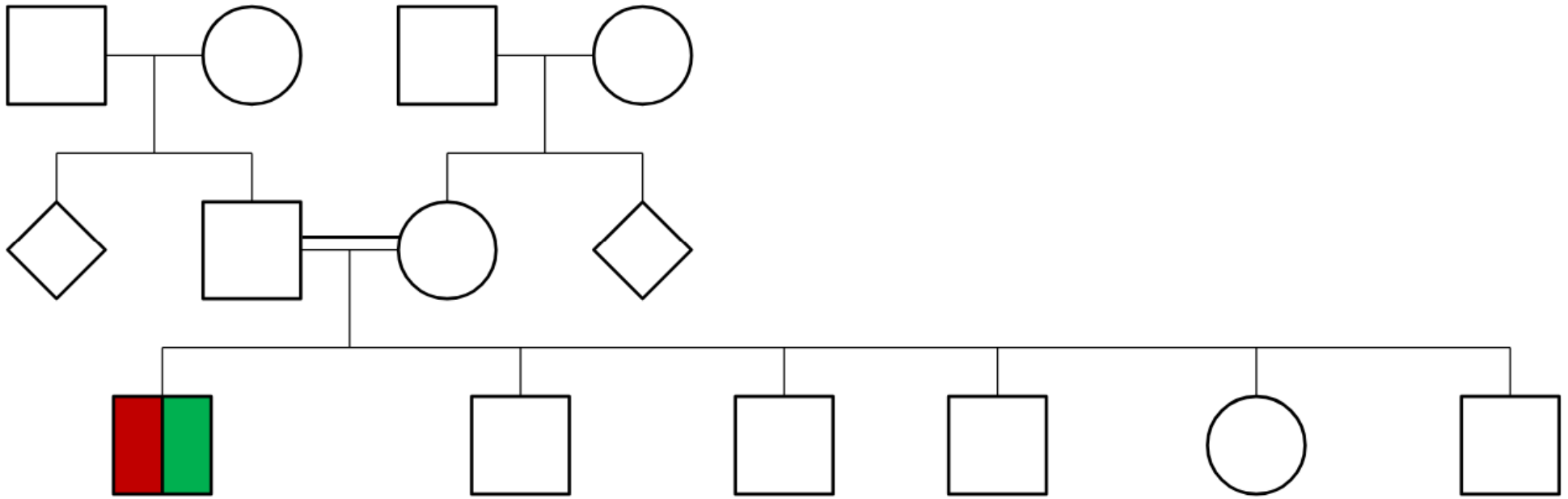
2017



F, 24 yrs
Elevated CPK
Rhabdomyolysis
Cardiomyopathy, 24 yrs
VT, 24 yrs

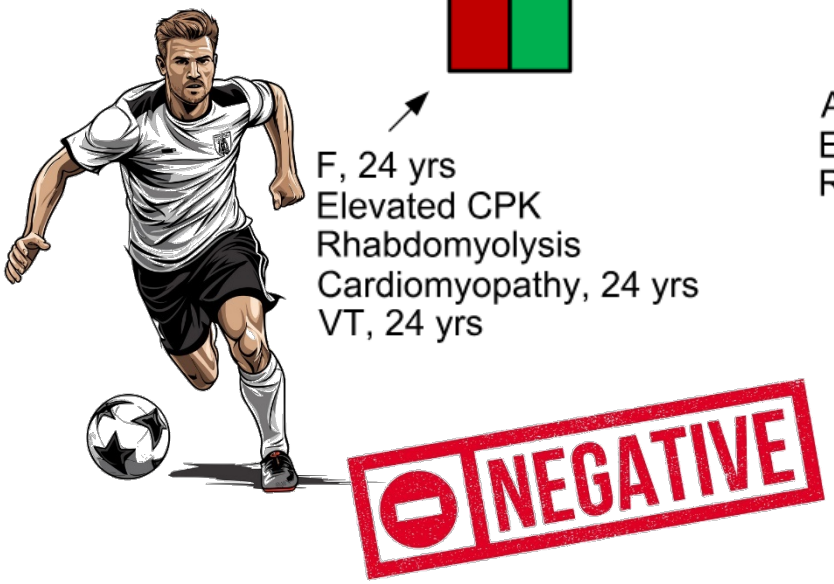
A, 21 yrs
Elevated CPK
Rhabdomyolysis

M, 18 yrs

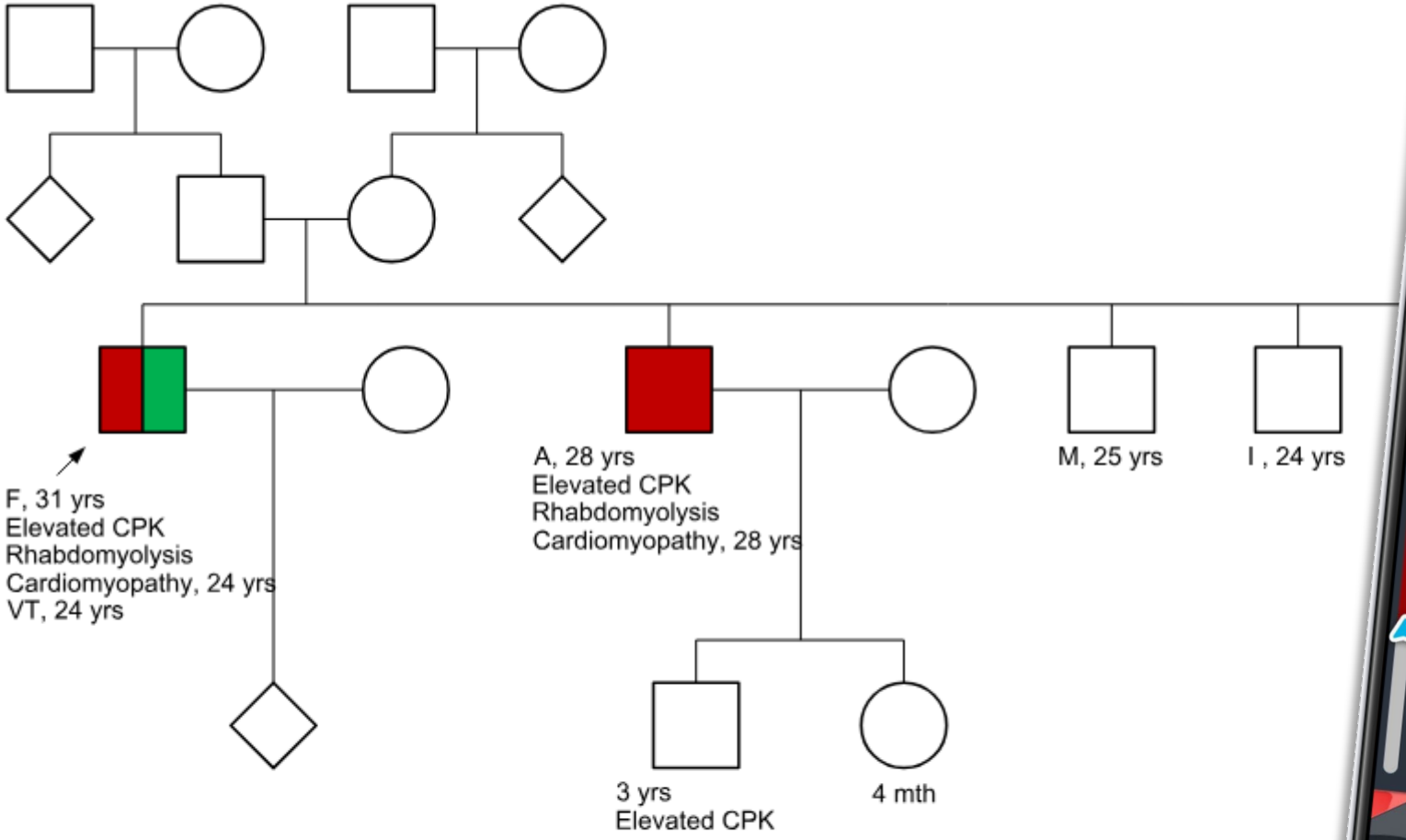
I , 17 yrs

Y, 10 yrs
Elevated CPK
Rhabdomyolysis

Y, 7 yrs



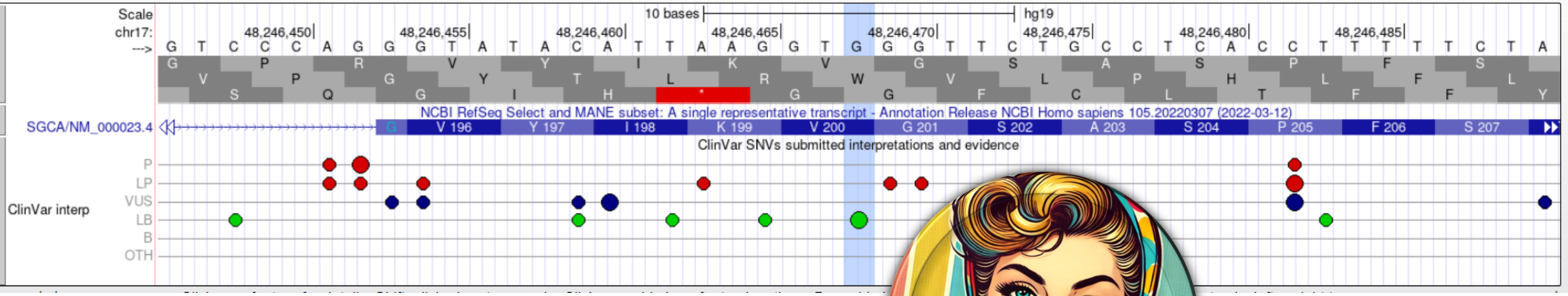
2024



Multiple Readmissions
PMVT

NEGATIVE

SGCA: c.600G>A, p.Val200=



Exon 6/10

- *SGCA* is a known cause of Muscular dystrophy, limb-girdle, autosomal recessive

Submissions - Germline

Classification (Last evaluated)	Review status (Assertion criteria)	Condition	Submitter	More information
