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Protocadherin-17 Expression and Function in Vertebrate Brain: A Literature Review

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Introduction:

The central nervous system (CNS) in vertebrates develops from a simple neural tube into a complex structure. The developmental steps to get to the complex structure have been examined extensively in the past few decades. To begin, the developing neural tube regionalizes into longitudinal and transverse subdivisions, with each subdivision undergoes further morphogenesis, and gives rise to a functional brain tissue (Redies, 1999).

During development, cell to cell adhesion plays a major role in the morphogenetic process. A type of molecules that is an important part in the process of cell adhesion are cadherins. Cadherins are transmembrane proteins that mediates cell to cell adhesion that is calcium dependent (Takeichi, 1991; Nollet et al., 2000; Basu et al., 2015). The cadherin superfamily can be classified into at least six different subfamilies based mainly on their extracellular and intracellular domain features. Two of these groups are classical cadherins and protocadherins (pcdhs) (Nollet et al., 2000).

Almost all members of the cadherin superfamily contain a large extracellular domain (called EC domain), a single pass transmembrane domain and a cytoplasmic domain (Takeichi, 1991). Members of the classical cadherin group have an EC domain consisting of five cadherin repeats, each about 110 amino acid residues in length (Suzuki, 1996). The two important cadherin repeats in the classical cadherins are the third and fifth repeats (EC3 and EC5). In comparison, pcdhs contain more than five EC repeats in their extracellular domains. Their domain sequences have been found to be similar to each other but different from those of the EC3 and EC5 of the classical cadherins (Suzuki, 1996). **Figure 1** depicts the structural differences between the two groupings of cadherins based on the extracellular domain.

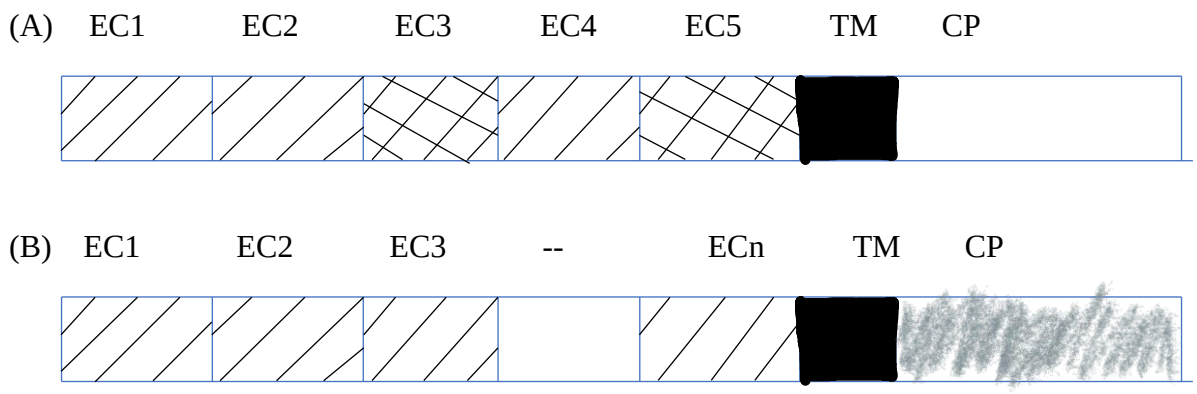

Figure 1. Panel A shows classical cadherins that contain EC3 and EC5 with specific characteristics denoted by the double zig-zag lines. Pcdhs (B) contain more than five EC repeats denoted by the ECn. The black boxed area in each drawing represents the transmembrane domain. CP stands for cytoplasmic domain, and TM stands for transmembrane domain

Pcdhs have been more recently discovered and studied (Redies et al., 2005). Within the pcdh family, there are more than 70 different genes that have been identified. These different pcdh genes can be organized into two different categories based on their genomic structure: clustered pcdhs and nonclustered pcdhs. The clustered pcdhs are named such because their genes are clustered in the genomes, whereas the nonclustered pcdhs have their genes spread out in the genomes, similar to most other protein-coding genes. The clustered pcdh group is the larger of the two, containing about 50 of the identified genes. The clustered pcdhs consist of the pcdhα, β, and γ groups (Morishita et al., 2007). The nonclustered pcdhs can be subdivided into two groups; pcdhδ and solitary pcdhs. The Pcdhδ group is characterized by containing highly conserved motifs in their cytoplasmic domains (Morishita et al., 2007). This group can be further divided into two types based on the number of their EC repeats, and conservation of amino acids motifs in their cytoplasmic domains (Redies et al., 2005; Morishita et al., 2007).

