BW, Carter Rowley J (1991) The vomeronasal (Jacobson's) organ in man: ultrastructure and frequency of occurrence. J Steroid Biochem Mol Biol 39:545–552

Morel A, Magnin M, Jeanmonod D (1997) Multiarchitectonic and stereotactic atlas of the human thalamus. J Comp Neurol 387:588–630

Mori T, Yuxing Z, Takaki H, Takeuchi M, Iseki K, Hagino S et al (2004) The LIM homeobox gene, *L3*/*Lhx8*, is necessary for proper development of basal forebrain cholinergic neurons. Eur J Neurosci 19:3129–3141

Morioka M, Marubayashi T, Matsumitsu T, Miura M, Ushio Y (1995) Basal encephaloceles with morning glory syndrome, and progressive hormonal and visual disturbances: a case report and review of the literature. Brain Dev 17:196–201

Morishima A, Aranoff GS (1986) Syndrome of septo-optic dysplasia: the clinical spectrum. Brain Dev 8:233–239

Muenke M, Beachy PA (2000) Genetics of ventral forebrain development and holoprosencephaly. Curr Opin Genet Dev 10:262–269

Muenke M, Beachy PA (2001) Holoprosencephaly. In: Scriver CR, Beaudet al, Sly WS, Valle D (eds) The metabolic & molecular bases of inherited disease, 8th edn. McGraw-Hill, New York, pp 6203–6230

Müller F, O'Rahilly R (1989a) The human brain at stage 16, including the initial development of the neurohypophysis. Anat Embryol (Berl) 179:551–569

Müller F, O'Rahilly R (1989b) The human brain at stage 17, including the appearance of the future olfactory bulb and the first amygdaloid nuclei. Anat Embryol (Berl) 180:353–369

Müller F, O'Rahilly R (1989c) Mediobasal prosencephalic defects, including holoprosencephaly and cyclopia, in relation to the development of the human forebrain. Am J Anat 185:391–414

Müller F, O'Rahilly R (2004) Olfactory structures in staged human embryos. Cells Tissues Organs 178:93–116

Müller F, O'Rahilly R (2006) The amygdaloid complex and the medial and lateral ventricular eminences in staged human embryos. J Anat (Lond) 208:547–564

Murray RC, Navi D, Fesenko J, Lander AD, Calof AL (2003) Widespread defects in the primary olfactory pathway caused by loss of *Mash1* function. J Neurosci 23:1769–1780

Muske LE (1993) Evolution of gonadotropin-releasing hormone (GnRH) neuronal systems. Brain Behav Evol 42:215–230

Muzio L, DiBenedetto B, Stoykova A, Boncinelli E, Gruss P, Mallamaci A (2002) Conversion of cerebral cortex into basal ganglia in *Emx2*$^{-/-}$ *Pax6*$^{Sey/Sey}$ double-mutant mice. Nat Neurosci 5:737–745

Nagai L, Li CH, Hsieh SM, Kizaki T, Urano Y (1984) Two cases of hereditary diabetes insipidus, with an autopsy finding in one. Acta Endocrinol 105:318–323

Nagasaki H, Ito M, Yuasa H, Saito H, Fukase M, Hamada K et al (1995) Two novel mutations in the coding region for neurophysin-II associated with familial central diabetes insipidus. J Clin Endocrinol Metab 80:1352–1356

Nakagawa Y, Shimogori T (2012) Diversity of thalamic progenitor cells and postmitotic neurons. Eur J Neurosci 35:1554–1562

Nakano KK (1973) Anencephaly: a review. Dev Med Child Neurol 15:383–400

Nanni L, Ming JE, Bocian M, Steinhaus K, Bianchi DW, de Die-Smulders C et al (1999) The mutational spectrum of the *Sonic hedgehog* gene in holoprosencephaly: SHH mutations cause a significant proportion of autosomal dominant holoprosencephaly. Hum Mol Genet 8:2479–2488

Nanni L, Croen LA, Lammer EJ, Muenke M (2000) Holoprosencephaly: molecular study of a California population. Am J Med Genet 90:315–319

Naruse I, Keino H (1995) Apoptosis in the developing CNS. Prog Neurobiol 47:135–155

Nassi JJ, Callaway EM (2009) Parallel processing strategies of the primate visual system. Nat Rev Neurosci 10:360–372

Nauta WJH, Haymaker W (1969) Hypothalamic nuclei and fiber connections. In: Haymaker W, Anderson E, Nauta WJH (eds) The hypothalamus. Thomas, Springfield, pp 136–209

Nery S, Fishell G, Corbin JG (2002) The caudal ganglionic eminence is a source of distinct cortical and subcortical populations. Nat Neurosci 5:1279–1287

Nieuwenhuys R (1977) Aspects of the morphology of the striatum. In: Cools AR, Lohman AHM, van den Bercken JHL (eds) Psychobiology of the striatum. Elsevier/North-Holland, Amsterdam, pp 1–19

