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Genes causing congenital hydrocephalus: Their chromosomal characteristics of telomere proximity and DNA compositions

Ian McKnight[a,1], **Christoph Hart**[a,1], **In-Hyun Park**[b], **Joon W. Shim**[a,*]

[a]Department of Biomedical Engineering, Marshall University, Huntington, WV 25755, USA

[b]Department of Genetics, Yale University School of Medicine, New Haven, CT 06519, USA

Abstract

Congenital hydrocephalus (CH) is caused by genetic mutations, but whether factors impacting human genetic mutations are disease-specific remains elusive. Given two factors associated with high mutation rates, we reviewed how many disease-susceptible genes match with (i) proximity to telomeres or (ii) high adenine and thymine (A + T) content in human CH as compared to other disorders of the central nervous system (CNS). We extracted genomic information using a genome data viewer. Importantly, 98 of 108 genes causing CH satisfied (i) or (ii), resulting in >90% matching rate. However, such a high accordance no longer sustained as we checked two factors in Alzheimer's disease (AD) and/or familial Parkinson's disease (fPD), resulting in 84% and 59% matching, respectively. A disease-specific matching of telomere proximity or high A + T content predicts causative genes of CH much better than neurodegenerative diseases and other CNS conditions, likely due to sufficient number of known causative genes ($n = 108$) and precise determination and classification of the genotype and phenotype. Our analysis suggests a need for identifying genetic basis of both factors before human clinical studies, to prioritize putative genes found in preclinical models into the likely (meeting at least one) and more likely candidate (meeting both), which predisposes human genes to mutations.

Keywords

Congenital hydrocephalus; Telomeres; A + T content; mutation; Chromosome; homologous recombination; familial Parkinson's disease; Alzheimer's disease

[*]**Corresponding author at:** Department of Biomedical Engineering, Marshall University, WAEC3005, 1676 Third Ave., Huntington, WV 25755, USA. shim@marshall.edu (J.W. Shim).

Author contributions

IM conducted the literature survey, wrote, and finalized the manuscript.

CH conducted the literature survey, wrote, and finalized the manuscript.

IP proposed an outline of all causative genes known so far in CH and edited the manuscript.

JWS conducted the literature survey, genomic data analysis, verified all data in the manuscript for accuracy and finalized the manuscript.

All authors have read and approved the submitted version of the manuscript.

[1]These authors contributed equally to the work and serve as co-first authors.

Conflict of interest

The authors declare no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.expneurol.2020.113523.

1. Introduction

Congenital hydrocephalus (CH) comprises one of the most common childhood brain disorders (Dewan et al., 2018) (~1 in 1000 worldwide births (Dewan et al., 2018; Isaacs et al., 2019)). CH, in which genetic variants are involved, may occur alone (non-syndromic) or as part of a syndrome with multiple anomalies (Zhang et al., 2006). If left untreated, hydrocephalus is fatal. The mainstay of treatments is surgical, through shunt insertion and a combination of endoscopic ventriculostomy and choroid plexus cauterization (Dewan and Naftel, 2017; Kulkarni et al., 2018; Vinchon et al., 2012). CH results in extremely poor neurological outcomes (McAllister 2nd, 2012) that are expensive to manage surgically (~$2 billion annually) with 29–15% failure rates (Lim et al., 2018; Ravindra et al., 2015; Wright et al., 2016).

Etiologically, CH is associated with developmental abnormalities such as genetic mutations linked to ciliopathies, neural tube defects, spina bifida, myelomeningocele, and exencephaly/anencephaly, while that with acquired form involves ischemia/hypoxia, hemorrhage, infection, trauma, and brain tumors. Collectively, all forms of hydrocephalus in children show hallmarks such as ventriculomegaly. The cause of this ventriculomegaly is claimed to be multi-factorial: excess CSF production, obstruction of CSF pathways, impaired CSF outflow, and/or imbalance of production and reabsorption at subarachnoid granulation (Ballabh, 2014; Bassan, 2009; Bateman, 2008; Bhattathiri et al., 2006; Garton et al., 2016; Kazan et al., 2005; Koschnitzky et al., 2018; Limbrick Jr. et al., 2010; Mbabazi-Kabachelor et al., 2019; McAllister 2nd, 2012; Murphy et al., 2002; Osterman et al., 2015; Perdaens et al., 2018; Radic et al., 2015; Rekate, 2007; Robinson, 2012; Romero et al., 2015; Shim et al., 2019; Shimada et al., 2019; Stoll et al., 2010; Zhang et al., 2006). Recent studies have identified that increases in the mutation rates of more than 100 distinct genes contribute directly to one or more of these causative factors, as well as the aforementioned developmental abnormalities, thus insinuating a strong correlation with the development of CH (Belal and Al Menabawy, 2017; de Paola et al., 2019; Fransen et al., 1995; Furey et al., 2018a; Furey et al., 2018b; Gable et al., 2019; Huh et al., 2009; Kousi and Katsanis, 2016; Rachel et al., 2015; Rowitch et al., 1999; Shim et al., 2019).

More specifically, a recent whole exome sequencing (WES) study suggests that CH results from impaired neurogenesis, leading to abnormal CSF drainage or obstruction of CSF flow (Furey et al., 2018b). One of the major neurodevelopmental pathways related with neurogenesis in CH is cilia/sonic hedgehog (SHH) signaling (Goetz and Anderson, 2010; Rohatgi et al., 2007). SHH is highly expressed in neural stem cells of the developing cortex, including the radial glia, intermediate progenitors, and outer radial astrocytes (Britto et al., 2002; Guemez-Gamboa et al., 2014; Han et al., 2008). The primary cilium, which is non-motile, is an essential organelle that mediates the SHH signaling. Using embryonic fibroblasts, it has been shown that when the ligand, SHH, binds to patched gene (PTCH) that blocks smoothened (SMO), SMO is released and translocates to cilia, which activates downstream signaling (Goetz and Anderson, 2010; Rohatgi et al., 2007). Mutations in a series of proteins that regulate the structure of cilia or SHH pathways have been implicated in CH as well. In a rat model of Meckel-Gruber Syndrome (MKS), mutated transmembrane protein 67 (TMEM67) resulted in CH with elongated primary cilia (Shim et al., 2019). The

TMEM67 gene encodes for Meckelin, a protein that functions in centriole migration to the apical membrane and formation of the primary cilium (Abdelhamed et al., 2015). ZCCHC8, the zinc finger CCHC-type domain containing 8 protein, which is reported to interact with the TR component (a non-coding RNA) of telomerase, has been shown to cause CH as well (Gable et al., 2019). Interestingly, ZCCHC8$^{-/-}$ mice showed significant upregulations of *transmembrane proteins (e.g. TMEM116)* and cilia-regulating genes (e.g. ccdc33) (Gable et al., 2019).

However, despite these neuroanatomical and clinical findings, as well as attempts to treat CH surgically, there is no effective cure for this disease. Moreover, the process by which mutations in TMEM67 and ZCCHC8 have occurred in their chromosomes— affecting cilia and SHH pathways—is largely unknown. Thus, an attempt to elucidate the mechanism underlying these high mutation rates is vitally important, thereby providing valuable insight into the root cause for CH, as well as likely leading to a more accurate diagnosis. To this end, we tested how many causative genes of CH meet the following two criteria: i) proximity to a telomere and ii) high A + T content. These two factors have been associated with a high mutation rate—causing genetic diseases (Nusbaum et al., 2006) such as CH—as indicated previously. We further tested whether genes causing other genetic disorders of the CNS would meet (i) or (ii) at a rate comparable to CH, in order to determine if these criteria provide a clear indication of genes causing neurological disorders.

2. Materials and methods

2.1. Database and open access software

The literature survey was centered on CH and associated genes. We used PubMed database. During the literature survey, we also utilized the publicly open genome data viewer (https://www.ncbi.nlm.nih.gov/genome/gdv/), Pubmed database of nucleotide accession number (https://www.ncbi.nlm.nih.gov/nucleotide/) and GC content calculators to obtain A + T content ((www.endmemo.com/bio/gc.php) and/or (https://www.biologicscorp.com/tools/GCContent/)).

2.2. Data plot and statistical methods

Prism was used to plot a bar graph and box and violin plot of the data obtained during analysis with genome data viewer. Statistical analyses were performed using Prism (version 8, GraphPad Software Inc.). Normal distribution of the data was confirmed using Shapiro-Wilk normality test ($\alpha < 0.05$). A two-sided unpaired *t*-test was used for comparison of two different groups, unless stated differently. Tukey's multiple comparisons test following one-way analysis of variance was used for comparison of more than two groups. The difference between data sets was considered significant at $P < 0.05$; P values are identified in the figures and legends as *P < 0.05, **$P < 0.01$, ***$P < 0.005$.

3. Results

3.1. Most cases of CH belong to a type of neural tube defects

Our first question was how phenotypes of TMEM67 mutant rats (Shim et al., 2019), which were reported recently, might be linked to pediatric patients we studied previously (Shim et al., 2013). We reanalyzed the data (Shim et al., 2013) and sorted them based on the diagnosis. Interestingly, among seventy individual data points (31 controls & 35 children with hydrocephalus included; 4 babies with tumors excluded), more patients were diagnosed as non-hemorrhagic hydrocephalus as compared to PHH. Importantly, 40% of neonatal hydrocephalus at age ≤ 3 yr belongs to a broad classification of neural tube defects: spina bifida & hydrocephalus (23%), myelomeningocele & hydrocephalus (13%), and encephalocele & hydrocephalus (3%) (Fig. 1A). We then sorted the data by age (Fig. 1B). We found a significant number of patients belonged to 'Not PHH' such as CH, while 'PHH' occupied 26% of all patients. In the cohort of 'age younger than 3 years', encephalocele (Shim et al., 2019) was found in the 'Not PHH' group. This suggests a linkage to mutations in ciliopathy-related genes (Abdelhamed et al., 2015; Shim et al., 2019; Taulman et al., 2001). The aforementioned diagnosis by clinicians also highlighted the significance of CH associated with a form of spina bifida reported in Bardet Biedl syndrome (BBS) (Carter et al., 2012; Leitch et al., 2008; Smith et al., 2006) and our recent studies concerning TMEM67 defects (Shim et al., 2019; Smith et al., 2006). However, this diagnosis alone for pediatric patients was insufficient to uncover rationale of a high mutation rate in CH. Even in this single center study, we noticed that spina bifida (23%) was as frequent as PHH (26%) (Fig. 1A–B).

In all ages studied, male-female ratio was almost equal when sorted into control vs. hydrocephalus (Shim et al., 2013). As patients with hydrocephalus were further divided into PHH and 'Not PHH', however, there were more females in non-hemorrhagic hydrocephalus and fewer female patients in PHH (Fig. 1C). We then asked how abnormal neurogenesis was proposed as a cause of CH in recent literatures (Furey et al., 2018a; Rodriguez and Guerra, 2017). Previously (Shim et al., 2016), we reported that trajectories of doublecortin (DCX)-expressing young neurons in hydrocephalus were different in TMEM67$^{-/-}$ mutants as compared to WT during neonatal period (postnatal day 17, P17). A disorganized and widespread GFAP+ cells in the vicinity of radially and tangentially migrating neural progenitors in hydrocephalus is consistent with several previous studies by others (Doetsch and Alvarez-Buy 11a, 1996; Doetsch et al., 2002; Sawamoto et al., 2006; Shim et al., 2016) (Bothwell et al., 2019). In breeding animals, it has come to our attention that TMEM67$^{-/-}$ rats at P12 die in less than 10 days (~P21), even if many young neurons migrate postnatally in the presence of CH (Shim et al., 2019; Smith et al., 2006).

