



XXX

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

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

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

**Test(s) requested: Whole Exome Sequencing (CentoXome GOLD®)**

### CLINICAL INFORMATION

The proband is asymptomatic.

We performed whole exome sequencing for the child of the proband. Please refer to our report xxx (name).

**This report reflects exclusively the segregation information for the proband in the context of the family analysis.**



**CARRIER STATUS**  
**Pathogenic variant identified**

### INTERPRETATION

The proband is a heterozygous carrier of a pathogenic variant in the BBS1 gene. As a consequence the proband and her partner have an increased risk of having children affected with Bardet-Biedl syndrome type 1.

### RECOMMENDATIONS

- Genetic counselling is recommended.

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**RESULT SUMMARY**

GENE	VARIANT COORDINATES	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
BBS1	Chr11(GRCh37):g.66278561G>A NM_024649.4:c.124+1G>A  Intron 2	Het	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation: nt weak 3/3 likely splice effect	gnomAD: - ESP: - 1000 G: - CentoMD: -	Substitution Pathogenic (class 1)

Variant description based on Alamut Batch (latest database available). \* AlignGVGD: C0: least likely to interfere with function, C65: most likely to interfere with function, splice prediction tools: SSF, MaxEnt, HSF. \*\* Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD® (latest database available). \*\*\* based on ACMG recommendations

**VARIANT INTERPRETATION**

**BBS1, c.124+1G>A**

The BBS1 variant c.124+1G>A is predicted to disrupt the highly conserved donor splice site of exon 2. The consequence of this change is not predictable, but a skip of exon 2 is very likely. According to HGMD Professional 2017.3, this variant has previously been described as disease causing for Bardet-Biedl syndrome by Harville et al., 2010 (PMID: 19797195) and Abu Safieh et al., 2010 (PMID: 19858128). It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

Pathogenic variants in the BBS1 gene are known to cause autosomal recessive Bardet-Biedl syndrome type 1 (OMIM®: 209900).

**INCIDENTAL FINDINGS**

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

**ANALYSIS STATISTICS WES**

AVERAGE COVERAGE (X)	% TARGET BP COVERED					
	0X	≥ 1X	≥ 5X	≥ 10X	≥ 20X	≥ 50X
109.79	0.32	99.68	99.35	98.69	96.21	78.65

**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

**METHODS**

RNA capture baits against approximately 60 Mb of the Human Exome (targeting >99% of regions in CCDS, RefSeq and Gencode databases) is used to enrich regions of interest from fragmented genomic DNA with Agilent’s SureSelect Human All Exon V6 kit. The generated library is sequenced on an Illumina platform to obtain an average coverage depth of ~100x. Typically, ~97% of the targeted bases are covered >10x. An end to end in-house bioinformatics pipeline including base calling, alignment of reads to GRCh37/hg19 genome assembly, primary filtering out of low quality reads and probable artefacts, and subsequent annotation of variants, is applied. All disease causing variants reported in HGMD®, in ClinVar or in CentoMD® as well as 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. 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 into classes 1 - 5 (see above). All variants related to the phenotype of

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the patient, except benign or likely benign variants, are reported.

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.

## 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.

Specific genetic events like copy number variants, translocations and repeat expansions may not be reliably detected with Exome Sequencing. In addition, due to limitations in technology, certain regions may either not be covered or may be poorly covered, where variants cannot be confidently detected.

## 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](mailto: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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