# 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 | Inh. | Disease Associations |
|---|---|---|---|---|
| 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] |

| Syndrome / Type of Malformation | Gene | Protein | Inh. | Disease Associations |
|---|---|---|---|---|
| | *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<br>10% of classic lissencephaly<br>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]<br>~60% of Van Maldergem syndrome[22] |
| | *FKRP*** | Fukutin-related protein | AR | ~2% of cobblestone lissencephaly[28,29]<br>9% of alpha-dystroglycanopathies[30]<br>6% of limb-girdle MD[31] |
| | *FKTN* | Fukutin | AR | ~7% of alpha-dystroglycanopathies[32]<br>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]<br>~30% of Walker-Warburg syndrome and ~11% of alpha-dystroglycanopathies[37,38]<br>Rare in LGMD[39] |

| Syndrome / Type of Malformation | Gene | Protein | Inh. | Disease Associations |
|---|---|---|---|---|
| | *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]<br>~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]<br>8-10% of alpha-dystroglycanopathies[30,32] |
| | *POMGNT2 (GTDC2)* | Protein O-Mannose Beta-1,4-N-Acetylglucosaminyltransferase 2 | AR | Rare in alpha-dystroglycanopathies[57] |

| Syndrome / Type of Malformation | Gene | Protein | Inh. | Disease Associations |
|---|---|---|---|---|
| | *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]<br>9-21% of alpha-dystroglycanopathies[30,32] |
| | *POMT2* | Protein O-Mannosyltransferase 2 | AR | 8-11% of cobblestone lissencephaly[28,29]<br>9-11% of alpha-dystroglycanopathies[30,32] |
| | *PQBP1* | Polyglutamine binding protein 1 | XL | Unknown in PVNH[60]<br>~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]<br>Rare in alpha-dystroglycanopathies[57] |
| | *TUBA1A** | Tubulin, Alpha-1A | AD | 1% of classic lissencephaly<br>30% of lissencephaly with cerebellar hypoplasia[69,70]<br>~43% of complex cortical malformations[71] |

| Syndrome / Type of Malformation | Gene | Protein | Inh. | Disease Associations |
|---|---|---|---|---|
| | *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] |

| Syndrome / Type of Malformation | Gene | Protein | Inh. | Disease Associations |
|---|---|---|---|---|
| | *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 |

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|---|---|---|---|---|
| | | | | 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] |

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|---|---|---|---|---|
| | 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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