PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA
Centro Congressi
di Confindustria
Auditorium
della Tecnica

9ª Edizione

30 Settembre
1 Ottobre
2022

DIAGNOSTICA NELLE CARDIOMIOPATIE NON ISCHEMICHE

GENETICA NELLE CARDIOMIOPATIE: QUALI CRITICITÀ E QUALI APPLICAZIONI CLINICHE

Maria Iascone

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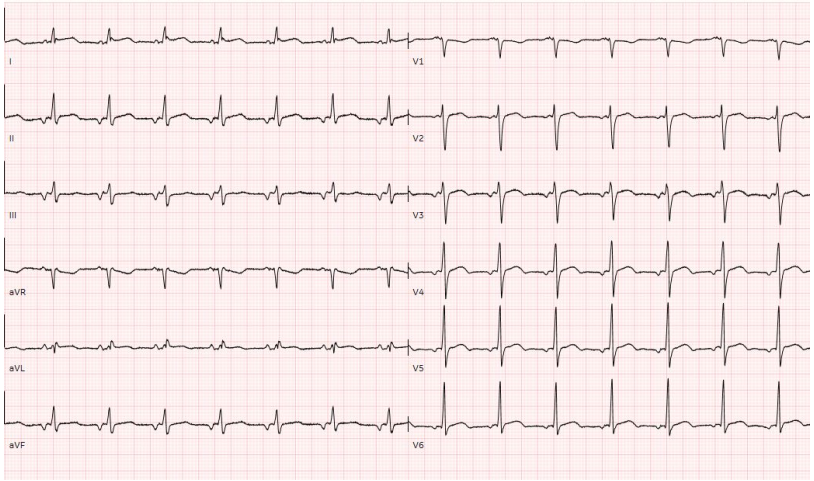
M.N. 26 yrs, male

