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Marked intrafamilial phenotypic variability of MYH7 p.Arg719Gln in a four-generation family with a history of multiple premature sudden deaths

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) due to sarcomeric variants shows age-dependent penetrance and wide intrafamilial variability. The *MYH7* p.Arg719Gln variant has been labelled "malignant," a label current guidelines no longer support because genotype is excluded from validated sudden cardiac death risk models.

Case Presentation: A four-generation Moroccan family was referred after five premature sudden deaths in young relatives. The pathogenic *MYH7* c.2156G>A (p.Arg719Gln) variant, first identified in the proband, was found in seven relatives (five female). Only three carriers - the proband and her two sisters, all women - met diagnostic criteria for HCM (non-obstructive hypertrophy, maximal septal thickness 15.5-17 mm). The remaining four carriers, aged 7-19 years, did not: two had sub-diagnostic septal z-scores (≈1.5 and ≈1.0) and two, including a 19-year-old woman, had no hypertrophy, yet the youngest showed markedly increased electrocardiography voltage out of proportion to wall thickness. Non-carriers were released from surveillance.

Conclusion: This family shows both the yield and the limits of cascade testing. Because none of the deceased was genotyped, the variant cannot be assumed to have caused the deaths; management, including defibrillator decisions, must rest on validated, age-specific risk assessment rather than on genotype.

Keywords: Cardiomyopathy, hypertrophic, MYH7 protein, human, death, sudden, cardiac, genetic testing, pedigree; ohenotype.

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Background

Hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous myocardial disease defined by increased left ventricular (LV) wall thickness not explained solely by loading conditions. Pathogenic variants in sarcomere genes, chiefly *MYH7* and *MYBPC3*, are transmitted in an autosomal dominant manner, with age-dependent, highly variable expression [1-3]. The *MYH7* p.Arg719Gln missense variant, first described in 1994 [4], affects a conserved arginine in the myosin head and has been reported in more than 30 unrelated affected individuals [5,6]. It was judged benign in the family in which it was first identified [4] but malignant in later kindreds ascertained through heavy premature mortality [5,7] - a contradiction that is itself instructive. Current guidance regard the prognostic usefulness of genotype in HCM as uncertain rather than absent [2,8], and neither European nor North American guidelines incorporate genotype into validated sudden cardiac death (SCD) risk calculators [1,2,8]; the p.Arg719Gln genotype alone should not be used to determine individual SCD risk or the need for an implantable cardioverter-defibrillator (ICD). We describe systematic screening of a severely affected family and use it to delineate what cascade testing did, and did not, resolve.

Case Presentation

The proband, a 38-year-old woman with HCM, was referred because of premature sudden death in the family. She reported five sudden deaths among young relatives: three sisters (at 12, 18 and 24 years), a maternal aunt (36 years), and the aunt's son (18 years) (Table 1; Figure 1). Two deaths had been examined at autopsy, which confirmed HCM; none of the deceased was genotyped and no molecular autopsy was performed, so the deaths cannot be attributed to the variant with certainty. Her blood relatives were screened with clinical examination, 12-lead electrocardiography (ECG) with the Sokolow–Lyon index, echocardiography and targeted genetic testing, performed in the first half of 2025 as part of routine cardiology follow-up. In adults, HCM required a maximal wall thickness ≥15 mm (with lower thresholds in the familial context); in children, a wall-thickness *z*-score ≥2 relative to body surface area (BSC) [1,2].

Ages and relationships are from the proband's family history and are consistent with the pedigree (Figure 1).

[a] Autopsy was performed in two of the five (both confirmed HCM); the source does not specify which individuals (ND, not documented per individual). None was genotyped.

Genetic testing

The *MYH7* variant NM_000257.4:c.2156G>A (p.Arg719Gln; exon 19; locus 14q11.2-q12) was first identified in the proband and then in six relatives - seven carriers among 20 individuals genotyped (18 blood relatives and two spouses); the variant was excluded in the remainder. It is absent from gnomAD and classified as pathogenic by the ClinGen Cardiomyopathy Variant Curation Expert Panel (ClinVar Variation ID 14107) [6,9]. The original molecular report could not be retrieved, so the initial analytical method is not described.

