Cardiomyopathy Clinical Case

Παρχαρίδου Δέσποινα

Επιμελήτρια Β

Α Καρδιολογική κλινική, ΠΓΝΘ ΑΧΕΠΑ

Presentation

- Woman 59 yo
- Presented at emergency department
- Dyspnea – orthopnea (a week ago). Epigastric discomfort
- Under antibiotics for respiratory tract infection (3 days ago - dyspnea considered to be bronchitis)
- Not under HF treatment
- Troponinemia (private lab blood test) 121 pg/ml

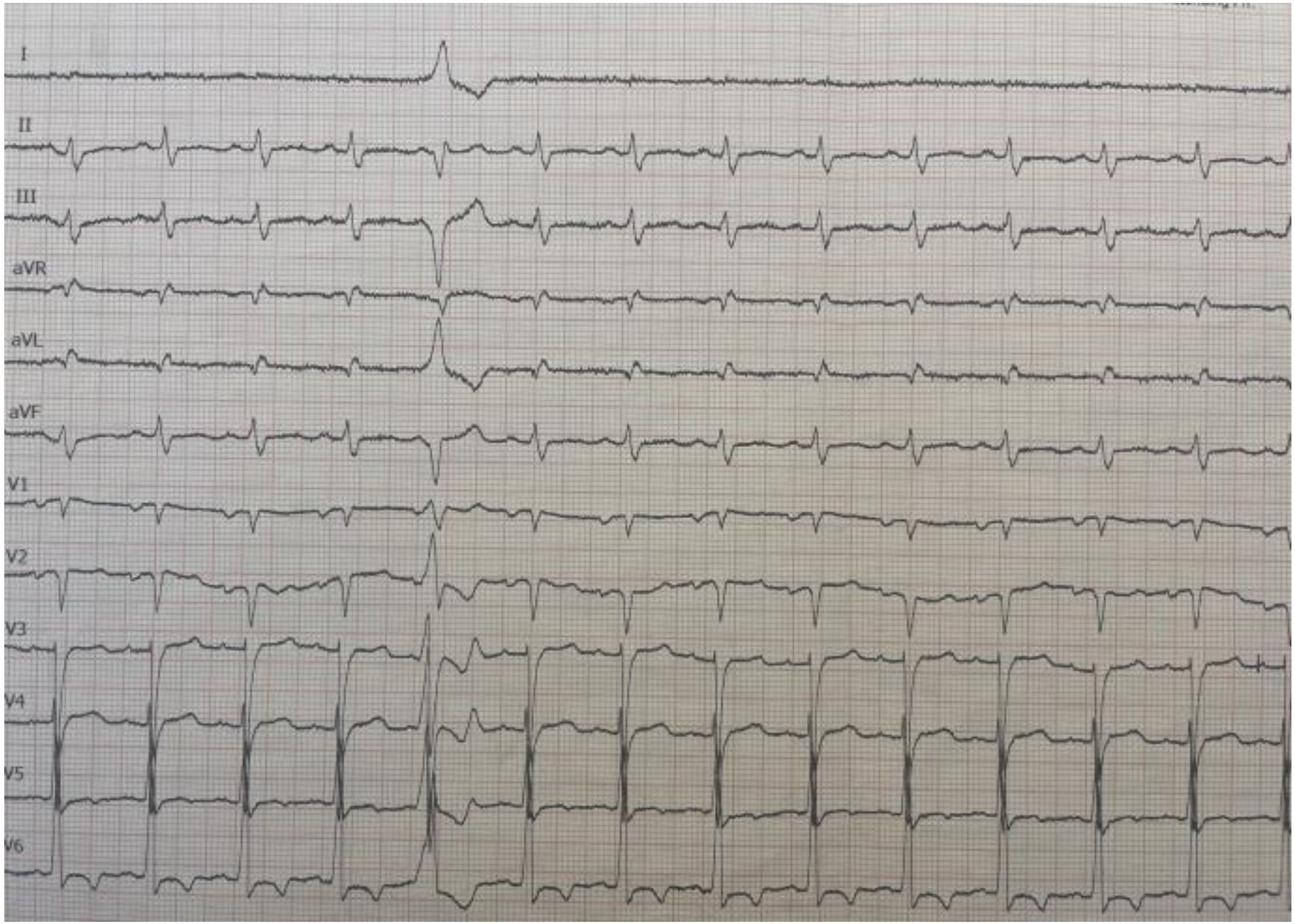
- **Claims she was asymptomatic before (working daily)**

Emergency Room department

- Pulmonary edema (lung crackles)
- SAT 90%
- 98 bpm
- BP 90 -70 mmHg

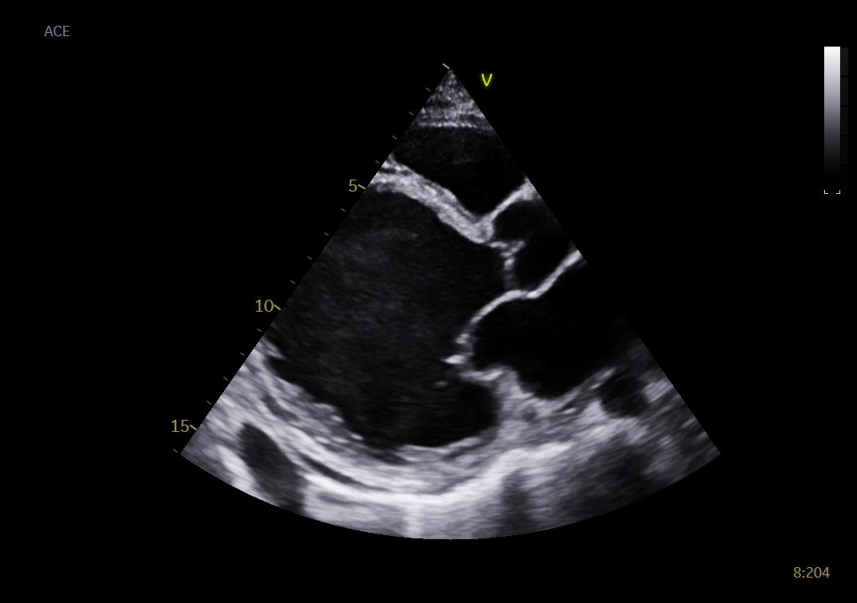
Troponin 98 pg/ml
NT-pro BNP 16.817 pg/ml
Normal renal and liver function

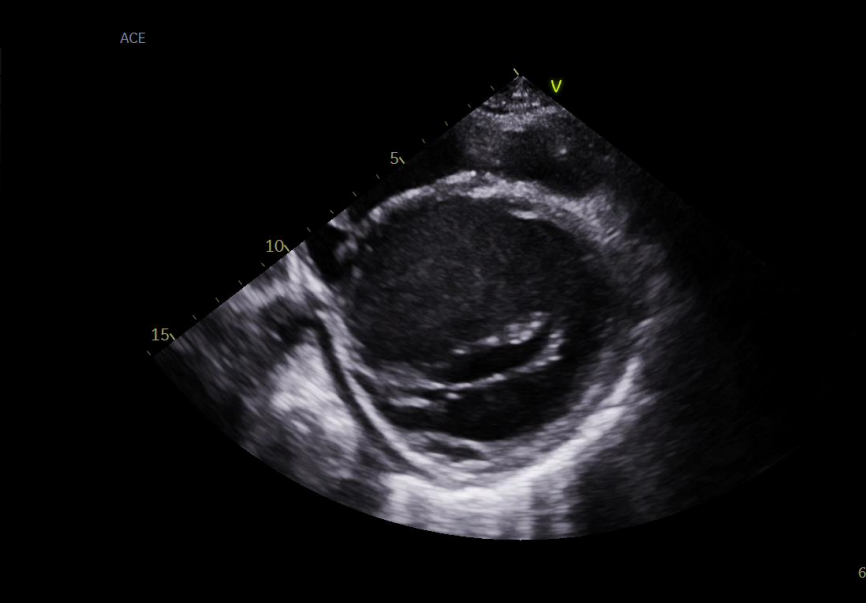
- Cardiology Intensive Care Unit admission (dobutamine, noradrenaline, diuretics IV)

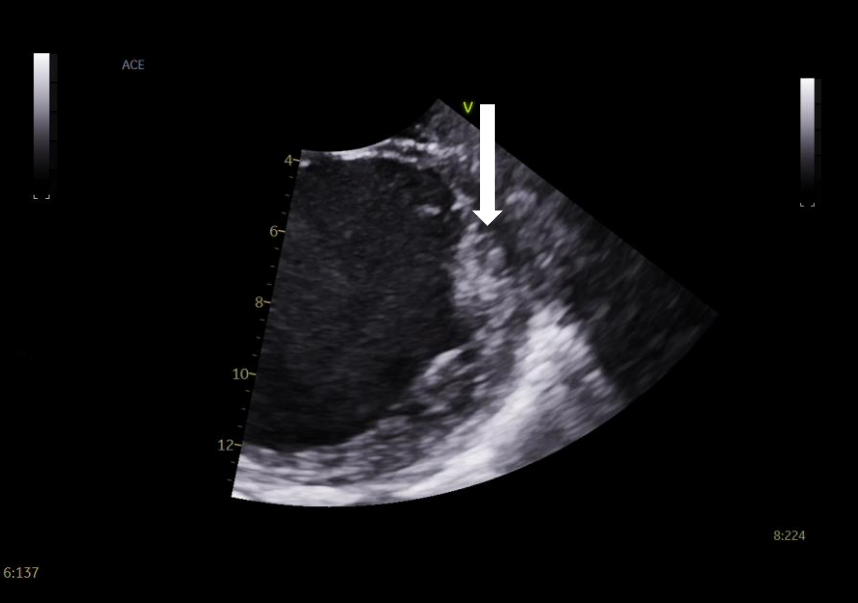


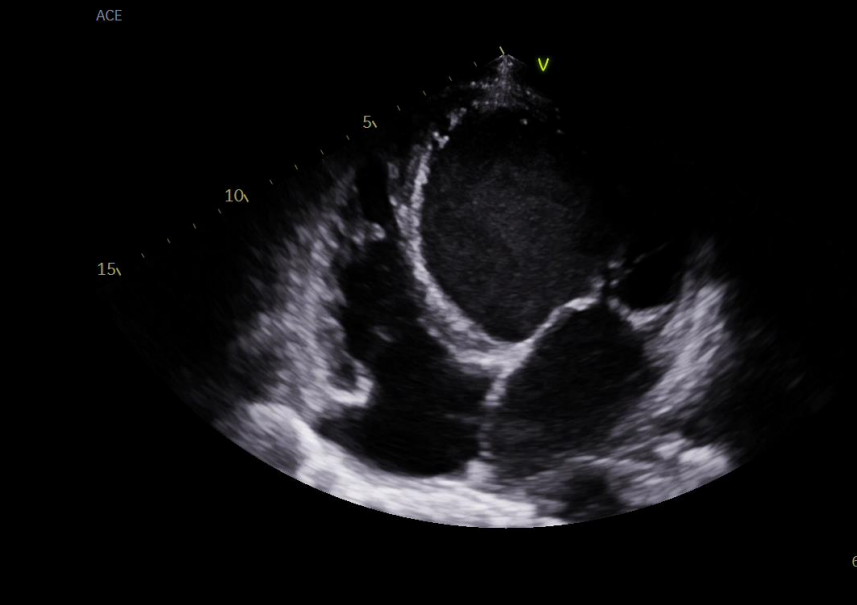
Holter monitoring/24h

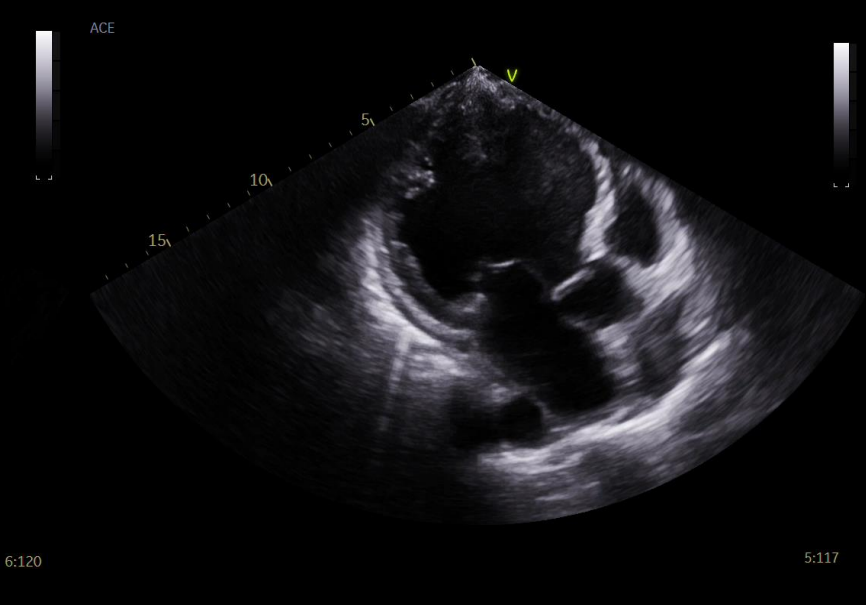
- PVCs multifocal (9.400/24h)
- NSVT (1 episode- 4 beats)

