Genetics of Cardiomyopathies

Genetics of cardiomyopathies

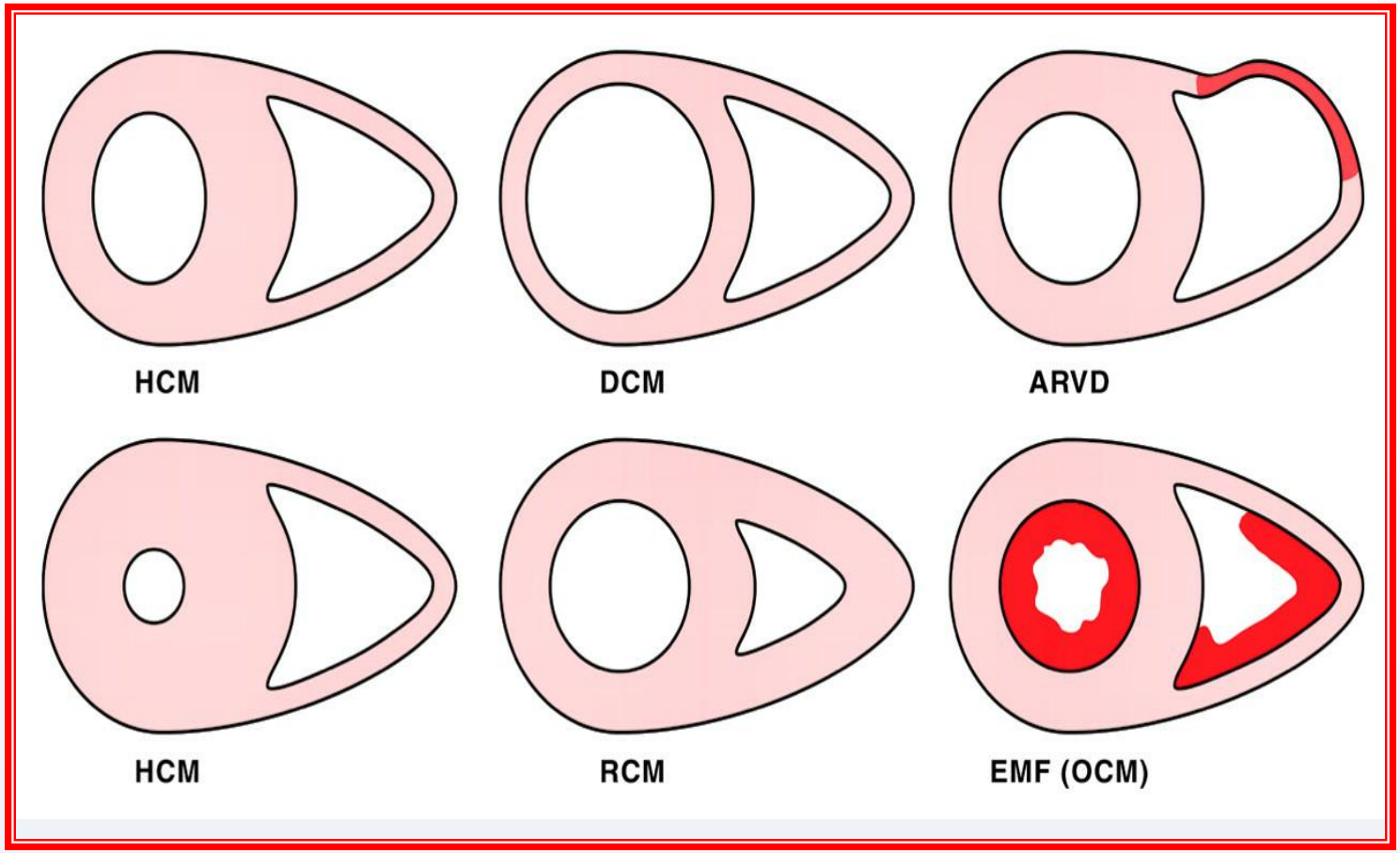
- Existing genetic paradigm for common forms of cardiomyopathy
- Role of genetic testing in clinical management
- Potential for new therapies
- Future challenges

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)

Classification of Cardiomyopathies

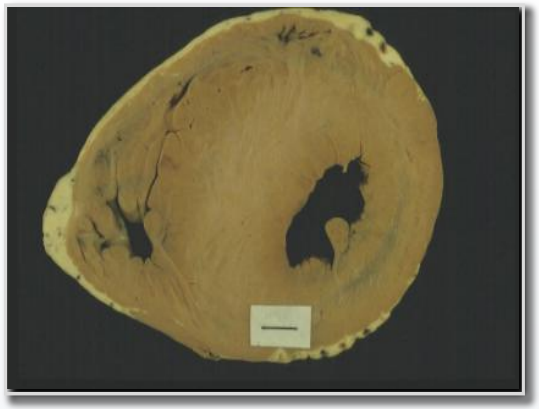


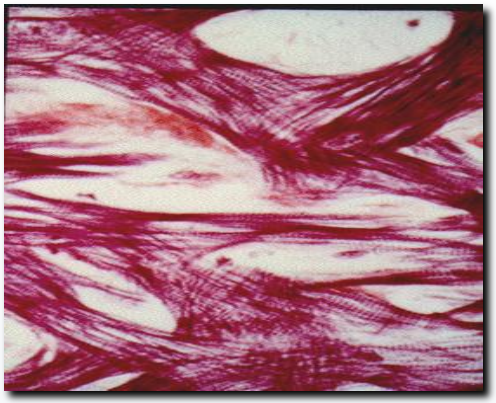
Davies M. Heart 2000;83:469-474

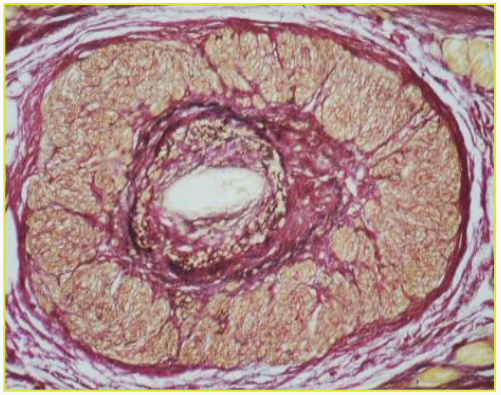
Key Points

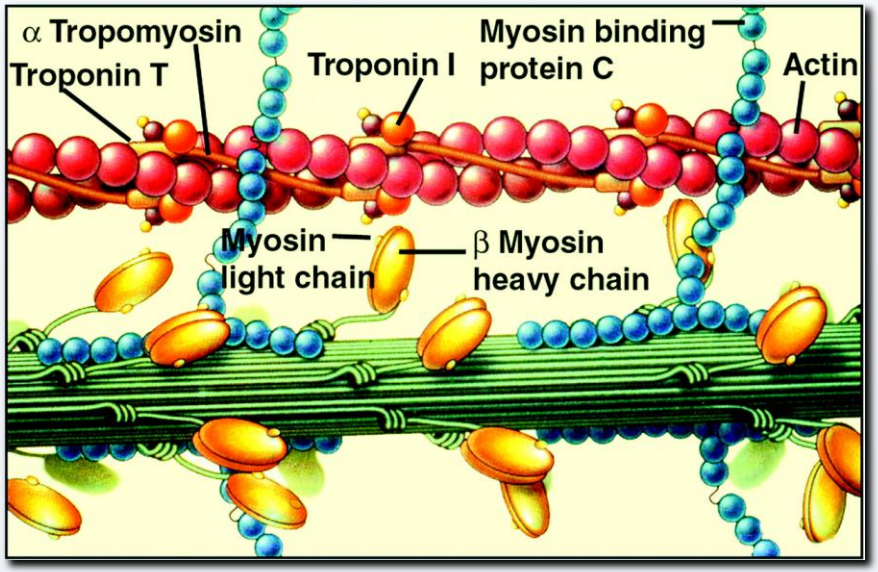
- All cardiomyopathies can be inherited
- Most are autosomal dominant
- Age related penetrance is usual
- Variable clinical expression

Hypertrophic Cardiomyopathy



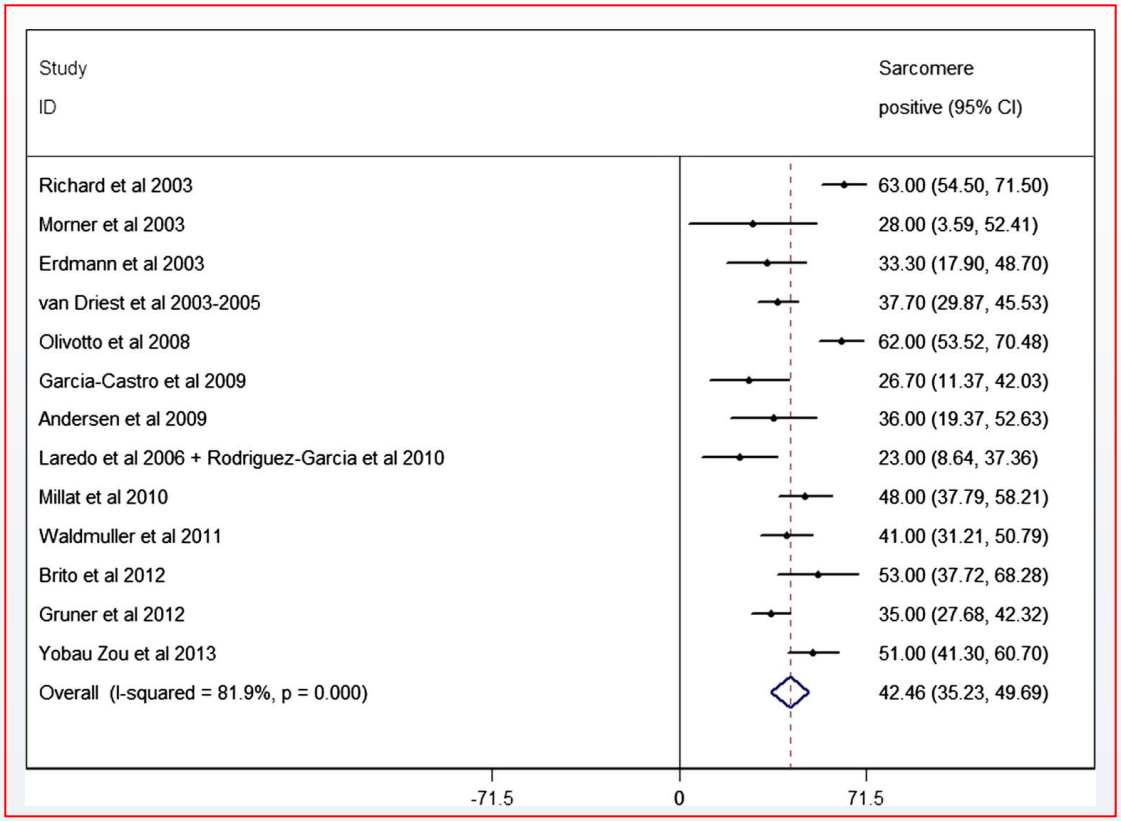






A systematic review and meta-analysis of genotype–phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations

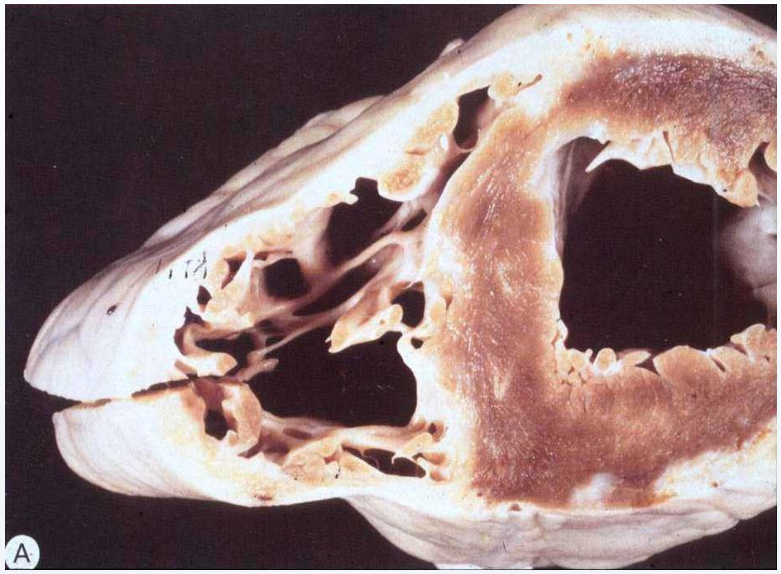
Luís R Lopes,[1] M Shafiqur Rahman,[2] Perry M Elliott[1]

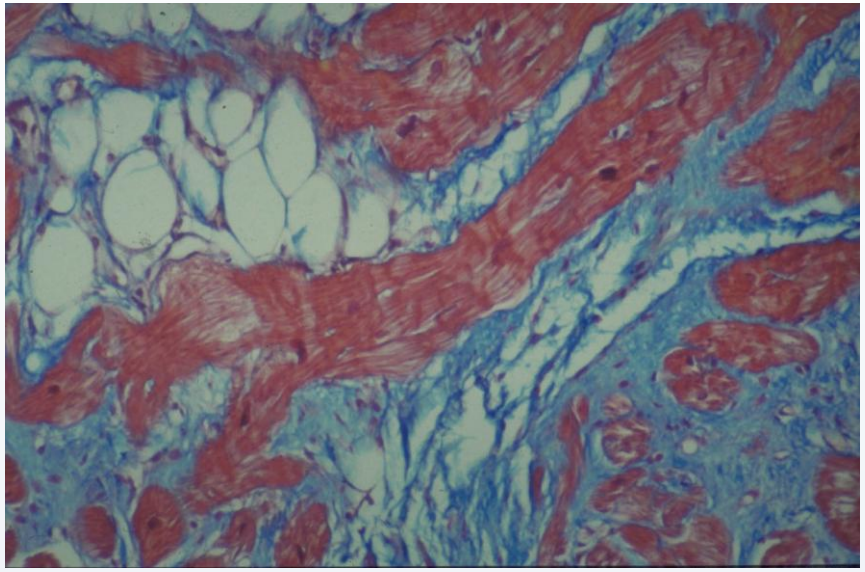


42.5%
(95% CI 35.2% to 49.7%).

