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The Genetic Basis of Hydrocephalus

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Annu. Rev. Neurosci. 2016. 39:409–35

First published online as a Review in Advance on May 2, 2016

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

This article's doi: 10.1146/annurev-neuro-070815-014023

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Keywords

ventriculomegaly, cerebrospinal fluid, aqueductal stenosis, multifactorial disorder

Abstract

Studies of syndromic hydrocephalus have led to the identification of >100 causative genes. Even though this work has illuminated numerous pathways associated with hydrocephalus, it has also highlighted the fact that the genetics underlying this phenotype are more complex than anticipated originally. Mendelian forms of hydrocephalus account for a small fraction of the genetic burden, with clear evidence of background-dependent effects of alleles on penetrance and expressivity of driver mutations in key developmental and homeostatic pathways. Here, we synthesize the currently implicated genes and inheritance paradigms underlying hydrocephalus, grouping causal loci into functional modules that affect discrete, albeit partially overlapping, cellular processes. These in turn have the potential to both inform pathomechanism and assist in the rational molecular classification of a clinically heterogeneous phenotype. Finally, we discuss conceptual methods that can lead to enhanced gene identification and dissection of disease basis, knowledge that will potentially form a foundation for the design of future therapeutics.

Contents

DEFINITION

The first documentation of cases of hydrocephalus is attributed to Hippocrates (ca. 460–ca. 370 BC), who postulated that the observed enlargement of patients' heads was secondary to fluid collection in the brain. The Roman physician Galen (129–ca. 200 AD) delineated the clinical and pathological signs of the disorder further through his neuroanatomical observations and pioneered surgical procedures for treating hydrocephalus. Since then, many definitions have been proposed in an effort to best describe this heterogeneous disorder. Broadly, hydrocephalus is defined as the abnormal accumulation of cerebrospinal fluid (CSF) within the ventricles and the subarachnoid space of the brain, causing accelerated head growth and, in most cases, requiring surgical intervention (Schrander-Stumpel & Fryns 1998). More recently, Rekate (2008) sought to develop a consensus statement, defining hydrocephalus as "an active distension of the ventricular system of the brain resulting from inadequate passage of cerebrospinal fluid from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation."

ANATOMY AND PHYSIOLOGY OF HYDROCEPHALUS

CSF is produced continuously starting at the sixth week of gestation by the choroid plexus and flows within the lateral, third, and fourth ventricles (**Figure 1*a***). Interstitial fluid from the brain parenchyma also contributes to the final CSF volume in the human brain (40–50 mL in neonates, 65–140 mL in children, and 140–170 mL in adults); in total, 500–600 mL of CSF is produced daily at a rate of 0.4 mL/min, a fluid production rate comparable only to that of the cells of the renal proximal tubule and pancreatic ducts (Burg & Orloff 1968, Cserr 1971).

The CSF path starts with secretion in the lateral ventricles, flow through the foramina of Monro into the third ventricle, and passage through the aqueduct of Sylvius into the fourth ventricle. CSF then exits the ventricular system via the foramina of Luschka and the medial aperture of the foramina of Magendie into the cisternae magna, toward the cortico-subarachnoid space and spinal subarachnoid space (**Figure 1*a***). Subsequently, CSF is absorbed, primarily by the arachnoid granulations of the subarachnoid space, and is drained into the venous sinuses; a small

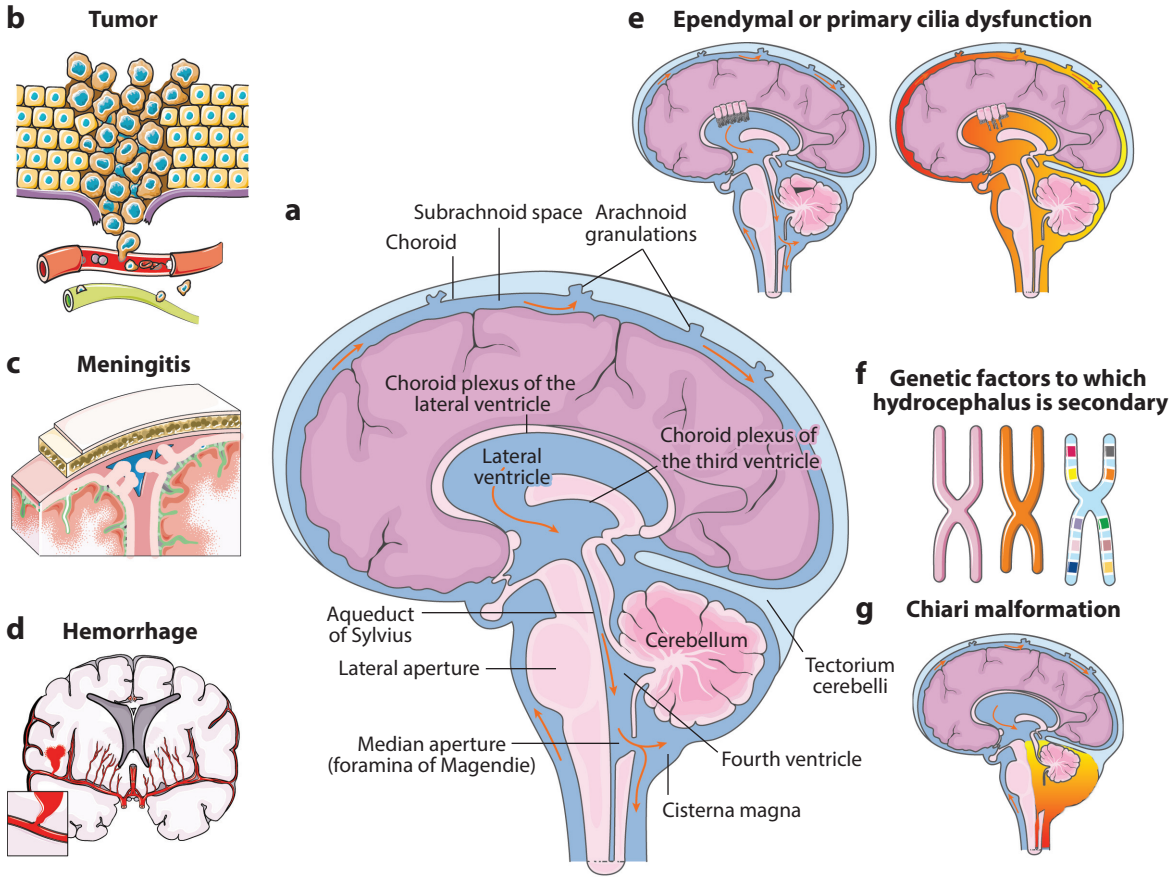


Figure 1

Schematic of causes of hydrocephalus. (*a*) Hydrocephalus can arise owing to obstruction of the CSF flow anywhere across the ventricular path that starts from the choroid plexus, where CSF is produced, and concluding with the spinal cord, where it is reabsorbed. Orange arrows highlight the path across which CSF flows in the ventricular system. Hydrocephalus is a multifactorial disorder that can arise as a result of genetic and/or environmental insults. Among the most common environmental causes underlying hydrocephalus are plexus or other tumors (*b*); infections of the ventricular system by agents such as enterovirus, cytomegalovirus, toxoplasmosis, or lymphocytic choriomeningitis (*c*); and cryptic microhemorrhages or other parenchymal hemorrhages that are especially common in premature infants (*d*). (*e*) Occlusion of the CSF flow can arise owing to abnormal or asynchronous beating of the ependymal cilia lining the ventricular system. (*f*,*g*) Finally, hydrocephalus can develop in the context of several genetic disorders (*f*) in which it can either comprise a primary clinical feature or develop secondary to other structural central nervous system malformations, as is the case in neural tube defects (*g*). This figure was prepared using Servier Medical Art (**http://www.servier.com/Powerpoint-image-bank**).

amount of CSF is also reabsorbed through the nerve roots of the spine. Given this travel path, hydrocephalus has been thought to occur whenever there is blockage in the ventricular system, subarachnoid space, or venous sinuses or defects in the direction of flow. Recently, clearance of CSF was shown to depend not only on the traditional unidirectional CSF flow but also on cardiac pulsatile movements directing CSF through the foramen magnum, into the spinal arachnoid space, and back into the skull into the brain parenchyma (Iliff et al. 2012). Perturbations in the pulsatile movements have been described in both human and murine hydrocephalus, although researchers still debate whether this dysfunction is the cause of hydrocephalus or a consequence of the disease (Qvarlander et al. 2013).

CLINICAL STRATIFICATION OF HYDROCEPHALUS

Investigators have proposed several different classification systems for hydrocephalus over the past years, guided primarily by clinical characteristics (reviewed in Oi 2011).

1. Onset: Hydrocephalus can be recognized either prenatally or postnatally. The latter can be subdivided further into neonatal, infantile, childhood, or adult types. Different ages at onset are considered indicative of different underlying causes: Fetuses and neonates are thought likely to present with hydrocephalus owing to intraventricular hemorrhage or genetic causes, whereas infants are more likely to have hydrocephalus owing to congenital malformations such as aqueductal stenosis or Chiari or Dandy-Walker malformation. In older children, the cause can be either idiopathic or acquired, with tumors being one of the main determinants (Corns & Martin 2012). Finally, in elder patients, hydrocephalus is almost always acquired through causes such as subarachnoid hemorrhage, trauma, infection, tumor, inflammation, or complications from surgery.
2. Location of lesion: The differentiation between nonobstructive or communicating hydrocephalus and obstructive or noncommunicating hydrocephalus was introduced over a century ago and remains in common use to describe clinical features (Dandy & Blackfan 1913). Distinction between the two conditions is based on whether CSF is communicating freely between the ventricles and the subarachnoid space or whether this flow is obstructed because of a discrete lesion. Although seemingly straightforward, such binary dichotomization has proved limiting in cases of developmental forms of hydrocephalus in which multiple points of obstruction are present. To overcome this challenge, Tully & Dobyns (2014) proposed that, in children with hydrocephalus, one should specify whether the primary point of obstruction is proximal (third ventricle or aqueduct) or distal (fourth ventricle or foramen magnum).
3. Intracranial pressure dynamics: Most cases of hydrocephalus are associated with elevated intracranial pressure. In contrast, normal pressure hydrocephalus (NPH), which occurs commonly in the elderly, is associated with enlarged ventricles but not elevated intracranial pressure. The causes leading to NPH are usually acquired; furthermore, this form of hydrocephalus is described usually in conjunction with other symptoms, such as gait disturbance, cognitive decline, and urinary incontinence (Hakim & Adams 1965).
4. Contribution of nongenetic causes: Hydrocephalus caused by another condition such as neoplasm, infection, trauma, or hemorrhage is usually referred to as acquired (or secondary) hydrocephalus (**Figure 1*b–d***). Hemorrhage is the most common cause of hydrocephalus prenatally and can be caused either by intraventricular hemorrhage or by cryptic microhemorrhages (Lategan et al. 2010, Morioka et al. 2006). Infections by agents such as enterovirus, cytomegalovirus, toxoplasmosis, or lymphocytic choriomeningitis are the second leading cause of acquired hydrocephalus, especially in infants (Chow et al. 2000, Simeone et al. 2013, Wright et al. 1997). Tumors can also account for a significant fraction of acquired hydrocephalus, with the posterior fossa, cerebellar astrocytomas, brainstem gliomas, and ependymomas being among the most common neoplastic sites observed in children. Finally, medication taken during pregnancy is another common source of infantile hydrocephalus, with isotretinoin being the best-documented drug associated with prenatal hydrocephalus, followed by misoprostol, metronidazole, and antidepressants (Munch et al. 2014).
5. Presence of additional clinical features (syndromic hydrocephalus): In contrast to nonsyndromic hydrocephalus that is caused frequently by extrinsic factors, syndromic forms are mostly genetic (**Figure 1*e–g***). However, this categorization is not deterministic; hydrocephalus driven by mutations in the L1 cell adhesion molecule (*L1CAM*), the most commonly

documented hydrocephalus-associated gene, can be both syndromic and nonsyndromic (Schrander-Stumpel & Fryns 1998, Verhagen et al. 2011). To classify the plethora of genetic syndromes of which hydrocephalus is a component, studies have proposed the classification to be based on the predominant clinical sign, such as muscular deficiencies in protein *O*-mannosyltransferase 2 (*POMT2*)-positive patients that present with muscle weakness and wasting, or brain abnormalities in the case of *L1CAM*-positive patients that also harbor other central nervous system defects such as corpus callosum agenesis (Verhagen et al. 2011).

