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Versatile Roles of the Chromatin Remodeler CHD7 during Brain Development and Disease

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CHD7 (Chromo-Helicase-DNA binding protein 7) protein is an ATP-dependent chromatin remodeler. Heterozygous mutation of the *CHD7* gene causes a severe congenital disease known as CHARGE syndrome. Most CHARGE syndrome patients have brain structural anomalies, implicating an important role of CHD7 during brain development. In this review, we summarize studies dissecting developmental functions of CHD7 in the brain and discuss pathogenic mechanisms behind neurodevelopmental defects caused by mutation of *CHD7*. As we discussed, CHD7 protein exhibits a remarkably specific and dynamic expression pattern in the brain. Studies in human and animal models have revealed that CHD7 is involved in multiple developmental lineages and processes in the brain. Mechanistically, CHD7 is essential for neural differentiation due to its transcriptional regulation in progenitor cells.

Keywords: CHD7, chromatin remodeler, CHARGE syndrome, brain development, mouse models

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HETEROZYGOUS MUTATION OF *CHD7* LEADS TO BRAIN DEVELOPMENTAL ANOMALIES

The human *CHD7* (Chromo-Helicase-DNA binding protein 7) is a long gene spanning approximately 189 kb at chromosome 8, containing 38 exons encoded for a large protein (2997 aa, about 336 kD). CHD7 protein is a member of CHD family of ATP-dependent chromatin remodelers. These enzymes utilize the energy from ATP hydrolysis to mobilize or relocate nucleosomes, thereby control DNA accessibility of chromatin. Chromatin remodeling is crucial for DNA-related biological processes such as transcription, chromosome segregation, DNA replication, and DNA repair (Clapier and Cairns, 2009). Not surprisingly, most chromatin remodelers are indispensable for normal development (Ho and Crabtree, 2010).

CHARGE syndrome (OMIM #214800), initially described in 1979 (Hall, 1979; Hittner et al., 1979) and named in 1981 (Pagon et al., 1981), is a congenital disease with severe developmental defects in multiple organ systems. Two decades later, *de novo* mutations in the *CHD7* gene were identified in CHARGE syndrome patients (Vissers et al., 2004), which turn out to be the major cause of this disease. Over 90% of patients with clinically typical CHARGE syndrome have heterozygous mutations in the *CHD7* gene (Bergman et al., 2011). Moreover, mutations of *CHD7* have also been identified in about 6% of Kallmann syndrome (OMIM #308700), a developmental disease characterized with IHH (idiopathic hypogonadotropic hypogonadism) and anosmia (Kim et al., 2008; Balasubramanian et al., 2014; Marcos et al., 2014). Up to now, 554 pathogenic *CHD7* mutations have been identified in CHARGE syndrome patients.[1] About 90% of these mutations

[1]www.chd7.org

are nonsense, frame shift, and splice site mutations, which result in truncated CHD7 protein (Basson and van Ravenswaaij-Arts, 2015). In contrast, more than 70% of *CHD7* mutations in Kallmann syndrome are missense mutations (Balasubramanian et al., 2014; Marcos et al., 2014), which correlate with mild phenotypes in these patients as compared to CHARGE syndrome.

Several earlier review articles have comprehensive summarized the developmental roles of CHD7 in multiple organs affected in CHARGE syndrome patients (Layman et al., 2010; Zentner et al., 2010; Bergman et al., 2011). This review focuses on the function of CHD7 during brain development. Multiple structural defects in the brain of CHARGE syndrome patients have been reported, such as hypoplasia of olfactory bulb and cerebellum, agenesis of the corpus callosum, microcephaly and atrophy of the cerebral cortex (Lin et al., 1990; Tellier et al., 1998; Becker et al., 2001; Johansson et al., 2006; Sanlaville et al., 2006; Legendre et al., 2012; Yu et al., 2013; Hale et al., 2016). Among them, deficiency of olfactory bulb and sulci is the most frequent brain defect in CHARGE syndrome patients, as shown by Magnetic Resonance Imaging (MRI) (Chalouhi et al., 2005; Pinto et al., 2005; Blustajn et al., 2008). Because only small cohorts of patients were being examined in these studies and the phenotype of CHARGE syndrome is very heterogeneous, the overall percentage of patients having brain developmental anomalies is still not known. Nevertheless, brain structural defect has recently been proposed as minor criteria for the diagnosis of CHARGE syndrome (Hale et al., 2016). Consistent with defects in the brain, most CHARGE syndrome patients have certain degree of intellectual deficiency (Bergman et al., 2011). In Kallmann syndrome patients with *CHD7* mutations, the common brain phenotype is hypoplasia of olfactory bulb and reduced number of GnRH (gonadotropin-releasing hormone) neurons in the hypothalamus (Marcos et al., 2014). Together, these observations clearly demonstrate that CHD7 is haploinsufficient for brain development.

