Prolonged QT Interval

January, 2004
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UTHSCSA and ALMMVAH
Measurement of QT interval

• Lead with large T wave with distinct end
• Best: maybe V2-V3
• Varies with heart rate, longer in women, longer in evening and night
• Bazett formula
  - \( QTc = \frac{QT}{\sqrt{RR \text{ interval}}} \)
• \( QTc \approx 0.40 \) for men, \( \approx 0.415 \) for women, ULN \( \approx 0.44 \) or 0.46 for men and 0.47 for women
  - Not universally accepted
• Marked PQT is >125% (0.50 men, 0.52 women), moderate PQT is 115-125% (0.46, 0.48)

Surawicz B et al. Chou’s 5th ed. P. 22-3, 555
Causes of Prolonged QT interval

- **Congenital**
  - Jervell-Lange-Nielson
  - Romano-Ward
  - Sporadic

- **Acquired**
  - Ischemia*, infarction*
  - MVP, cardiomyopathy*
  - CNS dz*, esp ICH
  - Autonomic NS surg

- **Acquired (contd)**
  - Metabolic (lo Ca*, Mg, K*, liquid protein diet, intracoronary contrast)
  - Drugs (I-A*, III*, I-C, Amio, phenothiazine, tricyclic, antihistamine-combo, pentamidine)
  - lo thyroid*, temp, pheo, organophosphate

* = may show less severe prolongation
Causes of Short QT Interval

• High Ca, K, digoxin, acidosis, ? beta-blockade
Causes of Abnormal U Wave

• Prominent U Wave
  – Definition: >1.5-2mm
  – Lo HR, K, Mg, hi Ca,
  – I-A, III, digoxin, phenothiazine, Epi
  – CNS disease
  – LVH
  – Hi thyroid
  – MVP, Long QT syndrome

• Inverted U Wave
  – Specific for heart disease
  – LVH (I, V5, V6)
  – RVH (V1, V2, II, III)
  – Ischemia/infarction
    • resting ECG
    • during anginal episode
    • exercise-induced
T and U Waves and Fusion

- Normal: U wave begins at end of T at baseline, synchronous with S2, with early beat, T and U may fuse
- If QT lengthens by less than about 0.10 sec, U is still discernable
- Notched T vs T-U:
  - Notch generally has short distance between peaks, where aT-aU interval is usually 0.17-0.22 sec
  - Notch nadir generally > 2mm, and U onset usually < 2 mm above baseline
  - Look at I aVL and aVR where there is usually no U to evaluate end of T wave

Surawicz B et al. Chou’s 5th ed. P. 561
Electrolyte Disturbances with Significant ECG Effects

- Hyperkalemia, hypokalemia
- Hypercalcemia, hypocalcemia
- Hypothermia
- Hypermagnesemia (depress AV and IV conduction)
- Acidosis or alkalosis usually have altered K or Ca, independent effects uncertain
Hyperkalemia

- T waves become tall and peaked (>5.5)
- QRS widens uniformly (>6.5)
- QRS axis may shift either left or right
- Advanced hyperkalemia is indistinguishable from dying heart
- Advanced hyperkalemia may give ST elevation
- P wave amplitude decreases, PR interval prolongs
- Sinoventricular conduction
- Concomitant hypercalcemia mitigates changes
- Concomitant hyponatremia worsens changes and hypernatremia mitigates
Hyperkalemia with ST elevation

Pt with DKA and K 6.9, morphology resembles monophasic action potential

Surawicz, p. 520
Hypokalemia

- Progressive ST segment depression > 0.5 mm
- Decrease in T wave amplitude
- Increase in U wave amplitude
  - >1 mm
  - >T wave height in same lead
- If K<2.7, ECG is “typical” (all 3 features) in 78% and “compatible” in 11%
- If K 2.7-3.0, ECG is “typical” in 35% and “compatible” in 35%
- No change in QT interval if measured before U wave
- Advanced hypokalemia – T and U are fused
- Concomitant hypocalcemia: aggravates findings

