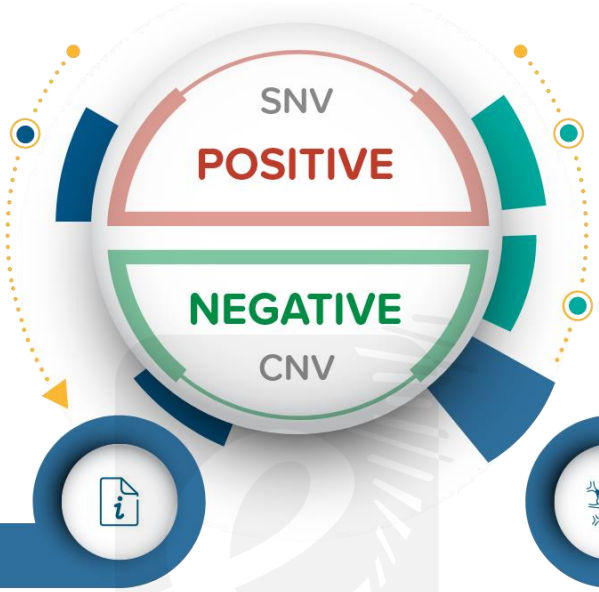
ExoSeq®
human exome sequencing

PATIENT		TEST ORDERED BY		SAMPLE DETAILS		PERFORMED BY	
Name:	Masah Suliman	Name:	Dr. Mahmoud Alhissi	ID:	SS2683_S8474	Laboratory:	Agiomix Labs
DOB:	04/08/2020	License #:	NA	Type:	DNA	License #:	3650734
Gender:	Female	Authority:	NA	Origin:	Blood	Authority:	DHA
Ethnicity:	Saudi	Center Name:	Delta Medical Laboratories	Receipt Date:	07/10/2024		
Report ID:	26271728304759	Center Address:	Saudi Arabia	Report Date:	24/10/2024		

ExoSeq® Comp + CNV

TEST INFORMATION

ExoSeq COMP - Whole Exome Sequencing using Next Generation Sequencing Technology of the Proband and also Copy Number Variation (CNV) Analysis.



SAMPLE QUALITY
PASSED

DATA QUALITY
PASSED

CLINICAL INFORMATION

4-year-old female with global developmental delay and autism. Unknown family history.

DETECTED SNV VARIANTS

Gene/ID#	Variant	Zygosity	Disorder	Inheritance	Variant Classification
USP7 NM_003470.3	c.2452A>C p.Asn818His	Heterozygous	Hao-Fountain Syndrome (HAFOUS)	Autosomal Dominant	Uncertain Significance

DETECTED CNV VARIANTS

No Copy Number Variants that match the phenotype has been detected

ExoSeq®
human exome sequencing

MEDICAL INTERPRETATION

Hao-Fountain syndrome (HAFOUS) is a neurodevelopmental disorder characterized by **global developmental delay**, variably impaired intellectual development with significant speech delay, **behavioral abnormalities, such as autism**, and mild dysmorphic facies. Additional features are variable, but may include hypotonia, feeding problems, delayed walking with unsteady gait, hypogonadism in males, and ocular anomalies, such as strabismus. Some patients develop seizures and some have mild white matter abnormalities on brain imaging. **Clinical correlation is recommended.**

Fountain et al. (2019) reported 11 patients, including 2 sibs, with a similar developmental disorder. The patients were ascertained from several different laboratories or institutions through collaborative efforts, after clinical genome or exome sequencing identified putative USP7 mutations. Reverse phenotyping was performed. **All patients had global developmental delay** with variably impaired intellectual development and significant speech delay; 2 were nonverbal. They had delayed motor development with walking achieved at about 3 years (range 17 to 156 months), but many had an abnormal gait, and 1 patient was nonambulatory. IQ, measured in a few patients, ranged from 52 to 80. **Most patients had behavioral abnormalities, including autism, autistic features**, impulsivity, compulsivity, temper tantrums, attention-deficit hyperactivity disorder, aggression, and manipulative behavior. Four patients had seizures. Additional variable features included hypotonia, feeding difficulties with gastroesophageal reflux, constipation, or diarrhea, sleep disturbances, asthma, short stature, scoliosis, kyphosis, and small hands or feet. Males tended to have hypogonadism with cryptorchidism and micropenis. Almost all patients had mildly dysmorphic facial features, including deep-set eyes and prominent nasal septum extending below the alae nasi, but there was no recognizable pattern. Eye abnormalities, including esotropia, myopia, strabismus, and nystagmus, were commonly observed. Five patients had abnormal brain MRI with decreased white matter, enlarged ventricles, nonspecific white matter abnormalities, thin corpus callosum, and mild gyral anomalies, but a few patients had normal brain imaging. Three additional patients with a similar phenotype were also reported, but each had additional genetic variants that may have contributed to the phenotype. Two more patients had larger de novo heterozygous deletions affecting USP7. In all, there were 16 patients with the disorder confirmed by genetic analysis, allowing refinement of the phenotype.

No Copy Number Variants that match the phenotype has been detected. Additionally, no variants of interest in mitochondrial DNA were detected.

