PROGRAMME

hypertrophiccardiomyopathyACoruna.com

V International Workshop on Cardiomyopathies

HYPERTROPHIC CARDIOMYOPATHY 2025

18th-19th SEPTEMBER

A Coruña (Spain)

Venue: Palexco

SERVIZO GALEGO DE SAÚDE
ÁREA SANITARIA DA CORUÑA E CEE
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UNIVERSIDADE DA CORU

ORGANIZED BY

SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA

Sección de Cardiopatías Familiares y Genética Cardiovascular

Spanish Group in Inherited Heart Diseases
and Cardiovascular Genetics of the Spanish Society of Cardiology

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Centro de Investigación Biomédica en Red (CIBERCV).
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SPAIN

James Ware
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Arash Yavari
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THURSDAY, SEPTEMBER 18TH

15:30 - 15:45	**Presentation** Antonio Gómez Caamaño. *Regional Minister of Health, Government of Galicia* Luis Verde Remeseiro. *Director of the Health Area of A Coruña and Cee* Eduardo Villacorta *President of the Spanish Group in Inherited Heart Diseases and Cardiovascular Genetics of the Spanish Society of Cardiology* Jose Manuel Vázquez *Head of Cardiology, C.H.U. de A Coruña*
15:45 - 15:50	**Welcome to Hypertrophic Cardiomyopathy in A Coruña** William J. Mckenna and Roberto Barriales-Villa
15:50 - 16:45	**GENETIC BASIS OF HCM ON 2025** Moderators: Philippe Charron and James Ware
15:50 - 15:55	**Clinical case:** María Valverde
15:55 - 16:05	**Is PRS in HCM ready for the primetime?** Connie Bezzina
16:05 - 16:15	**Between a rock and a hard place: intermediate effect variants and semi-dominance in HCM** Juan P. Ochoa
16:15 - 16:25	**Familial HCM with negative NGS: what is the next step?** Jodie Ingles
16:25 - 16:50	**Panel Discussion:** Speakers and Luis Lopes
16:50 - 17:30	**GENE THERAPY IN HCM** *JOINT SESSION WITH INDUSTRY* Moderators: Jodie Ingles and William Mckenna
16:50 - 17:00	**Tenaya Therapeutics (MyPeak-1 Phase 1b clinical trial)** Natalia Paterson-Sonicheva
17:00 - 17:10	**Lexeo Therapeutics (Gene Therapy for Cardiomyopathy Associated with Friedreich's Ataxia)** Gregory Aubert
17:10 - 17:30	**Panel Discussion:** Speakers, Juan P. Kaski and Perry Elliott
17:30 - 18:10	**Coffee break**

THURSDAY, SEPTEMBER 18TH

18:10 - 19:05	**CARDIAC MYOSIN INHIBITORS: AN EVOLVING STORY** Moderators: Albert Hagege and Nuno Cardim
18:10 - 18:15	**Clinical case:** Fernando Dominguez
18:15 - 18:25	**CMI in obstructive HCM** Iacopo Olivotto
18:25 - 18:35	**CMI in non-obstructive HCM** Anjali Owens
18:35 - 18:45	**Factors that influences the response to CMI** Ahmad Masri
18:45 - 19:05	**Panel Discussion:** Speakers and Michelle Michels
19:05 - 19:50	**INVASIVE SEPTAL REDUCTION THERAPIES IN 2025?** Moderators: Maite Tomé and Luis Ruiz-Guerrero
19:05 - 19:10	**Clinical case:** Ana García
19:10 - 19:20	**New surgical myectomy techniques: when to do?** Eduard Quintana
19:20 - 19:30	**Percutaneous interventions for the treatment of obstruction in HCM: established and novel therapies** Hubert Seggewiss
19:30 - 19:50	**Panel Discussion:** Speakers, Juan Ramón Gimeno and JM García Pinilla
19:50	End of the day

FRIDAY, SEPTEMBER 19TH

9:00 - 9:55	**NEW ORAL TREATMENTS IN HCM** *(JOINT SESSION WITH INDUSTRY)* Moderators: Juan R. Gimeno and Maite Tomé
9:05 - 9:15	**Edgewise Therapeutics (EDG-7500 in HCM, CIRRUS-HCM trial)** Robert Blaustein
9:15 - 9:25	**Imbria Pharmaceuticals (Ninerafaxtat in non obstructive HCM; FORTITUDE-HCM)** Arash Yavari
9:25 - 9:35	**Lexicon Pharmaceuticals (Sotaglifozin in HCM, SONATA-HCM trial)** Carolyn Ho
9:35 - 9:55	**Panel Discussion:** Speakers and Martin Maron
9:55 - 10:50	**CONTROVERSIES IN HYPERTROPHIC CARDIOMYOPATHY RISK STRATIFICATION** Moderators: José Rodríguez-Palomares and Anjali Owens
9:55 - 10:00	**Clinical case:** María Ángeles Espinosa-Castro
10:00 - 10:15	**AHA/ACC criteria are more precise** Martin Maron
10:15 - 10:30	**ESC criteria are enough** Perry Elliott
10:30 - 10:50	**Panel Discussion:** Speakers, Lorenzo Monserrat and Iacopo Olivotto
10:50 - 11:30	**Coffee break** *(POSTER EXHIBITION)*
11:30 - 12:15	**EXERCISE IN HYPERTROPHIC CARDIOMYOPATHY** Moderators: María L. Peña-Peña and Juan P. Kaski
11:30 - 11:35	**Clinical case:** Cayetana Barbeito-Caamaño
11:35 - 11:45	**Exercise in HCM patients: when to say no** María Sanz
11:45 - 11:55	**Potencial value of CPET in HCM** Caroline Coats
11:55 - 12:15	**Panel Discussion:** Speakers, Juan R. Gimeno and Eduardo Villacorta

FRIDAY, SEPTEMBER 19TH

12:15 - 13:00	**ATRIAL FIBRILLATION IN HYPERTROPHIC CARDIOMYOPATHY** Moderators: Enrique Berrios and José María Larrañaga-Moreira
12:20 - 12:25	**Clinical case:** Jorge Garrido
12:25 - 12:35	**Challenges in the medical management of atrial fibrillation** Elena Arbelo
12:35 - 12:45	**Challenges in the interventional management of atrial fibrillation** Juan Jiménez-Jaimez
12:45 - 13:00	**Panel Discussion:** Speakers, Michelle Michels and Albert Hagege
13:00 - 13:20	**KEYNOTE LECTURE** Moderator: Roberto Barriales-Villa **Frontiers in HCM research: what´s the future should be?** Perry Elliott
13:20 - 14:30	**Cocktail Lunch** *(POSTER EXHIBITION)*
14:35 - 15:30	**ATTR AMYLOIDOSIS: TREATMENT UPDATE** Moderators: Marisa Crespo and Tomás Ripoll
14:35 - 14:40	**Clinical case:** Gonzalo Barge
14:40 - 14:50	**TTR synthesis suppression** Ahmad Masri
14:50 - 15:00	**TTR stabilization** Esther González-López
15:00 - 15:10	**TTR amyloid degradation** Pablo García-Pavía
15:10 - 15:30	**Panel Discussion:** Speakers and José González-Costello
15:35 - 16:30	**CONTROVERSIES IN FABRY DISEASE** Moderators: Olga Azevedo and Javier Limeres
15:35 - 15:40	**Clinical case:** María Luisa Peña-Peña
15:40 - 15:50	**Substrate reduction and gene therapy in Fabry disease** Juan Ramón Gimeno
15:50 - 16:00	**Does immunogenicity play a role in the patient's treatment?** Juan Politei
16:00 - 16:10	**When to start treatment in woman?** Alberto Ortiz
16:10 - 16:30	**Panel Discussion:** Speakers and Tomás Ripoll

FRIDAY, SEPTEMBER 19TH

16:30 - 17:00	**AWARD CEREMONY FOR THE BEST POSTER** MODERATORS: Congress Organizing Committee and the Program Committee Presentation of the best posters
17:00	**Closing**

01. THIN-FILAMENT HYPERTROPHIC CARDIOMYOPATHY IS ASSOCIATED WITH HEART FAILURE OUTCOMES

Chumakova, Olga (1); Baklanova, Tatiana (1); Zateyshchikov, Dmitry (1)

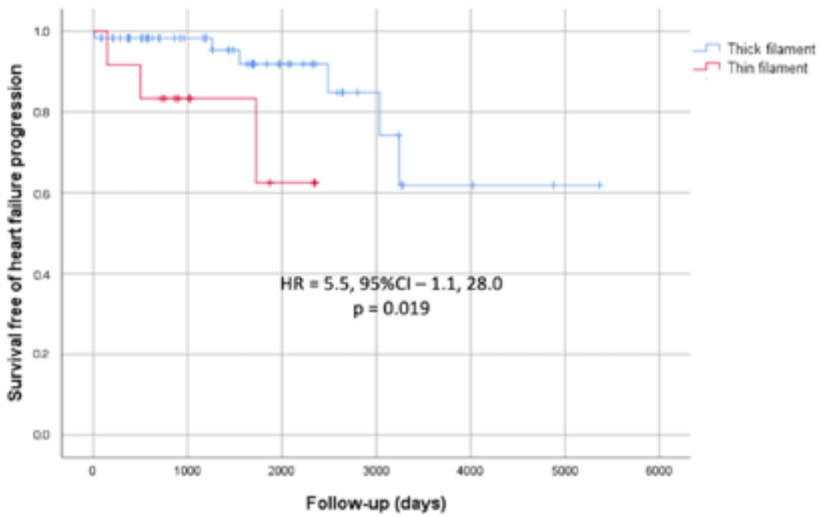
(1)City Clinical Hospital #17

Background/Objectives: Pathogenic/likely pathogenic (P/LP) variants in thin-filament genes are uncommon in hypertrophic cardiomyopathy (HCM) cohorts, and prospective follow-up data on thin-filament HCM remain limited (1-3). Notably, recent studies suggest distinct pathogenic mechanisms in HCM associated with thin-filament variants (4). This study aimed to provide a comparative analysis of prospective outcomes in patients with thin-filament versus thick filament HCM.

Methods: Sarcomere-positive HCM patients were enrolled from an ongoing single-center prospective study. Follow-up data, including HCM-related events and all-cause mortality, were collected. Comparative analyses were performed between patient groups carrying P/LP variants in thin-filament versus thick-filament genes.

Results: Of 230 genotyped HCM patients, 82 (age 46 ± 14 years; 52% male) carried single sarcomeric P/LP variants (36%), including 15 in thin-filament genes (6.5%). The thin-filament group did not differ from the thick-filament group in baseline characteristics, except for lower left ventricular wall thickness (median 17 versus 21 mm, p = 0.024). During a mean follow-up of 4.7 ± 2.3 years, adverse event rates were low and similar between groups. However, patients with thin-filament HCM showed significantly faster progression to advanced heart failure (Figure), with Kaplan-Meier estimated survival of 5.2 ± 0.64 versus 11.8 ± 1.04 years (p = 0.018). Notably, no malignant arrhythmic events were observed in the thin-filament group.

Conclusions: Thin-filament HCM is associated with faster progression to advanced heart failure in adults than thick-filament HCM. This emphasizes the importance of closely monitoring these patients for heart failure. Data on a higher risk of malignant arrhythmias in thin-filament HCM remain inconsistent across studies and rather depend on the specific genotype.



02. HYPERTROPHIC CARDIOMYOPATHY PHENOTYPE IN CARRIERS OF A FOUNDER PKP2 VARIANT: REALITY OR FICTION?

Huetos Pérez, Silvia (1)

(1)CiberCV

Recent findings challenge the established genotype–phenotype associations in hereditary cardiomyopathies. We report nine cases of individuals carrying the PKP2 frameshift variant p.Ser329Argfs*23, all diagnosed with hypertrophic cardiomyopathy (HCM) and with no other identifiable genetic cause. PKP2, typically linked to arrhythmogenic right ventricular cardiomyopathy (ARVC), is not commonly associated with HCM, a condition usually involving sarcomeric gene mutations.

The variant, identified primarily in unrelated families from the Galician region of Spain, suggests a potential founder effect. Clinical presentations varied, including apical, non-obstructive, asymmetric septal, and obstructive HCM forms. This study aims to assess the pathogenicity and penetrance of the variant and explore its potential role in expanding the phenotypic spectrum of PKP2. If confirmed, these findings may have implications for genetic screening and diagnostic criteria in specific populations.

03. COEXISTENCE OF HYPERTROPHIC CARDIOMYOPATHY AND SUBAORTIC MEMBRANE: A DIAGNOSTIC CHALLENGE

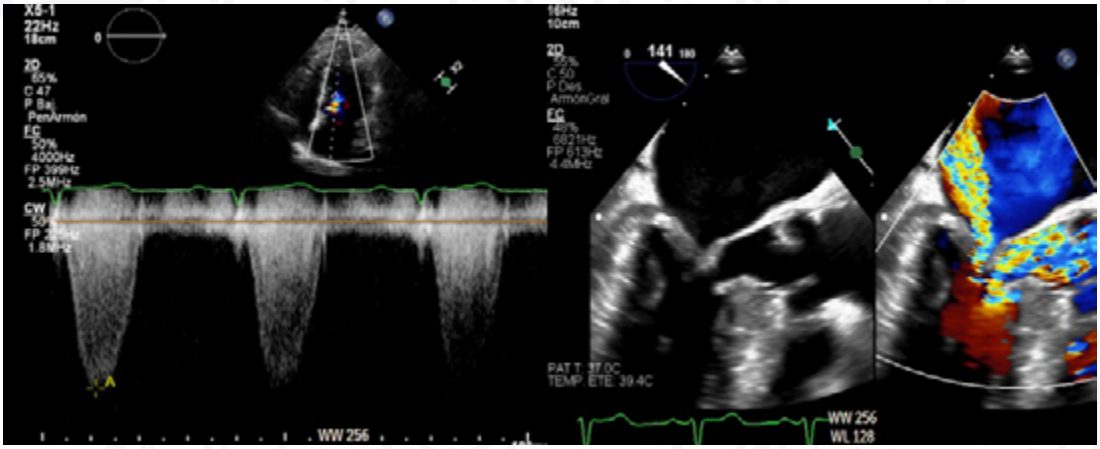
Altadill Balsells, Francesc (1); Triguero Llonch, Laura (1); De Antonio Ferrer, Marta (1); Fernández Martínez, Juan (1); Rodríguez Pérez, álvaro (1); Campreciós Crespo, Marta (1)

(1)Hospital de la Santa Creu i Sant Pau

The coexistence of hypertrophic cardiomyopathy (HCM) and subaortic membrane (SAMb) presents a diagnostic challenge and an increased risk of heart failure. Proper management is essential to better characterize the mixed left ventricular outflow tract (LVOT) obstruction before considering surgery.

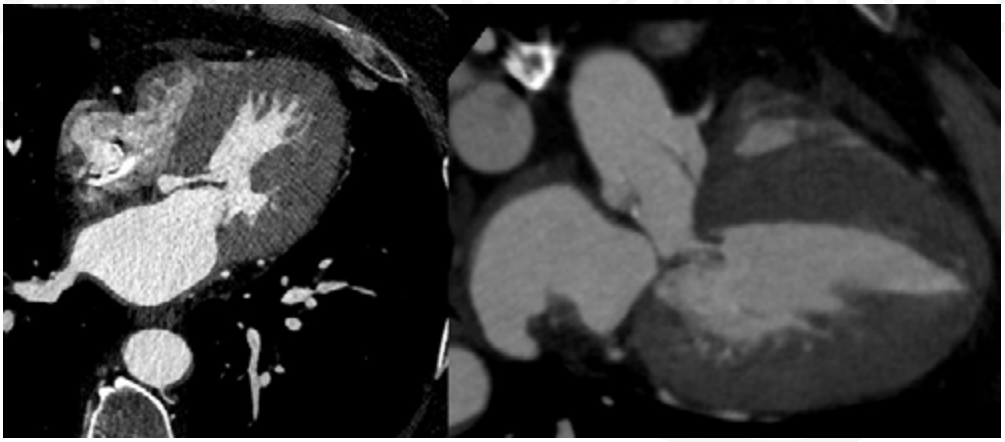
We report the case of a 67-year-old man evaluated for hypertension. Echocardiography showed a non-dilated left ventricle with preserved ejection fraction and septal hypertrophy of 16 mm. A significant LVOT gradient of 130 mmHg was detected, with a parabolic morphology suggesting mixed obstruction: fixed subvalvular and dynamic from hypertrophy **(Image 1)**.

Transesophageal echocardiography confirmed a laminar structure at the basal septum; consistent with an incomplete SAMb protruding into the ventricle. High-velocity turbulent outflow-tract systolic flow was predominantly due to systolic anterior motion (SAM). Severe mixed mitral regurgitation due to valvular degeneration and moderate SAM were observed **(Image 1)**.



