CYGENEX
A precision medicine solutions company

Patient Information: Accession: Physician: Laboratory:

Draft Report

TEST PERFORMED

Parkinson-Alzheimer-Dementia - 35 Genes
(35 Gene Panel; gene sequencing with deletion and duplication analysis)

RESULTS:

A heterozygous pathogenic variant consistent with a molecular diagnosis of a *PSEN1*-related condition was identified.

Clinically significant Variants

Gene Info		Variant Info		
GENE	INHERITANCE	VARIANT	ZYGOSITY	CLASSIFICATION
PSEN1 NM_000021.3	Autosomal Dominant	c.617G>C p.Gly206Ala	Heterozygous	**Pathogenic**

Additional Variants of Potential Clinical Relevance
None

INTERPRETATION:

Notes and Recommendations:

- This analysis included Repeat Expansion analysis of the C9orf72 gene, performed by repeat-primed PCR (rpPCR) and amplicon length analysis. The results for this individual's alleles are within the normal range.
- Children, siblings, and each parent of this individual are at risk of harboring the pathogenic variant reported. Testing of at risk family members for this variant is available.
- Gene specific notes and limitations may be present. See below.
- These results should be interpreted in the context of this individuals clinical findings, biochemical profile, and family history.
- Genetic counseling is recommended. Contact your physician about the available options for genetic counseling.

About *PSEN1*

Autosomal dominant mutations in PSEN1 have been associated with early-onset familial Alzheimer disease (AD3), frontotemporal dementia with or without parkinsonism, spastic paraparesis (SP), Pick disease, dilated cardiomyopathy, familial acne inversa (ACNINV3) (PubMed: 20301340, 27614114, 0301414, 20301486; OMIM: 104311).

The gene product of the *PSEN1* gene is a protein called Presenilin 1. See OMIM gene entry for *PSEN1* (OMIM: 104311) for further information.

PSEN1 NM_000021.3:c.617G>C (p.Gly206Ala)

Classification: **Pathogenic**

Zygosity and Inheritance

- This heterozygous Pathogenic variant is consistent with autosomal dominant inheritance of a *PSEN1*-related condition.

Variant Type

- Genomic change: Chr14(GRCh37):g.73659420G>C.
- This variant is in the dbSNP database: rs63750082
- This variant is predicted to result in a single amino acid substitution (missense) of **Gly** to **Ala** at codon 206 in exon 7 of the *PSEN1* gene.

Variant in Cases

- This variant, p.Gly206Ala, has been previously reported in multiple patients and families with early-onset familial Alzheimer disease and dementia (PubMed: 11710891, 23114514).
- This variant is classified as a "Disease Mutation" (DM) in the Human Gene Mutation Database (HGMD).
- This variant has one or more entries in ClinVar: RCV000518563.1, RCV000640609.2, RCV000019773.28

Variant in Controls

- This variant has been observed at a frequency of less than 0.01% (3/282886 alleles).
- The highest allele frequency at which this variant has been observed at in any sub-population with available data is 0.01% in the Other population.
- There are no homozygous control individuals for this variant.
- The Broad Institute gnomAD database (>120,000 Individuals with no known severe, pediatric onset disease) was used for this analysis.

Other Variant Information

- Analysis of amino acid conservation indicates that the wild-type amino acid Gly is completely conserved across vertebrate species, suggesting that a change at this position may not be tolerated and could adversely affect the structure and/or function of the protein.
- Amino acid conservation data:
  - Primates: 11 out of 11 match the wild type.
  - Mammals: 60 out of 60 match the wild type.
  - Vertebrates: 98 out of 98 match the wild type.
- The physiochemical difference between Gly and Ala as measured by Grantham's Distance is 60. This score is considered a "moderate" change. (PubMed: 4843792, 6442359).
- Computational predictions for p.Gly206Ala (2P/0B AGVGD, SIFT/).

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GENES TESTED:

Parkinson-Alzheimer-Dementia - 35 Genes

35 genes tested (99.44% at >20x).

APOE, APP, ATP13A2, ATP1A3, C9orf72, CSF1R, DCTN1, DNMT1, EIF4G1, FBXO7, GBA, GCH1, GRN, HTRA2, LRRK2, MAPT, NOTCH3, PARK7, PINK1, PLA2G6, POLG, PRKN, PRKRA, PRNP, PSEN1, PSEN2, SLC6A3, SNCA, SNCB, TAF1, TH, TREM2, TYROBP, UCHL1, VPS35

Gene Specific Notes and Limitations

APOE

The *APOE* gene was tested for this individual. The E4/E4 or E3/E4 genotypes associated with Alzheimer's disease risk may not be reported if deemed not clinically relevant based on patient age, medical history, and/or panel ordered. NOTE: this limitation does not apply to panels specific for Alzheimer and/or dementia (e.g. Parkinson-Alzheimer-Dementia Panel).

GBA

Significant pseudogene interference and/or reciprocal exchanges between the GBA gene and its pseudogene, GBAP1, have been known to occur and may impact results. As such, the relevance of variants reported in this gene must be interpreted clinically in the context of this individual's clinical findings, biochemical profile, and family history. The current testing method cannot detect copy-neutral rearrangements between the pseudogene and the functional gene, which have been reported in very rare cases of Gaucher disease (PubMed: 21704274).

