Chapter 1
Embryologic and Genetic Disorders of the Pituitary Gland

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Hypothalamo-Pituitary Development

The mature pituitary gland is a central regulator responsible for controlling growth, metabolism, reproduction and development and homeostasis through the regulation and function of other endocrine glands in the body [1]. The pituitary gland is situated within the sella turcica recess of the sphenoid bone at the base of the brain and consists of three lobes derived from two adjacent ectodermal layers: the anterior and intermediate lobes from the oral ectoderm and the posterior lobe from the neural ectoderm [2, 3]. Hypothalamo-pituitary (HP) development is dependent on the communication between the oral ectoderm and the overlying neural ectoderm. This occurs through a complex spatio-temporal genetic cascade of transcription factors and signalling molecules that may be either intrinsic or extrinsic to the developing Rathke's pouch, the primordium of the anterior pituitary (AP) [4]. A series of tightly regulated steps that result in cell proliferation and differentiation give rise to the five different specialized AP cell types that secrete six hormones: somatotrophs [growth hormone (GH)], thyrotrophs [thyroid-stimulating hormone (TSH)], gonadotrophs [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)], lactotrophs [prolactin (PRL)] and the corticotrophs [adrenocorticotropic hormone (ACTH)] [5] (Fig. 1.1).

The synthesis of each one of the six anterior pituitary hormones is regulated by specific hypothalamic peptides. Many of these ligands travel via the hypophyseal portal system from the hypothalamus into the bloodstream, a transport system that allows rapid communication and migration of hormones to the anterior pituitary. The ligands bind to their respective receptors on each specific anterior pituitary cell type, giving rise to the six hormones that have targets elsewhere in the body, and play distinct roles in endocrine regulation (Fig. 1.1).

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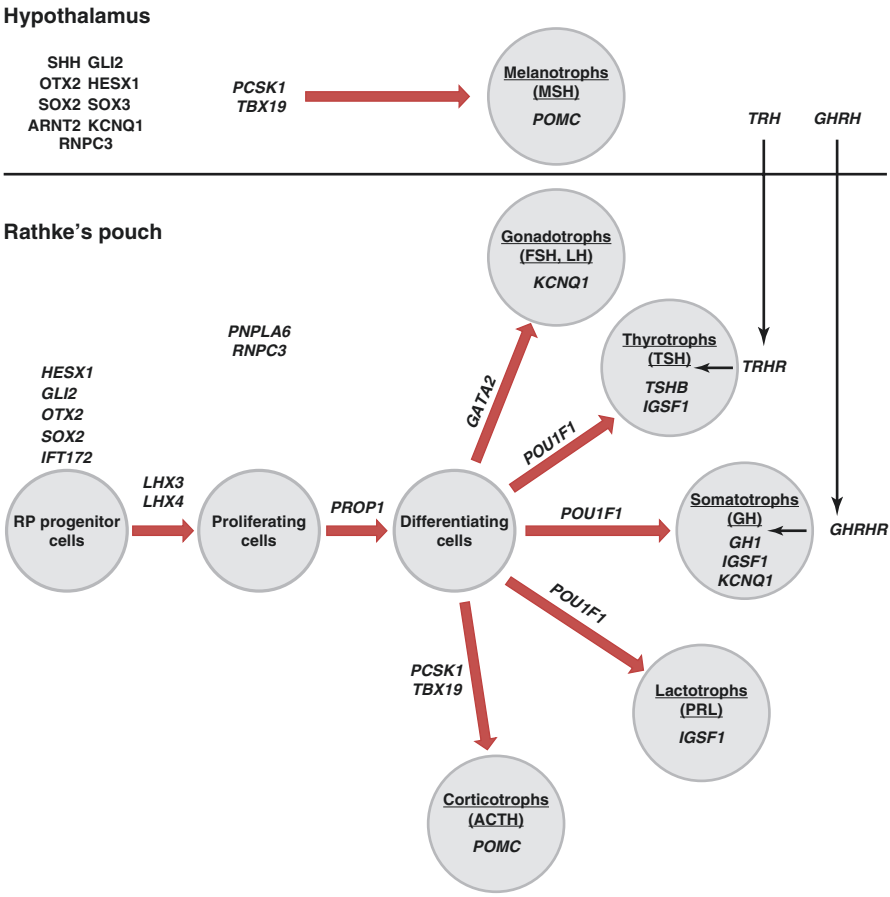

Fig. 1.1 A flowchart illustrating human embryonic hypothalamo-pituitary development. A complex spatio-temporal genetic cascade of transcription factors and signalling molecules, intrinsic or extrinsic, to the developing Rathke's pouch. A series of tightly regulated steps result in cell proliferation and differentiation to give rise to the five different specialized anterior pituitary cell types that secrete six hormones. Specific peptides derived from the hypothalamus regulate the synthesis of these hormones by binding to their respective receptors on each anterior pituitary cell type

Human Conditions Arising from Disordered Hypothalamo-Pituitary Development

Congenital hypopituitarism (CH) is characterized by deficiencies in one or more of these six hormones, with GH being the most frequently occurring hormone deficiency and often seen in isolation [4]. It is a syndrome with a wide variation in severity and may present early in the neonatal period or later in childhood. Midline and craniofacial structural abnormalities are often associated with CH, giving rise to a range of highly variable disorders, ranging from fatality to holoprosencephaly

(HPE), septo-optic dysplasia (SOD) and Kallmann syndrome (KS), characterized by hypogonadotropic hypogonadism (HH) with anosmia [6]. Thus, disordered embryogenesis can cause variable phenotypes involving a range of craniofacial midline defects, associated with HP disorders. All causative genes for congenital hypopituitarism and related disorders and their inheritance patterns are listed in Table 1.1 and are discussed throughout this chapter.

