Long QT-3 and Flecainide

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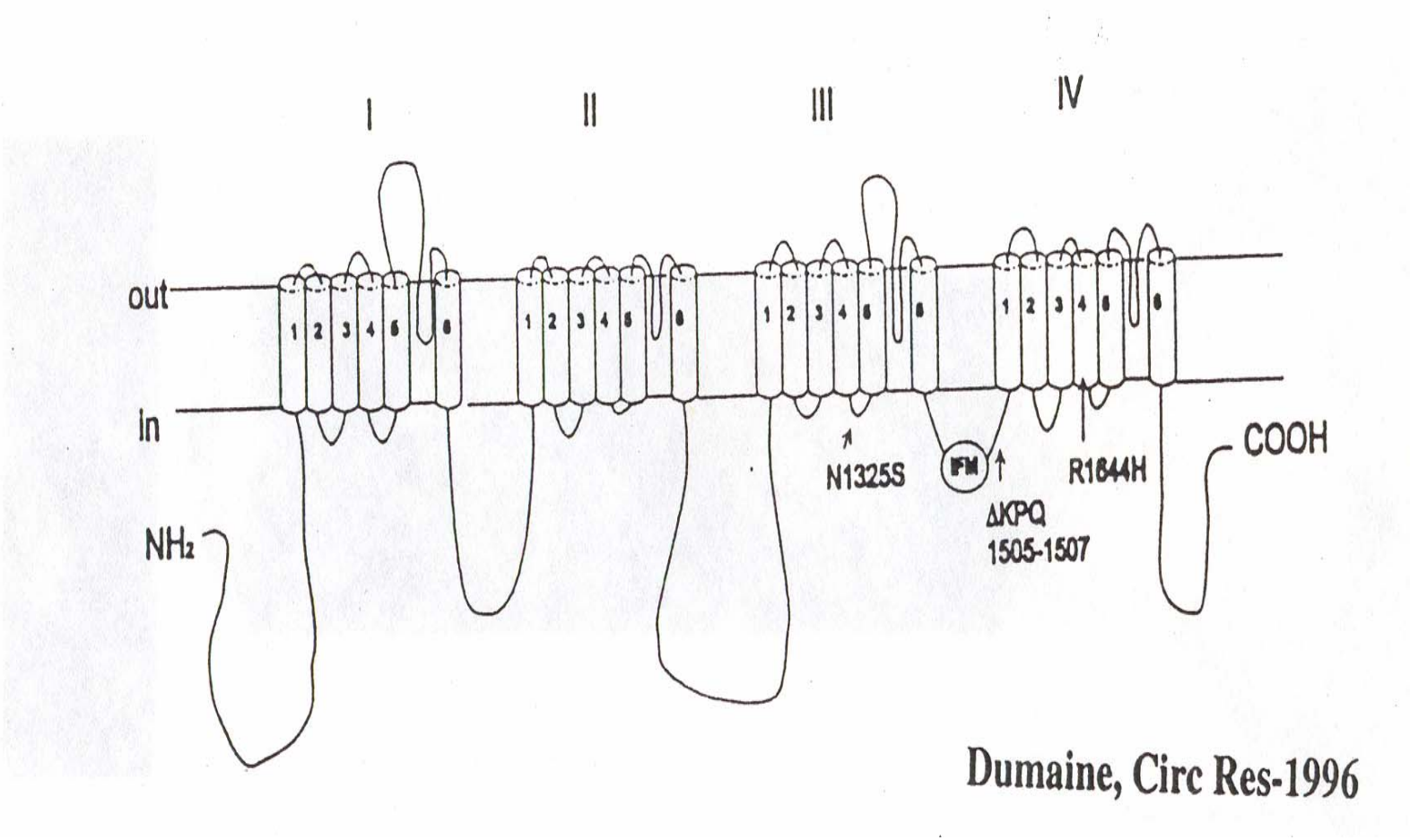
The Long QT syndrome is a genetic channelopathy with potentially life-threatening implications. Recent genetic and expression studies have helped us define a spectrum of genetic defects we now classify as the Long QT syndrome. This presentation will delineate the findings in five patients with a specific genotype of the Long QT syndrome, the ΔKPQ deletion of the SCN5A sodium channel gene. This abnormality is classified as the Long QT or LQT3 syndrome. Following a surprising discovery of QT shortening in one patient, the effect of the antiarrhythmic agent, flecainide, on the duration of the QT interval and the morphology of the T wave was systematically evaluated.

