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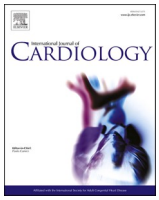

Autosomal recessive hypertrophic cardiomyopathy associated with variants in *TRIM63*

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Background: Hypertrophic cardiomyopathy (HCM) is typically linked to dominant variants in sarcomeric genes, but rare minor genes, including *TRIM63* coding for an E3 ubiquitin-protein ligase, have recently emerged as potential causes of recessive HCM.
Methods and results: Among 517 adult patients with clinical HCM who underwent next-generation sequencing, we found six index cases carrying biallelic *TRIM63* variants—four homozygous and two compound heterozygous. They presented with early-onset disease, marked concentric hypertrophy, diffuse myocardial fibrosis, and progressive left ventricular dysfunction. One patient underwent heart transplantation. No cardiac disease was found in heterozygous relatives.
Conclusions: TRIM63-related HCM is rare but clinically distinct. Early identification of *TRIM63* homozygous and two compound heterozygous variants in HCM is crucial and warrants proactive clinical surveillance.
Take home messages:

- TRIM63-related HCM is a rare autosomal-recessive subtype with early onset and severe phenotypes.
- Rapid disease progression is common, with extensive fibrosis and frequent transition to hypokinetic-dilated end-stage cardiomyopathy.
- Early genetic diagnosis supports proactive management, including timely ICD implantation for arrhythmia risk and reproductive counselling for families due to the recessive inheritance.

Abbreviations: ACGS, Association for Clinical Genomic Science; ACMG, American college of medical genetics and genomics; CMR, Cardiac magnetic resonance; ECG, Electrocardiogram; gDNA, Genomic DNA; gnomAD, Genome aggregation database; HCM, Hypertrophic cardiomyopathy; HGMD, Human gene mutation database; ICD, Implantable cardioverter-defibrillator; LGE, Late gadolinium enhancement; LP, Likely pathogenic; MuRF1, Muscle-specific RING finger protein 1; NGS, Next-generation sequencing; NSVT, Non-sustained ventricular tachycardia; *TRIM63*, Tripartite motif-containing protein 63.

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Table 1
Genetic variants and clinical features detected in TRIM63 gene in our cohort.

	Origin Sex	Variant (HGVS)	Variant Type	ACMG	Age at dx	Clinical course	LVEF	Hypertrophy	Other CMR findings	LVOTO
1.	North African F	c.224G>A p.(Cys75Tyr) HO	Missense	LP	< 40	Long-standing dyspnea. Progression toward restrictive physiology	50 %	Concentric hypertrophy	CMR not performed	No
2.	Caucasian M	c.739C>T p.(Glu247*) HO	Nonsense	LP	19	Complaining dyspnea and fatigue	50 %	Mid-to-apical concentric hypertrophy	Extensive transmural LGE in hypertrophied areas	Yes- up to 80 mmHg with Valsalva
3.	Caucasian M	c.739C>T p.(Glu247*) HE c.224G>A p.(Cys75Tyr) HE	Nonsense Missense	LP LP	18	Severe progression to end-stage with HF, SVT episodes, ICD implantation, listed for heart transplantation	35 %	Concentric massive hypertrophy (up to 40 mm)	Extensive transmural LGE and oedema in hypertrophied areas, apical aneurysm with thrombus	No
4.	Caucasian M	c.270C>A p.(Tyr90*) HE c.645_677delins21 p.(Leu216_Glu226delinsTrpMetArgArgLysValMet) HE	Nonsense Inframe	LP LP	27	Multiple NSVT, ICD implantation for primary prevention	35 %	Progression to dilated end-stage phenotype	Extensive transmural LGE of IVS and apex	No
5.	Caucasian M	c.739C>T p.(Glu247*) HO	Nonsense	LP	19	NSVT Documented, ICD implantation for primary prevention	45 %	Concentric hypertrophy	Extensive transmural LGE in hypertrophied areas and apical aneurysm	No
6.	Caucasian F	c.526 A>T p.(Met176Leu) HO	Missense	VUS	82	Supraventricular arrhythmias, no HF symptoms	55 %	Concentric hypertrophy (++apical septum)	Mild pericardial effusion, apical LGE	No

Clinical and imaging characteristics of six index patients carrying homozygous or compound heterozygous TRIM63 variants.
Abbreviations: ACMG: American College of Medical Genetics; CMR: cardiovascular magnetic resonance; dx: diagnosis; F: female; HF: heart failure; HE: heterozygous; HO: homozygous; ICD: implantable cardioverter-defibrillator; IVS: interventricular septum; LGE: late gadolinium enhancement; LV: left ventricle; LVEF: left ventricular ejection fraction; LVOTO: left ventricular outflow tract obstruction; M: male; MWST: maximal wall thickness; NSVT: non-sustained ventricular tachycardia; SVT: supraventricular tachycardia.

