PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA
Centro Congressi
di Confindustria
Auditorium
della Tecnica

9ª Edizione

30 Settembre
1 Ottobre
2022

CARDIOMIOPATIA ARITMOGENA: WHAT'S NEW?

FENOTIPO-GENOTIPO NELLA DISPLASIA ARITMOGENA LEFT-DOMINANT

Mango Ruggiero

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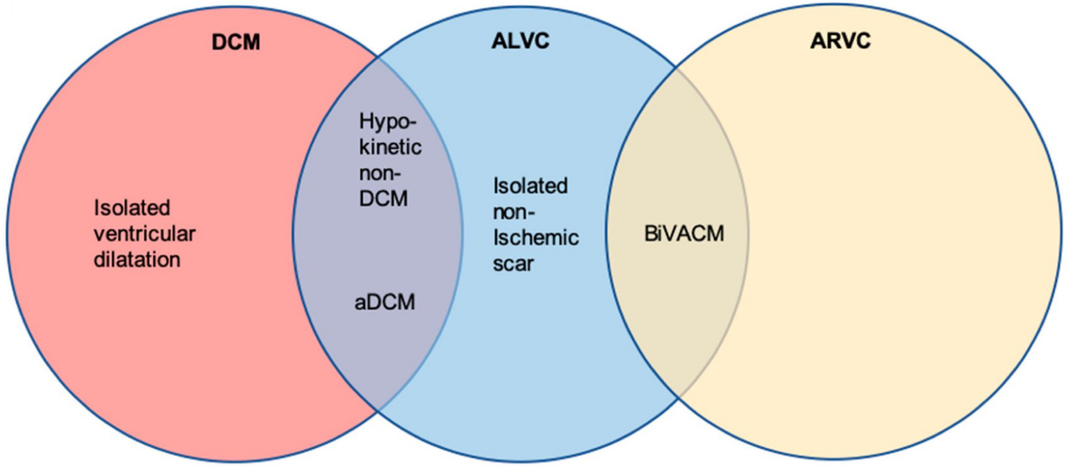
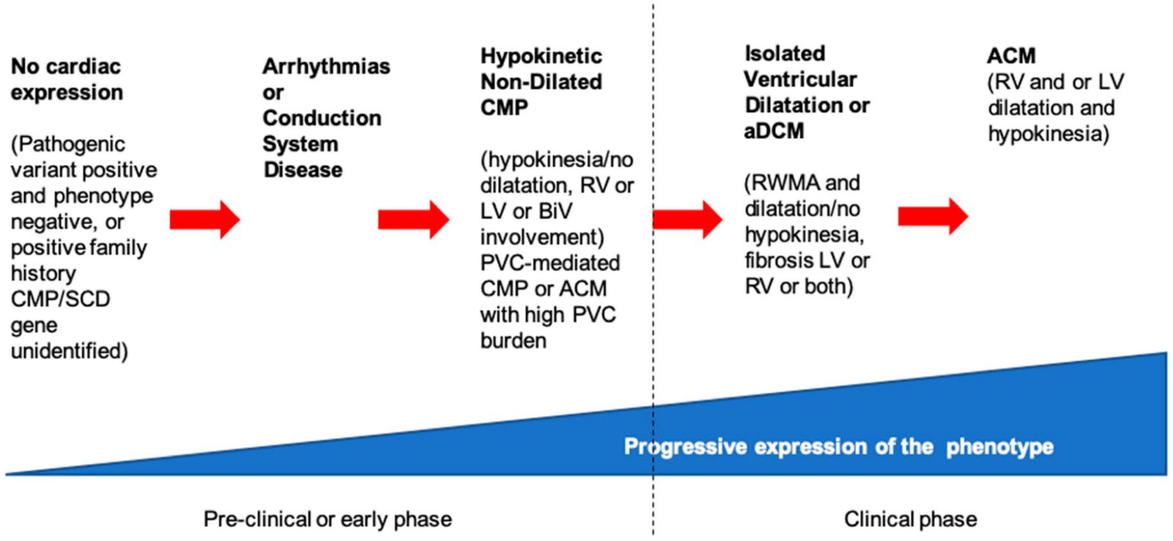
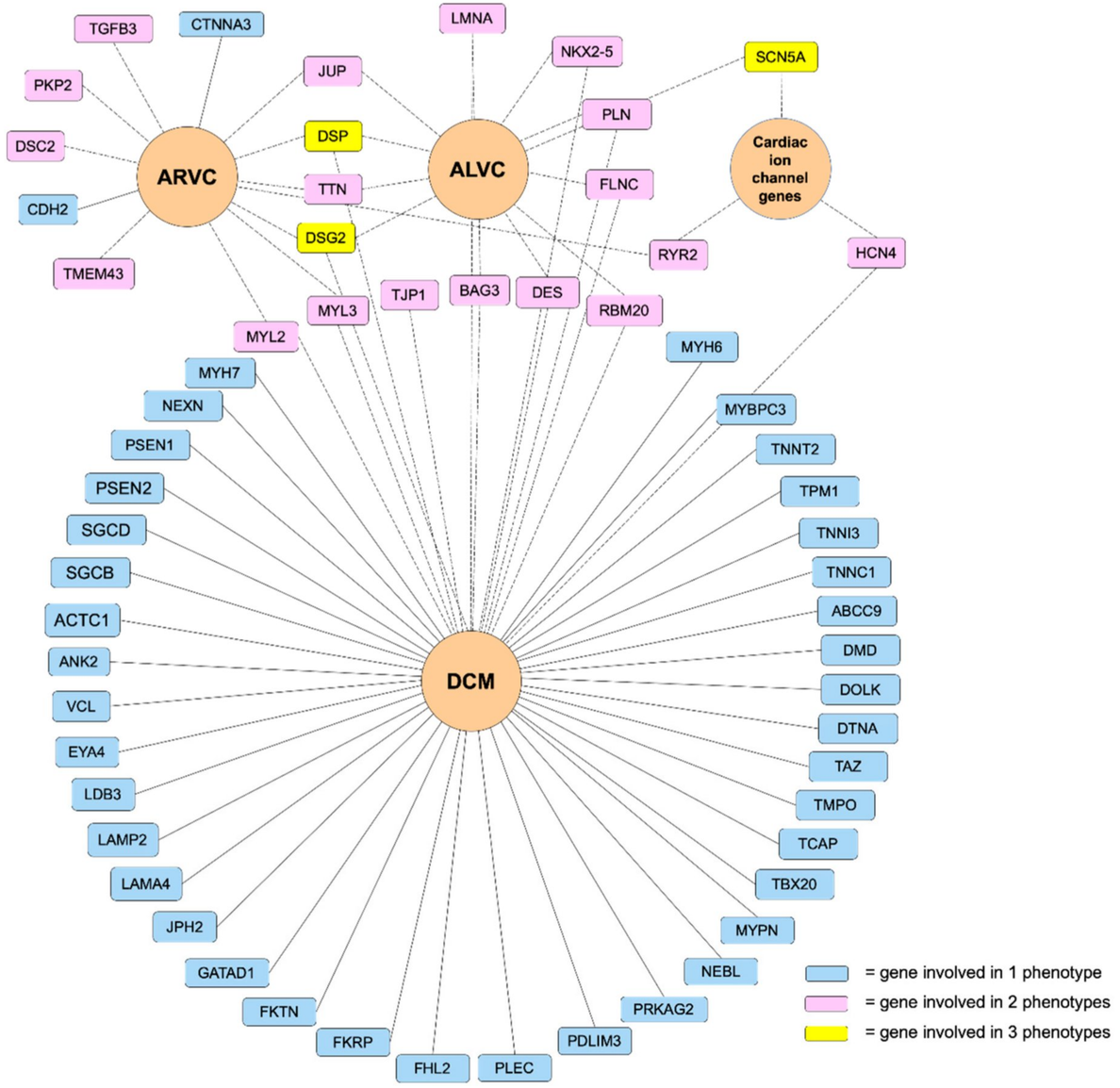
INTRODUCTION