SCN-5A sodium channel

To better understand the potential role of flecainide in the long QT syndrome, I will review some key developments in our understanding of this condition.

The following slide depicts the SCH5A sodium channel as delineated in the work of Dumaine and colleagues. This channel defect is located on Chromosome 3 and is a deletion mutation of residues 1505-1507 (the ΔKPQ segment).

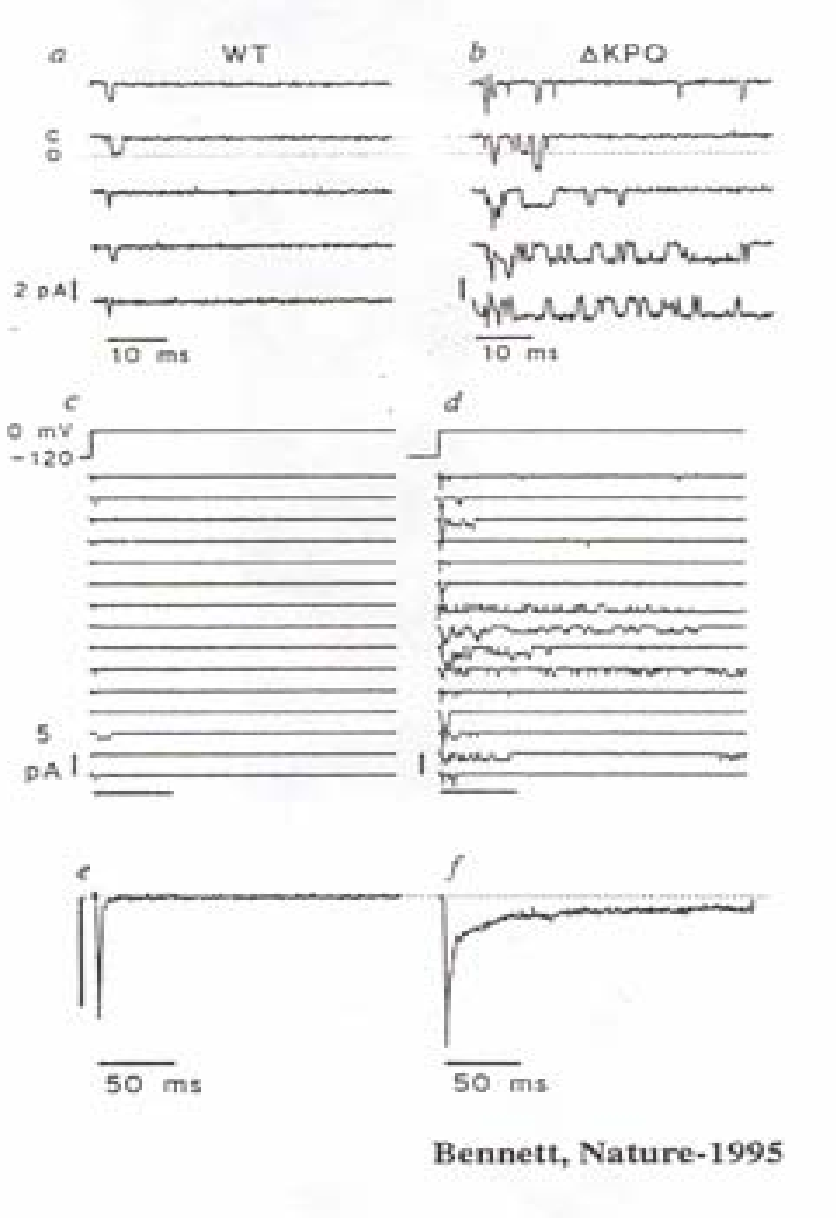
Genetics Studies in LQT3



Patch clamping studies

Using expressed human heart sodium channels; patch clamp studies by Bennett et al demonstrated the differences in sodium channel conduction between normal or (wild type) and channels with the ΔKPQ deletion. Note the increased number of duration of channel openings in the expressed ΔKPQ deletion experiment. As shown in e) and f), the net effect of the ΔKPQ deletion is an increased and prolonged inward sodium current which would be expressed on the surface electrocardiogram as a prolonged QT interval.

Patch Clamp Studies



Bennett, Nature-1995

Flecainide

Flecainide is an oral antiarrhythmic agent approved for use in atrial fibrillation and paroxysmal supraventricular tachycardias. It is also known to have profound effects on PVCs.