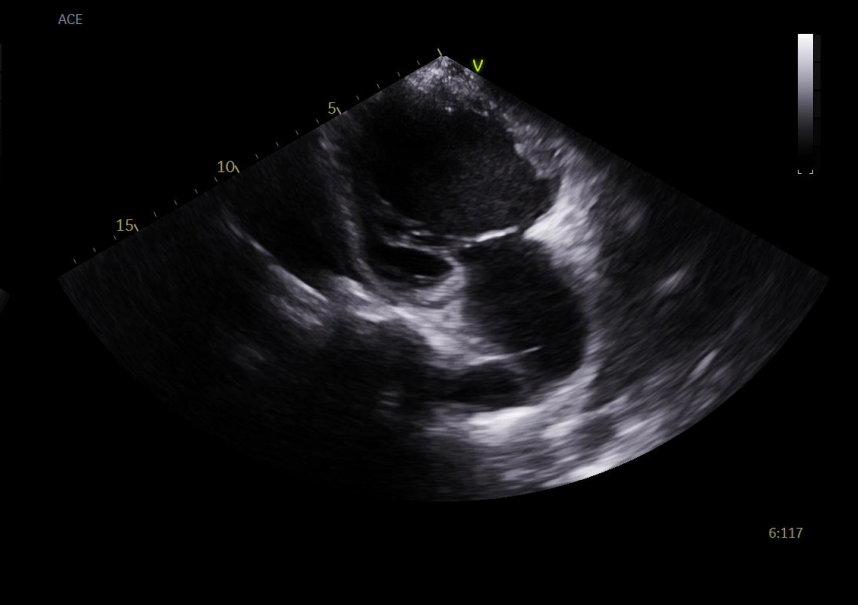

ACE
5
10
15
8:204

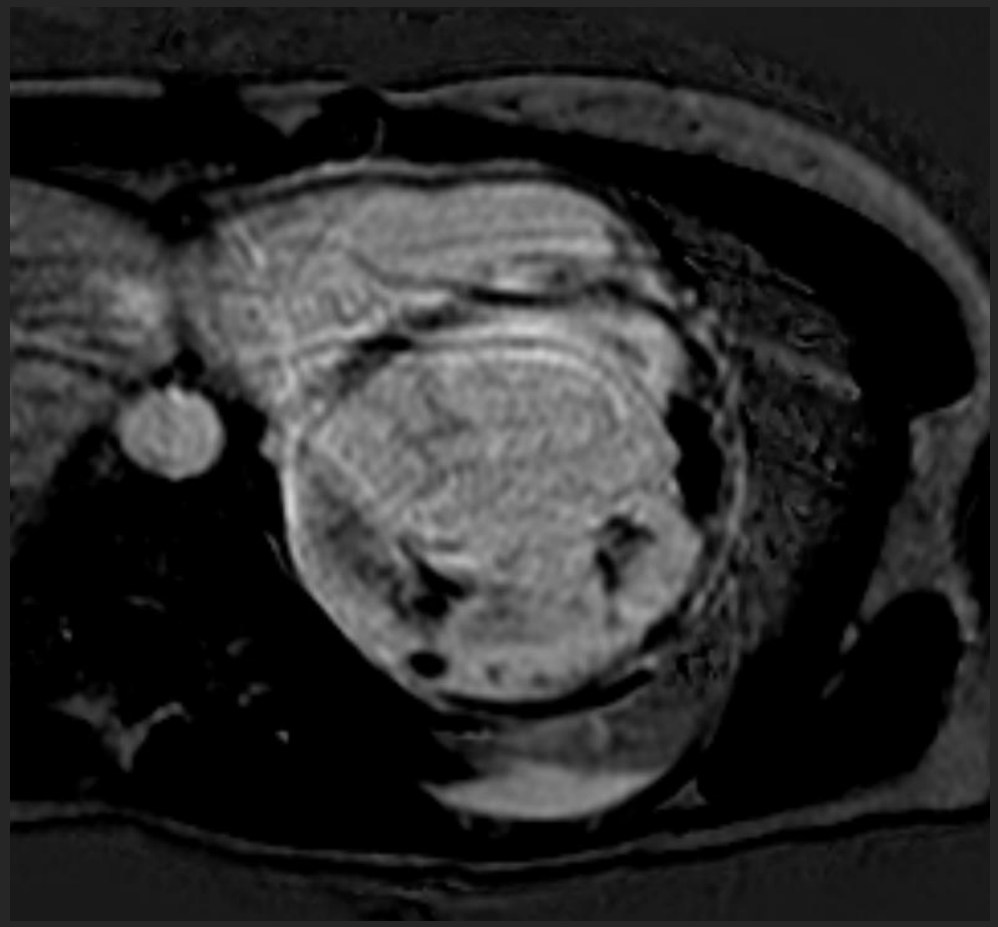

ACE
5
10
15
6:137


ACE
4
6
8
10
12
8:224


ACE
5
10
15
6:120


ACE
5
10
15
5:117


ACE
5
10
15
6:117



Discharge

- NYHA II
- HF medication
- ICD recommendation
- Referral to Onassis transplant center outpatient clinic→ proceed with ICD implantation
  plan for pre-transplant work up

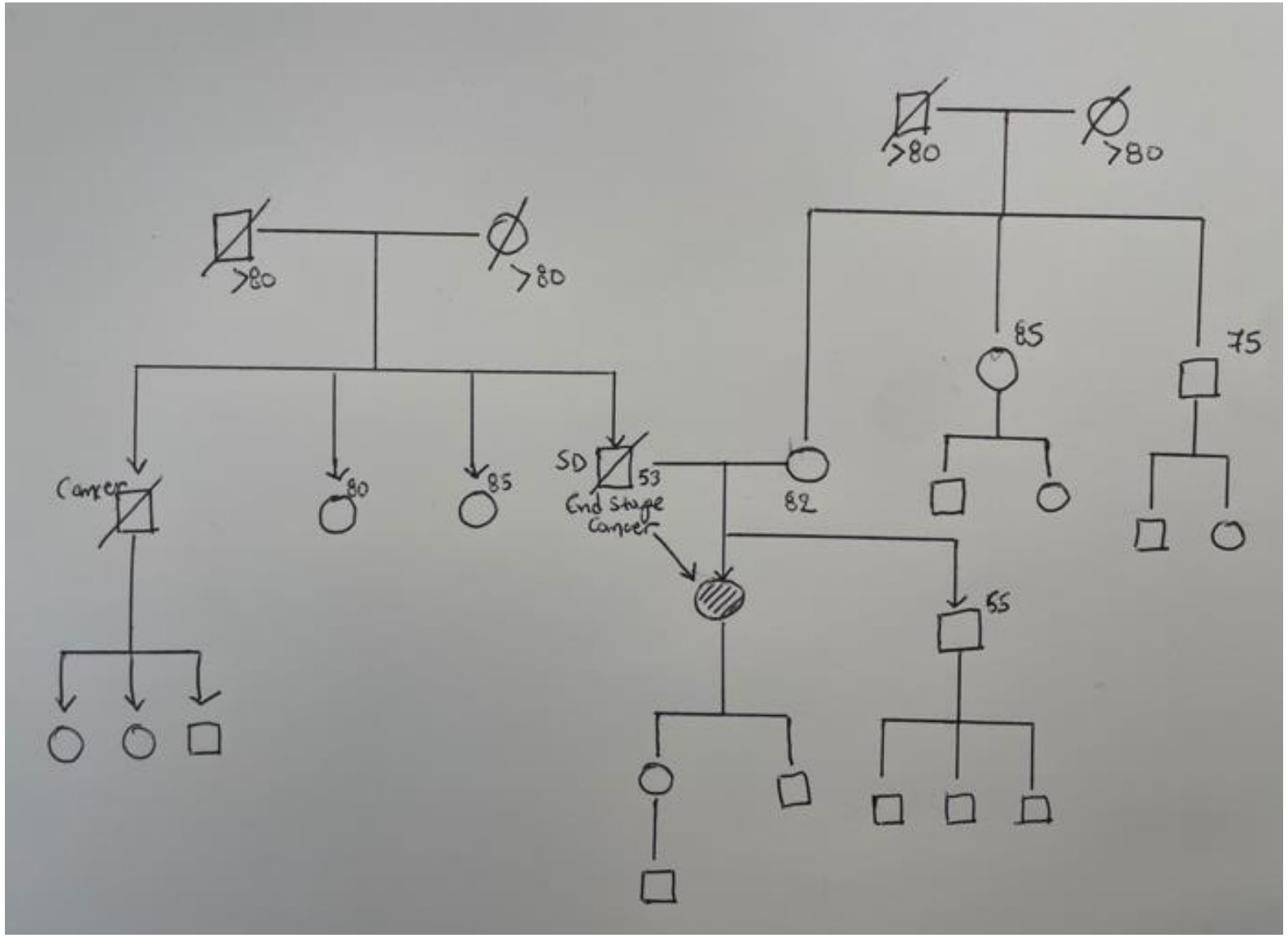
Patient claims she feels well

She doesn’t accept the severity of her condition

- ICD implantation after one month (NYHA II)

- 2nd hospitalization (15 days after ICD implantantion) due to low cardiac output and lower respiratory tract infection, unstable under dobutamine and noradrenaline

  Intraortic balloon pump (IABP) → Death (after 1 week)

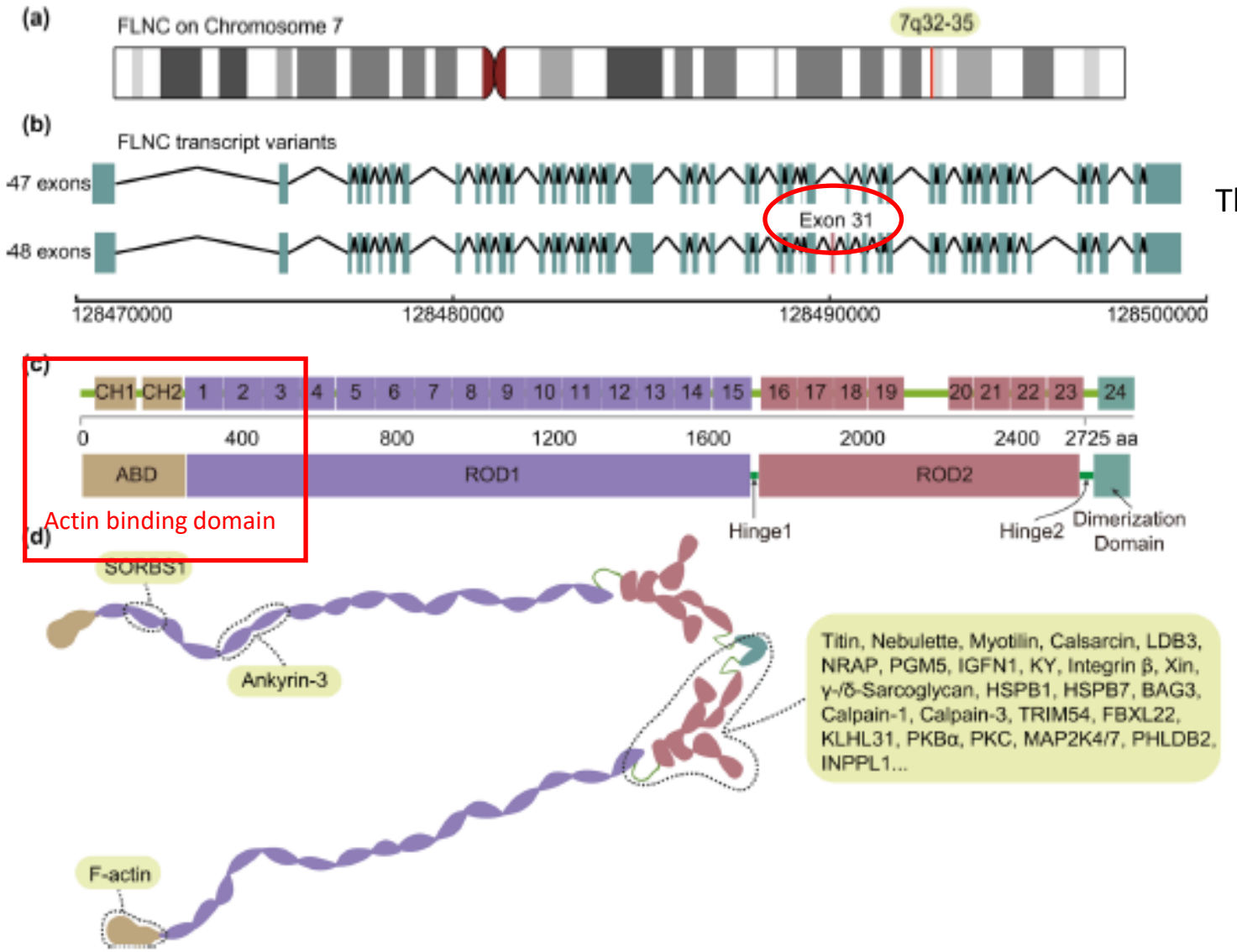


According to the patient history nobody in the family has cardiac problems

Genetic test

Γονίδιο	Μετάλλαξη	Ζυγωτία	Τρόπος κληρονόμησης	Κατάταξη*
FLNC (Exon 25)	*NC_000007.13: g.128487820TGGGGG>TGGGG NM_001458:c.4363del p.(Ala1455Leufs*61)*	*Ετεροζυγωτία*	*Αυτοσωμικός επικρατής*	*Πιθανώς παθογόνος*

