IntelligeneDx Cancer Genomics

Hereditary Cancer Panel

Patient Name:	Patient ID:
Patient DOB:	Sample Received Date:
Ordering Physician:	Report Delivery Date:

Breast and Ovarian Cancer Panel II

Test Indication: Predictive Test in Patient with Familial History of Cancer.

Results: POSITIVE – an established cancer predisposition was identified.

Pathogenic Mutation(s) Detected:

Gene	Zygose	Type	Mutation
MSH6	HETEROZYGOSE	Point Mutation G to T	c.3367G>T - Exon 5

Interpretation Summary

- This individual carries one previously published pathogenic mutation for Lynch syndrome (a missense mutation in *MSH6*).
- Lynch syndrome is typically inherited in an autosomal dominant pattern. Each first-degree relative (parents, siblings and children) has a 50% (or 1 in 2) chance of inheriting a pathogenic variant of *MSH6*.
- Mutations in this gene are associated with overall cancer risk to age 70 of 29% for men and 49% for women.
- Colorectal cancer risk is 25% for men, and 19% for women. Uterus cancer risk is up to 70%. Other cancers have increased risk as well.
- Disease penetrance and severity can vary due to modifier genes and/or environmental factors. The significance of a variant should therefore be interpreted in the context of the individual's clinical manifestations.

Recommendations Based on the Results

- It is recommended that this individual and any 1st degree relative receive continued clinical evaluation and follow-up for cancer prevention, including cancer screening, and risk reduction measures.
- Genetic counseling is highly recommended for this individual and their family to discuss the implications of this test results. For assistance in locating nearby genetic counseling services please contact the IntelligeneDx at (913) 258-2300.
- Genetic testing of this individual's biological parents and other family members, particularly those who are affected, may help to clarify the significance and relative contributions of the detected variants.
- Please note that the classification of variants of unknown significance may change over time if additional information becomes available. Please contact IntelligeneDx at (913) 258-2300 once a year for any updates regarding the status of these variants.

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Additional DNA Variants identified:

Gene	Zygose	Variant	Classification
MSH2	HETEROZYGOSE	c.118G>A exon 1	Uncertain Significance
MSH2	HETEROZYGOSE	c.146A>T exon 1	Uncertain Significance
BRCA2	HOMOZYGOSE	c.7397C>T exon 14	Uncertain Significance

Comment(s) on Individual Variants

Glu1123Ter in Exon 5 of MSH6 (NM_000179.2) Pathogenic.

- The mutation found in the MSH6 gene is classified as pathogenic in the Leiden Open Variation DataBase (LOVD).
- Individuals with this mutation are at an increased risk of Hereditary Nonpolyposis Colorectal Cancer (HNPCC) or Lynch Syndrome.
- Mutations in the MSH6 gene are associated with atypical HNPCC that do not fulfill Amsterdam criteria.
- In addition, mutations in MSH6 gene have been associated with Endometrial Cancer.

The MSH6 gene is a member of a set of genes known as the mismatch repair (MMR) genes. The MSH6 gene provides instructions for making a protein that plays an essential role in repairing DNA. This protein helps fix mistakes that are made when DNA is copied (DNA replication) in preparation for cell division. The MSH6 protein associates with another protein called MSH2 (produced from the MSH2 gene) to form a protein complex. This complex identifies locations on the DNA where mistakes have been made during DNA replication. Another group of proteins, the MLH1-PMS2 protein complex, then repairs the errors.

Gly40Ser in Exon 1 of MSH2 (NM_172244.2) Uncertain Significance.

The mutation c.118G>A in the gene MSH2 is described in the Leiden Open Variation DataBase (LOVD) as “classification 3: uncertain”. Yamada et al, 2003 report that this mutation can affect hMSH2 protein function, which is an atypical precursor to microsatellite instability (MSI). Changes in the MSH2 gene are the primary cause of MSI in HNPCC, however, few cases are related to inherited mutations

Asp49Val in Exon 1 of MSH2 (NM_172244.2) Uncertain Significance.

The mutation c.118G>A in the gene MSH2 is described in the Leiden Open Variation DataBase (LOVD) as “classification 3: uncertain. Changes in the MSH2 gene are the primary cause of MSI in HNPCC, however, few cases are related to inherited mutations

A2466Val in Exon 14 of BRCA1 (NM_000059.3) Uncertain Significance.

The c.7397c>T mutation in the BRCA2 gene was submitted in May 2003 to the NCBI by the Breast Cancer Information Core (BIC) with uncertain clinical significance. However, the laboratory GENEDX, on September 2013, classified the variant as benign and thus non-pathogenic.

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Methodology

Genes Analyzed:

APC, ATM, BAP1, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51, RAD51, RET, SDHB, SDHC, SLX4, SMAD4, STK11, TP53, VHL.

- Genomic DNA from the submitted specimen was extracted and enriched for the genes analyzed (above).
- Next-generation automated sequencing was performed on the Illumina MiSeq platform.
- The alignment of the sequences generated was performed on the respective reference coding sequences deposited in the GenBank NCBI coding sequence and its flanking regions containing splice sites. Variant calls are generated using the Burrows-Wheeler Aligner (bwa) followed by GATK analysis.
- The same regions were also evaluated to find large deletions and/or insertions.
- This test detects 100% of substitution variants (95%CI=82-100) and 95% of small insertions and deletions (95%CI=98.5-100).
- Sanger sequencing is used to provide data for bases with insufficient coverage. Clinically significant and novel variants are confirmed by independent Sanger sequencing.
- Variants classified as likely benign or benign are not confirmed.
- This test was developed and its performance characteristics determined by IntellegeneDx (CLIA#1 17D2097343). It has not been cleared or approved by the U.S Food and Drug Administration (FDA).

Considerations:

- This genetic test does not exclude the presence of any other change (mutation), pathogenic or not, present in gene regions not analyzed by this test.
- In some cases, the classification and interpretation of such mutations may change as new scientific information becomes available.
- The classification and interpretation of the mutations identified in this test reflect the current state of scientific understanding at the time that the result was issued.

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REFERENCES:
Frebourg T, et al. Am J Hum Genet 1995; 56:608; Hwang SJ, et al. Am J Hum Genet 2003; 72:975; Bendig I, et al. Cancer Genet.Cytogenet 2004; 154:22.

DATA BASES CONSULTED:

BreastCancerInformation Core (BIC)
Available in: http://research.nhgri.nih.gov/projects/bic/
Accessed: 02/20/2015

Kathleen Cuningham Foundation Consortium for researchinto Familial Breastcancer (kConFab)
Available in: http://www.kconfab.org/Progress/Mutations.aspx
Accessed: 02/20/2015

NCBI - National Center for BiotechnologyInformation
Available in: http://www.ncbi.nlm.nih.gov/
Accessed: 02/20/2015

PubMED
Available in: http://www.ncbi.nlm.nih.gov/pubmed/
Accessed: 02/20/2015

LOVD - Leiden Open VariationDatabase
Available in: http://databases.lovd.nl/genomed/home -
Accessed: 02/20/2015

This report was reviewed and approved on June, 23rd 2015 by Flavia C. Costa, Ph.D.

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