Inhera™ Colorectal Cancer

Inhera™: Colorectal Cancer Final Report
Genomics Core Laboratory
600 S. Medical Drive
St. George, UT 84790
Email: Genomics@imail.org
Questions? Call 435.251.5780

Intermountain® Precision Genomics

Patient

Patient Name: John Smith
Date of Birth: 08/10/1965
Accession ID: 12646-29-826-4925
Age: 55
Sex: Male

Specimen

Specimen Type: Buccal Swab
Collection Date: 11/04/2020
Received Date: 11/09/2020

Ordering Provider

Provider: THOMAS D. WISE
Report Date: December 17, 2020

Indication for Testing

C18.9 – malignant neoplasm of colon, unspecified

Test Result

⊕ Positive Result Pathogenic/Likely pathogenic variant(s) detected.

Pathogenic/Likely Pathogenic

GENE	VARIANT	POSITION	ZYGOSITY	CLASSIFICATION
MSH6	c.3934_3937dup p.Ile1313SerfsTer7	g.48033721A>AAGTT	Heterozygous	Pathogenic

Pathogenic/Likely Pathogenic Summary

***MSH6* p.Ile1313SerfsTer7**

This patient is heterozygous for variant p.Ile1313SerfsTer7 in the *MSH6* gene. This sequence change creates a premature translational stop signal in the MSH6 gene (NM_000179.3) at amino acid 1313 within the last Pfam domain of total 1324 amino acids. Though the variant will not result in nonsense mediated decay, this frameshift termination will result in the disruption of the C-terminal portion of the MSH2 interaction domain of the MSH6 protein (residues Ala1302-Leu1360) (PMID: 9774676, 12019211). This variant is listed as pathogenic (two star) in ClinVar (VCV000418610.9) and in the Human Gene Mutation Database. This variant is not present in population databases (Exac no frequency). The p.Ile1313SerfsTer7 has been reported as homozygous in an individual diagnosed with constitutional mismatch repair deficiency syndrome (PMID: 28369758), and also reported in patients with suspected Lynch Syndrome (PMID: 25980754, 26681312). Functional analysis of this variant has been reported to impact MSH6 protein function by disrupting the MSH2 interaction domain of MSH6 (PMID: 9774676), however the actual biological significance of the variant is yet to be identified. A founder mutation p.Leu1330Valfs*12 similar to this mutation has been reported as pathogenic in Lynch Syndrome (PMID: 19851887) indicating that this variant also might have similar effects. In summary, this variant meets criteria to be classified as pathogenic based on ACMG guidelines and ClinVar classification, its presence in affected individuals, absence from the general population, established pathogenic reports and the predicted impact on the protein.

Pathogenic/Likely Pathogenic Summary (CONT.)

This gene encodes a member of the DNA mismatch repair MutS family. In E. coli, the MutS protein helps in the recognition of mismatched nucleotides prior to their repair. A highly conserved region of approximately 150 aa, called the Walker-A adenine nucleotide binding motif, exists in MutS homologs. The encoded protein heterodimerizes with MSH2 to form a mismatch recognition complex that functions as a bidirectional molecular switch that exchanges ADP and ATP as DNA mismatches are bound and dissociated. Mutations in this gene may be associated with hereditary nonpolyposis colon cancer, colorectal cancer, and endometrial cancer. Transcripts variants encoding different isoforms have been described. [provided by RefSeq, Jul 2013]

Test results reviewed and approved by:

Jeremy Wallentine, MD

December 17, 2020

Test Disclaimer

The following genes were evaluated by sequencing (*, including CNVs): *APC*, ATM*, BLM, BMPR1A*, CDH1*, CHEK2*, EPCAM*, MLH1*, MSH2*, MSH6*, MUTYH*, PMS2*, POLD1, POLE, PTEN*, SMAD4*, STK11*, TP53**. Positive CNV calls are confirmed by MLPA. Results are negative unless stated in the Test Results section of the report. Note: A negative result, meaning no DNA variants of consequence were detected, does not entirely exclude a diagnosis of a specific hereditary condition as some DNA variants (i.e., some intronic variants, large deletions and duplications, and chromosomal rearrangements) associated with the condition may not always be detected. Benign and likely benign variants are not included in this report. Variants in other genes not included in this study and nongenetic factors, including diet and lifestyle, may also influence this risk. We strongly recommend that you discuss these results with a genetic counselor and/or your health care provider.

Test Methodology

The Inhera™-Colorectal Cancer provides comprehensive coverage of 18 genes (*APC, ATM, BLM, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53*) associated with an increased risk of inherited colorectal cancer. Genomic DNA (gDNA) is isolated from a patient specimen. The quality/quantity of the gDNA is assessed prior to Next Generation Sequencing (NGS) library preparation. NGS library preparation utilizes unique indexes to generate targeted libraries of approximately 500 base pairs (bp). The enrichment workflow enriches 350-650 bp centered symmetrically around the midpoint of the probe, providing coverage of exons (coding regions) and up to 50 bp of flanking intronic (non-coding) regions. All targeted regions are sequenced by NGS on Illumina's MiSeq or NextSeq platform. Reads are aligned to human genome reference sequence (GrCh37) using our in-house bioinformatics pipeline Hereditary Cancer Panel Pipeline version 3.3. During assay validation, Intermountain Precision Genomics (IPG) established the mean depth of coverage for all targeted regions to be > 500x. Sequence changes are identified using a clinical bioinformatics pipeline, and the clinical pathogenicity of each genetic variant is established based on the American College of Molecular Genetics (ACMG) scoring criteria[1]. To generate the low coverage table, we calculate the percentage of the gene that is covered below 30X for the regions covered by the assay. Low coverage is reported on exons that contribute to more than 5% of the gene covered below 30X. The bioinformatics pipeline includes a copy number variant (CNV) caller to detect large deletions and/or duplications in the genes listed above in bold. Any positive CNV calls are confirmed by MLPA (Multiplex Ligation-dependent Probe Amplification) analysis before reporting.

Regulatory Disclosures

This test was developed by Intermountain Precision Genomics (IPG). Its performance characteristics are determined by IPG. The methods have not been cleared or approved by the U.S. Food and Drug Administration. IPG is certified under CLIA-88 and accredited by the College of American Pathologists as qualified to perform high-complexity testing. This test is used for clinical purposes and should not be regarded as investigational or research.

References

Richards S, Aziz N, Bale S, Bick D, et al. Genetics in medicine : official journal of the American College of Medical Genetics. 2015, May. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. (PMID: 25741868)

Goldberg Y, Porat RM, Kedar I, Shochat C, et al. Familial cancer. 2010, Jun. An Ashkenazi founder mutation in the MSH6 gene leading to HNPCC. (PMID: 19851887)

Guerrette S, Wilson T, Gradia S, Fishel R. Molecular and cellular biology. 1998, Nov. Interactions of human hMSH2 with hMSH3 and hMSH2 with hMSH6: examination of mutations found in hereditary nonpolyposis colorectal cancer. (PMID: 9774676)

Polubothu S, Scott RH, Vabres P, Kinsler VA. The British journal of dermatology. 2017, 11. Atypical dermal melanocytosis: a diagnostic clue in constitutional mismatch repair deficiency syndrome. (PMID: 28369758)

Kariola R, Raevaara TE, Lönnqvist KE, Nyström-Lahti M. Human molecular genetics. 2002, May 15. Functional analysis of MSH6 mutations linked to kindreds with putative hereditary non-polyposis colorectal cancer syndrome. (PMID: 12019211)