LV Non-compaction: A Distinct Genetic Cardiomyopathy? Perhaps Less Frequent and Less Threatening than Previously Advertised

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DISCLOSURES : None

LV Trabeculation: from "healthy hearts" to cardiomyopathies

Healthy Hearts

- Noore et al. Quantifying left ventricular trabeculae function - application of image-based fractal analysis. Physiol Rep 2013;1:e00068.
- **3D-printing** could theoretically provide serial models

LVNC cardiomyopathy

- AHA: Primary genetic cardiomyopathy
- ESC: Unclassified→unclear whether it represents a distinct disease process or a morphologic trait shared by many, phenotypically different cardiomyopathies
- Unresolved→ while waiting for precise indications → descriptive nosology
- Captur et al. Canadian J Cardiol 2015

common, cardiomyopathy-associated variant. A proposed nosology could be: 'isolated LVNC' and then 'DCM with LVNC' and 'CHD with LVNC' as recently proposed from the **M**orpho-functional Phenotype, Involved **O**rgans, **G**enetic, **E**tiology, Functional **S**tatus (MOGE[S]) classification.[48]

LVNC: a distinct disease?

Definition

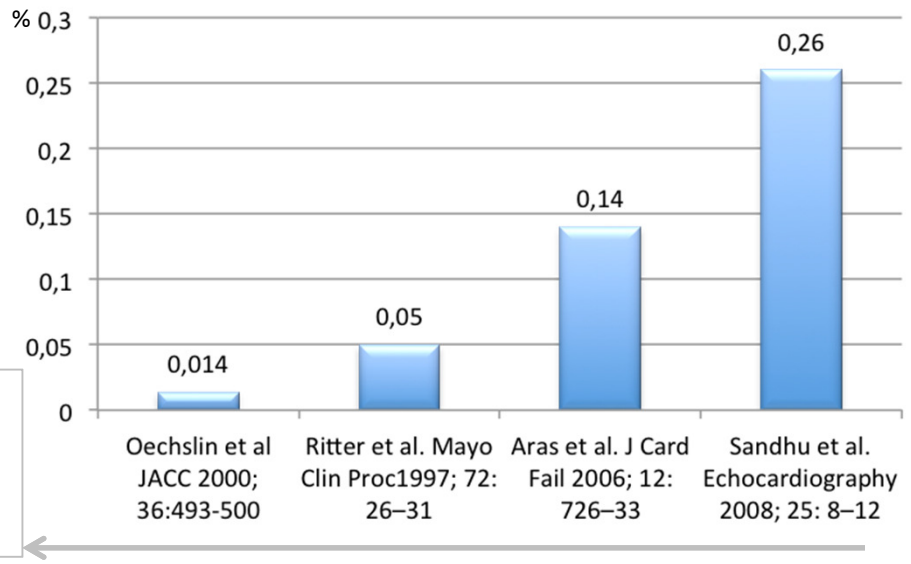
Left ventricular non-compaction is an imaging-based diagnosis defined by 3 markers:

1. **prominent left ventricular trabeculae**
2. **thin compacted layer**
3. **deep intertrabecular recesses.**

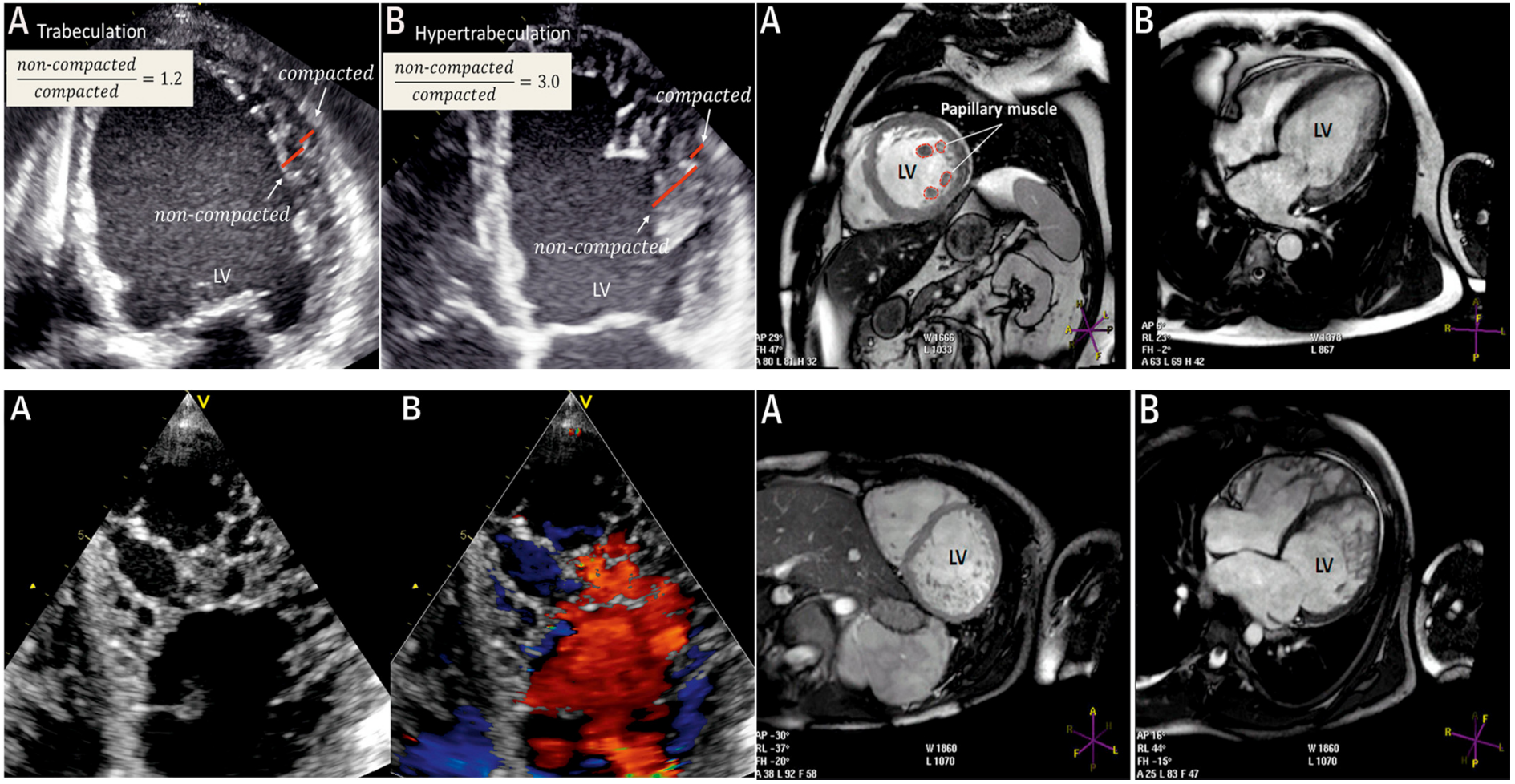
Belanger et al. Am J Cardiol 2008; 102: 92-6. Maximum linear length of NC/C and the planimetered area of LVNC on apical 4-chamber view: 60/380 ***→15,8%***

Prevalence

- ***Difficult determination; Echo and CMR diagnostic criteria are not standardized***
- ***CMR: 8 different methods (Canadian J Cardiol 2015:1-13)***



Diagnosis: Echo and CMR
NC/C RATIO



Arbustini E, Weidemann F, Hall JL. JACC 2015; 64: 1840-50

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3-1, proband: MYBPC3 p.(Thr957Ser) + *NEBL* c.1008+5A>G Homozygous

