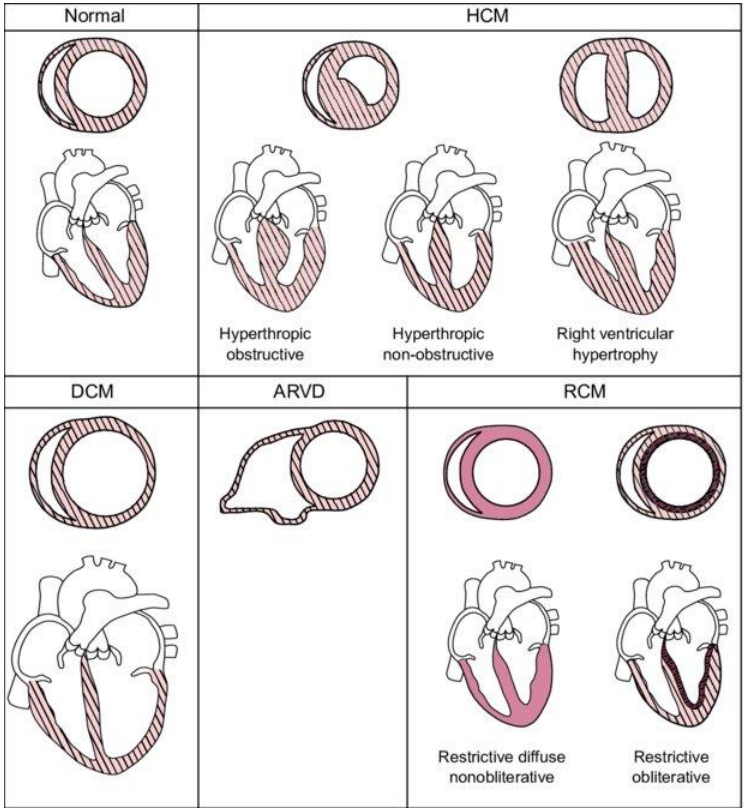
Cardiomyopathies

Hypertrophic, dilated and neuromuscular disorders

Emeline Van Craenenbroeck
Antwerp University Hospital, Belgium

Cardiologist, Antwerp University Hospital, Belgium
Associate professor, Cardiovascular Diseases, GENCOR, University of Antwerp, Belgium

Cardiomyopathy: Classification



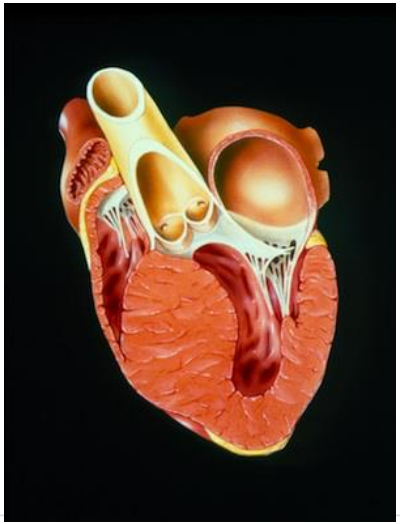
" A myocardial disorder in which ***the heart muscle is structurally and functionally abnormal,*** *in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality."*

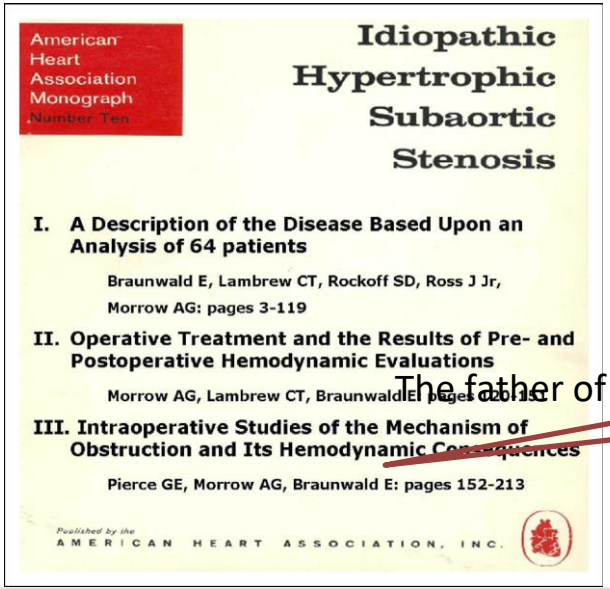
ESC Working group on Myocardial and Pericardial Diseases (Elliott T et al EHJ 2007)

Hypertrophic cardiomyopathy

Idiopathic hypertrophic subaortic stenosis

- Described for the first time in 1960
- Occurs in 1:500 in the general population

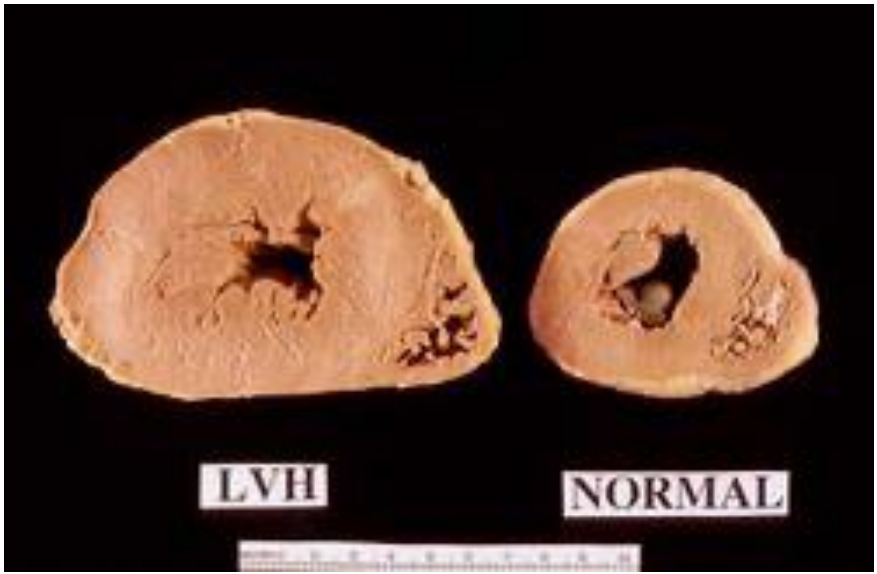




The father of HCM

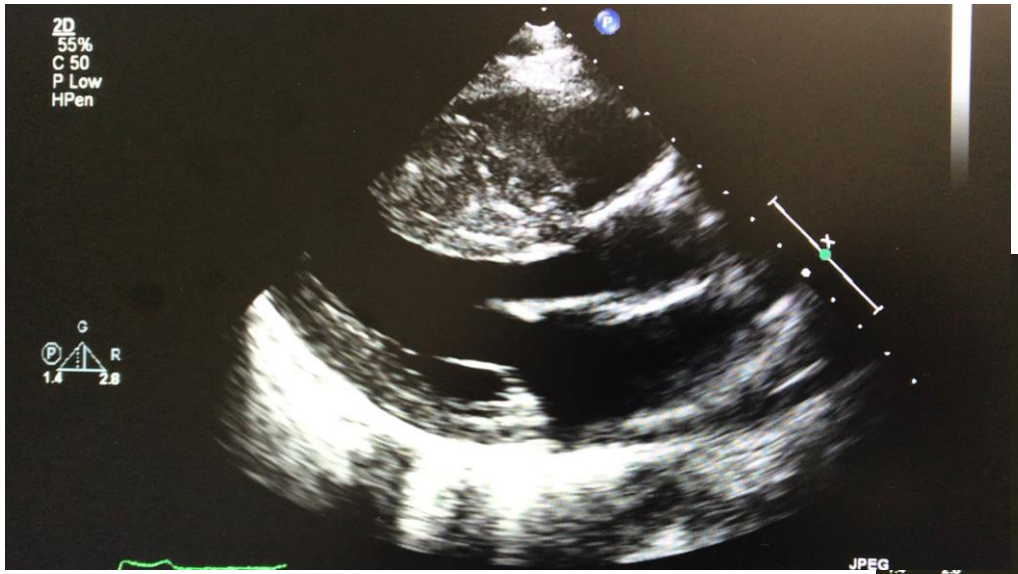
1. Hypertrophic cardiomyopathy: Diagnosis

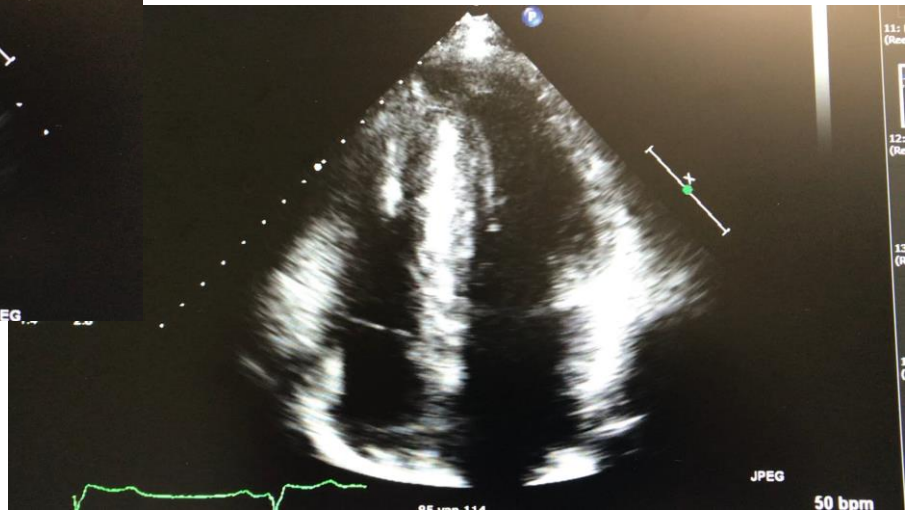
Definition: Left ventricular hypertrophy (lvsd > 15 mm) ***unexplained by abnormal loading conditions***



ESC Working group on Myocardial and Pericardial Diseases (Elliott T et al EHJ 2007)

1. Hypertrophic cardiomyopathy: Diagnosis





1. Hypertrophic cardiomyopathy: Diagnosis

- Presence of left ventricular hypertrophy (≥13 mm septal thickness)
  - In the absence of abnormal loading conditions or secondary causes such as
    - Arterial hypertension
    - Aortic stenosis
    - Physiological hypertrophy of athletes

- A cut-off of 15 mm has been recommended by the ESC working group to prevent overdiagnosis

- Co-existence
  - Hypertension/AS in patients with HCM can develop.
  - HCM can develop in patients with secondary causes. In this case, look at:
    - distribution of hypertrophy (asymmetric)
    - LVOT obstruction
    - ***Genetics***

2. HCM molecular genetic basis

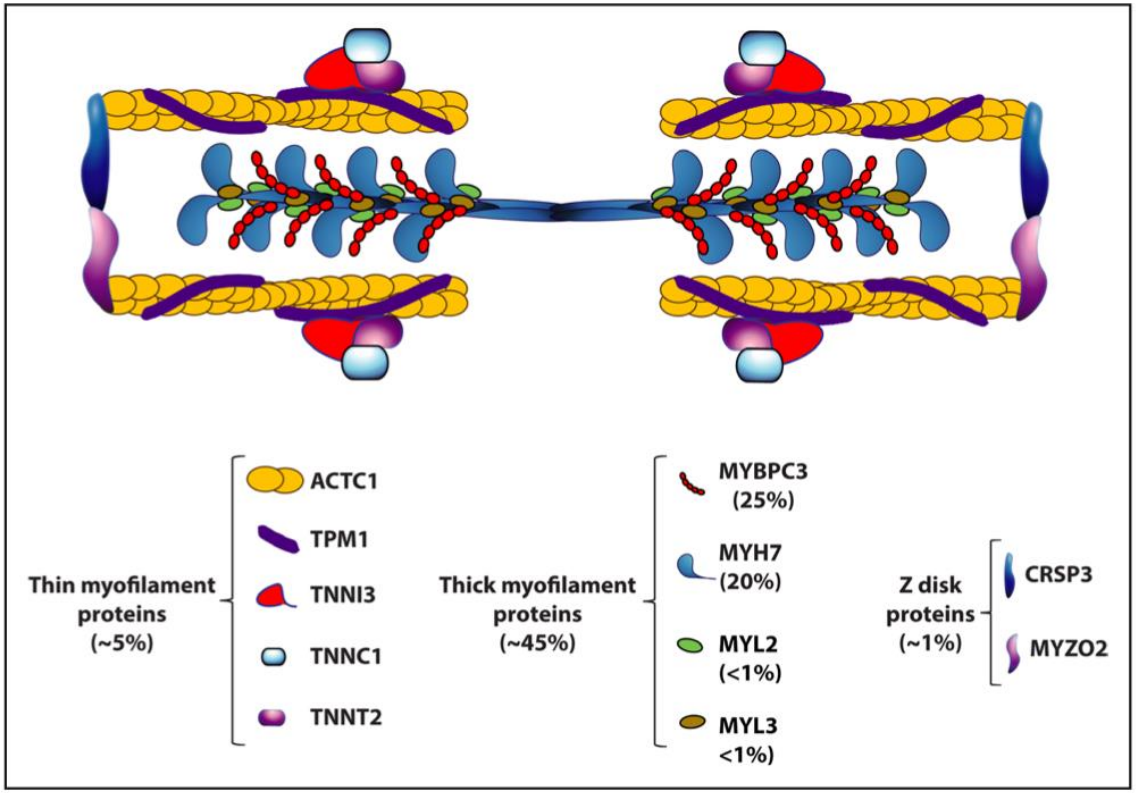


Figure 1. Hypertrophic cardiomyopathy (HCM) as a disease of sarcomere proteins. A schematic structure of a sarcomere composed of thick and thin filaments and Z discs is depicted along with its protein constituents involved in HCM. Established causal genes for HCM and their population frequencies are listed.

2. HCM molecular genetic basis

Table 1. Breakdown of the Original Linkage Studies Demonstrating the Co-Segregation of Genetic Variants and Hypertrophic Cardiomyopathy in Large Pedigrees and Incontrovertibly Associating Sarcomeric Genes With HCM

Gene	Protein	Demonstrated Associations	Year	Reference No.	Inheritance	N Pedigrees—(Total Size)	Max LOD	Notes
MYH7	Beta-myosin heavy chain	Locus 14q1	1989	7	AD	1 (96)	9.37	···
		Locus 14q11-12	1990	8		1 (96)	4.62	···
		Gene	1990	9		1 (96)	15.9	···
		Genetic heterogeneity of HCM	1990	10		4 (173)	10.85	···
TNNT2	Cardiac troponin T	Locus 1q3	1993	11	AD	3 (97)	8.47	···
		Gene	1994	12		1 (70)	6.3	···
MYBPC3	Myosin-binding protein C	Locus 11p13-q13	1993	13	AD	1 (54)	4.98	···
		Gene	1995	14		2 (46)	3.74	···
TPM1	Alpha tropomyosin	Locus 15q2	1993	15	AD	2 (87)	6.02	···
		Gene	1994	12		2 (87)	6.94	···
MYL3	Essential myosin light chain 3	Gene	1996	16	AD	1 (53)	6.2	···
TNNI3	Cardiac troponin I	Gene	1997	17	AD	1 (18)	3.1	···
MYL2	Regulatory myosin light chain 2	Gene	1998	18	AD	3 (47)	2.41 (estimated)	a
ACTC1	Alpha actin (cardiac muscle) 1	Gene	1999	19	AD	1 (22)	3.6	···

8 sarcomeric genes

2. HCM molecular genetic basis

Other non-sarcomeric genes

Table 3. Other Genes Classified as With Moderate/Strong/Definitive Evidence for Isolated HCM (or Multiple Conditions Including Isolated HCM) by ClinGen,[48] or With Convincing Evidence for HCM Causation Published After the ClinGen Curation Effort (Table view)

Gene	Protein	Disease	Year	Reference No.	Inheritance	ClinGen Classification	Notes
TNNC1	Troponin C type 1 (slow)	Isolated HCM	2001	36	AD	Moderate	···
PLN	Phospholamban	HCM, DCM, and ARVC	2003	37	AD	Definitive	···
CSRP3	Cysteine and glycine-rich protein 3 (cardiac LIM protein)	Isolated HCM	2003	38	AD	Moderate	···
JPH2	Junctophilin 2	Isolated HCM	2007	39	AD	Moderate	···
ACTN2	Actinin, alpha 2	HCM, LVH, LVNC, DCM, idiopathic VF	2010	40	AD	Moderate	···
FLNC	Filamin C, gamma	HCM, myofibrillar myopathy	2014	41	AD	Definitive	···
ALPK3	Alpha-kinase 3	HCM, DCM (infant-onset)	2016	42	AR	Strong	···
FHOD3	Formin homology 2 domain containing 3	HCM	2018	43	AD	···	a

2. HCM molecular genetic basis

Phenocopy genes

Table 2. Phenocopy Conditions for Hypertrophic Cardiomyopathy

Phenotype	Gene	Protein	Phenotypic Clue
AMPK-mediated glycogen storage	*PRKAG2*	Protein kinase A, γ subunit	Normal or reduced left ventricular systolic function, pre-excitation pattern
Pompe disease	*GAA*	α-1,4-glucosidase (acid maltase)	Autosomal recessive, multiorgan disease, pre-excitation pattern
Anderson–Fabry disease	*GLA*	α-galactosidase A	X-linked, multisystem also involving skin, kidney, and peripheral nerves
Danon disease	*LAMP2*	Lysosome-associated membrane protein 2	X-linked dominant, proximal muscle weakness, intellectual disability, short PR on ECG, elevated CK levels
Amyloidosis	*TTR*	Transthyretin	Low QRS voltage, other organ involvement, subendothelial LGE
Kearns–Sayre syndrome	*mtDNA*	Mitochondrial protein	Multisystem disease
Friedreich ataxia	*FRDA*	Frataxin	Autosomal recessive, neurodegeneration
Myotonic dystrophy	*DMPK*	Myotonin protein kinase	Myotonia, muscular dystrophy, cataract, and frontal baldness
	ZNF9	Zinc finger factor 9	
Noonan/LEOPARD syndromes (rasopathies)	*PTPN11*	Protein tyrosine phosphatase, nonreceptor type 11	Congenital heart defects, lentigines, Café-au-lait spots
	SOS1 and *SOS2*	Son of sevenless	
	RAF1	Murine leukemia viral oncogene homolog 1	
	KRAS	Kirsten rat sarcoma virus homolog	
	Others (*A2ML1*, *BRAF*, *CBL*, *MAP2K1*, *MAP2K2*, *NRAS*, *RIT1*, *RRAS*, and *SHOC2*)		
Neimann–Pick disease	*NPC1*	Neimann–Pick	Autosomal recessive neurodegenerative disease
Refsum disease	*PAHX (PHYH)*	Phytanoyl-CoA hydroxylase	Retinitis pigmentosa, peripheral neuropathy, and ataxia
Deafness	*MYO6*	Unconventional myosin 6	Autosomal dominant deafness

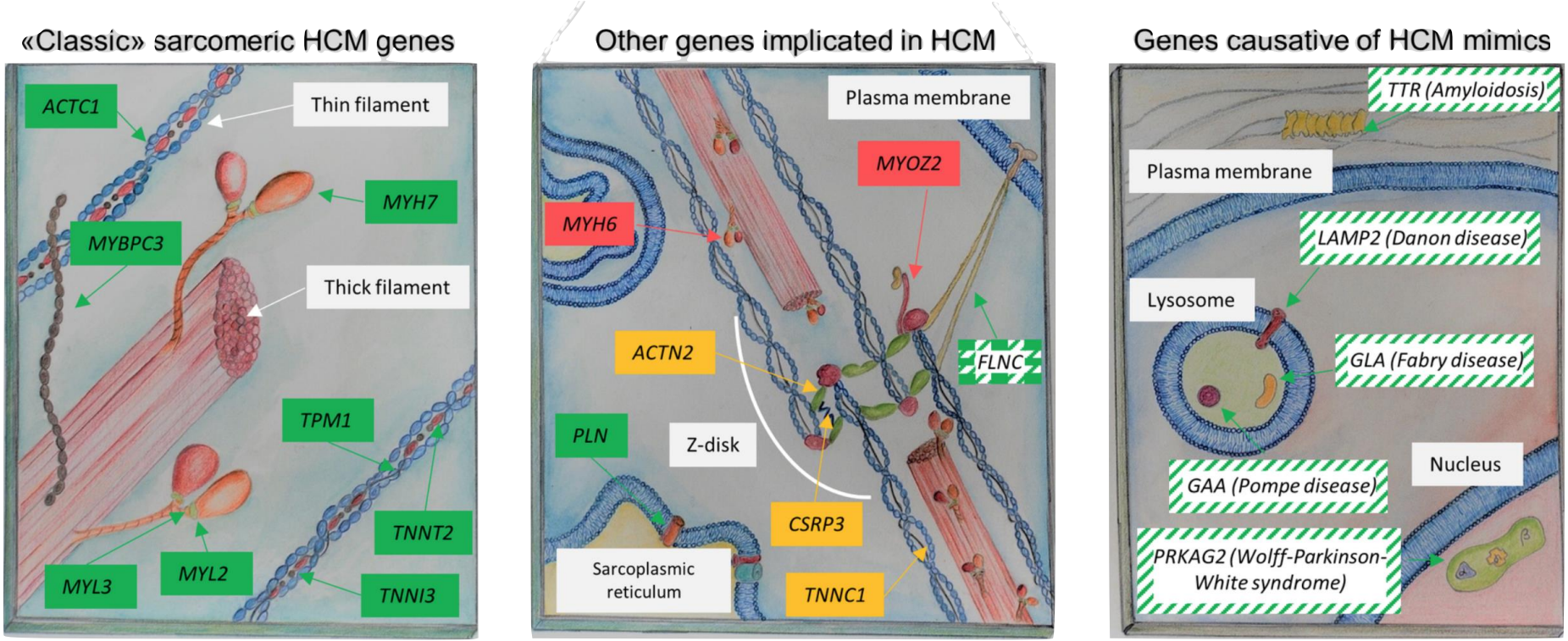
CK indicatescreatine kinase; and LGE, late gadolinium enhancement.