A specific example of the nonclustered pcdhδ is pcdh17. Like most classical cadherins, it contains three domains, extracellular, transmembrane and cytoplasmic domainsUnlike the classical cadherins, it contains six instead of five EC repeats (Liu et al., 2015). Expression patterns and/or function of this molecule have been studied in zebrafish (Biswas and Jontes, 2009; Liu et. al., 2009), mouse (Hoshina et al., 2013; Hayashi et al., 2014), rat (Kim et al., 2007)and humans (Abrahams et al., 2007; Chang et al., 2018). Despite their large evolutionary distance, the amino acid sequences of pcdh17/PCDH17 in zebrafish, mouse and humans are quite similar, over 73% identical in their coding regions (Liu et al. 2009), as shown in **figure 2** and **figure 3.**

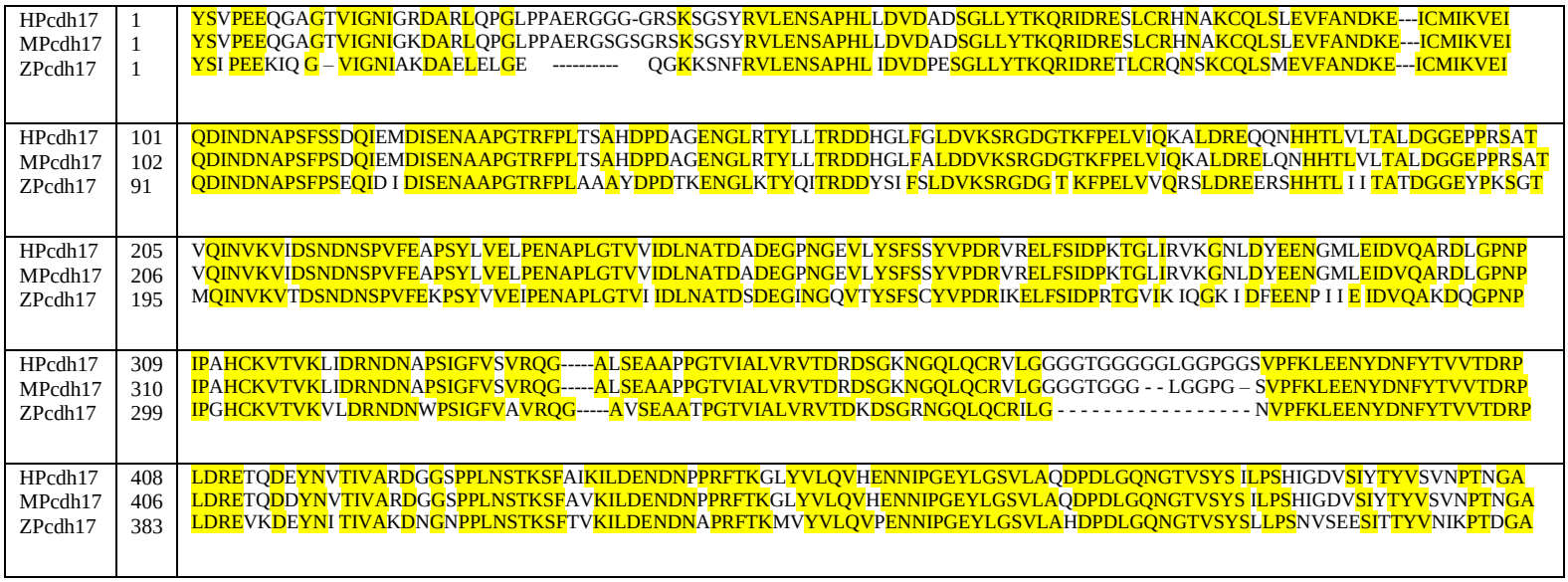

Figure 2. Amino acid sequence alignment of human protocadherin-17 (HPcdh17), mouse protocadherin-17 (MPcdh17), and zebrafish protocadherin-17 (ZPcdh17). Identical sequences among the three species are highlighted by the yellow shade. (Adapted from Liu et al., 2009)

The comparisons of the amino acid sequences of zebrafish, mice, and human were attained by using ClustalW2.

