THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Cerebral Cortical Malformations

Cerebral cortical malformations include a diverse group of developmental disorders that are common causes of neurodevelopmental delay and epilepsy[1]. These disorders include lissencephaly, pachygyria, polymicrogyria and microcephaly[2]. Numerous genes are associated with malformations of cortical developmental, which might disrupt each of the main stages of cell proliferation and specification, neuronal migration and late cortical organization. The disruption of these steps produces characteristic morphologic anomalies, typically abnormal sulcation and gyral patterns[3].

Our Cerebral Cortical Malformation Panel includes mutation analysis of the 70 genes listed below.

Cerebral Cortical Malformations Panel						
ACTB	CCND2	EML1	KATNB1	PAFAH1B1 (LIS1)	RAB3GAP2	TUBA8
ACTG1	CDK5	FKRP	KIAA1279	PHGDH	RELN	TUBB
AKT3	CIT	FIG4	KIF2A	PIK3R2	RTTN	TUBB2A
ARFGEF2	COL18A1	FKTN	KIF5C	POMGNT1	SNAP29	TUBB2B
ARX	COL3A1	FLNA	LAMA2	POMGNT2	SON	TUBB3
ASNS	CRADD	GMPPB	LAMC3	POMK	SRD5A3	TUBB4A
ATP6V0A2	DAG1	GPR56	LARGE	POMT1	TBC1D20	TUBG1
B3GALNT2	DCX	GPSM2	NEDD4L	POMT2	TMEM5/ RXYLT1	VLDLR
B3GNT1	DMRTA2	GRIN2B	NDE1	RAB18	TMTC3	WDR62
BICD2	DYNC1H1	ISPD	OCLN	RAB3GAP1	TUBA1A	

Gene	Inheritance Pattern	Clinical Features and Molecular Pathology
ACTB *ACTG1*	AD	Baraitser-Winter syndrome is a developmental disorder characterized by congenital ptosis, high-arched eyebrows, hypertelorism, ocular colobomata and anterior- predominant lissencephaly. Other features include postnatal short stature, microcephaly, ID, seizures and hearing loss[4]. Mutations in both *ACTB* and *ACTG1*, which code for cytoplasmic actin, have been identified in patients with Baraitser-Winter syndrome.
AKT3	AD	Heterozygous de novo mutations in the *AKT3* gene have been associated with Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 2[5,6]. Somatic mosaicism for mutations in the *AKT3* gene have been associated with hemimegalencephaly; these variants may not be detected unless pathological tissue is tested and the mutation is present in a high percentage of cells in that tissue[5].
ARFGEF2	AR	Periventricular heterotopia with microcephaly, autosomal recessive (ARPHM) is characterized by periventricular nodules of cerebral grey matter intensity on brain MRI, cerebral atrophy, and acquired microcephaly. Other features include severe developmental delay, seizures, failure to thrive, and recurrent infections[7]. Affected individuals have been found to have compound heterozygous or homozygous mutations in the *ARFGEF2* gene including frameshift, splice site and missense mutations[7].
ARX	X-linked	*ARX* mutations cause various phenotypes including XLAG, X-linked infantile spasms, and non-syndromic X-linked mental retardation[8-10]. Females with more