Efforts to map familial cases of hydrocephalus and generate relevant animal models, together with the advances in sequencing technologies, have resulted in the identification of four bona fide genes associated with isolated hydrocephalus and >100 genes that are thought to drive pleiotropic genetic disorders (**Table 1**). In the subsequent sections, we summarize the genetic findings and group hydrocephalus-associated genes and disorders into modules defined by the known function of mutated proteins as a means to (*a*) highlight some of the key developmental pathways that contribute to this pathology and (*b*) assist the rational classification of the phenotype, based not on clinical endpoints but on causative physiological drivers.

GENETICS OF HYDROCEPHALUS

Clinical entities associated with isolated hydrocephalus are rare. Among those, the most common heritable form is caused by mutations in *L1CAM* and accounts for up to 10% of males with X-linked isolated idiopathic hydrocephalus (Adle-Biassette et al. 2013). Empiric risk rates for isolated hydrocephalus, excluding the X-linked form, caused by *L1CAM* range from <1% to 4% (Bay et al. 1979, Burton 1979). Despite reports of several pedigrees with isolated hydrocephalus (e.g., Chow et al. 1990, Teebi & Naguib 1988, Zlotogora et al. 1994), to date, bona fide mutations have been described in only four genes [*L1CAM*; adaptor-related protein complex 1, sigma-2 subunit (*AP1S2*); multiple PDZ domain protein (*MPDZ*); and coiled-coil domain-containing protein 88C (*CCDC88C*)] (Al-Dosari et al. 2013, Ekici et al. 2010, Rosenthal et al. 1992, Tarpey et al. 2006). In most instances, hydrocephalus is a component of a defined syndrome. Overall, as of late 2015, over 100 genes have been described to be mutated in syndromic hydrocephalus cases (**Table 1** and **Supplemental Table 1**; follow the **Supplemental Materials link** from the Annual Reviews home page at **http://www.annualreviews.org**); several of these appear to aggregate in discrete, sometimes overlapping pathway modules (**Figure 2**).

Supplemental Material

NEURONAL ADHESION AND *L1CAM*-ASSOCIATED HYDROCEPHALUS

Mutations in *L1CAM* cause both X-linked hydrocephalus with stenosis of the aqueduct of Sylvius and a broader spectrum of pathology that includes isolated agenesis of the corpus callosum, hypoplasia of corticospinal tracts, hypoplasia of the anterior cerebellar vermis, fusion of the thalami, and X-linked spastic paraplegia (L1 syndrome) (Willems et al. 1987). The gene harbors both point mutations (Rosenthal et al. 1992) and genomic duplications (Van Camp et al. 1993). To date, >200 *L1CAM* mutations have been reported (Adle-Biassette et al. 2013). However, genotype-phenotype correlations have not been particularly informative: The only correlation that could be drawn with confidence reported that children bearing a truncating mutation are more likely to die prior to three years of age (52%) when compared to children with missense mutations (8%) (Vos et al. 2010).

As a neuronal adhesion molecule encoded by a transmembrane glycoprotein that belongs to the immunoglobulin superfamily of cell adhesion molecules, L1CAM mediates functions such as cell-cell adhesion, growth cone morphology, guidance of neurite outgrowth, myelination, axon

Table 1 Genes encoding major pathway components mutated in isolated or syndromic hydrocephalus

Disorder	OMIM ID	Genetic locus	Major clinical features	Mode of inheritance	Reference(s)
Neuronal adhesion					
X-linked hydrocephalus with aqueductal stenosis	307000	*L1CAM*	Adducted thumbs, corpus callosal atrophy	X-linked	Rosenthal et al. 1992
MASA/CRASH syndrome	303350	*L1CAM*	Mental retardation, aphasia, shuffling gait, adducted thumbs	X-linked	Jouet et al. 1994, Vits et al. 1994, Yamasaki & Kanemura 2015
Vesicle trafficking					
Pettigrew syndrome (Fried-type syndromic mental retardation)	304340	*AP1S2*	Intellectual disability	X-linked	Tarpey et al. 2006
Wnt signaling pathway					
Nonsyndromic autosomal recessive hydrocephalus, 1	236600	*CCDC88C*	Seizures, psychomotor delay	AR	Ekici et al. 2010
Dystroglycanopathies					
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	236670, 613155, 609308	*POMT1*	Brain and eye anomalies, mental retardation, limb-girdle	AR	Beltrán-Valero de Bernabé et al. 2002
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	613150, 613156, 613158	*POMT2*	Brain and eye anomalies, mental retardation, limb-girdle	AR	van Reeuwijk et al. 2005
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	253280, 613151, 613157	*POMGNT1*	Brain and eye anomalies, mental retardation, limb-girdle	AR	Yoshida et al. 2001
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	611615, 253800, 613152, 611588	*FKTN*	Dilated cardiomyopathy, brain and eye anomalies, mental retardation, limb-girdle	AR	Kobayashi et al. 1998
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	613153, 606612, 607155	*FKRP*	Brain and eye anomalies, mental retardation, limb-girdle	AR	Brockington et al. 2001a
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	614643, 616052	*ISPD*	Brain and eye anomalies, limb-girdle	AR	Roscioli et al. 2012, Willer et al. 2012
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	615249	*POMK*	Brain and eye anomalies	AR	Di Costanzo et al. 2014

(*Continued*)

Table 1 (*Continued*)

Disorder	OMIM ID	Genetic locus	Major clinical features	Mode of inheritance	Reference(s)
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	615181	*B3GALNT2*	Brain and eye anomalies	AR	Stevens et al. 2013
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	613154	*LARGE*	Brain and eye anomalies	AR	van Reeuwijk et al. 2007
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	616538	*DAG1*	Brain and eye anomalies	AR	Geis et al. 2013, Riemersma et al. 2015
Walker-Warburg syndrome (muscular dystrophy–dystroglycanopathy)	615287	*B3GNT1*	Brain and eye anomalies	AR	Buysse et al. 2013
Peters-plus syndrome	261540	*B3GALTL*	Eye anomalies, short stature	AR	Lesnik Oberstein et al. 2006
Lissencephaly 5	615191	*LAMB1*	Brain malformations	AR	Radmanesh et al. 2013
Congenital disorder of glycosylation, type Is	300884	*ALG13*	Seizures, hepatomegaly, recurrent infections	X-linked	Timal et al. 2012
Ciliopathies					
Bardet-Biedl syndrome/Meckel syndrome 4	615991, 611134	*CEP290*	Obesity, retinitis pigmentosa, kidney dysfunction, polydactyly, renal cystic dysplasia, developmental anomalies, postaxial polydactyly	AR	Baala et al. 2007
Kartagener syndrome	244400, 608644	*DNAI1*, *DNAH5*	Primary ciliary dyskinesia, situs inversus, dextrocardia	AR	Pennarun et al. 1999, Olbrich et al. 2002
Primary ciliary dyskinesia 25	615482	*DYX1C1*	Situs inversus, bronchiectasis, upper and lower airway disease	AR	Tarkar et al. 2013
Primary ciliary dyskinesia 31	616369	*CENPF*	Agenesis of corpus callosum, cerebellar hypoplasia, cleft palate	AR	Waters et al. 2015
Short-rib thoracic dysplasia 10 with polydactyly	615630	*IFT172*	Polydactyly, long-bone shortening	AR	Halbritter et al. 2013
Short-rib thoracic dysplasia 14 with polydactyly	616546	*KIAA0586*	Cerebral anomalies, polydactyly, long-bone shortening	AR	Alby et al. 2015

(*Continued*)

Table 1 (*Continued*)

Disorder	OMIM ID	Genetic locus	Major clinical features	Mode of inheritance	Reference(s)
Meckel syndrome 1	249000	*MKS1*	Renal cystic dysplasia, developmental anomalies, postaxial polydactyly	AR	Kyttälä et al. 2006
Meckel syndrome 3	607361	*TMEM67*	Renal cystic dysplasia, developmental anomalies, postaxial polydactyly	AR	Smith et al. 2006
Joubert syndrome 2	608091	*TMEM216*	Developmental delay, hindbrain malformations, breathing abnormalities	AR	Edvardson et al. 2010
Joubert syndrome 9	612285	*CC2D2A*	Retinitis pigmentosa, mental retardation	AR	Noor et al. 2008
Ventriculomegaly with cystic kidney disease	219730	*CRB2*	Renal cystic disease	AR	Slavotinek et al. 2015
Hydrolethalus syndrome 1	236680	*HYLS1*	Central nervous system malformations, postaxial polydactyly	AR	Mee et al. 2005
Hydrolethalus syndrome 2	614120	*KIF7*	Malformations of the mid- and hindbrain, postaxial polydactyly	AR	Putoux et al. 2011
Greig cephalopolysyndactyly syndrome	175700	*GLI3*	Craniosynostosis, postaxial syndactyly	AD	Wild et al. 1997
Nephronophthisis 18	615862	*CEP83*	Nephronophthisis, hepatic cytolysis, retinitis	AR	Failler et al. 2014
Orofaciodigital syndrome 1	311200	*OFD1*	Facial and digit malformations	X-linked	Ferrante et al. 2001
X-linked VACTERL association	306955	*ZIC3*	Dextrocardia and cardiac malformations	X-linked	Gebbia et al. 1997
VATER association with macrocephaly and ventriculomegaly	276950	*PTEN*	Vertebral anomalies, anal atresia, cardiac disease, renal anomalies	AR	Porteous et al. 1992
Marfan syndrome	154700	*FBN1*	Skeletal, ocular, cardiovascular, and fibrous connective tissue anomalies, arachnodactyly	AD	Hogue et al. 2013

(*Continued*)

Table 1 (*Continued*)

Disorder	OMIM ID	Genetic locus	Major clinical features	Mode of inheritance	Reference(s)
Osteopetrosis, autosomal recessive 8	615085	*SNX10*	Osteopetrosis, macrocephaly, hepato- and/or splenomegaly	AR	Mégarbané et al. 2013
Holoprosencephaly 5	609637	*ZIC2*	Holoprosencephaly	AD	Brown et al. 1998
RASopathies					
Neurofibromatosis, type I	162200	*NF1*	Fibromatous skin tumors	AD	Wallace et al. 1990
Costello syndrome	218040	*HRAS*	Distinctive facial appearance, failure to thrive, short stature	AD	Aoki et al. 2005
Noonan syndrome	163950	*PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS*, *SHOC2*, *CBL*	Distinctive facial appearance, heart defects, short stature	AD	Reviewed in Rauen 2013
Cardio-facio-cutaneous syndrome	115150	*BRAF*	Distinctive facial appearance, heart defects, mental retardation	AD	Niihori et al. 2006
Neurocutaneous melanosis, somatic	249400	*NRAS*	Neurocutaneous melanosis, seizures	Somatic mutations	Kinsler et al. 2013
Otopalatodigital syndrome, type II	304120	*FLNA*	Craniofacial dysmorphisms	X-linked	Robertson et al. 2003
Coffin-Lowry syndrome	303600	*RPS6KA3*	Intellectual disability, skeletal malformations	X-linked	Delaunoy et al. 2006
PI3K-AKT-mTOR pathway					
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 1	603387	*PIK3R2*	Polymicrogyria, polydactyly	AD	Rivière et al. 2012
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 2	615937	*AKT3*	Polymicrogyria, polydactyly	AD	Rivière et al. 2012
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 3	615938	*CCND2*	Polymicrogyria, polydactyly	AD	Mirzaa et al. 2014

(*Continued*)

Table 1 (*Continued*)

