

The University of Chicago Genetic Services Laboratories



5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES ☐ (888) 824 3637
Local: (773) 834 0555 ☐ FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu ☐ dnatesting.uchicago.edu
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TUBB2B Sequencing for Asymmetric Polymicrogyria

Clinical Features:

The hallmark feature seen in patients with *TUBB2B* mutations is asymmetric polymicrogyria (PMG) [OMIM #610031]. PMG is a brain malformation with numerous small gyri separated by shallow sulci, creating a cobblestone appearance. PMG in these patients is usually bilateral, asymmetric, and more striking in the frontal and temporal lobes. Other findings on MRI include absence of the corpus callosum, abnormal basal ganglia and cerebellum, and hypoplasia of the brainstem. Most patients also have microcephaly, severe mental retardation and seizures (1, 2).

Dr. William Dobyns at the Seattle Children's Research Institute is available to review MRI scans and give recommendations regarding genetic testing. Please contact Dr. Dobyns (wbd@uw.edu) or his coordinators, Carissa Adams (carissa.adams@seattlechildrens.org) and Brandi Bratrude (brandi.bratrude@seattlechildrens.org) to arrange this, if desired.

Molecular Genetics:

Mutations of the *TUBB2B* [OMIM #612850] gene, or β -tubulin, have been identified in patients with asymmetrical PMG (1). *TUBB2B* has 5 coding exons and is located at 6p25.2. *TUBB2B* is expressed in post-mitotic neurons during neuronal migration and differentiation (3). The *TUBB2B* protein forms alpha/beta tubulin heterodimers with *TUBA1A*. Jaglin XH, et al [2009] reported four unrelated individuals and one fetus with asymmetrical PMG and *de novo* mutations in *TUBB2B* (1). All mutations were missense mutations in highly conserved residues in exon 4. These mutations result in haploinsufficiency and aberrant heterodimer assembly. Mutations in the alpha-subunit, *TUBA1A*, cause a large spectrum of lissencephaly and pachygyria phenotypes (4). Interestingly, patients with mutations in *TUBA1A* also have absence of the corpus callosum, abnormal basal ganglia and cerebellum, and hypoplasia of the brainstem.

Inheritance:

Mutations in *TUBB2B* are autosomal dominant and all mutations, to date, have been *de novo*. Recurrence risk for parents is less than 1%, based on the theoretical risk for germline mosaicism.

Test Methods:

The University of Chicago Laboratory offers mutation analysis of all 5 coding exons and intron/exon boundaries of *TUBB2B* by direct sequencing of amplification products in both the forward and reverse directions. Deletion/duplication analysis of the *TUBB2B* gene is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory. This test is also offered as part of a panel (see website for pricing of panel test)

TUBB2B sequencing may be ordered alone, or as part of our Polymicrogyria panel which includes sequencing of a total of 7 genes. Please see our information sheet on our Polymicrogyria Next Generation Sequencing Panel for more details.

TUBB2B sequencing analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81404
Turn-around time:	4 weeks

TUBB2B deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81403
Turn-around time:	4 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. Jaglin XH, Poirier K, Saillour Y et al. Mutations in the beta-tubulin gene TUBB2B result in asymmetrical polymicrogyria. Nat Genet 2009: 41: 746-752.
2. Tischfield MA, Cederquist GY, Gupta ML et al. Phenotypic spectrum of the tubulin-related disorders and functional implications of disease-causing mutations. Curr Opin Genet Dev 2011: 21: 286-294.
3. Uribe V. The beta-tubulin gene TUBB2B is involved in a large spectrum of neuronal migration disorders. Clin Genet 2010: 77: 34-35.
4. Poirier K, Keays DA, Francis F et al. Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in tubulin alpha 1A (TUBA1A). Hum Mutat 2007: 28: 1055-1064.

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