



ROMA, 25 - 27 Giugno 2026

Valutazione clinica e stratificazione del rischio aritmico nei pazienti con mutazioni da **LMNA**



Andrea Igoren Guaricci

School of Medicine - University of Bari "Aldo Moro"

Division of University Cardiology,

Asclepios III, A.O.U.C. Policlinico di Bari, Italy



Agenda

- Background
- Genetics
- Phenotypic spectrum of Laminopathies
- Physiopathology
- Arrhythmic risk stratification

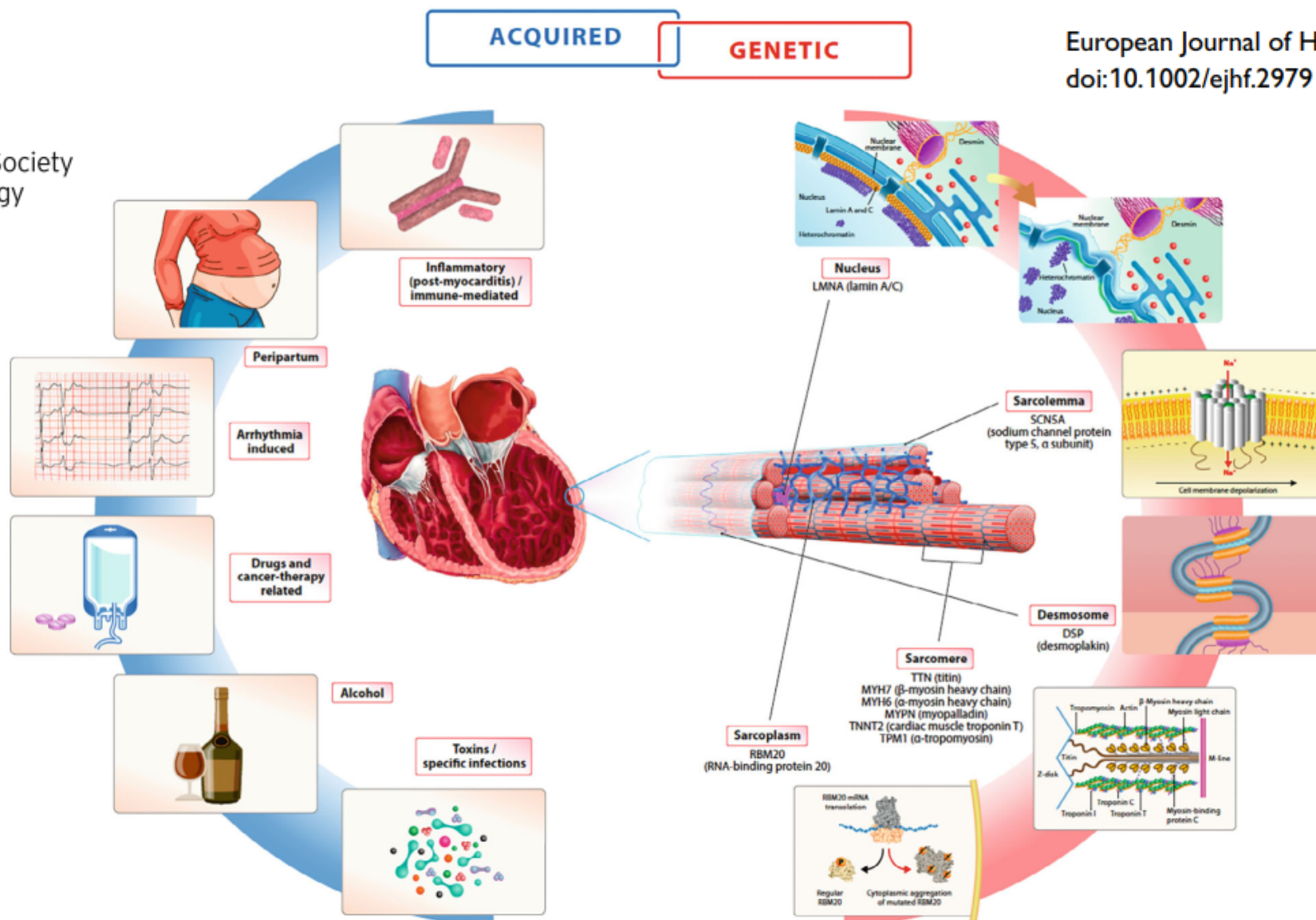
EPIDEMIOLOGY

CM phenotype	Adults	Children
HCM	Prevalence: 0.2%	Childhood incidence: 0.002–0.005% Childhood prevalence: 0.029%
DCM	Prevalence: 0.036 – 0.400%	Childhood incidence: 0.003–0.006% Childhood prevalence: 0.026% Infantile incidence: 0.038–0.046%
NDLVC	To be determined	To be determined
ARVC	Prevalence: 0.078%	Very rare in infancy and early childhood; to be determined in older children and adolescents
RCM	Rare	Childhood incidence: 0.0003%



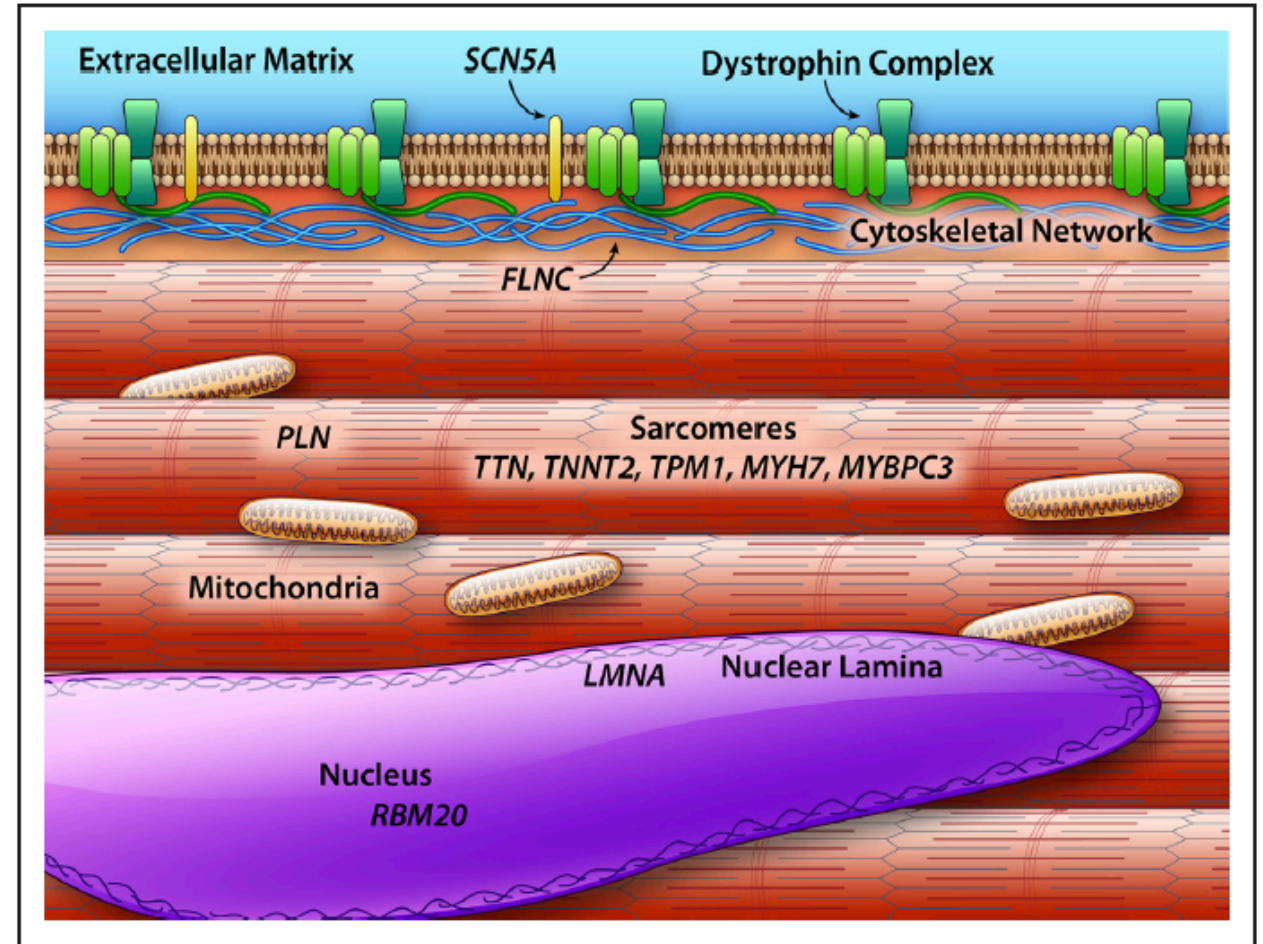
2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

DILATED CARDIOMYOPATHY - DEFINITION



DCM: genotypes

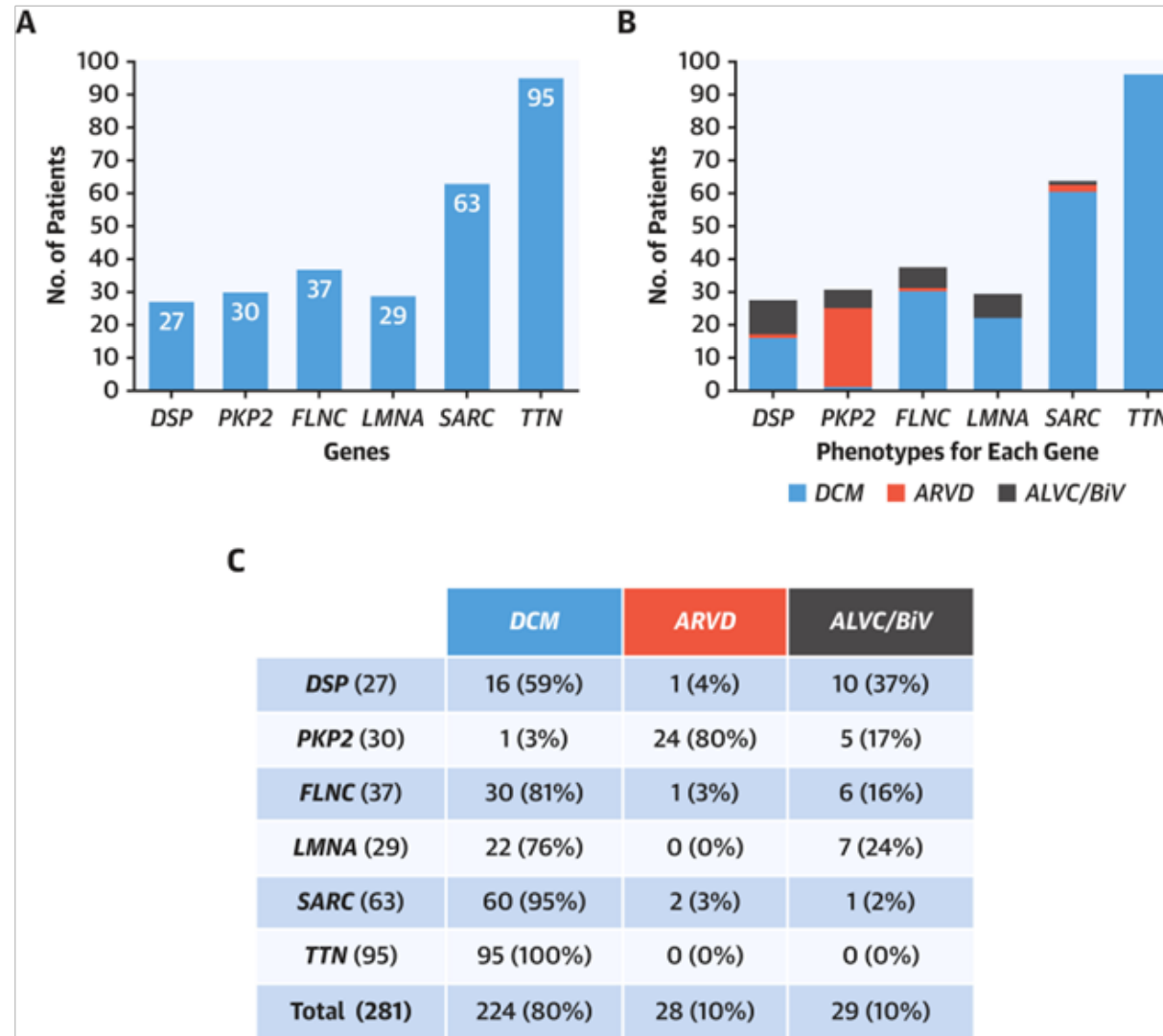
- ***TTN**tv*** (11-25%)
- ***LMNA*** (4-8%)
- **Sarcomero: *TNNT2*** (3%)
- ***FLNC*** (2-4%)
- ***RBM20*** (1-5%)
- ***SCN5A*** (2-3%)



