



## Mitochondrial and Molecular Medicine

Richard G. Boles, M.D.  
Medical Genetics  
Pasadena, California

### Mitochondrial & Molecular Medicine NeuroGenomics Service Peer-to-Peer Genomic Consultation Notes

Client: Rita, Rogério R., MD [rogeriorita@hotmail.com]  
Date: 6/9/2025  
Patient: França, Isaac  
DOB: 11/6/2018 (6y)  
Service level: Basic Standard **Comprehensive**  
Test/lab: WGS trio / Variantyx  
Off-target: Requested by parent  
Online: Dr. Rogério Rita  
Location: Provider: Brazil

*Summary of the discussion:*

Referral:

From parent 1/13/2025: I am writing to request a consultation with Dr. Richard Boles for my son, Isaac França, a 6-year-old autistic child. We have been struggling for an accurate diagnosis and effective treatment since he is 18 months old. Dr. Rogério Rita, Isaac's doctor here in Brazil, has been following his case and strongly recommended that we seek Dr. Boles's expertise. Dr. Rita is willing to collaborate closely and is looking forward to joining the consultation via videoconference to provide medical background and assist in implementing any recommendations locally.

As mentioned, Dr. Rogério Rita will coordinate Isaac's care locally. He is ready to assist with any necessary tests or treatments that Dr. Boles recommends. He will also join the consultation virtually to ensure clear communication and follow-up. This collaboration means Isaac will have continuous medical supervision in Brazil to carry out Dr. Boles' plan.

Since we will be traveling to the United States, we would also like to take advantage of this opportunity to perform any specialized tests that may not be available in Brazil, should Dr. Boles deem them necessary.

Patient information:

Chief complaints: Behavior (agitation), circadian sleep disorder, speech delay  
Present: ADHD, hypotonia, cognitive level delayed/unclear  
Absent: regression: seizures, fatigue, pain  
GI: loose stools in past

### Supplements as of May 2025:

- Gut permeability formula, 1 scoop 1 x/day mixed with juice or food (Peptan 4.5 g; Taurine 0.5 g; L-Glycine 1000 mg; Glucosamine sulfate 500 mg; Curcumin 95% 0.5 g; Fibregum 2.0 g; MSM 0.5 g; Orthosilicic acid 50 mg)
- L-Theanine 500 mg + GABA 500 mg + Memantine 5 mg + Inositol 500 mg + Citicoline 200 mg + 5-HTP 50 mg: 5ml twice a day (reduce dose if sedation occurs)
- Melatonin DUO 2 mg, 1 sublingual capsule diluted in a small amount of liquid before bedtime
- Methylcobalamin 1000 mcg, 1 drop in the morning and 1 at noon
- ProSleep 250 mg, try 1 to 2 capsules before bedtime
- Super Omega 3 liquid (1080 mg EPA + 720 mg DHA), 5ml once a day
- Taurine 500 mg, 1 capsule before bedtime
- Vitamin D3 3000 IU + Vitamin A 2000 IU + Vitamin E 50 IU + Tocopherol mix 50 mg + Vitamin K2 20 mcg: 5 drops/day
- Vitamin formula, 5ml after lunch (Vitamin B1 10 mg; B2 5 mg; B5 10 mg; B6 15 mg; Biotin 50 mcg; Zinc 20 mg; Selenium 50 mcg; Chromium 50 mcg; Manganese 0.5 mg; Magnesium ascorbate 300 mg; Betaglucan Plus 200 mg; Hydroxocobalamin 500 mcg; Siliciumax 150 mg; Lithium 50 mcg; Nicotinamide 15 mg)

### Clinical summary:

- **Diagnosis:** Autism Spectrum Disorder (ASD) confirmed around 2 to 2.5 years of age.
- **Detailed history:** on this link you can find a searchable list of all the exams that Isaac did

**Clinical History:** Isaac França is a 5-year-old male diagnosed with Autism Spectrum Disorder (ASD) around the age of 2.5 years. The initial concerns arose when he was approximately 18 months old, as his speech development was delayed, and he showed a lack of response when called by name. He has never developed functional speech and continues to have significant challenges in using spoken language to communicate. While he has a big vocabulary and can sing many different songs, he lacks the ability to use language with the intention to communicate. Recently, there has been some progress, as Isaac has started to verbalize simple words to express basic needs (e.g., chocolate, sleep, juice). Despite these small advances, he remains largely non-verbal and continues to wear diapers.

Isaac's motor development is strong; he is physically healthy and enjoys running, demonstrating good coordination and strength. However, he exhibits hyperactivity, often struggling to sit still or focus on tasks. Socially, Isaac prefers solitary play and has difficulty engaging with other children or adults. He tends to use toys in a non-functional manner and finds it challenging to participate in shared play activities.

**Current Situation:** Isaac remains in good health. Of course there is the ongoing concern regarding his communication abilities and the impact this has on his learning and development. Despite slow progress, recent improvements in his ability to verbalize basic needs have been encouraging. Isaac continues to receive specialized educational support, including the recent addition of a therapeutic assistant at school, which has shown promise in providing more individualized attention.

**Treatment and Interventions:** Isaac has been undergoing a combination of behavioral therapies and biomedical interventions. His current therapeutic regimen includes:

- **Dietary Modifications:** Gluten-free, dairy-free, and sugar-free diet, with occasional deviations, on gluten and sugar.
- **Behavioral Therapies:** Occupational therapy, music therapy, Applied Behavior Analysis (ABA).
- **Supplements:** Melatonin, taurine, a multivitamin complex, GABA, and others. Notably, he tried cannabidiol (CBD), but it was discontinued due to poor tolerance.
- **Hyperbaric Oxygen Therapy:** He underwent a few sessions of hyperbaric therapy, which provided temporary improvement that regressed after the treatment stopped.

### Family history:

**Family History:** There is a known family history of autism on the paternal side, with one adult cousin diagnosed with ASD. However, given the large family size, this may or may not be directly relevant to Isaac's condition.

Father: Computer scientist

Mother: Educated

No known chronic pain, fatigue, GI issues

### Non-genetic test results:

Normal testing: FRAT, EEG x2, MR brain

3/23/2025:

- Platelet Count – 301,000
- Mean Platelet Volume - 10.1
- ALT - 15
- GGT - 8
- Copper - 114
- CRP - <0.03
- Ionized Calcium - 1.27
- Mg - 2.1
- Vit A - 0.5
- Lead - <1.0
- Lipid Panel - 194/70/113/36
- Vit D - 59

### Genetic test results:

Chromosomal Microarray 11/1/2021: XY

Resultado:

Cromossomos sexuais: XY

ISCN: arr[GRCh38] 3q26.31q26.32(175364178\_176001139)x1

Tipo: deleção

Tamanho: 637 kb

Classificação: Provavelmente benigna

T-Exom 7/7/2023:

**Genetic Testing and Examinations:** Isaac has undergone one exome analyses, which were looked into by two labs:

1. **Tismoo - Exome Analysis (2023-04-18)**
  - Variant of Unknown Significance (VUS) identified in the MED13 gene.

- No pathogenic or likely pathogenic variants identified.
2. **Bioraras - Exome Analysis (2024-01-23)**
  - Pathogenic variant identified in the **GALT** gene, associated with Galactosemia.
  - Six variants of uncertain significance in the **MED13, ASS1, TAT, DLGAP1, and FHL1** genes.

These findings have not yet provided a definitive explanation for Isaac's clinical presentation.

**T-Exom®****Análise de dados do Exoma completo**

Nome do Paciente:	Isaac Lobato França	Código do Paciente:	TM968
Data de Nascimento:	06/11/2018	Local de Coleta:	Domicílio
Sexo:	Masculino	Tipo de Amostra:	Saliva (swab bucal)
Solicitado por:	Dr. Rogério Rodrigues Rita CRM-SC 4.538	Recebimento da Amostra:	18/04/2023
		Emissão do Relatório:	07/07/2023

**Exame Solicitado**

Sequenciamento e análise dos dados brutos do Exoma completo de Isaac Lobato França.

**Indicação Clínica**

Paciente com diagnóstico de Transtorno do Espectro do Autismo (TEA).

**RESULTADOS OBTIDOS**

A análise genética do Exoma completo de Isaac Lobato França foi realizada a partir da amostra de saliva, sob responsabilidade da TISMOO BIOTECH LABORATÓRIO LTDA (SP, Brasil). Uma variante genética de significado clínico desconhecido foi identificada no gene **MED13**, associado a transtornos do neurodesenvolvimento (Tabela 1). Esta análise genética não identificou variantes genéticas associadas a outras condições de saúde como achados incidentais e/ou secundários.

Na análise do Exoma completo de Isaac Lobato França, foi identificada uma variante genética de significado clínico desconhecido (VUS) no gene **MED13** como evento genético de extrema raridade populacional. Devido as características clínicas do paciente e desta alteração genética específica, sugere-se a investigação nos progenitores para verificar a possibilidade de mutação *de novo*, quer dizer, alteração genética que não foi herdada. Esta análise genética não identificou variantes genéticas associadas a outras condições de saúde como achados incidentais e/ou secundários.

