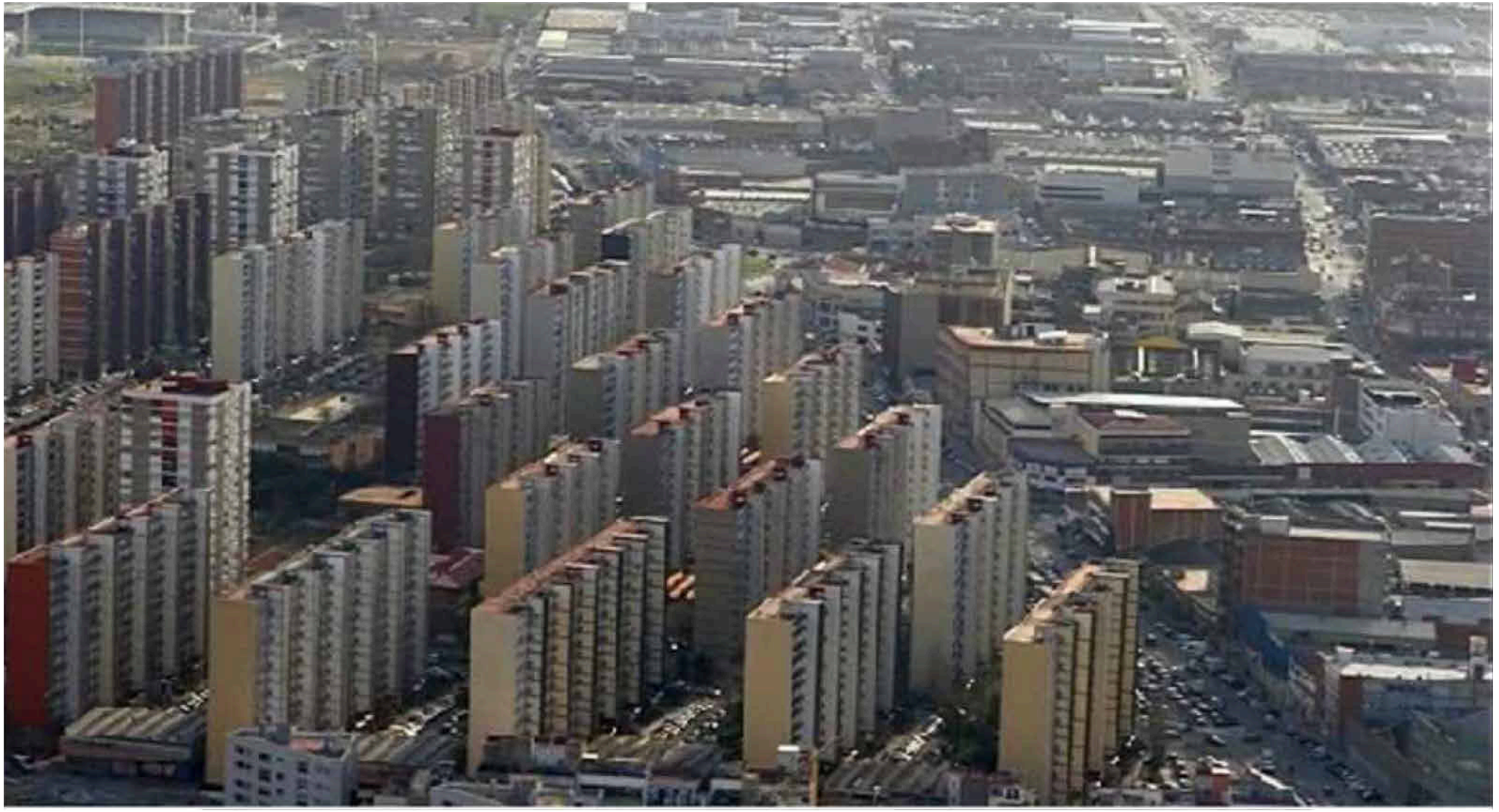
¿A quién pedir y cómo interpretar un estudio genético?

Joel Salazar-Mendiguchía

Health in Code

A Coruña

Conflicto de intereses



European Heart Journal (2013) **34**, 2381–2411
doi:10.1093/eurheartj/eht234

CURRENT OPINION

ESC Core Curriculum for the General Cardiologist (2013)

European Society of Cardiology

Committee for Education

- the major monogenic cardiovascular diseases, such as
  - cardiomyopathies;
  - familial aortopathies;
  - familial arrhythmias;
  - trisomies, in particular trisomy 21;
  - familial dyslipidaemias.

Skills

The ability to:

- evaluate relevant family history and construct a family pedigree;
- counsel index cases and family members at risk on the probability of being affected by a genetic cardiovascular disorder;
- recognize problems with pedigree interpretation such as incomplete penetrance, variable expressivity, and age-related patterns of expressivity;
- manage the uncertainties associated with genetic testing;
- direct patients and families when appropriate to major centres with a specialized interest in their particular disorder.

Pasos previos al estudio genético

September 2015

Author
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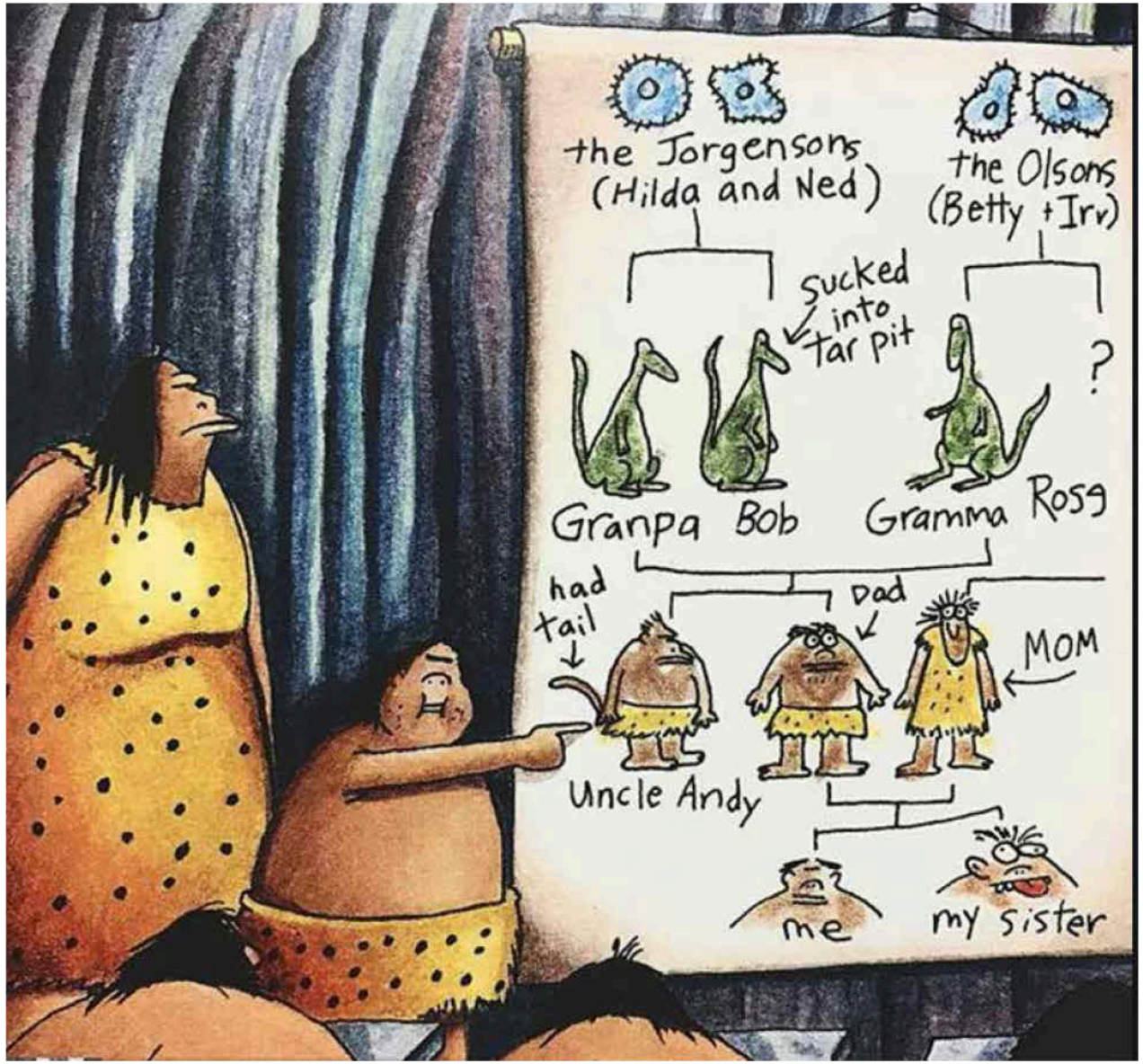
Phenotyping patients for genomic diagnostics

The realisation of genomic medicine in clinical practice rests on efficient and accurate interpretation of genomic data. Descriptions of a patient's clinical features - their 'phenotypes' - are essential to drive and target the correct analysis of this data. Maximising the benefits of genomic testing and managing the increasing demand for genetic tests depends on significant improvements in capturing and exchanging the appropriate phenotypic information across the NHS.


the Jorgensons
(Hilda and Ned)
the Olsons
(Betty + Irv)
sucked into tar pit
?
Granpa Bob
Gramma Rosa
had tail
dad
MOM
Uncle Andy
me
my sister


COUNSELOR
CARTOONSTOCK
.com
Search ID: rmon3130
RON MORGAN
"Your domestic problems seem to be genetic
due to the fact your parents reproduced."

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

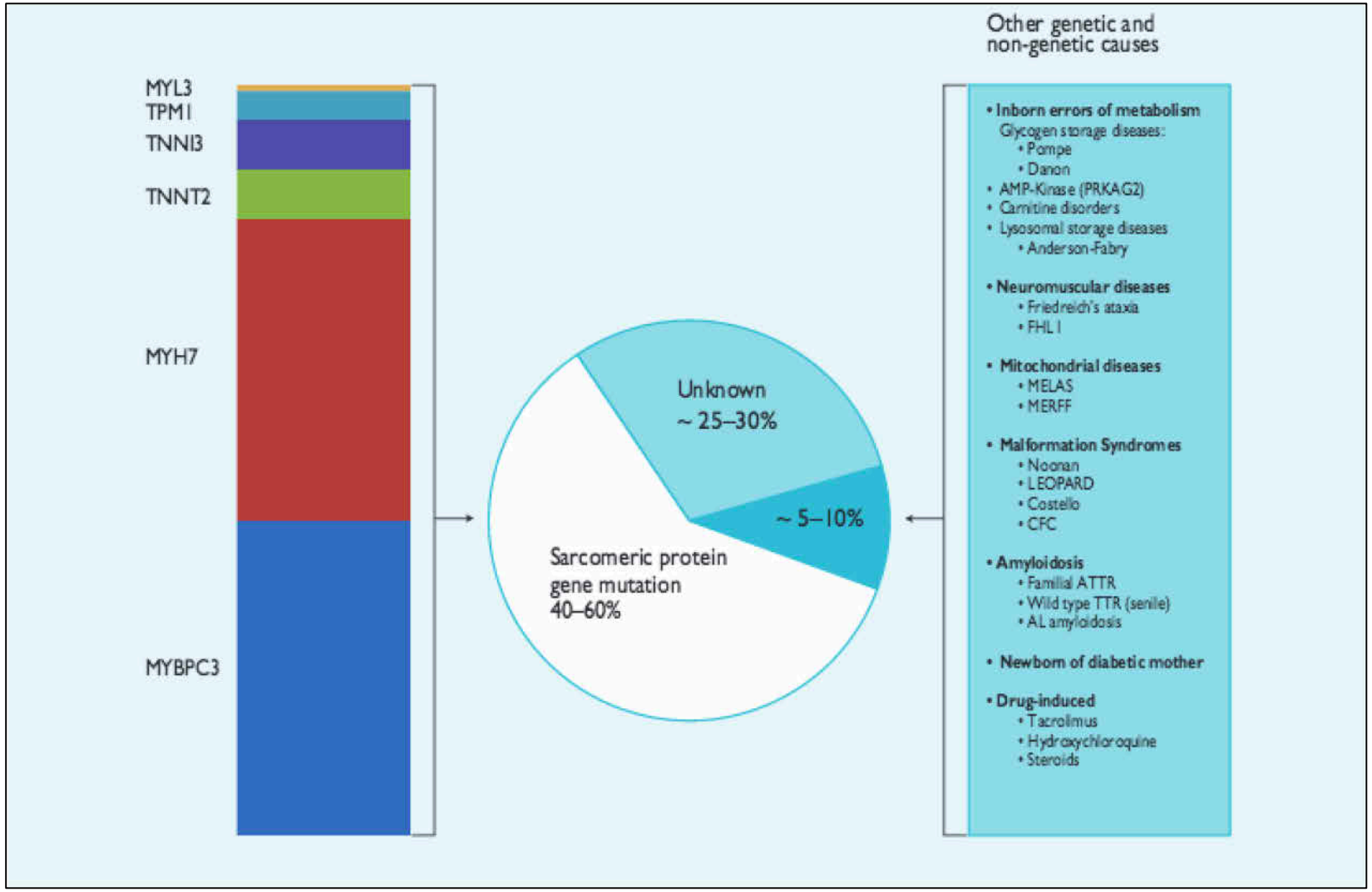
Section # – Disease	Diagnostic	Prognostic
Section VII – HCM	+++	++
Section VIII – ACM/ARVC	+	+/–
Section IX – DCM	+/–	–
Section IX – DCM + CCD	++	++
Section X – LVNC	+	–
Section XI – RCM	+	+

