Test requested: CentoCloud Genome Solo

CLINICAL INFORMATION
Female infertility; Hypercholesterolemia; Hypertension; Hypertriglyceridemia; Hypothyroidism; Renal cell carcinoma
(Clinical information indicated above follows HPO nomenclature)
Family history: Unknown.
Consanguineous parents: Unknown.

NEGATIVE RESULT

INTERPRETATION
No clinically relevant variants related to the described phenotype were detected.

RECOMMENDATIONS
• Reevaluation of the sequence dataset is recommended every 12 months or if there are phenotypic changes.
• Genetic counselling is recommended.
RESEARCH FINDINGS

Research variants (with potential relevance to the described phenotype) are variants in genes with no or only partial experimental evidence for their involvement in human disease.

The data was analyzed focusing on variants affecting protein function (nonsense, frameshift, conserved splice site and missense with high pathogenicity predictions) in genes with supporting evidence on zygosity, segregation or functional importance of the gene. Available literature or experimental data on expression and/or animal models were considered.

However, no such variants could be identified for the patient.

SECONDARY (INCIDENTAL) FINDINGS

If consent is provided, in line with ACMG recommendations for reporting of secondary (incidental) findings in clinical exome and genome sequencing (Genetics in Medicine, 2021; PMID: 34012068), we report secondary (incidental) findings, i.e., pathogenic variants (class 1) and likely pathogenic variants (class 2) in the recommended genes for the indicated phenotypes.

We did not detect any class 1 or 2 variants in the genes, for which secondary (incidental) findings are reported.

CARRIERSHIP FINDINGS

In this table we list sequence variants previously ascertained or evaluated and classified in CENTOGENE as "pathogenic" and "likely pathogenic", in selected genes associated with recessive severe and early-onset Mendelian diseases. As only in-house classified variants are presented, it should not be considered a comprehensive list of variants in these genes and does not provide a complete list of potentially relevant genetic variants in the patient. The complete gene list can be found at www.centogene.com/carriership-findings (please contact CENTOGENE customer support if the gene list has been updated after this report was issued). Orthogonal validation was not performed for these variants. Therefore, if any variant is used for clinical management of the patient, confirmation by another method needs to be considered. Furthermore, the classification of these variants may change over time, however reclassification reports for these variants will not be issued. CENTOGENE is not liable for any missing variant in this list and/or any provided classification of the variants at a certain point of time. As the identified variants may indicate (additional) genetic risks or diagnoses in the patient and/or family and/or inform about reproductive risks, we recommend discussing these findings in the context of genetic counselling.

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT COORDINATES</th>
<th>AMINO ACID CHANGE</th>
<th>SNP IDENTIFIER</th>
<th>ZYGOSITY</th>
<th>IN SILICO PARAMETERS*</th>
<th>ALLELE FREQUENCIES**</th>
<th>TYPE AND CLASSIFICATION***</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEXA</td>
<td>NM_001318825:1:c.1307_1310dup</td>
<td>p.(Tyr438Ilefs*5)</td>
<td>rs387906309</td>
<td>heterozygous</td>
<td>PolyPhen: - Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation_nt: N/A Conservation_aa: N/A</td>
<td>gnomAD: 0.00074 ESP: 0.0010 1000 G: 0 CentoMD: 0.0010</td>
<td>Frameshift Pathogenic (class 1)</td>
</tr>
<tr>
<td>MMUT</td>
<td>NM_000255.3:c.1399C&gt;T</td>
<td>p.(Arg467*)</td>
<td>rs774159791</td>
<td>heterozygous</td>
<td>PolyPhen: - Align-GVGD: N/A SIFT: N/A MutationTaster: Disease causing Conservation_nt: high Conservation_aa: N/A</td>
<td>gnomAD: 0.00068 ESP: - 1000 G: 0.000065 CentoMD: 0.00067</td>
<td>Nonsense Pathogenic (class 1)</td>
</tr>
</tbody>
</table>
CentoCloud® Genome Solo

**ANALYSIS STATISTICS**

| Targeted nucleotides covered | ≥ 10x | 99.02% |

**LIMITATIONS**

The genetic results are interpreted in the context of the provided clinical findings, family history, and other laboratory data. Only variants in genes potentially related to the proband’s medical condition are reported. Misinterpretation of results may occur if the provided genetic data or patient information is inaccurate and/or incomplete. If the obtained genetic results are not compatible with the clinical findings, additional testing should be considered.

The genes with mapping issues in GRCh37/hg19 genome assembly, the non-protein-coding disease-associated genes, and genomic regions that are hard to sequence by current technology and are without evidenced relevance for monogenic disorders, are excluded from this analysis. More complex genetic events such as inversions, translocations, and repeat expansions, are not analyzed in this test. In addition, due to technology limitations, certain regions may be poorly covered, or not covered at all. In these regions and others encompassing repetitive, high-homology (such as pseudogene homology), and GC-rich sequences, relevant variants can be missed. Extremely low-coverage calls are expected to be artifacts based on our extensive validations and are consequently not considered during the analysis. The CNV detection sensitivity is decreased for repetitive and homologous regions, such as pseudogenes. It is expected that lower quality samples (prenatal, product of conception, blood from patients with hematologic disorders, and highly degraded DNA) may generate lower quality NGS data; in these cases, CNV analysis may not be reported, with the exception of known pathogenic splicing variants evidenced by external sources.

**CENTOGENE VARIANT CLASSIFICATION (BASED ON ACMG RECOMMENDATIONS)**

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

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

This test was developed, and its performance was validated, by CENTOGENE. 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 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 (customer.support@centogene.com) in the future to determine if there have been any changes in classification of any reported variants.

DISCLAIMER

The CentoCloud® from CENTOGENE provides state-of-the-art bioinformatic services applying a validated diagnostic pipeline to filter variants from the sequencing raw data provided by our customers. Although regularly and extensively tested and monitored, the CentoCloud® system – like any software product including bioinformatic analyses and particularly as third-party software is included - might contain unforeseeable errors which may lead to misalignment, incorrect base calls, and mis-annotation of variants and thus may have an impact on the accuracy of the medical interpretation of results.

Although CENTOGENE monitors and reviews the received sequencing raw data and its quality insofar as technically possible, it is not responsible for any errors resulting from the preparation and sequencing of a sample by its customers (including, but not limited to, sample identification and/or sample swap). Such errors are then already contained within the raw data and will lead to an erroneous result. CENTOGENE shall only be responsible for providing a fully annotated variant list in the range and format as agreed with its customers. Any filtering criteria may be subject to further modification at the partner’s site in accordance with clinical information or family information. The selection of highlighted variants by CENTOGENE does not preclude any other variant within the variant list that should be considered for medical interpretation.

Any clinical interpretation and conclusion of variants highlighted in this report is the responsibility of the customer. Test results should always be interpreted in the context of clinical findings, family history, and any other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. Please note, rare polymorphisms exist that could lead to false negative or positive results. If results obtained do not match the clinical findings, additional testing of samples through CENTOGENE’s laboratory should be considered, this also applies for a confirmative analysis of any positive result.

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