Diamond-Blackfan Anemia (DBA) Panel

Disorder also known as: Blackfan-Diamond Anemia; Aase Syndrome; Aase-Smith Syndrome II; Pure hereditary red cell aplasia

Panel Gene List: RPS19, RPL5, RPS26, RPL11, RPL35A, RPS10, RPS24, RPS17, RPS7, RPL15, RPS29, RPL26, GATA1

Clinical Features: Diamond-Blackfan anemia usually presents with hypoplastic anemia in early infancy. Hematologic examination shows macrocytosis and a decrease in erythroid precursors. At least 40% of affected children have congenital anomalies including malformations of the thumb and upper limbs, craniofacial abnormalities including cleft lip and palate, heart defects and growth retardation. Affected individuals are at increased risk to develop leukemia. Defects in multiple ribosomal proteins have been implicated.

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less

than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Gene-specific exclusions for exon-level deletion/duplication testing for this panel are: RPS17 gene, only whole gene deletions or duplications may be detected; RPL15 gene, no copy number testing.

Inheritance Pattern, Variant Spectrum, Test Sensitivity:

Gene	Protein	Inheritance Pattern	Variant Spectrum	Frequency in DBA
RPS19	Ribosomal protein S19	AD	Missense, nonsense, splice-site, frameshift, large deletions, gross deletions (10%)	25%[1-3]
RPL5	Ribosomal protein L5	AD	Missense, nonsense, splice-site, frameshift, large deletions	~7%[4-6]
RPS26	Ribosomal protein S26	AD	Missense, splice-site, frameshift, gross deletions, one nonsense	~6.4%[8,11]
RPL11	Ribosomal protein L11	AD	Nonsense, splice-site, frameshift, large deletions, one missense	~5%[4-6]
RPL35A	Ribosomal protein L35A	AD	Large deletions, one missense, one nonsense, one small deletion, one splice-site	~3%[7,12]
RPS10	Ribosomal protein S10	AD	One frameshift, one missense, one nonsense	~2.6%[8,12]
RPS24	Ribosomal protein S24	AD	Nonsense, one missense, splice-site, one small deletion, one small in/del	~2%[8,9]
RPS17	Ribosomal protein S17	AD	Missense, small/large deletions, one nonsense	~1%[8,10]
RPS7	Ribosomal protein S7	AD	Splice-site	~1%[4,8]
RPL15	Ribosomal protein L15	AD	Two large deletions	Rare[13,14]
RPS29	Ribosomal protein S29	AD	Two missense	Rare[15]
RPL26	Ribosomal protein L26	AD	One small deletion	Rare[16]
GATA1	Gata-binding protein 1	X-linked	Missense, one splice-site, one small deletion, one small in/del	Rare[17,18]

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