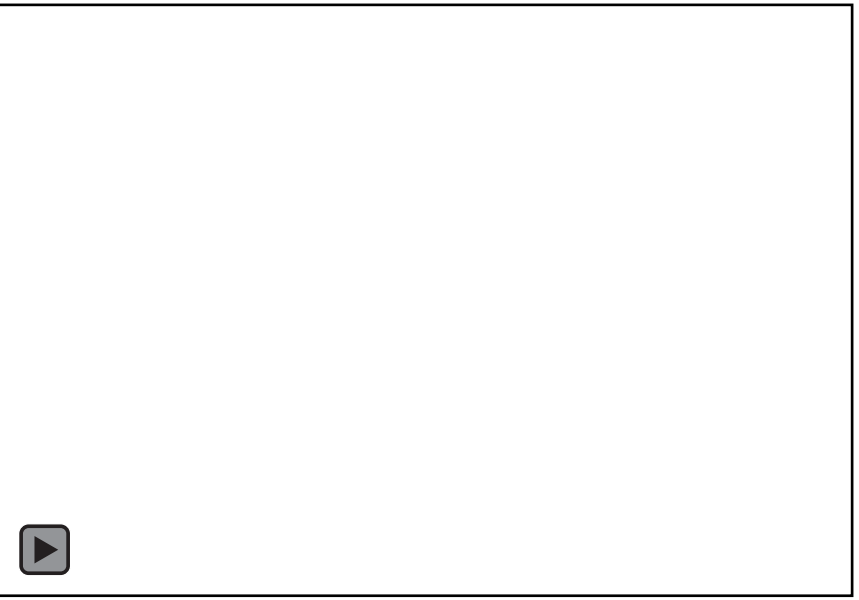
Ackerman et al. Europace. 2011

Recommendations	Class[a]	Level[b]	Ref.[c]
Genetic counselling is recommended for all patients with HCM when their disease cannot be explained solely by a non-genetic cause, whether or not clinical or genetic testing will be used to screen family members.	I	B	169–173
Genetic counselling should be performed by professionals trained for this specific task working within a multidisciplinary specialist team.	IIa	C	168–173

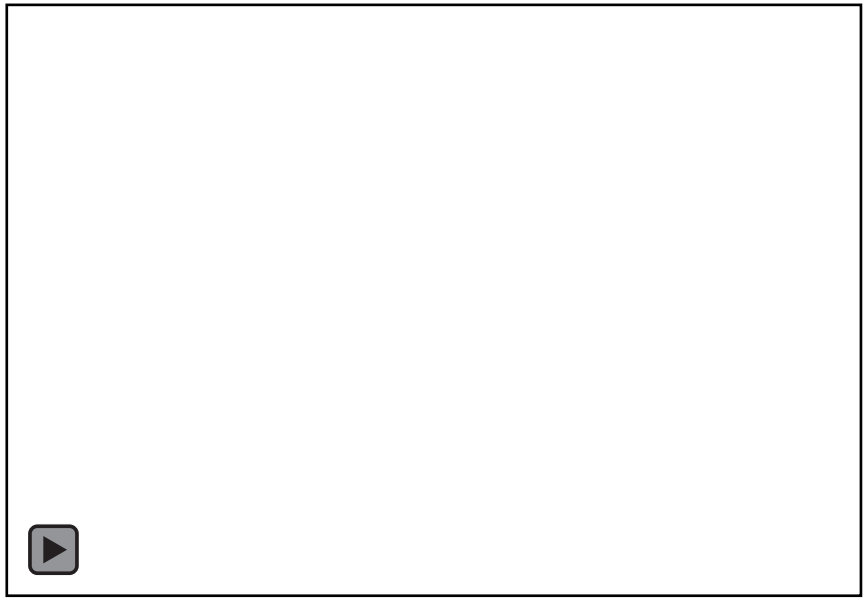
Recommendations	Class[a]	Level[b]	Ref.[c]
Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.	I	B	24,175 178–180
It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations.	I	C	168,172,183
In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis.	I	B	36–40, 43–46,67
Genetic testing in patients with a borderline[d] diagnosis of HCM should be performed only after detailed assessment by specialist teams.	IIa	C	168
Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives.	IIa	C	181,182

Elliott PM, Eur Heart J. 2014


MYL3
TPM1
TNNI3
TNNT2
MYH7
MYBPC3
Unknown
~ 25–30%
~ 5–10%
Sarcomeric protein
gene mutation
40–60%
Other genetic and
non-genetic causes
• Inborn errors of metabolism
Glycogen storage diseases:
• Pompe
• Danon
• AMP-Kinase (PRKAG2)
• Carnitine disorders
• Lysosomal storage diseases
• Anderson-Fabry
• Neuromuscular diseases
• Friedreich's ataxia
• FHL1
• Mitochondrial diseases
• MELAS
• MERFF
• Malformation Syndromes
• Noonan
• LEOPARD
• Costello
• CFC
• Amyloidosis
• Familial ATTR
• Wild type TTR (senile)
• AL amyloidosis
• Newborn of diabetic mother
• Drug-induced
• Tacrolimus
• Hydroxychloroquine
• Steroids



- 18 años
- SIV 15 mm / AI 45 mm / Grad pico 45 mmHg
- MS familiar



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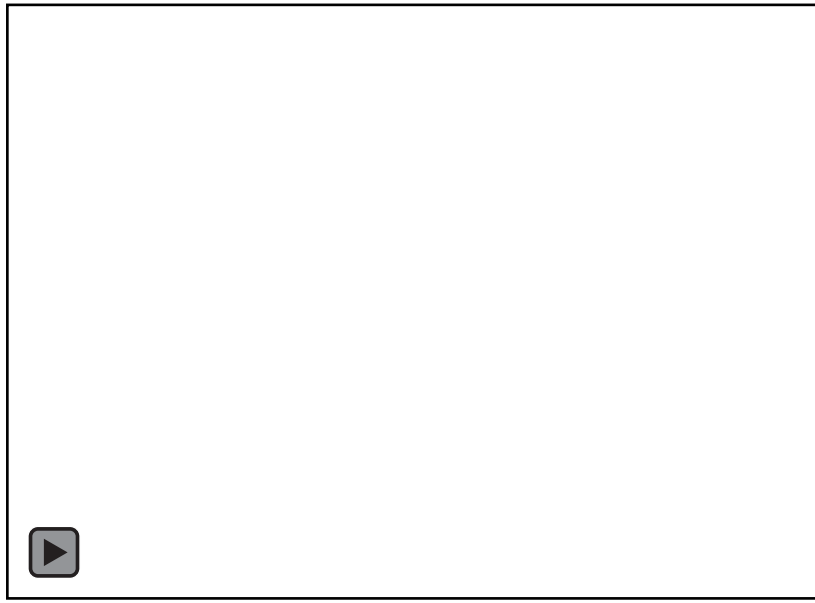
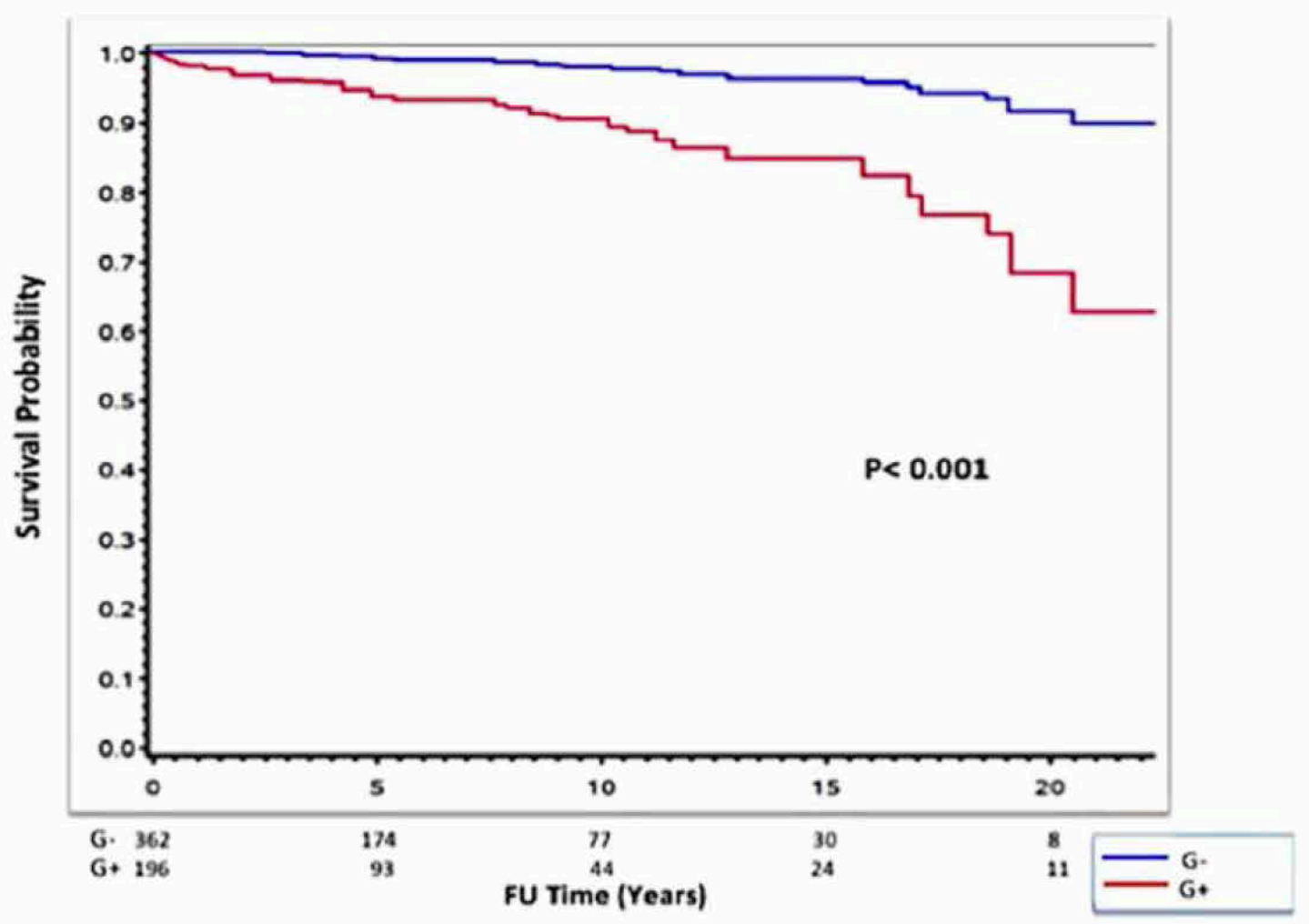
- MS familiar



- 18 años
- SIV 15 mm / AI 45 mm / Grad pico 45
- MS familiar

Risk of SCD at 5 years (%):	4.93
ESC recommendation:	ICD may be considered

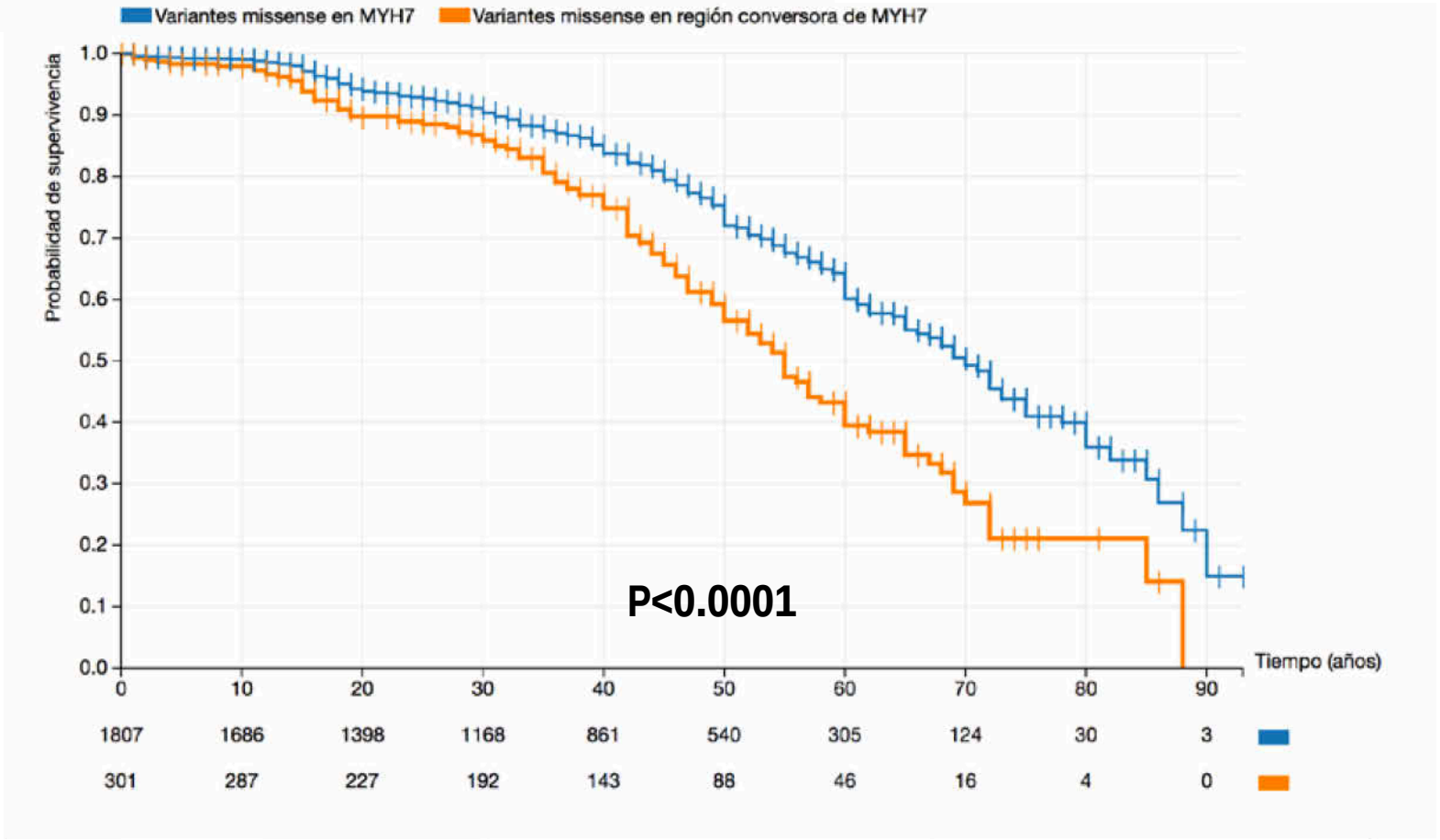
Miocardiopatía hipertrófica



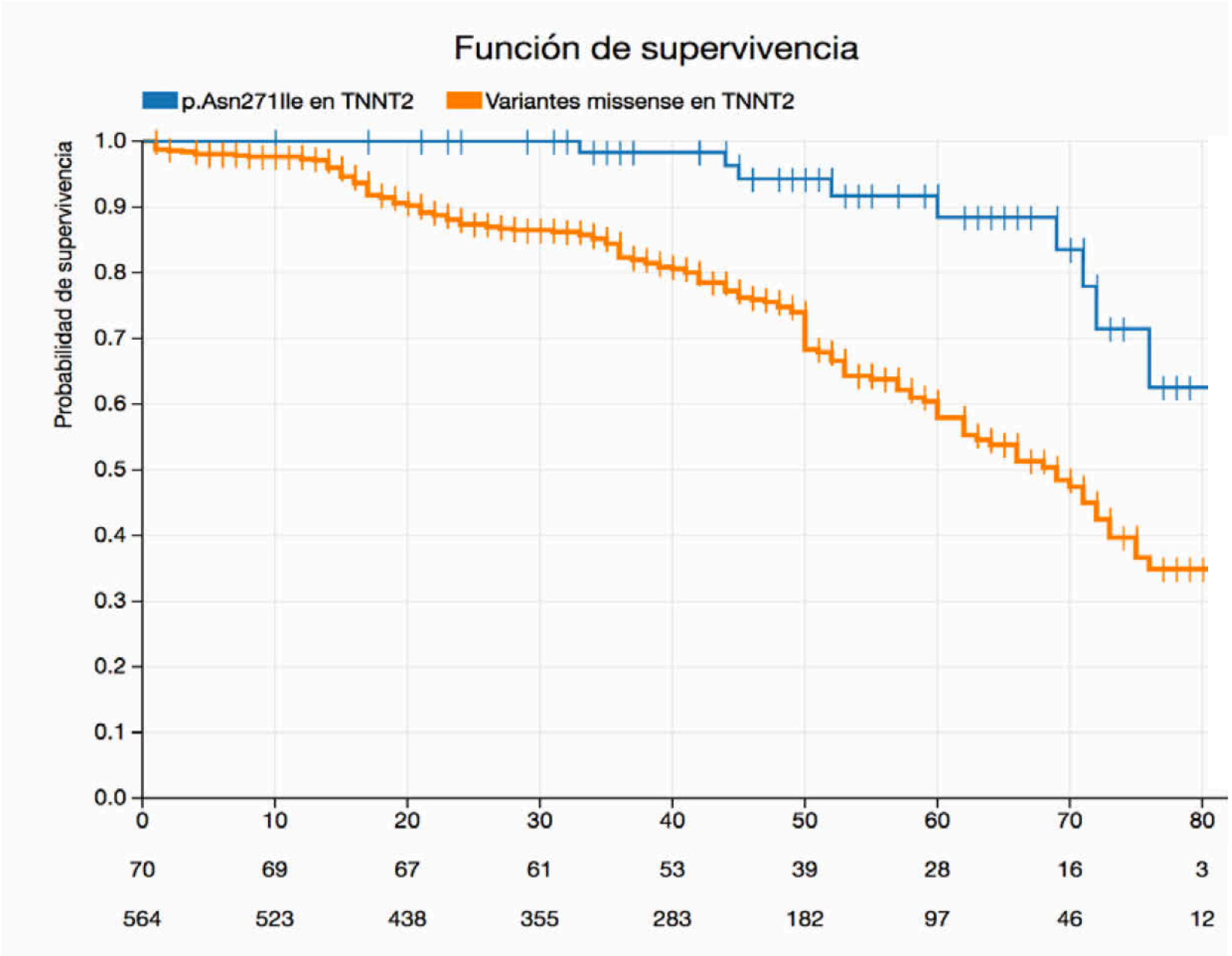
Li, et al. Circulation 2014

ORIGINAL ARTICLE

Phenotype and prognostic correlations of the converter region mutations affecting the β myosin heavy chain



García-Giustiani, et al. Heart. 2015


Función de supervivencia
p.Asn271Ile en TNNT2
Variantes missense en TNNT2
Probabilidad de supervivencia
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 10 20 30 40 50 60 70 80
70 69 67 61 53 39 28 16 3
564 523 438 355 283 182 97 46 12

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Section # – Disease	Diagnostic	Prognostic
Section VII – HCM	+++	++
Section VIII – ACM/ARVC	+	+/–
Section IX – DCM	+/–	–
Section IX – DCM + CCD	++	++
Section X – LVNC	+	–
Section XI – RCM	+	+

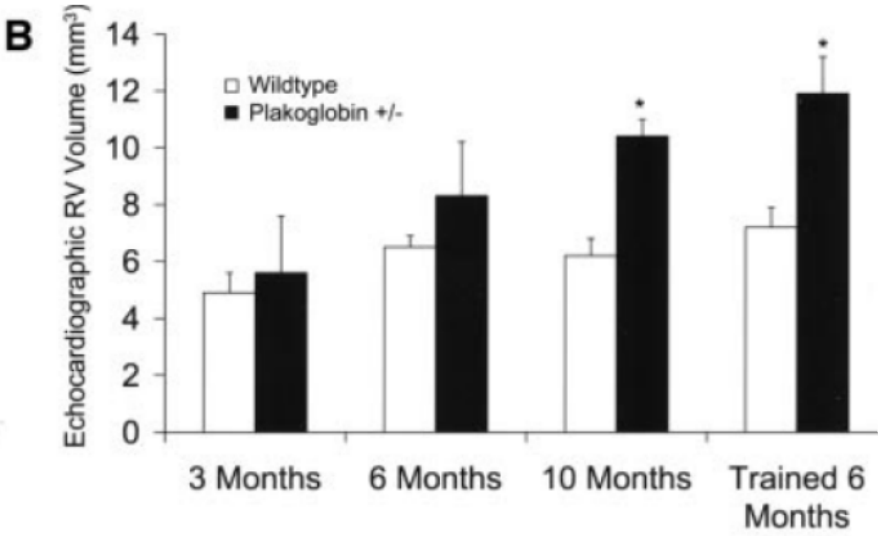
Ackerman et al. Europace. 2011

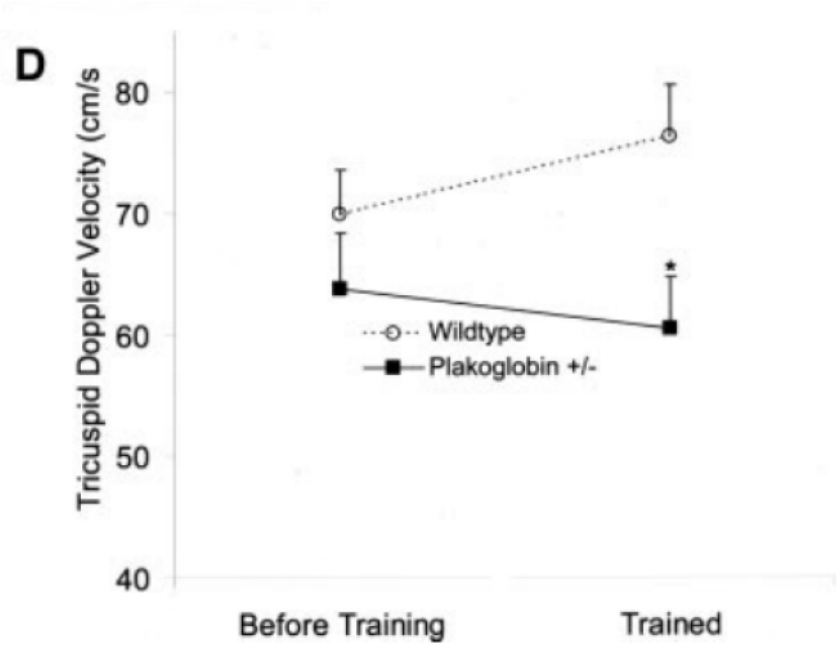
Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia

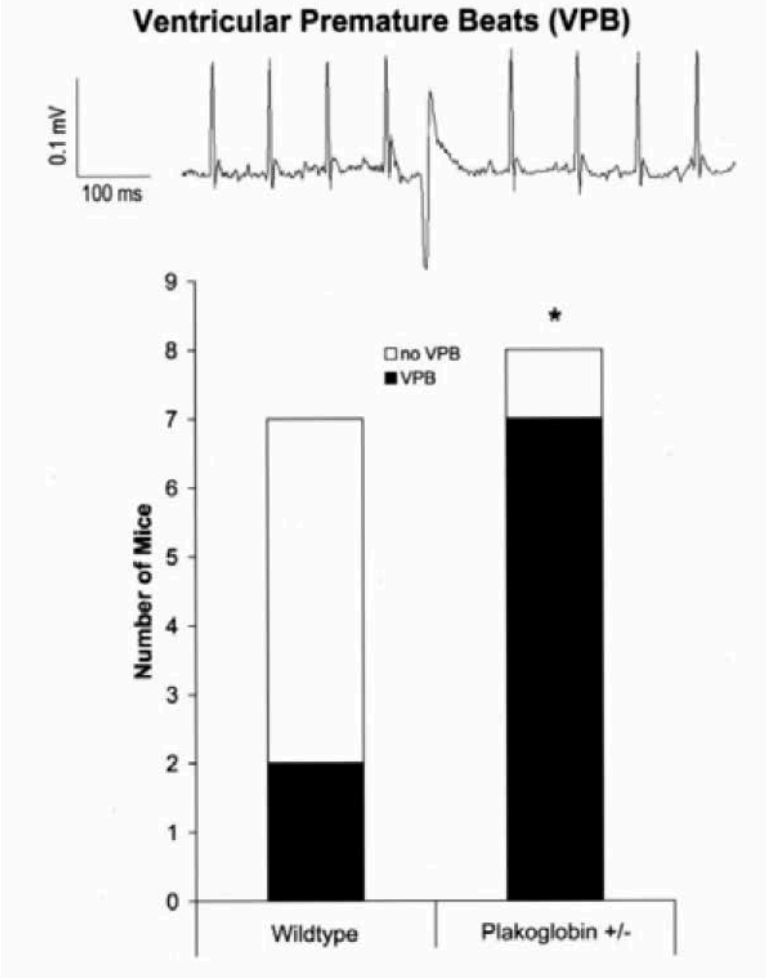
Major criteria

- ARVC/D confirmed in a first-degree relative who meets current Task Force criteria
- ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
- Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation

Age- and Training-Dependent Development of Arrhythmogenic Right Ventricular Cardiomyopathy in Heterozygous Plakoglobin-Deficient Mice

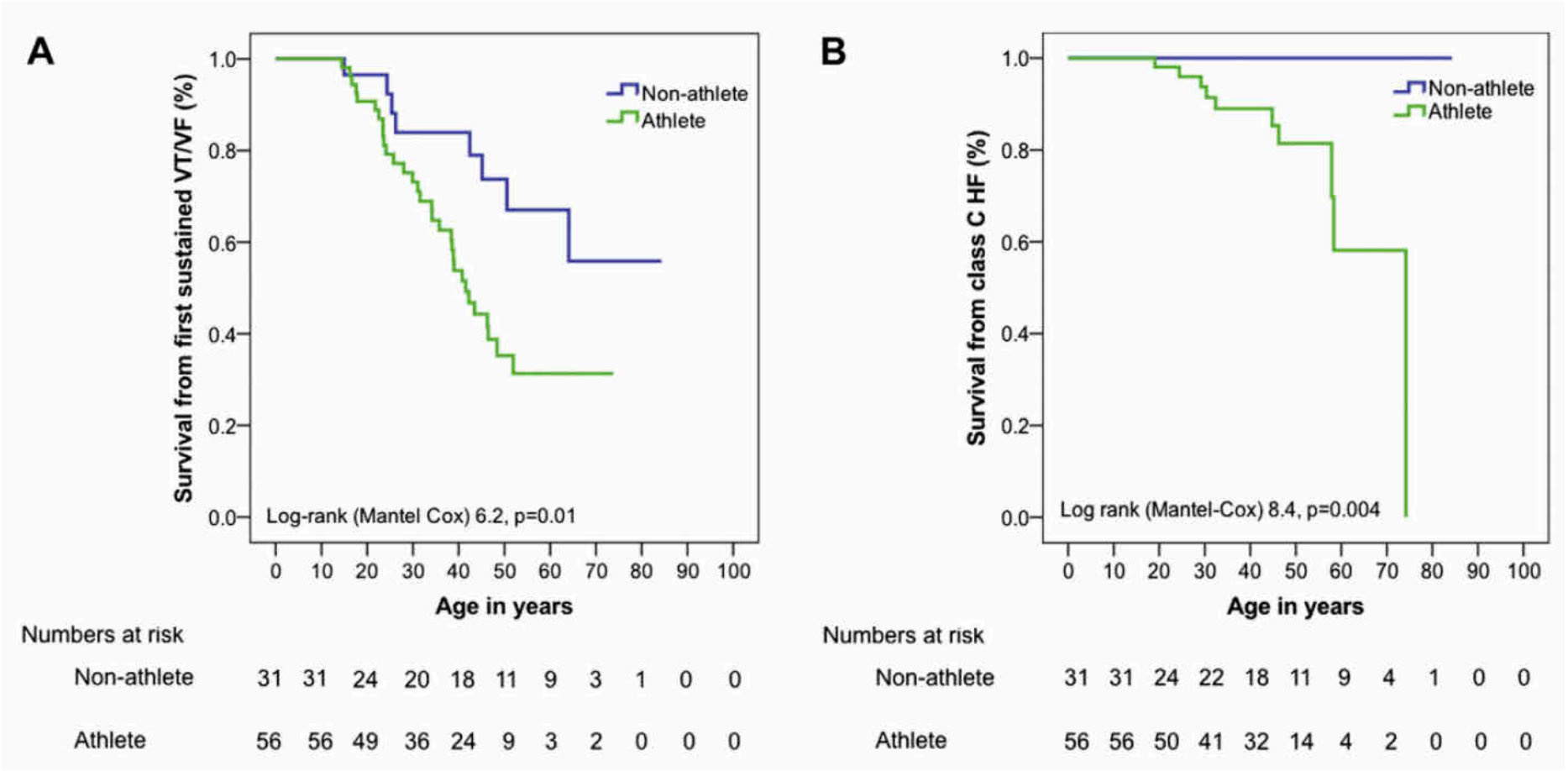






Kirchhof, et al. Circulation. 2006

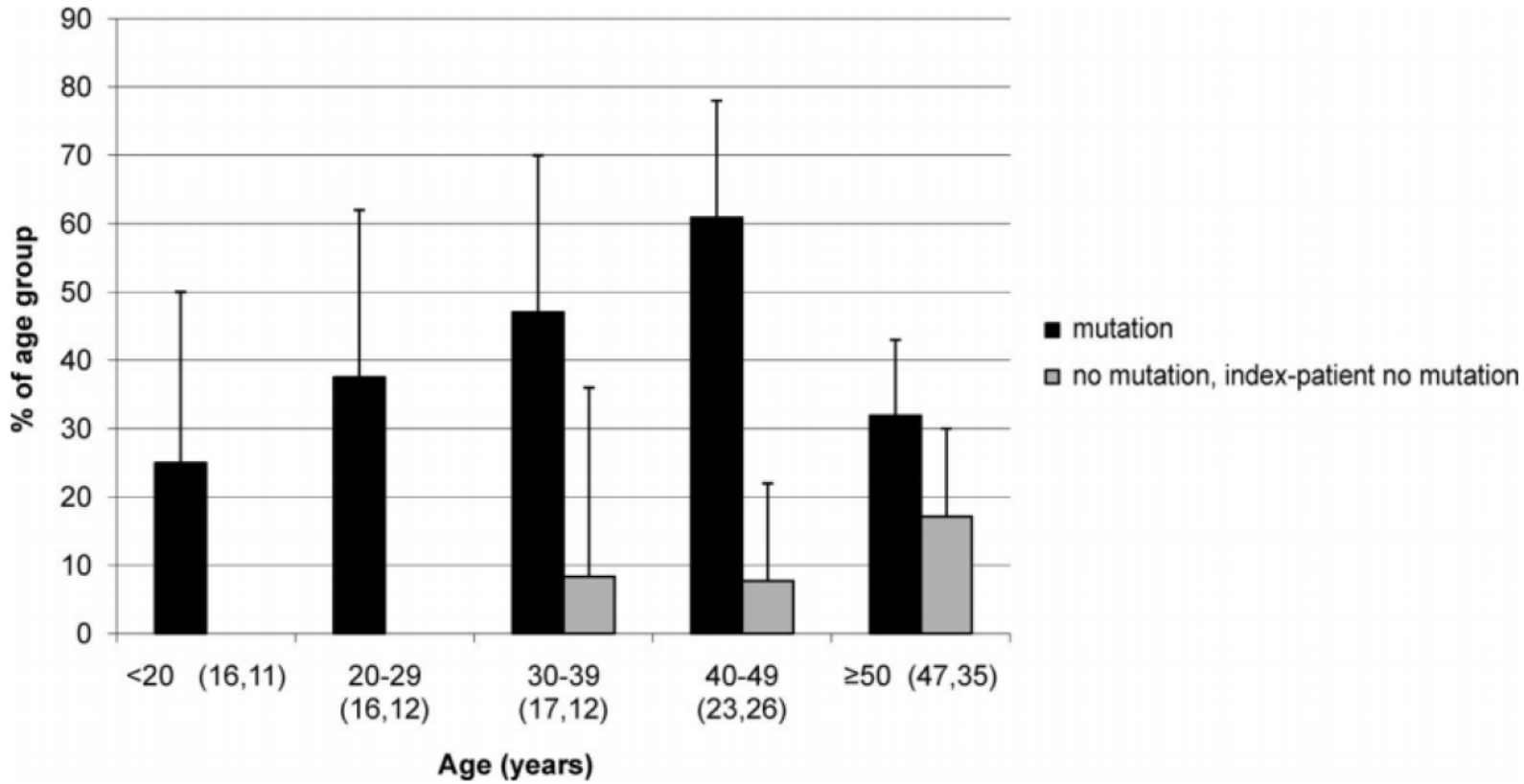
Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy–Associated Desmosomal Mutation Carriers



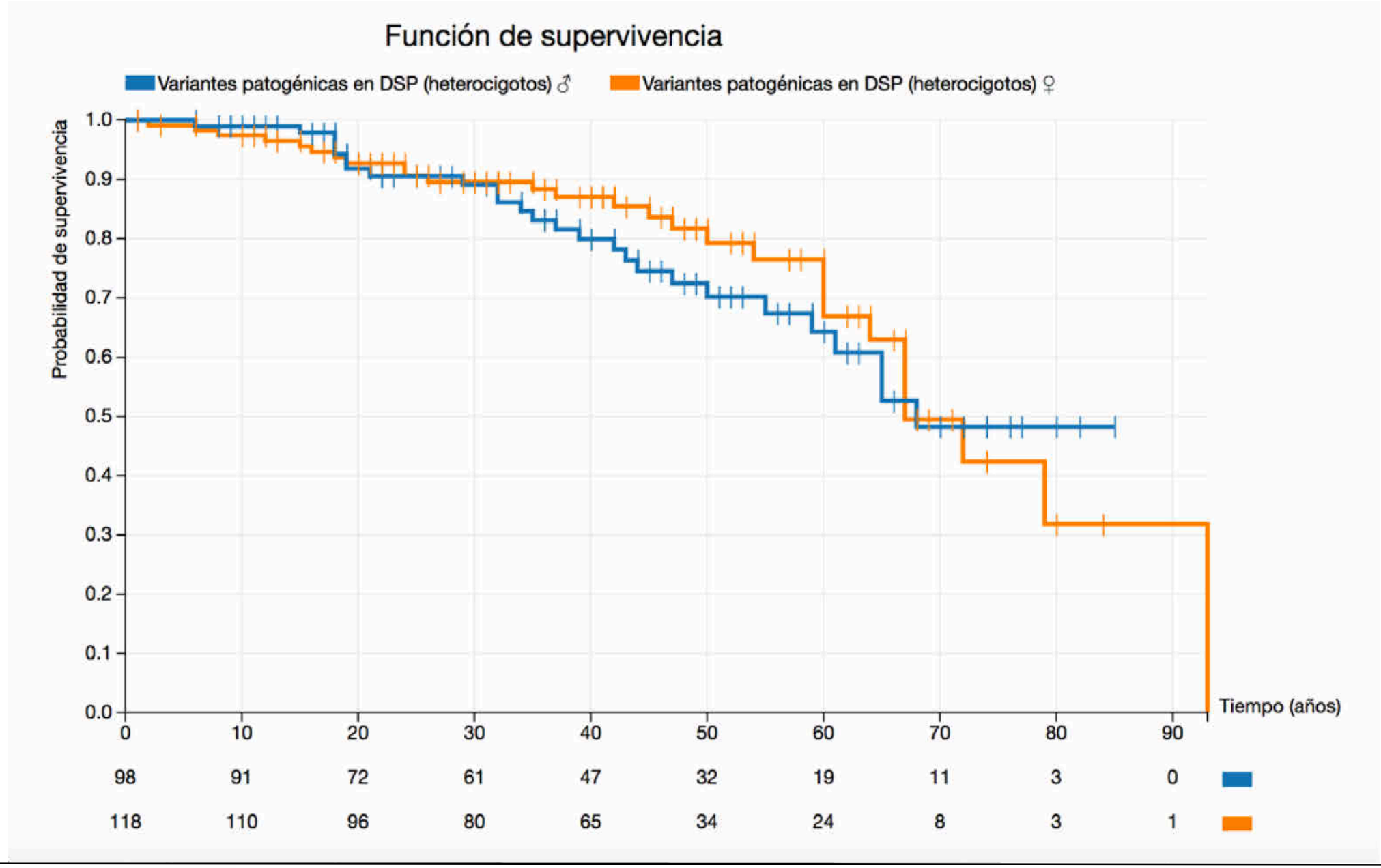
James, et al. J Am Coll Cardiol. 2013

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

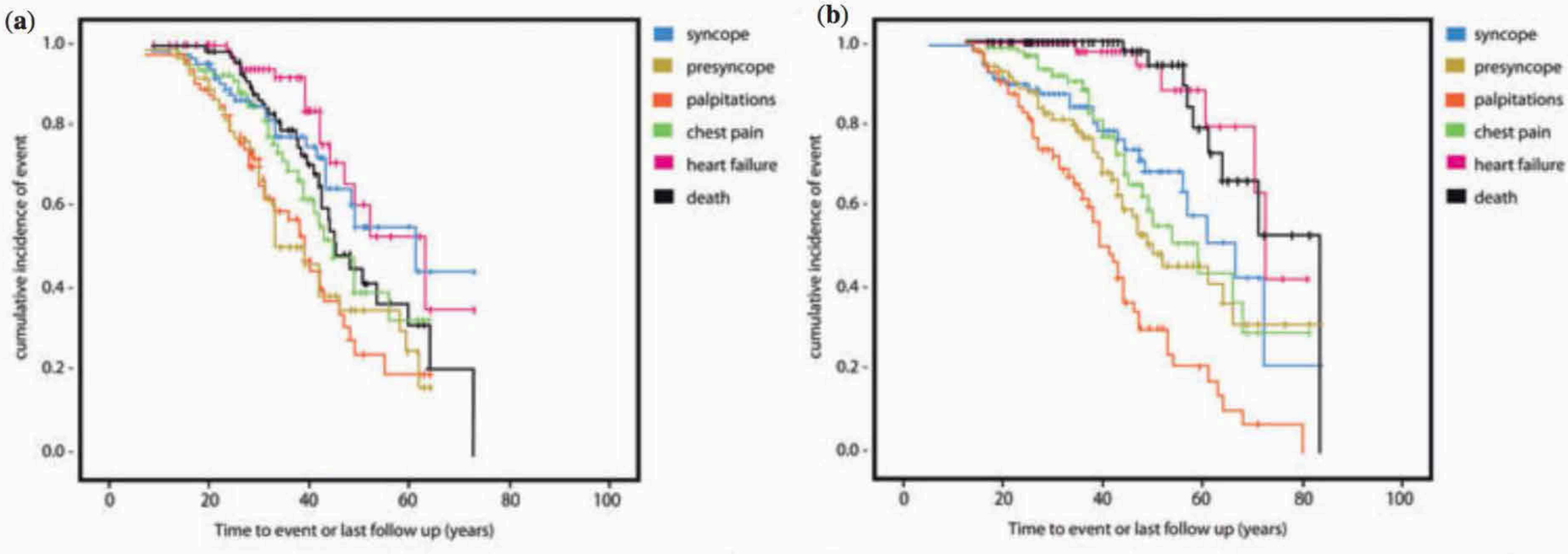
Pathogenic Desmosome Mutations in Index-Patients Predict Outcome of Family Screening: Dutch Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Genotype-Phenotype Follow-Up Study



Cox et al. Circulation. 2011


Función de supervivencia
Variantes patogénicas en DSP (heterocigotos) ♂
Variantes patogénicas en DSP (heterocigotos) ♀
Probabilidad de supervivencia
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Tiempo (años)
0 10 20 30 40 50 60 70 80 90
98 91 72 61 47 32 19 11 3 0
118 110 96 80 65 34 24 8 3 1

The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in TMEM43



Hodgkinson et al. Clin Genet. 2013

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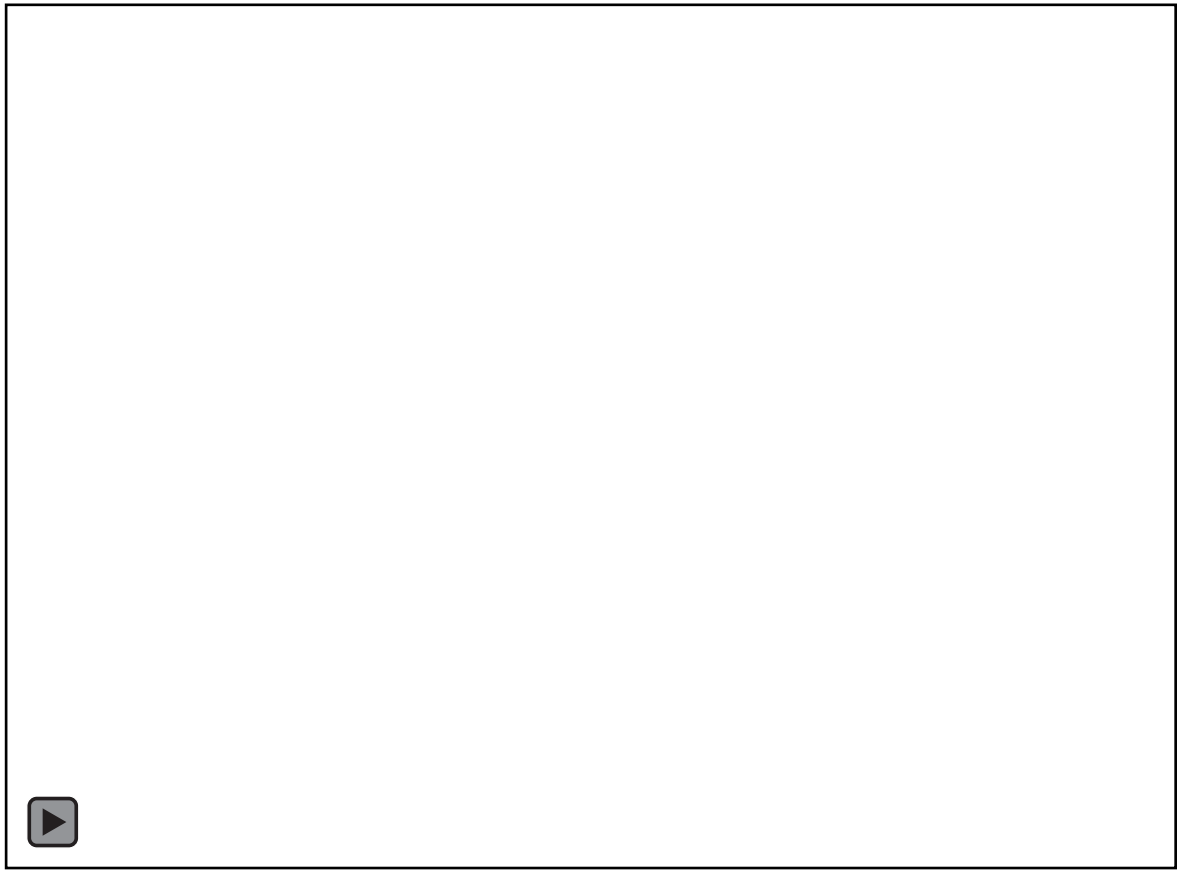
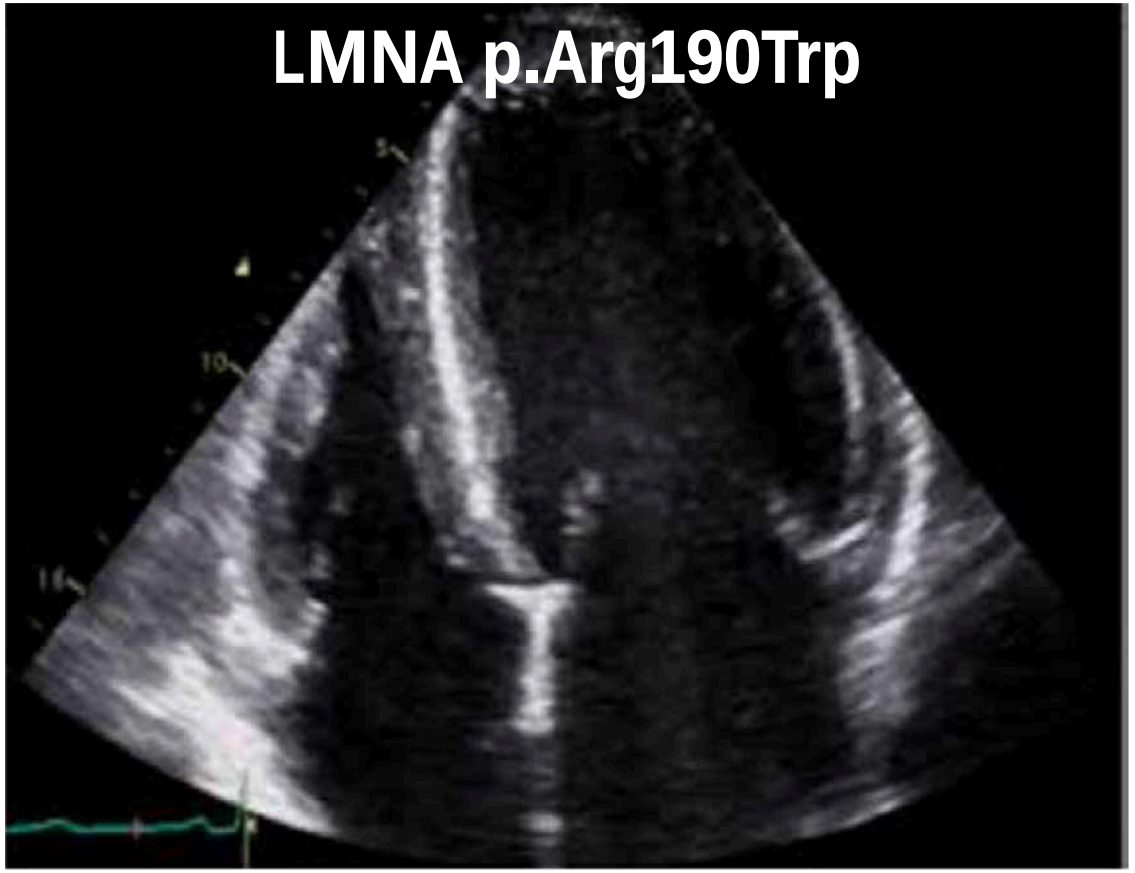
Ackerman et al. Europace. 2011

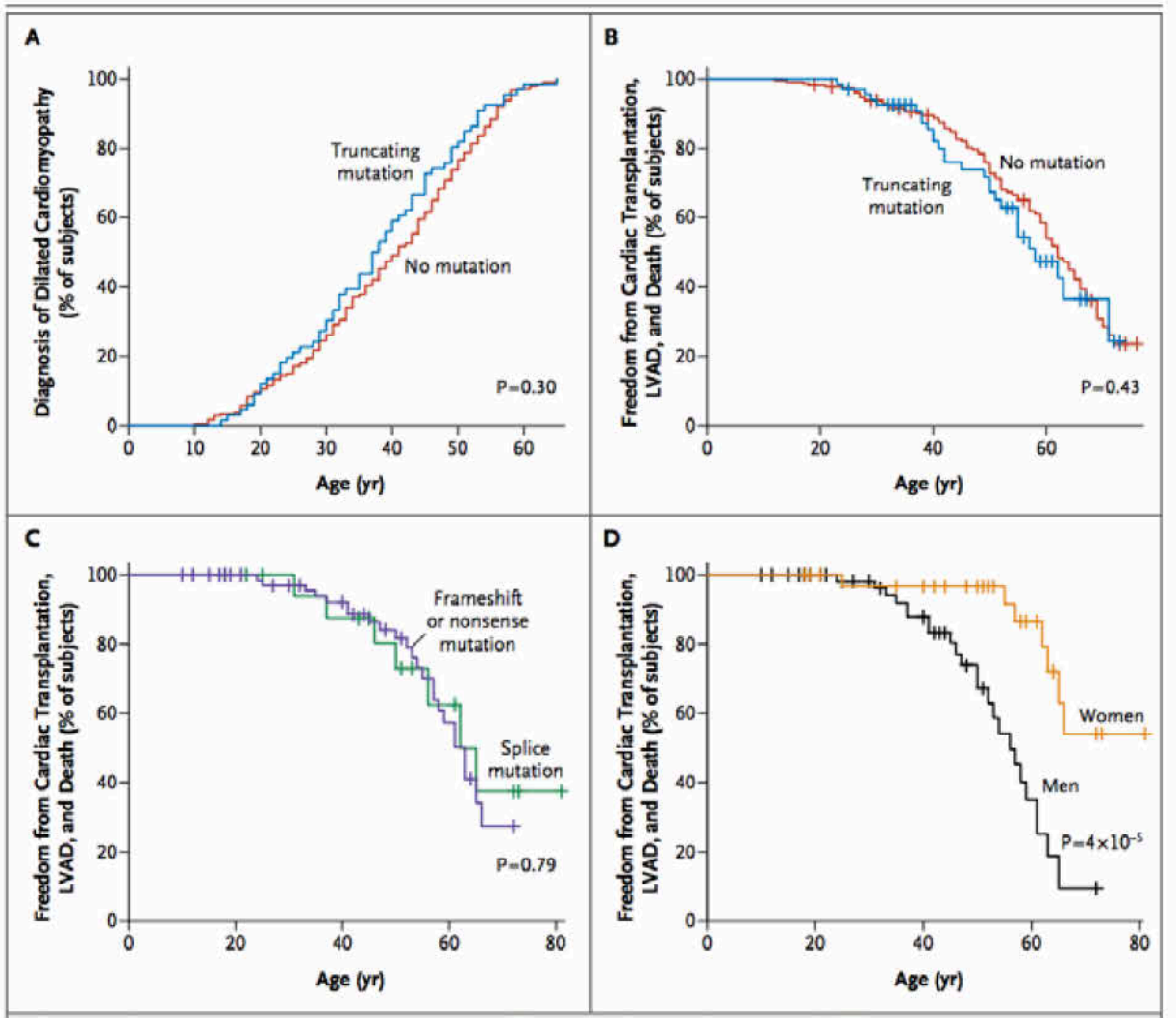


- Varón 40 años
- Disfunción ventricular izquierda severa
- Antecedentes familiares de muerte súbita

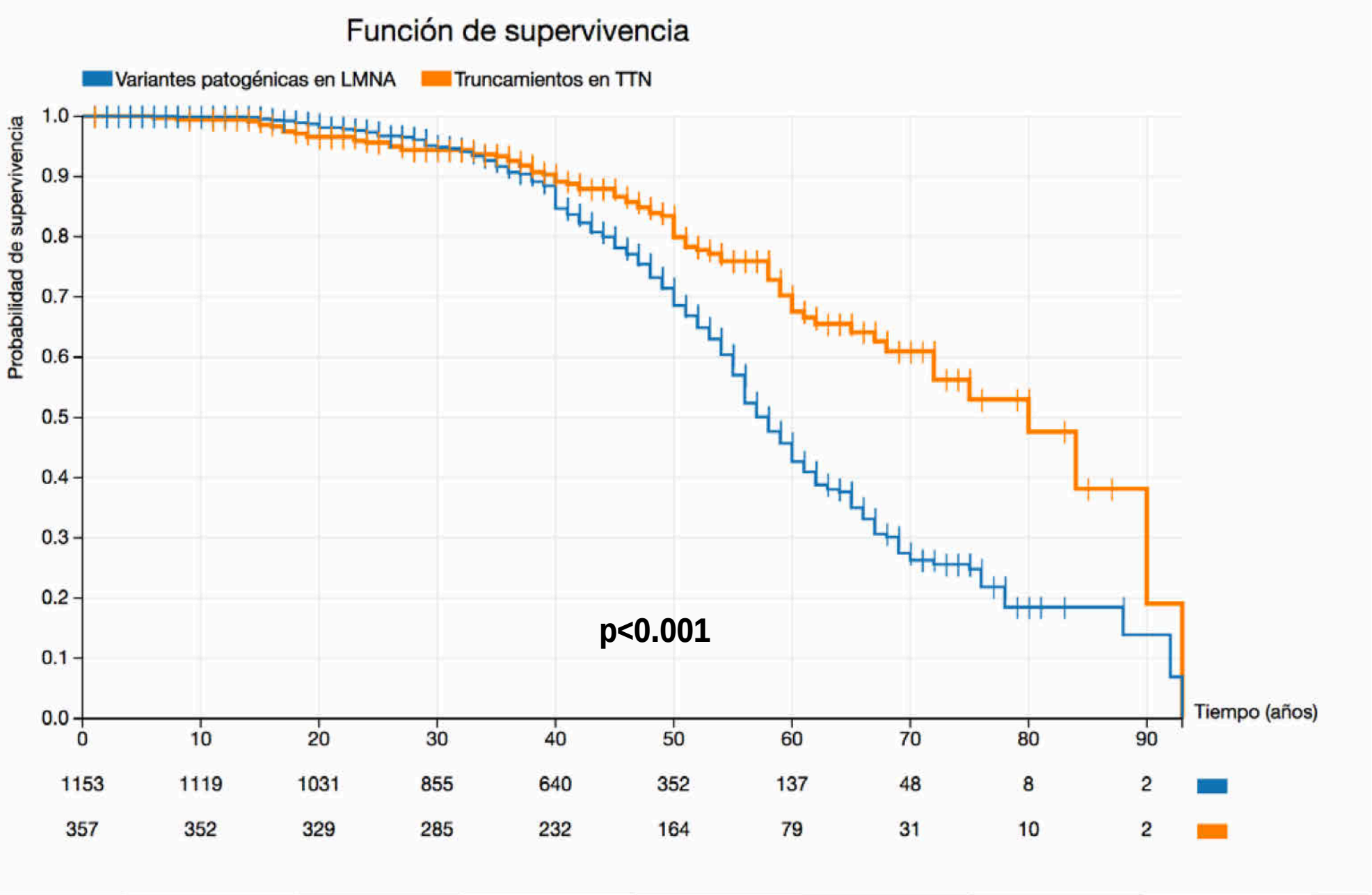


- Varón 40 años
- Disfunción ventricular izquierda moderada
- Sin antecedentes familiares de muerte súbita

Truncations of Titin Causing Dilated Cardiomyopathy



Herman et al. N Engl J Med. 2012



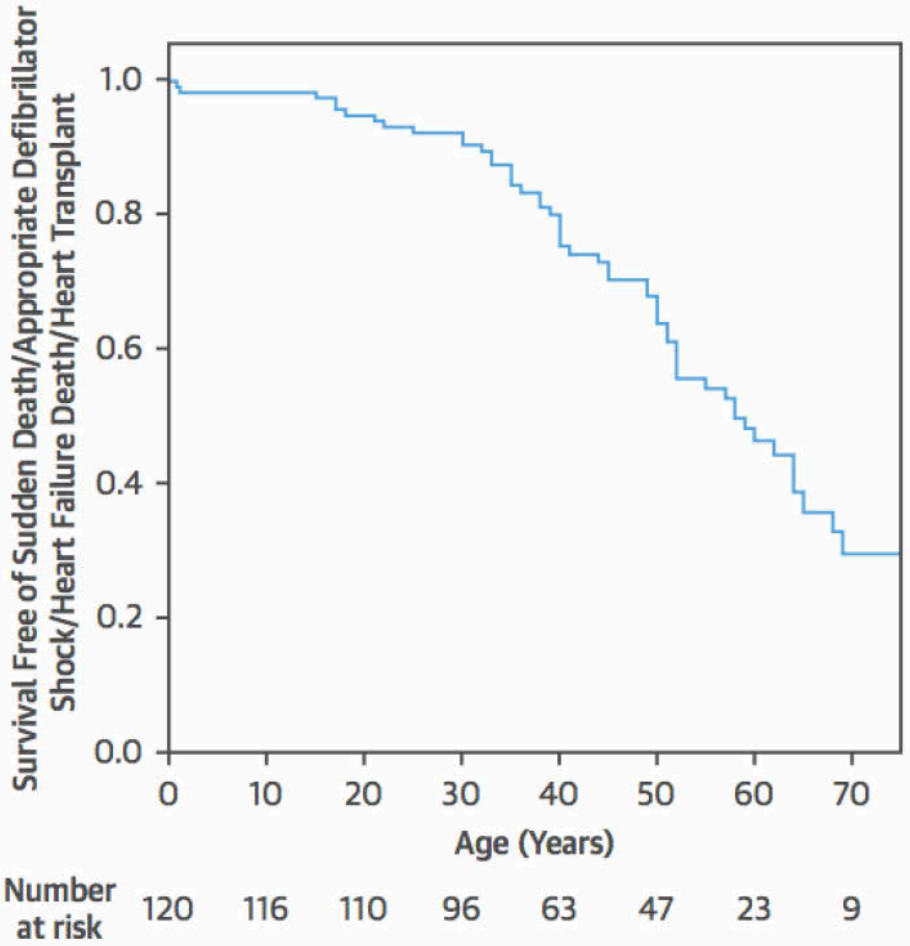
Health in Code. Unpublished data

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 68, NO. 22, 2016

PUBLISHED BY ELSEVIER
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.09.927

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

CONCLUSIONS Truncating mutations in *FLNC* caused an overlapping phenotype of dilated and left-dominant arrhythmogenic cardiomyopathies complicated by frequent premature sudden death. Prompt implantation of a cardiac defibrillator should be considered in affected patients harboring truncating mutations in *FLNC*.
(J Am Coll Cardiol 2016;68:2440-51)



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Section IX – DCM	+/–	–
Section IX – DCM + CCD	++	++
Section X – LVNC	+	–
Section XI – RCM	+	+

Section # – Disease	Diagnostic	Prognostic
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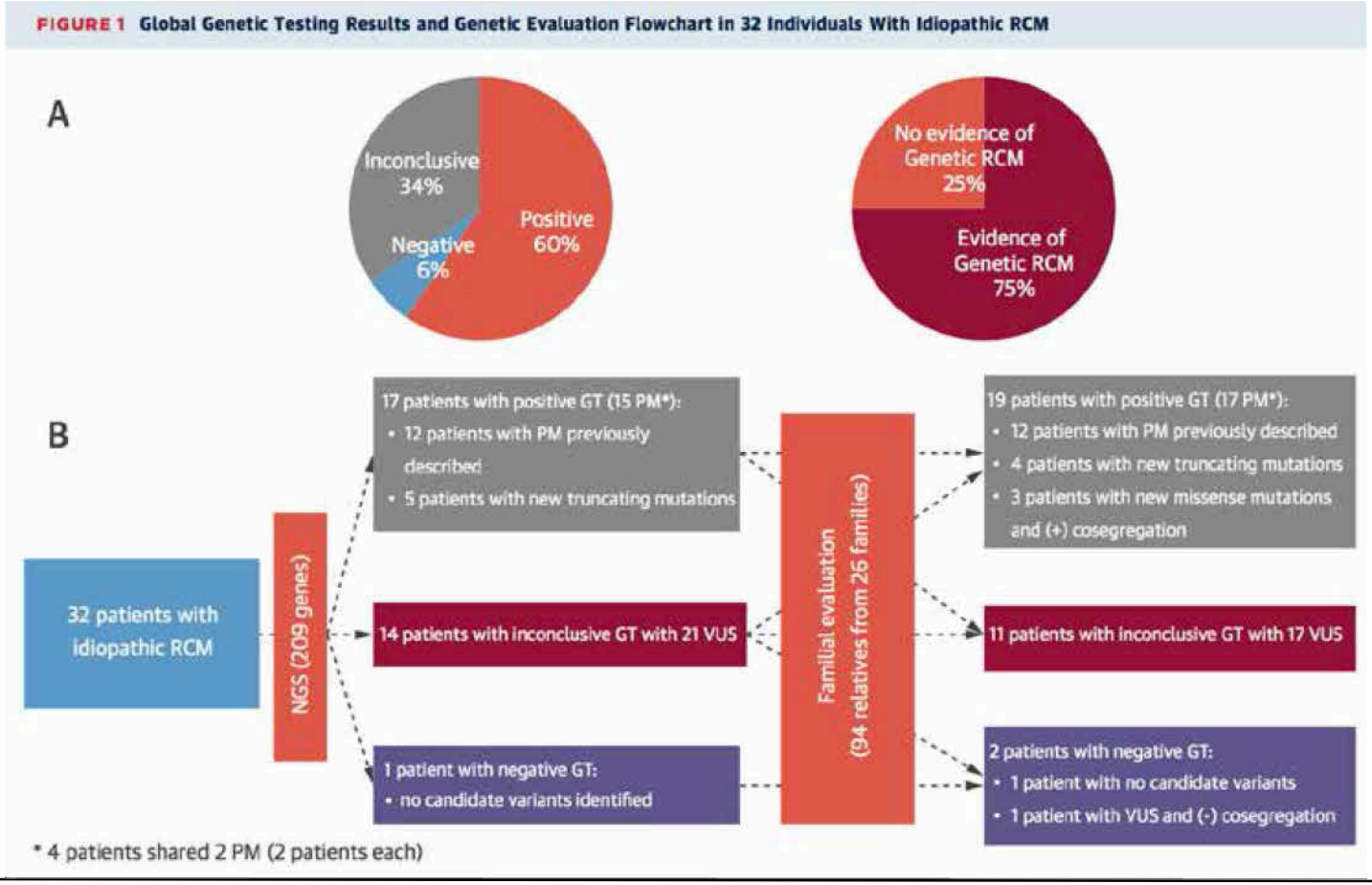
Section VIII – ACM/ARVC	+	+/–
Section IX – DCM	+/–	–
Section IX – DCM + CCD	++	++
Section X – LVNC	+	–
Section XI – RCM	+	+

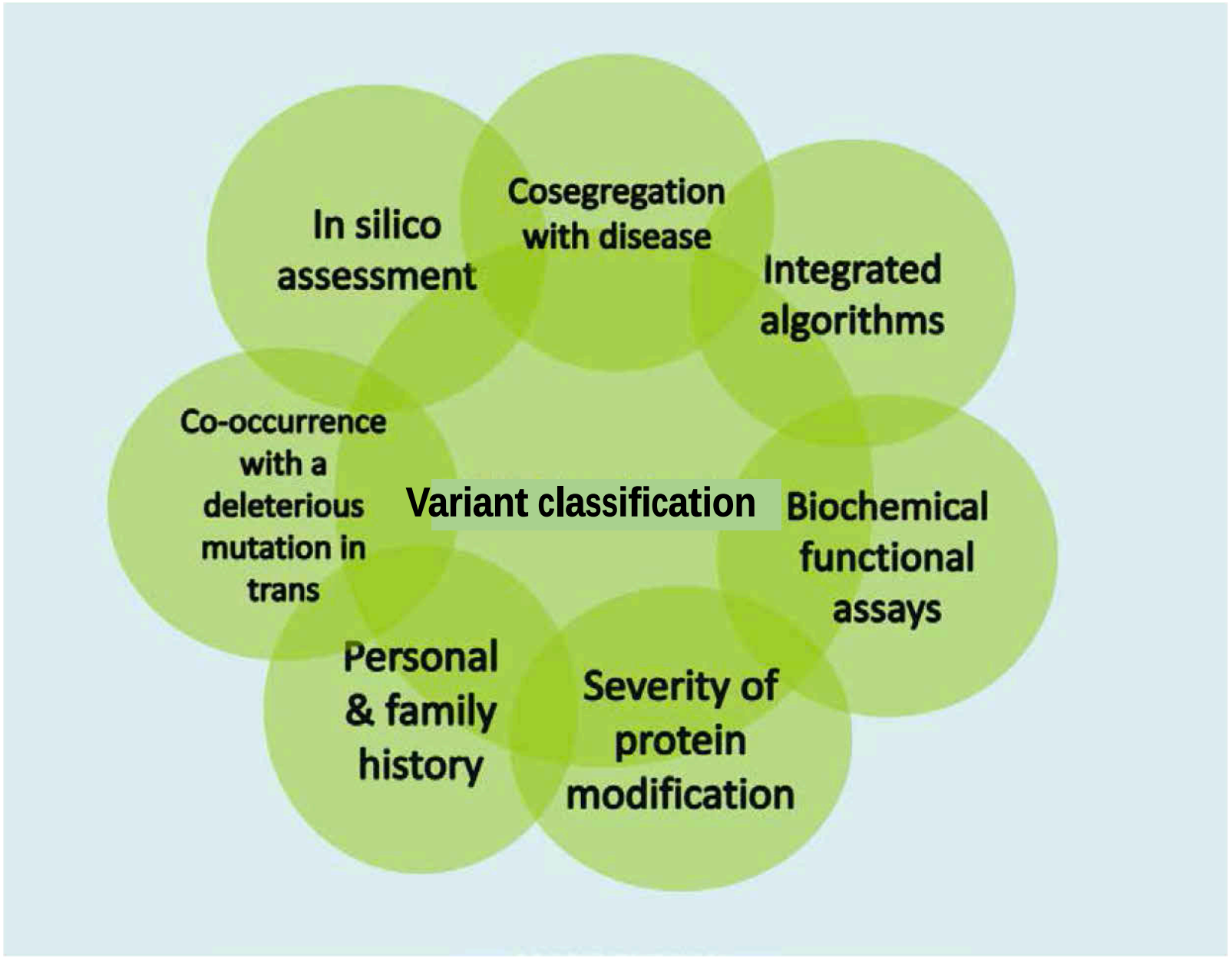
Idiopathic Restrictive Cardiomyopathy Is Primarily a Genetic Disease

FIGURE 1 Global Genetic Testing Results and Genetic Evaluation Flowchart in 32 Individuals With Idiopathic RCM



Gallego-Delgado, et al. J Am Coll Cardiol. 2016

Pedir un estudio genético es muy sencillo...
Lo importante es darle una interpretación


In silico assessment
Cosegregation with disease
Integrated algorithms
Co-occurrence with a deleterious mutation in trans
Variant classification
Biochemical functional assays
Personal & family history
Severity of protein modification

Nephrol Dial Transplant (2008) 23: 4044–4048
doi: 10.1093/ndt/gfn370
Advance Access publication 2 July 2008

Original Article

NDT
Nephrology Dialysis Transplantation

Two-tier approach for the detection of alpha-galactosidase A deficiency in kidney transplant recipients

Gert De Schoenmakere[1,2,*], Bruce Poppe[3,*], Birgitte Wuyts[4], Kathleen Claes[3], David Cassiman[5], Bart Maes[6,2], Dierik Verbeelen[6,7], Raymond Vanholder[1], Dirk R. Kuypers[8], Norbert Lameire[1], Anne De Paepe[3] and Wim Terryn[1,9,*]

278 hombres – 395 mujeres
1 caso (varón) – Ala143Thr

ily members has AFD-related signs or symptoms. Despite the delayed diagnosis, treatment with recombinant human AGALA is planned for the index patient. The results of

Lenders *et al. Orphanet Journal of Rare Diseases* (2016) 11:54
DOI 10.1186/s13023-016-0441-z