		severe mutations may be affected as well, and have agenesis of the corpus callosum and seizures[11].
ASNS	AR	Biallelic mutations in *ASNS* are associated with cortical atrophy, seizures, microcephaly, severe developmental delays and microcephaly[12].
ATP6V0A2	AR	Homozygous or compound heterozygous mutations in the *ATP6V0A2* gene cause autosomal recessive cutis laxa type IIA (ARCL2A). This condition is characterized by overfolding and wrinkling of the skin and dysmorphic craniofacial features. Individuals with ARCL2A have early developmental delays, and seizures associated with a neurodegenerative course[13]. Van Maldergem et al. (2008) reported cortical malformations reminiscent of Walker-Warburg syndrome in 8 patients with ARCL2A[13].
BICD2	AD	A recurrent *de novo* variant in *BICD2* has been reported in two unrelated patients with arthrogryposis multiplex congenita, hypotonia and bilateral perisylvian polymicrogyria[14]. Other variable features included congenital fractures, hip dislocation, micrognathia, respiratory insufficiency, and microcephaly.
B3GALNT2 *B3GNT1* *DAG1* *FKTN* *FKRP* *GMPPB* *LARGE POMGNT1* *POMGNT2* *POMK* *POMT1* *POMT2*	AR	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies type A (MDDGA) is a genetically heterogeneous group of autosomal recessive conditions caused by defective glycosylation of *DAG1*. Features of these conditions include brain and eye malformations, cognitive impairment, and congenital muscular dystrophy. Brain malformations seen in MDDGA include cobblestone lissencephaly, polymicrogyria, hydrocephalus, and cerebellar hypoplasia. The phenotypic spectrum of MDDGA includes Walker Warburg syndrome (WWS), muscle-eye-brain (MEB) disease, and Fukayama congenital muscular dystrophy (FCMD)[15].
CCND2	AD	Heterozygous mutations in *CCND2* have been reported in patients with megalencephaly, polymicrogyria, polydactyly and hydrocephalus (MPPH)[16]. One of the affected individuals had a mother with large head circumference and borderline intelligence, who was found to carry a *CCND2* variant in the mosaic state.
CDK5	AR	In a consanguineous family with individuals affected by severe lissencephaly, cerebellar hypoplasia and agenesis of the corpus callosum, Magen et al (2015) identified a homozygous truncating variant in the *CDK5* gene[17].
CIT	AR	Biallelic mutations in the *CIT* gene have been reported in individuals with severe congenital microcephaly, and variable abnormalities on brain MRI including lissencephaly, simplified gyral pattern, and cerebellar/brainstem hypoplasia[18,19].
COL18A1	AR	Biallelic mutations in *COL18A1* have been associated with Knobloch syndrome, which is typically characterized by eye abnormalities such as vitreoretinal degeneration and retinal detachment and occipital skull defects such as occipital encephalocele. More recently, multiple unrelated cases of biallelic *COL18A1* mutations associated with polymicrogyria, in addition to other findings such as epilepsy, myopia and retinal detachment, have been reported[20-22].
COL3A1	AR	Biallelic variants in *COL3A1* have been described in individuals with a cobblestone-like cortical malformation on brain MRI, white matter changes and cerebellar dysplasia. Additional findings may include developmental delay, easy bruising, arterial dissections and joint hypermobility[23].
CRADD	AR	A "thin" lissencephaly variant characterized by megalencephaly, frontal predominant pachygyria, intellectual disability, and seizures has been described in patients with biallelic mutations in the *CRADD* gene[24].
DCX	X-linked	*DCX* abnormalities result in severe lissencephaly or subcortical band heterotopia (SBH) in boys and a less severe SBH in girls25. *DCX* abnormalities are generally associated with an a>p gradient. In males, *DCX* mutations are present in approximately 30% with SBH and approximately 10% with lissencephaly. In females, *DCX* mutations are present in approximately 80% with SBH, especially those with diffuse bands or bilateral frontal only bands. Intragenic deletions of the *DCX* gene are present in approximately 10% of female patients with SBH in whom no mutations were identified by *DCX* sequencing[26,27].