PRKRA

Due to pseudogene interference, deletion/duplication analysis will not be performed for this gene.

PRNP

Unless otherwise specified, analysis of octapeptide region insertions are not evaluated. PCR amplification and fragmentation of the octapeptide region of PRNP is expected to be a reliable method for detecting insertions in this region similar to those that have been previously published (PubMed: 12023426, 15258222). Insertions larger than those previously reported and more complex rearrangements are not evaluated and cannot be excluded.

TAF1

The present analysis is not designed to detect the SVA retrotransposon insertion in this gene (PubMed: 20301662).

METHODS:

Genomic DNA was isolated from the submitted specimen indicated above (if cellular material was submitted). DNA was barcoded, and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing technology. Following alignment to the human genome reference sequence (assembly GRCh37), variants were detected in regions of at least 10x coverage. For this specimen, 99.59% and 99.44% of coding regions and splicing junctions of genes listed had been sequenced with coverage of at least 10x and 20x, respectively, by NGS or by Sanger sequencing. The remaining regions did not have 10x coverage, and were not evaluated. Variants were interpreted manually using locus specific databases, literature searches, and other molecular biological principles. To minimize false positive results, any variants that do not meet internal quality standards are confirmed by Sanger sequencing. Variants classified as pathogenic, likely pathogenic, unknown significance, or risk allele which are located in the coding regions and nearby intronic regions (+/- 20bp) of the genes listed above are reported. Variants outside these intervals may be reported but are typically not guaranteed. When a single pathogenic or likely pathogenic variant is identified in a clinically relevant gene with autosomal recessive inheritance, the laboratory will attempt to ensure 100% coverage of coding sequences either through NGS or Sanger sequencing technologies ("fill-in"). All genes listed were evaluated for large deletions and/or duplications. However, single exon deletions or duplications will not be detected in this assay, nor will copy number alterations in regions of genes with significant pseudogenes. Putative deletions or duplications identified by NGS are confirmed by an orthogonal method (qPCR or MLPA), unless exceeding an internally specified and validated quality score, beyond which deletions and duplications are considered real without further confirmation. New York patients: diagnostic findings are confirmed by Sanger, MLPA, or qPCR; exception SNV variants in genes for which confirmation of

NGS results has been performed >=10 times may not be confirmed if identified with high quality by NGS. Bioinformatics: The Fulgent Germline v2019.2 pipeline was used to analyze this specimen.

LIMITATIONS:

These test results and variant interpretation are based on the proper identification of the submitted specimen, accuracy of any stated familial relationships, and use of the correct human reference sequences at the queried loci. In very rare instances, errors may result due to mix-up or co-mingling of specimens. Positive results do not imply that there are no other contributors, genetic or otherwise, to this individual's phenotype, and negative results do not rule out a genetic cause for the indication for testing. Official gene names change over time. Fulgent uses the most up to date gene names based on HUGO Gene Nomenclature Committee (https://www.genenames.org) recommendations. If the gene name on report does not match that of ordered gene, please contact the laboratory and details can be provided. Result interpretation is based on the available clinical and family history information for this individual, collected published information, and Alamut annotation available at the time of reporting. This assay is designed and validated for detection of germline variants only. It is not designed or validated for the detection of low-level mosaicism or somatic mutations. This assay will not detect certain types of genomic aberrations such as translocations, inversions, or repeat expansions (eg. trinucleotide or hexanucleotide repeat expansion). DNA alterations in regulatory regions or deep intronic regions (greater than 20bp from an exon) may not be detected by this test. Unless otherwise indicated, no additional assays have been performed to evaluate genetic changes in this specimen. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions. Our laboratory uses a sensitive detection algorithm, however these types of alterations are not detected as reliably as single nucleotide variants. Rarely, due to systematic chemical, computational, or human error, DNA variants may be missed. Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the confounding contribution of pseudogene sequences or other highly-homologous sequences, sometimes these may still interfere with the technical ability of the assay to identify pathogenic alterations in both sequencing and deletion/duplication analyses. Deletion/duplication analysis can identify alterations of genomic regions which are two or more contiguous exons in size; single exon deletions or duplications may occasionally be identified, but are not routinely detected by this test. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether the predicted product will remain in-frame or not. Unless otherwise indicated, deletion/duplication analysis has not been performed in regions that have been sequenced by Sanger.

SIGNATURE:

Example Director, Ph.D., CGMBS, FACMG on
Electronically signed

DISCLAIMER:

This test was developed and its performance characteristics determined by **Fulgent Genetics**. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Since genetic variation, as well as systematic and technical factors, can affect the accuracy of testing, the results of testing should always be interpreted in the context of clinical and familial data. For assistance with interpretation of these results, healthcare professionals may contact us directly at **(626) 350-0537** or **info@fulgentgenetics.com**. It is recommended that patients receive appropriate genetic counseling to explain the implications of the test result, including its residual risks, uncertainties and reproductive or medical options.