



XXX

Order no.: xxx
Order received: xxx
Sample type: DNA
Sample collection date: xxx
Report type: Final Report
Report date: xxx

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

Additional report recipient(s): xxx

Test(s) requested: Whole Genome Sequencing (CentoGenome®)

CLINICAL INFORMATION*

Decreased patellar reflex, Difficulty climbing stairs, Difficulty running, EMG: neuropathic changes, Gowers sign, Juvenile onset, Lower limb muscle weakness, Mildly elevated creatine phosphokinase, Motor delay, Muscle weakness, Toe walking

*: Clinical information indicated above follows HPO nomenclature.

Age of Manifestation: 15th months

Please also see our reports for the family members: xxx and xxx (xxx).



POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

A homozygous deletion encompassing exon 7 and 8 of the SMN1 gene has been identified by whole genome sequencing and confirmed by MLPA.

This finding is consistent with a genetic diagnosis of autosomal recessive spinal muscular atrophy.

RECOMMENDATIONS

- Genetic counselling is recommended.

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RESULT SUMMARY

GENE (METHOD)	OUTCOME
SMN1 (WGS and MLPA)	homozygous deletion encompassing exon 7 and 8

VARIANT INTERPRETATION

SMN1, deletion of exon 7 and 8

We detected a large deletion encompassing exons 7 and 8 of the SMN1 gene. Similar deletions as well as deletions of the entire SMN1 gene have been described as disease-causing for spinal muscular atrophy by several authors (HGMD Professional 2017.4). The variant is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

Pathogenic variants in the SMN1 gene are associated with autosomal recessive spinal muscular atrophy, which is characterized by muscle weakness and atrophy resulting from progressive degeneration and loss of the anterior horn cells in the spinal cord (i.e., lower motor neurons) and the brain stem nuclei. The onset of weakness ranges from before birth to adolescence or young adulthood. The weakness is symmetric, proximal > distal, and progressive. Before the genetic basis of SMA was understood, it was classified into clinical subtypes; however, it is now apparent that the phenotype of SMN1-associated SMA spans a continuum without clear delineation of subtypes. Poor weight gain with growth failure, restrictive lung disease, scoliosis, joint contractures, and sleep difficulties are common complication (PMID: 20301526).

INCIDENTAL FINDINGS

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

ANALYSIS STATISTICS WGS

AVERAGE COVERAGE (X)	% TARGET BP COVERED					
	0X	≥ 1X	≥ 5X	≥ 10X	≥ 20X	≥ 50X
42.08	0.27	99.73	99.51	99.22	96.39	17.75

CENTOGENE VARIANT CLASSIFICATION (BASED ON ACMG RECOMMENDATIONS)

- Class 1** – Pathogenic
- Class 2** – Likely pathogenic
- Class 3** – Variant of uncertain significance (VUS)
- Class 4** – Likely benign
- Class 5** – Benign

Additionally, other types of clinical relevant variants can be identified (e.g. risk factors, modifiers).

METHODS

Genomic DNA was fragmented by sonication and Illumina adapters were ligated to generated fragments for subsequent sequencing on the HiSeqX platform (Illumina) to yield an average coverage depth of ~30X. An end to end in-house bioinformatics pipeline including base calling, primary filtering of low quality reads and probable artefacts, and annotation of variants was applied. CNV calling is based on HAS pipeline. All disease causing variants reported in HGMD®, in ClinVar or in CentoMD® in addition to all variants with minor allele frequency (MAF) of less than 1% in gnomAD database are considered. Evaluation is focused on coding exons along with flanking +/-20 intronic bases, however extended to the complete gene region for candidate genes or in search for a second previously described variant in AR inheritance pattern. 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 (see above). All variants related to the phenotype of the patient, except benign or likely benign variants, are reported. CNVs of unknown significance are not reported. Reported CNVs are confirmed with another method such as MLPA and qPCR.

Variants of relevance identified by NGS are continuously and individually in-house validated for quality aspects; those variants which meet our internal QC criteria (based on extensive validation processes) are not validated by Sanger.

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MLPA (multiplex ligation-dependent probe amplification) analyses were performed using SALSA MLPA probemix P021-A2 provided by MRC-Holland to test for deletions or duplications within or including the SMN1 gene(s).

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.

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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