Cardiomyopathies

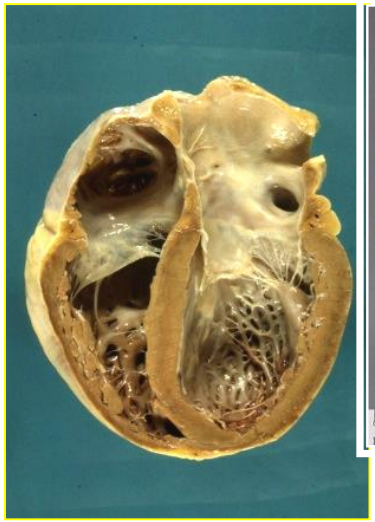
Prevalenza: 1/500 – 1/4000

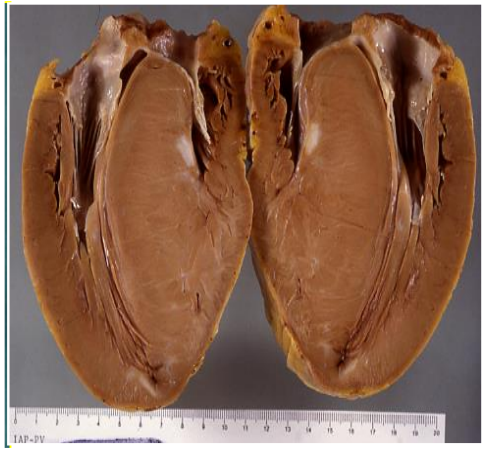
Storia Naturale

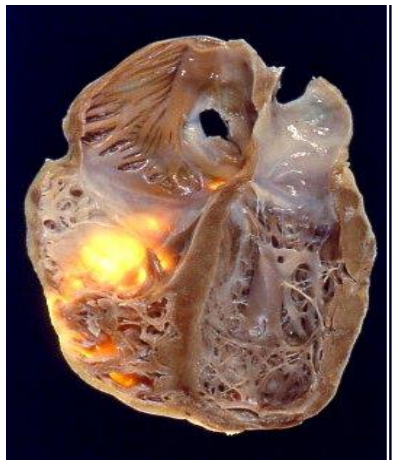
- variabile
- SCC, aritmia, MI, trapianto

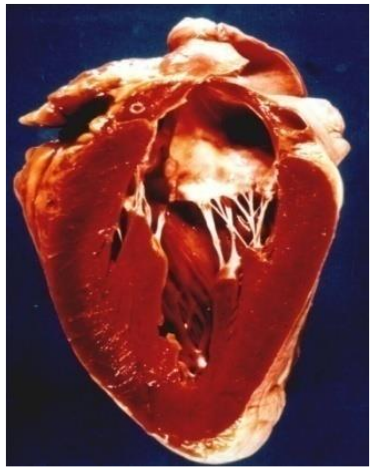
Genetica

- Forme "Familiare" 20 – 50%
- AD, AR, XL, matrilineare
- Penetranza correlata all'età







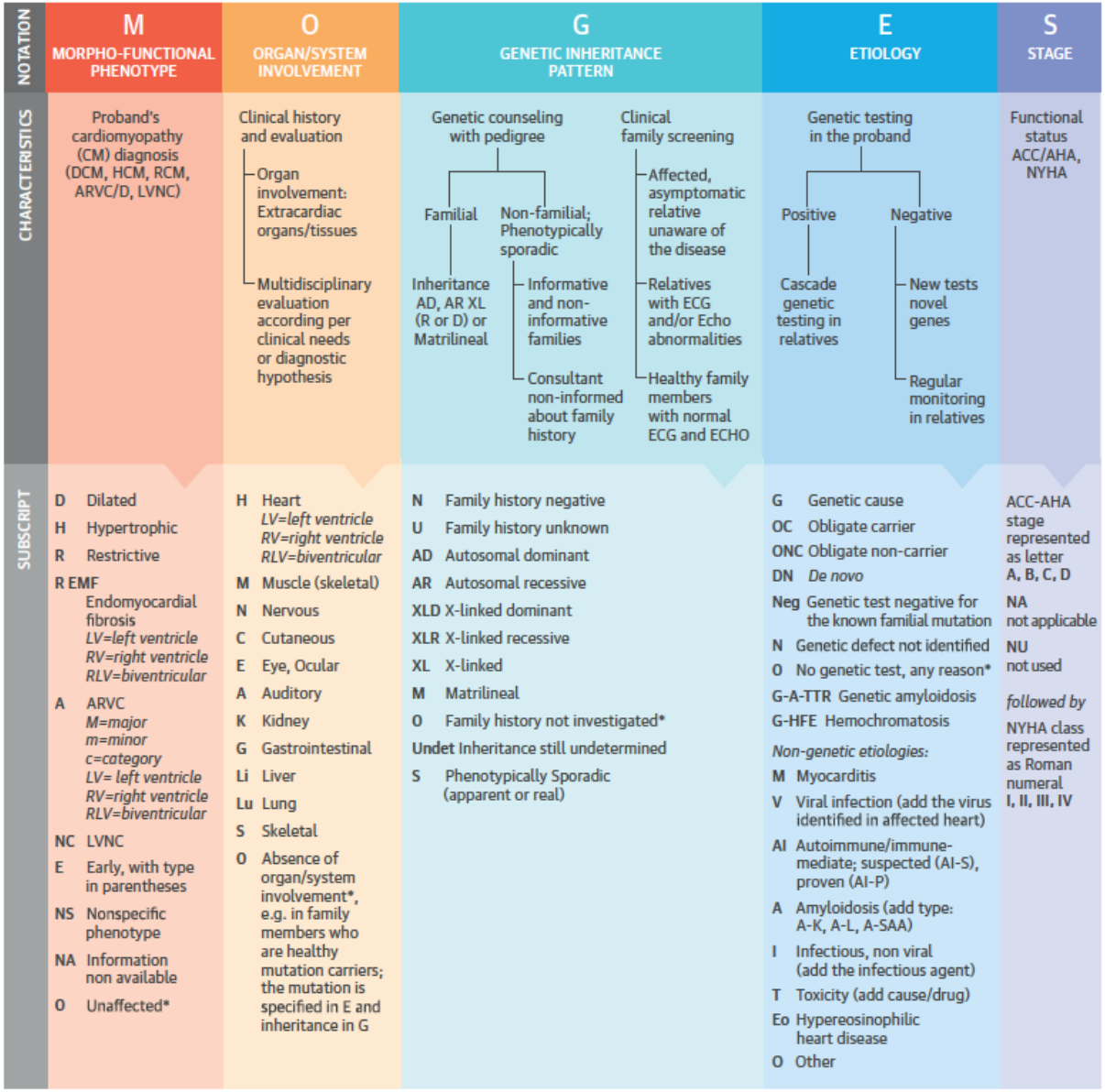


HEART MUSCLE DISEASE REGISTRY OF TRIESTE (UPDATE – 12/2016)

	DCM	HCM	ARVD	MYOC.
N° of pts	**1184**	304	127	117
Mean age (years)	**45±15**	46±19	37±16	38±16
Males (%)	**70**	64	69	70
Follow-up (months)	**125±83**	79±90	139±115	97±67
Years of enrolment	**1978-2016**	1983-2016	1976-2016	1981-2016
N° Follow-up (approx.)	**> 7500**	> 1000	700	500

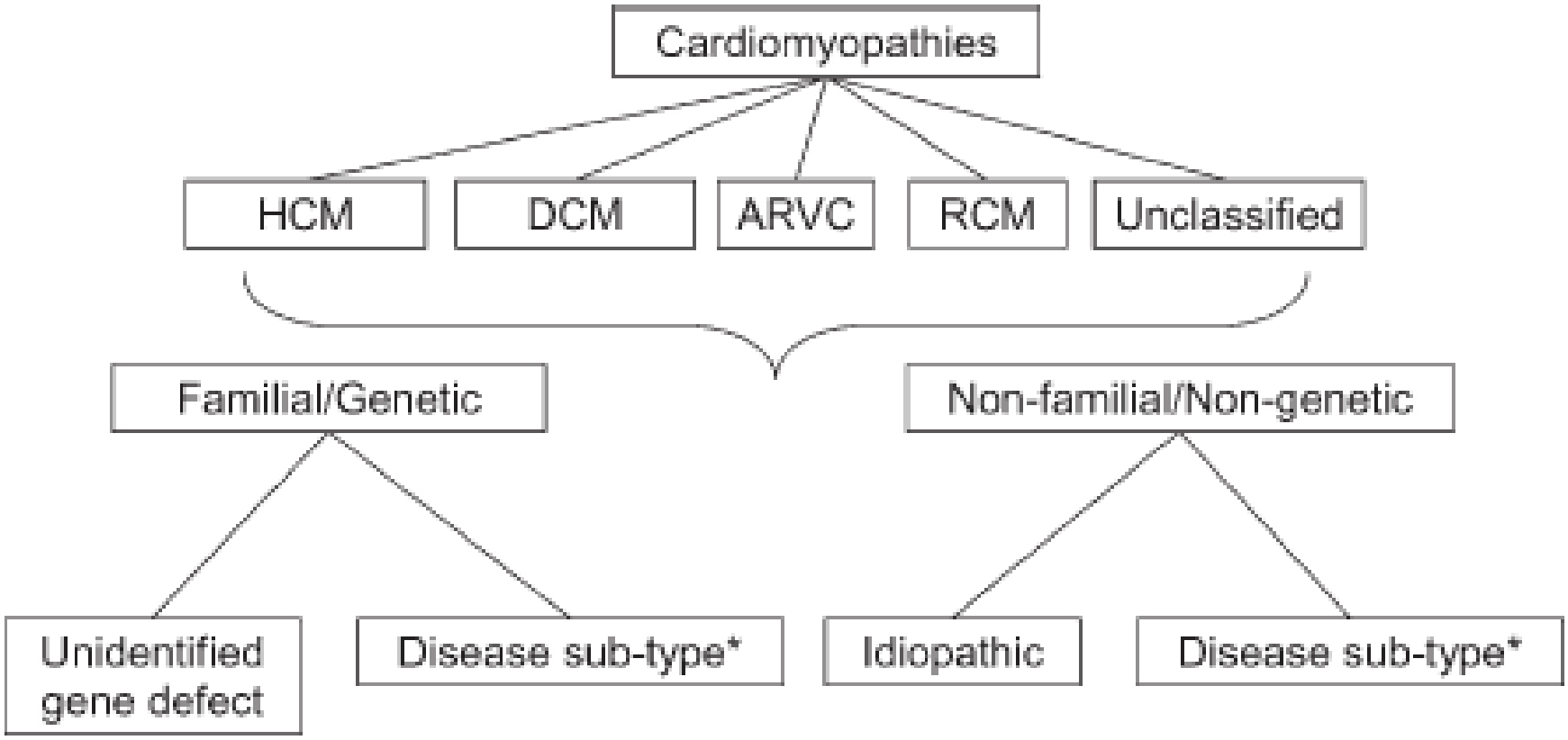
The MOGE(S) Classification of Cardiomyopathy for Clinicians

