CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE GmbH • Am Strande 7 • 18055 Rostock • Germany

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**

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

CLINICAL INFORMATION

Congenital onset; Hearing impairment; Small nail
(Clinical information indicated above follows HPO nomenclature.)

Family history: Yes.
Consanguineous parents: Yes.

POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

A heterozygous pathogenic variant was identified in the *ATP6V1B2* gene. **The genetic diagnosis of autosomal dominant congenital deafness with onychodystrophy is confirmed.**

In the remainder of the panel genes, no clinically relevant variant, including copy number variations, were identified.

RECOMMENDATIONS

- Genetic counselling is recommended.
- Parental carrier testing is recommended to determine if the variant is inherited or de novo.

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

RESULT SUMMARY

SEQUENCE VARIANTS							
GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
ATP6V1B2	NM_001693.3:c.1516C>T	p.(Arg506*)	rs794729667	heterozygous	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: weak Conservation_aa: N/A	gnomAD: - ESP: - 1000 G: - CentoMD: -	Nonsense Pathogenic (class 1)

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

ATP6V1B2, c.1516C>T p.(Arg506*)

The *ATP6V1B2* variant c.1516C>T p.(Arg506*) creates a premature stop codon. According to HGMD Professional 2020.3, this variant has previously been described as disease causing for Dominant deafness-onychodystrophy syndrome by Yuan et al., 2014 (PMID: 24913193), Menendez et al., 2017 (PMID: 28396750). It is classified as pathogenic (class 1) according to the recommendations of CENTOGENE and ACMG (please, see additional information below).

Pathogenic variants in the *ATP6V1B2* gene are associated with autosomal dominant congenital deafness with onychodystrophy (DDOD). The DDOD syndrome is characterized congenital deafness and onychodystrophy (e.g. absent/hypoplastic finger and toenails). Conical, hypoplastic teeth is also a feature (OMIM®: 124480).

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).

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 CentoHear (sequencing including NGS-based CNV analysis), 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 in the appendix of this report or at www.centogene.com/ngspanels-medical-reporting as part of our panel portfolio (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, a specificity of >99.9% for all reported variants is warranted.
The copy number variation (CNV) detection software has a sensitivity of above 85% for all homozygous/hemizygous deletions, as well as heterozygous deletions/duplications and homozygous/hemizygous duplications spanning at least three consecutive exons.

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ANALYSIS STATISTICS

CentoHear (sequencing including NGS-based CNV analysis)

Targeted nucleotides covered	≥ 20x	99.82%

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 (such as pseudogene homology), and GC-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 exon-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 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

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 Scientific Officer
Human Geneticist

Clinical Scientist

> Contact Details
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APPENDIX

CentoHear (sequencing including NGS-based CNV analysis)

ABHD12, ACTB, ACTG1, ADCY1, ADGRV1, AIFM1, ANKH, ATP2B2, ATP6V1B1, ATP6V1B2, BCS1L, BDP1, BSND, BTD, CABP2, CACNA1D, CCDC50, CD151, CD164, CDC14A, CDH23, CDKN1C, CEACAM16, CEP78, CHD7, CHSY1, CIB2, CISD2, CLDN14, CLIC5, CLPP, CLRN1, COCH, COL11A1, COL11A2, COL2A1, COL4A3, COL4A4, COL4A5, COL4A6, COL9A1, COL9A2, COL9A3, CRYM, DCAF17, DCDC2, DIABLO, DIAPH1, DIAPH3, DLX5, DMXL2, DNMT1, DSPP, EDN3, EDNRB, ELMOD3, EPS8, EPS8L2, ESPN, ESRP1, ESRRB, EYA1, EYA4, FDXR, FGF3, FGFR1, FGFR2, FGFR3, FOXI1, GAB1, GATA3, GIPC3, GJA1, GJB2, GJB3, GJB6, GPRASP2, GPSM2, GRHL2, GRXCR1, GRXCR2, GSDME, HARS1, HARS2, HGF, HOMER2, HOXB1, HSD17B4, ILDR1, KARS1, KCNE1, KCNJ10, KCNQ1, KCNQ4, KIT, KITLG, LARS2, LHFPL5, LOXHD1, LRP2, LRTOMT, MAN2B1, MANBA, MARVELD2, MCM2, MET, MGP, MITF, MPZL2, MSRB3, MYH14, MYH9, MYO15A, MYO3A, MYO6, MYO7A, NARS2, NDP, NLRP3, OPA1, OSBPL2, OTOA, OTOF, OTOG, OTOGL, P2RX2, PAX3, PCDH15, PDZD7, PEX1, PEX26, PEX6, PJVK, PMP22, PNPT1, POLR1C, POLR1D, POU3F4, POU4F3, PRPS1, RDX, RMND1, ROR1, RPS6KA3, S1PR2, SALL1, SALL4, SEMA3E, SERPINB6, SIX1, SIX5, SLC12A1, SLC17A8, SLC19A2, SLC26A4, SLC26A5, SLC29A3, SLC33A1, SLC44A4, SLC52A2, SLC52A3, SLITRK6, SMAD4, SMPX, SNAI2, SOX10, SOX2, SPATA5, STRC, SUCLA2, SUCLG1, SYNE4, TBC1D24, TBX1, TCOF1, TECTA, TFAP2A, TIMM8A, TJP2, TMC1, TMIE, TMPRSS3, TNC, TPRN, TRIOBP, TRMU, TSPEAR, TWNK, TYR, USH1C, USH1G, USH2A, VCAN, WBP2, WFS1, WHRN

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