McNally & Mestroni, *Circ Res.* 2017

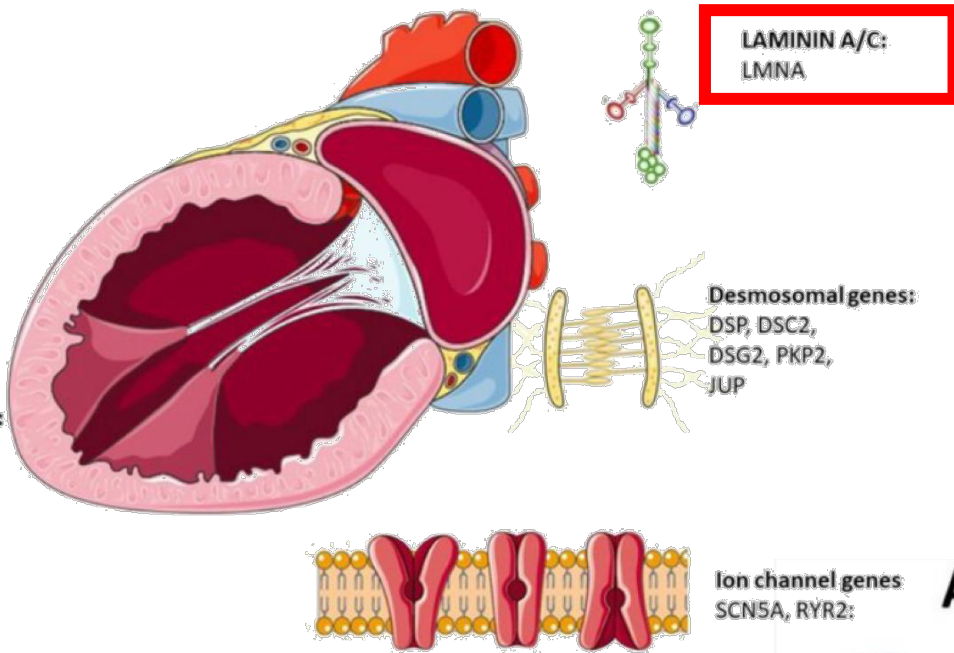
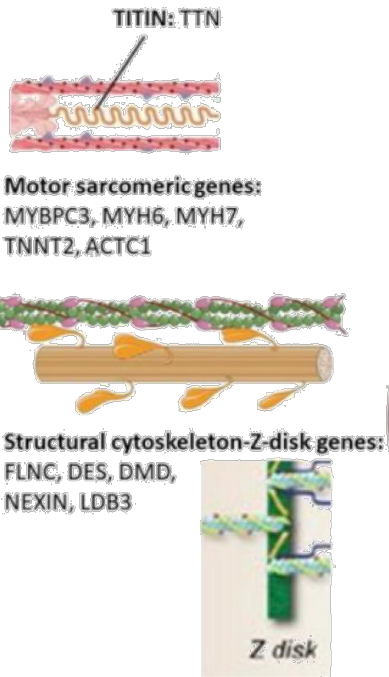
Genotype – centered approach

TTN and SARC variants were mostly associated with the DCM phenotype, whereas PKP2 variants were mostly associated with ARVC or ALVC/BiV. A more heterogeneous phenotypic distribution was detected for: DSP, LMNA, FLNC

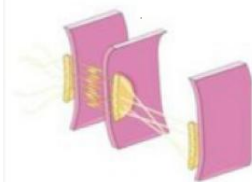


Notably, at the end of the follow-up period, 39 patients with DCM (17% of the DCM cohort) met the criteria for ALVC/BiV diagnosis. In particular, TTN (17%), DSP (15%), LMNA (21%), and FLNC (22%) carriers initially affected by DCM tended to convert their

DILATED CARDIOMYOPATHY

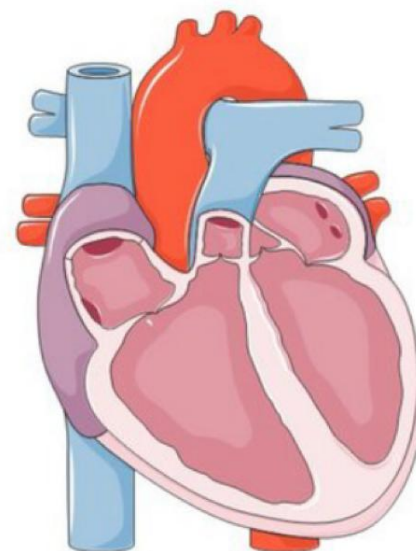


ARRHYTHMOGENIC CARDIOMYOPATHY



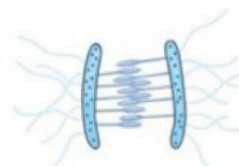
Desmosomal genes
Frequency 40-50% :

- JUP - Plakoglobin
- PKP2 - Plakophilin-2
- DSP - Desmoplakin
- DSG2 - Desmoglein-2
- DSC2 - Desmocollin-2



Non-desmosomal genes:
Frequency 20 – 30%

- RYR2 - Cardiac Ryanodine Receptor 2
- TGFB3 - Transforming growth factor β 3
- TMEM43 - Transmembrane Protein 43
- DES - Desmin
- PLN - Phospholamban
- TTN - Titin
- **LMNA - Lamin A/C**
- CTNNA3 - Alpha-T-catenin

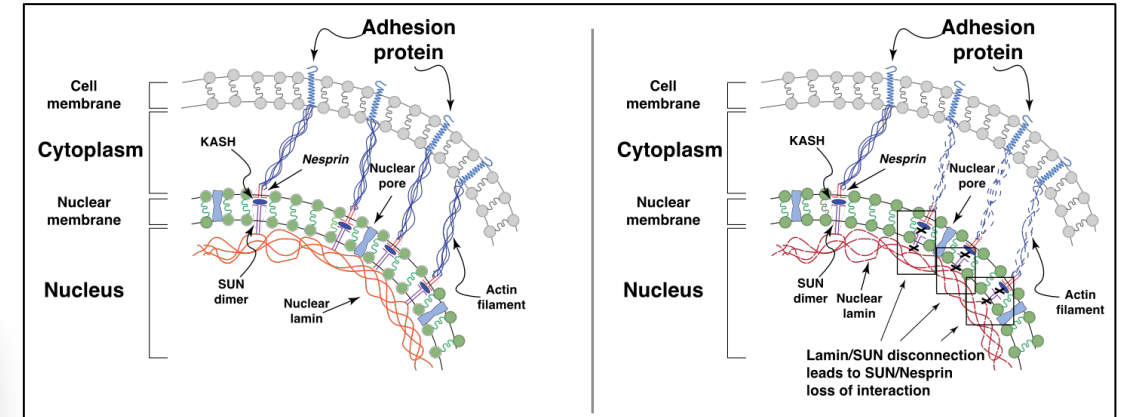
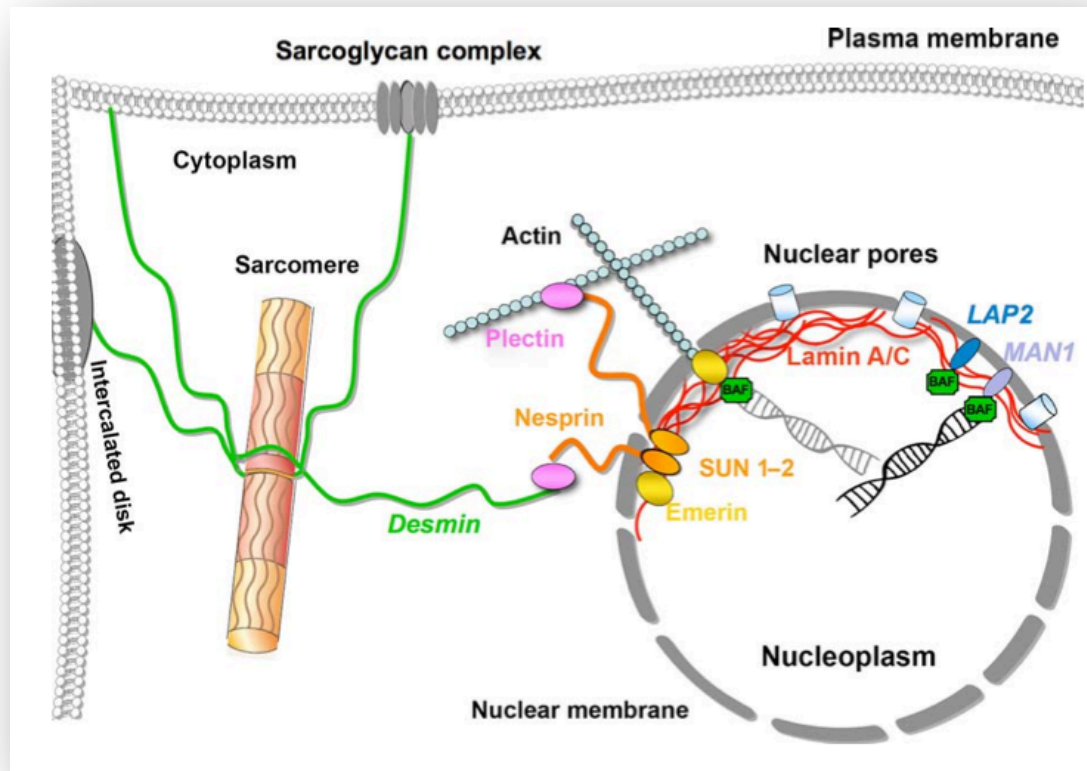


Agenda

- Background
- **Genetics**
- Phenotypic spectrum of Laminopathies
- Physiopathology
- Arrhythmic risk stratification

Lamin A/C

- 664 amino acids, 12 exons, 74139 Da
- High penetrance
- Missense and LoF



- Structural support for the core
- Maintenance of nuclear structural integrity and organization

Resistance to mechanical stress

DNA replication and repair processes

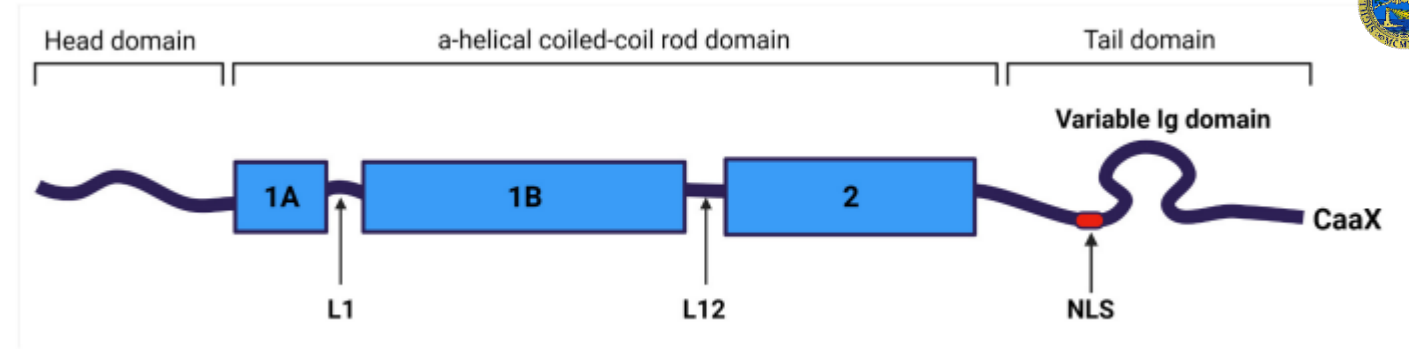
Regulation of gene expression and signaling