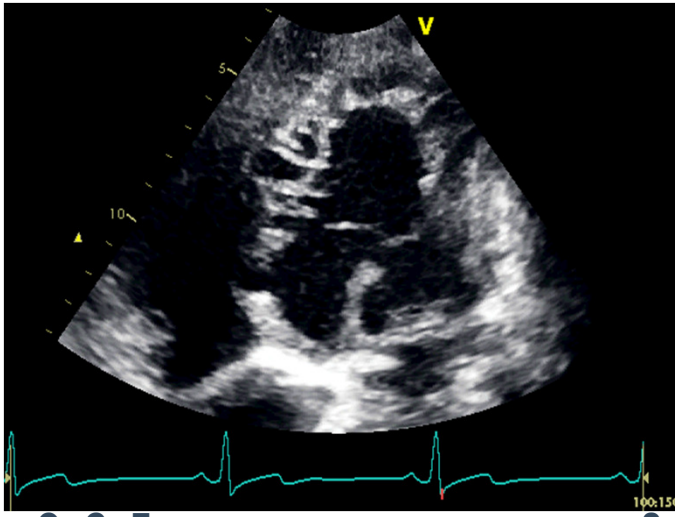
LVNC as isolated And non-isolated trait/disease

- *Isolated LVNC (iLVNC)*
- *LVNC associated with LV dilation & dysfunction at onset → tafazzinopathies (Barth syndrome)*
- ***LVNC in hearts fulfilling the diagnostic criteria for DCM, HCM, RCM, or ARVC***
- *LVNC associated with CHDs*
- *Syndromes with LVNC (or syndromic LVNC),* either sporadic or familial
  - Monogenic syndromes
  - Chromosomal defects
- ***Acquired isolated LVNC***
  - ***Athletes***
  - ***Pregnancy***
  - ***Chronic renal failure***
  - ***Sickle cell anemia***

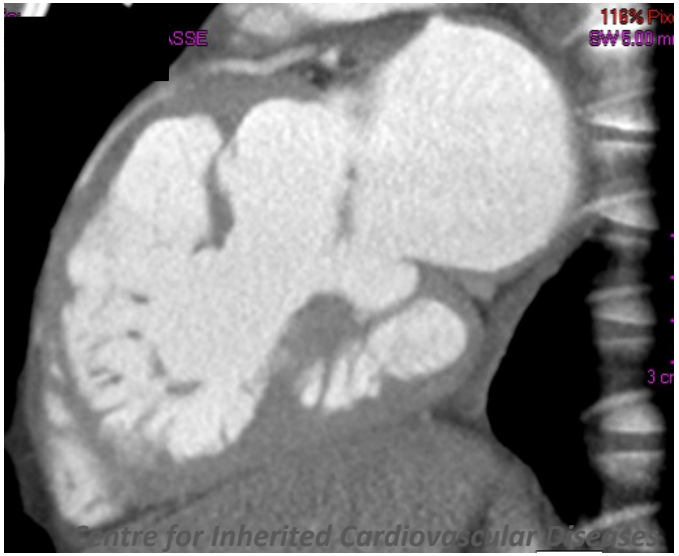
GENETICS and LVNC

- *Genes associated with LVNC (i.e. G4.5)**; no mutations reported to date in cardiomyopathies without LVNC***
- *Genes associated with **cardiomyopathies and LVNC** (overlapping genes: sarcomere, nuclear envelopathies, etc.)*
- *Monogenic syndromes with major **extra-cardiac traits and cardiac involvement** (Fabry, Danon, Sotos, Coffin-Lowry, etc.)*
- ***Mitochondrial DNA mutations** reported as associated with cardiac phenotypes including LVNC (Including MELAS)*
- *Large structural **chromosomal variations** like aneuploidies and deletion syndromes.*

Isolated LVNC, follow-up → clinically stable → 2006-2015

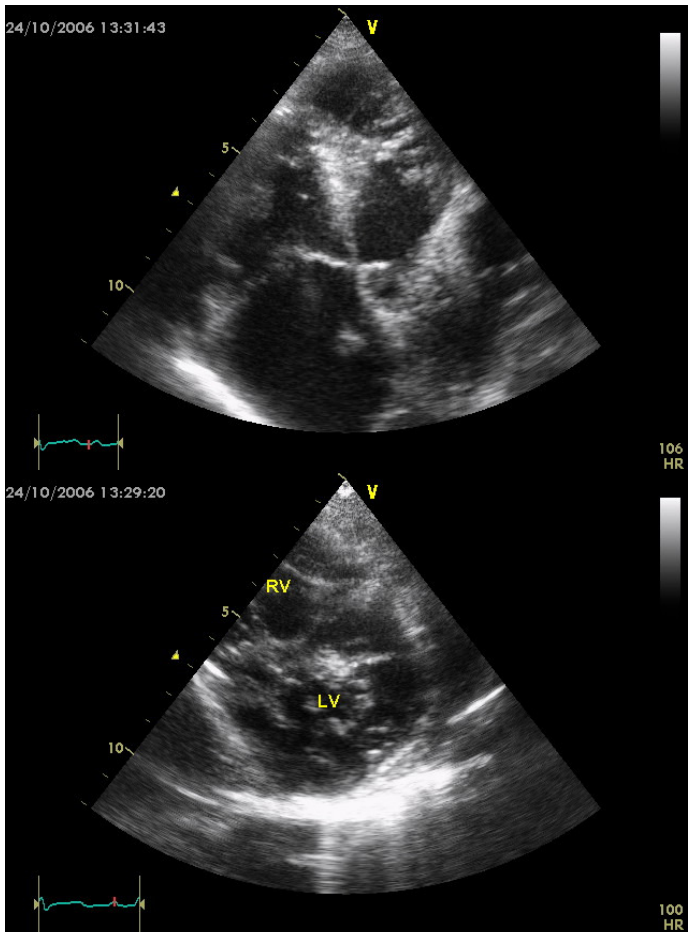


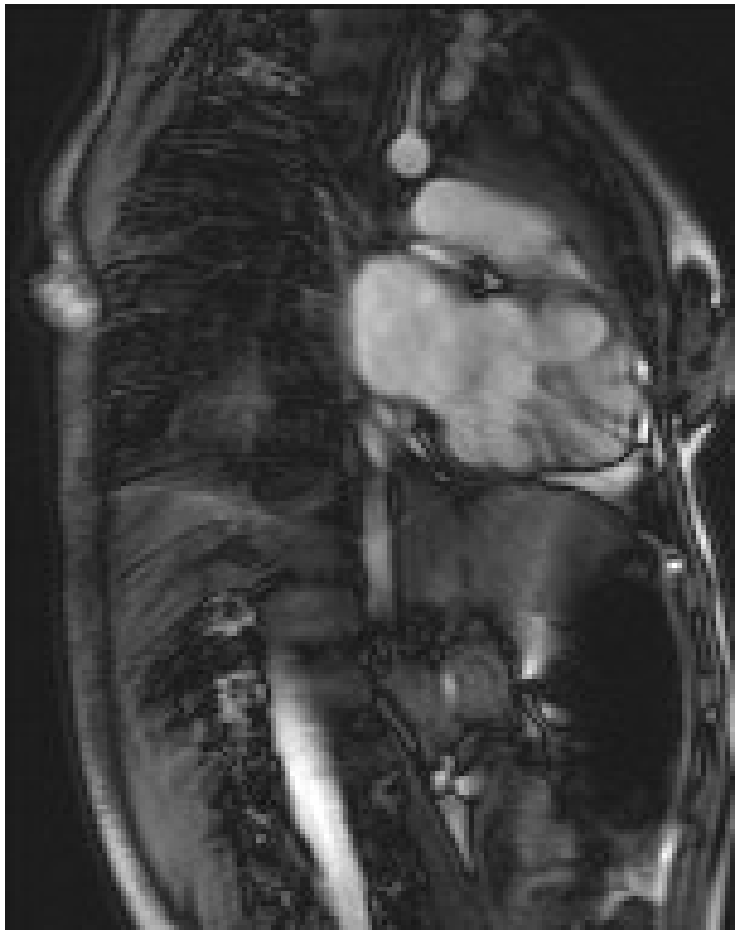
$M_{NC}\ O_{H}\ G_{U}\ E_{G\text{-}TXNRD2[p.Pro498Ser]\ +\ MYBPC3\ [p.Arg326Gln]}\ S_{X\text{-}I}$



