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Cadherins in Cerebellar Development: Translation of Embryonic Patterning into Mature Functional Compartmentalization

Christoph Redies · Franziska Neudert · Juntang Lin

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Abstract Cadherins are cell adhesion molecules with multiple morphogenic functions in brain development, for example, in neuroblast migration and aggregation, axon navigation, neural circuit formation, and synaptogenesis. More than 100 members of the cadherin superfamily are expressed in the developing and mature brain. Most of the cadherins investigated, in particular classic cadherins and δ-protocadherins, are expressed in the cerebellum. For several cadherin subtypes, expression begins at early embryonic stages and persists until mature stages of cerebellar development. At intermediate stages, distinct Purkinje cell clusters exhibit unique rostrocaudal and mediolateral expression profiles for each cadherin. In the chicken, mouse, and other species, the Purkinje cell clusters are separated by intervening raphes of migrating granule cells. This pattern of Purkinje cell clusters/raphes is, at least in part, continuous with the parasagittal striping pattern that is apparent in the mature cerebellar cortex, for example, for zebrin II/aldolase C. Moreover, subregions of the deep cerebellar nuclei, vestibular nuclei and the olivary complex also express cadherins differentially. Neuroanatomical evidence suggests that the nuclear subregions and cortical domains that express the same cadherin subtype are connected to each other, to form neural subcircuits of the cerebellar system. Cadherins thus provide a molecular code that specifies not only embryonic structures but also functional cerebellar compartmentalization. By following the implementation of this code, it can be revealed how mature functional architecture emerges from embryonic patterning during cerebellar development. Dysfunction of some cadherins is associated with psychiatric diseases and developmental impairments and may also affect cerebellar function.

Keywords Cell adhesion · Granule cell · Purkinje cell · Cell migration · Parasagittal organization · Neural circuits

C. Redies (✉) · F. Neudert · J. Lin
Institute of Anatomy I, University of Jena School of Medicine,
Jena University Hospital,
Teichgraben 7,
07743 Jena, Germany
e-mail: redies@mti.uni-jena.de

Expression and Role of Cadherins in the Central Nervous System

Cadherins are a large superfamily of cell adhesion molecules with more than 100 members that play multiple roles in nervous system development (for reviews, see [1–4]). Subgroups of cadherins include the classic cadherins [2, 5], the clustered protocadherins (α-, β-, and γ-subgroups) [5, 6], the nonclustered δ-protocadherins [1], desmosomal cadherins, and various smaller subgroups [5]. In the present review, we will focus on the subgroups of classic cadherins and δ-protocadherins because they have been studied in detail in the cerebellum. Before turning to the cerebellum, we will briefly summarize what is known about cadherins from the study of other parts of the brain.

Comprehensive expression mapping has revealed that, in most parts of the brain, classic cadherins and δ-protocadherins show a highly restricted expression pattern in particular brain regions, fiber tracts, and cell types at all stages of the central nervous system (CNS) development [2]. For example, multiple cadherins have been mapped in the nuclei of the forebrain [7–9], in the basal ganglia of the mouse [10], and in the visual system of the ferret [11, 12]. Results from these and other studies demonstrate that the expression pattern of each cadherin is distinct and differs from that of other cadherins, although partial overlap of expression between cadherins is observed [7–12]. Because cadherins confer differential adhesiveness to cell surface membranes [3, 4],

they are thought to represent a molecular code that specifies adhesive properties of brain structures. In particular, cadherins are differentially expressed by the histogenetic fields (neuromeres) of the early embryonic brain, by brain nuclei, regions, layers, and different types of cells in the CNS (for reviews, see [2, 3]). Last but not least, cadherins are markers for specific fiber tracts, neural circuits, and subtypes of synapses in the vertebrate brain [2, 4, 13, 14].

The expression pattern of each cadherin is relatively stable during development and, for many cadherins, it persists in the mature brain. The detailed mapping of cadherin expression during development allows following the development and functional maturation of brain regions in considerable detail [8–12].

Most cadherins bind to cadherin molecules of the same type (homotypic adhesion), but some cadherins also bind to other types of cadherins (heterotypic binding), although more weakly in general (for reviews, see [2, 3]). The preferentially homotypic binding between cadherins was proposed to form a molecular basis for the establishment of neural circuits by mediating specific binding between pre- and postsynaptic neural structures [14, 15]. Besides qualitative differences in cadherin expression, quantitative differences in the expression of a single cadherin subtype also cause a selective aggregation of cells and may further contribute to the role of cadherins in the selective association of cells and their surface membranes [16].

The cadherin-based adhesive code is a combinatorial one because multiple cadherins can be co-expressed both at the regional level [7–11] and at the single-cell level [17]. The combinatorial expression of multiple members of the cadherin superfamily may thus contribute to the great complexity of CNS architecture.

Cadherins play multiple roles during CNS development and in the mature brain. Experimental studies demonstrated that classic cadherins and δ-protocadherins are involved in the following processes: neuroepithelial histogenesis [18–20], embryonic patterning and emergence of histogenetic fields [21], axon outgrowth [22–24], axonal guidance and neural circuit formation [25, 26], dendritic sprouting [27], and synapse formation and plasticity [28–32].

Cadherins in Early Cerebellar Development

Cadherin expression in the cerebellar anlage is observed from the earliest stages of development. Throughout the brain, including the upper rhombencephalic lip, the neuroepithelium expresses Cdh2 (N-cadherin) ubiquitously [33]. Cdh2 continues to be expressed by granule cell precursors during their migration from the upper rhombencephalic lip [34, 35] in zebra fish and during their differentiation in mice [36]. Another cadherin expressed in early cerebellar anlage is Cdh1 (E-cadherin). In the E12.5 mouse, this cadherin is found in dorsal regions of the upper rhombencephalic lip [37] in a population of Neph3-positive cells that are likely to be precursors for Purkinje cells [38]. At E14, when Purkinje cells cease to be born, Cdh1 expression subsides in this region [37, 38].

As the cerebellar anlage develops, other cadherins begin to be expressed in the differentiating mantle layer. For example, expression of Cdh4 (R-cadherin), Cdh6B and Cdh7 in restricted regions of the cerebellar mantle layer sets in at around E5 (stage 27 [39]) in chicken [40]. The development of the Cdh6B and Cdh7 expression patterns on the surface of the cerebellum is shown in Fig. 1. Initially, expression of Cdh6B and Cdh7 is observed in transverse cerebellar domains that are distinct for each cadherin, but overlap partially. Subsequently, the domains become fragmented into patches that elongate in a rostrocaudal direction into distinct parasagittal stripes. This staining pattern can be attributed to the differential expression of the cadherins by Purkinje cell clusters [40]. A similar transition from transverse to parasagittal expression patterns has been observed for transcription factors [41] and reflects the developmental rotation of the cerebellar anlage [42]. In parallel, differential expression of Cdh4, Cdh6 and Cdh7 can also be observed in outgrowing fiber tracts within the cerebellar white matter and in the deep cerebellar nuclei [40].

The importance of the cadherin-based adhesion system during early cerebellar development has been demonstrated in mice homozygous for the cerebellar deficient folia (cdf) mutation [43]. In this mutant, the gene encoding for Catna2 (αN-catenin) is deficient. The Catna2 protein links classic cadherins to the neuronal cytoskeleton. Catna2-deficient mice are ataxic, display cerebellar dysplasia and abnormal lobulation of the cerebellum. A large number of Purkinje

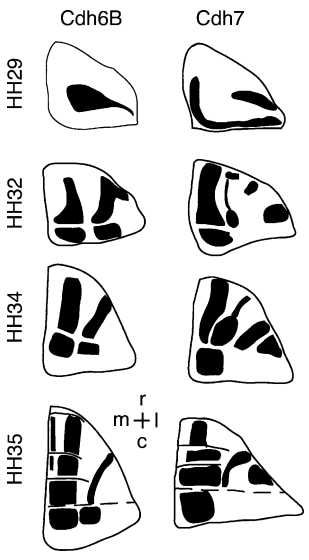


Fig. 1 Developmental expression of Cdh6B and Cdh7 on the surface of the chicken cerebellum (*dorsal views*). Early embryonic zones of expression, which are oriented transversely, gradually transform into multiple rostrocaudally oriented stripes of expression, which are typical for intermediate stages of cerebellar development. Embryonic stages according to Hamburger and Hamilton [39] are indicated on the *left side of each row*. Data are modified after the study by Arndt and Redies [40]. *Abbreviations*: *c* caudal, *l* lateral, *m* medial, *r* rostral

cells is found ectopically in the cerebellar white matter and in the inner granular layer [43].

At the end of early embryonic patterning, the expression of gene regulatory factors and cadherins both reflect the compartmentalization of the cerebellum into parasagittal Purkinje cell clusters, which are described in more detail in the next section.

