Lesch-Nyhan Syndrome: HPRT1 Gene Deletion/Duplication

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**Condition Description**

Lesch-Nyhan syndrome (LNS) is an X-linked condition caused by mutation in the *HPRT1* gene (Xq26-q27.2). The features of LNS are intellectual disability, spastic cerebral palsy, hyperuricemia (uric acid overproduction), and choreoathetosis. The hallmark features of the disease are behavioral disturbances such as self-destructive biting of fingers, lips, and cheeks, and banging of the head or limbs. Developmental delay and hypotonia are evident by ages three to six months. Behavioral disturbances and cognitive impairment arise between ages two and three years. Related disorders with less severe manifestations include hyperuricemia with neurologic dysfunction but no self-injurious behavior (HRND) and hyperuricemia alone, sometimes with acute renal failure (HRH).

The *HPRT1* gene encodes the production of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). This enzyme plays a controlling role in purine metabolism. Virtually complete deficiency of HPRT (residual activity less than 1.5%) is diagnostic of classic LNS in males. HPRT activity of 1.5% to 8% is associated with a neurological variant of LNS, with uric acid overproduction and neurologic disability that varies from minor clumsiness to debilitating extrapyramidal and pyramidal motor dysfunction. Partial HPRT deficiency (residual enzyme activity of at least 8%) is associated with Kelley-Seegmiller syndrome (KSS). Renal stones, uric acid nephropathy, and renal obstruction are often the presenting symptoms of Kelley-Seegmiller syndrome, but rarely of LNS. While LNS is characterized by abnormal metabolic and neurologic manifestations, KSS is usually associated only with the clinical manifestations of excessive purine production. Measurement of HPRT enzyme activity for carrier detection in females is technically demanding and not widely used.

Sequence analysis of the *HPRT1* gene in males with full LNS phenotype has been shown to identify the majority of mutations (218 mutations identified in 271 families in one study). Twenty-one to twenty-four percent of mutations have been shown to be large deletions. Each family generally has a unique mutation. The prevalence of LNS is approximately 1:380,000. It appears to occur in all populations that have been studied, and with relatively equal frequency.

For patients with suspected LNS, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

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**Genes**

*HPRT1*

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**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of LNS in an individual in whom sequencing analysis was negative
- Carrier testing in adult females with a family history of LNS in whom sequencing analysis was negative

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**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.

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**Detection**

For individuals with full LNS phenotype, the mutation detection rate is believed to be approximately 80%. 21-24% of mutations have been shown to be large deletions. Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

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**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™ 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. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

### Related Tests

Sequence Analysis of HPRT1 Gene is available and is required before deletion/duplication analysis (RM).

CGH array-based test for Deletion/Duplication Analysis of 64 different X-linked intellectual disability genes is available (OL).

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.