LVNC and CHD

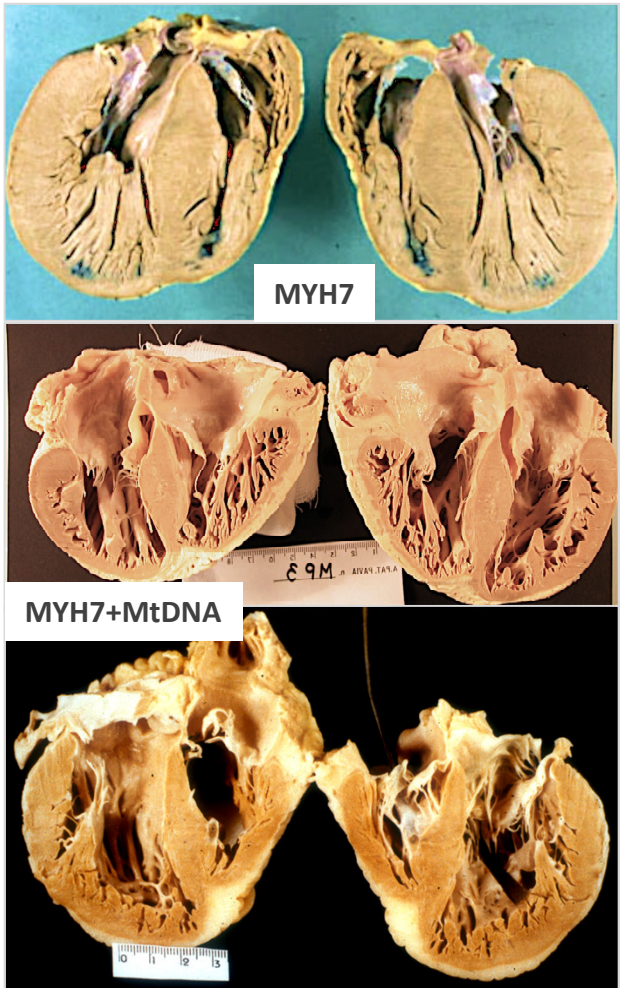
M$_{\text{R+NC + (CHD:ASD,VSD,PDA)}}$ **O**$_{\text{H+Contractural Arachnodactily}}$ **G**$_{\text{U}}$ **E**$_{\text{G-}}$*AKAP9* [p.Arg3377Ter]+*RYR2*[p.Tyr904Cys]+*FBN1*[p.Glu1297Gly] **S**$_{\text{B-I}}$