Cadherins at Intermediate Stages of Cerebellar Cortical Development

Cadherins Provide an Adhesive Code for Parasagittal Purkinje Cell Domains

Feirabend was the first to describe parasagittal clusters of Purkinje cells on histological grounds in the embryonic chicken cerebellum [44, 45]. At intermediate stages of development and in the mature cerebellum, parasagittal cerebellar organization is mirrored by various biochemical markers and the expression of large variety of genes by specific Purkinje cell clusters. Some of these molecules display highly restricted and complex parasagittal patterns. Examples are aldolase C/zebrin II [46], gene transcription factors [41, 47], intracellular signaling molecules (CaBP, cGK [48]; Pcp2/L7 [49–51]); ephrins, and Eph receptors [47, 52]; and members of the cadherin superfamily (see below).

The cadherin superfamily, in particular the subgroups of classic cadherins and δ-protocadherins, contains multiple genes that are expressed differentially in parasagittal Purkinje cell domains. Cadherin-expressing Purkinje cell domains were first visualized in the chicken cerebellum for Cdh4 (R-cadherin [53]), followed by many other cadherins in chicken, mouse, ferret and other species (for a detailed list and references, see Table 1).

As an example, Fig. 2 shows the differential expression of nine cadherins in the cerebellar cortex of the embryonic chicken. In general, each cadherin is expressed by a restricted subset of Purkinje cell clusters, although partial overlap of the expression domains is observed between cadherins. Abrupt changes of expression often coincide with granule cell raphes (Fig. 2b, d, j, and m; see "Granule Cell Raphes Delineate Cadherin-Expressing Purkinje Cell Domains"). Vice versa, each Purkinje cell domain is characterized by the expression of a specific subset of cadherins (Fig. 2m).

Figure 3 depicts whole mount preparations of embryonic chicken cerebella from rostral, dorsal and caudal views. Specimens were incubated in situ with probes for Cdh4 (Fig. 3a, e, and i [53]), Cdh6 (Fig. 3b, f, and j [54]), Cdh7 (Fig. 3c, g, and k [54]), Cdh8 and Pcdh7 (Fig. 3d, h, l, m, q, and u [13]), Pcdh9 (Fig. 3n, r, and v), and Pcdh17 (Fig. 3p, t, and x) or with an antibody against Pcdh10 (Fig. 3o, s, and w [13]). Each cadherin displays a unique and spatially restricted expression profile with a prominent parasagittal elongation (stripes) of the expression domains. A schematic reconstruction of the complete expression profiles for three of the cadherins (Cdh8, Pcdh7, and Pcdh10; [13]) is depicted in Fig. 4. The parasagittal striping patterns exhibit differences between individual lobules, suggesting that cadherins specify not only mediolateral domains but also rostrocaudal domains. Figure 4 confirms the precise complementarity of expression for pairs of cadherins in some regions (for example, for Cdh8/Pcdh7 in lateral parts of lobules II–VI; Fig. 4a, b), whereas other regions show partial overlap (for example, Pcdh7/Pcdh10 in lobules VII–IXa, b; Fig. 4b, c). Within Purkinje cell clusters, gradual changes in cadherin expression or partial expression can be found [54], providing evidence for additional pattern formation within clusters, thereby increasing the complexity of gene expression even further.

In conclusion, cadherins provide a combinatorial molecular code that specifies the identity of mediolateral and rostrocaudal Purkinje cell domains at intermediate stages of cerebellar development in the chicken [13, 54, 55]. Similar results were obtained for the expression of cadherins in the cerebellar cortex of the mouse [1, 56, 57] and the ferret [57]. For the postnatal mouse, Fig. 5 shows examples of partially overlapping Purkinje cell domains positive for Cdh8, Pcdh7, and Pcdh10. Figure 6 displays schematic diagrams that represent complete reconstructions of the parasagittal striping pattern for Pcdh7 and Pcdh10 expression in the postnatal cerebellum of mouse and ferret [57]. In both species, the patterns are largely complementary and mark specific mediolateral and rostrocaudal Purkinje cell domains. In the rostrocaudal dimension, changes in spatial expression patterns are more pronounced between lobules V/VI, lobules VII/VIII, and lobules IX/X, corresponding to the boundaries between an anterior zone (lobules I–V), a central zone (lobules VI–VII), a posterior zone (lobules VIII–IX), and a nodular zone (lobule X) of cerebellar patterning [58, 59].

Granule Cell Raphes Delineate Cadherin-Expressing Purkinje Cell Domains

In his seminal work on the cerebellum of the chicken embryo, Feirabend noted that the clusters of Purkinje cells are interrupted by intervening bands of migrating granule cells ("raphes" [44, 45]). Granule cell raphes represent *cell-dense* structures that are visible at intermediate stages of chicken embryonic development (about 9–15 days of incubation) and later disappear. They were also called "ribbons" by some authors [52, 54, 56] and should not be confused [55, 56] with the *cell-poor* medullary raphes that represent myeloarchitectural differentiations in the developing and mature cerebellum of several mammals [60, 61].

Table 1 Expression of classic cadherins and δ-protocaderins by cell types of the developing and mature cerebellum

Cadherin	Species	Stage	Granule cells	Inter-neurons	Purkinje cells	DCN neurons	References
Cdh1 (E-cadherin)	Mouse	E12–E14					[37]
Cdh2 (N-cadherin)	Zebrafish	Embryonic–larval	+				[34, 115]
	Chicken	E14, E18	+		+	+	J. Lin and C. Redies (unpublished data)
	Mouse	P0–adult	+		+	+	[33, 35, 38]
Cdh4 (R-Cadherin)	Zebrafish	Larval–adult			+		[115]
	Chicken	E11–E19	+ (r)	+	+ (d)	CbL	Figs. 2a, b and 3a, e, i [53, 54]
	Mouse	P0–adult	+ (r)	+	+ (d)	+	Fig. 10b, j, l [35, 56]
Cdh6	Chicken	E11–E19	−	−	+ (d)	CbM, CbL	Figs. 2c, d and 3b, f, j [53, 54]
	Mouse	P0/P2	−	−	−	M, IntP	[90]
Cdh7	Chicken	E11–E19	+ (r)	−	+ (d)	CbM, CbL	Figs. 2e and 3c, g, k [53, 54]
	Mouse	Adult	+	+	−	+	C. Redies (unpublished data)
Cdh8	Chicken	E12–E18	+ (r)	−	+ (d)	M, I, L	Figs. 2f and 3d, h, l; 4 [13]
	Mouse	E18–adult	+	−	+ (d)	M, Int, L	Figs. 5a and 8e [56, 57, 89, 90]
	Ferret	P2	+	−	+ (d)	Int, L	[57]
Cdh10	Chicken	E8–E16	+ (r)		+ (d)	+	[63]
Cdh11	Chicken	E12–E18	+ (r)		+ (d)	+	Fig. 2g; J. Lin and C. Redies (unpublished data)
	Mouse	P0–adult	+ (r)	−	+ (d)	−	Fig. 10c [56, 90]
Cdh14/18	Chicken	E14, E18	+		−	+	J. Lin and C. Redies (unpublished data)
	Mouse	Adult	+	−	+ (d)	+	Fig. 10d
Cdh15 (M-cadherin)	Mouse	P9–adult	+	−	−		[35, 102, 116]
Cdh20	Chicken	E14–E18	+(r)		−	+	J. Lin and C. Redies (unpublished data)
	Mouse	E11.5	+				[117]
Pcdh1	Chicken	E12–E18	−	−	+ (d)	+	Fig. 2h; J. Lin and C. Redies (unpublished data)
	Mouse	P5–adult	+	−	−		C. Redies (unpublished data)
Pcdh7	Chicken	E12–E18	+ (r)	+	+ (d)	M, I, L	Figs. 3m, q, d u and 4 [13]
	Mouse	P1–adult	+	+	+ (d)	M, IntA, L	Figs. 5b, 6, and 10g and i [1, 57]
	Rat	P3					[118]
	Ferret	P2	+		+ (d)	M, IntA, L	Fig. 6 [57]
Pcdh8	Chicken	E14, E18	+	−	+ (d)	+	J. Lin and C. Redies (unpublished data)
	Mouse	Adult	+	+	+ (d)	+	Fig. 10e
Pcdh9	Chicken	E12–E18	+	+	+ (d)	+	Figs. 2i and j; 3n, r and v; J. Lin and C. Redies (unpublished data)
	Mouse	P1–adult	+	+	+ (d)	+	Fig. 10f [1]
Pcdh10	Chicken	E12	−	−	+ (d)	M, I, L	Figs. 2k, 3o, s and w, 4, and 9a [13]
	Mouse	E15–adult	−	+	+ (d)	M, IntP, L	Figs. 5c, 6, and 8b, d [13, 56, 119, 120]
	Rat	P3					[118]
	Ferret	P2			+ (d)	M, IntP	Fig. 6 [13]
Pcdh17	Chicken	E12–E18	+	−	+ (d)	+	Figs. 2l and 3p, t, and x; J. Lin and C. Redies (unpublished data)
	Mouse	Adult	−	+	+ (d)	+	C. Redies (unpublished data)
	Rat	P3			+ (d)		[118]
Pcdh18	Rat	P3					[118]
Pcdh19	Chicken	E14, E18	+	−	+ (d)	+	J. Lin and C. Redies (unpublished data)
	Mouse	Adult	+	−	+ (d)	+	C. Redies (unpublished data)

r expression also in granule cell raphes, *d* expression in specific parasagittal Purkinje cell domains, *CbM* medial cerebellar nucleus (chicken), *CbL* lateral cerebellar nucleus (chicken) [121], *M* medial cerebellar nucleus (chicken, mouse, and ferret), *I* interposed cerebellar nucleus (chicken), *L* lateral cerebellar nucleus (chicken, mouse, and ferret) [122–124], *IntA* anterior part of the interposed nucleus (mouse and ferret), *IntP* posterior part of the interposed nucleus (mouse and ferret) [125]

