Cortical Brain Malformations Panel
Sequence Analysis and Exon-Level Deletion/Duplication Testing of 61 Genes

Panel Gene List: ACTB*, ACTG1, ADGRG1, AKT3, ARFGEF2, ARX*, ASPM, ATP6V0A2, B3GALNT2, B4GAT1**, CCND2, CIT, CUL4B, DCHS1*, DCX, DYNC1H1, FAT4, FKRP**, FKTN, FLNA, GMPPB, GPSM2, ISPD, KATNB1, KIF1BP, KIF2A, KIF5C, LAMB1, LAMC3, LARGE1, NDE1, NEDD4L, OCLN*^, PAFAH1B1, PIK3CA, PIK3R2, POMGNT1*, POMGNT2, POMK, POMT1, POMT2, PQBP1, RAB18, RAB3GAP1, RAB3GAP2, RELN, RTTN, SRD5A3, SRPX2, TBC1D20, TMEM5, TUBA1A*, TUBA8, TUBB, TUBB2A*, TUBB2B, TUBB3, TUBB4A*, TUBG1, VLDLR, WDR62

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

Clinical Features:

Abnormal neuronal migration leads to a variety of brain malformation disorders, including lissencephalies and subcortical band or periventricular nodular heterotopias.[1-4] MRI is necessary to detect and classify the abnormality in this group of cortical brain malformation disorders. While the neuroradiologic examination often delineates the specific type of malformation in an individual, lissencephaly, heterotopias, and polymicrogyria can sometimes be coincident.[5-7]

Lissencephaly is characterized by a thickened cortex and the absence of folds or gyri (agyria) or the presence of abnormally wide gyri (pachygyria). Lissencephalies can present in different forms and with varying severity, ranging from complete agyria to mixed agyria and pachygyria, or simplified gyri with subcortical band heterotopia (double cortex) (SBH). Lissencephalies uniformly cause developmental delay, epilepsy, and intellectual disability.[8]

Periventricular nodular heterotopia (PVNH) is characterized by the presence of uncalcified nodules of gray matter along the lateral ventricles.[1,9] X-linked PVNH is typically lethal in males, and affected females mainly present with focal seizures. A more severe phenotype, including microcephaly, intellectual disability, epilepsy, and quadriparesis is seen in a rare autosomal recessive form of PVNH.

Polymicrogyria results from abnormal folding of the cerebral cortex, leading to an excessive number of small gyri that can be distinguished from the absence of gyri and thickened cortex in lissencephaly.[1,4,10] Polymicrogyria restricted to a specific region of the cortex (focal polymicrogyria) can cause minimal neurologic impairment, but when it is widespread (generalized polymicrogyria) the phenotype is very severe and can consist of intractable epilepsy, intellectual disability, and cerebral palsy.

Genetics:
The various forms of cortical brain malformations demonstrate clinical and genetic heterogeneity.[11] Classic lissencephaly occurs as an autosomal dominant, autosomal recessive, or X-linked trait.[1,4] PAFAH1B1 (LIS1) is among the most prominent genes mutated in individuals with lissencephaly. Loss of PAFAH1B1 alone causes epilepsy and developmental delay, but with absence of severe dysmorphism. Deletion of this gene along with adjacent ones in the terminal end of the short arm of chromosome 17 causes Miller-Dieker syndrome, characterized by epilepsy, dysmorphic features, severe developmental delay and, occasionally, heart defects and omphalocele. Somatic variants in PAFAH1B1 and DCX have been described.[9,10] Cobblestone lissencephaly and lissencephaly with cerebellar hypoplasia segregate as autosomal recessive disorders and lissencephaly with agenesis of the corpus callosum is an X-linked disorder. Lissencephaly can sometimes occur together with heterotopias or polymicrogyria, depending on the affected gene and the type of pathogenic variant. PVNH most often presents as an X-linked dominant trait, but a rare autosomal recessive form also exists.[9] Polymicrogyria can present as an isolated finding or can appear alongside other brain malformations, depending on the gene affected and the type of pathogenic variant.[10] There are autosomal dominant as well as recessive forms of polymicrogyria.

