Peutz-Jeghers Syndrome: STK11 Gene Sequencing

Test Code: VL
Turnaround time: 4 weeks
CPT Codes: 81479 x1

Condition Description

Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation. Peutz-Jeghers-type hamartomatous polyps are most common in the small intestine (in order of prevalence: in the jejunum, ileum, and duodenum) but can also occur in the stomach and large bowel. Gastrointestinal polyps can result in chronic bleeding and anemia and cause recurrent obstruction and intussusception requiring repeated laparotomies and bowel resections. Variable expressivity is common; some affected individuals in families with PJS may have only polyps or perioral pigmentation.

The age at onset for symptoms from polyps is variable, with some individuals developing symptoms within the first few years of life. Significant interfamily variability is observed in the age at which polyps are first observed, suggesting that the natural history of polyps in a family may be a predictor of severity for offspring. In studies from MD Anderson Cancer Center, the median age at first GI symptoms was ten years, while the median age at first polypectomy was age 13 years. A report from Korea indicated a mean age of onset for GI symptoms of 12.5 years. In a review of 32 kindreds with PJS, laparotomy for bowel obstruction was performed in 30% of individuals by age ten years and in 68% by age 18 years.

Mucocutaneous hyperpigmentation presents in childhood as dark blue to dark brown macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa. Hyperpigmented macules on the fingers are common. The macules may fade in puberty and adulthood. Individuals with Peutz-Jeghers syndrome are at increased risk for malignancies (colorectal, gastric, pancreatic, breast, and ovarian cancers). Females are at risk for sex cord tumors with annular tubules (SCTAT), a benign neoplasm of the ovaries, and adenoma malignum of the cervix, a rare aggressive cancer. Males occasionally develop calcifying Sertoli cell tumors of the testes, which secrete estrogen and can lead to gynecomastia.

The diagnosis of Peutz-Jeghers syndrome is based on clinical findings. In individuals with a clinical diagnosis of PJS, molecular genetic testing of the STK11 (LKB1) gene (19p13.3) reveals disease-causing mutations in approximately 100% of individuals who have a positive family history and approximately 90% of individuals who have no family history of PJS.

About 50% of probands have an affected parent and about 50% have no family history of PJS, but the proportion of cases caused by de novo gene mutations is unknown as the frequency of subtle signs of the disorder in parents has not been thoroughly evaluated and molecular genetic data are insufficient. Parents of affected individuals with no known family history of PJS should be evaluated clinically, and with molecular genetic testing if a disease-causing STK11 mutation has been identified in the proband.

For patients with suspected PJS, 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.

Genes

STK11

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of PJS
- Individuals at-risk for PJS due to family history

Methodology

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PCR amplification of 9 exons contained in the \textit{STK11} gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are 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, and does not detect large deletions.

**Detection**

Clinical Sensitivity: Approximately 100% of individuals who have a positive family history and approximately 90% of individuals who have no family history of PJS. 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

* 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.

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**

- Deletion/duplication analysis of the \textit{STK11} gene by CGH array is available for those individuals in whom sequence analysis is negative (VM).
- 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 individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.