Informed Genomics

FORENSIC GENOMICS INNOVATION HUB

Status: FINAL

Comprehensive Hereditary Cancer Panel

Client Details

Name:
Date of Birth:
Gender: Female
Lab ID: Pathogenic Report Test v1.1

Requested By:
Referral ID:
Referral Centre:

Specimen

Specimen: Saliva
Collection Date: 04/04/2023
Receipt Date: 18/04/2023
Report Date: 25/05/2023

Result Summary: Clinically significant variant(s) DETECTED

A pathogenic variant associated with hereditary cancer susceptibility was detected in the BRCA2 gene. The identification of this variant significantly increases the risk of developing BRCA2 related cancers during your lifetime.

Variant Details

Gene	Transcript	Genotype	Protein Change	Exon
BRCA2	NM_000059.4	c.2701delC g.32337056delC	p.Ala902fs*2	11

Results

Variant Impact

This test is designed to detect genetic changes that indicate a significantly increased risk of developing certain types of cancer. A pathogenic heterozygous variant has been detected in this sample in the BRCA2 gene. BRCA2 is a tumour suppressor gene involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis.

Heterozygous BRCA2 pathogenic variants are strongly associated with cancer susceptibility (OMIM:604370 and 614320). The presence of this variant increases the risk of developing cancer, in particular breast or ovarian cancer, although BRCA2 mutations are also associated with susceptibility to other cancers.

Implications

Since genetic changes are often shared within families, any offspring will be at a 50% risk of inheriting this variant and therefore have increased susceptibility to associated disorders. There is also a chance that other relatives are at risk of having inherited this variant.

Whilst having this variant increases your cancer risk, BRCA2 mutations do not have a 100% penetrance which means that not everyone with a variant in BRCA2 will develop an associated cancer in their lifetime.

Recommended Actions

There is an increased risk of developing BRCA2 associated tumours in your lifetime, and therefore you should be monitored appropriately. Genetic counselling has been arranged, which will provide further information regarding your individual risk and what preventative measures are available.

It is possible to investigate other family members regarding the variant identified in the BRCA2 gene. We recommend that you inform your relatives, so that they may have the opportunity to be proactive in their cancer risk management.

Panel Performance

For robust variant calling a minimum read depth of 30X is required. If a region of interest does not reach this threshold, then variant calling can be compromised. For a sample to pass >99% of the panel must reach a minimum read depth of 30X

% Coverage of panel genes sequenced to a minimum 30X = 99.6%

Genes Tested

APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, MUTYH, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL

Reviewed and Approved : Dr Matthew Smith (Principal Clinical Scientist)
Approved on: 25/05/2023

Methods and Limitations

Basis of test

This test is designed to detect genetic changes that indicate a significantly increased risk of developing certain types of cancer. The genes included in this test have been selected based upon their strength as candidate genes and their inclusion in testing guidelines. These are actionable genes where preventative measures are available. Cancer susceptibility variants may exist in genes not covered by this test.

Genomic DNA is enriched for target regions using Nonacus Cell3TM Target hybridisation technology and sequenced using Illumina sequencing by synthesis chemistry. Screening for large deletions and duplications is performed using comparative depth of coverage of next generation sequencing data. Bioinformatics pipeline HCPv1.0. The assay achieved >99% sensitivity and specificity for single nucleotide variants (SNV) and indels (1-28bp) (95% Confidence Interval of >98% (SNV) and >92% (indel)) based on validation studies. CNV analysis determines copy number with high sensitivity (>97%).

Variant classification is performed according to the Cancer Variant Interpretation Group-UK consensus specification for Cancer Susceptibility (PMID: 32170000 http://www.canvaruk.org/) which is based on the American College of Medical Genetics and Genomics (ACMG PMID 25741868) and Association for Clinical Genomic Science (ACGS https://www.acgs.uk) guidelines. Variants are classified as pathogenic, likely pathogenic, variants of unknown significance (VUS), likely benign and benign. IGL does not routinely report VUS, likely benign or benign. All variants reported using HGVS nomenclature and interpreted in the context of the matched annotation (MANE) transcript using GRCh38. Variant interpretation supported using QIAGEN Clinical Insight (QCI) clinical decision support software 9.1.1.20230406.

Test Limitations

This test detects and reports single nucleotide variants (SNVs), small insertion/deletions (INDELS) and copy number variants (CNV) within selected genes (see genes tested section and reduced analysis list below). This test is not validated to detect inversions (such as the MSH2 exons 1-7 inversion) or mosaicism. It does not interrogate promoters, untranslated regions, and other non-coding regions. This test is not designed to detect chromosomal aneuploidy or complex rearrangements such as translocations. Clinically significant variants may exist in the tested genes that the technology is not designed to detect or within regions of these genes not covered by this test. Sensitivity can be impacted by mutation type, repetitive regions, GC content, homopolymers and the presence of pseudogenes. Regions of interest limited to exonic sequences and to a maximum +/- 20 intronic sequence.

PMS2 and its pseudogene PMS2CL share high sequence homology for exons 12-15. This test does not distinguish whether variants seen in these exons originate from PMS2 or PMS2CL. Further testing may be required to disambiguate any variants found in PMS2.

Analysis of the VHL, HOXB13, NF1, NTHL1 gene does not include CNV detection. Non-coding exons are not sequenced by this panel. This may impact on naming CNV variants.

Targeted Gene Analysis

Due to limited clinical data on the impact of certain variant types, reporting is restricted in several genes to certain variant types and loci. ATM (Truncating, frameshift and the c.7271T>G missense variant). CHEK2 (Truncating and frameshift). HOXB13 (c.251G>A missense variant). EPCAM (Exon 8 to 9 deletion).

The laboratory operates robust Quality control however all sources of error cannot be fully excluded and can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent changes in scientific understanding and updates to variant classification systems. DNA has been stored as per IGL DNA storage procedure.
PMID is a unique identifier referring to a published, scientific paper. Search PMID at http://www.ncbi.nlm.nih.gov /pubmed.