CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE AG Am Strande 7 • 18055 Rostock • Germany

XXX

Order no.: xxx
Order received: xxx
Sample type: blood, filter card
Sample collection date: xxx
Report type: Final Report
Report date: xxx

Patient no.: **xxx**, First Name: **xxx**, Last Name: **xxx**
DOB: **xxx**, Sex: **female**, Your ref.: **xxx**

Test(s) requested: BRCA1, BRCA2 panel (sequencing)

CLINICAL INFORMATION

Patient with history of ovarian cancer.

POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

A heterozygous pathogenic variant was identified in the BRCA1 gene. **The genetic diagnosis of autosomal dominant familial breast-ovarian cancer type 1 is confirmed. The proband has increased genetic susceptibility of breast cancer.**
In the BRCA2 gene, we have not detected any clinically relevant variant by sequencing.

RECOMMENDATIONS

- Testing of further relevant family members at risk might be considered.
- Genetic counselling is recommended.

> Contact Details
Tel.: +49 (0)381 80113 416
Fax: +49 (0)381 80113 401
dmqc@centogene.com
www.centogene.com

RESULT SUMMARY

GENE	VARIANT COORDINATES	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
BRCA1	Chr17(GRCh37):g.41245489G>A NM_007300.3:c.2059C>T p.(Gln687*) Exon 10	Het	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation: nt weak	gnomAD: - 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

BRCA1, c.2059C>T p.(Gln687*)

The BRCA1 variant c.2059C>T p.(Gln687*) creates a premature stop codon. According to HGMD Professional 2017.3, this variant has previously been described as disease causing for Breast and/or ovarian cancer by Worsham et al., 1998 (PMID: 9836072), Xiong et al., 2015 (PMID: 25525159). ClinVar lists this variant as pathogenic (clinical testing/research, Variation ID: 54448). It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

Pathogenic germline variants in BRCA1 gene are associated with familial breast-ovarian cancer type 1, 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 (46%-87%), ovarian cancer (39%-63%), prostate cancer (9%), and pancreatic cancer (1%-3%), 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

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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.

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 (dmqc@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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Chief Medical Director

Clinical Scientist