Laboratory Investigation Report

Patient Name	: Mast. Namish Mittal	Centre	: 1060 - Max Hospital Shalimar Bagh
Age/Gender	: 15 Y 0 M 7 D /Male	OP/IP No/UHID	: 314419
MaxID/Lab ID	: NHWZ.222783/0789012406962	Collection Date/Time	: Jan 06, 2024, 12:35 PM
Ref By	: Dr.A.J Chitkara	Reporting Date/Time	: Feb 10, 2024, 04:45 PM

SIN No:SB1851744

TEST REQUESTED: PANCREATITIS GENE PANEL (CFTR, CTRC, PRSS1, SPINK1)

METHOD USED

Next Generation Sequencing

CLINICAL INFORMATION / FAMILY HISTORY

15-year-old boy presented with recurrent pancreatitis. An increased value of Serum lipase and amylase noted. He has been evaluated for related genetic etiology.

TEST RESULTS

No significant variant related to patient phenotype has been detected

Single nucleotide variant unrelated to patient's phenotype have been detected

Sequence Variants Not Related to Phenotype (Incidental Finding)

Gene (Transcript)	Location	DNA/ Protein Change	Zygosity	Inheritance	Classification	Associated Diseases / OMIM
NR0B2 (-) NM_021969	Exon 1	C.227del p.Phe76Serfs*30	Heterozygous	Autosomal Dominant Autosomal Recessive	Pathogenic	Obesity, mild, early-onset (#601665)
HBB (-) NM_000518	Intron 1	c.92+5G>C p.?	Heterozygous	Autosomal Recessive	Pathogenic	β-thalassemia (#613985)
DIAPH3 (-) NM_001042517	Exon 24	c.2971A>T p.Lys991*	Heterozygous	Autosomal Dominant	Likely Pathogenic	Auditory neuropathy, autosomal dominant 1 (#609129)

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INTERPRETATION SUMMARY (Incidental Findings)

Variant-1

NR0B2: c.227del;p.Phe76Serfs*30

The heterozygous frameshift variant p.Phe76Serfs*30 also known as c.227del has been detected in the NR0B2 gene on chromosomal position chr1:26913713:GA>G. This variant is noted to have a total depth of 48X. It is located in exon 1 of the transcript NM_021969 and it leads to change in amino acid phenylalanine to serine at codon 76 of the NR0B2 protein followed by termination at codon 30 of the new reading frame. Loss of function is a known mechanism of disease for the frameshift variant of gene NROB2. This variant has been reported in Clinvar as Pathogenic (VCV000636300.2) and in dbSNP database (rs779783209). This variant has been reported in population frequency databases such as gnomAD (MAF- 0.0064%) and ExAC (MAF- 0.0115%). However, this variant has been reported in the South Asian population at frequency (0.1089%). As per ACMG classification the variant can be classified as pathogenic with criteria PM2, PVS1 and PP5.With the currently available evidence, this variant can be classified as pathogenic. Kindly correlate clinically.

Disease Details:

obesity is predominantly a polygenic and multifactorial trait. Genetic variation in NRB02 gene has been associated with susceptibility to obesity as a monogenic trait.

Variant-2

HBB c.92+5G>C; p.?

The heterozygous intronic splice site variant c.92+5G>C, has been detected in the HBB gene on chromosomal position chr11:5226925:C>G. This variant is noted to have a total depth of 91X. It is located in intron 1 of the transcript NM_000518 and it leads to splice defect. This variant has been reported in ClinVar as pathogenic (VCV000015447.91) and in dbSNP databases (rs33915217) This variant has been reported in population frequency databases such as gnomAD (MAF- 0.0237%) and ExAC (MAF- 0.0717%). This variant has a high frequency in the South Asian population (0.72%). This variant is predicted to be deleterious by in silico prediction tools such as SpliceAI, dbscSNV Ada, and dbscSNV RF. Aggregated prediction score for the variant is 0.8 which suggests it to be deleterious. As per ACMG classification the variant can be classified as pathogenic with criteria PM2, PS3, PP3, and PP5. This variant has been observed in individuals with beta thalassemia (PMID: 18294253, 19000664, 22392582, 23162295, 27263053). It is commonly reported in individuals of Pakistani and Indian ancestry (PMID: 18294253, 19000664, 22392582, 23162295, 27263053). This variant is also known as IVS-I-5, IVSI-5, and IVS1-5. Studies have shown that this variant alters mRNA splicing and is expected to lead to the loss of protein expression (PMID: 6188062). With the currently available evidence, this variant can be classified as pathogenic. Kindly correlate clinically.

Note: Since the second variant in the gene has not been detected, it is likely that the individual is a carrier for the variant. Please correlate this clinically.

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Disease Details

β-thalassemia is a genetic condition resulting from decreased or absence of production in the β chain of haemoglobin. Beta-thalassemia is caused by homozygous or compound heterozygous mutation in the beta-globin gene on chromosome 11p15.

This disorder is characterised by reduced production of hemoglobin A, which results from the reduced synthesis of beta-globin chains relative to alpha-globin chain, thus causing an imbalance in globin chain production and hence abnormal erythropoiesis and severe anaemia.

β-thalassemia is predominantly an inherited autosomal recessive disorder with mutated alleles from both parents contributing to the homozygous or compound heterozygous disease status of the affected child. The HBB variant found in the patient sample is in a heterozygous state which results in thalassemia minor phenotype.

