Genetics in heart disease

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Disclosures

I have nothing to disclose
Inherited cardiovascular disease

- According to the American Heart Association, ~50% of adults in the US have CVD.
- Heart disease causes almost 1 in 4 deaths in the U.S.
- Most CVD traits are polygenic or multifactorial (CAD, MI, ischemic stroke, AF).
- Inherited CVD has an estimated prevalence of 3% in the general population.
- Some inherited forms of CVD have a single or a few causal genes (hypercholesterolemia).
- Cardiomyopathies, aortopathies, channelopathies are heterogeneous disorders and are a major cause of cardiac morbidity and mortality.
- Younger onset of CVD or strong family history – higher risk of genetic etiology.
Inherited cardiovascular disease

- Understanding the genetics behind the onset and development of CVD is a critical part of the prevention and management.

- Precise molecular diagnosis can help predict prognosis and may guide treatment.

- Identifying a pathogenic variant in a patient allows screening other family members at risk.

- There may be different expressivity within the same family (age of onset, severity).

- Genotype-phenotype correlation remains complex for many disorders.

- Mutations in a single gene can influence multiple phenotypic traits (ex. TTN is the main disease-causing gene in DCM and is also involved in the pathogenesis of HCM and ARVC).

- Considerable phenotypic overlap between cardiomyopathies and arrhythmic syndromes.
Familial hypercholesterolemia

- Most common inherited cardiovascular disease, prevalence of 1:200-250
- Accounts for 2%-3% of myocardial infarctions in individuals < 60 years old
- Severely elevated LDL cholesterol levels that lead to atherosclerotic plaque deposition in the coronary arteries and proximal aorta at an early age
- Untreated men are at a 50% risk for a fatal or non-fatal coronary event by age 50 years
- Untreated women are at a 30% risk by age 60 years
- Xanthomas (patches of yellowish cholesterol buildup) around the eyelids and within the tendons of the elbows, hands, knees, and feet
- Autosomal dominant disorder
- **LDLR** (60-80%), **APOB** (1-5%), **PCSK9** (1-3%)
Marfan syndrome

- Face: Downslanted palpebral fissures, high arch palate, small chin, malar hypoplasia
- Eyes: Ectopia lentis, high myopia
- Heart: Aortic dilatation, valvular dyplasia, MVP
- Other: Arachnodactyly, scoliosis, chest deformity, flat feet, stretch marks, pneumothorax
- Autosomal dominant, mutations in FBN1 gene
Marfan syndrome

Diagnostic criteria:
When no family history, the diagnosis can be established in 4 scenarios:
- Aortic root enlargement (Z-score ≥2.0) and one of the following:
  - Ectopia lentis
  - A pathogenic FBN1 mutation
  - A systemic score ≥7
- Ectopia lentis and a FBN1 mutation associated with aortic enlargement

With family history the diagnosis can be established in 3 scenarios:
- Ectopia lentis
- Systemic score ≥7
- Aortic root enlargement (Z-score ≥2.0 if ≥20 years or ≥3.0 if <20 years)
<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist and thumb sign</td>
<td>3</td>
</tr>
<tr>
<td>Wrist or thumb sign</td>
<td>1</td>
</tr>
<tr>
<td>Pectus carinatum deformity</td>
<td>2</td>
</tr>
<tr>
<td>Pectus excavatum or chest asymmetry</td>
<td>1</td>
</tr>
<tr>
<td>Hindfoot deformity</td>
<td>2</td>
</tr>
<tr>
<td>Flat foot (pes planus)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>2</td>
</tr>
<tr>
<td>Protrusio acetabulae</td>
<td>2</td>
</tr>
<tr>
<td>Reduced upper segment / lower segment and increased arm span/height ratios</td>
<td>1</td>
</tr>
<tr>
<td>Scoliosis or thoracic column kyphosis</td>
<td>1</td>
</tr>
<tr>
<td>Reduced elbow extension</td>
<td>1</td>
</tr>
<tr>
<td>3 of 5 facial features</td>
<td>1</td>
</tr>
<tr>
<td>Skin striae</td>
<td>1</td>
</tr>
<tr>
<td>Myopia</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>
Marfan syndrome

