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

Physician: Doctor, Example

Patient: Patient, Example

DOB	7/24/1993
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Familial Transthyretin Amyloidosis (TTR) Sequencing

ARUP test code 2014035

TTR FGS Spec: Whole Blood

TTR FGS Interpretation: **Positive** *

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TEST PERFORMED - 2014035
TEST DESCRIPTION - Familial Transthyretin Amyloidosis (TTR)
Sequencing
INDICATION FOR TEST - Predictive Testing

RESULT
One pathogenic variant was detected in the TTR gene.

DNA VARIANT
Classification: Pathogenic
Gene: TTR
Nucleic Acid Change: c.238A>G; Heterozygous
Amino Acid Alteration: p.Thr80Ala

INTERPRETATION
According to information provided to ARUP, this individual has a
family history of familial amyloidosis with previous testing in
the family identifying an unspecified TTR variant. One copy of
the pathogenic variant, c.238A>G; p.Thr80Ala, was detected in
the TTR gene by sequencing. Although this molecular result is
consistent with a diagnosis of familial transthyretin
amyloidosis, clinical manifestations are variable; penetrance
for developing clinical symptoms may be variant specific and may
vary by geographic region or ethnic group for each variant
(Sekijima 2018). Offspring of this individual have a 50 percent
chance to inherit the pathogenic variant and would be at risk
for developing the clinical symptoms associated with familial
transthyretin amyloidosis.

Evidence for variant classification: The TTR c.238A>G;
p.Thr80Ala variant (rs121918070), also known as p.Thr60Ala, is
reported in the literature in multiple individuals and families
affected with hereditary amyloidosis, associated mainly with
amyloidotic cardiomyopathy and a poor prognosis (Altland 2007,
Dohrn 2013, Fontana 2015, Ihse 2013, Lachmann 2002, Pilebro
2016, Swiecicki 2015, Waits 1995, Wallace 1986). This variant is
the most common pathogenic TTR variant in the United Kingdom,
and has high prevalence in northwest Ireland (Reilly 1995,
Sattianayagam 2012). This variant is reported as pathogenic by
multiple laboratories in ClinVar (Variation ID: 13421), and is
only observed on one allele in the Genome Aggregation Database,
indicating it is not a common polymorphism. The threonine at
codon 80 is moderately conserved, but computational analyses
(SIFT, PolyPhen-2) predict that this variant is tolerated.
However, functional analyses of the variant protein show a
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reduction in stability compared to the wild-type protein (Cendron 2009, Sekijima 2005). Based on available information, the p.Thr80Ala variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation, including a discussion of medical screening and management, is recommended. This molecular result should be correlated with the TTR variant identified in other family members and the segregation of clinical manifestations in carriers. At-risk family members should be offered targeted testing for the identified variant (Familial Mutation, Targeted Sequencing; ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_000371.3 (TTR)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

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

Wallace MR et al. Biochemical and molecular genetic characterization of a new variant prealbumin associated with hereditary amyloidosis. J Clin Invest. 1986 Jul;78(1):6-12.

This result has been reviewed and approved by Steven Steinberg, Ph.D.

BACKGROUND INFORMATION: Familial Transthyretin Amyloidosis (TTR) Sequencing
CHARACTERISTICS: Familial Transthyretin Amyloidosis is caused by pathogenic variants of the TTR gene resulting in abnormal amyloid accumulation in various tissues and is generally categorized into three phenotypes: 1) familial amyloid polyneuropathy, a slowly progressive sensorimotor and autonomic neuropathy; 2) familial amyloid cardiomyopathy, a restrictive cardiomyopathy with cardiomegaly, conduction block, angina, congestive heart failure and aortic dissection/dilatation; and 3) leptomeningeal amyloidosis, primarily affecting the CNS, causing dementia, visual impairment, seizures, ataxia, psychosis, hemorrhage, and hydrocephalus. TTR variants can also be associated with benign familial euthyroid hyperthyroxinemia.
INCIDENCE: 1 in 568 individuals from Northern Portugal; 1 in 100,000 individuals of Northern European ancestry.
INHERITANCE: Autosomal dominant.
PENETRANCE: Incomplete.
CAUSE: Pathogenic TTR gene variants.
CLINICAL SENSITIVITY: 99 percent for Familial TTR Amyloidosis.
METHODOLOGY: Bidirectional sequencing of all coding regions and intron-exon boundaries of the TTR gene.
ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region variants, deep intronic variants and large deletions/duplications in TTR will not be detected.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
TTR FGS Spec	19-205-108892	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
TTR FGS Interpretation	19-205-108892	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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