

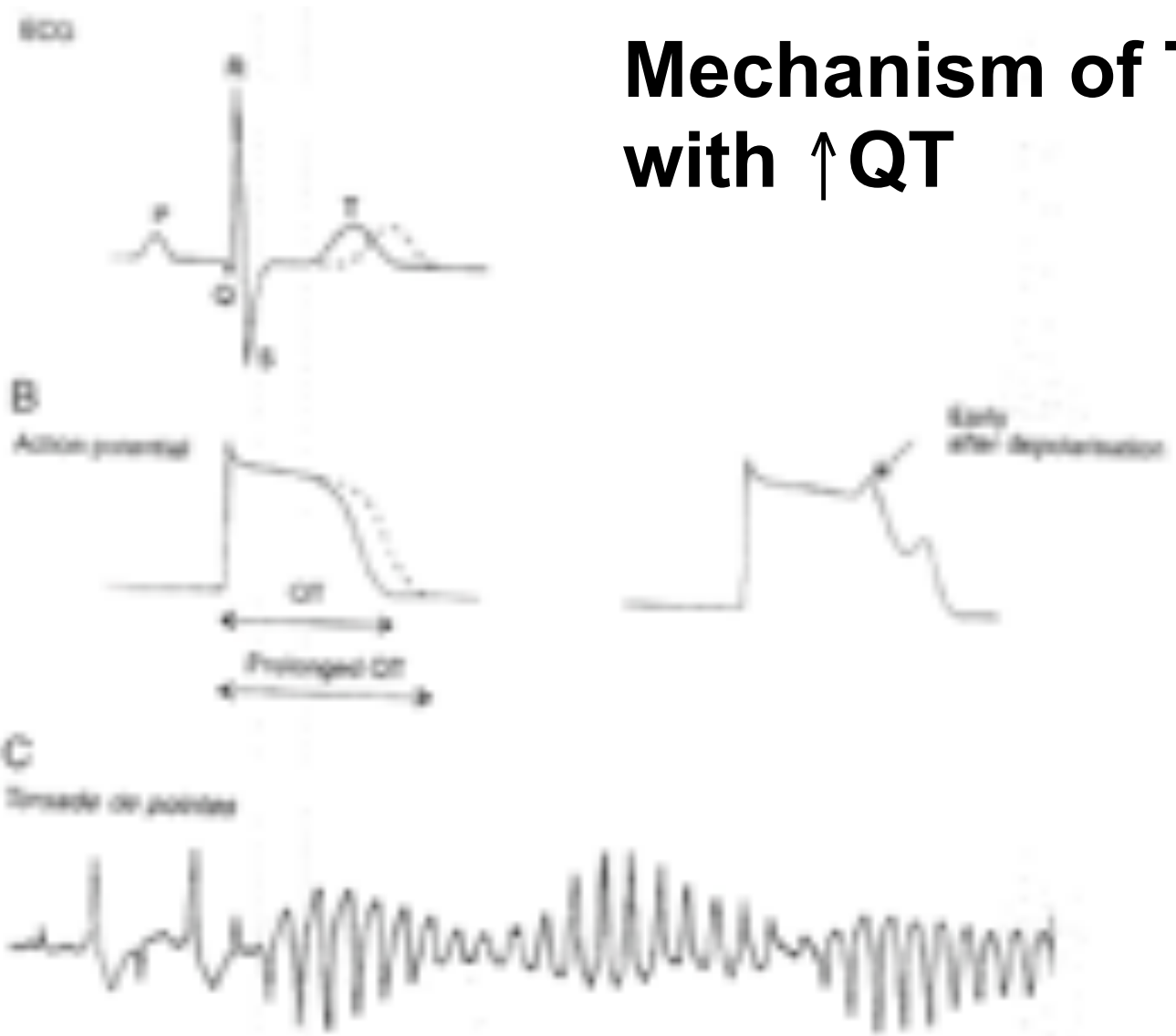
LQTS As A Paradigm for Drug-induced QT Prolongation

