Genetics of Inherited Sudden Death

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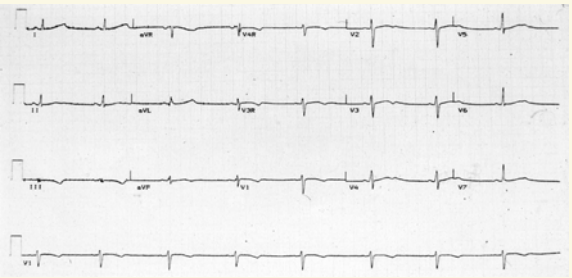
Mini Medical School 03/31/15

Disclosures: None

Clinical Case

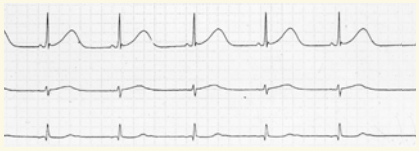
ECG of a 15 Year Old Girl Who Fainted



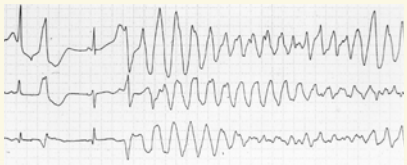
Clinical Case

24 Hour ECG Recording Strips

Baseline



3:30 AM
Nightmare



Cardiac Arrhythmias

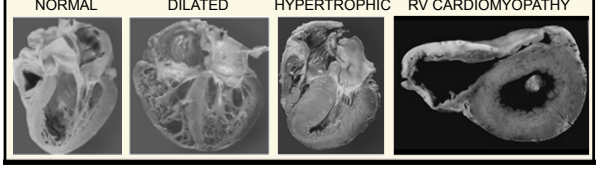
- Major cause of morbidity and mortality
- At least 250,000 sudden deaths per year in the United States
- Treatment is inadequate
- Most sudden death is associated with structural heart disease (MI, CHF)
- We have learned a lot from the rare genetic syndromes with simple inheritance (long QT & Brugada syndromes)

Inherited Arrhythmia Syndromes

• Long QT Syndrome	1:2500
• Short QT Syndrome	very rare
• Brugada Syndrome	1:5000
• Early Repolarization Syndrome	unknown
• Catecholaminergic Polymorphic VT	rare
• Familial Atrial Fibrillation	rare
• Conduction Defects: Lev, Lenegre	rare
• WPW	very rare

Inherited Cardiomyopathies With Arrhythmias

• Hypertrophic Cardiomyopathy	1:500
• Dilated Cardiomyopathy	1:500 (?)
• Arrhythmogenic RV Cardiomyopathy	rare
• LV Noncompaction	very rare
• Restrictive Cardiomyopathies	rare



Why Study Inherited Arrhythmia Syndromes?

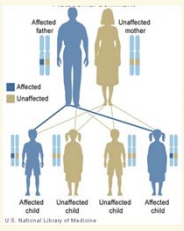
- Identifying the gene and the mutation helps with the diagnosis and treatment of the families with the rare disorders
- We hope that the lessons learned about arrhythmia and sudden death can be applied to the more common causes of arrhythmia and sudden death

DNA and Genetics

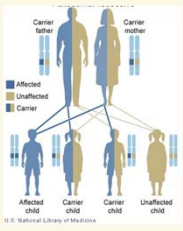
- Everyone has ~3 billion base pairs of DNA on 23 chromosomes, 2 copies each
- DNA encodes ~30,000 genes, which are copied into RNA and code for proteins
- DNA, RNA, and proteins are further modified
- Inherited diseases result from mutations (mistakes) in the DNA
- Book analogy