Structure of the FLNC gene and filamin C protein



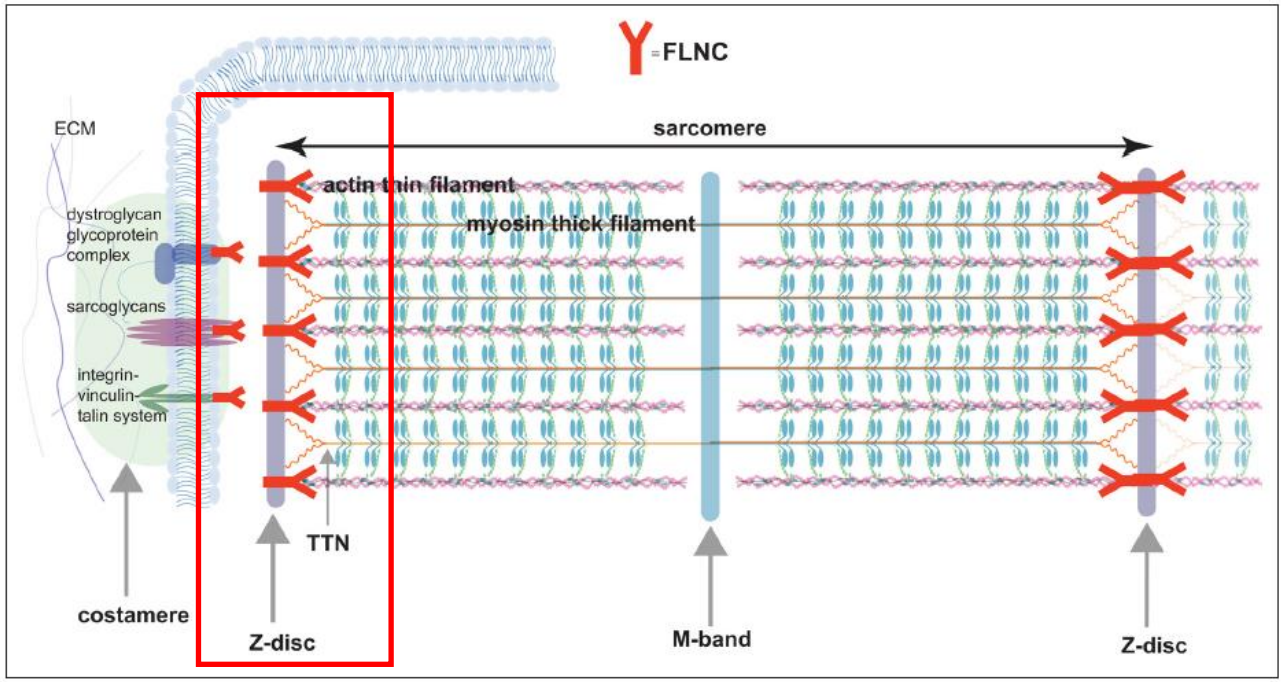
FLNC is located on chromosome 7q32-35

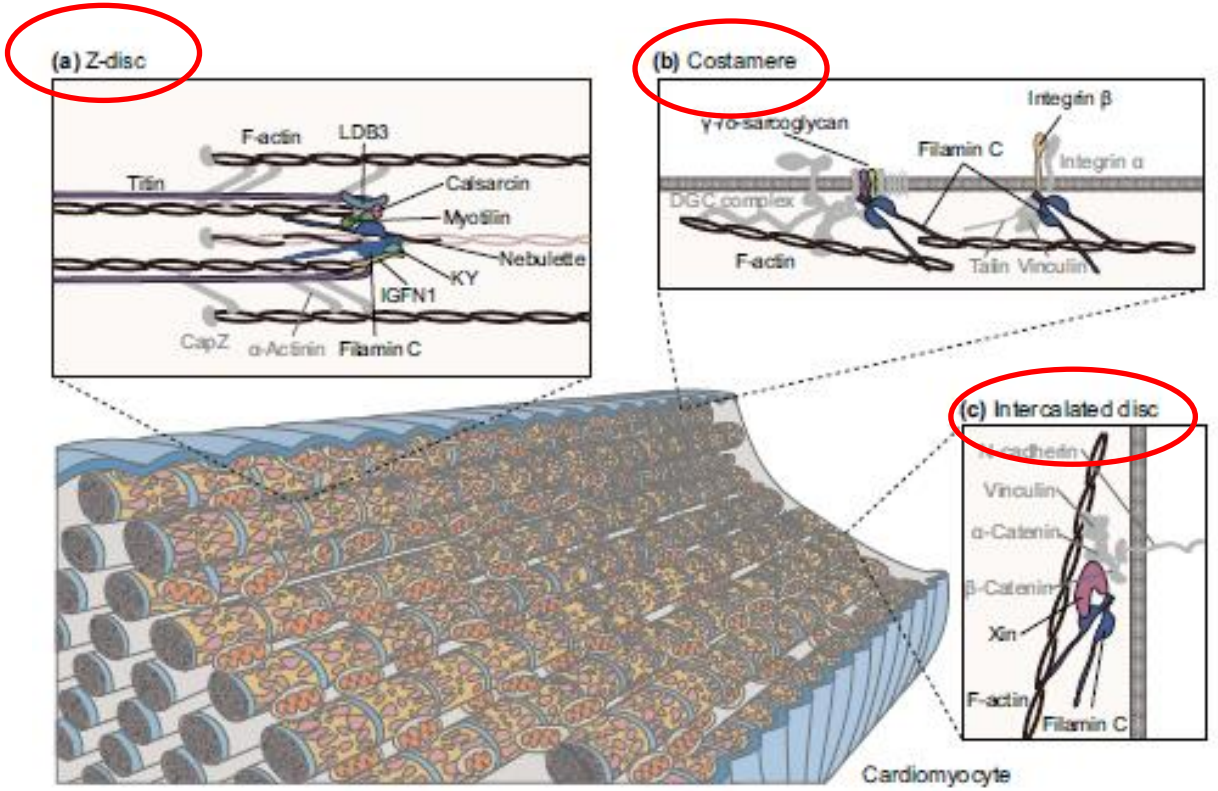
The FLNC gene has two known full-length mRNA isoforms

The hinge domains allow the protein to bend, so that when it dimerizes, the structure is similar to a “V.”

Song S, Heart Failure Reviews (2022)

FLNC has vital role in bridging the cytoskeleton and extracellular matrix in cardiomyocytes





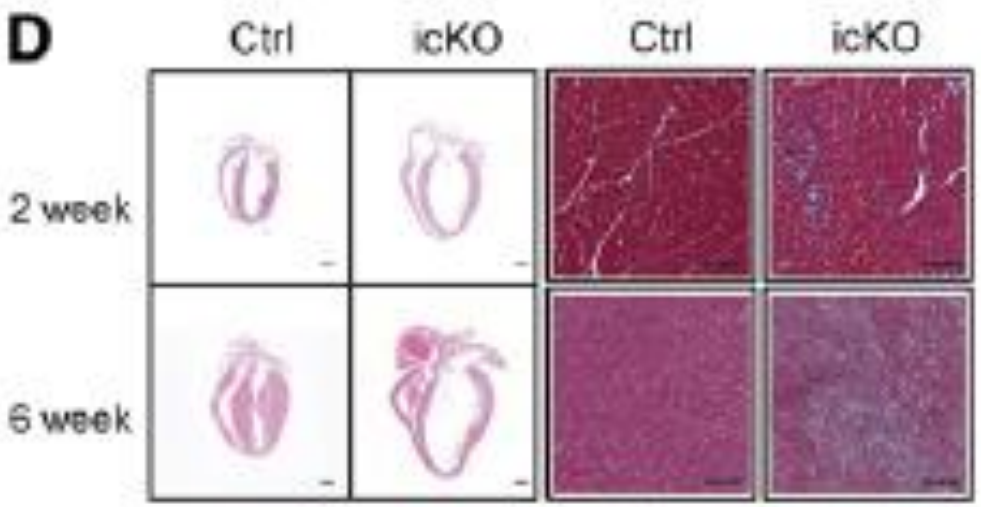
FLNC (red) localizes primarily to Z-discs, where it crosslinks actin

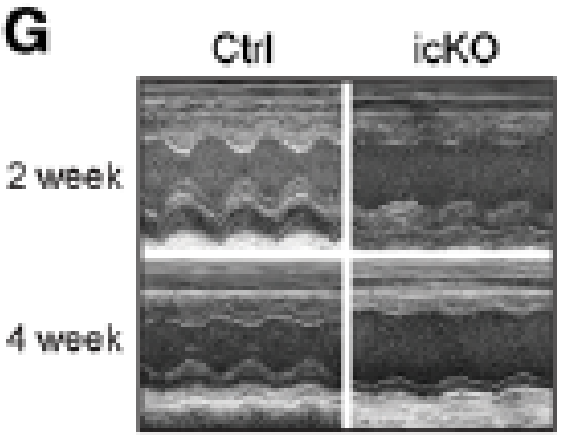
Smaller amounts of FLNC also localize to costameres (light green oval), and intercalated discs

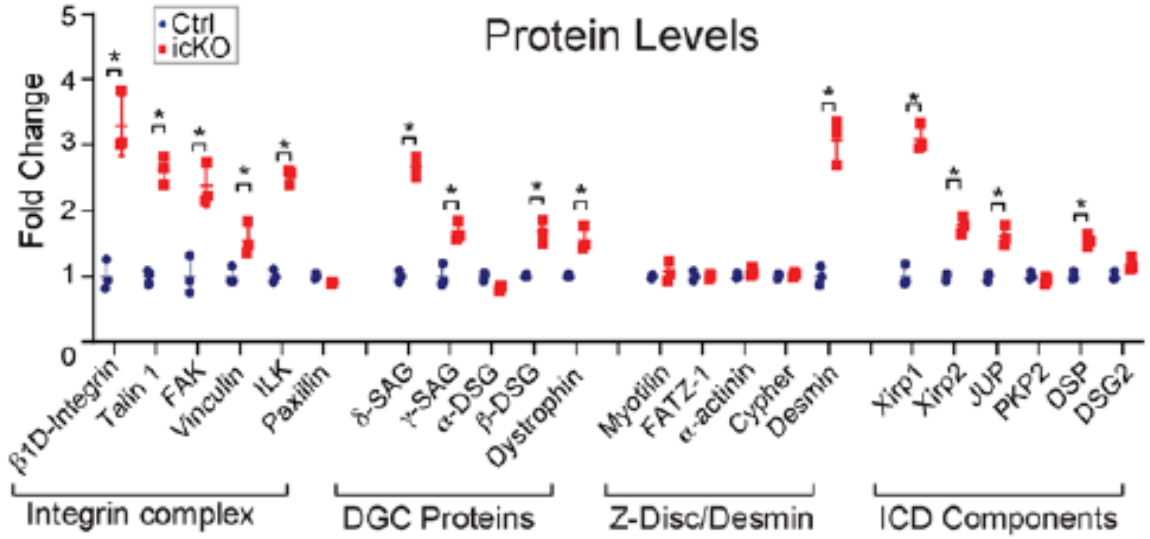
Song S, Heart Failure Reviews (2022)
Agarwal R, Circulation Research. 2021

Loss of Filamin C Is Catastrophic for Heart Function

icKO mice (inducible cardio myocyte- specific knockout)



