Pelizaeus-Merzbacher Disease: PLP1 Gene Deletion/Duplication

**Test Code:** RR  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81404 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 80-95% 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, full gene sequencing is appropriate.

Please click here for the GeneReviews summary on this condition.

### Genes

**PLP1**

### Indications

This test is indicated for:
- Confirmation of a clinical/biochemical diagnosis of PMD or SPG2.
- Carrier testing in adult females with a family history of PMD or SPG2.

### Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

### Detection

Between 80-95% of males with PMD or SPG2 have an identifiable alteration in PLP1. Duplication of a genomic region that includes PLP1 is the most frequent mutation associated with PMD, seen in 50-75% of males with PMD. Deletions of the entire PLP1 gene occur in fewer than 2% of individuals with PMD.

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations.

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### Specimen Requirements

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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:

Oragen™ 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**

Please submit copies of diagnostic biochemical test results along 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**

- Pelizaeus-Merzbacher Disease: PLP1 Gene Sequencing (RQ) is available for those individuals in whom deletion analysis is negative.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.