Heart. 2013 May 14. [Epub ahead of print]

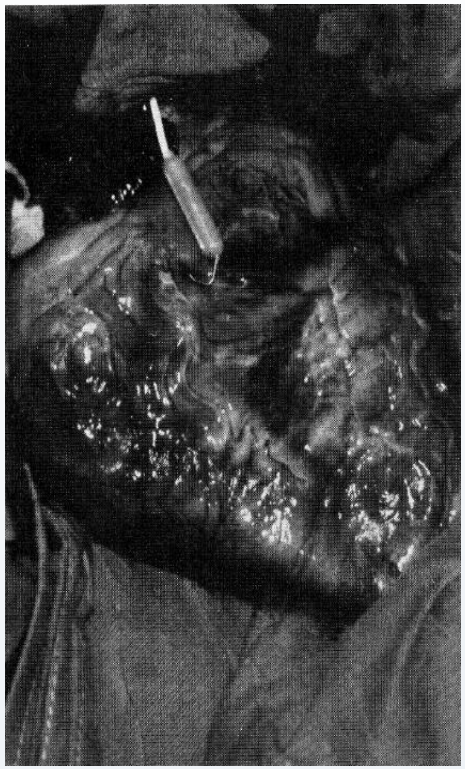
Arrhythmogenic right ventricular cardiomyopathy

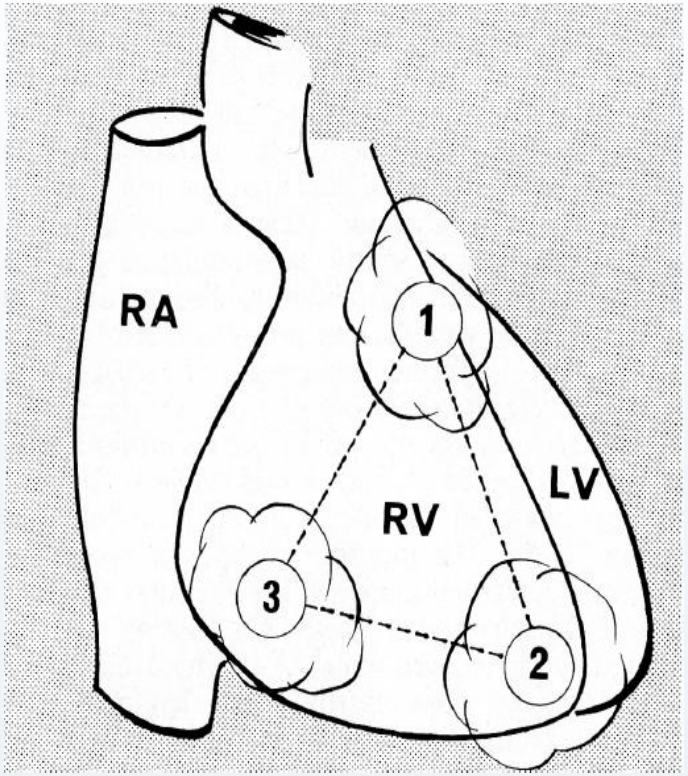


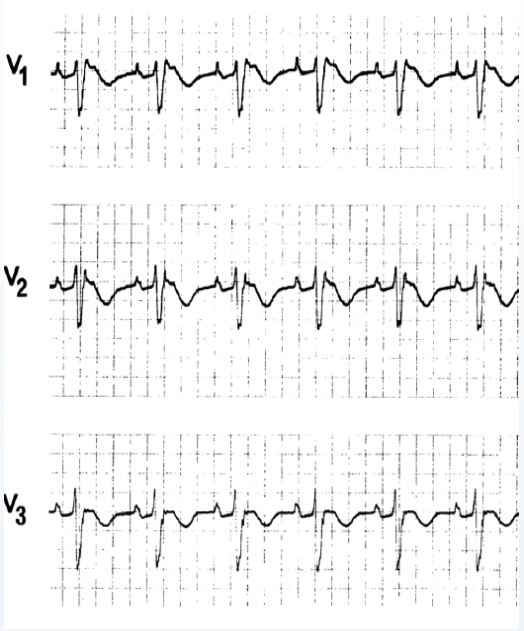


Right Ventricular Dysplasia: A Report of 24 Adult Cases

FRANK I. MARCUS, M.D., GUY H. FONTAINE, M.D., GERARD GUIRAUDON, M.D., ROBERT FRANK, M.D., JEAN L. LAURENCEAU, M.D., CHRISTINE MALERGUE, M.D., AND YVES GROSGOGEAT, M.D.







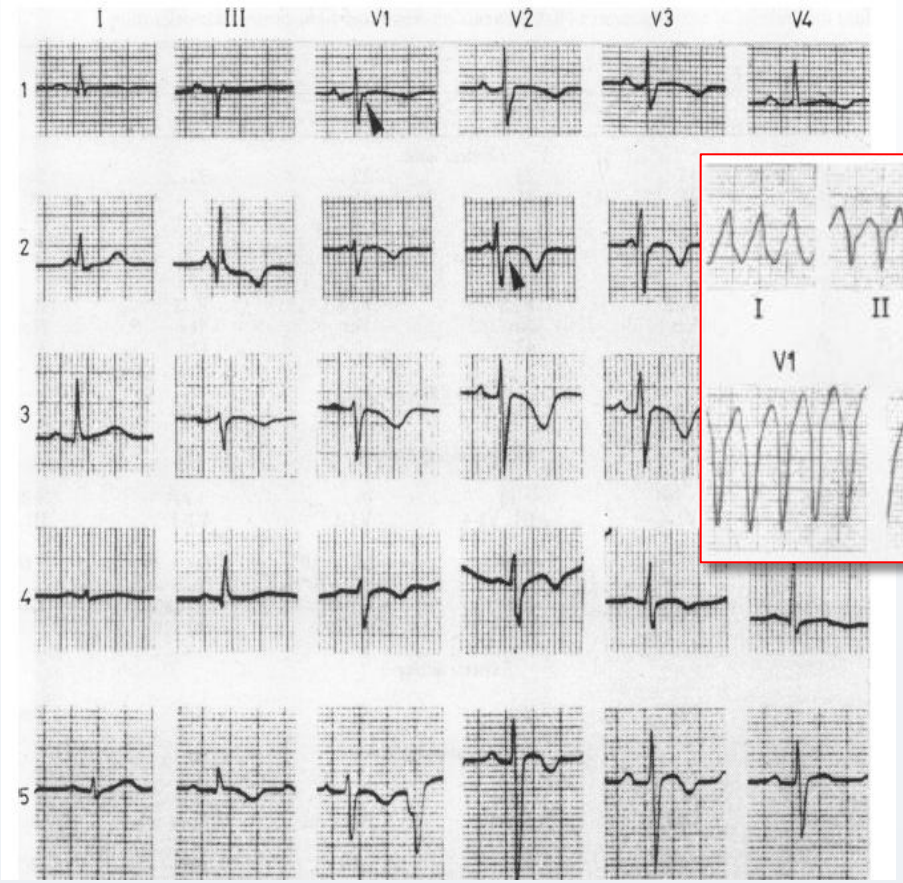
Circulation 1982;2:65

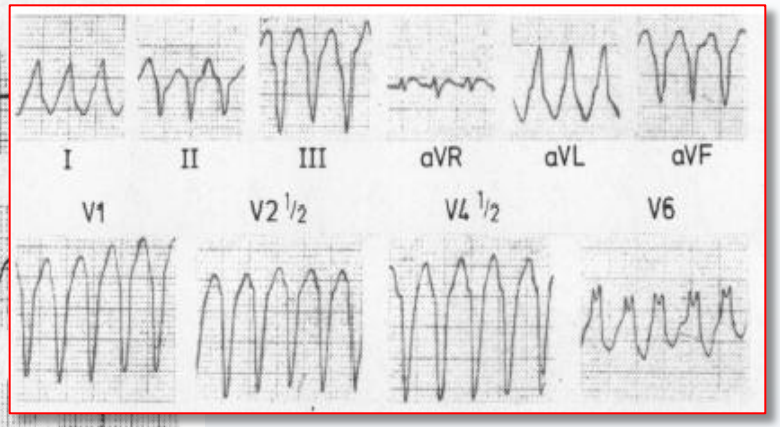
Ventricular tachycardia of left bundle branch block configuration in patients with isolated right ventricular dilatation

Clinical and electrophysiological features

EDWARD ROWLAND,* WILLIAM J McKENNA,† DECLAN SUGRUE, ROBIN BARCLAY, RODNEY A FOALE, DENNIS M KRIKLER

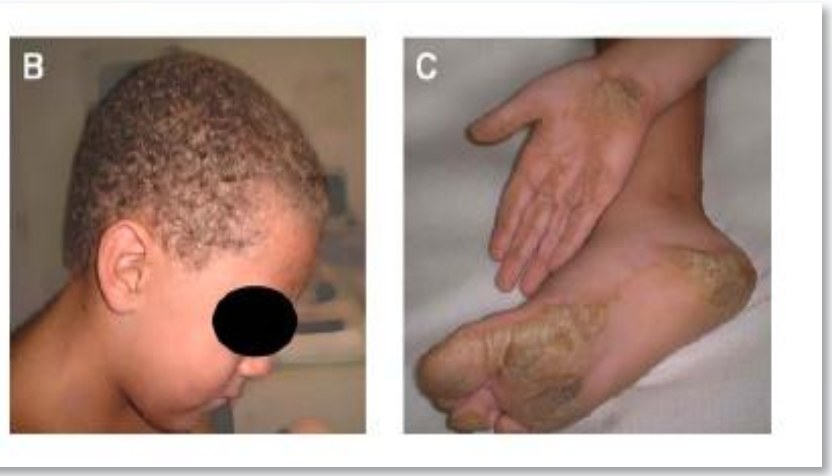
From the Division of Cardiovascular Disease, Royal Postgraduate Medical School, Hammersmith Hospital, London

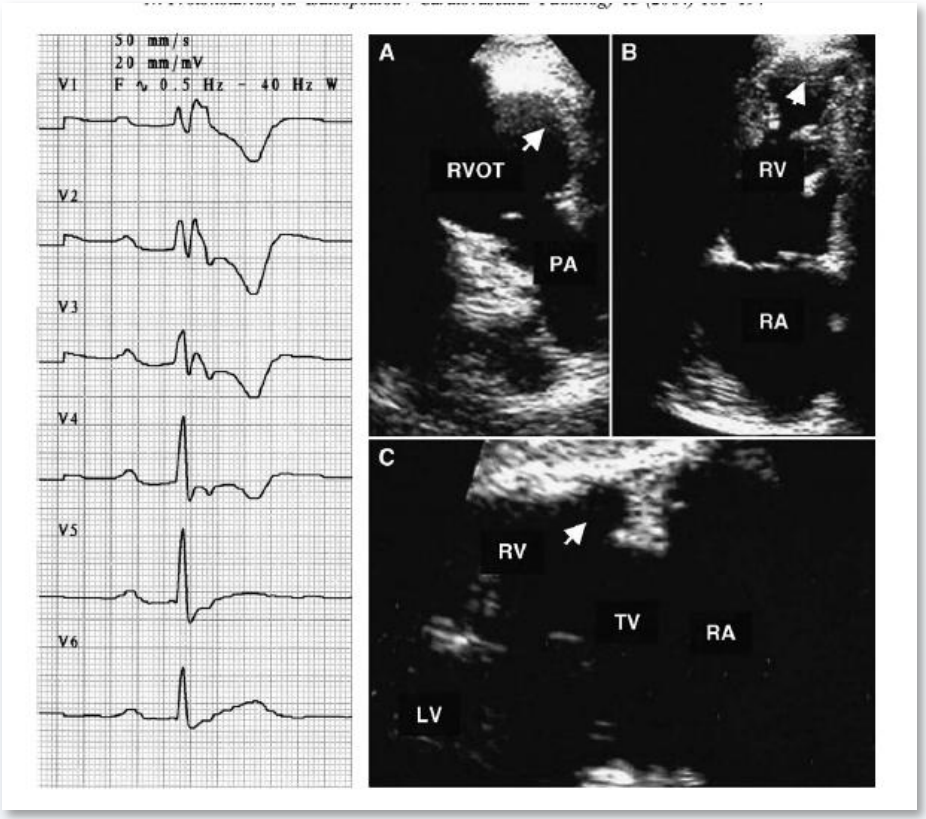




Br Heart J 1984 51: 15-24

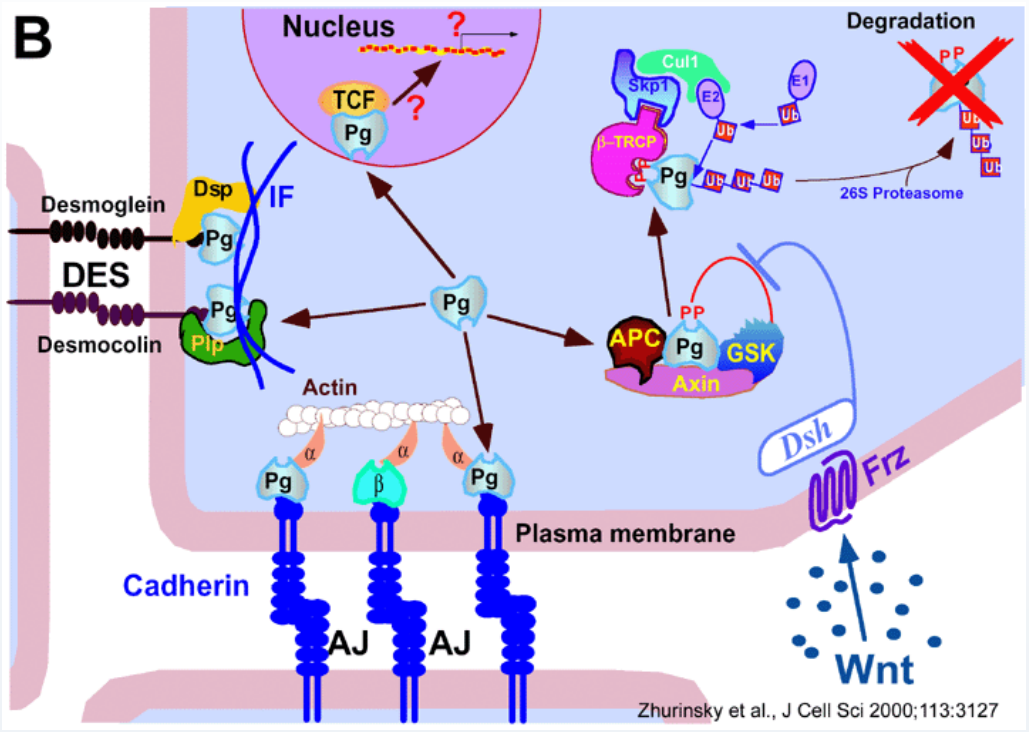
Cardiocutaneous syndromes ("Naxos disease")





Protonarious N and Tsatsopoulou A. Cardiovas Res 2004;13:185-194

ARVC: A Disease of Cell-to Cell Adhesion?

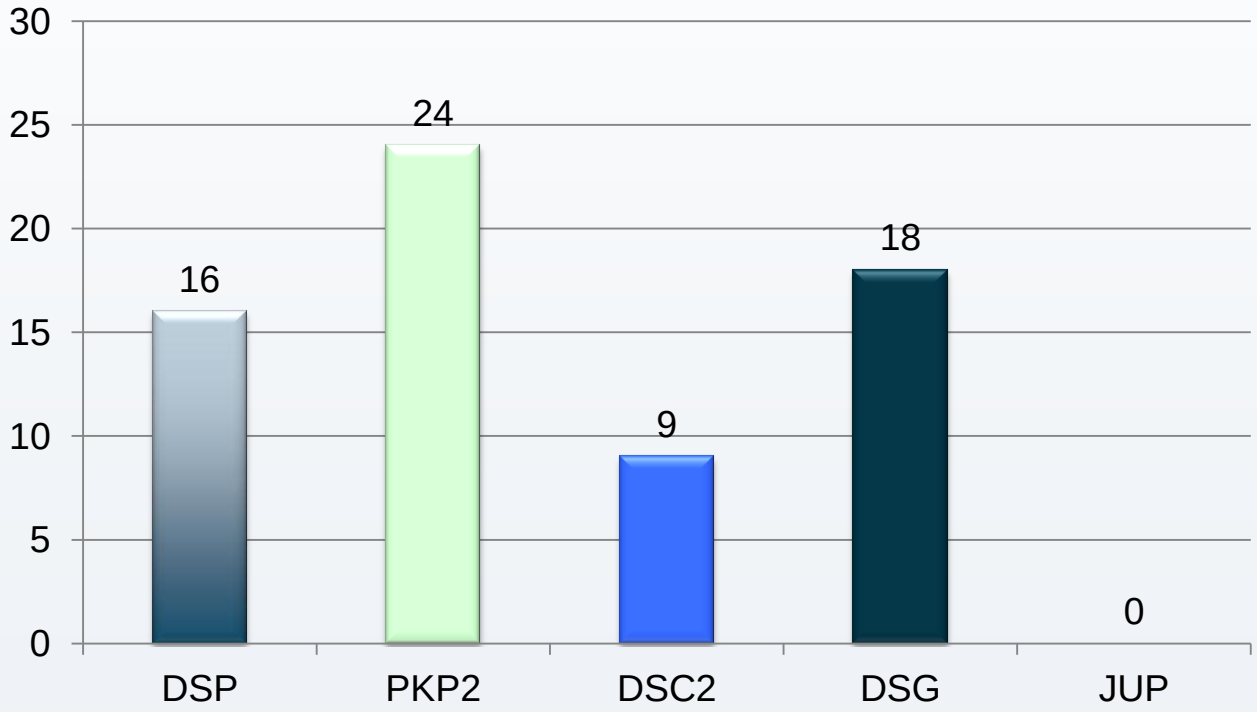


Plakoglobin
Desmoplakin
Plakophilin 2
Desmoglein 2
Desmocollin 2

Familial Evaluation in Arrhythmogenic Right Ventricular Cardiomyopathy

Impact of Genetics and Revised Task Force Criteria

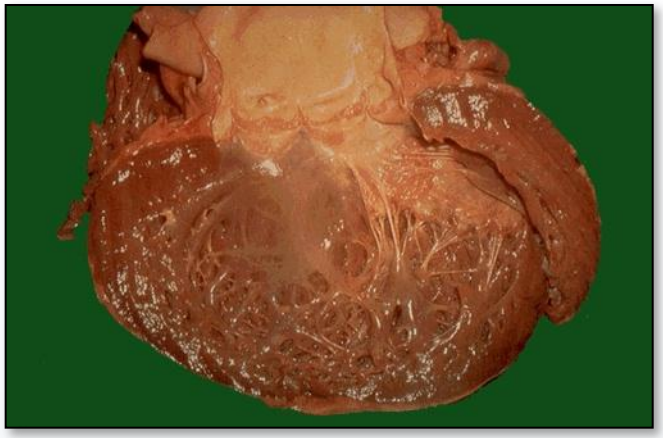
Giovanni Quarta, MD; Alison Muir, MD, MRCP; Antonios Pantazis, MD; Petros Syrris, PhD; Katja Gehmlich, PhD; Pablo Garcia-Pavia, MD; Deirdre Ward, MBBS, MRCPI; Srijita Sen-Chowdhry, MBBS, MD (Cantab); Perry M. Elliott, MBBS, MD, FRCP; William J. McKenna, MD, DSc, FRCP