1. Introduction

The *MYH7* gene, which encodes cardiac myosin heavy chain ß, was the first gene associated with Hypertrophic Cardiomyopathy (HCM) discovered in 1990. Since then, HCM has been called "the disease of the sarcomere" due to the identification of hundreds of variants in more than 20 genes [1,2]. Traditionally, HCM has been classified as an autosomal dominant Mendelian disease, with incomplete penetrance and variable expressivity. Despite extensive research efforts to expand the knowledge on the genetics of HCM, the current diagnostic yield of genetic testing ranges from 30 % to 50 % [3,4]. HCM in patients with negative genetic testing is believed to arise from a complex genetic architecture encompassing Mendelian forms, determined primarily by an ultrarare large-effect genetic variant, and polygenic forms [5]. Beyond the classic sarcomeric genes, several additional genes (*ACTN2, ALPK3, CSRP3, FHOD3, FLNC, JPH2, KLHL24, PLN* and *TRIM63*) encode non-sarcomeric proteins with diverse functions and have been proven to be disease-causing in a small subset of HCM patients. For this reason, these genes are referred to as "minor" genes, and investigating these pathways provides new insights into cardiomyopathy pathophysiology [6]. For most of these genes, the associated phenotype remains poorly characterized, and the mode of inheritance spans from autosomal dominant to recessive [7]. Among minor genes, *KLHL24* and *TRIM63* are responsible for ubiquitylation and protein degradation. In addition, these genes exhibit complex genotype-phenotype correlations across different variant classes (common regulatory and rare missense, truncating and biallelic loss-of-function variants), with distinct associations often observed for hypertrophic and dilated cardiomyopathy [6]. A recently published paper classifies 18 genes with robust recessive association with Cardiomyopathies, four of which are associated with HCM [7]. These findings emphasize the heterogeneous genetic basis of HCM and highlight the need for a refined classification of minor genes, which could ultimately impact genetic counselling and personalized treatment strategies.

