Booked on	01/12/2018	Patient ID	011812010010	Printed on	14/01/2019
Name	Smita Jain	Age	40 Years	Sex	F
Ordering Physician					

Clinical Exome Analysis

Sample Information

Sample Type: Whole Blood

Clinical Information

The patient presents with invasive ductal carcinoma (ER-PR positive). Age of manifestation: 40 years. Positive family history of mother affected with invasive ductal carcinoma at the age of 60 years.

Results

Gene	Variant	Zygosity	*In Silico* Parameters*	Allele Frequency	Classification**
RAD54L	Chr1(GRCh37):g.46733135_46733138dup NM_001142548.1:c.896_899dup p.(Leu301Glnfs*6) Exon 10	Heterozygous	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A	gnomAD: 0.0000040 ESP: - 1000 G: -	Frameshift Likely Pathogenic

Variant description based on Alamut Batch (latest database available). * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function, splice prediction tools: SSF, MaxEnt, HSF. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). *** based on ACMG recommendations.

> **LIKELY PATHOGENIC VARIANT IDENTIFIED.**

A heterozygous likely pathogenic variant was identified in the *RAD54L* gene. **The obtained result is compatible with the genetic diagnosis of invasive ductal breast cancer, with an autosomal dominant inheritance**.

Interpretation

RAD54L, c.896_899dup p.(Leu301Glnfs*6)

The *RAD54L* variant c.896_899dup p.(Leu301Glnfs*6) creates a shift in the reading frame starting at codon 301. The new reading frame ends in a stop codon 5 positions downstream. This variant has been confirmed by Sanger sequencing. It is classified as likely pathogenic according to the recommendations of ACMG (please, see additional information below).

Pathogenic variants in many genes are associated with high risk of developing familial breast cancer. An example is the *RAD54L* are associated with invasive ductal breast cancer (OMIM®: 603615). Breast cancer (referring to mammary carcinoma, not mammary sarcoma) is histopathologically and almost certainly etiologically and genetically heterogeneous. Important genetic factors have been indicated by familial occurrence and bilateral involvement (OMIM®: 114480).

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
132.86	0.39	99.61	99.35	99.02	97.68	87.81

Recommendations

- We recommend carrier testing for all informative/at risk family members to establish whether the detected variant is associated with the disorder or not. Basic clinical information and relationship for each analyzed family member is needed for a comprehensive evaluation of the data.
- Genetic and oncologic counselling is also recommended.

Report Released by:

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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.