**Tabela 1:** Variantes raras em genes associados ao desenvolvimento de quadros fenotípicos similares ao do paciente.

Gene	Localização (GRCh38)	Variante	Zigosidade (Ref/Alt)	Classificação (ACMG)	Condições associadas (Herança)	dbSNP (Origem)
GALT	Chr9 34647858	NM_000155:c.C404T (p.S135L)	Heterozigoto C/T	Patogênica	Galactosemia – AR (OMIM: 230400)	rs111033690 (N/D)
MED13	Chr17 62031587	NM_005121:c.A866T (p.D289V)	Heterozigoto T/A	Significado Incerto (PM2, PP3, BP1)	Transtorno de desenvolvimento intelectual – AD (OMIM: 618009)	rs925249026 (N/D)
ASS1	Chr9 130458525	NM_054012:c.G299A (p.R100H)	Heterozigoto G/A	Significado Incerto (PM1, PM2, PM5, PP5, BP4)	Citrulinemia - AR (OMIM: 215700)	rs138279074 (N/D)
TAT	Chr16 71570312	NM_000353:c.G998A (p.R333H)	Heterozigoto C/T	Significado Incerto (PM2, BP4)	Tirosinemia, tipo II – AR (OMIM: 276600)	rs771408463 (N/D)
FHL1	ChrX 136208570	NM_001159699:c.A665G (p.Q222R)	Hemizigoto A/G	Significado Incerto (PM2, BP4, PM1)	Distrofia muscular de Emery-Dreifuss, tipo 6 – LXR Miopatia corporal redutora, tipo 1A – LXD (OMIM: 300717) Miopatia corporal redutora, 1B – LX (OMIM: 300718) Miopatia escapuloperoneal – LXD (OMIM: 300695)	rs915687031 (N/D)

**AD:** Autossômica Dominante; **AR:** Autossômica Recessiva; **LXR:** Ligada ao X recessiva; **LXD:** Ligada ao X dominante; **XL:** Ligada ao X;  
**Ref:** Referência; **Alt:** Alterado; **N/D:** não determinada.

**Tabela 2:** Variantes raras em genes de susceptibilidade ao Transtorno do Espectro Autista (TEA).

Gene	Localização (GRCh38)	Variante	Zigosidade (Ref/Alt)	Classificação (ACMG)	Condições associadas (Score)	dbSNP (Origem)
DLGAP1	Chr18 3879219	NM_001242761:c.A850G (p.T284A)	Heterozigoto T/C	Significado Incerto (PM2, PP2, BP4)	TEA (SCORE: 2)	rs200178260 (N/D)
MED13	chr17 62031587	NM_005121:c.A866T (p.D289V)	Heterozigoto T/A	Significado Incerto (PM2, PP3, BP1)	TEA (SCORE: 1)	rs925249026* (N/D)

**Score (SFARI):** Classificação de evidência científica para associação entre o gene descrito e o risco de desenvolvimento de autismo (Score 1: Associação comprovada; Score 2: Forte candidato à associação).

\* Variante descrita na Tabela 1.

## MitoSwab Plus 8/1/2023:

**Name:** Isaac Franca      **Date of Birth:** 11/06/2018      **Dr.:** Burch, Mary

**MITOswab test:** - *Mitochondrial respiratory chain complexes (RC-I and RC-IV) activities and Citrate Synthase (CS) enzyme activity are measured in patient's buccal cells to evaluate the mitochondrial function in the buccal cells sample.*

### Result Values- (Observations)

Activity name	Value *	^Normal Range ^({mean ± SD})
Total Buccal Protein yield (micrograms)	703	
Citrate Synthase <sup>§</sup>	29.24 (242%)	4.4 – 22 ( <b>12.1 ±5.1</b> )
RC-IV (RC-IV/CS) <sup>¶</sup>	0.140 (45%)	0.15 -- 0.6 ( <b>0.31 ±0.1</b> )
RC-I (RC-I/CS) <sup>¶</sup>	3.6 (54%)	3.4 -- 11.9 ( <b>6.8 ±2.0</b> )

#### MITOswab test analysis reveals -

- The overall content of mitochondria was significantly above the normal range as indicated by the citrate synthase activity value (242% of the normal mean activity level) in test buccal sample.
- The activity of Respiratory Chain Complex-IV (RC-IV) (45% of the normal mean value) was below the normal range.
- The activity of Respiratory Chain Complex-I (RC-I) (54% of the normal mean value) was in the normal range.

#### Interpretation-

- Biochemical analysis results of subject's buccal sample suggest that it has marginally decreased activity of RC-IV and normal range activity of RC-I, but CS activity was increased significantly above the normal range.
- Almost 2.5-fold higher (than Normal mean value) CS activity may suggest a compensatory function in response to the mitochondrial dysfunction that may be present due to decreased activities of RC-IV.
- The RC-IV deficiency found in the test buccal sample was statistically non-significant.
- Periodic monitoring of mitochondrial enzyme assessment is strongly suggested.

#### Additional Information:-

The activity assay for mitochondrial respiratory chain complexes RC-II and RC-II+III were performed.

Activity name	Value *	^ Normal Range ^(mean ±SD)
RC-II (activity/CS) <sup>‡</sup>	0.121 (63%)	0.03 -- 0.35 ( <b>0.194 ±0.08</b> )
RC-II+III (activity/CS) <sup>†</sup>	0.018 (19%)	0.032 – 0.152 ( <b>0.092 ±0.03</b> )

#### Official laboratory report:

**VariantX** Genomic Unity® Whole Genome Analysis

Patient Name <b>Isaac França</b>	Date of Birth <b>Jun 6, 2018</b>	Test <b>202806864 / 99658</b>	Report Date <b>May 2, 2025</b>	MRN <b>-</b>
<b>Test Information</b>		<b>Indication for Testing</b>	<b>Included Analyses</b>	
Genetic Counselors	Rogerio R Rita and Richard Boles	Autism, Delayed speech and language development	> Small Sequence Variants > Mitochondrial Genome > Structural Variants > Short Tandem Repeats	
Cohort	Trio			
Sample Type	Saliva			
Sample Collection Date	Sep 7, 2024			
Sample Received Date	Sep 11, 2024			
Processed Date	Mar 19, 2025			
Ordering Clinician	Rogério Rogério Rita		ACMG Secondary Findings	Opted in
NPI	N/A		Actionable Findings	Opted in
<b>Results   Other Variants of Interest</b>				
<input type="radio"/> Primary	<input type="radio"/> ACMG Secondary	<input type="radio"/> Actionable	<input type="radio"/> Carrier	<input checked="" type="radio"/> Other Variants
<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

## Summary of Findings

\*\*\*\*\* Re-Analysis \*\*\*\*\*

This report is a re-analysis of the report that was issued on Dec 14, 2024. Please note that some variants may have been removed, added, altered, or reclassified. Such modifications could result from updates to databases, medical literature and published guidelines.

No pathogenic or likely pathogenic variants sufficient to cause disease were identified that have been associated with the clinical symptoms provided.

No variants were identified in the American College of Medical Genetics and Genomics (ACMG) list of genes to be reported as secondary findings.

Variant(s) were identified in this analysis that were not considered to impact the interpretation of this report and are listed in the table(s) below: 'Other Variants of Interest', 'Previously Reported Results'.

Findings	Location	Variant	Mode of Inheritance / Disease	Classification
Other Variants	<i>MED13</i> NM_005121.3	c.866A>T p.Asp289Val rs925249026 Heterozygous in proband Heterozygous in father Not detected in mother	Autosomal dominant intellectual developmental disorder G1	Uncertain Significance PP3_Moderate, PM2_Supporting
Supplementary (Previously Reported)	<i>GALT</i> NM_000155.4	c.404C>T p.Ser135Leu rs11033690 Heterozygous in proband Not detected in father Heterozygous in mother	-	-
Supplementary (Previously Reported)	<i>ASS1</i> NM_054012.4	c.299G>A p.Arg100His rs138279074 Heterozygous in proband Not detected in father Heterozygous in mother	-	-

## Summary of Findings (Continued)

Findings	Location	Variant	Mode of Inheritance / Disease	Classification
Supplementary (Previously Reported)	<i>TAT</i> NM_000353.3	c.998G>A p.Arg333His rs771408463 Heterozygous in proband Not detected in father Heterozygous in mother	-	-
Supplementary (Previously Reported)	<i>FHL1</i> NM_001159702.3	c.617A>G p.Gln206Arg rs915687031 Hemizygous in proband Not detected in father Heterozygous in mother	-	-
Supplementary (Previously Reported)	3q26.31q26.32	668.17 kb deletion Heterozygous in proband Heterozygous in father Not detected in mother	-	-

## Follow Up Recommendations

Genetic counseling is recommended to review both positive and negative results. Test results may benefit from periodic reevaluation for new clinical associations to variants and updated variant classification.

## Primary Findings

No findings were identified.

## ACMG Secondary Findings

No variants meeting the ACMG recommendations for reporting secondary findings were identified. Note that in some cases variants in genes listed by the ACMG may be reported in other sections of this report if the associated disorder is consistent with the patient's phenotype.

## Actionable Findings

No other actionable findings were identified at the time of reporting.

## Carrier Findings

No carrier findings were identified at the time of reporting.

## Other Variants Findings

This section of the report includes variants not considered causative of the primary indication for testing based on the clinical information provided. Examples include variants in genes of uncertain significance (GUS), variants in genes with no or limited correlation to the patient's phenotype, and variants associated with the family history.

Findings	Location	Variant	Mode of Inheritance / Disease	Classification
Other Variants	<i>MED13</i> NM_005121.3	c.866A>T p.Asp289Val rs925249026  Heterozygous in proband Heterozygous in father Not detected in mother	Autosomal dominant intellectual developmental disorder 61	Uncertain Significance PP3_Moderate, PM2_Supporting

## Supplementary Findings

This section of the report includes variants that were identified in the analysis, but were not interpreted, which includes runs or regions of homozygosity (ROH) and/or previously reported variants (PRVs), if applicable.