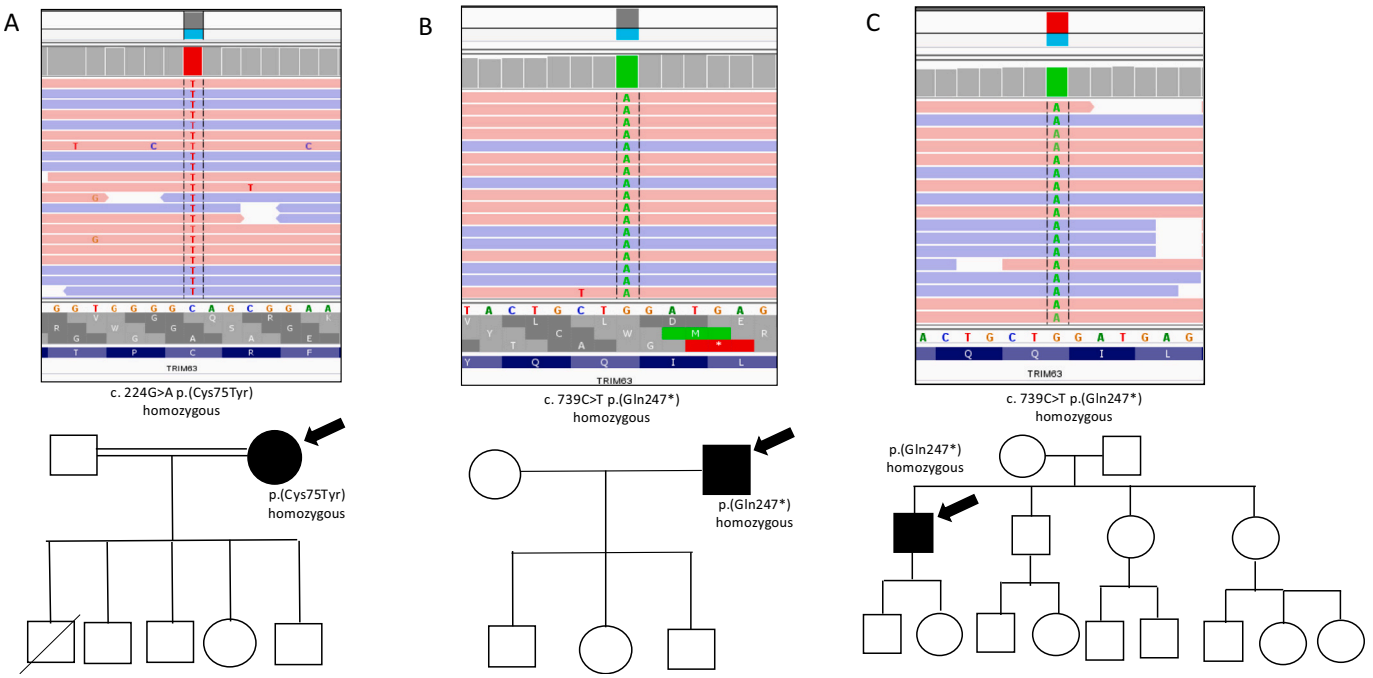

Fig. 1. Sequencing data and pedigrees of patients 1 (A), 2 (B), and 5 (C). Next-generation sequencing identified a homozygous c.224G > A p.Cys75Tyr) variant in patient 1, a North African woman. The family history was negative for cardiomyopathy, but the pedigree revealed consanguinity, supporting a recessive inheritance pattern. This variant, identified in homozygosity, has been previously described in adult patients with recessive HCM as likely pathogenic (LP). In patient 2, of Caucasian origin, molecular testing confirmed a homozygous c.739C>T p.(Gln247*) variant in TRIM63. His family history was negative for cardiomyopathy, and no relatives underwent genetic testing. The c.739C > T p. (Gln247*) variant has been described in adult patients with recessive HCM. In patient 5, also of Caucasian origin, the same homozygous c.739C > T p. (Gln247*) variant was detected. Family investigation suggested consanguinity, as both parents originated from the same geographically isolated village, making a shared ancestry highly probable.

1.1. TRIM63

TRIM63 is a rare, minor gene that was recently identified as a cause of HCM with autosomal recessive inheritance, and moderate association with HCM by ClinGen expert panels [8,9] [10]. The *TRIM63* gene (Genbank accession no. NM_032588) is considered tolerant to loss of function (LoF) and missense variants. *TRIM63* encodes an E3 ubiquitin-protein ligase known as muscle-specific RING-finger protein 1 (MuRF1), which belongs to a family of proteins with RING zinc-finger motifs. It is mainly found at the *Z*-disk and M-line of the sarcomere, where it interacts with several sarcomeric proteins. MuRF1 plays an essential role in regulating sarcomeric protein degradation through the ubiquitination pathway and linking myofibril components with intermediate filaments and microtubules [9]. Its expression is upregulated by atrophic stimuli, and *TRIM63* knockout mouse models exhibit an exaggerated hypertrophic response to stress, as well as an increase in hypertrophy biomarkers [11]. Genetic variants in *TRIM63* were first suggested as a possible cause of HCM following the identification of two missense variants (p.A48V and p.I130M) and a nonsense variant p.(Gln247*), in patients but not in controls [12], while more recently, three papers confirmed the association with autosomal recessive HCM and *TRIM63* variants in a few patients showing progressively marked hypertrophy, extensive fibrosis [8,13,14].

2. Materials and methods

TRIM63 was sequenced using next-generation sequencing (NGS) in a cohort of 517 adult index cases with a clinical diagnosis of HCM, of whom more than 95 % were Caucasian. The phenotype was established by the referring centres before the genetic testing. Written informed consent was obtained from all participants during genetic counselling.

A targeted panel of 29 cardiac genes implicated in HCM was analyzed by NGS (10). Specifically, genomic DNA was automatically extracted from whole-blood samples using QIAsymphony DSP DNA Kits (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Gene libraries were prepared from DNA using a commercial Illumina DNA Prep with Enrichment kit (Illumina Inc., San Diego, CA, USA) and Twist Custom Panel Cardio_V3 probes (Twist). The sequencing step was performed on an Illumina NextSeq 550 platform, targeting 151 bp pair-end reads, and achieving a mean sequencing coverage of above 600×. Variant analysis was performed by BaseSpace Sequence Hub with (DRAGEN Enrichment App -Illumina Inc., San Diego, CA, USA) and the platform eVAI (EnGenome S.R.L. Pavia, Italy). Sanger sequencing was used to confirm clinically relevant detected variants (forward and/or reverse strand). All variants were classified according to the American College of Medical Genetics (ACMG) classification and the Association for Clinical Genomic Science (ACGS) [15,16]. All patients provided written informed consent before participation. The Institutional Review Board approved the study protocol and conforms to the ethical guidelines of the 1975 Declaration of Helsinki (as revised in 2013).

