Key Principles of Human Genetics and their application to Cardiovascular Disease (CVD)

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Disclosures

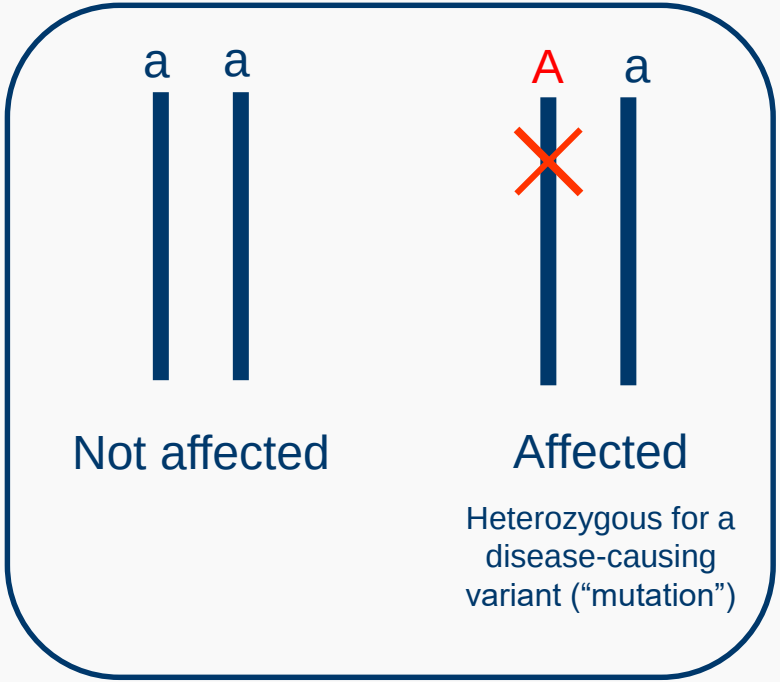
- Nothing to disclose.

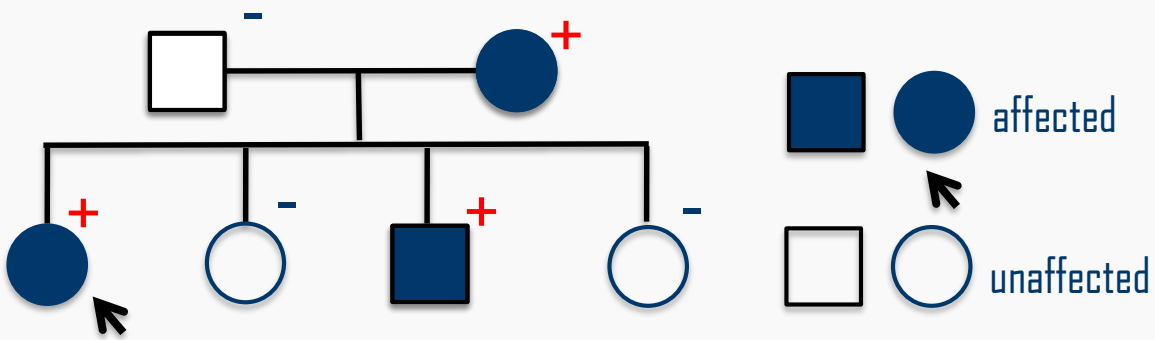
Outline

1) Define the most common mode of inheritance observed in genetic CVD
2) Outline current variant classification nomenclature
3) Explore how reduced penetrance, variable expression, gene-environment interactions, and genetic/phenotypic heterogeneity complicates clinical presentation
4) Describe the diagnostic yield gap with current CVD genetic testing

Most genetic CV disease is inherited in an autosomal dominant pattern.

- Disease inherited in an **autosomal dominant** pattern requires only one abnormal copy in a gene pair for disease to occur
  - 50% risk to first degree relatives (parents, siblings, children) to also share abnormal copy of gene
- Autosomal recessive and X-linked inheritance also reported, particularly in pediatric cases, but are less commonly observed in adult onset CVD





How do you determine what variants are clinically relevant for diagnosis and risk prediction in family members?