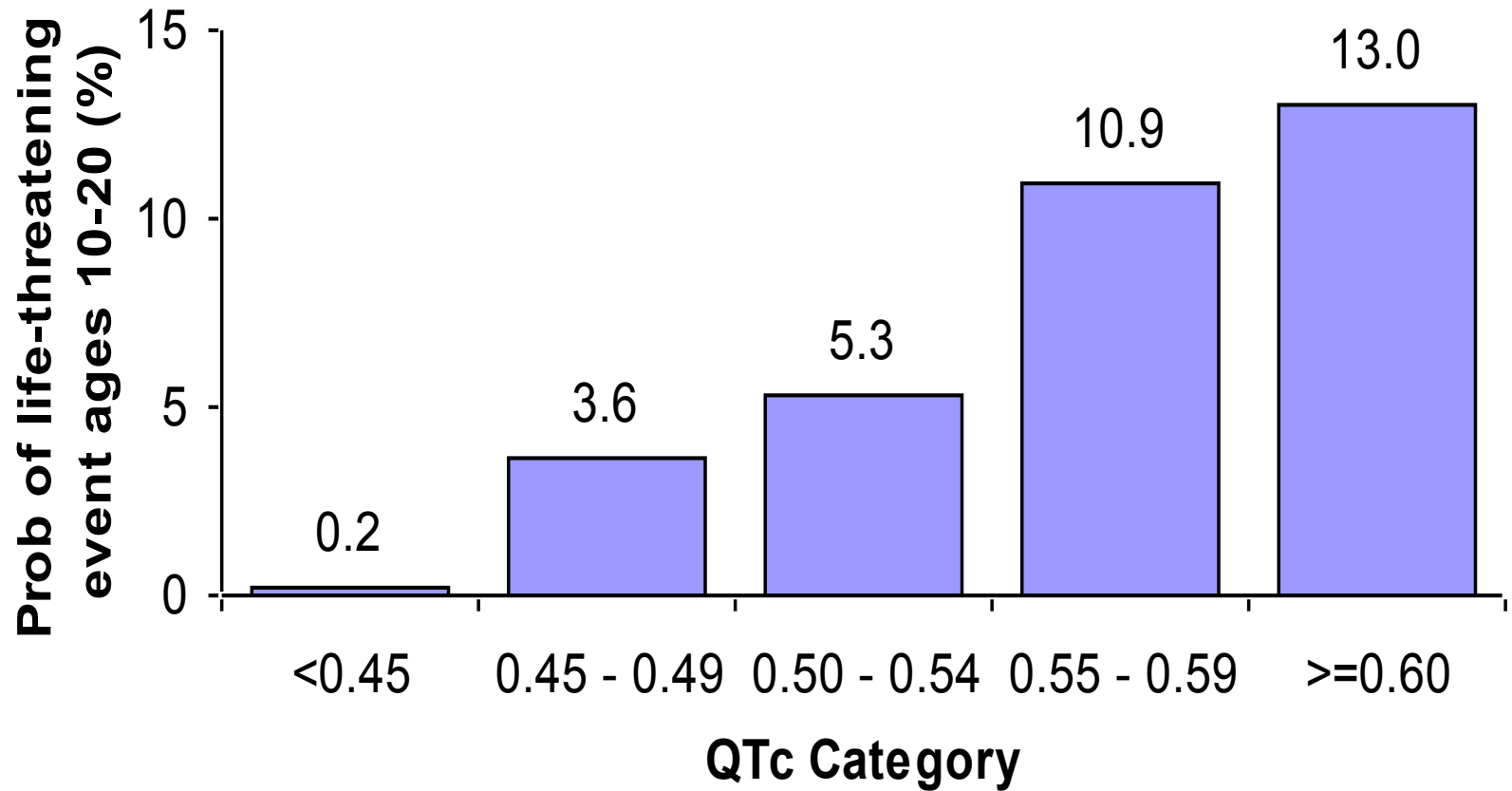
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CONFLICT OF INTEREST