Disorder	OMIM ID	Genetic locus	Major clinical features	Mode of inheritance	Reference(s)
Megalencephaly-capillary malformation-polymicrogyria syndrome somatic	602501	*PIK3CA*	Polymicrogyria, syndactyly	n/a	Rivière et al. 2012
Macrocephaly/ megalencephaly syndrome, autosomal recessive	248000	*TBC1D7*	Macrocephaly	AR	Capo-Chichi et al. 2013
Planar cell polarity and neural tube defects					
Susceptibility to neural tube defects	182940	*VANGL1*	Neural tube defects, craniorachischisis	AD	Kibar et al. 2001
Neural tube defects	182940	*VANGL2*	Neural tube defects, myelomeningocele	AD	Kibar et al. 2011
Susceptibility to spina bifida	182940	*CCL2*	Spina bifida	AD	Chambers et al. 1998
Neural tube defects	182940	*FUZ*	Neural tube defects	AD	Seo et al. 2011
Hajdu-Cheney syndrome	102500	*NOTCH2*	Skeletal anomalies	AD	Simpson et al. 2011
Nonsyndromic autosomal recessive hydrocephalus, 2	615219	*MPDZ*	Hydrocephalus	AR	Al-Dosari et al. 2013
Adams-Oliver syndrome 1	100300	*ARHGAP31*	Developmental delay, aplasia cutis congenital, limb defects, vascular anomalies	AD	Wild et al. 1997
Chudley-McCullough syndrome	604213	*GPSM2*	Sensorineural deafness, brain anomalies	AR	Walsh et al. 2010
Lysosomal storage disorders					
Mucopolysaccharidosis type VI	253200	*ARSB*	Short stature, hepatosplenomegaly, cardiac abnormalities, facial dysmorphisms	AR	Wicker et al. 1991
Gaucher disease, type IIIC	231005	*GBA*	Cardiac and neurological anomalies	AR	Chabás et al. 1995
Growth factors					
Apert syndrome	101200	*FGFR2*	Craniosynostosis	AD	Wilkie et al. 1995
Achondroplasia	100800	*FGFR3*	Dwarfism	AD	Rousseau et al. 1994, Shiang et al. 1994
Shprintzen-Goldberg syndrome	182212	*SKI*	Skeletal, neurological, cardiovascular, and connective tissue anomalies	AD	Doyle et al. 2012
Loeys-Dietz syndrome 1	609192	*TGFBR1*	Aortic aneurysm syndrome	AD	Loeys et al. 2005

(*Continued*)

Table 1 (*Continued*)

Disorder	OMIM ID	Genetic locus	Major clinical features	Mode of inheritance	Reference(s)
Transcription factors					
DiGeorge syndrome	188400	*TBX1*	Hypocalcemia, cardiac defects	AD	Yagi et al. 2003
Cousin syndrome	260660	*TBX15*	Dwarfism, facial dysmorphisms, skeletal anomalies	AR	Lausch et al. 2008
Ayme-Gripp syndrome	601088	*MAF*	Congenital cataracts, sensorineural hearing loss, intellectual disability, seizures, facial dysmorphisms	AD	Niceta et al. 2015

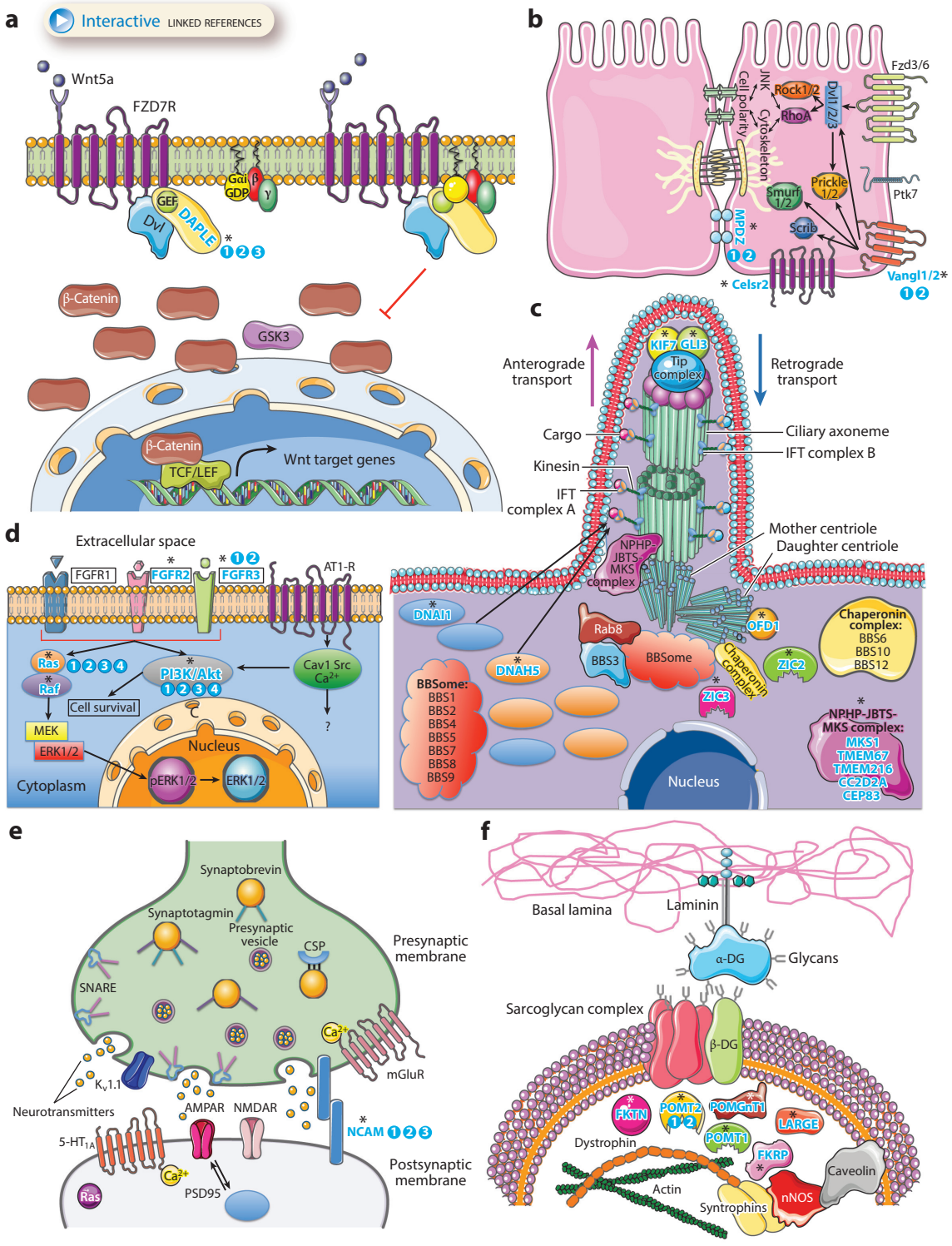
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MASA syndrome, mental retardation, aphasia, shuffling gait, and adducted thumbs syndrome; CRASH syndrome, corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus syndrome; Wnt, wingless/integrated.

bundling and pathfinding, long-term potentiation, neuronal cell survival and migration, and synaptogenesis (Adle-Biassette et al. 2013). Mutations in *L1CAM* cause an almost invariably neurological phenotype, characterized by several brain malformations that obstruct CSF flow, most commonly at the level of the aqueduct (Finckh et al. 2000). Nevertheless, *L1CAM* is not uniquely expressed in the nervous system, with transcripts lacking exons 2 and 27 having been identified in other sites such as the intestinal crypt cells (Thor et al. 1987), the male urogenital tract (Kujat et al. 1995), leukocytes (Kowitz et al. 1992), and kidney tubule epithelia (Debiec et al. 1998). To date, the precise mechanism(s) through which *L1CAM* defects lead to ventricular dilatation remain poorly understood, with only putative hypotheses existing. As such, mutations in *L1CAM* can (*a*) mediate the decrease in white matter elasticity, increasing CSF pressure and ventricular vulnerability, and (*b*) cause abnormal development of the midline structure and narrowing of the CSF pathway.

Analyses of multiple, large, hydrocephalus-patient series for *L1CAM* mutations concluded that the likelihood of identifying an *L1CAM* mutation in a patient with hydrocephalus increases in (*a*) the setting of a positive family history, (*b*) the presence of more than three *L1CAM* cardinal signs (hydrocephalus, adducted thumbs, spastic paraplegia, intellectual disability, or agenesis or hypoplasia of the corpus callosum), and (*c*) the absence of *L1CAM* atypical signs (cleft palate, brain hemorrhage, metabolic disorder, or heart malformation). No single finding, or combination of findings, can confirm or exclude the diagnosis. As such, genetic analysis of *L1CAM* is suggested in males with isolated or idiopathic hydrocephalus and is advised for patients who, in addition to hydrocephalus, have a positive family history of adducted thumbs (Tully & Dobyns 2014).

WINGLESS/INTEGRATED (WNT) SIGNALING PATHWAY

The first bona fide nonsyndromic hydrocephalus gene was identified through homozygosity mapping in a consanguineous pedigree from Algeria with two affected fetuses. Among the 25 positional candidate genes, priority was assigned to those expressed in the brain. Sequencing revealed a homozygous splice-affecting mutation that results in deletion of 290 bp and premature termination in *CCDC88C* (Ekici et al. 2010). *CCDC88C* encodes the segment polarity protein disheveled homolog (DVL)-binding protein DAPLE and acts as a negative regulator of the noncanonical Wnt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Interactive LINKED REFERENCES
Wnt5a
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γ
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Dvl
DAPLE
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β-Catenin
TCF/LEF
Wnt target genes
b
Fzd3/6
JNK
Cell polarity
Cytoskeleton
Rock1/2
RhoA
Dvl1/2/3
Prickle 1/2
Smurf 1/2
Ptk7
MPDZ 1 2
Scrib
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Vangl1/2* 1 2
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Anterograde transport
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KIF7
GLI3
Tip complex
Cargo
Kinesin
IFT complex A
Ciliary axoneme
IFT complex B
Mother centriole
Daughter centriole
NPHP-JBTS-MKS complex
DNAI1
DNAH5
Rab8
BBS3
BBSome
OFD1
Chaperonin complex
ZIC2
ZIC3
Chaperonin complex: BBS6 BBS10 BBS12
BBSome: BBS1 BBS2 BBS4 BBS5 BBS7 BBS8 BBS9
NPHP-JBTS-MKS complex: MKS1 TMEM67 TMEM216 CC2D2A CEP83
Nucleus
d
Extracellular space
FGFR1
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AT1-R
Ras
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1 2 3 4
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Cell survival
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Synaptotagmin
Presynaptic vesicle
CSP
SNARE
Presynaptic membrane
Ca2+
mGluR
Kv1.1
Neurotransmitters
AMPAR
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NCAM 1 2 3
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Ca2+
PSD95
Ras
Postsynaptic membrane
f
Basal lamina
Laminin
α-DG
Glycans
Sarcoglycan complex
β-DG
FKTN
POMT2 1 2
POMGnT1
LARGE
POMT1
Dystrophin
FKRP
Caveolin
Actin
nNOS
Syntrophins

signaling pathway through its homooligomer interaction with the PDZ domain of *Dishevelled* (Ishida-Takagishi et al. 2012, Oshita et al. 2003). Subsequently, Drielsma et al. (2012) reported a second familial case with two affected individuals, both of whom had a homozygous truncating mutation in *CCDC88C*. Of note, mouse mutants for components of the noncanonical Wnt signaling pathway, such as the *hGFAP-Cre;Dvl1*$^{-/-}$;*2*$^{flox/flox}$;*3*$^{+/-}$ mouse, can also manifest hydrocephalus, lending functional support and intimating a link between this pathway and CSF movement. It was hypothesized that hydrocephalus owing to DAPLE defects occurs through interaction of multiple paracrine signaling pathways that ultimately induce subtle planar cell polarity defects and aberrant CSF flow through defective cilia orientation (Ohata et al. 2014).