Pre-excitation

Microvoltage on ECG

myotonia

2. HCM molecular genetic basis: overview



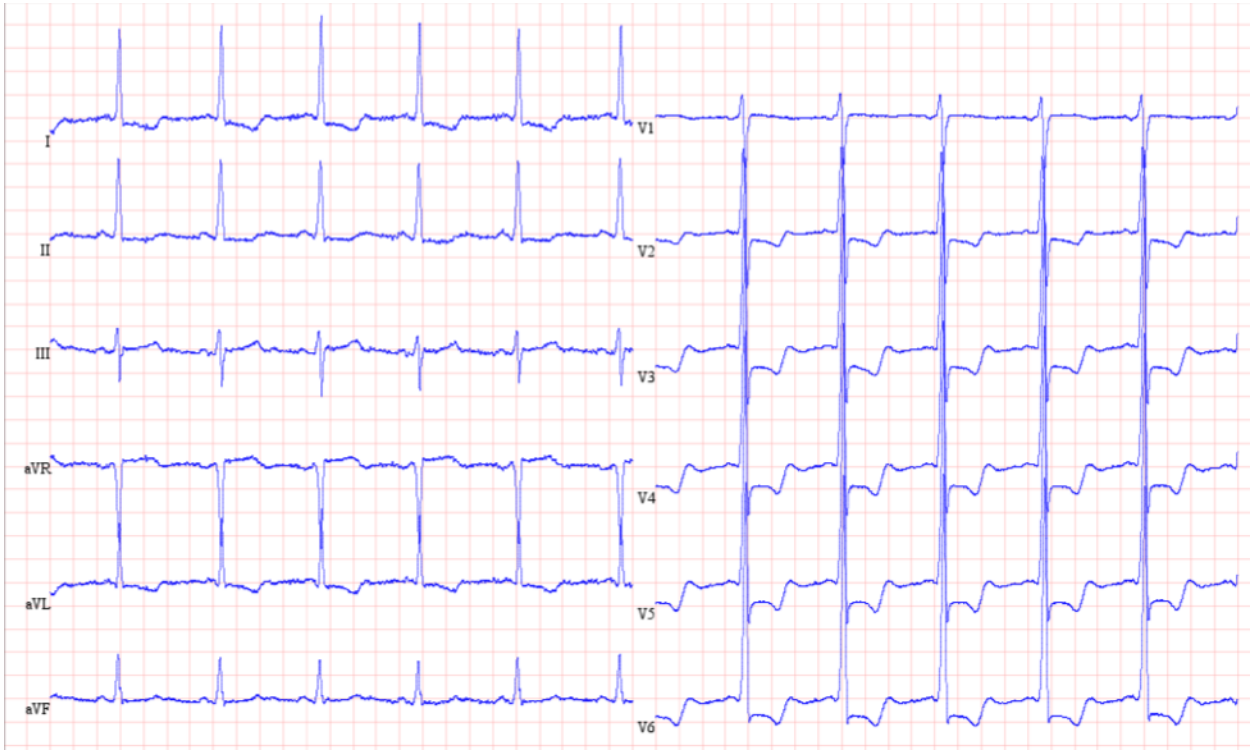
2. HCM molecular genetic basis: Phenocopy conditions

Table 2. Phenocopy Conditions for Hypertrophic Cardiomyopathy

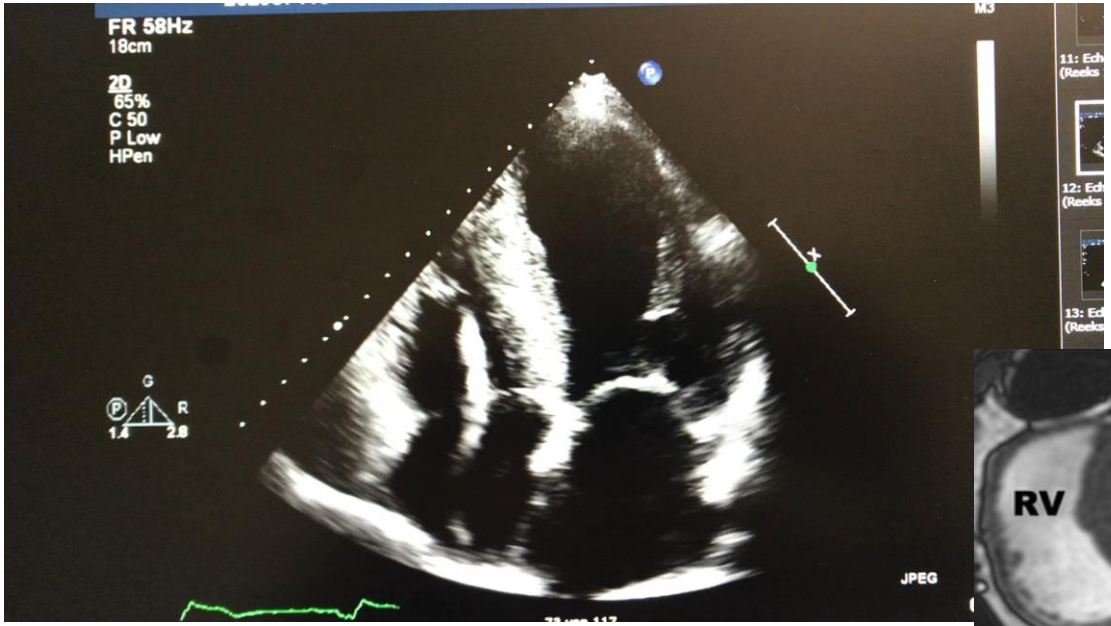
Phenotype	Gene	Protein	Phenotypic Clue
AMPK-mediated glycogen storage	*PRKAG2*	Protein kinase A, γ subunit	Normal or reduced left ventricular systolic function, pre-excitation pattern
Pompe disease	*GAA*	α-1,4-glucosidase (acid maltase)	Autosomal recessive, multiorgan disease, pre-excitation pattern
Anderson–Fabry disease	*GLA*	α-galactosidase A	X-linked, multisystem also involving skin, kidney, and peripheral nerves
Danon disease	*LAMP2*	Lysosome-associated membrane protein 2	X-linked dominant, proximal muscle weakness, intellectual disability, short PR on ECG, elevated CK levels
Amyloidosis	*TTR*	Transthyretin	Low QRS voltage, other organ involvement, subendothelial LGE
Kearns–Sayre syndrome	*mtDNA*	Mitochondrial protein	Multisystem disease
Friedreich ataxia	*FRDA*	Frataxin	Autosomal recessive, neurodegeneration
Myotonic dystrophy	*DMPK*	Myotonin protein kinase	Myotonia, muscular dystrophy, cataract, and frontal baldness
	ZNF9	Zinc finger factor 9	
Noonan/LEOPARD syndromes (rasopathies)	*PTPN11*	Protein tyrosine phosphatase, nonreceptor type 11	Congenital heart defects, lentigines, Café-au-lait spots
	SOS1 and *SOS2*	Son of sevenless	
	RAF1	Murine leukemia viral oncogene homolog 1	
	KRAS	Kirsten rat sarcoma virus homolog	
	Others (*A2ML1*, *BRAF*, *CBL*, *MAP2K1*, *MAP2K2*, *NRAS*, *RIT1*, *RRAS*, and *SHOC2*)		
Neimann–Pick disease	*NPC1*	Neimann–Pick	Autosomal recessive neurodegenerative disease
Refsum disease	*PAHX (PHYH)*	Phytanoyl-CoA hydroxylase	Retinitis pigmentosa, peripheral neuropathy, and ataxia
Deafness	*MYO6*	Unconventional myosin 6	Autosomal dominant deafness

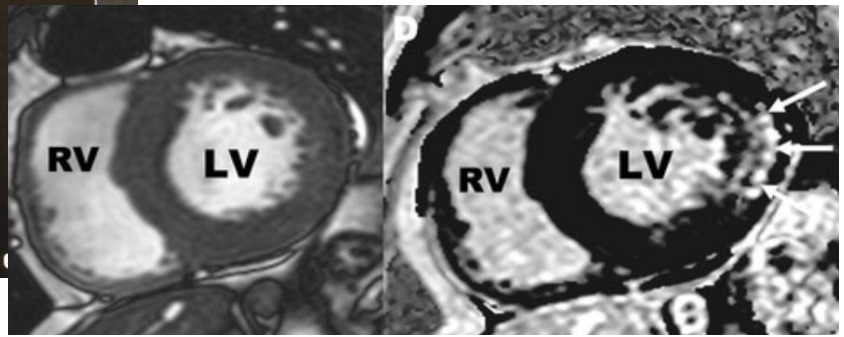
CK indicatescreatine kinase; and LGE, late gadolinium enhancement.

Differential diagnosis: PRKAG2: LVH and WPW



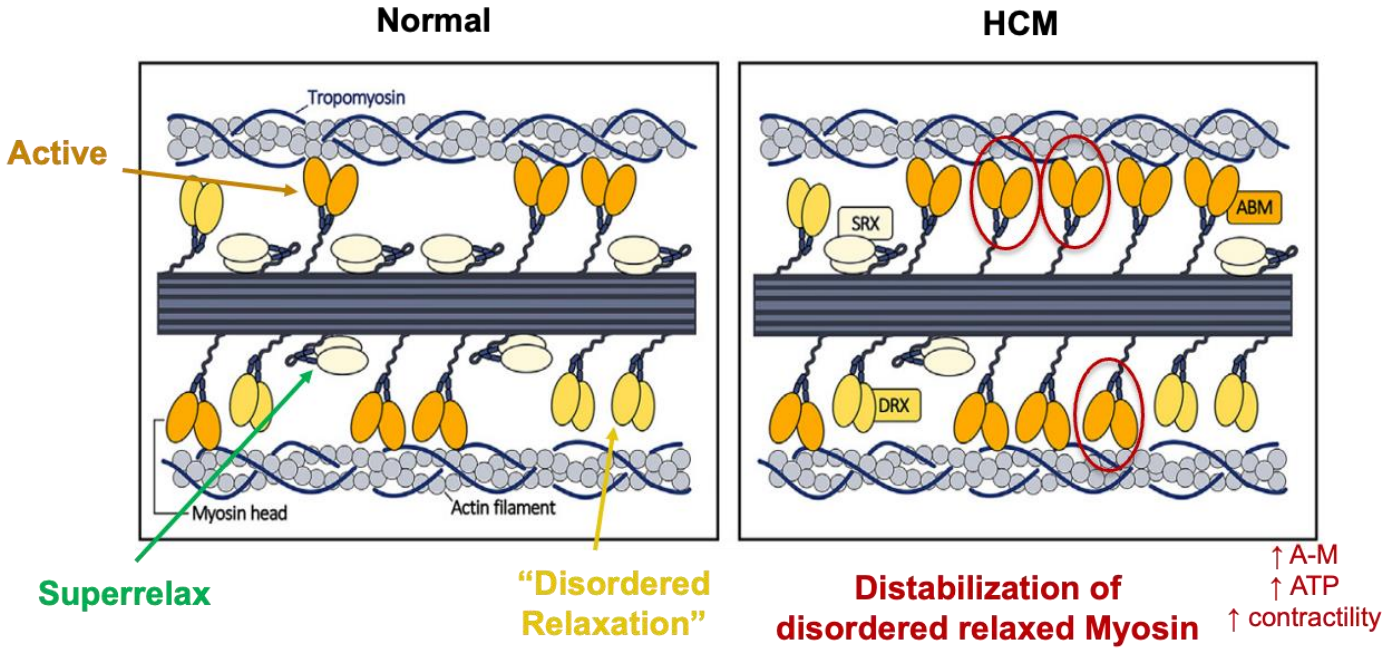
Differential diagnosis: Fabry disease (*GLA*)





3. Pathophysiology

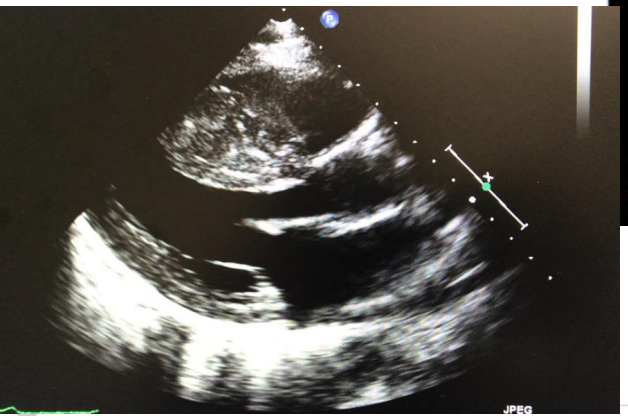
- Hypercontractility
- Decreased relaxation
- LVOT obstruction
- Interstitial fibrosis & myocyte disarray

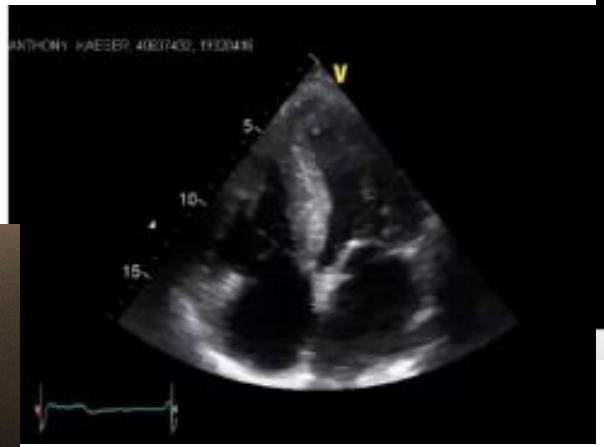


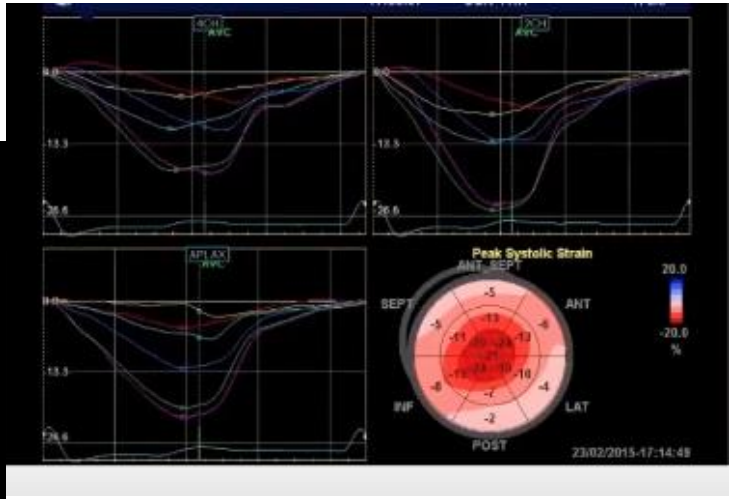
Ostrominski et al. JACC Heart Fail. 2023

3. Phenotypic characteristics: Imaging

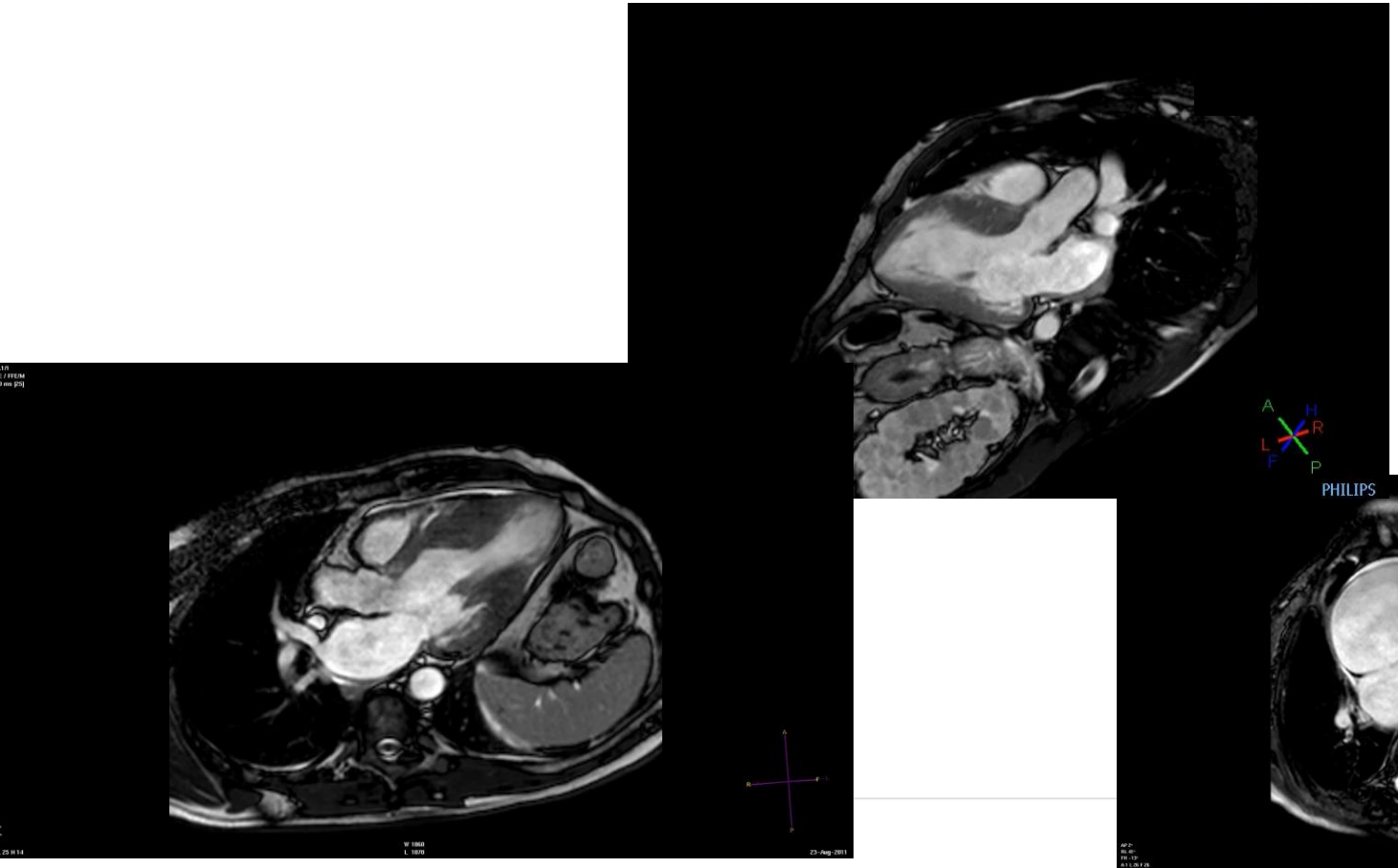
- **Echocardiography**





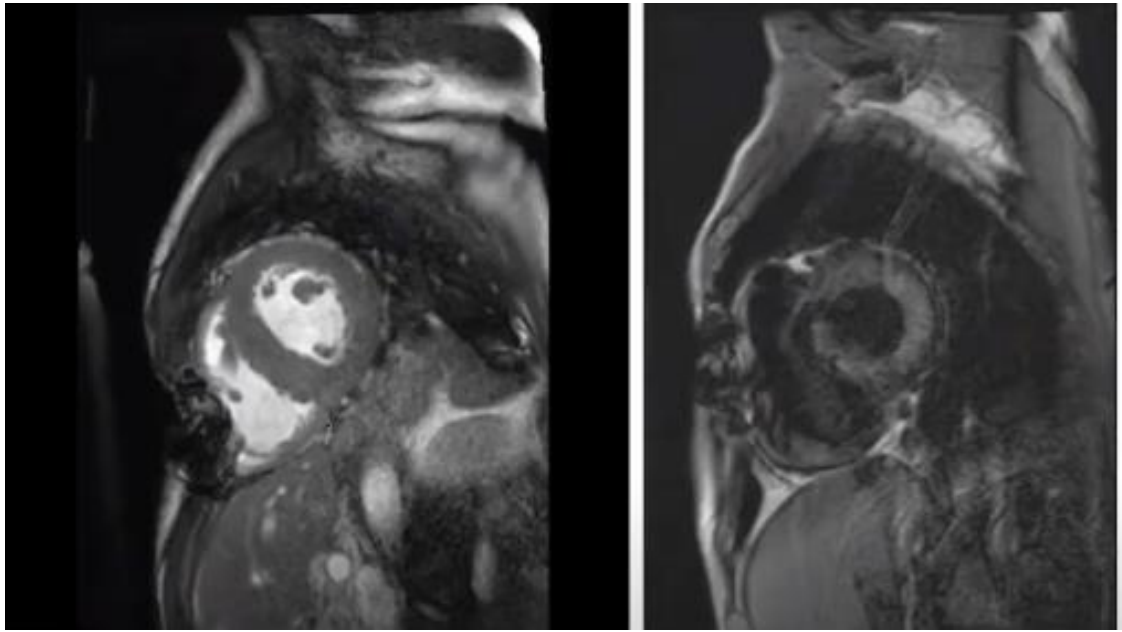


3. Phenotypic characteristics: Imaging



3. Phenotypic characteristics: Imaging

- **Cardiac MRI**
  - Structure in great detail
  - Tissue of the heart
    - infiltration
    - scarring



3. Phenotypic characteristics: Imaging

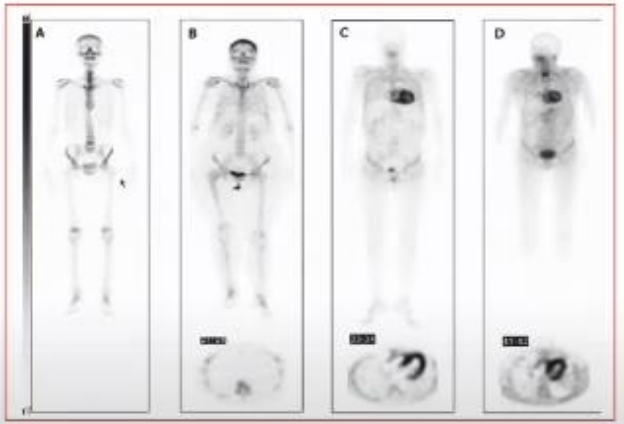
- **Bone scintigraphy**
  - ATTR- cardiac amyloidosis

Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis Using ^{99m}Tc-3,3-Diphosphono-1,2-Propanodicarboxylic Acid Scintigraphy

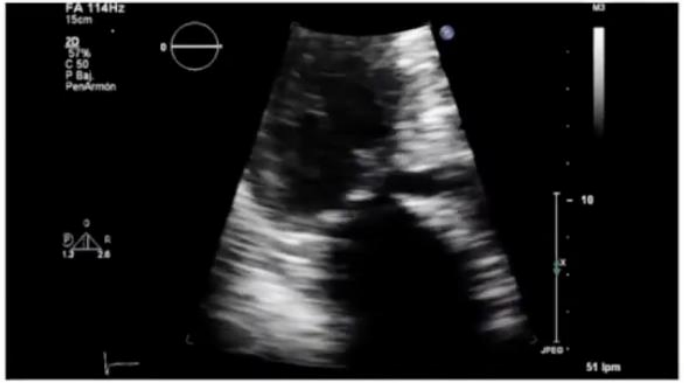
Enrica Perugini, MD,* Pier Luigi Guidalotti, MD,† Fabrizio Salvi, MD,‡ Robin M. T. Cooke, MA,* Cinzia Pettinato, MD,† Letizia Riva, MD,* Ornella Leone, MD,§ Mohsen Farsad, MD,† Paolo Ciliberti, MD,* Letizia Bacchi-Reggiani, MSc, MBIOSTAT,* Francesco Fallani, MD,* Angelo Branzi, MD,* Claudio Rapezzi, MD*
Bologna, Italy

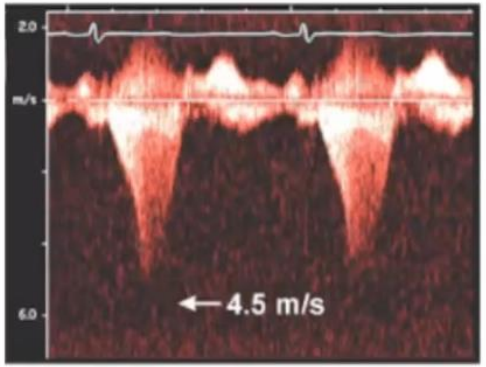
Diagnosis of amyloidosis was defined by histologic documentation of Congo-red staining and apple-green birefringence under cross-polarized light in at least one involved organ

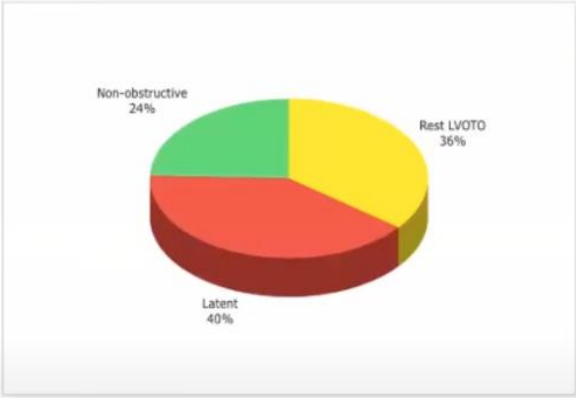
JACC Vol. 46, No. 6, 2005

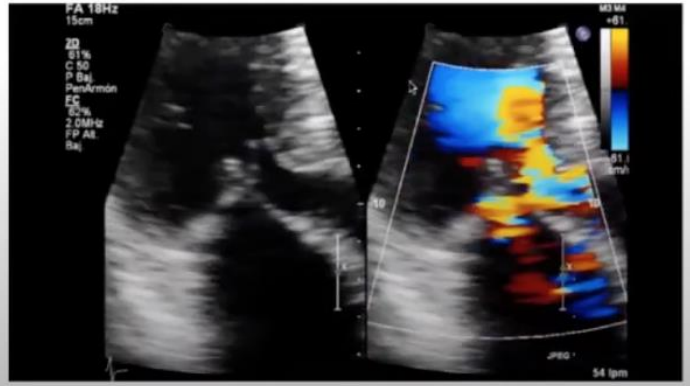


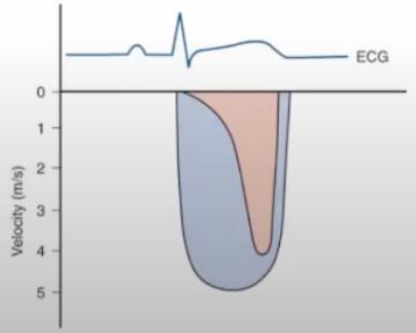
3. Phenotypic characteristics: LVOT obstruction



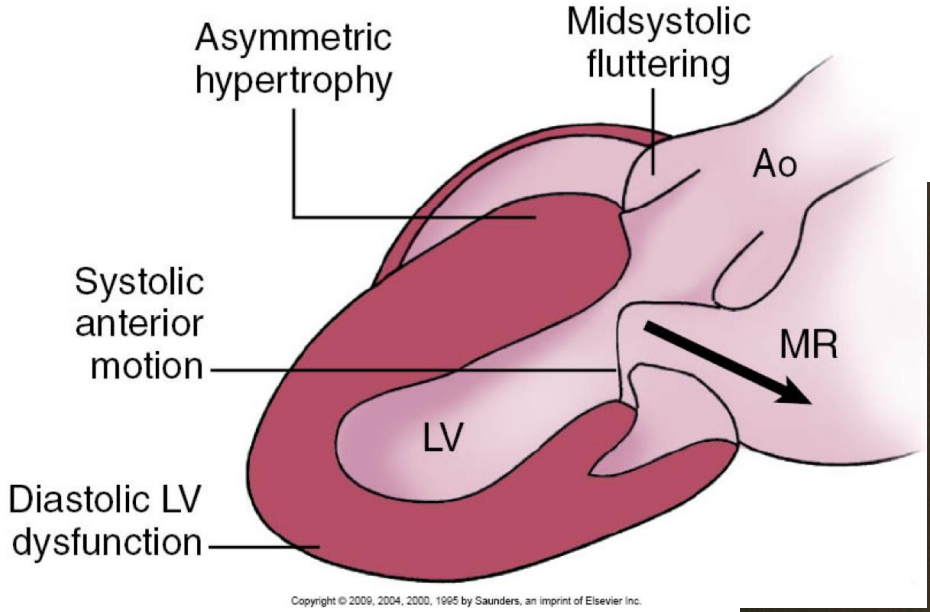


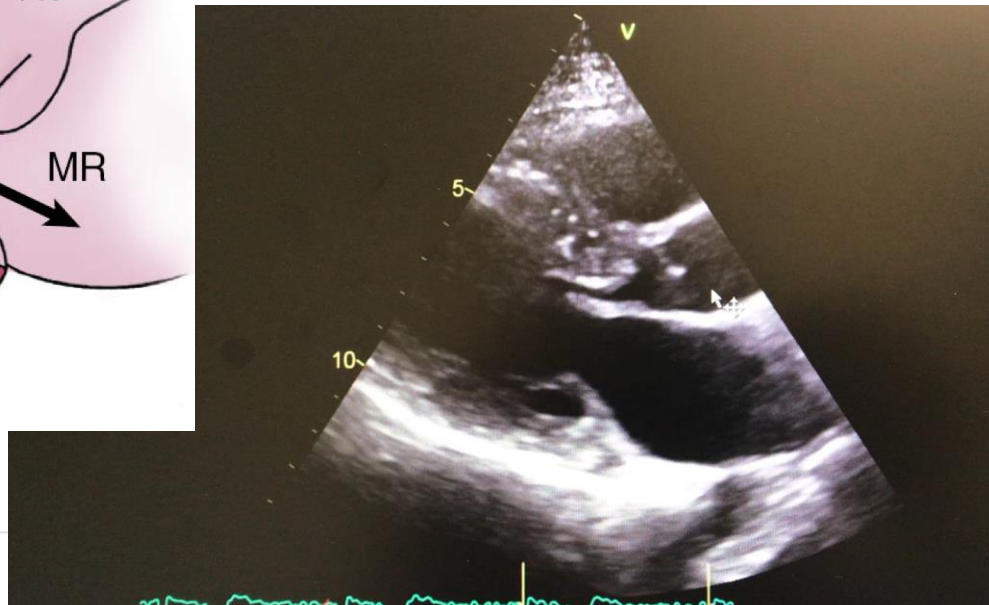




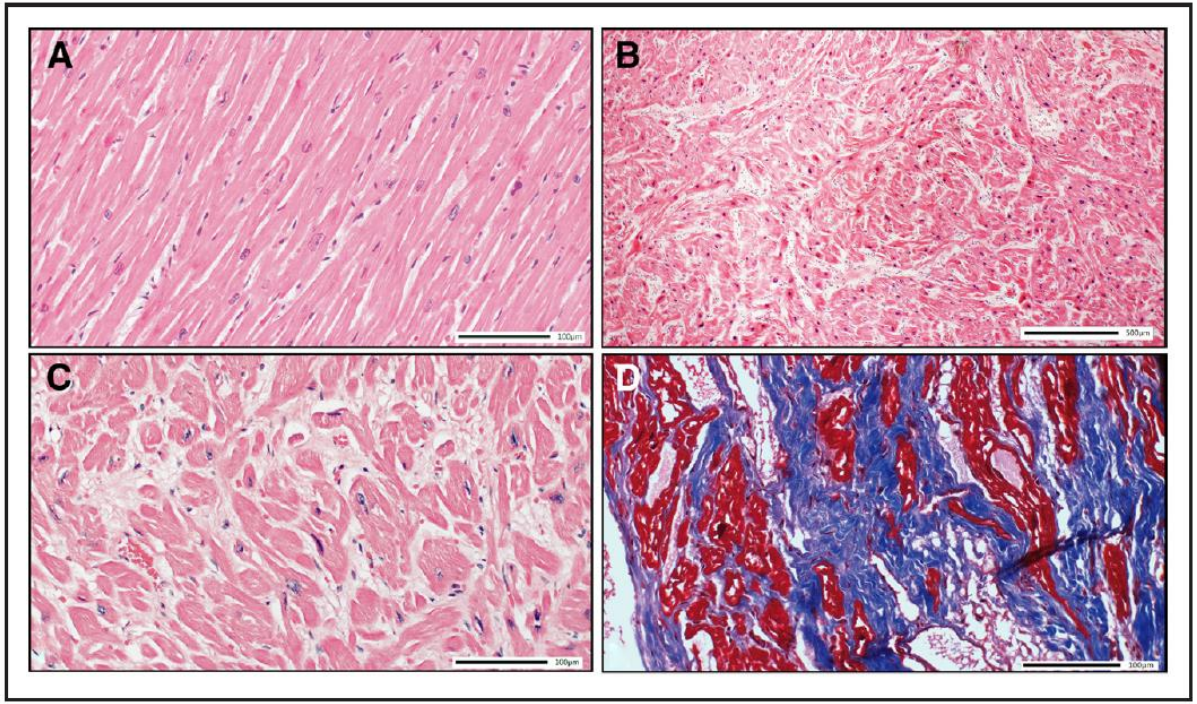


3. Phenotypic characteristics: LVOT obstruction

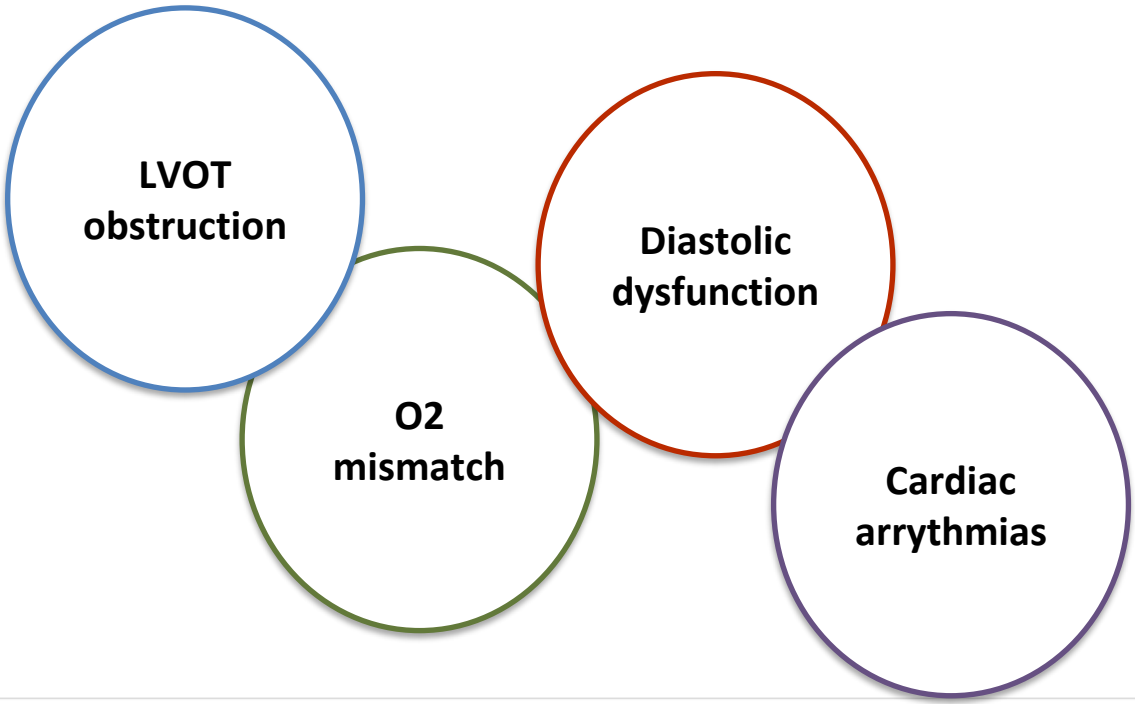




3. Phenotypic characteristics: Pathology



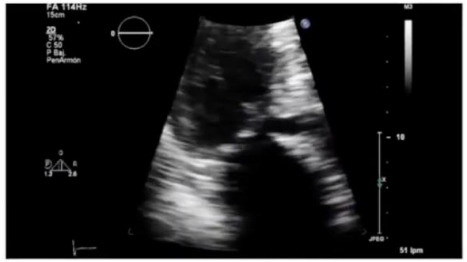
4. Clinical manifestations

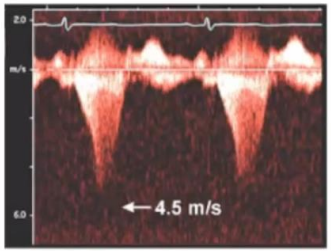


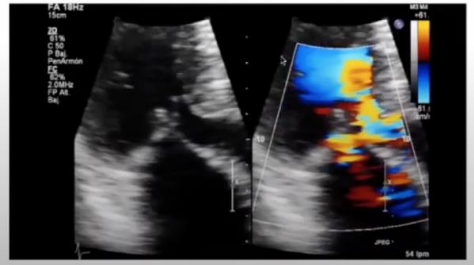
4. Clinical manifestations: LVOT obstruction

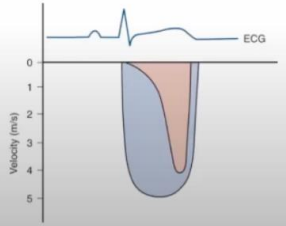
- Exertional or post-exertional syncope
- Exertional dyspnea and heart failure

  - LVOT obstruction at rest 1/3
  - LVOT obstruction during exercise 1/3
  - No LVOT obstruction 1/3









- Mechanisms
  - dependent on preload
  - dependent on force of contraction
  - SAM

- Physical exam
  - Midsystolic grade 3-4/6 systolic murmur, increasing during valsalva

4. Clinical manifestations: Chest pain

- Chest pain
  - typical or atypical
  - at rest or during exercise

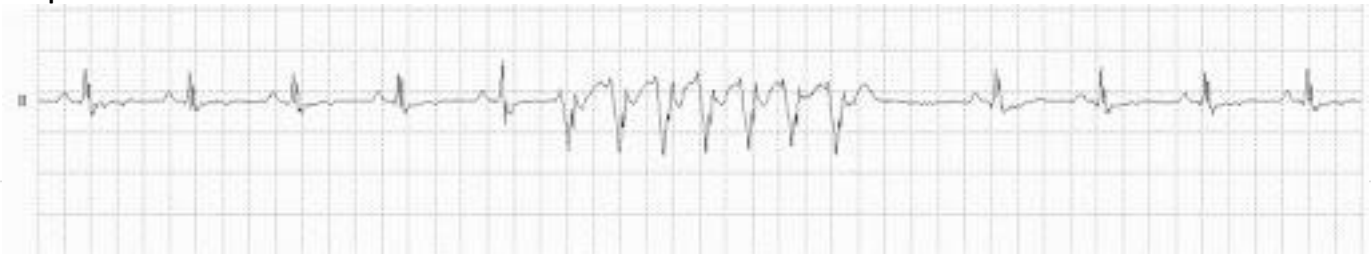
- Mechanisms
  - imbalance between myocardial oxygen supply and demand
  - myocardial hypoperfusion due to reduced blood flow through the thickened LV <-> increased oxygen demand of the LV

4. Clinical manifestations: Ventricular arrhythmias

- Palpitations, presyncope and syncope
  - (Non)-sustained ventricular tachycardia
    - 20-30% of patients
    - major risk factor for SCD
  - supraventricular PVC
  - ventricular PVC

- Mechanisms
  - interstitial fibrosis
  - myocardial ischemia
  - myocyte disarray

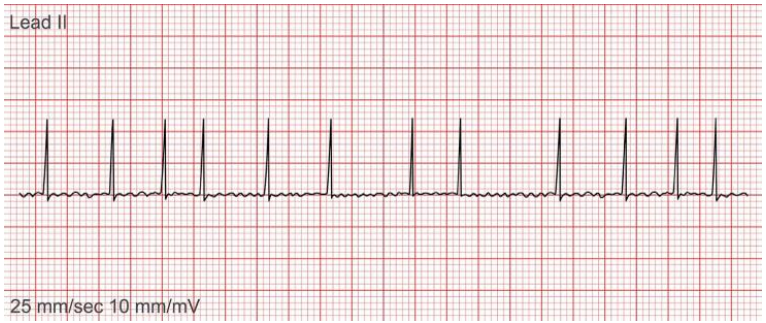
- !! dd severe LVOT obstruction may also cause syncope



4. Clinical manifestations: Supraventricular arrhythmias

- Atrial fibrillation (Palpitations, dyspnea)
  - 25% of patients
  - often poorly tolerated since loss of atrial contraction to ventricular filling results in further elevation of LV diastolic pressure
  - Major risk factor for thrombo -embolic events
  - LA size and LVOT obstruction are major risk factors for AF

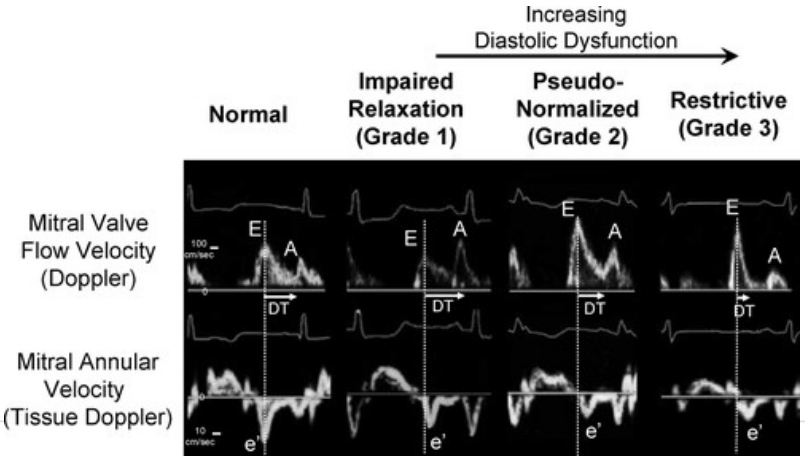
- Mechanisms
  - atrial enlargement and stretch due to diastolic dysfcuntion
  - atrial fibrosis



4. Clinical manifestations: Diastolic dysfunction

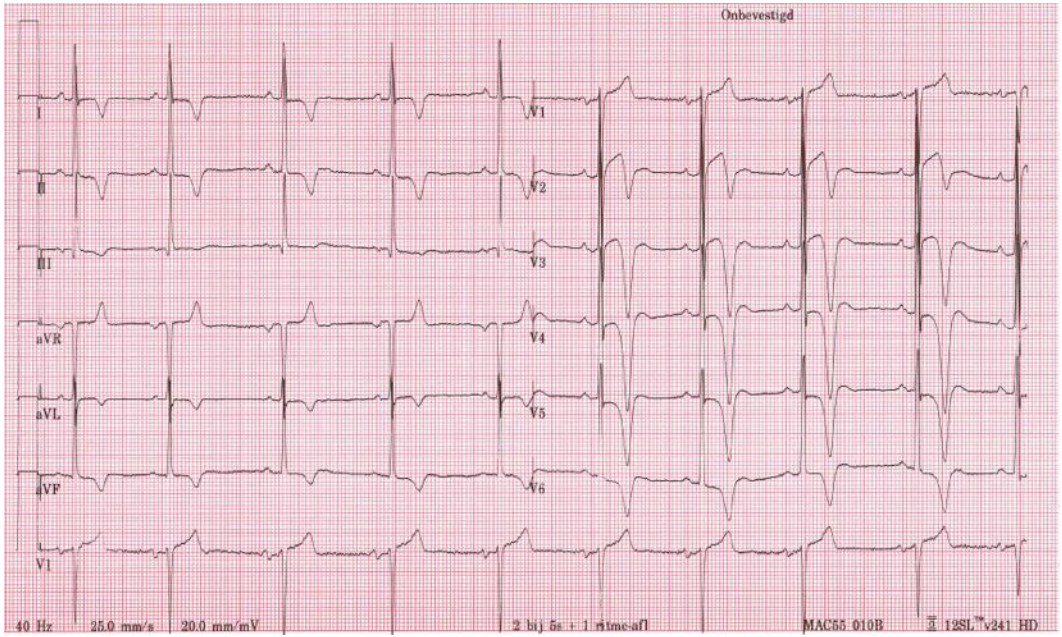
- exertional dyspnea
- exercise intolerance
- orthopnea
- peripheral edema
- HFpEF