Cell cycle regulation, chromatin organization

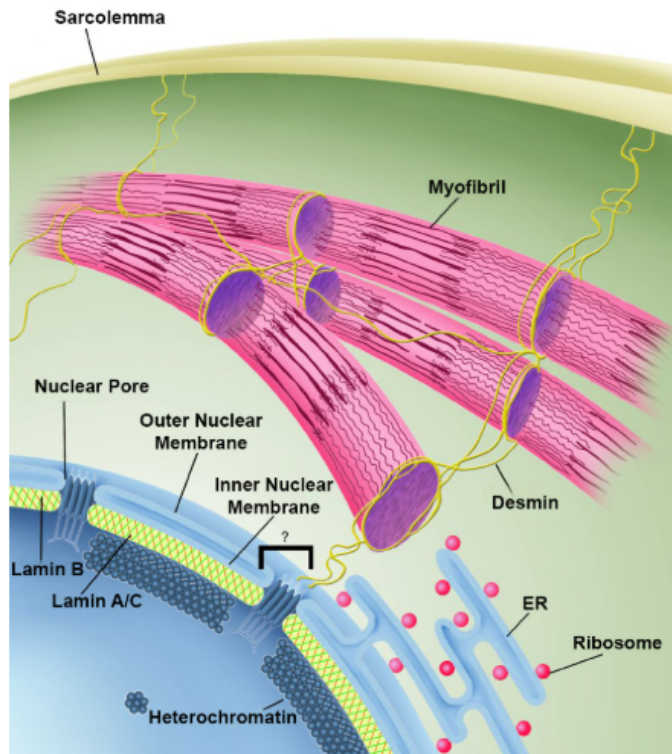
Cell differentiation and apoptosis

Taylor et al. JACC 2003; Carmosino M et al. Biol. Cell 2014; Maggi L et al. Int J Mol

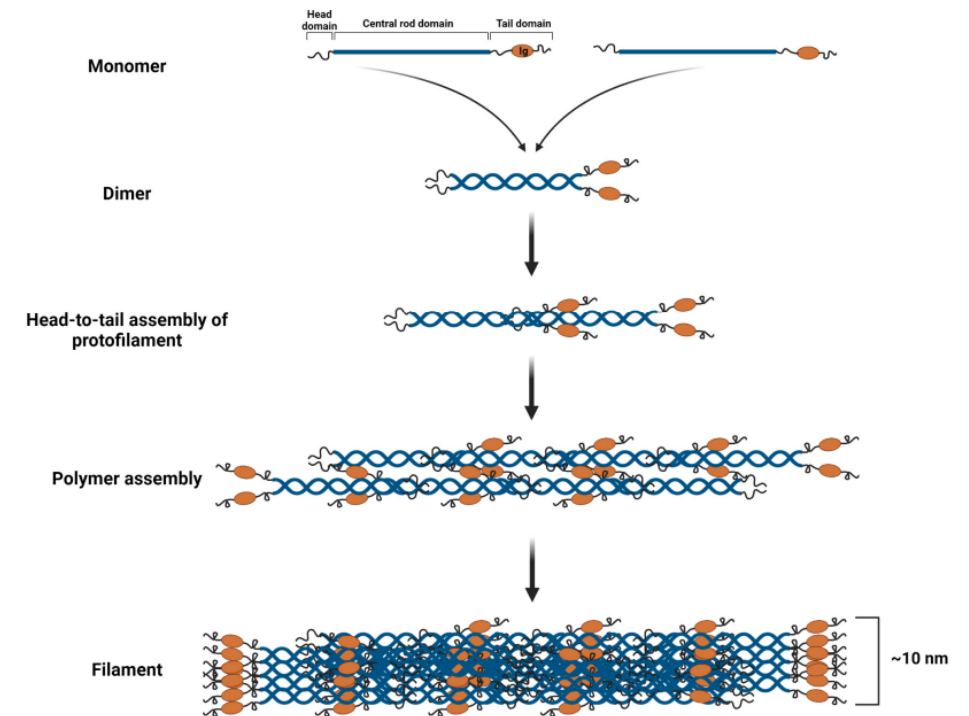
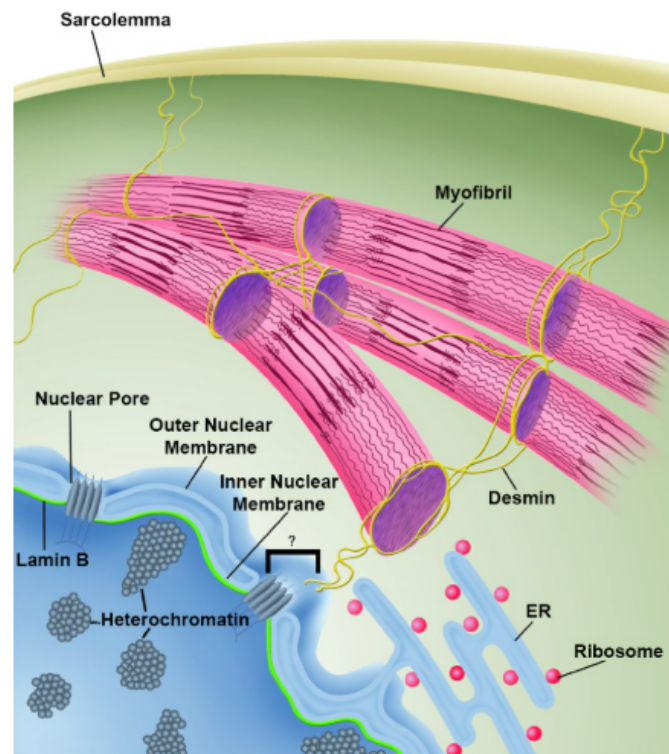
LMNA gene



A) Normal Myocyte

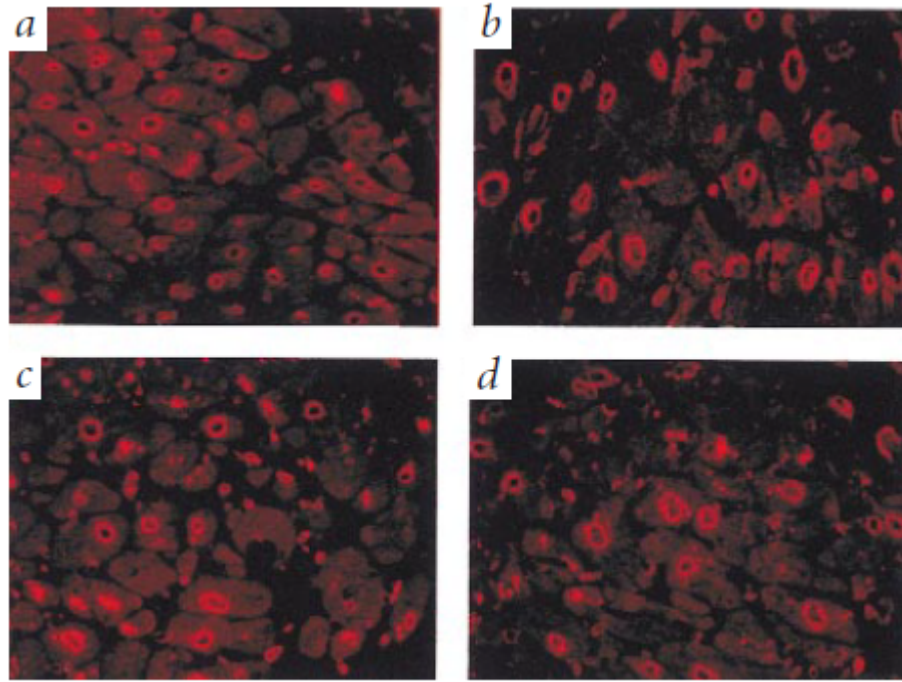


B) Myocyte Lacking Lamins A/C



Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy

Gisèle Bonne¹, Marina Raffaele Di Barletta^{1,3}, Shaïda Varnous¹, Henri-Marc Bécane², El-Hadi Hammouda², Luciano Merlini⁴, Francesco Muntoni⁵, Cheryl R. Greenberg⁶, Françoise Gary⁷, Jon-Andoni Urtizberea², Denis Duboc^{2,8}, Michel Fardeau^{1,2}, Daniela Toniolo³ & Ketty Schwartz¹

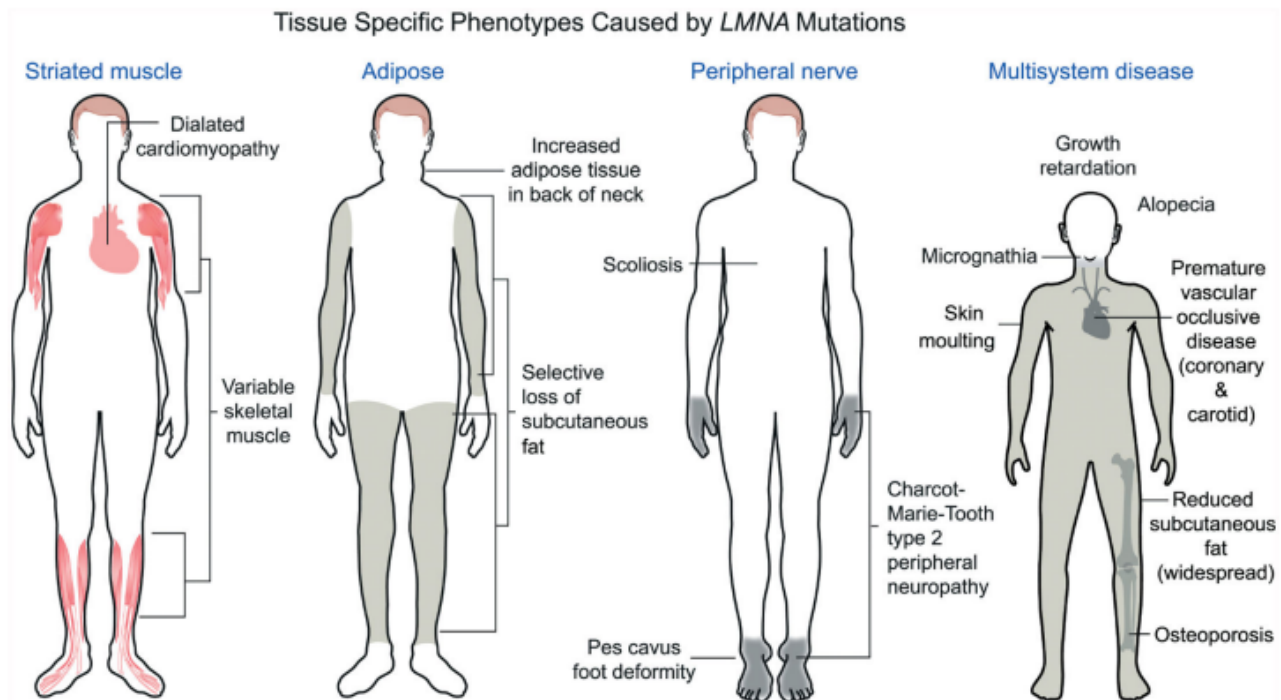
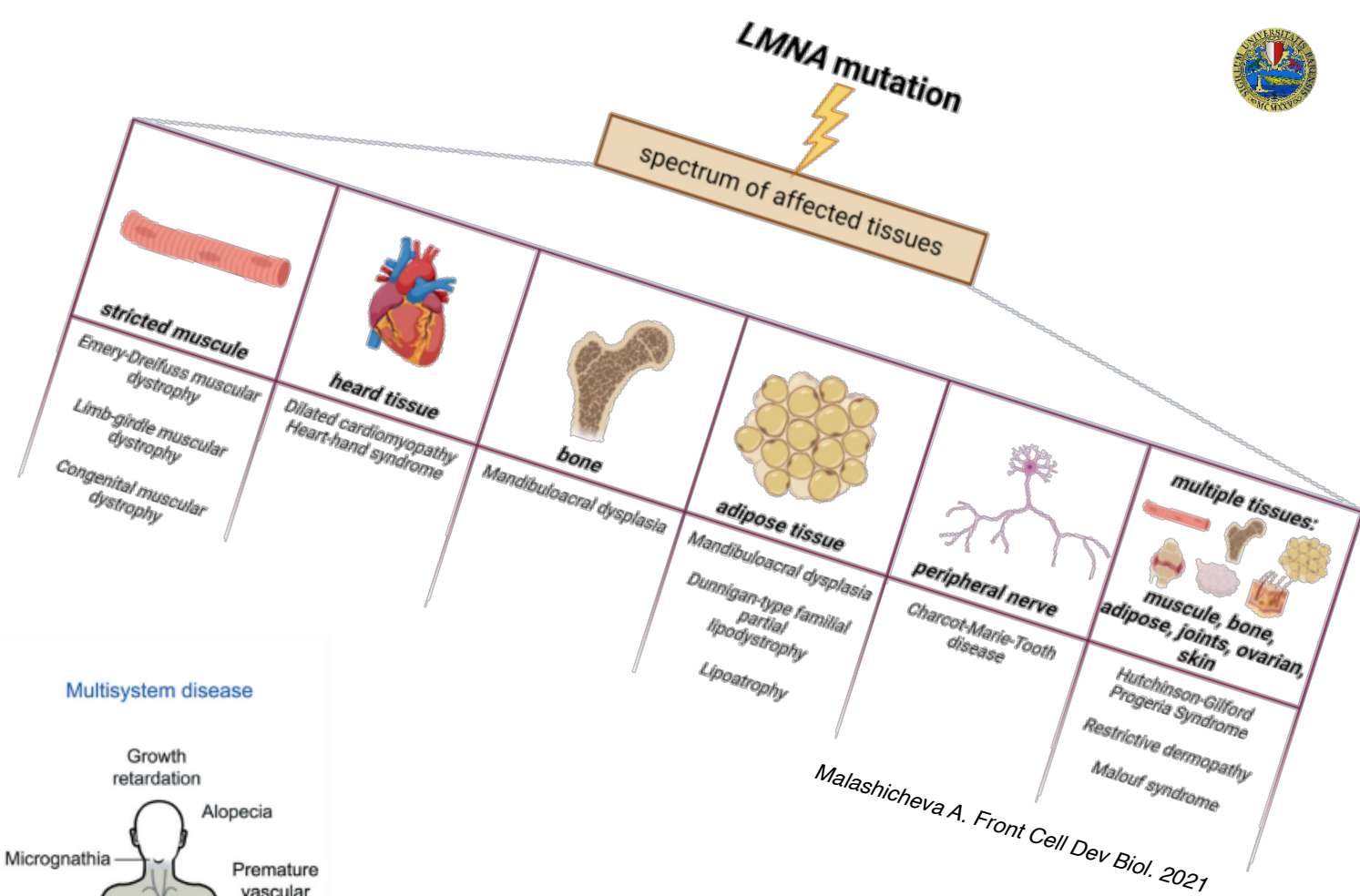


