

# Case Demonstrations in Congenital and Acquired Long QT Syndrome Can You Make A Correct ECG Interpretation?

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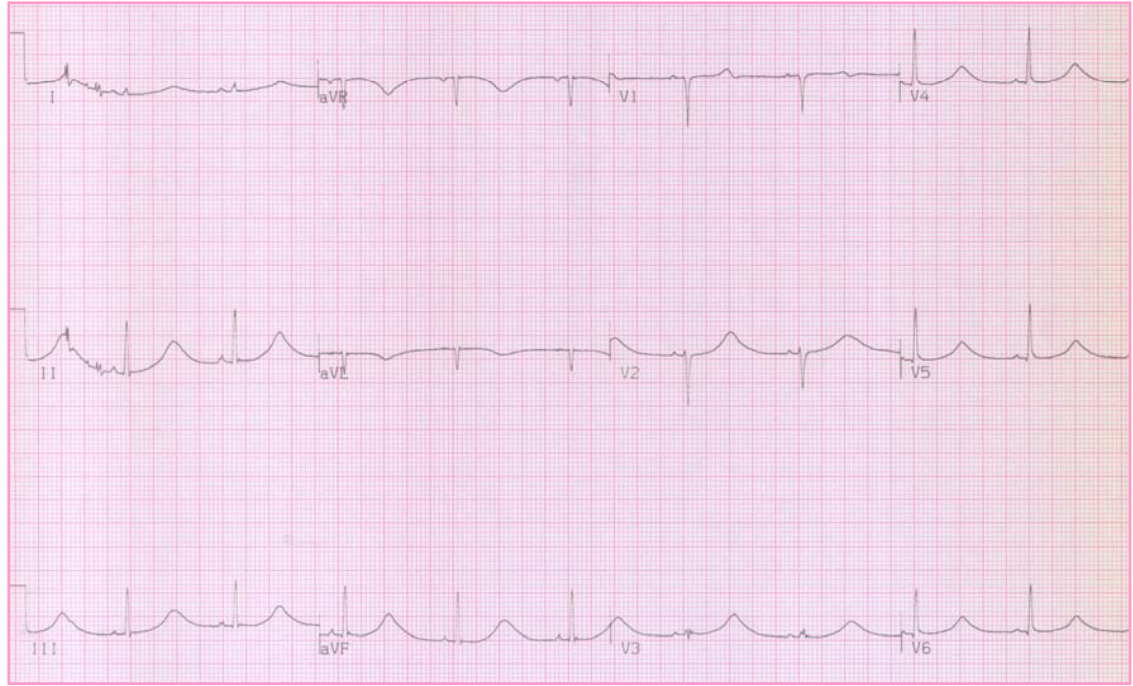
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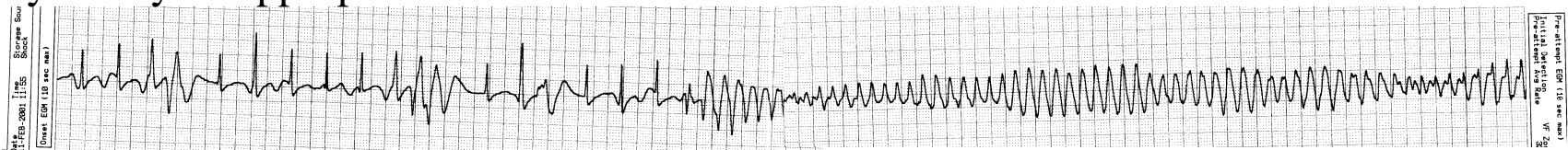
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## Case 1.

A 34 y.o. Caucasian female with a history of syncopal episodes had cardiac arrest at a Mexico beach during a family vacation. The paramedics found her in ventricular fibrillation (VF). Luckily she was resuscitated successfully. She had a markedly slow heart rate (<45 bpm) and was intolerable to beta-blockers thus an implantable cardioverter defibrillator (ICD) was implanted .



Three years later she experienced one inappropriate ICD discharge during a thunderstorm. On the fifth year of wearing an ICD she collapsed in the middle of skiing. Her ICD revealed following rhythm which was converted into sinus rhythm by an appropriate treatment.

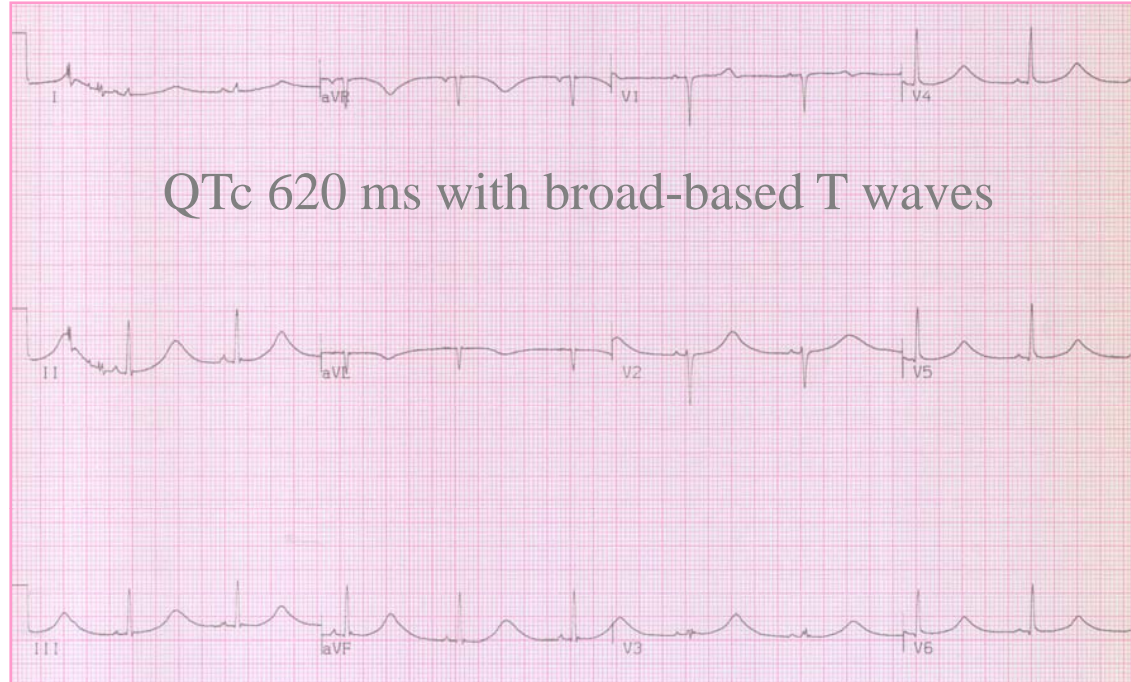


**What is your diagnosis?**

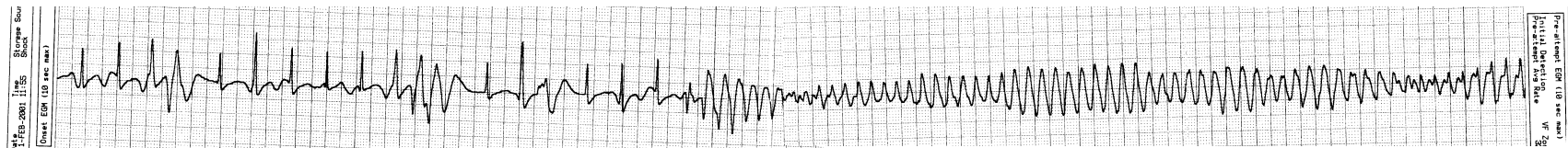
## Answer for case 1

1. Her 12-lead ECG showed sinus rhythm (rate 60 bpm), markedly prolonged QT interval (QTc 620 ms in V2) with broad-based T waves in the most of 12 leads.

Family ECG screening identified five asymptomatic affected members (QTc 470-500 ms) among 1<sup>st</sup>- and 2<sup>nd</sup>-degree relatives. Beta-blocker medication was recommended to the affected individuals.



2. ICD tracing revealed frequent PVCs, TdP which immediately degenerated into VF.

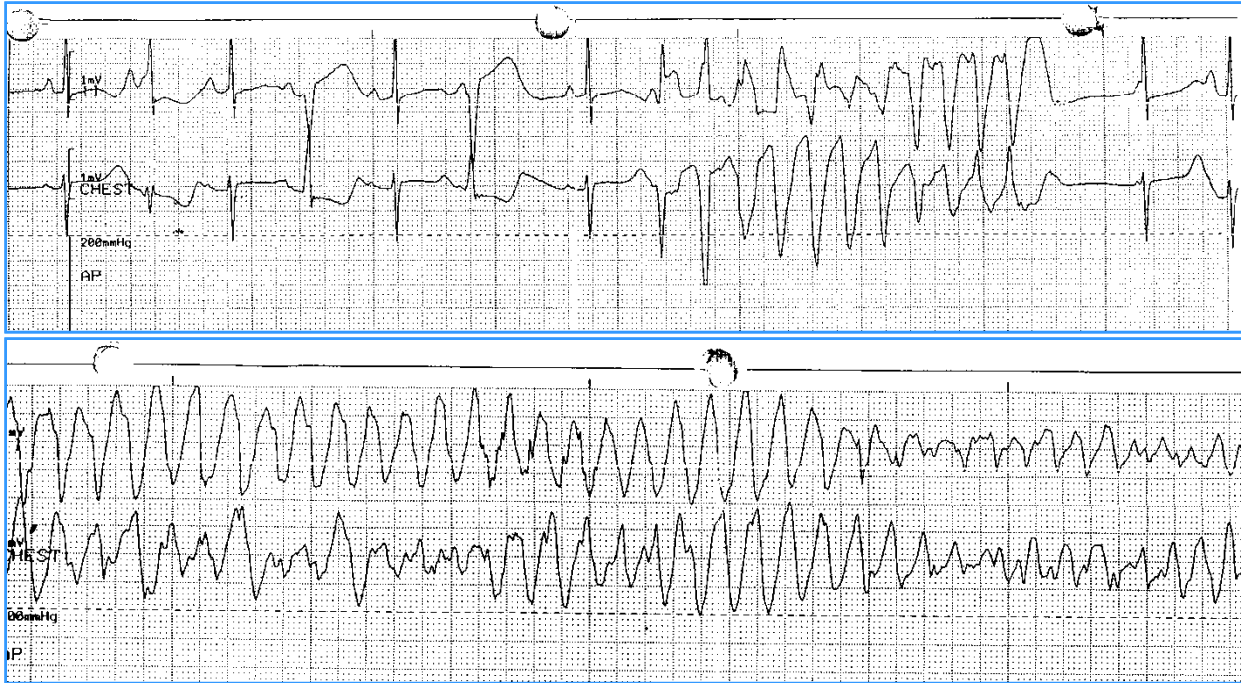


3. Based on the ECG patterns and the nature of cardiac events this patient was predicted as a possible LQT1 gene mutation carrier. A *KCNQ1* mutation was identified a few years later from the proband and affected family members.