Surawicz, p. 523
Hypokalemia

K = 2.4

Surawicz, p. 525
Calcium

- Ionized calcium, so correct for albumin level
- Mainly change in ST segment duration, little change in T wave morphology or P or QRS or PR or U
- Hypercalcemia shortens ST segment, so shortens the QaT (onset of QRS to apex of T)
  - If QaTc is 0.27 sec or less, then Ca is high 90% of time
- Hypocalcemia lengthens ST segment (rarely more than 140% normal)
Hypercalcemia

29-year old woman with lymphoma and bone involvement with Calcium 17.4; heart normal at autopsy, short QT interval, ST segment almost absent, flat T waves may or may not be related to hypercalcemia

Surawicz, p. 529
Hypercalcemia and Hypokalemia

41-year old man with multiple myeloma with absent ST segment and prominent U wave (V3), later normal K and Ca and ECG

Surawicz, p. 530

\[ Ca = 7.6 \]
\[ K = 2.9 \]
Hypocalcemia

31-year old man with chronic renal failure
Calcium 5.8 and K 3.3

PQT, esp ST segment, prominent U waves

Surawicz, p. 528
31-year old man with chronic renal failure
Calcium 5.8 and K 3.3

K now down to 2.8, U waves more prominent and mostly superimposed on T wave

Surawicz, p. 528
K now up to 3.5 and Calcium up to 6.5; ST segment is shorter and U less prominent

Surawicz, p. 528
Situations that Don’t Affect the ECG

- Hyponatremia, hypernatremia
- Hypomagnesemia, hypermagnesemia
- Hyperthermia
- Alkalosis, acidosis
- Alcohol, coffee, tobacco
Hypothermia

Heart rate 32, some baseline oscillation is somatic muscle tremor; long QT and ST depression as well as J wave (“Osborne wave”)
CNS Disorders

- Diffuse T inversion
- Particularly giant T inversion in precordial leads
- Prolongation of QT interval
- Can also have ST segment elevation or depression
- LV wall motion abnormalities have been described
CNS: Subarachnoid Bleed

3 women with subarachnoid hemorrhage, prolonged QT and increased amplitude of an upright or inverted T wave
Figure 1. Prolonged QT and QTc intervals, T wave alternans, and pulsus alternans.

Figure 2. Pseudo 2:1 AV block with hypotension.

49 year old woman with complete heart block receiving quinidine for ventricular arrhythmia

Hurst, 1998, Myerburg et al. P. 923
25 year old woman with Jervell and Lange-Nielson, and exercise-induced palpitations and syncope. Note the QTc of 610msec

Hurst, 1998, Myerburg et al. P. 923
25 year old woman with Jervell and Lange-Nielson, and exercise-induced palpitations and syncope. Note on this treadmill tracing T wave alternans induced by exercise.
25 year old woman with Jervell and Lange-Nielson, and exercise-induced palpitations and syncope. Note on this treadmill tracing T wave alternans followed by Torsades de Pointes

Hurst, 1998, Myerburg et al. P. 924
78 year old woman on telemetry service.
43 year old man in emergency center.
73 year old woman with COPD with chest discomfort. History of atrial arrhythmia on digoxin and quinidine.

ECG-SAP 1995, p. 56
85 year old woman found unresponsive at home, brought to the ED

ECG-SAP 1995, p. 28
85 year old woman found unresponsive at home, brought to the ED. QT interval 0.62. Intracerebral hemorrhage (neurogenic or “CNS T-wave” pattern), maybe from overactivity of the sympathetic NS. Catecholamine-induced myocardial necrosis. DDX: NQMI, quinidine.
56 year old woman receiving diuretic therapy presents to the ER

ECG-SAP 1995, p. 36
56 year old woman receiving diuretic therapy presents to the ER. QT 0.60. V2-3 with prominent U or bifid T, hypokalemia.

ECG-SAP 1995, p. 36
23 year old man on chronic hemodialysis.

