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Developmental Biology of the Meninges

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Abstract

The meninges are membranous layers surrounding the central nervous system. In the head, the meninges lie between the brain and the skull, and interact closely with both during development. The cranial meninges originate from a mesenchymal sheath on the surface of the developing brain, called primary meninx, and undergo differentiation into three layers with distinct histological characteristics: the dura mater, the arachnoid mater, and the pia mater. While genetic regulation of meningeal development is still poorly understood, mouse mutants and other models with meningeal defects have demonstrated the importance of the meninges to normal development of the calvaria and the brain. For the calvaria, the interactions with the meninges are necessary for the progression of calvarial osteogenesis during early development. In later stages, the meninges control the patterning of the skull and the fate of the sutures. For the brain, the meninges regulate diverse processes including cell survival, cell migration, generation of neurons from progenitors, and vascularization. Also, the meninges serve as a stem cell niche for the brain in the postnatal life. Given these important roles of the meninges, further investigation into the molecular mechanisms underlying meningeal development can provide novel insights into the coordinated development of the head.

Keywords

meninges; head mesenchyme; calvaria; brain development; craniofacial development

1. Introduction

The vertebrate central nervous system (CNS) is encased with three layers of membranes called the meninges (Greek: *meninx-membrane).* The meninges provide a protective cover to the underlying soft neural tissue of the brain and the spinal cord. Furthermore, they attach the CNS parenchyma to the bony skull or the vertebral column. The meninges also contain space through which cerebrospinal fluid (CSF) travels around CNS. In addition to these structural roles, a growing body of evidence has indicated that the meninges are actively involved in development of the brain and the calvaria (the top part of the skull), and even serve as a stem cell niche postnatally (Adeeb *et al.,* 2012; Decimo *et al.,* 2012; Gagan *et al.,* 2007; Siegenthaler and Pleasure, 2011; Richtsmeier and Flaherty, 2013). From a medical perspective, defects in the meninges are thought to underlie two neurodevelopmental

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disorders in humans, Dandy-Walker malformation and cobblestone lissencephaly (Siegenthaler and Pleasure, 2011). Both conditions impair the function of the brain.

Despite the profound importance of the meninges, we have very limited information about the formation, differentiation, and the molecular characteristics of this tissue. In this review, we summarize the current understanding of the process of meningeal development, interactions between the meninges and the developing calvaria, and interactions between the meninges and the developing brain. As such, the focus is on the cranial meninges covering the brain. Discussions of the spinal meninges can be found in other reviews (Lopes, 2009; Nagel *et al.,* 2018; Sakka *et al.,* 2016).

2. Organization of the meninges

In adult mammals, the meninges are made of three distinct layers (Fig. 1): the outermost dura mater *(dura-* tough, *mater-mother),* the middle arachnoid mater *(arachne-*spider), and the innermost pia mater *(pia-* tender), each named for their histological appearances. The dura mater is also referred to as pachymeninx (*pachy-*thick), while the arachnoid mater and the pia mater are together called leptomeninx *(lepto-* thin) (Adeeb *et al.,* 2012; Vanderah and Gould, 2015).

The dura mater is a thick and dense collagenous membrane attached to the inner surface of the skull. It is made of two layers - the outer layer (called endosteal layer/dura or periosteal layer/dura) serves as the periosteum of the internal surface of the skull bone. The inner layer (called meningeal layer/dura or dura mater proper) is fused to the endosteal layer in most regions, and they are separated only at the sites of dural venous sinuses for the drainage of venous blood from the brain. The dura mater folds and invaginates into the cranial cavity at major boundaries between the sub-regions of the brain. These folds are called dural reflections. For example, falx cerebri separates the two cerebral hemispheres along the midline, and tentorium cerebelli separates the cerebral hemispheres posteriorly from the cerebellum. The dura mater, especially the endosteal layer, contains numerous blood vessels, which are mainly involved in supplying blood to the calvaria (Adeeb *et al.,* 2012; Vanderah and Gould, 2015). In addition, the lymphatic vessels within the dura mater serve as a drain for CSF from the CNS (Aspelund *et al.,* 2015; DiNuoscio and Atit, 2019; Louveau *et al.,* 2015).

The arachnoid mater is a thin, translucent membrane containing a few layers of flattened cells. Underneath this membrane is arachnoid trabeculae, which is spongy connective tissue made of collagen fibers and fibroblasts. Openings in this meshwork constitute the subarachnoid space, and blood vessels and CSF travel through this space (Decimo *et al.,* 2012; Lopes, 2009; Vanderah and Gould, 2015).

The pia mater has a delicate, single cell-layer membrane that closely adheres to the surface of the brain. In addition, blood vessels branch out from the subarachnoid space through the pia mater into the brain. These blood vessels, as well as their perivascular connective tissue and perivascular space, are all considered a continuation of the pia mater (Decimo *et al.,* 2012; Lopes, 2009; O'Rahilly and Muller, 1986; Vanderah and Gould, 2015). The pial

basement membrane is a sheet of extracellular matrix (ECM) immediately internal to the pia mater. It contains diverse ECM proteins including laminins, collagen IV, heparan sulfate proteoglycans, and nidogen (also known as entactin) (Halfter *et al.,* 2002). The pial basement membrane forms the border between the meninges and the brain parenchyma, and it is closely involved in brain development (discussed below).

3. Development of the meninges

3.1 Histological description of the process

Embryonic development of the meninges has been described in multiple species by many researchers, with some works dating back over 200 years (Adeeb *et al.,* 2012). Here, we will focus on the description of the process in mammals based on studies of human, mouse, and rat (Adeeb *et al.,* 2012; Angelov and Vasilev, 1989; Decimo *et al.,* 2012; Lopes, 2009; McLone and Bondareff, 1975; O'Rahilly and Muller, 1986).

During early embryogenesis, mesenchyme cells begin to surround the hindbrain at the time of neural tube closure, and continue to spread to the midbrain and the forebrain levels (O'Rahilly and Muller, 1986). As a result, a mesenchymal sheath is established over the brain by Carnegie stage 15 in humans (5th week of gestation) and embryonic day (E) ~E9.5 in mice (Angelov and Vasilev, 1989; McLone and Bondareff, 1975; O'Rahilly and Muller, 1986). This sheath is the primary meninx (also known as primitive meninx or meninx primitiva), and it is the primordium for the meninges, skull, and the scalp (O'Rahilly and Muller, 1986). The primary meninx also contains a vascular plexus along the surface of the brain (perineural vascular plexus), which will develop into the blood vessels embedded in the meninges and those entering the brain (Decimo *et al.,* 2012). The nascent pia mater is already histologically discernable over some parts of the brain as cells intervening the vascular plexus and the wall of the brain (O'Rahilly and Muller, 1986). Fibroblasts in the pia mater produce ECM proteins to lay down the pial basement membrane that will separate the meninges and the brain.