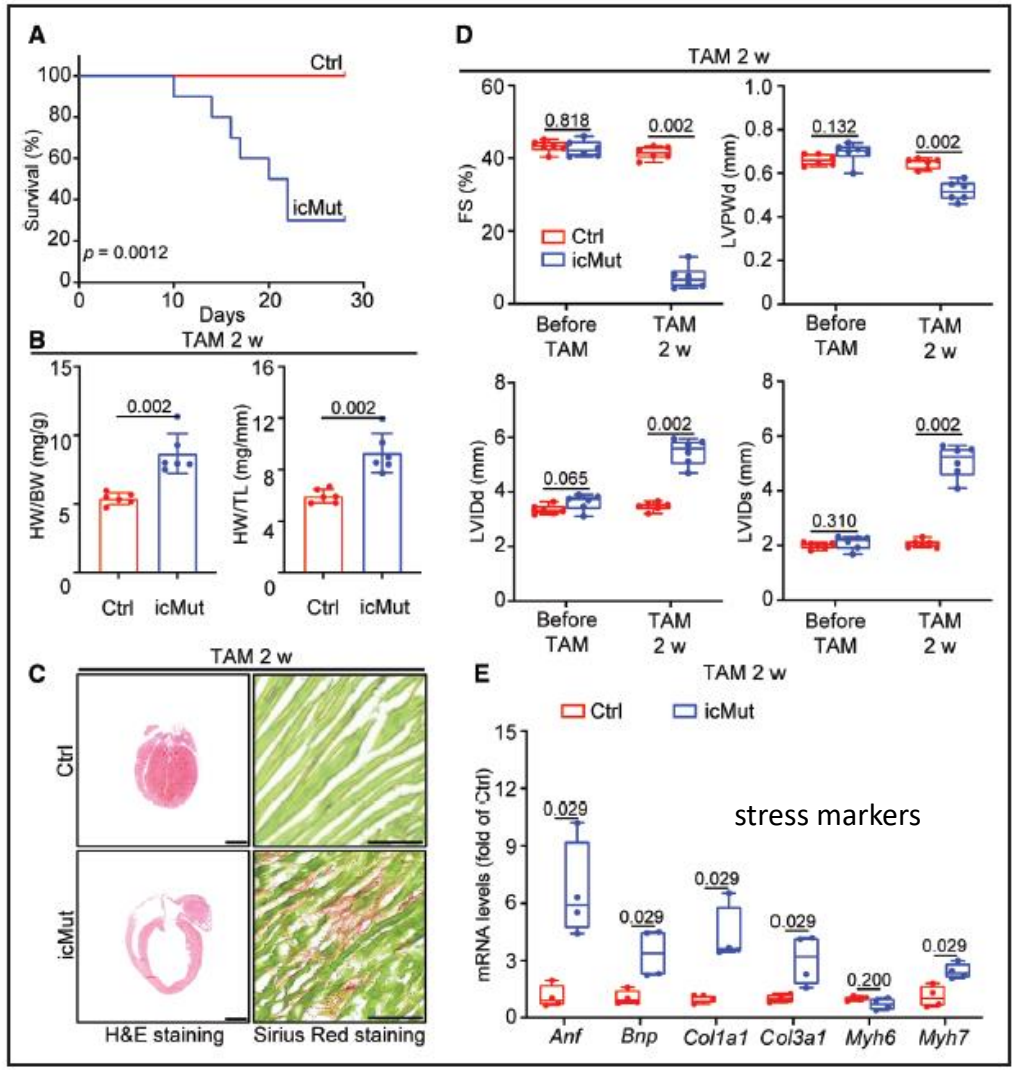




Loss of FLNC was accompanied by upregulation of multiple proteins, including those that directly interact with FLNC, representing components of the costamere and ICD, and the intermediate filament protein desmin

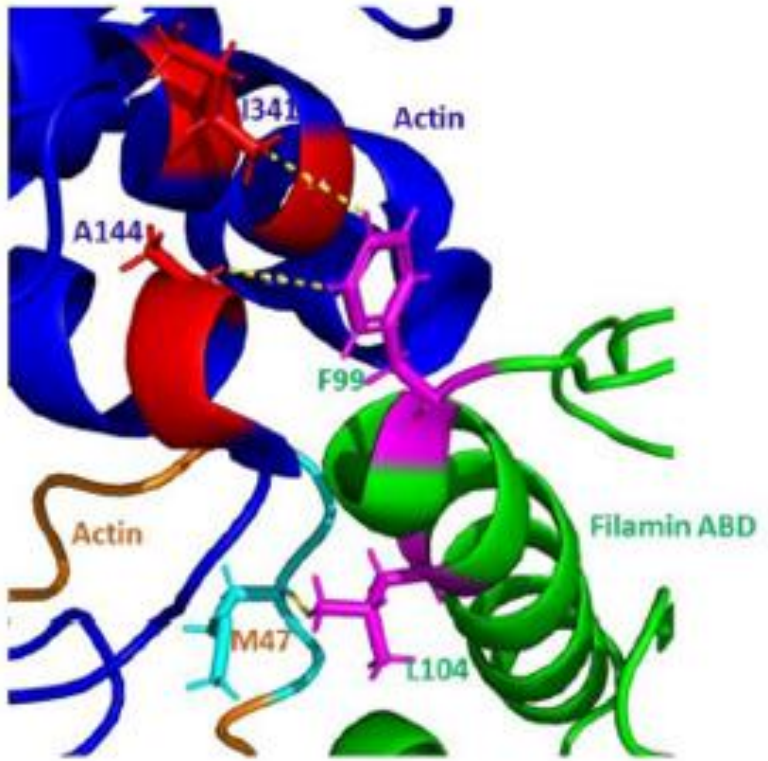
Zhou Y, Circulation 2020

Impairment of FLNC (filamin C)-actin interaction in adult (mutant mice) cardiomyocytes leads to DCM



Upregulation of cardiac stress markers indicating an ongoing pathological remodeling in icMut hearts

FLNC F93A/L98E mutations completely disrupted the inter action between FLNC and actin

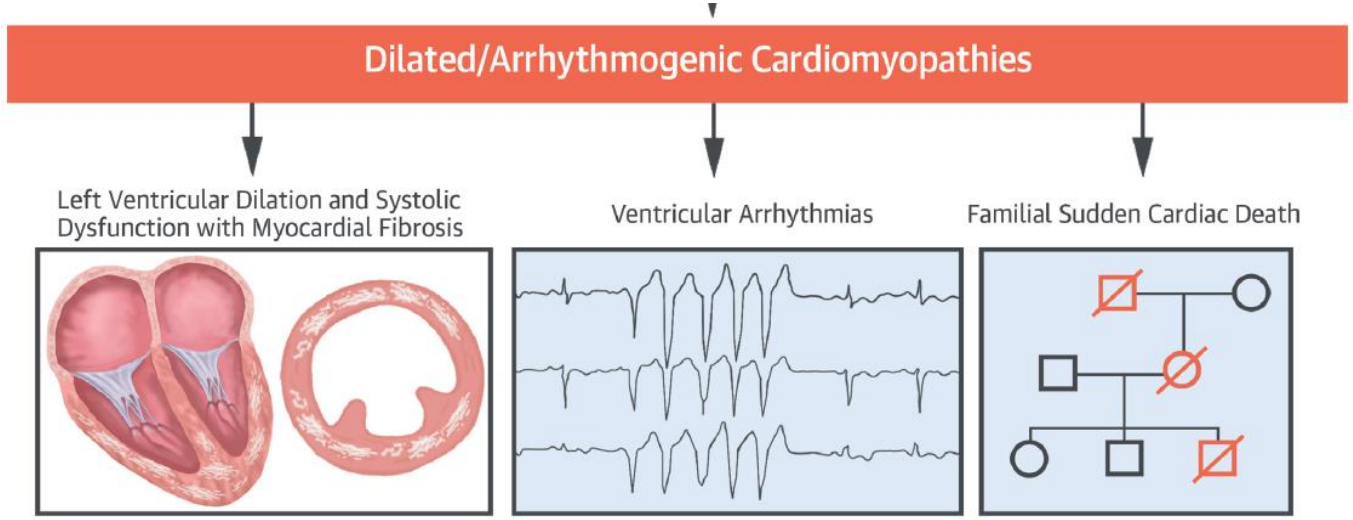


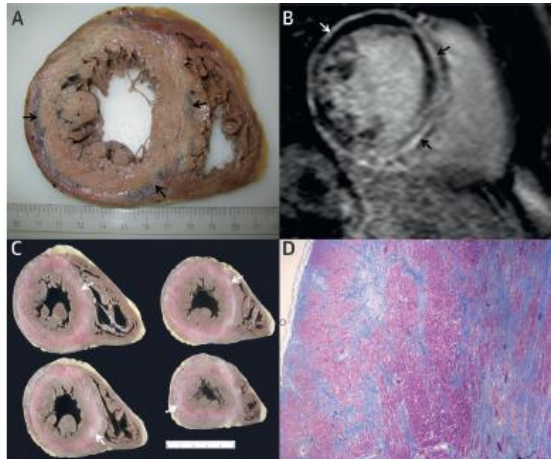
Zhou X, Circulation Research 2023

Filamin C Truncation Mutations Are Associated With Arrhythmogenic Dilated Cardiomyopathy and Changes in the Cell–Cell Adhesion Structures

Rene L. Begay, MS,[a] Sharon L. Graw, PhD,[a] Gianfranco Sinagra, MD,[b] Angeliki Asimaki, PhD,[c]

28 unrelated probands with truncating mutations in FLNC

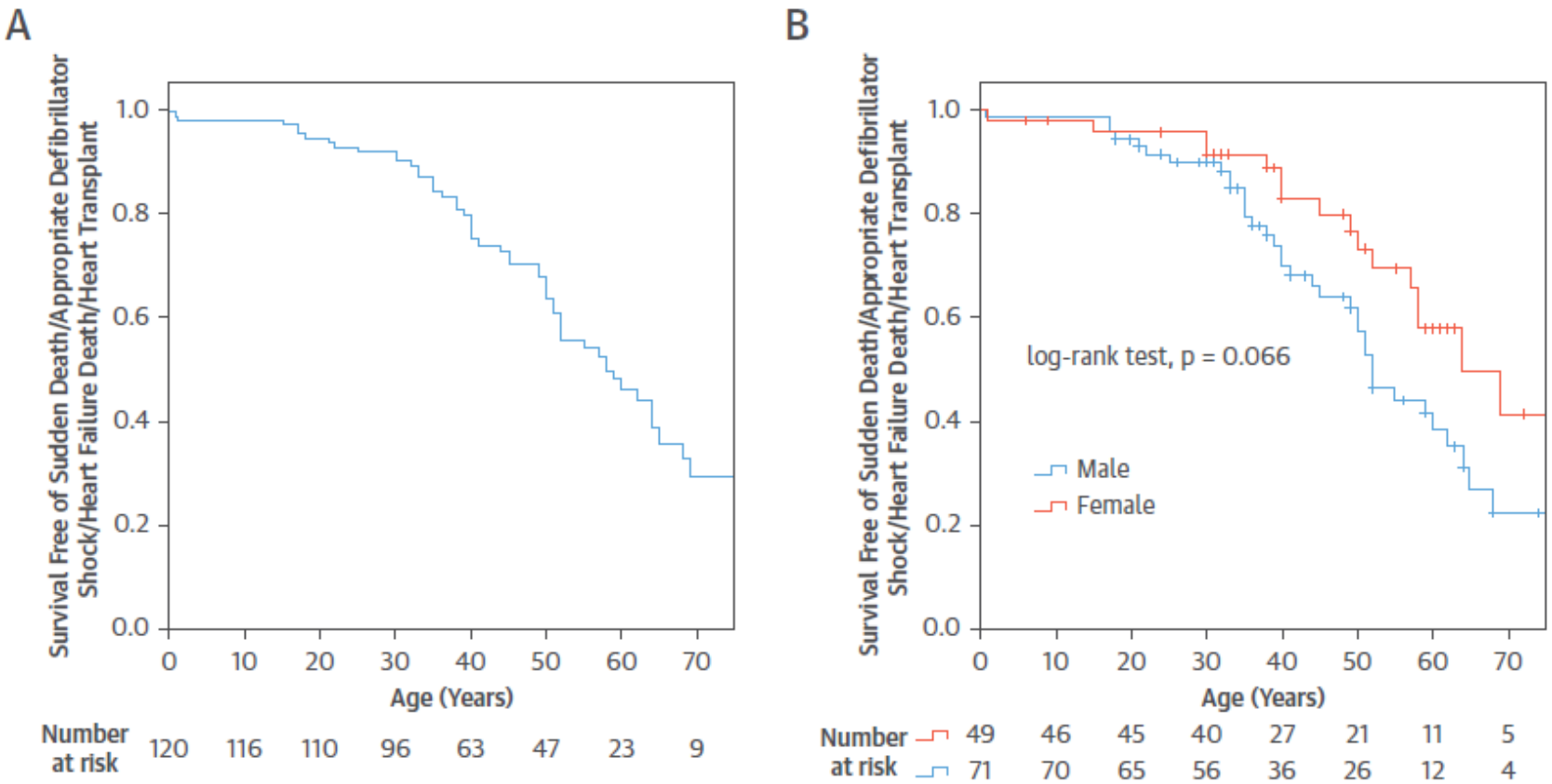




	Probands (n = 28; 17 Male)		
	Evaluated	Positive Finding	%
ECG			
Sinus rhythm	27	22	81
Atrial fibrillation	27	4	15
Pacemaker (atrial)	27	1	4
Cardiac conduction defects*	27	8	30
Low voltages	25	9	36
Negative T-wave all locations	21	13	62
Left precordial negative T-wave	21	6	29
Right precordial negative T-wave	21	0	0
Left + right precordial negative T-wave	21	0	0
Inferior negative T-wave	21	2	10
Inferior + left precordial negative T-wave	21	4	19
Cardiac structural affection			
LV dilation	27	19	70
EF <55%	27	26	96
MLVWT ≥12 mm	27	5	19
MLVWT ≥15 mm	27	0	0
LV hypertrabeculation	27	2	7
RV dilation/akinesia/dyskinesia/systolic dysfunction	28	10	36
Myocardium fibrosis	20	15	75
LV fibrosis	19	14	74
RV fibrosis	20	1	5

