Early-Onset Alzheimer's Panel, Sequencing

Alzheimer's disease (AD) is characterized by progressive memory loss leading to dementia. Up to 25% of AD may be hereditary. Less than 2% of cases are the early-onset familial form, defined as a diagnosis of AD before age 65, while 15-25% of cases are a late-onset familial form. Although symptoms of familial early-onset AD are similar to late-onset (sporadic AD), there is a greatly increased chance of identifying a genetic etiology with early-onset AD. Diagnosis of AD requires autopsy or a molecular genetic confirmation.

Disease Overview

Symptoms of Early-Onset AD

Symptom onset typically occurs between 30 and 60 years of age. Duration of disease is ~8-10 years.

- Progressive dementia beginning as subtle failure of memory (mild cognitive impairment)
- Confusion
- Poor judgment
- Loss of language skills
- Agitation
- Depression and withdrawal
- Hallucination
- Occasionally: seizures, Parkinson-like movements, hypertonia, and other movement disorders

Prevalence

Less than 2% of individuals with a diagnosis of AD have the early-onset familial form diagnosed before age 65.[1]

Etiology

Pathogenic variants in the *APP*, *PSEN1*, and *PSEN2* genes

Inheritance

Autosomal dominant

Genotype-Phenotype Correlation

PSEN2 has been shown to have reduced penetrance.[2]

Test Description

See Genes Tested table for genes included in this panel.

Tests to Consider

Early-Onset Alzheimer's Panel, Sequencing 3001585

Method: Massively Parallel Sequencing

- Confirm diagnosis of early-onset AD in symptomatic individuals
- Perform presymptomatic testing in individuals with a family history of early-onset AD
- Contraindications for ordering:
  - Test should not be ordered in individuals whose symptoms developed later than age 65

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial sequence variant previously identified in a family member
- A copy of family member's test result documenting the known familial variant is required

Related Tests

Apolipoprotein E (APOE) Genotyping, Alzheimer Disease Risk 2013341

Method: Polymerase Chain Reaction/Fluorescence Monitoring

- Recommended test to support to a clinical diagnosis of late-onset, familial AD in symptomatic individuals
- Pretest genetic counseling and informed consent are recommended in as well as posttest discussion of results
- NOT recommended for predicting risk for AD in asymptomatic individuals

Clinical Sensitivity

This test will identify a cause for familial early-onset AD in approximately 60-80% of cases. Clinical sensitivity is inversely related to age of onset.[3]

Familial early-onset AD is due to pathogenic variants in the following genes:

- *PSEN1* (20-70%)
- *APP* (10-15%)
- *PSEN2* (5%)
- Unknown (20-40%)[4]

Limitations

- A negative result does not exclude a heritable form of early-onset Alzheimer's disease.
- This assay only detects variants within the coding regions and intron-exon boundaries of the targeted genes.
- Regulatory region variants and deep intronic variants will not be identified. Non-coding transcripts will not be analyzed.
- Deletions/duplications/insertions of any size may not be detected by massive 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 and 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 allogeneic stem cell transplantation.
- The following regions are not sequenced due to technical limitations of the assay: APP (NM_001136016.3) exon 1

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are 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

Testing Strategy

Genes Tested			
Gene	MIM Number	Disorder and Subtype (Abbreviation)	Inheritance
APP	104300	Familial Alzheimer disease 1	AD
PSEN1	607822	Alzheimer disease, type 3	AD

Gene	MIM Number	Disorder and Subtype (Abbreviation)	Inheritance
PSEN2	606889	Alzheimer disease-4	AD

References

1. Knopman DS, Petersen RC, Cha RH, et al. Incidence and causes of nondegenerative nonvascular dementia: a population-based study. Arch Neurol. 2006; 63 (2): 218-21. PubMed

2. Jayadev S, Leverenz JB, Steinbart E, et al. Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. Brain. 2010; 133 (Pt 4): 1143-54. PubMed

3. Schellenberg GD, Montine TJ. The genetics and neuropathology of Alzheimer's disease. Acta Neuropathol. 2012; 124 (3): 305-23. PubMed

4. Pasanen P, Myllykangas L, Pöyhönen M, et al. Genetics of dementia in a Finnish cohort. Eur J Hum Genet. 2018; 26 (6): 827-837. PubMed

Related Information

Early-Onset Alzheimer Disease

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