Understanding and managing variable drug actions: from the ECG to population genomics (Chapter 1: the QT)

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Disclosures

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• Scientific Advisory Boards
  • Science and Industry Advisory Committee, Genome Canada
  • International Scientific Advisory Board, Biobank UK
  • Genomic Medicine Working Group, National Human Genome Research Institute
  • Department of Veterans Affairs Genomic Medicine Program Advisory Committee (Chair)
  • Science Committee, All of Us Research Program
Presentation plan

• Drug-induced arrhythmia syndromes: what we think we know
  • Chapter 1: drug-induced torsades de pointes
  • Chapter 2: arrhythmias induced by sodium channel blockers
• A digression that turns out to be interesting for many genetic arrhythmia syndromes: attacking the “variant of uncertain significance problem”.
• Baby steps to implementing Genomic Medicine
KCNQ1 (LQT1)

G269D

1000
100
10
1.0
0.1

81 6 2 4

time after dose (hr)

25 mg

"Here's my sequence…"
Case presentation
An “idiosyncratic” drug response

AR, 78 year old male
• Chronic coronary artery disease, heart failure
• Normal baseline QT. Paroxysmal AF.
• 2 days after starting the very potent QT–prolonging antiarrhythmic dofetilide ...

No personal or family history of syncope, sudden death
The general problem of variable drug response

%Δ LDL cholesterol with simvastatin 40 mg

Δ diastolic BP with HCTZ (AA population)
Rare serious adverse drug effects

- Angioedema (ACE inhibitors; more common with African ancestry)
- Myositis (statins)
- Hemolytic anemia in patients with G6PD deficiency exposed to antimalarials (more common with African ancestry)
- Intracerebral hemorrhage (many)
- Toxic epidermal necrolysis/ Stevens-Johnson Syndrome
Asked to see a young woman for arrhythmias

>600 msec
Drug-induced torsades de pointes
QT prolongation indicates that at least some ventricular action potentials are prolonged.
A primer in QT pathophysiology (2/4)

Prolonged repolarization = ↓net outward current.

Understanding the genetic basis of the congenital long QT syndromes has been the key starting point

↑inward current
- ↑“late” $I_{Na}$ ($SCN5A$)
- ↑$I_{Ca}$ ($CACNA1C$)
- ...

↓outward current
- ↓$I_{Kr}$ ($KCNH2$, aka HERG)
- ↓$I_{Ks}$ ($KCNQ1$+KCNE1)
- ↓$I_{K1}$ ($KCNJ2$)
- ...

Conventional wisdom, and lots of data, have told us that most drugs prolonging QT do so by blocking $I_{Kr}$
A primer in QT pathophysiology (3/4)

Prolonged repolarization = ↓ net outward current.
Understanding the genetic basis of the congenital long QT syndromes has been the key starting point.

↑ inward current
• ↑ "late" $I_{Na}$ (SCN5A)
• ↑ $I_{Ca}$ (CACNA1C)
• ...

↓ outward current
• ↓ $I_{Kr}$ (KCNH2, aka HERG)
• ↓ $I_{Ks}$ (KCNQ1+KCNE1)
• ↓ $I_{K1}$ (KCNJ2)
• ...

-120 mV
-30 mV
1 msec

increased late sodium current:
• defective channel function (congenital syndromes)
• altered cell signaling (more later)
24 cases of quinidine-induced LQTS define the major clinical risk factors: each one has been fodder for interesting translational/mechanistic science

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Count</th>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>Structural heart disease (especially LVH)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
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Roden et al., 1986
24 cases of quinidine-induced LQTS define the major clinical risk factors: each one has been fodder for interesting translational/mechanistic science.

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Unusual to get torsades during AF; high risk in the first few hours after cardioversion.

