Inherited Cardiomyopathies
Molecular genetics and Clinical genetic testing

Dr Shagun Aggarwal
Associate Professor, Department of Medical Genetics
Nizam’s Institute of Medical Sciences
Adjunct Scientist, Centre for DNA Fingerprinting & Diagnostics
Hyderabad
Cardiomyopathies

- The cardiomyopathies is a collection of myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular or congenital heart disease sufficient to cause the observed myocardial abnormality.
Classification

Morphofunctional phenotype (M)
Organ(s) involvement (O)
Genetic inheritance pattern (G)
Etiological annotation (E) including genetic defect or underlying disease/substrate
The functional status (S) of the disease using both the American College of Cardiology/American Heart Association stage and New York Heart Association functional class.
Rhythm disorders
Cardiomyopathies
Monogenic cardiac malformations

Ischemic heart disease
Heart failure
Peripheral arterial disease

Cardiac malformations
Ultrastructure of cardiac muscle
Figure 1: Classification of Inherited Cardiomyopathy According to Morphological Features

Inherited Cardiomyopathy

- HCM
- DCM
- ARVC
- RCM
- Unclassified
  - LVNC
  - Takotsubo

Prevalence
- HCM: 1:500
- DCM: 1:2500
- ARVC: 1:5000
- RCM: Rare

Defective gene
- Sarcomere
- Cytoskeleton
- Desmosome

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVNC = left ventricular non-compaction cardiomyopathy; RCM = restrictive cardiomyopathy. Adapted from Elliot et al. 5
Echocardiography in HCM
DAGGER SHAPED LVOT DOPPLER SPECTRUM
CASE 2 - APICAL HCM
CASE 3- MID CAVITORY HCM
HCM

- 1 in 500
- Left ventricular hypertrophy in absence of systemic condition or other cardiac disease
- Onset: infancy to old age
- Usual: post adolescence
- Leading cause of sudden cardiac death in young
- Asymptomatic- range of symptoms
- 5-10% progress to heart failure
### Common symptoms
- Shortness of breath (exacerbated by exertion)
- Chest pain
- Palpitations
- Orthostasis (low blood pressure when standing)
- Presyncope and syncope

### Diagnostic criteria

<table>
<thead>
<tr>
<th><strong>Left ventricular hypertrophy (LVH)</strong> in non-dilated ventricle (in the absence of other known causes e.g. hypertension aortic stenosis athlete's heart)</th>
<th><strong>Most commonly asymmetric septal (≥15 mm; 13-14 mm=borderline)</strong>&lt;br&gt;<strong>Less frequently concentric and apical</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic echocardiographic findings</strong></td>
<td><strong>Systolic anterior motion (SAM) of the mitral valve with associated left ventricular outflow tract obstruction and mitral regurgitation</strong>&lt;br&gt;<strong>Midventricular obstruction as a result of systolic cavity obliteration</strong>&lt;br&gt;<strong>Diastolic dysfunction including restrictive physiology</strong></td>
</tr>
<tr>
<td><strong>Pathognomonic histopathology</strong></td>
<td><strong>Myocyte disarray</strong>&lt;br&gt;<strong>Myocyte hypertrophy</strong>&lt;br&gt;<strong>Increased myocardial fibrosis</strong></td>
</tr>
</tbody>
</table>

### Other findings suggestive of HCM
- Fourth heart sound  
  Prominent left ventricular apical impulse/lift
- Brisk carotid upstroke  
  Left ventricular outflow tract/Intracavitary obstruction
- Abnormal ECG: Pattern consistent with LVH
- Pattern consistent with left atrial enlargement
- Prominent Q-waves in inferior and lateral leads
- Diffuse T-wave inversions
Genetics of HCM

• Strong genetic basis
• Autosomal dominant inheritance
• Incomplete penetrance- age dependent
• Variable expressivity
Pedigree showing autosomal dominant inheritance
50% recurrence risk in offspring
Genetics of HCM

