NEURAZON
WELLNESS STARTS WITH YOU

From:
Neurazon INC.
Precision Health Analysis Department - Children with Autism and Developmental Disorders
Quebec, Canada

Case no: 1167492
First Name: Fahed
Last Name: Dahman
DOB: 14.11.2018
Sex: Male

Test requested: Precision Health Analysis®

Results:
True Autism Spectrum Disorder Variants: NEGATIVE
Acquired Autism Spectrum Disorder Variants: NEGATIVE
Attention-Deficit/Hyperactivity Disorder Variants: NEGATIVE
Information Processing and Brain Development Variants: NEGATIVE
White Matter Delays Variants: POSITIVE
Methylation Variants: NEGATIVE
Metabolic and Mitochondrial Function Variants: POSITIVE
Neurotransmitters, Synaptic Health, and Behavior Variants: POSITIVE
Immune System Variants: NEGATIVE
Potential Digestive System Variants: NEGATIVE
Epigenetic Regulation Variants: NEGATIVE
Potential Uncontrolled Electrical Activity: NEGATIVE

Recommended Interpretation:

- Please note any clinically relevant variants detected that are associated with the described phenotype, if present.
- Review all variants listed in the attached report, if applicable.
- We recommend reevaluating the sequence dataset every 12 months or when there are changes in the phenotype.
- Reassessment by a multidisciplinary team is advised every 3 months to monitor any observed phenotypic changes using artificial intelligence.
- A tailored intervention plan should be developed and supervised by a multidisciplinary team.

ADDITIONAL INFORMATION

This assessment was developed and validated using the AI model of NEURAZON, based on the findings outlined in the attached report. The U.S. Food and Drug Administration (FDA) has determined that clearance or approval for this method is not required; therefore, neither has been sought. All test results are thoroughly reviewed, interpreted, and reported by our team of scientific and medical experts. For full details, please refer to the attached report.

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Recommended Homeopathy Plan

Step: 1st
step Name: Fahed Dahman
DOB: 14.11.2018

	Item name	Ingredient	Purpose	Quantity	Duration	Details
1	Centovita: NEUROMYELOGEN FORMULA: NEUROPLASTICITY AND BRAIN'S WHITE MATTER HEALTH SUPPORT	Multiple	Variant found	2 ml in the morning	4 months	www.centovita.com or amazon
2	Centovita: EASYSPEAK BRAIN BOOST: BRAIN AND SPEECH SUPPORT FOR CHILDREN	Multiple	Variant found	2 ml in the morning	4 months	www.centovita.com or amazon
3	Centovita: PEACEFUL MINDS: CALM & FOCUS MAGNESIUM HERBAL FORMULA FOR CHILDREN	Multiple	Variant found	0.5 ml in the morning 0.5 ml at night	4 months	www.centovita.com or amazon
4	Centovita: B-METHYLATION BOOST: LIQUID B COMPLEX AND METHYLATION SUPPORT FOR CHILDREN	Multiple	Variant found	1 ml in the morning	4 months	www.centovita.com or amazon

ADDITIONAL INFORMATION

Recommendations: The provided guidance includes safe, non-drug, natural treatments intended to support the child's development. These recommendations are not a replacement for professional rehabilitation and training sessions and should always be followed under the supervision of a qualified specialist. Progress and improvement depend on the individual child, the underlying causes, and their response to the interventions, with recommendations adjusted based on regular evaluations every three months. If any signs of an allergic reaction occur, discontinue the treatment immediately and consult with a healthcare provider to modify the treatment plan accordingly.

Reevaluation: A reevaluation is necessary after the specified duration to reassess development using the AI model or as recommended by the professional team.

Next Steps: Begin the second phase of the protocol after the timeframe indicated in the treatment plan.

This assessment was developed and its performance validated using the AI model of NEURAZON, as detailed in the attached report. Based on the U.S. Food and Drug Administration (FDA) guidelines, this method does not require clearance or approval, and none has been pursued. This test is intended for clinical purposes. All results are thoroughly reviewed, interpreted, and reported by our team of scientific and medical experts. Please refer to the attached report for comprehensive details.

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Order no: 1167492
Report Type: Final report

Case no : 1167492
First Name: FAHED
Last Name: DAHMAN
DOB: 14.11.2018
Sex: Male

Requested Test: WES (Whole Exome Sequencing)
Clinical Information/Indication: The analysis was performed according to the demand of referal center to identify variants in relevant genes associated with neurological disorders.
Result:

Table:

Main Findings:

A class 2 variant; c.19426+2T>A in the TTN gene was identified.
A class 3 variant; c.3317C>T / p.Pro1106Leu in the SBF1 gene was identified.
A class 3 variant; c.167C>A / p.Thr56Asn in the HHAT gene was identified.

