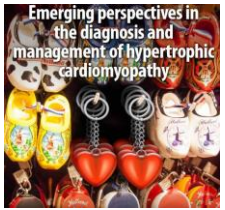
Hypertrophic Cardiomyopathy: Understanding the Condition

Perry Elliott, MD

London, United Kingdom

Emerging perspectives in the diagnosis and management of hypertrophic cardiomyopathy



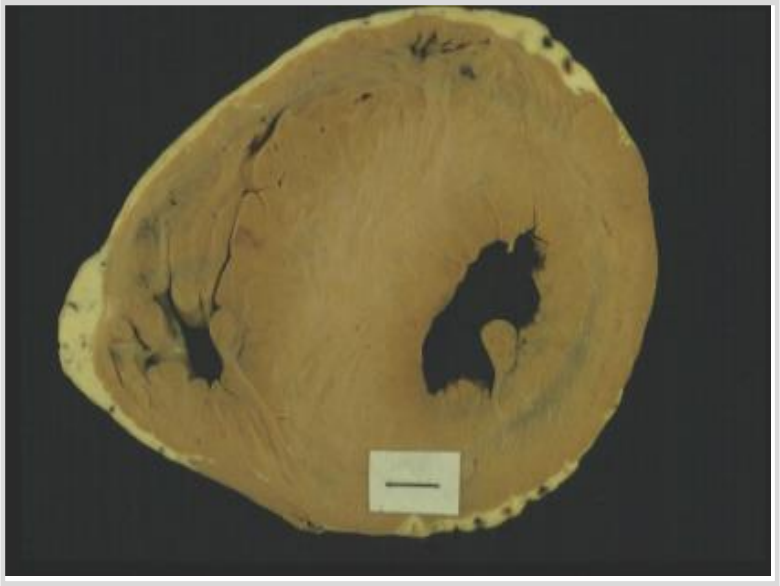
PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION
PACE-CME

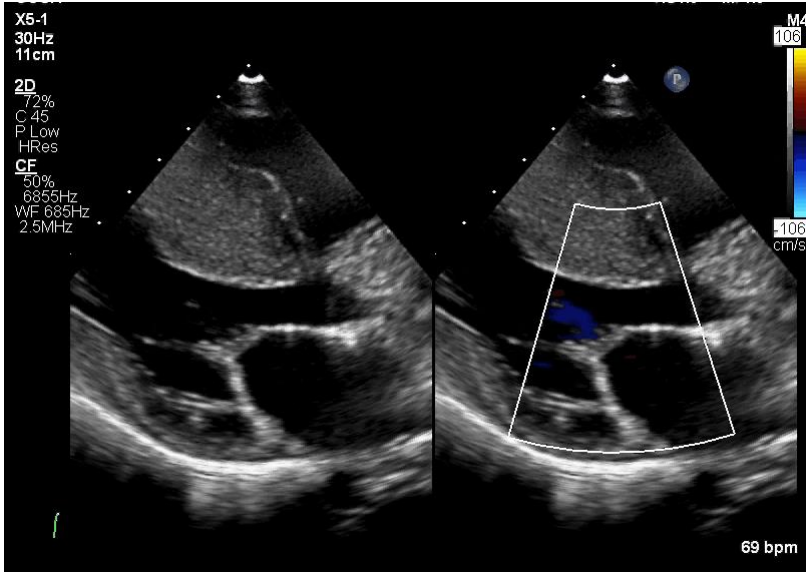
Declaration of interest

Consultancies/Ad Board:

- MyoKardia (BMS)
- Pfizer
- Sanofi-Genzyme
- DinaQor
- Astra Zeneca
- Sarepta
- Freeline

Hypertrophic Cardiomyopathy



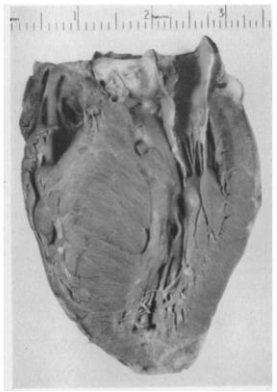


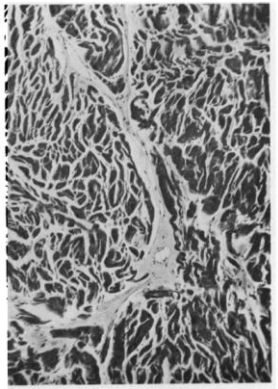
William Harvey
(1654–1720)

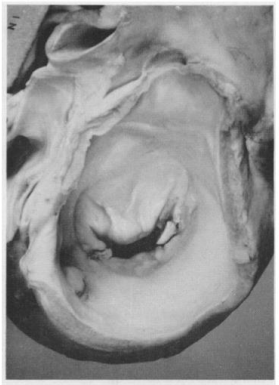
René Laënnec
(1781–1826)

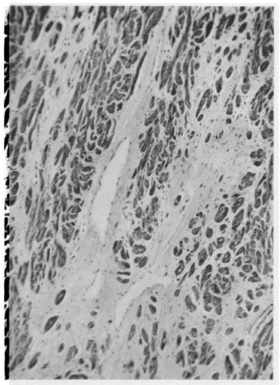
Edmé Félix Alfred Vulpian
1826 –1887)

