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

Case no: 271601
First Name: Daniel-sam
Last Name: Khati·b
DOB: 07.03.2015
Sex: Male

Test requested: Precision Health Analysis®

Results:
True Autism Spectrum Disorder Variants: POSITIVE
Acquired Autism Spectrum Disorder Variants: POSITIVE
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: NEGATIVE
Neurotransmitters, Synaptic Health, and Behavior Variants: POSITIVE
Immune System Variants: NEGATIVE
Potential Digestive System Variants: NEGATIVE
Epigenetic Regulation Variants: NEGATIVE
Potential Uncontrolled Electrical Activity: POSITIVE

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: Daniel-sam Khati·b
DOB: 07.03.2015

	Item name	Ingredient	Purpose	Quantity	Duration	Details
1	Kirkman Labs, Alpha Lipoic Acid, 50 mg	Alpha Lipoic Acid	White matter Development	Capsule every other day mornings. Dissolve in water, juice, honey	4 months	Can be purchased from iherb amazon
2	Planetary Herbals, Calm Child™ Herbal Syrup, 4 fl oz (118.28 ml)	Multiple	Behaviour improvement	1.0 ml at night and 1.0 ml mornings	4 months	Can be purchased from iherb amazon
3	Joyspring Burst B12	Multiple	White matter Development	1.0 ml every day in the morning	4 months	Can be purchased from iherb amazon

4) Superior Source, GABA, 100 mg, 100 MicroLingual® Instant Dissolve Tablets
1 tablet at night dissolved in water (4 months)

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: 271601
Report Type: Final report

Case no: 271601
First Name: DANIEL-SAM
Last Name: KHAT·B
DOB: 07.03.2015
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:
Heterozygous class 3 variant; c.2818G>C / p.Ala940Pro in the SHANK3 gene was identified.
Heterozygous class 3 variant; c.3265C>T / p.Arg1089Cys in the SHANK2 gene was identified.
Heterozygous class 3 variant; c.73G>T / p.Ala25Ser in the GABBR1 gene was identified.

Gene (transcript)	Location	Nucleotide (protein) dbSNP	Zygosity	Variant Classification	Disease (OMIM#, Inheritance)
SHANK3 NM_001372044.2	Exon 22	c.2818G>C p.Ala940Pro	Heterozygous	Class 3	SHANK3 Related Disease OMIM: 606230 Autosomal Dominant
SHANK2 NM_012309.5	Exon 26	c.3265C>T p.Arg1089Cys	Heterozygous	Class 3	Autism Susceptibility 17 OMIM: 613436 Autosomal Dominant
GABBR1 NM_021903.3	Exon 1	c.73G>T p.Ala25Ser rs1377844232	Heterozygous	Class 3	Neurodevelopmental Disorder With Language Delay and Variable Cognitive Abnormalities OMIM: 620502 Autosomal Dominant

Details About Gene and Variants:
SHANK3: This gene is a member of the Shank gene family. Shank proteins are multidomain scaffold proteins of the postsynaptic density that connect neurotransmitter receptors, ion channels, and other membrane proteins to the actin cytoskeleton and G-protein-coupled signaling pathways. Shank proteins also play a role in synapse formation and dendritic spine maturation. Mutations in this gene are a cause of autism spectrum disorder (ASD), which is characterized by impairments in social interaction and communication, and restricted behavioral patterns and interests. Mutations in this gene also cause schizophrenia type 15, and are a major causative factor in the neurological symptoms of 22q13.3 deletion syndrome, which is also known as Phelan-McDermid syndrome. [provided by RefSeq, Mar 2012]

The SHANK3 variant c.2818G>C / p.Ala940Pro was detected in heterozygous state. It is classified as Variant of Unknown Significance (VUS/class 3) according to the recommendations of ACMG. This variant is associated with autosomal dominant SHANK3 Related Disease (OMIM: 606230).

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SHANK2: This gene encodes a protein that is a member of the Shank family of synaptic proteins that may function as molecular scaffolds in the postsynaptic density of excitatory synapses. The alternative splicing demonstrated in Shank genes has been suggested as a mechanism for regulating the molecular structure of Shank and the spectrum of Shank-interacting proteins in the postsynaptic densities of the adult and developing brain. Alterations in the encoded protein may be associated with susceptibility to autism spectrum disorder. [provided by RefSeq, Feb 2014]

The SHANK2 variant c.3265C>T/p.Arg1089Cys was detected in heterozygous state. It is classified as Variant of Unknown Significance (VUS/class 3) according to the recommendations of ACMG. This variant is associated with autosomal dominant Autism Susceptibility 17 (OMIM: 613436).

GABBR1: This gene encodes a receptor for gamma-aminobutyric acid (GABA), which is the main inhibitory neurotransmitter in the mammalian central nervous system. This receptor functions as a heterodimer with GABA(B) receptor 2. Defects in this gene may underlie brain disorders such as schizophrenia and epilepsy. [provided by RefSeq, Jan 2016]

The GABBR1 variant c.73G>T/p.Ala25Ser was detected in heterozygous state. It is classified as Variant of Unknown Significance (VUS/class 3) according to the recommendations of ACMG. This variant is associated with autosomal dominant Neurodevelopmental Disorder With Language Delay And Variable Cognitive Abnormalities (OMIM: 620502).

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 for main findings and carriership findings to evaluate familial risks.
- Genetic counseling is recommended.

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.

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.

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.

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Table:

Gene (transcript)	Location	Nucleotide (protein) dbSNP	Zygosity	Variant Classification	Disease (OMIM#, Inheritance)
FLG NM_002016.2	Exon 3	c.3757G>T p.Gly1253* rs199895224	Heterozygous	Class 1	FLG Related Disease OMIM: 135940 Autosomal Recessive/ Autosomal Dominant
ALPL NM_000478.6	Exon 5	c.407G>A p.Arg136His rs121918011	Heterozygous	Class 1	ALPL Related Disease OMIM: 171760 Autosomal Recessive / Autosomal Dominant

Method:
Whole Exome Sequencing is performed by 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 Exome 2.0 kit. The generated library is sequenced on the MGI DNBSEQ-G400 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 format. Whole Exome Sequencing analysis is performed 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:

Percent of target covered (depth>=20)	94.3%
Average Depth (targeted regions)	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.

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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.

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.

Approved By: Dr. Alexandre Ruso

Technician: Kate S. Mandery

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