DMRTA2	AR	A homozygous truncating variant in *DMRTA2* has been described in affected individuals from a consanguineous family with a severe prenatal neurodevelopmental disorder characterized by fronto-parietal pachygyria/ lissencephaly, agenesis of the corpus callosum and progressive severe microcephaly[28].
DYNC1H1	AD	Mutations in *DYNC1H1* are associated with autosomal dominant mental retardation – 13 (MRD13). The key features of MRD13 are cognitive impairment and cortical brain malformations. Other variable features include dysmorphic features, seizures, and peripheral neuropathy. Poirier *et al.* (2013) identified *DYNC1H1* mutations in 1 familial and 8 sporadic cases of malformations of cortical development[2].
EML1	AR	Subcortical heterotopia secondary to biallelic mutations in the *EML1* gene has been identified in two families[29]. Other reported characteristic features include congenital macrocephaly, developmental delay, severe intellectual disability, epilepsy, severe congenital hydrocephalus and abnormal MRI findings such as polymicrogyria and agenesis of the corpus callosum[29]. Studies in mice have supported the role of *EML1* in neuronal migration defects[30]. A homozygous truncating variant in *EML1* has also been identified in a family with congenital hydrocephalus[30].
FLNA	X-linked	Mutations in *FLNA* are associated with a disorder of neuronal migration called periventricular nodular heterotopia[32]. *FLNA* is an X-linked gene, most affected individuals are female, and the disorder is typically lethal in males. Affected females can have epilepsy, but are typically of normal intelligence.
FIG4	AR	A homozygous mutation in the *FIG4* gene has been reported in one consanguineous family with bilateral occipital polymicrogyria. Studies of *FIG4*-null mice showed post- migration brain abnormalities, consistent with the mechanism underlying polymicrogyria in humans[33].
GPR56	AR	Bilateral frontoparietal polymicrogyria (BFPP) consists of polymicrogyria with multiple and fused small gyri, an irregular limit between white and grey matter, white matter abnormalities and cerebellar hypoplasia[34]. These radiological findings overlap with the features observed in cobblestone complex brain malformations such as muscle-eye- brain disease [OMIM#613153][34]. *GPR56* encodes a G protein-coupled receptor which is thought to be involved in regulating the maintenance of the pial basement membrane integrity in the forebrain and cerebellum[34]. Bahi-Buisoon et al. (2010) identified *GPR56* homozygous mutations in 15 out of 30 patients with radiological findings of BFPP. *GPR56* mutations are associated with clinical findings of hypotonia and pseudomyopathic behavior, moderate to severe intellectual disability, seizures, abnormal eye movements and bilateral pyramidal and cerebellar signs[34].
GPSM2	AR	Chudley-McCullough syndrome (CMS) is characterized by early onset severe to profound sensorineural hearing loss and brain abnormalities including frontal polymicrogyria, partial agenesis of the corpus callosum, grey matter heterotopia, and cerebellar dysplasia[35]. Cognitive impairment and seizures are rarely reported in individuals with CMS.
GRIN2B	AD	Heterozygous mutations in the *GRIN2B* gene have been identified in patients with a neurodevelopmental phenotype characterized by intellectual disability, autism spectrum behavioral issues, severe developmental delays, cortical malformations, epileptic encephalopathy, focal seizures and hyperkinetic movement disorders[36,37].
ISPD	AR	Biallelic mutations in *ISPD* have been identified in patients with Walker Warberg syndrome (WWS) and MEB like phenotype[38,39]. The reported characteristic features include cobblestone lissencephaly, hydrocephalus, hypoplasia of corpus callosum, cerebellar anomalies, brain stem atrophy/hypoplasia, brain vascular anomalies, ocular anomalies and muscular dystrophy/hypotonia[38-40]. Milder phenotypic presentations such as congenital muscular atrophy and LGMD like phenotype without brain involvement have also been reported[41].
KATNB1	AR	Homozygous mutations in *KATNB1* have been identified in multiple unrelated consanguineous families with variable malformations in cortical development, including lissencephaly, pachygyria, and hypoplasia of the corpus callosum[42].