JACC
Journal of the American College of Cardiology

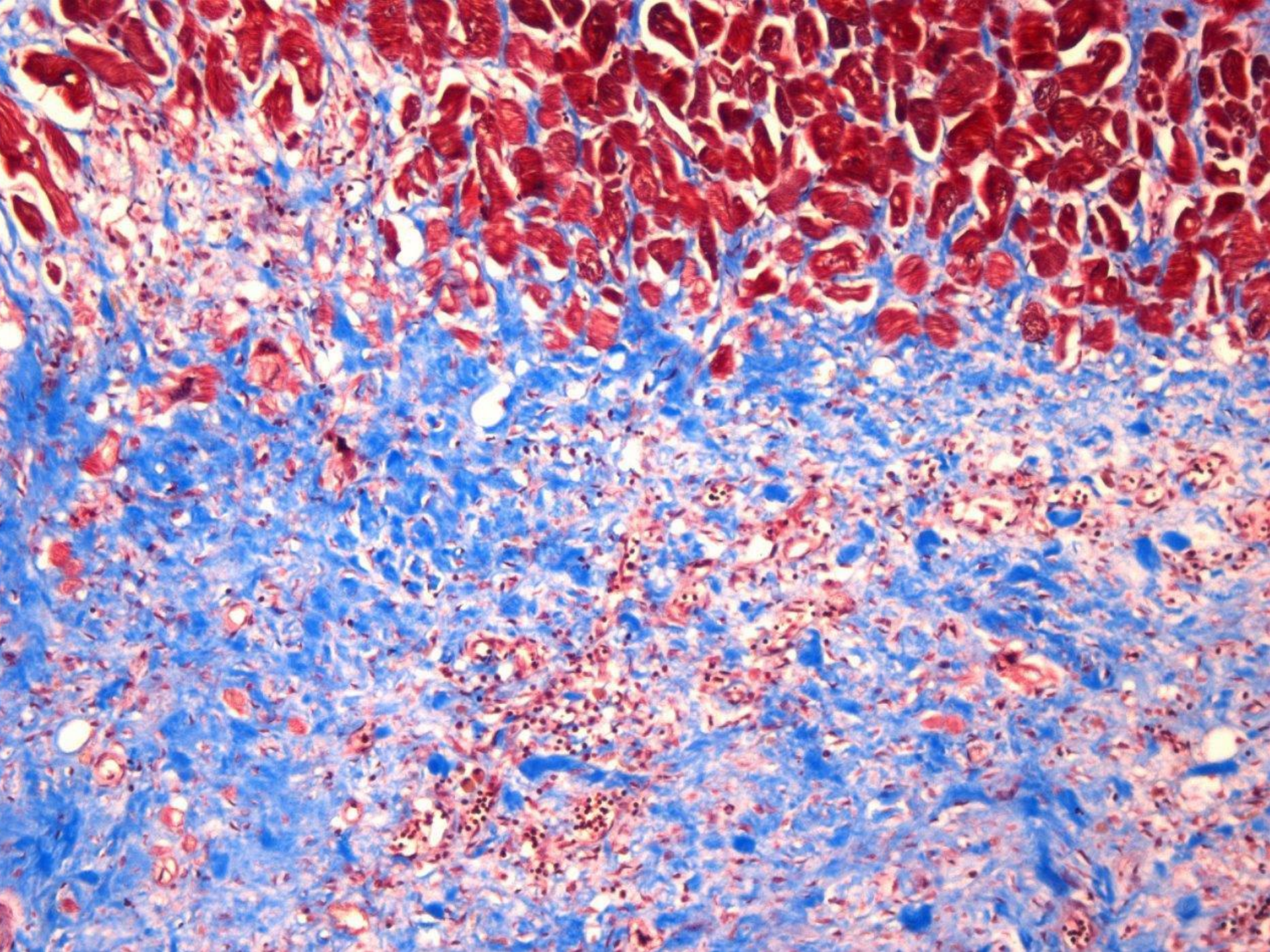


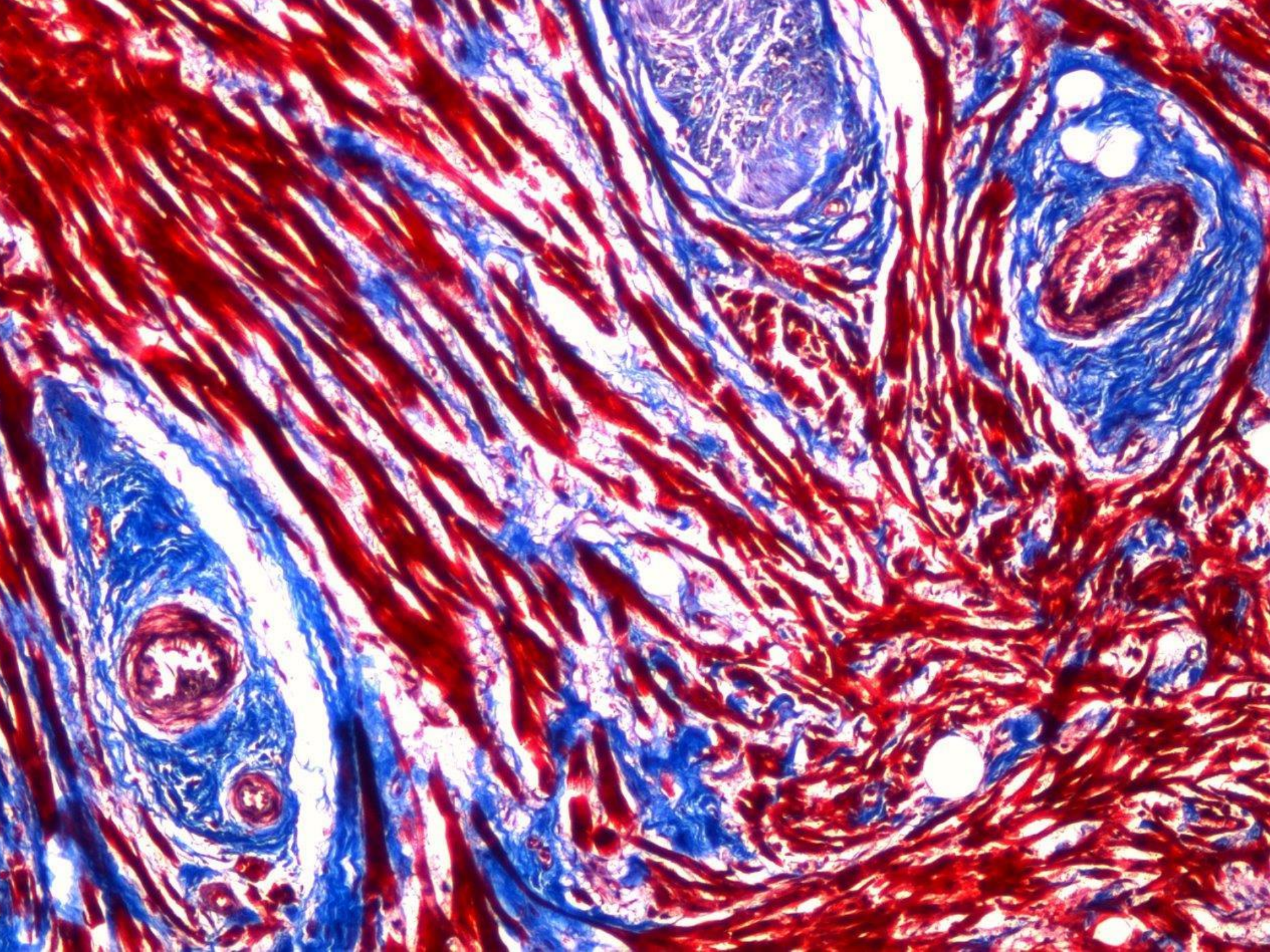
Arbustini et al.J Am Coll Cardiol 2014;64:304–18

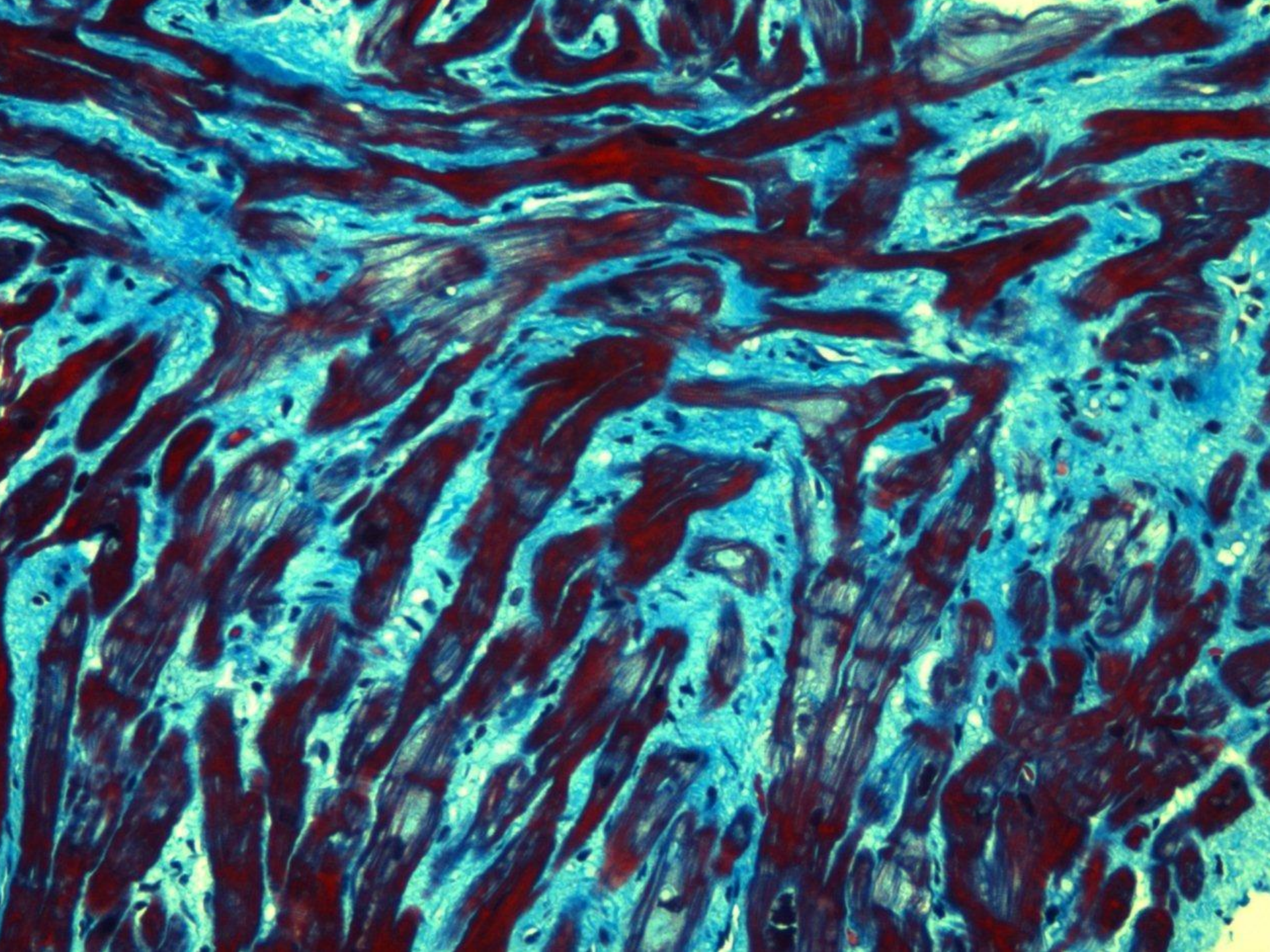
Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