Subsequently, the primary meninx is divided into an outer dense layer and an inner reticular layer at ~E10.5 in mice (Fig. 1). The inner layer is considered to be the meningeal mesenchyme although it has not been proven whether this layer gives rise to all three meninges including the dura mater. By stage 17 in humans (6th week of gestation) and ~E13 in mice, the mesenchyme around the brain is organized into multiple distinct layers (Fig. 1): the most external layer is the dermal layer. The next layer is what has been called a 'skeletogenic' layer, for giving rise to the skull (O'Rahilly and Muller, 1986). However, more recent studies have found that the mesenchyme cells in this layer on the apical side of the head may contribute to the sutures (soft tissue joints) but not the bone plates of the calvaria (Roybal *et al.,* 2010; Yoshida *et al.,* 2008). Therefore, the term 'calvarial' layer (Siegenthaler and Pleasure, 2011) is more appropriate in that it includes the precursors of the sutures as well as the bone. Internal to the calvarial layer, the meningeal primordium begins to be separated into pachymeninx (dura mater) and leptomeninx (arachnoid mater and pia mater) by the dural limiting layer. Pachymeninx contains longitudinally arranged fibroblasts, while leptomeninx is a meshwork of loosely organized cells. Dural limiting layer itself is a sheet of condensed cells, and it is thought to contribute to both the dura mater and the

arachnoid mater ultimately. Thus, the external portion of the dural limiting layer is usually included in the definition of pachymeninx (Lopes, 2009; O'Rahilly and Muller, 1986). Differentiation of the meningeal layers progresses from basal to apical direction (Vivatbutsiri *et al.,* 2008). During this process, leptomeninx undergoes cavitation to make the arachnoid trabeculae and the subarachnoid space. The dura mater gets filled with accumulating collagen fibers (Angelov and Vasilev, 1989), and the lymphatic vessels in the dura mater develop in the early postnatal life (Antila *et al.,* 2017).

3.2. Origins of the meningeal cells

Early experiments on quail and chick chimeras showed that neural crest-derived cells, generated from the caudal forebrain and the midbrain levels, contributed to the meninges associated with the forebrain. In contrast, mesoderm-derived cells gave rise to the meninges of the midbrain and the hindbrain (Fig. 2) (Couly and Le Douarin, 1987; Couly *et al.,* 1992; Le Douarin and Kalcheim 1999). However, in all areas of the meninges, the endothelial cells of the blood vessels were strictly of mesoderm origin (Le Douarin and Kalcheim 1999). Histological observations in human fetuses also suggested that the cranial meninges originated from both the neural crest (which is derived from the ectoderm) and the mesoderm. Furthermore, the prechordal plate and the paraxial mesoderm were named as the source of the mesodermal cells (O'Rahilly and Muller, 1986).

In mice, Cre-loxP technology and Cre-dependent reporter lines have enabled long-term lineage tracing of specific groups of cells (Soriano, 1999). Using this tool, several studies have examined the contribution of neural crest versus mesoderm cells to various tissues of the craniofacial area. The results in the meninges were consistent with those from the avian studies. Using *Wnt1-Cre,* which is active in the neural crest (Danielian *et al.,* 1998), Jiang et al (Jiang *et al.,* 2002) found neural crest-derived cells in all 3 layers of the meninges associated with the forebrain cerebral hemispheres, but not in the meninges covering the midbrain or the hindbrain. Another study (Yoshida *et al.,* 2008) used mesoderm-specific *Mesp1-Cre* (Saga *et al.,* 1999) in conjunction with *Wnt1-Cre,* to provide positive evidence that the meninges of the midbrain and the hindbrain were of mesoderm origin whereas the meninges of the forebrain were of neural crest origin (except for the endothelial cells).

3.3. Regulation of meningeal development

Molecular genetic regulation of meningeal development is poorly understood. Table 1 lists genes expressed in the developing meninges of mouse embryos during early stages (E10.5-E13.5) based on our literature search and Gene Expression Database query (C. M. Smith *et al.,* 2014). Among these, a few genes with functional importance have been identified from studies of mice exhibiting meningeal defects. Other candidates for regulators of meningeal development would be the genes associated with cobblestone lissencephaly and Dandy-Walker malformation in humans (discussed below), and they are listed in Table 2 and Table 3.

Foxc1 (formerly known as *Mf1),* encoding a forkhead/winged helix transcription factor, is the most extensively studied gene in the context of meningeal development. Mouse *Foxc1* is expressed throughout the primary meninx from its first appearance (Kume *et al.,* 1998;

Mishra *et al.,* 2016), and continues to be expressed in all three layers of the meninges (Zarbalis *et al.,* 2007). *Foxc1* was first linked to the meninges through a spontaneous mutation in mice called *congenital hydrocephalous (ch)* (Gruneberg, 1943), which turned out to be a point mutation in *Foxc1* creating a truncated protein (Kume *et al.,* 1998). *ch* homozygote pups ($Foxc1^{ch/ch}$) died at birth, suffering from an enlarged and hemorrhaging brain, loss of the calvaria, and other defects throughout the body. Severe meningeal defects were noted in $Foxc1^{ch/ch}$ mutants, and the hydrocephaly was attributed to the failure in development of the subarachnoid space (Green, 1970). Based on later histological examination and transmission electron microscopy, the defects were evident in $Foxc1^{ch/ch}$ mutants from E13.5, when the meningeal mesenchyme appeared abnormally compact. The three layers of the meninges initially differentiated on the baso-lateral side of the brain, but only the pia mater continued to develop. Expression of several genes were lost or reduced in the apical meningeal mesenchyme at E13.5-E14.5, and the arachnoid mater and the dura mater failed to form here (Vivatbutsiri *et al.,* 2008).