Nieuwenhuys R (1996) The greater limbic system, the emotional motor system and the brain. Prog Brain Res 107:551–580
Nobin A, Björklund A (1973) Topography of the monoamine neuron systems in the human brain as revealed in fetuses. Acta Physiol Scand Suppl 388:1–40
Norman RM (1947) État marbré of the corpus striatum following birth injury. J Neurol Psychiatry 10:12–25
Norman MG, McGillivray BC, Kalousek DK, Hill A, Poskitt PJ (1995) Congenital malformations of the brain. Pathologic, embryologic, clinical, radiologic and genetic aspects. Oxford University Press, New York
Nornes HO, Dressler GR, Knapik EW, Deutsch U, Gruss P (1990) Spatially and temporally restricted expression of Pax2 during murine neurogenesis. Development 109:797–809
Northcutt RG, Muske LE (1994) Multiple embryonic origins of gonadotropin-releasing hormone (GnRH) immunoreactive neurons. Brain Res Dev Brain Res 78:279–290
O'Rahilly R (1966) The early development of the eye in staged human embryos. Contrib Embryol Carnegie Instn 38:1–42
O'Rahilly R, Müller F (2001) Human embryology & teratology, 3rd edn. Wiley-Liss, New York
O'Rahilly R, Müller F, Hutchins GM, Moore GW (1988) Computer ranking of the sequence of appearance of 40 features of the brain and related structures in staged human embryos during the seventh week of development. Am J Anat 182:295–317
Oelschläger HA, Buhl EH, Dann JF (1987) Development of the nervus terminalis in mammals including toothed whales and humans. Ann NY Acad Sci 519:447–464
Ogren MP, Rakic P (1981) The prenatal development of the pulvinar in the monkey: ^{3}H-thymidine autoradiographic and morphometric analyses. Anat Embryol (Berl) 162:1–20
Ohkubo Y, Chiang C, Rubinstein JLR (2002) Coordinate regulation and synergistic actions of BMP4, SHH and FGF8 in the rostral prosencephalon regulate morphogenesis of the telencephalic and optic vesicles. Neuroscience 111:1–17
Oliveira LM, Semimara SB, Beranova M, Hayes FJ, Valkenburgh SB, Schipani E et al (2001) The importance of autosomal genes in Kallmann syndrome: genotype-phenotype correlations and neuro-endocrine characteristics. J Clin Endocrinol Metab 86: 1532–1538
Olson L, Seiger Å (1972) Early prenatal ontogeny of central monoamine neurons in the rat: fluorescence histochemical observations. Z Anat Entwicklungsgesch 137:301–316
Olson L, Seiger Å, Fuxe K (1972) Heterogeneity of striatal and limbic dopamine innervation: highly fluorescent islands in developing and adult rats. Brain Res 44:283–288
Olson L, Boreus LO, Seiger Å (1973) Histochemical demonstration and mapping of 5-hydroxytryptamine and catecholamine-containing neuron systems in the human fetal brain. Z Anat Entwicklungsgesch 139:259–282
Olsson M, Campbell K, Wictorin K, Björklund A (1995) Projection neurons in fetal striatal transplants are predominantly derived from the lateral ganglionic eminence. Neuroscience 69:1169–1182
Olsson M, Björklund A, Campbell K (1998) Early specification of striatal projection neurons and interneuronal subtypes in the lateral and medial ganglionic eminence. Neuroscience 84:867–876
Onye C (1990) Thalamus. In: Paxinos G (ed) The human nervous system. Academic, San Diego, pp 439–468
Opitz JM (1993) Blastogenesis and the "primary field" in human development. Birth Defects Orig Artic Ser 29:3–37
Opitz JM, Wilson GN, Gilbert-Barness E (1997) Abnormalities of blastogenesis, organogenesis, and phenogenesis. In: Gilbert-Barness E (ed) Potter's pathology of the fetus and infant. Mosby, St. Louis, pp 65–105
Ortmann R (1989) Über Sinneszellen am fetalen vomeronasalen Organ des Menschen. HNO 37:191–197
Ottersen OP, Storm-Mathisen J (1984) GABA-containing neurons in the thalamus and pretectum of the rodent. An immunocytochemical study. Anat Embryol (Berl) 170:197–207
Padberg G, Bruyn GW (1986) Chorea: differential diagnosis. Handb Clin Neurol 5:549–564
Panganiban G, Rubinstein JLR (2002) Developmental functions of the *Distal-less*/*Dlx* homeobox genes. Development 129:4371–4386
Parent A, Hazrati L-N (1995) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Rev 20:91–127
Parent A, Côté P-Y, Lavoie B (1995) Chemical anatomy of primate basal ganglia. Prog Neurobiol 46:131–197
Parnavelas JG (2000) The origin and migration of cortical neurones: new vistas. Trends Neurosci 23:126–131
Paroder V, Miller I, Shanske AL, Shiota K, Khan MN, Cohen MM Jr (2013) Hidden pituitary gland: implications for accessment. Am J Med Genet A 161A:630–631
Parsa CF, Goldberg MF, Hunter DG (2002) Papillorenal ("renal coloboma") syndrome. Am J Ophthalmol 134:300–301
Pasternak JF, Predey TA, Mikhael ME (1991) Neonatal asphyxia: vulnerability of basal ganglia, thalamus and brainstem. Pediatr Neurol 7:147–149
Pearson AA (1941a) The development of the nervus terminalis in man. J Comp Neurol 75:39–66
Pearson AA (1941b) The development of the olfactory nerve in man. J Comp Neurol 75:199–217
Pearson AA (1942) The development of the olfactory nerve, the nervus terminalis, and the vomeronasal nerve in man. Ann Otol Rhinol Laryngol 51:317–333
Pearson J, Brandeis L, Goldstein M (1980) Appearance of tyrosine hydroxylase immunoreactivity in the human embryo. Dev Neurosci 3:140–150
Pellegrini M, Monsouri A, Simeone A, Boncinelli E, Gruss P (1996) Dentate gyrus formation requires *Emx2*. Development 122:3893–3898
Percheron G (2004) Thalamus. In: Paxinos G, Mai JK (eds) The human nervous system, 2nd edn. Elsevier, Amsterdam, pp 592–675
Pichaud F, Desplan C (2002) Pax genes and eye organogenesis. Curr Opin Genet Dev 12:430–434
Pickel VM, Specht LA, Sumal KK, Joh TH, Reis DJ, Hervonen A (1980) Immunocytochemical localization of tyrosine hydroxylase in the human fetal nervous system. J Comp Neurol 194: 465–474
Pilavdzic D, Kovacs K, Asa SL (1997) Pituitary morphology in anencephalic human fetuses. Neuroendocrinology 65:164–172
Pineda-Alvarez DE, Solomon BD, Roessler E, Balog JZ, Hadley DW, Zein WM et al (2011) A broad range of ophthalmologic anomalies is part of the holoprosencephaly spectrum. Am J Med Genet A 155:2713–2720
Pinto G, Abadie V, Mesnage R, Blustajn J, Cabrol S, Amiel L et al (2005) CHARGE syndrome includes hypogonadotropic hypogonadism and abnormal olfactory bulb development. J Clin Endocrinol Metab 90:5621–5626
Pooh R (2009) Neuroscan of congenital brain abnormality. In: Kurjak A, Pooh R (eds) Fetal neurology. Jaypee, St Louis, pp 59–139
Porteus MH, Bulfone A, Liu JK, Puelles L, Lo LC, Rubinstein JLR (1994) DLX-2, MASH-1, and MAP-2 expression and bromodeoxyuridine incorporation define molecularly distinct cell populations in the embryonic mouse forebrain. J Neurosci 14:6370–6383
Prader A, Labhart A, Willi H (1956) Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myotonieartigem Zustand im Neugeborenenalter. Schweiz Med Wochenschr 86:1260–1261
Price JL (1990) Olfactory system. In: Paxinos G (ed) The human nervous system. Academic, San Diego, pp 979–990
Price JL, Drevets WC (2011) Neural circuits underlying the pathophysiology of mood disorders. Trends Neurosci 16:61–71

Price MG, Yoo JW, Burgess DL, Deng F, Hrachovy RA, Frost JD Jr, Noebels JR (2009) A triplet repeat expansion genetic mouse model of infantile spasm syndrome, Arx (GCG)10+7, with interneuronopathy, spasms in infancy, persistent seizures, and adult cognitive and behavioral impairment. J Neurosci 29:8752–8763

Probst FP (1979) The prosencephalies, morphology, neuroradiological appearances and differential diagnosis. Springer, Berlin/Heidelberg/New York

Prosser J, van Heyningen V (1998) *PAX6* mutation review. Hum Mutat 11:93–108

Provis JM, van Driel D, Billson FA, Russell P (1985a) Development of the human retina: patterns and mechanisms of cell distribution and redistribution in the ganglion cell layer. J Comp Neurol 233:429–451

Provis JM, van Driel D, Billson FA, Russell P (1985b) Human fetal optic nerve: overproduction and elimination of retinal axons during development. J Comp Neurol 238:92–100

Puelles L (1995) A segmental morphological paradigm for understanding vertebrate forebrains. Brain Behav Evol 46:319–337

Puelles L, Rubinstein JLR (2003) Forebrain gene expression domains and the evolving prosomeric model. Trends Neurosci 26:469–476

Puelles L, Verney C (1998) Early neuromeric distribution of tyrosine-hydroxylase-immunoreactive neurons in human embryos. J Comp Neurol 394:283–308

Puelles L, Amat JA, Martínez de la Torre M (1987) Segment-related, mosaic neurogenetic pattern in the forebrain and mesencephalon of early chick embryos. I. Topography of AChE-positive neuroblasts up to stage HH18. J Comp Neurol 266:247–268

Puelles L, Kuwana E, Puelles E, Bulfone A, Shimamura K, Keleher J et al (2000) Pallial and subpallial derivatives in the embryonic chick and mouse telencephalon, traced by the expression of the genes Dlx-2, Emx-1, Nkx-2.1, Pax-6, and Tbr-1. J Comp Neurol 424:409–438