Isolated Growth Hormone Deficiency

Growth hormone-releasing hormone (GHRH) is released from the hypothalamus and binds to its receptor (GHRHR) on somatotroph cells. This results in the synthesis and release of GH, in the presence of the transcription factor POU1F1 [7]. GH then binds to its receptors on target tissues, primarily the liver, leading to the release of insulin-like growth factor 1 (IGF1) and its binding protein, IGFBP3. The most common isolated deficiency is congenital isolated GH deficiency (IGHD) that has an incidence between 1/4000 and 1/10,000 live births. The majority of cases are sporadic, with a small percentage (3–30%) of familial cases, the aetiology being unknown in most patients [8, 9]. Short stature, ranging from moderate to severe, is the essential phenotypic feature in IGHD and is associated with a poor growth velocity with delayed skeletal maturation. Children with GHD are usually treated with recombinant human GH (rhGH) and generally respond well [9]. A number of genetic forms of GHD have been described. Autosomal recessive IGHD type IA patients present with severe growth failure in the first 6 months of life with undetectable GH concentrations. These patients frequently develop anti-GH antibodies after receiving exogenous GH, which prevent the growth response anticipated after rhGH therapy [10]. Heterogeneous homozygous *GH1* deletions, most frequently measuring 6.7 kb in length, were first described and remain the most common *GH1* gene alteration in patients with IGHD type IA [11], with other severe loss-of-function *GH1* mutations described subsequently (Table 1.1).

Type IB GHD is associated with recessive mutations in *GH1* and *GHRHR*, the latter also known as Sindh dwarfism [12]. Missense, frameshift, nonsense or splice site mutations may occur in *GH1* in patients from consanguineous pedigrees and specific ethnic backgrounds, for example, IVS4 + 1G → T, p.G120 V and p.C182X, respectively [5, 13, 14]. Type IB GHD due to *GHRHR* mutations is not a classical IGHD phenotype, in that these patients have minimal facial hypoplasia and no microphallus but do manifest anterior pituitary hypoplasia (APH) on magnetic resonance imaging (MRI) [15]. Patients that harbour *GHRHR* mutations are usually from consanguineous pedigrees from Brazil or the Indian subcontinent [16]. The vast majority of *GHRHR* mutations are associated with complete loss of function, for example, p.W273S and p.A176V [8, 17], and usually affect cAMP production, such as the p.K329E substitution that fails to show any cAMP response following GHRH treatment in in vitro studies [18]. The first, and still the most common, *GHRHR* mutation is p.E72X resulting in a truncated protein devoid of both the

Table 1.1 Genes associated with congenital hypopituitarism and related phenotypes, and their inheritance patterns

Gene	Phenotype	Inheritance
GH1	IGHD type IA	Autosomal recessive
	IGHD type IB	Autosomal recessive
	IGHD type II	Autosomal dominant
GHRHR	IGHD type IB	Autosomal recessive
RNPC3	IGHD	Autosomal recessive
TSHB	TSHD	Autosomal recessive Compound heterozygous
TRHR	TSHD	Autosomal recessive Compound heterozygous
IGSF1	TSHD, hypoprolactinemia, transient GHD; usually with macroorchidism	X-linked
TBL1X	TSHD	X-linked
TBX19	IAD	Autosomal recessive
POMC	IAD; early-onset obesity and red hair pigmentation	Autosomal recessive
PCSK1	IAD, GHD, TSHD, DI	Compound heterozygous Autosomal dominant
TCF7L1	SOD	Autosomal dominant
HESX1	IGHD	Autosomal dominant Autosomal recessive
	CPHD	
	SOD	
SOX2	HH, anophthalmia/microphthalmia	Autosomal dominant
	Hypothalamo-pituitary tumour	
SOX3	CPHD and absent infundibulum GHD	X-linked
OTX2	SOD	Autosomal dominant: haploinsufficiency or dominant negative
	CPHD	
	IGHD	
LHX3	CPHD, short neck with limited rotation	Autosomal recessive
LHX4	CPHD	Autosomal dominant Autosomal recessive
PROP1	CPHD	Autosomal recessive
POU1F1	CPHD	Autosomal dominant Autosomal recessive
PROKR2	HH/KS	Autosomal recessive Autosomal dominant
	SOD	
FGFR1	HH/KS	Autosomal dominant
	SOD	
FGF8	HH/KS	Autosomal dominant Autosomal recessive
	HPE	
	SOD	
KAL1	HH/KS	X-linked
	SOD	
	KS	

Table 1.1 (continued)

Gene	Phenotype	Inheritance
GLI2	HPE	Autosomal dominant: Haploinsufficiency
	IGHD/ CPHD	
	HH	
CDON	PSIS	Autosomal dominant
GPR161	PSIS	Autosomal recessive
ROBO1	PSIS	Autosomal dominant
ARNT2	CPHD	Autosomal recessive
PNPLA6	Oliver–McFarlane and Laurence–Moon syndrome	Autosomal recessive
KCNQ1	GHD, maternally inherited gingival fibromatosis	Autosomal dominant
IFT172	GHD, retinopathy, metaphyseal dysplasia, renal failure (ciliopathies)	Compound heterozygous

IGHD isolated growth hormone deficiency, *TSHD* thyroid-stimulating hormone deficiency, *IAD* isolated adrenocorticosteroid hormone deficiency, *DI* diabetes insipidus, *SOD* septo-optic dysplasia, *CPHD* combined pituitary hormone deficiency, *HH* hypogonadotropic hypogonadism, *KS* Kallmann syndrome, *HPE* holoprosencephaly, *PSIS* pituitary stalk interruption syndrome

transmembrane and intracellular domains (Wajnrajch et al. 1996). A recent study described a novel partial loss-of-function homozygous *GHRHR* mutation, p.P79L, which gives rise to an unusually mild form of IGHD in two unrelated families. The patients were compound homozygous, with a second homozygous variant in *GHRHR*, p.R4Q, which was not associated with functional impairment [19].