			R453W ↓			R527P ↓	L530P ↓	
EMD2	Lamin A/C	445	VDEEGKFVRLRNKSNEQ	//	WGCNLSLRTALINSTGEE	537		
EMD4, 6	Lamin A/C	445	VDEEGKFVRLRNKSNEQ	//	WGCNLSLPTALINSTGEE	537		
EMD7	Lamin A/C	445	VDEEGKFVRLRNKSNEQ	//	WGCNLSLRTAPINSTGEE	537		
Human	Lamin A/C	445	VDEEGKFVRLRNKSNEQ	//	WGCNLSLRTALINSTGEE	537		
Mouse	Lamin A/C	445	VDEEGKFVRLRNKSNEQ	//	WCGSSLRTALINSTGEE	537		
Rat	Lamin A	445	VDEEGKFVRLRNKSNEQ	//	WCGTSLRTALINSTGEE	537		
Chicken	Lamin A	446	VDLEGRFVRLRNKSNEQ	//	WGSGLSLRTALINSTGEE	538		
<i>Xenopus</i>	Lamin A	442	VDPEGKYVRLRNKSNEQ	//	WGTGDSIRTLTSSNEE	534		
<i>D. mel</i>	Dmo	478	LDPEGKFVRLFNKGSEEV	//	WVSADNTRTILNSEEAE	570		
Human	Lamin B2	374	IDLEGGKFVQLKNNSEKQ	//	WGTGESFRTVLVNADGEE	466		
Mouse	Lamin B2	451	VDPEGRFVRLKNNSEKQ	//	WGPGESFRTALVSADGEE	543		
Chicken	Lamin B2	462	IDLEGGKYVQLKNNSEKQ	//	WGTGNIIRTYLVNSDGEE	554		
<i>Xenopus</i>	Lamin LLII	485	IDLEGGKYVHLKNNSEKQ	//	WGTGNIIRTYLVNTEEEE	577		
Human	Lamin B1	446	IDVDGKFIRLKNTSEQDQ	//	WGTGEDVKVILKNSQGEE	538		
Mouse	Lamin B1	447	IDVDGKFIRLKNTSEQDQ	//	WGTGEDVKVILKNSQGEE	539		
Chicken	Lamin B1	445	IDVDGKFIRLKNTSEQDQ	//	WGTGEDVKVILKNSQGEE	537		
<i>Xenopus</i>	Lamin LLI	446	VDVDGKYIRLKNNSEKDH	//	WGTGNIIRTYLVNTEEEE	577		

Agenda

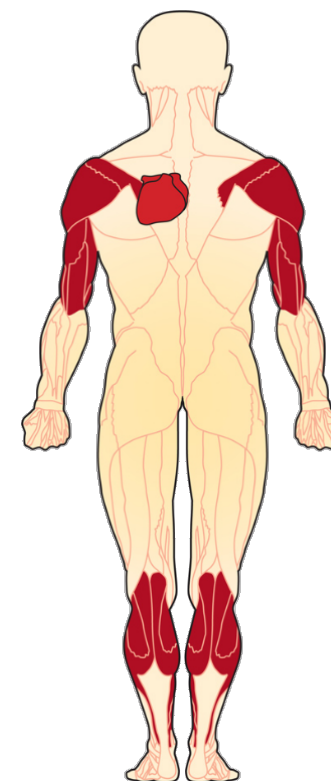
- Background
- Genetics
- Phenotypic spectrum of Laminopathies
- Physiopathology
- Arrhythmic risk stratification

Laminopathies spectrum



Worman HJ. J Pathol. 2012

Coinvolgimento Neurologico

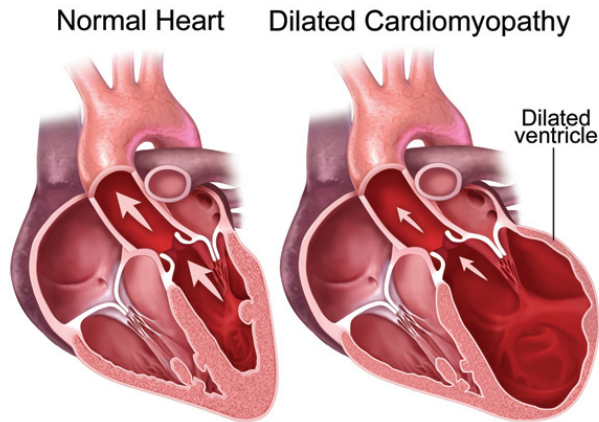


EDMD2



LGMD1B

Cardiolaminopathies



DILATED CARDIOMIOPATHIES – LMNA RELATED.

- More aggressive natural history compared with other forms of NICM
- Autosomal dominant (AD) inheritance, with variable penetrance and age-dependent expressivity



MYOPATY

CONDUCTION ABNORMALITIES

First-, second-, and third-degree atrioventricular (AV) block; right bundle branch block (RBBB), left bundle branch block (LBBB), and left anterior fascicular block (LAFB).

The most common and often the earliest cardiac manifestation.



SUPRAVENTRICULAR ARRHYTHMIAS

FA, FLUTTER.

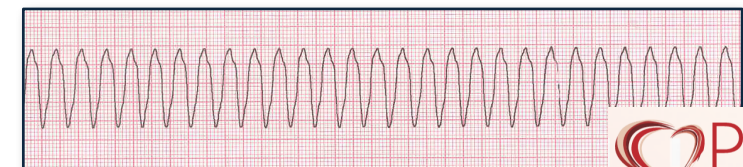
>> THROMBOEMBOLIC RISK



VENTRICULAR ARRHYTHMIAS

TV, TVS, FV.

>> SCD RISK.



Red Flags della cardiolaminopatia



- **Conduction disease:** **LMNA**
- **Supraventricular arrhythmias:** **SCN5A, LMNA**
- **Ventricular Arrhythmias/SCD:** **LMNA, RBM20, DSP, FLNC, SCN5A**
- **Muscle involvement/dystrophy:** **DMD, LMNA**
- **LVNC:** **TTN, MYH7**

