Clinical Genetics in Cardiomyopathies

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Καρδιολογίας ΑΠΘ

No conflict of interest
Basic Science and Molecular Cardiology

Patterns of Inheritance of a Disease

Autosomal Recessive Inheritance

Autosomal Dominant Inheritance

X-linked Inheritance

Mitochondrial Inheritance

Carrier  Unaffected  Affected
Genetic terms

- **Proband**: The first individual diagnosed in a family
- **Mutation**: A pathogenic gene variant
- **Modifier**: Gene variants or environmental factors
- **Penetrance**: phenotype positive/genotype positive
- **Phenotypic heterogeneity**: Phenotypic variability among individuals with similar genotype
- **Genotypic heterogeneity**: Genetic variability among individuals with similar phenotypes
- **Phenocopy**: A phenotype that mimics the disease phenotype
Types of mutation

- Missense mutation
- Nonsense mutation (Truncated mut)
  - Insertion/deletion
  - Frameshift mutation
  - Abnormal mRNA splicing
- Duplication
- Repeat expansion
Genetics of Hypertrophic Cardiomyopathy After 20 Years
Clinical Perspectives

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Figure 1  HCM Landmarks

Genetic and clinical advances over the >50-year history of hypertrophic cardiomyopathy (HCM). ICD = implantable cardioverter-defibrillator; SD = sudden death.
Prevalence of HCM

Advanced Imaging (CMR) Identifies Some Echo-Negative Patients

Autosomal Dominant Familial Inheritance with Multiple Affected Relatives

1:500 (0.2%) CARDIA

Current HCM Prevalence

Gene (+) Phenotype (-) Gene Carriers

Pathogenic Sarcomere Mutations (general population genetics)

0.6%

>1:500

Revised Estimate of HCM Prevalence


Christopher Semsarian et al. JACC 2015;65:1249-1254
Etiology of HCM

- Sarcomere mutations
  - Autosomal dominant
  - Earlier presentation
  - FH HCM/SCD more frequent
  - More severe phenotype
  - ?Poorer prognosis
  - 5% double mutation
- Metabolic disorders
  - Autosomal recessive/X-linked
- Neuromuscular disorders
  - Rarely HCM
- Malformation syndromes
  - Mainly diagnosed during childhood
### Molecular Substrate of HCM

<table>
<thead>
<tr>
<th>Strongest evidence for pathogenicity</th>
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<tbody>
<tr>
<td><strong>Thick filament</strong></td>
</tr>
<tr>
<td>1. β-myosin heavy chain</td>
</tr>
<tr>
<td>2. Regulatory myosin light chain</td>
</tr>
<tr>
<td>3. Essential myosin light chain</td>
</tr>
<tr>
<td><strong>Thin filament</strong></td>
</tr>
<tr>
<td>4. Cardiac troponin T</td>
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<tr>
<td>5. Cardiac troponin I</td>
</tr>
<tr>
<td>6. Cardiac troponin C</td>
</tr>
<tr>
<td>7. α-tropomyosin</td>
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<tr>
<td>8. α-cardiac actin</td>
</tr>
<tr>
<td><strong>Intermediate filament</strong></td>
</tr>
<tr>
<td>9. Cardiac myosin-binding protein C</td>
</tr>
<tr>
<td><strong>Z-disc</strong></td>
</tr>
<tr>
<td>10. α-actinin 2</td>
</tr>
<tr>
<td>11. Myозенin 2</td>
</tr>
<tr>
<td><strong>Lesser evidence for pathogenicity</strong></td>
</tr>
<tr>
<td><strong>Thick filament</strong></td>
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<tr>
<td>12. α-myosin heavy chain</td>
</tr>
<tr>
<td>13. Titin</td>
</tr>
<tr>
<td><strong>Z-disc</strong></td>
</tr>
<tr>
<td>14. Muscle LIM protein</td>
</tr>
<tr>
<td>15. Telethonin</td>
</tr>
<tr>
<td>16. Vinculin/metavinculin</td>
</tr>
<tr>
<td><strong>Calcium handling</strong></td>
</tr>
<tr>
<td>17. Calsequestrin</td>
</tr>
<tr>
<td>18. Junctophilin 2</td>
</tr>
</tbody>
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HCM = hypertrophic cardiomyopathy.
Clinical Applications of Genetic Testing

- Prevalence of HCM Genes in Probands
Types of mutations

- **Missense** (δυσυνθετικές) 90%
  Single amino acid substitution
- **Frame shift** (αλλαγή αναγνωστικού πλαισίου)
- **Deletions/Insertions** of nucleic acids
- **Shortened truncated proteins**
- **Pathogenic mutations**, severe disease
- **MYBPC** gene
Targeted genetic screening
Echocardiography-guided genetic testing
Septal Morphologies in HCM

Role of genetics in prognosis

**Figure 3**
Relation of Genetic Test Status to Outcome in Patients With Hypertrophic Cardiomyopathy

- **Panel A**: Free of CV Death, Ischemic Stroke, and Progression to NYHA Class III-IV (%)
  - Myofilament-Negative
  - Myofilament-Positive
  - Follow-Up after Genetic Testing (Yrs)
  - $p = 0.002$

- **Panel B**: Free of Systolic Dysfunction (%)
  - Myofilament-Negative
  - Myofilament-Positive
  - Age (Yrs)
  - $p = 0.021$

