

Neurabilities NeuroGenomics Service Peer-to-Peer Notes

Client:

Date: 3/20/2023

Patient:

DOB: 1/3/1942 (81y)

Service level: Basic Standard **Comprehensive**

Test/lab: WGS singleton/Variantyx

Off-target: Requested by adult patient, Dr.

Summary of the discussion:

Referral:

8/7/22

Dr. Boles,

I am referring this patient for genetic testing recommendation with Variantyx and then peer-to-peer consult.

Patient has an extensive past history of “unusual” symptoms and testing. He keeps an indexed website of the history of his symptoms, testing, and treatment (unusalsymptom.info) which is fairly thorough - especially so for the period before 2013, when I began to see him. Below is a list of interventions/treatments and their impact on his main symptoms. Main symptoms:

1. **Fatigue:** He started with vague, slowly progressive fatigue symptoms in the 1960's, with post-exertional malaise, muscle discomfort, and fibromyalgia. Onset of fatigue was not associated with any specific illness or events. When he started seeing me in 2013, his fatigue had progressed to the point that he was on total disability and essentially had 4 hours of 50-60% functionality per day and could walk approximately 1 square block. Now, he has 8 hours per day of >75% function and can walk >1 mi on level. He cannot do any aerobic exercise.
He has lived in the same rent-controlled apartment for over 40 years. The apt flooded roughly once per year for 30 years, but not has not flooded for the last 4-5 years, after the sewer drainage for the building was fixed. No other water damage and no visible mold. He has 2 HEPA filters in his house, which helped his fatigue and muscle “buzzing” a little.
2. **Muscle “Buzzing”:** Beginning in 1971, he developed onset of complex muscle “buzzing”/tightness/discomfort/pain/fatigue with washing. This complex effect on the muscles in the area washed is not stimulated by dry washing or rubbing (ie. it requires

water), is not affected by temperature of water or the absence/presence of soaps or shampoos, in the past, he would intermittently have red lines/dermatographia in the pattern of the washing/rubbing (but this stopped in the early 2000's). Improvements in his mood and general fatigue have not improved this symptom. No urticaria or paresthesias other than the buzzing/vibration effect in the muscles along with pain/tightness/fatigue. This symptom progressed to the point that by 2007 he was washing only small parts of his body in rotation every 5 days, since that was how long the pain and fatigue would last after the washing and he would be able to wash another part of his body. Starting Lamictal and supplementation with oral and IM magnesium, after RBC levels of magnesium were found to be low, all improved this symptom so that by 2013 he was able to take a full shower once per week with 5 days of decreasing fatigue after washing and 1-2 small, regional washes during the week. At that time, he was still requiring opiate pain medication when he washed but this has not been needed over the last 5-6 years, with gradual overall improvements.

~~not neuropathy.~~

3. Depression – long-standing for over 40 years, onset roughly correlating to the onset of his fatigue. See below for impact of multiple medications and other interventions on this.
4. Misc:
 - a. Urological – he has had gradually increasing prostate size over the last 10-15 years. Despite treatment with medications, he now he has 3-4x/night nocturia, persistent large residual urine volumes, and frequent low-grade UTI's, of which only symptomatic ones are treated with antibiotics.

Patient information:

Chief complaints:

1. Fatigue
2. Myalgia/buzzing

Family history:

None; no chronic pain, no immunodeficiency phenotype

Non-genetic test results:

Carnitine: low by report prior to supplementation

MitoSwab: RC-I 1.4 low, RC-IV 0.44 nl, CS 4.56 low nl

NCV/EMG: normal

Genetic test results:

Official laboratory report:

Patient Name
THOMAS RUBENS

Date of Birth
Jan 3 1942

Test
202502269 / 52795

Genetic Sex
Male

Results: NEGATIVE

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

Ordering Physician
Dr. Michael Cantwell

NPI
1760500011

Provider
MCMD

Test Performed
Singleton

Type
Swab

Collected
Oct 13 2022

Received
Oct 17 2022

Processed
Oct 31 2022

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.

Indication for testing (phenotype)

Chronic fatigue, Exercise intolerance, Myalgia, Chronic constipation, Diarrhea, Barrett esophagus, angina, Angina pectoris, Colorectal polyposis

Comprehensive Sequence Re-analysis - Variants of potential interest:

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

SCN9A c.4156A>C, p.Lys1386Gln, ch2:166,228,741, heterozygous:

✓

SCN9A_c.4156A>C

p.Lys1386Gln | chr2:166,228,741 | Exonic (Nonsynonymous SNV)

Pop Freq (HET | HO)

0.0000263 (4 | -)

Inheritance

AD,AR

Zygosity

Heterozygous

SCN9A

➤ Autosomal dominant primary erythralgia

➤ Autosomal dominant paroxysmal extreme pain disorder

➤ Autosomal dominant small fiber neuropathy

➤ Autosomal recessive congenital insensitivity to pain

SCN9A

➤ Autosomal dominant Erythralgia, primary

➤ Autosomal recessive Insensitivity to pain, congenital

➤ Autosomal dominant Small fiber neuropathy

➤ Autosomal dominant Paroxysmal extreme pain disorder

➤ Autosomal recessive Neuropathy, hereditary sensory and autonomic, type IID

➤ Autosomal dominant and autosomal recessive SCN9A-related disorders

Variant Comments

• PM2_supporting: MET for AR disease - MAF Latino/American admixture 0.0001963

• PP3: MET - aggregate predicted severity score = 1

• PM1: NOT MET - per Uniprot, variant is in a repeat region

• PP5: NOT MET - 2 star variant in ClinVar; VUS per Invitae in 4/20

• No literature associated with this variant so no clinical observations, segregation, de novo, or functional data.

