Predicting Drug-HERG Interactions

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DRUGS and HERG

- Congenital LQTS may be due to mutations in at least 8 possible genes coding for ion channels and related proteins.

- One of these (~15-20% of cases), is the HERG potassium channel

- Acquired LQTS (due to drugs), is almost always due to drug blockade of the HERG channel

Why do so many Drugs bind to HERG?

- The HERG channel is particularly adept at binding drugs that vary widely in their structure and application, including: conventional antiarrhythmics, antibiotics, antihistamines and antipsychotics

- Finding drugs that do not inhibit HERG has become a major hurdle for drug development in every clinical discipline

Drug Binding Sites

- Recent studies suggest that there may be multiple drug binding sites on HERG

- Binding occurs within the channel pore.

- Systematic mutagenesis of the pore-lining residues has led to the identification of three residues at the base of the selectivity filter (Thr 623, Ser 624, and Val 625) and two aromatic residues (Tyr 652 and Phe 656) in the S6 domain that are important in this respect.

- Different drugs are likely to bind to different combinations of these residues rather than to one particular arrangement but the precise combination of residues that promote binding has not been identified for all drugs that prolong the QT interval.
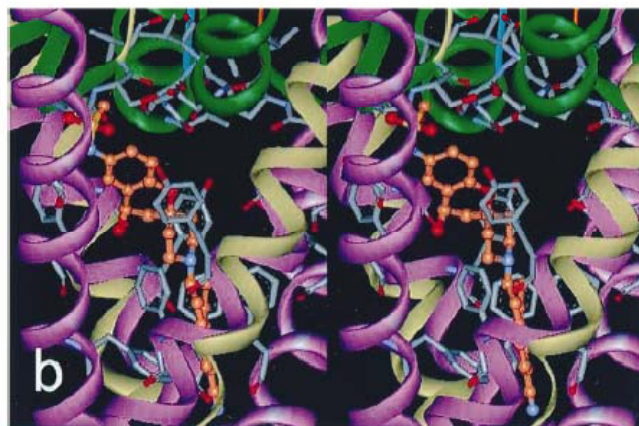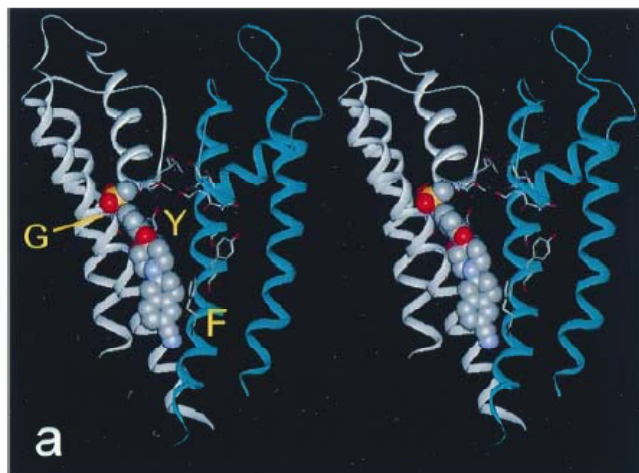
Fig. 3. Docking of a MK-499 molecule within the cavity of the homology model of the HERG K+ channel. (a) Stereoview of the S5-S6 domains of two HERG subunits with docked molecule of MK-499 (shown as a space-filling
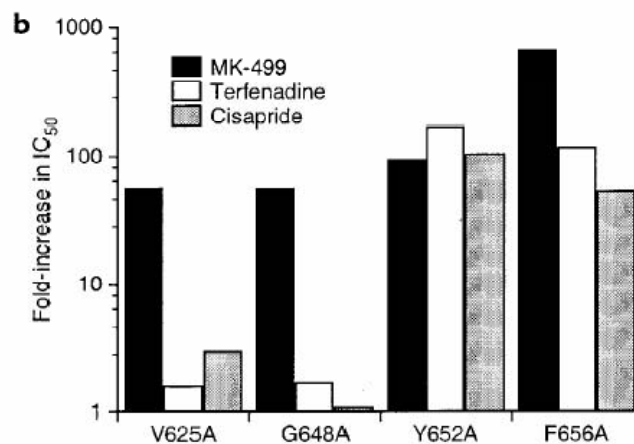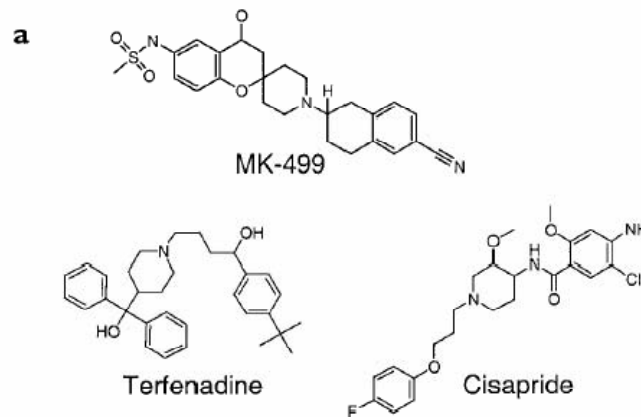
Fig. 4. Mutations of HERG that affect potency for block of HERG channels by MK-499, cisapride, and terfenadine. (a) Structures of the three compounds. (b) -Fold increase in IC$_{50}$ determined for each mutant channel plotted on a logarithmic scale. The IC$_{50}$ was 0.134 ± 0.019 μM for terfenadine ($n = 5$) and