3.2. TMEM67 mutations detected in almost all exons of MKS and BBS patients with CH

It was not until recently that the spatial status of TMEM67 had been demonstrated in the ciliary zone close to basal body along with tectonicl, tectonic2, and Cc2d2a/MKS6, which collectively form a transition zone complex (Garcia-Gonzalo et al., 2011; Yang et al., 2015). In the DNA sequencing of five individuals with MKS, three types of mutations—namely, frameshift (exon 3 & exon6), splice site (exon 9 & exon 15), and missense mutation (exon

11)—were associated with neurological (encephalocele and Dandy Walker malformation), renal (polycystic kidney), and hepatic (fibrosis and ductal plate malformation) phenotypes (Smith et al., 2006). Using Wistar polycystic kidney (Wpk) rats, a missense mutation in exon 12 of TMEM67 has been shown, which results in a gene-dose dependent neurological and renal phenotype consistent with the aforementioned clinical report (Iannicelli et al., 2010). Specifically, hemorrhage in the dorsomedial subarachnoid space at birth, encephalocele-like protrusion, and late-onset hydrocephalus during adulthood were reported in TMEM67 heterozygous mutants, while the affected phenotype exhibited early-onset CH, polycystic kidney, and neonatal mortality before weaning age. This was observed with 100% penetrance of hydrocephalus in Wpk rats with TMEM67 homozygous mutant alleles (Shim et al., 2019). As pointed out recently, in comparison with twelve cases of MKS human fetuses in a wider ethnic background (United States, France, Italy, Algeria, and Morocco) than the prior report with limited ethnic identities (Oman and Pakistan) (Smith et al., 2006), there is no overt hepatic phenotype in the rat model of TMEM67 mutations (Iannicelli et al., 2010; Shim et al., 2019). As found in extra-renal organs, these TMEM67$^{+/-}$ rats developed late-onset hydrocephalus (Shim et al., 2019). Moreover, increasing evidence (Table S1) (Dempsey et al., 2017; Deveault et al., 2011; Doherty et al., 2010; Parisi, 2009) suggests that the correlation of genotype-phenotype is not simple and that TMEM67-involved MKS shares clinical features with Jourbert syndrome (JS), COACH syndrome, and BBS (Iannicelli et al., 2010; Leitch et al., 2008).

3.3. ZCCHC8 gene, whose KO mice develop CH, is in the vicinity of its telomere

The zinc finger CCHC-type domain containing 8 protein (ZCCHC8) is a component of the nuclear exosome targeting complex. Gable and colleagues recently showed that ZCCHC8 is required for the maturation of TR, a component of telomerase that is a specialized non-coding RNA (also known as TERC). They uncovered two distinct RNA dysregulation disease phenotypes caused by partial and complete loss of nuclear RNA exosome targeting. Genotypically, ZCCHC8$^{+/-}$ mice displayed lung disease, similar to human idiopathic pulmonary fibrosis related with defects in telomere length, while ZCCHC8$^{-/-}$ mice exhibited abnormal neurogenesis during embryonic development and CH in adulthood. The authors have claimed that hydrocephalus in ZCCHC8$^{-/-}$ mice is reminiscent of human mutation carriers with intellectual disability, although the presence of hydrocephalus in patients of that type has not been reported (Gable et al., 2019). Interestingly, transmembrane proteins (TMEMs) are upregulated in the RNA transcriptome analysis of ZCCHC8$^{-/-}$ mice, but whether or not they are related with cilia remains undetermined. Specifically, TMEM151a, TMEM151b, TMEM253, and TMEM116 were upregulated in their RNA-seq. Analysis. None of these four TMEMs have yet been shown to localize in the ciliaiy transition zone. Their interpretation of the mechanism by which CH develops in this model is built on three premises: 1) ZCCHC8 expression is low in the brain but detected in ependymal cells, 2) three TMEMs transcripts, one of which may be related with the ciliary transition zone, were upregulated, and 3) genes reported to regulate motile cilia, cede family proteins, were upregulated. Among TMEMs they uncovered, ‘the ciliary body’ connected to the dorsal iris of the eye, in which TMEM116 was highly expressed, could be considered a potential link to the cilia of the central nervous system (CNS) (Sousounis et al., 2013). Thus, clarification is warranted if, for example, TMEM116 upregulated in ZCCHC8$^{-/-}$ mice with

CH is detected as one of transition zone complexes, similar to TMEM67, in conjunction with ‘ependymal’ ZCCHC8, which they briefly described (Gable et al., 2019).

3.4. An outline of genes causing CH

In the prior section, we compared two recently reported genes evoking CH. Similarly, here, we reviewed more than 100 genes causing CH and summarized the basic information (Table 1). Here, we found that 108 genes causing CH might be classified into four categories: 1) neurulation, 2) cilia, 3) syndromes, and 4) others. For more detailed classification, readers are recommended to visit the references (REF) listed in Table 1.

While this classic summary of genotype-phenotype (Table 1) is appreciated, we additionally asked which fundamental characteristics of these genes are associated with mutations leading to CH. To find the answer to this question, we first examined the human ZCCHC8 gene using the genome data viewer. Interestingly, ZCCHC8 is located very close to its telomere (<50 Mbp) on chromosome 12. We also found that the human TMEM67 gene is located slightly farther than 50 Mbp from its telomere on human chromosome 8 (Table S2).

3.5. Mapping of select genes on human chromosomes: I. proximity to telomeres

During literature surveys of SHH signaling related with CH, we found that a gene located adjacent to a telomere in a chromosome interacts with genes located in the same chromosome and can also affect the expression of genes that are further apart. For example, when the ligand SHH (in chromosome 7) binds to its receptor, PTCH1 (in chromosome 9) that blocks SMO (in chromosome 7), SMO is released and translocated to cilia to activate the downstream signaling (Goetz and Anderson, 2010; Rohatgi et al., 2007). Here, both SHH (q36.3) and SMO (q32.1) are located at the long arm of chromosome 7. If two genes are in the same chromosome, their genetic linkage can alter recombination frequency. Therefore, we sought a way to identify which chromosome has which gene, pinpointing where each gene lies on its chromosome via genetic mapping.

Previously, the biological basis for the apparently high mutation rate in human chromosome 8, on which TMEM67 is located, has been described. A group of colleagues led by Eric Lander have proposed that three factors are associated with high mutation rates, highlighting i) proximity to telomeres, ii) high recombination rate, and iii) high A + T content (Chimpanzee and Analysis, 2005; Hellmann et al., 2005; Nusbaum et al., 2006). Strictly speaking, a high recombination rate (Chimpanzee and Analysis, 2005; Hellmann et al., 2005; Nusbaum et al., 2006) is obtained when exchanged nucleotide sequences of F2 offspring from homologous recombination of FI parent chromosomes are discerned. However, if we apply the rule of thumb of 1 centimorgan (cM) ~1 million base pair (Mbp) (Hastbacka et al., 1992), then measuring the distance between two genes will allow the recombination frequency (Ritter et al., 1990) or rate (Nusbaum et al., 2006) to be calculated. As a result, we examined two of the three factors mentioned above—focusing on the position of a gene and its distal end locus of each arm on a chromosome where the telomere lies—using the following premise:

If recombination frequency (Ritter et al., 1990) is less than (≤) 50 cM, genes are linked: (1)

if recombination frequency is higher than 50 cM, genes are not linked, (2)

where 1 centimorgan (cM) 1 million base pair (Mbp) (Hastbacka et al., 1992).

First, we retrieved each transcript using the genome data viewer and checked the position in the short (p) or long (q) arm of the chromosome relative to the telomere (the distal end of the p or q arm depends on where a gene is located) of select genes readily known in clinical and animal studies of CH (Table S2)(Botfield et al., 2013). We found that three causative genes of CH located at chromosome X (L1CAM) and chromosome 12 (ZCCHC8 and MKS4/cep290) met the first condition of 'proximity to telomeres' within 50 Mbp (Nusbaum et al., 2006). Interestingly, we found that three other genes related with CH are also located within this proximity (<50 Mbp) to their telomeres—namely, TMEM116, TRPV4, and decorin (DCN) (Bothwell et al., 2019; Gable et al., 2019). In addition, Orail, MYC, and IGF1, which mediate store-operated Ca^{2+} signaling (Miao et al., 2017), induction of pluripotency (Park et al., 2008), and ciliary signaling in embiyonic ventricular surface (Lehtinen et al., 2013), respectively, are located at less than 50 Mbp to telomeres of the q arm on either chromosome 8 or chromosome 12. Intriguingly, however, TMEM67 and BBS10—which are known to cause CH and BBS—are slightly farther than 50 Mbp from their telomeres (Forsythe and Beales, 2013; Forsythe et al., 2018; Shim et al., 2019; Smith et al., 2006). Inversely, GLI1, which is known to mediate SHH signaling (Swiderski et al., 2014), and alpha tubulin (TUBAB1) gene—a marker for tufts of cilia (Mirzadeh et al., 2008)—are clearly far from their telomeres. In comparison, WNT1 and LRRK2, both known to regulate PCP signaling (Bengoa-Vergniory and Kypta, 2015; Meng et al., 2015) and familial Parkinson's disease (fPD) (Kluss et al., 2019), are much closer to the centromere (Fig. 2A) within chromosome 12 rather than the telomeres. Taken together, four genes known to cause CH or BBS (L1CAM, ZCCHC8, MKS4, and TMEM67) are noteworthy. However, an explanation other than 'proximity to telomeres' is sought to better correlate the genotype (mutations) with the reported phenotype in humans (CH or other syndromic diseases). Thus, we examined the % composition of guanine and cytosine (GC content) within all these gene transcripts to obtain the % composition of adenine and thymine (A + T content) (Nusbaum et al., 2006).

3.6. Mapping of 108 genes causing CH on human chromosomes: II. A + T content

The A + T content of 16 genes were obtained using a GC content calculator, after which we sorted the data by nucleotide size, in terms of full-length base pair number (bp). As is evident from Table S3, nucleotides longer than 6000 bp tended to show higher A + T content at >60%, which is higher than the threshold of 59% as proposed previously (Nusbaum et al., 2006). However, as the size of the nucleotide shortens, A + T content becomes less consistent across CH-related genes located on chromosome X, chromosome 8, and chromosome 12 (Table S3). As the sets of genes in Table S3 are compared to those of Table S2, despite having low A + T content (≤59%), two classic and relatively new causative genes of CH—L1CAM and ZCCHC8—demonstrated exemplary proximity (≤50Mbp) to their telomeres. In contrast, high A + T content (>59%) may have prevailed over insufficient proximity to telomeres in two marginally located genes, TMEM67 and BBS10. Although the select genes listed here may be a result of our unintended bias, TMEM67 and ZCCHC8, along with the aforementioned series of associated genes, have appeared to uncover that

either proximity to telomeres or high A + T content might suffice to predict if human CH develops—based on CH found in mutant animals. To test this idea, we extended our analysis to 108 causative genes (4 in Table S2–S3 + 104 in Table S4) of CH, reported previously (Buysse et al., 2013; Belal and Al Menabawy, 2017; Chabas et al., 1995; de Paola et al., 2019; Fransen et al., 1995; Furey et al., 2018a; Furey et al., 2018b; Gable et al., 2019; Huh et al., 2009; Iliescu et al., 2011; Kibar et al., 2001; Konishi et al., 2020; Kousi and Katsanis, 2016; Liu et al., 2016b; Rachel et al., 2015; Rowitch et al., 1999; Shaheen et al., 2017; Shim et al., 2019; Sironen et al., 2011; Vogel et al., 2012; Wicker et al., 1991; Wild et al., 1997).

In assessing the list of 108 causative genes of CH in Tables S2–S4, we summarized the survey of the distance between each gene locus and its telomere, defining it as the first factor or F(i) (Fig. 2B). As we went through each of these genes with the genome data viewer, it became obvious that if a causative gene of CH is located on chromosome 22, the 2nd shortest chromosome in physical length (Morton, 1991), “distance to a telomere” will almost always be within a 50 Mbp reach. This technically fulfills the first factor, F(i), indicating a higher mutation rate (Nusbaum et al., 2006), though it is less assertive than that indicated by longer chromosomes. By examining the known length of all chromosomes (Morton, 1991) and our data, we found that human chromosomes 18 to 22 had an absolute length less than 100 Mbp, meaning that their genes were unlikely to be >50 Mbp from the telomere, since the centromere is located between p- and q-arm (Fig. 2C), thereby easily meeting F (i). This implies that clinicians will have a different suggestion for patients with CH whose causative genes lie in chromosome 18, 19, 20, 21, 22, and Y—because any gene within these short chromosomes will likely have a range of distance from its telomere within 50 Mbp (Fig. 2A–C).