Findings	Location	Variant
Supplementary (Previously Reported)	<i>GALT</i> NM_000155.4	c.404C>T p.Ser135Leu rs111033690  Heterozygous in proband Not detected in father Heterozygous in mother
Supplementary (Previously Reported)	<i>ASS1</i> NM_054012.4	c.299G>A p.Arg100His rs138279074  Heterozygous in proband Not detected in father Heterozygous in mother
Supplementary (Previously Reported)	<i>TAT</i> NM_000353.3	c.998G>A p.Arg333His rs771408463  Heterozygous in proband Not detected in father Heterozygous in mother
Supplementary (Previously Reported)	<i>FHL1</i> NM_001159702.3	c.617A>G p.Gln206Arg rs915687031  Hemizygous in proband Not detected in father Heterozygous in mother
Supplementary (Previously Reported)	3q26.31q26.32	668.17 kb deletion  Heterozygous in proband Heterozygous in father Not detected in mother

## Patient Genotype

Gene	Genotype	Metabolizer Status
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*17	Rapid Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*1/*4	Intermediate Metabolizer
CYP3A5	*3/*3	Poor Metabolizer

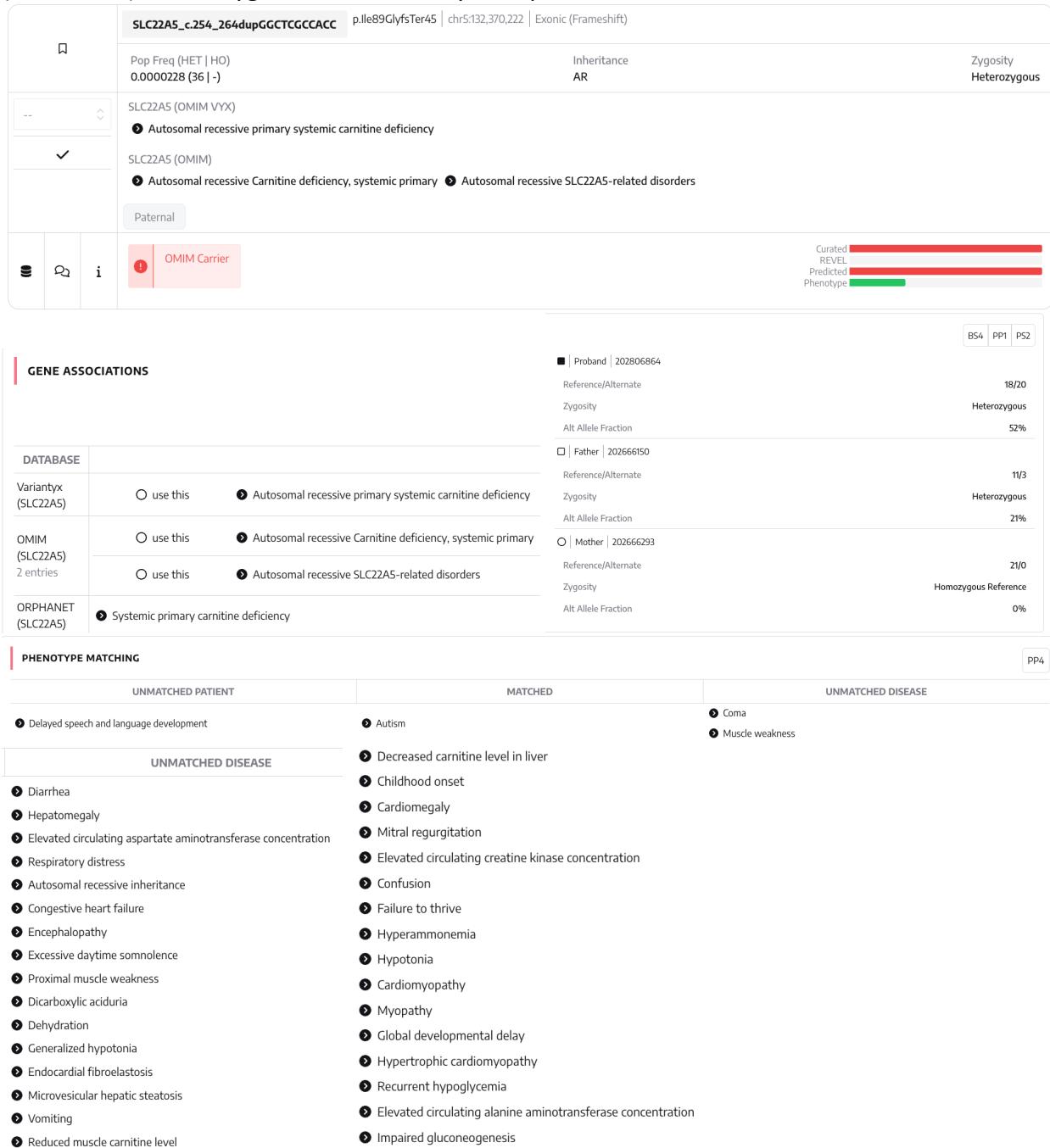
## Patient Genotype (Continued)

Gene	Genotype	Metabolizer Status
CYP4F2	*1/*1	Indeterminate
DYPD	c.85T>C (*9A)/c.1896T>C	Normal Metabolizer
NAT2	*4/*5	Indeterminate
NUDT15	*1/*1	Normal Metabolizer
SLCO1B1	*1/*14	Normal Function
TPMT	*1/*1	Normal Metabolizer
UGT1A1	*1/*36	Normal Metabolizer
VKORC1	Reference/Reference	Indeterminate

## Comprehensive Sequence Re-analysis - Variants of potential interest:

### *De novo* small variants:

SLC22A5 c.254\_264dupGGCTGCCACC, p.Ile89GlyfsTer45, chr5:132,370,222, Exonic (Frameshift), heterozygous, *de novo*, likely with paternal mosaicism:



HGMD																	
Phenotype	Carnitine deficiency, primary																
Variant Type	DM																
Accession	CI014475																
PMID &P	PATHOGENICITY SUPPORT	CITATION TYPE	PMID NOTES		ADDITIONAL PHENOTYPE	PUBLICATION											
11715001 Copy	PRI				Carnitine deficiency, primary	Wang <i>et al.</i> (2001) <i>Genet Med</i> 3:387											
31980526 Copy	✓	APR	Dataset 1, tab3, classified:Pathogenic [B:S132370222:T:TACCGGCTGCCChg38]		Carnitine deficiency	Hou <i>et al.</i> (2020) Precision medicine integrating whole-genome sequencing, comprehensive metabolomics, and advanced imaging. <i>PNAS</i> 117:3053											
38585546 Copy	✓	ACR				Basan <i>et al.</i> (2024) A Rare Treatable Cause of Cardiomyopathy: Primary Carnitine Deficiency. <i>MOL SYN</i> 15:156											

## ClinVar: Pathogenic x11

POPULATION DATA									
Date Range Specific PAF	Specify date range	DIY	D2Y	BA1	BS1	BS2	PM2	PS4	
Pop Freq	gnomAD Frequency	0.0000228							
0.0000228	gnomAD Heterozygous								
Variantx Frequency	36								
-	gnomAD Homozygous								
Variantx PDK Count									
-	gnomAD NF Frequency	0.0002207							
	gnomAD NF Population								
	Latino/Admixed American								

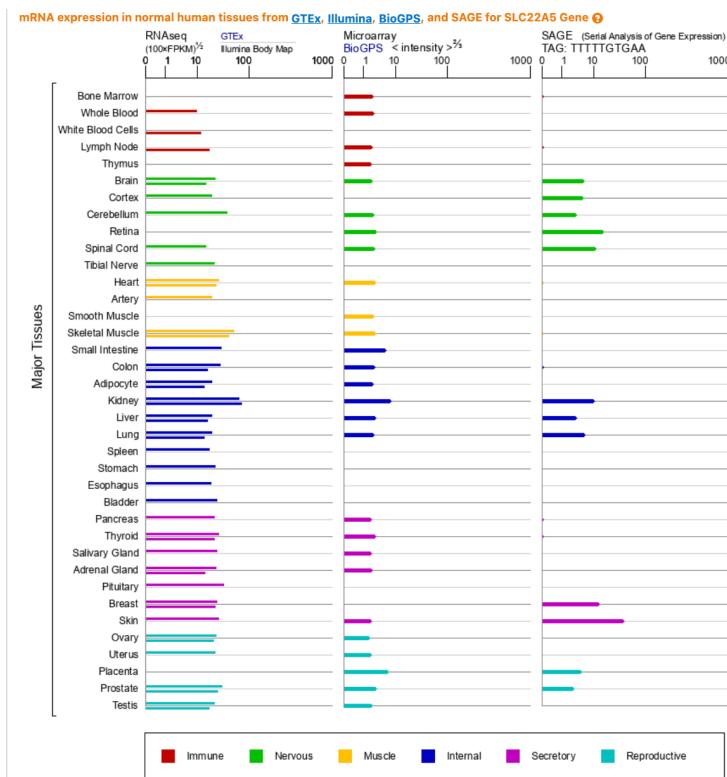
## SLC22A5: solute carrier family 22 member 5

Gene Other Names: OCTN2, SCD

Function Description: Sodium-ion dependent, high affinity carnitine transporter. Involved in the active cellular uptake of carnitine. Transports one sodium ion with one molecule of carnitine. Also transports organic cations such as tetraethylammonium (TEA) without the involvement of sodium. Also relative uptake activity ratio of carnitine to TEA is 11.3.

