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. Geetika Mohan
Sex: Female
Date of Birth/Age: 34 years
Disease: Asymptomatic

Clinician

Clinician Name: Dr Amit Verma
Medical Facility: Dr AV Institute of Personalized Cancer Therapy and Research
Pathologist: Not Provided

Specimen

Booking ID: 012208280048
Site: NA
Sample Type: Blood
Date of Collection: 28-08-2022
Date of Booking: 28-08-2022

CLINICAL SYNOPSIS

The index patient, Dr. Aditi Srivastava (Sample ID: 7614893), is an operated case of grade III, ER/Her2 Neu negative, PR positive, metastatic invasive ductal carcinoma left breast, diagnosed in September 2021. Sha has previously been operated for stage IIIc high grade serous carcinoma bilateral ovaries in 2017. She has a family history of breast cancer with her maternal uncle, maternal aunt, maternal cousin and younger sister affected. Dr. Aditi Srivastava was found to harbour a heterozygous variant, c.2806_2809del in the *BRCA2* gene. Daughter of index patient is being evaluated for the same variant.

RESULTS

Variant is confirmed to be present by Sanger sequencing.

Gene (Transcript) #	Location	Variant	Relationship to Index Patient	Clinical condition of family member	Variation reported in family member*
BRCA2 (ENST00000380152.8)[1]	Exon 11	chr13:g.32337161_32337164del (HET); c.2806_2809del; (p.Ala938ProfsTer21)	Daughter	Asymptomatic	Present (Heterozygous)

*The exon number and nucleotide numbers will differ based on the reference file chosen and the database used.

CLINICAL CORRELATION AND VARIANT INTERPRETATION

Variant description: A heterozygous 4 base pair deletion in exon 11 of the *BRCA2* gene (**chr13:g.32337161_32337164del; c.2806_2809del**) that results in a frameshift and premature truncation of the protein 21 amino acids downstream to codon 938 (**p.Ala938ProfsTer21**) was detected in the index patient (Sample ID: 7614893; Report Dated: 14th July 2022) by NGS and was further validated by Sanger sequencing (Figure 1A).

The same pathogenic variant is detected in heterozygous condition in the asymptomatic daughter of the index patient, Ms Geetika Mohan (Figure 1B). Reduced penetrance and variable age of onset have been reported in *BRCA2* gene variants[2].

The variant detected in the test and its significance needs to be carefully correlated with the clinical indications of the index patient.

RECOMMENDATION

Genetic counselling is recommended to interpret the significance of the results.

REFERENCES

1. ENSEMBL: http://www.ensembl.org.
2. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2022 May 26]. In: Adam MP,

Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.

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APPENDIX 1: TEST METHODOLOGY

Method

Targeted gene Sanger sequencing: Exon 11 of the *BRCA2* gene was PCR-amplified, and the product was sequenced using Sanger sequencing. In case of mosaicism in leucocytes, the detection limits of Sanger sequencing for presence of variant are ~20%. The sequence was aligned to available reference sequence ENST00000380152.8[1] to detect variant using variant analysis software programs. Variant classification follows the tenets of American College of Medical Genetics (ACMG) guidelines[2].

DISCLAIMER

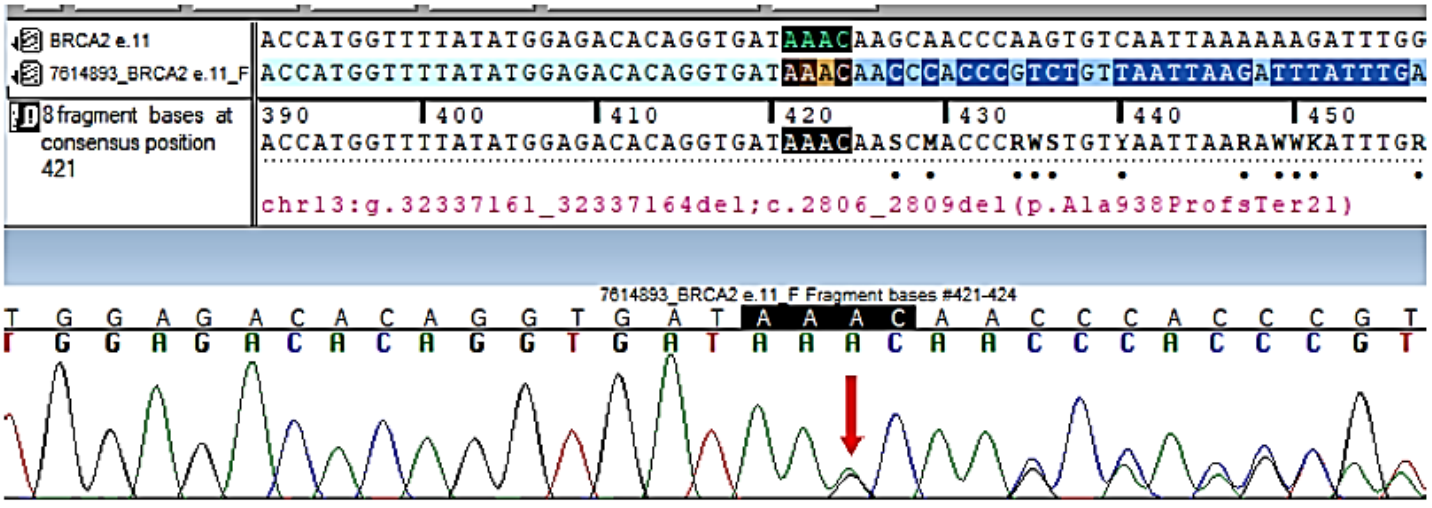
About 0.44% of total cases are susceptible to allele dropout/dropin phenomenon, which can lead to misdiagnosis[3].

REFERENCES

3. ENSEMBL: http://www.ensembl.org.
4. 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. Genet Med. 2013 Jul;15(7):565-74
5. Blais, Jonatan et al. Risk of Misdiagnosis Due to Allele Dropout and False-Positive PCR Artifacts in Molecular Diagnostics. The Journal of Molecular Diagnostics, Volume 17, Issue 5, 505 – 514.

Figure 1: Sequence chromatogram and alignment to the reference sequence showing the variant in exon 11 of the *BRCA2* gene (chr13:g.32337161_32337164del; c.2806_2809del; p.Ala938ProfsTer21) detected in heterozygous condition in the index patient, Dr. Aditi Srivastava (A) and detected in heterozygous condition in Ms. Geetika Mohan (B).

A. 7614893: The index patient (Dr. Aditi Srivastava)



B. 7681442: Daughter of the index patient (Ms. Geetika Mohan)