Mended Hearts: Savings Lives of Heart Patients Through Genetic Testing

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Why Genetics is Important in Heart Disease: Taking Heredity to Heart
We all have genetic predispositions

Some genes associated with sudden cardiac death: This image of human chromosomes shows the genes known to be responsible for several inherited conditions that can cause arrhythmias. The name of the condition is followed by the gene abbreviation, indicated in parentheses. See page 3 for full condition names. Often, more than one gene can be associated with a disorder, or different genes can be associated with variations of a disorder. This is the case with Long QT Syndrome. (Adapted from a Mayo Medical Laboratories image)
Common Inherited Forms of Heart Disease

- **Arrhythmias (isolated and syndromic)**
  - Long QT syndrome (LQTS)
  - Brugada syndrome
  - Catecholaminergic polymorphic ventricular tachycardia (CPVT)
  - Familial atrial fibrillation

- **Cardiomyopathies (isolated and syndromic)**
  - Dilated cardiomyopathy (DCM)
  - Hypertrophic cardiomyopathy (HCM)
  - Restrictive cardiomyopathy (RCM)
  - Arrhythmogenic right ventricular cardiomyopathy (ARVC)
  - Left ventricular noncompaction (LVNC)

- **Aneurysm syndromes**
  - Familial thoracic aortic aneurysm and dissection syndromes
  - Marfan, Loeys-Dietz, and other connective tissue disorders

- Familial coronary artery disease and dyslipidemias
- Congenital heart disease
Genetic markers of CHDs and other heritable heart diseases

CHDs are caused by
- Chromosome abnormalities
- Microdeletion/duplication syndromes
- Single gene disorders (syndromic and nonsyndromic)
- Somatic mutations?
- Others?
  - The cause for most nonsyndromic CHDs remains unknown – future research utilizing next-generation DNA sequencing may provide more accurate genetic risk information

Congenital heart defects (CHDs)

- The most common group of birth defects
  - Account for ~25% of all birth defects
  - CHDs affect ~36,000 children each year in the U.S.

- Multiple studies show CHDs have
  - High heritability
  - Increased recurrence risks (RR)
    - The overall RR of nonsyndromic CHDs is ~2-10%

- A search of the Online Mendelian Inheritance in Man (OMIM) database reveals that the number of genetic syndromes with cardiac involvement is greater than 1300
Mutations in the same gene can be associated with diverse cardiac phenotypes

- Prime example: *NKX2.5* gene
Cardiac Disorders Predisposing to SCA

**TABLE 1 Cardiac Disorders Predisposing to Pediatric and Young Adult SCA**

<table>
<thead>
<tr>
<th>Structural/functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypertrophic cardiomyopathy*</td>
</tr>
<tr>
<td>2. Coronary artery anomalies</td>
</tr>
<tr>
<td>3. Aortic rupture/Marfan syndrome*</td>
</tr>
<tr>
<td>4. Dilated cardiomyopathy or restrictive cardiomyopathy*</td>
</tr>
<tr>
<td>5. Myocarditis</td>
</tr>
<tr>
<td>6. Left ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>7. Mitral valve prolapse</td>
</tr>
<tr>
<td>8. Coronary artery atherosclerotic disease</td>
</tr>
<tr>
<td>9. Arrhythmogenic right ventricular cardiomyopathy*</td>
</tr>
<tr>
<td>10. Postoperative congenital heart disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrical</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. LQTS*</td>
</tr>
<tr>
<td>12. Wolff-Parkinson-White syndrome</td>
</tr>
<tr>
<td>13. Brugada syndrome*</td>
</tr>
<tr>
<td>14. Catecholaminergic polymorphic ventricular tachycardia*</td>
</tr>
<tr>
<td>15. Short QT syndrome*</td>
</tr>
<tr>
<td>16. Complete heart block</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Drugs and stimulants; some prescription medications</td>
</tr>
<tr>
<td>18. Primary pulmonary hypertension*</td>
</tr>
<tr>
<td>19. Commotio cordis</td>
</tr>
</tbody>
</table>

* Familial/genetic.
Cardiovascular Genetic and Genomic Medicine Program

- Comprehensive, multidisciplinary program at the Richard M. Ross Heart Hospital
- CV Genetic and Genomic Medicine Clinic
  - Dr. Ray Hershberger
  - Multidisciplinary clinic for cardiomyopathies, familial hypercholesterolemia, aortopathies, congenital heart disease, others
- Inherited Arrhythmia Clinic
  - Dr. Raul Weiss
  - Multidisciplinary clinic for genetic types of arrhythmias
- To schedule an appointment, please call 614-293-6694
Specialized Multidisciplinary CV Genetic and Genomic Medicine Clinic Model

Family with hereditary heart disease

Cardiologist

Pathologist

Genetic counselor

Nurse

Medical geneticist

Patient support groups

Genetic testing laboratories

Researchers

Coroner/Medical Examiner

Adapted from Semsarian and Hamilton *Heart Rhythm* 2012 and Ingles et al *Heart Rhythm* 2011
Taking an Informative Pedigree
Essential Tool for CV Genetic Medicine

- ≥3 generations

Questions should include:
1. Current ages
2. Health status and age at diagnosis
3. Age and cause of death
4. Focus on red flags (e.g. syncope)