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested 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, OCLN, POMGNT1, TUBA1A, TUBB2A and TUBB4A genes, only whole gene deletions or duplications may be detected.

Gene	Protein	Inh.	Disease Associations
*ACTB**	Actin, Beta	AD	Up to 80% of Baraitser-Winter syndrome[12]
ACTG1	Actin, Gamma-1	AD	Up to 20% of Baraitser-Winter syndrome[12]
ADGRG1 (GPR56)	Adhesion G protein-coupled receptor G1	AR	Up to 100% of typical of bilateral frontoparietal polymicrogyria[13,14]
AKT3	V-AKT murine thymoma viral oncogene homolog 3	AD	~30% of megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH)[15]
ARFGEF2	ADP ribosylation factor guanine nucleotide exchange factor 2	AR	Rare in PVNH[16,17]
*ARX**	Aristaless-related homeobox protein	XL	70-95% of XLAG[18,19], 3-10% in XLID[20,21]
ASPM	Abnormal spindle-like, microcephaly-associated protein	AR	25-50% of MCPH[22]
ATP6V0A2	Lysosomal H(+)-ATPase V0 subunit A2	AR	21-24% of autosomal recessive cutis laxa type II[23,24]
B3GALNT2	Beta-1,3-N-Acetylgalactosaminyltransferase 2	AR	Rare in alpha-dystroglycanopathies[25]
*B4GAT1 (B3GNT1)***	Beta-1,4-Glucuronyltransferase 1	AR	Rare in alpha-dystroglycanopathies[26,27]
CCND2	Cyclin D2	AD	~30% of MPPH[15]
CIT	Citron rho-interacting serine/threonine kinase	AR	Rare in MCPH[28,29,30]
CUL4B	Cullin 4B	XL	2-3% in XLID[31,32]

Gene	Protein	Inh.	Disease Associations
*DCHS1**	Dachsous cadherin-related 1	AD/ AR	~40% of Van Maldergem syndrome[33]
DCX	Doublecortin	XL	Up to 100% XL lissencephaly,10% of classic lissencephaly, 85% females and ~30% males with SBH[8,19,34]
DYNC1H1	Dynein, cytoplasmic 1, heavy chain 1	AD	5% of malformations of cortical development (MCD)[35]
FAT4	FAT atypical cadherin 4	AR	~20% of Hennekam syndrome[36] ~60% of Van Maldergem syndrome[33]
*FKRP***	Fukutin-related protein	AR	~2% of cobblestone lissencephaly[37,38], 9% of alpha-dystroglycanopathies[39], 6% of limb-girdle MD[40]
FKTN	Fukutin	AR	~7% of alpha-dystroglycanopathies[41] Does not include the Japanese founder mutation in the 3' UTR[42]
FLNA	Filamin A	XL	49% of PVNH[17]
GMPPB	GDP-Mannose Pyrophosphorylase B	AR	Rare in alpha-dystroglycanopathies[43,44]
GPSM2	G protein signaling modulator 2	AR	Up to 100% of Chudley-McCullough syndrome[45]
ISPD	Isoprenoid synthase domain-containing protein	AR	~6% of cobblestone lissencephaly[38], ~30% of Walker-Warburg syndrome and ~11% of alpha-dystroglycanopathies[46,47] Rare in LGMD[48]
KATNB1	Katanin regulatory subunit B1	AR	<1% of MCD[49,50]
KIF1BP (KIAA1279)	KIF1 binding protein	AR	Up to 100% of Goldberg-Shprintzen megacolon syndrome[51,52]

