JSC Exit Presentation

Rebecca McFadden
Florida Institute of Technology
Dr. Virginia Wotring
Pharmacology
EFFECTS OF GENETICS AND MUTATIONS ON ACQUIRED LONG QT SYNDROME

Rebecca McFadden
Space Life Sciences Summer Research Institute
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BACKGROUND
WHAT IS LONG QT?

[Diagram of the heart with labeled parts: Sinoatrial (SA) Node, Anterior intermodal Tract, Middle intermodal Tract, Posterior intermodal Tract, Atrioventricular (AV) Node, Right Bundle Branch.

Comparison of Normal EKG and Long-QT EKG.

- Normal EKG:
  - P wave
  - PR interval
  - QRS complex
  - T wave
  - QT interval

- Long-QT EKG:
  - P wave
  - PR interval
  - QRS complex
  - T wave
  - QT interval

Graphs showing RR intervals and T waves, highlighting differences in QT duration.

-right bundle branch
WHAT’S THE HARM?

❖ LQTS is either inherited or acquired
  ❖ Inherited occurs in 1/2,500 live births
    ❖ Caused by channel gene defects
  ❖ Cannot be determined only by ECG
    ❖ Diagnostic criteria useful, but not always accurate
❖ Causes 3000-4000 deaths annually in children and young adults in the US alone

1993 LQTS diagnostic criteria (Schwartz, 2006).
ACQUIRED LQTS

- Caused by medications
  - Can lead to Torsade de Pointes, ventricular tachycardia, ventricular fibrillation, and arrhythmia
  - Antiarrhythmics, antidepressants, antipsycotics, and antiemetics
  - Associated with 90 noncardiovascular drugs

- Most common cause of relabeling/withdrawal of market drugs in last decade
  - 1990-2001: 21 withdrawn

- Unclear why diverse compounds block HERG channels

- 2005: FDA released a Guidance for Industry
  - Drugs produced before this date have not been tested
Currently unpredictable
   Occurs in 1-8% of patients receiving antiarrhythmic drugs (Yang, 2002)
Risk factors include:
   Female gender
   Hypokalemia
   Hypomagnesaemia
   Bradycardia
   High drug concentrations
   Heart failure

But what about genetic/inherited predisposition?
FINDINGS
SILENT MUTATIONS

- 9 genotyped probands without clinically affected family members entered the study
- 46 family members examined; none affected by LQTS on ECG
- Molecule diagnosis revealed 15 family members were gene carriers
  - This was missed by ECG and the clinical scale
  - Possible to be a gene carrier without a prolonged interval
- 13 mutations have been identified
- These individuals are predisposed to the possible occurrence of drug-induced Torsade de Pointes
SCN5A GENE

- Provides instructions for making sodium channels
- One patient exposed to cisapride
  - Had normal QT interval prior
  - Developed prolonged QT interval, severe bradycardia, and repetitive torsade de pointes
  - Return to normal 6 days after discontinuation
  - Due to a genetic mutation in a sodium channel
- Possesses a polymorphism more prevalent in aLQTS
  - 23 family members examined of the proband
  - 11 members carry the allele
- Knowing these could allow the identification of at-risk individuals
THE GENETIC LINK

- Acquired LQTS shares many features with congenital
  - Genetic factors may determine susceptibility

- Three main genes: KCNQ1, KCNH2, and SCN5A
  - Overall, ten associated

- Quinidine study
  - LQTS occurs in individuals who are genetically predisposed, but requires an additional stressor

- Genetic re-sequencing
  - In 31 subjects, 20 carried missense variants across a set of 79 genes
  - Further, 23% carry previously identified cLQTS genes
  - Findings suggest overlap between cLQTS and aLQTS may be greater than previously reported
FUTURE PROSPECTS
WHERE DO WE GO?

- With the proper knowledge, many of these cases are preventable
- Genetic screening
  - Genotyping costs need to fall
  - Genotype- based pharmacotherapy
  - More significantly robust genomic markers necessary
- A perfectly healthy individual can be a gene carrier for a lethal syndrome
OTHER PROJECTS
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Daniel Gazda
Jeffrey Rutz
Lauren Merkle
Ron McNeel
Rebecca McFadden
Florida Institute of Technology
rmcfadden2012@my.fit.edu
rebecca.s.mcfadden@nasa.gov