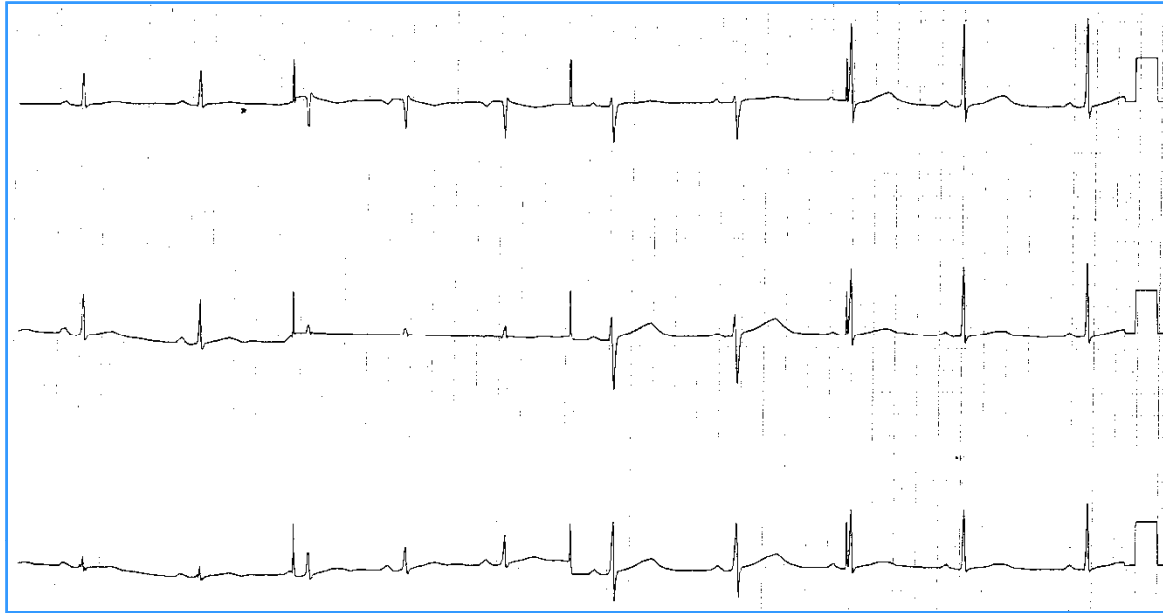
## Case 2.

A 32-y.o. Caucasian female with five syncopal episodes was admitted to ER. The ECG monitoring captured TdP which degenerated into VF. She regained consciousness after the DC shock.

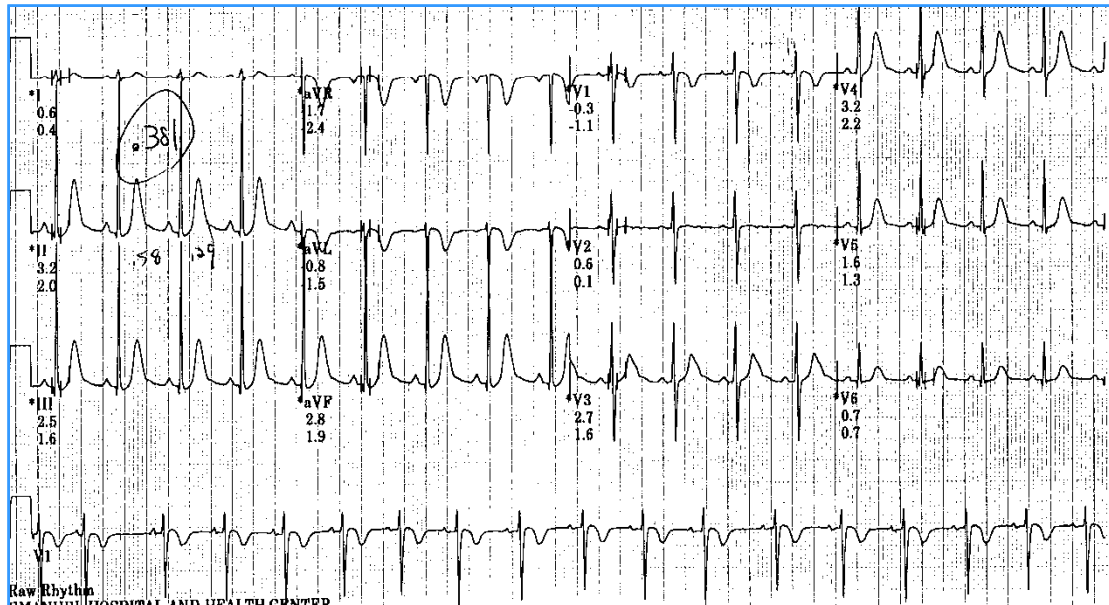


She had 5 years of syncopal episodes/seizures attacks mostly triggered by loud noise or emotional stress. Both cardiac (serial ECGs, Holter, tilt table test and echo) and neurology evaluation (EEG with sleep deprivation and head CT) were indicated as negative in her previous records.

# Resting ECG



1 minute after exercise



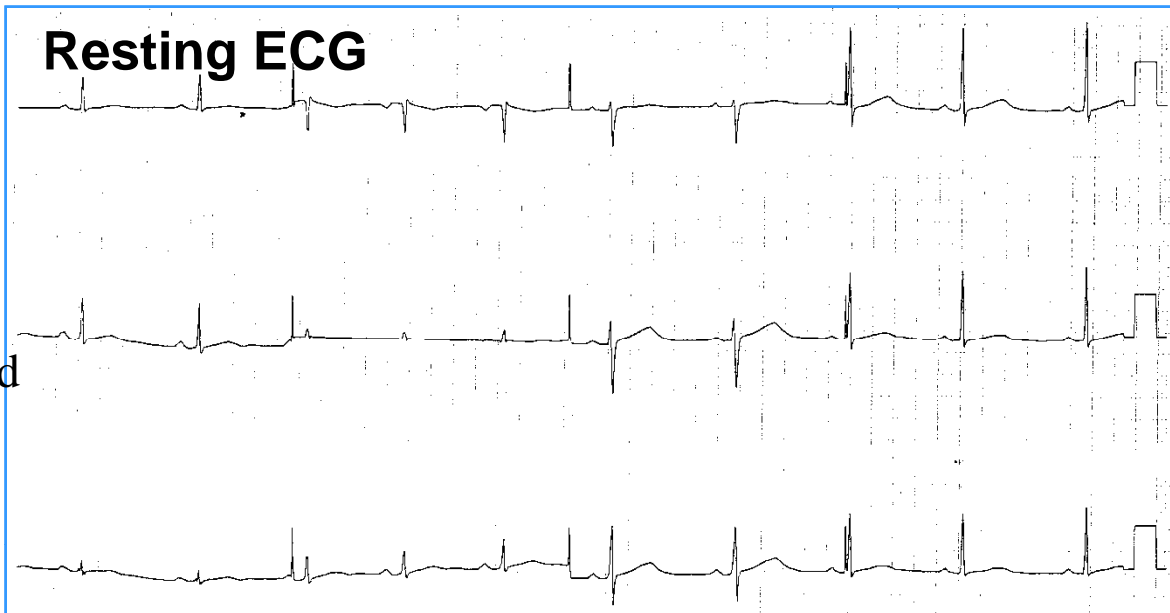
What is your ECG interpretation and clinical diagnosis?

## Answer for case 2

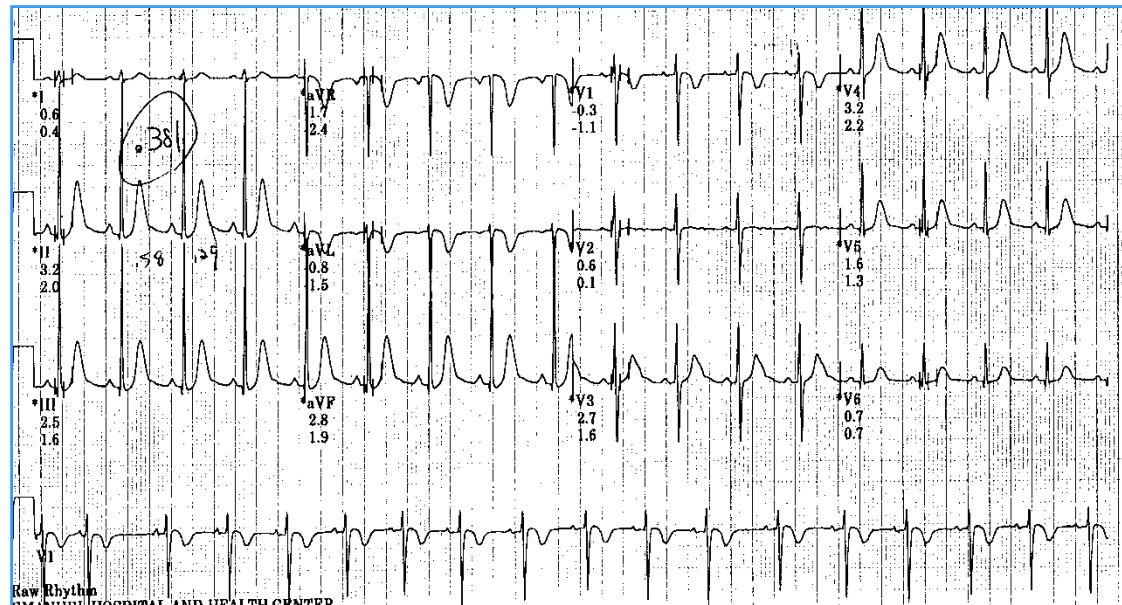
The resting ECG showed a prolonged QT interval (QTc 530 ms in V2) and subtle bifid T waves in most of 12 leads.

Her QT interval shortened dramatically during exercise (QTc 380 ms) and T waves became peaked at 1-min recovery.

The T wave morphology, QT response to exercise and the nature of cardiac events indicate this patient is a possible LQT2 gene mutation carrier. Genetic testing has confirmed the ECG prediction 3 years later.



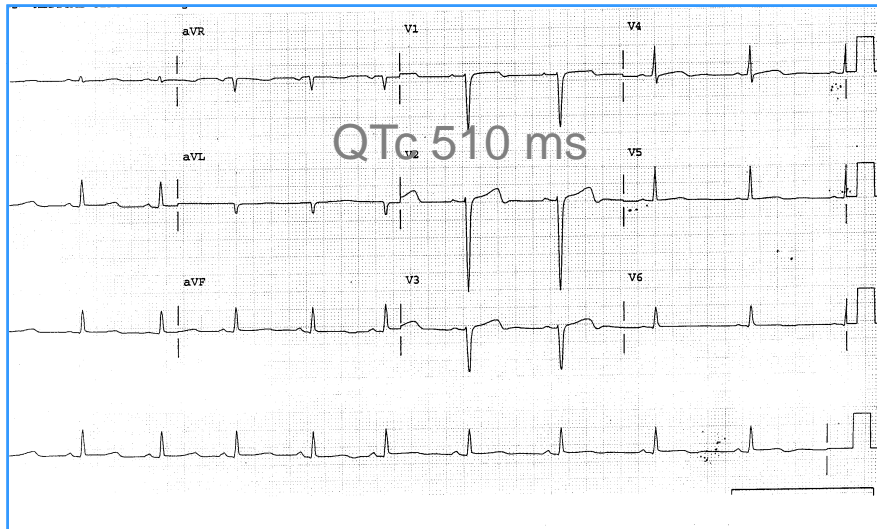
### 1 min after exercise



### Case 3.

A 33 y.o. Caucasian female elite athlete developed cardiac arrest due to torsade de pointes and ventricular fibrillation while taking a QT prolonging drug (QTc 500 ms/370 ms on/off trimethoprim sulfa). She refused beta-blocker medication and ICD and died suddenly at a 3rd cardiac arrest while she was taking another QT prolonging drug Sertraline for depression.

