GENETIC TESTING AND HEART DISEASE

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• 1860: inherited characteristics of peas
WATSON AND CRICK

- 1953: Double Helix structure of DNA
HUMAN GENOME PROJECT

- 2003: complete sequence of human DNA reported
- 3 billion base pairs
- We have about 25,000 genes
- Which comprise only 2% of total DNA
GENETICS AND CARDIAC DISEASE

• Many cardiac diseases have a genetic basis (sometimes!)
• Diagnosis confirmation of the index patient
• Prognosis of the index patient (??)
• Diagnosis (yes/no) of family members (prior to onset of disease!?)
• Embryonic and Prenatal Diagnosis
• Pharmacogenetics
WE ARE MORE COMPLICATED THAN A PEA

- Many genes and mutations for most phenotypes
- Not all people with disease have a mutation
- Not all mutations cause disease
- Not all people with a mutation develop disease
- Mutation usually does not determine outcome
- Genetic Counseling Issues
- Cost
GENETIC ANALYSIS

- Commercial Genetic Testing Lab
- Informed consent
- Blood or Tissue Sample
- Sequencing of relevant gene panel
- Gene copy analysis: deletions/duplications
- Results:
  - Positive result-disease specific mutation
  - Negative result-known mutation absent
  - Variant of unknown significance: these are frequent
CARDIAC DISEASE WITH GENETIC BASIS

- Dilated Cardiomyopathy
- Hypertrophic Cardiomyopathy
- Marfan Syndrome and Other Aortopathies
- Long QT Syndrome
- Brugada Syndrome

- There are many others, and research continues!
DILATED CARDIOMYOPATHY

- Common +/- conduction system disease: heart failure, sudden death
- 20-50% is genetic
  - Titin, alpha and beta myosin heavy chain, troponin T, many others
- Mostly autosomal dominant
- About 50% of familial dilated cardiomyopathy will have a specific gene diagnosis
HYPERTROPHIC CARDIOMYOPATHY

- Common: angina, heart failure, sudden death
- Other Causes of Hypertrophic Phenotype
  - Hypertension
  - Athlete’s Heart
- Many genes and mutations identified
  - Troponins, myosins, titin, others
- About 60% have disease causing mutation detected
- Fabry’s disease
- Mutant transthyretin amyloidosis
MARFAN SYNDROME

- Aortic root dilation/dissection and mitral valve prolapse
- Many other associated abnormalities
- Fibrillin-1 gene mutation in 90% (>1800 recorded mutations)
- Autosomal dominant
- Other similar phenotypes with different gene mutations
  - Loeys-Dietz Syndrome: TGFBR
LONG QT SYNDROME

- Sudden Death
- Approximately 12 genes identified
- Romano-Ward: autosomal dominant, normal hearing
  - Mostly potassium channel mutations
  - Some sodium channel mutations
- Jervell and Lange-Nielsen: autosomal recessive, deafness
  - Potassium channel mutations
BRUGADA SYNDROME

- Sudden Death
- Autosomal Dominant
- Marked male predominance
- Sodium channel gene mutations and others
- Approximately 40% have positive genetic test
Many drugs have genetic variations in metabolism and effect
  - Warfarin
  - Clopidogrel

However utility needs to be proven in clinical trials
  - Warfarin pharmacogenetic analysis did not demonstrate improvement in therapy
PRIMARY CARE PRESENTATIONS

- Index Case of Genetic Disease
- Family Member
- Prenatal Evaluation
PRIMARY CARE

- Family History
- ECG
- Echocardiogram
- Cardiology Referral
- Genetic Counseling Referral
  - Patient Teaching
  - Adverse effect of early diagnosis
  - Adverse effect of negative result
POTENTIAL BENEFITS OF GENETIC TESTING

- Confirmation of diagnosis
- Early diagnosis and intervention in family member
- Prenatal and embryonic diagnosis