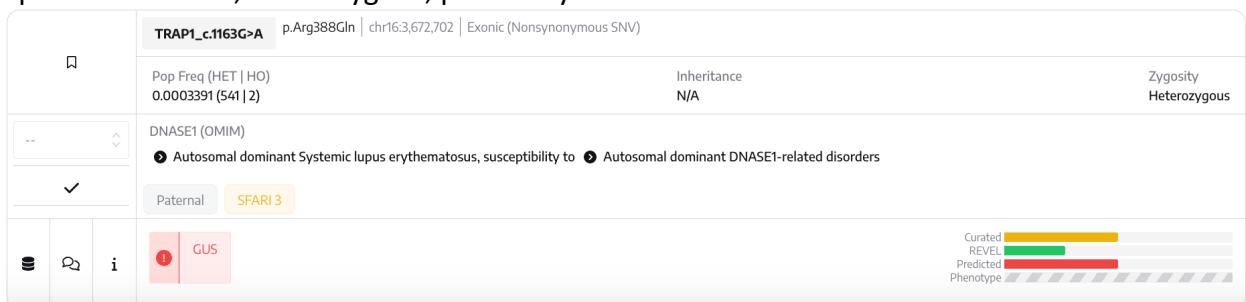


## GeneCards: 557 amino acids



Functional disease gene list: ATP1A2, ATP1A3, ATXN8OS, CACNA1A, CACNA1S, CDK8, CHAMP1, CLCN1, CNR1, COQ2, GFAP, GLA, GLS2, GRIN3B, HMBS, INF2, KCNH2, KCNJ18, KCNK18, KIF1B, KLK15, MAP1B, MEFV, OCM, OPRM1, OTC, PMP22, POGZ, POLG, PPM1D, PRRT2, PRX, RYR2, SCN1A, SCN2A, SCN4A, SCN9A, SCN10A, SCN11A, SH3TC2, SLC1A3, SLC2A1, TNFRSF1A, TNFRSF1B, TNXB, TRAP1, TRPA1, TRPC3, TRPM4, TRPV1, TUBB3:

TRAP1 c.1163G>A, p.Arg388Gln, chr16:3,672,702, Exonic (Nonsynonymous SNV), probable splice-site variant, heterozygous, paternally inherited:



## GENE ASSOCIATIONS

DATABASE	
HGMD (TRAP1) 12 entries	<ul style="list-style-type: none"> <li>● Congenital anomalies of the kidney and urinary tract/CAKUT in VACTERL</li> <li>● Cyclic vomiting syndrome</li> <li>● Developmental disorder</li> <li>● Focal segmental glomerulosclerosis</li> <li>● Autoinflammatory disease</li> <li>● Cardiovascular disease trait</li> <li>● Rubinstein-Taybi syndrome</li> <li>● Congenital anomalies of kidney and urinary tract</li> <li>● Hirschsprung disease</li> <li>● Juvenile idiopathic arthritis</li> <li>● Neurodevelopmental disorder</li> <li>● Parkinson disease, late-onset</li> </ul>
	ClinVar (TRAP1) 2 entries
	<ul style="list-style-type: none"> <li>● Congenital anomalies of kidney and urinary tract 1</li> <li>● Congenital anomaly of kidney and urinary tract</li> </ul>
	ClinVar (DNASE1) 2 entries
	<ul style="list-style-type: none"> <li>● Systemic lupus erythematosus</li> </ul>
	OMIM (DNASE1) 2 entries
	<p><input type="radio"/> use this      <input checked="" type="radio"/> Autosomal dominant Systemic lupus</p>
	<p><input type="radio"/> use this      <input checked="" type="radio"/> Autosomal dominant DNASE1-related</p>
	ORPHANET (DNASE1) 2 entries
	<ul style="list-style-type: none"> <li>● Systemic lupus erythematosus</li> <li>● Autosomal systemic lupus erythematosus</li> </ul>

		BS4	PP1	PS2
■   Proband   202806864				
Reference/Alternate		22/23		
Zygosity			Heterozygous	
Alt Allele Fraction				51%
<input type="checkbox"/>   Father   202666150				
Reference/Alternate		9/12		
Zygosity			Heterozygous	
Alt Allele Fraction				57%
<input checked="" type="radio"/>   Mother   202666293				
Reference/Alternate		21/0		
Zygosity			Homozygous Reference	
Alt Allele Fraction				0%

CLINVAR		BS3	BP6	PP5	PMS	PS1	PS3
HGVS Coding ↗		NM_016292.3:c.1163G>A		TRAP1			
Gene ↗							
INCLUDE IN REPORT	DISEASE	SEVERITY	OMIM	REVIEW STATUS			
<input type="checkbox"/>	not provided	Uncertain significance	.	criteria provided, single submitter (1/4)			
COMPUTATIONAL AND PREDICTIVE							
Curated Severity Score <b>4</b>	MutationTaster <b>10.0</b>	SIFT <b>0.015.D</b>	MetaLR <b>0.0579.T</b>				
REVEL <b>0.266</b>	PhyloP <b>0.892.D</b>	FATHMM <b>2.93.T</b>	GERP++ <b>535.D</b>				
Aggregate Predicted Severity Score <b>0.5</b>	PhastCons <b>0.742.B</b>	LRT <b>0.0.D</b>	MetaSVM <b>-1.166.T</b>				
	MutationAssessor <b>2.385.D</b>	Siphy <b>18.3915.B</b>	SpliceRF <b>0.75</b>				
			SpliceADA <b>0.897307727515607</b>				

POPULATION DATA		BA1	BS1	BS2	PM2	PS4
Date Range Specific PAF						
Specify date range <input type="text"/> ⏴ 1Y ⏴ 2Y						
Pop Freq 0.0004115	gnomAD Frequency 0.0003391	gnomAD Exomes Frequency -				
Variantyx Frequency 0.0004115	gnomAD Heterozygous 541					
Variantyx PDK Count 2430	gnomAD Homozygous 2	gnomAD NF Frequency 0.0004240				
	gnomAD NF Population South Asian					

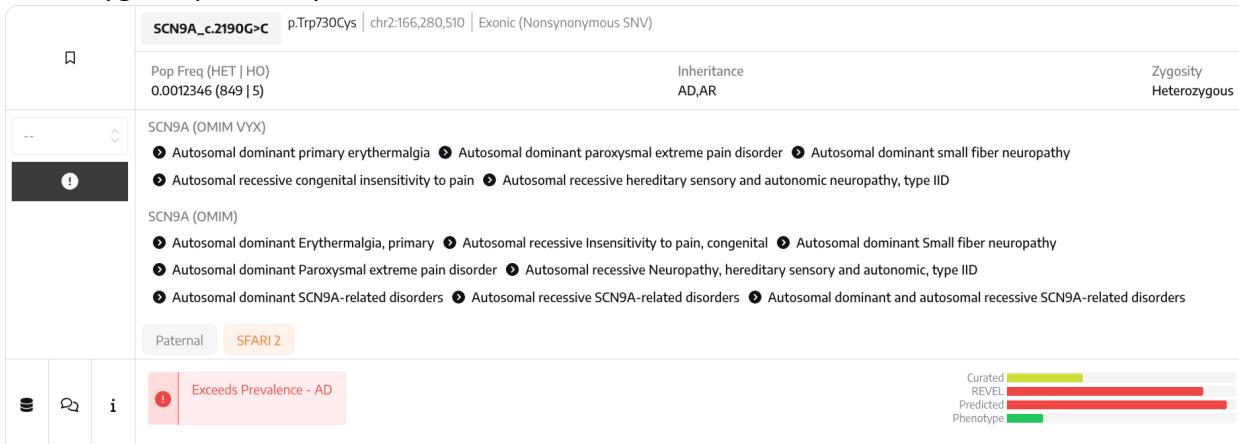
### IGV checked

TRAP1: TNF receptor associated protein 1

Gene Other Names: HSP75, HSP90L

Function Description: Chaperone that expresses an ATPase activity. Involved in maintaining mitochondrial function and polarization, most likely through stabilization of mitochondrial complex I. Is a negative regulator of mitochondrial respiration able to modulate the balance between oxidative phosphorylation and aerobic glycolysis. The impact of TRAP1 on mitochondrial respiration is probably mediated by modulation of mitochondrial SRC and inhibition of SDHA.

SCN9A c.2190G>C, p.Trp730Cys, chr2:166,280,510, Exonic (Nonsynonymous SNV), heterozygous, paternally inherited:



## GENE ASSOCIATIONS

DATABASE		
Variantyx (SCN9A) 5 entries	<input type="radio"/> use this	● Autosomal dominant primary erythermalgia
	<input type="radio"/> use this	● Autosomal dominant paroxysmal extreme pain disorder
	<input type="radio"/> use this	● Autosomal dominant small fiber neuropathy
	<input type="radio"/> use this	● Autosomal recessive congenital insensitivity to pain
	<input type="radio"/> use this	● Autosomal recessive hereditary sensory and autonomic neuropathy, type IID
OMIM (SCN9A) 8 entries	<input type="radio"/> use this	● Autosomal dominant Erythermalgia, primary
	<input type="radio"/> use this	● Autosomal recessive Insensitivity to pain, congenital
	<input type="radio"/> use this	● Autosomal dominant Small fiber neuropathy
	<input type="radio"/> use this	● Autosomal dominant Paroxysmal extreme pain disorder
	<input type="radio"/> use this	● Autosomal recessive Neuropathy, hereditary sensory and autonomic, type IID
	<input type="radio"/> use this	● Autosomal dominant SCN9A-related disorders
	<input type="radio"/> use this	● Autosomal recessive SCN9A-related disorders
	<input type="radio"/> use this	● Autosomal dominant and autosomal recessive SCN9A-related disorders
HGMD (SCN1A-AS1) 4 entries		● Congenital insensitivity to pain
		● Autism
		● Autism spectrum disorder
		● Neuropathic pain, in diabetic peripheral neuropathy
ClinVar (SCN9A) 13 entries		● Generalized epilepsy with febrile seizures plus, type 7...Neuropathy, hereditary sensory and autonomic, type 2A
		● Channelopathy-associated congenital insensitivity to pain, autosomal recessive
		● Primary erythermalgia
		● Paroxysmal extreme pain disorder
		● Inborn genetic diseases
		● Childhood epilepsy with centrotemporal spikes
		● Neuropathy, hereditary sensory and autonomic, type 2A
		● Small fiber neuropathy
		● Pain insensitivity
		● Acute episodes of neuropathic symptoms...Abnormality of pain sensation
		● Generalized epilepsy with febrile seizures plus, type 7
		● Neuropathy, hereditary sensory and autonomic, type IID
		● SCN9A-related peripheral neuropathies associated with increased pain
ClinVar (SCN1A-AS1) 2 entries		● Early infantile epileptic encephalopathy with suppression bursts
		● Severe myoclonic epilepsy in infancy