- **Panel C**: Free of Restrictive LV Filling (%)
  - Myofilament-Negative
  - Myofilament-Positive
  - Age (Yrs)
  - $p = 0.018$

- **Panel D**: Free of Systolic Dysfunction and Restrictive LV Filling (%)
  - Thick Filament
  - Thin Filament
  - Double Heterozygous
  - Age (Yrs)
  - *$p < 0.05$*
Family T

A. 73y/F
- MYBPC3 Q998E (CAG>GAG) het

B. 77y/M
- VS
- TNNI3 R145W (CGG>TGG) het

C. 37y/M
- MYBPC3 Q998E (CAG>GAG) het
- MYBPC3 Glu998Glu
- TNNI3 Arg145Trp

No Risk Factors

Figure 8 Double Mutations as a Potential Risk Factor in HCM
Dilated Cardiomyopathy

- Dilated LV and RV
- Reduced EF
- Absence of CAD, abnormal load
- 30-50% genetic origin
Familial Dilated Cardiomyopathy (FDC)

- Incidence: 30% (familial history)
- Patterns of inheritance: autosomal dominant, autosomal recessive, X-linked, matrilineal (mitochondrial DC)
Criteria for the diagnosis of Familial Dilated Cardiomyopathy

1. Presence of 2 or more affected individuals in a single family
2. Presence of a first-degree relative of a dilated cardiomyopathy patient, with well documented unexplained sudden death at <35 years of age
The phenotype can be characterized by an isolated cardiac dysfunction (isolated DCM) include conduction defects (atrioventricular block or sinus node dysfunction) skeletal muscular disorders
Genetic causes and phenotypes of DCM
Genetic causes and phenotypes of DCM

**Sarcomere (10%)**
- β-Myosin heavy chain (*MYH7*)
- Troponin T (*TNNT2*)
- Troponin I (*TNNI3*)
- Troponin C (*TNNC1*)
- Cardiac actin (*ACTC*)
- Tropomyosin (*TPM1*)
- Myosin-binding protein C (*MYBPC3*)

*force generation*
Sarcomere and Z-disc associated proteins

- Titin (TTN)
- Titin-cap/telethonin (TEL)
- Muscle LIM protein (CRP3)
- Metavinculin (VCL)
- Cypher/ZASP (LDB3)

Genetic causes and phenotypes of DCM
CONCLUSIONS

TTN truncating mutations are a common cause of dilated cardiomyopathy, occurring in approximately 25% of familial cases of idiopathic dilated cardiomyopathy and in 18% of sporadic cases. Incorporation of sequencing approaches that detect TTN truncations into genetic testing for dilated cardiomyopathy should substantially increase test sensitivity, thereby allowing earlier diagnosis and therapeutic intervention for many patients with dilated cardiomyopathy. Defining the functional effects of TTN truncating mutations should improve our understanding of the pathophysiology of dilated cardiomyopathy. (Funded by the Howard Hughes Medical Institute and others.)
Genetic causes and phenotypes of DCM

**Cytoskeleton**
- Dystrophin (*DMD*)
- Sarcoglycan (*SGCD*)
- Intermediate filaments
- Desmin (*DES*)
- Lamin A/C (*LMNA*)
Lamin A and C mutations

- Dilated cardiomyopathy and conduction disease alone
- Dilated cardiomyopathy and muscular dystrophies
- Muscular dystrophies
Lamin A/C mutations
Natural history

- Atrial arrhythmia, progressive AV block
- VT/VF
- LV dilation, systolic dysfunction (3th decade)
- Permanent pacing (>50%, A-V block)
  

- Event free survival rate: 30% vs 75% at the age of 45 years compared to other forms of DCM
  
  *(Taylor MR et al. JACC 2003;41:771-80)*
Predictors of sudden death

- nonsustained ventricular tachycardia
- LVEF < 45%
- male sex
- non-missense mutations (ins-del/truncating, or splicing mutations)
Genetic causes and phenotypes of DCM

**Channel and channel-associated proteins**

- Cardiac sodium channel (SCN5A)
- ATP-sensitive potassium channel (SUR2A/ABCC9)
- Phospholamban (PLN)
Mitochondria

- Tafazzin (G4.5) respiratory chain reaction proteins: energy production

Genetic causes and phenotypes of DCM
Arrhythmogenic right ventricular cardiomyopathy (ARVC)
GENETICS in ARVC

- Two patterns of inheritance
- autosomal dominant
- autosomal recessive
Autosomal recessive disease

- Naxos disease: Plakoglobin gene
- Carvajal syndrome: Desmoplakin gene
Autosomal dominant disease

- Desmoplakin gene
- Plakophilin-2 gen
- Desmoglein-2 gene
- Desmocollin-2 gene
- TMEM43 gene
- RyR2 gene
- TGF-beta-3 gene
Figure 6  Arrhythmogenic right ventricular cardiomyopathy is a desmosomal disease, namely a disease of the intercellular junction.
The ARVD/C Genetic Variants Database: 2014 Update
Conclusions

Genetic screening in Cardiomyopathies

- Rapid progress in last years
- Determination of results with caution
- Very important in special cases (Laminopathies)
- Genetic-based experimental therapies