A structural basis for drug-induced long QT syndrome

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Molecular Determinants of hERG Channel Block

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Predicting Drug Binding to hERG
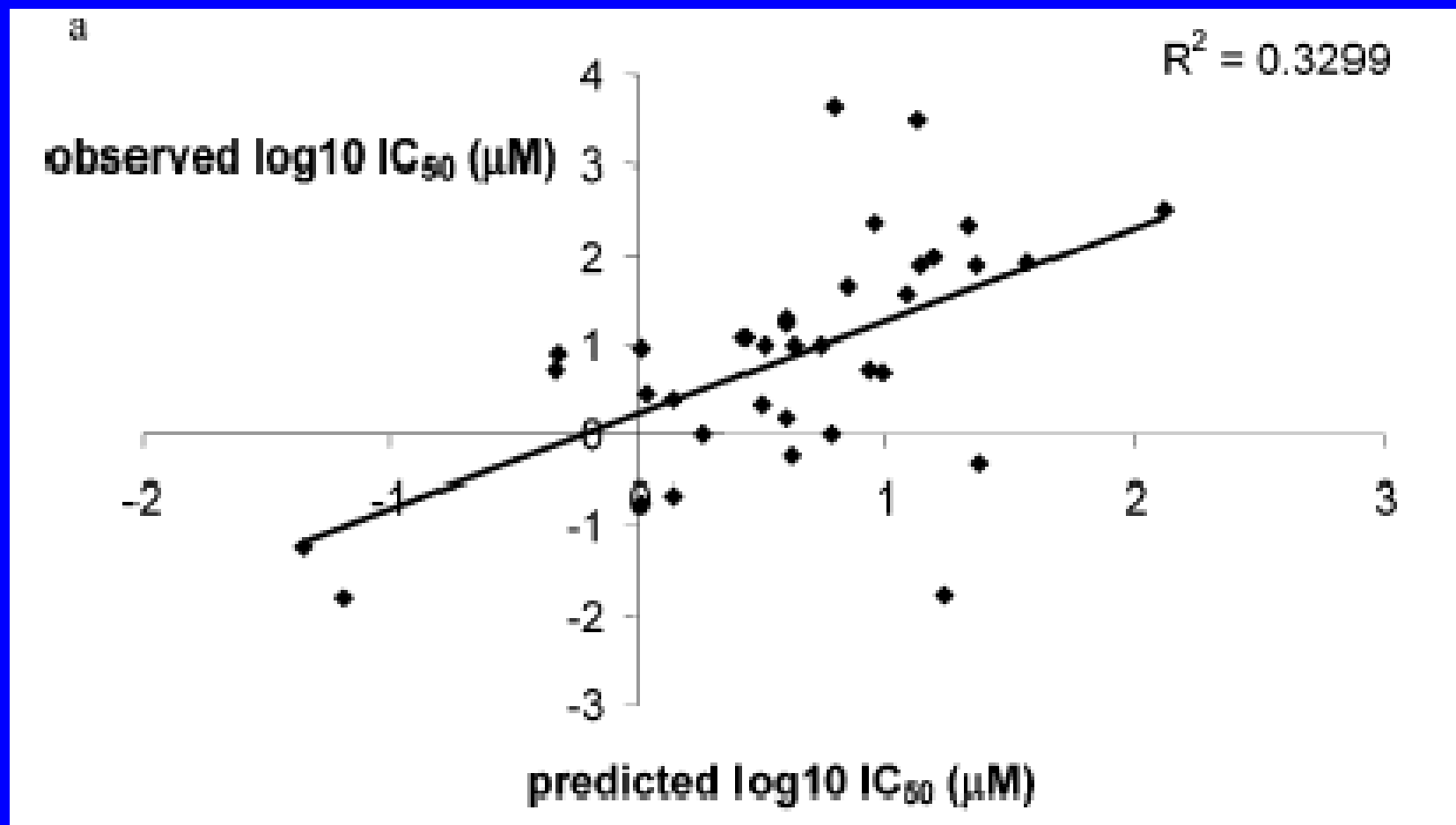
- **Insights for Human Ether-a-Go-Go-Related Gene Potassium Channel Inhibition Using Recursive Partitioning and Kohonen and Sammon Mapping Techniques**