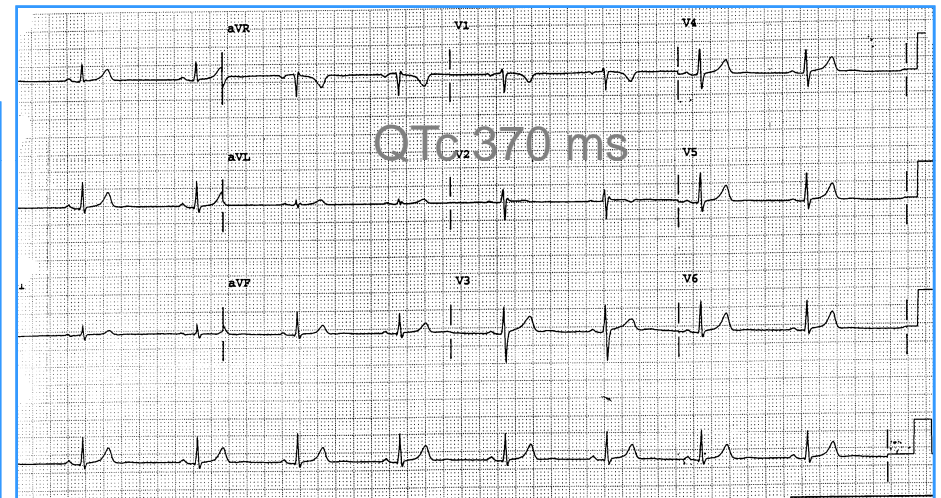
**On trimethoprim: QTc lengthened (510 ms) with biphasic T Waves**



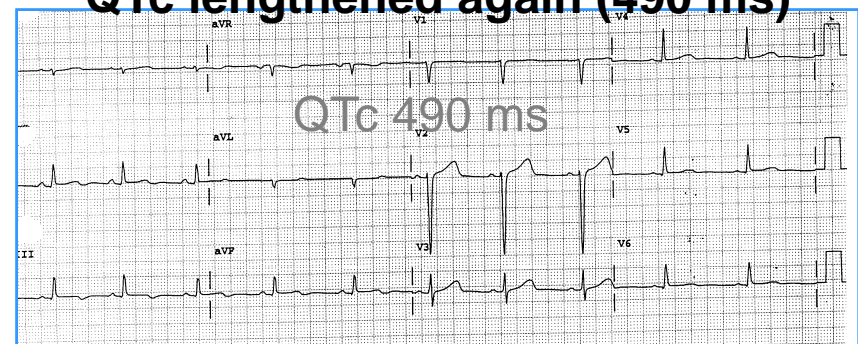
**On trimethoprim: TdP developed**



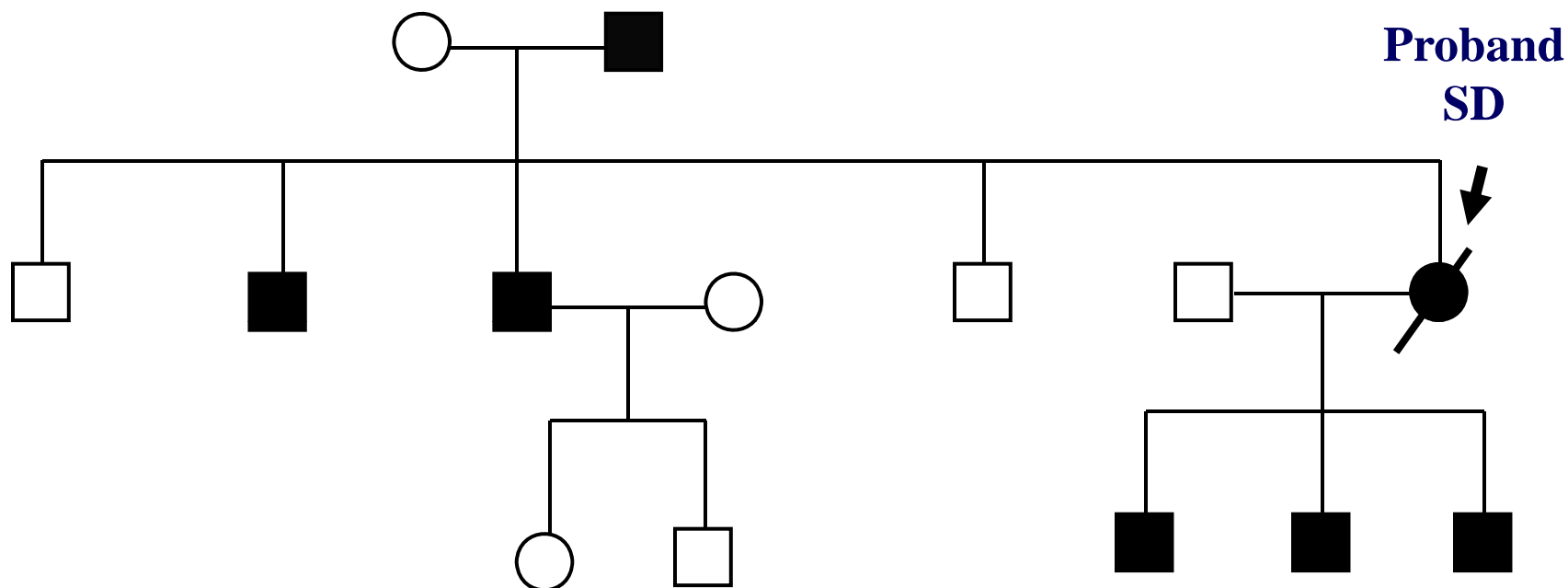
**Off trimethoprim: QTc shortened to 370 ms**



**Restarted trimethoprim: QTc lengthened again (490 ms)**



## Family pedigree



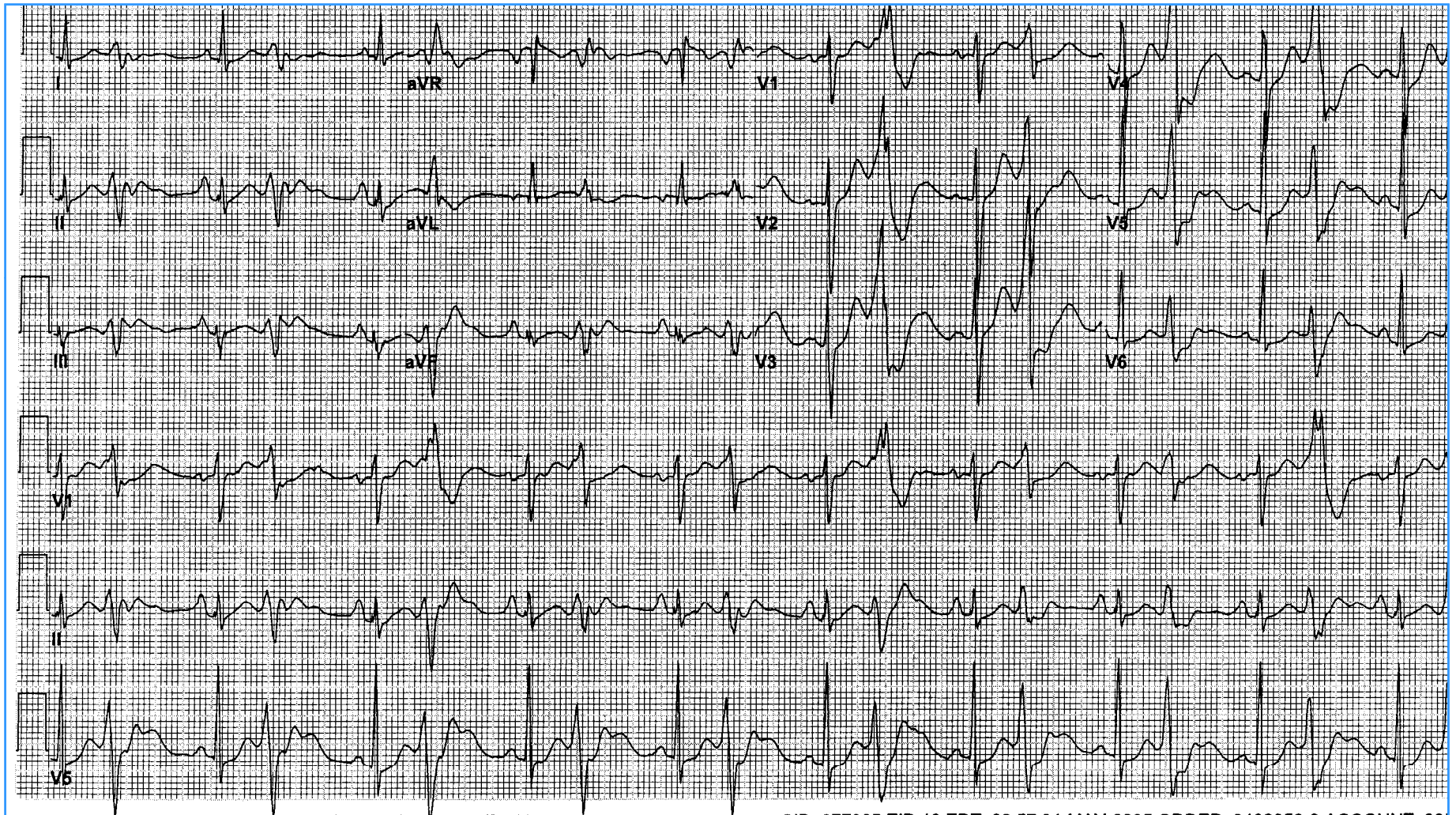
- ● A SCN5A mutation identified in 7 affected members (QTc  $424 \pm 22$  ms).  
□ ○ Unaffected family members.

Comments: Genetic predisposition is the underlying cause of drug induced long QT and the sudden death of the proband.

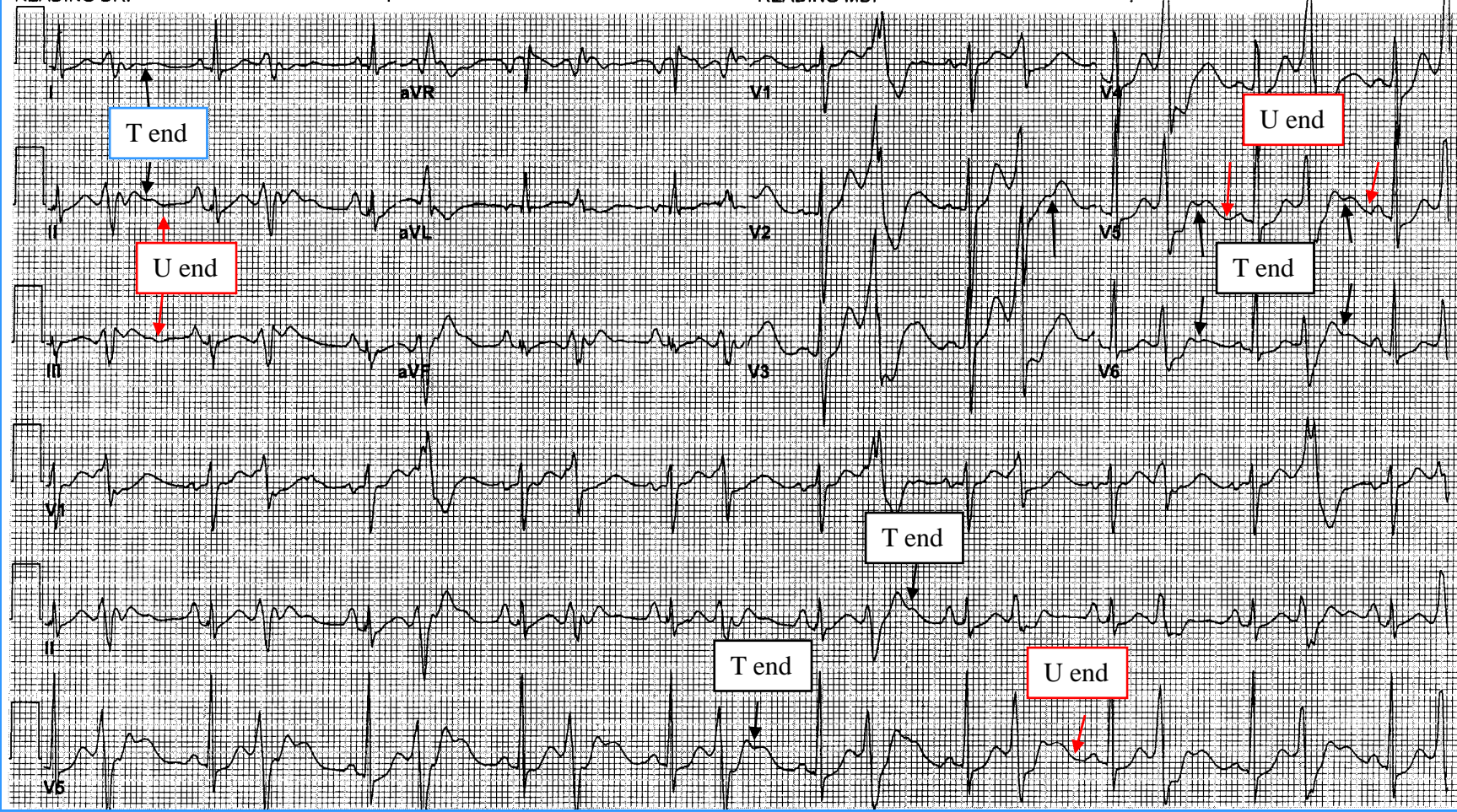


## Case 4.

A 34 y.o. Caucasian male developed recurrent syncope while taking methadone. VT/VF were documented by paramedics and polymorphic bigeminy PVCs were seen on admission.