The granule cell raphes are visible on nuclear stains and Nissl stains [44, 45]. Not all raphes are equally prominent in all sections (Fig. 2). The raphes regularly coincide with abrupt changes of cadherin-expressing Purkinje cell clusters (Figs. 2b, d, and j; 5 [54]). They connect the external and internal granular layer and thus interrupt the Purkinje cell

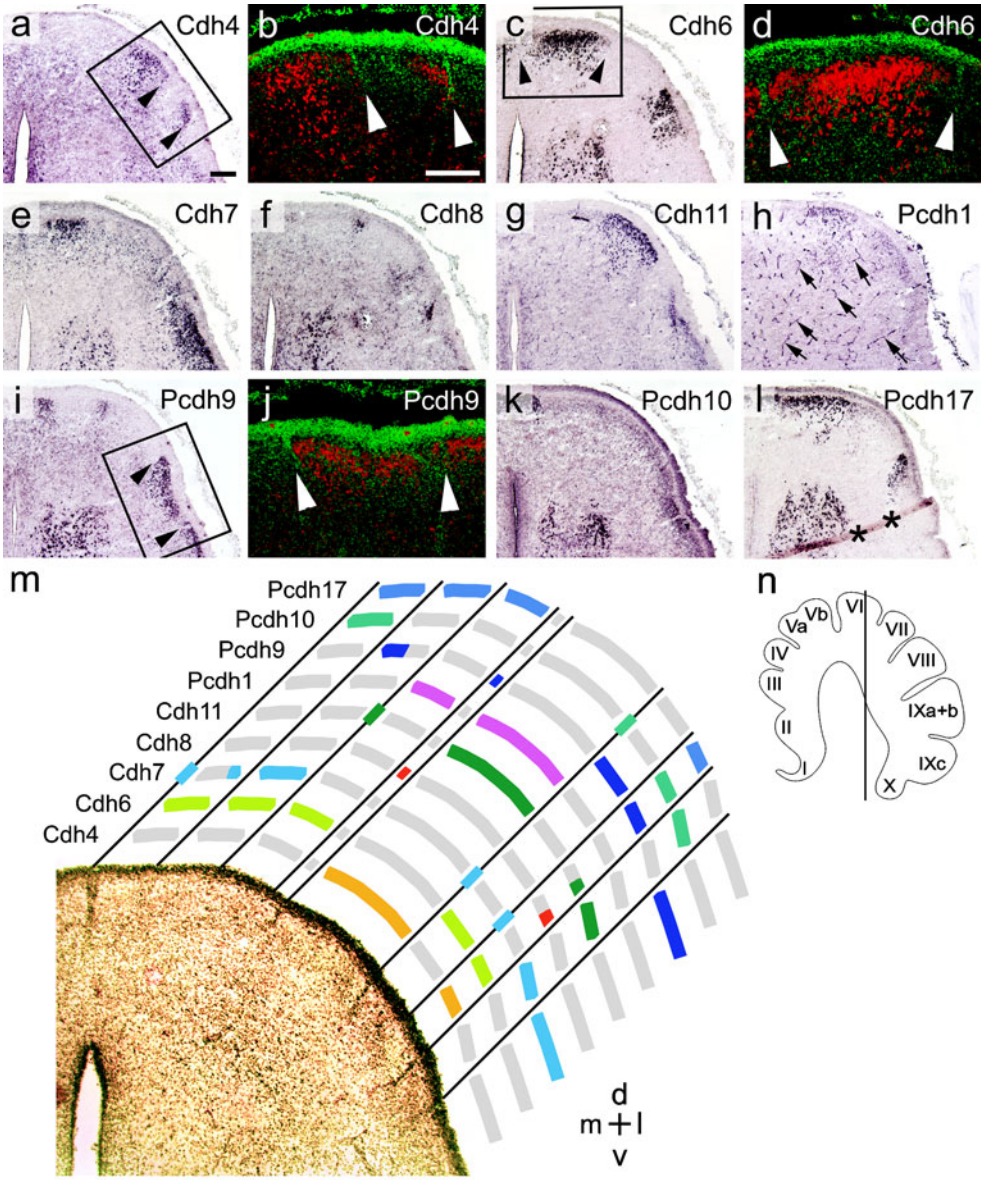


Fig. 2 Cadherin expression in transverse sections through chicken cerebellum at intermediate stages of development (12 days incubation). **a**–**l** Adjacent sections hybridized in situ with digoxigenin-labeled cRNA probes for Cdh4 (**a**, **b**), Cdh6 (**c**, **d**), Cdh7 (**e**), Cdh8 (**f**), Cdh11 (**g**), Pcdh1 (**h**), Pcdh9 (**i**,**j**), Pcdh10 (**k**), and Pcdh17 (**l**). **b**, **d**, Enlargements of the areas *boxed* in **a**, **c**, **i**, respectively, doubly stained with cadherin probe (*red*) and nuclear dye Hoechst 33258 (*green*). The *arrowheads* in **a**/**b**, **c**/**d**, **i**/**j** point to corresponding granule cell raphes. The *arrows* in **h** point to Pcdh1-positive blood vessels. The *asterisks* in **l** indicate an artefact (tissue fold). **m** Schematic diagram of the results. *Colors* indicate expression of the cadherin given on the *left upper side* of the diagram. *Gray color* indicates no expression. The *black lines* represent the position of the granule cell raphes, some of which are visible in the transverse section at this level. At positions, where the *lines* are replaced by *thicker colored lines*, granule cell raphes express the respective cadherin (for Cdh7, Cdh11, and Pcdh10). **n** Schematic diagram for the position of the sections displayed in a-l. The lobules are numbered by Roman numerals (*I*–*X*). *Abbreviations*: *d* dorsal, *l* lateral, *m* medial, *v* ventral. *Scale bars* 200 μm (in **a** for **a**, **c**, **e**–**i**, **k**, **l**; and in **b** for **b**, **d**, **j**)

layer, as is evident by gaps in the expression of calbindin, a marker for Purkinje cells [54, 62]. The raphe cells have a cytoarchitecture and gene expression profile identical to granule cells [44, 45, 47, 54], although some migrating interneurons can also be found in the raphes [54]. The raphes can be visualized with granule cell-specific markers, for example Zic-1 and Pax-6 [47, 62]. Some raphes express specific cadherins (for example, Cdh7 [54]; Cdh8 [13]; Pcdh7, Fig. 4c [13]; Cdh10 [63]; and Cdh11 [56]).

Granule cell raphes are not only found in chicken [44, 45, 47, 52, 54, 62] and other avian species [47], but also in mouse [55, 56, 64], rabbit and cat [65], and monkey [62]. In the mouse, the raphes are less obvious on histological grounds than in chicken [56, 62] and were erroneously reported to be absent in this species [47]. Like in the chicken, the mouse raphes are transient structures that occur at intermediate stages of cerebellar development (from about P0 to P6 in mouse [56]). The presence of raphes in species ranging from birds to higher mammals suggests that they represent an evolutionary conserved morphogenic feature [62].

In both chicken and mouse, there is a prominent midline raphe. About eight raphes, which are symmetrical about the midline, extend rostrocaudally across lobules on each side [44, 45, 47, 54, 56, 64]. The raphe patterns differ slightly between lobules. Occasionally, two raphes merge along their rostrocaudal course to continue as a single one [44, 45, 47, 64].

