Genetics for preventative cardiology

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Objectives

• To describe inherited heart diseases
• To explain relevant genetic principles
• To illustrate the importance of family history
• To describe the benefits and limitations of genetic testing
• To demonstrate the utility genetic counseling
• To examine common psychosocial issues and ethical considerations

HEART DISEASE COMES IN MANY FORMS!
Leading Causes of Death
(Males and Females)

Source: CDC/NCHS

Prevalence of CV Genetic Disorders

Types of Heart Conditions:
Acquired (non-genetic) vs. genetic

- Cardiomyopathies - Heart muscle problems
  - Hypertrophic Cardiomyopathy (HCM)
- Arrhythmias - Heart Rhythm problems
  - Long QT syndrome
- Congenital heart defects
- Aneurysm/Dissection (Enlargement/tearing of artery) and Valve problems
  - Marfan syndrome
- Sudden cardiac death/sudden unexplained death
- Coronary artery disease (CAD)/ Lipid disorders
  - Familial Hypercholesterolemia (FH)

Diagnosing Inherited Heart Conditions

- Genetic Testing
- Electrocardiogram (ECG) and Signal Average ECG
- Holter Monitor
- Echocardiogram
- Cardiac MRI
- Stress Test
- Cardiac Biopsy

Invasive Testing:
- Electrophysiology Test
- Angiography
Signs of inherited arrhythmias

• Personal history:
  – Unexplained fainting, cardiac symptoms.

• Family history:
  – Multiple family members with the same type of arrhythmia, particularly at a young age.
  – Fainting or palpitations without explanation.
  – Sudden unexplained death, SIDS.

Signs of inherited cardiomyopathy

• Personal history:
  – Shortness of breath especially with exertion, swelling, fatigue, dizziness, fainting, irregular heart beat.

• Family history:
  – Multiple family members with the same type of cardiomyopathy young age.
  – Heart failure, transplants, sudden death

Signs of inherited vascular disease

• Personal history:
  – Enlargement/aneurysm of the aorta or other arteries (usually asymptomatic)
  – Syndromic forms include characteristic facial appearances, skeletal, skin, vision abnormalities, and/or rupture of organs.

• Family history:
  – Family members aneurysms and/or syndromic features.
  – Sudden death

Treatment

• May include:
  – Close follow up only
  – Lifestyle modification
  – Medication
  – Procedures/Interventions
  – Implantable defibrillators
  – Surgery
  – Transplantation
Prognosis

- Variable- dependent upon:
  - Severity at diagnosis,
  - Compliance with recommendations,
  - Response to therapy.
- With early effective treatment most patients live normal, long, healthy lives.
- Sudden death is preventable with treatment.

INTRODUCTION TO GENETICS

Chromosomes, DNA, and Genes

Gene Mutation = Misspelling

Normal DNA Sequence: AGT CGA

Point Mutations:
- Base Substitution: AGTAGA
- Frameshift Mutations:
  - Insertion: ATG TCGA
  - Deletion: ATCGA
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Chromosomes

23 pairs of homologous chromosomes

Egg or Sperm production

SEX

Inheritance

46

23 pairs of homologous chromosomes

Egg or Sperm production

SEX

23

Autosomal dominant Inheritance

Inheritance

46

23 pairs of homologous chromosomes

Egg or Sperm production

SEX

23

46
How Do Families Come to the Geneticist’s Attention?

A Cardiologist Suspects a Heritable Condition and Refers

The “Proband”
The affected person in the family who brings the family to the attention of the Geneticist

Common questions in Hereditary Heart Disease

• What’s my risk?
• Who else is at risk?
• Is there any way to treat/prevent the condition?
• Does everyone with the familial mutation get the condition?
• Will everyone with the mutation have abnormal cardiac testing?
• Will this affect my lifestyle?

Genetic heart disease is treatable and sudden death is preventable with the right medical care.