- Strong genetic basis
- Autosomal dominant inheritance
- Incomplete penetrance - age dependent
- Variable expressivity
- Sarcomere genes most commonly involved
- 50-60% FHCM found to have mutations
- 20-30% of sporadic HCM
Figure 1: Schematic presentation of sarcomere with protein mutations causing HCM according to their frequency:

1: MYH7: Beta Myosin Heavy Chain: 40%
3: TNNT2: Troponin T2: 5%
5: TNNC1: Troponin C1: rare
7: ACTC: Alpha Actin: rare
9: MYL3: Myosin Light Chain 3: 1%
11: MYOZ2: Myozelin 2: rare

2: MYBPC3: Myosin Binding Protein C 3: 40%
4: TNNI: Troponin I 3: 5%
6: TPM: Tropomyosin: 2%
8: MYL2: Myosin Light Chain 2: rare
10: ACTN2: Alpha 2 Actinin: rare
<table>
<thead>
<tr>
<th>Gene</th>
<th>% of established mutations</th>
<th>Location</th>
<th>Name (HGNC)</th>
<th>Phenotype</th>
<th>OMIM</th>
<th>Muscular component</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td>40</td>
<td>14q11.2</td>
<td>Myosin, heavy chain, cardiac muscle, Beta</td>
<td>CMH1 (192600)</td>
<td>160760</td>
<td>Sarcomere, thick filament</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>40</td>
<td>11p11.2</td>
<td>Myosin binding protein, cardiac</td>
<td>CMH4 (115197)</td>
<td>600958</td>
<td>Sarcomere, intermediate filament</td>
</tr>
<tr>
<td>TNNT2</td>
<td>5</td>
<td>1q32.1</td>
<td>Troponin T type 2 (cardiac)</td>
<td>CMH2 (115195)</td>
<td>191045</td>
<td>Sarcomere, thin filament</td>
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<tr>
<td>TNNI3</td>
<td>5</td>
<td>19q13.42</td>
<td>Troponin I, type 3</td>
<td>CMH3 (613690)</td>
<td>191044</td>
<td>Sarcomere, thin filament</td>
</tr>
<tr>
<td>TPM1</td>
<td>2</td>
<td>15q22.2</td>
<td>Tropomyosin 1 (α)</td>
<td>CMH 3 (115196)</td>
<td>191010</td>
<td>Sarcomere, thin filament</td>
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<tr>
<td>MYL2</td>
<td>?</td>
<td>12q24.11</td>
<td>Myosin, light chain 2, regulatory, cardiac, slow</td>
<td>CMH 10 (608758)</td>
<td>160781</td>
<td>Sarcomere, thick filament</td>
</tr>
<tr>
<td>MYL3</td>
<td>1</td>
<td>3p21.31</td>
<td>Myosin, light chain 3, alkali, ventricular, skeletal slow</td>
<td>CMH 8 (608751)</td>
<td>160790</td>
<td>Sarcomere, thick filament</td>
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<tr>
<td>ACTC1</td>
<td>?</td>
<td>15q14</td>
<td>Actin, alpha, cardiac muscle 1</td>
<td>CMH 11 (612098)</td>
<td>102540</td>
<td>Sarcomere, thin filament</td>
</tr>
<tr>
<td>ACTN2</td>
<td>?</td>
<td>1q43</td>
<td>Actinin, α2</td>
<td>612158</td>
<td>102573</td>
<td>Z-disc</td>
</tr>
<tr>
<td>TNNC1</td>
<td>?</td>
<td>3p21.1</td>
<td>Troponin C type 1 (slow)</td>
<td>CMH 8 (613243)</td>
<td>191040</td>
<td>Sarcomere, thin filament</td>
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<tr>
<td>MYOZ2</td>
<td>?</td>
<td>4q26</td>
<td>Myozenin 2</td>
<td>CMH 16 (613838)</td>
<td>605602</td>
<td>Z-disc</td>
</tr>
</tbody>
</table>
Case

• 8 month old female
• Consanguineous parents
• Recurrent respiratory tract infections and labored breathing since 3 months age
• Predominant motor delay- partial neck holding, unable to sit with support
• Generalised hypotonia
• Hepatomegaly 2 cm
Serum CPK: 733 IU/l

