Dr. Amit Verma
Molecular Quest Healthcare
Laboratory
Gurugram
India

Order no.: 62596160
Order received: 31 May 2019
Sample type: blood, filter card
Sample collection date: 24 May 2019
Report date: 24 Jun. 2019
Report type: Final Report

Patient no.: **1400658**, First Name: **Manjula**, Last Name: **Tiwari**
DOB: **15 Sept. 1950**, Sex: **female**, Your ref.: **-**

Additional report recipient(s): Dr. Sunil K. Tadepalli, Centogene India PVT. LTD., Management, 107, Wegmans Business Park, Knowledge Park - III, 201308 Surajpar-Kasna Road, Greater Noida, India

Test(s) requested: Whole Exome Sequencing (CentoXome GOLD®)

CLINICAL INFORMATION

Myelodysplasia, Ovarian carcinoma
*: Clinical information indicated above follows HPO nomenclature.

Age of manifestation: 63 years.

⊕ POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

A heterozygous pathogenic variant was identified in the RAD50 gene. **This result is consistent with the genetic diagnosis of autosomal dominant RAD50-related susceptibility for cancer.**

RECOMMENDATIONS

- Parental carrier testing is requested (if possible) to establish whether the detected variant is inherited or *de novo*.

- Genetic counselling is also recommended.

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RESULT SUMMARY

GENE	VARIANT COORDINATES	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
RAD50	Chr5(GRCh37):g.131923329C>T NM_005732.3:c.832C>T **p.(Arg278*)** **Exon 6**	Het	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation: nt weak	gnomAD: 0.000044 ESP: - 1000 G: - CentoMD: -	stop gain Pathogenic (class 1)

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

VARIANT INTERPRETATION

RAD50, c.832C>T p.(Arg278*)

The RAD50 variant c.832C>T p.(Arg278*) creates a premature stop codon. According to HGMD Professional 2018.4, this variant has previously been described as disease causing for Breast cancer by Couch et al., 2015 (PMID: 25452441), Lowery et al., 2018 (PMID: 29506128). ClinVar lists this variant as Pathogenic (clinical testing, Variation ID: 408402). It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

RAD50 is a cycle cell control gene. Couch et al., 2015 (PMID: 25452441) detected deleterious variant in the RAD50 gene in one patient with Triple-Negative Breast Cancer. Lowery et al., 2018 (PMID: 29506128) identified variant in the RAD50 gene in patient with exocrine pancreatic neoplasms.

INCIDENTAL FINDINGS

We did not detect any class 1 or 2 variants in the genes for which incidental findings are reported based on the ACMG guidelines.

ANALYSIS STATISTICS WES

% TARGET NUCLEOTIDES COVERED			
0X	**≥ 10X**	**≥ 20X**	**≥ 50X**
0.20	99.67	99.45	95.64

CENTOGENE VARIANT CLASSIFICATION (BASED ON ACMG RECOMMENDATIONS)

Class 1 – Pathogenic

Class 2 – Likely pathogenic

Class 3 – Variant of uncertain significance (VUS)

Class 4 – Likely benign

Class 5 – Benign

Additionally, other types of clinical relevant variants can be identified (e.g. risk factors, modifiers).

METHODS

Double stranded DNA capture baits against approximately 36.5 Mb of the human coding exome (targeting >98% of the coding RefSeq and Gencode v28 regions, which was obtained from the human genome build GRCh37/hg19 on May 2018) were used to enrich target regions from fragmented genomic DNA with the Twist Human Core Exome Plus kit . The generated library is sequenced on an Illumina platform to obtain at

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least 20x coverage depth for >98% of the targeted bases. An in-house bioinformatics pipeline, including read alignment to GRCh37/hg19 genome assembly, variant calling and annotation, and comprehensive variant filtering is applied. All disease-causing variants reported in HGMD®, in ClinVar and in CentoMD® as well as all variants with minor allele frequency (MAF) below 1% in gnomAD database are considered. The investigation for relevant variants is focused on coding exons and flanking +/-20 intronic bases. All potential modes of inheritance patterns are considered. In addition, provided family history and clinical information are used to evaluate identified variants with respect to their pathogenicity and causality, and are categorized into classes 1 - 5 (see above). All variants related to the phenotype of the patient, except benign or likely benign variants, are reported.

Centogene has established stringent quality criteria and validation processes for variants detected by NGS. Low quality single nucleotide variants and all relevant deletion/insertion variants are confirmed by Sanger sequencing. Consequently, we warrant a specificity of >99.9% for all reported variants.

LIMITATIONS

The genetic results are interpreted in the context of the provided clinical findings, family history, and other laboratory data. Only variants in genes potentially related to the proband's medical condition are reported. Misinterpretation of results may occur if the provided information is inaccurate and/or incomplete. If the obtained genetic results do not concur with the clinical findings, additional testing should be considered.

Complex genetic events such as copy number variants, inversions, translocations and repeat expansions, may not be reliably detected with Exome Sequencing. In addition, due to technology limitations, certain regions may be either not or poorly covered. In these regions variants cannot be confidently detected. Extremely low coverage calls (homo/hemizygous or heterozygous calls with less than three or four reads, respectively) are expected to be artifacts based on our extensive validations and consequently are not considered during the analysis.

ADDITIONAL INFORMATION

This test was developed and its performance validated by CENTOGENE AG. 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 our scientific and medical experts.

In line with ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (Genetics in Medicine, 2017; PMID: 27854360), we report incidental findings, i.e. pathogenic variants (class 1) and likely pathogenic variants (class 2) only in the recommended genes for the recommended phenotypes. For children (<15 years old), pathogenic and likely pathogenic variants in BRCA1/2, MLH1, MSH2, MSH6, PMS2 and MUTYH genes related to adult onset phenotypes are not reported.

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 CENTOGENE (customer.support@centogene.com) 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 CENTOGENE 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 CENTOGENE or in cases where any test provided by CENTOGENE fails for unforeseeable or unknown reasons that cannot be influenced by CENTOGENE in advance. In such cases, CENTOGENE 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 CENTOGENE in advance.

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