ROLE OF GENETIC TESTING

Goals of genetic testing

• To make a diagnosis,
• To identify the underlying cause,
• To define risk,
• To determine the optimal treatment,
• To determine which family members are at risk,
• To guide individualized surveillance recommendations for each family member.
Role of genetic testing: Proband

- Confirm diagnosis:
  - medically (ex. LQTS)
  - Psychological benefit
- Determine diagnosis, prognosis, treatment:
  - Ex: LQTS, Marfan syndrome, SCD
- Unexpectedly change diagnosis and management:
  - Ex. HCM genocopies – Fabry, DCM/ARVC
- No impact at all on diagnosis, prognosis, treatment
  - Ex. Familial DCM, primary HCM, Brugada syndrome

Value of genetic testing of the proband is different for different conditions

Types of Genetic Testing

Confirm a genetic change that is already known to be present in the family. Called a “Single Site Test”
- We look at one location in one gene to see if the change is present
- Used for testing relatives in a family with a known mutation

Search for a genetic change in a set of genes known to be associated with a particular disorder (long QT, cardiomyopathy, etc.). Called a “Panel”
- Used when trying to find a genetic change in the first person affected in the family

Search ALL ~20,000 genes for a genetic change that could be responsible for a particular disorder. Called a “Whole Exome”
- Used when we are trying to discover a new gene in which a change could cause the disease. Often done as part of a research project.

Outcomes of Genetic Testing

There are three possible outcomes whenever we do a genetic test
1. We find a disease-causing (“pathogenic”) mutation
2. We find no change in a gene or genes that would explain the condition
3. We find a change but we do not know if it is disease causing or not (“Variant of Uncertain Significance” or “VUS”)

Without genetic testing…

…we don’t know which family members are at risk for the genetic heart disease.

Ongoing surveillance recommended for all family members.
- Has symptoms and diagnosed with a genetic heart condition
- Does not have signs of condition but may be at risk
With Genetic testing

Can determine which family members are at increased risk and which are not.

- Has symptoms, diagnosis, and a positive genetic test result.
- Inherited the genetic alteration, but has not developed the heart condition. Needs cardiology follow up.
- Did not inherit the genetic alteration, will not develop the heart problem. Does not need cardiology follow up.

Role of genetic testing: at-risk relatives

- Diagnostic - (Ex. Arrhythmias)
  - If negative:
    - Reassure not at increased risk - discharge from screening
  - If positive:
    - Screening recommendations
    - Lifestyle modifications
    - Medical therapies
    - ICD

Genetic counseling

- Educate about the condition, risk, and screening recommendations.
- Explain the role genetic testing.
- Interpret and explain genetic test results:
  - Implications for the patient
  - Family members
- Discuss who needs to know this information and how to tell them.
- Provide psychosocial support, referrals, patient resources.
When to seek genetic counseling?

- When you or a family member is diagnosed with a known or suspected genetic condition.
- When a family member has a positive genetic test.
- When planning a family.
- When you have questions or concerns about a genetic condition in your family.

Limitations/Complexities

- Clinical genetic testing does not always find the genetic cause.
- Genetic test results can be inconclusive.
  - Sometimes requires testing multiple family members.
- Sometimes despite all efforts, questions remain.
- Family members should still have cardiology screening.
- Ongoing research is key in furthering knowledge of inherited heart disease.

Insurance

- Commercial insurance covers genetic counseling and genetic testing.
  - Many labs have patient friendly billing policies that make genetic testing affordable for families.
  - Limited coverage for those with MediCare, MediCal.
- What about genetic discrimination?
- Laws to protect from genetic discrimination.
- Pre-existing conditions.
- Medical, life, long-term disability insurance.