3. Results

3.1. Genetic findings

Out of the 517 patients, a total of 6 (0.9 %) index cases were identified with a genotype consistent with an autosomal recessive mode of inheritance by *TRIM63* variants (Table 1). In the other patients of the

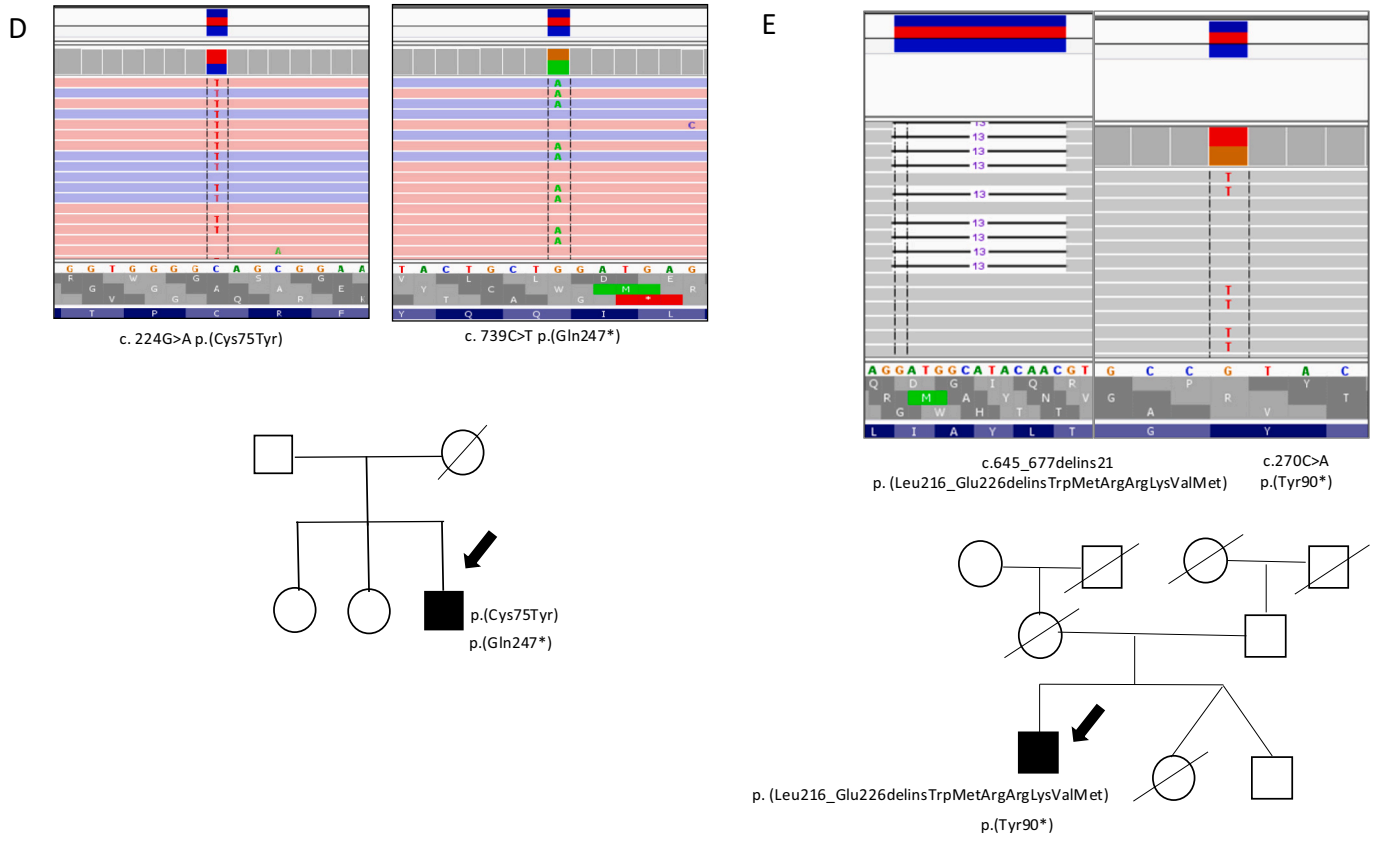

Fig. 2. Sequencing data and pedigrees of patient 3 (D) and patient 4 (E). In patient 3, genetic testing revealed a complex genotype with TRIM63 variants: c.739C>T p.(Gln247*), and c.224G>A p.(Cys75Tyr).
In patient 4, two heterozygous TRIM63 variants were detected: c.270C>A p.(Tyr90*) and c.645_677delins21 p.(Leu216_Glu226delinsTrpMetArgArgLysValMet). The latter represents an in-frame event (deletion of 33 nucleotides with insertion of 21) not previously described and classified as LP. The family history was unremarkable, although the proband's mother died suddenly at 51 years.

cohort, 171/517 (33 %) carried a causative variant in major sarcomeric genes (*MYBPC3, MYH7, MYL3, MYL2, TNNT2, TNNI3, TPM1, ACTC1, TNNC1*), compatible with autosomal dominant transmission. No other monoallelic *TRIM63* heterozygous variants were identified in the remaining index cases. There aren't any patients in our cohort who harbor both sarcomeric P/LP variants and TRIM63 variants. (See Figs. 1–3.)

