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

Physician: Doctor, Example

Patient: Patient, Example

DOB	1/8/1975
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

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_000435.3)
Nucleic Acid Change: c.3016C>T; Heterozygous
Amino Acid Alteration: p.Arg1006Cys
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.3016C>T; p.Arg1006Cys, 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.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification: The NOTCH3 c.3016C>T; p.Arg1006Cys variant (rs1555727942) is reported in the literature in several individuals affected with CADASIL (Cappelli 2009, Gonzalez 2020, Hu 2021, Joutel 1997, Ni 2022). This variant is also reported in ClinVar (Variation ID: 447823), but is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. Computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.569). However, 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 this variant is consistent with the predominant mechanism of disease in NOTCH3. 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 NOTCH3 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. 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
Cappelli A et al. High recurrence of the R1006C NOTCH3 mutation in central Italian patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Neurosci Lett. 2009 Sep 22;462(2):176-8. PMID: 19576955.

Gonzalez F et al. Non-convulsive status epilepticus as the initial manifestation in a family with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Neurologia (Engl Ed). 2020 Oct 2:S0213-4853(20)30214-0. English, Spanish. PMID: 33020014.

Hu Y et al. NOTCH3 Variants and Genotype-Phenotype Features in Chinese CADASIL Patients. Front Genet. 2021 Jul 15;12:705284. PMID: 34335700.

Joutel A et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. Lancet. 1997 Nov 22;350(9090):1511-5. PMID: 9388399.

Ni W et al. Genetic spectrum of NOTCH3 and clinical phenotype of CADASIL patients in different populations. CNS Neurosci Ther. 2022 Nov;28(11):1779-1789. PMID: 35822697.

Rutten JW et al. Interpretation of NOTCH3 mutations in the diagnosis of CADASIL. Expert Rev Mol Diagn. 2014 Jun;14(5):593-603. PMID: 24844136.

This result has been reviewed and approved by [redacted]

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

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	23-297-402571	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
CADASIL (NOTCH3) Interp	23-297-402571	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