Comprehensive Brain Malformations Panel Sequence Analysis and Exon-Level Deletion/Duplication Testing of 103 Genes

PANEL GENE LIST

ACTB, ACTG1, ADGRG1, AHI1, AKT3, AMPD2, ARFGEF2, ARL13B, ARX*, ASPM, ATP6V0A2, B3GALNT2, B4GAT1**, B9D1, B9D2, C5orf42, CASK, CC2D2A, CCND2, CEP41, CEP104, CEP120, CEP290, CHMP1A*, CIT, CSPP1, CUL4B, DCHS1*, DCX, DYNC1H1, EXOSC3, FAT4, FKRP**, FKTN, FLNA, GMPPB, GPSM2, IFT172, INPP5E, ISPD, KATNB1, KIAA0586, KIF1BP,KIF2A, KIF5C, KIF7*, LAMB1, LAMC3, LARGE1, MKS1, NDE1, NEDD4L, NPHP1, NPHP3, OCLN*^, OFD1, OPHN1, PAFAH1B1, PIK3CA, PIK3R2, POMGNT1*, POMGNT2, POMK, POMT1, POMT2, PQBP1, RAB18, RAB3GAP1, RAB3GAP2, RARS2, RELN, RPGRIP1L, RTTN, SEPSECS, SRD5A3, SRPX2, TBC1D20, TCTN1, TCTN2, TCTN3, TMEM5, TMEM67, TMEM138, TMEM216, TMEM231, TMEM237, TSEN2, TSEN15, TSEN34, TSEN54, TTC21B, TUBA1A*, TUBA8, TUBB, TUBB2A*, TUBB2B, TUBB3, TUBB4A*, TUBG1, VLDLR, VPS53, VRK1, WDR62*

*Only large deletion/duplications may be detected for the *ACTB, ARX, CHMP1A, DCHS1, KIF7, OCLN, POMGNT1, TUBA1A, TUBB2A and TUBB4A* genes

**No deletion/duplication analysis for the *B4GAT1* and *FKRP* genes

^No sequencing of exons 5-9 of the *OCLN* gene

CLINICAL FEATURES

Structural brain malformations result from disturbances in normal brain development and are associated with significant clinical variability depending on the location and nature of the malformation. This group of disorders is often associated with developmental and neurological symptoms such as intellectual disability, epilepsy, and movement disorders. In recent years, advances in neuroimaging have enabled better classification systems for the various types of structure brain malformations and assisted with the identification of the genetic etiology for many of these disorders, including cortical malformations, Joubert syndrome, and pontocerebellar hypoplasia.

Cortical brain malformations caused by abnormal neuronal migration lead to lissencephaly, subcortical band heterotopia, or periventricular nodular heterotopias, while abnormal folding of the cerebral cortex leads to polymicrogyria. Pathogenic variants in different genes causing cortical malformations can lead to overlapping clinical phenotypes, often including epilepsy, intellectual disability, and cerebral palsy.

Joubert syndrome is characterized by the presence of a midbrain and hindbrain abnormality called a molar tooth sign, which results from cerebellar hypoplasia, thickened superior cerebellar peduncles, and a deepened interpeduncular fossa. Individuals with Joubert syndrome typically exhibit hypotonia, developmental delay, and variable cognitive impairment, sometimes also associated with breathing abnormalities and oculomotor apraxia. Variant forms of this disorder can also include retinal dystrophy, renal disease, occipital encephalocele, polydactyly, hepatic fibrosis, or other abnormalities.

Pontocerebellar hypoplasia (PCH) results from a combination of a developmental defect of the ventral pons and progressive atrophy of the cerebellum during prenatal development. There are multiple different types of PCH that share overlapping clinical features, including hypotonia, developmental delay, seizures, and movement disorders. Specific subtypes of PCH are also associated with spinal muscular atrophy, progressive microcephaly, severe generalized clonus, hyperekplexia, camptodactyly, and micrognathia.

GENETICS

The genetic brain malformation disorders demonstrate significant clinical and genetic heterogeneity. These disorders are inherited in an autosomal dominant, autosomal recessive, or X-linked manner.

TEST METHODS

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

TEST SENSITIVITY

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype. Specific information about the diagnostic yield for each gene in selected populations is summarized in the following table(s). The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. For the OCLN gene, sequencing of exons 5-9 was not performed. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: B4GAT1 and FKRP genes, no copy number testing, ACTB, ARX, CHMP1A, DCHS1, KIF7, OCLN, POMGNT1, TUBA1A, TUBB2A and TUBB4A genes, only whole gene deletions or duplications may be detected.

