The Genetics and Genomics of Familial Heart Disease

Bringing Precision Medicine to Life!

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No conflicts, nothing to disclose

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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

The Explosion of Human Genetics and Genomics in Clinical Practice

Driven by high throughput sequencing

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- **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**

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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

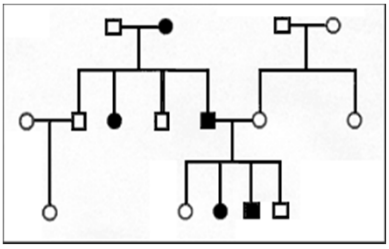
Classic Mendelian Inheritance

- **Autosomal Dominant**
- **Autosomal Recessive**
- **X-linked (dominant / recessive)**

Mitochondrial

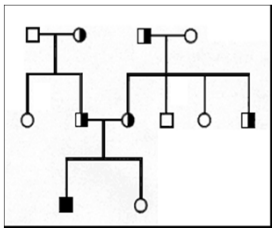
Mendelian Inheritance

Classic Mendelian Inheritance - Autosomal Dominant



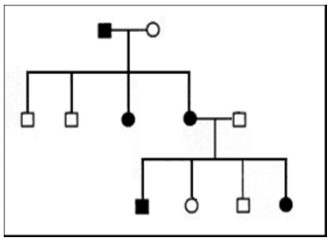
Mendelian Inheritance

Classic Mendelian Inheritance - Autosomal Recessive



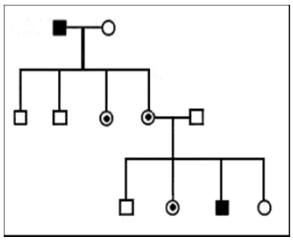
Mendelian Inheritance

Classic Mendelian Inheritance - X-linked (dominant)

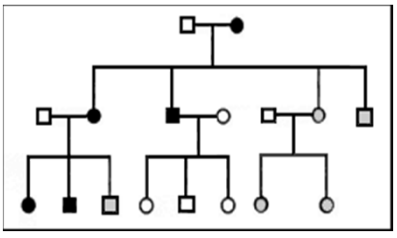


Mendelian Inheritance

Classic Mendelian Inheritance X-linked (recessive)



Mitochondrial Inheritance



Other Types of Genetic Variation

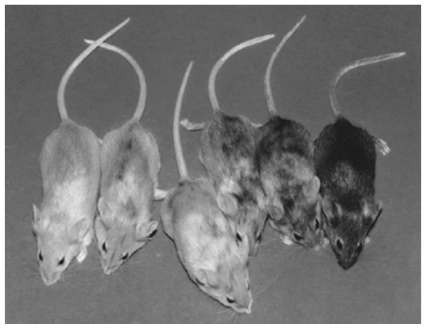
Chromosomal abnormalities

- 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



Whitelaw, Nature Genetics 2001:27:361-65

Genetic Evaluation: Purpose, Timing

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-

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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

Comprehensive family history

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Counseling about the condition:

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Counseling about the condition:
- **That it may have a genetic basis**

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- **May have a variable age of onset**

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

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Genetic testing, if feasible and indicated:

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Recommend baseline clinical screening of at-risk 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, J Cardiovasc Trans Research, 2008:1:137-43
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

Cardiomyopathies - DCM, HCM, RCM, ARVC, LVNC

Channelopathies - Long QT, Short QT, Brugada, CPVT (catecholaminergic polymorphic ventricular tachycardia), Timothy syndrome, others

Aortopathies: Marfan, Loeys-Dietz, Thoracic Aortic Aneurysm and Dissection (TAAD), others

Familial Hypercholesterolemia (FH); other heritable lipid disorders

Pulmonary Hypertension, congenital heart disease, others

Rules of the Road for Genetic Testing

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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**

HCM Gene Ontology

Gene ontology for HCM

Sarcome

MYH7
MYBPC3

TNNT2
TNNC1
TNNI3
TPM1
ACTC
MYL2
MYL3

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a genetic disease of sarcomeric proteins