THE EXPRESSION OF *CHD7* IN THE BRAIN IS VERY SPECIFIC AND DYNAMIC

Consistent with specific brain defects caused by *CHD7* mutations, the *CHD7* gene exhibits a spatial- and temporal-specific expression pattern during brain development. Expression of *CHD7* in the human brain has been observed throughout development (Sanlaville et al., 2006). More detailed analysis of the expression of *Chd7* has been done in mouse brain. Using *in situ* hybridization analysis, one study demonstrates that *Chd7* is expressed as early as E8.5 (Embryonic day 8.5) in mouse brain regions including forebrain and midbrain neural fold, neural tube, and neuroepithelial prominence (Jiang et al., 2012). At E12.5 and E14.5, *Chd7* is highly expressed in frontal cortex, medial ganglionic eminence, ventricular zone of medulla, and external granule zone of cerebellum (Bosman et al., 2005). A similar expression pattern of *Chd7* was observed in $Chd7^{Gt/+}$ (Gt: Gene-trap) embryo, where the expression of β-galactosidase reporter closely mimics endogenous *Chd7* (Hurd et al., 2007). One common observation from these studies is that the expression level of *Chd7* is higher in the proliferating ventricular zone compared to the differentiated areas of the neuroepithelium (**Figure 1A**). In adult mouse brain, *Chd7* shows a very specific and dynamic expression pattern in the adult neurogenic region subgranular zone (SGZ) in hippocampal dentate gyrus (DG) (**Figure 1B**). With immunostaining analysis, CHD7 is found to be expressed upon the activation of adult neural stem cells (NSCs), and is upregulated in transit progenitor cells and neuroblasts. In contrast, the expression of *Chd7* is completely switched off in granule neurons in DG (Feng et al., 2013; Jones et al., 2015). This dynamic expression pattern of *Chd7* in DG was confirmed in a recent single-cell RNA sequencing study whereas transcriptomes of EdU pulse-labeled individual neuronal cells were analyzed (Habib et al., 2016). Consistent with *in vivo* data showing the upregulation of *Chd7* upon activation of adult NSCs, *Chd7* is downregulated in cultured NSCs upon BMP4-induced quiescence (Martynoga et al., 2013).

In cerebellum, immunostaining results show that CHD7 is highly expressed in cerebellar granule cells throughout development and persists in adult cerebellum, in contrast to almost no expression in Purkinje neurons and Bergmann glia cells (Feng et al., 2017). In contrast to granule neurons in DG, the expression level of Chd7 is even higher in differentiated cerebellar granule neurons compared to granule neuron progenitors (GNPs) (Feng et al., 2017) (**Figure 1C**). Besides neuronal cells in the brain, while Chd7 is barely expressed in astrocytes, Chd7 is broadly expressed in oligodendrocyte (OL) lineage (He et al., 2016). Similar to cerebellar granule cells, the expression level of *Chd7* in differentiated oligodendrocytes is higher than oligodendrocyte precursor cells (OPCs) (**Figure 1C**). With such a specific and dynamic expression pattern in the brain, the expression of *Chd7* is expected to be tightly regulated. Mechanism behind is currently not known, however.