Common Inheritance Patterns

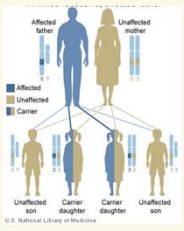
AUTOSOMAL DOMINANT



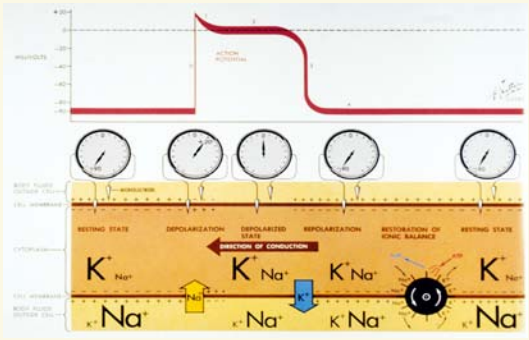
AUTOSOMAL RECESSIVE



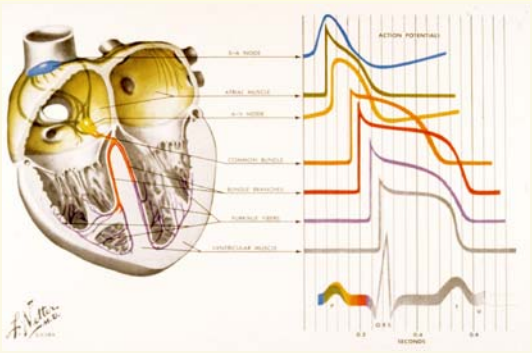
X-LINKED RECESSIVE



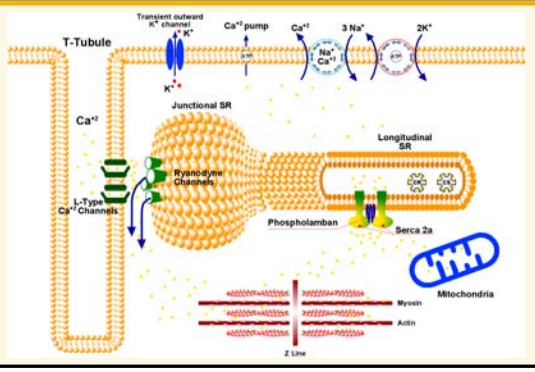
Heart Cells are Batteries



The ECG Measures the Spread of Cardiac Electrical Activity



Electrical Activity Triggers Contraction in the Heart



Brugada Syndrome: Clinical Characteristics

- Rare, 1:5000
- Characterized by a right bundle branch block pattern and ST segment elevation in electrocardiogram (ECG) leads V_1-V_3 (Brugada & Brugada, 1992)
- ECG pattern can vary from day to day
- No structural heart disease
- Can cause fainting & sudden cardiac death
- More common in Southeast Asia (Bangungut, Pokkuri, Lai Tai, SUDS).

Brugada Syndrome: Clinical Characteristics

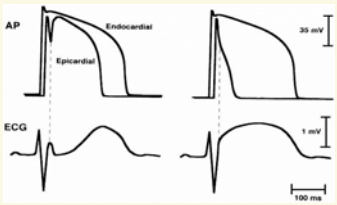
- Autosomal dominant inheritance pattern with variable penetrance
- Sodium channel blockers (e.g. procainamide, ajmaline) exacerbate the ECG findings and are used diagnostically (Brugada et al., 2000)
- Fevers exacerbate the ECG pattern & arrhythmias
- Associated with conduction disease
- Implantable Cardioverter Defibrillator (ICD) is only proven treatment

Brugada Syndrome: Genetics and Mechanism

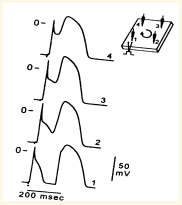
- Autosomal dominant inheritance pattern with variable penetrance
- Mutations of the cardiac sodium (Na^+) channel (SCN5A) that decrease inward cause ~20% of Brugada syndrome cases (Chen et al., 1998)
- Reduced inward sodium or calcium depolarizing currents in the right ventricle, where outward currents are large, lead to the ECG changes and arrhythmias (Antzelevitch, 1998)