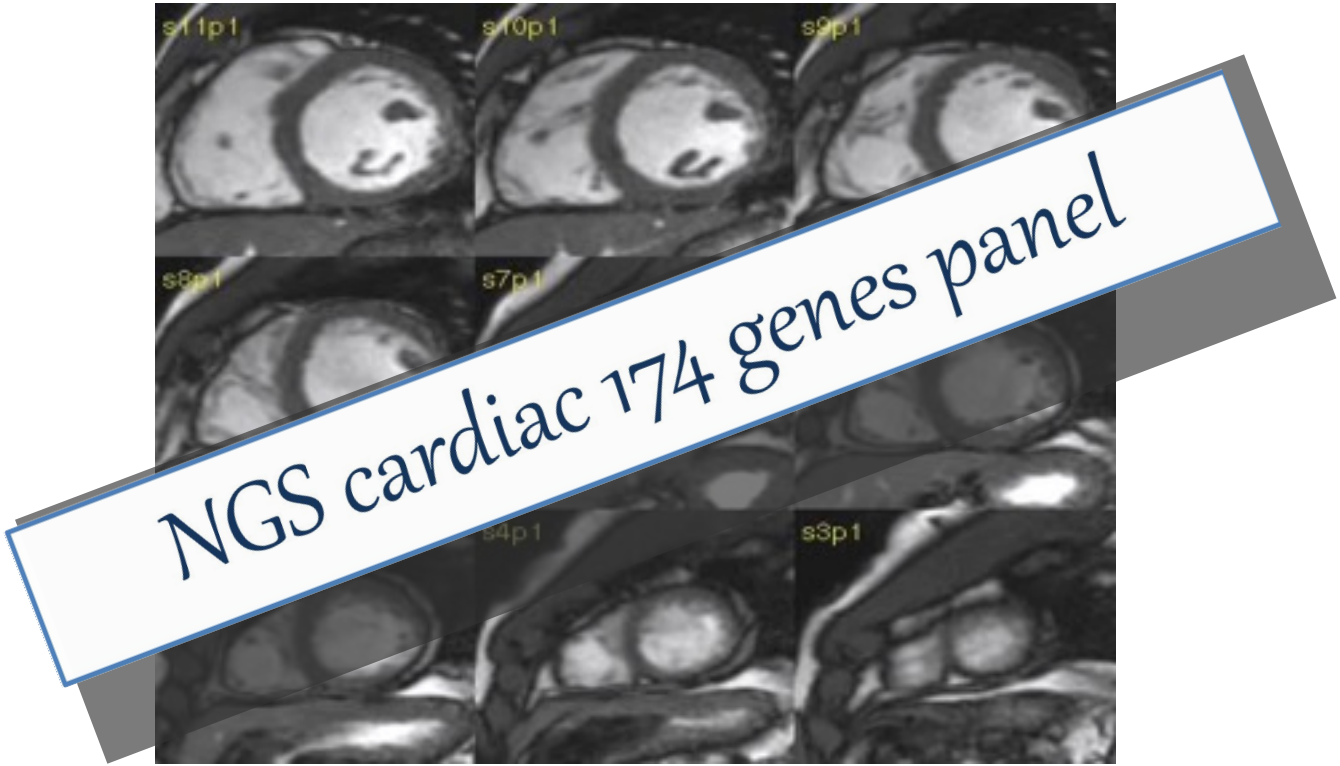
November 2020

- Admitted to Emergency Unit for dyspnoea and fever

- *No past medical history*
- *No family history of sudden cardiac death or cardiomyopathy*
- Blood test: BNP 264 pg/mL; TnI: 900; PCR 4



M.N. 26 yrs, male



Genetic testing for suspected ARVD requested

M.N. 26 yrs, male

- Due to the persistence of the inflammatory state and the high troponin level (PCR 22, fever, myalgia, hS-TnI 1200), he underwent a myocardial biopsy which revealed **myocarditis**.

Meanwhile…
the genetic test shows a variant of uncertain significance (VUS) in the ANK2 gene

le

After t

- MRI reve d dilatation, a itration was confirmed.

Genetic testing ers

Th old), or instr e, carriers of VU

e follow-up was indica

ANK2

View Gene Facts

3	2	0	0	0 / 0	Follow Gene
Gene-Disease Validity Classifications	Dosage Sensitivity Classifications	Clinical Actionability Assertions	Variant Pathogenicity Assertions	CPIC / PharmGKB High Level Records	

Curation Summaries | Status and Future Work (1) | External Genomic Resources | ClinVar Variants

Gene-Disease Validity

Group By Activity | Group By Gene-Disease Pair

Gene	Disease	MOI	Expert Panel	Classification	Report & Date
ANK2	complex neurodevelopmental disorder MONDO:0100038	AD	Intellectual Disability and Autism GCEP	Definitive	12/15/2020
ANK2	Brugada syndrome MONDO:0015263	AD	Brugada Syndrome GCEP	Disputed	11/21/2017
ANK2	catecholaminergic polymorphic ventricular tachycardia MONDO:0017990	AD	Catecholaminergic Polymorphic Ventricular Tachycardia GCEP	Disputed	01/20/2021

Dosage Se

Gene	Disease	Report & Date
ANK2		05/22/2019
		05/22/2019

A VUS should not be used to facilitate cascade screening; rather, clinical screening is required.