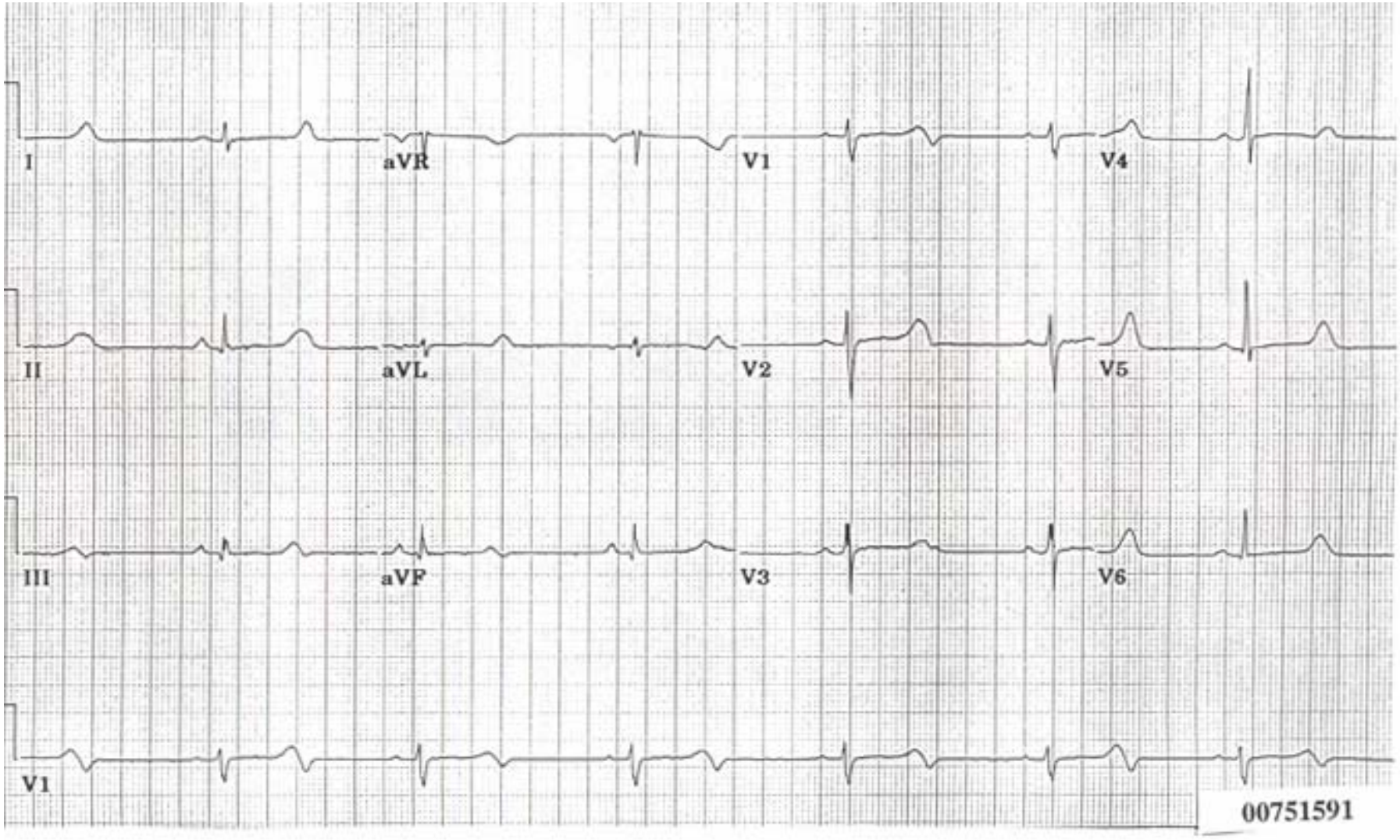
Studies by Anno and Hondeghem demonstrated that flecainide has a high affinity for, and persistent binding with the activated (open) sodium channel. It fits into the Vaughn Williams classification scheme as a Class 1C agent.

Baseline ECG

Our initial patient presented with syncope and torsades des pointes. He received and ICD and remained on beta blockers. Two years after his initial presentation he developed symptomatic palpitations. To our surprise he had paroxysmal atrial fibrillation.