Donald Teare
1911-1979

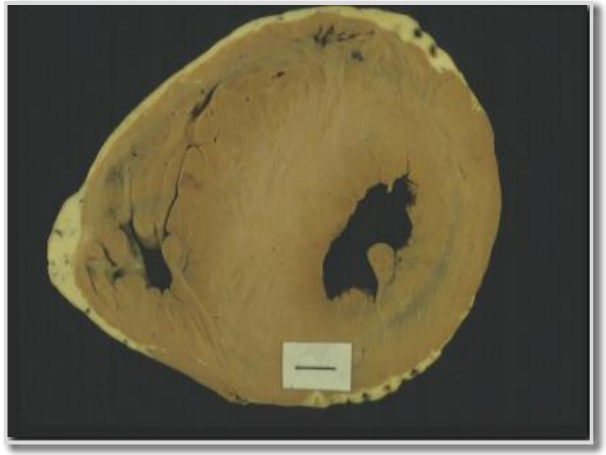


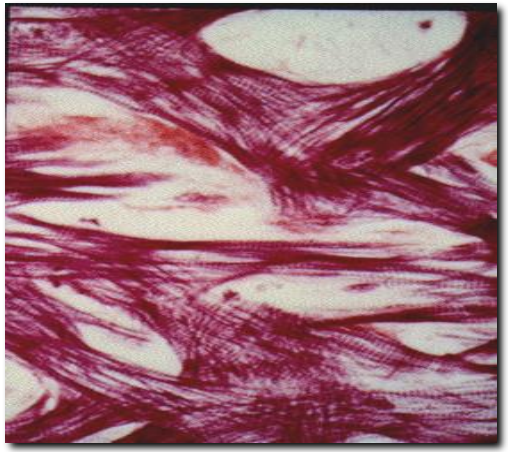


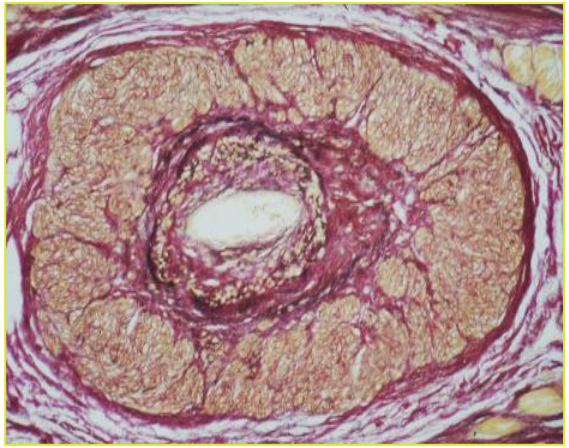




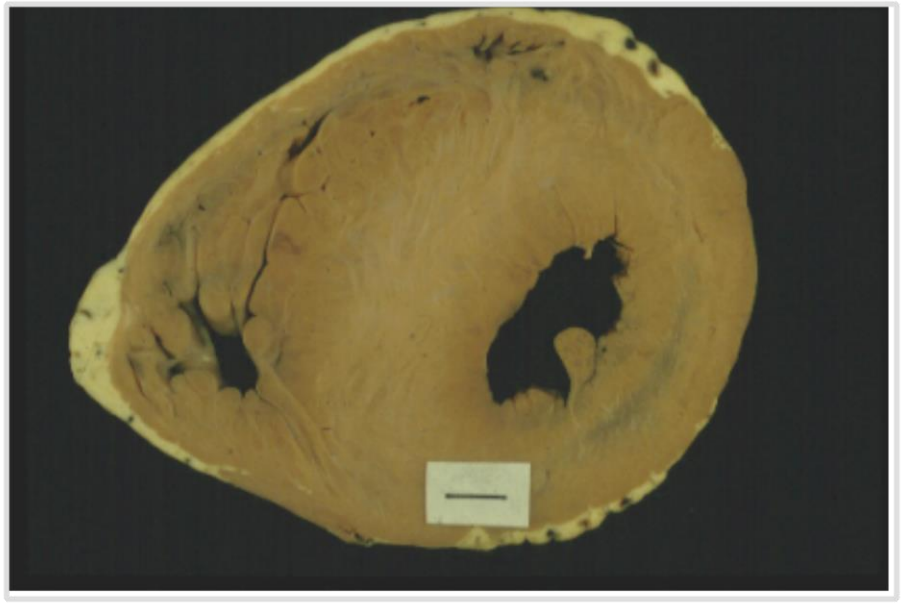
Teare D. Heart 1958;20;1-8







Hypertrophic Cardiomyopathy



Personal data: Prof Elliott

