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Order no.: 62497221  
Order received: 06 Aug. 2018  
Sample type: blood, EDTA  
Sample collection date: 02 Aug. 2018  
Report date: 15 Aug. 2018  
Report type: Final Report



Patient no.: **1311191**, First Name: **Uma**, Last Name: **Sharma**  
DOB: **07 Jun. 1960**, 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: BRCA1, BRCA2 panel (sequencing)**

#### CLINICAL INFORMATION

**no clinical information has been provided.**

Please note that the quality of the interpretation of patient's genetic data can be negatively influenced by missing clinical information.



**UNCLEAR RESULT**  
**Variant of uncertain significance (VUS) identified**

#### INTERPRETATION

A heterozygous variant of uncertain significance was identified in the BRCA2 gene. **A genetic diagnosis of hereditary breast and ovarian cancer syndrome type 2 is possible.**

#### RECOMMENDATIONS

- We recommend carrier testing for all informative 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 counselling is recommended.

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**RESULT SUMMARY**

GENE	VARIANT COORDINATES	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
BRCA2	Chr13(GRCh37):g.32918739A>C NM_000059.3:c.6886A>C  p.(Ile2296Leu) Exon 12	Het	PolyPhen: Benign Align-GVGD: C0  SIFT: Deleterious MutationTaster: Polymorphism  Conservation: nt weak/aa weak	gnomAD: 0.00017  ESP: -  1000 G: 0.00040  CentoMD: 0.000086	Missense  Uncertain significance (class 3)

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**

**BRCA2, c.6886A>C p.(Ile2296Leu)**

The BRCA2 variant c.6886A>C p.(Ile2296Leu) causes an amino acid change from Ile to Leu at position 2296. ClinVar lists this variant as likely benign and uncertain (clinical testing, Variation ID: 142797). It is classified as variant of uncertain significance (class 3) according to the recommendations of Centogene and ACMG (please, see additional information below).

Pathogenic germline variants in the BRCA2 gene are associated with familial breast-ovarian cancer type 2, also known as hereditary breast and ovarian cancer syndrome (HBOC), an autosomal dominant disorder. It is characterized with an increased life time risk for breast cancer (38%-84%), ovarian cancer (16.5%-27%), prostate cancer (15%), and pancreatic cancer (2%-7%), and possibly also melanoma. Breast cancer is one of the most common forms of cancer, accounting for about 25% of all cancers in women. It is 100 times more common in women than in men, although men tend to have poorer outcomes due to delays in diagnosis. About 5 to 10% of all breast cancers are inherited, and most of them are associated with BRCA1 and BRCA2 genes.

**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**

Genomic DNA is enzymatically fragmented and regions of interest are selectively enriched using capture probes targeted against coding regions of panel genes. Libraries are generated with Illumina compatible adaptors and sequenced on an Illumina platform. For the BRCA1, BRCA2 panel, the entire coding region of the BRCA1, BRCA2 genes including 10 bp of flanking intronic sequences are targeted. Our Plus Panel includes analysis of all reported disease causing deep intronic and regulatory mutations described outside the coding +/-10 boundary. Due to limitations of the method, the targeted sequences within the requested panel may not be covered 100%. Missing regions or regions of poor quality are completed with classical Sanger sequencing to achieve 100% coverage of all genes within this panel. 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. All identified variants are evaluated with respect to their pathogenicity and causality, and these 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. Structural changes (i.e. CNVs, inversions, repeat expansions etc.) are not assessed with the NGS data.

**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

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purposes. All test results are reviewed, interpreted and reported by our scientific and medical experts.

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](mailto: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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