Table 1. *Premature sudden deaths reported in the family.*

RELATIONSHIP TO PROBAND	SEX	AGE AT DEATH, Y	PRIOR HCM DIAGNOSIS	AUTOPSY
Sibling (sister)	F	12	None documented	ND[a]
Sibling (sister)	F	18	None documented	ND[a]
Sibling (sister)	F	24	None documented	ND[a]
Maternal aunt	F	36	None documented	ND[a]
Maternal cousin (aunt's son)	M	18	None documented	ND[a]

Phenotype of the carriers

Of the seven carriers, three - the proband and her two sisters (36 and 43 years), all women - met diagnostic criteria for HCM. All three had non-obstructive LV hypertrophy (maximal septal thickness 15.5-17 mm), preserved ejection fraction, and no systolic anterior motion (SAM) or resting outflow-tract obstruction; all were symptomatic, one in atrial fibrillation with right heart failure, and all had left atrial dilatation (Table 2). The remaining four carriers were genotype-positive without diagnostic hypertrophy (G+/P−): a 12-year-old girl (BSC 1.30 m²) had a subclinical septal *z*-score of ≈1.5, and a 13-year-old boy (1.44 m²) one of ≈1.0 - both below the pediatric threshold of $z \geq 2$ [10] - while a 19-year-old woman and a 7-year-old boy had no hypertrophy. The two youngest carriers additionally had very high ECG voltage (Sokolow–Lyon index 72 and 80 mm) out of proportion to their echocardiographic