NONE

Mechanism of TdP with \uparrow QT

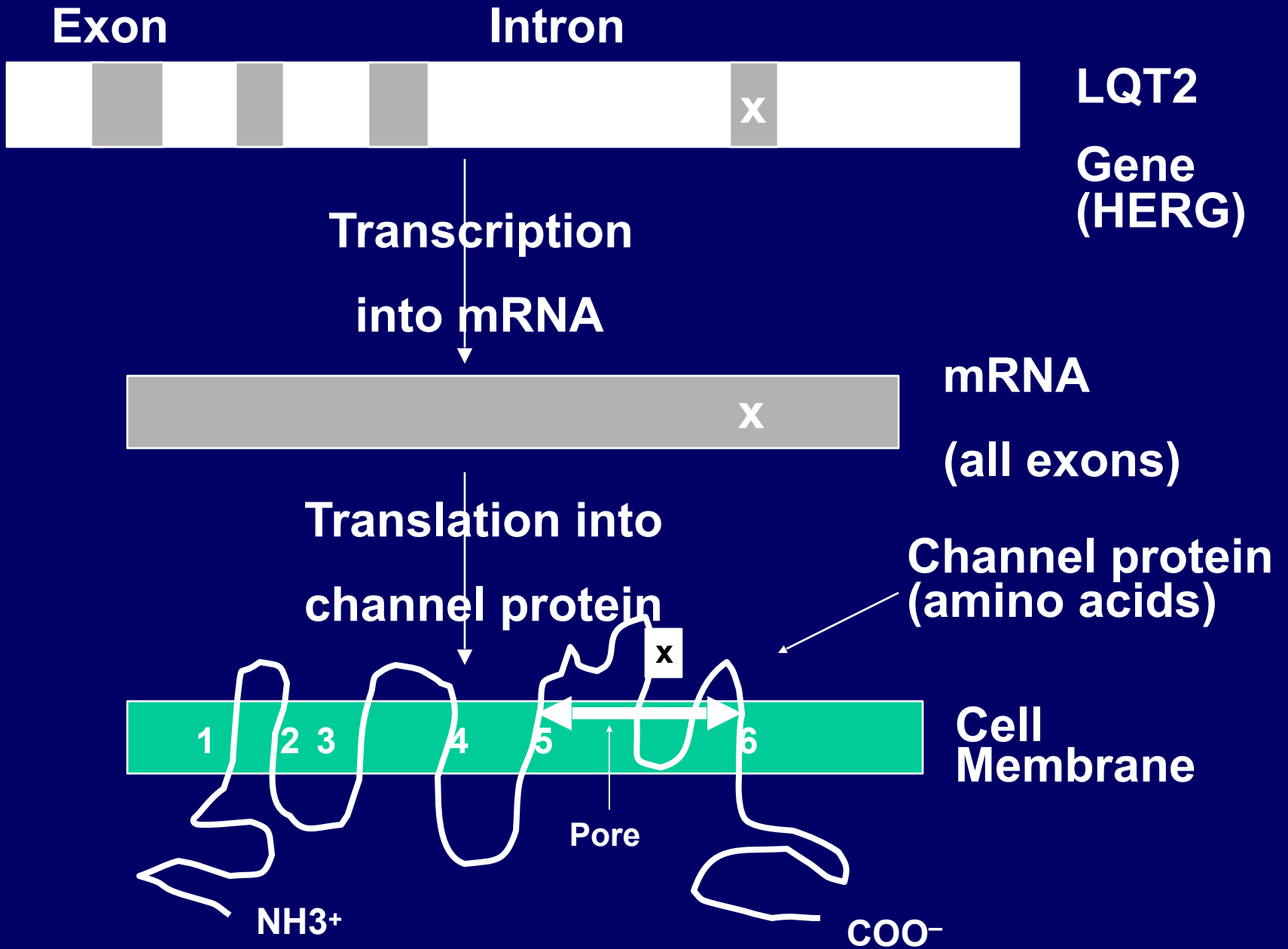


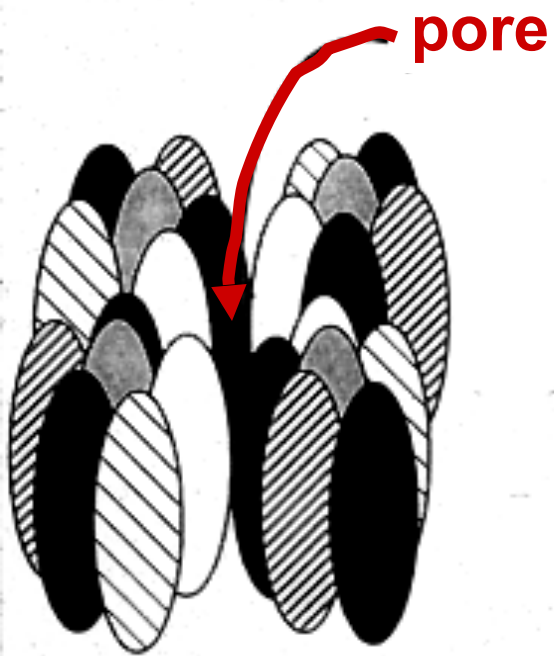
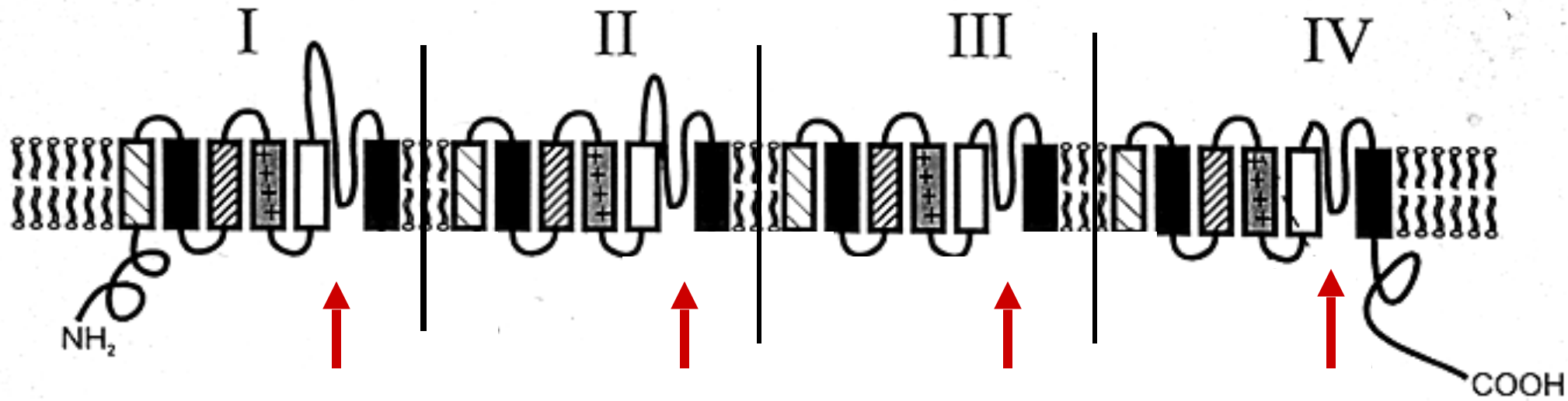


