NeurAbilities NeuroGenomics Service Peer-to-Peer Notes

Client:	Frye, Richard, MD, PhD
Date:	2/23/2024
Patient:	Qemali, Albana
DOB:	11/13/2013 (10y)
Service level:	Basic Standard **Comprehensive**
Test/lab:	WGS trio / Variantyx
Off-target:	Requested by adult patient
Online:	Dr. Frye

Summary of the discussion:

Referral:

Trim Qemali <trimqemali@gmail.com>
Fri 8/18/2023 9:34 PM
To:Neurogenomics Coordinator <Neurogenomics@neurabilities.com>;Frye Euro Office <fryeeuroautismcare@gmail.com>

Hi Elizabeth,

Here is an update regarding Albana's current status:

Albana is a 9-year-old with an extensive medical history spanning the last three years. Condensing the details into a single email proves challenging due to the volume of information.

Between August 2021 and December 2022, Albana was under the care of Dr. Matsev in Kiev, Ukraine. During this period, she underwent an intensive medical regimen. Dr. Maltsev diligently pursued resolution for various medical concerns, conducting comprehensive assessments throughout her body. Notably, when Albana was 7 years old at the time, she was prescribed a substantial array of medications as part of her treatment plan.

- Intravenous administration of Rituximab and Flammengis was employed to suppress the immune system effectively to a state of complete depletion. Concomitantly, ABX antibiotics were administered to address potential bacterial infections. Chelation therapy was utilized for detoxification purposes. In the end within the last 3 month she received 3 x 2g per KG IVIG.. IVIG exhibited promising results in terms of mitigating the symptoms associated with her Autism Spectrum Disorder (ASD). It has proven to be a particularly efficacious intervention in alleviating her condition.
- Simultaneously, an extensive pharmacological regimen was employed. The list of medications administered during this period is considerable. These medications include Propesum (administered intramuscularly, alternating between buttocks), Inflamafertinum (also administered intramuscularly, with alternating buttocks), Forsliv (administered as one tablet during meals), Karliv (administered as one tablet during meals), Artesunate (administered as a 50 mg tablet after eating), Medrol, a range of probiotics, kiprada, atoxil, antrax, and numerous others, to attack viruses found in blood such as TT, EBV, HH6 & HH7, keep care of the liver and so on.
- Additionally, nootropic agents were incorporated into the treatment protocol. Noteworthy examples include Cerebrocurin, which was administered via intramuscular injection at a dosage of 2.0 ml. Pantogam, at the same dosage previously prescribed, was also administered. Kiprada was provided in tablet form following meals. Furthermore, Valargin, at a dosage of 3000 mg, was administered as a tablet after dissolution in water and consumption alongside food.

Luckily she took everything well. Anyways, war started a month later and Albana received the last dosage of IVIG in Jan 2022.

In June 2022, the medical oversight for Albana was transitioned to Dr. Kiril Shlyapnikov. According to his assessment, the root cause appeared to lie within her mitochondria. Dr. Shlyapnikov's therapeutic approach primarily consisted of a regimen of supplements. Concurrently, to manage the anticipated hyperactivity resulting from the mitochondrial cocktail, Albana was prescribed risperidone for tranquility. Additionally, she was administered tegretol, an antiepileptic medication, despite the absence of a history of epilepsy. Dr. Shlyapnikov's rationale for this was to regulate a specific brain region associated with pain perception. It was a much lighter treatment program compared to Dr. Maltsev, however, discernible benefits did not manifest during this phase. Consequently, a pivotal shift in the treatment strategy occurred, prompting a consultation with Dr. Frye in November 2022.

Subsequently, we transitioned to the treatment protocol prescribed by Dr. Frye, which has proven notably effective. This regimen entails the administration of a judiciously low-dosage mitochondrial cocktail, in stark contrast to the approach previously advocated by Dr. Shlyapnikov. This protocol is complemented by periodic B12+Leucovorin injections. Notably, this course of action yielded a level of stability and modest yet discernible advancements in Albana's condition.

On the 14th of April 2023, following consultations with both Dr. Frye and Dr. Shlyapnikov, a decision was reached to initiate a regimen of bumetanide for Albana. It is pertinent to highlight that the dosage was deliberately maintained at a very low level (1 x 0.5 mg), as opposed to the originally suggested dosage of 2 x 0.5 mg by Dr. Frye. Within a mere two-week span, remarkable strides were observed. Albana exhibited heightened focus, displayed a heightened interest in

acquiring new knowledge, and notably commenced uttering phrases composed of 2, 3, and even 4 words—a developmental milestone previously unprecedented.

A period of smooth progress persisted until the conclusion of June 2023, when Albana began to articulate complaints of stomach discomfort. Notably, manifestations of stomach reflux were evident, accompanied by frequent hiccup episodes. Her daily food intake progressively diminished, resulting in a weight reduction of 2 kilograms. This compelled us to temporarily suspend the administration of all supplements. Following a noticeable improvement in her eating habits, we reinstated the supplement regimen from its initial stage. Regrettably, the resumption of stomach pain coincided with the recent introduction of TruNiagen and MagMind in the evening. We are presently engaged in a process of verification to ascertain whether these additions are indeed the root cause of her discomfort.

Since January 2023, an ongoing concern has been urinary tract infections. Commencing with an E. Coli infection in January-February 2023, this issue was succeeded by an Enterococcus infection in June 2023. A concerning development has been the emergence of self-harming behaviors, particularly hand biting, which has become more pronounced in recent times. Despite our efforts, we have yet to definitively identify the underlying trigger for this behavior. Encouragingly, Albana's verbal communication skills have exhibited satisfactory progress thus far. However, in the past three weeks, there has been a recurrence of sleep disturbances—a challenge that had been effectively managed for over a year. Albana's sleep duration currently spans around 6 to 7 hours, after which she awakens.

Once Dr. Boles undertakes a comprehensive review of Albana's genetics, I intend to bring to his attention the pertinent information that Albana exhibits an unfavorable response to B6 pyridoxine. Specifically, she experiences tremors and involuntary movements of her body and head immediately before falling asleep, particularly when subjected to elevated doses of B6. It is noteworthy, however, that there are no adverse effects when Albana consumes B6 in lower quantities, such as those found in Energyneeds by Neuroneeds, prescribed by Dr. Frye

In June 2023, we conducted a series of blood tests as part of Dr. Frye's treatment program, yielding remarkable outcomes. Notably, we attained nearly normal results on a laboratory test, marking a significant milestone. The corresponding file can be accessed through the following link:
https://albana.spa.mk/wp-content/uploads/2023/08/May2023.pdf

Additional results spanning the period from June 2022 to January 2023 are available for review at the following link in a comparison table:
https://albana.spa.mk/wp-content/uploads/2023/08/Results-Jun22-Jan23.pdf

A mitochondrial genome report from 2021, obtained through an alternate DNA sequencing process, which could potentially provide valuable insights for Dr. Boles, can be accessed through the following link:
https://albana.spa.mk/wp-content/uploads/2022/11/Genom-Mito-1.pdf

Please note the additional resources and information that are available to Albana's health records website at https://albana.spa.mk.A comprehensive array of materials, including FRAT tests, Cunningham Panel results, MRI and EEG reports, and more. Should Dr. Boles require further clarification or access to any specific materials feel free to contact me by email or phone at any time. I hope that I have included the most important information to share in this message.

Patient information:

Dr. Frye:

Date of Visit: Oct 31 2023

Aberrant Behavior Checklist Results

Report Date: 10/24/2023 Age: 9.9 Completed By: Father

	Scores by Category		Interpretation
18	Irritability		Mild
7	Social Withdrawal		None
3	Stereotypy		None
16	Hyperactivity		None
0	Innapropriate Speech		None

Reference Scales

	None	Mild	Moderate	Severe
Irritability	0-16	17-26	27-36	37+
Soc W/D	0-15	16-26	27-38	39+
Stereotypy	0-8	9-12	13-16	17+
Hyperactivity	0-23	24-31	32-39	40+
Inapp Speech	0-5	6-7	8-9	10+

Social Responsive Scale Survey Results

Report Date: 10/24/2023 Age: 9.9 Completed By: Father
Gender: Female

Raw	Scores by Category	T-Score	Interpretation
8	Awareness	58.8	None
19	Cognition	77.0	Severe
26	Communication	68.6	Moderate
16	Motivation	70.6	Moderate
14	Mannerisms	55.4	None
Raw	Overall Assessment	T-Score	Interpretation
69	SCI Total	73.0	Moderate
83	Total	73.0	Moderate

Reference Scales

Total T Score	Interpretation
0 - 59	None
60 - 65	Mild
66 - 75	Moderate
76 - 90+	Severe

Gastrointestinal Survey Results

Report Date: 10/24/2023 Age: 9.9 Completed By: Father

No Survey Taken - Descriptive info below, if provided

	Responses
Constipation	5+/wk
Diarrhea	2-3/day
Average Stool Consistency	Formed
Stool Smell	Normal
Flatulence	Normal

Developmental history:

Mama / dada said specifically at 36 months.
Walked at 20 months.
Pointed at 44 months.
Neurodevelopmental Regression: None
Developmental problem first suspected at: 2 years of age.
Diagnosis of autism made at 3 years of age months.
Other Developmental Diagnoses Include: Speech, motor and global delay at 2 years
Therapies started included ABA.

FOLLOW UP IN PERSON CONSULTATION

General Changes from Nov 7 2022:

May – bumex – within two weeks – more focused and language
July – weight loss and loss of appetite along with UTIs, stopped medication (except mB12/FA injections) without regression but did not improve appetite
Restarted bumex with improvements again
TruNigen
EnergyNeeds 3 Capsule BID – full dose tremors
Vit D and C
B12/FA EOD
Leucovorin 15mg once a day

Self-harm has resolved.

Bed 9pm – 30 min – awake at 2am and turns on light stays up for 1hr. Wakes up at 5am does not go back to sleep. Not tired in the morning. Lots of energy

BM daily normal. Gradually started rejecting food, first fries and then noodles. Eats fruits and drinks ok and chocolate. Omeprazole for 1 week without improvement. Lots of hiccups.

Current Medications
1. Risperidone 1mg/ml Oral Solution, take 0.5ml once a day at 20:00.
2. Carbamazepine retard 200mg 2 times a day (200mg in morning at 200mg at night).
3. Cromoglycic acid (or sodium cromoglicate – Allergoval) 200mg 3 times a day before the
main meals.
4. Leukovorin tablets 15 mg twice a day.

Current Supplements :
Immunoglobulins IgG, IgM, IgA for oral intake
Mitochondrial cocktail" – metabolic supplements for regular use
1. Vitamin D 5000 IU daily.
2. Ubiquinol 200mg 3 times a day.

Examination
Wt: 28 kg

Crying and wants to leave. Friendly and poor eye contact. Few words. Relatively calm but inattentive and impulsive. Decreased bulk. Tone and DTR reduced. MMM, EOMI, CTA, RRR without murmur. No rash or neurocutaneous stigmata.

IMPRESSION:

The following problems seems to be:
Mitochondrial Dysfunction given biomarkers, motor delays. Mitochondrial dysfunction can compromise transport of folate into the nervous system.

