Pelizaeus-Merzbacher Disease: PLP1 Gene Sequencing

**Test Code:** RQ  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81479 x1

**Condition Description**

Mutations in the *PLP1* gene (Xq22) are associated with disorders of nervous system myelin formation. Phenotypes range from Pelizaeus-Merzbacher disease (PMD) to spastic paraplegia 2 (SPG2). PMD manifestations in infancy or early childhood typically include nystagmus, hypotonia, and cognitive impairment; severe spasticity and ataxia appear as the findings progress. Affected children with PMD have a shortened life span. SPG2 manifests as spastic paraparesis with or without CNS involvement, and affected individuals usually have a normal life span. PLP1-related disorders are inherited in an X-linked recessive manner mainly affecting males. Female carriers may manifest mild to moderate signs of the disease. Varying phenotypes can coexist in the same kindred or sibship. Males with the PMD phenotype do not reproduce; males with the SPG2 phenotype may reproduce.

The *PLP1* gene encodes a 276-amino acid myelin proteolipid protein (PLP). PLP is the predominant protein constituent of central nervous system myelin, constituting about 50% of the myelin protein mass. Duplication of a genomic region that includes *PLP1* is the most frequent mutation associated with PMD, seen in 50-75% of males with PMD. Duplications are typically tandem duplications occurring at Xq22, but insertion at at least four other sites have been reported: Xp22, Xq28, 19qtel, and in the Y chromosome. Duplication of *PLP1* presumably results in overexpression of myelin proteolipid protein (PLP), leading to dysfunction and death of oligodendrocytes, the myelin-forming cells in the CNS. Deletions of the entire *PLP1* gene occur in fewer than 2% of individuals with PMD. Point mutations account for approximately 15-25% of *PLP1* mutations.

Between 80% and 95% of males with PMD or SPG2 have an identifiable alteration in *PLP1*. Most mothers of a proband are carriers of *PLP1* mutations. De novo mutations have been reported for several point mutations, but not for *PLP1* duplications, which appear to arise in the male germline. In the US, the prevalence of PMD is estimated to be approximately 1/200,000 to 1/500,000. A study in Germany reported the incidence there to be about 0.13 per 100,000 live births. In the Czech Republic, *PLP1* mutations have been reported in 1/90,000 births.

For patients with suspected PMD or SPG2, deletion/duplication analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by deletion/duplication analysis, sequence analysis is appropriate.

Click [here](#) for the GeneReviews summary on this condition.

**Genes**

*PLP1*

**Indications**

- Confirmation of a clinical/biochemical diagnosis of PMD or SPG2 in an individual in whom deletion/duplication analysis was negative
- Carrier testing in adult females with a family history of PMD or SPG2 in whom deletion/duplication analysis was negative

**Methodology**

PCR amplification of 7 exons contained in the *PLP1* gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence deoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements. Large deletions are not detected by this analysis.

**Detection**

Clinical Sensitivity: Between 80% and 95% of males with PMD or SPG2 have an identifiable alteration in *PLP1*. Point mutations account for approximately 15-25% of *PLP1* mutations. Mutations in the promoter region, some mutations in the introns, and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. 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*

**Type: Whole Blood (EDTA)**

Specimen Requirements:
- EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
- Older Children & Adults: 5-10 ml
- Autopsy: 2-3 ml unclotted cord or cardiac blood

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Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Special Instructions
Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed. Deletion/duplication analysis by targeted CGH array is recommended before sequence analysis. If deletion/duplication analysis is performed outside of EGL Genetics, please submit a copy of the report with the test requisition.

Related Tests
- Deletion/Duplication Analysis of PLP1 Gene by CGH array is available and is recommended before sequence analysis (RR).
- CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- 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 females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.