J Am Coll Cardiol 2016

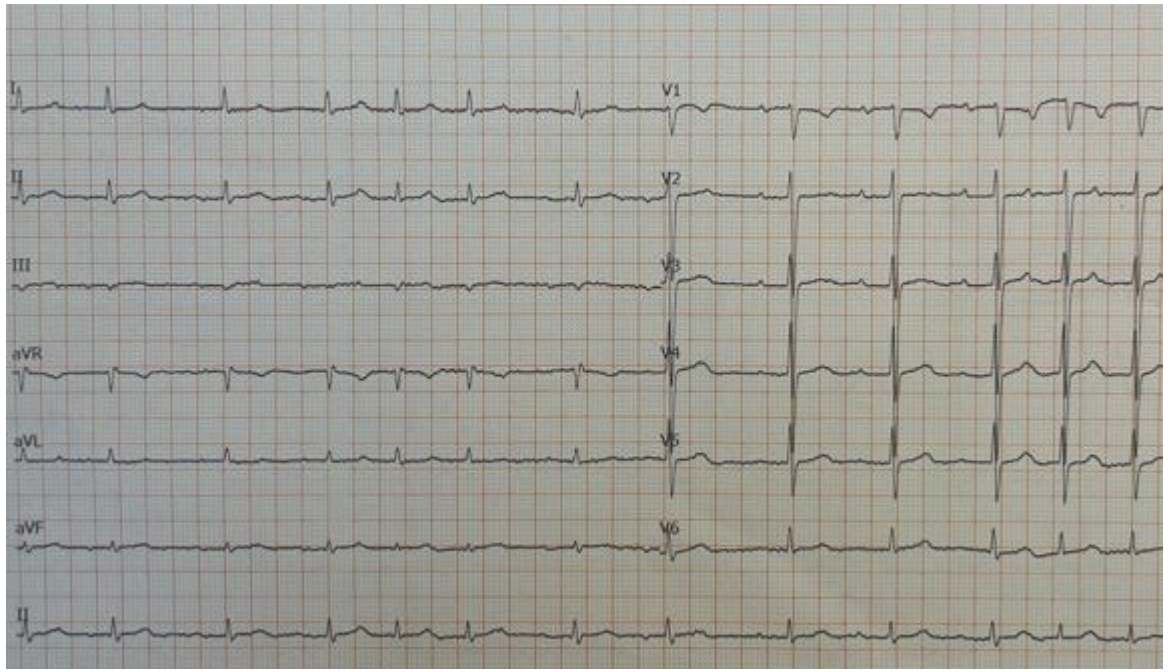
Truncating *FLNC* Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies

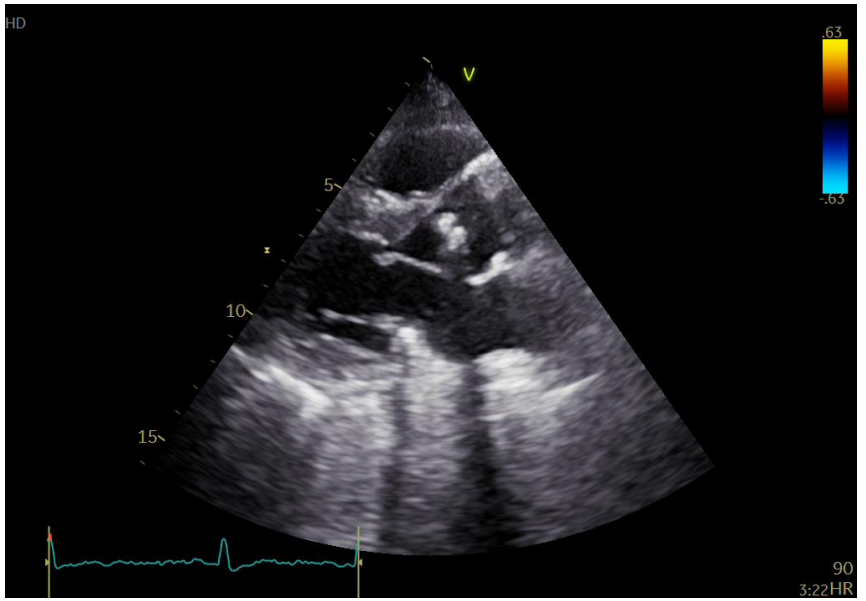


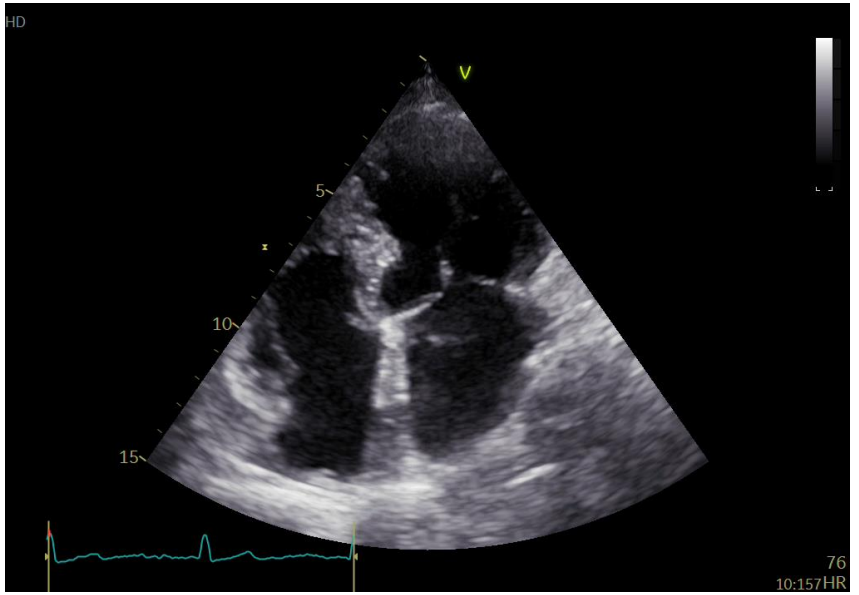
Free from major Cardiovascular Events

J Am Coll Cardiol 2016

Mother, 81 yo





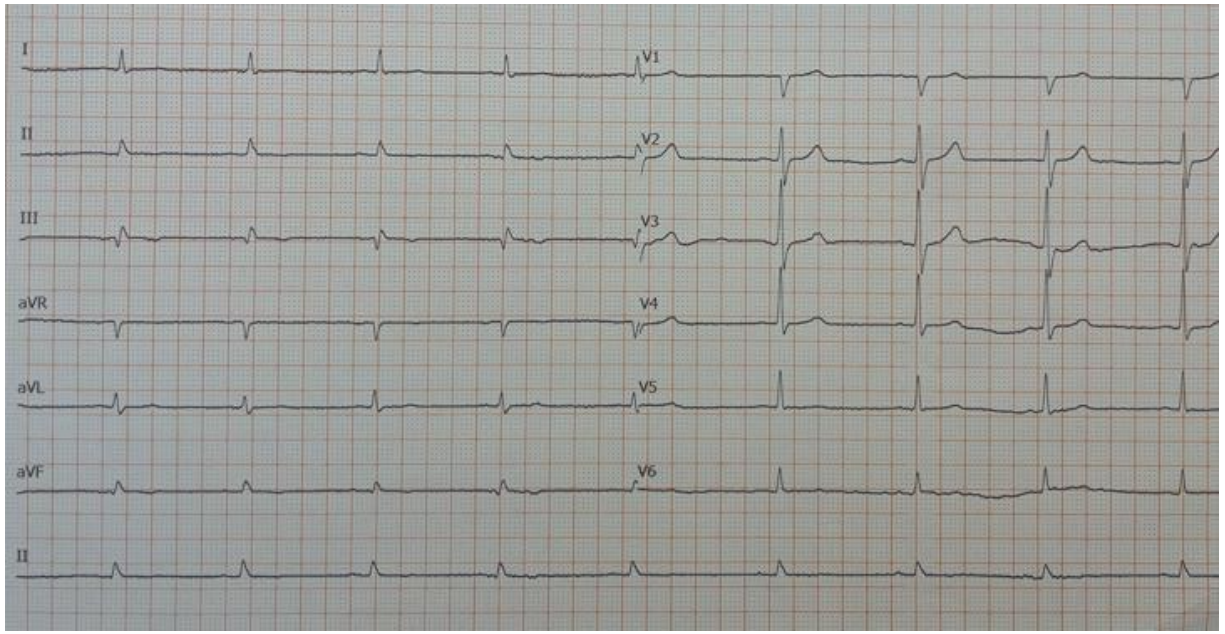


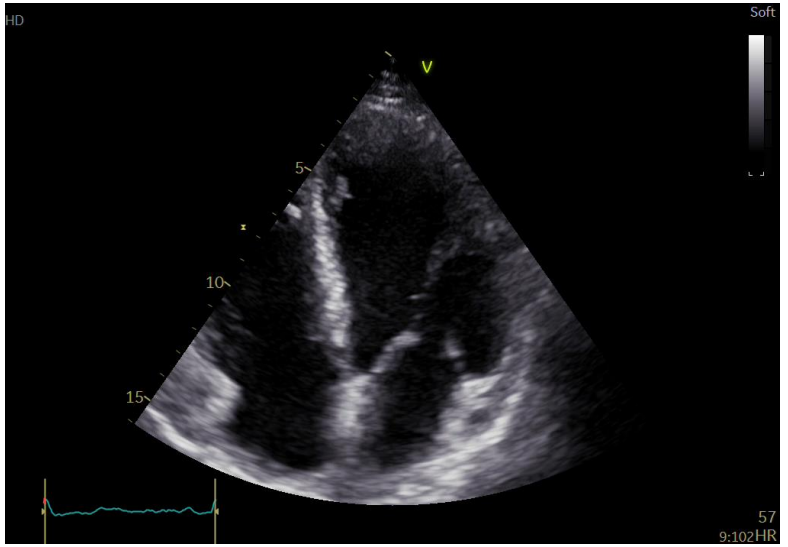
Syncope (-)
Palpitations (-)
NYHA II
Angina (-)

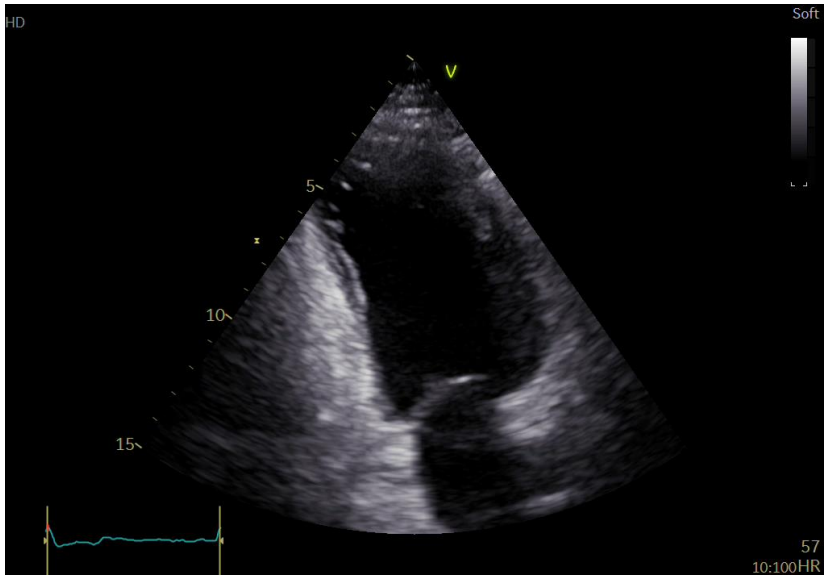
Genetic test pending

She is grieving the death of her daughter and is not willing to continue with running tests

