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 Dilatativa Non Ischemica

UTILITÀ DEL TEST GENETICO NEI PAZIENTI CON CARDIOMIOPATIA DILATATIVA NON ISCHEMICA

Sangiuolo Federica

PRIMEVIEW

DILATED CARDIOMYOPATHY

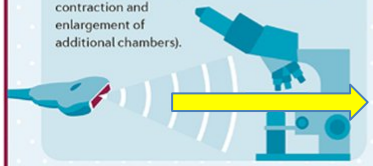
nature REVIEWS DISEASE PRIMERS

For the Primer, visit doi:10.1038/s41572-019-0084-1

Dilated cardiomyopathy (DCM) is a disease of the myocardium (heart muscle), with structural (dilation of the ventricles) and functional (impaired contractility) abnormalities. DCM can eventually lead to heart failure and life-threatening arrhythmias.

DIAGNOSIS

The signs and symptoms of DC mainly relate to the extent of ventricular systolic dysfunction and can include dyspnoea, fatigue and chest pain. Dilation is assessed with echocardiography, and cardiac MRI can identify the presence of fibrosis and oedema. Individuals with suspected inflammatory DCM should undergo endomyocardial biopsy. Analyses of biopsy samples with histology, immunohistochemstry and molecular biology techiques can determine the type of inflammatory infiltrate and the underlying aetiology, potentially guiding management choices. Factors that can worsen the prognosis include a left ventricular ejection fraction <35% and adverse remodelling characteristics (such as functional mitral valve regurgitation, myocardial fibrosis, dyssynchronous ventricular contraction and enlargement of additional chambers).



PATHOPHYSIOLOGY

GENETIC MUTATIONS

Up to 30% of DCM cases are caused by mutations in genes encoding proteins of the sarcomere (the basic contractile unit) or desmosome (a cell-to-cell adhesion structure)

INFLAMMATION

The activation of inflammatory pathways and the recruitment of immune cells result in fibrosis and remodelling, which cause dilation

AUTOIMMUNITY

Cardiac-specific autoantibodies have been isolated from patients with DCM, and, rarely, some autoimmune diseases (such as systemic lupus erythematosus, systemic sclerosis and rheumatoid arthritis) can cause DCM

ENLARGED VENTRICLES

Sex hormones alter cardiac function by binding to androgen and oestrogen receptors on cells. Women have higher levels of oestrogen receptors than men, and activation of these receptors prevents cardiomyocyte apoptosis, inhibits oxidative damage and reduces cardiac hypertrophy and fibrosis

EPIDEMIOLOGY

The 2015 Global Burden of Disease study estimated a global prevalence of cardiomyopathy of 2.5 million cases. In a multi-site study in the United States and Canada, DCM was the most common form of cardiomyopathy among children. The relative risk of mortality from DCM is higher in black individuals than in white individuals. DCM occurs more frequently in men than in women, and men also tend to have worse outcomes.

MANAGEMENT

Treatment aims at reducing symptoms of heart failure and improving cardiac function. Several pharmacological options are available, including angiotensin-converting enzyme inhibitors and β-blockers. Cardiac resynchronization therapy with a pacemaker or an implantable cardioverter defibrillator might also be indicated. Additional aetiology-based therapies, such as immunosuppressive and antiviral therapies, might be appropriate in patients with biopsy-confirmed myocarditis or infection, respectively.

INFECTIONS

Myocarditis (inflammation of the myocardium) can be caused by infection with several pathogens, especially viruses

CHEMICAL AND TOXIN EXPOSURE

Long-term abuse of alcohol or cocaine can lead to DCM, which can also occur as an adverse effect of cancer chemotherapeutic agents, such as anthracyclines

OUTLOOK

Advances in imaging techniques (such as speckle-tracking echocardiography) have the potential to detect systolic dysfunction before DCM develops. New sera biomarkers might not only aid diagnosis and indicate the risk of heart failure but also identify the underlying pathology and thereby help inform treatment. Improving our understanding of the contribution of infection, inflammation and autoimmunity to cardiac damage and remodelling in the pathogenesis of DCM could lead to the development of new therapeutic opportunities.

