Genetics and Cardiovascular diseases

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Outlines

• Basic understanding of cardiovascular genetics
• Modes of disease inheritance
• Genetic basis of cardiomyopathies, e.g. hypertrophic cardiomyopathy and arrhythmogenic disorders, e.g. long QT syndrome
• The clinical and genetic basis of sudden cardiac death in the young
• Clinical scenarios of potential genetic arrhythmogenic disorders
• Screening strategies for early detection of patients at risk
DNA changes

Cause of disease  Susceptibility to diseases
Gene and CVS diseases

- Improved diagnosis
- Understanding of disease pathogenesis
- Disease presentation
- Guiding therapy
- Pharmacogeneomics
The Many questions

• Why did my son/daughter die?
• How can we stop this ever happening in our family?
• What are the causes of sudden death in the young?
• How do we care for these families?
• How can we prevent sudden death in our communities?

We are making progress in the answers
## Causes of sudden cardiac death in the young

<table>
<thead>
<tr>
<th>Structural</th>
<th>Arrhythmogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>Long QT syndrome</td>
</tr>
<tr>
<td>CAD</td>
<td>Idiopathic VF</td>
</tr>
<tr>
<td>Coronary anomalies</td>
<td>Brugada syndrome</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>CPVT/ Exercise induced</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Others</td>
</tr>
<tr>
<td>ARVD</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Abnormal Postmortem</strong></td>
<td><strong>Negative postmortem</strong></td>
</tr>
</tbody>
</table>
Cardiomyopathy (CMP)
Cardiomyopathy (CMP)

- **Definition:**
  - Deterioration of the function of the myocardium (i.e., the actual heart muscle) for any reason.
Types of Cardiomyopathy

Fig. 2. Cardiomyopathies: three major functional types. Two-dimensional and Doppler echocardiography play central roles in the identification of the three major functional types of the cardiomyopathies. Major distinguishing features of these classes are listed in Table 1. Ao, aorta; LA, left atrium; LV, left ventricle.
Hypertrophic Cardiomyopathy

- 1:500 general population
- Most common genetic heart disease
- Clinical heterogeneity
- No symptoms to heart failure/ sudden death
- L.V hypertrophy
- LVOT obstruction and AF in 25% of HCM
- Most devastating complications
Genetic basis of HCM

- Familial type caused by mutation in one of the genes currently known to encode different components of the sarcomere.

- Characterized by left ventricular hypertrophy (LVH) in the absence of predisposing cardiac conditions (e.g., aortic stenosis) or CV conditions (e.g., long-standing hypertension)
14 genes defect cause familial HCM
## Genetic basis of HCM

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>%</th>
<th>Gene</th>
<th>Protein</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td>Myosin heavy chain, cardiac muscle beta isoform</td>
<td>40</td>
<td>MYL3</td>
<td>Myosin light polypeptide 3</td>
<td>1</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Myosin-binding protein C, cardiac-type</td>
<td>40</td>
<td>ACTC1</td>
<td>Actin, alpha cardiac muscle 1</td>
<td>UK</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CSRP3</td>
<td>Cysteine and glycine-rich protein 3, muscle LIM protein</td>
<td>UK</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Troponin T, cardiac muscle</td>
<td>5</td>
<td>TTN</td>
<td>Titin</td>
<td>UK</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACTN2</td>
<td>Alpha-actinin-2</td>
<td>UK</td>
</tr>
<tr>
<td>TNNI3</td>
<td>Troponin I, cardiac muscle</td>
<td>5</td>
<td>MYH6</td>
<td>Myosin heavy chain, cardiac muscle alpha isoform</td>
<td>UK</td>
</tr>
<tr>
<td>TPM1</td>
<td>Tropomyosin 1 alpha chain</td>
<td>2</td>
<td>TCAP</td>
<td>Telothonin</td>
<td>UK</td>
</tr>
<tr>
<td>MYL2</td>
<td>Myosin regulatory light chain 2, ventricular/cardiac muscle isoform</td>
<td>UK</td>
<td>TNNC1</td>
<td>Troponin C, slow skeletal and cardiac muscles</td>
<td></td>
</tr>
</tbody>
</table>
Other differential diagnosis

• **Environmental (Acquired) Causes of Left Ventricular Hypertrophy**

• **Inherited disorders with multisystem involvement**
  – Adult onset disease
    • Metabolic cardiomyopathies
    • Cardiac amyloidosis
  – Childhood onset disease
    • Inborn errors of metabolism
    • Malformation syndromes
    • Neuromuscular disorders
Metabolic genetics causes of Cardiomyopathy

- Many metabolic disorders can cause cardiomyopathy
  - Glycogen storage diseases: Pompe disease
  - Lysosomal storage disorders: Fabry disease, GM1 gangliosidosis
  - Mucopolysaccharidosis
  - FAOD and OA
  - Oligosaccharidosis
Case 1