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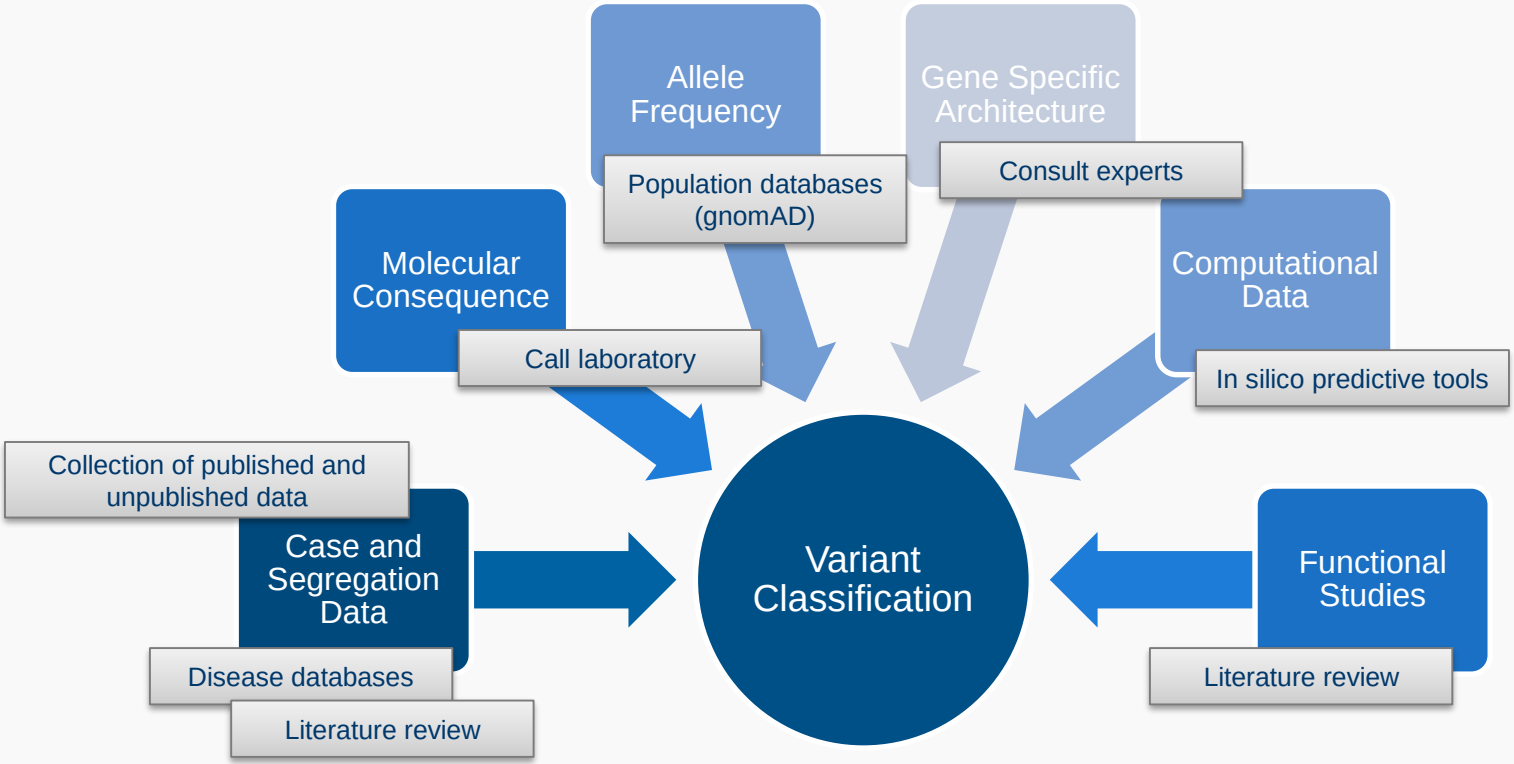
Pathogenic and Likely Pathogenic variants are clinically significant

American College of Medical Genetics (ACMG)-classified P/LP variants are considered monogenic (single gene) causes of disease.