LOSS-OF-FUNCTION STUDY IN MOUSE MODEL REVEALS AN IMPORTANT ROLE OF *CHD7* DURING BRAIN DEVELOPMENT

While xenopus (Bajpai et al., 2010), drosophila (Melicharek et al., 2010), and zebrafish models (Patten et al., 2012) have been established, mouse model is currently the predominant animal model for functional study of CHD7 and CHARGE syndrome. As shown in CHARGE syndrome patients, data from mouse studies confirm that CHD7 is haploidinsufficient for brain development (**Table 1**). Mice carrying germline loss-of-function mutation of *Chd7* have been generated with both ethylnitrosourea (ENU)-induced mutations and the gene-trap approaches. While homozygous loss-of-function mutation of *Chd7* is embryonic lethal at E10.5, heterozygous mutant mice are viable but show phenotypes closely mimicking CHARGE syndrome (Bosman et al., 2005; Hurd et al., 2007). Analysis of E10.5 *Chd7* homozygous gene-trap mutant embryo shows a reduction of the thickness of neuroepithelium in telencephalon and midbrain (Hurd et al., 2007), indicating that *Chd7* is required

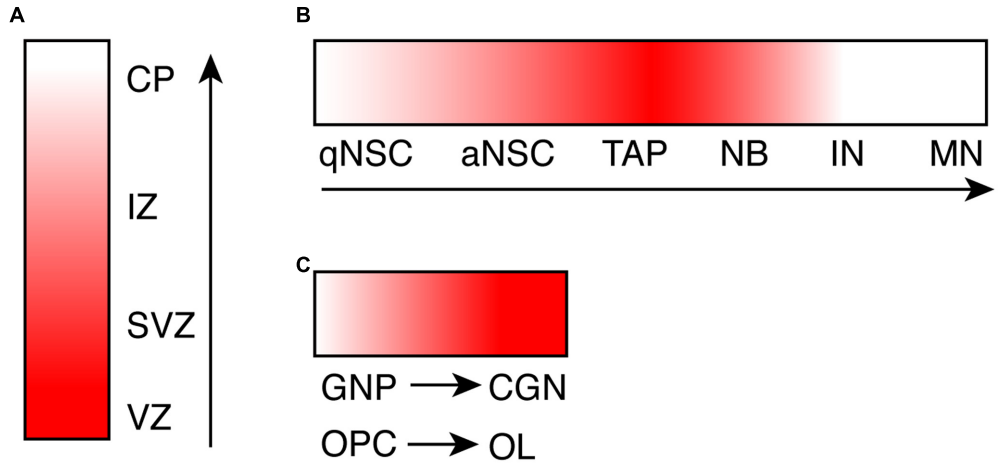

FIGURE 1 | The dynamic expression pattern of CHD7 during neurogenesis and oligodendrogenesis. **(A)** A cartoon shows the expression level of *Chd7* transcript during embryonic neurogenesis, based on *in situ* hybridization data. **(B)** A cartoon shows the expression level of CHD7 protein in adult neurogenic lineage in hippocampal dentate gyrus, based on immunostaining results. **(C)** A cartoon shows the increase of CHD7 expression upon differentiation of GNP and OPC, based on immunostaining results. The degree of redness reflects the expression level of *Chd7*. Arrows show the direction of differentiation. VZ, ventricular zone; SVZ, subventricular zone; IZ, intermediate zone; CP, cortical plate; qNSC, quiescent neural stem cell; aNSC, active NSC; TAP, transit amplifying progenitor; NB, neuroblast; IN, immature neuron; MN, mature neuron; GNP, granule neuron progenitor; CGN, cerebellar granule neuron; OPC, oligodendrocyte precursor cell; OL, oligodendrocyte.

TABLE 1 | Brain phenotype in *Chd7* loss-of-function mutant mouse models.