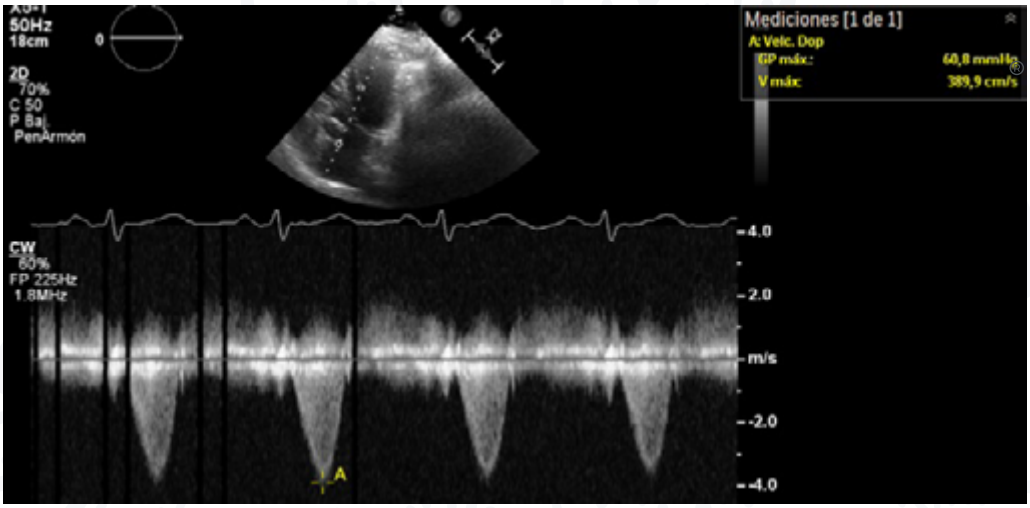
Beta-blockers were initiated but not tolerated, so calcium channel blockers were prescribed.

CT scan confirmed the SAMb causing significant subvalvular LVOT and SAM (Image 2) with a normally functioning tricuspid aortic valve. Cardiac MRI revealed minimal nonspecific septal fibrosis.



Despite treatment, the LVOT gradient remained elevated at 160 mmHg and the patient persists in NYHA functional class II with functional capacity below average in ergometry. After the Heart Team discussion, Mavacamten was started to reduce the dynamic gradient component, postponing the decision of surgery to the evolution.

Four weeks later, the gradient dropped to 60 mmHg, ejection fraction was kept preserved, and mitral regurgitation improved to mild **(Image 3)**.



04. CIRRUS-HCM: A MULTIPLE-DOSE PHASE 2 STUDY OF SAFETY, TOLERABILITY, AND EFFECTS ON HEMODYNAMICS AND FUNCTIONAL CAPACITY OF THE NOVEL CARDIAC SARCOMERE MODULATOR EDG-7500 IN HYPERTROPHIC CARDIOMYOPATHY

Owens, Anjali T (1); Abraham, Theodore P (2); Wharton, Ronald (3); Bhatia, Ankit (4); Harper, Mariko W (5); Dufton, Christopher (6); Gretler, Daniel D (6); Silverman, Jeffrey A (6); Mok, Marilyn M (6); Madden, Molly (6); Macdougall, James (6); Hawryluk, Natalie (6); Semigran, Marc J (6)

(1)University of Pennsylvania, Philadelphia PA; (2)University of California, San Francisco CA; (3)Northwell Health, New Hyde Park, NY; (4)The Christ Hospital Health Network, Cincinnati OH; (5)Virginia Mason Franciscan Health, Seattle WA; (6)Edgewise Therapeutics, Boulder CO

Background: EDG-7500 is a first-in-class cardiac sarcomere modulator designed to selectively decrease the rate of myocardial contractility during isovolumic contraction and increase diastolic relaxation for the treatment of patients with hypertrophic cardiomyopathy (HCM). It was well tolerated in a Phase 1 study of healthy adults (NCT06011317) and in a single-dose study of participants with obstructive HCM (oHCM) (CIRRUS-HCM Part A, NCT06347159). In CIRRUS-HCM Part A, acute reductions in resting and provoked left ventricular outflow tract (LVOT) peak gradient were observed without reductions in LV ejection fraction (LVEF). An acute dose-dependent reduction in NT-proBNP was observed within 24 hours of dosing, suggestive of an improvement in myocardial diastolic function.

Methods: CIRRUS-HCM Parts B and C are ongoing dose-ranging studies to evaluate the safety, tolerability, echocardiographic response as well as effects on functional capacity after 4 weeks of daily dosing of EDG-7500 in participants with oHCM and nHCM, respectively. Depth and durability of response will be assessed across a range of dose levels.

Results: The results of multiple-dose administration of EDG-7500 in participants with oHCM and nHCM will be presented.

Conclusions: The ongoing Phase 2 dose-ranging studies will provide the first data demonstrating the effects of daily administration of EDG-7500 on safety, tolerability, pharmacodynamics, dose and exposure response, and functional capacity in participants with oHCM and nHCM, and are anticipated to inform the design of subsequent Phase 3 studies.

05. EFFECT OF AFICAMTEN TREATMENT FOR UP TO 72 WEEKS ON CARDIAC STRUCTURE AND FUNCTION IN PATIENTS WITH OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY: THE SEQUOIA-HCM AND FOREST-HCM CMR SUB-STUDIES

Masri, Ahmad (1); Cardoso, Rhanderson (2); Nassif, Michael E. (3); Merkely, Bela (4); Oreziak, Artur (5); Abraham, Theodore P. (6); Barriales-Villa, Roberto (7); Coats, Caroline (8); Elliott, Perry (9); Owens, Anjali Tiku (10); Saberi, Sara (11); Solomon, Scott (2); Melloni, Chiara (12); Kramer, Christopher M. (13); Kwong, Raymond Y. (2); Maron, Martin S. (15)

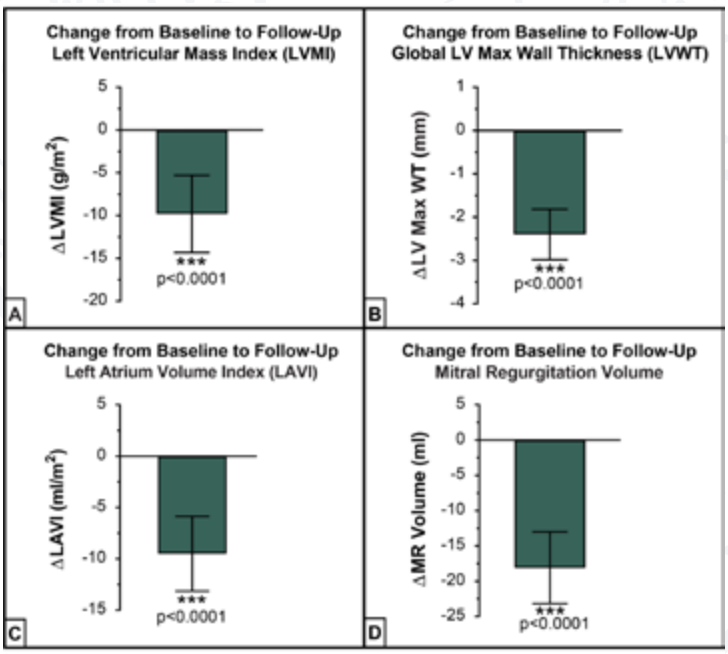
(1)Hypertrophic Cardiomyopathy Center, Knight Cardiovascular Institute, Oregon Health and Science University, Portland, OR; (2)Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; (3)University of Missouri Kansas City Healthcare Institute for Innovations in Quality and Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; (4)Heart and Vascular Center, Semmelweis University, Budapest, Hungary; (5)National Institute of Cardiology, Warsaw, Poland; (6)University of California San Francisco, San Francisco, CA, USA; (7)Complexo Hospitalario Universitario A Coruña, INIBIC, CIBERCV-ISCIII, A Coruña, Spain; (8)School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; (9)Department of Inherited Cardiovascular Diseases, St. Bartholomew's Hospital; Institute of Cardiovascular Science, University College London, United Kingdom; (10)University of Pennsylvania, Philadelphia, PA, USA; (11)University of Michigan Health, Ann Arbor, MI, USA; (12)Cytokinetics Incorporated, South San Francisco, CA, USA; (13)Cardiology Division, Department of Medicine, University of Virginia Health System Charlottesville VA, USA; (15)Lahey Hospital and Medical Center, Burlington, MA, USA

Background. Aficamten is a next-in-class cardiac myosin inhibitor in development for the treatment of hypertrophic cardiomyopathy (HCM). FOREST-HCM, an open-label extension study evaluating long term efficacy and safety of aficamten includes a 5-year cardiac magnetic resonance (CMR) imaging sub-study.

Methods. Between May 2021 and February 2025, 350 patients with obstructive HCM were enrolled in FOREST-HCM. Of these, 102 (29%) were currently enrolled in the CMR sub-study and 64 patients (60 ±11 years, 47% female) completed both baseline and follow-up CMR. Of these, 36 were from SEQUOIA-HCM with baseline CMR at the start of that study (follow-up 72 weeks) and 28 had baseline CMR at start of FOREST-HCM (follow-up 48 weeks).

Results. After 48-72 weeks of aficamten treatment, there were significant reductions from baseline in Left Ventricular (LV) mass index (-10 ±18 g/m2), maximal LV wall thickness (-2 ±2 mm), Left Atrial (LA) volume (-18 ±28 mL), mitral regurgitation (MR) volume (-18 ±19 mL), MR fraction (-14% ±16); all p<0.0001 (Figure). These changes were accompanied by stable LV late gadolinium enhancement mass (-0.3 ± 5 g, p=0.52) and global extracellular volume (-1.2% ±2.8, p=0.0002), while native T1 value decreased (-36.6 ±56 ms, p<0.0001). There was a modest decrease in LVEF by -3 ±6% (p<0.0001) from a baseline of 68 ±6%.

Conclusion. Longer-term treatment with aficamten over 48-72 weeks resulted in favorable cardiac remodeling with reduction in LV mass, LA volume, and MR while myocardial fibrosis remained stable.



06. GLOBAL REMODELING CHANGES WITH AFICAMTEN IN PATIENTS WITH OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY: AN ANALYSIS OF THE SEQUOIA-HCM TRIAL

Owens, Anjali T. (1); Abraham, Theodore P. (2); Claggett, Brian L. (3); Coats, Caroline J. (4); Hegde, Sheila M. (3); Januzzi, James L. (5); Maron, Martin S. (6); Masri, Ahmad (7); Miao, Zi Michael (3); Olivotto, Iacopo (8); Solomon, Scott D. (3); Jacoby, Daniel L. (9); Heitner, Stephen B. (9); Michels, Michelle (10); Sequoia-hcm Study Investigators, On Behalf Of The (1)

(1)University of Pennsylvania, Philadelphia, PA, USA; (2)University of California San Francisco, San Francisco, CA, USA; (3)Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; (4)School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; (5)Baim Institute for Clinical Research; Cardiology Division, Massachusetts General Hospital; Harvard Medical School; Boston MA; (6)Lahey Hospital and Medical Center, Burlington, MA, USA; (7)Oregon Health & Science University, Portland, OR, USA; (8)Meyer Children's Hospital, Istituto di Ricovero e Cura a Carattere Scientifico, Florence, Italy; (9)Cytokinetics, Incorporated, South San Francisco, CA, USA; (10) Erasmus Medical Center, Cardiovascular Institute, Thoraxcenter, Department of Cardiology, Rotterdam, The Netherlands

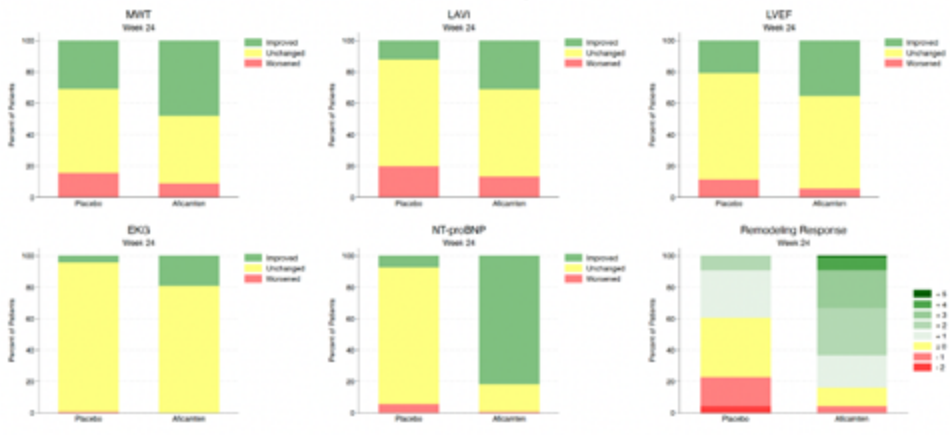
Background: The effect of aficamten on myocardial remodeling may impact progression of obstructive HCM (oHCM). We report an integrative analysis of myocardial remodeling with aficamten treatment.

Methods: SEQUOIA-HCM recruited 282 patients with symptomatic oHCM randomized to aficamten (n=142) or placebo (n=140) for 24 weeks. Global remodeling response (Week 24) was assessed across five domains: 1) maximal wall thickness (MWT) decrease of ≥1.5 mm; 2) change in categorical degree of left atrial (LA) enlargement according to LA volume index (LAVI) (normal [16–34 mL/m^2], mild [35–41 mL/m^2], moderate [42–48 mL/m^2], severe [>48 mL/m^2]); 3) hyperdynamic LVEF (≥72%); 4) left ventricular hypertrophy (LVH); 5) N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction ≥50% from baseline.

Results: At baseline, there were no differences between groups in the domains. Significant improvements in individual remodeling domains were observed for aficamten: MWT (68/142 [47.9%] vs 43/140 [30.7%] placebo, p=0.003), improvement by ≥1 category in LAVI among patients with abnormal LAVI (>34 mL/m^2) at baseline (44/94 [46.8%] vs 17/91 [18.7%], p<0.001), resolution of hyperdynamic LVEF (50/142 [35.2%]%] aficamten vs 29/140 [20.7%]%] placebo, p=0.007), resolution of strain pattern (27/142 [19.0%] vs 6/140 [4.3%] placebo, p<0.001), and ≥50% decrease in NT-proBNP (116/142 [81.7%] vs 10/140 [7.1%] placebo, p<0.001). Overall, 119/142 (83.8%) aficamten treated patients had beneficial remodeling in ≥1 domain vs 55/140 (39.3%) on placebo (p<0.001) (FIGURE); number needed to treat 2.2.

Conclusions: Aficamten treatment resulted in beneficial changes in indices of global remodeling assessed by domains encompassing cardiac structure and function, electrophysiology and biochemistry.

FIGURE: Global Remodeling Clinical Domains



*The full analysis set of 282 patients (140 placebo; 142 aficamten) are displayed for each domain.
EKG = electrocardiogram; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; MWT = maximal wall thickness; NT-proBNP = N-terminal pro-B-type natriuretic peptide.
For each metric the remodeling response was assigned a +1 if improvement was noted, 0 if no change was seen, and -1 if the metric worsened.

07. AFICAMTEN VERSUS METOPROLOL AS MONOTHERAPY FOR SYMPTOMATIC OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY: RESULTS FROM MAPLE-HCM

García-Pavía, Pablo (1); Fifer, Michael A. (2); The Maple-hcm Study Investigators, On Behalf Of (3)

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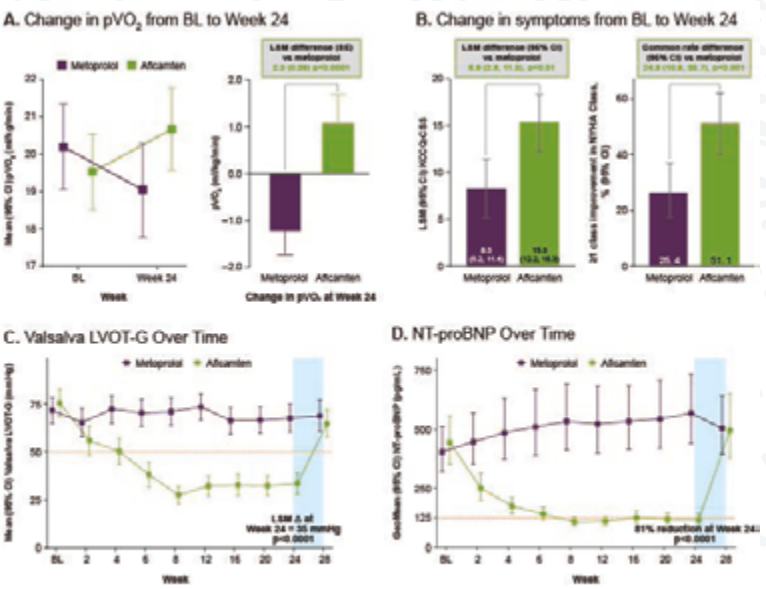
Methods: MAPLE-HCM (NCT05767346) is a multicenter phase 3, double-blind trial in symptomatic oHCM. Adult participants were randomized 1:1 to aficamten (5- 20 mg) or metoprolol (50-200 mg) after stopping HCM standard-of-care medications, if necessary. Primary endpoint: change in peak oxygen uptake (pVO2) at Week 24. Secondary endpoints: changes in New York Heart Association class, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score (KCCQ–CSS), Valsalva left ventricular outflow tract (LVOT) gradient, N-terminal pro-brain natriuretic peptide (NT-proBNP), echo-derived left atrial volume index (LAVI) and left ventricular mass index (LVMI).

