Germline Cancer Predisposition Panel Focused- *BRCA1* and *BRCA2*

Test Description

The MolQ *BRCA* Germline mutation test on Next Generation Sequencing is a targeted sequencing approach that is restricted to the protein-coding regions of selected genes viz., *BRCA1* and *BRCA2*, which have been implicated in breast and ovarian cancers. This panel utilizes 167 amplicons to analyze the coding region of both *BRCA1* and *BRCA2* genes.

Patient Demographic

Name: Mr. Amit Saini
Sex: Male
Date of Birth/Age: 48 years
Disease: Breast Carcinoma

Clinician

Clinician Name: Dr Amit Verma
Medical Facility: Max Hospital
Pathologist: Not Provided

Specimen

Booking ID: 012411290121
Site: NA
Sample Type: Blood
Date of Collection: 29-11-2024
Date of Booking: 29-11-2024

CLINICAL SYNOPSIS

Amit Saini, is diagnosed with breast carcinoma and has been evaluated for pathogenic variations in the *BRCA1* and *BRCA2* genes.

RESULTS

No pathogenic or likely pathogenic variant causative of the reported phenotype are detected

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.

GENE SUMMARY

BRCA1

This gene encodes a 190 kD nuclear phosphoprotein that plays a role in maintaining genomic stability, and it also acts as a tumor suppressor. The *BRCA1* gene contains 22 exons spanning about 110 kb of DNA. The encoded protein combines with other tumor suppressors, DNA damage sensors, and signal transducers to form a large multi-subunit protein complex known as the BRCA1-associated genome surveillance complex (BASC). This gene product associates with RNA polymerase II, and through the C-terminal domain, also interacts with histone deacetylase complexes. This protein thus plays a role in transcription, DNA repair of double-stranded breaks and recombination. Mutations in this gene are responsible for approximately 40% of inherited breast cancers and more than 80% of inherited breast and ovarian cancers. Alternative splicing plays a role in modulating the subcellular localization and physiological function of this gene. Many alternatively spliced transcript variants, some of which are disease-associated mutations, have been described for this gene, but the full-length natures of only some of these variants has been described. A related pseudogene, which is also located on chromosome 17, has been identified.

BRCA2

Inherited mutations in *BRCA1* and this gene, *BRCA2*, confer increased lifetime risk of developing breast or ovarian cancer. Both BRCA1 and BRCA2 are involved in maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair. The largest exon in both genes is exon 11, which harbors the most important and frequent mutations in breast cancer patients. The *BRCA2* gene was found on chromosome 13q12.3 in human. The BRCA2 protein contains several copies of a 70 aa motif called the BRC motif, and these motifs mediate binding to the RAD51 recombinase which functions in DNA repair. *BRCA2* is considered a tumor suppressor gene, as tumors with *BRCA2* mutations generally exhibit loss of heterozygosity (LOH) of the wild-type allele.

RECOMMENDATIONS

- We recommend confirming the presence of variants by Sanger Sequencing.
- *BRCA1* and *BRCA2* Multiplex Ligation-dependent Probe Amplification (MLPA) study is recommended to analyze deletion/duplications in the sample.
- The results should be interpreted in the context of the patient's medical evaluation. Correlation of the genetic findings with the clinical condition of the patient is required to arrive at accurate diagnosis, prognosis or for therapeutic decisions.
- The classification of variants of unknown significance (VUS) can change over time. Please contact MolQ laboratory at a later date for any change.
- For questions about this report, or for assistance please contact the Laboratory: contact@molq.in.
- Genetic counselling is recommended to discuss the implications of the test results.

Jatinder Kaur, PhD
Head, Molecular Biology & Genomics

Dr. Gulshan Yadav, MD
Head, Pathology

APPENDIX 1: TEST METHODOLOGY

Method

DNA isolated from Peripheral Blood or Buccal Swab is used for NGS Library preparation. The libraries were sequenced to mean depth: >150x on next generation sequencing platform. The raw read sequences obtained from NGS are processed to remove adapters and filter poor quality reads.
Clinically relevant germline mutations were identified and annotated using published variants in literature and a set of diseases databases. Clinically relevant mutations are annotated using published variants in literatures and a set of diseases databases - ClinVar, OMIM, HGMD. The effect of non-synonymous variant is calculated using multiple prediction algorithms such as PolyPhen, SIFT, Mutation Taster2.

Genetic test results are reported based on the variant classification recommendations of American College of Medical Genetics[8], 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.

DISCLAIMER

- This test is limited to *BRCA1* and *BRCA2* genes analysis only. It should be noted that this test does not sequence all bases in a human genome, not all variants have been identified or interpreted, and this report is limited only to variants with evidence for causing or contributing to disease/clinical details provided MolQ laboratory.
- This assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications.
- 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.
- The reported gene variations have not been confirmed by Sanger sequencing.
- 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

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