# 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: **female**, Your ref.: **XXX**

**Additional report recipient(s):** XXX

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

## CLINICAL INFORMATION

The patient has a horseshoe kidney, renal cyst, glucosuria, G6PD and alpha thalassemia trait and short stature on GH since 09/2017. She also has acute rheumatic fever with no cardiac involvement. The parents are consanguineous.

⊖ **NEGATIVE RESULT**

## INTERPRETATION

**We did not detect any copy number variation (CNV) relevant for the described phenotype of the patient. We detected a normal female, arr(1-22,X)x2.**

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

## RECOMMENDATIONS

- Proceeding to whole exome or whole genome trio sequencing is recommended (including the parents for segregation analysis).
- Genetic counselling is recommended.

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## REGIONS WITH ABSENCE OF HETEROZYGOSITY (AOH):

| CHROMOSOMAL REGION* | SIZE (KB) |
|---|---|
| arr[GRCh37] 1q41q42.2(216247219_230712124) | 14465 |
| arr[GRCh37] 3p21.31p21.2(48531739_51874861) | 3343 |
| arr[GRCh37] 4q32.3q35.1(169784759_183805438) | 14021 |
| arr[GRCh37] 5q11.1q11.2(49560858_56346338) | 6785 |
| arr[GRCh37] 7q33q34(134075709_141606098) | 7530 |
| arr[GRCh37] 8p23.1p22(11745734_17029975) | 5284 |

* according to ISCN 2016

| CHROMOSOMAL REGION* | SIZE (KB) |
|---|---|
| arr[GRCh37] 11p15.1p12(19312901_42315501) | 23003 |
| arr[GRCh37] 11q14.3q21(89082501_93005938) | 3923 |
| arr[GRCh37] 12q13.13q15(52644742_69577670) | 16933 |
| arr[GRCh37] 12q21.2q23.1(79421728_96455871) | 17034 |
| arr[GRCh37] 13q13.3q33.1(37031243_101833450) | 64802 |
|  |  |

* 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 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.

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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.

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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.

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