Is There a Genomic Basis to Acquired Channelopathic disease

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No Disclosures
Acquired Long QT Syndrome

Acquired implies an etiology for QT prolongation that is not genetic / congenital

QT prolongation can still result in torsades de pointes (TdP)
Acquired Long QT Syndrome

- **Drugs**
  - Hypokalemia, hypomagnesemia, hypocalcemia

- Metabolic disorders (anorexia nervosa, starvation, liquid protein diets, hypothyroidism)
- Bradyarrhythmias (sinus node dysfunction, AV block)
- Myocardial ischemia / infarction
- Intracranial disease
- HIV
- Hypothermia
- Connective tissue disease with anti-Ro/SSA antibodies
Acquired LQTS perspective

- Up to 3% of all drug prescriptions are for medications that may unintentionally cause TdP

- TdP develops in 1 – 8% of patients receiving QT prolonging drugs, such as quinidine, sotalol, ibudilife and dofetilide

- For a given patient receiving any of the drugs that may affect the QT interval, the chance of developing TdP is very small.
  - However, the total number of patients receiving at least one of these different medications is enormous

- Small chance of developing TdP may explain why the LQTS-inducing effect of a drug often only becomes visible once a drug is already on the market

Acquired LQT

Virtually all of the drugs that produce LQTS act by blocking $I_{KR}$ (rapid component of the delayed rectifier potassium current)

$I_{KR}$ encoded by the KCNH2 gene; aka hERG (human ether-a-go-go related gene)

- $I_{KR}$ Involved in phase 3 of cardiac action potential
- Inhibition of $I_{KR}$ prolongs action potential duration

Greatest cause of drug withdrawal and labelling restrictions during the last decade

Since 1982, relationship to Congenital LQTS

Moss AJ, Schwartz PJ. Delayed repolarization (QT or QTU prolongation) and malignant ventricular arrhythmias. Mod Concepts Cardiovasc Dis 1982;51:85–90.
Drugs involved in Acquired LQT

Antiarrhythmic Drugs:

- Quinidine (TdP in 0.6 – 1.5%)
- Disopyramide
- Procainamide (likely due to N-acetylprocainamide (NAPA) metabolite)
- Sotalol (TdP in 2% men, 4% women)
- Dofetilide (TdP in 0.9% with recent MI, 3.3% in heart failure)
- Ibutilide (TdP in 5.4% with heart failure versus 0.8 % without)
- Amiodarone – prolongs QTc, but rarely associated with torsades (<1%) unless taken with class 1a antiarrhythmic or when hypokalemia is present.

Berul et al. Acquired Long QT Syndrome. UptoDate
Drugs involved in Acquired LQT

- Haloperidol (FDA alert in 2007)
- Methadone (black box label 2006)
- Cisapride (torsades in 5.7%)
- Erythromycin
  - 2x risk of sudden cardiac death
  - especially with diltiazem, verapamil, azole antifungals
    » same CYP3A4 (5x risk)
- CredibleMeds.com (formerly arizonacert)

