PMP22 Gene Sequence Analysis in Hereditary Neuropathy with Liability to Pressure Palsy (HNPP) and Charcot-Marie-Tooth 1E (CMT1E)

Clinical Features:

Hereditary neuropathy with liability to pressure palsy (HNPP): is characterized by recurrent episodes of sensory and motor neuropathy in a single nerve. While any nerve in the peripheral nervous system can be affected, the ulnar, peroneal, median, brachial plexus and radial nerves are most commonly affected[1]. Almost all affected individuals show prolongation of distal nerve conduction latencies. Other features include: reduced or absent tendon reflexes, pes cavus, episodic foot drop, atrophy and weakness of the hands, carpal tunnel syndrome, and pain, while less common features include: motor brachial paralysis, proximal muscle atrophy, respiratory insufficiency, white matter lesions on brain MRI, hypoglossal nerve paralysis of the tongue, and scapuloperoneal syndrome. An episode can last from minutes to months. Individuals typically present in the 2nd or 3rd decade, although the age of onset can range from neonatal period into the 7th decade.[1]

Charcot-Marie-Tooth type 1E (CMT1E): has been associated with a spectrum of clinical features ranging from mild, episodic neuropathy, similar to HNPP, to severe, early onset demyelinating Dejerine-Sottas syndrome[6]. Typical features include: delays in motor development, distal muscle weakness, foot deformities, loss of deep tendon reflexes, and sensory defects, a small subset of patients with *PMP22* point variants present with axonal neuropathy[6]. Deafness, pressure palsies, and vestibular abnormalities are also reported. Nerve conduction velocities are often very reduced (under 10 m/s) [5], and pathogenic variants causing CMT1E are typically associated with a more severe clinical presentation than *PMP22* duplications[6-7].

Genetics:

Autosomal dominant with variable expressivity. HNPP is caused by loss of function variants in the *PMP22* gene. The most common cause of HNPP is a 1.5 Mb deletion on the short arm of chromosome 17, which includes the *PMP22* gene. While approximately 80% of individuals with HNPP have this recurrent deletion, the remaining 20% have point variants in the *PMP22* gene[1]. CMT1E is also caused by point variants in the *PMP22* gene; however, less than 5% of all CMT1 is caused by *PMP22* point variants[6]. Therefore, for individuals presenting with CMT1, we recommend the Hereditary Neuropathy panel, Demyelinating CMT panel, CMT panel, or Core CMT panel, which contain other genes for which point variants account for higher percentages of CMT1 cases. Deletion/duplication analysis of the *PMP22* gene is also available as a single gene test and is included in the Neuropathy panels (see the Hereditary Neuropathy Panel).

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.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the gene(s) included in this panel depends in part on the patient's clinical phenotype. Approximately 20% of individuals with HNPP do not have the recurrent *PMP22* deletion but instead have a pathogenic variant in *PMP22* detectable by sequence analysis[1]. Less than 5% of patients with CMT1 will have a point variant in *PMP22*[2]. The technical sensitivity of the sequencing test is estimated to be 98%. Deletions involving more than 20 bp and insertions involving more than 10 bp are not reliably detected by the sequencing methodology.

References:

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