"Progress in science depends on new techniques, new discoveries and new ideas, probably in that order" **Sydney Brenner**



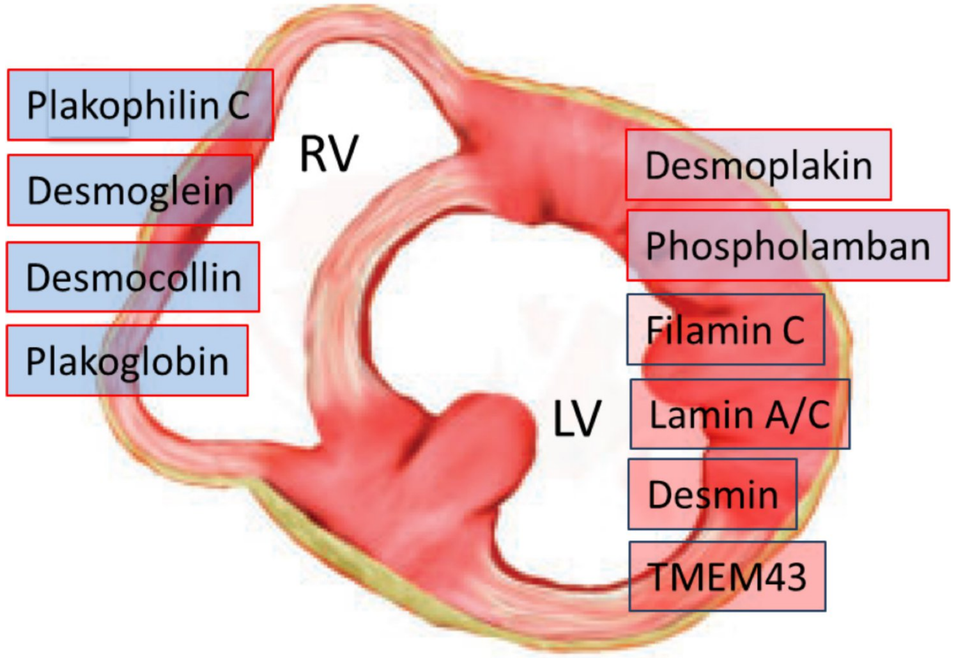




Patel et al., Int. J. Mol. Sci. 2020

State of Genetic testing for ALVC

Gene	Locus	Phenotype/syndrome	Protein (Cellular complex)	Frequency	ClinGen c
PKP2	12p11.21	Classic ARVC. BiVACM and ALVC in a minority of cases.	Plakophilin 2 (desmosome)	20–45%	Definite
DSP	6p24.3	Frequent BiVACM and ALVC. Occasional hair and skin features. Rare homozygous variants—Carvajal Syndrome.	Desmoplakin (desmosome)	2–15%	Definite
DSG2	18q12.1	Frequent BiVACM and ALVC.	Desmoglein 2 (desmosome)	4–15%	Definite
DSC2	18q12.1	ARVC. Less frequent BiVACM and ALVC.	Desmocollin 2 (desmosome)	2–7%	Definite
FLNC	7q32.1	ALVC. Right ventricular involvement is rare	Filamin-C (cytoskeleton)	3%	Definite[a]
JUP	17q21.2	Naxos disease (cardioectodermal)	Plakoglobin (desmosome)	<1% (higher in Naxos, Greece)	Definite
TMEM43	3p25.1	ARVC and BiVACM	Transmembrane protein 43 (nuclear envelope)	<1% (higher in Newfoundland)	Definite
PLN	6q22.31	Frequent ALVC/DCM	Phospholamban (sarcoplasmic reticulum; calcium handling)	1% (10–15% in Netherlands)	Definite[a]
DES	2q35	Frequent ALVC. Right ventricular involvement is also possible. Conduction system abnormalities common. Skeletal myopathy possible.	Desmin (cytoskeleton)	1–2%	Moderate



DSP FLNC DES PLN

Corrado D and Basso C, Heart 2022
Bariani et al., J. Clin. Med. 2022
ESC Consensus Statement on the state of genetic testing for cardiac diseases, 2022

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GENOTYPE-PHENOTYPE STUDIES

Myocardial fibrosis in ACM: a genotype–phenotype correlation study

		Non-desmosomal (25)	Desmosomal (13)	Negative (6)	*P*-value
LV-LGE positive, *n* (%)		20 (80)	10 (76.9)	5 (83.3)	0.94
Distribution	LV-LGE, *n* (%)	Subepicardial 20 (100)	Subepicardial 9 (90) Mesocardial 1 (10)	Subepicardial 4 (80) Mesocardial 1 (20)	0.17
Extension	LV-LGE annular, *n* (%)	14 (56)	4 (30.8)	0 (0)	0.02
RV-LGE, *n* (%)		10 (40)	10 (76.9)	2 (33.3)	*0.06*
LGE pattern, *n* (%)					
Isolated LV		11 (44)	1 (7.7)	3 (50)	*0.27*
Isolated RV		3 (12)	1 (7.7)	0 (0)	
Biventricular		9 (36)	9 (69.2)	2 (33.3)	
No		2 (8)	2 (15.4)	1 (16.7)	

Desmosomal and non-desmosomal mutation carriers showed different morphofunctional features but similar LV LGE presence.

