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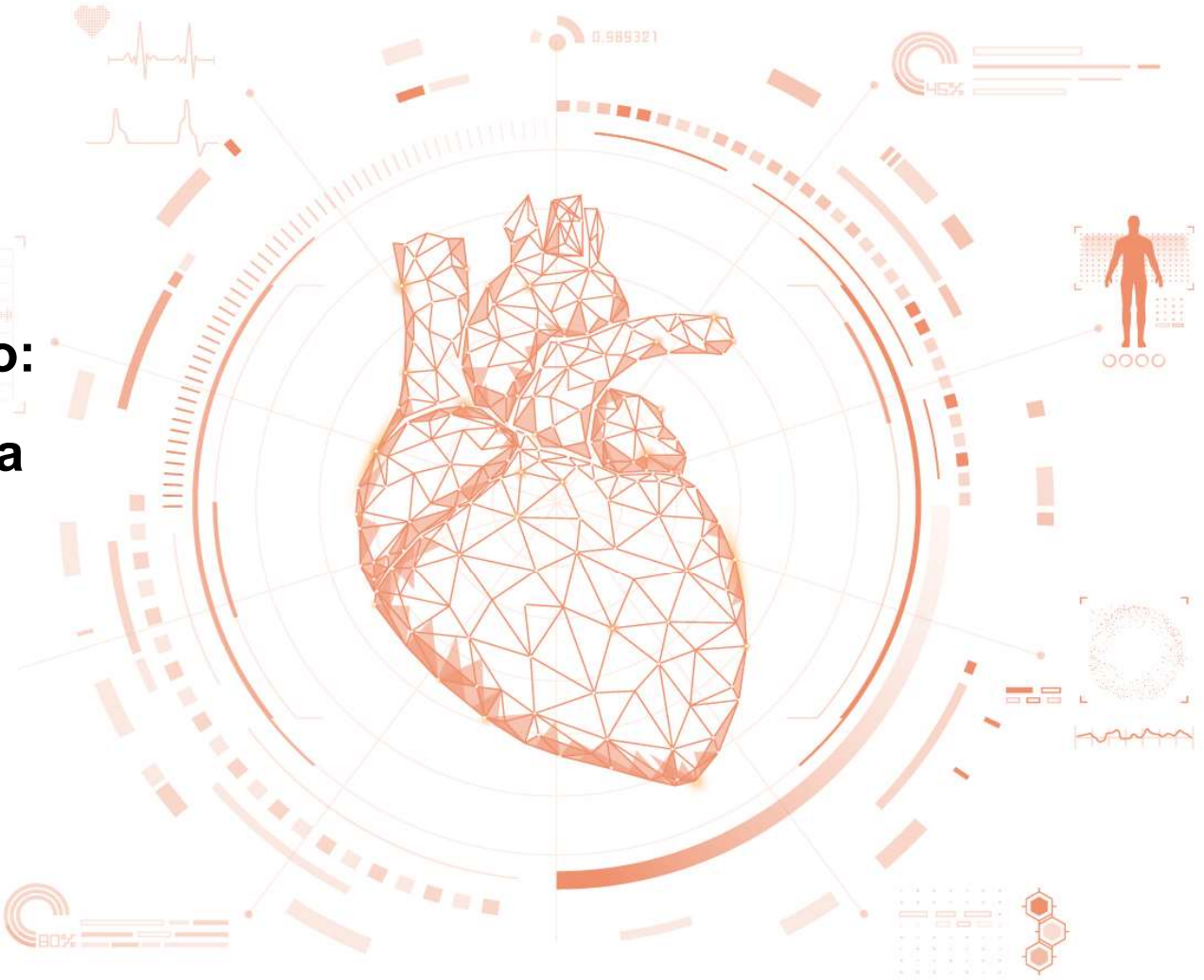
Genética para el cardiólogo clínico: Cardiopatías en las que la genética nos cambiará su manejo

Dr. Tomás Ripoll Vera
Unidad de Cardiopatías Familiares
Hospital Universitario Son Llatzer
Palma de Mallorca

Formación online en actualizaciones en Cardiología

Genética para el cardiólogo clínico: Cardiopatías en las que la genética nos cambiará su manejo



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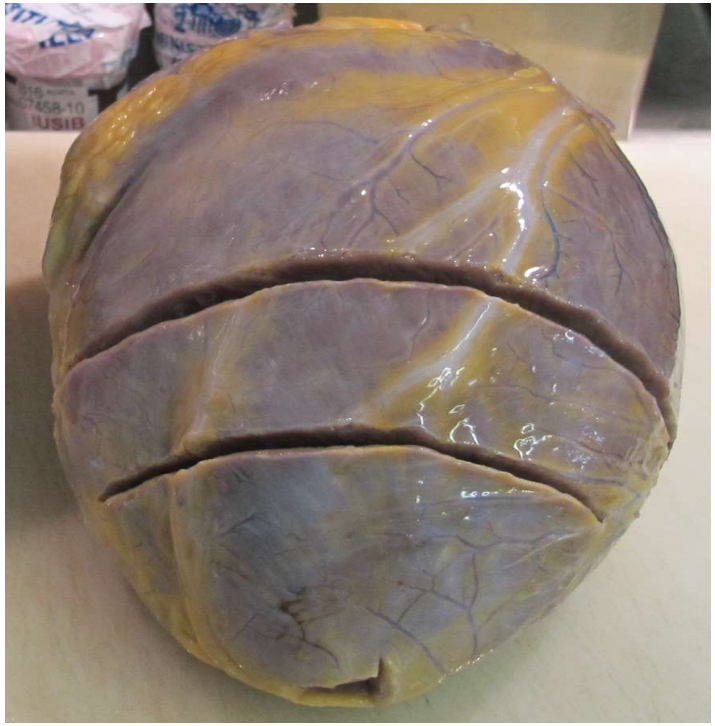
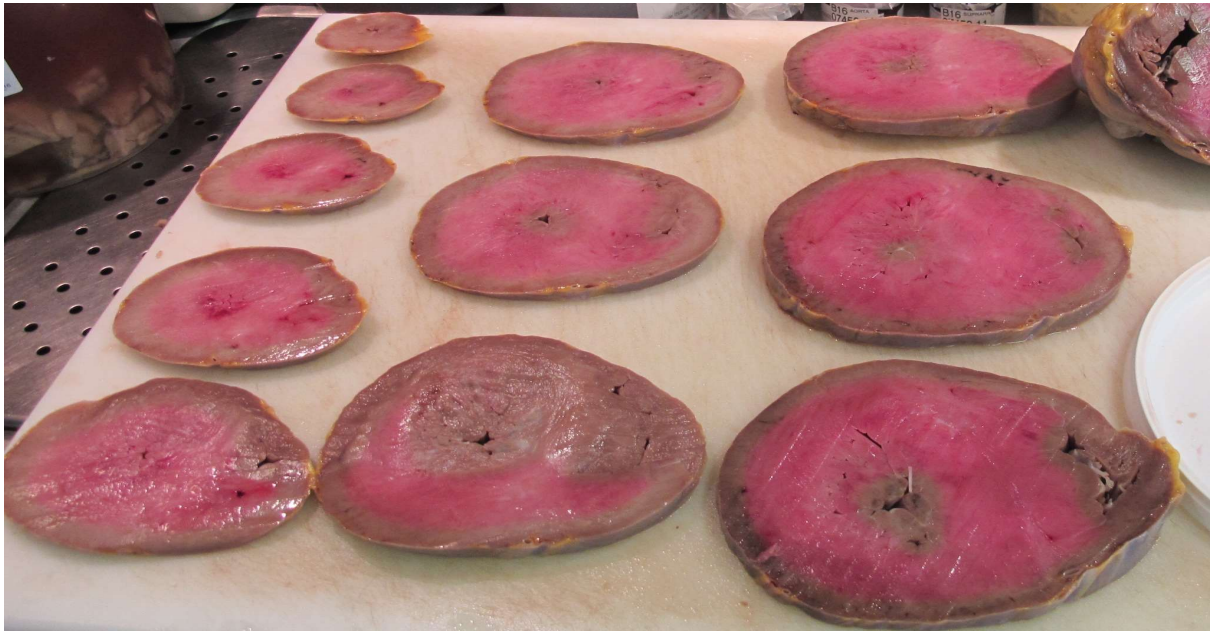
¿Cómo la genética nos cambia el manejo en la Miocardiopatía hipertrófica?





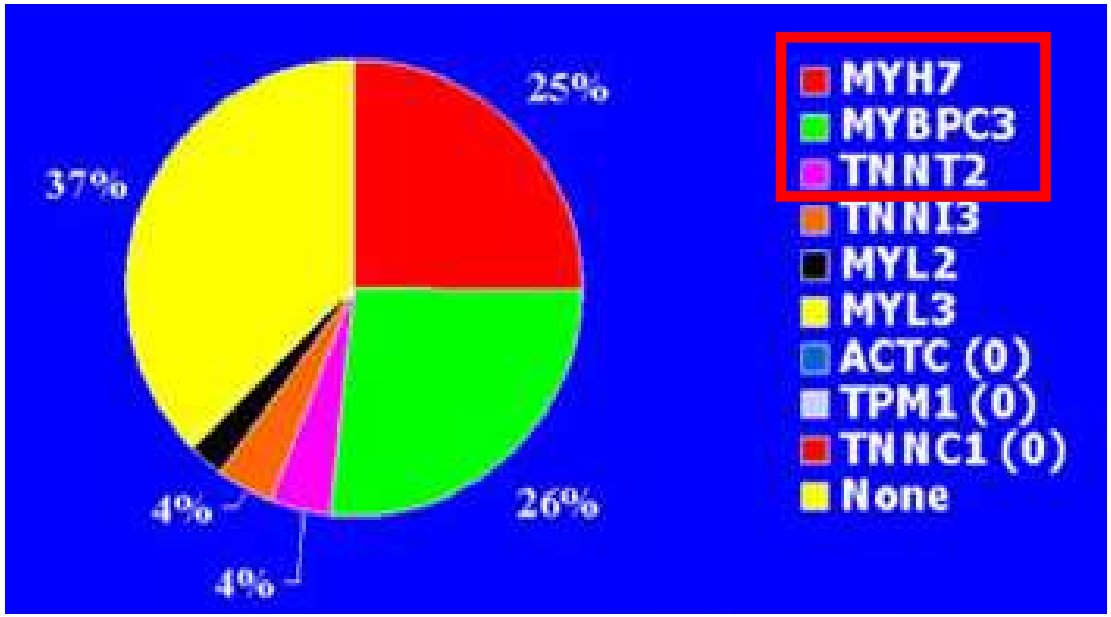
Indicación del estudio genético

Tabla 2
Recomendaciones y nivel de evidencia de los estudios genéticos en las guías y los documentos de consenso publicados

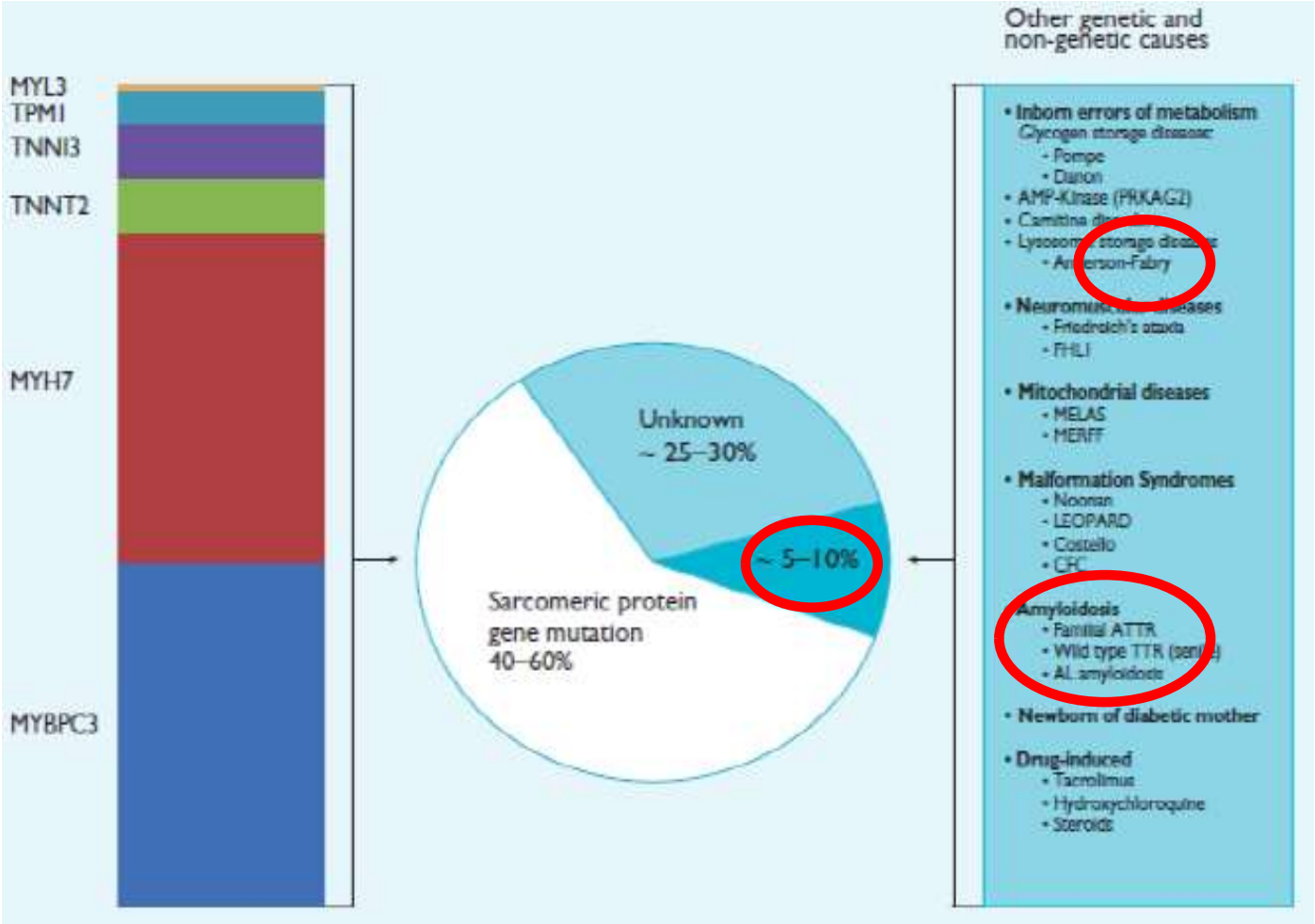
Estudio genético	Nivel de recomendación[a]
Miocardiopatía hipertrófica (Elliott et al[2], Ackerman et al[4])	I
	I
Miocardiopatía dilatada (Ackerman et al[4])	I[b]
	IIa[c]
Miocardiopatía restrictiva (Ackerman et al[4])	IIb
Miocardiopatía no compactada (Ackerman et al[4])	IIa
Miocardiopatía arritmogénica (Ackerman et al[4])	IIa (incluido en los criterios diagnósticos)
Síndrome de Brugada (Ackerman et al[4])	IIa
Taquicardia ventricular polimórfica catecolaminérgica (Ackerman et al[4])	I (incluido en los criterios diagnósticos)
Síndrome de QT largo (Ackerman et al[4])	I (incluido en los criterios diagnósticos)
Síndrome de QT corto (Ackerman et al[4])	IIb (incluido en los criterios diagnósticos)
Síndrome de Marfan (Loeys et al[5])	Incluido en los criterios diagnósticos
Síndrome de Loeys-Dietz (Arslan-Kirchner et al[6])	Incluido en los criterios diagnósticos