- Mechanisms
  - LVH
  - increased LV end-diastolic pressure
  - increased LA pressure
  - increased pulmonary capillary pressure



4. Clinical manifestations: the ECG

- Voltage changes of left ventricular hypertrophy
- ST-T wave changes
- deep Q waves
- LA enlargement
- (Pre-excitation)



5. Prognosis

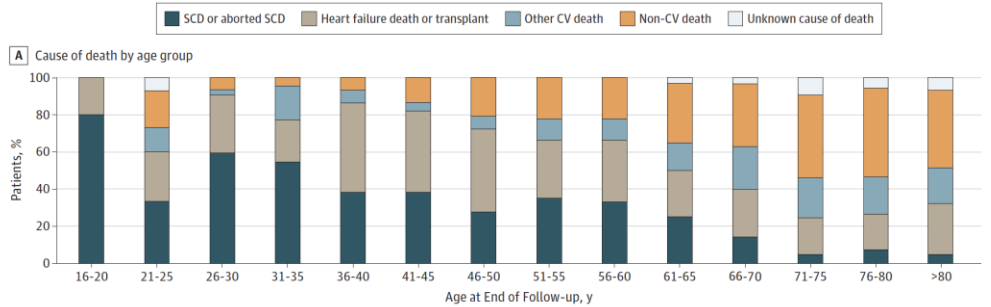
- HCM
  - 2/3 of of patients have normal life span without significant morbidity
  - especially patients without LVOT obstruction have excellent prognosis
  - Excess mortality

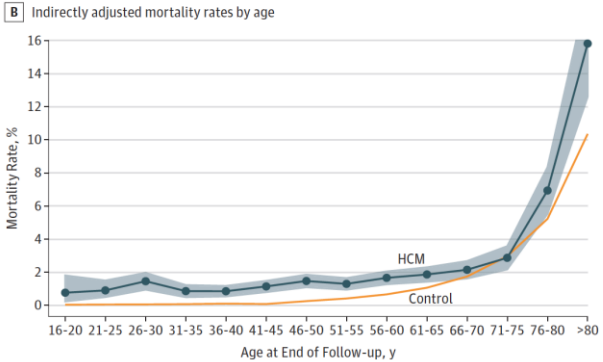
JAMA Cardiology | Original Investigation

Mortality Among Referral Patients With Hypertrophic Cardiomyopathy vs the General European Population

Massimiliano Lorenzini, MD, PhD; Zacharias Anastasiou, MSc; Constantinos O'Mahony, MD, PhD; Oliver P. Guttman, MD, PhD; Juan Ramon Gimeno, MD, PhD; Lorenzo Monserrat, MD, PhD; Aristides Anastasakis, MD; Claudio Rapezzi, MD; Elena Biagini, MD, PhD; Pablo Garcia-Pavia, MD, PhD; Giuseppe Limongelli, MD, PhD; Menelaos Pavlou, MSc, PhD; Perry M. Elliott, MD; for the Hypertrophic Cardiomyopathy Outcomes investigators

Figure 2. Cause of Death by Age Group and Event Rates According to Age at Presentation in the Study Population





6. Genetic testing

- Proband: Using WES/ panel analysis
  - causal variants in ≈30% to 50% of probands with HCM
  - **Caveat! /**
    - ca 50% without genetic diagnosis
    - Interpretation of these variants is challenging, particulary in a single affected individuals

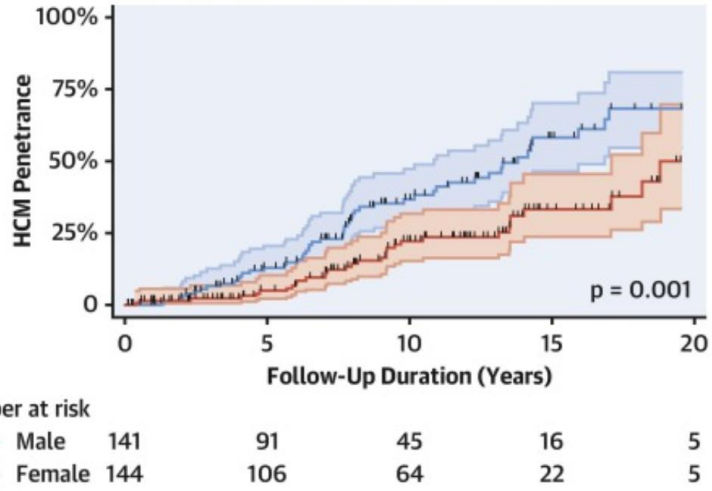
6. Genetic testing

- Genetic testing contributes to
  - establishing the diagnosis in case of doubt (dd athletes' heart, hypertensive heart disease)
  - SCD risk estimation
  - exclude phenocopy conditions- requiring a different managment (eg. enzyme replacement therapy in Fabry disease)
  - cascade testing in first degree relatives

6. Genetic testing

285 adult and pediatric carriers of pathogenic/likely pathogenic sarcomere protein variants with no hypertrophic cardiomyopathy (HCM)

Penetrance of HCM at 15-year follow-up: 46% (95% CI: 38%-54%)



Risk factors for HCM

Male
HR: 2.91
(95% CI: 1.82-4.65)

Abnormal ECG
HR: 4.02
(95% CI: 2.51-6.44)

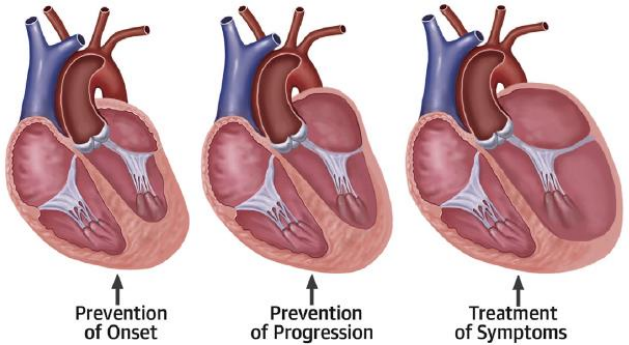
Lowest risk for HCM

TNNI3 variants
HR: 0.19
(95% CI: 0.07-0.55)

Lorenzini, M. et al. J Am Coll Cardiol. 2020;76(5):550-9.

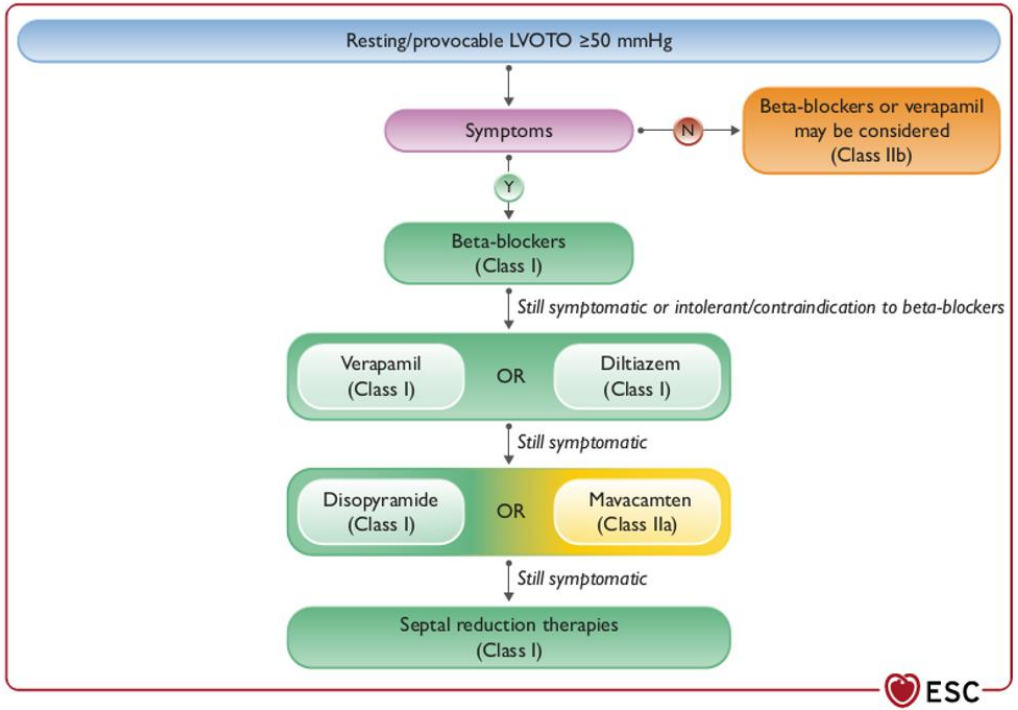
7. Management of asymptomatic patients

- Regular follow-up (eg. yearly)
- No pharmocological therapy so far
- Counseling on the genetic nature of the disease
- Avoid participation in competitive sports or intensive exercise (!! a moderate-intensity recreational exercise program is not only safe, but should be encouraged for most patients with HCM)



2020 ACC/AHA Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

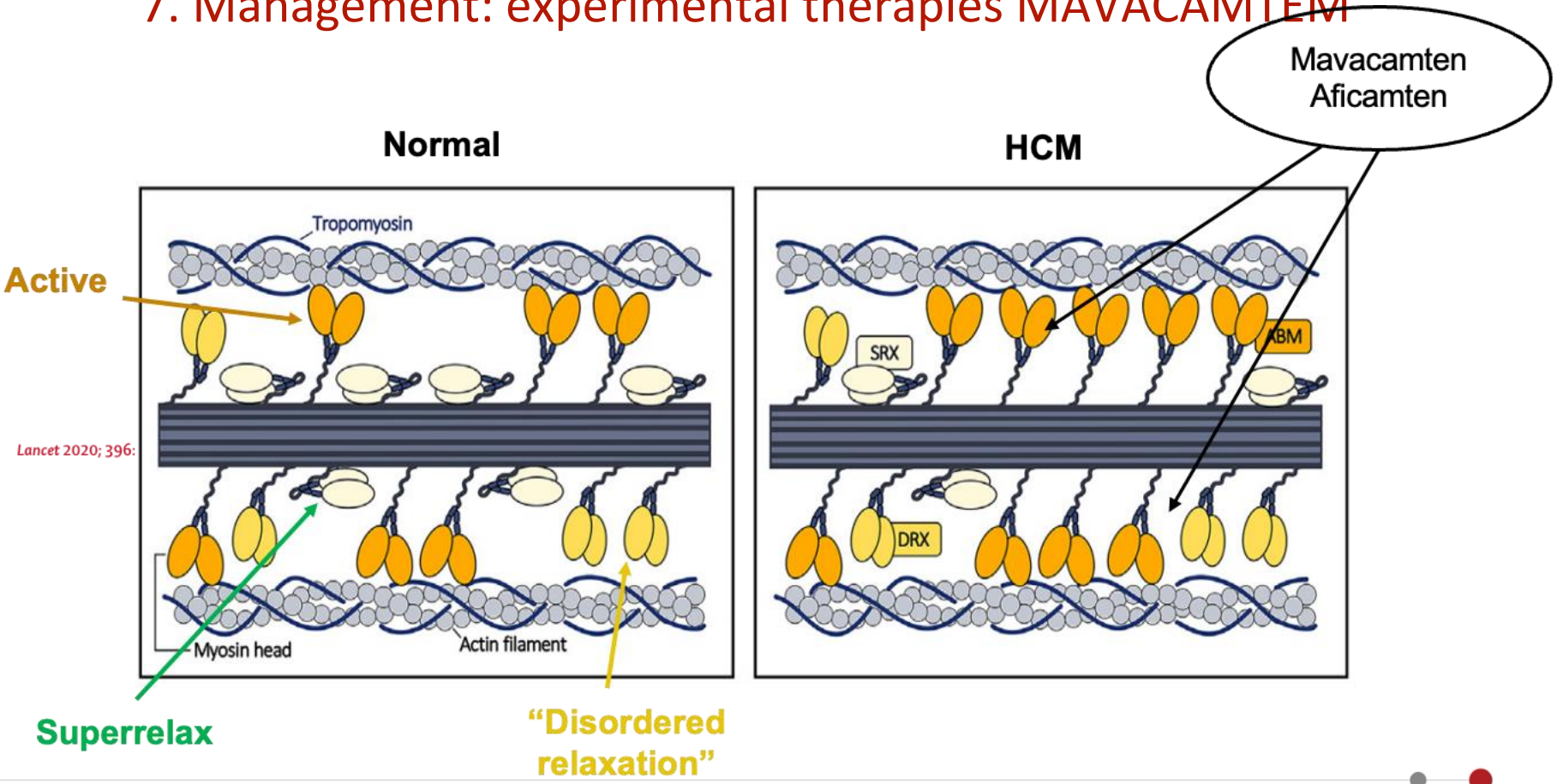
7. Management: symptomatic patients



Recommendations	Class[a]	Level[b]
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in adult patients with resting or provoked[c] LVOTO.[622,642–646]	IIa	A
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered as monotherapy in symptomatic adult patients with resting or provoked[c] LVOTO (exercise or Valsalva manoeuvre) who are intolerant or have contraindications to beta-blockers, verapamil/diltiazem, or disopyramide.[622,644–646]	IIa	B

Arbelo et al., Eur Heart J. 2023 Oct 1;44(37):3503-3626.

7. Management: experimental therapies MAVACAMTEM



Lancet 2020; 396:

7. Management: experimental therapies MAVACAMTEM

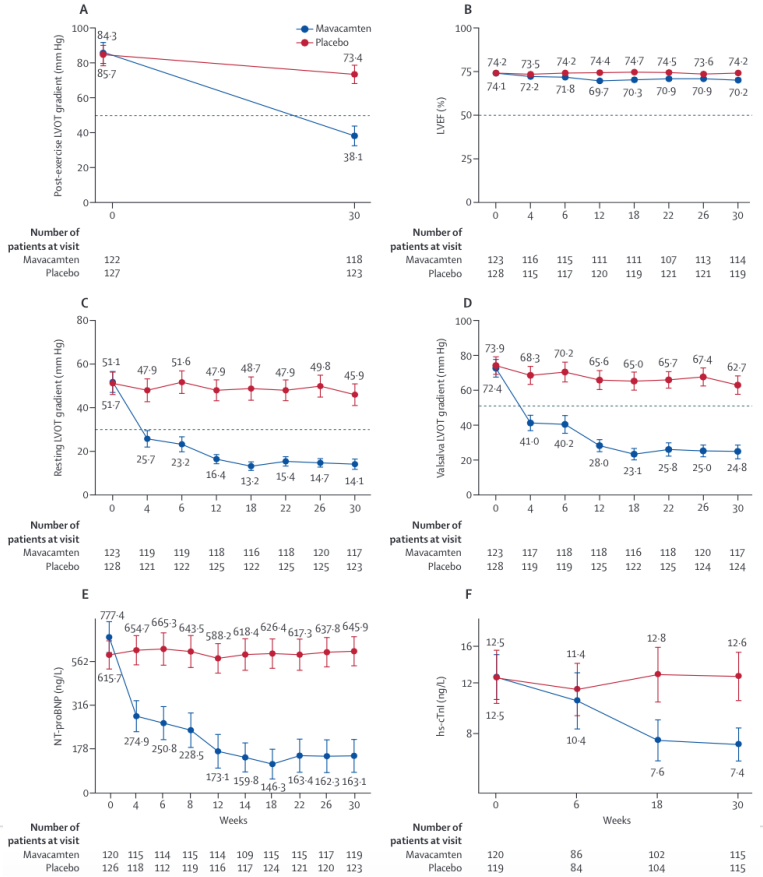
Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

Iacopo Olivotto, Artur Oreziak, Roberto Barriales-Villa, Theodore P Abraham, Ahmad Masri, Pablo Garcia-Pavia, Sara Saberi, Neal K Lakdawala, Matthew T Wheeler, Anjali Owens, Milos Kubanek, Wojciech Wojakowski, Morten K Jensen, Juan Gimeno-Blanes, Kia Afshar, Jonathan Myers, Sheila M Hegde, Scott D Solomon, Amy J Sehnert, David Zhang, Wanying Li, Mondira Bhattacharya, Jay M Edelberg, Cynthia Burstein Waldman, Steven J Lester, Andrew Wang, Carolyn Y Ha, Daniel Jacoby, on behalf of EXPLORER-HCM study investigators*

Summary

Lancet 2020; 396: 759–69

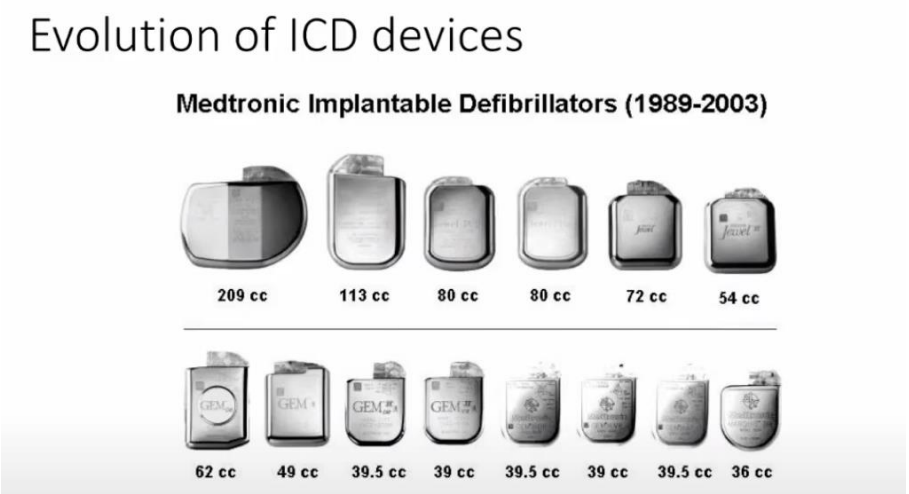
Mavacamtem MYK-461
- orally administered
- small molecule
- allosterically inhibits myosin ATPase activity



7. Management: patients at risk of SCD

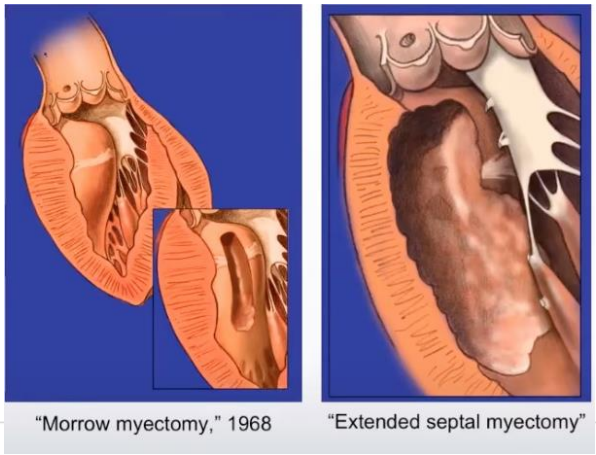
- Risk of SCD ranges from **0.5%-2%/year** in adults with HCM
- Particular risk in competitive athletes

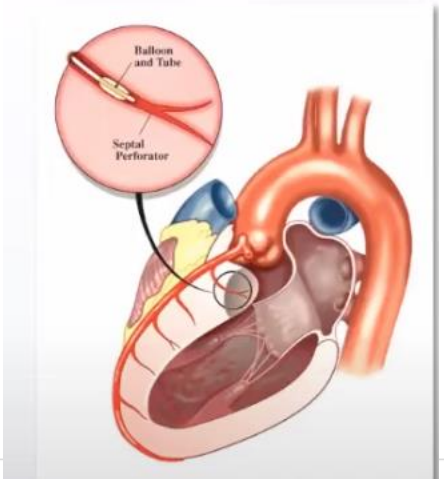
- VT/VF treated with internal cardioverter defibrillator (ICD)



7. Management: patients with LVOT obstruction and heart failure

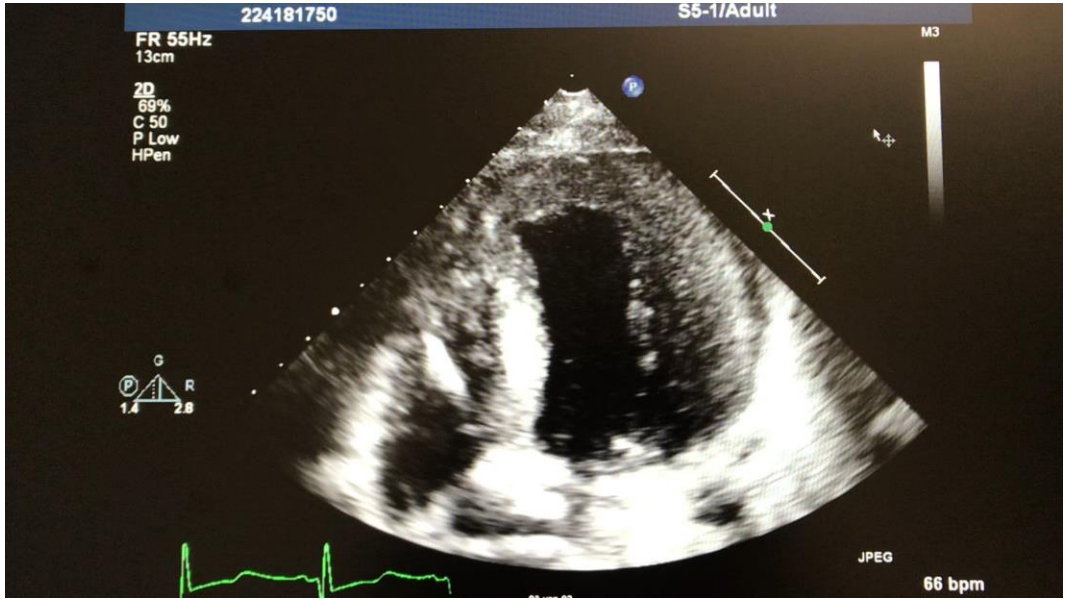
- LVOT obstruction
  - Betablocker/Disopyramide
  - If persistent symptomatic and IV gradient (≥50 mm Hg at rest or with provocation)
    - Septal myectomy/Morrow myectomy
    - alcohol septal ablation