A similar phenotype was found in a mutant with targeted null alleles of *Foxc1* ($Foxc1^{lacZ/lacZ}$), namely, lack of the arachnoid mater and the dura mater over the cerebral hemispheres (Siegenthaler *et al.,* 2009). From E12.5, the apical side of the mutant forebrain was deficient in meningeal fibroblasts, though the pia mater seemed to be present judging from the staining for the laminin in the pial basement membrane (Hecht *et al.,* 2010). The pial basement membrane was eventually disintegrated in the mutants at late fetal stages, but it was thought to be a secondary consequence of the early meningeal defects (Hecht *et al.,* 2010). In the hindbrain area of the $Foxe1^{lacZ/lacZ}$ mutant, the prospective arachnoid mater was thin and dense, and the prospective dura mater was disorganized at E12.5-E13.5 (Kume *et al.,* 1998). An additional insight into the role of *Foxc1* was provided by a hypomorphic mutation in mice named *hole in the head* (*hith*), recovered from a chemical mutagenesis screen (Zarbalis *et al.,* 2007). $Foxc1^{hith/hith}$ mutants showed a highly localized meningeal deficiency at the apex of the head at E18.5, together with defects in the skull and the brain at this location. The fact that the meninges were preferentially affected on the apical side suggested that *Foxc1* was particularly important for the apical progression of meningeal differentiation. Combined, the findings from various *Foxc1* mutants have established that this gene is a crucial, intrinsic regulator of early development of the meninges. However, the molecular and cellular mechanism of its function in the process remains unknown.

Zic family genes encode zinc finger domain transcription factors important for diverse events of embryonic development (Diamand *et al.,* 2018). In mice, *Zic1, Zic2,* and *Zic3* are expressed in the meninges (Inoue *et al.,* 2008), and *Zic1/3* double mutation caused a decrease in proliferation of the meningeal fibroblasts at E15.5. Expression of several genes was also reduced in the mutant meninges including *Lamc1* (encoding laminin subunit gamma 1), and the pial basement membrane was disrupted by E17.5 (Inoue *et al.,* 2008). Interestingly, *Foxc1* was down-regulated in the meninges of *Zic1/3* mutants, and thus *Foxc1* may be a downstream mediator of ZIC function in the meningeal development. However, it is unknown whether *Zic1/3* mutants have early meningeal defects as *Foxc1* mutants do. *Twist1* (twist basic helix-loop-helix transcription factor 1) is another transcription factor gene implicated in meningeal development. It is expressed broadly in the head mesenchyme including the meningeal layer (Tischfield et al. 2017). Deletion of *Twist1* in the meninges

led to hypoplasia of the dura mater and the arachnoid mater, and compaction of the subarachnoid space (Tischfield et al. 2017).

Among intercellular signaling pathways, there is direct evidence that transforming growth factor β (TGFβ) signaling is required for normal development of the meninges. *Tgfbr2,* which encodes a receptor component, is expressed in the meningeal mesenchyme from early stages (Wang *et al.,* 1995). In mouse embryos with neural crest-specific deletion of *Tgfbr2,* the forebrain meninges failed to develop; at E14.5, it was replaced with only a single layer of cells that did not proliferate (Ito *et al.,* 2003). In addition, wingless-integrated (WNT)/β-catenin signaling and retinoic acid (RA) signaling were shown to influence meningeal development. Constitutive activation of WNT/β-catenin pathway in the head ectoderm induced the expression of *Wnt6,* which in turn activated WNT/β-catenin pathway in the neural crest-derived meninges over the forebrain. This led to increased cell proliferation and expansion of the meningeal layer at E14.5 (Choe *et al.,* 2012). In a later study, β-catenin was directly activated or removed in the neural crest-derived cells, and the results suggested that WNT/β-catenin signaling promoted the general expansion of the head mesenchyme cells rather than regulating the specification of the meningeal cells (Choe, Zarbalis, *et al.,* 2014). Interestingly, removing β-catenin in the non-meningeal head mesenchyme also caused hypoplasia of the meninges on the baso-lateral side of the brain, indicating that WNT/β-catenin pathway uses a non-cell autonomous mechanism here (DiNuoscio and Atit, 2019). Contrary to the phenotype from excess WNT, treating mouse embryos with exogenous RA at E10 led to thin and discontinuous meninges (Jiang *et al.,* 2002). However, removing endogenous RA from ~E11.5 did not significantly affect the meninges (Haushalter *et al.,* 2017). Therefore, RA signaling may be dispensable for normal development of the meninges although its over-activation is deleterious.

Disruption of the pial basement membrane has been reported in mouse mutants of several genes for ECM or cell adhesion complex components, including *Apbb1* and *Apbb2* (amyloid beta (A4) precursor protein binding, family B, member 1 and member 2) (Guenette *et al.,* 2006), *Col4a1* (collagen type IV alpha 1) (Labelle-Dumais *et al.,* 2011), *Lama1* (laminin alpha 1) (Ichikawa- Tomikawa *et al.,* 2012), *Lamc1* (laminin gamma 1) (Halfter *et al.,* 2002), and Ptk2 (protein tyrosine kinase 2, previously called focal adhesion kinase or FAK) (Beggs *et al.,* 2003) (reviewed in Siegenthaler and Pleasure, 2011). However, these genes are likely required for maintaining the structural integrity of the meninges and the basement membrane, rather than regulating development of the meninges.

4. Influence of the meninges on calvarial development

The mammalian calvaria comprises five pieces of bone, namely, a pair of frontal bones, a pair of parietal bones, and a piece of interparietal bone, joined by soft connective tissue of the sutures (Fig. 2) (Ferguson and Atit, 2018; Ishii *et al.,* 2015). Like the meninges, the calvaria develops from the embryonic head mesenchyme surrounding the brain, and thus its progenitors are presumably included in the primary meninx described earlier. The calvaria is also of dual origin (Fig. 2) (Jiang *et al.,* 2002; Yoshida *et al.,* 2008): the frontal bone is mostly made of neural crest-derived cells with a minor contribution from mesodermal cells, while the parietal bone is entirely made of mesodermal cells. The interparietal bone contains

both groups of cells. At the end of development, the calvaria and the meninges are almost continuous in that the outer layer of the dura mater makes the periosteum on the inner surface of the calvarial bone.

