THE GENETICS OF CARDIOMYOPATHY: OPTIMIZING PATIENT AND FAMILY CARE BY IDENTIFYING DISEASE ETIOLOGY

The Ohio-ACC Spring Summit
April 18, 2012
Erin M. Miller, MS, CGC
The Heart Institute
Objectives

• Understand the variety of multi-gene panels available for cardiomyopathies

• Identify the utility of genetic testing for cardiomyopathy with regard to screening, diagnosis and management

• Determine appropriate genetic testing and/or referrals for patients with cardiomyopathies
Overview

• Genetic Counseling
• Review of published guidelines for genetic testing and screening of at-risk individuals
• Disease specific overview - HCM, DCM, RCM, ARVC, and LVNC
  • Etiology
  • Clinical genetic testing
  • Case examples
Genetic Counseling

• ...process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.

• In practice
  • Clinical care and support to families
    • Prenatal, Cancer, Pediatric, Adult, *Cardiovascular*
  • Education
  • Research
  • Policy

• Education:
  • M.Sc. in Genetic Counseling/Medical Genetics
    • 2-3 yr full time program, thesis requirement
  • Certification by the ABGC
  • Continuing Education

nsgc.org
A Contemporary Approach to Hypertrophic Cardiomyopathy
Carolyn Y. Ho and Christine E. Seidman
Circulation 2006;113:e858-e862

Guidelines for the Diagnosis and Management of Hypertrophic Cardiomyopathy
Christopher Semsarian, PhD, FRACP, a,b Members of the CSANZ Cardiovascular Genetics Working Group

Genetic diagnostics and genetic counselling in Hypertrophic Cardiomyopathy (HCM)

doi:10.1093/eurheartj/ehq327

Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases
Philippe Charron 1, Michael Arad 2, Eloisa Arbustini 3, Cristina Basso 4, Zofia Bilinska 5, Perry Elliott 6, Tiina Helio 7, Andre Keren 8, William J. McKenna 6, Lorenzo Monserrat 9, Sabine Pankuweit 10, Andreas Perrot 11, Claudio Rapezzi 12, Arsen Ristic 13, Hubert Seggewiss 14, Irene van Langen 15, and Luigi Tavazzi 16
HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

Michael J. Ackerman, MD, PhD, Silvia G. Priori, MD, PhD, Stephan Willems, MD, PhD, Charles Berul, MD, FHR, CCDS, Ramon Brugada, MD, PhD, Hugh Calkins, MD, FHR, CCDS, A. John Camm, MD, FHR, Patrick T. Ellinor, MD, PhD, Michael Gollob, MD, Robert Hamilton, MD, CCDS, Ray E. Hershberger, MD, Daniel P. Judge, MD, Hervè Le Marec, MD, William J. McKenna, MD, Eric Schulze-Bahr, MD, PhD, Chris Semsarian, MBBS, PhD, Jeffrey A. Towbin, MD, Hugh Watkins, MD, PhD, Arthur Wilde, MD, PhD, Christian Wolpert, MD, Douglas P. Zipes, MD, FHR
Genetic testing recommended:
HCM- confirmed clinical diagnosis
DCM- confirmed clinical diagnosis and CCD and/or family history of SUD
HCM, DCM, ARVC, RCM, LVNC- known mutation testing for relatives

Genetic testing can be useful:
ARVC- patients meeting the 2010 task force criteria
DCM- familial DCM to confirm the dx, recognize those at highest risk of arrhythmia, facilitate cascade screening
LVNC- confirmed clinical diagnosis

Genetic testing may be considered:
ARVC- patients with possible dx
RCM- clinical diagnosis