The coincidence of granule cell raphes with boundaries of gene expression by Purkinje cells was first described for cadherins [54] and subsequently for several other types of genes, such as ephrins and Eph receptors [47, 52], gene

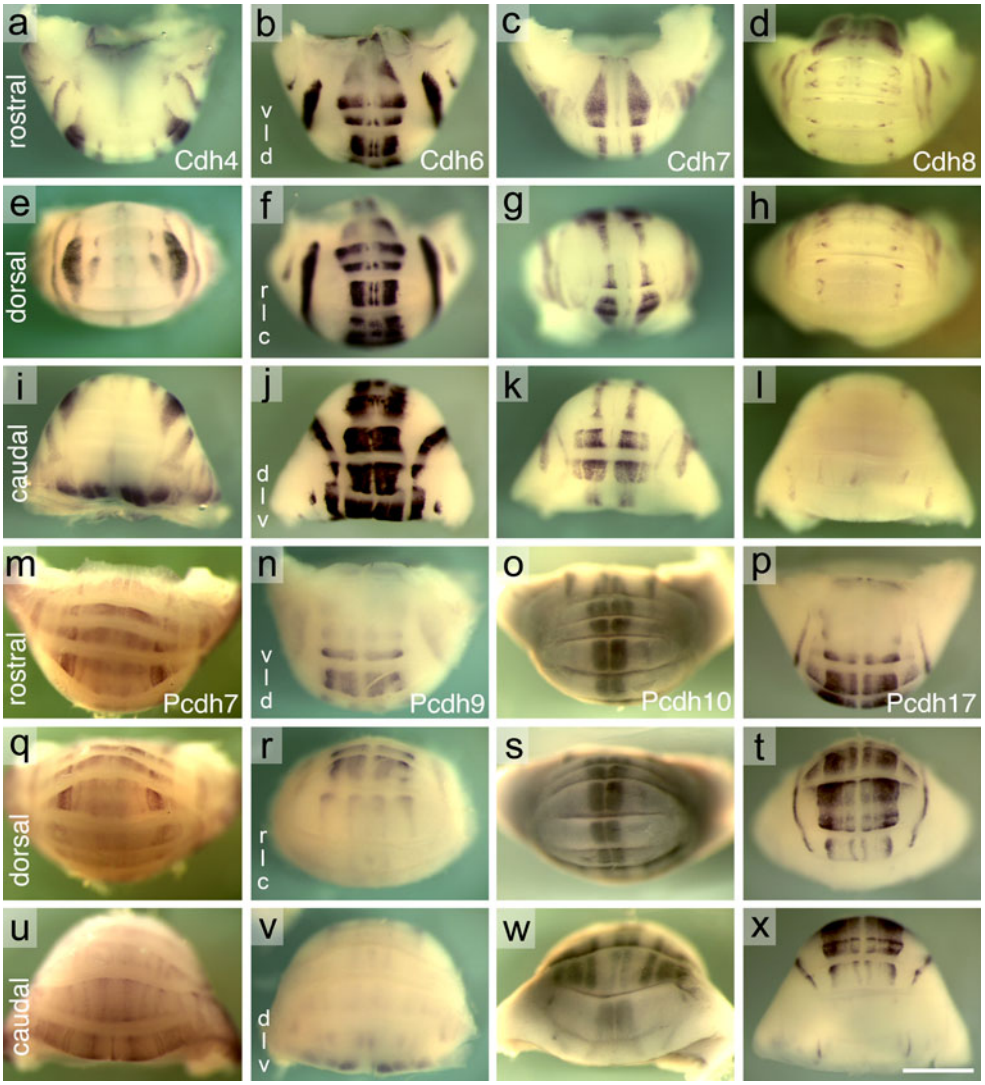


Fig. 3 Cadherin expression at the surface of chicken cerebella at intermediate stages of development (12 days incubation), viewed from rostral (**a**–**d**, **m**–**p**), dorsal (**e**–**h**, **q**–**t**) and caudal directions (**i**–**l**, **u**–**x**). Whole mount preparations were incubated in situ with digoxigenin-labeled cRNA probes for Cdh4 (**a**, **e**, **i**), Cdh6 (**b**, **f**, **j**), Cdh7 (**c**, **g**, **k**), Cdh8 (**d**, **h**, **l**), Pcdh7 (**m**, **q**, **u**), Pcdh9 (**n**, **r**, **v**) or Pcdh17 (**p**, **t**, **x**), or incubated with an antibody against Pcdh10 (**o**, **s**, **w**), as described previously [13]. Dark precipitate represents cadherin expression. Data displayed for Cdh8, Pcdh7 and Pcdh10 are from the study of Neudert and Redies [13]. *Abbreviations*: *c* caudal, *d* dorsal, *r* rostral, *v* ventral. *Scale bar*, 1 mm (in **x** for all panels)

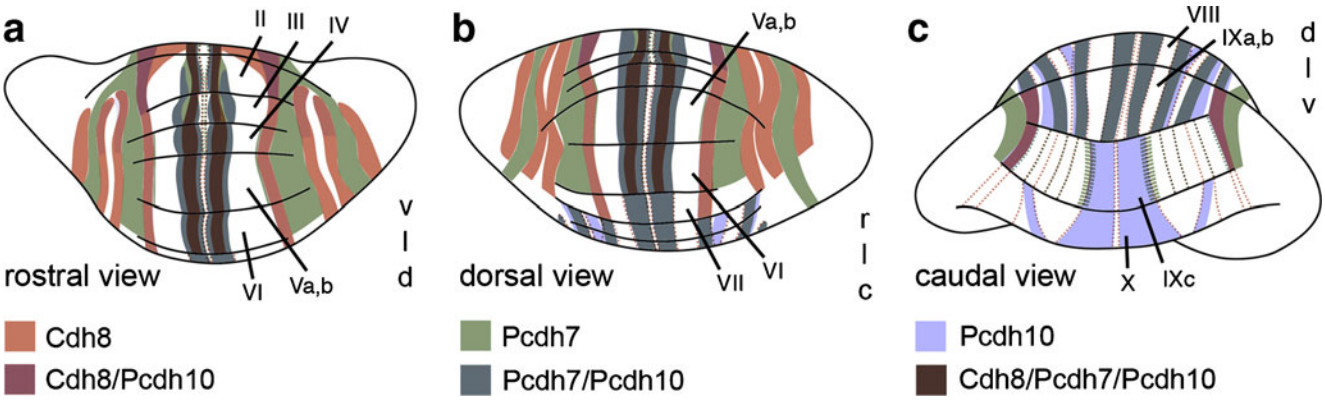
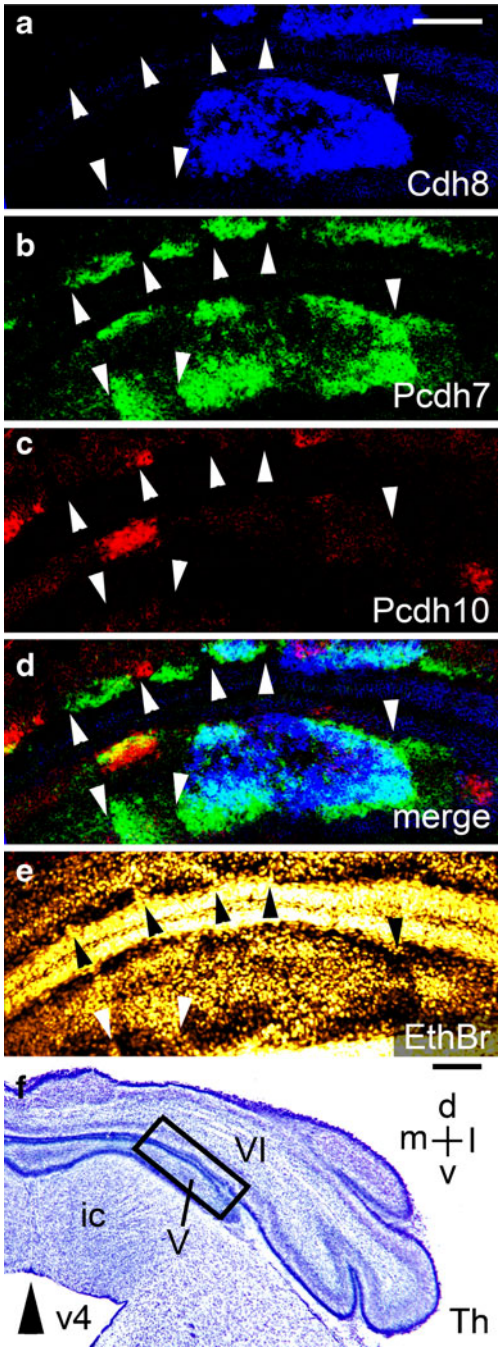


Fig. 4 *Color-coded* schematic diagrams that represent the expression of Cdh8 mRNA (compare with Fig. 3d, h, and l), Pcdh7 mRNA (compare with Fig. 3m, q, and u), and Pcdh10 protein (compare with Fig. 3o, s, and w) at the cerebellar surface of a chicken embryo at intermediate stages of development (12 days incubation). Views from a rostral (**a**), dorsal (**b**), and caudal direction (**c**) are displayed. The *color* coding is given below the panels. The number of the lobules is indicated by Roman numerals (*II*–*X*). Modified after the study by Neudert and Redies [13]. *Abbreviations*: *c* caudal, *d* dorsal, *r* rostral, *v* ventral



◀ **Fig. 5** Segments of cadherin-expressing Purkinje cell clusters are separated by granule cell raphes at intermediate stages of cerebellar development. **a**–**c** Adjacent horizontal sections through P3 mouse cerebellum were hybridized in situ with digoxigenin-labeled cRNA probes for Cdh8 (**a**), Pcdh7 (**b**), and Pcdh10 (**c**). **d** *Color-coded overlay* of the three panels displayed in **a**–**c**. **e** Nuclear counterstain with ethidium bromide (EthBr) of the section shown in (**b**). The *arrowheads* in **a**–**e** indicate the position of granule cell raphes that coincide with the borders of cadherin-expressing Purkinje cell clusters. **f** Nissl (thionin, Th) stain of an adjacent section. The *boxed* area is shown at a higher magnification in **a**–**e**. The number of the lobules is indicated by Roman numerals (*V, VI*). The *arrowhead* indicates position of the midline. *Abbreviations*: *d* dorsal, *ic* inferior colliculus, *l* lateral, *m* medial, *v* ventral, *v4* fourth ventricle. *Scale bars*, 100 μm (in a for **a**–**e**) and 250 μm (**f**)

regulatory factors (En-1, En-2, Shh, Gli-2/4, and Bmp-7; [47, 54]), and the adhesion molecule SC1 [54].