Since the calvaria and the meninges form in close apposition, it is expected that there would be extensive regulatory interactions between the two structures during development (Fig. 3). This topic was first studied through surgical manipulations (removals and transplantations) of the meninges in late fetal, neonatal, or young postnatal rats and rabbits (reviewed in Grova *et al.,* 2012; Lenton *et al.,* 2005). In these experiments, the dura mater was found necessary and sufficient for re-ossification after the calvarial bone was removed or injured (Hobar *et al.,* 1996; Mabbutt and Kokich, 1979), which indicated that the dura mater was a source of osteogenic signals. On the other hand, the dura mater from underneath a normally patent suture was necessary and sufficient to maintain the patency (Levine *et al.,* 1998; Opperman *et al.,* 1993). A similar result was obtained in mouse embryos in late gestation (E16.5) (Kim *et al.,* 1998). Various secreted molecules, including members of TGFβ, FGF (fibroblast growth factor), and BMP (bone morphogenetic protein) family, were expressed in the dura mater, and thought to mediate the interaction with the calvaria (Kim *et al.,* 1998; Lenton *et al.,* 2005; Levi *et al.,* 2012; Spector *et al.,* 2002; Warren *et al.,* 2003). Together, these studies have shown that the dura mater has an instructive role toward calvarial patterning and morphogenesis late in development.

In comparison to the late stages, interactions between the meninges and the calvaria during early development have received much less attention. The current evidence for such interaction is mostly based on correlation of normal developmental events or mutant phenotypes between the two structures. Around stage 17 (6th week of gestation) in humans and ~E13 in mice, the dural limiting layer appears on the baso-lateral side of the brain, marking the differentiation of the meninges into pachymeninx and leptomeninx (O'Rahilly and Muller, 1986; Vivatbutsiri *et al.,* 2008). Subsequently, the meningeal differentiation progresses toward the apex. Interestingly, the frontal bone and the parietal bone of the calvaria also arise from the mesenchyme on the baso-lateral side of the brain (called supra-orbital mesenchyme for its location above the eyes) at ~E12.5 in mice, and undergo apical expansion over the following days (Fig. 3) (Deckelbaum *et al.,* 2012; Ferguson *et al.,* 2018; Ishii *et al.,* 2015; Twigg and Wilkie, 2015). Furthermore, the growth of the skull bone correlated closely with the extent of the dural limiting layer during the expansion (O'Rahilly and Muller, 1986). This observation raised an intriguing possibility that the nascent dura mater guides calvarial bone growth.

More support for the above idea came from *Foxc1* mutant mice. As described earlier, *Foxc1*$^{ch/ch}$ and *Foxc1*$^{lacZ/lacZ}$ mutants had severe meningeal defects, in which the arachnoid mater and the dura mater failed to form on the apical side of the brain. In addition, the calvarial bone was missing from the apical side at birth (Kume *et al.,* 1998; Rice *et al.,* 2003). In these mutants, the calvarial bone development was arrested at E13.5, shortly after initiation of osteogenesis in the supraorbital mesenchyme (Rice *et al.,* 2003; Vivatbutsiri *et al.,* 2008). The bone rudiments showed decreased cell proliferation and apical growth (Machida *et al.,* 2014; Rice *et al.,* 2003). Importantly, during normal development, *Foxc1* is not expressed in the bone rudiments at this age, but instead it is strongly expressed in the

underlying meninges (Rice *et al.,* 2003). Moreover, the onset of the calvarial defect in *Foxc1* mutants was preceded by the meningeal defect (E12.5 according to Hecht *et al.,* 2010). These data indicated that *Foxc1* regulated the early growth of the calvarial bone indirectly, through an interaction between the meninges and the calvaria. The molecular identity of this interaction is still unknown.

Similar to *Foxc1* mutants, neural crest-specific *Tgfbr2* knockout mutants had severe meningeal defects (discussed above), which were accompanied by calvarial defects (Ito *et al.,* 2003). Both the frontal bone and the parietal bone failed to develop in these mutants. Because the parietal bone is of mesoderm origin, this phenotype indicated that *Tgfbr2* regulated development of the parietal bone in a cell non-autonomous manner. During normal development, the parietal bone is in contact with the neural crest-derived meninges covering the cerebral hemispheres (Fig. 2). Therefore, the parietal bone defect in neural crest-specific *Tgfbr2* mutants was attributed to the loss of the underlying meninges, which implied that signals from the meninges were essential to development of the parietal bone (Ito *et al.,* 2003).

In the aforementioned experiment where RA treatment of mouse embryos led to meningeal defects, the embryos exhibited a partial to complete loss of the parietal bone and the interparietal bone at E17.5 (Jiang *et al.,* 2002). Because the degree of the calvarial defects correlated with the severity of the meningeal defects in different animals, the calvarial phenotype was interpreted as a consequence of the loss of the meninges (Jiang *et al.,* 2002). However, a recent study has suggested a more direct effect of RA on calvarial development (Ferguson *et al.,* 2018). They found that RA treatment up-regulated expression of anti-osteogenic genes *HoxA1* (homeobox A1), *HoxC8* (homeobox C8), and *Hand2* (heart and neural crest derivatives expressed 2) in the calvarial mesenchyme to inhibit osteogenic specification. Notably, the meninges produce RA from ~E12.5 (Siegenthaler *et al.,* 2009), which plays an important role in brain development (discussed below). Therefore, the adverse effect of RA on calvarial osteogenesis would suggest that a mechanism to curb RA signaling is crucial to normal development of the calvaria. Indeed, calvarial mesenchyme expresses an RA-degrading enzyme Cyp26b1 (cytochrome P450, family 26, subfamily b, polypeptide 1) at E14.5 (Visel *et al.,* 2004), and inactivation of this gene resulted in severe hypoplasia of the calvarial bone (Maclean *et al.,* 2009).

5. Influence of the meninges on brain development

The meninges play multiple crucial roles in development of the brain, and the list continues to grow (Fig. 3).

First, the meninges are thought to provide trophic factors necessary to the survival of the cells in the brain. When the neural crest was ablated in early chick embryos to preclude development of the forebrain meninges, the forebrain neuroepithelium experienced massive apoptosis and subsequent degeneration (Etchevers *et al.,* 1999). However, it is unknown which factor(s) from the meninges mediate this function.

Second, the meninges regulate the migration and positioning of neurons by secreting molecules that can attract or repel cells. The meninges express a chemoattractant CXCL12 (chemokine (C-X-C motif) ligand 12, also known as SDF-1), through direct transcriptional activation by FOXC1 (Borrell and Marin, 2006; Zarbalis *et al.,* 2012). Thus, neurons and neural progenitors expressing the receptors, CXCR4 and CXCR7, are guided to and retained in the marginal zone of the brain immediately underneath the meninges. Examples of the cells subject to this control include Cajal-Retzius cells and interneurons of the cerebral cortex, neural progenitors in the dentate gyrus of the forebrain, and neural progenitors in the cerebellum (Bagri *et al.,* 2002; Borrell and Marin, 2006; Klein *et al.,* 2001; Li *et al.,* 2009; Ma *et al.,* 1998; Paredes *et al.,* 2006; Stumm *et al.,* 2003; Zhu *et al.,* 2002). On the other hand, BMP4, BMP7, and TGFβ1 from the meninges repel oligodendocyte precursor cells from the ventral forebrain to direct them into the cerebral cortex (Choe, Huynh, *et al.,* 2014). RA signaling also regulates the migration of cortical neurons. Upon deletion of an RA-synthesizing enzyme expressed in the meninges, altered migration of the neurons led to abnormal layering in the cerebral cortex (Haushalter *et al.,* 2017).