Variant-3

DIAPH3: c.2971A>T; p.Lys991*

The heterozygous nonsense variant c.2971A>T; p.Lys991*, has been detected in the DIAPH3 gene on chromosomal position chr13:59833163:T>A. This variant is noted to have a total depth of 88X. It is located in exon 24 of the transcript NM_001042517 and it leads to protein truncation at codon 991. The total length of the wild type protein is 1193 amino acids. This variant has not been reported in ClinVar but has been reported in dbSNP databases (rs531346416). This variant has been reported in population frequency databases such as gnomAD (MAF- 0.0002%) and ExAC (MAF- 0.0017%). This variant is predicted to be deleterious by in silico prediction tools such as Mutation Taster, DANN, and BayesDel. As per ACMG classification the variant can be classified as likely pathogenic with criteria PVS1, and PM2. With the currently available evidence, this variant can be classified as likely pathogenic. Kindly correlate clinically.

Disease Details

Autosomal dominant auditory neuropathy-1 (AUNA1) is caused by heterozygous mutation in the DIAPH3 gene (614567) on chromosome 13q21.

Auditory neuropathy is a type of hearing loss defined by the preservation of cochlear outer hair cell function and abnormal or absent auditory brainstem responses

RECOMMENDATIONS

- Clinical correlation of the identified gene variant and the proband's clinical phenotype is recommended.
- Further testing of the reported variant in parents, other affected and unaffected family members may be recommended, to assist in understanding of the clinical significance.
- Genetic Counselling is recommended for further understanding of the reported variant.

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DATA QUALITY STATISTICS

Total data generated (Gb)	12.78
Reads aligned (%)	99.94
Q30 data (%)	90.89
Mean Target coverage	48.61

TEST DESCRIPTION

The Pancreatitis Gene Panel sequences 4 genes (CFTR, CTRC, PRSS1, SPINK1). Pancreatitis Gene Panel germline testing is a comprehensive exome sequencing test that sequences all the protein-coding regions of the targeted genes. Pancreatitis is typically inherited in an autosomal dominant pattern.

This test uses Next Generation Sequencing (NGS) technology to detect the cause of genetic disorders. It utilizes the paternal and maternal genotype information to detect the causative variants. It assists the clinician in identifying the underlying cause of the disorder with certainty, solving the diagnostic odyssey for the patient. The clinician can personalize the treatment as per the clinical diagnosis of the patient.

TEST METHODOLOGY

Genomic DNA was extracted from the submitted specimen and the Twist comprehensive kit was used to target the exon regions of the targeted genes. These targeted regions were sequenced using the Illumina sequencing platform with paired-end reads. The DNA sequence was mapped to, and analyzed in comparison with, the published human genome build UCSC hg19 reference sequence. The targeted coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage and data quality threshold values. The possible causative variants were prioritised based on the variant's predicted pathogenicity, frequency of occurrence in population and patient's phenotype with known disease causing genes from human and model organisms data. Analysis results are reported based on the recommendations of American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP), as described below:

Class 1	Pathogenic	This variant may directly contribute to the development of disease.
Class 2	Likely Pathogenic	There is a high likelihood that this variant is disease-causing. Additional evidence is expected to confirm this assertion of pathogenicity
Class 3	Variant of Uncertain Significance (VUS)	There is not enough scientific evidence at this time to support a more definitive classification of this variant.
Class 4	Likely Benign	As per current scientific evidence, this variant is not expected to have a major effect on disease. Additional evidence is expected to confirm this assertion. New evidence may demonstrate that this variant can contribute to disease.
Class 5	Benign	The variant does not cause disease.

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In line with ACMG-AMP recommendations for reporting of secondary findings in clinical exome and genome sequencing, we report pathogenic variants and likely pathogenic variants only in the recommended genes for the recommended phenotypes.

LIMITATIONS

Inaccurate and/or incomplete information might lead to misinterpretation of results. Only the variants located in genes that are potentially related to the proband's clinical phenotype are reported. Absence of a plausible explanation for the reported phenotype by exome sequencing does not exclude a genetic basis of the patient's condition. Intronic variants, repeat expansions, copy number variations or chromosomal rearrangements may not be reliably detected with exome Sequencing and therefore are not assessed. Due to technology limitations, certain genes may be poorly covered impacting the test results. It is possible that the genomic region where a disease causing mutation exists in the proband was not captured using the current technologies and therefore was not detected. Additionally, it is possible that a particular genetic abnormality may not be recognized as the underlying cause of the genetic disorder due to incomplete scientific knowledge about the function of all genes in the human genome and the impact of variants in those genes. Only variants in genes associated with the medical condition, or thought to be clinically relevant potentially for the proband's medical condition, are reported here.

DISCLAIMERS

This report provides information about the patient's mutations that may aid the physician's decision making process, but this test should not be the sole source of information for making decisions on patient care and treatment. The test should be interpreted in the context of standard clinical, laboratory, and pathological findings. Identification of a mutation in one or more of these genes does not guarantee activity of the drug in a given indication. Benign mutations in the intronic regions have not been included in this report. The information provided in this report was collected from various sources that we believe to be reliable and quality control procedures have been put in place to ensure the information provided is as accurate, comprehensive, and current as possible. The information provided should only be utilized as a guide or aid and the decision to select any therapy option based on the information reported here resides solely with the discretion of the treating physician. Patient care and treatment decisions should only be made by the physician after taking into account all relevant information available including but not limited to the patient's condition, family history, findings upon examination, results of other diagnostic tests, and the current standards of care. This report should only be used as an aid and the physician should employ clinical judgment in arriving at any decision for patient care or treatment.

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2. David T. Miller et. al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 2021; 23:1391–1398

(DR ATUL THATAI)
Director Molecular & Cytogenomics

(DR NITIN DAYAL)
Prin. Cons. and Head Hematopathology

(DR PRIYANKA AGARWAL)
Sr. Manager
Genomics & Molecular