Mouse lines	Mouse brain phenotype	Relevant CHARGE phenotype	Reference
$Chd7^{Gt(S20-7E1)/Gt(S20-7E1)}$ (Gene-trap reporter inserted in exon 1)	E10.5 lethal, hypoplasia of the neuroepithelium	Cognitive disability	Hurd et al., 2007
$Chd7^{Gt(S20-7E1)/+}$	Small olfactory bulb (OB)	Hyposmia	Layman et al., 2009
$Chd7^{Whi/+}$ (p.W973X) $Chd7^{Gt(S20-7E1)/+}$	OB hypoplasia; decreased GnRH neurons in the hypothalamus	Anosmia; Genital hypoplasia; Puberty delay	Bergman et al., 2010; Layman et al., 2011
$Chd7^{COA1/+}$ (p.K719X)	Hypoplasia of OB; Telencephalic midline defects; Reduced cerebral cortex	Hyposmia; Cognitive disability	Jiang et al., 2012
Nestin-CreERT2::Chd7 $^{f/f}$ *Ubc-CreERT2::Chd7* $^{f/f}$ *Glast-CreERT2::Chd7* $^{f/f}$	Defects of adult neurogenesis	Cognitive disability; Hyposmia	Feng et al., 2013; Micucci et al., 2014; Jones et al., 2015
$Chd7^{Gt(XK403)/+}$ (Gene-trap reporter inserted in intron 36) *Atoh1-Cre::Chd7*$^{f/f}$ *Nestin-Cre::Chd7*$^{f/f}$	Vermis hypoplasia; Purkinje cell heterotopia	Vermis hypoplasia; Purkinje cell heterotopia	Yu et al., 2013; Feng et al., 2017; Whittaker et al., 2017
Olig1-Cre::Chd7 $^{f/f}$ *Pdgfr-CreERT2::Chd7* $^{f/f}$	Defect of myelination	White matter defects	He et al., 2016

for early brain development. Heterozygous *Chd7* loss-of-function mutant mice show defects in different brain regions. The most frequent defect is the absence or hypoplasia of olfactory bulb (Layman et al., 2009; Bergman et al., 2010; Jiang et al., 2012). Other brain anomalies identified in these mice include reduced number of GnRH neurons in the hypothalamus (Layman et al., 2011), defects in the development of telencephalic midline and reduction of the thickness of cerebral cortex (Jiang et al., 2012).

Ablation of *Chd7* in germline is embryonic lethal at E10.5, which prevents the study of its function in brain development during later stage. In order to further dissect the function of *Chd7* in brain development, several labs have applied *Chd7* conditional knockout (CKO) mouse lines ($Chd7^{flox/flox}$) (**Table 1**). Two $Chd7^{flox/flox}$ mouse lines have been used, with either exon 2 or 3 being floxed (Hurd et al., 2010; Feng et al., 2013). Upon cre-mediated recombination, the CHD7 protein is ablated in CKO mouse. Compared to mice carrying germline loss-of-function mutation of *Chd7*, key advantage of *Chd7* CKO mouse line is that it allows researchers to dissect the function of *Chd7* in specific cell lineage during brain development in a spatial- and temporal-specific manner. As discussed below, crucial functions of *Chd7* in adult neurogenesis, cerebellar development, and CNS myelination have been revealed by the CKO approach.

Adult neurogenesis occurs in restricted mouse brain regions including SGZ of DG in hippocampus and subventricular

zone (SVZ) of lateral ventricle (Gage, 2000). Given neurogenic mechanism in adult is similar to embryonic stage, adult neurogenesis provides an ideal system to study neurodevelopment. Moreover, while germline homozygous loss-of-function mutations of many neurodevelopmental genes are embryonic lethal, adult neurogenesis, in the other hand, allows the study of homozygous gene-silencing mutations because majority of them do not affect animal survival. Three independent studies demonstrated that loss of *Chd7* in adult NSCs leads to a decline of adult neurogenesis (Feng et al., 2013; Micucci et al., 2014; Jones et al., 2015). In *Chd7* CKO brain, the number of newborn neurons reduces, and mutant neurons show clear defects in dendritic development. Strikingly, voluntary running, a positive stimulus of adult neurogenesis in hippocampus, could rescue hippocampal neurogenic defects, including both the amount and the dendritic development of newborn neurons in *Chd7* CKO mice (Feng et al., 2013). Mutation of *Chd7* in adult NSCs was also shown to result in a loss of quiescent stem cells in DG, thereby an exhaustion of NSC pool (Jones et al., 2015). Dissecting mechanism behind the adult neurogenic defect in *Chd7* CKO mice reveals the function of CHD7 in neurodevelopment, which may help us to understand the cognitive deficiency that is frequently observed in CHARGE syndrome patients.

