PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA
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di Confindustria
Auditorium
della Tecnica

9ª Edizione

30 Settembre
1 Ottobre
2022

Morte improvvisa: Alla ricerca del sacro graal

GENETICA E STRATIFICAZIONE DEL RISCHIO NELLE CARDIOMIOPATIE: LUCI ED OMBRE

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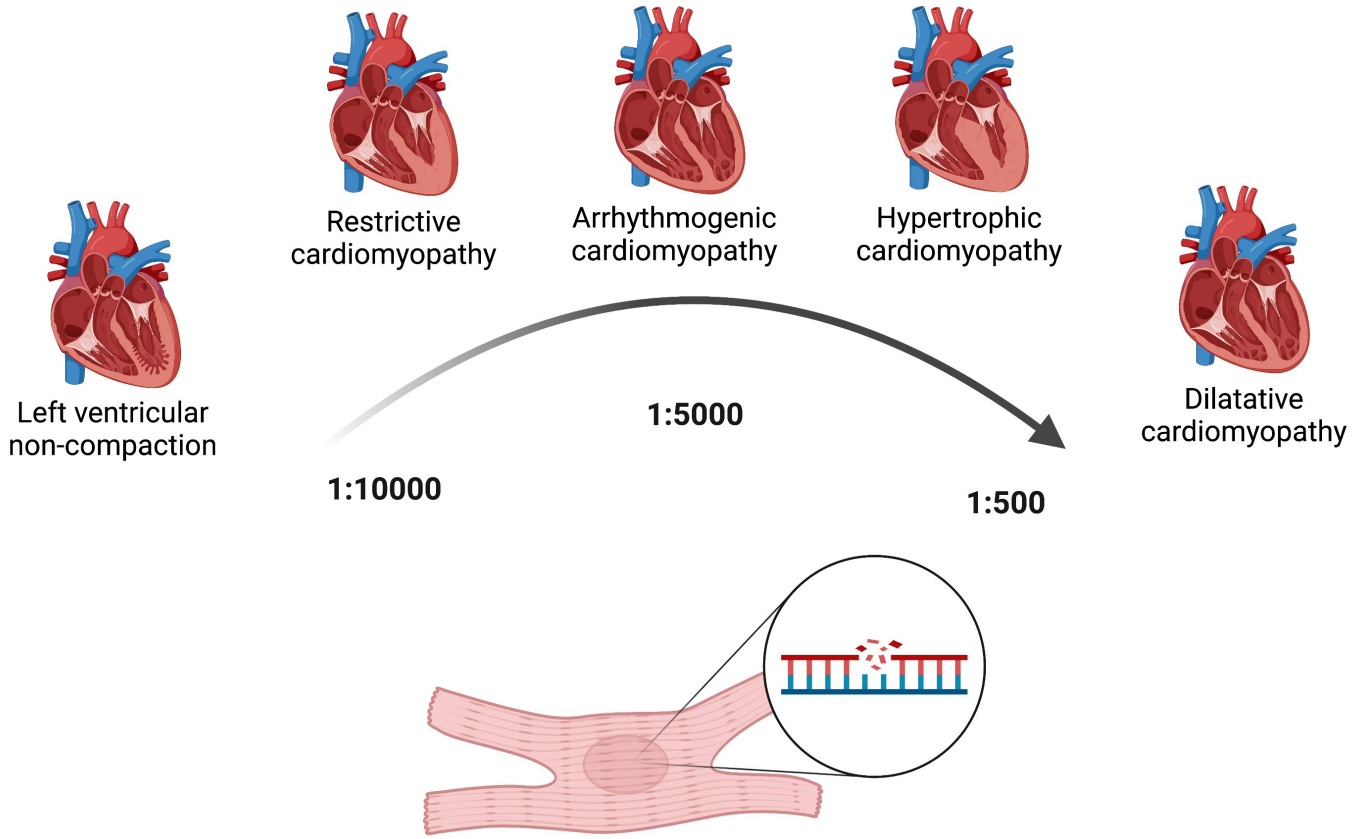
University of Pavia
IRCCS ICS Maugeri, Pavia, Italy
Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain

World of Cardiomyopathies



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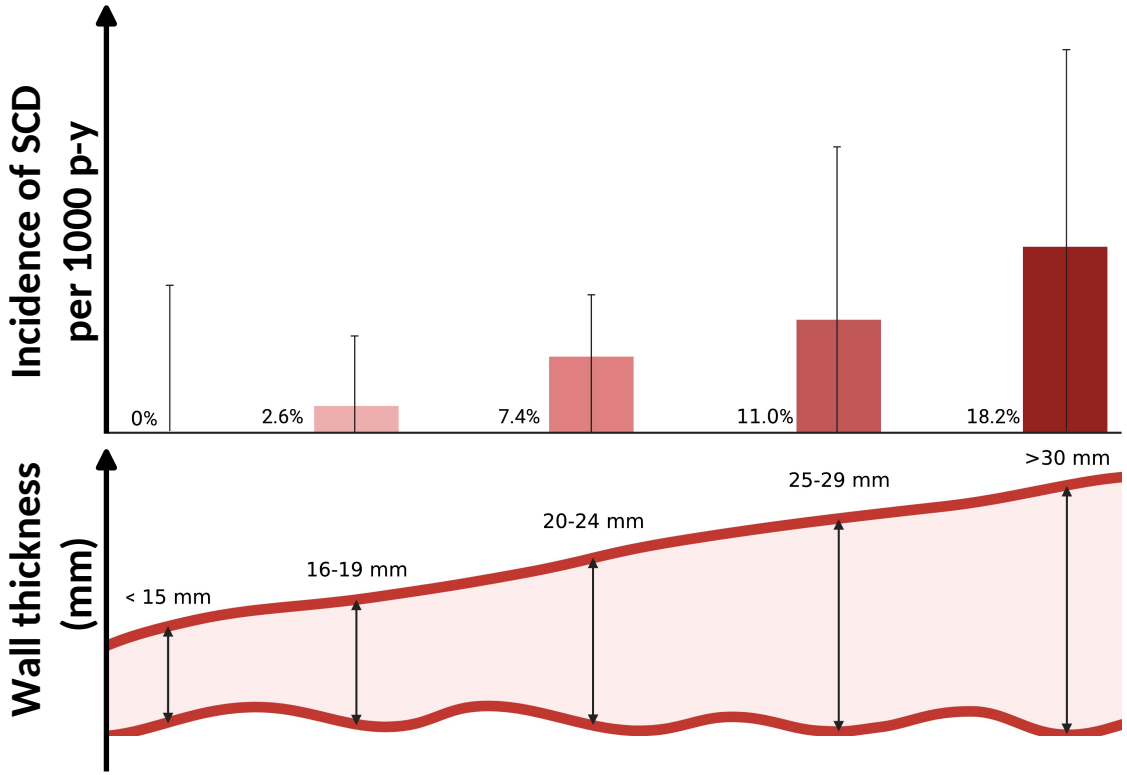
Interplay between Phenotype Severity and Arrhythmic Risk



Spirito P et al. **Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy.**
N Engl J Med. 2000 Jun 15;342(24):1778-85.