## PHENOTYPE MATCHING

UNMATCHED PATIENT	MATCHED	UNMATCHED DISEASE	PP4
<input checked="" type="checkbox"/> Autism <input checked="" type="checkbox"/> Delayed speech and language development		● Urinary incontinence ● Impaired temperature sensation ● Impaired tactile sensation ● Hypohidrosis ● Autosomal recessive inheritance ● Abnormal autonomic nervous system physiology ● Hyposmia ● Painless fractures due to injury ● Anosmia ● Intellectual disability ● Impaired proprioception ● Pain insensitivity ● Abnormal nerve conduction velocity ● Paresthesia ● Anhidrosis ● Hyporeflexia ● Congenital onset	

■ | Proband | 202806864

Reference/Alternate 26/31

Zygosity Heterozygous

Alt Allele Fraction 54%

□ | Father | 202666150

Reference/Alternate 29/26

Zygosity Heterozygous

Alt Allele Fraction 47%

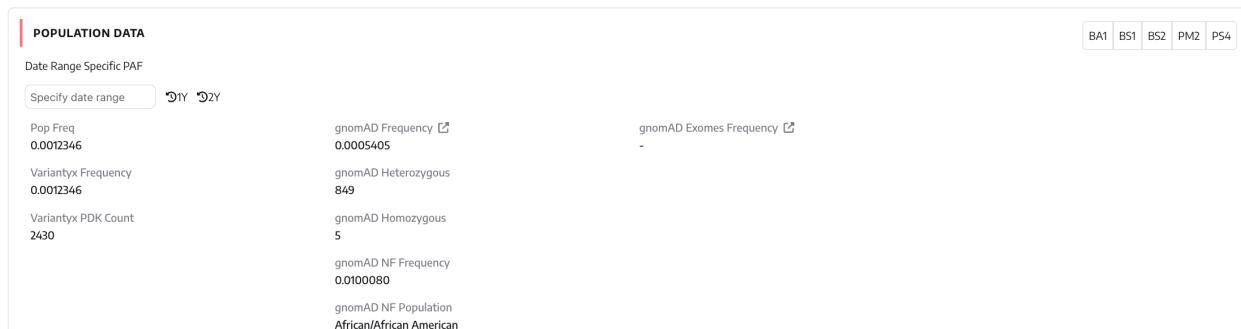
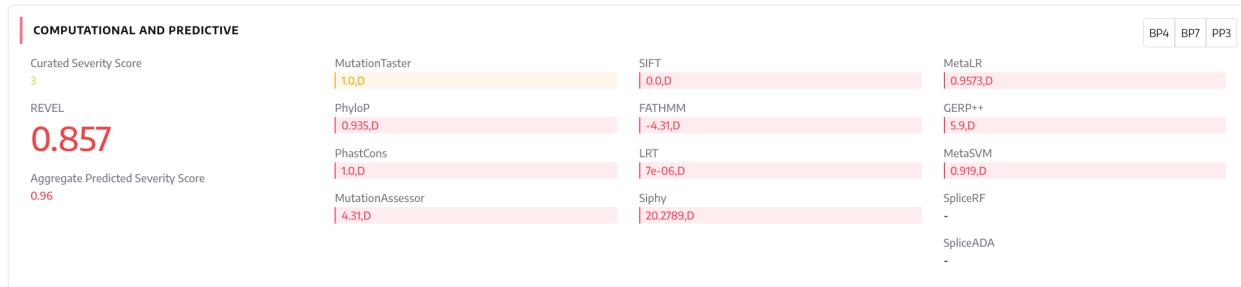
○ | Mother | 202666293

Reference/Alternate 26/0

Zygosity Homozygous Reference

Alt Allele Fraction 0%

ClinVar: Likely benign x7, Benign x2



### IGV checked

SCN9A: sodium voltage-gated channel alpha subunit 9

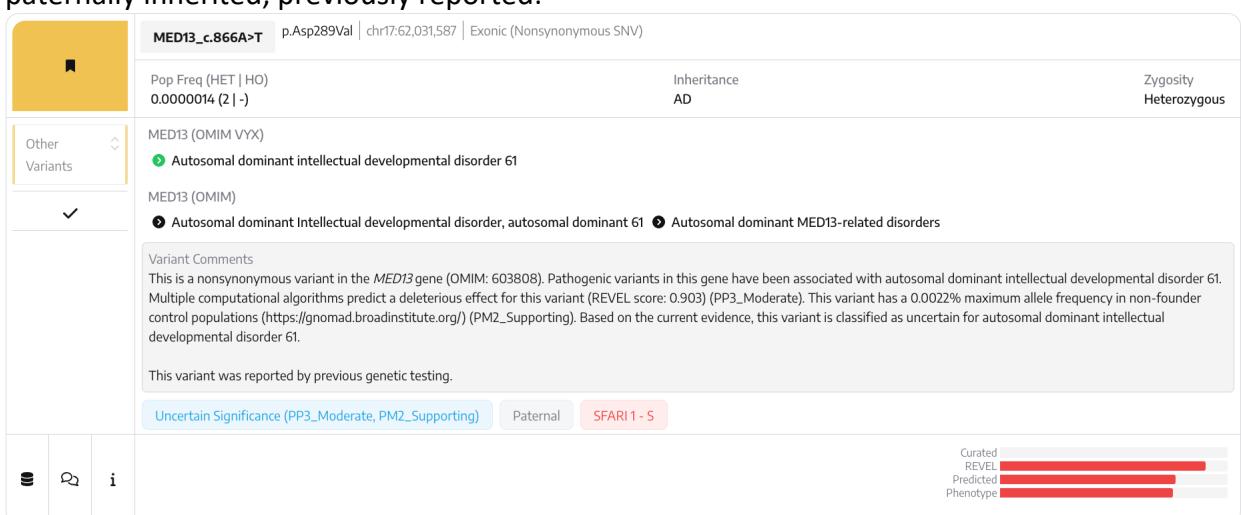
Gene Other Names: Nav1.7, PN1, NE-NA, NENA, ETHA

Function Description: Mediates the voltage-dependent sodium ion permeability of excitable membranes.

Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which Na(+) ions may pass in accordance with their electrochemical gradient. It is a tetrodotoxin-sensitive Na(+) channel isoform. Plays a role in pain mechanisms, especially in the development of inflammatory pain (By similarity).

### Other inherited small variants:

MED13 c.866A>T, p.Asp289Val, chr17:62,031,587, Exonic (Nonsynonymous SNV), heterozygous, paternally inherited, previously reported:



## GENE ASSOCIATIONS

DATABASE	CL	
Variantyx (MED13)	<input checked="" type="radio"/> on report	<input checked="" type="radio"/> Autosomal dominant intellectual developmental disorder 61
OMIM (MED13) 2 entries	<input type="radio"/> use this	<input checked="" type="radio"/> Autosomal dominant Intellectual developmental disorder, autosomal dominant 61
	<input type="radio"/> use this	<input checked="" type="radio"/> Autosomal dominant MED13-related disorders
ORPHANET (MED13)	<input checked="" type="radio"/> Non-specific syndromic intellectual disability	
	<input checked="" type="radio"/> Autism spectrum disorder	
	<input checked="" type="radio"/> Intellectual disability/developmental delay & speech delay/disorder	
	<input checked="" type="radio"/> Developmental disorder	
	<input checked="" type="radio"/> Neurodevelopmental disorder	
	<input checked="" type="radio"/> Autism	
	<input checked="" type="radio"/> Intellectual disability	
	<input checked="" type="radio"/> Congenital diaphragmatic hernia	
	<input checked="" type="radio"/> Developmental and epileptic encephalopathy with infantile spasms	
	<input checked="" type="radio"/> Developmental delay and dysmorphic features	
HGMD (MED13) 16 entries		
ClinVar (MED13) 7 entries		<input checked="" type="radio"/> Developmental language disorder <input checked="" type="radio"/> Intellectual developmental disorder 61 <input checked="" type="radio"/> Intellectual developmental disorder, autosomal dominant 61 <input checked="" type="radio"/> Microcephaly <input checked="" type="radio"/> Moderate intellectual disability, speech delay, ADHD, pervasive dev <input checked="" type="radio"/> Multiple congenital abnormalities <input checked="" type="radio"/> Sarcoma  <input checked="" type="radio"/> Intellectual developmental disorder 61 <input checked="" type="radio"/> Inborn genetic diseases <input checked="" type="radio"/> Autosomal dominant isolated somatotropin deficiency <input checked="" type="radio"/> MED13-related disorder <input checked="" type="radio"/> CDK8-kinase module-associated disorder <input checked="" type="radio"/> Neurodevelopmental disorder <input checked="" type="radio"/> See cases

## PHENOTYPE MATCHING

UNMATCHED PATIENT	MATCHED	UNMATCHED DISEASE
	<input checked="" type="radio"/> Delayed speech and language development <input checked="" type="radio"/> Autism	<input checked="" type="radio"/> Narrow palpebral fissure <input checked="" type="radio"/> Speech apraxia <input checked="" type="radio"/> Prominent nasal bridge <input checked="" type="radio"/> Generalized myoclonic-ataxic seizure <input checked="" type="radio"/> Wide mouth <input checked="" type="radio"/> Autosomal dominant inheritance <input checked="" type="radio"/> Periorbital fullness <input checked="" type="radio"/> Thin upper lip vermillion <input checked="" type="radio"/> Synophrys <input checked="" type="radio"/> Smooth philtrum <input checked="" type="radio"/> Hypertelorism <input checked="" type="radio"/> Wide nasal bridge <input checked="" type="radio"/> Chronic constipation <input checked="" type="radio"/> Hypotonia <input checked="" type="radio"/> Global developmental delay <input checked="" type="radio"/> Duane anomaly <input checked="" type="radio"/> Delayed gross motor development