Puelles L, Martínez S, Martínez de la Torre M (2008) Neuroanatomía. Médica Panamericana, Buenos Aires/Madrid (in Spanish)

Puelles L, Martinez-de-la-Torre M, Bardet S, Rubinstein JLR (2012a) Hypothalamus. In: Watson C, Paxinos G, Puelles L (eds) The mouse nervous system. Elsevier, Amsterdam, pp 221–312

Puelles L, Martinez-de-la-Torre M, Ferran J-L, Watson C (2012b) Diencephalon. In: Warson C, Paxinos G, Puelles L (eds) The mouse nervous system. Elsevier, Amsterdam, pp 313–316

Puelles L, Harrison M, Paxinos G, Watson C (2013) A developmental ontology for the mammalian brain based on the prosomeric model. Trends Neurosci 36:570–578

Pulitzer SB, Simon EM, Crombleholme TM, Golden JA (2004) Prenatal MR findings of the middle interhemispheric variant of holoprosencephaly. AJNR Am J Neuroradiol 25:1034–1036

Pyatkina GA (1982) Development of the olfactory epithelium in man. Z Mikrosk Anat Forsch 96:361–372

Qiu M, Bulfone A, Martinez S, Meneses JJ, Shimamura K, Pedersen RA, Rubinstein JLR (1995) Null mutations of Dlx-2 results in abnormal morphogenesis of proximal first and second branchial arch derivatives and abnormal differentiation in the forebrain. Genes Dev 9:2523–2538

Quinton R, Duke VM, de Zoysa PA, Platts AD, Valentine A, Kendall B et al (1996) The neuroradiology of Kallmann's syndrome: a genotypic and phenotypic analysis. J Clin Endocrinol Metab 81:3010–3017

Rademakers RP, van der Knaap MS, Verbeeten B, Barth P, Valk J (1995) Central cortico-subcortical involvement: a distinct pattern of brain damage caused by perinatal and postnatal asphyxia in term infants. J Comput Assist Tomogr 19:256–263

Rakic P (1974) Neurons in rhesus monkey visual cortex: systematic relation between time of origin and eventual disposition. Science 183:425–427

Rakic P (1975) Timing of major ontogenetic events in the visual cortex of the rhesus monkey. In: Buchwald NA, Brazier MAB (eds) Brain mechanisms of mental retardation. Academic, New York, pp 3–40

Rakic P (1976) Prenatal genesis of connections subserving ocular dominance in the rhesus monkey. Nature 261:467–471

Rakic P (1977a) Prenatal development of the visual system in rhesus monkey. Philos Trans R Soc Lond B Boil Sci 278:245–260

Rakic P (1977b) Genesis of the dorsal lateral geniculate nucleus in the rhesus monkey: site and time of origin, kinetics of proliferation, routes of migration and pattern of distribution of neurons. J Comp Neurol 176:23–52

Rakić P, Sidman RL (1969) Telencephalic origin of pulvinar neurons in the fetal human brain. Z Anat Entwicklungsgesch 129:53–82

Rallu M, Machold R, Gaiano N, Corbin JG, McMahon AP, Fishell G (2002a) Dorso-ventral patterning is established in the telencephalon of mutants lacking both Gli3 and Hedgehog signaling. Development 129:4963–4974

Rallu M, Corbin JG, Fishell G (2002b) Parsing the prosencephalon. Nat Rev Neurosci 3:943–951

Rathke H (1838) Über die Entstehung der Glandula pituitaria. Arch Anat Physiol Wiss Med 1838:482–485

Rieger DK, Reichenberger E, MacLean W, Sidow A, Olsen BR (2001) A double-deletion mutation in the Pitx3 gene causes arrested lens development in aphakia mice. Genomics 72:61–72

Rittig S, Robertson GL, Siggaard C, Kovács L, Gregersen N, Nyborg J, Pedersen EB (1996) Identification of 13 new mutations in the vasopressin-neurophysin II gene in 17 kindreds with familial autosomal dominant neurohypophyseal diabetes insipidus. Am J Hum Genet 58:107–117

Robinson BH (2001) Lactic acidemia: disorders of pyruvate carboxylase and pyruvate dehydrogenase. In: Scriver CR, Beaudet al, Sly WS, Valle D (eds) The metabolic & molecular bases of inherited disease, 8th edn. McGraw-Hill, New York, pp 2275–2295

Roessler E, Muenke M (1998) Holoprosencephaly: a paradigm for the complex genetics of brain development. J Inherit Metab Dis 21:481–497

Roessler E, Muenke M (2001) Midline and laterality defects: left and right meet in the midline. Bioessays 23:888–900

Roessler E, Muenke M (2010) The molecular genetics of holoprosencephaly. Am J Med Genet C Semin Med Genet 154C:52–61

Roessler E, Belloni E, Gaudenz K, Jay P, Berta P, Scherer SW et al (1996) Mutations in the human *Sonic hedgehog* gene cause holoprosencephaly. Nat Genet 14:357–360

Roessler E, Du Y-Z, Mullor JL, Casas E, Allen WP, Gillessen-Kaesbach G et al (2003) Loss-of-function mutations in the human *GLI2* gene are associated with pituitary anomalies and holoprosencephaly-like features. Proc Natl Acad Sci U S A 100:13424–13429

Roessler E, Ouspenskaia MV, Karkera JD, Vélez JI, Kantipong A, Lacbawan F et al (2008) Reduced NODAL signaling strength via mutation of several pathway members including FOXH1 is linked to human heart defects and holoprosencephaly. Am J Hum Genet 83:18–29

Roessler E, Lacbawan F, Dubourg C, Paulussen A, Herbergs J, Hehr U et al (2009) The full spectrum of holoprosencephaly-associated mutations with the *ZIC2* gene in humans predicts loss-of-function as the predominant disease mechanism. Hum Mutat 39:E541–E544

Roessmann U, Schwarz JF (1973) Familial striatal degeneration. Arch Neurol 29:314–317

Roessmann U, Velasco ME, Small EJ, Hori A (1987) Neuropathology of "septo-optic dysplasia" (de Morsier syndrome) with immunohistochemical studies of the hypothalamus and pituitary gland. J Neuropathol Exp Neurol 46:597–608

Rohr KB, Barth KA, Varga ZM, Wilson SW (2001) The nodal pathway acts upstream of hedgehog signaling to specify ventral telencephalic identity. Neuron 29:341–351

Rubinstein JLR, Beachy PA (1998) Patterning of the embryonic forebrain. Curr Opin Neurobiol 8:18–26

Rubinstein JLR, Shimamura K, Martínez S, Puelles L (1998) Regionalization of the prosencephalic neural plate. Annu Rev Neurosci 21:445–477