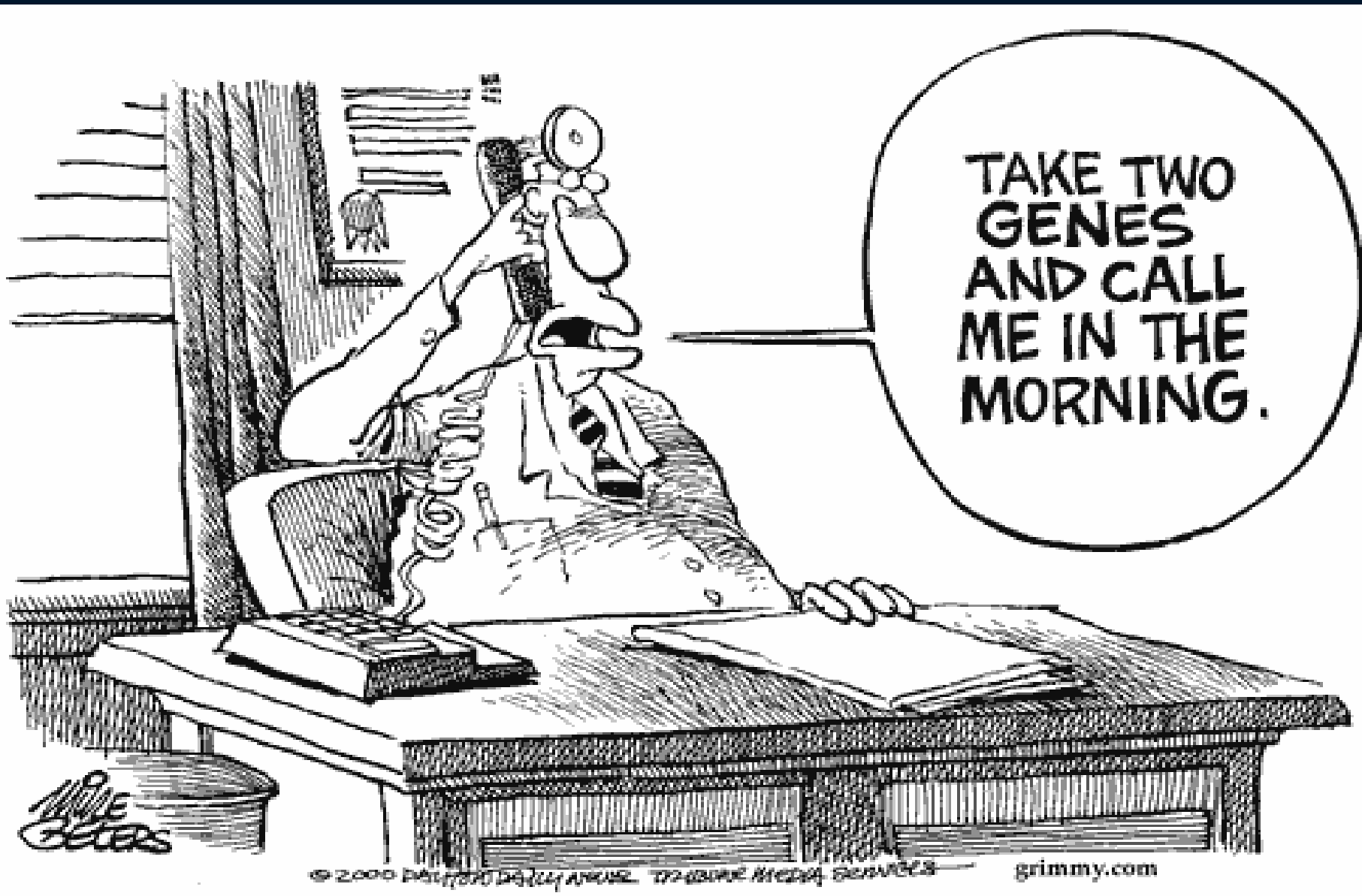


Elliot et al. European Heart Journal (2008) 29, 270–276

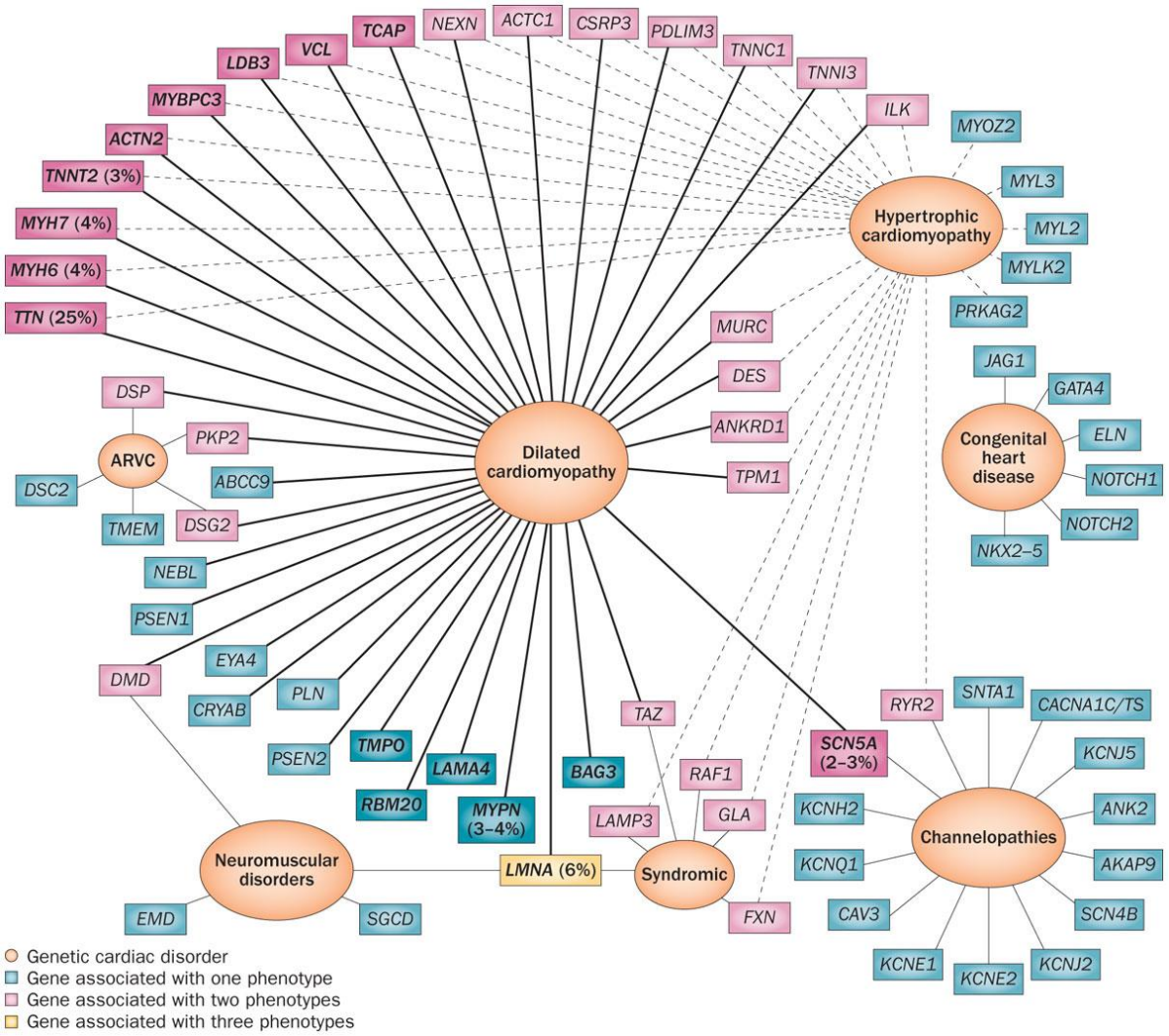




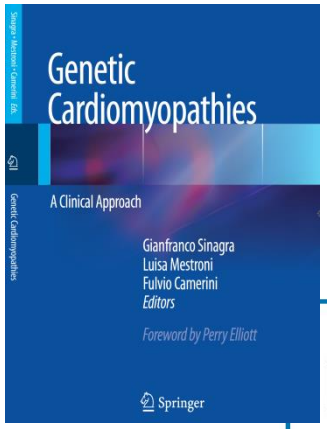



TAKE TWO GENES AND CALL ME IN THE MORNING.
grimmy.com

The Cardiomyopathies Phenome



*Hershberger, R. E. et al., Nat. Rev. Cardiol. 2013;*10:531–547



Cardiomyopathies and genetic complexity

Mutations within the same gene may cause different phenotypes

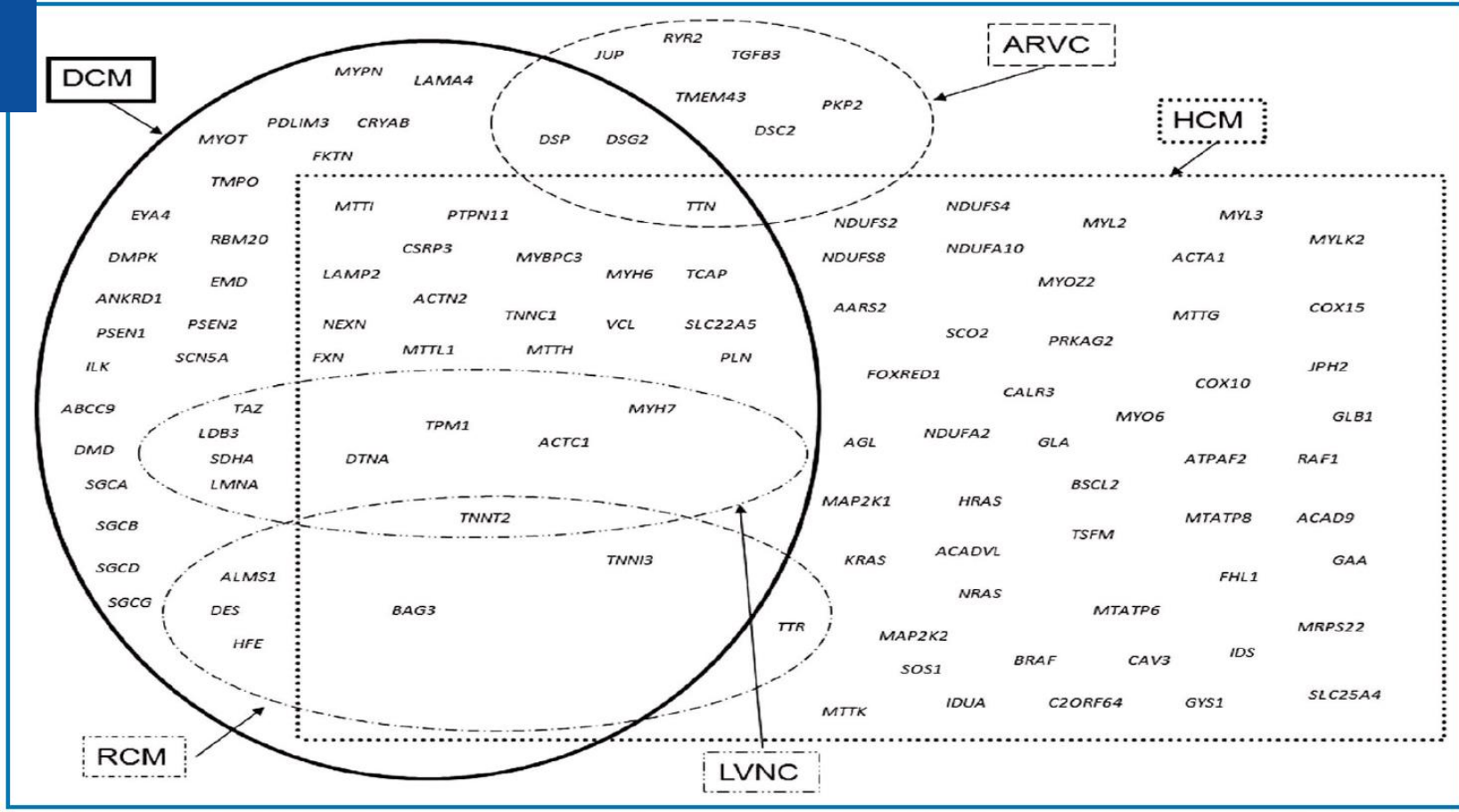
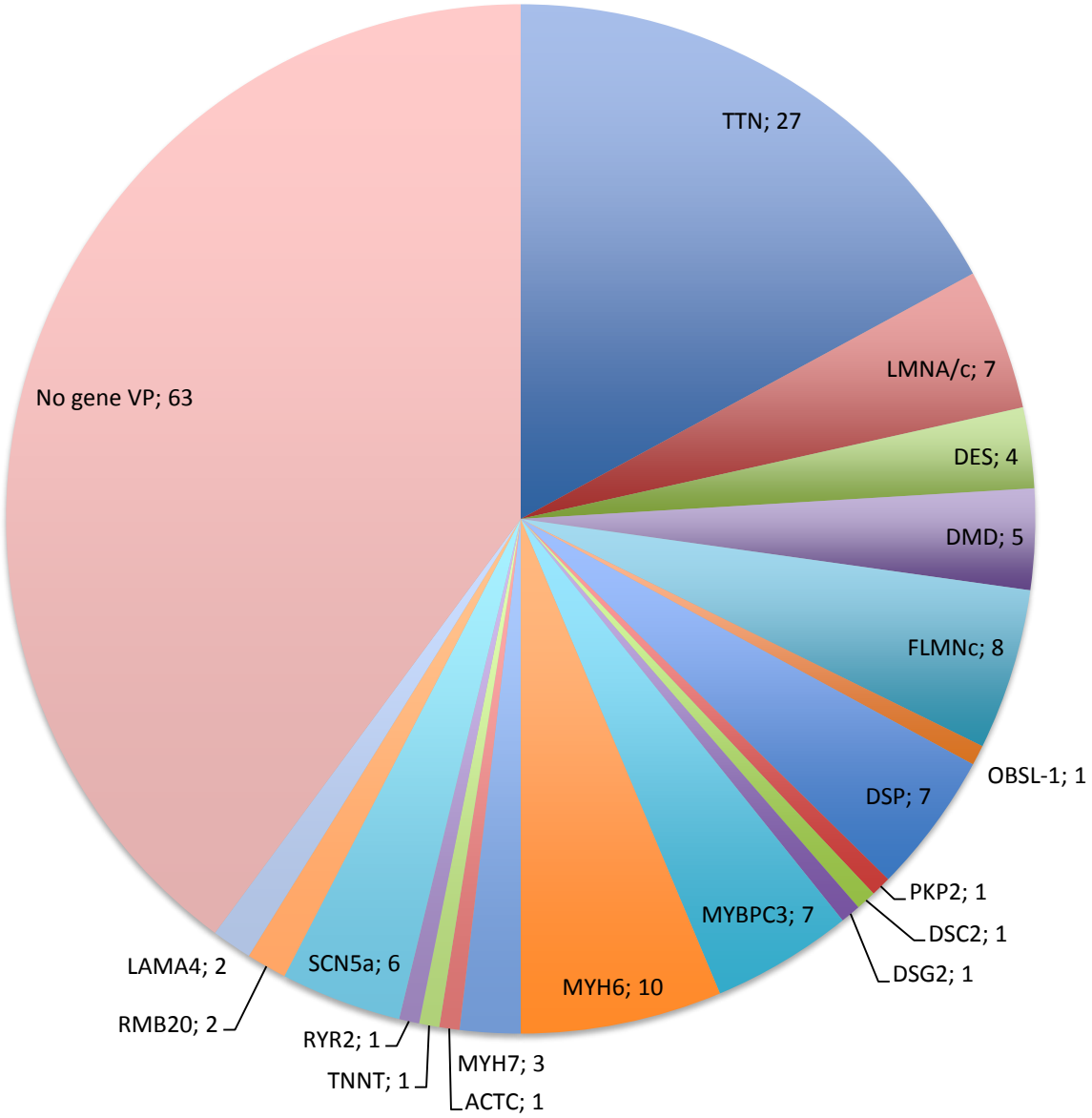


Fig. 1.1 Cardiomyopathies and genetic complexity. Mutations within the same gene may cause different phenotypes. Gene acronyms: see Tables 1.1–1.5 and Glossary. *ARVC*, arrhythmogenic right ventricular cardiomyopathy; *DCM*, dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *LVNC*, left ventricular non-compaction; *RCM*, restrictive cardiomyopathy

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies*,
DOI: 10.1007/978-88-470-2757-2_1, © Springer-Verlag Italia 2013

DCM genes (n 152; solo varianti P o LP)



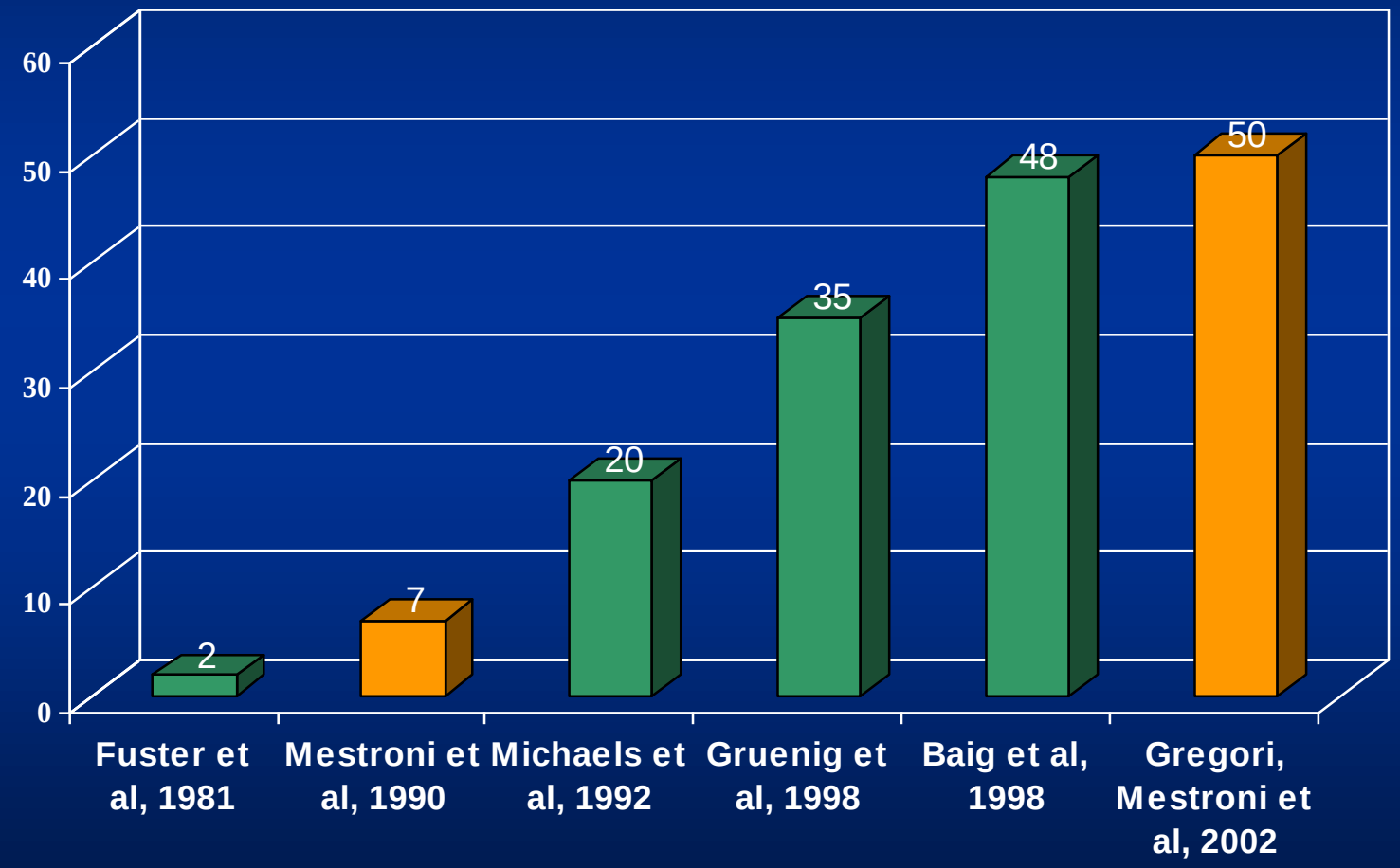
SPECIFIC GENES AVAILABLE FOR SCREENING BASED ON CARDIAC PHENOTYPE

Phenotype	Gene Tests Available	Yield of Positive Results
Hypertrophic (HCM)	MYH7, MYBPC7, TNNT2, TNNI3, TPMI, ACTC, MYL2, MYL3	MYH7, MYBPC3 = 60-80% of mutations, TNNT2 = 10-20%. Genetic cause identifiable in 35-45% overall. If family history is positive, 60-65%
Dilated (DCM)	LMNA,MYH7, TNNT2, SCN5A, DES, MYBPC3, TNNI3, TPMI, ACTC, PLN, LDB3, TAZ	LMNA = 5.5%, MYH7 = 4.2%, TNNT2 = 2.9%. All data from research cohorts
ARVD/C	DSP, PKP2, DSG2, DSC2	DSP = 6-16%, PKP2 = 11-43%, DSG2 = 12-40%
LVNC	Uncertain	Uncertain
Restrictive	Uncertain	Uncertain

Genetic evaluation of cardiomyopathy: HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010 Jun;16(6):e180-94.

Genetic determinants of dilated cardiomyopathy

FDC frequency in DCM



“Red flags approach”

European Heart Journal
doi:10.1093/eurheartj/ehs397

SPECIAL ARTICLE

Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

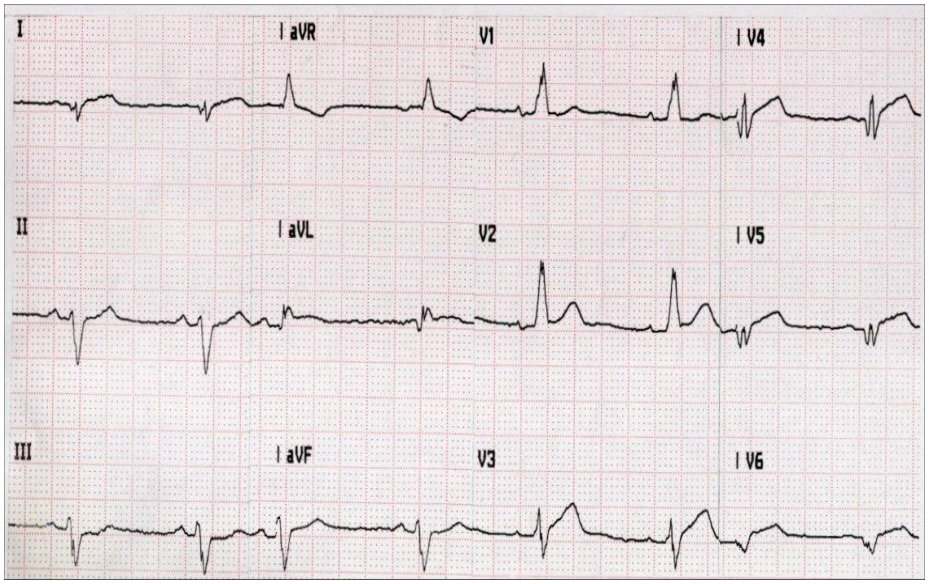
Claudio Rapezzi, Eloisa Arbustini, Alida L. P. Caforio, Philippe Charron, Juan Gimeno-Blanes, Tiina Heliö, Ales Linhart, Jens Mogensen, Yigal Pinto, Arsen Ristic, Hubert Seggewiss, Gianfranco Sinagra, Luigi Tavazzi, and Perry M. Elliott*