Brugada Syndrome: Mechanism

Truncated Epicardial APs



Phase 2 Reentry



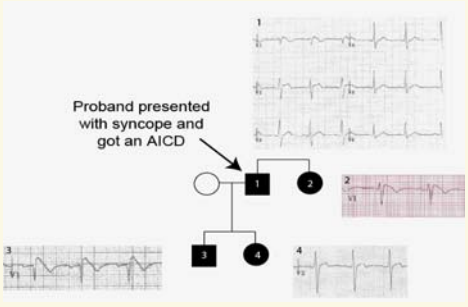
Brugada Syndrome: Known Genetic Causes

Locus	Protein	Gene	Current	Chromosome
BRGDA1	$Na_v1.5$	*SCN5A*	↓ I_{Na}	3p21
BRGDA2	GPD1-L	*GPD1L*	↓ I_{Na}	3p24
BRGDA3	$Ca_v1.2$	*CACNA1C*	↓ I_{Ca}	12p13.3
BRGDA4	$Ca_v\beta2$	*CACNB2B*	↓ I_{Ca}	10p12
BRGDA5	$Na_v\beta1$	SCN1B	↓ I_{Na}	19q13
BRGDA6	MiRP2	*KCNE3*	↑ I_{to}	11q13.4
BRGDA7	$Na_v\beta3$	*SCN3B*	↓ I_{Na}	11q24.1
BRGDA8	HCN4	*HCN4*	?	15q24.1
BRGDA9	Kv4.3	*KCND3*	↑ I_{to}	1p13.2

Other Genes: MOG1, FGF12

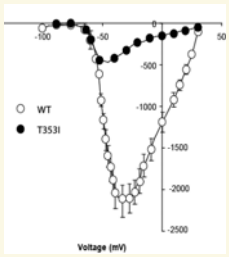
Brugada Syndrome: FM Family

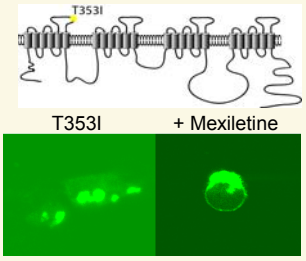
45 Year Old Man Who Fainted



Brugada Syndrome: FM Family

T353I Trafficking Mutation in SCN5A

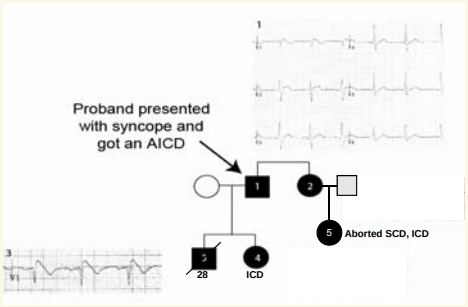




(Pfahnl et al., Heart Rhythm 2007; 4: 46-53)