Results: Participants received aficamten (n=88) or metoprolol (n=87). Mean age was 58 years, 58% were male, mean left ventricular ejection fraction (LVEF) was 68%, and mean resting and Valsalva LVOT gradients 47 and 74 mmHg, respectively. Mean pVO2 was 19.9 ml/kg/min and mean KCCQ-CSS was 65.8. At Week 24, mean pVO2 change was +1.1 mL/kg/min (95%CI: 0.5, 1.7) (aficamten) and −1.2 (95% CI: -1,7, -0.8) (metoprolol); least-squares mean difference: 2.3 mL/kg/min (95% CI: 1.5, 3.1; p<0.0001). The effect of aficamten on pVO2 was consistent across all prespecified subgroups. Secondary endpoints demonstrated statistically significant improvements with aficamten vs metoprolol (p<0.01), except LVMI (p=0.16). Aficamten was associated with changes in LVEF −4% (95%CI: −5%, −3%; P<0.001) vs metoprolol.

Conclusions: Aficamten monotherapy was superior to metoprolol with respect to exercise capacity, symptoms, health status, LVOT gradient, NT-proBNP, LAVI, and well tolerated.



08. FILAMIN C ASSOCIATED CARDIOMYOPATHY IN PEDIATRIC PATIENTS: A BELGIAN CASE SERIES AND LITERATURE REVIEW

Wannes, Renders (1); Evelien, Cansse (1); Luc, Bruyndonckx (2); Thomas, Salaets (3); Jelena, Hubrechts (4); Stéphane, Moniotte (4); Bert, Callewaert (1); Katya, De Groote (1); Laura, Muiño Mosquera (1)

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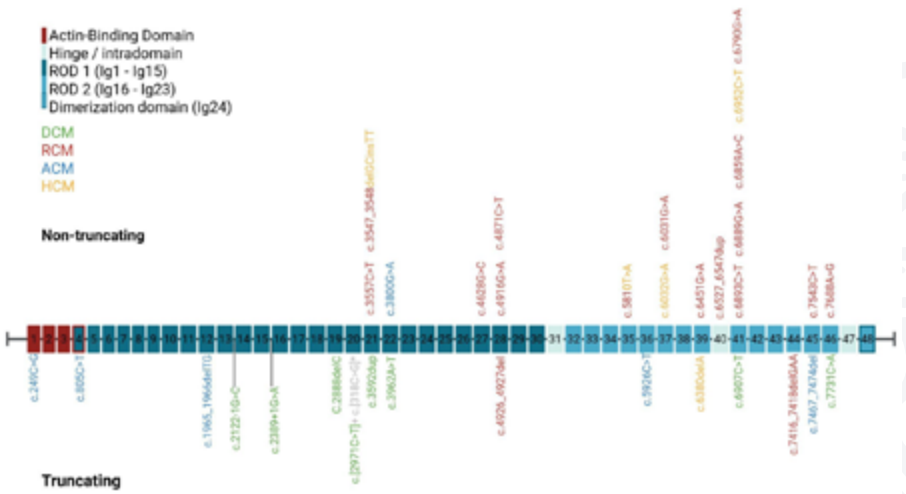
There is increasing interest in the role of Filamin C (FLNC) in cardiomyopathy. FLNC variants have been extensively described in skeletal myopathies and all types of cardiomyopathies. A contribution of 1-8% in CMP is reported in adults-max 8% in HCM cohorts. Interestingly, increasing literature discussing a childhood-onset form is published.

Aim: To study the cardiovascular outcome of children carrying a (likely) pathogenic variant in FLNC and evaluate genotype-phenotype correlations.

Methodology: Children diagnosed <18yrs, found via literature search or under follow-up in one of the participating Belgian centers were included. Demographic, genetic and cardiovascular data were collected.

Results: 60 children (63.3% male, mean age 6.9±6.1yrs) were included, with a positive family history in 58.3%. Restrictive CMP (RCM) was most frequent with 60%, followed by dilated CMP (DCM) in 20%. Only 11.7% of patients had arrhythmogenic CMP (ACM), and hypertrophic CMP (HCM) was the least frequent with just 8.3%. Genetically, RCM and HCM were mainly caused by missense variants, whereas DCM was solely associated with truncating variants. 50% of patients suffered a major cardiac event (mean age 10.5±8.6yrs, time to event 3±4.2yrs): 19 patients underwent heart transplantation, 4 received an ICD, and 5 patients suffered from sudden cardiac death at presentation.

Conclusion: FLNC-associated CMP can present at an early age and is marked by important morbidity and mortality. RCM is most frequently diagnosed in these early-onset cases, whereas the proportion of HCM is only limited. Highlighting a potential distinct entity of FLNC in children.



09. SINGLE-CENTRE EXPERIENCE OF GENETIC TESTING RESULTS REVEALS RARE SYNDROMIC CASES IN PAEDIATRIC PATIENTS WITH HCM.

Shcherbakova, Natalia (1); Brendel, Josephine (1); Rolfs, Nele (2); Seidel, Franziska (2); Klaassen, Sabine (2)

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Hypertrophic cardiomyopathy in children is a genetically heterogeneous condition which remains understudied compared to adults.

Methods: We conducted a retrospective review of health records and genetic data of paediatric patients with HCM at our centre over the last 10 years. All genetic data from cardiomyopathy panels and whole-exome sequencing were reanalysed and classified according to current international guidelines.

Results: We found 54 patients with a male-to-female ratio of 42 to 12 (78% to 22%, respectively), which is typical for HCM but not observed in other CMP cohorts at the centre, such as dilated or restrictive cardiomyopathy. The distribution of variants inherited from the father or mother was even. The diagnostic yield for genetic testing was 50% for LP/P variants, with the majority, 37%, located in the genes MYBPC3 and MYH7. Additionally, variants of unknown significance were found in 18.5% of probands. Among the 17 patients with negative genetic testing, 65% do not have a familial history, while among genetic-positive cases, only 33% were sporadic. A recessive type of inheritance was registered in 16% of cases with LP/P or VUS variants. Although the original cohort was primarily composed of isolated HCM cases, variants in genes associated with rare syndromic forms of HCM were found in 19%of patients. Retrospective analysis of medical records showed that patients could have subtle extracardiac manifestations of disease at presentation.

Conclusions. Genetic reanalysis identified causative variants in half of the probands, including syndromic forms that might have been missed clinically and could require expanded genetic testing.

10. CROSS-MODEL CONCORDANCE AND SERIAL REEVALUATION TO GUIDE ICD DECISIONS IN LOW-VOLUME PEDIATRIC HYPERTROPHIC CARDIOMYOPATHY

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Introduction: Risk stratification in pediatric hypertrophic cardiomyopathy (HCM) is challenged by limited cohort sizes and model discrepancies. Pediatric tools (PRIMaCY, HCM Risk-Kids) often classify more children as high-risk than adult models (ESC HCM Risk-SCD, AHA criteria). In small series, formal calibration is unfeasible, prompting the need for interpretable, pragmatic frameworks.

Objective: To evaluate the utility of cross-model concordance and yearly re-evaluation for guiding ICD decisions in low-volume pediatric HCM.

Methods: Twelve children (mean age 12.3 years; non-syndromic HCM) were prospectively followed (2019–2025). At baseline and annually, four risk tools were applied. Patients were grouped as:

1. High–High Concordance (both pediatric and adult tools high-risk);
2. High Concordance (both pediatric and an adult tool high-risk);
3. Discordance A (pediatric high, adult low);
4. Discordance B (pediatric low, adult high);
5. Low–Low Concordance.

The composite endpoint included sustained VT/VF, appropriate ICD shock, or sudden cardiac death (SCD).

Results: At diagnosis, 10/12 patients were high-risk by PRIMaCY, 7/12 by HCM Risk-Kids, 2/12 by ESC, and 3/12 by AHA. No patients were in the High–High concordance group. Two patients with High concordance had arrhythmic events; notably, only one showed extensive LGE on CMR. Two High concordance patients received ICDs and remained event-free. No events occurred in Discordance B or Low–Low groups.

Conclusions: In small pediatric cohorts, concordant high-risk classification across models may surrogate calibration. Serial re-evaluation supports clinical decisions, helping avoid overtreatment in pediatric-high/adult-low discordance. This qualitative framework aids risk-based ICD decisions when quantitative precision is limited.

11. VALIDATION OF THE HCM-AF SCORE TO PREDICT ATRIAL FIBRILLATION IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY AT A TERTIARY CENTER

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(1)Hospital Universitario Virgen de la Arrixaca

Background: Atrial fibrillation (AF) is the most common sustained arrhythmia in patients with hypertrophic cardiomyopathy (HCM), increasing their risk of morbidity and cardioembolic stroke. Early identification of high-risk individuals could improve preventive strategies such as anticoagulation.

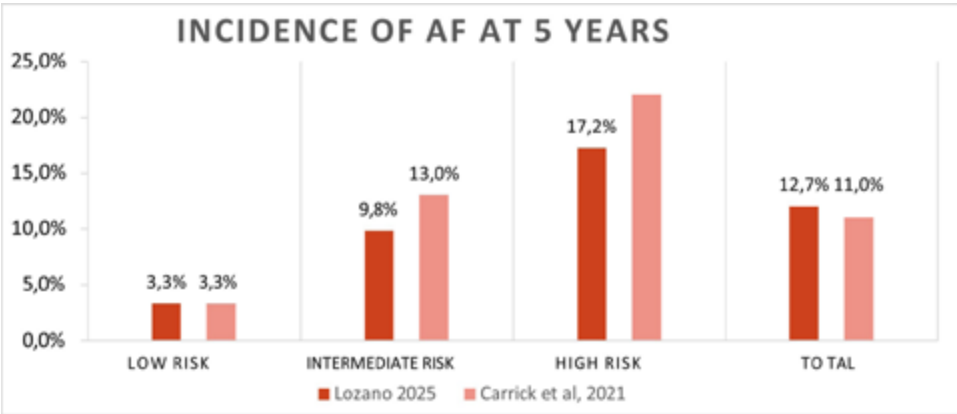
Objective: To assess the usefulness of the HCM-AF score to stratify the annual risk of AF in a large HCM cohort from a reference center in Murcia, Spain.

Methods: We conducted a retrospective observational study of 1,186 HCM patients (mean age 54.5 ± 16.7 years; 35.2% women) with a mean follow-up of 7.4 ± 5.5 years. Patients were categorized into low (<1%), intermediate (1–2%), or high (>2%) annual risk groups based on their HCM-AF score. Incidence rates were calculated and compared with those of the original score development cohort.

Results: The overall AF prevalence was 17.7% and the incidence was 2.2% per year. Incidence by risk group was: 0.7% (low), 2.6% (intermediate), and 4.4% (high). Predictors of AF in multivariate analysis were age at clinical evaluation (HR 1.03; 95% CI: 1.02–1.04), left atrial diameter (HR 1.09; 95% CI: 1.06–1.12), and left ventricular wall thickness (HR 1.06; 95% CI: 1.03–1.10). The HCM-AF score performed better than left atrial diameter >45 mm alone.

Conclusions: The HCM-AF score accurately classifies low- and high-risk HCM patients for AF, although it underestimates risk in the intermediate group. Despite this, it remains superior to single-parameter predictors and supports its clinical use for AF risk stratification in HCM.

Keywords: Atrial fibrillation, hypertrophic cardiomyopathy, HCM-AF score, risk stratification



12. HEALTHCARE ACCESS, SYMPTOM BURDEN, AND PSYCHOLOGICAL IMPACT IN HYPERTROPHIC CARDIOMYOPATHY: A MULTINATIONAL PATIENT-DRIVEN SURVEY

Tsenov, Emil (1); Maurizi Md, Niccolò (2); Van Der Velden Md Phd, Jolanda (3); Pinciroli, Matteo (4); Pieroni, Maurizio (5); Cecchi Md, Franco (4); Olivotto Md, Iacopo (6)

(1)European HCM Patient Foundation, Vienna, Austria; (2)Service of Cardiology, University Hospital of Lausanne (CHUV), Lausanne, Switzerland; (3)Department of Physiology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; (4)AICARM Italian Association for Cardiomyopathies, Florence, Italy; (5)Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy; (6)Meyer Children's Hospital IRCCS, Florence, Italy

Background and aims: Hypertrophic cardiomyopathy (HCM) is a complex genetic heart disease with significant patient implications. While research has focused on pathophysiology and treatment, patient-reported experiences remain underexplored.

Methods: A cross-sectional, multinational online survey was distributed in early 2025, targeting HCM patients in Europe. The questionnaire included sections on demographics, symptom burden, impact on daily life, medical management, and psychological well-being. Data were analyzed descriptively, with subgroup analyses based on geography, employment, and healthcare access.

Results: A total of 337 qualifying participants from 18 European countries completed the survey. Main reason for their diagnosis was symptoms (107, 42%). Specifically, shortness of breath and fatigue had an overall high impact on quality of life, both at diagnosis and at the time of survey (3.09/5 vs 2.93/5; 3.23/5 vs 3.46/5, respectively). With HCM diagnosis, the proportion of patients engaged in low to moderate activities increased significantly (87% vs 50%, p<0.01) and major psychological complaint was weight gain (71, 49%). Twenty-two (15%) patients reported having lost their job because of HCM; 46 (14%) reported a limitation in working hours as well as limitation in the kind of work performed (32, 9%), due to the disease. Despite a significant psychological burden access to mental health support was limited, as only 15% of patients regularly consulted a psychologist.

Conclusions: This survey highlights critical gaps in HCM management, including healthcare accessibility, persistent symptom burden, and unmet psychological needs. Improved care pathways, mental health integration, and workplace accommodations are essential to enhance patient-centered HCM management across Europe.

Figure 1 Evolution of perceived symptoms burden from diagnosis to present

Figure 2 Level of engagement in physical activity at diagnosis and at present across the cohort

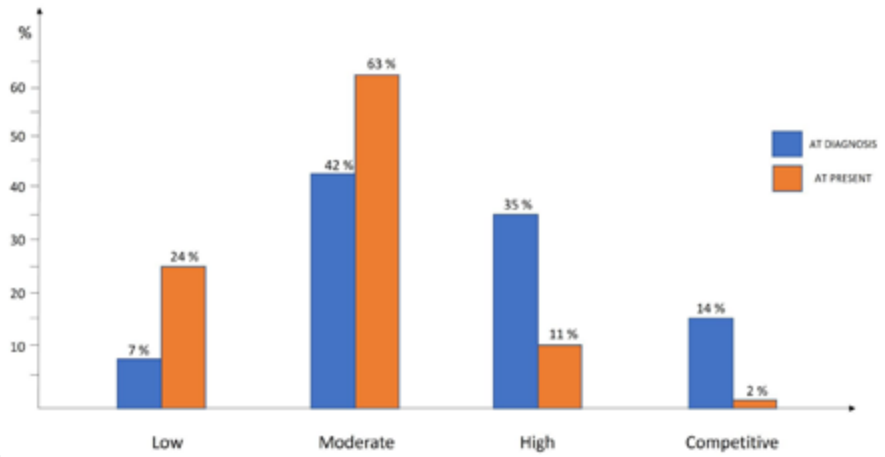
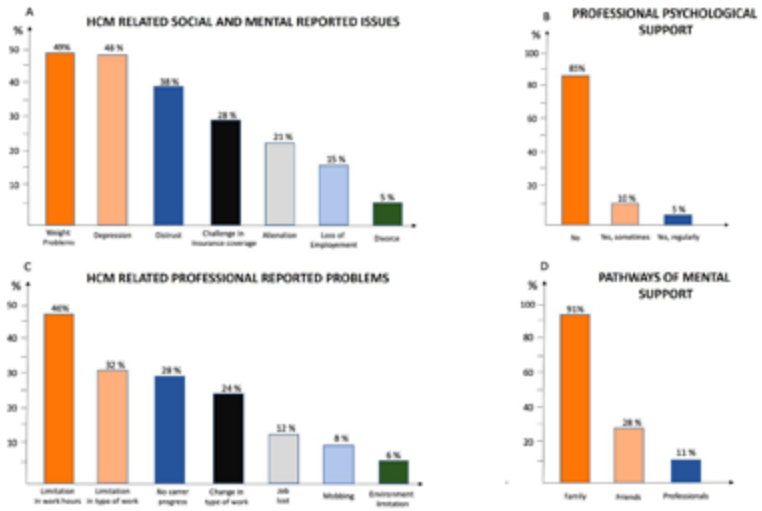


Figure 3 Psychological impact and pathways to seek mental support of the partecipants.