■ | Proband | 202806864

Reference/Alternate	33/36
Zygosity	Heterozygous
Alt Allele Fraction	52%

□ | Father | 202666150

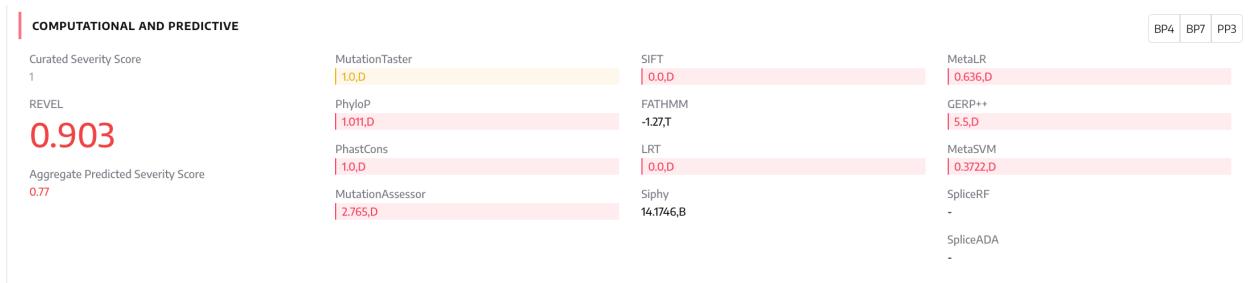
Reference/Alternate	17/10
Zygosity	Heterozygous
Alt Allele Fraction	37%

○ | Mother | 202666293

Reference/Alternate	20/0
Zygosity	Homozygous Reference
Alt Allele Fraction	0%

BS4 PP1 PS2

PP4



## IGV checked

MED13: mediator complex subunit 13

Gene Other Names: KIAA0593, TRAP240

Function Description: Component of the Mediator complex, a coactivator involved in the regulated transcription of nearly all RNA polymerase II-dependent genes. Mediator functions as a bridge to convey information from gene-specific regulatory proteins to the basal RNA polymerase II transcription machinery. Mediator is recruited to promoters by direct interactions with regulatory proteins and serves as a scaffold for the assembly of a functional preinitiation complex with RNA polymerase II and the general transcription factors.

HGMD Disease Count  
21

HGMD Diseases

DISEASE	COUNT	PUBLICATIONS
Autism spectrum disorder	16	Fu et al. (2022) <i>Nat Genet</i> 54:1320 Yuen et al. (2017) <i>Nat Neurosci</i> 20:602 Fu et al. (2022) Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. <i>NAT GENET</i> 54:1320 Trost et al. (2022) Genomic architecture of autism from comprehensive whole-genome sequence annotation. <i>CELL</i> 185:4409 Arteche-Lpez et al. (2021) <i>Genes (Basel)</i> 12:560
Intellectual disability/developmental delay & speech delay/disorder	12	Snijders Blok et al. (2018) <i>Hum Genet</i> 137:375 Kaplanis et al. (2020) Evidence for 28 genetic disorders discovered by combining healthcare and research data. <i>NATURE</i> 586:757 O'Brien et al. (2022) <i>Genet Med</i> 24:192
Autism	9	Wright et al. (2024) <i>Genet Med</i> 26:10120 Zhou et al. (2022) <i>Nat Genet</i> 54:1305 Sandoval-Talamantes et al. (2023) <i>Genes (Basel)</i> 14:
Developmental disorder	6	Kaplanis et al. (2020) <i>Nature</i> 586:757 Turner et al. (2019) <i>Am J Hum Genet</i> 105:1274 Kaplanis et al. (2020) Evidence for 28 genetic disorders discovered by combining healthcare and research data. <i>NATURE</i> 586:757
Neurodevelopmental disorder	4	Spataro et al. (2023) <i>Genes (Basel)</i> 14: Sanchis-Juan et al. (2023) <i>Am J Hum Genet</i> 110:1343 Pranav Chand et al. (2023) <i>Eur J Med Genet</i> 66:104730
OMIM Phenotypes		DISEASE
		Intellectual developmental disorder, autosomal dominant 61
		COUNT

OMIM:

\* 603808

## MEDIATOR COMPLEX SUBUNIT 13; MED13

*Alternative titles; symbols*

THYROID HORMONE RECEPTOR-ASSOCIATED PROTEIN 1; THRAP1  
THYROID HORMONE RECEPTOR-ASSOCIATED PROTEIN, 240-KD; TRAP240

**HGNC Approved Gene Symbol: MED13**

**Cytogenetic location:** 17q23.2 **Genomic coordinates (GRCh38):** 17:61,942,605-62,065,278 (from NCBI)

### Gene-Phenotype Relationships

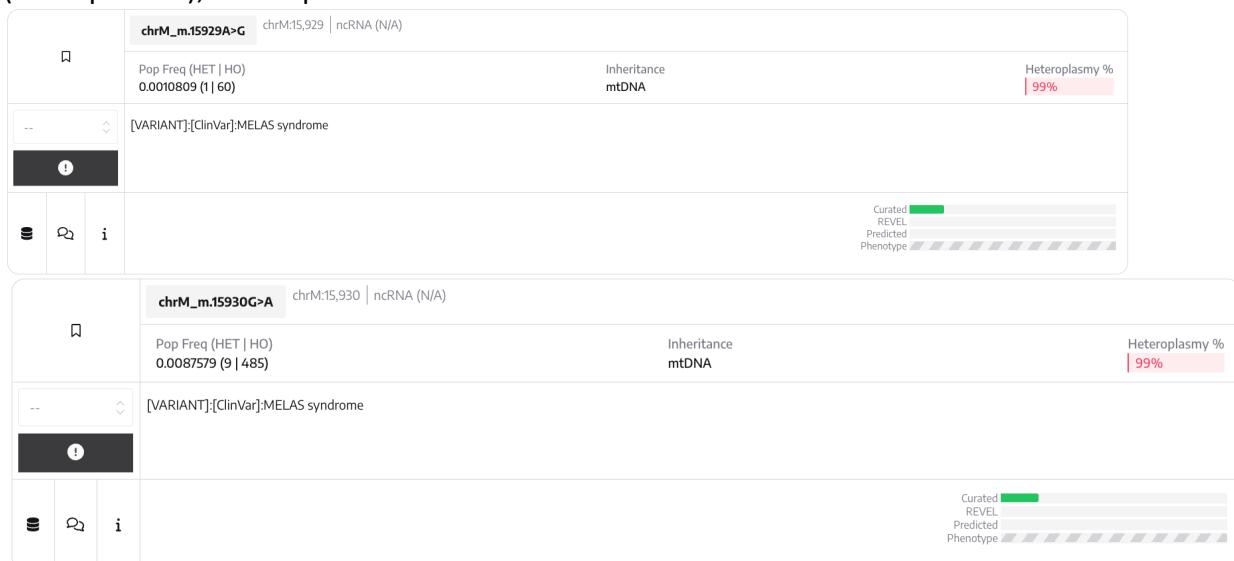
Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key
17q23.2	Intellectual developmental disorder, autosomal dominant 61	618009	AD	3

**Description:** MED13 is a subunit of the large Mediator complex that functions with DNA-binding transcription factors and RNA polymerase II (see 180660) for gene activation (summary by Sato et al., 2004).

**Description:** Autosomal dominant intellectual developmental disorder-61 (MRD61) is characterized by global developmental delay apparent in infancy with mildly impaired intellectual development, expressive speech delay, and behavioral abnormalities, including autism spectrum disorder and attention deficit-hyperactivity disorder (ADHD). Most affected individuals learn to walk on time or with some mild delay. Additional features are highly variable and may include nonspecific dysmorphic features, obstipation, ocular anomalies, and poor overall growth (Snijders Blok et al., 2018).

mtDNA variants:

MT-TT m.15929AG>GA, chrM:15,929, ncRNA (N/A), homoplasmic, maternally inherited (homoplasmic); stated prevalences are for each variant alone:



HAPLOGROUP	ALLEL NUMBER	HOMOPLASMIC AC	HOMOPLASMIC AF	HETEROPLASMIC AC	HETEROPLASMIC AF
A	2680	2	0.000746	0	0
B	1537	0	0	0	0
C	868	2	0.002304	0	0
D	603	0	0	0	0
E	34	0	0	0	0
F	282	0	0	0	0
G	91	0	0	0	0
H	14784	3	0.000203	1	0.000068
HV	701	0	0	0	0
I	934	0	0	0	0
J	3143	0	0	0	0
K	2732	0	0	0	0
L0	663	0	0	0	0
L1	2977	49	0.01646	0	0
L2	4724	0	0	0	0
L3	5671	0	0	0	0
L4	126	0	0	0	0
L5	1	0	0	0	0
M	1298	0	0	0	0
N	366	0	0	0	0
P	7	0	0	0	0
R	393	0	0	0	0
T	3080	0	0	0	0
U	6037	2	0.000331	0	0
V	1234	0	0	0	0
W	819	0	0	0	0
X	546	2	0.003663	0	0
Y	12	0	0	0	0
Z	89	0	0	0	0
HAPLOGROUP	ALLEL NUMBER	HOMOPLASMIC AC	HOMOPLASMIC AF	HETEROPLASMIC AC	HETEROPLASMIC AF
A	2679	4	0.001493	0	0
B	1537	10	0.006506	0	0
C	868	170	0.195853	0	0
D	603	4	0.006633	0	0
E	34	0	0	0	0
F	282	2	0.007092	0	0
G	91	4	0.043956	0	0
H	14781	48	0.003247	6	0.000406
HV	701	10	0.014265	0	0
I	932	1	0.001073	0	0
J	3143	4	0.001273	0	0
K	2732	14	0.005124	0	0
L0	663	6	0.00905	1	0.001508
L1	2974	29	0.009751	0	0
L2	4719	9	0.001907	0	0
L3	5668	105	0.018525	0	0
L4	126	0	0	0	0
L5	1	0	0	0	0
M	1298	5	0.003852	0	0
N	365	0	0	0	0
P	7	0	0	0	0
R	393	3	0.007634	0	0
T	3076	0	0	1	0.000325
U	6033	37	0.006133	1	0.000166
V	1234	16	0.012966	0	0
W	819	4	0.004884	0	0
X	546	0	0	0	0
Y	12	0	0	0	0
Z	89	0	0	0	0