The Heart Hospital, 16–18 Westmoreland Street, London W1G 8PH, UK

Pedigree	Autosomal dominant Autosomal recessive X-linked Matrilinear
Symptoms	Deafness Muscle pains/weakness Paraesthesia
Physical exam	Muscle weakness Postural hypotension Rash Ocular
ECG	Preexcitation a-v Block Pseudo-infarct pattern
Laboratory	Creatinine kinase Creatinine/Proteinuria Ferritin Lactate
Echo	Signs of infiltrative/storage diseases LVNC Presence/distribution of dyskinesias RV abn

Eur Heart J 2012, Rapezzi et al

Ospedali Riuniti di Trieste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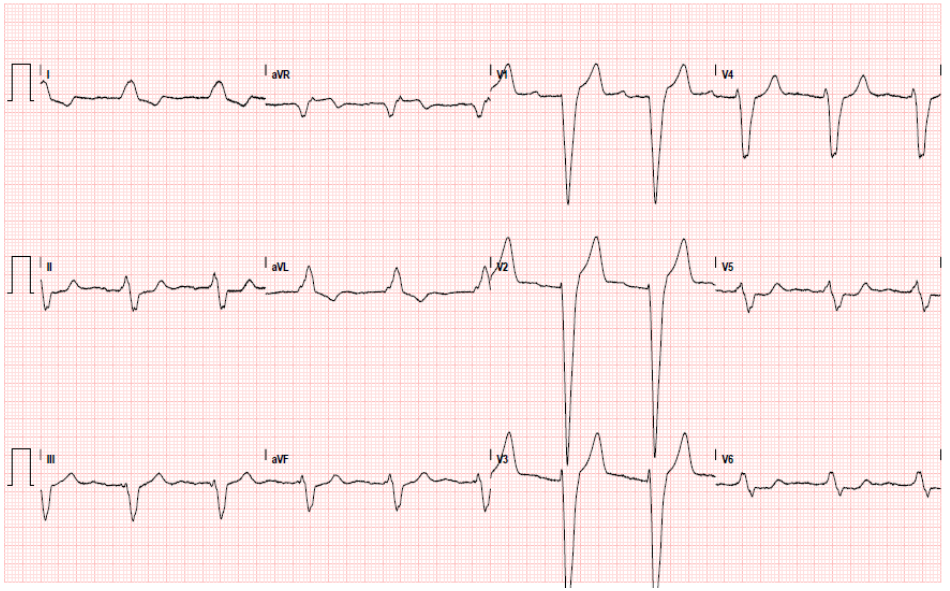
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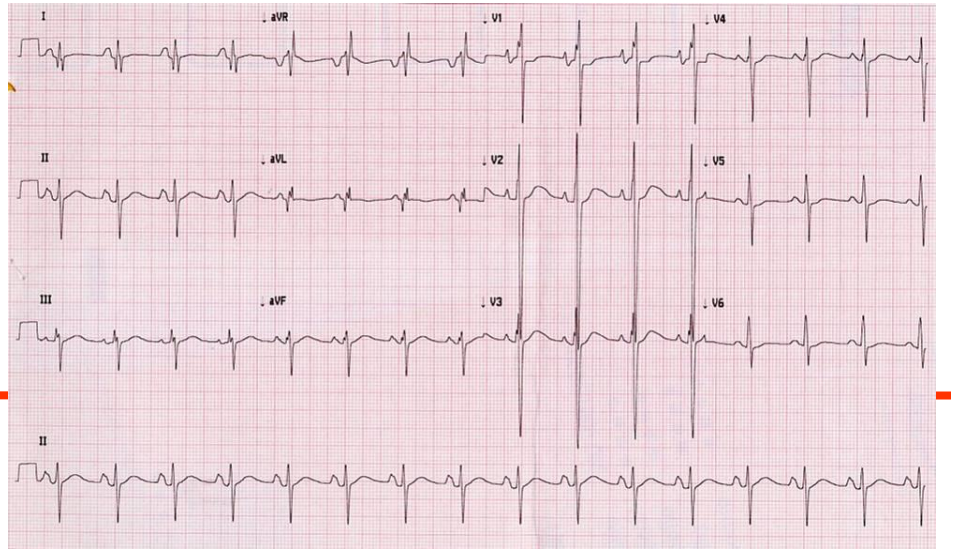
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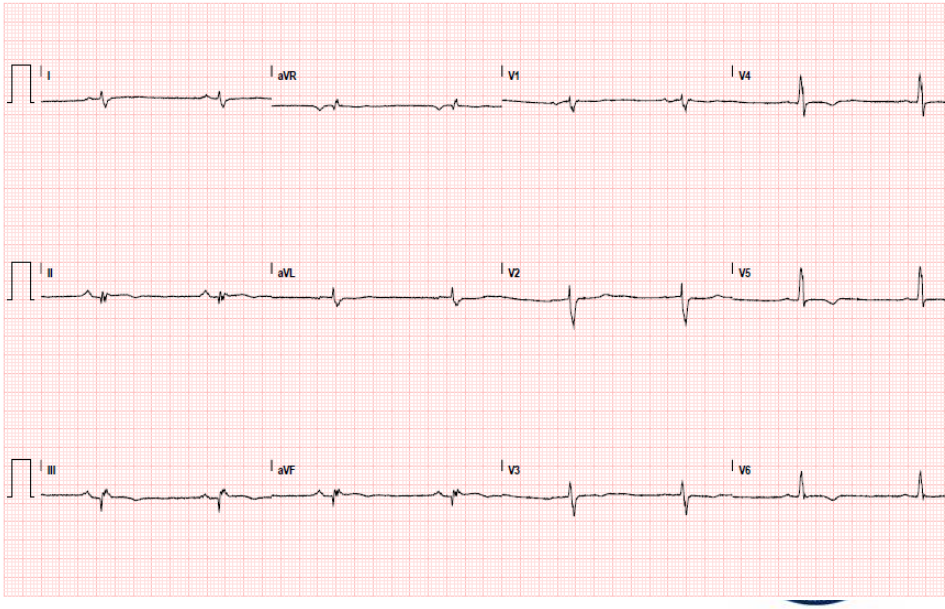
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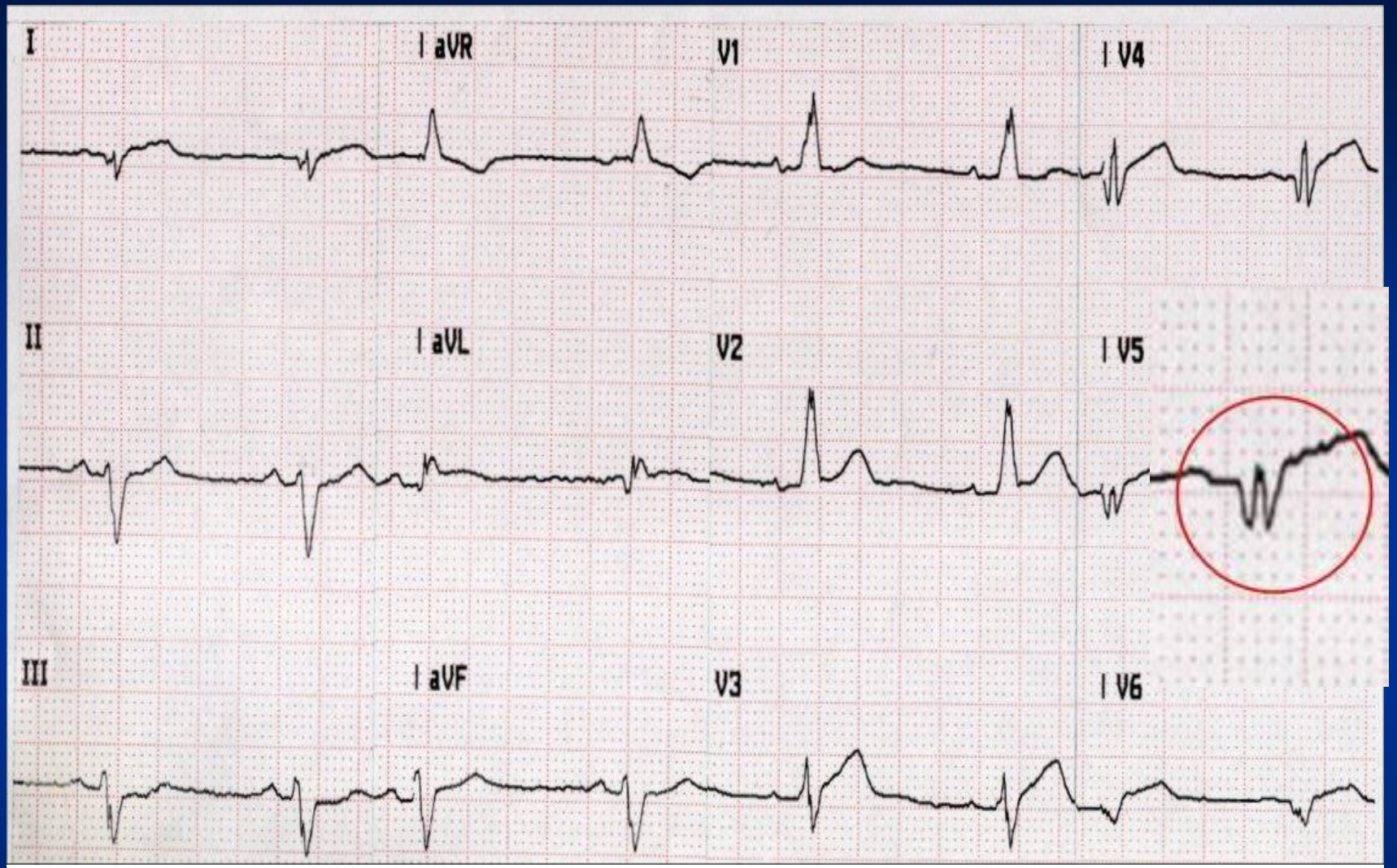

Fig. 5.3 Electrocardiogram of a patient with Becker muscular dystrophy and dilated cardiomyopathy. The electrocardiogram shows sinus bradycardia, P waves suggestive of left atrial enlargement, right bundle branch block, and "necrotic" Q waves in DI, aVL, V4–V6 with prominent R waves in V1–V2 suggestive of lateral and posterior necrosis

G. Sinagra, L. Mestroni, F. Camerini (eds.), *Genetic Cardiomyopathies*,
DOI: 10.1007/978-88-470-2757-2_1, © Springer-Verlag Italia 2013

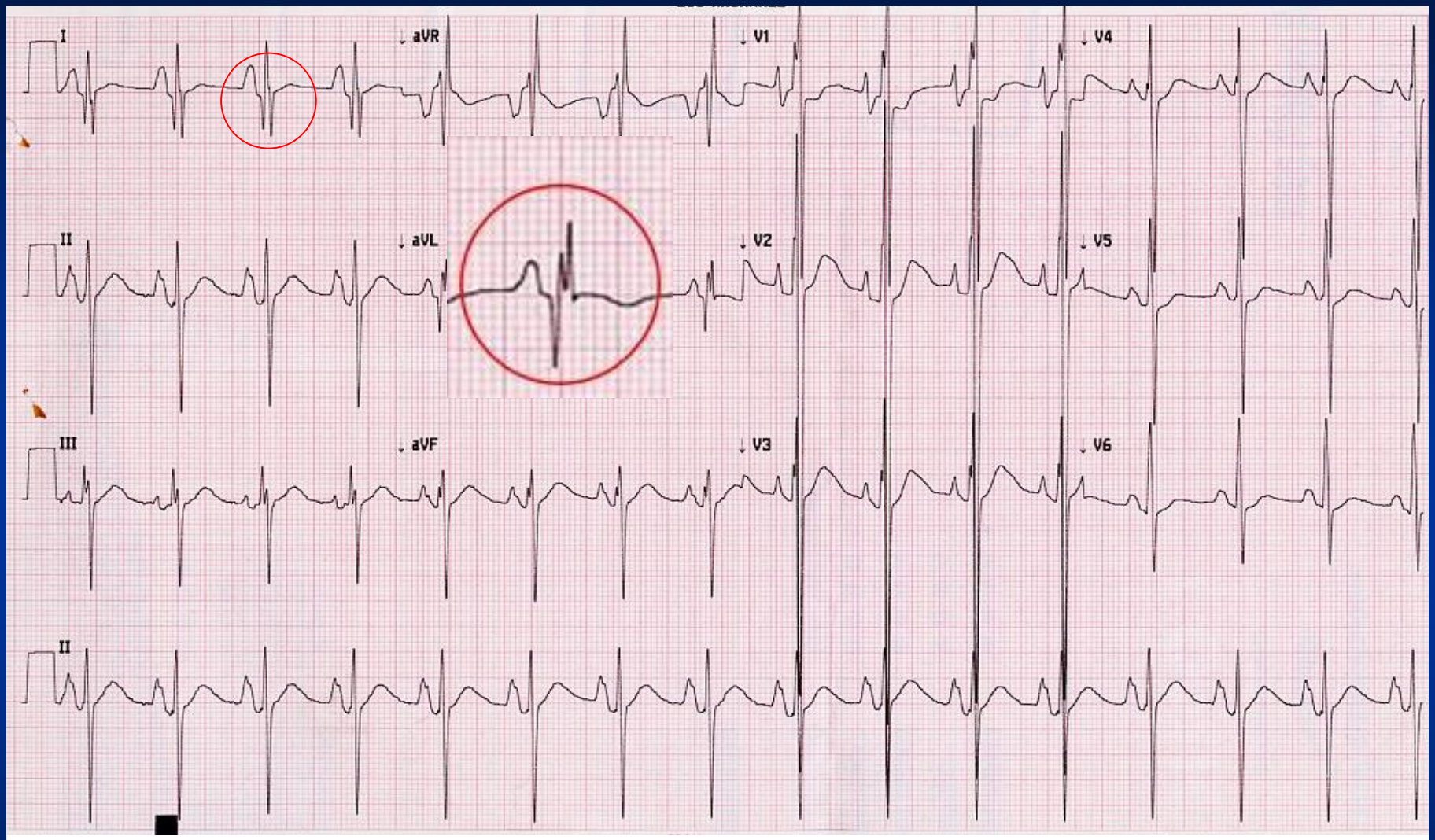

Fig. 5.2 Electrocardiogram of a 40-year-old woman with hypertrophic cardiomyopathy. The electrocardiogram shows sinus rhythm, biatrial dilatation, right ventricular conduction delay and biventricular hypertrophy. Note the high voltage and narrow Q waves in lead I and aVL

