Thyroid Genetics Panel

Patient		Specimen		Ordering Physician	
First Name:	John	Specimen Type:	Buccal Swab	Physician:	Test Doctor
Last name:	Doe	Collection Date:	04-01-2023	Institution:	Test Facility
Date of Birth:	09-31-9999	Received Date:	04-11-2023	Reported Date:	04-18-2023
Gender:	Male	Panel Coverage :	96.48%	Ref Accession:	N/A
Accession ID:	THY04172023	Average Read Depth:	211x		

Test Result:

Pathogenic / Likely Pathogenic variant detected on CST1 gene.

Gene & Transcript	Variant	Inheritance	Disorder or Phenotype	Criteria	Classification
CST1 NM_004993.6	c.916_917insC p.Gly306Alafs*12	Autosomal Dominant / Heterozygous	Machado-Joseph disease type 2	PM2, PVS1	Likely Pathogenic

Location	Allele State	Allelic Read Depths
Exon 10	Heterozygous	Ref(-): 5, Alt(G): 137, VAF: 96.48%

Genomic Position	Variant Frequency
Chr14:NC_000014.8:g.92537353_92537354insG	Not identified in large population studies

Thyroid Genetic Disease Risk Panel

Patient

Name : John Doe | Date of Birth: 09-31-9999 | Accession : THY04172023

Gene info	CST1 NM_004993.6
Variant Info	The Variant is found at Chr14:NC_000014.8:g.92537353_92537354insG location with a frameshift insertion c.916_917insC p.Gly306Alafs*12 change on the patient's CST1.
Variant interpretation	The frameshift insertion NM_004993.6(ATXN3):c.916_917insC (p.Gly306Alafs*12) has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. The p.Gly306Alafs*12 variant is novel (not in any individuals) in gnomAD All. The p.Gly306Alafs*12 variant is novel (not in any individuals) in 1kG All. This variant is predicted to cause loss of normal protein function through protein truncation caused a frameshift mutation. The frame shifted sequence continues 12 residues until a stop codon is reached. This variant is a frameshift variant which occurs in an exon of ATXN3 upstream of where nonsense mediated decay is predicted to occur. For these reasons, this variant has been classified as Likely Pathogenic. Overview: Machado-Joseph disease type 2 is a subtype of Machado-Joseph disease (SCA3/MJD) with intermediate severity characterized by an intermediate age of onset, cerebellar ataxia and external progressive ophthalmoplegia, with variable pyramidal and extrapyramidal signs.
Inheritance	Autosomal Dominant / Heterozygous
ACMG-Classification	Likely Pathogenic (PM2, PVS1)
Gene & Disorder or Phenotype	Machado-Joseph disease type 2
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.

OMNIHEALTH DIAGNOSTICS, LLC
CLIA: 45D2089485 | Address: 1840 N Greenville Ave, Suite 176, Richardson, TX 75081
Lab Director: Dr. Amy Gruszecki | Phone: 972.887.3444 | Fax: 972.887.3443

Thyroid Genetic Disease Risk Panel

Patient

Name : John Doe | Date of Birth: 09-31-9999 | Accession : THY04172023

Test Methodology

Thyroid Genetic Disease Risk Panel screens 46 genes on the Next Generation Sequencing (NGS) technology using the targeted gene enrichment chemistry on the IIlumina® MiniSeq platform. Genomic DNA 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 LLC Thyroid Genetic Disease screen, please contact us on Email: 12345@omnihealthdx.com

Computational analysis and variant calling were performed by Elite Clinical (www.elitelabs.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 LLC 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 LLC‘s Technical Supervisor or the General Supervisor.

Genes Evaluated

ATP1A2, CACNA1A, CST1, CST3, CSTB, CTNNB1, DUOX1, DUOX2, ESR1, FOXE1, G6PD, GLIS3, GNAQ, HAMP, HFE, HRAS, IGSF1, IRAK1, IRS4, IYD, KRAS, MECP2, NKX2-1, NRAS, PAX8, PIK3CA, PLCG2, PLN, PRKCG, SECISBP2, SLC16A2, SLC26A4, SLC40A1, SLC5A5, TBL1X, TFR2, TG, TGFBI, THRA, THRB, TP53, TPO, TRH, TSHB, TSHR, TTR..

Thyroid Genetic Disease Risk Panel

Patient

Name : John Doe | Date of Birth: 09-31-9999 | Accession : THY04172023

Test Limitations

Some Genes/variations for the following 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 and pseudogenes. 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 Thyroid Genetic Disease, nor is the absence of such variants a guarantee that an individual will not develop a 'Thyroid Genetic Disease'. The results of this genetics screening is strictly meant 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 screening for Thyroid Disease predisposition 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 Thyroid Genetic 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 LLC 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.