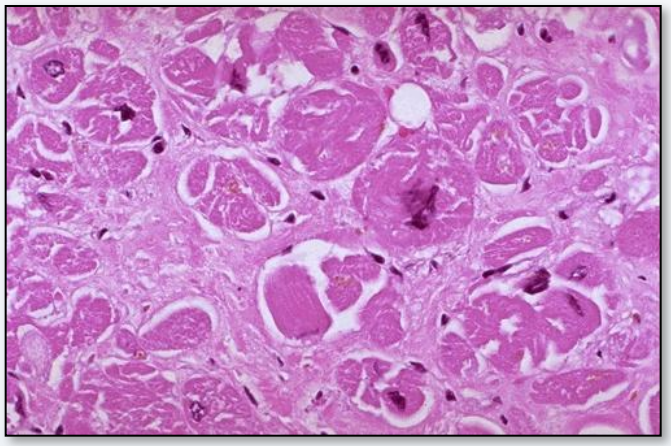


56/100 families ≥1 definite or probable mutation (6 digenic)

Circulation. 2011 Jun 14;123(23):2701-9

Dilated Cardiomyopathy





Author	n	Familial disease (%)
Fuster 1981	104	2
Michels 1985	169	6
Fragola 1988	12	33
Griffin 1988	32	10
Valentine 1989	184	9
Mestroni 1990	165	7
Michels 1992	59	20
Zachara 1993	105	13
Keeling 1995	40	25
Honda 1995	117	25
Gregori 1996	100	30

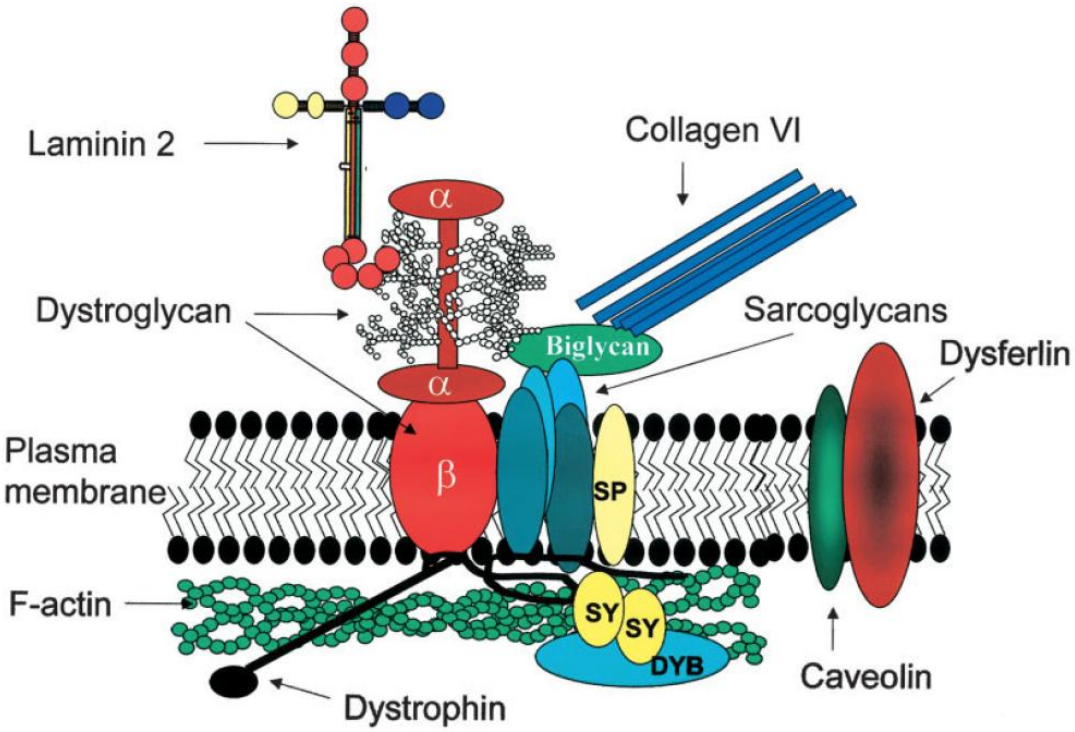
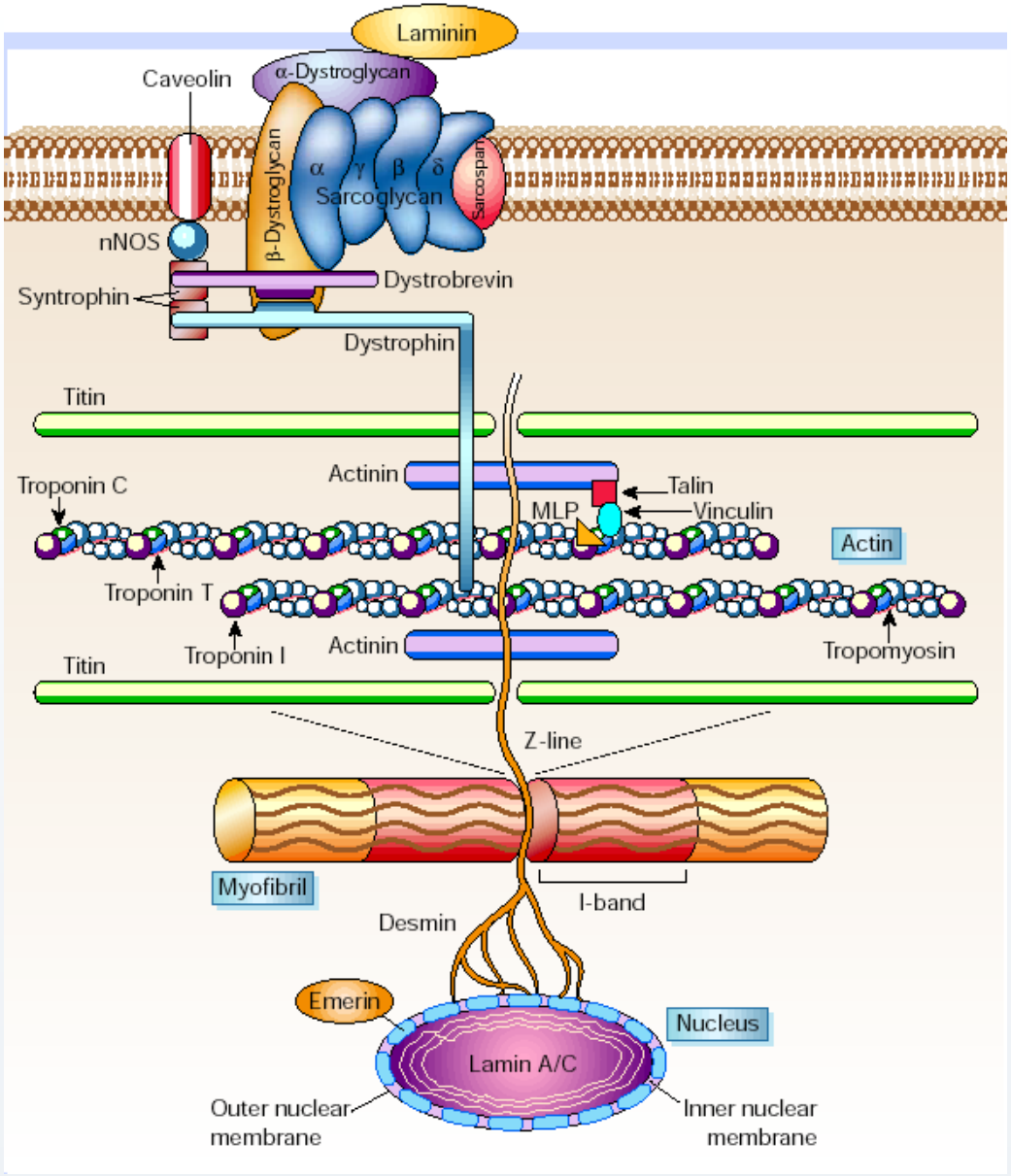


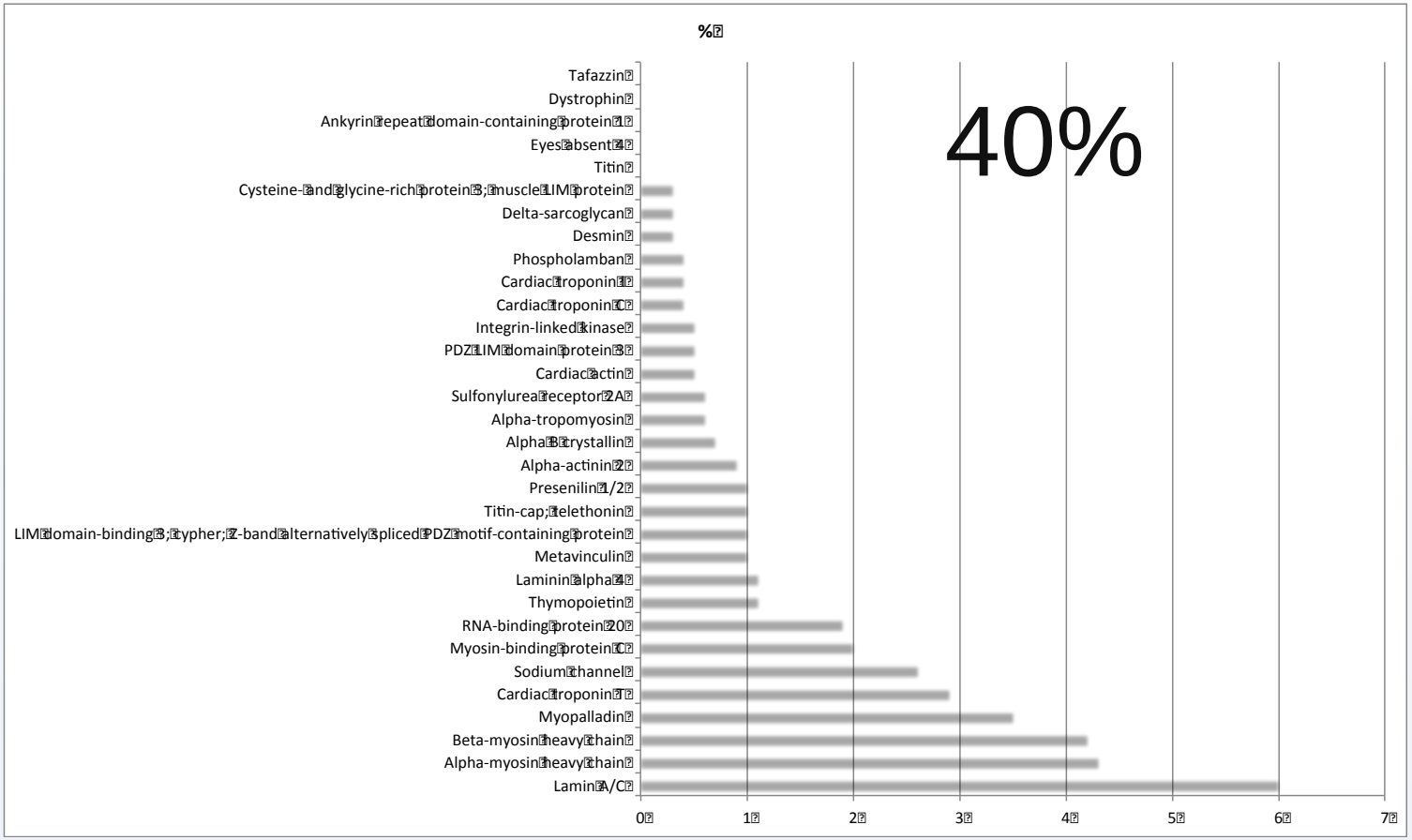
FIGURE 1. Scheme of the main proteins discussed in this review. DyB, dystrobrevin; SP, sarcospan; SY, syntrophin.

Goodwin, F. C., & Muntoni, F. (2005). Muscle & nerve, 32(5), 577–588.

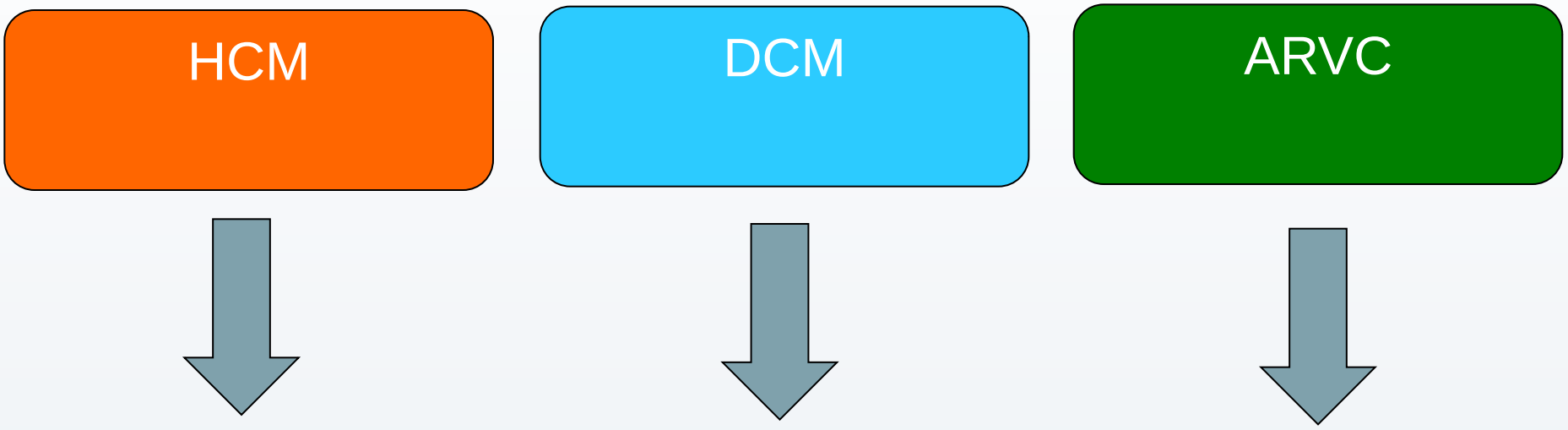
Genetics of DCM



Dilated Cardiomyopathy



J Am Coll Cardiol 2011;57:1641–9)

