Oculopharyngeal Muscular Dystrophy (OPMD): **PABPN1** GCN Repeat Analysis

**Condition Description**

Oculopharyngeal muscular dystrophy (OPMD) is characterized by late-onset ptosis (eyelid drooping), dysphagia (swallowing difficulty), and a positive family history with involvement of two or more generations. OPMD can be inherited in an autosomal dominant or autosomal recessive manner. The symptoms are the same in both inherited forms, but age of onset tends to be earlier in the autosomal dominant form. In one study of autosomal dominant OPMD, the mean age of onset for ptosis was 48 years and for dysphagia was 50 years. All individuals were symptomatic by age 70 years. Age of onset for autosomal recessive OPMD is often in the sixties. Other signs observed as the disease progresses are tongue atrophy and weakness, proximal lower extremity weakness, dysphonia, limitation of upward gaze, facial muscle weakness, and proximal upper extremity weakness. Severe cases represent 5% to 10% of all cases. These individuals have earlier onset of ptosis and dysphagia (<45 years) and an incapacitating proximal leg weakness that starts before age 60 years. Some individuals eventually need a wheelchair. Life expectancy is not reduced.

Serum CK concentration elevation two to seven times the normal value has been reported in individuals with OPMD with severe leg weakness. In most cases, however, serum CK concentration is normal or up to twice the upper normal value. Previously the diagnosis of OPMD was based on the presence of intranuclear inclusions (INI) on muscle biopsy; now muscle biopsy is only warranted in those individuals with normal results on DNA analysis. The molecular diagnosis of autosomal dominant and autosomal recessive OPMD depends upon detection of larger than normal "GCN" trinucleotide repeat in the first exon of the **PABPN1** gene (also called **PABP2**) at 14q11.2. The normal allele has ten GCN repeats (GCN)\textsuperscript{10} (previously referred to as the (GCG)\textsubscript{6} normal allele). Autosomal dominant alleles contain 12 to 17 GCN repeats -- (GCG)\textsubscript{12-17}. The autosomal recessive allele has 11 GCN repeats -- (GCN)\textsubscript{11} (previously referred to as (GCN)\textsubscript{7}). Individuals inheriting an autosomal dominant mutation from an affected parent and an autosomal recessive mutation [(GCN)\textsubscript{11}] from the other parent will develop a severe form of OPMD. The most severe OPMD presentation is reported for individuals who are homozygotes for an autosomal dominant OPMD mutation. Clinical anticipation is not observed with this disease.

The prevalence of autosomal dominant OPMD has been estimated to be 1:100,000 in France, 1:1000 in the French-Canadian population of the province of Quebec, and 1:600 among Bukhara Jews living in Israel. In the United States, the majority of affected individuals are of French-Canadian extraction, though a large number are also of other backgrounds, including Jewish Ashkenazi and Spanish American in Texas and California. The predicted prevalence of the autosomal recessive form should be in the order of 1:10,000 in France, Quebec, and Japan based on the allele frequency of the (GCN)\textsubscript{11} autosomal recessive mutation in these populations.

For patients with suspected OPMD, GCN repeat analysis is recommended.

**Click here** for the GeneTests summary on this condition.

**Genes**

PABP2, **PABPN1**

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of OPMD
- Carrier testing in adults with a family history of OPMD

**Methodology**

Analysis of GCN repeat number is detected by PCR amplification of exon 1 of the **PABPN1** gene and sequencing of the resulting fragments.

**Detection**

Clinical Sensitivity: Unknown. This analysis involves exon 1 only. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:
In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene\textsuperscript{TM} Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

**Related Tests**

- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.

- Prenatal testing is available to adult individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.