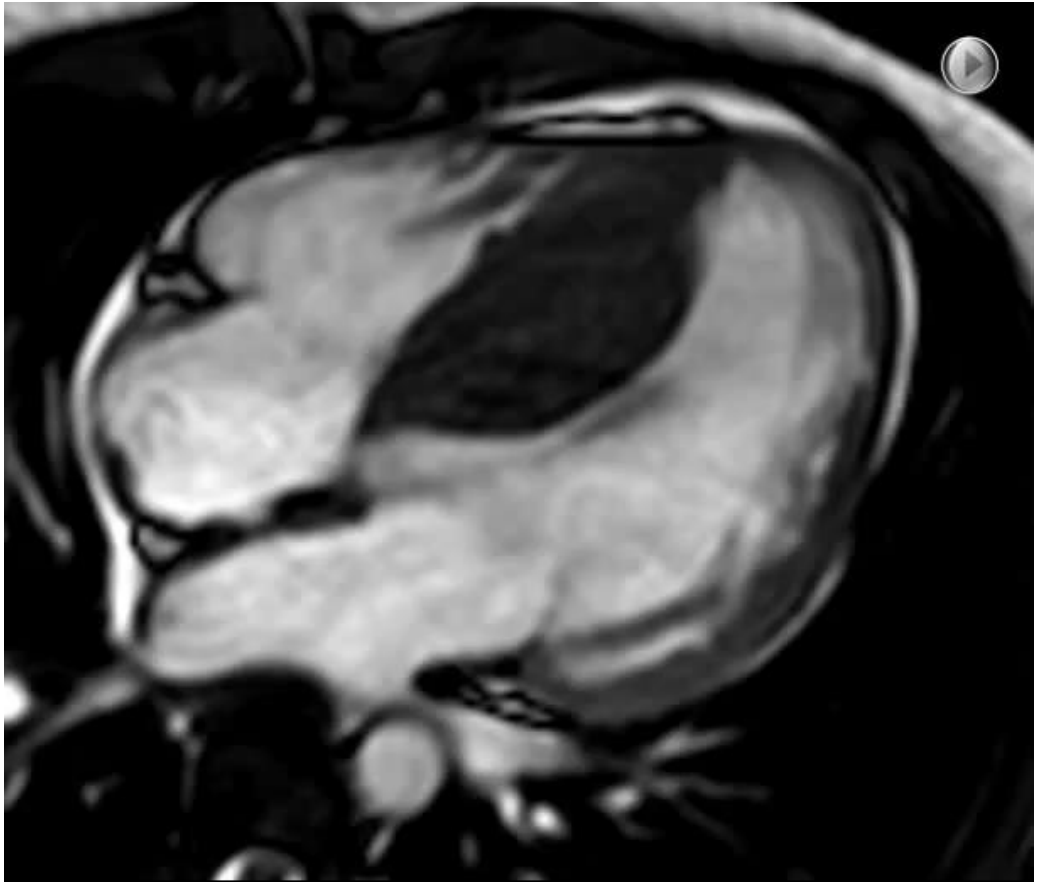
Increased left ventricular wall thickness not solely explained by abnormal loading conditions

ADULTS:

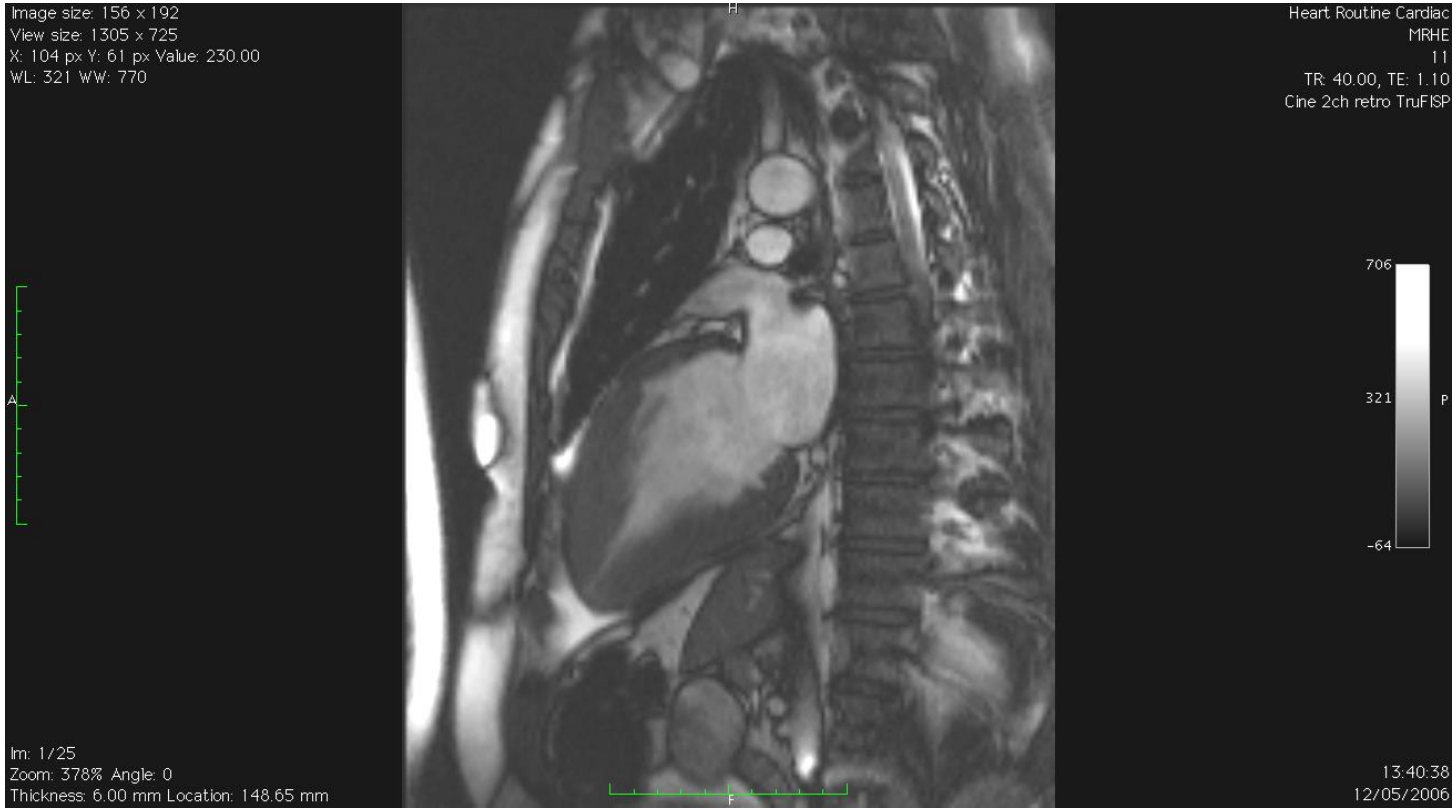
LV wall thickness ≥15 mm in one or more LV myocardial segments measured by any imaging technique