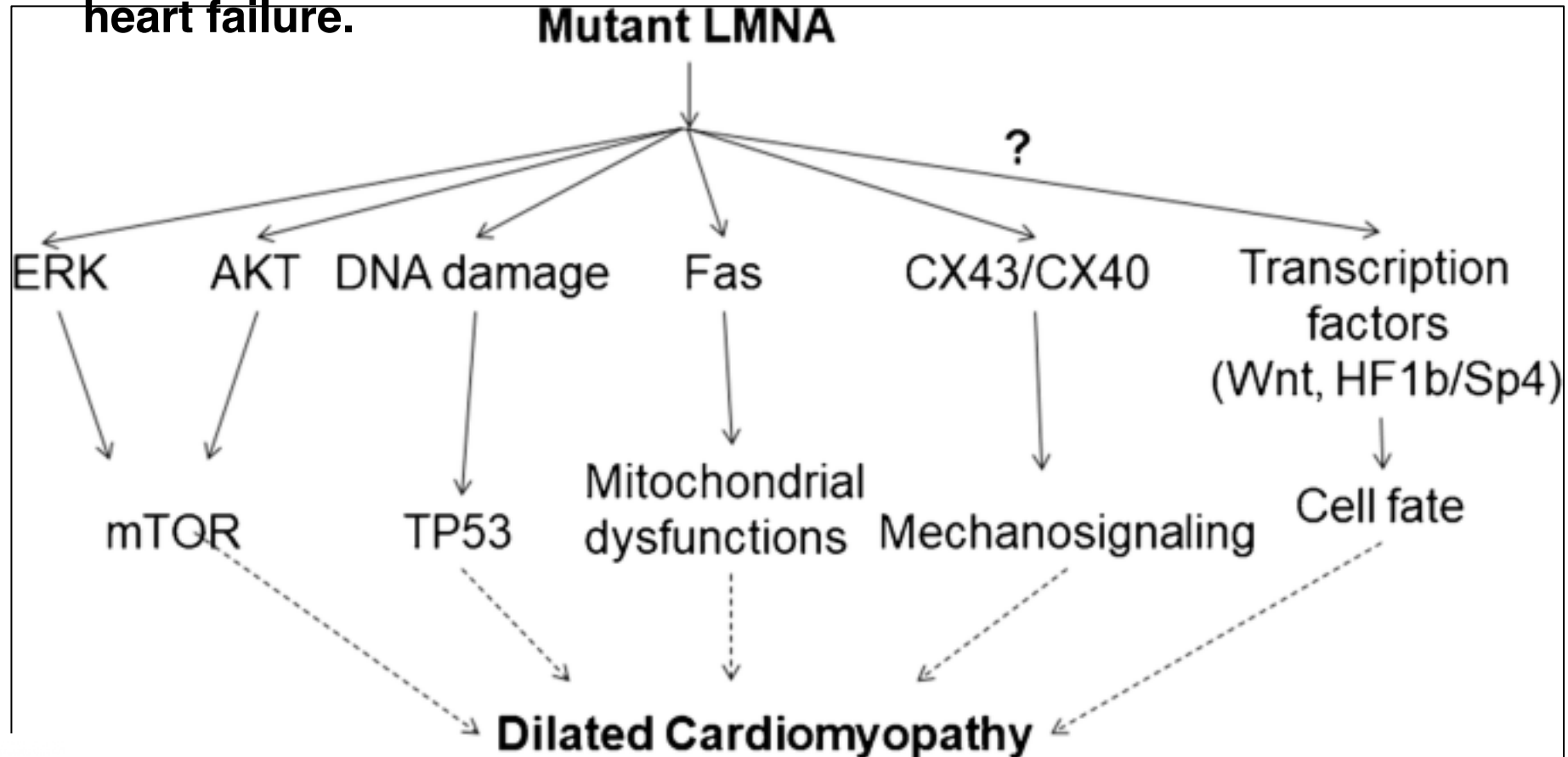


Agenda

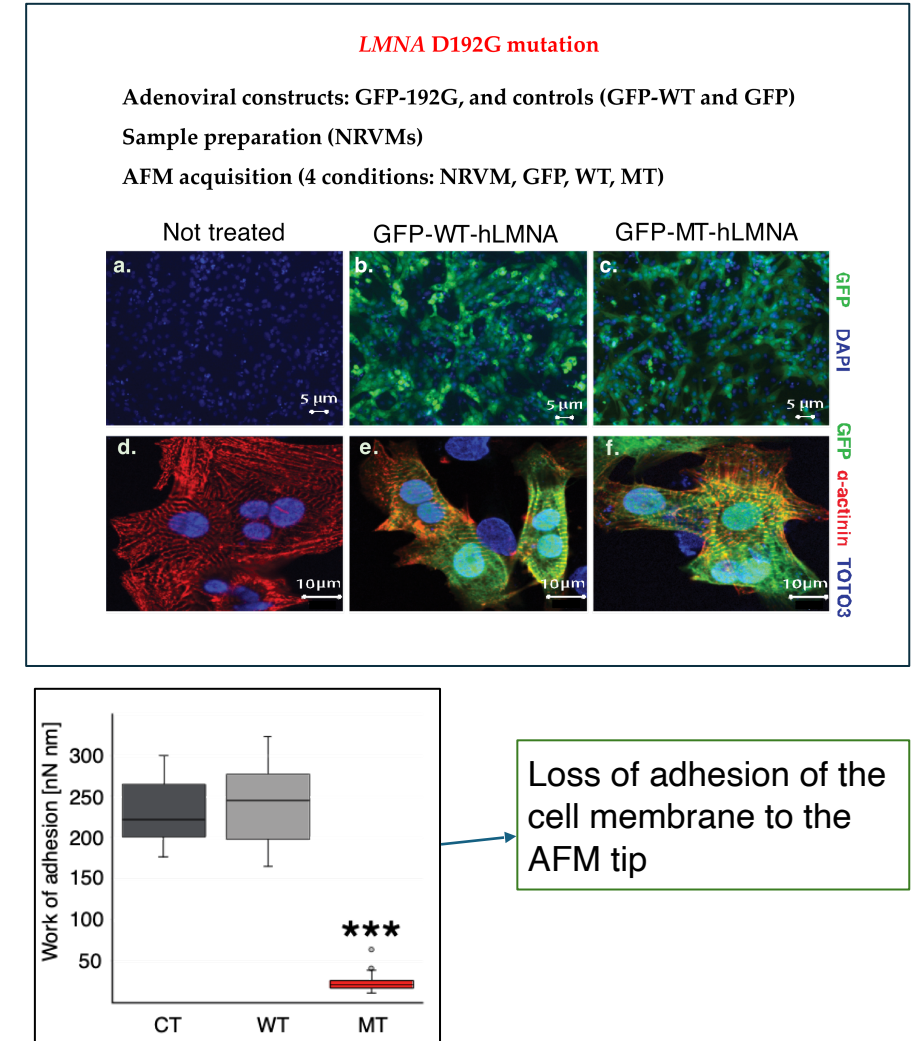
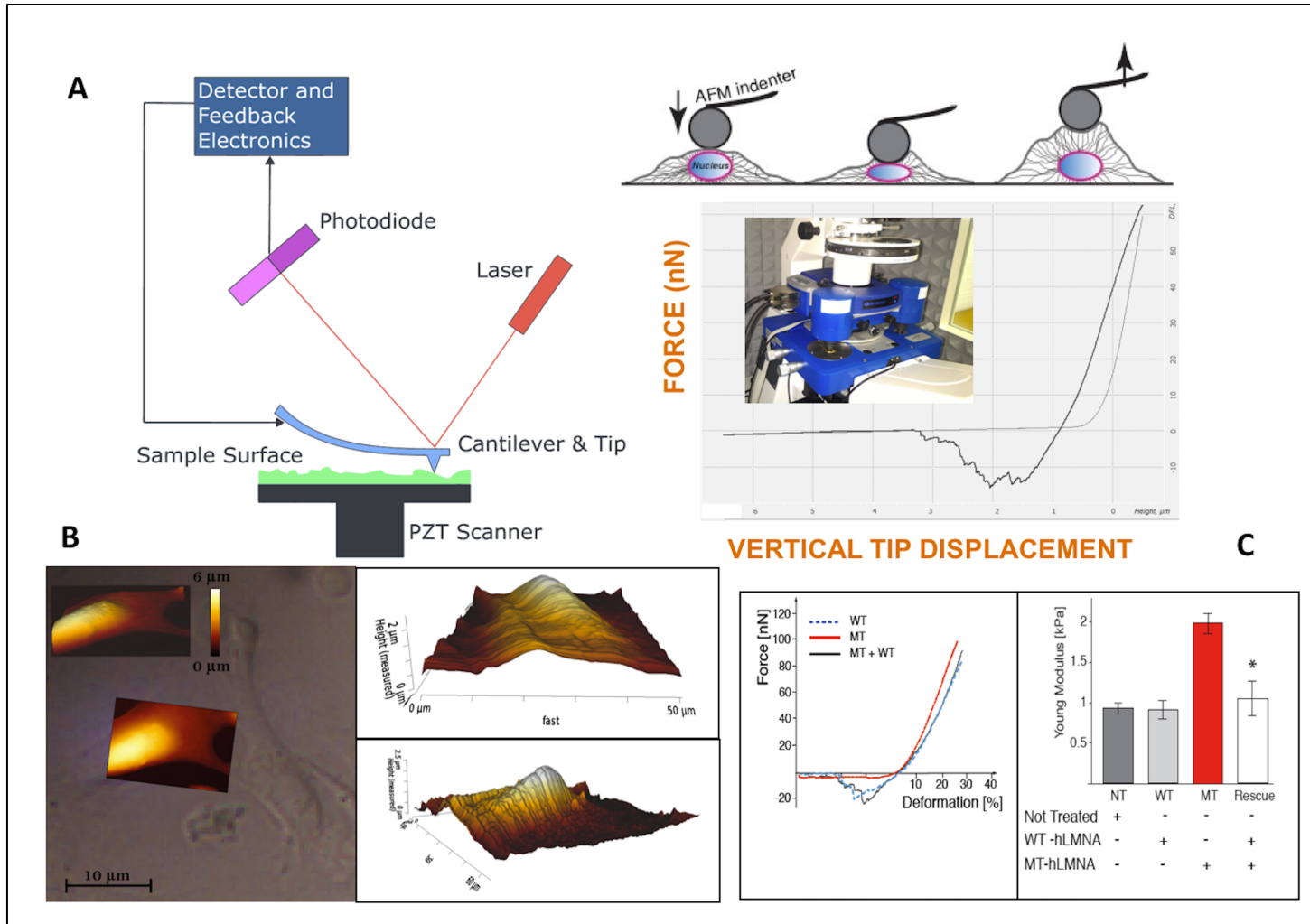
- Background
- Genetics
- Phenotypic spectrum of Laminopathies
- **Physiopathology**
- Arrhythmic risk stratification

LMNA

LMNA mutations cause cardiomyopathy through multiple mechanisms, including impaired mechanotransduction, nuclear dysfunction, DNA damage, apoptosis, and electrical remodeling, ultimately leading to fibrosis, arrhythmias, and heart failure.

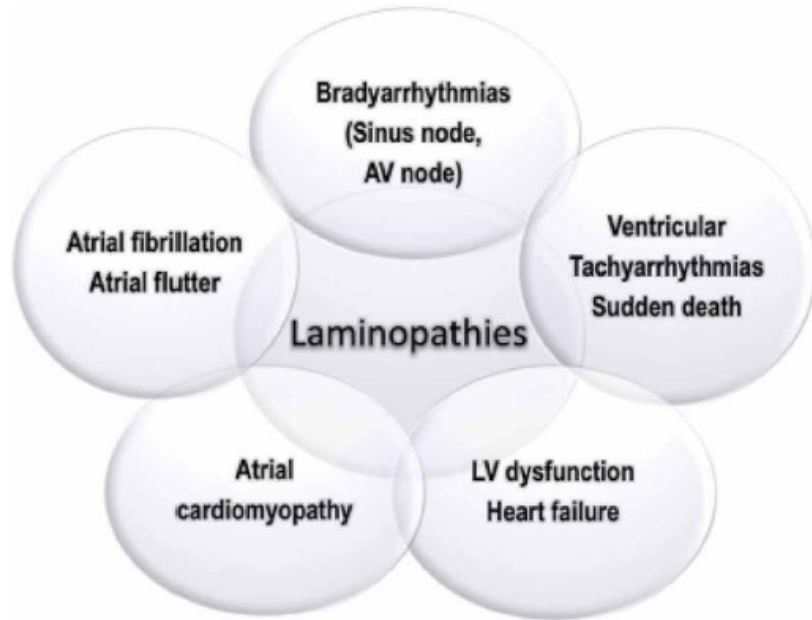


Altered biomechanics of *LMNA* mutant cardiomyocytes

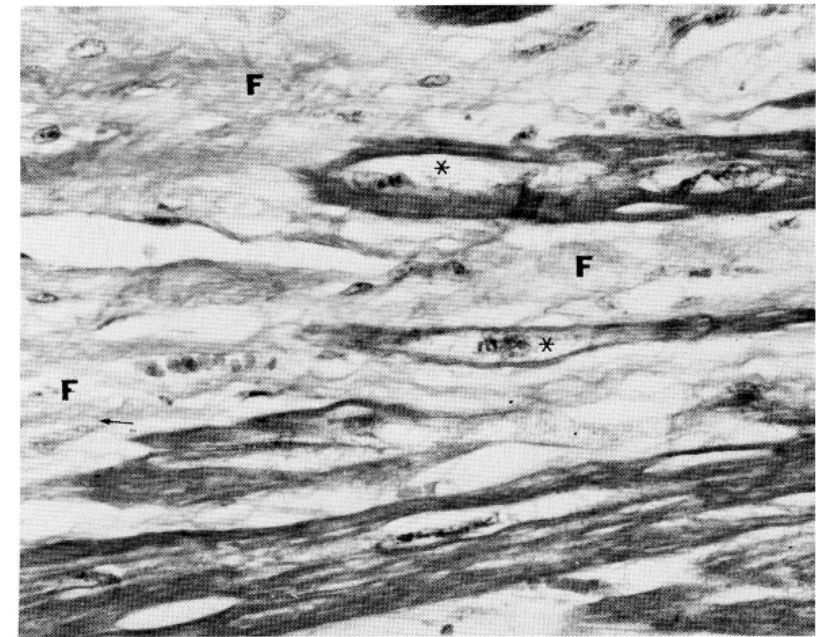


Lanzicher, et al., Nucleus 2015
Lanzicher, et al., Sci Rep 2015
Laurini et al., Cardio Res 2018

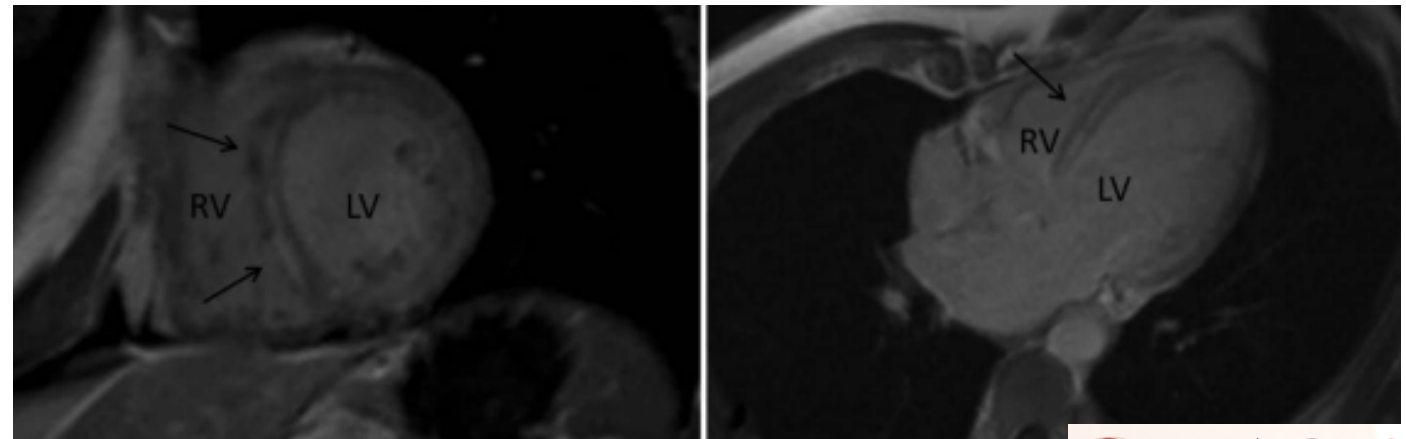
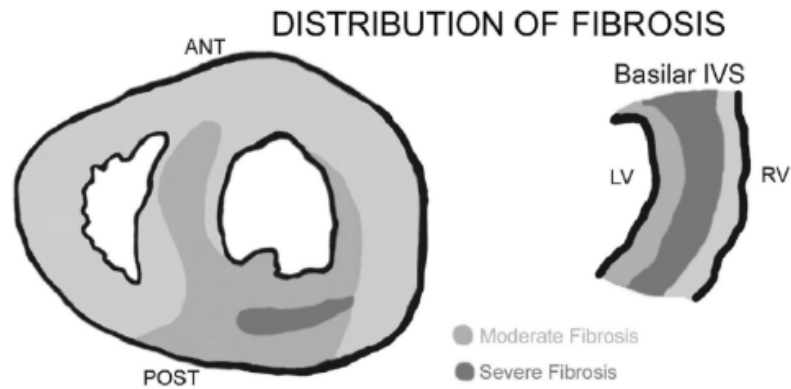
Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy



Boriani G. Nucleus. 2018

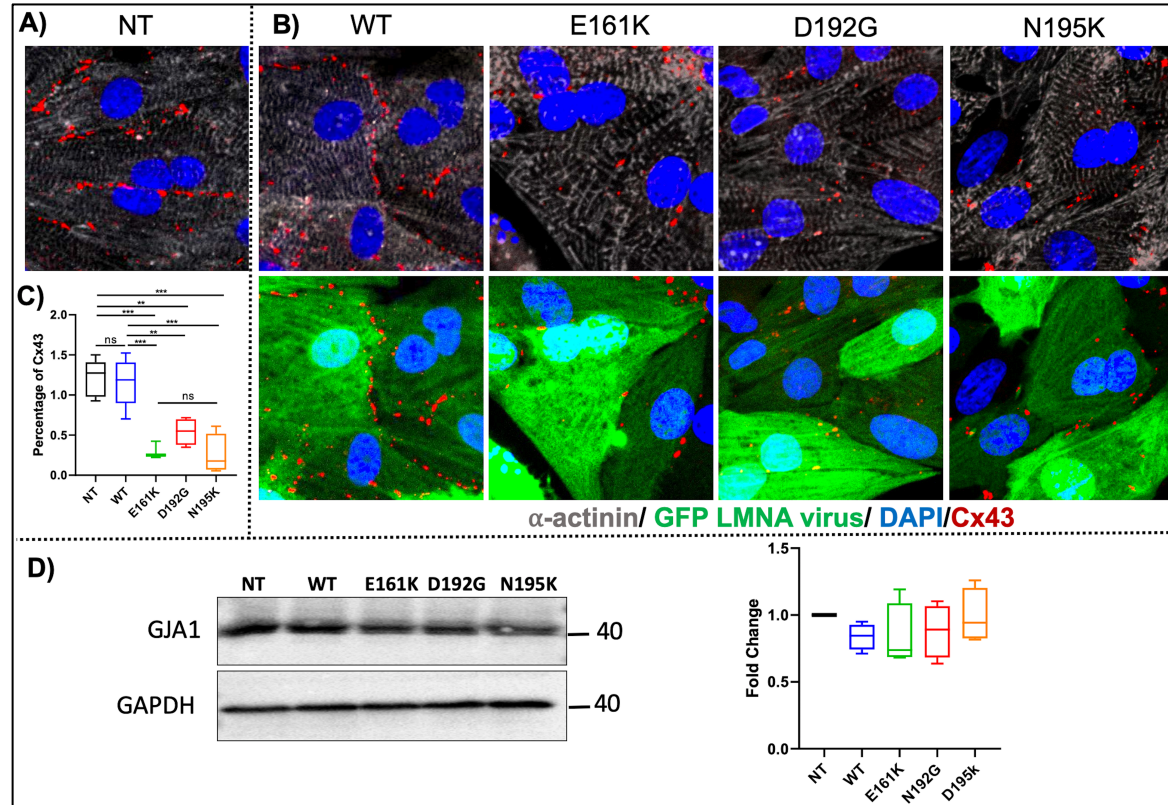


Graber HL. Circulation. 1986



Ollila L. Open Heart. 2017

LMNA: molecular mechanisms of arrhythmia



Altered hemichannels localization (Connexin 43) in mutant *LMNA*

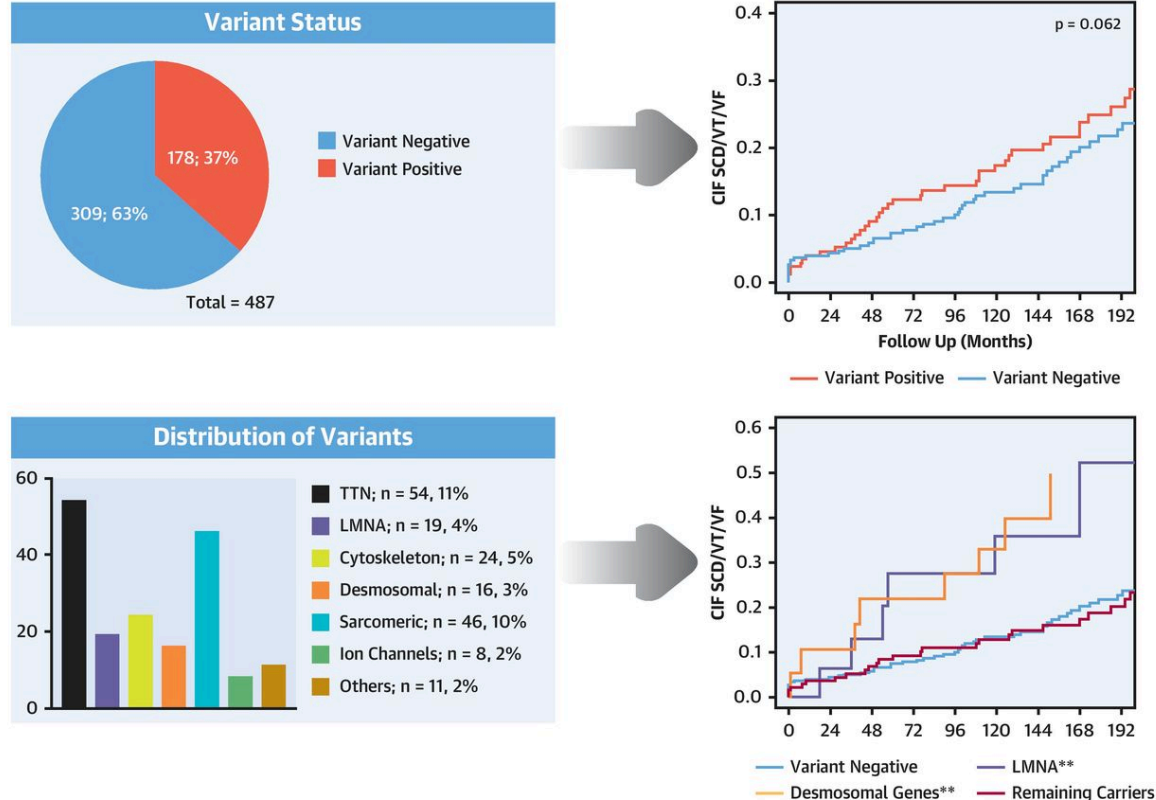
- Cx43 localization is defective in LMNA mutant cardiomyocytes
- Microtubules network and actin network (Cx43 trafficking machinery, “zip code”) disrupted

Agenda

- Background
- Genetics
- Phenotypic spectrum of Laminopathies
- Physiopathology
- Arrhythmic risk stratification

LMNA e geni desmosomiali che causano ACM

CENTRAL ILLUSTRATION: Effect of Genotype on Outcome in Dilated Cardiomyopathy



Gigli, M. et al. J Am Coll Cardiol. 2019;74(11):1480-90.

Positive variant carriers

➤ Trend toward worse SCD/VA outcome

LMNA gene and Desmosome variant carriers

➤ Highest SCD/VA risk

Circulation

ORIGINAL RESEARCH ARTICLE

Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies

444 pts
5-year risk of **MVA** $\geq 10\%$



Karim Wahbi, MD, PhD
et al

Circulation Wahbi 2019

RISK FACTORS
TVNS
MUTATIONS NOT MISSENSE
MALE
FEVS $\leq 45\%$
AV CONDUCTION DISORDERS



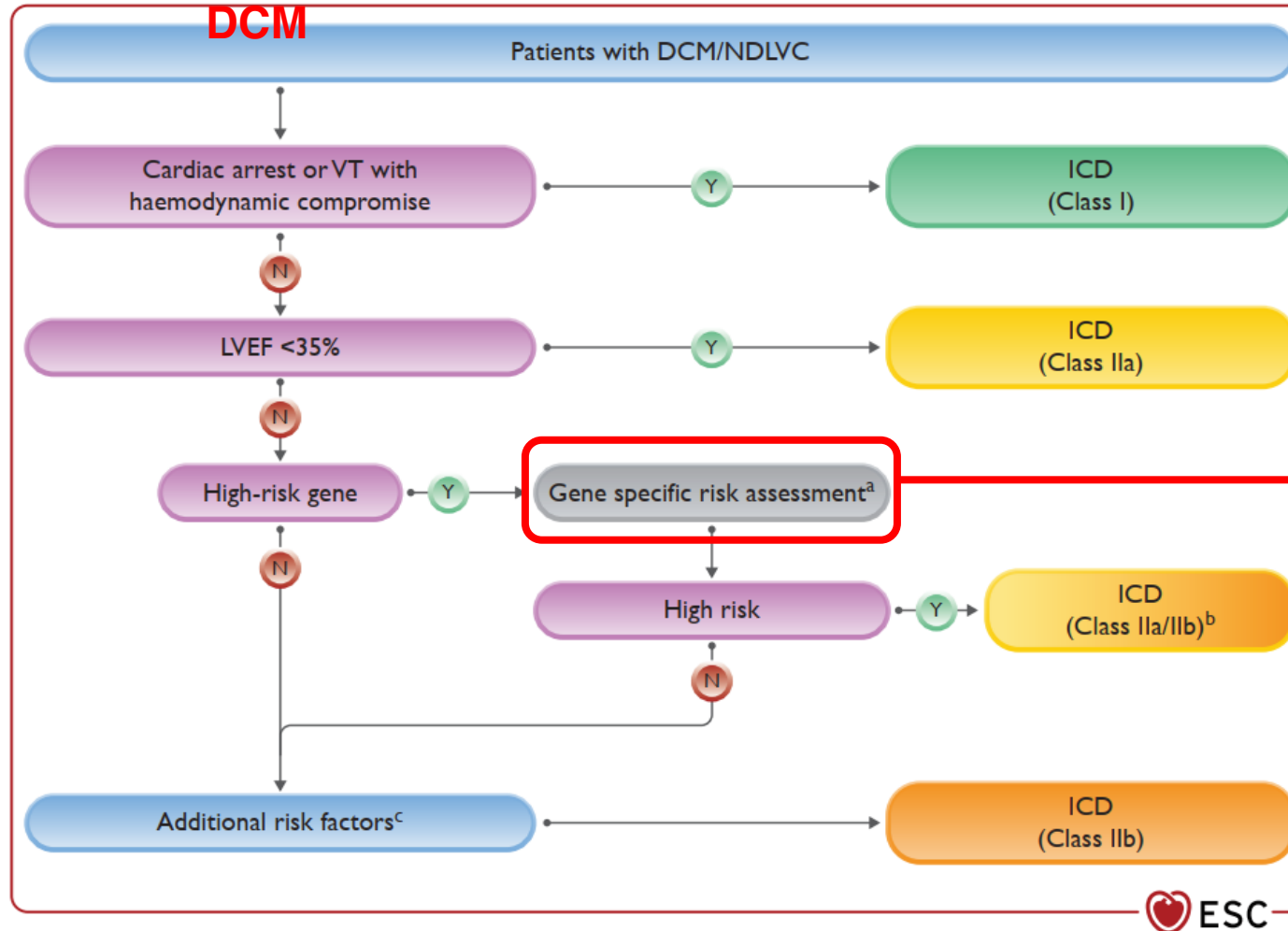
Risk calculator (<https://lmna-riskvta.fr/>) to predict the risk of ventricular arrhythmias potentially fatal