- You are seeing a 6 months old boy brought to cardiology clinic because of long standing history of hypertrophic cardiomyopathy based on echocardiogram finding. On examination you noticed that he has large tongue and hypotonic. You look at Electrocardiogram (ECG) and interestingly it showed short PR interval. What is the most likely disorder causing such presentation?
  - Fabry
  - GM1 gangliosidosis
  - Hurler
  - Pompe
<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical hints</th>
<th>Biochemical hint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GSD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pompe disease</td>
<td>Macroglossia + central hypotonia + hepatomegaly + short PR interval on ECG</td>
<td>Alpha glucosidase in dried blood spot</td>
</tr>
<tr>
<td>Danon disease (pseudopompe)</td>
<td>Present after 1st decade + mental retardation (70%) + muscle weakness</td>
<td>Molecular testing LAMP2</td>
</tr>
<tr>
<td>GSDIIIa</td>
<td>Myopathy, hepatomegaly, variable hypoglycemia, mild hepatocellular dysfunction</td>
<td>Debranching enzyme in liver and/or muscle (fibroblasts, lymphoblasts), CK</td>
</tr>
<tr>
<td>GSDIV Neuromuscular form (4 type)</td>
<td>Myopathy, hypotonia, mild liver involvement Muscle biopsy shows typical foci of polyglucosan bodies</td>
<td>Branching enzyme in liver and/or muscle (fibroblasts, lymphoblasts), CK</td>
</tr>
</tbody>
</table>
Metabolic causes of Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Disorders of Sphingolipid metabolism</th>
<th>Fabry disease</th>
<th>GM1 gangliosidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiokeratoma, Neuropathic pain, corneal dystrophy, renal dysfunction, stroke</strong></td>
<td>Alpha galactosidase def. in plasma or serum, leukocytes or cultured skin fibroblasts or lymphoblast</td>
<td><strong>Macroglossia, hepatosplenomegaly, cherry red spot, psychomotor retardation</strong></td>
</tr>
</tbody>
</table>
Case 2

- 20 years old girl with history of recurrent pain in the legs and found to have this skin rash. What is the most likely diagnosis?
Mode of inheritance

• For metabolic cardiomyopathies and neuromuscular disorders
  – AR, AD, XL, Mitochondrial

• For Familial HCM:
  – AD
Autosomal Dominant inheritance

Autosomal dominant

- **Autosomal:** the gene in question is located on one of the numbered, or non-sex, chromosomes.
- **Dominant:** single copy of the disease-associated mutation is enough to cause the disease. This is in contrast to a recessive disorder, where two copies of the mutation are needed to cause the disease.
Autosomal dominant

• What is the risks of sibs?
• If one of parents has the disease, what is the risk of offspring?
Autosomal dominant

Father with abnormal gene on autosomal chromosome

Mother with normal autosomal chromosome

Parents: AA

Offspring: AA AA AA AA

Each pregnancy bears a 50-50 chance of carrying the abnormal gene
Case 3

• You are seeing an affected parent with an autosomal dominant disease. What is the risk for having affected children?

  – 25%
  – 50%
  – 75%
  – 100%
Role of genetic testing in HCM

• Identify the cause
• Genetic counseling
• Disease targeted management
Role of genetic testing in HCM

- Currently population genetic testing not practical option given too many genes rarely identified in the family.
Risk stratification in HCM

• **Highest risk factors:**
  – Family history of sudden death
  – LVH ≥ 30mm
  – Previous resuscitated cardiac death
  – Syncope

• **Other risk factors:**
  – Non-sustained VT
  – Abnormal BP response to exercise
  – ? LVOT obstruction
  – ? Mutation
Diagnostic strategies

- Family history
- Screening of first-degree relatives for HCM
- Molecular genetic testing
- Invasive procedures like cardiac biopsy
Management

- Supportive
- No treatments to prevent or decrease disease development or to reverse established manifestations currently exist.
Case 4

• You are seeing a 30 year old woman with history of heart palpitations, syncope and positive family history of sudden death of her brother at 32 year of age. ECG showed epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V1-V3) Echocardiogram showed severe right ventricular dilation and reduction of right ventricular function with no left ventricular impairment. What is the most likely diagnosis?

A. ARVD
B. JLNS
C. RWS
D. Brugada syndrome
ARVD

• Detailed of diagnostic criteria could be found at
8 genes cause ARVD

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RYR2</strong></td>
<td>Ryanodine receptor 2</td>
<td>50-70%</td>
</tr>
<tr>
<td><strong>DSP</strong></td>
<td>Desmoplakin</td>
<td>6-16%</td>
</tr>
<tr>
<td><strong>TMEM43</strong></td>
<td>transmembrane protein 43</td>
<td></td>
</tr>
<tr>
<td><strong>TGFB3</strong></td>
<td>Transforming growth factor beta-3 gene</td>
<td></td>
</tr>
<tr>
<td><strong>PKP2</strong></td>
<td>The essential armadillo-repeat protein of the cardiac desmosome, plakophilin-2</td>
<td></td>
</tr>
<tr>
<td><strong>DSG2</strong></td>
<td>desmoglein-2</td>
<td></td>
</tr>
<tr>
<td><strong>DSC2</strong></td>
<td>desmocollin-2</td>
<td></td>
</tr>
<tr>
<td><strong>JUP</strong></td>
<td>The junction plakoglobin protein also known as gamma catenin</td>
<td></td>
</tr>
</tbody>
</table>
Case 5

