CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE AG Am Strande 7 • 18055 Rostock • Germany

XXX

Order no.: xxx
Order received: xxx
Sample type: blood, filter card
Sample collection date: xxx
Report type: Final Report
Report date: xxx

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

Test(s) requested: Clinical Exome Sequencing (CentoDX™)

CLINICAL INFORMATION

Cleft palate, Coarctation of aorta, Hearing impairment, Hypoplastic left heart, Seizures
*: Clinical information indicated above follows HPO nomenclature.
Her parents are consanguineous.

NO GENETIC DIAGNOSIS

INTERPRETATION

No clinically relevant variant to the described phenotype has been detected.

RECOMMENDATIONS

- We recommend proceeding with chromosomal microarray analysis to screen for clinically relevant large deletions or duplications.
- Genetic counselling is recommended.

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CLIA registration 99D2049715; CAP registration 8005167. Scientific use of these results requires permission of CENTOGENE. If you would like to download your reports from our web portal, please contact us to receive your login and password. More information is available at www.centogene.com or support@centogene.com.

RESULT SUMMARY

By clinical exome sequencing, we did not detect any variant clinically relevant to the described phenotype of the patient. Please see below for the list of specifically analyzed genes. Although no relevant variant has been identified in these genes, pathogenic variants cannot be completely excluded since not all exons were fully covered due to limitations of the method. For these genes, an overall coverage of 98.49% was achieved (>20x), with 3634 missing base pairs (coding region including +/- 10bp). Note that clinical exome sequencing for diagnostic purposes does not provide full coverage for all genes and cannot detect large deletions/duplications. If needed, it is possible to test for every single gene that might likely explain the given phenotype.

specifically analyzed genes included in our panels for Cleft lip/palate, Congenital heart defects, and non-syndromic sensorineural deafness:
ACTG1, BMP4, CCDC50, CDH23, CFC1, CITED2, CLDN14, COCH, COL11A2, CRELD1, CRYM, DIABLO, DIAPH1, DIAPH3, ESPN, ESRRB, EYA4, FOXH1, FOXI1, GATA4, GATA6, GDF1, GIPC3, GJB2, GJB3, GJB6, GPSM2, GRHL2, GRXCR1, GSDME, HGF, ILDR1, IRF6, KCNJ10, KCNQ4, LHFPL5, LOXHD1, LRTOMT, MARVELD2, MIR96, MSRB3, MSX1, MYH14, MYH9, MYO15A, MYO3A, MYO6, MYO7A, NECTIN1, NKX2-5, NOTCH1, OTOA, OTOF, PCDH15, PJVK, POU3F4, POU4F3, PRPS1, PTPRQ, RDX, SERPINB6, SIX1, SLC12A1, SLC17A8, SLC26A4, SLC26A5, SMPX, STRC, SUMO1, TBX1, TBX20, TECTA, TJP2, TMC1, TMIE, TMPRSS3, TP63, TPRN, TRIOBP, USH1C, WFS1, WHRN, ZFPM2

INCIDENTAL FINDINGS

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

ANALYSIS STATISTICS for the offered genes

AVERAGE COVERAGE (X)	% TARGET BP COVERED					
	0X	≥ 1X	≥ 5X	≥ 10X	≥ 20X	≥ 50X
155.67	0.23	99.77	99.54	99.36	98.61	93.02

METHODS

Genomic DNA is enzymatically fragmented and regions of interest are selectively enriched using capture probes targeted against coding regions of ~6700 genes with known clinical significance. Libraries are generated with Illumina compatible adaptors and sequenced on an Illumina platform.
Evaluation is focused on coding exons along with flanking +/-10 intronic bases within the captured region. Due to limitations of the method, the target region is not covered 100%. Raw sequence data analysis, including base calling, demultiplexing, alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37) and variant calling is performed using validated in-house software. Relevant 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. All pertinent inheritance patterns are considered. In addition, provided family history and clinical information are used to evaluate eventually identified variants. All identified variants are evaluated with respect to their pathogenicity and causality, and these are categorized in classes 1 - 5. All variants related to the phenotype of the patient, except benign or likely benign variants, are reported. Any relevant variant(s) identified by NGS is(are) Sanger sequenced to exclude NGS artefacts before being reported.

LIMITATIONS

Test results are interpreted in the context of clinical findings, family history and other laboratory data. Only variations in genes potentially related to the proband's medical condition are reported. Rare polymorphisms may lead to false negative or positive results. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. If results obtained do not match the clinical findings, additional testing should be considered.
Due to limited read length and other contributing technical limitations, repeat expansions (i.e. in the Huntington gene, the SCA-genes, the myotonic dystrophy repeat region, and other similar regions) cannot be assessed with the applied method. Of note, CNV calls from Whole Genome Sequencing have a limited accuracy and sensitivity, and structural changes below 2 kb at a genome-wide level are not called by our pipeline.

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.

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In line with ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (Genetics in Medicine, 2016), 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.

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 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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