DUO CARRIER SCREENING REPORT

Patient Details

Gender:	Male	Female
Full Name:	**xxxx**	**xxx**
Age/ Date of Birth:	31 Years	25 Years
Kit ID:	**xxxx**	**xxxx**
Sample Type:	Blood in EDTA tube	Blood in EDTA tube
Date and time of Sample Collection:	06/03/2023; NA	06/03/2023; NA
Date and time of Sample Receipt:	09/03/2024; 10. 20 AM	09/03/2024; 10. 20 AM
Date and time of Report:	19/04/2024; 10:00 AM	
Test Requested:	**Whole Exome Sequencing -Duo**	
Test Requested by:	**xxxx**	

Clinical diagnostics/History

XXX is non-consanguineously married to XXX, and their first child died with clinical suspicion of renal tubular acidosis or congenital adrenal hyperplasia. They have been evaluated for carrier status of pathogenic/ likely pathogenic variations.

Test Result

Significant carrier variants were detected in the couple.

Table 1: Carrier variants identified in this couple.

A. Primary Findings

Gene (Transcript)	Variant	Location	Disease (OMIM)	Inheritance	Mr. Abid Ahmad (zygosity)	Mrs. Afsha Abid (zygosity)	Classification
HSD3B2 (NM_000198.4)	c.818_819del; **(p.Lys273ArgfsTer7)**	Exon 4	Congenital adrenal hyperplasia (CAH) due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency (OMIM#201810)	Autosomal Recessive	**Heterozygous**	**Heterozygous**	**Pathogenic**
CFTR (NM_000492.4)	c.350G>T (**p.Arg117Leu**)	Exon 4	Cystic fibrosis (OMIM#219700)	Autosomal Recessive	**Not detected**	**Heterozygous**	**Pathogenic**
CFTR (NM_000492.4)	c.358G>A (**p.Ala120Thr**)	Exon 4	Cystic fibrosis (OMIM#219700)	Autosomal Recessive	**Heterozygous**	**Not detected**	**Uncertain significance**

Table 2: Carrier variants identified only in Mr. XXX UDTAK8344

Gene (Transcript)	Variant	Location	Zygosity	Inheritance	Disease (OMIM)	Classification
SMPD1 (NM_000543.5)	c.1267C>T; **(p.His423Tyr)**	Exon 4	Heterozygous	Autosomal Recessive	Niemann-Pick disease, type A (OMIM#257200) Niemann-Pick disease, type B (OMIM#607616)	**Likely Pathogenic**

Table 3: Carrier variants identified only in Mrs. XXX UDTAK8337

Gene (Transcript)	Variant	Location	Zygosity	Inheritance	Disease (OMIM)	Classification
TMPRSS3 (NM_001256317.3)	c.323-6G>A (3' splice site)	Intron 4	Heterozygous	Autosomal recessive	Deafness, autosomal recessive 8/10 (OMIM#601072)	**Likely Pathogenic**

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant 1: (HSD3B2)

Variant description: A heterozygous two base pairs deletion in exon 4 of the **HSD3B2** gene **(chr1-119964940 CAA>C)** that results in a frameshift and premature truncation of the protein 7 amino acids downstream to codon 273 **(p.Lys273ArgfsTer7; NM_000198.4)** was detected (Table). This variation is reported in individual(s) with 3-beta-hydroxysteroid dehydrogenase deficiency [PMID: 34628416]. This variation is documented as pathogenic in ClinVar database [ClinVar ID: VCV000586031.7]. The minor allele frequency of this variation is 0.0032%, 0.0025% in gnomAD(exome) and ExAC databases respectively, and is absent in the 1000 Genomes database. The reference region is conserved across species.

OMIM phenotype: Congenital adrenal hyperplasia (CAH) due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency is caused by homozygous or compound heterozygous mutation in the HSD3B2 gene (613890) on chromosome 1p12 [PMID: 18842627].

Based on the evidence, **this HSD3B2 gene variation is classified as a pathogenic variant and both partners are heterozygous carriers of this variation.**

Variant 2: (CFTR)

Variant description: A heterozygous missense variation in the exon 4 of the **CFTR** gene **(chr7-117171029 G>T)** that results in the amino acid substitution of Leucine for Arginine at codon 117 **(p.Arg117Leu; NM_000492.4)** was detected (Table). The observed variation lies in the ABC membrane domain of the CFTR protein. This variant has previously been reported in patients with Cystic Fibrosis [PMID: 20706124, 27738188]. Experimental studies have shown that this missense change affects CFTR function [PMID: 11278813, 30046002]. This variant is reported as pathogenic/likely pathogenic/variant of uncertain significance variant in the ClinVar database [ClinVar ID: VCV000053765.19]. The variant is not reported in the 1000 Genome database and has a minor allele frequency of 0.001% in both ExAC and gnomAD (Exome) databases. The in silico predictions of the variant is damaging by SIFT, PolyPhen-2, Mutation Taster, FATHMM, and DANN tools. The reference codon is conserved across species.

Based on the evidence**, this CFTR gene variation is classified as pathogenic and XXX is a heterozygous carrier of this variant.**

Variant 3: (CFTR)

Variant description: A heterozygous missense variation in the exon 4 of the **CFTR** gene **(chr7-117171037 G>A)** that results in the

amino acid substitution of Threonine for Alanine at codon 120 **(p.Ala120Thr; NM_000492.4)** was detected (Table). The observed variation lies in the ABC membrane domain of the CFTR protein. This variant has previously been reported in compound heterozygous state in patients with Cystic Fibrosis [PMID: 28830496, 31916691, 33572515]. This variant is reported with conflicting classifications of pathogenicity [Likely pathogenic(1); Uncertain significance(10)] in the ClinVar database [ClinVar ID: VCV000053774.38]. The variant is not reported in the 1000 Genome database and has a minor allele frequency of 0.01% in both ExAC and gnomAD (Exome) databases. The in silico predictions of the variant is damaging by PolyPhen-2, Mutation Taster, and DANN and uncertain by SIFT, and FATHMM. The reference codon is conserved across species.