Pathogenic	**Disease-causing variant**
Likely Pathogenic	**>95% confidence disease-causing**
Variant of Uncertain Significance	**Unknown if disease-causing or not**
Likely Benign	**>95% confidence NOT disease-causing**
Benign	**Not disease-causing**


Allele Frequency
Population databases (gnomAD)
Gene Specific Architecture
Consult experts
Molecular Consequence
Call laboratory
Computational Data
In silico predictive tools
Collection of published and unpublished data
Case and Segregation Data
Disease databases
Literature review
Variant Classification
Functional Studies
Literature review

ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

lines for the interpretation of sequence
ensus recommendation of the American
cal Genetics and Genomics and the
on for Molecular Pathology

iz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5],
, Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12],
ctor, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15];

Official journal of the American College of Medical Genetics and Genomics

SPECIAL ARTICLE | Genetics inMedicine

Open

Adaptation and validation of the ACMG/AMP variant classification framework for *MYH7*-associated inherited cardiomyopathies: recommendations by ClinGen's Inherited Cardiomyop

Melissa A. Kelly, MS[1], Colleen Caleshu, MS[2],
Steven M. Harrison, PhD[1], Stuart Cook
Eden Haverfield, PhD[5], Jan D.H. Jongbloe
Kate Orland, MS[9], Gabriele Richard, MD[7],
Kate Thomson, BSc[12,13], Lisa M. Vincent, P
Nicola Whiffin, PhD[4,14], Jodie Ing
Christopher Semsarian, MBBS PhD[15], Jame
Birgit Funke, PhD[1,17,18]; for the ClinGe

Circulation: Genomic and Precision Medicine

ORIGINAL ARTICLE

Variant Interpretation for Dilated Cardiomyopathy

Refinement of the American College of Medical Genetics and Genomics/ ClinGen Guidelines for the DCM Precision Medicine Study

Ana Morales, MS; Daniel D. Kinnamon, PhD; Elizabeth Jordan, MS; Julia Platt, MS; Matteo Vatta, PhD; Michael O. Dorschner, PhD; Carl A. Starkey, PhD; Jonathan O. Mead, BS; Tomohiko Ai, MD, PhD; Wylie Burke, MD, PhD; Julie Gastier-Foster, PhD; Gail P. Jarvik, MD, PhD; Heidi L. Rehm, PhD; Deborah A. Nickerson, PhD; Ray E. Hershberger, MD; on behalf of the DCM Precision Medicine study of the DCM Consortium*

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ON EDUCATION

Clinical Cardiovascular Genetic Counselors Take a Leading Role in Team-based Variant Classification

Chloe Reuter[1] · Megan E. Grove[2,3] · Kate Orland[4] · Katherine Spoonamore[5] · Colleen Caleshu[1,2]

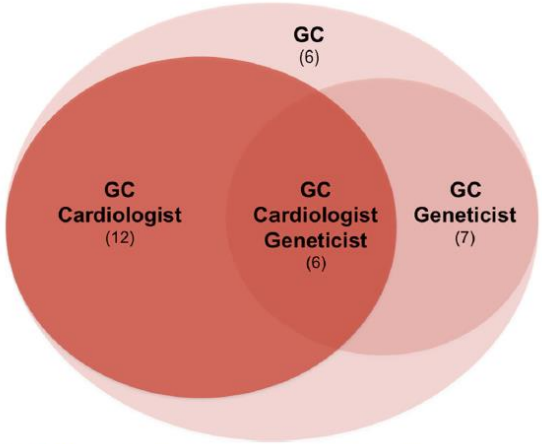


Fig. 2 Variant classification is team-based. 25/31 (81%) of genetic counselors who classify variants do so in a team-based fashion either with a cardiologist (12/31 (39.0%)), a geneticist (7/31 (23.0%)), or both (6/31 (17.0%)). 6/31 (19.0%) are the only provider involved in variant classification and all of those participants work with a cardiologist specialized in inherited disease. GC = genetic counselor

The clinical presentation of a genetic CVD can be complicated

Penetrance

- The percentage of people with

Expressivity

- The severity of a phenotype

This presents a challenge the clinician.

When genotype positive individuals have only absent, sub-clinical, or mild phenotypes, they may appear or be reported as "healthy" which can confuse or complicate the genetic risk assessment.