Structural defects in cerebellum occur frequently in CHARGE syndrome patients (Becker et al., 2001; Sanlaville et al., 2006; Legendre et al., 2012; Yu et al., 2013). Recent mouse studies have provided valuable insights into mechanism behind the pathogenesis of cerebellar anomalies caused by loss-of-function of *Chd7*. Heterozygous gene-trap mutation of *Chd7* leads to reduced expression of key signaling molecule Fgf8 (Fibroblast growth factor 8) in isthmus organizer (IsO), an organizer region that directs cerebellar development during early embryonic stage (between E8 and E9). Importantly, heterozygous loss-of-function mutations of both *Chd7* and *Fgf8* show a synergistic effect in cerebellar development, resulting in severe vermis aplasia (Yu et al., 2013). While this study provides evidence showing the important role of *Chd7* during early embryonic development of cerebellum, recent studies have revealed that *Chd7* is also required for cerebellar development at later stages. Using the *Atoh1-Cre::Chd7* $^{flox/flox}$ mouse line to knockout *Chd7* specifically in GNPs, two independent studies clearly reveal that *Chd7* mutant animals exhibit cerebellar hypoplasia and massive Purkinje cell heterotopia (Feng et al., 2017; Whittaker et al., 2017). Importantly, highly similar phenotypes were observed in CHARGE syndrome pre-fetuses and patients (Legendre et al., 2012; Yu et al., 2013). Ablation of *Chd7* in Purkinje cell progenitors in the *Ptf1a-Cre::Chd7*$^{flox/flox}$ mice does not result in any obvious cerebellar developmental defect (Feng et al., 2017), excluding an essential role of *Chd7* in Purkinje cell lineage. Together, these findings strongly implicate that dysfunction of CHD7 in cerebellar granule cell lineage leads to cerebellar defects in CHARGE patients.

Consistent with the specific expression of *Chd7* in OL lineage, CHD7 has been shown to play a crucial role in myelination during brain development and remyelination after drug-induced demyelination in adult mice (He et al., 2016). Further mechanistic study show that *Chd7* is required for differentiation and maturation of OLs. The function of CHD7 in oligodendrogenesis may help to explain the structural defects in white matter and corpus callosum of CHARGE syndrome patients.

LOSS OF *CHD7* IN THE MOUSE BRAIN CAUSES COMMON CELLULAR PHENOTYPE

As discussed above, CHD7 is involved in both neurogenesis and oligodendrogenesis, highlighting its versatile roles during brain development. On the other hand, loss of *Chd7* in different cell lineages in mouse brain causes similar cellular phenotype. **First**, loss of *Chd7* leads to defect in terminal differentiation of mouse neural progenitor cells. Ablation of *Chd7* in mouse adult NSCs or cerebellar GNPs impairs terminal differentiation of granule neurons in DG and cerebellum, respectively (Feng et al., 2013, 2017). Similarly, ablation of *Chd7* in mouse OPCs leads to defects in the differentiation of OLs (He et al., 2016). **Second**, Chd7 seems to be dispensable for both the generation and the proliferation of neural progenitor cells. Actually, ablation of *Chd7* in adult NSCs in both *Nestin-CreERT2::Chd7*$^{flox/flox}$ and *Glast-CreERT2::Chd7*$^{flox/flox}$ mice leads to a mild increase of cell proliferation in the SGZ (Feng et al., 2013; Jones et al., 2015). The specification and proliferation of cerebellar GNPs are not affected in *Atoh1-Cre::Chd7*$^{flox/flox}$ mice (Feng et al., 2017). Knockout of *Chd7* in OL lineage in *Olig1-Cre::Chd7*$^{flox/flox}$ mice, does not affect the generation and proliferation of OPCs (He et al., 2016). **Third**, loss of *Chd7* in neural progenitor cells leads to increased cell death. Increased cell death was observed upon loss of *Chd7* in both adult neurogenic regions and cerebellum in mouse (Feng et al., 2013, 2017; Whittaker et al., 2017). Cultured *Chd7* mutant mouse GNPs are more prone to cell death upon differentiation (Feng et al., 2017). Interestingly, loss of *Chd7* was shown to activate p53-dependent induction of apoptosis during embryonic development, and inhibition of p53-dependent apoptosis could partially rescue developmental defects in *Chd7* knockout embryo (Van Nostrand et al., 2014). Whether p53-dependent activation of cell death occurs during adult neurogenesis and cerebellar development need to be tested. In summary, CHD7 seems to have a similar cellular function in different cell lineages during brain development. CHD7 is essential for both neurogenesis and oligodendrogenesis via controlling the differentiation of neural progenitor cells. Loss of *Chd7* in progenitor cells has mild effect on cell proliferation, but leads to the increase of cell death.