His baseline electrocardiogram from 1997 is shown in the next slide. Note the marked sinus bradycardia and the profound QT-interval prolongation especially the prolonged ST segment and the large T wave. These ECG changes are typically found in the LQT3 patients

Electrocardiogram in LQT3

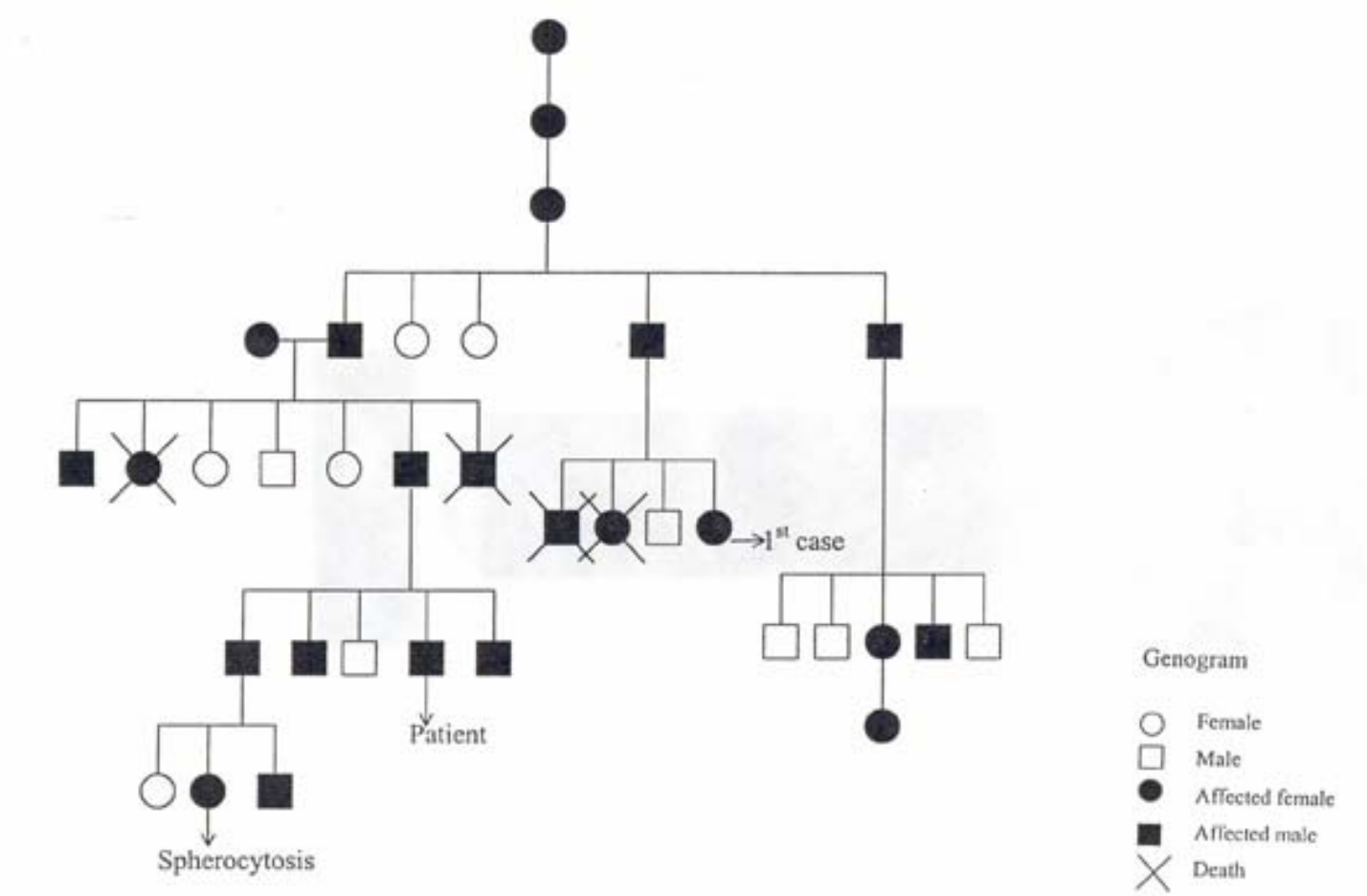


Family Tree

Communication with Dr. Arthur Moss of the University of Rochester Medical Center was established and revealed that this patient was part of the International Long QT registry and had already been genotyped.

Genotyping revealed this patient and affected family members (noted in black on this slide) as carrying the ΔKPQ deletion of the SCN5A sodium channel.