Brother, 55 yo



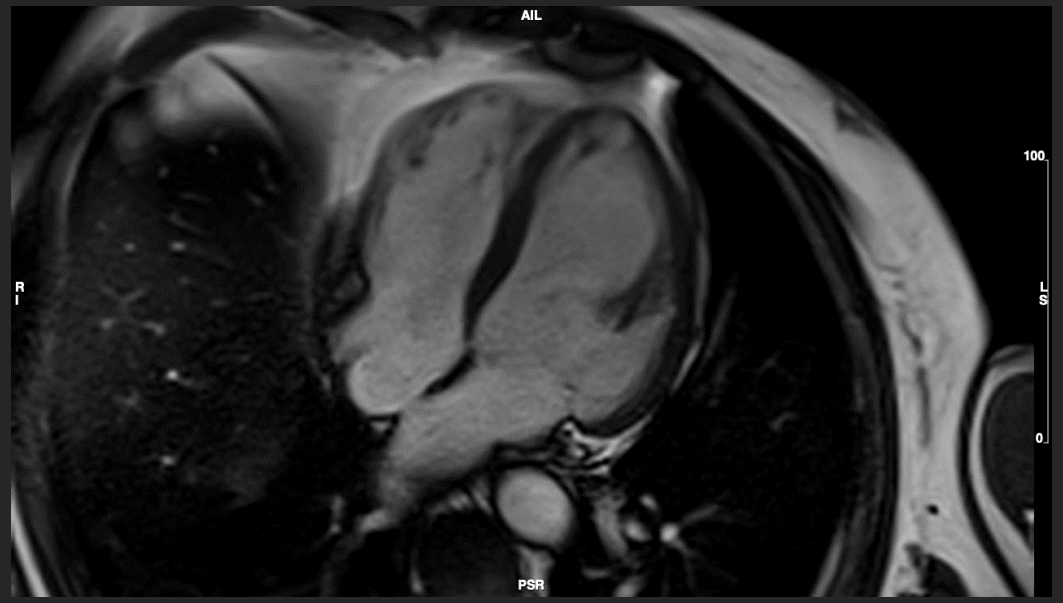


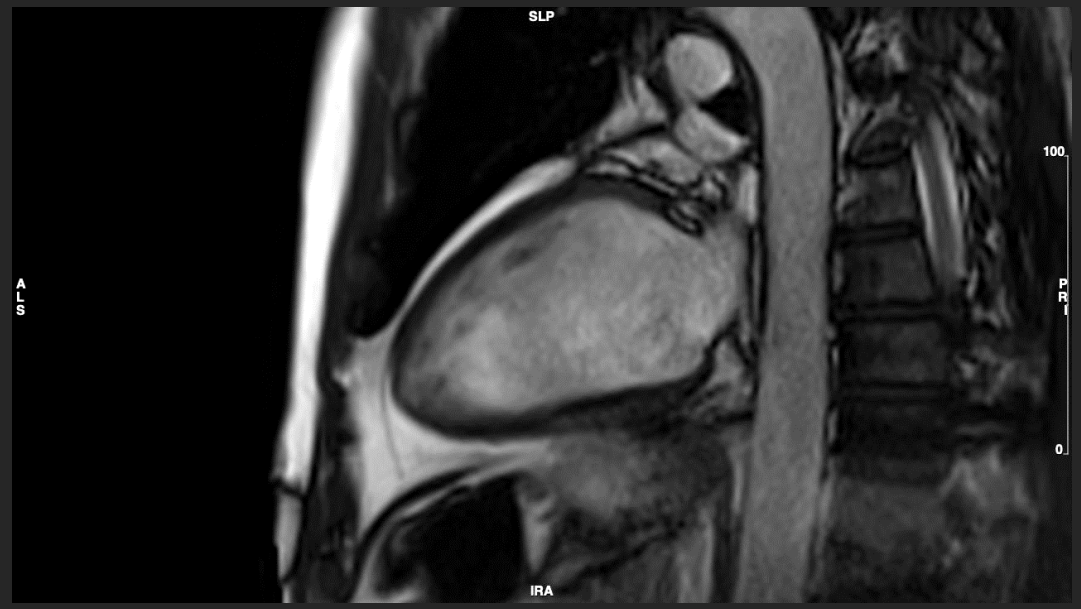


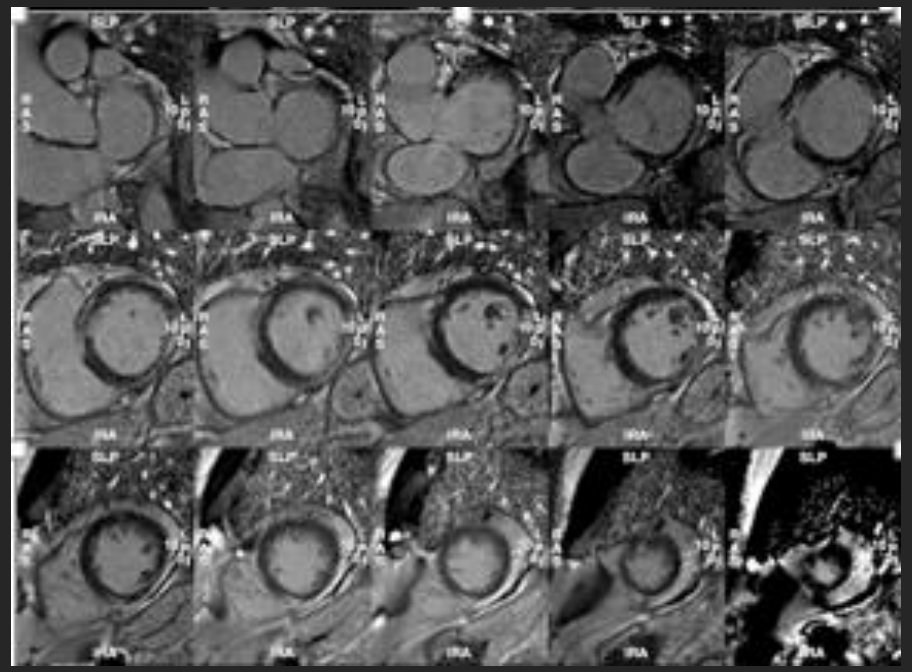
Syncope (-)
Palpitations (+)
NYHA I
Angina (-)

Holter 5846 PCVs
Due to PVCs his cardiologist recommedend CA (normal)

Genetic test pending







Imaging provided by Th Karamitsos

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Genetic test is pending
What about ICD?
Should we wait for the genetic result?

Risk stratification and primary prevention of SCD		
ICD implantation should be considered in patients with DCM/HNDCM, symptomatic heart failure (NYHA class II–III), and LVEF ≤35% after ≥3 months of OMT.[357,359,635,650]	IIa	A
ICD implantation should be considered in DCM/HNDCM patients with a pathogenic mutation in *LMNA* gene, if the estimated 5-year risk of life-threatening VA is ≥10%[c] *and* in the presence of NSVT or LVEF < 50% or AV conduction delay.[80,652,653]	IIa	B
ICD implantation should be considered in DCM/HNDCM patients with a LVEF <50% and ≥2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in *LMNA*,[d] *PLN*, *FLNC*, and *RBM20* genes).	IIa	C
In DCM/HNDM patients, electrophysiological evaluation should be considered when syncope remains unexplained after non-invasive evaluation.[661,668]	IIa	C

EF 52%
Risk factors
- No syncope
- LGE on CMR √
- No EP study done
- Genetic test pending

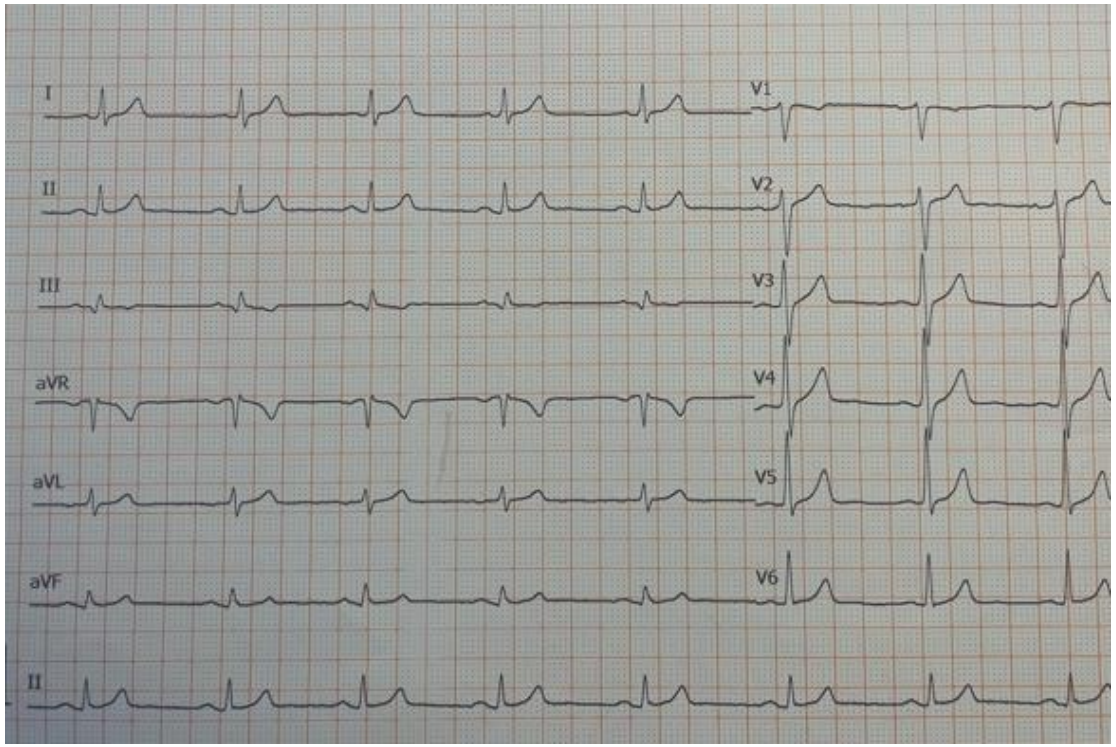
2023 ESC Guidelines for the management of cardiomyopathies

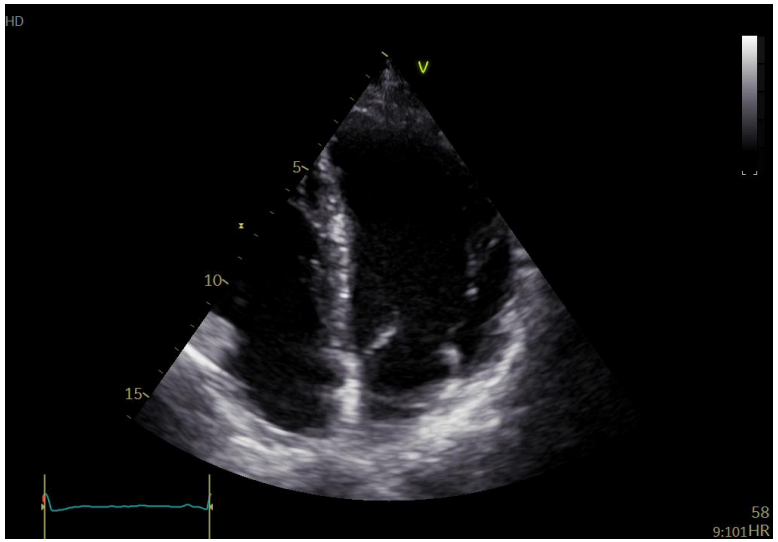
An ICD should be considered in patients with DCM with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors (see *Table 21*).[541,542,867,869,873,878,881,886]	IIa
An ICD may be considered in selected patients with DCM with a genotype associated with high SCD risk and LVEF >35% without additional risk factors (see *Table 21*).[869,873,881,886]	IIb
An ICD may be considered in patients with DCM without a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors.[c,138,873,874]	IIb

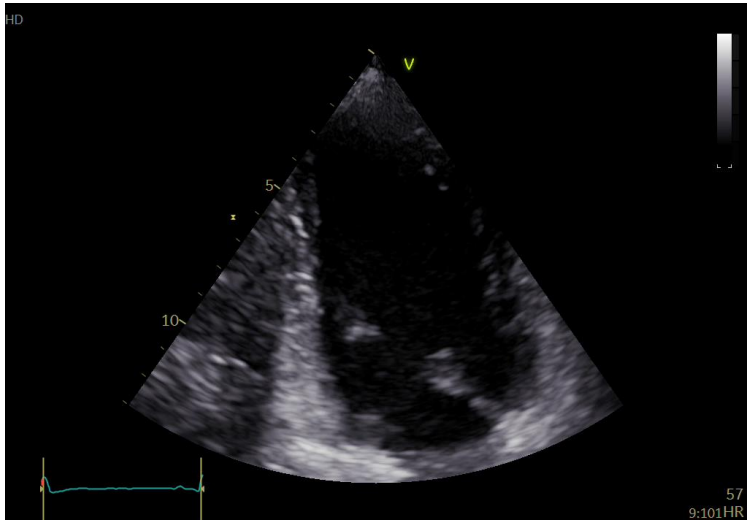
Additional risk factors

Gene	Annual SCD rate	Predictors of SCD
FLNC-truncating variants[866,867,880]	5–10%	LGE on CMR LVEF < 45%