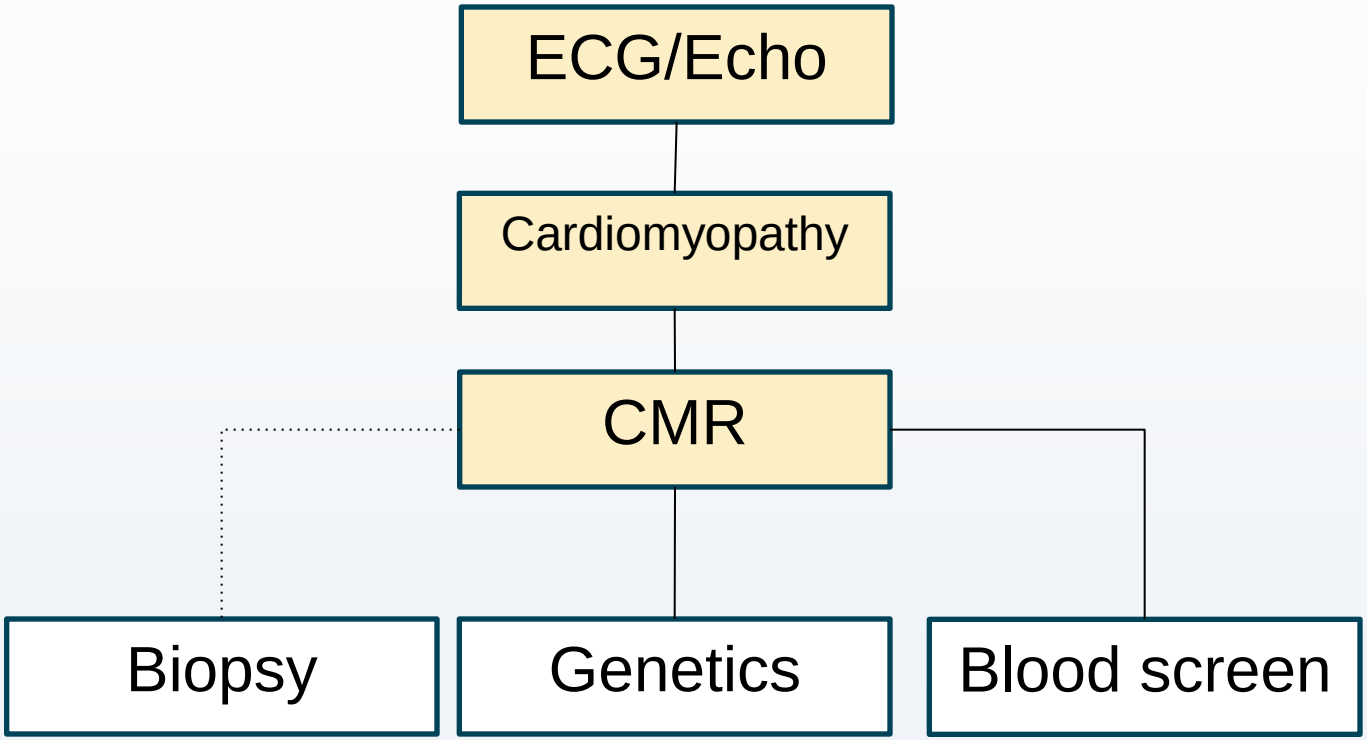

HCM
DCM
ARVC
Sarcomere
Cytoskeleton
Sarcomere
Nuclear
envelope…
Desmosome

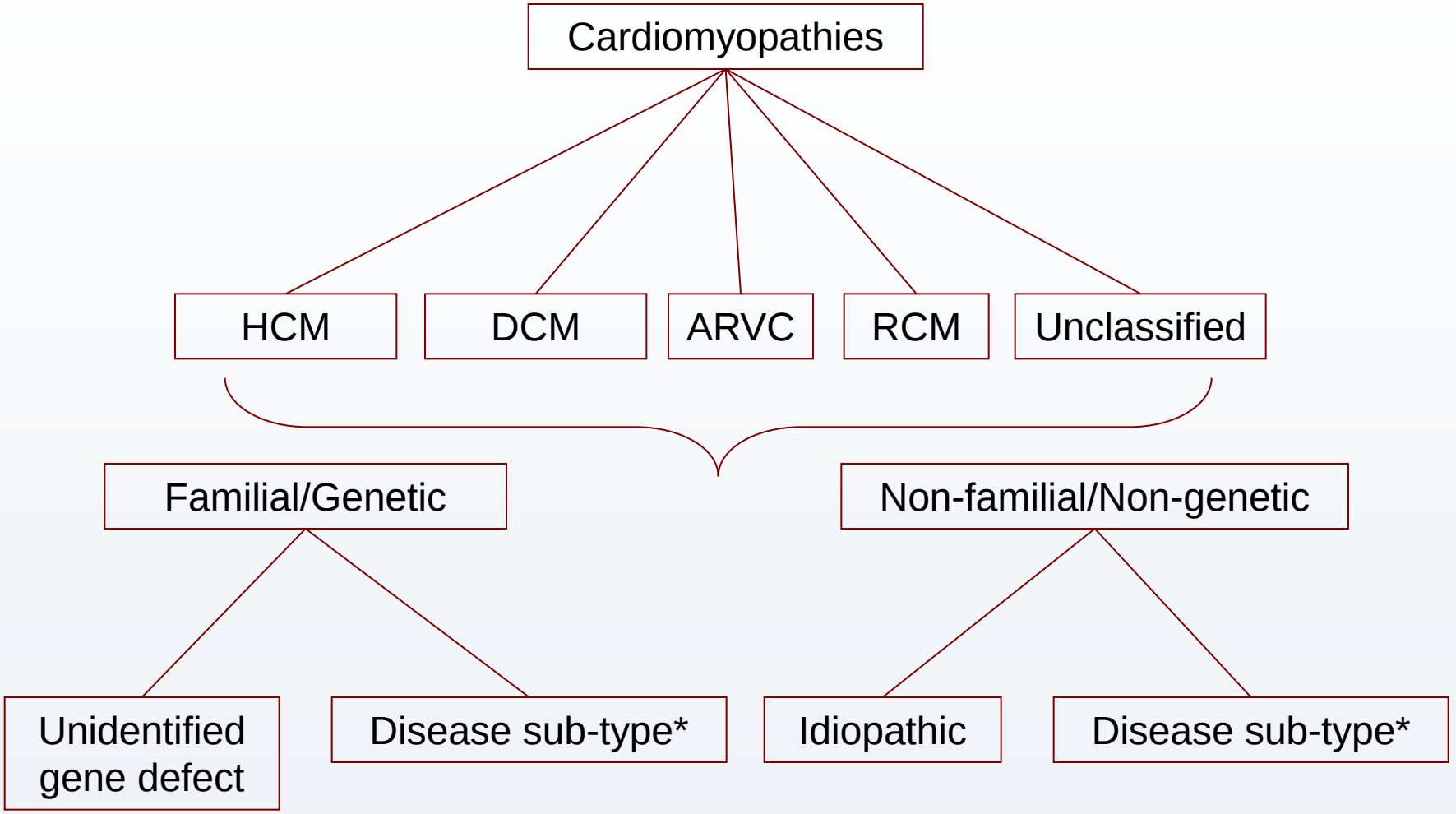
WHY OFFER GENOTYPING?

Why Offer Genotyping?

- Confirmation of Diagnosis?
- Management?
- Screening/management of family?

Cardiomyopathy is a clinical diagnosis





Elliott P et al Eur Heart J. 2008 Jan;29(2):270-6

Table 1 Examples of different diseases that cause cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations ß myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin-T α-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin α-myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedermann syndrome Swyer's syndrome Other Phospholamban promoter Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy	Familial, unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor-β3 (TGFβ3)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/− HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desminopathy Pseuxanthoma elasticum Haemochromatosis Anderson–Fabry disease Glycogen storage disease	Left ventricular non-compaction Barth syndrome Lamin A/C ZASP α-dystrobrevin
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid (AL/prealbumin)	Myocarditis (infective/toxic/immune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chromosomal cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (anthracyclines)	Tako Tsubo cardiomyopathy

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

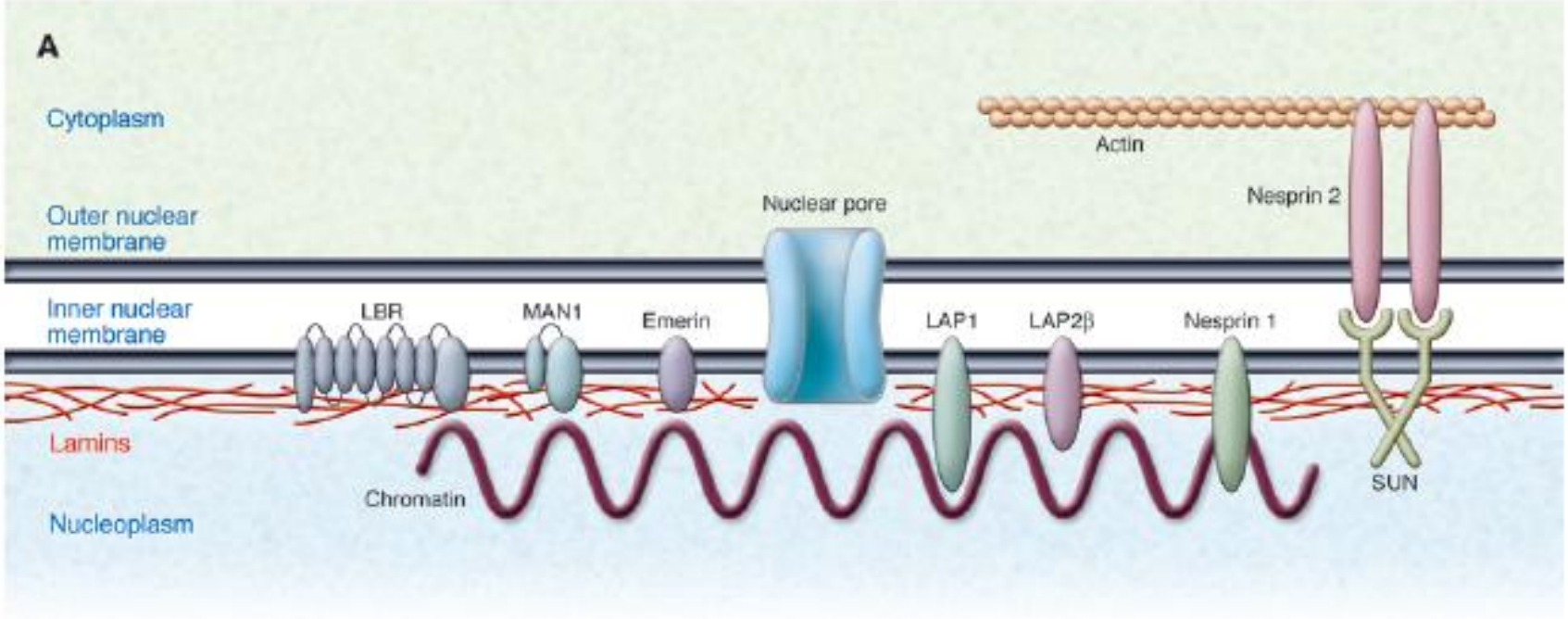
Elliott P et al Eur Heart J. 2008 Jan;29(2):270-6

DOES A (GENETIC) DIAGNOSIS ALTER MANAGEMENT?

Genetic “guided” therapies in cardiomyopathy

- Pompe ERT
- Anderson-Fabry Disease ERT
- ATTR Amyloid Diflunisal, stabilisers, Tx…

Lamin AC


A
Cytoplasm
Outer nuclear membrane
Inner nuclear membrane
Lamins
Nucleoplasm
Actin
Nesprin 2
Nuclear pore
LBR
MAN1
Emerin
LAP1
LAP2β
Nesprin 1
SUN
Chromatin

Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study

(J Am Coll Cardiol 2012;59:493–500

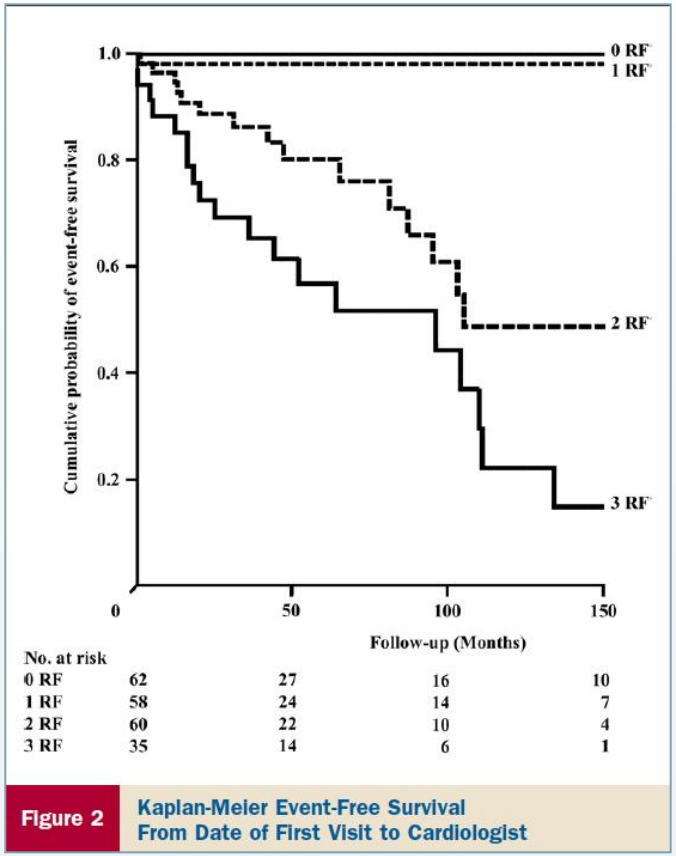


Figure 2 Kaplan-Meier Event-Free Survival From Date of First Visit to Cardiologist

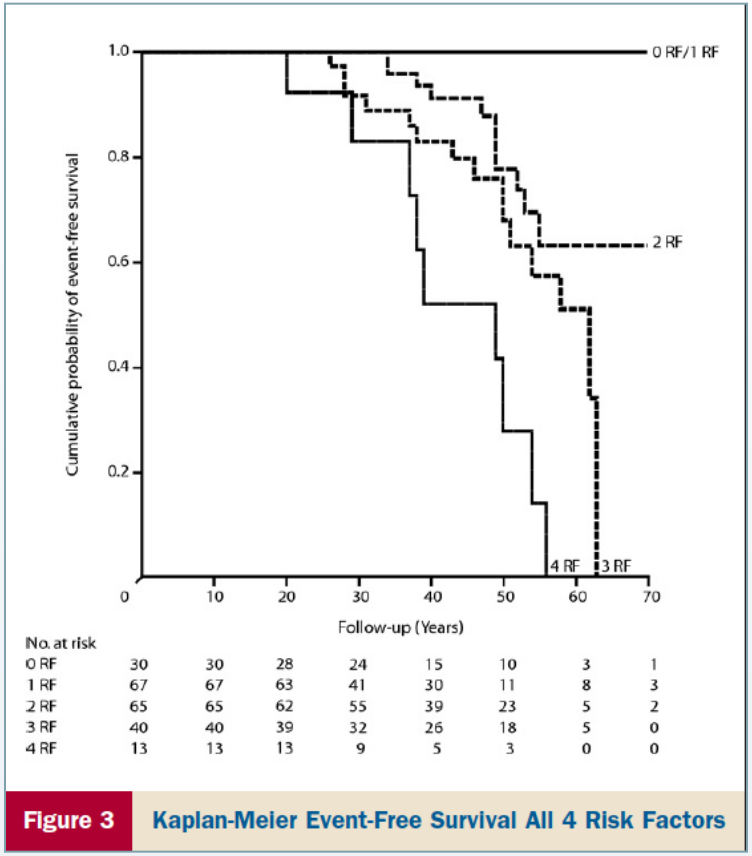


Figure 3 Kaplan-Meier Event-Free Survival All 4 Risk Factors

NSVT, LVEF 45%, male

+ non-missense mutations (ins-del/truncating or mutations affecting splicing)