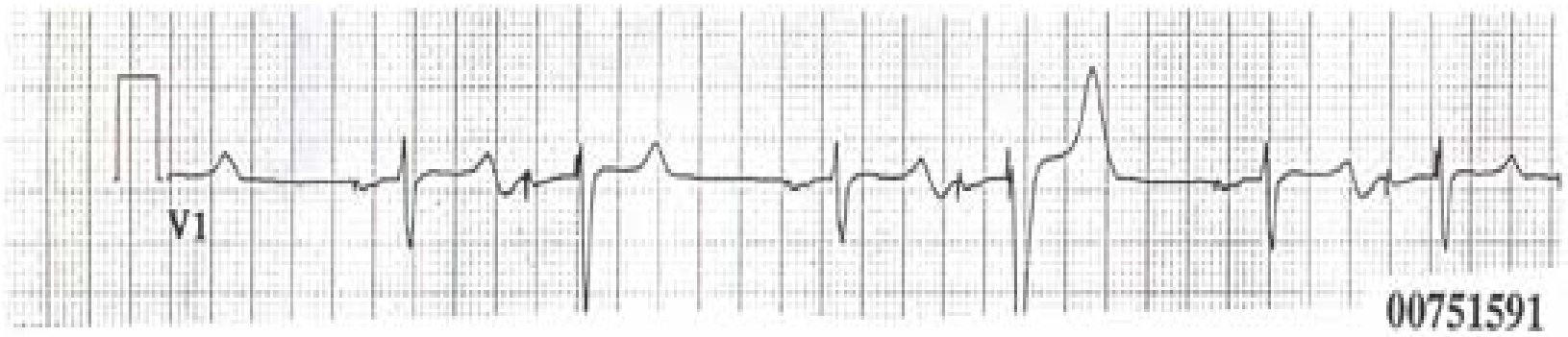
Family History-LQT3



ECG Rhythm Strip-Lead V_1

The following ECG rhythm strip was obtained at the time of his admission for treatment of his atrial fibrillation. He is in an atrial-paced rhythm with his dual chamber ICD was programmed to 70 beats/minute. Note, however, the rate is less than 70 because of over-sensing of the large amplitude T waves.

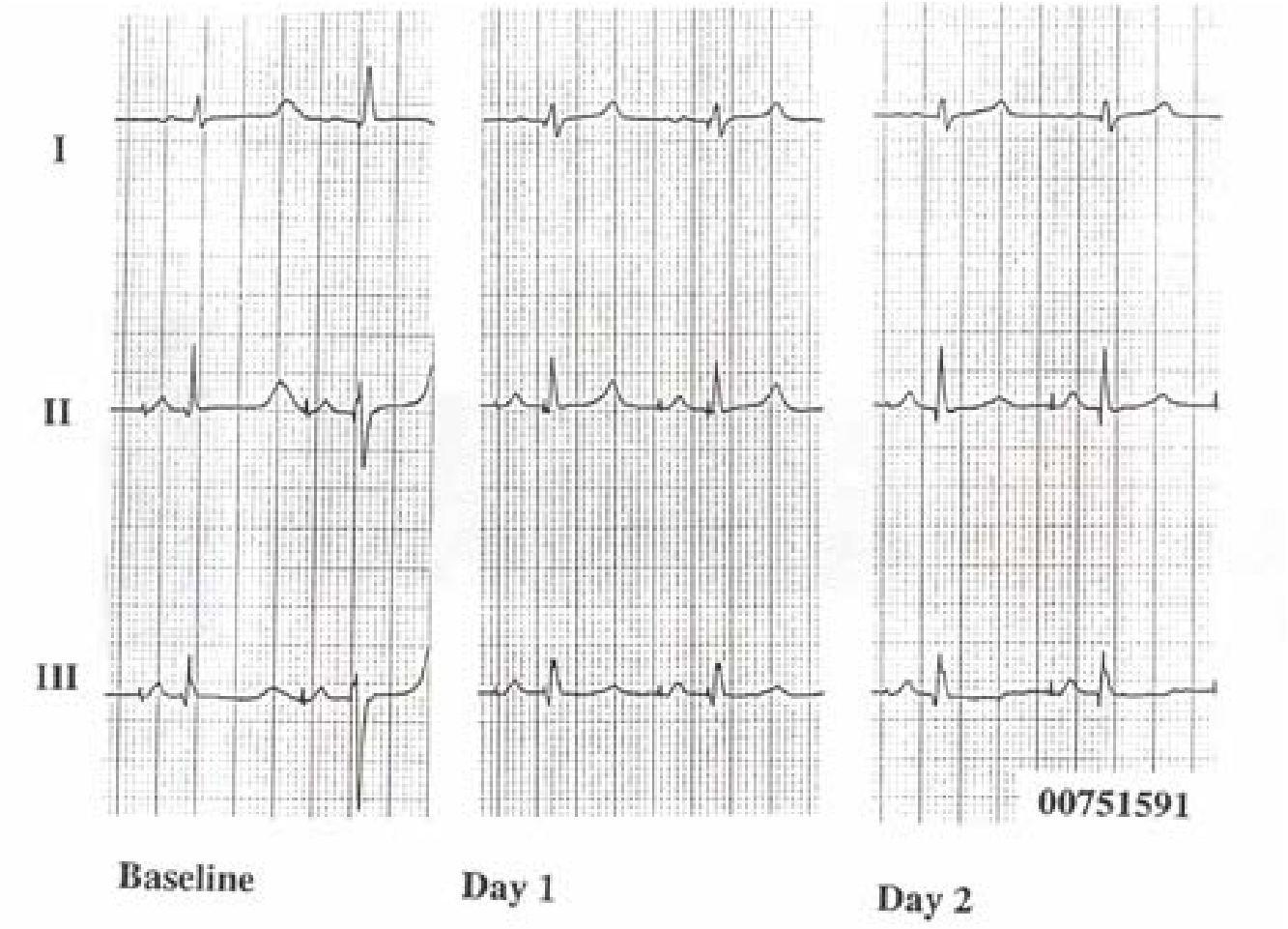
Electrocardiogram in LQT3
T-wave over-sensing