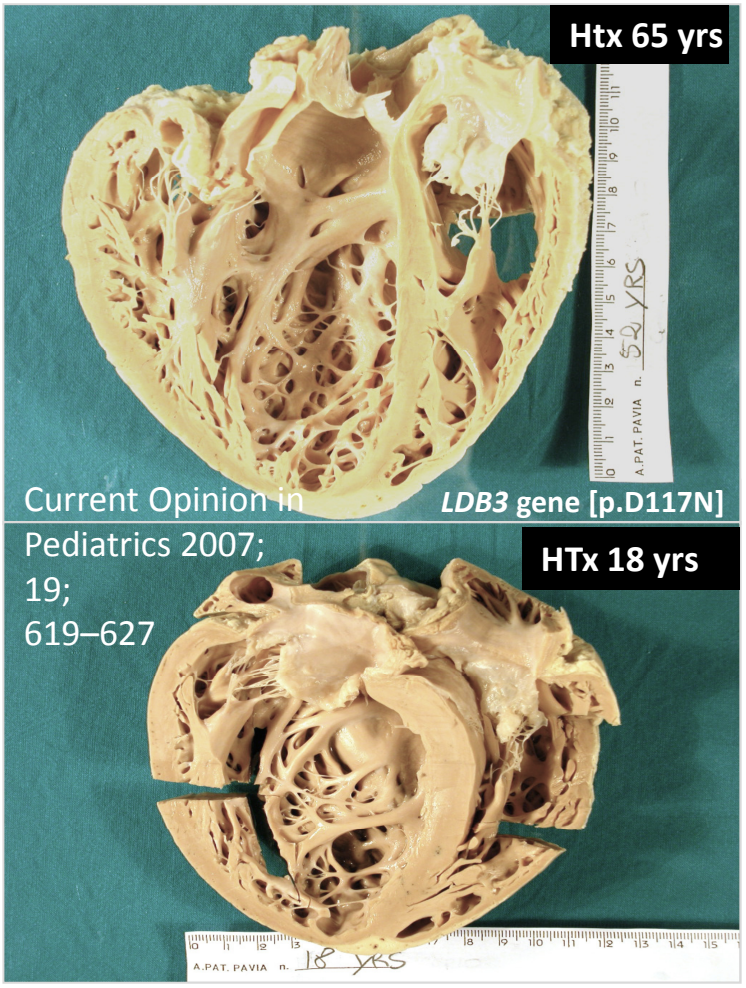


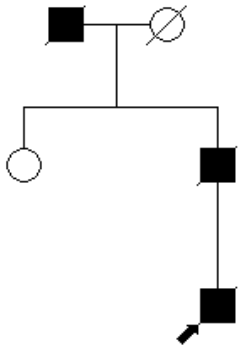
LVNC associated with Cardiomyopathy

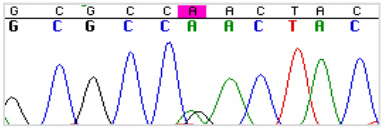
HCM



DCM



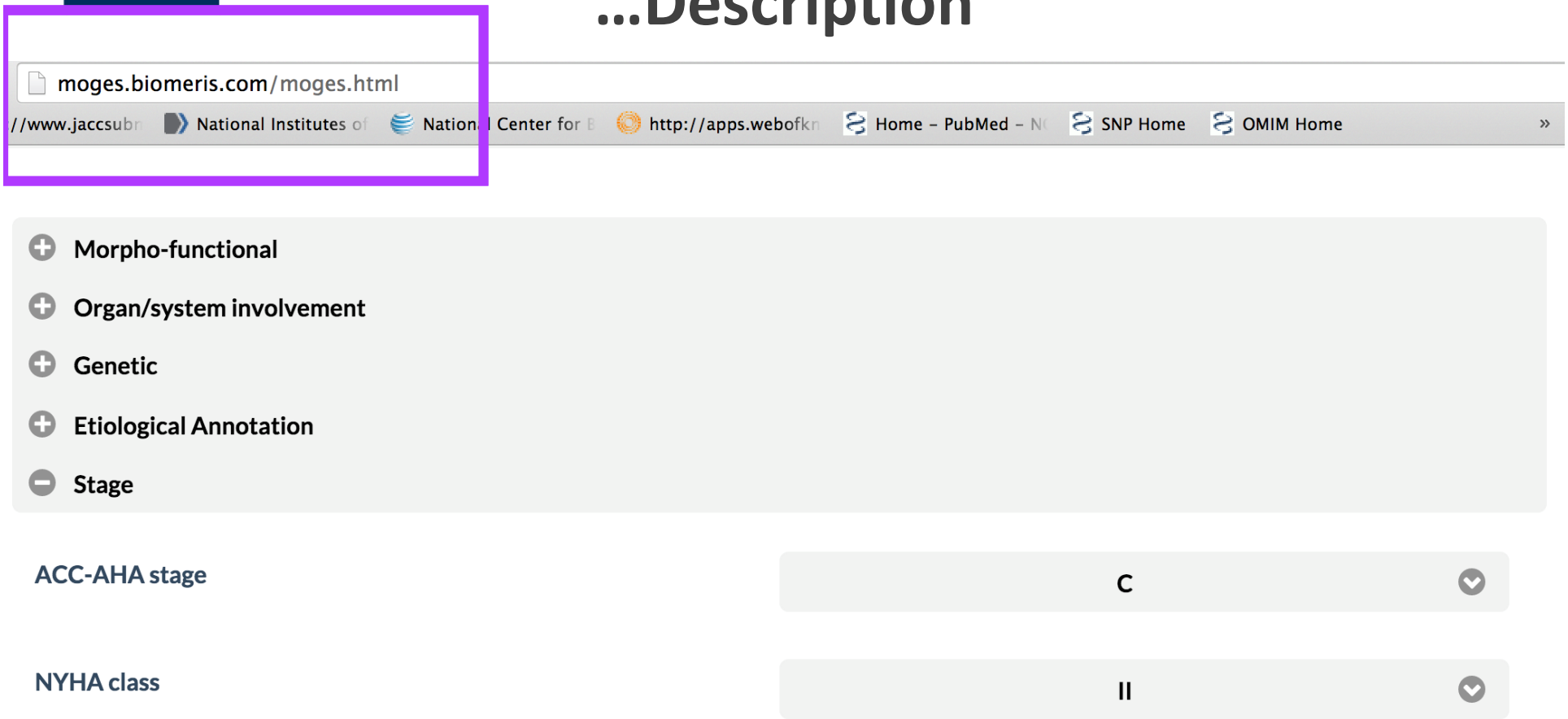




LDB3 → *DCM with LVNC*
Vatta el al. JACC
2003;42:2014–2027.

TNNT2:p.Lys217dup

Why forcing a diagnosis of NC?
…Description



$M_{D+NC}\ O_{H+M}\ G_{XLR}\ E_{G\text{-}G4.5[p.Glu202ValfsX15]}\ S_{C\text{-}II}$

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Phenotype-based diagnosis of CMP

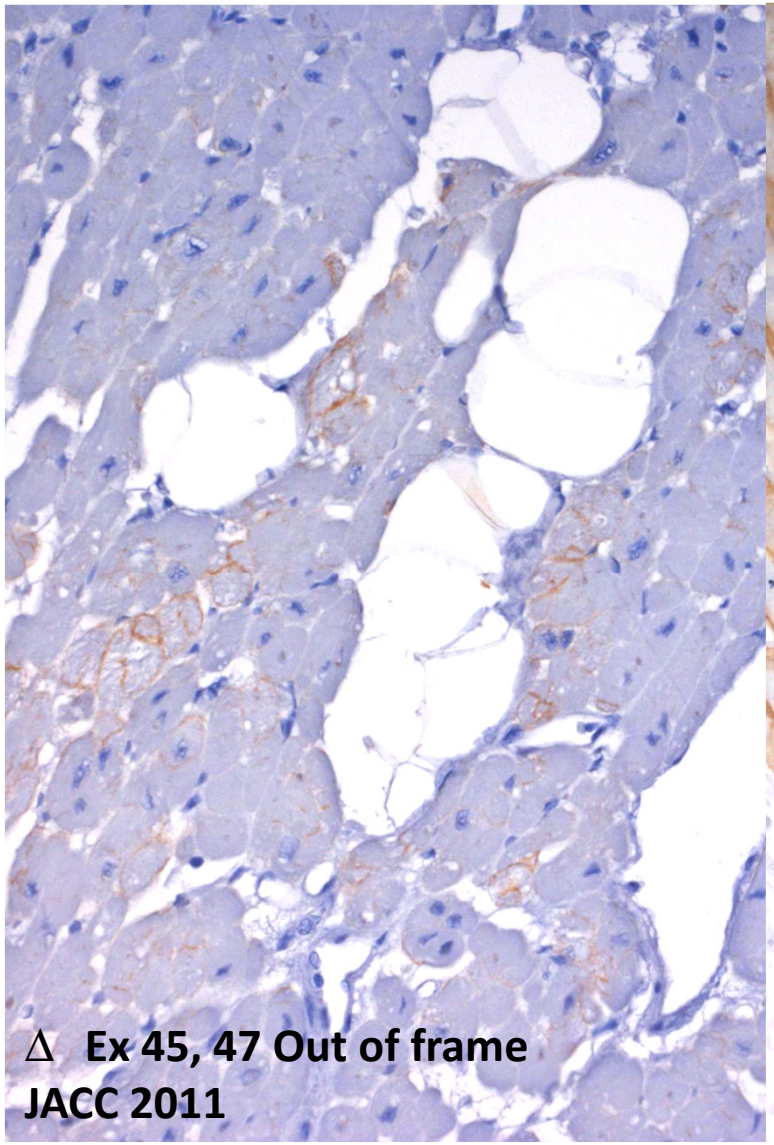
- Inheritance
- Cardiac traits
  - ECG
  - Echocardiography
    - LVNC
- Extracardiac traits: ocular, auditory, skeletal, nervous, cutaneous, etc.
- Biochemical markers: >sCPK, >lactacidemia, hypocholesterolemia, organic acidurias, etc.
- CMR
- Pathology: DYS; DES; LMNA; LAMP2, etc.
- Age of onset: amyloid unlikely in children!
- Combined information
  Probands and relatives

Genetic and clinical red flags contributing to the hypothesis of a specific diagnosis

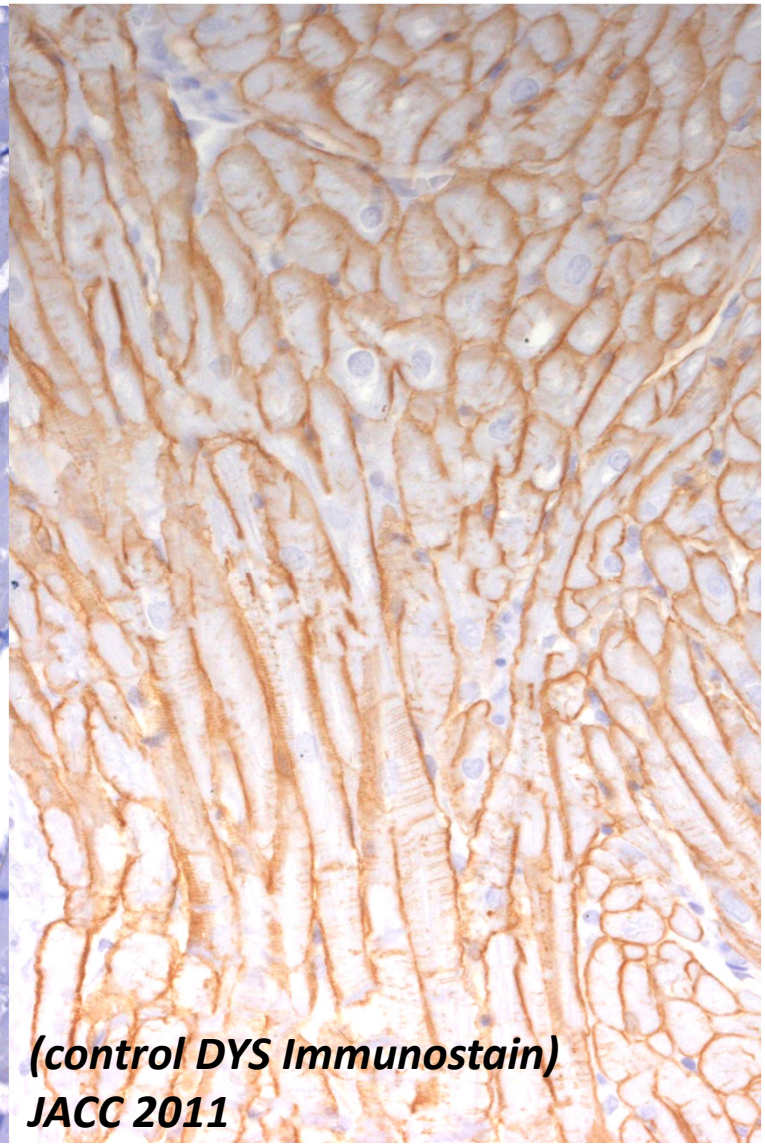
Rapezzi, Arbustini et al Eur Heart J. 2013;34:1448-58.