13. GENOTYPE-PHENOTYPE CORRELATION AND CLINICAL OUTCOMES IN ANDERSON-FABRY DISEASE WITH THE ARG301GLN GLA VARIANT

Blanco, Rocio (1); Ripoll-vera, Tomas (1); Rico, Yolanda (2); Hermida, Alvaro (3); Abdullah, I (4); Kolia, L (5); Alvarez, Jorge (1); Fortuny, Elena (2); Nowak, Albina (4); Nordbeck, Peter (5); Pons, Jaume (2); Bosch, Teresa (2); Alamar, Marta (1); Ruiz-pizarro, Virginia (1); Heine, Damian (2)

(1)H. U. Son Llatzer; (2)H. U. Son Espases; (3)H. U. Santiago de Compostela; (4)University Hospital Zurich; (5)Clinic Wurzburg Mitte

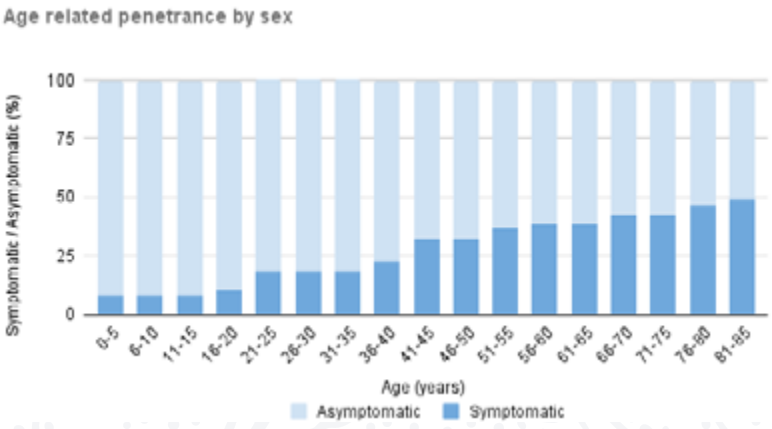
Resumen: Background: Anderson-Fabry disease (AFD) is a genetic condition that affects the enzyme α-Galactosidase A, leading to abnormal glycosphingolipid deposition in lysosomes, and involving multiple organs. The Arg301Gln variant in the GLA gene is poorly described, with limited reports showing varied patterns of classical and non-classical AFD, the latter with later onset and milder organ damage.

Purpose: To analyse the penetrance, clinical phenotype, and biochemical profile of the largest cohort of patients with the Arg301Gln GLA variant.

Methods: Observational, international, retrospective cohort case series of patients carrying the Arg-301Gln variant.

Results: Forty-nine Arg301Gln GLA carriers were included, 41% male. Penetrance was 63%, 1.5 times higher in men. Mean symptom onset was at 41 years; men presented earlier and were diagnosed sooner than women. Classic presentation affected only 20%, with no gender differences. During follow-up, nearly 20% experienced non-fatal cardiovascular and renal events (e.g., stroke, dialysis, heart failure, arrhythmias requiring devices), predominantly in men. Only a few women had normal α-galactosidase A activity; most showed residual levels. The combined incidence of events, including all-cause mortality, was 33%, with 9% mortality.

Conclusions: The Arg301Gln GLA variant is associated with high cardiorenal penetrance, typically with onset in middle age. Few patients displayed the classical AFD phenotype. As in other X-linked conditions, males were more prone to severe events. This genotype-phenotype correlation has clinical relevance for patient management and decision-making.



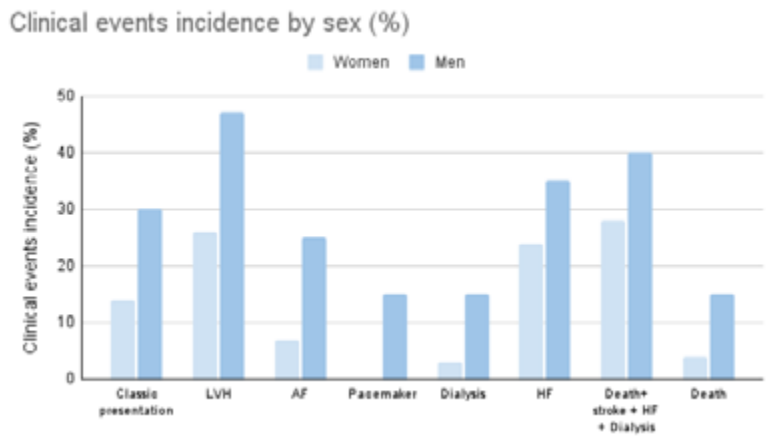


Figure 5. Combined Kaplan–Meier curve of events during follow-up.

15. DANON DISEASE IN INFANTS

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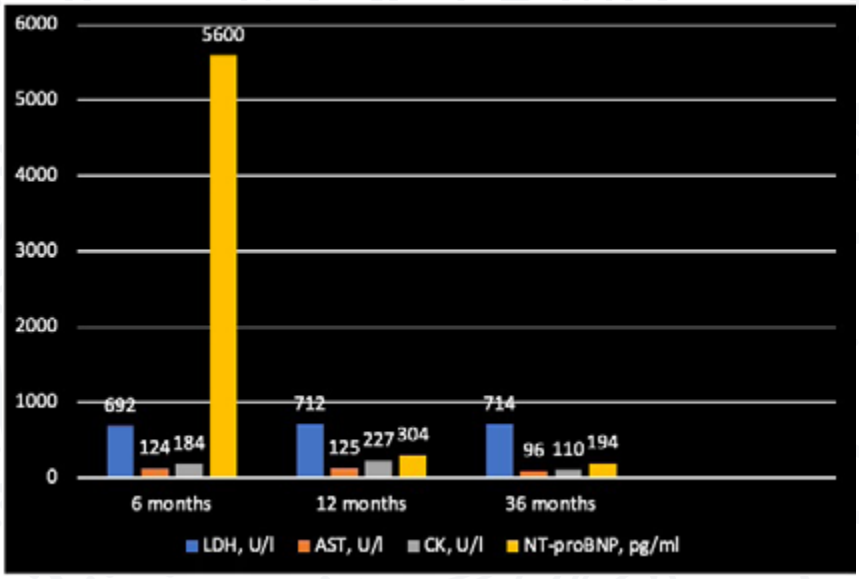
(1)National Medical Research Center for Children's Health, Moscow, Russia; (2)Tenaya Therapeutics, San Francisco, CA, USA

Background/Objectives: Danon disease is a rare X-linked cardiomyopathy caused by truncating variants in the LAMP2 gene, leading to reduced protein expression. Males typically present earlier and more severely, while females show variable onset and course due to differences in X-chromosome inactivation. We present a case of early-onset Danon disease in a female infant with a de novo LAMP2 variant (c.507G>A, p.W169*).

Methods: Clinical, pedigree and genetic evaluations were assessed at the National Medical Research Center of Children's Health (Russia) from 2023 to present.

Results: A full-term girl born to healthy parents developed elevated transaminases by day 3 of life and supraventricular tachycardia (SVT) with reduced LV ejection fraction (EF 23%) on day 4. SVT resolved by day 12, EF normalized by day 7, but lab abnormalities persisted. At 3 months, symmetric LV hypertrophy was present without outflow obstruction. At 6 months, further evaluation showed elevated cardiac markers, symmetrical LVH 10–14 mm, PWT 11–14 mm, RV wall 4.4 mm, EF 85%, and mild diastolic dysfunction. ECG/Holter revealed sinus rhythm, intra-atrial conduction delay, supraventricular ectopic beats, repolarization abnormalities, and QTc 410 ms. Liver ultrasound showed mild diffuse changes. Whole exome sequencing identified a heterozygous de novo LAMP2 pathogenic variant (p.W169*), not found in gnomAD, but listed in HGMD.

Conclusions: Danon disease can manifest early in girls. Its variable course may delay diagnosis. Persistent liver enzyme elevation provides an early disease marker. Genetic testing including LAMP2 is essential, especially in infants with hypertrophy or arrhythmia. Emerging gene therapies highlight the importance of early identification.



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16. CARDIOPULMONARY, VENTILATORY, AND METABOLIC ADAPTATIONS IN HCM PATIENTS FOLLOWING HIGH-INTENSITY TRAINING

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(1)Universidad de Murcia; (2)Hospital General Universitario de Caravaca; (3)Hospital Virgen de la Arrixaca - Unidad de Cardiología; (4)Hospital Virgen de la Arrixaca, Inherited Cardiac Disease Unit (CSUR)

Aim: The main aim of this study was to assess the effect of 12 weeks of concurrent high intensity resistance and cardiorespiratory training on cardiopulmonary, vntilatory and metabolic parameters in patients with hypertrophic cardiomyopathy (HCM).

Methods & Results: en HCM patients were evaluated before and after 12 weeks of individualized concurrent training which consisted of 2 sessions/week with a resistance training part followed by cadiorespiratory training on a treadmill. Exercise selection was based on general HCM recommendations and performed with a moderate level of effort with 50-70% of the estimated 1 repetition maximum (1RM) weight and executing approximately only half of the repetitions that could be potentially completed. Cardiorespiratory training consisted of one session of continuous workload 5-10 beats per minute (bpm) abote VT1 and second fartlek-style session with 4-7 blocks of 2-5 minutes of a workload corresponding to 5-10 bpm below the VT2 interspersed with 1-3 minutes rest at VT1 pace. Training promoted an increase in functional capacity (+4 mL·kg−1·min−1), oxygen consumption at both ventilatory thresholds, VE/VCO2, metabolic response to exerciseand other CPET-derived variables associated with a better prognosis and long- term survival. Neither detrimental effects nor cardiac events ocurred during training or cardiorespiratory testing.

Conclusions: The results show a positive effect of concurrent high intensity resistance and cardiorespiratory training on patients' cardiopulmonary function, metabolic and ventilatory efficiency that may improve their functional class, quality of life, and long- term prognosis. The replication of this protocol in a larger cohort of patients is warranted to confirm these preliminary results.

17. CONDUCTION CHANNELS IN HYPERTROPHIC CARDIOMYOPATHY: A NOVEL MARKER FOR ARRHYTHMOGENIC RISK?

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(1)Hospital Clínic de Barcelona

In 25 hypertrophic cardiomyopathy (HCM) patients, post-processing, semi-automatic analysis with a dedicated software of routine LGE-CMR revealed that Conduction Channels (corridors of intermediate-density scar) are strong predictors of ventricular arrhythmias. Patients with at least one channel had a 14-fold higher risk of sustained/non-sustained ventricular tachycardia or ventricular fibrillation, and risk rose with the number and summed length of channels. Incorporating these metrics may improve risk assessment and potentially guide ablation strategies in HCM.

Variable	With events	Without events	Hazard Ratio (95% CI)	p-value
Conduction channel present (yes)	7/8 (88%)	2/17 (12%)	14.45 (1.73–120.93)	**0.01**
Number of channels	1.5 [1.0–2.2]	0.0 [0.0–0.0]	1.95 (1.12–3.39)	**0.02**
Total channel length (mm)	25.2 [8.4–41.1]	0.0 [0.0–0.0]	1.02 (1.00–1.04)	0.08
Mean channel length (mm)	22.5 ± 9.3	20.7 ± 6.7	1.05 (0.92–1.21)	0.44
Maximum channel length (mm)	28.3 ± 13.1	27.4 ± 16.2	1.02 (0.92–1.12)	0.75
Maximum transmurality (%)	20.0 ± 17.9	5.0 ± 7.1	1.02 (0.96–1.08)	0.52
Total LV mass (g)	165.8 [139.5–201.7]	104.3 [70.1–120.8]	1.01 (1.00–1.02)	**0.03**
BZ + Core mass (g)	19.6 [10.7–30.6]	6.6 [4.7–8.0]	1.04 (0.99 – 1.09)	0.08
BZ + Core (%)	11.9 ± 6.0	7.7 ± 5.4	1.06 (0.94 – 1.20)	0.32
BZ mass (g)	13.6 [9.0–22.3]	4.5 [3.2–6.4]	1.05 (1.00–1.11)	0.06
BZ (%)	9.4 ± 5.1	5.8 ± 4.0	1.10 (0.95–1.28)	0.19
Core mass (g)	3.0 [1.9–5.8]	1.3 [0.8–2.3]	1.10 (0.89–1.35)	0.39
Core (%)	1.8 [1.4–2.7]	1.4 [1.0–2.8]	0.94 (0.56–1.58)	0.81

Figure 1. Univariate Cox analysis of Late Gadolinium Enhancement Cardiac Magnetic Ressonance (LGE-CMR) variables for arrhythmic events. *LV: Left ventricle; BZ: Borderzone.*

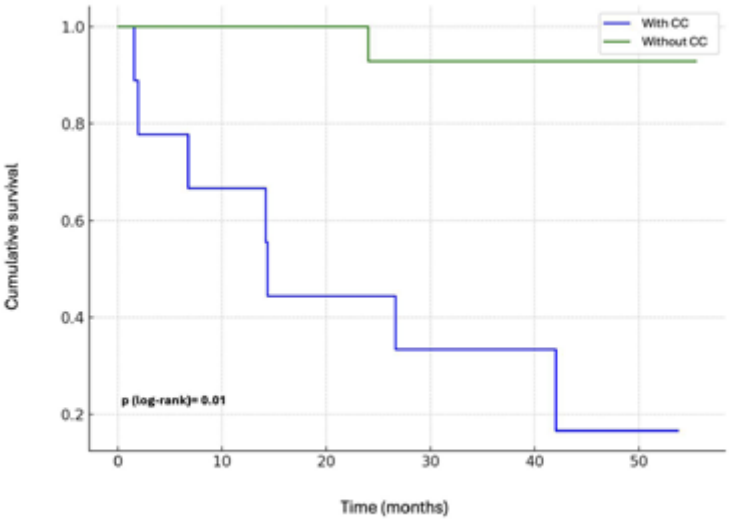


Figure 2. Kaplan–Meier curves for arrhythmia-free survival in patients with conduction channels (blue) and without conduction channels (green). *CC: Conduction channel.*

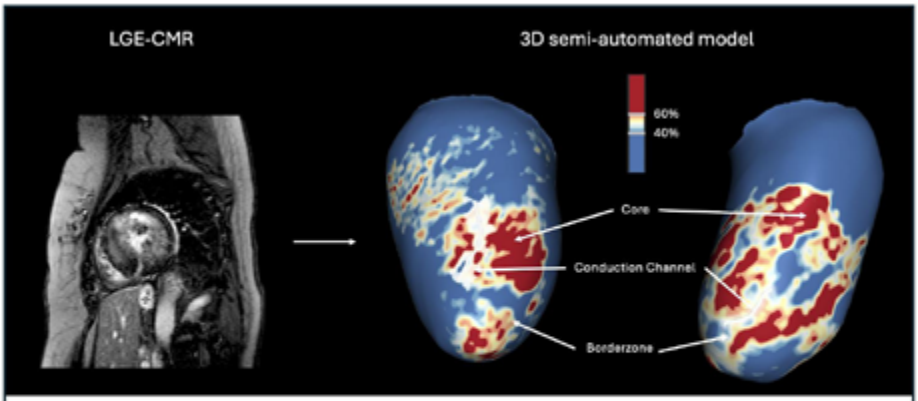


Figure 3. Visual summary of the post-processing analysis. Late Gadolinium Enhancement-Cardiac Magnetic Resonance (LGE-CMR) images are sequenced using a dedicated semi-automated software, driven by a pixel-intensity algorithm. Core scar is defined as pixels with greater than 60% of maximum intensity and Borderzone is defined as between 40 and 60%. Conduction channels are borderzone areas that connect healthy myocardium and are surrounded by core scar.