Third, the pial basement membrane plays a structural role to control the migration and positioning of neurons (Decimo *et al.,* 2012; Siegenthaler and Pleasure, 2011). During normal development of the brain, a special population of cells called radial glia send out processes from the ventricular zone toward the surface of the brain (Chou *et al.,* 2018). These processes serve as a scaffold for radial migration of the neurons. The endfeet of the radial glial processes attach to the pial basement membrane to obtain physical stability, and the migrating neurons are stopped in the marginal zone by the pial basement membrane. In mouse mutants with defects in the pial basement membrane (discussed above), the radial endfeet became detached prematurely, and the distribution of the neurons became abnormal in the cerebral cortex and the cerebellum (Beggs *et al.,* 2003; Guenette *et al.,* 2006; Halfter *et al.,* 2002; Ichikawa-Tomikawa *et al.,* 2012; Inoue *et al.,* 2008; Labelle-Dumais *et al.,* 2011; Zarbalis *et al.,* 2007).

Fourth, the meninges regulate generation of neurons from neural progenitors (neurogenesis), which occurs through asymmetric cell divisions of the progenitors. This function has been elucidated mainly from the studies of *Foxc1* mutants lacking most of the meninges (Siegenthaler *et al.,* 2009). In the cerebral cortex of E14.5 $Foxc1^{lacZ/lacZ}$ mutants, symmetric divisions increased and asymmetric divisions decreased compared with control animals. As a consequence, the cerebral cortex became elongated but contained fewer differentiated neurons than normal. Importantly, the cortical phenotype was partially rescued by in utero RA treatment at E10.5-E13.5, while the meningeal defects were unchanged. This result led to a model that the meninges-derived RA is important for cortical neurogenesis (Siegenthaler *et al.,* 2009). The rescue of *Foxc1* cortical defects clearly indicates that RA is *sufficient* to promote neurogenesis in the absence of the meninges. Whether the meningeal RA is *necessary* for cortical neurogenesis during normal development, in the presence of the meninges, has been debated (Chatzi *et al.,* 2013; Haushalter *et al.,* 2017). In addition to the cerebral cortex, the meninges regulate the neurogenesis in the embryonic dentate gyrus. Here, BMP7 from the meninges has been identified as a key factor (Choe *et al.,* 2013). For the cerebellum, CXCL12 from the meninges suppresses neuronal differentiation while promoting proliferation (Haldipur *et al.,* 2014).

Fifth, the meninges regulate development of the blood vessels of the brain. In *Foxc1*$^{ch/ch}$ and *Foxc1*$^{lacZ/lacZ}$ mutants, blood vessels in the cerebral cortex were increased in diameter but decreased in density at E14.5 (Mishra *et al.,* 2016). Once again, this phenotype was attributed to the meninges deficiency and the consequent loss of RA. Consistently, inactivation of an RA synthesis enzyme caused similar cerebrovascular defects as *Foxc1* mutation (Bonney *et al.,* 2016). In this context, RA signaling had dual effects on the activity of WNT/β-catenin pathway in the endothelial cells, to allow normal growth of the vasculature while preventing inappropriate growth (Bonney *et al.,* 2016). A recent study investigated development of the cerebral veins specifically. They found that TWIST1-controlled production of BMP2 and BMP4 from the endosteal dura mater and the calvarial bone were important for the growth and remodeling of the cerebral veins (Tischfield *et al.,* 2017).

Sixth, the meninges affect formation of the corpus callosum, a thick bundle of axons in the dorsal midline of the brain connecting the two cerebral hemispheres. BMP7 produced by the meninges inhibited outgrowth of the callosal axons, and WNT3 from the neurons antagonized the effect of BMP7 to allow development of the corpus callosum (Choe *et al.,* 2012).

Finally, the meninges form a niche for neural stem cells (reviewed in Decimo *et al.,* 2012). A group of cells expressing Nestin, a marker of stem/progenitor cells, were found in the leptomeninges of rats from a late fetal stage to adulthood (Bifari *et al.,* 2009; Bifari *et al.,* 2015). A lineage-tracing experiment confirmed that they were indeed stem cells for cortical neurons (Bifari *et al.,* 2017). The role of the meninges as a stem cell niche is thought to be related to the presence of fractones, which are specialized ECM structures enriched with growth factors (Bifari *et al.,* 2015).

As expected from the profound influence of the meninges on brain development, defects in the meninges have been linked to neurodevelopmental disorders in humans. Cobblestone lissencephaly is a condition where the surface of the cerebral cortex lacks the normal ridges and grooves but has small bumps (Devisme *et al.,* 2012; Verrotti *et al.,* 2010). This phenotype occurs when the integrity of the pial basement membrane is compromised, allowing over-migration of the neurons into the meningeal layers. Mutations underlying cobblestone lissencephaly have mostly been identified in the genes associated with ECM (Table 2) (Devisme *et al.,* 2012; Verrotti *et al.,* 2010). Dandy-Walker malformation is characterized by hypoplasia of the cerebellum and hydrocephaly (accumulation of CSF inside the brain) (Imataka *et al.,* 2007), and *FOXC1* is one of the genes associated with this condition in humans (Table 3) (Aldinger *et al.,* 2009). Because studies in mice have shown that *Foxc1* is expressed in the meninges but not in the brain (Aldinger *et al.,* 2009; Kume *et al.,* 1998), Dandy-Walker malformation is thought to result from meningeal defects. Although the meningeal phenotype is unknown for most of the human patients, imaging studies on those with *FOXC1* mutations have found evidence of meningeal deficiency (Aldinger *et al.,* 2009).

6. Conclusion

In this review, we have discussed the current understanding of the process of meningeal development, and the role of the meninges in regulating development of the neighboring structures. The pervasive defects in mouse *Foxc1* mutants have clearly illustrated the critical role of the meninges in development of the head as a whole. The presence of the meninges is essential to normal development of the calvaria and the brain. At the same time, there are examples where the meninges have adverse effects (inhibition of calvarial osteogenesis by RA, and inhibition of corpus callosum development by BMP7), which need to be antagonized. Thus, the interactions with the meninges should be closely considered when the molecular regulation of calvarial development or brain development is studied.

