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

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by pathogenic variants in the *NOTCH3* gene. This condition is primarily characterized by subcortical ischemic events, such as transient ischemic attacks (TIAs) and strokes. Individuals with CADASIL may also present with cognitive impairment and dementia, migraines, psychiatric and mood disorders, and epilepsy. Age of onset and clinical presentation are highly variable.

Disease Overview

Prevalence

2-4/100,000

Age of Onset

Variable and age dependent; symptoms may present from the 3rd-8th decade

Symptoms

- 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)

Prognosis

- CADASIL is a progressive disease with no known effective treatment
- Disease progression is more rapid in males than females
- Median age for loss of ambulation is 60 years
- Median age of death is 68 years

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

Pathophysiology

Reduced cerebral blood flow leads to degeneration of vascular smooth muscle and neurological and psychiatric impairment.

Tests to Consider

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, CADASIL (NOTCH3), Sequencing 3000531

Method: Polymerase Chain Reaction/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

Genetics

Gene

NOTCH3

Inheritance

Autosomal dominant

Penetrance

100%, with variable expressivity and age of onset

De novo Variants

Rare

Variants

>300 pathogenic variants identified; the majority are missense

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: 95%[,]
- Analytical sensitivity: 99%

Results

- Positive
  - One copy of a pathogenic *NOTCH3* gene variant detected predicts a diagnosis of CADASIL
- Negative
  - No pathogenic *NOTCH3* gene variant detected; CADASIL diagnosis unlikely, but not excluded
- Inconclusive
  - *NOTCH3* gene variant of uncertain significance detected; whether variant is benign or pathogenic is unknown

Limitations

- Diagnostic errors may occur due to rare sequence variations
- Large deletions and duplications are not detected
- Deep intronic and promoter variants will not be detected

References

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5. 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. PubMed

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