Syndrome/Type of Malformation	Gene	Protein	Inheritance	Disease Association
Cortical brain malformations	*ACTB**	Actin, Beta	AD	Up to 80% of Baraitser-Winter syndrome[1]
	ACTG1	Actin, Gamma-1	AD	Up to 20% of Baraitser-Winter syndrome[1]
	ADGRG1 (GPR56)	Adhesion G protein-coupled receptor G1	AR	Up to 100% of typical of bilateral frontoparietal polymicrogyria[2,3]
	AKT3	V-AKT murine thymoma viral oncogene homolog 3	AD	~30% of megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH)[4]
	ARFGEF2	ADP ribosylation factor guanine nucleotide exchange factor 2	AR	Rare in PVNH[5,6]

	*ARX**	Aristaless-related homeobox protein	XL	70-95% of XLAG[7,8], 3-10% in XLID[9,10]
	ASPM	Abnormal spindle-like, microcephaly-associated protein	AR	25-50% of MCPH[11]
	ATP6V0A2	Lysosomal H(+)-ATPase V0 subunit A2	AR	21-24% of autosomal recessive cutis laxa type II[12,13]
	B3GALNT2	Beta-1,3-N-Acetylgalactosaminyltransferase 2	AR	Rare in alpha-dystroglycanopathies[14]
	*B4GAT1 (B3GNT1)***	Beta-1,4-Glucuronyltransferase 1	AR	Rare in alpha-dystroglycanopathies[15,16]
	CCND2	Cyclin D2	AD	~30% of MPPH[4]
	CIT	Citron rho-interacting serine/threonine kinase	AR	Rare in MCPH [17,18,19]
	CUL4B	Cullin 4B	XL	2-3% in XLID[20,21]
	*DCHS1**	Dachsous cadherin-related 1	AR	~40% of Van Maldergem syndrome[22]
	DCX	Doublecortin	XL	Up to 100% XL lissencephaly 10% of classic lissencephaly 85% females and ~30% males with SBH[8,23,24]
	DYNC1H1	Dynein, cytoplasmic 1, heavy chain 1	AD	5% of malformations of cortical development (MCD)[25]
	FAT4	FAT atypical cadherin 4	AR	~20% of Hennekam syndrome[26] ~60% of Van Maldergem syndrome[22]
	*FKRP***	Fukutin-related protein	AR	~2% of cobblestone lissencephaly[28,29] 9% of alpha-dystroglycanopathies[30] 6% of limb-girdle MD[31]
	FKTN	Fukutin	AR	~7% of alpha-dystroglycanopathies[32] Does not include the Japanese founder mutation in the 3' UTR[33]
	FLNA	Filamin A	XL	49% of PVNH[6]
	GMPPB	GDP-Mannose Pyrophosphorylase B	AR	Rare in alpha-dystroglycanopathies[34,35]

	GPSM2	G protein signaling modulator 2	AD	Up to 100% of Chudley-McCullough syndrome[36]
	ISPD	Isoprenoid synthase domain-containing protein	AR	~6% of cobblestone lissencephaly[29] ~30% of Walker-Warburg syndrome and ~11% of alpha-dystroglycanopathies[37,38] Rare in LGMD[39]
	KATNB1	Katanin regulatory subunit B1	AR	<1% of MCD[40,41]
	KIF1BP (KIAA1279)	KIF1 binding protein	AR	Up to 100% of Goldberg-Shprintzen megacolon syndrome[42,43]
	KIF2A	Kinesin heavy chain member 2A	AD	1% of MCD[25,44]
	KIF5C	Kinesin family member 5C	AD	Rare in MCD[25,45,46]
	LAMB1	Laminin, Beta-1	AR	Rare in cobblestone lissencephaly[47]
	LAMC3	Laminin gamma-3	AR	Rare in pachygyria[48]
	LARGE1	LARGE xylosyl- and glucuronyltransferase 1	AR	2-5% of cobblestone lissencephaly[28,29] ~1% of alpha-dystroglycanopathies[30,32]
	NDE1	nudE neurodevelopment protein 1	AR	Rare[49,50,51]
	NEDD4L	Neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase	AD	Unknown in PVNH[52]
	OCLN^*	Occludin	AR	Up to 100% of bilateral band-like calcification and polymicrogyria[53,54]
	PAFAH1B1 (LIS)	Platelet-Activating Factor Acetylhydrolase 1b, Regulatory Subunit 1	AD	~40-65% of classic lissencephaly[23,55]
	PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	AD	~40% of megalencephaly-capillary malformation (MCAP)[56]
	PIK3R2	Phosphoinositide-3-kinase regulatory subunit 2	AD	~40% of MPPH[4]
	*POMGNT1**	Protein O-Mannose Beta 1-2-N-Acetylglucosaminyltransferase	AR	11-18% of cobblestone lissencephaly[28,29]