PRECISE DIAGNOSIS

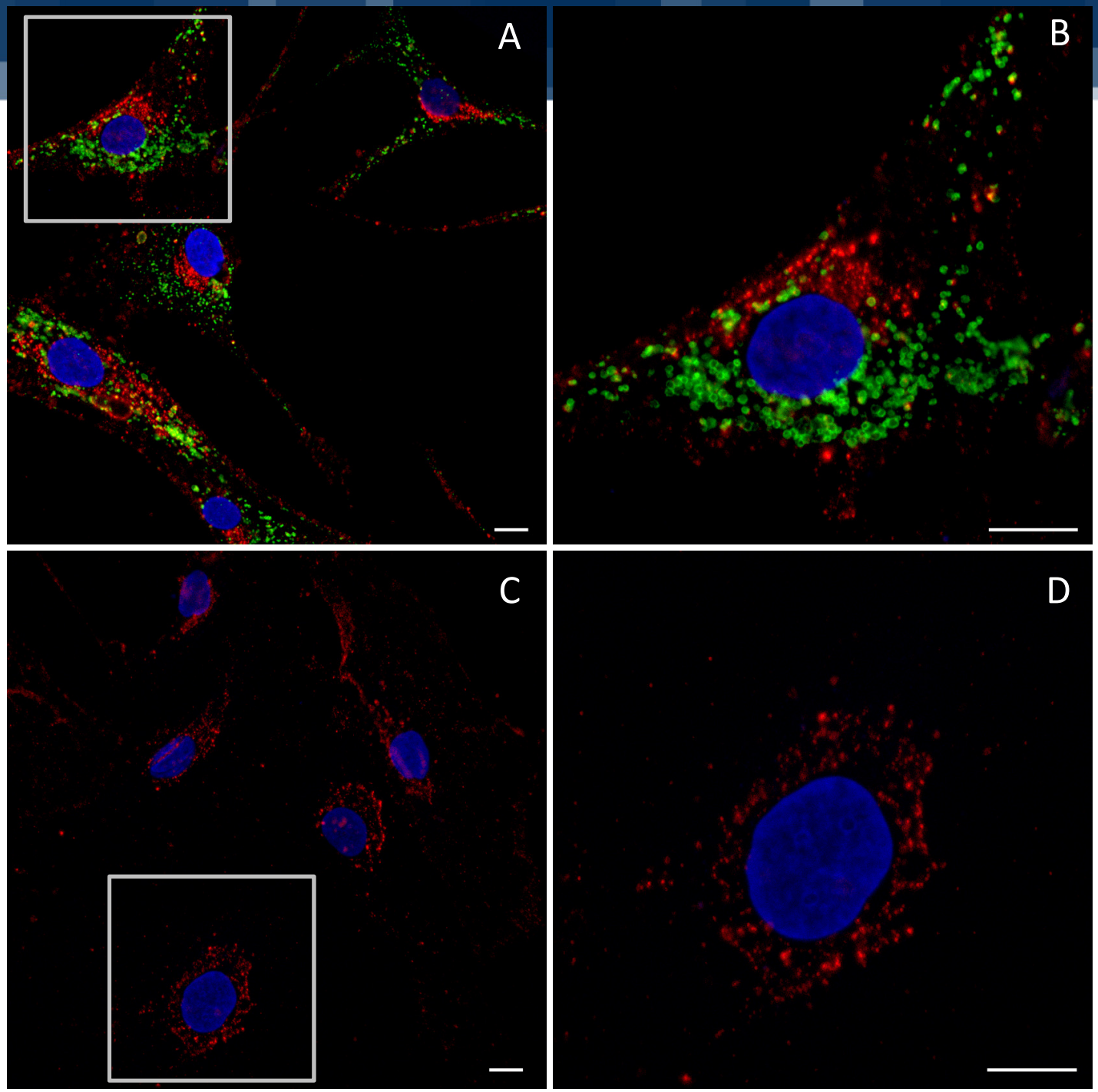
DYS:
28%
LVNC



Δ Ex 45, 47 Out of frame
JACC 2011



(control DYS Immunostain)
JACC 2011



Expression of the mutated protein LAMP2 (green) Lysosome marker in red Male

CTRL

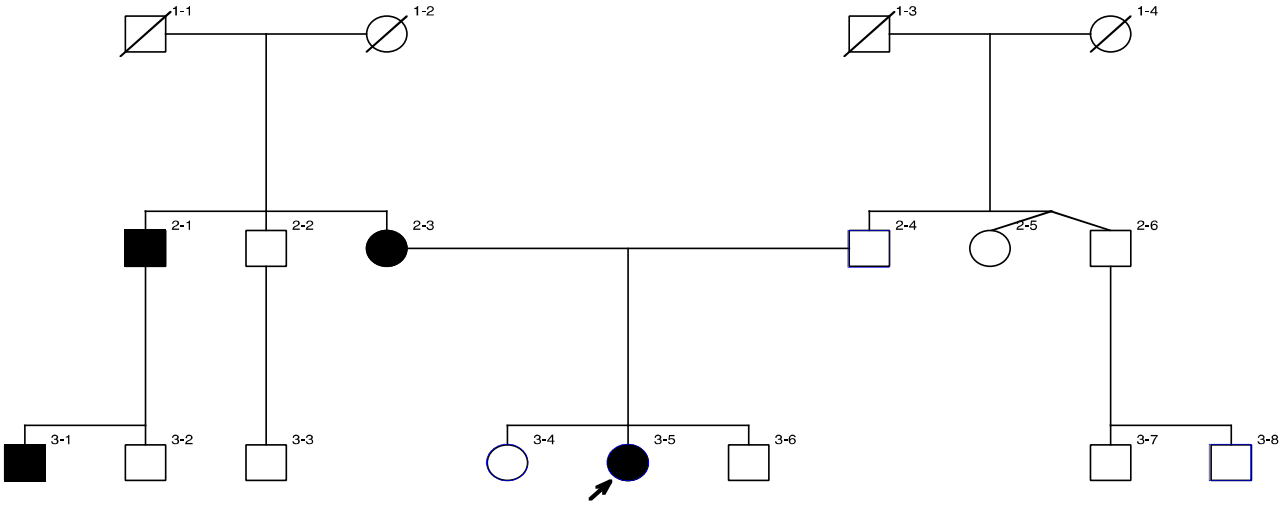
Mutated

Family screening in the diagnostic work-up

- Genetic evaluation**, both counseling and genetic testing**, is recommended in
  - patients diagnosed with one of the syndromes in which LVNC may recur
  - individuals in which LVNC is incidentally identified during medical screening
- The **medical genetic examination** explores anthropometric profiles, faces, skin, eyes, hairs, skeletal, and nervous system.
- ECG, echocardiography and CMR, biochemical information, along with extra-cardiac traits are potentially useful for phenotype characterization of patients and families (*red flags*)
- Family **pedigrees give a "graphic" view** of the mode of inheritance of the disease
- **Affected members of a same family may demonstrate different or combined cardiac phenotypes, with isolated LVNC in some relatives, and CMP with or without LVNC in others**