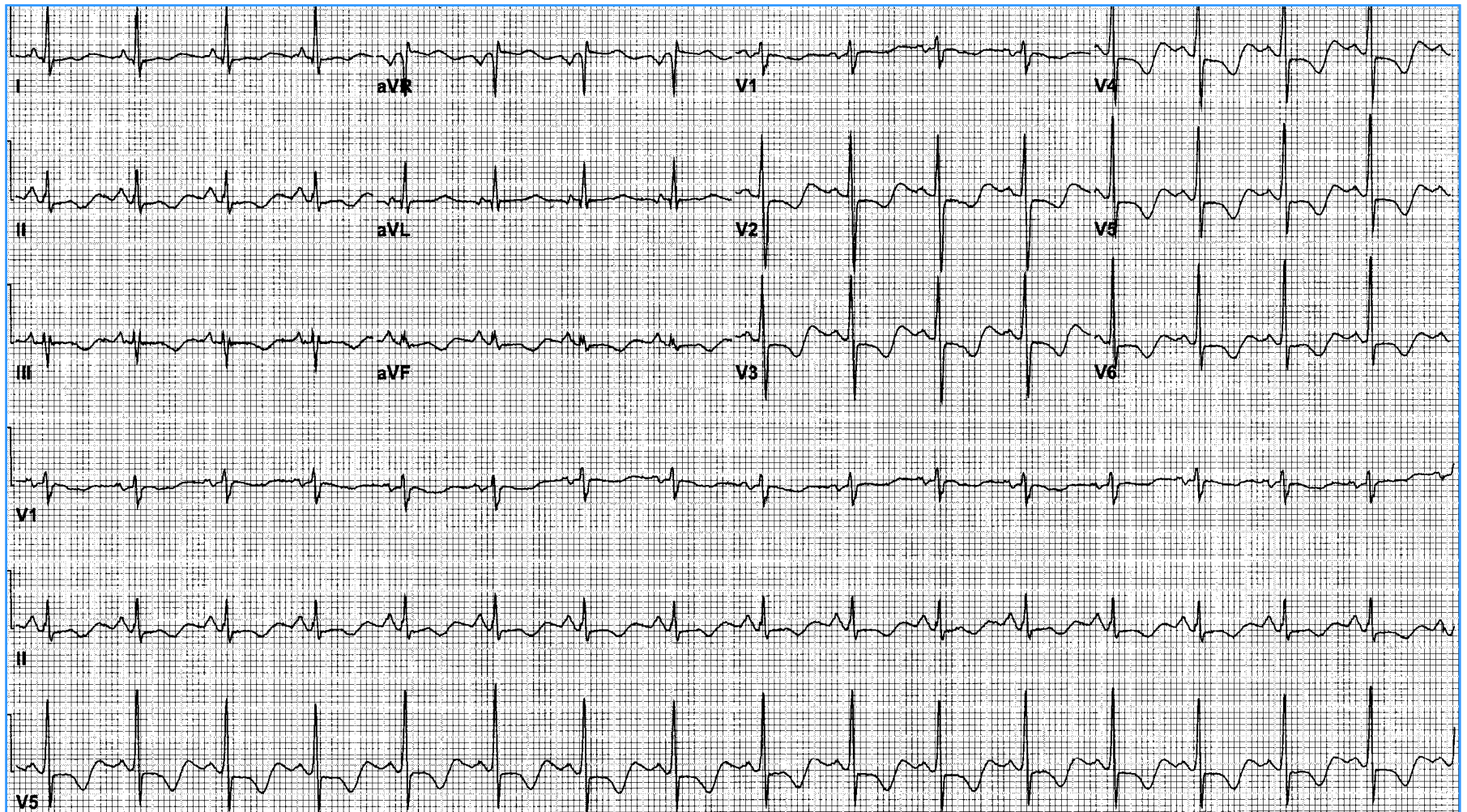


Case 4. His serum potassium level was 2.5 mEq/L. Medical history revealed that he had beta-thalassemia.

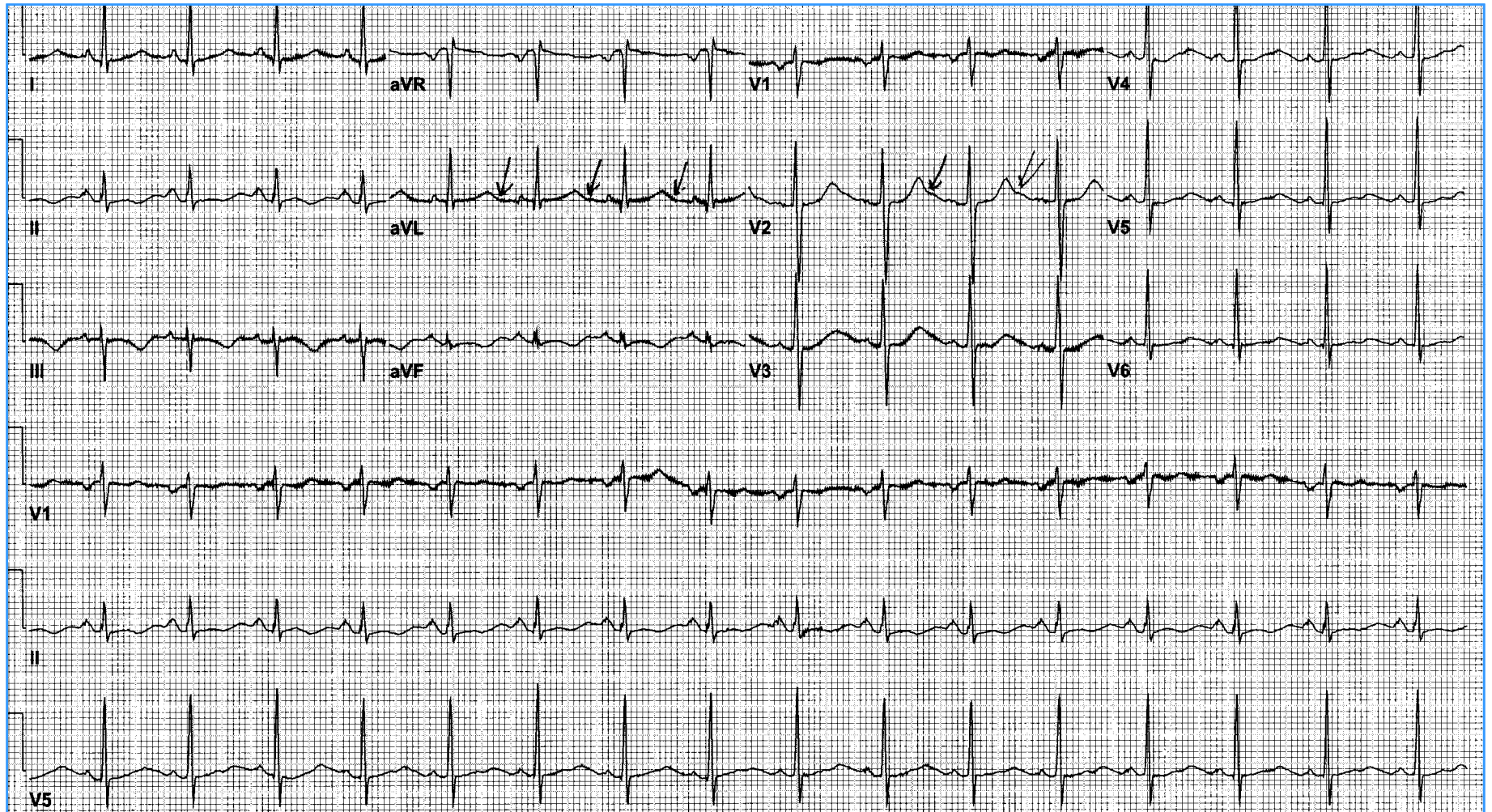




Case 4. QTU was 570 ms one week later. The enlarged U wave might be related to the lower level of magnesium and potassium seen in beta-thalassemia. The use of QT prolonging drug further delayed repolarization and caused arrhythmic syncope.

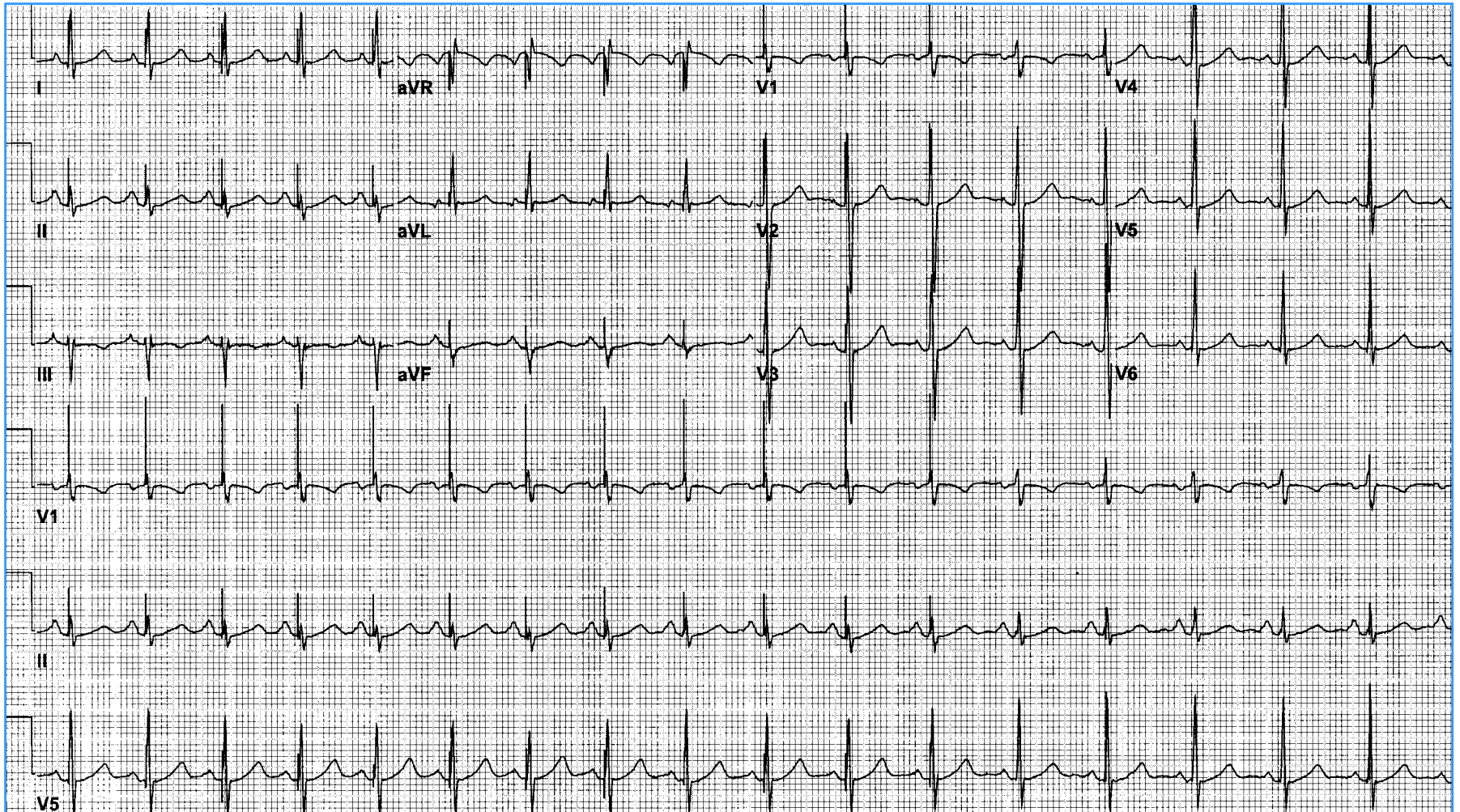


# Reduced U wave amplitude after treated with potassium and magnetism supplements





Case 4. QTc 420 ms with normalized T-U morphology two weeks later.