Genetic counseling *is recommended* for all patients and relatives with familial heart disease
<table>
<thead>
<tr>
<th>Section – Disease</th>
<th>Yield of Genetic Test*</th>
<th>% of Controls with a Rare VUS#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section I – LQTS</td>
<td>75% (80%)</td>
<td>4%</td>
</tr>
<tr>
<td>Section II – CPVT</td>
<td>60% (70%)</td>
<td>3%</td>
</tr>
<tr>
<td>Section III – BrS</td>
<td>20% (30%)</td>
<td>2% (just SCN5A)</td>
</tr>
<tr>
<td>Section IV – CCD</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Section V – SQTS</td>
<td>Unknown</td>
<td>3%</td>
</tr>
<tr>
<td>Section VI – AF</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Section VII – HCM</td>
<td>60% (70%)</td>
<td>~5% (unpublished data)</td>
</tr>
<tr>
<td>Section VIII – ACM/ARVC</td>
<td>60%</td>
<td>16%</td>
</tr>
<tr>
<td>Section IX – DCM</td>
<td>30%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Section IX – DCM + CCD</td>
<td>Unknown</td>
<td>4% (for SCN5A and LMNA)</td>
</tr>
<tr>
<td>Section X – LVNC</td>
<td>17%–41%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Section XI – RCM</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Logistics of genetic testing

• Large multi-gene panels
  • Multiple laboratories offer testing, specific panels may vary
  • [www.genetests.org](http://www.genetests.org)

• Test the most severely affected individual when possible
  • Blood, spit, tissue

• Turn around time typically 6-8 weeks
  • Communicated to the ordering provider

• Result interpretation
  • Positive, negative, variant of uncertain significance, other
  • Interpretation may vary between laboratories, and may change
  • Mutation prediction models, conserved amongst species, frequency in healthy control population, previous reports/publications
Clinical Screening Recommendations


• Clinical screening for cardiomyopathy is recommended
  • Asymptomatic at-risk relatives who are known to carry the disease-causing mutation(s)
  • Asymptomatic at-risk FDRs when genetic testing has not been performed or has not identified a disease-causing mutation
Clinical Screening Caveats

• Screening should also be initiated at any time signs or symptoms appear
• At-risk FDRs with any abnormal clinical screening tests (regardless of genotype) should be considered for repeat clinical screening at one year
• Clinical screening for HCM has also been recommended in “athletic SDRs” when genetic testing has not been performed or has not identified a disease-causing mutation*

Inheritance, Penetrance and Disease Expression

- **Primarily autosomal dominant inheritance**
  - Mitochondrial, X-linked and AR inheritance observed

- **Penetrance**
  - Incomplete
  - Age-dependent

- **Variable disease expression**
  - Diverse clinical spectrum ranging from asymptomatic individuals, cardiovascular symptoms, congestive heart failure requiring transplant or resulting in death, and SCA/SCD
  - Heart muscle disease may present with overlapping features

- **Diverse etiologies and historically high rates of idiopathic disease**
  - Inability to identify underlying etiology has inhibited appropriate treatment, counseling and understanding of disease.
Aims:
- Determine spectrum of etiologic diagnoses in PCM
- Determine clinical diagnostic testing yield in a non-selected outpatient clinic population

Methods:
- Retrospective analysis of clinical test results
- 98 consecutive probands
- Excluded neuromuscular disease, chemotherapy mediated, and rhythm induced cardiomyopathies
- All patients evaluated in Multidisciplinary Clinic
  - Full cardiac work-up including appropriate imaging
  - Clinical genetics evaluation
  - Molecular testing as indicated

Genetic Diagnosis in Pediatric Cardiomyopathy Patients
Etiology in 98 Probands

- **Idiopathic**: 70%
- **Myocarditis**: 26%
- **Syndromic**: 15%
- **Metabolic**: 38%
- **Familial**: 55%

- **PCMR**: (98)
- **All**: (52)
- **HCM**: (29)
- **DCM**: (4)
- **RCM**: (11)
- **LVNC**: (2)
- **ARVC**: (1)

Phenotype:
- Idiopathic
- Myocarditis
- Syndromic
- Metabolic
- Familial
Results

- Significantly increased etiologic diagnosis
  \[p < 0.01\] when compared to PCMR data
- Familial disease most common etiology (42%)
  True across phenotypic groups
  Familial disease in infants in HCM and DCM
  All RCM probands were familial
- Significant rates of metabolic and syndromic disease
  All phenotypes: Metabolic = 17% Syndromic = 12%
  Higher rates in HCM and DCM populations
Hypertrophic Cardiomyopathy (HCM)

- Unexplained cardiac hypertrophy with systolic and possible diastolic dysfunction
  - Outflow tract obstruction possible