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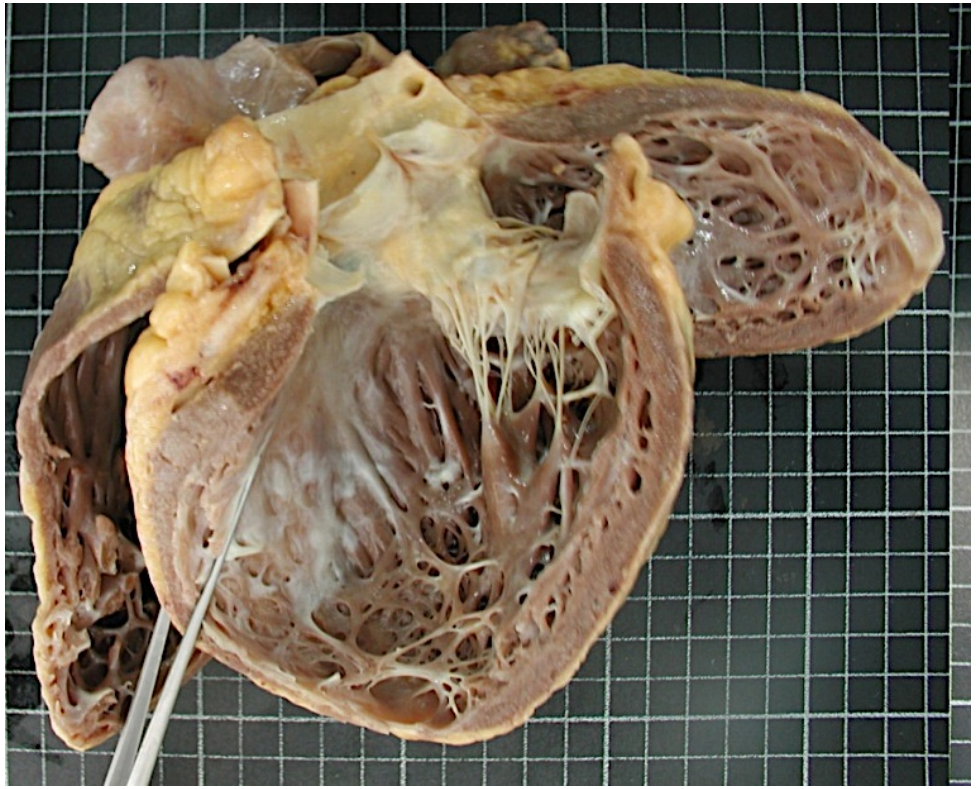
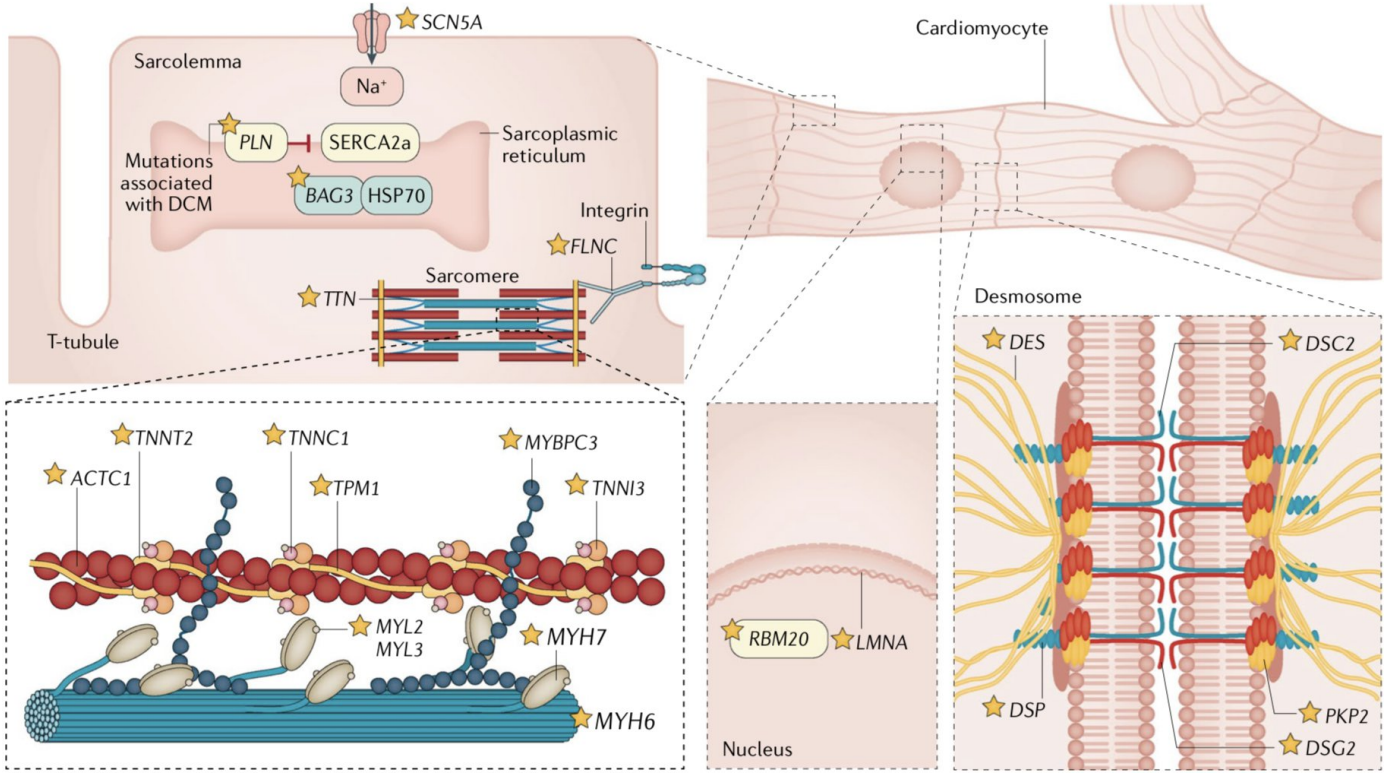


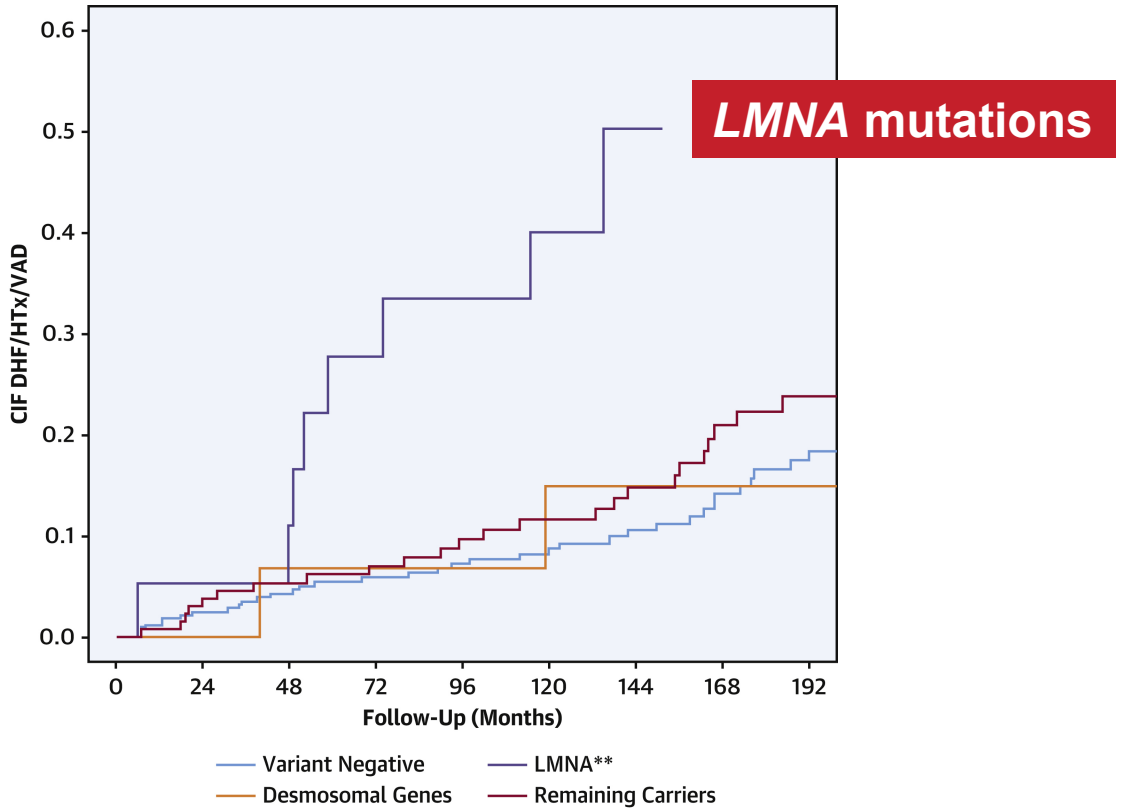
DILATATIVE CARDIOMYOPATHY

DCM:
A Genetically Heterogenous Disease



Schultheiss HP et al.
Dilated cardiomyopathy.
Nat Rev Dis Primers. 2019 May 9;5(1):32.

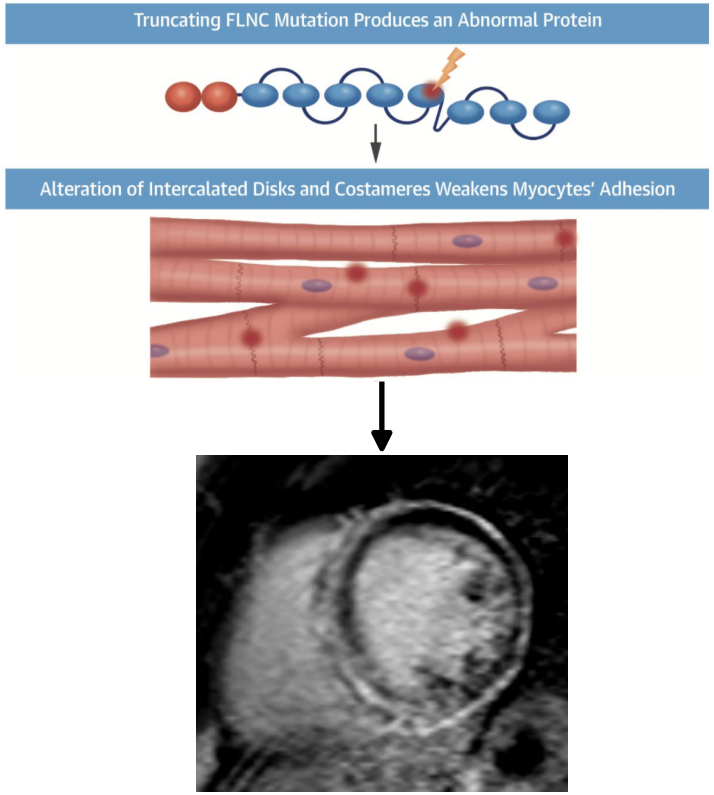
Genetics Impact Survival...