## **Using QT prolonging drugs is also a common cause of cardiac events in patients with congenital LQTS**

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In a preliminary study, we found that of 202 LQT1 patients prior to beta-blocker medication, 26 had cardiac arrest. Among them 10/26 (38%) were taking a QT prolonging drug at the time of the event, and all ten were female.

Vincent, et al. *Circulation* 2003;108:17 (Abstract No. 2307).

# Diagnosis of Congenital Long QT Syndrome

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## Clinical Dx

ECG: QT prolongation and characteristic ST-T-U changes

Medical history: Syncope, cardiac arrest and sudden death.

Gene-specific trigger effects

Family history, pedigree analysis and ECG screening help identify obligate/asymptomatic gene carriers

## Genetic testing

>650 mutations have been identified in *LQT1-9*.  
Mutation screening costs \$5000/proband in the United States. About 30% LQTS with solid clinical diagnosis obtained negative results. At present we recommend expert screening before ordering genetic testing conducted in a commercial lab.

## QT Interval

$$QTc = \frac{QT}{\sqrt{R-R}}$$

(Bazett' formula)

◆ Average from 2-3 consecutive beats in lead II, V5, or the lead with the longest QT interval.

◆ U wave should be excluded in the QT measurement.

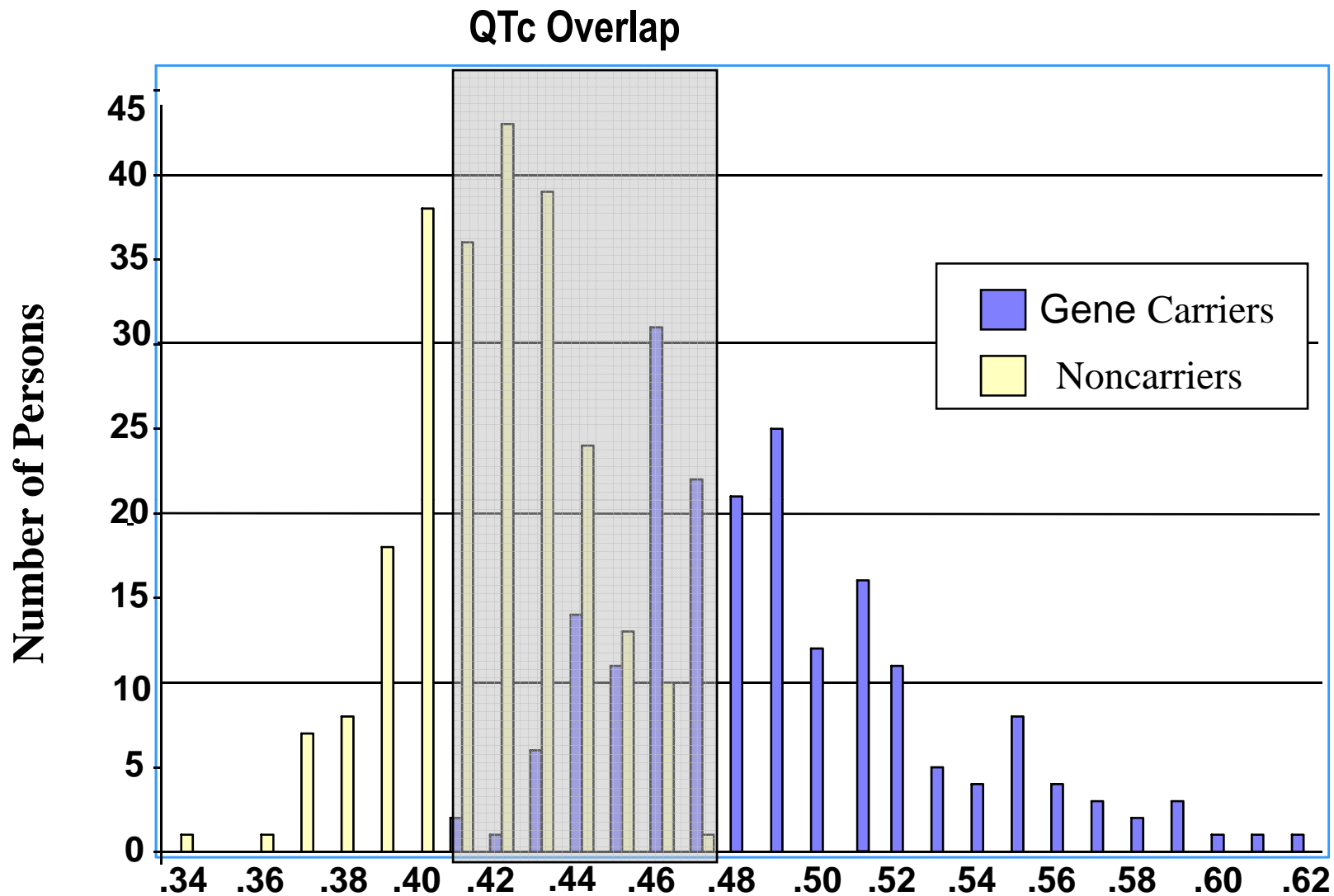
◆ LQTS:  $QTc \geq 0.48$  s in females;  $QTc \geq 0.47$  s in males

◆  $QTc$  0.46 s (F) or 0.45 s (M): high probability LQTS

◆ Borderline  $QTc$ : 0.44-0.46 s

◆ Normal  $QTc$   $< / = 0.44$  s (present in 12-30% of LQTS gene carriers)



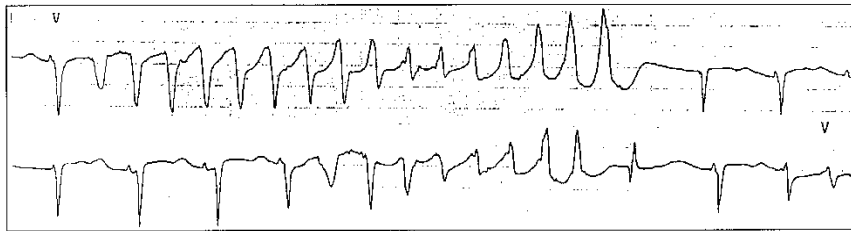
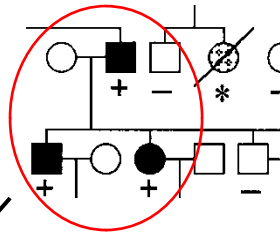


1/3 of LQTS gene carriers have QTc < 0.47 s, and 12% have QTc < 0.45 s.  
**The large QT overlap range with normal subjects complicates LQTS diagnosis.**

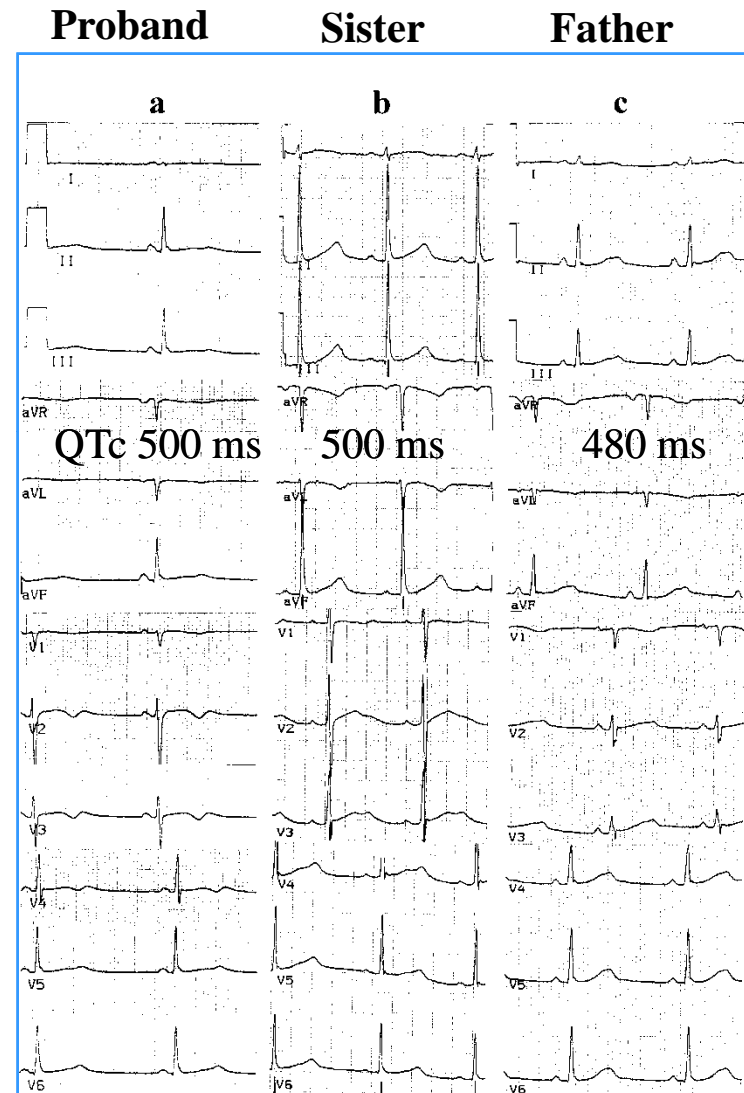
Vincent, et al. NEJM 1992;327:846-52

# Family Pedigree Analysis in LQTS Diagnosis

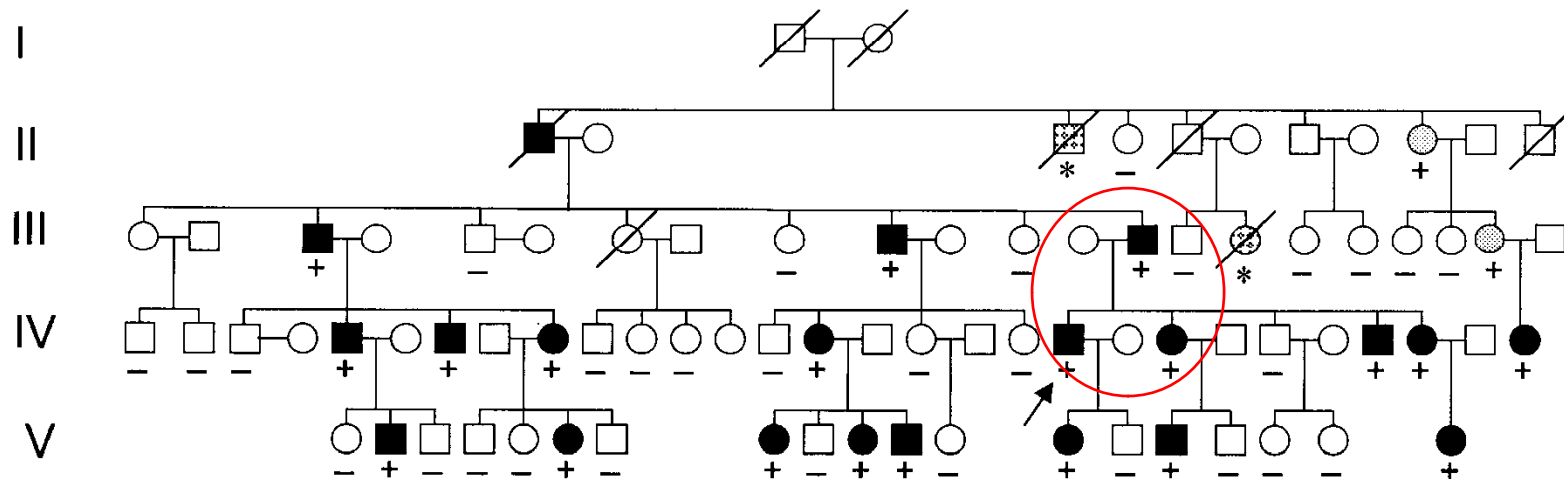
## The nuclear family



- The 1<sup>st</sup> cardiac event of the 27 y.o. proband was cardiac arrest. TdP was recorded in ER post DC shocks.
- Nuclear family ECG screening revealed typical LQT2 ECG patterns.