ECG-SAP 1995, p. 38
23 year old man on chronic hemodialysis. QT borderline 0.44. ST segment prolonged but T wave normal duration. Hypocalcemia. T’s are peaked suggesting hyperkalemia (chest leads half standard.) ECG for hyperkalemia is 0.85 spec, sens only 0.60.

ECG-SAP 1995, p. 38
77 year old woman: CHF, palpitations and weakness, digitalis, diuretics
77 year old woman: CHF, palpitations and weakness, digitalis, diuretics, AFib, Junctional rhythm, AV block, low K+, long QT, digitalis toxicity.

ECG-SAP 1995, p. 86
69 year old man with low back pain in the Emergency Department
69 year old man with low back pain in the Emergency Department
Short QT 0.32, low P amplitude, absent ST segment, normal T, normal U
Hypercalcemia from Multiple Myeloma Ca >12 mg/dl shortens phase 2 of action potential

ECG-SAP 1995, p. 82
65 year old man in MICU
80 year old man with syncope for 2 weeks, with ECG showing complete AV block. No MI. K 3.8. Cure: pacemaker.

Sandoe, Sigurd, Arrhythmia - A guide to clinical electrocardiology 1991
25 year old woman with 1000 mg thioridazine overdose (100 pills). Third day, QT normalized.

13 year old girl with syncope: alarm clock: Romano-Ward
betablocker ended symptoms

Alarm clock ring - sinus rate rises

torsade onset

termination

30 sec later

Sandoe, Sigurd
Alarm clock ring - sinus rate rises
torsade onset
termination 30 sec later

No symptoms for at least 8 years after initiation with beta-blocker

Sandoe, Sigurd, Arrhythmia - A guide to clinical electrocardiology 1991
Treatment of Torsade de Pointes

• Depends on cause: remove offender of drug or bradycardia or lyte disturbance for acquired

• Acute and chronic: beta-blockade, Mg++ (2gm over 2 min, then 2-20 mg/min), Pacing, lidocaine, potential K+ channel opener, possibly Left cardiac sympathetic denervation, ICD if resistant, possibly mexilitene
Fig. II. A simplified representation of the cardiac myocyte action potential and the role and timing of the currents implicated as causatory in the long QT syndrome (LQTS). Abnormalities of \( I_{Ca} \), the L-type inward \( Ca^{2+} \) ion current, and \( I_{to} \), the transient outward \( K^{+} \) current, have not been identified as yet in congenital LQTS. Figure was supplied by Michael C. Sanguinetti. Reproduced, with permission, from Cell Press [30].
Model of Cardiac Ventricular Cell, with Ion Channels and Pumps
Circles indicate beta adrenergic augmentation

18 Currents in a Cardiac Ventricular Cell:

- INa indicates fast sodium current;
- ICa(L), calcium current through L-type calcium channels;
- ICa(T) calcium current through T-type calcium channels;
- IKr, fast component of delayed rectifier potassium current;
- IKs, slow component of delayed rectifier potassium current;
- IK1, inward rectifier potassium current;
- IKp, plateau potassium current;
- IK(ATP), ATP-sensitive potassium current;
- INaK, sodium-potassium pump current;
- INaCa, sodium-calcium exchange current;
- Ip(Ca), calcium pump in sarcolemma;
- INa,b, sodium background current;
- ICa,b, calcium background current;
- Ins(Ca), nonspecific calcium-activated current;
- Iup, calcium uptake from myoplasm to network sarcoplasmic reticulum (NSR);
- Irel, calcium release from junctional sarcoplasmic reticulum (JSR);
- Ileak, calcium leakage from NSR to myoplasm; and
- Itr, calcium translocation from NSR to JSR.

Calmodulin, troponin, and calsequestrin are calcium buffers.

