The Genetics and Genomics of Familial Heart Disease
Bringing Precision Medicine to Life!

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Director, Division of Human Genetics
Joint Appointment, Division of Cardiovascular Medicine
The Ohio State University Wexner Medical Center

No conflicts, nothing to disclose
I. The Explosion of Human Genetics and Genomics
II. What is Familial Heart Disease?
   • Mendelian (heritable) vs Complex (non-Mendelian) heart disease
III. What you need to know about a genetic evaluation
   • What is a genetic evaluation?
   • Common conditions needing genetic evaluation
   • Rationale for genetic evaluation
   • Molecular genetic testing
   • Results interpretation and return
   • Cascade clinical screening and molecular testing for families
IV. A Case Presentation of Dilated Cardiomyopathy
V. Discussion

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Driven by high throughput sequencing
The Explosion of Human Genetics and Genomics in Clinical Practice

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• 10 years ago – challenging to routinely sequence anyone

• 5 years – 2-3 genes possible (HCM 5 – 8 genes)
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- 3 years – gene panels emerging (5-20 genes)

- 2 years – larger panels (10-40; pan-cardio – 76)
# The Explosion of Human Genetics and Genomics in Clinical Practice

Driven by high throughput sequencing

- 10 years ago – challenging to routinely sequence anyone
- 5 years – 2-3 genes possible (HCM 5 – 8 genes)
- 3 years – gene panels emerging (5-20 genes)
- 2 years – larger panels (10-40; pan-cardio – 76)
- 1 year ago – clinical exome emerges
  - exome = 19,000 – 20,000 genes encoding proteins

## Now – selective clinical exome sequencing:
- 3 or more affecteds
- negative panel
- insurance coverage
Common terminology of genetic variation

Categories of Genetic Variation:

• Nucleotide: single nucleotide polymorphism (SNP), single nucleotide variant (SNV)

• Genome organization: copy number variation (CNVs), inversions, deletions, translocations

• Epigenetics: changes in the regulation of gene activity/expression that are not dependent on gene sequence (e.g., methylation, retrotransposons)

Genetic Variation - Nucleotide

Frequency
• Common: > 5% of the population
• Rare < 1%, <0.5% of the population
• Very Rare <0.1%, <0.01%
• Observed one time, ‘private’ mutation

Type
• Synonymous (no change in amino acid)
• Missense (amino acid changed)
• Nonsense (stop codon)
• Short Insertions/Deletions
• Splice Site
• Truncating variants – nonsense, indels, splice site
• Terminology: ‘mutation’ versus ‘variant’
### Familial Heart Disease is usually ‘Mendelian’

**Mendelian**
- Usually familial
- Usually identifiable pattern of inheritance (e.g., autosomal dominant, recessive, X-linked)
- Usually one gene
- Usually rare variants causal

### Complex disease
- No discernable pattern of inheritance
- Uncommonly familial (1-2%)
- Many genes involved, common variants each with minimal impact
- Hypertension, diabetes, coronary artery disease
Mendelian Inheritance

Classic Mendelian Inheritance
• Autosomal Dominant
• Autosomal Recessive
• X-linked (dominant / recessive)

Mitochondrial

Mendelian Inheritance

Classic Mendelian Inheritance - Autosomal Dominant
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Mendelian Inheritance

Classic Mendelian Inheritance - X-linked (dominant)
Mendelian Inheritance

Classic Mendelian Inheritance  X-linked (recessive)

Mitochondrial Inheritance
Other Types of Genetic Variation

Chromosomal abnormalities
  • Translocations
  • Duplications
  • Deletions

Epigenetics: heritable changes in gene expression with no underlying changes in gene sequence
  • gene methylation
  • transcriptionally competent retrotransposons
  • others

Epigenetic Variation in an Isogenic Strain

The purpose of a genetic evaluation is to:

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- Provide a rationale and a plan of action to deal with it

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# Genetic Evaluation: Purpose, Timing

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- Provide a rationale and a plan of action to deal with it

This is especially relevant:

- In unaffected at-risk relatives
- If history of early death or significant morbidity (e.g., sudden cardiac death, myocardial infarction, heart failure, aortic rupture, etc)
**Genetic Evaluation: Purpose, Timing**

