THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Donnai-Barrow Syndrome: Mutation Analysis of *LRP2*

Clinical Features

Donnai-Barrow syndrome [DBS, OMIM#222448] is characterized by agenesis of the corpus callosum, congenital diaphragmatic hernia, facial dysmorphism, ocular anomalies, sensorineural hearing loss and developmental delay (1). DBS has clinical overlap with facio-oculo-acoustico-renal syndrome [FOAR, OMIM#227920], however FOAR syndrome is typically reported as having proteinuria but lacking agenesis of the corpus callosum and congenital diaphragmatic hernia (1). No one clinical feature is pathognomonic for DBS. The diagnosis should be considered when several of the clinical features are present in combination (2).

Molecular Genetics

Homozygous and compound heterozygous mutations in the *LRP2* [OMIM#600073] gene cause DBS/FOAR syndrome (1). Indels, splice site, nonsense and missense mutations have been described. *LRP2* is a member of a family of receptors with structural similarities to the low density lipoprotein receptor.

Inheritance

LRP2-related DBS/FOAR syndrome is inherited in an autosomal recessive pattern. Parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *LRP2* gene is performed. Targets of interest are enriched and amplified using the Agilent SureSelect System. The constructed genomic DNA library 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 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 20bp. 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.

LRP2 sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405 81406
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.

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

References:

1. Kantarci S, Al-Gazali L, Hill RS et al. Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico-renal syndromes. Nat Genet 2007: 39: 957-959.
2. Kantarci S, Ragge NK, Thomas NS et al. Donnai-Barrow syndrome (DBS/FOAR) in a child with a homozygous LRP2 mutation due to complete chromosome 2 paternal isodisomy. Am J Med Genet A 2008: 146A: 1842-1847.

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