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.:**	650000352
Patient no.:	10000030	**Reference no.:**	IV178099
DOB:	yyyy/mm/dd	**Specimen collected:**	yyyy/mm/dd
Sex:	Female	**Date approved:**	yyyy/mm/dd
Sample type:	Blood	**Date reported:**	yyyy/mm/dd

TEST REQUEST: JAG1 (OMIM: 601920) sequencing analysis; Alagille syndrome (OMIM: 118450); inheritance: autosomal dominant.

CLINICAL INFORMATION: Infant male presenting with cholestasis and renal dysplasia. Ophthalmology pending.

A diagnosis of Alagille syndrome can be genetically confirmed.

TEST RESULT:

Gene (OMIM)	Inheritance	Variant	Classification
JAG1 (601920)	Autosomal dominant	**Heterozygous c.1234G>A (p.Arg5678Cys)**	**Class 1 – pathogenic variant**

INTERPRETATION:

We detected a heterozygous variant in exon 16 of the JAG1 gene (c.1234G>A, p.Arg5678Cys). This variant has previously been reported in association with Alagille syndrome (ALGS1; OMIM: 118450) by Scientist *et al*., 2010 (HGMD Professional 2015.1 - PMID: 1234567). Additionally, this variant has been shown to reduce protein function in a functional assay by Researcher *et al.*, 2014 (PMID: 1234568). This variant is reported without carrier frequency information by NCBI 1000 Genomes (rs12345678). It has not previously been reported by NHLBI Exome Sequencing Project, but is reported at a frequency of 0.000023 by the Exome Aggregation Consortium (ExAC). Additionally, this variant has been classified as 'pathogenic' by CentoMD™, ClinVar, and LOVD databases. Finally, the variant occurs at a highly conserved nucleotide position within the tuberin protein domain, and is predicted to have a pathogenic effect by SIFT, MutationTaster, Align GVGD, and PolyPhen-2 algorithms. Based on this information, and in accordance with ACMG 2015 guidelines (PMID: 25741868), **we classify this as a class 1 pathogenic variant. We recommend proceeding to parental testing.**

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.

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RECOMMENDATIONS:

-Parental testing for the detected variant.
-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 **JAG1** gene was analysed by PCR and sequencing of both DNA strands of the entire coding region and the highly conserved exon-intron splice junctions. The reference sequence of the **JAG1** gene is: **NM_000214.2**. **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).