Sean Ekins,*,†,#,‡ Konstantin V. Balakin,§,‡ Nikolay Savchuk,§ and Yan Ivanenkov§

ACT LLC, 601 Runnymede AVenue, Jenkintown, PennsyNania 19046, Department of Pharmaceutical Sciences, UniVersity of Maryland,

20 Penn Street, Baltimore, Maryland 21201, and Chemical DiVersity, Inc., 11558 Sorrento Valley Road, San Diego, California 92121

- The human ether-a-go-go related gene (hERG) can be inhibited by marketed drugs, and this inhibition may lead to QT prolongation and possibly fatal cardiac arrhythmia. We have collated literature data for 99 diverse hERG inhibitors to generate Kohonen maps, Sammon maps, and recursive partitioning models. Our aim was to investigate whether these computational models could be used either individually or together in a consensus approach to predict the binding of a prospectively selected test set of 35 diverse molecules and at the same time to offer further insights into hERG inhibition. The recursive partitioning model provided a quantitative prediction, which was markedly improved when Tanimoto similarity was included as a filter to remove molecules from the test set that were too dissimilar to the training set ($r2$) 0.83, Spearman rho) 0.75, p) 0.0003 for the 18 remaining molecules, >0.77 similarity). This model was also used to screenand prioritize a database of drugs, recovering several hERG inhibitors not used in model building.

Themapping approaches used molecular descriptors required for hERG inhibition that were not reported previouslyand in particular highlighted the importance of molecular shape. The Sammon map model provided the bestqualitative classification of the test set (95% correct) compared with the Kohonen map model (81% correct),and this result was also superior to the consensus approach. This study illustrates that patch clamping datafrom various literature sources can be combined to generate valid models of hERG inhibition for prospectivepredictions

<u>Lessons for Clinicians</u>

- Given the difficulty in predicting accurately what drugs will block HERG, what should the clinician bear in mind when treating patients in order to minimise the likelihood of devastating consequences?