Management of laminopathies

- Anti-failure therapy
- Anticoagulation
- ICD when bradycardia/AVB/ventricular arrhythmia
- Transplantation

Will it help the family? (Predictive/Cascade Testing)

Reasons for PT in HCM

- **Prevention of Complications**
  - Sudden Death
  - Stroke
  - (Heart failure)

- **Psychosocial**
  - select career, sports activities
  - relieve uncertainty
  - time to adjust
  - Family “well being” – anxious parents etc

Economic

A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy

Jodie Ingles,[1,2] Julie McGaughran,[3,4] Paul A Scuffham,[5] John Atherton,[4,6] Christopher Semsarian[1,2,7]

Euro 587 per quality-adjusted life-year gained,

Euro 9509 per additional life-year gained

Ingles J et al. Heart. 2012 Apr;98(8) 625-30

DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model

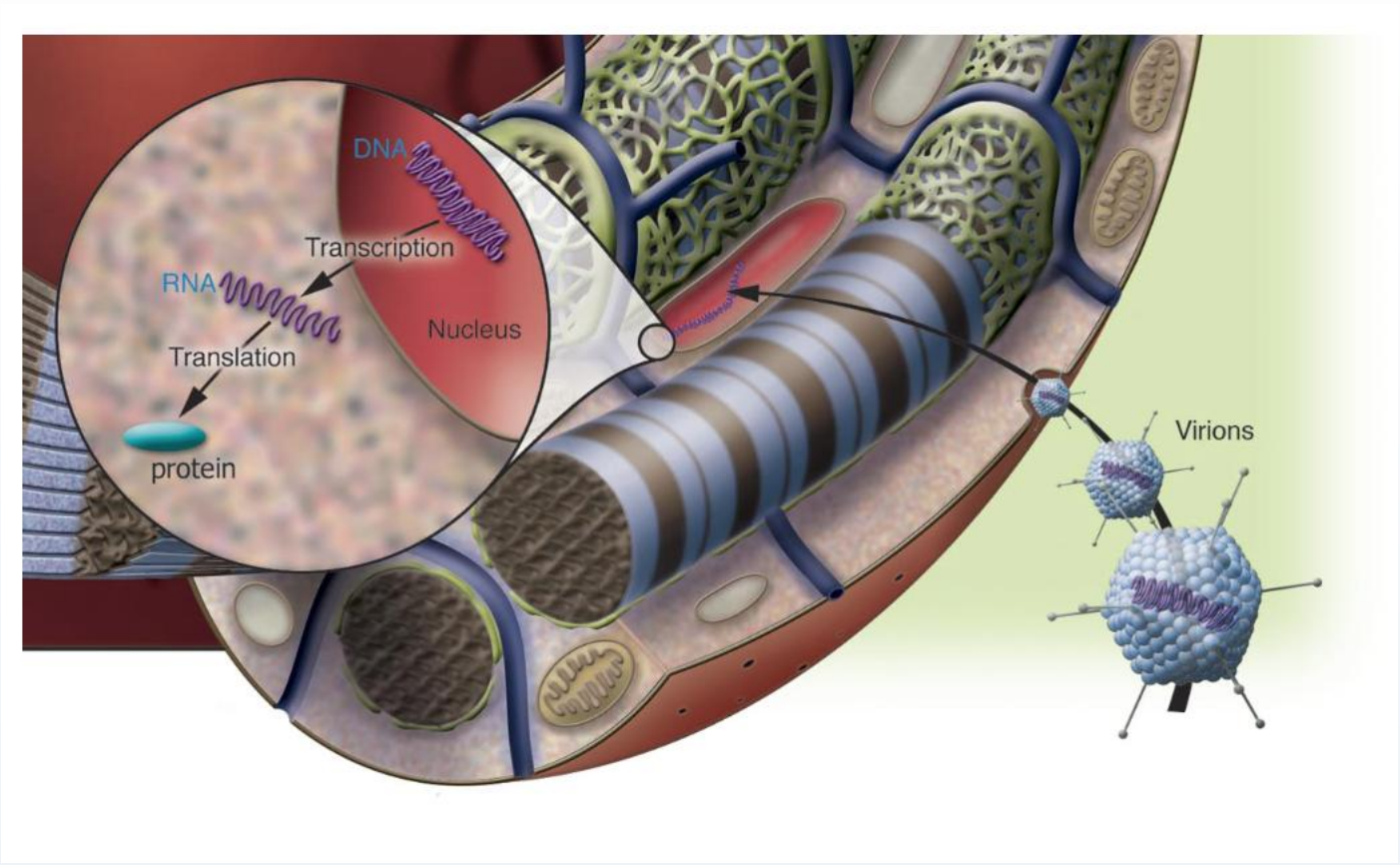
Sarah Wordsworth[1*], José Leal[1], Edward Blair[2,3], Rosa Legood[4], Kate Thomson[5], Anneke Seller[5], Jenny Taylor[6], and Hugh Watkins[3]

The incremental cost per life year saved was Euro 14 397

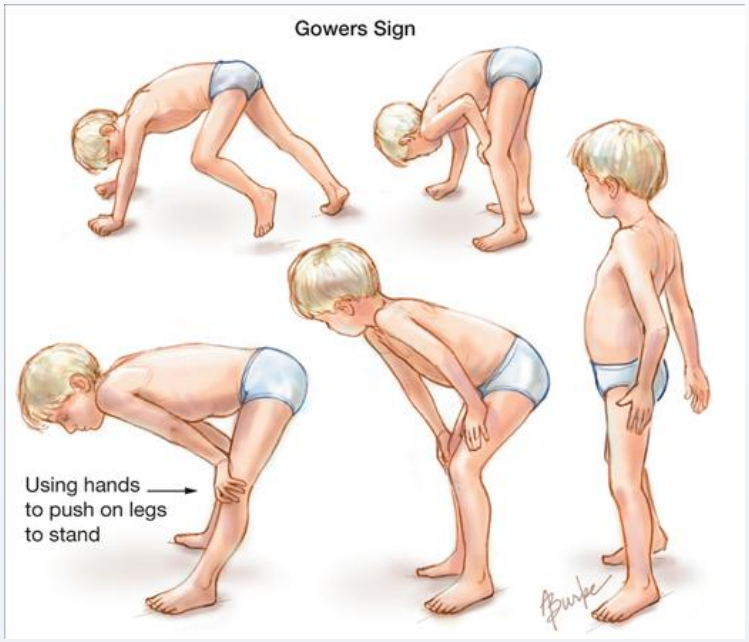
Wordsworth S et al. Eur Heart J. 2010 Apr;31(8):926-35

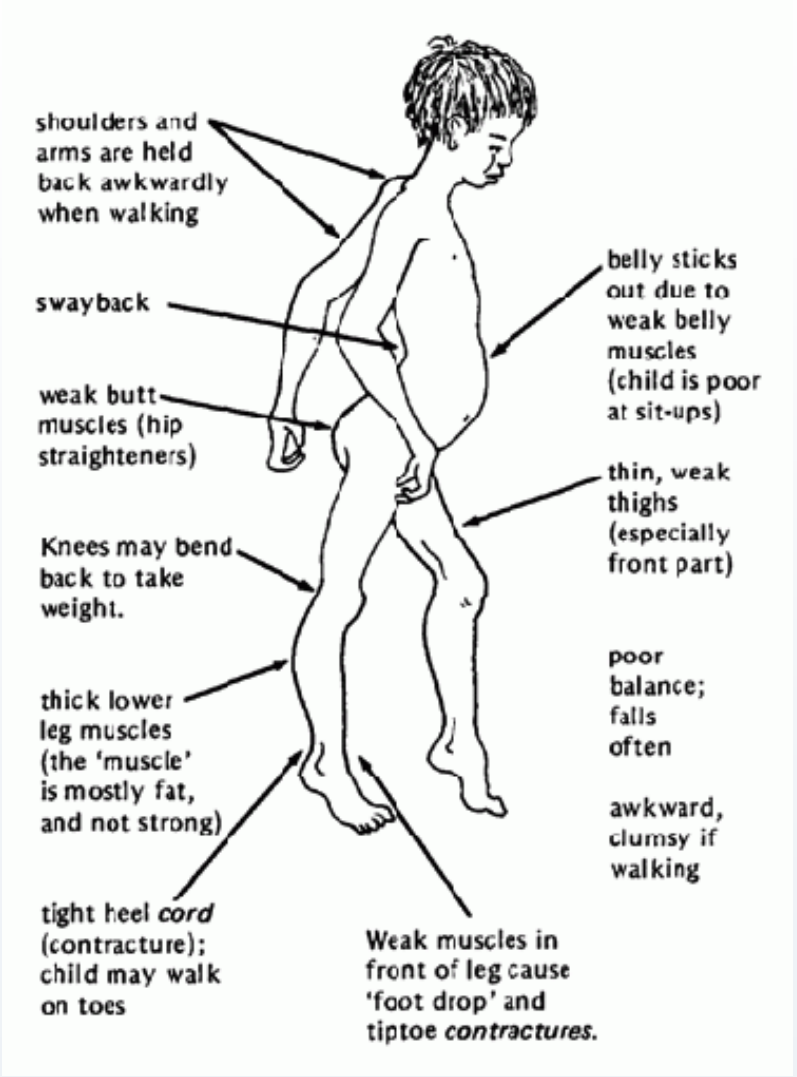
MUTATION GUIDED THERAPY?

Gene transfer: Viral Vectors



Duchenne Muscular Dystrophy





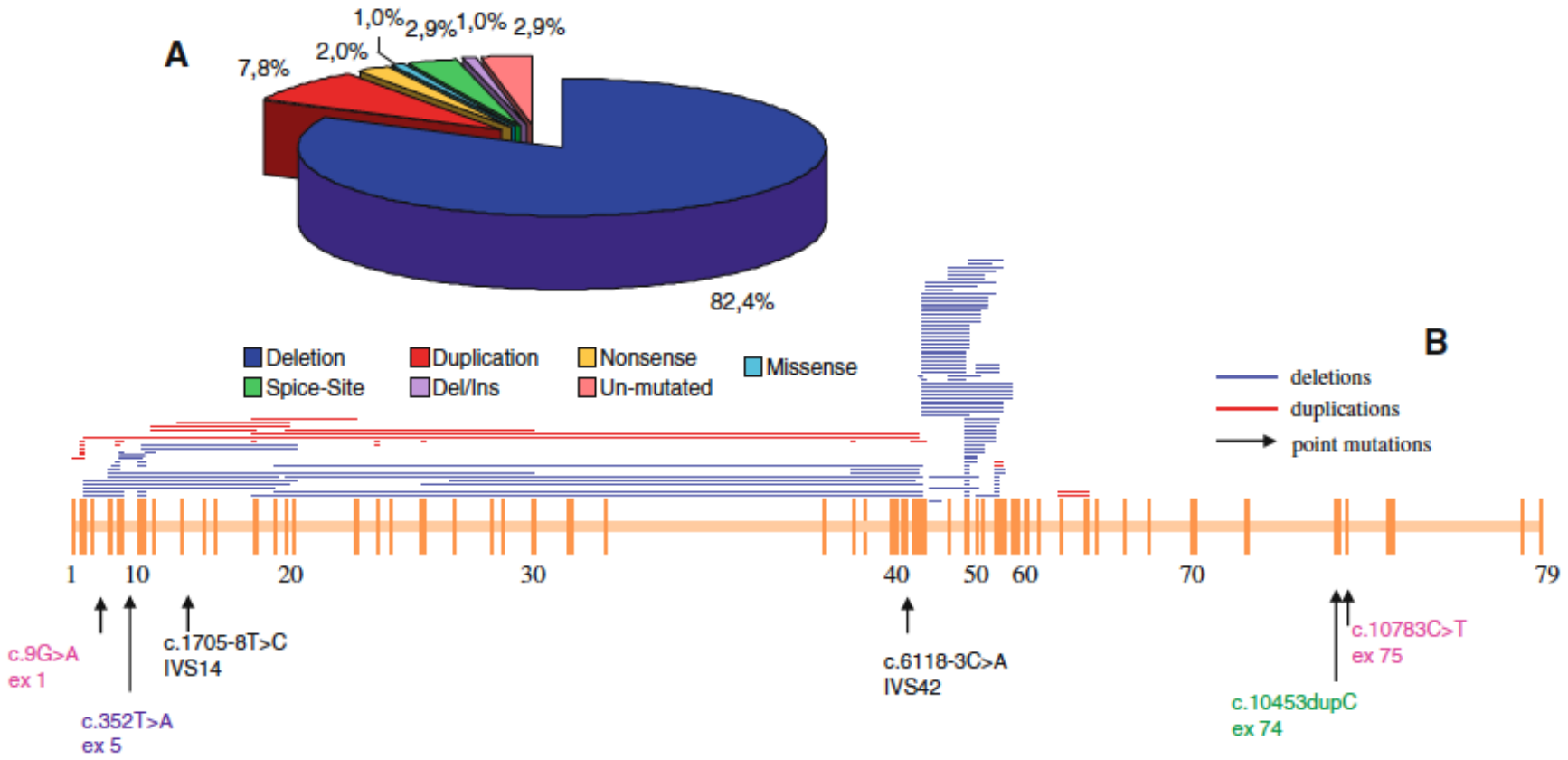
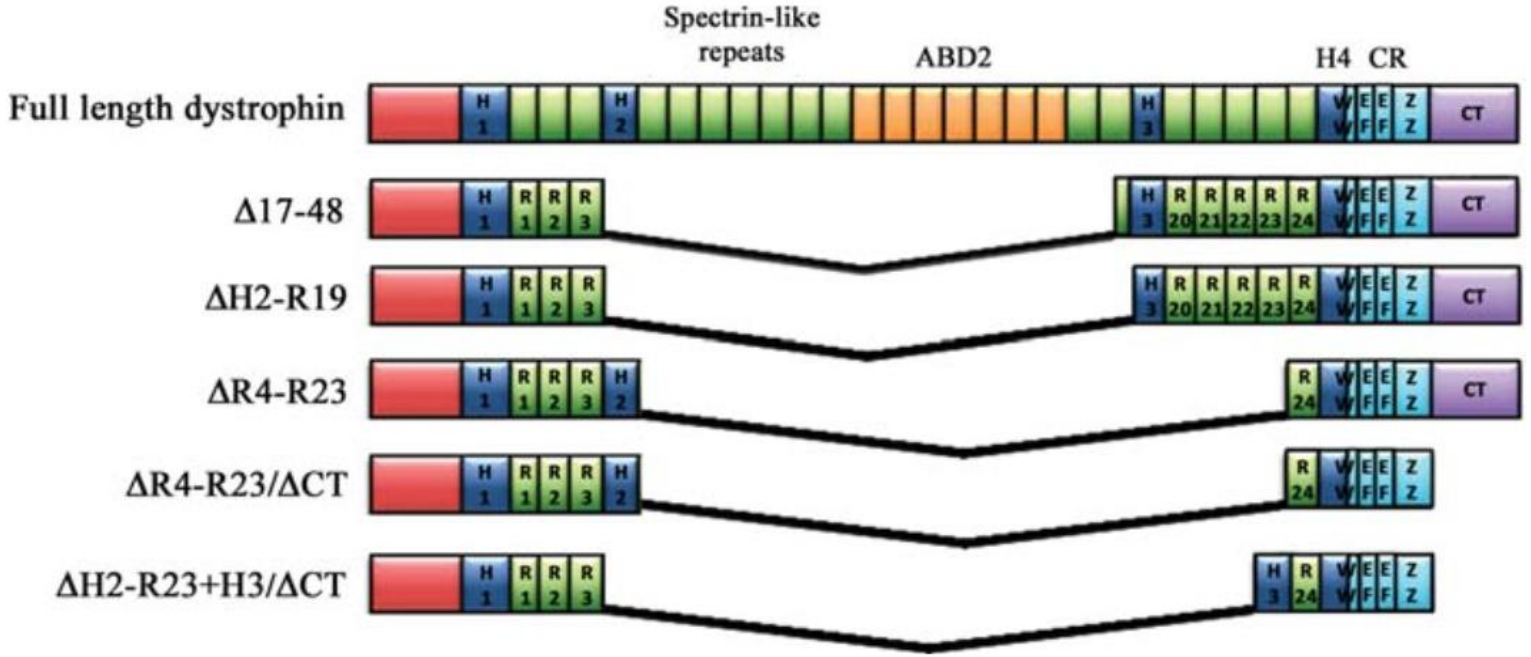