	ZPcdh17	**HPcdh17**	**MPcdh17**
ZPcdh17		73.50%	74.16%
HPcdh17			98.25%
MPcdh17			

Figure 3: Sequence comparisons between zebrafish, human, and mouse PCDH17/pcdh17 sequences. Abbreviations are the same as in figure 2. The figure is adopted from Liu et al., 2009.

This review focuses on the expression patterns and major functions of pcdh17 in the vertebrate brain by, first, reviewing the expression of pcdh17 in different brain regions of zebrafish, rat and/or mice, and humans and, second, discussing functional studies in those organisms.

Pcdh17 Expression in major brain regions

Pcdh17 in the telencephalon

The vertebrate telencephalon is located in the most anterior part of the brain and becomes the largest and most sophisticated region in higher vertebrates such as birds and mammals. The telencephalon plays a crucial role in memory, attention, sensory integration, and voluntary motor control (Sugahara et al., 2013). It includes the pallium (cortex in mammals) and subpallium, or basal ganglia (Sugahara et al., 2013). Because of the importance of functions this division provides, it is crucial to understand how pcdh17/PCDH17 is expressed in developing and adult organisms.

The zebrafish telencephalon consists of a pair of olfactory bulbs and two hemispheres. Expressional studies were performed to determine pcdh17 mRNA (*pcdh17*) expression in

developing zebrafish embryos (Liu et al., 2009) and adult zebrafish (Liu et al., 2015). *Pcdh17* is found in the forebrain (it later develops into telencephalon and diencephalon) of zebrafish embryos 12-13 hours post fertilization (hpf). Major brain regions have become distinct by 24 hpf in zebrafish (Kimmel et al., 1995). In zebrafish telencephalon of 24 hpf zebrafish, *pcdh17* shows highest expression in the lateroventral regions (Liu et al., 2009). Its expression in the telencephalon remains similar in 36 hpf zebrafish, and its expression domains become enlarged to almost the entire telencephalon in embryos of 50-72 hpf. In the adult zebrafish telencephalon, *pcdh17* shows expression in the internal cellular layer of the olfactory bulb, as well as the external cellular and glomerular layers, which is in the more peripheral regions of the olfactory bulb (Liu et al. 2015). In the hemispheres of the telencephalon, *pcdh17* expression is detected in most regions, with higher levels of expression, based on staining intensity, in the dorsomedial and ventricular regions.

In developing rat brain (post-natal day 3), *pcdh17* expression is found to be similar to that of the zebrafish, in the olfactory bulb and numerous regions of the cerebral hemispheres, including frontal cortex, parietal cortex, basal ganglia, amygdala, and hippocampus (Kim et al., 2007). In developing mice (P10), pcdh17 protein is detected in the olfactory bulb, prefrontal cortex, and basal ganglia (Hoshina et al., 2013). High levels of pcdh17 expression is found in both pre- and postsynaptic neurons in the medial prefrontal cortex and anterior striatum (receptive regions of the basal ganglia). *Pcdh17* is also found in the amygdala (Hayashi et al., 2014). There is no published reporting, to the best of my knowledge, on pcdh17 expression in adult rat or mice. There is no detailed and comprehensive study on distribution of PCDH17 in developing human brains, except a brief mentioning of its being enriched in focal regions of the prefrontal cortex of 19-20 weeks old human brains (Abrahams et al., 2007). In adult humans,

PCDH17 expression is found in Brodmann's area 46 (Dean et al., 2007), and in other cortical regions (Chang et al., 2018).

Comparing the expression patterns with fish and mammals in the telencephalon, *pcdh17* is expressed in the olfactory bulb in zebrafish, rats, and mice, *Pcdh17* is expressed in the cortex of mice and rats, as well as the pallium, which is the fish homologous region of the mammal cortex. Pcdh17 is also detected in the basal ganglia of mammals and the subpallium (ventral half of the telencephalon) in zebrafish. Furthermore, both the hippocampus of the mice and rat, and the dorsolateral telencephalon region, the fish homologous region for zebrafish, show *pcdh17* expression. Lastly, both the amygdala in mice and rats, and the dorsomedial telencephalon, the corresponding zebrafish region, contain many *pcdh17* expressing cells.