- Pathophysiology
  - Myocyte disarray
  - Fibrosis

- Prevalence 1 in 500
  - Most common inherited cardiac disorder
  - Major cause of sudden cardiac death (SCD) in competitive athletes
  - Acquired causes include systemic hypertension, athletes heart, etc.
HCM: A Disease of the Sarcomere

Seidman et al 1995
**Genes Associated with HCM**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Frequency in patients with HCM</th>
<th>Associated phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td>β-Myosin heavy chain</td>
<td>25–35%</td>
<td>Mild or severe HCM</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Myosin-binding protein C (cardiac type)</td>
<td>20–30%</td>
<td>Expression similar to MYH7, late onset</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Troponin T (cardiac muscle)</td>
<td>3–5%</td>
<td>Mild hypertrophy, sudden death</td>
</tr>
<tr>
<td>TNNI3</td>
<td>Troponin I (cardiac muscle)</td>
<td>&lt;5%</td>
<td>Extreme intrafamilial heterogeneity, no sudden death without severe disease</td>
</tr>
<tr>
<td>TPM1</td>
<td>Tropomyosin 1α</td>
<td>&lt;5%</td>
<td>Variable prognosis, sudden death</td>
</tr>
<tr>
<td>MYL2</td>
<td>Regulatory myosin light chain 2 (ventricular/cardiac-muscle isoform)</td>
<td>&lt;5%</td>
<td>Skeletal myopathy</td>
</tr>
<tr>
<td>MYL3</td>
<td>Essential myosin light chain 3</td>
<td>Rare</td>
<td>Skeletal myopathy</td>
</tr>
<tr>
<td>ACTC</td>
<td>α-Cardiac actin 1</td>
<td>Rare</td>
<td>Apical hypertrophy</td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
<td>Rare</td>
<td>Typical HCM</td>
</tr>
<tr>
<td>TNNC1</td>
<td>Troponin C, slow skeletal and cardiac muscles</td>
<td>Rare</td>
<td>Typical HCM</td>
</tr>
<tr>
<td>MYH6</td>
<td>α-Myosin heavy chain</td>
<td>Rare</td>
<td>Late onset</td>
</tr>
<tr>
<td>CSRPR3</td>
<td>Muscle LIM protein</td>
<td>Rare</td>
<td>Late onset, variable penetrance</td>
</tr>
<tr>
<td>MYLK2</td>
<td>Myosin light chain kinase 2</td>
<td>Rare</td>
<td>Early onset</td>
</tr>
<tr>
<td>LDB3</td>
<td>LIM binding domain 3</td>
<td>Rare</td>
<td>Mainly sigmoidal HCM</td>
</tr>
<tr>
<td>TCAP</td>
<td>Telethonin</td>
<td>Rare</td>
<td>Typical HCM, variable penetrance</td>
</tr>
<tr>
<td>VCL</td>
<td>Vinculin/metavinculin</td>
<td>Rare</td>
<td>Obstructive midventricular hypertrophy</td>
</tr>
<tr>
<td>ACTN2</td>
<td>α-Actinin 2</td>
<td>Rare</td>
<td>Mainly sigmoidal HCM</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>Rare</td>
<td>Typical HCM, variable penetrance</td>
</tr>
<tr>
<td>MYOZ2</td>
<td>Myozinenin 2</td>
<td>Rare</td>
<td>Typical HCM</td>
</tr>
<tr>
<td>JPH2</td>
<td>Junctophilin 2</td>
<td>Rare</td>
<td>Typical HCM</td>
</tr>
</tbody>
</table>

Abbreviation: HCM, hypertrophic cardiomyopathy.
Genetic Testing- HCM

- Clinical testing available through 6 clinical laboratories within the United States
  - HCM gene panel

- Large multi-gene panels due to significant genetic heterogeneity
  - Number of genes range from 8-18
  - MYBPC3 and MYH7 account for majority of cases;
    - many private mutations
    - Majority are inherited, de novo mutations reported
  - Heterozygous for two disease causing mutations in 3-5% of cases
  - Current detection rates vary; average 40% for isolated cases and 70% for cases with FH of HCM or SCD
Case Example 1 (KFM testing)

- d. 49 Cerebral hemorrhage
- 46 yo
- 21 yo dx. 14 atenolol
- 19 yo dx 16 s/p ICD
- 29 yo dx 18 s/p ablation
- 33 yo No echo
- 50 yo s/p ICD
- 4 yo Nml echo and ecg
- 21 mo Nml echo and ecg
HCM Gene Panel