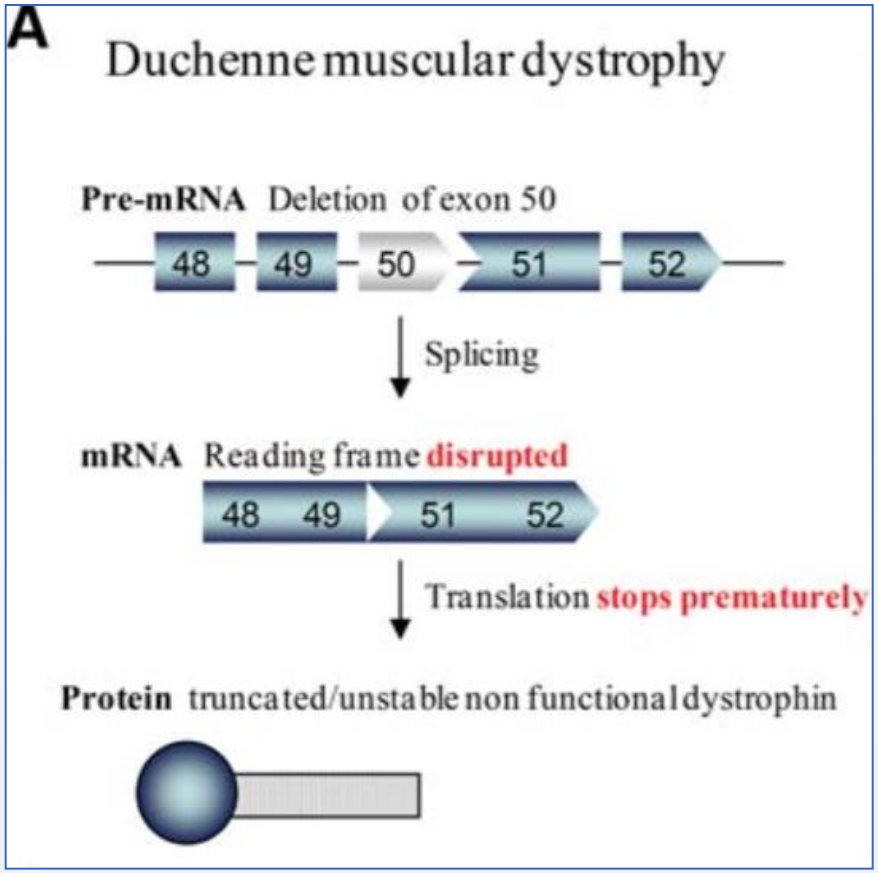
Fig. 4 Molecular characteristics of BMD. **a** Relative frequencies of different *DMD* mutations in the BMD patient population. **b** Distribution of mutations along the *DMD* gene. Deletions (*blue*) and duplications (*red*) are mapped in the upper part of the figure. *Arrows* indicate point mutations (Nonsense mutations in *pink*, small insertions/deletions in *green*, splicing mutations in *black*)

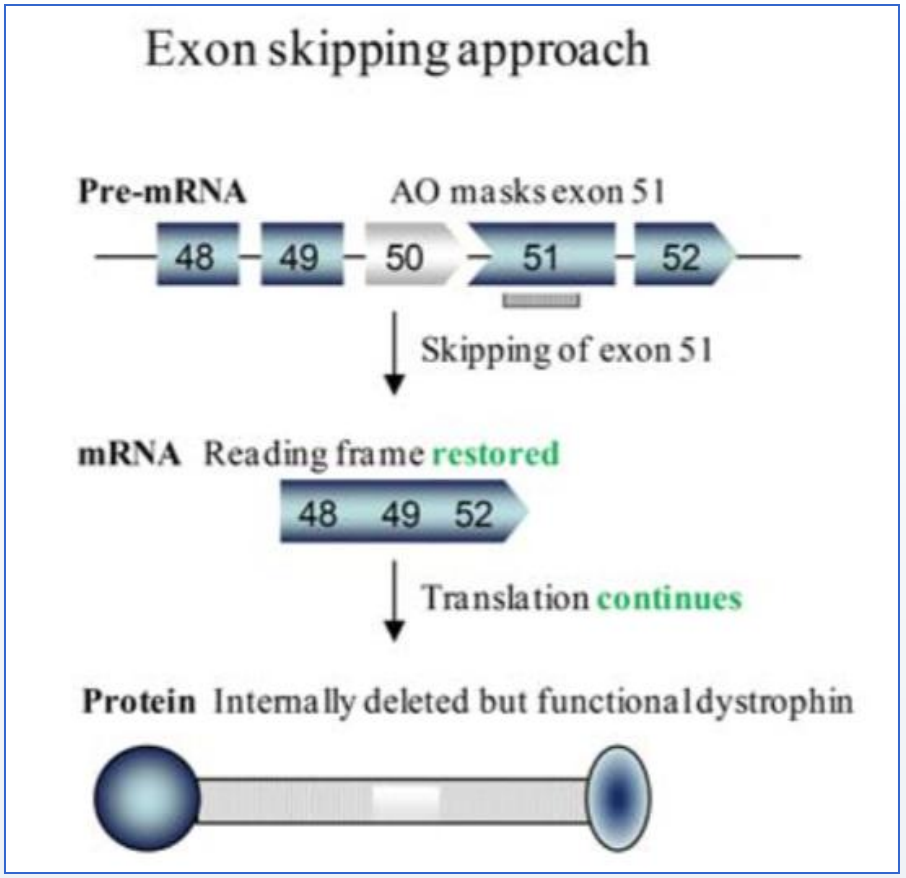
Gene Transfer: DMD



Human Molecular Genetics, 2011, Vol. 20,

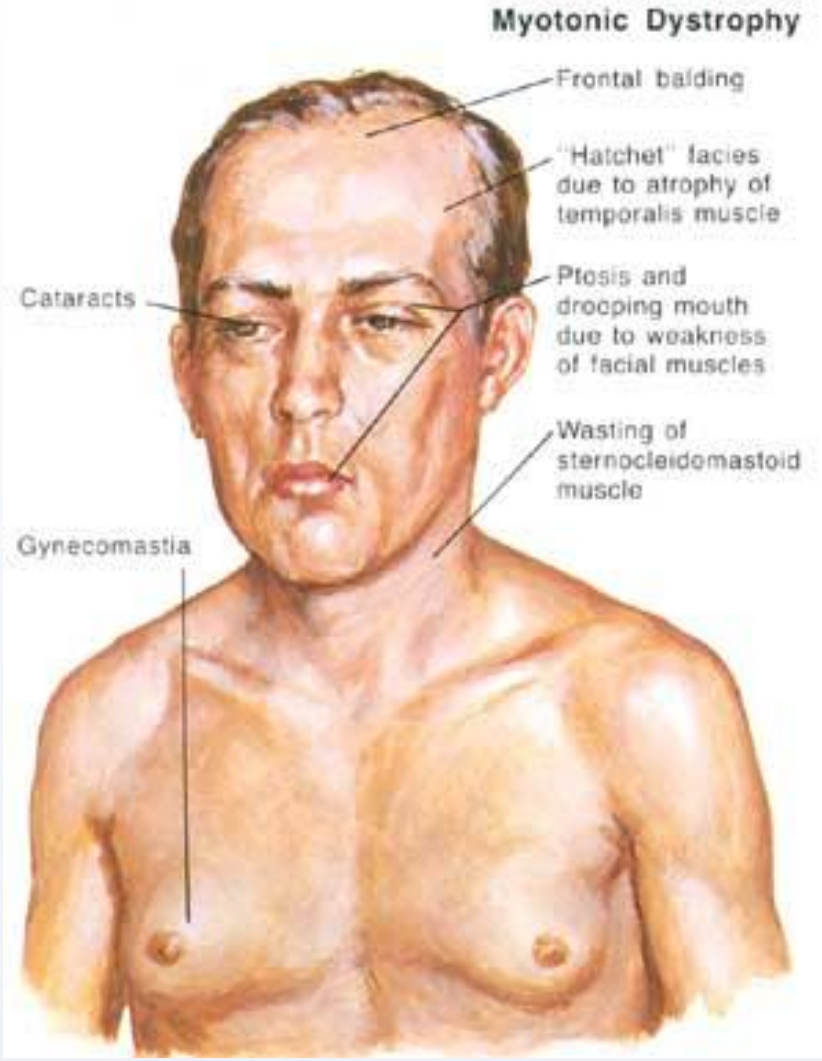
Exon Skipping



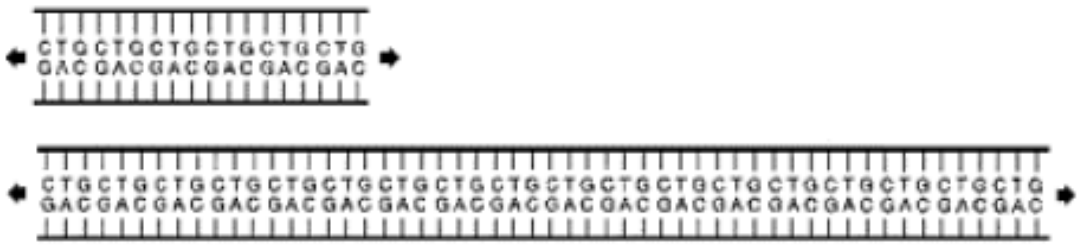


Myotonic Dystrophy

Systemic involvement in DM1	
Eye	▶ Cataract
Endocrine system	▶ Diabetes ▶ Thyroid dysfunction ▶ Hypogonadism
Gastrointestinal tract	▶ Dysphagia ▶ Constipation ▶ Gallbladder stones ▶ Pseudo-obstruction
Central nervous system	▶ Cognitive impairment ▶ Mental retardation ▶ Attentive disorders
Heart	



Genetics

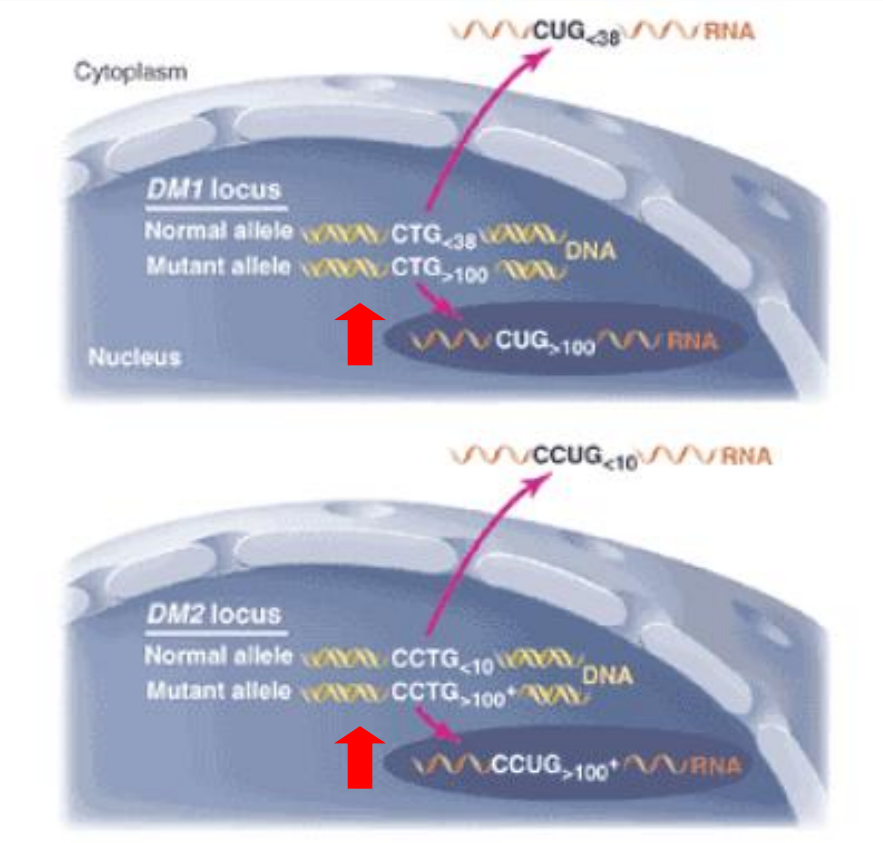


DM1 Chromosome 19q 13.3

DM Protein kinase (DMPK)