Pcdh17 in the diencephalon

The diencephalon is important in the vertebrate nervous system with functions that include a crucial relay and integration, modulation of sensory, motor, and cognitive functions, control of endocrine and reproductive functions, food and water intake, and regulation of circadian rhythms (Chatterjee and Li, 2012). The vertebrate diencephalon consists of the thalamus, epithalamus, and hypothalamus (Sugahara et al., 2013). With the diencephalon playing such important and diverse roles, it would be interesting to learn its molecular markers including pcdh17 in this region.

Pcdh17 expression is found in both the embryonic zebrafish (Liu et al., 2009) and adult zebrafish (Liu et al., 2015). As mentioned above, *pcdh17* is found in the forebrain (precursors of both telencephalon and diencephalon) of 12-13 hpf zebrafish embryos. In 24 hpf zebrafish, *pcdh17* expression is mainly detected in lateral and ventral diencephalon. A similar pattern of

pcdh17 expression is found in the diencephalon of 34 hpf embryos. *Pcdh17* continues to be expressed in older embryos of 50 and 70 hpf, and its expression, both in space and staining intensity, is increased in the older embryos compared to that in the younger embryos. In adult zebrafish, *pcdh17* has expression in the habenula and dorsal saccus of the epithalamus, in the preoptic area, suprachiasmatic nucleus of the anterior hypothalamus, in periventricular regions of the hypothalamus, and in the dorsal and ventral thalamus (Liu et al. 2015).

In developing rat diencephalon, *pcdh17* expression is located in the habenula of the epithalamus, in most regions of the hypothalamus, and in anteroventral, ventromedial and lateral thalamus (Kim et al., 2007). In developing mice (P10), pcdh17 protein is detected in epithalamus, thalamus and hypothalamus (higher level) (Hoshina et al., 2013). The epithalamus structure expressing pcdh17 is lateral habenula nucleus. In the thalamus, pcdh17 is found in the mediodorsal thalamus and paraventricular thalamus. There is no published report, to the best of my knowledge, on PCDH17 expression in human diencephalon.

The expression pattern of *pcdh17* in the zebrafish and mammal diencephalon are similar. *Pcdh17* is expressed in the epithalamus (e.g. habenula), hypothalamus (e.g. suprachiasmatic nucleus), and thalamus (e.g. wide expression) in the three species.

Pcdh17 in the midbrain

The vertebrate midbrain, also called the mesencephalon, is located between the diencephalon and hindbrain (Saladin, 2018). The midbrain consists of the optic tectum in nonmammals, and superior and inferior colliculi in mammals. Another part of this region is the tegmentum, which contains structures such as periaqueductal grey area, red nucleus and reticular formation. The optic tectum plays an important role for visual processes in nonmammals. The

superior colliculi functions in orienting the head and eyes toward visual and/or auditory stimuli. On the other hand, the inferior colliculi functions in processing auditory information (Kinkhabwala et al., 2011; Saladin, 2018). The tegmentum is important for brain functions that regulate breathing, cardiovascular activities, arousal, consciousness, and movement coordination. Any information about *pcdh17* expression in this brain region can help us understand the nature of this region.

Pcdh17 expression is found in areas of the midbrain in both embryonic zebrafish (Liu et al., 2009) and adult zebrafish (Liu et al., 2015). There is no obvious *pcdh17* expression in the midbrain of embryonic zebrafish 12-13 hpf. At 24 hpf, there is some expression in the tegmentum (Biswas & Jontes, 2009). Expression of *pcdh17* in the midbrain of 34 hpf embryos increases in the areas of the optic tectum and tegmentum. In older embryos, 50 to 72 hpf, expression intensity increased even more in both the tectum and the tegmentum (Liu et al., 2009). In adult zebrafish brain, the midbrain shows *pcdh17* expression in the stratum periventricular (SPV) throughout the tectum (Liu et al., 2015). There is also expression in the torus longitudinalis (TL) and the dorsal tegmental nucleus (DTN) (Liu et al., 2015).

Similar to zebrafish, there is *pcdh17* expression in developing rat midbrain in the areas of the of superior and inferior colliculi (Kim et al., 2007). In P10 day mice, pcdh17 protein appears to be expressed in both the superior and inferior colliculi and tegmentum, based on images in Hoshina et al. (2013), although its expression in the midbrain was not discussed. *PCDH17* expression is also reported in the human midbrain (Redies et al., 2005), but no information on its spatial distribution in the midbrain was provided.

