| Procedure | Result | Units | Ref Interval | Accession | Collected | Received | Reported/ Verified |
|---|---|---|---|---|---|---|---|
| Alzheimer's Specimen | Whole Blood | | | 19-309-104003 | 05-Nov-19 09:53:00 | 05-Nov-19 09:53:00 | 06-Nov-19 09:07:48 |
| Alzheimer's Interp | Positive  f | | | 19-309-104003 | 05-Nov-19 09:53:00 | 05-Nov-19 09:53:00 | 06-Nov-19 09:07:48 |

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05-Nov-19 09:53:00   Alzheimer's Interp:
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
Alzheimer's disease type 3 (MIM: 607822). This result is consistent with a diagnosis of early onset Alzheimer's
disease. This individual's 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 Alzheimer's 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 Alzheimer's
disease (Kim 2012, Thordardottir 2018). Based on available information, the p.His163Arg variant is considered to
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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 05-Nov-19 09:53:00  Alzheimer's Interp:

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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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