Desafios diagnósticos en enfermedades cardiovasculares de origen hereditario

Dr. Luis Enrique Gómez

Hospital de Agudos “Juan A. Fernández”

Agenda para hoy

Temario

-Enfermedades cardiovasculares hereditarias

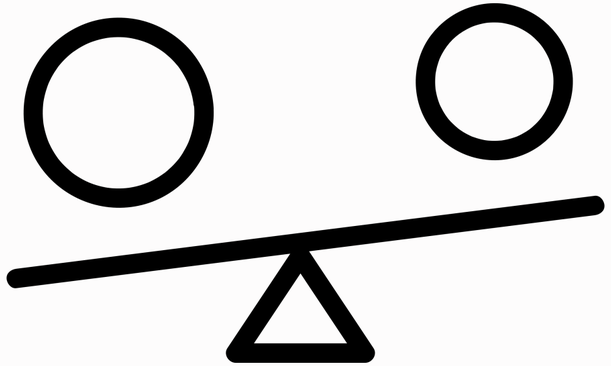
-Tipos de ECH

- Arritmias Hereditarias

- Miocardiopatias

- Mensajes finales

ENFERMEDADES CARDIOVASCULARES HEREDITARIAS



ENFERMEDADES CARDIOVASCULARES HEREDITARIAS

ABEBE BIKILA. ROMA 1960

SHERPA

YAK

ENFERMEDADES CARDIOVASCULARES HEREDITARIAS

ABEBE BIKILA. ROMA 1960

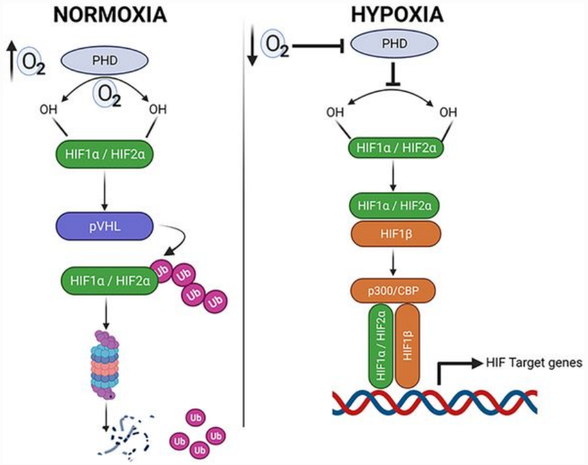
BEKOJI ESTÁ A 2.800 METROS

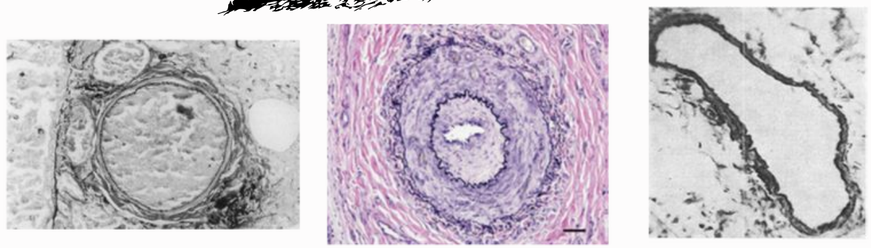
SHERPA

NO SHERPA

VACA

YAK





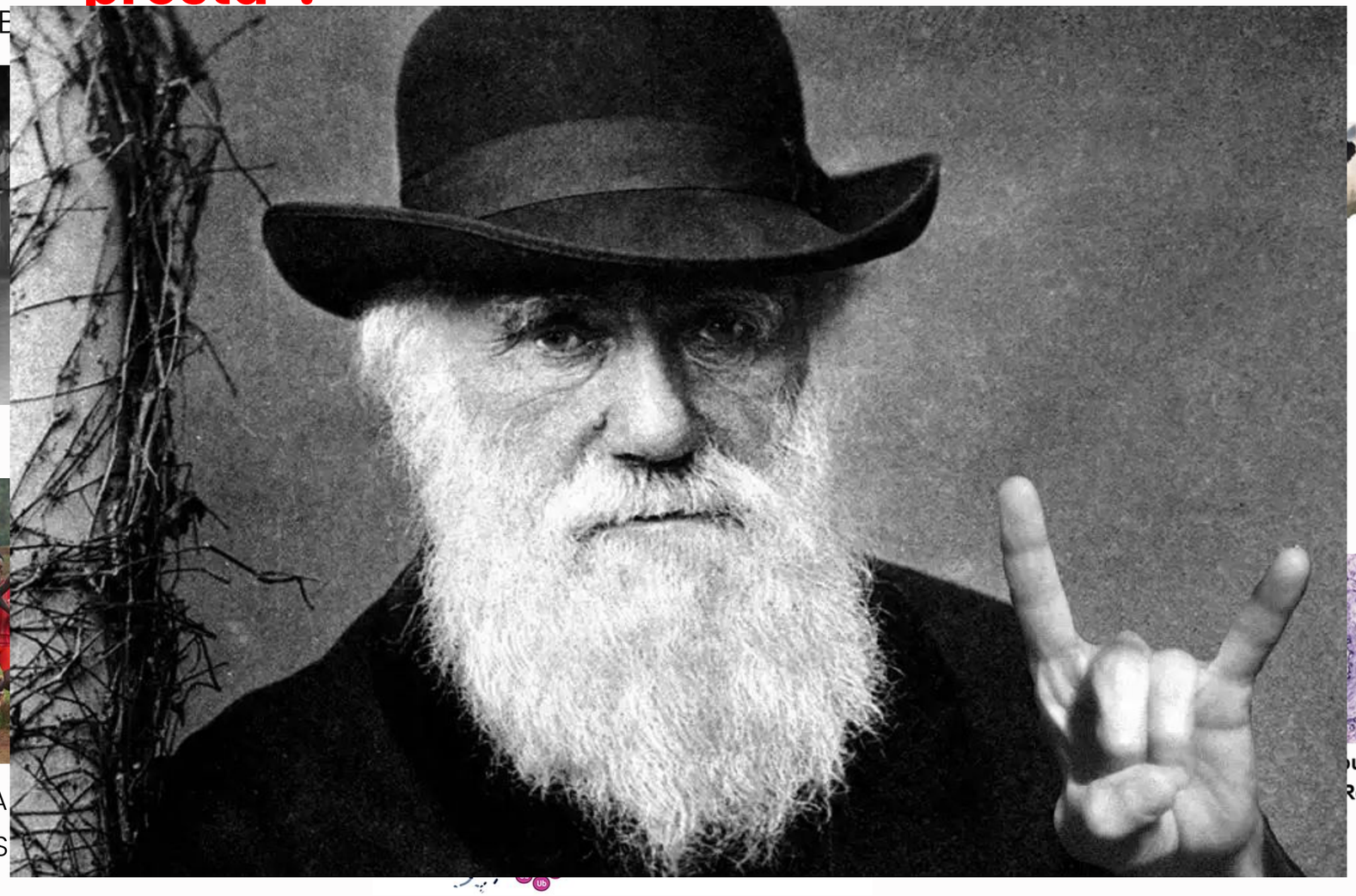
Gupta ML.Lack of smooth muscle in the small pulmonary arteries of the native Ladakhi. Is the Himalayan highlander adapted? Am Rev Respir Dis 145: 1201–1204, 1992

“Lo que natura no da Salamanca non presta”.

ABEBE E

BEKOJI ESTÁ A

METROS



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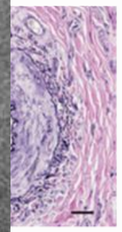
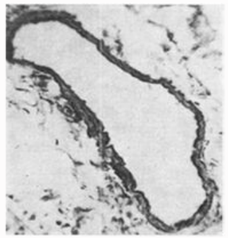
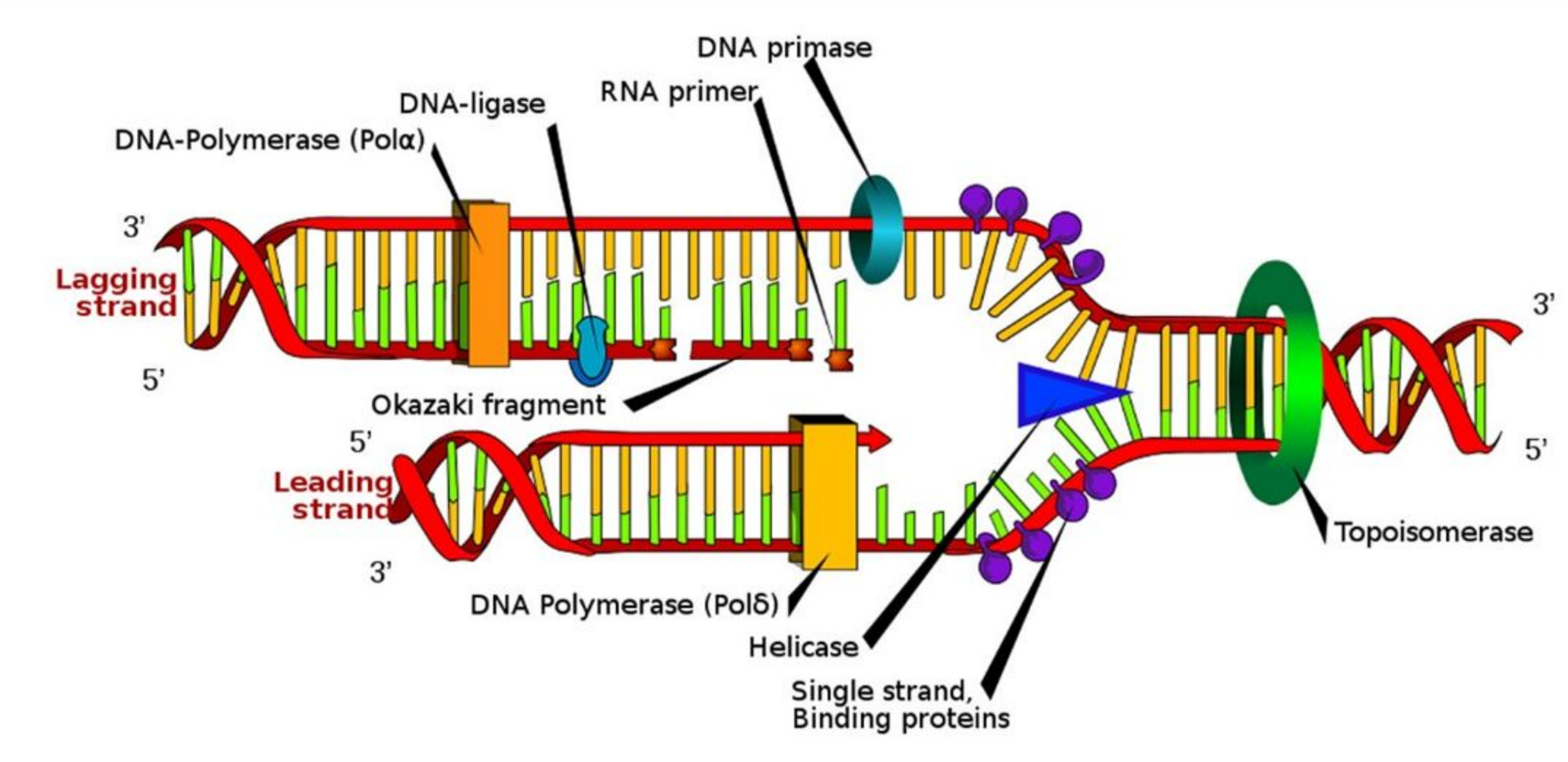




ulmonary arteries of the native Ladakhi. Is
Rev Respir Dis 145: 1201–1204, 1992

ENFERMEDADES CARDIOVASCULARES HEREDITARIAS



1 error cada 100 millones de nucleótidos. Tasa de error 1,3 x 10 -8

Kong A. Nature 2012;488:471-475.

Caracteristicas ECH

Presentación familiar

- Evaluar a los miembros de la familia si una persona está afectada.
- Posibilidad de variante genética heredada.

Base genetica

- Diagnóstico genético posible, aunque no siempre se identifica la variante causal.
- Aumento en la identificación de nuevas variantes.
- Considerar penetrancia incompleta y expresividad variable de los cambios génicos.

Muerte súbita

- En ocasiones como forma de presentación de la enfermedad.
- Son causa frecuente en menores de 35 años sean deportistas o no

Herencia y Riesgo

Monogenico

↑↓

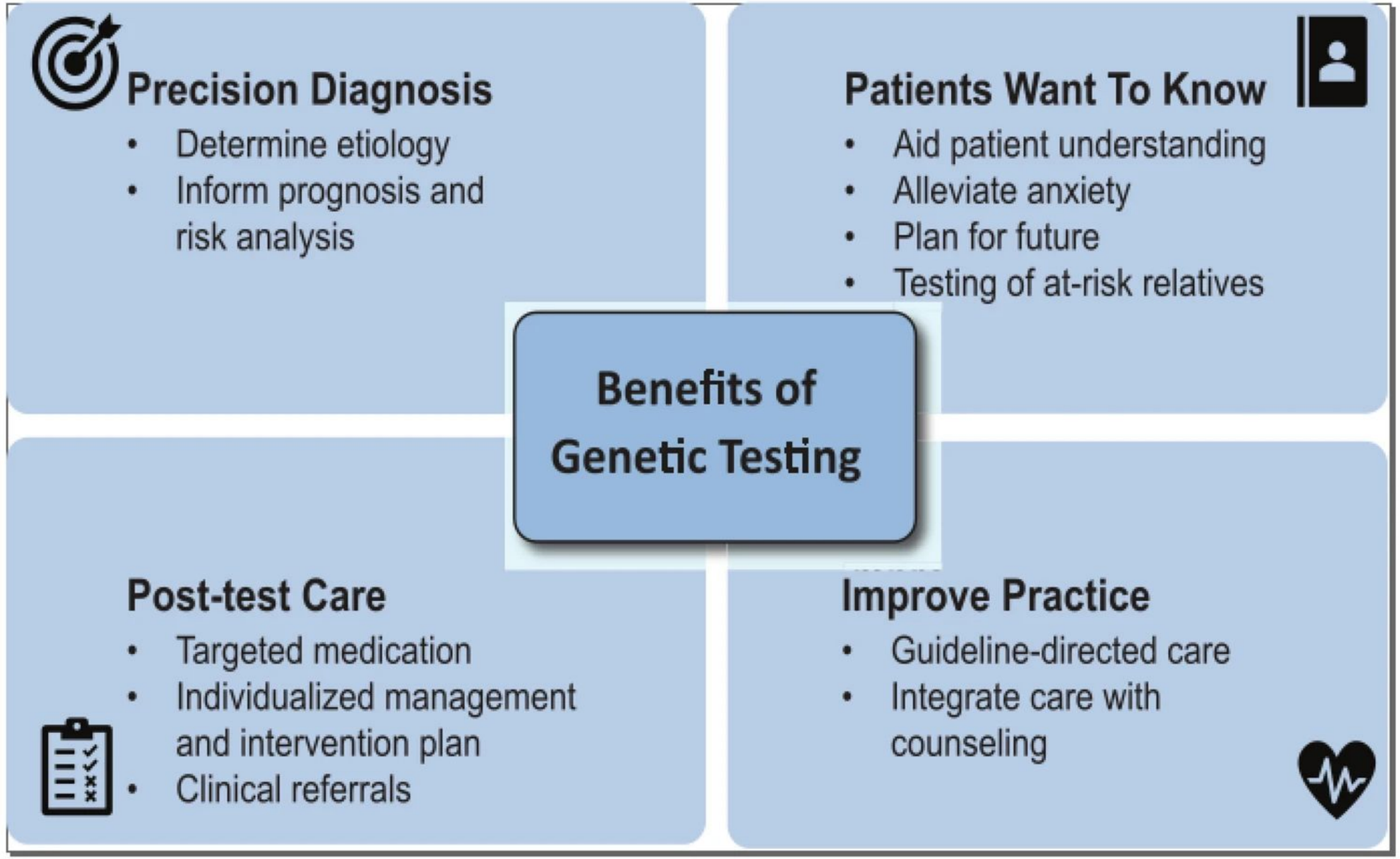
Poligenico

Condición Clínica

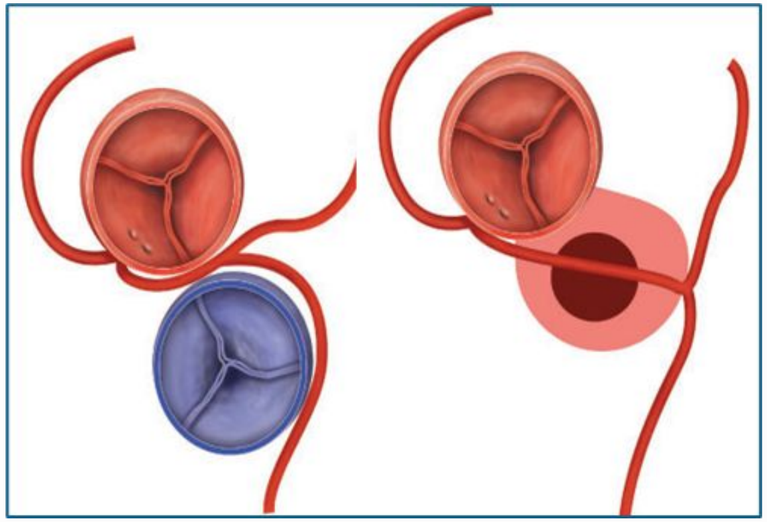
↑↓

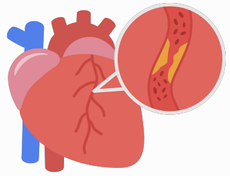
Rasgo familiar

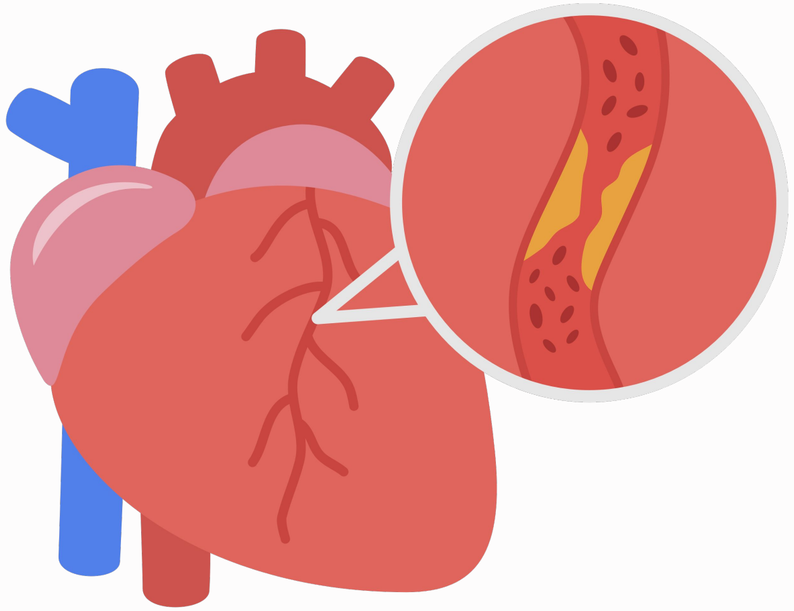
Factor de Riesgo

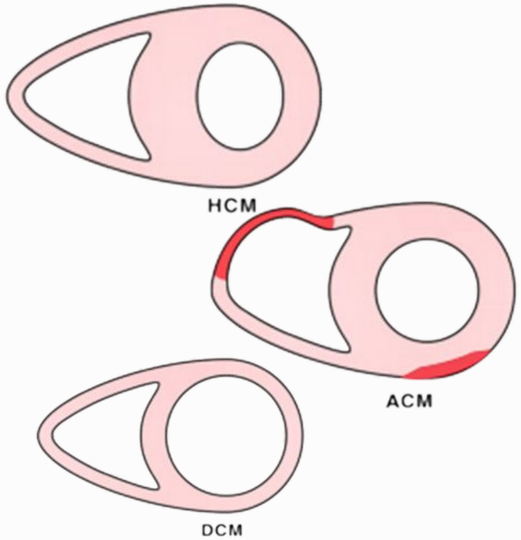

Precision Diagnosis
Determine etiology
Inform prognosis and risk analysis
Patients Want To Know
Aid patient understanding
Alleviate anxiety
Plan for future
Testing of at-risk relatives
Benefits of Genetic Testing
Post-test Care
Targeted medication
Individualized management and intervention plan
Clinical referrals
Improve Practice
Guideline-directed care
Integrate care with counseling

Muerte súbita cardíaca









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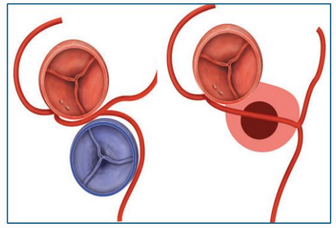
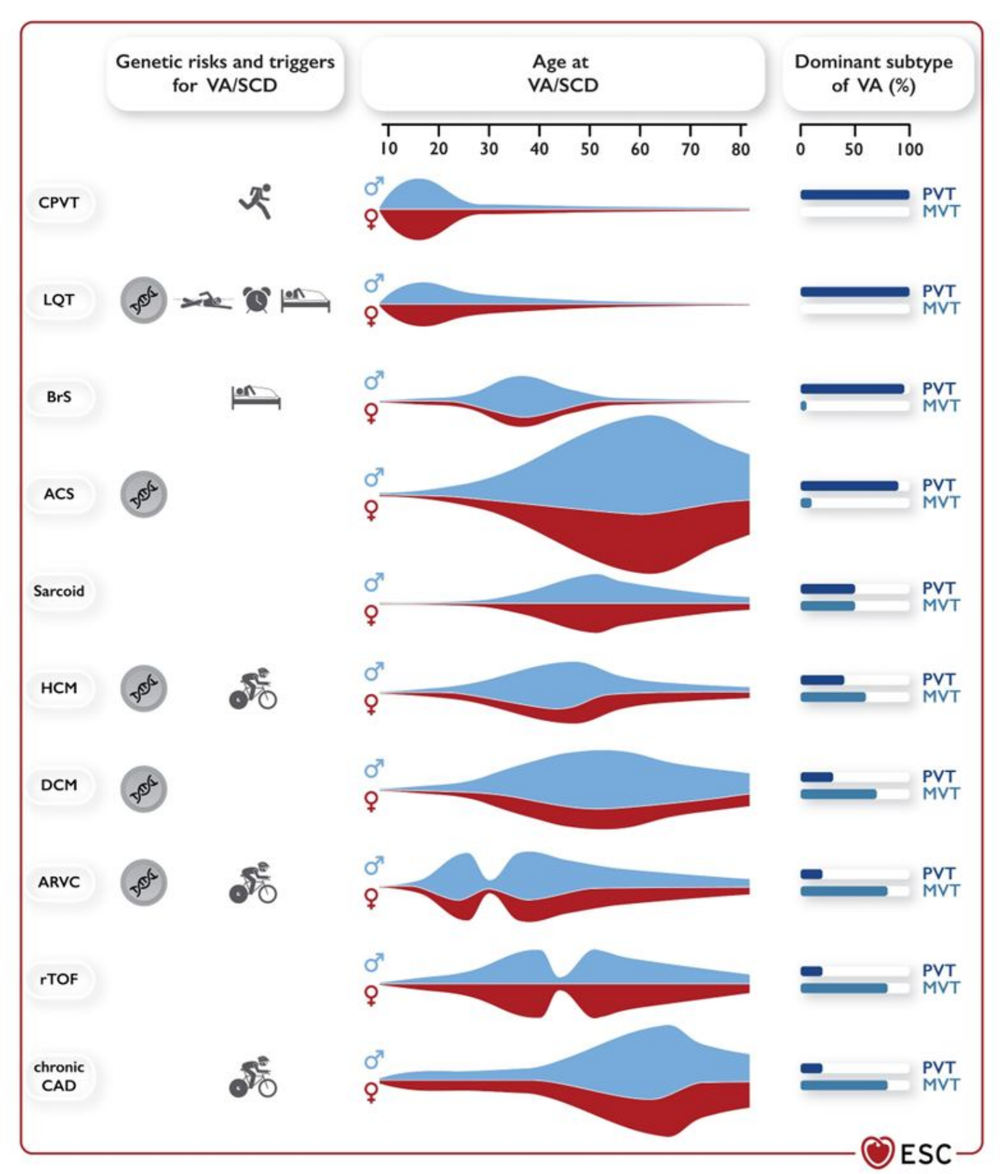
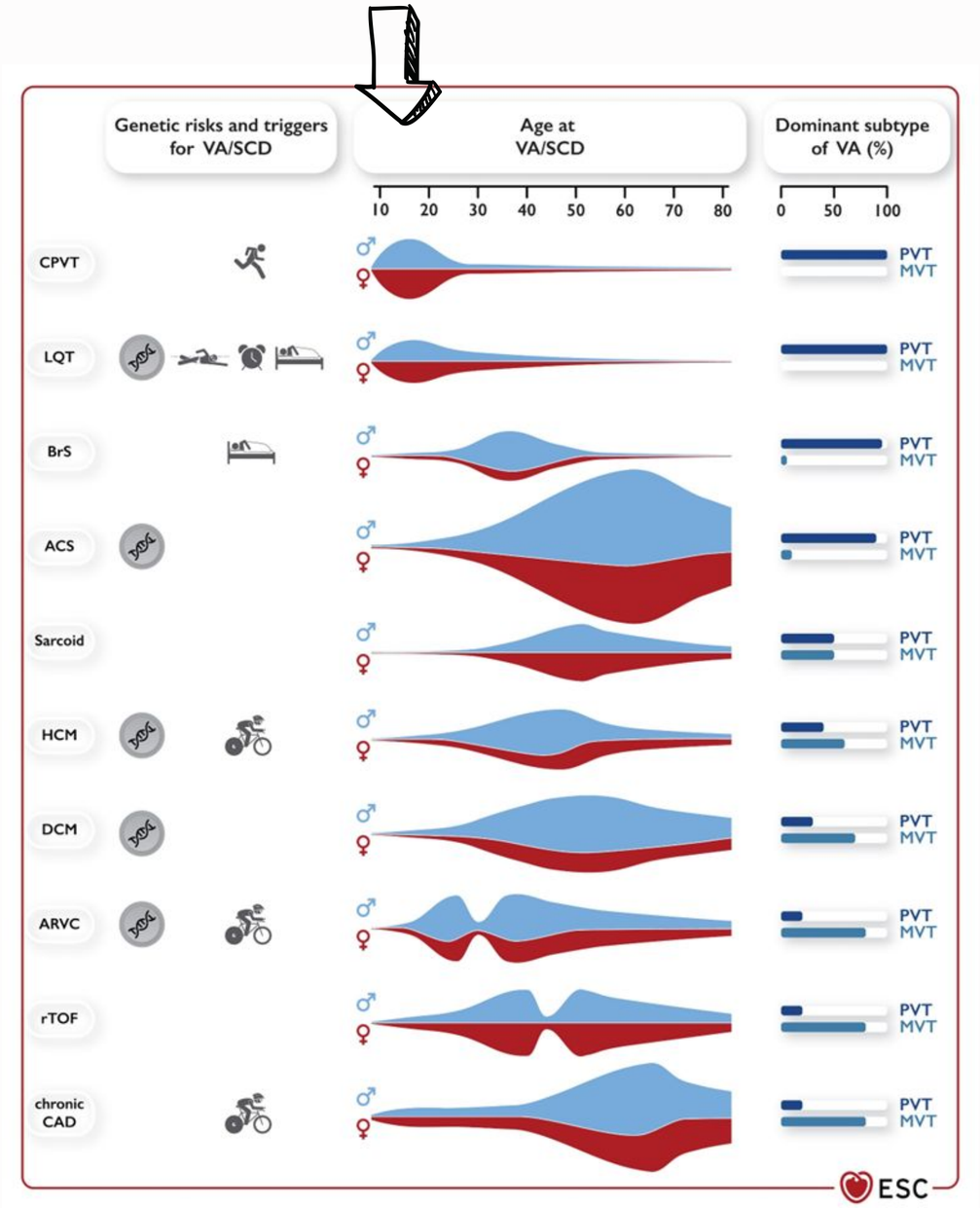




Etiología MSC

Grupos etarios

KATJA ZEPPENFELD, ET AL, 2022 ESC GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VENTRICULAR ARRHYTHMIAS AND THE PREVENTION OF SUDDEN CARDIAC DEATH: .EUROPEAN HEART JOURNAL, VOLUME 43, ISSUE 40, 21 OCTOBER 2022, PAGES 3997–4126



ARRITMIAS PRIMARIAS

MIOCARDIOPATÍAS

MIOCARDITIS

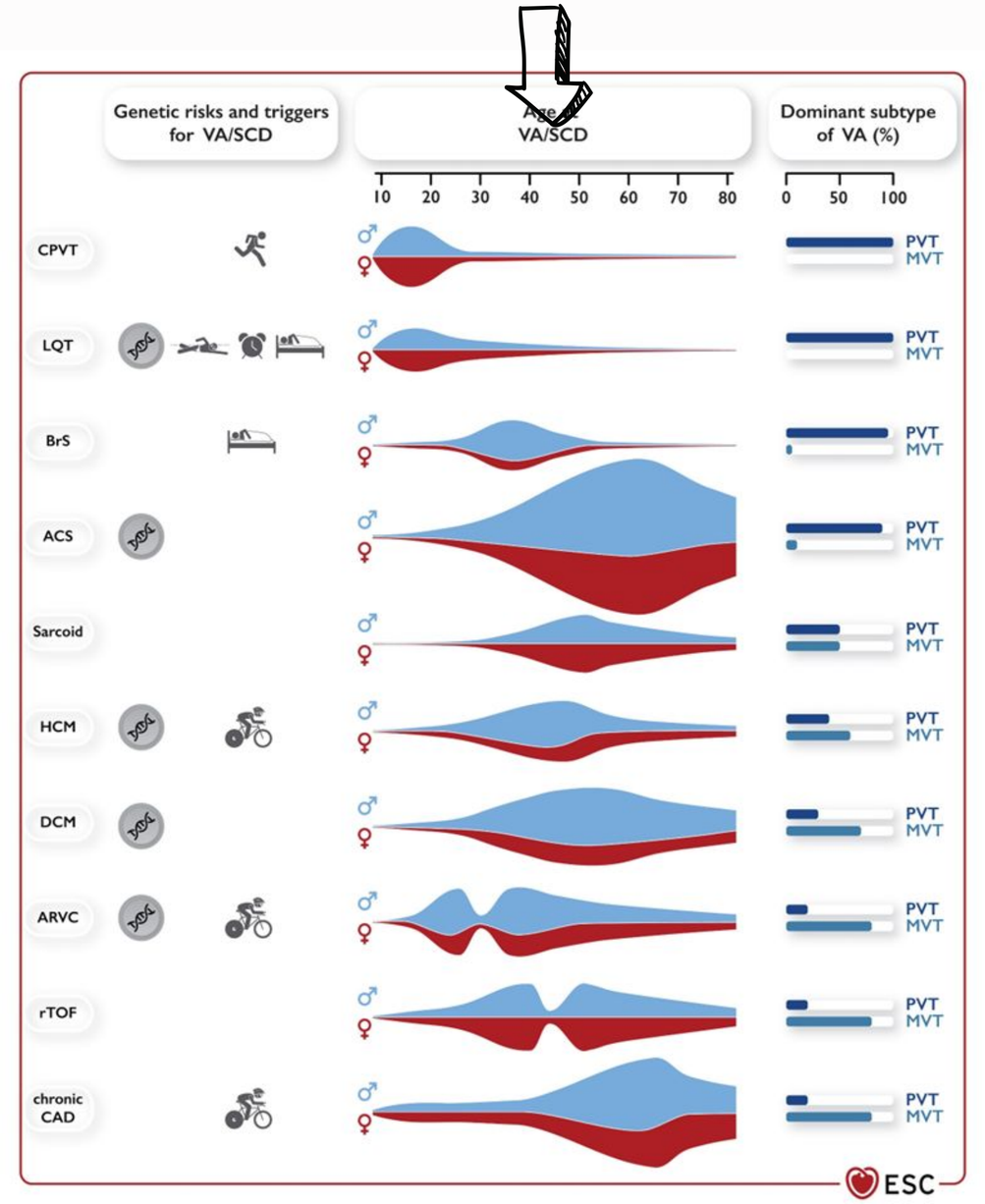
ANOMALÍAS CORONARIAS

CPVT

LQT

ARVC

KATJA ZEPPENFELD, ET AL, 2022 ESC GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VENTRICULAR ARRHYTHMIAS AND THE PREVENTION OF SUDDEN CARDIAC DEATH: .EUROPEAN HEART JOURNAL, VOLUME 43, ISSUE 40, 21 OCTOBER 2022, PAGES 3997–4126



BRS

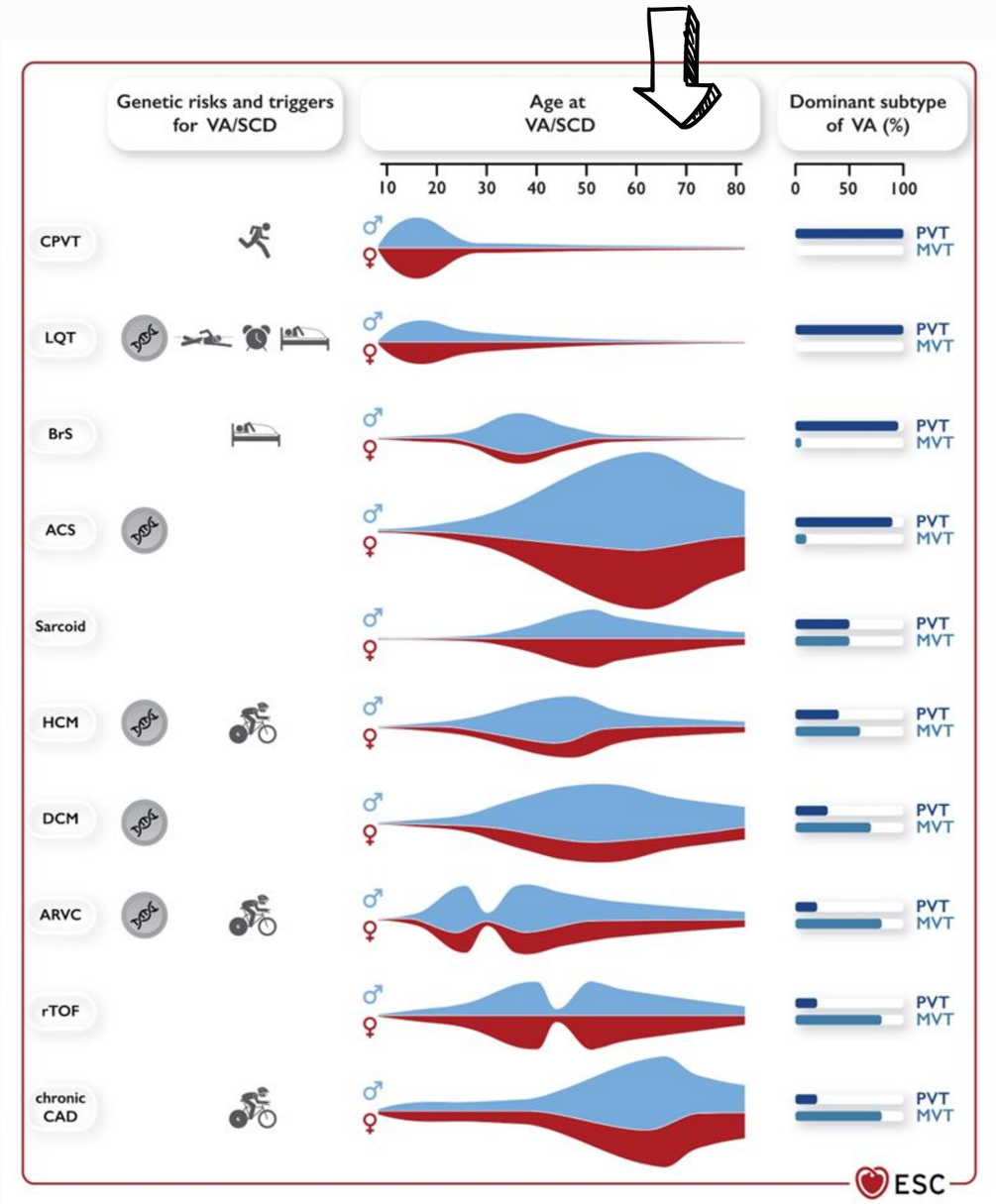
HCM

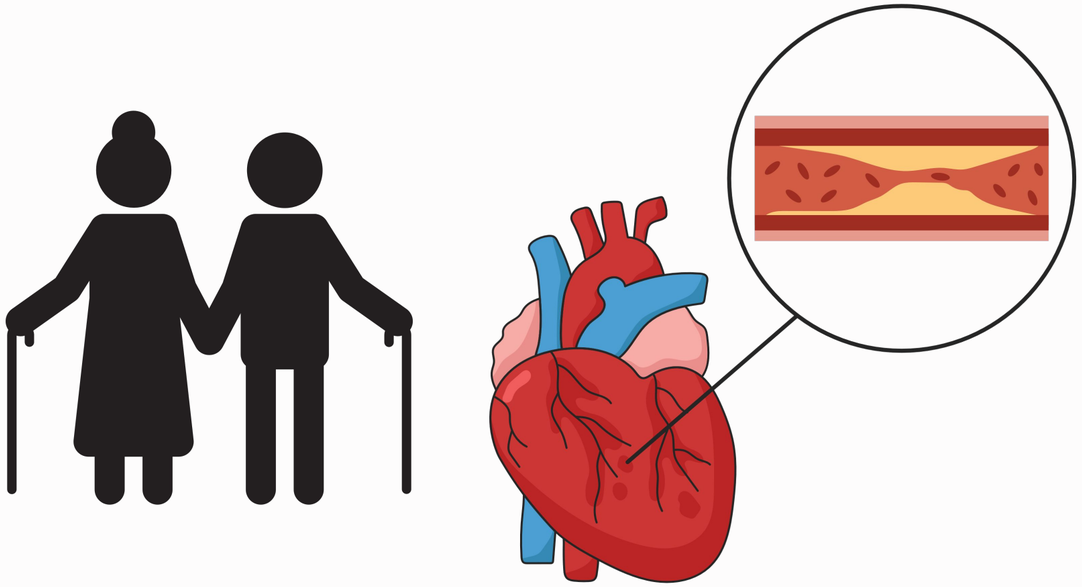
DCM

ARVC

SCA

KATJA ZEPPENFELD, ET AL, 2022 ESC GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH VENTRICULAR ARRHYTHMIAS AND THE PREVENTION OF SUDDEN CARDIAC DEATH: .EUROPEAN HEART JOURNAL, VOLUME 43, ISSUE 40, 21 OCTOBER 2022, PAGES 3997–4126





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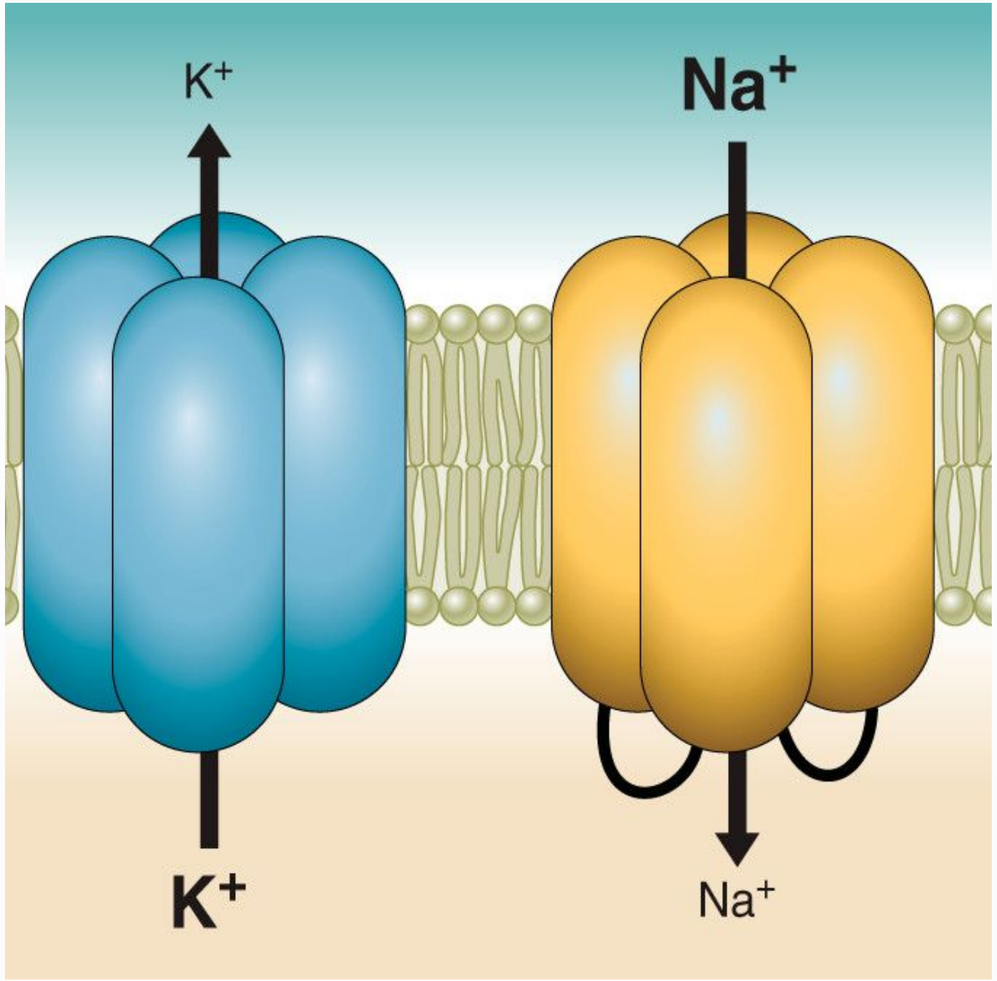


Arritmias de origen hereditario

Qt Largo

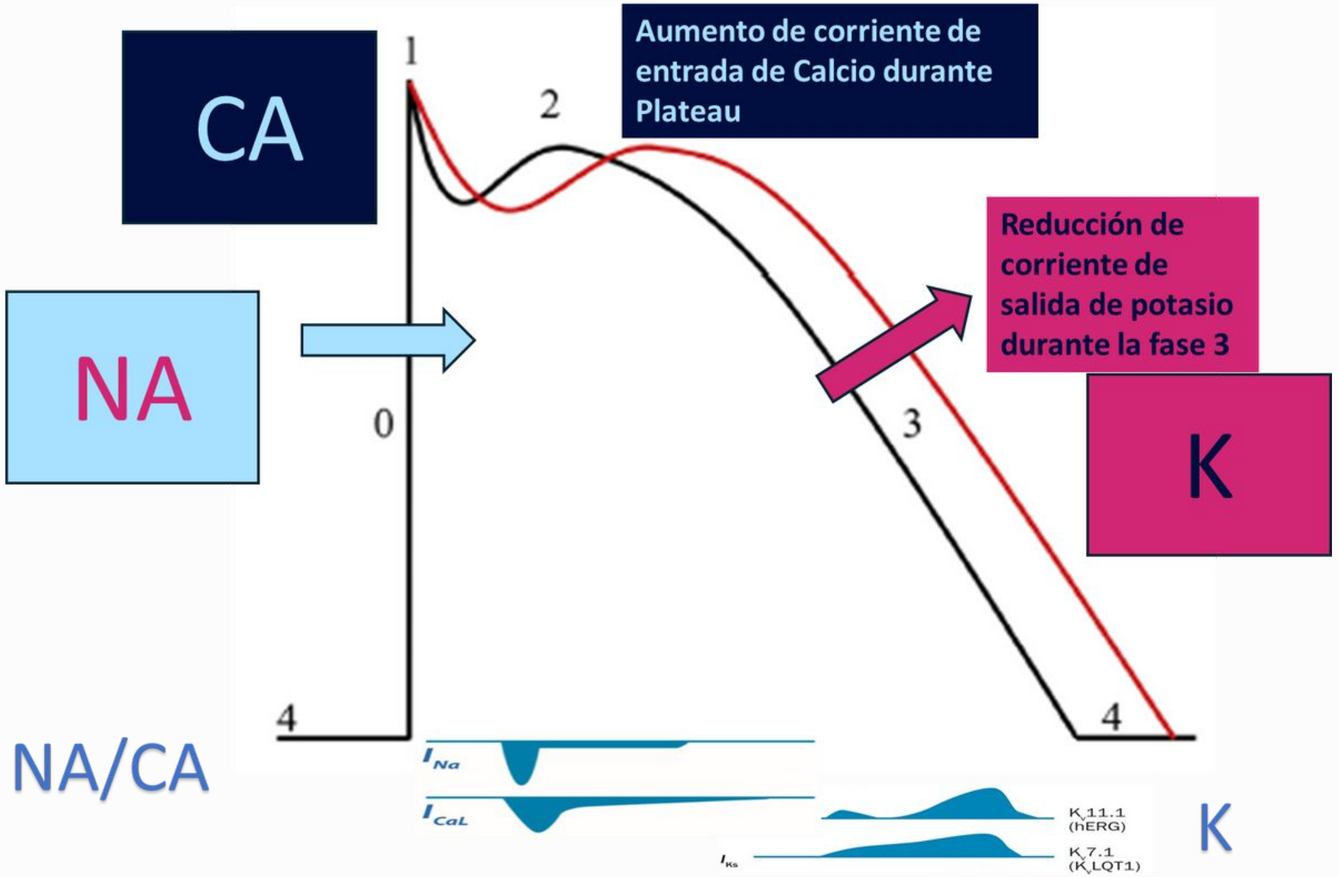
PATRONES DE HERENCIA

AD 1/2000 **ROMANO-WARD**

AR 1/4000000 **JERVELL LANGE NIELSEN**

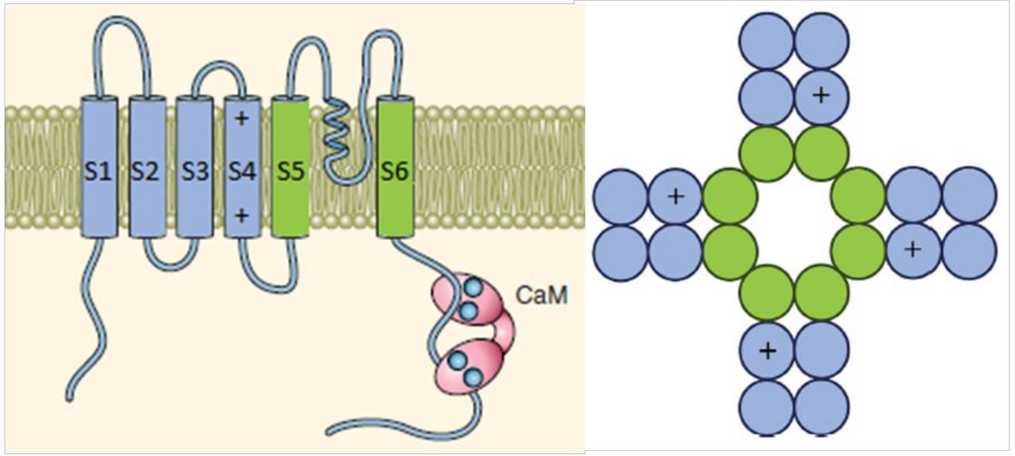
MORTALIDAD

50% **SINTOMATICOS**



↓ Corriente de Potasio

Canal Potasio

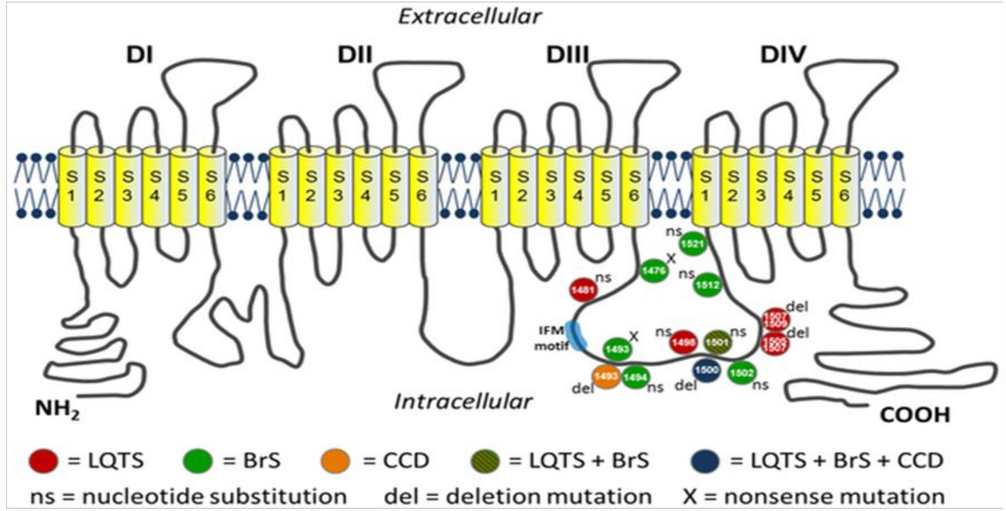


Lento	Rapido
Kv7.1 (Iks)	Kv11,1 (Ikr)
KCNQ1 Sub α	KCNH2 Sub α

Variantes con Perdida de Función 80%*

Persistencia de la corriente de Sodio

Canal Sodio



SCN5A

Variantes con Ganancia de Función*

*Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):868-77

Qt Pretest

Presentacion Clinica		
Tipo 1	Tipo 2	Tipo 3
Estrés Emocional		

Historia Fliar, Síntomas.
ECG
Holter
Ergometria
Imagenes

Confirmacion manual de la duración QTc ≥ 480 mseg ♀ ≥ ♂ 470 mseg (excluir U, formula Bazet, evaluar anomalías onda T)

PT.Score de riesgo QTL*

QTC≥500 mseg

≤ 1 | **1,5-3** | **≥ 3,5**

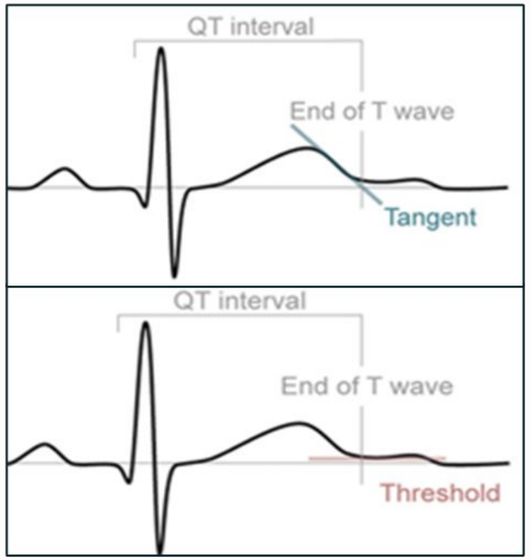
Test Provocación**

*Schwartz score
**Test provocación, ergometría, pararse abruptamente, Epinefrina, estrés aritmetico

Clase I

Test Genético

Test Genético



Vink AS, et al.Circulation. 2018;138:2345–2358.

Long QT syndrome
Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
LQTS	+++	+++	+++

Europace (2022) 24, 1307–1367

Qt

QTL

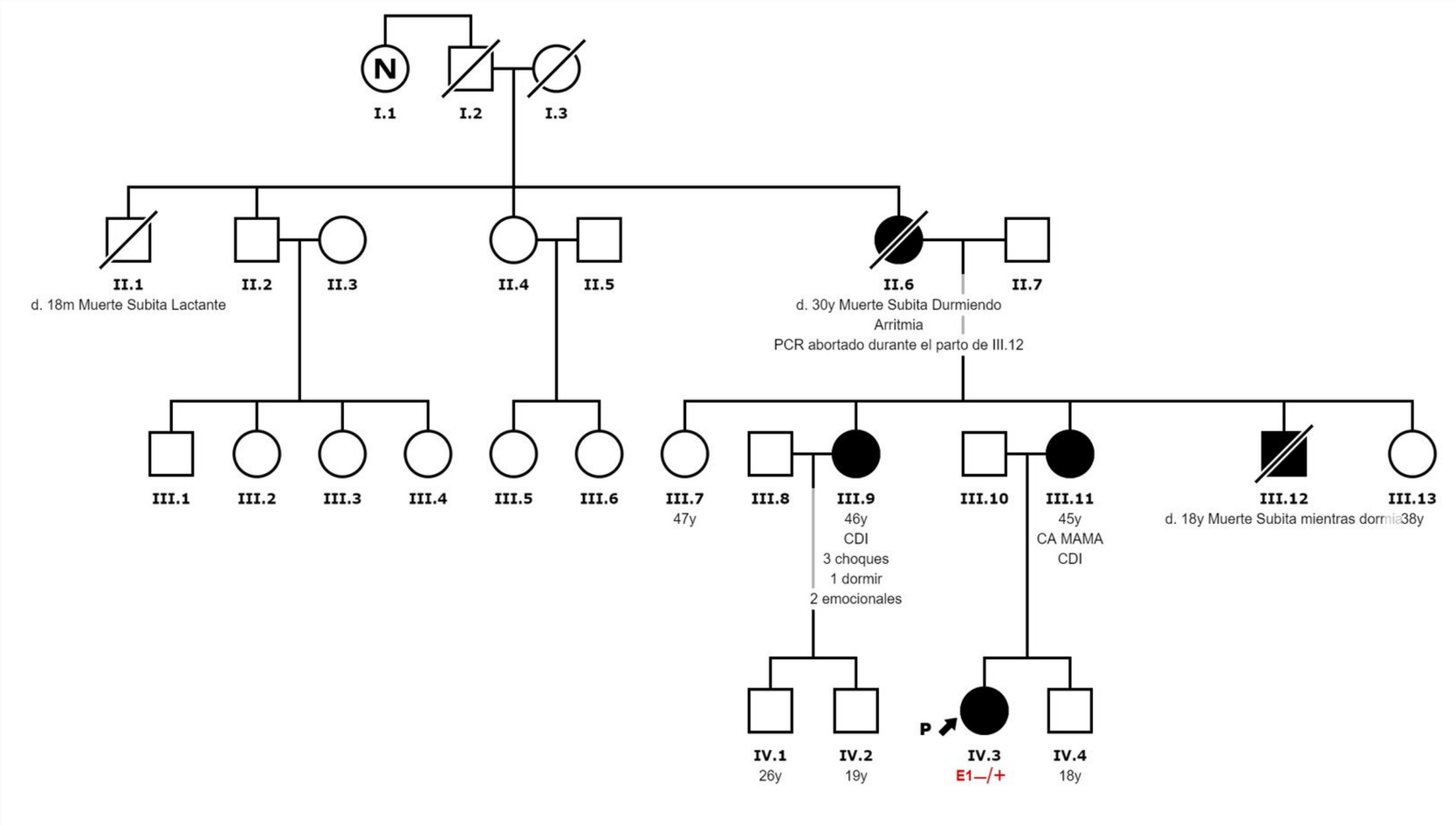
Score de Scwartz ≥3,5

Dismorfismos faciales y TEA

Debilidad Muscular. Esqueleto anormal

KCNQ1 KCNH2 SCN5A CALM 1,2,3	CACNA1C KCNE1	KCNQ1 KCNE1	CACNA1C, AD	TRDN AR	KCNJ2 AD
		AR. Jervell Lange Nielsen	**Síndrome de Timothy**	**Síndrome KO TRD**	**Síndrome de Andersen Tawil**

Expert Consensus Statement on the state of genetic testing for cardiac disease. Europace (2022) 24, 1307–1367



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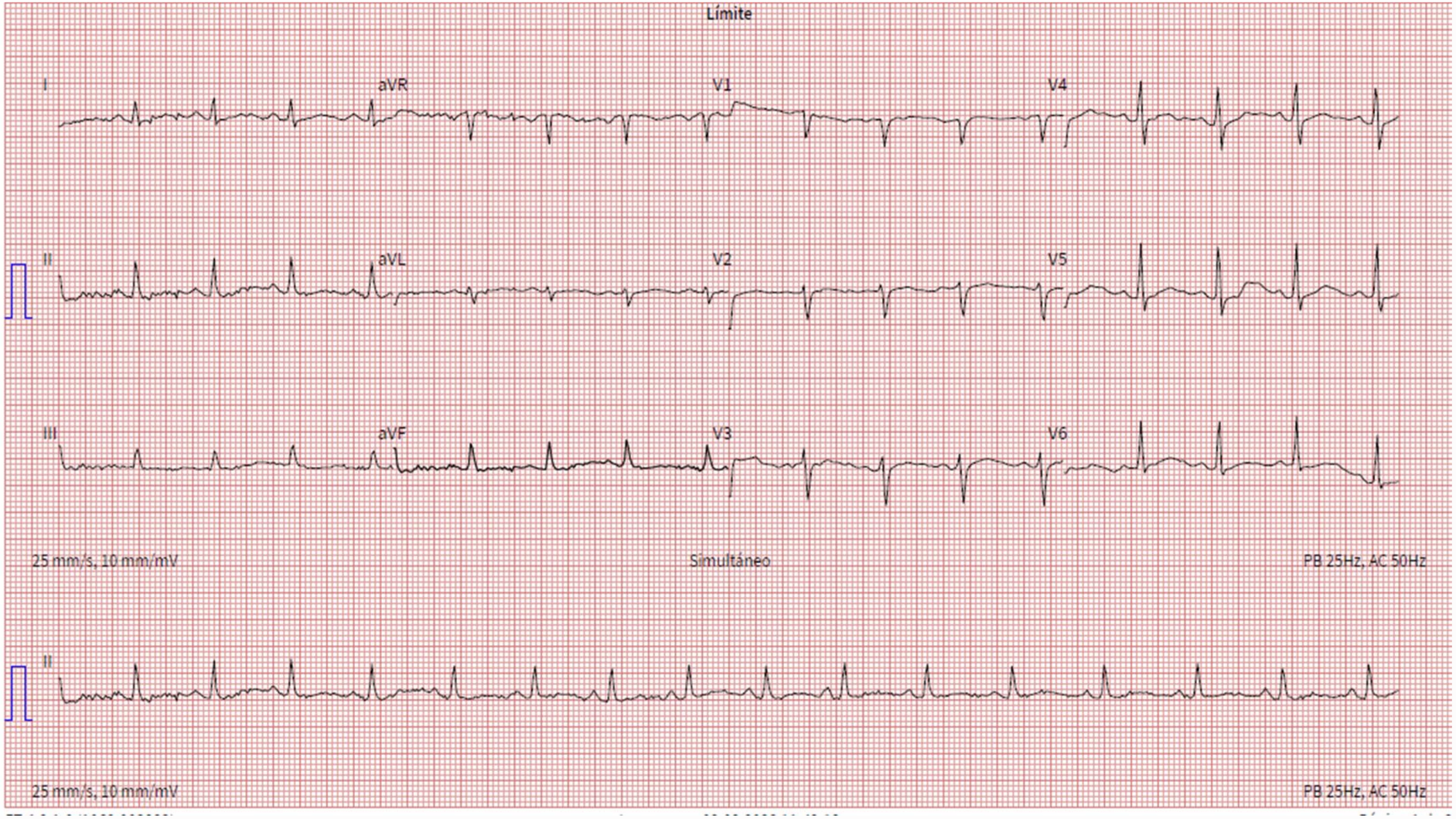
Qt



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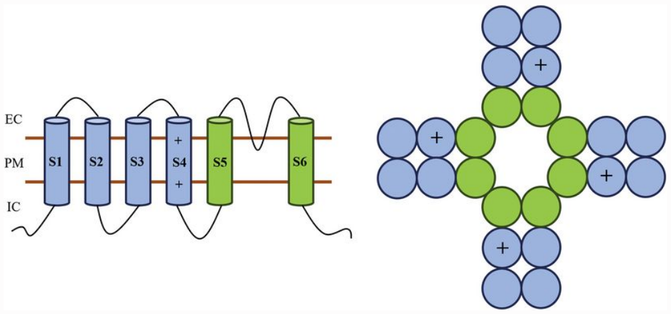
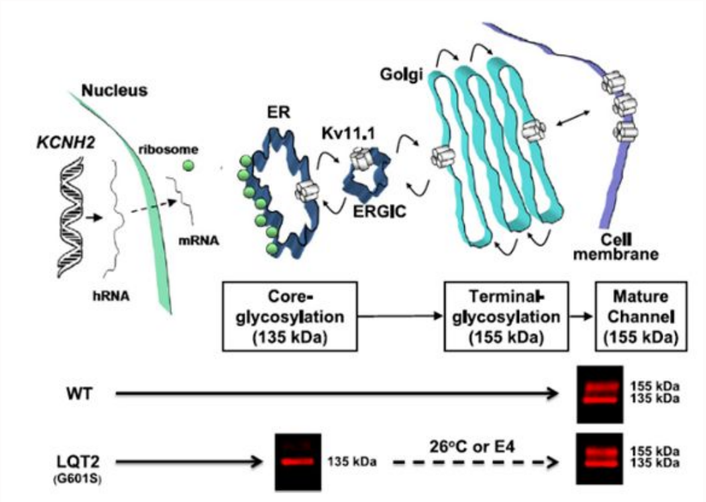
Qt

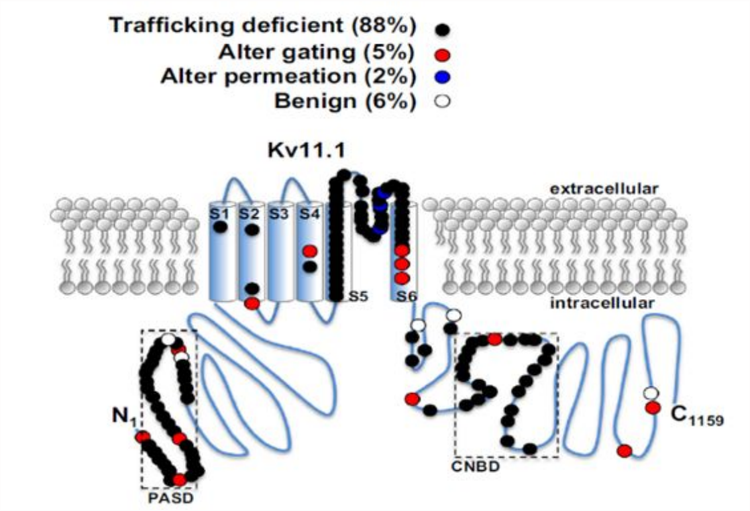
UCT HOSPITALARIA PATAGONICA

HOSPITALES DE ALTA COMPLEJIDAD HOSPITAL GOBERNADOR CEPERNIC PRESIDENTE KIRCHNER

GEN	CAMBIO DE NUCLEÓTIDO	CAMBIO DE AMINOÁCIDO	CIGOSIDAD	CLASIFICACIÓN ACMG
KCNH2	c.1814C>A (NM_000238.4)	p.(Pro605His)	Heterocigota	Posiblemente Patogénica







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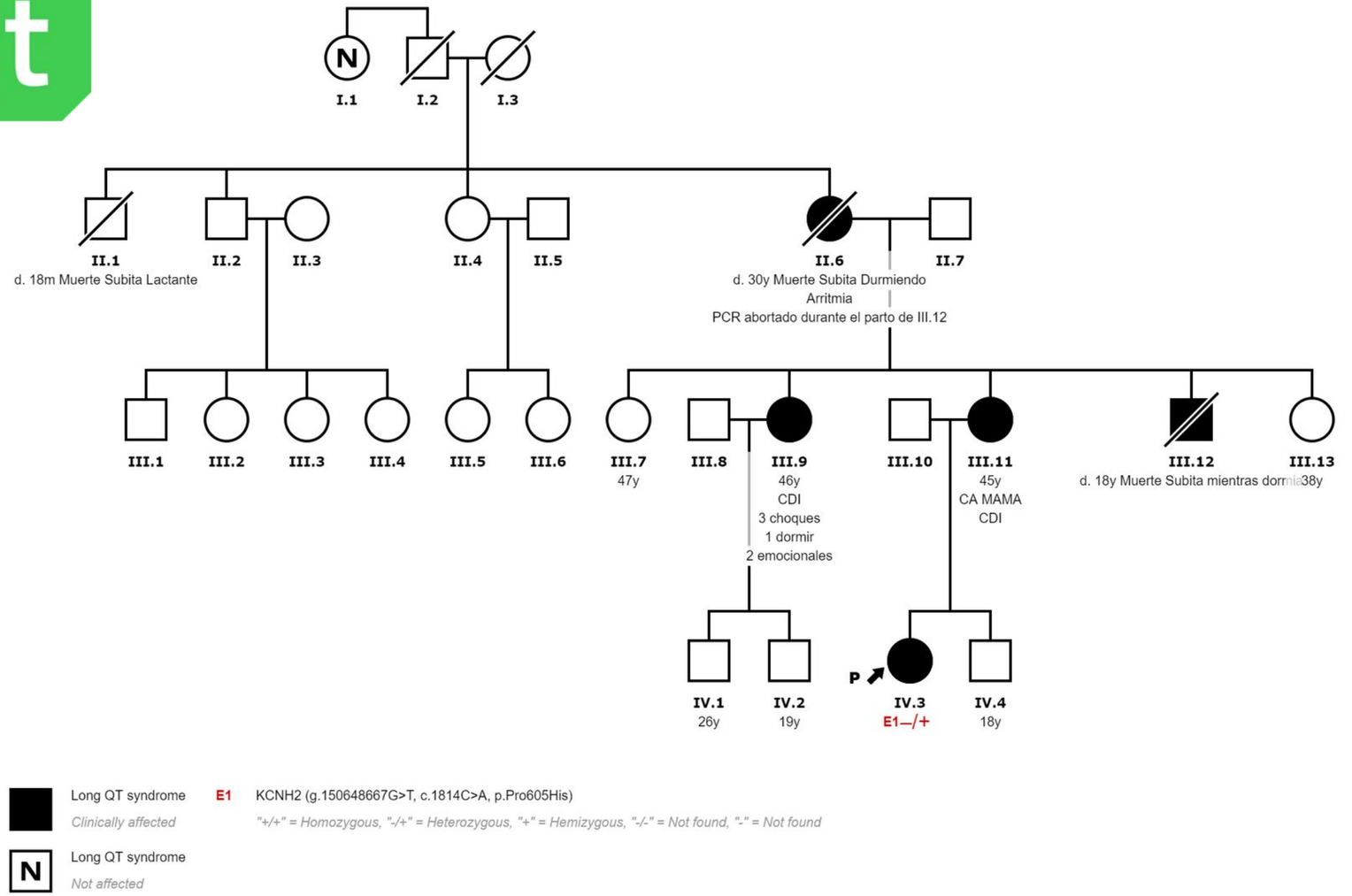
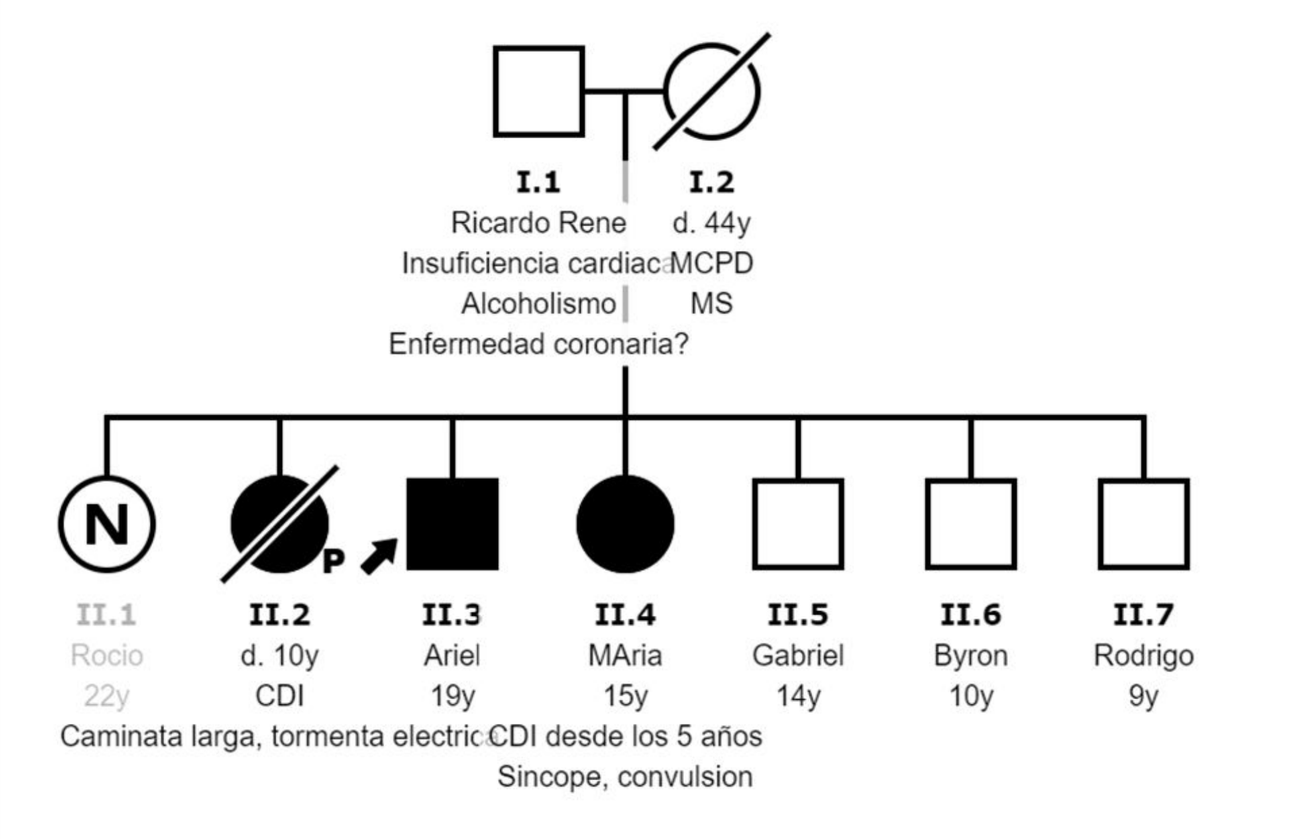
Qt



BETABLOQUEANTES

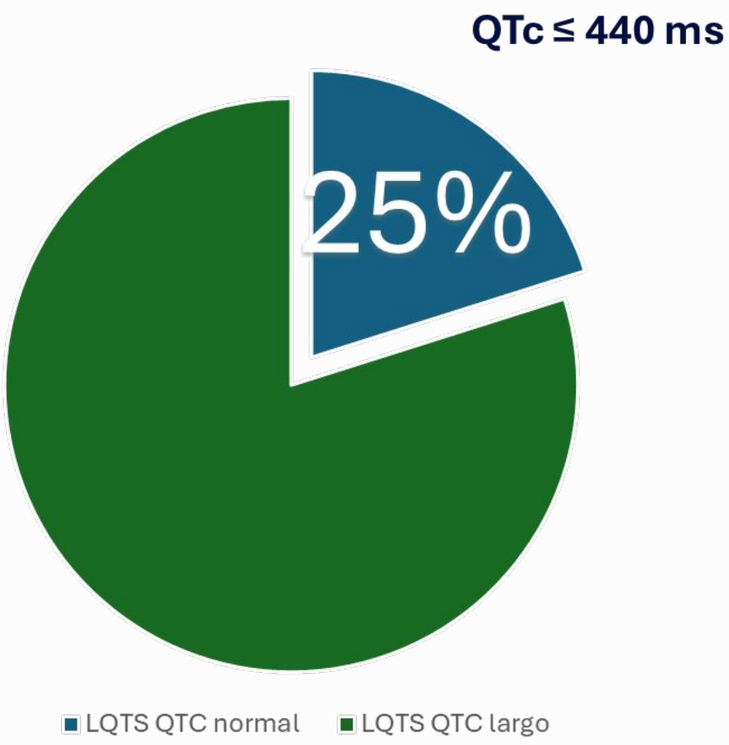
Qt

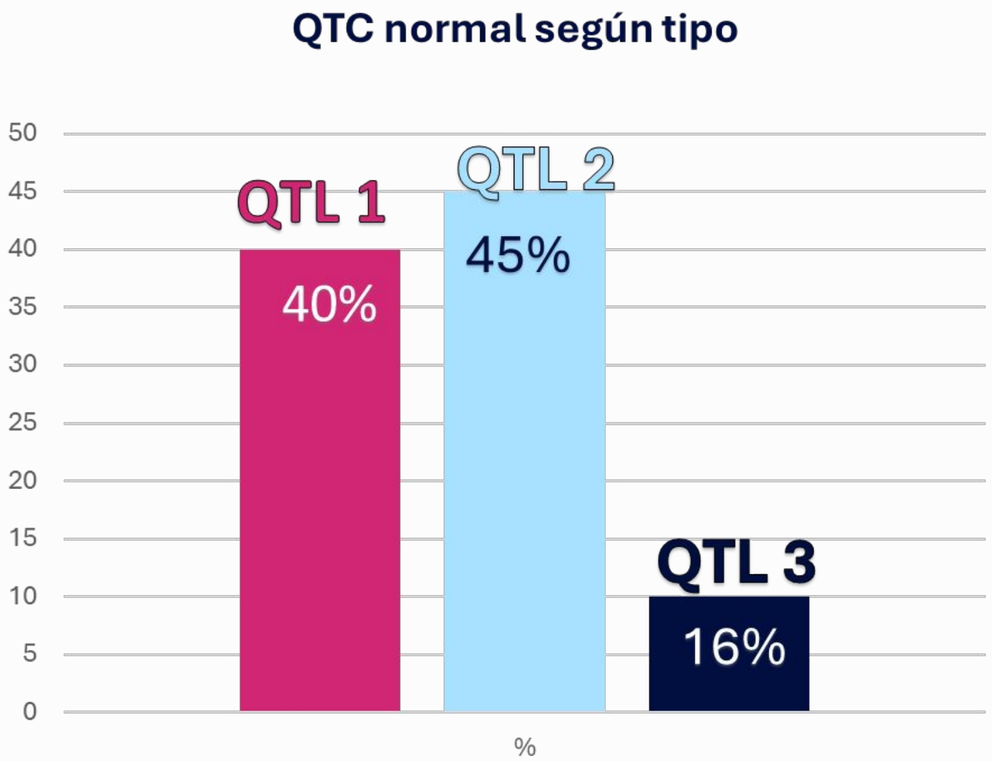


SINCOPE

ECG NORMAL

Qt

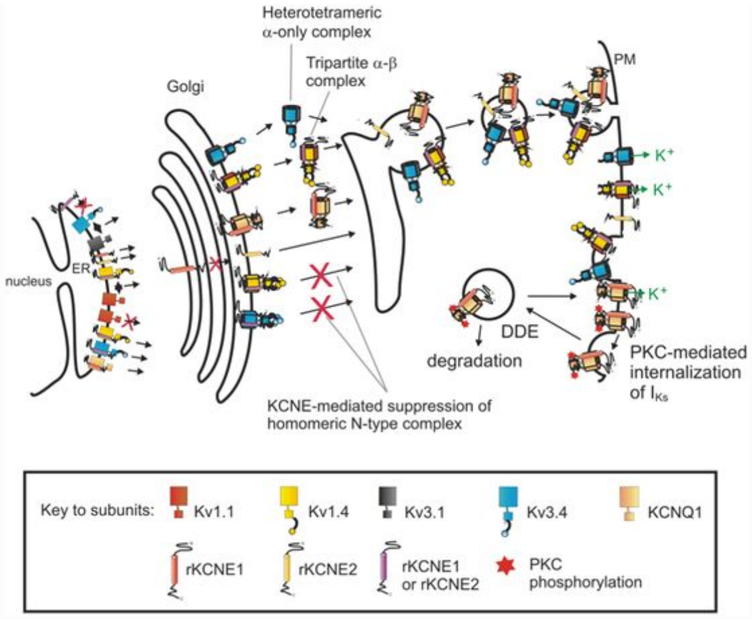


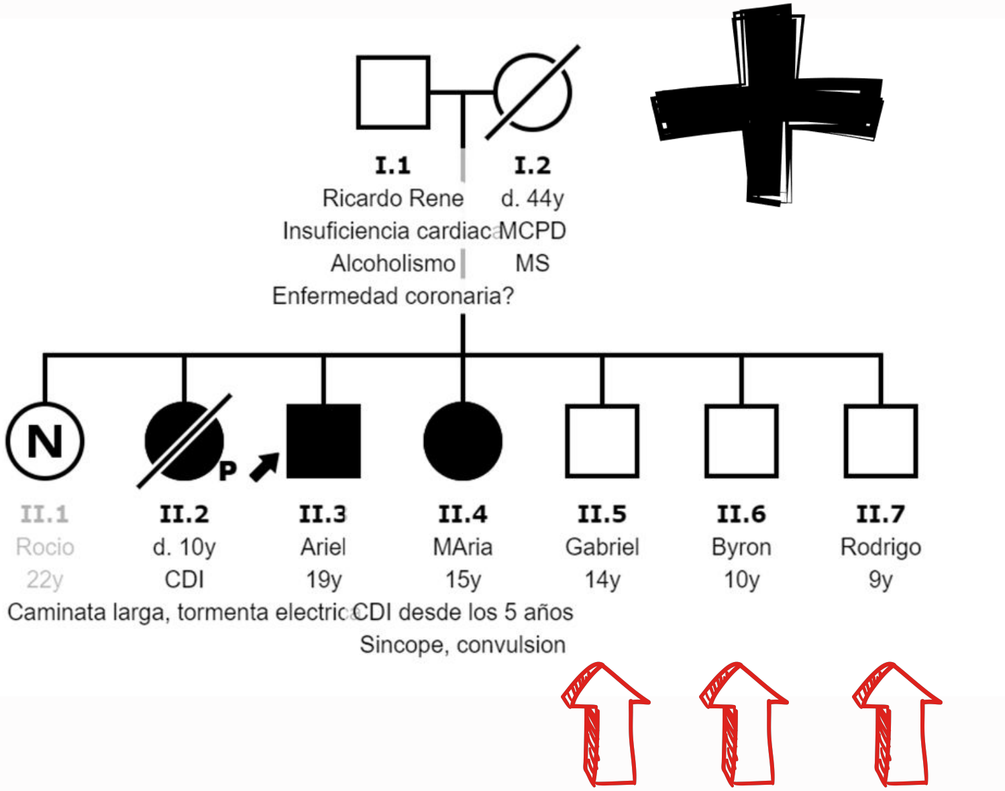


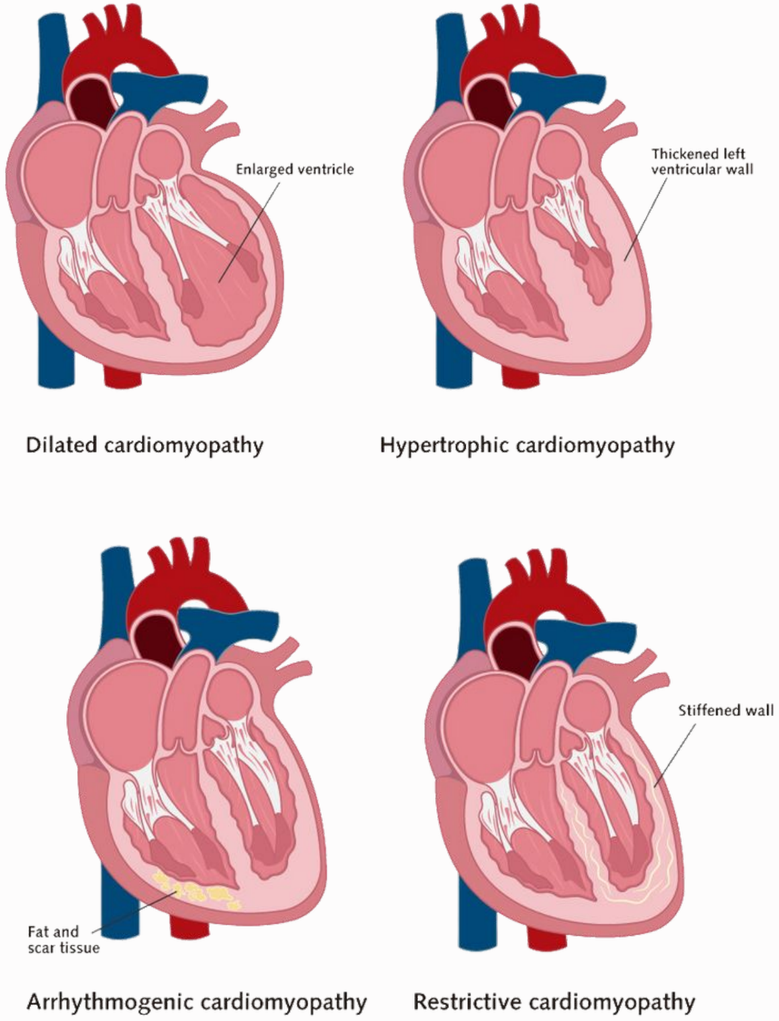
Goldenberg I et al. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. J Am Coll Cardiol. 2011;57:51–9.

BETABLOQUEANTES

GEN	CAMBIO DE NUCLEÓTIDO	CAMBIO DE AMINOÁCIDO	CIGOSIDAD	CLASIFICACIÓN ACMG
KCNQ1	c.535G>A (NM_000218.3)	p.Gly179Ser	Heterocigota	**Patogénica**

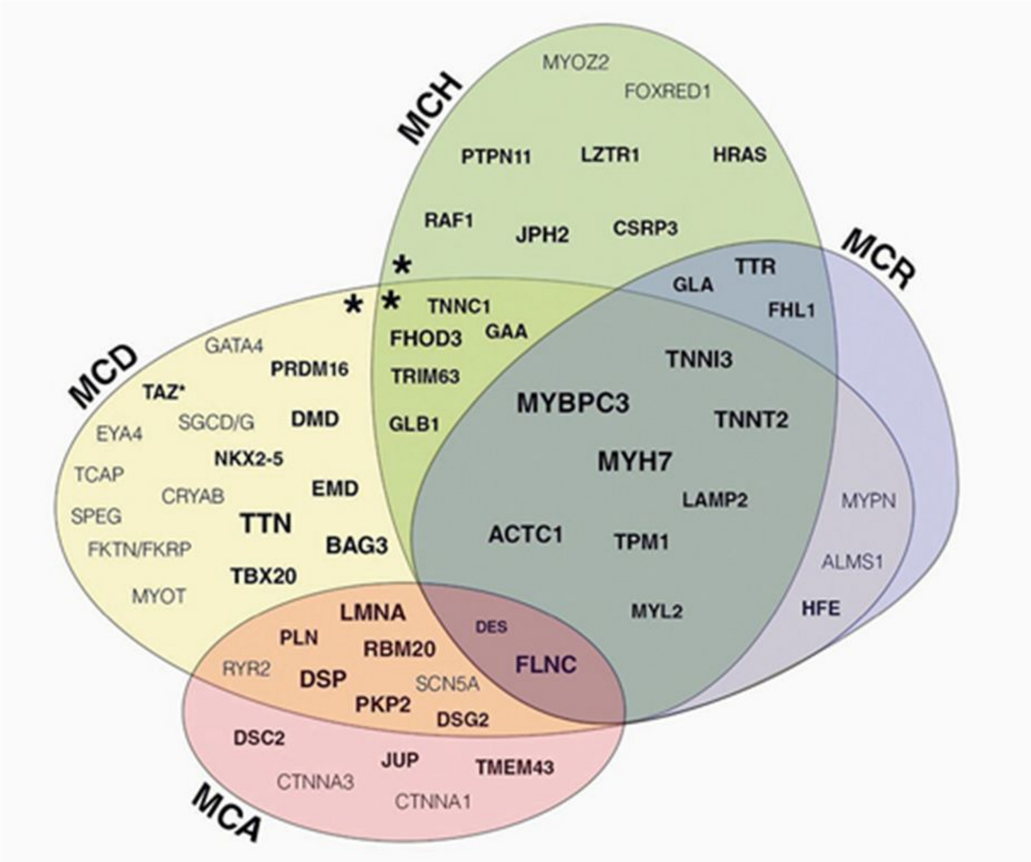


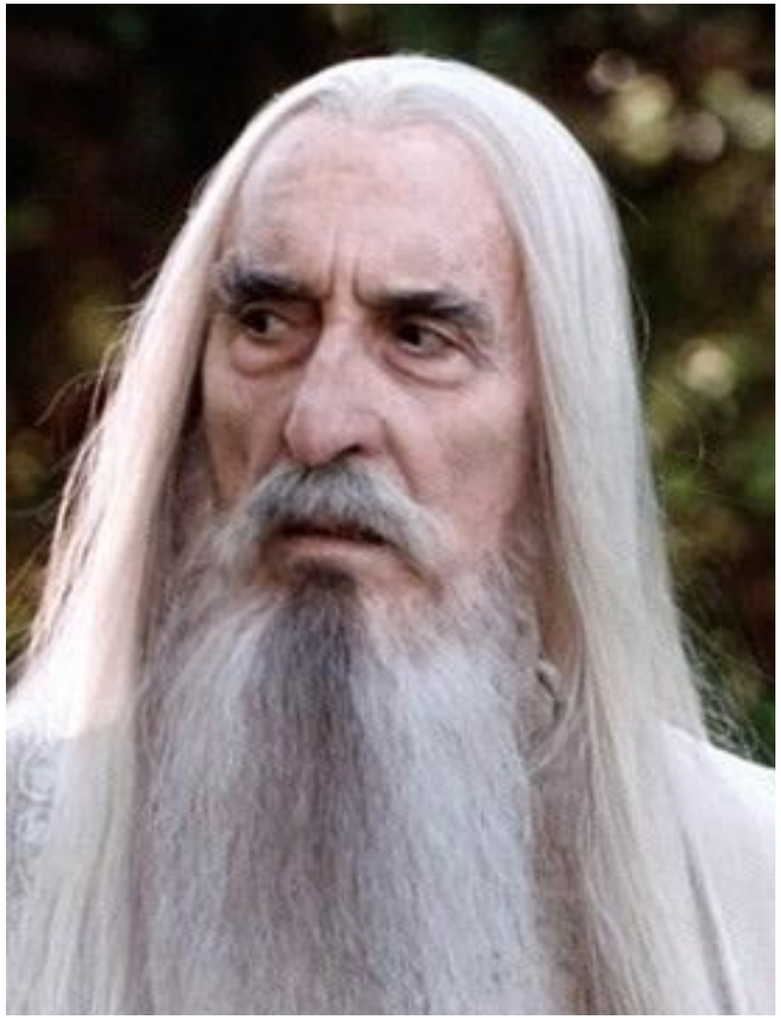




Miocardiopatías

Fenotipos solapados





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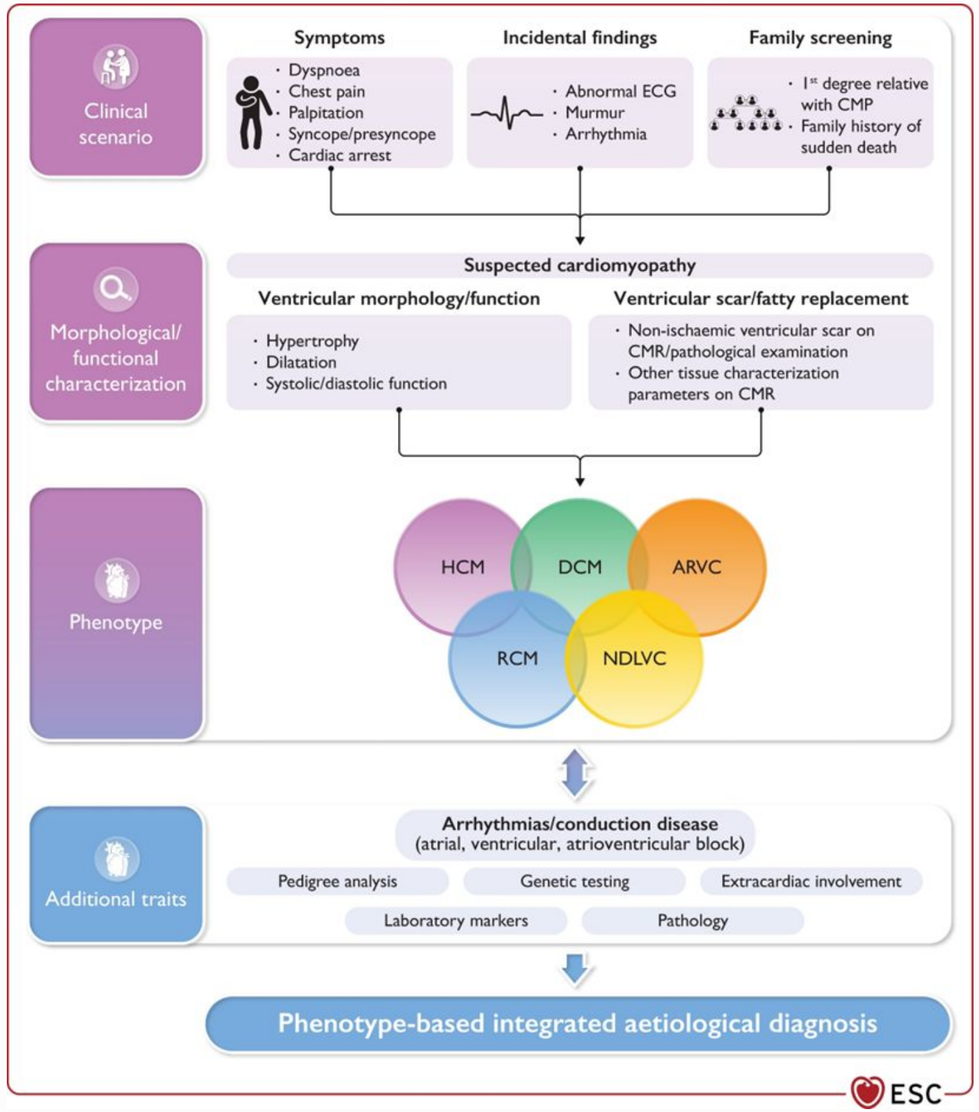

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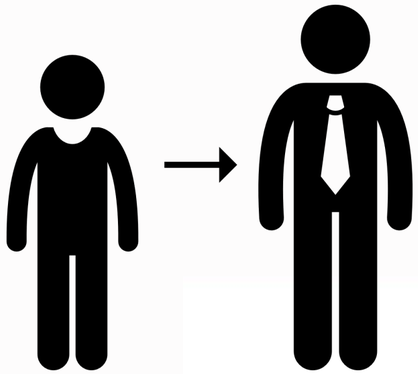
Miocardiopatia Hipertrofica

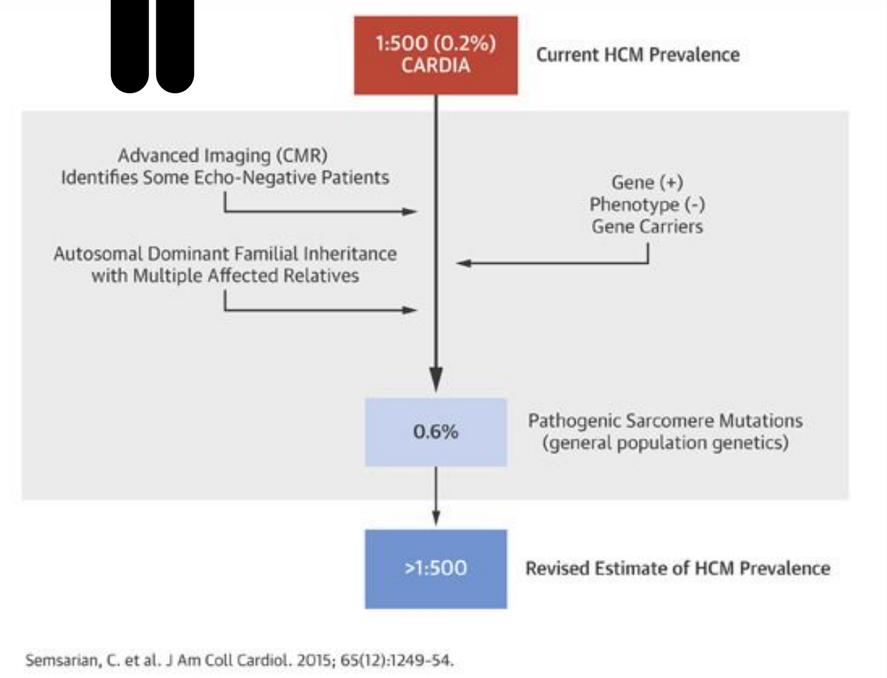


0.2%

Prevalencia:

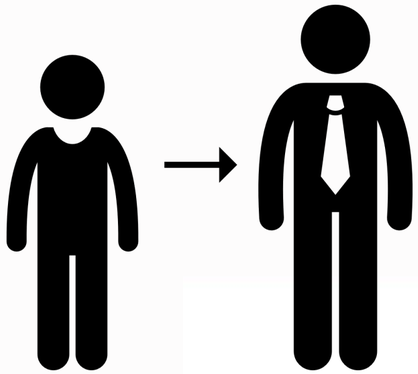
0.029%

Arola A, et al. Am J Epidemiol. 1997 Sep 1;146(5):385-93.



Semsarian, C. et al. J Am Coll Cardiol. 2015; 65(12):1249-54.

Miocardiopatia Hipertrofica



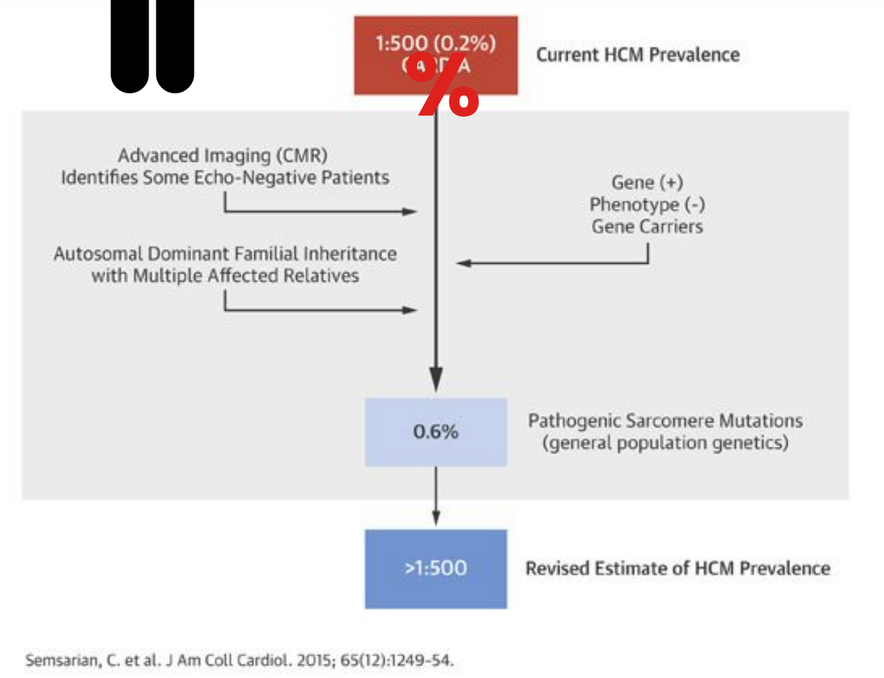
Prevalencia:

0.029%

Arola A, et al. Am J Epidemiol. 1997 Sep 1;146(5):385-93.

Inicio: 15%

0.2 %



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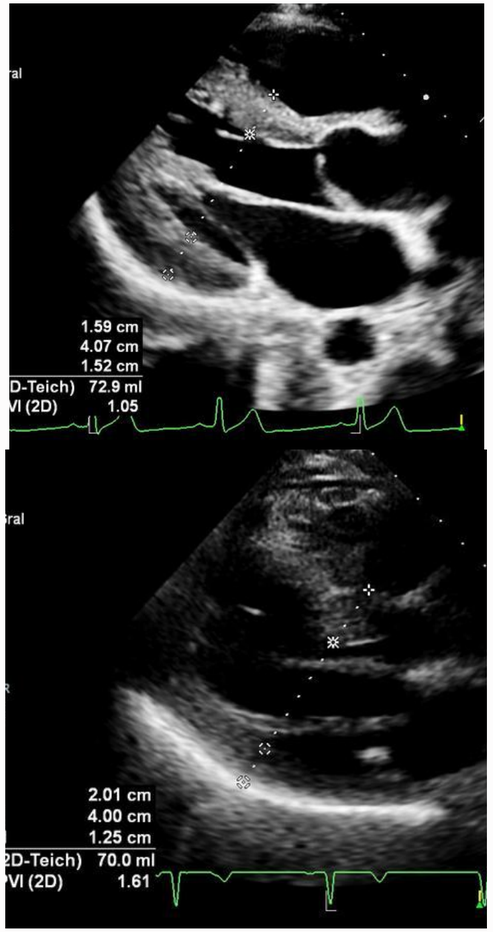


Espesor parietal en uno o mas segmentos miocardicos

≥15 mm

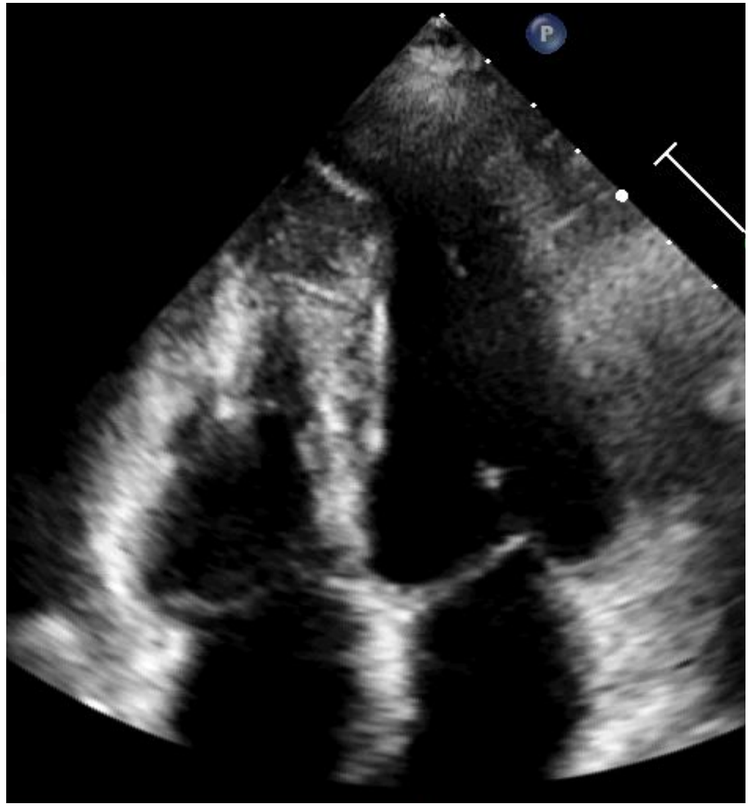
Z-score ≥2.5

o

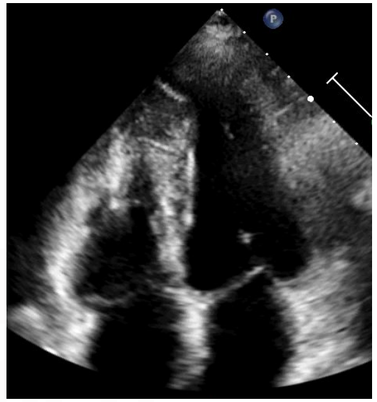
≥13 mm

Z-score ≥2

Ausencia otras causas de engrosamiento parietal, sistémicas, sindrómicas o metabólicas.



Ausencia otras causas de engrosamiento parietal, sistémicas, sindrómicas o metabólicas.



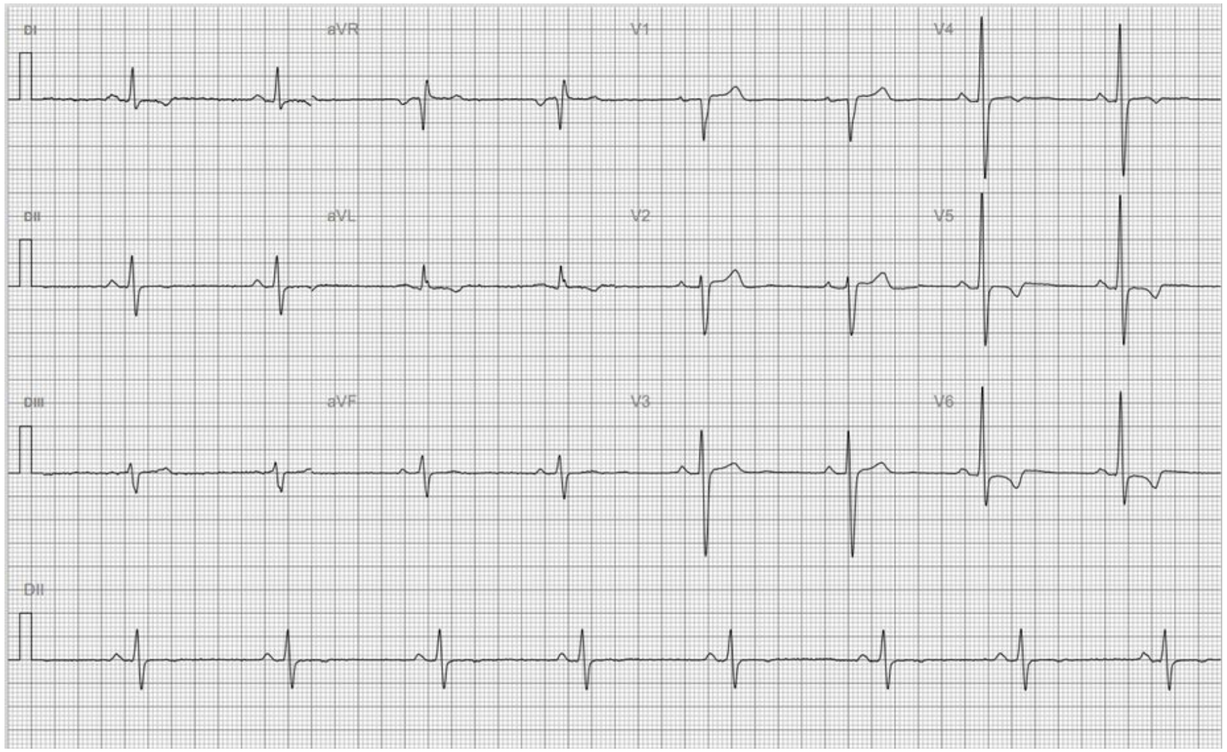
BITGENIA

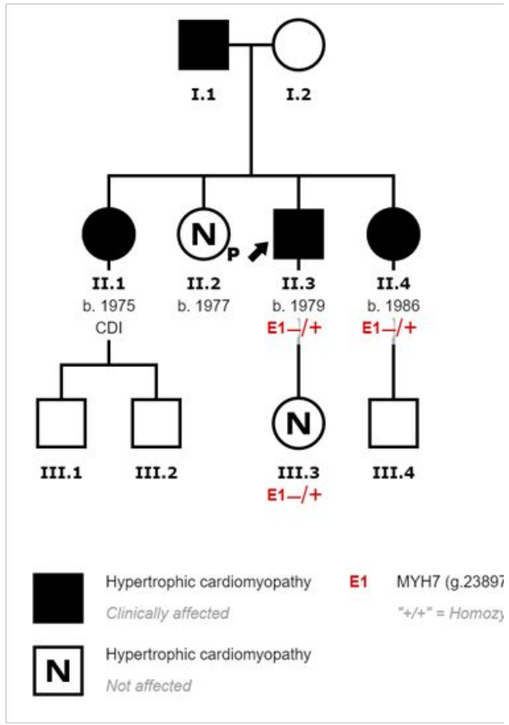
RESULTADOS

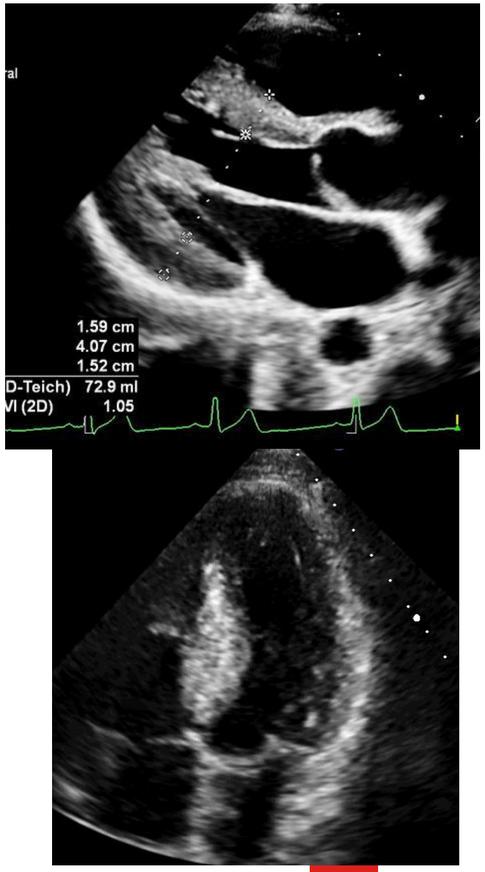
Se informa una variante **Patogénica** en el gen ***PTPN11*** asociado con Síndrome de Noonan, Síndrome de Noonan con múltiples léntigos y Metacondromatosis, todos de herencia autosómica dominante.

PTPN11 NM_002834.5							
POSICIÓN	CAMBIO DE NUCLEÓTIDO	CAMBIO EN LA PROTEÍNA	EFECTO	GENOTIPO	PROF.	INFO EXTERNA	CLASIFICACIÓN ACMG
12:112489068	C > T c.1492C>T	p.(Arg498Trp)	*Missense Variant*	HET	51/123	rs397507541	5

5 Patogénica 4 Probablemente Patogénica 3 Significado incierto (VUS)

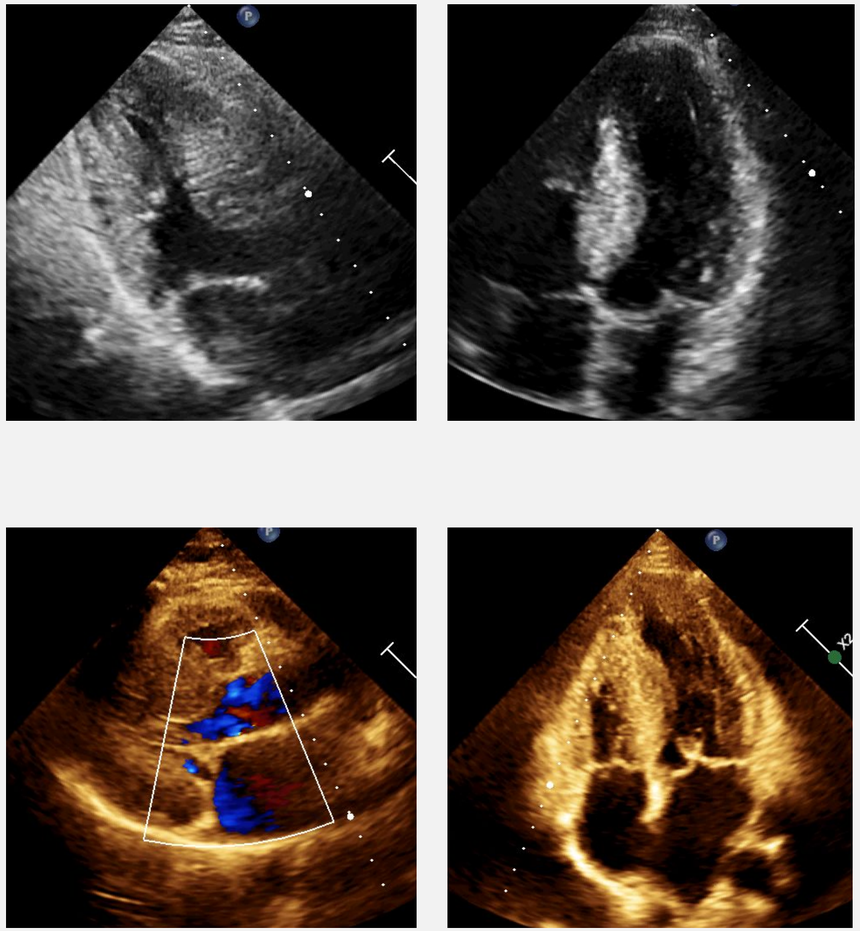


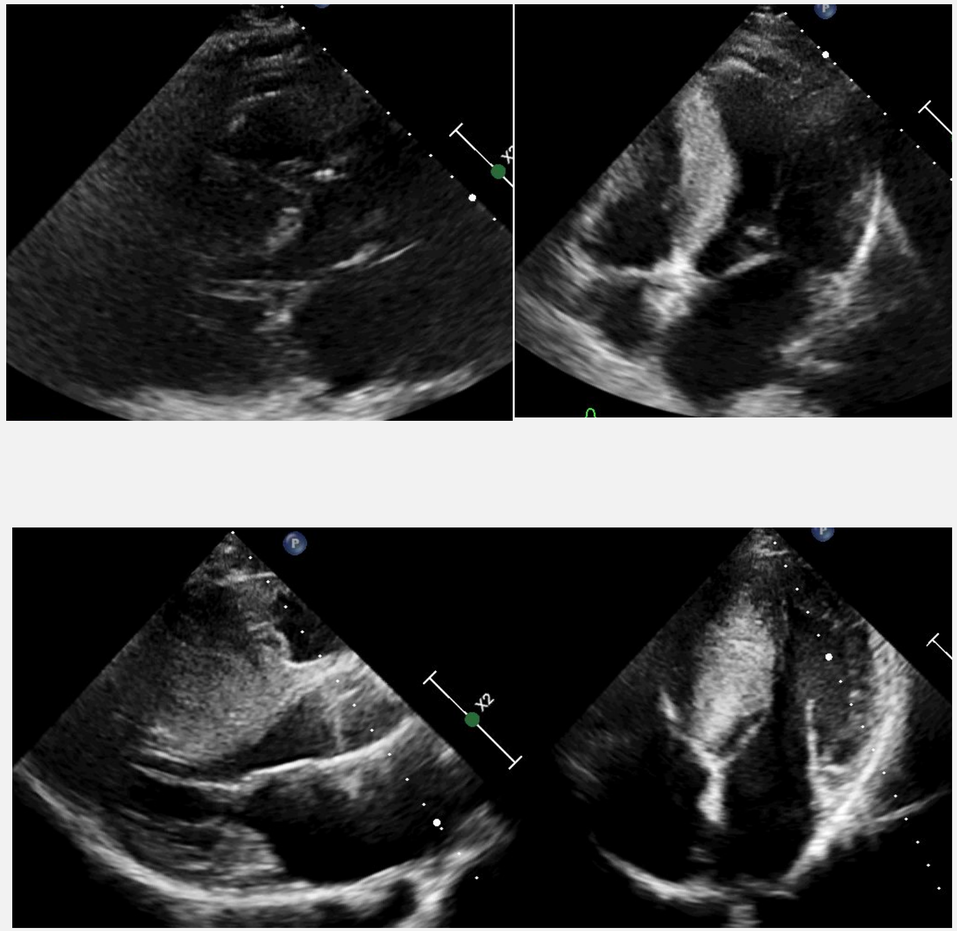




Desafíos diagnósticos en enfermedades cardiovasculares de origen hereditario. Dr Luis Enrique Gómez

MCH y?

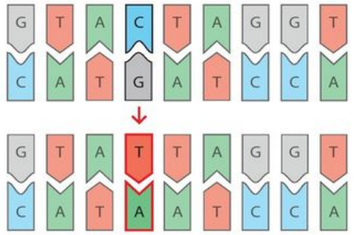




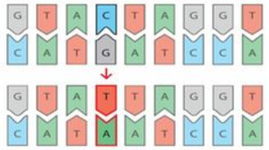
MCH y genética

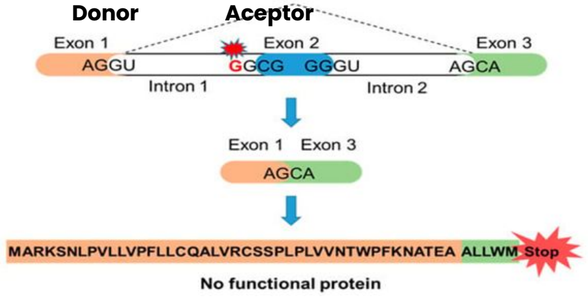
III JORNADAS DE GENÓMICA CLÍNICA

SNV

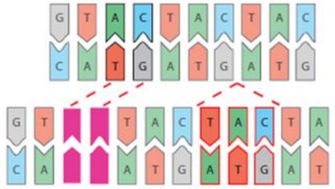


SNV

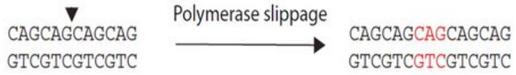




Indel



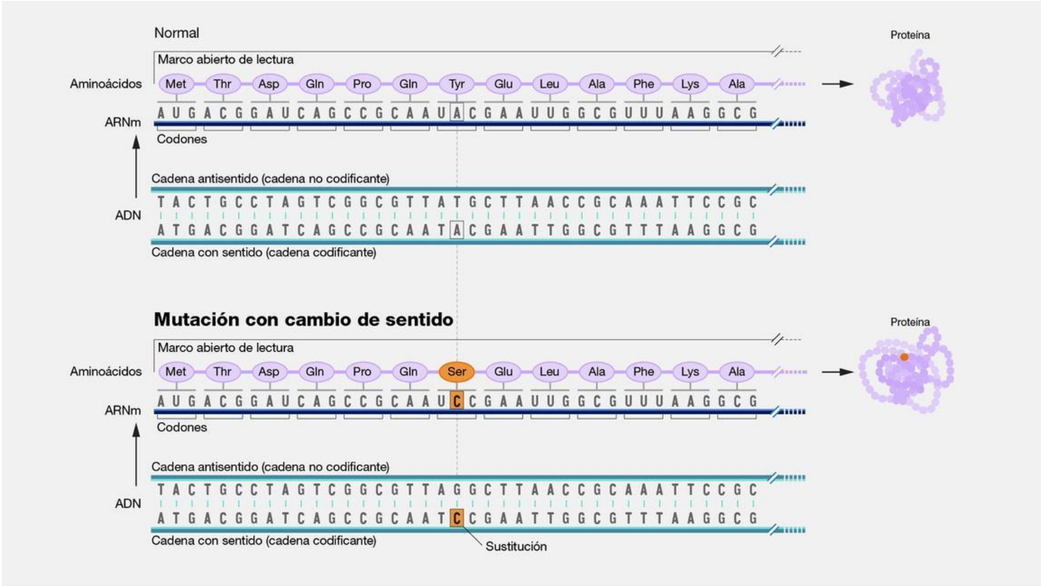
Deslizamiento de la ADN Pol*

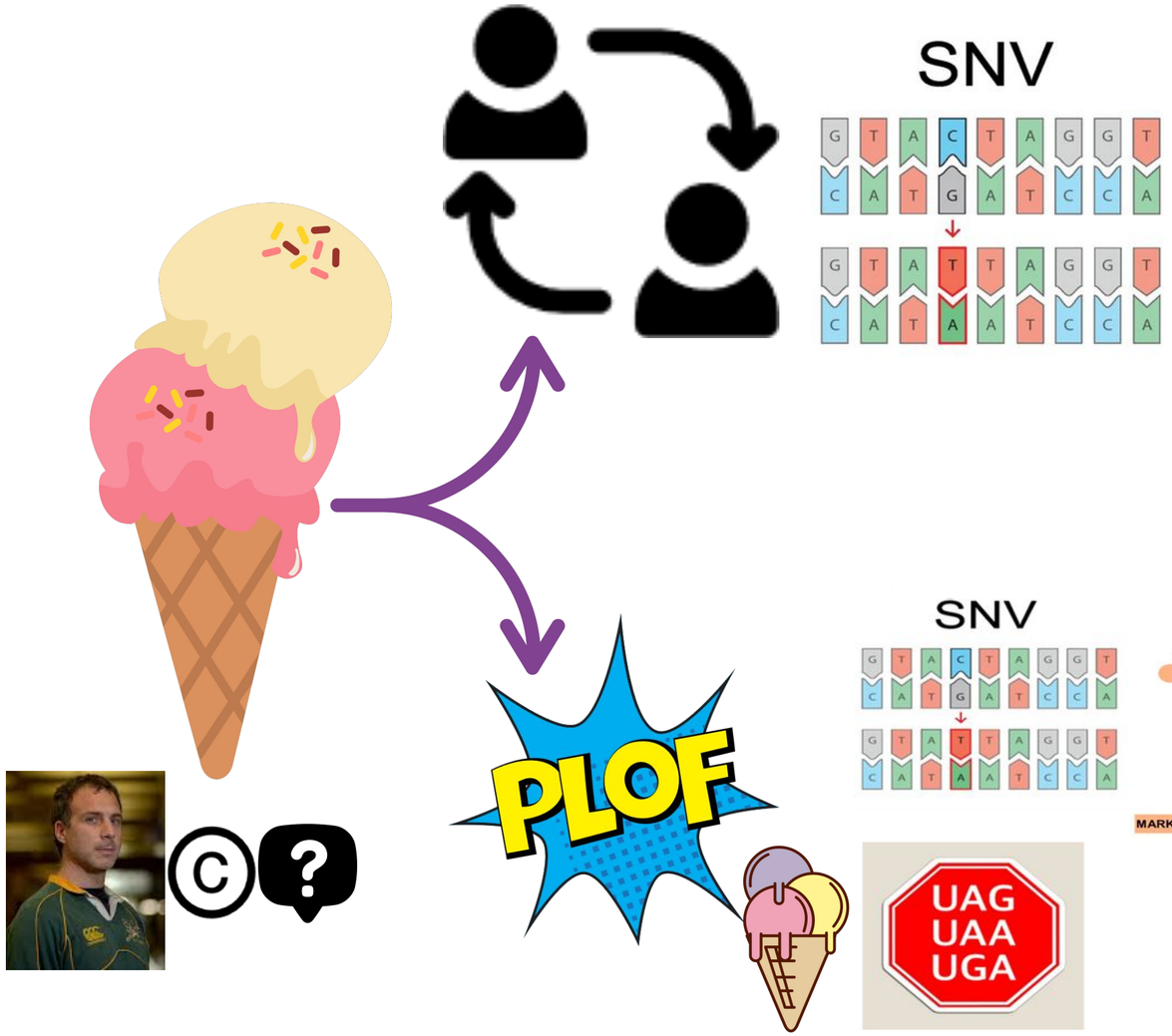


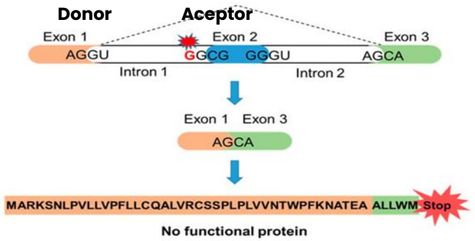
Streisinger G. Cold Spring Harb Symp Quant Biol. 1966;31:77-84

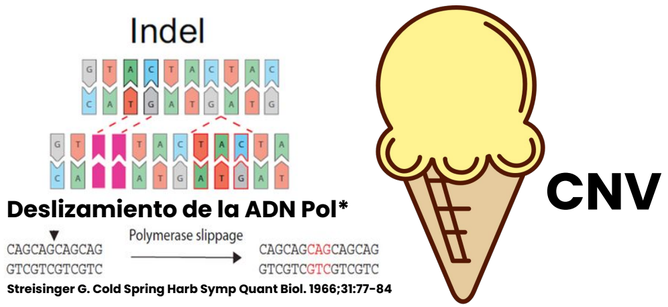
Desafíos diagnósticos en enfermedades cardiovasculares de origen hereditario. Dr Luis Enrique Gómez

MCH y genética

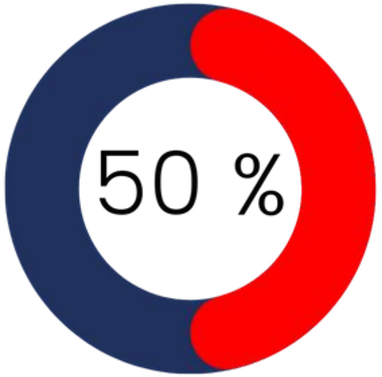








Genética, organicemos chango



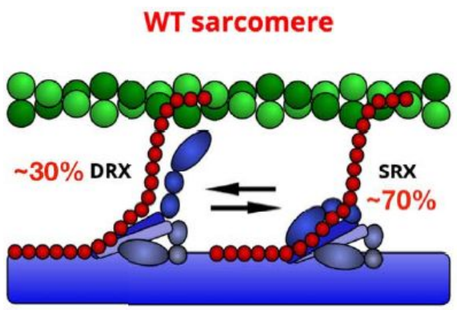
REDITO DIAGNOSTICO

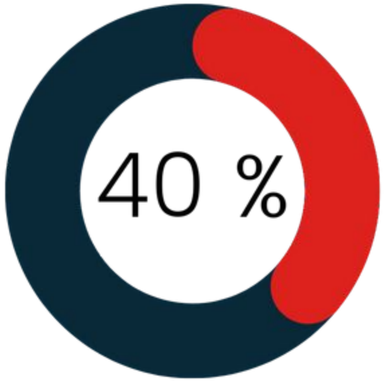
Dosage Sensitivity

Gene	Disease	Working Group	HI Score & TS Score
MYH7		Dosage Sensitivity WG	0 (No Evidence for Haploinsufficiency) 0 (No Evidence for Triplosensitivity)

Dosage Sensitivity

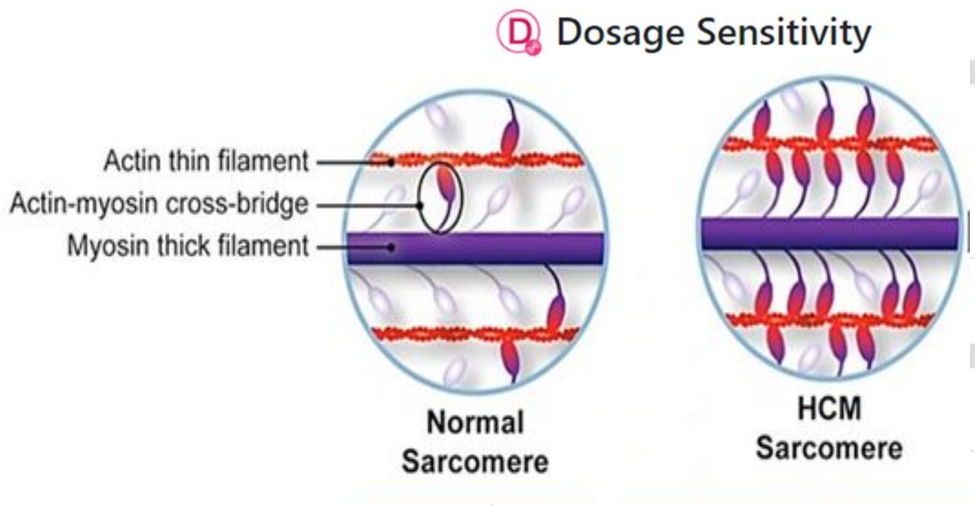
Gene	Disease	Working Group	HI Score & TS Score
MYBPC3	hypertrophic cardiomyopathy 4 MONDO:0007268	Dosage Sensitivity WG	3 (Sufficient Evidence for Haploinsufficiency)
MYBPC3		Dosage Sensitivity WG	0 (No Evidence for Triplosensitivity)

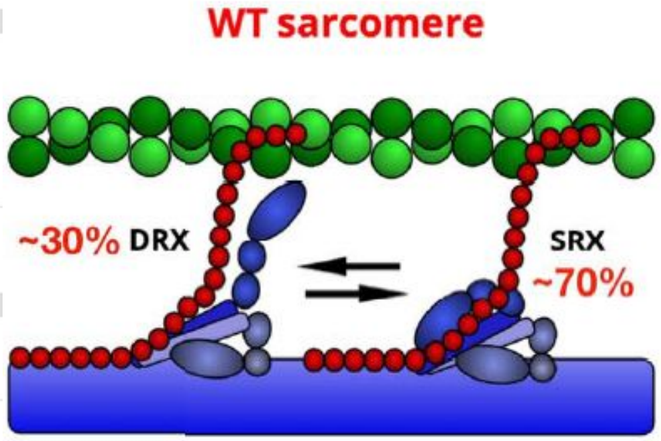




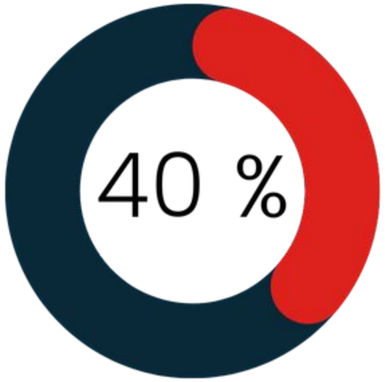
MYH7 Y MYBPC3

Genética, organicemos chango

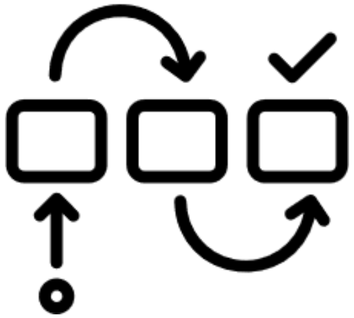




REDITO DIAGNOSTICO



MYH7 Y MYBPC3

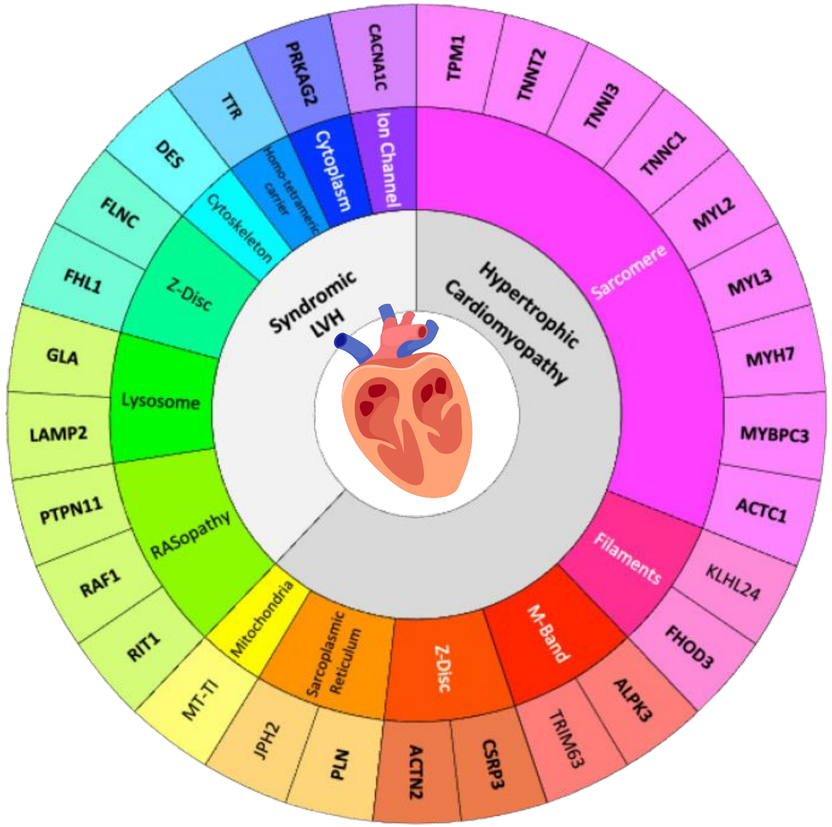


POPULATION EVIDENCE (POP)
POP_FRQ Population Freq.

CLINICAL EVIDENCE (CLN)
CLN_CCR Case:control ratio
CLN_COB Case observation counts
CLN_LNK Linkage
CLN_PHE Specific Phenotype
CLN_DNV De novo

MOLECULAR IMPACT EVIDENCE (IMP)
IMP_NMD Predicted to undergo NMD
IMP_CDS Impact to coding sequence
IMP_MSS Missense variants
IMP_SYN Synonymous
IMP_INF In-frame delins
IMP_SPL Splicing assessment
IMP_FXN Variant-specific Funct Assays

Al final del dia...



Hespe S, Waddell A, Ingles J. ClinGen Hereditary Cardiovascular Disease Gene Curation Expert Panel: Reappraisal of Genes associated with Hypertrophic Cardiomyopathy. medRxiv [Preprint]. 2024 Jul 31:2024.07.29.24311195.

Sarcomero

MYBPC3,MYH7,TPM1,TNNT2,ACTC1,MYL2,MYL3,TNNC1

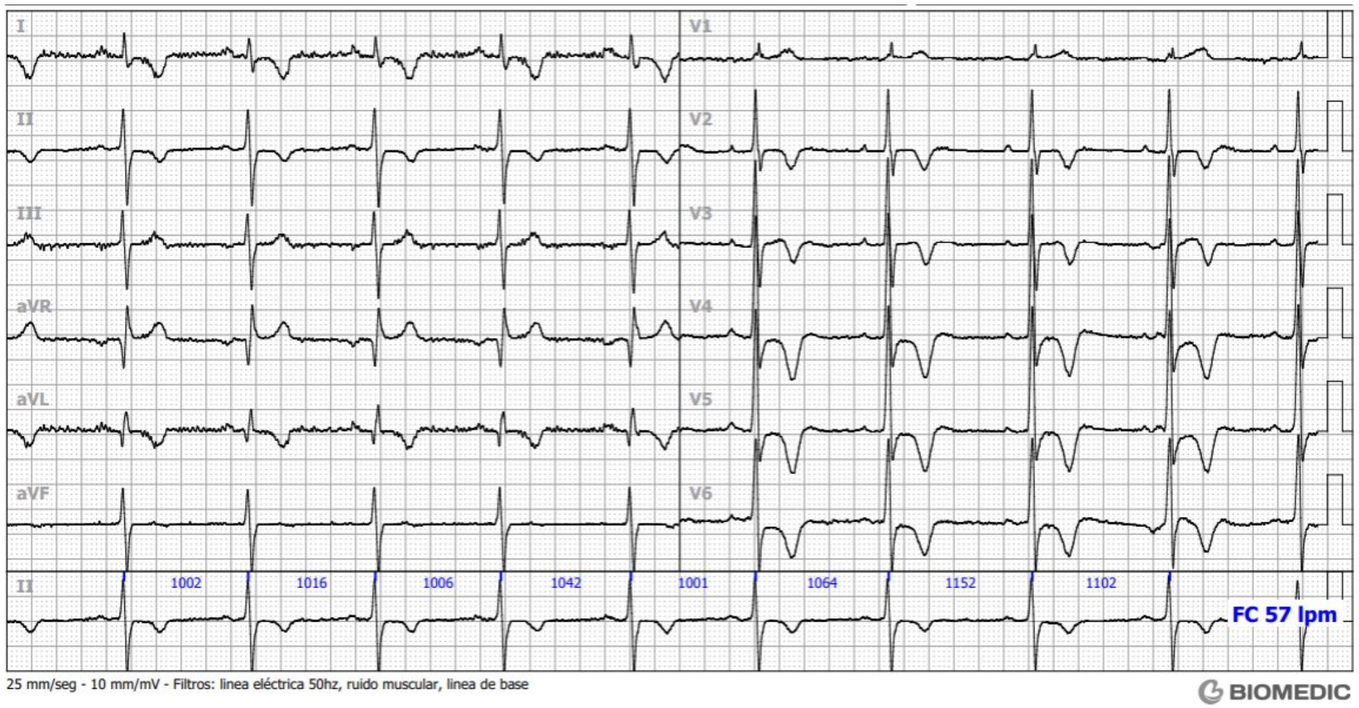
Otros monogenicos

FHOD3,KLHL24,TRIM63,CSRP3,PLN,ACTN2,JPH2,MT-TI

Sindromico

Rasopatias: PTPN11, RAF1, RIT1
Danon: LAMP2
Fabry: GLA
Amiloidosis: TTR
Emery Dreifuss: FHL1
Miopatia miofibrilar: FLNC
Desminopatia: DES
PRKAG2: PRKAG2
Sme. Timothy: CACNA1C

Poligenico



30 Años.

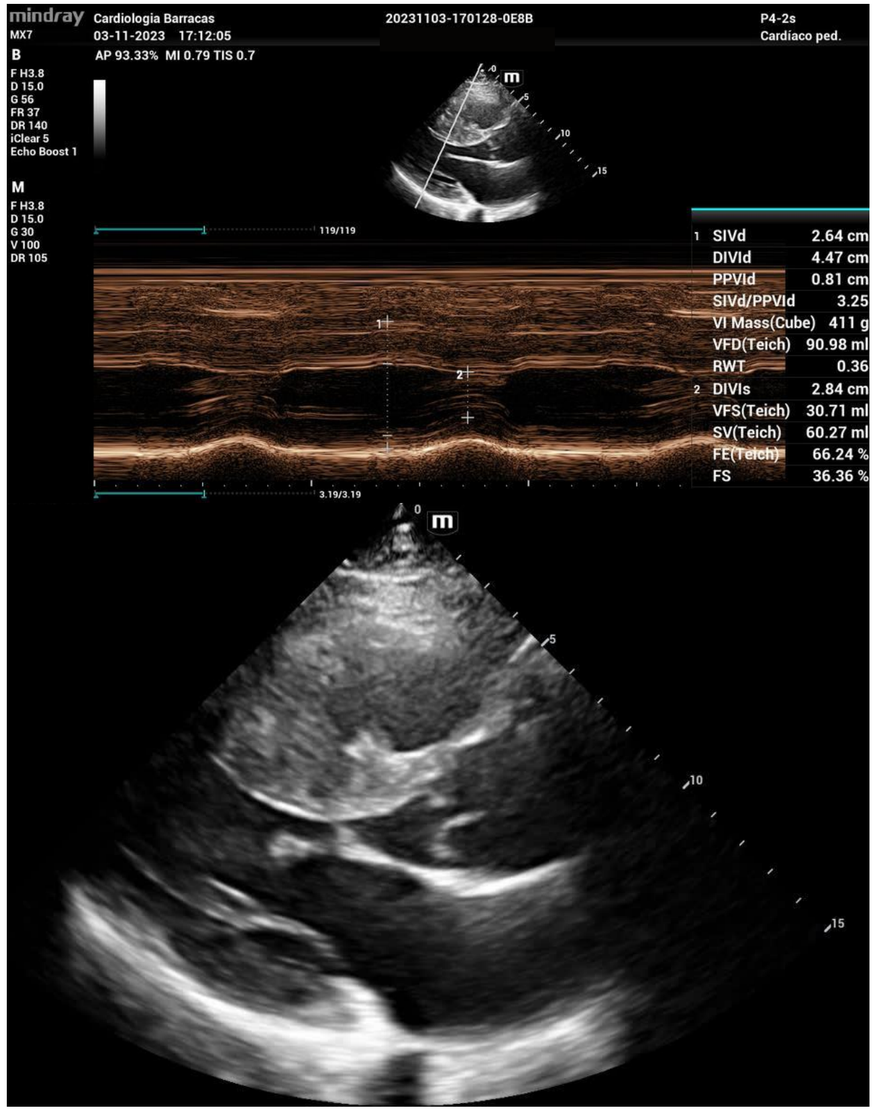
Apto físico

Antecedentes fliares

desconoce

Sintomas

asintomatico



Ecodopper

Diagnostico

Miocardiopatia Hipertrofica Septal

Asimetrica no obstructiva

1

Estudio genético

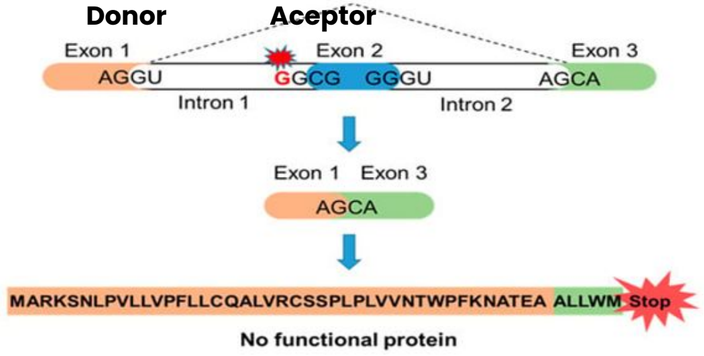
BITGENIA
TRANSCENDING GENOMICS

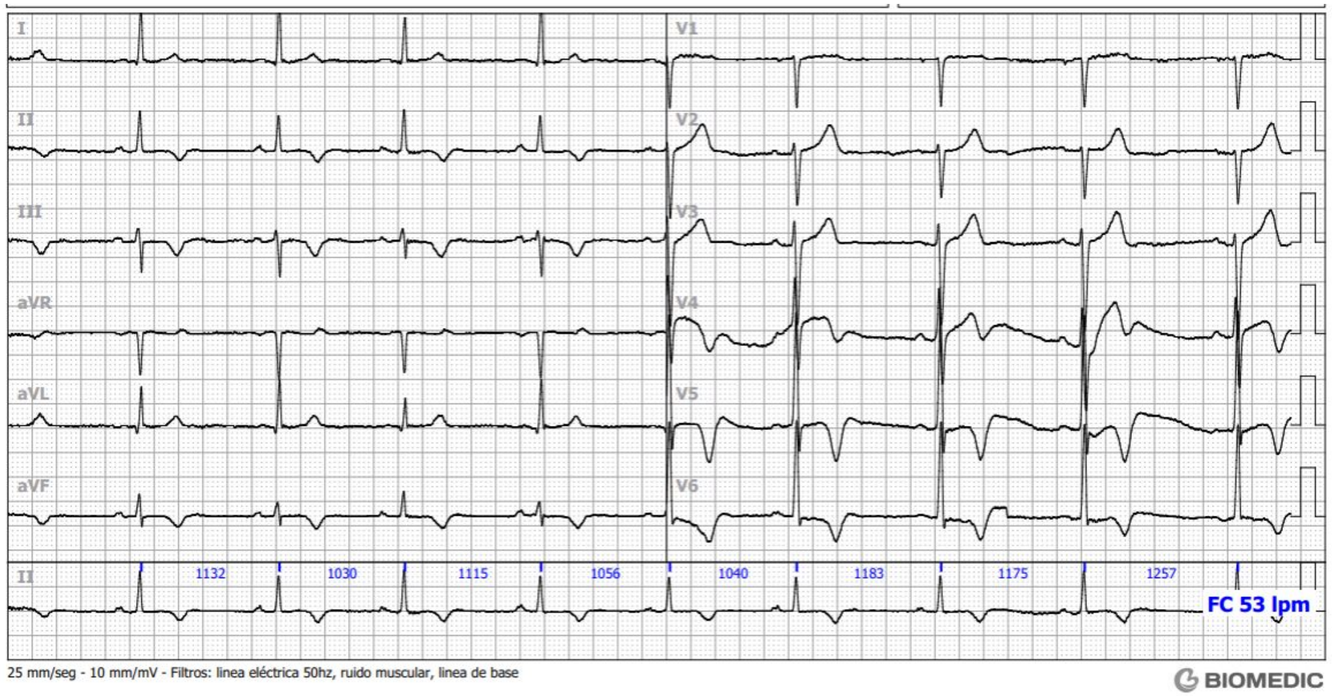
RESULTADOS

Se informa una variante **Patogénica** en el gen ***MYBPC3*** asociado con Cardiomiopatía Hipertrófica (autosómico dominante/ autosómico recesivo) y Cardiomiopatía Dilatada (autosómico dominante).

MYBPC3 NM_000256.3							
POSICIÓN	**CAMBIO DE NUCLEÓTIDO**	**CAMBIO EN LA PROTEÍNA**	**EFECTO**	**GENOTIPO**	**PROF.**	**INFO EXTERNA**	**CLASIFICACIÓN ACMG**
11:47339792	T>C c.1928-2A>G	p.(?)	*Splice Acceptor Variant*	HET	50/107	rs397515937	**5**

5 Patogénica 4 Probablemente Patogénica 3 Significado incierto (VUS)





36 Años.

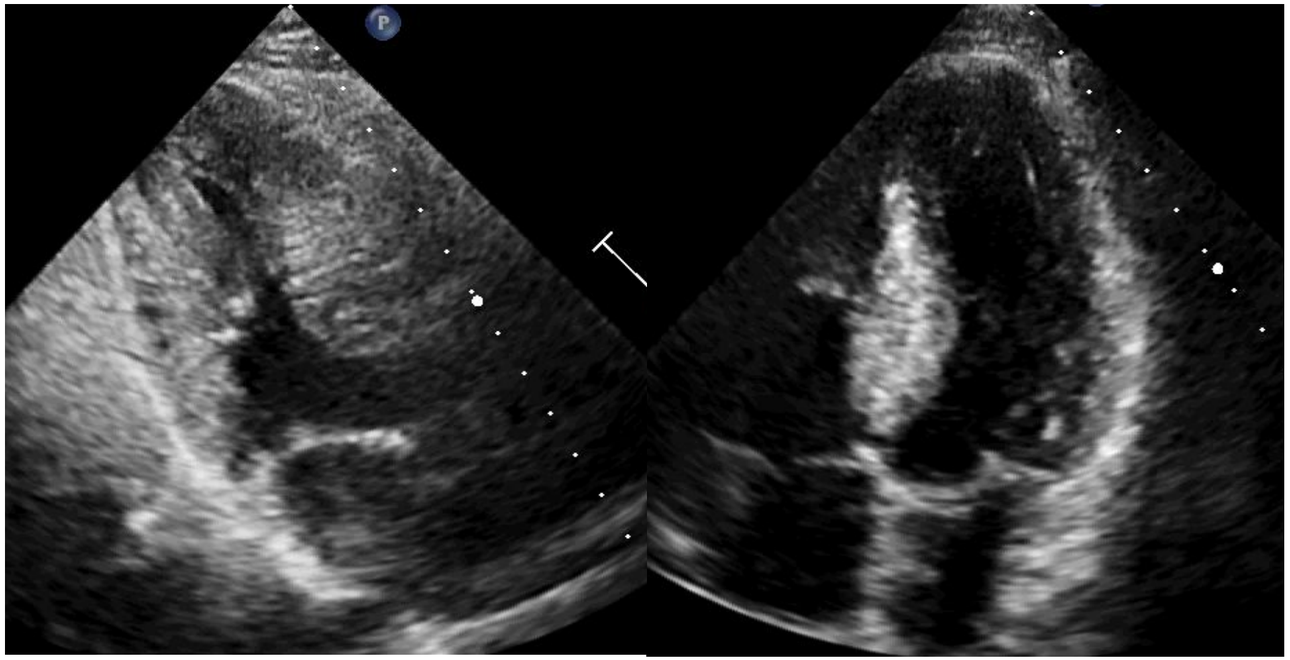
Colega

Antecedentes fliares

Madre MCH

Sintomas

Disnea esfuerzo



36 Años. Control

Antecedentes fliares

Madre MCH

Sintomas

Disnea esfuerzo

Estudio genético

2

INVITAE

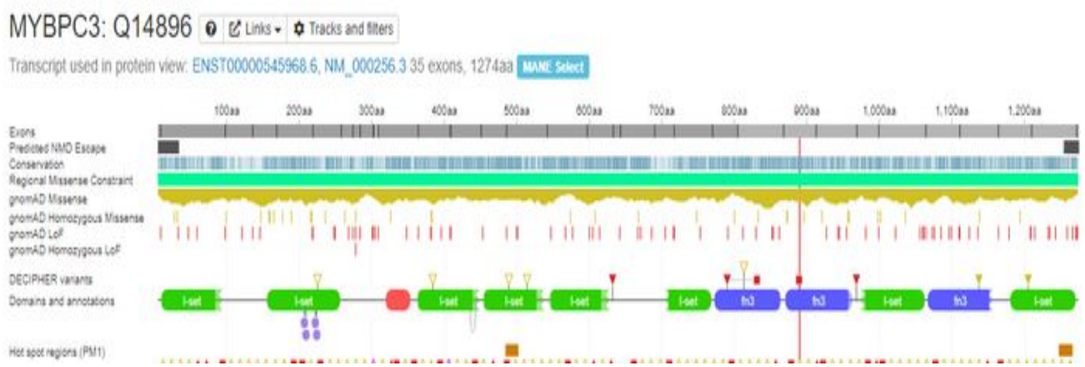
RESULT: POSITIVE

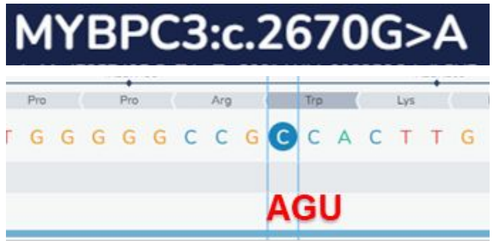
One Pathogenic variant identified in MYBPC3. MYBPC3 is associated with a spectrum of autosomal dominant cardiomyopathy conditions.

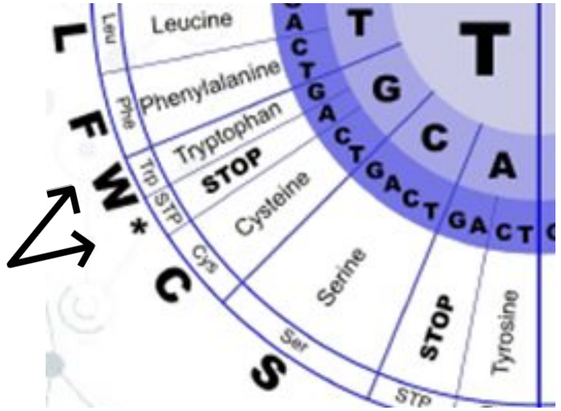
GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
MYBPC3	c.2670G>A (p.Trp890*)	heterozygous	PATHOGENIC
GAA	c.2065G>A (p.Glu689Lys)	heterozygous	Benign (Pseudodeficiency allele)

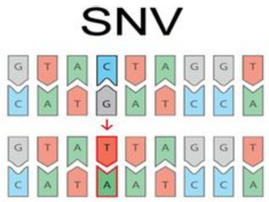
About this test

This diagnostic test evaluates 157 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

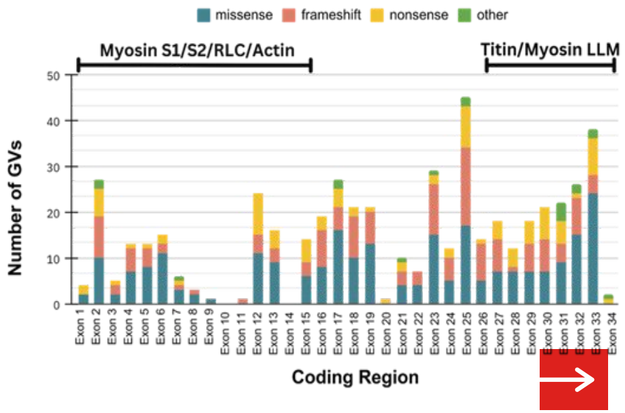


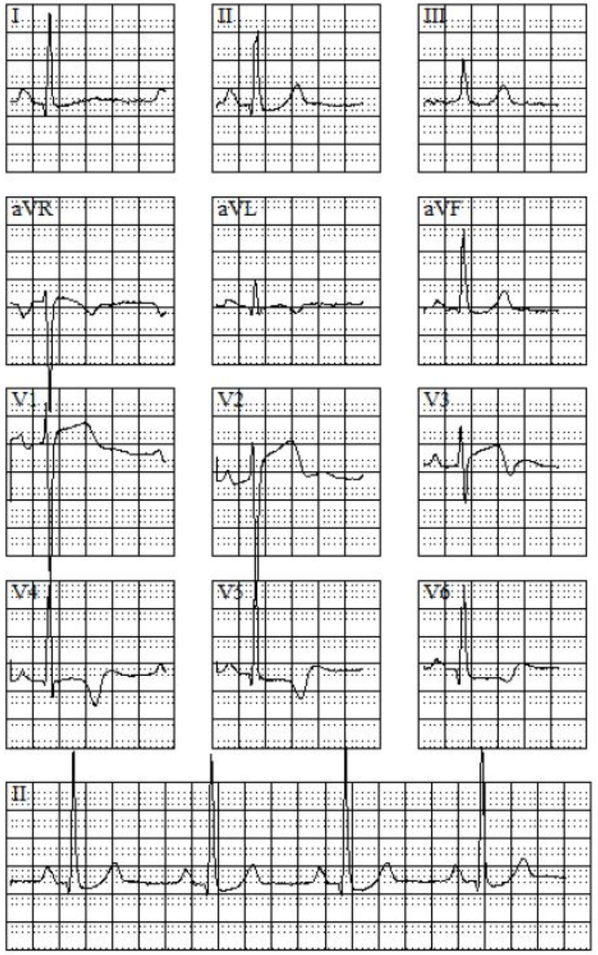






EXON 26





LPM:
FC: 57 LPM

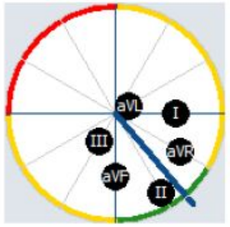
Intervalos:
Ancho QRS: 96 ms
Ancho P: 152 ms
RR: 1056 ms
Intervalo QT: 467 ms
Intervalo QTc: 455 ms

Segmento PR:
PR seg: 60 ms
PR int: 212 ms

Segmento ST:
Intervalo ST: 96 ms
J0 : 0.029 mV
J20: -0.084 mV
J60: -0.089 mV
J80: -0.089 mV

Elev ST: -0.058 mV
Pend ST: -004.6 uV/ms

Eje electrico: 50°



38Años.

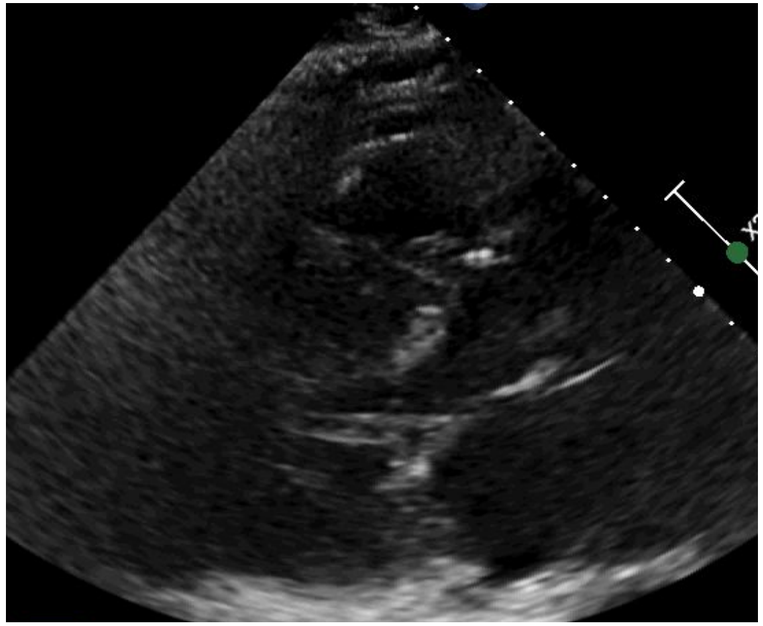
MDQ

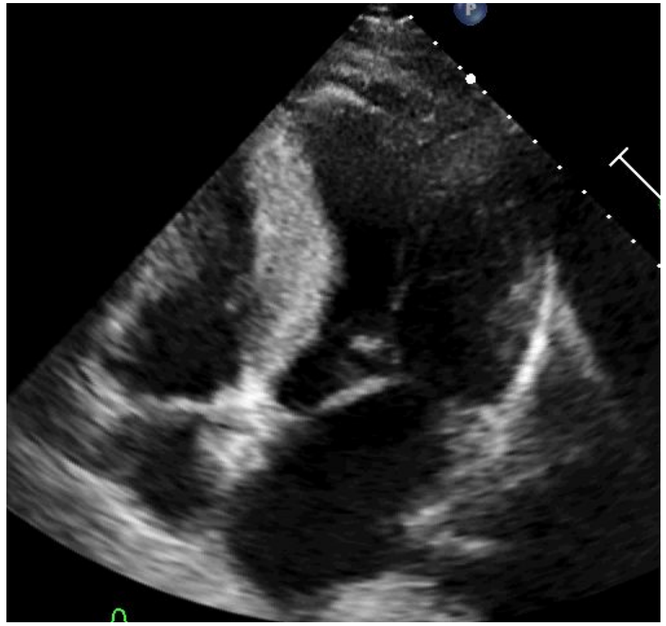
Antecedentes fliares

MCH/CDI

Sintomas

Disnea





MCH septal asimetrica

Septo-invertido

Estudio genético

3

UCT HOSPITALARIA PATAGONICA

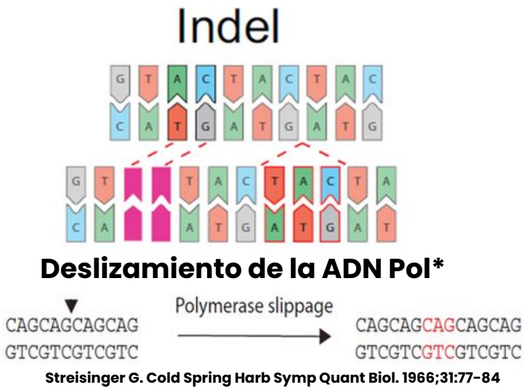
HOSPITALES DE ALTA COMPLEJIDAD HOSPITAL GOBERNADOR CEPERNIC PRESIDENTE KIRCHNER

GEN	CAMBIO DE NUCLEÓTIDO	CAMBIO DE AMINOÁCIDO	CIGOSIDAD	CLASIFICACIÓN ACMG
MYBC3	c.362del (NM_000256.3)	p.Pro121Argfs*38	Heterocigota	**Patogénica**

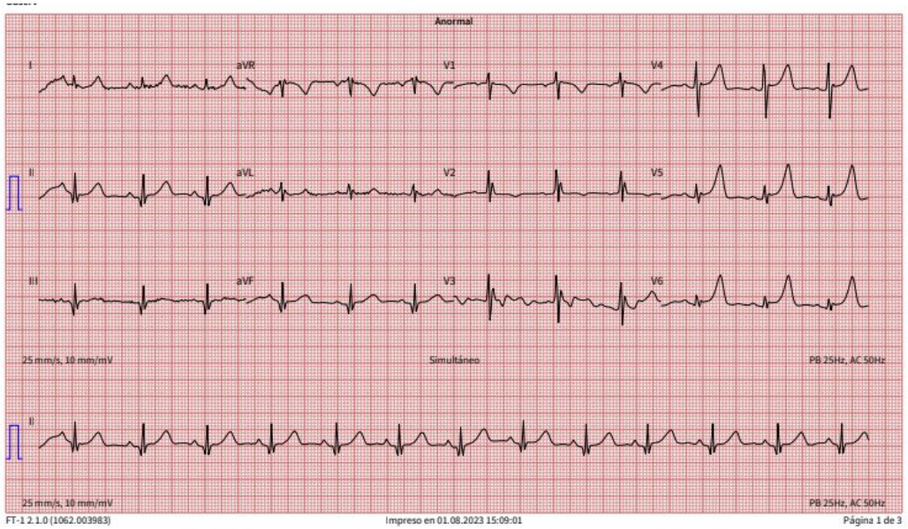
MYBPC3:c.362del

CHR11-47372096 CG>C

p.Pro121Argfs*38



Streisinger G. Cold Spring Harb Symp Quant Biol. 1966;31:77-84



16 Años.

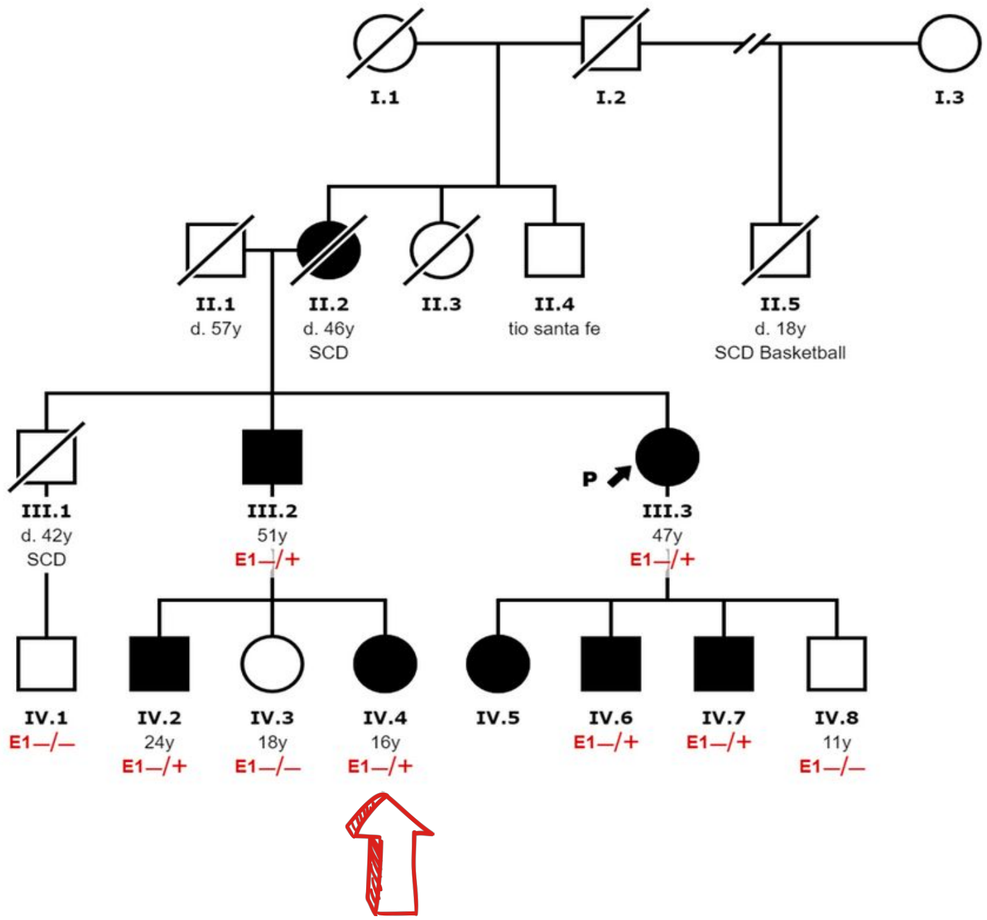
Cribado Fliar

Antecedentes fliares

Tia MCH. MYH7 val606met

Sintomas

asintomatica. rugby competitivo


I.1
I.2
I.3
II.1
d. 57y
II.2
d. 46y
SCD
II.3
II.4
tio santa fe
II.5
d. 18y
SCD Basketball
III.1
d. 42y
SCD
III.2
51y
E1—/+
P
III.3
47y
E1—/+
IV.1
E1—/—
IV.2
24y
E1—/+
IV.3
18y
E1—/—
IV.4
16y
E1—/+
IV.5
IV.6
E1—/+
IV.7
E1—/+
IV.8
11y
E1—/—

Pedigree

Estudio genético

INVITAE

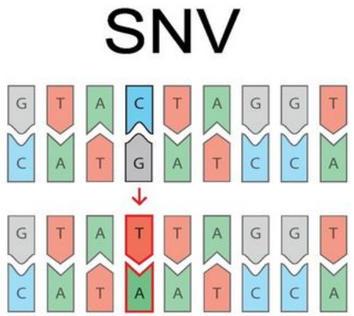
RESULT: POSITIVE

One Pathogenic variant identified in MYH7. MYH7 is associated with a spectrum of autosomal dominant and recessive cardiac and neuromuscular conditions.

One Pathogenic variant identified in SLC22A5. SLC22A5 is associated with autosomal recessive primary carnitine deficiency.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
MYH7	c.1816G>A (p.Val606Met)	heterozygous	PATHOGENIC
SLC22A5	c.34G>A (p.Gly12Ser)	heterozygous	PATHOGENIC
NEBL	c.1322C>G (p.Ser441Cys)	heterozygous	Uncertain Significance
NF1	c.169G>A (p.Gly57Ser)	heterozygous	Uncertain Significance



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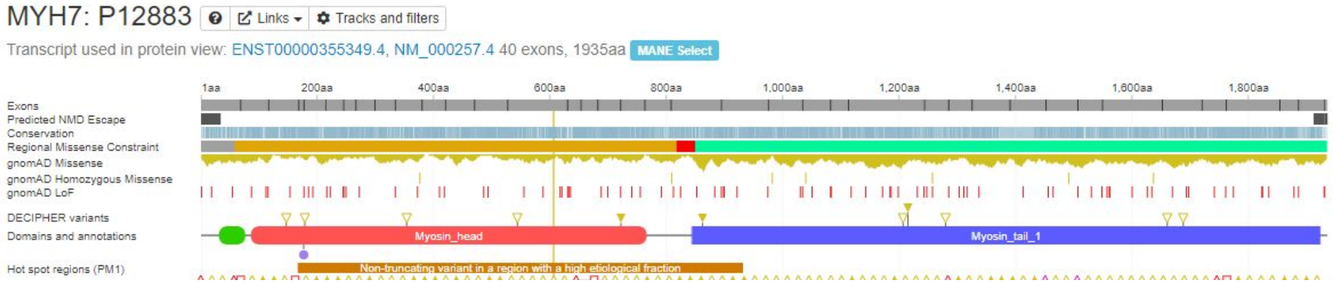
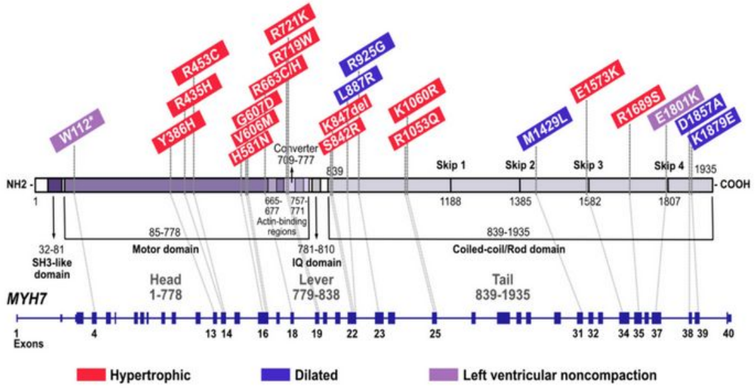
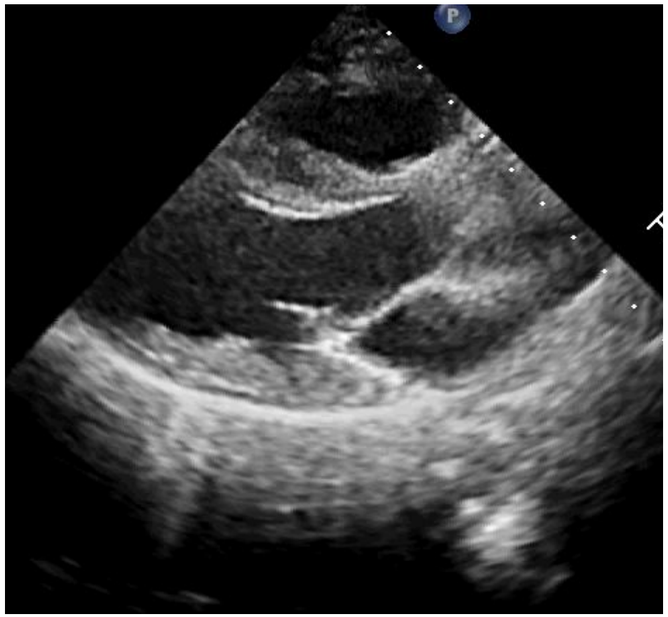
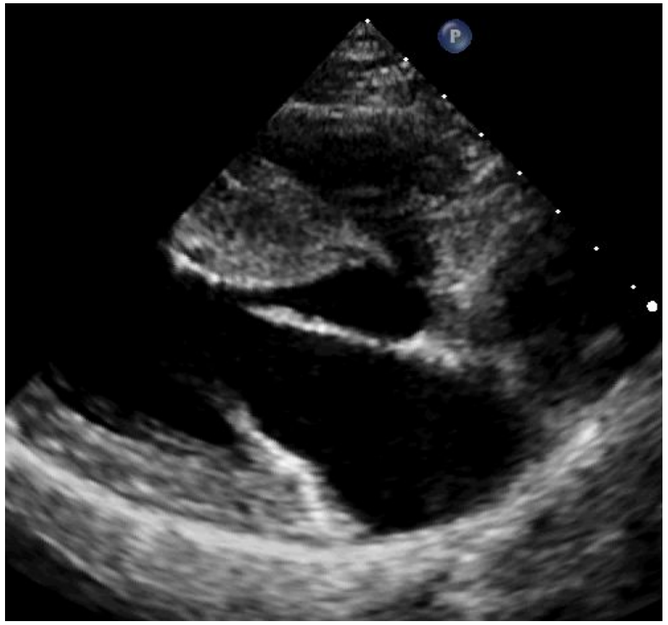


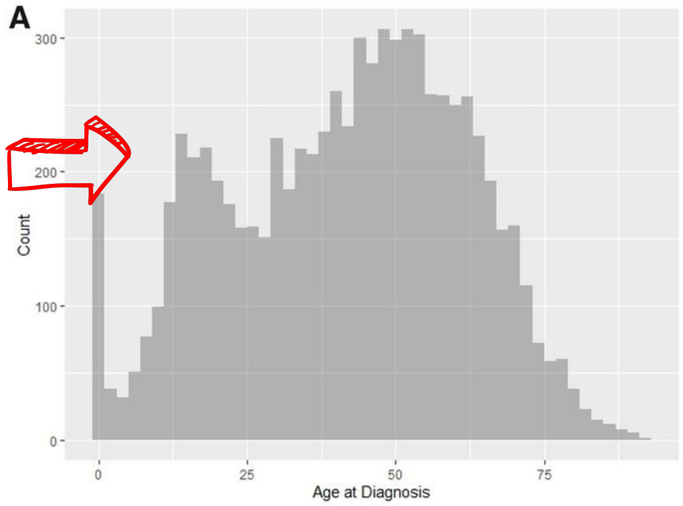


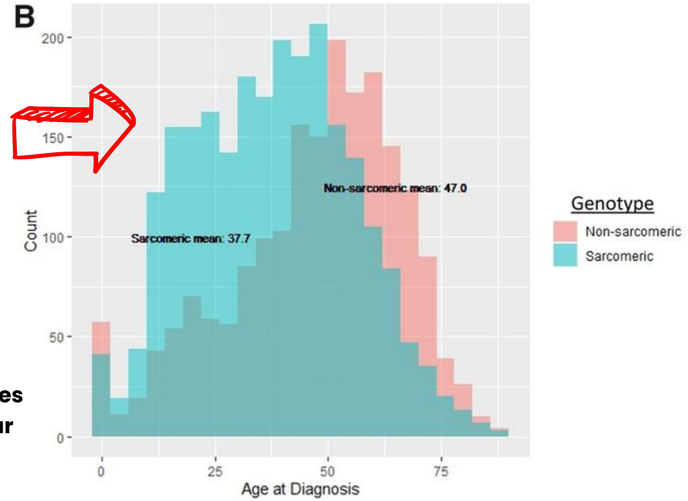




Fenotipo evolutivo

15 % INICIO EN LA ADOLESCENCIA

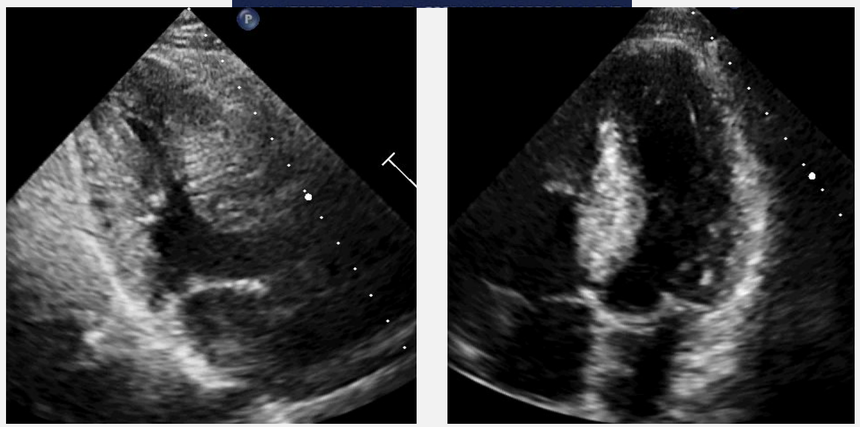




Marston NA, et al. Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. Eur Heart J. 2021 May 21;42(20):1988-1996.

PLOF

MYBPC3:c.2670G>A



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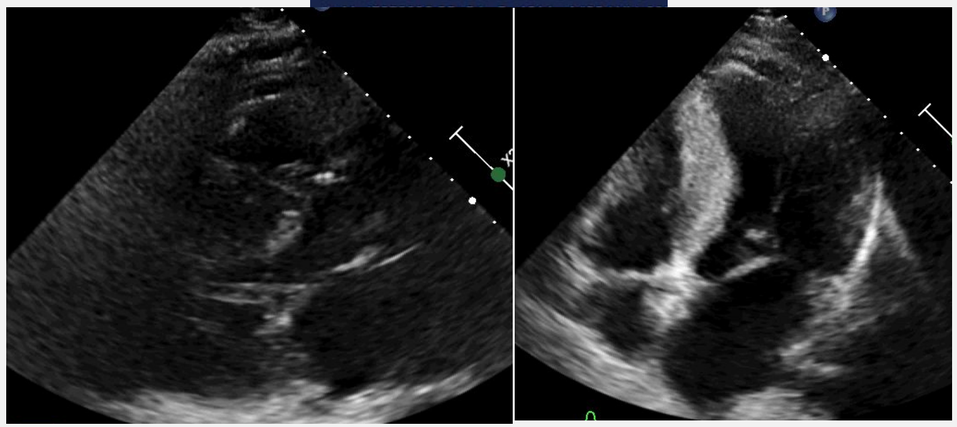

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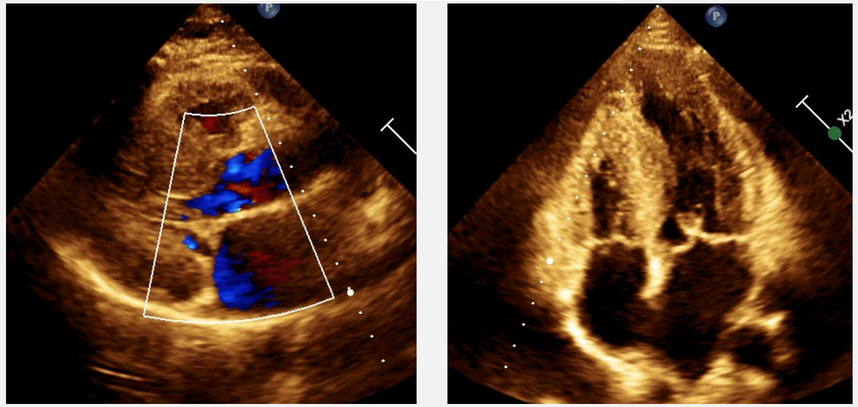

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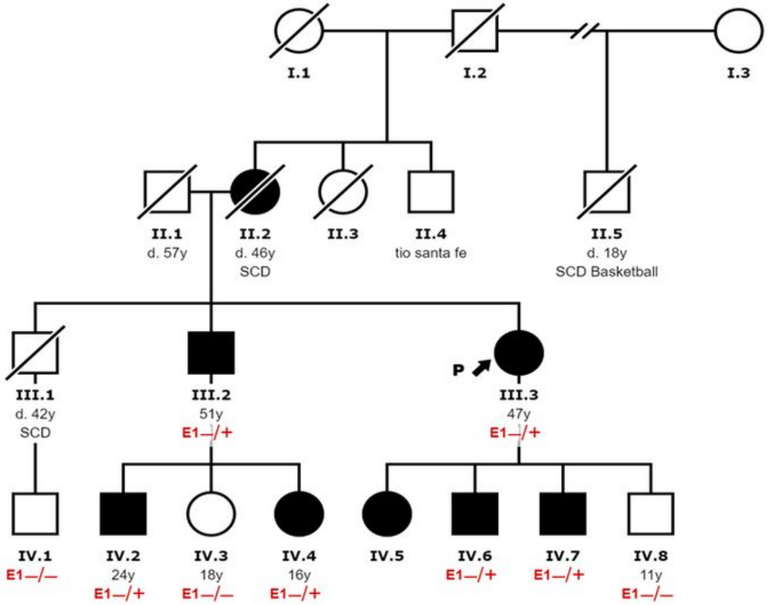
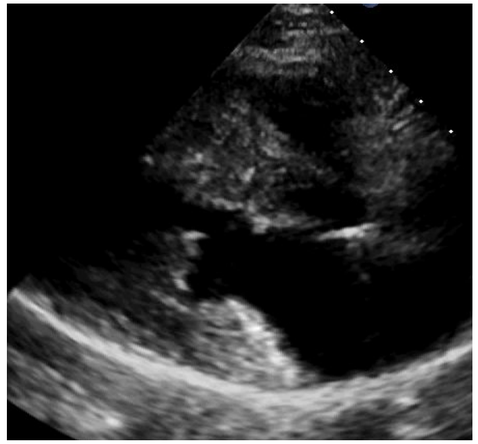
MCH Y FENOTIPO



MYH7:c.1816G>A

chr14-23896866 C>T | p.Val606Met | NM_000257.4

IV.4



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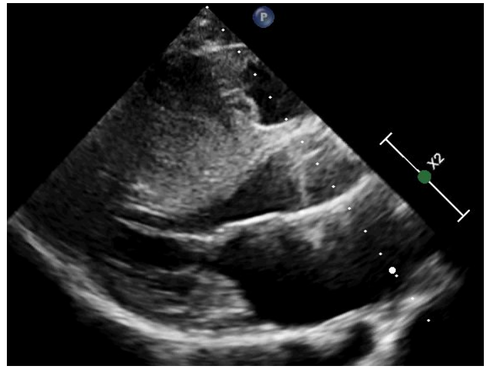

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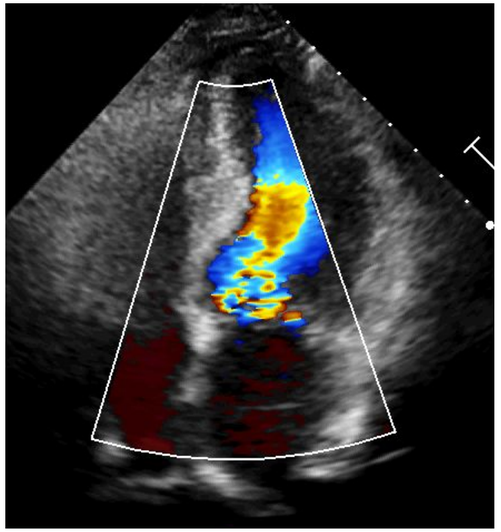
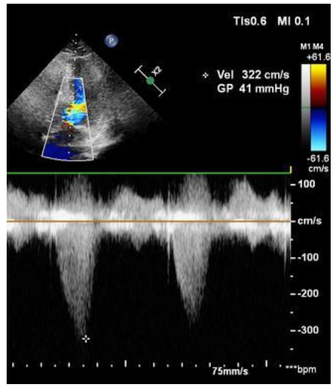
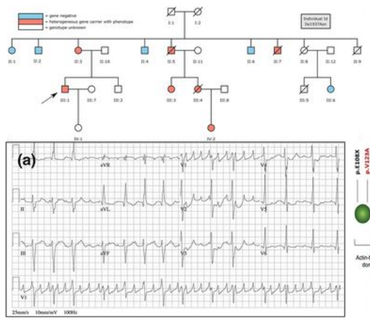


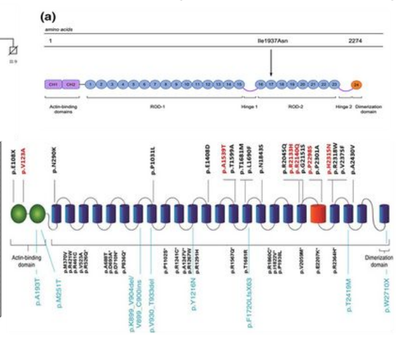


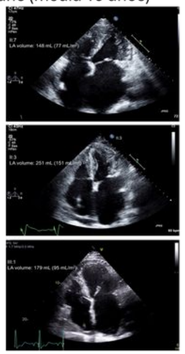
RIESGO MSC

FLNC* Ile1937Asn**

Insuficiencia cardiaca que require TX 43%
Muerte subita 29%
Miopatia auricular de inicio temprano (media 19 años)







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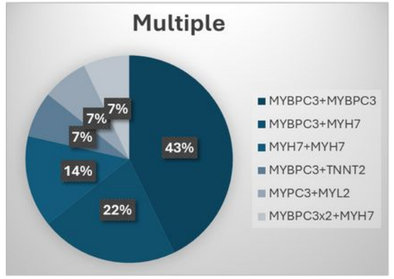
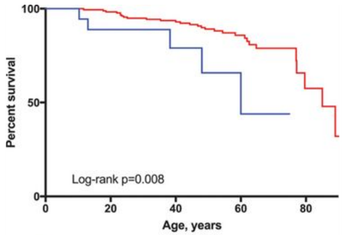
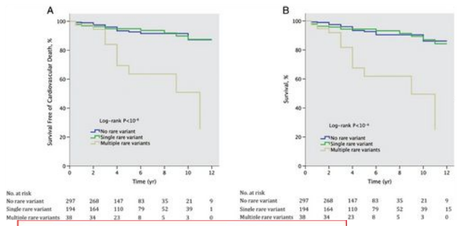
*Valdés-Mas R. Nat Commun. 2014 Oct 29;5:5326. Gómez J, Circ Cardiovasc Genet. 2017 Apr;10(2):e001584.



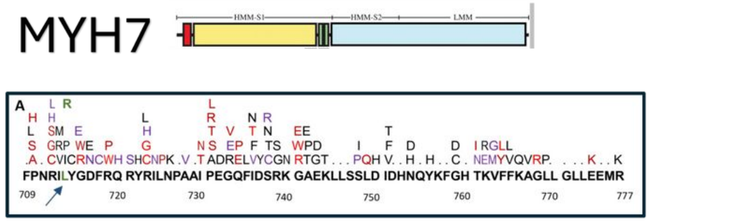


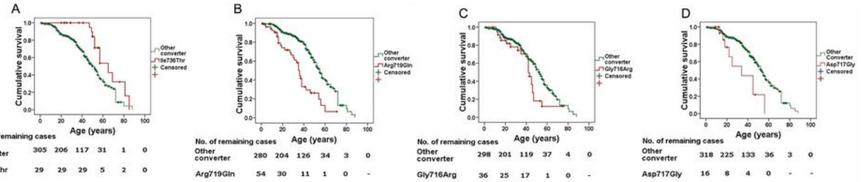
Burns C. Multiple Gene Variants in Hypertrophic Cardiomyopathy in the Era of Next-Generation Sequencing. Circ Cardiovasc Genet. 2017 Aug;10(4):e001666



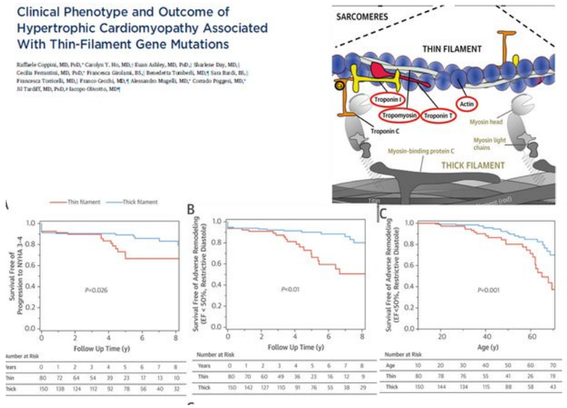
Wang, J. Malignant effects of multiple rare variants in sarcomere genes on the prognosis of patients with hypertrophic cardiomyopathy. Eur J Heart Fail, 16: 950-957.

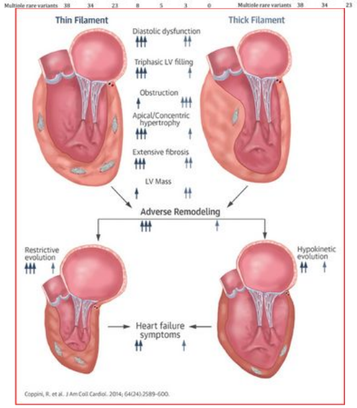
MYH7

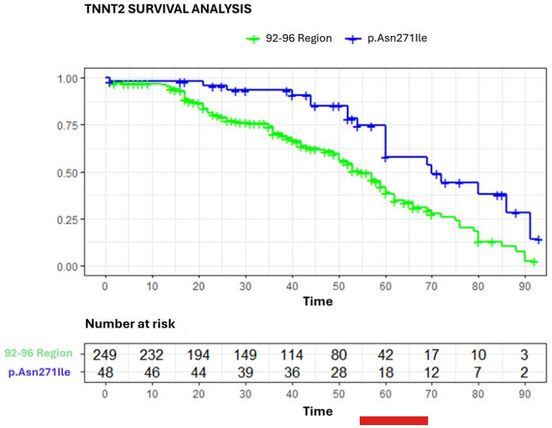




García-Giustiniani D, Arad M, Ortiz-Genga M, Barriales-Villa R, Fernández X, Rodríguez-García I et al. Phenotype and prognostic correlations of the converter region mutations affecting the β myosin heavy chain. Heart 2015;101(13):1047-53



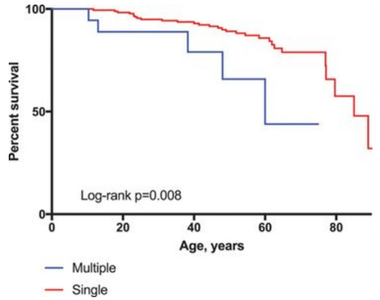




Desafíos diagnósticos en enfermedades cardiovasculares de origen hereditario. Dr Luis Enrique Gómez

MCH Y RIESGO MSC

Gen	Variante	Resultado	Patogenicidad
MYBPC3	NP_000247.2:p.Arg845Gly NM_000256.3:c.2533C>G NC_000011.9:g.47359011G>C	Heterocigosis	Variante de significado incierto (?)
	NP_000247.2:p.Cys566Ser NM_000256.3:c.1696T>A NC_000011.9:g.47363636A>T	Heterocigosis	Variante de significado incierto (?)



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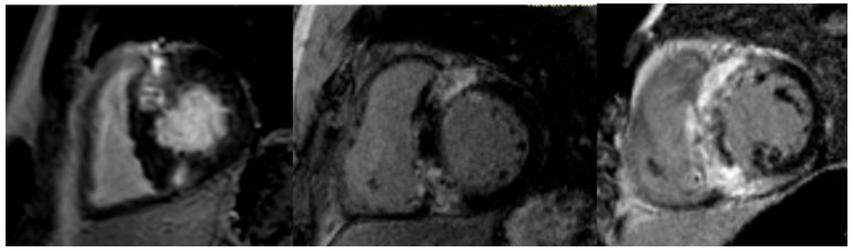
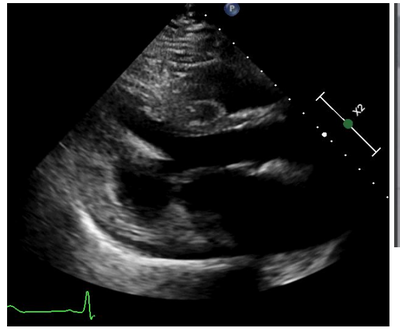




POSICIÓN	GEN	CAMBIO DE NUCLEÓTIDO/ PROTEÍNA	EFECTO	FENOTIPO ASOCIADO (PATRÓN DE HERENCIA)	INFO EXTERNA	GENO-TIPO	PROF.	CLASIFICA-CIÓN
15:63044099	*TPM1* NM_001018005.2	c.187G>A p.(Ala63Thr)	*Missense Variant*	- Miocardiopatía dilatada (MIM: 611878; AD) - Miocardiopatía hipertrófica 3 (MIM: 115196; AD) - No compactación ventricular izquierda 9 (MIM: 611878; AD)	rs1064796782 ClinVar ID: 424074[1]	HET	119/278	3

5 Patogénica 4 Probablemente Patogénica 3 Significado incierto (VUS)

HCM Risk-SCD

Assess risk of sudden cardiac death and need for ICD in hypertrophic cardiomyopathy

Questions

1.	Age?	60 Years
2.	Maximum LV Wall Thickness?	18 mm
3.	Left Atrial Size?	57 mm
4.	LVOT Gradient?	5 mmHg
5.	Family History of Sudden Cardiac Death?	Yes
6.	Non-sustained VT?	Yes
7.	Unexplained Syncope?	Yes

Risk of Sudden Cardiac Death at 5 years

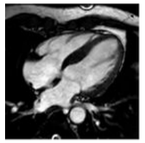
14.18%

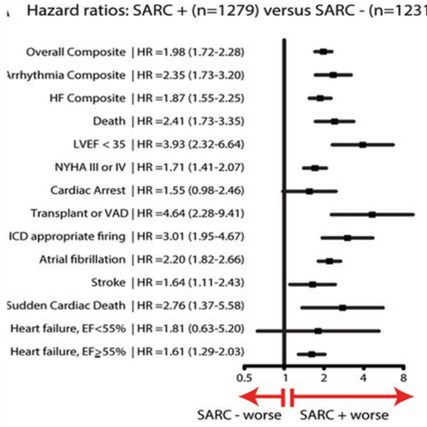
ESC Recommendation

ICD should be considered

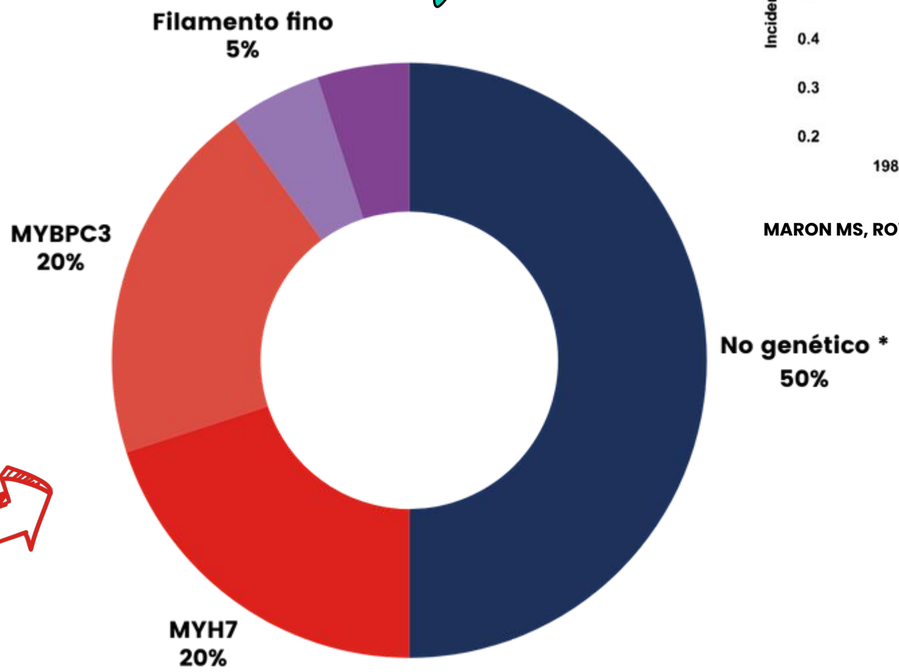
MCH Y RIESGO MSC

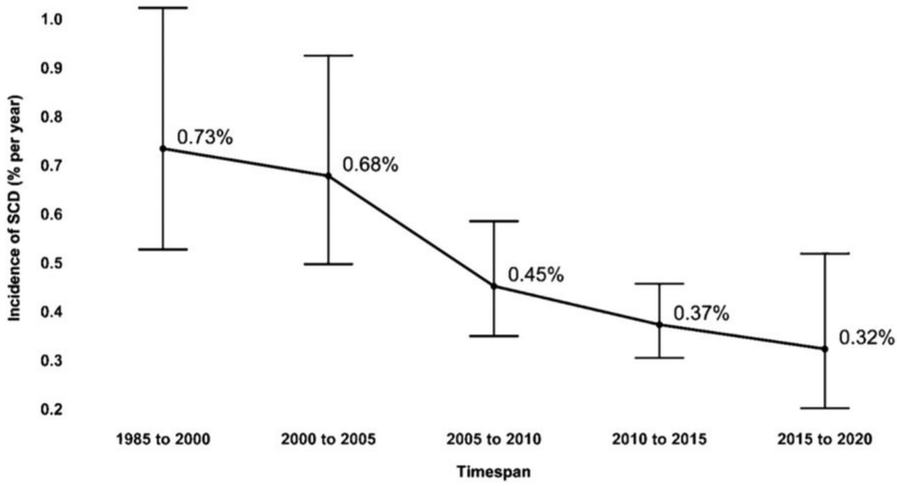
Poblaciones distintas. Mayores eventos en SARC+





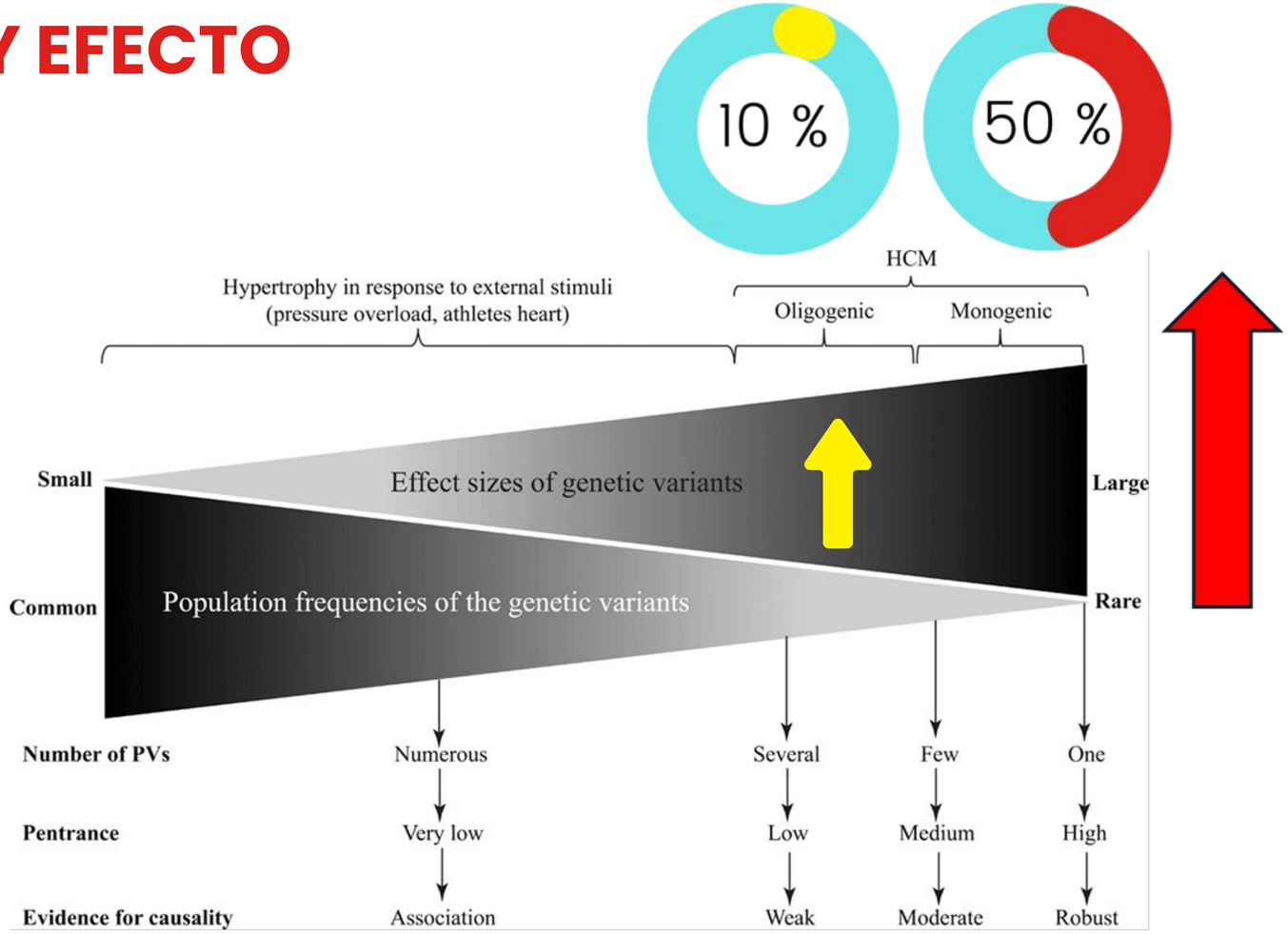
Ho CY et al. Circulation. 2018 Oct 2;138(14):1387-1398.





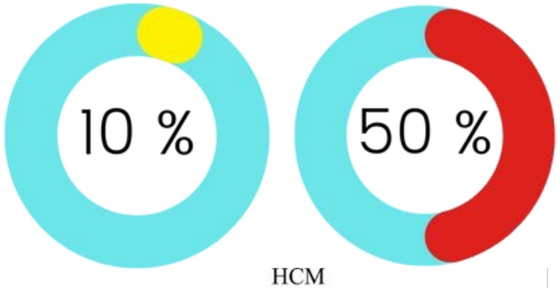
MARON MS, ROWIN EJ, MARON BJ. THE PARADIGM OF SUDDEN DEATH PREVENTION IN HYPERTROPHIC CARDIOMYOPATHY. AM J CARDIOL. 2024 FEB 1;212S:S64-S76.

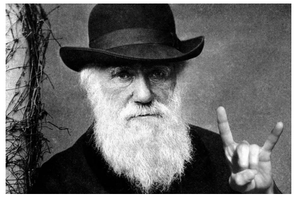
VARIANTE Y EFECTO

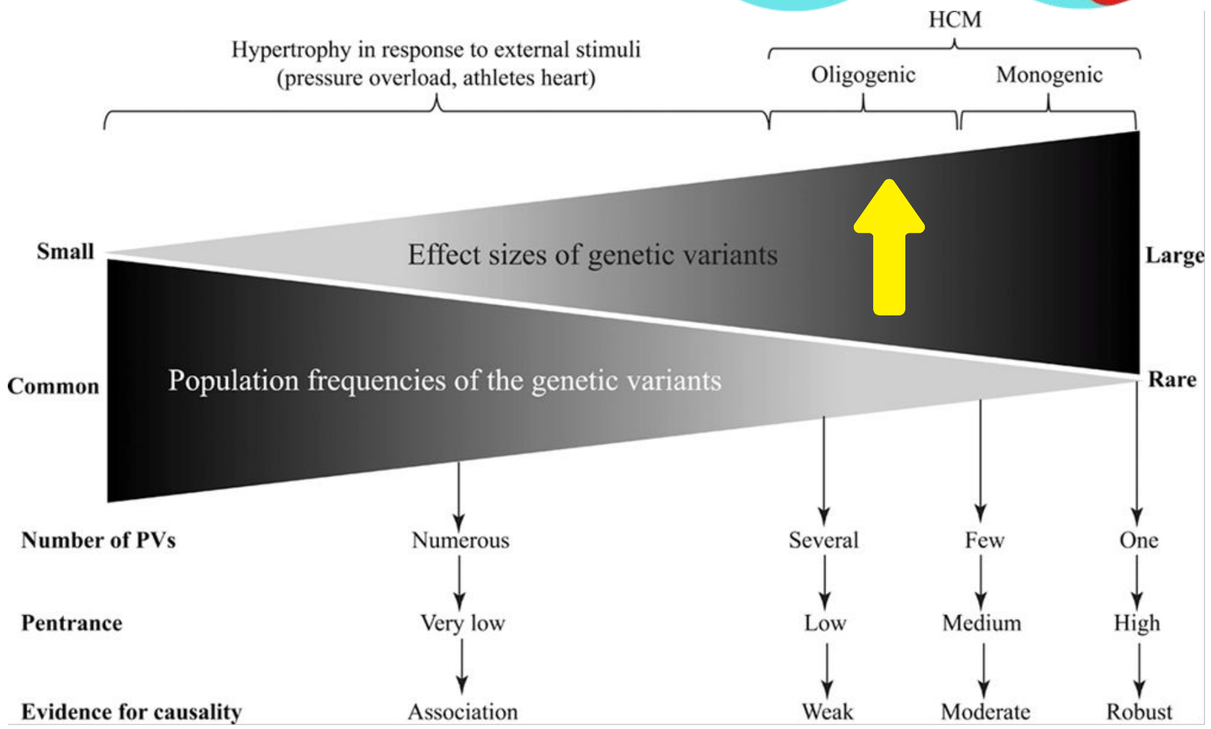


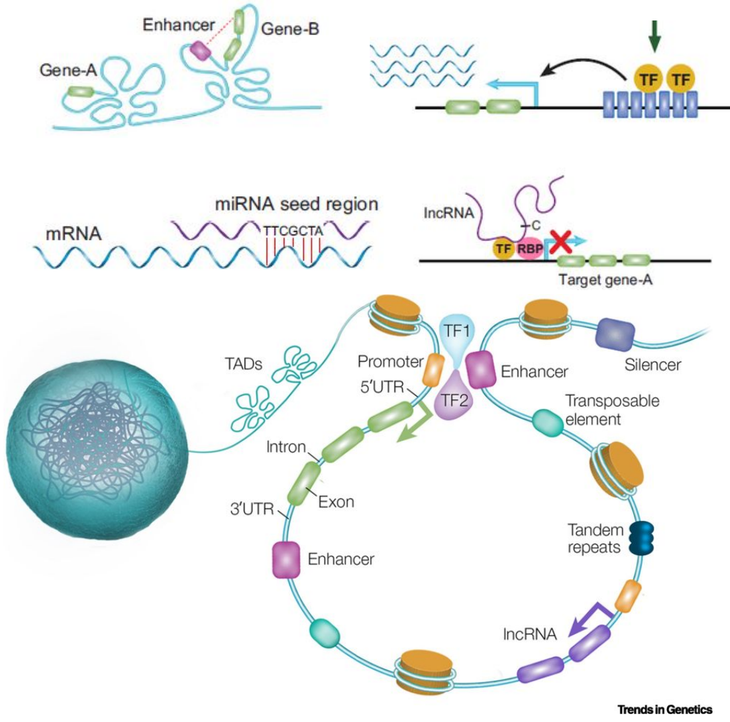
Marian AJ. Circulation Research. 2021;128:1533–1553

VARIANTE Y EFECTO...

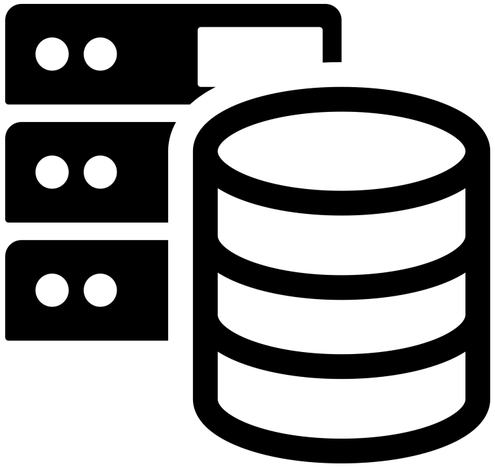


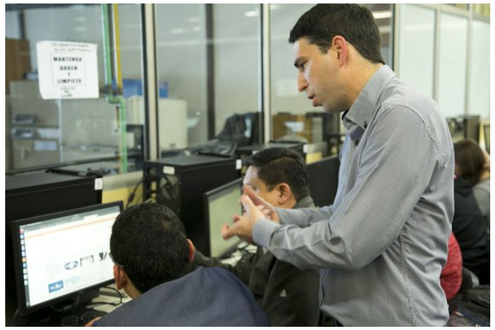






Marian AJ. Circulation Research. 2021;128:1533–1553

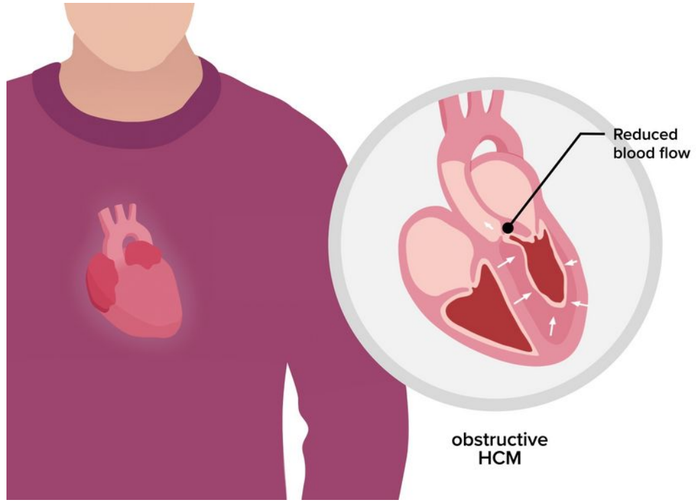


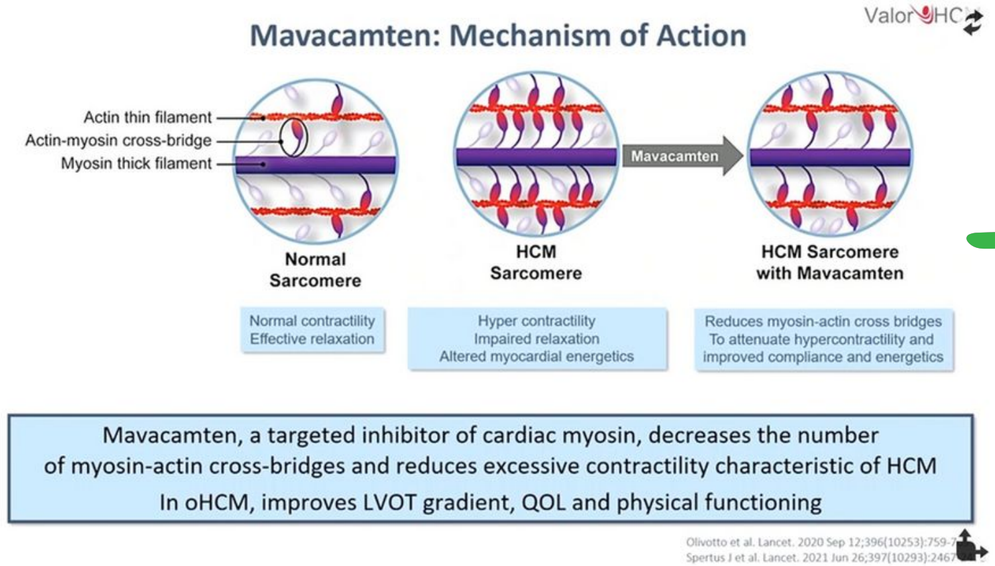


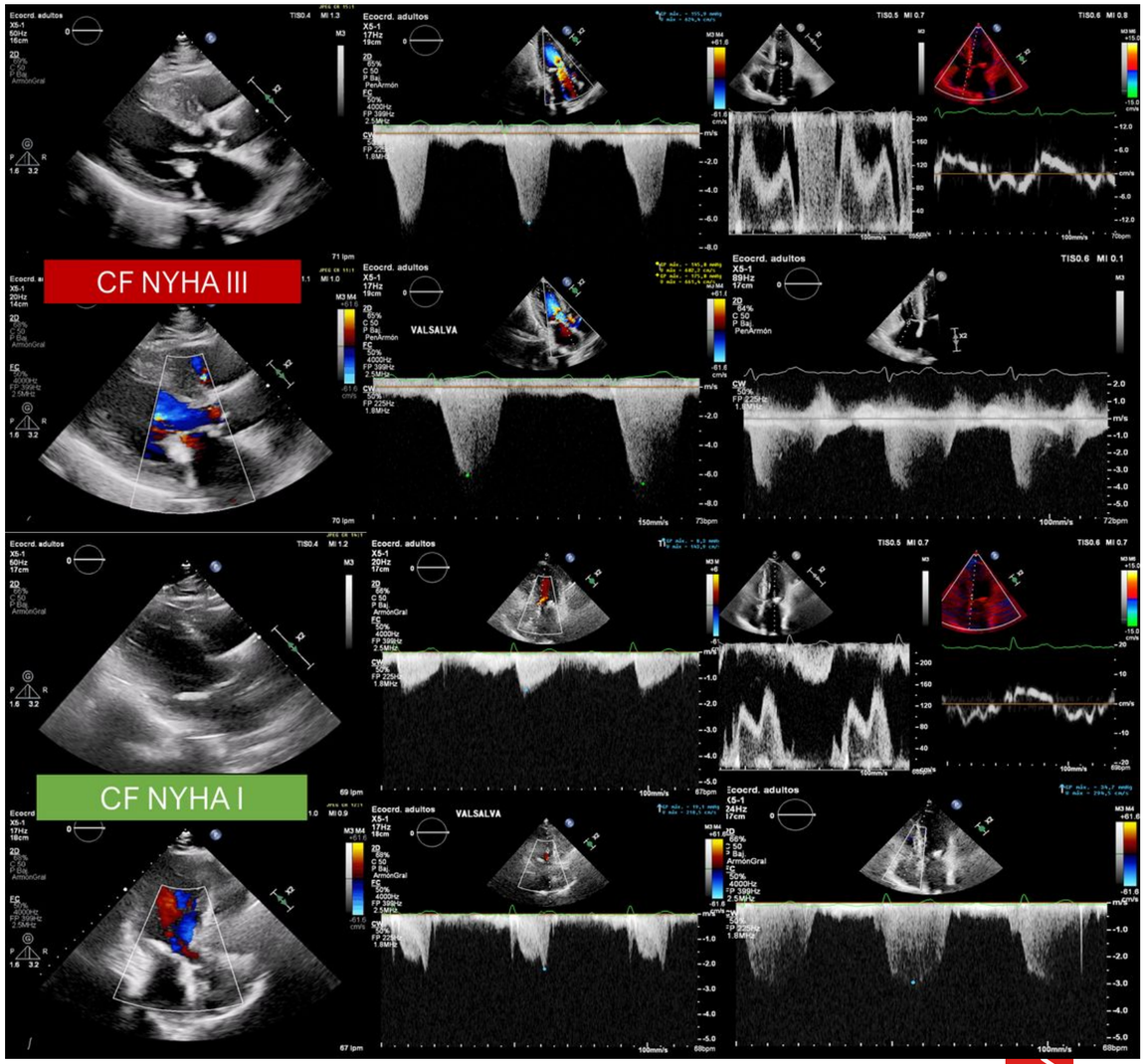
Desafíos diagnósticos en enfermedades cardiovasculares de origen hereditario. Dr Luis Enrique Gómez

NUEVOS TRATAMIENTOS. El Futuro llego

III JORNADAS DE GENÓMICA CLÍNICA



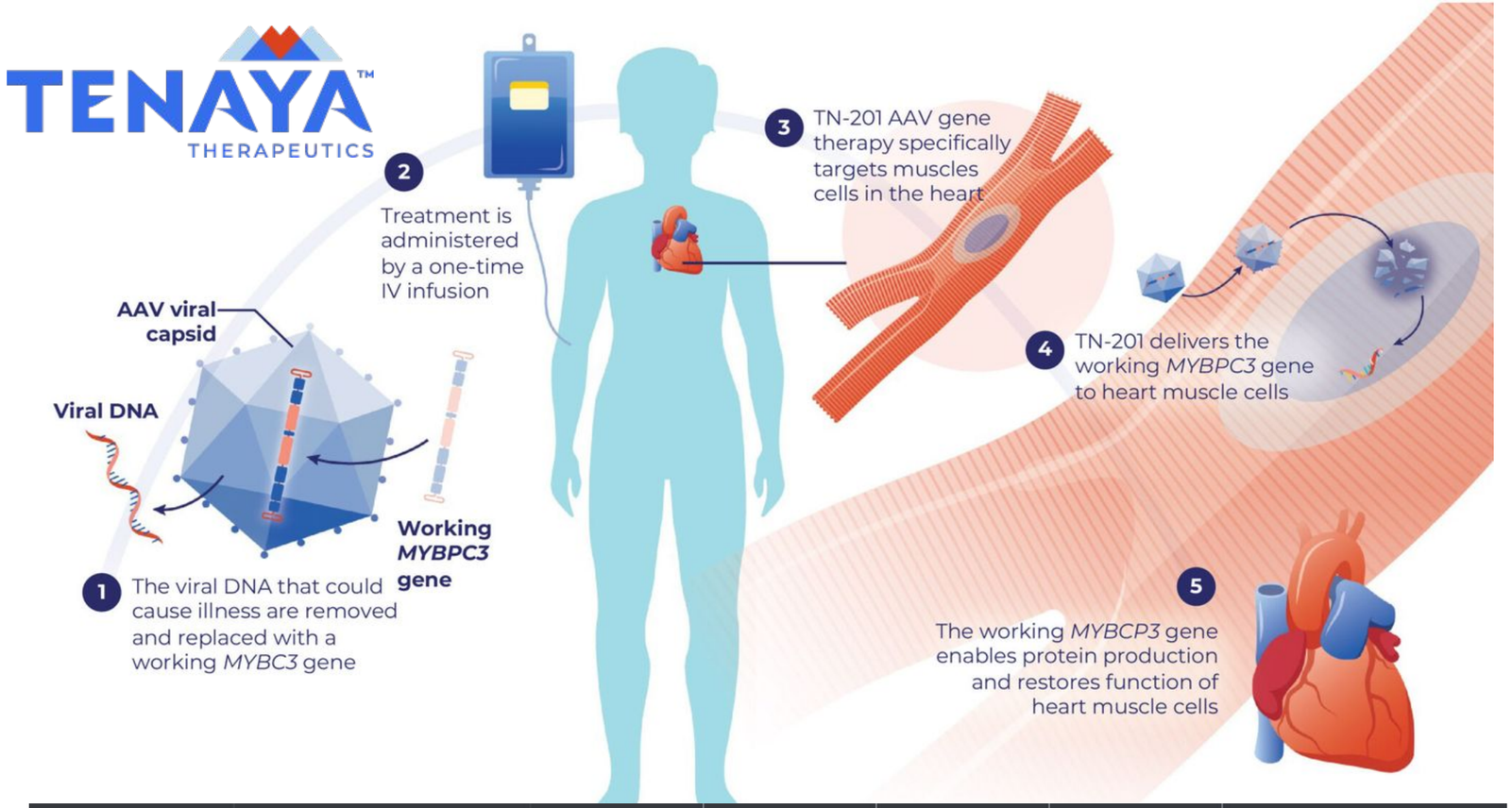




CORTESIA DR ROBERTO BARRIALES

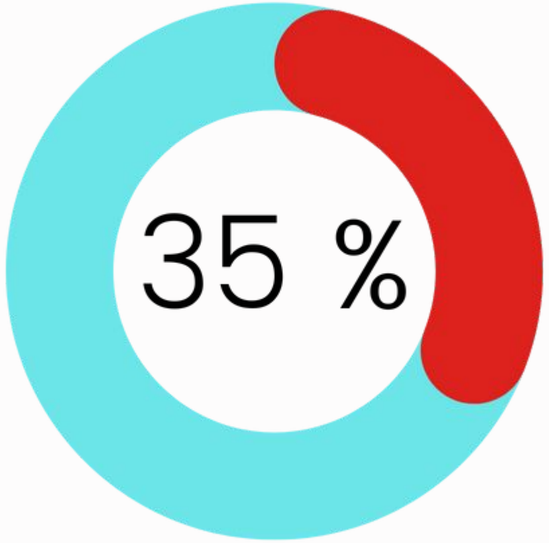
Desafíos diagnósticos en enfermedades cardiovasculares de origen hereditario. Dr Luis Enrique Gómez

NUEVOS TRATAMIENTOS. Hace rato



Program	Indication(s)	Discovery	Preclinical	Phase 1	Phase 2/3	US Prevalence
Gene Therapy						
TN-201	MYBPC3 HCM					> 115K
TN-401	PKP2 ARVC					> 70K

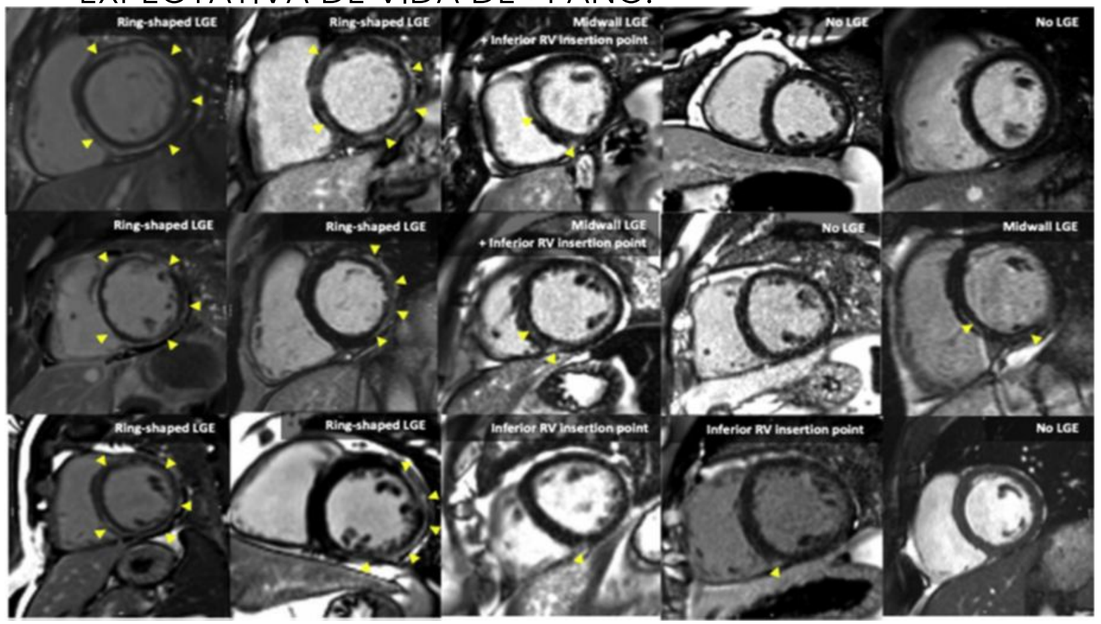
Miocardiopatia Dilatada



- **PREVALENCIA 1:250-400**
- APARICIÓN TARDÍA DE LA ENFERMEDAD
- INCIDENCIA 5-7/100 000 PERSONAS /AÑO.

MCD Y RIESGO MSC

- FEY ≤ 35 %
- CF II-III
- TTO OPTIMO
- EXPECTATIVA DE VIDA DE >1 AÑO.



LMNA

FLNC

TMEM43

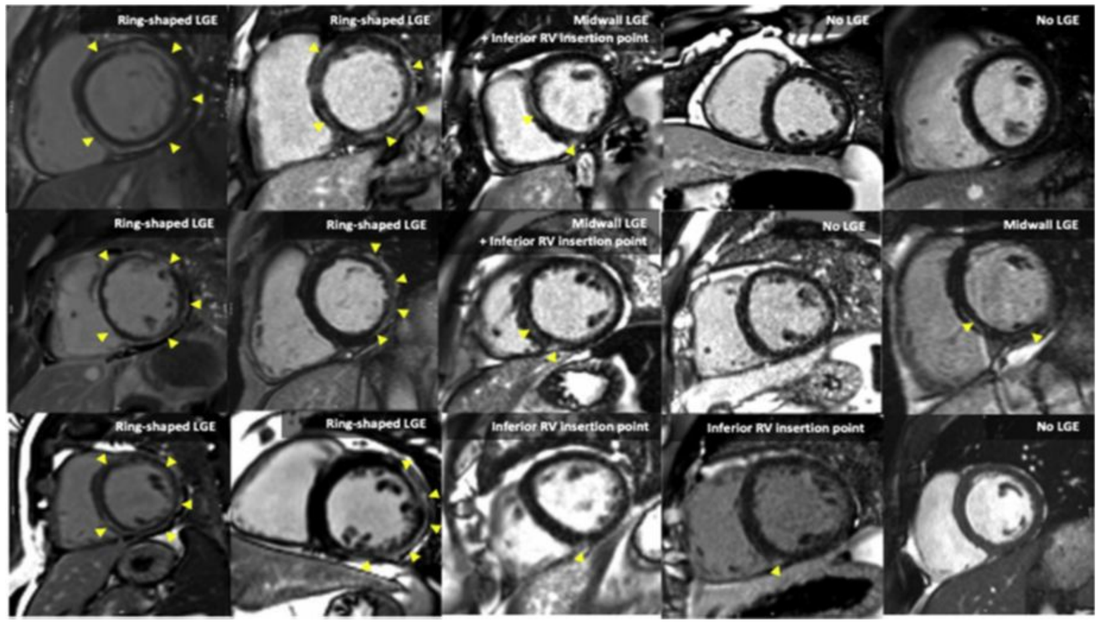
PLN

DSP

RBM20

MCD Y RIESGO MSC

- FEY ≤ 35 %
- CF II-III
- TTO OPTIMO
- EXPECTATIVA DE VIDA DE >1 AÑO.



DSP FLNC TTN BAG3 LAMINA A/C

LMNA

FLNC

TMEM43

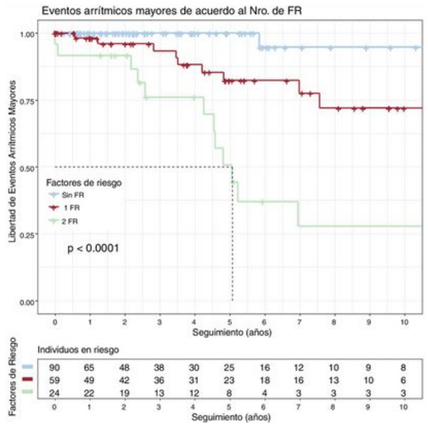
PLN

DSP

RBM20

MCD Y RIESGO MSC

LMNA



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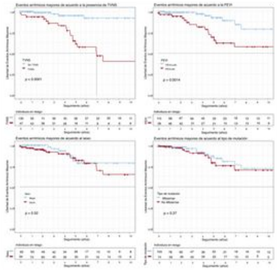
FEY ≤45%
TVNS



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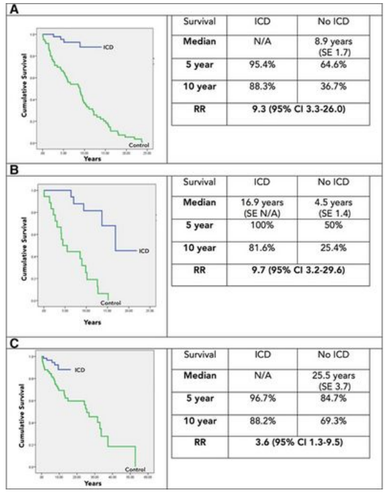
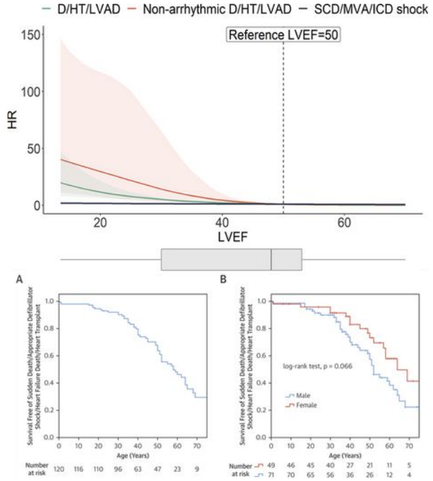


Hodgkinson Kaet al. Long-Term Clinical Outcome of Arrhythmogenic Right Ventricular Cardiomyopathy in Individuals With a p.S358L Mutation in TMEM43 Following Implantable Cardioverter Defibrillator Therapy. Circ Arrhythm Electrophysiol. 2016 Mar;9(3):e003589.

FLNC



Gigli M, et al. Phenotypic Expression, Natural History, and Risk Stratification of Cardiomyopathy Caused by Filamin C Truncating Variants. Circulation. 2021 Nov 16;144(20):1600-1611.

FEY ≤45%

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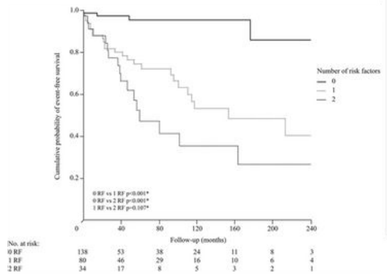
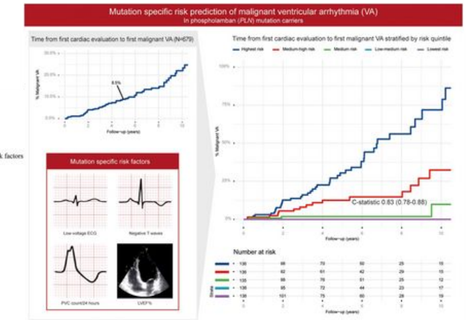
PLN

FEY ≤45%
TVNS
TVS



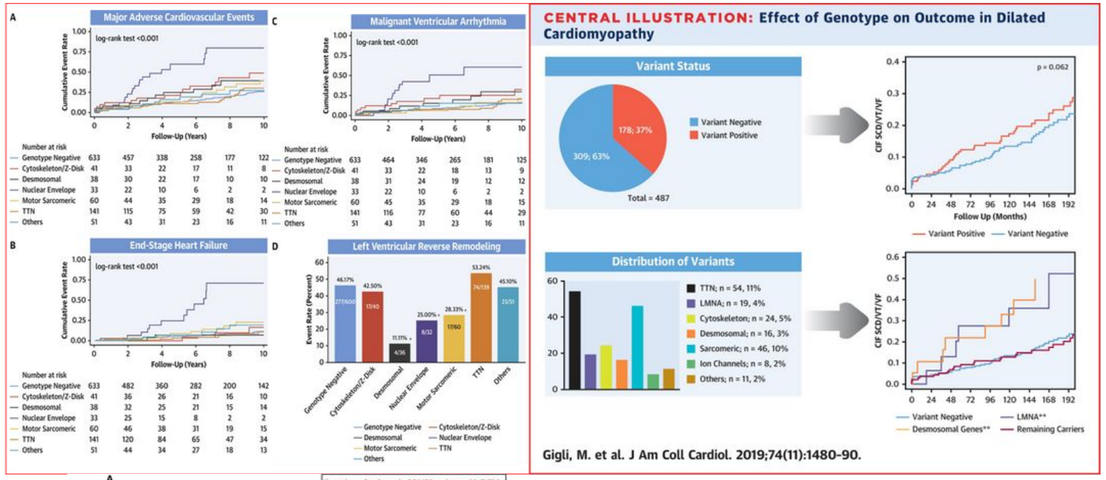
van Rijsingen IA, et al. Outcome in phospholamban R14del carriers: results of a large multicentre cohort study. Circ Cardiovasc Genet. 2014 Aug;7(4):455-65.

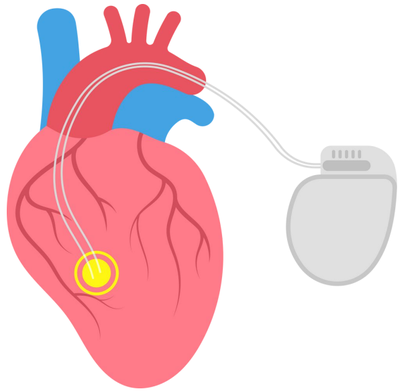


Verstraelen TE, et al. Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers-reaching the frontiers of individual risk prediction. Eur Heart J. 2021 Jul 31;42(29):2842-2850.

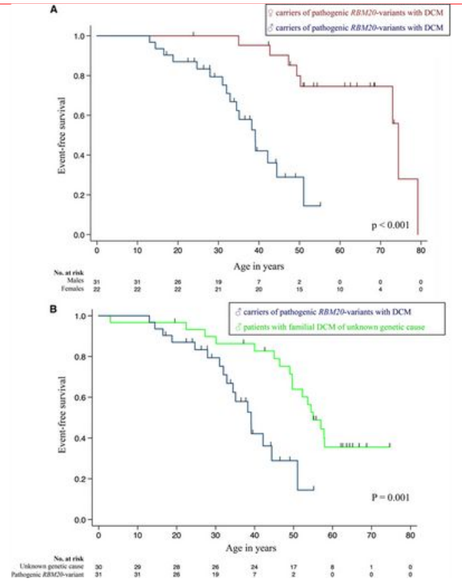
MCD Y RIESGO MSC

DSP





RBM20

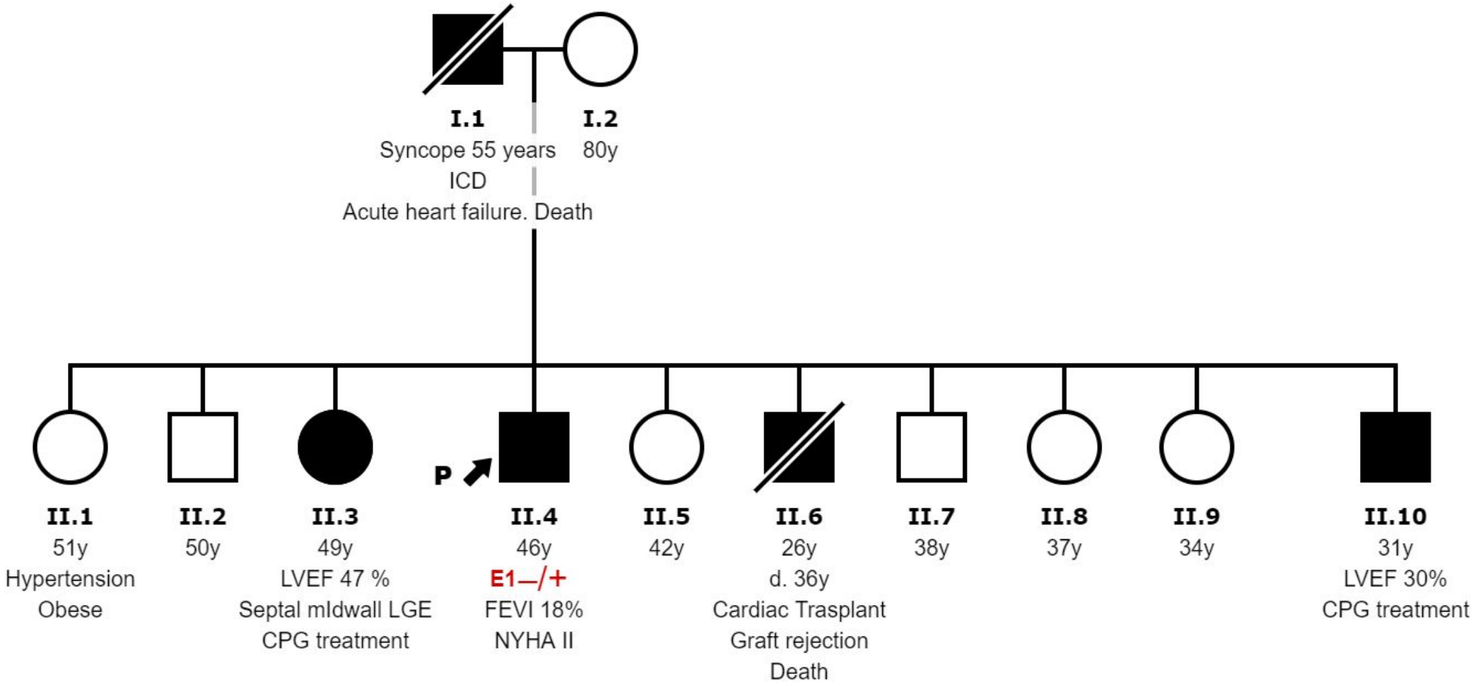


RTG en RM
FEY <45%

Hey TM, et al. Pathogenic RBM20-Variants Are Associated With a Severe Disease Expression in Male Patients With Dilated Cardiomyopathy. Circ Heart Fail. 2019 Mar;12(3):e005700

Gen	Riesgo Anual MS	Predictores MS
LMNA	5-10%	LMNA risk score. www. https://lmna-risk-vta.fr/
FLNC	5-10%	RTG en RM/FEY<45%
TMEM43	5-10%	Hombre/Mujer +FEY<45%/TVNS/RTG en RM,>200EV holter
PLN	3-5%	PLN risk score https://plnriskcalculator.shinyapps.io/final_shiny/ RTG en RM/FEY <45%/TVNS
DSP	3-5%	RTG en RM/FEY <45%
RBM20	3-5%	RTG en RM/FEY <45%

MCD Y RIESGO MSC



MCD Y RIESGO MSC

UCT HOSPITALARIA PATAGONICA

HOSPITAL GOBERNADOR CEPERNIC PRESIDENTE KIRCHNER

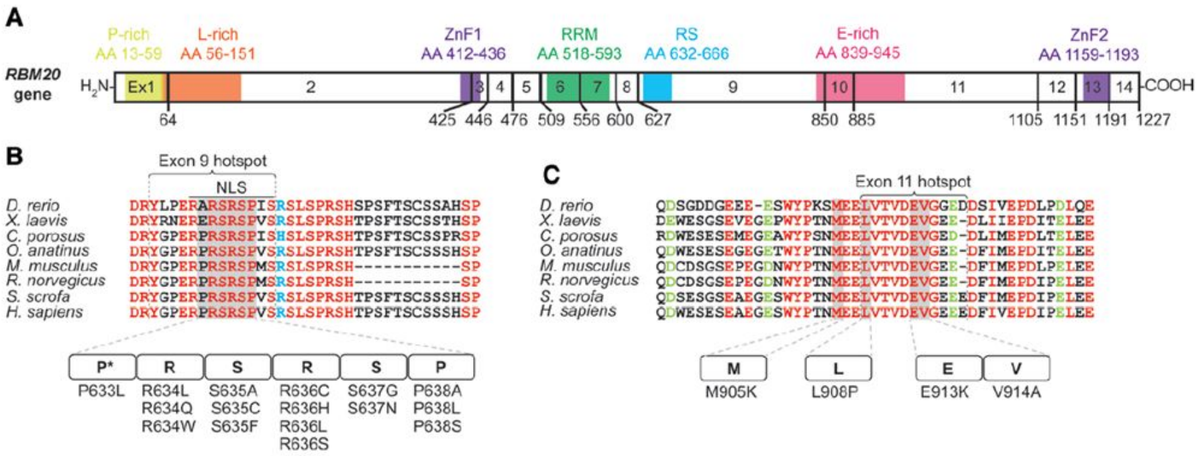
SERVICIO DE DIAGNÓSTICO MOLECULAR

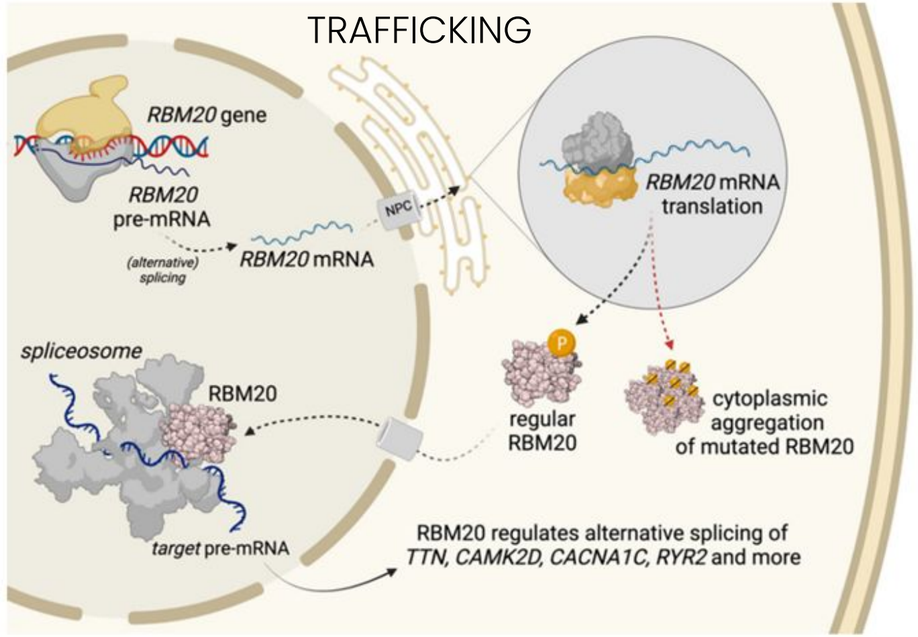
UNIDAD DE CONOCIMIENTO TRASLACIONAL HOSPITALARIA PATAGÓNICA

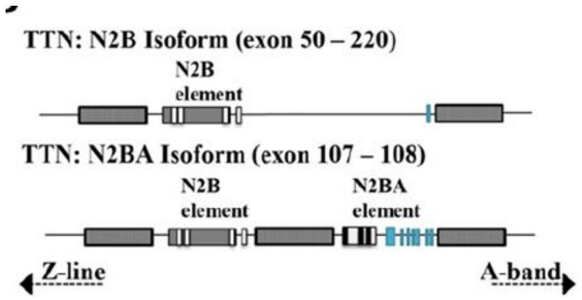
HOSPITAL DE ALTA COMPLEJIDAD EL CALAFATE S.A.M.I.C.

Jefe De Servicio: Dr. Guillermo Corró - MP: 329, MN: 11055
Email: diagnostico.molecular@hospitalelcalafate.gob.ar Tel: 02902491831 Int: 4003

GEN	CAMBIO DE NUCLEÓTIDO	CAMBIO DE AMINOÁCIDO	CIGOSIDAD	CLASIFICACIÓN ACMG
RBM20	c.1906C>A (NM_001134363.3)	p.Arg636Ser	Heterocigota	Patogénica







Desafíos diagnósticos en enfermedades cardiovasculares de origen hereditario. Dr Luis Enrique Gómez

Miocardiopatia Arritmogenica

- **PREVALENCIA 1:2000-5000**

50% ARRITMIA VENTRICULAR

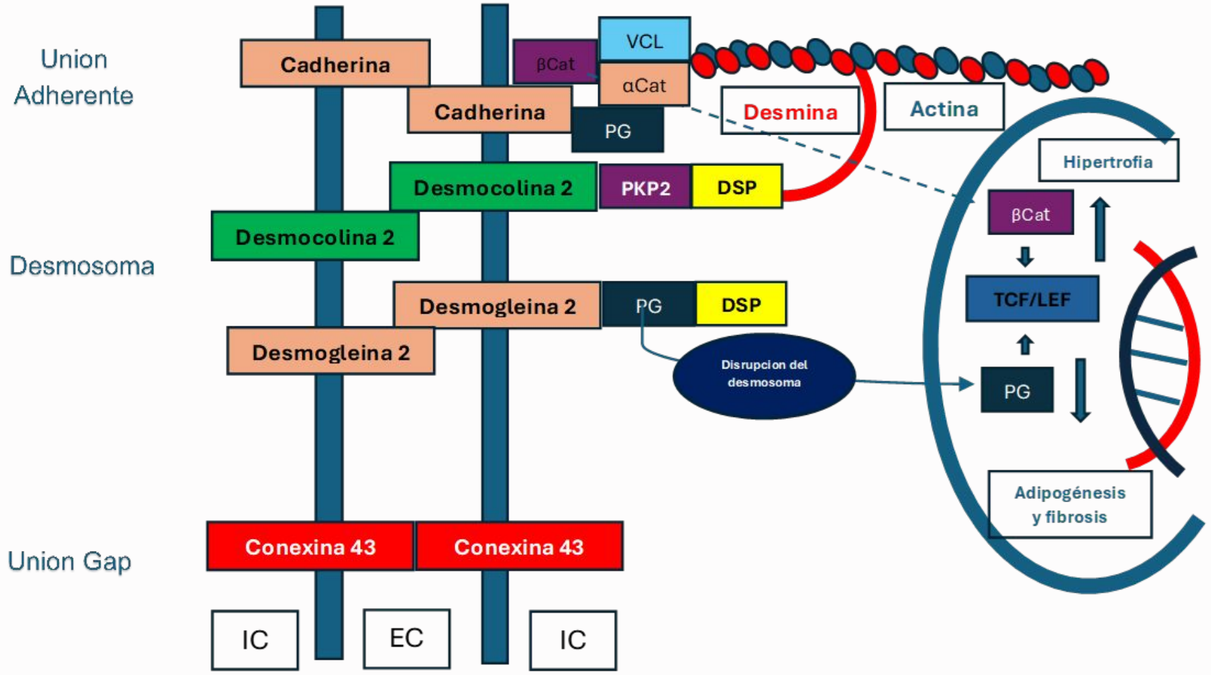


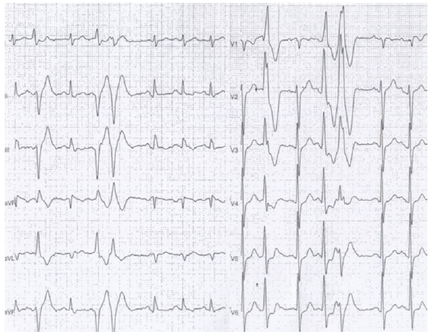
Fig.2. Mecanismo molecular

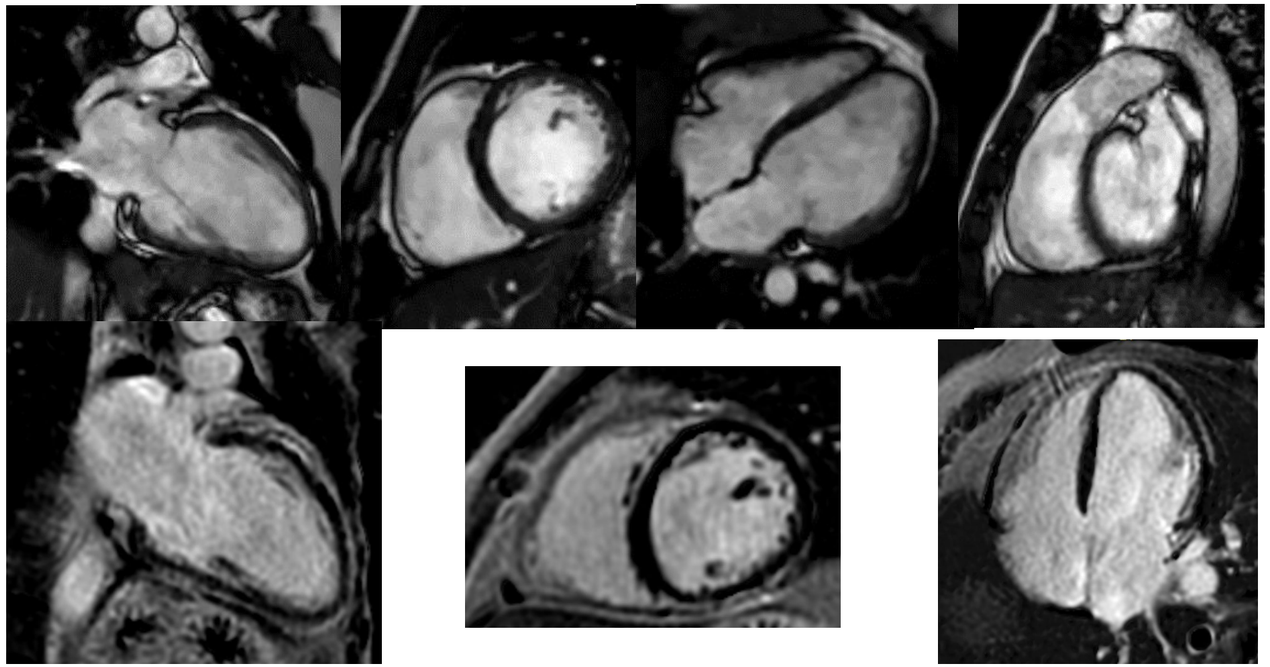
MCA Y RIESGO MSC

Gen	Proteina	Prevalencia	Fenotipo	Otros fenotipos	ClinGen
Genes desmosomicos					
PKP2	Plakophilin-2	20-46%	MAVD		Definitivo
DSP	Desmoplakin	3-20%	MNDVI, MABV, MAVD	Síndrome de fragilidad cutánea-cabello lanoso (pelo lanoso o hipotricosis, queratodermia palmoplantar)[13]	Definitivo
DSG2	Desmoglein-2	3-20%	MAVD		Definitivo
DSC2	Desmocolin-2	1-15%	MAVD		Definitivo
JUP	Plakoglobin	0-1% (> Naxos)	Enfermedad de NAXOS		Definitivo
Variantes Fundadoras					
PLN	Phospholamban	0-4%(> países bajos)	MAVD	R14del mas común, peor en ♀	Moderado
TMEM43	Transmembrane protein43	0-2% (> Newfoundland)		Jóvenes, Varones, arritmia ventricular letal (Newfoundland, Canada)	Definitivo
Genes de Fenotipos solapados					
SCN5A	Nav1.5	2%	MAVD	Solapamiento con MCD, Sme Brugada y QT largo	Limite
LMNA	Lamin A/C	0-4%	MCA	Solapamiento con MCD. Distrofia muscular esquelética. Disfunción del nódulo sinusal y anomalías del sistema de conducción.	Limite
TTN	Titin	0-10%	MCA	Solapamiento con MCD	Limite
FLNC	Filamin C	0-3%	MCA	Predominante izquierda, Distrofia muscular esquelética	Limite
DES	Desmin	0-3%	MCA	Distrofia muscular esquelética. Anomalías del sistema de conducción.	Limite
Genes Emergentes					
CTNNA	Alpha-Catenina	0-2%	MAVD		Limite
CDH2	Cadherin-2	0-2%	MAVD		Limite
TJP1	Tight junction protein 1	0-4%	MCA		Limite
ANK2	Ankyrin-B	0-5%	MCA		Limite

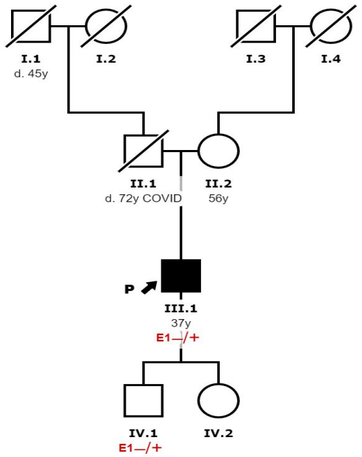
Gen	Riesgo Anual MS	Predictores MS
LMNA	5-10%	LMNA risk score. www. https://lmna-risk-vta.fr/
FLNC	5-10%	RTG en RM/FEY<45%
TMEM43	5-10%	Hombre/Mujer +FEY<45%/TVNS/RTG en RM,>200EV holter
PLN	3-5%	PLN risk score https://plnriskcalculator.shinyapps.io/final_shiny/ RTG en RM/FEY <45%/TVNS
DSP	3-5%	RTG en RM/FEY <45%
RBM20	3-5%	RTG en RM/FEY <45%

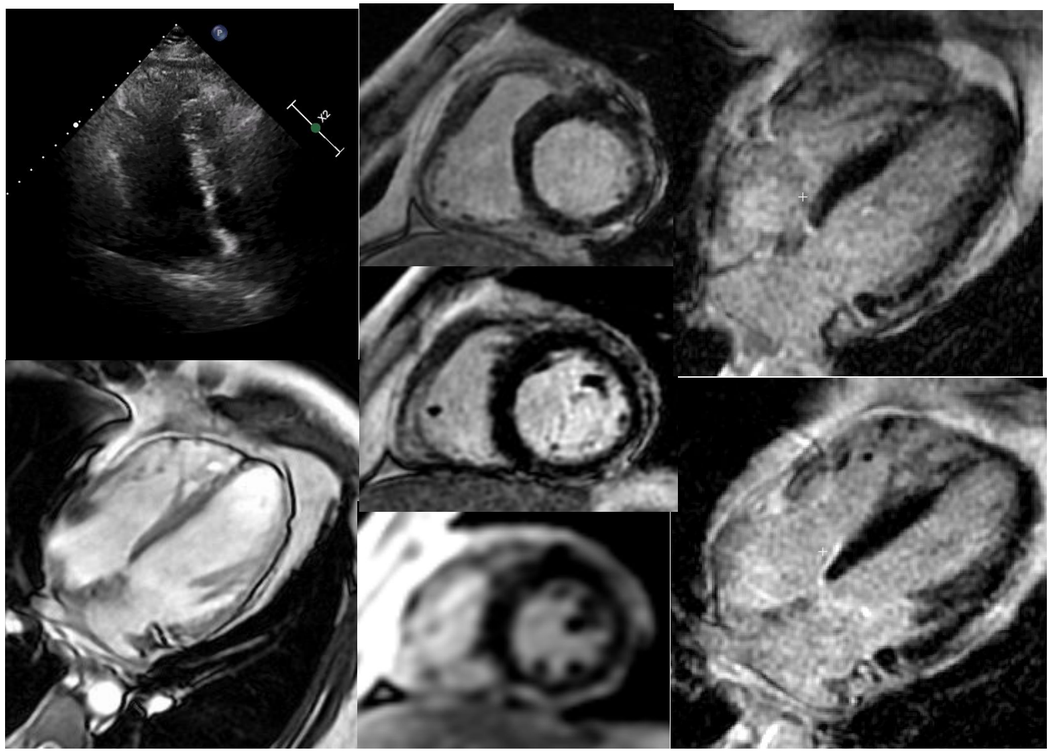
MCA Y RIESGO MSC

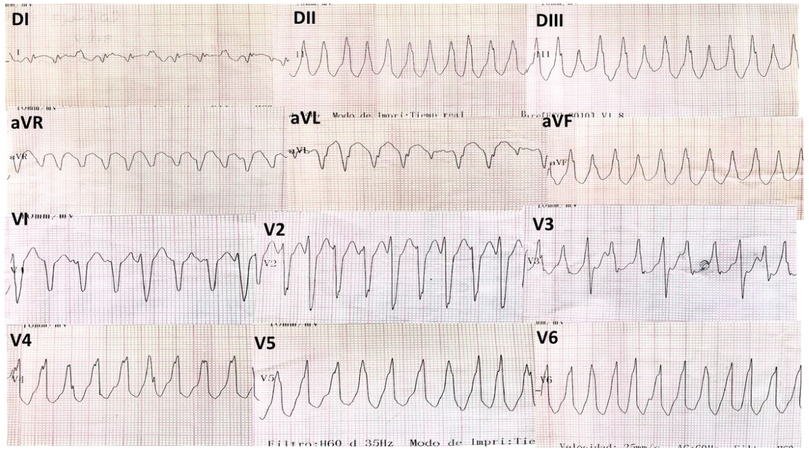




MCA Y RIESGO MSC

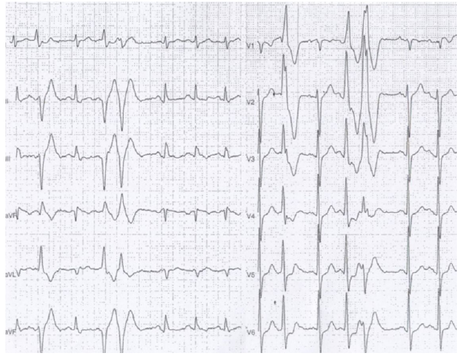


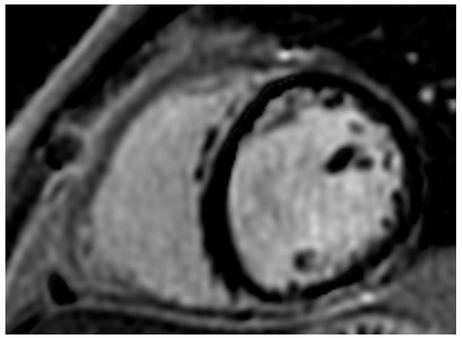




MCA Y RIESGO MSC

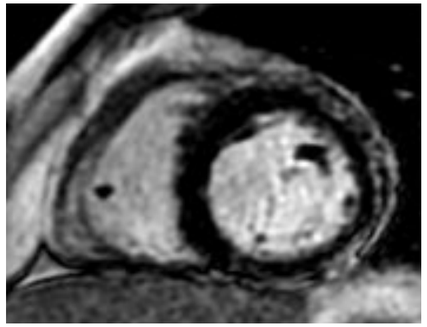
Running recreativo
Palpitaciones

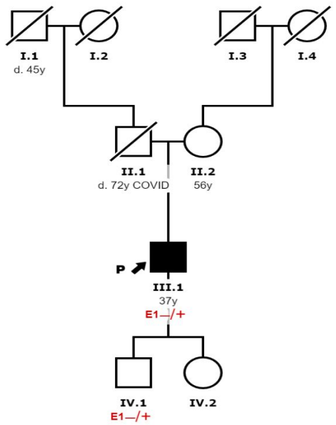




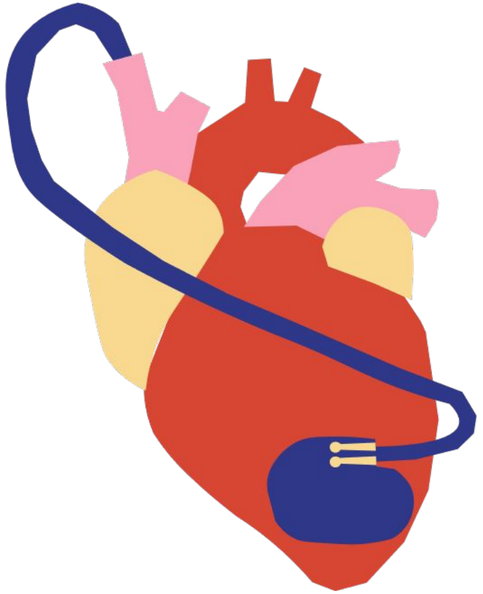
DSP c.250C>T (p.Arg84*)

TV-CVE CDI

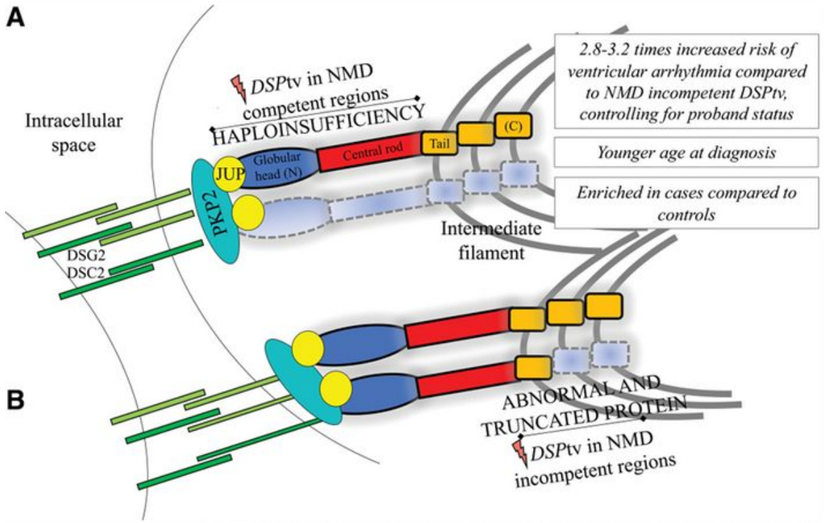




DSP c.1009_1010dup (p.Leu338Serfs*36)



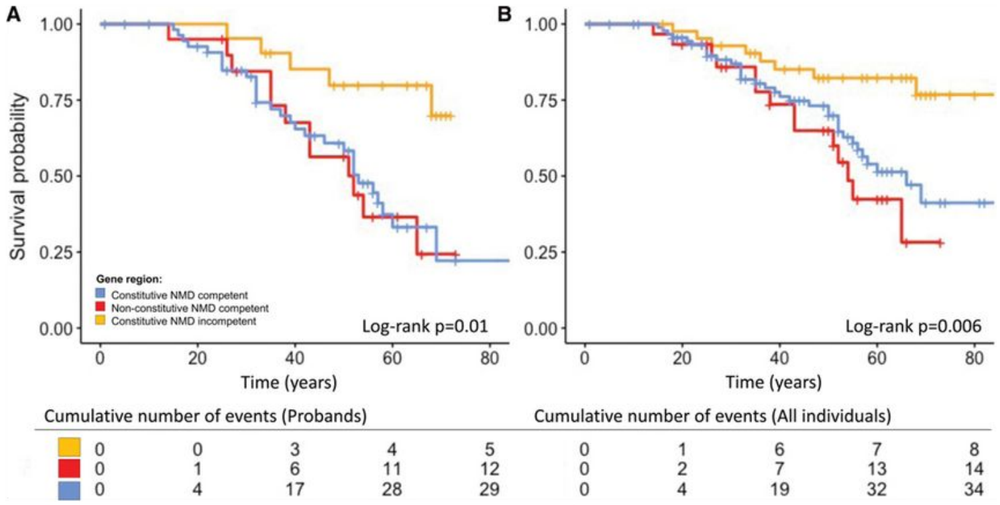
MCA Y RIESGO MSC



2.8-3.2 times increased risk of ventricular arrhythmia compared to NMD incompetent DSPtv, controlling for proband status

Younger age at diagnosis

Enriched in cases compared to controls



Hoorntje ET. Variant Location Is a Novel Risk Factor for Individuals With Arrhythmogenic Cardiomyopathy Due to a Desmoplakin (DSP) Truncating Variant. Circ Genom Precis Med. 2023 Feb;16(1):e003672.

Mensajes Finales

1.EL EG CONFIRMA EL DIAGNOSTICO ETIOLOGICO.

2.EL EG ES FACTIBLE Y ACCESIBLE!?

3.EN OPORTUNIDADES ES UN MARCADOR DE RIESGO Y DEFINE CONDUCTAS

4. LA INTERPRETACION DEBE REALIZARSE POR UN EQUIPO MULTIDISCIPLINARIO.

5.MEDICINA TRASLACIONAL.

Gracias