Heterozygous mutations in the *GH1* gene commonly affect splicing resulting in exon skipping, leading to the most common autosomal dominant form of GHD, known as type II GHD [20] (Table 1.1). The shorter 17.5 kDa GH isoform, resulting from the skipping of exon 3, has been reported to exert a dominant negative effect on GH secretion, with expression levels directly related to severity of the disorder [21, 22]. Heterozygous *GH1* missense mutations, such as p.E32A, p.R178H and p.R183H, have also been described in GHD type II. These patients have variable height deficit and severity, occasionally with a height within the normal range, and may develop additional pituitary hormone deficiencies over time, including ACTH, TSH and gonadotrophin deficiencies [8]. To date, no mutations in *GHRH* have been described in association with IGHD.

In addition to *GH1* and *GHRHR*, mutations have recently been reported in *RNPC3* in patients with GHD. The RNA-binding region (RNA recognition motifs [RRM]) containing 3 on chromosome 1 encodes a 65 K protein component of the U12-type spliceosome. It contains two bipartite nuclear targeting sequences important for nuclear targeting for proteins, especially those functioning in the cell nucleus itself, and its two RRM motifs suggest that it may contact one of the small nuclear RNAs of the minor spliceosome [23]. Biallelic mutations in *RNPC3* have been described in three sisters with severe IGHD and pituitary hypoplasia, where anomalies were identified in U11/U12 di-snRNP formation and the splicing of multiple U12-type introns in these patient cells [24]. Through RNA sequencing the

authors identified a list of 21 genes with significantly decreased U12/U2 ratios in patient cells, as well as aberrant processing events including exon skipping and activation of cryptic U2-type splice sites [24]. A subset of the 21 genes were found to encode proteins with relevant functions in pituitary development, such as *SPCS2* and *SPCS3* that encode subunits of the signal peptidase complex, implicated in post-translational processing of preprohormones such as preproghrelin to proghrelin [24, 25], thus themselves becoming candidates for GHD. However, the exact mechanism underlying the GH deficiency remains to be established.

No murine model for *Rnpc3* loss of function exists; however studies using a zebrafish mutant model with an induced lethal point mutation in *rnpc3* have provided a useful and specific model of aberrant U12-type splicing in vivo. Results showed that the formation of aberrant U11- and U12-containing snRNAs sufficiently impaired the efficiency of U12-type splicing to cause arrested development in the intestine, liver and pancreas. Analysis of the zebrafish transcriptome revealed that efficient mRNA processing is a critical process for the growth and proliferation of cells during vertebrate development [26]. Additionally, mutations have occasionally been described in IGHD patients in genes encoding early (*HESX1*, *SOX2*, *SOX3* and *OTX2*) or late (*PROP1* and *POU1F1*) transcription factors implicated in murine and human pituitary development [9, 27, 28].

Other Isolated Hormone Deficiencies and Abnormalities

Congenital functional failure of a single lineage has been reported for all pituitary cell types, giving rise to isolated hormone deficiencies other than IGHD, such as isolated TSH deficiency (TSHD), isolated hypogonadotropic hypogonadism [IHH; LH and FSH deficiency] that may be part of KS, isolated ACTH deficiency (IAD) and, very rarely, isolated PRL deficiency (PRLD) [29]. Interestingly, an increased prolactin is more likely to occur in children with congenital hypopituitarism, particularly those with midline defects, as opposed to a decrease. Although rare, isolated PRLD also known as hypoprolactinaemia clinically manifests only in women as puerperal alactogenesis, namely, the failure of milk production during breastfeeding [30]. One such familial case involved a mother and daughter that had eight pregnancies cumulatively, all followed by puerperal alactogenesis resulting from isolated PRLD [31]. The aetiology of isolated PRLD is as yet unknown, and candidate genes often screened are those found to be mutated in patients with PRLD as part of combined pituitary hormone deficiency (CPHD) and that are known to be involved in the lineage differentiation of lactotrophs, such as *POU1F1*, *PROP1*, *LHX3*, *LHX4*, *HESX1* and *OTX2* [32] (Table 1.1).

In TSHD, inadequate thyroid hormone biosynthesis occurs due to defective stimulation of the thyroid gland by TSH, therefore causing central, or secondary, hypothyroidism in the affected patients. In some rare cases, mutations in genes regulating TSH biosynthesis and secretion, namely, *TSHB*, *TRHR* and more recently *IGSF1,* have been described in patients with isolated TSHD [33, 34]. In addition, a homo-

zygous frameshift mutation in *PROP1* in a pedigree has been reported to be associated with isolated central hypothyroidism presenting at a young age [35], indicating that this well-known CPHD causative gene should also be considered in the diagnosis of TSHD.

Mutations in *TSHB*, encoding the TSHβ subunit, have previously been identified in hypothyroid patients, with TSH concentrations that are highly variable, and not always detectable [36, 37]. The most frequently occurring *TSHB* mutation, c.373delT (C105Vfs114X) [37], causing secondary hypothyroidism is known as a mutational 'hotspot' in *TSHB* and has been identified in homozygous form in several populations worldwide [38]. It has also been identified in compound heterozygosity with p.Q49X [39], a 5.4kb *TSHB* deletion (c.1-4389_417*195delinsCTCA) and a missense p.M1P variant [40], amongst others. Screening using both T_4 and TSH is a highly sensitive method for detecting congenital hypothyroidism in neonates and helps prevent mental retardation, which could be a consequence of delayed diagnosis [41].