Barriales-Villa R et al. Rev Esp Cardiol. 2016;69(3):300–309

MUTACIONES EN GENES SARCOMÉRICOS EN 197 MCH



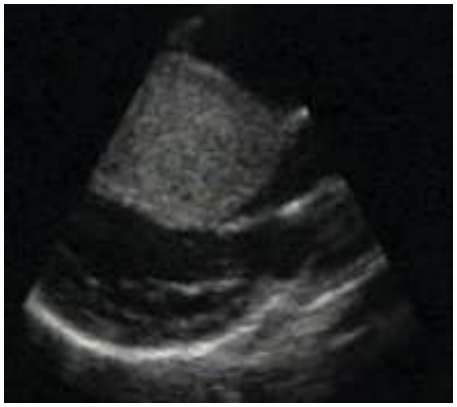
Richard P et al. Circulation 2003



Authors/Task Force members et al. Eur Heart J 2014;35:2733-2779

Mutación en MHY7 (β-Miosina)

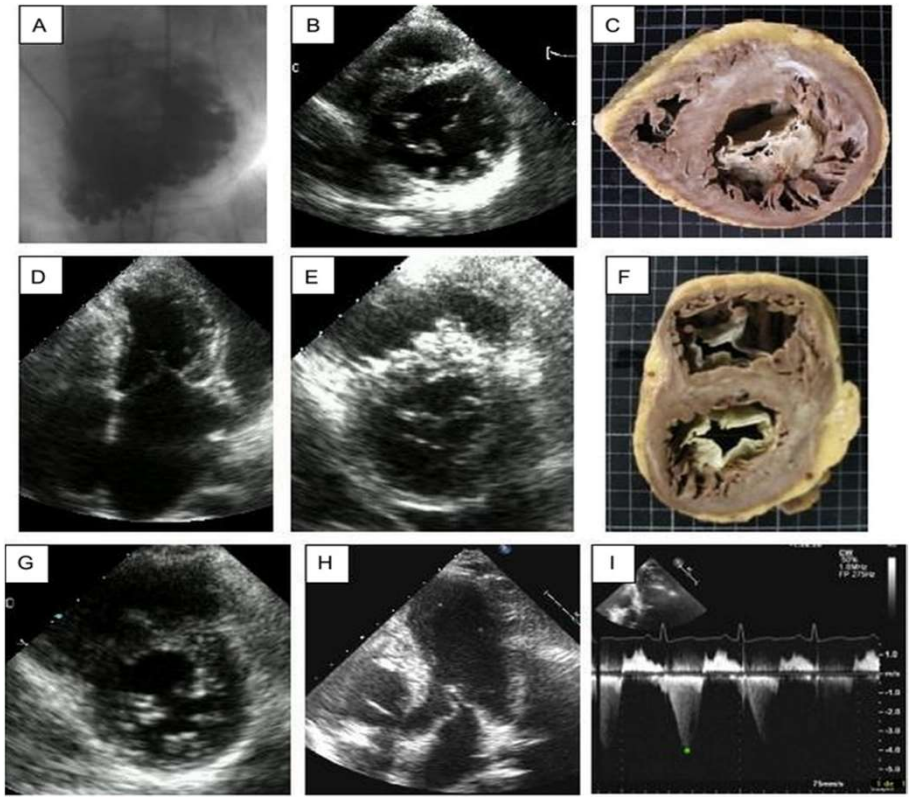
- 15-30%
- HVI severas,
- a edad temprana (adolescencia),
- fenotipo más maligno → peor pronóstico
- Mayor penetrancia → > casos familiares

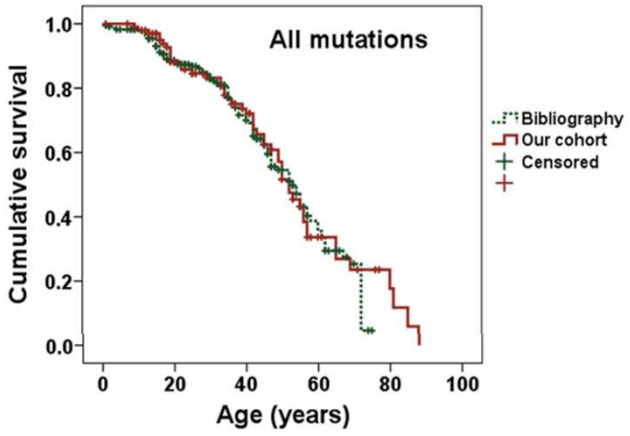


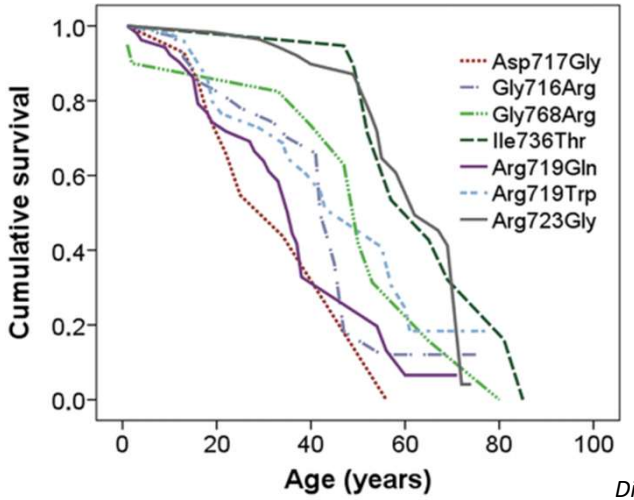
Richard 2003. Van Driest 2004

Pronóstico

MYH7







Diego García et al. Heart 2015

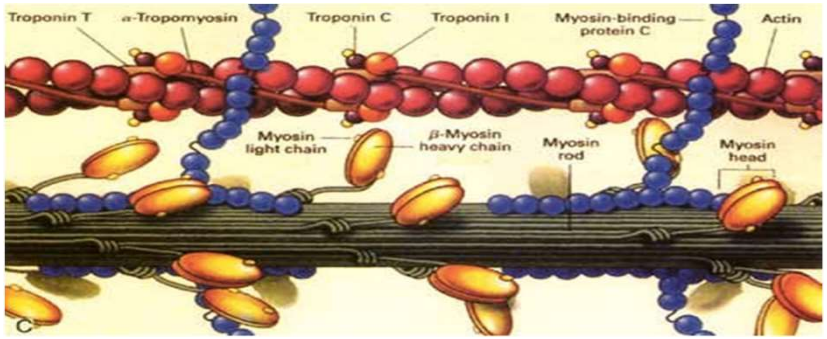
Mutación en MYBPC3
(Prot C de unión a la Miosina)

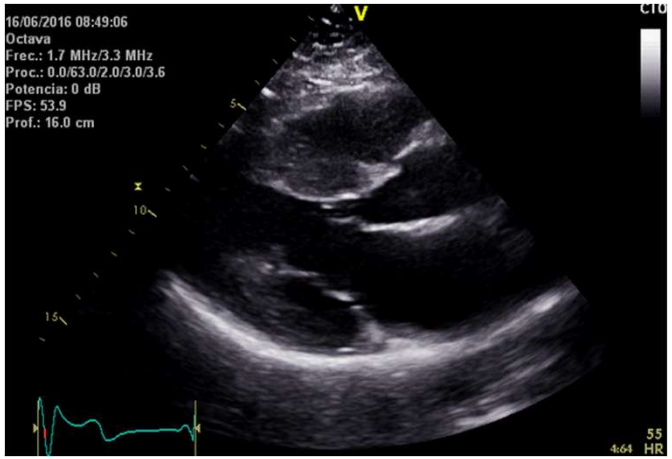
- 15-30%
- HVI moderadas,
- Bajo riesgo de MS
- Penetrancia depende de la edad. Más frecuente a edades tardías.
- >% de casos esporádicos

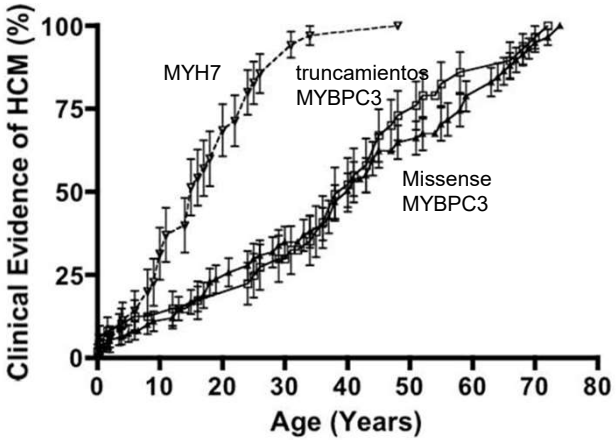
Wolfgang-M F. Lancet 2001; 358:1627

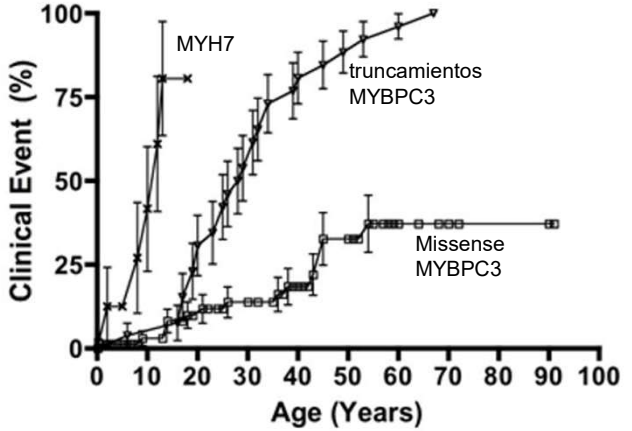
Pronóstico

MYBPC3









Landstrom AP et al. Circulation 2010;122:2441-45

Mutación en TNNT2

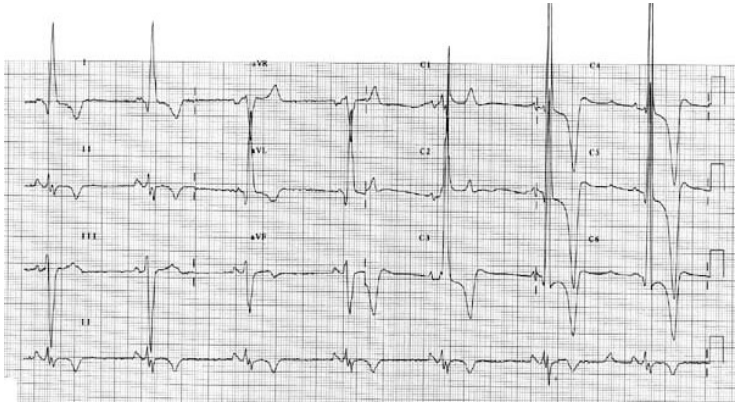
(Troponina T)

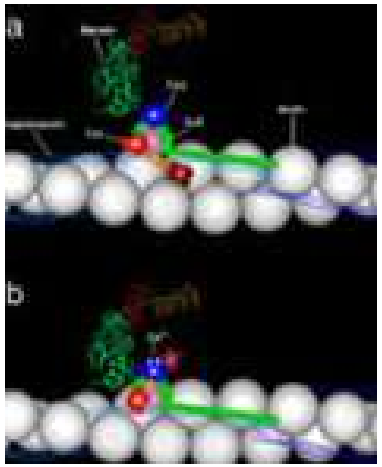
- ≈ 5%

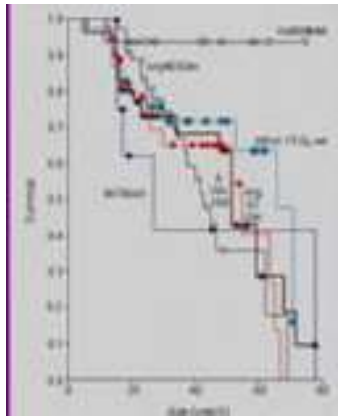
- HVI moderadas ó leves (incluso ausente)….más “disarray”

- Mal pronóstico por alto riesgo de MS (incluso en ausencia de HVI)

- Expresión en adolescencia.



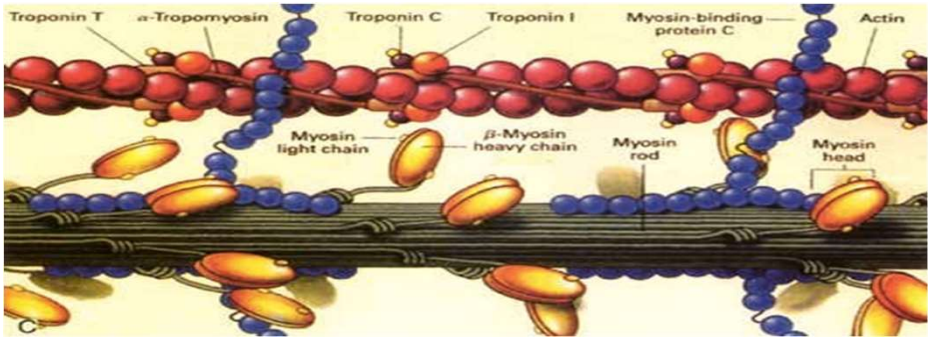


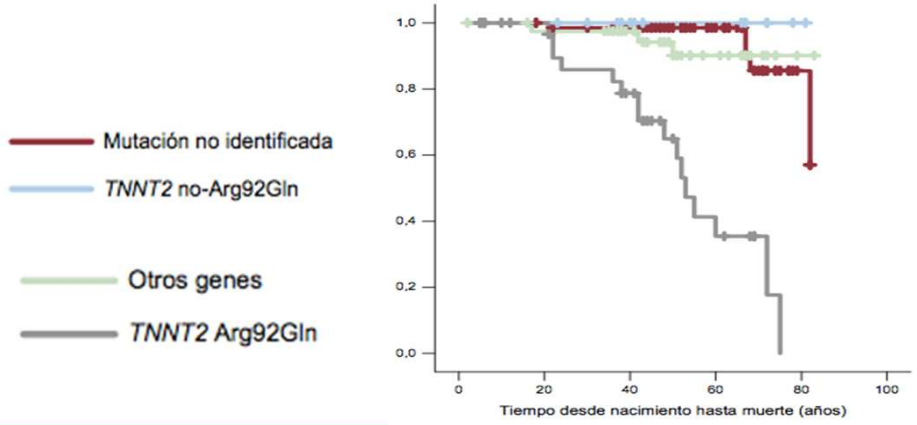


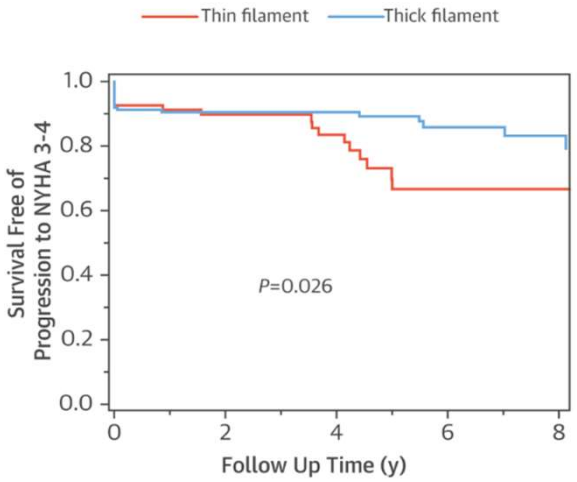
Watkins et al. NEJM 1995

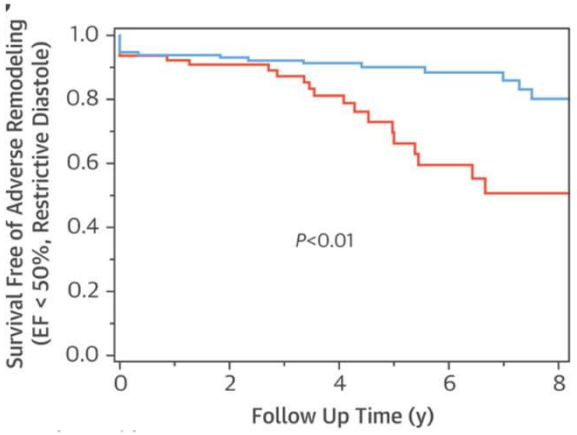
Pronóstico

TNNT2









Ripoll-Vera T et al, Rev Esp Cardiol 2016

Rev Esp Cardiol. 2016;69(2):149–158

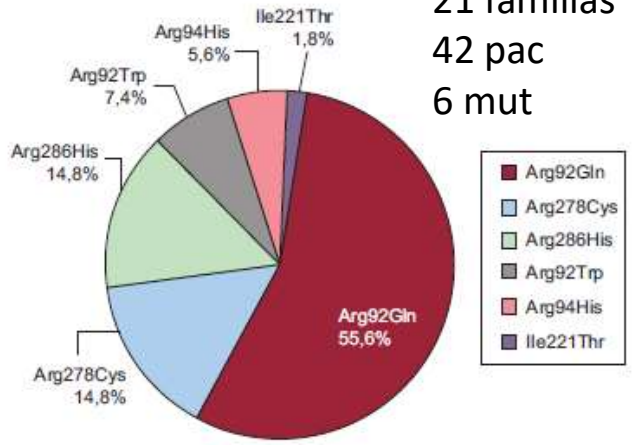
Original article

Clinical and Prognostic Profiles of Cardiomyopathies Caused by Mutations in the Troponin T Gene

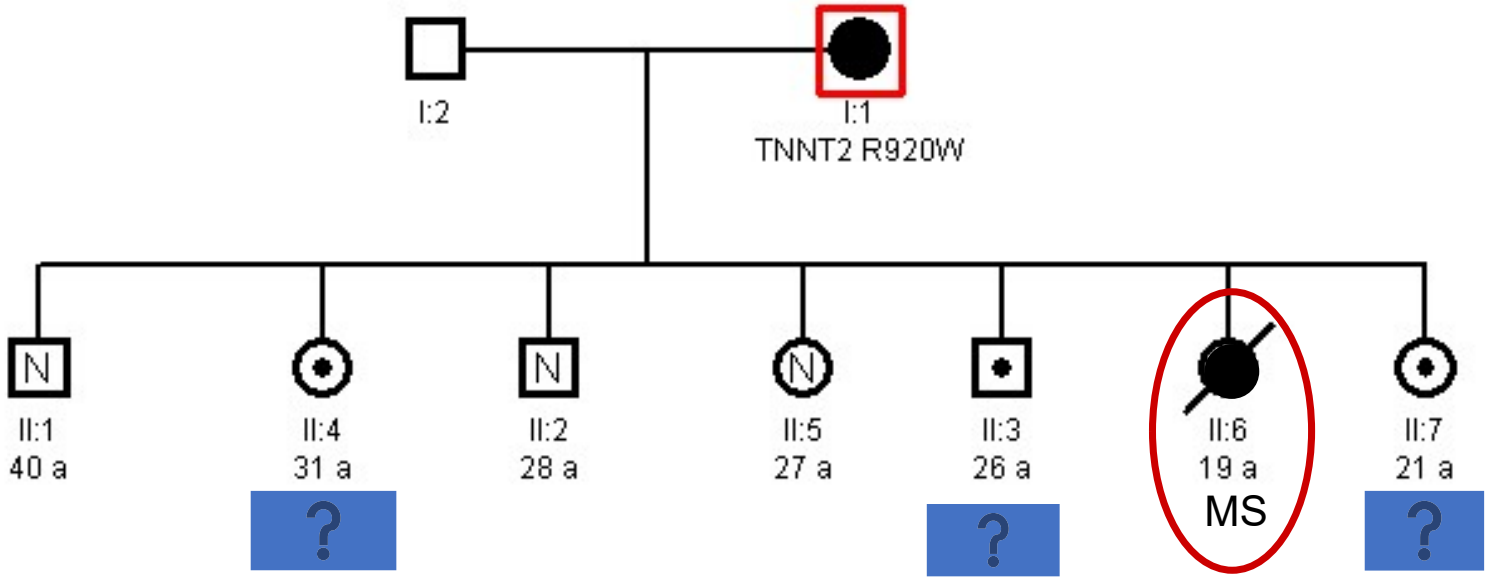
Tomás Ripoll-Vera,[a,*] José María Gámez,[a] Nancy Govea,[b] Yolanda Gómez,[a] Juana Núñez,[a] Lorenzo Socías,[a] Ángela Escandell,[a] and Jorge Rosell[b]

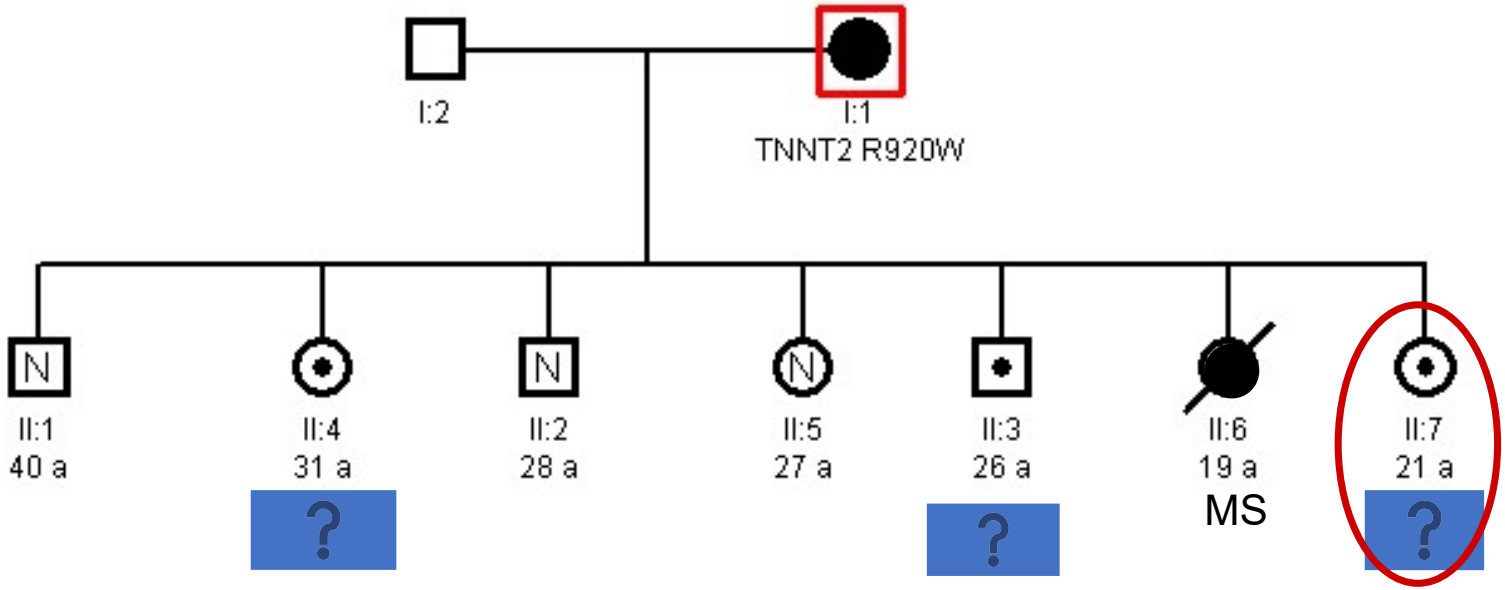
[a] Servicio de Cardiología, Hospital Son Llàtzer, IdISPa, Ciberobn, Palma de Mallorca, Balearic Islands, Spain
[b] Sección de Genética, Hospital Son Espases, Palma de Mallorca, Balearic Islands, Spain

21 familias
42 pac
6 mut



- 10 familias R92Q
- 54 pacientes.


I:2
I:1
TNNT2 R920W
N
II:1
40 a
II:4
31 a
?
N
II:2
28 a
N
II:5
27 a
II:3
26 a
?
II:6
19 a
MS
II:7
21 a
?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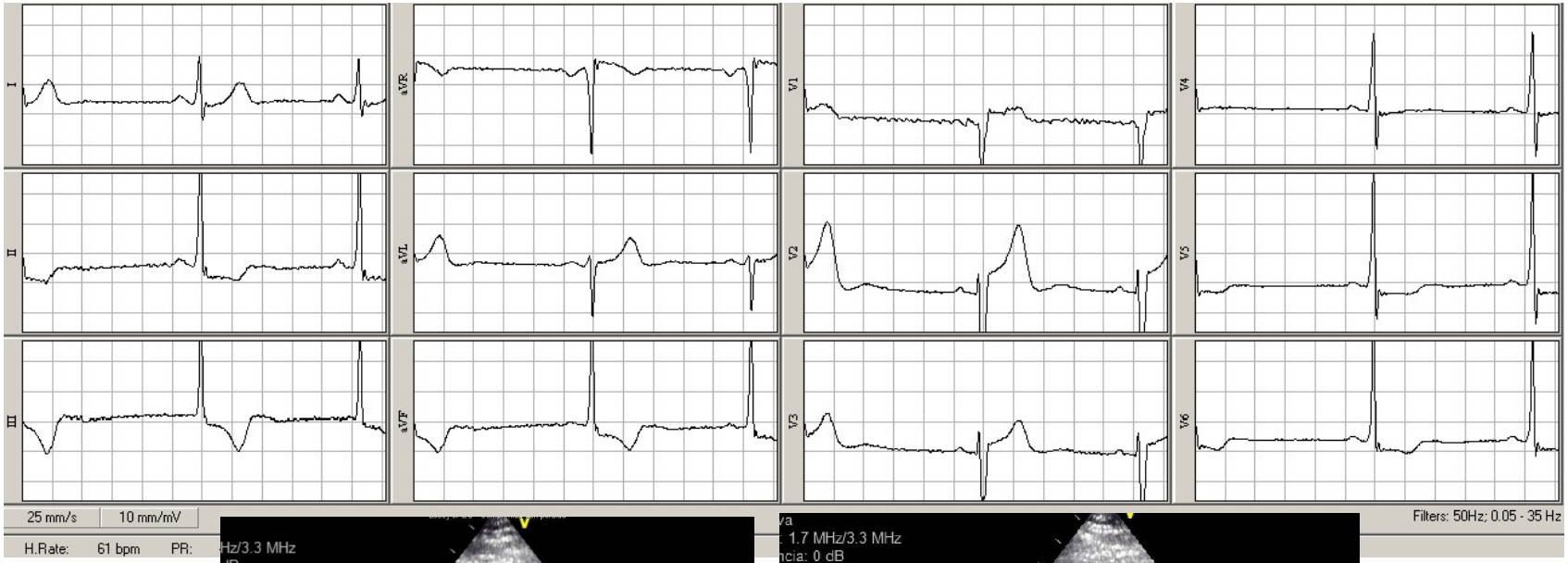
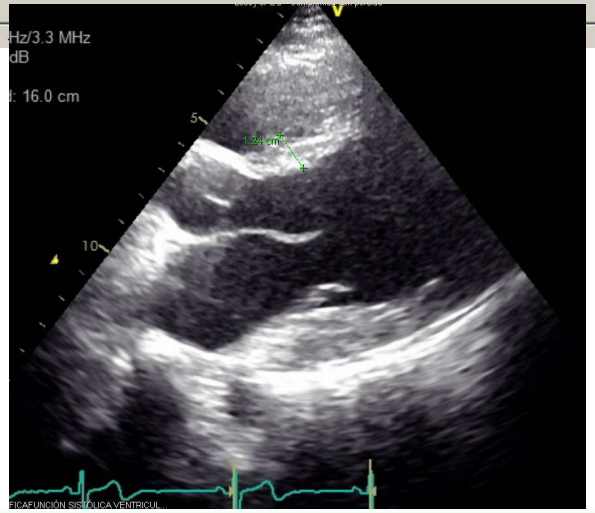
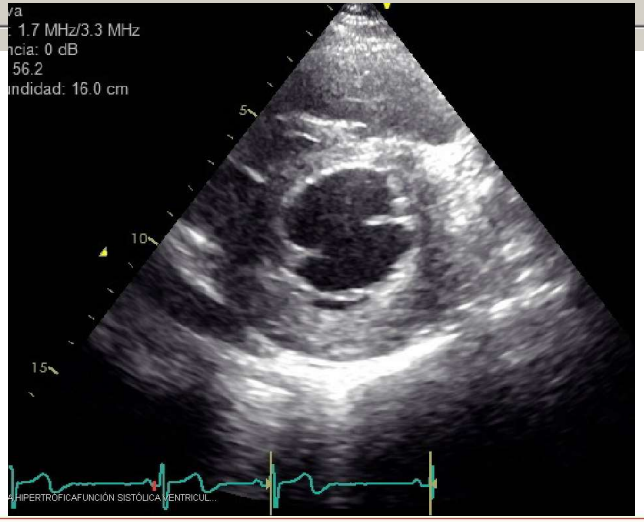
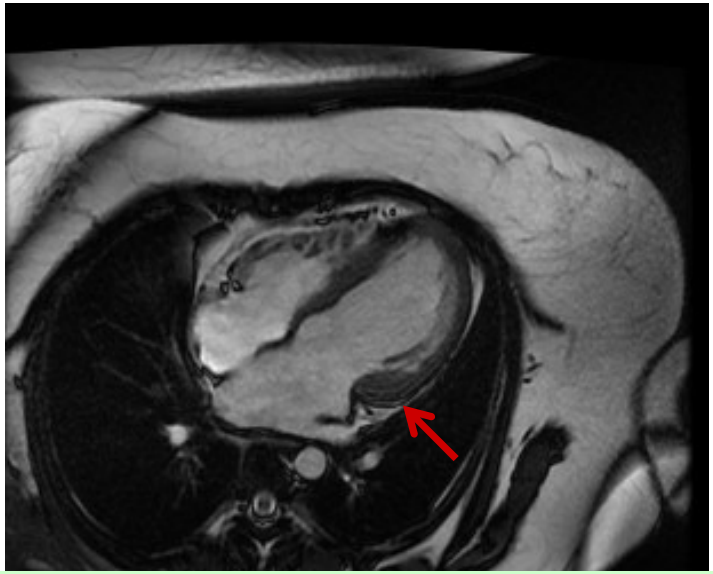
II:6
19 a
MS
II:7
21 a
?

Mujer de 21 años

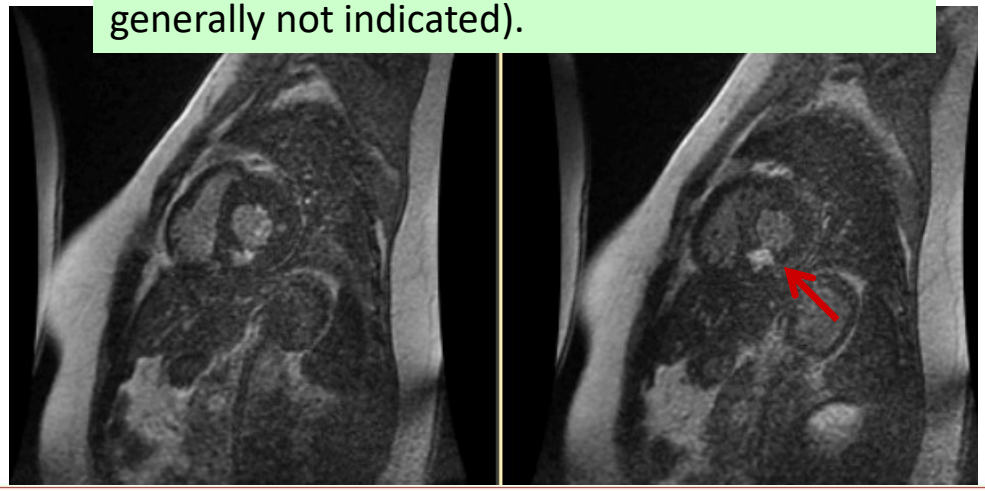




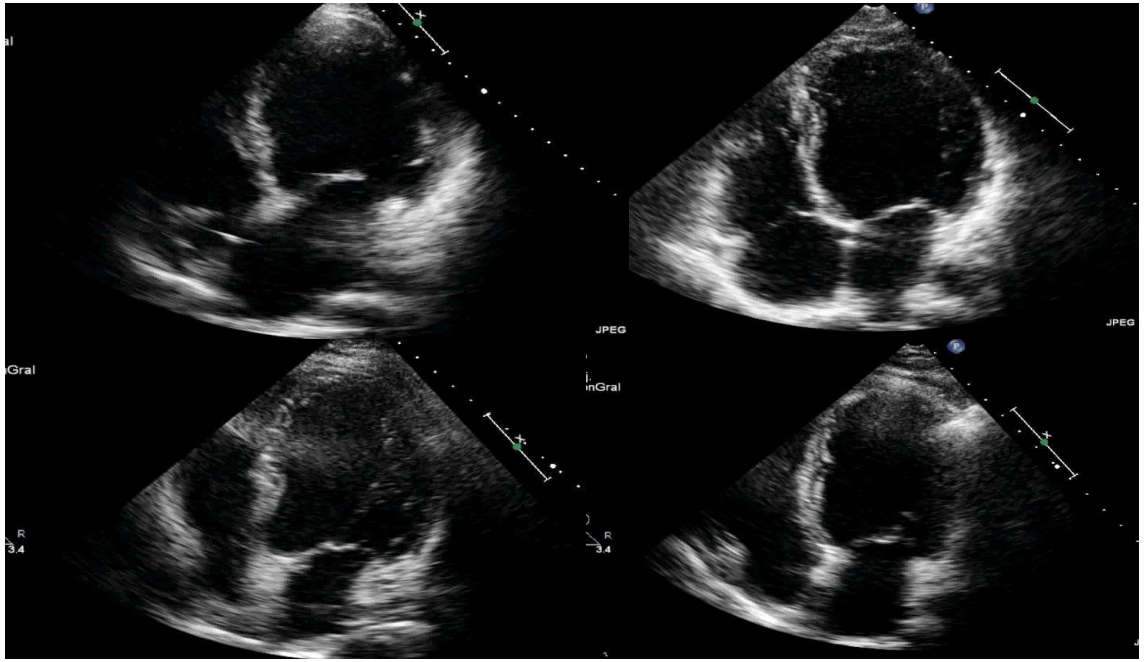




Risk score ESC (SCD at 5 years): 3.04 % (ICD generally not indicated).



¿Cómo la genética nos cambia el manejo en la Miocardiopatía dilatada?



Indicación del estudio genético

Tabla 2
Recomendaciones y nivel de evidencia de los estudios genéticos en las guías y los documentos de consenso publicados

Estudio genético	Nivel de recomendación[a]
Miocardiopatía hipertrófica (Elliott et al[2], Ackerman et al[4])	I
	I
Miocardiopatía dilatada (Ackerman et al[4])	I[b]
	IIa[c]
Miocardiopatía restrictiva (Ackerman et al[4])	IIb
Miocardiopatía no compactada (Ackerman et al[4])	IIa
Miocardiopatía arritmogénica (Ackerman et al[4])	IIa (incluido en los criterios diagnósticos)
Síndrome de Brugada (Ackerman et al[4])	IIa
Taquicardia ventricular polimórfica catecolaminérgica (Ackerman et al[4])	I (incluido en los criterios diagnósticos)
Síndrome de QT largo (Ackerman et al[4])	I (incluido en los criterios diagnósticos)
Síndrome de QT corto (Ackerman et al[4])	IIb (incluido en los criterios diagnósticos)
Síndrome de Marfan (Loeys et al[5])	Incluido en los criterios diagnósticos
Síndrome de Loeys-Dietz (Arslan-Kirchner et al[6])	Incluido en los criterios diagnósticos

Barriales-Villa R et al. Rev Esp Cardiol. 2016;69(3):300–309

¿Cuándo hacer estudio genético en MCD?

Europace (2011) 13, 1077–1109
doi:10.1093/europace/eur245

HRS/EHRA EXPERT CONSENSUS STATEMENT

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

STATE OF GENETIC TESTING FOR DILATED CARDIOMYOPATHY (DCM)	
Class I (is recommended)	Comprehensive or targeted (*LMNA* and *SCN5A*) DCM genetic testing **is recommended** for patients with DCM **and** significant cardiac conduction disease (i.e. first, second, or third degree heart block) and/or a family history of premature unexpected sudden death.
	Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case.
Class IIa (can be useful)	Genetic testing **can be useful** for patients with **familial** DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.

MCD con trastornos de conducción (bloqueo AV de 1º,2º ó 3º grado)

MCD con algún familiar con MS prematura

MCD familiar

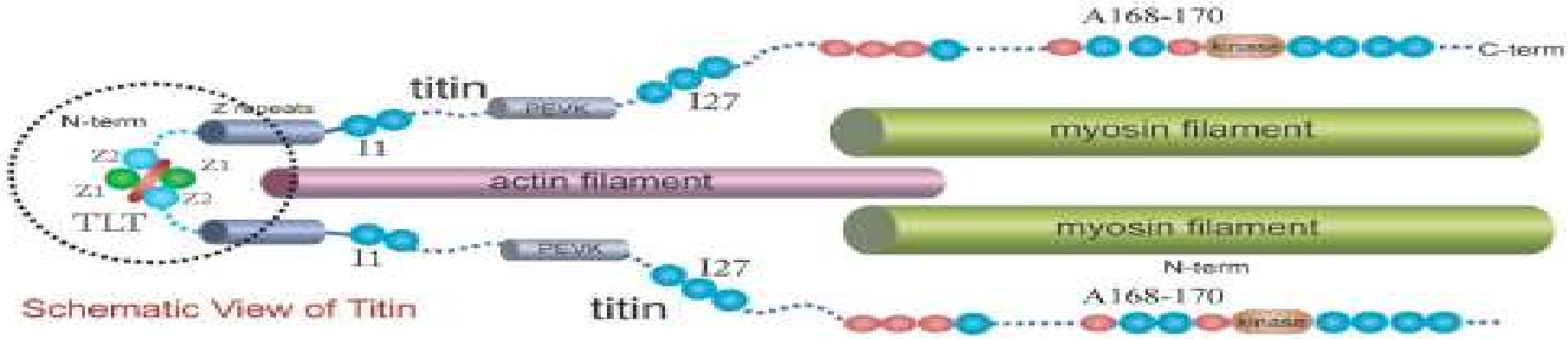
Ackerman MJ et al. Europace 2011

MIOCARDIOPATIA DILATADA isquémica VS no isquémica o idiopática:

- Genética → 50%
- Taquimiocardiopatía
- Enfermedades de depósito
- Enfermedades infecciosas: virus, Chagas…
- Tóxicos: alcohol, ~~cocaína~~ → **10% genética**
- QT: antraciclinas, trastuzumab, doxorrubicina, ciclofosfamida, imatinib… → **7,5% genética**
- Miocarditis
- Déficits nutricionales: selenio
- Enfermedades autoinmunes: LES, sarcoidosis
- Enfermedades endocrinológicas (tiroides, feocromocitoma)
- Miocardiopatía periparto → **10% genética**

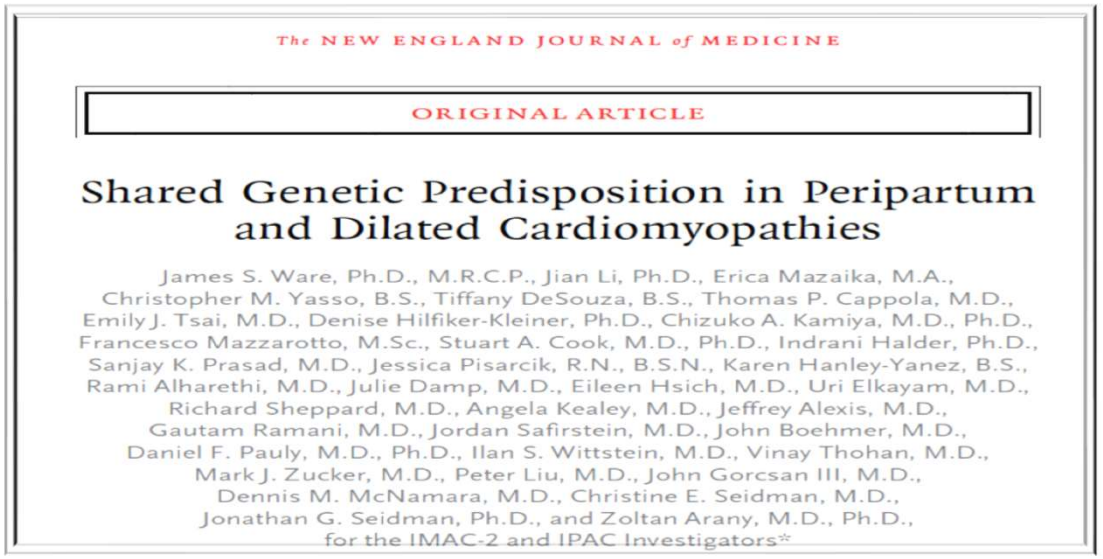
MUTACIONES EN TITINA (TTN)

- TTN, el gen que codifica la proteína Titina del sarcómero, se había analizado poco en miocardiopatías debido a su enorme tamaño.
- Causa más frecuente de MCD (25% en casos familiares y 18% en casos esporádicos).
- Alta penetrancia.
- Mutaciones missense muy frecuentes y en general NO patogénicas.



Hermann DS et al. NEJM 2012;366:7

Mutaciones TTNtv muy frecuentes en M. PERIPARTO



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies

James S. Ware, Ph.D., M.R.C.P., Jian Li, Ph.D., Erica Mazaika, M.A., Christopher M. Yasso, B.S., Tiffany DeSouza, B.S., Thomas P. Cappola, M.D., Emily J. Tsai, M.D., Denise Hilfiker-Kleiner, Ph.D., Chizuko A. Kamiya, M.D., Ph.D., Francesco Mazzarotto, M.Sc., Stuart A. Cook, M.D., Ph.D., Indrani Halder, Ph.D., Sanjay K. Prasad, M.D., Jessica Pisarcik, R.N., B.S.N., Karen Hanley-Yanez, B.S., Rami Alharethi, M.D., Julie Damp, M.D., Eileen Hsich, M.D., Uri Elkayam, M.D., Richard Sheppard, M.D., Angela Kealey, M.D., Jeffrey Alexis, M.D., Gautam Ramani, M.D., Jordan Safirstein, M.D., John Boehmer, M.D., Daniel F. Pauly, M.D., Ph.D., Ilan S. Wittstein, M.D., Vinay Thohan, M.D., Mark J. Zucker, M.D., Peter Liu, M.D., John Gorcsan III, M.D., Dennis M. McNamara, M.D., Christine E. Seidman, M.D., Jonathan G. Seidman, Ph.D., and Zoltan Arany, M.D., Ph.D., for the IMAC-2 and IPAC Investigators*

CONCLUSIONS

The distribution of truncating variants in a large series of women with peripartum cardiomyopathy was remarkably similar to that found in patients with idiopathic dilated cardiomyopathy. *TTN* truncating variants were the most prevalent genetic predisposition in each disorder.

Ware JS et al; NEJM 2016

TTN truncating variants - 2nd hit cardiomyopathies

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Genetic Etiology for Alcohol-Induced Cardiac Toxicity

James S. Ware, MRCP, PhD,[a,b,c,*] Almudena Amor-Salamanca, MD,[d,*] Upasana Tayal, MRCP, PhD,[a,b,*] Risha Govind, MSc,[a,b,e,*] Isabel Serrano, MD,[f] Joel Salazar-Mendiguchía, MD,[g,h] Jose Manuel García-Pinilla, MD, PhD,[i,j] Domingo A. Pascual-Figal, MD, PhD,[i,k] Julio Nuñez, MD, PhD,[i,j] Gonzalo Guzzo-Merello, MD, PhD,[d] Emiliano Gonzalez-Vioque, PhD,[m] Alfredo Bardaji, MD, PhD,[f] Nicolas Manito, MD, PhD,[g] Miguel A. López-Garrido, MD,[i,j] Laura Padron-Barthe, PhD,[d,i] Elizabeth Edwards, PhD,[a,b] Nicola Whiffin, PhD,[a,b,c] Roddy Walsh, MSc, PhD,[a,b] Rachel J. Buchan, MSc,[a,b] William Midwinter, BSc,[a,b] Alicja Wilk, BSc,[a,b] Sanjay Prasad, MD,[a,b] Antonis Pantazis, MD,[b] John Baski, MRCP, PhD,[b] Declan P. O'Regan, MRCP, PhD,[c] Luis Alonso-Pulpon, MD, PhD,[d,i] Stuart A. Cook, MRCP, PhD,[a,c,n,o] Enrique Lara-Pezzi, PhD,[i,p] Paul J. Barton, PhD,[a,b,*] Pablo Garcia-Pavia, MD, PhD[d,i,q,*]

10% of patients with ACM present TTNtv

DCM +TTNtv + excessive alcohol

- more prone to **decline in LVEF** than those who drink less or lack these genetic variants

Ware et al. JACC 2018

Circulation

ORIGINAL RESEARCH ARTICLE

Genetic Variants Associated With Cancer Therapy–Induced Cardiomyopathy

BACKGROUND: Cancer therapy–induced cardiomyopathy (CCM) is associated with cumulative drug exposures and preexisting cardiovascular disorders. These parameters incompletely account for substantial interindividual susceptibility to CCM. We hypothesized that rare variants in cardiomyopathy genes contribute to CCM.

Pablo Garcia-Pavia, MD, PhD*
Yuri Kim, MD, PhD*
Maria Alejandra Restrepo-Cordoba, MD*

7.5% of patients with CCM present TTNtv
(vs. 1.1% in reference cancer population)

CCM +TTNtv

- more AF, HF and impaired myocardial recovery compared to CCM without TTNtv

Garcia-Pavia et al. Circulation 2019

LAMINOPATÍAS (*LMNA*)

Miocardiopatía Dilatada

- ***Dilatación ventricular izquierda (VI) leve***
- ***Disfunción sistólica VI severa → Trasplante cardiaco***
- ***Trastornos de la conducción A-V frecuentes → Marcapasos/DAI***
- ***Afectación de músculo esquelético variable***

Distrofia muscular AR Emery-Dreifuss

Distrofia muscular de cinturas AD

Neuropatía axonal Charcot-Marie-Tooth tipo 2
Lipodistrofia familiar parcial
Progreria de Hutchinson-Gilford

Metaanálisis de 299 pac con Mutaciones en LMNA

Table 2 Age and mode of death of patients with *LMNA* mutation leading to Emery-Dreifuss or limb girdle muscular dystrophy (with muscular dystrophy) or dilated cardiomyopathy (without muscular dystrophy)

	Muscular dystrophy	No muscular dystrophy	All patients
No of patients died	44	32	76
Age at death (years)	45	59	46
Sudden death	19	16	35
With pacemaker	6	10	16
Without pacemaker	13	6	19
Due to heart failure	5	4	9
With pacemaker	1	2	3
Without pacemaker	4	2	6
unclassified death	20	12	32
With pacemaker	10	3	13
Without pacemaker	10	9	19

Van Berlo JH, et al. J Mol Med 2005;83:79-83.

Primary Prevention of Sudden Death in Patients with Lamin A/C Gene Mutations

19 patients LMNA + conduction defects

↓

Offered an ICD instead of PCM

↓

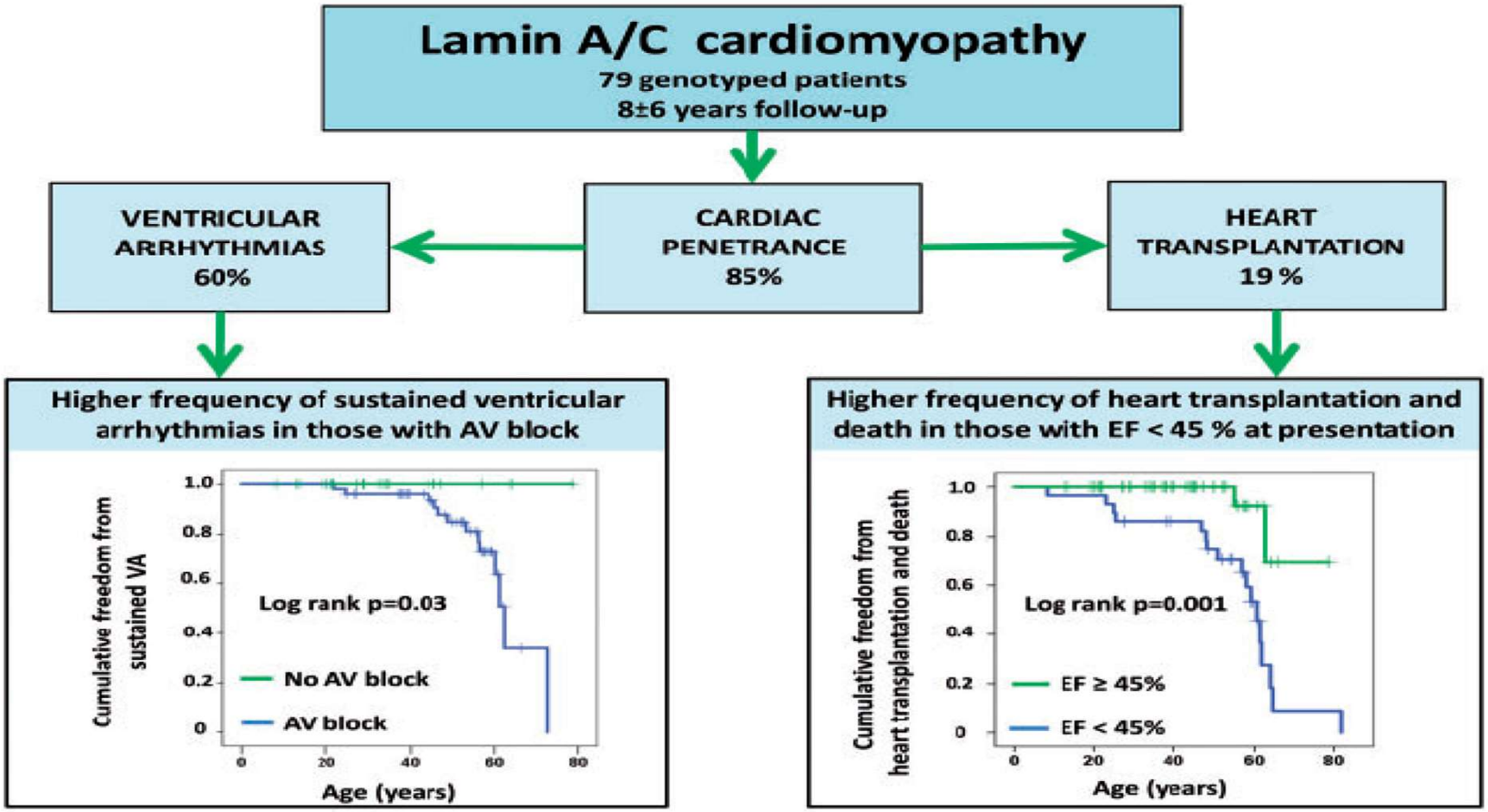
FU 34 months

↓

8 (42%) had appropiate ICD therapy

In conclusion, ICD implantation in patients with a lamin A/C mutation who are in need of a pacemaker is effective in treating possibly lethal tachyarrhythmias. The implantation of an ICD, rather than a pacemaker, should be considered for these patients.

Meune et al. NEJM 2006;354:209-10.



Hasselberg NE et al EHJ 2017

LMNA

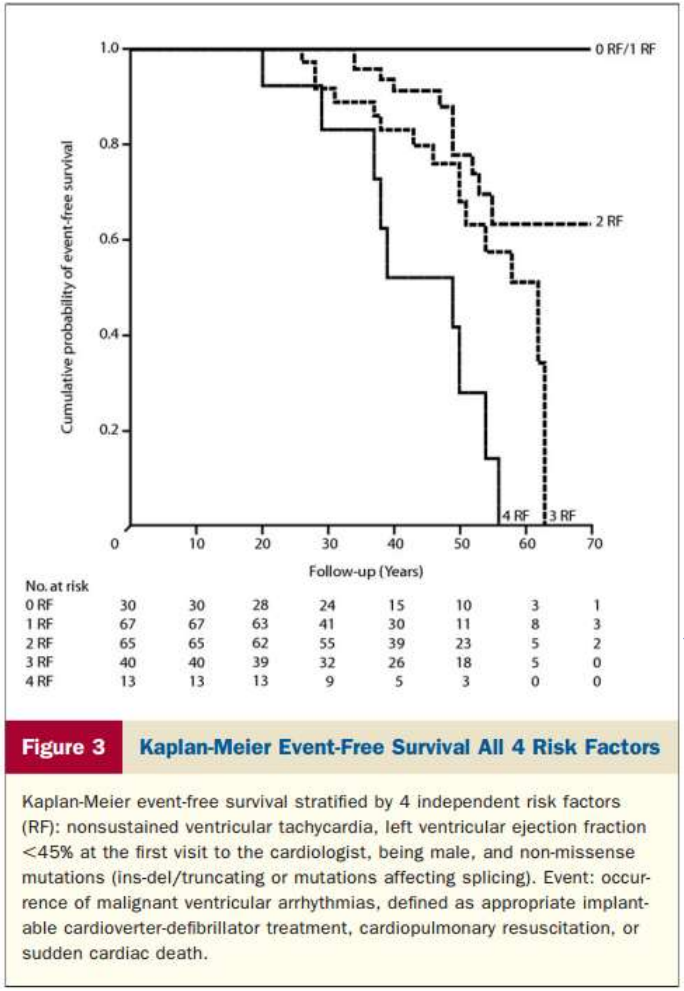


Figure 3 **Kaplan-Meier Event-Free Survival All 4 Risk Factors**

Kaplan-Meier event-free survival stratified by 4 independent risk factors (RF): nonsustained ventricular tachycardia, left ventricular ejection fraction <45% at the first visit to the cardiologist, being male, and non-missense mutations (ins-del/truncating or mutations affecting splicing). Event: occurrence of malignant ventricular arrhythmias, defined as appropriate implantable cardioverter-defibrillator treatment, cardiopulmonary resuscitation, or sudden cardiac death.

van Rijsingen IAW, JACC 2012

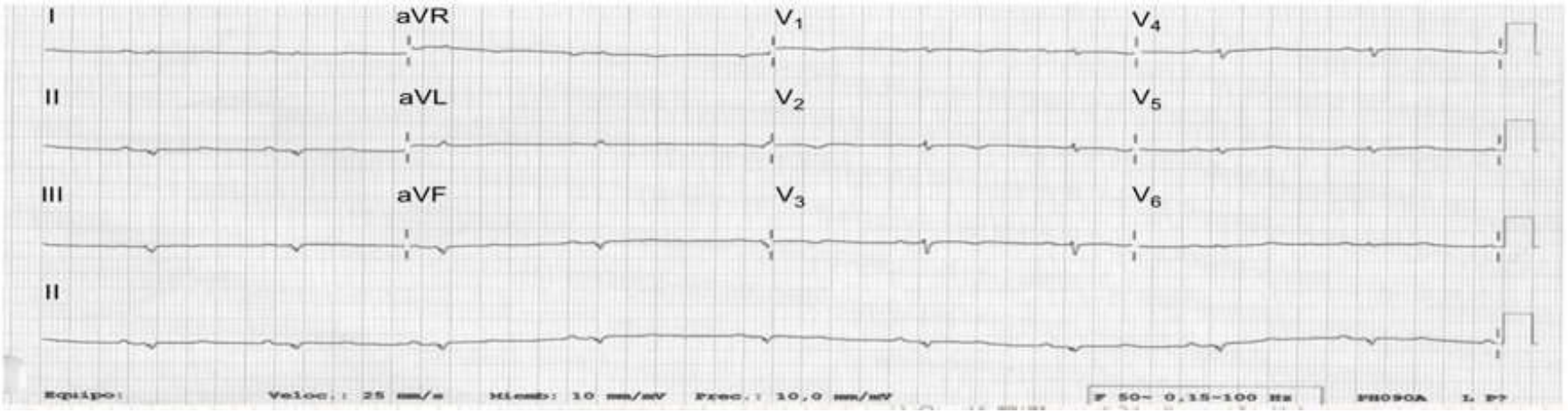
Recommendations	Class[a]	Level[b]	Ref.[c]
Optimal medical therapy (ACE inhibitors, beta-blockers and MRA) is recommended in patients with DCM to reduce the risk of sudden death and progressive HF.	I	A	8
Prompt identification and treatment of arrhythmogenic factors (e.g. pro-arrhythmic drugs, hypokalaemia) and co-morbidities (e.g. thyroid disease) is recommended in patients with DCM and VA.	I	C	8
A coronary angiography is recommended in stable DCM patients with an intermediate risk of CAD and new onset VA.	I	B	8
An ICD is recommended in patients with DCM and haemodynamically not tolerated VT/VF, who are expected to survive for >1 year with good functional status.	I	A	151–154
An ICD is recommended in patients with DCM, symptomatic HF (NYHA class II–III) and an ejection fraction ≤35% despite ≥3 months of treatment with optimal pharmacological therapy who are expected to survive for >1 year with good functional status.	I	B	64, 313, 316, 317, 354
Catheter ablation is recommended in patients with DCM and bundle branch re-entry ventricular tachycardia refractory to medical therapy.	I	B	8,208, 345, 346
An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.[d]	IIa	B	71
Amiodarone should be considered in patients with an ICD that experience recurrent appropriate shocks in spite of optimal device programming.	IIa	C	229
Catheter ablation may be considered in patients with DCM and VA not caused by bundle branch re-entry refractory to medical therapy.	IIb	C	355
Invasive EPS with PVS may be considered for risk stratification of SCD.	IIb	B	115
Amiodarone is not recommended for the treatment of asymptomatic NSVT in patients with DCM.	III	A	313, 354
Use of sodium channel blockers and dronedarone to treat VA is not recommended in patients with DCM.	III	A	129, 356, 357

ESC guidelines 2015

GEN PHOSPHOLAMBAN (PLN)

PLN es esencial para la contracción miocárdica. Función reguladora de la homeostasis del calcio.

- Mal pronóstico
- Se asocia con MCD y MS…considerar DAI !!



Ceholski DK. J Biol Chem 2012
Ha KN. Proc Natl Acad Sci USA 2011

GEN FILAMINA C (*FLNC*)

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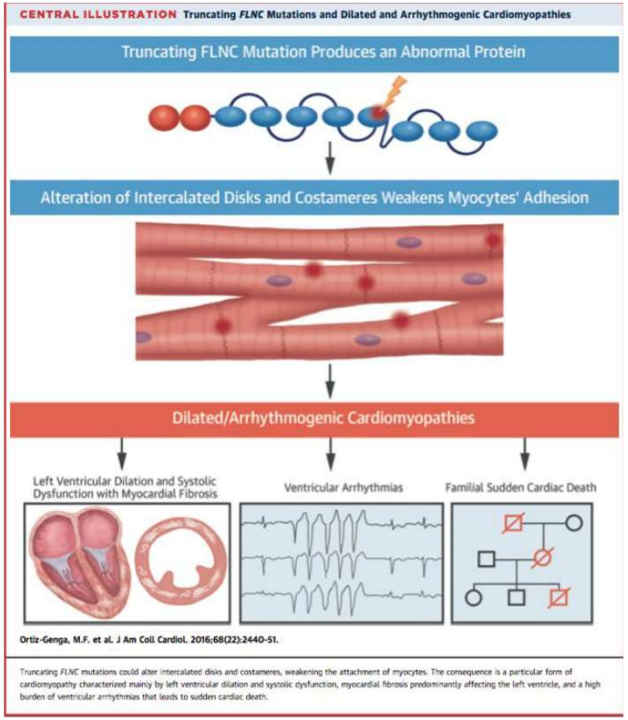
Truncating *FLNC* Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies

Martín F. Ortiz-Genga, MD,[a,b] Sofía Cuenca, MD, PhD,[c] Matteo Dal Ferro, MD,[d] Esther Zorio, MD, PhD,[e] Ricardo Salgado-Aranda, MD,[f] Vicente Climent, MD,[g] Laura Padrón-Barthe, PhD,[h] Iria Duro-Aguado, MD,[i] Juan Jiménez-Jáimez, MD, PhD,[j] Víctor M. Hidalgo-Olivares, MD,[k] Enrique García-Campo, MD,[l] Chiara Lanzillo, MD, PhD,[m] M. Paz Suárez-Mier, MD, PhD,[n] Hagith Yonath, MD,[o] Sonia Marcos-Alonso, MD, PhD,[p] Juan P. Ochoa, MD,[b] José L. Santomé, BSc,[b] Diego García-Giustiniani, MD,[b] Jorge L. Rodríguez-Garrido, MD,[b,p] Fernando Domínguez, MD,[c] Marco Merlo, MD,[d] Julián Palomino, MD, PhD,[l] María L. Peña, MD,[q] Juan P. Trujillo, MD, PhD,[b] Alicia Martín-Vila, PharmD,[l] Davide Stolfo, MD,[d] Pilar Molina, MD, PhD,[r] Enrique Lara-Pezzi, PhD,[h,s] Francisco E. Calvo-Iglesias, MD, PhD,[l] Eyal Nof, MD,[o] Leonardo Calò, MD,[m] Roberto Barriales-Villa, MD, PhD,[a,p] Juan R. Gimeno-Blanes, MD, PhD,[t] Michael Arad, MD, PhD,[o] Pablo García-Pavía, MD, PhD,[c,u] Lorenzo Monserrat, MD, PhD[a,b]



MUTACIONES en *FILAMINA C*

MISSENSE

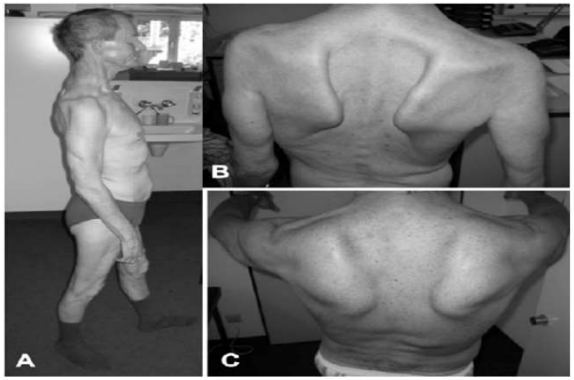
TRUNCAMIENTOS

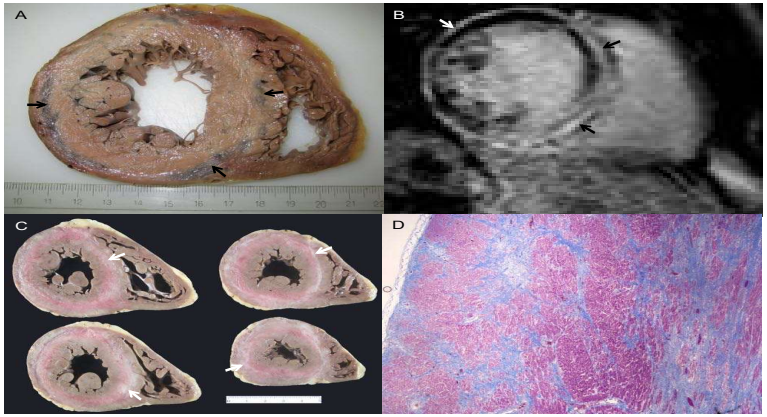
HIPERTRÓFICA

RESTRICTIVA

DILATADA-ARRITMOGÉNICA

MIOPATÍA MIOFIBRILAR



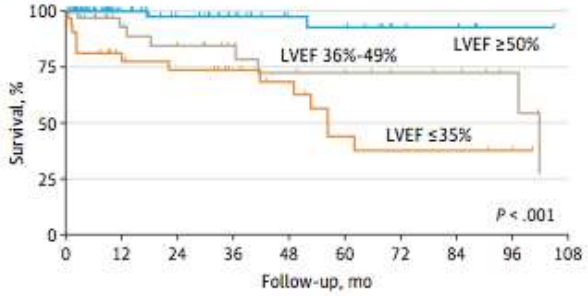


Ortiz-Genga M et al. JACC 2016;68:2440

JAMA Cardiology | Original Investigation

Association of Left Ventricular Systolic Dysfunction Among Carriers of Truncating Variants in Filamin C With Frequent Ventricular Arrhythmia and End-stage Heart Failure

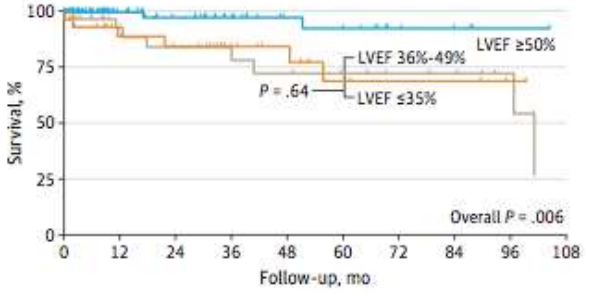
A Survival free from primary composite end point



No. at risk

LVEF ≥50%	95	50	38	28	20	19	13	12	9	8
LVEF 36%-49%	36	22	19	15	12	10	8	7	4	1
LVEF ≤35%	33	21	19	15	12	7	6	6	4	3

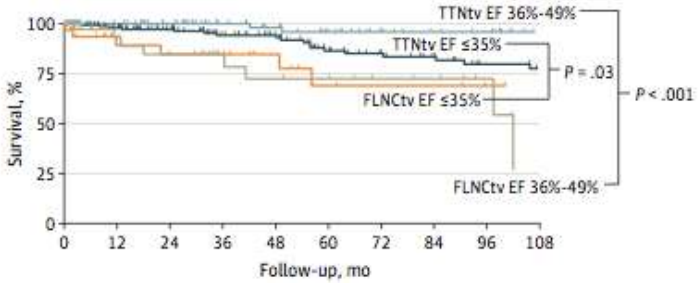
B Survival free from secondary composite arrhythmic end point



No. at risk

LVEF ≥50%	95	50	38	28	20	19	13	12	9	8
LVEF 36%-49%	36	22	19	15	12	10	8	7	4	1
LVEF ≤35%	33	21	19	15	12	7	6	6	4	3

C Survival free from secondary composite arrhythmic end point, by genetic variant



No. at risk

TTNtv EF 36%-49%	86	81	71	55	46	37	28	24	22	13
FLNCtv EF 36%-49%	36	22	19	15	12	10	8	7	4	1
TTNtv EF ≤35%	158	129	108	89	79	60	53	46	39	36
FLNCtv EF ≤35%	33	21	19	15	12	7	6	6	4	3

AKHTAR, JAMA CARDIOL 2021

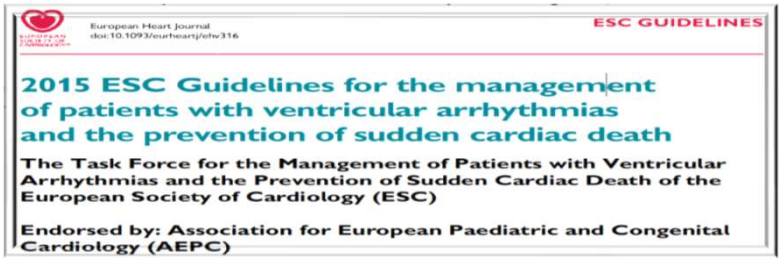
PRONÓSTICO

Gen	Frecuencia	Pronóstico
Titina *(TTN)*	25%	Similar incidencia de eventos que MCD general (no genotipada). Alta tasa de reversión de disfunción VI[1]
Lamina *(LMNA)*	6%	**Mal pronóstico**. Alta tasa de arritmias fatales con fenotipos leves. Evolución a disfunción severa que requiere Tx cardíaco[2]
Fosfolambán (*PLN)*	<1%	**Mal pronóstico.** Alta tasa de arritmias y MS[3]
Filamina C *(FLNC)*	?	Truncamientos. **Mal pronóstico.** Alta tasa de arritmias y MS[4]
Distrofina *(DMD)*	?	Baja tasa de eventos arrítmicos. Alta tasa de evolución a IC avanzada[5]
Desmina *(DES)*	<1%	**Mal pronóstico**. Fenotipo arrítmico. Sustitución grasa[6]

[1]Roberts AM et al. *Sci Transl Med*. 2015; Ware JS et al; NEJM 2016; Ware JS et al, JACC 2018
[2]Tobita et al. Sci Rep. 2018
[3]López-Ayala et al. Rev Esp Cardiol. 2015;68(4):343–354
[4]Ortiz-Genga M et al. JACC 2016;68:2440
[5]Diegoli M, et al. JACC 2011;58:925-34
[6]Ripoll-Vera T et al. Rev Esp Cardiol. 2015;68(11):1027–1038

TRATAMIENTOS ESPECÍFICOS:

Mutaciones en Lamina A/C



An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.[d]	IIa	B

[d]Risk factors in patients with a confirmed *LMNA* mutation: NSVT during ambulatory electrocardiogram monitoring, LVEF <45% at first evaluation, male sex and non-missense mutations (insertion, deletion, truncations or mutations affecting splicing).

Investigación: Inhibidores p38 MAPK

Clinical Study ARRAY-797-301

A Phase 3, Multinational, Randomized, Placebo-controlled Study of ARRY-371797 in Patients with Symptomatic Dilated Cardiomyopathy Due to a Lamin A/C Gene Mutation

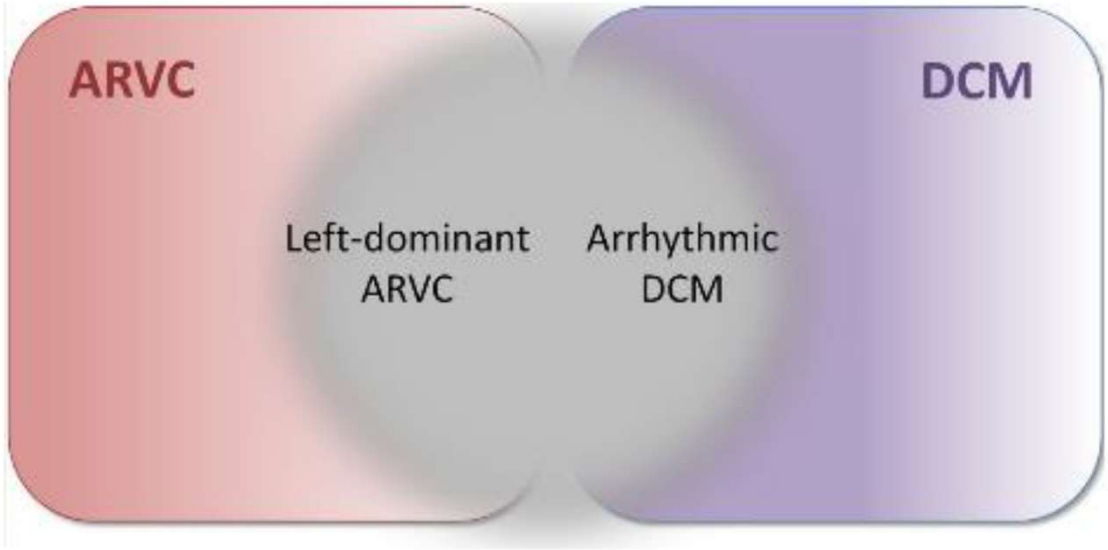
¿Cómo la genética nos cambia el manejo en la Miocardiopatía arritmogénica?

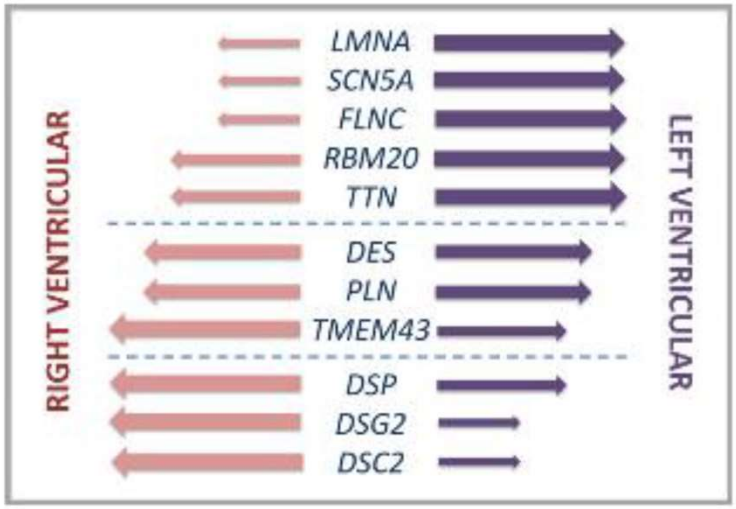
Indicación del estudio genético

Tabla 2
Recomendaciones y nivel de evidencia de los estudios genéticos en las guías y los documentos de consenso publicados

Estudio genético	Nivel de recomendación[a]
Miocardiopatía hipertrófica (Elliott et al[2], Ackerman et al[4])	I
	I
Miocardiopatía dilatada (Ackerman et al[4])	I[b]
	IIa[c]
Miocardiopatía restrictiva (Ackerman et al[4])	IIb
Miocardiopatía no compactada (Ackerman et al[4])	IIa
Miocardiopatía arritmogénica (Ackerman et al[4])	IIa (incluido en los criterios diagnósticos)
Síndrome de Brugada (Ackerman et al[4])	IIa
Taquicardia ventricular polimórfica catecolaminérgica (Ackerman et al[4])	I (incluido en los criterios diagnósticos)
Síndrome de QT largo (Ackerman et al[4])	I (incluido en los criterios diagnósticos)
Síndrome de QT corto (Ackerman et al[4])	IIb (incluido en los criterios diagnósticos)
Síndrome de Marfan (Loeys et al[5])	Incluido en los criterios diagnósticos
Síndrome de Loeys-Dietz (Arslan-Kirchner et al[6])	Incluido en los criterios diagnósticos

Barriales-Villa R et al. Rev Esp Cardiol. 2016;69(3):300–309





Peters et al. Heart LungCirc. 2018
Gandjbkhahc et al JACC 2018

Patrones específicos de RTG en base a la genética: estudio de correlación genotipo-fenotipo

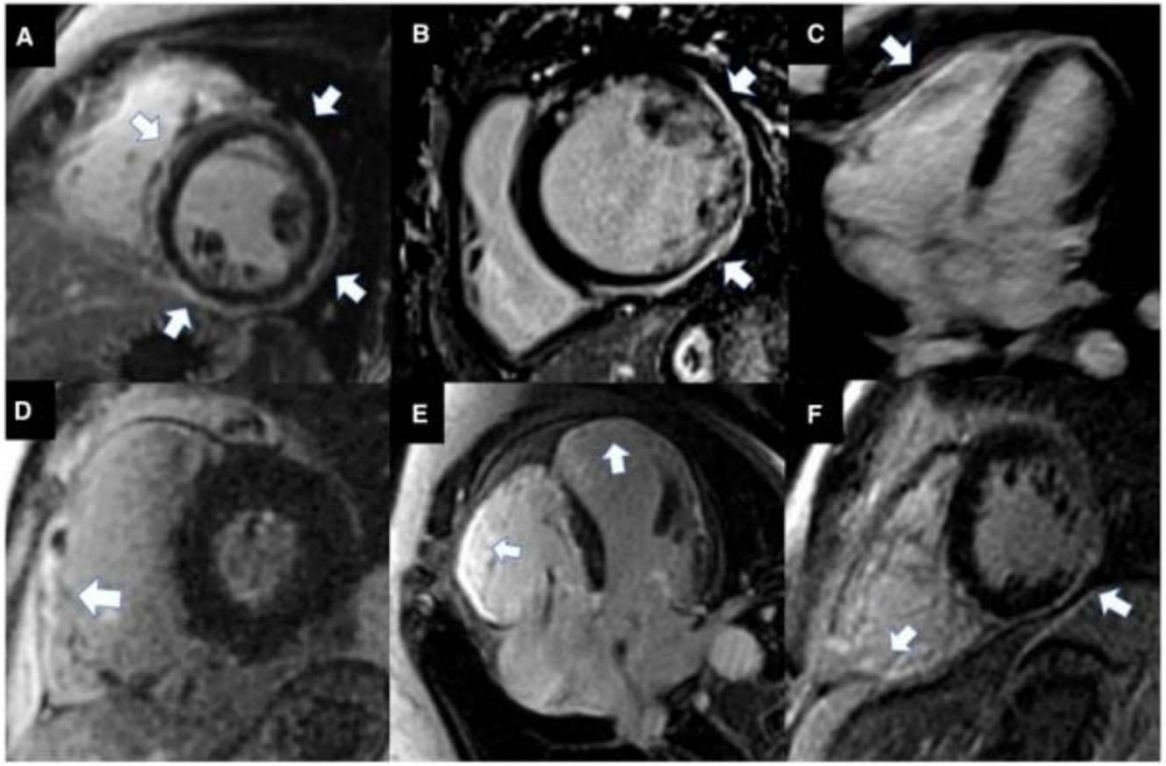


Figure 2 Representative late gadolinium enhancement images from non-desmosomal mutations (upper panels) and desmosomal mutations (lower panels). The white arrows show the enhancement zones. (*A*) *DES* mutation with circumferential LV enhancement. (*B*) *FLNC* mutation with lateral LV enhancement. (*C*) *TMEM43* mutation patient with RV enhancement. (*D*) *PKP-2* mutation with RV enhancement. (*E*) *DSG-2* mutation with biventricular enhancement. (*F*) *DSP* mutation with biventricular enhancement.

Segura D et al. Eur Heart J CV Imaging 2019

Clinical characteristics and determinants of the phenotype in *TMEM43* arrhythmogenic right ventricular cardiomyopathy type 5

Fernando Dominguez, MD, PhD,[*†] Esther Zorio, MD, PhD,[†‡§] Juan Jimenez-Jaimez, MD, PhD,[‖] Rafael Salguero-Bodes, MD,[†¶] Robert Zwart, PhD,[#] Esther Gonzalez-Lopez, MD, PhD,[*†] Pilar Molina, MD, PhD,[§**] Francisco Bermúdez-Jiménez, MD, PhD,[‖] Juan F. Delgado, MD, PhD,[†¶] Aitana Braza-Boïls, PhD,[‡§] Belen Bornstein, MD, PhD,[††] Jorge Toquero, MD, PhD,[*] Javier Segovia, MD, PhD,[*†] J. Peter Van Tintelen, MD, PhD,[‡‡] Enrique Lara-Pezzi, PhD,[†§§‖‖] Pablo Garcia-Pavia, MD, PhD[*†¶¶]

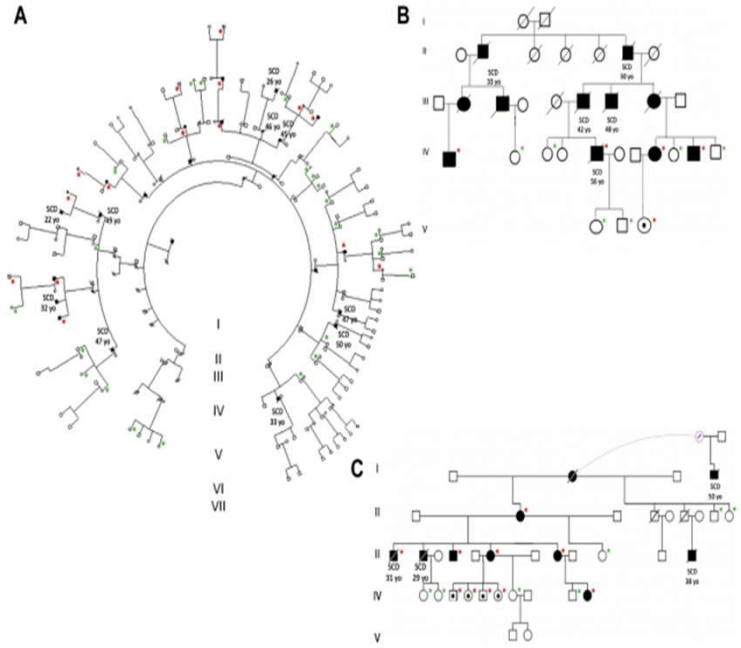
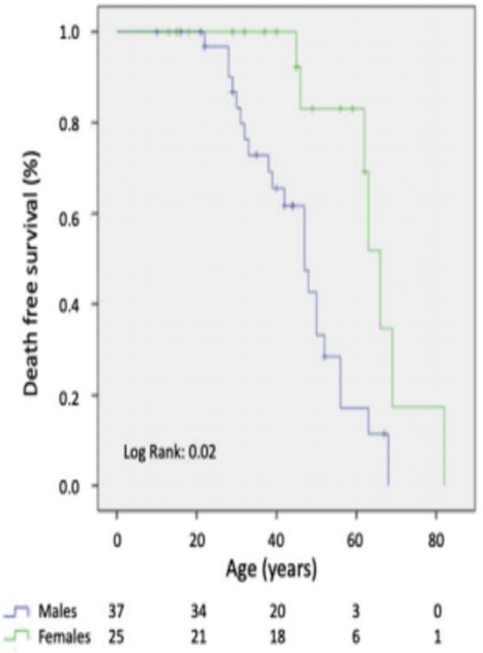


Table 1 Clinical, electrocardiographic, and echocardiographic

Variable	Affected		
	Male	Female	Total
Number of subjects	37 (59.7)	25 (40.3)	62
Age (y)	36.5 ± 14.9	43.1 ± 20.9	39.1 ± 17.6
SCD	20/37 (54.0)	4/25 (14.0)	24/62 (38.7)
SCD ≤50 y	17/37 (45.9)	2/25 (8.0)	19/62 (30.6)
SCD age (y)	41.8 ± 11.5	61.0 ± 15.7	44.6 ± 14.3
Heart failure	3/21 (14.3)	4/16 (25.0)	7/37 (18.9)