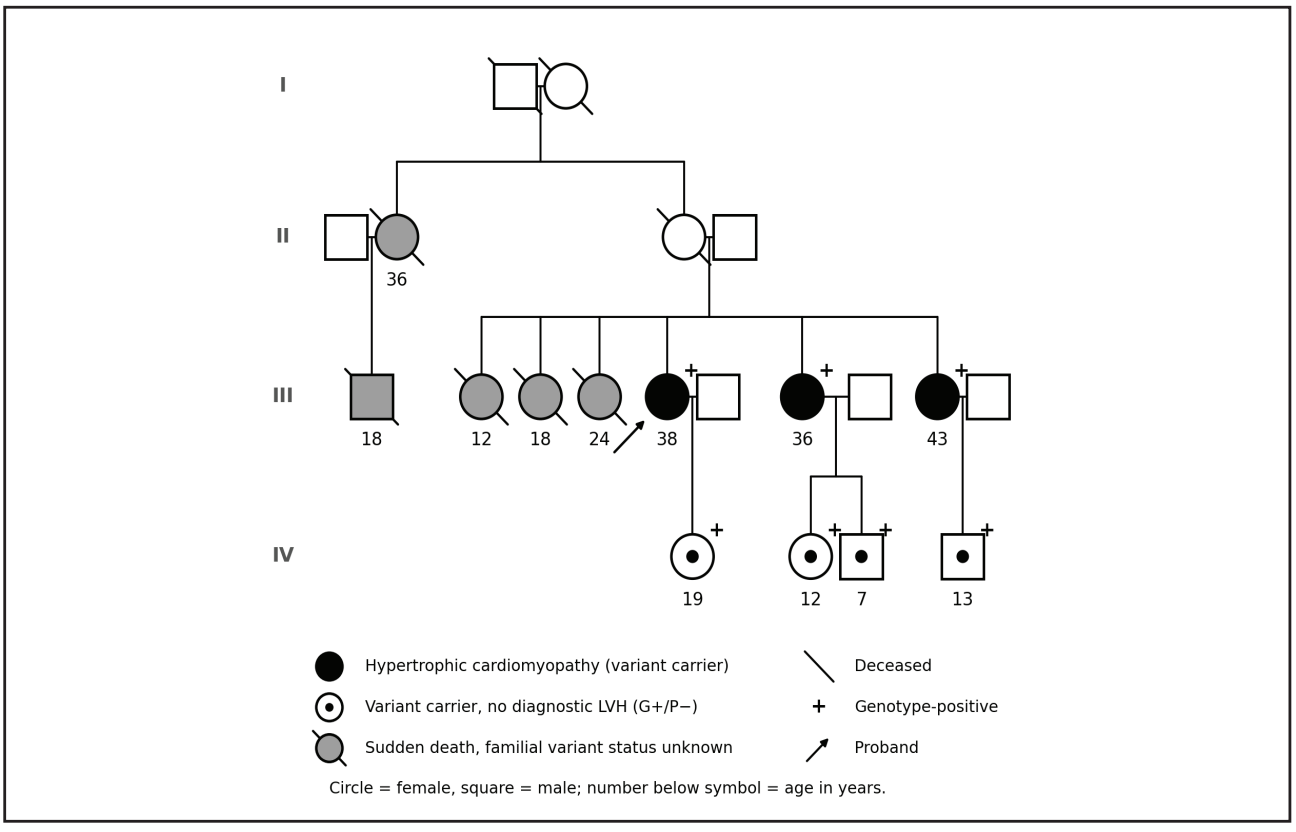


Figure 1. *De-identified four-generation pedigree. Circles denote women and squares men. Black symbols indicate variant carriers meeting diagnostic criteria for HCM; a central dot indicates a genotype-positive carrier without diagnostic LV hypertrophy. Gray symbols indicate relatives who died suddenly and were not genotyped (familial variant status unknown). A diagonal line denotes a deceased individual, a plus sign a genotype-positive carrier, and the arrow the proband. Numbers below symbols are ages in years (age at death for the deceased). The familial variant is MYH7 p.Arg719Gln.*

Table 2. *Per-patient characteristics of the seven carriers of* ***MYH7*** *p.Arg719Gln.*

CHARACTERISTIC	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7
Relationship	Proband	Sister	Sister	Daughter	Niece	Nephew	Nephew
Age, years	38	36	43	19	12	7	13
Sex	F	F	F	F	F	M	M
NYHA dyspnea	II-III	II	II	II	II	—	—
Palpitations	+	+	+	+	+	—	—
Systolic murmur	2/6	3/6	—	—	—	—	—
ECG Sokolow index, mm	—[a]	40	36	42	80	72	45
Other ECG	iLBBB, LAE	AF	Deep Q	—	—	—	Deep Q
IVS, mm	15.5	17	15.5	9.9	10.8	7.4	10.3
Posterior wall, mm	13	15	10.4	8.4	8.4	5.6	7.7
BSA, m²/septal z [b]	—	—	—	—	1.30/≈1.5	—	1.44/≈1.0
LVEF, %	60	60	58	77	77	64	61
SAM/LVOT obstruction	—	—	—	—	—	—	—
Left atrial area, cm²	45	62	41	ND	ND	ND	ND
Left atrial diameter, mm [d]	57	68	52	ND	ND	ND	ND
Mitral regurgitation	Trivial	Moderate	Mild	—	—	—	—
24-h Holter	NSSVT[c]	—	—	Normal	—	Normal	Normal
Treatment	BB + Am	BB + Am + D + A	BB + Am	BB	BB	BB	BB
Phenotype	HCM	HCM	HCM	G+/P–	G+/P– [b]	G+/P–	G+/P–[b]

Cases 1-3 are the affected adults; Cases 5 and 7 are carriers with septal *z*-scores below the pediatric diagnostic threshold; Cases 4 and 6 have no hypertrophy - together; Cases 4–7 are genotype-positive without diagnostic HCM (G+/P–).AF, atrial fibrillation; Am, amiodarone; A, oral anticoagulant; BB, beta-blocker; D, diuretic; G+/P–, genotype-positive/phenotype-negative; iLBBB, incomplete left bundle branch block; IVS, interventricular septum; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; ND, not documented; NSSVT, non-sustained supraventricular tachycardia.

[a]Not recorded numerically (incomplete left bundle branch block and left atrial enlargement).

[a]BSC (Mosteller) and septal *z*-score by the Detroit pediatric nomogram [10]; $z \geq 2$ corresponds to ≈12.1 and ≈12.7 mm, respectively.

[a]Non-sustained supraventricular tachycardia with frequent supraventricular ectopy and >200 ventricular ectopic beats/24 hours.

[a]Parasternal long-axis left atrial diameter, used with maximal wall thickness, LVOT gradient, family history, and rhythm/syncope status to calculate the HCM Risk-SCD estimates reported in the text.

findings - a subclinical electrical abnormality that is distinct from, and should not be equated with, diagnostic HCM. Relatives without the variant were discharged from surveillance [1,2,11].