Segura-Rodriguez et al., EHJ Cardiovascular Imaging 2020

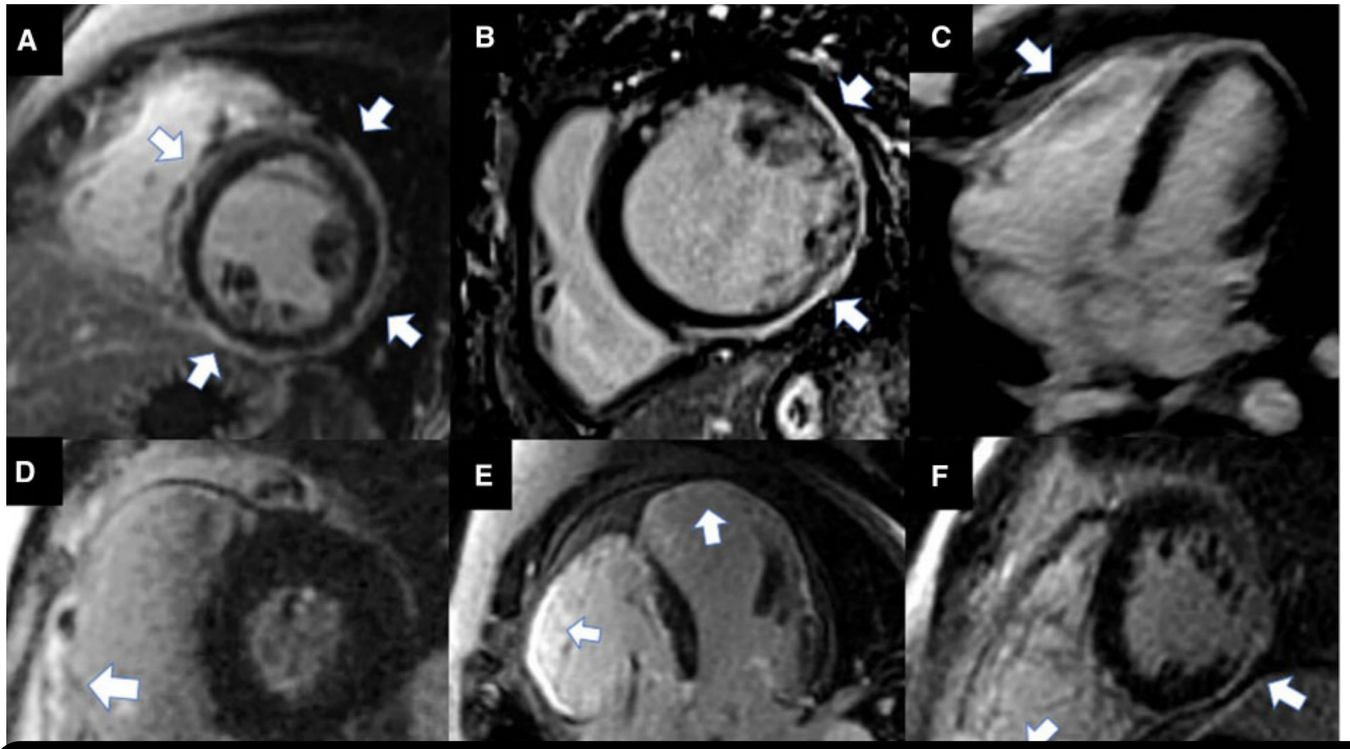
Patients' phenotypes by gene mutation and CMR pattern

Gene	Protein	Nucleotide change	Protein change	Carriers	LV RWMA	RV RWMA	LGE phenotype	LGE LV extension
DES	*Desmin*	c.1203G>C	Missense	16	11	8	RV 1	Annular 13
							LV 6	Inferolateral 2
							BV 9	Inferior 1
DSP	*Desmoplakin*	c.3133C>T	Nonsense	7	2	6	LV 1	Annular 3
		c.7697_7698insG	Frameshift				BV 6	Septum 1
								Inferolateral 2
								Lateral 1
FLNC	*Filamin C*	c.4288 + 2T>G	Nonsense	7	3	2	LV 5	Inferolateral 3
		c.581_599delTGGTGG ACAACTGCGCCCC	Nonsense				RV 1	Lateral 2
							None 1	
DSG-2	*Desmoglein2*	c.875G>A	Missense	5	3	4	BV 3	Annular 1
		c.535delA	Nonsense				None 0	Lateral 2
PKP-2	*Plakophilin2*	c.1643delG	Nonsense	1	None	1	1	
LMNA	*Lamin A/C*	c.1541G>A	Missense	1	None	None	None	
TMEM43	*Luma*	c.1073C>T	Missense	1	None	1	RV 1	
Negative				6	2	5	LV 3	
							BV 2	
							None 1	