Examples

- Arrhythmias
- Cardiomyopathies
Genetic arrhythmias

- Structurally normal heart but problems with the heart’s electrical system
- Symptoms:
  - Fainting (syncope), palpitations, sudden death
  - Similar for all but triggers differ and can be very important for diagnosis
- Diagnosis: EKG’s, stress tests, Holter monitoring, EP study
- Treatment: medications, ablation, CRT, ICD’s

Long QT syndrome

**Prevalence:** 1:2-3000

**Phenotype:**
- Syncope, palpitations, none
  - Symptom misdiagnosis common - seizures, anxiety
- Risk dependent on severity, genotype
- Triggers based on genotype
- Intermittent symptoms and ECG

**Onset:** variable

**Diagnosis:** ECG, holter monitor, exercise test, family history

**Treatment:** based on symptoms, age, risk factors, genotype
- Medication (beta-blockers)
- ICD - implantable cardioverter defibrillator
- Avoid triggers: strenuous exercise, alarming noises, QT-prolonging drugs, dehydration

Other genetic arrhythmias

- Brugada, CPVT, Short QT syndrome, others
- Similarities:
  - Symptoms: syncope, palpitations, sudden death
  - AD inheritance, variable expression, incomplete penetrance
  - Treatment based on patient’s presentation, SCD risk
  - Genetic testing principles/issues
- Differences:
  - Genes but there is overlap
  - Age of onset, severity
- Work with EP to establish a clinical and genetic diagnosis based on clinical and family history
Cardiomyopathies

- Diseases of the cardiac muscle cause abnormal structure and function (pump)
- Hypertrophy, dilatation, stiffness
  - Reduced efficiency leads to symptoms of SOB, dizziness/lightheadedness, syncope often with exertion
- Abnormal heart rhythms
  - Syncope, SCD

Dilated Cardiomyopathy

- Prevalence: not well defined
- Enlarged, weak left ventricle
- Risk for arrhythmias
- Secondary:
  - Coronary artery disease
  - Viral
  - Toxins
- Primary: ~30% familial
- Treatment
  - Medications for heart failure
  - Heart transplant
  - ICDs to prevent fatal arrhythmias

HCM Family

Dilated Cardiomyopathy

- ~20-50% of idiopathic DCM cases are believed to have a genetic basis
  - Overlap with other types of cardiomyopathy in families (RCM, ARVC).
- The familial cases are generally inherited as autosomal dominant, reduced penetrance, variable expressivity
- Many genes:
  - Genetic testing for DCM will find a mutation in ~40% of familial DCM cases
Aortic aneurysm/dissection

- Aortic aneurysm:
  - Dilatation or aortic wall
  - Asymptomatic
  - Progressive
  - Treatment: medications, preventive surgery based on size and expansion over time
- Aortic dissection:
  - Tear in one or more layers of the aorta
  - High mortality
  - Treatment: emergency surgery
  - Cause of SCD

Symptoms of TAAD

Aneurysm: None

Dissection:

- Pain:
  - Severe and persistent
  - Chest, jaw, neck and upper back, abdomen.
- Shortness of breath
- Coughing
- Hoarseness
- Sometimes there are no symptoms

Aortic aneurysm/dissection

- Genetic: more likely thoracic aorta, absence of risk factors (age, smoking, HTN, atherosclerosis)
- Syndromes:
  - Marfan
  - Loeys-Dietz
  - Ehlers-Danlos IV
- Non-syndromic: must r/o syndrome first
  - Thoracic aortic aneurysm and dissection (TAAD)
  - Autosomal dominant
- Genetic diagnosis: Medical Geneticist, Cardiologist, other specialties and genetic testing key to diagnosis

TAAD: Autosomal Dominant with Variable Expression and Incomplete Penetrance

- Proband presented with isolated aortic dissection at age 36
- After eval and GT, family members with aortic dilatation and/or mutation carriers were identified
- Genetic testing can guide management recommendations
Importance of family history

Family history

- Cardiac history unreliable and vague (often referred to as “heart attack,” “heart thing,” “heart disease”)
  - Frequent need to confirm with records.
  - Heart disease most poorly reported of all common disease (Fazio et al ASHG 2009)
- Sudden unexplained death
  - SIDS
  - Accidents, drowning - odd/unexplained?
- Symptoms (syncope, SOB, etc)
  - Often misdiagnosed (asthma in HCM, seizures in genetic arrhythmias)
  - Context, prior symptoms, evaluation
  - Subjective, common and associated with other more common conditions (syncope, palpitations, dizziness)