Rugarli EI (1999) Kallmann syndrome and the link between olfactory and reproductive development. Am J Hum Genet 65:943–948
Rugarli EI, Lutz B, Kuratani SC, Wawersik S, Borsani G, Ballabio A, Eichele G (1993) Expression pattern of the Kallmann syndrome gene in the olfactory system suggests a role in neuronal targeting. Nat Genet 4:19–26
Rutherford MA (2002) Magnetic resonance imaging of injury in the immature brain. In: Squier W (ed) Acquired damage to the developing brain: timing and causation. Arnold, London, pp 166–192
Rutherford MA, Pennock JM, Murdoch-Eaton DM, Cowan FM, Dubowitz LM (1992) Athetoid cerebral palsy with cysts in the putamen after hypoxic-ischemic encephalopathy. Arch Dis Child 67:846–850
Rutherford MA, Pennock JM, Schwieso JE, Cowan FM, Dubowitz LM (1995) Hypoxic ischemic encephalopathy: early magnetic resonance imaging findings and their evolution. Neuropediatrics 26: 183–191
Sachdeva R, Traboulsi EI (2012) Aniridia. In: Traboulsi EI (ed) Genetic diseases of the eye, 2nd edn. Oxford University Press, Oxford, pp 109–123
Sailaja K, Gopinath G (1994) Developing substantia nigra in human: a qualitative study. Dev Neurosci 16:44–52
Sanger TD (2003) Pathophysiology of pediatric movement disorders. J Child Neurol 18:S9–S24
Sanlaville D, Etchevers HC, Gonzalez M, Martinovic J, Clément-Ziza M, Delezoide A-L et al (2006) Phenotypic spectrum of CHARGE syndrome in fetuses with CHD7 truncating mutations correlates with expression during human development. J Med Genet 43: 211–217
Santos A, Traboulsi EI (2012) Congenital abnormalities of the retinal pigment epithelium. In: Traboulsi EI (ed) Genetic diseases of the eye, 2nd edn. Oxford University Press, Oxford, pp 150–162
Saper CB (2004) Hypothalamus. In: Paxinos G, Mai JK (eds) The human nervous system, 2nd edn. Elsevier Academic, San Diego, pp 514–550
Sarnat HB (2000) Molecular genetic classification of central nervous system malformations. J Child Neurol 15:675–687
Sarnat HB, Flores-Sarnat L (2001) Neuropathologic research strategies in holoprosencephaly. J Child Neurol 16:918–931
Sato K, Mano T, Sakurai M, Furukawa T (1975) Isolated thyrotropin deficiency: a case with abnormal leukocytes function. Clin Endocrinol 23:525–529
Savic I, Berglund H, Gulyas B, Roland P (2001) Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. Neuron 30:661–668
Schier AF (2001) Axis formation and patterning in zebrafish. Curr Opin Genet Dev 11:393–404
Schmahl W, Knoedlseder M, Favor J, Davidson D (1993) Defects of neuronal migration and the pathogenesis of cortical malformations are associated with small eye (Sey) in the mouse, a point mutation at the Pax-6-locus. Acta Neuropathol (Berl) 86:126–135
Scholpp S, Lumsden A (2010) Building a bridal chamber: development of the thalamus. Trends Neurosci 33:373–380
Schumann CM, Amaral DG (2006) Stereological analysis of amygdala neuron number in autism. J Neurosci 26:7674–7679
Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, Buonocore MH et al (2004) The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neurosci 24:6392–6401
Schuurmans C, Guillemot F (2002) Molecular mechanisms underlying cell fate specification in the developing telencephalon. Curr Opin Neurobiol 12:26–34
Schwalbe G (1880) Beiträge zur Entwicklungsgeschichte des Zwischenhirns. Sitz Ber Jen Ges Med Naturwiss 20:2–7
Schwanzel-Fukuda M, Pfaff DW (1989) Origin of luteinizing hormone releasing hormone neurons. Nature 338:161–164
Schwanzel-Fukuda M, Bick D, Pfaff DW (1989) Luteinizing hormone releasing hormone (LHRH)-expressing cells do not migrate in an inherited hypogonadal (Kallmann) syndrome. Mol Brain Res 6:311–326
Schwanzel-Fukuda M, Crossin KL, Pfaff DW, Bouloux PMG, Hardelin J-P, Petit C (1996) Migration of luteinizing hormone-releasing hormone (LHRH) neurons in early human embryos. J Comp Neurol 366:547–557
Schwind JL (1928) The development of the hypophysis cerebri of the albino rat. Am J Anat 41:295–315
Schwob JE, Price JL (1984) The development of axonal connections in the central olfactory system of rats. J Comp Neurol 223:177–202
Seibt J, Schuurmans C, Gradwhol G, Dehay C, Vanderhaeghen P, Guillemot F, Polleux F (2003) *Neurogenin2* specifies the connectivity of thalamic neurons by controlling axon responsiveness to intermediate target clues. Neuron 39:439–452
Seiger Å, Olson L (1973) Late prenatal ontogeny of central monoamine neurons in the rat: fluorescence histochemical observations. Z Anat Entwicklungsgesch 140:281–318
Selemon LD, Goldman-Rakic PS (1985) Longitudinal topography and interdigitation of corticostriatal projections of the rhesus monkey. J Neurosci 5:776–794
Semina EV, Reiter RS, Murray J (1997) Isolation of a new homeobox gene belonging to the Pitx/Rieg family: expression during lens development and mapping to the aphakia region on mouse chromosome 19. Hum Mol Genet 6:2109–2116
Semina EV, Ferrell RE, Mintz-Hittner HA, Bitoun P, Alward WLM, Reiter RS et al (1998) A novel homeobox gene *PITX3* is mutated in families with autosomal-dominant cataracts and ASMB. Nat Genet 19:167–170
Sergi C, Schmitt HP (2000) The vesicular forebrain (pseudoaprosencephaly): a missing link in the teratogenic spectrum of defective brain anlage and its discrimination from aprosencephaly. Acta Neuropathol (Berl) 99:277–284
Shanmugalingam S, Houart C, Picker A, Reifers F, Macdonald R, Barth A et al (2000) Ace/Fgf8 is required for forebrain commissure formation and patterning of the telencephalon. Development 127:2549–2561
Shatz CJ (1983) The prenatal development of the cat's retinogeniculate pathway. J Neurosci 3:482–499
Shatz CJ, Luskin MB (1986) Relationship between the geniculocortical afferents and their cortical target cells during development of the cat's primary visual cortex. J Neurosci 6:3655–3668
Shatz CJ, Rakic P (1981) The genesis of efferent connections from the visual cortex of the fetal rhesus monkey. J Comp Neurol 196:287–307
Shatz CJ, Ghosh A, McConnell SK, Allendoerfer KL, Friauf E, Antonini A (1990) Pioneer neurons and target selection in cerebral cortical development. Cold Spring Harb Symp Quant Biol 55:469–480
Sheng HZ, Westphal H (1999) Early steps in pituitary organogenesis. Trends Genet 15:236–240
Sheng HZ, Moriyama K, Yamashita T, Li H, Potter SS, Mahon KA, Westphal H (1997) Multistep control of pituitary organogenesis. Science 278:1809–1812
Shepherd GM, Greer CA (1990) Olfactory bulb. In: Shepherd GM (ed) The synaptic organization of the brain, 3rd edn. Oxford University Press, New York, pp 133–169
Shih J, Fraser SE (1996) Characterizing the zebrafish organizer: microsurgical analysis at the early shield stage. Development 122: 1311–1322
Shimamura K, Rubinstein JLR (1997) Inductive interactions direct early regionalization of the mouse forebrain. Development 124: 2709–2718
Shimamura K, Hartigan DJ, Martínez S, Puelles L, Rubinstein JLR (1995) Longitudinal organization of the anterior neural plate and neural tube. Development 121:3923–3933

Shimogori T, Lee DA, Miranda-Angulo A, Yang Y, Wang H, Jiang L et al (2010) A genomic atlas of mouse hypothalamic development. Nat Neurosci 13:767–775

Shiota K (1993) Teratothanasia: prenatal loss of abnormal conceptuses and the prevalence of various malformations during human gestation. Birth Defects Orig Artic Ser 29:189–199

Shiota K, Yamada S (2010) Early pathogenesis of holoprosencephaly. Am J Med Genet C Semin Med Genet 154C:22–28

Shipley MI, McLean JH, Ennis M (1995) Olfactory system. In: Paxinos G (ed) The rat nervous system, 2nd edn. Academic, San Diego, pp 899–926

