LifeLabs Genetics™

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R. F. Carter, PhD, FCCMG
Lab Director

Dr. Jane Doe
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Final Report

Patient name:	PATIENT, SAMPLE	**Order no.:**	650000821
Patient no.:	10000054	**Reference no.:**	IV293710
DOB:	yyyy/mm/dd	**Specimen collected:**	yyyy/mm/dd
Sex:	Female	**Date approved:**	yyyy/mm/dd
Sample type:	Blood, EDTA	**Date reported:**	yyyy/mm/dd

TEST REQUEST: Charcot-Marie-Tooth (CMT) Axonal panel – sequencing analysis.

CLINICAL INFORMATION: Patient presenting with symptoms of Charcot-Marie-Tooth neuropathy.

Based on an intronic variant with possible splicing effect in DNM2, a genetic diagnosis of Charcot-Marie-Tooth neuropathy is possible. However, further analyses are suggested in order to evaluate the clinical significance of this variant.

TEST RESULT:

Gene (OMIM)	Inheritance	Variant	Classification
DNM2 (602378)	Autosomal dominant	**Heterozygous c.1234-5G>T**	**Class 3 - VUS**

No significant variants detected for: AARS, ARHGEF10, DYNC1H1, GAN, GARS, GDAP1, HSPB1, HSPB8, KIF1B, LMNA, MED25, MFN2, MPZ, NEFL, RAB7A, SLC12A6, TRPV4, or YARS genes.

INTERPRETATION:
An unknown proportion of Charcot-Marie-Tooth (CMT) cases are caused by mutations in the DNM2 gene (NCBI GeneReviews 2015; PMID: 20301532). **In your patient, we detected a heterozygous variant of uncertain clinical significance (VUS) in the DNM2 gene.** Additional analyses are recommended.

We detected a previously unreported heterozygous variant in intron 15 of the DNM2 gene (c.1234-5G>T). This variant has not been reported by NCBI 1000 Genomes, NHLBI Exome Sequencing Project, or Exome Aggregation Consortium population frequency databases. It has not been reported by HGMD, ClinVar, or CentoMD™ mutation databases to date. However, a small deletion affecting this genomic region (c.1234-3_1234-5delATG) has previously been reported as disease-causing for CMT dominant intermediate type B (CMTDIB) by Scientist, 2012 (HGMD Professional 2015.1 – PMID: 123456789). Additionally, software analyses by MaxEntScan, SpliceSiteFinder, and Human Splicing Finder predict an aberrant effect on splicing is possible. **Based on this information, and in accordance with ACMG 2015 guidelines (PMID: 25741868), we consider this a class 3 VUS** (please see additional information below for classification details).

As several lines of evidence are in favour of clinical relevance for the detected variant, we suggest further assessment by familial testing in informative relatives, and mRNA analysis. Please note that the classification of a VUS can change over time; feel free to contact LifeLabs Genetics in the future regarding any updates.

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Our genetic counsellors are available to assist you with interpretation of these results. Alternately, to locate genetic services near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca.

RECOMMENDATIONS:

-Testing for the detected intronic variant in informative relatives may be advisable to clarify its significance. mRNA studies are also suggested.
-Genetic counselling.

Please note that any further analyses will result in additional costs.

ADDITIONAL INFORMATION:

This test has been developed and validated for clinical purposes by Centogene AG and LifeLabs Genetics. Variants are classified on the basis of multiple private and public databases – including CentoMD™, NCBI 1000 genomes, NHLBI Exome Sequencing Project, Exome Aggregation Consortium and HGMD® Professional – and in accordance with ACMG 2015 guidelines (PMID: 25741868).

Scientific use of these results requires permission from Centogene and LifeLabs Genetics. More information is available at www.lifelabsgenetics.com or Ask.Genetics@LifeLabs.com.

Categories of variant classification (ACMG categories):
Class 1 - Pathogenic variant (sufficient evidence for pathogenicity)
Class 2 - Likely pathogenic variant (strong evidence for pathogenicity)
Class 3 - Variant of uncertain clinical significance (insufficient or conflicting evidence regarding variant effect)
Class 4 - Likely benign variant (strong evidence for neutrality)
Class 5 - Benign variant (sufficient evidence for neutrality)

METHODS:

The **AARS, ARHGEF10, DNM2, DYNC1H1, GAN, GARS, GDAP1, HSPB1, HSPB8, KIF1B, LMNA, MED25, MFN2, MPZ, NEFL, RAB7A, SLC12A6, TRPV4, YARS** genes were analysed by PCR and next-generation sequencing of both DNA strands of the entire coding region and the highly conserved exon-intron splice junctions. PCR-based amplicon library capture was utilized. We have a minimum coverage of 30x for every amplicon. The reference sequences of the **AARS, ARHGEF10, DNM2, DYNC1H1, GAN, GARS, GDAP1, HSPB1, HSPB8, KIF1B, LMNA, MED25, MFN2, MPZ, NEFL, RAB7A, SLC12A6, TRPV4, YARS** genes are: **NM_001605.2, NM_014629.2, NM_001005360.2, NM_001376.4, NM_022041.3, NM_002047.2, NM_018972.2, NM_001540.3, NM_014365.2, NM_015074.3, NM_170707.3, NM_030973.3, NM_014874.3, NM_000530.6, NM_006158.4, NM_004637.5, NM_133647.1, NM_021625.4, NM_003680.3. Please note that large deletions, duplications, and novel deep intronic variants may not be detectable by the techniques applied**

All **Class 1 and 2** pathogenic variants are confirmed by forward and reverse Sanger sequencing of an independent aliquot of DNA.

Please note:

- Analysis and interpretation are based upon the assumption that the patient's medical and family history is accurate as described.
- Common polymorphisms have not been included in this report. A complete list of any detected Class 4 and 5 variants is available upon request.
- All technical protocols have limitations that affect specificity. Polymorphic/normal genomic variation in the patient sample may interfere with mutation detection, and lab error is a rare but possible occurrence. Please contact us if these results appear inconsistent with the clinical evidence.
- Results and interpretation are based upon current technologies, methodologies and medical literature, which may change over time with progress in the field. Please stay in contact with us to remain up to date on options for follow-up testing.

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LifeLabs Genetics is licensed by the Ontario Ministry of Health and Long-Term Care to operate as a clinical genetic laboratory: MOHLTC license 5806. If you have any questions or would like to inquire about additional analyses, please do not hesitate to contact us at **Ask.Genetics@lifelabs.com** or call us at **1-84-GENE-HELP** (1-844-363-4357).