Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: arup, arup

Patient: PROD, ATP7B NGS 2

DOB
Sex: Male
Patient Identifiers: 36630
Visit Number (FIN): 36949
Collection Date: 2/24/2022 10:23

Wilson Disease (ATP7B) Sequencing

ARUP test code 3004411

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

RESULT
One pathogenic variant was detected in the ATP7B gene.

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

INTERPRETATION
Two copies of a pathogenic variant, 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.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

Evidence for variant classification: The ATP7B c.3207C>A; p.His1069Gln variant (rs76151636), also known as His714Gln, has been reported 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. At-risk family members should be offered testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). This individuals future reproductive partner should be

offered genetic testing to determine carrier status.

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not included in this report.

REFERENCES
Cocos R, et al. Genotype-phenotype correlations in a mountain population community with high prevalence of Wilson's disease: genetic and clinical homogeneity. PLoS One. 2014 9(6):e98520.

Duc HH, et al. His1069Gln and six novel Wilson disease mutations: analysis of relevance for early diagnosis and phenotype. Eur J Hum Genet. 1998 6(6):616-23.

Morgan C, et al. The distinct functional properties of the nucleotide-binding domain of ATP7B, the human copper-transporting ATPase: analysis of the Wilson disease mutations E1064A, H1069Q, R1151H, and C1104F. J Biol Chem. 2004 279(35):36363-71.

Payne A, et al. Functional expression of the Wilson disease protein reveals mislocalization and impaired copper-dependent trafficking of the common H1069Q mutation. Proc Natl Acad Sci U S A. 1998 95(18):10854-9.

Rodriguez-Granillo A, et al. Stability and ATP binding of the nucleotide-binding domain of the Wilson disease protein: effect of the common H1069Q mutation. J Mol Biol. 2008 383(5):1097-111.

Tanzi R, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet. 1993 5(4):344-50.

van den Berghe P, et al. Reduced expression of ATP7B affected by Wilson disease-causing mutations is rescued by pharmacological folding chaperones 4-phenylbutyrate and curcumin. Hepatology. 2009 50(6):1783-95.

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	22-055-103050	2/24/2022 10:23:00 AM	2/24/2022 10:23:39 AM	2/24/2022 10:33:00 AM
Wilson Disease (ATP7B) Interp	22-055-103050	2/24/2022 10:23:00 AM	2/24/2022 10:23:39 AM	2/24/2022 10:33:00 AM

END OF CHART