Table 2. Examples of commonly used medications that cause QT prolongation

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Amiodarone (Cordarone)</td>
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<tr>
<td></td>
<td>Disopyramide (Norpace)</td>
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<td></td>
<td>Dofetilide (Tikosyn)</td>
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<td></td>
<td>Ibutilide (Corvert)</td>
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<td></td>
<td>Procainamide (Pronestyl)</td>
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<td></td>
<td>Quinidine (Quinaglute)</td>
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<td></td>
<td>Sotalol (Betapace)</td>
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<td>Antipsychotics</td>
<td>Chlorpromazine (Thorazine)</td>
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<td></td>
<td>Clozapine (Clozaril)</td>
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<td></td>
<td>Haloperidol (Haldol)</td>
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<td></td>
<td>Quetiapine (Seroquel)</td>
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<td></td>
<td>Risperidone (Risperdal)</td>
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<td></td>
<td>Thioridazine (Mellaril)</td>
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<tr>
<td>Antibiotics</td>
<td>Azithromycin (Zithromax)</td>
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<tr>
<td></td>
<td>Ciprofloxacin (Cipro)</td>
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<td></td>
<td>Clarithromycin (Biaxin)</td>
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<td></td>
<td>Ketoconazole (Nizoral)</td>
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<td></td>
<td>Levofloxacin (Levaquin)</td>
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<td>Moxifloxacin (Avelox)</td>
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<td>Ofloxacin (Floxin)</td>
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<td></td>
<td>Sparfloxacin (Zagam)</td>
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<td></td>
<td>Telithromycin (Ketek)</td>
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<td></td>
<td>Trimethoprim-Sulfa (Bactrim)</td>
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<tr>
<td>Antidepressants</td>
<td>Amitriptyline (Elavil)</td>
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<tr>
<td></td>
<td>Citalopram (Celexa)</td>
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<td></td>
<td>Desipramine (Pertofrane)</td>
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<td></td>
<td>Doxepin (Sinequan)</td>
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<td></td>
<td>Fluoxetine (Prozac)</td>
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<td></td>
<td>Imipramine (Norprinil)</td>
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<td></td>
<td>Nortriptyline (Pamelor)</td>
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<td></td>
<td>Paroxetine (Paxil)</td>
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<td></td>
<td>Sertraline (Zoloft)</td>
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<td></td>
<td>Venlafaxine (Effexor)</td>
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<tr>
<td>Antiemetics</td>
<td>Ondansetron (Zofran)</td>
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<td></td>
<td>Prochlorperazine (Compazine)</td>
</tr>
</tbody>
</table>

Berul et al. Acquired Long QT Syndrome. UptoDate
Ayad et al, Proc (Bayl univ Med Cent) 2010; 23:250-255
Risk factors for events with drug-induced LQTS

- Higher doses of the drugs
- Concurrent use of multiple drugs or same metabolic pathways
- Diuretic treatment (electrolyte abnormalities)
- Baseline QTc prolongation
- Marked QTc prolongation (>500) during therapy
- Bradycardia (“reverse use dependence“) – fall in local extracellular potassium concentration leads to enhanced drug-induced inhibition of $I_{KR}$
- Electrolyte disturbances: hypokalemia, hypomagnesemia, less often hypocalcemia
- Impaired hepatic or renal function
- Underlying heart disease (heart failure, MI, LVH)
- Recent conversion from atrial fibrillation
- Female Sex
- Older age
- Congenital LQTS

Berul et al. Acquired Long QT Syndrome. UptoDate
K, Mg, Ca

- Virtually all drugs acting on QT do so by blocking $I_{KR}$ current mediated by potassium channel encoded by KCNH2 gene.

- Enhanced drug block of $I_{KR}$ with hypokalemia related to decreased $I_{KR}$ activity
  - upon removal of extracellular K+, the magnitude of outward HERG current amplitude is reduced, which may lead to a prolongation of the ventricular repolarization.\(^1\)

- In 92 patients with drug induced LQTS, 27 percent had hypokalemia or hypomagnesiam.\(^2\)

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Berul et al. Acquired Long QT Syndrome. UptoDate
Multiple redundant repolarizing currents are involved in maintaining normal cardiac repolarization.

Reduced reserve from subtle defects in one or more repolarizing currents may remain subclinical at baseline due to the additional compensatory repolarizing mechanisms.

Presence of stressors, such as drugs, unmask the low reserve.

Likely to have a significant heritable component.

Relatives of patients with LQTS have propensity to develop drug-induced repolarization abnormalities.

Normal QTc does not mean normal

- Normal QT interval does not rule out the presence of disease-associated mutations

- Congenital long-QT family members who are identified mutation carriers can have normal QT intervals.

- Normal ECGs have been identified in family members with autosomal recessive Jervell-Lange-Neilsen syndrome.
  - Severe symptoms arise in probands (two abnormal alleles, one from each parent)
  - Parents are phenotypically “normal” (carry long-QT syndrome–associated mutations)
  - Are asymptomatic mutation carriers might be at increased risk for TdP on exposure to drugs or other stressors?
    » Splawski et al. reported sudden death in an otherwise healthy young Jervell-Lange-Neilsen parent with severe psychic stress

Screening for Congenital LQTS

- Genes encoding pore-forming channel proteins evaluated
  - KCNQ1 (LQT1), KCNH2 (LQT2) and SCN5A (LQT3)

- Cohort of 92 patients with acquired LQTS (aLQTS)

- Controls: Middle Tennessee (71) and US populations (90).