# Family Pedigree Expansion and ECG Phenotyping



- ● Male and female with LQTS phenotype
- ○ Male and female without LQTS phenotype
- \* Sudden death before the LQTS diagnosis
- Obligate carrier
- Proband
- + T1945+6C heterozygous carrier
- T1945+6C non-carrier

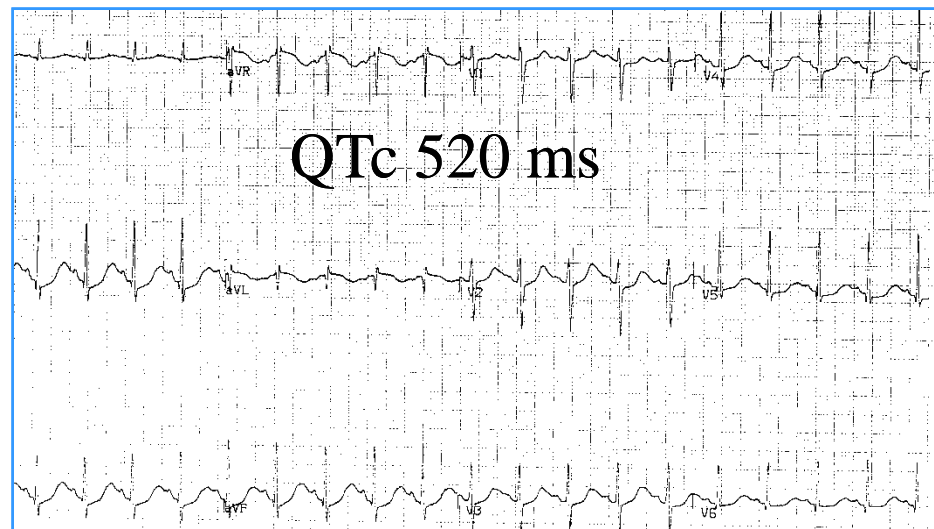
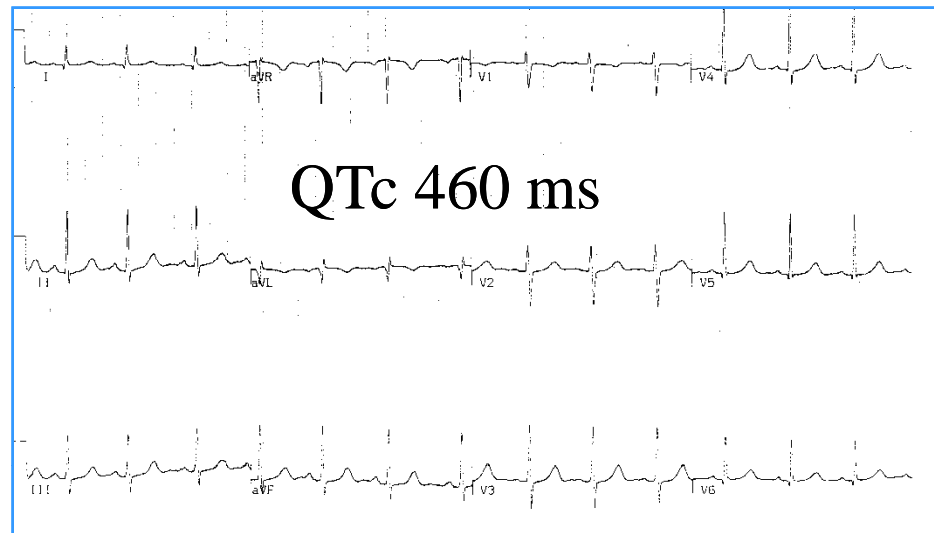
Although 35% of affected members showed normal to borderline QT interval ( $\leq 0.46$  s), T wave pattern evaluation and family pedigree expansion identified 23 affected members. Genetic testing and functional study identified the LQTS-causing intronic mutation.

(Zhang, et al JACC 2004;44:1283-91)

## Exercise tests in LQTS diagnosis

II-2 in the pedigree:

- Asymptomatic, F, 32 y.o  
Baseline QTc 0.46 s.  
Normal appearing T wave
- At 1-min recovery after 15 min of bicycle exercise test: QTc lengthened to 0.52 and T wave became broad-based
- Genetic testing revealed that she was a *KCNQ1* (LQT1) mutation C1022A carrier



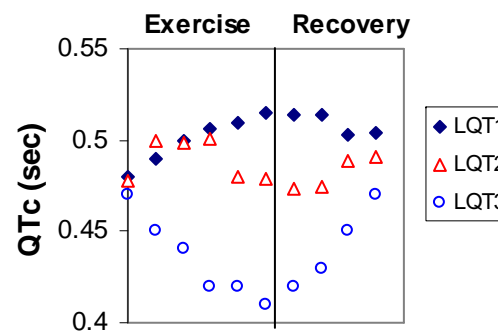


In LQT1, the QT is often longest during the peak stage of exercise and/or in the early stages of recovery (30 sec-3 min post exercise). The T wave often becomes broad based in the early stages of recovery.

# Exercise tests in LQTS diagnosis

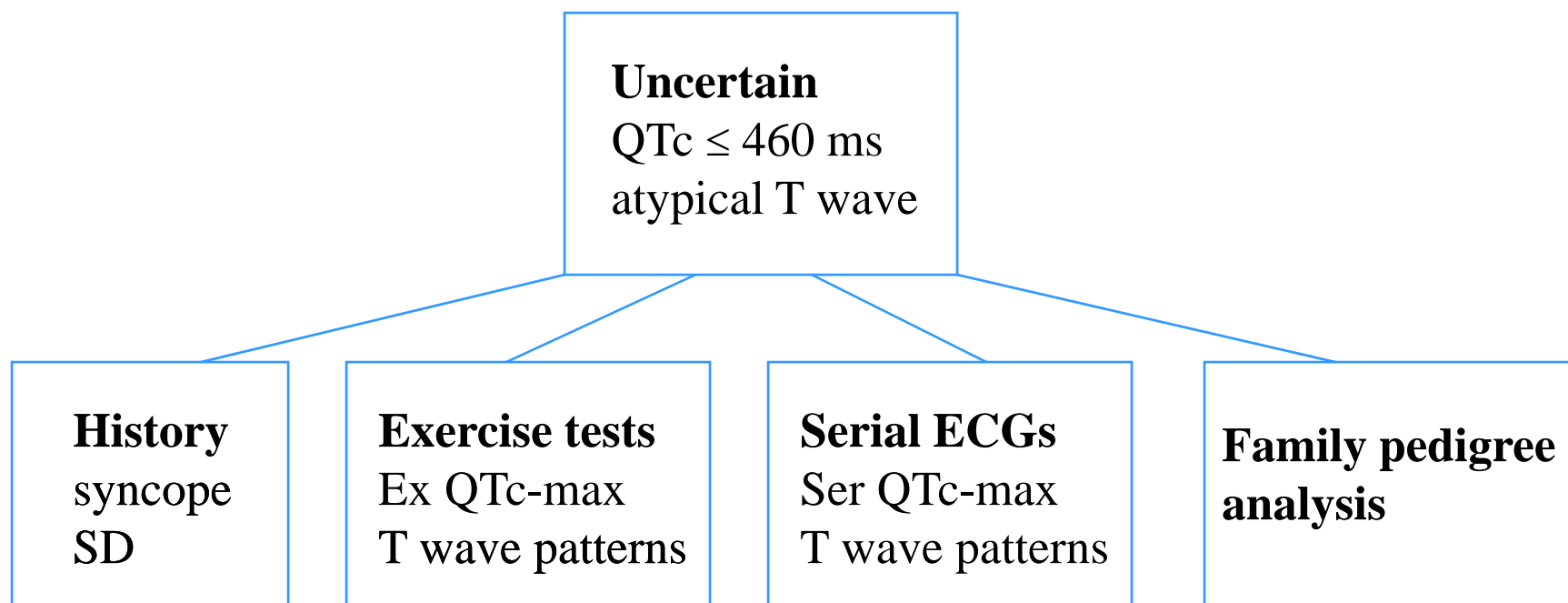
## Differential QT Response to Exercise by Genotype

- ♥ QTc changes were different during Ex and recovery in LQT1-3,
- ♥ LQT1: QTc  $\uparrow$  during Ex and early recovery.
- ♥ LQT3: QTc  $\downarrow$  in Ex and early recovery.
- ♥ LQT2: More heterogeneous; general pattern-QTc  $\uparrow$  in early Ex, variable during later Ex and early recovery,  $\uparrow$  in later recovery.



## Enhanced ECG criteria in LQTS diagnosis

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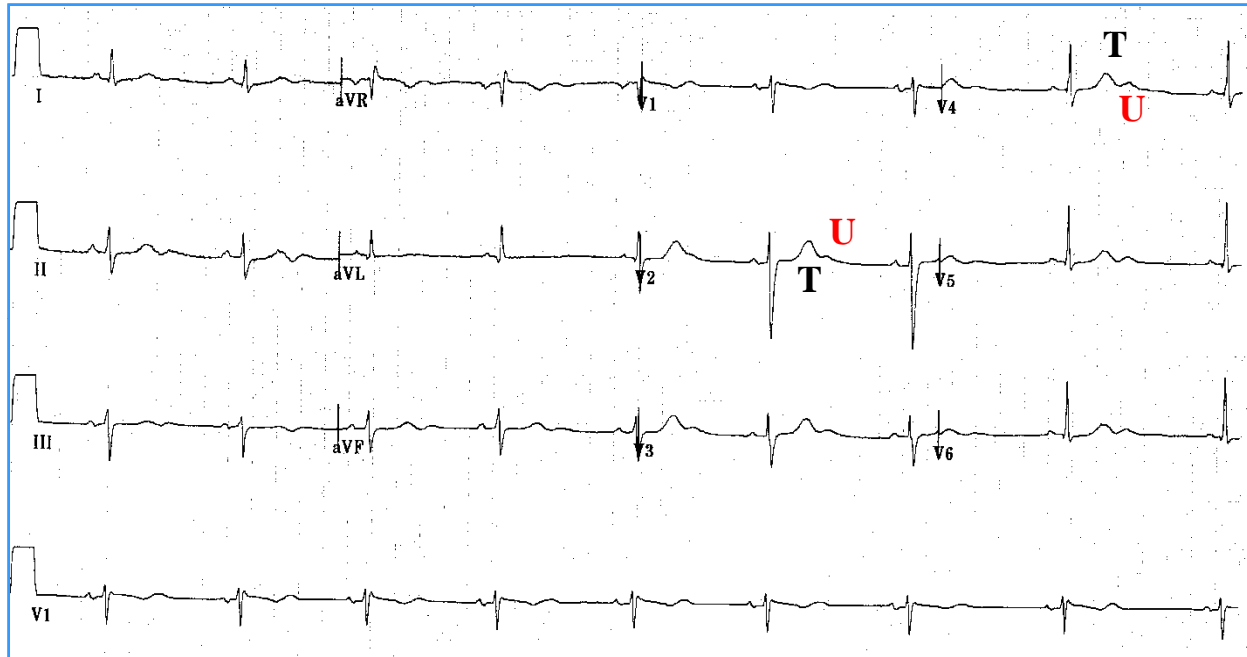


(Zhang, et al JACC 2004)

Based on our experience the medical history evaluation, exercise testing, serial ECG follow-up and family pedigree analysis increase the diagnostic accuracy in patients with normal to borderline QT interval.