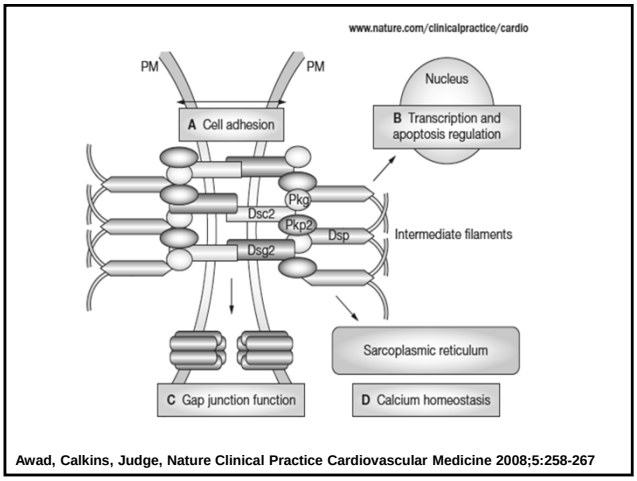
MYBPC3	**(myosin binding protein C)**	**40%**
MYH7	**(beta myosin heavy chain)**	**40%**
TNNT2	**(troponin T, others)**	**10-15%**

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disease of the desmosome

Gene ontology for ARVC

Desmosome

PKP2
DSG2
DSC2
DSP
TNNI3



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

DCM Gene Ontology

Gene ontology for DCM

Sarcome	Cytoskeleton	Z-disc	Nuclear envelope
ACTC	*DMD*	*TCAP*	*LMNA*
MYH7	*DES*	*CSRP3*	*TMPO*
MYH6	*LDB3*	*ACTN2*	**Gamma secretase activity**
MYBPC3	*SGCD*	*MYPN*	*PSEN1*
TNNT2	*PDLIM3*	*ANKRD1*	*PSEN2*
TNNC1	*VCL*	*NEBL*	**Sarcoplasmic reticulum**
TNNI3	*RYAB*	*NEXL*	*PLN*
TPM1	*ILK*	*MURC*	**Transcription factor**
TTN	*LAMA4*		*EYA4*
			RNA binding
Ion Channel	**Mitochondrial**		*RBM20*
ABCC	*TAZ/G4.5*		**Co-chaperone, heat shock protein**
SCN5A			*BAG3*

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

Dilated Cardiomyopathy

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

TTN	**~20%**
LMNA	**5-8%**
MYH7	**4%**
MYPN	**3.5%**
TNNT2	**3%**
SCN5A	**3%**
BAG3	**3%**
MYPBC3	**3%**

and many others. . . . .

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

Channelopathy Gene Ontology

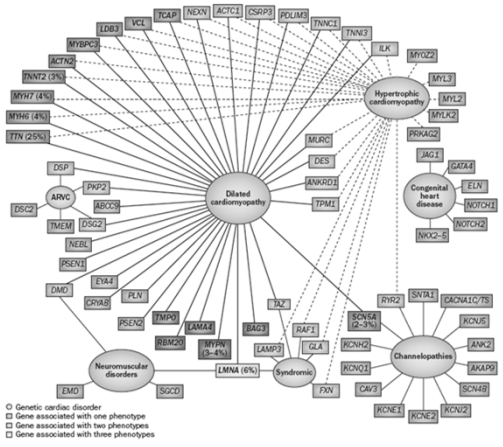
Gene ontology for Channelopathies

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%)

Ackerman et al Heart Rhythm 2011;8:1308-39



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

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- Information regarding test sensitivity:
  - DCM – 30-40%
  - HCM – 50-75% if familial; 30-40% sporadic
  - ARVC – ~50%
  - Long QT – 75%

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Testing cost is a one-time event

- Many insurers now cover genetic testing
- Test panels are rapidly expanding at same cost

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- **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.**

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- **ICD in place, no shocks**

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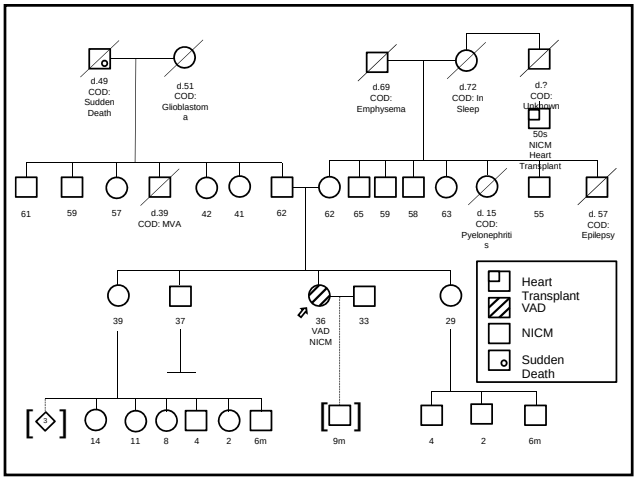
The Ohio State University Wexner Medical Center