CHILDREN:

LV wall thickness more than two standard deviations above the predicted mean (z-score >2)

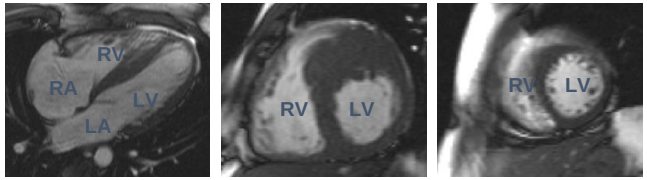


Personal data: Prof Elliott

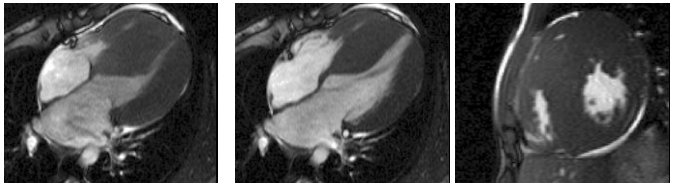


Personal data: Prof Elliott

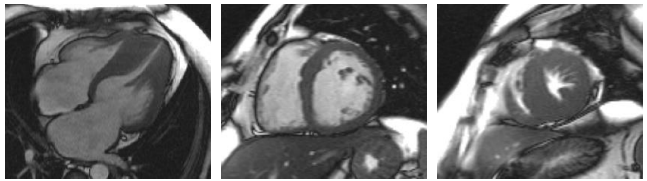
Asymmetrical septal hypertrophy



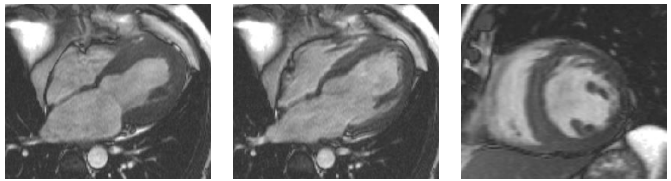
Bi-ventricular hypertrophy



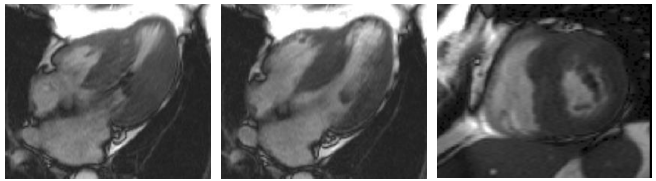
Apical hypertrophy



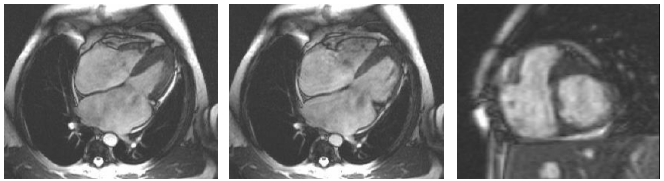
“End-stage” dilatation



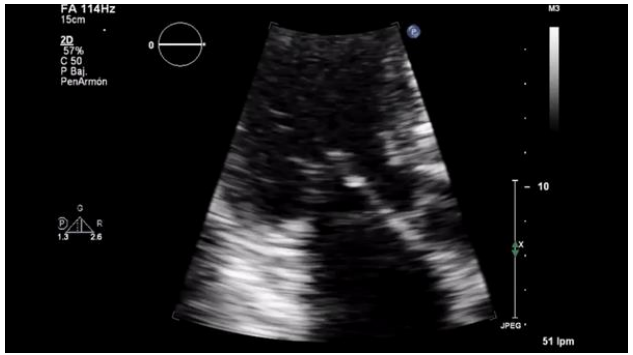
Mid-cavity obstruction

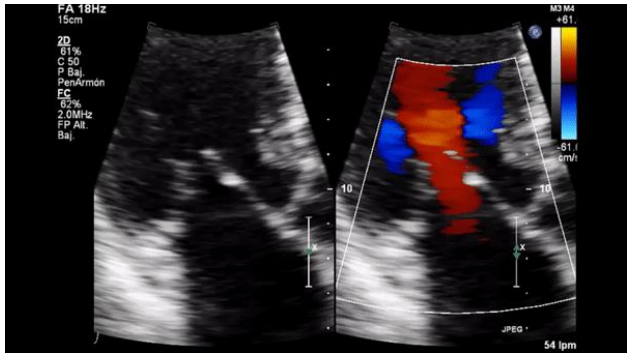


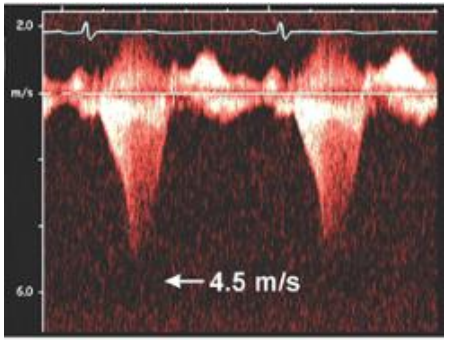
Restrictive cardiomyopathy

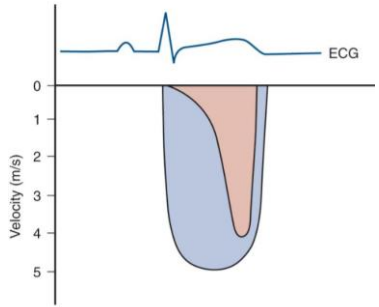


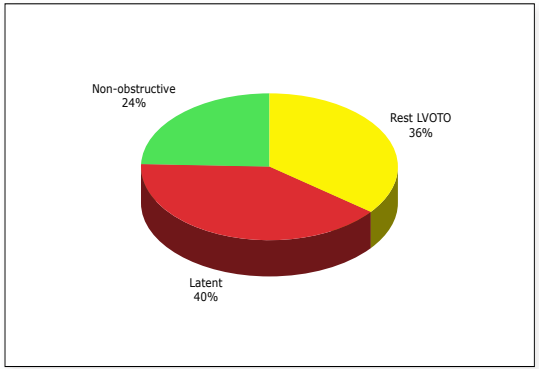
Echo features of HCM











Courtesy K. Savvatis, Barts

Mapping the gene for HCM to chromosome 14q1

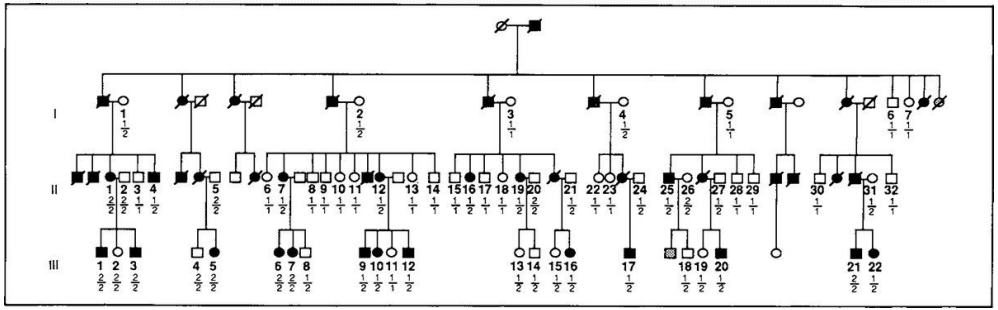
1372 THE NEW ENGLAND JOURNAL OF MEDICINE Nov. 16, 1989

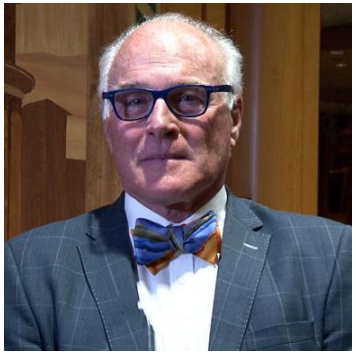
MAPPING A GENE FOR FAMILIAL HYPERTROPHIC CARDIOMYOPATHY TO CHROMOSOME 14q1

JOHN A. JARCHO, M.D., WILLIAM MCKENNA, M.D., J.A. PETER PARE, M.D., SCOTT D. SOLOMON, M.D., RANDALL F. HOLCOMBE, M.D., SHAUGHAN DICKIE, TATJANA LEVI, D.D.S., HELEN DONIS-KELLER, PH.D., J.G. SEIDMAN, PH.D., AND CHRISTINE E. SEIDMAN, M.D.

Abstract To identify the chromosomal location of a gene responsible for familial hypertrophic cardiomyopathy, we used clinical and molecular genetic techniques to evaluate the members of a large kindred. Twenty surviving and 24 deceased family members had hypertrophic cardiomyopathy; 58 surviving members were unaffected. Genetic-linkage analyses were performed with polymorphic DNA loci dispersed throughout the entire genome, to identify a locus that was inherited with hypertrophic cardiomyopathy in family members. The significance of the linkage detected between the disease locus and polymorphic loci was assessed by calculating a lod score (the logarithm of the probability of observing coinheritance of two loci, assuming that they are genetically linked, divided by the probability of detecting coinheritance if they are unlinked).