Rare recessive biallelic inactivating mutations in *TRHR*, namely, p.S115-T117del and p.A118T, have been reported in three affected individuals from two unrelated pedigrees with central congenital hypothyroidism (CCH), with absent TSH and prolactin responses to exogenous TRH [42, 43]. More recently, the p.P81R missense mutation described in isolated CCH highlights the importance of the second transmembrane helix in mediating TRH receptor activation via hormone binding, making it the first deleterious missense TRHR defect that gives rise to CCH [44]. In addition, a recently identified novel homozygous mutation, p.I131T, that decreases TRH affinity was identified in an overweight patient with CCH and normal stature [33].

More recently, *IGSF1* mutations have been associated with an X-linked form of central hypothyroidism associated with macroorchidism; mutations include missense, nonsense, frameshift and submicroscopic gene deletions incorporating *IGSF1* [34, 45]. *Igsf1* is expressed in murine pituitary thyrotroph, lactotroph and somatotroph cells [34] and in Leydig and germ cells in murine/human testes, with very low levels in Sertoli cells [46]. Furthermore, the latter study implies that IGSF1 stimulates transcription of TRHR by negative modulation of the TGFβ1-Smad signalling pathway, thereby enhancing TSH synthesis and biopotency. In contrast, IGSF1 is suggested to downregulate the activin-Smad pathway, leading to reduced expression of *FSHB* secreted by gonadotropes. The authors describe a large hemizygous 207.873 Kb deletion on Chr. Xq26.2 associated with hypothyroidism with reduced TSH biopotency, increased secretion of FSH in neonatal minipuberty and macroorchidism from 3 years of age [46]. Macroorchidism does not appear to be a phenotypic feature in all patients with *IGSF1* mutations [47], and interestingly, heterozygous female carriers of these *IGSF1* mutations may sometimes manifest mild hypothyroidism [48]. *Igsf1*-deficient male mice (Igsf1_ex1male) show diminished pituitary and serum TSH concentrations, pituitary TRH receptor expression and triiodothyronine concentrations and increased body mass [34]. Recent studies have shown that *Igsf1*-deficient male mice with a loss-of-function mutation in the C-terminal domain exhibit reduced expression of the TSH subunit genes as well as

TSH and TRH proteins. Addition of exogenous TRH resulted in TSH release, albeit to a significantly lesser extent than wild-type littermates [49].

The X-linked transducin β-like protein 1 (*TBL1X*) gene is a component of the thyroid hormone receptor-corepressor complex, mutations in which have been previously associated with sensorineural hearing loss [50]. In a recent study, six mutations in unrelated pedigrees with congenital isolated central hypothyroidism have been identified [51]. Like *IGSF1*, *TBL1X* is associated with an X-linked form of TSHD.

Isolated ACTH deficiency (IAD) is a very rare and heterogeneous condition making diagnosis very difficult due to the varied clinical presentation. It may be lethal due to the hypocortisolism and has also been associated with neonatal hypoglycaemia, convulsions, hypercalcaemia [52] and/or cholestasis that can be associated with a 20% mortality rate if unrecognized [53, 54]. IAD patients have also presented with an empty sella and severe hyponatraemia [55]. *TBX19*, formally known as *TPIT*, plays a critical role in the terminal differentiation of the pituitary pre-pro-opiomelanocortin (POMC) lineages, namely, corticotrophs and melanotrophs. Mutations in *TBX19* have been associated with early-onset IAD [56] and have been found in up to 2/3 of neonatal cases, with complete or severe loss of function as exemplified by studies of DNA binding and/or transactivation [57]. These *TBX19* mutations are most often substitutions in the DNA-binding Tbox domain, thereby resulting in impaired DNA binding or protein-protein interaction. However, premature stop codons, aberrant splicing and chromosomal deletions have also been reported in this gene [58]. A recent study described compound heterozygosity in *TBX19*, with a novel frameshift p.Arg222Lysfs*4 mutation and the previously described p.R286X mutation, respectively, in a patient with IAD combined with recurrent respiratory tract infections. The authors concluded that adrenal insufficiency should be considered in patients with unexplained recurrent infections to prevent a delay in diagnosis [59].

The serial cleavage of POMC by prohormone convertases (PCs) generates ACTH in corticotrophs (PC1) and melanocyte-stimulating hormone (αMSH) in melanotrophs (PC2) that bind to the melanocortin receptors (MC2-R, MC1-R and MC4-R, respectively) [60–62]. *POMC* mutations have been reported in association with IAD. MC1-R function is known to contribute towards hair and skin pigmentation in both mice and humans [63]. ACTH is the only known ligand for MC2-R located in the adrenals [64]. Antagonistic studies on MC4-R signalling have revealed its involvement in the regulation of food intake and in the aetiology of severe obesity in mice [65], which occurs in the absence of the MC4-R ligand α-MSH. Therefore patients with *POMC* mutations usually have the distinct phenotypic hallmarks of early-onset obesity and red hair, in addition to adrenal insufficiency with hypocortisolism and hypoglycaemia. The first *POMC* mutations described were the compound heterozygous p.G7013 T/p.C7133Δ and the homozygous p.C3804A identified, respectively, in such patients [66]. Compound heterozygosity has also been described in *PCSK1*, encoding PC1, in a female patient with ACTH and gonadotrophin deficiency, with severe obesity and glucose dysregulation [67]. PC1 has since been described as being essential for the normal absorptive function of the

