CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE AG Am Strande 7 • 18055 Rostock • Germany

XXX

Order no.: XXX
Order received: XXX
Sample type: XXX
Sample collection date: XXX
Report date: XXX
Report type: Final Report

Patient no.: **XXX**, First Name: **XXX**, Last Name: **XXX**
DOB: **XXX**, Sex: **unknown**, Your ref.: **XXX**

Test(s) requested: Chromosomal microarray analysis (CMA; CentoArrayCyto™ – 750K incl. SNP test)

CLINICAL INFORMATION

Dysmorphic abortus.

POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

We detected a 1 copy loss of X chromosome.

This result is consistent with a genetic diagnosis of monosomy X (Turner syndrome).

RECOMMENDATIONS

- Genetic counselling is recommended.

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

RESULT SUMMARY

CNV DESCRIPTION*	SIZE (KB)	GENE COUNT**	INTERPRETATION***	PATIENT RELEVANT PHENOTYPE
arr[GRCh37]Xp22.33q28(168551_155233098)x1	155065	1125	pathogenic	Monosomy X (Turner syndrome)

* according to ISCN 2016; ** genes are listed at the end of the report; *** according to ACMG 2011, modified

VARIANT INTERPRETATION

We detected a 1 copy loss of chromosome X. This copy number variation (CNV) is classified as pathogenic according to the recommendations of Centogene and ACMG (please see additional information below).

Turner syndrome is a chromosomal disorder associated with the complete or partial absence of an X chromosome. Clinical features are heterogeneous and typical physical anomalies are often mild or absent. Short stature is present in all cases. Ovarian failure, with variable onset depending on the chromosomal anomalies, is frequent. Other visceral manifestations (bone anomalies, lymphoedema, deafness, and cardiovascular, thyroid and gastrointestinal involvement) are less common but should be screened for at diagnosis, then monitored during adolescence and adulthood. During gestation, typical forms with associated malformations can be diagnosed by ultrasound examination, but mild forms are discovered incidentally following amniocentesis performed for another indication (for example, advanced maternal age) (ORPHA: 881).

REGIONS WITH ABSENCE OF HETEROZYGOSITY (AOH):

CHROMOSOMAL REGION*	SIZE (KB)
arr[GRCh37] 2p23.3p23.2(24800155_28358774)	3559
arr[GRCh37] 6p22.2p22.1(26473982_29711041)	3237
arr[GRCh37] 19q13.2q13.31(40933980_44040253)	3106

* according to ISCN 2016

CENTOGENE CLASSIFICATION OF CMA DETECTED COPY NUMBER VARIANTS

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

The classification of copy number variants at Centogene is based on the ACMG standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants (2011). Copy number variants are evaluated based on the patient's reason for referral for this genomic screening. Comprehensive reporting of heterozygous recessive variants is outside the scope of the intended use of this test. Therefore, recessive carrier status might not be disclosed. Any clinical concern for recessive disorders should be communicated to the reporting laboratory for appropriate consideration.

1 copy loss – heterozygous/hemizygous deletion
2 copy loss – homozygous deletion
1 copy gain – heterozygous/hemizygous duplication
2 copy gain – homozygous duplication or triplication

METHODS

Chromosomal microarray analysis (CMA; CentoArrayCyto™- 750K)
250 ng of genomic DNA were fragmented, amplified and hybridized to the array according to manufacturer`s guidelines. The Cytoscan 750K array (Affymetrix) contains 750,000 markers, including 200,000 SNP markers, across the whole genome covering 80% of the genes. It enables the detection of copy number variations and/or large deletions/duplications. The results were analyzed with the Chromosome Analysis suite (ChAS, Affymetrix). Copy number variations with a minimum of 25 markers and a size of more than 50kb (deletions) and 200kb (duplications) are reported. The SNP component of this array allows analyzing absence of heterozygosity (AOH). The presence of AOH in multiple chromosomes might be consistent with inheritance from a shared ancestor. For homozygous deletions, analysis was performed for all

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

aberrations with at least 5 aberrant markers and a size of more than 1kb. These and eventually identified deletions below the given thresholds are only reported if a clear phenotypic overlap of affected genes is observed. The results were interpreted using the DGV and Decipher databases and additional available databases.

LIMITATIONS

CMA method is recommended for the purpose of identifying DNA copy number variations (CNVs) associated with chromosomal imbalances and for the detection of absence/loss of heterozygosity (AOH/LOH), regions of homozygosity (ROH), or long contiguous stretches of homozygosity (LCSH). CMA can only detect large genomic copy number imbalances and AOH in the nuclear genome. It cannot detect balanced chromosomal rearrangements such as balanced inversions, reciprocal translocations and inversions. CMA cannot detect imbalances in the mitochondrial genome, repeat sequences such as segmental duplications, complete uniparental heterodisomy for the entire chromosome, point mutations and indels, low levels of mosaicism for regions 15 Mb in size or below 30% mosaicism, genomic copy number changes 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. There might be abnormalities present in that region that are not detectable by the CMA technology.

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.
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 (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.

COPYRIGHT NOTICE

Chief Medical Director

Medical Reporter

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