3.7. Causative genes of CH: III. Proximity to telomeres vs. A + T content

To further test our idea, we obtained the specific A + T (Fig. 3A) content of all of the aforementioned genes reported to cause CH. These 108 causative genes were found in almost all of the chromosomes except three (chromosome 18, 20, 21). Although a majority of these genes had less than 59% A + T content (dashed vertical lines in Fig. 3B), 32 of 108 genes with A + T content >59% (Fig. 3B; Table S2–S4). We defined this condition as the second factor or F(ii). When we counted the number of these factors to match with CH, >90% of genes causing CH satisfied the proximity to telomeres ($n = 92/108$) or high A + T content ($n = 32/108$). Furthermore, 20% of known genes met F(i) and F(ii) alike, while less than 10% (10 of 108 genes) met neither F(i) nor F(ii) (Fig. 3C). This raises the possibility that the disease-specific success rate of the previously proposed factors successfully projects CH, regardless of the particular locus on a certain chromosome (e.g. 8p) (Nusbaum et al., 2006).

3.8. Genes causing CH uncovering the factor-nucleotide size relationship

During the survey of nucleotide base pairs of the 108 genes, data entries suggest that the full-length size of a gene, if it is larger than 6000 bp, likely leads to the said gene having high A + T content at >59%. The Pearson coefficient ($r = 0.24$) suggests that there is a correlation ($P = 0.01$) between the full-length size and A + T content in CH (Fig. 4A–B). We further organized factors (i) and (ii) with respect to the base pair number (bp) of each gene,

by grouping into three categories with an approximately equal number per sub-group at 1–3000 bp (n = 40), 3001–6000 bp (n = 39), and 6001–15,000 bp (n = 29), respectively (total N = 108 causative genes of CH; Table S2, S3, and S4). Statistical analysis suggests that there is no significant overall difference in proximity to telomeres with respect to the gene full-length size. However, pair-wise comparisons using Tukey's post-hoc test after one-way ANOVA suggest that there is a significant difference (P = 0.0075) in A + T content with respect to the full-length size (bp) in the shortest and the longest gene group. Genes with a full-length size longer than 6000 bp have a 41% chance (12/29) of harboring A + T content at >59%, compared to the two other groups with shorter sizes (20% and 24% chances for 1–3000 bp and ≥ 6001 bp group, respectively) (Fig. 4C–D).

3.9. Genes associated with AD

We next checked the position of the p or q arm of the chromosome relative to the telomere of 70 genes associated with Alzheimer's disease (AD) (Table S5)(Seshadri et al., 2010; Bird, 1993). In assessing these genes, we surveyed the distance between each gene locus and its telomere using the first factor, or F(i) (Fig. 5A). As we identified the 70 gene loci listed in Tables S5, it was evident that—in chromosomes of short physical length such as chromosome 19, 20, and 21—the "distance to a telomere" will almost always be within 50 cM, thereby fulfilling F(i). This is consistent with the previous result (Fig. 2B–C) above. Again, this confirms that clinicians can provide a convincing explanation for patients with AD whose susceptible genes lie on chromosome 19, 20, 21, 22 and Y—where mutations are highly likely due to the short chromosomal length (blue asterisk in Fig. 5A).

To further test our hypothesis, we obtained the A + T content (Fig. 5B) of genes reported to be susceptible to AD. The majority of genes susceptible to AD were distributed on chromosomes 2 and 19, forming a dense cluster. When we examined 70 genes of AD, 84% satisfied the proximity to telomeres (n = 53/70) or high A + T content (n = 8/70) conditions. Furthermore, 1 of these genes met both F(i) and F(ii), while less than 20% (11 of 70 genes) met neither F(i) nor F(ii) (Fig. 5C). This supports the idea that disease-specific matching of the previously proposed two factors can predict genetic disorders of the CNS—telomere proximity or A + T content might suffice to predict both diseases, although mismatch is higher for AD (84% matching) than CH (>90% matching).

We then organized the factors (i) and (ii) with respect to the base pair number (bp) of each gene. Consistent with the previous analysis (Fig. 4), we grouped the genes into three categories: 1–3000 bp (n = 39), 3001–6000 bp (n = 22), and 6001–15,000 bp (n = 9), respectively (total N = 70 genes susceptible to AD; Table S5; Fig. 5D–D'). Statistical analysis suggests that there is no significant difference in proximity to telomeres with respect to the gene full-length size. However, pair-wise comparisons using Tukey's post-hoc test after one-way ANOVA suggest that there is a significant difference (P = 0.031) in A + T content with respect to the full-length size (bp) in the shortest and the longest gene group. Genes with a full-length size longer than 6000 bp have a 33% chance (3/9) of having >59% A + T content, compared to the two other groups with shorter sizes (3% and 14% chances for 1–3000 bp and ≥ 6001 bp group, respectively). (Fig. 5E–F).

3.10. Matching rate of two factors with other genetic diseases

We next analyzed the percentage of these two factors matching with familial Parkinson's disease (fPD), since the series of causative genes was readily available: namely, PARK 1 to PARK 18. Using 17 genes of fPD identifiable via the genome data viewer, we found that less than 60% of genes associated with fPD satisfied either F(i) or F(ii) while no genes met F(i) and F(ii) at the same time. Inversely, we found that 41% of genes associated with fPD met neither proximity to telomeres nor high A + T content (Fig. 6A–C; Table S6)(Kumar et al., 2012; Le et al., 2003; Nichols et al., 2009). Statistical analysis suggests that there is no significant difference in proximity to telomeres with respect to the gene full-length size (Fig. 6D). Consistent with the previous assessment with CH, pair-wise comparisons using Tukey's post-hoc test after one-way ANOVA indicate that A + T content of the fPD genes with molecular size higher than 6000 bp is significantly different than other groups ($P < 0.01$). However, fPD genes with full-length size longer than 6000 bp have only a 20% chance (1/5) of having A + T content at >59% while the two other groups of fPD genes showed a 0% likelihood (Fig. 6E).

Consistent with fPD, we found a similar trend of moderate success—an overall 62.5% matching rate—in other CNS genetic conditions including neurofibromatosis (NF), tuberous sclerosis (TSC), BBS, Huntington's disease (HD) and malformations with agenesis of corpus callosum (cc) (Fig. 6F; Table S7)(Ferner and Gutmann, 2013; Hjortshoj et al., 2008; Ivanovski et al., 2018; Khalifa et al., 2015; Liu et al., 2019; Ly and Blakeley, 2019; Meczekalski et al., 2013; Nishimura et al., 2004; Rius et al., 2018; Sathasivam et al., 2013; Sheffield et al., 2018; Siegler et al., 2018; Tsai et al., 2012; Tyburczy et al., 2015; Uytingco et al., 2019; Zhang et al., 2011). Both tests of fPD and other CNS disease at ~60% matching rate were contrasted with the >90% rate generated from the 108 genes of CH (Fig. 3C vs. Fig. 6C&F). A mechanistic study elucidating disease-specific alterations of high mutation rates associated with proximity to telomeres and A + T content—as well as why CH demonstrates >90% accuracy while other genetic conditions of the CNS remain at ~60%—is warranted.

4. Discussion

We checked the two factors of telomere proximity and DNA composition focusing on AT-rich sequences in CH, fPD, AD, and a group of other genetic diseases—including neurofibromatosis (NF), tuberous sclerosis (TSC), Bardet-Biedl syndrome (BBS), and corpus callosum malformation (Fig. 1–6E and Fig. 6F). Chromosomal DNAs adjacent to telomeres are to some extent vulnerable to DNA damage or mutagenesis (Nusbaum et al., 2006). In this study, we considered this as being within 50 Mb from the chromosome ends (Nusbaum et al., 2006; Ritter et al., 1990). The threshold of 59% in A + T content is a genome-wide average reported in humans (Nusbaum et al., 2006). Telomeres, essentially characterized by a unique chromatin environment (Blasco, 2007), are composed of 3–20 kb of AT-rich repeats flanked by subtelomeric regions extending up to 300 kb into the chromosome (Misteli, 2014). In addition, tandem repeats of short GT-rich sequences are characteristic of almost all eukaryotic telomeres (McKnight and Shippen, 2004). Despite this repeated sequence and the number of repeats varying between species, human telomeres

range in size from 2 to 50 kb and consist of 300–8000 precise repeats of the sequence CCCTAA/TTAGGG. Moreover, a common feature of all telomeres is the orientation of the G-rich strand. In all cases, this strand comprises the 3′-end of the chromosome, while its terminal part is single-stranded, generating a G-tail (Blackburn et al., 2006). It is also noted that genes in close proximity to telomeres are silenced due to the repressive nature of specific telomere-binding proteins such as heterochromatin (Misteli, 2014). The degree of repression declines with distance from the telomere, limited to ~100 kb (Kulkarni et al., 2010). Taken together, telomeres are the specialized mechanisms protecting chromosomes, since cells do not tolerate the presence of unprotected chromosome ends (McClintock, 1941) (O'Connor, 2008).

Our detailed analysis using the aforementioned two criteria associated with high mutation rate is primarily dedicated to CH (Fig. 2–4), AD (Fig. 5), and fPD (Fig. 6) because these diseases have multiple genes involved, rather than a small number of genes reported. We found that a genetic disease can have multiple genes with several types of mutations: i) point mutation, ii) indels, iii) transpositions, iv) inversions, v) nondisjunctions, and vi) changes in the ploidy level (Loewe and Hill, 2010). For instance, Down Syndrome is the most common genetic disorder by prevalence (1 in 1000 live births worldwide). But it is not single or multiple genes with type i (point mutation) through type v (nondisjunctions) mutations, but the presence of a third copy of chromosome 21 that causes this syndrome. In this situation (type vi—the ploidy level mutations) (Loewe and Hill, 2010), our analysis is inappropriate.

Previously, we characterized three different models of hydrocephalus starting from human CSF assays (Shim et al., 2016; Shim et al., 2013; Shim et al., 2019). Hence, our genomic analysis was centered on factors associated with high mutation rates (Nusbaum et al., 2006) in hydrocephalus resulting from genetic mutations. One of the critical physiological parameters determining the diagnosis of hydrocephalus is intracranial pressure (ICP) (Eide et al., 2010), which is associated with a rapid increase in head circumference or macrocephaly (Robinson et al., 2018), the most obvious sign of hydrocephalus in infants. Elevated ICP, a primary symptom manifested as macrocephaly, distinguishes neonatal hydrocephalus from similar types of the brain conditions with ventriculomegaly such as periventricular leukomalacia found in cerebral palsy (Albright et al., 2005; Limbrick Jr. and Park, 2006). However, a rise in ICP in hydrocephalus should not be confused with idiopathic intracranial hypertension, or pseudotumor cerebri (Friedman and Jacobson, 2002). Interestingly, unlike the SLC12A7 gene as we surveyed in CH (Table 1), a splicing mutation in SLC12A3 gene is linked to idiopathic intracranial hypertension (Godefroid et al., 2006). This suggests that there might be a novel population of undiscovered genes causing intracranial hypertension in the absence of hydrocephalus.