**MYBPC3, IVS11-9 G>A**

<table>
<thead>
<tr>
<th>Genes Evaluated</th>
<th>Disease: Protein (Gene)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM1: Myosin Heavy Chain (MYH7)</td>
<td>HCM/DCM: Troponin C1 (TNNC1)</td>
</tr>
<tr>
<td>HCM2: Troponin T2 (TNNT2)</td>
<td>HCM: Caveolin 3 (CAV3)</td>
</tr>
<tr>
<td>HCM3: Troponym 1 (TPM1)</td>
<td>Dano disease: Lysosomal-associated Membrane Protein 2 (LAMP2)</td>
</tr>
<tr>
<td>HCM4: Myosin-binding Protein C (MYBPC3)</td>
<td>Fabry disease: Alpha-galactosidase (GLA)</td>
</tr>
<tr>
<td>HCM7: Troponin I (TNNI3)</td>
<td>Glycogen Storage Disease:</td>
</tr>
<tr>
<td>HCM8: Myosin light chain 3 (MYL3)</td>
<td>Protein Kinase AMP-activated Gamma 2 (PRKAG2)</td>
</tr>
<tr>
<td>HCM10: Myosin light chain 2 (MYL2)</td>
<td>Mitochondrial HCM: tRNA glycine (MTTG)</td>
</tr>
<tr>
<td>HCM11: Alpha Actin Cardiac (ACTC)</td>
<td>Mitochondrial HCM: tRNA isoleucine (MTTL)</td>
</tr>
<tr>
<td>Transthyretin amyloidosis: Transthyretin (TTR)</td>
<td>Mitochondrial HCM: tRNA lysine (MTTK)</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial HCM: tRNA glutamine (MTTQ)</td>
</tr>
</tbody>
</table>

**Result:**

**ABNORMAL (POSITIVE):**

Heterozygous for IVS11-9 G>A in the MYBPC3 gene; published, disease-causing mutation (1).

A heterozygous G>A nucleotide substitution was identified in intron 11 of the MYBPC3 gene, which is predicted to cause abnormal gene splicing. This mutation is denoted IVS11-9 G>A or c.927-9 G>A at the cDNA level.

No other disease-causing mutations were detected by sequence analysis of the 18 genes tested in this individual.

**Interpretation:**

This individual is heterozygous for a published splice site mutation in the MYBPC3 gene, consistent with an autosomal dominant form of HCM.
Case Example 1 (KFM testing)

- **d. 49** Cerebral hemorrhage
- **46 yo**
- **21 yo dx. 14 atenolol** MYBPC3 +
- **19 yo dx 16 s/p ICD**
- **29 yo dx 18 s/p ablation**
- **33 yo** No echo
- **50 yo** s/p ICD
- **4 yo** Nml echo and ecg
- **21 mo** Nml echo and ecg
- **KFM -**
- **KFM -**
Uptake of Genetic Testing and Cardiac Screening among HCM and DCM Families

• METHODS
  • Recent guidelines recommend genetic testing and cascade screening for at-risk relatives, clinical utility remains uncertain

• Reviewed >250 patients evaluated for cardiomyopathy between 10/2006 and 08/2010
  • Excluded patients with a genetic syndrome, underlying metabolic disease, myocarditis, chemotherapy induced CHF or other acquired causes
  • Excluded patients with RCM, ARVC and LVNC
  • 57 probands with a confirmed diagnosis of HCM or DCM who underwent genetic testing
  • 46 HCM, 11 DCM
• All patients underwent:
  • Full cardiac work-up including appropriate imaging
  • Clinical genetics evaluation and genetic counseling
  • Molecular genetic testing was discussed and offered as indicated
• IRB approval
Uptake of Cardiac Screening Among Relatives

57 probands with HCM/DCM

- Screening indicated: 177 first degree relatives
  - Screening completed: 135 first degree relatives (76%)

- Screening indicated: 302 relatives
  - Screening completed: 173 relatives (57%)

- Screening indicated: 125 second degree relatives
  - Screening completed: 38 second degree relatives (30%)

Clinical diagnosis of HCM/DCM: 43 relatives (25%)
Uptake of Known Familial Mutation Testing Among Relatives

