ELITE CLINICAL LABORATORY

Pulmonary Disease Risk Panel

Patient		Specimen		Ordering Physician	
First Name:	XXXXX	Specimen Type:	Buccal Swab	Physician:	XXXXXXXXXXX
Last name:	XXXXXXX	Collection Date:	XX-XX-XXXX	Institution:	XXXXXXXXXXXXXX
Date of Birth:	XX-XX-XXXX	Received Date:	XX-XX-XXXX	Reported Date:	XX-XX-XXX
Gender:	XXXXXX	Panel Coverage :	96.5%	Ref Accession:	N/A
Accession ID:	XXXXXXXXXXX	Average Read Depth:	191x%		

Test Result:

+Positive : For Likely Pathogenic Variant on SCN4A gene.

Gene & Transcript	Variant	Inheritance	Disorder or Phenotype	Criteria	Classification
SCN4A NM_000334.4	c.4484T>C p.Ile1495Thr	Autosomal Dominant / Heterozygous	Unspecified	PM2, PP2, PP3	Likely Pathogenic

Location	Allele State	Allelic Read Depths
Exon 24	Heterozygous	Ref(A): 185, Alt(G): 179, VAF: 49.18%

Genomic Position	Variant Frequency
Chr17:NC_000017.10:g.62019158A>G	Not identified in large population studies

Patient

Name : XXXXXXXXXXXX Date of Birlh: XX-XX-XXXX Accession : XXXXXXXXXX

Gene info 	SCN4A NM_000334.4
Variant Info 	The Variant is found at Chr17:NC_000017.10:g.62019158A>G location with a missense variant c.4484T>C p.Ile1495Thr change on the patient's SCN4A
Variant interpretation 	The missense variant NM_000334.4(SCN4A):c.4484T>C (p.Ile1495Thr) has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. The p.Ile1495Thr variant is novel (not in any individuals) in gnomAD All. The p.Ile1495Thr variant is novel (not in any individuals) in 1kG All. There is a moderate physicochemical difference between isoleucine and threonine. The gene SCN4A has a low rate of benign missense variation as indicated by a high missense variants Z-Score of 1.56. The gene SCN4A contains 76 pathogenic missense variants, indicating that missense variants are a common mechanism of disease in this gene. The p.Ile1495Thr missense variant is predicted to be damaging by both SIFT and PolyPhen2. The isoleucine residue at codon 1495 of SCN4A is conserved in all mammalian species. The nucleotide c.4484 in SCN4A is predicted conserved by GERP++ and PhyloP across 100 vertebrates. For these reasons, this variant has been classified as Uncertain Significance.
Inheritance 	Autosomal Dominant / Heterozygous
ACMG-Classification	Likely Pathogenic (PM2, PP2, PP3)
Gene & Disorder or Phenotype	Unspecified
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 Birlh: XX-XX-XXXX Accession : XXXXXXXXXX

Test Methodology

Pulmonary Risk Factor Screening 68 gene panel screening performed at Elite Clinical Laboratory utilizes Next-Generation Sequencing technology using Nextera Flex chemistry on the IIIumina MiniSeq and NextSeq platforms. Genomic DNA is extracted from Buccal swabs (Dry and Wet) are tagemented 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 Pulmonary Disease screen, please contact .

Computational analysis and variant calling is performed by ipseity (www.ipseitys.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 gnom AD 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 varinats 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

ABCA3, CCDC39, CCDC40, CFTR, CHAT, CHRNA1, CHRNB1, CHRND, CHRNE, COLQ, CSF2RA, CSF2RB, DKC1, DNAAF1, DNAAF2, DNAH1, DNAH5, DNAH11, DNAI1, DNAI2, DNAL1, EDN3, EFEMP2, ELMOD2, ELN, FBLN5, FLCN, FOXF1, GAS8, GLRA1, HPS1, HPS4, ITGA3, LTBP4, MECP2, NAF1, NF1, NKX2-1, NME8, PARN, PHOX2B, PIH1D3, RAPSN, RET, RSPH3, RSPH4A, RSPH9, RTEL1, SCN4A, SCNN1A, SCNN1B, SERPINA1, SFTPA1, SFTPA2, SFTPB, SFTPC, SLC6A5, SLC7A7, SLC34A2, SMAD4, SMPD1, STAT3, TERC, TERT, TINF2, TSC1, TSC2, ZEB2.

Test Limitations

Some variations in these genomic regions may not be reported such as: large genomic rearrangements greater than 50 bp in length, rare (low frequency) mutations, or structural (non-coding) variations. 8 genomic regions were observed to have mean coverage depths that did not meet clinical sufficiency thresholds. These regions are excluded from tertiary analysis and reporting, and include:

chr16:2097989:2098066:TSC2:5'UTRExon(254723602)

chr9:135779797:135779841:TSC1:Exon(254722795)

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 pulmonary disorder, nor is the absence of such varian ts a guarantee that an individual will not develop a pulmonary disorder. The results of this screen are meant strictly to guide a physician in the management of their patient's health.

Patient

Name : XXXXXXXXXXXX Date of Birlh: XX-XX-XXXX Accession : XXXXXXXXXX

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 Pulmonary Disease, nor is the absence of such variants a guarantee that an individual will not develop a Pulmonary 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).

Regulatory Disclosures

Genetic-based hereditary Pulmonary 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 Pulmonary 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 necessi ty 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.