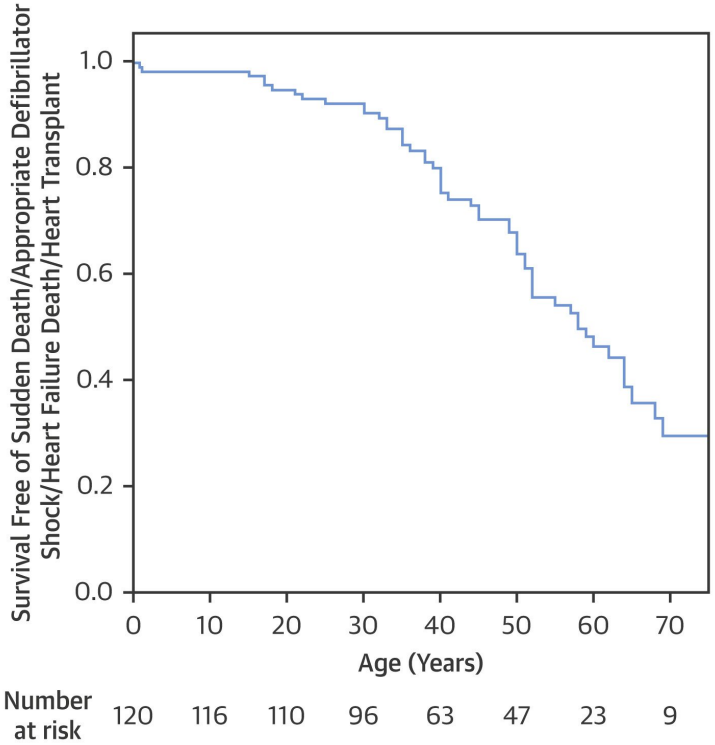


***LMNA* mutations**

Gigli M et al.
Genetic Risk of Arrhythmic Phenotypes in Patients With Dilated Cardiomyopathy.
J Am Coll Cardiol. 2019 Sep 17;74(11):1480-1490.

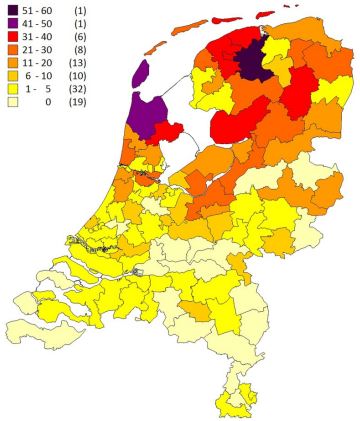
FLNC: Arrhythmogenic DCM

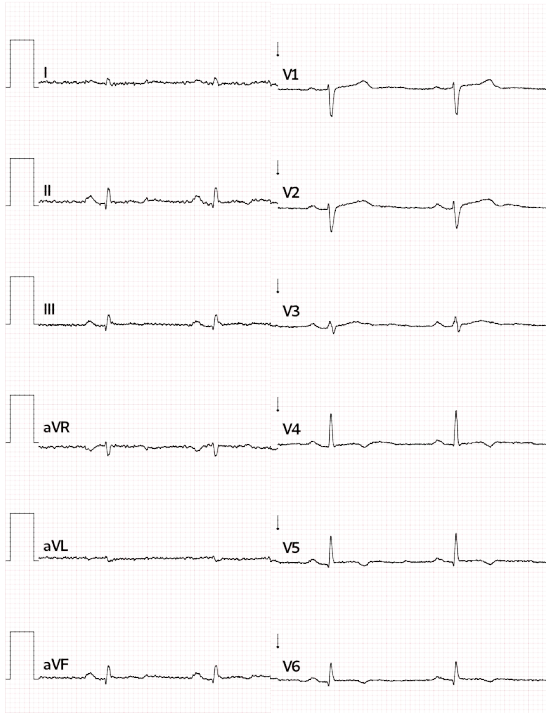




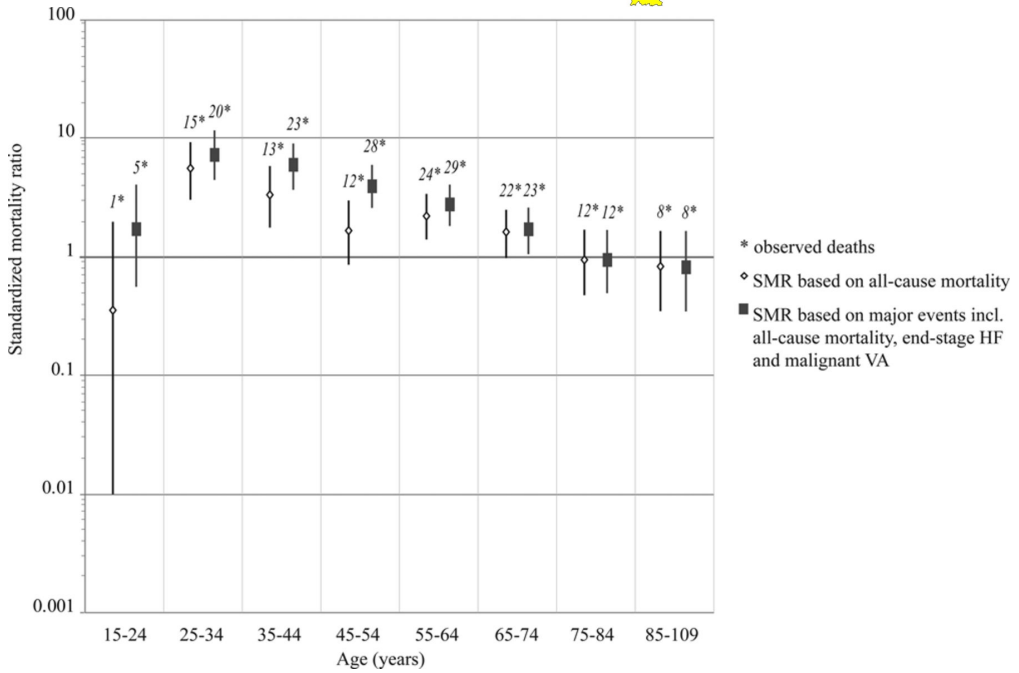
Ortiz-Genga MF et al.
Truncating *FLNC* Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies.
J Am Coll Cardiol. 2016 Dec 6;68(22):2440-2451.

PLN Cardiomyopathy:
p.R14del



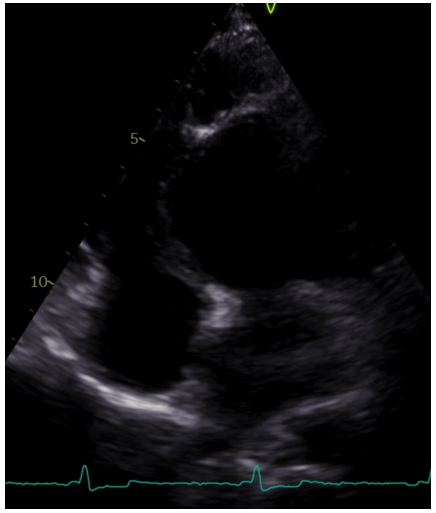


Hof IE et al.
Prevalence and cardiac phenotype of patients with a phospholamban mutation.
Neth Heart J. 2019 Feb;27(2):64-69.



van Rijsingen IA et al.
Outcome in phospholamban R14del carriers: results of a large multicentre cohort study.
Circ Cardiovasc Genet. 2014 Aug;7(4):455-65.

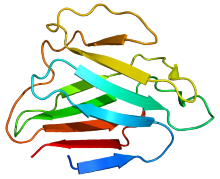
Genetics and Risk Stratification



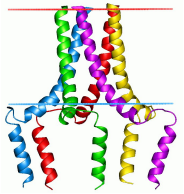
LVEF < 50%

+

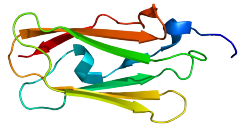
Mutation carriers of:



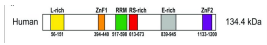
LMNA mutation



PLN mutation



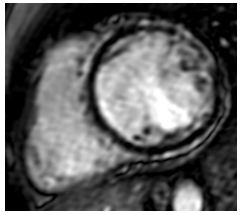
FLNC mutation



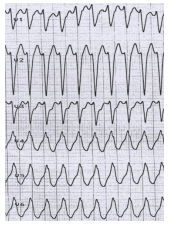
RMB20 mutation

≥1 of the following:

