



XXX

Order no.: xxx documented by: xxx

Order received: xxx

Sample type: blood, CentoCard®

Sample collection date: xxx

Report date: xxx

Report type: Final Report

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

Additional report recipient(s): xxx

Test(s) requested: CentoBreast® (sequencing including NGS-based CNV analysis)

CLINICAL INFORMATION

Breast carcinoma; Ductal carcinoma in situ
(Clinical information indicated above follows HPO nomenclature.)

Age of onset: 58 year(s). Diagnosed condition(s): invasive ductal carcinoma. Previous external genetic testing, results negative: immunohistochemistry right breast (PR, HER2). Previous external genetic testing, results positive: immunohistochemistry right breast (ER), immunohistochemistry left breast (ER, PR, HER2).

Family history: Yes.

Father : Brain neoplasm; Maternal aunt 1: Breast carcinoma; Maternal aunt 2: Uterine neoplasm; Maternal male cousin : Neoplasm of the lung; Niece : Breast carcinoma; Paternal aunt : Breast carcinoma; Paternal female cousin 1: Breast carcinoma; Paternal female cousin 2: Breast carcinoma; Paternal female cousin 3: Breast carcinoma; Paternal male cousin : Sudden death; Paternal uncle : Neoplasm of the lung; Sister : Neoplasm
Consanguineous parents: Yes, first cousins.



POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

A heterozygous pathogenic variant was identified in the *BRCA2* gene. **This finding is consistent with the increased genetic risk to autosomal dominant familial breast-ovarian cancer type 2 associated cancers.**

In the remainder of the panel genes (see methods), no other clinically relevant sequence or copy number variant was identified.

RECOMMENDATIONS

- Carrier testing of further at-risk family members is recommended.
- Oncology counseling is recommended to discuss possible therapeutic options.
- Genetic counseling is recommended.

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RESULT SUMMARY

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
BRCA2	NM_000059.3:c.755_758del	p.(Asp252Valfs*24)	N/A	heterozygous	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: N/A Conservation_aa: N/A	gnomAD: 0.000081 ESP: - 1000 G: 0.000022 CentomD: 0.000018	Frameshift Pathogenic (class 1)

Variant annotation based on OTFA (using VEP v93). * AlignGVD: C0: least likely to interfere with function, C65: most likely to interfere with function; splicing predictions: Ada and RF scores. ** Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentomD® (latest database available). *** based on ACMG recommendations.

VARIANT INTERPRETATION

BRCA2, c.755_758del p.(Asp252Valfs*24)

The *BRCA2* variant c.755_758del p.(Asp252Valfs*24) creates a shift in the reading frame starting at codon 252. The new reading frame ends in a stop codon 23 positions downstream. According to HGMD Professional 2019.4, this variant has previously been described as disease causing for Breast cancer by Tavtigian et al., 1996 (PMID: 8589730), Schrader et al., 2016 (PMID: 26556299), Park et al., 2017 (PMID: 28111427). ClinVar lists this variant as pathogenic (clinical testing/research, Variation ID: 38103). It is classified as pathogenic (class 1) 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. *BRCA1/BRCA2* germline mutations might also have implications in cancer therapy which should be discussed with the oncologist/gynecologist (OMIM®:612555).

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 enriched using DNA capture probes. The final indexed libraries are sequenced on an Illumina platform. As the enriched target regions cover all panel genes and usually include more genes due to enlarged wet lab backbones, the downstream bioinformatic analysis and the report may include clinically relevant findings exceeding the selected gene panel.

For the CentoBreast® (sequencing including NGS-based CNV analysis) panel(s), the coding regions of the panel genes, 10 bp of flanking intronic sequences, and known pathogenic/likely pathogenic variants within these genes (coding and non-coding) are targeted for analysis. The panel gene list can be obtained here: www.centogene.com/ngspanels-medical-reporting (please contact CENTOGENE customer support if the gene list has been updated after this report was issued). Data analysis, including alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37), variant calling and annotation is performed using validated in-house software. All identified variants are evaluated with respect to their pathogenicity and causality, and are categorized into five classes (pathogenic; likely pathogenic; VUS; likely benign; benign). All potentially clinically relevant variants are reported. VUSs are not reported in the following cases: the described phenotype(s) is already explained by a detected pathogenic or likely pathogenic variant(s); the detected VUSs are not related to the described phenotype(s); lack of clinical information; for oncogenetic panels. CENTOGENE has established stringent quality criteria and validation processes for variants detected by NGS. Variants with low quality and/or unclear zygosity are confirmed by orthogonal methods. Consequently,

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a specificity of >99.9% for all reported variants is warranted.

The copy number variation (CNV) detection software has a sensitivity of above 80% for all homozygous deletions and heterozygous deletions/duplications spanning at least three consecutive exons.

ANALYSIS STATISTICS

Centobreast® (sequencing including NGS-based CNV analysis)

Targeted nucleotides covered	≥ 20x	99.66%
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LIMITATIONS

The genetic results are interpreted in the context of the provided clinical findings, family history, and other laboratory data. 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.

The used method is not designed to, and therefore cannot, detect complex genetic events such as inversions, translocations and repeat expansions. In addition, due to technology limitations, certain regions may be either not or poorly covered. In these regions and others encompassing repetitive, high homology, and high CG-rich sequences, variants can be missed. 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 are consequently not considered during the analysis.

Potential aberrant splicing is assessed with splice prediction tools. Synonymous variants and intronic variants that are beyond 10 nucleotides from exons-intron boundaries are not considered for aberrant splicing analysis. However, pathogenic splicing variants evidenced by external sources will be reported.

Heterozygous CNVs spanning less than three exons cannot reliably be detected, are therefore excluded from routine analysis, and will only be inspected and reported upon medical or technical indication. The sensitivity is decreased for repetitive and homologous regions, such as pseudogenes.

ADDITIONAL INFORMATION

This test was developed and its performance validated by CENTOGENE GmbH. 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.

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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