- Frequency of three common nonsynonymous coding region polymorphisms similar between aLQTS and controls.

- Missense mutations in 5 of 92 patient (absent in controls)

- MinK 7% among drug-induced compared to 2-4% controls

- 10-15% of affected individuals (aLQTS) with genetic mutations

More screening in aLQTS...

- 32 patients with drug-induced aLQTS
- 32 healthy controls
- KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), KCNE2 (LQT6)
- Missense mutations in 4 patients [KNCH2, KCNE1 (2), KCNE2]
  - 13% of aLQTS
- Three other mutations in both patients and controls

### Table 2: Clinical characteristics of the aLQTS patient population.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>32</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 (12–84)</td>
<td>75 (24–82)</td>
<td>70 (12–84)</td>
</tr>
<tr>
<td>QTc at rest (ms)</td>
<td>425 (378–490)</td>
<td>422 (378–470)</td>
<td>433 (397–490)</td>
</tr>
<tr>
<td>QTc after drug intake (ms)</td>
<td>537 (428–640)</td>
<td>539 (428–640)</td>
<td>533 (456–600)</td>
</tr>
<tr>
<td>Trigger drugs (number of cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Quinidine</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Relevant concurrent therapy (number of cases)</td>
<td>11</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Either more than one drug that blocks LQTS related ion channels, or a secondary drug inhibiting the metabolism of the QT prolonging drug*

Paulussen et al, J Mol Med 2004; 82:182-8
Mutations in aLQTs versus cLQTS

188 with acquired (aLQT) compared to 101 congenital (cLQT) probands.

- Considered symptomatic if they exhibited TdP, pre-syncpe, syncope, cardiac arrest, or ventricular fibrillation, or as asymptomatic if they had a prolonged QTc ≥480 ms (86% of aLQT patients)

- In aLQTs, 53 disease-causing mutation carriers (51 single gene, 2 compound heterozygotes) = 28%, CI 22-35%

- 13 in KCNQ1, 29 in KCNH2, 3 in SCN5A, 1 in KCNE1, 1 in KCNE2

Itoh et al. European Heart Journal 2016 37: 1456-64
Control QTc durations

- Congenital LQTS
- Acquired LQTS
- Non-carrier family members

Itoh et al. European Heart Journal 2016 37: 1456-64
True versus Unmasked

- **Unmasked:** QTc > 460 ms in females and > 450 ms in males

- **112 (60%)** true aLQTS
  - 23% gene positive

- **76 (40%)** unmasked cLQTS
  - 36% gene positive

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Table 2  Prevalence of mutation carriers according to baseline features of the 188 aLQTS subjects

<table>
<thead>
<tr>
<th>Demographic/clinical variable</th>
<th>Mutation carriers (n = 55)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blacks</td>
<td>0/2</td>
<td>0.09</td>
</tr>
<tr>
<td>Caucasians</td>
<td>16/39 (41)</td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>37/147 (25)</td>
<td></td>
</tr>
<tr>
<td>Age of onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>20/49 (41)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥40 years</td>
<td>33/139 (24)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>11/48 (23)</td>
<td>0.46</td>
</tr>
<tr>
<td>Females</td>
<td>42/140 (30)</td>
<td></td>
</tr>
<tr>
<td>Secondary factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>19/81 (23)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>17/42 (40)</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>5/17 (29)</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>11/43 (26)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1/5 (20)</td>
<td></td>
</tr>
<tr>
<td>Control QTc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True aLQTS</td>
<td>26/112 (23)</td>
<td>0.07</td>
</tr>
<tr>
<td>Unmasked LQTS</td>
<td>27/76 (36)</td>
<td></td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>52/162 (32)</td>
<td>0.002</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1/26 (4)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are n/N (%).
LQTS, long QT syndrome; aLQTS, acquired long QT syndrome.