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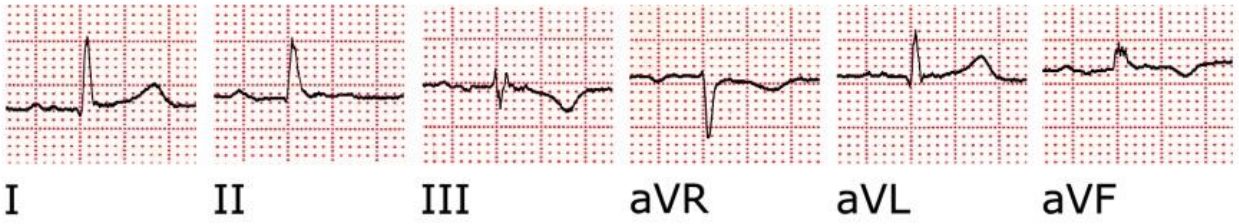
DOI: 10.1007/978-88-470-2757-2_1, © Springer-Verlag Italia 2013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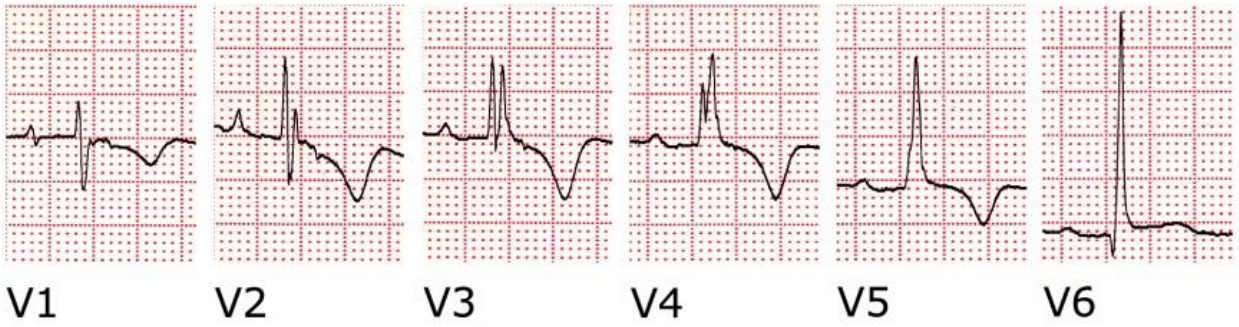
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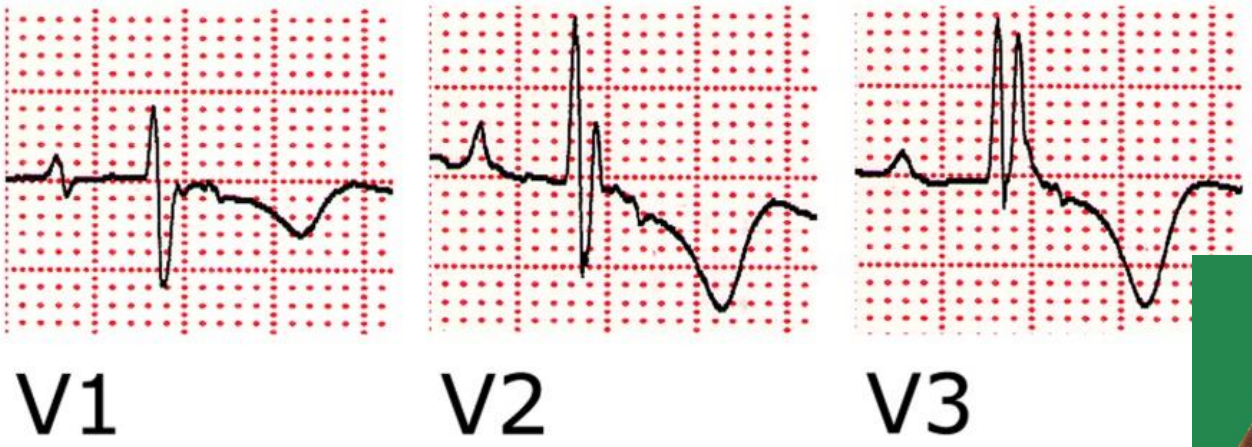
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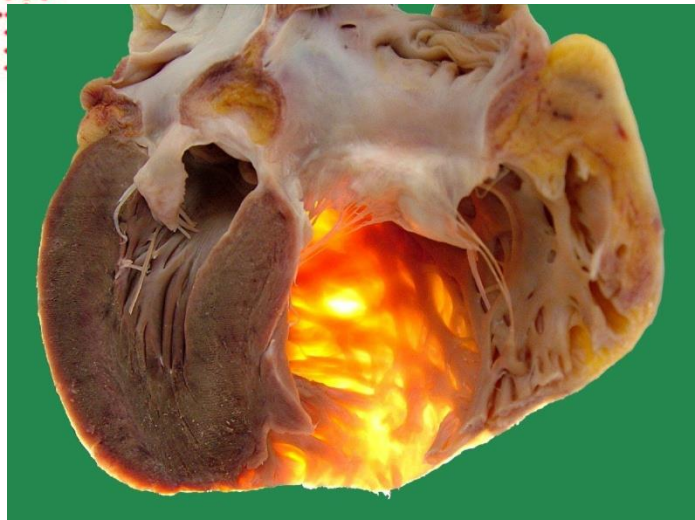
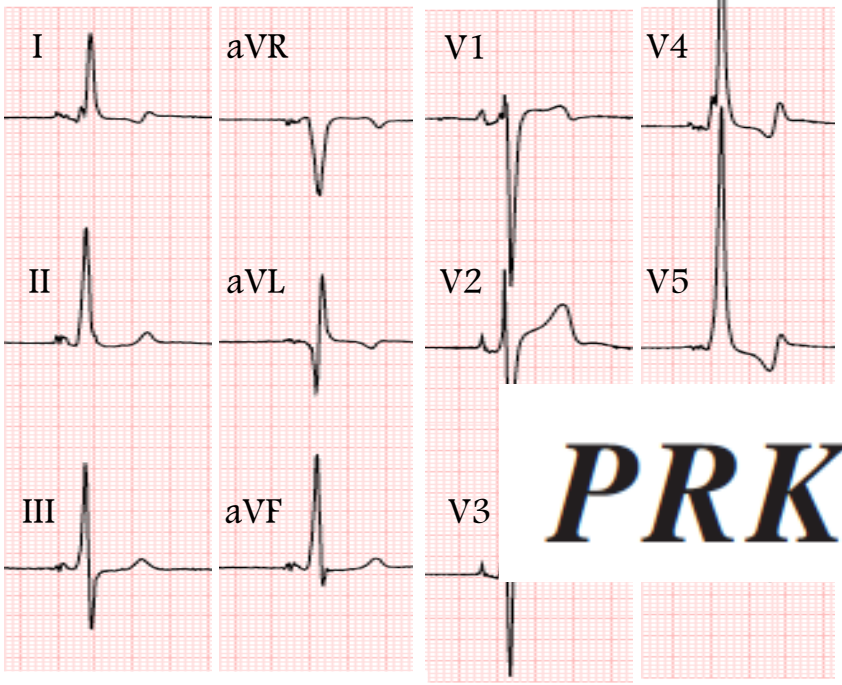


A 17-year-old asymptomatic man.

The father: unexplained left ventricular hypertrophy and received a PM at age 35 for SSS.

A



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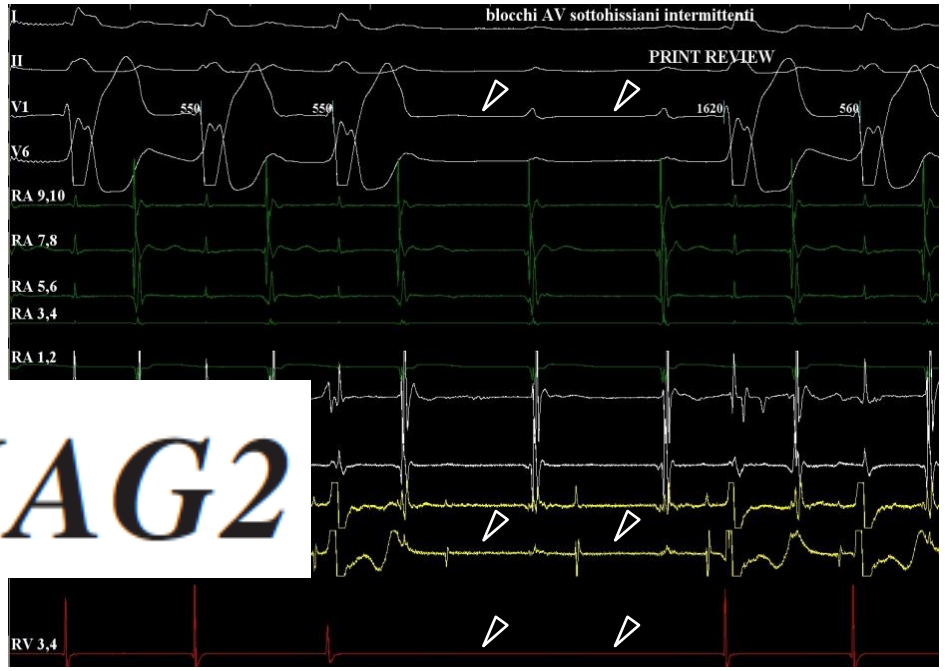

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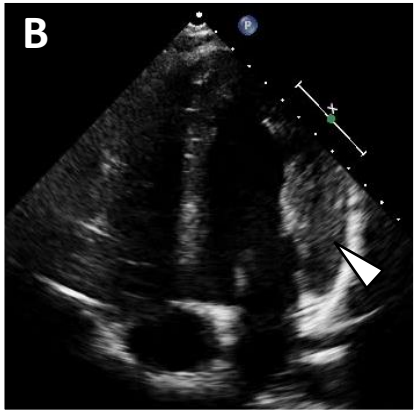

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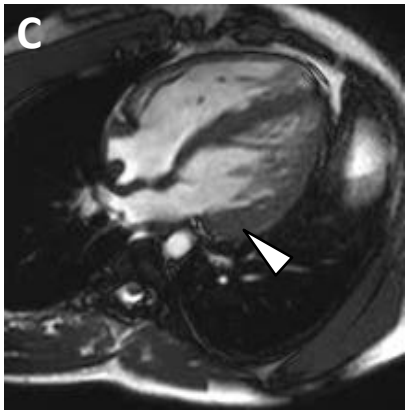

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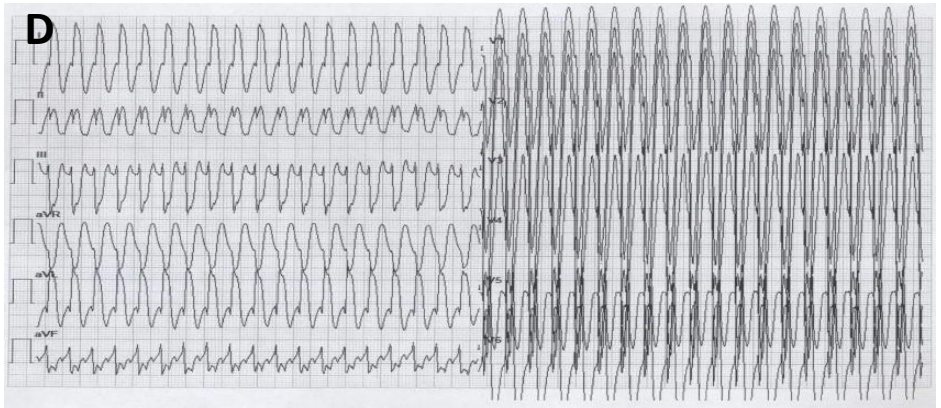
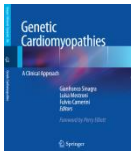


Cardiomyopathies and Arrhythmias



DCM with initial symptomatology characterized by
- ✓ supraventricular arrhythmias,
- ✓ atrioventricular conduction delay
- ✓ and elevated creatine kinase levels.

LMNA gene mutation should be considered highly likely.

Patients with **DCM** and peculiar phenotype characterized by an arrhythmogenic trait

- ✓supraventricular arrhythmias
- ✓atrial fibrillation
- ✓sick sinus syndrome

→ ***SCN5A*** gene mutations
(approximately 2% of patients with DCM)

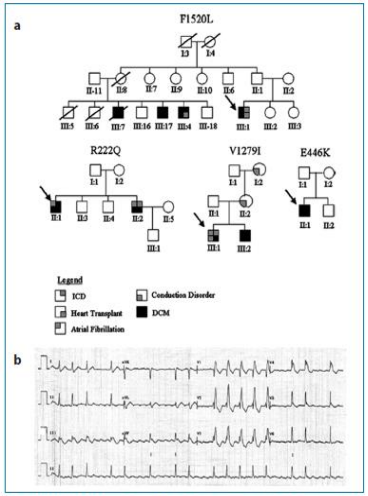


Fig. 4.1 Dilated cardiomyopathy in sodium channel mutations. **a** Pedigrees of patients with dilated cardiomyopathy and *SCN5A* mutations. Generations are denoted by *roman numerals*. *Black arrows* show probands for each pedigree. **b** Early arrhythmia in *SCN5A* mutation carriers. Electrocardiogram of an affected individual, showing atrial fibrillation when the patient had a normal left ventricular ejection fraction (74%). Modified from McNair et al. [22], with permission

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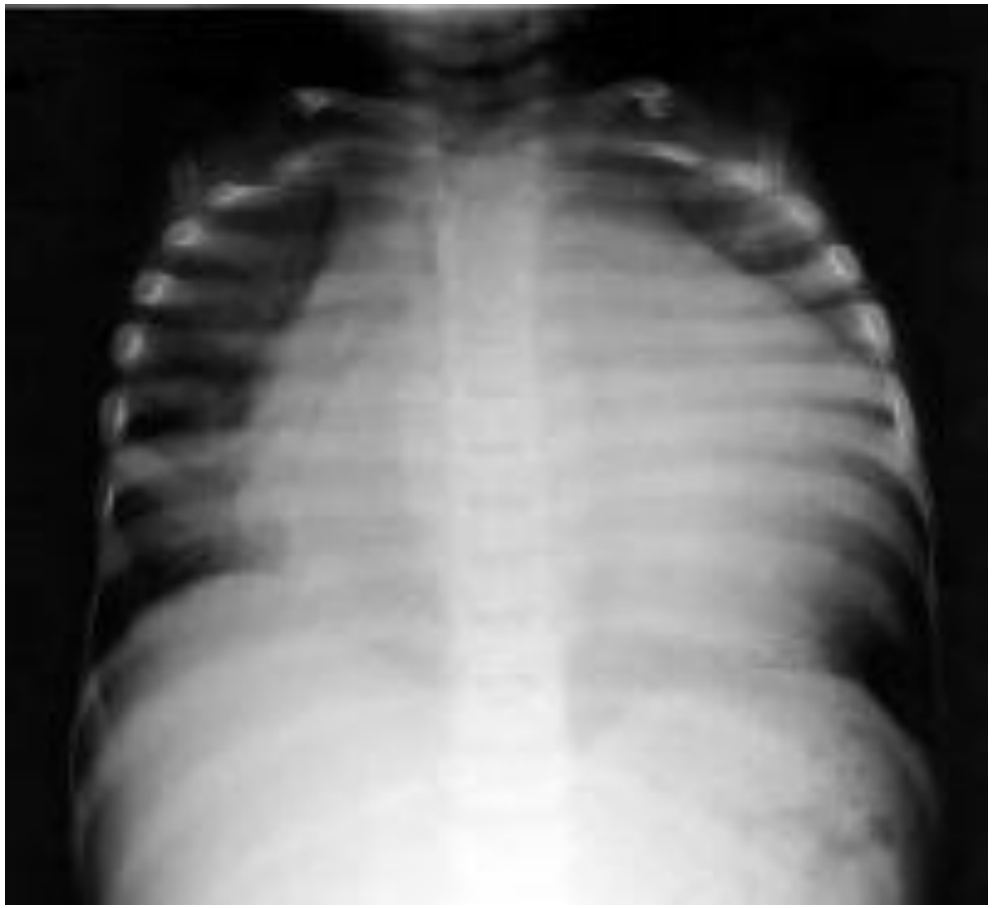
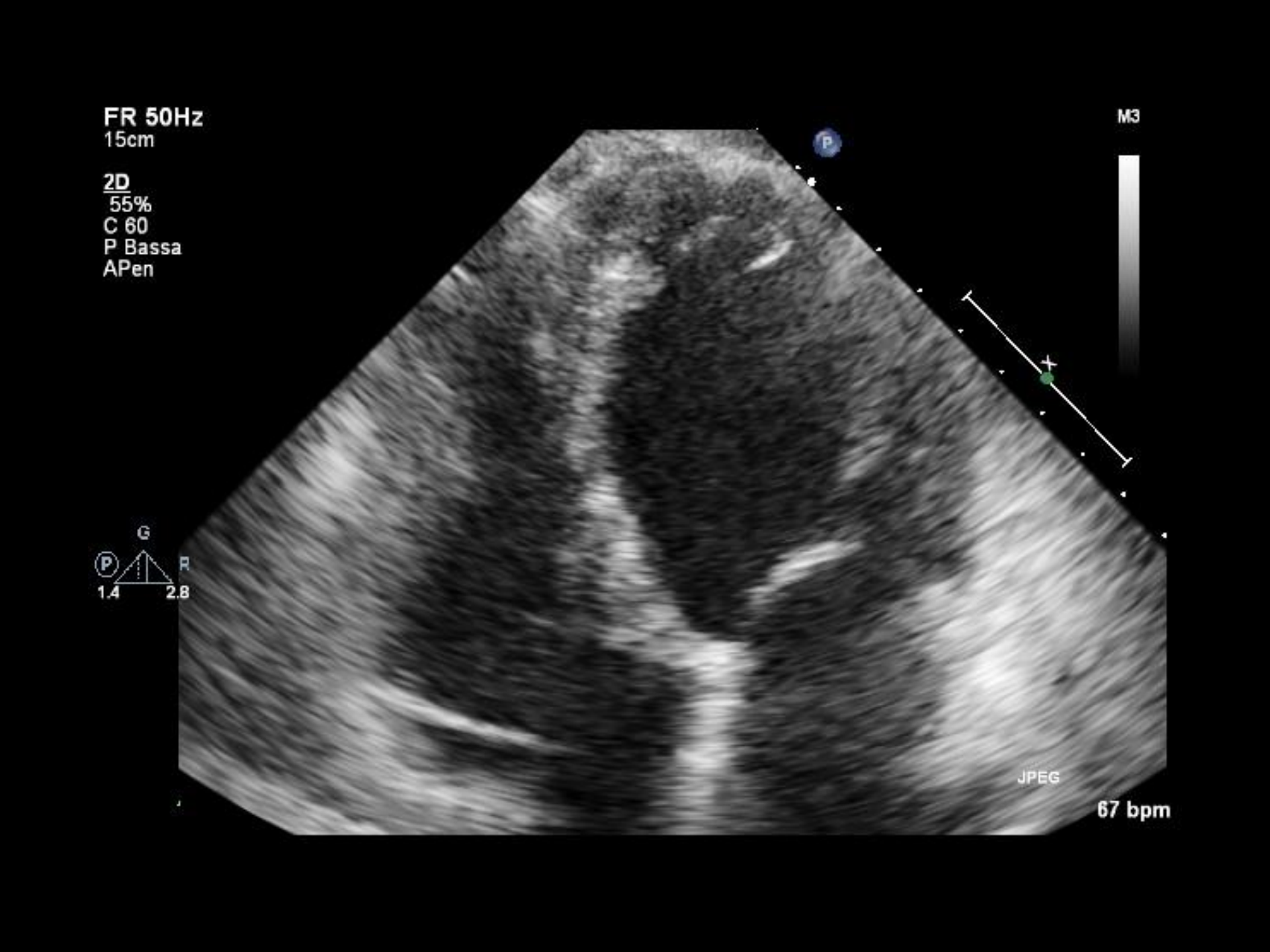
DOI: 10.1007/978-88-470-2757-2_1, © Springer-Verlag Italia 2013