VESICLE TRAFFICKING

Pettigrew syndrome was thought originally to be allelic to L1 syndrome (Fried 1972) but was recognized later as a distinct clinical entity that differs from *L1CAM*-associated hydrocephalus in that patients with Pettigrew syndrome present with intellectual disability, choreoathetosis, Dandy-Walker malformation(s), and diagnostic calcium or iron depositions in the basal ganglia (Cacciagli et al. 2014, Strain et al. 1997). Linkage in a four-generation pedigree mapped a 6-Mb critical interval on Xq22; within this interval, *AP1S2* was found to harbor mutations in three families with

Figure 2

Schematic of select pathways disrupted in hydrocephalus. Several pathways with overlapping functions have been implicated in the pathophysiology of hydrocephalus. (*a*) The Wnt signaling pathway was highlighted through the identification of mutations in *CCDC88C/DAPLE* in patients with nonsyndromic autosomal recessive hydrocephalus. (*b*) The importance of tight junction integrity and planar cell polarity have been documented through the study of both nonsyndromic (*MPDZ*-caused) and syndromic forms of hydrocephalus. (*c*) The role of primary and ependymal cilia in the maintenance and regularity of CSF flow has been highlighted in numerous observations. Cilia not only are involved in the production of CSF flow, but through their synchronous beating, they generate a steady directional CSF flow that is required to maintain the patency of the aqueduct during brain development. (*d*) Lesions in the growth factor signaling pathways that signal to the PI3K-AKT-mTOR pathway have also been implicated in the formation of hydrocephalus through the spectrum of syndromic disease forms. (*e*) *L1CAM* is a bona fide nonsyndromic X-linked hydrocephalus gene that harbors mutations in 10% of males reported to present hydrocephalus and has highlighted the importance of the integrity of neuronal adhesion. (*f*) The dystroglycanopathies that arise owing to defects in proteins that add sugar groups to the dystroglycans are a group of disorders in which hydrocephalus is often the first clinical sign to be recognized. The genetic defects leading to this devastating group of disorders are thought to abolish the proper interaction and anchoring of the cell to the extracellular matrix and disrupt tissue organization and homeostasis. Proteins known to give rise to hydrocephalus when defective are indicated with a black asterisk. Links to references can be found by clicking on the protein names that are highlighted in cyan; proteins with multiple links have circled numbers that are linked to each reference. This figure was prepared using Servier Medical Art (**http://www.servier.com/Powerpoint-image-bank**). Abbreviations: 5-HT$_{1A}$, 5-hydroxytryptamine 1A; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AKT, protein kinase B; AT1-R, angiotensin II receptor type 1; BBS, Bardet-Biedl syndrome; CC2D2A, coiled-coil and C2 domain containing 2A; CCDC88C, coiled-coil domain-containing protein 88C; CELSR2, cadherin EGF LAG seven-pass G-type receptor 2; CEP83, centrosomal protein 83kDa; CSF, cerebrospinal fluid; CSP, chemosensory protein; DG, dystroglycan; DNAH5, dynein axonemal heavy chain 5; Dvl, disheveled segment polarity protein; FGFR, fibroblast growth factor receptor; FKRP, fukutin-related protein; FKTN, fukutin; FZD7R, frizzled class receptor 7; GDP, guanosine 5′-diphosphate; GEF, guanine nucleotide exchange factor; GLI3, Gli-Kruppel family member 3; IFT, intraflagellar transport; JBTS, Joubert-Boltshauser syndrome; JNK, c-JUN N-terminal kinase; KIF7, kinesin family member 7; LARGE, acetylglucosaminyltransferase-like protein; LEF, lymphoid enhancer-binding factor; L1CAM, L1 cell adhesion molecule; mGluR, metabotropic glutamate receptor; MKS, Meckel-Gruber syndrome; MPDZ, multiple PDZ domain protein; NCAM, neuronal cell adhesion molecule; NMDAR, *N*-methyl-D-aspartate receptor; nNOS, neuronal nitric oxide synthase; NPHP, nephronophthisis; PI3K, phosphoinositide 3-kinase; POMGnT1, protein *O*-mannose β-1,2-*N*-acetylglucosaminyltransferase; POMT1, protein *O*-mannosyltransferase 1; PSD95, postsynaptic density protein 95; PTK7, protein tyrosine kinase 7; RHOA, Ras homolog family member A; ROCK, Rho-associated protein kinase; SCRIB, scribbled planar cell polarity protein; SMURF, SMAD specific E3 ubiquitin protein ligase; SNARE, synaptosome-related; SRC, proto-oncogene protein tyrosine kinase; TCF, transcription factor; TMEM67, transmembrane protein 67; VANGL1, vang-like 1 (van gogh, Drosophila); Wnt5α, wingless/integrated subunit 5$^{\alpha}$; ZIC2, zinc finger protein 2.

Pettigrew syndrome (Tarpey et al. 2009). Subsequent studies expanded the mutational spectrum of *AP1S2* (Cacciagli et al. 2014). *AP1S2* encodes the sigma 2 subunit of the AP1 adaptin protein, one of the major regulators of lysosomal protein sorting that is known to pack in vesicles and transport proteins between the *trans* Golgi network and the endosomes (Reusch et al. 2002). Tully & Dobyns (2014) recommended that males presenting with hydrocephalus, intellectual disability, and iron or calcium depositions be tested for mutations in *AP1S2*.

The role of vesicular trafficking in ventricular homeostasis has been demonstrated further in murine studies. Lethal giant larvae, drosophila, homolog of, 1 (*Lgl1*) hemizygous null mutant mice die shortly after birth owing to severe hydrocephalus (Klezovitch et al. 2004). The defective protein in this model encodes a protein that promotes trafficking of membrane precursor vesicles whose fusion with the plasmalemma is crucial for axonal growth (Wang et al. 2011). Further, one of the first spontaneous mouse mutants reported to display severe hydrocephalus, the *hyh* mouse, bears a missense mutation in the soluble N-ethylmaleimide-sensitive factor (NSF) attachment protein α (αSNAP), a component of the apical vesicle transport machinery that is responsible for vesicular docking, mediating the membrane fusion of vesicles that shuttle between the *trans* Golgi network and the apical membrane (Chae et al. 2004). Studies of the *hyh* model have hypothesized further that aberrant trafficking regulates cell fate with premature withdrawal from the cell cycle of neuronal progenitors, leading to increasing numbers of early-born, deep-layer cerebral cortical neurons and depletion of the cortical progenitor pool (Chae et al. 2004).

DYSTROGLYCAN-ASSOCIATED HYDROCEPHALUS (WALKER-WARBURG SYNDROME)

The dystroglycanopathies are a heterogeneous group of autosomal recessive disorders characterized by defective glycosylation of α-dystroglycan (Godfrey et al. 2007). The clinical phenotypes invariably involve muscular dystrophy and can range in severity from the almost-always-lethal Walker-Warburg syndrome and muscle-eye-brain disease to the less severe limb-girdle muscular dystrophy with no associated brain or eye involvement (Brockington et al. 2001b, van Reeuwijk et al. 2005). In dystroglycanopathies, hydrocephalus often develops as early as the sixth month of gestation, driven typically by aqueductal obstruction (Dobyns et al. 1989). Other neurological features involve a cobblestone cortex with abnormal white matter in cerebral hemispheres, brainstem abnormalities, cerebellar cysts, and eye malformations (Dobyns et al. 1989). Several genes that cause different subtypes of this group of disorders have been identified. All encode known or predicted glycosyltransferases and are thought to mediate the addition of carbohydrate residues onto the α-dystroglycan backbone, either via the process of *O*-mannosylation [i.e., *POMT1*, *POMT2*, protein *O*-mannose β-1,2-*N*-acetylglucosaminyltransferase (*POMGnT1*)] (Akasaka-Manya et al. 2004, Manya et al. 2003, Yoshida et al. 2001) or via other not yet fully characterized mechanisms [fukutin (*FKTN*), fukutin-related protein (*FKRP*), acetylglucosaminyltransferase-like protein (*LARGE*)] (Brockington et al. 2005, de Paula et al. 2003, Xiong et al. 2006). The dystroglycans are expressed in several cell types, mediating the myelination and nodal architecture of peripheral nerves (Saito et al. 2003), epithelial morphogenesis (Durbeej et al. 2001), cell adhesion (Matsumura et al. 1997), synaptogenesis (Montanaro et al. 1998), and signaling through several pathways that include protein kinase B (AKT), Ras, and epidermal growth factor (EGF) receptor signaling (Langenbach & Rando 2002, Poulton & Deng 2006, Spence et al. 2004). When appropriately glycosylated, dystroglycans provide a direct link between the cytoplasmic cytoskeleton and the extracellular matrix. Defects in the interaction between dystroglycan-ligand and neuronal overmigration cause aberrations in the integrity of basement membranes in the brain, suggesting

that these functions may be some of the underlying mechanisms that give rise to hydrocephalus (Satz et al. 2008).

CILIOPATHIES AND HYDROCEPHALUS

Studies performed in animal models first and subsequently in humans have established an intimate link between ciliary defects and the formation of hydrocephalus. Among the first models developed was the H-Tx rat model that develops congenital hydrocephalus owing to ciliary defects (Kiefer et al. 1998). Evidence from subsequent mouse models has shown that hydrocephalus can arise from defects in either motile or primary cilia (Sotak & Gleeson 2012). For example, a dynein, axonemal heavy-chain 5 (*Dnahc5*) null mouse model displays both hydrocephalus and random left-right axis specification, as well as chronic respiratory infections. The same is true for several additional models, such as sperm-associated antigen 6 (*Spag6*); hydrocephalus-inducing, mouse, homolog of (*hydin*); primary cilia dyskinesia protein 1 (*Pcdp1*); and hepatocyte nuclear factor-3/forkhead homologue 4 (*Hfh4*), all of which carry null mutations in genes and proteins essential for motile cilia assembly and function (Chen et al. 1998, Ibañez-Tallon et al. 2004, Lee et al. 2008, Sapiro et al. 2002). Finally, a recent study that generated and analyzed 4,650 knockout mouse lines through a high-throughput mutagenesis and phenotyping process identified 12 novel mutants with autosomal recessive hydrocephalus (Vogel et al. 2012). The mutation underlying the hydrocephalic phenotype was determined in eight of these lines; strikingly, all eight affected proteins were shown to be required for motile ciliogenesis and function (Vogel et al. 2012).

Ependymal cilia line the ventricles and interventricular connections. Through their synchronous beating, they generate a directional flow of CSF, termed ependymal flow (Ibañez-Tallon et al. 2004). A steady ependymal flow is required to maintain the patency of the aqueduct during brain development; the absence of this flow results in secondary aqueduct stenosis during early postnatal brain development and, subsequently, in hydrocephalus. Nevertheless, cilia not only regulate the directional flow of CSF but are also involved in the regulation of CSF production. The latter offers a rational explanation as to why murine models with defects in nonmotile primary cilia are also associated with the development of ventriculomegaly. Exemplars of primary cilia–mediated hydrocephalus involve the E2F transcription factor 5 (*E2f5*) model, in which increased secretory activity of the choroid plexus causes communicating congenital hydrocephalus, and the *Tg737*^{orpk} model, in which CSF overproduction leads to the development of hydrocephalus prior to the formation of motile cilia (Banizs et al. 2005, Lindeman et al. 1998). In humans, at least 20 genes encoding proteins that are required for either the biosynthesis or proper function of the cilium have been reported to be associated with syndromic hydrocephalus (**Table 1**). Select examples involve the Kartagener syndrome, defined by the presence of situs inversus, primary ciliary dyskinesia, sperm motility defects, and hydrocephalus; mutations in kinesin family member 7 (*KIF7*) that cause hydrolethalus syndrome, which presents with hydrocephalus, exencephaly, polydactyly, club feet, cerebellar malformations, heart and lung defects, and cleft palate; and Joubert and Meckel-Gruber syndromes, both of which are associated with congenital hydrocephalus in humans (Badano et al. 2006, Putoux et al. 2011, Sotak & Gleeson 2012).

NEURAL TUBE DEFECTS AND PLANAR CELL POLARITY

Neural tube defects (NTDs) are common, severe congenital malformations that involve the failure of neural tube closure (Mitchell 2005). Several disorders fall under the umbrella of NTDs, including spina bifida, anencephaly, Dandy-Walker malformation, Chiari malformations, and osteopetrosis. The majority of patients with NTDs have hydrocephalus (Copp & Greene 2010).

Mechanistically, hydrocephalus is thought to occur by occluding CSF flow through tethering, which pulls the cerebellum into the foramen magnum as the vertebral column lengthens. Causally, given that NTDs are multifactorial, with contribution from both genetic and environmental factors, hydrocephalus induced by underlying NTD pathology may also be of multifactorial origin (Greene & Copp 2014). Among the nongenetic factors are teratogenic agents such as valproic acid, the fungal product fumonisin, maternal obesity and diabetes, and the historical link with low blood levels of the B vitamin folate (Correa et al. 2003, Missmer et al. 2006, Smithells et al. 1976, Wlodarczyk et al. 2012). To date, the identification of the NTD-associated fuzzy planar cell polarity protein (*FUZ*), vang-like1 (van gogh, Drosophila) (*VANGL1*), and vang-like2 (*VANGL2*) genes has implicated the planar cell polarity pathway as one of the biological processes underlying this group of disorders (Kibar et al. 2011, Murdoch et al. 2001, Seo et al. 2011). Recently, a tight junction protein that regulates planar cell polarity, MPDZ (also known as *MUPP1* for multi-PDZ domain protein-1), was reported to cause autosomal recessive nonsyndromic communicating hydrocephalus in two unrelated consanguineous families (Al-Dosari et al. 2013, Assémat et al. 2013). Although no reports of additional cases with mutations in *MPDZ* exist, mutations in *MPDZ* do not seem to be associated with NTD-like phenotypes (Al-Dosari et al. 2013). The same is true for other planar cell polarity genes, such as cadherin EGF LAG seven-pass G-type receptor 2 (*CELSR2*), that are not associated with NTDs and yet cause hydrocephalus (Al-Dosari et al. 2013, Tissir et al. 2010) through a mechanism that involves ependymal cilia dysfunction (Sotak & Gleeson 2012). Although the precise mechanisms through which disruption of the planar cell polarity pathway results in the clinical manifestation of hydrocephalus are not fully elucidated, defects in this pathway are broadly detrimental to ventricular formation.