doi:10.1038/s41572-019-0088-x

Written by Lucia Brunello; designed by Laura Marshall

Timeline of genetic variant discovery in DCM

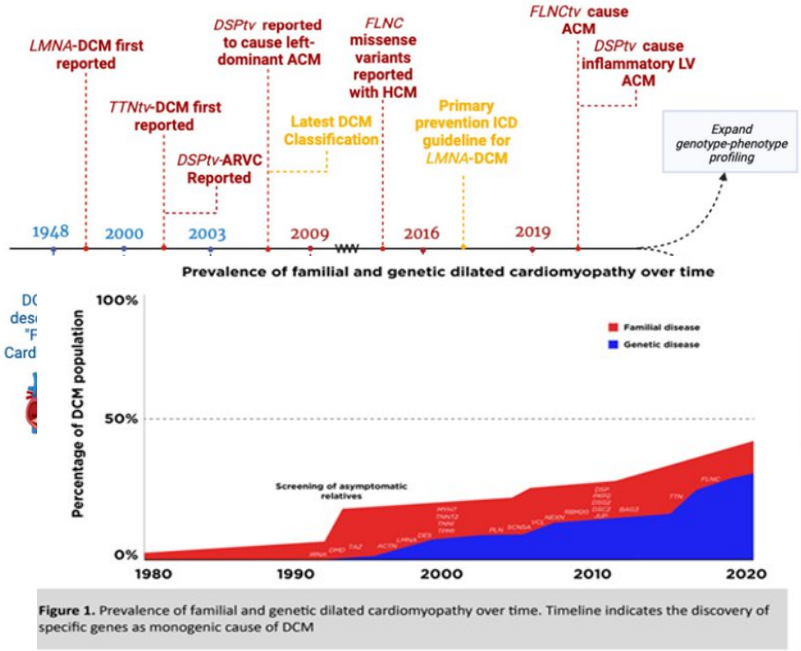
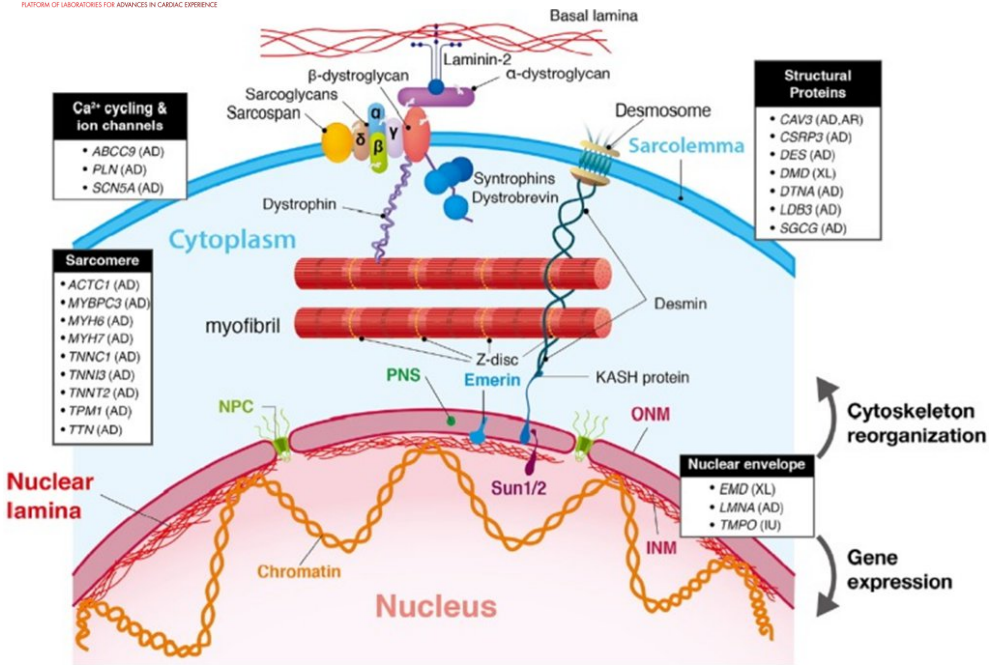


Figure 1. Prevalence of familial and genetic dilated cardiomyopathy over time. Timeline indicates the discovery of specific genes as monogenic cause of DCM

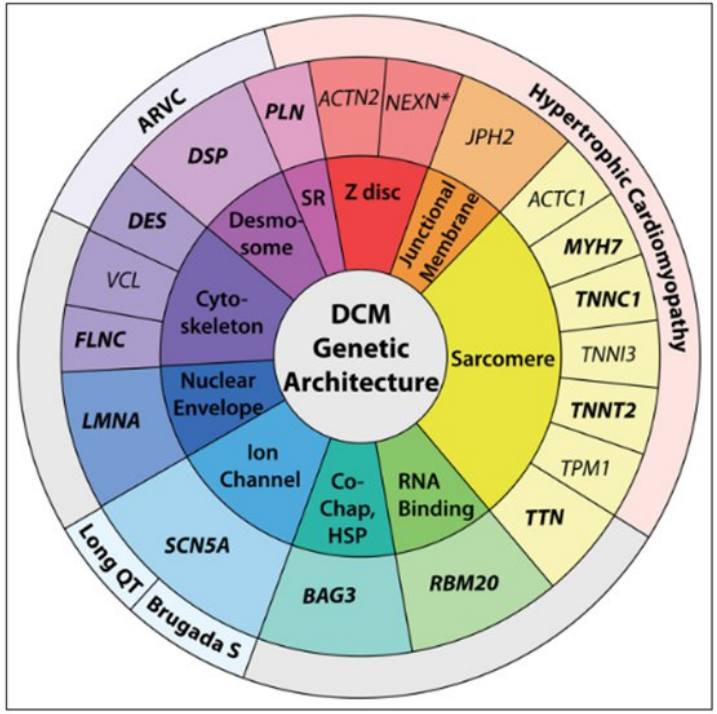
267 genes

DCM inheritance: AD pattern, X-linked, AR and mitochondrial patterns

Penetrance in AD DCM is age-dependent (a normal phenotypic assessment by echocardiogram and ECG does not exclude the possibility of later onset disease)
Variable expressivity



Mol Cells. 2016 Oct;39(10):722-727. doi: 10.14348/molcells.2016.0061.



Circulation. 2021 Jul 6;144(1):7-19. doi: 10.1161/CIRCULATIONAHA.120.053033.

Co-Chap, HSP, Co-chaperone, heart shock protein;
SR, sarcoplasmic reticulum.

Table 5 Impact of genetic testing for the proband

Disease	Diagnostic	Prognostic	Therapeutic
Arrhythmia syndromes			
Long QT syndrome	+++	+++	+++
CPVT	+++	+	+
Brugada syndrome	+	+	+
Progressive cardiac conduction disease	+	+	+
Short QT syndrome	+	+	+
Sinus node disease	–	+	–
Atrial fibrillation	–	+	–
Early repolarization syndrome	–	–	–
Cardiomyopathies			
Hypertrophic cardiomyopathy	+++	++	++
Dilated cardiomyopathy	++	+++	++
Arrhythmogenic			

++: can be recommended/can be useful.
+: may be considered/may be useful.
–: is not recommended/is not indicated nor useful.

ESC European Society of Cardiology

Europace (2022), 00, 1–61
https://doi.org/10.1093/europace/euac030

POSITION PAPER

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

ESC European Society of Cardiology
Europace (2022), 00, 1–61
https://doi.org/10.1093/europace/euac030
POSITION PAPER