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- In unaffected at-risk relatives
- If history of early death or significant morbidity (e.g., sudden cardiac death, myocardial infarction, heart failure, aortic rupture, etc)
- For timely drug/device intervention

**Timing:** A genetic evaluation is indicated with a new diagnosis of cardiomyopathy (DCM, HCM, ARVC, restrictive), channelopathy, aortopathy, dyslipidemia/premature coronary artery disease.
## Components of a genetic evaluation

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### Components of a genetic evaluation

- **Comprehensive family history**
- **Counseling about the condition:**  
  - That it may have a genetic basis  
  - May have a variable age of onset  
  - Its associated symptoms, outcomes, etc

### Components of a genetic evaluation

- Genetic testing, if feasible and indicated:
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Genetic testing, if feasible and indicated:
- If positive, return of results
- If positive, cascade genetic testing of relatives
Components of a genetic evaluation

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- If positive, cascade genetic testing of relatives
- If negative, consider exome sequencing if 3 or more affecteds, or if trio for possible *de novo* or recessive

Recommend baseline clinical screening of at-risk relatives
Components of a genetic evaluation

Genetic testing, if feasible and indicated:
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• If positive, cascade genetic testing of relatives
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Recommend baseline clinical screening of at-risk relatives
Periodic clinical rescreening of at-risk relatives

Guidelines and Other Information Sources
Genetic Evaluation of Cardiovascular Disease

Guidelines:
• Cardiomyopathies – Heart Failure Society of America, 2009; Heart Rhythm Society, 2011
• Channelopathies – Heart Rhythm Society, 2011

GeneReviews (online NCBI/NLM resource)
• Hypertrophic Cardiomyopathy – Cirino, Ho
• Arrhythmogenic Right Ventricular Cardiomyopathy – McNally, McLeod, Dellefave-Castillo
• Thoracic Aortic Aneurysms and Dissection – Milewicz, Regalado
• Dilated Cardiomyopathy – Hershberger, Morales
• Catecholaminergic Polymorphic Ventricular Tachycardia – Napolitano, Priori, Bloise
• Brugada Syndrome – Brugada, Campuzano, Brugada
• . . .and others
Indications for a Cardiovascular Genetic Evaluation

- New diagnosis of a known genetic condition with or without a positive family history
  - Cardiomyopathy
  - Channelopathy
  - Aortopathy
  - Familial Hypercholesterolemia, severe hyperlipidemia

- Clear family history of a morbid or lethal phenotype: sudden death, cardiomyopathy, aneurysm, pacemakers, bleeding, clotting, stroke, early myocardial infarction

Rationale for Genetic Referral, Genetic Testing, in Cardiovascular Genetic Medicine

Pre-symptomatic diagnoses enables:
- Improved surveillance for disease presentation
- Early treatment to decrease morbidity and mortality

By:
- Preventing disease progression (drugs, specific Rx)
- Improved timing of interventions (drugs, devices)
- Averting heart failure and arrhythmic events

Burkett, Hershberger, J Am Coll Cardiol 2005; 45:969-81
Hershberger, Morales, Siegfried, Genetics in Med 2010;12:655-667
Hershberger, Siegfried, J Am Coll Cardiol 2011; 57: 1641-49
## Disorders with Genetic Testing Available

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
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<tr>
<td>Cardiomyopathies - DCM, HCM, RCM, ARVC, LVNC</td>
<td></td>
</tr>
<tr>
<td>Channelopathies - Long QT, Short QT, Brugada, CPVT (catecholaminergic polymorphic ventricular tachycardia), Timothy syndrome, others</td>
<td></td>
</tr>
<tr>
<td>Aortopathies: Marfan, Loeys-Dietz, Thoracic Aortic Aneurysm and Dissection (TAAD), others</td>
<td></td>
</tr>
<tr>
<td>Familial Hypercholesterolemia (FH); other heritable lipid disorders</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension, congenital heart disease, others</td>
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## Rules of the Road for Genetic Testing

- Phenotypes follow gene ontologies – inform test selection
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- Mutations -- almost always unique to a pedigree - ‘private’ – make interpretation challenging

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- Mutations -- almost always unique to a pedigree - ‘private’ – make interpretation challenging

- Most genes have mutations scattered throughout coding sequence – entire genes need to be sequenced
Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a genetic disease of sarcomeric proteins