LMNA-risk VTA calculator

Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies

2023 ESC Guidelines for the management of cardiomyopathies

PREVENTION of UNEXPECTED DEATH in DCM



LMNA
 FLNC truncating variant
 TMEM43
 PLN
 DSP
 RBM20

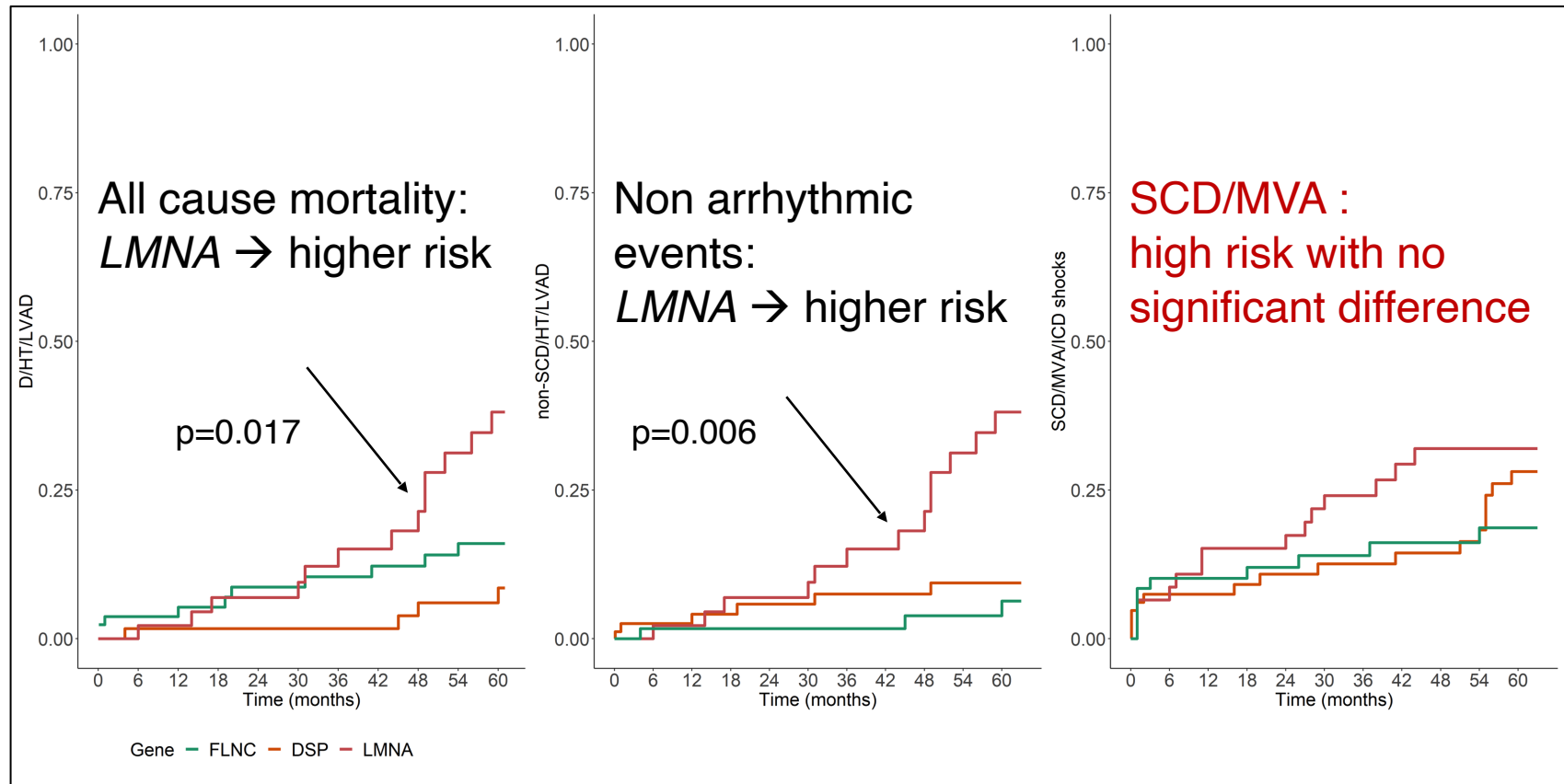
LMNA-risk VTA calculator
 Risk Prediction Score for Life-Threatening Ventricular
 Tachyarrhythmias in Laminopathies

Arbello et al, European Heart Journal (2023) 00, 1–124
<https://doi.org/10.1093/eurheartj/ehad194>

ACM outcome:
comparison of *FLNC*tv with *LMNA* and *DSP*

Study cohorts:

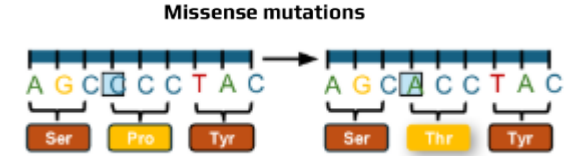
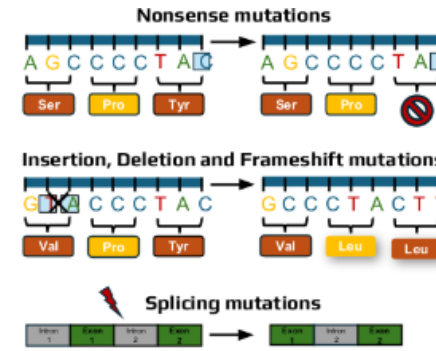
*FLNC*tv 85 cases
LMNA 46 cases
DSP 60 cases



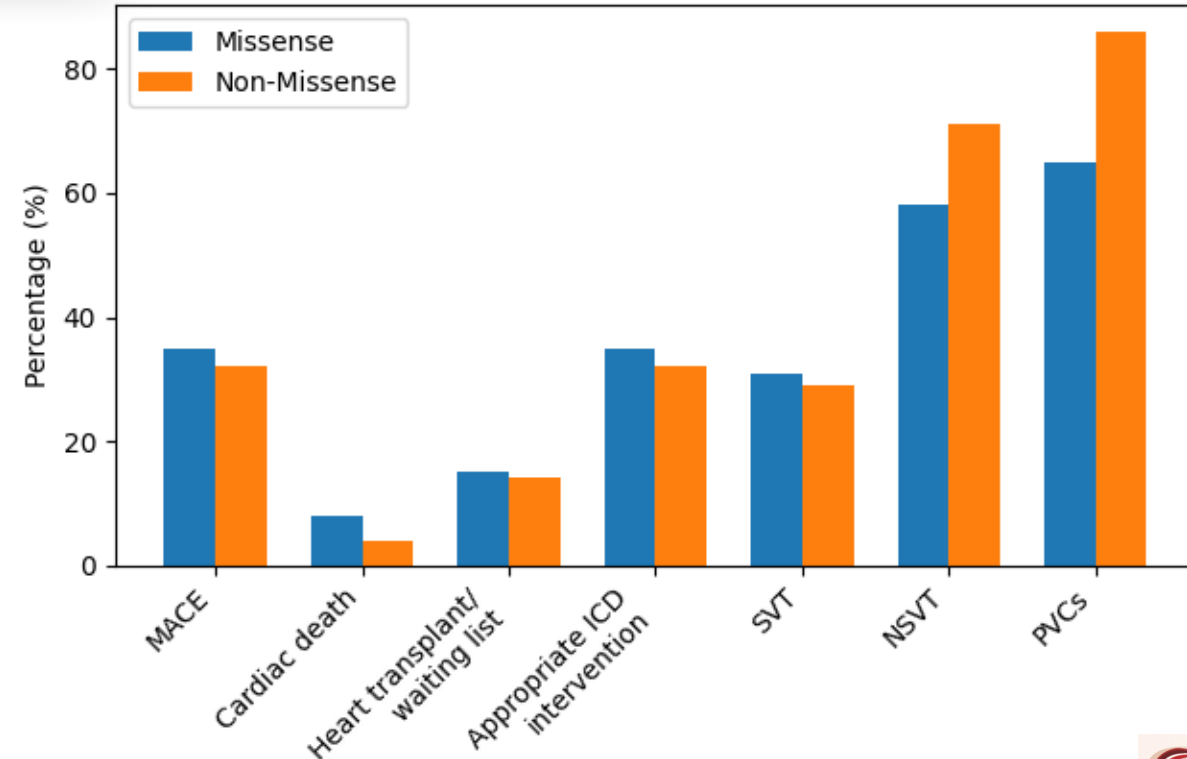
Article

Missense and Non-Missense Lamin A/C Gene Mutations Are Similarly Associated with Major Arrhythmic Cardiac Events: A 20-Year Single-Centre Experience

Cinzia Forleo ^{1,*}, Maria Cristina Carella ^{1,2}, Paolo Basile ^{1,2}, Eugenio Carulli ^{1,2}, Michele Luca Dadamo ¹, Francesca Amati ¹, Francesco Loizzi ¹, Sandro Sorrentino ¹, Ilaria Dentamaro ¹, Marco Maria Dicorato ¹, Stefano Ricci ¹, Rosanna Bagnulo ³, Matteo Iacoviello ³, Vincenzo Ezio Santobuono ¹, Carlo Caiati ¹, Martino Pepe ¹, Jean-Francois Desaphy ⁴, Marco Matteo Ciccone ¹, Nicoletta Resta ^{3,†} and Andrea Igoen Guaricci ^{1,†}



Comparison of cardiac manifestations related to non-missense vs. missense LMNA mutations

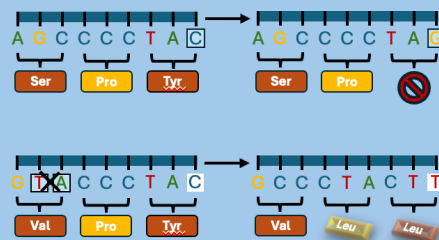


Cardiovascular prognostic impact of missense vs nonmissense lamin A/C variants: A systematic review and meta-analysis ^e

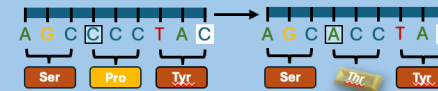
Andrea Igoren Guaricci, MD, PhD, FESC,^{1,23} Andrea Faggiano, MD,^{2,3,23} Karim Wahbi, MD, PhD,^{4,5} Roberto Barriales-Villa, MD, PhD,⁶ Maria Cristina Carella, MD, PhD,¹ Stefano Carugo, MD,^{2,3,7} Alex Hørby Christensen, MD, PhD,⁸ Cinzia Forleo, MD, PhD,¹ Elisa Gherbesi, MD,^{2,3} Kristina H. Haugaa, MD, PhD,^{9,10,11} Marco Merlo, MD,¹² José M. Larranaga-Moreira, MD,⁶ Saima Mushtaq,¹³ Valeria Novelli, MD, PhD,¹⁴ Giovanni Peretto, MD,^{15,16} Nicoletta Resta, MD, PhD,¹⁷ Christine Rootwelt-Norberg, MD, PhD,^{18,19} Rabah Ben Yaou, MD,^{20,21} Marco Matteo Ciccone,¹ Gianfranco Sinagra, MD,¹² Gianluca Pontone, MD, PhD^{13,22}

GENETIC TESTING

Non-missense mutations (N=849)



Missense mutations (N=969)

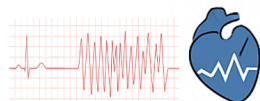


OUTCOME



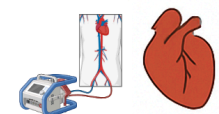
Main CV outcome $\downarrow$ 30.5% vs 21.3%

