



SCG5/GREM1 Targeted Duplication Testing for Hereditary Mixed Polyposis Syndrome

Clinical Features

Hereditary mixed polyposis syndrome (HMPS) [OMIM#601228] is a rare condition characterized by the development of colorectal polyps with multiple, mixed morphologies, and increased risk of colorectal cancer (1). Polyp types observed in affected individuals include serrated lesions, Peutz-Jeghers polyps, juvenile polyps and conventional adenomas (2). Without screening and intervention, these polyps can eventually become cancerous. The lifetime risk of colorectal cancer in patients with HMPS is unknown, but is thought to be increased compared to the general population risk of 5%. To date, no extra-colonic features of HMPS have been described (2).

Molecular Genetics

Jaeger *et al.* (2012) identified a heterozygous 40-kb duplication at 15q13.3 that extended from intron 2 of the *SCG5* gene to a site upstream of the *GREM1* locus and just upstream of the CpG island of the *GREM1* gene, [OMIM#603054], in multiple families of Ashkenazi Jewish descent with HMPS. There was perfect concordance between the presence of the duplication and affected status in the families studied (2). Screening for the duplication in 718 colorectal cancer patients and 935 controls identified an additional affected male of Ashkenazi Jewish descent with a history consistent with HMPS (2). The duplication was not identified in any control patients, and was only identified in individuals of Ashkenazi Jewish descent, suggesting this is a founder mutation in this population (2). The duplication is thought to lead to over-expression of *GREM1* which causes reduced activity of the bone morphogenetic protein pathway and is thought to be the mechanism that drives tumorigenesis in these patients.

Inheritance

HMPS is inherited in an autosomal dominant manner. Recurrence risk for children of an affected individual is 50%.

Test methods

A PCR-specific assay is used to test for the 40-kb duplication region at 15q13.3 in HMPS patients. PCR primers are used to amplify the duplication boundary of the 40-kb duplicated region that produces a unique specific amplification product in the presence of the duplication.

SCG5/GREM1 targeted duplication testing

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| Sample specifications: | 3 to 10 cc of blood in a purple top (EDTA) tube |
| Cost: | \$500 |
| CPT codes: | 81402 |
| Turn-around time: | 3-4 weeks |

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

- Whitelaw SC, Murday VA, Tomlinson IP *et al.* Clinical and molecular features of the hereditary mixed polyposis syndrome. *Gastroenterology* 1997; 112: 327-334.
- Jaeger E, Leedham S, Lewis A *et al.* Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist *GREM1*. *Nat Genet* 2012; 44: 699-703.

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