CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE AG Am Strande 7 • 18055 Rostock • Germany

XXX

Order no.: xxx
Order received: xxx
Sample type: xxx
Sample collection date: xxx
Report type: Final Report
Report date: xxx

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

Test(s) requested: CentoScreen™ Paired PACK panel

CLINICAL INFORMATION

The proband is unaffected. Family history: consanguinity.

Please also see our concurrent report for the proband's partner (xxx).

NEGATIVE RESULT

INTERPRETATION

Please note that for CentoScreen™ Paired PACK panel we test the second partner only for clinically relevant variants in genes, in which we detected a clinically relevant variant in the first partner.

Therefore, based on the result for the proband's partner, we analysed the GCDH gene:

We did not detect any clinically relevant variant in the GCDH gene by sequencing. For the GCDH gene an overall coverage of 100% was achieved (>20x), with no missing base pairs (coding region including +/- 10bp).

Please note that the GCDH gene is not included in the panel genes that are tested for copy number variation (see limitations).

RECOMMENDATIONS

- We recommend proceeding to deletion/duplication analysis of the GCDH gene to exclude a second possibly pathogenic variant in this family.
- Genetic counselling is recommended.

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

ANALYSIS STATISTICS

An overall coverage of 99.64% was achieved (coding region including +/- 10bp).

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

METHODS

Custom RNA capture baits against 331 panel genes (covering >99% of regions in CCDS and sequence variants including known deep intronic pathogenic variants, splicing, regulatory, any known mutation in CentoMD® 4.0 or HGMD® Professional 2017.3) are used to enrich regions of interest from fragmented genomic DNA. The generated library is sequenced on an Illumina HiSeq 4000 platform. Typically, over 99% of the targeted bases are covered >20x. An end to end in-house bioinformatics pipeline including base calling, alignment of reads to GRCh37/hg19 genome assembly, primary filtering out of low quality reads and probable artefacts, and subsequent annotation of variants, is applied. All disease causing variants reported in HGMD®, in ClinVar or in CentoMD® as well as all variants with minor allele frequency (MAF) of less than 1% in gnomAD database are considered. Evaluation is focused on coding exons along with flanking +/-20 intronic bases and all identified variants are evaluated with respect to their pathogenicity and causality, and these are categorized into classes 1 - 5 (please see https://www.centogene.com/genetic-testing/reporting-at-centogene.html). Only Class 1 and Class 2 variants along with few selected risk factor variants are reported. Variants of relevance identified by NGS are continuously and individually in-house validated for quality aspects; those variants which meet our internal QC criteria (based on extensive validation processes) are not validated by Sanger.

LIMITATIONS

CentoScreen® is a screening test designed to assess the risk for the proband's offspring to be affected with an autosomal recessive or X-linked recessive disorder. It is not intended to establish a genetic diagnosis for the proband – unaffected or affected. However, the test result may include information about a medical condition of the proband that requires medical follow-up. Please note that a negative result for this panel does not rule out the possibility of a genetic condition in the proband, the proband's partner and/or their offspring. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. If results obtained do not match the clinical or family history, additional testing should be considered.
CentoScreen® panel focuses on 331 genes (list available at www.centogene.com) related to frequently occurring disorders within the population. Pathogenic or likely pathogenic variants outside the panel genes will not be detected. Variants of uncertain significance within the targeted region are not reported. Please note that they may become better understood and reclassified over time.
Copy number variations (CNVs) assessment with NGS is limited to 34 genes (ABCC6, ALDH3A2, COL4A5, CTNS, DBT, DMD, EDA, F8, FANCA, FKTN, GAA, GALC, GBE1, GJB6, GLDC, HBA1, HBA2, HBB, HEXB, HPRT1, HPS3, HSD17B4, IDS, MCOLN1, NEB, OTC, PAH, PCCA, PCDH15, PDHA1, RAPSN, SGCB, STS and XPC) within the Panel. Any CNVs lying outside the coding regions of these genes will not be reported.
Specific genetic events like translocations and repeat expansions may not be reliably detected with Next Generation Sequencing. Recombination of GBA with its pseudogene and inversion of Intron 1 and Intron 22 within F8 gene is not directly assessed and hence may be missed. Analysis of variants lying within repetitive regions of NEB and TTN may have limitations when only sequenced with NGS. 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.
Repeat Expansion testing may not be able to detect exact number of repeats beyond 200. Mosaic expansions may be missed.
Deletions other than exon 7 in SMN1 are not covered within the assay.

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.
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

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

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.

COPYRIGHT NOTICE

Chief Medical Director

Clinical Scientist

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