CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE • Am Strande 7 • 18055 Rostock • Germany

Order no.:
Order received: DD/MM/YYYY
Sample type / Sample collection date:
CentoCloud / no material / not available
Report date: DD/MM/YYYY
Report type: Final Report

Patient no.: , First Name: , Last Name:
DOB: **DD/MM/YYYY**, Sex: , Your ref.:

Test(s) requested: CentoCloud Exome Trio

CLINICAL INFORMATION

Unaffected
(Clinical information indicated above follows HPO nomenclature.)

Consanguineous parents: unknown.

The proband is the parent of the index patient.

We analyzed whole exome sequencing data for the child of the proband. Please refer to our report [ID Order, Name].
This report reflects exclusively the segregation information for the proband in the context of the family analysis.

CARRIER STATUS CONFIRMED

Likely pathogenic variant identified

INTERPRETATION

A heterozygous likely pathogenic variant was identified in the *POMT2* gene. **The carrier status of the *POMT2* variant is confirmed.**

Considering the result of the partner, with each pregnancy of this couple there is a 25% risk for the offspring of being affected.

RECOMMENDATIONS

- Genetic counselling, including reproductive counselling (discussing prenatal and preimplantation diagnoses, if relevant) is recommended.

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MAIN FINDINGS

SEQUENCE VARIANTS							
GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
POMT2	NM_013382.5:c.1900del	p.(Gln634Argfs*23)	N/A	heterozygous	PolyPhen: - Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: N/A Conservation_aa: N/A	gnomAD: - ESP: - 1000 G: - CentoMD: -	Frameshift Likely Pathogenic (class 2)

Variant annotation based on OTFA (using VEP v94). * 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

POMT2, c.1900del p.(Gln634Argfs*23)

The *POMT2* variant c.1900del p.(Gln634Argfs*23) creates a shift in the reading frame starting at codon 634. The new reading frame ends in a stop codon 22 positions downstream. It is classified as likely pathogenic (class 2) according to the recommendations of CENTOGENE and ACMG (please, see additional information below).

Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies (type A), which includes both the more severe Walker-Warburg syndrome (WWS) and the slightly less severe muscle-eye-brain disease (MEB), is an autosomal recessive disorder with characteristic brain and eye malformations, profound mental retardation, congenital muscular dystrophy, and death usually in the first years of life. It represents the most severe end of a phenotypic spectrum of similar disorders resulting from defective glycosylation of DAG1 (128239), collectively known as 'dystroglycanopathies' (van Reeuwijk et al., 2005; PMID:15894594).
Mode of Inheritance: Autosomal recessive (OMIM®: 613150)

SECONDARY (INCIDENTAL) FINDINGS

If consent is provided, in line with ACMG recommendations for reporting of secondary (incidental) findings in clinical exome and genome sequencing (Genetics in Medicine, 2021; PMID: 34012068), we report secondary (incidental) findings, i.e., pathogenic variants (class 1) and likely pathogenic variants (class 2) in the recommended genes for the indicated phenotypes.

We did not detect any class 1 or 2 variants in the genes, for which secondary (incidental) findings are reported.

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 clinically relevant variants can be identified (e.g. risk factors, modifiers).

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METHODS

An in-house bioinformatics pipeline, including read alignment to GRCh37/hg19 genome assembly, variant calling, annotation, and comprehensive variant filtering is applied. All variants with minor allele frequency (MAF) of less than 1% in gnomAD database, and disease-causing variants reported in HGMD®, in ClinVar or in CentoMD® are evaluated. The investigation for relevant variants is focused on coding exons and flanking +/-10 intronic nucleotides of genes with clear gene-phenotype evidence (based on OMIM® information). All potential patterns for mode of inheritance are considered. In addition, provided family history and clinical information are used to evaluate identified variants with respect to their pathogenicity and disease causality. Variants are categorized into five classes (pathogenic, likely pathogenic, VUS, likely benign, and benign) along ACMG guidelines for classification of variants. All relevant variants related to the phenotype of the patient are reported. CENTOGENE has established stringent quality criteria and validation processes for variants detected by NGS. Variants with low sequencing quality and/or unclear zygosity are confirmed by orthogonal methods only when a DNA sample has been provided. In such cases, a specificity of > 99.9% for all reported variants is warranted.

ANALYSIS STATISTICS

CentoCloud® Exome Trio

Targeted nucleotides covered	≥ 20x	98.25%

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 genetic data or patient information is inaccurate and/or incomplete. If the obtained genetic results are not compatible with the clinical findings, additional testing should be considered.
The genes with mapping issues in GRCh37/hg19 genome assembly, the non-protein-coding disease-associated genes, and genomic regions that are hard to sequence by current technology and are without evidenced relevance for monogenic disorders, are excluded from this analysis. More complex genetic events such as inversions, translocations, and repeat expansions, are not analyzed in this test. In addition, due to technology limitations, certain regions may be poorly covered, or not covered at all. In these regions and others encompassing repetitive, high-homology (such as pseudogene homology), and GC-rich sequences, relevant variants can be missed. Sequence variants with a coverage less than 20 reads are not considered for evaluation. The higher the percentage of the target regions covered less than 20 reads, the higher the likelihood of missing a potentially relevant variant. Potential aberrant splicing is assessed with splice prediction tools. Intronic variants that are beyond 10 nucleotides from exon-intron boundaries are not considered for aberrant splicing analysis, with the exception of known pathogenic splicing variants evidenced by external sources.

ADDITIONAL INFORMATION

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

The CentoCloud® from CENTOGENE provides state-of-the-art bioinformatic services applying a validated diagnostic pipeline to filter variants from the sequencing raw data provided by our customers. Although regularly and extensively tested and monitored, the CentoCloud® system – like any software product including bioinformatic analyses and particularly as third-party software is included - might contain unforeseeable errors which may lead to misalignment, incorrect base calls, and mis-annotation of variants and thus may have an impact on the accuracy of the medical interpretation of results.
Although CENTOGENE monitors and reviews the received sequencing raw data and its quality insofar as technically possible, it is not responsible for any errors resulting from the preparation and sequencing of a sample by its customers (including, but not limited to, sample identification and/or sample swap). Such errors are then already contained within the raw data and will lead to an erroneous result.
CENTOGENE shall only be responsible for providing a fully annotated variant list in the range and format as agreed with its customers. Any filtering criteria may be subject to further modification at the partner's site in accordance with clinical information or family information. The selection of highlighted variants by CENTOGENE does not preclude any other variant within the variant list that should be considered for medical interpretation.

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Any clinical interpretation and conclusion of variants highlighted in this report is the responsibility of the customer. Test results should always be interpreted in the context of clinical findings, family history, and any other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. Please note, rare polymorphisms exist that could lead to false negative or positive results. If results obtained do not match the clinical findings, additional testing of samples through CENTOGENE's laboratory should be considered, this also applies for a confirmative analysis of any positive result.

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Chief Genomic Officer Human Geneticist	Human Geneticist	Clinical Scientist