KIAA1279	AR	Goldberg-Shprintzen syndrome (GOSHS) is an autosomal recessive multiple malformation disorder characterized by Hirschsprung megacolon, microcephaly, hypertelorism, submucous cleft palate, short stature, and intellectual disability[43]. Brooks *et al.* (2005) identified a homozygous nonsense mutation in *KIAA1279* in all affected individuals of a Moroccan family with polymicrogyria and a clinical diagnosis of GOSHS. The function of the KIAA1279 protein product is unknown, however it's mRNA has been identified as localizing in the adult central nervous system, including in the cerebellum[43].
KIF2A *KIF5C* *TUBB TUBB2A* *TUBB3 TUBG1*	AD	Complex cortical dysplasia with other brain malformations (CDCBM) is a neuronal migration disorder associated with axon guidance defects. Clinically, patients have mild to severe intellectual disability, strabismus, axial hypotonia, and spasticity. Malformations seen on brain MRI include polymicrogyria, gyral disorganization, fusion of the basal ganglia, thin corpus callosum, hypoplastic brainstem, and abnormal cerebellar vermis[2,44].
LAMA2	AR	*LAMA2*-related muscular dystrophy is an autosomal recessive group of conditions ranging from late-onset proximal weakness and motor delays to profound neonatal hypotonia, failure to thrive, ophthalmoparesis, and respiratory failure. A small proportion of individuals with early-onset *LAMA2*-related muscular dystrophy have brain malformations, including pachygyria and cortical dysplasia[45]. The majority of affected individuals have normal cognitive abilities and cognitive development is not consistently correlated with brain MRI findings[46].
LAMB1	AR	In two consanguineous families with cobblestone lissencephaly, Radmanesh *et al* (2013) identified two different homozygous loss-of-function mutations in the *LAMB1* gene. Radmanesh *et al.* noted that although the brain malformations were similar to those identified in patients with muscular-dystrophy-dystroglycanopathies, these patients did not have significant eye or muscle disease[47].
LAMC3	AR	Barak et al (2011) identified a homozygous frameshift mutation in *LAMC3* in a patient with bilateral occipital pachygyria. Further screening of the *LAMC3* gene in 12 individuals with various malformations of cortical development (including lissencephaly and polymicrogyria), identified a homozygous truncating mutation in 1 patient with occipital pachygyria[48].
NDE1	AR	Mutations in NDE1 have been reported in children with severe congenital microcephaly (with brains smaller than 10 SD below the mean) with simplified gyri, profound developmental handicap, and normal body growth. Patients may also have lissencephaly or microhydraencephaly. Paciorkowski, et al. (2013) reported a patient with a full gene deletion and a truncating mutation in NDE1 who had severe microcephaly, agenesis of the corpus callosum, and a cortical dysplasia with a polymicrogyria-like appearance[49]. NDE1 is highly expressed in the developing human and mouse cerebral cortex, particularly at the centrosome, and has a role in mitotic spindle assembly during early neurogenesis. Deficiency of NDE1 therefore appears to cause failure of neurogenesis and a deficiency of cortical lamination.
NEDD4L	AD	De novo missense mutations in NEDD4L have been reported in multiple patients with periventricular nodular heterotopia, a form of cortical malformation[50]. One patient with a de novo NEDD4L mutation and polymicrogyria in addition to periventricular nodular heterotopia has been reported[51].
OCLN	AR	Band-like calcification with simplified gyration and polymicrogyria (BLC-PMG) is a rare autosomal recessive disorder characterized by bilateral, symmetrical polymicrogyria, a prominent band of gray matter calcification on brain imaging, and calcification in the cerebellum and basal ganglia[52]. Clinical features include early onset seizures, severe microcephaly and developmental arrest. O'Driscoll et al. (2010) identified *OCLN* mutations in 9 patients from 6 families with a BLC-PMG phenotype. *OCLN* encodes for occludin, which is a key component of tight junctions in the brain, which are functional in cerebral blood vessels in early fetal development[52].
PAFAH1B1 (LIS1)	AD	*PAFAH1B1 (LIS1)* abnormalities cause the most severe form of lissencephaly and are generally associated with a p>a gradient[53]. *PAFAH1B1* mutations are present

