SagePath®
Excellence In Health Care

DEPARTMENT OF MOLECULAR DIAGNOSTICS

BRCA1, *BRCA2* Germline

Next Generation Sequencing

Clinical Indication: Not Available
Specimen: EDTA P. Blood

Results

POSITIVE
One pathogenic variant was detected in *BRCA1* gene in the tested sample

Variant Details

Gene	Chromosome locus/ Transcript	Variant coding/ Protein coding	Exon	Variant Interpretation
BRCA1	chr17:41244365/ NM_007294.4	c.3182delT/ p.Ile1061LysfsTer12	10	Pathogenic

Interpretation

One pathogenic variant in *BRCA1* gene has been identified in the individual. The variant p.Ile1061LysfsTer12 is reported in databases as rs886040101. This variant is classified as "Pathogenic" in ClinVar.
BRCA1 and *BRCA2* genes play critical role in DNA repair of double strand breaks and maintenance of genomic stability. Mutations in BRCA1/2 genes are associated with increased risk for breast, ovarian, prostate and pancreatic cancers. Breast cancer patients with germline mutations in BRCA1 can benefit from PARP inhibitors like Olaparib, Talazoparib.

Recommendation

1. Confirmation of reported variant by Sanger sequencing technique.
2. Testing of related family members to access cancer predisposition.
3. Genetic Counselling

NGS Statistics

Coverage	Coverage Uniformity	Depth
98.42%	**99.74%**	**183**

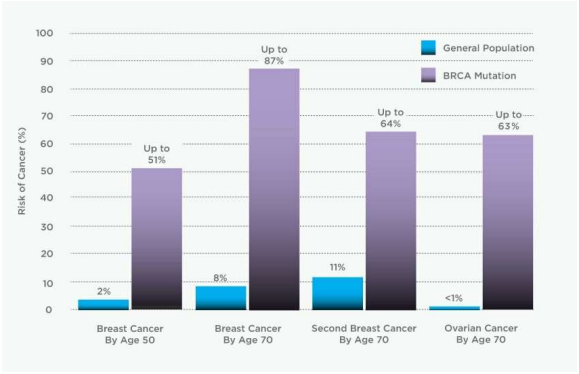
Guidelines

Classification of Variant	Remarks

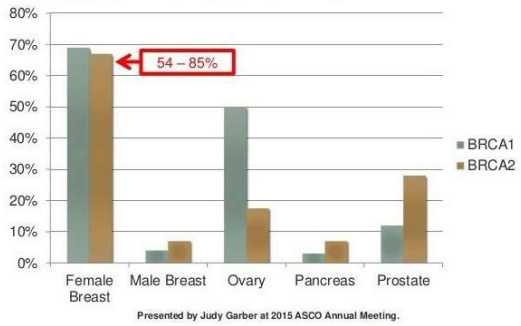
Pathogenic	The variant has been shown to directly contribute to the development of disease. The subject is at significantly increased risk for developing Breast & / or ovarian cancer as compared to general population.
Likely Pathogenic	There is a high likelihood (greater than 90% certainty) that this variant is disease-causing. Additional evidence is expected to confirm this assertion of pathogenicity; but there is a small chance that new evidence may demonstrate that this variant does not have clinical significance
Likely Benign	This variant is not expected to have a manor effect on disease; however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion, but we cannot fully rule out the possibility that new evidence may demonstrate that this variant can contribute to disease.
Benign	This variant does not contribute to cause disease.
Variant of Unknown Significance (VUS)	There is not enough information at this time to support a more definitive classification of this variant.

General Information:

Risk of developing HBOC with BRCA1 and BRCA 2 mutation: Specific inherited mutations in BRCA1 and BRCA2 genes increases the risk of HBOC (1, 5)The lifetime risk of Breast cancer with the pathogenic variant of BRCA1 and BRCA 2 is 46% to 87%. Also, BRCA germline pathogenic variants confer an excessive risk for ovarian cancer ranging from 16.5% to 63%. The lifetime risk of prostate cancer with germline pathogenic variants in BRCA genes ranges from 20-30%.



Elevated Risk of other Cancers with BRCA Mutations



The testing of these mutations is usually recommended only when the person's individual or family history suggests the possible presence of a harmful mutations in BRCA1 or BRCA2, as it can influence the disease management decisions by proper genetic counselling.