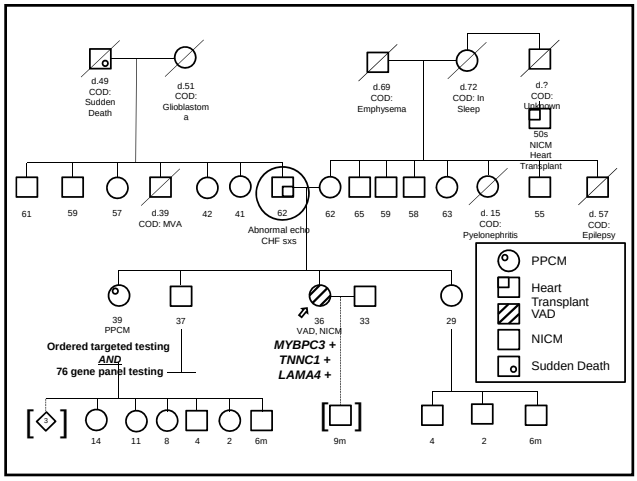


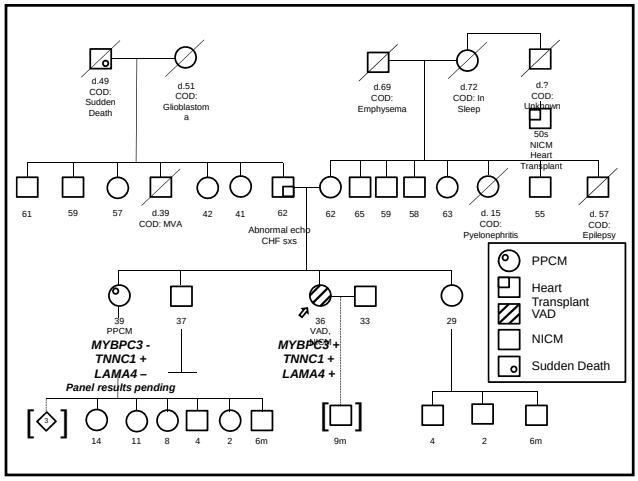
MJ – Genetic testing results (76 gene "Comprehensive Cardiomyopathy" panel)

Gene	cDNA	Protein effect	MAF	CLIA lab's interpretation
*MYBPC3**	c.26-2A>G	IVS1-2A>G	.01% (EA)	Disease-causing mutation
*TNNC1^*	c.446A>G	Asp149Gly	0% (EA)	Variant, likely disease-causing
LAMA4~	c.4624A>T	Asn1542Tyr	.02% (EA)	Variant of unknown significance (VUS)

MJ – Genetic testing results (76 gene "Comprehensive Cardiomyopathy" panel)

- ***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**





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  - **Our exome data suggests that multiple variants may be more common than previously thought.**
    - ***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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Patient Case 2: JA

This 57 year old Caucasian male with ischemic cardiomyopathy, coronary artery disease treated at an outside hospital

- **first stent 2005,**
- **clopedigrel stopped after 1 year, late in-stent thrombosis 2006, large MI, recovered to normal systolic function**
- **2006 restented; clopedigrel again stopped, large MI 2007, EF 20%.**

Patient Case 2: JA

This 57 year old Caucasian male with ischemic cardiomyopathy, coronary artery disease treated at an outside hospital

