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

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a condition in which reduced cerebral blood flow leads to the degeneration of vascular smooth muscle, causing neurologic and psychiatric impairment. It is primarily characterized by subcortical ischemic events, such as transient ischemic attacks (TIAs) and strokes. Age of onset and clinical presentation are highly variable, and symptoms may present from the third to the eighth decade of life. This condition is progressive and there is currently no known effective treatment. Pathogenic variants in the *NOTCH3* gene are causative for CADASIL.

## Featured ARUP Testing

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, CADASIL (NOTCH3), Sequencing 3004383

**Method:** Massively Parallel Sequencing

- Preferred test for genetic confirmation of a clinical diagnosis of CADASIL
- Informed consent is required for testing. See ARUP Genetics Consent Forms.
- Testing of asymptomatic minors (<18 years of age) is not available at ARUP.
- If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

## Disease Overview

### Common Clinical Features

- Subcortical ischemic events (85% of affected individuals)
  - TIAs
  - Strokes
- Cognitive defects/dementia (75% of affected individuals)
- Migraines (35% of affected individuals)
- Psychiatric disorders (33% of affected individuals)
- Epilepsy (10% of affected individuals)

### Diagnostic Criteria

- Clinical signs
- Family history
- Brain imaging
  - White matter hyperintensities first appear in anterior temporal lobes
    - May be visible by magnetic resonance imaging (MRI) as early as 21 years of age
  - Cerebral microbleeds may be detected by echo imaging
- Skin biopsy
  - Immunohistochemistry demonstrating a positive *NOTCH3* staining of the vessel wall
  - Electron microscopy showing granular osmophilic material within vascular media close to vascular smooth muscle cells

### Prevalence

2-4/100,000

## Genetics

### Gene

*NOTCH3* (NM_000435)

### Inheritance

Autosomal dominant

## Penetrance

Pathogenic variants in epidermal growth factor (EGF)-like domains 1-6 are generally 100%, with variable expressivity and age of onset; pathogenic variants in EGF-like domains 7-34 exhibit variable penetrance and expressivity.

## De novo Variants

Rare

# Test Interpretation

## Clinical Sensitivity

95%

## Analytical Sensitivity

For massively parallel sequencing:

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) | Analytical Sensitivity (PPA) 95% Credibility Region[a] (%) |
|---|---|---|
| SNVs | >99 | 96.9-99.4 |
| Deletions 1-10 bp | 93.8 | 84.3-98.2 |
| Deletions 11-44 bp | >99 | 87.8-100 |
| Insertions 1-10 bp | 94.8 | 86.8-98.5 |
| Insertions 11-23 bp | >99 | 62.1-100 |

[a]The gene included on this test is a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

## Results

| Results as Reported in Patient Chart | Variant(s) Detected | Clinical Significance |
|---|---|---|
| Positive | One pathogenic or likely pathogenic variant detected | Confirms or predicts a diagnosis of CADASIL |
| See note | One variant of uncertain significance detected | Unknown if variant is disease causing or benign |
| Negative | No pathogenic variants detected | Diagnosis of CADASIL unlikely, though not excluded |

## Limitations

- Diagnostic errors may occur due to rare sequences.
- Large deletions and duplications are not detected.
- Deep intronic and promoter variants will not be detected.
- A negative result does not exclude a diagnosis of CADASIL.
- The following regions are not sequenced due to technical limitations of the assay: *NOTCH3* (NM_000435) exon(s) 1.