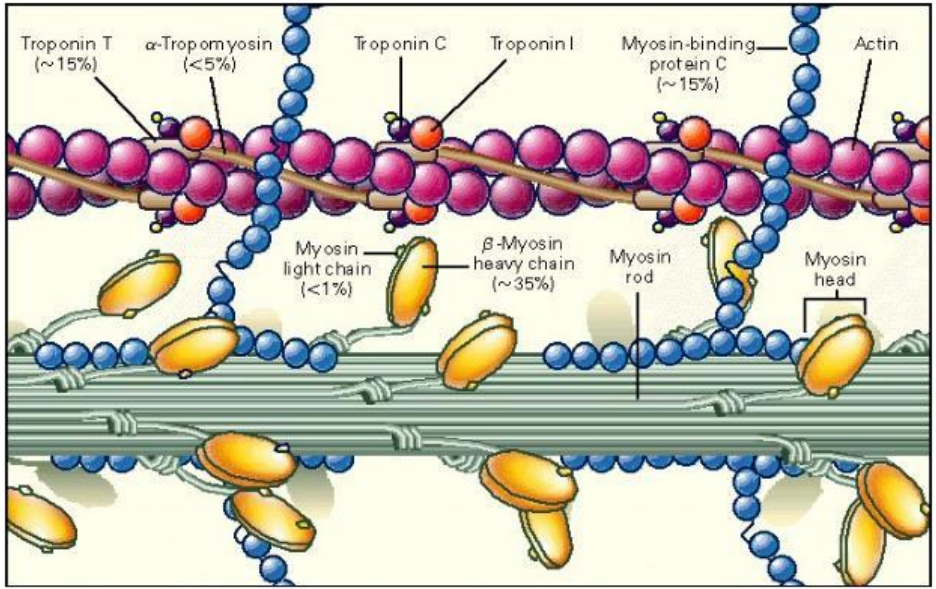
A DNA locus (D14S26), previously mapped to chromosome 14 and of unknown function, was found to be coinherited with the disease in this family. No instances of recombination were observed between the locus for familial hypertrophic cardiomyopathy and D14S26, yielding a lod score of +9.37 ($\theta = 0$). These data indicate that in this kindred, the odds are greater than 2,000,000,000:1 that the gene responsible for familial hypertrophic cardiomyopathy is located on chromosome 14 (band q1). (N Engl J Med 1989; 321:1372-8.)





N Engl J Med 1989;321:1372–8.

The evolving story of genetics in HCM



Gene	Protein	Frequency (%)
Cardiac myosin-binding protein C	MYBPC3	30–40%
β cardiac myosin heavy chain	MYH7	20–30%
Cardiac troponin T	TNNT2	5–10%
Cardiac troponin I	TNNI3	4–8%
Regulatory myosin light chain	MYL2	2–4%
Essential myosin light chain	MYL3	1–2%
α tropomyosin	TPM1	<1%
α cardiac actin	ACTC1	<1%
Muscle LIM protein	CSRP3	<1%

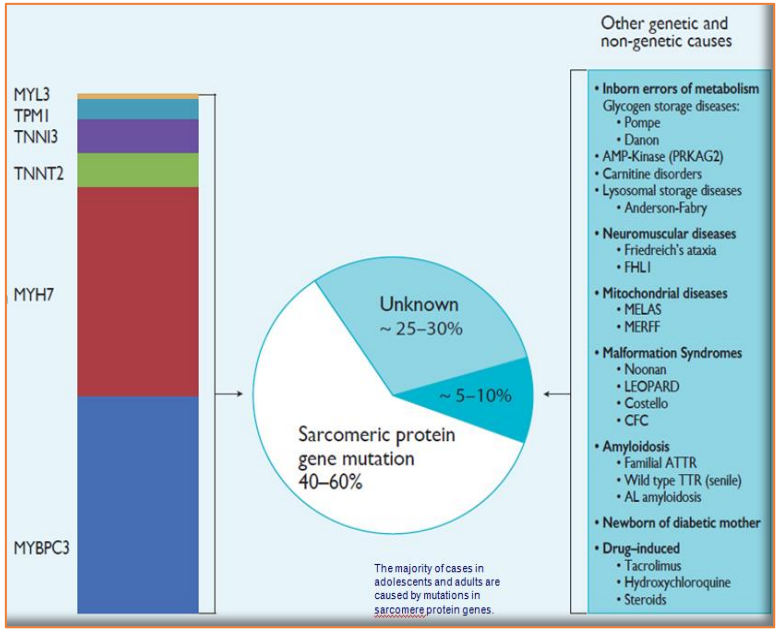
Spirito P, Seidman CE, McKenna WJ, Maron BJ. N Engl J Med. 1997 Mar 13;336(11):775-85.
Liew AC et al. J. Clin. Med. 2017, 6, 118;

Formin Homology 2 Domain Containing 3 *(FHOD3)* Is a Genetic Basis for Hypertrophic Cardiomyopathy

JACC 2018; 72: 2457-2467

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

Heart 2020;106:1342–1348.