35% of genetic and familial DCM

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

Table 14 Genes implicated in dilated cardiomyopathy

Gene	Locus	Phenotype–syndrome	Protein (functional effect)	Frequency	
TTN	2q31.2	DCM	Titin	~15–25%	
LMNA	1q22	DCM, ACM	Lamin A/C	~4–7%	Definitive
MYH7	14q11.2	HCM	Bêta Myosin heavy chain	~3–5%	Definitive
TNNT2	1q32.1	HCM, DCM	Troponin T	~2%	Definitive
RBM20	10q25.2	DCM	RNA-binding motif protein 20	~2%	Definitive
PLN	6q22.31	DCM, ACM	Phospholamban	~1% (*more in Netherlands*)	Definitive
FLNC	7q32.1	DCM≫BiVACM	Filamin-C	~1%	
BAG3	10q26.11	DCM, myopathy	BAG family molecular chaperone regulator 3	~2%	
DSP	6p24.3	ARVC, DCM	Desmoplakin	1–3%	
TPM1	15q22.1	HCM, DCM	alpha-tropomyosin	~1–2%	
ACTC1	15q11q14	HCM, DCM	Cardiac alpha-actin	<1%	Moderate
ACTN2	1q43	HCM, DCM, LVNC	Alpha-actinin-2	<1%	Moderate
DES	2q35	DCM, Myopathy, ACM	Desmin	<1%	Definitive
JPH2	20q13.12	DCM, HCM	Junctophilin 2	<1%	Moderate
NEXN	1p31.1	DCM, HCM	Nexilin	<1%	Moderate
SCN5A	3p22.2				Definitive
TNNC1	3p21.1				Definitive
TNNI3	19q13.4				Moderate
VCL	10q22.2				Moderate

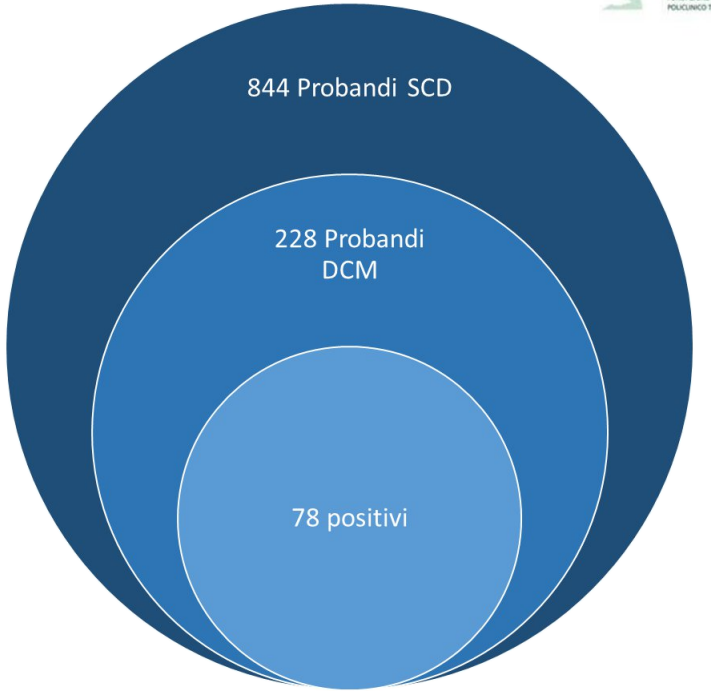
ACM, arrhythmogenic cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy

Truncating variants in titin gene (TTN) are the most frequent in DCM, accounting for up to 20% of cases

High genetic and allelic heterogeneity

Genes that do not have sufficient evidence to date as single-gene causes for disease should not receive variant interpretations

ACTC1
CAV3
DES
DSP
DMD
DSC2
DSG2
FLNC
GLA
JUP
LAMP2
LDB3
LMNA
MYBPC3
MYH7
MYL2
MYL3
PKP2
PLN
PRKAG2
RBM20
RYR2
SCN5A
TAZ
TNNC1
TNNI3
TNNT2
TPM1
TTN



ABOUT 30% IS VARIANT-POSITIVE

Approccio PHENOTYPE-FIRST

PATHOGENIC VARIANT: genotype-negative family members of a genotype-positive patient may be cautiously released from screening
A genetic diagnosis can be useful for reproductive planning
Variant positive but unaffected relatives should be monitored in a way depending on the specific gene or family history

NOT PATHOGENIC VARIANT: unaffected family members also require clinical screening at regular intervals because there is considerable phenotypic heterogeneity in age of onset and disease progression within members of the same family.