Current

<table>
<thead>
<tr>
<th>Current</th>
<th>Probable clone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ current</td>
<td>SCN5A (hH1)*</td>
</tr>
<tr>
<td>L-type Ca²⁺ current</td>
<td>dihydropyridine receptor*</td>
</tr>
<tr>
<td>T-type Ca²⁺ current</td>
<td>Na⁺-Ca²⁺ exchanger</td>
</tr>
<tr>
<td>Na⁺-Ca²⁺ exchange</td>
<td>Ca²⁺ exchanger</td>
</tr>
<tr>
<td>I_TO 1 (4-AP-sensitive)</td>
<td>Kv1.2, 1.4, 1.5, 2.1+/or 4.2/3*</td>
</tr>
<tr>
<td>I_TO 2 (Ca²⁺-activated)</td>
<td>--</td>
</tr>
<tr>
<td>IKS</td>
<td>KvLQT1 + IsK (minK)</td>
</tr>
<tr>
<td>IKr</td>
<td>HERG</td>
</tr>
<tr>
<td>IKur</td>
<td>possibly Kv1.5*</td>
</tr>
<tr>
<td>ICl or / Kp</td>
<td>CFTR (Cl), TWIK/ORK1 (K) family</td>
</tr>
<tr>
<td>inward rectifiers</td>
<td>Kir2 (IK₁), Kir3.1+3.4 (IK-Ach); Kir6+SUR (IK-ATP)</td>
</tr>
<tr>
<td>Ih (pacemaker current)</td>
<td>--</td>
</tr>
</tbody>
</table>

*subunits also identified
Pore-forming K+ channel subunits in man and rodent. grey box=heart
Interactive Processes in a Cell

Congenital QT Prolongation

• Diagnostic Criteria:
  – Asymptomatic patient, QTc>470msec
  – OR: Male with QTc>440 or female with QTc>460 PLUS:
    • Stress-related syncope
    • Torsade de pointes
    • Family history of early (<35yo) SCD
  – These criteria are neither totally sensitive or specific

### Table 1

Diagnostic criteria for long QT syndrome

<table>
<thead>
<tr>
<th>Features</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG findings</strong></td>
<td></td>
</tr>
<tr>
<td>QTc</td>
<td></td>
</tr>
<tr>
<td>≥0.48 s</td>
<td>3</td>
</tr>
<tr>
<td>0.46-0.47 s</td>
<td>2</td>
</tr>
<tr>
<td>0.45 s</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes**</td>
<td>2</td>
</tr>
<tr>
<td>T wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T wave in three leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age**</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Clinical History</strong></td>
<td></td>
</tr>
<tr>
<td>Syncope**</td>
<td></td>
</tr>
<tr>
<td>With stress</td>
<td>2</td>
</tr>
<tr>
<td>Without stress</td>
<td>1</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
</tr>
<tr>
<td>Family members with definite LQTS^</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained sudden cardiac death before age 30 among immediate family members</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Scoring:** ≤ 1 point, low probability of LQTS; 2–3 points, intermediate probability of LQTS; ≥ 4 points, high probability of LQTS. ^Findings in the absence of medications or disorders known to affect these ECG findings. QTc calculated by Bazett’s formula, where QTc = QT/√RR. **Mutually exclusive. **Resting heart rate below the second percentile for age. ***The same family member cannot be counted for both of these criteria. Reprinted with permission from ref. 6.
## Congenital QT Prolongation (LQTS)