Our projection of genes causing CH highlights distinct biological processes over time: neurogenesis and neurodegeneration. CH is found in children as an early onset, mostly. However, some forms of genetically driven hydrocephalus are late-onset and found in young adults as well. Thus, we thought that hydrocephalus from genetic mutations is not always as a result of birth defects, because a set of patients with NPH (usually found in elderly persons) is known to have hydrocephalus arising from genetic defects (Morimoto et al., 2019). As such, other than age, we have sought what other critical factors can better explain

CH. Since CH is primarily a CNS disease related with ‘abnormal neurogenesis’ or ‘generation’ as recently proposed (Furey et al., 2018a), we enthralled the idea that a CNS disease associated with ‘degeneration’ could potentially provide a valuable comparison. Thus, familial PD (fPD) was chosen, since there are more than 15 genes so far defined as PARK family genes.

In our investigation of these familial genes for fPD, we analyzed the dataset and found that it might be more meaningful to compare CH and “PD” with another type of degenerative disorder to investigate where each disease stands from a low-to-high matching rate standpoint with respect to the two factors utilized in this study. Hence, we have additionally surveyed Alzheimer’s Disease (AD). Surprisingly, AD was much more similar to CH than fPD was when comparing the matching rate using (i) proximity to telomeres and (ii) high A + T content—even though both AD and fPD are degenerative diseases of the CNS. Our interpretation is that genetic mutations that are highly associated with these two factors are sufficient to drive development of CH and AD in a similar manner. However, these factors might not be sufficient to explain the mutations detected in fPD, suggesting the involvement of ‘bigenic mechanisms’—such as environmental and genetic factors (Warner and Schapira, 2003). However, this observed discrepancy in fPD as compared to CH and/or AD does not exclude the possibility of acquired mutations (Veeriah et al., 2010) such as somatic mitochondrial DNA mutation (Coxhead et al., 2016).

Other than the two criteria tested in this study, linking a mutation to the disease through specific mediators might deepen our scientific understanding of the subject. For example, a more thorough evaluation of the phenotype revealing ‘hemorrhage’ in CH (Emmert et al., 2019; Shim et al., 2016; Shim et al., 2019) may shed light on mechanisms underlying PHH. Similarly, finding a phenotype of ‘age-related loss or toxin-induced injury in neural connectivity (Luk et al., 2012; Henderson et al., 2019)’ along the nigrostriatal pathway might better explain how genetic and environmental factors alike can contribute to the pathogenesis of fPD.

5. Conclusions

- Per the criteria of <50 Mbp proximity to telomeres and A + T content at >59%, the TMEM67 gene is associated with mutations causing CH due primarily to a high A + T content of 64% with a marginal proximity to telomeres. In contrast, the ZCCHC8 gene is associated with mutations causing CH due primarily to proximity to telomeres.
- Our results using the first factor suggests that causative genes located on chromosomes 18 to 22 more likely achieve a proximity to telomeres (<50 Mbp) due to short chromosomal length.
- Factor-nucleotide size relationships suggest that the full-length size of a gene causing CH, if it is longer than 6000 bp, likely shows high A + T content at >59%.
- If genes causing genetic diseases with mutations do not satisfy the two criteria or the factors according to the previous suggestions (Nusbaum et al., 2006):

- Causative mutations may be found in a region that is less likely to be mutated or
- Off-target effects (mutations) might dominate in an animal study or
- During evolution, genes causing CH in animals have not survived in humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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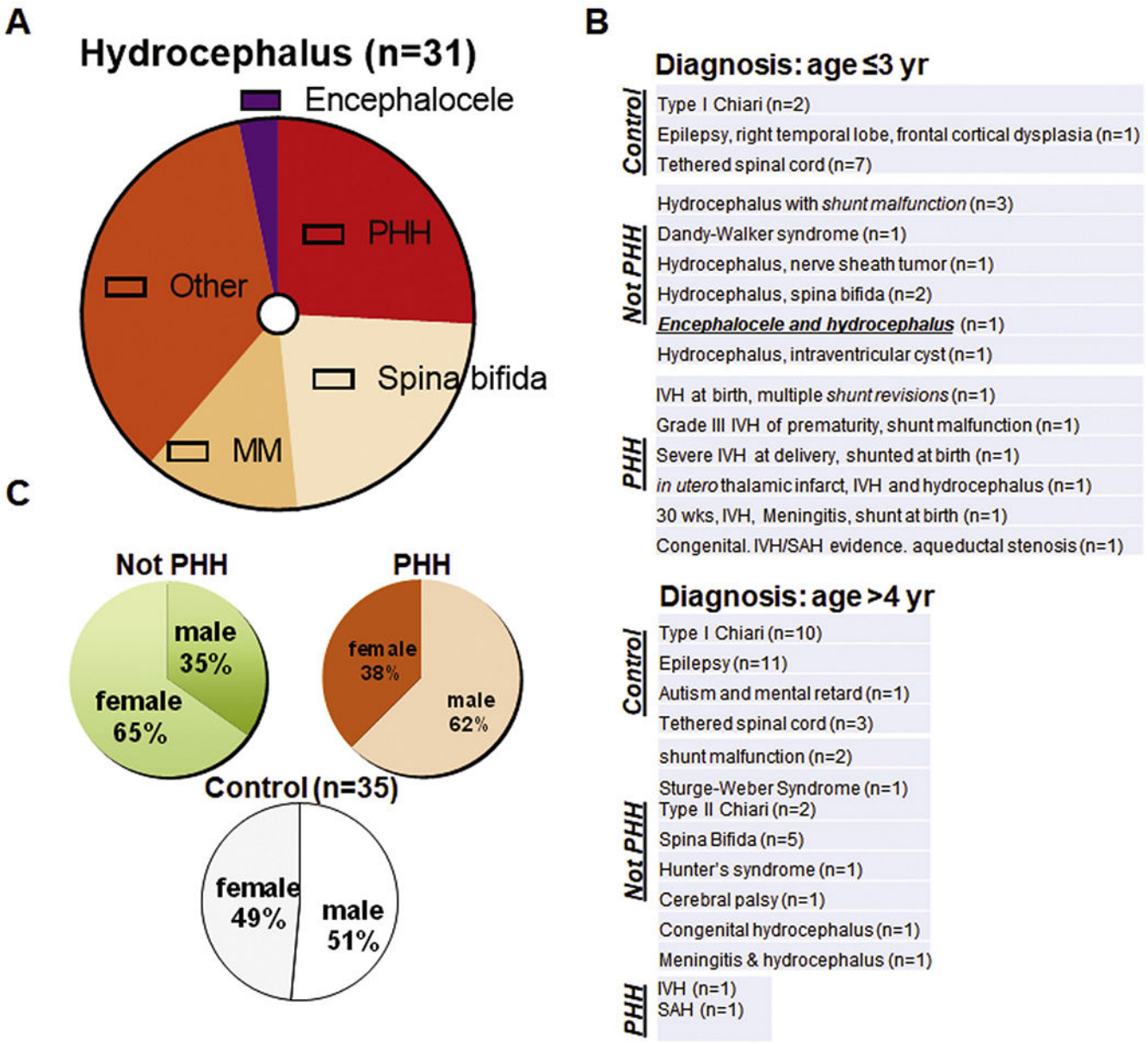

Fig. 1. Classification of pediatric hydrocephalus

(A) Diagram summarizing sub-classification of hydrocephalus in children into post-hemorrhagic hydrocephalus (PHH) and not-PHH group involving diagnosis such as spina bifida (23%), myelomeningocele (MM; 13%), encephalocele (3%) and other conditions. Secondary causes such as hemorrhage leading to post-hemorrhagic hydrocephalus (PHH) accounted for fewer than one in three cases (26%). Collectively, 71% patients at age 0–26 years (n = 31) were diagnosed as hydrocephalus other than PHH (Not PHH). (B) Summary showing the gist of diagnosis for younger (upper) and older (lower) age group. (C) Sex was evenly distributed within control (n = 35) and hydrocephalus group (n = 31). However, when hydrocephalus group was sub-divided into two, female-male ratio became not even in Not PHH and PHH group (age 0–26 years). Single center study (Shim et al., 2013).

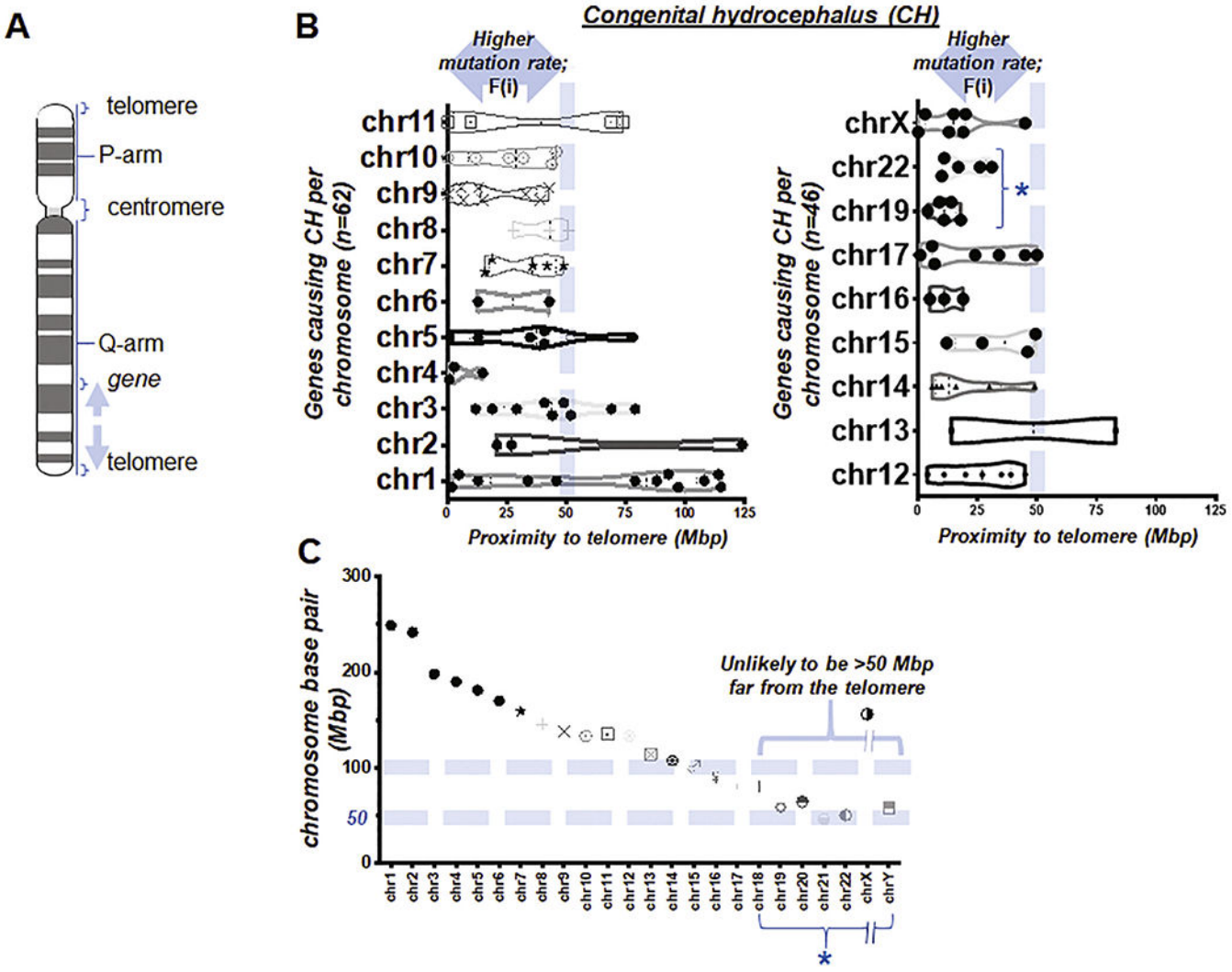

Fig. 2. Proximity to telomeres in genes known to cause CH

(A) Illustration simplified to indicate relative positions of telomeres, centromere, each arm, and a gene in a human chromosome (Nusbaum et al., 2006). Arrows indicate a distance between the gene and a telomere. (B) Box and violin plots showing the full distribution of the gene proximity to its telomere over chromosome (chr) 1 to 11 (left) and 12 to X (right). F(i) and * indicate 'the first factor or proximity to telomeres' and 'the group of chromosomes unlikely to be >50 Mbp distant from the telomere due to their short physical size (Morton, 1991)' (C) Length of all human chromosomes reported previously (Morton, 1991). * indicates the same in (B).