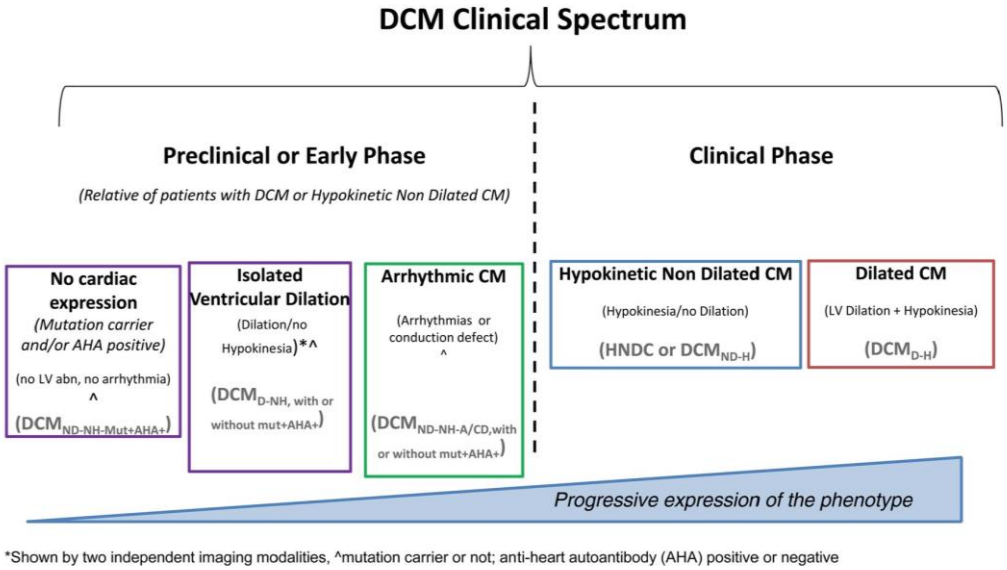
7. Management: patients with LVOT obstruction and heart failure

- Advanced heart failure
  - cardiac transplantation



Dilated cardiomyopathy

Definition and etiology



Specific aetiologies of DCM

- Genetic
  - cardiac
  - neuromuscular
- Drugs
  - antineoplastic
  - psychiatric
- Toxins
  - alcohol
  - cocaine
- Myocarditis
  - infectious
  - autoimmune
- Peripartum
- Nutritional

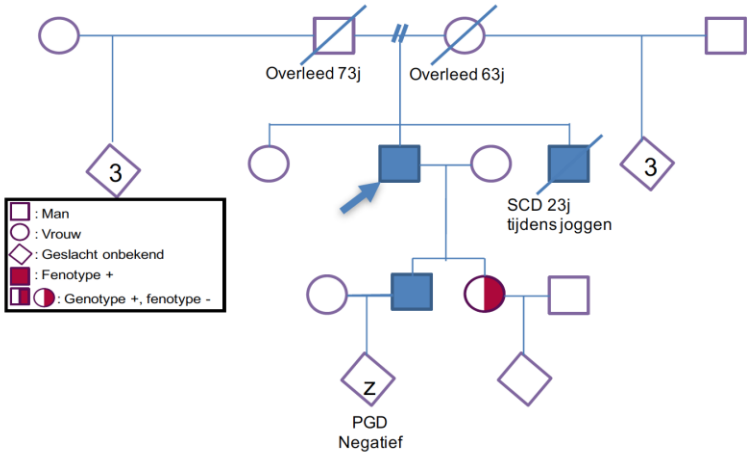
Pinto *et al* 2016

Left ventricular or biventricular systolic dysfunction and dilatation, that is not explained by abnormal loading conditions or coronary artery disease

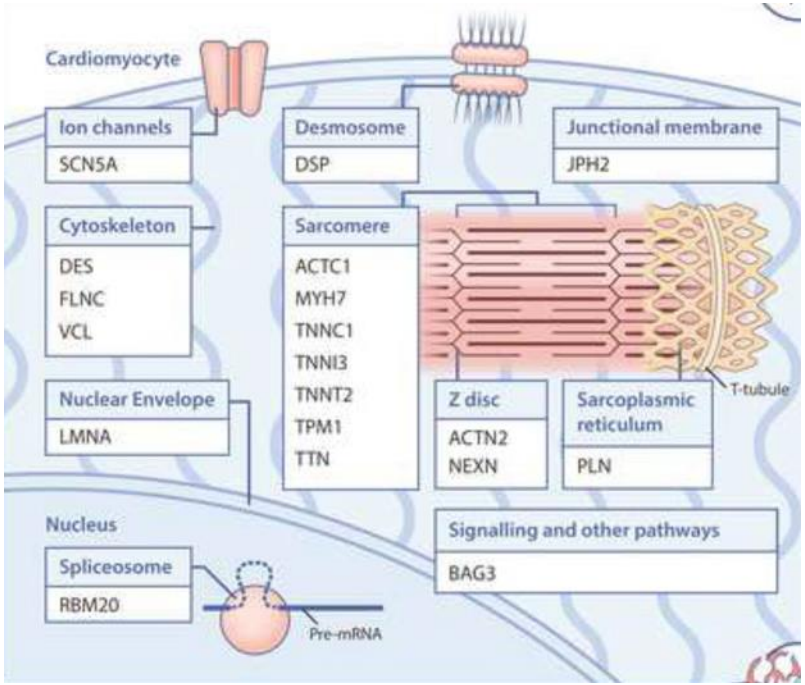
ESC position statement, Eur Heart J, 2016:37(23);1850–1858

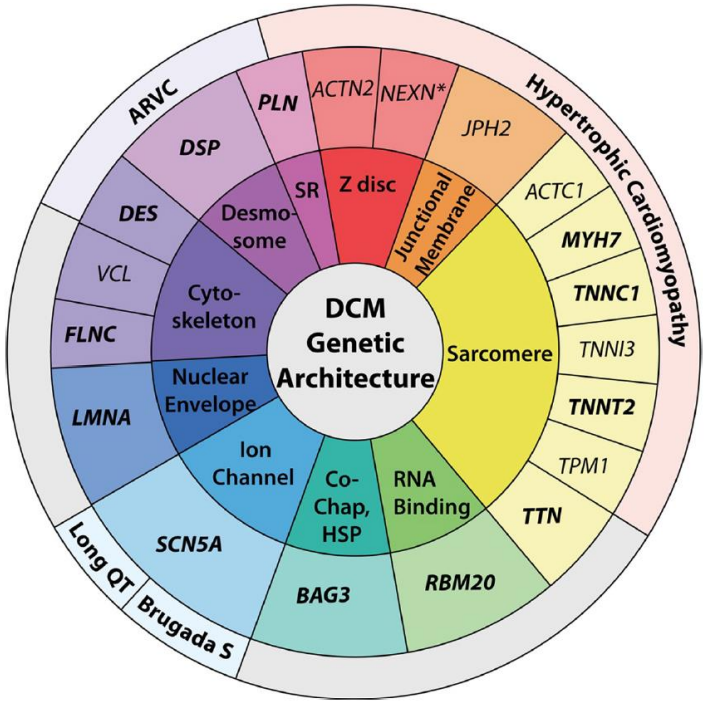
Genetic basis of DCM

- 20-30% of DCM is familial (positive familial history)
  - Identifiable monogenic cause in 25-40%
  - inheritance is usually autosomal dominant
  - genetically heterogeneous
  - variable & age-related penetrance



Monogenic dilated cardiomyopathy: key genes





Jordan et al, Circulation 2021

TTN variants

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

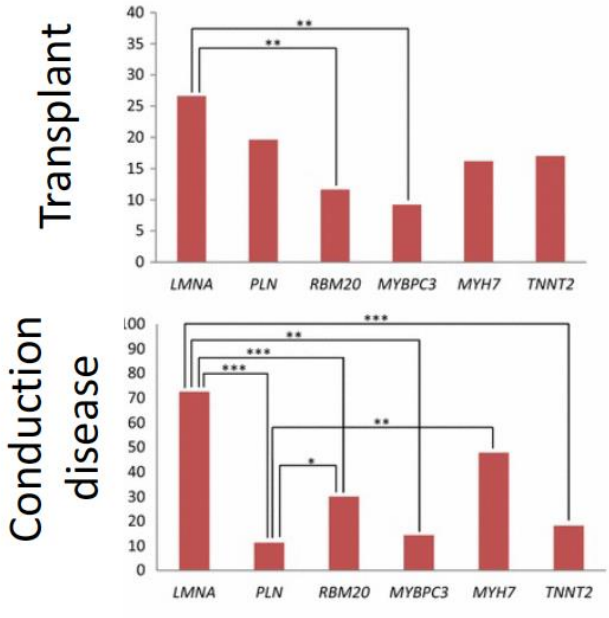
Truncations of Titin Causing Dilated Cardiomyopathy

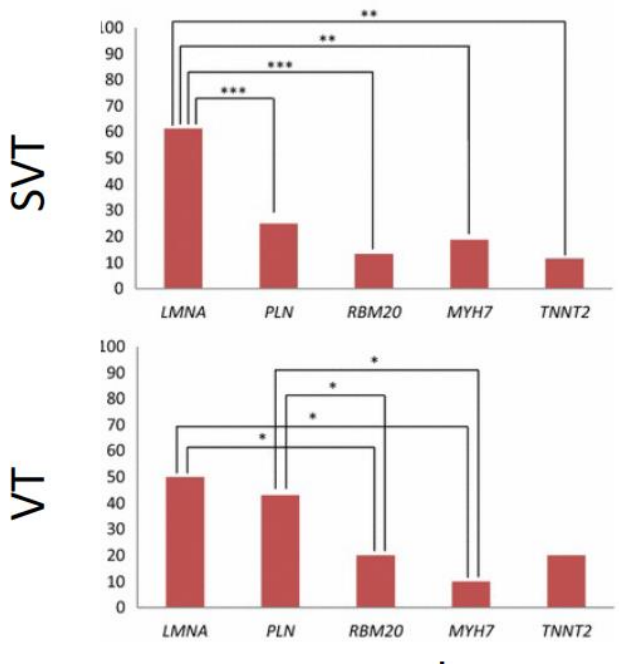
Daniel S. Herman, Ph.D., Lien Lam, Ph.D., Matthew R.G. Taylor, M.D., Ph.D., Libin Wang, M.D., Ph.D., Polakit Teekakirikul, M.D., Danos Christodoulou, B.S., Lauren Conner, B.S., Steven R. DePalma, Ph.D., Barbara McDonough, R.N., Elizabeth Sparks, R.N.P., Debbie Lin Teodorescu, M.A., Allison L. Cirino, C.G.C., Nicholas R. Banner, F.R.C.P., Dudley J. Pennell, M.D., Sharon Graw, Ph.D., Marco Merlo, M.D., Andrea Di Lenarda, M.D., Gianfranco Sinagra, M.D., J. Martijn Bos, M.D., Ph.D., Michael J. Ackerman, M.D., Ph.D., Richard N. Mitchell, M.D., Ph.D., Charles E. Murry, M.D., Ph.D., Neal K. Lakdawala, M.D., Carolyn Y. Ho, M.D., Paul J.R. Barton, Ph.D., Stuart A. Cook, M.D., Luisa Mestroni, M.D., J.G. Seidman, Ph.D., and Christine E. Seidman, M.D.

" TTN truncating mutations are a common cause of dilated cardiomyopathy, occurring in approximately 25% of familial cases of idiopathic dilated cardiomyopathy and in 18% of sporadic cases "

Herman DS et al, NEJM 2012

Prognostication by genotype



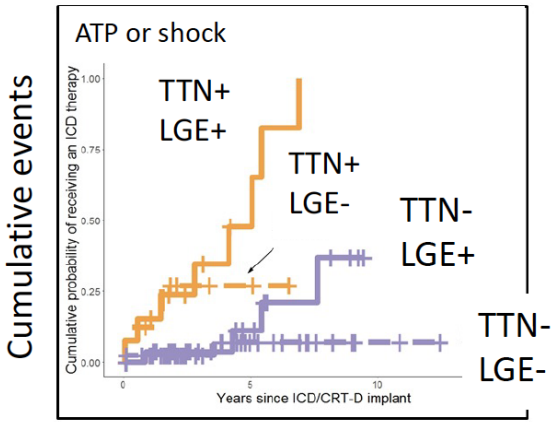


Kayvanpour et al, 2017

Prognostication by genotype

117 DCM patients with ICD in situ

TTN variants predict ICD therapies for VT (> 200bpm) or VF



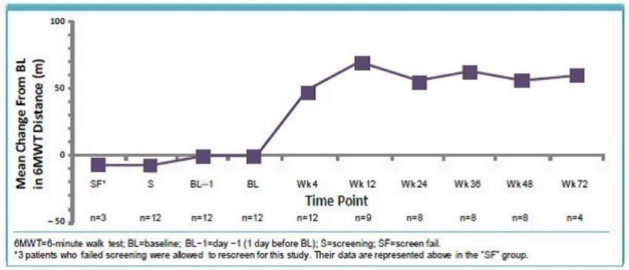
TTNtv + / LGE +
vs.
TTNtv - / LGE –

HR = 16.6
(3.5-79)
P<0.0001

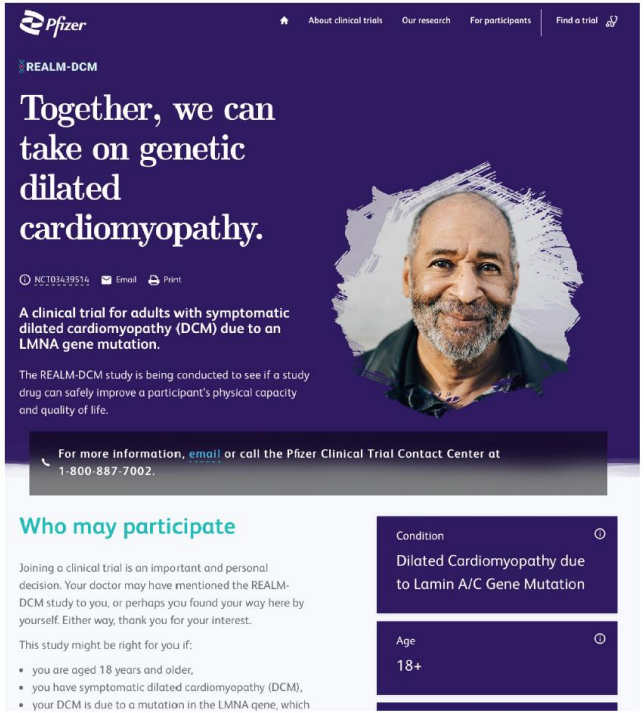
Corden et al , JAMA Netw Open

Genotype targeted therapies

Targeted therapies for LMNA DCM

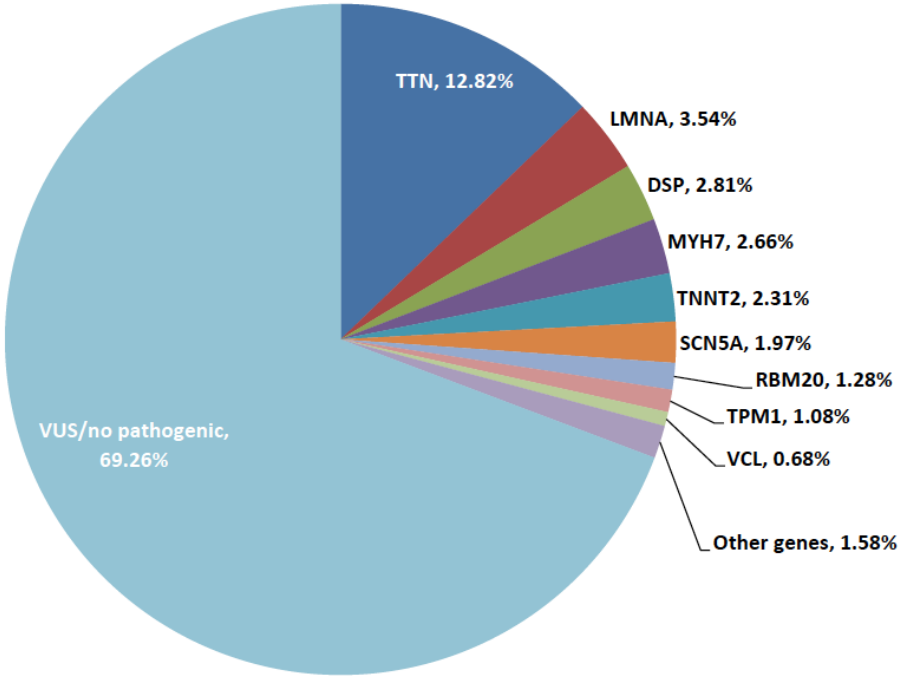


Phase 2 results: improved 6 minute walk test



Arry-371797
MAPK inhibitor

Current challenges in DCM

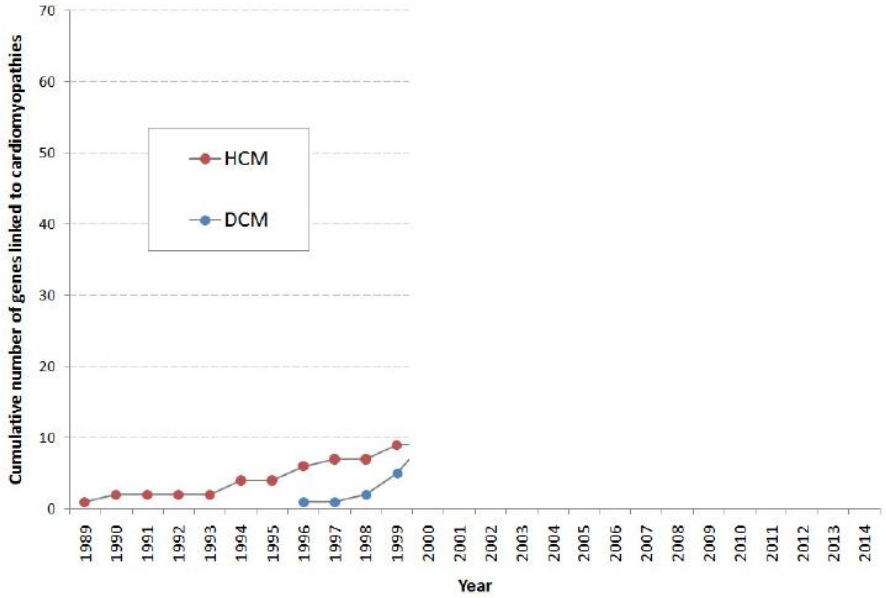


60-70% familial DCM is genetically unexplained

Walsh, Thomson *et al*, Genetics in Medicine 2016

Current challenges in DCM

Rapid gene discovery….