2 D echo: Left ventricular hypertrophy and dilatation
Global hypokinesia of LV

### DBS Enzyme Activity:

<table>
<thead>
<tr>
<th>Test</th>
<th>Acid α-glucosidase with acarbose (A)</th>
<th>Total neutral α-glucosidase (B)</th>
<th>Ratio B/A</th>
<th>% Inhibition by acarbose</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Glucosidase (pmol/punch/h)</td>
<td><strong>0.55</strong></td>
<td>18.4</td>
<td>33.4</td>
<td>89.5</td>
<td>Deficient</td>
</tr>
<tr>
<td>Normal ref range</td>
<td>7.4 – 50</td>
<td>14 - 95</td>
<td>1.4 - 13.5</td>
<td>32 - 73</td>
<td></td>
</tr>
<tr>
<td>Late onset/Carriers</td>
<td>2.8 – 7.2</td>
<td>12 - 60</td>
<td>3 - 25</td>
<td>36 - 80</td>
<td></td>
</tr>
<tr>
<td>Patient ref range</td>
<td>&lt; 1.2</td>
<td>15 - 78</td>
<td>13 - 70</td>
<td>60 - 98</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis

• Pompe disease (Glycogen storage disorder type 2)
• Poor prognosis in absence of therapy
• ERT available
• Autosomal recessive disorder
• 25% recurrence risk
Noonan syndrome
## RAS-MAPK pathway disorders

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>GENE</th>
<th>PROPORTION CAUSED BY THE GENE</th>
<th>HEART DEFECTS</th>
<th>ASSOCIATED FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noonan Syndrome</td>
<td>PTPN11</td>
<td>50%</td>
<td>Pulmonary valve stenosis (PS), Hypertrophic cardiomyopathy (HOCM), ASD</td>
<td>Short stature, down slanting palpebral fissures, webbing of neck, pectus carinatum, pectus excavatum, cryptorchidism</td>
</tr>
<tr>
<td></td>
<td>KRAS</td>
<td>&lt;5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOS1</td>
<td>10 to 13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAF1</td>
<td>3 to 17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>1 in 1000-2500</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costello Syndrome</td>
<td>HRAS</td>
<td>80 to 90%</td>
<td>HOCM, Atrial Arrhythmia, PS</td>
<td>Warts/papillomata, Noonan like face</td>
</tr>
<tr>
<td>Cardio-facio-cutaneous Syndrome</td>
<td>BRAF</td>
<td>70 to 80%</td>
<td>HOCM, PS, ASD</td>
<td>Noonan like face, sparse curly hair, large head, coarse facies, short stature, mental retardation</td>
</tr>
<tr>
<td></td>
<td>MAP2K1</td>
<td>10 to 15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAP2K2</td>
<td>&lt;5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KRAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LÉOPARD Syndrome</td>
<td>PTPN11</td>
<td>80-90%</td>
<td>PS, HOCM</td>
<td>Multiple Lentigens, Hypertelorism, Deafness, Conduction defects of heart, Pulmonary Stenosis</td>
</tr>
<tr>
<td></td>
<td>RAF1</td>
<td>Few</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Other syndromic hypertrophic cardiomyopathies

<table>
<thead>
<tr>
<th>Gene mutation</th>
<th>Protein mutation</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRKAG2</td>
<td>Gamma subunit of AMP-dependant protein kinase 2</td>
<td>Autosomic recessive</td>
<td>7q36.1</td>
<td>Hypotonia; failure to thrive; Hypoglycemia; Hepatomegaly; growth retardation</td>
</tr>
</tbody>
</table>
| GLA           | Alpha galactosidase | X linked         | Xq22.1 | **Fabry disease**  
|               |                   |                  |        | Fatigue; acroparesthesia; proteinuria; renal failure, corneal opacity, anhidrosis; angiokeratoma; neuropathy |
| LAMP2         | Lysosome associated membrane protein 2        | X linked         | Xq24   | **Danon disease**  
|               |                   |                  |        | Proximal myopathy; raised CPK; cognitive impairment, visual impairment; WPW |
# Fabry disease