Sie LTL, van der Knaap MS, Oostings J, de Vries L, Lafeber HN, Valk J (2000) MR pattern of hypoxic-ischemic brain damage after prenatal, perinatal or postnatal asphyxia. Neuropediatrics 31:128–136

Siebert JR, Warkany J, Lemire RJ (1986) Atelencephalic microcephaly in a 21 week human fetus. Teratology 34:9–19

Siebert JR, Kokich VG, Warkany J, Lemire RJ (1987) Atelencephalic microcephaly: craniofacial anatomy and morphologic comparisons with holoprosencephaly and anencephaly. Teratology 36:279–285

Siebert JR, Cohen MM Jr, Sulik KK, Shaw C-M, Lemire RJ (1990) Holoprosencephaly: an overview and atlas. Wiley-Liss, New York

Silver J, Robb RM (1979) Studies on the development of the eye cup and optic nerve in normal mice and in mutants with congenital optic nerve aplasia. Dev Biol 68:175–190

Simeone A, Acampora D, Gulisano M, Stornaiuolo A, Boncinelli E (1992) Nested expression domains of four homeobox genes in developing rostral brain. Nature 358:687–690

Simeone A, Acampora D, Mallaci A, Stornaiuolo A, D'Apice MR, Nigro V, Boncinelli E (1993) A vertebrate gene related to orthodenticle contains a homeodomain of the bicoid class and demarcates anterior neuroectoderm in the gastrulating mouse embryo. EMBO J 12:2735–2747

Simon EM, Hevner RF, Pinter JD, Kinsman SL, Hahn J, Barkovich AJ (2000) Assessment of the deep gray nuclei in holoprosencephaly. AJNR Am J Neuroradiol 21:1955–1961

Simon EM, Hevner RF, Pinter JD et al (2001) The dorsal cyst in holoprosencephaly and the role of the thalami in its formation. Neuroradiology 43:787–791

Simon EM, Hevner RF, Pinter JD, Clegg NJ, Delgado M, Kinsman SL et al (2002) The middle interhemispheric variant of holoprosencephaly. AJNR Am J Neuroradiol 23:151–155

Sisodiya SM, Free SL, Williamson KA, Mitchell TN, Willis C, Stevens JM et al (2001) *PAX6* haplo-insufficiency causes cerebral malformations and olfactory dysfunction in humans. Nat Genet 28: 214–216

Skidmore JM, Cramer JD, Martin JF, Martin DM (2008) *Cre* fate mapping reveals lineage specific defects in neuronal migration with loss of *Pitx2* function in the developing mouse hypothalamus and subthalamic nucleus. Mol Cell Neurosci 37:696–707

Smart IH, Dehay C, Giroud P, Berland M, Kennedy H (2002) Unique morphological features of the proliferative zones and postmitotic compartments of the neural epithelium giving rise to striate and extrastriate cortex in the monkey. Cereb Cortex 12:37–53

Smidt MP, van Schaick HSA, Lanctôt C, Tremblay JJ, Cox JJ, van der Kleij AAM et al (1997) A homeodomain gene *PITX3* has highly restricted brain expression in mesencephalic dopaminergic neurons. Proc Natl Acad Sci U S A 94:13305–13310

Smidt MP, Asbreuk CH, Cox JJ, Chen H, Johnson RL (2000) A second independent pathway for development of mesencephalic dopaminergic neurons requires Lmxb1. Nat Neurosci 3:337–341

Smith JEH, Traboulsi EI (2012) Malformations of the anterior segment of the eye. In: Traboulsi EI (ed) Genetic diseases of the eye, 2nd edn. Oxford University Press, Oxford, pp 92–108

Smith-Fernández A, Pieau C, Repérant J, Boncinelli E, Wassef M (1998) Expression of the *Emx-1* and *Dlx-1* homeobox genes define three molecularly distinct domains in the telencephalon of mouse, chick, turtle and frog embryos: Implications for the evolution of telencephalic subdivisions in amniotes. Development 125:2099–2111

Soffer D, Amir N, Elpeleg ON, Gomori JM, Shalev RS, Gottschalk-Sabeg S (1992) Striatal degeneration and spongy myelinopathy in glutaric aciduria. J Neurol Sci 107:199–204

Solomon BD, Pineda-Alvarez DE, Mercier S, Raam MS, Odent S, Muenke M (2010) Holoprosencephaly flashcards: a summary for the clinician. Am J Med Genet C Semin Med Genet 154C:3–7

Sousa VH, Fishell G (2010) Sonic hedgehog functions through dynamic changes in temporal competence in the developing forebrain. Curr Opin Genet Dev 20:391–399

Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA et al (2002) Brain structural abnormalities in young children with autism spectrum disorder. Neurology 59:184–192

Specht LA, Pickel VM, Joh TH, Reis DJ (1981a) Light-microscopic immunocytochemical localization of tyrosine hydroxylase in prenatal rat brain. I. Early ontogeny. J Comp Neurol 199:233–253

Specht LA, Pickel VM, Joh TH, Reis DJ (1981b) Light-microscopical immunocytochemical localization of tyrosine hydroxylase in prenatal rat brain. II. Late ontogeny. J Comp Neurol 199:255–276

Squier W (2002) Pathology of fetal and neonatal brain damage: Identifying the timing. In: Squier W (ed) Acquired damage to the developing brain: timing and causation. Arnold, London, pp 110–127

Stein J, Walsh V (1997) To see but not to read; the magnocellular theory of dyslexia. Trends Neurosci 20:147–152

Steingrimsson E, Moore KJ, Lamoreux ML, Ferré-D'Amaré A, Burley SK, Zimring DCS et al (1994) Molecular basis of mouse *microphthalmia* (*mi*) mutations helps explain their developmental and phenotypic consequences. Nat Genet 8:256–263

Stenman J, Yu RT, Evans RM, Campbell K (2003) *Tlx* and *Pax6* cooperate genetically to establish the pallio-subpallial boundary in the embryonic mouse telencephalon. Development 130:1113–1122

Stephan H (1975) Allocortex. Handbuch der mikroskopischen Anatomie des Menschen, vol 4, Teil 9. Springer, Berlin/Heidelberg/New York

Stephan H, Andy OJ (1977) Quantitative comparison of the amygdala in insectivores and primates. Acta Anat (Basel) 98:130–153

Stoykova A, Fritsch R, Walther C, Gruss P (1996) Roles of Pax-genes in developing and adult brain as suggested by expression patterns. J Neurosci 14:1395–1412

Stoykova A, Treichel D, Hallonot M, Gruss P (2000) *Pax6* modulates the dorsoventral patterning of the mammalian telencephalon. J Neurosci 20:8042–8050

Stühmer T, Anderson SA, Ekker M, Rubinstein JLR (2002) Ectopic expression of the Dlx genes induces glutamic acid decarboxylase and Dlx expression. Development 129:245–252

Suda Y, Hossain ZM, Kobayashi C, Hatano O, Yoshida M, Matsuo I, Aizawa S (2001) *Emx2* directs the development of diencephalon in cooperation with *Otx2*. Development 128:2433–2450

Suh H, Gage PJ, Drouin J, Camper SA (2002) Pitx2 is required at multiple stages of pituitary organogenesis: pituitary primordium formation and cell specification. Development 129:329–337

Sundin OH (2012) Embryology of the eye and the role of developmental genes. In: Traboulsi EI (ed) Genetic diseases of the eye, 2nd edn. Oxford University Press, Oxford, pp 5–22

Sur M, Leamey CA (2001) Development and plasticity of cortical areas and networks. Nat Rev Neurosci 2:251–262

Sussel L, Marín O, Kimura S, Rubinstein JLR (1999) Loss of *Nkx2.1* homeobox gene function results in a ventral to dorsal molecular respecification within the basal telencephalon: evidence for a transformation of the pallidum into the striatum. Development 126:3359–3370

Swaab DF (1997) Neurobiology and neuropathology of the human hypothalamus. In: Bloom FE, Björklund A, Hökfelt T (eds) Handbook of chemical neuroanatomy, vol 13, The primate nervous system. Part I. Elsevier, Amsterdam, pp 39–137

Swaab DF (2003) The human hypothalamus: basic and clinical aspects, part 1: nuclei of the human hypothalamus. Handb Clin Neurol 79

Swaab DF (2004) The human hypothalamus: basic and clinical aspects, part 2: neuropathology of the human hypothalamus and adjacent structures. Handb Clin Neurol 80

Swaab DF, Fliers E (1985) A sexually dimorphic nucleus in the human brain. Science 228:1112–1115

Swaab DF, Hofman MA (1988) Sexual differentiation of the human hypothalamus: ontogeny of the sexually dimorphic nucleus of the preoptic area. Brain Res Dev Brain Res 44:314–318

Swaab DF, Hofman MA, Lucassen PJ, Purba JS, Raadsheer FC, van de Nes JAP (1993) Functional neuroanatomy and neuropathology of the human hypothalamus. Anat Embryol (Berl) 187:317–330

Switzer RC, Hill J, Heimer L (1982) The globus pallidus and its rostroventral extension into the olfactory tubercle in the rat: a cyto- and chemoarchitectural study. Neuroscience 7:1891–1904

Szeto DP, Rodriguez-Esteban C, Ryan AK, O'Connell SM, Liu F, Kioussi C et al (1999) Role of the bicoid-related homeodomain factor Pitx1 in specifying hindlimb morohogenesis and pituitary development. Genes Dev 13:484–494

Takahashi H, Ohama E, Naito H et al (1988) Hereditary dentato-rubropallido-luysian atrophy: clinical and pathologic variants in a family. Neurology 38:1065–1070

Tamamaki N, Fujimori KE, Takauji R (1997) Origin and route of tangentially migrating neurons in the developing neocortical intermediate zone. J Neurosci 17:8313–8323

Tan SS, Kalloniatis M, Sturm K, Tam PP, Reese BE, Faulkner-Jones B (1998) Separate progenitors for radial and tangential cell dispersion during development of the cerebral cortex. Neuron 21:295–304

Tassabehji M, Newton VE, Read AP (1994) Waardenburg syndrome type 2 caused by mutations in the human microphthalmia (*MITF*) gene. Nat Genet 8:251–255

ten Donkelaar HJ, Cruysberg JRM (2011) The visual system. In: ten Donkelaar HJ (ed) Clinical neuroanatomy: brain circuitry and its disorders. Springer, Berlin/Heidelberg/New York, pp 331–365

ten Donkelaar HJ, Dederen PJW (1979) Neurogenesis in the basal forebrain of the Chinese hamster (*Cricetulus griseus*). I. Time of neuron origin. Anat Embryol (Berl) 156:331–348

ten Donkelaar HJ, Hori A (2011) The hypothalamus and hypothalamohypohysial systems. In: ten Donkelaar HJ (ed) Clinical neuroanatomy: brain circuitry and its disorders. Springer, Berlin/Heidelberg/New York, pp 603–631

ten Donkelaar HJ, Lammers GJ, Gribnau AAM (1979) Neurogenesis in the amygdaloid nuclear complex in a rodent (the Chinese hamster). Brain Res 165:348–353

ten Donkelaar HJ, van de Warrenburg B, Willemsen M, Küsters B, Hashizume Y, Hori A (2011) Basal ganglia. In: ten Donkelaar HJ (ed) Clinical neuroanatomy: brain circuitry and its disorders. Springer, Berlin/Heidelberg/New York, pp 495–564

Tennyson VM, Barrett RE, Cohen G, Côté L, Heikkila R, Mytilineou C (1972) The developing neostriatum of the rabbit: correlation of fluorescence histochemistry, electron microscopy, endogenous dopamine levels, and [^{3}H] dopamine uptake. Brain Res 46:251–285

Theil T, Alvarez-Bolado G, Walter A, Ruther U (1999) *Gli3* is required for *Emx* gene expression during dorsal telencephalic development. Development 126:3561–3571

Theiler K (1972) The house mouse – development and normal stages from fertilization to 4 weeks of age. Springer, Berlin/Heidelberg/New York

Theiler K, Varnum DS, Nadeau JH, Stevens LC, Cagianut B (1976) A new allele of *ocular retardation*: early development and morphogenetic cell death. Anat Embryol (Berl) 150:85–97

Thomas PQ, Dattani MT, Brickman JM, McNay D, Warne G, Zacharin M et al (2001) Heterozygous *HESX1* mutations associated with isolated congenital pituitary hypoplasia and septo-optic dysplasia. Hum Mol Genet 10:39–45

Tole S, Goudreau G, Assimacopoulos S, Grove E (2000a) *Emx2* is required for growth of the hippocampus but not for hippocampal field specification. J Neurosci 20:2618–2625

Tole S, Ragsdale CW, Grove EA (2000b) Dorsoventral patterning of the telencephalon is disrupted in the mouse mutant *extratoes* (*J*). Dev Biol 217:254–265

Toresson H, Campbell K (2001) A role for *Gsh1* in the developing striatum and olfactory bulb of *Gsh* mutant mice. Development 128:4679–4689

Toresson H, Potter S, Campbell K (2000) Genetic control of dorsal-ventral identity in the telencephalon: opposing roles for *Pax6* and *Gsh2*. Development 127:4361–4371

Torres M, Gomez-Pardo E, Gruss P (1996) *Pax2* contributes to inner ear patterning and optic nerve trajectory. Development 122:3381–3391

Towfighi J, Ladda RL, Sharkey FE (1987) Purkinje cell inclusions and 'atelencephaly' in 13q-chromosomal syndrome. Arch Pathol Lab Med 111:146–150

Treier M, O'Connell S, Gleiberman A, Price J, Szeto DP, Burgess R et al (2001) Hedgehog signaling is required for pituitary glandular development. Development 128:377–386

Trottier D, Eloit C, Wassef M, Talmain G, Bensimon JL, Døving KB, Ferrard J (2000) The vomeronasal cavity in adult humans. Chem Senses 25:369–380

Truslove GM (1962) A gene causing ocular retardation in the mouse. J Embryol Exp Morphol 10:652–660

Truwit CL, Barkovich AJ, Grumbach MM, Martini JJ (1993) MR imaging of Kallmann syndrome, a genetic disorder of neuronal migration affecting the olfactory and genital sytems. AJNR Am J Neuroradiol 14:827–838

Tulinius M, Moslemi A-R, Darin N, Westerberg B, Wiklund L-M, Holme E, Oldfors A (2003) Leigh syndrome with cytochrome-c oxidase deficiency and a single T insertion nt 5537 in the mitochondrial $tRNA^{Trp}$ gene. Neuropediatrics 34:87–91

Tuttle R, Nakagawa Y, Johnson JE, O'Leary DDM (1999) Defects in thalamocortical axon pathfinding correlate with altered cell domains in *Mash-1*-deficient mice. Development 1256:1903–1916