RASOPATHIES

The RASopathies are a clinically defined group of syndromes caused by germline mutations in genes that encode components or regulators of the Ras/mitogen-activated protein kinase (MAPK) pathway. Ras proteins are small guanosine GTPases that function as a signaling hub within the cell, regulating the cell cycle and cellular growth, differentiation, and senescence (Rauen 2013). Neurofibromatosis type 1, Noonan syndrome, Costello syndrome, and cardio-facio-cutaneous (CFC) syndrome are among the disorders that belong under the umbrella of RASopathies and are associated with hydrocephalus (Rauen 2013). The hydrocephalus reported in the context of these syndromes is thought to be multifactorial and to either be a direct manifestation caused by the genetic defect or be a secondary symptom. Despite the phenotypic mimicry observed among RASopathy disease entities owing to the common underlying Ras/MAPK pathway dysregulation, the mechanisms underlying a phenotype common across disorders such as hydrocephalus differ. For example, hydrocephalus in patients diagnosed with neurofibromatosis type 1 is likely due to a combination of brain overgrowth and obstructive hamartomas that develop in the ventricular system (Dinçer et al. 2011). Patients with Noonan syndrome have likewise been described with hydrocephalus, in addition to and possibly secondary to hindbrain herniation(s) and cervical intracord cysts, which could obstruct CSF flow at either the brain or spinal cord level (Heye & Dunne 1995). Researchers have documented cerebellar overgrowth, which is likely to lead to obstruction and CSF flow abnormalities, in Costello syndrome (Gripp et al. 2010). Finally, in CFC syndrome instances of cervical stenosis, torticollis and Chiari malformation(s) are thought to account for a fraction of cases with hydrocephalus (Reinker et al. 2011). Of note, CFC, Noonan, and Costello syndromes are also associated with structural heart disease; Tully & Dobyns (2014) have hypothesized that elevated venous pressures may create a pressure gradient that impedes absorption of CSF into the systemic circulation.

PI3K-AKT-MTOR PATHWAY

The PI3K-AKT-mTOR pathway has been increasingly recognized as an underlying cause of a spectrum of megalencephaly-associated syndromes (Mirzaa et al. 2012). Mutations in four genes of the PI3K-AKT-mTOR pathway have been reported to cause different syndromes: the MPPH syndrome that encompasses a constellation of symptoms including primary (congenital or early postnatal) megalencephaly, polymicrogyria, syndactyly with or without postaxial polydactyly, and ventriculomegaly that may progress to hydrocephalus with asymmetry especially of the lateral ventricles (Garavelli et al. 2007, Mirzaa et al. 2004, Pisano et al. 2008), as well as the MCAP (megalencephaly-capillary malformation) syndrome that involves cutaneous vascular malformations in addition to the MPPH symptoms (Garavelli et al. 2005). De novo germline activating mutations in RAC-gamma serine/threonine-protein kinase (*AKT3*), cyclin D2 (*CCND2*), phosphoinositide-3-kinase regulatory subunit 2 (*PIK3R2*), and phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), four core PI3K-AKT-mTOR pathway genes, have been associated with MPPH (Lee et al. 2012, Mirzaa et al. 2014, Nakamura et al. 2014, Rivière et al. 2012). De novo activating mutations in several components of the PI3K-AKT-mTOR pathway upstream of *CCND2* lead to overlapping megalencephaly syndromes associated with hydrocephalus in nearly half of reported individuals. Nevertheless, the underlying mechanism(s) for this observation remains to be explored. Recently, one putative mechanism proposed the aberrant stabilization of CCND2 in neuronal precursors within the developing cerebral cortex, which results in an expansion of the radial glial cells and intermediate progenitor cells (IPCs) (Mirzaa et al. 2014). IPCs allow for geometric expansion of cellular output from the subventricular zone and are thus important drivers of brain size (Nonaka-Kinoshita et al. 2013). Studies in mice electroporated with mutant *CCND2* showed that these proliferating progenitor populations are overproduced, whereas only a small fraction of progenitors exit the cell cycle, thereby suggesting an excess of proliferation that manifests as megalencephaly (Mirzaa et al. 2014). Megalencephaly can induce cortical malformation polymicrogyria and cerebellar overgrowth, leading to posterior fossa crowding and cerebellar tonsillar ectopia or herniation, which causes an obstruction of CSF flow (Mirzaa et al. 2012).

GROWTH FACTOR SIGNALING

Syndromes associated with skeletal anomalies such as craniosynostosis in Apert syndrome and dwarfism in achondroplasia have been linked to progressive hydrocephalus (Fukumitsu et al. 2000, Ohmiya et al. 2001). The mutations in these syndromes affect proteins that participate in the growth factor signaling pathways, including fibroblast growth factor (FGF) and transforming growth factor beta (TGFB) signaling, crucial for cell proliferation, differentiation, survival, and motility. In addition to the identification of patients with mutations in FGF receptor 2 (*FGFR2*), *FGFR3*, and TGFB receptor 1 (*TGFBR1*) who have hydrocephalus as a comorbidity, a contributory role of growth factor defects in the development of ventriculomegaly has also been supported by the finding that growth factor concentration appears to be increased in the CSF of hydrocephalic patients (Killer et al. 2010, Loeys et al. 2005, Rousseau et al. 1994, Wilkie et al. 1995). Animal models have corroborated this association further. First, administration of *Fgf2* to embryonic mouse brains induced the formation of hydrocephalus through aberrant neuronal differentiation in the postnatal cerebral cortex (Ohmiya et al. 2001). Later, stable models lent further evidence for this association; transgenic mice that overexpress *Tgfb1* in their astrocytes develop hydrocephalus, as does the THX rat, in which increased levels of *Tgfb3* contribute to the manifestation of the phenotype (Li et al. 2005).

Two mechanisms have been proposed to explain these observations. The first is that the skeletal and predominantly cranial changes induced by defects in the growth factor signaling cascade obstruct CSF flow and reduce absorption into the systemic circulation by increasing venous pressure (Bristol et al. 2004). The second proposed mechanism involves the excessive brain overgrowth that can lead to hydrocephalus by compounding other brain structures that then induce CSF flow blockage, similar to PI3K-AKT-mTOR pathway–associated megalencephaly (Hevner 2005, Khonsari et al. 2012).

CONCLUSIONS AND FUTURE PROSPECTS

Hydrocephalus is a complex condition influenced by both genetic and environmental factors. The complexity of this disorder is highlighted further by the fact that it can occur either in isolation (congenital or pure hydrocephalus) or in conjunction with other genetic anomalies. The concern of whether hydrocephalus is a phenomenon observed as a cause or as a consequence challenges our ability to dissect the pathways responsible for altering normal CSF flow and inducing ventriculomegaly. The advent of novel sequencing technologies has contributed to the significant progress made in the identification of genes associated with both idiopathic and syndromic forms of this condition. Nevertheless, only four bona fide pure hydrocephalus genes have been identified to date. These genes do not seem to belong to a sole biological pathway but rather highlight different cellular processes involving neural cell adhesion, planar cell polarity, the Wnt signaling pathway, or vesicle transport within the cell, hampering our ability to comprehend the mechanisms underlying this disorder.

To understand the molecular mechanisms of ventriculomegaly better, researchers have generated several congenital hydrocephalus animal models. Strikingly, the majority of genes identified to be causative of hydrocephalus in mice encode ciliary proteins, highlighting the relevance of the cilium in the context of the disorder through a postulated mechanism in which the synchronous beating of the cilia dictates CSF flow across the ventricular system, and if defects arise in the flow, then ventriculomegaly occurs (Banizs et al. 2005, Vogel et al. 2012). Another conclusion drawn from the animal models is that the inheritance and penetrance of hydrocephalus is likely orchestrated by more than one gene and the presence of genetic modifiers, with specific congenic strains being more susceptible to the development of the condition than others. For instance, the C57BL/6 strain is now understood to be a background susceptible to the development of congenital hydrocephalus. Supporting this conclusion, studies on mouse models of *L1cam* (Adle-Biassette et al. 2013) have shown that *L1cam*-deficient mice develop hydrocephalus only after backcrossing to the C57BL/6 strain, with the mutation becoming embryonic lethal after several generations (Itoh et al. 2004). Similarly, *Naglu* mice (the murine model for Sanfilippo syndrome type B) display the disease hallmark features, including hydrocephalus only in the C57BL/6 strain (Gografe et al. 2003). Finally, both *nm1054*- and *fyn*- deficient mice develop hydrocephalus in the C57BL/6J background; hydrocephalus is either mild or absent in the 129S6/SvEvTac or a mixed background (Goto et al. 2008, Lee et al. 2008). These findings support the notion that hydrocephalus is the likely product of genetic interactions whose relationships are as yet unclear. We speculate that such architecture will also likely be true in humans, in whom variable penetrance and expressivity of hydrocephalus is the well-documented norm rather than the exception.

The observation that lesions in several crucial biological pathways can give rise to ventriculomegaly challenges our ability to focus on the role of alleles within a discrete niche of genetic loci that are likely to interact. An alternative is to utilize combinatorially the plethora of tools developed thus far. Toward this end, establishing a complete genetic profile of sporadic individuals sampled in the context of cohort studies through higher throughput technologies

such as whole-exome or whole-genome sequencing seems necessary, suggesting that the view of disorders as pure monogenic entities represents an underestimation of the genetic architecture of these phenotypes. This approach is more likely to uncover the primary drivers leading to hydrocephalus and offers the opportunity to mine the same data set multiple times to discover genetic determinants that are likely to either attenuate or exacerbate disease expressivity among patients with the same primary genetic lesion. Aggregation of genetic and clinical data will facilitate the discovery of such modifying alleles, which will in turn offer opportunities for targeted therapies. The usefulness of adequate sampling coupled with the combinatorial use of diverse research methodologies was highlighted recently in a study that identified *Jagged-1* as a protective locus that can mask fully the symptoms of Duchenne muscular dystrophy (Vieira et al. 2015). Aggregating detailed clinical information from multigenerational pedigrees and large cohorts of idiopathic cases and coupling this information with a complete genetic and ideally transcriptional profile is not only paramount to identifying novel hydrocephalus-causing or -associated genes but also the only way through which (*a*) a more insightful comprehension of the affected processes, (*b*) a better understanding of the basis of this disorder, (*c*) improved prognosis, and (*d*) an efficient path toward designing new therapeutic paradigms can be achieved.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We apologize to our colleagues whose work we were unable to cite owing to space constraints. We thank Dr. Erica Davis and Dr. Edwin Oh for critical review of the manuscript and the members of the Center for Human Disease Modeling for helpful discussions and suggestions.