Syncope



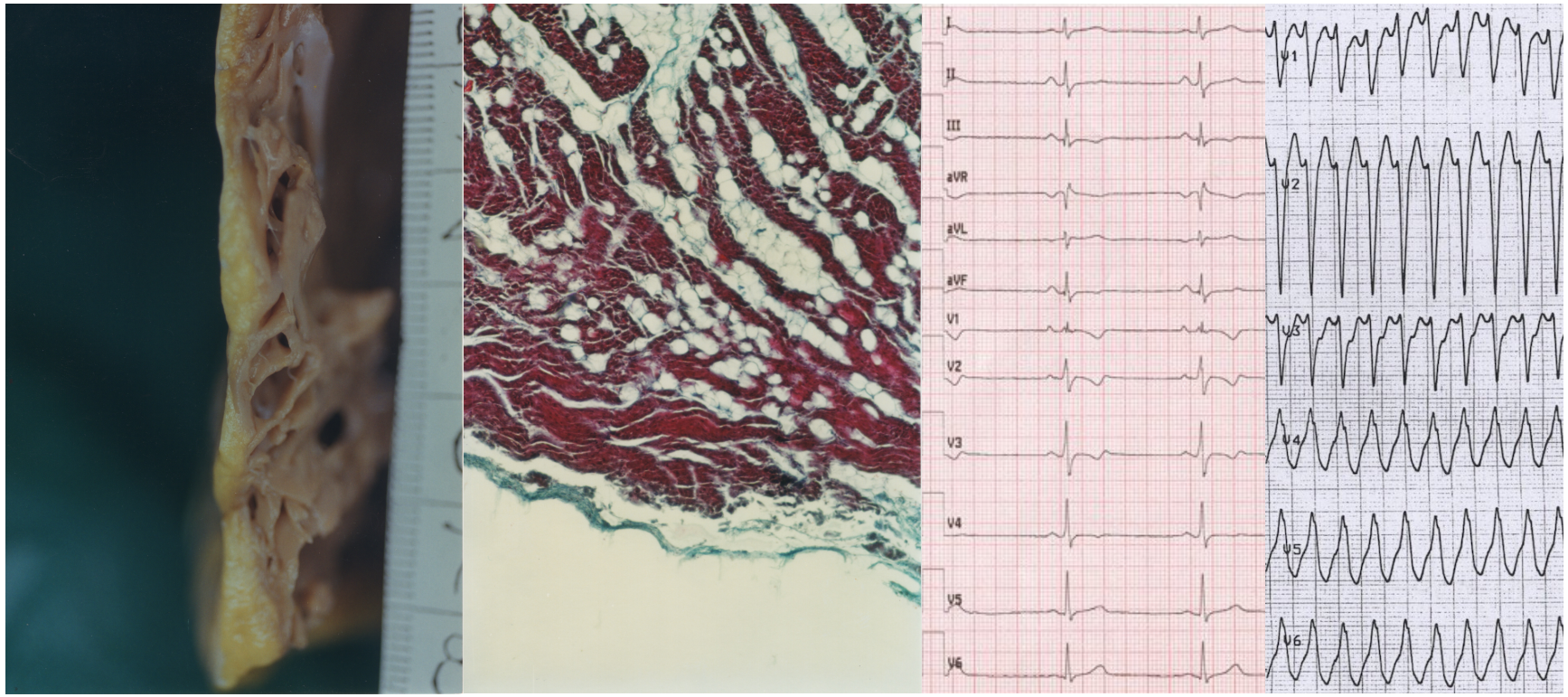
LGE



SMVT

Zeppenfeld K et al.
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.
Eur Heart J. 2022 Aug 26:ehac262.

ICD implantation should be considered in DCM/HNDCM patients with a LVEF <50% and ≥2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in *LMNA*,[d] *PLN*, *FLNC*, and *RBM20* genes).	IIa	C



ARRHYTHMOGENIC CARDIOMYOPATHY

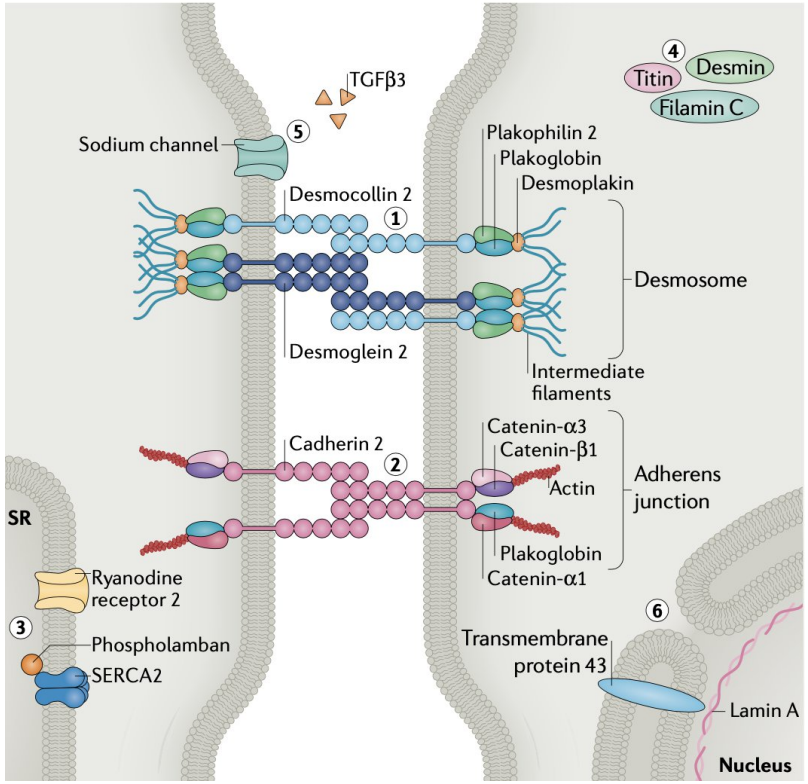
The Disease of the Desmosome

PKP2

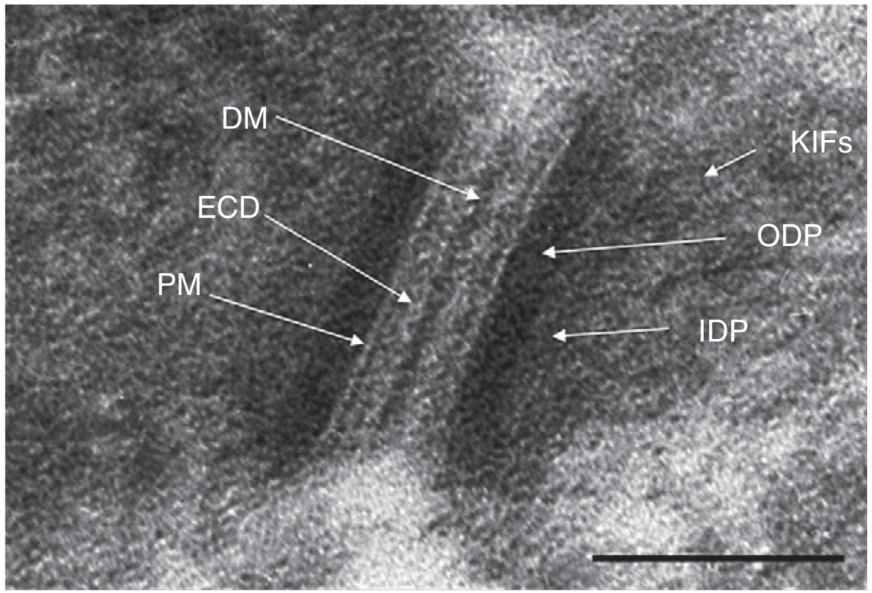
DSP

DSG2

DSC2



Austin KM, Trembley MA, Chandler SF, et al. **Molecular mechanisms of arrhythmogenic cardiomyopathy**. Nat Rev Cardiol. 2019;16(9):519-537.



Scothern, A. & Garrod, D. B. T.-M. in C. B. Chapter 18 Visualization of Desmosomes in the Electron Microscope. in Introduction to Electron Microscopy for Biologists 88, 347–366 (Academic Press, 2008).

Complexity of Desmosomal Variants: Double Hit, Double the Trouble

- As many as 48% of people with a confirmed diagnosis may have at least 2 different genetic mutations.
- In general, persons who have 2 mutations have more severe signs and symptoms of ARVC

Compound and Digenic Heterozygosity Contributes to Arrhythmogenic Right Ventricular Cardiomyopathy

Tianhong Xu, PHD,* Zhao Yang, MD, PHD,†‡ Matteo Vatta, PHD,‡

Comprehensive Desmosome Mutation Analysis in North Americans With Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

A. Dénise den Haan, Boon Yew Tan, Michelle N. Zikusoka, Laura Ibañez Lladó, Rahul Jain, Amy Daly, Crystal Tichnell, Cynthia James, Nuria Amat-Alarcon, Theodore Abraham, Stuart D. Russell, David A. Bluemke, Hugh Calkins, Darshan Dalal and Daniel P. Judge

Circ Cardiovasc Genet 2009;2;428-435; originally published online Jun 3, 2009;

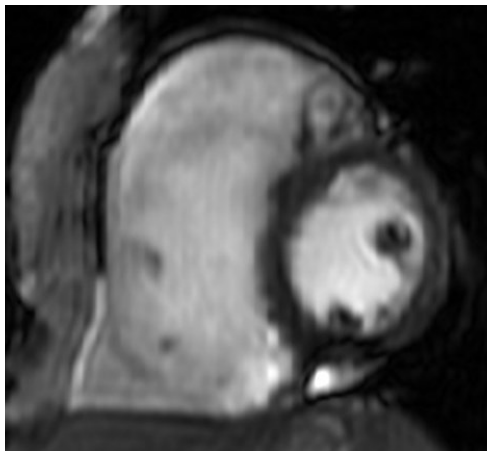
JMG

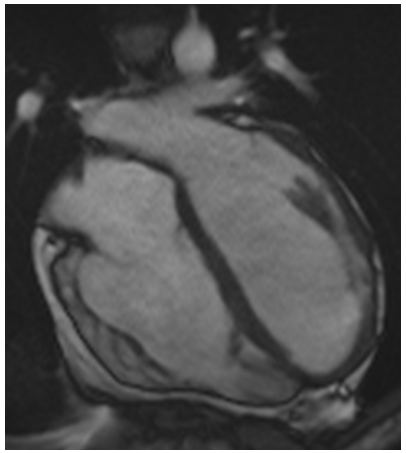
Wide spectrum of desmosomal mutations in Danish patients with arrhythmogenic right ventricular cardiomyopathy

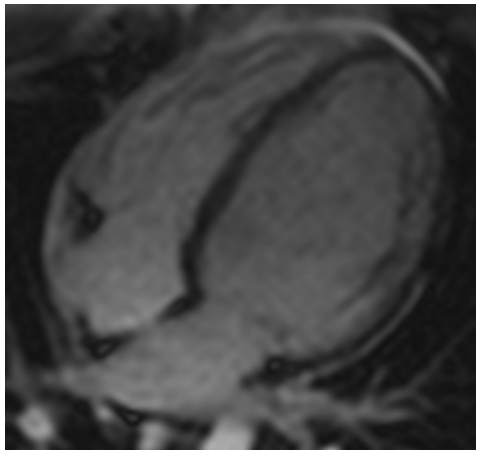
A H Christensen, M Benn, H Bundgaard, et al.

Xu T et al. *J Am Coll Cardiol*. 2010; 55(6):587-97 den Haan AD et al. *Circ Cardiovasc Genet*. 2009; 2(5):428-35. Christensen AH et al. *J Med Genet*. 2010; 47(11):736-44

Phenotypic Spectrum of Arrhythmogenic CM



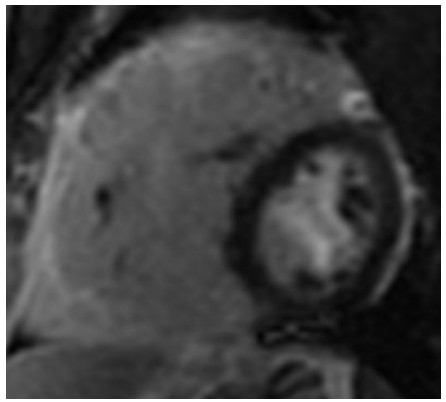


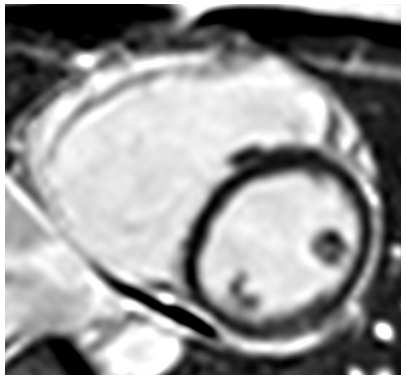


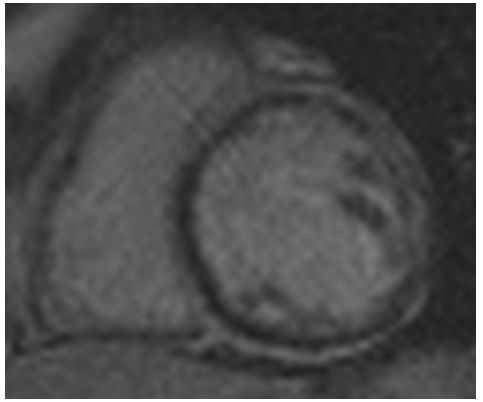
Right ventricular involvement → 39%

Biventricular involvement → 56%

Left ventricular involvement → 5%

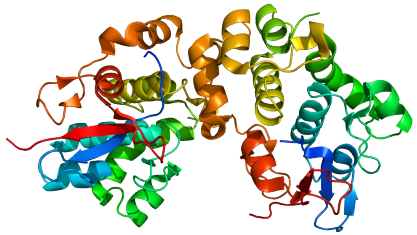


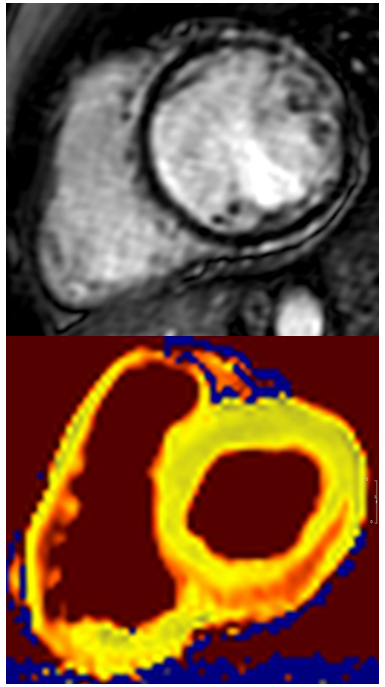


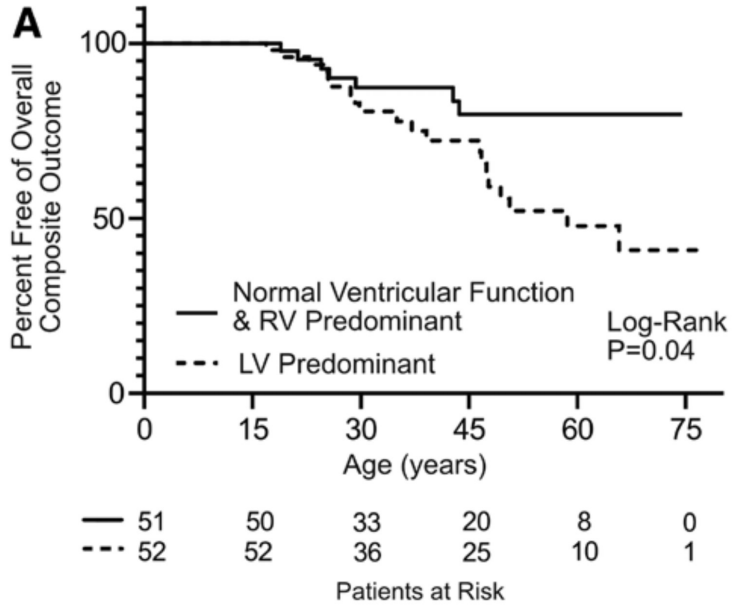


Sen-Chowdhry S et al. Circulation. 2007 Apr 3;115(13):1710-20.

DSP Cardiomyopathy: An Inflammatory and Fibrotic Left Ventricular Cardiomyopathy



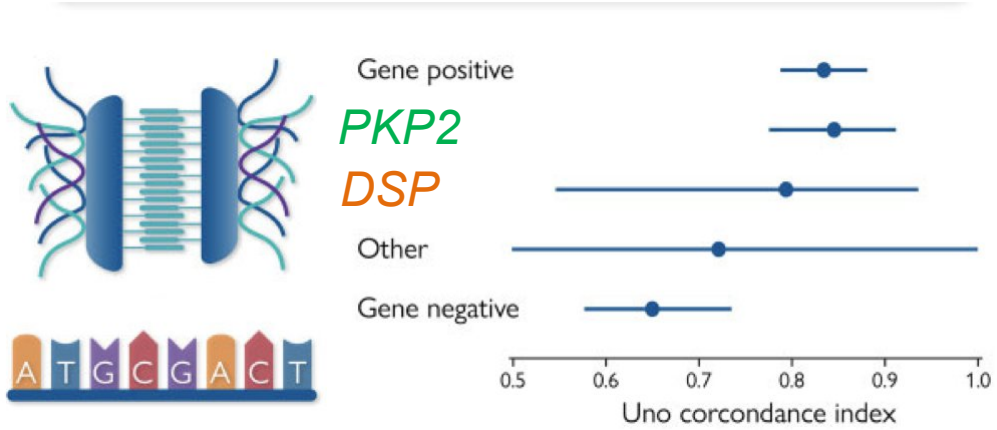




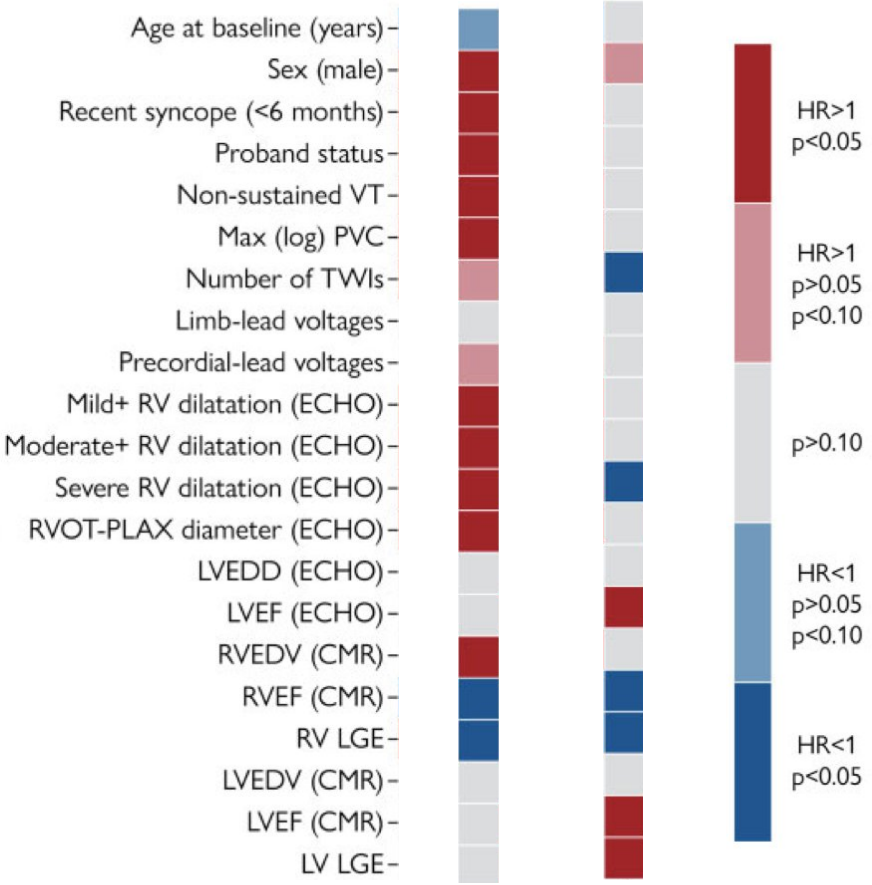
Smith ED et al.
Desmoplakin Cardiomyopathy, a Fibrotic and Inflammatory Form of Cardiomyopathy Distinct From Typical Dilated or Arrhythmogenic Right Ventricular Cardiomyopathy.
Circulation. 2020 Jun 9;141(23):1872-1884.

Risk Calculators and Genotype

ARVC Risk Score Performance Varies With Genotype



Genotype-Specific – Risk Factors



Protonotarios A et al.
Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator.
Eur Heart J. 2022 Aug 21;43(32):3053-3067.

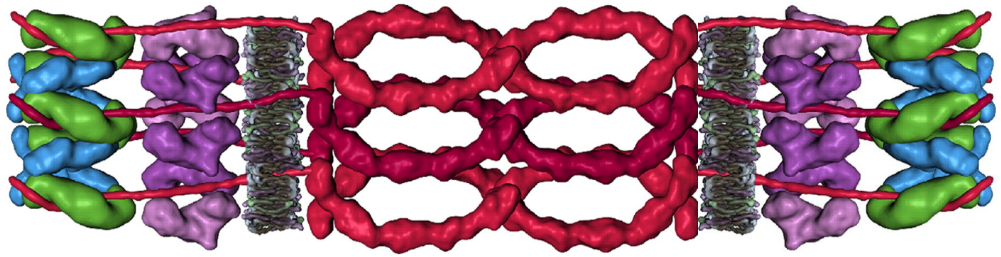
THANK YOU FOR YOUR ATTENTION!

Plakoglobin, *JUP*

McKoy G et al.
Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease).
Lancet. 2000 Jun 17;355(9221):2119-24.

Plakophilin, *PKP2*

Gerull B et al.
Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy.
Nat Genet. 2004 Nov;36(11):1162-4.



Desmoplakin, *DSP*

Rampazzo A et al.
Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy.
Am J Hum Genet. 2002 Nov;71(5):1200-6.

Desmoglein, *DSG2*

Pilichou K et al.
Mutations in desmoglein-2 gene are associated with arrhythmogenic right ventricular cardiomyopathy.
Circulation. 2006;113(9):1171-1179

Desmocollin, *DSC2*

Syrris P et al.
Arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in the desmosomal gene desmocollin-2.
Am J Hum Genet. 2006;79(5):978-984

Al-Amoudi A et al.
The three-dimensional molecular structure of the desmosomal plaque.
Proc Natl Acad Sci U S A. 2011 Apr 19;108(16):6480-5.

Conclusions

- **Genetic studies** contribute to the management of patients with inheritable arrhythmogenic disorders, allowing a more precise **etiological diagnosis** and providing **insights for risk stratification** and **therapeutic decisions**.

Arrhythmogenic Cardiomyopathy

NEW!

Genetic testing + Genetic counselling

In patients with a suspected or definite diagnosis of ARVC, genetic counselling and testing are recommended.[672,673]	I	B

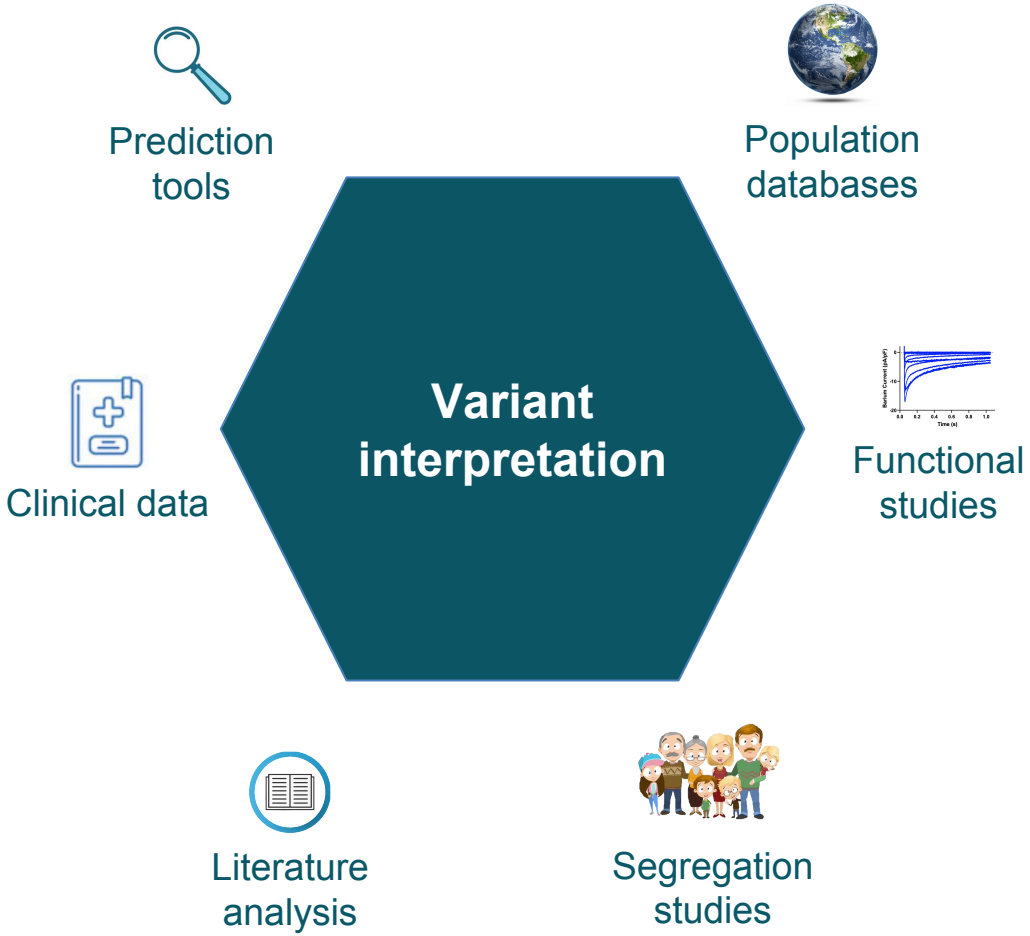
Zeppenfeld K et al.
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.
Eur Heart J. 2022 Aug 26:ehac262.

Arrhythmogenic Cardiomyopathy:
High Intensity Exercise

Avoidance of high-intensity exercise is recommended in patients with a definite diagnosis of ARVC.[683–685]	I	B
Avoidance of high-intensity[c] exercise may be considered in carriers of ARVC-related pathogenic mutations and no phenotype.[683,687]	IIb	C

Zeppenfeld K et al.
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.
Eur Heart J. 2022 Aug 26:ehac262.

Variant Interpretation

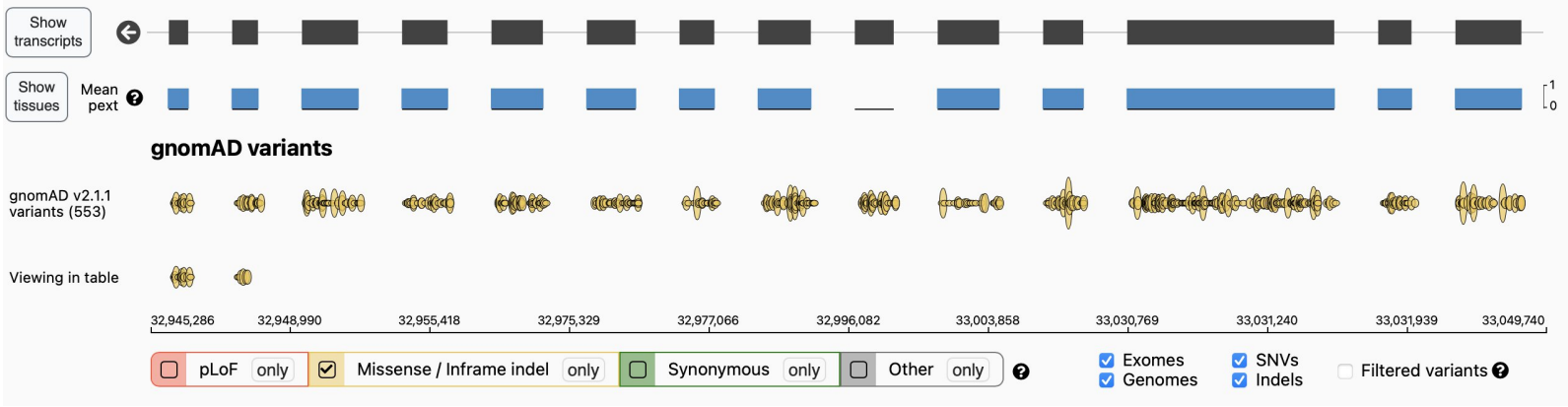


ACMG
American College of Medical Genetics and Genomics

Richards S et al. **Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.**
Genet Med. 2015 May;17(5):405-24.

Problem of Variant Interpretation:
Missense *PKP2* variants

- *PKP2* is a **highly polymorphic gene** with a high rate of missense variants.
- Prevalence of missense variants in *PKP2* that might be compatible with the prevalence of ACM is **1 in 56**.
- **The same proportion of patients clinically affected by ACM may therefore host a missense variant without clinical significance**



Dilatative Cardiomyopathy

Genetic testing

Genetic testing (including at least *LMNA*, *PLN*, *RBM20*, and *FLNC* genes) is recommended in patients with DCM/HNDCM and AV conduction delay at <50 years, or who have a family history of DCM/HNDCM or SCD in a first-degree relative (at age <50 years).[641–645]	I	B

- LMNA A/C
- FLNC
- PLN
- RBM20

Zeppenfeld K et al.
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.
Eur Heart J. 2022 Aug 26:ehac262.

LMNA-Specific Risk Calculator

LMNA-risk VTA calculator

Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies

Sex	○ Male ○ Female	
Non-missense LMNA mutation	○ Yes ○ No	*Non-missense mutations include insertions, deletions, truncating mutations or mutations affecting splicing*
Atrio-ventricular block	○ Absent ○ 1st degree ○ High degree	*Please select the highest degree. 1st degree AV block corresponds to ≥0.20 sec PR interval and high degree AV block to type II 2nd degree or 3rd degree (and not type I 2nd degree)*
Non-sustained ventricular tachycardia	○ Yes ○ No	*NSVT corresponds to ≥3 consecutive ventricular complexes at a rate ≥120 bpm on 24-h ambulatory electrocardiographic monitoring*
Left ventricular ejection fraction	[ ] %	*Left ventricular ejection fraction measurement derived from echocardiogram*

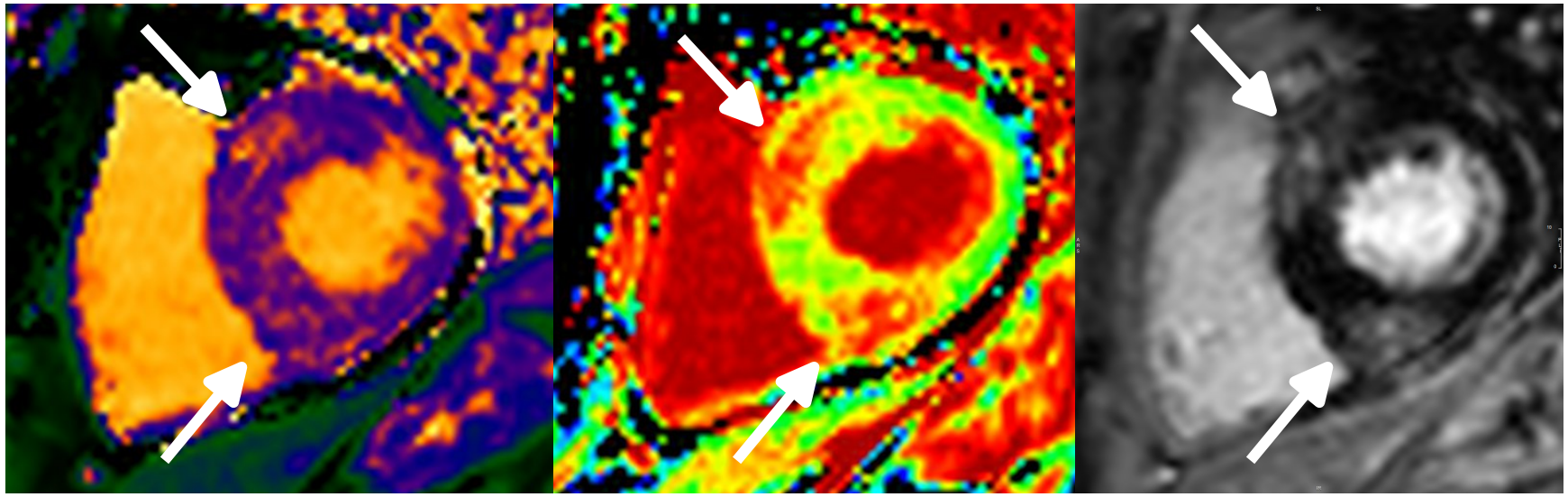
Risk of Life-Threatening Ventricular Tachyarrhythmias at 5 years

___ %

Reset

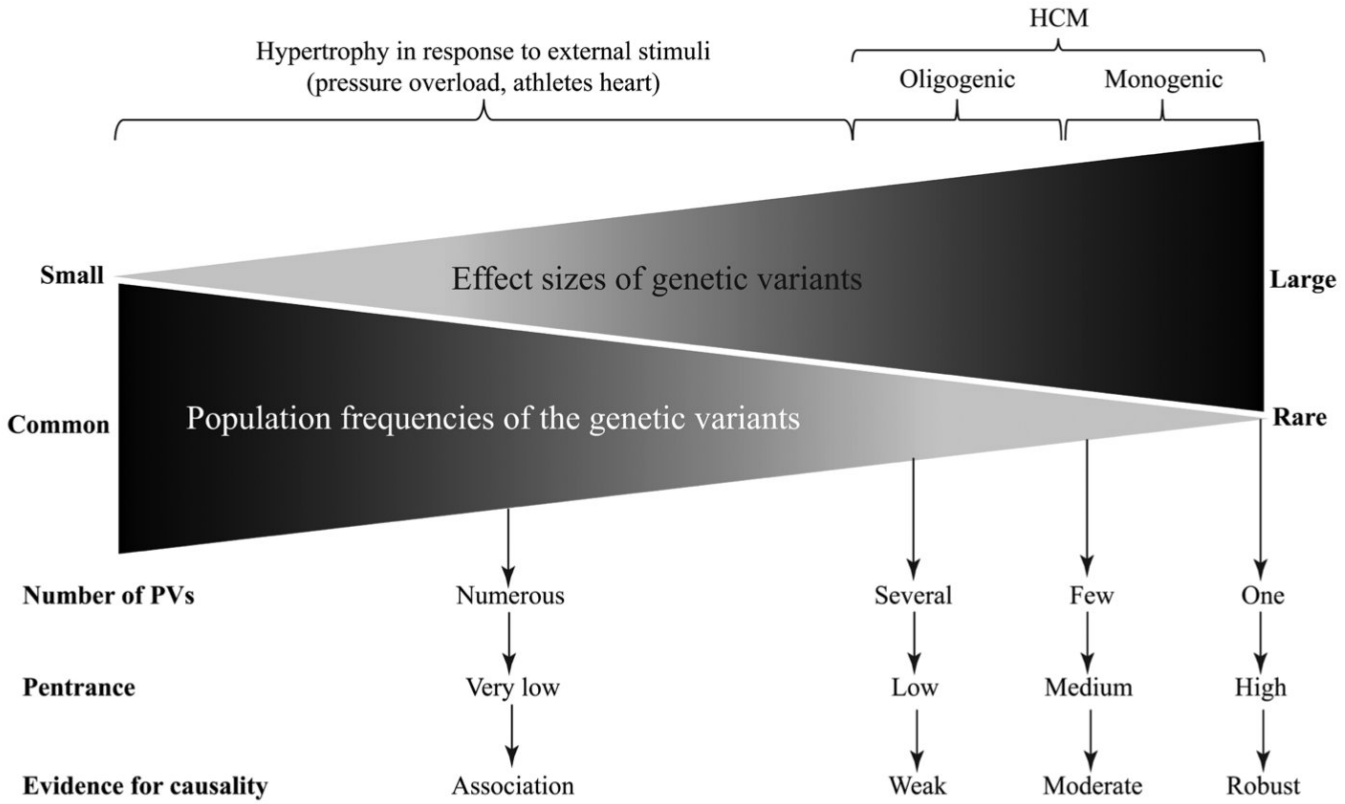
Wahbi K et al.
Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies.
Circulation. 2019 Jul 23;140(4):293-302.