MT-ND1 m.3397A>G, p.Met31Val, chrM:3,397, Exonic (Nonsynonymous SNV), homoplasmic, maternally inherited (homoplasmic):

**chrM\_m.3397A>G** p.Met31Val | chrM:3,397 | Exonic (Nonsynonymous SNV)

Pop Freq (HET | HO)  
0.0015241 (1 | 85)

Inheritance  
mtDNA

Heteroplasmy %  
100%

[VARIANT]:[Mitomap]:ADPD / possibly LVNC-cardiomyopathy associated / resistance to high altitude pulmonary edema[ClinVar]:Leigh syndrome; Alzheimer disease; Parkinson disease, late-onset

Curated  
REVEL  
Predicted  
Phenotype

**CLINVAR**

HGVS Coding ▾  
Gene ▾

chrM:m.3397A>G  
MT-ND1

INCLUDE IN REPORT	DISEASE	SEVERITY	OMIM	REVIEW STATUS
<input type="checkbox"/>	Parkinson disease, late-onset	Pathogenic	168600	no assertion criteria provided (0/4)
<input type="checkbox"/>	Leigh syndrome	Benign	256000	criteria provided, single submitter (1/4)
<input type="checkbox"/>	Alzheimer disease	Pathogenic	.	no assertion criteria provided (0/4)

BS3 BP6 PPS PMS PS1 PS3

IGV checked

**Conservation**

PhyloP 100v	8.729 ⓘ
PhastCons 470way	0.036 ⓘ
PhyloP 470way	0.58 ⓘ
PhastCons 100v	1 ⓘ

**Pathogenicity predictors ⚠ 5**

PolyPhen2	Benign ⓘ
VEST	Neutral ⓘ
MutationTaster	.
CADD	Neutral ⓘ
EFIN SP	Damaging ⓘ
PANTHER	.
SIFT	Neutral ⓘ
MitoClass 1	Damaging ⓘ
fathmm	.
PROVEAN	Damaging ⓘ
EFIN HD	Neutral ⓘ
PhD-SNP	Disease ⓘ
SIFT4G	Damaging ⓘ
SNPDryad	Neutral ⓘ
AlphaMissense	Likely benign ⓘ
Mutation Assessor	Medium ⓘ
MLC	Neutral ⓘ

**Pathogenicity meta-predictors ⚠ 3**

APOGEE1	Pathogenic ⓘ
Condel	Deleterious ⓘ
DEOGEN2	.
APOGEE2	Vus+ ⓘ
COVEC WMV	Neutral ⓘ
Meta SNP	Disease ⓘ
CAROL	Neutral ⓘ
MtoolBox	Neutral ⓘ

## Structural variants:

3q26.31q26.32x1(175,361,471-176,029,643), 668.17kbp, Exonic, (Deletion), heterozygous, paternally inherited; previously reported:

**3q26.31q26.32x1(175,361,471-176,029,643)** 668.17kbp | Exonic | ((Deletion))

Pop Freq 0.0000804 Genes (Prioritized) NAALADL2, MIR4789... +6 more Genotype Heterozygous Depth Call (Overlap) 0.50000 (1.000000)

Previously Reported [HGMD]: Craniofacial anomalies and learning difficulties/developmental delay

Comments for report  
This is a paternally inherited heterozygous interstitial deletion of 668.17 kb within the region of chromosome 3q26.31 to 3q26.32. The genes within the region can be retrieved from the UCSC browser using the coordinates chr3:175,361,472-176,029,643 (GRCh38).

This deletion may correlate with a previously reported result from another diagnostic laboratory. It is recommended to review this result in the context of any prior molecular testing that has been done for this individual. Any differences in size, genomic coordinates and/or chromosomal bands may be attributed to comparisons between the genome build, testing methodology and/or bioinformatic analysis platforms used.

Read Based Structural Variants Paternal

Phenotype 

IGV / SVP 

GROUP ZYGOSITY					
<input checked="" type="checkbox"/> Proband   202806864		Zygosity	Heterozygous		
<input type="checkbox"/> Father   202666150		Zygosity	Heterozygous		
<input type="checkbox"/> Mother   202666293		Zygosity	Homozygous Reference		

ON REPORT	GENE	OMIM PHENOTYPES	TRANSCRIPT	EXON RANK START	EXON RANK STOP	AFFECTED CDS
<input type="radio"/> use this	NAALADL2		ENST00000454872 (NM_207015.3) Total # of Exons: 14	6	14	1298 / 2388 (54.36%)
<input type="radio"/> use this	MIR4789		ENST00000577469 (NM_039952.1) Total # of Exons: 1	1	1	Non-Coding
<input type="radio"/> use this	RNU6-1233P		ENST00000362922 (-) Total # of Exons: 1	1	1	Non-Coding
<input type="radio"/> use this	RNU4-91P		ENST00000364778 (-) Total # of Exons: 1	1	1	Non-Coding
<input type="radio"/> use this	UBE2V1P2		ENST00000397758 (-) Total # of Exons: 1	1	1	Non-Coding
<input type="radio"/> use this	RNU6-1317P		ENST00000364582 (-) Total # of Exons: 1	1	1	Non-Coding
<input type="radio"/> use this	NAALADL2-AS1		ENST00000426315 (-) Total # of Exons: 3	1	3	Non-Coding
<input type="radio"/> use this	ACTG1P23		ENST00000437653 (-) Total # of Exons: 1	1	1	Non-Coding

**NAALADL2: N-acetylated alpha-linked acidic dipeptidase like 2**  
Function Description: May be catalytically inactive

## DISEASE PHENOTYPES

HGMD Disease Count

1

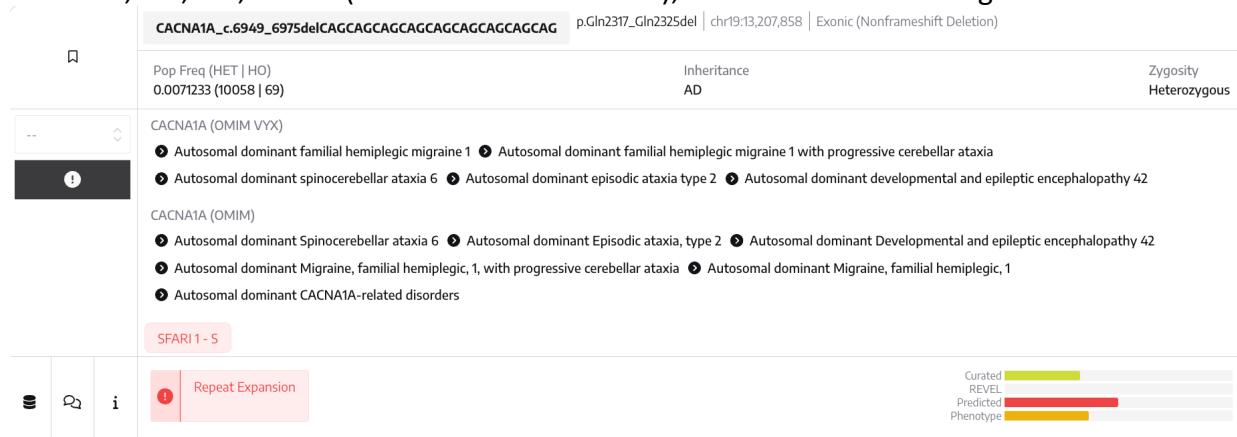
HGMD Diseases

DISEASE	COUNT	PUBLICATIONS
Developmental disorder	4	Kaplanis <i>et al.</i> (2020) <i>Nature</i> 586:757
Autism spectrum disorder	2	Fu <i>et al.</i> (2022) <i>Nat Genet</i> 54:1320
Cornelia de Lange syndrome	2	Kaur <i>et al.</i> (2023) <i>Am J Med Genet A</i> 191:2113
Mllerian, renal & cervicothoracic abnormalities	1	Backhouse <i>et al.</i> (2019) <i>Sex Dev</i> 13:26
Cardiovascular disease trait	1	Glicksberg <i>et al.</i> (2019) <i>BMC Med Genomics</i> 12:

SVPlots checked

Short tandem repeats:

CACNA1A c.6949\_6975delCAGCAGCAGCAGCAGCAGCAGCAG, p.Gln2317\_Gln2325del, chr19:13,207,858, Exonic (Nonframeshift Deletion); variant of uncertain significance:



CACNA1A 4/11 CAG repeats

Checked by GAV

Off-target/incidental variants: No variants of interest

Per our discussion today:

*No variants were identified that are highly likely to be disease causal by themselves. However, multiple variants were identified that may or may not be disease related, and some of them may suggest therapeutic options.*

*Disease is likely polygenic and multifactorial. The postulated mechanism of disease is mitochondrial dysfunction. Variants in the mother contribute to mitochondrial dysfunction on the supply side, while variants from the fathers contribute to mitochondrial dysfunction on the demand side, as well as protecting mitochondrial proteins in a highly oxidative environment.*

- SLC22A5 c.254\_264dupGGCTGCCACC, p.Ile89GlyfsTer45, chr5:132,370,222, Exonic (Frameshift), heterozygous, *de novo*, likely with paternal mosaicism:
  - This is a *de novo* loss-of-function Pathogenic variant in a gene generally considered to have recessive inheritance.
    - The variant is very rare (5 in 100K) in humans.
    - Paternal gonadal mosaicism is likely.
  - The protein encoded by this gene is a carnitine transporter, including on the renal epithelium, brain, muscle, and most other tissues (not liver).
  - Variants in this gene have been reported in carnitine uptake deficiency, a severe autosomal-recessive disorder appearing in infancy. However, relatively mild degrees of carnitine deficiency have been seen in heterozygote parents (carriers), who sometimes have mild symptoms in my experience, and anecdotally can benefit from carnitine supplementation.
  - This *de novo* variant is a good candidate for being disease related in Isaac as a risk factor.
- TRAP1 c.1163G>A, p.Arg388Gln, chr16:3,672,702, Exonic (Nonsynonymous SNV), probable splice-site variant, heterozygous, paternally inherited:
  - This variant is highly likely to alter protein function, as it is predicted to alter a splice site.
    - This is also a missense variant. It is uncommon (0.7%) in humans, conserved in vertebrates, and variably predicted as such by (6/10) computer algorithms.
  - The protein encoded by this gene is a mitochondrial chaperone that protects proteins in the mitochondria in high oxidative situations.
  - The phenotype regarding variants in this gene has not been well delineated. In particular, the loss-of-function phenotype is poorly delineated. Cases are reported in a variety of neurodevelopmental and morphological disorders. In particular, this gene has been associated with autism.
  - This variant is a very good candidate for being disease related in Isaac as a risk factor.