18. OFF-LABEL MAVACAMTEN IN A CHILD WITH OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY (HOCM): A CASE REPORT

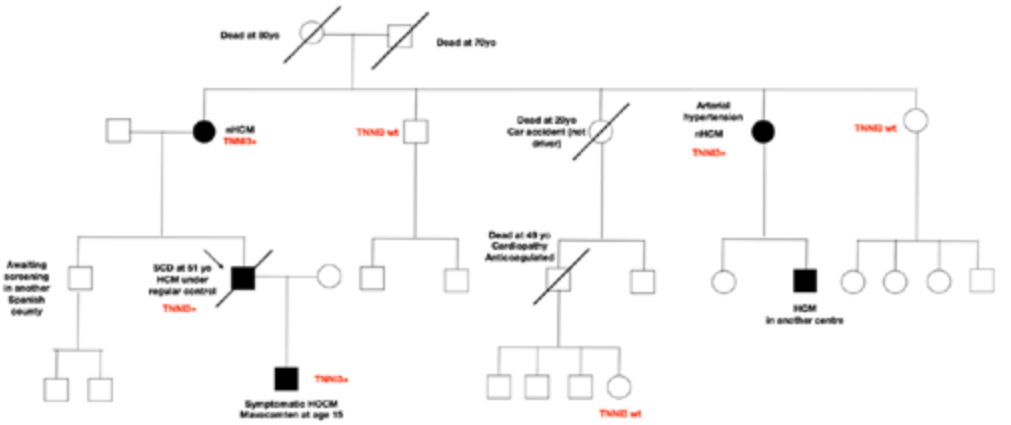
Beltrán Martínez, Susana (1); Ruiz, Eladio (2); Peiró, Esteban (2); Insa, Beatriz (2); Muñoz, Gloria (3); Company Langa, Mireia (1); Astudillo Sacoto, Ana Elisa (1); Rad García, Guillermo (1); Gil Molina, Marta (1); Murillo Varona, Guillermo (1); Huélamo Montoro, Sara (1); Fernández, Nerea (1); Llau García, Jorge (1); Braza-boïls, Aitana (4); Martínez-dolz, Luis (5); Zorio, Esther (4)

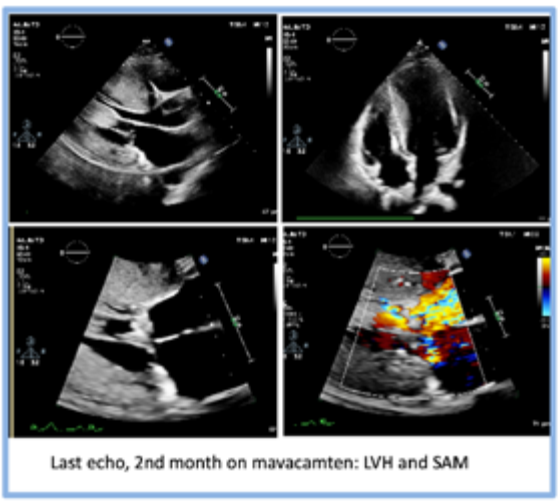
(1)Cardiology Department at the Hospital Universitario y Politécnico La Fe , Valencia, Spain; (2)Pediatric Cardiology, Hospital Universitario y Politécnico La Fe, Valencia, Spain; (3)Pediatric Cardiology, Hospital La Ribera, Alzira, Valencia, Spain; (4)CAFAMUSME Research Group at the IIS La Fe, Valencia, Spain; (5) Cardiology Department at the Hospital Universitario y Politécnico La Fe , Valencia, Spain, Medicine Department at the Medicine School of the Universitat de Valènica, Valencia, Spain, CIBERCV, Madrid, Spain;

Introduction: Mavacamten is currently recommended for symptomatic obstructive hypertrophic cardiomyopathy (HOCM) in adults (Class IIA per ESC, Class I per AHA 2024 guidelines).

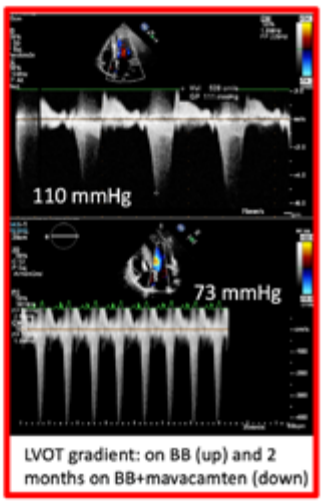
Case Report: We present a 15-year-old male with symtomatic HOCM, heterozygous for the pathogenic TNNI3 c.485G>C (p.Arg162Pro) variant. Family history included sudden cardiac death (SCD) in his father and his father's cousin. Diagnosed with HOCM phenotype at age 10, he showed rapid disease progression. At 15, his weight and height were comparable to adults (96 kg, 185 cm), and despite bisoprolol, he presented with with advanced NYHA Class III symptoms, NT-proBNP 2208 pg/mL, severe left ventricular (LV) hypertrophy (30 mm), a maximal left ventricular outflow tract obstruction (LVOTO) gradient of 100 mmHg, LV ejection fraction of 90%, and moderate-to-severe mitral regurgitation. Neither non-sustained ventricular tachycardia or late gadolinium enhancement were detected. Thus, his estimated 5-year SCD risk was 7.86%, prompting cardioverter-defibrillator (ICD) implantation. Disopyramide was unavailable due to national shortages. Given his intermediate metabolizer status, off-label mavacamten 5 mg was initiated alongside beta-blockers. After two months, he showed significant clinical and mild echocardiographic and biomarker improvement (NYHA Class II; LVOTO gradient reduced to 73 mmHg; NT-proBNP reduced to 689 pg/mL), with no side effects. He remains under close monitoring to guide ongoing treatment.

Discussion: While mavacamten's efficacy is established in adults, pediatric data are limited. Our case supports its potential off-label use in selected adolescents with severe, and refractory HOCM. Ongoing trials like SCOUT-HCM will modify the natural history of the disease in children.

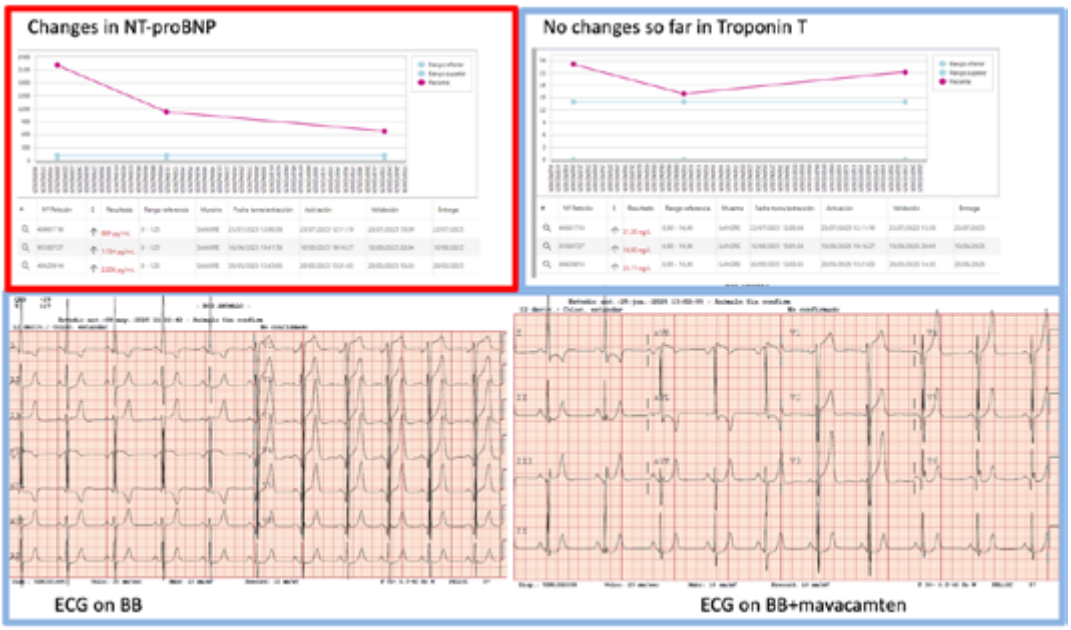




Last echo, 2nd month on mavacamten: LVH and SAM



LVOT gradient: on BB (up) and 2 months on BB+mavacamten (down)



19. RE-CLASSIFICATION OF HYPERTROPHIC CARDIOMYOPATHY GENETIC VARIANTS IN PATIENTS FROM THE SARCOMERIC HUMAN CARDIOMYOPATHY REGISTRY (SHARE)

Hespe, Sophie (1); Powell, George (2); Stevens, Chelsea (3); Catto, Laura (1); Stewart, Natalie (1); Baker, Amy (1); Krishnan, Neesha (1); Mitchell, Lucas A (1); Henden, Natasha (1); Theotokis, Pantazis (2); Buchan, Rachel (2); Mcgurk, Kathryn (2); Sarcomeric Human Cardiomyopathy Registry Investigators, Share (4); Ho, Carolyn Y (3); Ware, James S (2); Ingles, Jodie (1)

(1)Genomics and Inherited Disease Program, Garvan Institute of Medical Research, and UNSW Sydney, Sydney, NSW, Australia; (2)National Heart and Lung Institute and Medical Research Council Laboratory of Medical Sciences, Imperial College, London, United Kingdom; (3)Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; (4)Sarcomeric Human Cardiomyopathy Registry; SHaRe

Background: Genetic testing is a powerful tool for identifying family members at risk of developing disease and is dependent on accurate variant interpretation where classifications reflect our knowledge at a point in time.

Aim: Re-classify hypertrophic cardiomyopathy (HCM) variants from a large multi-center international registry of genetically characterised HCM patients (Sarcomeric Human Cardiomyopathy Registry; SHaRe).

Methods: SHaRe participants were clinically evaluated and enrolled at international sites. Data were entered from genetic reports performed between 1989 and 2020. Variants were systematically re-evaluated with the American College of Medical Genetics and Genomics criteria.

Results: Of 12,187 HCM patients, 8083 had genetic testing and 4407 (45%) had a variant identified in a clinically significant HCM gene. There were 1606 unique variants identified: 737 underwent expedited curation, 205 (25%) retained their classification of P/LP, 55 (7%) as B/LB and 477 (36%) as VUS. 869 (21%) were manually curated. 304/1606 (18%) had a change or clarification in classification. 197 (12%) were downgraded, including 107 (7%) classifications from LP/P to VUS (majority MYH7 missense variants); 82 (5%) VUS to LB/B; and 8 (<1%) P/LP to B/LB. 69 (4%) were upgraded, including 57 LP/P (3%) for 170 patients. Classification was clarified for 31(2%) variants with conflicting classifications within SHaRe.

Conclusion: 304 (18%) variants seen in 672 individuals had a change or clarification in classification upon re-evaluation. Evidence informing variant classification evolves over time and periodic re-evaluationis critical. Public sharing of case data remains a key factor in reclassification.

20. CHARACTERISATION OF HYPERTROPHIC CARDIOMYOPATHY IN FEMALES WITH CHILDHOOD-ONSET DANON DISEASE

Lim, Zhia Ning (1); Norrish, Gabrielle (1); Field, Ella (2); Arbos, Sophie (2); Cervi, Elena (2); Kaski, Juan Pablo (1)

(1)Great Ormond Street Hospital Centre for Inherited Cardiovascular Diseases, UCL Centre for Paediatric Inherited and Rare Cardiovascular Disease; (2)Great Ormond Street Hospital Centre for Inherited Cardiovascular Diseases

Danon disease (DD) is a rare X-linked multisystem disorder characterised by severe cardiomyopathy, skeletal myopathy, and intellectual difficulties. Males often present in childhood with severe left ventricular hypertrophy (LVH) and are at high risk of sudden cardiac death and progression to heart failure by the 3rd decade, whereas females have a more protracted course, with milder clinical features in childhood. However, the natural history of DD-related cardiomyopathy in girls has not been well-characterised.

Longitudinal clinical data from 7 girls with a genetically-confirmed LAMP2 pathogenic/likely pathogenic variant consistent with DD were collected.

Seven girls were referred at a median age of 10 (5-12). Five (71.4%) had a diagnosis of hypertrophic cardiomyopathy (HCM) at baseline and 1 (14.3%) during follow up, at a median age of 8.5 (5-13.5). Of those with a cardiac phenotype, 4 (66.7%) had pre-excitation and 5 (83.3%) had extreme LVH at baseline. Three (50%) had concurrent right ventricular hypertrophy (RVH) and 3 (50%) had obstructive HCM. Three (50%) had late gadolinium enhancement on cardiac MRI. During a median follow up of 3 (1.5-7.5) years, 3 (42.9%) experienced supra-ventricular arrhythmias and 4 (57.1%) had non-sustained ventricular tachycardia. Four (57.1%) underwent primary prevention cardioverter defibrillator implantation. One (14.3%) progressed to a dilated hypokinetic phase and underwent heart transplantation at 15 years old.

Girls with DD can present with severe HCM with rapid progression to dilated hypokinetic phase, akin to the male phenotype. DD should be considered in girls with HCM with additional features like pre-excitation and extreme LVH.

21. PERFORMANCE OF ARTIFICIAL INTELLIGENCE VERSUS CLINICIAN MAXIMUM WALL THICKNESS SEGMENTATION OF CARDIAC MRI FOR MORTALITY PREDICTION

Joy, George (1); Meredith, Benjamin (2); Pierce, Iain (2); Shiwani, Hunain (2); Kellman, Peter (3); Treibel, Ta (2); Manisty, C (2); Hughes, Ad (2); Tome, M (1); Moon, Jc (2); Davies, Rh (2)

(1)City St George's University of London; (2)University College London, UK; (3)National Institutes of Health, USA

Background: Maximum wall thickness (MWT), reflects left ventricular hypertrophy and adverse prognosis in multiple diseases. In hypertrophic cardiomyopathy (HCM), MWT is a key marker in diagnosis and risk. AI derived MWT reduces observer variability thereby improving precision; how this translates to outcome is incompletely understood. We hypothesized that a deep-learning AI segmentation of MWT obtained from cardiac MRI outperforms expert clinician segmentation for the prediction of all-cause mortality.

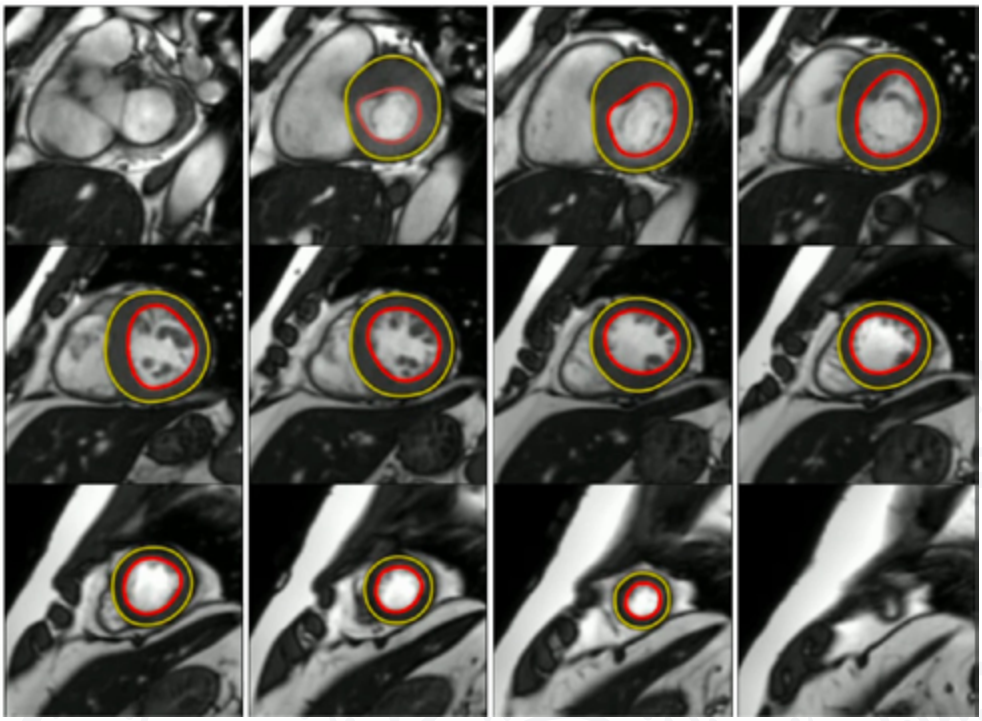
Methods: We studied a retrospective cohort of 10,382 consecutive patients who underwent cardiac MRI (CMR) in our centre. Mortality data was obtained from a national database. The median follow-up was 5.9 years (IQR 4.8–7.4), during which 1,743 patients (17%) died. A subgroup analysis was conducted in hypertrophic cardiomyopathy (HCM), n=1,699, of which 250 (14%) died.

AI segmentation was performed on all CMR studies, and Cox proportional hazards models were fitted to compare the prognostic value of AI-derived MWT with those derived from clinician segmentation used in clinical care.

Results: Compared to clinician segmentation, AI-derived MWT had higher prediction for all-cause mortality in all-comers ($p<0.001$) and HCM ($p=0.005$). Differences remained after adjusting for age and sex (both $p<0.001$). Machine analysis was performed at 20s per participant.

Conclusion: Compared to clinician experts, AI-derived MWT shows superior prediction of mortality in all-comer patients and in patients with HCM. AI segmentation is delivered at high speed and low-cost. Findings support the superseding of clinician-derived MWT with AI.

