PMP22 Gene Deletion/Duplication Analysis in Hereditary Neuropathy with Liability to Pressure Palsy (HNPP) and Charcot-Marie-Tooth 1A (CMT1A)

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 1A (CMT1A): is a progressive disorder characterized by slow nerve conduction velocity (less than 38m/s), distal muscle weakness and atrophy, depressed deep tendon reflexes, sensory loss, pes cavus, hammertoes, and bilateral foot drop. Hearing loss and hip dysplasia may also be present[2,5]. Approximately 85% of individuals with CMT1A present with initial symptoms before age 20.[3]

Genetics:

Autosomal dominant with variable expressivity and reduced penetrance; approximately 80% of individuals with *PMP22* deletions inherited the deletion from a parent, while approximately 66% of individuals with *PMP22* duplications inherited the duplication from a parent[1,2]. HNPP is most commonly caused by 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]. The reciprocal duplication of *PMP22* is the most common cause of Charcot-Marie-Tooth disease. Approximately 70% of CMT1 is caused by the recurrent *PMP22* duplication[2]. Other causes of demyelinating CMT include: point variants in *PMP22*, and pathogenic variants in *MPZ*, *LITAF*, *EGR2*, and *NEFL*. Sequence and deletion/duplication analysis of the 53 genes associated with inherited neuropathy, including *PMP22*, is available at GeneDx (see the Hereditary Neuropathy Panel).

Test Methods:
Targeted array CGH analysis with exon-level resolution is performed to evaluate for a deletion or duplication of one or more exons of the gene. The presence of any potentially disease-associated copy number alteration(s) is confirmed by quantitative PCR or another appropriate method. Sequencing and deletion/duplication analysis of the remaining genes on the Hereditary Neuropathy Panel is available as a separate test if this test negative.

Test Sensitivity:
Exon-level array CGH will detect partial and whole gene deletions and duplications of the *PMP22* gene. Approximately 80% of individuals with a HNPP will have a deletion of *PMP22*, while approximately 70% of individuals with CMT1 will have a duplication of the *PMP22* gene[1,4].

References:

1. Bird (Updated September 2014). Hereditary Neuropathy with Liability to Pressure Palsies. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010. Available at http://www.genetests.org.
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3. Li, J (2012) Semin Neurol. 32(3): 204-214.
4. Nelis et al. (2006) Eur J Hum Genet 4(1): 25-33.
5. Siskind et al. (2013) J Genet Counsel 22:422-436.