Family history is imperative in:
1) aiding diagnosis
2) determining inheritance pattern
3) identifying at-risk relatives
4) selecting the most informative family member for genetic testing initiation
A Few General Rules of Thumb

- **Most** Inherited Cardiovascular Conditions
  - Relatively common diseases
    - **Younger** age of onset
    - More **severe**
  - Autosomal dominant
    - However…pedigree may not look dominant
    - Phenotype may not be in every generation
    - Lack of additional diagnoses in family even when genetic due to
      - Reduced penetrance
      - Smaller family sizes
      - Variable expression of signs and symptoms
Family History Red Flags

- “Heart attack”, <55 yrs men, <65 yrs women
  - Arrhythmia, aortic dissection, cardiomyopathy, early onset CAD
- Sudden death, unexplained & accidental (drowning, unexplained single MVA)
  - Arrhythmia, aortic dissection, cardiomyopathy, early onset CAD
- Syncope or pre-syncope
  - Arrhythmia, cardiomyopathy
- Exercise intolerance
  - Arrhythmia, cardiomyopathy
- Heart transplantation
  - Cardiomyopathy
- Heart failure <60 yrs
  - Cardiomyopathy
- Multiple family members with pacemakers and/or ICDs
  - Arrhythmia, cardiomyopathy
- Sudden Infant Death Syndrome (SIDS)
  - Emerging data suggests ~10-15% of SIDS deaths are associated with mutations in several genes associated with cardiac ion channelopathies
- Seizures
CV Genetic/Genomic Medicine Consultation

- Medical history
- Family history
  - Collection and review of family members’ medical records, autopsy reports, etc.
- Physical examination
  - Cardiologist, electrophysiologist, medical geneticist
- Risk assessment
- Education
- Genetic and genomic testing options – now MANY!
  - Informed consent, discussion of possible results, sample collection, insurance preauthorization
- Genetic test result interpretation and disclosure
- Screening/management recommendations
Additional Services

- Psychosocial counseling and anticipatory guidance for issues related to hereditary disease, genetic testing results, etc.
- Referral to support groups and advocacy organizations
- Connection with families with the same condition
- Coordination of DNA banking for future use of patients, families and possibly researchers
- Discussion of available genetics research study options
- Evaluation of at-risk family members

Cascade genetic testing and clinical screening
Genetic testing
<table>
<thead>
<tr>
<th>Test</th>
<th>Type</th>
<th>Method</th>
<th>Laboratory</th>
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<tbody>
<tr>
<td>Cardiomyopathy (Hypertrophic) Multi-Gene Panel</td>
<td>Panel</td>
<td></td>
<td>Harvard Medical School and Partners Healthcare, Laboratory for Molecular Medicine - Cambridge, MA, USA</td>
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<tr>
<td>Cardiomyopathy (Hypertrophic) Multi-Gene Panel</td>
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<td>Health in Code S.L. - A Coruña, Spain</td>
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<tr>
<td>Cardiomyopathy (Hypertrophic) Multi-Gene Panel</td>
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<td>Centogene AG, Rare Disease Company - Roetgen, Germany</td>
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<tr>
<td>Cardiomyopathy (Hypertrophic) Multi-Gene Panel</td>
<td>Panel</td>
<td></td>
<td>University Hospitals of Geneva - Genetic Medicine, Genetic Oncology - DiagMol - Geneva, Switzerland</td>
</tr>
<tr>
<td>Cardiomyopathy (Hypertrophic) Multi-Gene Panel</td>
<td>Panel</td>
<td></td>
<td>Baylor College of Medicine, John Welsh Cardiovascular Diagnostic Laboratory - Houston, TX, USA</td>
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<td></td>
<td>GeneDx - Gaithersburg, MD, USA</td>
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<td></td>
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GTR:
Genetic Testing Registry
Genetic and Genomic Testing Advances

- Next-generation DNA sequencing
  - Rapid analysis of large panels of disease-specific genes
- “Design Your Own” Panels
  - 1,000 genes for $1,000
- Pan Cardio Panels (~80 genes)
- Cardiomyopathy Panels (>70 genes)
- Arrhythmia Panels (>30 genes)
- Whole exome sequencing
  - Information on coding sequence of all ~24,000 genes
  - Clinically available and have ordered on several patients now
- Whole genome sequencing
Doctors Sift Through Patients’ Genomes To Solve Medical Mysteries

by ROB STEIN

Listen to the Story
Morning Edition

21

Ending the diagnostic odyssey, with and without treatment ramifications

North County Twins Cured After Whole Genome Sequencing

By Chris Chan | Saturday, Aug 25, 2012 | Updated 11:03 AM PDT

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Sara Terry’s first clue that something was wrong with her son, Christian, came just three weeks after he was born.

“We went to check on him, just like any parents go and check on their kids just to make sure they’re breathing,” says Terry, 34, of Spring, Texas. “And we found him in his crib, and he wasn’t breathing. He was blue.”

Erin Kayne for NPR

Sara Terry and her son, Christian, in Spring, Texas. After sequencing Christian’s genome, doctors were able to diagnose him with a Noonan-like syndrome.
DNA from two family members were analyzed by WES

>2000 rare variants were shared

Of these, 55 were predicted to affect a protein

None completely segregated with CHD

MYH6 Ala290Pro was identified in all but one affected individual