- SCN9A c.2190G>C, p.Trp730Cys, chr2:166,280,510, Exonic (Nonsynonymous SNV), heterozygous, paternally inherited:
  - This variant is likely to alter protein function, as it is uncommon (just > 0.1%) in humans, highly conserved in vertebrates, and predicted as such by (10/10) computer algorithms.
  - This gene encodes for one subunit of the NaV1.7 sodium channel that transmits electrical signals in nociceptors, which are the peripheral nerve cells that transmit pain signals.
  - Disease manifestations are generally autosomal dominantly-inherited, chronic pain conditions resulting from hyperactive mutant channels in which an increase in sodium ion influx enhances the transmission of pain signals. These conditions, termed erythromelalgia, paroxysmal extreme pain disorder, and small fiber neuropathy, all have in common episodes of severe noxious stimuli (often pain, but can be burning, itching, etc., often with allodynia).
    - Signs and symptoms can be localized or generalized, often associated with erythema, swelling, and warmth, sometimes accompanied with an extended peripheral (e.g., autonomic, enteric, sensory) neuropathy, and occasionally associated with seizures or degeneration.
  - This variant is a good candidate for being disease related in Isaac as a risk factor for behavioral meltdowns, which may be associated with noxious signaling such a pain, nausea, heat, etc.
- MED13 c.866A>T, p.Asp289Val, chr17:62,031,587, Exonic (Nonsynonymous SNV), heterozygous, paternally inherited, previously reported:
  - This variant is likely to alter protein function, as it is extremely rare (3 in a million) in humans, highly conserved in vertebrates, and predicted as such by (8/10) computer algorithms.
  - The protein encoded by this gene is mediator complex subunit 13
    - “Function Description: Component of the Mediator complex, a coactivator involved in the regulated transcription of nearly all RNA polymerase II-dependent genes. Mediator functions as a bridge to convey information from gene-specific regulatory proteins to the basal RNA polymerase II transcription machinery. Mediator is recruited to promoters by direct interactions with regulatory proteins and serves as a scaffold for the assembly of a functional preinitiation complex with RNA polymerase II and the general transcription factors.”
    - “MED13 is a subunit of the large Mediator complex that functions with DNA-binding transcription factors and RNA polymerase II (see 180660) for gene activation (summary by Sato et al., 2004).” [OMIM]
  - Variants in this gene have been associated with a neurodevelopmental disorder, autosomal dominant intellectual developmental disorder-61 (MRD61). This disorder “is characterized by global developmental delay apparent in infancy with mildly impaired intellectual development, expressive speech delay, and behavioral abnormalities, including autism spectrum disorder and attention deficit-hyperactivity disorder (ADHD). Most affected individuals learn to walk on

- time or with some mild delay. Additional features are highly variable and may include nonspecific dysmorphic features, obstipation, ocular anomalies, and poor overall growth (Snijders Blok et al., 2018)." [OMIM]
- This variant is a good candidate for being disease related in Isaac as a risk factor.
  - MT-TT m.15929AG>GA, chrM:15,929, ncRNA (N/A), homoplasmic, maternally inherited (homoplasmic); prevalence is for m.15929A>G alone:
    - This mtDNA-encoded, dinucleotide missense variant is highly likely to alter protein function as one of the nucleotide substitutions is very-highly conserved in mammals.
      - The prevalence of this change is unclear as the computer determine the prevalence for each nucleotide variance separately. They are both commonly found in mtDNA haplogroup A, which the patient belongs to.
    - The protein encoded by this gene is a tRNA in mitochondrial protein translation.
    - Variants in this gene have been reported in a wide variety of predominantly neuromuscular conditions associated with mitochondrial disease.
      - Autism this also associated with mitochondrial disease.
    - This variant is a good candidate for being disease related in Isaac as a risk factor.
  - MT-ND1 m.3397A>G, p.Met31Val, chrM:3,397, Exonic (Nonsynonymous SNV), homoplasmic, maternally inherited (homoplasmic):
    - This mtDNA-encoded variant is likely to alter protein function, as it is uncommon (0.15%) in humans, highly conserved in vertebrates, and mostly predicted as such by computer algorithms.
    - The protein encoded by this gene is a subunit of complex one of the respiratory chain, part of the oxidative-phosphorylation complex.
    - Variants in this gene have been reported in a wide variety of predominantly neuromuscular conditions associated with mitochondrial disease.
      - Autism this also associated with mitochondrial disease.
    - This variant is a good candidate for being disease related in Isaac as a risk factor.
  - 3q26.31q26.32x1(175,361,471-176,029,643), 668.17kbp, Exonic, (Deletion), heterozygous, paternally inherited; previously reported:
    - This variant is a deletion of 668,000 nucleotides including 54% of the NAALADL2 gene, and this is a loss-of-function variant for that gene. Seven non-coding genes of unknown function are also included in the deletion.
      - This deletion is uncommon (1.6 in 10K) in humans.
    - The protein encoded by the NAALADL2 gene has unknown function. It is similar to N-acetylated alpha-linked acidic dipeptidase. This protein may be catalytically inactive.
    - The phenotype regarding variants in this gene has not been well delineated. HGMD has 10 listings, 8 are neurodevelopmental disorders.
      - This gene is associated with autism as category 2 by SFARI.
    - This variant is a very good candidate for being disease related in Isaac as a risk factor.

- CACNA1A c.6949\_6975delCAGCAGCAGCAGCAGCAGCAGCAG, p.Gln2317\_Gln2325del, chr19:13,207,858, Exonic (Nonframeshift Deletion); variant of uncertain significance:
  - This variant is a 27-nt deletion in a trinucleotide repeat, resulting in loss of nine glutamate amino acids.
  - It is an uncommon variant of uncertain significance.
  - The protein encoded by this gene is a neuronal calcium transporter.
  - Variants in this gene have been reported in wide variety of paroxysmal neurological conditions, in particular migraine.
  - This variant is a possible candidate for being disease related in Isaac as a risk factor.

Potential management issues for consideration:

- Mitochondrial-related (SLC22A5, TRAP1, SCN9A, MT-TT, MT-ND1, CACNA1A):
  - Supplements:
    - Dietary supplements aimed at increasing mitochondrial energy metabolism.
    - In particular, supplementation with carnitine due to the variant in SLC22A5.
    - Dietary supplements with antioxidants.
    - Dietary supplements that are neuroprotective.
    - The conflict-of-interest with the above was discussed.
  - Blood testing for free carnitine, coenzyme Q10, 25-hydroxyvitamin D, potassium, and magnesium levels.
- SCN9A-related:
  - No treatment is consistently effective. However, the diagnosis is often helpful in understanding that the pain is “real”, and not driven by neurosis or secondary gain. Additionally, a diagnosis suggests that chronic treatment of neuropathic pain is indicated, and not a “course” of narcotics.
  - Therapies shown to be effective in relieving pain in some individuals include avoidance of triggers, cooling of the extremities, gabapentin, serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine), selective serotonin reuptake inhibitors (e.g., sertraline), tricyclic antidepressants (e.g., amitriptyline), carbamazepine, and sodium channel blockers, among several others.
  - Functional medicine approaches might include neuroprotective agents such as supplementation with antioxidants or magnesium.
- Consider a high-potassium diet to force sodium and calcium out of cells.
- Follow-up in 6 months.



Richard G. Boles, M.D.  
Medical Geneticist  
Mitochondrial & Molecular Medicine  
Cell: 310-869-6332  
Fax: 626-270-4272  
[drboles@molecularmito.com](mailto:drboles@molecularmito.com)

*This "Service" is performed as part of the Mitochondrial & Molecular Medicine NeuroGenomics Service, and some information regarding the nature and limitations of the Service are found at <http://molecularmitomd.com>. In particular, this Service involves a discussion among professionals of potential diagnoses and/or management options, but does not constitute the practice of medicine, and no physician-patient relationship is provided or inferred by this Service.*

*Disclosure: I am the Chief Medical & Scientific Officer for NeuroNeeds LLC, the start-up company that makes SpectrumNeeds®, EnergyNeeds®, QNeeds®, OmegaNeeds®, CalmNeeds®, FocusNeeds®, and ActivNeeds®. As such, I may receive financial compensation based upon my efforts and/or the success of the company. However, I receive no appreciable additional compensation based on if you buy this product. My primary interest herein is as your child's physician. You are under no obligation to purchase this or any product, whether recommended by myself (Dr. Boles) or another health care provider. As always, it is recommended that you contact your physician regarding any changes to disease management.*

*California Law: For informational purposes only, a link to the federal Centers for Medicare and Medicaid Services (CMS) Open Payments web page is provided here (<https://openpaymentsdata.cms.gov>). The federal Physician Payments Sunshine Act requires that detailed information about payment and other payments of value worth over ten dollars (\$10) from manufacturers of drugs, medical devices, and biologics to physicians and teaching hospitals be made available to the public.*