This review has also highlighted numerous questions that are yet to be answered regarding meningeal development. How do the head mesenchyme cells of the primary meninx become specified into the meningeal, calvarial, or dermal fate? Among the cells to become the meninges, how are they divided into the components of the dura mater, the arachnoid mater, or the pia mater? Do the meninges regulate similar aspects of calvarial development as they do for the brain, including cell migration, vascularization, and differentiation from progenitor cells? What factor(s) mediate the influence of the meninges on calvarial development? Are the interactions between the meninges and the surrounding tissues reciprocal - in other words, does the calvaria or the brain influence development of the meninges? To address the issue of specification and differentiation of meningeal cells, it would be important to identify distinct populations of cells from the primary meninx and follow their segregation in terms of the molecular characteristics over the course of development. This can be achieved by single cell RNA sequencing and clustering (Griffiths *et al.,* 2018). Elucidating the signaling interactions between the meninges and the calvaria would be facilitated by tools to dissect tissue-specific roles of a gene, such as mouse lines expressing Cre recombinase in one tissue but not the other. To our knowledge, there is no published Cre line fitting this description. Applying these and other modern investigative techniques will greatly improve our knowledge of meningeal development, which could also advance our understanding of calvarial development and brain development.

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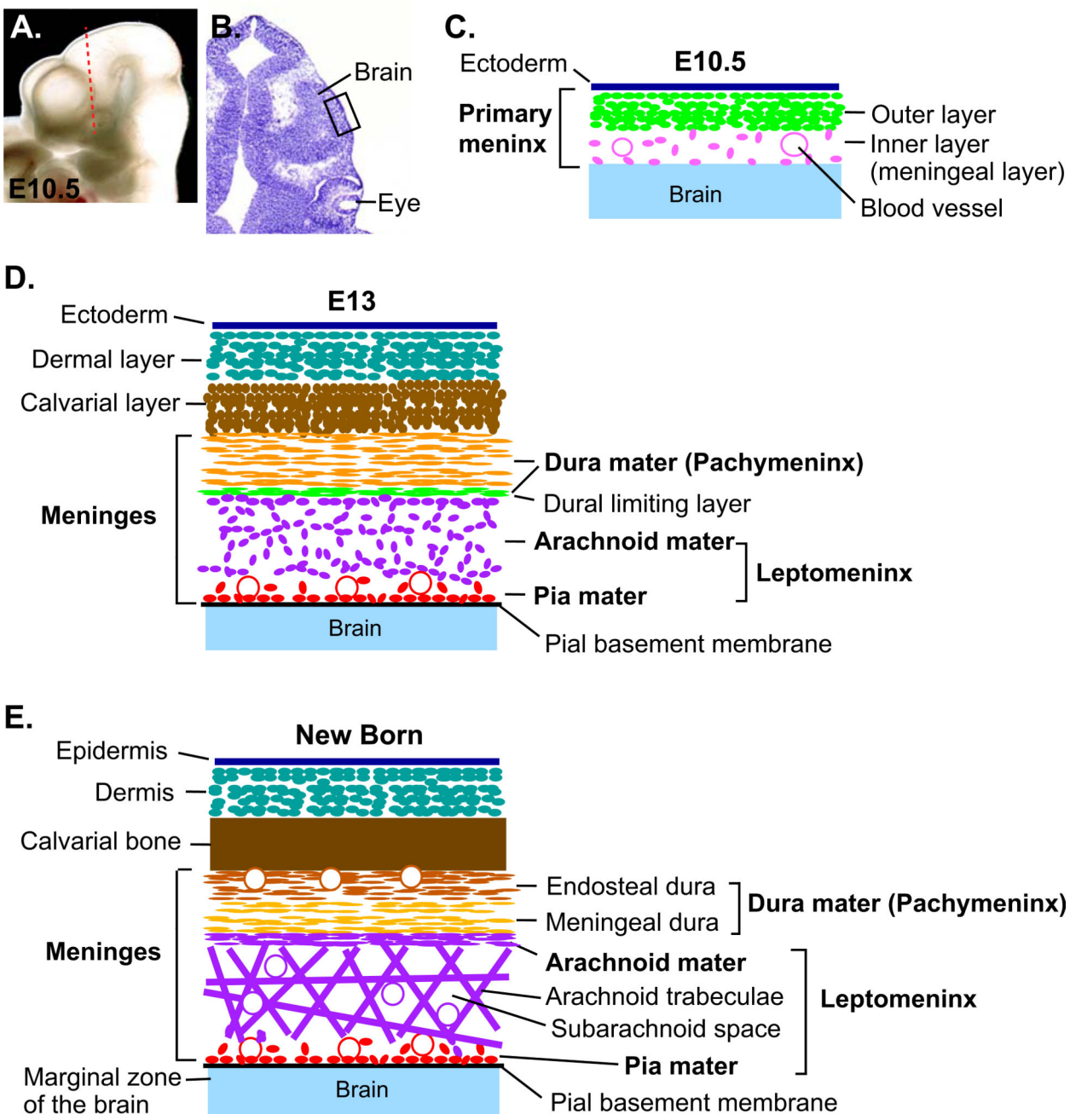

Figure 1. Development of the meninges

(A) Lateral view of the head of E10.5 mouse embryo. **(B)** A coronal section through the head of E10.5 mouse embryo at a position shown in A (dotted line). The section was stained with cresyl violet to show the morphology. **(C)** A schematic of the tissue layers from the boxed area in B. After the primary meninx is established around the brain at ~E9.5, the mesenchyme becomes divided into an outer dense layer and an inner reticular layer (meningeal layer) at ~E10.5. **(D)** Around E13, the meninges begin to differentiate into the pachymeninx (dura mater) and the leptomeninx (arachnoid mater and pia mater) separated by dural limiting layer. **(E)** Later, the dura mater appears as two tightly attached layers, the

endosteal dura and the meningeal dura. The endosteal dura serves as periosteum of the inner surface of the calvarial bone. The cavitation of the leptomeninges generates arachnoid trabeculae made of collagen fibers and the fibroblasts, and the subarachnoid space inside the trabeculae.