### Table 2
Molecular and cellular mechanisms of cardiac arrhythmias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene (alternate name)</th>
<th>Protein</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT-1</td>
<td><em>KVLQT1</em> (<em>KCNQ1</em>)</td>
<td>$I_{Ks}$ $K^+$ channel $\alpha$ subunit</td>
<td>28</td>
</tr>
<tr>
<td>LQT-2</td>
<td><em>HERG</em> (<em>KCNH2</em>)</td>
<td>$I_{Kr}$ $K^+$ channel $\alpha$ subunit</td>
<td>29</td>
</tr>
<tr>
<td>LQT-3</td>
<td><em>SCN5A</em></td>
<td>$I_{Na}$ $K^+$ channel $\alpha$ subunit</td>
<td>30</td>
</tr>
<tr>
<td>LQT-4</td>
<td><em>ANKB</em></td>
<td>ANKRIN-$\beta$</td>
<td>31</td>
</tr>
<tr>
<td>LQT-5</td>
<td><em>minK</em> (<em>KCNE1</em>)</td>
<td>$I_{Ks}$ $K^+$ channel $\beta$ subunit</td>
<td>32</td>
</tr>
<tr>
<td>LQT-6</td>
<td><em>MiRP1</em> (<em>KCNE2</em>)</td>
<td>$I_{Kr}$ $K^+$ channel $\beta$ subunit</td>
<td>33</td>
</tr>
<tr>
<td>LQT-7</td>
<td><em>KCNJ2</em></td>
<td>$I_{Kr}$ $K^+$ channel $\alpha$ subunit</td>
<td>34</td>
</tr>
</tbody>
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Molecular and cellular mechanisms of cardiac arrhythmias

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<tbody>
<tr>
<td>LQT-1</td>
<td>KVLQT1 (KCNQ1)</td>
<td>I\textsubscript{Ks} K\textsuperscript{+} channel α subunit</td>
<td>28</td>
</tr>
<tr>
<td>LQT-2</td>
<td>HERG (KCNH2)</td>
<td>I\textsubscript{Kr} K\textsuperscript{+} channel α subunit</td>
<td>29</td>
</tr>
<tr>
<td>LQT-3</td>
<td>SCN5A</td>
<td>I\textsubscript{Na} K\textsuperscript{+} channel α subunit</td>
<td>30</td>
</tr>
<tr>
<td>LQT-4</td>
<td>ANKB</td>
<td>ANKRIN-β</td>
<td>31</td>
</tr>
<tr>
<td>LQT-5</td>
<td>minK (KCNE1)</td>
<td>I\textsubscript{Ks} K\textsuperscript{+} channel β subunit</td>
<td>32</td>
</tr>
<tr>
<td>LQT-6</td>
<td>MiRP1 (KCNE2)</td>
<td>I\textsubscript{Kr} K\textsuperscript{+} channel β subunit</td>
<td>33</td>
</tr>
<tr>
<td>LQT-7</td>
<td>KCNJ2</td>
<td>I\textsubscript{Kr} K\textsuperscript{+} channel α subunit</td>
<td>34</td>
</tr>
</tbody>
</table>

Subtype of LQTS

<table>
<thead>
<tr>
<th>Subtype of LQTS</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Current (I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>11</td>
<td>KCNQ1</td>
<td>I\textsubscript{Ks} α-subunit</td>
</tr>
<tr>
<td>LQT2</td>
<td>7</td>
<td>KCNH2</td>
<td>I\textsubscript{Kr} α-subunit</td>
</tr>
<tr>
<td>LQT3</td>
<td>3</td>
<td>SCN5A</td>
<td>I\textsubscript{Na} α-subunit</td>
</tr>
<tr>
<td>LQT4</td>
<td>4</td>
<td>AnkyrinB</td>
<td>Unknown</td>
</tr>
<tr>
<td>LQT5</td>
<td>21</td>
<td>KCNE1</td>
<td>I\textsubscript{Ks} β-subunit</td>
</tr>
<tr>
<td>LQT6</td>
<td>21</td>
<td>KCNE2</td>
<td>I\textsubscript{Kr} β-subunit</td>
</tr>
<tr>
<td>LQT7 (Andersen’s)</td>
<td>17</td>
<td>KCNJ2</td>
<td>I\textsubscript{K1}</td>
</tr>
</tbody>
</table>

*Abbreviation: LQTS, long QT syndrome.