Salem et al., 2018

Hypogonadism as a Reversible Cause of Torsades de Pointes in Men

Salem et al., 2018

Roden et al., 1986
Plasma quinidine and serum potassium

For almost all other drugs, high concentrations or overdose increase risk
Plasma quinidine and serum potassium

<table>
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<th>Plasma Quinidine (μg/ml)</th>
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<td>15</td>
</tr>
<tr>
<td>2.5 - 4.5</td>
<td>10</td>
</tr>
<tr>
<td>&gt;4.5</td>
<td>5</td>
</tr>
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<th>Serum Potassium (mEq/L)</th>
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<td>&lt;3.0</td>
<td>Potassium wasting diuretics</td>
</tr>
<tr>
<td>3.0 - 3.4</td>
<td>3</td>
</tr>
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Other possible risk factors: each one has an underlying mechanistic story

- Some $I_{Kr}$ blockers carry much higher risk than others
  - dofetilide: 1.7%; moxifloxacin: 1/1,000,000
- Inflammatory states
- Cirrhosis
- Autoimmune conditions
- Common DNA variants
Hypokalemia and bradycardia/pauses are common in torsades

Canine Purkinje fiber action potentials at slow rates after exposure to quinidine and low $K^+$
Improving Prediction of Drug Action
http://www.pgrn.org/predicting-drug-action.html
Improving Prediction of Drug Action
http://www.pgrn.org/predicting-drug-action.html

Found 'Torsade' in Progress Note - Internal Medicine written on by Damilola Daniel Phillips MRN = 31349616;
https://vpen.app.vumc.org/scripts/portfolio/index.pl?uniq=fmqc58h00
An “idiosyncratic” drug response

AR, 78 year old male

- Chronic coronary artery disease
- Normal baseline QT. Paroxysmal AF.
- 2 days after starting the very potent $I_{Kr}$ blocker dofetilide ...

- KCNQ1 variant leading to R583C identified
- In vitro: $\downarrow I_{Ks}$
- Not found in >400 ethnically-matched controls
- ∴ this is likely subclinical congenital Long QT Syndrome

No personal or family history of syncope, sudden death
Why did AR only get Torsades after ~2,000,000,000 heart beats?
The concept of reduced repolarization reserve

Patient 1

Patient 2

Same QT-prolonging drug
Repolarization reserve: a simulation example

- 75% $I_{Kr}$ block
- Minimal $I_{Kr}$ lesion (e.g. R583C)
- Minimal $I_{Ks}$ lesion + $I_{Kr}$ drug block
The genomics of drug-induced long QT syndrome and torsades de pointes, to summarize several decades of work...

- 10-20% of patients have Congenital Long QT syndrome disease gene variants
- A common (allele frequency 0.8-2.4%) $KCNE1$ variant (D85N) confers an odds ratio of ~10
- Genome-wide association $\rightarrow$ no common variants mediating risk
Understanding the multiple components of normal QT can inform risk for drug-induced long QT

Arking, Newton-Cheh and 248 co-authors, 2014
Understanding the multiple components of normal QT can inform risk for drug-induced long QT

- $P = 10^{-213}$
- effect size: 3.5 msec/allele

Arking, Newton-Cheh and 248 co-authors, 2014
Genetic risk scores: putting lots of common genetic variants together

\[ \text{GRS}_i = \sum_{j=1}^{k} \begin{cases} 2 & \text{if } i_j \geq 2 \\ 1 & \text{if } i_j = 1 \\ 0 & \text{if } i_j = 0 \end{cases} \cdot \omega_j \]

- Score for subject \( i \)
- Add up terms for \( k \) variants
- #of risk alleles carried by subject \( i \) at locus \( j \)
- Effect size for any given variant
What we want from a genetic risk score
What we want from a genetic risk score

P<10⁻⁷

Strauss et al., 2017
Question 1: Which one of the following statements regarding drug-induced torsades de pointes is most correct?

a. The majority of cases occur in patients with unrecognized congenital long QT syndrome
b. A common polymorphism in the cardiac calcium channel increases risk 10-fold
c. A genetic risk score based on multiple common polymorphisms can distinguish patients at risk
d. Hyperkalemia is a risk factor
e. Male sex is a risk factor
Question 1: Which one of the following statements regarding drug-induced torsades de pointes is most correct?