"*incomplete*" penetrance

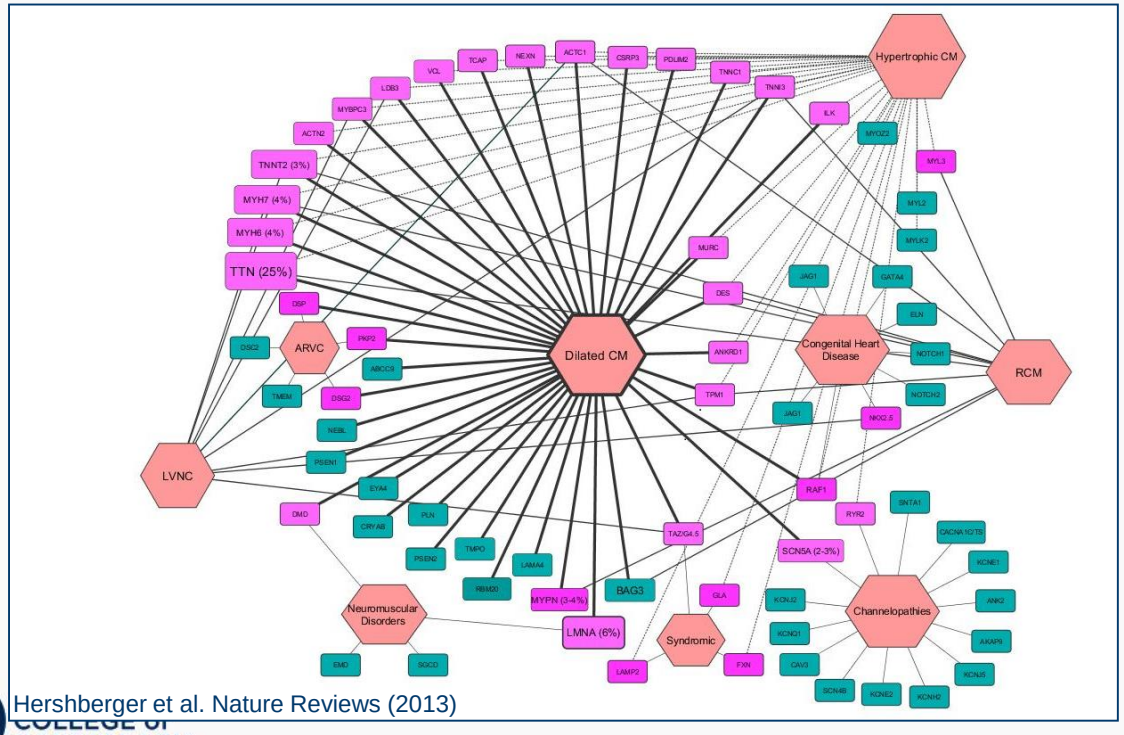
Nussbaum RL, et al. *Thompson & Thompson Genetics in Medicine*. 8Th ed. / ed. Philadelphia: Saunders/Elsevier; 2016.

The clinical presentation of a genetic CVD can be complicated

- Environment can modify penetrance and expression resulting from unique **gene-environment (GxE) interactions** among individuals, even within the same family.
- Such as:
  - Cardiotoxicity, alcoholism, and pregnancy in genetic DCM
  - Smoking, diabetes, and other conventional coronary artery disease risk factors in individuals with FH
  - Exercise in people with genetic predisposition to ACM/ARVC
  - Others…

The clinical presentation of a genetic CVD can be complicated

Marked **genetic and phenotypic heterogeneity** has also been described.



Hershberger et al. Nature Reviews (2013)

Jordan et al. Circulation May 2021

Sensitivity of genetic testing is not 100%.

Cardiomyopathy	Channelopathy	Familial Hypercholesterolemia	Aortopathy

A negative result does not exclude genetic cause. Family members could still be at risk!

Genes yet to be identified, regions of the genome that are not currently analyzed or well understood, complex multiple or common variant mechanisms, etc. may in part hold the remaining unsolved genetic background of CVD.

Key Takeaways

1) A majority of genetic CVD is due to pathogenic or likely pathogenic variants inherited in an autosomal dominant pattern
2) Reduced penetrance, variable expression, genetic/phenotypic heterogeneity, and GxE interactions can complicate clinical presentation of a patient/family
3) The complete genetic background of CVD remains unsolved, leaving family members still at risk

Thank you

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