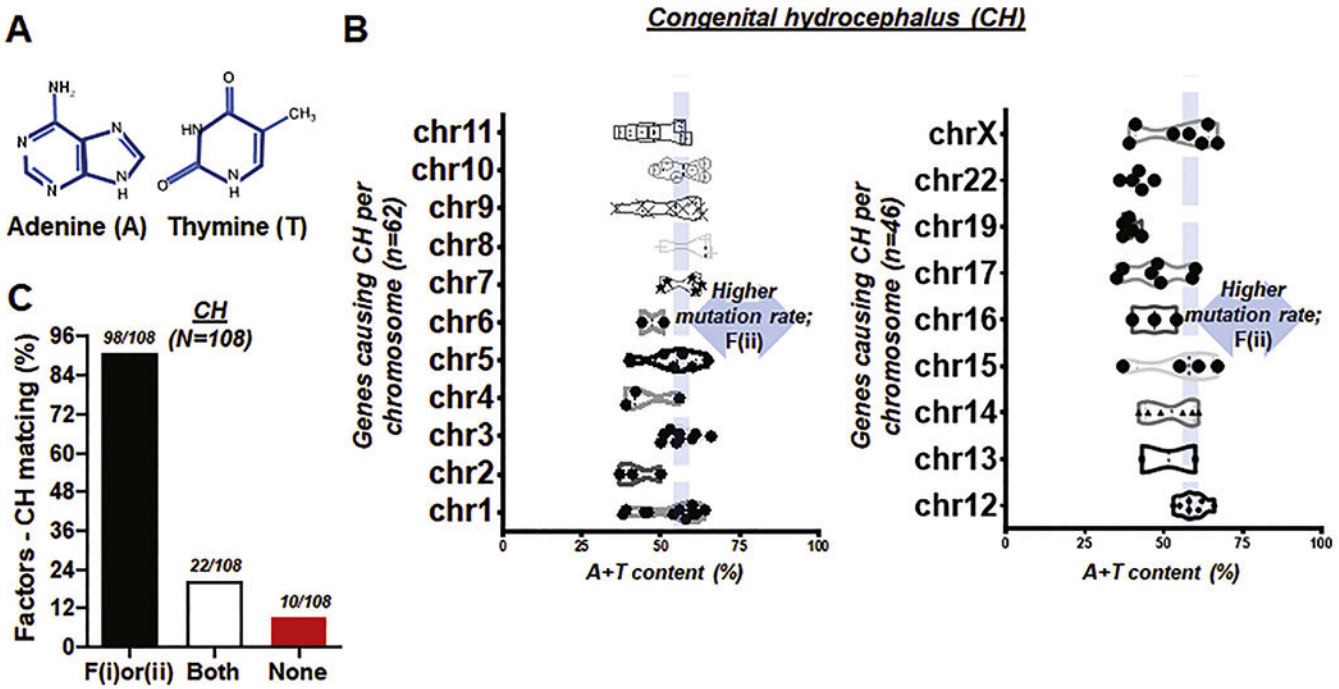

Fig. 3. A + T content of genes and factors-CH matching rate

(A) Illustration showing two of four chemical bases comprising DNA, adenine (A) and thymine (T) whose combined content is associated with high mutation rate in human chromosomes (Nusbaum et al., 2006). (B) Box and violin plots showing the full distribution of A + T content over chromosome (chr) 1 to 11 (left) and 12 to X (right). F(ii) indicates 'the second factor or A+T content' (C) Bar graph demonstrating factors-CH matching rate. 'F(*i*)or(ii)' represents the genes causing CH satisfying either proximity to telomeres within 50 Mbp or A + T content higher than 59%; 'Both' represents the genes meeting two factors alike. Total number of genes, $N = 108$. Matching rate at >90%.

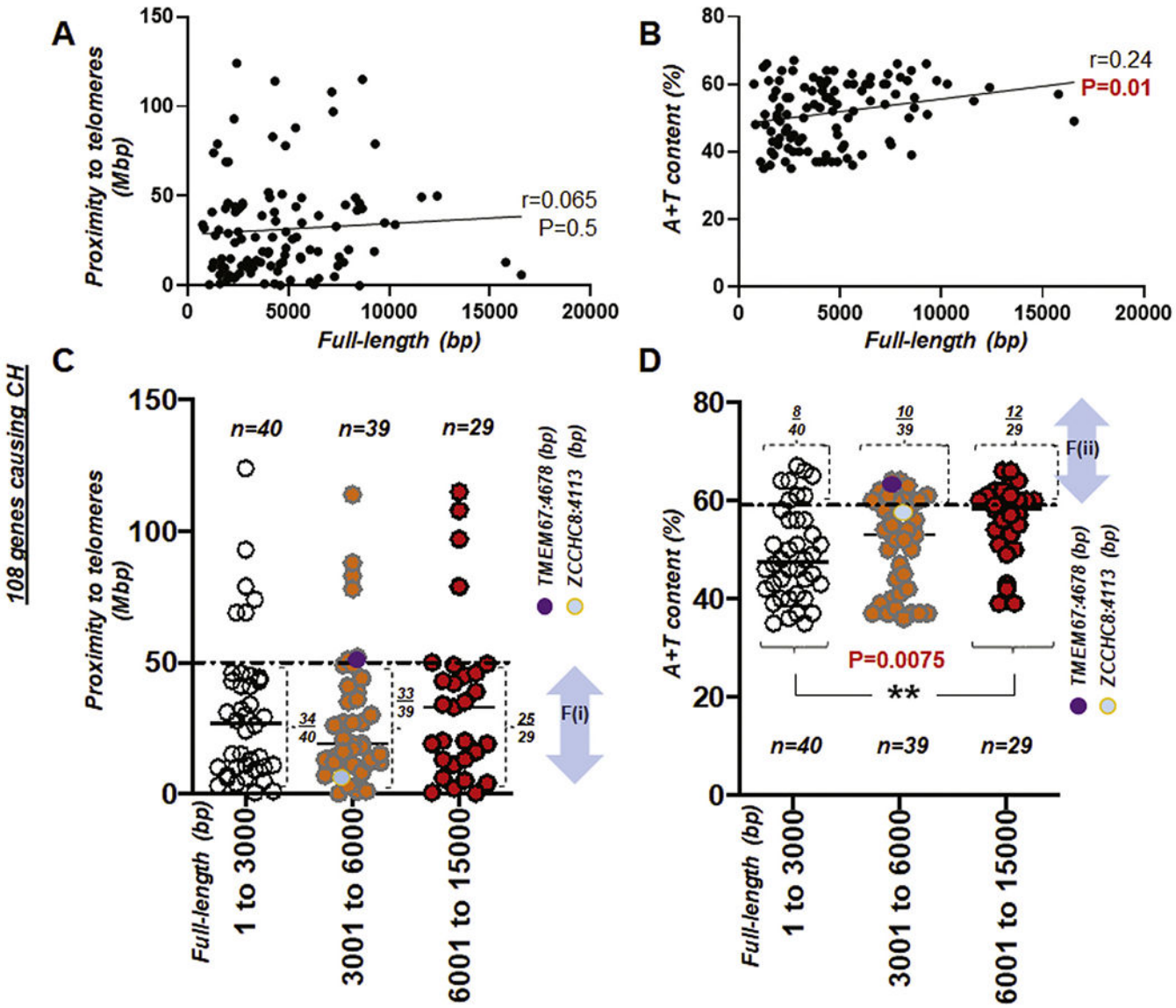

Fig. 4. Proximity to telomere and A + T content over gene length (bp)

(A) Scattered plot showing the Pearson correlation between the full length (bp) of genes causing CH and proximity to telomeres. (B) Scattered plot showing the Pearson correlation between the full length (bp) of genes causing CH and A + T content. r: Pearson coefficient (A-B). (C) Scattered plot showing 108 genes causing CH with proximity to telomeres over full-length size of the gene (bp). A horizontal dotted line indicates 50 Mbp. (D) Scattered plot summarizing 108 genes causing CH with A + T content over full-length size of the gene (bp). A horizontal dotted line indicates A + T content at 59%. F(i) and F(ii) indicate the first and second factor, respectively. Note that circles in purple and light blue indicate TMEM67 and ZCCHC8 gene in (C) and (D). **, $P < 0.01$.

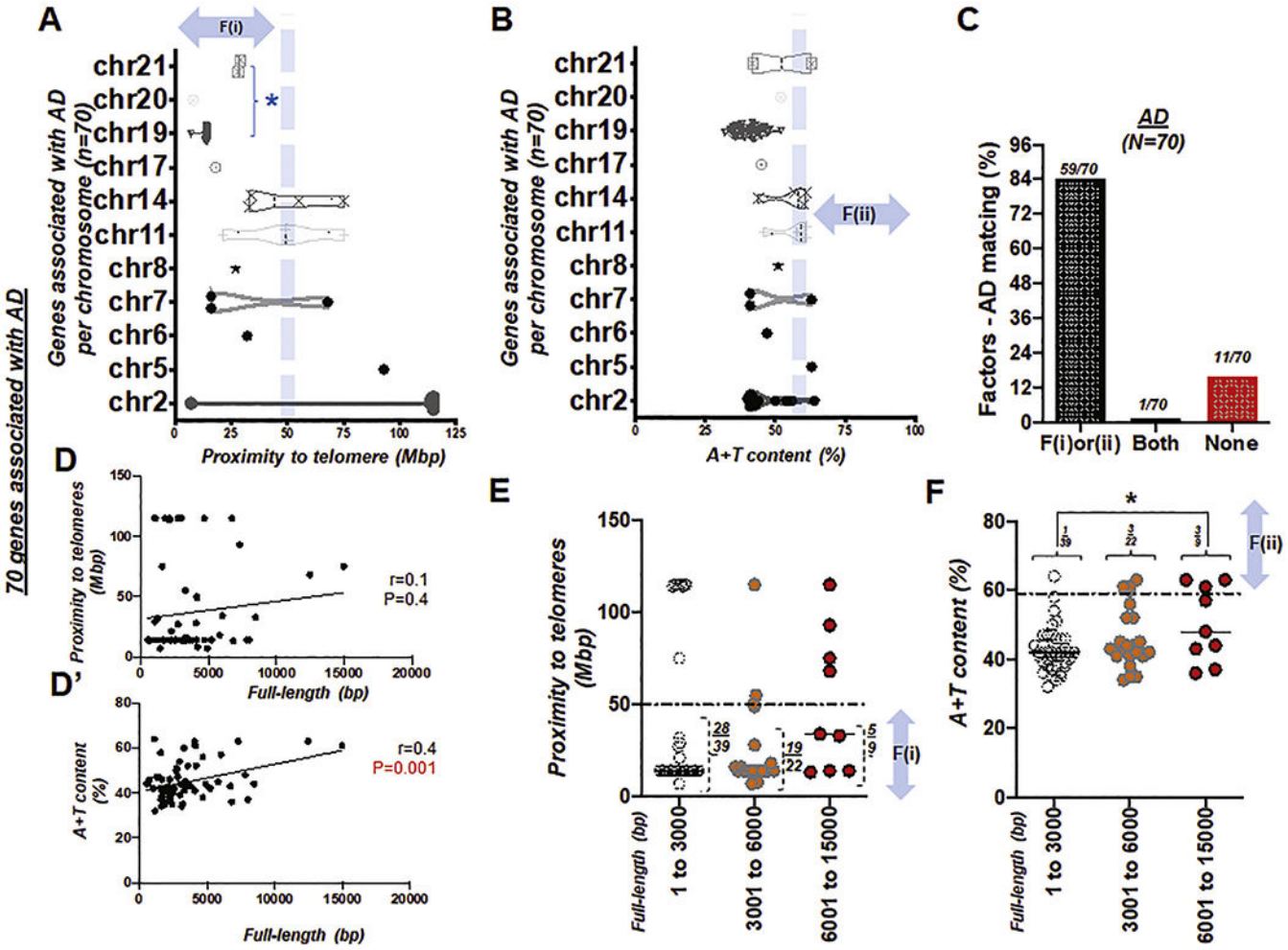

Fig. 5. Genes associated with Alzheimer's disease (AD), satisfying either proximity to telomeres or high A + T content

(A) Box and violin plots showing the full distribution of the gene proximity to its telomere over chromosome (chr) 1 to 21. An asterisk in blue, *, indicates 'the group of chromosomes unlikely to be >50 Mbp distant from the telomere due to their short physical size (Morton, 1991)' (B) Box and violin plots showing the full distribution of A + T content over chromosome (chr) 1 to 21. (C) Bar graph demonstrating factors-AD matching rate. Total number of genes, $N = 70$. Success (matching) rate at 84%. (D) Scattered plot showing the Pearson correlation between the full length (bp) of genes associated with AD and proximity to telomeres. (D') Scattered plot showing the Pearson correlation between the full length (bp) of genes associated with AD and A + T content, r: Pearson coefficient (D-D'). (E) Scattered plot showing 70 genes of AD with proximity to telomeres over full-length size of the gene (bp). A horizontal dotted line indicates 50 Mbp. (F) Scattered plot summarizing 70 genes of AD with A + T content over full-length size of the gene (bp). A horizontal dotted line indicates A + T content at 59%. F(i) and F(ii) indicate the first and second factor, respectively. An asterisk in black, *, $P < 0.05$.