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nerves</td>
<td>Acroparasthesias</td>
</tr>
<tr>
<td>Superficial vessels</td>
<td>Angiokeratoma</td>
</tr>
<tr>
<td>Kidney</td>
<td>Isothenuria, hypertension, renal insufficiency/failure</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Strokes, transient ischemic attacks</td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td>Hypohydrosis, diarrhea, vasomotor instability</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Coronary insufficiency, hypertrophic myocardiopathy</td>
</tr>
</tbody>
</table>

3-10% males with HOCM have Fabry disease ERT available
• AS A GENETICIST HOW DO YOU APPROACH A CASE OF HCM.
Approach to patient with HOCM

• History and examination
• Dysmorphic assessment and systemic evaluation
• Echocardiography and Ancillary testing
• Three generation family history with attention to sudden cardiac deaths esp. young age, heart failure, syncopal attacks
• Cardiac evaluation of family members- first degree relative
First diagnosed left ventricular hypertrophy

- Clinical familial screening + TTE
- Family and personal history, physical examination, TTE

HCM/phenocopies likely

- High probability of secondary hypertrophy of non genetic cause

Genetic testing

- No mutation
  - Clinical follow-up
  - Consider repeating test according to genetic progress

- Mutation +
  - VUS
  - Mutation causative of HCM/phenocopies
    - Familial screening for the identified mutation
  - Mutation +
    - Regular follow-up
    - Counselling
    - Risk stratification
  - Mutation -
    - HCM/Phenocopies ruled out
      - No follow up
Relevance of genetic testing

- Identification of true positive and negative family members
- Prenatal diagnosis: 50% recurrence risk
- Optimise M/m using knowledge of genotype-phenotype correlation
- 23 bp deletion in intron of MYBPC3 gene has increased risk of heart failure (OR 7)
- TNNT2 mutations - less hypertrophy, more arrhythmia
- MYH7 mutations - LVH by 2nd decade, increase risk of sudden death & heart failure
- Identification of systemic disease with specific Rx
- Prophylactic pharmacotherapy in presymptomatic mutation +: Diltiazem, ACE/ARBs
CASE 5 - DILATED CARDIOMYOPATHY
DCM

- DCM is defined by LV dilatation and systolic dysfunction i.e. a reduction in myocardial force generation characterized by an ejection fraction of <50%
- 1 in 2500
- 30-50% have family history
- Heart failure, thromboembolism and SCD
• Genetically heterogeneous
• >50 genes known
• AD/AR/XL
• Incomplete penetrance
• Acquired etiologies also common
• Occurs as part of clinical spectrum of various genetic neuromuscular disorders
**Sarcomere genes**
MYH7, MYH6, MYL3, MYL2, TPM1, TNNT2, TNNI3, TNNC1, ACTC, MYBPC3

**Z disk**
TTN, LBD3, VCL, CSRP3, TCAP, TTID

**Mitochondrial**
TTR, FRA, Cox15, HFE

**Cytoskeletal-Membrane Linkers**
DMD, SGCG, SGCD, SGCB, SGCA, FKRP

**Nuclear**
TAZ, LMNA, EMD, EYA4, SYNE1, TMPO, RBM20
Sequencing of 20 genes in DCM has a diagnostic yield of 17-30% only.
Common clinical conditions associated with DCM

- Duchenne & Becker’s muscular dystrophy-probands as well as carrier mothers
- Limb girdle muscular dystrophy
- Emery-Dreifuss muscular dystrophy
- Mitochondrial myopathy
- Peripartum cardiomyopathy
Approach to a patient with DCM

• History (with special attention to heart failure symptoms, arrhythmias, presyncope and syncope)
• Three generation family history- special attention to X linked inheritance pattern
• Physical examination (with special attention to the cardiac and skeletal muscle systems)
• Electrocardiogram
• Echocardiogram
• CK-MM (at initial evaluation only)
Genetic testing