**Treatment:**

- Annual echo to monitor ascending aorta
- More frequent when aortic root diameter >4.5 cm or the rate of dilation >0.5 cm/year
- Surgical repair when aortic root diameter > 5.0 cm, the rate of increase ~ 1.0 cm/year, or progressive aortic regurgitation
- More aggressive therapy when family history of early aortic dissection
- For now beta-blockers should be primary medical therapy
- Losartan is a reasonable treatment option in patients who cannot tolerate beta-blockers
- Avoid isometric exercise and competitive sports
Loeys-Dietz syndrome

- Generalized arterial tortuosity with aneurisms

- Overlap with Marfan syndrome - bifid uvula/cleft palate, scoliosis, chest deformity, arachnodactyly, joint laxity, easy bruising, dystrophic scars

- Dilatation or dissection of the aorta (> 95%), dissection occurs at smaller aortic diameters than in Marfan syndrome

- Tortuosity is often most prominent in head and neck vessels

- Autosomal dominant

- TGFBR2 (55-60%), TGFBR1 (20-25%), few other genes

- At least annual echocardiography
- MRA or CT scan with 3D reconstruction from head to pelvis
- Early and aggressive surgical intervention
Thoracic Aortic Aneurysms and Aortic Dissections

- Dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta or both
- Dissections of the thoracic aorta involving ascending or descending aorta
- Vascular manifestations can be the only findings
- Exclusion of syndromic causes (Marfan, etc)
- Autosomal dominant
- At least 16 known genes
- Medical treatment and surgical repair similar to Marfan patients
Dilated cardiomyopathy

- Established by left ventricular enlargement and systolic dysfunction
- Results in heart failure, arrhythmias, thromboembolic disease
- Onset usually occurs in adults in the fourth to sixth decade
- 30-50% of isolated DCM have a genetic basis
- Can be autosomal dominant (90%), autosomal recessive or X-linked
- Genetically heterogeneous, >60 genes ($TTN$ – 10-20%, $LMNA$ – 6%, others < 5%)
- Most genes code for proteins responsible for cardiac muscle contraction
- Genetic testing should be offered to every individual of any age with nonischemic DCM, including those with peripartum or pregnancy-associated cardiomyopathy
DCM phenotype-genotype correlation

- *TTN* truncating variants increases the risk of DCM to 100% by age of 70

- Higher prevalence of sudden cardiac death, cardiac transplantation, ventricular arrhythmias in *LMNA* and *PLN* mutation carriers

- Frequency of ventricular arrhythmia with *LMNA* is 50% and *PLN* is 43%

- Heart transplantation rate highest in *LMNA* mutation carriers (27%)

- *RBM20* mutation carriers transplanted at a markedly younger age (mean 28.5 years)

Left ventricular non-compaction

- LVNC can share the same clinical presentation as DCM

- Echo - abnormal trabeculations in the left ventricle, frequently at the apex

- Affects less than 0.3% of the population

- 20-25% of cases of LVNC have a genetic basis

- R/o metabolic and mitochondrial causes (primary carnitine deficiency, fatty acid oxidation disorders, Barth disease) when neonatal/childhood cases

- DCM/LVNC can be a feature of various genetic syndromes, including Danon disease, Carvajal Syndrome, Emery-Dreifuss muscular dystrophy

- Inheritance: autosomal dominant/recessive, X-linked, or mitochondrial
DCM/LVNC panel

Test Information Sheet

Dilated Cardiomyopathy/Left Ventricular Noncompaction Panel

Disorders also known as: Idiopathic Dilated Cardiomyopathy (IDC); Familial Dilated Cardiomyopathy (FDC); Left Ventricular Noncompaction Cardiomyopathy (LVNC)

