Germline Cancer Predisposition Panel-focused

Test Description

The MolQ *BRCA* Germline mutation test helps assess your risk of developing cancer by detecting a potentially harmful change (mutation) in *BRCA1* and *BRCA2* genes.

Patient Demographic

Name: Ms. Hajira Mohseni
Sex: Female
Date of Birth/Age: 57 years
Disease: Ovarian Carcinoma

Clinician

Clinician Name: Dr Amish Vora
Medical Facility: HOPE Clinic
Pathologist: Not Provided

Specimen

Booking ID: 011910170163
Site: NA
Sample Type: Blood
Date of Collection: 17-10-2019
Date of Booking: 17-10-2019

CLINICAL SYNOPSIS

Hajira Mohseni, is a case of carcinoma ovary and has been evaluated for pathogenic variations in the *BRCA1* and *BRCA2* genes.

RESULTS

Pathogenic variant causative of the reported phenotype is detected.

Gene (Transcript) #	Location	Variant	Zygosity	Disease	Inheritance	Classification
BRCA1 (-) (ENST00000471181.2)	Exon 12	c.4327C>T (p.Arg1443Ter)	Heterozygous	Breast-ovarian cancer, familial, 1	Autosomal dominant	Pathogenic

$Genetic test results are reported based on the recommendations of American College of Medical Genetics[1].

ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) DETECTED

No other variant that warrants to be reported was detected. Variations with high minor allele frequencies which are likely to be benign will be given upon request.

The *BRCA1* and *BRCA2* genes are 100% covered in this assay.

CLINICAL CORRELATION AND VARIANT INTERPRETATION

***BRCA1* p.Arg1443Ter**
Overall depth: 92X

Variant description: A heterozygous nonsense variation in exon 12 of the ***BRCA1*** gene (**chr17:g.41234451G>A; Depth: 92x**) that results in a stop codon and premature truncation of the protein at codon 1443 (**p.Arg1443Ter; ENST00000471181.2**) was detected (Table). The observed variation (**also referred to as c.4446C>T**) has previously been reported in the individuals with hereditary breast and ovarian cancer[2-5] and documented as pathogenic in Clinvar database[6]. The **p.Arg1443Ter** variant has not been reported in the 1000 genomes databases and has a minor allele frequency of 0.002% and 0.005% in the ExAC and our internal database, respectively. The *in-silico* prediction# of the variant is damaging by MutationTaster-2 tool. The reference codon is conserved in primates.

OMIM phenotype: Susceptibility to familial breast-ovarian cancer-1 (OMIM#604370) is caused by mutations in the *BRCA1*

gene (OMIM*113705)[7].

Based on the above evidence[$], ***this BRCA1 variation is classified as a pathogenic variant and needs to be carefully correlated with the clinical symptoms***.

RECOMMENDATIONS

- The sensitivity of NGS based assays to detect large heterozygous deletions/duplications, complex rearrangements (>10 bp) and copy number variations (CNVs) is low (70-75%) as it uses short-read sequencing data. Therefore, an alternate method such as Multiplex Ligation-dependent Probe Amplification (MLPA) is recommended to detect such structural variants in *BRCA1* and *BRCA2* genes. Kindly consult with your clinician and contact MolQ Laboratory for this test.
- Genetic counselling is advised for interpretation on the consequences of the variant(s).