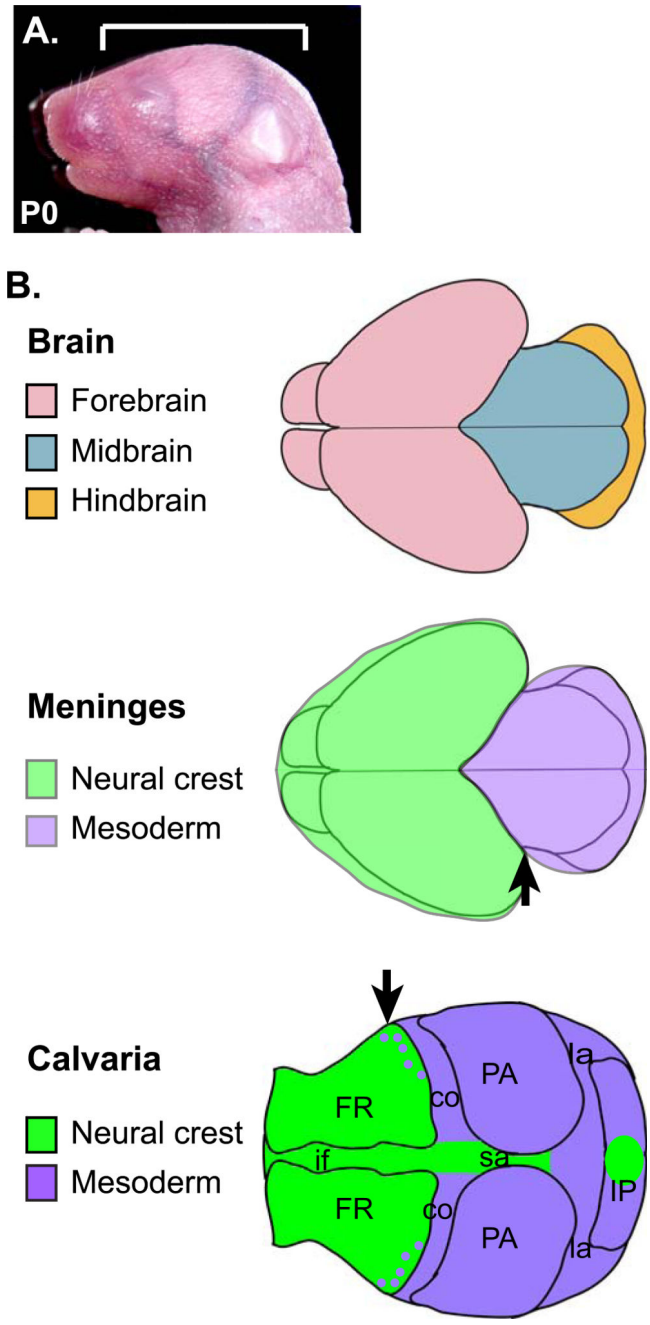

Figure 2. Contribution of the cells from the neural crest and the mesoderm to the meninges and the calvaria

A) Lateral view of the head of a newborn mouse. The bracket indicates the area depicted in B. **B)** Dorsal views of the head showing the three components of the head. Note the difference in the rostro-caudal positions of the neural crest-mesoderm boundary in the meninges and in the calvaria (arrows). co: coronal suture, FR: frontal bone, if: interfrontal suture, IP: interparietal bone, la: lambdoidal suture, PA: parietal bone, sa: sagittal suture.

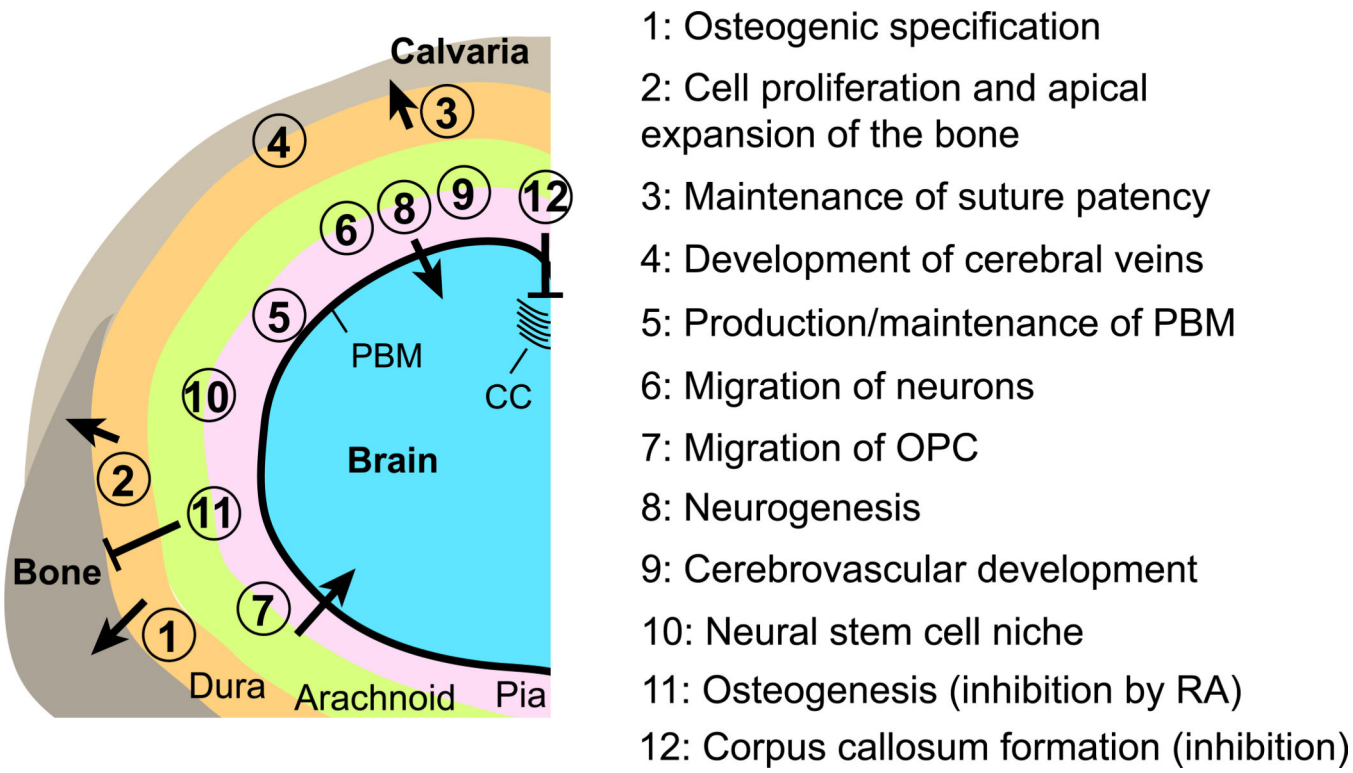

Figure 3. Influences of the meninges to development of the calvaria and the brain

A schematic representation of a coronal section of the head of mouse embryos at late gestation stages (>E12.5). The left-dorsal quadrant of the head is shown. The positions of the circled numbers indicate the meningeal component thought to be responsible for each interaction. For the numbers straddling the arachnoid mater and the pia mater, there is not enough evidence to assign the function to only one layer or the other, and both layers are likely involved. CC: corpus callosum, OPC: oligodendrocyte precursor cells, PBM: pial basement membrane, RA: retinoic acid.

