Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/8/1989
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Wilson Disease (ATP7B) Sequencing

ARUP test code 3004411

Wilson Disease (ATP7B) Specimen	Whole Blood
Wilson Disease (ATP7B) Interp	Positive

RESULT
Two pathogenic variants were detected in the ATP7B gene.

PATHOGENIC VARIANT
Gene: ATP7B (NM_000053.4)
Nucleic Acid Change: c.2332C>T; Heterozygous
Amino Acid Alteration: p.Arg778Trp
Inheritance: Autosomal recessive

PATHOGENIC VARIANT
Gene: ATP7B (NM_000053.4)
Nucleic Acid Change: c.3207C>A; Heterozygous
Amino Acid Alteration: p.His1069Gln
Inheritance: Autosomal recessive

INTERPRETATION
Two pathogenic variants, c.2332C>T; p.Arg778Trp, and c.3207C>A; p.His1069Gln, were detected in the ATP7B gene by massively parallel sequencing. Pathogenic ATP7B variants are inherited in an autosomal recessive manner and are associated with Wilson disease (MIM: 606882). This result is consistent with a diagnosis of Wilson disease. Although the identified variants have not previously been reported to occur on the same chromosome, parental testing could confirm they are located on opposite chromosomes.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The ATP7B c.2332C>T; p.Arg778Trp variant (rs137853284) is reported in homozygous and compound heterozygous state in several individuals with Wilson disease (Butler 2001, Coffey 2013, Kumar 2007, Shah 1997) and is described as segregating with disease (Coffey 2013). The variant is listed in the ClinVar database (Variation ID: 456553) and in the general population with an overall allele frequency of 0.005% (13/249,436 alleles) in the Genome Aggregation Database. The arginine at codon 778 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.877). In support of this prediction, this variant has been shown to have reduced function (Kumar 2007). Additionally, other amino acid substitutions at this codon (p.Arg778Gln, p.Arg778Gly, p.Arg778Leu) have been reported in individuals with Wilson disease and are considered pathogenic (Dong 2016, Forbes 1998, Kumar 2007, Schushan 2012).

H=High, L=Low, *=Abnormal, C=Critical

Considering available information, this variant is classified as pathogenic.

The ATP7B c.3207C>A; p.His1069Gln variant (rs76151636), also known as His714Gln, has been reported in the homozygous and compound heterozygous state in numerous individuals diagnosed with Wilson disease (Cocos 2014, Duc 1998, Tanzi 1993). Functional studies indicate that the variant protein has altered subcellular localization (Payne 1998, van den Berghe 2009), reduced affinity to ATP (Morgan 2004, Rodriguez-Granillo 2008) and reduced half-life (Payne 1998). Cells expressing the variant protein show reduced viability when exposed to increased levels of copper (Payne 1998). This variant is reported in ClinVar (Variation ID: 3848) and is found in the general population with an overall allele frequency of 0.10% (286/280766 alleles) in the Genome Aggregation Database. The histidine at codon 1069 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.909). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Parental testing should be considered to confirm the chromosomal origin of the identified variants (Familial Targeted Sequencing, ARUP test code 3005867). At-risk family members should be offered testing for the variant in their family lineage. This individual's reproductive partner should be offered Wilson Disease (ATP7B) Sequencing (ARUP test code 3004411) to determine carrier status.

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

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This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: Wilson Disease (ATP7B) Sequencing

CHARACTERISTICS: Wilson disease is a disorder of copper metabolism caused by pathogenic variants in the ATP7B gene. Toxic accumulation of copper in body tissues, particularly the liver and central nervous system, causes progressive disease that is eventually lethal if untreated. The clinical presentation of Wilson disease is highly variable and age dependent. Symptoms, including Kayser-Fleischer rings, liver disease, neurologic findings, and psychiatric disease, may present at any time from early childhood to late adulthood.

PREVALENCE: 1 in 10,000 to 1 in 30,000.

CAUSE: Pathogenic germline variants in ATP7B.

INHERITANCE: Autosomal recessive.

PENETRANCE: Age dependent.

CLINICAL SENSITIVITY: 98 percent.

GENE TESTED: ATP7B (NM_000053)
Deletion/duplication analysis is not available for this gene.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of Wilson disease. This test only detects variants within the coding regions and intron-exon boundaries of the ATP7B gene. Regulatory region variants and deep intronic variants will not be identified, including the Sardinian founder variant, c.-436_-422del15. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Wilson Disease (ATP7B) Specimen	23-097-401597	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Wilson Disease (ATP7B) Interp	23-097-401597	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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