111 genes tested for DCM in commercial laboratories

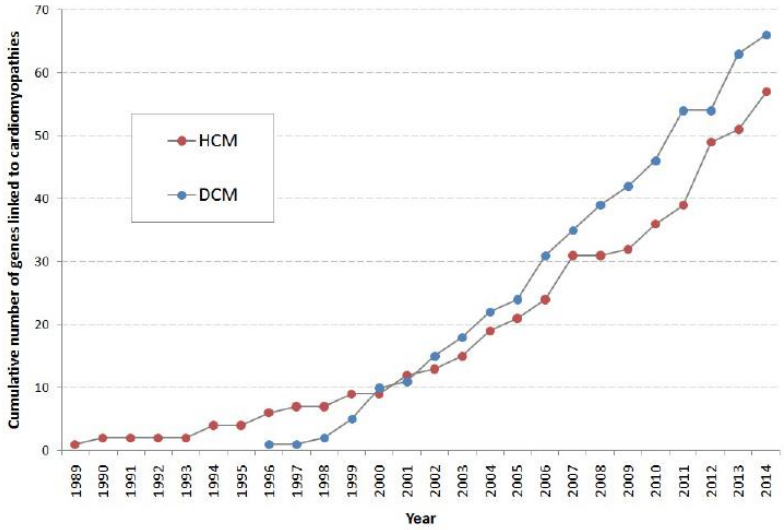
ABCC9	**ACTC1**	**ACTN2**	AGL1	ALMS1	ALPK3	**ANKRD1**	**BAG3**	BRAF
CACNA1C	CALR3	CASQ2	**CAV3**	**CHRM2**	**CRYAB**	**CSRP3**	CTF1	CTNNA3
DES	**DMD**	**DOLK**	**DSC2**	**DSCG2**	**DSP**	**DTNA**	**EMD**	EYA4
FHL1	**FHL2**	FKRP	FKTN	FLNC	FXN	**GATAD1**	GATA4	GATA6
GAA	**GLA**	HCN4	HRAS	**ILK**	**JPH2**	**JUP**	KRAS	**LAMA4**
LAMP2	**LDB3**	**LMNA**	LRRC10	MAP2K1	MAP2K2	MIB1	MTND1	MTND5
MTND6	MTTD	MTTG	MTTH	MTTI	MTTK	MTTL1	MTTL2	MTTM
MTTQ	MTTS1	MTTS2	**MURC**	**MYBPC3**	**MYH6**	**MYH7**	**MYL2**	**MYL3**
MYLK2	**MYOM1**	**MYOZ2**	**MYPN**	**NEBL**	**NEXN**	NKX2-5	NPPA	NRAS
PDLIM3	**PKP2**	PLKHM2	**PLN**	**PRDM16**	**PRKAG2**	**PTPN11**	**RAF1**	**RBM2**
RIT1	**RYR2**	**SCN5A**	**SGCD**	**SLC22A5**	**SOS1**	**TAZ**	TBX20	**TCAP**
TGFB3	**TMEM43**	**TMPO**	**TNNC1**	**TNNI3**	**TNNT2**	**TPM1**	TRDN	**TTN**
TTR	**TXNRD2**	**VCL**						

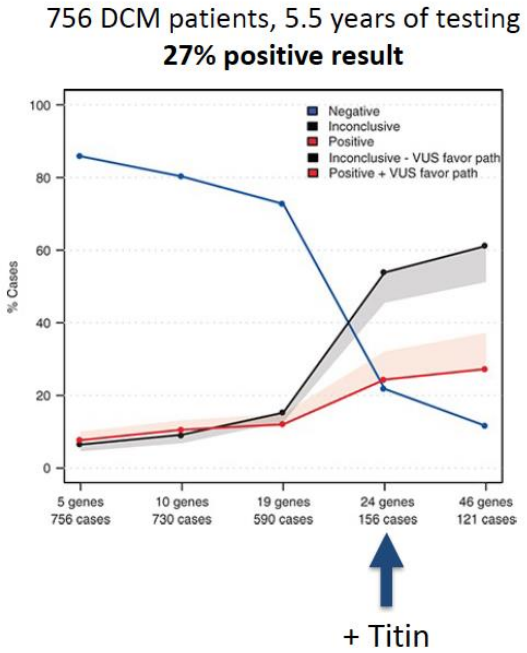
Found only on one panel and reflect genes implicated in Noonan, mitochondrial, neuromuscular

McNally & Mestroni Circ Res. 2017;121:731

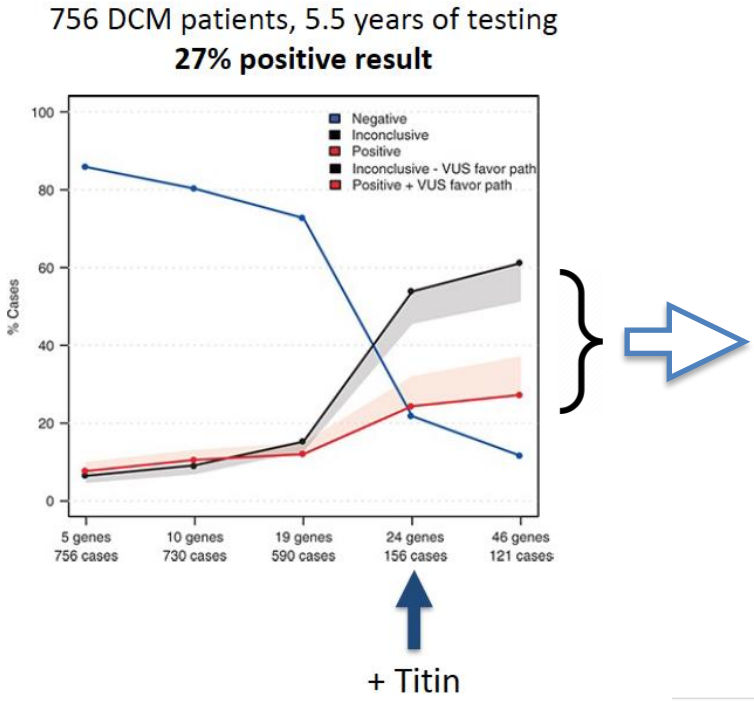
Current challenges in DCM

Rapid gene discovery…. but with little benefit





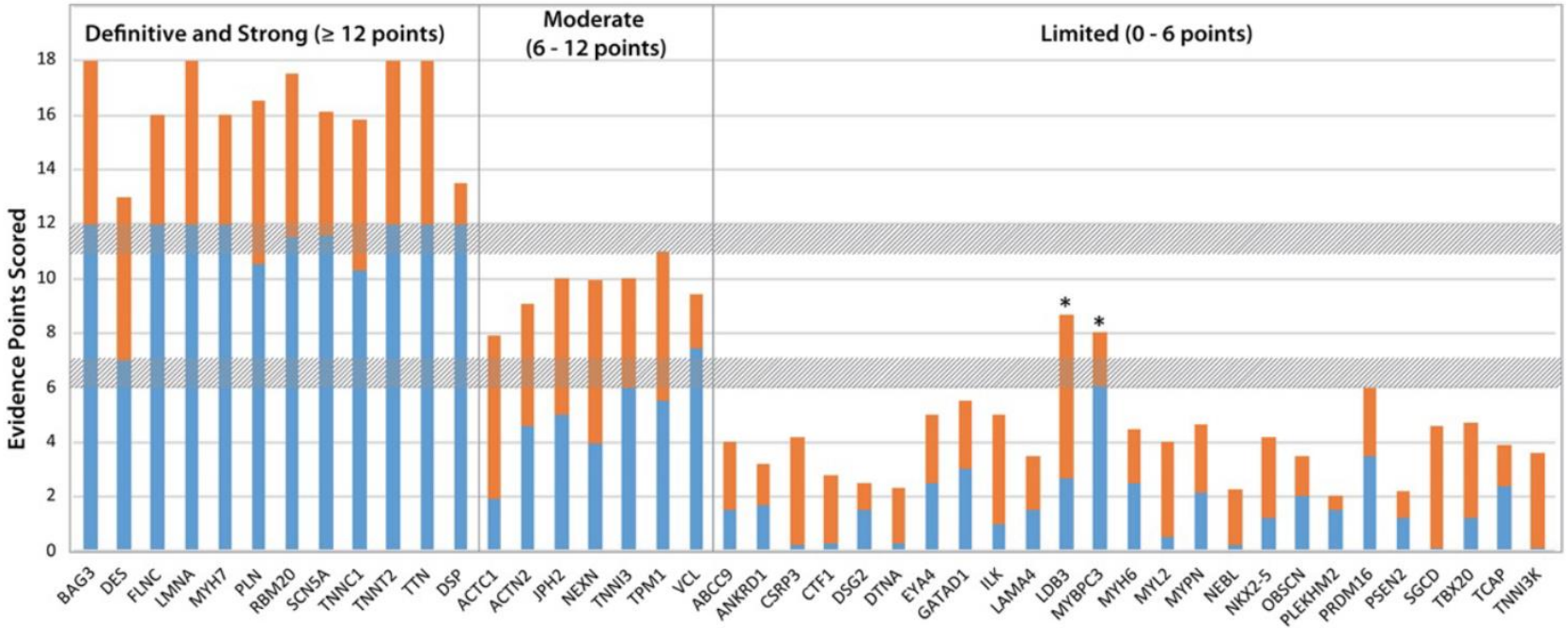
Current challenges in DCM



Many variants difficult to interpret

Current challenges in DCM

Most genes in DCM are spurious

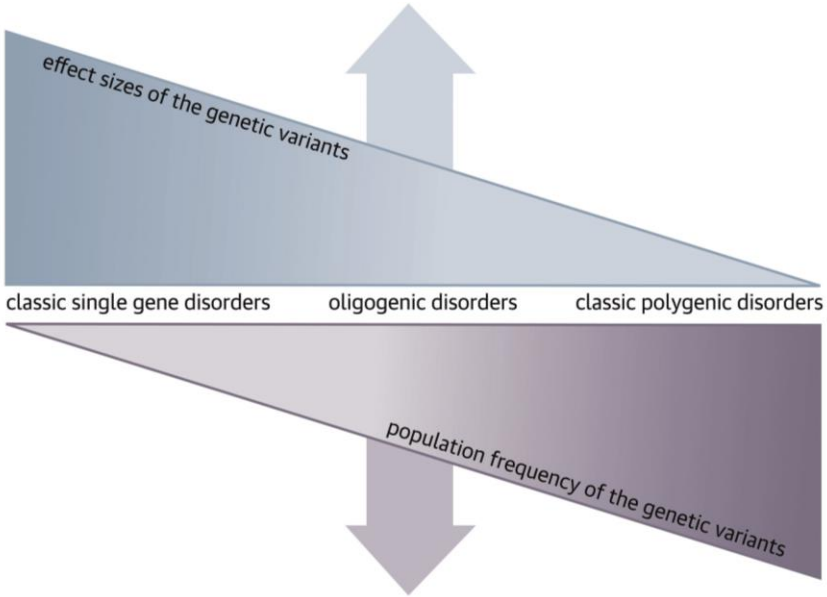


Jordan et al, Circulation 2021

How to explain these gene-elusive DCM?

Not monogenic disease?

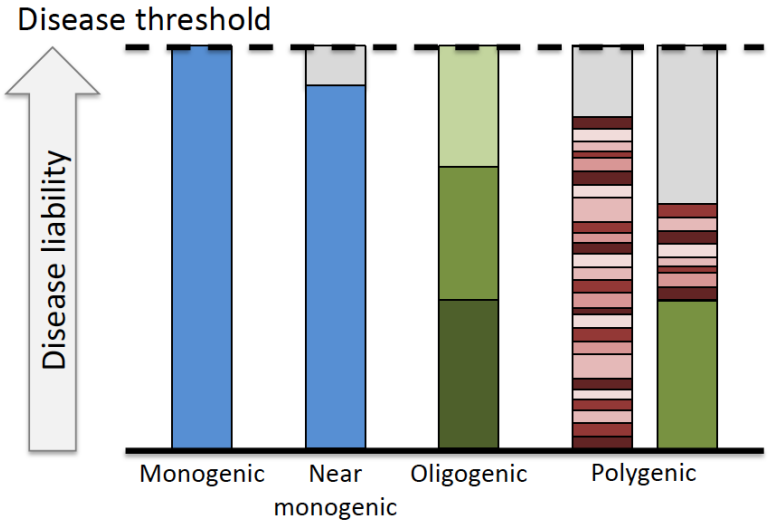
Very rare variants with large effect sizes



Multiple common variants with small effect size

Marian AJJ, JACC 2020

Genetic modifiers and polygenic risk



rare variants - individually large effect
common variants – collectively large effect
environmental and other exposures

Large effect variants (rare)
Intermediate effect variants
Common variants
Environment

Adapted from Bezzina Circ Res 2015

Environmental modifiers

Genetic Etiology for Alcohol-Induced Cardiac Toxicity

Truncating variants in TTN in 9.9 % of the patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies

Truncating variants in TTN in 10% of the patients compared to 1.4% of the reference population

Circulation
Volume 140, Issue 1, 2 July 2019; Pages 31-41
https://doi.org/10.1161/CIRCULATIONAHA.118.037934

American Heart Association.

ORIGINAL RESEARCH ARTICLE

Genetic Variants Associated With Cancer Therapy–Induced Cardiomyopathy

Truncating variants in TTN in 7.5 % of the patients

2016 2018 2016 2019

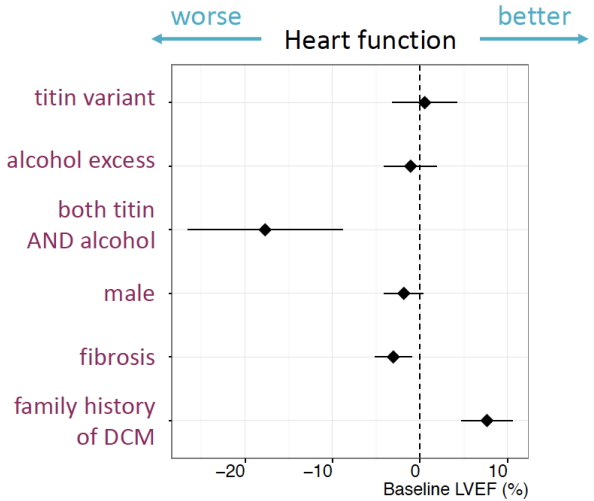
Genetic etology of alcohol induced CMP

	Alcohol CM (n=141)	Dilated CM (n=366)	Healthy Volunteer (n=445)
TTNtv	14 (9.9%)	44 (12%)	3 (0.7%)

JACC 2018

Genetic Etiology for Alcohol-Induced Cardiac Toxicity

a self-reported history of alcohol intake of >80 g/day over a period of at least 5 years



Ware JS et al, JACC 2018

Genetic etology of peripartum CMP

- 172 women with PPCM
  - Truncating variants in *TTN* in 10% of the patients compared to 1.4% of the reference population ($P=2.7\times10^{-10}$);
  - Yield of genetic testing in PPCM is similar compared to a cohort of patients with DCM[7].
  - This suggest that at least a subset of PPCM has a genetic etiology

Table 1. Demographic Characteristics of the Patients in Each Cohort and the Prevalence of Truncating Variants at Baseline.*

Characteristic	Group A (N=10)	Group B (N=26)	Group C (N=10)	Group D (N=9)	Group E (N=34)	Group F (N=83)	All Patients (N=172)
	Temple University	University of Pennsylvania	University of Hannover, Germany	Japan	IMAC-2	IPAC	
Age — yr	34.2±7.6	34.1±7.4	34.3±6.7	30.8±3.4	31.2±6.8	29.8±6.3	31.3±6.7
African descent — no. (%)†	5 (50)	16 (62)	5 (50)	0	11 (32)	24 (29)	61 (35)
Left ventricular ejection fraction — %	10.0±3.9	30.1±13.5	27.6±10.8	29.1±10.1	27.2±7.4	29.8±9.7	28.6±10.4
Patients with truncating variants — no. (%)							
Any	2 (20)	1 (4)	1 (10)	1 (11)	6 (18)	15 (18)	26 (15)
TTN	0	0	1 (10)	1 (11)	4 (12)	11 (13)	17 (10)

* Plus–minus values are means ±SD. IMAC-2 denotes Intervention in Myocarditis and Acute Cardiomyopathy 2, and IPAC Investigations in Pregnancy Associated Cardiomyopathy.
† Ancestry was defined genetically by means of principle-component analysis of all common variants that were sequenced.

Ware J et al. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. NEJM 2016

Genetic etology of anthracylin-induced CMP

Circulation
Volume 140, Issue 1, 2 July 2019; Pages 31-41
https://doi.org/10.1161/CIRCULATIONAHA.118.037934

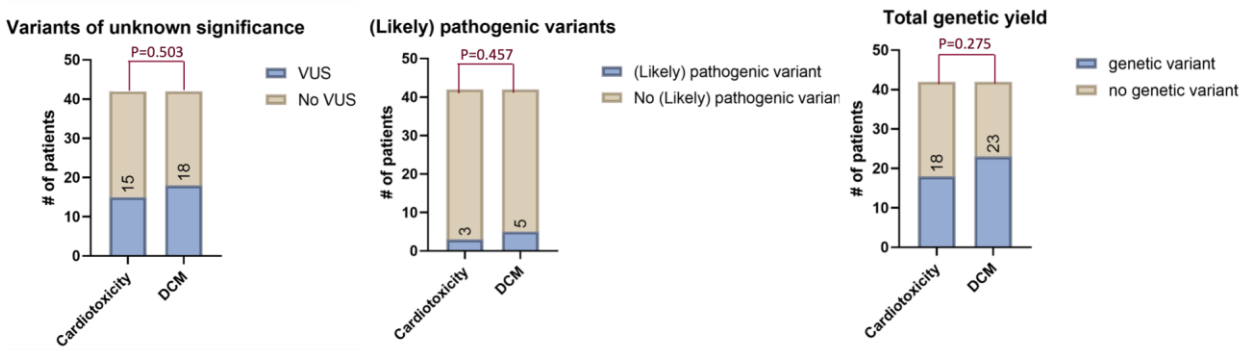
ORIGINAL RESEARCH ARTICLE

Genetic Variants Associated With Cancer Therapy–Induced Cardiomyopathy

Truncating variants in TTN in 7.5 % of the patients

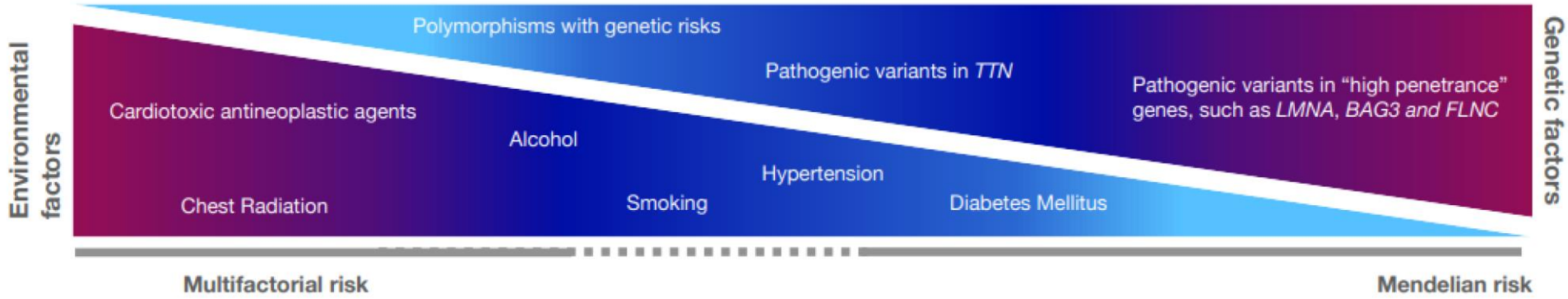
42 Cardiotoxicity patients

42 DCM controls

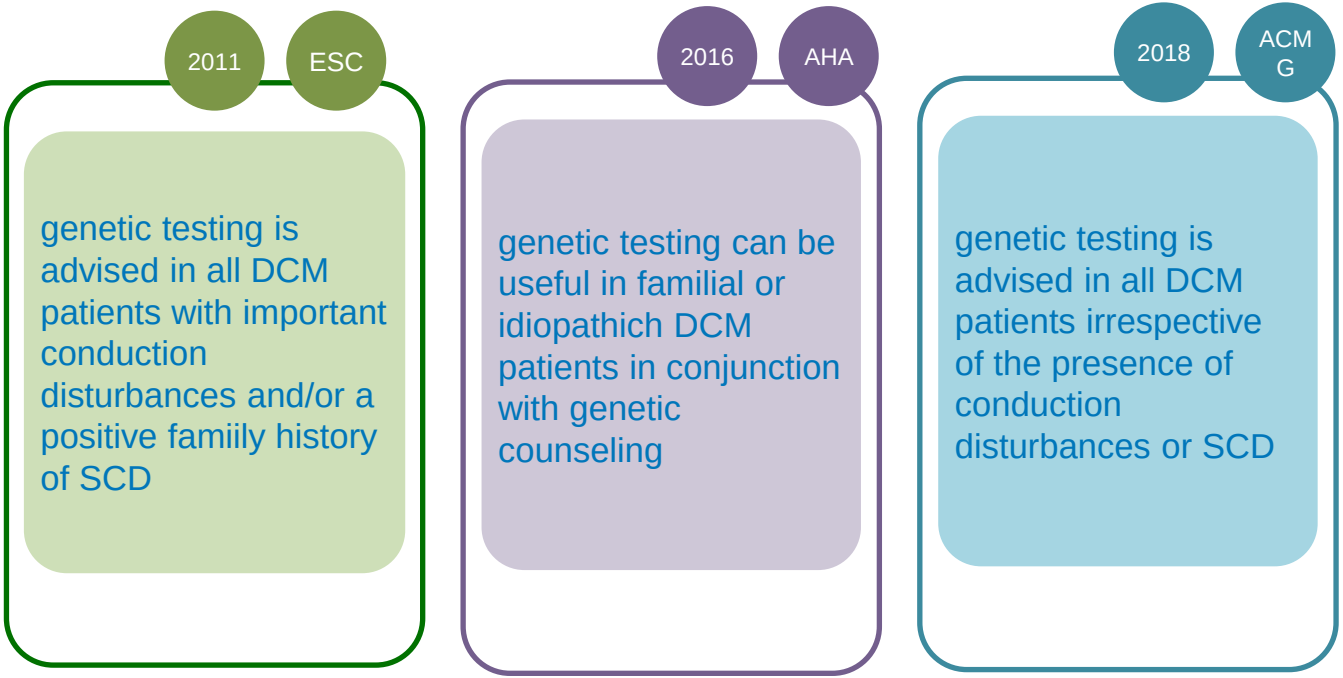


Garcia Pavia P et al Circulation 2019

Genetic architecture of DCM is complex



Genetic testing in DCM: who to refer?



Ackerman MJ et al, *Heart Rhythm.* 2011;8(8):1308-1339. 2. Bozkurt et al *Circulation* 2016 3. Hershberger RE et al. *Genet Med.* 2018;20(9):899-909.

Genetic testing in DCM: who to refer?