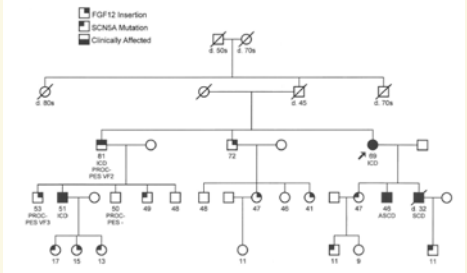
Brugada Syndrome: FM Family

13 Years Later



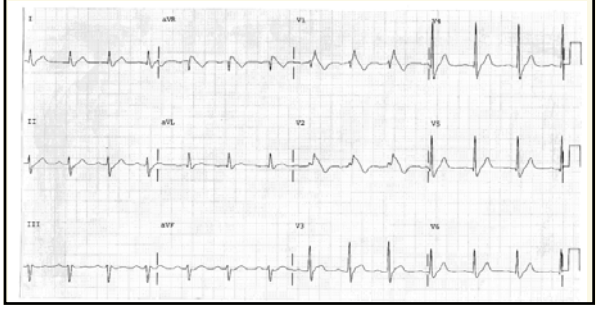
Brugada Syndrome: FF Family

58 Year Old Woman Who Presents after the Sudden Death of her 2nd Son



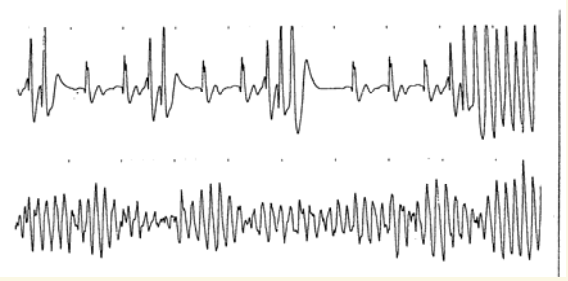
Brugada Syndrome: FN Family

55 Year Old Man With Fainting



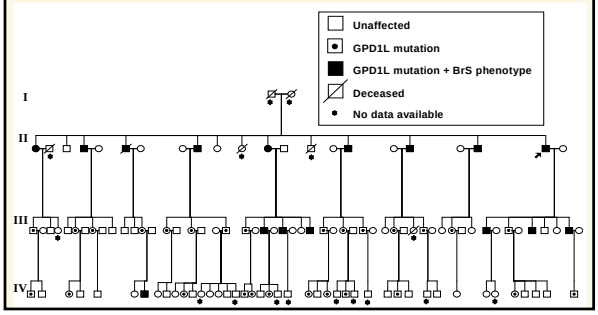
Brugada Syndrome: FN Family

Electrogram from ICD Shock



Brugada Syndrome: FN Family

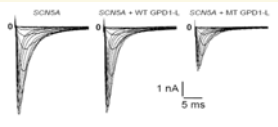
Pedigree of FN Family



Brugada Syndrome: FN Family

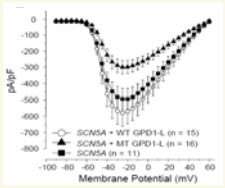
GPD1-L Mutation Decreases Na^+ Current

Na Current in HEK Cells



The GPD1-L mutant leads to a 60% decrease in Na current

Current-Voltage Curves



Inherited Sudden Death: Clinical Screening

- Who? All first degree relatives (or closest available) and all symptomatic blood relatives; then cascade screening
- How? History, Family History, ECG, Echocardiogram, +/- MRI, +/- Stress Test, +/- Drug Challenge
- Why? Treatments including follow-up, avoiding medications, avoiding competitive sports, medications, ICDs

Inherited Sudden Death: Genetic Screening

- Efficacy: LQTS (~60%), Brugada (~30%), CPVT (>50%), ARVD (~50%), HCM (>60%), DCM (>40%)
- Who to screen if mutation is not known? a definitively affected family member
- Who to screen if mutation known? all first degree relatives (or closest available) and all symptomatic blood relatives; then cascade screening

Inherited Sudden Death: Genetic Screening

- Advantages:
  - Carriers: Avoid drugs that exacerbate, exercise
  - Carriers: Potential to guide treatments
  - Asymptomatic Carriers: Therapies, Follow-up
  - Non-carrier of known mutation: Peace of mind
- Problems:
  - Cost: Variable coverage by insurance
  - Useless if definitive mutation is not found
  - Carriers: Can damage careers, insurability
  - Conclusions may be wrong

Acknowledgments

University of Iowa

Shengchuan Dai MD
Xiaodong Zhu PhD
Rebecca Gutmann RN BS
Kaikobad Irani MD PhD
Haider Mehdi PhD
Gina Morgan
Jin-Young Yoon PhD
Ajit Vikran PhD

University of Pittsburgh

Samir Saba MD
Ryan Aleong MD
Alaa Shalaby MD
Christopher Lewarchik PhD
Indrani Halder PhD
Marwan Refaat MD
Laurie Kerchner BS
Asma Navqi
Laurie Kerchner
Madhur Singh MD

Emory University

Samuel Dudley MD PhD
Heather Bloom MD

Washington U. in St. Louis

Jeanne Nerbonne PhD

Mass General

Patrick Ellinor MD PhD

Ohio State

Raul Weiss MD

Mayo Clinic

Michael Ackerman MD PhD

Funded by NIH R01HL62300, R01HL77398, R01HL115955