# “LQT4” – ECG spectrum in patients with *ANKB* mutations

1



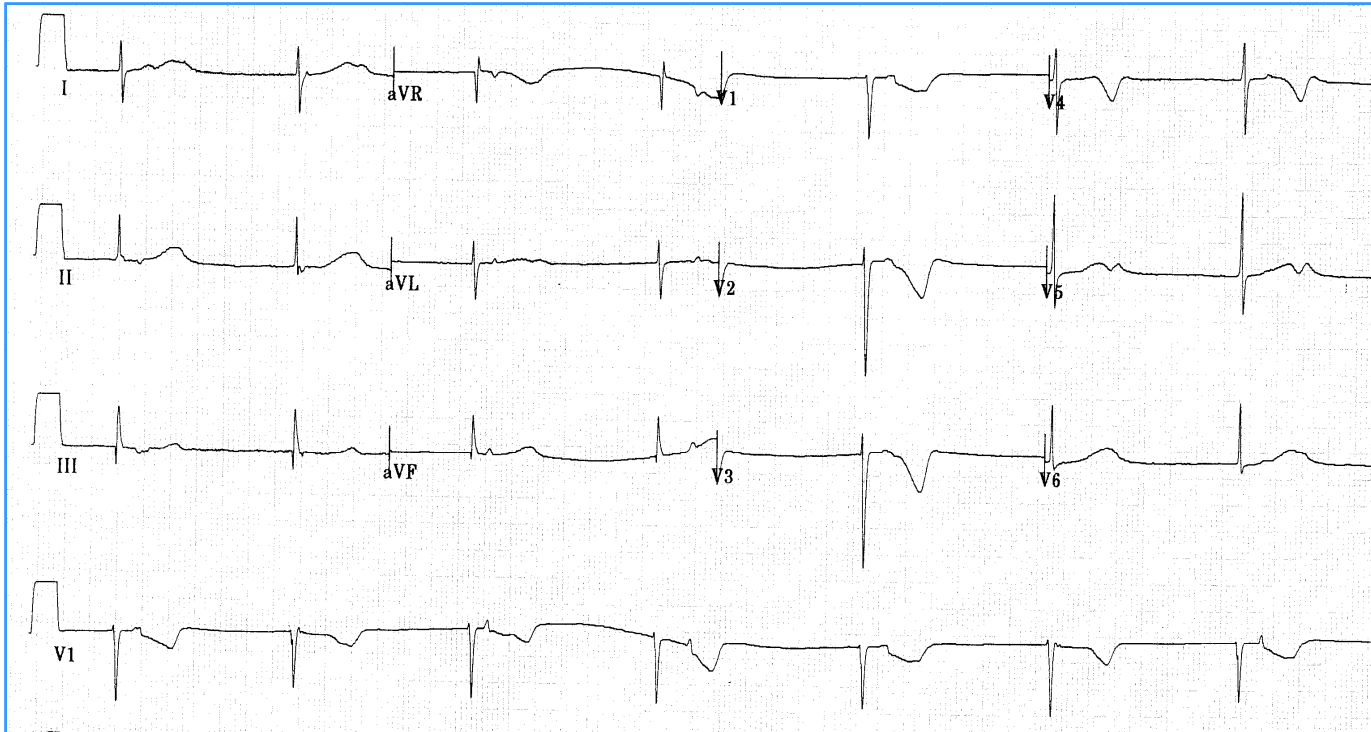
A 28 y.o. asymptomatic female E1425G carrier presents with sinus bradycardia, borderline QTc (450 ms) and prominent U waves.

(ECG tracing was contributed by Dr. Vincent Probst)



## “LQT4” – ECG spectrum in patients with *ANKB* mutations

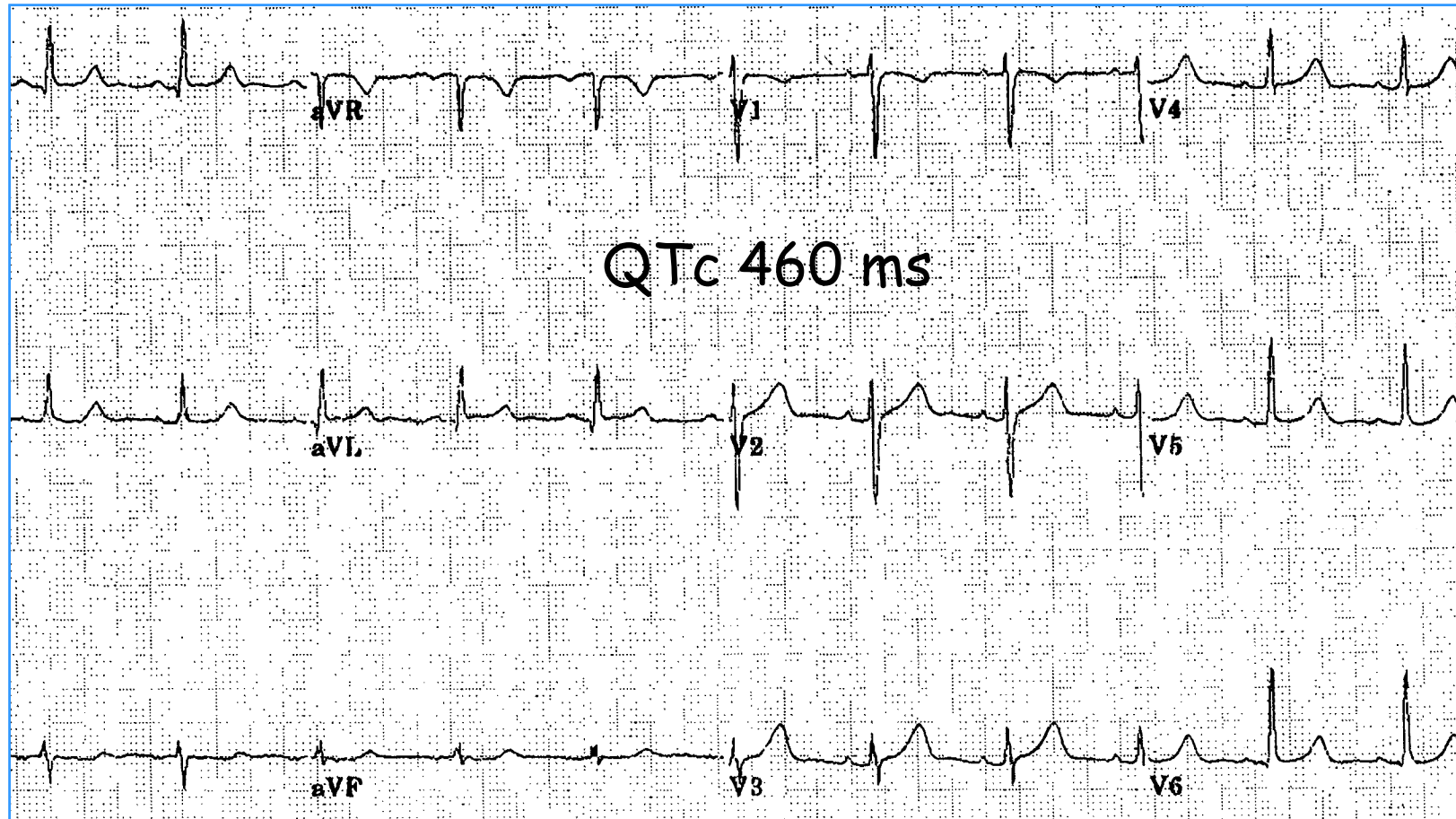
2



A 5 y.o. asymptomatic male E1425G carrier presents with AV disassociation due to a remarkable sinus bradycardia (42 bpm), bizarre T waves and prolonged QT interval.

(ECG tracing was contributed by Dr. Vincent Probst)

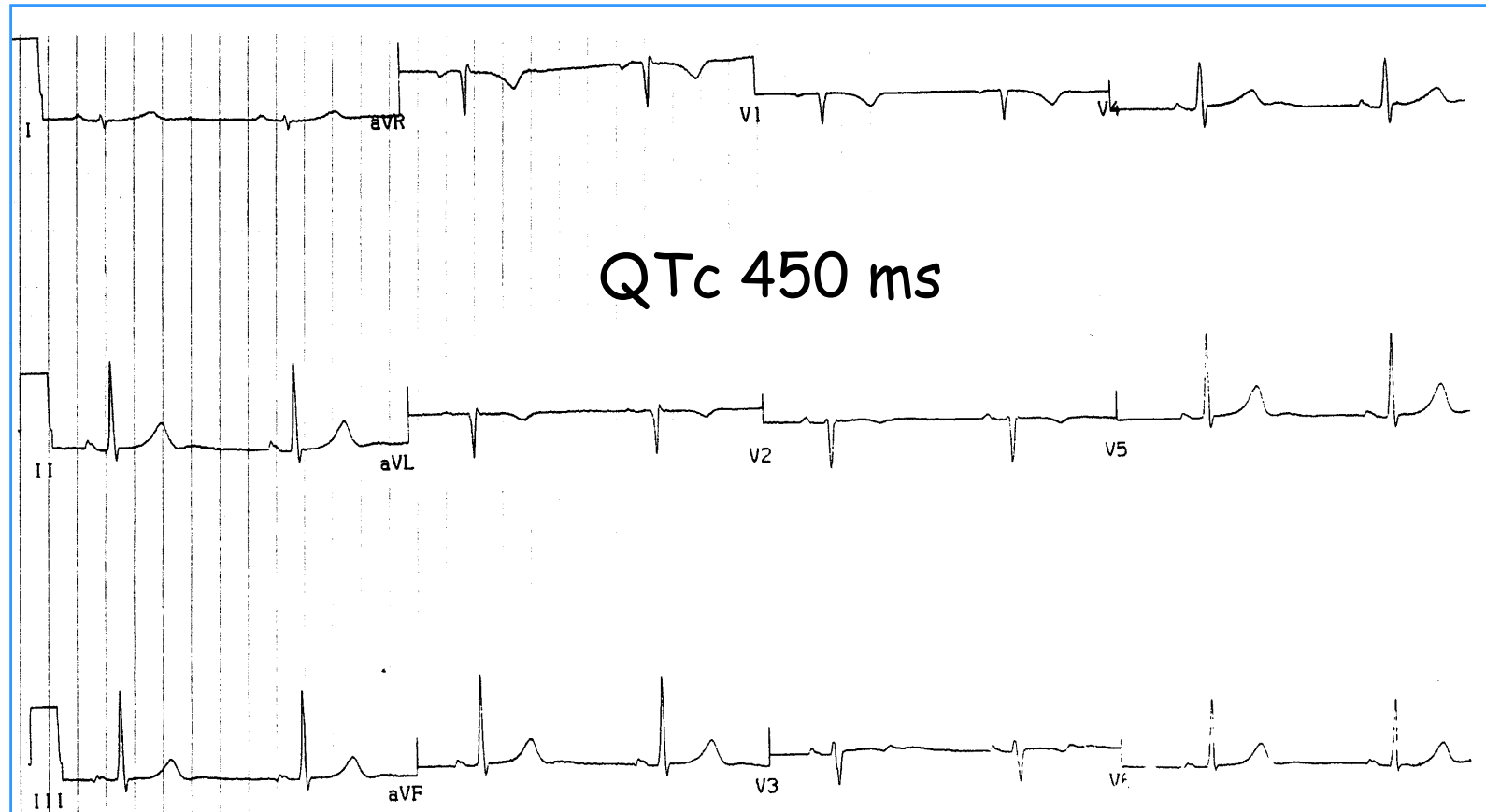
## ECG manifestation in patients with LQT5



A 32 y.o. female *Mink* gene mutation carrier with borderline QT prolongation

Due to the limited number of cases studied, we are unable to characterize the ECG phenotype characteristics in LQT5 and LQT6 patients.