Pcdh17 in the hindbrain

The vertebrate hindbrain is important for controlling and coordinating movement. The hindbrain is also home to the cerebellum, medulla oblongata, and pons. These areas help with functions that are crucial for survival (Kinkhabwala et al., 2011; Saladin 2018). The hindbrain is responsible for controlling movements, balance, respiration, cardiovascular activities, and conveying sensory information to higher brain regions. With being associated with such important functions, the hindbrain is a crucial part of the vertebrate CNS. Anything we can learn about *pcdh17* expression in this region can help us understand more about the molecular nature of the hindbrain. With that, examining *pcdh17* expression in this region is an important study.

Pcdh17 expression is found in the hindbrain in both embryonic zebrafish (Liu et al., 2009) and adult zebrafish (Liu et al., 2015). *Pcdh17* expression in the brain of zebrafish embryos is seen as early as 12-13 hpf., but no obvious expression in the hindbrain (Liu et al., 2009). By 24 hpf, *pcdh17* is found in the hindbrain of zebrafish embryos. Small clusters of *pcdh17* expressing cells are found in ventrolateral regions. *Pcdh17* expression is found to become increased in the hindbrain in embryos of 34 hpf, with a similar pattern, confined mainly to the ventrolateral regions, but with expanded domains, forming two columns of cells lateral to the midline of the hindbrain. In older embryos, 50 to 72 hpf, *pcdh17* continues to be expressed in the hindbrain, with its expression domains expand further, both in dorsoventral and lateromedial directions (Liu et al., 2009). In adult zebrafish, *pcdh17* is expressed in major regions of the cerebellum including the cerebellar body and lateral granular eminence (Liu et al., 2015). Moreover, cells at the border between the granular and molecular layers of the cerebellar body show stronger labeling. These cells are likely Purkinje cells based on their location and size. *Pcdh17* has a wide distribution in the medulla. Nuclei of six cranial nerves (fifth to tenth) all contain *pcdh17* expressing cells.

Strongly labeled cells are found in the superficial regions of both facial and vagal lobes. The inferior reticular formation also contains many *pcdh17* expressing cells.

In the brain of P3 rat brain, *pcdh17* expression is strong throughout the hindbrain. Moreover, its expression in this region appears to have a stripe-patchy pattern (Kim et al., 2007). In developing mice hindbrain (P10), pcdh17 protein expression is found mainly in the ventral regions (Hoshina et al., 2013). In humans, *PCDH17* expression is detected in regions of the hindbrain in the areas of the cerebellum, pons, and medulla oblongata (Redies et al., 2005), but more specific spatial distribution pattern in the hindbrain was not provided.

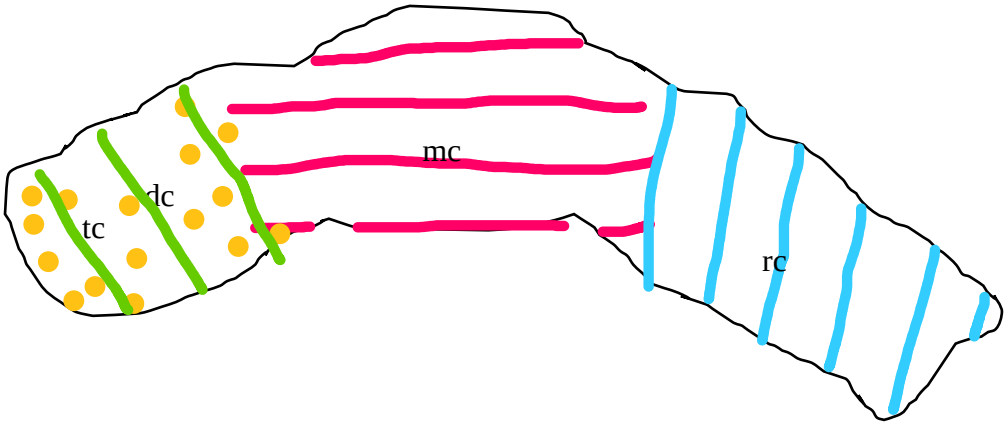

Figure 4 shows a schematic, sagittal representation of a 12-13 hpf embryonic zebrafish brain, highlighting some of the major areas where *pcdh17* is found. (green – forebrain/telencephalon, diencephalon; red – midbrain, blue – hindbrain) Yellow dots represent regions with high level of *pcdh17* expression.

