Sudden cardiac death
Heart muscle fibrosis and genetics

Inherited and rare diseases unit
Onassis Cardiac Surgery Centre
Cardiomyopathies

- HCM
- DCM
- ARVC
- RCM
- Unclassified

- Familial / Genetic
  - Unidentified gene defect
  - Disease subtype*

- Non-familial / Non-genetic
  - Idiopathic
  - Disease subtype*

European WG on Myocardial and Pericardial Diseases (EHJ2008)
Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases

Yigal M. Pinto1, Perry M. Elliott2, Eloisa Arbustini3, Yehuda Adler4, Aris Anastasakis5, Michael Böhm6, Denis Duboc7, Juan Gimeno8, Pascal de Groote9,10, Massimo Imazio11, Stephane Heymans12,13, Karin Klingel14, Michel Kornajda11, Giuseppe Limongelli15, Ales Linhart16, Jens Mogensen16, James Moon17, Petronella G. Pieper18, Petar M. Seferovic19, Stephan Schueler20, Jose L. Zamorano21, Alda L.P. Caforio22, and Philippe Charron13,23
CASE

- 28 Y OLD – SUDDEN DEATH
- ECG: SR, LOW VOLTAGE
- FATHER WITH PALPITATION

POST MORTEM

SEGMENTAL, REGIONAL FIBROSIS WITHOUT OTHER SPECIFIC HISTOLOGICAL FINDINGS
Male, 28 years of age

ECG: 3 years ago

LOW VOLTAGE
70y  
No cardiac reason

>90y

90y

94y  
Arrhythmia (?)

85y

Dyslipidemia  
AY – 80y

6 brothers  
alive

Ca

Ca

60y  
Ca

76y

Ca

Ca

40d

28y - SCD

POST MYOCARDITIS?

= SCD – Rest ECG abnormalities

= Normal person

+ = Person that was genetically tested and a mutation was identified

- = Person that was genetically tested and a mutation was not identified
Relatives’ clinical data – Father
CORONARY ANGIOGRAPHY NORMAL
FAMILY CLINICOGENETIC APPROACH

- **SCD** – Rest ECG abnormalities
- **Person with indication of cardiomyopathy**
- **Normal person**
- **Person that was genetically tested and a mutation was identified**
- **Person that was genetically tested and a mutation was not identified**

**Disease causative genetic mutation**

p.Arg25Cys of gene PLN (phospholabane)

**Mild DCM arrhythmogenic**

**FAMILY CLINICOGENETIC APPROACH**

- **70y No cardiac reason**
- **>90y**
- **90y Arrhythmia (?)**
- **85y Dyslipidemia AY – 80y**
- **6 brothers alive**
- **Ca**
- **60y Ca**
- **76y Ca**
- **Reported normal**
- **40Y**
- **28y – SCD**
- **PREGNANCY**

**Person with indication of cardiomyopathy**

Gene PLN (phospholabane)

**Mild DCM arrhythmogenic**

- **Person that was genetically tested and a mutation was identified**
- **Person that was genetically tested and a mutation was not identified**
Disease causative genetic mutation

p.Arg25Cys of gene PLN (phospholabane)
A founder mutation in the *PLN* gene, which encodes phospholamban, a protein with an important role in calcium homeostasis, has been associated with profound arrhythmic tendencies in patients with DCM and in those without structural phenotypes. These studies suggest that mutations in genes controlling calcium handling, also known to cause DCM, may influence arrhythmic risk independently of structural changes.

**IN DEPTH**

**Personalizing Risk Stratification for Sudden Death in Dilated Cardiomyopathy**

*The Past, Present, and Future*

Brian P. Halliday, MB ChB, John G.F. Cleland, MD PhD
Jeffrey J. Goldberger, MD Sanjay K. Prasad, MD

Flowchart of the potential techniques that may be used to improve risk stratification.
Reduced and age-dependent penetrance and variable expressivity illustrate the importance of environmental modifiers such as viral triggers or excess alcohol consumption, which may unmask the phenotype.
The Genetic Basis of DCM

Familial DCM is defined as idiopathic DCM in at least 2 closely related relatives and is thought to account for 25% to 50% of idiopathic DCM.

The majority of mutations occur in autosomal genes, with a small number of Xlinked and mitochondrial mutations identified.

Cases with reduced penetrance, variable expressivity, and multiple mutations are not infrequent.

The most common mutations occur in genes encoding sarcomeric proteins and in genes related to the nuclear envelope and the cytoskeleton.

Considering that DCM is often diagnosed late and occasionally at postmortem, genetic screening enabling early diagnosis and risk stratification is attractive.
ΣΥΖΗΤΗΣΗ

► ΠΟΙΑ ΕΙΝΑΙ Η ΔΙΑΓΝΩΣΗ ΚΑΙ ΓΙΑΤΙ;

► ΣΕ ΤΙ ΚΑΤΗΓΟΡΙΑ ΚΙΝΔΥΝΟΥ ΑΝΗΚΕΙ ΣΥΜΦΩΝΑ ΜΕ ΤΑ ΚΛΑΣΣΙΚΑ ΚΡΙΤΗΡΙΑ ΔΙΑΣΤΡΩΜΑΤΩΣΗΣ ΚΙΝΔΥΝΟΥ.

► ΕΧΕΙ ΣΗΜΑΣΙΑ ΝΑ ΕΚΛΕΓΧΘΕΙ Η ΟΙΚΟΓΕΝΕΙΑ;