

## STK11 Gene Analysis in Peutz-Jeghers Syndrome

**Disorder also known as:** Peutz-Touraine-Jeghers syndrome; Hamartomatous intestinal polyposis

### Clinical Features:

Peutz-Jeghers syndrome (PJS) is characterized by the combination of a distinct type of gastrointestinal hamartomatous polyp, called Peutz-Jeghers polyps, and a distinctive pattern of mucocutaneous hyperpigmentation. Polyps are most prevalent in the small intestine, but also appear in the stomach, colon, and nasal passages. Hyperpigmented macules associated with PJS are found on the buccal mucosa, around the mouth, eyes, nostrils, in the perianal area, and on the tips of the fingers and toes. They are dark blue to dark brown in color, typically present in infancy or childhood, and may fade with age. Individuals with PJS have an increased risk to develop cancers of the breast, colon, pancreas, stomach, small bowel, uterus, lung, and endocervical glands.<sup>1,2</sup> Females with PJS have a risk to develop sex cord tumors with annular tubules (SCTAT), a benign ovarian neoplasm, and affected males can develop calcifying Sertoli cell tumors of the testes.<sup>1</sup> The largest study of cancer risks associated with PJS estimated the risk of developing any cancer to be 85% by age 70.<sup>2</sup>

### Inheritance Pattern:

PJS is inherited in an autosomal dominant manner. While *de novo* (new) cases have been reported, the percentage of cases due to *de novo* pathogenic variants is unknown.<sup>3-6,17</sup>

### Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of *STK11* are PCR amplified and capillary sequencing is performed. Bi directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method is used to confirm all variants with clinical or uncertain significance. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. All sequence alterations are described according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Concurrent deletion/duplication testing is performed using either exon-level array CGH or MLPA. Confirmation of copy number changes is performed by MLPA, qPCR, or repeat aCGH analysis. Data analysis is performed using gene-specific filtering. The array is designed to detect most single-exon deletions and duplications. Array CGH alterations are reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. Benign and likely benign variants, if present, are not reported but are available upon request.

## Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of *STK11* depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of Peutz-Jeghers syndrome as outlined above. Sequencing and deletion/duplication analysis is expected to identify pathogenic variants in approximately 95% of individuals with a clinical diagnosis of Peutz-Jeghers syndrome, with large deletions accounting for up to 30% of pathogenic variants.<sup>7,8</sup>

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while array CGH will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or array CGH.

## References:

- Giardiello, F. M. *et al.* Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology* **119**, 1447–1453 (2000).
- Hearle, N. *et al.* Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **12**, 3209–3215 (2006).
- Gao, Y. *et al.* A De Novo mutation of STK11 gene in a Chinese patient with Peutz-Jeghers syndrome. *Dig. Dis. Sci.* **55**, 1032–1036 (2010).
- Yoo, J.-H. *et al.* A novel de novo mutation in the serine-threonine kinase STK11 gene in a Korean patient with Peutz-Jeghers syndrome. *BMC Med. Genet.* **9**, 44 (2008).
- Liu, W.-L. *et al.* Identification of a novel de novo STK11 mutation in a Chinese child with Peutz-Jeghers syndrome. *J. Int. Med. Res.* **39**, 2033–2038 (2011).
- Hernan, I. *et al.* De novo germline mutation in the serine-threonine kinase STK11/LKB1 gene associated with Peutz-Jeghers syndrome. *Clin. Genet.* **66**, 58–62 (2004).
- Aretz, S. *et al.* High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. *Hum. Mutat.* **26**, 513–519 (2005).
- Resta, N. *et al.* Cancer risk associated with STK11/LKB1 germline mutations in Peutz-Jeghers syndrome patients: results of an Italian multicenter study. *Dig. Liver Dis. Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver* **45**, 606–611 (2013).
- Amos, C. I. *et al.* Genotype-phenotype correlations in Peutz-Jeghers syndrome. *J. Med. Genet.* **41**, 327–333 (2004).
- Young, R. H. Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. *Mod. Pathol. Off. J. U. S. Can. Acad. Pathol. Inc* **18 Suppl 2**, S81-98 (2005).
- Hearle, N. C. M. *et al.* Exonic STK11 deletions are not a rare cause of Peutz-Jeghers syndrome. *J. Med. Genet.* **43**, e15 (2006).
- van Lier, M. G. F. *et al.* High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am. J. Gastroenterol.* **105**, 1258–1264; author reply 1265 (2010).
- Beggs, A. D. *et al.* Peutz-Jeghers syndrome: a systematic review and recommendations for management. *Gut* **59**, 975–986 (2010).
- van Lier, M. G. F., Mathus-Vliegen, E. M. H., Wagner, A., van Leerdam, M. E. & Kuipers, E. J. High cumulative risk of intussusception in patients with Peutz-Jeghers syndrome: time to update surveillance guidelines? *Am. J. Gastroenterol.* **106**, 940–945 (2011).
- Banno, K. *et al.* Hereditary gynecological tumors associated with Peutz-Jeghers syndrome (Review). *Oncol. Lett.* **6**, 1184–1188 (2013).
- Tomlinson, I. P. & Houlston, R. S. Peutz-Jeghers syndrome. *J. Med. Genet.* **34**, 1007–1011 (1997).
- McGarrity, T. J., Amos, C. I. & Baker, M. J. Peutz-Jeghers Syndrome. in *GeneReviews*(®) (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).