None of the three affected adults had extreme hypertrophy (≥30 mm) or resting LV outflow-tract obstruction; unexplained syncope was not documented in the retrospective record, and the only ventricular-tachycardia surveillance finding was non-sustained supraventricular (not ventricular) tachycardia in one patient, which does not itself count as a risk factor in validated SCD-risk models. All three had a strong family history of premature sudden death. Applying the HCM Risk-SCD model [12] retrospectively - using left atrial diameter (57, 68, and 52 mm for Cases 1-3, respectively, Table 2), maximal wall thickness, a resting LV outflow tract (LVOT) gradient of 0 mmHg, positive family history, and the absence of documented non-sustained ventricular tachycardia or syncope - the calculated 5-year SCD risk was 3.8% (Case 1), 5.7% (Case 2) and 3.1% (Case 3): low to intermediate by the model's own thresholds (<4%, ICD generally not indicated; 4-<6%, ICD may be considered; ≥6%, ICD should be considered). This is a retrospective application of a model that postdates the historical treatment decisions in this family and could not have informed them; no adult in fact received a primary-prevention defibrillator, and the specific clinical reasoning documented at the time could not be retrieved. A beta-blocker was combined with amiodarone in the three adults, reflecting a historical regimen that preceded contemporary risk-stratified management, although atrial fibrillation - the usual indication for amiodarone - was documented in only one of them (Case 2, who also received a diuretic and an oral anticoagulant, Table 2); the specific indication in the other two could not be reconstructed from the archival records. The children received a beta-blocker alone, and no cardioverter-defibrillator had been implanted in any family member.

Discussion

Screening identified seven carriers - three with definite HCM and four carriers without diagnostic hypertrophy - and released the non-carriers. Both results have practical value: once a causal variant is known, genotype-negative relatives can leave lifelong surveillance, concentrating resources on those who remain at risk [11]. What cascade testing did not do was predict the disease course. Within a single sibship a 12-year-old girl had borderline hypertrophy while her 7-year-old brother had a structurally normal heart, and a 19-year-old carrier remained phenotype-negative - variability characteristic of sarcomeric HCM [3].

This bears on the "malignant mutation" question. Pathogenicity and individual prognostic value must be kept apart: for p.Arg719Gln the first is settled by expert-panel curation [4,6,9]; the second is not. The same variant was judged benign by its first describers [4] and malignant in a later kindred [5], both ascertained through catastrophic mortality. Our family invites the same caution against itself: none of the deceased was genotyped, and a kindred referred for exceptional mortality is, by construction, a biased sample. The deaths are real; their attribution to the variant remains an inference [2,8].

Two features deserve note. First, a female preponderance - all three affected adults, five of the seven carriers, and four of the five deceased were female - contrary to the male predominance usually reported for SCD in HCM; with these numbers this is an observation, not a finding. Second, the dissociation between electrical and morphological expression in the youngest carriers is hypothesis-generating rather than proof that electrical change precedes hypertrophy.

Because genotype alone does not reliably stratify individual risk, primary-prevention defibrillator decisions must use validated, age-appropriate tools - the HCM Risk-SCD model in adults and pediatric tools (HCM Risk-Kids, and PRIMaCY) with *z*-score-indexed measures in children [1,2,12-14] - supported by cardiac magnetic resonance, which was unavailable here. The historical beta-blocker–amiodarone regimen predates current practice and should not be read as a recommendation. This retrospective report is limited by small numbers, archival data of variable completeness - including an assumption of absent syncope where it was not explicitly documented, and a retrospective HCM risk-SCD calculation performed outside the timeframe of the original treatment decisions - absence of molecular autopsy, and lack of cardiac magnetic resonance; the deaths were documented from family history rather than certificates, though consistent with the pedigree.

Conclusion

Cascade screening identified *MYH7* p.Arg719Gln across four generations and disclosed the full span of sarcomeric expression, from an isolated electrical signature in young carriers to overt adult disease, consistent with incomplete, age-dependent penetrance. A pathogenic variant establishes who needs watching, but not who will die, nor by itself who should receive a defibrillator, and it cannot assign a cause to deaths in relatives who were never tested. Validated, age-specific risk assessment must guide management.

List of Abbreviations

BSA	Body surface area
ECG	Electrocardiogram
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter-defibrillator
LV	Left ventricular
LVOT	Left ventricular outflow tract
NYHA	New York Heart Association
SAM	Systolic anterior motion
SCD	Sudden cardiac death.

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Conflict of interest

The authors declare no conflict of interest.

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None.

Consent for publication

Written informed consent was obtained from all participating relatives, and from the parents or legal guardians of the participating minors, for their clinical and genetic information and the de-identified pedigree to be reported. Names and initials are not published.

Ethical approval

This retrospective study was conducted in accordance with the Declaration of Helsinki. In 2026, the institutional research ethics committee of the participating hospital raised no objection to the study or to publication of the de-identified data (non-objection statement on file, dated 2026, available to the editor on request).

Author contributions

M.G. and J.N. conceived the report and drafted the manuscript. H.H. collected and analyzed the clinical and genetic data. H.B. and A.B. provided senior supervision and critically revised the manuscript for important intellectual content. All authors approved the final version and agree to be accountable for the work.

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