"Risk Factors" for aLQTS

- ## Risks due to particular drugs

  -Many agents (cardiac and non-cardiac)

  -Well covered in resources such as www.torsades.org

  -Now pre-empted in drug development

- ## Risks due to patient

  -Not so well recognised

  -Provides easy method of harm-minimisation

  -Particularly relevant to use of high-risk drugs, BUT most drugs are not high-risk, and most events are probably due to medium-low risk drugs given to "higher-risk patients"

Higher-Risk Patients

- Bradycardia (spontaneous or drug-related)
- Polypharmacy
- Chronically ill (incl Mentally ill)
- Age
- ↓Renal function
- Female gender
- Those with Minor ↑QT at baseline
- Those with pre-existing Heart Disease
- *Formes frustes* of cLQTS
- Combinations

Higher-Risk Patients

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<u>AGE</u>

- Subjects >65 years are three times more likely to have ↑QTc (95% CI 1.1-8.3)- Reilly et al Lancet 2000, (similar observations in Rotterdam Study)

- Once again this is clearly likely to be due to a mixture of subclinical genetic reductions in repolarisation reserve added to various acquired causes

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QT INTERVAL - SEX DIFFERENCES

- Two-thirds of reported cases of drug-induced torsades occur in women

- QT_c in male & female infants and children are equal.

- QT_c in males shortens by about 20ms at about the time of puberty and this difference persists for life.

- Males and females with LQTS genotypes have longer QT_c than males and females without, but:

- Within both the genotypic LQTS group and normals, male QT_c is approx 20ms shorter than female QT_c.

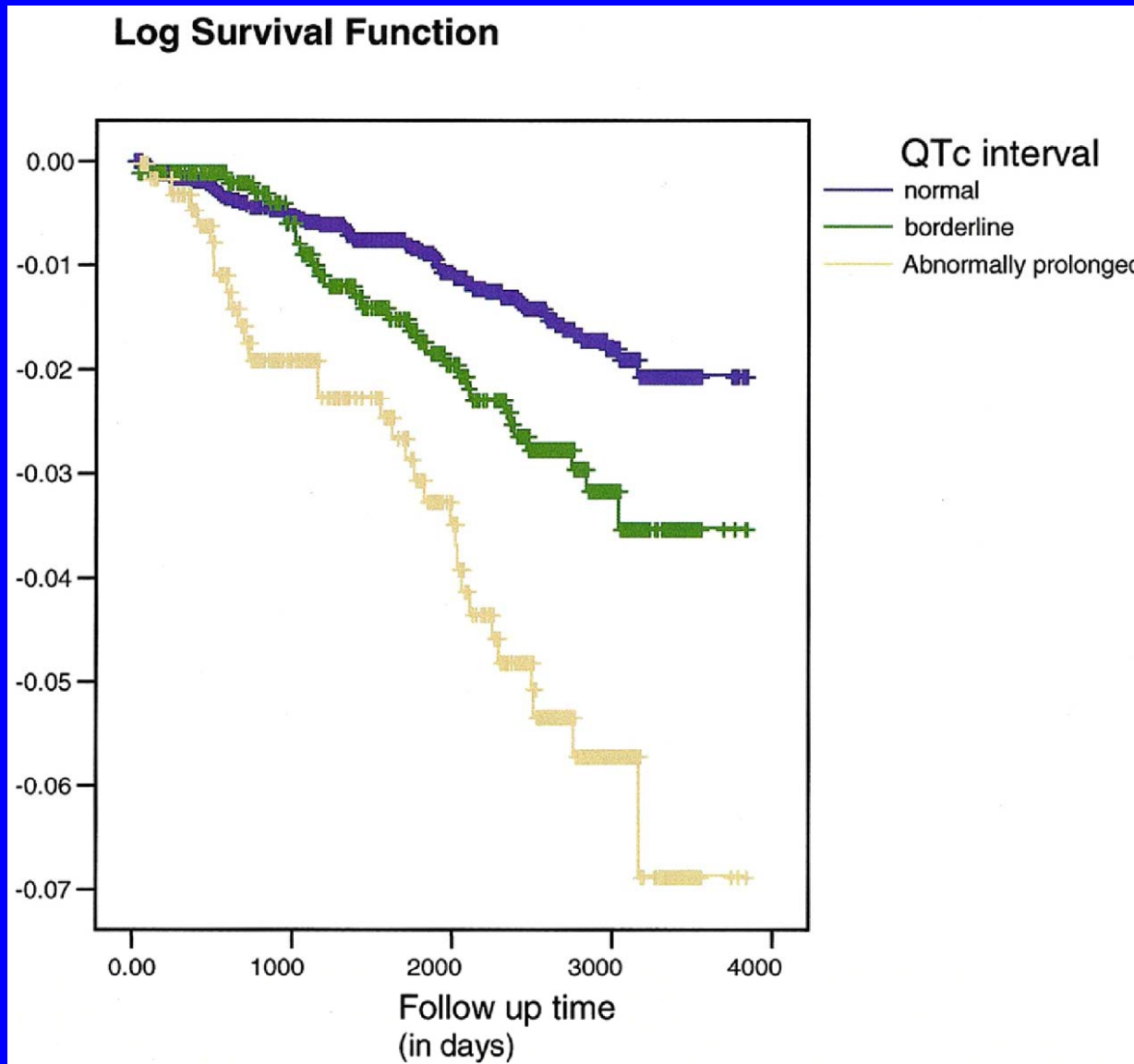- These differences are more prominent at HR $\leq$ 60.