3.1.1. *TRIM63: c.224G>A p.(Cys75Tyr) variant*

This missense variant was identified in homozygosity in patient 1, a North African woman with reported consanguinity, and in heterozygosity as part of a complex genotype in patient 3 (Table 1). The variant has been previously described in adult patients with recessive HCM and is annotated in ClinVar (variation ID 222847) and HGMD Professional (CM2015313). In gnomAD (v4.1.0) it is reported with an allele frequency of 0.00009 in heterozygotes and no homozygotes. According to ACMG/ACGS guidelines, in homozygosity this variant is classified as likely pathogenic (LP). The activated criteria are PM2 (moderate), PS4 (moderate), PM3 (supporting), and PP3 (supporting).

3.1.2. *TRIM63: c.739C>T p.(Gln247*) variant*

This nonsense variant was detected in homozygosity in two Caucasian males (patients 2 and 5). In patient 5, consanguinity was suspected, as both parents originated from the same geographically isolated village. The same variant was also identified in heterozygosity in patient 3, in association with another *TRIM63* variant (Table 1). The c.739C>T p.(Gln247*) variant has been reported in adult patients with recessive HCM, is annotated in ClinVar (variation ID 222849) and HGMD Professional (CM128455). In gnomAD (v4.1.0), it is present with an allele frequency of 0.0006 in heterozygotes and no homozygotes. In homozygosity, it is classified as LP. The activated criteria are PVS1 (very strong), PM2 (moderate).

3.1.3. *TRIM63: c.270C>A p.(Tyr90*) variant*

This nonsense variant was identified in heterozygosity in patient 4 (Table 1). It has not been previously reported, is not annotated in ClinVar or HGMD Professional, and is absent from gnomAD (v4.1.0). According to ACMG/ACGS guidelines, in homozygosity, this variant is classified as likely pathogenic (LP). The activated criteria are PVS1 (very strong), PM2 (moderate).

3.1.4. *TRIM63: c.645_677delins21 p.(Leu216_Glu226delinsTrpMetArgArgLysValMet) variant*

This deletion-insertion (delins), consisting of a 33-nucleotide deletion and a 21-nucleotide insertion, that replaces eleven amino acid residues with seven other amino acid residues, was identified in heterozygosity in patient 4 (Table 1). It has not been previously reported, is not annotated in ClinVar or HGMD Professional, and is absent from gnomAD (v4.1.0). According to ACMG/ACGS guidelines, in homozygosity, this variant is classified as likely pathogenic (LP). The activated

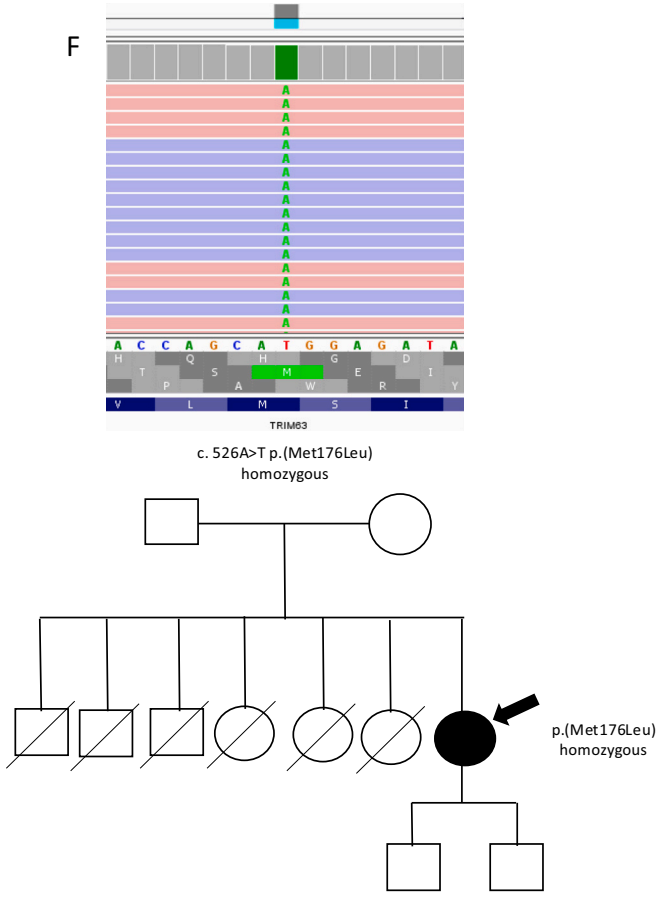

Fig. 3. Sequencing data and pedigree of patient 6. Next-generation sequencing identified a homozygous c.526 A>T p.(Met176Leu) variant in the TRIM63 gene in a Caucasian woman. This variant, previously reported only in heterozygous individuals, has not been described and is not annotated in HGMD Professional or ClinVar databases. In homozygosity, this variant is classified as a Variant of Uncertain Significance (VUS). Family history was negative for cardiomyopathy.