Methodology

This panel tests for variations in the entire coding and certain intronic regions of *BRCA1* and *BRCA2* genes using Next Generation sequencing. This assay is used for identifying the SNVs and Indels in the exons of *BRCA1* and *BRCA2* genes. Average coverage of the targeted region obtained was around 1000X.Genomic DNA was isolated from blood sample using commercial kit according to manufacturer's instructions and the target regions of interest were amplified using the Ampliseq™ BRCA Panel. Library preparation was performed using the Ion AmpliSeq™ Library Kit Plus. The sequencing was performed on the GeneStudio S5. The FASTQ reads were aligned against the hg19 in the Torrent suite software (v5.10). Variant calling was done using Ion Reporter (v5.14). The variants were annotated using BRCA Research Assay Germline Annotations v1.4 and ACMG guidelines was followed for variant classification.

Database versions used

5000Exomes (Source Version:20161108), Canonical RefSeq Transcripts(Source Version:v95), ClinVar(Source Version:20190909), dbSNP(Source Version:153), DGV(Source Version:20160515), DrugBank(Source Version:20190723), ExAC(Source Version:1), Gene Ontology(Source Version:20190930), Named Variants(Source Version:1), Pfam(Source Version:32), PhyloP Scores(Source Version:20160919), RefSeq Gene Functional Canonical Transcripts Scores(Source Version:10), RefSeq GeneModel(Source Version:95), CitelineTrialTrove.

Limitation and Disclaimer

Clinical decision regarding care and treatment of customers should not be solely based on this Test. Treatment decisions are the responsibility of the Clinician/ Hospital.

All investigations have their limitation which is imposed by the limits of sensitivity and specificity of individual assay procedures as well as the quality of the specimen received at Oncquest Laboratories Ltd.

Mutations in the other regions of the *BRCA1/BRCA2* gene like deep intronic regions are not covered. Large insertions, deletions, duplications, inversions, repeat expansions and complex rearrangements cannot be characterized accurately by NGS as it uses shortread sequencing data. Such structural variants have a much higher false-positive and false-negative rate than seen for SNVs (single nucleotide variant).

In case of germline mosaicism, there is a risk of the disease recurrence in the family. However, due to technical limitation

of this test, germline mosaicism cannot be determined by this test. Additionally, it is possible that a particular genetic abnormality may not be recognized as the underlying cause of the genetic disorder due to incomplete scientific knowledge about the function of all genes in the human genome and the impact of variants on those genes. Not all variations detected may be listed in the report. Inclusion of variations is dependent upon our assessment of their significance. The quality of sequencing and coverage varies between regions. Many factors such as homopolymers, GC-rich regions etc. influence the quality of sequencing and coverage. This may result in an occasional error in sequence reads or lack of detection of a particular genetic lesion. These test results should be interpreted only in conjunction with the patient's clinical history and other test results.

A report on all variants present is available upon request, please contact the laboratory. Data from this test is based on currently available scientific information. This data can be re-assessed for the presence of any variants that may be newly linked to be associated with cancer. The physician can request reanalysis of the data.

References

1. Richards S et al. 2015. 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. Genet Med 17 (5):405-424 [PMID:25741868]
2. American College of Medical Genetics and Genomics 2013. Incidental findings in clinical genomics: a clarification. Genet. Med.15 (8):664-6[PMID: 23828017].
3. BRCA Mutations: Cancer Risk and Genetic Testing Fact Sheet - National Cancer Institute
4. Jee-Soo Lee et al., 2018.Reclassification of BRCA1 and BRCA2 variants of uncertain significance: A multifactorial analysis of multicenter prospective cohort. jmedgenet-2018-105565.
5. Amanda Ewart Toland et al.,2018. Clinical testing of BRCA1 and BRCA2: a worldwide snapshot of technological practices. (2018) 3:7; doi:10.1038/s41525-018-0046-7. Npg Genomic Medicine.

Note: The performance of this test has been evaluated at Oncquest Laboratories Ltd.

***** End Of Report *****

Disclaimer: All Results released pertain to the specimen submitted to the lab
1. Test results are dependent on the quality of the sample received by the lab
2. Tests are performed as per schedule given in the test listing and in any unforeseen circumstances, report delivery may be delayed
3. Test results may show interlaboratory variations
4. All dispute and claims are subjected to local jurisdiction only. Clinical correlation advised.
5. Test results are not valid for medico legal purposes
6. For all queries, feedbacks, suggestions, and complaints, please contact customer care support +0124 665 0000