Likely benign (Nov 08, 2016)	★☆☆☆ (GeneDx Variant Classification (06012015)) Method: clinical testing	not specified Affected status: yes Allele origin: germline	GeneDx Accession: SCV000533178.4 First in ClinVar: Mar 08, 2017 Last updated: Mar 08, 2017	
Likely benign (Aug 26, 2022)	★☆☆☆ (Invitae Variant Classification Sherloc (09022015)) Method: clinical testing	Autosomal recessive limb-girdle muscular dystrophy type 2D Affected status: unknown Allele origin: germline	Invitae Accession: SCV002488508.2 First in ClinVar: Apr 08, 2022 Last updated: Feb 07, 2023	
Likely benign (Feb 08, 2023)	★☆☆☆ (ACMG Guidelines, 2015) Method: clinical testing	Autosomal recessive limb-girdle muscular dystrophy type 2D Affected status: unknown Allele origin: germline	Genome-Nilou Lab Accession: SCV003931686.1 First in ClinVar: Jun 17, 2023 Last updated: Jun 17, 2023	

Comment:
This variant is considered likely benign or benign based on one or more of the following criteria: it is a conservative change, it occurs at a poorly conserved position in the protein, it is predicted to be benign by multiple in silico algorithms, and/or has population frequency not consistent with disease. (less)