a. The majority of cases occur in patents with unrecognized congenital long QT syndrome (~20%)

b. A common polymorphism in the cardiac calcium channel increases risk 10-fold (*KCNE1*, potassium channel subunit)

c. A genetic risk score based on multiple common polymorphisms can distinguish patients at risk

d. Hyperkalemia is a risk factor (hypokalemia)

e. Male sex is a risk factor (females)
A word about treatment

046457463 2/16/19; 2:49 am. 58 year old man with alpha\textsubscript{1}-antitrypsin deficiency, NASH, 1 day s/p liver transplant complicated by intra-operative cardiac arrest
A word about treatment

046457463 2/16/19; 3:45 am. 58 year old man with alpha$_1$-antitrypsin deficiency, NASH, 1 day s/p liver transplant complicated by intra-operative cardiac arrest
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046457463 2/16/19; 3:45 am. 58 year old man with alpha₁-antitrypsin deficiency, NASH, 1 day s/p liver transplant complicated by intra-operative cardiac arrest
Management

- Recognize
- Withdraw offending drugs
- Correct hypokalemia to >4
- Empiric magnesium

- Get rid of pauses: isoproterenol, pacing
- ?Testosterone
- Long-term (congenital long QT):
  - Beta blockade
  - Pacing/ICD in high risk patients
Presentation plan

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- Baby steps to implementing Genomic Medicine
A Long QT genetic test result

<table>
<thead>
<tr>
<th>Gene</th>
<th>cDNA</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Classification</th>
</tr>
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<tbody>
<tr>
<td>KCNH2 (aka HERG)</td>
<td>c.26 C&gt;T</td>
<td>p.Ala9Val (A9V)</td>
<td>Heterozygous</td>
<td>Variant of unknown significance</td>
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No definitive disease-causing mutations were detected by sequence analysis of the 12 genes in this individual.

**Interpretation:**
This individual is **heterozygous for a novel variant of unknown significance** in the KCNH2 gene.
The VUS problem
variant of unknown significance

Approaches to solving this problem

- *In silico* predictors
- *In vitro* study, one variant at a time, or many variants at a time
- Family or population studies: do variant carriers have a phenotype?

variant frequencies in 125,000 exomes/15,000 whole genomes

https://gnomad.broadinstitute.org/

Starita et al., 2017
One approach to the VUS problem...

A family with Brugada Syndrome

- No variants in the cardiac sodium channel gene SCN5A, but a rare variant, G145R in TBX5
- Loss of TBX5 function causes Holt Oram Syndrome
- TBX5 is a known regulator of SCN5A expression
- G145R absent in gnomAD. Marked loss of function in vitro.

How do we prove that a rare variant in a transcription factor gene causes Brugada syndrome in this family?
One approach to the VUS problem...

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- TBX5 is a known regulator of SCN5A expression
- G145R absent in gnomAD. Marked loss of function in vitro.

How do we prove that a rare variant in a transcription factor gene causes Brugada Syndrome in this family?
TBX5$^{G145R/WT}$ cardiomyocytes have reduced SCN5A transcripts and reduced peak sodium current
CRISPR-cas9 correction of G145R rescues the decreased $I_{Na}$ phenotype
TBX5^{G145R/WT} iPSC-cardiomyocytes display other (unexpected) arrhythmogenic features
To make a very long story short...

↓ $\text{SCN5A}$ transcription
↓ Reduced peak sodium current
↓ Brugada syndrome
↓ $\text{TBX5}$ transcriptional activity
↓ transcription of multiple tyrosine kinase receptors and ligands
↓ $\text{PI3K}$

$\text{G145R} \rightarrow 97\%$ decrease in $\text{TBX5}$ transcriptional activity

Cardiac sodium channel

Early sodium current

Bersell et al., AHA 2017
Other possible risk factors: each one has an underlying mechanistic story

- Some $I_{Kr}$ blockers carry much higher risk than others
  - dofetilide: 1.7%; moxifloxacin: 1/1,000,000
- Inflammatory states
- Cirrhosis
- Autoimmune conditions
- Common DNA variants
Very potent $I_{Kr}$ blockers also enhance late sodium current by inhibiting PI3-kinase

Yang et al., 2014
Question 2: Which one of the following actions is the commonest mechanism causing drug-induced QT prolongation in humans?

a. Calcium channel block  
b. Sodium channel block  
c. Potassium channel block  
d. PI 3-Kinase inhibition
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• Baby steps to implementing Genomic Medicine
Implementing Genomic Medicine

It says here I have a high genetic risk score for QT prolongation. My doctor just prescribed sotalol – should I worry?

