

Lesch-Nyhan Syndrome: *HPRT1* Gene Sequencing

Test Code: RM

Turnaround time: 4 weeks

CPT Codes: 81479 x1

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.

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

Genes

[HPRT1](#)

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of LNS
- Carrier testing in adult females with a family history of LNS

Methodology

PCR amplification of 9 exons contained in the *HPRT1* gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy 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: 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. 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

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

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.

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.

Special Instructions

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

Related Tests

Deletion/Duplication Analysis of HPRT1 Gene by CGH array is available for those individuals in whom sequence analysis is negative (RN).

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.