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. Vaanishka Kapoor
Sex: Female
Date of Birth/Age: 12 years
Disease: Osteosarcoma

Clinician

Clinician Name: Dr P. K. Julka
Medical Facility: Max Institute of Cancer Care
Pathologist: Not Provided

Specimen

Booking ID: 011906230277
Site: NA
Sample Type: Blood
Date of Collection: 23-06-2019
Date of Booking: 23-06-2019

CLINICAL SYNOPSIS

Vaanishka Kapoor, is a case of metastatic Osteosarcoma. She has a family history of cancer, paternal aunt was diagnosed with carcinoma Breast and a known carrier of BRCA1 mutation.

She has been evaluated for pathogenic variations in the *BRCA1* and *BRCA2* genes.

RESULTS

Likely Pathogenic variant causative of the reported phenotype is detected.

Gene (Transcript) #	Location	Variant	Zygosity/ Disease	Inheritance	Classification
BRCA1 (-) (ENST00000471181.2)	Exon 2	Chr17:41276034-?_41276113+?del c.(?_-119)_(80+1_81-1)del (exon 2 deletion)	Heterozygous/ Breast-ovarian cancer, familial, 1	Autosomal dominant	Likely 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 c.(?_-119)_(80+1_81-1)del (exon 2 deletion)

Variant description: The identified heterozygous variant causes deletion of exon 2 in the *BRCA1* gene. This deletion was identified by copy number variation (CNV) analysis of the NGS data, which detects large deletion/duplication in the tested genes. When the CNV analysis of all amplicons from the 3 tested genes in the specimen DNA was performed and compared with other DNA specimens, we detected a heterozygous deletion of exon 2 in the *BRCA1* gene in the specimen DNA. In the

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BRCA1 gene, exon 2 harbors the translation initiation site. Thus, in the resulting transcript (if any) due to the identified deletion, the translation initiation site will be lacking, thus will likely result in loss-of-function.
Large genomic deletions spanning exon 1 and 2 of the *BRCA1* gene have been reported several times across various ethnic groups with respect to breast and/or ovarian cancer [1], [3], [4].
In a study, deletion of exon 2 in the *BRCA1* gene (represented as g.3792_6326del, in the article) was detected in a patient of British origin affected with ovarian cancer and with family history of breast and ovarian cancer [5]. In another study on breast and ovarian cancer patients, *BRCA1* (exons 1–2) deletion co-segregated with disease in the family and it was suggested to have a pathogenic role [6]. The identified heterozygous deletion is predicted to result in loss-of-function. In addition, heterozygous deletions spanning exon 2 have been previously reported in patients affected with breast cancer/ovarian cancer. Thus, this variant has been labelled as 'likely pathogenic (likely disease-causing)'.

REFERENCES

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3. van den Ouweland AM, Dinjens WN, Dorssers LC, van Veghel-Plandsoen MM,Brüggenwirth HT, Withagen-Hermans CJ, Collée JM, Joosse SA, Terlouw-KromosoetoJN, Nederlof PM. 2009. Deletion of exons 1a-2 of BRCA1: a rather frequent pathogenicabnormality. Genet Test Mol Biomarkers :13(3):399-406. [PMID: 19405878].

4. Mazoyer S. 2005. Genomic rearrangements in the BRCA1 and BRCA2 genes. Hum Mutat.: 25(5):415-22. [PMID: 15832305].

5. Ramus SJ, Harrington PA, Pye C, DiCioccio RA, Cox MJ, Garlinghouse-Jones K, Oakley-Girvan I, Jacobs IJ, Hardy RM, Whittemore AS, Ponder BA, Piver MS, PharoahPD, Gayther SA.2007. Contribution of BRCA1 and BRCA2 mutations to inherited ovarian cancer. Hum Mutat.: 28(12):1207-15. [PMID: 17688236].

6. Veschi S1, Aceto G, Scioletti AP, Gatta V, Palka G, Cama A, Mariani-Costantini R, Battista P, Calò V, Barbera F, Bazan V, Russo A, Stuppia L. 2007. High prevalence of BRCA1 deletions in BRCAPRO-positive patients with high carrier probability. Ann Oncol.: 18(6), 86-92.

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APPENDIX 1: TEST METHODOLOGY

Method

Sample preparation: Genomic DNA isolated from saliva, blood or any other standard tissue source is used for preparation of the 'DNA sequencing-ready' library. The DNA is quantified using Qubit Fluorometer and 50 ng is taken for library preparation. "Nextera" library preparation uses a transposon-based shearing of the genomic DNA. The Nextera protocol allows the DNA to be "tagmented" (fragmented and tagged simultaneously in the same tube). Limited cycle PCR step allows the incorporation of adaptors, platform-specific tags and barcodes to prepare the DNA sequencing libraries.
Target Enrichment: The tagged and amplified sample libraries are checked for quality and quantified. Approximately 500 ng of each library is used in this step and any deviation from the recommended amount results in over or under representation of the sample and greater or less mean coverage. For this panel, up to 12 libraries can be combined into a single tube and set up for enrichment, to generate adequate coverage total sequencing for each sample on a MiSeq sequencer. Two simultaneous enrichment steps are performed to optimize the pull down of the regions of interest using target specific probes. Target libraries are amplified using limited PCR steps and 6-10 pM are loaded for sequencing.
Sequencing Details: Sequencing is performed using a standard v2 kit on Illumina MiSeq with the expected data output of 4-5 GB. For this panel, the output size is 0.253 MB, optimum cluster density to be achieved during sequencing is 750-1000 clusters/sqmm.
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 (test outsourced to reference laboratory).

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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.