criteria are PM2 (moderate), PM4 (moderate), and PM3 (moderate).

3.1.5. TRIM63: c.526 A>T p.(Met176Leu) variant

This missense variant was identified in homozygosity in patient 6, a Caucasian woman with a negative family history (Table 1). It has not been described in the literature and is not annotated in ClinVar or HGMD Professional. In gnomAD (v4.1.0), it is reported with a heterozygous allele frequency of 0.00002 in heterozygotes and no homozygotes. According to ACMG/ACGS guidelines, in homozygosity, it is classified as a Variant of Uncertain Significance (VUS). The activated criteria are PM2 (moderate) and PM3 (supporting).

3.2. Imaging findings and clinical implications

Patients are typically symptomatic, including exertional dyspnoea, or even show signs of heart failure at the onset of the disease. In our cohort of individuals with TRIM63-related HCM, all patients at echocardiography displayed a concentric pattern of LV hypertrophy, with prominent thickening of the interventricular septum and apical segments, often accompanied by left atrial enlargement as exemplified in Fig. 4A; in one case, wall thickness exceeded 40 mm, representing an extreme phenotype. Left ventricular outflow tract obstruction was documented in only one patient, whereas the others exhibited non-obstructive forms at diagnosis (Table 1).

While echocardiography remains the primary diagnostic modality, complementary findings may emerge from cardiac magnetic resonance (CMR). Of significance, a unifying and striking feature of this unique cardiomyopathy is the presence of severe myocardial fibrosis. In our case series, five out of the six patients underwent CMR imaging, and all showed extensive fibrosis (Late Gadolinium Enhancement-LGE) in the hypertrophied areas. Conversely, none of these patients underwent an endomyocardial biopsy due to unwarranted clinical indications. LGE involves several myocardial regions, predominantly the interventricular septum and apex, with varied distributions ranging from subendocardial to transmural (Fig. 5). This diffuse fibrotic remodeling reflects the core pathological substrate of the disease and progressively alters ventricular structure and function [17]. Mechanistically, TRIM63 encodes MuRF1, an ubiquitin-protein ligase involved in sarcomeric protein turnover through the ubiquitin–proteasome system, and the loss of MuRF1 function may impair degradation of key sarcomeric proteins, leading to their accumulation, activation of hypertrophy-related signaling pathways, and progressive myocardial fibrosis [9]. These processes likely contribute to the adverse remodeling, systolic dysfunction, and apical aneurysm formation.

In our series, two patients (cases 3 and 4) showed progression toward a hypokinetic-dilated end-stage phase, and one of them was ultimately listed for heart transplantation. Two patients (cases 3 and 5) developed a distinct apical aneurysm, while all individuals demonstrated at least moderate diastolic dysfunction. The progression to an end-stage, hypokinetic-dilated phase is characterized by LV dilation, global hypokinesia, and biventricular involvement, alongside atrial as exemplified in Fig. 4B.

Early identification of *TRIM63* mutations enables proactive surveillance using echocardiography and CMR for early detection of hypertrophy progression or fibrotic remodeling. Patients with biallelic mutations may exhibit more severe disease trajectories—including early onset, advanced diastolic dysfunction, and extensive fibrosis—warranting consideration of device therapy, such as implantable cardioverter-defibrillators (ICDs), as indicated in reported cases [13].

Patients who display more severe or rapidly progressive disease phenotypes may require other therapeutic interventions, such as optimal heart failure management and timely consideration for advanced therapies, such as mechanical circulatory support or heart transplantation, particularly in cases evolving toward end-stage heart failure. Of note, one patient in our cohort with a homozygous *TRIM63* variant classified as VUS presented a milder and atypical phenotype. This highlights that genetic findings should always be interpreted alongside clinical features, family history, and disease trajectory, as genotype–phenotype correlations may vary substantially.

Given the recessive inheritance pattern, genetic counselling must be tailored to include reproductive risk assessment for at-risk family members. Some of our patients were suspected of having consanguinity, which should always be taken into account [18]. Further studies are needed to understand the natural history of *TRIM63*-related disease, the risk of developing arrhythmias, and potential strategies for preventing further disease progression.

