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Cardiovascular Genomics

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Myocardial Infarction/ Coronary Artery Disease

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Stroke

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Sudden Cardiac Death

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Racial/Ethnic and Gender Differences in CVD

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Myocardial Infarction (MI) Coronary Artery Disease (CAD)

- There has been an explosion of studies examining genetic markers in MI/CAD
  - Genetic linkage analyses of families
  - Candidate gene
  - Genome-wide association studies (GWAS)

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Genetic Linkage Analyses of Families

- Several chromosomal regions harboring MI/CAD genes have been identified
- Mutations affected only a single family or had no functional relevance in other studies
- *ALOX5AP* (arachidonate 5-lipoxygenase-activating protein) gene at chromosome 13q12–13 ↔ Inflammation (MI, CAD, Stroke)

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• Helgadottir, A., et al. *(2005). Am J Hum Genet, 76(3), 505.*
• *H*elgadottir, A., et al. (2004). *Nat Genet, 36(3), 233.*

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Candidate Gene Approach

- *> 150 candidate genes have been analyzed*
- Both positive and negative associations were found for nearly all genes
- Genes affecting LDL-C (e.g. *APO E)* ↔ MI/CAD

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• Yamada, Y., et al. (2008). Genomic Med, 2(1–2), 7.
• Schunkert, H., et al. (2010). *Eur Heart J, 31(8), 918.*

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Genome-Wide Association Studies (GWAS)

- Chromosome 9p21.3 ↔ MI/CAD
  - Helgadottir et al., 2007
  - McPherson et al., 2007
  - Samani et al., 2007
- Antisense noncoding RNA in the INK4 locus called ANRIL

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• Helgadottir, A., et al. (2007). . Science, 316(5830), 1491.
• McPherson, R., et al. (2007). *Science, 316(5830), 1488.*
• Samani, N. J., et al. (2007). NEJM, 357(5), 443
• Schunkert, H., et al. (2008). *Circulation, 117(13), 1675.*

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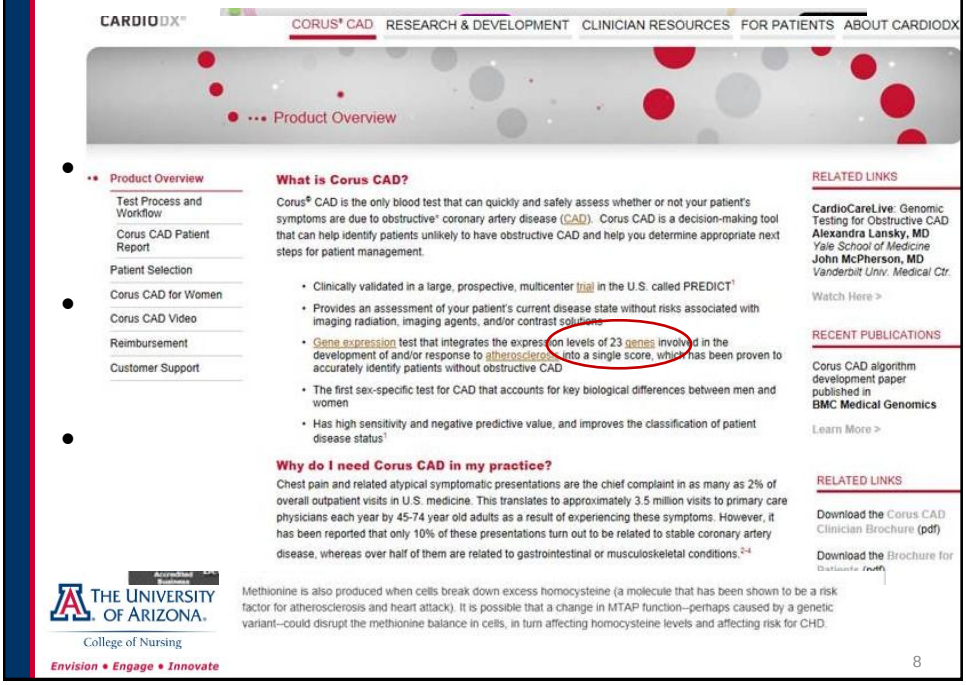
CARDIoGRAM

- A global consortium
  - Discovered 13 novel and confirmed 10 previously reported chromosomal loci
    - Not associated with traditional CAD risk factors
    - Only able to explain a limited fraction of CAD heritability

• Schunkert, H., et al. (2011). *Nat Genet, 43(4), 333.*



Stroke

- 4th Leading Cause of Death
- Leading cause of adult disability
- 87% are ischemic stroke

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Stroke

- Risk factors
- Family History
- Twin Studies
- Prevalence of stroke
- Genetic research in stroke

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Stroke

- Genes that have been associated with stroke.
- Rare genetics disorders associated with stroke
- Testing for genetics disorders
- Direct to consumer (DTC genetic tests)

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Inherited Channelopathies and Cardiomyopathies

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Sudden Cardiac Death (SCD)

- ~1 million deaths per year, leading cause of death in the world.
- Most cases related to ischemic heart disease.
- Genetic etiology of many of these cardiac monogenetic conditions are now known.
- There are 2 broad categories of inherited cardiac diseases channelopathies and cardiomyopathies.