ESC European Society of Cardiology

Europace (2022) 24, 1307–1367
https://doi.org/10.1093/europace/euac030


WHO
WHY
WHERE
WHAT
HOW
WHEN

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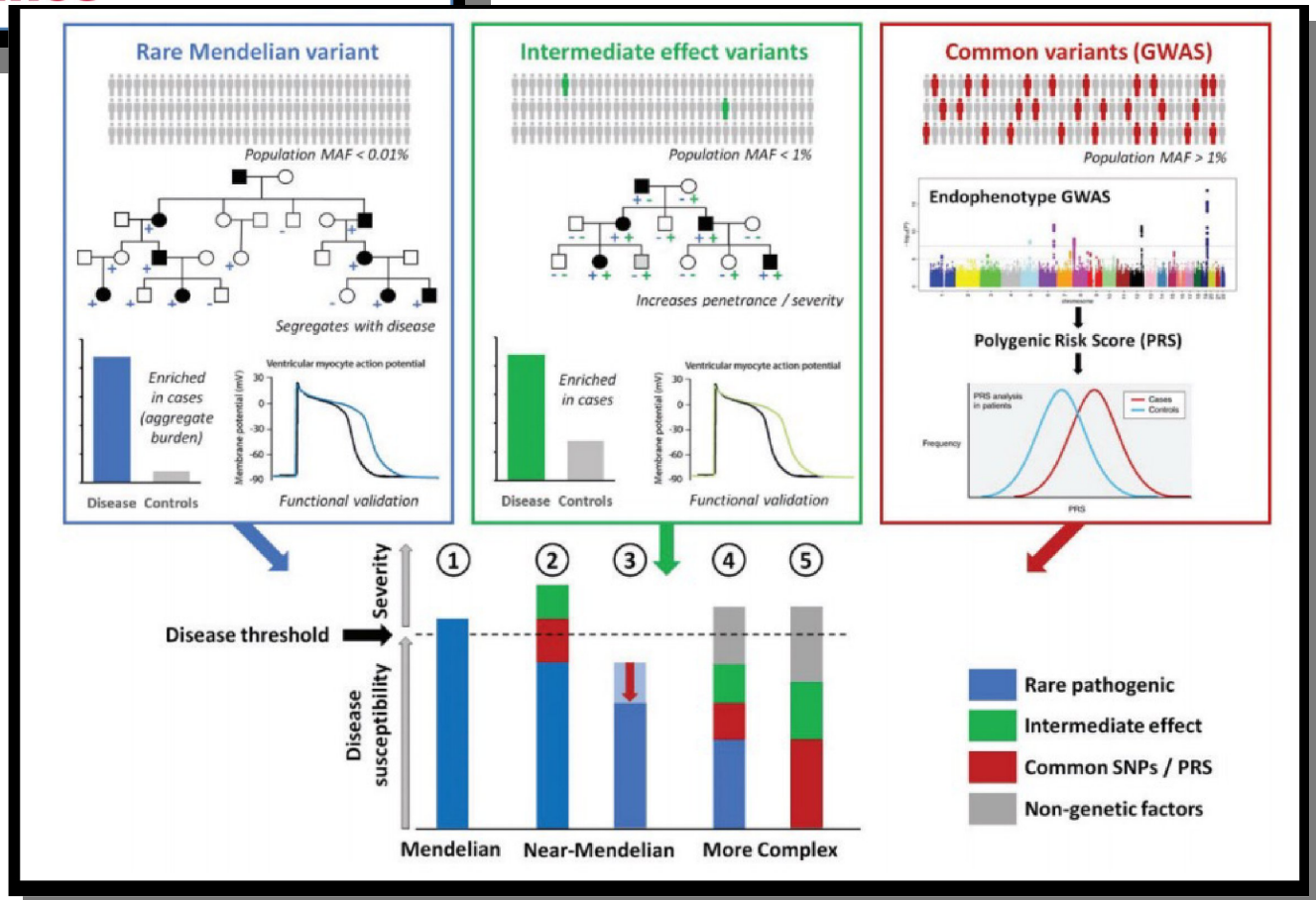
POSITION PAPER