Prevalence of Anderson-Fabry Disease in Male Patients With Late Onset Hypertrophic Cardiomyopathy

Circulation. 2002;105:1407-1411

Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness

European Heart Journal 2016;37:1826-1834

ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–124
https://doi.org/10.1093/eurheartj/ehad194

ESC GUIDELINES

2023 ESC Guidelines for the management of cardiomyopathies

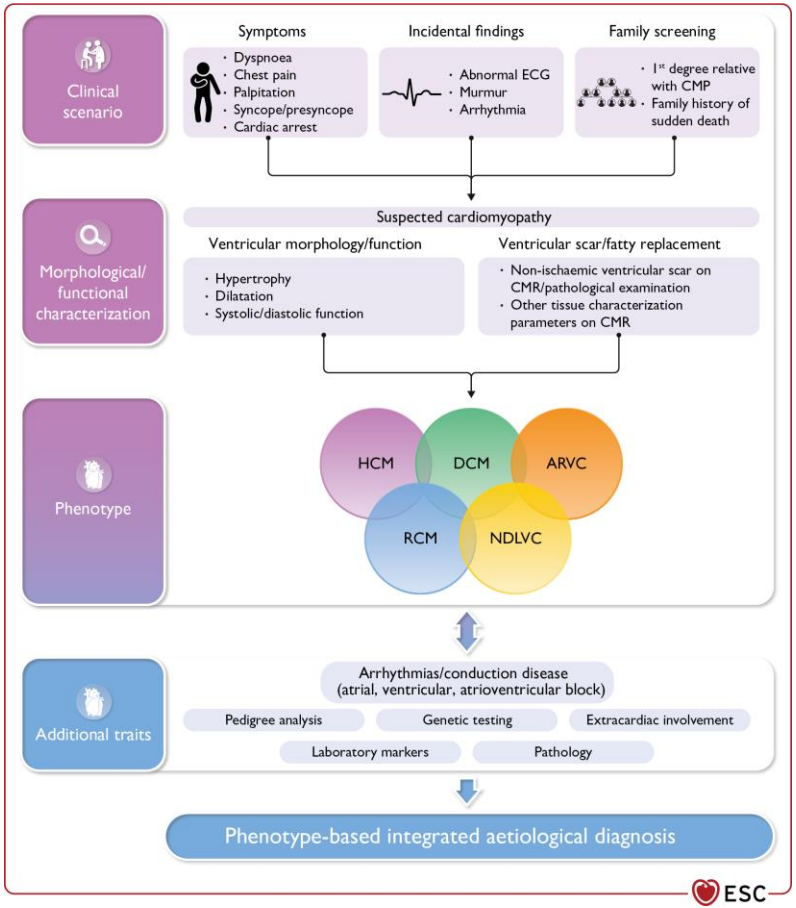
Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

Cardiomyopathy: Definition

- *"A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality."*

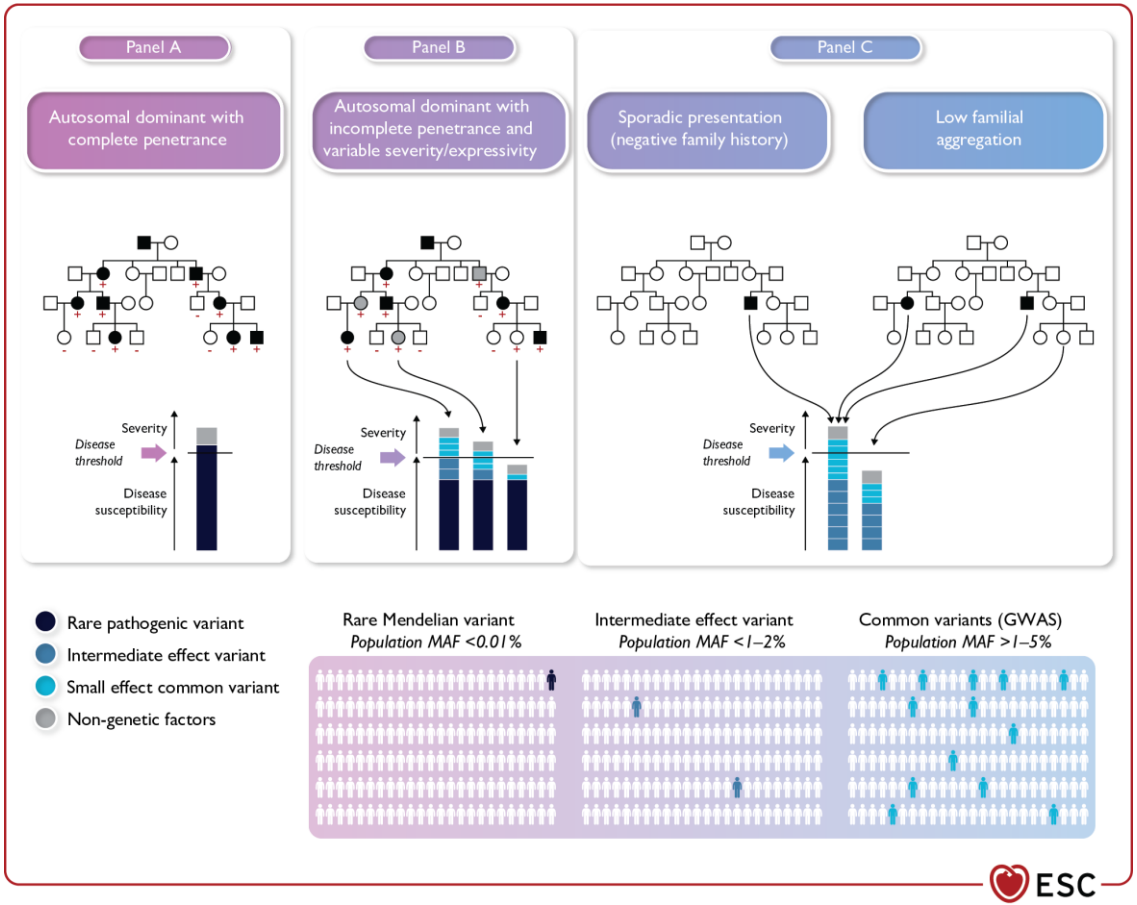
ESC Working Group on Myocardial Pericardial Diseases (Elliott P et al. EHJ 2007)