GENETIC INTERPRETATION

Variant Details	
Gene ID	USP7
Transcript	NM_003470.3
Location	Chr16:8993472
HGVSc and HGVSp	c.2452A>C p.Asn818His
Coverage	28:29
Zygosity	Heterozygous
Inheritance Pattern	Autosomal Dominant
Disease	Hao-Fountain Syndrome (HAFOUS)
Classification	Uncertain Significance
Classification Database	Franklin, Varsome

A heterozygous missense variant **(c.2452A>C, p.Asn818His)** has been detected in **USP7 gene** which is located at **exon 22** out of 31 total exons. This variant has been classified as a variant of uncertain significance in Franklin database using the following ACMG criteria; it is a missense variant in a gene with low rate of benign missense mutations and high number of pathogenic missense variants in this gene for which missense mutation is a common mechanism of a disease [PP2], and it is found in extremely low frequency in gnomAD population databases [PM2]. Varsome database classified this variant as a variant of uncertain significance using the following ACMG criteria [PM2, BP4]. Mutation Taster also predict this variant to be disease causing as the amino acid sequence changed, splice site changes and protein features might be affected. However, no data available for this variant in ClinVar. Since this variant is currently classified as a variant of uncertain significance, **we do not know what this variant may mean for the patient. Detailed functional and family studies are needed to determine its impact.**

This variant might be inherited form one of the parent or occurred as a de-novo (new) variant, testing the parents is recommended to help establish the meaning of the variant for this patient and help with calculating the recurrent risk, although germline mosaicism cannot be excluded. **Genetic counselling is recommended.**

ExoSeq®
human exome sequencing

RECOMMENDATION

We recommend:

1. Follow-up with referring Physician.
2. Appropriate genetic counselling.
3. Checking the **USP7** variant in the parents and other family members.
4. **Detailed functional and family studies are recommended to determine the impact of this variant.**
5. **If the detected variant is not favorable, chromosomal microarray analysis to look for large deletions and duplications that could be missed by NGS based analysis along with Whole genome sequencing to investigate for non-coding and regulatory region variants might be considered.**
6. This report should be evaluated together with clinical and other laboratory data.
7. Karyotype of the parents to determine if they carry a balanced translocation and genetic counselling for risk of recurrence in future pregnancies if appropriate.

SECONDARY FINDING

No pathogenic or potentially significant variants in the remainder of gene(s) have been identified.

(BIBLIOGRAPHY/CITATIONS):

This test was developed and its performance was validated by the performing lab. The test is meant for clinical purposes. All the results are reviewed, interpreted and reported by our scientific personal. Should there be any further information required from the performing lab, it would result in extra costs. In accordance with the ACMG Guidelines for the reporting of the secondary findings, in clinical whole exome sequencing, variants classified as Class 1 or Class 2 (previously reported and unreported pathogenic and likely pathogenic variants) in the following genes are included in this report if consent is indicated on the requisition form.

Variant classification can change over time as further information become available. For updates regarding classification of variants of unknown significance, please contact Agiomix at a later date (reports@agiomix.com) to find out if there have been any changes in the classification of the reported variants.

All the results are reviewed, interpreted and reported by our scientific personnel.
In accordance with the ACMG Guidelines for the reporting of the secondary findings, in clinical whole exome sequencing (Ref.& Cit.), variants classified as Class 1 or Class 2 (previously reported and unreported pathogenic and likely pathogenic variants) in the following genes are included in this report if consent is indicated on the requisition form.

References:

1. ClinGen: https://www.clinicalgenome.org/, ClinGen Dosage Sensitivity Curation Page: https://dosage.clinicalgenome.org/
2. UNIQUE Database: http://www.rarechromo.org
3. OrphaNet: http://www.orpha.net
4. Database of Genomic Variants: http://dgv.tcag.ca
5. ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/
6. HGMD® (Human Gene Mutation Database) Public
7. OMIM (Online Mendelian Inheritance in Man): https://www.omim.org/
8. dbSNP: https://www.ncbi.nlm.nih.gov/snp/
9. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Riggs ER er al., 2020 Genet Med. 22(2):245-257 (PMID: 31690835).
10. Fountain MD, Oleson DS, Rech ME, Segebrecht L, Hunter JV, McCarthy JM, Lupo PJ, Holtgrewe M, Moran R, Rosenfeld JA, Isidor B, Le Caignec C, Saenz MS, Pedersen RC, Morgan TM, Pfotenhauer JP, Xia F, Bi W, Kang SL, Patel A, Krantz ID, Raible SE, Smith W, Cristian I, Torti E, Juusola J, Millan F, Wentzensen IM, Person RE, Küry S, Bézieau S, Uguen K, Férec C, Munnich A, van Haelst M, Lichtenbelt KD, van Gassen K, Hagelstrom T, Chawla A, Perry DL, Taft RJ, Jones M, Masser-Frye D, Dyment D, Venkateswaran S, Li C, Escobar LF, Horn D, Spillmann RC, Peña L, Wierzba J, Strom TM, Parenti I, Kaiser FJ, Ehmke N, Schaaf CP. Pathogenic variants in USP7 cause a neurodevelopmental disorder with speech delays, altered behavior, and neurologic anomalies. Genet Med. 2019 Aug;21(8):1797-1807. doi: 10.1038/s41436-019-0433-1. Epub 2019 Jan 25. PMID: 30679821; PMCID: PMC6752677.

PERFORMING LAB AUTHORIZATION DETAILS

Authorized By:

Dr. Umut Fahrioğlu, PhD MSc Genetics and Genetic Counselling

DHA License - 88670961-001

Performed/Supervised By:

Iryna Volobuieva, MSc Genetics

DHA License - 12660477-001

PERFORMING LAB

Agiomix® next generation diagnostics

PERFORMING LAB ACCREDITATION

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS | Licensed by: DUBAI HEALTH AUTHORITY | ACCREDITED BASED ON ISO 27001:2022 INFORMATION SECURITY MANAGEMENT SYSTEM | ACCREDITED BASED ON ISO 9001:2015 QUALITY MANAGEMENT SYSTEM

METHODS/LIMITATIONS/ DISCLAIMER

COUNSELLING