Accession ID:	**1347**
Sample Type:	Blood
Patient's Name:	**APD-Sample-test**
Gender/Age:	Male/54 Years

NEUR

ALZHEIMER-PARKINSON DEMENTIA

Data Uploaded On:		**Report Generated On:**	

CLINICAL INDICATIONS / PHENOTYPE:

Dementia

RESULTS:

List of clinically significant mutations (CSM)

GENE	VARIANT	ZYGOSITY	DISEASE	INHERITANCE	INTERPRETATION
GRN (NM_002087.4)	Exon 11 **c.1365del (p.Cys456fs)**	Heterozygous	**Neuronal ceroid lipofuscinosis 11** (OMIM#614706) **Primary progressive aphasia** (OMIM#607485) **GRN-related frontotemporal lobar degeneration with Tdp43 inclusions** (OMIM#607485)	AR, AD	**Uncertain Significance**

***Genetic test results are reported based on the recommendations of American College of Medical Genetics.**
****Sanger validation is recommended for the above listed variants.**
*****The significance/classification of the variant(s) may change based on genetic testing in the parents and other family members.**
******Data revaluation performed upon the up gradation of databases used and results may vary in accordance.**

INTERPRETATION:

GRN;c.1365del(p.Cys456fs)

Genomic location: chr17:44352198 AC>A
Variant type: Loss of function
Depth: total 98; alt 46 (47%)
Inheritance: The variant was identified in the Heterozygous state in the patient.
Frequency: The variant is very rare, absent from the gnomAD reference population dataset.
Prediction tools: Computational tools yield conflicting predictions of the impact of the variant on the gene or gene product.
Clinical evidence: To date, the variant has not been described by reputable sources or in the primary literature.

INCIDENTAL FINDINGS: No variants were identified.

RECOMMENDATIONS:

- Genetic counseling is advised for interpretation on the consequences of the variant(s).
- If results obtained do not match the clinical findings, additional testing should be considered as per referring clinician's recommendation.

METHODOLOGY:

The Genes2Me Alzheimer-Parkinson-Dementia NGS panel was used for sequencing that screens for 101 clinically relevant genes (coding regions of the genome) for diseases associated with genetic mutations. It covers all major mutations like SNV, InDels & CNV adding up to a target size of 392 Kb with hybridization-based target capture technique.

After raw data generation, we follow the GATK best practices framework for identification of variants in the sample, starting with raw data quality check using the FastQC followed by BWA read aligner for mapping/aligning to human reference genome GRCh37. After the alignment, GATK HaplotypeCaller algorithm is used for variant calling. Annotation of the variants is performed using open-source available software SnpEff. Further, clinically relevant mutations are annotated using published variants in literature and set of diseases databases – ClinVar, OMIM and HPO. The 1000Genome, gnomAD, dbSNP and 100K Genome Asia databases are used for annotation of variants for their minor allele frequency. The dbNSFP database is used for annotation and functional prediction of all potential non-synonymous variants.

TECHNICAL INFORMATION:

VARIANT CLASSIFICATION AS PER "ACMG GUIDELINES":

Variant is a permanent change in the sequence of DNA that makes up a gene that could be pathogenic – causing a disease or benign – not causing a disease.

1. Pathogenic Variant
   The variant is responsible for causing disease with ample scientific research to support the disease – gene – variant association. These variants are often referred to as mutations.
2. Likely Pathogenic Variant
   The variant is very likely responsible to contribute to the development of disease with insufficient scientific evidences to prove the association. Additional evidences and testing is expected to confirm this assertion of pathogenicity.
3. Variant of Uncertain Significance
   The variant whose impact is difficult to classify based on current available scientific evidences. Further testing of the patient or family members is recommended.

LIMITATIONS:

- Genetic testing is an important part of the diagnostic process however it may not always give a definitive answer. In some cases, a genetic variant may be missed due to the limitations in existing medical knowledge and testing technology. Accurate interpretation of test results is dependent on the availability of biological & medical information (clinical history) of the family, failing to this may leads to incorrect result interpretation and diagnosis.
- Test results are interpreted in the context of clinical findings, available scientific evidences, family history and other laboratory data. The variation(s) which is/are potentially relevant – significant related to the patient's provided medical history is/are reported.
- Genetic testing is highly accurate but rarely inaccurate results may occur for various reasons like mislabeling of samples, inaccurate clinical/medical family history, rare technical errors or unusual

circumstances such as bone marrow transplantation, blood transfusion or the presence of change(s) in such a small percentage of cells that may not be detectable (mosaicism).

DISCLAIMER:

- The interpretation of variants in this report is performed to the best knowledge of the scientific & medical information available at the time of reporting. The classification of variants is based on ACMG (American College of Medical Guidelines) guidelines. The re-analysis of sample data in light of new evidence is not routinely performed but can be done upon request.
- As of the inherent technological limitations of the sequencing assay, some of the coding regions can't be properly sequenced, so, variations in these regions may not be identified & interpreted. It is possible that variants not identified by the assay may be associated with the provided phenotypes of the patient.
- It is possible due to insufficient phenotypic information, a gene – variant may be present in data but not selected for analysis and interpretation.
- The mutations have not been confirmed by Sanger sequencing.
- The incidental or secondary findings (if any) that meet the ACMG guidelines can be given upon request.
- The report shall be generated within a specified TAT (Turn Around Time), however, it may vary, depending upon the complexity of test(s) requested. Genes2Me under no circumstances will be liable for any delay beyond aforementioned TAT.
- Genes2Me clarify that the generated report(s) of the test(s) doesn't provide any kind of diagnosis or opinion or recommendation for any disease and its cure in any manner. It is therefore recommended that the patient and/or the guardian(s) of the patient must take the consultation of the clinician or a certified physician or doctor for further course of
  action.
- If the provided material quality and/or quantity not up to the desired level, further procedures will be completed only after
  getting confirmation from referring clinician/physician only, so, in that case, test(s) result(s) may be misleading or even wrong,
  therefore, Genes2Me hereby disclaims all liability arising in this connection with the test(s) and report(s).
- This is a laboratory developed test and the development and the performance characteristics of this test are determined by Genes2Me only.

REFERENCES:

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***For any further technical queries please contact at contact@genes2me.com**