4. Limitations

Many clinical and genetic features suggest autosomal recessive inheritance in our cohort but confirming this requires genetic testing and clinical assessments of the parents. This was not feasible due to reasons like parents living abroad (e.g., patient 1 in Morocco), being deceased, or refusing participation due to age or personal circumstances.

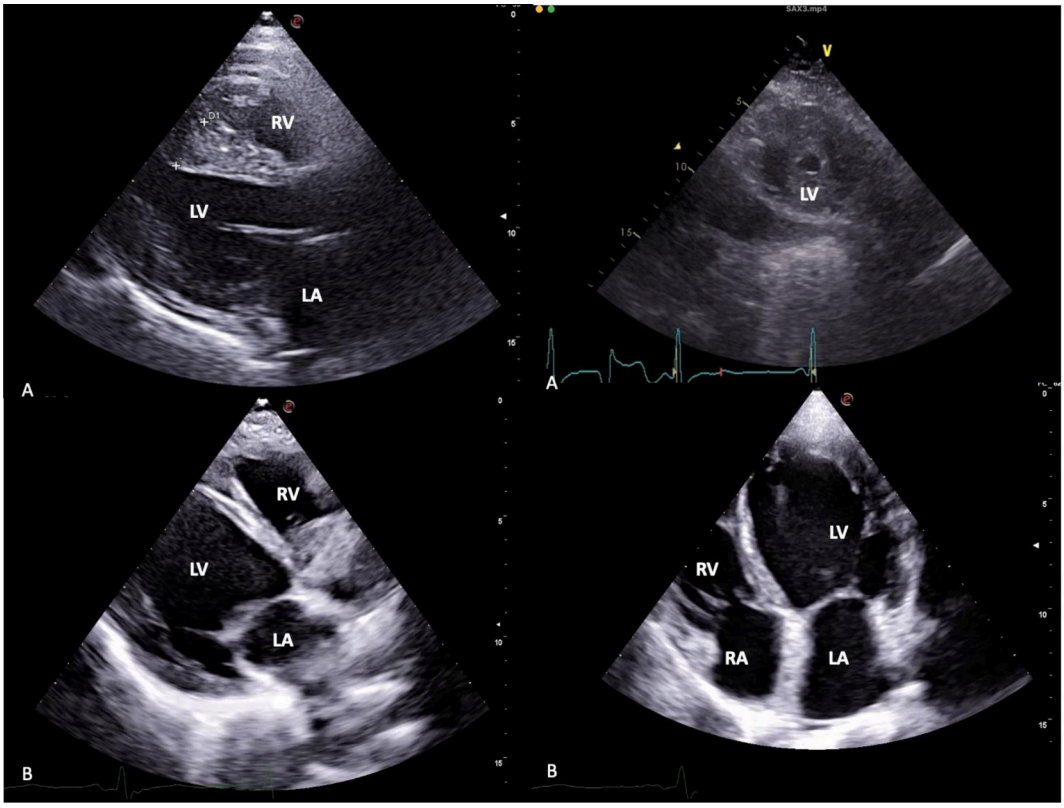

Fig. 4. Echocardiographic features in two patients with *TRIM63*-related HCM at different disease stages. Top panel: Echocardiographic images from a recently diagnosed patient with *TRIM63*-related HCM. Parasternal long-axis (left) and short-axis (right) views show concentric left ventricular hypertrophy, with marked thickening of the interventricular septum and apical segments. Left atrial enlargement is also noted. Bottom panel: Echocardiographic images from a patient with TRIM63-related HCM in the end-stage phase. There is left ventricular dilatation and global hypokinesia with biventricular involvement, consistent with a hypokinetic-dilated evolution. Four-chamber and parasternal views demonstrate dilatation of the left and right atria. Abbreviations: LV: left ventricle; RV: right ventricle; LA: left atrium; RA: right atrium; HCM: hypertrophic cardiomyopathy.

Nonetheless, the absence of a documented family history or affected individuals in at least three generations aligns with an autosomal recessive pattern.

In addition in our study was not possible to investigate the phenotype of individuals with monoallelic heterozygous P/LP *TRIM63* variants except for the consanguineous partner of the patient 1: he carries the c.224G>A p.(Cys75Tyr) variant in the heterozygous state and he did not show any signs of HCM.

Finally, the very small size of our cohort inherently limits the generalisability of the observed imaging–clinical correlations and the proposed trajectory of disease progression. While the consistency of findings across individual cases suggests a reproducible pattern, these data should be interpreted with caution, as they likely represent the more advanced end of the phenotypic continuum. Larger, multicentre studies will be necessary to confirm features of TRIM63-related cardiomyopathy.