Role of Cadherins in Migration of Cerebellar Precursors

Luo et al. [66] overexpressed either of two classic cadherins, Cdh6 and Cdh7, in Purkinje cell precursors by in vivo electroporation of chicken embryos [67]. The cadherin-overexpressing cells migrated along precise pathways. After their initial radial migration from the ventricular layer to the mantle layer, the leading processes of the migratory Cdh7-transfected cells (arrowheads in Fig. 7a) oriented themselves along pre-existing Cdh7-positive neurite fascicles (arrows in Fig. 7a). Migration followed these neurite fascicles to cortical domains that expressed the same cadherin endogenously. The leading processes of Cdh6B-transfected cells oriented themselves along different subsets of neurites that expressed Cdh6B and originated from Cdh6B-positive domains (Fig. 7b). As a consequence, cadherin-expressing cells distributed preferentially to cortical Purkinje cell domains that expressed the same cadherin endogenously. Control cells that did not overexpress cadherins did not show such selective migratory pathways and postmigratory positions (Fig. 7c). Cadherin type-specific induction of apoptosis and cell sorting cannot explain the observed patterns of distribution to the cortical domains. Rather, the differential distribution is compatible with a model, in which cadherins guide tangential migrating neurons along neurites that express the same molecules (Fig. 7d). In this model, the leading processes of migratory neurons orient themselves along pre-existing neurites by a preferentially contact-dependent homotypic adhesive mechanism. A similar cadherin-based mechanism for selective axonal tracking has been found for the guidance of migrating axons in the tectofugal system of the chicken embryo [25].

Experimental evidence for a role of cadherins in the tangential migration of neuronal precursors has also been established for precerebellar neurons [68]. Here, four classic cadherins are expressed by cells in the migratory stream of the lateral reticular nucleus and external cuneate nucleus. While overexpressing Cdh2 and Cdh11 has no effect on cell migration in this stream, overexpressing dominant negative constructs slows down migration [68]. Cdh2 (N-cadherin) is also required for chain migration of early granule cell precursors from the cerebellar upper lip in zebra fish embryos [34]. The lack of Cdh2 in granule cells leads to impaired directional migration, failure of differentiation, and malpositioning of granule cells. Moreover, the orientation of the leading edge and the position of the centromere in the direction of migration is lost in the Cdh2-deficient cells [34].

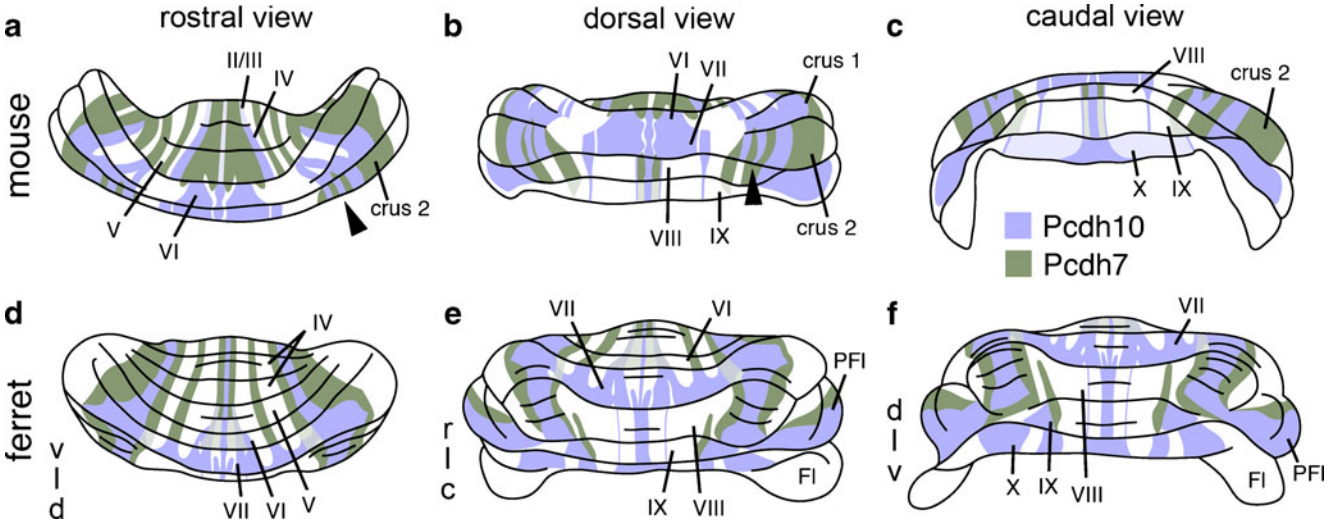


Fig. 6 Complementary expression of Pcdh7 and Pcdh10 at the surface of the mouse cerebellum (**a**–**c**) and ferret cerebellum (**d**–**f**) at postnatal day (P)3 and P2, respectively. Rostral (**a**, **d**), dorsal (**b**, **e**), and caudal views (**c**, **f**) are shown. *Colors* represent cadherin staining, as indicated. The *arrowheads* in **a**, **b** point to the lateral A zone, which is unique to rodents [82]. The lobules are indicated by Roman numbers (*II–X*). Modified after the study by Neudert et al. [57]. *Abbreviations*: *c* caudal, *d* dorsal, *Fl* flocculus, *PFl* paraflocculus, *r* rostral, *v* ventral