Clinical diagnostic workflow of cardiomyopathy



2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

The genetic architecture of the cardiomyopathies

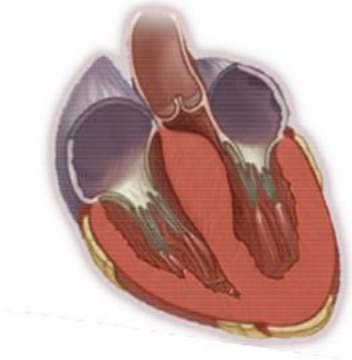


2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

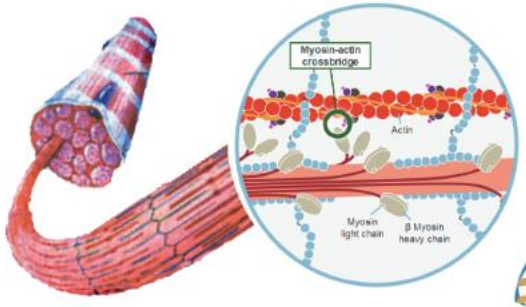
Hypertrophic cardiomyopathy: the future of treatment

C. Vaughan Tuohy, Sanjiv Kaul, Howard K. Song, Babak Nazer, and Stephen B. Heitner*

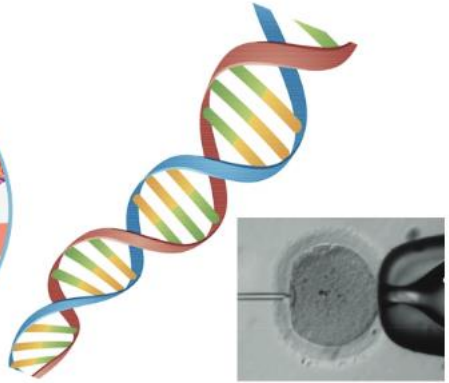
Structural Derangements:
- Septal hypertrophy
- Mitral leaflet abnormalities
- Subvalvular abnormalities
- SAM/LVOT obstruction
- Mitral regurgitation



Molecular Derangements:
- Actin-myosin cross-bridging
- Myocardial metabolism
- Sodium and calcium channels
- Hyperdynamic LV function, impaired LV relaxation and compliance
- Myocardial disarray, fibrosis, and adverse remodeling



Genetic Derangements:
- Genetic mutations in sarcomeric proteins

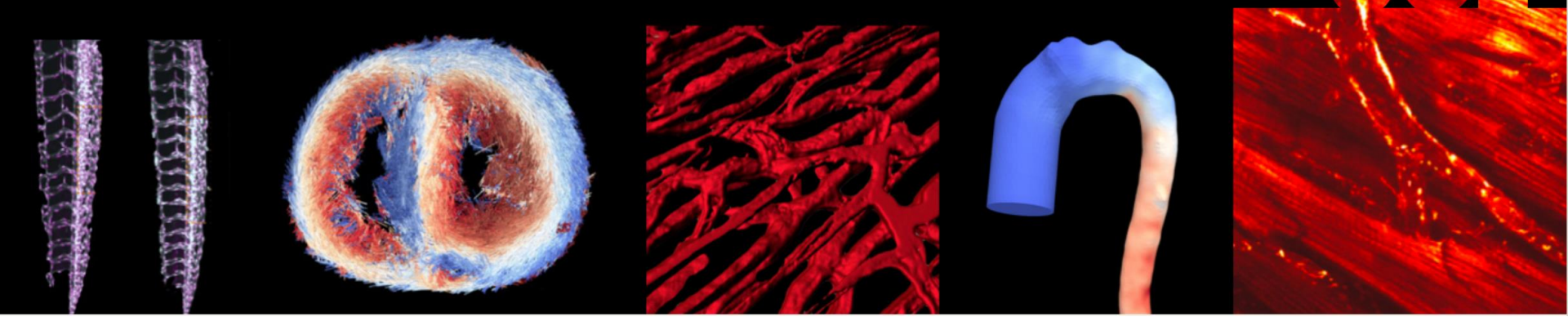


Novel Procedures:
- Surgical papillary muscle realignment, chordae removal, and mitral valve repair
- Apical myectomy
- Transcatheter mitral valve repair
- Radiofrequency septal ablation
- High-intensity focused ultrasound septal ablation

Novel Pharmacotherapies:
- Mavacamten, CK-274
- Perhexiline, Trimetazidine
- Ranolazine, Eleclazine
- N-Acetylcysteine
- ARBs, aldosterone antagonists
- Statins

Gene-Based Therapies:
- Allele-specific gene silencing
- Embryonic gene repair using CRISPR/Cas9

European Journal of Heart Failure (2020)22, 228–240



Thank You

Cardiomyopathy UK the heart muscle charity
Barts Health NHS NHS Trust
Queen Mary University of London
British Heart Foundation
NHS National Institute for Health Research
wellcome
ACT