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

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.

Tests to Consider

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.

Related Tests

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

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.

Additional Resources

Dichgans M, Herzog J, Gasser T. NOTCH3 mutation involving three cysteine residues in a family with typical CADASIL. *Neurology*. 2001;57(9):1714-1717.

Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol*. 1998;44(5):731-739.

Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. *Neurology*. 2002;59(8):1134-1138.

Opherk C, Peters N, Herzog J, et al. Long-term prognosis and causes of death in CADASIL: a retrospective study in 411 patients. *Brain*. 2004;127(Pt 11):2533-2539.

Peters N, Opherk C, Bergmann T, et al. Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. *Arch Neurol*. 2005;62(7):1091-1094.

Rutten JW, Dauwerse HG, Gravesteijn G, et al. Archetypal *NOTCH3* mutations frequent in public exome: implications for CADASIL. Ann Clin Transl Neurol. 2016;3(11):844-853.

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