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Next Generation Sequencing Panel for Polymicrogyria

Clinical Features:

Polymicrogyria (PMG) is a cortical brain malformation which is characterized by an excessive number of small irregular gyri separated by shallow sulci, which leads to an irregular cortical surface [1]. PMG varies widely in extent and location in the brain depending on the underlying etiology or syndrome, and can be isolated to a single region of one hemisphere, bilateral and asymmetric, bilateral and symmetric, or diffuse [1]. Depending on the extent, subtype, and underlying etiology of PMG, clinical manifestations may range from selective impairment of cognitive function to severe encephalopathy with intractable epilepsy [1]. PMG may be isolated, or observed as part of a multiple congenital anomaly syndrome. It may be associated with a genetic etiology, or may be due to exogenic causes such as infection, or impaired hemodynamic disturbances [1].

Our Polymicrogyria Panel includes all six genes listed below.

Polymicrogyria					
GPR56	KIAA1279	OCLN	TUBA8	TUBB2B	TUBB3

Gene / Condition	Clinical and Molecular Findings
GPR56 [OMIM# 604110] Bilateral Frontoparietal Polymicrogyria [OMIM# 606854]	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 [2]. These radiological findings overlap with the features observed in cobblestone complex brain malformations such as muscle-eye-brain disease [OMIM#613153] [2]. *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 [2]. Bahi-Buisoon *et al*. (2010) identified *GPR56* mutations in 15 out of 20 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 [2].
KIAA1279 [OMIM# 609367] Goldberg-Shprintzen Megacolon syndrome [OMIM# 609460]	Goldberg-Shprintzen megacolon syndrome is an autosomal recessive multiple malformation disorder characterized by Hirschsprung megacolon, microcephaly, hypertelorism, submucous cleft palate, short stature, and intellectual disability [3]. Brooks *et al.* (2005) identified a homozygous nonsense mutation in *KIAA1279* in an affected family which had bilateral generalized polymicrogyria as a consistent feature and Hirschprung disease as a variable feature. The family was considered to have a clinical diagnosis of Goldberg-Shprintzen megacolon syndrome, although polymicrogyria had not previously been described as a feature of this syndrome [3]. 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 [3].
OCLN [OMIM# 602876] Band-Like Calcification with Simplified Gyration and Polymicrogyria [OMIM#251290]	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 [4]. Clinical features include early onset seizures, severe microcephaly and developmental arrest. O'Driscoll *et al.* (2010) identified *OCLN* mutations in 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 [4].

TUBA8 [OMIM# 605742] Polymicrogyria with Optic Nerve Hypoplasia [OMIM#613180]	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 [5]. The affected individuals did not have any noted dysmorphic features [5]. The *TUBA8* protein is widely expressed in neural tissues, and is thought to have a role in cortical organization and regulation of brain development [5].
TUBB2B [OMIM #612850] Asymmetric Polymicrogyria [OMIM #610031]	Patients with *TUBB2B* mutations typically have bilateral, asymmetric polymicrogyria, which is more striking the frontal and temporal lobes [6]. Other findings on MRI include absence of the corpus callosum, abnormal basal ganglia and cerebellum, and hypoplasia of the brainstem [6]. Most patients also have microcephaly, severe mental retardation and seizures [6]. Mutations of the *TUBB2B* gene, or α-tubulin, have been identified in patients with asymmetrical polymicrogyria [6]. *TUBB2B* is expressed in post-mitotic neurons during neuronal migration and differentiation [7]. Jaglin *et al*. (2009) reported four unrelated individuals and one fetus with asymmetrical PMG and autosomal dominant *de novo* mutations in *TUBB2B*.
TUBB3 [OMIM #602661] Complex Cortical Dysplasia with Other Brain Malformations [OMIM#614039]	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 [8]. Cortical malformations seen on brain MRI include polymicrogyria, gyral disorganization, fusion of the basal ganglia, thin corpus callosum, hypoplastic brainstem, and abnormal cerebellar vermis [8]. Autosomal dominant mutations of the *TUBB3* gene were reported in 10% (12/120) of patients with CDCBM who were previously negative for mutations in *LIS1, DCX, TUBA1A, TUBB2B*, and *GPR56*. *TUBB3* encodes a neuronal betatubulin subunit [8].

Inheritance:

GPR56, KIAA1279, OCLN and *TUB8A* mutations are inherited in an autosomal recessive pattern. Parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

TUBB2B and *TUBB3* mutations are inherited in an autosomal dominant pattern. All *TUBB2B* mutations described to date have been *de novo* in nature. The recurrence risk for parents is less than 1%, based on the theoretical risk for germline mosaicism. Both *de novo* and inherited mutations in *TUBB3* have been described. The recurrence risk for unaffected parents of an isolated case is <1%. The recurrence risk for affected parents is 50%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are amplified using highly parallelized and multiplexed PCR reactions assembled with the Raindance System. DNA is sequenced 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 novel and/or potentially 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 8 bp.

Next Generation Sequencing Polymicrogyria Panel

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3700
CPT codes:	83891, 83900, 83901 X13, 83904 X12, 83912
Turn-around time:	8 – 10 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory. Only fresh blood samples are accepted for this testing.

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	83891, 83898 x2, 83894, 83912
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	83891, 83898 x4, 83894, 83912
Turn-around time:	1-2 weeks

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.

References:

1. Aronica E *et al.*, "Malformations of Cortical Development." (2012) Brain Pathology 22: 380-401.
2. Bahi-Buisson N *et al.*, "GPR56-related bilateral frontoparietal polymicrogyria: further evidence for an overlap with the cobblestone complex." (2010) Brain 133: 3194-209.
3. Brooks A *et al.*, "Homozygous Nonsense Mutations in KIAA1279 Are Associated with Malformations of the Central and Enteric Nervous Systems." (2005) 77: 120-6.
4. O'Driscoll M et al., "Recessive Mutations in the Gene Encoding the Tight Junction Protein Occuldin Cause Band-Like Calcification with Simplified Gyration and Polymicrogyria." (2010) Am J Hum Genet 87: 354-64.
5. Abdollahi M *et al.*, "Mutation of the Variant α-Tubulin TUBA8 Results in Polymicrogyria with Optic Nerve Hypoplasia." (2009) Am J Hum Genet 85: 737-44.
6. Jaglin XH, *et al.* "Mutations in the α-tubulin gene TUBB2B result in assymetrical polymicrogyria". (2009) Nature Genetics 41: 746-752.
7. Uribe V. "The α-tubulin gene TUBB2B is involved in a large spectrum of neuronal migration disorders." (2010) Clin Genetics 77: 34-5
8. Poirier K, *et al.* "Mutations in the neuronal □-tubulin subunit TUBB3 result in malformation of cortical development and neuronal migration defects". (2010) Hum Molec Genet 19(22): 4462-4473.

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