Mitochondrial Support

- Continue Ubiquinol 100mg twice a day
- Start EnergyNeeds by Neuroneeds (https://www.neuroneeds.com/product/energyneeds/) 3 capsules twice a day
- Start NAD+ – TruNiagen 300mg once a day

Central Folate Leucovorin

- Continue Leucovorin 30mg twice a day

Methylation Support

- Continue B12 SQ 1250mcg every other day

General Changes from Nov 7 2022:
November was one of the best months before starting treatment.
Dec 15 she had tooth issue and nocturnal enuresis and increased repetitive behavior and increased anxiety and increase SIBs and decreased verbal communication and eye contact. Found to have E Coli UTI and treated with Nitrofurantoin and continue with prolonged course and now urine negative.

B-Complex Life Extension – Tremor
Liposomal B12 – no tremors
B12 shots – went well for two weeks with improvements with verbal communication – then got flu and virus and stopped.

3. Acetyl-L-carnitine 750mg 3 times a day before meals.
4. Ascorbic acid 50mg a day.
5. Alfa lipoic acid 150mg / day.
6. Vitamin E 100 IU daily.
7. Citrulline malate take 2 grams at morning and evening.
8. Glutathione take 100mg in morning and evening.
9. Resveratrol 500-600mg daily.
10. Niacinamide 500mg daily in morning.
11. Inosine take 500mg 3 tablets a day.

PLAN:

GI
- Gastroenterologist Evaluation – Dr Krigsman
- Digestive Enzymes – Houston Enzymes Trienza with meals
- Biocidin®LSF – 1 pump per day

Genetics Workup:
- Whole Genome Sequencing Trio (Variantyx)
- Dr Richard Boles Neurogenetics (molecularmitomd.com)
- Possible genes ACAD9, COQ4, ATP8

Mitochondrial Support
- Restart Ubiquinol 100mg twice a day
- Start EnergyNeeds by Neuroneeds (https://www.neuroneeds.com/product/energyneeds/) 3 capsules twice a day
- Start NAD+ – TruNiagen 300mg once a day
- MitoSynergy Original Formula
- https://mitosynergy.com/collections/all-products/products/mitoactivator-original
- Designs for Health L-Carnitine 800mg twice a day

Central Folate Leucovorin
- Increased Leucovorin 30mg twice a day

Methylation Support
- Continue B12/FA SQ every other day
- Coastal Compounding

Neurotransmitters
- Bumex 0.5 tablet twice a day
- Memantine 10mg tablet twice a day. Start at 5mg (1/2 tablet) twice a day for 2 weeks and then increase to 1 tablet twice a day.

Follow-Up: 3 months zoom

Time: 1hr face to face

Diagnostic Codes
Encephalopathy [G93.40 (348.30)]
Mixed receptive and expressive developmental Language Disorder [F80.2]
Sleep disorder [G47.9 (780.50)]

PFO spontaneously closed, lipoma removed from back, strabismus

Family history:

Mother late talker.
No family history of autism.
No family history of seizure or other neurological disorders

No family history of mitochondrial disease
Mom dx Sjogren's syndrome, otherwise no other family history of lupus, rheumatoid arthritis, Crohn's disease, ulcerative colitis, or celiac disease
Diabetes on mom's side

Non-genetic test results:

Previous Recommendations and Results

Fasting before breakfast
- Ammonia – slightly elevated 51 (17-50) / Normal 45
- Complete Metabolic Panel (CMP) – normal
- lactic acid – 3,8 (H)
- Acylcarnitine profile – summary normal
  Carnitine slightly elevated free on supplementation
- Pyruvate – not done
- homocysteine – normal 6.1
- Amino acids analysis, Plasma(Quantitative) – A/L 2.8 (H)
- Urine Organic Acids – Succinic high, 2-oxogluteraric low, hydroxybutyric high
- Urinary orotic acid
  NSE 16 – normal x 2
  S-100 0.242 (<0.105)
  CRP 0.2 (<5)
  IL-1B <5
  IL-8 normal
  CH-50 normal
  Vit D 57
  TSH ok

Repeat after a large protein meal (protein shake: Premier Protein Shake 30g protein)
- Ammonia – 68 (18-72)
- Complete Metabolic Panel (CMP)
- lactic acid – 3.4 (H)
- Acylcarnitine profile – not calculated
- Pyruvate
- homocysteine
- Amino acids analysis, Plasma(Quantitative) – Alanine 1034, A/L 4.4, Citrulline 62 (1-46) and Arginine 269 (10-140)
- Urine Organic Acids – hydroxybutyric, Fumaric, 3-methylcrotonylglycine, Tiglylglycine high
- Urinary orotic acid

Labs
Q10 high
Pyruvate normal
Lysosomal oligosaccharides normal
S100B 0.14 (<0.1.05)

Mito Swab
CS 177%
C4 25%
C1 15%
C2 68%

Previous Recommendations

Workup for possible CONGENITAL DISORDER OF DEGLYCOSYLATION 1
- Urine oligosaccharides
- Blood alpha-fetoprotein

Workup for possible COQ4 deficiency
- CoQ10 level after one week without supplementation.

Possible ACAD9 - Complex I Deficiency
- Avoid Aspirin
- Consider Riboflavin Supplementation
- Mito-Swab to look for complex I deficiency

Endocrine:
Total T4 ok

Immune abnormalities:
NSE and S100B were elevated initially but improved.
ANA normal
C3c, C4 ok
IgG ok
EST ok
Neutrophil myeloperoxidase activity low initially but then improved with therapy
Cunningham Panel: Elevated D! and Anti-Tubulin. CamKinase II 170.

Neurologic
MRI: Left temporal arachnoid cyst.
EEG: Low amplitude.

Metabolic:
Homocysteine normal
MTHFR Homozygous for 1298
MTRR meter for 66 A>G
Ammonia elevated
Lactate and L/P elevated
Amino Acids overall low.
FRAT double negative
Self Restricts meat

Nutritional:
Vit D: low normal

Genetic test results:

Report: Life Diagnostic
Patient: Albana Qemali
Date: 01.06.2023

G-Life
www.g-life.care
e-mail:contact@g-life.care

Analysis - Annotation with **Franklin** by **Genoox**, Palo Alto, CA, USA on raw FASTAQ files, created by Dante labs.

Result: Nine variants have been detected, one pathogenic, one likely pathogenic, and the rest are with uncertain significance.
Two of these variants are shared with the mother, two others are shared with the father.

Nr.	Gene / region	Variant	Variant type	Zygosity	Variant classification
1.	***CYP24A1***	CYP24A1:c.428_430delAAG (p.Glu143del) (rs777676129)	InDel, inframe deletion	Heterozygote	**Pathogenic**
2.	***CYP24A1***	CYP24A1:c.849A>T (p.Lys283Asn)	SNV, Missense	Heterozygote	**Uncertain significance**
3.	***SNC10A***	SCN10A:c.2485C>T (p.Arg829Cys) (rs755974168)	SNV, Missense	Heterozygote	**Likely Pathogenic**
4.	***SNC10A***	SCN10A:c.4089G>A (p.Val1363Val)	SNV, Splice region	Heterozygote	**Uncertain significance (Likely Patogenic)**
5.	***CLPB***	CLPB:c.1717C>T (p.Arg573Cys) (rs186989806)	SNV, Missense	Heterozygote	**Uncertain significance (leaning pathogenic)**
6.	***MT-ATP8***	MT-ATP8:c.116C>T chrM-8481 C>T (p.Pro39Leu) (rs1603221521)	SNV, Missense	Heterozygote	**Uncertain significance (leaning pathogenic)**
7.	***CACNA1G***	CACNA1G:c.4987G>C (p.Val1663Leu) (rs1450618466)	SNV, Missense	Heterozygote	**Uncertain significance (leaning pathogenic)**
8.	***ERF***	ERF:c.205G>A (p.Val69Ile) (rs745819984)	SNV, Missense	Heterozygote	**Uncertain significance (leaning pathogenic)**
9.	***KMT2C***	KMT2C:c.7443-7_7443-6delTT (rs746018833)	InDel, Intron variant	Heterozygote	**Uncertain significance (leaning benign)**
10.	***2q12.1 Deletion***	PANTR1|POU3F3	Deletion3.105 bp	Heterozygote	**Pathogenic**

Interpretation:

1. **Variant in the gene CYP24A1:c.428_430delAAG (p.Glu143del), Exon 2, autosomal recessive**

Official laboratory report:

Variantyx

Genomic Unity®
Whole Genome Analysis
Report Date: Jan 22 2024

Patient Name	Date of Birth	Test	Genetic Sex
Albana Qemali	Nov 13 2013	202639147 / 70147	Female

Results: NEGATIVE

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.

However, variants were identified in this analysis that were not considered to impact the interpretation of this report and are listed in the supplementary tables below: 'Previously Reported Results' and 'Regions of Homozygosity (ROH)'.

Ordering Physician
Richard Frye

NPI
1891730461

Provider
Neurodevelopmental Precision Medicine

Test Performed
Trio

Type
Blood

Collected
Nov 21 2023

Received
Nov 24 2023

Processed
Jan 18 2024

Additional Information

The patient's clinical notes mentioned that previous genetic testing from another diagnostic laboratory identified variants in the following genes: *NGLY1, CLPB, DHTKD1, CSGALNACT1, ACAD9, CPS1, COQ4, BSCL2*. However, these variants could not be identified with the information provided and, therefore, are not included in this report. This report includes analysis and classification of any variants that meet our reporting criteria.

Follow Up Recommendations

Genetic counseling is recommended to review both positive and negative results, as well as secondary and incidental findings, if identified. Test results may benefit from periodic reevaluation for new clinical associations to variants and updated variant classification.

Consider family studies for UPD should there be any clinical correlation with conditions that arise due to UPD of chromosome 11.

Indication for Testing (Phenotype)

Behavioral abnormality, Cognitive impairment, Arachnoid cyst, Delayed speech and language development, Insomnia, Feeding difficulties, Recurrent singultus, Autism, EEG abnormality, Skeletal muscle atrophy, Hypotonia, Hyporeflexia, Encephalopathy, Global developmental delay, Recurrent ear infections

Likely Diagnostic Findings

This section contains variant(s) in genes partially or fully consistent with the clinical phenotype.
No findings were identified.

ACMG Secondary Findings

This section of the report includes variants identified in a list of genes recommended by the American College of Medical Genetics and Genomics (ACMG) for reviewing and reporting 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.

Regions of Homozygosity (ROH)

Regions of homozygosity, also known as loss of heterozygosity (LOH) or absence of heterozygosity (AOH), are genomic segments showing a continuous stretch of homozygous variants with no statistically significant intervening heterozygous variants. ROH may be representative of uniparental disomy (UPD), ancestral homozygosity or regions inherited from a more recent common ancestor that are identical by descent (IBD). If the analysis includes sequence analysis, these regions will be interrogated for homozygous pathogenic or likely pathogenic variants and reported as indicated. Consider family studies for UPD if there is clinical correlation with the reported imprinted chromosome. Reporting ROH follows the ACMG guidelines for ROH and UPD (PMID: 23328890, 32296163).

