PABPN1 Gene Analysis for Oculopharyngeal Muscular Dystrophy

DISORDER ALSO KNOWN AS
OPMD

CLINICAL REATURES
Oculopharygeal muscular dystrophy (OPMD) is characterized by slow progressive muscle weakness that results in difficulty swallowing (dysphagia) and drooping of the eyelids (ptosis). The onset of disease is from 40-50 years of age and it usually presents with ptosis, followed by dysphagia, which progresses overtime. As the weakness progresses there can be an increased risk of potentially lifethreatening aspiration pneumonia and poor nutrition. OPMD can also present with tongue weakness and atrophy, vocal changes (wet voice due to pooling of saliva), facial muscle weakness, limitation of upward gaze, weight loss, proximal weakness in the lower extremities, and less commonly, proximal weakness in the upper extremities. Individuals with severe lower extremity weakness will also have creatine phosphokinase (CK) concentrations that are elevated two to seven times the normal value. Previously, the diagnosis of OPMD was made based on histopathology of intranuclear inclusions (INI) and dystrophic changes to the muscle; however, these findings are neither necessary for, nor specific to, the diagnosis of OPMD. Evidence of a myopathic process can be observed on EMG, but is thought to be nonspecific for OPMD.[6]

INHERITANCE PATTERN/GENETICS
OPMD is usually inherited in an autosomal dominant manner; autosomal recessive inheritance of a particular allele has been documented.

Oculopharygeal muscular dystrophy is caused by expansion of the alanine repeat (GCN trinucleotide, where N represents any nucleotide) in the first exon of the PABPN1 gene. Normal alleles contain ten GCN trinucleotide repeats. Autosomal dominant forms of OPMD result from alleles carrying 12-17 repeats. The autosomal recessive form of OPMD results from homozgosity of an allele with 11 repeats; it is characterized by later onset and milder disease.[5] The proportion of de novo repeat expansions is unknown, but reported to be small.[6] The PABPN1 trinucleotide repeat is stable during mitosis and meiosis so expansion is rare and therefore, anticipation is not observed in this disease.[5] The prevalence of OPMD ranges from1:600 to 1:100,000 with higher prevalence in French-Canadian and Bukhara Jewish populations.[3,4,5].

TEST METHODS
Using genomic DNA obtained from blood (2-10 mL in EDTA), analysis is performed by bi-directional Sanger sequencing of exon 1, specifically covering the alanine repeat starting at amino acid 2. Repeat number is evaluated by visual inspection of the sequence and counting the number of repeats. Test results are confirmed by repeat Sanger sequencing.

TEST SENSTIVITY
The clinical sensitivity of sequence analysis for the trinucleotide repeat in the PABPN1 gene depends on the phenotype of the patient. In those individuals with OPMD, 99% have an expansion of the alanine repeat in exon 1 of the PABPN1 gene, which is detectable by targeted sequence analysis.[1,2] One pathogenic single nucleotide variant (p.G12A) has been associated with OPMD and is detectable by this test.[7] The technical sensitivity of Sanger sequencing is estimated to be greater than 95%.

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