human small intestine, with compound heterozygosity identified in a second patient with malabsorptive severe refractory neonatal diarrhoea as the predominant phenotype. This patient, similar to the first, also had obesity, hypoadrenalism, reactive hypoglycaemia and elevated circulating levels of specific prohormones [68]. PC1-null mice confirm defective POMC and proinsulin processing seen in PC1-deficient humans; however, mice are growth retarded rather than obese [69]. Subsequent *PCSK1* mutations have since been identified in patients, such as the nonsense p.Arg80* loss-of-function mutation, which produces a truncated protein with only 2 exons out of 14, and that co-segregated with obesity in a three-generation family [70]. Furthermore, recent studies have generated *PCSK1* (PC1)-deficient human embryonic stem cell (hESC) lines, differentiated into hypothalamic neurons, to investigate POMC processing. Results showed that unprocessed POMC increased and processed POMC-derived peptides in *PCSK1* knockout hESC-derived neurons decreased in cells, which phenotypically copies the POMC processing reported in PC1-null mice and PC1-deficient patients [71]. PC1/3-deficient patients often manifest hypothyroidism and hypocortisolism. However some patients may also present with an elevated TSH and ACTH, respectively [72]. In rare cases, GHD and diabetes insipidus may also occur in these patients, thus broadening disease manifestation in *PCSK1* insufficient patients [73].

Septo-Optic Dysplasia

SOD, also known as de Morsier syndrome, occurs in 1/10,000 live births with equal prevalence in males and females. It is a heterogeneous disorder with a variable phenotype, loosely defined by any combination of the triad of optic nerve hypoplasia (ONH), midline neuroradiological abnormalities (such as agenesis of the corpus callosum and absence of the septum pellucidum) and pituitary hypoplasia with consequent endocrine deficits [74, 75]. Approximately 40% of SOD patients may actually present with normal endocrinology. Intriguingly, SOD is associated with a younger maternal age, when compared with mothers of children with isolated defects of the HP axis [76]. The reason for this maternal age effect is unknown but has been suggested to be associated with increased maternal drug and alcohol abuse [77, 78]. Approximately 75–80% of patients exhibit ONH, which may be unilateral or, more commonly, bilateral (88% as compared with 12% unilateral cases), and may be the first presenting feature with later onset of endocrine dysfunction [79]. In rare cases, the eye abnormality may be more severe, resulting in microphthalmia or anophthalmia [80], where one or both of the eyes are abnormally small or completely absent, respectively. The association of midline abnormalities with hypopituitarism has long been established, suggesting a common developmental origin of the hypothalamus and pituitary and the midline structures within the brain [81]. Mutations in the gene encoding the transcriptional repressor HESX1 were the first to be associated with the pathogenesis of rare cases of SOD [82, 83]. Significant insights into the pathogenesis of the disorder were provided

by the original studies, whereby murine transgenesis resulted in murine phenotypes highly reminiscent of SOD. Thereafter, human mutations have been cloned into mouse models and studied in depth, such as the first *HESX1* mutation (p.R160C) identified [84]. More recently, *SOX2*, *SOX3* and *OTX2* have been shown to be mutated in rarer forms of SOD, with severe bilateral eye defects including microphthalmia or anophthalmia in patients with *SOX2* and *OTX2* mutations, and abnormalities of the hypothalamus, pituitary and the infundibulum as well as the corpus callosum in patients with *SOX3* mutations [85] (Table 1.1). Recently, mutations in genes implicated in KS have also been linked with SOD; for example, two heterozygous *KAL1* mutations were identified in three females from two unrelated families with SOD [86]. Prior to this, three patients with SOD were reported to have heterozygous mutations in *FGFR1* that altered receptor signalling, with one predicted to affect splicing [87]. The same report also identified a heterozygous loss-of-function mutation, p.R268C, in *PROKR2*. This variant had previously been implicated in normosmic HH and KS. The heterozygous missense *FGF8* mutation, p.Q216E, has also been described in an SOD patient with microcephaly and neurological defects. Interestingly, *FGF8* has also been implicated in a patient with semilobar HPE, diabetes insipidus and TSH and ACTH insufficiency [6], making this KS gene a new candidate for both SOD and HPE. More recently, a defined role for *TCF7L1* in the aetiology of SOD has been described. Conditional deletion of murine *Tcf7L1* results in forebrain defects and partially penetrant dwarfism [88]. Heterozygous missense *TCF7L1* variants were then subsequently identified in two unrelated SOD patients [88].

SOD can be associated with a wide range of phenotypic variability, highlighting the complexity of the disorder and suggesting the impact of both genetic and environmental factors involved in the aetiology of the disease [89]. Other associated features include developmental delay, seizures, visual impairment, sleep disturbance, precocious puberty, obesity, anosmia, sensorineural hearing loss and cardiac anomalies [77]. The majority of cases remain aetiologically unexplained. The following section describes the role of the genes linked with this disorder and other CH syndromes to date.