LOCATION	VARIANT	DISEASE / INHERITANCE
11p11.2p11.11 NC_000011.10: g.45,800,981_51,182,410	5.38 Mb	Region of Homozygosity

Previously Reported Results

This section of the report includes variants reported by previous genetic testing, either in this individual or in a family member, that do not otherwise meet our clinical diagnostic reporting criteria. Disease associations for the gene(s) in this table are not provided in the absence of clinical and/or molecular correlation. Variants are only included in the report if sufficient variant information was provided at the time of testing. For previously reported structural variants, if identified, see additional comments below. Any previously reported variants that meet our clinical diagnostic reporting criteria will appear in other sections of this report. Any differences in variant nomenclature from previous results may be due to differences in reference transcript, genome build, testing methodology, and/or bioinformatics platforms used.

LOCATION	VARIANT
MTHFR NM_005957.5	c.1286A>C p.Glu429Ala rs1801131 Homozygous in proband Heterozygous in father Heterozygous in mother
MTRR NM_002454.3	c.66A>G p.Ile22Met rs1801394 Heterozygous in proband Not detected in father Heterozygous in mother

Sample Information

PATIENT	SEX	DATE OF BIRTH	SPECIMEN TYPE	DATE COLLECTED	DATE RECEIVED
Proband Albana Qemali 202639147	F	Nov 13 2013	Blood	Nov 21 2023	Nov 24 2023
Mother 202639129	F	-	Blood	Nov 21 2023	Nov 24 2023
Father 202639138	M	-	Blood	Nov 21 2023	Nov 24 2023

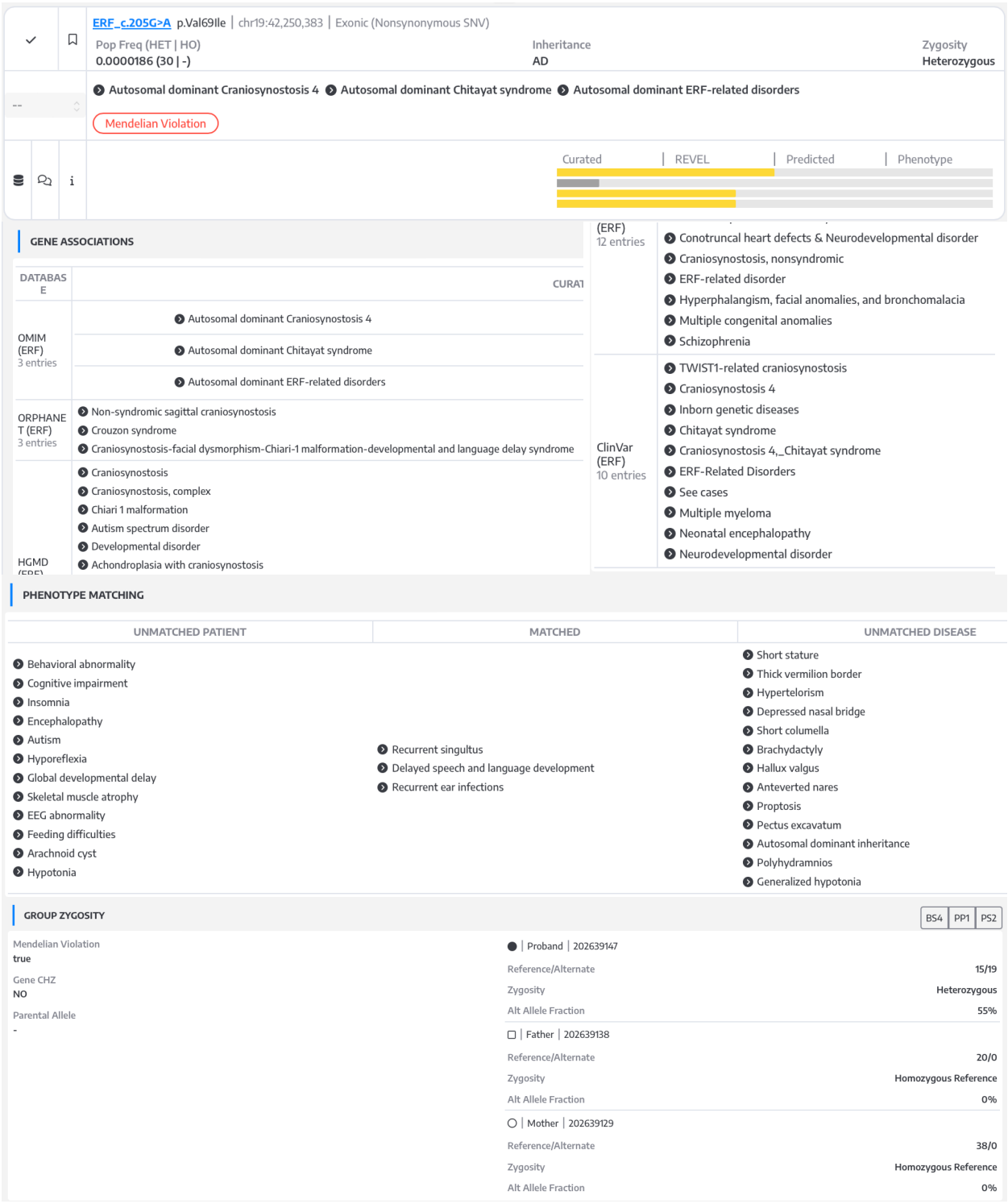
Patient Genotype

GENE	GENOTYPE	METABOLIZER STATUS
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*17	Rapid Metabolizer
CYP2C9	*1/*2	Intermediate Metabolizer
CYP2D6	*1/*4	Intermediate Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
CYP4F2	*1/*3 (V433M)	Indeterminate
DPYD	Reference/Reference	Normal Metabolizer
NAT2	*6/*6	Indeterminate
NUDT15	*1/*1	Normal Metabolizer
SLCO1B1	*1/*15 (521C)	Decreased Function
TPMT	*1/*1	Normal Metabolizer
UGT1A1	*1/*80+*28	Intermediate Metabolizer
VKORC1	Reference/rs9923231 (-1639G>A)	Indeterminate

Comprehensive Sequence Re-analysis - Variants of potential interest:

De novo small variants:

ERF c.205G>A, p.Val69Ile, chr19:42,250,383, Exonic (Nonsynonymous SNV), heterozygous, *de novo*:



CLINVAR

BS3 | BP6 | PP5 | PM5 | PS1 | PS3

HGVS Coding: NM_006494.4:c.205G>A

Gene: ERF

INCLUDE IN REPORT	DISEASE	SEVERITY	OMIM	REVIEW STATUS
☑	not provided	Uncertain significance	.	criteria provided, single submitter (1/4)