- Diagnostic yield is considerablen even in **isolated cases**!
  - 15-25% pathogenic variants in isolated cases
  - 25-40% in patients with positive family history

- Genetic testing should be considered in '**acquired DCM**'
  - alcoholic CMP
  - peripartum CMP
  - Anthracyclin- induced CMP

Understanding the genetics of adult-onset dilated cardiomyopathy: what a clinician needs to know

Upasana Tayal, James S Ware, Neal K Lakdawala, Stephane Heymans, Sanjay K Prasad ✉

European Heart Journal, Volume 42, Issue 24, 21 June 2021, Pages 2384–2396, https://doi.org/10.1093/eurheartj/ehab286
Published: 21 June 2021 **Article history** ▾

Take home messages

Clinical utility of genomics in HCM/DCM

- Benefit for the patient: genetic testing contributes to
  - establishing the diagnosis in case of doubt
  - Precision medicine
    - SCD risk estimation
    - Stratified therapy
  - exclude phenocopy conditions- requiring a different managment (eg. enzyme replacement therapy in Fabry disease)
- Benefit for the family
  - Genetic counselling
  - Cascade screening and (early) diagnosis
  - Reproductive counselling and prenatal diagnosis

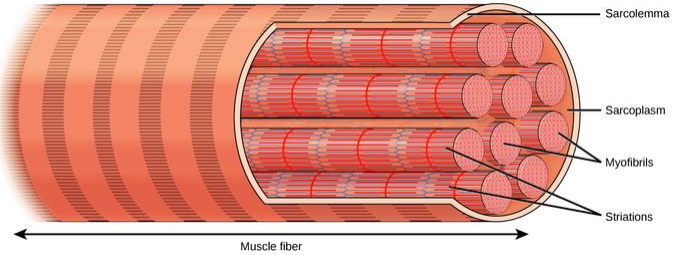
ESHG Training course on Cardiogenetics
5th October 2021

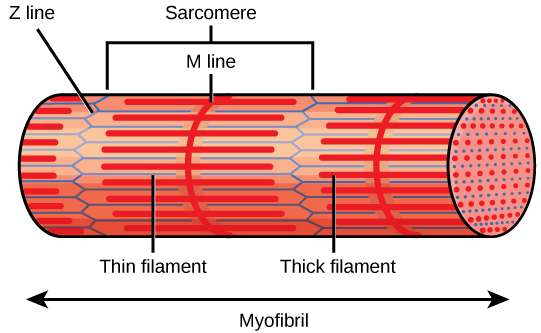
Neuromuscular cardiomyopathy

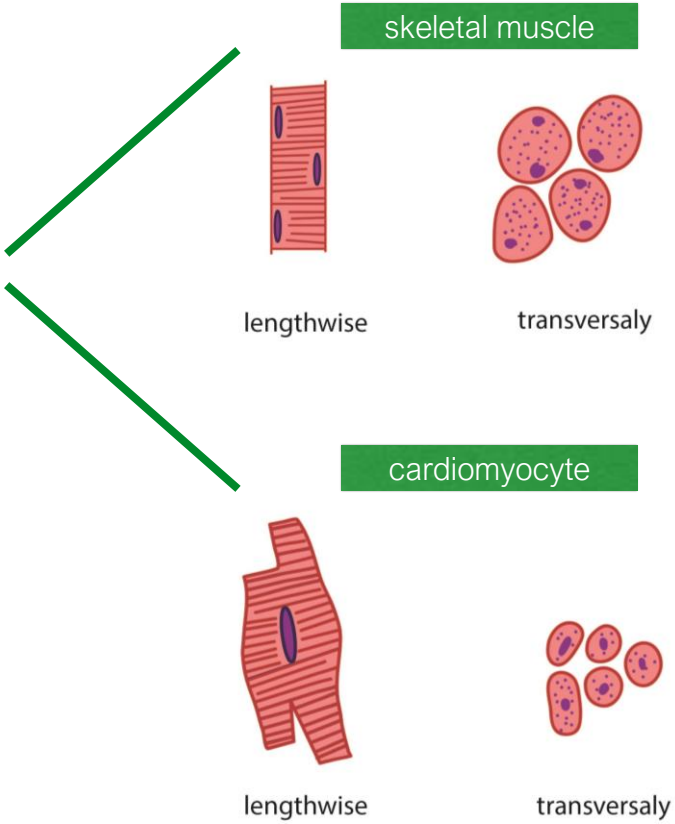
Emeline Van Craenenbroeck
Cardiologist UZA
Heart Failure, transplantation and cardiogenetics

Cardiac involvement in neuromuscular disorders

Overview


Sarcolemma
Sarcoplasm
Myofibrils
Striations
Muscle fiber


Z line
Sarcomere
M line
Thin filament
Thick filament
Myofibril


skeletal muscle
lengthwise
transversaly
cardiomyocyte
lengthwise
transversaly

NMDs that are associated with cardiac disease

A. Myotonic dystrophy
B. Dystrophinopathies: Becker and Duchenne muscular dystrophy
C. Emery-Dreifuss muscular dystrophy
D. Limg girdle muscular dystrophy (miscellaneous)
E. Myofibrillar myopathy
F. Facioscapulohumeral muscular dystrophy
G. Friedreich ataxia

NMDs that are associated with cardiac disease

A. Myotonic dystrophy

B. Dystrophinopathies: Becker and Duchenne muscular dystrophy

C. Emery-Dreifuss muscular dystrophy

D. Limg girdle muscular dystrophy (miscellaneous)

E. Myofibrillar myopathy

F. Facioscapulohumeral muscular dystrophy

G. Friedreich ataxia

3. NMDs associated with cardiac disease

Myotonic dystrophy (DM)

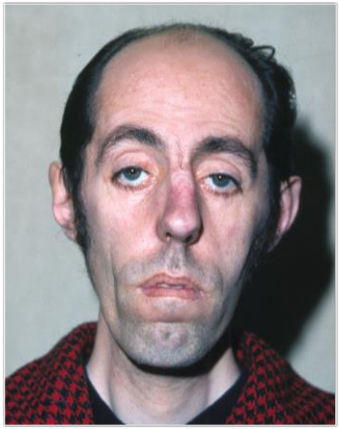
- Prevalence: most common muscular dystrophy, DM1 affects1 in 8000 persons
- Genetics: AD
- DM1 (Steinert disease)
    - CTG-repeat expansion >48 repeats in a non-coding sequence of the dystrophia myotonica protein kinase gene (DMPK gene) on chromosome 19q 13.3.
    - The length of the CTG repeat expansion is moderately correlated with disease severity and age of onset: Mild 50-150 repeats, classic 50-1000 repeats, congenital > 1000 repeats
- DM2 (Proximal myotonic myopathy, PROMM)
    - CCTG repeat expansioin in ZNF9 gene
    - No correlation between repeat length and disease severity

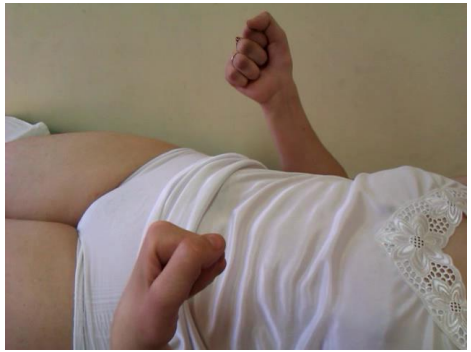
3. NMDs associated with cardiac disease

Myotonic dystrophy (DM)

Neurological and extra-muscular presentation

- DM2 milder phenotype compared to DM1
- Muscular characteristics: progressive myopathy characterized by both distal and facial weakness and muscle atrophy, myotonia
- Extra-muscular characteristics: frontal balding, cataract, low intelligence, infertility en hypogonadism, insulin resistance, irritable bowel disease, OSAS





3. NMDs associated with cardiac disease

Myotonic dystrophy (DM)

Cardiac phenotypes in DM1

1. Electrical disturbances +++

- 1st degree AV block is seen in up to **40%** cases. BBB, long QT, ST-T modifications and axis deviations are other possible findings
- Supraventricular tachycardia is very common with up to **25%** patients presenting atrial fibrillation or and/or atrial flutter
- Ventricular tachycardia is frequent. 50% of patients who have a pacemaker (PM) for AV block, develop VT and are at risk of SCD

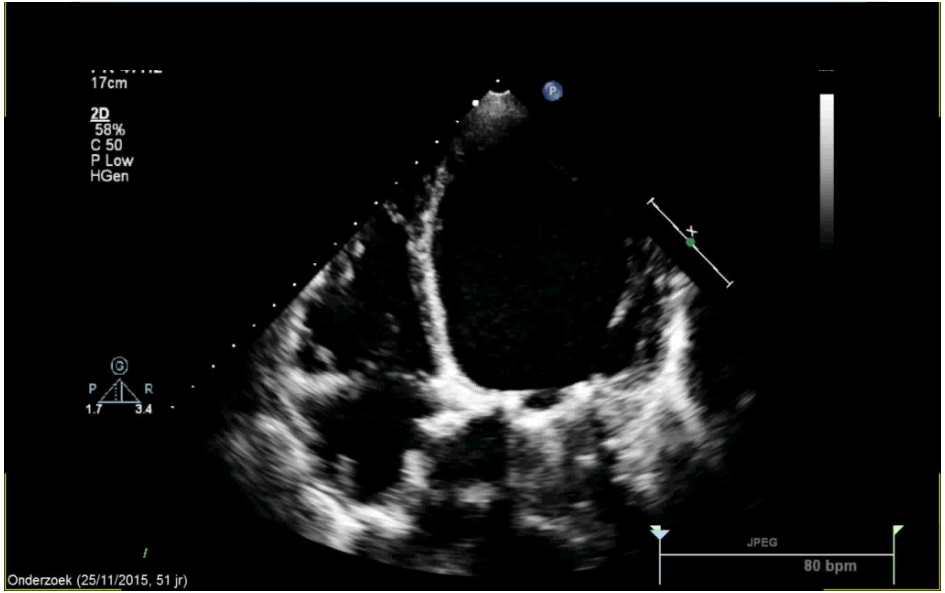
2. Cardiomyopathy +

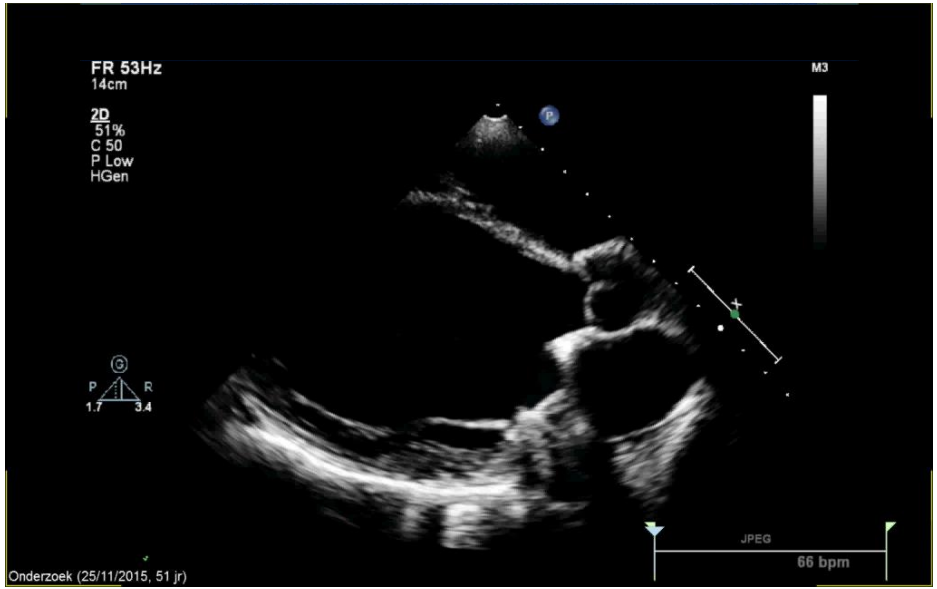
- DCM, HCM or non-compaction CM

3. NMDs associated with cardiac disease

Myotonic dystrophy (DM)

Male, 53 y





3. NMDs associated with cardiac disease

Myotonic dystrophy (DM)

Pathophysiology of cardiac phenotypes in Steinert disease

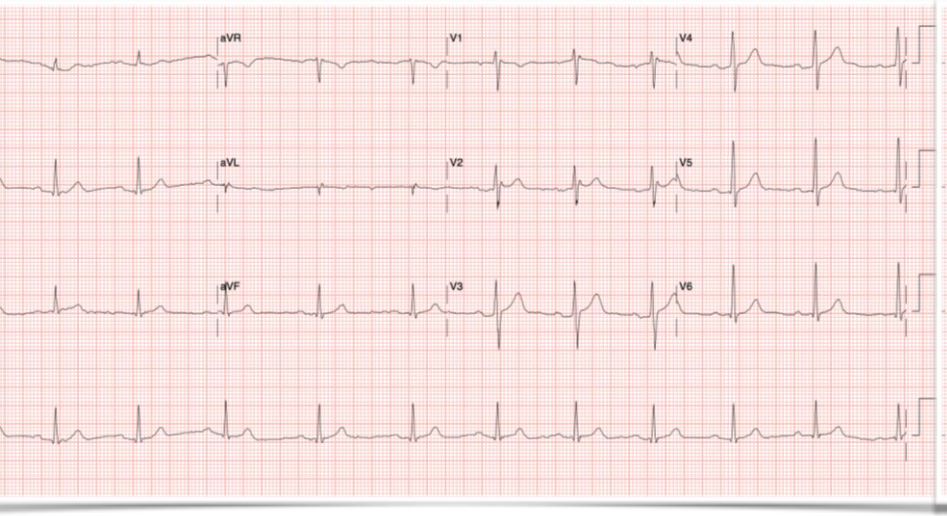
- Myocardial fibrosis
- Degeneration, fibrosis, and fatty infiltration of the cardiac conduction tissue
- DM1 is the prototype of a RNA-mediated disease
    - The pathologically expanded DMPK mRNA transcript has a polyadenylated (CUG) tail that confers a toxic gain-of-function via sequestration of RNA-binding proteins and interference with the alternative splicing of numerous other genes (return to fetal splicing)
    - *INSR, CLCN1, CACNA1S, RYR1, SCN5A*

3. NMDs associated with cardiac disease

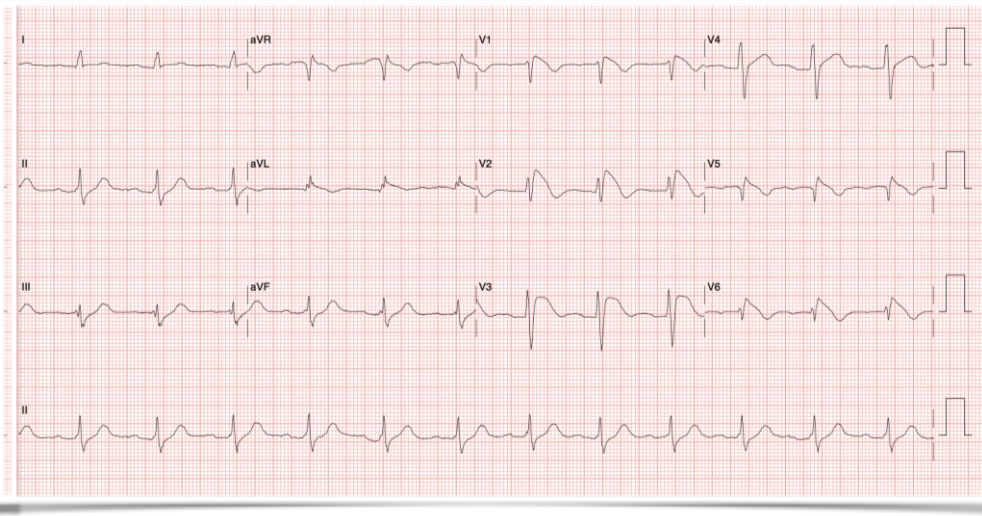
Myotonic dystrophy (DM)

Male, 36 y

ECG at rest



After Ajmaline infusion



3. NMDs associated with cardiac disease

Myotonic dystrophy (DM)

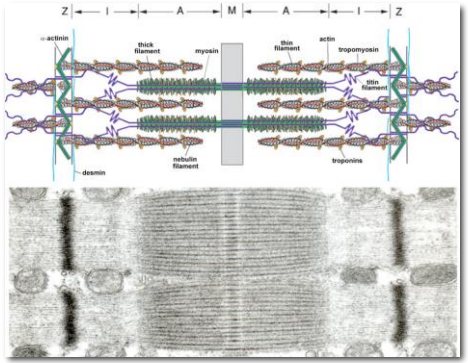
SCD in Steinert disease

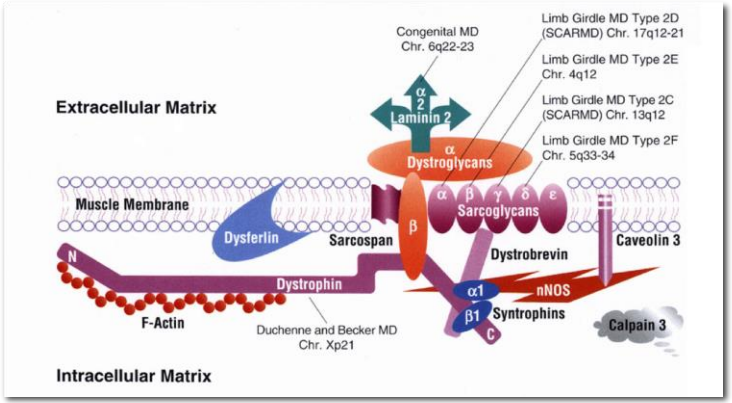
- Cardiovascular Events (LV dysfunction, ischemic heart disease, pulmonary emboli or SCD) represents 30% of mortality
- Sudden death due to cardiac arrhythmia is nearly as common a cause of death in DM1 (29%), as are complications of neuromuscular respiratory failure (31%)
- Steinert is the NMD with highest prevalence of SCD
- 1/4 patients has positive family history for SCD
- Risk factors: myocardial fibrosis, atrial tachyarrytmia, PR-interval >240 msec, aberrant QRS conduction and any degree of AV-block
- The annual risk of sudden cardiac death is estimated at 0.56%

3. NMDs associated with cardiac disease

Dystrophinopathies

- Incidence: 1 in 4000 male births
- Terminology
  - Becker muscular dystrophy (BMD): later onset and milder clinical course
  - Duchenne muscular dystrophy (DMD): more severe phenotype
- Genetics: X-linked
  - deletions of one or more exons (65-70%), duplications (5-10%) and point mutations in dystrophin (DMD) gene
- Muscle fiber degeneration is the primary pathologic process





NMDs that are associated with cardiac disease

A. Myotonic dystrophy

B. Dystrophinopathies: Becker and Duchenne muscular dystrophy

C. Emery-Dreifuss muscular dystrophy

D. Limg girdle muscular dystrophy (miscellaneous)

E. Myofibrillar myopathy

F. Facioscapulohumeral muscular dystrophy

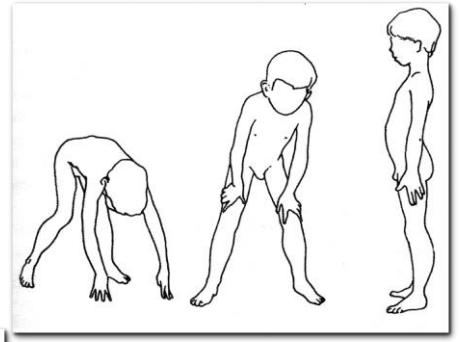
G. Friedreich ataxia

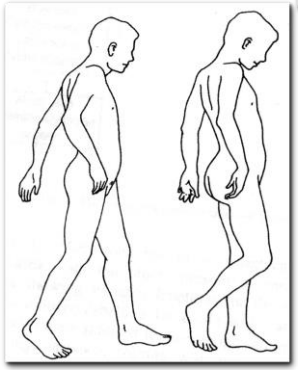
3. NMDs associated with cardiac disease

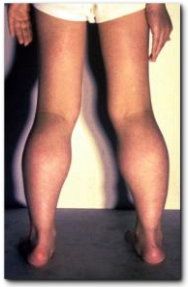
Dystrophinopathies

Neurological presentation

- Muscle weakness proximal > distal, lower> upper extremities
- Gowers' sign: using hand support to get into upright position
- Waddling gait, lumbar lordosis
- Pseudohypertrophy



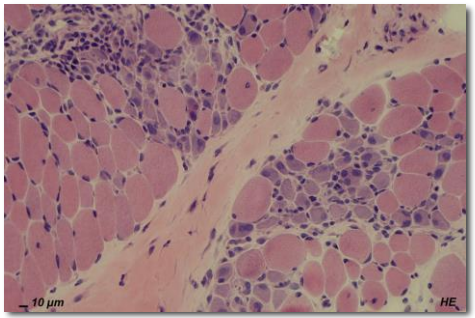


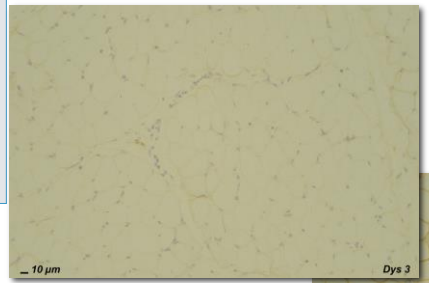


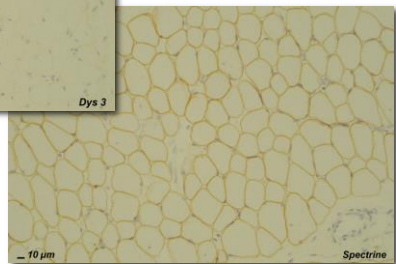
3. NMDs associated with cardiac disease

Dystrophinopathies

	Clinical features	Pathological features
Duchenne	- Onset: 2-5 yrs - Pseudohypertrophy - Reduced IQ - Cardiac involvement - Death by age 20-30 yrs	- Absent dystrophin on immunohistochemistry - WB: Dystrophin <5% of normal amount
Becker	- Onset: variable - More benign course	- Reduced dystrophin on immunohistochemistry - WB: Dystrophin > 20% of normal amount







3. NMDs associated with cardiac disease

Dystrophinopathies

Cardiac phenotype

1. Dilated cardiomyopathy ++

- *Fibrosis* of the posterobasal left ventricular wall
- ECG: characteristic ECG with tall right precordial R waves, Q waves inferolateral
- TTE: severe mitral regurgitation due to involvement of the posterior papillary muscle
- DMD-associated dilated cardiomyopathy (DCM): heart is primarily affected and skeletal muscle is spared