HESX1

The transcription factor HESX1 is a member of the paired-like class of homeodomain proteins which acts as a transcriptional repressor essential for pituitary organogenesis [83]. Binding partners of human HESX1 such as transducing-like enhancer of split 1 (TLE1) (ortholog of Groucho in *Drosophila*), the nuclear corepressor (N-COR) and DNA methyltransferase 1 (DNMT1) can all form complexes to enable it to exert its repressive activity [90, 91]. *Hesx1* is one of the earliest markers of murine pituitary development, expressed initially during gastrulation in the region fated to form the forebrain and ventral diencephalon, and is then restricted to Rathke's pouch by embryonic day (E) 9.0 [92]. *Hesx1* continues to be

expressed in the developing AP until E12, when it then disappears in a spatio-temporal sequence that corresponds to progressive pituitary cell differentiation [4]. *Hesx1* transcripts have totally disappeared from the entire ventral portion by E13, giving rise to the anterior lobe of the pituitary [93]. A homozygous null mutation in mice results in a phenotype that resembles SOD, with 5% of *Hesx1* null mice exhibiting a severe phenotype with no AP [90]. This is consistent with an insertion mutation in exon 3 in the 'Alu' element of *HESX1* which was identified in a patient with a retinal coloboma associated with aplasia of the AP. The reported patient had undetectable concentrations of all AP hormones [94]. Patients with *HESX1* mutations have variably penetrant phenotypes ranging from isolated GHD, evolving hypopituitarism in the absence of midline and eye defects, through to SOD and pituitary aplasia [95]. *Hesx1* null mice show great phenotypic variability with features that include a reduction in forebrain tissue, craniofacial dysplasia with a short nose and absence of developing optic vesicles. These mice also have a significantly decreased head size, absence of telencephalic vesicles, absence of olfactory placodes, hypothalamic and infundibular abnormalities, and aberrant morphogenesis of Rathke's pouch [83]. Rathke's pouch formation was variably affected, and abnormal bifurcations were apparent, resulting in multiple pituitary glands in a proportion of the mice [82, 83, 96]. Although of variable severity, both neonatal and adult homozygous mutant mice manifested phenotypes that presented with eye defects such as microphthalmia and anophthalmia, with abnormalities of the septum pellucidum and corpus callosum, closely resembling SOD in humans.

SOX2 and SOX3

SOX2 and *SOX3* are members of the *SOXB1* subfamily of '*SRY-related HMG box*' transcription factors. They have an N-terminal domain of unknown function, a DNA- binding high mobility group (HMG) box domain and a longer C-terminal domain involved in transcriptional activation [97]. Members of the *SOXB1* subfamily are expressed throughout the CNS and are amongst the earliest neural markers that play a role in neuronal determination [98]. Murine *Sox3* is shown to be involved in neurogenesis through its expression in actively dividing undifferentiated neural progenitor cells, and this expression is maintained throughout development [99]. Expression of *Sox3* is also seen in the ventral diencephalon, infundibulum and presumptive hypothalamus, a similar expression pattern to that of *Wnt5a* expression [100]. *Sox3*-deficient mice exhibit expanded BMP and FGF signalling domains as well as abnormalities in Rathke's pouch [101], suggesting a possible mechanism underlying the hypopituitary phenotype in these mutants [102]. The mutant mice exhibited variable complex phenotypes including craniofacial abnormalities, midline CNS defects and a reduction in size and fertility [101]. Mutations in *SOX3* are usually associated with infundibular hypoplasia and an ectopic or undescended PP and have been shown to result in aggresome formation and impaired transactivation

[103]. Duplications within the Xq24-q27.3 region [104], incorporating *SOX3,* have long been associated with X-linked hypopituitarism and mental retardation. *SOX3* was the only gene that was found to be expressed in the murine infundibulum out of three annotated in the smallest duplication (690Kb) to date. Submicroscopic *SOX3*-spanning duplications at position Xq27.1 have since been described in patients with variable hypopituitary phenotypes including CPHD, absence or hypoplasia of the infundibulum and an abnormality of the corpus callosum [85]. Polyalanine expansions of *SOX3* were initially associated with X-linked mental retardation and IGHD in a French pedigree that harboured an in-frame duplication of 33 bp encoding for 11 alanines in the *SOX3* gene [105]. A further *SOX3* polyalanine expansion was later associated with loss of function in a transcriptional assay in an X-linked pedigree with hypopituitarism [85]. Additionally, a 2.31-Mb deletion on Xq27, again incorporating *SOX3*, was identified in a patient with haemophilia B due to the loss of factor IX and CH due to loss of *SOX3*, with the unusual phenotype of a persistent craniopharyngeal canal on MRI [106], a phenotype that was replicated in *Sox3* null mice. Furthermore, an 18 bp deletion in the polyalanine tract of *SOX3* (p.A243_A248del6) was identified in a CH patient, resulting in an increase in transcriptional activation [107]. These data highlight the critical gene dosage of *SOX3* in normal development of the diencephalon and infundibulum and consequently the AP.

SOX2 is expressed in neural progenitor populations throughout the developing and adult CNS and is necessary to maintain their progenitor identity [108]. After gastrulation, murine *Sox2* expression is restricted to the presumptive anterior neuroectoderm and, by E9.5, is expressed throughout the CNS, brain, sensory placodes, branchial arches, gut endoderm, oesophagus and trachea. Homozygous null *Sox2* mice fail to survive and die shortly after implantation [109], whereas heterozygous mice manifest hypoplasia and abnormal morphology of the AP, with subsequent reduction in GH, LH, ACTH and TSH concentrations [110]. Other studies have shown that retinal progenitor cells with conditionally ablated *Sox2* lose competence to both proliferate and terminally differentiate. Additionally, *Sox2* hypomorphic/null mice, with a 40% reduction of *Sox2* expression compared to wild-type (WT) mice, present with variable microphthalmia as a result of aberrant neural progenitor differentiation. Furthermore, this study suggests that *Sox2/SOX2* activity functions in a dose-dependent manner in retinal progenitor cell differentiation [111]. The first description of *SOX2* mutations in humans was in a cohort of individuals with severe eye phenotypes. De novo mutations were associated with bilateral anophthalmia, or severe microphthalmia, with accompanying developmental delay, learning difficulties, oesophageal atresia and genital abnormalities in males [112]. *SOX2* expression in humans is observed throughout the human brain, including the developing hypothalamus as well as Rathke's pouch and the eye [80]. Following on from these studies, *SOX2* mutations have also been associated with AP hypoplasia and hypogonadotropic hypogonadism (HH) [110] and are usually associated with loss of function. These de novo mutations result in a loss of DNA binding, nuclear localization or transcriptional activation, suggesting that the phenotypes arise as a result of haploinsufficiency of *SOX2* during development. Conditional deletion of *Sox2* mutant mice in the hypothalamus and pituitary is associated with impaired gonado-