LQTS1 Mechanism

Phosphorylation of S27 causes increase in function of $I_{Ks}$:

- Increase current density with depolarization
- Delayed inactivation after activation, so open channels can accumulate

Mechanism

LQT1

A – normal association of KCNQ1 with yotiao and SNS-responsive elements

B – loss of association due to disruption of the LIZ motif, now not SNS-responsive

Gene SCN5A is cardiac Na channel, defect is incomplete inactivation

Gene SCN1A is neuronal Na channel, associated with epilepsy has similar functional abnormality

Kass RS & Moss AJ. J Clin Invest. 2003;112:810
LQTS4: Ankyrin dysfunction

- Autosomal dominant; one French kindred, 25 affected patients, SCD related to physical exertion or emotional stress (SCD in 2 pts)
- Phenotype: Sinus node dysfunction/bradycardia, LQTS and SCD, penetrance is high but not complete

Mohler PJ et al. Nature. 2003;421:634
Ankyrin Proteins

- Ankyrins are ubiquitously expressed intracellular adaptor proteins that target diverse proteins to specialized membrane domains, in 3 classes
  - Ankyrin R: restricted distribution (RBC, some neurons, striated muscle)
  - Ankyrin B: broadly expressed
  - Ankyrin G: giant size and general expression
- Structure: membrane-binding domain (24 ANK repeats), spectrin-binding domain, death domain, and C-terminal domain
- Ankyrins associate with ion channels, calcium release channels, cell adhesion molecules, and cytoplasmic proteins such as clathrin and tubulin

Ankyrin Proteins

- ANK repeats: 33-AA motif involved in protein recognition, found in over 325 human proteins, they fold into stacks of antiparallel α-helices connected by exposed loops

- Membrane-binding domain (24 ANK repeats) are multivalent and can interact with multiple proteins so may assemble multiprotein complexes at specific sites: Ankyrin B -/- cardiomyocytes display downregulation and mis-sorting of Calcium release channels (ryanodine and I-P3 receptors) in the endoplasmic reticulum, mediated by the C-terminal domain

Ankyrin Structure

Ankyrin Structure

Erythrocyte membrane

- Actin
- α-Spectrin
- β-Spectrin
- Anion-exchanger dimers
- 210 kDa Ankyrin-R

Axon initial segment

- Voltage-gated Na⁺ channel
- L1 CAMs
- Actin
- 480/270 kDa Ankyrin-G
- αIIβI/V spectrin

Ankyrin Connections

- Ankyrin-associated proteins
  - Cell adhesion molecules: CD44, L1CAMs: L1, LAD-1, NrCAM, NgCAM, neuroglian, neurofascin

- Ion channels
  - Anion exchanger (1-3)
  - Voltage-sensitive NaCh (β1,2)
  - Na⁺/K⁺-ATPase
  - H⁺/K⁺-ATPase
  - Na⁺/Ca²⁺ exchanger

- Calcium-release channels
  - Ryanodine receptor
  - Ins(1,4,5)P₃ receptor

- Cytoplasmic
  - Tubulin
  - Clathrin
  - β spectrin I-IV

LQTS4: Ankyrin dysfunction

• Autosomal dominant (heterozygote mice have disease phenotype)
• Disrupted cellular organization of:
  – Sodium pump
  – Sodium-Calcium exchanger
  – Inositol 1,4,5 triphosphate receptor
• Lower delivery to transverse tubules and lower protein level

K+ Channels

- The 2 key delayed rectifier currents are $I_{ks}$ and $I_{kr}$, both potassium.
- $I_{ks}$ is $\alpha$ and $\beta$ subunits, (LQTS1-KVLQT1=KCNQ1 and LQTS5-minK=KCNE1 respectively).
- $I_{ks}$ is strongly regulated by SNS stimulation.
- KCNQ1/KCNE1 channel forms a macromolecular signalling complex.
  - Coupled to yotiao, an adaptor protein that binds to protein kinase A (PKA) and to protein phosphatase 1 (PP1) and facilitates phosphorylation of Ser$^{27}$ and increase conductance.
  - SNS stimulation $>$ cAMP $>$ increase $I_{ks}$ $>$ faster repolarization = shorter APD, balanced against PKA stimulation of L type Ca channels that prolong APD.
  - Dysfunction of the channel leads to an arrhythmogenic inequity in SNS-stimulated phosphorylation of the channel, can give EADs.