KEY TARGET GENES OF CHD7 DURING BRAIN DEVELOPMENT

Consistent with the known function of chromatin remodelers in transcriptional regulation, a common molecular function of CHD7 in neural cells is controlling gene expression. Multiple target genes of CHD7 during brain development have been

TABLE 2 | Key target genes of CHD7 in mouse neural cells.

Target genes	Neural cells	Direct binding of CHD7	Rescue	Reference
Jag1, Gli2, Gli3, *MycN, Hes5*	Neural stem cells (NSCs)	Promoter and enhancer, ChIP-seq	n.d.	Engelen et al., 2011
Sox4, *Sox11*	Adult NSCs	Promoter, ChIP-qPCR	Yes	Feng et al., 2013
Rarb, Rxrg, Neurod1	Subventricular zone (SVZ) NSCs	Promoter, ChIP-qPCR	Yes	Micucci et al., 2014
Hes5	Subgranular zone (SGZ) NSCs; NSCs	Promoter, ChIP-seq	Yes	Engelen et al., 2011; Jones et al., 2015
Osterix, Creb3l2	Oligodendrocytes	Promoter and enhancer, ChIP-seq	Yes	He et al., 2016
Otx2, *Gbx2*	Cells in rhombomere 1	Enhancers, ChIP-qPCR	n.d.	Yu et al., 2013
Reelin	Cerebellar GNPs	Enhancers, ChIP-seq	Yes	Feng et al., 2017; Whittaker et al., 2017

identified (**Table 2**). Using shRNA-mediated gene knock down approach in cultured mouse NSCs, Engelen et al. (2011) show that CHD7 functions as a cofactor of the SoxB family of transcription factor SOX2 to activate multiple developmental disease-relevant genes like *Jag1*, *Gli2*, *Gli3,* and *MycN*. In adult mouse NSCs, CHD7 is required for the activation of two SoxC family of transcription factors SOX4 and SOX11, and overexpression of SOX4 and SOX11 could largely rescue the neuronal differentiation defect in *Chd7* mutant NSCs (Feng et al., 2013). Another study show that CHD7 activates the expression RA (retinoic acid) signaling receptors *Rarb* and *Rxrg*, and RA treatment could partially rescue neuronal differentiation defect in neurosphere derived from the SVZ of *Chd7* CKO mice (Micucci et al., 2014). Also, CHD7 was shown to activate Notch effector HES5 in quiescent adult mouse NSCs, which is known to be required for the maintenance of NSC quiescence (Jones et al., 2015). During early cerebellar development, CHD7 was found to activate and repress the expression of *Gbx2* and *Otx2*, respectively, which results in the downregulation of *Fgf8* in IsO (Yu et al., 2013). During postnatal development of cerebellum, two independent studies reported *reelin*, an essential gene for neuron migration, as a key target gene of Chd7 (Feng et al., 2017; Whittaker et al., 2017). Using the *Nestin-Reln* mouse line, Whittaker et al. (2017) show that overexpression of *reelin* during brain development partially rescues defects of *Chd7* mutant cerebellum. Using RNA-seq and ChIP-seq (Chromatin immunoprecipitation with high throughput sequencing) analysis in differentiating OLs, CHD7 was found to regulate genes like *Osterx* and *Creb3l2*, both of them are required for both OL differentiation and bone formation (He et al., 2016). Except the *Otx2* gene, CHD7 functions as a transcriptional activators for its target genes. Genome-wide analysis including RNA-seq and ChIP-seq in GNPs and OLs support the notion that CHD7 is required for the activation of gene expression during neural differentiation (He et al., 2016; Feng et al., 2017).

