CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE GmbH • Am Strande 7 • 18055 Rostock • Germany

Dr. (Physician)
Institution
Address
Country

Order no.:
Order received: DD-MM-YYYY
Sample type / Sample collection date:
blood, CentoCard® / DD-MM-YYYY
Report date: DD-MM-YYYY
Report type: Final Report

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

Test(s) requested: CentoArray®

CLINICAL INFORMATION

Abnormality of the face; Atrial septal defect; Truncus arteriosus; Ventricular septal defect.
(Clinical information indicated above follows HPO nomenclature.)

Family history: Unknown.
Consanguineous parents: Unknown.

POSITIVE RESULT
Pathogenic CNV identified

INTERPRETATION

An interstitial heterozygous loss of 2597 kb (copy number state: 1, classification: pathogenic) within the 22q11.21 chromosomal cytoband was identified. **The genetic diagnosis of 22q11.2 deletion syndrome is confirmed.** Variable expressivity has been described for 22q11.2 deletion syndrome, so a carrier parent could be mildly affected (McDonald-McGinn et al., 2020; PMID: 20301696).

Please note that regions with absence of heterozygosity (AOH) were detected (listed below).

RECOMMENDATIONS

- If possible, parental targeted testing (by CMA or MLPA) is recommended as establishing the origin of the CNV, inherited or *de novo*, is important for familial genetic counselling. Additionally, targeted testing for all affected and at-risk family members, if any, is recommended.
- Genetic counselling, including reproductive counselling is recommended.

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RESULT SUMMARY

COPY NUMBER VARIATIONS				
CNV DESCRIPTION*	SIZE (KB)	GENE COUNT**	INTERPRETATION***	RELATED DISORDER
arr[GRCh37] 22q11.21(18877787_21475334)x1	2597	74	Pathogenic	22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (includes TBX1)

* according to ISCN 2020; ** genes are listed below; *** according to ACMG 2020, modified

GENES INCLUDED IN THE DETECTED CNVs:

CNV DESCRIPTION*	RefSeq GENES
arr[GRCh37] 22q11.21(18877787_21475334)x1	*FAM230F, DGCR6, PRODH, DGCR5, DGCR11, DGCR2, TSSK2, ESS2, GSC2, LINC01311, SLC25A1, CLTCL1, HIRA, MRPL40, C22orf39, UFD1, CDC45, CLDN5, LINC00895, SEPTIN5, SEPT5-GP1BB, GP1BB, TBX1, GNB1L, RTL10, TXNRD2, COMT, MIR4761, ARVCF, MIR185, TANGO2, MIR3618, MIR1306, DGCR8, TRMT2A, MIR6816, RANBP1, SNORA77B, ZDHHC8, CCDC188, LINC02891, LINC00896, MIR1286, RTN4R, DGCR6L, FAM230A, GGTLC3, TMEM191B, PI4KAP1, RIMBP3, FAM230J, FAM230G, ZNF74, SCARF2, KLHL22, MED15, POM121L4P, TMEM191A, SERPIND1, PI4KA, SNAP29, CRKL, LINC01637, AIFM3, LZTR1, THAP7, THAP7-AS1, TUBA3FP, P2RX6, SLC7A4, MIR649, P2RX6P, LRRC74B, BCRP2*

* according to ISCN 2020

VARIANT INTERPRETATION

arr[GRCh37] 22q11.21(18877787_21475334)x1

We detected an interstitial heterozygous 2597 kb large copy loss on the long arm of chromosome 22 including 74 genes (listed above). The detected CNV encompasses the critical region (chr22:18912231-21465672, genomic coordinate according to the Human genome assembly GRCh37/h19) associated to the 22q11.2 deletion syndrome (DGS/VCFS, (proximal, A-D, including TBX1, ISCA-37446).

22q11.2DS is an autosomal dominant contiguous gene deletion syndrome. Affected individuals can present with a wide range of features that are highly variable, even within families. The major clinical manifestations include congenital heart disease, particularly conotruncal malformations (ventricular septal defect, tetralogy of Fallot, interrupted aortic arch, and truncus arteriosus), palatal abnormalities (velopharyngeal incompetence, submucosal cleft palate, bifid uvula, and cleft palate), immune deficiency, characteristic facial features, and learning difficulties. Hearing loss can be sensorineural and/or conductive. Laryngotracheoesophageal, gastrointestinal, ophthalmologic, central nervous system, skeletal, and genitourinary anomalies also occur. Psychiatric illness and autoimmune disorders are more common. In 22q11.2DS caused by a 3.0 (2.54)-Mb deletion, the deletion is de novo in more than 90% of individuals and inherited from a heterozygous parent in about 10% of individuals (McDonald-McGinn et al., 2020 - PMID: 20301696). This CNV is classified as pathogenic according to the recommendations of CENTOGENE and ACMG (please see additional information below).