• Complicated by multiple genes
• No single gene contributes significantly except Titin
• Genotype-phenotype is important
• LMNA mutations: SCD frequency as high as 46% due to conduction system defects
• ICD should be considered
• SCN5A mutations also predispose to arrhythmia
Lamin A/C Gene

LMNA mutations

- Emery-Dreifuss muscular dystrophy
- Limb-girdle muscular dystrophy 1B
- Dilated cardiomyopathy with conduction defects

Congenital muscular dystrophy
Relevance of genetic testing

• Identification of true positive and negative family members
• Identification of asymptomatic female carriers in X linked inheritance
• Prenatal diagnosis
• Optimise M/m using knowledge of genotype-phenotype correlation
• ICD in LMNA mutations
• Identification of systemic disease with M/m of comorbidities
Arrhythmogenic RVCM

- ARVC is defined by myocyte loss and fibrofatty infiltration of the myocardium and is associated with an increased susceptibility to arrhythmias and sudden death
- Involvement of LV also reported
- Male predominance
- Onset around 40 years
- T wave inversion in precordial leads
- 1 in 2000-5000
- Leading cause of SCD <35 years age
• Early, “concealed” phase is characterized by propensity toward ventricular arrhythmia in the setting of preserved morphology, histology, and ventricular function
• Later stages: myocyte loss, inflammation, and fibroadiposis become evident
• Morphologically DCM
• Ventricular arrhythmia mc presentation
• Late stages: heart failure
Genetics of ARVCM

- Upto 60% have identifiable genetic mutations

Majority involve components of the desmosome
AD/AR forms
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Gene</th>
<th>Location</th>
<th>Recessive form</th>
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</thead>
<tbody>
<tr>
<td>ARVC1</td>
<td>TGFB3</td>
<td>14q24.3</td>
<td></td>
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<tr>
<td>ARVC2</td>
<td>RYR2</td>
<td>1q43</td>
<td></td>
</tr>
<tr>
<td>ARVC3</td>
<td>Unknown</td>
<td>14q12-q22</td>
<td></td>
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<tr>
<td>ARVC4</td>
<td>TTN</td>
<td>2q32.1-q32.3</td>
<td></td>
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<tr>
<td>ARVC5</td>
<td>TMEM43</td>
<td>3p25.1</td>
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<tr>
<td>ARVC6</td>
<td>Unknown</td>
<td>10p14-p12</td>
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<tr>
<td>ARVC7</td>
<td>DES</td>
<td>2q35</td>
<td></td>
</tr>
<tr>
<td>ARVC8</td>
<td>DSP</td>
<td>6p24.3</td>
<td>6-16% Carvajal syndrome</td>
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<tr>
<td>ARVC9</td>
<td>PKP2</td>
<td>12p11</td>
<td>11-43%</td>
</tr>
<tr>
<td>ARVC10</td>
<td>DSG2</td>
<td>18q12.1</td>
<td>12-40%</td>
</tr>
<tr>
<td>ARVC11</td>
<td>DSC2</td>
<td>18q12.1</td>
<td>2-7%</td>
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<td>ARVC12</td>
<td>JUP</td>
<td>17q21.2</td>
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<tr>
<td>Others</td>
<td>PLN</td>
<td>6q22.1</td>
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<tr>
<td></td>
<td>LMNA</td>
<td>1q22</td>
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<td></td>
<td>SCN5A</td>
<td>3p21</td>
<td></td>
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<tr>
<td></td>
<td>CTNNA3</td>
<td>10q 22.2</td>
<td></td>
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</tbody>
</table>
Approach

- Similar to HCM & DCM
- Signal Averaged ECG (SAECG) in ARVD only
- Holter monitoring
- Magnetic resonance imaging in ARVD
- Genetic testing may contribute to diagnosis in early stages
• Compound heterozygosity and double heterozygosity common
• Significance of some previously reported mutations not known
• S358L mutation in TMEM43 in the Newfoundland founder population: fully penetrant, nonclassic form, high incidence of SCD and heart failure
• Cardiac ryanodine receptor (RyR2): distinct clinical entity, ARVC2,
• Characterized by juvenile SCD and effort-induced polymorphic ventricular tachycardia
• Definite Genotype –phenotype information not available at present
• No definite guidelines on mutation specific m/m
• Animal studies and anecdotal clinical reports suggest that prolonged and intense physical activity, particularly endurance training, may accelerate disease progression: ? M/m of presymptomatic individuals
Left ventricular Non compaction

