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 extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. 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. For the RPS17 and RPL15 genes, sequencing but not deletion/duplication analysis is performed.

Inheritance Pattern, Variant Spectrum, Test Sensitivity:

Gene	Inheritance Pattern	Variant Spectrum	Frequency in DBA
RPS19	Autosomal dominant	Missense, nonsense, splice-site, frameshift, large deletions, gross deletions (10%)	25%[1-3]
RPL5	Autosomal dominant	Missense, nonsense, splice-site, frameshift, large deletions	~7%[4-6]
RPS26	Autosomal dominant	Missense, splice-site, frameshift, gross deletions, one nonsense	~6.4%[8,11]
RPL11	Autosomal dominant	Nonsense, splice-site, frameshift, large deletions, one missense	~5%[4-6]
RPL35A	Autosomal dominant	Large deletions, one missense, one nonsense, one small deletion, one splice-site	~3%[7,12]
RPS10	Autosomal dominant	One frameshift, one missense, one nonsense	~2.6%[8,12]
RPS24	Autosomal dominant	Nonsense, one missense, splice-site, one small deletion, one small in/del	~2%[8,9]
RPS17	Autosomal dominant	Missense, small/large deletions, one nonsense	~1%[8,10]
RPS7	Autosomal dominant	Splice-site	~1%[4,8]
RPL15	Autosomal dominant	Two large deletions	Rare[13,14]
RPS29	Autosomal dominant	Two missense	Rare[15]
RPL26	Autosomal dominant	One small deletion	Rare[16]
GATA1	X-linked	Missense, one splice-site, one small deletion, one small in/del	Rare[17,18]

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