CMPD “sindromica”

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G
P
R
1.4
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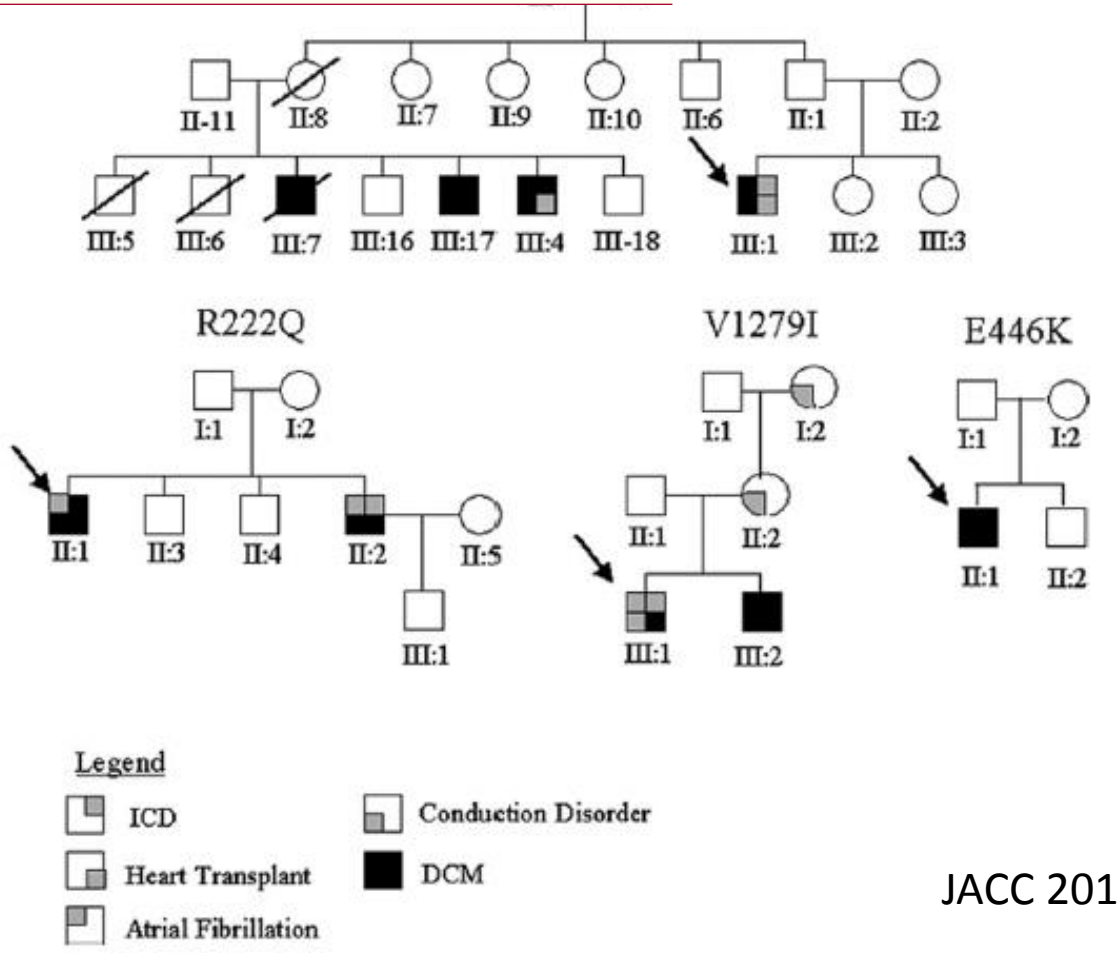
67 bpm

SCN5A Mutations Associate With Arrhythmic Dilated Cardiomyopathy and Commonly Localize to the Voltage-Sensing Mechanism

William P. McNair, PHD,* Gianfranco Sinagra, MD,§ Matthew R. G. Taylor, MD, PHD,*†
Andrea Di Lenarda, MD,§ Debra A. Ferguson, MS, ANP,* Ernesto E. Salcedo, MD,*
Dobromir Slavov, PHD,* Xiao Zhu, BS,* John H. Caldwell, PHD,‡ Luisa Mestroni, MD,*†
and the Familial Cardiomyopathy Registry Research Group

Aurora, Colorado; and Trieste, Italy



JACC 2011;57:2160-8.

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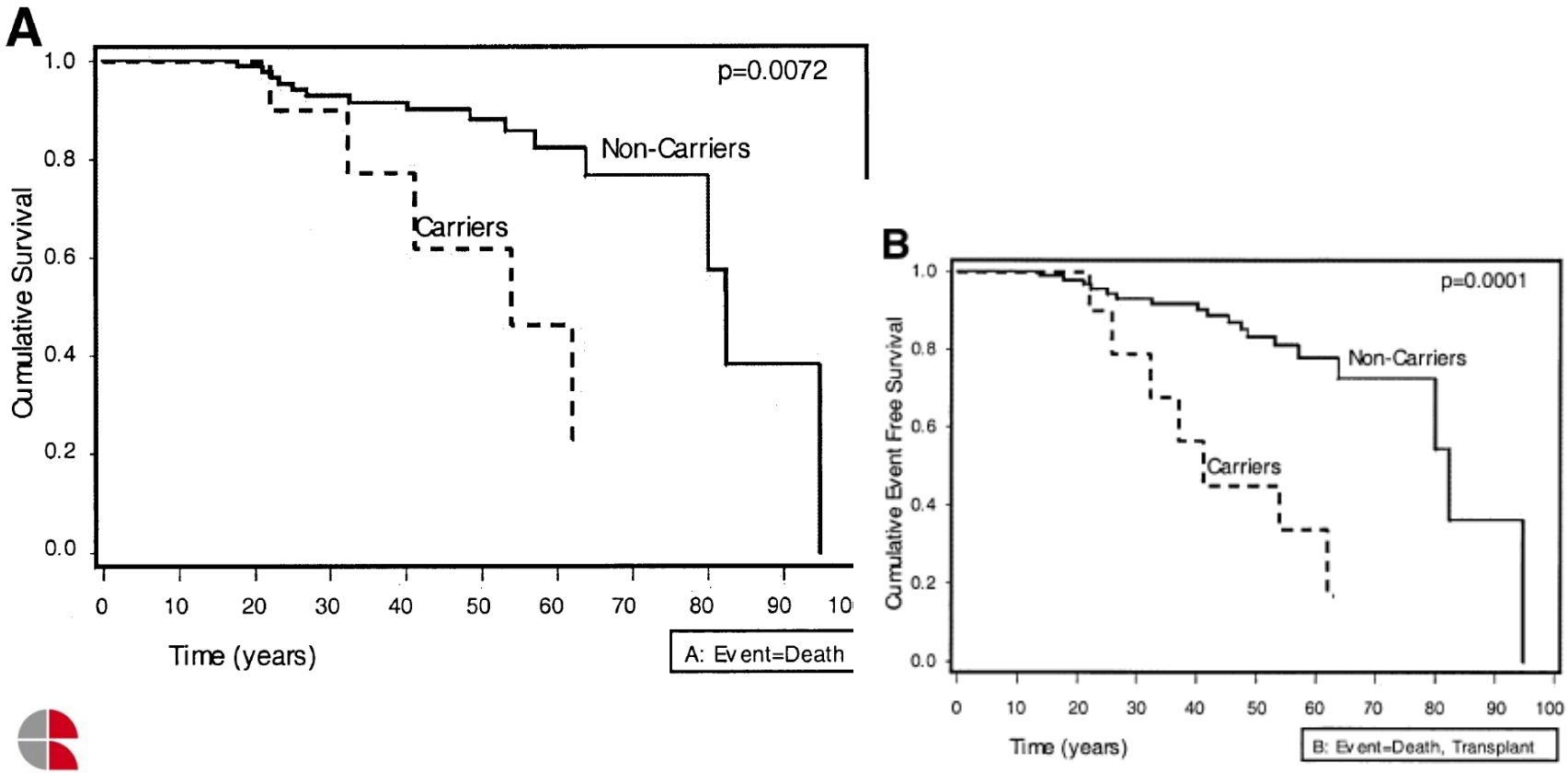
Cardiomyopathy

Natural History of Dilated Cardiomyopathy Due to Lamin A/C Gene Mutations

Matthew R. G. Taylor, MD,* Pamela R. Fain, PHD,*†‡ Gianfranco Sinagra, MD, FESC,§ Misi L. Robinson,‖ Alastair D. Robertson, PHD,* Elisa Carniel, MD,§ Andrea Di Lenarda, MD, FESC,§ Teresa J. Bohlmeyer, MD,* Debra A. Ferguson, MS,* Gary L. Brodsky, PHD,* Mark M. Boucek, MD,*¶ Jean Lascor, MS,¶ Andrew C. Moss, BA,* Wai-Lun P. Li, BS,*† Gary L. Stetler, PHD,† Francesco Muntoni, MD, FRCPCH,# Michael R. Bristow, MD, PHD, FACC,* Luisa Mestroni, MD, FACC, FESC,* Familial Dilated Cardiomyopathy Registry Research Group

Denver, Colorado; Trieste, Italy; Omaha, Nebraska; and London, United Kingdom



LMNA mutations in Dilated Cardiomyopathy

Study design:

- multicenter cohort of **269** *LMNA* mutation carriers

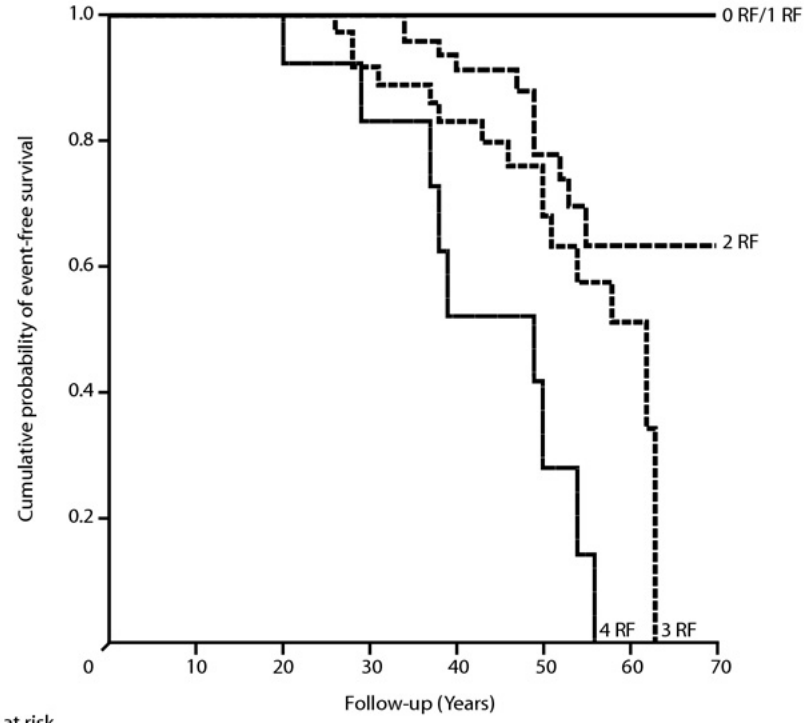
Results:

LMNA carriers with MVA: 18%

- 11 cardiopulmonary resuscitation
- 25 appropriate ICD treatment
- 12 SD

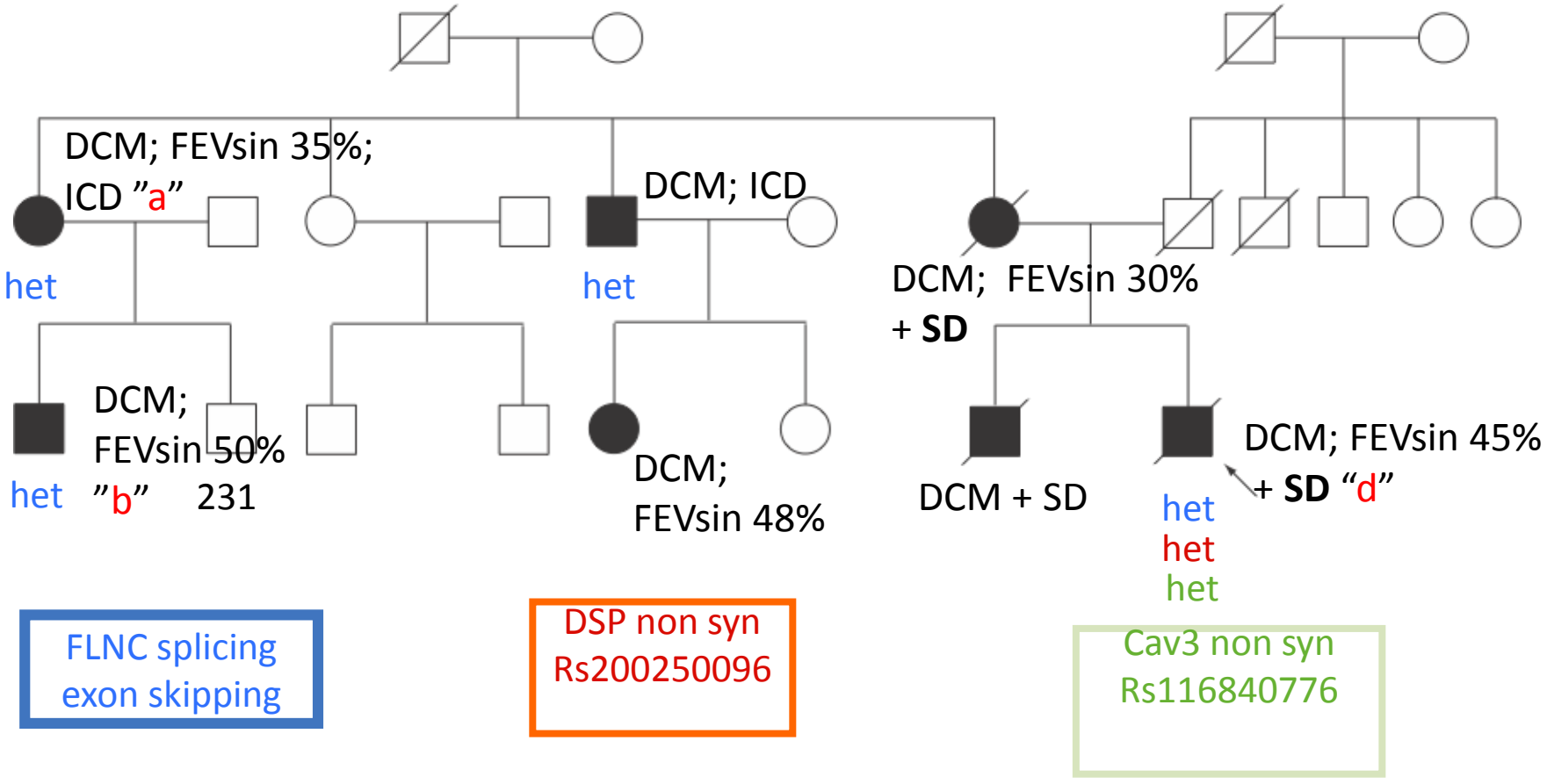
4 independent Risk Factors, cumulative risk:

- nonsustained ventricular tachycardia
- LVEF < 45%
- Male gender
- Truncating mutations



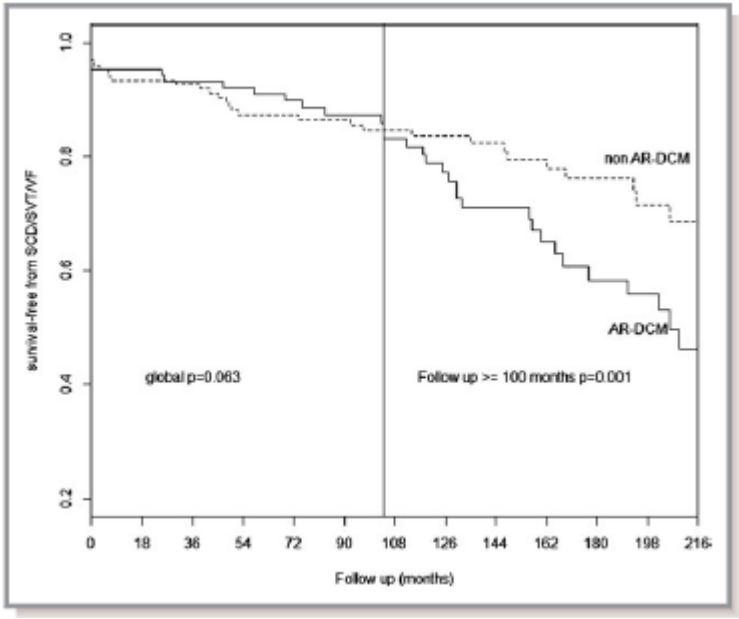
Rijsingen et al., J Am Coll Cardiol 2012;59:493–500

FAM#225:
DCM – Sudden death



Arrhythmogenic Phenotype in Dilated Cardiomyopathy: Natural History and Predictors of Life-Threatening Arrhythmias

Anita Spezzacatene, MD; Gianfranco Sinagra, MD; Marco Merlo, MD; Giulia Barbati, PhD; Sharon L. Graw, PhD; Francesca Brun, MD; Dobromir Slavov, PhD; Andrea Di Lenarda, MD; Ernesto E. Salcedo, MD; Jeffrey A. Towbin, MD; Jeffrey E. Saffitz, MD, PhD; Frank I. Marcus, MD; Wojciech Zareba, MD; Matthew R. G. Taylor, MD, PhD; Luisa Mestroni, MD, FACC, FAHA, FESC; on behalf of the Familial Cardiomyopathy Registry



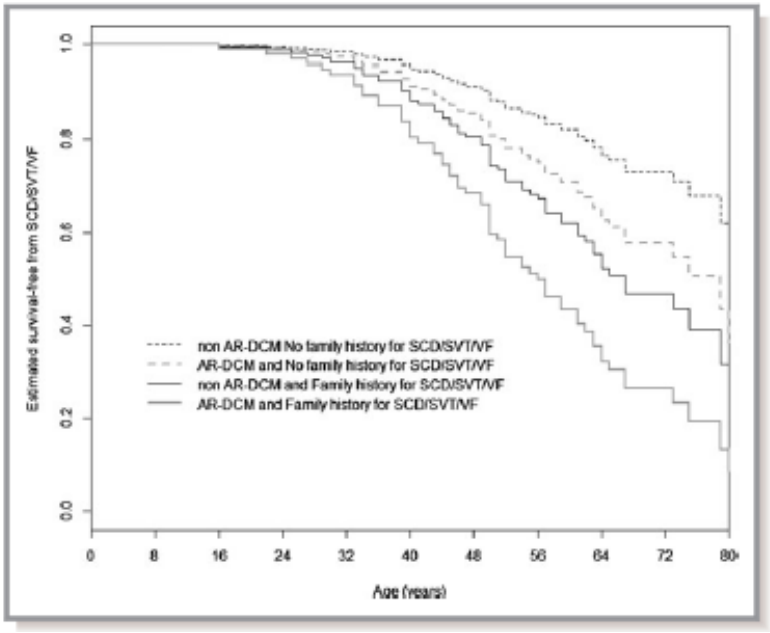


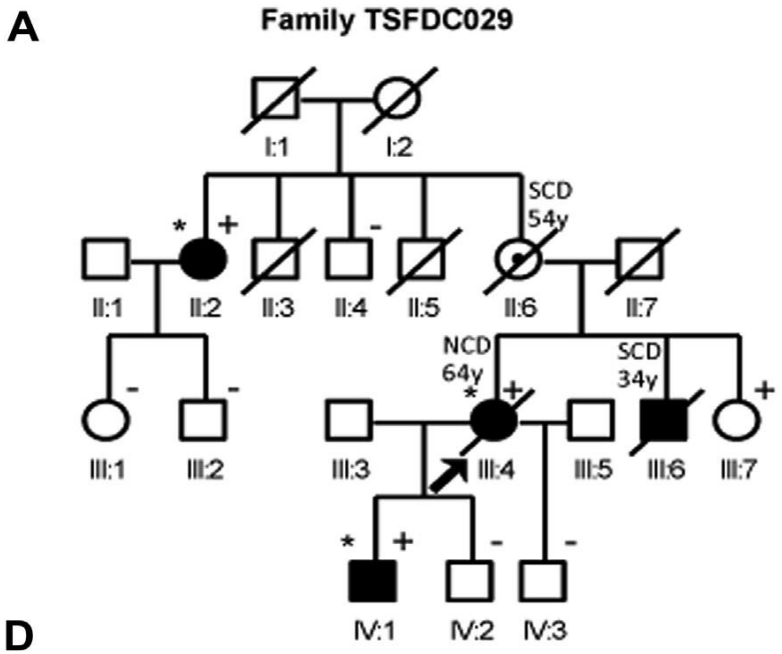
Table 1. Arrhythmic Profile of 109 AR-DCM Patients

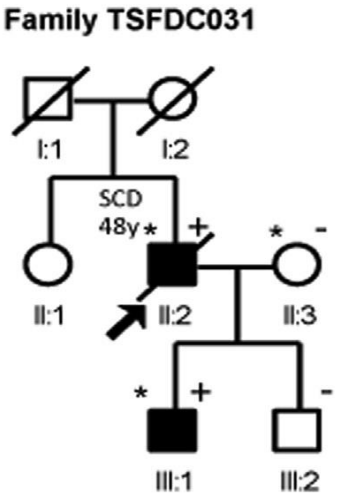
Criteria	AR-DCM Patients, n (%)
NSVT (≥5 beats, ≥150 bpm)	43 (39.4)
≥1000 PVCs/24 h	90 (82.6)
≥50 Couplets/24 h	40 (36.7)
Syncope	8 (7.3)

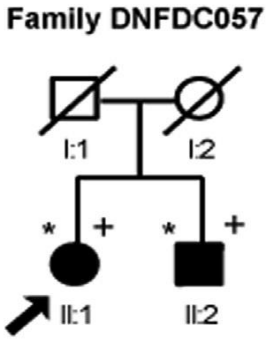
Am Heart Assoc. 2015 Oct 16;4(10):e002149.

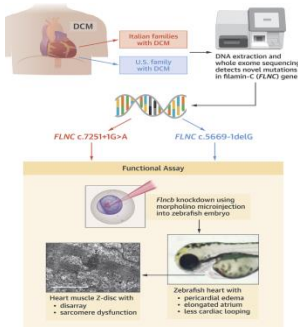
FLNC Gene Splice Mutations Cause Dilated Cardiomyopathy

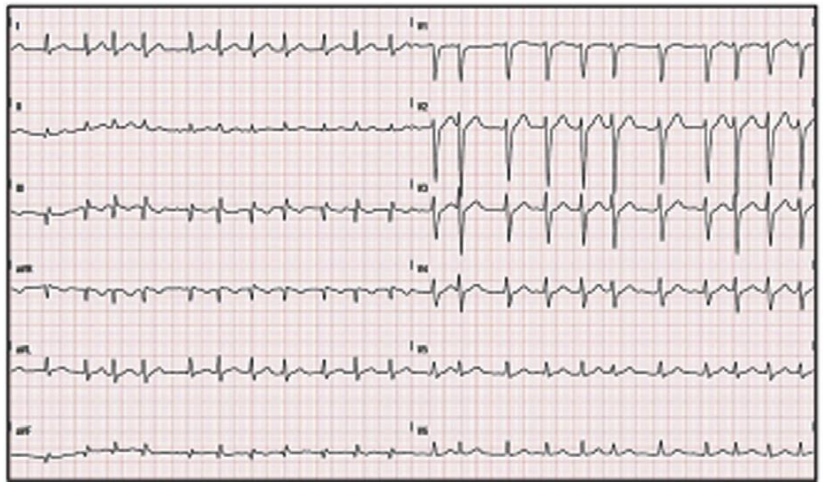
JACC
Basic to Translational Science

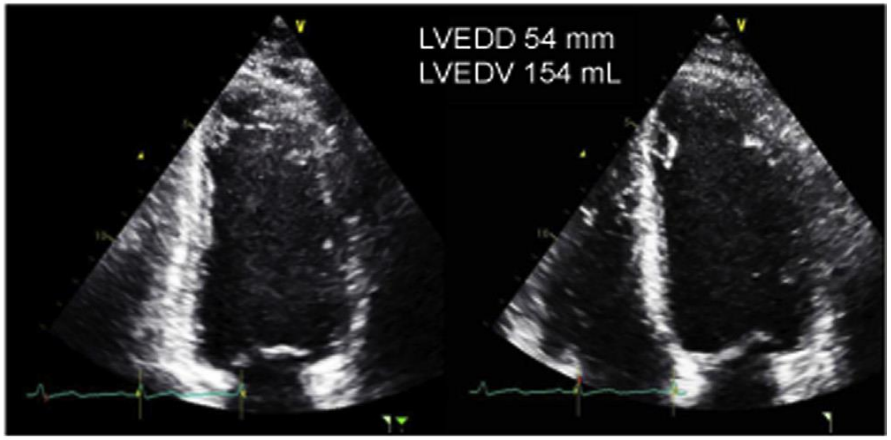












Begay, Sinagra, Mestroni at al

JACC: BASIC TO TRANSLATIONAL SCIENCE
http://dx.doi.org/10.1016/j.jacbts.2016.05.004

Truncating *FLNC* Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies

JACC
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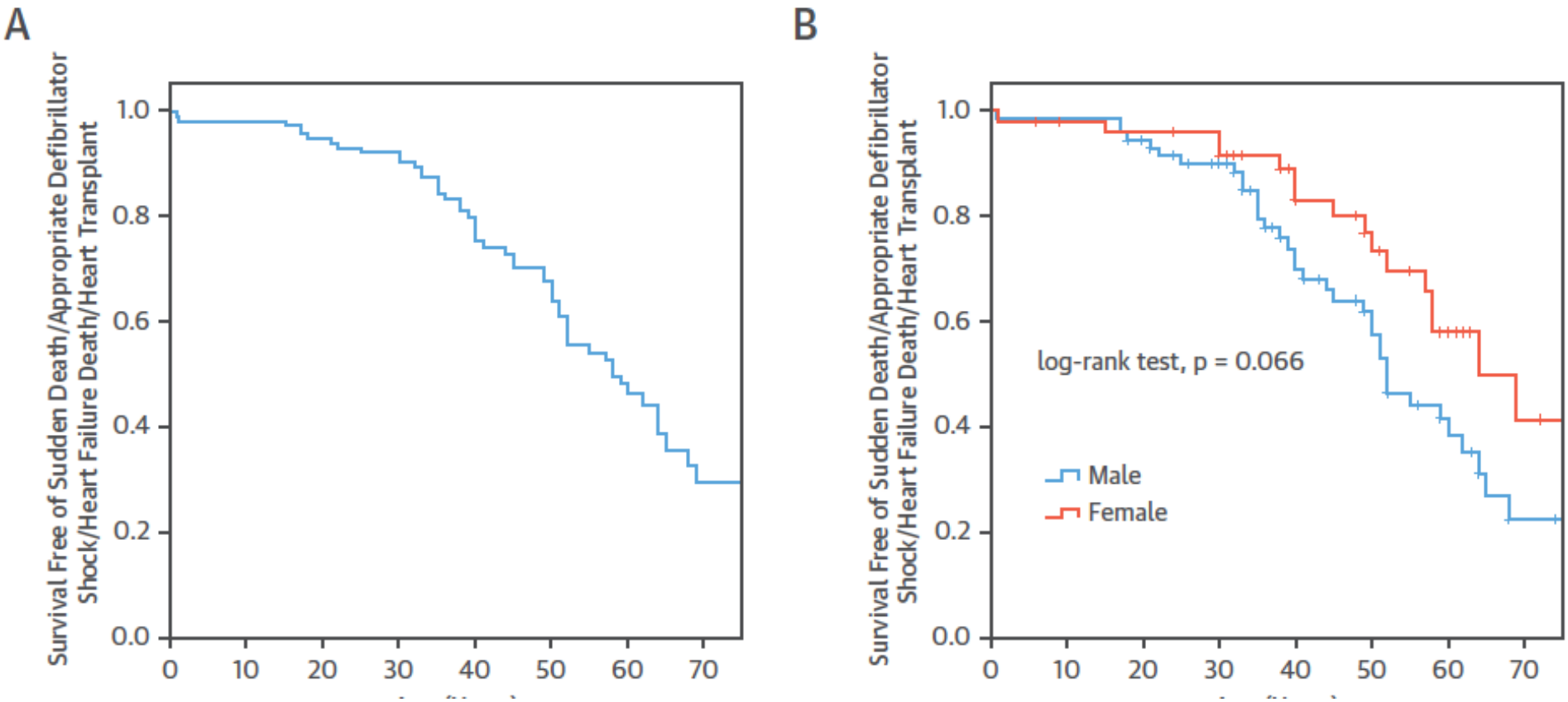
Major Cardiovascular Events



In families with truncating FLNC mutations, freedom from sudden death, appropriate defibrillator shock, heart failure death, or heart transplantation in all clinically or genetically affected subjects (A) and discriminated by sex (B) decreased as subjects aged.