Gene (Transcript)	Location	Nucleotide (protein) dbSNP	Zygosity	Variant Classification	Disease (OMIM#, Inheritance)
TTN NM_001267550.2	Intron 66	c.19426+2T>A rs727505178	Heterozygous	Class 2	TTN Related Disorder [1] [2] OMIM: 188840 Autosomal Dominant/ Autosomal Recessive
SBF1 NM_002972.4	Exon 26	c.3317C>T p.Pro1106Leu rs368716467	Homozygous	Class 3	Charcot-Marie-Tooth Disease, Type 4B3 OMIM: 615284 Autosomal Recessive
HHAT NM_018194.6	Exon 4	c.167C>A p.Thr56Asn rs867091715	Homozygous	Class 3	Nivelon-Nivelon-Mabille Syndrome OMIM: 600092 Autosomal Recessive

Details About Gene and Variants:
TTN: This gene encodes a large abundant protein of striated muscle. The product of this gene is divided into two regions, a N-terminal I-band and a C-terminal A-band. The I-band, which is the elastic part of the molecule, contains two regions of tandem immunoglobulin domains on either side of a PEVK region that is rich in proline, glutamate, valine and lysine. The A-band, which is thought to act as a protein-ruler, contains a mixture of immunoglobulin and fibronectin repeats, and possesses kinase activity. An N-terminal Z-disc region and a C-terminal M-line region bind to the Z-line and M-line of the sarcomere, respectively, so that a single titin molecule spans half the length of a sarcomere. Titin also contains binding sites for muscle associated proteins so it serves as an adhesion template for the assembly of contractile machinery in muscle cells. It has also been identified as a structural protein for chromosomes. Alternative splicing of this gene results in multiple transcript variants. Considerable variability exists in the I-band, the M-line and the Z-disc regions of titin. Variability in the I-band region contributes to the differences in elasticity of different titin

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isoforms and, therefore, to the differences in elasticity of different muscle types.

The TTN variant c.19426+2T>A was detected in heterozygous state. It is classified as Likely Pathogenic (LP/class 2) according to the recommendations of ACMG. This variant is associated with autosomal dominant / autosomal recessive TTN Related Disorder [1] [2] (OMIM: 188840).

SBF1: This gene encodes a member of the protein-tyrosine phosphatase family. However, the encoded protein does not appear to be a catalytically active phosphatase because it lacks several amino acids in the catalytic pocket. This protein contains a Guanine nucleotide exchange factor (GEF) domain which is necessary for its role in growth and differentiation. Mutations in this gene have been associated with Charcot-Marie-Tooth disease 4B3. Pseudogenes of this gene have been defined on chromosomes 1 and 8. [provided by RefSeq, Dec 2014]

The SBF1 variant c.3317C>T / p.Pro1106Leu was detected in homozygous state. It is classified as Variant of Unknown Significance (VUS/class 3) according to the recommendations of ACMG. This variant is associated with autosomal recessive Charcot-Marie-Tooth Disease, Type 4B3 (OMIM: 615284).

HHAT: 'Skinny hedgehog' (SKI1) encodes an enzyme that acts within the secretory pathway to catalyze amino-terminal palmitoylation of 'hedgehog' (see MIM 600725).[supplied by OMIM, Jul 2002]

The HHAT variant c.167C>A / p.Thr56Asn was detected in homozygous state. It is classified as Variant of Unknown Significance (VUS/class 3) according to the recommendations of ACMG. This variant is associated with autosomal recessive Nivelon-Nivelon-Mabille Syndrome (OMIM: 600092).

Recommendations:

- It is recommended to evaluate this patient's result together with clinical and laboratory findings.
- Genetic screening and clinical evaluation are recommended for family members.
- Genetic counseling is recommended.

[1]Rare mutations in the TTN gene have been identified with autism (O'Roak et al., 2011 & 2012).
O'Roak BJ, Deriziotis P, Lee C, Vives L, Schwartz JJ, Girirajan S, Karakoc E, Mackenzie AP, Ng SB, Baker C, Rieder MJ, Nickerson DA, Bernier R, Fisher SE, Shendure J, Eichler EE. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. Nat Genet. 2011 Jun;43(6):585-9. doi: 10.1038/ng.835. Epub 2011 May 15. Erratum in: Nat Genet. 2012 Apr;44(4):471. PMID: 21572417; PMCID: PMC3115696.

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[2]O'Roak BJ, Vives L, Girirajan S, Karakoc E, Krumm N, Coe BP, Levy R, Ko A, Lee C, Smith JD, Turner EH, Stanaway IB, VernotB, Malig M, Baker C, Reilly B, Akey JM, Borenstein E, Rieder MJ, Nickerson DA, Bernier R, Shendure J, Eichler EE. Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. Nature. 2012 Apr 4;485(7397):246-50. doi: 10.1038/nature10989. PMID: 22495309; PMCID: PMC3350576.

Additional Findings:
The variants reported as additional findings refer to pathogenic changes that are not related to the referred phenotype but can cause additional phenotype thus require genetic counseling and further clinical evaluation.