THE MOLECULAR FUNCTION OF CHD7 IN NEURAL CELLS

Data from several CHD7 ChIP-seq studies have shown that CHD7 protein preferentially binds to distal regulatory elements in different cells including ESCs (embryonic stem cells), NPCs, and GNPs (Schnetz et al., 2009, 2010; Ram et al., 2011; Feng et al., 2017). In particular, two studies have shown the association of CHD7 to super-enhancers in human ESCs and mouse GNPs (Hnisz et al., 2013; Feng et al., 2017). Given super-enhancers are associated with genes establishing cell identity, these findings implicate important role of CHD7 in cell fate determination. As an example, two super-enhancers are present at the *Chd7* gene in mouse GNPs (Feng et al., 2017), consistent with the important role of CHD7 in these cells. Using ATAC-seq (transposase-Accessible Chromatin with high throughput sequencing), Feng et al. (2017) show loss of *Chd7* leads to specific alteration of open chromatin structure in distal regulatory elements of *Chd7* target genes. How CHD7 is recruited to specific targets is still an open question. Given CHD7 protein does not have DNA binding specificity, it is believed that sequence-specific transcription factors recruit CHD7 to its target genes. Along with this line, several transcription factors have been reported to interact with CHD7. In mouse NSCs, knock down of *Sox2* impairs the binding of CHD7 to its target, indicating that Sox2 is involved in the recruitment of Chd7 (Engelen et al., 2011). In differentiating OLs, CHD7 is shown to interact with a SoxE family of transcription factor SOX10, and to colocalize with SOX10 genome-wide (He et al., 2016). The requirement of SOX10 for the targeting of CHD7 in OLs has not been shown in this study, however.

As expected, the chromatin remodeling activity is important for the function of CHD7 during development. Most of *CHD7* mutations in CHARGE syndrome patients result in truncated CHD7 protein that apparently lost its ATPase and chromatin remodeling activities. Importantly, Bouazoune and Kingston (2012) observed that several patients-derived missense *CHD7* mutations lead to reduction or loss of its ATPase and remodeling activity *in vitro*. Intriguingly, CHD7 interacts with other chromatin remodelers. Multiple evidences suggest a possible functional interaction between CHD7 and the BAF (Brg1/Brahma-associated factors) complex. **First**, in human neural crest cells, CHD7 is associated with multiple subunits of the PBAF (Polybromo- and Brg1/Brahma-associated factors) complex (Bajpai et al., 2010). CHD7 and PBAF colocalize to distal regulatory elements of key neural crest transcription factors, and synergistically activate neural crest gene expression (Bajpai et al., 2010). Consistently, in neural crest-derived melanocyte, Brg1-CHD7-containing PBAF complex interacts with and facilitates the function of the master transcription factor MITF (Microphthalmia-associated transcription factor) (Laurette et al., 2015). **Second**, in OLs, BRG1 was shown to activate the

expression of *Chd7* (He et al., 2016). **Third**, phenotypes of *Brg1* CKO brain in adult neurogenesis and cerebellar development (Ninkovic et al., 2013; Moreno et al., 2014) are similar to *Chd7* CKO brain. Moreover, yeast two-hybrid screening has identified CHD8, another CHD family chromatin remodeler, as an interacting partner of CHD7 (Batsukh et al., 2010). The interaction between CHD7 with BRG1 and CHD8 was confirmed in HEK293T cells using coimmunoprecipitation coupled to mass spectrometry (Feng et al., 2017). How chromatin remodelers function together is an open question. One stimulating study show that three chromatin remodelers BRG1, CHD4, and SNF2H colocalize to a substantial portion of sites on chromatin, and the DNA accessibility of many regions requires a combined activity of several remodelers (Morris et al., 2014). It is worthy to investigate the potential cooperative or counteractive functions of CHD7 with BRG1 and CHD8 during brain development.