Days 1-3

This next slide demonstrates leads I, II and III from electrocardiograms obtained at baseline as well as tracings obtained on day one after two doses of 50 mgs of flecainide and day two when the flecainide was increased to 100 mg twice daily. Note the dramatic reduction in QT interval duration. Further note the reduction of T wave amplitude and near normalization of the ST-segment by day 2. A pacing spike is noted after the onset of QRS complex.

Flecainide Effect on the Electroccardiogram in LQT3



ECG series patient 2

To discover whether the effects noted in this patient were secondary to flecainide and could apply to other patients with the ΔKPQ deletion, a systematic evaluation of four additional carriers was undertaken. All are males. The patient's brother, his two-year old nephew, and two additional patients followed by Dr. Moss were enrolled in this study.

Sequential tracings from patient 2 are displayed on the next slide. The tracings were obtained at baseline and days 1 and 2 following flecainide therapy at 50, then 100 mg twice daily. The patient was on naldolol 20 mg/day and had a dual chamber pacemaker inserted previously. The pacemaker was programmed to 70 beats/minutes. The baseline QTc was 521 milliseconds. On day 1 the QTc had shortened to 479 milliseconds and on day 2 further shortened to 440 milliseconds.

Flecainide Effect on the Electrocardiogram in LQT3

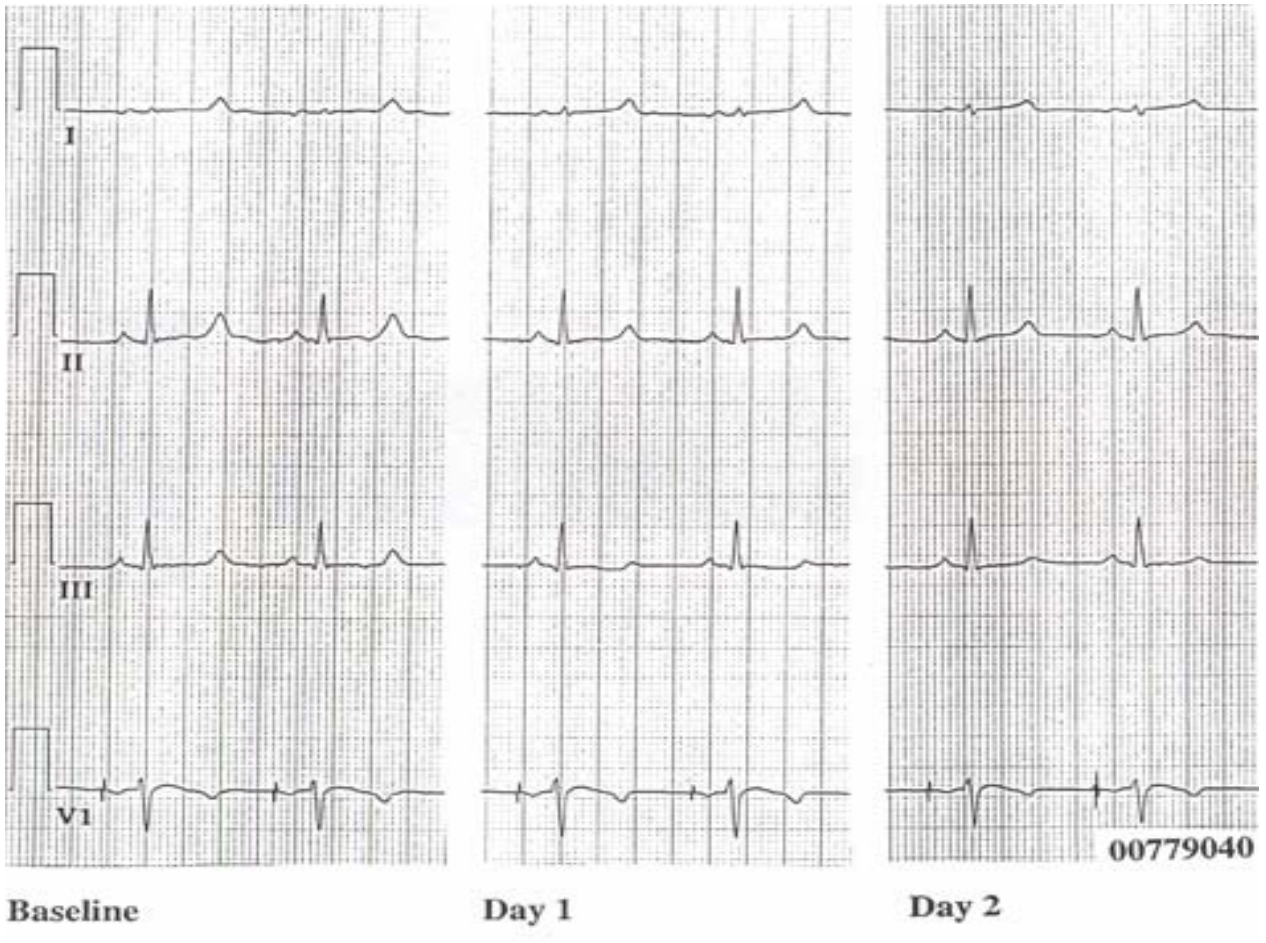


Table Flecainide in 5 patients

