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Booked on	06/08/2016	**Patient Id**	011608060042	**Printed on**	02/09/2016
Name	Mrs. Sudha Chugh	**Age**	52 Years	**Sex**	F
Ordering Physician	Dr Amit Verma Max Hospital				

BRCA1 and *BRCA2* Gene Analysis

Sample Information

Sample Type: Whole Blood, EDTA

Clinical Indications

Triple negative breast cancer

Results

BRCA1 (NM_007294.3, sequencing)	**heterozygous pathogenic variant c.3607C>T (p.Arg1203*)**
BRCA2 (sequencing)	**no pathogenic variant**

A diagnosis of familial breast and ovarian cancer syndrome based on the *BRCA1* variant is confirmed.

Interpretation

We detected a heterozygous variant in the *BRCA1* gene, c.3607C>T (p.Arg1203*). This variant has previously been described as disease-causing for breast-ovarian cancer by Friedman *et al.*, 1994 and later confirmed by Juwle *et al.*, 2012 and Amendola *et al.*, 2015 (HGMD Professional 2016.2 - PMIDs: 7894493, 22752604, and 25637381). It is listed in the ClinVar database several times as pathogenic in independent clinical entries (variation ID: 17671). The Exome Sequencing Project describes it with a frequency of 0.0002 in the African American population whereas it is absent European American population (ESP – Alamut v.2.7.1). To date, this variant is not described in the Exome Aggregation Consortium or the 1000 Genomes Browser. It is classified as pathogenic (class 1) according to the recommendations of ACMG (please, see additional information below).

Pathogenic germline variants in *BRCA1* cause familial/hereditary breast and ovarian cancer syndrome (HBOC). HBOC is characterized by an increased life time risk for breast cancer (87%), ovarian cancer (44%), prostate cancer (16%), and pancreatic cancer (van Asperen et al. 2005 PMID: 16141007, Tai YC, et al. 2007 PMID: 18042939, Ford et al. 1998 PMID: 9497246, Verhoog et al. 1999 PMID: 10550133.). Management and prevention of primary manifestations should be discussed individually with the treating physicians. Germline pathogenic variants in *BRCA1* are inherited in an autosomal dominant manner.

A diagnosis of familial breast and ovarian cancer syndrome based on the *BRCA1* variant is confirmed. Predictive analysis is now available. Genetic counselling of the patient and further family members is recommended.

Report Released by:

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Supplement Information Sheet

Comment

The classification of variants of uncertain clinical significance can change over time. Please feel free to contact MolQ Laboratory (contact@molq.in) in the future to determine if there have been any changes in classification of these variants. If you would like to enquire about any additional analyses, please do not hesitate to contact us (contact@molq.in).

Classification of the variants (based on ACMG recommendations):
Class 1 – Pathogenic
Class 2 – Likely pathogenic
Class 3 – Variant of uncertain clinical significance (VUS)
Class 4 – Likely benign
Class 5 – Benign
Class 6 – Disease-associated variant

Methodology

- The ***BRCA1, BRCA2*** genes were analyzed by PCR and sequencing of both DNA strands of the entire coding region and the highly conserved exon-intron splice junctions. The reference sequences of the ***BRCA2*** gene is: **NM_000059.3**
- There may be limited portions of either *BRAC1* or *BRACA*2 for which sequence determination can be performed only in the forward or reverse direction. Unequal allele amplification may result from rare polymorphisms under primer sites.

Analytical Sensitivity

The analytical sensitivity of DNA sequencing performed in both directions is estimated to be >99.98%. Failure to detect a genetic variant or mutation in the analyzed DNA regions may result from errors in specimen handling and tracking, amplification and sequencing reactions or computer-assisted analysis and data review. The rate of such errors is estimated from validation studies to be less than one Percent (<1%)

Overall Test Accuracy

For a patient with at least a 10 % probability of a positive test based on a personnel or family history of cancer, the chance of an incorrect test result is less than 1%.

Description of Nomenclature

All mutations and genetic variants are named according to the convention of Beaudet and Tsui. (Beaudet AL, Tsui LC. A suggested nomenclature for designating mutations. Hum Mut 1993: 2:245- 248). Nucleotide numbering starts at the first transcribed base of *BRCA1* and *BRCA2* based on Gen Bank entries U14680 and U43746, respectively.

Interpretive Criteria

The classification and interpretation of all variants identified in the assay reflects the current state of scientific understanding at the time the report is issued. In some instances, the classification and interpretation of variants may change as scientific information becomes available.

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Positive for a deleterious mutation
Includes clinically significant nonsense and frame shift mutations that prematurely truncate the protein. In addition, specific missense mutations and non- coding intervening sequence (IVS) mutations are recognized as deleterious on the basis of data derived from linkage analysis of high Risk families, functional assays, statistical analysis, biochemical evidence and / or demonstration of abnormal mRNA transcript processing.
Genetic variant, suspected deleterious
Includes genetic variants for which the available evidence indicates a likelihood, but not proof , that the mutation is deleterious . The specific evidence supporting such an interpretation will be summarized for individual variants on each such report.
Genetic variant favor polymorphism
Includes genetic variants for which available indicates that the variant is highly unlikely to contribute substantially to cancer. The specific evidence supporting such as interpretation will be summarized for individual variants on each such report.
Genetic variant of uncertain significance
Includes missense mutations and mutations that occur in analyzed intronic regions whose clinical significance has not yet been documented (Mazoyer S et al., Nature Genetics 1996: 14:253-254).
No deleterious mutation detected
Includes genetic variants for which published data demonstrate absence of substantial clinical significance. Includes truncating mutations in *BRCA* that occur at and distal to amino acid 3326 (Mazoyer S et al. Nature Genetics 1996: 14:253-254). Also includes mutations in the protein-coding region that neither alter the amino acid sequence nor are predicated to significantly affect exon splicing, and base pair alternations in non – coding portions of the gene that have been demonstrated to have no deleterious effect on the length or stability of the mRNA transcript.
Specific variant / mutation not identified
Indicates that specific and designed mutations or variants are not present in the individual being tested.