Primary Ciliary Dyskinesia (PCD) Panel

PCD PANEL GENE LIST

ARMC4, C21ORF59 [CFAP298], CCDC103, CCDC114, CCDC151, CCDC39, CCDC40, CCDC65, CCNO, CENPF, DNAAF1, DNAAF2, DNAAF3, DNAAF5 [HEATR2], DNAH11, DNAH5, DNAI1, DNAI2, DNAJB13, DRC1, DYX1C1 [DNAAF4], GAS8, LRRC6, PIH1D3, RSPH1, RSPH3, RSPH4A, RSPH9, SPAG1, ZMYND10.

CLINICAL FEATURES

Primary Ciliary Dyskinesia (PCD) is associated with abnormal ciliary structure and function leading to chronic otosinopulmonary disease, situs abnormalities, and reduced fertility. More than 75% of full-term neonates with PCD have neonatal respiratory distress and require supplemental oxygen for days to weeks[1-3]. Young children with PCD are susceptible to recurrent otitis media, which may impair speech development and cause transient or permanent hearing loss[4, 5]. Individuals with PCD are prone to recurrent airway infections that persist into adulthood and are characterized by chronic cough, nasal congestion and drainage, and sinusitis, resulting in bronchiectasis and progressive lung disease that sometimes requires transplant[1, 6-8]. Kartagener Syndrome, characterized by chronic sinusitis, bronchiectasis, and situs inversus totalis or other situs anomalies, is recognized in40-50% of individuals with PCD[9, 10]. Heterotaxy is observed in at least 12% of individuals with PCD[11, 12].Some affected women have normal fertility, however, reduced fertility and an increased risk for ectopic pregnancy has been reported, while nearly all men with PCD are infertile due to abnormal cilia causing impaired sperm motility[13, 14]. The estimated pan-ethnic prevalence of PCD is 1:10,000 –1:20,000 liveborns[10].

INHERITANCE PATTERN

PCD is inherited in an autosomal recessive manner, with complete penetrance associated with biallelic variants, while carriers of heterozygous variants are asymptomatic. The only exception is the PIH1D3 gene which is X-linked, and to date, hemizygous males exhibit symptoms, while affected heterozygous females have not been reported.

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.

TEST SENSIVITY

A PCD diagnosis can be established by clinical evaluation, combined with abnormal ciliary ultrastructural analysis (up to 30% of individuals with PCD have normal findings[5,15]), and/or the identification of pathogenic variants in one of the PCD-associated genes. Pathogenic variants in DNAI1 and DNAH5 are identified in up to 30% of affected individuals, however, diagnostic variants in one of the 30 genes on this panel, are expected to be identified in 50-75% of patients clinically diagnosed with PCD[15,16]. Detailed information regarding gene specific variant detection is summarized on the PCD supplemental sensitivity table.

This test comprises 30 genes that have been carefully vetted and selected for their relevance to PCD and the quality of the existing literature establishing a relationship between each gene and PCD. The clinical sensitivity of

the genes included in this test depends in part on the patient's clinical phenotype and family history. In general, the sensitivity of this test is highest for individuals with a laterality defect, unexplained neonatal respiratory distress, and early-onset chronic nasal congestion and wet cough[17].

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.

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