Based on the evidence**, this CFTR gene variation is classified as variant of uncertain significance and XXX is a heterozygous carrier of this variant.**

OMIM phenotype: Cystic fibrosis (CF) (OMIM#219700) is caused by homozygous or compound heterozygous variations in the CFTR gene (OMIM*602421) [PMID:18842627].

The detected CFTR variants are likey to occur in compound heterozygous condition in their to be offspring.

Variant 4: (SMPD1)

Variant description: A heterozygous missense variation in exon 4 of the **SMPD1** gene (**chr11-6414850 C>T**) that results in the substitution of amino acid Tyrosine for Histidine at codon 423 (**p.His423Tyr; NM_000543.5**) was detected (Table). This variation is reported in individual(s) with Niemann-Pick disease [PMID: 20301544, 28600779]. This variation is documented as pathogenic in ClinVar database [ClinVar ID: VCV000002992.59]. The minor allele frequency of this variation is 0.0008% in ExAC database and is absent in gnomAD(exome) and 1000 Genomes databases. The in silico prediction of the variant is damaged by Polyphen2, MutationTaster, and DANN and uncertain by SIFT and FATHMM tools. The reference codon is conserved across species.

OMIM phenotype: Niemann-Pick disease type A and Niemann-Pick disease type B, known as the 'visceral' form, are caused by homozygous or compound heterozygous mutation in the sphingomyelin phosphodiesterase-1 gene (SMPD1; 607608), which encodes acid sphingomyelinase (ASM), on chromosome 11p15 [PMID: 18842627].

Based on the evidence, **this SMPD1 gene variation is classified as a likely pathogenic variant and Abid Ahmad is a heterozygous carrier of this variation.**

Variant 5 (TMPRSS3 gene):

Variant description: A heterozygous splice variation in the intron 4 of the **TMPRSS3** gene **(chr21-43808641 C>T)** that affects the position 6 nucleotides upstream of the exon 4 **(c.323-6G>A; NM_001256317.3)** was detected (Table). The observed variation has previously been reported in patients with deafness [PMID: 11137999, 30622556, 34868270]. Studies have shown that this variant alters mRNA splicing and is expected to lead to the loss of protein expression [PMID: 11137999]. This variant is reported as Pathogenic/Likely pathogenic/Uncertain significance in the ClinVar database [ClinVar ID: VCV000046113.21]. The variant has a minor allele frequency of 0.02% in the 1000 Genomes database and 0.01% in the ExAC and gnomAD (Exome) database, respectively. The in silico predictions of the variant is damaging by SpliceAI, dbscSNV Ada and dbscSNV RF tools. The reference base is conserved in mammals.

OMIM phenotype: Autosomal recessive deafness-8 (DFNB8), also known as DFNB10 (OMIM#601072) is caused by homozygous or compound heterozygous variations in the TMPRSS3 gene (OMIM*605511) [PMID: 18842627].

Based on the evidence**, this TMPRSS3 gene variation is classified as likely pathogenic and Afsha Abid is a heterozygous carrier of this variant.**

Test Methodology used: Next Generation Sequencing

- Genetic counseling is recommended to discuss the implications of this finding for the patient.
- Sanger validation of the detected variants is recommended.

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Test Methodology

The extracted genomic DNA was fragmented and was used to perform targeted gene capture of human exome using a custom capture kit. The final indexed libraries were sequenced to 100X coverage with 2x150 chemistry on Illumina sequencing platform. The primary and secondary analysis were performed on Illumina DRAGEN platform. The sequences obtained were aligned to human reference genome (GRCh37/Hg19) using DRAGEN. Set of disease databases are used during tertiary analysis like ClinVar, OMIM, GWAS, HGMD and SwissVar. Common variants are filtered basedon allele frequency in 1000 Genome Phase 3, ExAC, EVS, dbSNP147. Non-synonymous variants effect is calculated using multiple algorithms such as PolyPhen-2, SIFT, Mutation Taster2, Mutation Assessor, and LRT. Silent variations that do not result in any change in amino acid in the coding region are not reported.

Disclaimers

- This test is used for clinical purposes and should be interpreted in context with other clinical findings. Any questions, suggestions, or concerns regarding the interpretation of results should be forwarded enquiries@getcheckedclinic.com.
- It is hereby clarified that the report generated from the test does not provide any diagnosis or opinion or recommends any cure in any manner. Getchecked Clinic hereby recommends the patient and/or the guardians of the patients, as the case may be, to take the assistance of the clinician or a certified physician or doctor, to interpret the report thus generated.
- Interpretation of variants in this report is performed to the best knowledge of the laboratory based on the information available at the time of reporting. The classification of variants is based on ACMG (American College of Medical Guidelines) guidelines.
- Genes with pseudo genes, para log genes and genes with low complexity may have decreased sensitivity and specificity of variant detection and interpretation due to the inability of the data and analysis tools to unambiguously determine the origin of the sequence data in such regions.
- Copy number variations/chromosomal rearrangements cannot be assessed using this method
- This is a laboratory developed test and the performance and characteristics of this test is determined by Getchecked Clinic.
- Deep intronic variants are not assessed by this method
- It is possible that the genomic region where a disease causing mutation exists in the provided specimen was not captured using the current technologies and therefore was not detected.

References

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