5. Conclusion

TRIM63 variants appear to be an uncommon cause of HCM, inherited in an autosomal-recessive manner (~1 %) and associated with severe hypertrophy, early onset HCM, and a high rate of Left ventricular (LV) dysfunction. Despite the small number of cases reported to date, several distinctive features of the disease could distinguish this form from the "classical" sarcomeric phenotype. In addition, the identification of a rare autosomal recessive form of HCM has important implications for the genetic counselling process and clinical management.

CRediT authorship contribution statement

Francesca Bonanni: Writing – original draft, Conceptualization. **Adelaide Ballerini:** Data curation. **Alessia Gozzini:** Methodology. **Alberto Marchi:** Resources, Investigation. **Eszter Dalma Palinkas:** Resources. **Valentina Barletta:** Validation. **Laura Dosa:** Visualization, Investigation. **Massimiliano Cecconi:** Visualization, Methodology. **Natascia Cerrato:** Data curation. **Mattia Zampieri:** Visualization. **Silvia Passantino:** Visualization. **Iacopo Olivotto:** Writing – review & editing, Validation. **Francesca Girolami:** Writing – review & editing, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

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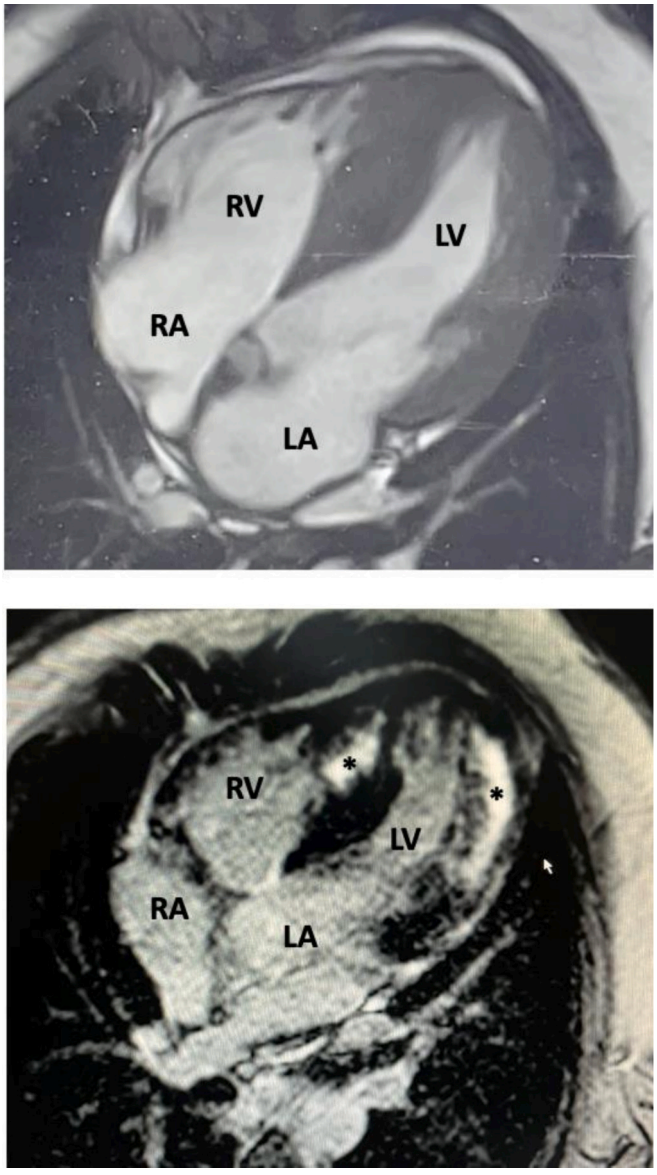

Fig. 5. Representative cardiac magnetic resonance images in a patient with *TRIM63*-related HCM Top panel: SSFP cine image, demonstrating marked concentric left ventricular hypertrophy with preserved global systolic function. Enlargement of both atria, particularly the left atrium, is also noted. Bottom panel: Four-chamber LGE image from a different patient in an advanced disease stage, showing extensive, confluent areas of transmural fibrosis involving the interventricular septum and anterior wall (indicated by asterisks). These images exemplify the progressive myocardial remodeling typical of *TRIM63*-related cardiomyopathy, from early hypertrophy to massive fibrotic evolution. Abbreviations: HCM: Hypertrophic Cardiomyopathy; LV: left ventricle; RV: right ventricle; LA: left atrium; RA: right atrium; LGE: late gadolinium enhancement; CMR; cardiac magnetic resonance; SSFP: steady-state free precession.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.134010.

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