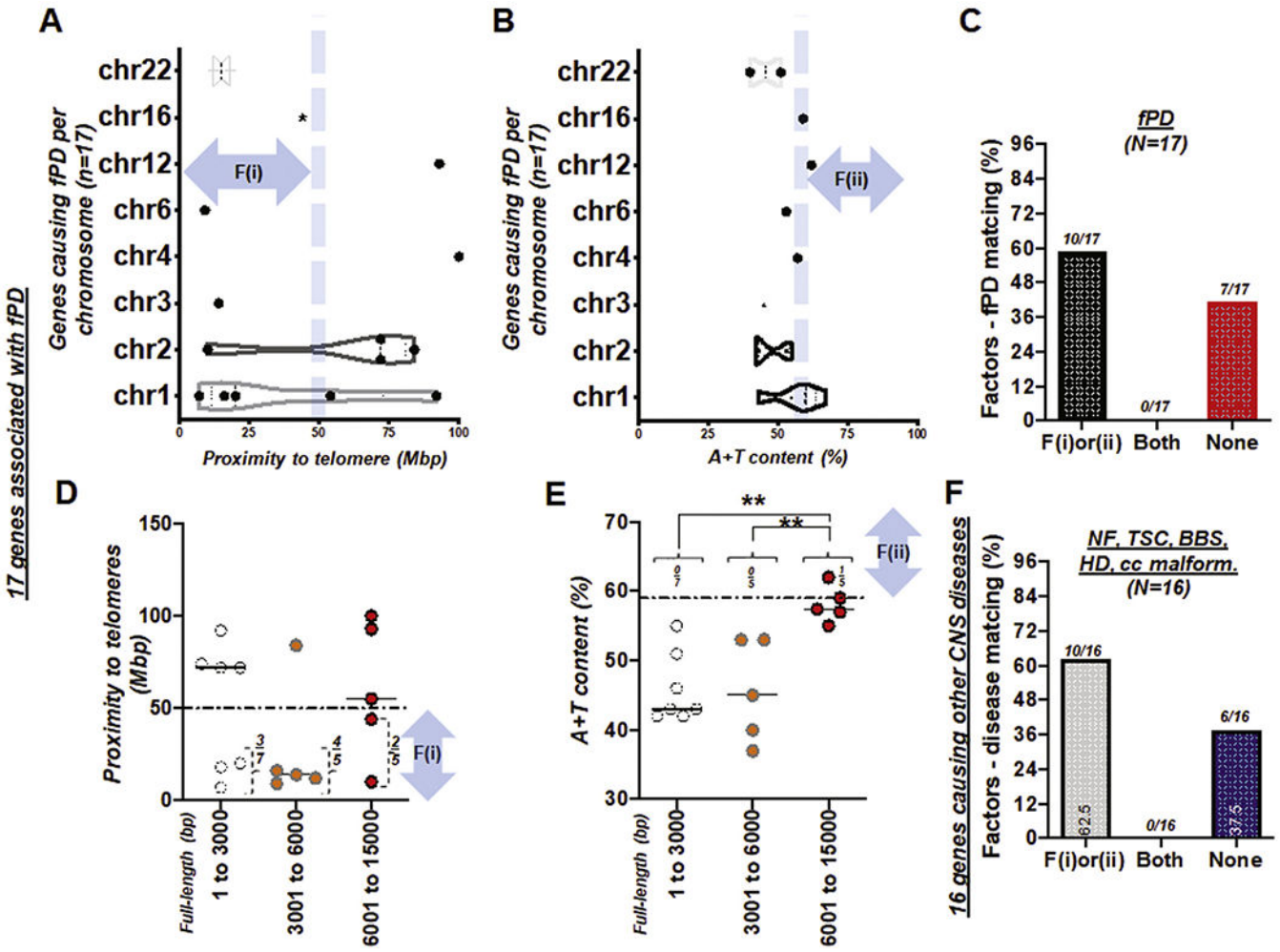

Fig. 6. Genes causing fPD and other genetic diseases of the CNS

(A) Box and violin plots showing the full distribution of the gene proximity to its telomere over chromosome (chr) 1 to 22. (B) Box and violin plots showing the full distribution of A + T content over chromosome (chr) 1 to 22. fPD: familial Parkinson's disease (A and B). (C) Bar graph demonstrating factors-fPD matching rate. Total number of genes, $N = 17$. Success (matching) rate at 59%. See also Table S6. (D) Scattered plot showing 17 genes causing fPD with proximity to telomeres over full-length size of the gene (bp). A horizontal dotted line indicates 50 Mbp. (E) Scattered plot summarizing 17 genes causing fPD with A + T content over full-length size of the gene (bp). A horizontal dotted line indicates A + T content at 59%. F(i) and F(ii) indicate the first and second factor, respectively. **, $P < 0.01$ (F) Bar graph demonstrating the factor-other diseases of the CNS matching rate. Total number of genes, $N = 16$. NF; neurofibromatosis ($n = 2$); TSC; tuberous sclerosis disease (n = 2); BBS ($n = 5$); HD ($n = 1$); CNS malformations involving agenesis of corpus callosum (cc; $n = 6$). Success (matching) rate at ~60%. See also Table S7.

Table 1

An outline of genes causing CH.

gene	class	protein	key functions	mutant phenotype	REF
AK7	2,4*	Adenylate Kinase 7	catalyzes the reversible phosphorylation of adenine nucleotides, and plays a role in energy homeostasis of cell	Primary ciliary dyskinesia, spermatogenic failure 27, non-syndromic male infertility due to sperm motility disorder, and CH	(Lores et al., 2018)
AK8	4	Adenylate Kinase 8	catalyzes the reversible transfer of the terminal phosphate group between nucleoside triphosphates and monophosphates	Reticular Dysgenesis, Fetal Akinesia Deformation Sequence 1, and CH	(Vogel et al., 2010)
AKT3	3	AKT Serine/Threonine Kinase 3	Regulator of the PI3K-AKT-mTOR pathway (especially in the nervous system) and is essential for the development of the brain and other parts of the body	Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome, other disorders	(Riviere et al., 2012)
ALG13	3,4	ALG13 UDP-N-Acetylglucosaminyltransferase Subunit	heterodimerizes with asparagine-linked glycosylation 14 homolog, helps to catalyze the second sugar addition of the highly conserved oligosaccharide precursor in endoplasmic reticulum N-linked glycosylation	Lennox-Gastaut syndrome, epileptic encephalopathy, and CH	(Epi et al., 2013)
AP1S2	3	Adaptor Related Protein Complex 1 Subunit Sigma 2	mediates the recruitment of clathrin to the membrane, as well as the recognition of sorting signals within the cytosolic tails of transmembrane receptors	Pettigrew syndrome, including choreoathetosis, Dandy-Walker malformation, seizures, iron/calcium deposition in the brain, and CH	(Cacciagli et al., 2014; Saillour et al., 2007)
ARHGAP31	3,4	Rho GTPase Activating Protein 31	Inactivates Cdc42 and Rac1 through stimulation of reaction to turn GTP into GDP	Adams-Oliver syndrome and CH	(Lehman et al., 1993)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
ARSB	4*	Arylsulfatase B	Removes sulfate group from dermatan sulfate and chondroitin sulfate to aid in lysosome digestion	mucopolysaccharidosis type VI and CH	(Valayannopoulos et al., 2010)
B3GALNT2	3,4	Beta-1,3-N-Acetylgalactosaminyltransferase 2	Involved in alpha-dystroglycan glycosylation	Walker-Warburg syndrome, cobblestone lissencephaly, eye malformations, profound mental disability, and CH	(Ducro et al., 2015)
B3GALTL	3	beta 3-glucosyltransferase	involved in a two-step glycosylation pathway to form a sugar structure made of fucose and glucose on a specific location of several different proteins	Peters plus syndrome (eye abnormalities, short stature, intellectual disability) and CH	(Schoner et al., 2013)
B3GNT1	4	*N*-acetyllactosaminide beta-1,3-*N*-acetylglucosaminyltransferase	Essential for the synthesis of poly-*N*-acetyllactosamine, a determinant for the blood group i antigen	Congenital muscular dystrophy and CH	(Czeschik et al., 2013)
BRAF	3,4	B-Raf proto-oncogene, serine/threonine kinase	The gene is also referred to as proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, while the protein is more formally known as serine/threonine-protein kinase B-Raf	a congenital anaplastic astrocytoma, a linear syringocystadenoma papilliferum, ocular abnormalities, and CH	(Watanabe et al., 2016)
CC2D2A	2,3,4	Coiled-Coil and C2 Domain Containing 2A	A coiled-coil and calcium binding protein that plays a critical role in cilia formation	Meckel syndrome type 6, Joubert syndrome type 9, and CH	(Bachmann-Gagescu et al., 2015)