				8-10% of alpha-dystroglycanopathies[30,32]
	POMGNT2 (GTDC2)	Protein O-Mannose Beta-1,4-N-Acetylglucosaminyltransferase 2	AR	Rare in alpha-dystroglycanopathies[57]
	POMK	Protein O-Mannose kinase	AR	Unknown in alpha-dystroglycanopathies[58,59]
	POMT1	Protein O-Mannosyltransferase 1	AR	27-34% of cobblestone lissencephaly[28,29] 9-21% of alpha-dystroglycanopathies[30,32]
	POMT2	Protein O-Mannosyltransferase 2	AR	8-11% of cobblestone lissencephaly[28,29] 9-11% of alpha-dystroglycanopathies[30,32]
	PQBP1	Polyglutamine binding protein 1	XL	Unknown in PVNH[60] ~1% of X-linked intellectual disability[61]
	RAB18	RAS-associated protein	AR	5% of Warburg Micro syndrome[62]
	RAB3GAP1	Rab3 GTPase-activating protein (catalytic subunit)	AR	41% of Warburg Micro syndrome[62]
	RAB3GAP2	Rab3 GTPase-activating protein (non-catalytic subunit)	AR	7% of Warburg Micro syndrome[62]
	RELN	Reelin	AR	Rare[63,64]
	RTTN	Rotatin	AR	Rare[65]
	SRD5A3	Steroid-5-alpha-reductase 3	AD	Up to 100% of SRD5A3-CDG[66]
	SRPX2	Sushi repeat-containing protein	XL	Rare[67]
	TBC1D20	TBC1 domain family, member 20	AR	5% of Warburg Micro syndrome[68]
	TMEM5	Transmembrane protein 5	AR	~6% of cobblestone lissencephaly[29] Rare in alpha-dystroglycanopathies[57]
	*TUBA1A**	Tubulin, Alpha-1A	AD	1% of classic lissencephaly 30% of lissencephaly with cerebellar hypoplasia[69,70] ~43% of complex cortical malformations[71]
	TUBA8	Tubulin, Alpha-8	AR	Rare[72]
	TUBB	Tubulin, Beta	AD	~3% of complex cortical malformations[71]
	*TUBB2A**	Tubulin, Beta-2A	AD	Rare[73]

	TUBB2B	Tubulin, Beta-2B	AD	~3% in cortical malformations including lissencephaly and polymicrogyria[69,74] ~17% of complex cortical malformations[71]
	TUBB3	Tubulin, Beta-3	AD	~10% of complex cortical malformations[71]
	*TUBB4A**	Tubulin, Beta-4A	AD	Rare in hypomyelinating leukodystrophy-6 (HLD6)[75]
	TUBG1	Tubulin, Gamma-1	AD	~3% of complex cortical malformations[71]
	VLDLR	Very low density lipoprotein receptor	AR	Rare cerebellar hypoplasia with simplified gyri[76,77]
	WDR62	WD repeat-containing protein 62	AR	Unknown[78]
Joubert syndrome and related disorders (JSRD)	*AHI1*	Abelson helper integration site 1 (Jouberin)	AR	6-16% of JSRD[79-83]
	ARL13B	ADP-ribosylation factor-like 13B	AR	Rare in JSRD[84,85]
	B9D1	B9 domain-containing protein 1	AR	Rare in JSRD[81,86,87]
	B9D2	B9 domain-containing protein 2	AR	Rare in JSRD[88,89]
	C5orf42	Chromosome 5 open reading frame 42	AR	7-25% of JSRD[79-81,90]; 45% of JSRD in French-Canadian[91]; 82% of Oral-facial-digital syndrome type 6 (OFDVI)[92]
	CC2D2A (MKS6)	Coiled-coil and C2 domains-containing protein 2A	AR	2-10% of JSRD[79,81,88,93-98]
	CEP41	Centrosomal protein, 41kDa	AR	Rare in JSRD[99]
	CEP104	Centrosomal protein, 104kDa	AR	Rare in JSRD[100]
	CEP120	Centrosomal protein, 290kDa	AR	Rare in JSRD[101,102]
	CEP290 (NPHP6)	Centrosomal protein, 290kDa	AR	2-25% of JSRD[79-81,97,98,103-108]; 50% in JSRD with cerebello-oculo-renal phenotype (CORS)[109]
	CSPP1	Centrosome and spindle pole associated protein 1	AR	2-5% of JSRD[79,88,110-112]
	IFT172	Intraflagellar transport 172	AR	Rare in JSRD[88,113,114]
	INPP5E	Inositol polyphosphate-5-phosphatase, 72kDa	AR	2-4% of JSRD[79,81,88,115,116]

