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**

**Test(s) requested: Hereditary hemorrhagic telangiectasia panel (sequencing)**

## CLINICAL INFORMATION

Patient is a first-time pregnant woman who is suspected of having Oslers disease due to repeated nosebleeds.

**POSITIVE RESULT**
**Likely pathogenic variant identified**

## INTERPRETATION

A heterozygous likely pathogenic variant was identified in the ENG gene. **The genetic diagnosis of autosomal dominant hereditary hemorrhagic telangiectasia type 1E is confirmed.**

In the remainder of the panel genes (see methods), no other clinically relevant variant has been identified.

## RECOMMENDATIONS

- Parental carrier testing is requested to establish whether the detected variant in the ENG gene 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*** |
|---|---|---|---|---|---|
| ENG | Chr9(GRCh37):g.130582178C>T<br>NM_001114753.1:c.1272+1G>A<br><br>Intron 9 | Het | PolyPhen: N/A<br>Align-GVGD: N/A<br>SIFT: N/A<br>MutationTaster: N/A<br>Conservation: nt moderate<br>3/3 likely splice effect | gnomAD: -<br>ESP: -<br>1000 G: -<br>CentoMD: - | Substitution<br>Likely pathogenic<br>(class 2) |

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

### ENG, c.1272+1G>A

The ENG variant c.1272+1G>A is predicted to disrupt the highly conserved donor splice site of exon 9. ClinVar lists this variant as pathogenic (clinical testing, Variation ID: 213209). It is classified as likely pathogenic (class 2) according to the recommendations of Centogene and ACMG (please, see additional information below).

Pathogenic variants in ENG gene are associated with hereditary hemorrhagic telangiectasia type 1 (HHT1), an autosomal dominant disorder. Hereditary hemorrhagic telangiectasia (HHT) is a vascular dysplasia leading to telangiectases and arteriovenous malformations of skin, mucosa, and viscera. Epistaxis and gastrointestinal bleeding are frequent complications of mucosal involvement. Visceral involvement includes that of the lung, liver, and brain.

## ANALYSIS STATISTICS

Please be aware that NGS panels do not give full coverage for all genes. An overall coverage of 99.87% was achieved, with 23 missing base pairs (coding region including +/- 10bp). At your request, it is possible to test for every fragment with missing bases.

## 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 panel genes. Libraries are generated with Illumina compatible adaptors and sequenced on an Illumina platform.
For the Hereditary hemorrhagic telangiectasia panel, the entire coding region of the ACVRL1, ADAM17, ENG, GDF2, PTPN14, RASA1, SMAD4 genes including 10 bp of flanking intronic sequences are targeted. Due to limitations of the NGS analysis alone, the targeted region within the requested panel may not reach 100% coverage. 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. 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.

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## 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.

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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