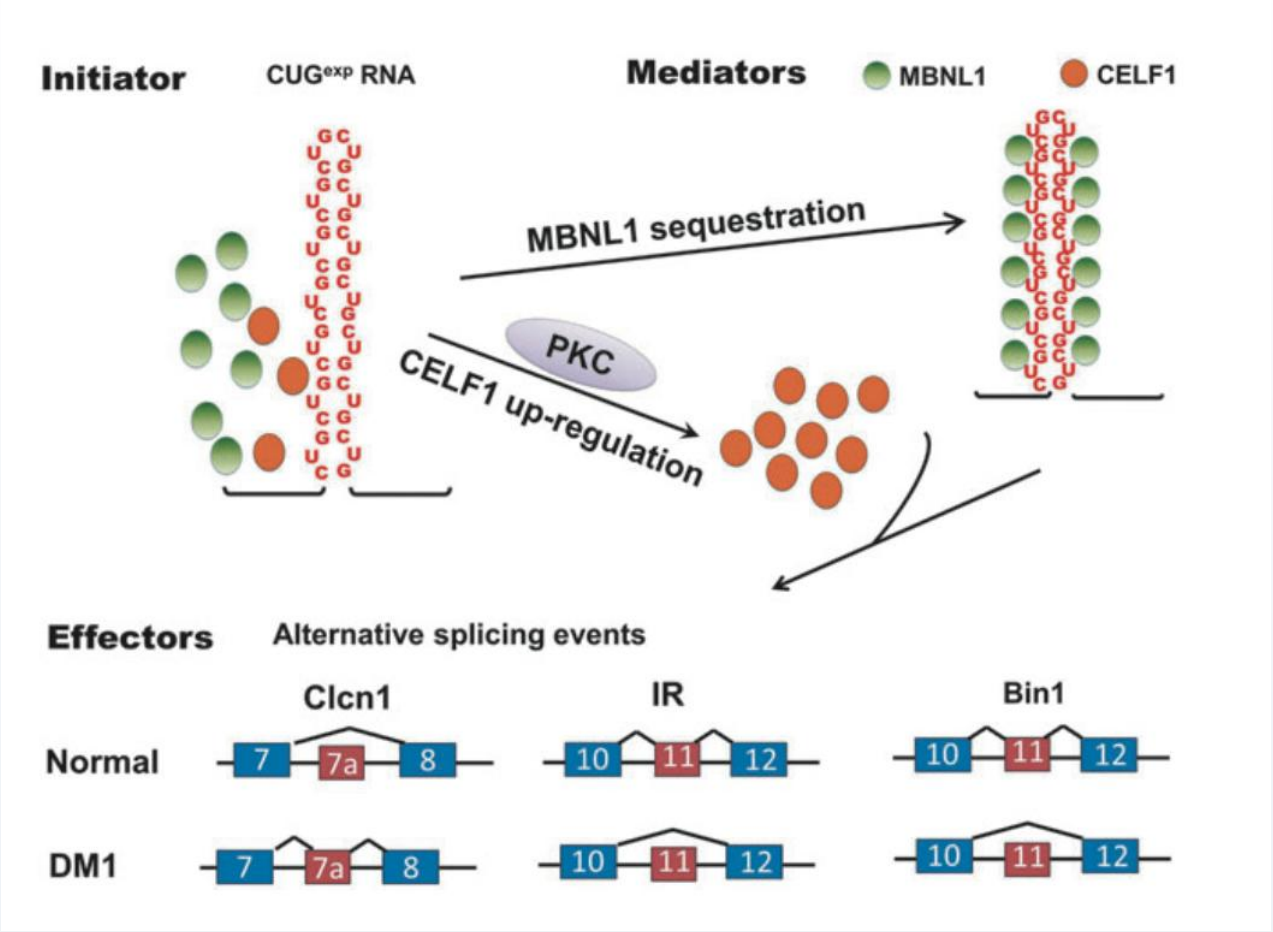
DM2 Chromosome 3q21

Zn Finger 9



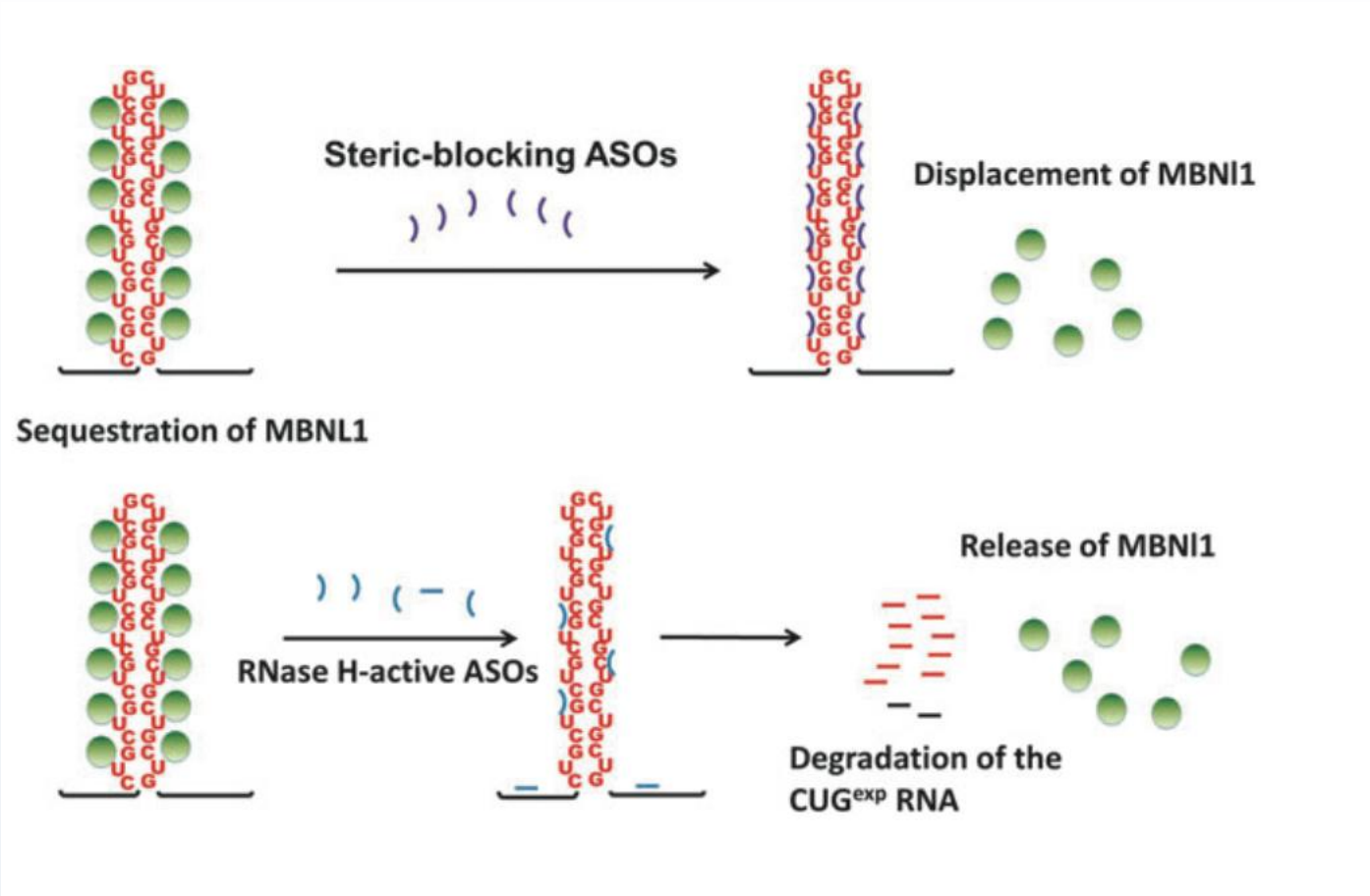
Science 2001: 293:816-17

RNA Toxicity



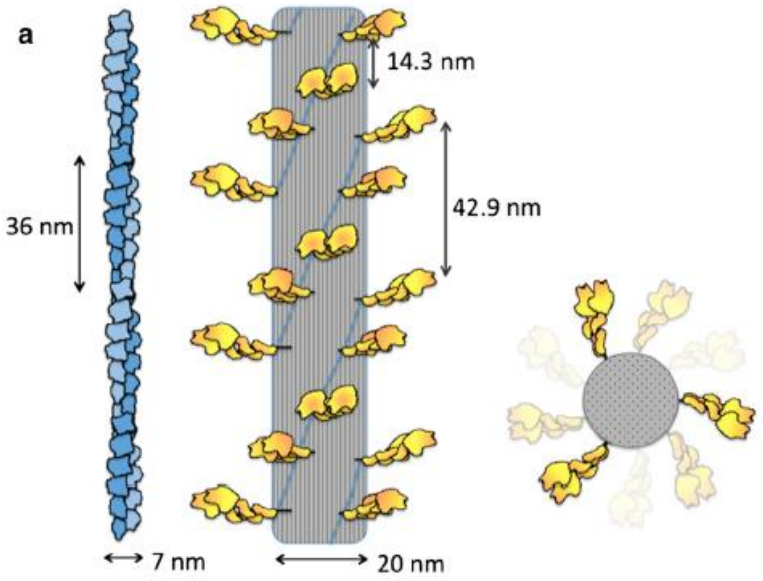
HUMAN GENE THERAPY 24:499–507 (May 2013)

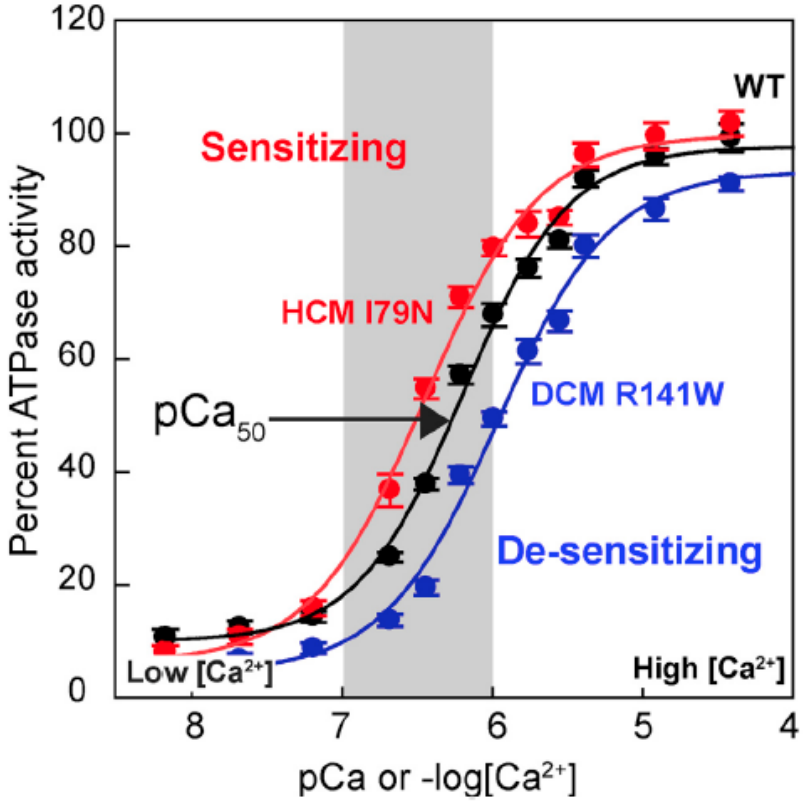
RNA Toxicity: DM1



HUMAN GENE THERAPY 24:499–507 (May 2013)

NOVEL THERAPIES IN SARCOMERE DISEASE





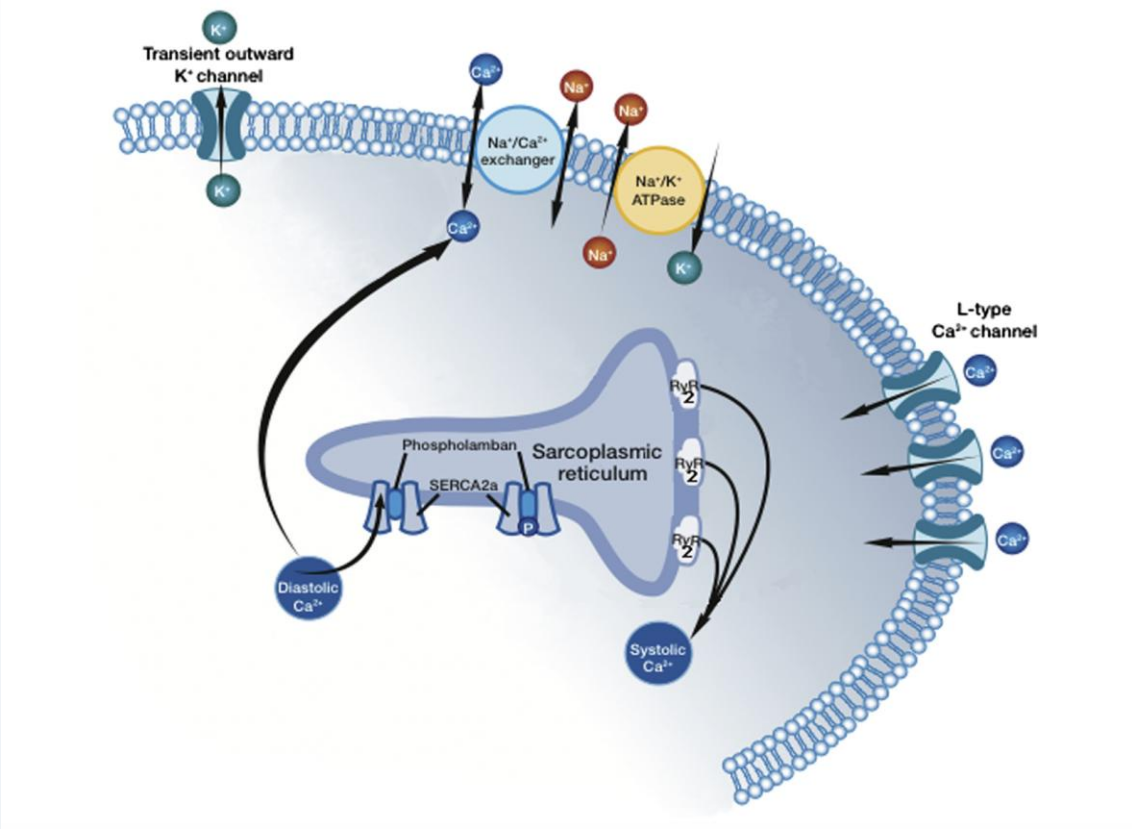
Spudich JA. Biophysical Journal Volume 106 March 2014 1236–1249

“Down-stream” targets

- Cross-bridge kinetics
- Calcium sensitivity & cycling
- Signalling pathways and protein degradation
- Cardiomyocyte-fibroblast cross-talk
- Energetics
- Gene therapy

Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure

The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b)

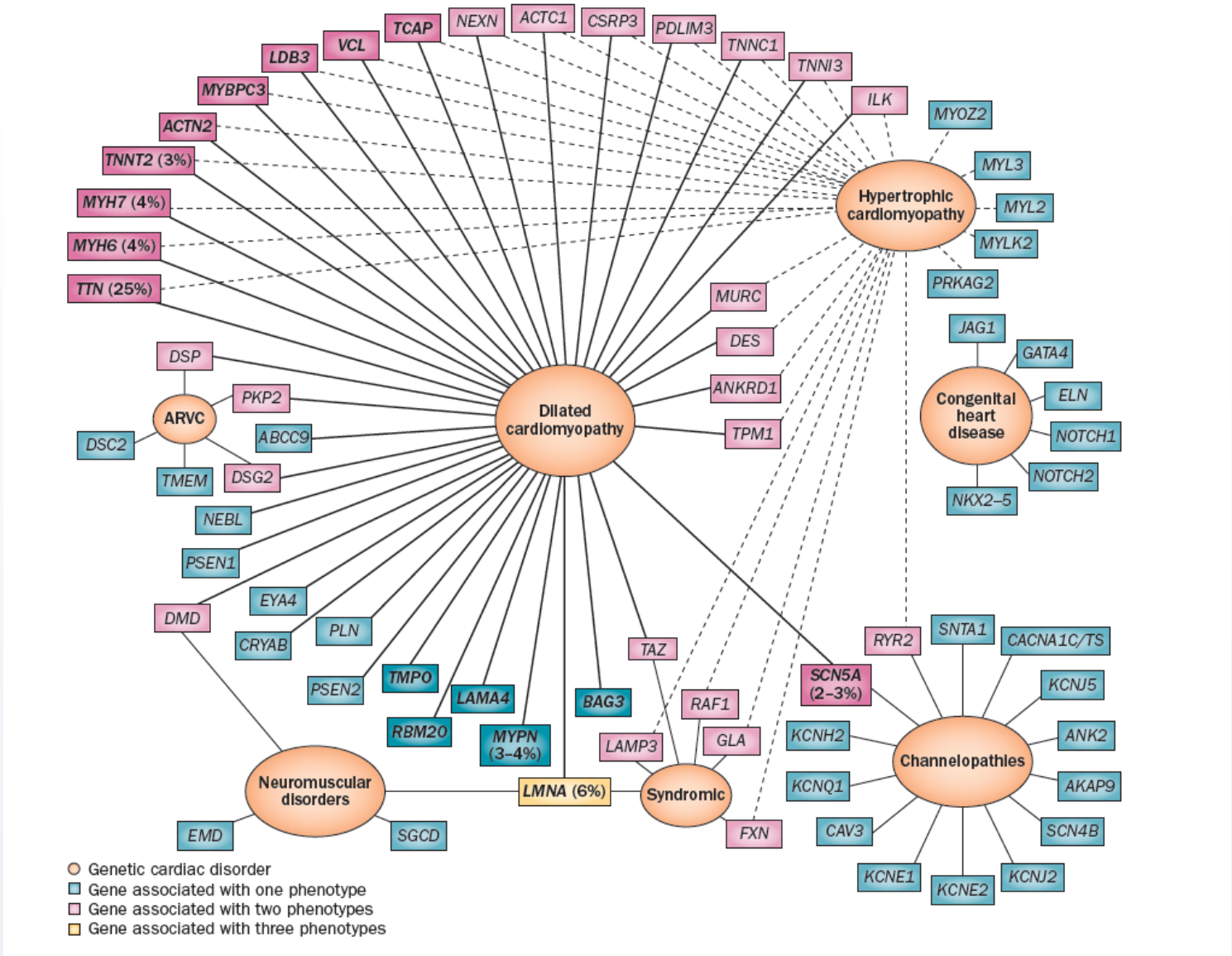


JACC: Heart Failure Vol. 2, No. 1, 2014

Key Message

- Aetiology and pathogenesis are critical in the development of new therapies

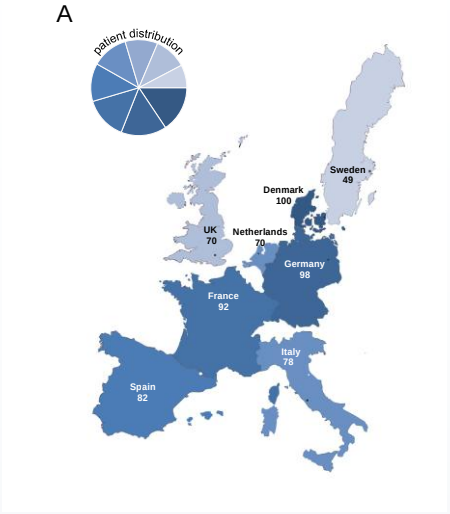
FUTURE CHALLENGES



Hershberger R et al. Nature Rev Cardiol 2013

The INHERITANCE Next-Generation Sequencing Study: A Comprehensive Atlas of the Genetics of Human Dilated Cardiomyopathy