COMPUTATIONAL AND PREDICTIVE

BP4 | BP7 | PP3

Curated Severity Score: 4

REVEL: 0.097

Aggregate Predicted Severity Score: 0.41

MutationTaster: 1.0,D

PhyloP: 0.935,D

PhastCons: 0.967,D

MutationAssessor: -0.52,T

SIFT: 0.423,T

FATHMM: 2.03,T

LRT: 1.6e-05,D

Siphy: 12.5983,B

MetaLR: 0.0179,T

GERP++: 4.52,D

MetaSVM: -0.9732,T

SpliceRF: -

SpliceADA: -

POPULATION DATA

BA1 | BS1 | BS2 | PM2 | PS4

Date Range Specific PAF

Specify date range | 1Y | 2Y

Pop Freq: 0.0000186

Variantyx Frequency: -

Variantyx PDK Count: -

gnomAD Frequency: 0.0000186

gnomAD Heterozygous: 30

gnomAD Homozygous: -

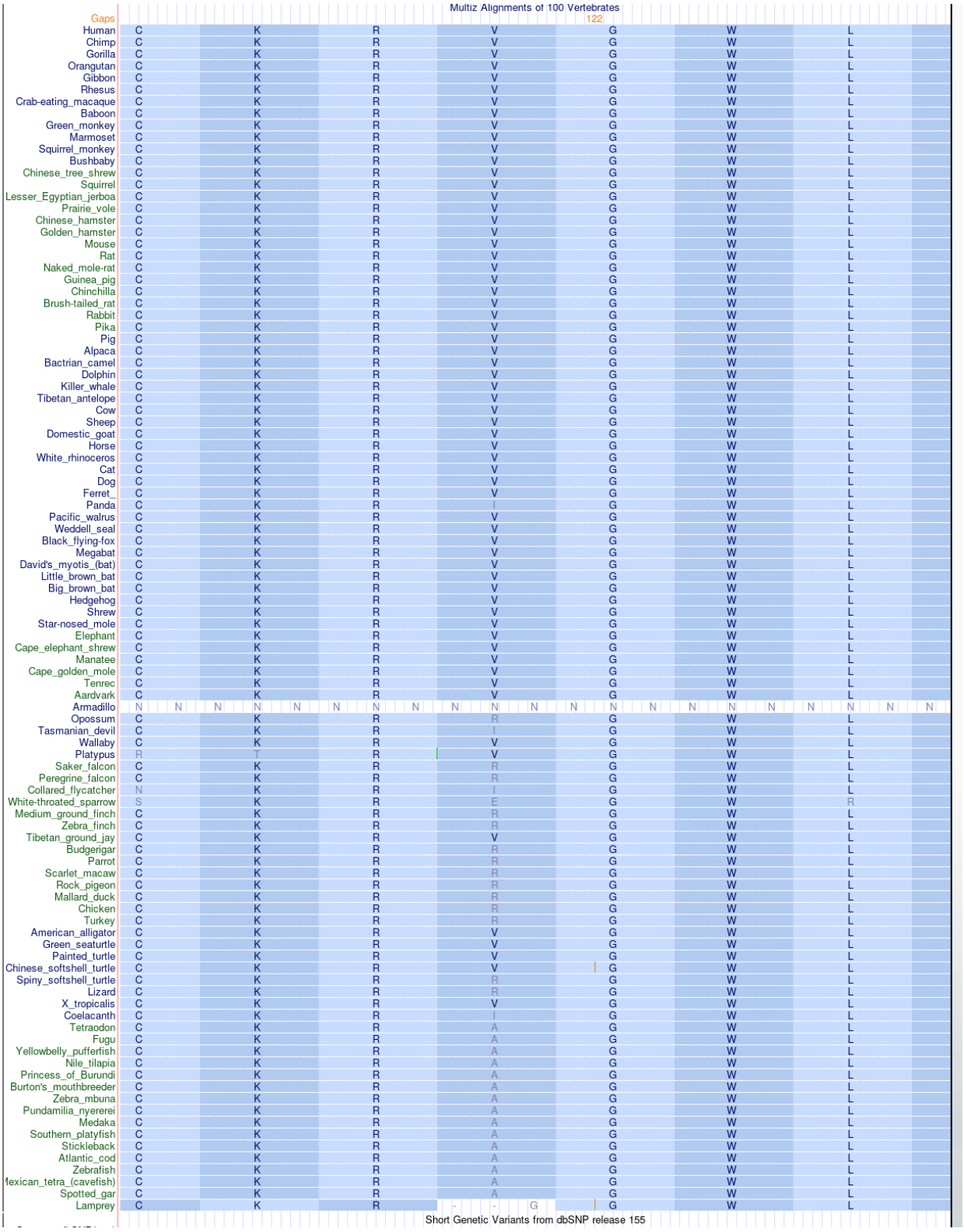
gnomAD NF Frequency: 0.0000333

gnomAD NF Population: Latino/Admixed American

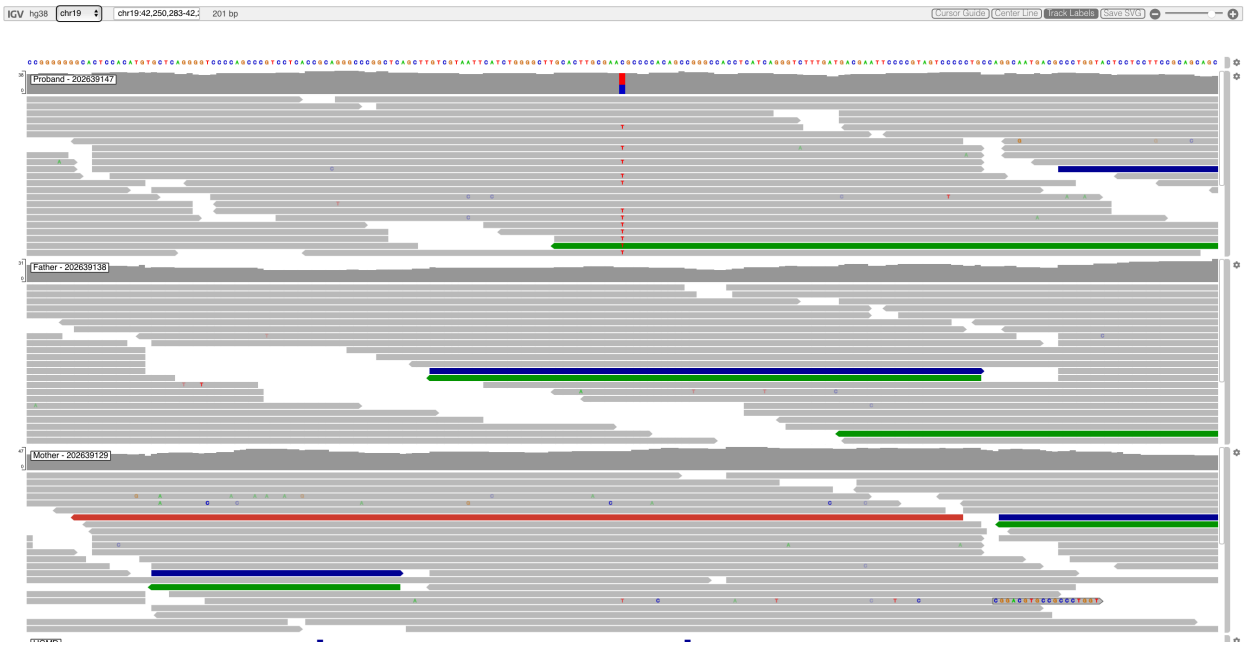
gnomAD Exomes Frequency: -

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Remaining	3	62468	0	0.00004802
Admixed American	2	60012	0	0.00003333
European (non-Finnish)	24	1180040	0	0.00002034
African/African American	1	74934	0	0.00001335
European (Finnish)	0	64024	0	0.000
Middle Eastern	0	5882	0	0.000
South Asian	0	91070	0	0.000
Ashkenazi Jewish	0	29604	0	0.000
East Asian	0	44886	0	0.000
Amish	0	912	0	0.000
XX	14	812342	0	0.00001723
XY	16	801490	0	0.00001996
Total	**30**	**1613832**	**0**	**0.00001859**

Include: ☑ Exomes ☑ Genomes



UCSC-GB: Valine is highly conserved in mammals, but not beyond that. Isoleucine is formed by a transition (common mutation), and is only found among mammals in panda and Tasmanian devil. This suggests that this variant may not be tolerated. Opossum has arginine, all others mammals have valine.



ERF: ETS2 repressor factor

HGMD Disease Count

40

HGMD Diseases

DISEASE	COUNT	PUBLICATIONS
Craniosynostosis	23	Glass *et al.* (2019) *Am J Med Genet A* 179:615 Yoon *et al.* (2019) *Neurosurgery* 87:294 Topa *et al.* (2020) *Am J Med Genet A* 182:348 Lee *et al.* (2017) *Genet Med* 20:1061 Chaudhry *et al.* (2015) *Am J Med Genet A* 167:2544
Craniosynostosis, complex	9	Twigg *et al.* (2013) *Nat Genet* 45:308 Glass *et al.* (2019) ERF-related craniosynostosis: The phenotypic and developmental profile of a new craniosynostosis syndrome. *AJMGA* 179:615 Krberg *et al.* (2020) A progressive and complex clinical course in two family members with ERF-related craniosynostosis: a case report. *BMC MG* 21:90
Chiari 1 malformation	3	Provenzano *et al.* (2021) *Hum Genet* 140:625
Developmental disorder	2	Turner *et al.* (2019) *Am J Hum Genet* 105:1274
Autism spectrum disorder	2	Fu *et al.* (2022) *Nat Genet* 54:1320

OMIM Phenotypes

DISEASE	COUNT
Craniosynostosis 4	
Chitayat syndrome	

Orphanet Diseases

DISEASE	INHERITANCE	AGE OF ONSET	AGE OF DEATH
Non-syndromic sagittal craniosynostosis	Autosomal dominant,Not applicable	Infancy,Neonatal	normal life expectancy
Crouzon syndrome	Autosomal dominant	Infancy,Neonatal	normal life expectancy
Craniosynostosis-facial dysmorphism-Chiari-1 malformation-developmental and language delay syndrome	.	.	.

OMIM:

* 611888

ETS2 REPRESSOR FACTOR; ERF

Alternative titles; symbols

PE2

HGNC Approved Gene Symbol: ERF

Cytogenetic location: 19q13.2 ***Genomic coordinates (GRCh38): 19:42,247,569-42,255,128*** (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype View Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
19q13.2	Chitayat syndrome	617180	AD	3
	Craniosynostosis 4	600775	AD	3

Description: Members of the ETS family of transcription factors, such as ERF, regulate cell proliferation and differentiation. They share a highly conserved DNA-binding domain, the ETS domain, that recognizes the sequence GGAA/T (de Castro et al., 1997). For further information on ETS transcription factors, see ETS1 (164720).

Gene Function-Using transfection assays of HeLa cells, Sgouras et al. (1995) found that ERF repressed the ETS2 promoter more than 30-fold. ERF also repressed the GATA1 (605371) promoter in the presence of its transactivator, GATA1. ERF suppressed the ETS-dependent transforming activity of the gag-myb (189990)-ets fusion oncogene of the avian E26 virus. The level of transcriptional repression by ERF was proportional to its affinity for the ERF target sequence in the promoter. The isolated DNA-binding domain of ERF strongly inhibited the ETS2 promoter, whereas removal of the DNA-binding domain of ERF abrogated its repressor activity. Sgouras et al. (1995) mapped the ERF repressor domain between amino acids 472 and 530. Although the ERF protein level remained constant throughout the cell cycle, ERF phosphorylation status was altered as a function of the cell cycle and after mitogenic stimulation. ERF was hyperphosphorylated in cells transformed by the activated Ha-ras (HRAS; 190020) and v-src (SRC; 190090) genes, and the transcription repressor activity of ERF was decreased after cotransfection with activated Ha-ras or the kinase domain of RAF1 (164760), indicating that ERF activity is probably regulated by the Ras/MAPK pathway. Consistent with the in vivo phosphorylation and inactivation by Ha-ras, ERF was efficiently phosphorylated in vitro by Erk2 (MAPK1; 176948) and CDC2 (116940)/cyclin B (see CCNB1; 123836) kinases at sites similar to those detected in vivo. Mutation of thr526 to ala eliminated a major ERF phosphoprotein in vivo, after phorbol ester induction, and in vitro, after ERK2 phosphorylation. Substitution of thr526 for glu also decreased the repression ability of ERF. Sgouras et al. (1995) concluded that ERF is involved in transcriptional regulation of genes activated during entry into G1 phase.

Bose et al. (2017) showed that ERF mutations in prostate cancer cause decreased protein stability and mostly occur in tumors without ERG (165080) upregulation. ERF loss recapitulated the morphologic and phenotypic features of ERG gain in normal mouse prostate cells, including expansion of the androgen receptor (AR; 313700) transcriptional repertoire, and ERF had tumor

suppressor activity in the same genetic background of PTEN (601728) loss that yields oncogenic activity by ERG. In the more common scenario of ERG upregulation, chromatin immunoprecipitation followed by sequencing indicated that ERG inhibits the ability of ERF to bind DNA at consensus ETS sites both in normal and in cancerous prostate cells. Consistent with a competition model, ERF overexpression blocked ERG-dependent tumor growth, and ERF loss rescued TMPRSS2 (602060)-ERG-positive prostate cancer cells from ERG dependency. Bose et al. (2017) concluded that their data provided evidence that the oncogenicity of ERG is mediated, in part, by competition with ERF, and raised the larger question of whether other gain-of-function oncogenic transcription factors might also inactivate endogenous tumor suppressors.

Molecular Genetics-Craniosynostosis 4: In 12 families with craniosynostosis (CRS4; 600775), Twigg et al. (2013) identified heterozygosity for mutations in the ERF gene (see, e.g., 611888.0001-611888.0005).

Chaudhry et al. (2015) analyzed the ERF gene in 40 patients with genetically undiagnosed multiple suture or sagittal synostosis, and identified 2 heterozygous mutations, one in the start codon (611888.0006) and the other in a splice site (611888.0007), in 2 affected boys. Chaudhry et al. (2015) noted that 2 (5%) of 40 patients in their study population had a pathogenic variant in the ERF gene, similar to the 3% frequency that was observed in a larger cohort (Twigg et al., 2013).

In a cohort of 182 Spanish craniosynostosis probands, Paumard-Hernandez et al. (2015) screened 7 craniosynostosis-associated genes, including the ERF gene, but did not detect any mutations in ERF. The authors suggested that the frequency of ERF mutations might be lower than previously reported.

Chitayat Syndrome: In 5 patients from 4 families with Chitayat syndrome (CHYTS; 617180), Balasubramanian et al. (2017) identified heterozygosity for a recurrent missense mutation in the ERF gene (Y89C; 611888.0008). The authors stated that it was unclear why the Y89C variant produced a different phenotype from that associated with previously reported mutations in the same region of ERF, such as R86C (611888.0003) and R65Q (611888.0004). [Albana V69I]

Description: Chitayat syndrome (CHYTS) is a rare condition characterized by respiratory distress presenting at birth, bilateral accessory phalanx resulting in shortened index fingers with ulnar deviation, hallux valgus, and characteristic facial features including prominent eyes, hypertelorism, depressed nasal bridge, full lips, and upturned nose (summary by Balasubramanian et al., 2017).