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

Genetic influences on disease and modes of inheritance

- HCM; LQT
- ARVC
- DCM; BrS



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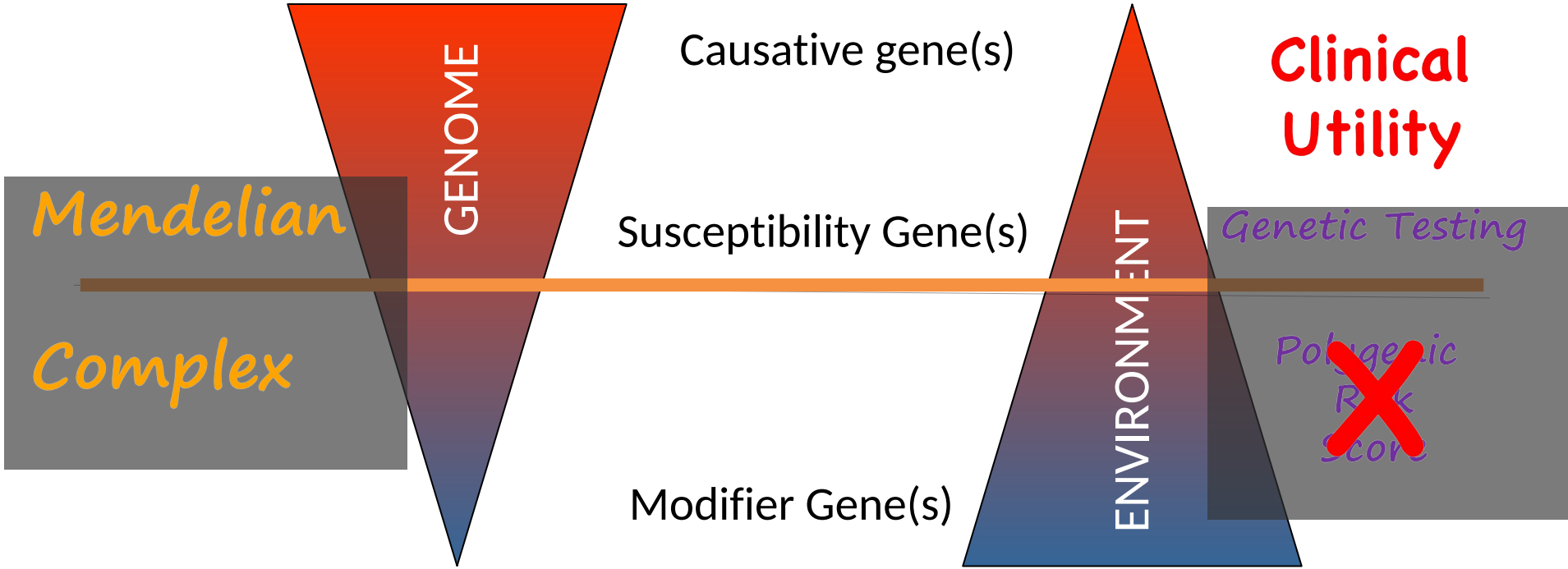
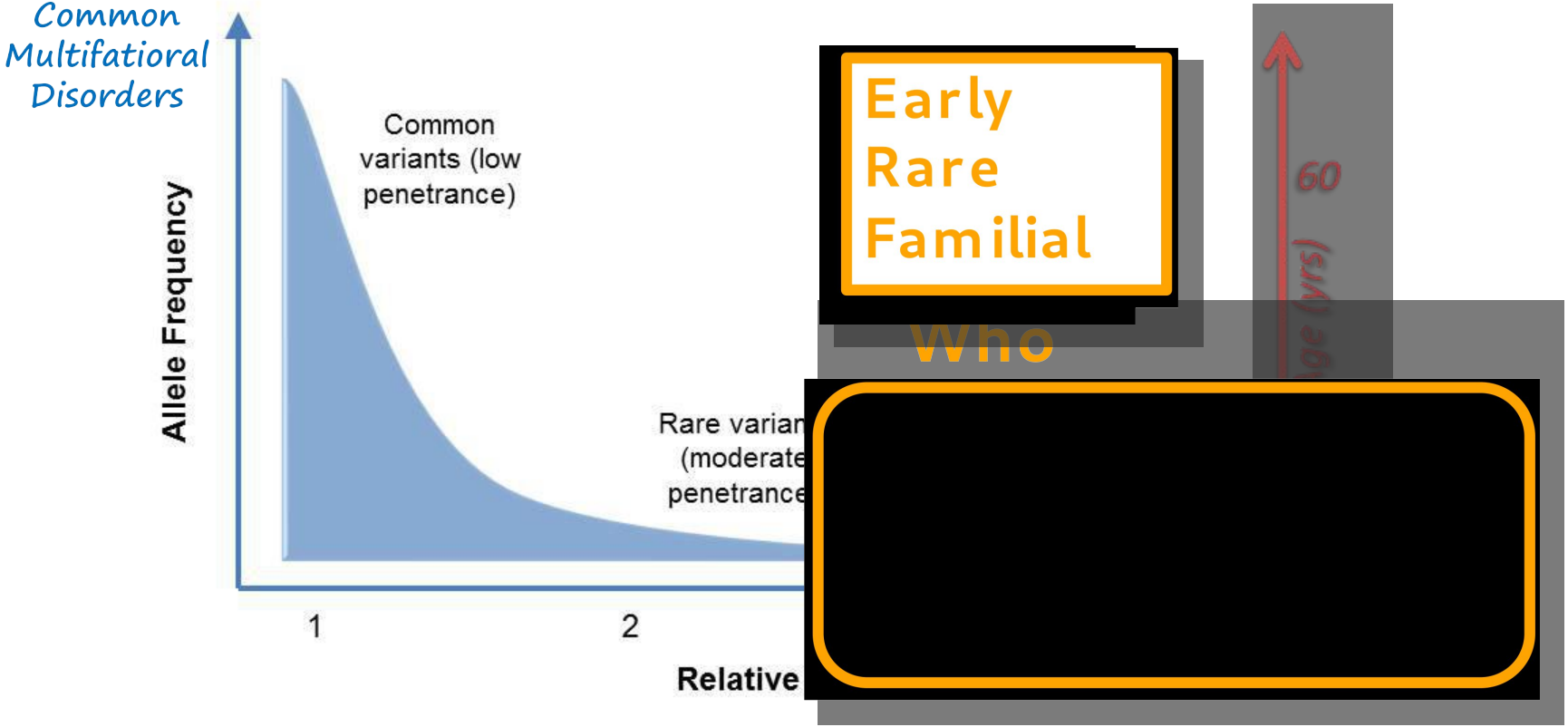
https://doi.org/10.1093/europace/euac030