No. Events	5	60	31	23	17
No. Subjects	2936	1901	652	237	148

Inherited LQTS Disorders (Channelopathies)

<u>Genes</u>	<u>Protein Channels</u>	<u>Ion Currents</u>
LQT1 & LQT5	KCNQ1-minK	I _{Ks}
LQT2 & LQT6	HERG-MiRP1	I_{Kr}
LQT3	SCN5A	I _{Na}



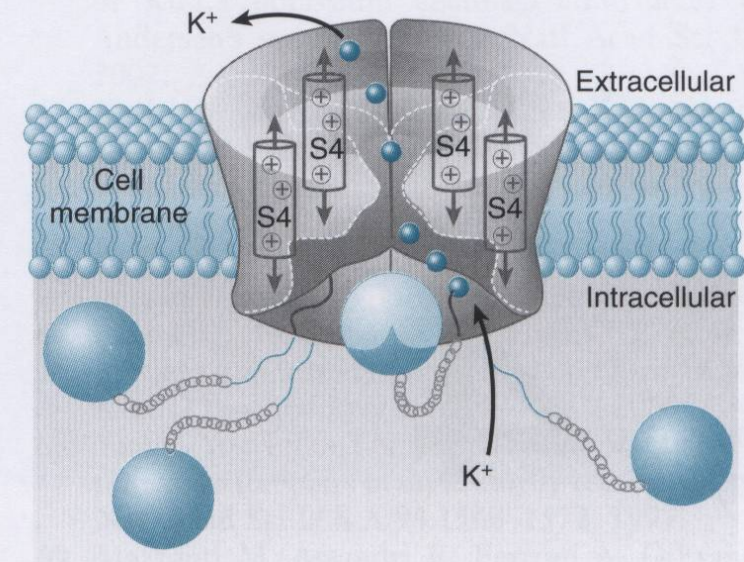
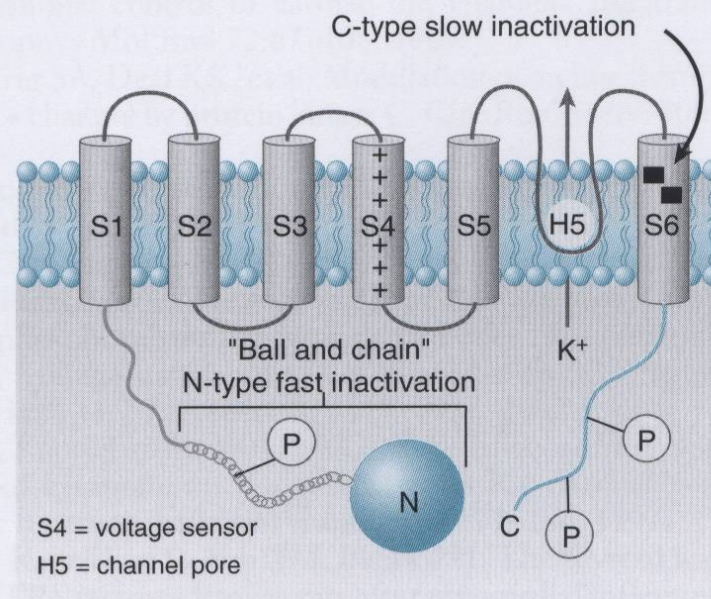