Gene	Protein	Inh.	Disease Associations
KIF2A	Kinesin heavy chain member 2A	AD	1% of MCD[34,53]
KIF5C	Kinesin family member 5C	AD	Rare in MCD[34,54,55]
LAMB1	Laminin, Beta-1	AR	Rare in cobblestone lissencephaly[56]
LAMC3	Laminin, Gamma-3	AR	Rare in pachygyria[57]
LARGE1	LARGE xylosyl- and glucuronyltransferase 1	AR	2-5% of cobblestone lissencephaly[37,38] ~1% of alpha-dystroglycanopathies[39,40]
NDE1	nudE neurodevelopment protein 1	AR	Rare[58,59,60]
NEDD4L	Neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase	AD	Unknown in PVNH[61]
OCLN^*	Occludin	AR	Up to 100% of bilateral band-like calcification and polymicrogyria[62,63]
PAFAH1B1 (LIS1)	Platelet-Activating Factor Acetylhydrolase 1b, Regulatory Subunit 1	AD	~40-65% of classic lissencephaly[8,64]
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	AD	~40% of megalencephaly-capillary malformation (MCAP)[65]
PIK3R2	Phosphoinositide-3-kinase regulatory subunit 2	AD	~40% of MPPH[15]
*POMGNT1**	Protein O-Mannose Beta 1-2-N-Acetylglucosaminyltransferase	AR	11-18% of cobblestone lissencephaly[37,38] 8-10% of alpha-dystroglycanopathies[39,40]
POMGNT2 (GTDC2)	Protein O-Mannose Beta-1,4-N-Acetylglucosaminyltransferase 2	AR	Rare in alpha-dystroglycanopathies[66]
POMK	Protein O-Mannose kinase	AR	Unknown in alpha-dystroglycanopathies[67,68]
POMT1	Protein O-Mannosyltransferase 1	AR	27-34% of cobblestone lissencephaly[37,38] 9-21% of alpha-dystroglycanopathies[39,40]
POMT2	Protein O-Mannosyltransferase 2	AR	8-11% of cobblestone lissencephaly[37,38] 9-11% of alpha-

Gene	Protein	Inh.	Disease Associations
			dystroglycanopathies[39,40]
PQBP1	Polyglutamine binding protein 1	XL	Unknown in PVNH[69] ~1% of X-linked intellectual disability[70]
RAB18	RAS-associated protein	AR	5% of Warburg Micro syndrome[71]
RAB3GAP1	Rab3 GTPase-activating protein (catalytic subunit)	AR	41% of Warburg Micro syndrome[71]
RAB3GAP2	Rab3 GTPase-activating protein (non-catalytic subunit)	AR	7% of Warburg Micro syndrome[71]
RELN	Reelin	AR	Rare[72,73]
RTTN	Rotatin	AR	Rare[74]
SRD5A3	Steroid-5-alpha-reductase 3	AR	Up to 100% of SRD5A3-CDG[75]
SRPX2	Sushi repeat-containing protein	XL	Rare[76]
TBC1D20	TBC1 domain family, member 20	AR	5% of Warburg Micro syndrome[77]
TMEM5	Transmembrane protein 5	AR	~6% of cobblestone lissencephaly[40] Rare in alpha-dystroglycanopathies[67]
*TUBA1A**	Tubulin, Alpha-1A	AD	1% of classic lissencephaly 30% of lissencephaly with cerebellar hypoplasia[5,78] ~43% of complex cortical malformations[79]
TUBA8	Tubulin, Alpha-8	AR	Rare[80]
TUBB	Tubulin, Beta	AD	~3% of complex cortical malformations[81]
*TUBB2A**	Tubulin, Beta-2A	AD	Rare[81]
TUBB2B	Tubulin, Beta-2B	AD	~3% in cortical malformations including lissencephaly and polymicrogyria[5,82] ~17% of complex cortical malformations[79]

Gene	Protein	Inh.	Disease Associations
TUBB3	Tubulin, Beta-3	AD	~10% of complex cortical malformations[79]
*TUBB4A**	Tubulin, Beta-4A	AD	Rare in hypomyelinating leukodystrophy-6 (HLD6)[83]
TUBG1	Tubulin, Gamma-1	AD	~3% of complex cortical malformations[79]
VLDLR	Very low density lipoprotein receptor	AR	Rare cerebellar hypoplasia with simplified gyri[84,85]
WDR62	WD repeat-containing protein 62	AR	Unknown[86]

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

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