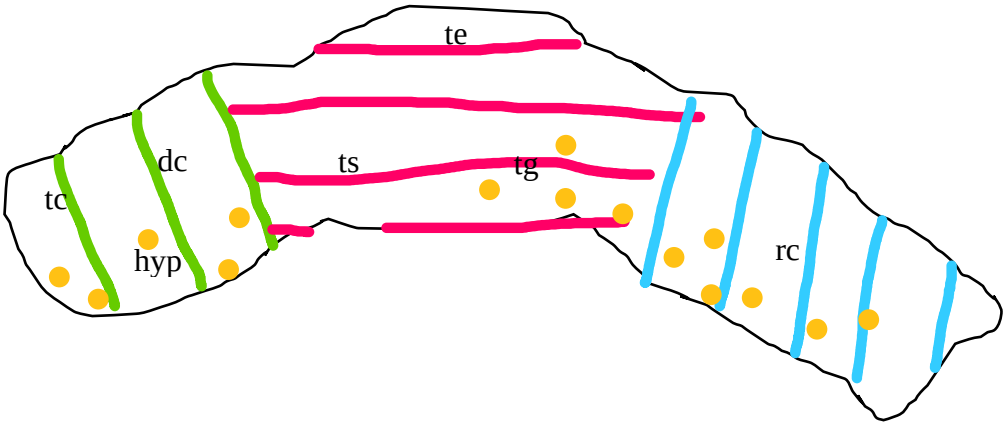

Figure 5 shows a schematic, sagittal representation of a 24 hpf embryonic zebrafish brain, highlighting some of the major areas where pcdh17 is found. (green – forebrain/telencephalon, diencephalon; red – midbrain; te-tectum; tg-tegmentum, blue – hindbrain) Yellow dots represent regions with high levels of *pcdh17* expression.

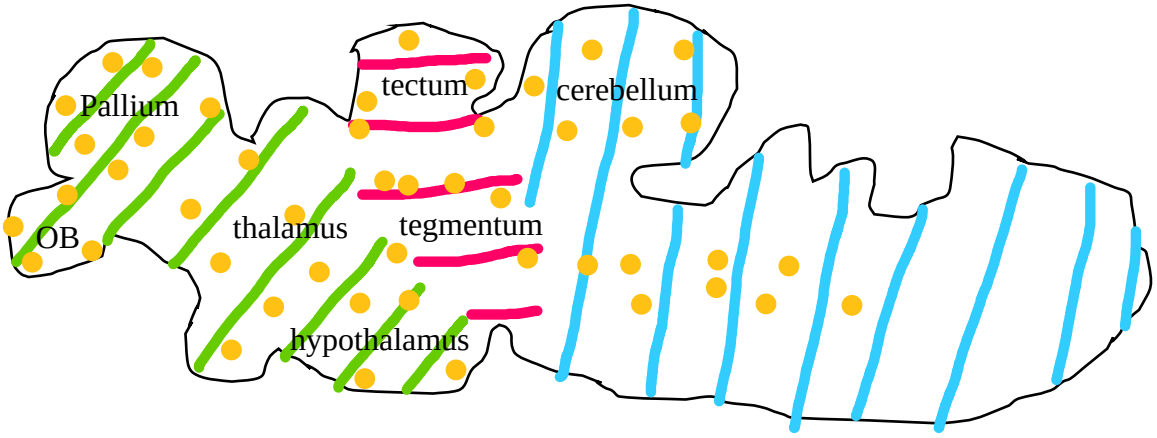

Figure 6 shows a schematic, sagittal representation of the adult zebrafish brain, highlighting some of the major areas where pcdh17 is found. (green – forebrain/telencephalon, diencephalon; red – midbrain, blue – hindbrain; OB – olfactory bulb). Yellow dots represent regions with high levels of *pcdh17* expression.