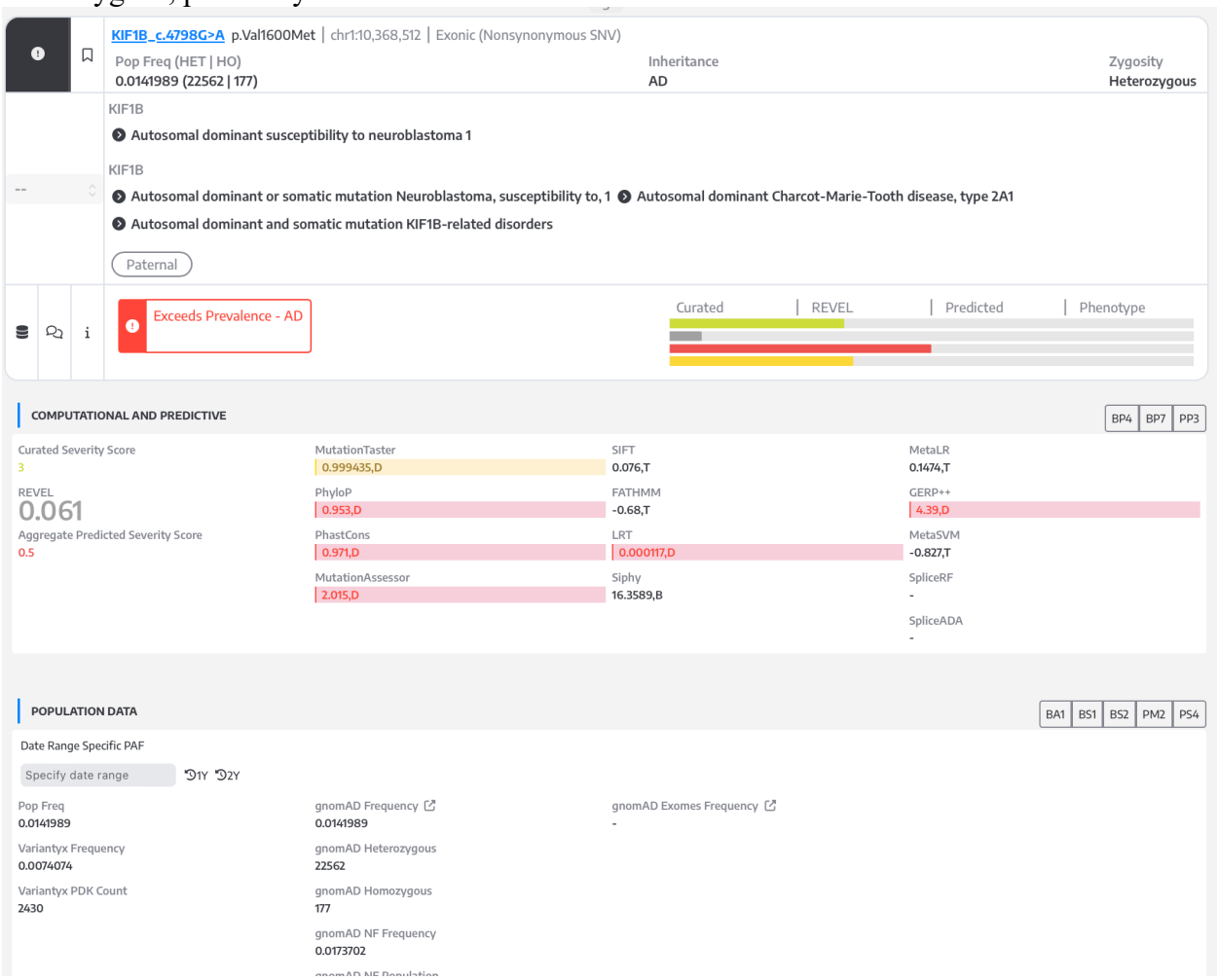
Animal Model: Papadaki et al. (2007) found that mouse Erf was expressed throughout embryonic development and adulthood. However, in situ hybridization of developing placenta showed that, after 7.5 days postcoitum, expression of Erf was restricted to extraembryonic ectoderm, and after 9.5 days postcoitum, it was restricted to a subpopulation of labyrinth cells. Erf +/- mice appeared normal and were fertile, but Erf -/- embryos died in utero at day 10 due to severe placenta defects. Erf -/- embryos failed to undergo chorioallantoic attachment and labyrinth development and instead had an expanded chorion layer that failed to further differentiate. These mice also failed to close the ectoplacental cone cavity. Erf -/- placentas had abnormalities in the giant cell and spongiotrophoblast layers. Erf -/- trophoblast stem cells showed delayed differentiation compared with wildtype cells and failed to express specific differentiation markers.

Twigg et al. (2013) generated mice with a conditional Erf allele and observed that mice heterozygous or homozygous for the conditional allele were grossly normal, whereas mice that were compound heterozygous for the conditional allele and a null allele had domed heads that

became apparent during the first 3 to 6 weeks of life. Micro-CT scanning showed craniosynostosis affecting multiple calvarial sutures. No other specific skeletal abnormalities were evident. Quantification of transcripts in embryonic day 16.5 calvaria showed up to 2-fold downregulation of multiple osteogenic markers in conditional/null mutants compared to wildtype littermates. Despite this mildly delayed embryonic ossification, by postnatal day 14 there was variable fusion of the cranial sutures of mutant, but not of wildtype, pups.

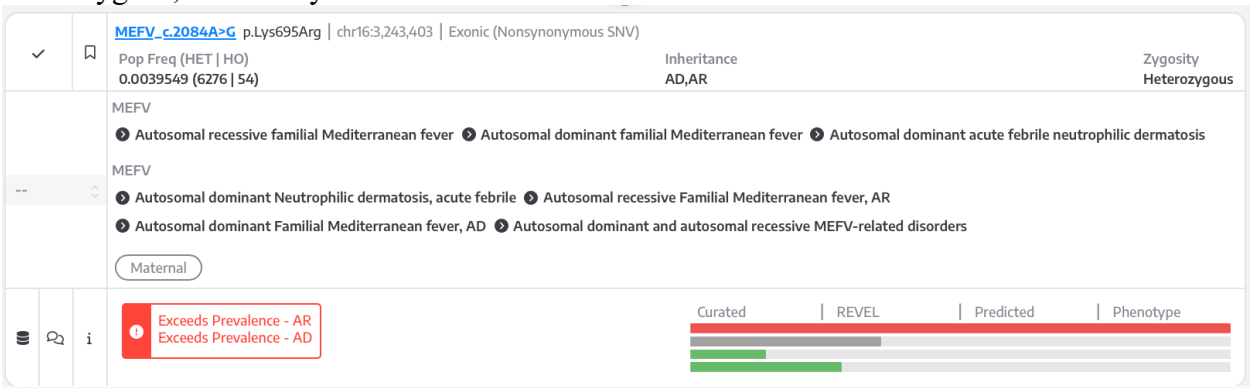
Functional disease gene list: ATP1A2, ATP1A3, ATXN8OS, CACNA1A, CACNA1S, CDK8, CHAMP1, CLCN1, CNR1, COQ2, GFAP, GLA, GLS2, HMBS, INF2, KCNH2, KCNJ18, KCNK18, KIF1B, MAP1B, MEFV, OCM, OPRM1, OTC, PMP22, POGZ, POLG, PPM1D, PRRT2, PRX, RYR2, SCN1A, SCN2A, SCN4A, SCN9A, SCN10A, SCN11A, SH3TC2, SLC1A3, SLC2A1,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

KIF1B c.4798G>A, p.Val1600Met, chr1:10,368,512, Exonic (Nonsynonymous SNV), heterozygous, paternally inherited:



IVG checked

MEFV c.2084A>G, p.Lys695Arg, chr16:3,243,403, Exonic (Nonsynonymous SNV), heterozygous, maternally inherited:



HGMD

BS3 | BP6 | PP5 | PM5 | PS1 | PS3 | PP1 | BS4 | PM3 | BP2

Phenotype	Mediterranean fever, familial
Variant Type	DM
Accession	CM981245

PMID	PATHOGENICITY SUPPORT	CITATION TYPE	PMID NOTES	ADDITIONAL PHENOTYPE	PUBLICATION
9668175 Copy		PRI		Mediterranean fever, familial	Bernot *et al.* (1998) *Hum Mol Genet* 7:1317
11175300 Copy	✓	SAR			Mansour *et al.* (2001) Familial Mediterranean fever in Lebanon: mutation spectrum, evidence for cases in Maronites, Greek orthodoxes, Greek catholics, Syriacs and Chiites and for an association between amyloidosis and M694V and M694I mutations. *EJHG* 9:51
11977178 Copy	✓	ACR			Gershoni-Baruch *et al.* (2002) Familial Mediterranean fever: the segregation of four different mutations in 13 individuals from one inbred family: genotype-phenotype correlation and intrafamilial variability. *AJMG* 109:198
14615741 Copy	✓	APR		Henoch-Schnlein purpura	Gershoni-Baruch *et al.* (2003) Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch-Schnlein purpura. *J PEDIAT* 143:658
18318646 Copy	✓	ACR			Chalevelakis *et al.* (2008) Different intrafamilial clinical presentation of FMF mutation carriers. *GENET TEST* 12:125
20041150 Copy	✓	APR		Fibromyalgia syndrome, association	Feng *et al.* (2009) Missense mutations in the MEFV gene are associated with fibromyalgia syndrome and correlate with elevated IL-1beta plasma levels. *PLOS ONE* 4:e8480
21228398 Copy	✓	SAR	Labelled as severe recessive disease-causing mutation. Supplementary table 9.		Bell *et al.* (2011) Carrier testing for severe childhood recessive diseases by next-generation sequencing. *STM* 3:65ra4
22975760 Copy	✓	SAR	Supplemental table B		Lazarin *et al.* (2013) An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *GENET MED* 15:178
23588594 Copy	✓	APR		Juvenile idiopathic arthritis	Comak *et al.* (2013) MEFV gene mutations in Turkish children with juvenile idiopathic arthritis. *EJP* 172:1061
23907647 Copy		SAR			Moradian *et al.* (2014) Patient management and the association of less common familial Mediterranean fever symptoms with other disorders. *GENET MED* 16:258
23981758 Copy	✓	APR		Henoch-Schnlein purpura	Altug *et al.* (2013) MEFV gene mutations in Henoch-Schnlein purpura. *IJRD* 16:347
24251727 Copy	✓	ACR			Sediv *et al.* (2014) Cluster of patients with Familial Mediterranean fever and heterozygous carriers of mutations in MEFV gene in the Czech Republic. *CLIN GENET* 86:564
27353043 Copy	✓	APR		Periodic fever	Fokstuen *et al.* (2016) Experience of a multidisciplinary task force with exome sequencing for Mendelian disorders. *HUM GENOM* 10:24
27364639 Copy	✓	SAR			Milenkovi *et al.* (2016) Distribution of MEFV gene mutations and R202Q polymorphism in the Serbian population and their influence on oxidative stress and clinical manifestations of inflammation. *PROJ* 14:39