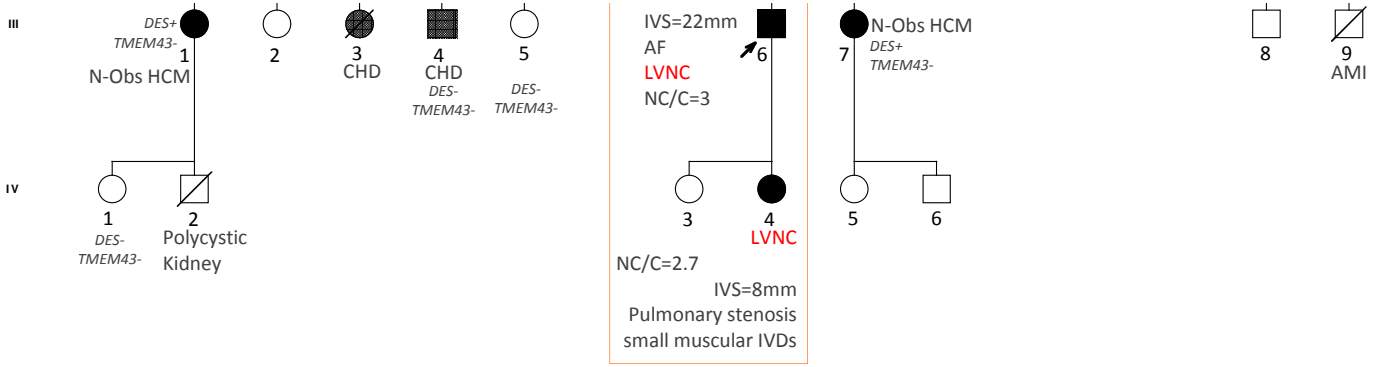
Segregation

HCM+ LVNC/hypertrabeculation → MYBPC3 + LBD3

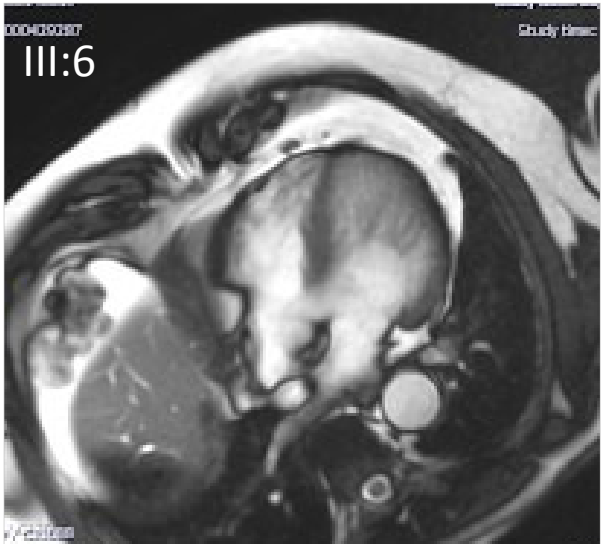


	MOGE(S)
3-5(P)	$M_{H\ (N\text{-}Obs)}$ (>trabeculation) O_H G_{AD} $E_{G\text{-}MYBPC3}$[p.Arg502Gln] + *LDB3*[p.Asp117Asn] $S_{B\text{-}I}$
2-1	$M_{H\ (N\text{-}Obs)}$ O_H G_{AD} $E_{G\text{-}MYBPC3}$[p.Arg502Gln] $S_{B\text{-}I}$
2-2	M_0 O_0 G_{Neg} $E_{G\text{-}MYBPC3}$[Neg] $S_{A\text{-}I}$
2-3	$M_{H\ (N\text{-}Obs)}$ O_H G_{AD} $E_{G\text{-}MYBPC3}$[p.Arg502Gln] $S_{B\text{-}II}$
2-4	$M_{0(>trabeculation)}$ O_H G_U $E_{G\text{-}LDB3}$[p.Asp117Asn] $S_{B\text{-}I}$
2-6	M_0 O_0 G_U $E_{G\text{-}LDB3}$[p.Asp117Asn] $S_{A\text{-}I}$
3-1	$M_{H\ (N\text{-}Obs)}$ O_H G_{AD} $E_{G\text{-}MYBPC3}$[p.Arg502Gln] $S_{B\text{-}I}$
3-2	M_0 O_0 G_{Neg} $E_{G\text{-}MYBPC3}$[Neg] $S_{A\text{-}I}$
3-4	$M_{0(>trabeculation)}$ O_H G_U $E_{G\text{-}LDB3}$[p.Asp117Asn] $S_{B\text{-}I}$
3-6	M_0 O_0 G_{Neg} $E_{G\text{-}MYBPC3}$[Neg] + *LDB3*[Neg] $S_{A\text{-}I}$
3-7	M_0 O_0 G_{Neg} $E_{G\text{-}LDB3}$[p.Asp117Asn] $S_{A\text{-}I}$
3-8	$M_{0(>trabeculation)}$ O_H G_{AD} $E_{G\text{-}LDB3}$[p.Asp117Asn] $S_{B\text{-}I}$

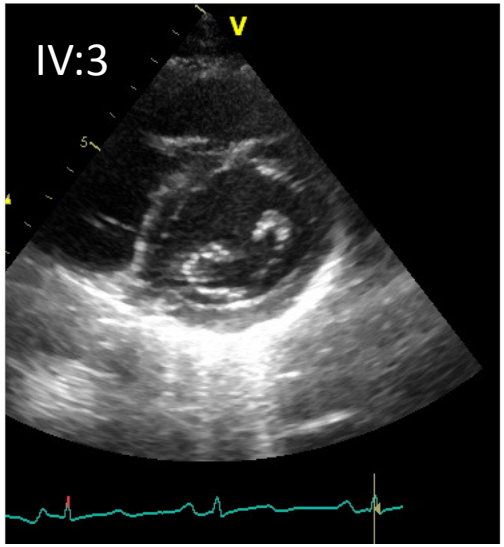
DES→HCM, TMEM43→NC



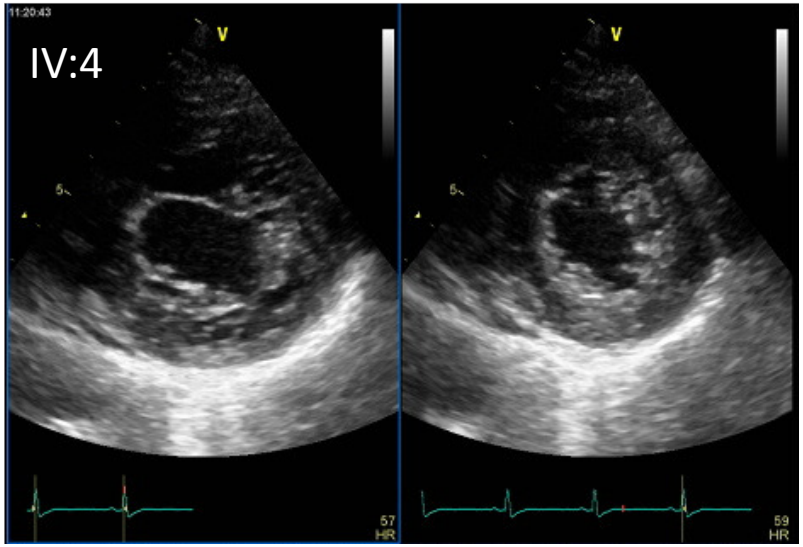
DES p.(Gly84Ser) + *TMEM43* p.(Arg28Trp)