Itoh et al. European Heart Journal 2016 37: 1456-64
Mutations in aLQTs versus cLQTS

Figure 3  Distribution of genetic subtypes in acquired long QT syndrome and congenital long QT syndrome. All acquired long QT syndrome mutation carriers are shown in A; they are then subdivided in B as ‘true acquired long QT syndrome’ or ‘unmasked congenital long QT syndrome’, according to the study definitions.
Scoring System (predicting positive gene testing)

1 point for each:
- <40 years
- Symptoms
- QTc >440

Figure 4. Proportions of mutation carriers/non-mutation carriers among the 188 patients according to increasing score values. Score 0 = age ≥ 40 years + asymptomatic + QTc ≤ 440 ms; score 3 = age < 40 years + symptomatic + QTc > 440 ms; Scores 1 and 2 represent the presence of one or of two factors. The number of mutation carriers increases with increasing score values (from 0 in the group with Score 0) and indicates that 89% of mutation carriers (47 of 53) are found within the Scores 2 and 3. Conversely, among the 52 patients with a score of 1, which represent 28% of the entire population, there were six mutation carriers; this means that while within the group with a score of 1, there is an 11% of mutation carriers, when looking at the entire population this percentage drops to 3%. This would be the percentage of mutation carriers missed if genetic screening would be limited to the groups with a score of 2 and 3.

Itoh et al. European Heart Journal 2016 37: 1456-64
Conclusions for Itoh et al.

- QTc (in absence of triggering factors) of aLQTS cases is shorter than cLQTS patients, but is significantly longer than that of controls.

- 28% of aLQTS subjects have mutations in cLQTS genes (23% in “true aLQTS”).

- Unlike with cLQTS, the most prevalent mutations in aLQTS are on the KCNH2 gene.

- Baseline QTc + simple clinical parameters allows identification of aLQTS subjects more likely to be carriers of LQTS mutations.

Itoh et al, European Heart Journal 2016 37: 1456-64
IV Quinidine was given to 14 relatives of patients who did not tolerate quinidine and 14 relatives of patients who did tolerate (controls).

QTc did not prolonged differently in the two groups.

Transmural dispersion of repolarization, as measured from the peak to the end of the T wave (TpTe) different in the two groups.

Risk of TDP is related to TpTe more than QT interval prolongation itself?
KCNQ1 mutations

10 cases of sudden death in Japanese patients administered psychotropic medications in which autopsy identified no clear cause of death.

G643S, missense polymorphism in KCNQ1 ($I_{KS}$)

- Found in 6 of 10 sudden death cases (60%)
- 11% of 381 Japanese controls with same polymorphism.

SCN5A variants

- Y1102 is a common SCN5A variant in Africans and African Americans.

- 22 African American patients with “arrhythmia or risk for arrhythmia”
  - Syncope, aborted sudden death, medication- or bradycardia-associated QTc prolongation, documented ventricular arrhythmias

- 100 healthy African American controls

- 56.6% of cases and 13% of controls with Y1102 mutation.

- Y1102 may cause a small but inherent and chronic risk of acquired arrhythmia???

Splawski et al, Science 2002; 297:1333-6
Some drugs may affect ion channel trafficking, leading to decreased availability of ion channels at the cell membrane.

Pentamidine (antiprotozoal) appears to reduce membrane expression of the hERG channel.

May be an important mechanism for drug induced QT prolongation and TdP.

Copy Number Variations

Background: 3-12% of congenital LQTS who were otherwise mutation negative carried CNV (Copy number variations – sections of the genome are repeated).

Williams, et al.: First exploration of CNVs in determining susceptibility to aLQTS…

• KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 examined
• Significant CNV in 1 of 90 aLQTS patients - KCNQ1 exon 13
  • functional characterization demonstrated impaired channel function
• 1 significant CNV in 197 controls

Williams et al, Europace 2015; 17:635-41
Conclusions

- Genetic variations have been discovered in 10-25% of acquired Long QT patients.

- Concept of “Repolarization Reserve” is appealing as we discover the complexity of acquired Long QT Syndrome

- Likely many other mechanisms (e.g., copy number variations, membrane expression) for acquired Long QT Syndrome that we have not yet elucidated
Thank you!