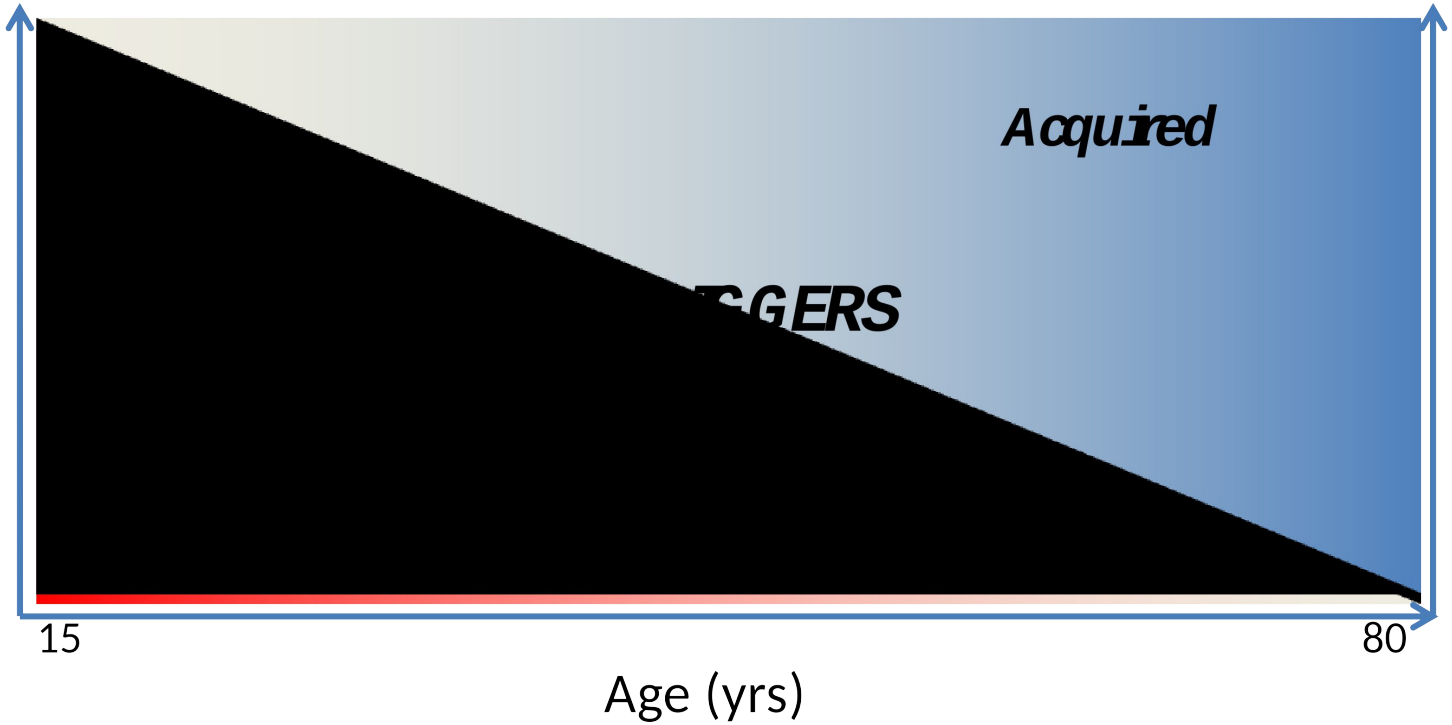
Human diseases aetiologies



Genetic Architecture of Human Diseases



LVOT Obstruction in HCM



Ferrazzi et al. J Am Coll Cardiol. 2020

Long QT syndrome

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
LQTS	+++	+++	+++

Why

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Europace (2022) 24, 1307–1367
https://doi.org/10.1093/europace/euac030