gene	class	protein	key functions	mutant phenotype	REF
CCDC85C	1,4	Coiled-Coil Domain Containing 85C	plays a role in cell-cell adhesion and epithelium development through its interaction with proteins of the beta-catenin family	Congenital disorder of glycosylation, Type lie, obstructive hydrocephalus, and CH	(Tanaka et al., 2015)
CCDC88C	1	coiled-coil domain containing 88C	interacts with the dishevelled protein and is a negative regulator of the Wnt signaling pathway	autosomal recessive, primary non-syndromic CH	(Ruggeri et al., 2018)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
CCL2	1,4*	chemokine (C–C motif) ligand 2	Through signaling via the binding/ activation of CCR2, instigates a powerful chemotactic response and mobilization of calcium ions in the cell	Alopecia areata, neural tube defects, and CH	(Snowden et al., 2012)
CCND2	3	G1/S-specific cyclin-D2	Regulates G1-S transition step in the mitotic cycle and is regulated by the PI3K-AKT-mTOR pathway, influencing protein synthesis, cell proliferation and survival, and brain development	Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome	(Mirzaa et al., 2014)
CENPF	3,4	centromere protein F	Plays a role in chromosome segregation during mitotis by associating with the kinetochore in late G2 and maintaining this association through early anaphase	Stromme syndrome, intestinal atresia, ocular anomalies, renal and cardiac abnormalities, and CH	(Filges et al., 2016)
CEP83	2	Centrosomal protein 83	A centriolar protein involved in primary cilium assembly	Infantile nephronophthisis, intellectual disability, and CH	(Failler et al., 2014)
CFAP43	2	cilia and flagella associated protein 43	involved in sperm flagellum axoneme organization and function	Normal pressure hydrocephalus, spermatogenic failure 19, and CH	(Morimoto et al., 2019)
CFAP54	2	Cilia- And Flagella-Associated Protein 54	Required for assembly and function of cilia and flagella	Primary ciliary dyskinesia and CH	(McKenzie et al., 2015)
CRB2	1	crumbs cell polarity complex component 2	A member of a family of proteins that are components of the Crumbs cell polarity complex; important in early embryonic development	Cerebral ventriculomegaly and congenital nephrosis	(Slavotinek et al., 2015)
DAG1	3,4	dystroglycan 1	involved in laminin/basement membrane assembly, sarcolemmal stability, cell survival, peripheral nerve myelination, nodal structure, cell migration, and epithelial polarization	Walker-Warburg syndrome, limb-girdle muscular dystrophy, and CH	(Leibovitz et al., 2018)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
DNAAF1	2*	dynein axonemal assembly factor 1	involved in the regulation of microtubule-based cilia and actin-based brush border microvilli	Primary ciliary dyskinesia and CH	(Ha et al., 2016)
DNAH5	2,3	Dynein Axonemal Heavy Chain 5	Produces the force within cilia necessary to cause movement	Primary ciliary dyskinesia heterotaxy syndrome, and CH	(Ibanez-Tallon et al., 2002
DPCD	2	Deleted In Primary Ciliary Dyskinesia Homolog (Mouse)	involved in the generation and maintenance of ciliated cells	Primary ciliary dyskinesia and CH	(Vogel et al., 2010)
DYX1C1/ DNAAF4	2,4	Dynein axonemal assembly factor 4	encodes a tetratricopeptide repeat domain-containing protein that interacts with estrogen receptors and heat shock proteins	involved in the generation and maintenance of ciliated cells	(Chandrasekar et al., 2013)

gene	class	protein	key functions	mutant phenotype	REF
EML1	3	echinoderm microtubule-associated protein-like 1	Modulates the assembly and organization of the microtubule cytoskeleton, as well as likely the orientation of mitotic spindle and plane of cell division	Band heterotopia and CH	(Collin et al., 2020)
EN1	1	homeobox protein engrailed-1; transcription factor	The human engrailed homologs 1 and 2 encode homeodomain-containing proteins and have been implicated in the control of pattern formation during development of the central nervous system	Ectopic expression leads to agenesis of subcommissural organ (SCO), ependymal differentiation defects in choroid plexus and CH	(Louvi and Wassef, 2000)
FBN1	3,4	fibrillin 1	Provides instructions for making fibrillin-1, which is transported out of cells into the extracellular matrix	Geleophysic dysplasia, aqueductal stenosis, and CH	(Porayette et al., 2014)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
FGFR2	3,4*	fibroblast growth factor receptor 2	Promotes cell growth/division, maturation/ differentiation, bone development, angiogenesis, wound healing, and embryonic development	Apert syndrome, Beare-Stevenson cutis gyrate syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome, breast cancer, cholangiocarcinoma, epidermal nevus, other cancers, and CH	(Wenger et al., 1993)
FGFR3	3,4	fibroblast growth factor receptor 3	Regulates bone growth through the limitation of ossification in long bones	Achondroplasia, Crouzon syndrome with acanthosis nigricans, epidermal nevus, hypochondroplasia, Muenke syndrome, SADDAN, multiple cancers, and CH	(Bodensteiner, 2019)
FKRP	3,4	fukutin-related protein	Like fukutin, adds a molecule called ribitol 5-phosphate to the chain of sugars attached to a protein called alpha (α)-dystroglycan	Walker-Warburg syndrome, limb-girdle muscular dystrophy, congenital muscular dystrophy type 1C, and CH	(Yis et al., 2007)
FKTN	3,4	Fukutin	adds a molecule called ribitol 5-phosphate to the chain of sugars attached to a protein called alpha (α)-dystroglycan	Fukuyama congenital muscular dystrophy, Walker-Warburg syndrome, limb-girdle muscular dystrophy, and CH	(Arora et al., 2019)
FLNA	3,4	Filamin A, alpha	participates in the anchoring of membrane proteins for the actin cytoskeleton	Periventricular heterotopia and CH	(Sheen et al., 2004)
FOXJ1	1,2	Forkhead Box J1	regulates the transcription of genes that control the production of motile cilia	Systemic lupus erythematosus, allergic rhinitis, and CH	(Wallmeier et al., 2019)
FUZ	1	Fuzzy Planar Cell Polarity Protein	involved in the creation of cilia and directional movement of cells	Neural tube defects and CH	(Kousi and Katsanis, 2016)
FZD3	4	Frizzled Class Receptor 3	encode seven-transmembrane domain proteins that are receptors for the wingless type MMTV integration site family of signaling proteins	Fallopian Tube Serous Adenocarcinoma and CH	(Wang et al., 2014)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
GBA	4*	Acid beta-glucocerebrosidase	Plays a role in lysosome digestion by breaking glucocerebroside into glucose and ceramide	Gaucher disease, Parkinson disease, dementia with Lewy bodies, and CH	(Cindik et al., 2010; Hruska et al., 2008)

gene	class	protein	key functions	mutant phenotype	REF
GLI3	1,3	GLI Family Zinc Finger 3	One of the C2H2-type zinc finger proteins subclass of the Gli family; DNA-binding transcription factor, mediating SHH signaling	Greig cephalopolysyndactyly syndrome and CH	(Babbs et al., 2008; Balk and Biesecker, 2008)
GPSM2	3,4	G-protein-signaling modulator 2	Plays a significant role in mitotic spindle pole organization, as well as in the development of normal hearing	Nonsyndromic hearing loss, Chudley-McCullough syndrome, and CH	(Koenigstein et al., 2016)
HB-EGF	4	Heparin-binding EGF-like growth factor	Influences cell cycle progression, cell migration, and angiogenesis	Subarachnoid hemorrhage and CH	(Shim et al., 2016)
HRAS	3,4	GTPase HRas transforming protein p21	Once bound to Guanosine triphosphate, H-Ras will activate a Raf kinase like c-Raf, the next step in the MAPK/ERK pathway	Costello syndrome, cerebellar tonsillar herniation, and CH	(Gripp et al., 2010)
HYDIN	2	axonemal central pair apparatus protein	Central pair-dynein adaptor	Missing central pair projection, ciliary motility defect, and CH	(Davy and Robinson, 2003)
HYLS1	2,3	Hydrolethalus syndrome protein 1	Incorporated into centrioles and required for the formation of cilia	Hydrolethalus syndrome, macrocephaly, midline cleft-lip, polydactyly, and CH	(Belengeanu et al., 2011)
IFT172	3,4	intraflagellar transport 172	encodes a subunit of the intraflagellar transport subcomplex IFT—B, which is necessary for ciliaryassembly and maintenance	Polydactyly, short-rib thoracic dysplasia, Joubert syndrome, and CH	(Friedland-Little et al., 2011)
ISLR2	4	Immunoglobulin Superfamily Containing Leucine Rich Repeat 2	Required for axon extension during neural development	Hernia, hiatus, chicken egg allergy, and CH	(Alazami et al., 2019)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
ISPD/crppa	3,4*	Isoprenoid Synthase Domain-Containing Protein/CDP-L-Ribitol Pyrophosphorylase A	helps produce ribitol 5-phosphate, which is added to alpha (α)-dystroglycan	Walker-Warburg syndrome, limb-girdle muscular dystrophy, and CH	(Roscioli et al., 2012)
KIAA0586	2,3	Homolog of TALPID3	A centrosomal protein required for ciliogenesis and Polydactyly, abnormal dorsal	Polydactyly, abnormal dorsal patterning of the neural tube and CH	(Alby et al., 2015)
KIF7	2,3	kinesin family member 7	Provides instructions for making primary cilia	Growth retardation, infantile spasms, acrocallosal syndrome, and CH	(Tunovic et al., 2015)
L1CAM	3,4	L1 protein family cell adhesion molecule	Cell migration and adhesion	L1 syndrome or CRASH (corpus callosum hypoplasia, retardation, aphasia, spastic paraplegia, and hydrocephalus)	(Fransen et al., 1995)
LAMB1	4	Laminin Subunit Beta 1	involved in cell attachment, chemotaxis, and binding to the laminin receptor, as well as capable of inhibiting metastasis	Lissencephaly 5 (seizures and severely delayed psychomotor development) and CH	(Radmanesh et al., 2013)
LARGE	3,4	LARGE xylosyl- and glucuronyltransferase 1	adds chains of sugar molecules composed of xylose and glucuronic acid to alpha (α)-dystroglycan	Walker-Warburg syndrome, congenital muscular dystrophy type 1D, and CH	(Kousi and Katsanis, 2016)
LRRC48	2,3	Leucine-Rich Repeat-Containing Protein 48	key regulator of ciliary/flagellar motility which maintains the alignment and integrity of the distal axoneme and regulates microtubule sliding in motile axonemes	Smith-Magenis syndrome, primary ciliary dyskinesia, and CH	(Ha et al., 2016)

gene	class	protein	key functions	mutant phenotype	REF
MAF	3,4	MAF BZIP Transcription Factor	Regulates development of embryonic lens fiber cell, increased susceptibility of T-cells to apoptosis, and terminal differentiation of chondrocytes	Coloboma, multiple myeloma, Aymegripp syndrome, Cataract 21-multiple types, and CH	(Niceta et al., 2015)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
MBOAT7	4*	Membrane Bound O-Acyltransferase Domain Containing 7	involved in the reacylation of phospholipids as part of the phospholipid remodeling pathway known as the Land cycle	Mental retardation (autosomal recessive 57), Autosomal Recessive Non-Syndromic Intellectual Disability, and CH	(Vogel et al., 2010)
MKS1	2,3	Meckel Syndrome Type 1	A part of the flagellar apparatus basal body proteome, required for cilium formation	Meckel syndrome, BBS, and CH	(Nabhan et al., 2015)
MKS4	2,3	Meckel syndrome type 4	a centrosomal protein that plays an important role in centrosome and cilia development	Suppression of ciliogenesis and hydrocephalus	(Rachel et al., 2015)
MPDZ	4	Multiple PDZ Domain Crumbs Cell Polarity Complex Component	Interacts with HTR2C receptor, causing potential clumping at cell surface	Hydrocephalus, congenital, 2, with or without brain or eye anomalies	(Yang et al., 2019)
MSX1	3	Msh homeobox 1; transcription factor	a transcriptional repressor during embryogenesis	SCO agenesis; neuroependymal denudation and CH	(Bach et al., 2003)
MYH9	4	Myosin Heavy Chain 9	involved in cytokinesis, cell migration, polarization and adhesion, maintenance of cell shape, and signal transduction	Macrothrombocytopenia, inclusion bodies, nephropathy, and CH	(Belal and Al Menabawy, 2017)
NAPA	4	Alpha-soluble NSF attachment protein	involved in the intra-cellular trafficking and fusing of vesicles to target membranes in cells	Hydrocephalus with hop gait; male hyh mice with a strongly reduced fertility	(Batiz et al., 2009)
NF1	4	Neurofibromatosis type 1	A GTPase-activating protein that negatively regulates RAS/MAPK by accelerating the hydrolysis of Ras-bound GTP	Macrocephaly, vasculopathy, aqueduct stenosis, cancer, and CH	(Nix et al., 2020)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
NME5	2,4*	NME/NM23 Family Member 5	Confers protection from cell death by Bax and alters the cellular levels of several antioxidant enzymes, including Gpx5	Nemaline myopathy 5, primary ciliary dyskinesia, and CH	(Anderegg et al., 2019)
NME7	4	NME/NM23 Family Member 7	catalyzes phosphate transfer from nucleoside triphosphates to nucleoside diphosphates	Venous thromboembolism, dextrocardia with situs inversus, deafness, and CH	(Vogel et al., 2010)
NRAS	3,4	Neuroblastoma Proto-Oncogene, GTPase	The N-ras proto-oncogene is a member of the Ras gene family. It is mapped on chromosome 1, and it is activated in HL60, a promyelocytic leukemia line	Congenital melanocytic nevus syndrome and CH	(Recio et al., 2017; Uguen et al., 2015)
OFD1	1	OFD1 Centriole and Centriolar Satellite Protein	Appears to play a role in the early development of the brain, limbs, and kidney	Joubert syndrome, polycystic kidney, and CH	(Field et al., 2012)
PAC1/klf6	4	pituitary adenylate cyclaseactivating polypeptide type I receptor	This gene encodes a member of the kinesin family of proteins. Members of this family are part of a multisubunit complex that functions as a microtubule motor in intracellular organelle transport.	Reduced neuronal proliferation, increased apoptosis in the developing cortex, reduced cerebral cortex, corpus callosu, and subcommissural organ with CH	(Lang et al., 2006; Picketts, 2006)
PAX6	1	Paired box protein 6	acts as a “master control” gene for the development of eyes and other sensory organs	SCO agenesis and CH	(Estivill-Torrus et al., 2001)