LITERATURE CITED

Adle-Biassette H, Saugier-Veber P, Fallet-Bianco C, Delezoide AL, Razavi F, et al. 2013. Neuropathological review of 138 cases genetically tested for X-linked hydrocephalus: evidence for closely related clinical entities of unknown molecular bases. *Acta Neuropathol.* 126:427–42

Akasaka-Manya K, Manya H, Kobayashi K, Toda T, Endo T. 2004. Structure-function analysis of human protein O-linked mannose β1,2-*N*-acetylglucosaminyltransferase 1, POMGnT1. *Biochem. Biophys. Res. Commun.* 320:39–44

Al-Dosari MS, Al-Owain M, Tulbah M, Kurdi W, Adly N, et al. 2013. Mutation in *MPDZ* causes severe congenital hydrocephalus. *J. Med. Genet.* 50:54–58

Alby C, Piquand K, Huber C, Mégarbané A, Ichkou A, et al. 2015. Mutations in *KIAA0586* cause lethal ciliopathies ranging from a hydrolethalus phenotype to short-rib polydactyly syndrome. *Am. J. Hum. Genet.* 97:311–18

Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, et al. 2005. Germline mutations in *HRAS* proto-oncogene cause Costello syndrome. *Nat. Genet.* 37:1038–40

Assémat E, Crost E, Ponserre M, Wijnholds J, Le Bivic A, Massey-Harroche D. 2013. The multi-PDZ domain protein-1 (MUPP-1) expression regulates cellular levels of the PALS-1/PATJ polarity complex. *Exp. Cell Res.* 319:2514–25

Baala L, Romano S, Khaddour R, Saunier S, Smith UM, et al. 2007. The Meckel-Gruber syndrome gene, *MKS3*, is mutated in Joubert syndrome. *Am. J. Hum. Genet.* 80:186–94

Badano JL, Mitsuma N, Beales PL, Katsanis N. 2006. The ciliopathies: an emerging class of human genetic disorders. *Annu. Rev. Genom. Hum. Genet.* 7:125–48

Banizs B, Pike MM, Millican CL, Ferguson WB, Komlosi P, et al. 2005. Dysfunctional cilia lead to altered ependyma and choroid plexus function, and result in the formation of hydrocephalus. *Development* 132:5329–39

Bay C, Kerzin L, Hall BD. 1979. Recurrence risk in hydrocephalus. *Birth Defects Orig. Artic. Ser.* 15:95–105

Beltrán-Valero de Bernabé D, Currier S, Steinbrecher A, Celli J, van Beusekom E, et al. 2002. Mutations in the O-mannosyltransferase gene *POMT1* give rise to the severe neuronal migration disorder Walker-Warburg syndrome. *Am. J. Hum. Genet.* 71:1033–43

Bristol RE, Lekovic GP, Rekate HL. 2004. The effects of craniosynostosis on the brain with respect to intracranial pressure. *Semin. Pediatr. Neurol.* 11:262–67

Brockington M, Blake DJ, Prandini P, Brown SC, Torelli S, et al. 2001a. Mutations in the fukutin-related protein gene (*FKRP*) cause a form of congenital muscular dystrophy with secondary laminin α2 deficiency and abnormal glycosylation of α-dystroglycan. *Am. J. Hum. Genet.* 69:1198–209

Brockington M, Torelli S, Prandini P, Boito C, Dolatshad NF, et al. 2005. Localization and functional analysis of the LARGE family of glycosyltransferases: significance for muscular dystrophy. *Hum. Mol. Genet.* 14:657–65

Brockington M, Yuva Y, Prandini P, Brown SC, Torelli S, et al. 2001b. Mutations in the fukutin-related protein gene (*FKRP*) identify limb girdle muscular dystrophy 2I as a milder allelic variant of congenital muscular dystrophy MDC1C. *Hum. Mol. Genet.* 10:2851–59

Brown SA, Warburton D, Brown LY, Yu CY, Roeder ER, et al. 1998. Holoprosencephaly due to mutations in *ZIC2*, a homologue of *Drosophila odd-paired*. *Nat. Genet.* 20:180–83

Burg MB, Orloff J. 1968. Control of fluid absorption in the renal proximal tubule. *J. Clin. Investig.* 47:2016–24

Burton BK. 1979. Empiric recurrence risks for congenital hydrocephalus. *Birth Defects Orig. Artic. Ser.* 15:107–15

Buysse K, Riemersma M, Powell G, van Reeuwijk J, Chitayat D, et al. 2013. Missense mutations in β-1,3-*N*-acetylglucosaminyltransferase 1 (*B3GNT1*) cause Walker-Warburg syndrome. *Hum. Mol. Genet.* 22:1746–54

Cacciagli P, Desvignes JP, Girard N, Delepine M, Zelenika D, et al. 2014. *AP1S2* is mutated in X-linked Dandy-Walker malformation with intellectual disability, basal ganglia disease and seizures (Pettigrew syndrome). *Eur. J. Hum. Genet.* 22:363–68

Capo-Chichi JM, Tcherkezian J, Hamdan FF, Décarie JC, Dobrzeniecka S, et al. 2013. Disruption of TBC1D7, a subunit of the TSC1-TSC2 protein complex, in intellectual disability and megalencephaly. *J. Med. Genet.* 50:740–44

Chabás A, Cormand B, Grinberg D, Burguera JM, Balcells S, et al. 1995. Unusual expression of Gaucher's disease: cardiovascular calcifications in three sibs homozygous for the D409H mutation. *J. Med. Genet.* 32:740–42

Chae TH, Kim S, Marz KE, Hanson PI, Walsh CA. 2004. The *hyh* mutation uncovers roles for αSnap in apical protein localization and control of neural cell fate. *Nat. Genet.* 36:264–70

Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. 1998. Maternal fever and birth outcome: a prospective study. *Teratology* 58:251–57

Chen J, Knowles HJ, Hebert JL, Hackett BP. 1998. Mutation of the mouse hepatocyte nuclear factor/forkhead homologue 4 gene results in an absence of cilia and random left-right asymmetry. *J. Clin. Investig.* 102:1077–82

Chow CW, McKelvie PA, Anderson RM, Phelan EM, Klug GL, Rogers JG. 1990. Autosomal recessive hydrocephalus with third ventricle obstruction. *Am. J. Med. Genet.* 35:310–13

Chow KC, Lee CC, Lin TY, Shen WC, Wang JH, et al. 2000. Congenital enterovirus 71 infection: a case study with virology and immunohistochemistry. *Clin. Infect. Dis.* 31:509–12

Copp AJ, Greene ND. 2010. Genetics and development of neural tube defects. *J. Pathol.* 220:217–30

Corns R, Martin A. 2012. Hydrocephalus. *Surgery* 30:142–48

Correa A, Botto L, Liu Y, Mulinare J, Erickson JD. 2003. Do multivitamin supplements attenuate the risk for diabetes-associated birth defects? *Pediatrics* 111:1146–51

Cserr HF. 1971. Physiology of the choroid plexus. *Physiol. Rev.* 51:273–311

Dandy WE, Blackfan KD. 1913. An experimental and clinical study of internal hydrocephalus. *J. Am. Med. Assoc.* 61:2216–17

de Paula F, Vieira N, Starling A, Yamamoto LU, Lima B, et al. 2003. Asymptomatic carriers for homozygous novel mutations in the FKRP gene: the other end of the spectrum. *Eur. J. Hum. Genet.* 11:923–30

Debiec H, Christensen EI, Ronco PM. 1998. The cell adhesion molecule L1 is developmentally regulated in the renal epithelium and is involved in kidney branching morphogenesis. *J. Cell Biol.* 143:2067–79

Delaunoy JP, Dubos A, Marques Pereira P, Hanauer A. 2006. Identification of novel mutations in the RSK2 gene (*RPS6KA3*) in patients with Coffin–Lowry syndrome. *Clin. Genet.* 70:161–66

Di Costanzo S, Balasubramanian A, Pond HL, Rozkalne A, Pantaleoni C, et al. 2014. *POMK* mutations disrupt muscle development leading to a spectrum of neuromuscular presentations. *Hum. Mol. Genet.* 23:5781–92

Dinçer A, Yener U, Özek MM. 2011. Hydrocephalus in patients with neurofibromatosis type 1: MR imaging findings and the outcome of endoscopic third ventriculostomy. *AJNR. Am. J. Neuroradiol.* 32:643–46

Dobyns WB, Pagon RA, Armstrong D, Curry CJ, Greenberg F, et al. 1989. Diagnostic criteria for Walker-Warburg syndrome. *Am. J. Med. Genet.* 32:195–210

Doyle AJ, Doyle JJ, Bessling SL, Maragh S, Lindsay ME, et al. 2012. Mutations in the TGF-β repressor *SKI* cause Shprintzen-Goldberg syndrome with aortic aneurysm. *Nat. Genet.* 44:1249–54

Drielsma A, Jalas C, Simonis N, Désir J, Simanovsky N, et al. 2012. Two novel CCDC88C mutations confirm the role of DAPLE in autosomal recessive congenital hydrocephalus. *J. Med. Genet.* 49:708–12

Durbeej M, Talts JF, Henry MD, Yurchenco PD, Campbell KP, Ekblom P. 2001. Dystroglycan binding to laminin α1LG4 module influences epithelial morphogenesis of salivary gland and lung in vitro. *Differ.; Res. Biol. Divers.* 69:121–34

Edvardson S, Shaag A, Zenvirt S, Erlich Y, Hannon GJ, et al. 2010. Joubert syndrome 2 (JBTS2) in Ashkenazi Jews is associated with a *TMEM216* mutation. *Am. J. Hum. Genet.* 86:93–97

Ekici AB, Hilfinger D, Jatzwauk M, Thiel CT, Wenzel D, et al. 2010. Disturbed Wnt signalling due to a mutation in *CCDC88C* causes an autosomal recessive non-syndromic hydrocephalus with medial diverticulum. *Mol. Syndromol.* 1:99–112

Failler M, Gee HY, Krug P, Joo K, Halbritter J, et al. 2014. Mutations of *CEP83* cause infantile nephronophthisis and intellectual disability. *Am. J. Hum. Genet.* 94:905–14

Ferrante MI, Giorgio G, Feather SA, Bulfone A, Wright V, et al. 2001. Identification of the gene for oral-facial-digital type I syndrome. *Am. J. Hum. Genet.* 68:569–76

Finckh U, Schroder J, Ressler B, Veske A, Gal A. 2000. Spectrum and detection rate of *L1CAM* mutations in isolated and familial cases with clinically suspected L1-disease. *Am. J. Hum. Genet.* 92:40–46

Fried K. 1972. X-linked mental retardation and/or hydrocephalus. *Clin. Genet.* 3:258–63

Fukumitsu H, Ohmiya M, Nitta A, Furukawa S, Mima T, Mori K. 2000. Aberrant expression of neurotrophic factors in the ventricular progenitor cells of infant congenitally hydrocephalic rats. *Child's Nerv. Syst.* 16:516–21

Garavelli L, Guareschi E, Errico S, Simoni A, Bergonzini P, et al. 2007. Megalencephaly and perisylvian polymicrogyria with postaxial polydactyly and hydrocephalus (MPPH): report of a new case. *Neuropediatrics* 38:200–3

Garavelli L, Leask K, Zanacca C, Pedori S, Albertini G, et al. 2005. MRI and neurological findings in macrocephaly-cutis marmorata telangiectatica congenita syndrome: report of ten cases and review of the literature. *Genet. Couns.* 16:117–28

Gebbia M, Ferrero GB, Pilia G, Bassi MT, Aylsworth A, et al. 1997. X-linked *situs* abnormalities result from mutations in *ZIC3*. *Nat. Genet.* 17:305–8

Geis T, Marquard K, Rodl T, Reihle C, Schirmer S, et al. 2013. Homozygous dystroglycan mutation associated with a novel muscle-eye-brain disease-like phenotype with multicystic leucodystrophy. *Neurogenetics* 14:205–13

Godfrey C, Clement E, Mein R, Brockington M, Smith J, et al. 2007. Refining genotype phenotype correlations in muscular dystrophies with defective glycosylation of dystroglycan. *Brain: J. Neurol.* 130:2725–35

Gografe SI, Garbuzova-Davis S, Willing AE, Haas K, Chamizo W, Sanberg PR. 2003. Mouse model of Sanfilippo syndrome type B: relation of phenotypic features to background strain. *Comp. Med.* 53:622–32

Goto J, Tezuka T, Nakazawa T, Sagara H, Yamamoto T. 2008. Loss of Fyn tyrosine kinase on the C57BL/6 genetic background causes hydrocephalus with defects in oligodendrocyte development. *Mol. Cell. Neurosci.* 38:203–12