Internal GeneMatcher for Novel Variants

Recent samples with variant 17:48246468 G>A

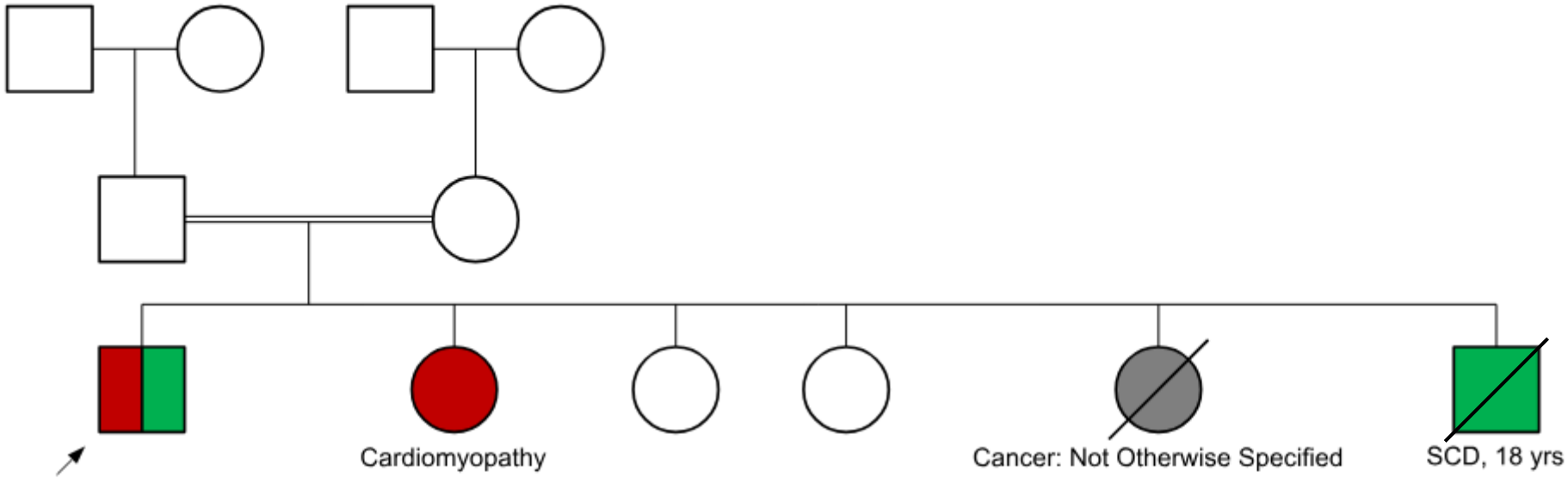
Backlog HOM: 3 Backlog HET: 17

Please note that the listed items do not include recent samples been marked with Exclude AF.

Showing a maximum of 100 records. For the full list, search in variant browser.

VCF SAMPLE	G	MODI...	Z	DP2	% ALT	ANALYSIS	PHENOTYPES	AFFE
38729.dragen.wes.grch37.202301...	Fe...	01/20...	HOM	0, 135	100.00	11876	Myopathy	
38493.dragen.wes.grch37.202301...	M...	01/07...	HOM	0, 99	100.00	11761 - Copy	"Elevated circulating creatine kina...	
38493.dragen.wes.grch37.202301...	M...	01/07...	HOM	0, 99	100.00	11761	"Elevated circulating creatine kina...	
35289.dragen.wes.grch37.202206...	M...	06/04...	HOM	0, 99	100.00	I-H221013122001	myopathy	
35289.dragen.wes.grch37.202206...	M...	06/04...	HOM	0, 99	100.00	I-H220608132405	myopathy CPK	
35289.dragen.wes.grch37.202206...	M...	06/04...	HOM	0, 99	100.00	10075		
9616-gatk-20201125-231708	M...	11/26...	HOM	2, 65	97.01	I-H240225171629	cardiomyopathy "muscle tissue di...	
9616-gatk-20201125-231708	M...	11/26...	HOM	2, 65	97.01	I-H230524120451		

2024



LEGEND

- Cardiomyopathy
- SCD
- Cancer: Not Otherwise Specified

From: Jessica Hoffman <jhoffman@genedx.com>
Sent: Tuesday, March 5, 2024 11:43 PM
To: הורוביץ סמדר - HOROWITZ SMADAR <smadarho@hadassah.org.il>
Subject: RE: Inquiry Regarding Variant NM_000023.4(SGCA):c.600G>A (p.Val200=)

Dear Smadar,

We identified the c.600 G>A: p.(Val200=) variant in trans with a LOF PATH variant in SGCA in a patient with muscular dystrophy, progressive muscle weakness, and muscle biopsy results consistent with a sarcoglycanopathy.

Was your patient homozygous or was there a second SGCA variant identified?

Best wishes,
Jessica

Jessica Hoffman, MS, CGC
Supervisor, Genomics Reporting
Genetic Counseling
Main: 301-519-2100 | Fax: 301-519-2892 | jhoffman@genedx.com
GeneDx | GeneDx.com

207 Perry Parkway
Gaithersburg, MD 20877

GeneDx

INVITAE

Genetic testing, simplified

Dear Smadar,

Thank you for your inquiry. Invitae has detected the variant, SGCA, Exon 6, NM_000023.2:c.600G>A (Silent) before and it is classified as likely benign. Please note that this classification was based on information available the last time we detected this variant. Our classification may change if we were to see the variant again today or in the future.

The evidence used in the classification is as follows:

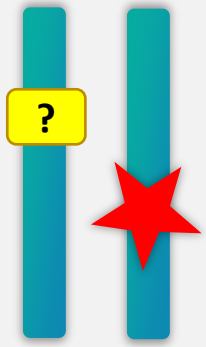
- 1 pathogenic point: Population:RECESSIVE: Allele count within pathogenic range (gnomAD)

Please note that internal Invitae cases were not used to reach this classification at this time. The affected/unaffected status and clinical information that we receive as a testing laboratory may be incomplete, absent, or otherwise limited.

Of note, the total points assigned are used to determine a variant classification of either: Pathogenic (5 pathogenic points), Likely Pathogenic (4 pathogenic points), Variant of Uncertain Significance (0-3 pathogenic points and 0-2 benign points), Likely Benign (3-4 benign points), or Benign (5 benign points). For additional information and a detailed review on our variant classification system, please visit our website, our publication in Genetics in Medicine, and our white paper.

An aggregate review of the prior cases indicates that we have seen this variant in the heterozygous state in the following:

At least 4 additional affected individuals with the same variant in comp with additional P/LP variant



SGCA phenotype

asymptomatic → severe phenotype

CARDIOVASCULAR:

Heart:

-Cardiomyopathy (rare) HP:0001638

SKELETAL:

-Contractures

SKELETAL:

Spine:

-Scoliosis may occur

MUSCLE SOFT TISSUE:

-Limb-girdle muscle weakness HP:0003325

-Limb-girdle muscle atrophy HP:0003797

-Unsteady gait HP:0002317

-Calf muscle hypertrophy HP:0008981

-Necrosis and degeneration seen on muscle biopsy

-Sadhalin deficiency seen on muscle biopsy

-Decreased immunostaining for alpha-sarcoglycan

-Myopathic changes seen on EMG HP:0003198

NEUROLOGIC:

Central Nervous System:

-Loss of reflexes due to myopathy

LABORATORY ABNORMALITIES:

-Increased serum creatine kinase HP:0003236

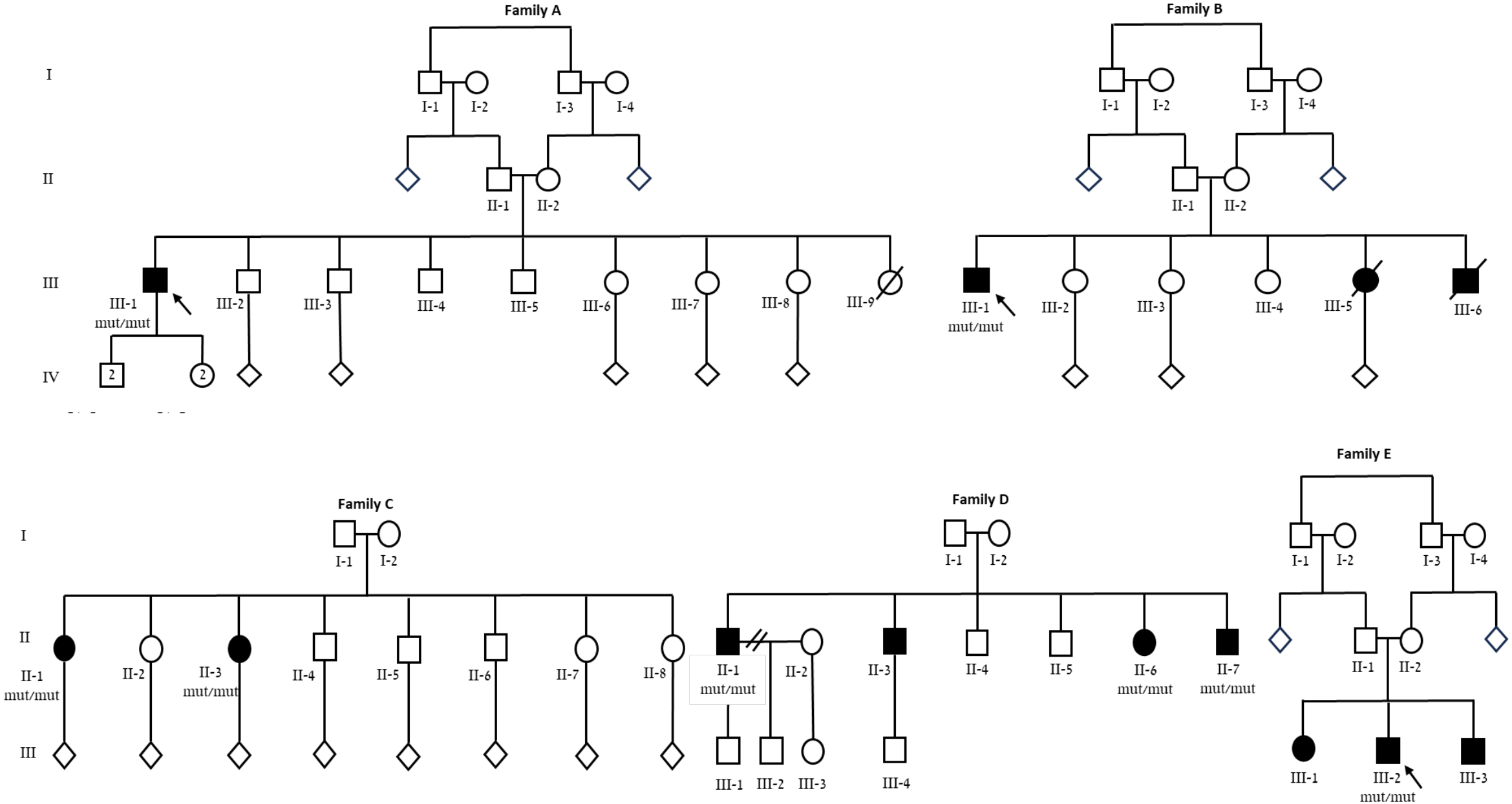
MISCELLANEOUS:

-Onset in childhood (3 to 10 years)

-Loss of independent walking by teenage years (in some)

-Progressive disorder HP:0003676

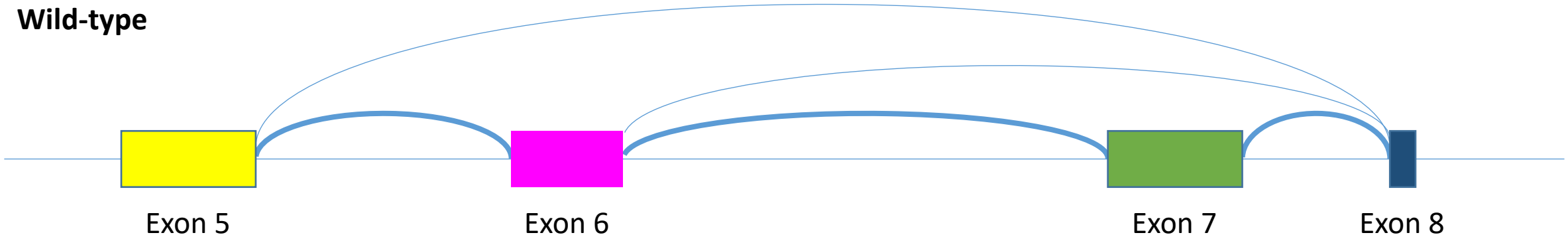
-Variable severity HP:0003828



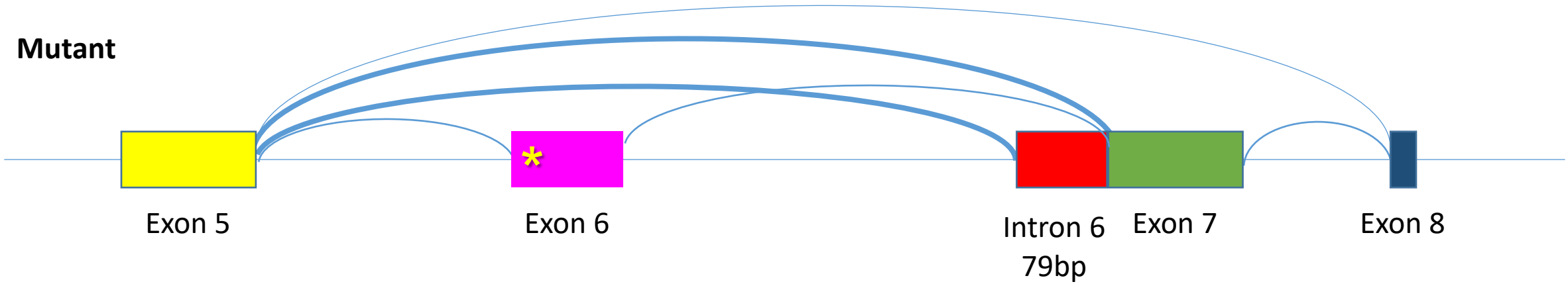
Unpublished data

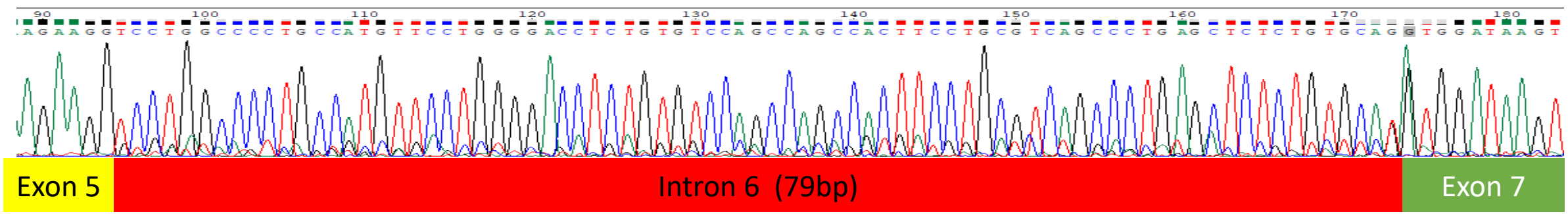
Family	Family A	Family B			Family C		Family D			Family E		Total
Individual	III-1	III-1	III-5	III-6	II-1	II-3	II-1	II-3	II-6	III-1	III-2	
Gender	M	M	F	M	F	F	M	M	F	*F*	M	
Age	45	28	30	18	46	40	31	28	17	13	10	
Genotype	HOM	HOM	?	?	HOM	HOM	HOM	HOM	?	HOM	HOM	
Myopathy	+	+	-	NA	+	+	-	-	+	+	-	**60%** (6/10)
Elevated CPK **Rhabdomyolysis**	+ -	+ -	+ -	NA	+ -	NA	++ +	+ +	+++ +	+ -	+ -	**100%** (9/9)
Cardiomyopathy (LVEF)	-	19%	48%	NA	NA	NA	38%	40%	-	NA	NA	**66%** (4/6)
Dilated LV	-	+++	-	NA	NA	NA	+	-	-	NA	NA	**33%** (2/6)
Abnormal ECG	-	+	-	NA	-	NA	+	+	NA	NA	NA	**50%** (3/6)
Abnormal CMR **LGE Lat. Wall** **LGE Inf. Wall**	NA	+ + +	+ + +	NA	NA	NA	+ + -	+ + +	NA	NA	NA	**100%** (4/4)
PVCs (24hrs)	580	19000	380	NA	NA	NA	NSVT	NA	NA	NA	NA	**50%** (2/4)
Sudden death (VT/VF)	-	+	-	+	-	-	+	-	-	-	-	**27%** (3/11)
ICD	-	+	-	NA	-	-	+	-	-	-	-	**20%** (2/10)

Wild-type



Mutant





Ronit Hoffman, Unpublished data

Clinical Implications

1. Enhanced family screening
2. Family planning Options
3. Tailored treatment approaches
   - Potential for gene-specific clinical trials
4. Improved risk stratification
   - Enhanced decision-making for interventions (e.g., ICD placement)

Key Takeaways:

1. Synonymous variants are not inherently benign.

2. Suspect these variants, especially in phenotype-relevant genes.

3. Examine internal, population-specific data.

4. Exercise caution with ClinVar classifications.

5. Regular data revision is essential.