Segura-Rodriguez et al., EHJ Cardiovascular Imaging 2020

Representative late gadolinium enhancement images

DES *FLNC* *TMEM43*

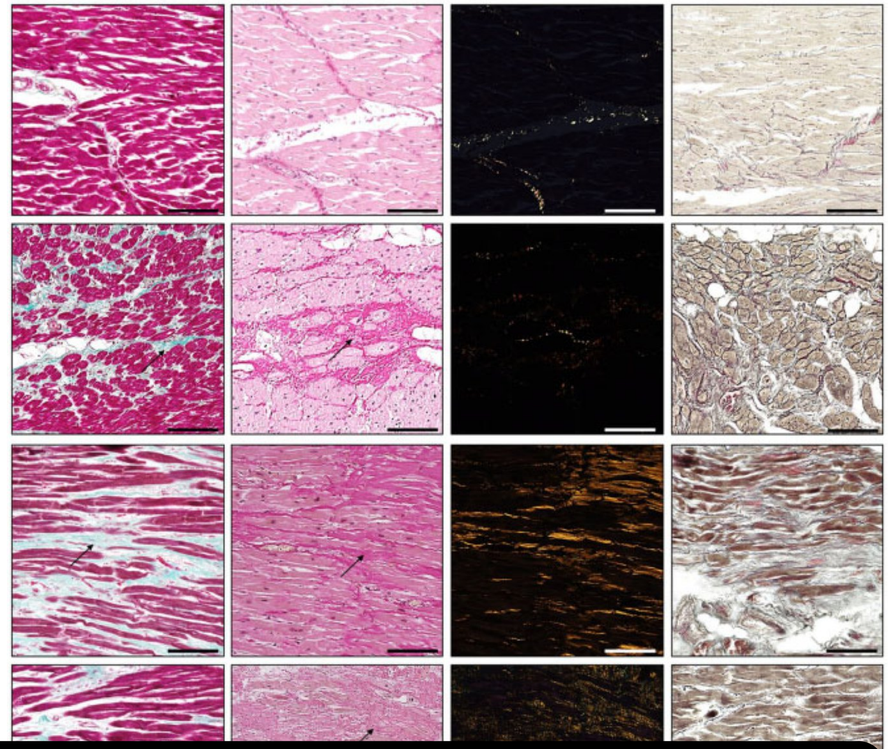


Histochemistry of fibrillar extracellular matrix components: increase in the fibrillar connective tissue and intercellular space

CONTROL

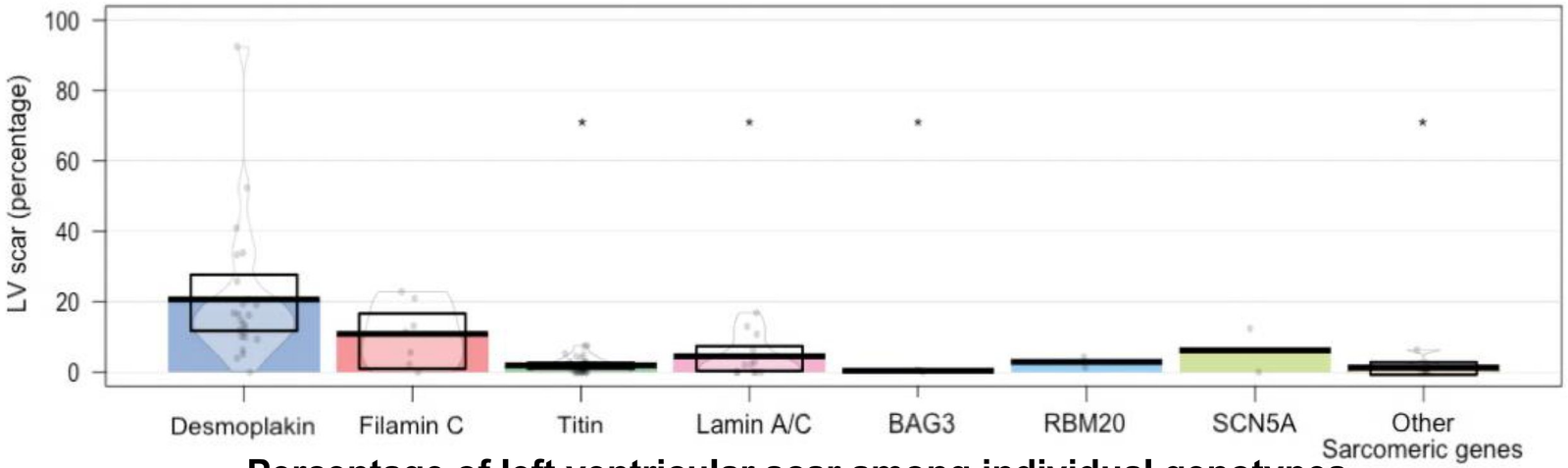
DES
39,45%

FLNC
51.42%
C.H.

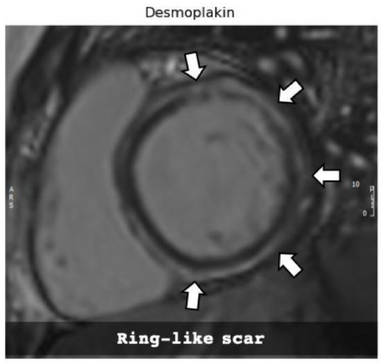


DES mutation carriers can be identified by a specific and extensive LV subepicardial circumferential LGE pattern.

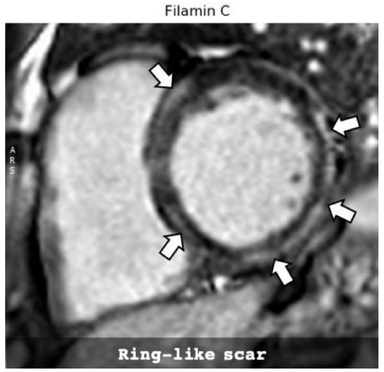
Dilated Cardiomyopathy and Arrhythmogenic Left Ventricular Cardiomyopathy: A Comprehensive Genotype-Imaging Phenotype Study