trophin secretion as well as TSH and GH deficiencies. This suggests a critical role for *Sox2* in the hypothalamus and/or the developing pituitary, particularly with respect to GnRH neuron specification [113]. In addition, *SOX2* haploinsufficiency has been implicated in the generation of slow-progressing pituitary tumours in patients [114]. Furthermore, a very recent study [115] has implicated a role for SOX2 in melanotrope cell fate acquisition, independent of its early role in promoting progenitor proliferation. This study showed that SOX2 is maintained at low levels in melanotropes [115] where its expression is likely regulated by P27 [116]. Murine cells expressing Sox2 and E-cadherin are found throughout the RP in embryos but persist scattered throughout the adult gland, predominantly within a narrow zone lining the pituitary cleft. These postnatal Sox2+ cells also express *Sox9* and *S100* [117]. Interestingly, both embryonic and adult Sox2+ pituitary progenitor/stem cells have shown the ability to differentiate into all hormone-producing lineages, contributing to organ homeostasis during postnatal life. Furthermore, the targeted expression of oncogenic β-catenin in Sox2+ cells gives rise to pituitary tumours [118]. Therefore Sox2+ pituitary stem/progenitor cells not only seem to be involved in long-term physiological maintenance of the adult pituitary, but they also appear accountable for driving tumorigenesis in vivo.

OTX2

OTX2 (orthodenticle homeobox 2) is a transcription factor that is required for the formation of anterior structures and maintenance of the forebrain and has been implicated in 2–3% of anophthalmia-/microphthalmia-related syndromes in humans [82]. In mice, the expression of *Otx2* is localized to developing neural and sensory structures of the brain such as the cerebellum, the eye, nose and ear and is required at multiple steps in brain development and neuronal differentiation [119]. Mice homozygous for mutations die from severe brain abnormalities after exhibiting malformations in both the forebrain and the eye due to impaired gastrulation. Heterozygous mice can display a range of phenotypes from normal to severe forms of eye/brain abnormalities such as anophthalmia and HPE [120]. During retinal development, *Otx2* regulates retinal pigment epithelium specification and photoreceptor and bipolar cell differentiation and maturation, with expression being maintained in these three cell types throughout life [121]. *Otx2* transcripts and protein are normally detectable at E10.5 in both the ventral diencephalon and Rathke's pouch. By E12.5 *Otx2* transcripts are undetectable in Rathke's pouch but persist in the ventral diencephalon until E14.5, and by E16.5, no *Otx2* transcripts are detected in either structure [122]. A previous study showed that *Otx2* expression persisted in Rathke's pouch until E16.5 in *Prop1*-mutant mice, 4 days after the peak of *Prop1* expression and 2 days after any pituitary defects become apparent [122]. This study suggests that Prop1 regulates expression of other factors that suppress *Otx2*, implying a role for Otx2 in murine pituitary development. Another study reported an HH phenotype in GnRH-neuron-*Otx2* knockout mice [123]. These murine data are

consistent with human *OTX2* phenotypes, which are highly variable and include IGHD, hypopituitarism and HH, usually, but not invariably, associated with severe ocular malformations [124]. Furthermore, OTX2 regulates expression of transcription factors *HESX1* and *POU1F1*, thereby influencing anterior pituitary development. In vitro functional analysis showed that mutant Otx2 abolished activation of the HESX1 promoter and was hypomorphic on the POU1F1 promoter [125]. Despite this knowledge, the precise role of *OTX2* in hypothalamo-pituitary development still remains unclear [3]. In addition, in vivo otocephaly gene suppression studies show that *OTX2* loss-of-function mutations modify otocephaly and/or dysgnathia phenotypes in humans when in the presence of a second known otocephaly gene mutation. This suggests that mutant *OTX2* contributes to the severity of craniofacial defects, such as those affecting the lower jaw [126].

GLI2

The *GLI family zinc finger 2* (*GLI2*) transcription factor is a component of the SHH signalling pathway, known to be implicated in HPE and other midline neurodevelopmental anomalies [127, 128]. Unlike mutated *SHH*, described to specifically cause HPE, mutated *GLI2* is also associated with CH in the absence of midline brain defects [129]. These patients have variable phenotypes ranging from IGHD to complex CPHD, in combination with variable polydactyly, cleft lip/palate, diabetes insipidus, dysmorphic features and an ectopic posterior pituitary on MRI [130–132]. Truncated GLI2 is often reported in such cases, for example, p.L788fsX794, p.L694fsX722 and p.E380X, respectively [130], with complete loss of the C-terminal activator domain. In addition, haploinsufficient missense mutations such as p.E518K [129] and p.R516P [133], for example, have been implicated in the aetiology of CH in these patients. Incomplete or variable penetrance may also be apparent for *GLI2* mutations, where a heterozygous mutation with functional consequences in the child is present in the unaffected parent or a parent with a mild form of the disease, respectively [129].