- 40 mutation positive probands
  - KFM testing indicated: 140 first degree relatives
    - KFM testing completed: 72 first degree relatives (51%)
      - 53 asymptomatic relatives (63%)
        - KFM negative: 32 relatives (60%)
        - KFM positive: 21 relatives (40%)
  - KFM testing completed: 84 relatives (39%)
    - KFM positive: 31 relatives (100%)
  - KFM testing indicated: 73 second degree relatives
    - KFM testing completed: 12 second degree relatives (16%)

PRECLINICAL
Family history status of patients with DCM and HCM

<table>
<thead>
<tr>
<th>Family History Status</th>
<th>FH status: Evaluation N (%)</th>
<th>FH status: Current N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Family History</td>
<td>28 (49)</td>
<td>41 (72)</td>
</tr>
<tr>
<td>Negative Family History</td>
<td>29 (51)</td>
<td>16 (28)</td>
</tr>
</tbody>
</table>

- 13 probands had additional family members diagnosed with cardiomyopathy after the initial evaluation
  - 9 probands; family members diagnosed as a direct result of recommendations for family screening
  - 2 probands; family members dx due to CV symptoms
  - 2 probands; uncertain why family members were dx
Summary: Uptake of Cardiac Screening and Genetic Testing

- 1st degree more likely than 2nd degree to complete screening and testing
- Uptake of cardiac surveillance was greater than genetic testing ($p<0.0001$)
- 40% of asymptomatic relatives were given a genetic diagnosis and 25% of relatives were given a clinical diagnosis
- 33 relatives negative KFM testing

- Data demonstrate role and utility of cascade screening and genetic testing

- Improved risk stratification
  - Psychological, economic and medical implications
    - Reduction in SCD, improved understanding of early signs/symptoms and disease progressing
Case Example 2 (confirming clinical dx)

• History:
  • Presented in infancy with a murmur
  • Status post resection of infundibular pulmonic stenosis and transannular patch enlargement of RV outflow tract (6/27/1994)
  • Surgical history: Status post ICD in July 2005

• Presented at 18 yoa in September of 2011

• Cardiac Evaluation:
  • HCM with severe asymmetric septal hypertrophy
  • LV mid-cavitary gradient of 7 mmHg, near obliteration of the LV cavity in systole
  • LV trabeculations
  • Supranormal LV systolic function, EF=72%
Relative short stature and Easy bruising
ADD, ADHD, difficult with reading comprehension
IEP in first grade; extra time for test taking
Nursing student
Differential Diagnosis

• Presentation of severe HCM in infancy with marked RV involvement
  • metabolic condition, inborn error of metabolism, genetic syndromic condition, or isolated (familial) cardiomyopathy.

• Familial HCM vs. Noonan syndrome
  • Some features of NS- PI, mild learning disabilities, easy bruising

• Noonan syndrome
  • CHD present in 50-80% (PVS 20-50%)
  • HCM present in 20-30% (present at birth, dev. in infancy
  • 1/3 have mild intellectual impairment, many normal cognitive function
  • Facial appearance changes considerably with age
    • Most striking in nb period, most subtle in adults
    • Low-set, posteriorly rotated ears, hypertelorism, thick or droopy eyelids
PTPN11 in 50% of affected individuals, SOS1 in approximately 13%, RAF1 in 3% to 17%, and KRAS in fewer than 5%. Other genes in which mutations have been reported to cause Noonan syndrome in fewer than 1% of cases include NRAS, BRAF, and MAP2K1.

Test(s) Requested: Comprehensive Resequencing Array for Noonan, LEOPARD, Cardio-Facio-Cutaneous, and Costello Syndromes

Genes Included: BRAF, HRAS, KRAS, MAP2K1, MAP2K2, PTPN11, RAF1, SHOC2, and SOS1

Result: **POSITIVE. Heterozygous for the M504V Mutation in the PTPN11 Gene**

This individual is heterozygous for the A>G nucleotide substitution in exon 13 of the PTPN11 gene, resulting in the replacement of a Methionine codon (ATG) with a Valine codon (GTG) at amino acid position 504. This mutation is denoted c.1510 A>G at the cDNA level or p.Met504Val (M504V) at the protein level.