28828621 Copy	✓	SAR			Barut *et al.* (2018) Familial Mediterranean fever in childhood: a single-center experience. *RI* 38:67
28927886 Copy	–	APR	Higher frequency than expected in patient cohort	Multiple sclerosis, childhood onset	Blaschek *et al.* (2018) TNFRSF1A and MEFV mutations in childhood onset multiple sclerosis. *EJPN* 22:72
29080837 Copy	✓	SAR			Procopio *et al.* (2018) Genotype-phenotype correlation in FMF patients: A "non classic" recessive autosomal or "atypical" dominant autosomal inheritance? *GENE* 641:279
29543225 Copy	✓	SAR			Kriegshuser *et al.* (2018) Clinical and genetic heterogeneity in a large cohort of Armenian patients with late-onset familial Mediterranean fever. *GENET MED* 20:1583
29977033 Copy	–	APR		Septic shock & hyperferritinaemia	Kernan *et al.* (2018) Adults with septic shock and extreme hyperferritinemia exhibit pathogenic immune variation. *GEN IMMUN* 20:520
30476936 Copy	✓	APR	Candidate pathogenic variant. Supplement 4. [B:16:3293403:T:C:hg19:rs104895094:K695R]	Kidney and/or genitourinary disorder	Rasouly *et al.* (2019) The Burden of Candidate Pathogenic Variants for Kidney and Genitourinary Disorders Emerging From Exome Sequencing. *AIM* 170:11
30513227 Copy	✓	APR		Henoch-Schonlein purpura	Ekinci *et al.* (2019) MEFV gene variants in children with Henoch-Schnlein purpura and association with clinical manifestations: a single-center Mediterranean experience. *PMED* 131:68
30783801 Copy	✓	APR		Systemic autoinflammatory disease	Karacan *et al.* (2019) Diagnostic utility of a targeted next-generation sequencing gene panel in the clinical suspicion of systemic autoinflammatory diseases: a multi-center study. *RI* 39:911
30826945 Copy	✓	APR		Henoch-Schnlein purpura	Cakici *et al.* (2019) MEFV gene mutations in children with Henoch-Schnlein purpura and their correlations-do mutations matter? *CLIN RHEUM* 38:1947
32199921 Copy	–	SAR			Bozgeyik *et al.* (2020) Next-generation screening of a panel of genes associated with periodic fever syndromes in patients with Familial Mediterranean Fever and their clinical characteristics. *GENOMICS* 112:2755
32597225 Copy	✓	APR	Patient also has c.3019dupC;p.Leu1007Profs*2 in NOD2 and c.1463G>A;p.Arg488His in SLC22A5.	Blau syndrome	Crdova-Fletes *et al.* (2020) Whole-exome sequencing in three children with sporadic Blau syndrome, one of them co-presenting with recurrent polyserositis. *AUTOIMM* 53:344
32853466 Copy	✓	SAR	See Table 1.		Umar *et al.* (2020) Genome sequencing unveils mutational landscape of the familial Mediterranean fever: Potential implications of IL33/ST2 signalling. *JCMM* 24:11294
33258288 Copy	✓	SAR	Likely Pathogenic. See Supplementary data.		Quaio *et al.* (2020) Diagnostic power and clinical impact of exome sequencing in a cohort of 500 patients with rare diseases. *AJMGCSMG* 184:955
33733382 Copy	×	FCR			Honda *et al.* (2021) Rapid Flow Cytometry-Based Assay for the Functional Classification of MEFV Variants. *JCIM* 41:1187
34426522 Copy	–	SAR	See Dataset S4.		Kars *et al.* (2021) The genetic structure of the Turkish population reveals high levels of variation and admixture. *PNAS* 118:e2026076118
35874679 Copy	–	APR	Classified as VUS. Suppl. table 3.	IgG subclass deficiency	Mrup *et al.* (2022) Added Value of Reanalysis of Whole Exome- and Whole Genome Sequencing Data From Patients Suspected of Primary Immune Deficiency Using an Extended Gene Panel and Structural Variation Calling. *FIMM* 13:906328

COMPUTATIONAL AND PREDICTIVE

BP4 BP7 PP3

Curated Severity Score 7	MutationTaster 1.0,N	SIFT 0.133,T	MetaLR 0.0998,T
REVEL 0.353	PhyloP 0.964,D	FATHMM 0.17,T	GERP++ 0.964,B
Aggregate Predicted Severity Score 0.14	PhastCons 0.609,B	LRT 0.965121,N	MetaSVM -0.9867,T
	MutationAssessor 1.245,T	Siphy 1.6328,B	SpliceRF -
			SpliceADA -

POPULATION DATA

BA1 BS1 BS2 PM2 PS4

Date Range Specific PAF

Specify date range 1Y 2Y

Pop Freq 0.0053498	gnomAD Frequency 0.0039549	gnomAD Exomes Frequency -
Variantyx Frequency 0.0053498	gnomAD Heterozygous 6276	
Variantyx PDK Count 2430	gnomAD Homozygous 54	
	gnomAD NF Frequency 0.0039067	

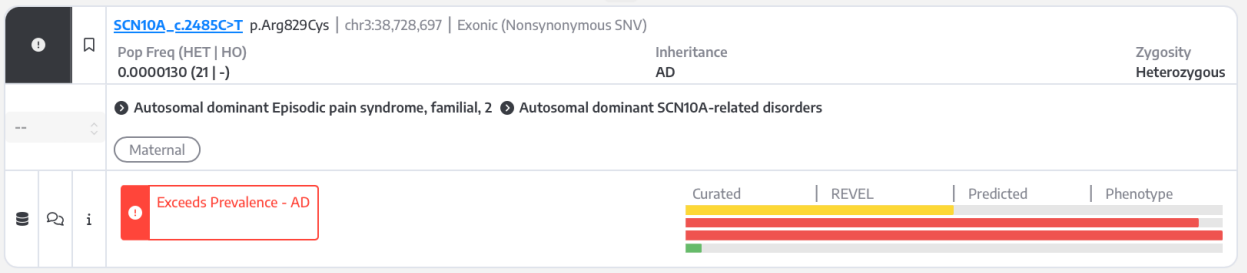
HGVS Coding NM_000243.3:c.2084A>G

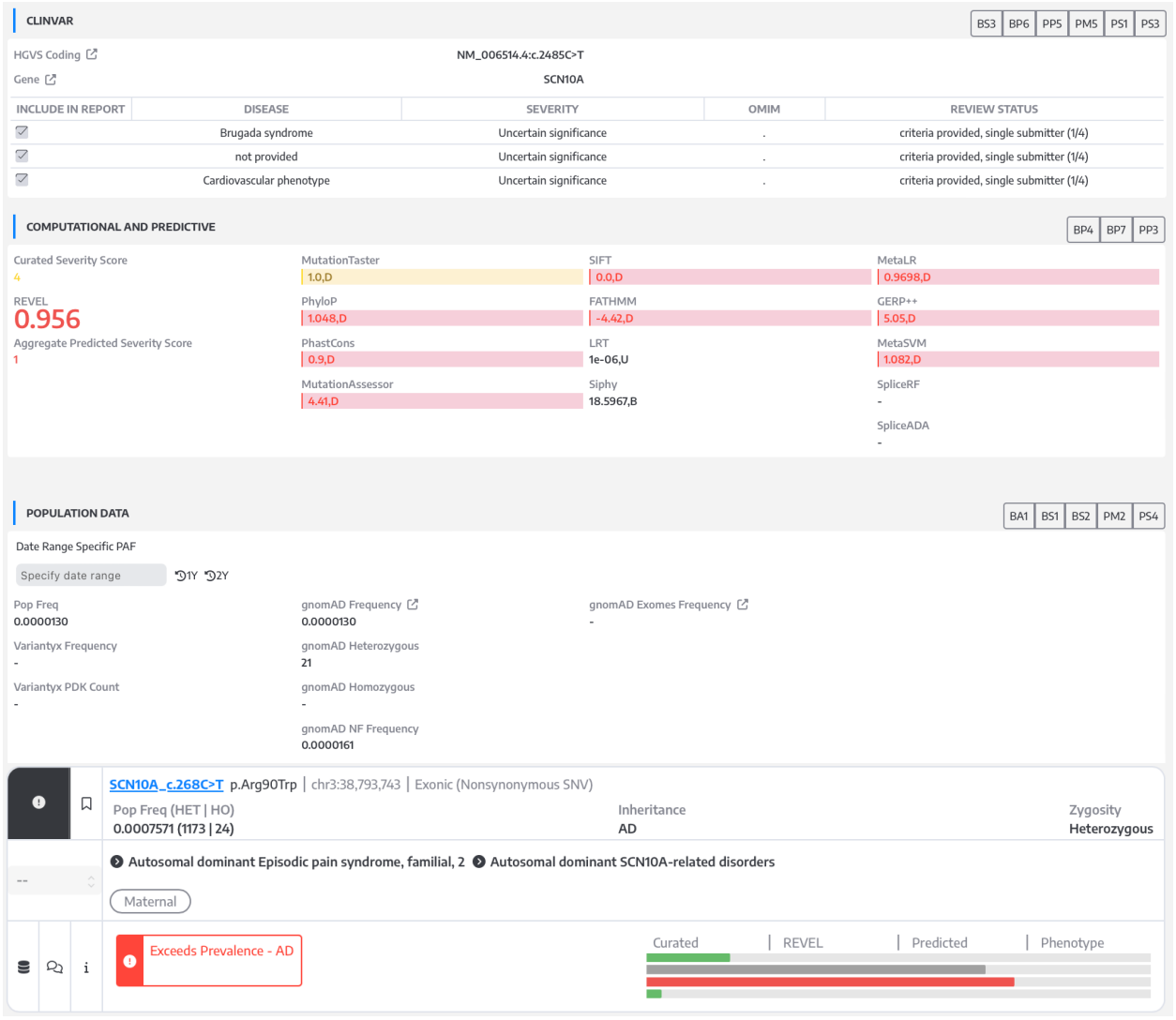
Gene MEFV

INCLUDE IN REPORT	DISEASE	SEVERITY	OMIM
☑	not provided	Pathogenic	.
☑	Familial Mediterranean fever	Uncertain significance	249100
☑	Familial Mediterranean fever	not provided	249100
☑	not provided	Likely pathogenic	.
☑	not provided	Uncertain significance	.
☑	not provided	Uncertain significance	.
☑	not provided	Uncertain significance	.
☑	Familial Mediterranean fever	Likely pathogenic	249100
☑	Familial Mediterranean fever	Likely pathogenic	249100
☑	not provided	not provided	.
☑	not provided	Likely pathogenic	.
☑	Cachexia,_Peripheral neuropathy,_Syncope,_Urticaria,_Intermittent diarrhea,_Abnormality of the dentition	Uncertain significance	.
☑	Familial Mediterranean fever	Uncertain significance	249100
☑	Familial Mediterranean fever,_Acute febrile neutrophilic dermatosis,_Familial Mediterranean fever, autosomal dominant	Uncertain significance	249100
☑	Renal insufficiency,_Abnormality of cardiovascular system morphology,_Heart, malformation of	Likely pathogenic	.
☑	Familial Mediterranean fever	Likely benign	249100
☑	not provided	Pathogenic	.
☑	Familial Mediterranean fever	not provided	249100
☑	not specified	Uncertain significance	.
☑	Inborn genetic diseases	Pathogenic	.
☑	not provided	Pathogenic	.
☑	Familial Mediterranean fever	Pathogenic	249100
☑	not provided	Likely pathogenic	.
☑	Familial Mediterranean fever,_Familial Mediterranean fever, autosomal dominant	Uncertain significance	249100
☑	Familial Mediterranean fever	Likely pathogenic	249100
☑	Familial Mediterranean fever	Pathogenic	249100
☑	not provided	Uncertain significance	.
☑	Familial Mediterranean fever	Pathogenic	249100
☑	not provided	Likely pathogenic	.
☑	Autoinflammatory syndrome	Likely pathogenic	.
☑	not provided	Likely pathogenic	.
☑	not provided	Likely pathogenic	.
☑	not specified	Uncertain significance	.