Wung et al. Genetics and Cardiac Channelopathies, 2010

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The Primary Electrical Diseases or Channelopathies

- LQTS, (1/3,000 people)
- SQTS, (Fewer than 30 cases since its discovery in 2000)
- Brugada syndrome, (~35/100,000 people)
- CPVT, (1/10,000 people)
- ARVD, (1/5,000 people)

- Identified by characteristic ECG abnormalities
- However, these characteristics are sometimes NOT present (due to low/incomplete penetrance)

Wung et al. Genetics and Cardiac Channelopathies, 2010

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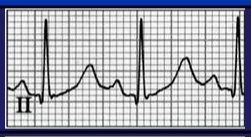
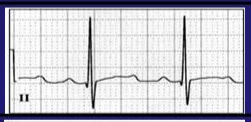
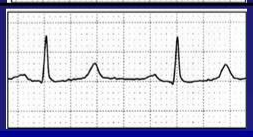
Types of Long QT Syndrome

Type	Genotype	ECG	Trigger	Incidence
LQT1	KCNQ1		swimming & exercise	30-35%
LQT2	KCNH2 HERG		auditory & emotional	25-30%
LQT3	SCN5A		resting & sleep-related	5-10%

Modi & Krahn. Sudden Cardiac Arrest Without Overt Heart Disease, 2011

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Inherited Cardiomyopathies

- Hypertrophic Cardiomyopathy (1 in 500 people)
- Dilated Cardiomyopathy (1 in 1,000 people)
- Restrictive Cardiomyopathy (Less than 5% in the west)

- Genetically heterogeneous.
  - Caused by mutations in a variety of gene encoding proteins of the cardiac sarcomere.

- 18 disease-causing genes and greater than 500 mutations have been identified.
- Many of these mutations are unique to individual families.
- B-myosin heavy chain and myosin-binding protein C genes account for the majority of identified mutations in HCM.

Wung et al. Genetics and Cardiac Channelopathies, 2010

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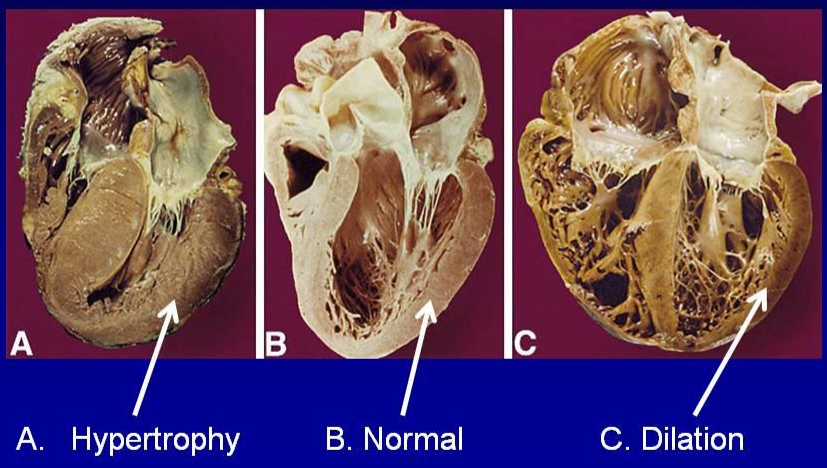
Types of Cardiomyopathies



Seidman & Seidman. The Genetic Basis for Cardiomyopathy: from Mutation Identification to Mechanistic Paradigms, 2001

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Recommendations for Genetic Testing & Counseling

- Genetic testing in the family can lead to identification of at-risk members who are clinically asymptomatic.
  - Negative results for HCM provides reassurance that the specific disease-causing mutation is not present.
  - However, negative results for channelopathies may not be truly negative for an inherited syndrome.

- ***Treatment decisions should NOT rely solely on an individual's genetic test result but rather comprehensive clinical evaluation and family history.

Wung et al. Genetics and Cardiac Channelopathies, 2010

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Nursing Implications

- Nurses play a pivotal role in cardiogenetics and are actively engaged in direct clinical care of patients and families with a wide variety of heritable conditions.
- Genetically trained nurses have been instrumental in recognizing genetic conditions, providing counseling, education, and support to patients and families.
- Educational efforts undertaken by nurses include counseling on the avoidance of potential arrhythmic triggers and explaining the rationale of prescribed therapies in protection against SCD.

Wung et al. Genetics and Cardiac Channelopathies, 2010

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Racial or Ethnic and Gender Differences in Genomics of Cardiovascular Disease

Genetic Similarities

- **AA, Asian, European (Men & Women)**
  - **SCN5A= ↑ prolonged PR interval on electrocardiogram**
  - **SNC10A = ↑ prolonged PR interval on electrocardiogram**
- **AA, Asian, European, Hispanic (Men & Women)**
  - **SCARB1 = ↑ CAC, common internal and carotid intimal medial thickness**
- **Mexican Women & Native American Women**
  - **FOCAD = ↑ heart rate**

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Summary

- Genetic testing for common CVD, like MI and stroke, is commercially available; however, genetic markers to comprehensively profile these diseases are still ongoing.
- Genetic testing for LQTS and HCM can provide valuable information for nurses to tailor prevention and management strategies for individuals at risk for SCD.

Clinical Resources

- Hypertrophic Cardiomyopathy Association
  - www.4hcm.org
- International Stroke Genetics Consortium
  - http://www.strokegenetics.org/
- Sudden Arrhythmia Death Syndrome Foundation
  - www.sads.org