Tvrdik P, Capecchi MR (2012) Gene targeting. In: Watson C, Paxinos G, Puelles L (eds) The mouse nervous system. Elsevier, Amsterdam, pp 19–35

Ulfig N (2002a) Ganglionic eminence of the human fetal brain – new vistas. Anat Rec 267:191–195

Ulfig N (2002b) Calcium-binding proteins in the human developing brain. Adv Anat Embryol Cell Biol 165:1–95

Ulfig N, Nickel J, Bohl J (1998) Transient features of the thalamic reticular nucleus in the human foetal brain. Eur J Neurosci 10:3773–3784

Ulfig N, Neudörfer F, Bohl J (2001) Development-related expression of AKAP79 in the striatal compartments of the human brain. Cells Tissues Organs 168:319–329

Ulfig N, Setzer M, Bohl J (2003a) Ontogeny of the human amygdala. Ann NY Acad Sci 985:22–33

Ulfig N, Bohl J, Setzer M (2003b) Expression of NMDAR1 in the human fetal amygdala and the adjacent ganglionic eminence. Neuroendocrinology 2:40–42

Vaizey MJ, Sanders MD, Wybar KC, Wilson J (1977) Neurological abnormalities in congenital amaurosis of Leber. Review of 30 cases. Arch Dis Child 52:399–402

van den Munckhof P, Luk KC, Ste-Marie L, Montgomery J, Blanchet PJ, Sadikot AF, Drouin J (2003) Pitx3 is required for motor activity and for survival of a subset of midbrain dopaminergic neurons. Development 130:2535–2542

Van der Kooy D, Fishell G, Krushel LA, Johnston JG (1987) The development of striatal compartments: from proliferation to patches. In: Carpenter MB, Jarayaman A (eds) The basal ganglia. Structures and concepts – current concepts. . Plenum, New York, pp 81–98

van Domburg PHMF, ten Donkelaar HJ (1990) The human substantia nigra and ventral tegmental area. A neuroanatomical study with

notes on aging and aging diseases. Adv Anat Embryol Cell Biol 121:1–132
van Eden CG, Mrzljak L, Voorn P, Uylings HBM (1989) Prenatal development of GABAergic neurons in the neocortex of the rat. J Comp Neurol 289:213–227
van Heyningen V, Williamson KA (2002) *PAX6* in sensory development. Hum Mol Genet 11:1161–1167
Van Heyningen V, Williamson KA (2008) *PAX6* and aniridia and related phenotypes. In: Epstein CJ, Erickson RP, Wynshaw-Boris A (eds) Inborn errors of development, 2nd edn. Oxford University Press, Oxford, pp 809–817
Van Hoesen GW, Yeterian EH, Lavizzo-Mourney R (1981) Widespread corticostriate projections from temporal cortes of the rhesus monkey. J Comp Neurol 199:205–219
van Overbeeke JJ (1991) The development of the variations of the human basal cerebral arteries. University of Utrecht, Thesis
van Overbeeke JJ, Hillen B, Vermeij-Keers C (1994) The arterial pattern at the base of arhinencephalic and holoprosencephalic brains. J Anat (Lond) 185:51–63
Vanderhaeghen P, Polleux F (2004) Developmental mechanisms patterning thalamocortical projections: intrinsic, extrinsic and in between. Trends Neurosci 27:384–391
Varga ZM, Wegner J, Westerfield M (1999) Anterior movement of ventral diencephalic precursors separates the primordial eye field in the neural plate and requires cyclops. Development 126:5533–5546
Vermeij-Keers C (1975) Primary congenital aphakia and the rubella syndrome. Teratology 11:257–266
Vermeij-Keers C (1987) 6.5-mm Human embryo with a single nasal placode: cyclopia or hypotelorism? Teratology 36:1–6
Verney C, Berger B, Adrien J, Vigny A, Gay MC (1982) Development of the dopaminergic innervation of the rat cerebral cortex. A light microscopic immunocytochemical study using anti-tyrosine hydroxylase antibodies. Brain Res 5:41–52
Verney C, Zecevic N, Nikolic B, Alvarez C, Berger B (1991) Early evidence of catecholaminergic cell groups in 5- and 6-week-old human embryos using tyrosine hydroxylase and dopamine-β-hydroxylase immunocytochemistry. Neurosci Lett 131:121–124
Verney C, Milosevic A, Alvarez C, Berger B (1993) Immunocytochemical evidence of well-developed dopaminergic and noadrenergic innervations in the frontal cerebral cortex of human fetuses at midgestation. J Comp Neurol 336:331–344
Verney C, El Amraoui A, Zecevic N (1996) Comigration of tyrosine hydroxylase- and gonadotrophin-releasing hormone-immunoreactive neurons in the nasal area of human embryos. Brain Res Dev Brain Res 97:251–259
Verney C, Zecevic N, Puelles L (2001a) Structure of longitudinal brain zones that provide the origin for the substantia nigra and ventral tegmental area in human embryos, as revealed by cytoarchitecture and tyrosine hydroxylase, calretinin, calbindin, and GABA immunoreactions. J Comp Neurol 429:22–44
Verney C, Zecevic N, Ezan P (2001b) Expression of calbindin D28K in the dopaminergic mesotelencephalic system in embryonic and fetal human brain. J Comp Neurol 429:45–58
Visser M, Swaab DF (1979) Life span changes in the presence of α-melanocyte-stimulating-hormone-containing cells in the human pituitary. J Dev Physiol 1:161–178
Voit T, Lemburg P, Neuen E, Lumenta C, Strork W (1987) Damage of thalamus and basal ganglia in asphyxiated fullterm neonates. Neuropediatrics 18:176–181
Volpe P, Campobasso G, De Robertis V, Rembouskos G (2009) Disorders of prosencephalic development. Prenat Diagn 29: 340–354
Voogd J, Nieuwenhuys R, van Dongen PAM, ten Donkelaar HJ (1998) Mammals. In: Nieuwenhuys R, ten Donkelaar HJ, Nicholson C (eds) The central nervous system of vertebrates. Springer, Berlin/Heidelberg/New York, pp 1637–2097
Voorn P, Kalsbeek A, Jorritsma-Byham B, Groenewegen HJ (1988) The pre- and postnatal development of the dopaminergic cell groups in the ventral mesencephalon and the dopaminergic innervation of the striatum of the rat. Neuroscience 25:857–887
Vortkamp A, Franz T, Gessler M, Grzeschik K-H (1992) Deletion of *GLI3* supports the homology of the human Greig cephalopolysyndactyly syndrome (GCPS) and the mouse mutant extra toes (*Xt*). Mamm Genome 3:461–463
Waclaw RR, Wang B, Pei Z, Ehrman LA, Campbell K (2009) Distinct temporal requirements for the homeobox gene GSX2 in specifying striatal and olfactory bulb neuronal fates. Neuron 63:451–465
Wallis DE, Roessler E, Hehr U, Nanni L, Wiltshire T, Richieri-Costa A et al (1999) Mutations in the homeodomain of the human *SIX3* gene cause holoprosencephaly. Nat Genet 22:196–198
Walther C, Gruss P (1991) *Pax-6*, a murine paired box gene, is expressed in the developing CNS. Development 113:1435–1449
Wang Q, Chen Q, Zhao K, Wang L, Trabouli EI (2001) Update on the molecular genetics of retinitis pigmentosa. Ophthalmic Genet 22:133–154
Warkany J (1971) Congenital malformations. Year Book Medical Publishers, Chicago
Warner TT, Lennox GG, Janota I, Harding AE (1994) Autosomal-dominant dentato-rubro-pallido-luysian atrophy in the United Kingdom. Mov Disord 9:289–296
Warner TT, Lennox GG, Walker RWH et al (1995) A clinical and molecular genetic study of dentatorubropallidoluysian atrophy in four European families. Ann Neurol 37:452–459
Watanabe YG (1982) Effects of brain and mesenchyme upon the cytogenesis of rat adenohypophysis *in vitro*. I. Differentiation of adrenocorticotropes. Cell Tissue Res 227:257–266
Watkins-Chow DE, Camper SA (1998) How many homeobox genes does it take to make a pituitary gland? Trends Genet 14:284–290
Wawersik S, Purcell P, Maas RL (2000) *Pax6* and the genetic control of early eye development. In: Fini ME (ed) Vertebrate eye development. Springer, Berlin/Heidelberg/New York, pp 15–36
Wichmann T, DeLong MR, Vitel JL (2000) Pathophysiological considerations in basal ganglia surgery: role of the basal ganglia in hypokinetic and hyperkinetic movement disorders. In: Lozano AM (ed) Movement disorder surgery, vol 15, Progress in neurological surgery. Karger, Basel, pp 31–57
Wichterle H, Garcia-Verdugo JM, Herrera DG, Alvarez-Buylla A (1999) Young neurons from medial ganglionic eminence disperse in adult and embryonic brain. Nat Neurosci 2:461–466
Wichterle H, Turnbull DH, Nery S, Fishell G, Alvarez-Buylla A (2001) In utero fate mapping reveals distinct migratory pathways and fates of neurons born in the mammalian forebrain. Development 128:3759–3771
Willnow S, Kiess W, Butenandt O, Dörr HG, Enders A, Strasser-Vogel B et al (1996) Endocrinbe disorders in septo-optic dysplasia (De Morsier syndrome) – evaluation and follow-up of 18 patients. Eur J Pediatr 155:179–184
Wolfram DJ (1938) Diabetes mellitus and simple optic atrophy among siblings: report of four cases. Proc Staff Meet Mayo Clin 13:715–718
Wray S, Nieburgs A, Elkabes S (1989a) Spatiotemporal cell expression of luteinizing hormone releasing hormone in the prenatal mouse: evidence for an embryonic origin in the olfactory pit. Brain Res Dev Brain Res 46:309–318
Wray S, Grant P, Gainer H (1989b) Evidence that cells expressing luteinizing hormone releasing hormone mRNA in the mouse are derived from progenitor cells in the olfactory placode. Proc Natl Acad Sci U S A 86:8132–8136
Wurst W, Bally-Cuif L (2001) Neural plate patterning: upstream and downstream of the isthmic organizer. Nat Rev Neurosci 2:99–108
Xu Q, Cobos I, De la Cruz E, Rubinstein JLR (2004) Origins of cortical interneuron subtypes. J Neurosci 24:2612–2622

