OMNIHEALTH DIAGNOSTICS

Primary Immunodeficiency 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:	PID04172023	Average Read Depth:	211x		

Test Result:

+Positive : For Likely Pathogenic Variant on MST1 gene.

Gene & Transript	Variant	Inheritance	Disorder or Phenotype	Criteria	Classification
MST1 NM_020998.4	c.1251-2A>C	Autosomal Dominant / Heterozygous	Progressive loss of naive T cells	PM2, PVS1,	Likely Pathogenic

Location	Allele State	Allelic Read Depths
Exon 11	Heterozygous	Ref(T): 99, Alt(G): 11, VAF: 10.00%

Genomic Position	Variant Frequency
Chr3:NC_000003.11:g.49723167T>G	Not identified in large population studies

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Patient

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Gene info	MST1 NM_020998.4
Variant Info	The Variant is found at Chr3:NC_000003.11:g.49723167T>G location with a splice acceptor variant c.1251-2A>C change on the patient's MST1
Variant interpretation	The splice acceptor variant NM_020998.4(MST1):c.1251-2A>C has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. Although the variant is present at 0.0016% in gnomAD All, it has the flag "RF" and may not represent the true population frequency. The c.1251-2A>C 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 (PMC3824282).
Inheritance	Autosomal Dominant / Heterozygous
ACMG-Classification	Likely Pathogenic (PM2, PVS1)
Gene & Disorder or Phenotype	MST1 & Progressive loss of naive T cells
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.

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Test Methodology

Immunodeficiency Risk Factor Screening 47 gene panel screening performed at Ipseity Diagnostics LLC utilizes Next Generation Sequencing (NGS) technology using 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 Ipseity Diagnostics LLC Immunodeficiency screen, please contact us on Email: 12345@omnihealthdx.com

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 Ipseity Diagnostics 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 Ent Scan, NN Splice, 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 AC MG 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 Ipseity Diagnostics LLC s Technical Supervisor or the General Supervisor.

Genes Evaluated

ATM, BLM, BRCA2, BTK, CDX1, CFTR, CYBA, CYBB, F13B, F5, F7, F9, FANCC, FGB, G6PC, G6PD, IFNGR1, IFNGR2, ITGB2, JAGN1, JAK2, MEFV, MPL, MSH6, MST1, MYD88, NCF1, NFKB2, NRAS, PALB2 , PIK3CD, PLCG2, PMS2, PTEN, PTPRC, RAG1, RAG2, RFXANK, RUNX1, SPINK5, STAT1, STAT3, STK4, TERT, TNFRSF13B, VPS13B.

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. MST1 gene and its variants detected on chromosome-3 are only considered for tertiary analysis and reporting. Pseudogene for the same gene on chromosome-1 is excluded from further analysis and reporting.

Excluded: MST1L macrophage stimulating 1 like (pseudogene)

Location: 1p36.13; chr 1 : NC_000001.10:17,080,142 - 17,091,958

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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 Immunodeficiency, nor is the absence of such variants a guarantee that an individual will not develop a 'Immunodeficiency'. The results of this genetics screening is 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 Immunodeficiency 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 Immunodeficiency 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 Ipseity Diagnostics 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.