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OCLN Sequencing for Band-like calcification with simplified gyration and polymicrogyria syndrome

Clinical Features:

Band-like calcification with simplified gyration and Polymicrogyria (BLC-PMG), or "pseudo-TORCH" syndrome, [OMIM#251290] is a rare autosomal recessive neurological disorder with highly characteristic clinical and neuroradiologic features. Affected individuals demonstrate early-onset seizures, severe microcephaly and developmental delay. Brain CT and MRI imaging show a prominent band of cortical gray matter calcification, as well as calcification in the cerebellum and basal ganglia, in addition to bilateral, symmetric polymicrogyria (PMG). These neuroradiologic features resemble those caused by congenital infections, hence the term "pseudo-TORCH" syndrome is used (1-3).

Molecular Genetics:

Intragenic deletions and mutations in the *OCLN* gene [OMIM#602876] have been identified in patients with the pseudo-TORCH syndrome (1). The *OCLN* gene encodes occludin, an integral component of tight junctions. Tight junctions are functional in cerebral blood vessels early in fetal development and continue to play a vital role in the maintenance of the blood-brain barrier during postnatal life (4). Neuropathological studies of affected individuals, as well as the mouse model of occludin deficiency demonstrated that calcifications and PMG were predominantly associated with the cerebral blood vessels in location and caused by vascular/ischemic insults, supporting the role of the *OCLN* gene in their pathogenesis (5, 6).

The *OCLN* gene maps to 5q13.1 and consists of 9 coding exons. Homozygous and compound heterozygous mutations in *OCLN* were identified in nine individuals from six families of Turkish, Egyptian, Mexican and British ancestry (1). Homozygous exonic deletions of the OCLN gene have also been identified in affected individuals of Turkish, Egyptian and Mexican origin. With the exception of an acceptor splice site mutation in intron 5, the remainder of missense and nonsense mutations identified to date are within exon 3 (1-3).

Inheritance:

BLC-PMG is inherited in an autosomal recessive pattern. Parents of an affected child are likely carriers. Recurrence risk for carrier parents is 25%.

Test methods:

We offer sequencing of coding exons 2-5 and their intron/exon boundaries only. The full-length *OCLN* gene has a pseudogene approximately 1.5 Mb in length containing a copy of *OCLN* exons 6-9 within a 500 kb-inverted duplication (1). Therefore, testing these latter exons is not available using our current methodology. Deletion/duplication analysis of the coding exons 2-5 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.

OCLN 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.

OCLN sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$875
CPT codes:	81405
Turn-around time:	4 weeks

OCLN deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81404
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. O'Driscoll MC, Daly SB, Urquhart JE et al. Recessive mutations in the gene encoding the tight junction protein occludin cause band-like calcification with simplified gyration and polymicrogyria. Am J Hum Genet 2010: 87: 354-364.
2. Abdel-Salam GM, Zaki MS. Band-like intracranial calcification (BIC), microcephaly and malformation of brain development: a distinctive form of congenital infection like syndromes. Am J Med Genet A 2009: 149A: 1565-1568.
3. Briggs TA, Wolf NI, D'Arrigo S et al. Band-like intracranial calcification with simplified gyration and polymicrogyria: a distinct "pseudo-TORCH" phenotype. Am J Med Genet A 2008: 146A: 3173-3180.
4. Ballabh P, Hu F, Kumarasiri M et al. Development of tight junction molecules in blood vessels of germinal matrix, cerebral cortex, and white matter. Pediatr Res 2005: 58: 791-798.
5. Saitou M, Furuse M, Sasaki H et al. Complex phenotype of mice lacking occludin, a component of tight junction strands. Mol Biol Cell 2000: 11: 4131-4142.
6. Virgintino D, Errede M, Robertson D et al. Immunolocalization of tight junction proteins in the adult and developing human brain. Histochem Cell Biol 2004: 122: 51-59.