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- **Cardiac MRI 2007: dilated LV, EF 23%; non-viable LAD territory; valves OK**
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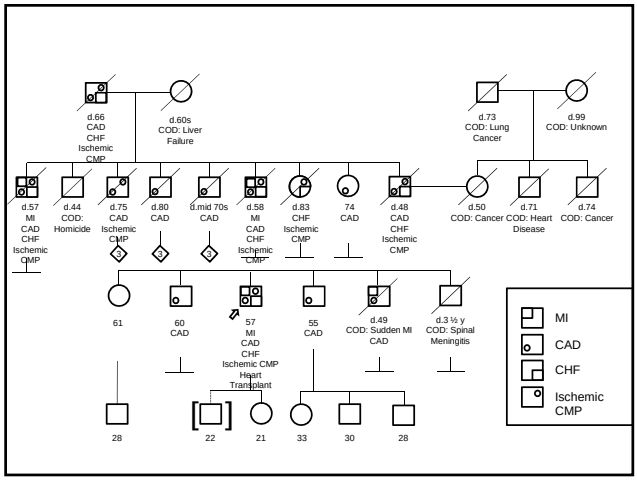
Heart transplant December 2011, now doing well

The Genetics and Genomics of Familial Heart Disease

Bringing Precision Medicine to Life!

Amy Sturm, LCGC
Associate Professor
Department of Internal Medicine
The Ohio State University Wexner Medical Center



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

Gene	cDNA	Protein effect	MAF	CLIA lab's interpretation
*MYH7**	c.4377G>T	Lys1459Asn	.01% (EA)	Disease-causing mutation
*PKP2^*	c.184C>A	Gln62Lys	.04% (EA)	Variant of unknown significance (VUS)
DSC2~	c.327A>G	Ile109Met	.01% (EA)	Variant of unknown significance (VUS)

JA – Genetic testing results (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**

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing

Trevor J. Pugh, PhD[1,2,3], Melissa A. Kelly, MS[1], Sivakumar Gowrisankar, PhD[1], Elizabeth Hynes, BA[1], Michael A. Seidman, MD, PhD[1,3], Samantha M. Baxter, MS[1], Mark Bowser, MS[1], Bryan Harrison, BA[1], Daniel Aaron, BA[1], Lisa M. Mahanta, BA[1], Neal K. Lakdawala, MD[4], Gregory McDermott, BA[1], Emily T. White, MS[1], Heidi L. Rehm, PhD[1,3], Matthew Lebo, PhD[1,3] and Birgit H. Funke, PhD[1,2]

Purpose: Dilated cardiomyopathy is characterized by substantial locus, allelic, and clinical heterogeneity that necessitates testing of many genes across clinically overlapping diseases. Few studies have sequenced sufficient individuals; thus, the contributions of individual genes and the pathogenic variant spectrum are still poorly defined. We analyzed 766 dilated cardiomyopathy patients tested over 5 years in our molecular diagnostics laboratory.

Methods: Patients were tested using gene panels of increasing size from 5 to 46 genes, including 121 cases tested with a multiple-cardiomyopathy next-generation panel covering 46 genes. All variants were reassessed using our current clinical-grade scoring system to eliminate false-positive disease associations that afflict many older analyses.

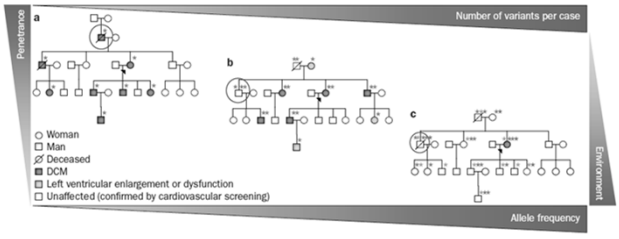
Results: Up to 37% of dilated cardiomyopathy cases carry a clinically relevant variant in one of 20 genes, titin (*TTN*) being the largest contributor (up to 14%). Desmoplakin (*DSP*), an arrhythmogenic right ventricular cardiomyopathy gene, contributed 2.4%, illustrating the utility of multidisease testing. The clinical sensitivity increased from 10 to 37% as gene panel sizes increased. However, the number of inconclusive cases also increased from 4.6 to 51%.

Conclusion: Our data illustrate the utility of broad gene panels for genetically and clinically heterogeneous diseases but also highlight challenges as molecular diagnostics moves toward genome-wide testing.

Genet Med advance online publication 6 February 2014

Key Words: cardiomyopathy; genetic heterogeneity; molecular diagnostics; next-generation sequencing; variants

Variations on the Typical Mendelian Disease Paradigm Relevant to DCM



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

Management and Screening Recommendations

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