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Subtle Prolongation of QT

- Rotterdam Study looked at 125 SCDs in 8000 subjects >55, followed for 6.7 yrs (Straus et al, JACC 47:362;2006)

- QTc increased with age and with comorbidities (HT,DM,CHD,CCF)

- After "correction" for these, association between QT and SCD remained

QTc versus Survival free of SCD

Log Survival Function

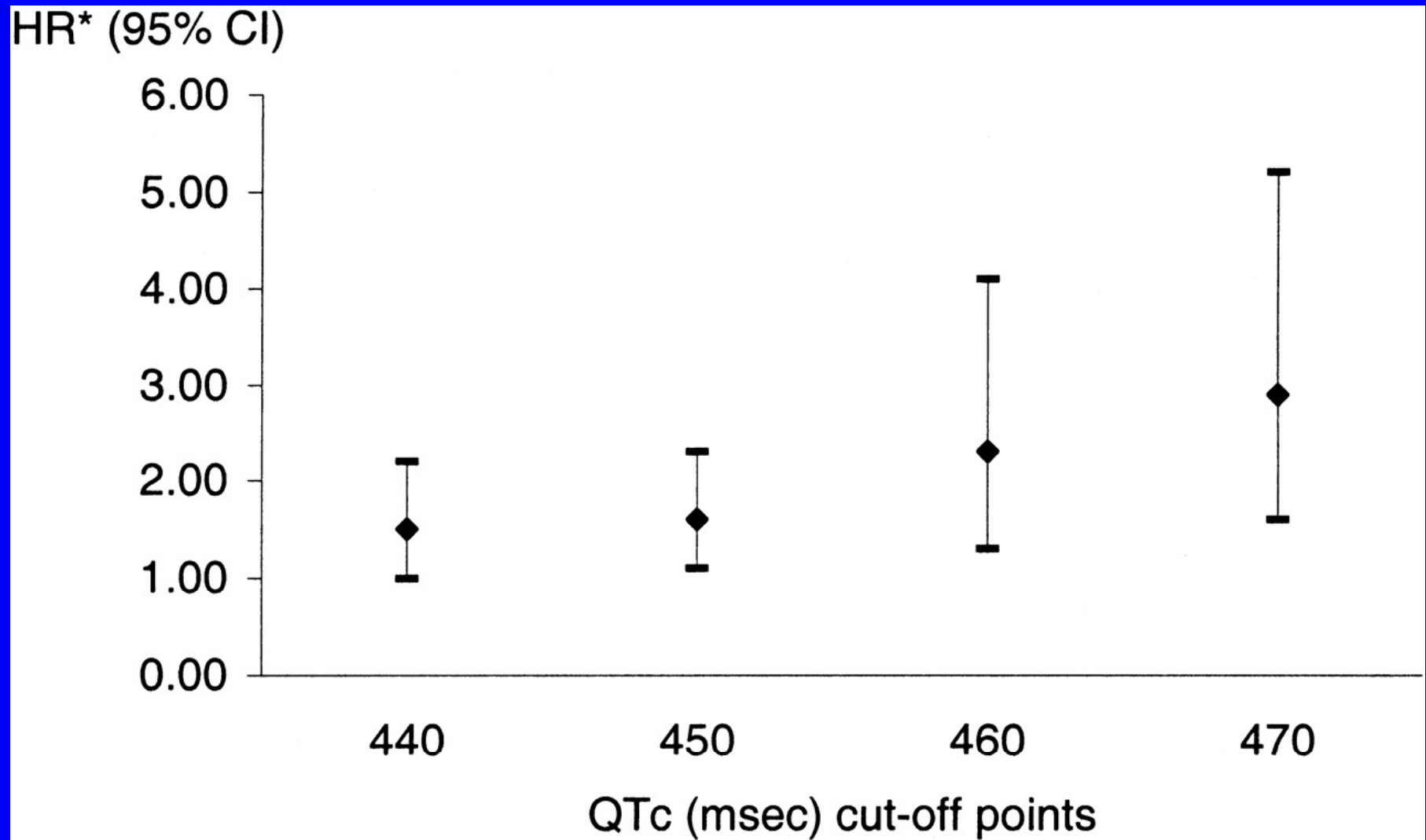QTc interval
- normal
- borderline
- Abnormally prolonged

Follow up time (in days)

Borderline=
-M 431-450
-F 451-470

Straus et al: JACC 47;362;2006

Prolonged QTc Interval and Risk of Sudden Cardiac Death in a Population of Older Adults

Sabine M.J.M. Straus, MD, PhD*, , , Jan A. Kors, PhD , Marie L. De Bruin, PhD , Cornelis S. van der Hooft, MD ,||, Albert Hofman, MD, PhD*, Jan Heeringa, MD*, Jaap W. Deckers, MD, PhD*, J. Herre Kingma, MD, PhD||,¶, Miriam C.J.M. Sturkenboom, PhD*, , Bruno H. Ch. Stricker, PhD*,||,* and Jacqueline C.M. Witteman, PhD*

Kaplan-Meier log survival plot of heart rate corrected QT (QTc) interval prolongation and sudden cardiac death.

Risk (HR) of SCD vs QTc

(Straus et al JACC 2006)

Risk of sudden cardiac death (SCD) at different heart rate corrected QT (QTc) interval cutoff points. *Adjusted for age, gender, body mass index, cholesterol/high-density lipoprotein ratio, smoking, hypertension, diabetes, myocardial infarction, and heart rate. CI = confidence interval; HR = hazard ratio.