Xu Q, Tam M, Anderson SA (2008) Fate mapping Nkx2.1-lineage cells in the mouse telencephalon. J Comp Neurol 506:16–29

Xuan S, Baptista CA, Balas G, Tao W, Soares VC, Lai E (1995) Winged helix transcription factor BF-1 is essential for the development of the cerebral hemispheres. Neuron 14:1141–1152

Yakovlev PI (1959) Pathoarchitectonic studies of cerebral malformations. III. Arrhinencephalies (holotelencephalies). J Neuropathol Exp Neurol 18:22–55

Yakovlev PI (1969) The development of the nuclei of the dorsal thalamus and the cerebral cortex. In: Locke S (ed) Modern neurology (papers in tribute to Professor Denny Derek-Brown). Little, Brown, Boston, pp 1–15

Yamada S, Uwabe C, Fujii S, Shiota K (2004) Phenotypic variability in human embryonic holoprosencephaly in the Kyoto collection. Birth Defects Orig Artic Ser 70:495–508

Yamada S, Samtani RR, Es L, Lockett E, Uwabe C, Shiota K et al (2010) Developmental atlas of the early first trimester human embryo. Dev Dyn 239:1585–1595

Yamadori T (1965) Die Entwicklung des Thalamuskerns mit ihren ersten Fasersystemen bei menschlichen Embryonen. J Hirnforsch 7:393–413

Yamanouchi H, Hirato J, Yokoo H, Nako Y, Morikawa A, Nakazato Y (1999) Olfactory bulb dysplasia: a novel subtype of neuronal migration disorder. Ann Neurol 46:783–786

Ye W, Shimamura K, Rubinstein JLR, Hynes MA, Rosenthal A (1998) FGF and Shh signals control dopaminergic and serotonergic cell fatwe in the anterior neural plate. Cell 93:755–766

Yilmaz Y, Alper G, Kilicoglu G, Celik L, Karadeniz L, Yilmaz-Degirmenci S (2001) Magnetic resonance imaging findings in patients with severe neonatal indirect hyperbilirubinemia. J Child Neurol 16:452–455

Yokochi K, Aiba K, Kodama M, Fujimoto S (1991) Magnetic resonance imaging in athetotic cerebral palsied children. Acta Paediatr Scand 80:818–823

Yoshida M, Suda Y, Matsuo I, Miyamoto N, Takeda N, Kuratani S, Aizawa S (1997) *Emx1* and *Emx2* functions in development of dorsal telencephalon. Development 124:101–111

Young RW (1985) Cell differentiation in the retina of the mouse. Anat Rec 212:199–205

Yun K, Potter S, Rubinstein JLR (2001) *Gsh2* and *Pax6* play complementary roles in dorsoventral paaterning of the mammalian telencephalon. Development 128:193–205

Zaki PA, Quinn JC, Price DJ (2003) Mouse models of telencephalic development. Curr Opin Genet Dev 13:423–437

Zečević N, Kostović I (1980) Synaptogenesis in developing neostriatum of the human fetus. Neurosci Lett Suppl 5:S311

Zecevic N, Verney C (1995) Development of the catecholamine neurons in human embryos and fetuses, with special emphasis on the innervation of the cerebral cortex. J Comp Neurol 351: 509–535

Zeki S (1993) A vision of the brain. Blackwell, Oxford

Zeki SM, Hollman AS, Dutton GN (1992) Neuroradiological features of patients with optic nerve hypoplasia. J Pediatr Ophthalmol Strabismus 29:107–112

Zeltser L, Larsen C, Lumsden A (2001) A novel developmental compartment in the forebrain regulated by Lunatic fringe. Nat Neurosci 4:683–685

Zetterstrom RM, Williams R, Perlmann T, Olson L (1996) Cellular expression of the intermediate early transcription factors Nurr1 and NGFI-B suggest a gene regulatory role in several brain regions including the nigrostriatal dopamine system. Mol Brain Res 41:111–120

Zetterstrom RH, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T (1997) Dopamine neuron agenesis in Nurr1-deficient mice. Science 276:248–250

Zeviani M, Bertagnolio B, Uziel G (1996) Neurological presentations of mitochondrial diseases. J Inherit Metab Dis 19:504–520

Zhao T, Szábo N, Ma J, Luo L, Zhou X, Alvarez-Bolado G (2008) Genetic mapping of Foxb1-cell lineage shows migration from caudal diencephalon to telencephalon and lateral hypothalamus. Eur J Neurosci 28:1941–1955

Zhu X, Rosenfeld MG (2004) Transcriptional control of precursor proliferation in the early phases of pituitary development. Curr Opin Genet Dev 14:567–574

Zschocke J, Quak E, Guldberg P, Hoffmann GF (2000) Mutation analysis in glutaric aciduria type 1. J Med Genet 37:177–181