REFERENCES

1. Richards S. et al., 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):405-24,2015.
2. Weitzel J. N. et al., Prevalence of BRCA mutations and founder effect in high-risk Hispanic families. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the AmericanSociety of Preventive Oncology (2005): 1055-9965.
3. Soumittra, N., et al. Molecular genetics analysis of hereditary breast and ovarian cancer patients in India. Hereditary Cancer in Clinical Practice, 7(1) (2009).
4. Weitzel, J., et al. Prevalence and Type of BRCA Mutations in Hispanics Undergoing Genetic Cancer Risk Assessment in the Southwestern United States: A Report from the Clinical Cancer Genetics Community Research Network. Journal of ClinicalOncology, 31(2) (2013): pp.210-216.
5. Cavallone L. et al., Comprehensive BRCA1 and BRCA2 mutation analyses and review of French-Canadian families with atleast three cases of breast cancer. Familial cancer (2010): 1573-7292.
6. https://www.ncbi.nlm.nih.gov/clinvar/variation/17675/
7. McKusick V.A., Mendelian Inheritance in Man. A Catalog of Human Genes and Genetic Disorders. Baltimore: Johns Hopkins University Press (12th edition), 1998.

Jatinder Kaur, PhD
Head, Molecular Biology & Genomics

Dr. Gulshan Yadav, MD
Head, Pathology

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APPENDIX 1: TEST METHODOLOGY

Method

The *BRCA1*, *BRCA2* gene(s) was/were analyzed by an amplicon-based next-generation sequencing approach. The amplicons cover the entire coding region and the highly conserved exon-intron splice junctions. We have a minimum coverage of >20x for every amplicon. Missing regions or regions of poor quality are completed with classical Sanger sequencing to achieve 100% coverage. Variants of relevance identified by NGS are continuously and individually in-house validated for quality aspects; those variants which meet our internal QC criteria (based on extensive validation processes) are not validated by Sanger.

Genetic test results are reported based on the variant classification recommendations of American College of Medical Genetics[1], as described in the table below:

Variant	A change in a gene. This could be disease causing (pathogenic) or not disease causing (benign).
Pathogenic	A disease causing variation in a gene which can explain the patient's symptoms has been detected. This usually means that a suspected disorder for which testing had been requested has been confirmed.
Likely Pathogenic	A variant which is very likely to contribute to the development of disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion of pathogenicity.
Variant of Uncertain Significance	A variant has been detected, but it is difficult to classify it as either pathogenic (disease causing) or benign (non-disease causing) based on current available scientific evidence. Further testing of the patient or family members as recommended by your clinician may be needed. It is probable that their significance can be assessed only with time, subject to availability of scientific evidence.

#The transcript used for clinical reporting generally represents the canonical transcript (according to Ensembl release 87 gene model), which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported.
Variants annotated on incomplete and nonsense mediated decay transcripts will not be reported.
#The *in-silico* predictions are based on Variant Effect Predictor, Ensembl release 91 (SIFT version - 5.2.2; PolyPhen - 2.2.2); LRT version - November, 2009 release from dbNSFPv3.1 and Mutation Taster2 based on build NCBI 37 / Ensembl 69.

For any further technical queries please contact contact@molq.in.

DISCLAIMER

- The variants in this report are interpreted based on information available in scientific literature at the time of reporting, therefore, an impact and classification of gene variation might change over time with respect to clinical indication. MolQ Laboratory cannot be held responsible for this, the clinician can request reanalysis of data on an annual basis at an additional cost.
- Variants in untranslated region, promoters and deep intronic regions are not analyzed in this test.
- Incidental or secondary findings (if any) that meet the ACMG guidelines[2] can also be given upon request.
- Test results are interpreted in the context of clinical findings, family history and other laboratory data. In the absence of detailed accurate clinical or family history of the patient, MolQ Laboratory cannot guarantee the accuracy of the interpretation of results.
- The results may be inaccurate in rare circumstances if the individual tested has undergone bone marrow transplantation or blood transfusion.
- MolQ Laboratory is not liable to provide diagnosis, opinion or recommendation related to disease, in any manner. MolQ Laboratory hereby recommends the Patient and/or the guardians of the Patient to contact clinician for further interpretation of the test results.
- This is a laboratory developed test and the development and the performance characteristics of this test was determined by the reference laboratory.

REFERENCES

1. Richards S., *et al.*, 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, Genetics in Medicine, 2015 May;17(5):405-24.
2. Green R. C., *et al.*, American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing.