Hypertrophic cardiomyopathy not only dominant inheritance

Bi allelic variants in TRIM63 a common cause for HCM

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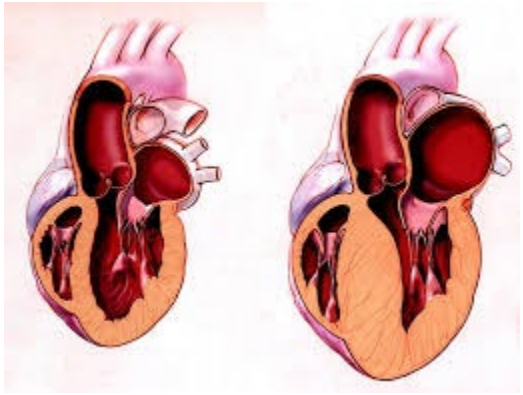
- Hypertrophic cardiomyopathy (HCM) is a prevalent hereditary heart disease, with an incidence of 1:500.

- HCM may be a multifactorial or monogenic disorder and is often transmitted in an autosomal dominant manner.



ESC European Society of Cardiology
Europace (2022) 24, 1307–1367
https://doi.org/10.1093/europace/euac030
POSITION PAPER

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

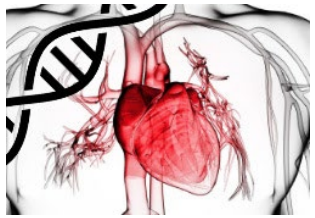


Table 13 Genes implicated in hypertrophic cardiomyopathy

Gene	Locus	Syndrome	Protein (functional effect)	Frequency	ClinGen classification
MYBPC3	11p11.2	Familial HCM	↓contractility due to ↓Ca^{2+} sensitivity	40–45%	Definite
MYH7	14q11.2-q12	Familial HCM	↓contractility due to ↓Ca^{2+} sensitivity	15–25%	Definite
TNNI3	19q13.4	Familial HCM	Loss of function (inhibitory)	1–7%	Definite
TNNT2	1q32.1	Familial HCM	Increase oxygen consumption	1–7%	Definite
TPM1	15q22.2	Familial HCM	Loss-of-function of the thin filament	1–2%	Definite
ACTC1	15q.14	Familial HCM	Gain-of-function causing high contractile phenotype	1–2%	Definite
MYL2	12q24.11	Familial HCM	Loss-of-function	1–2%	Definite
MYL3	3p21.31	Familial HCM	Loss-of-function	1–2%	Definite
Intrinsic cardiomyopathy genes					
ACTN2	1q43	LVH, LVNC, DCM, and idiopathic VF	Loss-of-function	<1%	Moderate
PLN	6q22.31	HCM, DCM, and ARVC	Loss-of-function of SERCA (Ca^{2+} overload) mitochondrial disease	<1%	Definite
JPH2	20q13.12	Familial HCM/ DCM	Unknown	<1%	Moderate
FHOD3	18q12.2	Familial HCM/ DCM	Actin filament polymerization disruption	0.5–2%	Not curated by ClinGen
CSRP3	11p15.1	Late onset familial HCM, DCM	Unknown (non-sarcomeric gene)	<1%	Moderate
TNNC1	3p21.1	Familial HCM	Disruption of Ca^{2+} handling	<1%	Moderate

Syndromic genes, where isolated LVH may be seen					
CACNA1C	12p13.33	Timothy syndrome, BrS, LQTS	Intracellular Ca (2+) overload	<1%	Definite
DES	2q35	Desminopathy (DCM), myofibrillar myopathy	Dysfunction through Z-disk and myofibril disintegration, followed by abnormal accumulation of intracellular proteins	<1%	Definite
FHL1	Xq26.3	Emery-Dreifuss MD, cardiac conduction abnormalities, arrhythmias, HCM	Dysfunction through Z-disk and myofibril disintegration, followed by abnormal accumulation of intracellular proteins	<1%	Definite
FLNC	7q32.1	Myofibrillar myopathy, HCM, RCM, distal myopathy	Dysfunction through Z-disk and myofibril disintegration, followed by abnormal accumulation of intracellular proteins	<1%	Not curated by ClinGen
GLA	Xq22.1	Fabry disease	Loss-of-function	<1%	Definite
LAMP2	Xq24	Danon disease	Loss-of-function	<1%	Definite
PRKAG2	7q36.1	PRKAG2 cardiomyopathy	Dysfunction of AMPK	1–2%	Definite
PTPN11	12q24.13	Noonan syndrome	RASopathy	<1%	Definite
RAF1	3p25.2	Noonan syndrome	RASopathy	<1%	Definite
RIT1	1q22	Noonan syndrome	RASopathy	<1%	Definite
TTR	18q12.1	Transthyretin amyloidosis	Loss-of-function causing amyloid deposition in peripheral nerves and heart	1–2%	Definite
ALPK3	15q25.3	Infant-onset HCM/DCM	Biallelic loss-of-function	<1%	Strong

TRIM 63

This gene encodes a member of the RING zinc finger protein family found in striated muscle and iris. The product of this gene is an E3 ubiquitin ligase that localizes to the Z-line and M-line lattices of myofibrils. This protein plays an important role in the atrophy of skeletal and cardiac muscle and is required for the degradation of myosin heavy chain proteins, myosin light chain, myosin binding protein, and for muscle-type creatine kinase.

* 606131

TRIPARTITE MOTIF-CONTAINING PROTEIN 63; TRIM63

Alternative titles; symbols

E3 UBIQUITIN PROTEIN LIGASE TRIM63
RING FINGER PROTEIN 28; RNF28
STRIATED MUSCLE RING ZINC FINGER PROTEIN; SMRZ
MUSCLE-SPECIFIC RING FINGER PROTEIN 1; MURF1

HGNC Approved Gene Symbol: *TRIM63*

Cytogenetic location: *1p36.11* ***Genomic coordinates (GRCh38):*** *1:26,051,301-26,067,630* (from NCBI)

Human molecular genetic and functional studies identify TRIM63, encoding Muscle RING Finger Protein 1, as a novel gene for human hypertrophic cardiomyopathy

Suet Nee Chen [1], Grazyna Czernuszewicz, Yanli Tan, Raffaella Lombardi, Jianping Jin, James T Willerson, Ali J Marian

Affiliations + expand

PMID: 22821932 PMCID: PMC3482312 DOI: 10.1161/CIRCRESAHA.112.270207

Free PMC article

Abstract

Rationale: A delicate balance between protein synthesis and degradation maintains cardiac size and function. TRIM63 encoding Muscle RING Finger 1 (MuRF1) maintains muscle protein homeostasis by tagging the sarcomere proteins with ubiquitin for subsequent degradation by the ubiquitin-proteasome system (UPS).

Objective: To determine the pathogenic role of TRIM63 in human hypertrophic cardiomyopathy (HCM).

Methods and results: Sequencing of TRIM63 gene in 302 HCM probands (250 white individuals) and 339 control subjects (262 white individuals) led to identification of 2 missense (p.A48V and p.I130M) and a deletion (p.Q247*) variants exclusively in the HCM probands. These 3 variants were absent in 751 additional control subjects screened by TaqMan assays. Likewise, rare variants were enriched in the white HCM population (11/250, 4.4% versus 3/262, 1.1%, respectively, P=0.024). Expression of the mutant TRIM63 was associated with mislocalization of TRIM63 to sarcomere Z disks, impaired auto-ubiquitination, reduced ubiquitination and UPS-mediated degradation of myosin heavy chain 6, cardiac myosin binding protein C, calcineurin (PPP3CB), and p-MTOR in adult cardiac myocytes. Induced expression of the mutant TRIM63 in the mouse heart was associated with cardiac hypertrophy, activation of the MTOR-S6K and calcineurin pathways, and expression of the hypertrophic markers, which were normalized on turning off expression of the mutant protein.

Conclusions: TRIM63 mutations, identified in patients with HCM, impart loss-of-function effects on E3 ligase activity and are probably causal mutations in HCM. The findings implicate impaired protein degradation in the pathogenesis of HCM.

TRIM63

p.Ala48Val

p.Ile130Met

p.Gln247Ter

Does p.Q247X in TRIM63 cause human hypertrophic cardiomyopathy?

Rafal Ploski [1], Agnieszka Pollak, Sonja Müller, Maria Franaszczyk, Ewa Michalak, Joanna Kosinska, Piotr Stawinski, Mateusz Spiewak, Hubert Seggewiss, Zofia T Bilinska

Affiliations + expand

PMID: 24436435 DOI: 10.1161/CIRCRESAHA.114.302662

Abstract

Rationale: Variants in TRIM63, including a nonsense mutation (p.Q247X), have been suggested recently to cause hypertrophic cardiomyopathy.

Objective: To verify pathogenicity of TRIM63 p.Q247X detected by whole-exome sequencing in a symptomless professional sports player seeking medical advice because of a prolonged QT interval found during a routine check-up.

Methods and results: Clinical studies were performed in the proband and his mother, who also carried TRIM63 p.Q247X. No evidence of hypertrophic cardiomyopathy was found in either person.

Conclusions: The p.Q247X variant in TRIM63 is not likely to be a highly penetrant variant causing hypertrophic cardiomyopathy.

Keywords: TRIM63 protein, human; cardiomyopathy, hypertrophic.

Homozygous Nonsense Mutation p.Q274X in TRIM63 (MuRF1) in a Patient with Mild Skeletal Myopathy and Cardiac Hypertrophy

Manu Jokela [1] [2], Peter Baumann [3], Sanna Huovinen [4], Sini Penttilä [1], Bjarne Udd [1]

Affiliations + expand

PMID: 30372688 DOI: 10.3233/JND-180350

Abstract

TRIM63 mutations have been described as a potential cause for cardiac and skeletal myopathy in only one family so far. We describe a new patient carrying the same homozygous TRIM63 nonsense mutation c.739 C>T p.Q247X, that was originally reported in two members of a Spanish family manifesting cardiac hypertrophy. One of these original patients also had an additional heterozygous mutation in TRIM54 and a much more severe phenotype also involving skeletal muscles, and a digenic inheritance was therefore suggested. Our case report confirms the role of TRIM63 as a new cardiac myopathy gene, although it is unclear whether the homozygous p.Q247X mutation alone is sufficient to cause an additional skeletal myopathy.

Keywords: MuRF1; Myopathy; TRIM63; cardiac hypertrophy; hypertrophic cardiomyopathy; myopathy with internalized capillaries.

Mutations in *TRIM63* cause an autosomal-recessive form of hypertrophic cardiomyopathy

Joel Salazar-Mendiguchía [1 2 3], Juan Pablo Ochoa [4], Julian Palomino-Doza [5 6], Fernando Domínguez [6 7], Carles Díez-López [8], Mohammed Akhtar [9], Soraya Ramiro-León [10], María M Clemente [11], Antonia Pérez-Cejas [12], María Robledo [13], Iria Gómez-Díaz [4], María Luisa Peña-Peña [14], Vicente Climent [15], Francisco Salmerón-Martínez [16], Celestino Hernández [17], Pablo E García-Granja [18], M Victoria Mogollón [19], Ivonne Cárdenas-Reyes [4], Marcos Cicerchia [4], Diego García-Giustiniani [4], Arsonval Lamounier Jr [4], Belén Gil-Fournier [10], Felícitas Díaz-Flores [12], Rafael Salguero [5], Luis Santomé [4], Petros Syrris [20], Montse Olivé [21], Pablo García-Pavía [6 7 22], Martín Ortiz-Genga [4], Perry M Elliott [9 20], Lorenzo Monserrat [4]; GENESCOPIC Research Group

Collaborators, Affiliations + expand

PMID: 32451364 PMCID: PMC7476281 DOI: 10.1136/heartjnl-2020-316913

Free PMC article

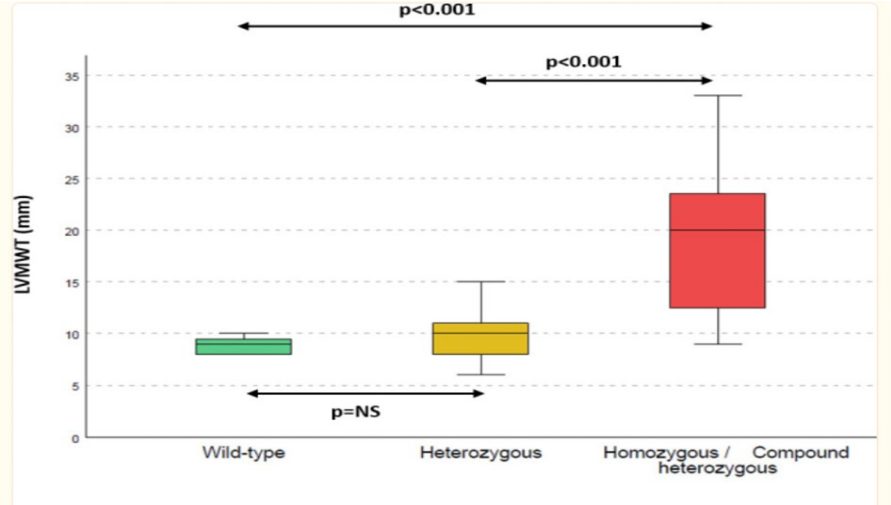
Abstract

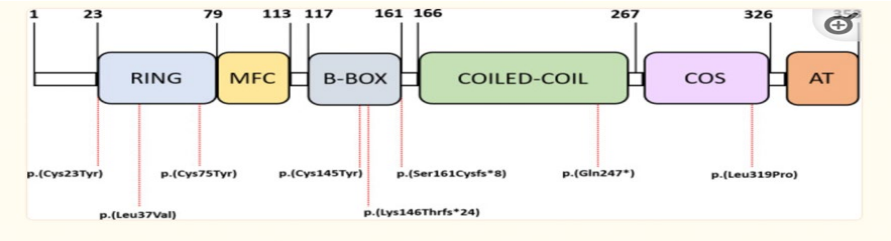
Objective: Up to 50% of patients with hypertrophic cardiomyopathy (HCM) show no disease-causing variants in genetic studies. *TRIM63* has been suggested as a candidate gene for the development of cardiomyopathies, although evidence for a causative role in HCM is limited. We sought to investigate the relationship between rare variants in *TRIM63* and the development of HCM.

Methods: *TRIM63* was sequenced by next generation sequencing in 4867 index cases with a clinical diagnosis of HCM and in 3628 probands with other cardiomyopathies. Additionally, 3136 index cases with familial cardiovascular diseases other than cardiomyopathy (mainly channelopathies and aortic diseases) were used as controls.

Results: Sixteen index cases with rare homozygous or compound heterozygous variants in *TRIM63* (15 HCM and one restrictive cardiomyopathy) were included. No homozygous or compound heterozygous were identified in the control population. Familial evaluation showed that only homozygous and compound heterozygous had signs of disease, whereas all heterozygous family members were healthy. The mean age at diagnosis was 35 years (range 15-69). Fifty per cent of patients had concentric left ventricular hypertrophy (LVH) and 45% were asymptomatic at the moment of the first examination. Significant degrees of late gadolinium enhancement were detected in 80% of affected individuals, and 20% of patients had left ventricular (LV) systolic dysfunction. Fifty per cent had non-sustained ventricular tachycardia. Twenty per cent of patients suffered an adverse cerebrovascular event (20%).

Conclusion: *TRIM63* appears to be an uncommon cause of HCM inherited in an autosomal-recessive manner and associated with concentric LVH and a high rate of LV dysfunction.





-concentric left ventricular hypertrophy (LVH)

-late gadolinium enhancement

-left ventricular (LV) systolic dysfunction

- non-sustained ventricular tachycardia

- adverse cerebrovascular event (20%)

Case Report: Two New Cases of Autosomal-Recessive **Hypertrophic Cardiomyopathy** Associated With **TRIM63**-Compound Heterozygous Variant.

Andreeva S, Chumakova O, Karelkina E, Lebedeva V, Lubimtseva T, Semenov A, Nikitin A, Speshilov G, Kozyreva A, Sokolnikova P, Zhuk S, Fomicheva Y, Moiseeva O, Kostareva A.

Front Genet. 2022 Feb 22;13:743472. doi: 10.3389/fgene.2022.743472. eCollection 2022.

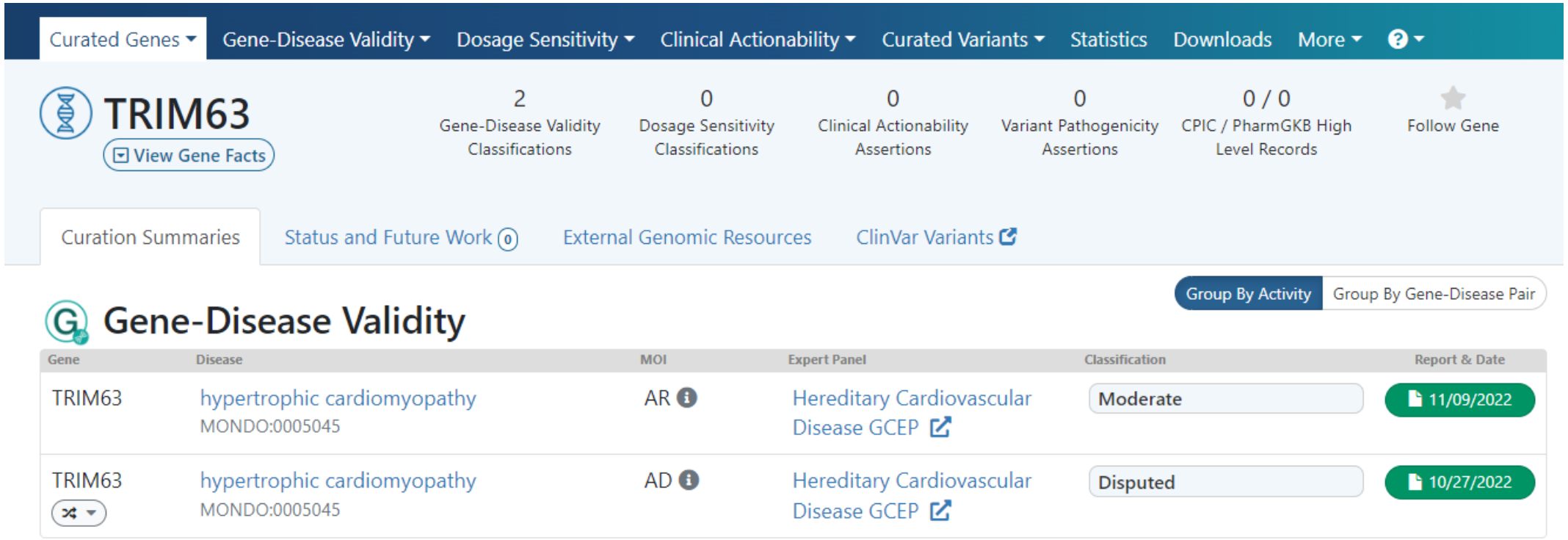
PMID: 35273634 **Free PMC article.**

Ethnicity, consanguinity, and genetic architecture of **hypertrophic cardiomyopathy**.

Allouba M, Walsh R, Afify A, Hosny M, Halawa S, Galal A, Fathy M, Theotokis PI, Boraey A, Ellithy A, Buchan R, Govind R, Whiffin N, Anwer S, ElGuindy A, Ware JS, Barton PJR, Yacoub M, Aguib Y.

Eur Heart J. 2023 Dec 21;44(48):5146-5158. doi: 10.1093/eurheartj/ehad372.

PMID: 37431535 **Free PMC article.**


Curated Genes
Gene-Disease Validity
Dosage Sensitivity
Clinical Actionability
Curated Variants
Statistics
Downloads
More
TRIM63
View Gene Facts
2
Gene-Disease Validity Classifications
0
Dosage Sensitivity Classifications
0
Clinical Actionability Assertions
0
Variant Pathogenicity Assertions
0 / 0
CPIC / PharmGKB High Level Records
Follow Gene
Curation Summaries
Status and Future Work 0
External Genomic Resources
ClinVar Variants
Group By Activity
Group By Gene-Disease Pair
Gene-Disease Validity
Gene
Disease
MOI
Expert Panel
Classification
Report & Date
TRIM63
hypertrophic cardiomyopathy
MONDO:0005045
AR
Hereditary Cardiovascular Disease GCEP
Moderate
11/09/2022
TRIM63
hypertrophic cardiomyopathy
MONDO:0005045
AD
Hereditary Cardiovascular Disease GCEP
Disputed
10/27/2022

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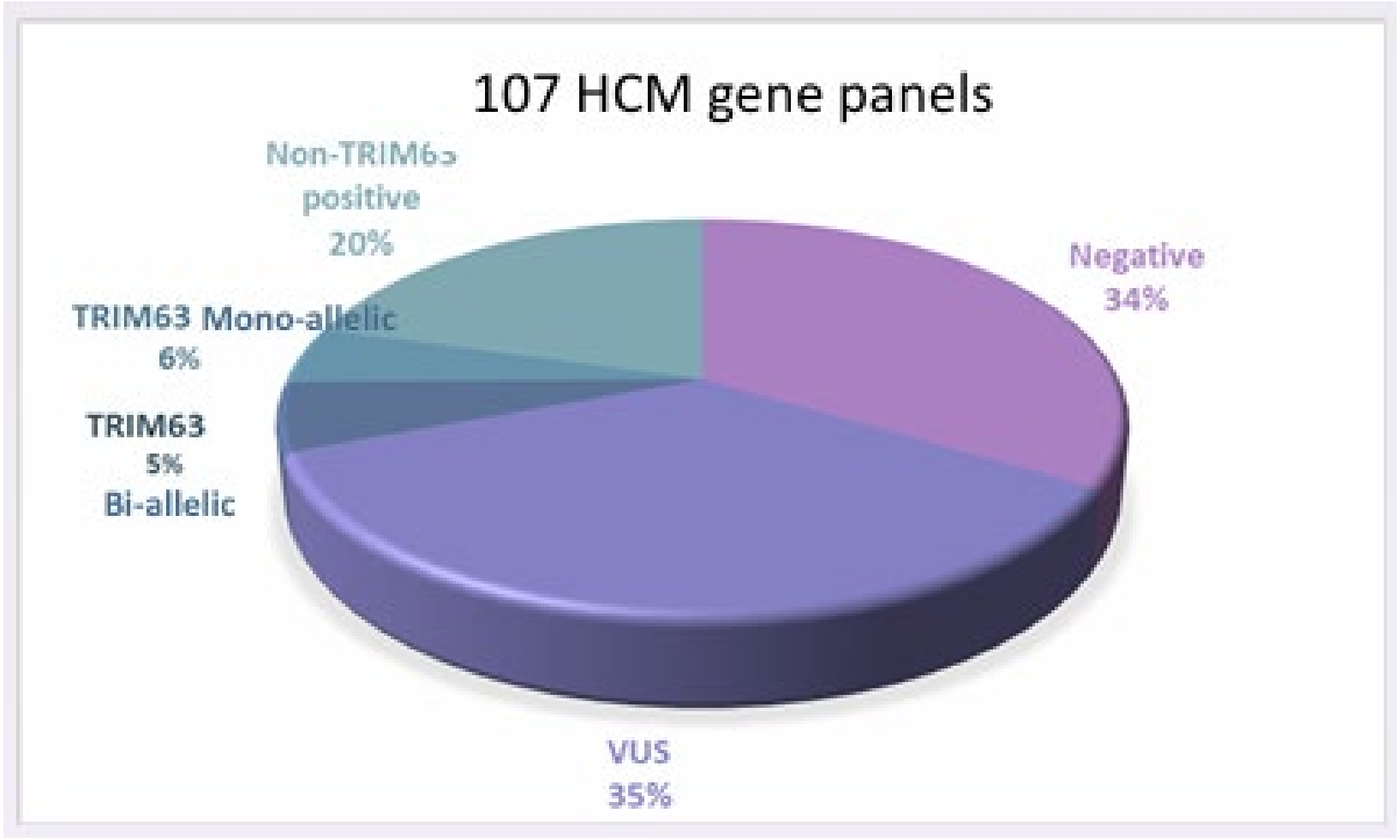
107 HCM patients

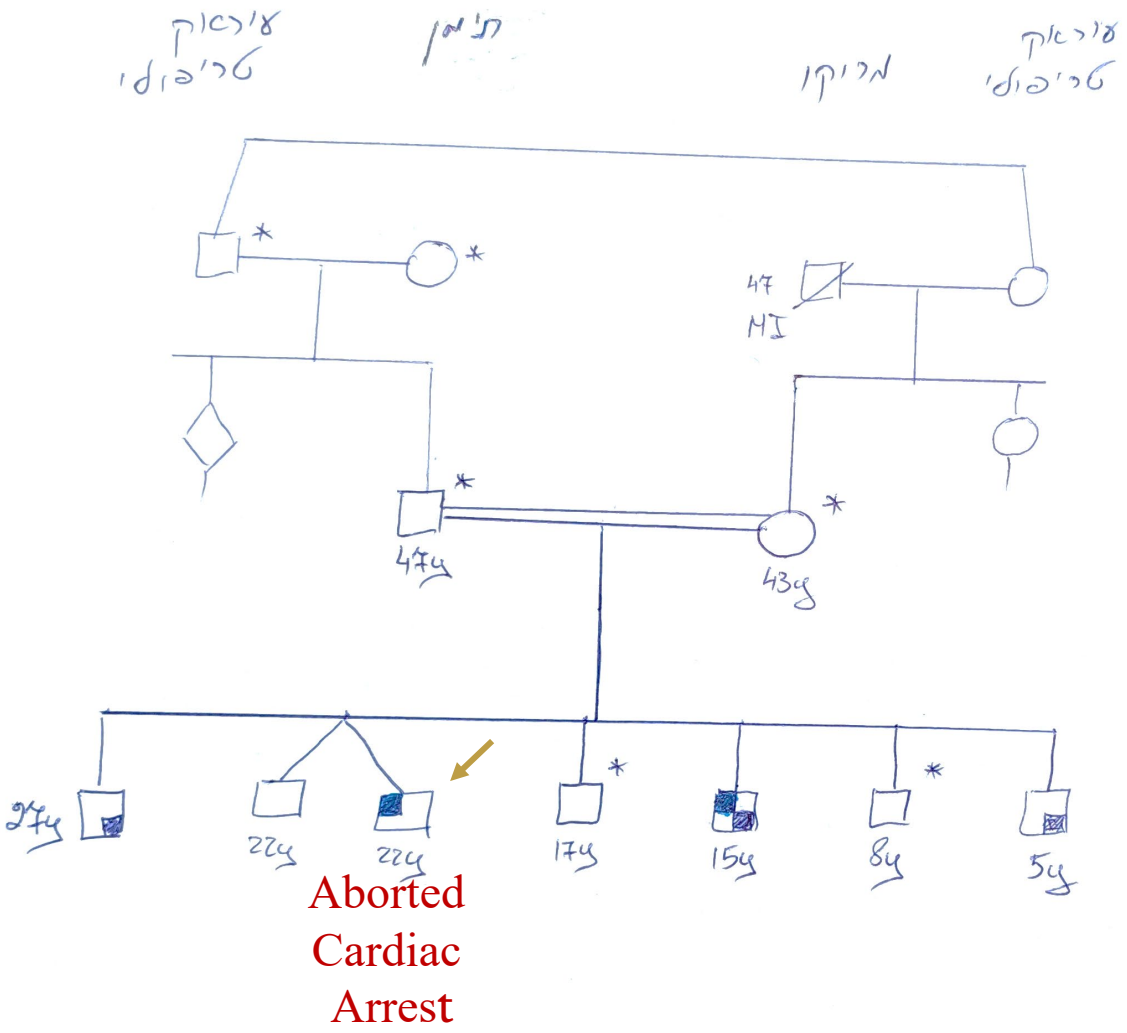
07/2022-10/2023

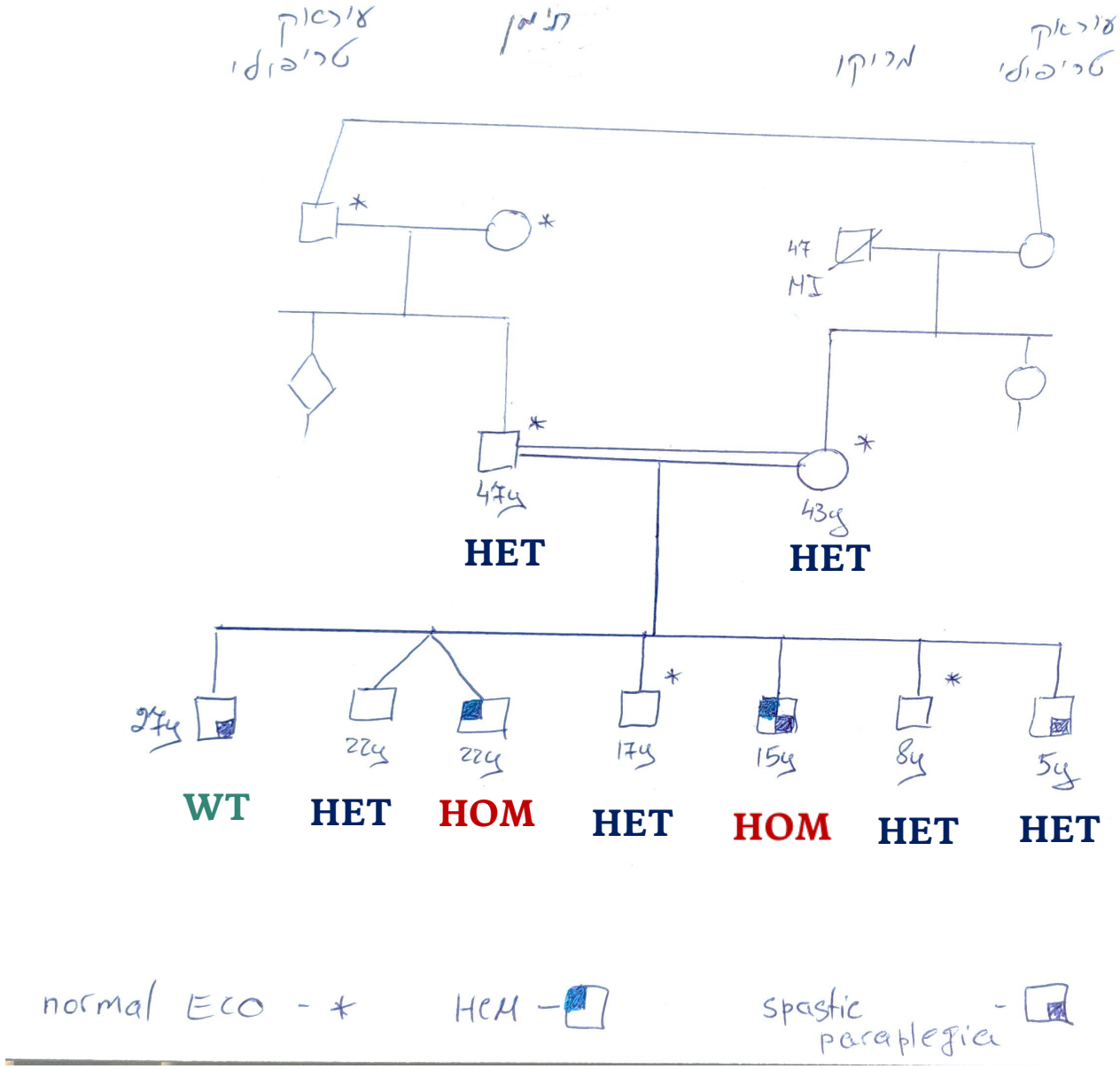
Virtual Exome based gene panel for HCM (including 116 genes)

11 Patients with mono or biallelic pathogenic variants in TRIM63


107 HCM gene panels
Non-TRIM63 positive 20%
Negative 34%
TRIM63 Mono-allelic 6%
TRIM63 Bi-allelic 5%
VUS 35%

Family 1


47
HI
47y
43y
27y
22y
22y
17y
15y
8y
5y
Aborted
Cardiac
Arrest
normal ECO - *
HCM -
Spastic
paraplegia -



Famly 1

TRIM63

c.277C>T
p.Gln93Ter

LP

Genetics	Gender	Origin	Age at dx	Arrhythmia	Morphology	LVMWT	EF	NYHA class
Gln93Ter/ Gln93Ter	M	Libyan Jewish	11	Sudden cardiac arrest	Concentric hypertrophy	35mm	55%	2
Gln93Ter/ Gln93Ter	M	Iranian Jewish	19	AFib NSVT	Concentric hypertrophy	20mm	50%	3
Gln93Ter/ Gln247Ter	M	Libyan Jewish	13-WPW 39-HCM	AVRT NSVT	Concentric hypertrophy	19mm	50%	2
Gln247Ter/ Gln247Ter	F	Libyan Jewish	25	AFib NSVT	Concentric hypertrophy	33mm	25%	2-3
Cys75Thr/ Cys75Thr	M	Bedouin	30	VPCS	Asymmetric LVH, Non obstructive	16 mm	60%	1

TRIM63:c.277C>T, p.Gln93*

0.0652%	**gnomAD (Max)** **Very Rare** variant in gnomAD (Max)	**4** Alleles of **6,136** **0** homozygote **N/A** Individuals
0.002%	**gnomAD (Aggregated)** **Very Rare** variant in gnomAD (Aggregated)	**5** Alleles of **251,354** **0** homozygote **N/A** Individuals
0.0033%	**ExAC** **Very Rare** variant in ExAC	**4** Alleles of **121,198** **0** homozygote **N/A** Individuals
0.002%	**gnomAD (Exome)** **Very Rare** variant in gnomAD (Exome)	**5** Alleles of **251,354** **0** homozygote **N/A** Individuals
N/A	**GME Variome** **No Observation** for this variant in GME Variome	**N/A** Alleles of **N/A** **N/A** homozygote **N/A** Individuals
0%	**gnomAD (Genome)** **No Observation** for this variant in gnomAD (Genome)	**0** Alleles of **0** **0** homozygote **N/A** Individuals
N/A	**India DB** **No Observation** for this variant in India DB	**N/A** Alleles of **N/A** **N/A** homozygote **N/A** Individuals
N/A	**Mexican DB** **No Observation** for this variant in Mexican DB	**N/A** Alleles of **N/A** **N/A** homozygote **N/A** Individuals
N/A	**ABraOM**	**N/A** Alleles of **N/A**

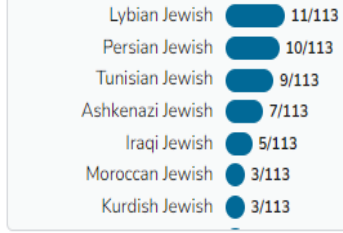
Franklin Community Frequency

113 cases
Very Rare variant in Franklin community

7
Homozygote

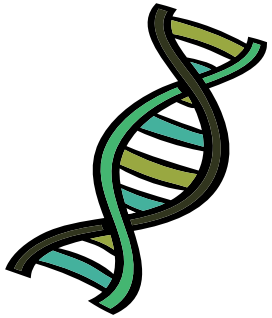
Quick filters: High Confidence | Homozygous Only | From my Country

Ethnicity Distribution | Associated Phenotype Systems



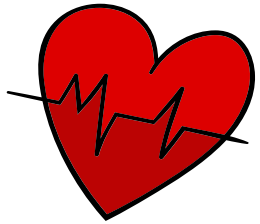
Unaffected Distribution

1:30 in Lybian Jewish population

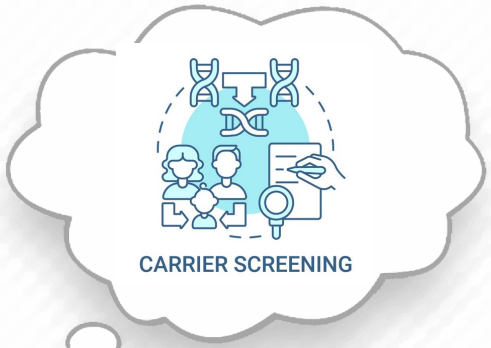


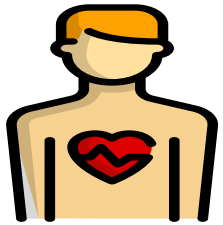
biallelic pathogenic variants in TRIM63 were identified in 5 individuals (4.7%).

The gene is not included in most of the commercial gene panels



Severe concentric hypertrophy
Young age of onset
Ventricular and supraventricular arrhythmias





Heterozygote variants in TRIM63 were found in additional 6/80 (8.6%).

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Noa Ruhrman Shahar
Dina Yagel
Rotem Greenberg
Ofer Isakov
Michal Naftali
Lily Bazak
Daniel Monakier
Alvit Veber
Nechama Shalva

Amitai Segev
Moti Haim
Lena Sagi-Dain
Lilach Benyamini
Adel Shalata
Sagi Josefsberg
Ben Yehoshua
Lina Basel Salmon
Sara Hoss
Shay Ben-Shachar