DES (Neg) + TMEM43 (Neg)

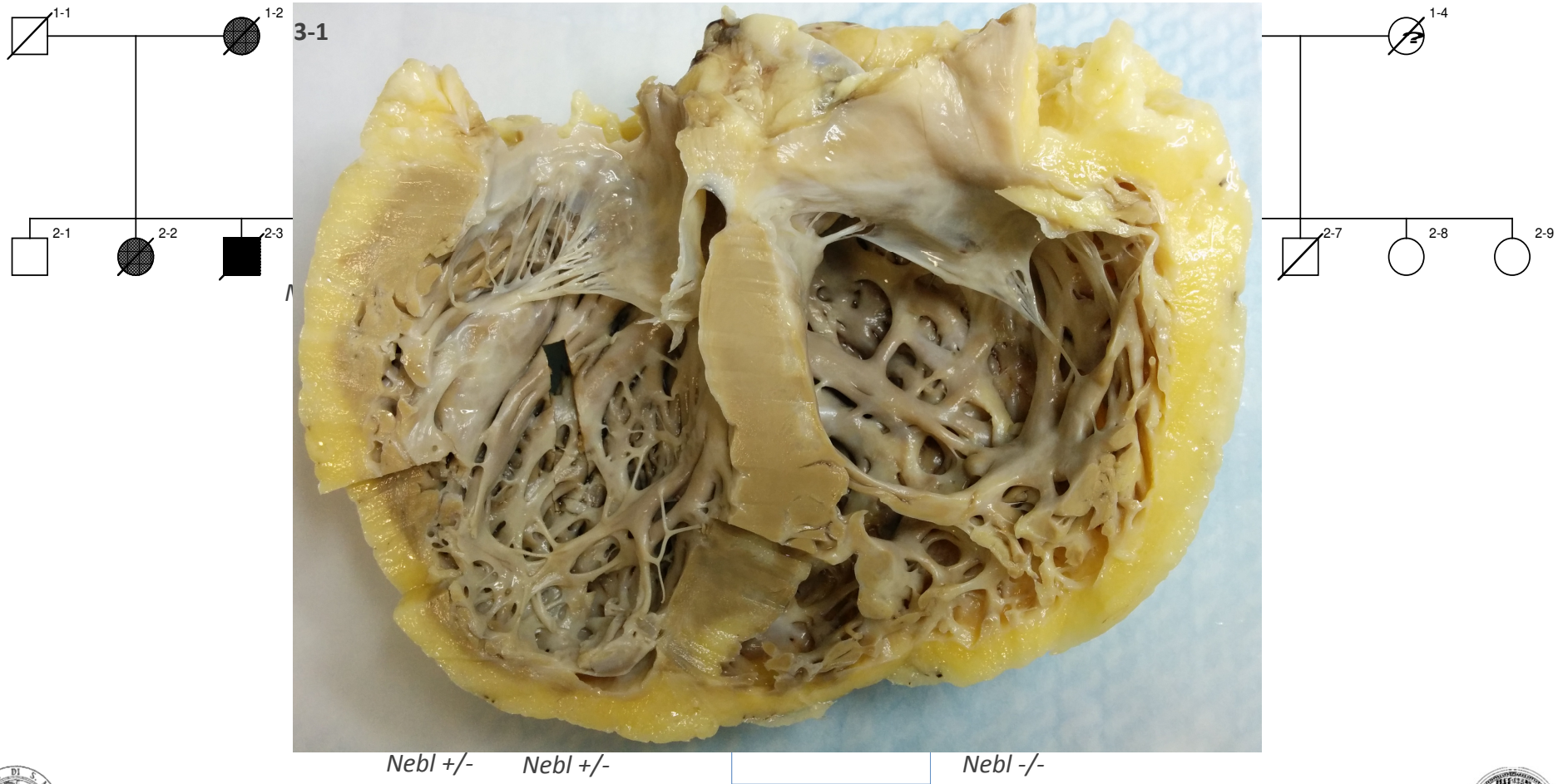


DES p.(Gly84Ser) + *TMEM43* p.(Arg28Trp)



Compactless DCM
MYBPC3 +/- NEBL +/+

3-1, proband: MYBPC3 p.(Thr957Ser) + *NEBL* c.1008+5A>G Homozygous



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Left Ventricular Noncompaction

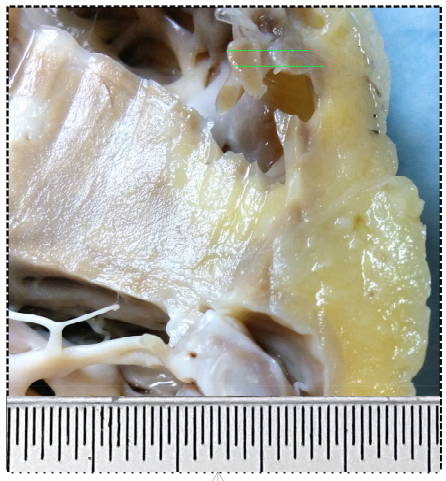
Prominent trabeculae /thick, non-compacted layer

+

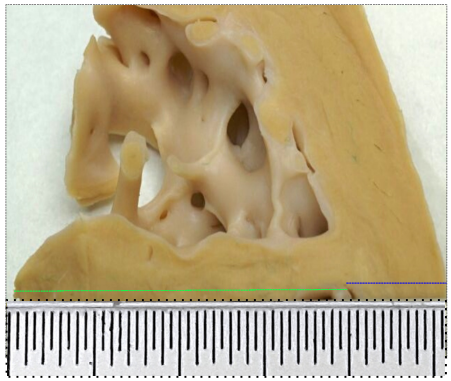
Thin compacted layer

+

Deep intertrabecular recesses



Diagnostic criteria based on NC/C ratio thickness, volume, mass: fulfilled in both examples



Causes: heterogeneous

- *Individual variability in hearts with normal LV size, function and thickness*
  - *In normal hearts*
- *Genetic Heterogeneous*
  - *"Isolated"*
  - *Associated with CMP*
  - *Associated with CHD*
  - *Associated with monogenic syndromes*
  - *Associated with chromosomal anomalies*
  - *Dynamic, > with disease progression (shown in cardiodystrophinopathies)*
  - *Emerging during the course of the disease (shown in ryanodinopathies)*
  - *Potentially reversible (shown in acquired LVNC)*
- *Non genetic*
  - *Sport*
  - *Pregnancy*
  - *Sickle cell anemia*
  - *Chronic renal failure*