Pituitary Stalk Interruption Syndrome

Pituitary stalk interruption syndrome (PSIS) is characterized by a thin or discontinuous pituitary stalk, pituitary gland insufficiency and APH and/or an EPP on MRI. Interestingly, a novel missense mutation in *CDON*, another member of the SHH signalling pathway that causes HPE, has been reported in a patient with PSIS, with neonatal hypoglycaemia and cholestasis associated with GH, TSH, and ACTH deficiencies, without HPE [134]. This again demonstrates how mutated members of this crucial pathway may elicit other hypopituitary-related phenotypes, aside from their more established association with HPE. *GPR161*, encoding the orphan G

protein-coupled receptor 161, a transmembrane protein, has also been implicated in PSIS. Whole exome sequencing revealed a homozygous missense mutation, p.L19Q, in a consanguineous family with two affected siblings with PSIS [135]. Despite the lack of functional analysis, prediction models and the hypothesis that GPR161 interacts with GLI2, GLI3 and the SHH pathway suggest a possible involvement of this gene in the aetiology of patients with PSIS [135]. ROBO1 is a receptor involved in Slit/Robo signalling that essentially controls embryonic axon guidance and branching in the nervous system during development [136]. *ROBO1* is another gene that has recently been implicated in PSIS; a novel heterozygous frameshift, a nonsense and a missense mutation (p.A977Qfs*40, p.Y1114* and p.C240S, respectively) were identified in five affected patients. Ocular anomalies including hypermetropia with strabismus and ptosis were present in four out of five patients with PSIS (two familial and one sporadic case) [137]. Known CH causative genes including *LHX4*, *OTX2*, *HESX1*, *SOX3*, and *PROKR2* have also been described to be mutated in rare cases of PSIS [28, 138, 139].

ARNT2

ARNT2 (aryl hydrocarbon receptor nuclear translocator 2) is a member of the basic helix-loop-helix-Per-Arnt-Sim (bHLH-PAS) superfamily of transcription factors. This protein forms heterodimers with sensor proteins from the same family that then bind regulatory DNA sequences. *Arnt2*(-/-) null murine embryos die perinatally and exhibit impaired hypothalamic development [140]. Recent studies showed expression of *ARNT2* within the CNS, including the hypothalamus, as well as the renal tract during human embryonic development. A homozygous frameshift *ARNT2* mutation has been described in several individuals born to a highly consanguineous pedigree with congenital hypopituitarism. These patients exhibit GH, TSH and ACTH deficiencies associated with diabetes insipidus, progressive neurological abnormalities with microcephaly, renal tract abnormalities and post-retinal visual pathway dysfunction, indicating the essential role of ARNT2 in HP development and postnatal brain growth [141]. The disorder appears to be lethal, with several individuals dying in the first few years of life.

PNPLA6

Mutations in the *PNPLA6* gene, , encoding neuropathy target esterase (NTE), are known to be associated with a spectrum of rare neurodegenerative conditions, including spastic paraplegia type 39 (SPG39), Gordon–Holmes syndrome (GHS) and Boucher–Neuhäuser syndrome (BNHS) [142, 143]. This gene has recently been implicated in two distinct neurodegenerative disorders: Oliver–McFarlane and Laurence–Moon syndromes. The phenotypes are characterized by

chorioretinopathy, spinocerebellar ataxia, spastic paraplegia, learning difficulties, and trichomegaly. These disorders include pituitary dysfunction with a small anterior pituitary on MRI, including variable GHD and HH. In humans, embryonic expression studies show *PNPLA6* transcript expression in the developing eye, pituitary and brain. Significant reduction of NTE enzymatic activity was observed in fibroblast cells derived from Oliver–McFarlane syndrome patients. Additionally, full rescue of the *pnpla6* morphant zebrafish was achieved using wild-type *PNPLA6* mRNA, compared to only partial rescue with mutant *PNPLA6* mRNAs [144]. These data signify that defective recessive *PNPLA6* alleles can give rise to rare distinct phenotypes with variable neurodegenerative manifestations (Table 1.1).

KCNQ1

The paternally imprinted gene *KCNQ1* encodes the alpha subunit of the voltage-gated ion channel Kv7.1, previously implicated in cardiac arrhythmia syndromes amongst other heart defects [145]. It is expressed in mouse and human somatotroph and gonadotroph cells in the postnatal pituitary, in hypothalamic GHRH neurons during murine development and in the human hypothalamus [146]. Mutations in *KCNQ1* (p.R116L and p.P369L) have recently been described in patients with GHD, maternally inherited gingival fibromatosis and accompanying mild craniofacial dysmorphic features [146] (Table 1.1). Phenotypic variability is apparent in patients harbouring mutations, even between monozygotic twins where one had more severe growth failure during childhood than the other. This study demonstrates how ion channels are clinically relevant regulators of pituitary function in humans, which supports previous data implicating voltage-gated potassium channel currents in pituitary cells [147–149].

IFT172

The *IFT172* gene encodes a subunit of the intraflagellar transport (IFT) subcomplex IFT-B, necessary for ciliary assembly and maintenance. Mutations in *IFT172* have previously been associated with skeletal ciliopathies, with or without polydactyly, that in turn are often associated with retinal, cerebellar or hepatorenal malformations [150–152]. Interestingly, a patient with early growth retardation, APH and an EPP on their MRI harboured compound heterozygous mutations in *IFT172*, p.C1727R and a novel splice site mutation in intron 4 and c.337–2A >C, identified through WES. This patient manifested retinopathy associated with metaphyseal dysplasia and hypertension with renal failure, indicative of a ciliopathy [153]. This was the first report of an *IFT172* mutation present in a patient who presented with GHD in early childhood, signifying the role of ciliary function in pituitary development and the bridge between early-onset growth failure and ciliopathies (Table 1.1).

Furthermore, Alström syndrome, a rare autosomal recessive disease characterized by multiorgan dysfunction and associated with GHD, is caused by a mutation in *ALMS1*, encoding a protein that localizes to the centrosomes and basal bodies of ciliated cells [154].

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