To summarize, *pcdh17* shows expression in all major regions of embryonic and adult zebrafish, mice, rat and humans. It is important to note that all the studies of *pcdh17*/*PCDH17* expression in the vertebrate brain show an anterior-posterior gradient, meaning that anterior regions (forebrain) shows more expression than posterior regions (hindbrain) (Liu et al., 2009). In other words, *pcdh17* expression in the vertebrate brain is conserved. In general, studies on expression in zebrafish is much more detailed than in rat, mice and humans.

Functional Studies in Zebrafish

To the best of my knowledge, there is only one published report on pcdh17 function in zebrafish development (Chen et al., 2013). Morpholino antisense oligonucleotide (MO) techniques were used to study the function of pcdh17 in developing zebrafish retinas. The study shows that the injected zebrafish embryos have similar body shape and size when compared to the control zebrafish, but have significantly reduced eye size (Chen et al., 2013). Further analysis of the eye reveals that the reduced eye size is likely due to reduced cell proliferating rates, instead of increased cell death. Despite the smaller eye size, there is no apparent defects in the differentiation of retinal cell types. There was no report on the effect of reduced pcdh17 expression on the zebrafish brain development.

Functional Studies in Mice

There are several studies on examining the function of pcdh17 in mice brain. Strong expression of pcdh17 in both the pre- and postsynaptic neurons in the anatomically connected corticobasal ganglia pathway in developing mice suggests its function in the development of

these brain circuits (Hoshina et al., 2013). An in vitro assay showed that pcdh17 mediates calcium-dependent homophilic cell-cell adhesion (Hoshina et al., 2013).

To better understand the function of pcdh17 in the mice brain development and function, pcdh17 mutant mice were generated, which showed 96% reduction in pcdh17 protein expression (Hoshina et al., 2013). Examination of the mutant mice shows that the mice have no gross defects in the architecture of the brain, and no detectable difference in overall axonal projections when compared to wild type mice (Hoshina et al., 2013). Specifically, there is no defect found in the corticobasal ganglia pathway where pcdh17 is expressed. Moreover, expression of synaptic markers such as N-cadherin, synaptophysin, PSD95, and glutamate receptors appears to be normal in the pcdh17 mutant mice. Next, the synaptic morphology of wild type and mutant mice was examined using electron microscopy. In excitatory synapses, there is a significant increase in the docked synaptic vesicles in the mutant mice. This increase is also observed in some inhibitory synapses in the corticobasal ganglia circuits. Therefore, pcdh17 appears to have an inhibitory effect on the accumulation of synaptic vesicles (Hoshina et al., 2013).

Electrophysiological analysis of the pcdh17 mutant mice shows no detectable changes in synaptic transmission mediated by glutamate (the major excitatory neurotransmitter in mammal brains) within the corticobasal ganglia circuits, suggesting that pcdh17 does not have an effect on the excitatory corticostriatal synaptic transmission. However, when similar analysis is performed on the GABAergic inhibitory synapses in the basal ganglia, an enhancement in the synaptic transmission is observed. One of the major contributing factors to reduced synaptic transmission or synaptic depression, is due to depletion of presynaptic vesicles after above normal activation of the synaptic transmission. Because there is increased number of presynaptic vesicles in pcdh17 mutant mice, they are less susceptible to the synaptic depression. This anti-depressant-

like phenotype known to be regulated by the corticobasal ganglia circuits, suggests that pcdh17 is involved in depressive behaviors (Hoshina et al., 2013). This speculation is tested by behavioral tests for evaluating sensory and motor functions, cognition, anxiety and depression. For example, tail suspension test and forced swim test show that pcdh17 mutant mice are less immobile than wild type mice, suggesting that pcdh17 mutant mice are less susceptible to depression than wild type mice (Hoshina et al., 2013).

Another study of pcdh17 function in mice brain demonstrates that pcdh17 is involved in development of efferent axons in amygdala (Hayashi et al., 2014). Pcdh17 was localized on axon fibers that extend from amygdala neurons. Ectopic expression of pcdh17 in amygdala axons that do not typically express pcdh17 results in their joining other axons that endogenously express pcdh17. This result suggests that pcdh17 is sufficient to induce rearrangement of axons, and that pcdh17 regulates grouping of axons through homophilic interactions of their extracellular domains (Hayashi et al., 2014). *S*everal amygdala nuclei, including the medial and basolateral amygdala, express *pcdh17* (Hayashi et al., 2014). Knockout mice for *pcdh17* were examined and their phenotypes were analyzed. In homozygous mutants. There is no noticeable abnormalities in the overall structure of the amygdala nuclei. Moreover, there is no significant difference between the wild type and *pcdh17* mutant mice in the number of Lhx6 (a transcription factor expressed by most neurons in the amygdala) labeled neurons. This suggests that knocking out pcdh17 in mice has no detectable effect on the formation of amygdala nuclei (Hayashi et al., 2014). However, in these homozygous mutant mice, the size of the stria terminalis is reduced. The stria terminalis is the major output pathway of the amygdala. Axonal labeling of this pathway reveals that axonal fibers in the stria terminalis are significantly reduced (30% in milder cases) or completely missing (in severe cases). By the use of electron microscopic analysis, it is