Son, 31yo





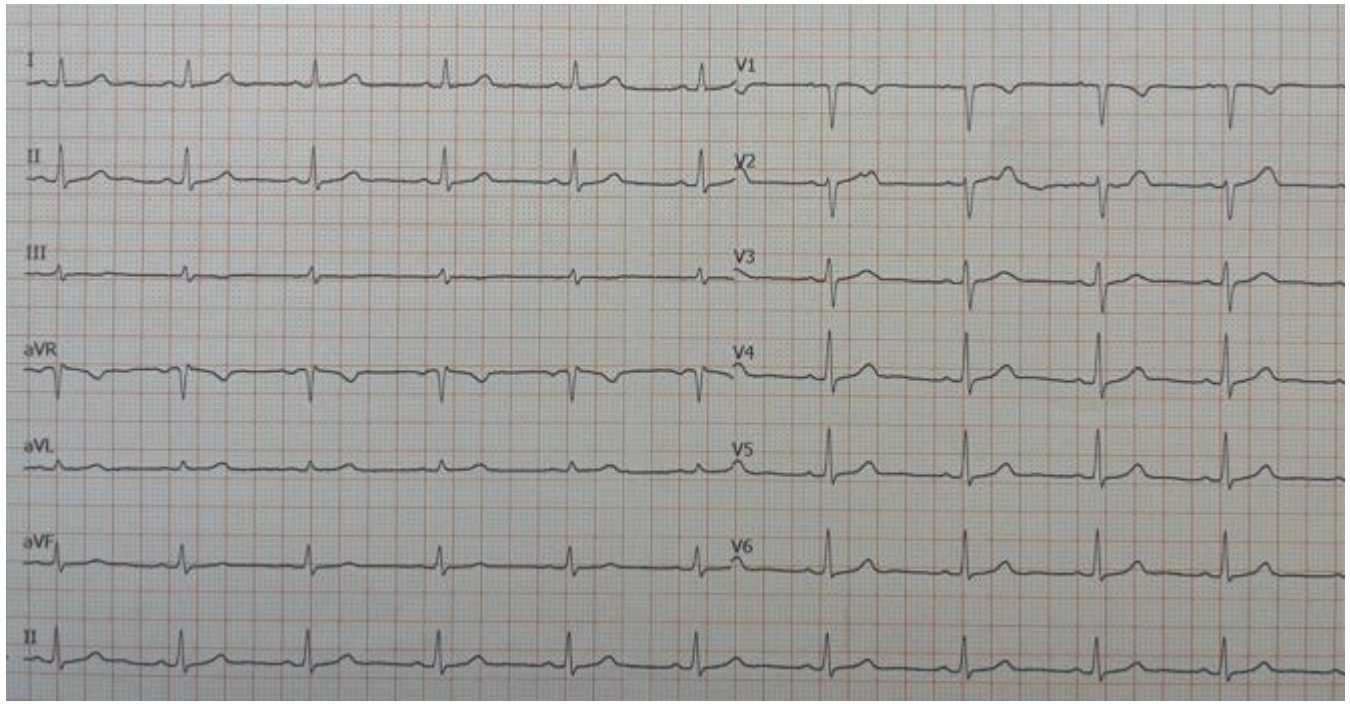


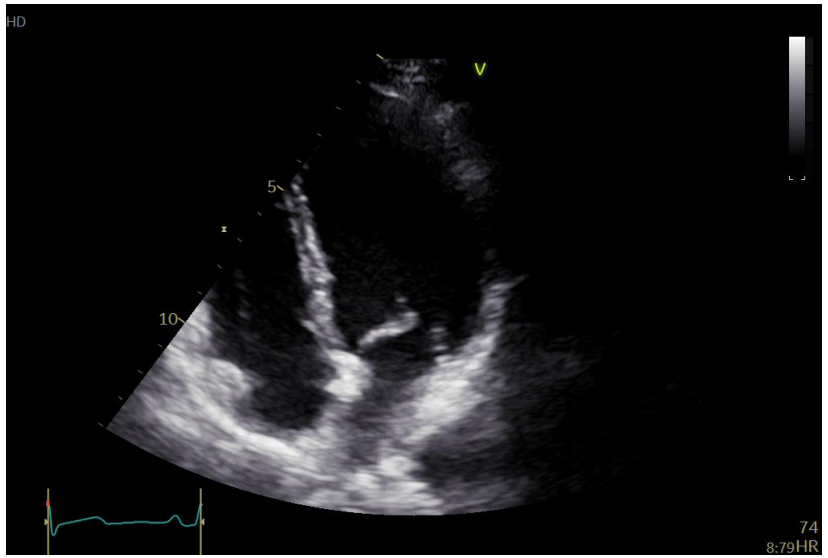
Syncope (-)
Palpitations (+)
NYHA I
Angina (-)

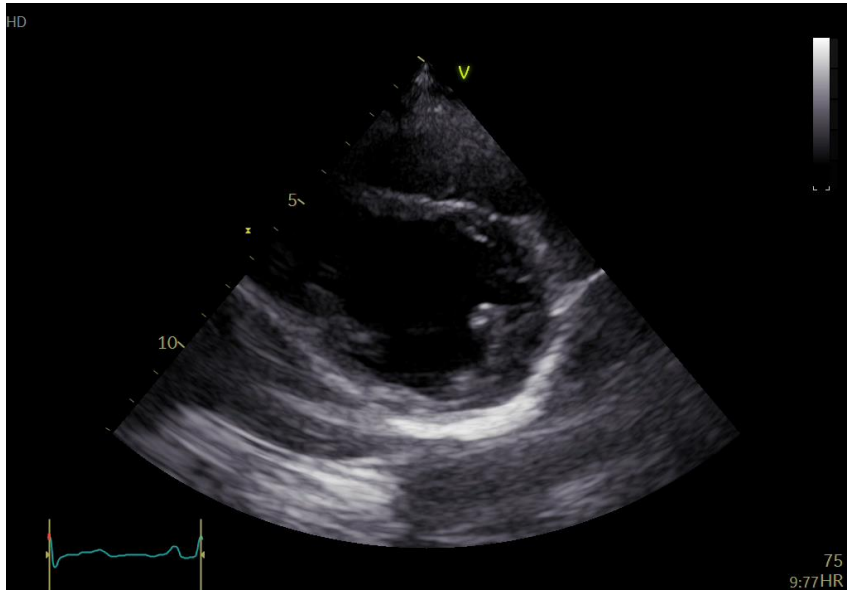
Holter 300 PCVs

Genetic test pending

Daughter, 34yo







Asymptomatic

Genetic test pending

Filamin C variants are associated with a distinctive clinical and immunohistochemical arrhythmogenic cardiomyopathy phenotype

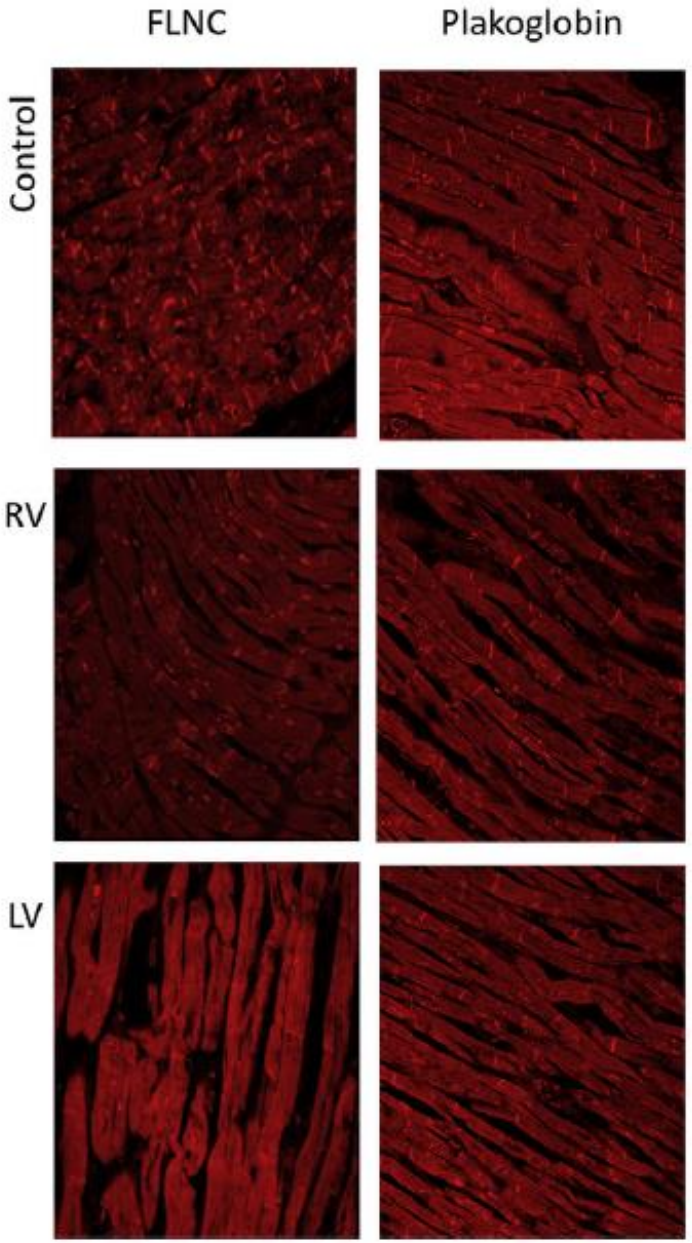
Charlotte L. Hall [a,1], Mohammed M. Akhtar [a,1], Maria Sabater-Molina [b,1], Marta Futema [a,1], Angeliki Asimaki [c,1], Alexandros Protonotarios [a,1], Chrysoula Dalageorgou [a,1], Alan M. Pittman [d,1], Mari Paz Suarez [e,1], Beatriz Aguilera [e,1], Pilar Molina [f,1], Esther Zorio [g,1], Juan Pedro Hernández [h,1], Francisco Pastor [i,1], Juan R. Gimeno [j,1], Petros Syrris [a,*,1], William J. McKenna [a,1]

FLNC null variant carriers (n=16)

ACM associated with FLNC variants presents with a distinctive phenotype characterized by Holter arrhythmia and LGE on CMRI with unremarkable ECG and echocardiographic finding

International Journal of Cardiology (2020)

Effects of FLNC mutations at the level of the intercalated disc from SD victims with FLNC variants sourced from another clinicopathology consortium (n=11)



FLNC displays a strong localization at the intercalated disc that decreases or is completely absent in patients carrying FLNC mutations

Staining for FLNC showed a decreased immunoreactive signal intensity in the LV in all 11 subjects highlighting a predominant LV disease

The signal for plakoglobin at the intercalated was strong and indistinguishable from controls in nine cases in both RV and LV samples

International Journal of Cardiology (2020)

Clinical characteristics of *FLNC* null variant carriers in families A-D. N=16

Family -Individual	*FLNC* Genotype	NYHA class/Symptoms	Age	Sex	ECG	Echocardiography Description	LVEF (%)	Arrhythmia 24 h VE count/type of arrhythmia	CMRI RV EDV (ml)	RVEF (%)	LV EDV (ml)	LVEF (%)	LGE distribution	Task Force Diagnostic Criteria (m, M)/Diagnosis
Family A II:2 (index case)	p.Arg991X	NYHA II	76	F	Permanent AF, low QRS voltage in limb leads Late potentials	Borderline LV dilatation with mild LV systolic dysfunction	50	19,248 Non-sustained VT	146	49	122	41	Basal lateral LGE	2 m and 1 M Definite
Family A III:2	p.Arg991X	Asymptomatic	44	F	Low QRS voltage in limb leads	Normal biventricular size and function	55–60	12,935	Normal	Normal	172	52	Normal/No LGE	1 m and 1 M Borderline
Family A IV:1	p.Arg991X	Palpitations	20	F	T-wave inversion inferior leads	Normal biventricular size and function	55–60	69 Sustained VT presentation, RBBB morphology	212	54	206	59	Basal lateral sub-epicardial LGE	2 m Possible
Family A IV:2	p.Arg991X	Asymptomatic	18	F	Unremarkable	Normal biventricular size and function	55–60	1	168	58	184	56	Normal/No LGE	1 m Unaffected
Family B II:1	c.7252-1G > A	Presyncope	64	M	Incomplete RBBB	Normal biventricular size and function	55–60	535						2 m Possible
Family B II:2 (index case)	c.7252-1G > A	Asymptomatic	62	M	Low QRS voltage	Normal biventricular size and function	55–60	22	210	61	209	65	Sub-epicardial LGE basal-mid anterolateral and inferolateral walls	1 M* Possible
Family C II:1	p.L1573X	Asymptomatic	76	M	Loss of inferior R waves	Normal biventricular size and function	59	0	147	67	156	64	Basal lateral epicardial LGE	None Unaffected
Family C III:1 (index case)	p.L1573X	Syncope	54	M	Low QRS voltage in limb leads	Non-dilated LV with mild LV dysfunction RV regional wall motion abnormality (dyskinetic RVOT and RV free wall)	45–50	Sustained VT of LBBB morphology with superior axis	211	51	183	51	Extensive basal to mid sub-endocardial LGE in the anterolateral and inferolateral walls	1 m and 1 M Borderline
Family C III:4	p.L1573X	Palpitations	50	F	T wave inversion V6	Normal biventricular size and function	60	166	Normal	Normal	112	70	Equivocal basal LGE	1 m Unaffected
Family C IV:1	p.L1573X	Asymptomatic	19	M	Unremarkable	Normal biventricular size and function	59	3	180	54	173	57	Normal/No LGE	None Unaffected
Family C IV:3	p.L1573X	Asymptomatic	26	F	Poor R-wave progression in anterior leads	Normal biventricular size and function	60	0	141	64	161	60	Normal/No LGE	None Unaffected
Family D II:1	p.Arg482X	Asymptomatic	73	M	Unremarkable	Non-dilated LV and mild LV dysfunction	45	1093	141	41	196	48	Circumferential basal LGE and mid-inferior and inferolateral LGE	1 m and 1 M Borderline
Family D II:4	p.Arg482X	NYHA II	SCD 71	M	T-wave inversion V6	Dilated LV and severe LV dysfunction	35	9249 Non-sustained VT	Normal	normal	257	52	Extensive inferior and inferolateral subepicardial basal LGE	2 m and 1 M Definite
Family D III:2	p.Arg482X	Asymptomatic	46	F	Unremarkable	Normal biventricular size and function	60–65	6 Non-sustained VT	131	71	149	68	Normal/No LGE	2 m Possible
Family D III:3	p.Arg482X	Asymptomatic	43	M	Unremarkable	Normal biventricular size and function	60–65	3	161	57	146	68	Subtle streak of non-ischaemic LGE in the basal inferolateral wall	1 m Unaffected
Family D III:6 (index case)	p.Arg482X	NYHA II	50	F	Low QRS voltage in precordial leads	Borderline LV dilatation with mild to moderate LV systolic dysfunction	40–45	5197	227	62	187	62	Basal inferolateral and inferior wall LGE	1 m and 1 M Borderline