		in approximately 30% of patients with *PAFAH1B1*-related lissencephaly and rarely in patients with SBH. Microdeletions involving 17p13.3 are present in 100% of patients with MDS and approximately 50% of patients with lissencephaly. Intragenic deletions of one or more exons of PAFAH1B1 are present in approximately 15% of patients with *PAFAH1B1*-related lissencephaly[54].
PHGDH	AR	Biallelic mutations in the *PHGDH* gene have been reported in individuals with Neu-Laxova Syndrome 1 (NLS-1) and *PHGDH* deficiency[55,56]. *PHGDH* deficiency is a serine biosynthesis disorder characterized by reduced L-serine concentrations, congenital microcephaly, intractable seizures and delayed psychomotor development. Neu-Laxova Syndrome 1 is a multiple congenital anomaly syndrome characterized by intrauterine fetal growth restriction, reduced fetal mobility, distinctive facial features, skeletal/limb malformations, icthyosis, brain developmental abnormalities (including microcephaly, lissencephaly, hypoplastic cerebellum, absent cerebellum vermis, etc) and perinatal lethality. It has been hypothesized that NLS represents the severe end of the spectrum for the serine metabolism deficiency[56,57].
RAB18 RAB3GAP1 RAB3GAP2 TBC1D20	AR	Warburg Micro syndrome [OMIM #600118] is a rare autosomal recessive condition characterized by ocular and neurodevelopmental abnormalities and hypothalamic hypogonadism[58,59]. Key clinical features include microphthalmia, microcornia, congenital cataracts, optic atrophy, microcephaly, cortical dysplasia and atrophy, congenital hypotonia, severe intellectual disability, and spastic diplegia[58,59]. Progressive joint contractures, growth failure, kyphoscoliosis and hypertrichosis have also been described in a proportion of affected individuals[58]. In addition to the characteristic ocular findings, common facial features include deep set eyes, wide nasal bridge and a narrow mouth[58]. Brain magnetic resonance imaging (MRI) of affected individuals consistently shows polymicrogyria in the frontal and parietal lobes, wide sylvian fissures, thin corpus callosum and increased subdural spaces[58].
PIK3R2	AD	Heterozygous mutations in the *PIK3R2* gene have been identified in patients with megalencephaly related overgrowth disorder called as megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 1 (MPPH)6. Reported spectrum of brain malformations include megalencephaly, perisylvian polymicrogyria, mega corpus callosum, cerebellar tonsillar ectopia (Chiari 1 malformation), hydrocephalus and dysmyelination. Other characteristic features are absence of vascular malformations, postaxial polydactyly, abnormal muscle tone, spasticity, epilepsy, mild dysmorphic features, developmental delays and intellectual disability5,6,60. Heterozygous mosaic variants have also been described in patients with these phenotypes61. *Our sequencing assay is designed to detect germline variants; variants present in the mosaic state may not be detected by this assay.*
RELN VLDLR	AR	*RELN* mutations have been identified in patients with a less severe form of lissencephaly with cerebellar hypoplasia (LCH)[62]. *VLDLR*-associated cerebellar hypoplasia (*VLDLR*-CH) falls within the LCH spectrum, and is characterized by non- progressive congenital ataxia, ID, dysarthria, strabismus and seizures. These patients have mild lissencephaly as well. *VLDR* is part of the reelin (*RELN*) signaling pathway, which guides neuroblast migration in the cerebral cortex and cerebellum. LCH is distinguished from *VLDLR*-CH by more severe lissencephaly with an a>p gradient, a small and malformed hippocampus, and profound cerebellar hypoplasia with complete absence of detectable folia[63].
RTTN	AR	Kheradmand Kia *et al* (2012) identified a homozygous mutation in *RTTN* in three members of a consanguineous family with polymicrogyria and seizures[64]. The polymicrogyria in these affected individuals was asymmetric extending from the frontal to the temporal, parietal and occipital lobes on brain MRI. *RTTN* is required for the early development of left-right specification and axial rotation and may play a role in notochord development.
SNAP29	AR	Sprecher *et al* (2005) identified a homozygous truncating mutation in two unrelated consanguineous Arab Muslim families with cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma (CEDNIK) syndrome. Individuals with CEDNIK syndrome have progressive microcephaly in conjunction with a range of