Another interesting molecular mechanism revealed from a recent study is the cooperative function of CHD7 and DNA topoisomerase TOP2B in transcriptional regulation (Feng et al., 2017). Increasing evidences show the cooperative role of chromatin remodelers and DNA topoisomerases. In mouse ESCs, BAF complex was shown to regulate DNA decatenation during mitosis by recruiting DNA topoisomerase TOP2A (Dykhuizen et al., 2013). One recent study from the same lab demonstrates that TOP2B synergizes with the BAF complex to resolve facultative chromatin to accessible chromatin (Miller et al., 2017). Another recent study shows that BRG1 is required for the recruitment of Topoisomerase 1 in B-cell line (Husain et al., 2016). Importantly, enzymatic activities of TOP1 and TOP2B are absolutely required for the transcription of long genes (>100 kb in gene length) in neurons (King et al., 2013). Many of expressed long genes in neurons are essential neuronal genes, with their dysfunction results in various human neurological disorders. Feng et al. (2017) demonstrate that CHD7 recruits TOP2B to facilitate the transcription of long genes in cerebellar granule neurons, including the *reelin* gene. Consistently, ablation of *Top2b* specifically in mouse forebrain results in a *reelin*-deficient phenotype in cerebral cortex (Lyu and Wang, 2003).

FUTURE PERSPECTIVE

One of remaining questions concerning the function of CHD7 in the brain is whether CHD7 is required for the function of mature neurons. As discussed before, the expression of *Chd7* is switched off in most types of mature neurons in the brain during neurogenesis. However, CHD7 is highly expressed in cerebellar granule neurons in adult mouse and human brain (Feng et al., 2017), and some interneurons in the olfactory bulb of adult mouse (Micucci et al., 2014). The selective expression of *Chd7* indicates that it may be involved in the function of these mature neurons. Studying the function of CHD7 in adult brain may help us to understand neuronal behavior abnormality frequent observed in CHARGE syndrome patients.

Several key questions regarding molecular function of CHD7 in the cell remains to be answered. **First,** what is pathogenic mechanisms of *CHD7* missense mutations? Study of missense mutations could provide important insight into the molecular and biochemical function of CHD7 protein. Recent development of structure analysis of chromatin remodelers may provide crucial mechanistic insight of missense mutations of CHD7. For instance, the chromo domain of CHD1 has been shown to be structurally required for the activity of its ATPase activity (Sundaramoorthy et al., 2017). Given the chromo domains in CHD family of chromatin remodelers are conserved, this finding may provide a mechanistic answer for the apparent loss of ATPase activity of one chromo domain mutation CHD7 S834F (Bouazoune and Kingston, 2012). **Second**, what is the exact function of CHD7 at enhancers? It is tempting to speculate that the nucleosome remodeling activity of CHD7 facilitates the transcription activity at enhancers. This hypothesis remains to be experimentally tested. **Third**, does CHD7 functions alone or within a complex? As examples, CHD1 functions as a monomer (Tran et al., 2000; Lusser et al., 2005), in contrast, CHD4 functions within the NuRD (Nucleosome remodeling Deacetylase) complex (Zhang et al., 1998). Solid biochemical assays need to be performed to answer this question.

It is worthy to notice that recent unprecedented development of technology in the field of human cell-based disease modeling. It has already become a routine practice to derive human induced pluripotent stem cells (iPSCs) from patients. The full reservoir of differentiation capacity enables iPSCs as an excellent cell model for disease modeling. Recent development of genome editing tools such as CRISPR-Cas technology has in principle enabled the genome editing at anywhere of the genome in any cell. In particular, genome editing in human iPSCs has enormous application in biomedical research (Hockemeyer and Jaenisch, 2016). Moreover, the recent development of 3D-based human brain organoid culture system has largely improved our ability to model human brain development in tissue culture dish (Lancaster et al., 2013). These state-of-art human cell-based technologies have been applied to model human brain development and neurological disorders. Study the function of CHD7 using this approach is expected to advance our understanding of role of CHD7 in brain development and disease.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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