• Patient's phenotypic features of muscle pain, fibromyalgia, and muscle buzzing do not correlate with SCN9A-associated AR conditions, which are insensitivities to pain. Patient's types of pain do not appear to overlap with the AD-associated conditions either.

Based on the available evidence, this variant is a VUS.
Not reporting.

Uncertain Significance (PP3, PM2_Supporting)

SFARI 2

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Exceeds Prevalence - AD

Curated

Predicted

Phenotype

GENE ASSOCIATIONS

PP4

DATABASE	CURATION
OMIM VYX (SCN9A) 4 entries	<div>➤ Autosomal dominant primary erythralgia</div> <div>➤ Autosomal dominant paroxysmal extreme pain disorder</div> <div>➤ Autosomal dominant small fiber neuropathy</div> <div>➤ Autosomal recessive congenital insensitivity to pain</div>
HGMD (SCN1A-)	<div>➤ Congenital indifference to pain</div> <div>➤ Congenital insensitivity to pain</div>

PHENOTYPE MATCHING

PP4

CLINVAR

BS3BP6PP5PM5PS1PS3

HGVS Coding

NM_001365536.1:c.4156A>C

Gene

SCN9A

INCLUDE IN REPORT	DISEASE	SEVERITY	OMIM	REVIEW STATUS
✓	Generalized epilepsy with febrile seizures plus, type 7_Neuropathy, hereditary sensory and autonomic, type 2A	Uncertain significance	613863	criteria provided, single submitter (1/4)
✓	not provided	Uncertain significance	.	criteria provided, single submitter (1/4)

Coverage 17/19

COMPUTATIONAL AND PREDICTIVE

BP4BP7PP3

Aggregate Predicted Severity Score

1

SpliceRF

-

SpliceADA

-

MutationTaster

0.999877,D

PhyloP

1.061,D

PhastCons

1.0,D

MutationAssessor

3.02,D

SIFT

0.001,D

FATHMM

-4.97,D

LRT

7e-06,D

Siphy

12.4612,B

MetaLR

0.962,D

GERP++

4.13,D

MetaSVM

1.0897,D

Curated Severity Code

4

POPULATION DATA

BA1BS1BS2PM2PS4

Date Range Specific PAF

Specify date range

1Y2Y

Pop Freq

0.0000263

Variantx Frequency

-

Variantx PDK Count

-

gnomAD Genomes Frequency

0.0000263

gnomAD Genomes Heterozygous

4

gnomAD Genomes Homozygous

-

gnomAD Genomes NF Frequency

0.0001963

gnomAD Genomes NF Population

Latino/Admixed American

gnomAD Exomes Frequency

0.0000146

gnomAD Exomes Homozygous

0

TNXB c.6074A>T, p.Asp2025Val, chr6:32,068,536, heterozygous:

✓

🔖

[TNXB_c.6074A>T](#) p.Asp2025Val | chr6:32,068,536 | Exonic (Nonsynonymous SNV)

Pop Freq (HET | HO)
0.0037098 (82 | -)

Inheritance
AD,AR

Zygosity
Heterozygous

TNXB

➤ Autosomal recessive classic-like Ehlers-Danlos syndrome 1 ➤ Autosomal dominant vesicoureteral reflux 8

TNXB

➤ Autosomal recessive Ehlers-Danlos syndrome, classic-like, 1 ➤ Autosomal dominant Vesicoureteral reflux 8

➤ Autosomal dominant and autosomal recessive TNXB-related disorders

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⚠

Exceeds Prevalence - AD

Curated

Predicted

Phenotype

PHENOTYPE MATCHING

PP4

UNMATCHED PATIENT

MATCHED

UNMATCHED DISEASE

➤ Exercise intolerance

➤ Colorectal polyposis
➤ Myalgia
➤ Angina pectoris
➤ Chronic constipation
➤ Chronic fatigue
➤ Diarrhea
➤ Barrett esophagus

➤ Joint hypermobility
➤ Bicornuate uterus
➤ Hyperextensible skin
➤ Unilateral renal agenesis
➤ Vesicoureteral reflux
➤ Proximal muscle weakness
➤ Muscle fiber splitting
➤ Ambiguous genitalia
➤ female
➤ Autosomal recessive inheritance
➤ Increased connective tissue
➤ Joint subluxation
➤ Proximal amyotrophy
➤ Soft skin