Interpretation: The M504V missense mutation observed in the submitted sample has been previously reported in association with Noonan syndrome and has also been seen many times at GeneDx (Tartaglia et al., 2001). The mutation lies within a region of the gene coding for the highly conserved PTP domain of the protein tyrosine phosphatase 11. The identification of the M504V mutation in this specimen is consistent with a diagnosis of autosomal dominant Noonan syndrome in the patient.
HCM

Case Example 1

Sarcomeric

Case Example 2

Noonan Syndrome
Dilated Cardiomyopathy (DCM)

- Left ventricular enlargement with systolic dysfunction

- The prevalence of DCM is ~1/2500, although it may be more common
  - 20-50% of individuals have a family history
  - Many acquired forms

- Common cause of CHF and cardiac transplantation
## Genes Associated with DCM

### Table 2. Genetic Causes of Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>OMIM</th>
<th>Frequency, Familial</th>
<th>Frequency, Sporadic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Dominant FDC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dilated Cardiomyopathy Phenotype</strong></td>
<td></td>
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<tr>
<td>ACTC</td>
<td>Cardiac actin</td>
<td>102540</td>
<td>rare</td>
<td>rare</td>
<td>5.5% overall (41/748, 6 studies, see text)</td>
</tr>
<tr>
<td>DES</td>
<td>Desmin</td>
<td>125660</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>LMNA</td>
<td>Lamin A/C</td>
<td>130330</td>
<td>7.3%</td>
<td>3.0%</td>
<td></td>
</tr>
<tr>
<td>SGCD</td>
<td>α-sarcoglycan</td>
<td>601411</td>
<td>rare</td>
<td>rare</td>
<td>4.8% overall (22/455, 3 studies)</td>
</tr>
<tr>
<td>MYH7</td>
<td>β-myosin heavy chain</td>
<td>160760</td>
<td>6.3%</td>
<td>3.2%</td>
<td>2.3% overall (15/644, 3 studies)</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Cardiac troponin T</td>
<td>191045</td>
<td>2.9%</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>TPM1</td>
<td>α-tropomyosin</td>
<td>191010</td>
<td>rare</td>
<td>rare</td>
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<tr>
<td>TTN</td>
<td>Titin</td>
<td>188840</td>
<td>?</td>
<td>?</td>
<td></td>
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<tr>
<td>VCL</td>
<td>Metavinculin</td>
<td>193065</td>
<td>rare</td>
<td>rare</td>
<td></td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Myosin-binding protein C</td>
<td>600958</td>
<td>?</td>
<td>?</td>
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</tr>
<tr>
<td>CSRP3</td>
<td>Muscle LIM protein</td>
<td>600824</td>
<td>rare</td>
<td>rare</td>
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<tr>
<td>ACTN2</td>
<td>α-actinin-2</td>
<td>102573</td>
<td>?</td>
<td>?</td>
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</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>172405</td>
<td>rare</td>
<td>rare</td>
<td></td>
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<tr>
<td>ZASP</td>
<td>Cypher/LIM binding domain 3</td>
<td>605906</td>
<td>?</td>
<td>?</td>
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<tr>
<td><strong>LDG3</strong></td>
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<tr>
<td>MYH6</td>
<td>α-myosin heavy chain</td>
<td>160710</td>
<td>?</td>
<td>?</td>
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</tr>
<tr>
<td>ABC9</td>
<td>SUR2A</td>
<td>601439</td>
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<tr>
<td>TNAC1</td>
<td>Cardiac troponin C</td>
<td>191040</td>
<td>?</td>
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<tr>
<td>TCFP</td>
<td>Titin-cap or telophosphorin</td>
<td>604488</td>
<td>rare</td>
<td>rare</td>
<td>2.3% overall (11/469, 2 studies)</td>
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<tr>
<td>SCN5A</td>
<td>Sodium channel</td>
<td>600163</td>
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<td>EYA4</td>
<td>Eyes absent 4</td>
<td>603580</td>
<td>?</td>
<td>?</td>
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<tr>
<td>TMPO</td>
<td>Tltrymopoietin</td>
<td>188380</td>
<td>?</td>
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<tr>
<td>PSEN1</td>
<td>Presenilin 1 / 2</td>
<td>104311</td>
<td>?</td>
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<tr>
<td>PSEN2</td>
<td></td>
<td>600759</td>
<td>?</td>
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<tr>
<td><strong>X-linked Familial Dilated Cardiomyopathy</strong></td>
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<td><strong>DM1</strong></td>
<td>Dystrophin</td>
<td>300377</td>
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<td><strong>TAZ/G4.5</strong></td>
<td>Tafazzin</td>
<td>300394</td>
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<tr>
<td><strong>Autosomal Recessive Familial Dilated Cardiomyopathy</strong></td>
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<tr>
<td>TNNB</td>
<td>Cardiac troponin I</td>
<td>191044</td>
<td>?</td>
<td>?</td>
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</tr>
</tbody>
</table>

