

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB: Unknown
Gender: Unknown
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 00/00/0000 00:00

Early-Onset Alzheimer's Panel, Sequencing

ARUP test code 3001585

Alzheimer's Specimen

whole Blood

Alzheimer's Interp

Positive

INDICATION FOR TESTING
Early-onset dementia.

RESULT

One pathogenic variant was detected in the PSEN1 gene.

PATHOGENIC VARIANT

Gene: PSEN1 (NM_000021.4)
Nucleic Acid Change: c.488A>G; Heterozygous
Amino Acid Alteration: p.His163Arg
Inheritance: Autosomal Dominant

INTERPRETATION

One pathogenic variant, c.488A>G; p.His163Arg, was detected in the PSEN1 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic variants in PSEN1 are associated with autosomal dominant Alzheimers disease type 3 (MIM: 607822). This result is consistent with a diagnosis of early onset Alzheimers disease. This individuals offspring have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:

The PSEN1 c.488A>G; p.His163Arg variant (rs63750590) is reported in the literature segregating with disease in multiple families affected with early-onset Alzheimers disease (see link to Alzforum database and references therein). This variant is reported in ClinVar (Variation ID: 18124), and is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. The histidine at codon 163 is highly conserved, and computational analyses (SIFT: tolerated, PolyPhen-2: possibly damaging) predict conflicting effects of this variant on protein structure/function. In vitro functional analyses demonstrate an increase in beta-amyloid peptide secretion and changes to cellular calcium homeostasis, among other cellular defects (Bojarski 2009, Citron 1997, Sun 2018). Additionally, other variants at this codon (c.487C>T; p.His163Tyr, c.488A>C; p.His163Pro) have been reported in individuals with early-onset Alzheimers disease (Kim 2012, Thordardottir 2018). Based on available information, the p.His163Arg variant is considered to

H=High, L=Low, *=Abnormal, C=Critical

be pathogenic.

RECOMMENDATIONS

Genetic and neurological consultations are indicated, including a discussion of medical screening and management. At risk family members may consider testing for the identified pathogenic PSEN1 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS

Likely benign and benign variants are not included in this report, but are available upon request.

REFERENCES

Link to Alzforum database for H163R:
<https://www.alzforum.org/mutations/psen1-h163r>

Bojarski L et al. Presenilin-dependent expression of STIM proteins and dysregulation of capacitative Ca²⁺ entry in familial Alzheimer's disease. *Biochim Biophys Acta*. 2009 Jun;1793(6):1050-7.

Citron M et al. Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice. *Nat Med*. 1997 Jan;3(1):67-72.

Kim J et al. A novel PSEN1 H163P mutation in a patient with early-onset Alzheimer's disease: clinical, neuroimaging, and neuropathological findings. *Neurosci Lett*. 2012 Nov 21;530(2):109-14.

Sun L et al. Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of Abeta42 and Abeta40 peptides by gamma-secretase. *Proc Natl Acad Sci U S A*. 2017 Jan 24;114(4):E476-E485.

Thordardottir S et al. Reduced penetrance of the PSEN1 H163Y autosomal dominant Alzheimer mutation: a 22-year follow-up study. *Alzheimers Res Ther*. 2018 May 10;10(1):45.

This result has been reviewed and approved by Hunter Best, Ph.D.

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BACKGROUND INFORMATION: Early-Onset Alzheimer's Panel, Sequencing

CHARACTERISTICS: Alzheimer's disease (AD) is characterized by progressive memory loss leading to dementia. Up to 25 percent of AD may be hereditary. Less than 2 percent is the early-onset familial form defined as a diagnosis of AD before age 65, while 15-25 percent is 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.

EPIDEMIOLOGY: Nearly 6 million individuals in the U. S. are affected with AD; approximately 200,000 are <65 yrs.

CAUSE: Pathogenic germline APP, PSEN1 and PSEN2 gene variants are causative of early-onset AD.

INHERITANCE: Autosomal dominant.

PENETRANCE: PSEN2 has reduced penetrance.

CLINICAL SENSITIVITY: 60-80 percent for familial early-onset AD.

GENES TESTED: APP*, PSEN1, PSEN2

*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of sequencing is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of early onset AD. This test 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. 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, 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 an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

The following region is not sequenced due to technical limitations of the assay:

APP (NM_001136016.3) exon 1

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Alzheimer's Specimen	19-309-104003	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Alzheimer's Interp	19-309-104003	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical