Unidades de Cardiopatías Heredables. Medicina siglo XXI

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Unidad de Cardiopatías Familiares

Hospital Universitario 12 de Octubre

LA CHARLA

- Un concepto: Heredable
- No es un área emergente
- Precio. Nuevas tecnologías NGS
- Recomendaciones-Guidelines
- Epidemiología
- Para que sirve? Por qué hacer un estudio genético
- Casos. Correlación genotipo fenotipo. Pronostico
- Convencidos?
- Cuál es el futuro. Conclusiones

Eventos heredables

- Es genético?
- La medida λ: Riesgo sobre población general. % Riesgo.

$\lambda = \%R$

%R= 50%
λ = 1000

Esquizofrenia

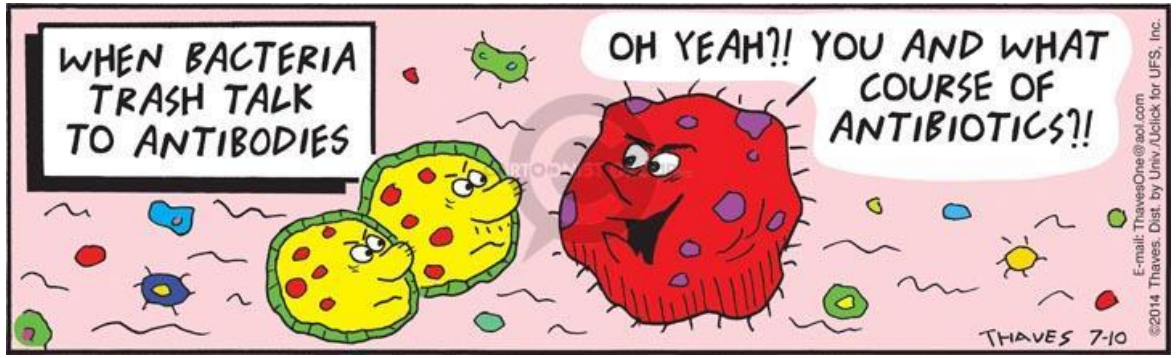
%R= 10%
λs = 10

Hipertensión

%R= 50%
λs = 6

%R= 0 ?
λ = 1

HITOS DE LA MEDICINA MODERNA

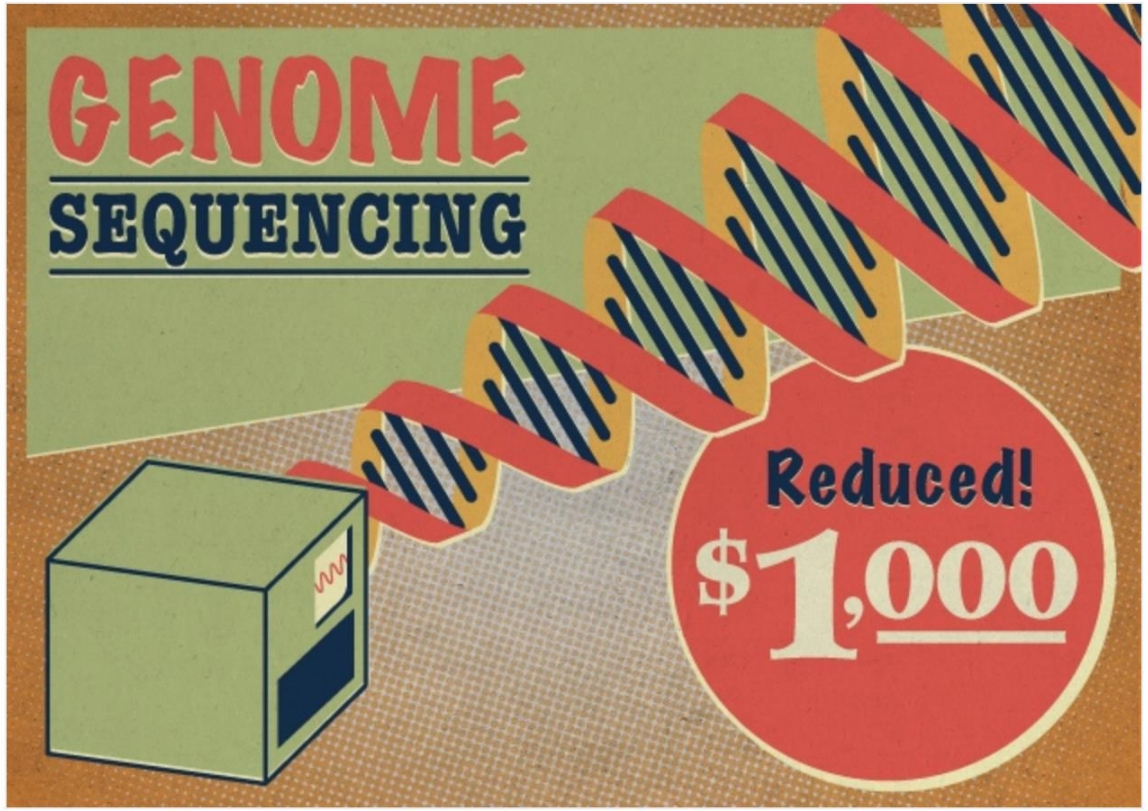


Technology: The $1,000 genome

With a unique programme, the US government has managed to drive the cost of genome sequencing down towards a much-anticipated target.

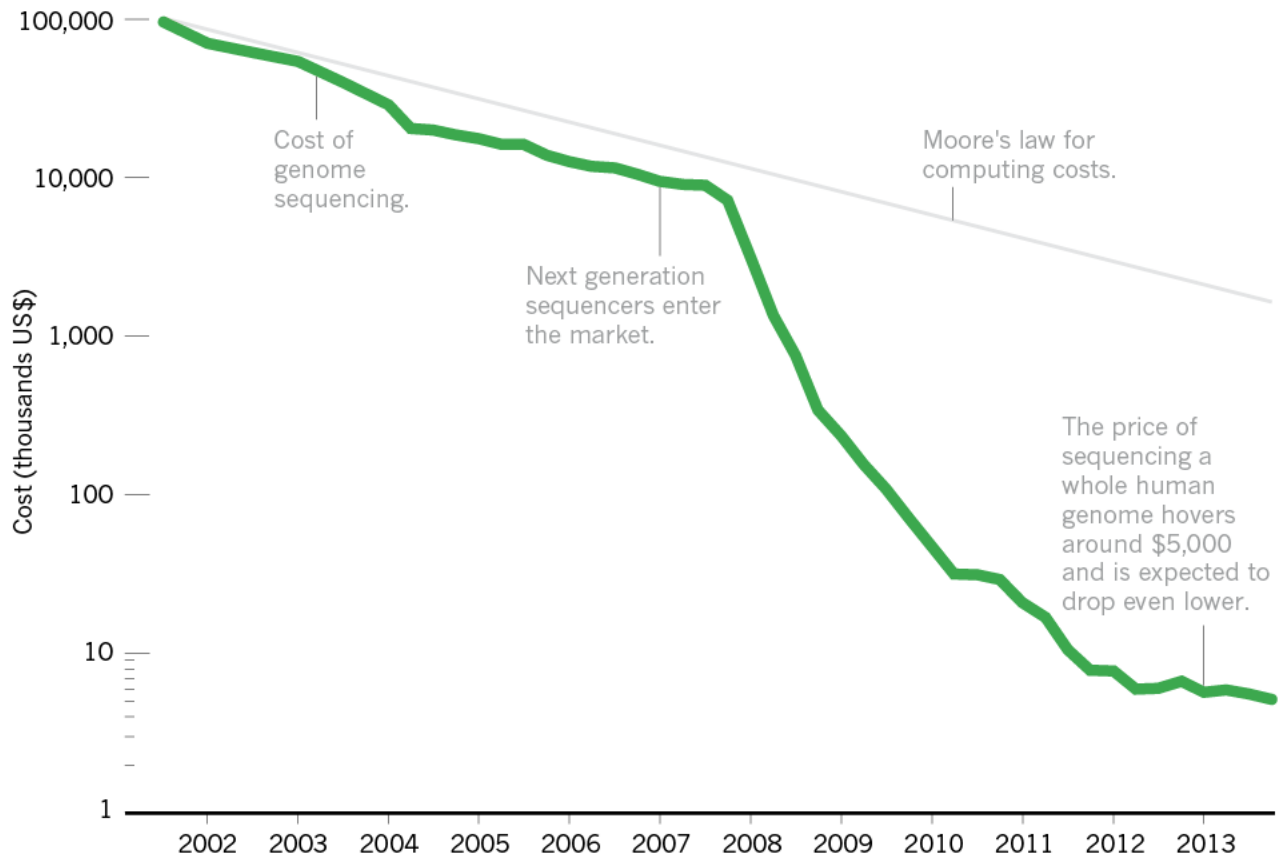
Erika Check Hayden

19 March 2014

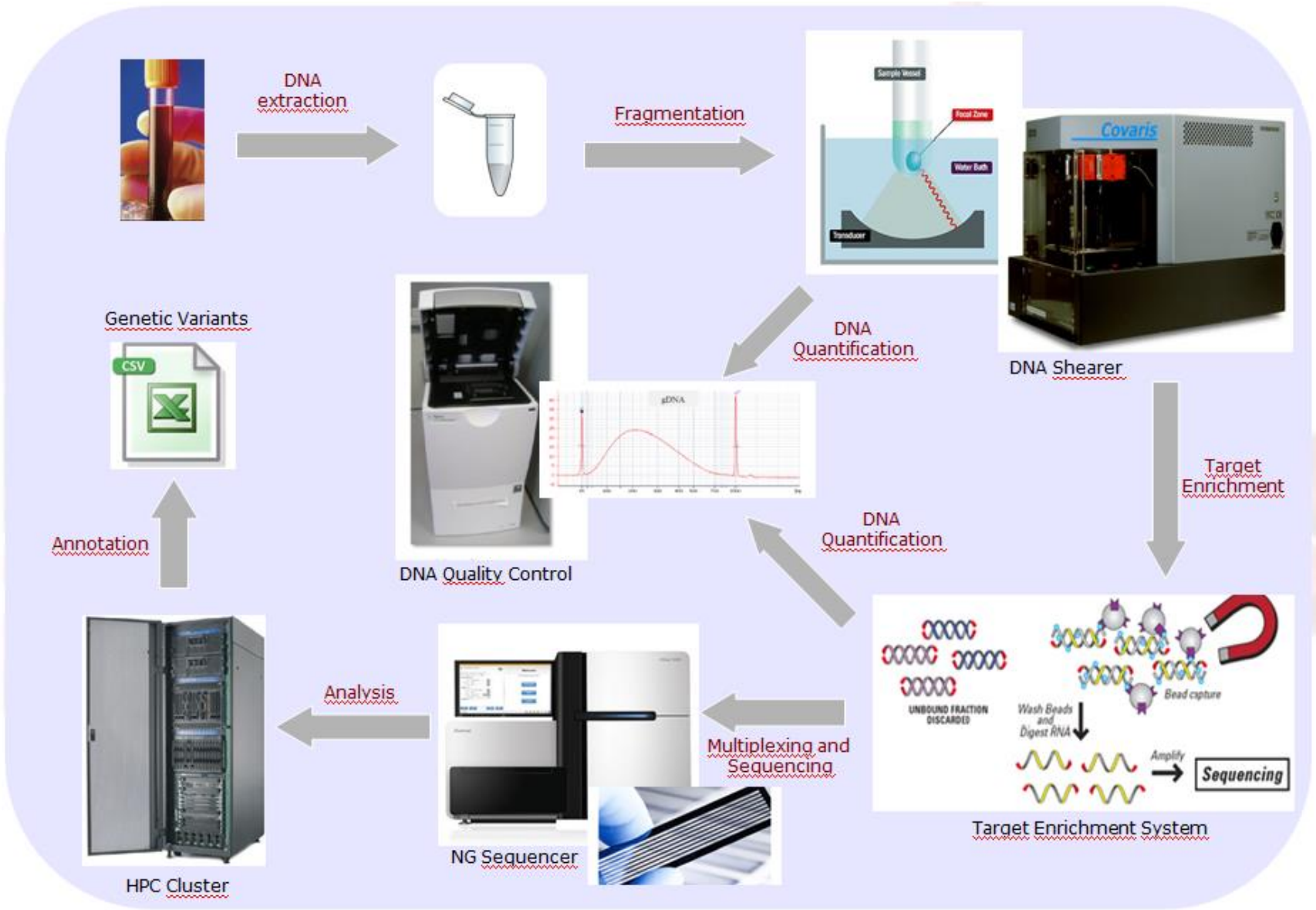


Falling fast

In the first few years after the end of the Human Genome Project, the cost of genome sequencing roughly followed Moore's law, which predicts exponential declines in computing costs. After 2007, sequencing costs dropped precipitously.



SECUENCIACION SANGER VS NGS (NEXT GENERATION SEQUENCING)



GENOM
E

Class I (is recommended)

Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.

Comprehensive or LQT1-3 (*KCNQ1, KCNH2*, and *SCN5A*) targeted LQTS genetic testing **is recommended** for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults).

Mutation-specific genetic testing **is recommended** for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.

Class IIb (may be considered)

Comprehensive or LQT1-3 (*KCNQ1, KCNH2*, and *SCN5A*) targeted LQTS genetic testing **may be considered** for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs.

STATE OF GENETIC TESTING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

Class I (is recommended)

Comprehensive or CPVT1 and CVPT2 (RYR2 and CASQ2) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion.

Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.

STATE OF GENETIC TESTING FOR BRUGADA SYNDROME (BrS)

Class I (is recommended)

Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.

Class IIa (can be useful)

Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.

Class III (is not indicated/recommended)

Genetic testing **is not indicated** in the setting of an isolated type 2 or type 3 Brugada ECG pattern.

STATE OF GENETIC TESTING FOR ARRHYTHMOGENIC CARDIOMYOPATHY (ACM)/ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

Class I (is recommended)

Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the ACM/ARVC-causative mutation in an index case.

Class IIa (can be useful)

Comprehensive or targeted (*DSC2, DSG2, DSP, JUP, PKP2*, and *TMEM43*) ACM/ARVC genetic testing **can be useful** for patients satisfying task force diagnostic criteria for ACM/ARVC.

Class IIb (may be considered)

Genetic testing **may be considered** for patients with possible ACM/ARVC (1 major or 2 minor criteria) according to the 2010 task force criteria (European Heart Journal).

Class III (is not indicated/recommended)

Genetic testing **is not recommended** for patients with only a single minor criterion according to the 2010 task force criteria.

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.

STATE OF GENETIC TESTING FOR LEFT VENTRICULAR NONCOMPACTION (LVNC)

Class I (is recommended)

Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of a LVNC-causative mutation in the index case.

Class IIa (can be useful)

LVNC genetic testing **can be useful** for patients in whom a cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype.

Ackerman MJ, Priori SG, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace. 2011;13:1077-109.

LQTS is diagnosed in the presence of a confirmed pathogenic LQTS mutation, irrespective of the QT duration.	I	C	This panel of experts

Targeted post-mortem genetic analysis of potentially disease-causing genes should be considered in all sudden death victims in whom a specific inheritable channelopathy or cardiomyopathy is suspected.	IIa	C	17,50, 51

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

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SaludMadrid
Comunidad de Madrid

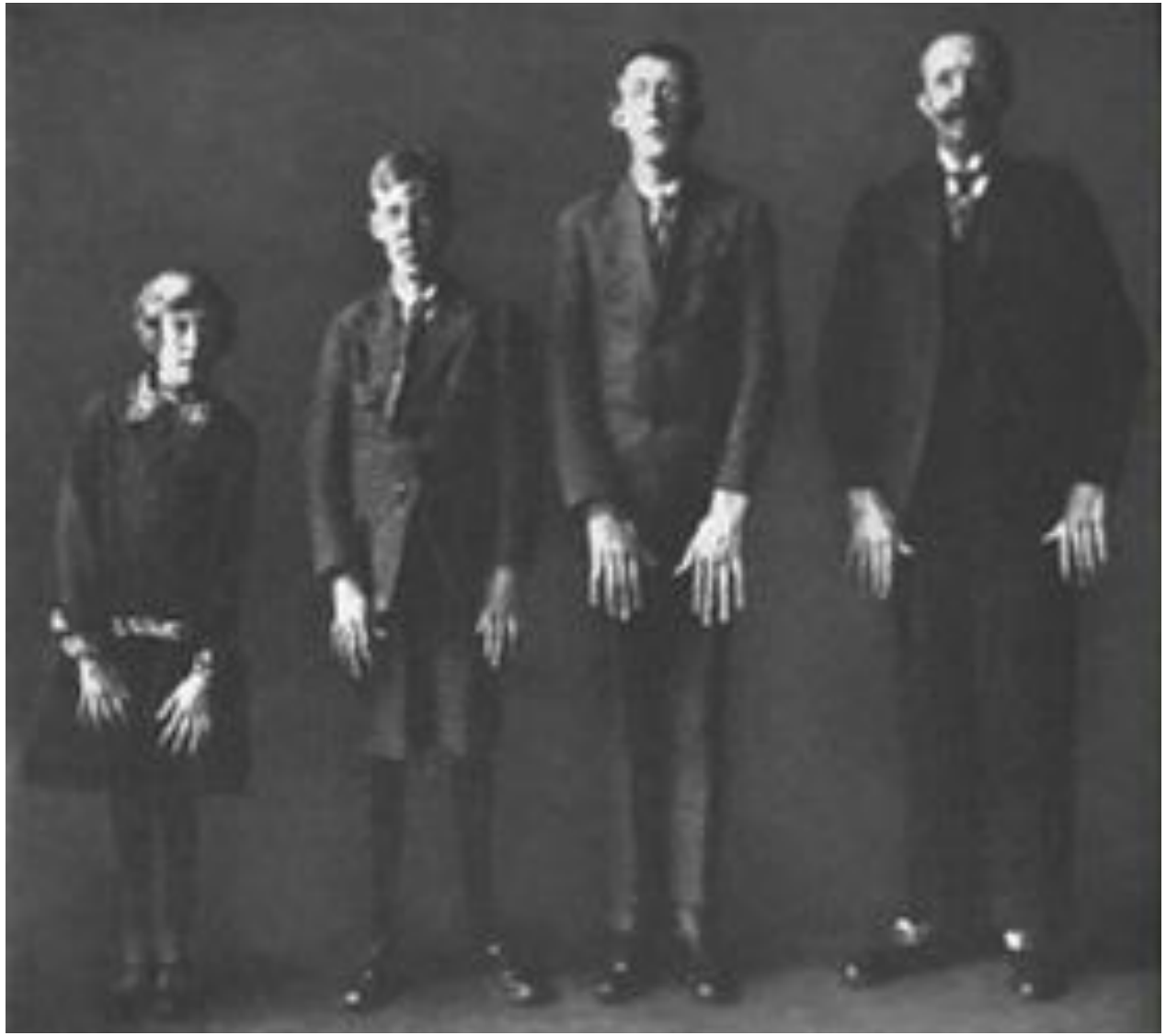
Major

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

In the absence of family history:
(1) Ao (Z ≥2) AND EL=MFS*
(2) Ao (Z ≥2) AND *FBN1*=MFS
(3) Ao (Z ≥2) AND Syst (≥7pts)=MFS*
(4) EL AND *FBN1* with known Ao=MFS

NUESTRAS PARTICULARIDADES

- La enfermedad cardíaca heredable como grupo es muy prevalente (0.2%)
- Lenguaje diferente. Hallazgos moleculares y su interpretación requieren un grupo de expertos (Clínica- imagen)
- Guías y generalidades habitualmente no aplicable

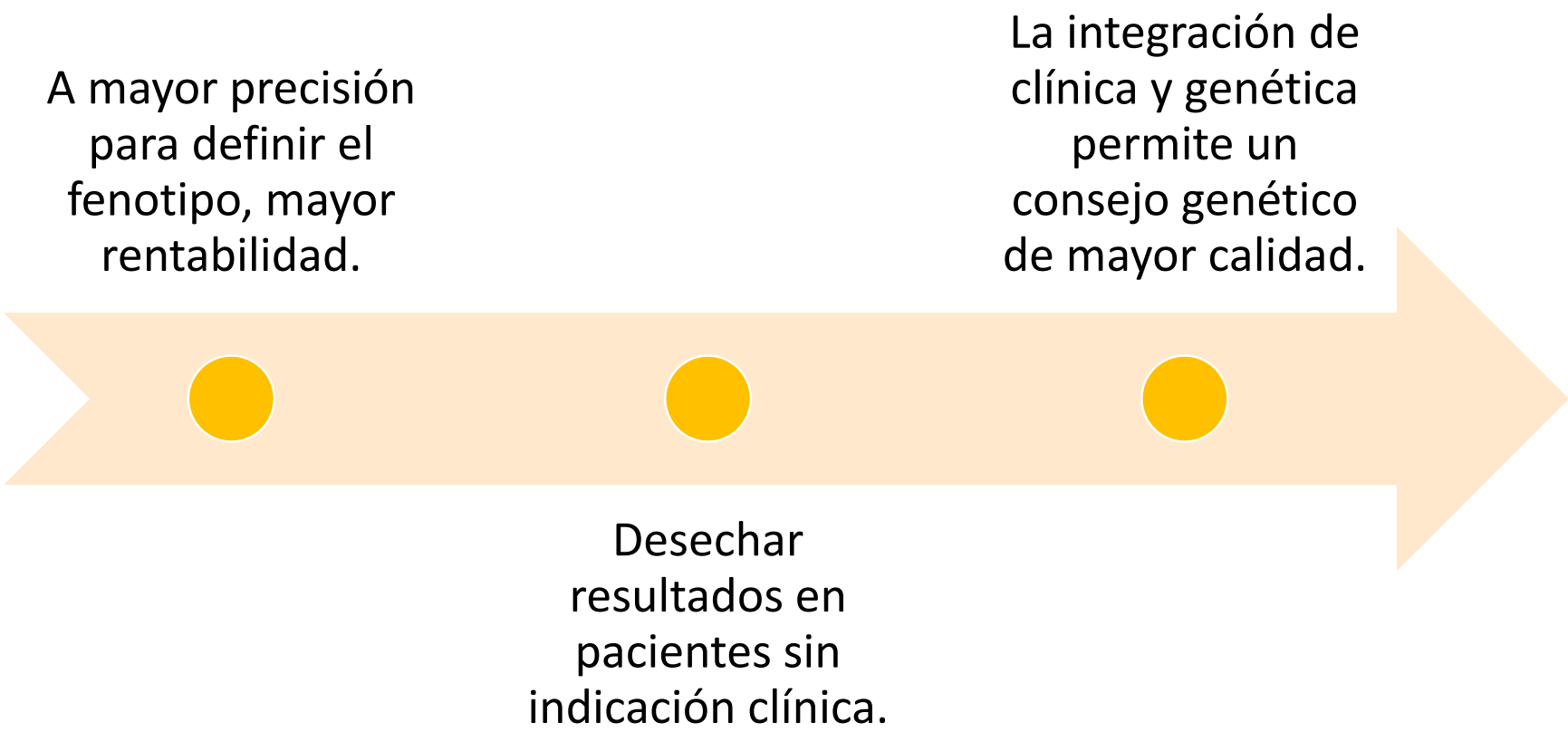


GESTION DE CASOS

Por qué hacer un estudio genético?

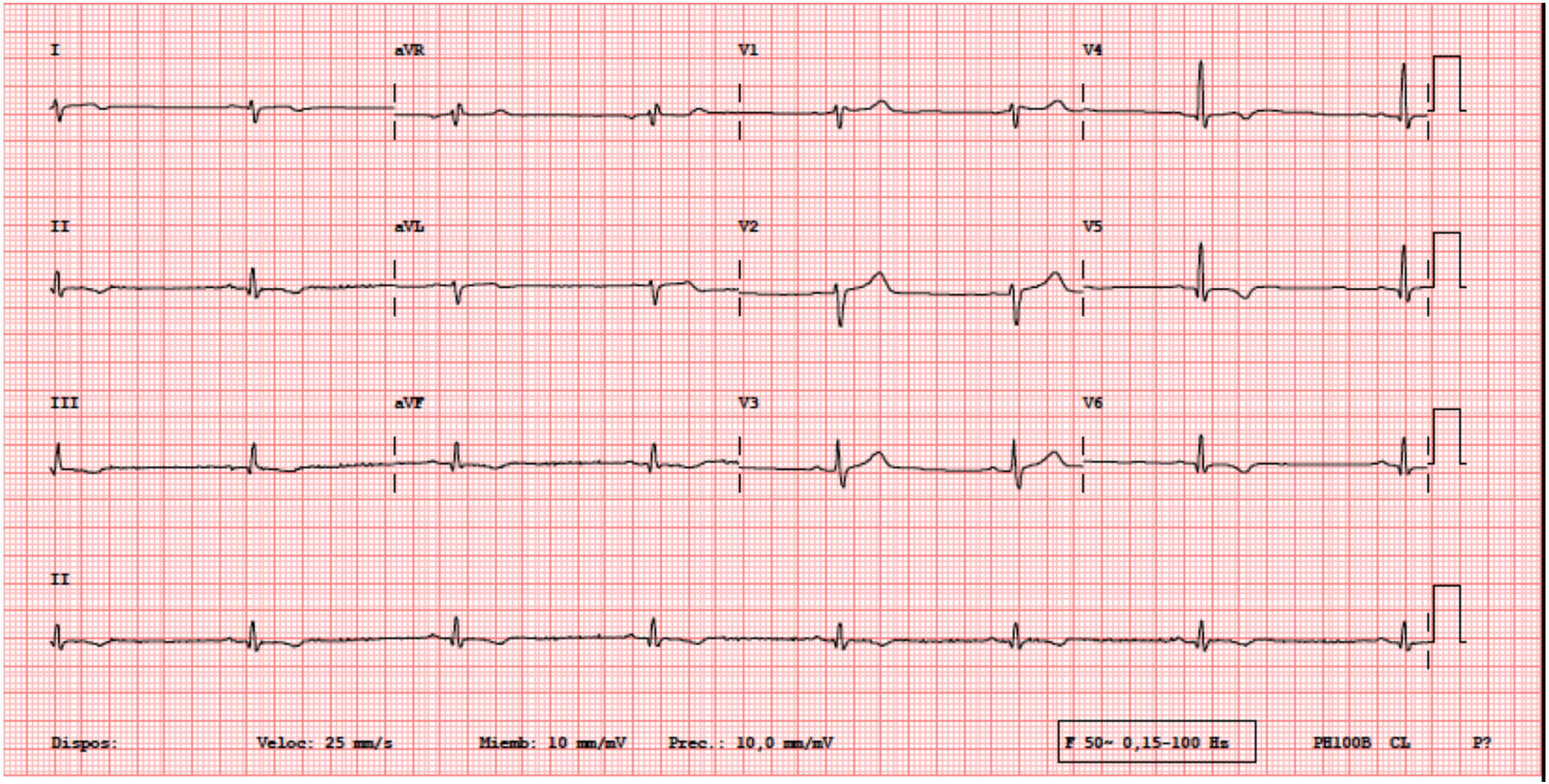
- Diagnóstico: índice y familiares
- Consejo genético
- Pronóstico
- Decisiones terapéuticas
- Investigación: Comprender la enfermedad y avanzar en su manejo

Siempre apoyarse en la clínica y generar unidades especializadas:

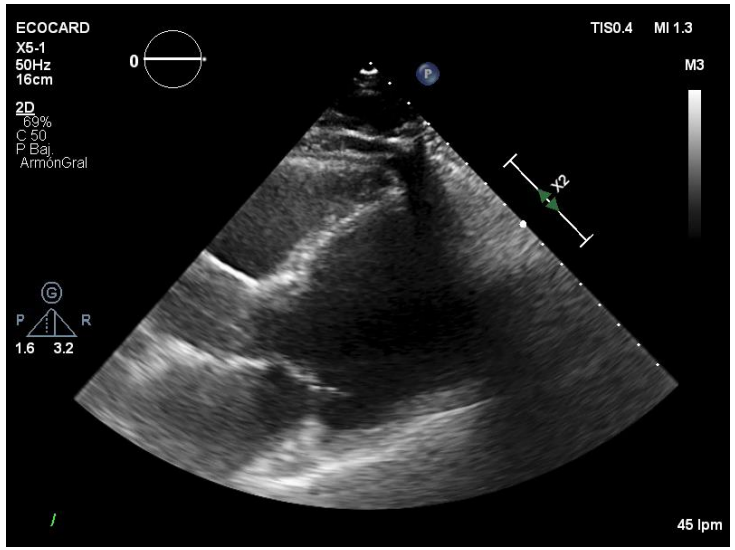


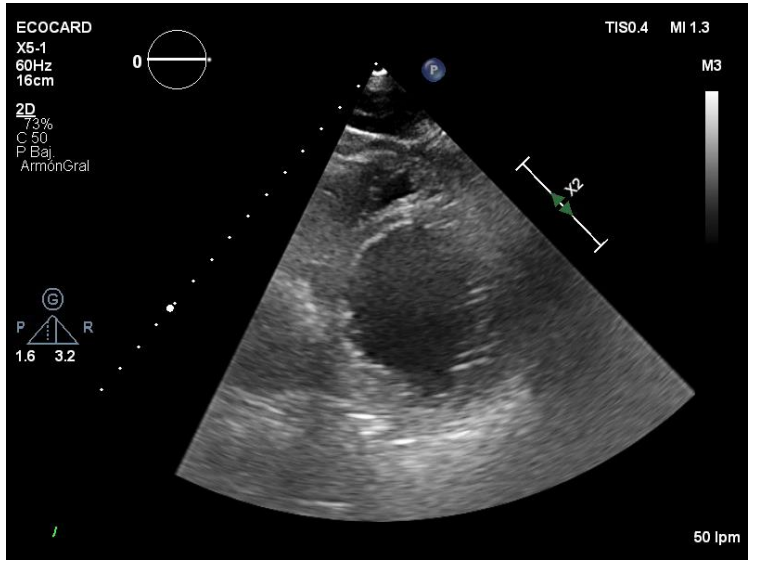
CASO 1. DIAGNOSTICO

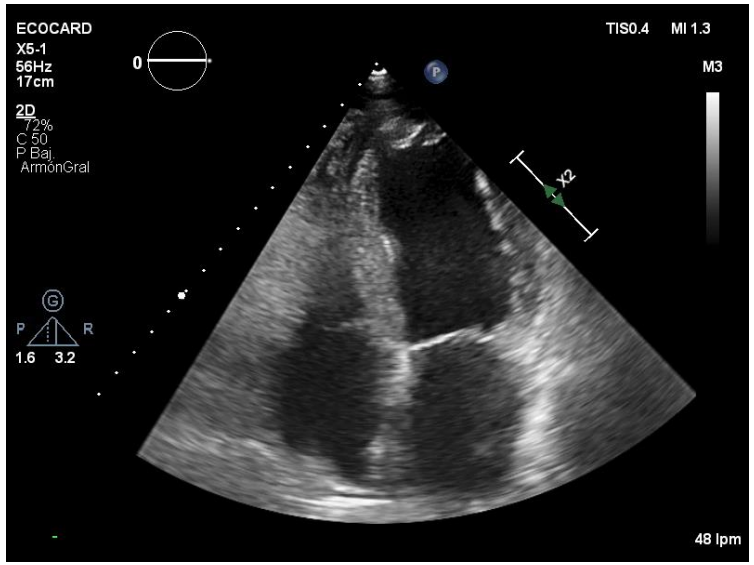
- Derivado en 2001 a Cardiología por ECG anómalo
- Diagnosticado de MCD “Idiopática”
- Seguido con múltiples tratamientos. Adiro. Ramipril, Carvedilol, Atenolol, etc.
- Asintomático
- CF I Deporte recreativo
- Entra en la espiral de familiares

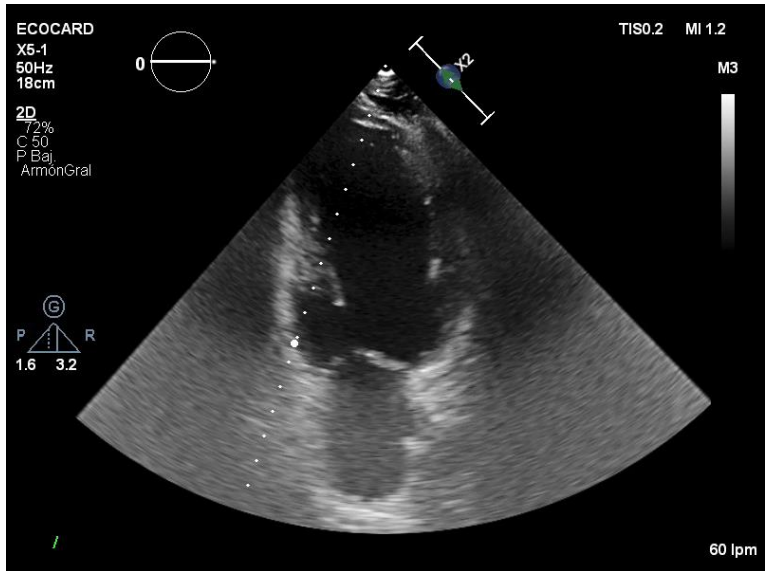

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Dispos:
Veloc: 25 mm/s
Miemb: 10 mm/mV
Prec.: 10,0 mm/mV
F 50~ 0,15-100 Hz
PH100B CL
P?

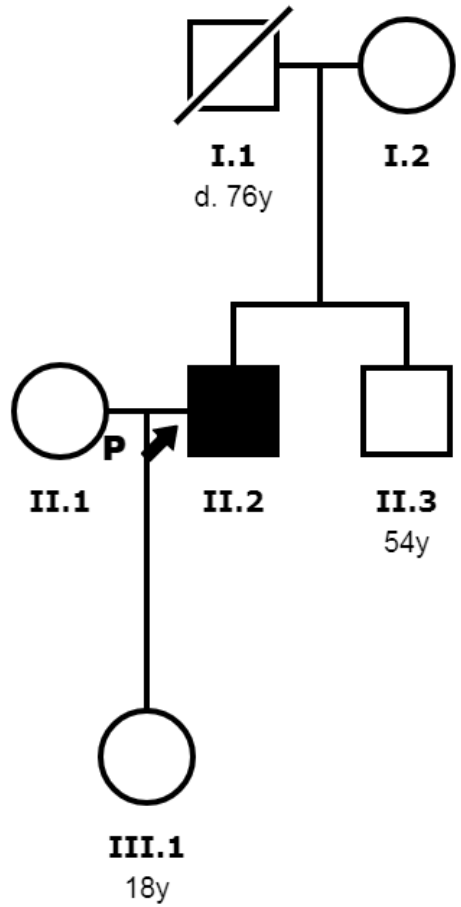
ECOCARDIOGRAMA









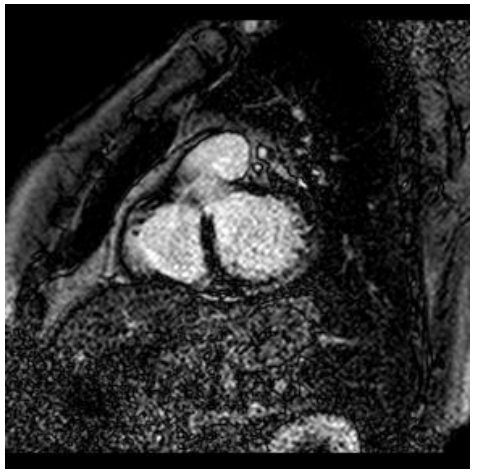


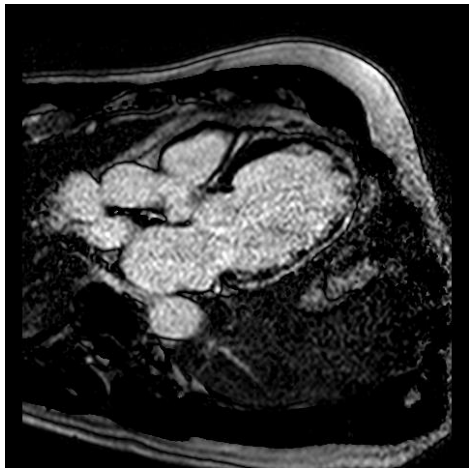
Dilated cardiomyopathy

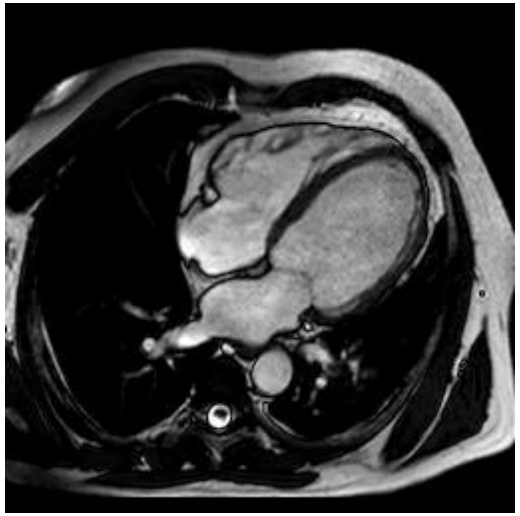
Clinically affected

CARDIOPATIAS FAMILIARES

- CPK Persistentemente elevada. 224 U/L
- Calambres musculares después del ejercicio
- Titulación de fármacos
- Holter inicial con racha de 4 latidos ventriculares. Morfología de BCRD
- Bisoprolol. Ramipril

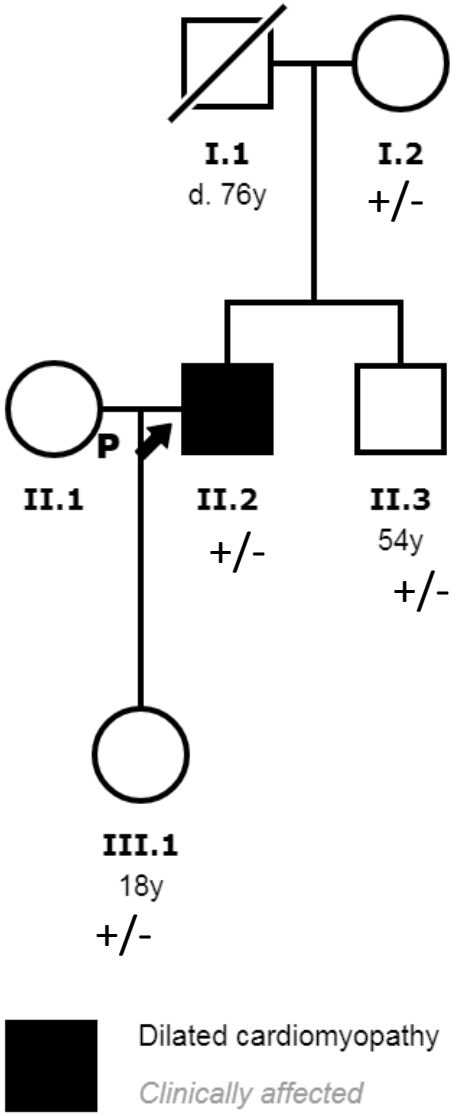






TEST GENETICO

- Panel NGS 96 genes
- Estudio genético Positivo
- DMD Deleción de los exones 3 a 9. NM_004006.2:c.93+49857_961-22489del
- CNV
- No presente en controles
- Haploinsuficiencia
- Reporte previo de variantes estructurales similares. Becker, Duchenne o MCD aislada
- Herencia recesiva ligada a X. Mujeres pueden tener fenotipos ligeros


I.1
d. 76y
I.2
+/-
P
II.1
II.2
+/-
II.3
54y
+/-
III.1
18y
+/-
Dilated cardiomyopathy
Clinically affected

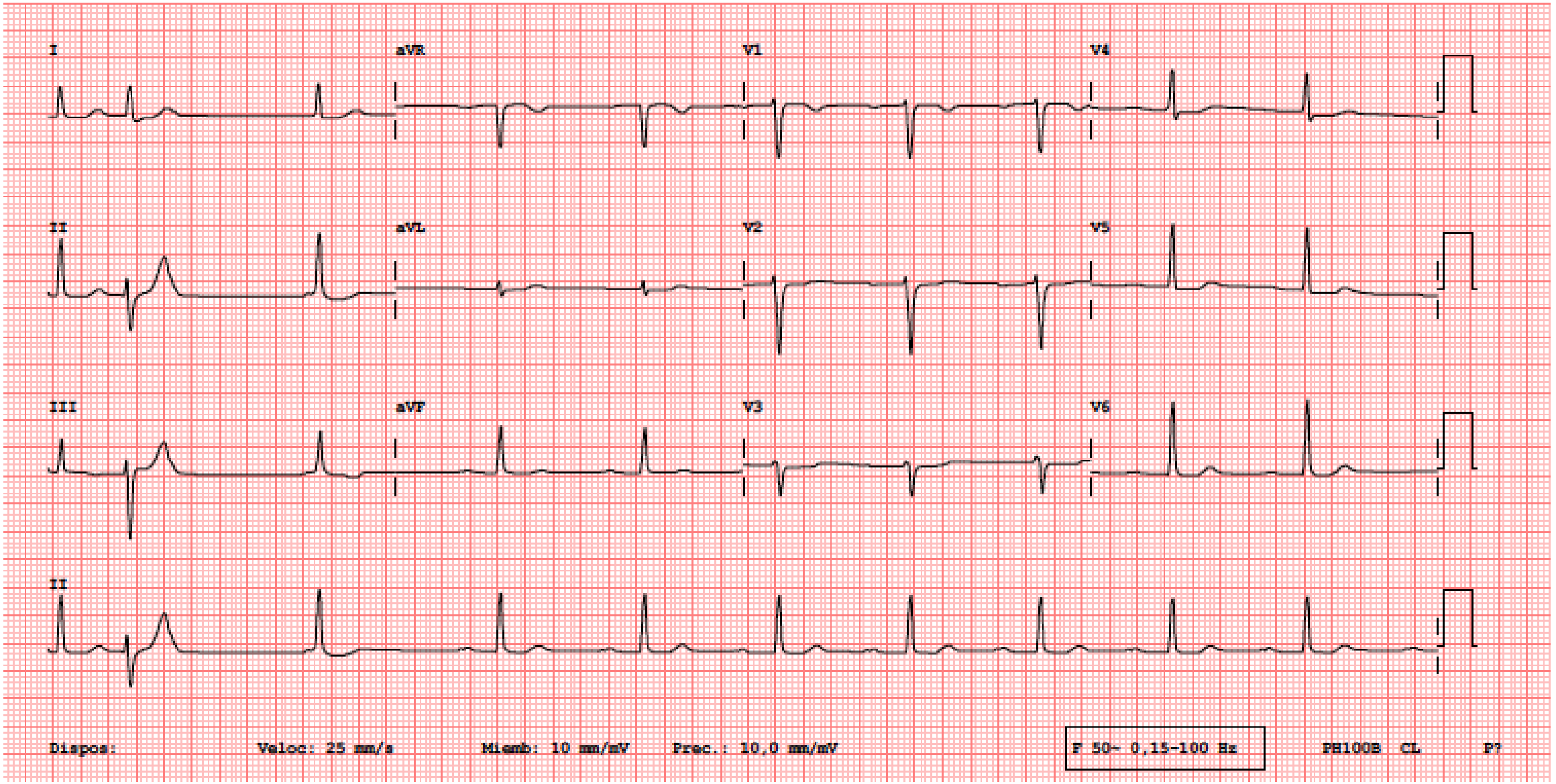

BABY
APPLE
JUICE
BEER

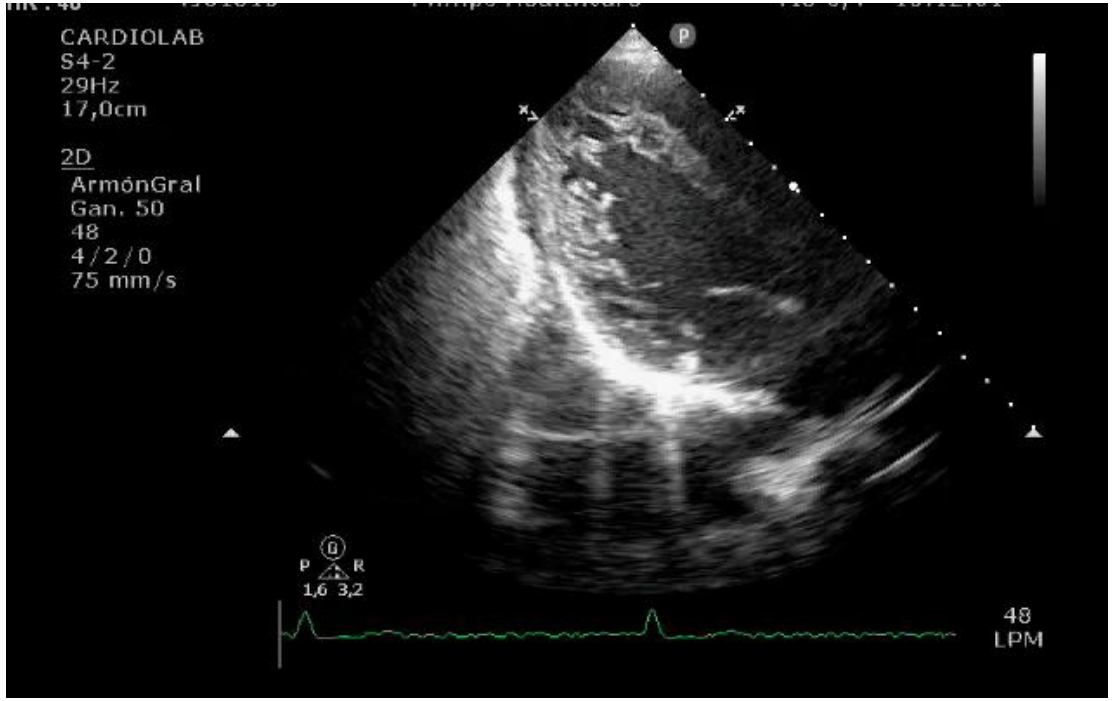
PRONOSTICO

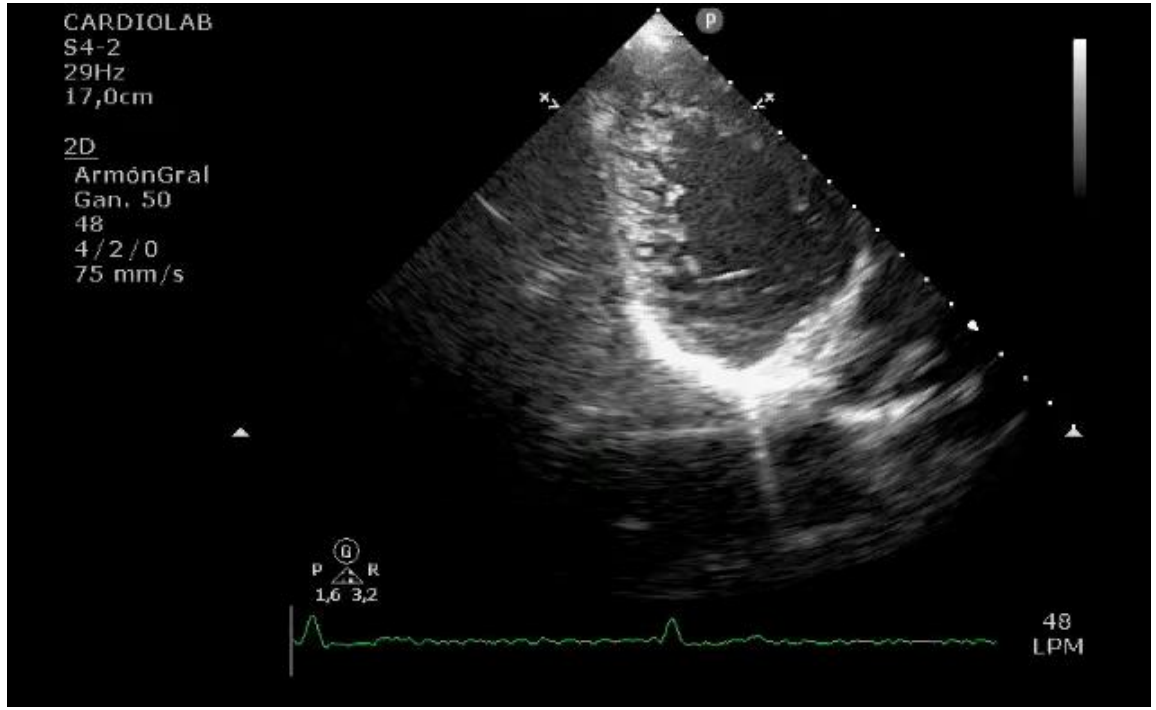
- Mujer de 30 años remitida para estudio a raíz de la muerte de su hermano
- Familiares: Abuelo materno fallecido durante el sueño a los 40 años. Hermana fallecida en edad pediátrica en el postoperatorio de comunicación interauricular.
- Hermano muerte súbita durante el sueño, 24 años. Primer ritmo asistolia. Tras RCP FV. Traslado a otro hospital
- Eco hermano: Dilatación VI. Disfunción VI moderada-severa. No compactación apical. Fallece encefalopatía hipóxico isquémica

EL CASO

- Padre y madre. Estudio con Eco y Holter 24h sin hallazgos
- Personales: Intervenida de CIA ostium secundum en la infancia
- Asintomática
- ECG: Bloqueo AV 1er grado
- Holter: Sin arritmias
- RM: FEVI en el límite inferior de la normalidad. No compactación inferolateral y apical
- Madre de dos varones (9 y 4 años). CIA Ostium Secundum. Intervenidos forma percutánea y abierta.

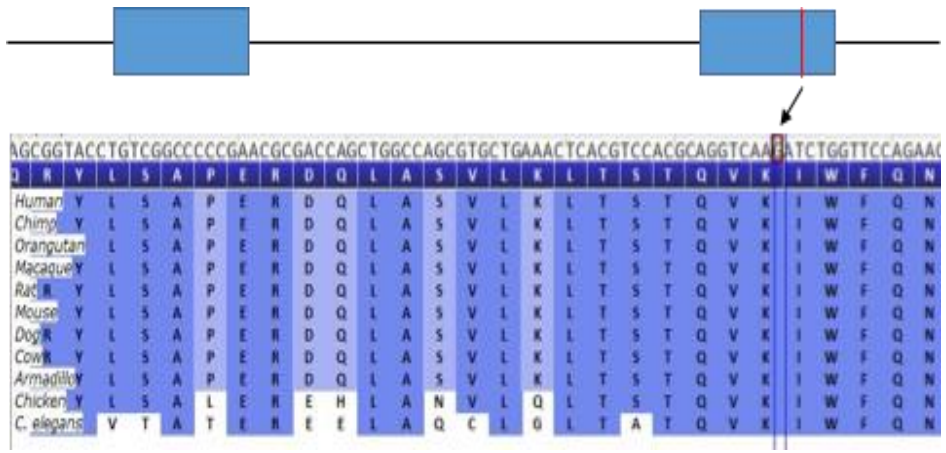

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Diapos:
Veloc: 25 mm/s
Miemb: 10 mm/mV
Prec.: 10,0 mm/mV
F 50- 0,15-100 Hz
PH100B CL
P?

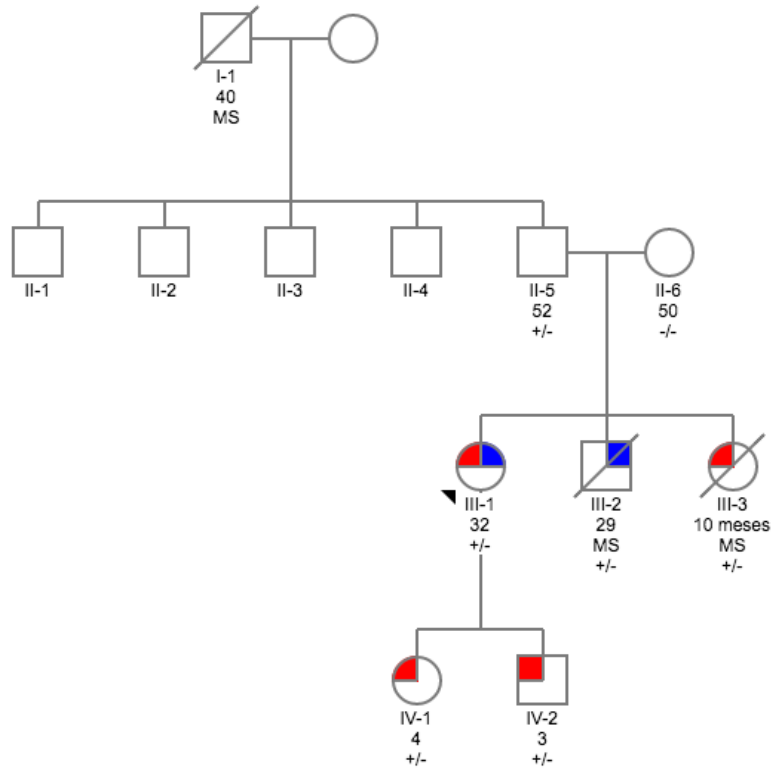

CARDIOLAB
S4-2
29Hz
17,0cm
2D
ArmónGral
Gan. 50
48
4/2/0
75 mm/s
P
P R
1,6 3,2
48
LPM


CARDIOLAB
S4-2
29Hz
17,0cm
2D
ArmónGral
Gan. 50
48
4/2/0
75 mm/s
P
P R
1,6 3,2
48
LPM

A ALGUIEN SE LE OCURRIO HACER GENETICA

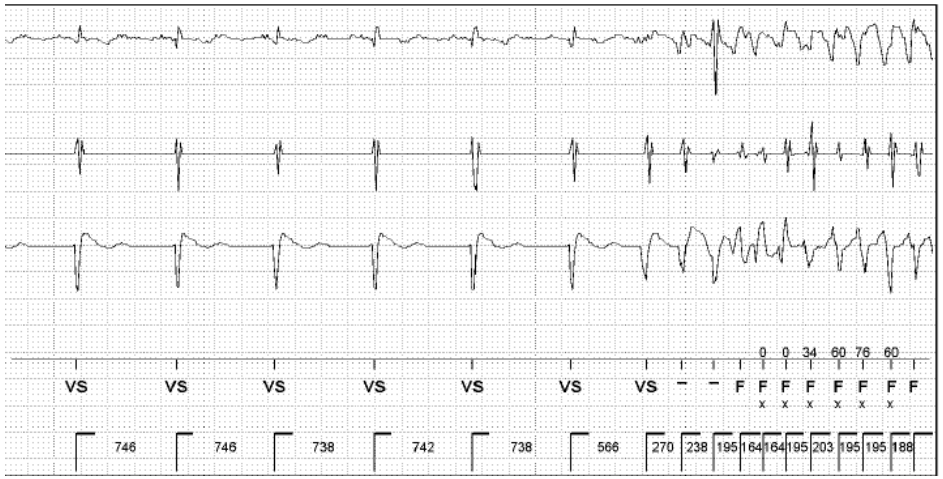
- Test genético al hermano fallecido
- Panel NGS 268 genes. Análisis bioinformático centrado en 16 genes (ACTC1, CASQ1, DMD, DTNA, HCN4, LDB3, LMNA, MYBPC3, MYH7, NKX2.5, SCN5A, TAZ, TNNI3, TNNT2, TPM1, VCL)
- POSITIVO
- NKX 2-5. p.Lys183Asn
- No reportada en bases de datos públicas
- No publicada
- Residuo conservado

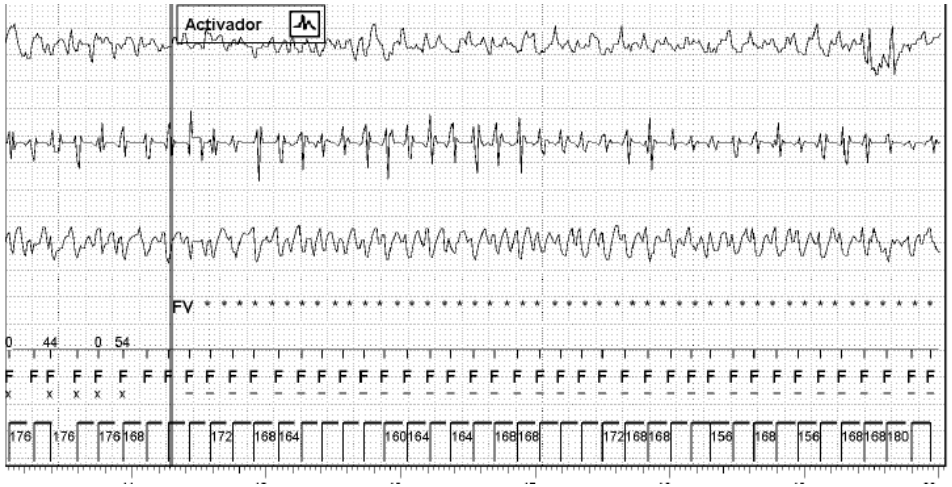

AGCGGTACCTGTCGGCCCCCGAACGCGACCAGCTGGCCAGCGTGCTGAAACTCACGTCCACGCAGGTCAAGATCTGGTTCCAGAAC
Q R Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Human Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Chimp Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Orangutan L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Macaque Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Rat R Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Mouse Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Dog R Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Cow R Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Armadillo Y L S A P E R D Q L A S V L K L T S T Q V K I W F Q N
Chicken Y L S A L E R E H L A N V L Q L T S T Q V K I W F Q N
C. elegans V T A T E R E E L A Q C L G L T A T Q V K I W F Q N


I-1
40
MS
II-1
II-2
II-3
II-4
II-5
52
+/-
II-6
50
-/-
III-1
32
+/-
III-2
29
MS
+/-
III-3
10 meses
MS
+/-
IV-1
4
+/-
IV-2
3
+/-

Y AHORA QUE?

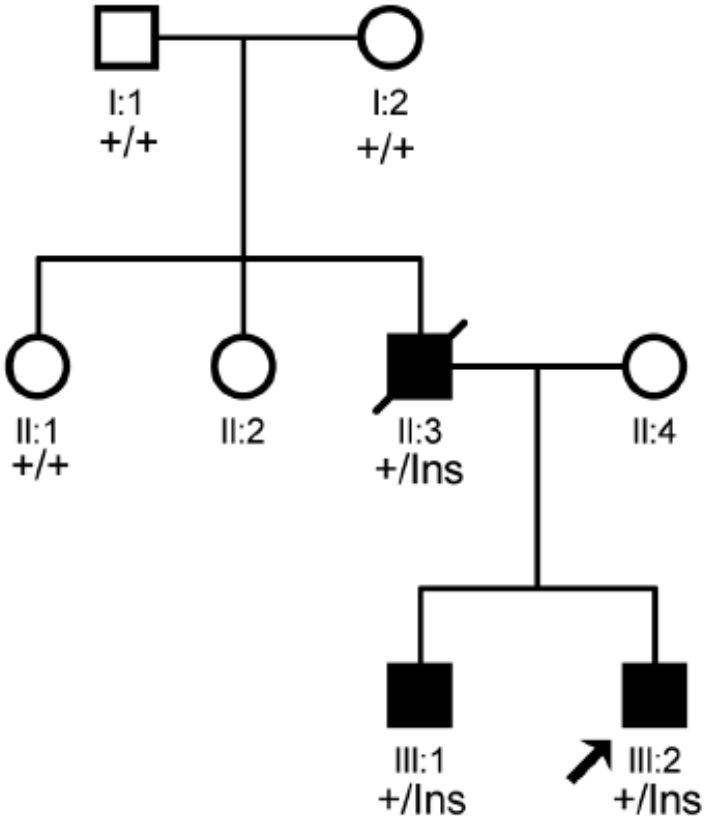
- Posiblemente patogénica
- Estudio de cosegregación: Patogénica con penetrancia incompleta
- Riesgo de muerte súbita?
- En aquel entonces se decidió implante de DAI





QUE NOS DICE LA GENETICA

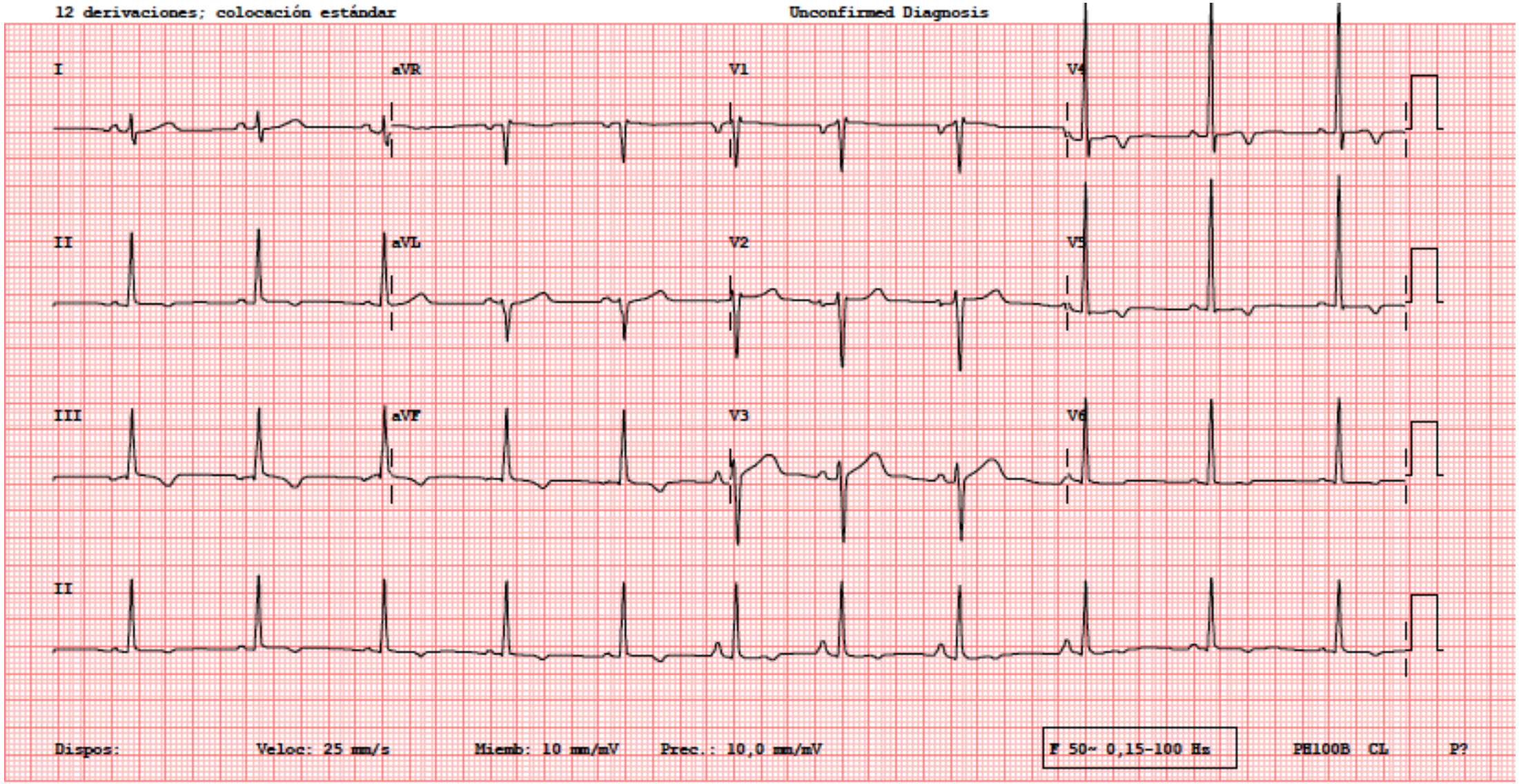
- No compactación y NKX2.5. Una sola referencia Ouyang (p.Leu171Argfs*7)
- No compactación, CIA y muerte súbita
- Bermudez et al. 2016. Mujer 48 años. TVNS. No compactación. CIA Ostium Secundum. BAV completo. p.Glu167Lys
- 48 pacientes (18 familias). 8 muertes súbitas. CIA 75% pacientes. 90% defectos de conducción. 42% MCP. 5 no compactación
- Pacientes Málaga, Ouyang y H12O. Misma región. Homeodomain



Ouyang, P., et al., A de novo mutation in NKX2.5 associated with atrial septal defects, ventricular noncompaction, syncope and sudden death. Clin Chim Acta, 2011. 412(1-2): p. 170-5

CASO 3

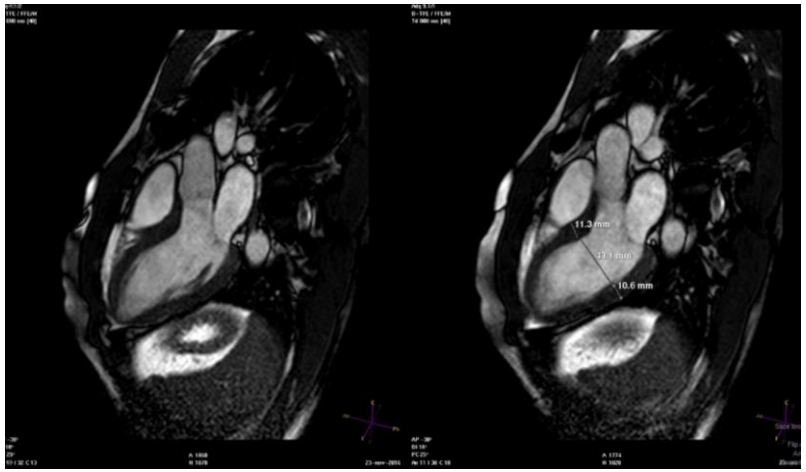
- Antecedentes familiares: Padre muerte súbita posible IAM en autopsia. Madre valvulopatía
- No FRCV
- Remitido por alteración ECG en reconocimiento empresa. Asintomático
- Deportista de competición en la juventud. Actualmente aproximadamente 100 Km cada 2 días de bici
- Exploración: Sin hallazgos


12 derivaciones; colocación estándar
Unconfirmed Diagnosis
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Dispos:
Veloc: 25 mm/s
Miemb: 10 mm/mV
Prec.: 10,0 mm/mV
F 50~ 0,15-100 Hz
PH100B CL
P?

Y LAS PRUEBAS

- Eco de consulta: Septo 13 mm. No otros hallazgos. No imágenes
- Dolor torácico tipo pinchazo en axila de reposo prolongado
- SPECT: 11.5 Mets. Detenida por disnea y alteraciones significativas del ST. En esfuerzo máximo descenso de ST horizontal en dichas derivaciones de hasta 2 mm que corrige en la recuperación inmediata. EV monomorfas aisladas asintomáticas.
- Defectos fijos de captación en pared anterior y pared inferior este ultimo con discreta reversibilidad. Artefactos por HVI?
- Ideas?

LA RMN


11.3 mm
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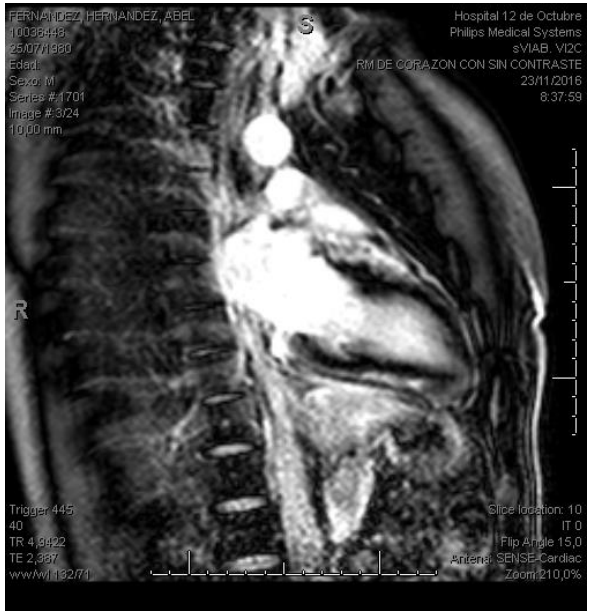
FERNANDEZ, HERNANDEZ, ABEL
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25/07/1980
Edad:
Sexo: M
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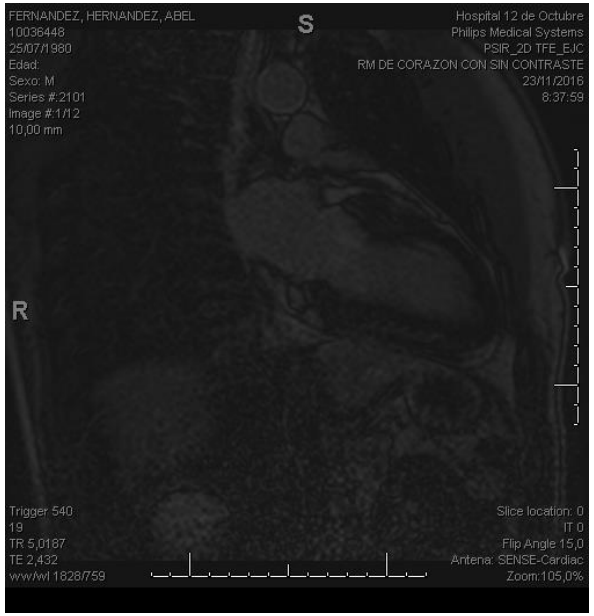
Image #:3/24
10,00 mm
S
Hospital 12 de Octubre
Philips Medical Systems
sVIAB. VI2C
RM DE CORAZON CON SIN CONTRASTE
23/11/2016
8:37:59
R
Trigger 445
40
TR 4,3822
TE 2,387
ww/wl 132/71
Slice location: 10
IT 0
Flip Angle 15,0
Antena: SENSE-Cardiac
Zoom:210,0%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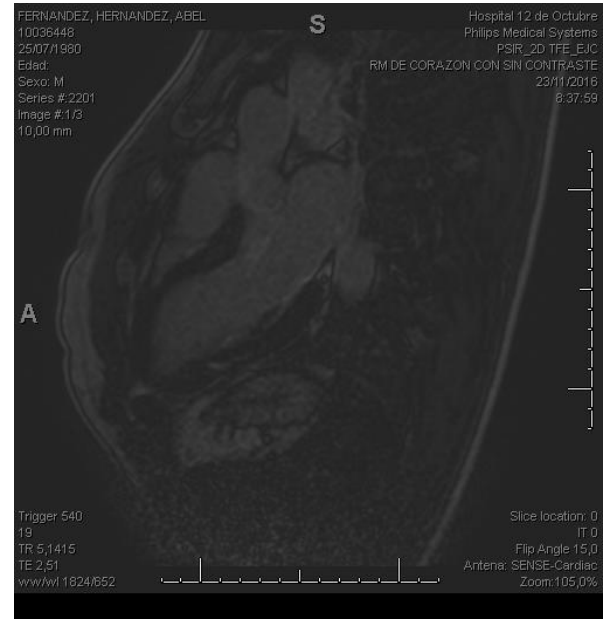
10,00 mm
S
Hospital 12 de Octubre
Philips Medical Systems
PSIR_2D TFE_EJC
RM DE CORAZON CON SIN CONTRASTE
23/11/2016
8:37:59
R
Trigger 540
19
TR 5,0187
TE 2,432
ww/wl 1828/759
Slice location: 0
IT 0
Flip Angle 15,0
Antena: SENSE-Cardiac
Zoom:105,0%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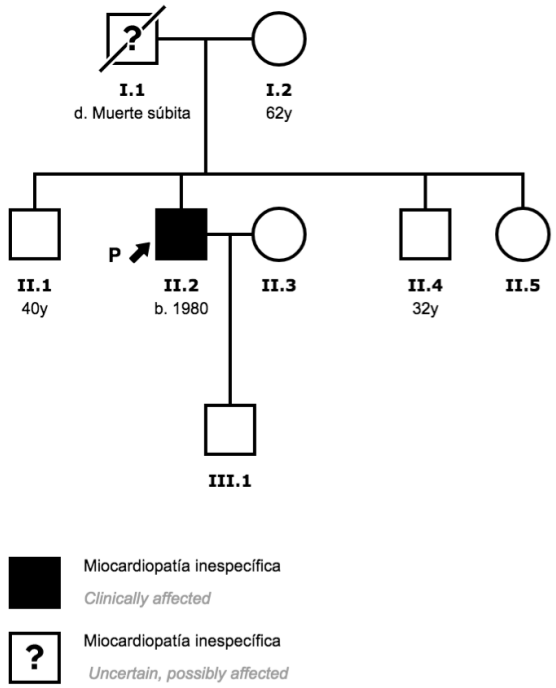
10,00 mm
S
Hospital 12 de Octubre
Philips Medical Systems
PSIR_2D TFE_EJC
RM DE CORAZON CON SIN CONTRASTE
23/11/2016
8:37:59
A
Trigger 540
19
TR 5,1415
TE 2,51
ww/wl 1824/652
Slice location: 0
IT 0
Flip Angle 15,0
Antena: SENSE-Cardiac
Zoom:105,0%

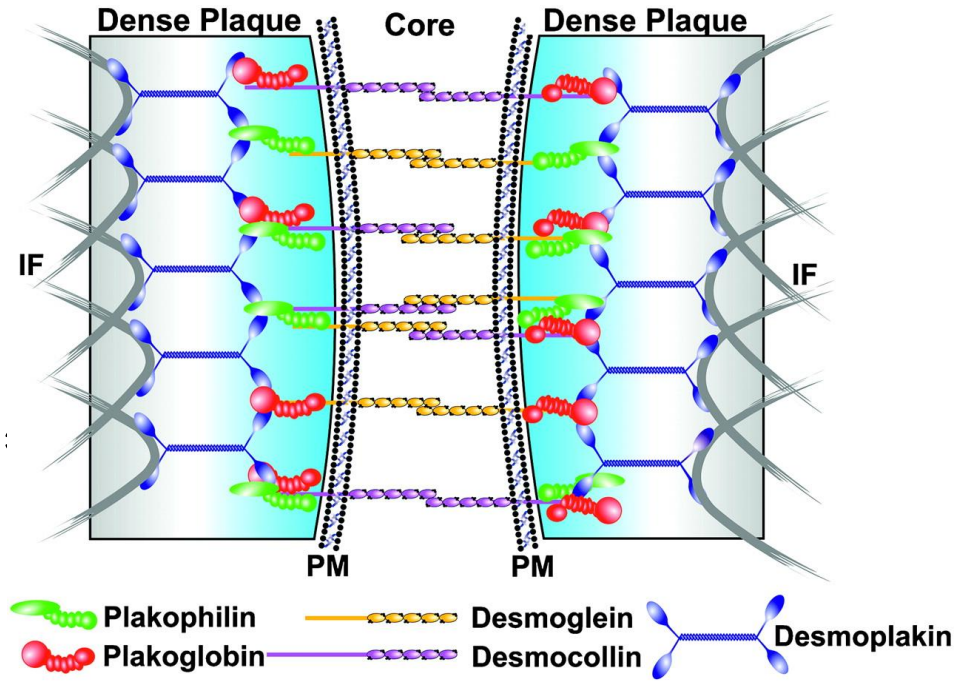
CON TODO ESTO… A FAMILIARES

- Coronariografía: Sin lesiones significativas
- Madre de 61 años. Padre fallecido a los 47 años de forma súbita catalogada de posible IAM (No tiene informes en el momento)
- Tres hermanos de 40, 32 y hermana de 30 años, sin cardiopatía conocida.
- Un hijo de 1 y 1/2 años
- Holter: Sin arritmias



Y AHORA?

- Cuál es el pronóstico de la paciente?
- Respuesta mágica: ESTUDIO GENETICO!!
- NGS. Panel 96 genes
- Positivo
- (Reordenamiento complejo) p.Ala1904Serfs
- Tipo variante?



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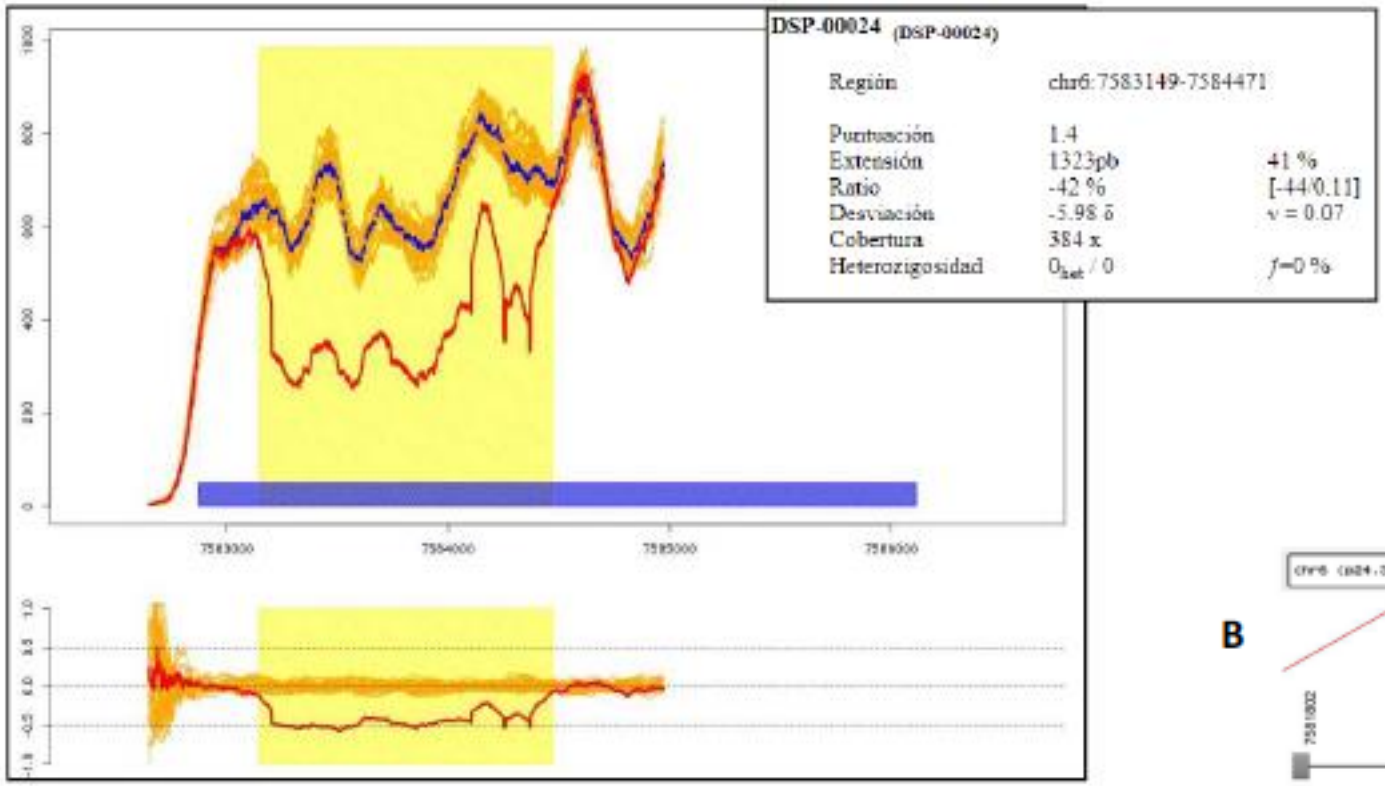

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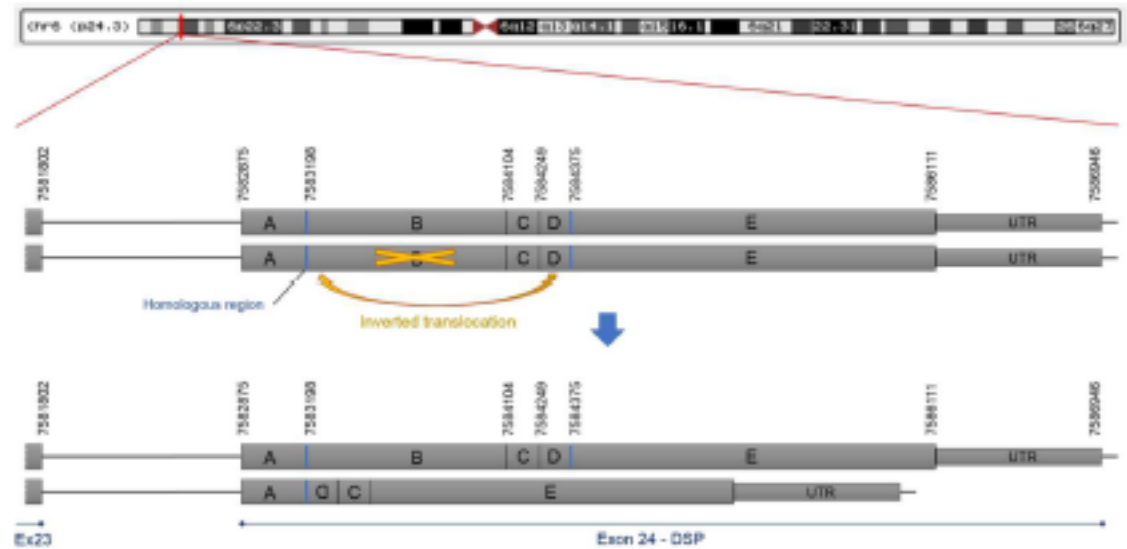
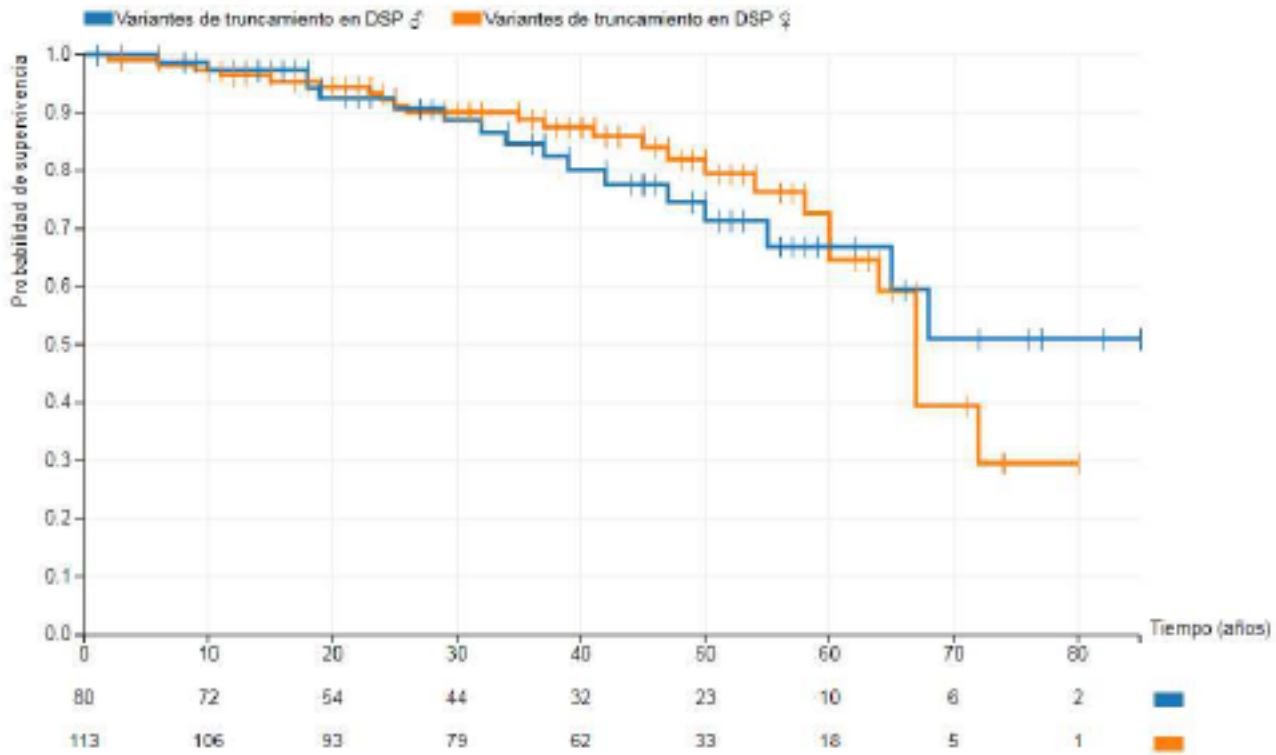
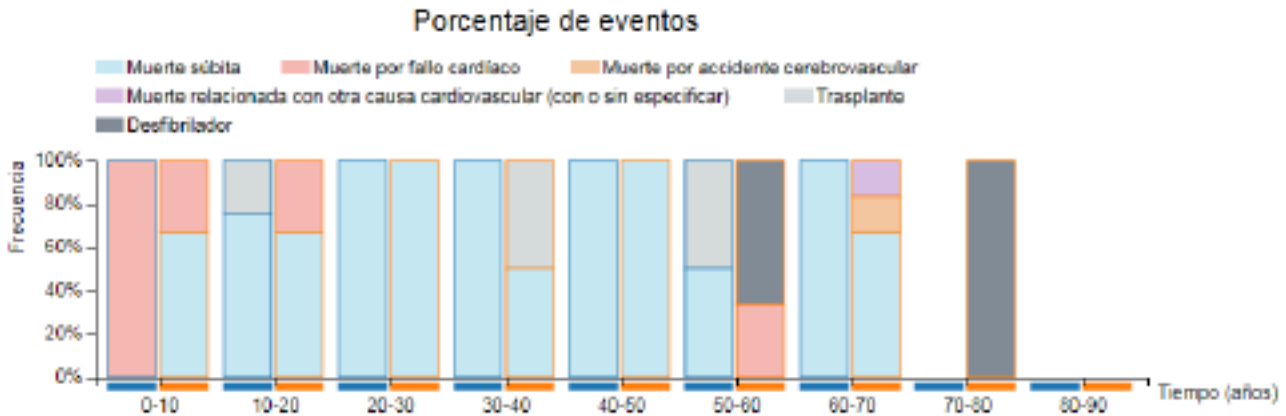
B



LA VARIANTE

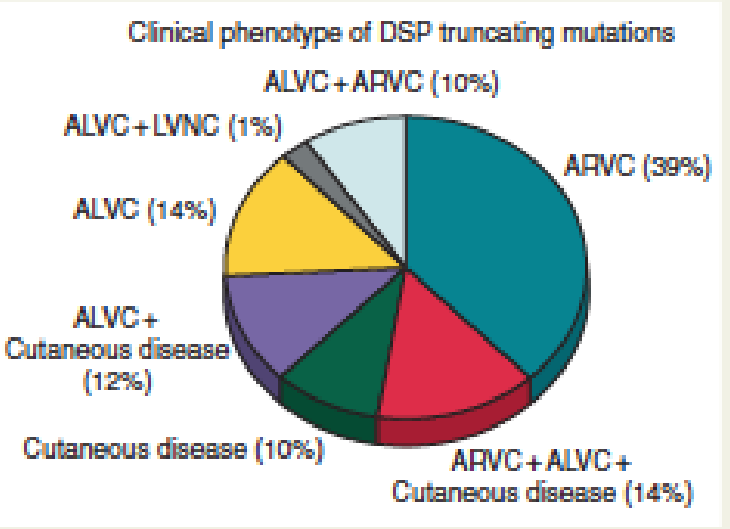
- No descrita en población general
- Truncamiento- Haploinsuficiencia. Proteína 1900 aminoácidos
- Conservación aminoácido- No aplica
- Que sabemos de los truncamientos en DSP?


Variantes de truncamiento en DSP ♂
Variantes de truncamiento en DSP ♀
Probabilidad de supervivencia
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
80
Tiempo (años)
80
72
54
44
32
23
10
6
2
113
106
93
79
62
33
18
5
1


Porcentaje de eventos
Muerte súbita
Muerte por fallo cardíaco
Muerte por accidente cerebrovascular
Muerte relacionada con otra causa cardiovascular (con o sin especificar)
Trasplante
Desfibrilador
Frecuencia
100%
80%
60%
40%
20%
0%
0-10
10-20
20-30
30-40
40-50
50-60
60-70
70-80
80-90
Tiempo (años)

Desmoplakin truncations and arrhythmogenic left ventricular cardiomyopathy: characterizing a phenotype

Jose María López-Ayala[1], Ivan Gómez-Milanés[2], Juan José Sánchez Muñoz[1], Francisco Ruiz-Espejo[2], Martín Ortíz[3], Josefa González-Carrillo[1], David López-Cuenca[1], M. J. Oliva-Sandoval[1], Lorenzo Monserrat[3], Mariano Valdés[1], and Juan R. Gimeno[1]*



Conclusion

We have reported on a novel mutation in desmoplakin (c.1339C>T) associated with a phenotype of ALVC and LVNC. Truncating mutations in desmoplakin seem to consistently cause extensive LV fibrosis with near normal RV performance. Ventricular arrhythmias and SCD occur in the absence of overt LV dysfunction or dilatation, and as a consequence, ICD implantation must be considered promptly. Genetic information seems to be of paramount prognostic value in this setting.

TRUNCAMIENTOS DESMOPLAQUINA

- Displasia de ventrículo izquierdo. Confundida con miocarditis o MCD idiopática
- Truncamientos en DSP altamente penetrantes. >80%
- Alta incidencia de MS. 15% portadores

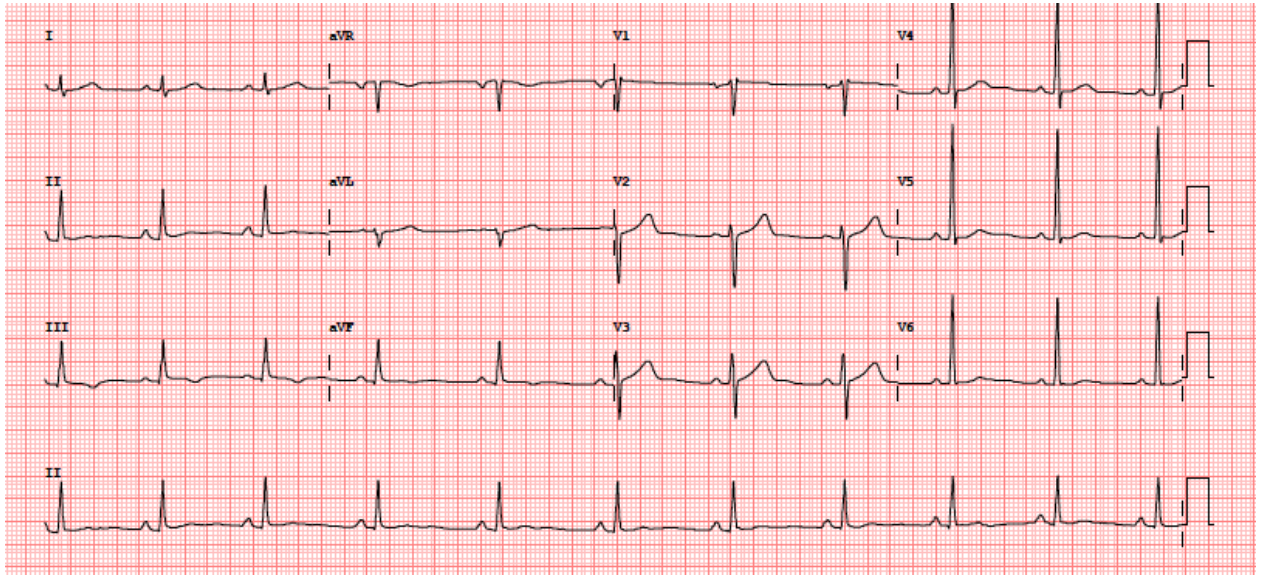
Table I Clinical characterization of DSP c.1339 C>T carriers

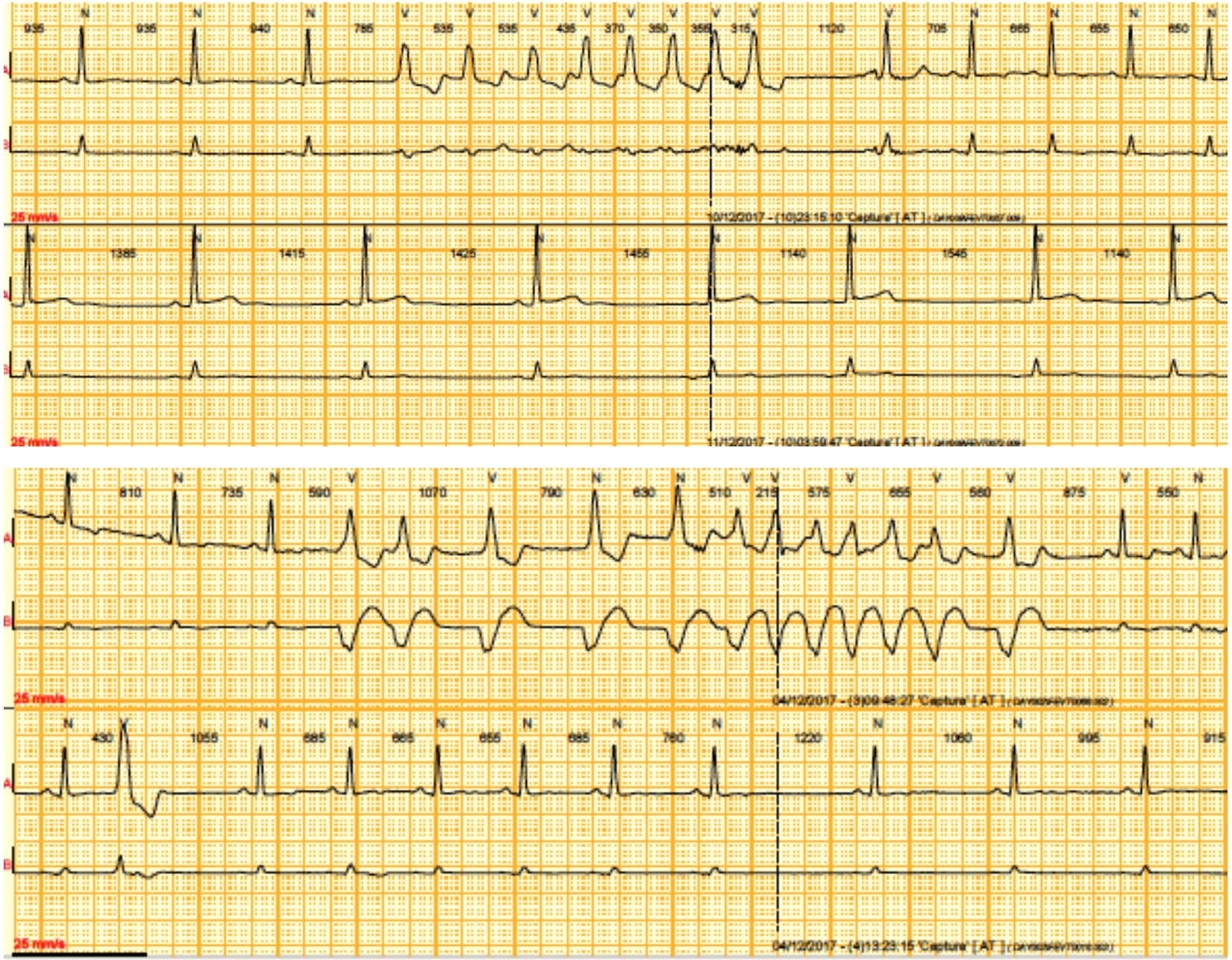
Case	Family	Pedigree	Age/ Sex	Syncope	Sustained VT	Morphology VT	CL (ms)	Non sustained VT	NYHA	ARVC diagnosis	LVEF	LGE distribution	Hypertrabeculation (CMR)
1	A	II.2	59F	Yes	Yes	RBBB	330	Yes	I	Borderline	40	NA	NA
2	A	II.3	65F	No	No	NA	No	No	II	Possible	40	NA	NA
3	A	III.1	55F	No	Yes	NA	NA	No	I	Definitive	64	NA	NA
4	A	III.6	45F	No	No	No	No	No	I	Definitive	40	Inferoposterior and lateral	Yes
5	A	III.4	44F	No	No	NA	NA	Yes	I	Borderline	50	Global	Yes
6	**A**	**III.5**	**36M**	**No**	**Yes**	**NA**	**NA**	**Yes**	**I**	**Definitive**	**30**	**NA**	**NA**
7	A	IV.4	38F	No	No	No	No	No	I	Possible	60	No	NA
8	A	IV.6	14M	No	No	No	No	No	I	Possible	45	Lateral	No
9	A	IV.7	19M	No	No	No	No	No	I	Possible	55	Lateral	No
10	B	I.1	72F	No	Yes	LBBB. Axis −30°	320	Yes	II	Definitive	30	NA	NA
11	B	II.2	49F	No	No	No	No	No	I	Possible	58	NA	NA
12	**B**	**II.1**	**42F**	**No**	**Yes**	**NA**	**NA**	**No**	**I**	**Definitive**	**40**	**NA**	**NA**
13	**C**	**II.1**	**62F**	**No**	**Yes**	**NA**	**NA**	**Yes**	**II**	**Definitive**	**43**	**Inferoposterior and lateral**	**No**
14	C	III.5	45M	No	Yes	NA	220	No	I	Definitive	42	Global	Yes
15	C	II.3	73M	No	No	No	No	No	I	Borderline	60	No	No
16	C	III.1	38F	No	No	No	No	No	I	Borderline	60	No	No
17	C	IV.1	13M	No	No	No	No	No	I	Borderline	66	No	Yes
18	C	IV.2	17F	No	No	No	No	No	I	Borderline	60	No	Yes

F, female; M, male; CL, cycle length; NA, not available. Probands are in bold.

CIERRE DEL CASO

- Asintomático
- Se ha prohibido deporte extenuante o competitivo
- Seguir estrechamente
- Holter de larga duración




25 mm/s
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11/12/2017 - (10)03:59:47 'Capture' [AT]
25 mm/s
04/12/2017 - (3)09:48:27 'Capture' [AT]
04/12/2017 - (4)13:23:15 'Capture' [AT]
25 mm/s

CUAL ES EL FUTURO?

- Colaboración académica. Principios de normalidad. Bases de datos
- Genotipado a gran escala. Captura heredabilidad. Nuevos genes
- Regiones más allá de los exones
- Interpretación de patogenicidad. Correlaciones solidas genotipo fenotipo- incluyendo pronostico
- Masificación de datos genómicos- Pen drive
- Aplicación de datos genómicos de forma consistente a enfermedades complejas o farmacogenomica
- Paso transcriptomica proteomica
- Aplicación terapéutica
- Clínicos deben aprender un mínimo de elementos

CONCLUSIONES

- No es una frontera ni el futuro. Es el presente
- Casi todos los rasgos son en algún grado heredables
- Enfermedad monogenicas o mendelianas son en conjunto comunes
- Exposición creciente a datos genéticos
- Genética hace parte actualmente de algoritmos diagnósticos y de la práctica clínica diaria
- Genética utilidad en múltiples dimensiones. Diagnostico, pronóstico, consejería, screening familiar
- La realidad apunta a que la genética va a estar presente en toda la práctica clínica
- Convencidos?