Wilson Disease (ATP7B) Sequencing
ARUP test code 2010716

ATP7B Sequencing Specimen: Whole Blood

ATP7B Sequencing Interpretation

Positive *

TEST PERFORMED - 2010716
TEST DESCRIPTION - Wilson Disease (ATP7B) Sequencing
INDICATION FOR TEST - Not Provided

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

DNA VARIANT
Classification: Pathogenic
Gene: ATP7B
Nucleic Acid Change: c.3809A>G; Homozygous
Amino Acid Alteration: p.Asn1270Ser

INTERPRETATION
Two apparent copies of a pathogenic variant, c.3809A>G; p.Asn1270Ser, were detected in the ATP7B gene by sequencing. The presence of two pathogenic variants, one in each copy of the ATP7B gene, is causative for Wilson disease; therefore, this molecular result is consistent with a clinical diagnosis of Wilson disease. Because sequence analysis is not able to detect large ATP7B deletions, this individual either has two copies of the detected pathogenic variant or a single copy of the variant with a large deletion on the opposite chromosome. Parental testing could determine which of the above scenarios is correct.

Evidence for variant classification: The ATP7B c.3809A>G; p.Asn1270Ser variant (rs121907990) is reported in the literature in numerous individuals affected with Wilson disease (Abuduxikuer 2015, Barada 2010, Daneshjoo 2018, Guggilla 2015, Hua 2016, Tanzi 1993, Todorov 2005, Wu 1999). It has been reported to cosegregate with disease in families, both in the homozygous state (Barada 2010, Tanzi 1993) and in trans to another pathogenic variant (Daneshjoo 2018). The asparagine at codon 1270 is highly conserved, it occurs in the well-conserved hinge region of the ATP7B ATPase domain (Tanzi 1993), and computational analyses (SIFT, PolyPhen-2) predict that this variant is deleterious. Biochemical analyses indicate this variant has severely reduced copper transport activity (Huster 2012), and it fails to rescue growth defects of mutant yeast to the extent of wildtype protein (Iida 1998). Other variants at this codon (p.Asn1270Asp, p.Asn1270Ile) are reported in Wilson disease patients, though their pathogenicity has not yet been fully demonstrated (Nemeth 2016, Tuan Pham 2017). The p.Asn1270Ser variant is reported as pathogenic by multiple

H=High, L=Low, *=Abnormal, C=Critical
laboratories in ClinVar (Variation ID: 3859), and it is found in the general population with an overall allele frequency of 0.019% (52/277208 alleles) in the Genome Aggregation Database. 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 is recommended to confirm the chromosomal origin of the identified variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Adult family members should be offered carrier testing for the variant in their family lineage. This individual's reproductive partner should be offered Wilson Disease (ATP7B) Sequencing (ARUP test code 2010716) to determine carrier status.

COMMENTS
Reference Sequence: GenBank # NM_000053.3 (ATP7B)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES

This result has been reviewed and approved by Steven Steinberg, Ph.D.
BACKGROUND INFORMATION: Wilson Disease (ATP7B) Sequencing

CHARACTERISTICS: Wilson disease is a disorder of copper metabolism caused by mutations 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-Fleisher rings, liver disease, neurologic findings, and psychiatric disease, may present at any time from early childhood to late adulthood.

INCIDENCE: 1/30,000 - 1/50,000

INHERITANCE: Autosomal recessive.

PENETRANCE: Age-dependent.

CAUSE: Pathogenic ATP7B gene mutations.

CLINICAL SENSITIVITY: 98 percent.

METHODOLOGY: Bidirectional sequencing of the entire ATP7B coding region and intron/exon boundaries.

ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.

LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations, deep intronic mutations, and large deletions/duplications will not be detected. Mutations in genes other than ATP7B are not evaluated.

See Compliance Statement C: www.arulab.com/CS

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