Figure Caption: Deep learning AI segmentation of maximum wall thickness in a patient with hypertrophic cardiomyopathy (end-diastole)



22. POLYGENIC SCORE ANALYSES IN A LARGE MULTINATIONAL HCM CLINICAL COHORT IDENTIFIES EFFECTS ON DISEASE PENETRANCE AND SEVERITY

Lipov, Alex (1); Jordà, Paloma (2); Gimeno, Juan R. (3); Castillo, Ismael Henarejos (2); Walsh, Roddy (4); Michels, Michelle (5); Paterson, Natasha (6); Roston, Thomas (7); Olivotto, Iacopo (8); Barriales-villa, Roberto (9); Jurgens, Sean J. (1); Cadrin-tourigny, Julia (2); Amin, Ahmad S. (1); Adler, Arnon (10); Tadros, Rafik (2); Bezzina, Connie R. (1)

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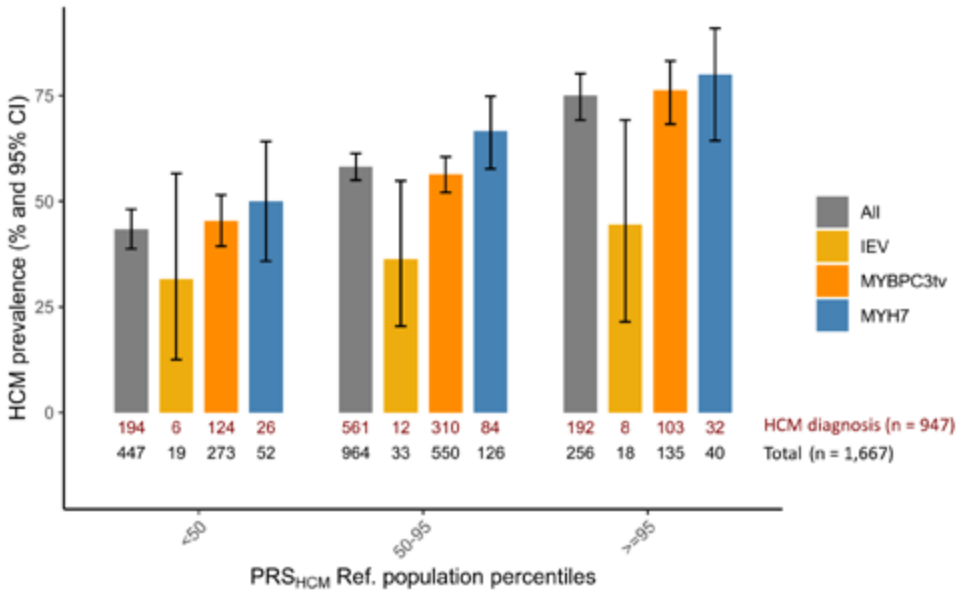
Disease expressivity in hypertrophic cardiomyopathy (HCM) varies widely, from unaffected genetically predisposed individuals to those with life-threatening complications. Polygenic scores (PGS) have been shown to predict the penetrance of HCM-causing rare genetic variants (HCMrv) and HCM-related outcomes in large biobank studies. However, their utility in clinical cohorts remains unclear.

We studied a clinical HCM cohort from Canada, Italy, the Netherlands and Spain, comprising 6,111 individuals with HCM and/or carrying an HCMrv. An ancestry-adjusted PGS, derived from the largest HCM genome-wide association study, was calculated for all individuals and tested for association with HCM penetrance, maximal left ventricular wall thickness (MLVWT) and major adverse clinical events (MACE).

Among 1,667 relatives carrying an HCMrv (age at last follow-up 47 ± 19; 49% females), the PGS was associated with HCM diagnosis (OR 1.6 per SD increase in PGS; 95% CI: 1.4-1.8). Male sex and hypertension also independently increased penetrance by 3-fold and 2-fold, respectively. The PGS was predictive across genetic subgroups, including pathogenic MYH7, truncating MYBPC3, and intermediate-effect variant carriers (Figure). In 4,949 affected individuals (age at diagnosis 48 ± 17; 33% female; 49% HCMrv carriers), each SD increase in PGS was associated with a 0.5 mm increase in MLVWT (95% CI: 0.3-0.6), and a 12% increase in lifetime risk of MACE (HR 1.12, 95% CI: 1.06-1.18).

PGS assessment may enhance risk stratification and personalize monitoring strategies—guiding the timing, frequency, and scope of clinical evaluations in both genetically predisposed individuals and patients with manifest HCM.



23. SUDDEN DEATH WITH (ALMOST) NO STRUCTURAL HEART DISEASE

Márquez Camas, Paloma (1); Robles Mezcua, Ainhoa (2); Jiménez Rubio, Clara (2); Pérez Cabeza, Alejandro (2); Díaz Expósito, Arancha (2); García Pinilla, José Manuel (2)

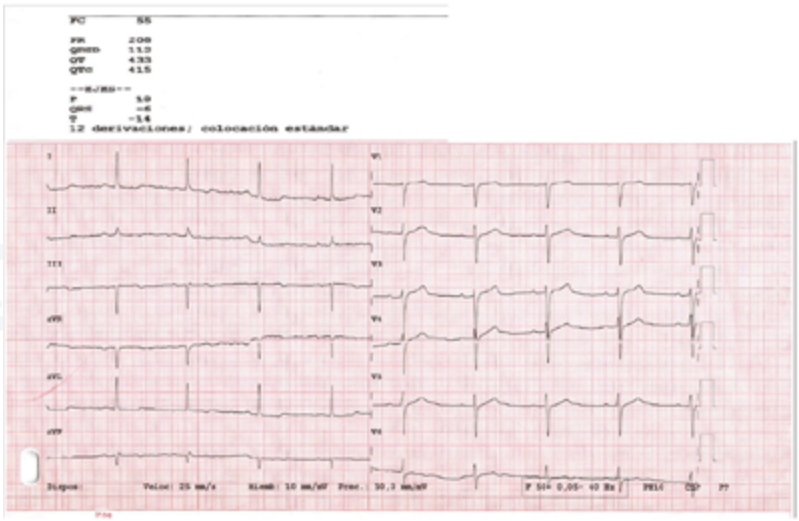
(1)H. Santa Ana; (2)H. Virgen de la Victoria

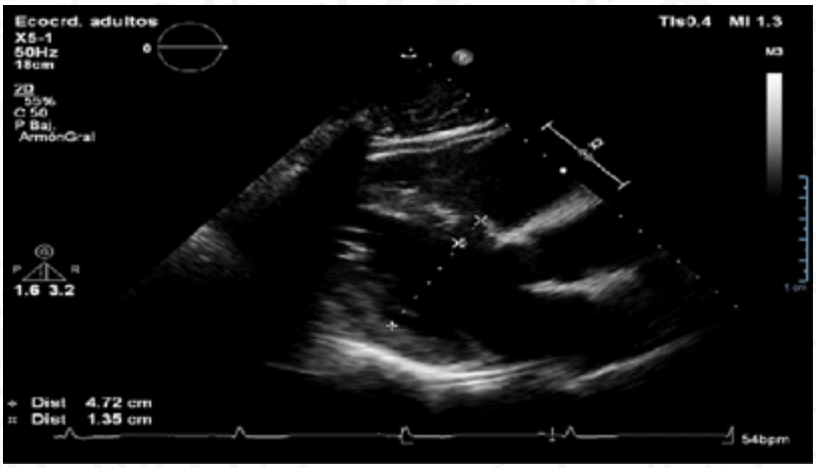
We present the case of a 67-year-old man with a history of hypertension, diabetes, and dyslipidemia who experienced a sudden syncope without prodromes while at a bar. Immediate assistance was provided, and emergency services identified ventricular fibrillation as the arrest rhythm, with successful defibrillation and return to sinus rhythm.

He was transferred to our center, where coronary angiography showed no significant lesions. He remained stable in the ICU without need for intubation or recurrence of arrhythmias. Further evaluation, including echocardiogram and cardiac MRI, revealed only mild left ventricular hypertrophy and left atrial dilatation. ECG showed anterior QS complexes, normal QTc, and no repolarization abnormalities. Continuous telemetry and 48-hour Holter monitoring were unremarkable.

Despite cardiovascular risk factors and signs suggestive of prior ischemia, acute coronary syndrome was ruled out. An implantable cardioverter-defibrillator (ICD) was placed for secondary prevention, and a genetic study was requested. Results confirmed a pathogenic variant in the **TNNT2** gene, associated with hypertrophic cardiomyopathy (HCM).

Upon receiving the results of this genetic study, it has been possible to reach a definitive diagnosis of the patient, this pathogenic variant is associated with the development of HCM, with incomplete penetrance and late expressivity. In these cases the carriers present a not very severe phenotype, but with severe and early fibrosis and myofibrillar disorganization, even with mild degrees of ventricular hypertrophy, being the cause of the dissociation between the degree of hypertrophy and the risk of ventricular arrhythmias. During follow-up, we completed the family history and initiated screening of at-risk relativ





24. CLINICAL CHARACTERISTICS AND OUTCOMES OF GENE ELUSIVE CHILDHOOD ONSET HYPERTROPHIC CARDIOMYOPATHY

Fico, Vera (1); Bonanni, Francesca (1); Macpherson, Nina (2); Field, Ella (2); Cervi, Elena (2); Norrish, Gabrielle (2); Kaski, Juan Pablo (2)

(1)Meyer Children's Hospital IRCCS, 50139 Florence, Italy.; (2)Centre for Inherited Cardiovascular Diseases, Department of Cardiology, Great Ormond Street Hospital, London, United Kingdom. Institute of Cardiovascular Sciences, University College London, London, United Kingdom.

Background: The yield of genetic testing for sarcomeric variants is high in childhood hypertrophic cardiomyopathy (HCM) but genetic testing is inconclusive or negative in 40-60.Adults with gene elusive disease are typically older at presentation with milder disease and better outcomes.The characteristics and natural history of childhood gene-elusive disease is unknown.

Objectives: To describe the clinical phenotype and outcomes of gene elusive childhood HCM .

Methods: Retrospective single centre study of HCM patients ≤ 18 Years classified as Sarc+ (pathogenic/likely pathogenic sarcomeric variant) or Sarc−(variant of unknown significance/no variants identified) following genetic testing.Outcomes included all-cause mortality or arrhythmic event.

Results: Of 259 HCM patients undergoing genetictesting,79 (30.5%) were classified as Sarc−.Compared to Sarc+ patients, Sarc− were younger at diagnosis (2 vs 9 years, p=0.006), more commonly the familial proband (72.2% vs 37.8%, p<0.001) and more often diagnosed incidentally (53.2% vs 20.6%, p<0.001). The cardiac phenotype differed with Sarc- patients more frequently having concentric hypertrophy (22.8% vs 12.2%, p<0.001) and obstructive disease (32.9% vs 14.4%, p<0.001). Over a median follow up of 14 [8-17] years, 13 (16.5%) expereinced an arrhythmic event (cardiac arrest, n=5, appropriate ICD

therapy n=5,sudden death (SCD) (n=3) and 8 (10.1%) died(Unknown 3(3.8%),SCD 2(2.55%),Heart Failure 2(2.5%),Non-cardiovascular Death 1(1.3%)).The incidence of mortality or arrhythmic outcomes did not significantly differ between Sarc– and Sarc+ groups (all p>0.05).

Conclusions: Gene elusive paediatric HCM patients presents at a young age without a family history.Despite differences in clinical phenotype, outcomes are not significantly different compared to sarcomeric disease.

25. WHOLE GENOME SEQUENCING AS EXTENSION OF THE ANALYSIS IN HYPERTROPHIC CARDIOMYOPATHY?

Sánchez-carmona, E (1); Blanco-verea, A (1); Ramos-luis, E (3); Gil, R (1); álvarez-barredo, M (4); López-abel, B (5); Sobrino, B (6); Walsh, R (7); Bezzina, Cr (7); Gonzale-juanatey, Jr (8); Carracedo, A (9); Brion, M (1)

(1)Xenética Cardiovascular, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Spain.; (3)Fundación Pública Galega de Medicina Xenómica (FPGMX), Santiago de Compostela, Spain; Unidade de Cardiopatías Familiares. Servizo de Cardioloxía, Hospital Clínico Universitario de Santiago de Compostela, Spain.; (4)Unidade de Cardiopatías Familiares. Servizo de Cardioloxía, Hospital Clínico Universitario de Santiago de Compostela, Spain; Servizo de Cardioloxía, Hospital Clínico Universitario de Santiago de Compostela, Spain; CIBERCV; (5)Unidade de Cardiopatías Familiares. Servizo de Cardioloxía, Hospital Clínico Universitario de Santiago de Compostela, Spain; Servizo de Pediatría, Hospital Clínico Universitario de Santiago de Compostela, Spain; (6)Fundación Pública Galega de Medicina Xenómica (FPGMX), Santiago de Compostela, Spain; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III (ISCIII), Spain.; (7)Department of Experimental Cardiology, Amsterdam Cardiovascular Sciences, University of Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands; (8)Servizo de Cardioloxía, Hospital Clínico Universitario de Santiago de Compostela, Spain; Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III (ISCIII), Spain.; (9)Fundación Pública Galega de Medicina Xenómica (FPGMX), Santiago de Compostela, Spain; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III (ISCIII), Spain; (10)Xenética Cardiovascular, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Spain; Unidade de Cardiopatías Familiares. Servizo de Cardioloxía, Hospital Clínico Universitario de Santiago de Compostela, Spain.; CIBERCV

Hypertrophic cardiomyopathy (HCM) is the second most prevalent cardiomyopathy (CM) and 2023 ESC Guidelines for the management of CM recommend sequencing robustly associated genes as a routine first-line test. Similarly, guidelines indicate an extended analysis for unsolved cases with high suspicion of a Mendelian cause.

This study starts from 26 HCM unsolved probands for a previous panel of genes associated with CM, that were selected for whole genome sequencing (WGS) based on a strong personal or familial history suggestive of a Mendelian cause. After detection and annotation processes, rare (likely) pathogenic single nucleotides variants for VarSome, ClinVar or InterVar, in 1999 putative cardiac related genes were filtered and evaluated with ACMG guidelines.

As a result, likely casual heterozygous variants were detected in 2 patients. One stop gained variant in ALPK3 for which the dominant association with HCM has been recently updated by ClinGen. The second proband carries a loss of function variant in SVIL, a type of variant that, recently, has been associated with an increased risk of HCM.

In addition, heterozygous pathogenic variants in genes with recessive inheritance and several variants of uncertain significance with possible HCM association were also detected.

These results emphasize the importance of reevaluating the first genetic test before extending the analysis, the advances of technologies and the emerging knowledge could elucidate an unsolved case. That reanalysis, together with the implementation of WGS, showed a putative positive diagnosis in approximately 8% of cases and identified new candidate genes and variants potentially amenable to further investigations.

26. SUDDEN DEATH IN HYPERTROPHIC CARDIOMYOPATHY: FEATURES IN A MULTIDISCIPLINARY, MULTICENTRIC STUDY.

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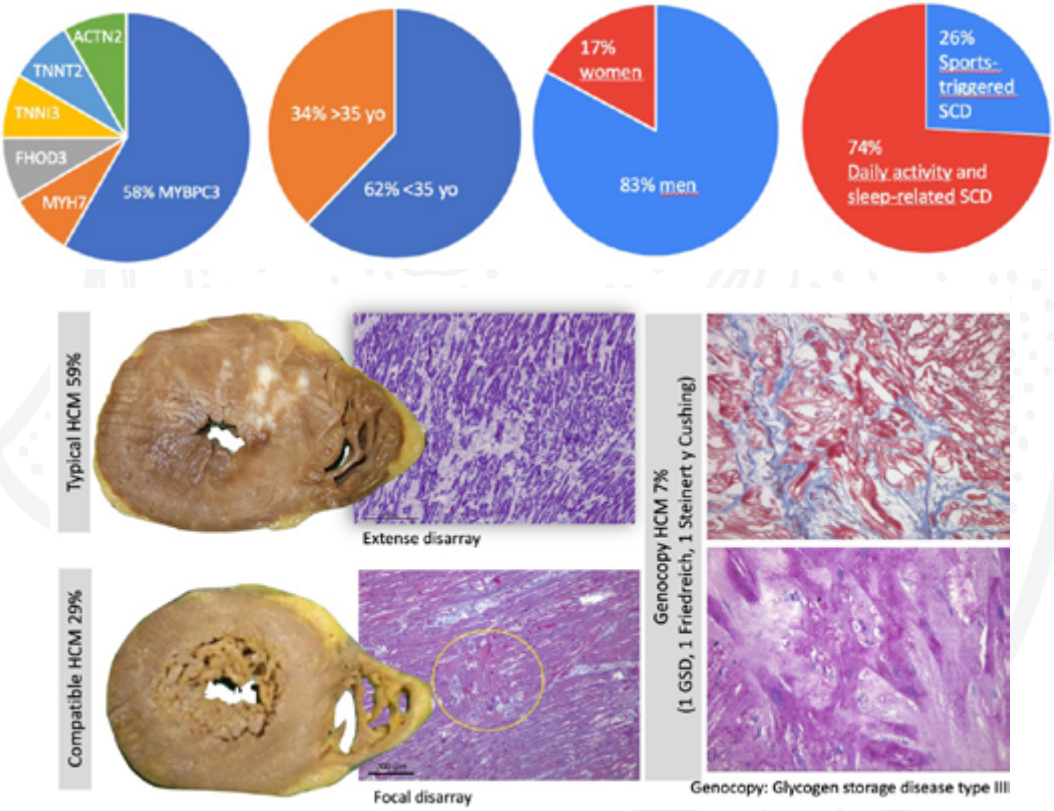
Background: Hypertrophic cardiomyopathy (HCM) is a leading cause of sudden cardiac death (SCD) in the young. This study analyzes pathological and genetic findings in SCD-HCM cases using a multidisciplinary forensic approach.