---

*Genes are ordered by publication year.

†Rare indicates less than 1%; frequencies are provided only with two or more publications.

‡Overall frequencies may include studies that did not distinguish between familial and sporadic cases.
Genetic Testing - DCM

• Clinical genetic testing available; 4 laboratories offer comparable gene panels
  • DCM gene panel, DCM/LVNC gene panel

• Extensive genetic heterogeneity
  • Largest gene panel includes 27 genes
  • Relatively low frequency of involvement of any one gene

• Current detection rate approximately 20-30%
Case Example 3 (idiopathic DCM)
Case Example 4 (Idiopathic DCM)
DCM gene panel results

Case Example 3

**MYH7, Gln1346Stop**
Novel, predicted to cause loss of protein function

Risk stratification of relatives

Case Example 4

**TPM1, Glu272Gly**
Novel, variant of uncertain significance

Likely de novo, confirms pathogenicity
Arrhythmogenic Right Ventricular Cardiomyopathy

- Characterized by progressive fibrofatty replacement of the myocardium predisposing to ventricular arrhythmia and sudden death
  - Bi-ventricular and LV presentation (20-40%) have been recognized
- Leading cause of ventricular arrhythmia and sudden cardiac in the young (<35 years)
- Prevalence unknown (1 in 1,250-5,000)
  - Approximately 50% have a positive family history
Genetic Basis of Disease

• ARVC regarded as a disease of the desmosome; form mechanical couplings that attach adjacent myocytes at the intercalated disc

DSG2, desmoglein-2; DSC2, desmocollin-2; PKP2, plakophilin-2; PKG, plakoglobin; DSP, desmoplakin.

Sen-Chowdhry S et al, JACC 2007
## Genes Associated with ARVC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Estimated Percentage of ARVC</th>
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<tbody>
<tr>
<td>TGFB3</td>
<td>Transforming growth factor beta-3</td>
<td>rare</td>
</tr>
<tr>
<td>RYR2</td>
<td>Ryanodine receptor</td>
<td>rare</td>
</tr>
<tr>
<td>DSP</td>
<td>Desmoplakin</td>
<td>6-16%</td>
</tr>
<tr>
<td>PKP2</td>
<td>Plakophilin-2</td>
<td>11-43%</td>
</tr>
<tr>
<td>DSG2</td>
<td>Desmoglein-2</td>
<td>12-40%</td>
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<tr>
<td>DSC2</td>
<td>Desmocollin-2</td>
<td>rare</td>
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<tr>
<td>TMEM43</td>
<td>Transmembrane protein 43</td>
<td>unknown</td>
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<tr>
<td>JUP</td>
<td>Plakoglobin</td>
<td>rare</td>
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</table>
Genetic Testing

• Clinical testing available for all 8 genes
  • ARVC gene panel

• 40-50% of cases will have an underlying genetic mutation
  • Compound heterozygosity and digenic heterozygosity identified in up to 10% of cases
  • Disease modifying vs. disease causing?