ACMG Findings (ACMG 81 Genes):
According to the ACMG guidelines (Genetics in Medicine, 2023; PMID: PMID: 37347242), Class 1 or 2 incidental changes in proposed diseases and genes are reported. Variants in the BRCA1/2, MLH1, MSH2, MSH6, PMS2, TMEM127, MAX and MUTYH genes associated with adult onset diseases in children (under 15 years of age) are not reported.

Carriership Findings:
Class 1 and class 2 variants in genes selected according to OMIM phenotypes associated with severe or early-onset diseases have been reported. The variants reported as carriership findings refer to pathogenic changes that are not related to the reported phenotype and require family screening in conjunction with genetic counseling due to potential carrier risk.

Table:

Gene (Transcript)	Location	Nucleotide (protein) dbSNP	Zygosity	Variant Classification	Disease (OMIM#, Inheritance)
DCAF17 NM_025000.4	Exon 4	c.436del p.Ala147Hisfs*9 rs797045038	Heterozygous	Class 1	Woodhouse-Sakati Syndrome OMIM: 241080 Autosomal Recessive
MCCC2 NM_022132.5	Exon 11	c.1015G>A p.Val339Met rs150591260	Heterozygous	Class 1	3-Methylcrotonyl-CoA Carboxylase 2 Deficiency OMIM: 210210 Autosomal Recessive

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CNV Table:

CNV Detected Genes and Region	Result	Disease (OMIM#, Inheritance)
ANO5 (Exons 1-17) chr11:22.215.029-22.284.600	Class 2, Heterozygous Deletion chr11:22.215.029-22.284.600 (69.6kb) ISCN: sseq[GRCh37] del(11)(p14.3) (22215029_22284600)	ANO5 Related Disease OMIM: 608662 Autosomal Dominant/ Autosomal Recessive

Method:
Whole Exome Sequencing is performed by DiagnoSeq using Twist Biosciences technology. First, approximately 36.5 Mb of Consensus Coding Sequences (CCS) (targeting> 98% of RefSeq and Gencode v28 regions derived from the human genome) are replicated from fragmented genomic DNA with the Twist Human Core Exome Plus kit. The generated library is sequenced on the Illumina Novaseq NGS platform to achieve a minimum reading depth of 20x for>98% of the targeted bases. As a result of sequencing, raw data is obtained in FASTQ and VCF formats. Whole Exome Sequencing analysis is performed on FASTQ data using the Franklin by Genoox analysis program. In addition to all disease-causing variants reported in the HGMD®, ClinVar, and CentoMD® databases as well as all variants with a Minor Allele Frequency (MAF) of less than 1% in the gnomAD database are considered. The research for related variables has focused on coding exons and surrounding +/- 20 intronic bases. All potential inheritance patterns are covered. In addition, the family history and clinical information provided are used to evaluate pathogenicity and variables defined by their cause of disease and are classified in Class 1 - 5 scoring **. All variables related to the patient's phenotype are reported, except for benign or possible benign variants. Low-quality single nucleotide variants and all related deletion/insertion variants are validated by Sanger sequencing.

Analysis Statistics:

Average Depth (RefSeq Exome)	160
Variant Quality	99%

Method Limitations:
Polymorphisms in primary binding and regions, CNV duplications and somatic microsatellite variations, tissue mosaic, high GC nucleotide content can lead to false positive / negative results. False positive findings may occur due to large deletion / point mutation combined heterozygosity. Variants in transcripts other than canonical transcripts cannot be eliminated, and differences may occur between exon numbers and mutation positions depending on the transcript type sequenced. This method does not show heterozygous deletions and duplications in rare exons and nucleotide changes in other regions of the gene.

Variants with the allele fraction below 30% for regions with a sensitivity of this test of 50X read count are not reported. Additionally, due to technology limitations, some regions may be either not covered or poorly covered. Variables in these regions cannot be reliably detected. Areas with extremely low readings are considered artifacts as a result of validation studies, and they were not taken into account during the analysis. Copy number changes, inversions, translocations and repeat sequence increases cannot be detected by the NGS method.

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The genetic results are interpreted in the context of the provided clinical findings, family history, and other laboratory data. Only variants in genes potentially related to the proband's medical condition are reported. Misinterpretation of results may occur if the provided information is inaccurate and/or incomplete. If the obtained genetic results do not concur with the clinical findings, additional testing should be considered.

****Variant Classification (According to American College of Medical Genetics ACMG)**
Class 1 – Pathogenic
Class 2 – Likely pathogenic
Class 3 – Variant of Unknown Significance -VUS
Class 4 – Likely benign
Class 5 – Benign

This test was analyzed by Neurazon, Canada.

Digitally Approved by:

Dr. Carmel Katz

Lead Scientist and Geneticist

Lead Bioinformatics Specialist

At Neurazon

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