Booked on	07/01/2017	**Patient ID**	011811150271	**Printed on**	15/11/2018
Name	Shilpam Rastogi	**Age**	34 Years	**Sex**	F
Ordering Physician					

Clinical Exome Analysis

Sample Information

Sample Type: Whole Blood

Clinical Information*

The patient with unilateral breast carcinoma diagnosed at the age of 34 years (invasive ductal carcinoma, ductal carcinoma in situ), neoplasm of the breast, fibroadenoma of the breast, lymphatic vessel neoplasm, pain, and jaundice. Family history includes paternal grandfather with pancreatic cancer diagnosed at the age of 70 years, and paternal aunt with breast cancer diagnosed at the of 60.

*: Clinical information indicated above follows HPO nomenclature

Results

Gene	Variant	Zygosity	Classification
XRCC3	Chr14(GRCh37):g.104173393A>G NM_001100118.1:c.353T>C **p.(Leu118Pro) Exon 5**	Heterozygous	Missense Uncertain significance

VARIANT OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED.

A heterozygous variant of uncertain significance was identified in the *XRCC3* gene. **The increased genetic susceptibility to autosomal dominant XRCC3-related breast cancer is possible.**

The clinical exome dataset was evaluated for variants clinically relevant to the described phenotype. We did not detect any further variant which could be indicative of the genetic diagnosis of your patient. In addition, no pathogenic or likely pathogenic variants that would be insufficient for a genetic diagnosis (e.g. heterozygous variants in genes related to autosomal recessive disorders), but would have led us to recommend further testing (e.g. deletion/duplication analysis) were detected. Furthermore, genes related to diseases having substantial overlap with the phenotype of the patient were re-evaluated. Again, no other clinically relevant variants were identified. Please be advised that clinical exome sequencing for diagnostic purposes cannot provide full coverage for all genes and cannot detect large deletions/duplications.

Interpretation

XRCC3, c.353T>C p.(Leu118Pro)

The *XRCC3* variant c.353T>C p.(Leu118Pro) causes an amino acid change from Leu to Pro at position 118. It is classified as variant of uncertain significance (class 3) according to the recommendations of ACMG.

Heterozygous germline pathogenic variants in the *XRCC3* gene have been associated with susceptibility to breast cancer, pancreatic cancer and further malignancies (OMIM®: 600675).

Incidental Findings

Incidental findings which we list according to the ACMG guidelines are not provided here due to the lack of consent.

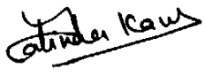
ANALYSIS STATISTICS FOR THE OFFERED GENES

Average Coverage (X)	% Target BP Covered					
	0X	≥ 1X	≥ 5X	≥ 10X	≥ 20X	≥ 50X
156.09	0.33	99.67	99.36	99.13	98.29	90.83

Recommendations

- Carrier testing in the other affected family members, if applicable, is recommended to further establish the causality of the detected variant.
- As large deletions and duplications are not detectable by sequencing, we recommend deletion/duplication analysis of the relevant genes, specially the *BRCA1* and *BRCA2* genes.
- Genetic counselling is recommended

Report Released by:



Dr. Jatinder Kaur, PhD
Head, Molecular Biology & Genomics

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Consultant, Pathology

Supplement Information Sheet

Comment

***Genetic test results are reported based on the recommendations of American College of Medical Genetics [1], as described 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 patients' 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.
Benign	A variant which is known not to be responsible for disease has been detected. Generally no further action is warranted on such variants when detected.
Likely Benign	A variant is not expected to have a major effect on disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion.
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.

Methodology

Genomic DNA is enzymatically fragmented and regions of interest are selectively enriched using capture probes targeted against coding regions of ~6700 genes with known clinical significance. Libraries are generated with Illumina compatible adaptors and sequenced on an Illumina platform.

Evaluation is focused on coding exons along with flanking +/-10 intronic bases within the captured region. Due to limitations of the method, the target region is not covered 100%. Raw sequence data analysis, including base calling, demultiplexing, alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37) and variant calling is performed using validated in-house software. Relevant variants reported in HGMD®, in ClinVar as well as all variants with minor allele frequency (MAF) of less than 1% in gnomAD database are considered. All pertinent inheritance patterns are considered. In addition, provided family history and clinical information are used to evaluate eventually identified variants. Laboratory has established stringent quality criteria and validation processes for variants detected by NGS. Lower quality single nucleotide or deletion insertion variants are thus being confirmed by Sanger. As a result of this specificity of >99.9% is warranted for all reported variants.

LIMITATIONS

Test results are interpreted in the context of clinical findings, family history and other laboratory data. Only variations in genes potentially related to the proband's medical condition are reported. Rare polymorphisms may lead to false negative or positive results. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. If results obtained do not match the clinical findings, additional testing should be considered.

Specific genetic events like copy number variants, translocations and repeat expansions may not be reliably detected with targeted Clinical Exome Sequencing. In addition, due to limitations in technology, certain regions may either not be covered or may be poorly covered, where variants cannot be confidently detected.

ADDITIONAL INFORMATION

This test was developed and its performance validated by the reference laboratory. The US Food and Drug Administration (FDA) has determined that clearance or approval of this method is not necessary and thus neither have been obtained. This test has been developed for clinical purposes. All test results are reviewed, interpreted and reported by their scientific and medical experts.

In line with ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (Genetics in Medicine, 2016), we report incidental findings, i.e. pathogenic variants and likely pathogenic variants only in the recommended genes for the recommended phenotypes.

To also exclude mistaken identity in your clinic, several guidelines recommend testing a second sample that is independently obtained from the proband. Please note that any further analysis will result in additional costs.

The classification of variants can change over the time. Please feel free to contact MolQ (contact@molq.in) in the future to

determine if there have been any changes in classification of any reported variants.

Disclaimer

- Any preparation and processing of a sample from patient material provided to laboratory by a physician, clinical institute or a laboratory (by a "Partner") and the requested genetic and/or biochemical testing itself is based on the highest and most current scientific and analytical standards. However, in very few cases genetic or biochemical tests may not show the correct result, e.g. because of the quality of the material provided by a Partner to laboratory or in cases where any test provided by laboratory fails for unforeseeable or unknow n reasons that cannot be influenced by laboratory in advance. In such cases, MolQ laboratory shall not be responsible and/or liable for the incomplete, potentially misleading or even wrong result of any testing if such issue could not be recognized by us in advance.
- The classification of variants of unknown significance can change over time and MolQ cannot be held responsible for this. Please contact MolQ at a later date to inquire about any changes.
- Intronic variants are not assessed using this method.
- Large deletions of more than 10 bp or copy number variations /chromosomal rearrangements cannot be assessed using this method.
- Certain genes may not be covered completely and few mutations could be missed.
- The mutations have not been validated by Sanger sequencing.