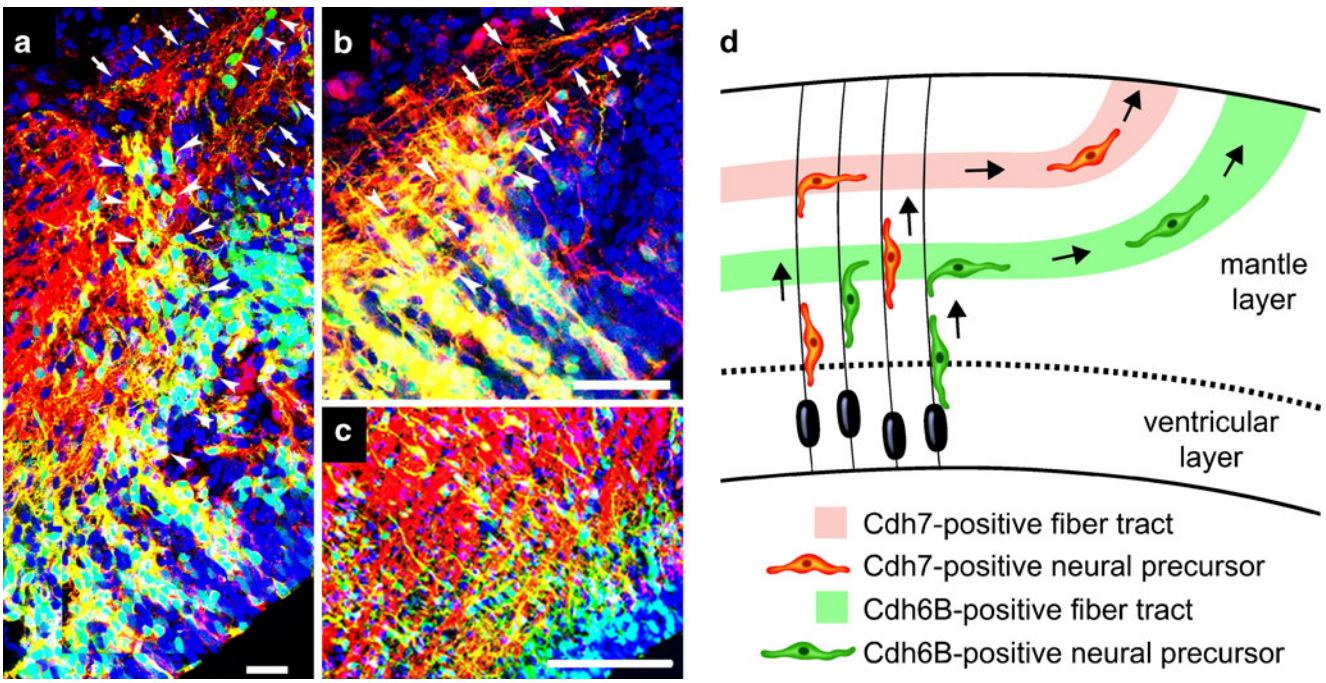


Fig. 7 Cdh6B and Cdh7 direct the migration of Purkinje cell precursors to cortical domains that express the same cadherin subtype in the chicken cerebellum. **a**–**c** Results of electroporation experiments with Cdh7 expression plasmid (**a**), Cadh6B expression plasmid (**b**), and control plasmid (**c**; GFP alone). *Red color* indicates Cdh7 immunostaining (**a**, **c**) and Cdh6B immunostaining (**b**), respectively. *Green color* represents GFP expression used as a marker for electroporated neural cells. *Blue color* indicates nuclear staining. Note that cadherin-overexpressing neurons (*arrowheads* in **a**–**b**) first migrate radially in the ventricular layer. The processes of the migrating cells then turn into a tangential direction in the mantle layer to migrate along pre-existing neurite fascicles that express the same cadherin subtype (*arrows* in **a**–**b**). The processes of electroporated control cells (**c**; GFP only) show no orientation along preexisting neurite fascicles. **d** Schematic diagram illustrating the homotypic adhesion mechanisms, by which migrating Purkinje cell precursors in the mantle zone are guided by neurites that express the same cadherin subtype, finally reaching specific cortical domains. The arrows in d indicate the direction of migration. Modified after the study by Luo et al. [66]. *Scale bars*, 50 μm in (**a** and **b**), and 100 μm in (**c**)

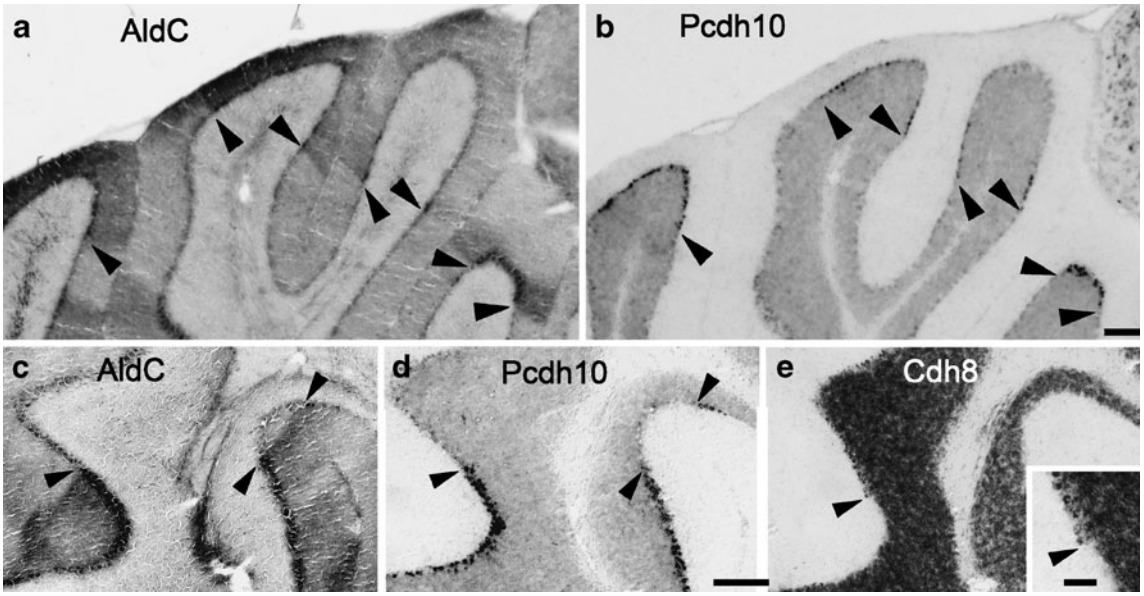


Fig. 8 Cadherin-expressing Purkinje cell domains in the adult mouse cerebellar cortex (**b**, **d**, **e**) relate to the zebrin II/aldolase C pattern (**a**, **c**). Consecutive transverse sections of an adult mouse cerebellum were hybridized with digoxigenin-labeled cRNA probes for Pcdh10 (**b**, **d**) and for Cdh8 (**e**), or immunostained with an antibody against zebrin II/aldolase C (AldC) protein (**a**, **c**). *Arrowheads* indicate borders of cadherin-expressing Purkinje cell domains that coincide with borders of zebrin II/aldolase C (AldC) expression. The insert in **e** shows an enlargement of the border of the Cdh8-positive domain (*arrowhead*). *Scale bars*, 200 μm (in **b** for **a**, **b**; in **d** for **c**–**e**) and 100 μm (insert in **e**)

In granule cells, Cdh2 is a target of nuclear factor I, a key regulator for granule cell development [36].

In summary, a complex pattern of discrete Purkinje cell clusters has formed at intermediate stages of development, as a result of embryonic patterning processes. The Purkinje cell clusters express differentially multiple members of the cadherin superfamily and various other types of genes, and are separated by raphes of migrating granule cells. The developmental role of the raphes, if any, remains unclear. It is conceivable that the raphes do not play a specific role in cerebellar development but are a passive phenomenon. Granule cells possibly prefer a migratory route between the Purkinje cell clusters at intermediate stages of development because cell adhesion is still strong within the cell-dense clusters, which contain several layers of Purkinje cells. Later, when the Purkinje cell clusters have dispersed into a sheet of single cells, granule cell migration might be less impeded by the tight adhesiveness within Purkinje cell clusters [54].

Cadherin Expression in the Mature Cerebellum

In the previous sections, we described the intricate histochemical and molecular patterning that reflects cerebellar compartmentalization during development. In this section, we will discuss evidence that this ontogenetic compartmentalization forms a basis for functional architecture and connectivity in the mature cerebellum.

Relation to Molecular Markers of Mature Cerebellar Architecture

Besides cadherins, there are several other well-studied molecular markers that are expressed differentially by Purkinje cells in restricted domains along the rostrocaudal and mediolateral dimensions. Many of these molecules are expressed either at intermediate developmental stages ("early-onset markers") or in the mature cerebellar cortex ("late-onset markers"; in mouse from P15 onwards; reviewed in Ref. [58]). Examples of early-onset markers are gene regulatory proteins, such as En-1, En-2, Pax2, Wnt-7b, Shh, Gli-2/4, and Bmp-7 [41, 47], ephrins and Eph receptors [47, 52], and cell adhesions molecules, such as SC1 [69] and FAR-2 [70]. Example of late-onset markers are aldolase C/zebrin II [46, 48, 71, 72], HNK-1 [46], and the heat shock protein 25 (HSP25) [73]. Late-onset markers generally display parasagittal striping patterns in the mature cerebellum.

How do the early ontogenetic compartmentalization of cerebellar cortex into discrete Purkinje cell cluster and the adult parasagittal striping pattern relate to each other? Given the paucity of gene markers that bridge both periods, this question remained unanswered for some time [58]. However, previous evidence already suggested a continuity between early and late patterns, for example, expression studies of transgenes like L7/pcp2-LacZ [49] and OMP-LacZ [74]. Also, the ectopic overexpression of the early-onset marker En-2 [75] and altered levels of cerebellar En-2 in mutant