Panel Gene List: ABCC9, ACTC1, ACTN2, ALMS1, ANKRD1, BAG3, CHRM2, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, FKTN, FLNC, GATAD1, HCN4, ILK, LAMA4, LAMP2, LDB3, LMNA, LRRC10, MIB1, MTND1, MTND5, MTND6, MTTD, MTTG, MTTH, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTS1, MTTS2, MYBPC3, MYH6, MYH7, MYPN, NEBL, NEXN, NKX2-5, PLN, PRDM16, RAF1, RBM20, RYR2, SCN5A, SGCD, TAZ, TBX20, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, TXNRD2, VCL

Additional genes from our cardiology test menu may be added to this panel by selecting test code J554C.
Hypertrophic cardiomyopathy

- The prevalence of HCM is 0.2%, males = females
- Variable clinical presentation; ranging from asymptomatic to sudden death
- Can be a presenting feature of Danon disease, Fabry disease, Noonan syndrome, mitochondrial cardiomyopathy
- 60%-70% of HCM patients have a disease causing mutation
- Genetically heterogeneous condition, mutations in at least 40 genes
- Many genes encode for sarcomeric proteins in the cardiac muscle
- MYH7 and MYBPC3 account for >70% of cases
- Typically inherited in an autosomal dominant manner
HCM phenotype-genotype correlation

- Heterogeneous nature of the disease precludes the establishment of precise genotype–phenotype relationships

- Sarcomere-related gene variants associated with an asymmetric septal hypertrophy, younger age of onset, sudden cardiac death, family history of HCM and female gender

- Lack of phenotypic differences between MYH7- and MYBPC3-associated HCM when assessed by cardiac MRI

- Toronto Genotype score and Mayo HCM Genotype Predictor scores – useful tools for clinicians to identify patients with the highest likelihood for positive genetic testing based on clinical characteristics (age of diagnosis, LV morphological subtype, LV wall thickness, and a family history)
Arrhythmogenic right ventricular cardiomyopathy (ARVC)

- Disorder of the intracellular desmosomal junctions of cardiomyocytes
- Prevalence is estimated at 1:1000 to 1:2500
- Caused by progressive fibrofatty replacement of the right ventricular myocardium
- Heart palpitations, syncope develop between 2nd and 5th decade (mean age ~31 years)
- Sudden cardiac death can be the first symptom, particularly in young athletes
- Many asymptomatic patients may be diagnosed only after routine ECG
- Typically inherited in an autosomal dominant manner
- At least 13 genes implicated, most common DSC2, DSG2, DSP, JUP, PKP2, TMEM43
- Rare syndromic autosomal recessive forms - Naxos and Carvajal syndromes
Channelopathies
Long QT Syndrome

- Delayed repolarization manifested by QT prolongation on ECG, increased propensity to syncope, ventricular tachyarrhythmias and sudden cardiac death

- Estimated prevalence of ~ 1 in 3,000

- The clinical course is quite variable, even within the same family

- Sudden death is the first and final symptom in 10-15% of fatal LQTS events

- Genetic causes in at least 75% of cases, many subtypes, mutations in >12 different genes

- Usually an autosomal dominant trait

- Beta-blockers is the primary treatment; possible implantable cardioverter-defibrillators (ICD) and/or left cardiac sympathetic denervation (LCSD)
# Long QT Syndrome

## Phenotype Correlations by Gene

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Average QTc</th>
<th>ST-T-Wave Morphology</th>
<th>Incidence of Cardiac Events</th>
<th>Cardiac Event Trigger</th>
<th>Sudden Death Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>KCNH2</em></td>
<td>LQTS type 2</td>
<td>480 msec</td>
<td>Bifid T-waves</td>
<td>46%</td>
<td>Auditory stimuli, emotion, exercise, sleep</td>
<td>6%-8%</td>
</tr>
<tr>
<td><em>KCNQ1</em></td>
<td>LQTS type 1</td>
<td>~490 msec</td>
<td>Broad-base T-wave</td>
<td>63%</td>
<td>Exercise, emotion</td>
<td>6%-8%</td>
</tr>
<tr>
<td><em>SCN5A</em></td>
<td>LQTS type 3</td>
<td>~490 msec</td>
<td>Long ST, small T</td>
<td>18%</td>
<td>Sleep</td>
<td>6%-8%</td>
</tr>
</tbody>
</table>
Catecholaminergic polymorphic ventricular tachycardia (CPVT)