	KIAA0586	TALPID3 protein	AR	2-7% of JSRD[117-121]
	*KIF7**	Kinesin family member 7	AR	Rare in JSRD, fetal hydrolethalus and acrocallosal syndromes[79,88,122-125]
	MKS1	MKS1 B9-domain containing protein (Meckel syndrome type 1 protein)	AR	1-2% of JSRD[79,87,88]; 7-30% of Meckel Gruber syndrome[98,126,127,128]
	NPHP1	Nephrocystin 1	AR	2-7% of JSRD (homozygous gene deletion)[129-132]
	NPHP3	Nephrocystin 3	AR	3% of JSRD[104,133-136]
	OFD1 (CXorf5)	Oral-facial-digital syndrome 1 protein	XL	Rare in JSRD[79,81,88,137-140]
	RGRIP1L (NPHP8)	RPGRIP1-like protein	AR	2-5% in Joubert syndrome (mostly cerebro-renal type)[79,81,88,94,98,141-144]
	TCTN1	Tectonic family member 1	AR	Rare in JSRD[79,80,145,146]
	TCTN2	Tectonic family member 2	AR	Rare in JSRD[79,88,140,147-149]
	TCTN3	Tectonic family member 3	AR	Rare in JSRD[79,147,150]
	TMEM67 (MKS3)	Transmembrane protein 67 (Meckelin)	AR	1-10% of JSRD[79,81,88,97,104,151-153]; 15-28% of Meckel Gruber syndrome[98,126]; 75-83% of JSRD with liver involvement (including COACH syndrome)[94]
	TMEM138	Transmembrane protein 138	AR	Rare in JSRD[79,98,154]
	TMEM216	Transmembrane protein 216	AR	3% of JSRD[88,154,155]; Up to 100% of JSRD in Ashkenazi Jewish[155,156]; Rare in Oral-facial-digital syndrome type 6 (OFDVI)[92]
	TMEM231	Transmembrane protein 231	AR	Rare in Joubert and Meckel Gruber syndromes[81,157-159]
	TMEM237 (ALS2CR4)	Transmembrane protein 237	AR	Rare in Joubert and Meckel Gruber syndromes[79,80,98,128,160]
	TTC21B	Tetratricopeptide repeat domain-containing protein 21B	AR	Unknown in JSRD[97,161-163]
Pontocerebellar hypoplasia	*AMPD2*	Adenosine monophosphate deaminase 2	AR	Rare[164,165]

	CASK	Calcium/calmodulin-dependent serine protein kinase	XL	~4% in cerebellar hypoplasia and intellectual disability[166-168]
	*CHMP1A**	Charged multivesicular body protein 1A	AR	Rare[169]
	EXOSC3	Exosome component 3	AR	~50% of PCH1[170]
	OPHN1	Oligophrenin 1	XL	12% in XLID with cerebellar hypoplasia; ~1% in XLID[171]
	RARS2	Arginyl-tRNA synthetase 2	AR	Rare[172-174]
	RELN	Reelin	AR	Rare[63,64]
	SEPSECS	O-phosphoserine tRNA-selenocysteine tRNA synthase	AR	Rare[175,176]
	TSEN2	tRNA splicing endonuclease 2	AR	~1-2% of PCH2 and PCH4[177,178]
	TSEN15	tRNA splicing endonuclease 15	AR	Rare[179]
	TSEN34	tRNA splicing endonuclease 34	AR	~2% of PCH2 and 4[177,178]
	TSEN54	tRNA splicing endonuclease 54	AR	~60% of PCH (A307S common)[168,174,177,178]
	TUBA1A	Tubulin, Alpha-1A	AD	~30% of lissencephaly with cerebellar hypoplasia[69,70]
	TUBA8	Tubulin, Alpha-8	AR	Rare[72]
	TUBB2B	Tubulin, Beta-2B	AD	~3% in cortical malformations including lissencephaly and polymicrogyria[69,74] ~17% of complex cortical malformations[71]
	TUBB3	Tubulin, Beta-3	AD	~10% of complex cortical malformations, including PCH[71]
	VLDLR	Very low density lipoprotein receptor	AR	Rare cerebellar hypoplasia with simplified gyri[76,77]
	VPS53	Vacuolar protein sorting 53	AR	Rare[180]
	VRK1	Vaccinia-related kinase 1	AR	Rare[181]

*Only large deletion/duplications may be detected for the ACTB, ARX, CHMP1A, DCHS1, KIF7, OCLN, POMGNT1, TUBA1A, TUBB2A and TUBB4A genes
**No deletion/duplication analysis for the B4GAT1 and FKRP genes
^No sequencing of exons 5-9 of the OCLN gene

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