REGIONS WITH ABSENCE OF HETEROZYGOSITY (AOH):

Segments showing continuous homozygosity with no intervening heterozygosity are termed ‘regions with absence of heterozygosity’. If they are copy number neutral (no deletion), these regions may represent uniparental disomy (UPD), ancestral homozygosity due to linkage disequilibrium, or regions inherited from a more recent common ancestor that are identical by descent. A high number of AOHs can be seen in offspring from related (consanguineous) parents (Sund and Rehder, 2014, PMID: 25060286). Regions with AOH might be indicative for the presence of homozygous single nucleotide variants related to recessive diseases.

CHROMOSOMAL REGION*	SIZE (KB)
arr[GRCh37] 7q21.2q22.1(92746570_103396611)x2 hmz	10650

* according to ISCN 2020

CHROMOSOMAL REGION*	SIZE (KB)
-	-

* according to ISCN 2020

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CENTOGENE LARGE COPY NUMBER VARIATION CLASSIFICATION

PATHOGENIC – CNV with sufficient evidence to classify as pathogenic
LIKELY PATHOGENIC – CNV with strong evidence in favor of pathogenicity
UNCERTAIN SIGNIFICANCE – CNV with limiting and/or conflicting evidence regarding pathogenicity
LIKELY BENIGN – CNV with strong evidence against pathogenicity
BENIGN – CNV with sufficient evidence to classify as benign; polymorphism
Additionally, other types of clinically relevant variants can be identified (e.g. risk factors, modifiers).

The classification of large copy number variations at CENTOGENE is based on the ACMG standards and guidelines for interpretation and reporting of constitutional copy number variations.

METHODS

The Infinium™ Global Diversity Array with Cytogenetics kit (Illumina) is used for this analysis. This kit contains ~1.8 million SNP markers distributed genome-wide, particularly for more than 4800 disease-associated genes with 99.9% exon coverage, enabling the detection of copy number variations (CNVs). Genomic DNA is amplified, fragmented, and hybridized to the array according to the manufacturer`s instructions. Results are analyzed using NxClinical Software (BioDiscovery). CNVs exceeding a size of 50 kb for losses and 200 kb for gains are reported. Identified losses below the given thresholds are only reported if a clear phenotypic overlap with affected genes is observed. Results are interpreted using DGV, DECIPHER and ClinGen databases and additional available resources. CNVs are classified into five classes (pathogenic, likely pathogenic, VUS, likely benign, and benign) along ACMG guidelines for classification of variants. Benign and likely benign CNVs are excluded from reporting. CNVs are evaluated based on the patient's reason for referral for this test and the clinical information provided. Comprehensive reporting of heterozygous CNVs in the context of recessive diseases is outside the scope of the intended use for this test. Therefore, carrier status might not be disclosed. Any clinical concern for recessive disorders should be communicated to the reporting laboratory for appropriate consideration. According to regulatory requirements in prenatal analyses, CENTOGENE only reports highly penetrant pathogenic and likely pathogenic CNVs. This array allows for the analysis of regions with absence of heterozygosity (AOH). The presence of AOH in multiple chromosomes may be consistent with inheritance from a common ancestor.

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 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.

Chromosomal microarray (CMA) is recommended for the identification of DNA copy number variations (CNVs), chromosomal imbalances, and areas with absence/loss of heterozygosity (AOH/LOH). CMA can only detect CNVs in the nuclear genome; it cannot detect CNVs in the mitochondrial genome. CMA cannot detect balanced chromosomal rearrangements such as translocations and inversions, repeat sequences such as segmental duplications, complete uniparental heterodisomy, point mutations and delins, low level mosaicism (< 30%), mosaicism for duplications with a high copy number (> 3 copies) and CNVs in the regions of the genome that are not represented on the microarray. Failure to detect an alteration at a specific locus does not exclude the diagnosis of a genetic disorder associated with that locus, as there may be abnormalities present in that region that are not detectable by CMA technology.

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.

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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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