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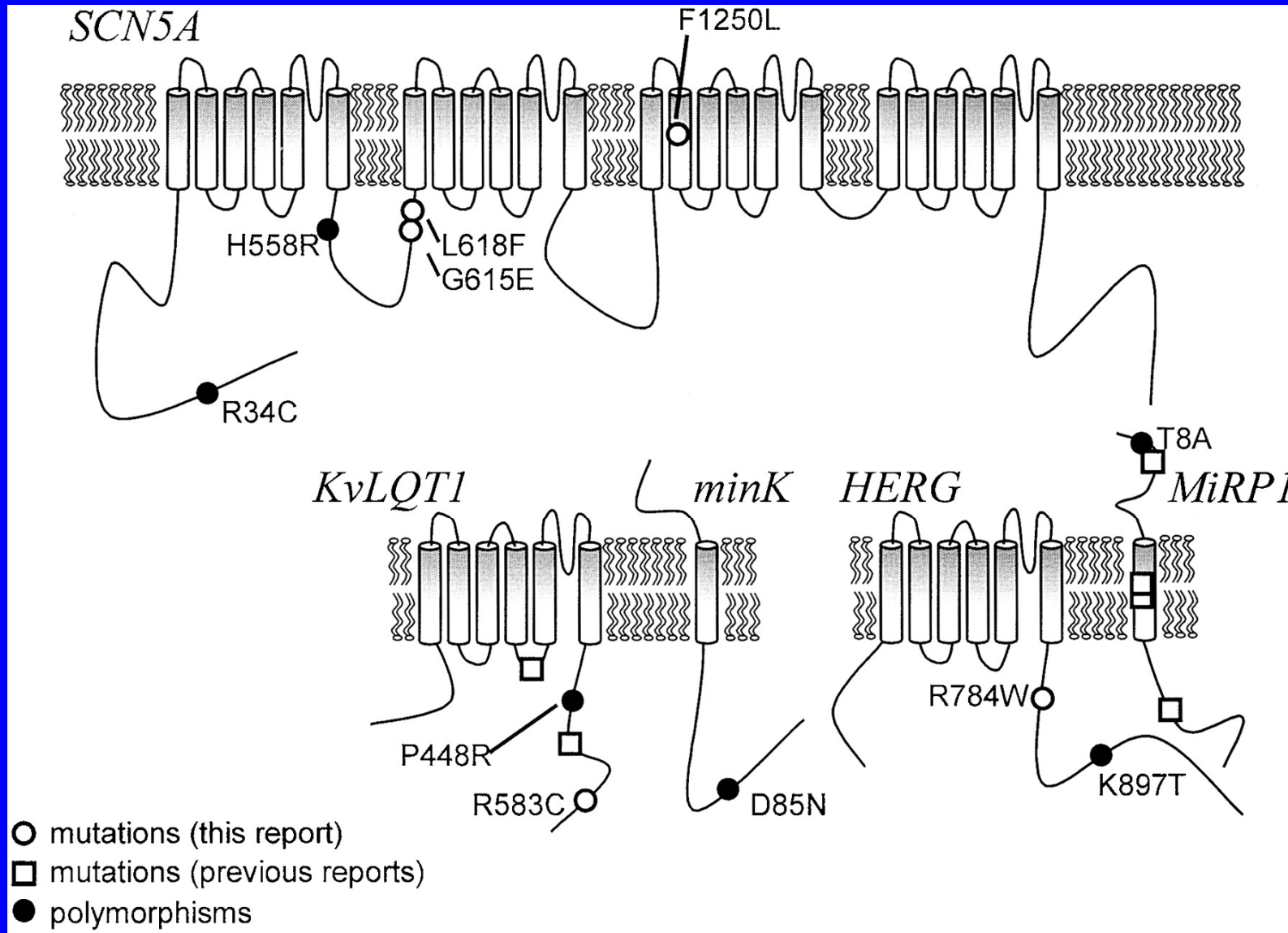- *Formes frustes* of cLQTS
- Combinations

Genomics vs Acquired Heart Disease?