Hypertrophic cardiomyopathy

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
HCM	+++	++	++

Dilated cardiomyopathy

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
DCM	++	+++	++

Arrhythmogenic cardiomyopathy

Disease	Diagnostic	Prognostic	Therapeutic
ACM	+++	++	++

Where & How

Choice of genetic tests and interpretation of variants

Recommendation	Consensus statement instruction	Ref.
Genetic testing in patients with a potential cardiogenetic condition is performed only with appropriate genetic counselling.		Expert opinion
In patients with a clear specific phenotype, it is appropriate to perform genetic testing analysing genes with definite or strong evidence supporting disease causation.		10,17,20,21,69

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Europace (2022) 24, 1307–1367
https://doi.org/10.1093/europace/euac030

A gradient of effect sizes…

ESC European Society of Cardiology

European Heart Journal (2022) 43, 1901–1916
https://doi.org/10.1093/eurheartj/ehab895

SPECIAL ARTICLE

Interpretation and actionability of genetic variants in cardiomyopathies: a position statement from the European Society of Cardiology Council on cardiovascular genomics

Eloisa Arbustini [1]*, Elijah R. Behr [2], Lucie Carrier [3,4], Cornelia van Duijn [5], Paul Evans[6], Valentina Favalli[7], Pim van der Harst [8], Kristina Hermann Haugaa [9,10], Guillaume Jondeau [11,12,13†], Stefan Kääb[14,15], Juan Pablo Kaski [16,17], Maryam Kavousi[18], Bart Loeys [19,20], Antonis Pantazis[21], Yigal Pinto[22], Heribert Schunkert[23,24], Alessandro Di Toro [1], Thomas Thum [25,26], Mario Urtis [1], Johannes Waltenberger [27,28], and Perry Elliott [29,30]

Variant Classification

- Class 5: pathogenic — >95%
- Class 4: likely pathogenic — >90%
- Class 3: VUS — 10-90%
- Class 2: likely benign — <10%
- Class 1: benign — <5%

…a certain amount of evidence is necessary

- Class 5: pathogenic
- Class 4: likely pathogenic

Genetic cascade screening in family members

- Class 3: VUS

Class 3 variants

VUS should be deemed "nonactionable"

Revaluation

2019 HRS Expert Consensus Statement

Sick or not sick

Diagnostic

Predictive

Diagnostic

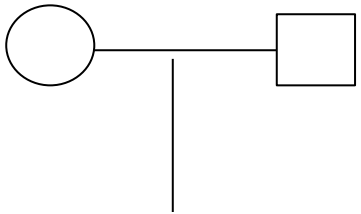
Overt clinical phenotype

Importance of extra-cardiac signs for differential diagnosis

As early as possible in affected subjects, after a careful clinical assessment, collecting all available biochemical/instrumental data

(*differential*) Diagnosis & Prognosis

Male, 10 years



Syncopal episodes

CK mild increase

Transition from C to T in exon 6.
Missense substitution.
Arg at position 406 is changed to Trp.

This variant is reported as pathogenic by HGMD - Phenotype: Myopathy, desmin related (CM000368).

This variant is known to ClinVar: RCV000018320.29 (Conflicting interpretations of pathogenicity* - Myofibrillar myopathy 1), RCV000056781.3 (Pathogenic* - not provided).

This variant is reported as possibly pathogenic by Uniprot (view report).

This variant is known to dbSNP: rs121913003 (validated dbSNP entry - Clinical significance: not_provided,pathogenic).

HGVS v2.0 Nomenclature

cDNA Level:	**NM_001927.3:c.1216C>T**
gDNA Level:	**Chr2(GRCh37):g.220286254C>T**
Protein Level:	**p.Arg406Trp**