Jan Haas[1,2], Karen S. Frese[1,2], Barbara Peil[3], Wanda Kloos[1], Andreas Keller[4], Rouven Nietsch[1,2], Zhu Feng[1], Sabine Müller[4], Elham Kayvanpour[1,2], Britta Vogel[1], Farbod Sedaghat-Hamedani[1,2], Wei-Keat Lim[6], Xiaohong Zhao[6], Dmitriy Fradkin[6], Doreen Köhler[1], Simon Fischer[1], Jennifer Franke[1], Sabine Marquart[1,2], Ioana Barb[1,2], Ali Amr[1,2], Philipp Ehlermann[1], Derliz Mereles[1,2], Tanja Weis[1,2], Andreas Kremer[6], Vanessa King[6], Emil Wirsz[6,5], Richard Isnard[10], Michel Komajda[10], Diego Garcia-Giustiniani[11], Martin Ortiz-Genga[11], Marisa Crespo-Leiro[11,17], Anders Waldenstrom[9], Martino Bolognesi[15], Riccardo Bellazzi[14], Stellan Mörner[16], Justo Lorenzo Bermejo [3], Lorenzo Monserrat[11,17], Eric Villard[10], Jens Mogensen[12], Yigal Pinto[13], Philippe Charron[10], Perry Elliott[8], Eloisa Arbustini[7], Hugo A. Katus[1,2], Benjamin Meder[1,2,#]



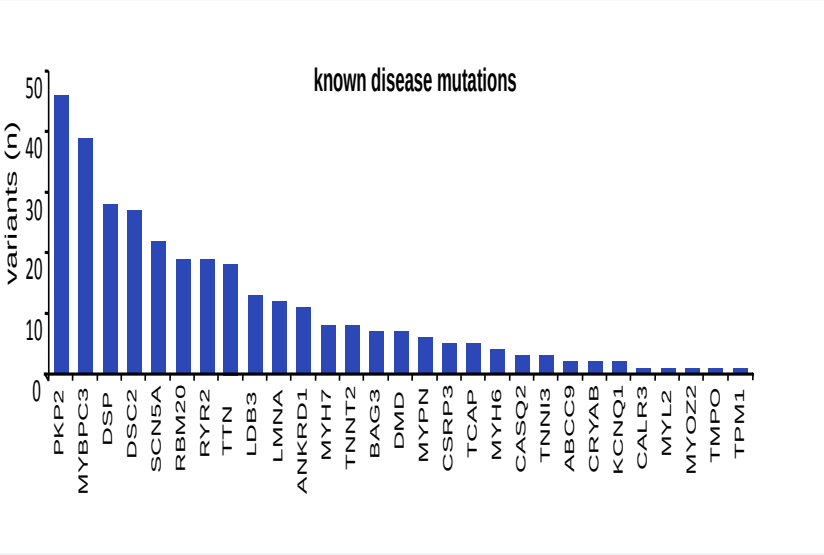


Table 2: Multiple mutations affecting single patients.

Number of mutations	HGMD[1] variant pos Patients, (%)	Category Ib-III[2] variant pos Patients, (%)
0	345 (54.0%)	171 (26.7%)
≥1	294 (46.0%)	468 (73.2%)
≥2	82 (12.8%)	243 (38.0%)
≥3	14 (2.2%)	82 (12.8%)
≥4	2 (0.3%)	16 (2.5%)

1 = category Ib. 2 = either category Ib or category II or category III.

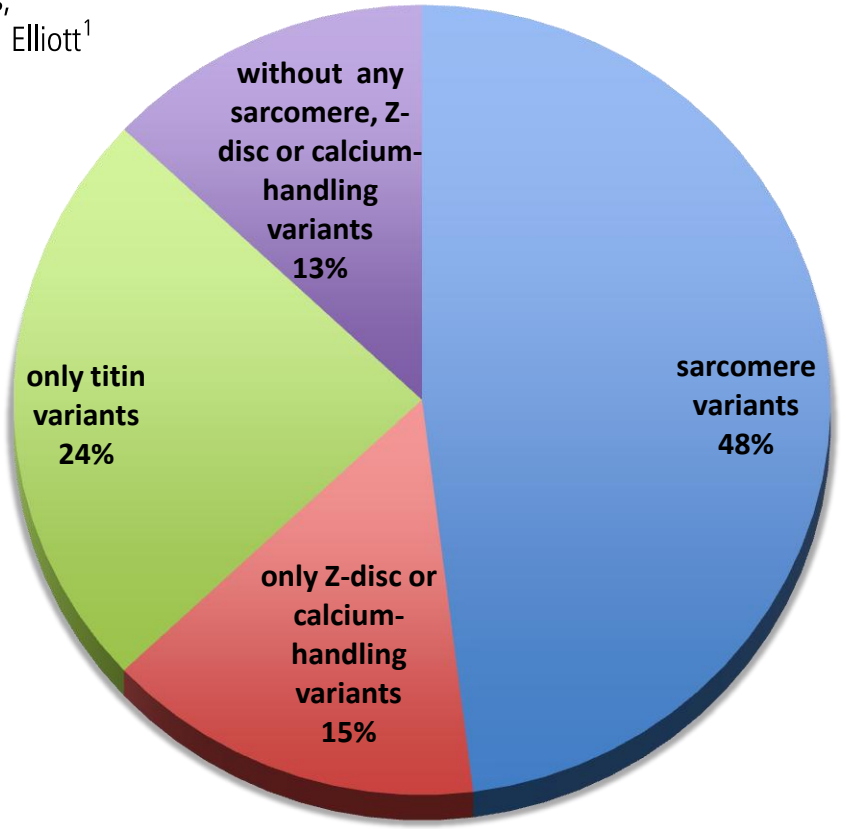
Unpublished Data

Genetic complexity in hypertrophic cardiomyopathy revealed by high-throughput sequencing

Luis R Lopes,[1] Anna Zekavati,[2] Petros Syrris,[1] Mike Hubank,[2] Claudia Giambartolomei,[3] Chrysoula Dalageorgou,[1] Sharon Jenkins,[1] William McKenna,[1] Uk10k Consortium,[4] Vincent Plagnol,[3] Perry M Elliott[1]

- **243 (48%) :** 173 distinct rare variants in the **8 sarcomeric protein genes most commonly associated with HCM**

- **317 (63%)** : 278 rare variants in genes previously associated **with HCM**



Lopes, L. R., et al. (2013). *Journal of Medical Genetics*, *50*(4), 228–239.

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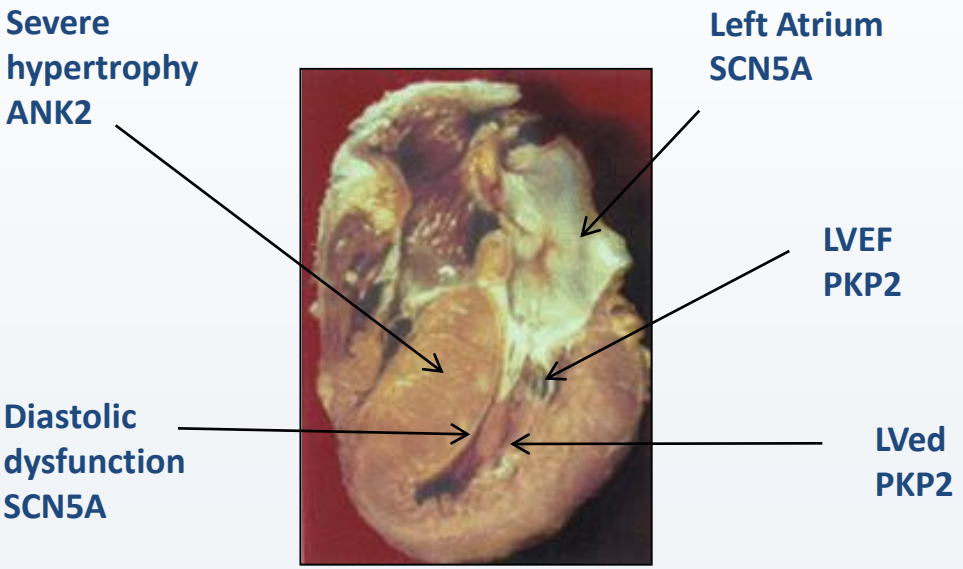
- 95 candidate variants in **desmosomal protein genes** in 122 patients (24%) [26 published]
- 121 rare variants in **ion-channel disease genes** in 133 patients (26%) [25 published]

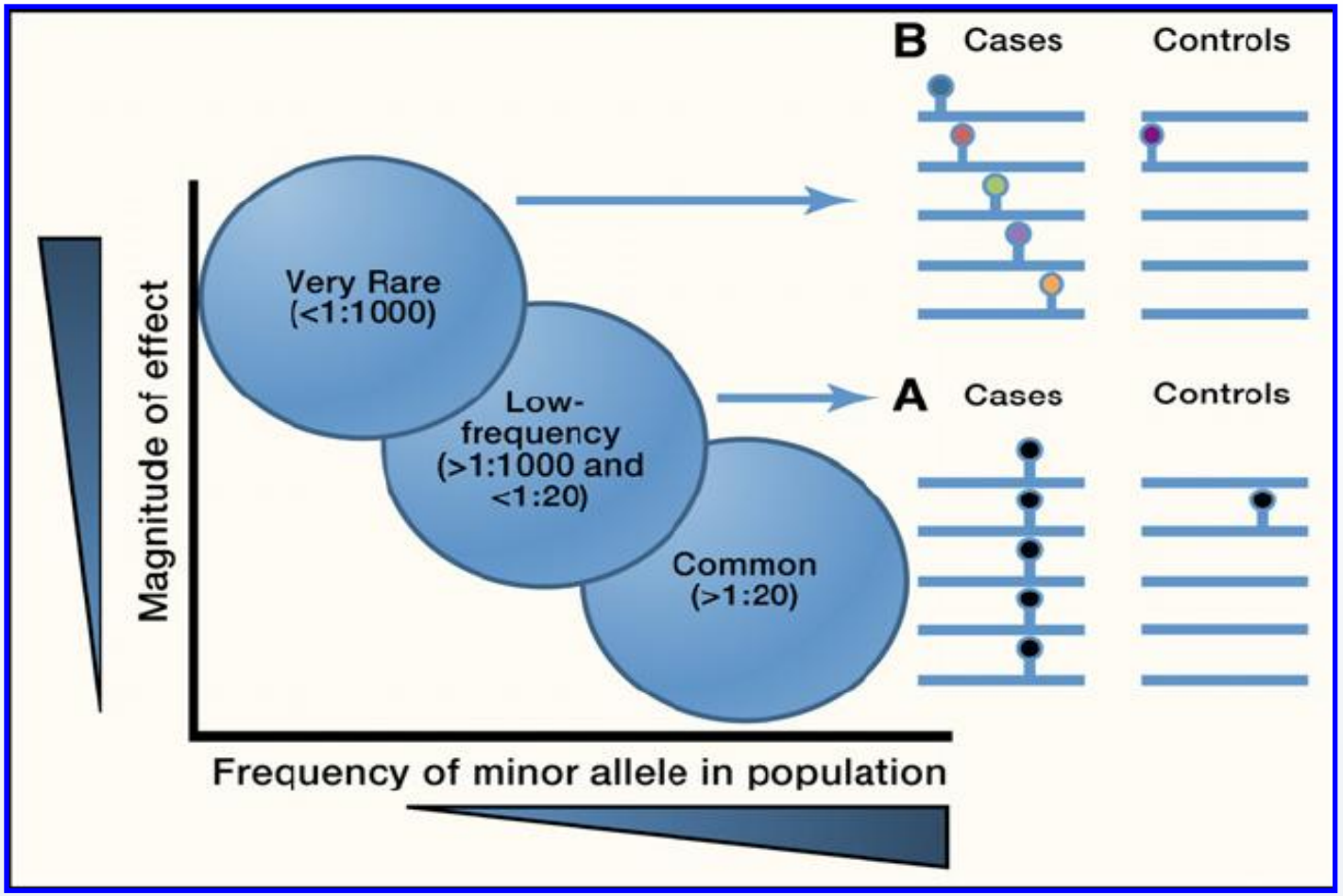
Lopes, L. R., et al. (2013). *Journal of Medical Genetics*, *50*(4), 228–239.

Genotype-phenotype associations : NON SARCOMERE genes

Phenotype	Gene	Gene-positive	Gene-negative	P-value
LA diameter (mm)	*SCN5A*	47.7±6.4	44.1±7.7	0.033
Moderate-severe diastolic dysfunction	*SCN5A*	45%	27.2%	0.035
LVOT gradient (mmHg)	*SCN5A*	62.4±57.5	32.9±40.6	0.035
LVOTO (>30 mmHg)	*SCN5A*	65%	34.8%	0.008
MLVWT >30mm	*ANK2*	10.9%	2%	0.003
MLVWT (mm)	*ANK2*	20.1±6.2	18.5±4.2	0.024
LV dilation (LVED >55mm)	*PKP2*	13.3%	4.2%	0.022
Systolic dysfunction (fractional shortening <25%)	*PKP2*	17.2%	2.9%	0.001
NSVT (baseline)	*PLN*	100%	25.4%	0.023
	ANK2	45.5%	24%	0.012



Lopes et al. Heart. 2015 Feb 15;101(4):294-301



Kathiresan et al. Cell 2012

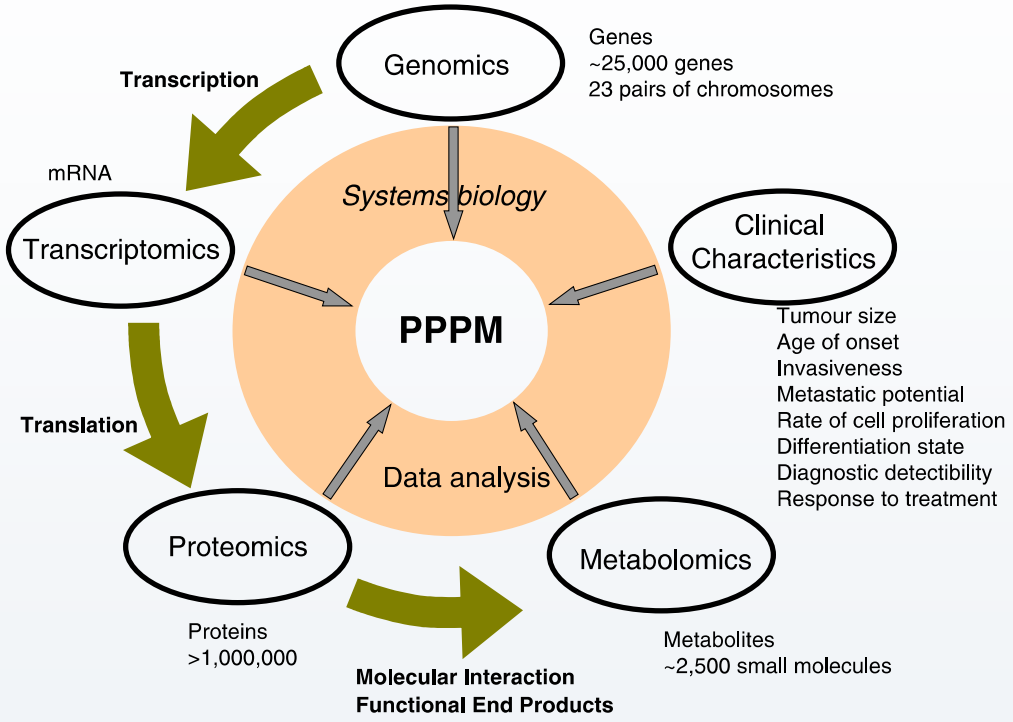


Figure 2 The contributions of 'omics' and systems biology to the practice of PPPM.