The University of Chicago Genetic Services Laboratories

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TUBB3 Sequence Analysis

Clinical Features:

Complex cortical dysplasia with other brain malformations (CDCBM) [OMIM#614039] is a neuronal migration disorder associated with axon guidance defects. Clinically, patients have mild to severe mental retardation, strabismus, axial hypotonia, and spasticity. Cortical malformations seen on brain MRI include: polymicrogyria, gyral disorganization, fusion of the basal ganglia, thin corpus callosum, hypoplastic brainstem, and abnormal cerebellar vermis (1).

Molecular Genetics:

Abnormalities of the *TUBB3* [OMIM #602661] gene were reported in approximately 10% (12/120) of patients with CDCBM (1). These patients were selected from a cohort of patients in the lissencephaly-pachygyria spectrum previously negative for mutations in all previously described lissencephaly and polymicrogyria genes (*LIS1*, *DCX*, *TUBA1A*, *TUBB2B*, and *GPR56*). Brain MRI findings in this group included: polymicrogyria, gyral disorganization and simplification syndromes with or without pontocerebellar defects. All six identified mutations were missense changes in exons 3 or 4. These novel changes all affected highly conserved amino acids and were not detected in 360 normal controls. *TUBB3* has four coding exons, is located at 16q24.3, and encodes a neuronal beta-tubulin subunit (1).

Mutations in *TUBB3* have also been reported in patients with congenital fibrosis of extraocular muscles-3A (CFEOM3A) [OMIM#600638]. These patients have a milder phenotype. They do not have cortical dysgenesis or gyral abnormalities, but rather have hypoplasia of oculomotor nerves and dysgenesis of the corpus callosum and the internal capsule (2). *TUBB3* mutations that cause CFEOM3A affect amino acids important in kinesin-microtubule interactions (3).

Inheritance:

TUBB3 mutations are inherited in an autosomal dominant pattern, with some reported cases occurring *de novo* and others inherited from an affected parent. Recurrence risk for unaffected parents of an isolated case is low (<1%), but germline mosaicism is possible. Recurrence risk for affected parents is 50%.

Test methods:

We offer mutation analysis of the four coding exons and intron/exon boundaries of *TUBB3* by direct sequencing of amplification products in both the forward and reverse directions. Deletion/duplication analysis of the *TUBB3* 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.

TUBB3 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.

TUBB3 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

TUBB3 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:

You will be informed of the results of your case as soon as it has been completed. 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. Poirier K, Saillour Y, Bahi-Buisson N et al. Mutations in the neuronal ß-tubulin subunit TUBB3 result in malformation of cortical development and neuronal migration defects. Hum Mol Genet 2010: 19: 4462-4473.
2. Tischfield MA, Baris HN, Wu C et al. Human TUBB3 mutations perturb microtubule dynamics, kinesin interactions, and axon guidance. Cell 2010: 140: 74-87.
3. 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.

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