Taking Heredity to the Heart: Genetics of Cardiomyopathy

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Objectives

- Review the genetic basis of HCM
- Discuss importance and indicators in the family history
- Discuss some issues surrounding genetic testing
- Briefly list other inherited cardiovascular conditions that are on our radar

No conflicts to disclose
Inheritance Patterns in Cardiac Disease
All Have a Genetic Basis

Familial CM
Familial Arrhythmias
Familial Aortopathies
Familial Hyperlipidemia

Simple/Mendelian:
Primary cause:
Single variant with large effect
(Autosomal Dominant)
Plus:
Multigenic influences
Environmental influences

Complex/Multigenic
Primary cause:
Multiple common variants, each with small but additive effects
Occasional:
Rare variants with larger effect size

Coronary disease
Hypertension
Typical hyperlipidemia
Autosomal Dominant Inheritance

- A single altered gene is passed on in a family
- 50% independent probability of gene being passed on (regardless of sex)
- Reduced penetrance and variable expressivity
- Nothing skips generations
16 y/o brother, Asymptomatic

20 y/o male diagnosed HCM age 4 mo
Myectomy age 11, Class II CHF, primary prevention ICD age 16, appropriate shock age 19

46 y/o father, Asymptomatic

TNNT2 Arg286Cys
Genetic basis for HCM: mutations in sarcomere contractile unit genes

- Improved Diagnosis of Familial Disease
- Prognosis
- Mechanistic Understanding
- Emerging Treatments Targeted to Mechanism


Ho, et al., Circ 2018
Genetic test results

Results

Known Pathogenic Mutation

Presumed Pathogenic

Novel (new) Mutation

Unknown Clinical Significance

Benign

Negative

Confirms diagnosis
Testing available for family
(cannot predict severity or age of onset)
Reproductive options

Analyze further
Parental testing

May or may not cause disease
Influence other variants?
Cannot be used to test unaffected relatives
Clinical co-relation essential; suspicious or not??
Affected relatives help clarify
Reclassification

Cannot rule out genetic cause
No genetic testing for family

Genetic test results should be interpreted in the context of clinical and family history information
Insurance reimbursement variable

Prices plummeted: $250 OOP for proband. May be no charge for family.

Comparison: Cost of clinical screening >$2000 per exam
Discrimination

‘Genetic Information Non-Disclosure Act’ (GINA) signed into law on May 21\textsuperscript{st}, 2008.

- Prohibits a group health plan for requesting, requiring, obtaining or using genetic testing results
- Prohibits employer from discriminating based on genetic information (hiring, firing, raises, promotions)
- Not included: life, disability & long-term care insurance
- Exceptions
Genetic Basis of DCM

- Genetic basis of DCM now established
- Negative family history does NOT rule out genetic DCM (variable expressivity)
- Genetic testing should be considered for DCM, even in setting of EtOH or peripartum
- Cardiomyopathy medications should not be stopped with EF recovery (the genetic substrate is still there)
- DCM patients’ family members should be screened even if negative FamHx.
Other Inherited Cardiovascular Indications for Genetic counseling and/or testing

- Dilated Cardiomyopathy
- Arrhythmogenic Cardiomyopathy
- Left Ventricular Non-Compaction
- Arrhythmias (Long QT, CPVT, Brugada)
- Aortic disease (Marfan syndrome, LDS, EDS, non-syndromic FTAAD)
- Vascular disease (SCAD, FMD)
- Familial Hypercholesterolemia
- Pulmonary Arterial Hypertension
- Neuromuscular disease with cardiac component