VUS: the absence of segregation of a VUS interpreted variant with a robust familial phenotype may lead to re-classifying to likely benign.
The segregation of a VUS with clinical phenotype reclassifies it as LP or P, as well as functional tests

PROGNOSTIC VALUE OF P or LP VARIANTS

- Patients with pathogenic LMNA variants have consistently been associated with a poor prognosis: high risk of SCD related either to conduction defect or ventricular arrhythmia and preventive pacemaker (PM) or ICD therapy should be considered

- Higher risk of SCD is also associated with truncated variants in FLNC, DES, RBM20, and PLN genes: preventive ICD implantation

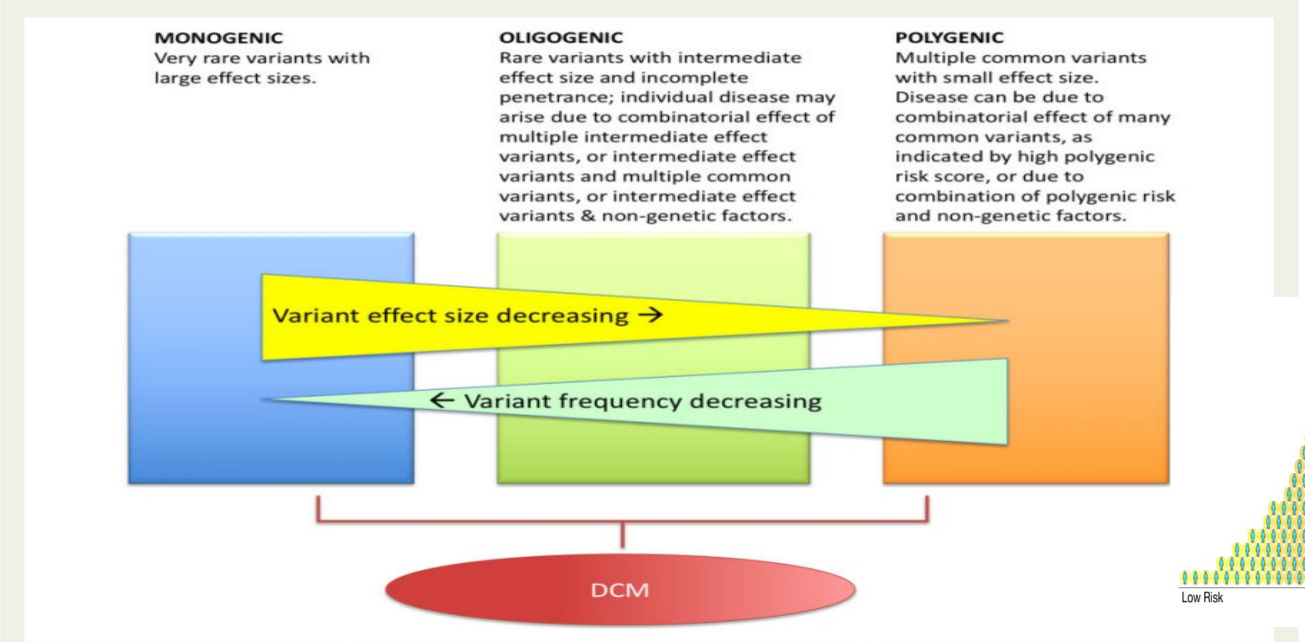
- Desmosomal pathogenic variants as well as in SCN5A gene are also associated with a greater risk of life-threatening ventricular arrhythmias/SCD.

- Patients with DCM are also at greater risk for heart failure and heart transplantation when they are carriers of pathogenic variants in LMNA, RBM20, and DSP genes.