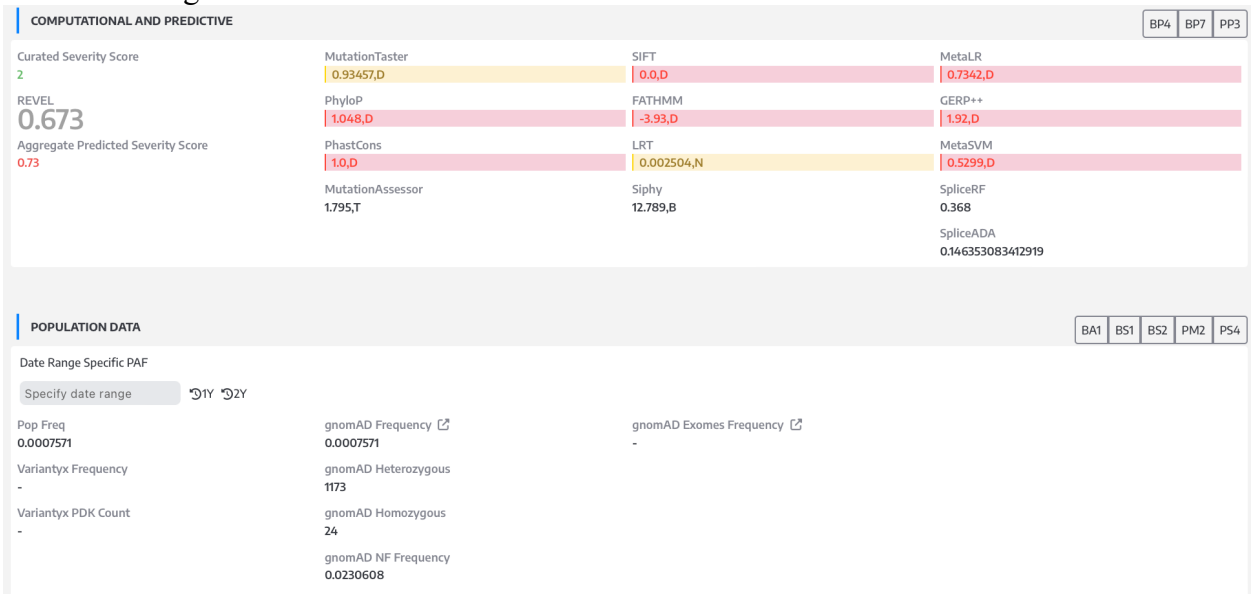
IGV checked: Patient is heterozygous, mother is homozygous

SCN10A c.2485C>T, p.Arg829Cys, chr3:38,728,697 & c.268C>T, p.Arg90Trp, chr3:38,793,743; both are Exonic (Nonsynonymous SNV), heterozygous, and maternally inherited:





ClinVar: Benign x3



OMIM (SCN10A) 2 entries	Autosomal dominant Episodic pain syndrome, familial, 2
	Autosomal dominant SCN10A-related disorders
ORPHANET (SCN10A) 6 entries	Congenital insensitivity to pain-anosmia-neuropathic arthropathy
	Primary erythromelalgia
	Romano-Ward syndrome
	Paroxysmal extreme pain disorder
	Sodium channelopathy-related small fiber neuropathy
	Brugada syndrome
	Brugada syndrome
	Sudden unexplained death
	Autism spectrum disorder
	Atrial fibrillation
	Atrial fibrillation & slow ventricular rates
	Atrioventricular nodal reentry tachycardia
	Cardiac conduction disease
	Kidney stone disease
	Neuromuscular disorder & eplieptic encephalopathy
	QRS interval, association with
	Small fibre neuropathy
	Sudden cardiac arrest
	Sudden unexpected nocturnal death
	Atrial fibrillation, early-onset
	Congenital harlequin syndrome
	Developmental disorder
	Erythromelalgia
	Infantile spasms
	Lennox-Gastaut syndrome
	Long QT syndrome
	Peripheral neuropathy, painful
HGMD (SCN10A) 45 entries	Reduced activity
	Refractory epilepsy & autism spectrum disorder
	Arrhythmia
	Autism
	Cardiomyopathy, dilated, modifier of
	Cardiomyopathy, primary fibrotic atrial
	Cardiovascular disease trait
	Congenital diaphragmatic hernia
	Conotruncal heart defects
	Hypoplastic left heart syndrome
	Intellectual disability
	Left ventricular obstruction & Neurodevelopmental disorder
	Neurodevelopmental disorder
	Neurodevelopmental disorder, severe
	PR interval, association with
	Painful sensory neuropathy
	Painful small fibre neuropathy with gastroparesis
	Peripheral neuropathy, association with
	Sensory and autonomic neuropathy
	Stillbirth
	Sudden cardiac death in J wave syndrome
	Sudden infant death syndrome
	Sudden unexpected nocturnal death, reduced risk
	Sudden unexplained death of youth
ClinVar (SCN10A) 3 entries	Episodic pain syndrome, familial, 2
	Brugada syndrome
	Impaired temperature sensation

PHENOTYPE MATCHING PP4

UNMATCHED PATIENT	MATCHED	UNMATCHED DISEASE
Behavioral abnormality		
Cognitive impairment		
Insomnia		
Autism		
Encephalopathy		
Hyporeflexia		
Global developmental delay		Autosomal dominant inheritance
Skeletal muscle atrophy		Adult onset
EEG abnormality		Hyperalgesia
Recurrent ear infections		
Feeding difficulties		
Recurrent singultus		
Delayed speech and language development		
Arachnoid cyst		
Hypotonia		

IGV checked x2

SCN10A: sodium voltage-gated channel alpha subunit 10

Gene Other Names: Nav1.8, hPN3, SNS, PN3

Function Description: Tetrodotoxin-resistant channel that 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 sodium ions may pass in accordance with their electrochemical gradient. Plays a role in neuropathic pain mechanisms.

HGMD Disease Count

128

HGMD Diseases

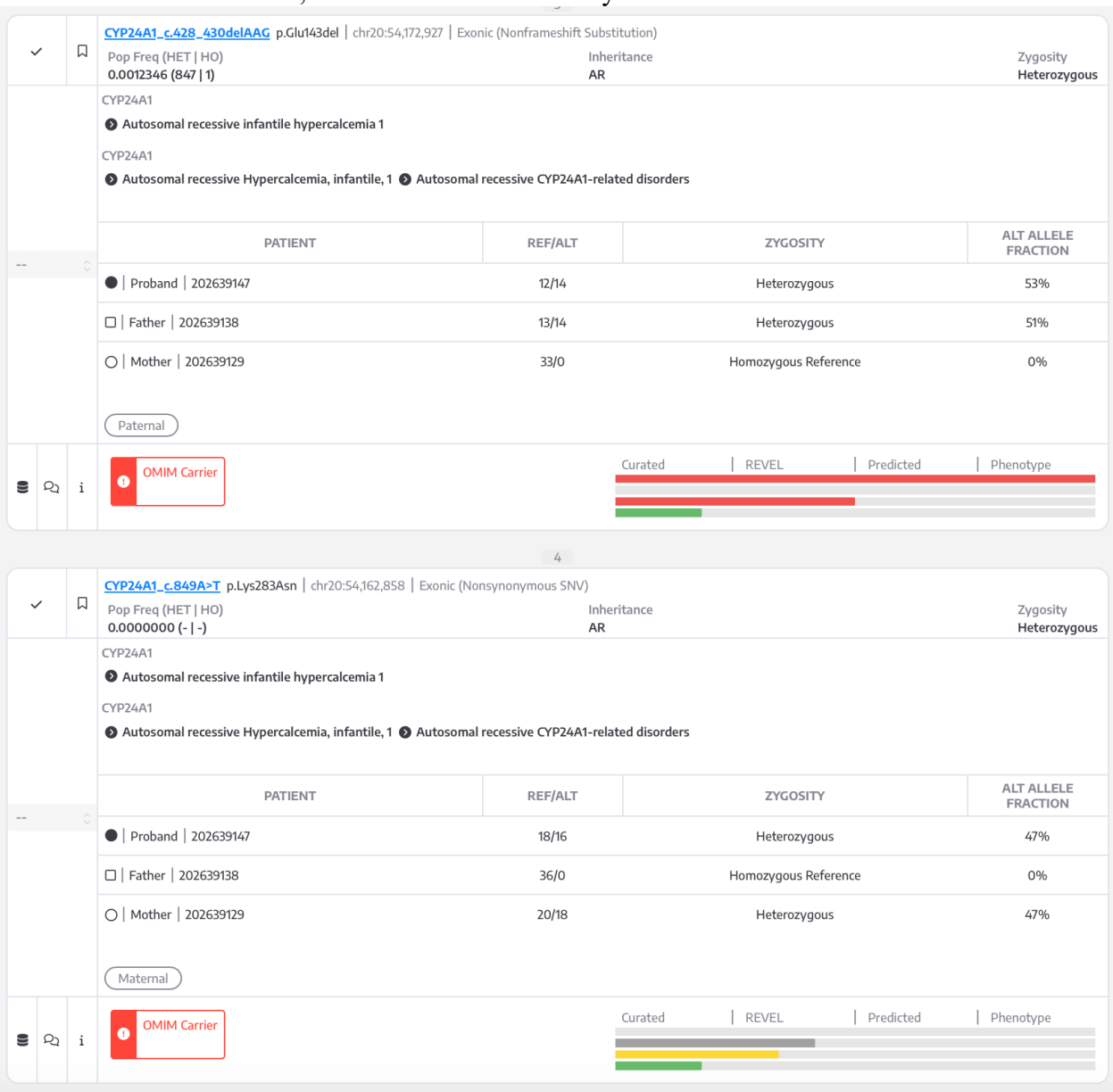
DISEASE	COUNT	PUBLICATIONS
Brugada syndrome	45	Campuzano *et al.* (2019) Genetic interpretation and clinical translation of minor genes related to Brugada syndrome. *HUM MUT* 40:749 Hu *et al.* (2014) *J Am Coll Cardiol* 64:66 Monasky *et al.* (2019) *Europace* 21:1550 Behr *et al.* (2015) *Cardiovasc Res* 106:520 Fukuyama *et al.* (2016) *Europace* 18:905
Sudden unexplained death	12	Lin *et al.* (2017) *Circ Cardiovasc Genet* 10:e001839 Gando *et al.* (2019) *Forensic Sci Int* 301:289 Neubauer *et al.* (2016) *Int J Legal Med* 130:1011 Gando *et al.* (2019) Functional characterization of SCN10A variants in several cases of sudden unexplained death. *FSI* 301:289
Autism spectrum disorder	11	Heinrichs *et al.* (2021) The Potential Effect of Na $_{v}$1.8 in Autism Spectrum Disorder: Evidence From a Congenital Case With Compound Heterozygous *SCN10A* Mutations. *FMN* 14:709228 Kambouris *et al.* (2017) *Ann Clin Transl Neurol* 4:26 Fu *et al.* (2022) *Nat Genet* 54:1320 Lee *et al.* (2021) *Front Genet* 12: Rabia *et al.* (2022) *Genes (Basel)* 13:1633
Atrial fibrillation	7	Jabbari *et al.* (2015) *Circ Cardiovasc Genet* 8:64 Savio-Galimberti *et al.* (2014) *Cardiovasc Res* 104:355 Hong *et al.* (2020) Pathogenic mutations perturb calmodulin regulation of $Na_V1.8$ channel. *BBRC* 533:168
Atrial fibrillation & slow ventricular rates	3	Savio-Galimberti *et al.* (2014) SCN10A/Nav1.8 modulation of peak and late sodium currents in patients with early onset atrial fibrillation. *CARDIO RES* 104:355 Kars *et al.* (2021) The genetic structure of the Turkish population reveals high levels of variation and admixture. *PNAS* 118:e2026076118