COMPUTATIONAL AND PREDICTIVE

BP4 BP7 PP3

Aggregate Predicted Severity Score
0.45

MutationTaster
0.999804,D

PhyloP
0.961,D

SpliceRF
-

SpliceADA
-

SIFT
0.014,D

FATHMM
0.29,T

LRT
0.00248,N

Siphy
12.8212,B

MetaLR
0.3428,T

GERP++
5.33,D

MetaSVM
-0.2614,T

Curated Severity Code
7

POPULATION DATA

BA1 BS1 BS2 PM2 PS4

Date Range Specific PAF

Specify date range 1Y 2Y

Pop Freq
0.0037098

gnomAD Genomes Frequency
0.0005388

gnomAD Exomes Frequency
0.0007915

Variantx Frequency
0.0037098

gnomAD Genomes Heterozygous
82

gnomAD Exomes Homozygous
1

Variantx PDK Count
2426

gnomAD Genomes Homozygous
-

gnomAD Genomes NF Frequency
0.0005236

gnomAD Genomes NF Population
Latino/Admixed American

TNFRSF13B c.204dupA, p.Leu69ThrfsTer12, heterozygous:

✓	🔖	TNFRSF13B_c.204dupA p.Leu69ThrfsTer12 chr17:16,948,978 Exonic (Frameshift) Pop Freq (HET HO) 0.0003090 (47 -)		Inheritance AD,AR	Zygosity Heterozygous
		TNFRSF13B ➤ Autosomal dominant or autosomal recessive Common variable immunodeficiency 2 ➤ Autosomal recessive Immunoglobulin A deficiency 2			
		TNFRSF13B ➤ Autosomal dominant or autosomal recessive Immunodeficiency, common variable, 2 ➤ Autosomal recessive Immunoglobulin A deficiency 2 ➤ Autosomal dominant and autosomal recessive TNFRSF13B-related disorders			
☰	💬	i	Curated Predicted Phenotype 		

CLINVAR					BS3	BP6	PP5	PM5	PS1	PS3
HGVS Coding 🔗		NM_012452.3:c.204dup								
Gene 🔗		TNFRSF13B								
INCLUDE IN REPORT	DISEASE	SEVERITY	OMIM	REVIEW STATUS						
<input checked="" type="checkbox"/>	Immunodeficiency, common variable, 1	Likely pathogenic	607594	no assertion criteria provided (0/4)						
<input checked="" type="checkbox"/>	Immunodeficiency, common variable, 2	Pathogenic	240500	criteria provided, single submitter (1/4)						
<input checked="" type="checkbox"/>	not provided	Pathogenic	.	criteria provided, single submitter (1/4)						
<input checked="" type="checkbox"/>	not provided	Pathogenic	.	criteria provided, single submitter (1/4)						
<input checked="" type="checkbox"/>	Immunodeficiency, common variable, 2	Likely pathogenic	240500	criteria provided, single submitter (1/4)						
<input checked="" type="checkbox"/>	Common Variable Immune Deficiency, Dominant	Uncertain significance	.	criteria provided, single submitter (1/4)						
<input checked="" type="checkbox"/>	not provided	Pathogenic	.	no assertion criteria provided (0/4)						

Per our discussion today:

- SCN9A c.4156A>C, p.Lys1386Gln, ch2:166,228,741, heterozygous:
 - This variant is highly likely to alter protein function as it is very rare in humans, highly conserved, and predicted as such by computer algorithms.
 - Variants in this gene can result in small fiber neuropathy with exaggerated sensation, including pain and fatigue. Other sensations I have seen in patients with variants in this gene include tinnitus and interstitial cystitis. Erythroderma is also then described.
 - This variant is an excellent fit for the disease in this patient, and thus is highly likely contributing in a polygenic/multifactorial manner.
- TNXB c.6074A>T, p.Asp2025Val, chr6:32,068,536, heterozygous:
 - This variant is likely to alter protein function as it is rare in humans, conserved, and predicted as variably such by computer algorithms.
 - Variants in this gene can result in Ehlers-Danlos syndrome-like issues, including dysautonomia.

- o This variant is a potential risk factor for fatigue in this patient, via vascular hypotension.
- TNFRSF13B c.204dupA, p.Leu69ThrfsTer12, heterozygous:
 - o This variant results in protein loss of function, and assessed as Pathogenic. o Variants in this gene can result in common variable immunodeficiency.
 - o This variant shows poor clinical correlation to the phenotype in this patient, however, it is possible that low immunoglobulin levels are a contributing factor in his disease.

Potential management issues for consideration:

- Consider SCN9A-targeted medications:
 - o Gabapentin, duloxetine, sertraline, amitriptyline
- Consider increasing mitochondrial cocktail. The potential conflict of interest was discussed.



Richard G. Boles, M.D.
 Medical Geneticist
 Director, Neurabilities NeuroGenomics
 Program Cell: 310-869-6332
 Fax: 626-270-4272
 rboles@neurabilities.com [https://
 neurabilities.com/neurogenomics](https://neurabilities.com/neurogenomics)

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