Table 1.

Genes expressed in the developing meninges in mice at early stages (E10 - E13.5)

Gene Symbol	Gene Name	References
Aldh1a2	aldehyde dehydrogenase family 1, subfamily A2	Siegenthaler *et al*., 2009
Alx4	aristaless-like homeobox 4	Rice *et al.,* 2003; Vivatbutsiri *et al.,* 2008
Ambp	alpha 1 microglobulin/bikunin precursor	Sanchez, Martinez, *et al*., 2002
Ano1	anoctamin 1, calcium activated chloride channel	Gritli-Linde *et al*., 2009
Ano6	anoctamin 6, calcium activated chloride channel	Gritli-Linde *et al*., 2009
Apod	apolipoprotein D	Sanchez, Ganfornina, *et al.,* 2002
Bmp4	bone morphogenetic protein 4	Thompson *et al.,* 2014
Bmp7	bone morphogenetic protein 7	Vivatbutsiri *et al.,* 2008
Cxcl12	chemokine (C-X-C motif) ligand 12	D. Daniel *et al.,* 2005; Borrell and Marin, 2006
Cxcr2	chemokine (C-X-C motif) receptor 2	Luan *et al*., 2001
Fli 1	friend leukemia integration 1	Hart *et al*., 2000
Foxc1	forkhead box C1	Kume *et al.,* 1998; Rice *et al.,* 2003; Mishra *et al.,* 2016
Foxc2	forkhead box C2	Rice *et al.,* 2003
Foxd2	forkhead box D2	Wu *et al.,* 1998
Fras1	fraser extracellular matrix complex subunit 1	Makrygiannis *et al.,* 2013
Gja1	gap junction protein, alpha 1	Vivatbutsiri *et al.,* 2008
Grn	granulin	R. Daniel *et al*., 2003
Hlf	hepatic leukemia factor	Hitzler *et al.,* 1999
Id1	inhibitor of DNA binding 1	Evans and O'Brien, 1993
Lamc1	laminin gamma 1	Makrygiannis *et al.,* 2013
Lamc3	laminin gamma 3	Barak *et al.,* 2011
Msx1	msh homeobox 1	MacKenzie *et al.,* 1992; Rice *et al.,* 2003; Thompson *et al.,* 2014
Msx2	msh homeobox 2	MacKenzie *et al.,* 1992
Nedd4	neural precursor cell expressed, developmentally down-regulated 4	Liu *et al.,* 2009
Rbp1	retinol binding protein 1, cellular	Ruberte *et al.,* 1993
Rdh10	retinol dehydrogenase 10	Romand *et al*., 2008
Sorcs2	sortilin-related VPS10 domain containing receptor 2	Boggild *et al.,* 2018
Sparc	secreted acidic cysteine rich glycoprotein	Vincent *et al.,* 2008
Tgfb1	transforming growth factor, beta 1	Heine *et al.,* 1987; Thompson *et al.,* 2014
Tgfbr2	transforming growth factor, beta receptor 2	Wang *et al.,* 1995
Vtn	vitronectin	Seiffert *et al.,* 1995
Wls	wntless WNT ligand secretion mediator	Yeung *et al.,* 2014
Zic1	zinc finger protein of the cerebellum 1	Thompson *et al.,* 2014
Zic2	zinc finger protein of the cerebellum 2	Thompson *et al.,* 2014
Zic3	zinc finger protein of the cerebellum 2	Thompson *et al.,* 2014

Table 2.

Genes associated with cobblestone lissencephaly in humans

Gene Symbol	Gene Name	References
LAMB1	Laminin, beta 1	Radmanesh *et al.*, 2013
TMTC3	Transmembrane and tetratricopeptide repeat domains- containing protein 3	Jerber *et al.*, 2016
ISPD	Isoprenoid synthase domain-containing protein	Vuillaumier-Barrot *et al.*, 2012
POMGNT2	Protein o-mannose beta-1,4-n- acetylglucosaminyltransferase 2	Manzini *et al.*, 2012
POMT1	Protein o-mannosyltransferase 1	Beltran-Valero de Bernabe *et al.*, 2002
RXYLT1	Ribitol xylosyltransferase 1	Vuillaumier-Barrot *et al.*, 2012
B3GALNT2	Beta-1,3-n-acetylgalactosaminyltransferase 2	Stevens *et al.*, 2013
B4GAT1	Beta-1,4-glucuronyltransferase 1	Buysse *et al.*, 2013

Table 3.

Genes associated with Dandy-Walker malformation in humans

Gene Symbol	Gene Name	References
ALG3	Alg3, S.cerevisiae, homolog of	Sun *et al.,* 2005
AP1S2	Adaptor-related protein complex 1, sigma 2 subunit	Cacciagli *et al.,* 2014
EBP	Emopamil-binding protein	Derry *et al.,* 1999
FOXC1	Forkhead box c1	Aldinger *et al.*, 2009
LAMC1	Laminin, gamma 1	Darbro *et al.,* 2013
LARGE1	Acetylglucosaminyltransferase-like protein	van Reeuwijk *et al.,* 2007
NID1	Nidogen 1	Darbro *et al.,* 2013
NPHP3	Nephrocystin 3	Bergmann *et al.*, 2008
PIEZO2	Piezo-type mechanosensitive ion channel component 2	McMillin *et al.,* 2014
POMT1	Protein o-mannosyltransferase 1	Beltran-Valero de Bernabe *et al.,* 2002
SLC45A1	Solute carrier family 45, member 1	Anazi *et al.,* 2017
TMEM138	Transmembrane protein 138	Lee *et al.,* 2012
TMEM67	Transmembrane protein 67	U. M. Smith *et al.,* 2006
ZIC1	Zic family, member 1	Grinberg *et al.,* 2004
ZIC4	Zic family, member 4	Grinberg *et al.,* 2004