- Rotterdam Study attempted to "correct" for the latter, but this sort of correction is always fraught

- Some almost certainly relates to undiscovered *formes frustes* of cLQTS

- It defies commonsense to argue against the notion that at least some of the hazard detected relates to subtle undetected heart disease (mild LVH etc) which can reduce "repolarisation reserve"

SNPs in Relevant Genes in aLQTS Patients

- "~10-15% of drug-associated aLQTS patients have DNA variants in the coding regions of genes associated with cLQTS"

- These are "predominantly in the genes encoding ancillary subunits"

Yang, Roden et al Circulation 105:1943;2002

SNPs Associated with aLQTS

Allelic Variants in Long-QT Disease Genes in Patients With Drug-Associated Torsades de Pointes

Ping Yang, PhD; Hideaki Kanki, MD; Benoit Drolet, PhD; Tao Yang, PhD; Jian Wei, MD PhD; Prakash C. Viswanathan, PhD; Stefan H. Hohnloser, MD; Wataru Shimizu, MD; Peter J. Schwartz, MD; Marshall Stanton, MD; Katherine T. Murray, MD; Kris Norris, RN; Alfred L. George, Jr, MD; Dan M. Roden, MD

Background— DNA variants appearing to predispose to drug-associated "acquired" long-QT syndrome (aLQTS) have been reported in congenital long-QT disease genes. However, the incidence of these genetic risk factors has not been systematically evaluated in a large set of patients with aLQTS. We have previously identified functionally important DNA variants in genes encoding K+ channel ancillary subunits in 11% of an aLQTS cohort.

Methods and Results— The coding regions of the genes encoding the pore-forming channel proteins KvLQT1, HERG, and SCN5A were screened in (1) the same aLQTS cohort (n=92) and (2) controls, drawn from patients tolerating QT-prolonging drugs (n=67) and cross sections of the Middle Tennessee (n=71) and US populations (n=90). The frequency of three common nonsynonymous coding region polymorphisms was no different between aLQTS and control subjects, as follows: 24% versus 19% for H558R (SCN5A), 3% versus 3% for R34C (SCN5A), and 14% versus 14% for K897T (HERG). Missense mutations (absent in controls) were identified in 5 of 92 patients. KvLQT1 and HERG mutations (one each) reduced K+ currents in vitro, consistent with the idea that they augment risk for aLQTS. However, three SCN5A variants did not alter INa, which argues that they played no role in the aLQTS phenotype.

Conclusions— DNA variants in the coding regions of congenital long-QT disease genes predisposing to aLQTS can be identified in 10% to 15% of affected subjects, predominantly in genes encoding ancillary subunits.

MiRP1 (KCNE2) and ACQUIRED LQTS

- MiRP1 speeds up deactivation of HERG currents and slightly decreases peak amplitude-both decrease integrated current flow

- Roden et al have found mutations/SNPs in this protein in 8-10% of patients with drug-induced aLQTS. This is well above expected frequency

Gene Variants and aLQTS

- May be "direct" or "indirect"
- Indirect variants reduce repol. reserve but do not prolong QT interval and do not alter drug binding. QT increases only when exposed to drugs
- Examples: A116V-MiRP1; Asian-specific G643S in KCNQ1 (11% in Japanese population); S1102Y in SCN5A-increased prevalence in people of West African origins

Gene Variants (cont.)

- Direct variants do not affect K current but increase sensitivity to drugs

Anantharam et al; JPET 307:831;2003
Sesti et al; PNAS 97:10613;2000

Gene variants and aLQTS

- 1.6% of Caucasian Americans carry T8A SNP in MiRP1. This is associated with enhanced sensitivity of sodium channel to sulfamethoxazole and hence with cases of arrhythmia associated with Bactrim

- 3% of African Americans carry Q9E in MiRP1 which is associated with clarithromycin-induced arrhythmias

Rescue of Phenotype by Coexisting Polymorphism

- Very recent report of common polymorphism (H558R), in SCN5A restoring normal trafficking of mutant (R282H), Nav 1.5 channels in HEK293 cells

- May explain some variability of expression/penetrance, incl some ethnic variability

- Needs to be confirmed in cardiomyocytes (as Priori notes in Editorial)

(Poelzing et al, Circulation 114:368;2006)