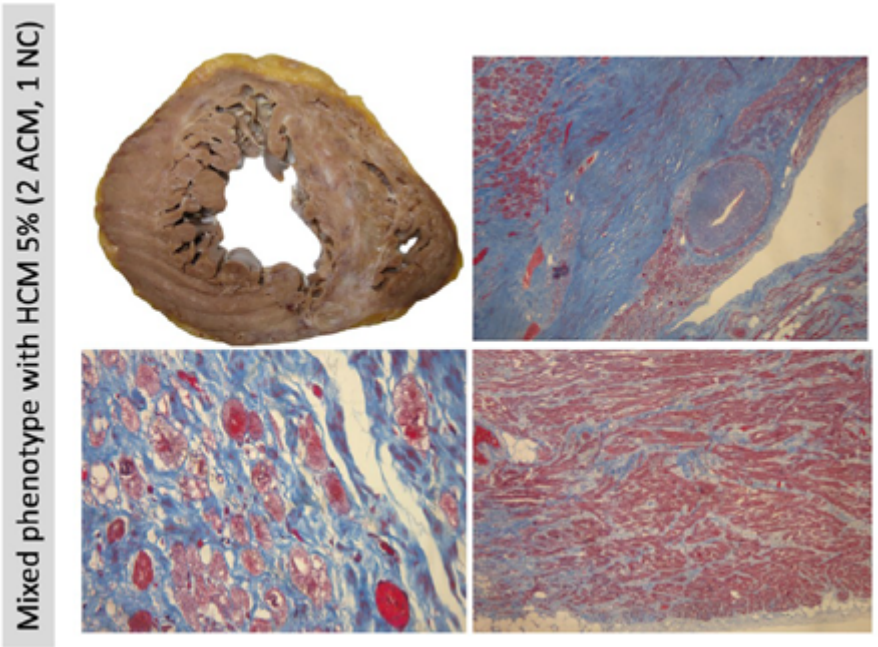
Methods: We retrospectively reviewed autopsies from 2008–2024 with SCD attributed to HCM or compatible conditions. Data included clinical history, autopsy, histology, toxicology, genetic testing, and family screening.

Results: 58 cases were included (median age 50; 83% male). Phenotypes included typical HCM (59%), compatible HCM (29%), mixed (5%), and genocopies (7%). Overweight/obesity was present in 63%. SCD occurred during routine activity (60%), sports (26%), or sleep (14%). Heart weight was increased in 79%; asymmetric LV hypertrophy in 93%. Myocardial disarray appeared in all cases; interstitial fibrosis (93%) and scarring (53%) were frequent. Small vessel disease was present in 85%. Toxicology was positive in 12%. Genetic testing (22 cases) showed pathogenic or likely pathogenic variants in 59%, mostly in MYBPC3. Family screening (107 relatives) identified 26 carriers, 20 with phenotype.

Conclusions: SCD in HCM can occur beyond the young adult age; 62% were over 35 years, suggesting that age should not be a limiting factor for multidisciplinary approach. Despite being an autosomic dominant trait, HCM SCD affected predominantly men (83%), as in other SCD causes. Obesity, though frequent clinically, was present in only 22%, questioning its presumed link to SCD in HCM. Postmortem findings highlight the value of multidisciplinary collaboration in understanding HCM-related SCD.

Keywords: hypertrophic cardiomyopathy, sudden cardiac death, forensic pathology, genetic testing, postmortem study.





27. EXPERIENCE WITH MAVACAMTEN IN OBSTRUCTIVE HYPERTROPHIC CARDIOPYOPATHY IN A NATIONAL REFERRAL CENTER

Alen Andres, Alberto (1); Fernandez Garcia, Maria (1); Nieves Ureña, Beatriz (1); Ptazinksy, Raul (1); Álvarez Gato, Andres (1); Sanchez Suarez, Manuel (1); Martinez Salgado, Ines (1); Suarez, Daniel (1); Salgado Barquinero, Maria (1); Rodriguez Reguero, Jose Julian (1); Lorca, Rebeca (1)

(1) Hospital Universitario Central de Asturias

Background: In Obstructive Hypertrophic cardiomyopathy (OHCM), symptom presence correlates with worse prognosis. Despite medical therapy, up to 50% of patients remain symptomatic and/or exhibit significant LVOT obstruction. Septal reduction therapies such as surgical myectomy or alcohol septal ablation are in those cases requiered—procedures carrying risks even in experienced centers. European cardiomyopathies guidelines have incorporated myosin ATPase inhibitors, such as mavacamten, as a novel alternative therapy.

Methods: A retrospective, single-center study was conducted including patients with HOCM treated with mavacamten. Clinical and demographic data were collected at baseline and during follow-up. Adherence and tolerance to therapy were assessed. Follow-up occurred at 4, 8, and 12 weeks, with extended data at 18 and 24 weeks for some patients.

Results: 8 patients were included. All started mavacamten at 5 mg/day. None required dose reduction due to LVEF deterioration, and the drug was well tolerated without significant adverse effects. All patients experienced marked clinical and functional improvement, with a reduction in LVOT gradients and NT-proBNP levels. Notably, all reached NYHA class I-II, and none required invasive septal reduction therapy (see table). The cohort was clinically and genetically heterogeneous, supporting the efficacy of the new treatment.

Conclusions: This case series demonstrates that mavacamten is a safe and effective non-invasive treatment option for symptomatic HOCM patients in a real-world setting. The observed improvements in clinical status, biomarkers, and echocardiographic parameters align with findings from clinical trials. Mavacamten may reduce the need for invasive septal reduction in appropriately selected patients.

Table

P	Sex	Age	Genetic test	Baseline situation			After treatment		
				FC (NYHA)	LVOTO (mmHg) Rest (Valsalva/ stress)	NTproBNP (pg/mL)	FC (NYHA)	LVOTO (mmHg) Rest (Valsalva/ stress)	NTproBNP (pg/mL)
1	F	51	*MYH7* p.Arg663Cys	III/IV	90 (90)	1178	I/IV	20	144
2	M	47	Negative	II-III/IV	20 (61)	-	I/IV	No	102
3	F	64	*MYL3* p.Leu137Pro	III/IV	53 (90)	2939	I/IV	20 (47)	657
4	F	54	*TNNC1* p.A8V	III/IV	36 (70)	1320	I/IV	No	682
5	M	58	Negative	II-III/IV	48 (84)	328	I-II/IV	No	138
6	F	81	*MYH7* p.Arg870His	III/IV	30(85)	6171	I-II/IV	No	1577
7	F	79	Negative	III/IV	30 (58)	453	II/IV	No	74
8	M	76	Negative	II-III/IV	20 (40)	711	II/IV	No	110

Patients data before and after the treatment. M: male; F: female; FC: functional class; LVOTO: left ventricular outflow tract obstruction.

28. NATURAL HISTORY AND CLINICAL OUTCOMES OF CHILDHOOD-ONSET NON-OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

Macpherson, Nina (1); Field, Ella (1); Barnes, Annabelle (1); Cervi, Elena (1); Norrish, Gabrielle (1); Kaski, Juan Pablo (1)

(1)Great Ormand Street Hospital, University College London

Background: Hypertrophic cardiomyopathy (HCM) causes morbidity and mortality across age groups. Although most children with HCM have non-obstructive HCM (nHCM), data on its pathophysiology and outcomes remain limited. This study investigated clinical presentation and natural history of paediatric nHCM.

Methods: Retrospective clinical data, including demographics, baseline and follow-up cardiac investigations and clinical outcomes from patients diagnosed with non-syndromic HCM <18 years at Great Ormond Street Hospital (1989-2024) were collected and analysed.

Results: Of 324 patients, 196 (60.5%) had nHCM [mean age 8yrs ± 6.2] vs 128 (39.5%) with HOCM [mean age 4yrs ± 5.4]. nHCM patients were more often referred via family screening (38.5% vs 16.1%, p=0.001), less frequently probands (47.3% vs 62.3%, p=0.001), and had lower median LVMWT z-scores at baseline (8.4 vs 11.8; p<0.001) and follow-up (7.8 vs 16.2; p<0.001).

At follow-up, fewer nHCM patients were medicated (44.4% vs 81.5%, p<0.001), but Class III antiarrhythmic use was higher (14.9% vs 4.0%, p=0.01). Chest pain was more prevalent in nHCM (52.6% vs 25.0%, p=0.012), though most remained NYHA I.

Life-threatening arrhythmic events were more frequent in nHCM (29.0% vs 13.1%, p=0.01), with higher rate of appropriate ICD shocks (9.7% vs 3.3%, p=0.02). ICDs were more commonly implanted for secondary prevention in nHCM (22.2% vs 6.6%, p=0.014).

Conclusions: Paediatric nHCM carries higher risk of life-threatening arrhythmias, despite milder cardiac phenotype and fewer symptoms overall. Symptomatic non-obstructive patients more frequently report chest pain and receive class III antiarrhythmic medications. Early treatment may prevent disease-related complications in children with severe, early-onset nHCM.

29. HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY (HOCM) AND LONG QT SYNDROME (LQTS), AN ULTRARE GENOCOPY CAUSED BY A NAA10 VARIANT: A FAMILIAL CASE REPORT.

Company Langa, Mireia (1); Ruiz, Eladio (2); Cano, Ana (2); Fernández-tudela, Belén (2); Peris, Franc (3); Rad García, Guillermo (1); Astudillo Sacoto, Ana Elisa (1); Murillo Varona, Guillem (1); Beltrán Martínez, Susana (1); Gil Molina, Marta (1); Domingo, Diana (4); Martínez-dolz, Luis (5); Zorio, Esther (6)

(1)Cardiology Department at Hospital Universitario y Politécnico La Fe, Valencia, Spain; (2)Pediatric Cardiology, Hospital Universitario y Politécnico La Fe, Valencia, Spain; (3)Hospital de Elda, Alicante, Spain; (4) CAFAMUSME Research Group at the IIS La Fe, Inherited cardiac diseases unit and Cardiology Department at the Hospital Universitario y Politécnico La Fe , Valencia, Spain.; (5)Cardiology Department at the Hospital Universitario y Politécnico La Fe , Valencia, Spain, Medicine Department at the Medicine School of the Universitat de Valènica, Valencia, Spain, CIBERCV, Madrid, Spain; (6)CAFAMUSME Research Group at the IIS La Fe, Inherited cardiac diseases unit and Cardiology Department at the Hospital Universitario y Politécnico La Fe , Valencia, Spain, Medicine Department at the Medicine School of the Universitat de Valènica, Valencia

Introduction: The NAA10 gene, located on the X chromosome, encodes the catalytic subunit of the N-terminal acetyltransferase A complex, essential for post-translational modification of cytosolic proteins. Pathogenic NAA10 variants cause a broad clinical spectrum, including Ogden syndrome, characterized by neurodevelopmental delay and cardiac abnormalities such as Long QT syndrome (LQTS) and hypertrophic obstructive cardiomyopathy (HOCM).

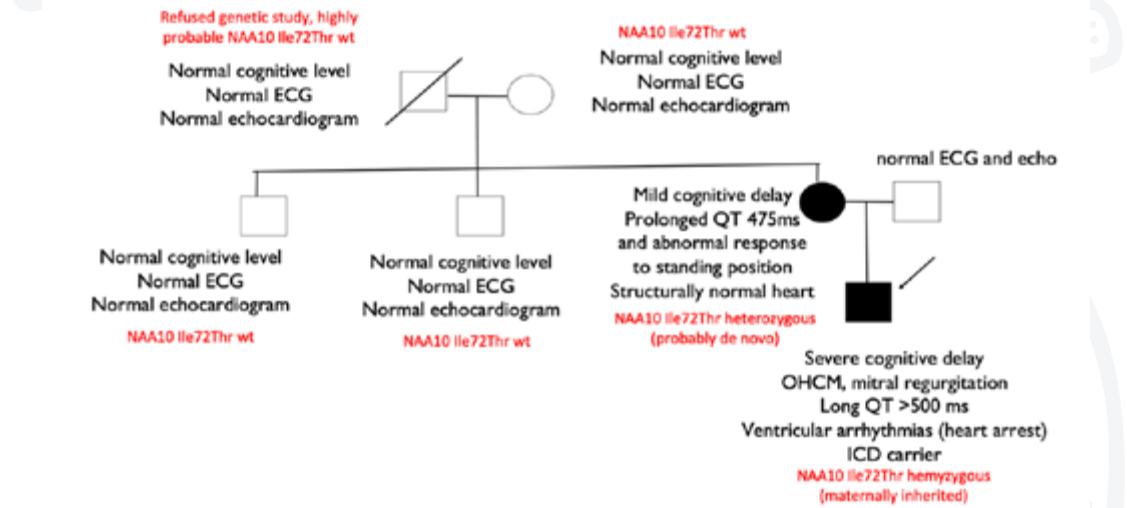
Case Report: We report two related carriers of the likely pathogenic NAA10 c.215T>C (p.Ile72Thr) variant.

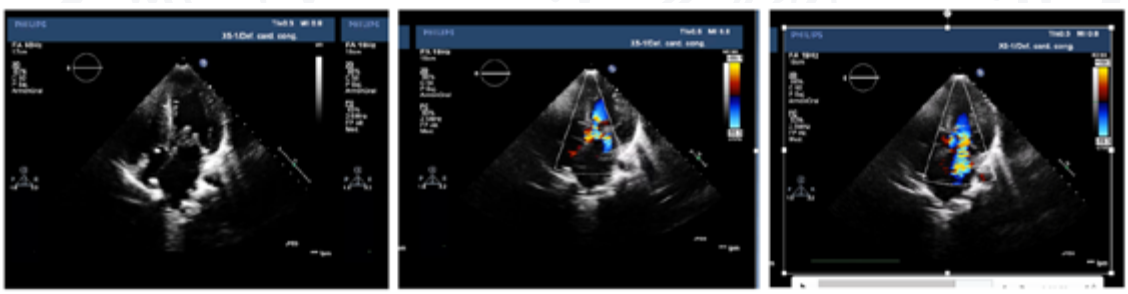
The proband, a hemizygous male, was first evaluated at 11 months for a heart murmur and was diagnosed with HOCM and LQTS. Propranolol was initiated. He also showed neurodevelopmental delay (at 8 years functioning at a 4-year-old level).

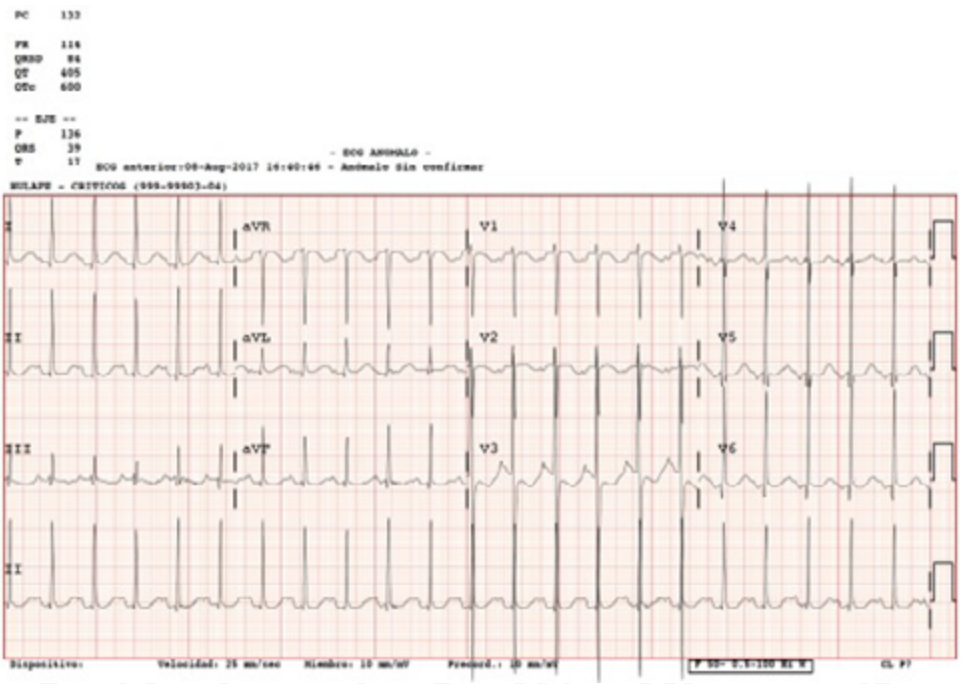
At 9 years, he suffered multiple torsades de pointes episodes with QTc up to 740 ms. Echocardiography at 8 years revealed asymmetric septal hypertrophy (16 mm), systolic anterior motion of the mitral leaflet causing left ventricular outflow tract obstruction (65 mmHg gradient), moderate mitral regurgitation, and focal myocardial fibrosis. Treatment included increased propranolol and ICD implantation, with no further cardiac events by 17 years.

His mother, a heterozygous carrier, exhibited a mild phenotype with QTc intervals of 470 ms supine, 494 ms standing, and 450 ms recovery during exercise. She showed no ventricular hypertrophy and had mild cognitive impairment.

Discussion: NAA10 mutations may cause complex phenotypes with structural and electrophysiological cardiac abnormalities. The coexistence of HOCM and LQTS in males should prompt consideration of NAA10-related disease. Further clinical data are needed to guide management of this ultrarare condition.