- Trabeculated/Spongy left ventricular wall
- May involve right ventricle
- Early onset disease
- Progressive poor cardiac outcome
- Ventricular hypertrophy
- Sudden Cardiac death
- Thromboembolism
- Asymptomatic
- 0.014-1.3% prevalence
CASE 6 - LV noncompaction
DEEP RECESSIONS NEAR APEX
Genetics

- Mutation in up to 25% (17-40%) individuals
- Syndromic associations
  1. Barth syndrome
  2. Mitochondriopathies
- LDB3 (5%), ACTC1, MYH7, MYBPC3, TNNT2, LMNA, DTNA mutations in isolated cases
- Overlap with HCM & DCM
- Relative contributions unknown
- No definite guidelines for M/m based on mutation
Restrictive cardiomyopathy

- RCM is characterized by increased stiffness of the ventricular chambers
- Progresses to heart failure and death in few years
- Upto 35% have genetic mutation
  - TNNI3 (18%), MYH7 (14%), and MYBPC3 (2%), TNNT2, ACTC1
- Syndromic associations: Gaucher disease, Fabry disease, Glycogen storage disease, amyloidosis
HYPERTROPHIC CARDIOMYOPATHY
- FXN
- GLA
- JPH2
- MYL2
- MYL3
- MYOZ2
- PRKAG2
- PTPN11

CARDIOMYOPATHY
- EMD
- CRYAB
- GATAD1
- ACTN2
- ANKRD1
- CSRP3
- LAMP2
- MYH6
- MYPN
- NEXN
- LDB3/ZASP
- TAZ

CARDIOMYOPATHY
- ABCC9
- BAG3
- DES
- DMD
- EYA4
- FKTN
- LAMA4
- DSG2
- DSP
- LMNA

DILATED CARDIOMYOPATHY
- NKX2.5
- RBM20
- SCN5A
- TBX20
- TMPO
- TTN
- TXNRD2

LEFT VENTRICULAR NON-COMPACTION

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA
- DSC2
- JUP
- PKP2
- RYR2
- TGFB3
- TMEM43
1. A careful family history for 3 generations is recommended for all patients with cardiomyopathy
   • Is it familial?
   • Identify individuals at risk
   • Inheritance pattern
   • May suggest the age of onset, penetrance, lethality, response to treatment
2. Clinical screening for cardiomyopathy in asymptomatic first-degree relatives is recommended

• Asymptomatic at-risk relatives who are known to carry the disease-causing mutation(s)

• Asymptomatic at-risk first-degree relatives when genetic testing has not been performed or has not identified a disease-causing mutation
• History (with special attention to heart failure symptoms, arrhythmias, presyncope and syncope)
• Physical examination (with special attention to the cardiac and skeletal muscle systems)
• Electrocardiogram
• Echocardiogram
• CK-MM (at initial evaluation only)
• Signal Averaged ECG (SAECG) in ARVD only
• Holter monitoring in HCM, ARVD
• Exercise treadmill testing in HCM
• Magnetic resonance imaging in ARVD
<table>
<thead>
<tr>
<th>Cardio-myopathy Phenotype</th>
<th>Interval if genetic testing is negative and/or if clinical family screening is negative</th>
<th>Screening interval if a mutation is present</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic</td>
<td>Every 3 years until 30 years of age, except yearly during puberty; after 30 years if symptoms develop</td>
<td>Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter</td>
<td>B</td>
</tr>
<tr>
<td>Dilated</td>
<td>Every 3–5 years beginning in childhood</td>
<td>Yearly in childhood; every 1–3 years in adults.</td>
<td>B</td>
</tr>
<tr>
<td>ARVD</td>
<td>Every 3–5 years after age 10</td>
<td>Yearly after age 10 to 50 years of age.</td>
<td>C</td>
</tr>
<tr>
<td>LVNC</td>
<td>Every 3 years beginning in childhood</td>
<td>Yearly in childhood; every 1–3 years in adults.</td>
<td>C</td>
</tr>
<tr>
<td>Restrictive</td>
<td>Every 3–5 years beginning in adulthood</td>
<td>Yearly in childhood; every 1–3 years in adults.</td>
<td>C</td>
</tr>
</tbody>
</table>