		brain malformations, including cortical dysplasia, pachygyria, absence of the corpus callosum, and perisylvian polymicrogyria. Additional features include dysmorphic facies, palmoplantar keratosis and ichthyosis, severe developmental delays, optic disc hypoplasia, and sensorineural hearing loss[65].
SON	AD	Haploinsufficiency of *SON* is hypothesized to cause defective RNA splicing of genes essential for neurodevelopment[66]. De novo heterozygous mutations in this gene have been identified in multiple individuals with severe developmental delays, brain malformations and intellectual disability[66,67]. Characteristic cerebral cortical malformations include abnormal gyration patterns, ventriculomegaly, Arnold-Chiari malformations, arachnoid cysts, and hypoplasia of the corpus callosum. Other findings include epilepsy, vision issues, musculoskeletal abnormalities (e.g. scoliosis or kyphosis, contractures, hypotonia, and hypermobility of the joints), hematological abnormalities, and distinctive facial features[66,67].
SRD5A3	AR	Mutations in *SRD5A3* are associated with congenital disorder of glycosylation type Iq (CDG1Q). CDG1Q is a rare autosomal recessive condition characterized by abnormal type 1 glycosylation in association with congenital eye malformations including ocular colobomas and optic disc hypoplasia, intellectual disabilities, and variable brain malformations. Al-Gazali *et al.* (2008) reported a consanguineous family with multiple affected individuals. Brain malformations seen in affected individuals included cerebellar vermis hypoplasia, hypoplasia of the corpus callosum, absent septum pellucidum, and bilateral frontal polymicrogyria68. Cantagrel et al. (2010) subsequently identified a homozygous mutation in *SRD5A3* in affected individuals in this family, as well as homozygous or compound heterozygous *SRD5A3* mutations in 5 other individuals[69].
TMEM5/RXYTL1	AR	*RXYLT1* (*TMEM5*) encodes a transmembrane protein with a predicted glycosyltransferase function. Vuillaumier-Barrot, *et al*., 2012, identified biallelic mutations in *TMEM5* in fetal cases with cobblestone lissencephaly from 5 unrelated families[40]. Other reported features include neural-tube defects, visceral malformations, and gonadal dysplasia. Since that time, mutations in this gene have been implicated in alpha-dystroglycanopathies with a wide clinical spectrum ranging from WWS/MEB like phenotype to milder form of congenital muscular dystrophy without any structural brain, ocular and systemic malformations[70,71].
TMTC3	AR	Jerber *et al.*, 2016 identified biallelic mutations in *TMTC3* in six unrelated consanguineous families with cobblestone lissencephaly and other brain malformations such as ventriculomegaly, brainstem and cerebellar hypoplasia. Other most commonly reported features were delayed psychomotor development with truncal hypotonia, variable appendicular spasticity, intellectual disability and seizures. Only minority of patients presented with ocular defects or elevated muscle creatine phosphokinase (CPK) which are one of the prominent features of other known congenital dystroglycanopathies[72].
TUBA1A	AD	*TUBA1A* mutations have been identified in patients with gyral malformations and are associated with two forms of lissencephaly. The first is lissencephaly with a p>a gradient similar to LIS1-associated lissencephaly, although this is rare cause of typical lissencephaly. The second is a severe form of lissencephaly associated with severe cerebellar hypoplasia (LCH) and often underdevelopment of the corpus callosum. About 30-40% of children with LCH have mutations in TUBA1A[73].
TUBA8	AR	Abdollahi *et al.* identified homozygous *TUBA8* mutations in two consanguineous families with extensive bilateral polymicrogyria and optic nerve hypoplasia. Clinical findings in the affected individuals included severe developmental delay, hypotonia and seizures[74]. The affected individuals did not have any noted dysmorphic features[74]. The *TUBA8* protein is widely expressed in neural tissues, and is thought to have a role in cortical organization and regulation of brain development[74].
TUBB2B	AD	Patients with *TUBB2B* mutations typically have bilateral, asymmetric polymicrogyria, which is more striking the frontal and temporal lobes[58]. Other findings on MRI include absence of the corpus callosum, abnormal basal ganglia and cerebellum, and hypoplasia of the brainstem[75]. Most patients also have microcephaly, severe mental retardation and seizures[75]. Mutations of the *TUBB2B*

		gene, or α-tubulin, have been identified in patients with asymmetrical polymicrogyria[75]. *TUBB2B* is expressed in post-mitotic neurons during neuronal migration and differentiation[76]. Jaglin et al. (2009) reported four unrelated individuals and one fetus with asymmetrical PMG and autosomal dominant de novo mutations in *TUBB2B*[76].
TUBB4A	AD	Mutations in *TUBB4A* are associated with hypomyelinating leukodystrophy-6 (HLD6). Individuals with HLD6 have infancy or childhood onset motor delays, followed by development of extrapyramidal movement disorders and progressive abnormalities on brain MRI. Brain MRI in affected individuals shows hypomylination in conjunction with other findings, including progressive atrophy of the basal ganglia and cerebellum, and atrophy or disappearance of the putamen. HLD6 is typically a sporadic condition due to de novo mutations in *TUBB4A*, but germline mosaicism has been reported in one family with two affected siblings[77].
WDR62	AR	Mutations in *WDR62* have been reported in a subset of patients with microcephaly, cortical malformations, and moderate to severe ID. Besides microcephaly, these patients had various brain malformations including callosal abnormalities, polymicrogyria, schizencephaly and subcortical nodular heterotopia. A subset has seizures[78]. Homozygous missense and frameshift mutations were first reported in seven consanguineous families. Like other autosomal recessive primary microcephaly genes, *WDR62* encodes a spindle pole protein that is expressed in neuronal precursor cells undergoing mitosis in the proliferative phase of neurogenesis[79].

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Cerebral Cortical Malformation Panel (71 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3500
CPT codes:	81406 81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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