determined that the axons passing the dorsal part of the stria terminalis are well-oriented in a parallel fashion in the wild type mice, whereas this alignment is disrupted with misoriented axons in mutant mice. This led to the conclusion that pcdh17 is required for normal axon extension from specific subdivisions of the amygdala (Hayashi et al., 2014).

PCH17 Function in Humans

Major mood disorders, or affective disorders, such as bipolar disorder, depressive disorder, and anxiety disorders, are mental health problems affecting millions of people and a leading cause of disability in this country (Evans & Charney, 2003). Studies have shown that PCDH17 is involved in the development of these mood disorders.

As in mice and rat, *PCDH17* is expressed in human amygdala, which is an important region for regulation of mood, anxiety, and fear. This suggests that PCDH17 may be involved in major mood disorders (Chang et al., 2018). A large scale clinical data analysis of single-nucleotide polymorphisms (SNPs) of more than 60,000 individuals, coupled with functional MRI analysis, RNA sequencing, cognitive assessment and personality traits measurements, and in vitro cell culture experiments, demonstrate a clear association between a particular PCDH17 allele and high risk of developing major mood disorders (Chang et al., 2018). The study showed that one SNP, rs9537793, located 3’ to *PCDH17* showed the highest association with mood disorders when compared to other SNPs tested.

Since PCDH17 is highly expressed in the amygdala and caudate nucleus of the basal ganglia, brain areas involved in emotional processing, it is hypothesized that this PCDH17 SNP is associated with mood and personality disorders. Individuals with this rs9537793 SNP are found to be associated with neuroticism, which is an important emotional trait for predicting

mood disorders (Chang et al., 2017). Moreover, individuals carrying the risk SNP have significantly decreased volumes of both the amygdala and hippocampus. These results lead to the hypothesis that the SNP may also be associated with amygdala function underlying negative emotional processing (Chang et al., 2017). Healthy individuals who are carriers for the risk SNP of *PCDH17* show significantly increased amygdala activity when presented with negative stimuli compared to those individuals who are not carriers of the particular risk allele. Furthermore, individuals who are homozygous carriers of the risk allele show the highest amount of amygdala activity, which is followed by heterozygotes, and the least amount of amygdala activity are seen in those homozygous for a protective allele.

The correlation between PCDH17 and major mood disorders is further supported by an RNA sequencing analysis, which showed that individuals with bipolar disorder had significantly increased PCDH17 mRNA expression (Chang et al., 2018). An in vitro experiment using induced pluripotent stem cells (iPSCs) derived from patients with bipolar disorder and those from healthy individuals show that both the iPSCs and neurons derived from them express higher levels of PCDH17 from bipolar disorder patients than those from healthy individuals, suggesting that PCDH17 plays a role in early brain development, and abnormal PCDH17 expression may cause mental disorders including bipolar mood disorder.

Conclusion

Studies of pcdh17 expression in zebrafish, mice, rat, and humans show that this cell adhesion molecule exhibits similar expression patterns in the major brain areas in both fish and mammals. Important regions expressing pcdh17/PCDH17 include frontal cortex, basal ganglia, hippocampus and amygdala. There is more data on the spatial distribution of *pcdh17* in zebrafish

brain than that in the other species, but there is more information on pcdh17/PCDH17 function in mice and humans. In both mice and humans, pcdh17/PCDH17 is involved in depression. In humans, PCDH17 is associated with major mood disorders, especially the bipolar disorder. Future functional studies may shed light on pcdh17/PCDH17 function in activities controlled by the diencephalon (e.g. regulation of reproduction) and hindbrain (e.g. control of movement).

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