Non Mendelian inheritance

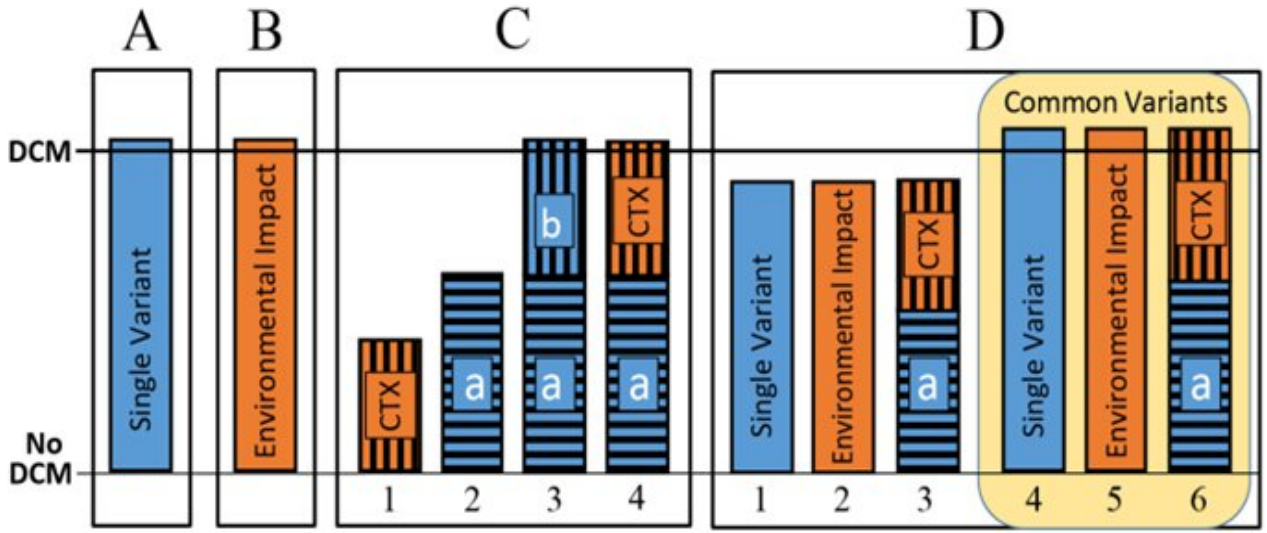
- Oligogenic: the coinheritance of these other genetic factors (rare variants) can exacerbate or attenuate the effect of the latter on the phenotype in terms of age at onset, variable expressivity (**genetic modifiers**: e.g. carrier of pathogenic variants in TTN).
- 30%- gene environment interaction: genetic predisposition interacts with extrinsic or environmental factors (EXPOSOME) resulting in mixed genetic/environmental causes, such as myocarditis, as well as peripartum, alcoholic, or chemotherapy-related cardiomyopathies.

Continuum of genetic complexity exists where at one end of the spectrum are Mendelian disorders determined primarily by the inheritance of an ultra-rare large-effect genetic defect, and at the other end are highly polygenic disorders determined by many genetic variants with additive effect.



DISEASE-CAUSING ⟶ **DISEASE CONTRIBUTING VARIANTS**

FROM MONOGENIC TO POLYGENIC INHERITANCE: GENE ENVIRONMENT INTERACTION



threshold for clinically detectable DCM

a,b: two moderate impact variants
common variants (yellow box)

MAJOR CHALLENGES YET TO BE RESOLVED IN DCM GENETICS

• The utility of DCM genetics—does genotype drive prognosis therapy? Studies need to be designed to test these questions.

R222Q in SCN5A: drug with sodium channel-blocking properties are highly effective

• What is the optimal approach to detect earliest clinical evidence of pre-DCM? Does this require an imaging approach, such as cardiac magnetic resonance imaging, or the measurement of some biologic marker?
• Will conventional drug treatment, effective for symptomatic DCM, prevent the development of pre-DCM in those who are genetically at-risk?
• Can an integrated approach to risk prediction incorporating variants across the allele frequency spectrum as well as environmental factors be developed?