• Some cases of autosomal recessive inheritance
  • Naxos disease
    • Palmoplantar keratoderma
    • Woolly, curly, dense, rough and bristly hair
    • Specific mutations in plakoglobin and desmoplakin
Case Example 5 (SCD and ARVC)

- SCD 18 yo d. Unk PM
- 22 yo Palpitaitons
- SCD 16 yo HCM?
- 17 yo Normal echo Epsilon wave on ECG S/P ICD
Genetic Testing Results

- Two variants were identified in DSP;
  - novel, disease-causing mutation, Arg2160Stop
  - variant of unknown significance, likely disease-causing, Arg315Cys.
Case Example 5 (SCD and ARVC)

- 22 yo Palpitations
- DSP + Arg2160Stop Arg315Cys
- S/P ICD
- DSP Arg2160Stop Arg315Cys
- 17 yo Normal echo Epsilon wave on ECG S/P ICD
Restrictive Cardiomyopathy

- RCM is characterized by impaired ventricular filling
  - Lack of flexibility, rigidity and stiffness
  - Normal LV wall thickness and systolic function
  - Atrial enlargement

- Rare- least common type of cardiomyopathy
  - Familial and Idiopathic cases
  - Infiltrative disease: Sarcoidosis, amyloidosis, Gaucher and Fabry disease
Genetics of RCM

- Genetic basis largely unknown
  - Least common type of cardiomyopathy
  - Less commonly presents with familial disease
- Genes associated with RCM
  - MYH7, TNNI3 and DES
  - TNNT2, ACTC, MYBPC3, *TPMI, *MYL2 and *MYL3

- Yield of testing unknown:
  - Kaski et al 2008 33% (4/12) of patients with idiopathic RCM had a mutation
  - Kubo et al 2007 53% (8/15) of patients with HCM and restrictive physiology had a mutation
  - Kindel et al 2012 (in press) 4 of 4 patients had positive FH, 1 with a mutation

*Caleshu C et al 2011*
Case Example 6 (RCM)

MYH7, G768R
Exon 21
aa 768 highly conserved
reported in literature as pathogenic
Adults with HCM – youngest age of dx 34

Ware, et al Clinical Genetics 2008
Left Ventricular Noncompaction (LVNC)

- Characterized by excessive prominent trabeculations and deep intratrabecular recesses of the normally smooth/compacted LV
- Recognized as a distinct form of cardiomyopathy in 2006*; previously referred to as spongiform or spongy myocardium
- Associated with heart failure, thromboembolism and arrhythmias

*Maron et al Circ 2006 ;113

J. A. Towbin and N. E. Bowles
Nature 415, 227-233(10 January 2002)
doi:10.1038/415227a
Genes Associated with LVNC

- Clinical Genetic Testing available
- 17-41%* will have an underlying mutation
  - Mutations in more than 15 genes identified
  - Sarcomeric, cytoskeletal and ion channel genes
  - Genes encoding the sarcomeric proteins most common
    - MYH7, ACTC1, TNNT2, MYBPC3, ZASP/LBD3

- Mitochondrial disease
- Barth syndrome
  - Mutations in TAZ result in x-linked form of LVNC and metabolic disease in infants

*Klaassen et al Circ 2008
Hoedemaekers et al Circ Cardiovasc Genet 2010
Case example 7

DCM/LVNC panel requested

d.23 SCD LVH and cardiomegaly on autopsy

- 9 yo LV trabeculations
  - MYH7, Thr1929Met

- 8 yo Nml echo and ecg
  - KFM +

- 7 yo Nml echo and ECG
  - KFM +

- 6 yo Nml echo and ECG
  - KFM -
Diagnostic Implications
Genetic testing

- Limited genotype-phenotype data given heterogeneity and frequency of private/novel mutations
- Challenges regarding result interpretation (i.e. multiple mutations, variants of uncertain significance, etc.)
- Confirmation of a clinical diagnosis and presumed etiology
  - Anticipation of syndromic features
- Identification of at-risk relatives when disease mutation identified
Prognostic and Therapeutic Implications
Genetic Testing

• Identification of the underlying gene and mutation has limited role in cardiovascular risk assessment and management of the affected individual
  • GLA associated with Fabry disease – availability of ERT
  • Increased risk of arrhythmia associated with mutations in TNNT2, DES and LMNA
  • TTR associated with RCM secondary to amyloidosis
  • LAMP2 associated with Danon disease (x-linked)
  • PRKAG2 associated with WPW and conduction abnormalities
  • Noonan syndrome associated with extracardiac features
  • ARVC; LV involvement more common with DSP and PKP2 associated with earlier onset of symptoms and arrhythmia
Acknowledgements

• The Cardiomyopathy/Heart Failure Team at CCHMC
• Patients and Families
• Cardiovascular Genetic Counseling Colleagues
QUESTIONS AND COMMENTS

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