Chronic Granulomatous Disease Test

CGD TEST GENE LIST

CYBA , CYBB, NCF1, NCF2, NCF4

CLINICAL FEATURES

CGD is a congenital immunodeficiency with recurrent severe infections including pneumonia, lymphadenitis, skin and hepatic abscesses, osteomyelitis and septicemia. Infections usually become apparent during the first year of life. Phagocytic neutrophils are unable to produce a bactericidal respiratory burst due to a deficiency of one of the component proteins of the NADPH oxidase complex. The oxidative burst test can be used to identify X-linked cases if female patients (or the carrier mothers of male patients) show the characteristic mosaic pattern caused by X-inactivation.

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. For the NCF1 gene, only sequencing of exon 2 is performed using capillary sequencing. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: NCF1 and NCF4 genes: no copy number testing, CYBA gene: only whole gene deletions or duplications may be detected.

TEST SENSITIVITY

Gene	Protein	Inheritance	Clinical Sensitivity
CYBB	p91-phox, beta subunit of cytochrome b	X-Linked	67%[2]
NCF1	p47-phox, neutrophil cytosol factor 1	AR	20%[1]
CYBA	p22-phox, alpha subunit of cytochrome b	AR	6%[1,3]
NCF2	p67-phox, neutrophil cytosol factor 2	AR	6%[1,3]
NCF4	p40-phox, neutrophil cytosol factor 4	AR	Rare[4]

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TEST SENSITIVITY

CYBA: Rare missense, nonsense, splice, frameshift, and large deletion variants are known.[1,3]
CYBB: In a large survey[2] , 90% of patients with pathogenic variants in CYBB had frameshift, nonsense, missense and splice site variants that would be easily detected by sequencing. The remaining 10% were primarily deletions of one or more exons, which are detectable by sequencing in males and by ExonArrayDx in females.
NCF1: The majority of pathogenic variants are a recurring gene conversion causing a GT deletion in exon 2.[1]
NCF2: Rare missense, nonsense, splice, frameshift, and large partial duplication variants are known.[1,3] Partial gene deletions have been observed.
NCF4: A missense and frameshift variant have been reported.[4]

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