The next slide demonstrates the results from all five subjects. In all five patients the QTc shortened by at least 60 milliseconds and ranged from 60 to 150 milliseconds with flecainide levels at the low end of the usually therapeutic range is .2 to 1.0 mg/L. No patient had side effects or proarrhythmia from the flecainide.

Flecainide Effect on the Electrocardiogram in LQT3

Patient	1	2	3	4	5
Age, years	17	19	64	31	2
QT_c-baseline(sec)	.59	.52	.54	.53	.52
QT_c-flecainide(sec)	.44	.44	.48	.45	.45
Flecainide Level (mg/L)	.3	.3	.4	.2	N/A

Flecainide versus Mexiletine

Patients 3 and 4 had previously received mexiletine. This table demonstrates the dose responses for flecainide and mexiletine in these patients. In patient 3, mexiletine produced a reduction of 50 milliseconds while flexainide reduced the QTc by 60 milliseconds. In patient 4, mexiletine again shortened the QTc by 50 milliseconds while flecainide shortened it by 80 milliseconds. While both sodium channel-blocking agents demonstrated shortening of the QTc, there was slightly greater effect with flecainide.

Conclusion

In conclusion, flecainide consistently shortened the QT interval in the five subjects studied who had the ΔKPQ deletion of the SCN5A sodium channel, Further, flecainide appears to reduce the duration of the ST-segment and the amplitude of the T-wave.

In the two patients who received both mexiletine and flecainide, flecainide appeared to be equal to or better than mexiletine.

While this small pilot study needs confirmation by larger trails to evaluate the safety and efficacy of flecainide, it indicated that flecainide may be a promising therapeutic agent in patients with the SCN5A:ΔKPQ mutation.