Genetic Cardiomyopathies: Idiopathic No More?

Cardiomyopathy

A heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilation, due to a variety of etiologies that frequently are genetic. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, and often lead to cardiovascular death or progressive heart failure-related disability.

This definition excludes myocardial involvement secondary to CAD, HTN, valvular and congenital heart disease.


Points to Remember

Genetic mutations are more common than you might think
Many cardiac cellular structures are affected
Demonstrate incomplete penetrance and phenotypic variation
Take care to unlock the family history
Skeletal myopathies may be present and subtle
Lots of arrhythmias may be a clue
CM may be part of a “two hit” model
LV dysfunction may be mild
Family screening can be life-saving


Cardiomyopathies--Classic

Dilated
Hypertrophic
Restrictive

Primary cardiomyopathies—disease processes solely or predominantly involve the myocardium
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Echocardiography Identifies Cardiomyopathy Phenotypes

Mutations of Cell Structures Lead to Gene Mediated Dilated Cardiomyopathy

The main proteins involved in cardiomyopathies

Left ventricular non-compaction cardiomyopathy

LV Non-Compaction

Genetic overlap of cardiomyopathy
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Massively parallel DNA sequencing has decreased the cost of sequencing.

Genetic Testing Can Give Three Results

Positive: Known pathologic gene identified

Negative: No Mutation Identified

Means: no genetic pathology OR pathologic gene mutation present but not identified

VUS: Variant of Uncertain Significance

Higher Probability: on a gene known to be associated with heart or cardiac pathology

Lower Probability: no known association with cardiac pathology

Diagnostic Approaches

History
Family History
ECG
Imaging
Echo
MRI
Biopsy
Labs
Genetic Testing

Genetic Mutations are Variously Expressed

Approach to the DCM Patient

Genetic Testing Panels

UT Health
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Phenotypic “Variation” Multiple Mutations May Be Present

Genetic Testing Samples Panels of Genes

AR Genotype and Family History Are Risk Factors for SCD and Life-threatening Arrhythmias

Titin, the Third Sarcomeric Filament

Truncations of Titin Causing Dilated Cardiomyopathy

Table 1. Subjects with TTN Truncating Variants, According to Cohort
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Genetic Etiology for Alcohol-Induced Cardiac Toxicity

Genetic Testing Samples Panels of Genes

VUS Number Varies by Population NU Biobank Cohort

Central Illustration: Alcohol Consumption and Genetic Background Act in Concert to Determine Cardiac Phenotype
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**Hypertrophic Cardiomyopathy**

Genetics

50% autosomal dominant with incomplete penetrance

Mutations of contractile proteins have been identified

- 50%: β-myosin heavy chain – Chromosome 14
- 15%: Troponin T – Chromosome 1
- 35%: α-tropomyosin – Chromosome 15

Phenotypic expression varies

- time of onset
- degree of hypertrophy
- risk of sudden death

**Restrictive Cardiomyopathy**

Non-infiltrative

- Idiopathic
- Scleroderma

**HCM Phenotypes**

- Sigmoidal HCM: 40–50%
- Reverse curve HCM: 30–40%
- Asymptomatic: < 15%
- Restrictive: >15%

**HCM Genes**

HCM Panel Gene List: ACTC1, ACTN2, ANKR01, CALR3, CAV3, CSR3, DES, FXN, GLA, JPH2, LAMP2, MYBP3, MYH6, MYH7, MYL2, MYL3, MYOM1, MYOZ2, NEXN, PLN, PKAG2, PTPN11, RAF1, TCAP, TNAC1, TNAC3, TNNT2, TPM1, TTN, TTR, VCL
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Restrictive Cardiomyopathy Etiologies

- Myocardial infiltration
- Amyloidosis
- Sarcoidosis
- Hemachromatosis
- Fabry’s Disease – glycosphingolipid deposits
  - α-galactosidase A deficiency
- Gaucher’s Disease – cerobroside deposits
  - α-glucosidase deficiency

Restrictive Cardiomyopathy Etiologies

- Endocardial Lesions
  - Endocardial fibrosis
    - Africa, Brazil, Columbia, Sri Lanka
- Carcinoid Heart Disease
- Loffler’s endocarditis
- Hypereosinophilic syndrome

Thank You!

Variation in SCN5A

SCN5A G1318V

Adapted from Ruan Y et al. (2009) Nat Rev Cardiol