Greene ND, Copp AJ. 2014. Neural tube defects. *Annu. Rev. Neurosci.* 37:221–42
Gripp KW, Hopkins E, Doyle D, Dobyns WB. 2010. High incidence of progressive postnatal cerebellar enlargement in Costello syndrome: brain overgrowth associated with *HRAS* mutations as the likely cause of structural brain and spinal cord abnormalities. *Am. J. Med. Genet. Part A* 152A:1161–68
Hakim S, Adams RD. 1965. The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. *J. Neurol. Sci.* 2:307–27
Halbritter J, Bizet AA, Schmidts M, Porath JD, Braun DA, et al. 2013. Defects in the IFT-B component IFT172 cause Jeune and Mainzer-Saldino syndromes in humans. *Am. J. Hum. Genet.* 93:915–25
Hevner RF. 2005. The cerebral cortex malformation in thanatophoric dysplasia: neuropathology and pathogenesis. *Acta Neuropathol.* 110:208–21
Heye N, Dunne JW. 1995. Noonan's syndrome with hydrocephalus, hindbrain herniation, and upper cervical intracord cyst. *J. Neurol. Neurosurg. Psychiatry* 59:338–39
Hogue J, Lee C, Jelin A, Strecker MN, Cox VA, Slavotinek AM. 2013. Homozygosity for a *FBN1* missense mutation causes a severe Marfan syndrome phenotype. *Clin. Genet.* 84:392–93
Ibañez-Tallon I, Pagenstecher A, Fliegauf M, Olbrich H, Kispert A, et al. 2004. Dysfunction of axonemal dynein heavy chain Mdnah5 inhibits ependymal flow and reveals a novel mechanism for *hydrocephalus* formation. *Hum. Mol. Genet.* 13:2133–41
Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, et al. 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid βa. *Sci. Translational Med.* 4:147ra11
Ishida-Takagishi M, Enomoto A, Asai N, Ushida K, Watanabe T, et al. 2012. The Dishevelled-associating protein Daple controls the non-canonical Wnt/Rac pathway and cell motility. *Nat. Commun.* 3:859
Itoh K, Cheng L, Kamei Y, Fushiki S, Kamiguchi H, et al. 2004. Brain development in mice lacking L1-L1 homophilic adhesion. *J. Cell Biol.* 165:145–54
Jouet M, Rosenthal A, Armstrong G, MacFarlane J, Stevenson R, et al. 1994. X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. *Nat. Genet.* 7:402–7
Khonsari RH, Delezoide AL, Kang W, Hébert JM, Bessières B, et al. 2012. Central nervous system malformations and deformations in *FGFR2*-related craniosynostosis. *Am. J. Med. Genet. Part A* 158A:2797–806
Kibar Z, Salem S, Bosoi CM, Pauwels E, De Marco P, et al. 2011. Contribution of *VANGL2* mutations to isolated neural tube defects. *Clin. Genet.* 80:76–82
Kibar Z, Vogan KJ, Groulx N, Justice MJ, Underhill DA, Gros P. 2001. *Ltap*, a mammalian homolog of *Drosophila Strabismus/Van Gogh*, is altered in the mouse neural tube mutant Loop-tail. *Nat. Genet.* 28:251–55
Kiefer M, Eymann R, von Tiling S, Muller A, Steudel WI, Booz KH. 1998. The ependyma in chronic hydrocephalus. *Child's Nerv. Syst.* 14:263–70
Killer M, Arthur A, Al-Schameri AR, Barr J, Elbert D, et al. 2010. Cytokine and growth factor concentration in cerebrospinal fluid from patients with hydrocephalus following endovascular embolization of unruptured aneurysms in comparison with other types of hydrocephalus. *Neurochem. Res.* 35:1652–58
Kinsler VA, Thomas AC, Ishida M, Bulstrode NW, Loughlin S, et al. 2013. Multiple congenital melanocytic nevi and neurocutaneous melanosis are caused by postzygotic mutations in codon 61 of *NRAS*. *J. Investig. Dermatol.* 133:2229–36
Klezovitch O, Fernandez TE, Tapscott SJ, Vasioukhin V. 2004. Loss of cell polarity causes severe brain dysplasia in *Lgl1* knockout mice. *Genes Dev.* 18:559–71
Kobayashi K, Nakahori Y, Miyake M, Matsumura K, Kondo-Iida E, et al. 1998. An ancient retrotransposal insertion causes Fukuyama-type congenital muscular dystrophy. *Nature* 394:388–92
Kowitz A, Kadmon G, Eckert M, Schirrmacher V, Schachner M, Altevogt P. 1992. Expression and function of the neural cell adhesion molecule L1 in mouse leukocytes. *Eur. J. Immunol.* 22:1199–205
Kujat R, Miragall F, Krause D, Dermietzel R, Wrobel KH. 1995. Immunolocalization of the neural cell adhesion molecule L1 in non-proliferating epithelial cells of the male urogenital tract. *Histochem. Cell Biol.* 103:311–21
Kyttälä M, Tallila J, Salonen R, Kopra O, Kohlschmidt N, et al. 2006. *MKS1*, encoding a component of the flagellar apparatus basal body proteome, is mutated in Meckel syndrome. *Nat. Genet.* 38:155–57

Langenbach KJ, Rando TA. 2002. Inhibition of dystroglycan binding to laminin disrupts the PI3K/AKT pathway and survival signaling in muscle cells. *Muscle Nerve* 26:644–53

Lategan B, Chodirker BN, Del Bigio MR. 2010. Fetal hydrocephalus caused by cryptic intraventricular hemorrhage. *Brain Pathol.* 20:391–98

Lausch E, Hermanns P, Farin HF, Alanay Y, Unger S, et al. 2008. *TBX15* mutations cause craniofacial dysmorphism, hypoplasia of scapula and pelvis, and short stature in Cousin syndrome. *Am. J. Hum. Genet.* 83:649–55

Lee JH, Huynh M, Silhavy JL, Kim S, Dixon-Salazar T, et al. 2012. De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly. *Nat. Genet.* 44:941–45

Lee L, Campagna DR, Pinkus JL, Mulhern H, Wyatt TA, et al. 2008. Primary ciliary dyskinesia in mice lacking the novel ciliary protein Pcdp1. *Mol. Cell. Biol.* 28:949–57

Lesnik Oberstein SAJ, Kriek M, White SJ, Kalf ME, Szuhai K, et al. 2006. Peters Plus syndrome is caused by mutations in *B3GALTL*, a putative glycosyltransferase. *Am. J. Hum. Genet.* 79:562–66

Li X, Miyajima M, Arai H. 2005. Analysis of TGF-β2 and TGF-β3 expression in the hydrocephalic H-Tx rat brain. *Child's Nerv. Syst.* 21:32–38

Lindeman GJ, Dagnino L, Gaubatz S, Xu Y, Bronson RT, et al. 1998. A specific, nonproliferative role for E2F-5 in choroid plexus function revealed by gene targeting. *Genes Dev.* 12:1092–98

Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, et al. 2005. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in *TGFBR1* or *TGFBR2*. *Nat. Genet.* 37:275–81

Manya H, Sakai K, Kobayashi K, Taniguchi K, Kawakita M, et al. 2003. Loss-of-function of an *N*-acetylglucosaminyltransferase, POMGnT1, in muscle–eye–brain disease. *Biochem. Biophys. Res. Commun.* 306:93–97

Matsumura K, Chiba A, Yamada H, Fukuta-Ohi H, Fujita S, et al. 1997. A role of dystroglycan in schwannoma cell adhesion to laminin. *J. Biol. Chem.* 272:13904–10

Mee L, Honkala H, Kopra O, Vesa J, Finnilä S, et al. 2005. Hydrolethalus syndrome is caused by a missense mutation in a novel gene *HYLS1*. *Hum. Mol. Genet.* 14:1475–88

Mégarbané A, Pangrazio A, Villa A, Chouery E, Maarawi J, et al. 2013. Homozygous stop mutation in the *SNX10* gene in a consanguineous Iraqi boy with osteopetrosis and corpus callosum hypoplasia. *Eur. J. Med. Genet.* 56:32–35

Mirzaa GM, Conway RL, Gripp KW, Lerman-Sagie T, Siegel DH, et al. 2012. Megalencephaly-capillary malformation (MCAP) and megalencephaly-polydactyly-polymicrogyria-hydrocephalus (MPPH) syndromes: two closely related disorders of brain overgrowth and abnormal brain and body morphogenesis. *Am. J. Med. Genet. Part A* 158A:269–91

Mirzaa GM, Dodge NN, Glass I, Day C, Gripp K, et al. 2004. Megalencephaly and perisylvian polymicrogyria with postaxial polydactyly and hydrocephalus: a rare brain malformation syndrome associated with mental retardation and seizures. *Neuropediatrics* 35:353–59

Mirzaa GM, Parry DA, Fry AE, Giamanco KA, Schwartzentruber J, et al. 2014. De novo *CCND2* mutations leading to stabilization of cyclin D2 cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome. *Nat. Genet.* 46:510–15

Missmer SA, Suarez L, Felkner M, Wang E, Merrill AH Jr., et al. 2006. Exposure to fumonisins and the occurrence of neural tube defects along the Texas-Mexico border. *Environ. Health Perspect.* 114:237–41

Mitchell LE. 2005. Epidemiology of neural tube defects. *Am. J. Med. Genet. Part C Semin. Med. Genet.* 135C:88–94

Montanaro F, Gee SH, Jacobson C, Lindenbaum MH, Froehner SC, Carbonetto S. 1998. Laminin and α-dystroglycan mediate acetylcholine receptor aggregation via a MuSK-independent pathway. *J. Neurosci.* 18:1250–60

Morioka T, Hashiguchi K, Nagata S, Miyagi Y, Mihara F, et al. 2006. Fetal germinal matrix and intraventricular hemorrhage. *Pediatr. Neurosurg.* 42:354–61

Munch TN, Rasmussen ML, Wohlfahrt J, Juhler M, Melbye M. 2014. Risk factors for congenital hydrocephalus: a nationwide, register-based, cohort study. *J. Neurol. Neurosurg. Psychiatry* 85:1253–59

Murdoch JN, Doudney K, Paternotte C, Copp AJ, Stanier P. 2001. Severe neural tube defects in the *loop-tail* mouse result from mutation of *Lpp1*, a novel gene involved in floor plate specification. *Hum. Mol. Genet.* 10:2593–601

Nakamura K, Kato M, Tohyama J, Shiohama T, Hayasaka K, et al. 2014. *AKT3* and *PIK3R2* mutations in two patients with megalencephaly-related syndromes: MCAP and MPPH. *Clin. Genet.* 85:396–98

Niceta M, Stellacci E, Gripp KW, Zampino G, Kousi M, et al. 2015. Mutations impairing GSK3-mediated MAF phosphorylation cause cataract, deafness, intellectual disability, seizures, and a Down syndrome-like facies. *Am. J. Hum. Genet.* 96:816–25

Niihori T, Aoki Y, Narumi Y, Neri G, Cavé H, et al. 2006. Germline *KRAS* and *BRAF* mutations in cardio-facio-cutaneous syndrome. *Nat. Genet.* 38:294–96

Nonaka-Kinoshita M, Reillo I, Artegiani B, Martínez-Martínez MA, Nelson M, et al. 2013. Regulation of cerebral cortex size and folding by expansion of basal progenitors. *EMBO J.* 32:1817–28

Noor A, Windpassinger C, Patel M, Stachowiak B, Mikhailov A, et al. 2008. *CC2D2A*, encoding a coiled-coil and C2 domain protein, causes autosomal-recessive mental retardation with retinitis pigmentosa. *Am. J. Hum. Genet.* 82:1011–18

Ohata S, Nakatani J, Herranz-Pérez V, Cheng J, Belinson H, et al. 2014. Loss of *Dishevelled*s disrupts planar polarity in ependymal motile cilia and results in hydrocephalus. *Neuron* 83:558–71

Ohmiya M, Fukumitsu H, Nitta A, Nomoto H, Furukawa Y, Furukawa S. 2001. Administration of FGF-2 to embryonic mouse brain induces hydrocephalic brain morphology and aberrant differentiation of neurons in the postnatal cerebral cortex. *J. Neurosci. Res.* 65:228–35

Oi S. 2011. Classification of hydrocephalus: critical analysis of classification categories and advantages of "Multi-categorical Hydrocephalus Classification" (Mc HC). *Child's Nerv. Syst.* 27:1523–33

Olbrich H, Häffner K, Kispert A, Völkel A, Volz A, et al. 2002. Mutations in *DNAH5* cause primary ciliary dyskinesia and randomization of left-right asymmetry. *Nat. Genet.* 30:143–44

Oshita A, Kishida S, Kobayashi H, Michiue T, Asahara T, et al. 2003. Identification and characterization of a novel Dvl-binding protein that suppresses Wnt signalling pathway. *Genes Cells: Devoted Mol. Cell. Mech.* 8:1005–17

Pennarun G, Escudier E, Chapelin C, Bridoux AM, Cacheux V, et al. 1999. Loss-of-function mutations in a human gene related to *Chlamydomonas reinhardtii* dynein IC78 result in primary ciliary dyskinesia. *Am. J. Hum. Genet.* 65:1508–19

Pisano T, Meloni M, Cianchetti C, Falchi M, Nucaro A, Pruna D. 2008. Megalencephaly, polymicrogyria, and hydrocephalus (MPPH) syndrome: a new case with syndactyly. *J. Child Neurol.* 23:916–18

Porteous MEM, Cross I, Burn J. 1992. VACTERL with hydrocephalus: One end of the Fanconi anemia spectrum of anomalies? *Am. J. Med. Genet.* 43:1032–34

Poulton JS, Deng WM. 2006. Dystroglycan down-regulation links EGF receptor signaling and anterior–posterior polarity formation in the *Drosophila* oocyte. *PNAS* 103:12775–80

Putoux A, Thomas S, Coene KLM, Davis EE, Alanay Y, et al. 2011. *KIF*7 mutations cause fetal hydrolethalus and acrocallosal syndromes. *Nat. Genet.* 43:601–6

Qvarlander S, Lundkvist B, Koskinen LO, Malm J, Eklund A. 2013. Pulsatility in CSF dynamics: pathophysiology of idiopathic normal pressure hydrocephalus. *J. Neurol. Neurosurg. Psychiatry* 84:735–41