OMIM Phenotypes

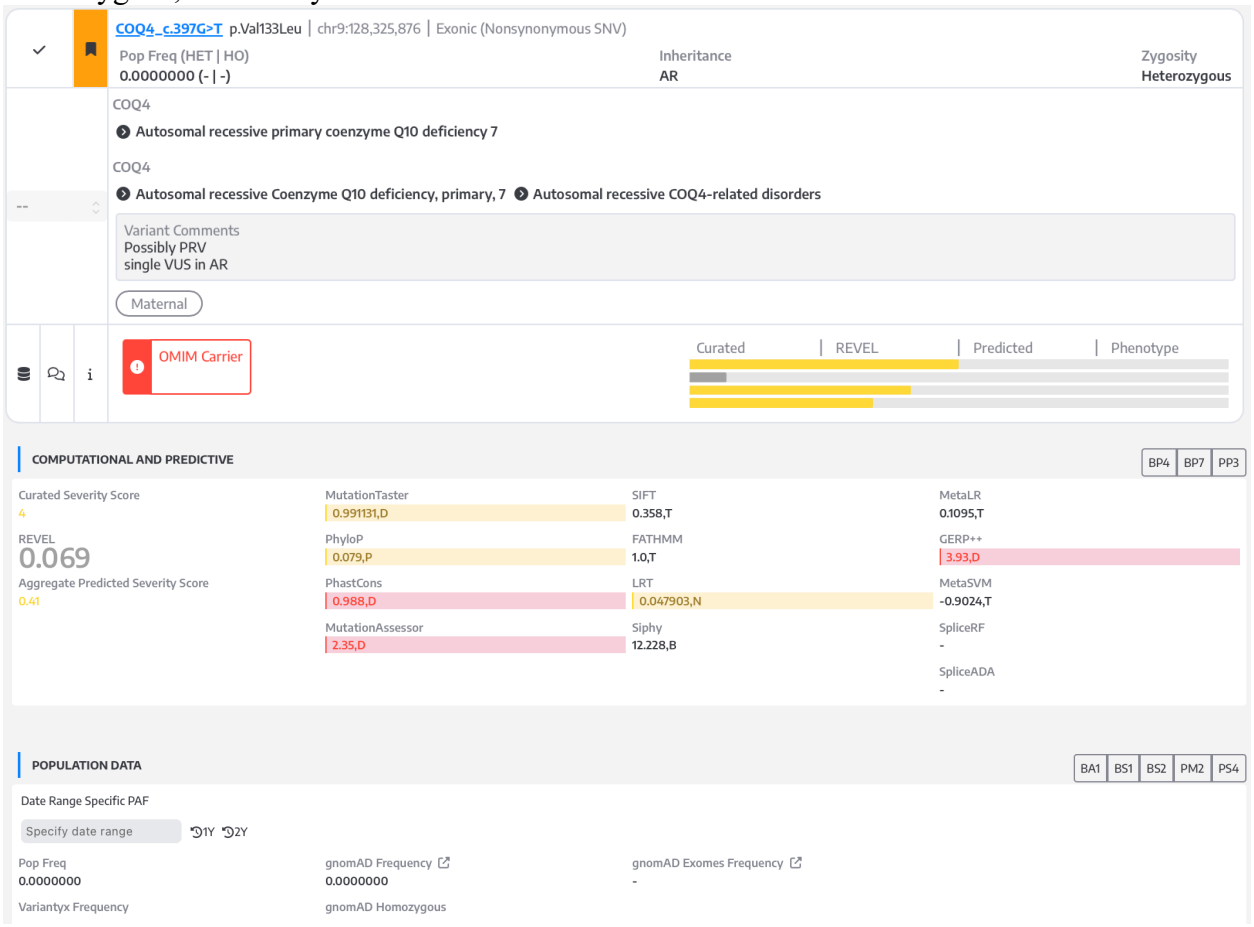
DISEASE	COUNT
Episodic pain syndrome, familial, 2	

Other inherited small variants:

Calcium level was normal, so these variants are likely not disease related in Albana:

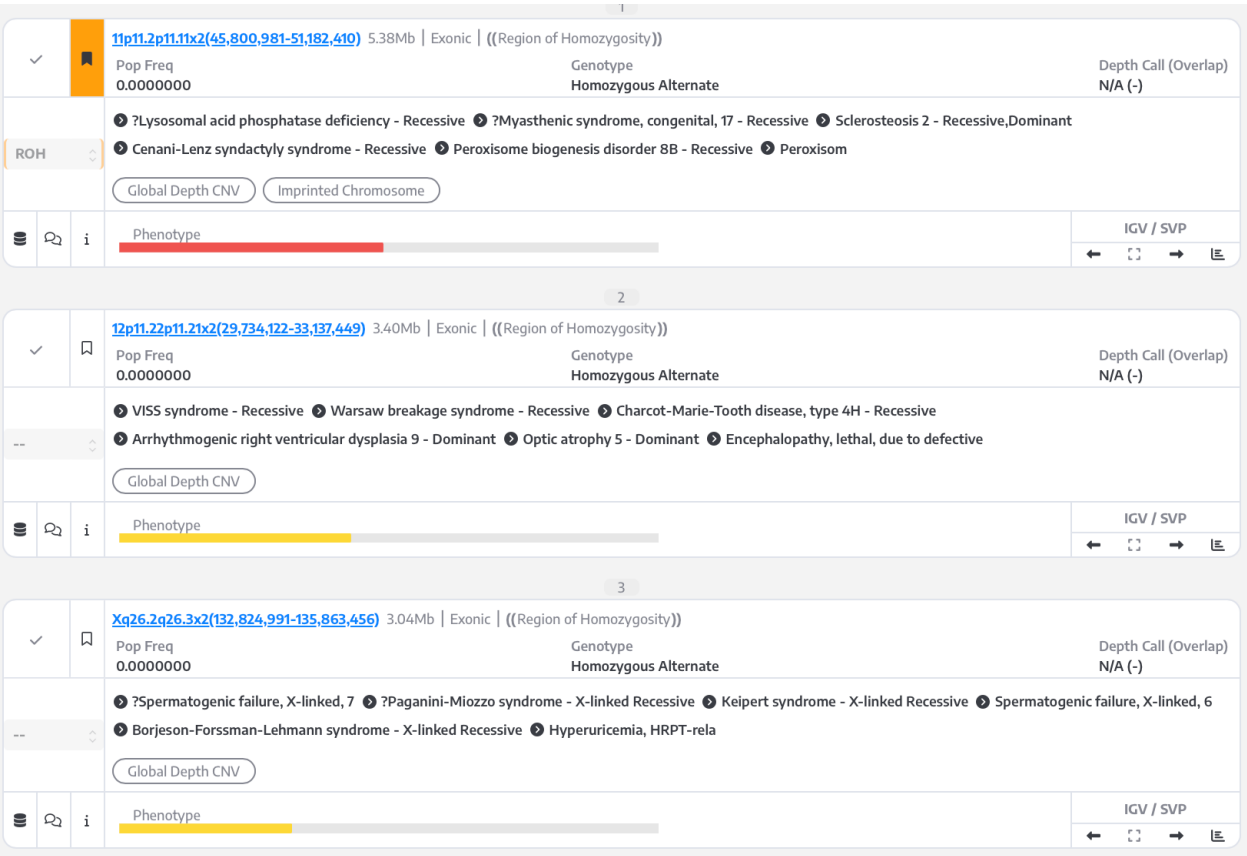


COQ4 c.397G>T, p.Val133Leu, chr9:128,325,876, Exonic (Nonsynonymous SNV), heterozygous, maternally inherited:



mtDNA variants: No variants of interest

Loss-of-heterozygosity:



Structural variants: No variants of interest

Short tandem repeats: No variants of interest; CACNA1A 11/13 CAG repeat by GAV = normal

Off-target/incidental variants: No variants of interest

Per our discussion today: All variants listed above were discussed, only those believed to be the most relevant are in this summary below:

- ERF c.205G>A, p.Val69Ile, chr19:42,250,383, Exonic (Nonsynonymous SNV), heterozygous, *de novo*:
    - This ***de novo*** variant is highly likely to alter protein function, as it is very rare in humans (3/100K people), well conserved in mammals, and variably predicted as such by computer algorithms.
    - The variant is in a hot spot for mutation in this gene.
    - The protein encoded by this gene is a transcriptional repressor.
    - Variants in this gene have been reported in craniosynostosis or autism/NDD.
    - This variant is an excellent candidate for being disease causal or related in this patient.

- SCN10A c.2485C>T, p.Arg829Cys, chr3:38,728,697 & c.268C>T, p.Arg90Trp, chr3:38,793,743; both are Exonic (Nonsynonymous SNV), heterozygous, and maternally inherited:
    - This variant is likely to alter protein function, as it is rare in humans, conserved in vertebrates, and variably predicted as such by computer algorithms.
    - The protein encoded by this gene is a sodium channel in noxious neurons.
    - Variants in this gene have been reported in chronic pain conditions. I have seen variants in this gene in patients with autism before likely associated with behavioral meltdowns, probably due to noxious symptoms.
    - This variant is a good candidate for being disease related in this patient, especially in regards to possible behavioral meltdowns.
- MEFV c.2084A>G, p.Lys695Arg, chr16:3,243,403, Exonic (Nonsynonymous SNV), heterozygous, maternally inherited:
    - This variant is common in humans.
    - The protein encoded by this gene is pyrin, in the inflammatory cascade.
    - Variants in this gene have been reported in autoinflammatory conditions, including FMF and fibromyalgia.
    - This variant is a good candidate for being disease related in this patient, especially in regards to improvement on therapies that decrease inflammation (e.g., IVIG).

Potential management issues for consideration:

- SCN10A-targeted therapies: In particular, mitochondrial-targeted dietary supplements, additional magnesium and zinc, gabapentin, and/or duloxetine
- MEFV-targeted therapies: In particular, NSAIDS – ibuprofen, naproxen, colchicine, ketorolac

Additional information regarding one of the above genes:

SCN10A: This gene encodes for one subunit of the NaV1.8 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. The SCN9A gene (NaV1.7 sodium channel) is a better-known cause of chronic pain, although SCN10A is thought to be similar. Conditions caused by these genes include erythromelalgia, paroxysmal extreme pain disorder, and small fiber neuropathy, all of which 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, enteral, sensory) neuropathy, and occasionally associated with seizures or degeneration. 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, selective serotonin reuptake inhibitors, tricyclic antidepressants, carbamazepine, and sodium channel blockers, among several others. Functional medicine approaches might include neuroprotective agents such as supplementation with antioxidants or magnesium.

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