



XXX

Order no.: xxx  
Order received: xxx  
Sample type: blood, filter card  
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

**Test(s) requested: Clinical Exome Sequencing (CentodX™)**

### CLINICAL INFORMATION

The patient is presenting since birth with dark blue sclerae and recurrent fractures. Suspicion of osteogenesis imperfecta. Parents are not related. No affected siblings reported.



**POSITIVE RESULT**  
**Pathogenic variant identified**

### INTERPRETATION

A heterozygous pathogenic variant was identified in the COL1A1 gene. **The genetic diagnosis of autosomal dominant COL1A1-related osteogenesis imperfecta is confirmed.**

### RECOMMENDATIONS

- Parental carrier testing is requested to establish whether the detect variant is inherited or de novo.
- Genetic counselling is recommended.

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**RESULT SUMMARY**

GENE	VARIANT COORDINATES	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
COL1A1	Chr17(GRCh37):g.48267264C>A  NM_000088.3:c.2569G>T p.(Gly857Cys) Exon 37	Het	PolyPhen: Probably damaging Align-GVGD: C65 SIFT: Deleterious MutationTaster: Disease causing Conservation: nt high/aa high	gnomAD: -  ESP: - 1000 G: - CentoMD: -	Missense  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**

**COL1A1, c.2569G>T p.(Gly857Cys)**

The COL1A1 variant c.2569G>T p.(Gly857Cys) causes an amino acid change from Gly to Cys at position 857. According to HGMD Professional 2017.3, this variant has previously been described as disease causing for Osteogenesis imperfecta III/IV by Marini et al., 2007 (PMID: 17078022) and Bardai et al., 2016 (PMID: 27509835). It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

COL1A1-related osteogenesis imperfecta (OI) is characterized by fractures with minimal or absent trauma, variable dentinogenesis imperfecta (DI), and, in adult years, hearing loss. The clinical features of COL1A1-related OI represent a continuum ranging from perinatal lethality to individuals with severe skeletal deformities, mobility impairments, and very short stature to nearly asymptomatic individuals with a mild predisposition to fractures, normal dentition, normal stature, and normal life span. Fractures can occur in any bone, but are most common in the extremities. DI is characterized by grey or brown teeth that may appear translucent and wear down and break easily. COL1A1-related OI has been classified into four types (I, II, III, and IV) based on clinical presentation and radiographic findings. This classification system can be helpful in providing information about prognosis and management for a given individual. The four OI types are now referred to as follows: OI type I: classic non-deforming OI with blue sclerae; OI type II: perinatally lethal OI; OI type III: progressively deforming OI; OI type IV: common variable OI with normal sclerae. COL1A1-related OI is inherited in an autosomal dominant manner. The proportion of cases caused by a de novo COL1A1 mutation varies by the severity of disease: approximately 60% of cases of classic non-deforming OI with blue sclerae or common variable OI with normal sclerae, virtually 100% of perinatally lethal OI, and close to 100% of progressively deforming OI are de novo (Steiner, et al., 2013 - PMID: 20301472).

**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.

**ANALYSIS STATISTICS for the offered genes**

AVERAGE COVERAGE (X)	% TARGET BP COVERED					
	0X	≥ 1X	≥ 5X	≥ 10X	≥ 20X	≥ 50X
137.69	0.11	99.89	99.70	99.40	98.17	89.52

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## 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 is enzymatically fragmented and regions of interest are selectively enriched using capture probes targeted against coding regions of ~6700 genes with known clinical significance. Libraries are generated with Illumina compatible adaptors and sequenced on an Illumina platform.

Evaluation is focused on coding exons along with flanking +/-10 intronic bases within the captured region. Due to limitations of the method, the target region is not covered 100%. Raw sequence data analysis, including base calling, demultiplexing, alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37) and variant calling is performed using validated in-house software. Relevant 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. All pertinent inheritance patterns are considered. In addition, provided family history and clinical information are used to evaluate eventually identified variants. 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 targeted Clinical 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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