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

Indications for Ordering

- Confirm diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Determine whether at-risk relatives have a pathogenic *NOTCH3* gene variant

Test Description

Bidirectional sequencing of *NOTCH3* gene coding regions and intron/exon boundaries

Tests to Consider

Primary test

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

- 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 test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

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)
  - Transient ischemic attacks (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
- 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
- Brain imaging
  - White matter hyperintensities first appear in anterior temporal lobes
  - May be visible by magnetic resonance imaging (MRI) as early as 21 years
  - Cerebral microbleeds may be detected by echo imaging

Pathophysiology

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

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% (Markus, 2002; Peters, 2005)
- 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

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