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Andersen-Tawil syndrome (ATS)

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ATS

- normo- or dyskalemic periodic paralysis
- ventricular arrhythmia (LQT 7)
- slight dysmorphic features in some patients
- no myotonia
- dominant mutations in $\textit{KCNJ2}$ encoding the $K_{ir2.1}$ K$^+$ channel

$\textit{KCNJ2}$ expressed in skeletal and cardiac muscle
Long QT syndromes
- episodic arrhythmias known as *torsade de points*
- conversion into ventricular fibrillation
- sudden death in young otherwise healthy individuals

LQT7 is similar to LQT1
Development of LQT arrhythmia by prolonged action potential

Arrhythmia improves at slight tachycardia

ECG

Torsade de pointes
Inwardly rectifying $K^+$ channel
Kir2.1

Mg$^{2+}$ outward current blocks pore

Andersen’s syndrome — deletion
Expression of the normal (WT) and/or the mutated gene in COS cells
Currents through the mutant Kir2.1 channel
A,B: Depolarization and hypokalemia at reduced Kir2.1 function
C,D: Serum K⁺ depends on individual slow Na⁺ channel inactivation

A) Increasing block of $g_{Kir}$ to destabilize the resting state

B) $g_{Kir}$ shut-off

C) $E_s = -100$ mV, $E_s = -90$ mV, $E_s = -80$ mV, $E_s = -70$ mV, $E_s = -60$ mV

D) $[K^+]_e$ vs. $t$ [s]

E) $E = -80$ mV, $[K^+]_e = 4$ mM, $[K^+]_e = 3$ mM, $[K^+]_e = 2$ mM

F) $K_{mNa}$ vs. $[K^+]_e$ [mM]
Reduced- and increased-function mutations are associated with different features

Hypertelorism

Hypotelorism

characteristic TU morphology

AT

R82W

G215R

V93I

G215R

V93I
ATS fibers were depolarized to -65 mV at 4.5 mM K+ and further at 1.5 mM
twitch force
## ATS patients: paralytic attacks

<table>
<thead>
<tr>
<th>Kir2.1 mutations</th>
<th>Sex M:f</th>
<th>onset</th>
<th>1st symptom</th>
<th>K⁺/mM paralysis</th>
<th>PP type</th>
<th>Maxim. duration</th>
<th>chronic weakness</th>
<th>Muscle histology</th>
<th>Reaction to CAI</th>
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</thead>
<tbody>
<tr>
<td>R67W</td>
<td>6;1</td>
<td>12</td>
<td>Para/Arrh</td>
<td>very low</td>
<td>HypoPP</td>
<td>Days</td>
<td>Yes (1/6)</td>
<td>Vacuoles</td>
<td>n.d.</td>
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<tr>
<td>D78G</td>
<td>0;1</td>
<td>8</td>
<td>Paralysis</td>
<td>low</td>
<td>HypoPP</td>
<td>Days</td>
<td>Yes (1/1)</td>
<td>Vacuoles</td>
<td>Beneficial</td>
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<td>R82W</td>
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<td>33</td>
<td>Para/Arrh</td>
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<td>HypoPP</td>
<td>Days</td>
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<tr>
<td>G215D</td>
<td>1;0</td>
<td>3</td>
<td>Paralysis</td>
<td>5.8</td>
<td>HyperPP</td>
<td>Days</td>
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<td>n.d.</td>
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<td>9,5</td>
<td>Paralysis</td>
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<td>Days</td>
<td>Yes (1/2)</td>
<td>Vacuoles</td>
<td>Worsening</td>
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<td>5.7</td>
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<td>Hours</td>
<td>No (6/6)</td>
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<td>9,3</td>
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<td>HypoPP</td>
<td>h/days</td>
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<td>1.9</td>
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<td>weeks</td>
<td>No (1/1)</td>
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<td>Kir2.1 mutation</td>
<td>Type of arrhythmia</td>
<td>ECG QT&lt;sub&gt;c&lt;/sub&gt;</td>
<td>Effective therapy</td>
<td>Provoked by</td>
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<td>&lt; 440</td>
<td>Exercise, no effective drug</td>
<td>Stress, work, CAI</td>
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<td>Hyperthyroidism</td>
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<td>R218W</td>
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<td>Exercise, β-blocker, amiodarone</td>
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<td>R218Q</td>
<td>PVC, VT, bigeminus</td>
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<td>amiodarone</td>
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Electrolyte and water dysequilibrium during paralytic attacks causes vacuolar myopathy.
At rest
Therapy of ATS

Therapy of paralytic attacks:
Hypokalemic paralytic attacks as in HypoPP
Hyperkalemic paralytic attacks as in HyperPP
If type of attack is unknown: try potassium since ingestion-induced hyperkalemia is much less dangerous to the heart than hypokalemia!

Therapy of arrhythmia:
Na\(^+\) channel blockers like propafenone (1st choice)
Imipramine according to old reports on HyperPP with arrhythmia
Amiodarone only in older patients (late side effects)
Pacemaker/defibrillator in drug-resistant ventricular tachycardia

Our experience: arrhythmias are improved by slight exercise but worsened by strenuous work