**HERG Channel:
tetramer of 4 identical
subunits**

CHANNEL ARCHITECTURE

A. Linear topology

B. Tetrameric assembly

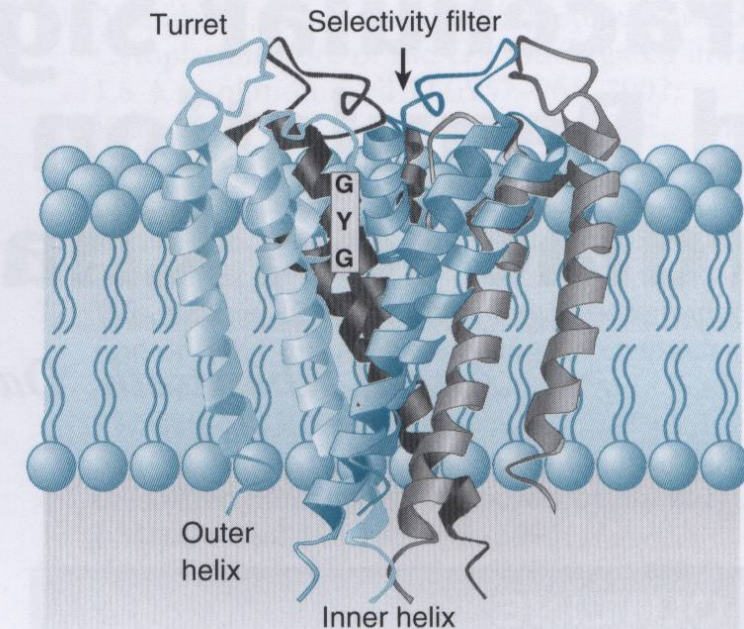
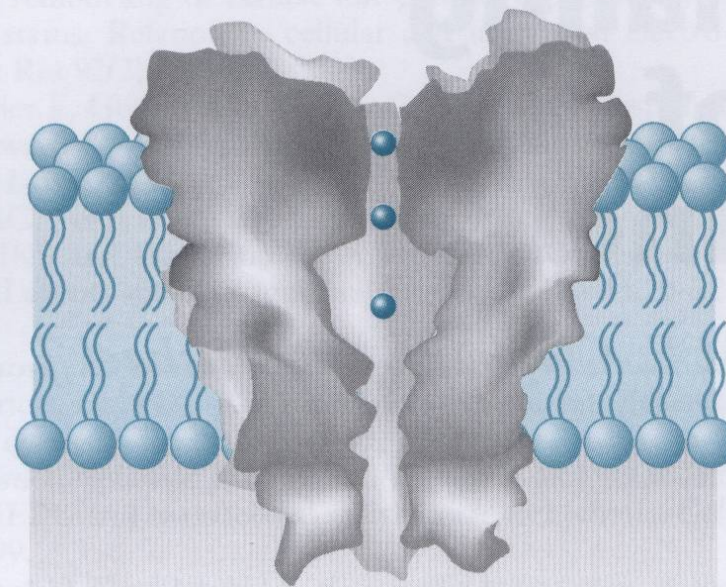