30. MEXICAN REGISTRY OF CARDIOMYOPATHIES (REMEMI) BASELINES DATA, DIAGNOSIS AND TREATMENT STRATEGIES IN MEXICO.

Berrios Barcenas, Enrique Alexander (1); Escalante Seyffert, Maria Cecilia (1)

(1)Instituto Nacional de Cardiología Ignacio Chávez

Background: The Mexican Registry of Cardiomyopathies (REMEMI) is a contemporary, prospective, observational, and national registry that includes consecutive patients with all four types of cardiomyopathies: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). We are reporting the clinical and therapeutic baseline characteristics of this patient group.

Methods and results: A total of 1,026 patients from most states in the Mexican Republic (19) were included, with 494 corresponding to DCM, 490 to HCM, 35 to RCM, and 7 to ARVC. We found significant differences among the various cardiomyopathy phenotypes ($p < 0.05$) in terms of coexistence with diabetes, the use of implantable defibrillators, the presence of ventricular tachycardia, and NYHA functional class ≥ 1. There were no significant differences in age and predominant gender among each group. When analyzing by phenotype, we found that patients with HCM have limited use of essential diagnostic methods, such as magnetic resonance imaging, Holter monitoring, and genetic testing in patients and their relatives.

Conclusion: The search for contemporary information through observational registries in Mexico presents a valuable opportunity to understand the characteristics of the methods employed in the study and treatment of diseases such as cardiomyopathies by Mexican physicians. It can provide us with insights for the implementation of management guidelines and strategies for disseminating findings, thereby enhancin healthcare in our country.

VARIABLES	Total (N = 1026)	HCM (n = 490)	DCM (n = 494)	RCM (n = 35)	ARCV (n = 7)	P
Male sex (n, %)	607 (59.2)	271 (55.2)	310 (62.8)	20 (57.1)	6 (85.7)	0.051
Age (y.o.)	57.5 ± 16.9	56.7 ± 17.8	58.3 ± 16.2	61.6 ± 13.7	41 ± 9.5	0.01
Diabetes (n, %)	100 (9.7)	83 (16.9)	6 (1.4)	11 (34.4)	0	<0.001
Hypertension (n, %)	312 (30.4)	194 (39.6)	104 (24.1)	14 (42.4)	0	<0.001
ICD (n, %)	181 (17.6)	44 (10.7)	130 (31.3)	4 (11.8)	3 (42.9)	<0.001
VT (n, %)	113 (11)	36 (7.3)	64 (12.9)	6 (17.1)	7 (100)	<0.001
AF (n, %)	182 (17.7)	98 (20)	70 (14.1)	13 (37.1)	1 (14)	0.07
NYHA ≥ 2	167 (16.2)	105 (21.4)	38 (7.6)	23 (65)	1 (14)	<0.001

DCM: Dilated cardiomyopathy, HCM: hypertrophic cardiomyopathy, RCM: restrictive cardiomyopathy, ARCV: arrhythmogenic right ventricular cardiomyopathy. ICD: Implantable cardiodesfibrilator, VT: ventricular tachycardia, AF: atrial fibrillation, NYHA: New York Heart Association.

31. TAMIZAJE DE ENFERMEDAD DE FABRY EN PACIENTES MEXICANOS CON MIOCARDIOPATIA HIPERTRÓFICA.

Berrios Barcenas, Enrique Alexander (1); Escalante Seyffert, María Cecilia (1)

(1)Instituto Nacional de Cardiología Ignacio Chávez

La enfermedad de Fabry es una enfermdad lisosomal causada por mutaciones del gen GLA el cual es responsable de la síntesis de alfagalactosidasa, enzima necesaria para degradar y eliminar esfingolípidos en el organismo. La acumulación de este sustrato produce manifestaciones diversas, incluyendo daño cardíaco, cuya manifestación más frecuente es la hipertrofia ventricular. Estudios en otras poblaciones demuestran prevalencia de enfermad de Fabry de 0.5-1% en pacientes con Miocardiopatía hipertrófica, sin embargo en la actualidad este no se realiza de forma rutinaria. El objetivo del estudio es determinar la prevalencia de enfermedad de Fabry en pacientes con Miocardiopatía hipertrófica.

32. GENETIC CHARACTERIZATION OF FELINE HYPERTROPHIC CARDIOMYOPATHY WITH THE USE OF HIGH-TROUGHPUT SEQUENCING.

Gil Ortuño, Cristina (1); Sebastián Marcos, Patricia (2); Nicolás Rocamora, Elisa (1); Gimeno Blanes, Gimeno Blanes (3); Fernández Del Palacio, Maria Josefa (2); Sabater Molina, María (4)

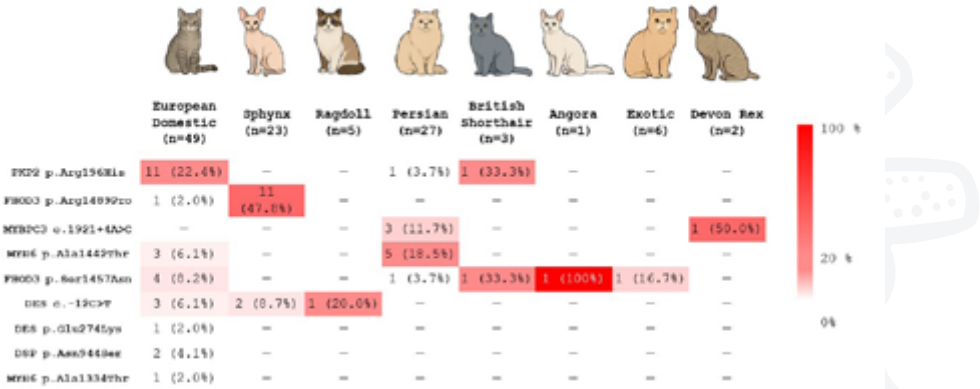
(1)Laboratorio de Cardiogenética (IMIB). Universidad de Murcia; (2)Servicio de Cardiología. Hospital Veterinario. Universidad de Murcia; (3)Unidad CSUR ERN Cardiopatias Familiares. Hospital Universitario Virgen Arrixaca. Murcia. Spain; (4)Laboratorio de Cardiogenética (IMIB). Departamento de Medicina Legal. Universidad de Murcia

Introduction: HCM is the most common heart disease in cats and a leading cause of morbidity and mortality affecting between 10-15% of cats. The aim of the study was to identify genetic variants in a cohort of cats diagnosed of HCM by using of NGS sequencing.

Methods: 76 HCM cats (6.5±4.1 years old, 46 (60.5%) males, 30 (39.5%) females) from 11 breeds were included. 58 cats (mean age 5.6 ± 3.6 years old, 31 (53.4%) males, 27 (46.6%) females) with normal wall thickness were selected as controls. Main cohort consisted of 48 cats (35 affected and 13 controls) that underwent NGS sequencing with a 27 genes panel. To confirm these findings, we expanded the study with an additional 86 cats in which 24 selected variants were analyzed by Sanger sequencing. In total, 134 cats were examined (76 affected and 58 controls).

Results: 50% of the HCM cats were carriers of 1 or more relevant variants. 11 (14.5%) cats carried 2 variants and 1 (1.3%) cat carried 3 variants. 9 genetic novel variants were classified as relevant in the MYBPC3, MYH6, FHOD3, DES, DSP and PKP2 genes. An additional variant in DSP not meeting selection criteria was significantly more prevalent in affected animals and was also included as possible modulator. Some genetic variants were pure-breed specific.

Conclusion: Relevant genetic variants affecting either sarcomeric or desmosomal genes were found in cats by a massive sequencing panel. The percentage of cats with two or more variants was high, suggesting an oligogenic cause.



33. DIFFERENCES IN HCM PHENOTYPES: SUB-ANALYSIS OF MEXICAN REGISTRY OF CARDIOMYOPATHIES

Berrios Barcenas, Enrique Alexander (1); Escalante Seyffert, Maria Cecilia (1)

(1)Instituto Nacional de Cardiología Ignacio Chávez

Background: Hypertrophic Cardiomyopathy (HCM) is the most common genetic cardiovascular disease, characterized by an increased thickness of the ventricular walls without another explanation. However, in the past few years, different phenotypes have been characterized based on the location of hypertrophy. This study analyzes the difference between the multiple hypertrophic cardiomyopathy phenotypes.

Methods and results: This is a subanalysis of the Mexican Cardiomyopathy Registry that includes 434 patients with HCM, subdivided into three phenotypes: obstructive (O, n=109), non-obstructive (nO, n=273), and midventricular-apical (M/Ap, n=52). The mean age is 56±17 years, with a male predominance (55%). Within the -O- subgroup, a significantly higher occurrence of syncope (22%, p<0.05), a history of surviving sudden cardiac death (5%, p=0.02), implantation of implantable cardioverter-defibrillators (ICDs) (16%, p<0.05), dyspnea (46%, p=0.04), and a longer QRS duration (110 ms, p=0.02) were observed. The M/Ap group exhibited an older age profile (64 years [56-72], p<0.05) and a higher prevalence of coexisting ischemic heart disease (17%, p<0.05). Moreover, no significant differences in interventricular septum thickness were observed between the -O- and -nO- groups (19.4 vs 18 mm, p: NS).

Conclusion: In patients with hypertrophic cardiomyopathy, clinical, morphological, and electrical differences are observed among the O, nO, and M/Ap phenotypes. These differences should be taken into account in the initial evaluation and follow-up of patients, considering hypertrophic cardiomyopathy as a heterogeneous group of presentations.

34. CHARACTERIZATION OF VARIANT MYBPC3-C.772G>A IN A HYPERTROPHIC CARDIOMYOPATHY COHORT: EVIDENCE OF A FOUNDER EFFECT IN MURCIA, SPAIN

Bernabé García, ángel (1); Munteanu, Serena (1); Wagih Gomez, Jesús (1); Júdez Serrano, Ángel (1); Olmo Conesa, Marí Carmen (2); Mustafá Hervas, Fátima (2); Muñoz Esparza, Carmen (2); Gimeno Blanes, Juan Ramón (3); Sabater Molina, María (4)

(1)Cardiogenetic Laboratory. Biomedical Research Institute of Murcia (IMIB), Murcia, Spain.; (3)Inherited Cardiac Disease Unit (CSUR), Virgen de la Arrixaca University Hospital, Murcia, Spain. European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN-Guard Heart), Amsterdam, The Netherlands. Department of Inte; (5)Department of Legal and Forensic Medicine, Faculty of Medicine, University of Murcia, 30110, Murcia, Spain. Cardiogenetic Laboratory, Biomedical Research Institute of Murcia (IMIB), Murcia, Spain. European Reference Network for Rare and Low Prevale

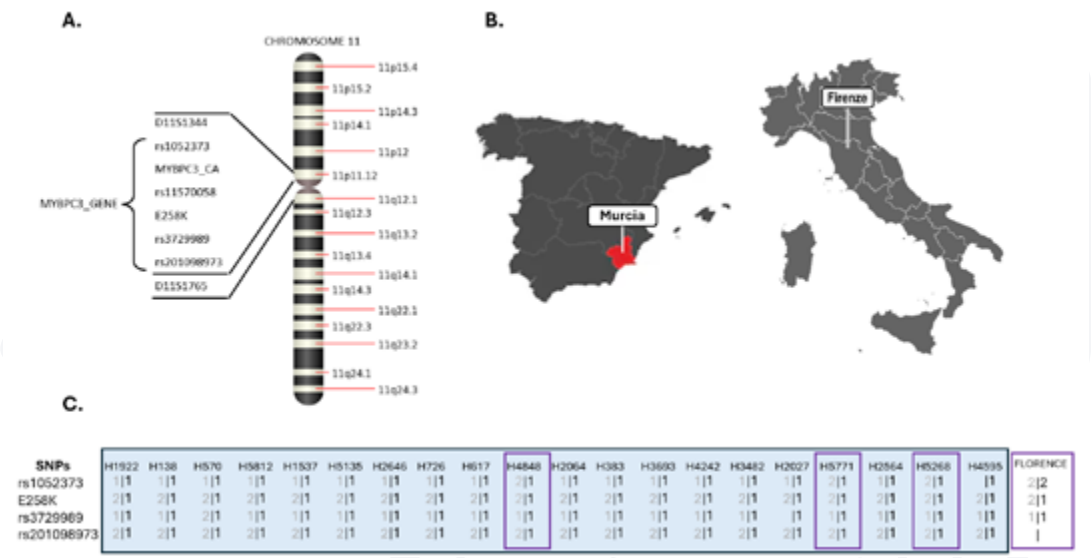
Background: Hypertrophic cardiomyopathy (HCM) is a disease with variable penetrance and clinical expression. The MYBPC3-c.772G>A variant (p.Glu258Lys, E258K) that affects splicing and causes a premature truncation has been identified as a founder variant in the region of Florence (Italy).

Objectives: The aim of the study was to confirm the presence of a founder effect in 20 apparently unrelated families from Murcia carrying the MYBPC3-c.772G>A variant and to determine the possibility of a common ancestor with the Florence families.

Methods: 136 individuals from 20 families from the Region of Murcia relatives from probands carrying the MYBPC3-c.772G>A variant were clinically evaluated with ECG and echocardiogram. 3 SNPs in MYPBC3 gene (rs3729989; rs1052373 and rs201098973) and 3 microsatellite markers STR (D11S1344, MYBPC3_CA and D11S1765) were selected to analyse identified carriers and assess the hypothesis of a founder effect. (Figure 1A and 1B)

Results: Based on the analysis of genetic markers, a shared haplotype was confirmed in 16 families. These results suggest the probability of a founder effect in Murcia region. Preliminary results based on two SNPs shared with the study conducted in Florence show that three families share the same haplotype, suggesting that it is unlikely that the families from Murcia and Florence share a common ancestor (Figure 1C). Further studies are required to confirm these observations.

Conclusions: Based on preliminary results, variant c.772G>A has a founder effect in Murcia. Florence and Murcia series seem to have an independent origin. These findings have important implications for diagnosis and screening strategies.



35. MITRAL VALVE ALTERATIONS IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Berrios Barcenas, Enrique Alexander (1); Escalante Seyffert, Maria Cecilia (1)

(1)Instituto Nacional de Cardiología Ignacio Chávez

Background: Hypertrophic cardiomyopathy (HCM) is one of the most common inherited heart diseases. Its broad morphological spectrum and clinical heterogeneity display diverse underlying pathological mechanisms. Although septal hypertrophy and systolic anterior motion (SAM) are pathophysiological features of the left ventricular outflow tract obstruction (LVOTO) in HCM, structural mitral valve abnormalities can also play a role in this mechanism. This study aims to describe the mitral valve components in HCM patients and its association with obstruction and symptoms.

TABLE 1: Mitral valve alterations between LVOTO and non-LVOTO

	Without LVOTO (n=27)	LVOTO (n=49)	*p* value
Anterior leaflet length (mm)	24 (22, 28)	28 (24, 30)	**0.03**
Posterior leaflet length (mm)	18 (15, 20)	18 (16, 20)	NS
Anterior leaflet thickness (mm)	3.1 (2.1, 4.4)	2.8 (2.4, 3.8)	NS
Posterior leaflet thickness (mm)	2.8 (2.2, 3.6)	3.1 (2.5, 3.6)	NS
Tenting area (cm^2)	1.24 ± 0.5	1.04 ± 0.38	NS
Mitral annulus diastole (mm)	28 (25, 35)	28 (24, 31)	NS
Mitral annulus systole (mm)	23 ± 6.1	21 ± 6.3	NS
Coaptation depth (mm)	0.61 ± 0.21	0.68 ± 0.19	NS
Accessory papillary muscle	20 (74%)	39 (79%)	NS
Accessory chordae tendineae	13 (48%)	30 (61%)	NS
Epicardium-anterior leaflet distance (mm)	12.5 (9, 18)	10 (4, 13)	**0.01**
Systolic anterior movement	2 (7%)	42 (85%)	**<0.001**
Moderate-severa mitral regurgitation	2 (7%)	21 (42%)	**<0.001**
Interventricular septum (mm)	20 (17, 23)	21 (18, 24)	NS

Bold emphasizes the p value <0.05. LVOTO: Left ventricular outflow tract obstruction. NS: Non-significant.

GENERAL INFORMATION

DATES

18th – 19th september 2025

VENUE

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REGISTRATION

Registration fees	Before 1st June 2025	After 1st June 2025
General registration	450 €	500 €
Fellow*	250 €	300 €
Nursery*	250 €	300 €
Streaming**	200 €	200 €

VAT Included

** In order to apply for this rate, it will be necessary to attach a certificate or official document from the entity/institution, signed by the head of service/supervisor.*

*** The streaming registration fee includes live viewing of the sessions and the possibility to watch them on demand from 10 days after the end of the congress until the end of January 2026.*

Registration deadline before the meeting:
Deadline for sending registrations to the technical secretariat is September 12th 2025. After that date registrations will only be accepted at the congress venue.

Cancellation policy

Before 30th June 2025	100% refund
After 1st July 2025	No refund

ACCOMMODATION

HOTEL	ADDRESS	PRICE
HOTEL EUROSTARS ATLÁNTICO**** Tel. 981 22 65 00	Av. Jardines de Méndez Núñez, s/n, 15006 A Coruña	Single: 170 € Doble: 180 €

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