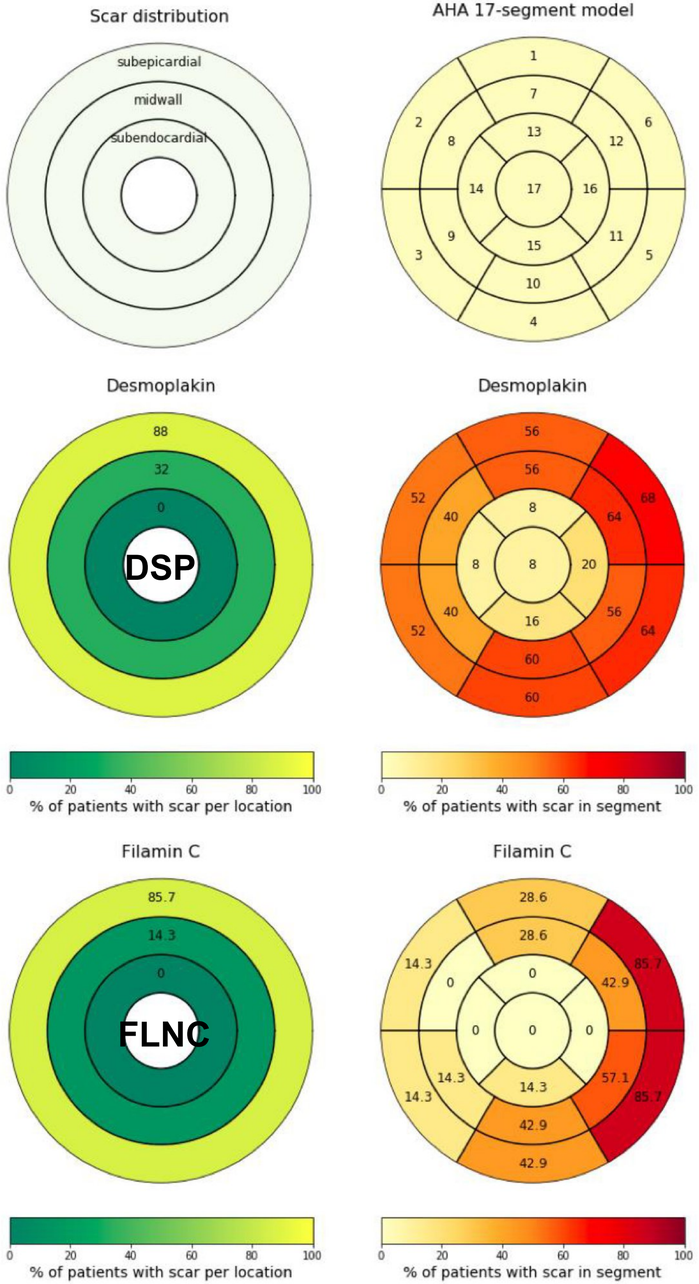
Percentage of left ventricular scar among individual genotypes



DSP



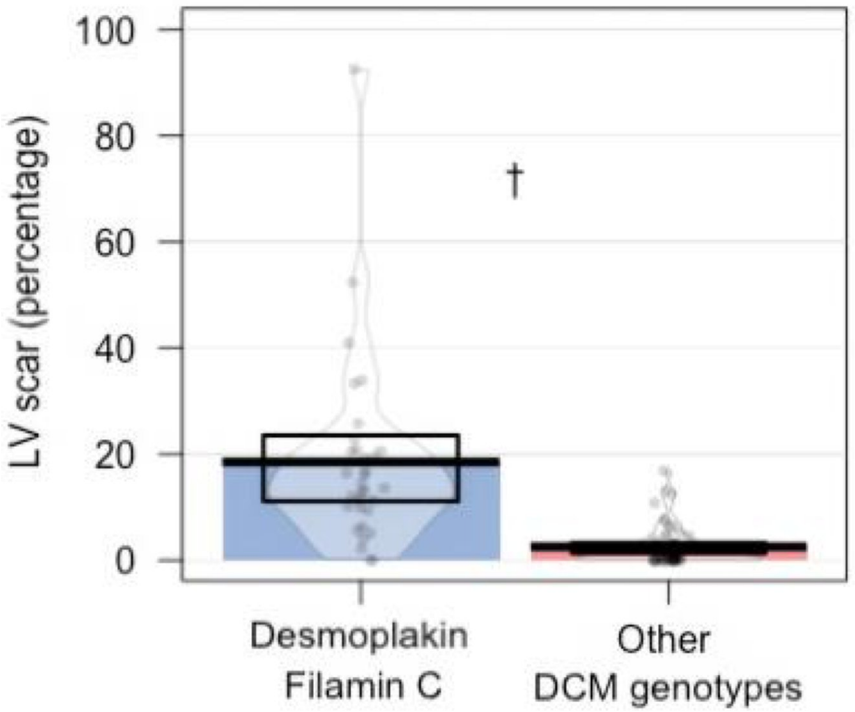
FLNC



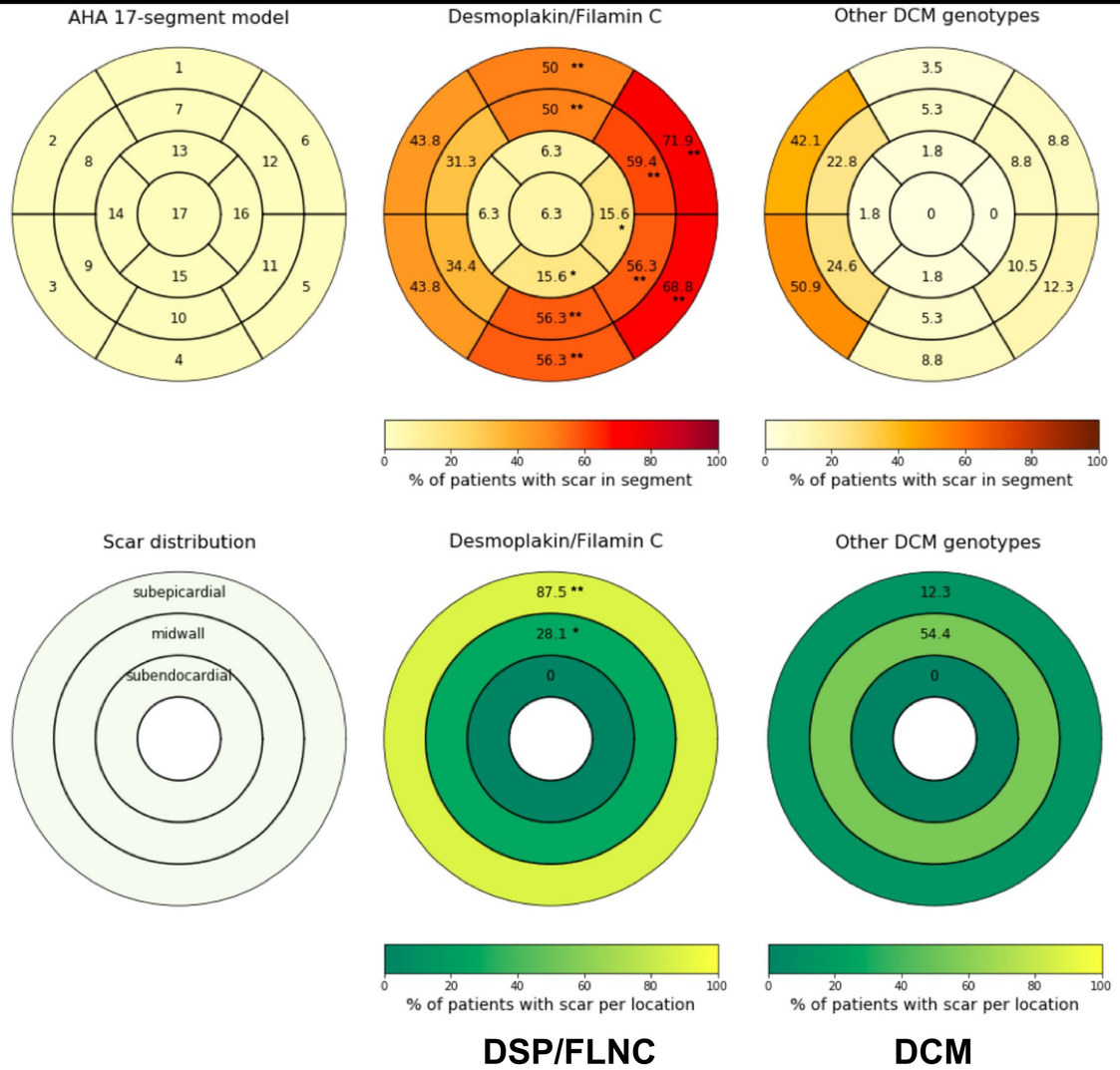
Distribution of left ventricular scar in myocardial layers and in bull's eye

