

Neuro Disease Risk Panel

Patient		Specimen		Ordering Physician	
First Name:	XXXXXXX	Specimen Type:	Buccal Swab	Physician:	XXXXXXXXXXXX
Last name:	XXXXXXXX	Collection Date:	XX-XX-XXXX	Institution:	XXXXXXXXXXXX
Date of Birth:	XX-XX-XXXX	Received Date:	XX-XX-XXXX	Reported Date:	XX-XX-XXXX
Gender:	XXXXXX	Panel Coverage :	88%	Ref Accession:	N/A
Accession ID:	XXXXXXXXXXXX	Average Read Depth:	21x%		



Test Result:

+ Positive : For Likely Pathogenic Variant on PRKRA gene.

Gene & Transcript	Variant	Inheritance	Disorder or Phenotype	Criteria	Classification
PRKRA NM_003690.5	c.515-2_515-1ins(57)	Autosomal Recessive / Heterozygous	Dystonia 16	PM2, PVS1	Likely Pathogenic

Location	Allele State	Allelic Read Depths
Exon 6	Heterozygous	Ref(-): 34, Alt(AGTTTCCATAAATGACTCTAGCCTGCAAATTGTAGTATATTCTCTCT ATGAGCAGG): 5, VAF: 12.82%

Genomic Position	Variant Frequency
Chr2:NC_000002.11:g.179306432_179306433insAGTTTCCATAAATGACTCTAGCCTGCAAATTGTAGTATATTCTCTCTTATGAGCAGG	Not identified in large population studies

Patient

Name : XXXXXXXXXXXX

Date of Birth: XX-XX-XXXX

Accession : XXXXXXXXXXXX

Gene info



PRKRA NM_003690.5

Variant Info



The Variant is found at
 Chr2:NC_000002.11:g.179306432_179306433insAGTTTCCATAAATGACTCTAGCCTGC
 AAATTGTAGTATATTCTCTTATGAGCAGG location with a splice acceptor variant
 c.515-2_515-1ins(57) change on the patient's PRKRA

Variant interpretation



The splice acceptor variant NM_003690.5(PRKRA):c.515-2_515-1ins(57) has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. The c.515-2_515-1ins(57) variant is novel (not in any individuals) in gnomAD All. The c.515-2_515-1ins(57) variant is novel (not in any individuals) in 1kG All. This variant mutates a splice-acceptor sequence and is predicted to disrupt the reading frame, resulting in nonsense mediated decay. This variant results in the loss of an acceptor splice site for the clinically relevant transcript. This variant disrupts the acceptor splice site for an exon upstream from the last coding exon resulting in a frameshift mutation that is predicted to cause nonsense mediated decay. For these reasons, this variant has been classified as Likely Pathogenic.

Inheritance



Autosomal Recessive / Heterozygous

ACMG-Classification

 Likely Pathogenic
(PM2, PVS1)

Gene & Disorder or Phenotype

Dystonia 16

What's next



Correlate the findings with clinical symptoms, biochemical profile and family history whilst closely monitoring the subject with periodical visits. Genetic counseling is recommended.

Patient

Name : XXXXXXXXXXXX

Date of Birth: XX-XX-XXXX

Accession : XXXXXXXXXXXX

Test Methodology

Neuro Disease Risk Factor Screening 118 gene panel screening performed at Elite Clinical Laboratory utilizes Next-Generation Sequencing technology using Nextera Flex chemistry on the Illumina MiniSeq and NextSeq platforms. Genomic DNA is extracted from Buccal swabs (Dry and Wet) are tagged and enriched for regions of interest using probes specific for each region specified in the BED (Browser Extensible Data) file. Positive (www.coriell.org) and Negative controls are included with each machine run to ensure the accuracy of amplicon preparation alongside targeted sequencing on coding regions and intronic/exonic boundaries of interest and precise finding of the variant on the positive control and negative control respectively. Exclusions from analysis are listed below. Sequences obtained are then aligned against a human reference genome and variants such as SNVs (Small Nucleotide Variants) and Indels (Insertions and Deletions) are noted. For a detailed list of regions covered and comprehensive statistics by Elite Clinical Laboratory Neuro Degenerative Disease screen, please contact .

