CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE AG Am Strande 7 • 18055 Rostock • Germany

XXX

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

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

Additional report recipient(s): xxx

Test(s) requested: CentoXome®

CLINICAL INFORMATION

Unaffected.
We performed sequencing analysis focusing on the affected child of the proband. **This report reflects exclusively the segregation information for the proband in the context of the family analysis.**
Please see our concurrent familial reports xxx and xxx.

CARRIER STATUS CONFIRMED

Pathogenic variant identified

INTERPRETATION

A familial pathogenic variant was identified in the CPLANE1 gene in a heterozygous state.

This finding and the result for the second parent confirm homozygosity of the variant for the index patient. Each of their progeny has a 25% risk of developing the associated autosomal recessive disorder.

RECOMMENDATIONS

- Genetic counselling is recommended.

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Patient no.: xxx
Order no.: xxxx

RESULT SUMMARY

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
CPLANE1	NM_023073.3:c.7778G>A	p.(Trp2593*)	rs863225159	heterozygous	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: Disease causing Conservation_nt: weak Conservation_aa:	gnomAD: - ESP: - 1000 G: 0.00031 CentoMD: 0.00026	Nonsense Pathogenic (class 1)

Variant description 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

CPLANE1, c.7778G>A p.(Trp2593*)

The CPLANE1 variant c.7778G>A p.(Trp2593*) creates a premature stop codon. According to HGMD Professional 2019.1, this variant has previously been described as disease causing for autosomal recessive Joubert syndrome (OMIM®: *614571) by Bachmann-Gagescu et al., 2015 (PMID: 26092869). ClinVar lists this variant as pathogenic (clinical testing/research, Variation ID: 217574). It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

INCIDENTAL FINDINGS

Incidental findings which we list according to the ACMG guidelines are not provided here due to the lack of consent.

ANALYSIS STATISTICS WES

% TARGET NUCLEOTIDES COVERED			
0X	**≥ 10X**	**≥ 20X**	**≥ 50X**
0.03	99.83	99.50	88.11

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 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.

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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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