Augusto et., Eur Heart J Cardiovasc Imaging 2020

Sub-epicardial LV late gadolinium enhancement with ring-like pattern (at least 3 contiguous segments in the same short axis slice) was observed in 78.1% of DSP/FLNC genotypes but was absent in the other DCM genotypes (p<0.001)

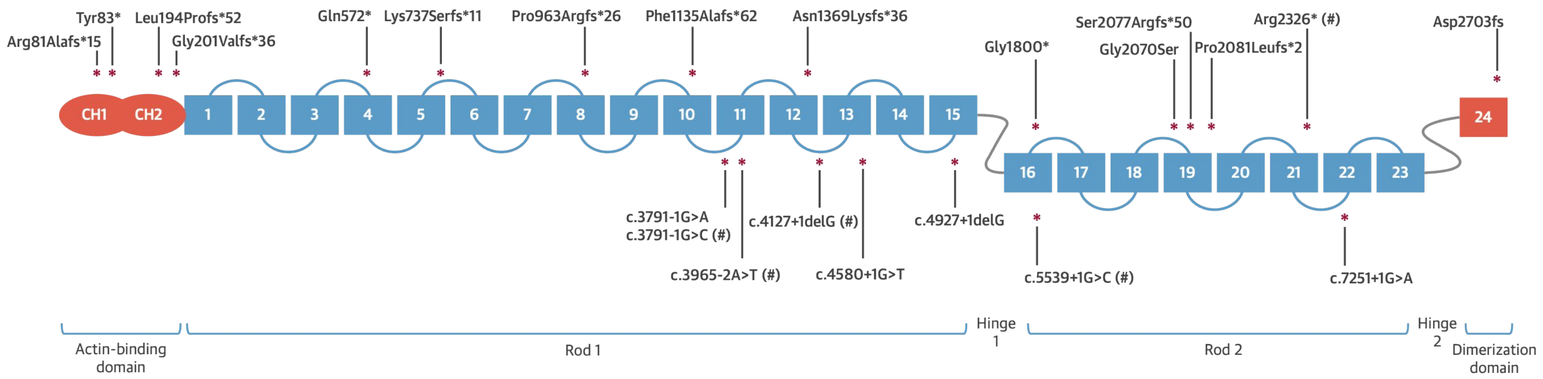


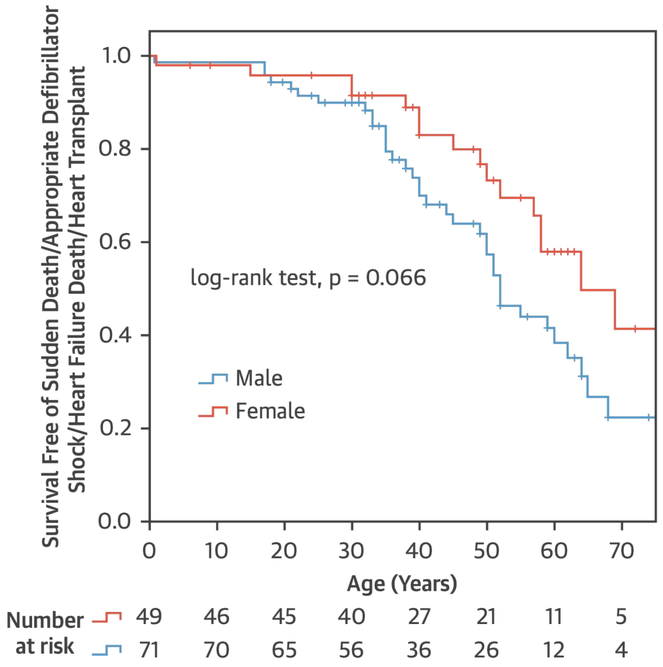
Percentage of left ventricular scar between grouped genotypes