Native T1 mapping | Extracellular volume | Late gadolinium enhancement



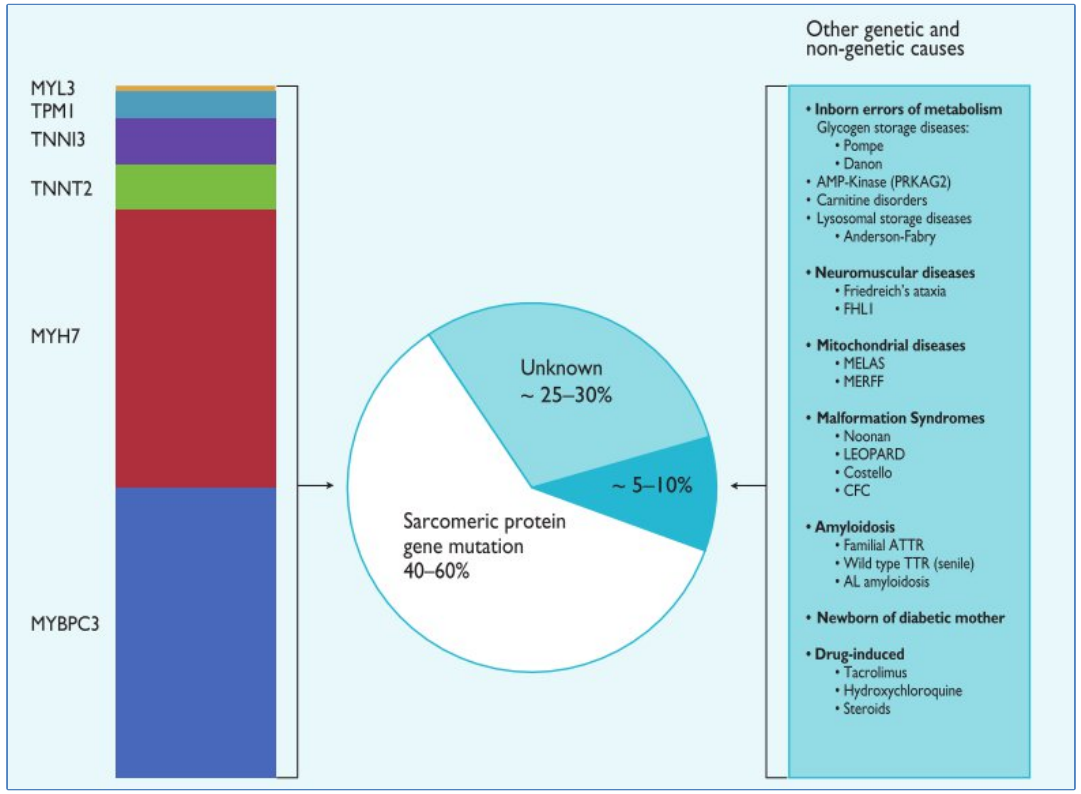
HYPERTROPHIC CARDIOMYOPATHY

Genetic Architecture of HCM



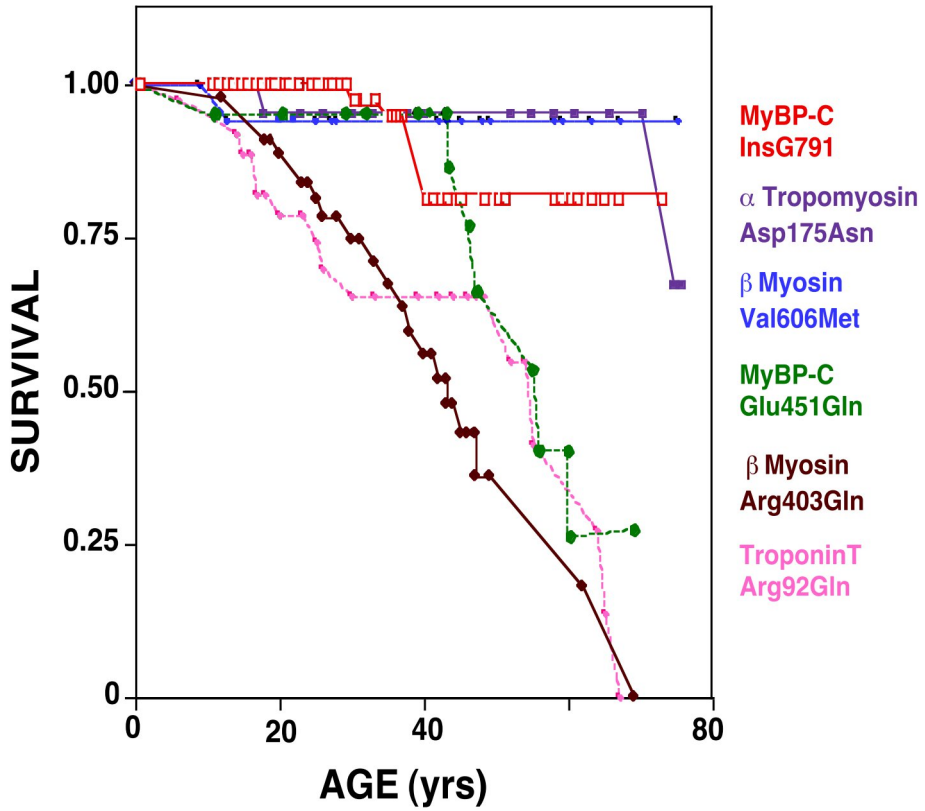
Marian AJ.
Molecular Genetic Basis of Hypertrophic Cardiomyopathy.
Circ Res. 2021 May 14;128(10):1533-1553.

Yield of Genetic Analysis in HCM



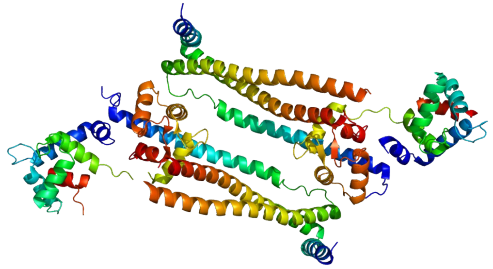
Elliott PM et al.
2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy.
Eur Heart J. 2014 Oct 14;35(39):2733-79.

Genotype & Prognosis in HCM

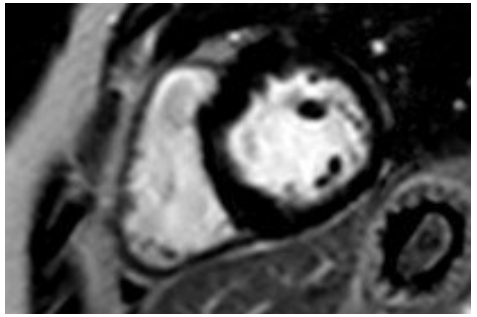


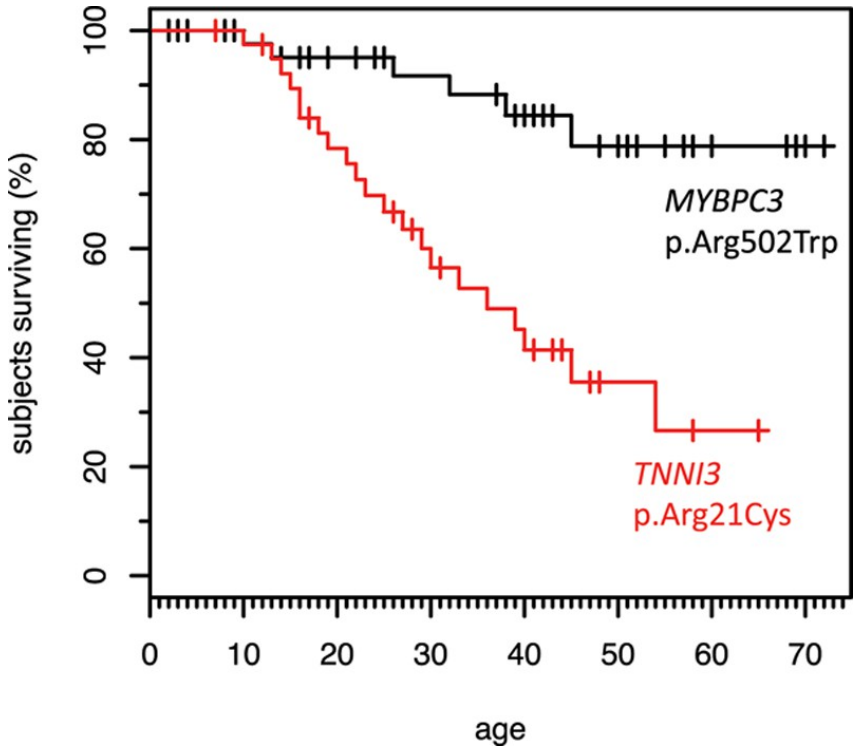
Watkins H et al.
Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy.
N Engl J Med. 1992 Apr 23;326(17):1108-14.

TNNI3: Malignant Hypertrophic Cardiomyopathy



27/57 (47%) subjects with clinical evidence of HCM





Fahed AC et al.
Founder Mutation in N Terminus of Cardiac Troponin I Causes Malignant Hypertrophic Cardiomyopathy.
Circ Genom Precis Med. 2020 Oct;13(5):444-452.

Utility of Genetic Testing: Cardiomyopathies

Disease	Diagnostic	Prognostic	Therapeutic
HCM	+++	+	+
ACM	++	+/-	-
DCM	++	+	+