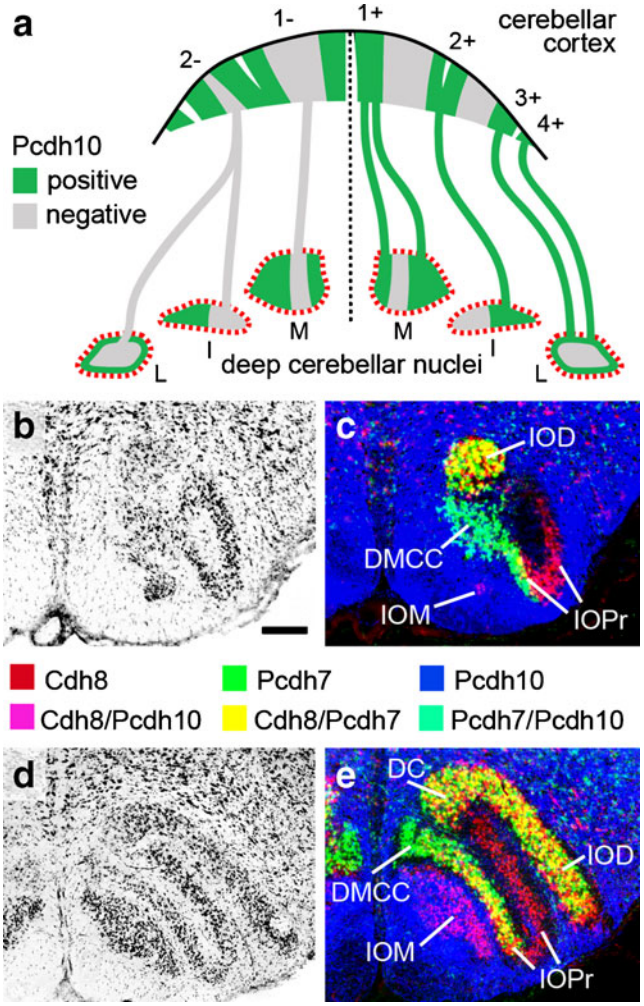


Fig. 9 **a** Comparison of anterograde axonal tracing and Pcdh10-expression in the cerebellar cortex and deep cerebellar nuclei of chicken embryos at intermediate stages of development (12 days' incubation). Colors indicate gray matter and connecting fiber tracts that express Pcdh10 (*in green*) or are Pcdh10-negative (*in gray*). Data are modified after the study of Neudert and Redies [13]. **b–e.** Cadherin expression in the ferret inferior olivary complex at postnatal day 2 (P2). Consecutive sections at a rostral level (**b**, **c**) and an intermediate level (**d**, **e**) were hybridized in situ with cRNA probes for Cdh8 or Pcdh7, immunostained with antibodies against Pcdh10, or stained with thionin (**b**, **d**). Results from in situ hybridization are shown in *color-coded overlays* (**c**, **e**). The *color coding* is given between the two panels. Data are modified after the study of Neudert et al. [57]. *Abbreviations*: *1+ to 4+* Pcdh10-positive domains in the cerebellar cortex, *1-* and *2-* Pcdh10-negative domains in the cerebellar cortex, *DC* dorsal cap, *DMCC* dorsomedial cell column, *I* interposed cerebellar nucleus, *IOD* dorsal accessory olive, *IOM* medial accessory olive, *IOPr* principal olive, *L* lateral cerebellar nucleus, *M* medial cerebellar nucleus. *Scale bar*, 200 μm (in **b** for **b**–**e**)

mice [76] have a dose-dependent effect on late cerebellar Purkinje cell patterning. Moreover, mediolateral compartmentalization of the cerebellum was related to the birthdate of Purkinje cells between E10.5 and E12.5 in the mouse [77].

Some cadherins, for example Cdh8 and Pcdh10, are suitable markers to answer the above question because they are expressed both at early/intermediate stages of cerebellar development and in the mature cerebellar cortex. In the mouse, expression of Cdh8 and Pcdh10 starts as early as E18 and E15, respectively, and persists in the mature cerebellum with only minor modifications of the striping pattern [56]. A comparison of the Pcdh10 and aldolase C expression directly visualized common mediolateral expression boundaries throughout development [56], bridging the gap between early-onset and late-onset markers [58, 78]. Figure 8 shows an example of how Purkinje cell clusters that persist from intermediate stages of development coincide with the aldolase C striping pattern to form common expression boundaries in the cerebellar cortex of the adult mouse. The conclusion that early-onset patterns and late-onset patterns closely relate to each other [56] has been confirmed by subsequent studies, for example, for neurogranin (expressed in mouse from E15 to P20 [78]) and for phospholipase C beta 4 (PLCbeta4; E18 to adult [79]). Further evidence for a relation between the expression of some cadherins and aldolase C can be derived from the study by Sarna et al. [80]. They showed that the aldolase C-immunopositive Purkinje cell domains are co-extensive with phospholipase Cbeta3 (PLCbeta3) expression in the adult mouse, whereas they are complementary to those of PLCbeta4. At late stages of cerebellar development, the expression of Pcdh10 overlaps with the aldolase C pattern to a large degree (Fig. 8a–d [56, 57]) and it is complementary to that of Pcdh7 (Fig. 6a, d [57]). In turn, the PLCbeta4 expression pattern [79] and the Pcdh7 expression pattern resemble each other in the anterior part of the postnatal mouse cerebellum [57]. However, there are also differences between the early embryonic patterning and the adult patterning, as is evident from the positions of distinct borders and gene expression data (for example, see [76]).

The cerebella of vertebrate species display large differences in their size, overall morphology and foliation pattern [60, 81]. For example, the cerebella of carnivores like cat and ferret exhibit a broad, well-developed vermis and relatively small but clearly demarcated hemispheres, whereas the vermis and cerebellar hemispheres of rodents like the mouse are less elaborate. Nevertheless, the expression patterns of two δ-protocadherins, Pcdh7 and Pcdh10, largely resemble each other in mouse and ferret at intermediate stages of development (Fig. 6 [57]), suggesting that (1) there is a similar cerebellar bauplan for the two species, and (2) differences in gross morphologies between the two species are more likely caused by differential growth of embryonic divisions of a common bauplan than by gross differences in early embryonic patterning. Some minor differences between the cadherin expression patterns between mouse and ferret were noted, however, and they might indicate true species-

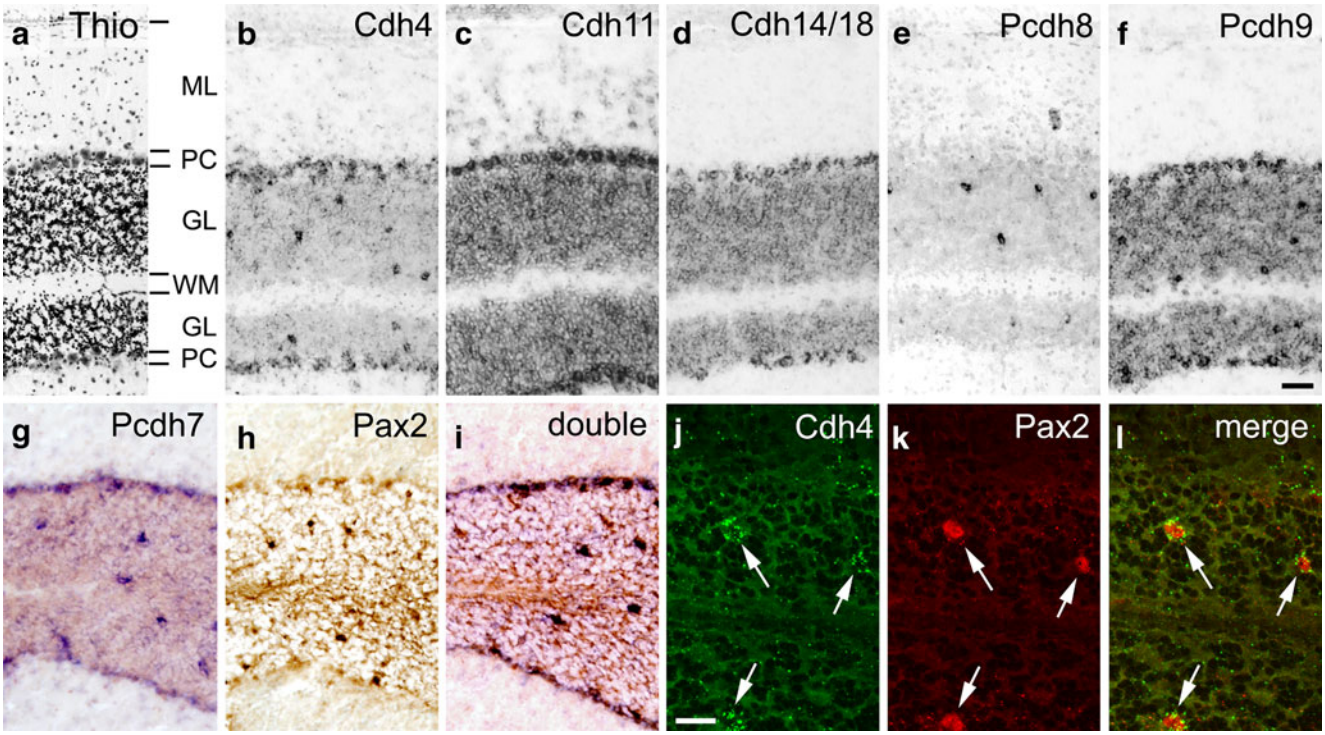


Fig. 10 Cell type-specific expression of cadherins and protocadherins in the adult mouse cerebellar cortex. **a** Nissl stain (Thio). **b**–**f** Consecutive sections were hybridized with digoxigenin-labeled cRNA probes for Cdh4 (**b**), Cdh11 (**c**), Cdh14/18 (**d**), Pcdh8 (**e**), or Pcdh9 (**f**). **g**–**i** Adjacent sections were hybridized with cRNA probes for Pcdh7 (**g**; *purple precipitate*), labeled with an antibody against the Pax2 protein (**h**; *brown precipitate*) or doubly labeled for both molecules (**i**; *brownish-purple precipitate*). Note that the Pcdh7-positive cells in the granule cell layer (**g**) have a distribution and density similar to the Pax2-positive cells (**h**) and co-express Pax2 (**i**). **j**–**l** A section was double-labeled with cRNA probe for Cdh4 (**j**) and an antibody against the Pax2 protein (**k**); the merged fluorescent image is displayed in l (merge). The *arrows* in j–l point at cells that co-express Cdh4 and Pax2. *Abbreviations*: *GL* granule cell layer, *ML* molecular layer, *PC* Purkinje cell monolayer, *WM* white matter. *Scale bars*, 50 μm (in f for **a**–**i**; in j for **j**–**l**)

specific differences in cerebellar differentiation [57]. For example, the lateral A zone [82], which seems to be unique to rodents, contains more numerous cadherin-positive stripes in the mouse (arrowheads in Fig. 6a, b). Cerebellar patterning between avian and mammalian species seems to be evolutionary more divergent because the expression profiles of corresponding cadherins in the chicken cerebellum (compare Fig. 4 to Fig. 6) can be less clearly related to that of mammals [13, 57]. These results suggest that the complex and unique expression profiles of multiple cadherins will be useful for future studies of interspecies differences in cerebellar architecture. Unlike cadherins, single molecules like aldolase C show a roughly similar striping pattern in different vertebrate species [83–86].