"Here's my sequence..."

New Yorker, 2000
PREDICT
Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment
Mephenytoin hydroxylation deficiency in Caucasians:
Frequency of a new oxidative drug metabolism polymorphism

P. J. Wedlund, Ph.D., W. S. Aslanian, M.D., C. B. McAllister, M.Sc.,
G. R. Wilkinson, Ph.D., and R. A. Branch, M.D. Nashville, Tenn.
Departments of Medicine and Pharmacology, Vanderbilt University

Cumulative urinary recovery of 4-hydroxy-mephenytoin (μmol)

normal metabolizer

poor metabolizer

Time (hours)
Fast forward 25 years: While we are designing PREDICT, the FDA adds pharmacogenetic information to the clopidogrel label.

S-mephenytoin hydroxylase = **CYP2C19**
The future is here
Drug-Gene Interaction

Clopidogrel Poor Metabolizer Rules

Genetic testing has been performed and indicates this patient may be AT RISK for inadequate anti-platelet response to clopidogrel (Plavix) therapy.

This patient has been tested for CYP2C19 variants, which has identified the presence of two copies of a risk allele which is associated with reduced metabolism of clopidogrel. Poor metabolizers treated with clopidogrel at normal doses exhibit higher rates of stent thrombosis/other cardiovascular events.

Treatment modification is recommended if not otherwise contraindicated:
- Prescribe prasugrel (EFFIENT) 10 mg daily
- Prescribe ticagrelor (BRILINTA) 90 mg twice daily

WARNING: Prasugrel should only be prescribed to patients weighing more than 60kg. This patient does not have a weight entered in the system - please ensure the patient meets the weight criteria before prescribing prasugrel.

Prasugrel should not be given to patients who:
- have a history of stroke or transient ischemic attack.

Ticagrelor should not be given to patients who:
- have a history of severe hepatic impairment or intracranial bleed.

External Link

The Vanderbilt P&T Committee has approved this recommendation based on the detailed review of the literature and consensus guidelines.

Remove the following orders?
- Remove clopidogrel (PLAVIX) 75 mg tablet
- Keep prasugrel (EFFIENT) tablet 10 mg
- Keep ticagrelor (BRILINTA) tablet 90 mg

Apply the following?
- Order prasugrel (EFFIENT) tablet 10 mg
- Do Not Order ticagrelor (BRILINTA) tablet 90 mg

Acknowledge Reason
- Contraindicated for alternatives
- Potential side effects
- Cost
- Other (specify)
CYP2C19 genotypes in 13,423 patients at Vanderbilt University Hospital

- **no variant**: 10,464
- **homozygous (2.7%)**: 361
  - At high risk for stent failure during clopidogrel
- **heterozygous (19.4%)**: 2,598
  - At modest risk for stent failure during clopidogrel

**CYP2C19 genotypes in 13,423 patients**

**gnomAD**
- 442 non-synonymous variants
- Only 9 are “common”: minor allele frequency >1% in at least one population

When we looked at 5 drug-gene pairs in the first 10,000 PREDICT participants, 91% had a genetic variant that modulates risk of drug response
Personalizing medicine

The good physician treats the disease; the great physician treats the patient who has the disease.

Sir William Osler
The Teams

The eMERGE Network
electronic Medical Records & Genomics
A consortium of biorepositories linked to electronic medical records data
for conducting genomic studies

Pharmacogenomics Research Network

All of Us
The Precision Medicine Initiative

Vanderbilt University Medical Center