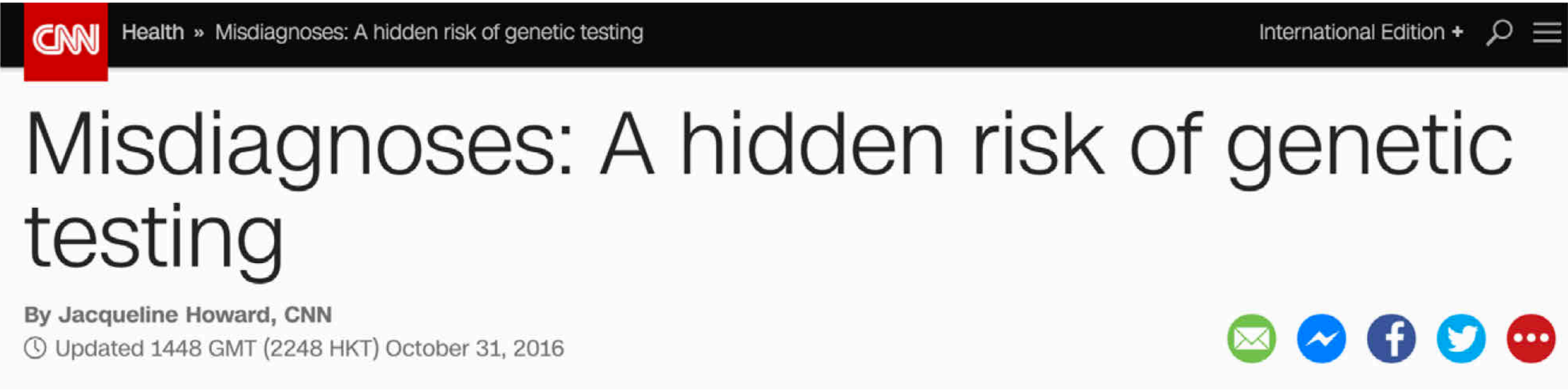
Orphanet Journal of Rare Diseases

RESEARCH

Open Access

Alpha-Galactosidase *A* p.A143T, a non-Fabry disease-causing variant

Malte Lenders[1], Frank Weidemann[2,3], Christine Kurschat[4], Sima Canaan-Kühl[5], Thomas Duning[6], Jörg Stypmann[7], Boris Schmitz[8], Stefanie Reiermann[1], Johannes Krämer[2,9], Daniela Blaschke[10], Christoph Wanner[2], Stefan-Martin Brand[8] and Eva Brand[1*]

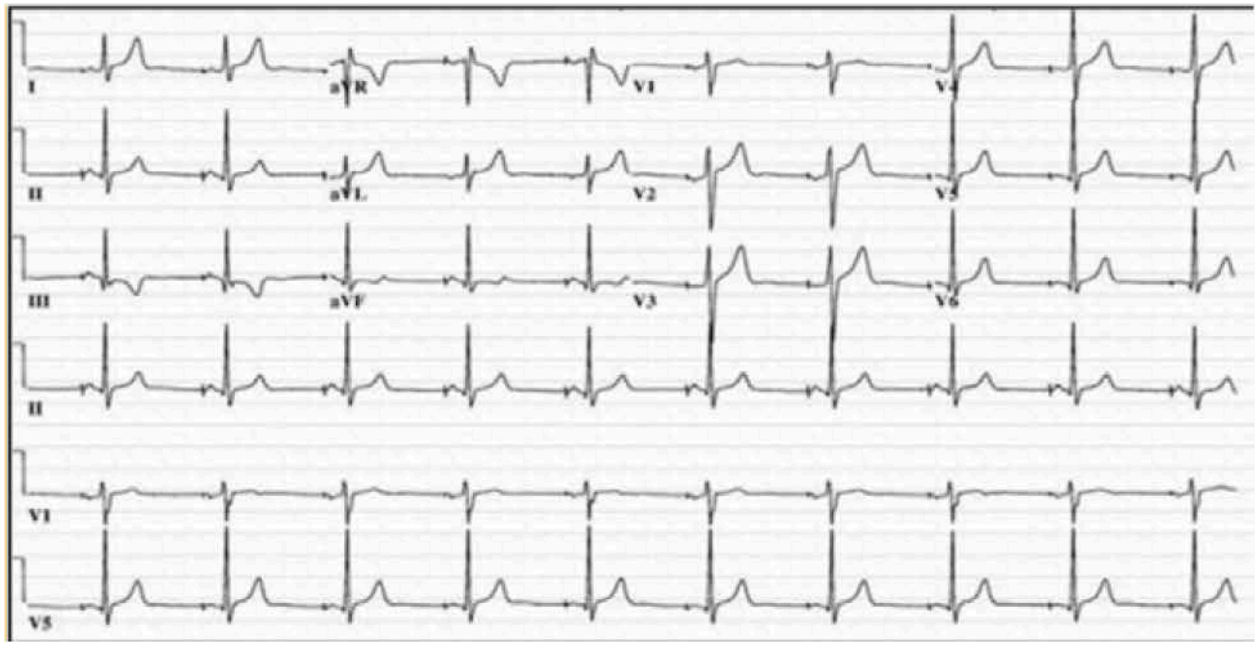

CNN
Health » Misdiagnoses: A hidden risk of genetic testing
International Edition +
Misdiagnoses: A hidden risk of genetic testing
By Jacqueline Howard, CNN
Updated 1448 GMT (2248 HKT) October 31, 2016

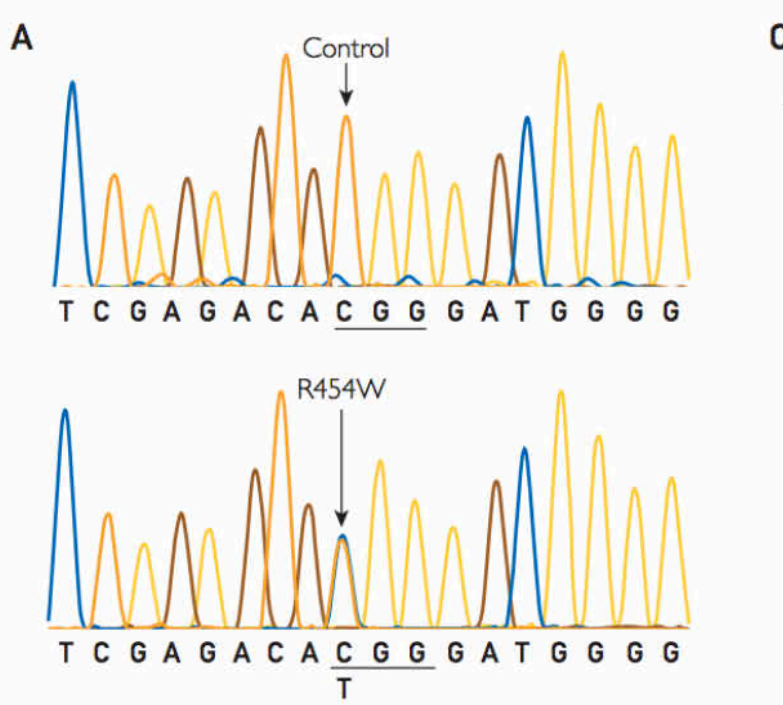
MAYO CLINIC

SPECIAL ARTICLE

The Promise and Peril of Precision Medicine

Jaeger P. Ackerman, BA; Daniel C. Bartos, PhD; Jamie D. Kapplinger, BS;
David J. Tester, BS; Brian P. Delisle, PhD; and Michael J. Ackerman, MD, PhD





C

	Pathogenic: Supporting	Moderate	Strong	Very strong
Population data		Absent in 1000G and ESP	Prevalence in affected individuals statistically significantly increased over controls	
Computational and predictive data	Multiple lines of computational evidence support a deleterious effect on the gene/gene product	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before In-frame INDELs in a nonrepeat region or stop-loss variants	Same amino acid change as an established pathogenic variant	Truncating variant in a gene where LOF is a known mechanism of disease
Functional data	Missense in gene with low rate of benign missense variants and pathogenic missense common		Well-established functional studies show a deleterious effect	
Segregation data	Co-segregation with disease in multiple affected family members	→ Increased segregation data		
***De novo* data**		*De novo* (without paternity and maternity confirmed)	*De novo* (paternity and maternity confirmed)	
Allelic data		For recessive disorders, detected in trans with a pathogenic variant		
Other database	Reputable database = pathogenic			
Other data	Patient's phenotype highly specific for gene			

MAYO CLINIC

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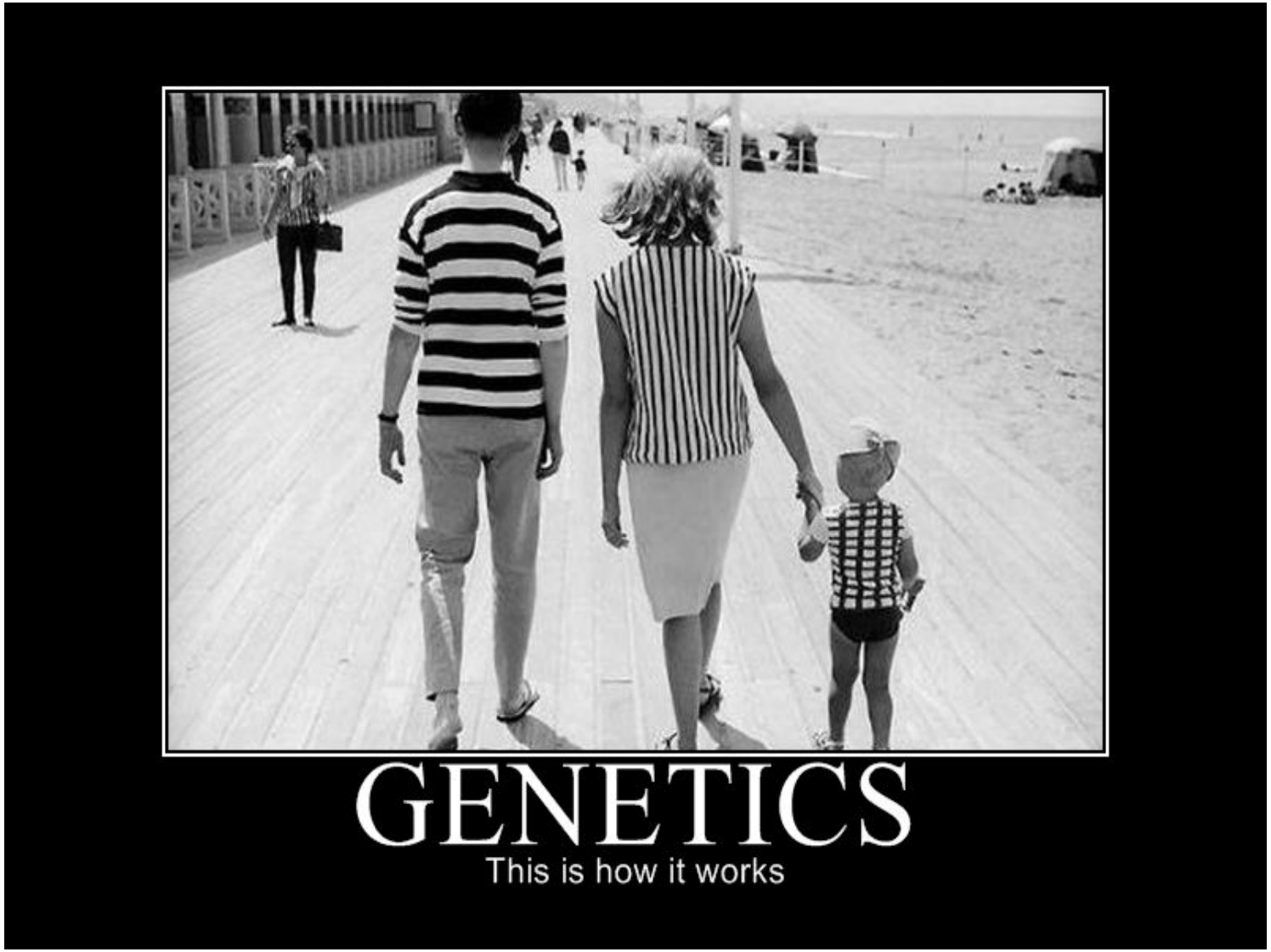
Conclusiones

- **El abordaje genético es mucho más que el estudio genético**
- **El estudio genético es útil a nivel diagnóstico, pronóstico, terapéutico y de aproximación a la familia**
- **La interpretación genética es compleja, requiere un abordaje multidisciplinar y alta especialización**

¡GRACIAS!



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