Booked on	15/04/2015	**Patient Id**	01150065	**Printed on**	11/05/2015
Name	Mrs. Bimla Devi	**Age**	54 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, Bilateral Breast Cancer

Results

BRCA1 - **No Pathogenic Mutation Detected**
BRCA2 - **No Pathogenic Mutation Detected**

A diagnosis of familial breast and ovarian cancer based on BRCA1/2 mutation cannot be genetically confirmed.

Recommendations

We recommend post-test genetic counselling.

Interpretation:

No pathogenic mutations are detected in the *BRCA1* or *BRCA2* genes by sequencing.

Germline mutations in *BRCA1* and *BRCA2* lead to familial/hereditary breast and ovarian cancer (HBOC) that is characterized by an increased life time risk for breast cancer (40 – 80%), ovarian cancer (11-40%), prostate cancer (1-10%), and pancreatic cancer (17%), and possibly also melanoma. An increased likelihood of a *BRCA1* or *BRCA2* mutation is suspected on the basis of personal and family history characteristics, but the diagnosis of HBOC is made based on molecular genetic testing. No currently available technique can guarantee the identification of all cancer-predisposing mutations in *BRCA1* or *BRCA2*. Furthermore, mutations of uncertain clinical significance may be identified. Management and prevention of primary manifestations should be discussed individually with the treating physicians. Germline mutations in *BRCA1* and *BRCA2* are inherited in an autosomal dominant manner. The vast majority of individuals with a *BRCA1* or *BRCA2* mutation have inherited it from a parent. However, because of incomplete penetrance, variable age of cancer development, cancer risk reduction resulting from prophylactic surgery, or early death, not all individuals with a *BRCA1* or *BRCA2* mutation have a parent affected with cancer. If HBOC is suspected, genetic counselling is recommended.

In cases of not identifying a mutation or identifying a variant of an unclear significance (VUS), other differential diagnosis may be considered. This includes mutations that lead to an elevated breast cancer risk (Li Fraumeni syndrome because of mutations in *TP53*, PTHS because of mutations in *PTEN*, Peutz-Jeghers syndrome because of mutations in *STK11*, *HDGC* because of mutations in *CDH1*, as well as mutations in other genes), or that lead to an elevated ovary cancer risk (mutations in *TP53*, Lynch syndrome because of mutations in *MSH2*, *MSH6*, *MLH1*, *PMS2*, and others).

Report Released by:

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Supplement Information Sheet

Comment

This result does not eliminate the possibility of hereditary cancer susceptibility. Further, genetic susceptibility to breast/ovarian cancer has also been suggested to be associated with mutations in genes other than *BRCA1* and *BRCA2* (at least 22 other genes, including *RAD51C (BROVCA3)* and *RAD51D (BROVCA4)*, and other susceptibility loci).

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 – Previously reported as disease-causing
Class 2 – Previously unreported, but of the type which can cause the disorder
Class 3 – Previously unreported, may or may not be the cause of the disorder (Variant of uncertain clinical significance)
Class 4 – Previously unreported and is likely neutral
Class 5 – Previously reported as neutral
Class 6 – Disease-associated SNPs

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 ***BRCA1, BRCA2*** genes are: **NM_007294.3, NM_007300.3, 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.