Clues and questions

- Heart failure
  - Shortness of breath, edema, fatigue
  - “asthma”
- Heart transplant
- “big heart,” “enlarged heart,” “old man’s heart”
- “pacemaker”
- Heart “surgery”
  - Open ended questions -- what type of surgery?
- Age of onset/procedure
- Medications

Family history considerations

- Often negative on initial evaluation:
  - Validity of reported history: “heart attack” may actually be SCD due to arrhythmia, cardiomyopathy or aortopathy. Import to confirm history via MRs, autopsy reports
  - No family history or no one has been screened?
    - Reduced/age related penetrance, undiagnosed disease, disregarded symptoms, premature death from other causes
    - Other explanations for SCD, symptoms
Counseling and ethical issues

Genetic evaluation: standard of care

- Guidelines:
  - AHA 2012 guidelines:
    - "Genetic counseling is uniformly recommended (for single gene disorders)."
  - HRS/EHRA 2010 guidelines:
    - "Genetic counseling is recommended for all patients and relatives with familial heart diseases and should include discussion of the risks, benefits, and options available for clinical testing and/or genetic testing."

Special Counseling and Management Issues

- At-risk relatives
  - Predictive testing or diagnostic testing?
  - Testing offered or recommended?
  - Testing minors – at what age?
  - "But I’m healthy"
  - Who is your patient?
- Sudden cardiac death (SCD)
  - Mortality, fear of SCD. "Ticking time bomb," "I could drop dead"
- Treatment side effects, impact on lifestyle
- Lifestyle modifications: identity, stigma, finding balance with exercise/activity
- Creating the worried well (low penetrance/event risk) Integrating genetic and clinical information when making management decisions

Ethical issues

- Duty to warn in sudden cardiac death syndromes
  - Preventable
  - Kids at risk
  - At-risk individuals in public safety positions
  - How far should we go to warn?
  - Who is your patient?
Take home messages

- Many types of inherited CV conditions
  - Arrhythmias, cardiomyopathies, aortopathies, CAD, CHD’s and syndromic
  - Family history often unknown/misreported
- Autosomal dominant inheritance
- Variability- wide range in age of onset, severity, penetrance
- Genetic testing is complicated:
  - Many genes + many mutations + massive human genetic variation = variant interpretation challenging
- Interdisciplinary care: Cardiology and Genetics

Questions?

Risk Assessment Using Common Single Nucleotide Polymorphisms (SNPs) Associated with Cardiovascular Disease

- Use of SNPs identified by Genome Wide Association Studies
- Currently, the Mainstay of Direct-To-Consumer DTC companies
Odds Ratios for coronary artery disease for having a G ("risk allele") over an A for one particular SNP (rs10757274)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OR (95% confidence)</th>
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<tbody>
<tr>
<td>GG</td>
<td>1.38 (1.12–1.70)</td>
</tr>
<tr>
<td>AG</td>
<td>1.25 (1.03–1.50)</td>
</tr>
<tr>
<td>AA</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The 25% increased risk of with having one G, the risk allele, and of 38% for having two G’s was confirmed two dozen studies.

How predictive is having 1 or 2 G’s for Coronary Artery Disease?

Risk for Coronary Artery Disease Events over the Next 10 Years

<table>
<thead>
<tr>
<th>9p21 Genotype Known</th>
<th>2 Risk Alleles</th>
<th>0 Risk Alleles</th>
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</thead>
<tbody>
<tr>
<td>65 year old male</td>
<td>11%</td>
<td>13.2%</td>
</tr>
<tr>
<td>No CAD risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 year old female</td>
<td>2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>No CAD risk factors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Palomaki et al.
13 SNP Loci Combined To Generate Genetic Risk Score for CAD

Fraction of the Population

Comparison of SNP risk score to Standard Framingham Risk Score