TABLE 1. CHARACTERISTICS OF 12 PATIENTS WITH DESMIN MYOPATHY.*

FAMILY OR PATIENT NO.	AGE (YR)/ SEX	AGE AT ONSET		SERUM CREATINE KINASE†	EXTENT OF SKELETAL-MUSCLE WEAKNESS‡	CHARACTERISTICS OF CM
		SM	CM			
		yr		U/liter		
Family 1						
Proband	50/M	20	42	Normal	Severe weakness, wheelchair-bound, 0–4/5 in distal and proximal muscles§	Conduction defects, right bundle-branch block, idioventricular rhythm
Sister	52/F	38	—	Normal	Moderate weakness, foot drop, 4/5 in other distal and proximal muscles§	—
Family 2						
Proband	29/F	22	2	428	Moderate weakness, foot drop, 4/5 in other distal and proximal muscles§	Conduction defects, syncopal episodes, implantation of pacemaker, heart failure
Brother	31/M	20	9	700	Moderate weakness, 4/5 in distal and proximal muscles	Conduction defects, syncopal episodes, implantation of pacemaker, sudden death
Brother	32/M	24	10	Normal	Moderate weakness, 4/5 in distal and proximal muscles	Conduction defects, syncopal episodes, implantation of pacemaker, heart failure, death
Family 3						
Proband	45/F	30	38	Normal	Severe weakness, wheelchair-bound, 0–3/5 in distal muscles, 3–4/5 in proximal muscles, respiratory-muscle weakness, with need for continuous positive airway pressure§	Mitral-valve prolapse, mitral and tricuspid regurgitation
Sister	49/F	35	—	Normal	Moderate weakness, foot drop, 4/5 in other distal and proximal muscles	—
Mother	69/F	25	—	Normal	Severe weakness, paralysis, dependent on respirator§	—
Family 4						
Proband	52/F	30	—	364	Severe weakness, wheelchair-bound, 0–3/5 in distal and proximal muscles§	—
Son	25/M	24	—	963	Mild weakness, 4/5 in foot and toe extensors	—
Patient 5	29/F	24	25	600	Severe weakness, 0–4/5 in distal and proximal muscles	Conduction defects, syncopal episodes, implantation of pacemaker
Patient 6	50/F	43	40	Normal	Moderate weakness, foot drop, 4/5 in other distal and proximal muscles	Conduction defects, syncopal episodes, implantation of pacemaker

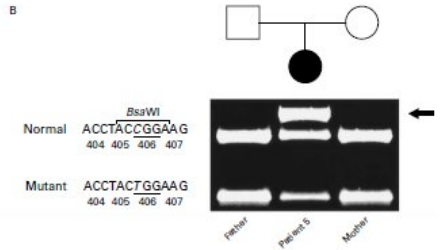
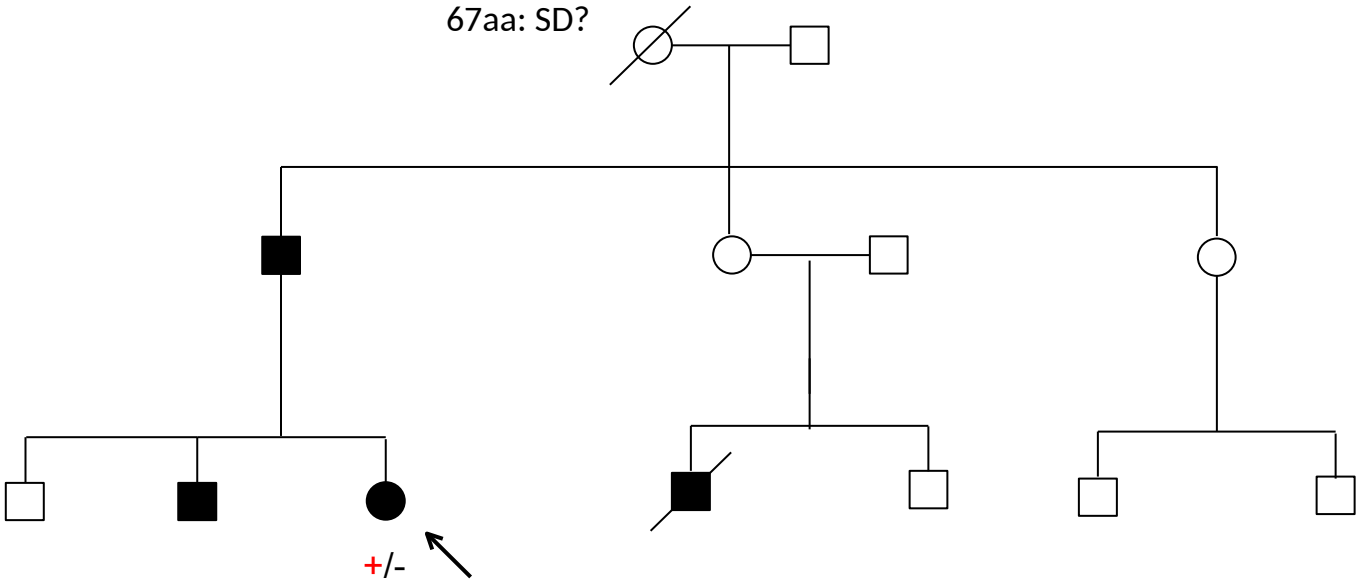