gene	class	protein	key functions	mutant phenotype	REF
PI3K	4	Phosphoinositide-3-kinase	A group of genes that produce an enzyme involved in cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking	Cancers, other disorders	(Roy et al., 2019)
PIK3CA	3,4	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha	Produces a subunit of an enzyme important for cell proliferation and migration, protein production, intracellular materials transport, and cell survival	Klippel-Trenaunay syndrome, megalencephaly-capillary malformation syndrome, epidermal nevus, cancers, other disorders	(Riviere et al., 2012)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
PLOD2	3*	procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	a membrane-bound homodimeric enzyme that is localized to the cisternae of the rough endoplasmic reticulum. The enzyme catalyzes the hydroxylation of lysyl residues in collagen-like peptides.	Abnormal neurogenesis and prenatal communicating CH	(Furey et al., 2018a; Furey et al., 2018b)
POMGNT1	3,4	protein O-linked mannose *N*-acetylglucosaminyltransferase 1	encodes a type II transmembrane protein that participates in O-mannosyl glycosylation and is specific for alpha linked terminal mannose. involved in the presentation of the laminin-binding	Walker-Warburg syndrome, limb-girdle muscular dystrophy, muscle-eye-brain disease, and CH	(Vervoort et al., 2004)
POMK	3,4	protein O-mannose kinase	O-linked carbohydrate chain of alpha-dystroglycan (a-DG), which forms transmembrane linkages between the extracellular matrix and the exoskeleton	Walker-Warburg syndrome, heteropia, limb-girdle muscular dystrophy, and CH	(Preiksaitiene et al., 2020)
POMT1	4	protein O-mannosyltransferase 1	Along with POMT2, helps modify α-dystroglycan through glycosylation via the addition of mannose; this anchors the structural framework of the cytoskeleton to the ECM	Walker-Warburg syndrome, limb-girdle muscular dystrophy, muscle-eye-brain disease, and CH	(Currier et al., 2005)
POMT2	4	protein O-mannosyltransferase 2	Along with POMT2, helps modify α-dystroglycan through glycosylation via the addition of mannose; this anchors the structural framework of the cytoskeleton to the ECM	Walker-Warburg syndrome, limb-girdle muscular dystrophy, muscle-eye-brain disease, and CH	(van Reeuwijk et al., 2005)
PTCH1	1,3	patched 1	Receptor of Sonic Hedgehog in SHH pathway, which is essential in early cell growth and specialization	Gorlin syndrome, nonsyndromic holoprosencephaly, coloboma, cancers, and CH	(Furey et al., 2018a)
PTEN	4	phosphatase and tensin homolog	Provides instructions for making an enzyme that acts as a tumor suppressor	Enlargement of midbrain structures and CH	(Ohtoshi, 2008)
PTPN11	3	protein tyrosine phosphatase, non-receptor type 11	helps regulate the RAS/MAPK signaling pathway	Noonan syndrome, cancers, and CH	(Zheng et al., 2018)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
RAF1	3,4*	Raf-1 proto-oncogene, serine/threonine kinase	part of the ERK1/2 pathway as a MAP kinase (MAP3K) that functions downstream of the Ras subfamily of membrane associated GTPases	Abnormal brain vasculature and CH	(Zarate et al., 2014)
RFX3	4	Regulatory factor X3	a transcriptional activator that can bind DNA as a monomer or as a heterodimer with other RFX family members.	neuroependymal defects and CH	(Baas et al., 2006)

gene	class	protein	key functions	mutant phenotype	REF
RFX4	4	Regulatory factor X4; transcription factor	a transcriptional repressor, which encodes transcription factors that contain a highly-conserved winged helix DNA binding domain	SCO agenesis; severe midline structure defects and CH	(Blackshear et al., 2003)
RPS6KA3	3,4	Ribosomal protein S6 kinase alpha-3	Involved in cellular proliferation, differentiation, and apoptosis and is important in pathways in the brain responsible for learning, the formation of long-term memories, and the survival of nerve cells	Coffin-Lowry syndrome,	(Kousi and Katsanis, 2016)
RSPH9	2	radial spoke head component 9	component of the axonemal radial spoke head	Primary ciliary dyskinesia and CH	(Zou et al., 2020)
RUVBL1	4	RuvB Like AAA ATPase 1	associates with several multisubunit transcriptional complexes and with protein complexes involved in both ATP-dependent remodeling and histone modification	Retinitis pigmentosa 50, hemangioma of spleen, and CH	(Dafinger et al., 2018)
SGSM3	4	small G protein signaling modulator 3	play a cooperative role in NF2-mediated growth suppression of cells	Protein-altering mutations found in human cases of CH	(Furey et al., 2018a)
SKI	3,4	Sloan-Kettering Institute (SKI) proto-oncogene	Controls TGF- β pathway by binding to certain SMAD proteins, thus interrupting pathway signaling	Shprintzen-Goldberg syndrome and CH	(O'Dougherty et al., 2019)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
SLC12A7	4*	Solute Carrier Family 12 Member 7	Mediates electroneutral potassium-chloride cotransport when activated by cell swelling	Agenesis of corpus callosum with peripheral neuropathy, renal tubular acidosis, and CH	(Jin et al., 2019)
SMARCB1	3,4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	regulates gene activity and expression by chromatin remodeling via the SWI/SNF protein complexes	Coffin-Siris syndrome, Rhabdoid tumor predisposition syndrome, Schwannomatosis, and CH	(Diets et al., 2019)
SMARCC1	1,4	SWI/SNF complex subunit	The encoded protein is part of the large ATP-dependent chromatin remodeling complex SWI/SNF and contains a predicted leucine zipper motif typical of many transcription factors	Abnormal neurogenesis and prenatal communicating CH	(Furey et al., 2018a; Furey et al., 2018b)
SNX10	4	Sorting Nexin 10	a member of the sorting nexin family, involved in intracellular trafficking	Osteopetrosis, corpus callosum hypoplasia and CH	(Megarbane et al., 2013)
SNX27	4	Sorting Nexin Family Member 27	involved in endocytosis of plasma membrane receptors and protein trafficking	Epileptic encephalopathy, epilepsy, and CH	(Wang et al., 2016)
SOCS7	4	Suppressor of cytokine signaling 7	a target gene of microRNA-145, regulating interferon-b	A smaller body size and early neonatal death due to CH	(Krebs et al., 2004)
SPEF2	2,4	Sperm Flagellar 2	Plays a role in localization of the intraflagellar transport protein IFT20 to the manchette, and required for correct axoneme development in spermatozoa	Spermatogenic failure 43, primary ciliary dyskinesia, and CH	(Finn et al., 2014)
STK36	2	Serine/Threonine Kinase 36	positive regulator of the GLI zinc-finger transcription factors	Primary ciliary dyskinesia and CH	(Merchant et al., 2005)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**

gene	class	protein	key functions	mutant phenotype	REF
TBC1D7	3*	TBC1 domain family member 7	Subunit of the TSC1-TSC2 complex and component of the TSC-TBC complex, regulates cell growth and differentiation, participates in the proper sensing of growth factors and glucose	Macrocephaly/megalencephaly syndrome (autosomal recessive)	(Lim and Crino, 2013)
TBX1	3,4	T-Box Transcription Factor 1	Aids formation of tissues and organs during embryonic development by binding to specific areas of DNA	22q11.2 deletion syndrome, heart defects, cleft palate, hearing loss, and CH	(Kousi and Katsanis, 2016)
TGFBR1	3,4	Transforming Growth Factor Beta Receptor 1	Forms part of the TGF- β signaling pathway	Loeys-Dietz syndrome, familial thoracic aortic aneurism and dissection, prostate cancer, other cancers, and CH	(Yang et al., 2008)
TMEM216	2,3	Transmembrane protein 216	Part of the tectonic-like complex which is required for tissue-specific ciliogenesis and may regulate ciliary membrane composition	Meckel syndrome type 2, Joubert syndrome 2 also known as Cerebello-oculorenal syndrome 2, and CH	(Edvardson et al., 2010; Kousi and Katsanis, 2016)
TMEM67	2,3	Meckelin or transmembrane protein 67	centriole migration to the apical membrane and formation of the primary cilium	Meckel syndrome type 3 (MKS3), Joubert syndrome type 6 (JBTS6), and hydrocephalus	(Shim et al., 2019; Smith et al., 2006)
TRIM71	1,4	Tripartite motif family protein 71	One of group 1 members, which possesses a variety of C-terminal domains, and are represented in both vertebrate and invertebrates	Abnormal neurogenesis and prenatal communicating CH	(Furey et al., 2018a; Furey et al., 2018b)
ULK4	4	unc-51 like kinase 4	Plays a role in neuronal growth and endocytosis, specifically in neurite branching, neurite elongation and overall neuronal migration	Schizophrenia, bipolar disorder, autism, and CH	(Liu et al., 2016a)
VANGL1	1	VANGL planar cell polarity protein 1	Mediates intestinal trefoil factor induced wound healing in intestinal mucosa	Caudal regression sequence, neural tube defect	(Yamasaki and Kanemura, 2015)
gene	**class**	**protein**	**key functions**	**mutant phenotype**	**REF**
VANGL2	1*	VANGL planar cell polarity protein 2	Involved in planar cell polarity (especially in the steriociliary bundles of the cochlea), neural plate development, and polarization and movement of myocardializing cells	Neural tube defect	(Bubenshchikova et al., 2012)
WASL/n-wasp	3,4	WASP Like Actin Nucleation Promoting Facto	interacts with several proteins involved in cytoskeletal organization, including cell division control protein 42 (CDC42) and the actin-related protein-2/3 (ARP2/3) complex	Wiskott-Aldrich Syndrome, Buruli Ulcer, and CH	(Jain et al., 2014)
WDR81	3,4	WD repeat domain 81	plays a role in endolysosomal trafficking	Cerebellar ataxia, severe mental disability, disequilibrium syndrome 2, and CH	(Cappuccio et al., 2017)
ZCCHC8	2,4	zinc finger CCHC domain-containing protein 8	an accessory factor to the nuclear RNA exosome complex	Pulmonary fibrosis and hydrocephalus	(Gable et al., 2019)
ZIC2	1	Zic family member 2	Provides instructions for making a protein that plays an important role in the development of the forebrain	Neural tube defect, holoprosencephaly and CH	(Yamasaki and Kanemura, 2015)
ZIC3	1,3	Zinc finger protein ZIC 2	A transcription factor in early stages of left-right axis formation	Dandy-Walker malformation, neural tube defects, and CH	Grinberg and Millen, 2005)

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* class 1–4 (neurulation, cilia, syndrome, others).