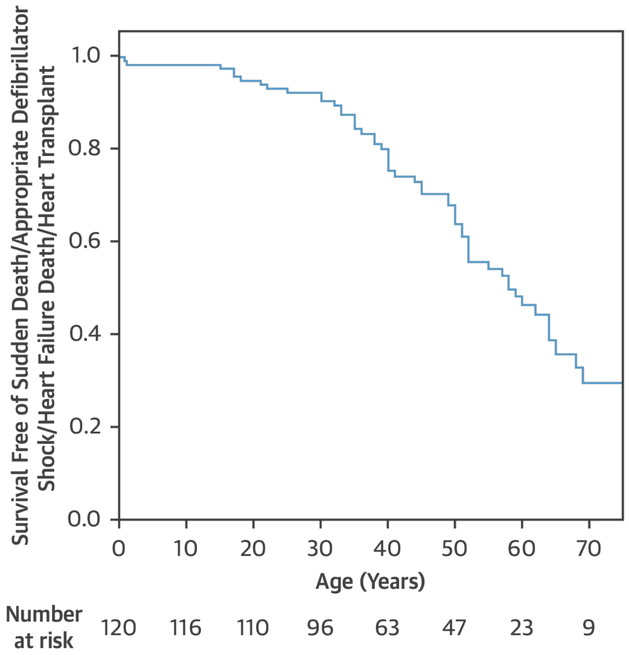


Augusto et., Eur Heart J Cardiovasc Imaging 2020

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







28 Probands and 54 relatives

- Left ventricular dilation (68%)
- Systolic dysfunction (46%)
- Myocardial fibrosis (67%)
- Inferolateral negative T waves and low QRS voltages on ECG (33%)
- Ventricular arrhythmias (82%)
- Frequent SD (40 cases in 21 of 28 families)
- Penetrance (>97% over 40 yo)

Ortiz-Genga et al., JACC 2016

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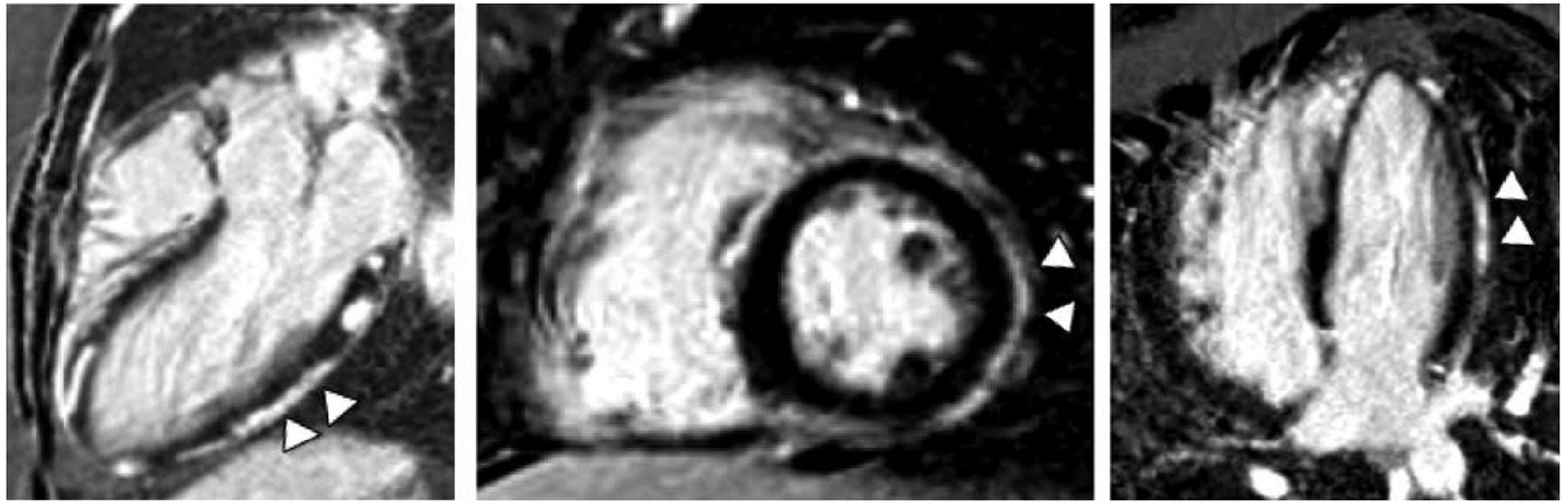
GENE-CENTRIC STRATEGIES WILL BE ESSENTIAL TO FURTHERING ACCURATE RISK ASSESSMENT

Desmoplakin Cardiomyopathy, a Fibrotic and Inflammatory Form of Cardiomyopathy Distinct From Typical Dilated or Arrhythmogenic Right Ventricular Cardiomyopathy

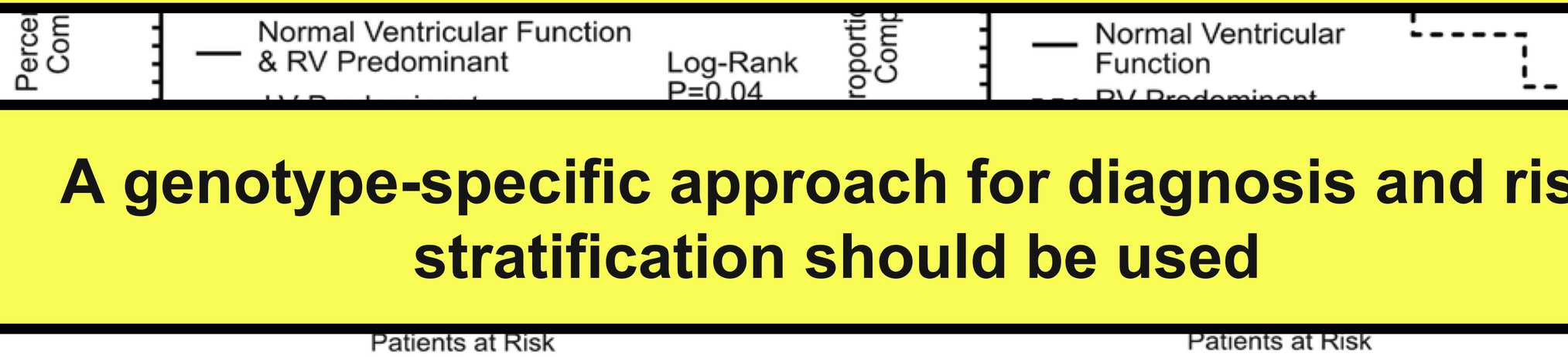


DSP cardiomyopathy is a distinct form of ACM characterized by episodic myocardial injury, left ventricular fibrosis that precedes systolic dysfunction, and a high incidence of ventricular arrhythmias.

Smith ED et al., Circulation 2020

Survival analysis of severe ventricular arrhythmia outcomes

The presence of any LV systolic dysfunction in DSP cardiomyopathy (LV ejection fraction <55%), particularly when associated with frequent premature ventricular contractions and LV late gadolinium enhancement, indicates a substantial risk for severe ventricular arrhythmias.