A

B

C. X-ray crystallographic structure

D. Resolution X-ray crystallographic structure



C

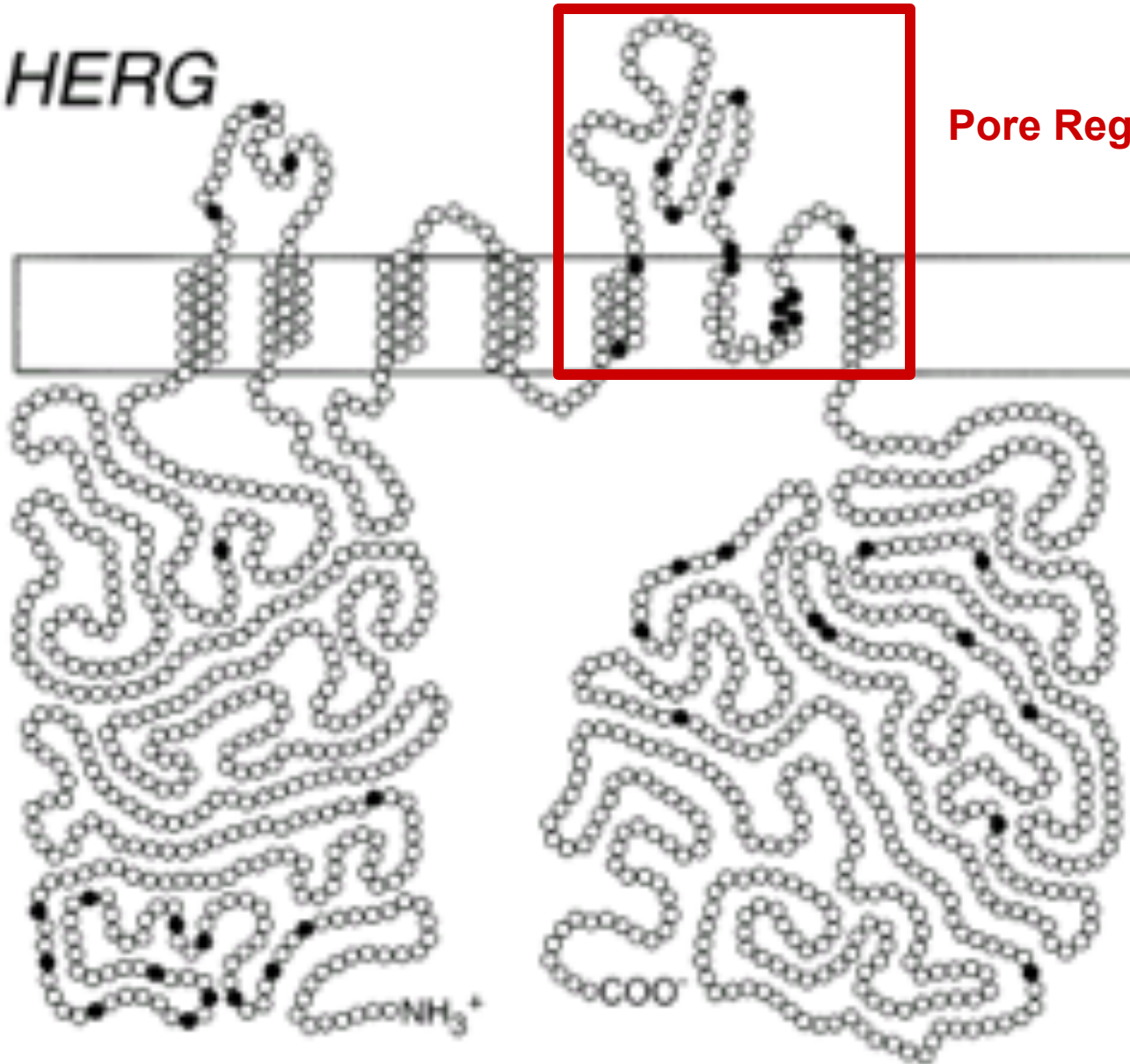
D

LQT2: HERG MUTATIONS

201 family members with HERG mutations

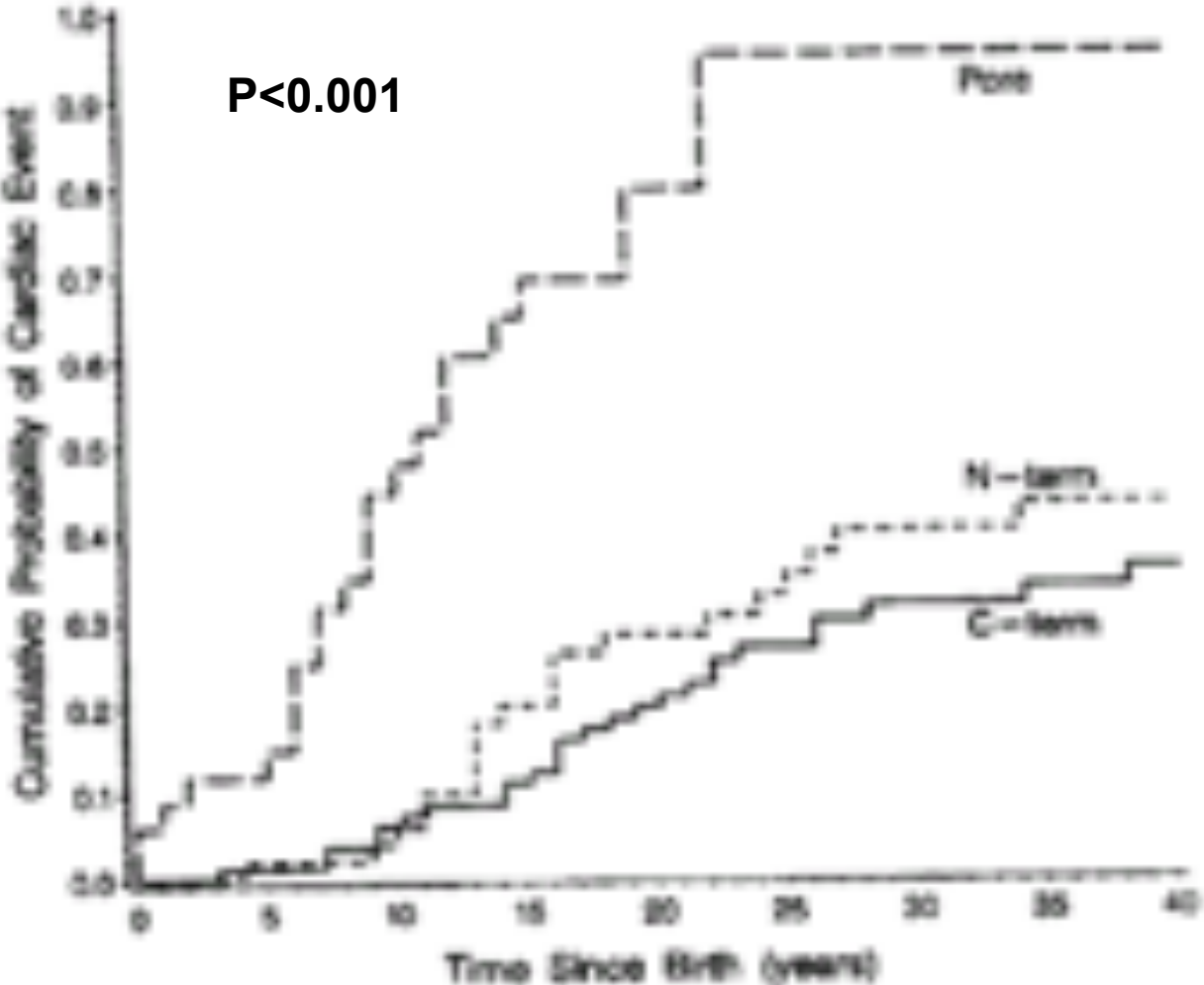
- 35 with mutations in the pore region**
- 166 with mutations in non-pore region**