Kass RS & Moss AJ. J Clin Invest. 2003;112:810
Potassium Channel Function

VGCC – voltage gated calcium channel
PKA – protein kinase A
PP1 – protein phosphatase 1
RyR2 – ryanodine receptor, the major SR Ca++ release channel in the heart

Ryanodine Receptor

- RyR1 is in skeletal muscle
- RyR2 is in cardiac muscle – has an extensive cytoplasmic domain that is a scaffold for regulatory proteins using LIZ (leucine-isoleucine zipper) motifs
  - FKBP12.6
  - PKA (reg and cat and mAKAP)
  - PP1 and spinophilin
  - PP2A and PR130
- Regulation is for the step of phosphorylation of Ser$^{2809}$ that causes dissociation of FKBP12.6 and more activity of Ca++ release (similar to $I_{\text{ks}}$)

Anderson’s Syndrome is a triad of dysmorphic features, cardiac arrhythmias and LQT, and periodic paralysis, and expression is variable.

Periodic paralysis syndromes are also channelopathies, but this syndrome shows combined abnormalities.

Inward rectification means that inward flux of K+ ions at a potential below Keq for K+ occurs more readily than efflux at a potential above Keq for K+; Kir2.1 is a strong rectifier.

Kir1.1 mutation produces Bartter’s syndrome and has analogous functional consequences as the Kir2.1 mutation explored.

Kir 2.1 has a pore region with a K+ selectivity filter GYG (gly-tyr-gly)

Kir 2.1 has been postulated to play an important, but not exclusive role as the inward rectifier current, \( I_{K1} \).

Congenital QT Prolongation

- **Jervell and Lange-Nielson** (1957): autosomal recessive, with deafness (KVLQT1 and minK also control inner ear endolymph homeostasis)
- These 2 syndromes are disturbances in the same genes and channels, except **Jervell and Lange-Nielson** patients are homozygous, and the **Romano-Ward** patients are heterozygous with variable penetrance
# Types of Congenital Prolonged QT Interval

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS1 (most common)*</td>
<td>KvLQT1</td>
<td>11p15.5</td>
<td>↓Iks (alpha subunit)</td>
</tr>
<tr>
<td>LQTS2</td>
<td>HERG</td>
<td>7q35-q36</td>
<td>↓Ikr</td>
</tr>
<tr>
<td>LQTS3 (rare)</td>
<td>SCN5A</td>
<td>3p21-p23</td>
<td>↑late INa</td>
</tr>
<tr>
<td>LQTS4</td>
<td>?</td>
<td>4q25-q27</td>
<td>?</td>
</tr>
<tr>
<td>LQTS5 (rare)*</td>
<td>minK (KCNE1)</td>
<td>21q22.1-q22</td>
<td>↓Iks (ancillary subunit)</td>
</tr>
<tr>
<td>LQTS6</td>
<td>KCNE2</td>
<td>?</td>
<td>↓Ikr</td>
</tr>
</tbody>
</table>

* Jervell and Lange-Nielson as well as Romano-Ward
### Adrenergic Effects in Congenital Prolonged QT interval

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Pharm Mimic</th>
<th>↑QT/ ↑TDR</th>
<th>Isoproterenol, +Propranolol</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS1</td>
<td>chromanol 293B</td>
<td>+/-</td>
<td>↑/↑, n/n</td>
<td>↓Iks</td>
</tr>
<tr>
<td>LQTS2</td>
<td>dofetalide, E-4031, d-sotalol</td>
<td>+/-</td>
<td>↑/↑↓, n/n</td>
<td>↓Ikr</td>
</tr>
<tr>
<td>LQTS3</td>
<td>anthopleurin A, ATX-II</td>
<td>+++/++</td>
<td>↓/↓, n/n</td>
<td>↑late INa</td>
</tr>
</tbody>
</table>

Experimentally: beta-blockade totally suppresses Tdp in LQT1, partially suppresses TdP in LQT2, and may provoke TdP in LQT3; but Na blocker may improve LQTS3, Mexiletine or flecainide.  

