THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Bardet-Biedl syndrome

Clinical Features:
Bardet-Biedl syndrome (BBS) is an autosomal recessive multi-systemic ciliopathy characterized by retinal dystrophy, obesity, postaxial polydactyly, leaning difficulties, renal involvement and genitourinary abnormalities [1]. Visual prognosis is poor, and the mean age of legal blindness is 15.5 years. Birth weight is typically normal but significant weight gain beigns within the first year. Renal disease is a major cause of morbidity and mortality. There is considerable interfamilial and intrafamilial variability in the clinical presentation [2].

Molecular Genetics:
Mutations in 16 BBS genes (*BBS1* through *BBS16*) account for approximately 80% of clinically diagnosed BBS patients [2]. In individuals of European and Caucasian ancestry, the majority of mutations are identified in *BBS1* and *BBS10* which account for 23% and 20% of identified mutations, respectively [2]. Two recurrent mutations have been identified in this population including a missense change (p.M390R) in *BBS1* and a frameshift (p.C91Lfs*5) in *BBS10* [2]. In Tunisian populations, pathogenic mutations are more likely to be described in *BBS1, BBS2* and *BBS8*, while in Saudi Arabian populations, pathogenic mutations are more likely to be described in *BBS1, BBS3* and *BBS4* [1]. For the majority of mutations identified no clear cut genotype-phenotype correlations have been estabilished. The BBS genes are all involved in some way in ciliogenesis.

Biallelic mutaitons in *IFT172* have been reported in four individuals from three unrelated familes with retinal degeneration and Bardet-Biedl syndrome. Variable severity was reported in these families, ranging from isolated retinal degeneration to Bardet-Biedl syndrome with cutaneous polydactyly [3].

In a study by Lindstrand *et al*, patient with Bardet-Biedel syndrome was identified to be compound heterozygous for loss of function mutations in the *IFT74* gene. In vivo fucntional studies in zebrafish resulted in gastrulation and renal defects [4].

Inheritance:
Generally speaking BBS is considered to be an autosomal recessive condition. There are several reported cases of a triallelic mode of inheritance where three mutations in BBS genes are required before the phenotype becomes apparent, or alternatively where a third disease locus acts as a disease modifier [1]. Triallelic inheritance is considered to be uncommon [5].

Our Bardet-Biedl Syndrome Panel includes analysis of the 18 genes listed below.

Bardet-Biedl Panel					
BBS1	BBS4	BBS7	BBS10	MKS1 (BBS13)	SDCCAG8 (BBS16)
BBS2	BBS5	TTC8 (BBS8)	TRIM32 (BBS11)	CEP290 (BBS14)	IFT172
ARL6 (BBS3)	MKKS (BBS6)	BBS9	BBS12	WDPCP (BBS15)	IFT74

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed 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 20 bp.

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.

Bardet-Biedl Syndrome Panel (18 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2000
CPT codes:	81406 81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

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. M'hamdi, O., I. Ouertani, and H. Chaabouni-Bouhamed, *Update on the genetics of bardet-biedl syndrome.* Mol Syndromol, 2014. **5**(2): p. 51-6.
2. Forsythe, E. and P.L. Beales, *Bardet-Biedl syndrome.* Eur J Hum Genet, 2013. **21**(1): p. 8-13.
3. Bujakowska, K.M., et al., *Mutations in IFT172 cause isolated retinal degeneration and Bardet-Biedl syndrome.* Hum Mol Genet, 2015. **24**(1): p. 230-42.
4. Lindstrand, A., et al., *Copy-Number Variation Contributes to the Mutational Load of Bardet-Biedl Syndrome.* Am J Hum Genet, 2016. **99**(2): p. 318-36.
5. Abu-Safieh, L., et al., *In search of triallelism in Bardet-Biedl syndrome.* Eur J Hum Genet, 2012. **20**(4): p. 420-7.

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