2. Electrical disturbances ++

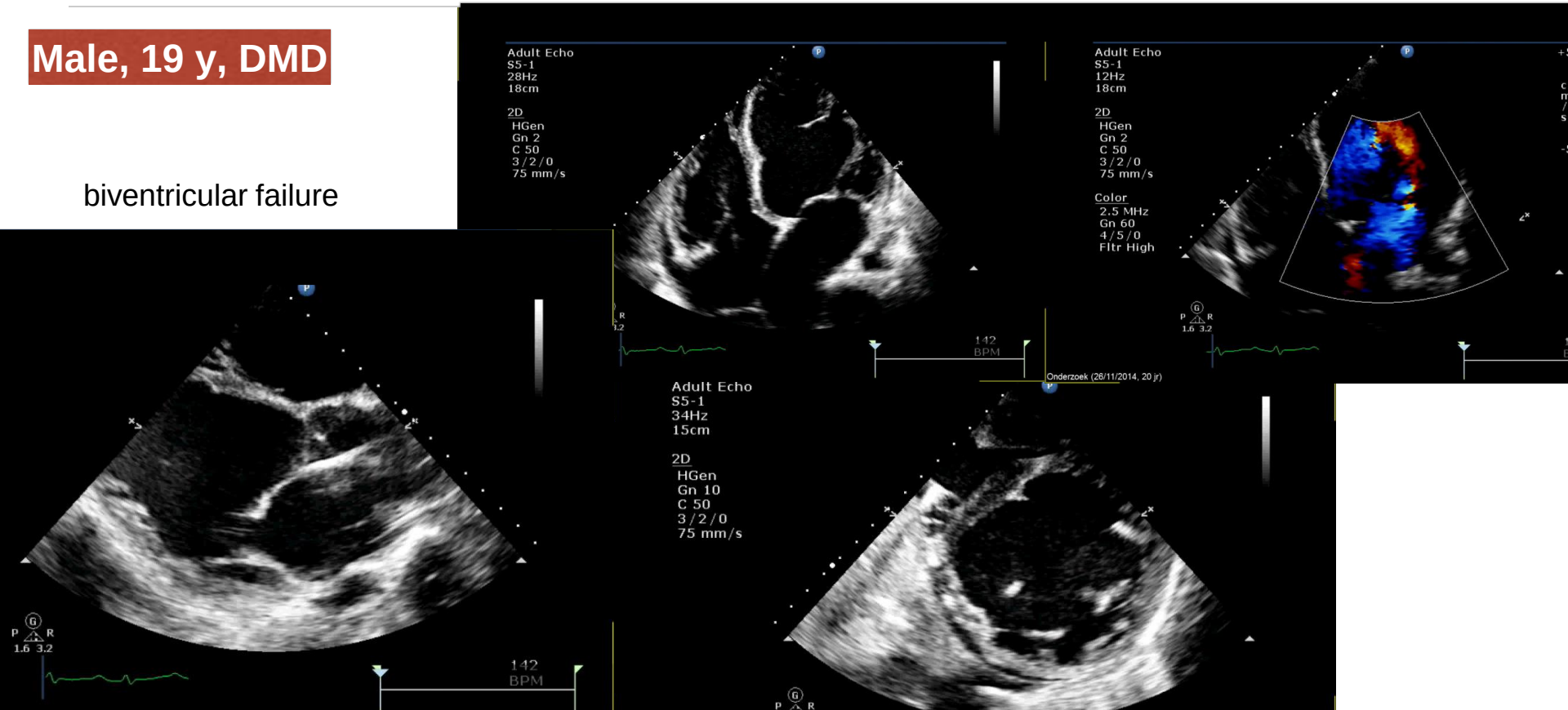
- conduction delay, especially atrial and AV node
- arrhythmias

3. NMDs associated with cardiac disease

Dystrophinopathies

Male, 19 y, DMD

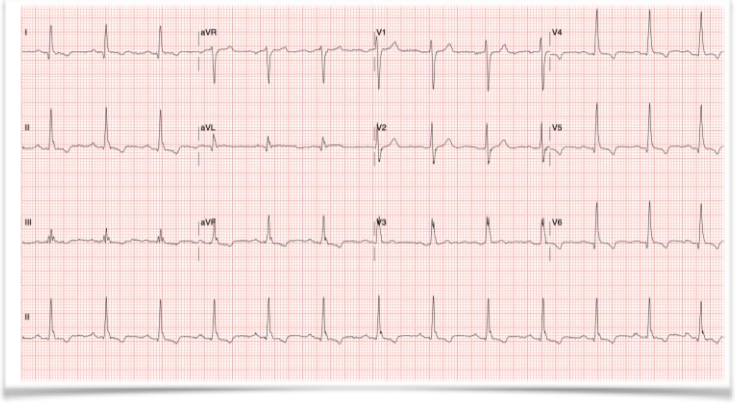
biventricular failure



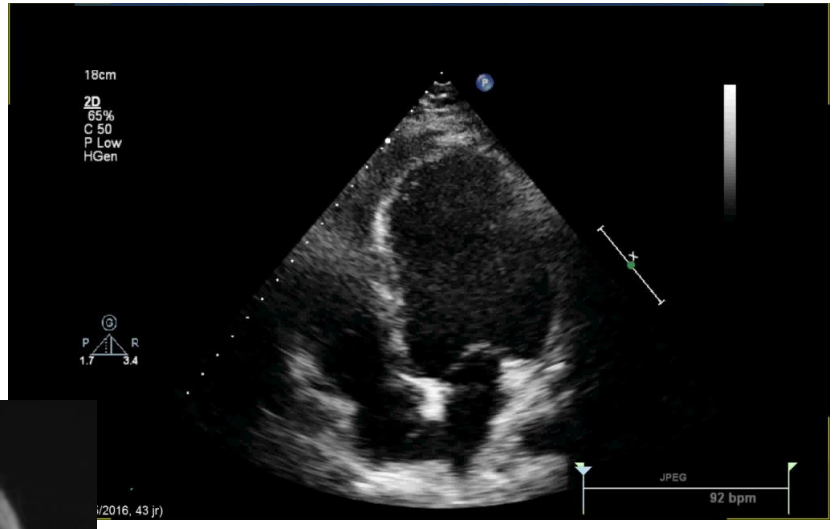
3. NMDs associated with cardiac disease

Dystrophinopathies

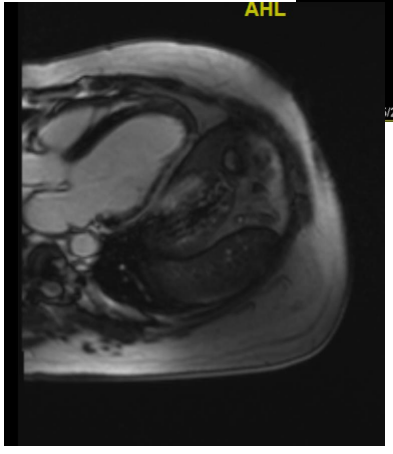
Male, 44 y, BMD



ECG: TWI inferolateral, Q waves lateral



TTE= LVEF 33%



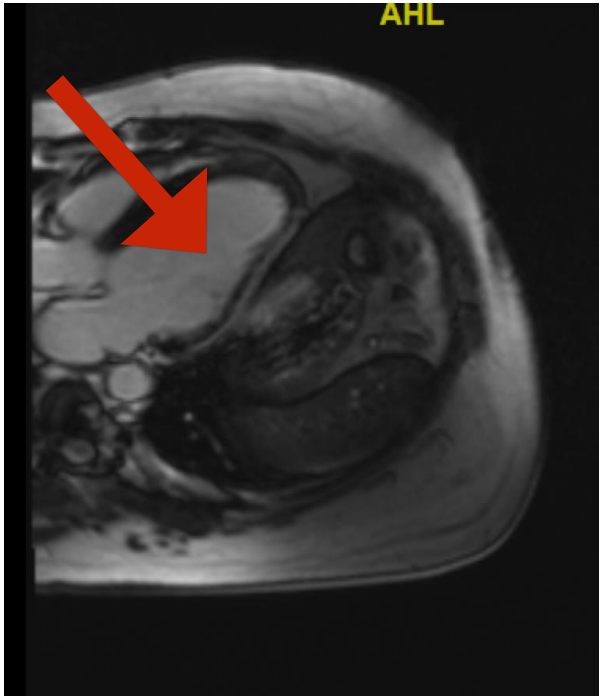
CMR: LGE lateral LV +++

3. NMDs associated with cardiac disease

Dystrophinopathies

SCD in Becker and Duchenne muscular dystrophy

- Risk factors:
    - increased LVEDD
    - low EF
    - fibrosis (LGE on CMR)
    - Large QT dispersion



CMR: LGE lateral LV +++

3. NMDs associated with cardiac disease

Emery-Dreifuss muscular dystrophy (EDMD)

- Incidence: rare disorder, estimated prevalence 1 per 100 000
- Genetics: heterogeneous disorder
- Mutations in genes encoding nuclear membrane proteins

	gene	inheritance
EDMD1	EMD (Emerin)	X-linked
EDMD2	LMNA (Lamin A/C)	AD
EDMD3	LMNA (Lamin A/C)	AR
EDMD4	SYNE1	AD
EDMD5	SYNE2	AD
EDMD6	FHL1	X-linked
EDMD7	TMEM43	AD

- Different resentation

NMDs that are associated with cardiac disease

A. Myotonic dystrophy

B. Dystrophinopathies: Becker and Duchenne muscular dystrophy

C. Emery-Dreifuss muscular dystrophy

D. Limg girdle muscular dystrophy (miscellaneous)

E. Myofibrillar myopathy

F. Facioscapulohumeral muscular dystrophy

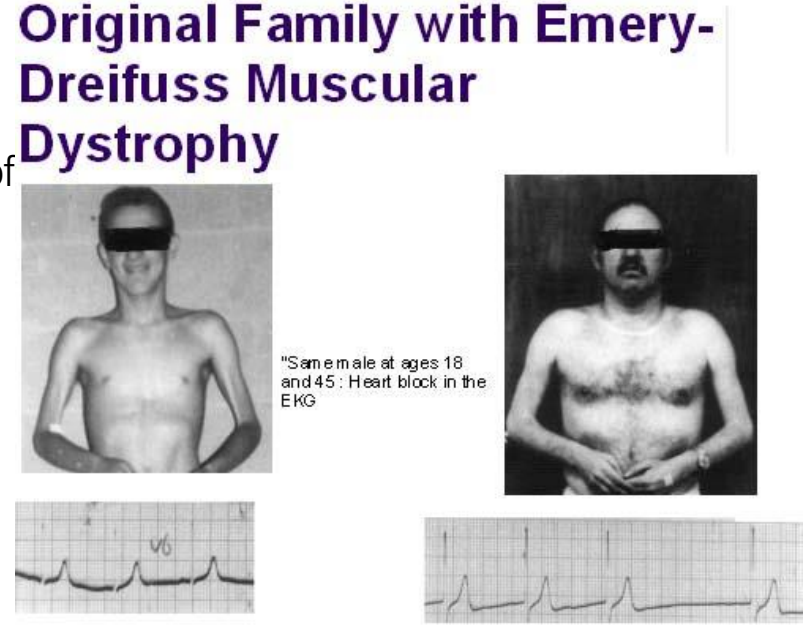
G. Friedreich ataxia

3. NMDs associated with cardiac disease

Emery-Dreifuss muscular dystrophy (EDMD)

Neurological presentation

- Onset: first or second decade of life
- Slowly progressive in the first three decades of life
- Contractures (elbows, achilles tendon) are often first manifestations of the disease
- Humeroperoneal muscular dystrophy: biceps>triceps>distal leg weakness



3. NMDs associated with cardiac disease

Emery-Dreifuss muscular dystrophy (EDMD)

Cardiac phenotype

1.Electrophysiological abnormalities +++

- Atrial standstill
- AF, Aflutter
- AV conduction block
- Ventricular arrhytmias (particularly in EDMD2)

2. Dilated cardiomyopathy ++

- Typically with AV conduction abnormalities
- Sinusbradycardia or supraventricular tachycardia can be early sign of cardiac involvement
- EDMD2 (LMNA mutation): arrhythmogenic DCM with ventricular arrhythmias

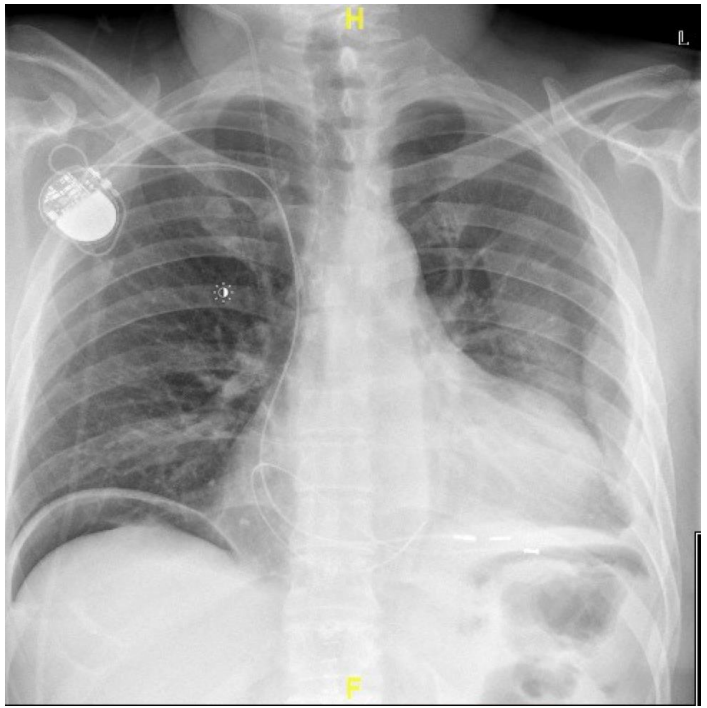
- Onset of cardiac phenotype usually in the third decade of life
- Often manifests before the onset of significant skeletal muscle weakness

3. NMDs associated with cardiac disease

Emery-Dreifuss muscular dystrophy (EDMD)

SCD in EDMD

- Occasionally described, rather rare
- Except for EDMD2 !!!



3. NMDs associated with cardiac disease

Limb girdle muscular dystrophy (LGMD)

- Prevalence: 1 in 20 000, fourth most common genetic cause of muscle weakness
- Characterized by proximal muscle weakness
- Genetics: AD or AR
- Overview of AD forms

	protein	additional clinical features
LGMD1A	Myotilin	dysarthria
LGMD1B	Lamin A/C	- DCM in 60% - associated with AV block
LGMD1C	Caveolin-3	HCM
LGMD1D	DNAJB6	
LGMD1E	Desmin	- arrhytmia, onset 20-25 yrs - DCM (30-50 yrs) - SCD
LGMD1F	TNPO3	

NMDs that are associated with cardiac disease

A. Myotonic dystrophy

B. Dystrophinopathies: Becker and Duchenne muscular dystrophy

C. Emery-Dreifuss muscular dystrophy

D. Limg girdle muscular dystrophy (miscellaneous)

E. Myofibrillar myopathy

F. Facioscapulohumeral muscular dystrophy

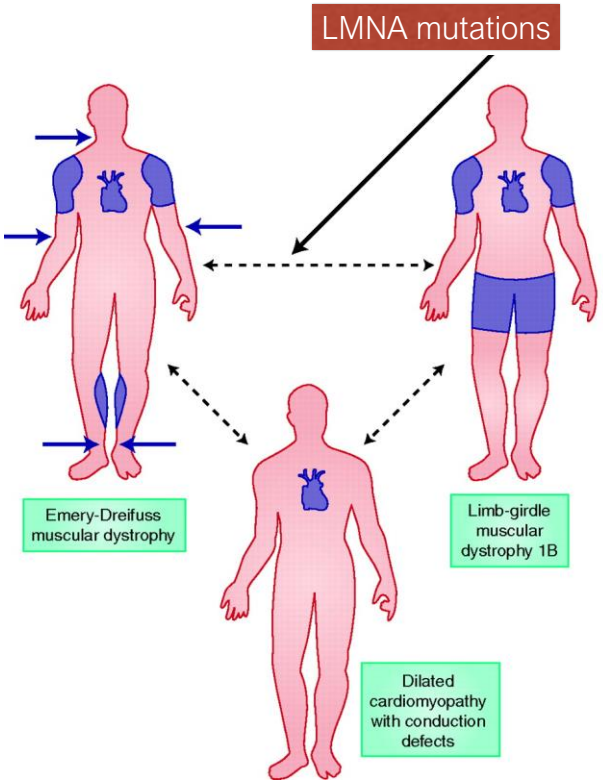
G. Friedreich ataxia

3. NMDs associated with cardiac disease

Summary laminopathies

Laminopathies

- Mutations in LMNA that encodes lamin A/C, can lead to three different cardio- neurologic phenotypes
  - Emery Dreifuss muscular dystrophy type 2 (EDMD2)
  - Limb-girdle muscular dystrophy type 1B (LGMD1B)
  - Dilated cardiomyopathy with conduction defects (CMD1A)



NMDs that are associated with cardiac disease

A. Myotonic dystrophy

B. Dystrophinopathies: Becker and Duchenne muscular dystrophy

C. Emery-Dreifuss muscular dystrophy

D. Limg girdle muscular dystrophy (miscellaneous)

E. Myofibrillar myopathy

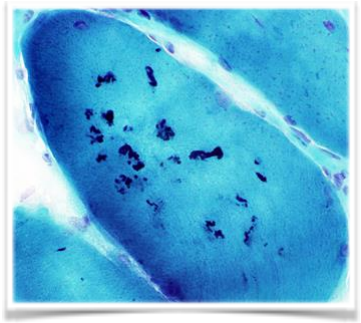
F. Facioscapulohumeral muscular dystrophy

G. Friedreich ataxia

3. NMDs associated with cardiac disease

Myofibrillar myopathy

- Proximal (limb girdle) or distal myopathy
- Pathological features: degradation of myofibrils
- Genetics: AD



	protein	additional clinical features
MFM1=LGMD1E	Desmin	60% cardiac involvement syncope
MFM2	AB crystallin	Arrhythmia, conduction block
MFM3	ZASP	27% DCM
MFM6	BAG3	HCM, RCM
Gowers' Laing	MYH7	HCM, DCM, LVNC

NMDs that are associated with cardiac disease

A. Myotonic dystrophy

B. Dystrophinopathies: Becker and Duchenne muscular dystrophy

C. Emery-Dreifuss muscular dystrophy

D. Limg girdle muscular dystrophy (miscellaneous)

E. Myofibrillar myopathy

F. Facioscapulohumeral muscular dystrophy

G. Friedreich ataxia

3. NMDs associated with cardiac disease

Fascioscapulohumoral muscular dystrophy (FSHD)

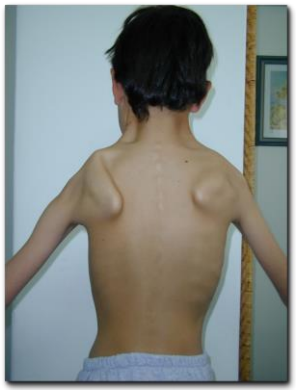
- Incidence: third most common hereditary muscle disorder after myotonic dystrophy and Duchenne muscular dystrophy
- Genetics: AD
    - D4Z4 repeat contraction, leading to transcriptional upregulation of DUX4 gene that is normally silenced in somatic tissue

3. NMDs associated with cardiac disease

Fascioscapulohumoral muscular dystrophy (FSHD)

Neurological presentation

- Age of onset: between 10 and 30 yrs
- Slow progression, quasi normal life expectancy
- Initially face and scapulae, followed by foot dorsiflexors and hip girdle



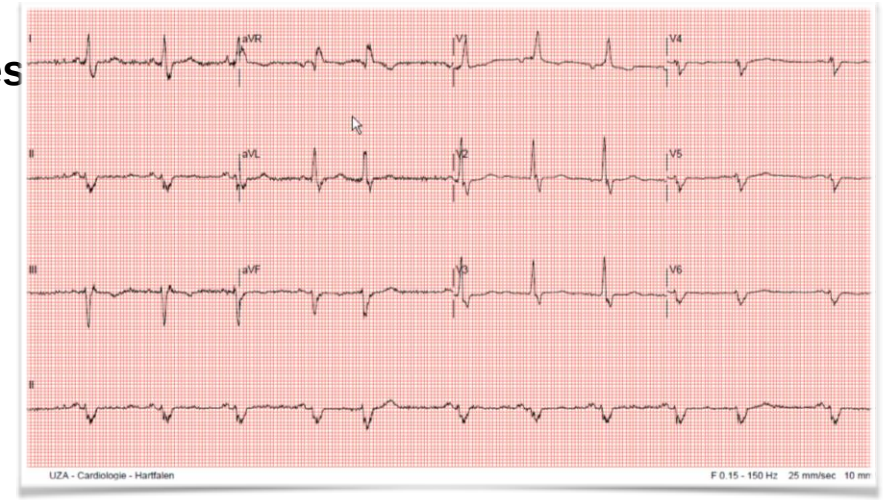
3. NMDs associated with cardiac disease

Fascioscapulohumoral muscular dystrophy (FSHD)

Cardiac involvement can occur, but is infrequent

1. Electrophysiological abnormalities

- P-wave abnormalities
- IV conduction delay
- supraventricular arrhythmia



NMDs that are associated with cardiac disease

A. Myotonic dystrophy

B. Dystrophinopathies: Becker and Duchenne muscular dystrophy

C. Emery-Dreifuss muscular dystrophy

D. Limg girdle muscular dystrophy (miscellaneous)

E. Myofibrillar myopathy

F. Facioscapulohumeral muscular dystrophy

G. Friedreich ataxia

3. NMDs associated with cardiac disease

Friedreich ataxia

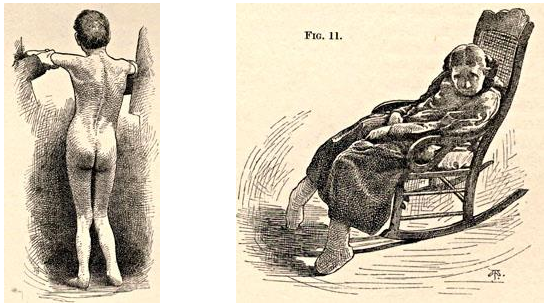
- Incidence: most common hereditary ataxia in caucasians, incidence 1 in 40 000 persons
- Genetics: AR
    - pathogenic expansion of a GAA trinucleotide repeat sequence in frataxin (FXN) gene
- Mixed sensory and cerebellar ataxia

3. NMDs associated with cardiac disease

Friedreich ataxia

Neurological presentation

- Age of onset: puberty
- Progressive gait ataxia of all 4 limbs and dysarthria
- Patients become wheelchair-bound about 10 years after disease onset



From Bramwell: Atlas of Clinical Medicine

3. NMDs associated with cardiac disease

Friedreich ataxia

Cardiac involvement is frequent, account for 60% of the mortality in Friedreich ataxia

1. Concentric LVH +++

- progressive impairment of systolic function, usually before 30 yrs
- patients die 20 years after disease onset, predominantly from cardiac complications
- LVH more frequent in males and related to number of repeat expansions

2. Sudden cardiac death= frequent cause of death ++

- due to arrhythmic complications related to HCM

3. NMDs associated with cardiac disease

Friedreich ataxia

Male, 25 yrs

TTE: concentric HCM