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

Physician: arup, arup

Patient: Genomics, Notch 1

DOB	
Sex:	Male
Patient Identifiers:	36436
Visit Number (FIN):	36755
Collection Date:	2/23/2022 10:16

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, CADASIL (NOTCH3), Sequencing

ARUP test code 3004383

CADASIL (NOTCH3) Specimen	Whole Blood
CADASIL (NOTCH3) Interp	Positive

RESULT
One pathogenic variant was detected in the NOTCH3 gene.

PATHOGENIC VARIANT
Gene: NOTCH3 (NM_000435.2)
Nucleic Acid Change: c.350G>T; Heterozygous
Amino Acid Alteration: p.Cys117Phe
Inheritance: Autosomal dominant

INTERPRETATION
One copy of a pathogenic variant, c.350G>T; p.Cys117Phe, was detected in the NOTCH3 gene by massively parallel sequencing. Pathogenic NOTCH3 variants are inherited in an autosomal dominant manner and are associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; MIM: 125310). This result is consistent with a diagnosis of CADASIL; clinical manifestations are variable and age dependent. This individual's offspring have a 50 percent chance of inheriting the causative variant.

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 a list of the genes analyzed and limitations of this test.

Evidence for variant classification: The NOTCH3 c.350G>T; p.Cys117Phe variant (rs773539041), also published as c.428G>T, is reported in the literature in multiple individuals affected with CADASIL (Dichgans 1999, Matsushima 2017, Opherk 2004). This variant is reported in ClinVar (Variation ID: 447838). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. Additionally, other amino acid substitutions at this codon (p.Cys117Trp, p.Cys117Tyr, p.Cys117Arg, p.Cys117Ser) have been reported in individuals with CADASIL and are considered pathogenic (Ampuero 2009, Chen 2017, Spinicci 2013, Qin 2019). The cysteine at codon 117 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.974). Most pathogenic NOTCH3 variants occur in exons 2-24 and either create or destroy a cysteine residue within an EGF-like domain (Rutten 2014), and thus the p.Cys117Phe variant is consistent with the predominant mechanism of disease in NOTCH3. Based on available information, this variant is considered to be pathogenic.

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

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).

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
Ampuero I et al. On the diagnosis of CADASIL. J Alzheimers Dis. 2009;17(4):787-94.

Chen S et al. Clinical features and mutation spectrum in Chinese patients with CADASIL: A multicenter retrospective study. CNS Neurosci Ther. 2017;23(9):707-716.

Dichgans M et al. Quantitative MRI in CADASIL: correlation with disability and cognitive performance. Neurology. 1999;52(7):1361-7.

Matsushima T et al. Genotype-phenotype correlations of cysteine replacement in CADASIL. Neurobiol Aging. 2017;50:169.e7-169.e14.

Opherk C et al. Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. Brain. 2004;127(Pt 11):2533-9.

Qin W et al. Clinical features of 4 novel NOTCH3 mutations of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in China. Med Sci Monit Basic Res. 2019;25:199-209.

Rutten JW et al. Interpretation of NOTCH3 mutations in the diagnosis of CADASIL. Expert Rev Mol Diagn. 2014;14(5):593-603.

Spinicci G et al. Unusual clinical presentations in subjects carrying novel NOTCH3 gene mutations. J Stroke Cerebrovasc Dis. 2013;22(4):539-44.

BACKGROUND INFORMATION: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, CADASIL (NOTCH3), Sequencing

CHARACTERISTICS: CADASIL is a condition characterized predominantly by subcortical ischemic events, including transient ischemic attacks (TIAs) and strokes. Other features of this condition include cognitive defects, dementia, migraines, psychiatric and mood disorders, and epilepsy. Age of onset and clinical presentation are highly variable.

PREVALENCE: 2-4 in 100,000; penetrance may be variable.

INHERITANCE: Autosomal dominant.

CAUSE: Pathogenic variants in the NOTCH3 gene.

CLINICAL SENSITIVITY: 95 percent.

GENE TESTED: NOTCH3 (NM_000435)
Exon 1 is not covered by sequencing.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted gene, followed by massively parallel sequencing. Sanger sequencing performed as necessary to fill in

regions of low coverage and confirm reported variants.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected by massively parallel sequencing, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of CADASIL. This test only detects variants within the coding regions and intron-exon boundaries of the specific gene. Regulatory region variants and deep intronic variants will not be identified. 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 in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
NOTCH3 (NM_000435) exon(s) 1

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
CADASIL (NOTCH3) Specimen	22-054-102869	2/23/2022 10:16:00 AM	2/23/2022 10:17:24 AM	2/23/2022 12:13:00 PM
CADASIL (NOTCH3) Interp	22-054-102869	2/23/2022 10:16:00 AM	2/23/2022 10:17:24 AM	2/23/2022 12:13:00 PM

END OF CHART

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