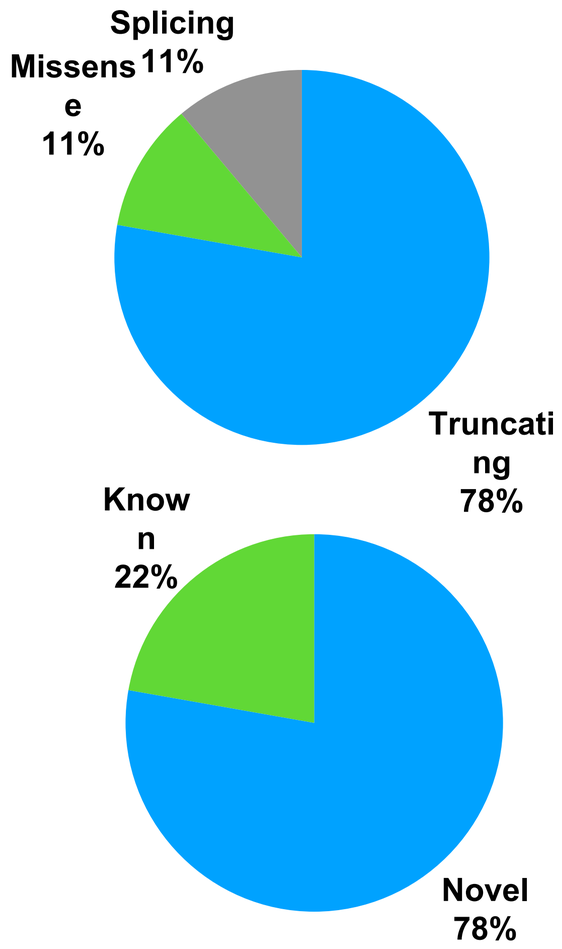


A genotype-specific approach for diagnosis and risk stratification should be used

Smith ED et al., Circulation 2020

Variants identified in desmoplakin (DSP NM_004415) gene in Policlinico Tor Vergata Genetics Division

Patients	HGVSc	HGVSp	Exon	dbSNP	ACMG	Literature
1	c.6154C>T	p.Gln2052Ter	24	-	Pathogenic	novel
2	c.2497C>T	p.Gln833Ter	18	rs1561693779	Pathogenic	novel
3	c.2848del	p.Ile950LeufsTer27	20	rs397516927	Pathogenic	PMID: 25157032
4	c. 1352G>C	p.Arg451Pro	11	-	Likely pathogenic	novel
5	c.5851C>T	p.Arg1951Ter	24	rs869025395	Pathogenic	PMID: 26899768
6	c.3203_3204 del	p.Glu1068ValfsTer19	23	rs1285329067	Pathogenic	novel
7	c.5210del	p.Gly1737AspfsTer16	23	rs1581819043	Pathogenic	novel
8	c.170+2T>G	p.(?)	-	rs1581777867	Likely pathogenic	novel
9*	c.5210del	p.Gly1737AspfsTer16	23	rs1581819043	Pathogenic	novel



Clinical characteristics of probands carrying LP or P variants in desmoplakin (DSP) gene.

Patients	Sex	Age at diagnosis (years)	MAEs	Syncope	Chest Pain	Palpitations	Myocarditis	NYHA Class	ICD	Family History of SCD	Family History of DCM
1	F	40	SVT	No	Yes	Yes	No	II	Yes	Yes	DCM
2	M	51	No	No	No	No	No	II	Yes	Yes	DCM
3	F	44	No	No	No	Yes	No	I	No	No	DCM, ACM
4	M	32	No	No	No	No	No	I	No	No	DCM
5	M	31	No	Yes	No	Yes	Yes	I	Yes	Yes	No

Age at diagnosis: 37.36

Palpitations 56%

Recurrent episodes of acute myocarditis among family members, or a personal history of acute myocarditis combined with a family history of cardiomyopathy or SCD, should raise the suspicion of LV variants of ACM, and tissue characterization and genetic testing should be advised

Imaging characteristics of probands carrying LP or P variants in desmoplakin (DSP) gene.

Patients	LVE	RVE	LVEF	RVEF	Cardiac wall motion	LGE	Localization
1	Moderate	Moderate	45%	27%	Global hypokinesia of LV and RV	Yes	(RVW and IVS)
2	Severe	n.d.	22%	68%	Global hypokinesia of LV	Yes	Subendocardial with transmural extension (LVW)
3	n.d.	n.d.	63%	54%	Normokinesia	Yes	Subepicardial (LVW)
4	Mild	Mild	51%	60%	Normokinesia	Yes	Subepicardial (LVW)
5	Moderate	n.d.	42%	42%	Global hypokinesia of LV	Yes	Intramural (IVS), Subepicardial (LVW)
6	n.d.	n.d.	54%	n.a.	Normokinesia	Yes	Epicardial (LVW, RVW, IVS)
7	n.d.	n.d.	55%	57%	Normokinesia	Yes	Subepicardial (LVW and IVS)
8	Mild	n.d.	55%	51%	Hypokinesia of anterior wall and mid-apical IVS	Yes	Subepicardial (LVW and IVS)
9	n.d.	n.d.	63%	56%	Normokinesia	Yes	Mid-Subepicardial (LVW)

Systolic dysfunction 44%

LGE 100%

LGE distribution: 88% SE

Ventricular arrythmias 67%

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CONCLUSIONS

The most defining genotype-phenotype characteristic of ALVC

genetic testing is valued not only for diagnostic purposes but also because it can stratify the arrhythmic risk of ACM patients

Very high penetrance of truncating variants

Sub-epicardial ringlike scar pattern in DSP/FLNC/DES

"hot phase”: chest pain, troponin release, and 12-lead electrocardiogram abnormalities with normal coronary arteries” especially in DSP variant carriers

High risk of SD and HF expecially in DSP/FLNC/DES/PLN

"Walking with the Ghosts of My Grandmothers"

a painting by Hollis Sigler

on the cover of
the journal *Science*
October, 1994

THANK YOU FOR YOUR ATTENTION

Cardiogenetics PTV
Prof. F. Sangiuolo
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R. Mango
Prof. G. Novelli

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