OR:2.22, p <0.001
Data from 12 studies and 1818 patients



Arrhythmic outcome $\uparrow$ 25.5% vs 18.9%

OR:2.37, p <0.001
Data from 10 studies and 1689 patients



HF-related outcome $\uparrow$ 18.2% vs 23.9%

OR:0.96, p =0.801
Data from 5 studies and 1044 patients with single-study effect

Arthur A.M. Wilde

Guaricci AI, et al Heart Rhythm 2025

Laminopathies: natural history and risk prediction of heart failure

Philippe Charron ^{1,2,3,*†}, Julie Proukhnitzky ^{1,2,3,†}, Rabah Ben Yaou^{4,5}, Pascale Richard⁶, Mohamed Dembélé⁷, Mario Urtis^{8,†}, Thomas Gossios⁹, Saurabh Kumar¹⁰, Konstantinos Savvatis ^{9,11}, Tanya Stojkovic⁴, Frédéric Anselme¹², Philippe Maury¹³, Estelle Gandjbakhch ^{1,2,3,†}, Raphaël Martins¹⁴, Frédéric Sacher ^{15,†}, Jean-Noel Trochu ^{16,†}, Stéphanie Rouanet³, Julie Lejeune⁷, Ghassan Moubarak ¹⁷, Abdallah Fayssol¹⁸, Eloi Marijon^{19,20}, Pascal Laforêt¹⁸, Anthony Béhin⁴, Sarah Leonard-Louis⁴, Guilhem Sole²¹, Fabien Labombarda²², Corinne Metay^{5,6}, Susana Quijano-Roy²³, Ivana Dabaj ²⁴, Didier Klug²⁵, Gilbert Habib ²⁶, Marie-Christine Vantyghem²⁷, Philippe Chevalier ^{28,†}, Emmanuelle Salort-Campana²⁹, Jean-Marc Sellal ³⁰, Xavier Waintraub ^{2,3,†}, Katja Zeppenfeld ³¹, Ahmad S. Amin ^{32,†}, Daria R. Kramarenko^{32,†}, Yigal M. Pinto^{32,†}, Andrew Landstrom ³³, Alessandra Serio^{8,†}, Cathy Chikhaoui^{4,5}, Nicolas Combes ³⁴, Christine Barnerias³⁵, Henri-Marc Bécane⁴, Eric Bieth³⁶, Franck Boccara ³⁷, Damien Bonnet ^{38,†}, Françoise Bouhour³⁹, Anne-Claire Brehin⁴⁰, Pascal Cintas⁴¹, François Roubille ⁴², Nicolas Lamblin²⁵, Pascal de Groote²⁵, Pierre-François Winum⁴³, Nicolas Piriou^{16,†}, Patricia Réant⁴⁴, Annachiara De Sandre-Giovannoli⁴⁵, Marion Masingue⁴, Isabelle Desguerre³⁵, Julien Durigneux⁴⁶, Andoni Echaniz-Laguna⁴⁷, Romain Eschalié ⁴⁸, Ana Ferreira^{4,5}, Mélanie Fradin⁴⁹, Bénédicte Gaborit⁵⁰, Arnaud Gay⁵¹, Albert Hagège ^{19,20,†}, Arnaud Isapof⁵², Isabelle Jeru⁵³, Emmanuelle Lagrue⁵⁴, Vincent Laugel⁵⁵, Arnaud Lazarus¹⁷, France Leturcq⁵⁶, Armelle Magot⁵⁷, Véronique Manel⁵⁸, Sandra Mercier⁵⁹, Christophe Meune ⁶⁰, Maud Michaud⁶¹, Marie-Christine Minot-Myhié⁶², Aleksandra Nadaj-Pakleza⁶³, Yann Péréon⁵⁷, Florence Petit⁶⁴, Julien Praline⁶⁵, Anne Rollin¹³, Catherine Sarret⁶⁶, Frederic Taithe⁶⁷, Céline Tard⁶⁸, Vincent Tiffreau⁶⁹, Laurent Fauchier⁷⁰, Camille Vatier ^{71,72}, Ulrike Walther-Louvier⁷³, Benjamin Schurr⁷⁴, Pierre Bobin⁶, Mohamed El Hachmi^{75,76}, Clarisse Billon⁷⁵, Bertrand Fontaine^{4,5}, Corinne Vigouroux^{71,72}, Neal K. Lakdawala ⁷⁷, Eloisa Arbustini ^{8,†}, Perry Elliott ⁹, Gisèle Bonne⁵, and Karim Wahbi ^{20,74,*}

• HF-MACE incidence: 9.7% at 5 years, 12.3% at 10 years

• Lifetime incidence: 17% by age 50, 45% by age 70

• Nearly one in two LMNA patients experiences a major HF event during lifetime

Take-home message:

Heart failure progression is a major determinant of prognosis in laminopathies.

Four Independent Predictors of HF-MACE

Male sex (HR 1.86)

LVEF <50% (HR 2.18)

Missense head/rod variants (HR 2.91)

Complete LBBB (HR 2.99)

Missense variants in **exons 1–6** emerged as the **strongest** genetic predictor of **HF progression**.

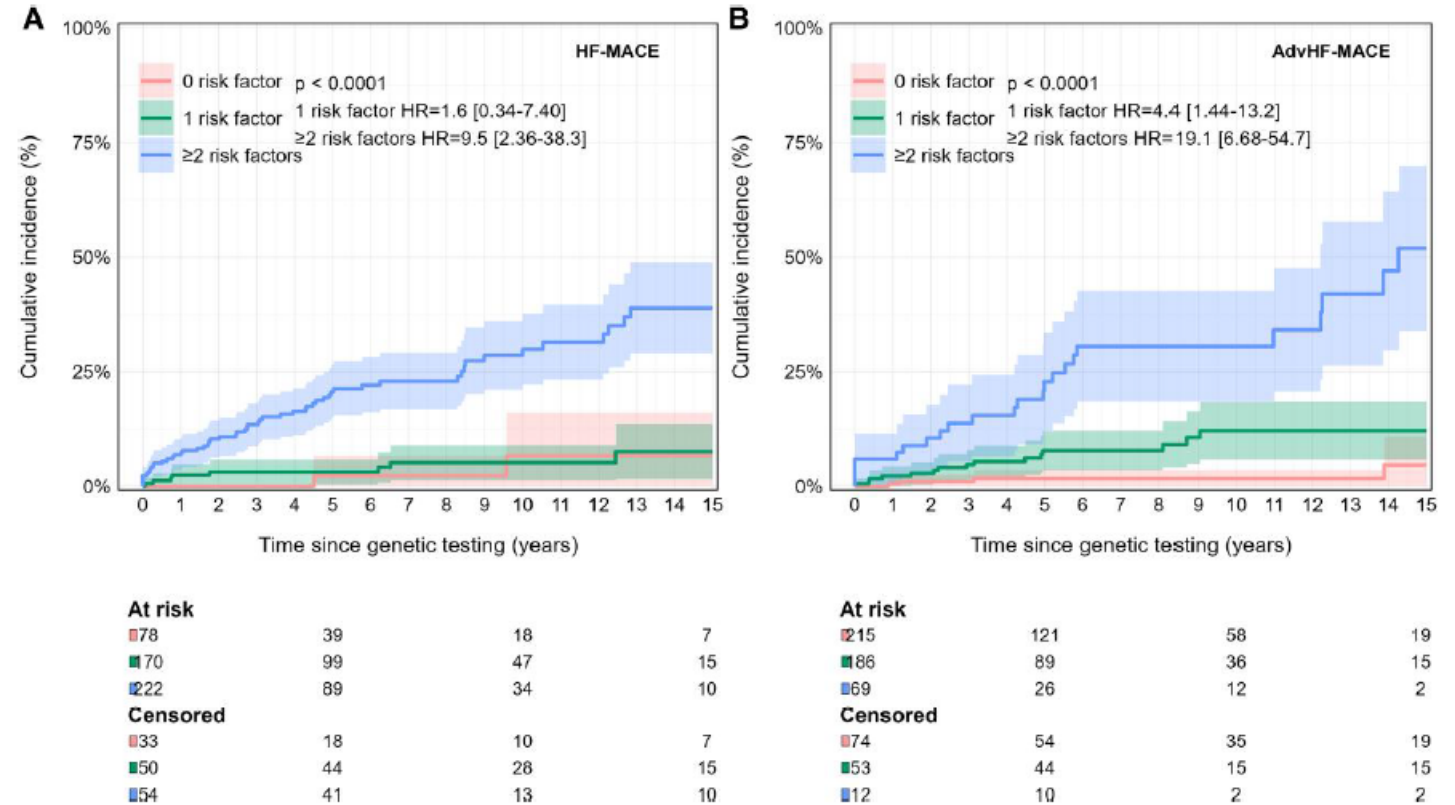
LMNA-HF Risk Score

0 RF → 1.5% HF-MACE at 5 years

1 RF → 5% HF-MACE at 5 years

≥2 RF → 22% HF-MACE at 5 years

LVEF <30%: 50% HF at 1 year, 72% at 5 years



Early referral to advanced HF and transplant programs is recommended.

**ESC**European Heart Journal (2026) 00, 1–14
<https://doi.org/10.1093/eurheartj/ehag104>**CLINICAL RESEARCH***Heart failure and cardiomyopathies*

Laminopathies: natural history and risk prediction of heart failure

Arrhythmic risk: NSVT, truncating variants, LVEF

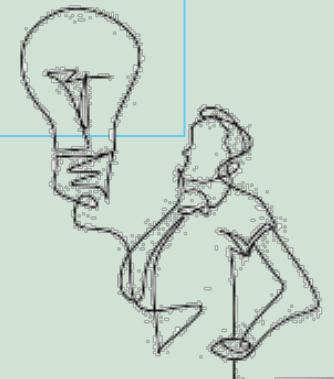
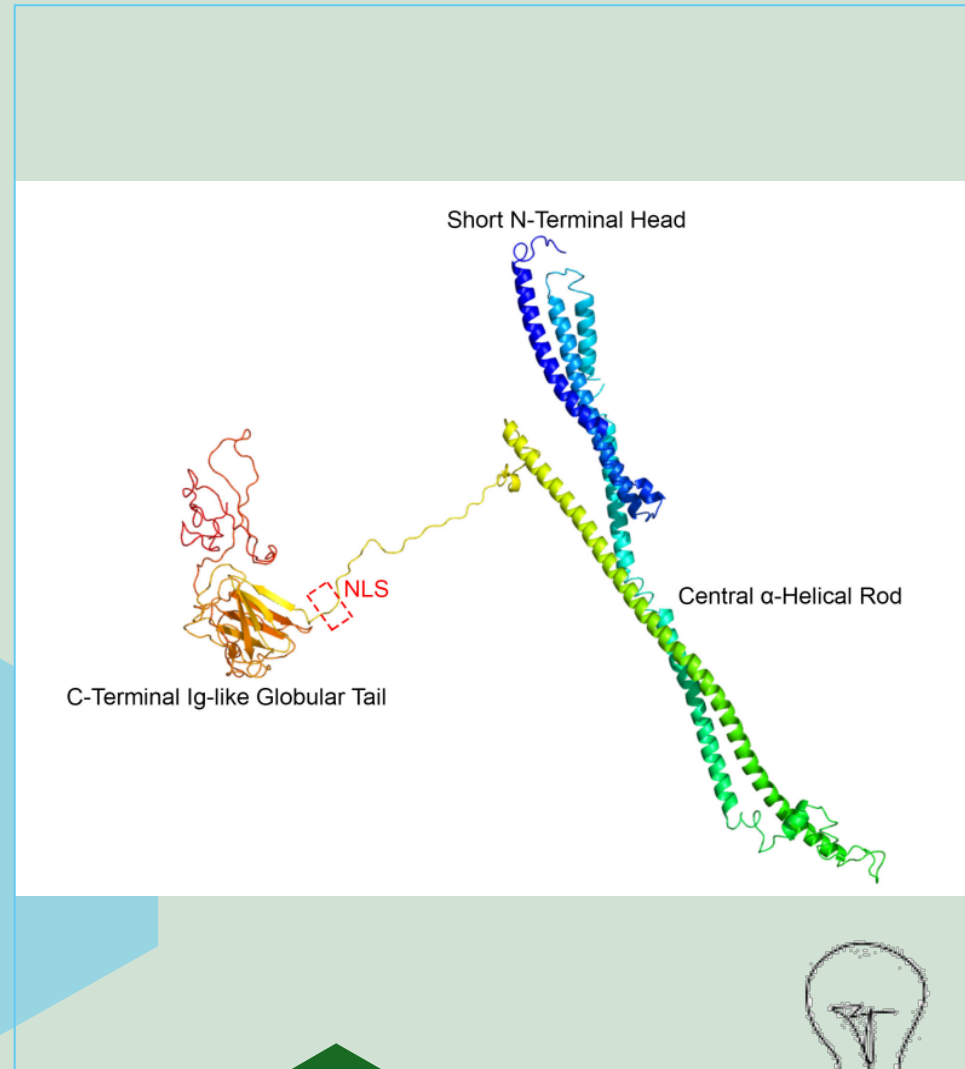
Heart failure risk: LVEF<50%, LBBB, head/rod missense variants

LMNA-HF score complements LMNA-VTA score



LMNA-related Cardiomyopathy Study

LAMIN-CarMyo
Study



yo Study

**Approximately 500
patients carrying P/
LP variants in the
LMNA gene**

Comitato Etico Locale IRCCS Istituto Oncologico
"Gabriella Serio"

Seduta COMITATO ETICO LOCALE del
03/11/2025

(D.G.R. Regione Puglia n.712 del 22/05/2023 e
rett. N. 806 del 12/06/2023)

Prot. 2561/CEL - Studio LAMIN CarMyo Study
Parere FAVOREVOLE



- U.O.C. Cardiologia Univ., A.O.U.C. Policlinico Bari – A.I. Guaricci
(*Centro Promotore*)
- U.O.C. Cardiologia Univ., ASUGI Trieste – M.Merlo
- Università Vita-Salute san Raffaele, Milano – G. Peretto
- Centro Cardiologico Monzino, IRCCS – G.Pontone
- Dipart. di Cardiologia, Ospedale Casilino, Roma – L. Calò
- Università della Campania Luigi Valvitelli, Napoli – G. Limongelli
- Università Politecnica delle Marche – A. Dello Russo
- Fondazione G. Monasterio CNR-Regione Toscana – A. Barison
- A.O.U. Careggi Firenze – I. Olivotto
- Università degli Studi di Padova – B.Bauce
- A.O.U. Sant'Orsola Bologna – E. Biagini
- Università Degli Studi di Roma Sapienza – C. Chimenti
- U.O.C. Cardiologia ASU FC Udine – M. Imazio



ROMA, 25 - 27 Giugno 2026

Grazie per l'attenzione!



Andrea Igoren Guaricci
School of Medicine - University of Bari "Aldo Moro"

**Division of University Cardiology,
Asclepios III, A.O.U.C. Policlinico di Bari, Italy**