5/16 normal ECG
Family members

11/16 normal echo
One index case

4/5 index case
EF>45%

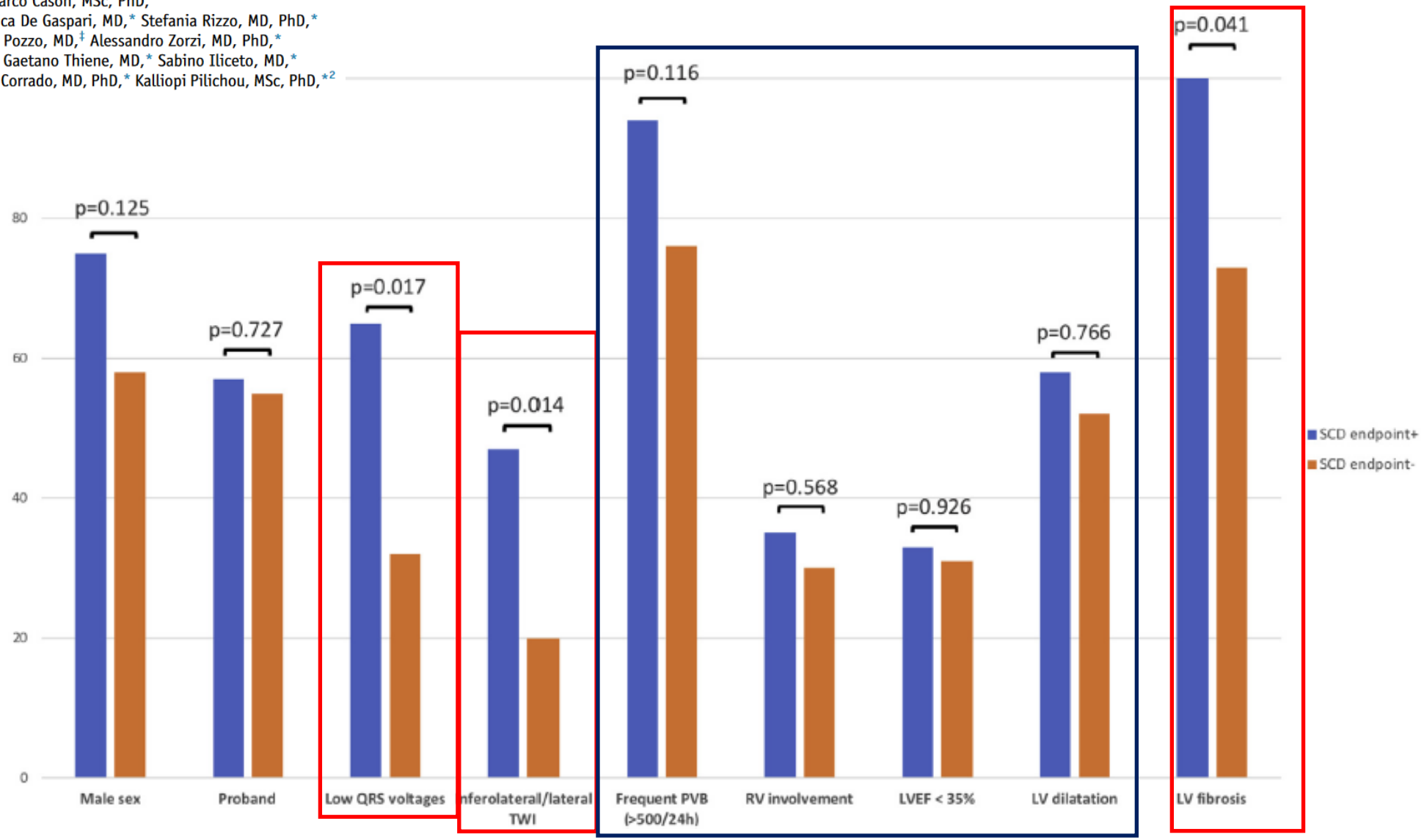
C.L. Hall et al. / International Journal of Cardiology (2020)

Filamin-C variant-associated cardiomyopathy: A pooled analysis of individual patient data to evaluate the clinical profile and risk of sudden cardiac death

Rudy Celeghin, MSc, PhD,[*1] Alberto Cipriani, MD,[*1] Riccardo Bariani, MD,[*] Maria Bueno Marinas, MSc, PhD,[*] Marco Cason, MSc, PhD,[*] Michela Bevilacqua, MD, PhD,[†] Monica De Gaspari, MD,[*] Stefania Rizzo, MD, PhD,[*] Ilaria Rigato, MD, PhD,[*] Stefano Da Pozzo, MD,[‡] Alessandro Zorzi, MD, PhD,[*] Martina Perazzolo Marra, MD, PhD,[*] Gaetano Thiene, MD,[*] Sabino Iliceto, MD,[*] Cristina Basso, MD, PhD,[*] Domenico Corrado, MD, PhD,[*] Kalliopi Pilichou, MSc, PhD,[*2] Barbara Bauce, MD, PhD[*2]

270 gene-elusive ACM probands, **12 (4.4%) had FLNC variants, and 13 additional family members** carried the same mutation (**25 patients**)

On invidual data pooled analysis, 145 patients with FLNC-associated cardiomyopathies were included



Risk factors associated with SCD

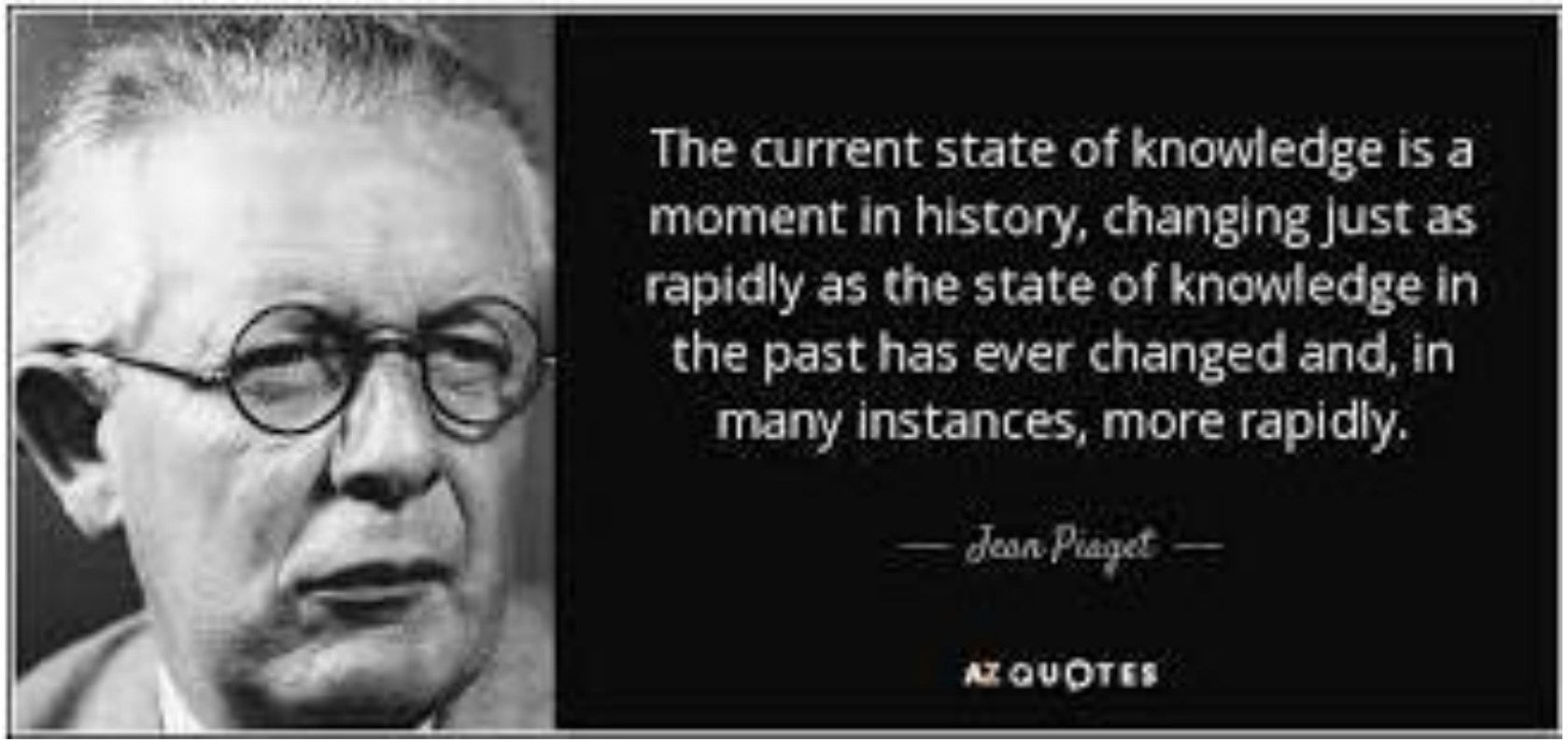
Celeghin R et al, Heart Rhythm 2022

Table 3 Demographic and clinical profile of patients with *FLNC* cardiomyopathy (pooled analysis)

	Overall sample (n = 145)	ACM (n = 60)	DCM (n = 85)	*P* value
Age (y)	43 ± 16	48 ± 17	40 ± 14	.017
≥35 y	101 (70)	45 (75)	56 (66)	.274
Male sex	89 (61)	40 (67)	49 (58)	.302
Proband	81 (56)	33 (55)	48 (57)	.867
Radical variant	133 (92)	49 (82)	84 (99)	<.001
Electrocardiographic characteristics				
Low (<0.5 mV) QRS voltages in limb leads	40/109 (37)	19/46 (41)	21/63 (33)	.426
TWI in V_1–V_3 ± V_4	11/120 (9)	9/56 (16)	2/64 (3)	.023
TWI in inferolateral/lateral leads	29/120 (24)	19/56 (34)	10/64 (16)	.032
Arrhythmic history				
Frequent PVB (>500/24 h)	94/119 (79)	41/53 (77)	53/66 (80)	.821
Sustained VT	30/107 (28)	15/53 (28)	15/54 (28)	1
Cardiac imaging findings				
LV dilation	69/131 (53)	15/57 (26)	54/74 (73)	<.001
LVEF (%)	42 ± 14	51 ± 11	36 ± 12	<.001
LVEF ≤35%	43/137 (29)	5/57 (9)	38/80 (48)	<.001
RV involvement	36/117 (31)	19/57 (33)	17/60 (28)	.689
LV LGE	50/67 (75)	38/44 (86)	12/23 (52)	.004
Full heart histopathological analysis				
LV fibrosis	11/12 (92)	7/7 (100)	4/5 (80)	.217
Outcome				
SCD composite endpoint	28 (19)	10 (17)	18 (21)	.498
Cardiac transplantation/heart failure death	8 (6)	1 (2)	7 (8)	.088

Celeghin R et al, Heart Rhythm 2022

Many thanks!



Keep an open mind