HERG

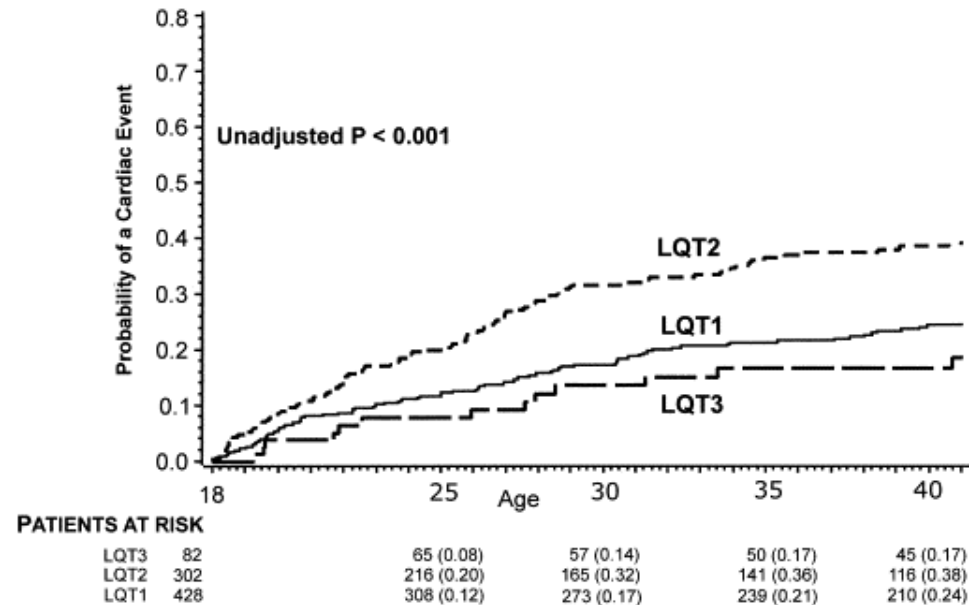
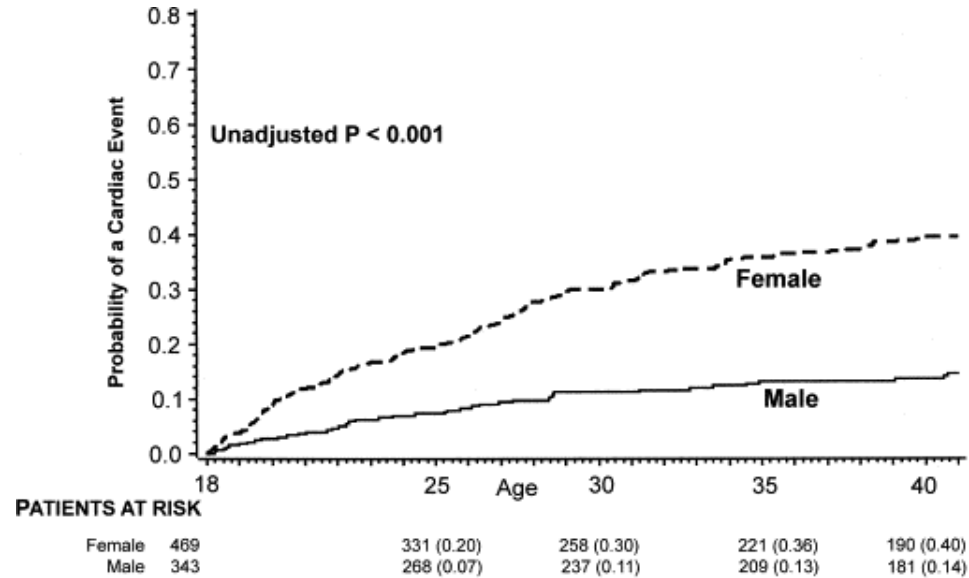