- **MYBPC3** (myosin binding protein C) 40%
- **MYH7** (beta myosin heavy chain) 40%
- **TNNT2** (troponin T, others) 10-15%

Gene ontology for HCM

Sarcome
- MYH7
- MYBPC3
- TNNT2
- TNNC1
- TNNI3
- TPM1
- ACTC
- MYL2
- MYL3
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disease of the desmosome

Gene ontology for ARVC
Desmosome
PKP2
DSG2
DSC2
DSP
TNNT1

Awad, Calkins, Judge, Nature Clinical Practice Cardiovascular Medicine 2008;5:258-267
**DCM Gene Ontology**

**Gene ontology for DCM**

<table>
<thead>
<tr>
<th>Sarcome</th>
<th>Cytoskeleton</th>
<th>Z-disc</th>
<th>Nuclear envelope</th>
</tr>
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<tbody>
<tr>
<td>ACTC</td>
<td>DMD</td>
<td>TCAP</td>
<td>LMNA</td>
</tr>
<tr>
<td>MYH7</td>
<td>DES</td>
<td>CRSP3</td>
<td>TMPO</td>
</tr>
<tr>
<td>MYH6</td>
<td>LDB3</td>
<td>ACTN2</td>
<td>Gamma secretase activity</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>SGCD</td>
<td>MYPN</td>
<td>PSEN1</td>
</tr>
<tr>
<td>TNNT2</td>
<td>PDLIM3</td>
<td>ANKRD1</td>
<td>PSEN2</td>
</tr>
<tr>
<td>TNNC1</td>
<td>VCL</td>
<td>NEBL</td>
<td>Sarcoplasmic reticulum</td>
</tr>
<tr>
<td>TNNI3</td>
<td>RYAB</td>
<td>NEXL</td>
<td>PLN</td>
</tr>
<tr>
<td>TPM1</td>
<td>ILK</td>
<td>MURC</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>TTN</td>
<td>LAMA4</td>
<td></td>
<td>EYA4</td>
</tr>
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**Ion Channel**

| ABCC     | TAZ/G4.5     | Co-chaperone, heat shock protein |
| SCN5A    |              | BAG3                     |

Hershberger, Siegfried, J Am Coll Cardiol 2011; 57: 1641-49

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**Dilated Cardiomyopathy**

Dilated Cardiomyopathy

is a genetic disease of diverse protein function that yields a final phenotype

<table>
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<tr>
<th>Gene</th>
<th>Percentage</th>
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<tr>
<td>TTN</td>
<td>~20%</td>
</tr>
<tr>
<td>LMNA</td>
<td>5-8%</td>
</tr>
<tr>
<td>MYH7</td>
<td>4%</td>
</tr>
<tr>
<td>MYPN</td>
<td>3.5%</td>
</tr>
<tr>
<td>TNNT2</td>
<td>3%</td>
</tr>
<tr>
<td>SCN5A</td>
<td>3%</td>
</tr>
<tr>
<td>BAG3</td>
<td>3%</td>
</tr>
<tr>
<td>MYPBC3</td>
<td>3%</td>
</tr>
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and many others.

Hershberger, Siegfried, J Am Coll Cardiol 2011; 57: 1641-49
Channelopathy Gene Ontology

Gene ontology for Channelopathies

Long QT
KCNQ1 (LQT1) 30-35%
KCNH2 (LQT2) 25-40%
SCN5A (LQT3) 5-10%

Catcholaminergic Polymorphic Ventricular Cardiomyopathy
RYR2 60%

Brugada Syndrome
SCN5A (20-30%)

Hershberger, Hedges, Morales. Nature Reviews Cardiology 10, 531-547 (September 2013)
### Additional comments on molecular genetic testing and counseling

Always start with the family member with the clearest and most compelling phenotype for testing

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- Obtain an extended family history
- Discuss heritability
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Genetic counselors:
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- Patient/family follow up especially for cascade evaluation, testing
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Genetic counselors:
- Obtain an extended family history
- Discuss heritability
- Coordinate testing and communicate results
- Patient/family follow up especially for cascade evaluation, testing
- Information regarding test sensitivity:
  - DCM – 30-40%
  - HCM – 50-75% if familial; 30-40% sporadic
  - ARVC – ~50%
  - Long QT – 75%