Mutations in LQTS Genes

• Each gene has multiple types of abnormalities, some are hot spots.
• Modifier genes?: identical gene defects have variability in clinical features.
• Modification of channel function:
  – Related to specific amino acid defect
  – KvLQT1, KCNE1 and HERG lose function
  – SCN5A gains function (defective inactivation)
Clinical Correlation in Congenital LQTS

• Manifestations
  – LQTS1: trigger of exercise
  – LQTS3: trigger with sleep or rest, shorten QT with exercise
  – LQTS2: both rest and exercise

• Management
  – Beta-blocker is first choice therapy
  – LQT3 usually improve with mexiletine
  – LQT2 may improve with mexiletine
ECG manifestations of LQTS

- Vary with genotype

Type 1

Type 2

Type 3

Circ, Dec 5, 2000... Wilde and Roden p 2797, Zhang et al, p.2849
Type 1

Circ, Dec 5, 2000... Wilde and Roden p 2797, Zhang et al, p.2849
Type 2

Circ, Dec 5, 2000… Wilde and Roden p 2797,
Zhang et al, p.2849
Type 3

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849
## Clinical Characteristics in Common Forms of LQTS

<table>
<thead>
<tr>
<th></th>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene mutated</td>
<td>KCNQ1 (KvLQT1)</td>
<td>KCNH2 (HERG)</td>
<td>SCN5A</td>
</tr>
<tr>
<td>Current affected</td>
<td>$k_s$</td>
<td>$k_r$</td>
<td>$k_{Na}$</td>
</tr>
<tr>
<td>Estimated prevalence (%)*</td>
<td>45</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Mean QTc†</td>
<td>490±43</td>
<td>495±43</td>
<td>510±48</td>
</tr>
<tr>
<td>% of events occurring with exercise or emotional stress‡</td>
<td>97</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td>Exercise-related trigger</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other triggers</td>
<td>Swimming</td>
<td>Loud noise</td>
<td></td>
</tr>
<tr>
<td>% with events to age 10†</td>
<td>40</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>% with events to age 40†</td>
<td>63</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Median age at 1st event†</td>
<td>9</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>QT shortening with exercise‡§</td>
<td>&lt;Normal</td>
<td>Normal</td>
<td>&gt;Normal</td>
</tr>
<tr>
<td>Efficacy of β-blockade to prevent events</td>
<td>+++</td>
<td>++</td>
<td>+(?)</td>
</tr>
<tr>
<td>Efficacy of mexiletine to shorten QT‡</td>
<td>−</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849
References:


• Sandoe, Sigurd, Arrhythmia - A guide to clinical electrocardiology Publishing Partners Verlags GmbH 1991


• Wilde et al. Circulation 2000;102:2799-2801
Keating M et al. Cell 2001; 104:569
CPVT-ECG

- ventricular premature beat
- ventricular bigemini
- ventricular bigemini and one doublet
- ventricular polymorphic triplet
- ventricular polymorphic doublet and triplet
- salvo of polymorphic ventricular tachycardia

Postma AV et al. Netherlands, presented at AHA Nov 2002
Ca\(^{2+}\) & excitation-contraction coupling

- Na\(^{+}\),K\(^{+}\) ATPase
- Na\(^{+}\) channel
- L-type Ca\(^{2+}\) channel
- Ca\(^{2+}\) ATPase
- SR Ca\(^{2+}\) release channel
- RYR2
- Sarcoplasmatic reticulum (SR)
- Ca\(^{2+}\) sequesterin
- CASQ2
- Na\(^{+}\)-Ca\(^{2+}\) exchanger
- Ca\(^{2+}\) release from SR

Postma AV et al. Netherlands, presented at AHA Nov 2002