



xxx

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

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

Test(s) requested: CentoMito™ Genome panel

CLINICAL INFORMATION

Sensorineural hearing loss, proximal muscle weakness, myoclonus epilepsy, CPK and lactate elevated, dysarthria; EMG shows chronic myopathy with distal symmetric axonal sensory polyneuropathy; onset at the age of three years; myoclonus epilepsy associated with ragged red fibers (MERFF) is suspected.



POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

A known pathogenic variant was identified in the MT-TK gene in a high-level heteroplasmic state.
A genetic diagnosis of MERFF with mitochondrial inheritance is thus confirmed.

RECOMMENDATIONS

- maternal carrier testing (ideally by next generation sequencing to detect low-level heteroplasmy)
- genetic counselling

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RESULT SUMMARY

GENE (TRANSCRIPT, METHOD)	OUTCOME
MT-TK (NC_012920.1, sequencing)	heteroplasmic variant m.8344A>G

VARIANT INTERPRETATION

MT-TK, m.8344A>G

The MT-TK variant m.8344A>G was detected in a heteroplasmic state (84.7% of 9061 NGS reads). The affected nucleotide position in the tRNA for Lysine is conserved and MitoTIP predicts a deleterious effect (<https://www.mitomap.org>) by alteration of the TψC loop of the encoded tRNA. This variant has previously been described as pathogenic for myoclonic epilepsy with ragged red fibers (MERRF) by Shoffner *et al.*, 1990 (PMID: 2112427), followed by several other authors. It is the most common pathogenic variant, present in more than 80% of affected individuals with typical findings of the disease (DiMauro and Hirano, 2015 - PMID: 20301693). It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG (please, see additional information below).

MERRF is a multisystem disorder characterized by myoclonus followed by generalized epilepsy, ataxia, weakness, and dementia. Onset is usually in childhood, occurring after normal early development. Common findings are hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White syndrome. The variant detected has also been associated with Leigh syndrome. Disorders caused by pathogenic variants in the mitochondrial genome are transmitted by maternal inheritance. The mother of a proband usually has the mtDNA pathogenic variant and may or may not have symptoms. A female with the pathogenic variant may transmit the pathogenic variant to all of her offspring; however, prediction of the phenotype from prenatal studies is not possible because the mutational load in tissues sampled prenatally may shift *in utero* or after birth (DiMauro and Hirano, 2015 - PMID: 20301693).

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

Targeted amplification of the entire mitochondrial genome is done using two overlapping long range PCRs. The amplicons are run on the Bioanalyzer to assess for any putative deletion within the mitochondrial genome. The amplified products are subsequently tagged and Illumina compatible adapters ligated to generate libraries that are sequenced on Illumina platforms to an average sequencing depth of 1000x or more.

Raw sequence data analysis, including base calling, demultiplexing, alignment to the Revised Cambridge Reference Sequence (rCRS) of the Human Mitochondrial DNA (NC_012920) and variant calling are performed using validated in-house software. Following the base calling and primary filtering of low quality reads, standard Bioinformatics pipeline was implemented to annotate detected variants and to filter out probable artefacts. The pipeline confidently detects heteroplasmy levels down to 15%.

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.

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.

Statistics (CentoMito Genome)

Overall, 100% of the target base pairs of the mitochondrial genes were covered at least 500x. The average cover was: 11944.66x.

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

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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 (customer.support@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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