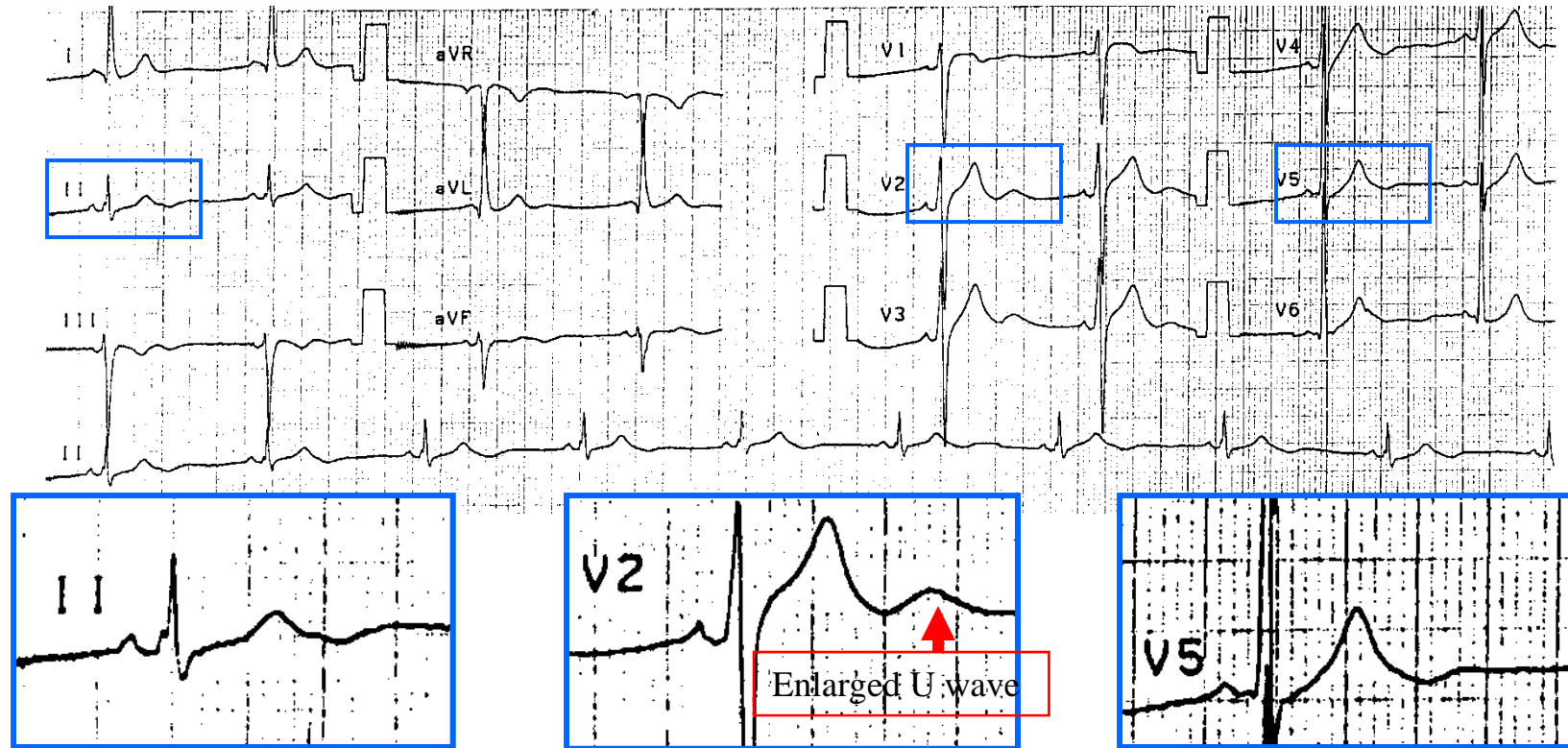
## ECG manifestation in patients with LQT6



A 41 y.o. female *MIRP1* mutation carrier with a borderline QT interval

# “LQT7”— ECG characteristics in patients with Andersen-Tawil syndrome

M, 50 y.o., N216H mutation carrier



QTc is normal (406 ms), but QUc is markedly prolonged (687 ms)  
with increased U wave amplitude (0.15 mV) and duration (240 ms)

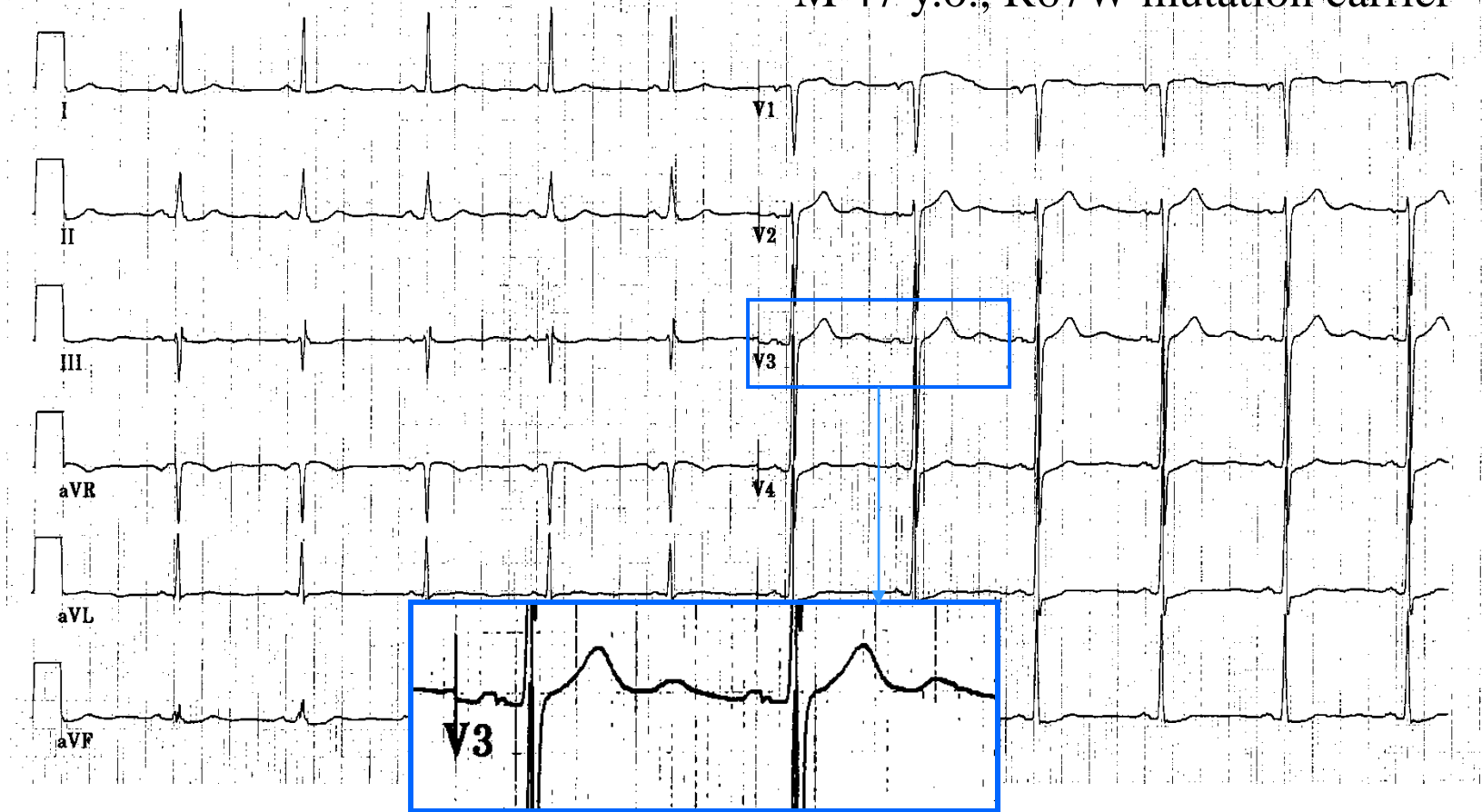
(Zhang, et al . Circulation 2005;111:2720-2726)



This ECG example is from a gene carrier. Given a closer look, we see a late T wave component in lead II, a slow T wave termination in V2 and V5 with enlarged U waves.

## “LQT7”— ECG characteristics in patients with Andersen-Tawil syndrome

M 47 y.o., R67W mutation carrier



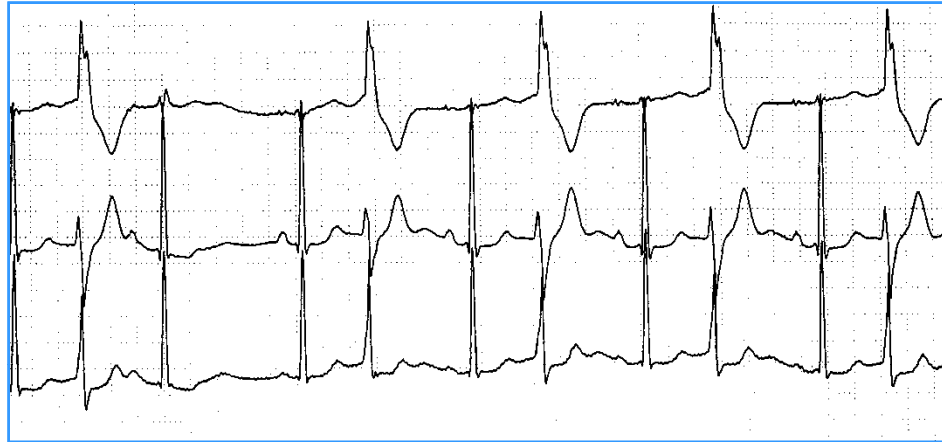
Enlarged U wave in V2-3 with a wide T-U junction or T-U separation  
QTc max 420 ms is normal but QUc 689 ms is markedly prolonged.

(Zhang, et al . Circulation 2005;111:2720-2726)

Terminal T wave abnormality is also observed in this patient with a different mutation. Prominent U wave is also evident. The T-U waves are pretty much separated in some of the leads. Compared to normals, KCNJ2 mutation carriers have a longer Tpeak to Upeak interval.

# ECG characteristics in patients with Andersen-Tawil syndrome

F, 19 y.o.  
G300V  
carrier



Frequent  
PVCs  
originating  
from LV

F, 11 y.o.  
R67W  
carrier



Bi-directional VT  
originating from LV

Frequent PVCs in bigeminy, and non-sustained VT are common in this entity.



## ECG characteristics in patients with Andersen-Tawil syndrome

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### Accuracy of genotype prediction by T-U wave patterns

<b>Sensitivity</b>	<b>Specificity</b>	<b>PPV</b>	<b>NPV</b>	<b>OPV</b>
<b>0.97</b>	<b>0.81</b>	<b>0.88</b>	<b>0.94</b>	<b>0.91</b>

Although the average QTc is within the upper normal limit, the majority of patients with type-1 Anderson-Tawil syndrome present with characteristic T-U morphology changes. Their *KCNJ2* genotype, therefore, can be predicted by typical ECG patterns.

(Zhang, et al . Circulation 2005;111:2720-2726)

Characteristic T-U wave patterns were present in 91% of *KCNJ2* gene mutation carriers, in whom an enlarged U wave is predominant in 73%. Using the T-U wave patterns, we successfully predicted the *KCNJ2* genotype in a random ECG mixture of 57 ATS1, 61 unaffected family members and 29 ATS without *KCNJ2* mutation subjects.