- Arrhythmogenic disorder induced by physical activity, stress, or catecholamine infusion
- Can deteriorate into ventricular fibrillation
- Recurrent syncope, seizures, or sudden death after physical activity or emotional stress
- Syncope usually is the first symptom in more than half of the patients
- If untreated, CPVT is highly lethal – 30% chance of cardiac arrest
- Individuals with CPVT do not have structural cardiac abnormalities
- Autosomal dominant condition
- 50-55% have a pathogenic variant in RYR2 (one of the largest ion channel proteins)
Proper genetic test utilization
When and how to perform genetic test

- Genetic testing should be offered to patients who fulfil diagnostic criteria for inherited CVD
- DNA testing should be performed in certified laboratory
- Do not “overshoot” genetic testing
- If you don’t know how to order or explain genetic test results - defer testing to geneticist
- Pre-test counseling to explain benefits and limitations of the test and the possible consequences of the test results
- Post-test genetic counseling to discuss test results directly with the patient
Understanding test results

- A negative genetic result does not guarantee that the disease is not genetic

- A negative result today may be positive in the future

- Variants of unknown significance (VUS) - not enough evidence to classify an alteration as deleterious or benign

- VUS should not be used in clinical decision-making before follow-up testing is completed

- Genetic laboratories frequently upgrade VUS to deleterious variant or downgrade to benign variant, based on novel data

- Genotype–phenotype correlation, if any
Family screening

- Family members should be screened only when a pathogenic gene variant has been found (not a VUS)

- Marked genetic and phenotypic heterogeneity observed in cardiomyopathy

- In general, the age at which predictive testing is conducted is determined by the likely age of onset of the cardiomyopathy and the risk of cardiac complications

- One should consider pattern of disease in the family, the practice of strenuous physical training or competitive sports, and the presence of symptoms or other clinical suspicion

- Careful consideration is needed when family members are asymptomatic minors

- Children cannot provide autonomous informed consent, may not understand the pros and cons of the screening process, and are at risk of psychological stress
**Figure 2** Organization of family screening. Asterisk (*) indicates additional cardiac examination in selected ...
## Pros & Cons of predictive screening

### Main outcomes associated with predictive diagnosis in cardiomyopathies

<table>
<thead>
<tr>
<th></th>
<th>If the mutation is present</th>
<th>If the mutation is absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive outcome</strong></td>
<td>Removal of uncertainty</td>
<td>Removal of uncertainty, and relief</td>
</tr>
<tr>
<td></td>
<td>Regular medical follow-up is organized which will improve the prognosis</td>
<td>No future development of the disease, and medical follow-up is no more required</td>
</tr>
<tr>
<td><strong>Negative outcome</strong></td>
<td>Anxiety because of future cardiac expression (risk of premature death)</td>
<td>Possible ‘survivor’ guilt</td>
</tr>
<tr>
<td></td>
<td>No treatment to begin at this stage in most disorders</td>
<td>No risk of transmission to offspring</td>
</tr>
<tr>
<td><strong>Uncertainties remaining</strong></td>
<td>Recommend environmental modifications? (exercise or alcohol restriction)</td>
<td>Not always easy to affirm that the mutation identified in the proband is the cause of the disorder in the family, especially if missense mutation</td>
</tr>
<tr>
<td></td>
<td>Medical costs?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insurability or professional concerns?</td>
<td></td>
</tr>
</tbody>
</table>
Follow-up

- Negative family history does NOT eliminate it being genetic
- Normal genetic testing does not completely excludes genetic etiology
- Consider reevaluation in a couple of years
- Diagnosis of a CVD in a child should prompt consideration of imaging family members: mother, father, siblings
- Phenotype/genotype correlation for confirmed cases
- Natural history of disease with appropriate up to date screening
- Counseling of family about potential recurrence risk
- Treatment, if any