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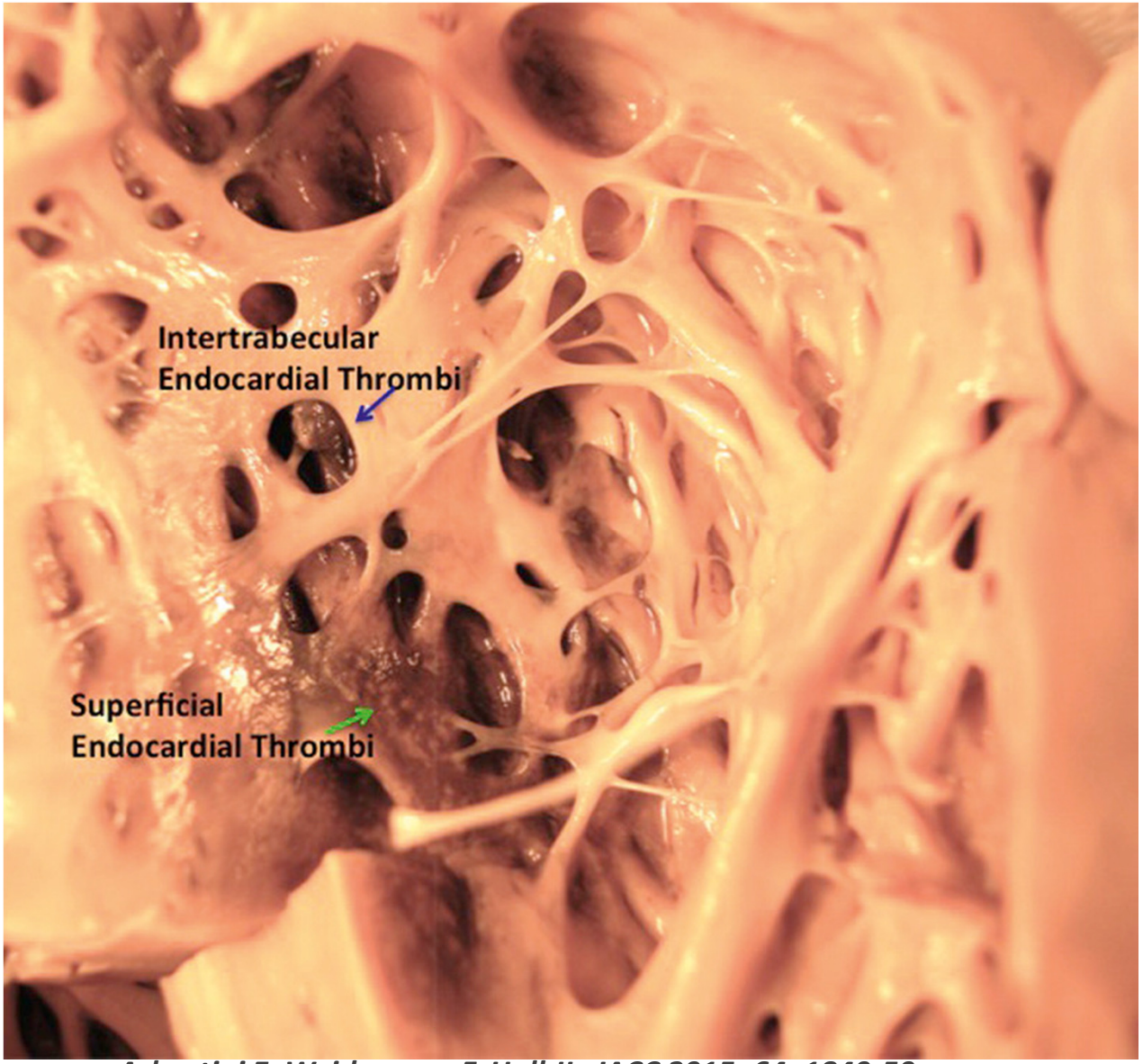

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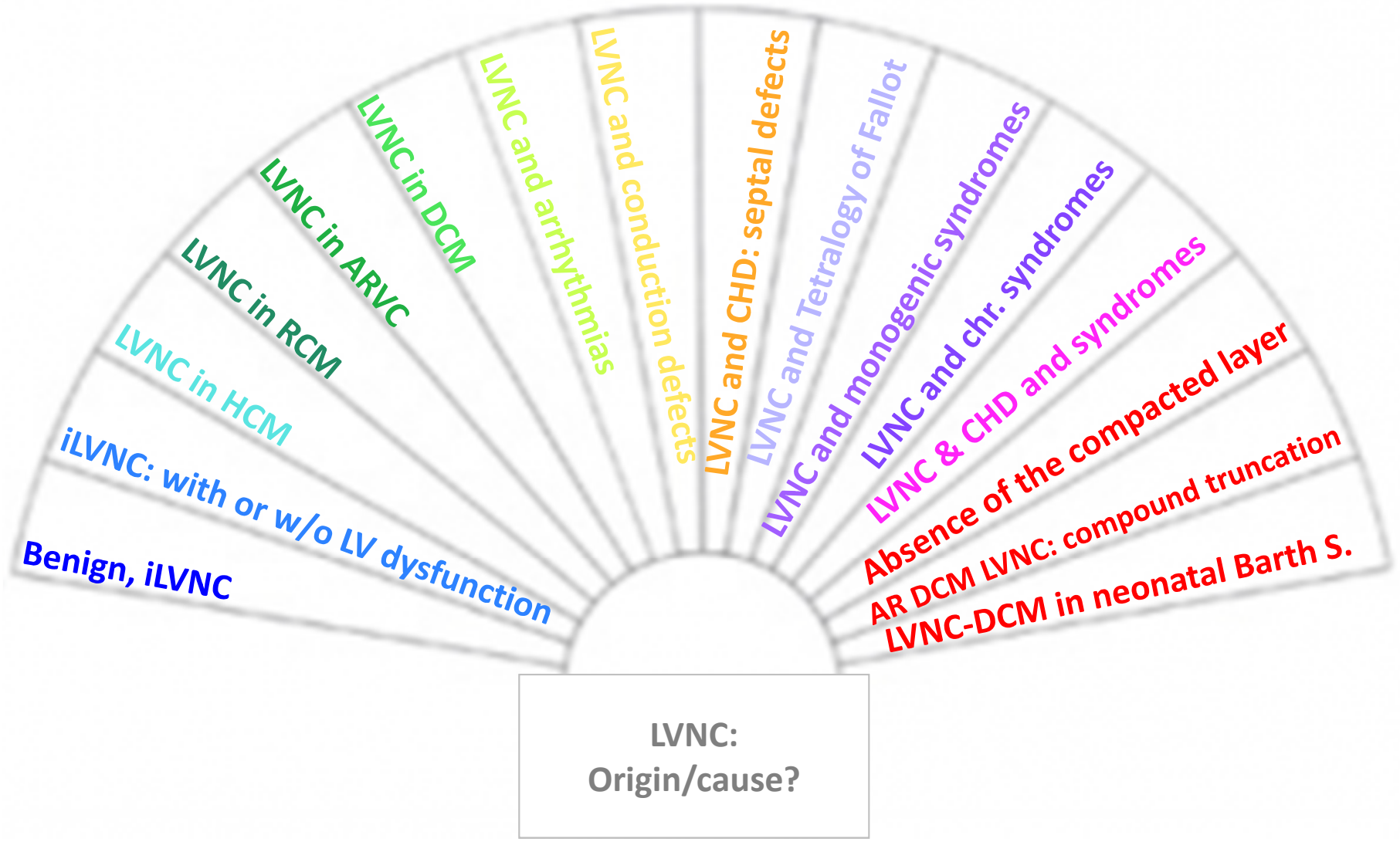
Benign, iLVNC
iLVNC: with or w/o LV dysfunction
LVNC in HCM
LVNC in RCM
LVNC in ARVC
LVNC in DCM
LVNC and arrhythmias
LVNC and conduction defects
LVNC and CHD: septal defects
LVNC and Tetralogy of Fallot
LVNC and monogenic syndromes
LVNC and chr. syndromes
LVNC & CHD and syndromes
Absence of the compacted layer
AR DCM LVNC: compound truncation
LVNC-DCM in neonatal Barth S.
LVNC:
Origin/cause?

CONCLUSION

- *Scientific Societies cannot ignore the problem*
- *Risks:*
  - *Overdiagnosis of NC*
  - *Misdiagnosis of CMP*
  - *Labeling healthy individuals as affected by CMP → athletes*
  - *Ethics of resources*

By it self LVNC / increased trabeculation does not define a CMP, is dynamic, potentially reversible.

- *Diagnostic work-up*
  - *Inclusion → clinical evaluation, "genetic visit", ECG, ECHO, Holte*
  - *Monitoring*
  - *Family screening*
  - *Genetic testing → CMP*