CENTOGENE
THE RARE DISEASE COMPANY

**CENTOGENE GmbH** • Am Strande 7 • 18055 Rostock • Germany

XXX

**Order no.:** xxx
**Order received:** xxx
**Sample type / Sample collection date:**
blood, EDTA / xxx
**Report date:** xxx
**Report type:** Final Report

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

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

**Test(s) requested: CentoArray®**

## CLINICAL INFORMATION

Almond-shaped palpebral fissure; Cryptorchidism; Feeding difficulties in infancy; Global developmental delay; Intellectual disability; Micropenis; Neonatal hypotonia; Obesity; Polyphagia; Short stature; Small hand
(Clinical information indicated above follows HPO nomenclature.)

Family history: No.

Consanguineous parents: No
Clinician suspects: Prader-Willi syndrome

**POSITIVE RESULT**
**Pathogenic copy number variation (CNV) identified**

## INTERPRETATION

A heterozygous loss of ~4.9 Mb (copy number state: 1, classification: pathogenic) within the 15q11.2q13 chromosomal region was identified. This loss overlaps with the recurrent 15q11.2q13 deleted region in Prader-Willi/Angelman syndromes subject to parental imprinting.

Attending to the provided clinical information, the genetic diagnosis of Prader-Willi syndrome is confirmed.

The detected genetic sex is male. Regions with absence of heterozygosity (AOH) are listed below.

## RECOMMENDATIONS

- Cytogenetic analysis (karyotyping and FISH) of the patient and father is recommended.
- Genetic counselling is recommended.

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## RESULT SUMMARY

| **COPY NUMBER VARIATIONS** | | | | |
|---|---|---|---|---|
| CNV DESCRIPTION* | SIZE (KB) | GENE COUNT** | INTERPRETATION*** | RELATED DISORDER |
| **arr[GRCh37] 15q11.2q13.1(23623542_28544359)x1** | **4914** | **113** | **Pathogenic** | **Prader-Willi syndrome** |

* 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] 15q11.2q13.1(23623542_28544359)x1 | *GOLGA6L2, MIR4508, MKRN3, MAGEL2, NDN, PWRN4, PWRN2, PWRN3, PWRN1, NPAP1, SNRPN, SNURF, SNORD107, PWARSN, SNORD64, PWAR5, SNORD108, PWAR6, SNORD109A, SNORD116-1, SNORD116-2, SNORD116-3, SNORD116-4, SNORD116-5, SNORD116-6, SNORD116-7, SNORD116-8, SNORD116-9, SNORD116-10, SNORD116-11, SNORD116-12, SNORD116-13, SNORD116-14, SNORD116-15, SNORD116-16, SNORD116-17, SNORD116-18, SNORD116-19, SNORD116-20, SNORD116-21, SNORD116-22, SNORD116-23, SNORD116-24, SNORD116-25, SNORD116-26, SNORD116-27, SNORD116-28, SNORD116-29, SNORD116-30, IPW, SNHG14, PWAR1, SNORD115-1, SNORD115-2, SNORD115-3, SNORD115-4, SNORD115-5, SNORD115-6, SNORD115-7, SNORD115-8, SNORD115-9, SNORD115-10, SNORD115-11, SNORD115-12, SNORD115-13, SNORD115-14, SNORD115-15, SNORD115-16, SNORD115-17, SNORD115-18, SNORD115-19, SNORD115-20, SNORD115-21, SNORD115-22, SNORD115-23, PWAR4, SNORD115-24, SNORD115-25, SNORD115-26, SNORD115-27, SNORD115-28, SNORD115-29, SNORD115-30, SNORD115-31, SNORD115-32, SNORD115-33, SNORD115-34, SNORD115-35, SNORD115-36, SNORD115-37, SNORD115-38, SNORD115-39, SNORD115-40, SNORD115-41, SNORD115-42, SNORD115-43, SNORD115-44, SNORD115-45, SNORD115-46, SNORD115-47, SNORD115-48, SNORD109B, UBE3A, ATP10A, MIR4715, LINC02346, LINC00929, GABRB3, GABRA5, GABRG3-AS1, GABRG3, OCA2, HERC2* |

* according to ISCN 2020

## VARIANT INTERPRETATION

### arr[GRCh37] 15q11.2q13.1(23623542_28544359)x1

A CNV that consists in the loss of 1 copy (heterozygous deletion) of ~4.9 Mb overlapping with the recurrent 15q11.2q13 region between breakpoints BP2-BP3 deleted in Prader-Willi/Angelman syndromes subjected to parental imprinting, was detected. This CNV is classified as pathogenic according to the recommendations of CENTOGENE and ACMG (please see additional information below)

Prader-Willi syndrome (PWS) is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity (unless eating is externally controlled). Motor milestones and language development are delayed. All individuals have some degree of cognitive impairment. A distinctive behavioral phenotype (with temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics) is common. Hypogonadism is present in both males and females and manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. Short stature is common (if not treated with growth hormone); characteristic facial features, strabismus, and scoliosis are often present (PMID: 20301505).

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## 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] 2q14.1q14.2(117884934_121147726)x2 hmz | 3262 |
| arr[GRCh37] 3p21.31p21.1(49040786_52852488)x2 hmz | 3811 |
| arr[GRCh37] 3q22.2q23(135292221_141380727)x2 hmz | 6088 |

* according to ISCN 2020

| CHROMOSOMAL REGION* | SIZE (KB) |
|---|---|
| arr[GRCh37] 6p12.3p12.1(47402355_53536029)x2 hmz | 613 |
| arr[GRCh37] 6q24.2q24.3(144761542_147934602)x2 hmz | 3173 |
| - | - |

* according to ISCN 2020

## 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, 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.

## 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



| **XXX** | **XXX** | **XXX** |
|---|---|---|
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