Oxford Molecular Genetics Laboratory

Hereditary Mixed Polyposis Syndrome

HMPS1 OMIM 601228, 603054 (*GREM1*); HMPS2 OMIM 610069, 601299 (*BMPR1A*)

INTRODUCTION

Hereditary mixed polyposis syndrome (HMPS) is characterised by polyps of multiple and mixed morphologies and an increased risk of colorectal carcinoma. Polyp types include; juvenile polyps, Peutz-Jeghers polyps, serrated polyps and adenomas. Inhertitance is autosomal dominant.

Altered expression of two genes is reported in association with HMPS. These are *GREM1* (HMPS1) and *BMPR1A* (HMPS2).

HMPS1 is caused by a ~40kb duplication of the region from exon 2 of *SCG5* (upstream of *GREM1*) to just upstream of the CpG island of *GREM1*. The duplication has so far only been identified on a specific haplotype and in HMPS patients of Ashkenazi Jewish heritage, (Jaeger *et al*, Nature Genetics, 44(6), June 2012).

HMPS2 is caused by loss of function variants in the *BMPR1A* gene (O'Riordan et al, Colorectal Disease, 12, 570-573, Cao et al, J. Med. Genet, 2006, 43, e130).

TESTING AND REFERRALS

Diagnostic:

- Clinically affected patients.
- UK referrals must be made through Clinical Genetics departments.

Pre-symptomatic test for Familial Mutation:

- Individuals at risk of developing HMPS. Clinically unaffected relatives of individuals in whom a HMPS causing pathogenic mutation has been identified.
- Referrals from Clinical Genetics only.
- Requests for pre-symptomatic testing should either be discussed with the laboratory in advance or be accompanied by details regarding the known pathogenic mutation in the family.

Prenatal:

- Prenatal testing is not usually requested.
- Prenatal requests would only be accepted from Clinical Genetics and must be discussed with the laboratory and arranged in advance.

STRATEGY & TECHNICAL INFORMATION

- Mutation screening in diagnostic referrals is undertaken as follows;

- *BMPR1A*; Next Generation Sequencing using the Custom Hereditary Cancer Solution (HCS) by Sophia Genetics, along with the Sophia DDM analytical platform (includes sequencing and dosage analysis). If a pathogenic/likely pathogenic is found using NGS, family testing can be undertaken using Sanger sequencing or MLPA as appropriate.

  GREM1 duplication; PCR and fragment analysis across the *GREM1* duplication breakpoint and /or Next Generation Sequencing using the Custom Hereditary Cancer Solution (HCS) by Sophia Genetics, along with the Sophia DDM analytical platform.

- When a pathogenic mutation has been identified in an individual, subsequent testing of family members (presymptomatic or diagnostic confirmation) involves testing for the familial mutation only.

TARGET REPORTING TIMES

Diagnostic test (*BMPR1A*):	42 calendar days
Diagnostic test (*GREM1*):	42 calendar days
Predictive testing for known familial variant:	14 calendar days
Diagnostic testing for known familial variant:	42 calendar days

N.B. Details are correct for the date of printing only – last updated 08/11/2019