Ortiz-Genga et al. J Am Coll Cardiol 2016;68:2440–51

Genetics and genotype–phenotype correlations in Finnish patients with dilated cardiomyopathy

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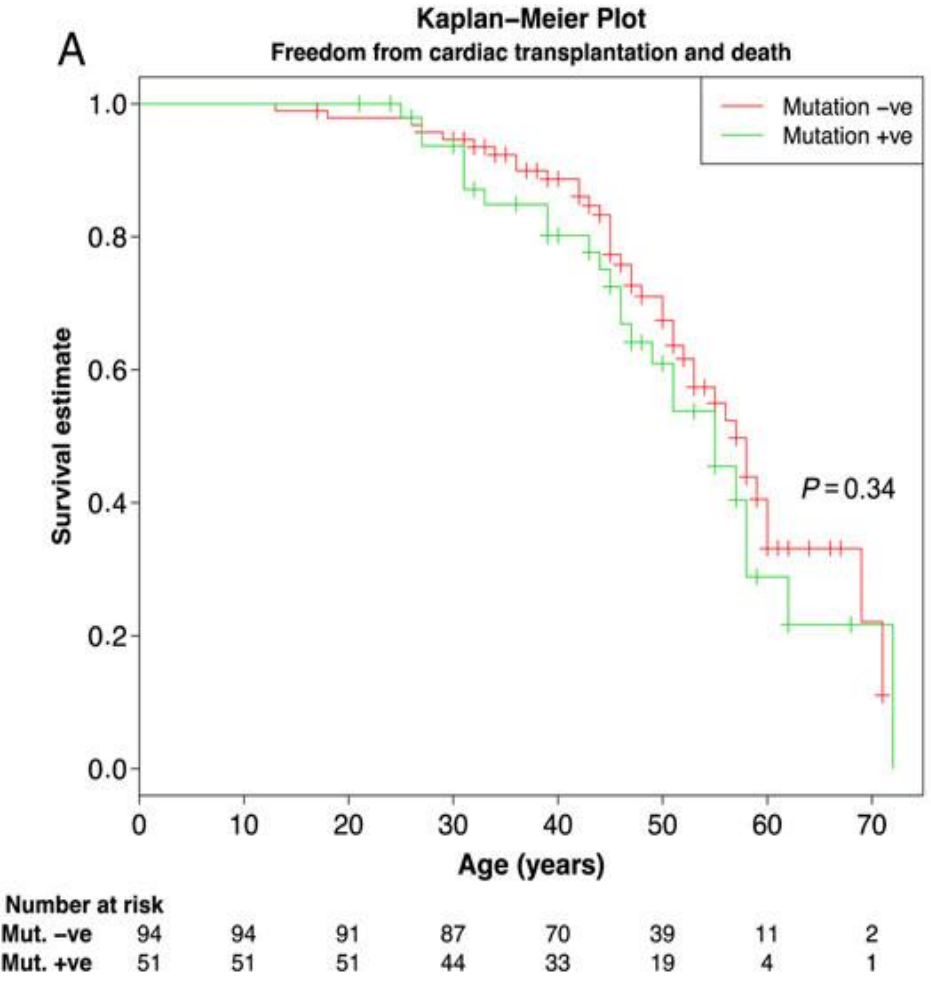
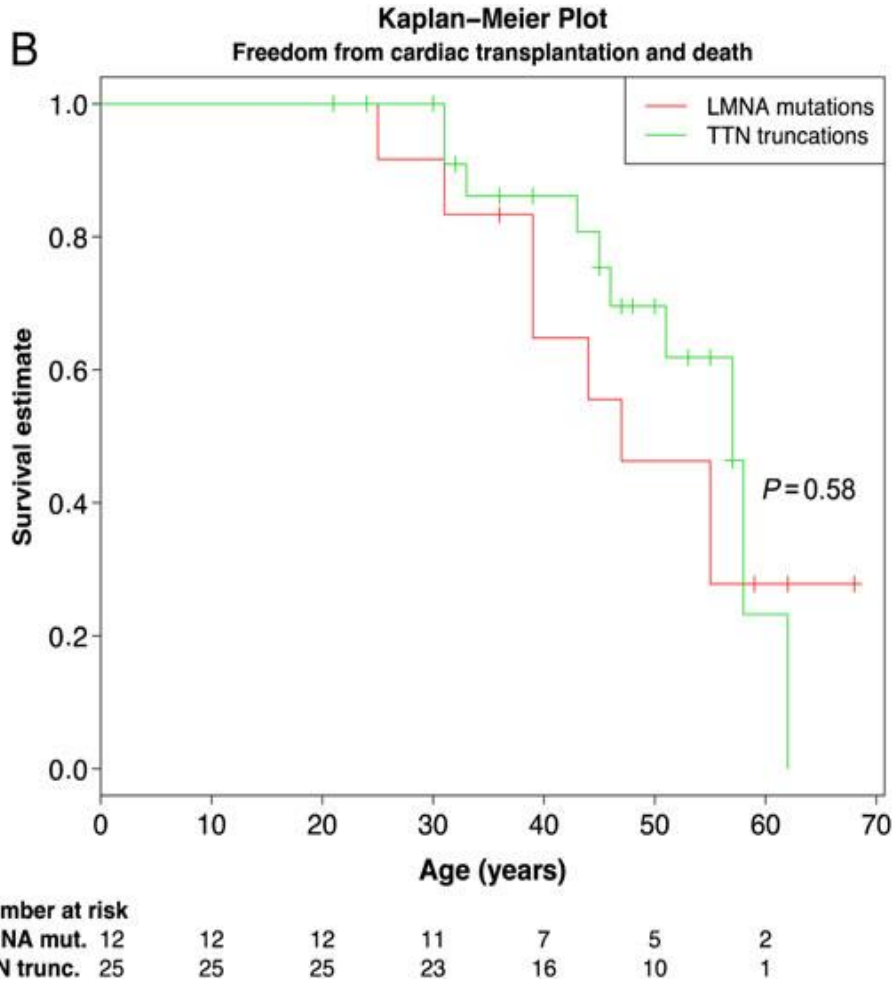
freedom from composite endpoint (HTx and death from cardiac causes)





European Heart Journal (2015) **36**, 2327–2337

Prognostic Relevance of Gene-Environment Interactions in Patients With Dilated Cardiomyopathy

Applying the MOGE(S) Classification

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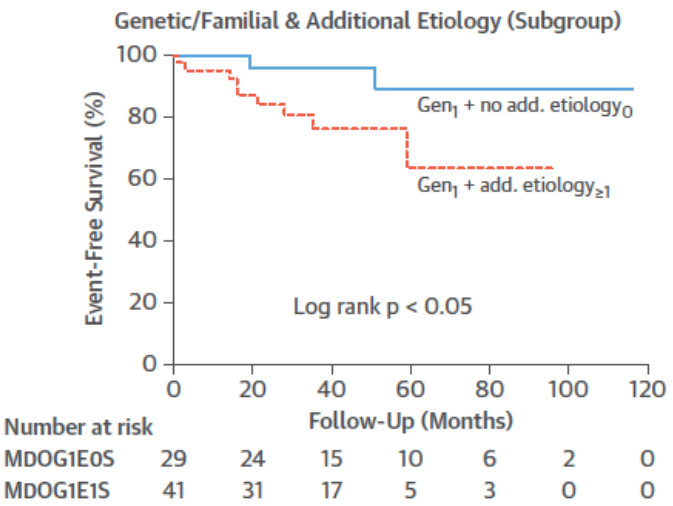
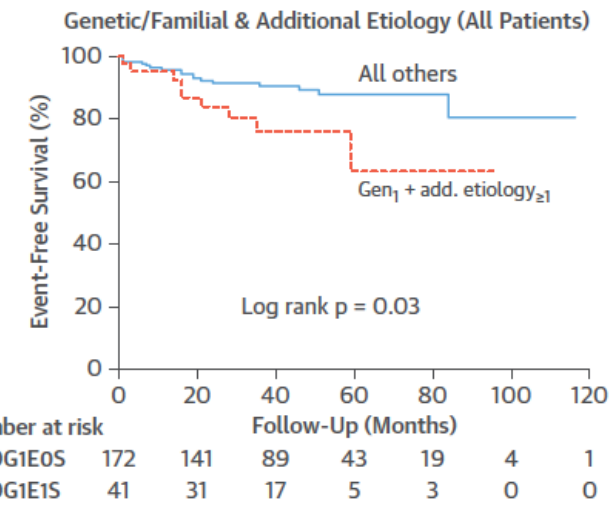
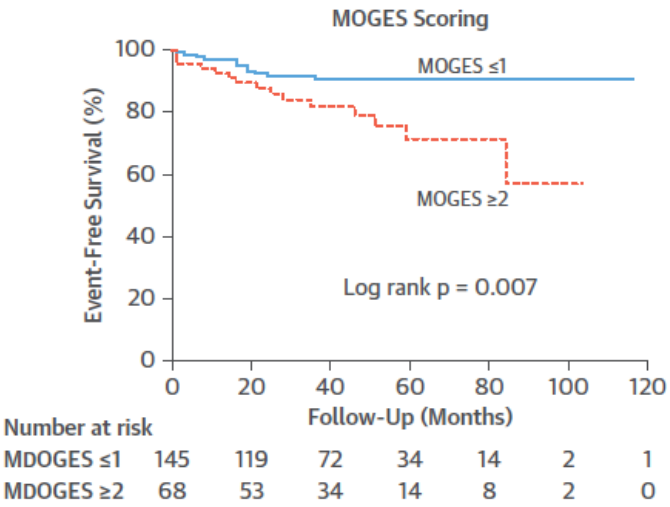
A



B



C



J Am Coll Cardiol 2015;66:1313–23

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

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ESC GUIDELINES

Risk stratification and management of patients with dilated cardiomyopathy

Recommendations	Class[a]	Level[b]	Ref.[c]
An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.[d]	IIa	B	71

doi:10.1093/eurheartj/ehv316

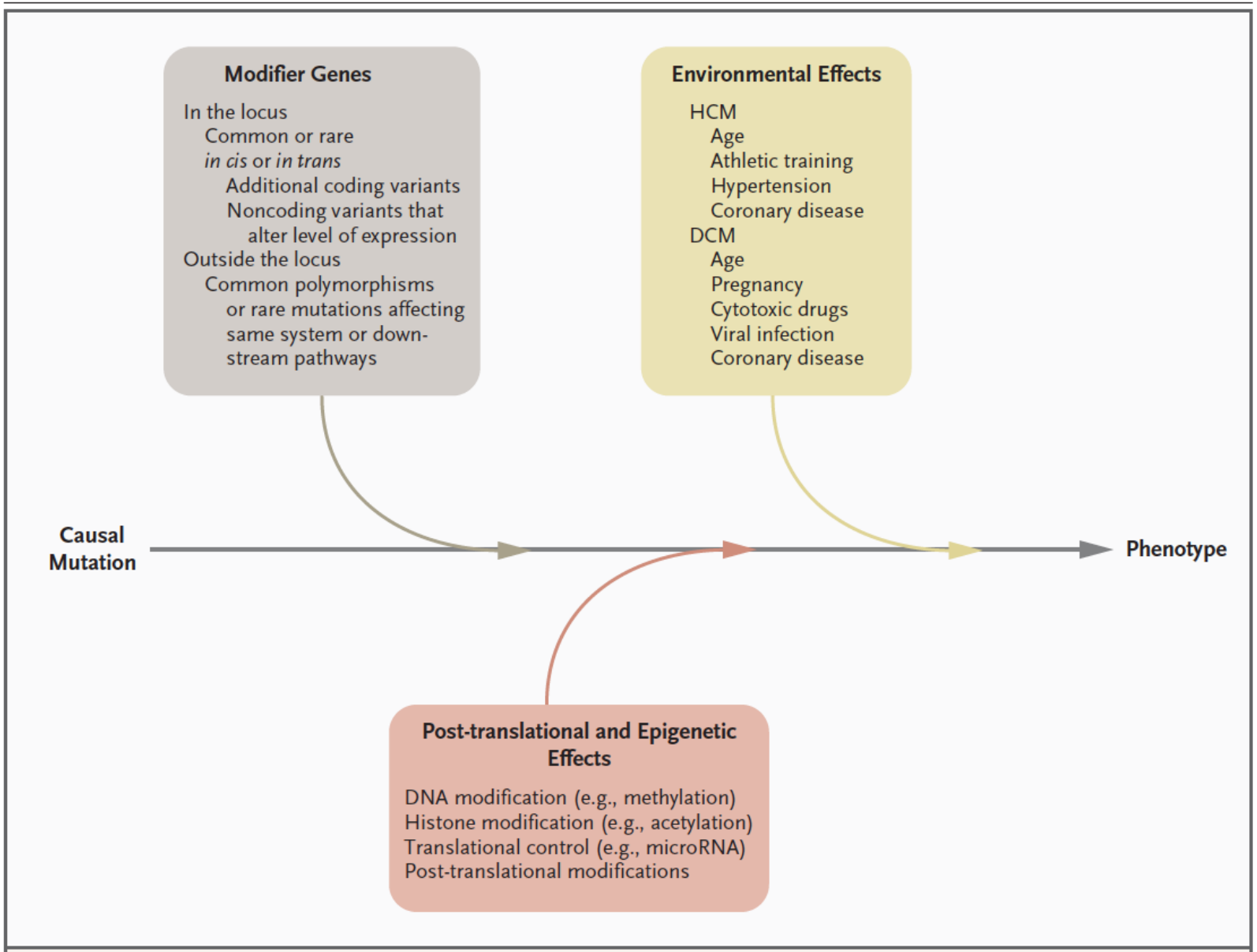

Figure 5. Complexities of the Genotype–Phenotype Relationship in Inherited Cardiomyopathies.

Watkins H. NEJM 2011;364:1643-56.

Genetica CMP

- **A chi?** forme accertatamente familiari per guidare lo screening/idoneità; casi controversi molto selezionati;
- **Quando?** Nei maggiorenni; casi minorenni molto selezionati;
- **Per quale uso?** Stratificazione prognostica; in casi selezionati per orientare la tp con device