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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/31/2023
Sex:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Wilson Disease (ATP7B) Sequencing

ARUP test code 3004411

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

RESULT
Two copies of a pathogenic variant were detected in the ATP7B gene.

PATHOGENIC VARIANT
Gene: ATP7B (NM_000053.4)
Nucleic Acid Change: c.865C>T; Homozygous
Amino Acid Alteration: p.Gln289Ter
Inheritance: Autosomal recessive

INTERPRETATION
Two apparent copies of a pathogenic variant, c.865C>T; p.Gln289Ter, 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; OMIM(R)). This result is consistent with a diagnosis of Wilson disease.

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.865C>T; p.Gln289Ter variant (rs121907999) is reported in the literature in homozygous and compound heterozygous individuals affected with Wilson disease (Couchonnal 2021, Manolaki 2009, Nayagam 2023, Panagiotakaki 2004, Waldenstrom 1996). This variant is also reported in ClinVar (Variation ID: 3864) and is found in the general population with an overall allele frequency of 0.003% (7/248088 alleles) in the Genome Aggregation Database (v2.1.1). This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. 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 future reproductive partner should be offered Wilson Disease (ATP7B) Sequencing (ARUP test code 3004411) to determine carrier status.

COMMENTS

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

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

REFERENCES
Couchonnal E et al. ATP7B variant spectrum in a French pediatric Wilson disease cohort. Eur J Med Genet. 2021 Oct;64(10):104305. PMID: 34400371.
Manolaki N et al. Wilson disease in children: analysis of 57 cases. J Pediatr Gastroenterol Nutr. 2009 Jan;48(1):72-7. PMID: 19172127.
Nayagam JS et al. ATP7B Genotype and Chronic Liver Disease Treatment Outcomes in Wilson Disease: Worse Survival With Loss-of-Function Variants. Clin Gastroenterol Hepatol. 2023 May;21(5):1323-1329.e4. PMID: 36096368.
OMIM(R) Copyright (C) 1996 - Present year, Johns Hopkins University All rights reserved.
Panagiotakaki E et al. Genotype-phenotype correlations for a wide spectrum of mutations in the Wilson disease gene (ATP7B). Am J Med Genet A. 2004 Dec 1;131(2):168-73. PMID: 15523622.
Waldenstrom E et al. Efficient detection of mutations in Wilson disease by manifold sequencing. Genomics. 1996 Nov 1;37(3):303-9. PMID: 8938442.

This result has been reviewed and approved by [redacted]

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	25-101-401389	4/11/2025 10:39:00 AM	4/13/2025 4:16:55 PM	4/21/2025 12:40:00 PM
Wilson Disease (ATP7B) Interp	25-101-401389	4/11/2025 10:39:00 AM	4/13/2025 4:16:55 PM	4/21/2025 12:40:00 PM

END OF CHART

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