At-risk first-degree relatives with any abnormal clinical screening tests (regardless of genotype) should be considered for repeat clinical screening at one year.
Rationale

• Early detection may delay disease presentation and progression, or averting life-threatening events, such as sudden cardiac death

• Variable age of onset and incomplete penetrance, adult onset: basis for screening age & interval

• At risk family members: caution about presyncope, syncope, other S/S
3. Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered.

Challenges

• Genetic heterogeneity
• Mutation heterogeneity
• Incomplete penetrance
• Variable expressivity
• Incomplete knowledge regarding genes involved & genotype-phenotype correlations
Challenges and limitations

- Deceased proband
- Incomplete information of clinical phenotypes
- Unavailable family members
- No definite therapeutic implications except LMNA mutations
- No definite prognostic implications
- No diagnostic utility in the affected person
4. Genetic testing should be considered for the most clearly affected person in a family. DNA from tissue of deceased person if available. Testing for unaffected at risk person – likely to be negative.

Choice of test:
1. Specific genetic panel
2. Targeted testing depending on phenotype
3. NGS based multigene panel
HRS/EHRA consensus statement 2011

• HCM: Recommended testing for MHY7, MYBPC3, TNNI3, TNNT2, TPM1 for all patients
• DCM-CCD: Recommended LMNA, SCN5A testing
• For all other cardiomyopathies: Can be useful but not recommended in index case
• Family targeted mutation testing recommended for all once index case mutation known
• Main limitation: Genetic heterogeneity, poor yield
Next Generation sequencing

High throughput sequencing techniques
Generate millions of base pair

Clinical exome panel: sequences all OMIM genes with known Mendelian phenotypes

Challenge: VUS
5. Genetic and family counseling is recommended for all patients and families with cardiomyopathy.

Pretest
Posttest
Preconceptional & Prenatal

A negative genetic test does not exclude genetic etiology/inherited cardiomyopathies.
Approach to genetic testing for Cardiomyopathies

Obtain family history. Identify the person who best meets diagnostic criteria. Test this person using a multi-gene panel.

- Pathogenic variant identified
  - Test at-risk family members for family-specific mutation
    - Absent: Dismiss from routine clinical cardiac evaluation
    - Present: Perform clinical cardiac evaluations at recommended intervals

- Likely pathogenic variant identified
  - Segregation study of selected family members
    - Pathogenicity supported: Perform clinical cardiac evaluations at recommended intervals on at-risk family members
    - Pathogenicity refuted or uncertain

- Variant of unknown significance identified

- No pathogenic variant identified

1. Additional details or considerations may be required for each step.
2. Segregation study is necessary to confirm the pathogenicity of the variant.
3. Timing and frequency of evaluations depend on clinical and family history.
Advantages of genetic testing

• Presymptomatic testing of relatives
• Prenatal diagnosis in at risk pregnancy
• Rarely diagnosis in some patients with non-definitive findings
• Identifies genetic vs acquired eg. in DCM
• Identification of underlying systemic condition or syndrome: surveillance of other findings
• Management in storage disorders: ERT
Take home messages

• Large majority of cardiomyopathies are of genetic etiology and show autosomal dominant inheritance
• Clinical presentations vary and SCD may be the first presentation
• Screening of first degree relatives is important
• Genetic testing helps in presymptomatic diagnosis and targeting surveillance
• Testing is difficult in view of genetic heterogeneity and missing genotype-phenotype correlations
• Next generation sequencing enables overcoming some of these drawbacks
Thank you