• A 4 year old deaf child who experiences syncopal episodes during periods of stress, exercise, or fright. ECG showed: long QT interval, what is the most likely diagnosis?
  A. Romano-Ward syndrome
  B. Jervell and Lange-Nielsen Syndrome
  C. Brugada syndrome
  D. Noonan syndrome
Inherited arrhythmogenic diseases eg: Long QT syndromes

- Characterized by prolong QT on ECG
- Syncope, cardiac arrest and sudden death
- Different genotypes eg: LQT1-LQT10
- Ion channelopathies
- Normal heart in postmortem analysis
Romano-Ward syndrome (RWS)

- AD
- QT prolongation and T-wave abnormalities on the ECG and the ventricular tachycardia torsade de pointes (TdP).
- TdP is usually self-terminating, thus causing a syncopal event
- Syncope typically occurs during exercise and high emotions
- Less frequently at rest or during sleep, and usually without warning.
- In some instances, TdP degenerates to ventricular fibrillation and causes aborted cardiac arrest (if the individual is defibrillated) or sudden death.
5 genes cause RWS

<table>
<thead>
<tr>
<th>Gene</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ1</td>
<td>58</td>
</tr>
<tr>
<td>KCNH2</td>
<td>35</td>
</tr>
<tr>
<td>SCN5A</td>
<td>5</td>
</tr>
<tr>
<td>KCNE1</td>
<td>1</td>
</tr>
<tr>
<td>KCNE2</td>
<td>1</td>
</tr>
</tbody>
</table>
Jervell and Lange-Nielsen Syndrome

- AR
- Congenital profound bilateral sensorineural hearing loss and long QTc, usually greater than 500 msec.
- Prolongation of the QTc interval is associated with tachyarrhythmias, including ventricular tachycardia, episodes of *torsade de pointes* ventricular tachycardia, and ventricular fibrillation
- Syncope or sudden death
- The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright.
- Fifty percent of individuals with JLNS had cardiac events before age three years. More than half of untreated children with JLNS die prior to age 15 years.
2 genes cause JLNS

- **KCNQ1** (90%)
- **KCNE2** (10%)
Autosomal Recessive inheritance
• **Autosomal:** the gene in question is located on one of the numbered, or non-sex, chromosomes.

• **Recessive:** 2 copy of the disease-associated mutation are needed to cause the disease.
Autosomal Recessive

• What are the risks of sibs?
• If one of the parents has the disease, what is the risk of offspring?
• If both parents have the disease, what are the risks to the offspring?
Autosomal Recessive
Genetics basis of Long QT syndrome

- LQTS1-LQT12
- 75% detection rate
- AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, SCN4B, SCN5A, SNTA1 which can be done in commercial lab
Case 6

- An ECG of 40 year old lady showed ST segment elevation in leads V₁-V₃, coved type. Family history showed multiple sudden death at similar age. What is the most likely diagnosis?
  A. ARVD
  B. Catecholaminergic Polymorphic Ventricular Tachycardia
  C. Progressive conduction system disease
  D. Brugada syndrome
Brugada syndrome

• Note presence of ST-segment elevation in leads $V_1$-$V_3$, coved type
8 genes can cause Brugada syndrome

- **SCN5A**, **GPD1L**, **CACNA1C**, **CACNB2**, **SCN1B**, **KCNE3**, **SCN3B**, and **HCN4**
Case 7

- 8 year old boy with history of recurrent syncope during exercise. ECG consists of ventricular tachycardia. What is the most likely diagnosis?

A. ARVD
B. Catecholaminergic Polymorphic Ventricular Tachycardia
C. Progressive conduction system disease
D. Brugada syndrome
2 genes causing CPVD

- RYR2 (autosomal dominant) encodes the cardiac ryanodine receptor channel
- CASQ2 (autosomal recessive) encodes calsequestrin, a calcium buffering protein of the sarcoplasmic reticulum (SR)
Screening Strategies for Early Detection of Patients at Risk
• The victim:
  – Clinical history
  – Circumstance of death
  – Detailed postmortem analysis

• The family:
  – Detailed family history
  – Counseling and educations
  – Clinical screening of at risk family members
  – All first-degree relatives of an affected individual should be evaluated with resting ECG, Holter monitoring, and, most importantly, with exercise stress testing
Multidisciplinary care

- Forensic/pathologist
- Cardiologist
- Counselor
- Gene testing centre
- Geneticist
- Research centre
- Patient support group
- Family
Summary

• Major advances in our understanding of genetics basis of many heart diseases
• Knowledge of genetic causes has led to improved and earlier diagnosis of at risk individuals in family/ screening program
• Earlier diagnosis has opened larger therapeutic window for prevention of disease complications e.g.: sudden death
• Genetics factors are likely to be very important in clinical trial settings in terms of response therapies and in development of targeted personalized medicine
• Remember family history and multidisciplinary approach