Cadherin-Expressing Purkinje Cell Domains Relate to Functional Connectivity

Cadherins are markers for specific neural circuits (reviewed in [2, 3]). For example, in the visual system, cadherins are expressed not only by specific gray matter regions, but also by their efferent fiber projections and target regions [14, 17, 25, 87, 88].

In the cerebellar system, the brain structures that are connected to the cerebellar cortex contain subregions, which express cadherins differentially. Examples are the deep cerebellar nuclei [13, 53, 54, 57, 89], the vestibular nuclei [53, 54, 57, 89], and the olivary complex (Fig. 9b–e [1, 13, 57, 63, 89, 90]). Evidence from the neuroanatomical literature suggested that many of the structures in the cerebellar system, that express the same cadherins, are selectively connected to each other (Cdh4 [53]; Cdh6 and Cdh7 [40, 54]; Cdh8, Pcdh7, and Pcdh10 [13, 57]). In several cases, immunostaining can be used to visualize directly cadherin-positive fiber tracts that connect cortical Purkinje cell domains with underlying deep cerebellar nuclei [13, 40, 54, 57] or other cerebellar targets [40, 54] that express the same cadherin subtype.

Neudert and Redies [13] investigated the relation between cadherin expression and the connectivity of Purkinje cell domains directly by combining axonal tracing and immunostaining for Pcdh10 in the chicken cerebellum. Their results

demonstrate that, in general, the Pcdh10-positive cortical domains are connected to Pcdh10-positive deep nuclear regions (Fig. 9a). Vice versa, Pcdh10-negative cortical domains are connected to Pcdh10-negative deep nuclear regions. This finding confirms directly that brain structures that express the same cadherin subtype can be selectively connected to each other.

The inferior olivary complex displays a particularly intricate pattern of differential cadherin expression (Fig. 9b–e). Each olivary division projects climbing fibers to distinct parasagittal domains in the cerebellar cortex (termed zones "A-D" [82, 91]). A detailed comparison of cadherin expression (Cdh8, Pdh7 and Pcdh10) in the olivary divisions and the cortical target zones indicated that the cadherin expression profiles parallel functional olivo-cerebellar connectivities in the mouse and the ferret [57].

Taken together, the above findings support the notion that the ontogenetic pattern of Purkinje cell clusters/granule cell raphes is directly translated into the parasagittal striping pattern of gene expression in the mature cerebellum, which, in turn, reflects functional connectivity [13, 58, 60, 91–94]. The pattern of Purkinje cell clusters/granule cell raphes can therefore be considered a primordial scheme of functional cerebellar compartmentalization. Future studies on the expression of cadherins and other molecules that are expressed throughout cerebellar development will provide more detail on how adult cerebellar compartmentalization evolves during cerebellar development. It is possible that molecular patterning and functional differentiation continue in parallel throughout cerebellar development, resulting in the gradual emergence of increasingly more complex cerebellar architecture. Alternatively, molecular patterning may be largely completed at intermediate stages and may subsequently be simply translated into functional patterns by morphogenic processes that regulate, for example, cell migration, axonal outgrowth and synaptogenesis.

Cell Type-Specific Expression of Cadherins in the Cerebellar Cortex

The previous sections focused on compartmentalized expression of cadherins by Purkinje cells, which form a sheet of single cells between the (outer) molecular layer and the (inner) granule cell layer in the adult cerebellar cortex (Fig. 10a). However, other types of cerebellar cells also express cadherins, as already mentioned for migrating granule cells. The internal granule cell layer contains small granule cells but also some larger interneurons [95]. The cells in the internal granule cell layer and the interneurons of the molecular layer (stellate cells and basket cells) show little or no evidence of regionalization with respect to gene expression, also for cadherins.

A comprehensive list of classic cadherins and δ−protocadherins and their expression patterns in cerebellar cortex of vertebrates is given in Table 1. Figure 10 shows examples of cell type-specific expression of cadherins in the mouse cerebellar cortex. A large majority of classic cadherins and δ-protocadherins are differentially expressed by specific Purkinje cell compartments (Figs. 2–6) at intermediate stages of development ("Cadherins Provide an Adhesive Code for Parasagittal Purkinje Cell Domains"). In the adult mouse cerebellum, Cdh2, Cdh11, and Cdh14/18 are expressed by most if not all Purkinje cells, whereas Cdh4, Cdh8 (Fig. 8e), Pcdh7, Pcdh8, Pcdh9, Pcdh10 (Fig. 8b and d), Pcdh17, and Pcdh19 are restricted to subsets of Purkinje cells in the mature cerebellum of chicken and/or mouse. Granule cells throughout the cerebellum are weakly to strongly positive for several cadherin subtypes (Table 1). Within the granule cell layer, there are also some scattered large cells that are strongly positive for Cdh4 (Fig. 10b, j, and l), Pcdh7 (Fig. 10g, i), Pcdh8 (Fig. 10e), Pcdh9 (Fig. 10f), and Pcdh17. Whether these large cells represent different subsets of interneurons [95] remains to be studied. Some cadherin-expressing cells have a distribution similar to Golgi II interneurons, which express the gene marker Pax2 in the young adult mouse [35, 95–97]. Double-labelling experiments with Pax2 confirmed that some Golgi II interneurons co-express Pcdh7 (Fig. 10g–i) and Cdh4 (Fig. 10j–l). In the developing chicken cerebellum, Cdh4-positive interneurons were also reported within the granule cell raphes at intermediate stages of development [54]. Oligodendrocytes in cerebellar white matter express Cdh19 [98]. Whether Bergmann glia express specific cadherins is unclear at present. Blood vessels in the cerebellum express specific cadherins, for example Cdh2 [14, 35], Cdh5 [35], and Pcdh1 (arrows in Fig. 2h [99]).

Last but not least, the persistence of cadherin expression in mature cerebellar neural circuits suggests a role of cadherins also in cerebellar synaptic function because cadherins are activity-dependent synaptic proteins [4, 29–32]. In the cerebellum, the following cadherins have been reported at synaptic locations, mostly in subsets of synapses: Cdh2 [31, 32, 100, 101], Cdh15 (M-cadherin) [102], Cdh4, and Cdh7 [54], and protocadherin-β16 [103]. The role of these and other cadherins in cerebellar synaptic function remains to be investigated.

Cadherins in Brain Disease

Cadherins are involved in tumorigenesis in many organs, including the brain, for example, by regulating the invasiveness of tumor cells [104]. In the mature CNS, postmitotic nerve cells do not give rise to tumors and the type of brain disease that might be associated with cadherin

dysfunction has remained largely elusive. Recent studies, however, indicate that neuropsychiatric disorders and developmental disturbance of brain function can be linked to cadherin genes.

The first cadherin genes implicated in psychosis was the gene pair Pcdh11X/Y, which has been duplicated during hominoid evolution and is thought to be a candidate gene for the evolution of hominoid-specific characteristics such as cerebral asymmetry [105, 106]. However, genetic screening studies did not confirm an association with psychosis [107]. Similarly, screens for mutations in Pcdh8 [108] and the seven-pass transmembrane cadherins CELSR [109] did not reveal any association with schizophrenia. Unlike these genes, the FAT cadherin gene locus contains a susceptibility gene for bipolar disorder [110] and single nucleotide polymorphisms (SNPs) near the Cdh7 gene are also associated with bipolar disorder. Moreover, mutations and SNPs of the Pcdh10 gene were found to be associated with autism-spectrum disorders [111, 112]. Female-limited infantile epileptic encephalopathy, which results in cognitive impairment, is caused by mutations in the X-linked Pcdh19 gene [113, 114].

Most classic cadherins and δ-protocadherins not only regulate embryonic and functional brain compartmentalization as well as the emergence of neural circuits in CNS development, but they continue to be expressed in neural circuits and synapses in the adult brain [1–3, 32]. It is therefore likely that, besides the examples mentioned above, other genetic brain diseases with a strong developmental component will be linked to cadherin genes in the future. Because most cadherins are simultaneously expressed in several brain areas, cadherin-associated brain disorders may globally affect several functional systems of the brain, even if perturbance in one specific system may dominate the clinical picture. Some of the disease-related cadherins mentioned above, for example Cdh7 and Pcdh10, are expressed during cerebellar development (Figs. 1–10, Table 1). It will be of interest to elucidate whether and how cerebellar functions are affected in these and other cadherin-linked brain disorders.

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