Computational analysis and variant calling is performed by ipseity (www.ipseity.com). Briefly, reads from the sequence output were aligned to the human reference genome (GRCh37) using the Burrows-Wheeler Aligner (BWA). Variants to the reference were called using the Genomic Analysis Tool Kit (GATK). The variants were annotated and filtered using the Elite Clinical Laboratory' analysis work flow implementing the ACMG guidelines for interpretation of sequence variants. This includes comparison against the gnomAD population catalog of variants in 123,136 exomes, the 1000 Genomes Project Consortium's publication of 2,500 genomes, the NCBI-ClinVar database of clinical assertions on variant's pathogenicity and multiple lines of computational evidence on conservation and functional impact. The following databases and insilico algorithms are used to annotate and evaluate the impact of the variant in the context of human disease: 1000 genomes, gnomAD, ClinVar, OMIM, dbSNP, NCIB Ref Seq Genes, ExAC Gene Constraints, VS-SIFT, VS PolyPhen2, PhyloP, GERP+, GeneSplicer, Max EntScan, NNSplice, PWM Splice Predictor. Analysis was reported using the HGVS nomenclature (www.hgvs.org/mutnomen) as implemented by custom transcript annotation algorithm. Only variants with an end ACMG classification of "Pathogenic" or "Likely Pathogenic" are reported and VUS/Benign/Likely Benign variants are not reported. Classification of pathogenicity is consistently updated by the National Institutes of Health and the information found within this report is consistent with the current knowledge base as the knowledge base changes, so may clinical interpretation of variants. All reports are reviewed prior to release by either Elite Clinical Laboratory's Technical Supervisor or the General Supervisor.

Genes Evaluated

APP, PSEN1, PSEN2, APOE, CLU, PICALM, CR1, BIN1, CD33, MS4A4A, MS4A6E, CD2AP, EPHA1, ABCA7, CASS4, CELF1, FERMT2, INPP5D, MEF2C, NME8, PTK2B, SLC24A4, RIN3, SORL1, ZCWPW1, TREM2, ADAM10, PVRL2, ABI3, PLCG2, CSF1R, TRIP4, TP53INP1, VPS35, SNCA, LRRK2, PRKRA, GBA, RAB39B, TMEM230, RAB7L1, GCH1, VPS13C, PARK2, PINK1, PARK7, ATP13A2, PLA2G6, FBXO7, SYNJ1, DNAJC6, SCARB2, CHCHD2, PANK2, POLG, TAF1, GAK, ADORA1, EIF4G1, ATP6AP2, GIGYF2, TBP, HTRA2, SOD1, TARDBP, OPTN, VCP, FUS, PFN1, SQSTM1, UBQLN2, CHMP2B, ANG, NEFH, TBK1, NEK1, CHCHD10, TUBA4A, UNC13A, SARM1, C21orf2, EPHA4, LMNB1, SPAST, DCTN1, FIG4, SETX, HNRNPA1, HNRNPA2B1, VAPB, ALS2, MAPT, GRN, TMEM106B, RAB38, CTSC, BTNL2, TOMM40, CLCN6, MARK2, MARK4, EP300, AKT1, SGTA, ELAVL1, TOR1A, THAP1, APTX, ATM, PRRT2, ANO3, TH, ATP1A3, DNMT1, ITM2B, NOTCH3, PRNP, TYROBP

Test Limitations

Rare diagnostics errors may occur if these mutations occur within the priming sequencing regions. Presence of a pathogenic/likely pathogenic variant does not guarantee that an individual will develop a Neuro Degenerative Disease, nor is the absence of such variants a guarantee that an individual will not develop a 'Neuro Degenerative Disease'. The results of this screen are meant strictly to guide a physician in the management of their patient's health. Any Likely pathogenic or Pathogenic variants detected in the report should be clinically correlated (As per Physicians Advice) and confirmed via the orthogonal testing platforms (Sanger Sequencing or PCR based tests).

Patient

Name : XXXXXXXXXXX

Date of Birth: XX-XX-XXXX

Accession : XXXXXXXXXXX

Regulatory Disclosures

Genetic-based hereditary Neuro Degenerative Disease Risk Factor screening is intended as a tool to guide physicians in the management of their patients and should NOT be treated as a diagnostic tool. NGS-based hereditary Neuro Degenerative Disease screening is considered a high-complexity laboratory-developed test (LDT) by CMS under the Clinical Laboratory Improvement Amendment (CLIA) and is not FDA-cleared. The test and performance metrics were validated in house by Elite Clinical Laboratory technical personnel (or designated scientific advisors) and approved by their Laboratory Director. The results are intended for use only by the ordering physician and/or designated healthcare provider. The ordering provider is responsible for 1) ascertaining the medical necessity of the ordered test, 2) resulting diagnoses, 3) management of the disease and/or decisions based on the data provided. Results rely on collection personnel following specified collection and shipment protocols.

REFERENCES

Richards, Sue, et al. "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." *Genetics in medicine* 17.5 (2015): 405. Exome Aggregation Consortium et al. "Analysis of Protein-Coding Genetic Variation in 60,706 Humans." *Nature* 536.7616 (2016): 285–291. PMC. Web. 13 May 2018. The 1000 Genomes Project Consortium. "A Global Reference for Human Genetic Variation." *Nature* 526.7571 (2015): 68–74. PMC. Web. 13 May 2018.

Testing was performed by Elite Clinical Laboratory 3600 S Gessner Road, Houston, TX, 77063 USA CLIA # 45D1061571. Laboratory Director: Dr Albert Chen MD.