CENTOGENE
THE RARE DISEASE COMPANY

CENTOGENE AG Am Strande 7 • 18055 Rostock • Germany

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: **female**, Your ref.: **xxx**

Additional report recipient(s): xxx

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

CLINICAL INFORMATION*

Abnormal facial shape, Abnormality of the ureter, Acute kidney injury, Bidirectional shunt, Depressed nasal bridge, Hydrometrocolpos, Hydronephrosis, Hypertelorism, Large for gestational age, Left-to-right shunt, Low-set ears, Patent ductus arteriosus, Patent foramen ovale, Pelvic kidney, Postaxial foot polydactyly, Prominent forehead, Pulmonary arterial hypertension, Pulmonary hypoplasia, Renal cyst, Short neck
*: Clinical information indicated above follows HPO nomenclature.

Please also see our concurrent reports concerning the parents of the patient xxx (name) and xxx (name).

POSITIVE RESULT
Pathogenic variants identified

INTERPRETATION

Two heterozygous pathogenic variants were identified in the BBS1 gene. Parental testing confirmed compound heterozygous state of these variants. **The genetic diagnosis of autosomal recessive Bardet-Biedl syndrome type 1 is confirmed.**

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)
BBS1	Chr11(GRCh37):g.66291105C>T NM_024649.4:c.951+58C>T Intron 10	Het	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation: nt moderate 2/3 likely splice effect	gnomAD: - ESP: - 1000 G: - CentoMD: 0.000095	Substitution Pathogenic (class 1)

Variant description based on Alamut Batch (latest database available). * AlignGVD: 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). This variant was detected in the mother in heterozygous state. It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

BBS1, c.951+58C>T

The BBS1 variant c.951+58C>T is predicted to create an intronic donor splice site, which is likely to cause a shift in the reading frame and a loss of function of the BBS1 protein. According to HGMD Professional 2017.3, this variant has previously been described as disease causing for Bardet-Biedl syndrome by Abu Safieh et al., 2010 (PMID: 19858128) and Scheidecker et al., 2015 (PMID: 25982971). This variant was detected in the father in heterozygous state. 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 Bardet-Biedl syndrome type 1 (OMIM®: 209900). Bardet-Biedl syndrome (BBS) is an autosomal recessive and genetically heterogeneous ciliopathy. It is characterized by rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, and renal abnormalities. The visual prognosis for children with BBS is poor. Night blindness is usually evident by age seven to eight years. Birth weight is usually normal, but significant weight gain begins within the first year and becomes a lifelong issue for most individuals. A majority of individuals have significant learning difficulties. Renal disease is a major cause of morbidity and mortality (PMID: 20301537).

INCIDENTAL FINDINGS

We did not detect any class 1 or 2 variants in the genes for which incidental findings are reported based on the ACMG guidelines.

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ANALYSIS STATISTICS WES

AVERAGE COVERAGE (X)	% TARGET BP COVERED					
	0X	≥ 1X	≥ 5X	≥ 10X	≥ 20X	≥ 50X
173.93	0.29	99.71	99.48	99.08	97.64	87.24

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

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 the patient, except benign or likely benign variants, are reported.
Centogene has established stringent quality criteria and validation processes for variants detected by NGS. Lower quality single nucleotide or deletion insertion variants are thus being confirmed by Sanger. As a result of this we warrant specificity of >99.9% for all reported variants.

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) 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,

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potentially misleading or even wrong result of any testing if such issue could not be recognized by CENTOGENE in advance.

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