Figure 2. Nucleotide Sequences of Desmin Gene Fragments from Two Members of Family 4 with Familial Autosomal Dominant Myopathy (Panel A) and from Patient 5, Who Had Sporadic Cardiac and Skeletal Myopathy, and Her Unaffected Parents (Panel B).

The alterations identified in codons 342 and 406 of the desmin gene are underlined, and the nucleotides affected are italicized. Restriction enzymes *Sbf*I and *Bsa*WI were used to screen for mutations. Bands associated with mutations on electrophoresis are indicated by the arrows.

The New England Journal of Medicine, 2016

Diagnostic and then…predictive

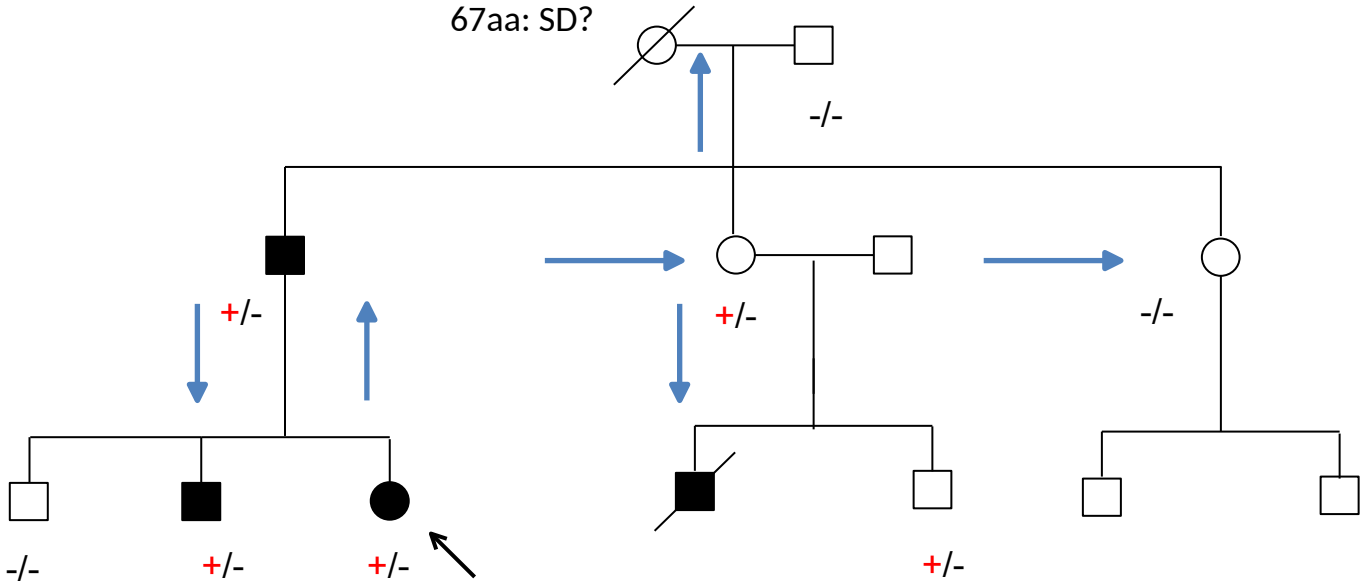


DCM & Ventricular arrhythmia

LMNA: p.Glu317Lys

PATHOGENIC

Diagnostic and then…predictive



DCM & Ventricular arrhythmia

LMNA: p.Glu317Lys

PATHOGENIC

In summary…

Genetic testing is a powerful tool that must be integrated with other clinical tools

Misuse can be harmful to the patient and the family

As with any other test in medicine, the *5 Ws* are essential for appropriate and valuable application

This is still an evolving field, and we are learning while we are going…

Gruppo di Lavoro CARDIO-ARITMIE

- Uniformare l'esecuzione dei test (lista dei geni, criteri di interpretazione, referti, consensi, etc)
- Discussione e confronto sull'interpretazione di casi complessi

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