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

Mendelian Inheritance in Man Number:
118220 (Charcot-Marie-Tooth disease, demyelinating type 1A; CMT1A); 162500 (Hereditary Neuropathy with Liability to Pressure Palsy; HNPP); 601097 (peripheral myelin protein 22 gene; PMP22)

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. 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.

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. Approximately 85% of individuals with CMT1A present with initial symptoms before age 20.

Inheritance pattern:
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.

Genetics:
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 mutations in the PMP22 gene. 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. Other causes of demyelinating CMT include: point mutations 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).

Reasons for referral:
1. Molecular confirmation of a clinical diagnosis
2. To assist with decisions about treatment and management of individuals with neuropathy
3. Testing of at-risk relatives for specific known pathogenic variants previously identified in an affected family member

Test method:
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\(^1,4\).

**Specimen Requirements and Shipping/Handling:**
- **Blood:** Whole blood in EDTA. Adults: 8-10 ml; Children: 4 ml; Infants: 2 ml. Ship blood overnight at ambient temperature, using a cool pack in hot weather. Blood specimens may be refrigerated for up to 7 days prior to shipping.
- **Oral Rinse:** Use GeneDx kit only; follow instructions at [http://www.genedx.com/order-a-test/specimen-requirements/](http://www.genedx.com/order-a-test/specimen-requirements/)
- **Extracted DNA:** Outside DNA is discouraged; however, high quality extracted DNA can be accepted. This test requires a minimum of 20 μg of DNA at a concentration of 50 ng/ul of DNA with a minimum volume of 400 ul.
- **Other specimens:** Buccal brushes and paraffin embedded tissue can NOT be used for this testing.

**Required Forms:**
- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

**References:**