Testing cost is a one-time event
- Many insurers now cover genetic testing
- Test panels are rapidly expanding at same cost
Patient Case 1: MJ

This 36 year old Caucasian female had new onset of Idiopathic Dilated Cardiomyopathy in 2009 at 31 years of age

• Symptom onset for a few weeks, without obvious trigger
Patient Case 1: MJ

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- Symptom onset for a few weeks, without obvious trigger
- Echo: 7.2 cm LVEDD, EF 10-15%
- ECG: LBBB, 144 msec; PR 134 msec; LAD
- Cardiac magnetic resonance: dilated LV, severe global hypokinesis, EF 19%; normal RV size, moderate RV systolic dysfunction; biatrial enlargement; moderate MR; minimal midwall fibrosis with gadolinium; no iron overload.

### Patient Case 1: MJ

Urgent/Emergent VAD placement August 2009
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- Treated medically

- Did well, improved
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  • ICD in place, no shocks
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[Family tree diagram with various symbols and dates indicating deaths with causes of death (COD).]

- d.49: COD: Sudden Death
- d.51: COD: Glioblastoma
- d.69: COD: Emphysema
- d.72: COD: In Sleep
- d.57: COD: Epilepsy
- d.39: COD: MVA
- d.36: COD: NICM Heart Transplant
- d.29: COD: NICM

[Other symbols and arrows indicating family relationships and ages.]
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<td>MYBPC3*</td>
<td>c.26-2A&gt;G</td>
<td>IVS1-2A&gt;G</td>
<td>.01% (EA)</td>
<td>Disease-causing mutation</td>
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<tr>
<td>TNNC1^</td>
<td>c.446A&gt;G</td>
<td>Asp149Gly</td>
<td>0% (EA)</td>
<td>Variant, likely disease-causing</td>
</tr>
<tr>
<td>LAMA4~</td>
<td>c.4624A&gt;T</td>
<td>Asn1542Tyr</td>
<td>.02% (EA)</td>
<td>Variant of unknown significance (VUS)</td>
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*Reported previously in association with HCM; destroys canonical splice acceptor site

^Novel variant; non-conservative amino acid substitution; conserved position; missense variants in nearby residues have been reported in HGMD in association with CMP (E134D, D145E, I148V)

~Novel variant; semi-conservative amino acid substitution; position not well conserved; no nearby variants reported in HGMD in association with CMP
Panel results pending
Research

• The family is enrolled our DCM Research Protocol.

• Our exome data suggests that multiple variants may be more common than previously thought.
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    ➢ Which variants cause DCM and which act as modifiers?
  • Our data also suggests that PPCM shares the same genetic basis with DCM.
    ➢ What is the molecular basis underlying pregnancy onset of DCM?

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<td>• Echo 2007: LVEDD 6.7 cm, EF 16%</td>
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<tr>
<td>• Cardiac MRI 2007: dilated LV, EF 23%; non-viable LAD territory; valves OK</td>
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First OSU notes 2007

- Echo 2007: LVEDD 6.7 cm, EF 16%
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- Close, careful follow up, full medical therapy
- Progressive disease

Heart transplant December 2011, now doing well

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JA – Genetic testing results
(76 gene “Comprehensive Cardiomyopathy” panel)

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<td>Gln62Lys</td>
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<td>Variant of unknown significance (VUS)</td>
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<td>c.327A&gt;G</td>
<td>Ile109Met</td>
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(76 gene “Comprehensive Cardiomyopathy” panel)

• *Reported previously in association with HCM and Ebstein’s anomaly; non-conservative amino acid substitution; conserved residue; missense variants in nearby residues have been reported in HGMD in association with CMP (A1454T, S1465L)
• ^Reported numerous times as VUS; has been present in ARVC patients with other variants
• ~Reported previously as VUS; reported in ARVC patient with other variant; conservative amino acid substitution; position not conserved
Variations on the Typical Mendelian Disease Paradigm Relevant to DCM

Management and Screening Recommendations

- Clinical screening of all first-degree relatives
- Segregation genetic testing in affected family members
- What about predictive testing?

Hershberger, Hedges, Morales. *Nature Reviews Cardiology* 10, 531-547 (September 2013)