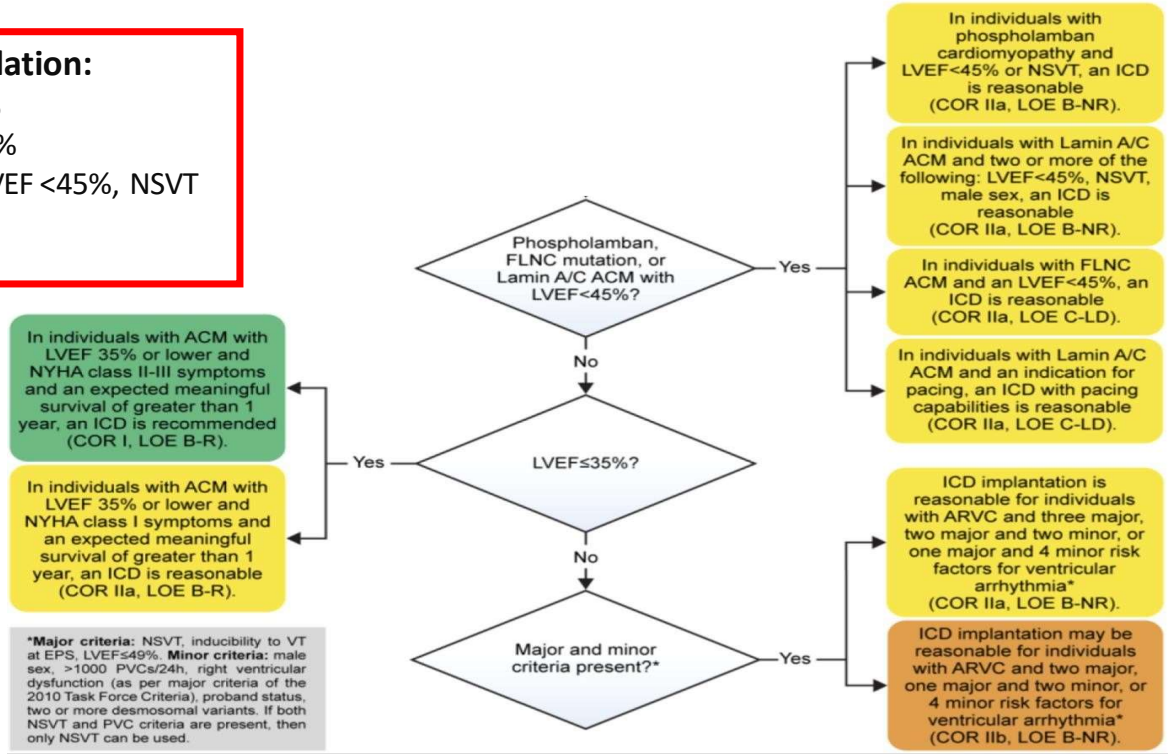
Domínguez F et al. Heart Rhythm 2020

HRS CONSENSUS EXPERT IN ARRHYTHMOGENIC CARDIOMYOPATHY 2019

ICD for primary prevention

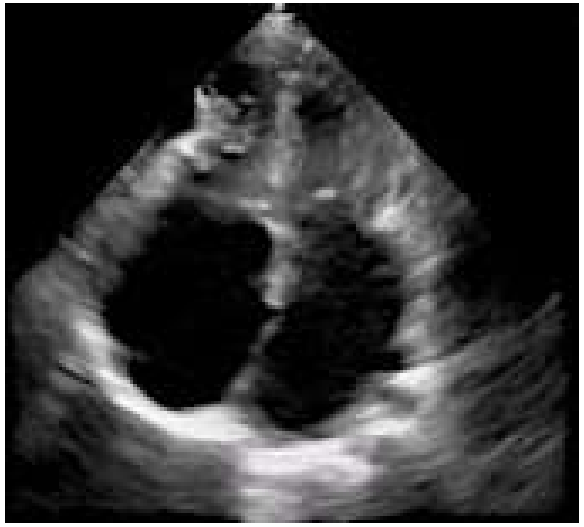
IIa recommendation:
PLN & LVEF <45%
FLNC & LVEF <45%
LMNA & male, LVEF <45%, NSVT

*TMEM43!!



Towbin et al. Heart Rhythm. 2019

¿Cómo la genética nos cambia el manejo en la Miocardiopatía restrictiva?



Causas de miocardiopatía restrictiva

- Idiopática
- Familiar
- No familiar

Familiar	Familiar (gen desconocido, AD) Sarcoméricas (*TNNI3, MYH7, MYL3, MYBPC3, TTN, FLNC*) (AD) Desminopatías (*DES, CRYAB*) (AD, AR) Amiloidosis familiar (*TTR, APOA1*) (AD) Hemocromatosis (*HFE*) (AR) Enfermedades por depósito lisosomal - Enfermedad de Fabry (*GLA*) (ligada al X) - Enfermedad de Danon (*LAMP2*) (ligada al X) - Enfermedad de Pompe (*GAA*) (AR) Pseudoxantoma elástico (*ABCC6*) (AD o AR)
No familiar	Amiloidosis (AL, prealbúmina) Esclerodermia Sarcoidosis Síndrome carcinoide Metástasis Radiación Tóxicos (antraciclinas)

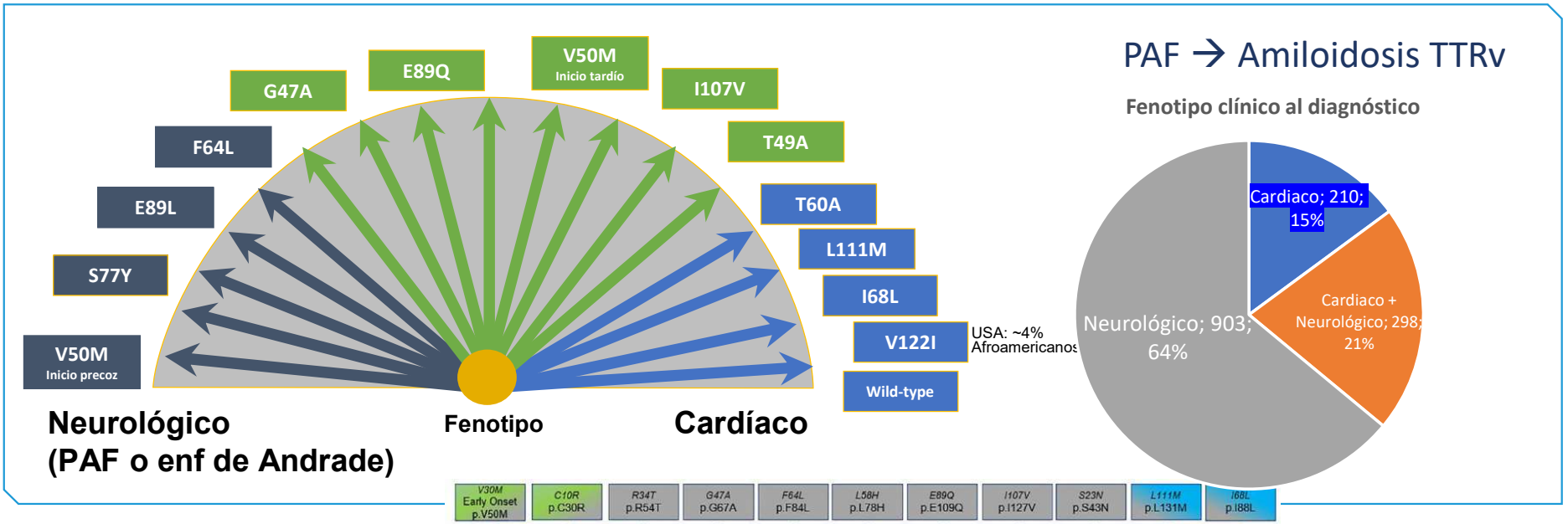
En cursiva principales genes responsables de cada enfermedad

Modificado de Elliott P et al. Eur Heart J. 2008;29:270-276

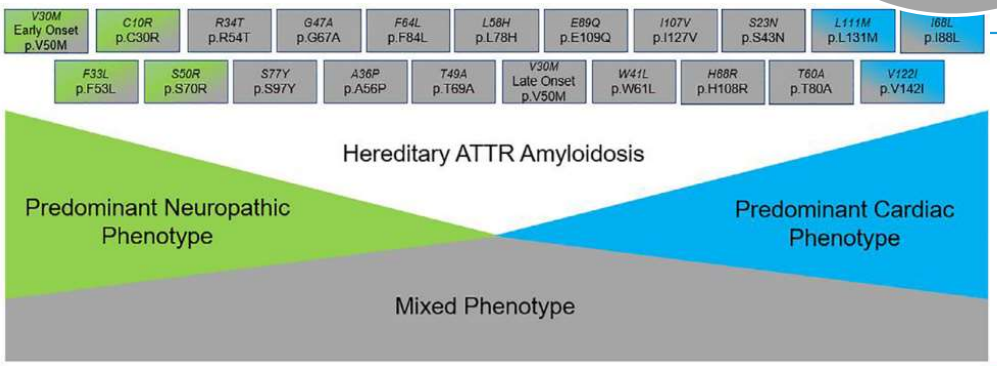
Desminopatías

- Gen DES. La mayoría AD.
- Miopatía esquelética (MMII) + miocardiopatía (restrictiva) con arritmias o trastornos en la conducción (1º).
- Muy elevada penetrancia a partir de la 3ª década.
- Todos los pacientes afectos suelen precisar marcapasos por BAV.
- IC en 3ª-4ª década.

Amiloidosis por Transtiretina (ATTRv)

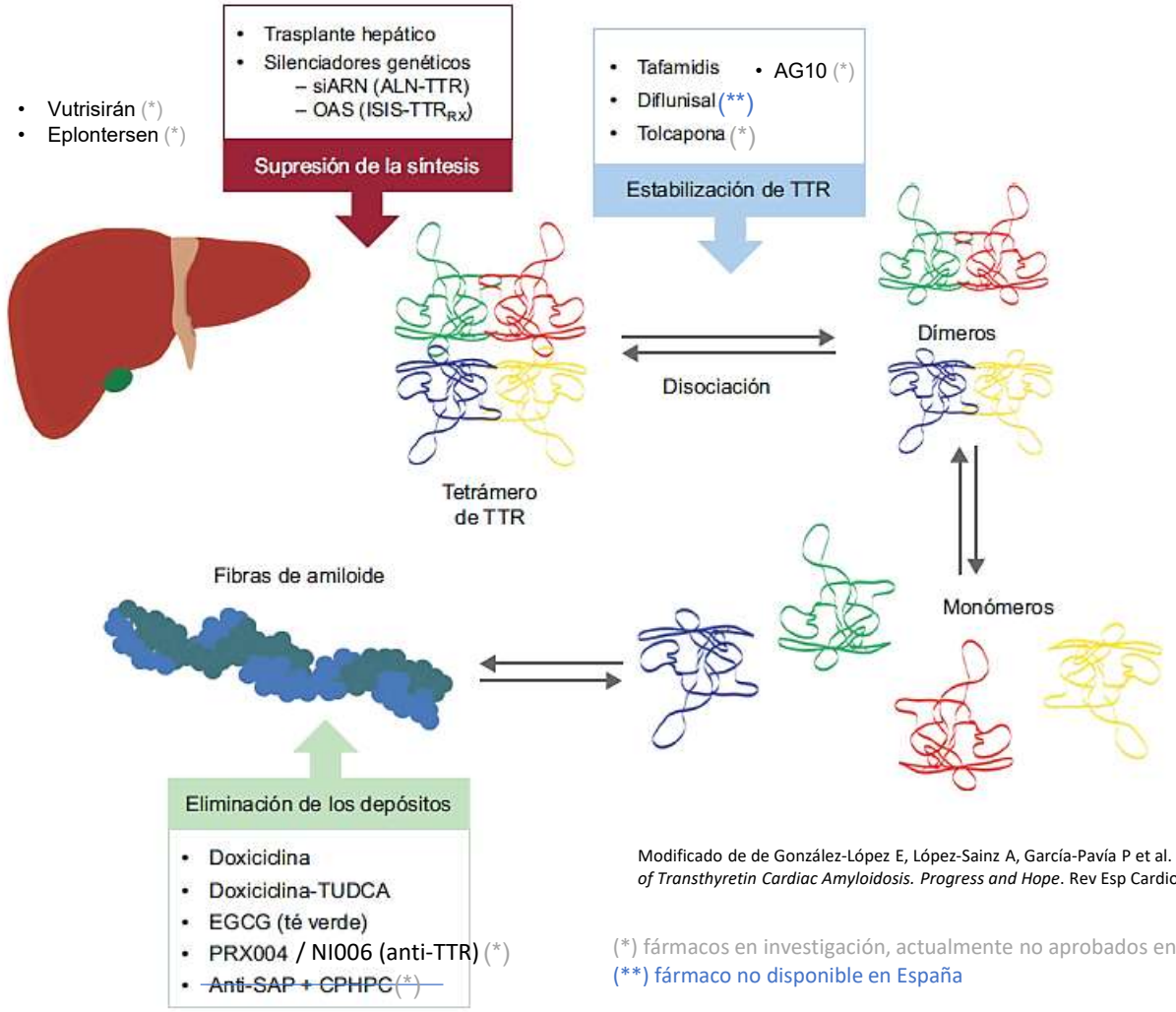


Basado en Rapezzi C, Quarta CC, Obici L, Perfetto F, Longhi S, Salvi F et al. Eur Heart J. 2013;34:520-8.



Extraído de Griffin JM, Maurer MS. Transthyretin cardiac amyloidosis: a treatable form of heart failure with preserve ejection fraction. Trends in Cardiovascular Medicine. 2019;17:36.

ATTRv: posibles opciones terapéuticas



Modificado de de González-López E, López-Sainz A, García-Pavía P et al. *Diagnosis and Treatment of Transthyretin Cardiac Amyloidosis. Progress and Hope*. Rev Esp Cardiol 2017;70:991-1004

(*) fármacos en investigación, actualmente no aprobados en España
(**) fármaco no disponible en España

CONCLUSIONES

- Los estudios genéticos son imprescindibles en el manejo de pacientes con cardiopatías familiares, tanto para el pacientes índice como para focalizar el seguimiento en los portadores.

- Una correcta interpretación clínica, realizada por equipos especializados, y apoyada por herramientas de gestión del conocimiento es esencial para obtener su máximo beneficio.

- Ofrecen ya hoy en día información pronóstica muy útil.

- Tratamientos dirigidos en base a la vía patogénica afectada permitirán aliviar la expresión del fenotipo y realizar medicina personalizada.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