Radmanesh F, Caglayan AO, Silhavy JL, Yilmaz C, Cantagrel V, et al. 2013. Mutations in *LAMB1* cause cobblestone brain malformation without muscular or ocular abnormalities. *Am. J. Hum. Genet.* 92:468–74

Rauen KA. 2013. The RASopathies. *Annu. Rev. Genom. Hum. Genet.* 14:355–69

Reinker KA, Stevenson DA, Tsung A. 2011. Orthopaedic conditions in Ras/MAPK related disorders. *J. Pediatr. Orthop.* 31:599–605

Rekate HL. 2008. The definition and classification of hydrocephalus: a personal recommendation to stimulate debate. *Cerebrospinal Fluid Res.* 5:2

Reusch U, Bernhard O, Koszinowski U, Schu P. 2002. AP-1A and AP-3A lysosomal sorting functions. *Traffic* 3:752–61

Riemersma M, Mandel H, van Beusekom E, Gazzoli I, Roscioli T, et al. 2015. Absence of α- and β-dystroglycan is associated with Walker-Warburg syndrome. *Neurology* 84:2177–82

Rivière JB, Mirzaa GM, O'Roak BJ, Beddaoui M, Alcantara D, et al. 2012. De novo germline and postzygotic mutations in *AKT3*, *PIK3R2* and *PIK3CA* cause a spectrum of related megalencephaly syndromes. *Nat. Genet.* 44:934–40

Robertson SP, Twigg SR, Sutherland-Smith AJ, Biancalana V, Gorlin RJ, et al. 2003. Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. *Nat. Genet.* 33:487–91

Roscioli T, Kamsteeg EJ, Buysse K, Maystadt I, van Reeuwijk J, et al. 2012. Mutations in *ISPD* cause Walker-Warburg syndrome and defective glycosylation of α-dystroglycan. *Nat. Genet.* 44:581–85

Rosenthal A, Jouet M, Kenwrick S. 1992. Aberrant splicing of neural cell adhesion molecule L1 mRNA in a family with X-linked hydrocephalus. *Nat. Genet.* 2:107–12

Rousseau F, Bonaventure J, Legeai-Mallet L, Pelet A, Rozet JM, et al. 1994. Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. *Nature* 371:252–54

Saito F, Moore SA, Barresi R, Henry MD, Messing A, et al. 2003. Unique role of dystroglycan in peripheral nerve myelination, nodal structure, and sodium channel stabilization. *Neuron* 38:747–58

Sapiro R, Kostetskii I, Olds-Clarke P, Gerton GL, Radice GL, Strauss IJ. 2002. Male infertility, impaired sperm motility, and hydrocephalus in mice deficient in sperm-associated antigen 6. *Mol. Cell. Biol.* 22:6298–305

Satz JS, Barresi R, Durbeej M, Willer T, Turner A, et al. 2008. Brain and eye malformations resembling Walker–Warburg syndrome are recapitulated in mice by dystroglycan deletion in the epiblast. *J. Neurosci.* 28:10567–75

Schrander-Stumpel C, Fryns JP. 1998. Congenital hydrocephalus: nosology and guidelines for clinical approach and genetic counselling. *Eur. J. Pediatr.* 157:355–62

Seo JH, Zilber Y, Babayeva S, Liu J, Kyriakopoulos P, et al. 2011. Mutations in the planar cell polarity gene, Fuzzy, are associated with neural tube defects in humans. *Hum. Mol. Genet.* 20:4324–33

Shiang R, Thompson LM, Zhu YZ, Church DM, Fielder TJ, et al. 1994. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell* 78:335–42

Simeone RM, Rasmussen SA, Mei JV, Dollard SC, Frias JL, et al. 2013. A pilot study using residual newborn dried blood spots to assess the potential role of cytomegalovirus and *Toxoplasma gondii* in the etiology of congenital hydrocephalus. *Birth Defects Res. Part A Clin. Mol. Teratol.* 97:431–36

Simpson MA, Irving MD, Asilmaz E, Gray MJ, Dafou D, et al. 2011. Mutations in *NOTCH2* cause Hajdu-Cheney syndrome, a disorder of severe and progressive bone loss. *Nat. Genet.* 43:303–5

Slavotinek A, Kaylor J, Pierce H, Cahr M, DeWard SJ, et al. 2015. *CRB2* mutations produce a phenotype resembling congenital nephrosis, Finnish type, with cerebral ventriculomegaly and raised alpha-fetoprotein. *Am. J. Hum. Genet.* 96:162–69

Smith UM, Consugar M, Tee LJ, McKee BM, Maina EN, et al. 2006. The transmembrane protein meckelin (*MKS3*) is mutated in Meckel-Gruber syndrome and the wpk rat. *Nat. Genet.* 38:191–96

Smithells RW, Sheppard S, Schorah CJ. 1976. Vitamin deficiencies and neural tube defects. *Arch. Dis. Child.* 51:944–50

Sotak BN, Gleeson JG. 2012. Can't get there from here: cilia and hydrocephalus. *Nat. Med.* 18:1742–43

Spence HJ, Dhillon AS, James M, Winder SJ. 2004. Dystroglycan, a scaffold for the ERK-MAP kinase cascade. *EMBO Rep.* 5:484–89

Stevens E, Carss KJ, Cirak S, Foley AR, Torelli S, et al. 2013. Mutations in *B3GALNT2* cause congenital muscular dystrophy and hypoglycosylation of α-dystroglycan. *Am. J. Hum. Genet.* 92:354–65

Strain L, Wright AF, Bonthron DT. 1997. Fried syndrome is a distinct X linked mental retardation syndrome mapping to Xp22. *J. Med. Genet.* 34:535–40

Tarkar A, Loges NT, Slagle CE, Francis R, Dougherty GW, et al. 2013. DYX1C1 is required for axonemal dynein assembly and ciliary motility. *Nat. Genet.* 45:995–1003

Tarpey PS, Smith R, Pleasance E, Whibley A, Edkins S, et al. 2009. A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation. *Nat. Genet.* 41:535–43

Tarpey PS, Stevens C, Teague J, Edkins S, O'Meara S, et al. 2006. Mutations in the gene encoding the sigma 2 subunit of the adaptor protein 1 complex, *AP1S2*, cause X-linked mental retardation. *Am. J. Hum. Genet.* 79:1119–24

Teebi AS, Naguib KK. 1988. Autosomal recessive nonsyndromal hydrocephalus. *Am. J. Med. Genet.* 31:467–70

Thor G, Probstmeier R, Schachner M. 1987. Characterization of the cell adhesion molecules L1, N-CAM and J1 in the mouse intestine. *EMBO J.* 6:2581–86

Timal S, Hoischen A, Lehle L, Adamowicz M, Huijben K, et al. 2012. Gene identification in the congenital disorders of glycosylation type I by whole-exome sequencing. *Hum. Mol. Genet.* 21:4151–61

Tissir F, Qu Y, Montcouquiol M, Zhou L, Komatsu K, et al. 2010. Lack of cadherins Celsr2 and Celsr3 impairs ependymal ciliogenesis, leading to fatal hydrocephalus. *Nat. Neurosci.* 13:700–7

Tully HM, Dobyns WB. 2014. Infantile hydrocephalus: a review of epidemiology, classification and causes. *Eur. J. Med. Genet.* 57:359–68

Van Camp G, Vits L, Coucke P, Lyonnet S, Schrander-Stumpel C, et al. 1993. A duplication in the *L1CAM* gene associated with X-linked hydrocephalus. *Nat. Genet.* 4:421–25

van Reeuwijk J, Brunner HG, van Bokhoven H. 2005. Glyc-O-genetics of Walker–Warburg syndrome. *Clin. Genet.* 67:281–89

van Reeuwijk J, Grewal PK, Salih MAM, Beltrán-Valero de Bernabé D, McLaughlan JM, et al. 2007. Intragenic deletion in the *LARGE* gene causes Walker-Warburg syndrome. *Hum. Genet.* 121:685–90

Verhagen JMA, Schrander-Stumpel CTRM, Krapels IPC, de Die-Smulders CEM, van Lint FHM, et al. 2011. Congenital hydrocephalus in clinical practice: a genetic diagnostic approach. *Eur. J. Med. Genet.* 54:e542–47

Vieira NM, Elvers I, Alexander MS, Moreira YB, Eran A, et al. 2015. Jagged 1 rescues the Duchenne muscular dystrophy phenotype. *Cell* 163:1204–13

Vits L, Van Camp G, Coucke P, Fransen E, De Boulle K, et al. 1994. MASA syndrome is due to mutations in the neural cell adhesion gene *L1CAM*. *Nat. Genet.* 7:408–13

Vogel P, Read RW, Hansen GM, Payne BJ, Small D, et al. 2012. Congenital hydrocephalus in genetically engineered mice. *Vet. Pathol.* 49:166–81

Vos YJ, de Walle HE, Bos KK, Stegeman JA, Ten Berge AM, et al. 2010. Genotype-phenotype correlations in L1 syndrome: a guide for genetic counselling and mutation analysis. *J. Med. Genet.* 47:169–75

Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, et al. 1990. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. *Science* 249:181–86

Walsh T, Shahin H, Elkan-Miller T, Lee MK, Thornton AM, et al. 2010. Whole exome sequencing and homozygosity mapping identify mutation in the cell polarity protein GPSM2 as the cause of nonsyndromic hearing loss DFNB82. *Am. J. Hum. Genet.* 87:90–94

Wang T, Liu Y, Xu XH, Deng CY, Wu KY, et al. 2011. Lgl1 activation of rab10 promotes axonal membrane trafficking underlying neuronal polarization. *Dev. Cell* 21:431–44

Waters AM, Asfahani R, Carroll P, Bicknell L, Lescai F, et al. 2015. The kinetochore protein, *CENPF*, is mutated in human ciliopathy and microcephaly phenotypes. *J. Med. Genet.* 52:147–56

Wicker G, Prill V, Brooks D, Gibson G, Hopwood J, et al. 1991. Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): an intermediate clinical phenotype caused by substitution of valine for glycine at position 137 of arylsulfatase B. *J. Biol. Chem.* 266:21386–91

Wild A, Kalff-Suske M, Vortkamp A, Bornholdt D, Kônig R, Grzeschik KH. 1997. Point mutations in human *GLI3* cause Greig syndrome. *Hum. Mol. Genet.* 6:1979–84

Wilkie AOM, Slaney SF, Oldridge M, Poole MD, Ashworth GJ, et al. 1995. Apert syndrome results from localized mutations of *FGFR2* and is allelic with Crouzon syndrome. *Nat. Genet.* 9:165–72

Willems PJ, Brouwer OF, Dijkstra I, Wilmink J. 1987. X-linked hydrocephalus. *Am. J. Med. Genet.* 27:921–28

Willer T, Lee H, Lommel M, Yoshida-Moriguchi T, Beltrán-Valero de Bernabé D, et al. 2012. *ISPD* loss-of-function mutations disrupt dystroglycan O-mannosylation and cause Walker-Warburg syndrome. *Nat. Genet.* 44:575–80

Wlodarczyk BJ, Palacios AM, George TM, Finnell RH. 2012. Antiepileptic drugs and pregnancy outcomes. *Am. J. Med. Genet. Part A* 158A:2071–90

Wright R, Johnson D, Neumann M, Ksiazek TG, Rollin P, et al. 1997. Congenital lymphocytic choriomeningitis virus syndrome: a disease that mimics congenital toxoplasmosis or cytomegalovirus infection. *Pediatrics* 100:E9

Xiong H, Kobayashi K, Tachikawa M, Manya H, Takeda S, et al. 2006. Molecular interaction between fukutin and POMGnT1 in the glycosylation pathway of α-dystroglycan. *Biochem. Biophys. Res. Commun.* 350:935–41

Yagi H, Furutani Y, Hamada H, Sasaki T, Asakawa S, et al. 2003. Role of *TBX1* in human del22q11.2 syndrome. *Lancet* 362:1366–73

Yamasaki M, Kanemura Y. 2015. Molecular biology of pediatric hydrocephalus and hydrocephalus-related diseases. *Neurol. Med.-Chir.* 55:640–46

Yoshida A, Kobayashi K, Manya H, Taniguchi K, Kano H, et al. 2001. Muscular dystrophy and neuronal migration disorder caused by mutations in a glycosyltransferase, POMGnT1. *Dev. Cell* 1:717–24

Zlotogora J, Sagi M, Cohen T. 1994. Familial hydrocephalus of prenatal onset. *Am. J. Med. Genet.* 49:202–4