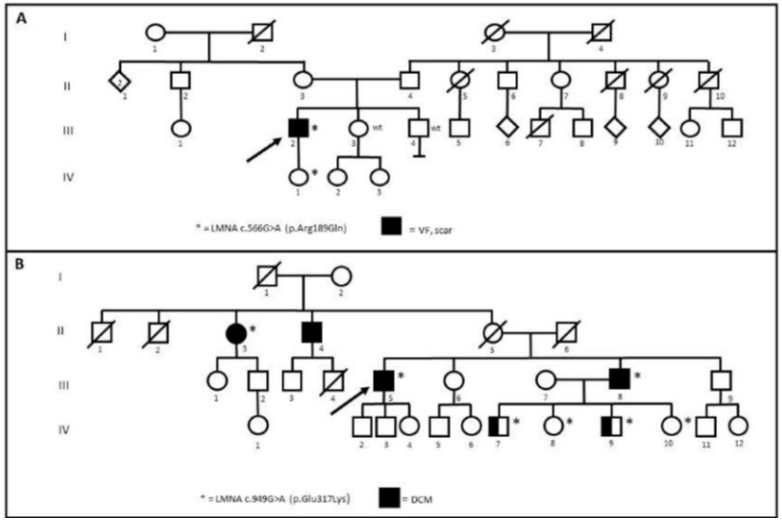
dott R Mango
dott.ssa E Marchionni
dott.ssa V Ferradini
dott. A Latini
dott.ssa F Di Lorenzo
dott.ssa V Visconti
Prof. G Novelli

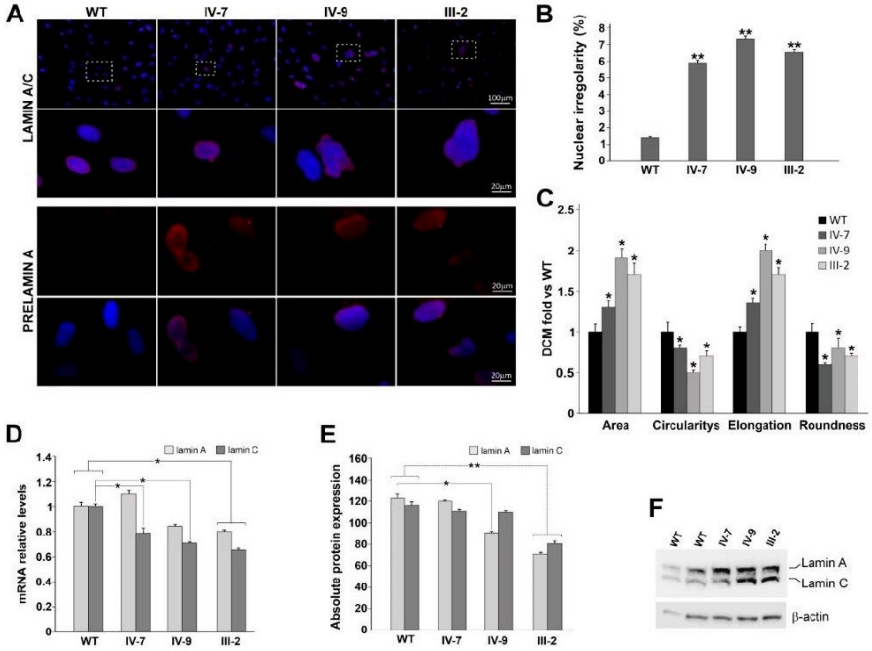
PTV
FONDAZIONE PTV
POLICLINICO TOR VERGATA

UNIVERSITÀ degli STUDI di ROMA
TOR VERGATA

the genetic architecture of DCM is broader in scope and more complex than previously understood.

Common variants of small effect and intermediate effect variants may, to varying extents, influence penetrance in individuals with Mendelian genetic defects by pushing the genetic burden towards the threshold of disease, as well as influence severity of disease.
While their incorporation into genetic testing approaches is expected to increase the sensitivity of genetic testing, the identification of such modulatory variants is still a matter of intense research and therefore currently not clinically applicable.


A
I
II
III
IV
* = LMNA c.566G>A (p.Arg189Gln)
= VF, scar
B
I
II
III
IV
* = LMNA c.949G>A (p.Glu317Lys)
= DCM


A
WT
IV-7
IV-9
III-2
LAMIN A/C
PRELAMIN A
100μm
20μm
B
Nuclear irregolarity (%)
C
DCM fold vs WT
WT
IV-7
IV-9
III-2
Area
Circularitys
Elongation
Roundness
D
lamin A
lamin C
mRNA relative levels
E
Absolute protein expression
F
Lamin A
Lamin C
β-actin