Pore Region (S5-S6)

Mutation Location and Cardiac Events



LQTS: Age 18-40 Years



DRUG-INDUCED \uparrow QTc

DRUGS WITHDRAWN: ↑ QT & TdP

<u>Drug*</u>	<u>Class</u>	<u>Date Withdrawn</u>
Terfenadine	Antihistamine	Feb 1998
Sertindole	Antipsychotic	Dec 1998
Astemizole	Antihistamine	Jun 1999
Grepafloxacin	Antibiotic	Nov 1999
Cisapride	GI Prokinetic	July 2000

*All block the HERG channel

DRUG-INDUCED QT PROLONGATION AND THE HERG CHANNEL

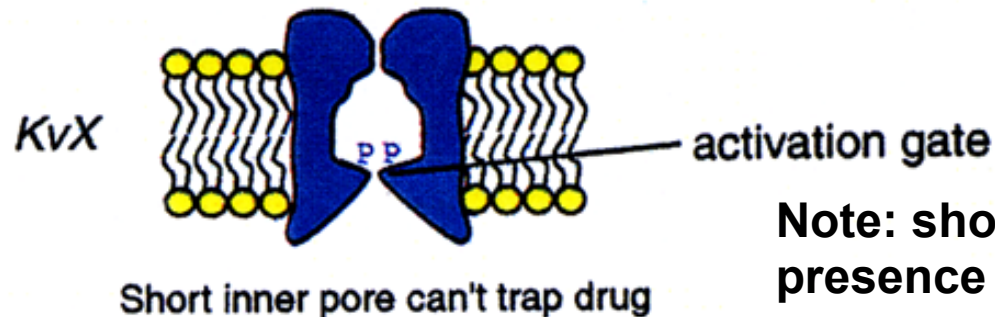
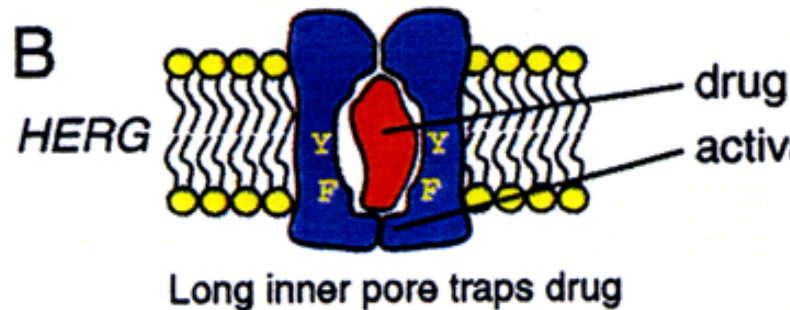
**Why is HERG channel unusually
susceptible to nonspecific binding of
drugs?**

A	<u>Channel</u>	<u>S6 domain sequence</u>
	<i>Kv1.1</i>	AGVLTIALPVPVIV
	<i>Kv1.5</i>	AGVLTIALPVPVIV
	<i>Kv2.1</i>	AGVLVIALPVPVII
	<i>Kv3.1</i>	AGVLTIAMPVIV
	<i>Kv4.1</i>	SGVLVIALPVPVIV
	<i>Kv4.2</i>	SGVLTIALPVPVIV
	<i>Kv4.3</i>	SGVLTIALPVPVIV
	<i>KVLQT1</i>	FAISFFALPAGILG
	<i>HERG</i>	IGSLMYASIFGNVS

HERG Features

1. Long pore cavity d/t lack of proline residues

2. Unique Y (tyrosine) and F (phenylalanine) drug-binding sites



Note: short inner pore d/t presence of proline (P)

HERG: Structural Basis for Drug-Induced QT Prolongation

- 1. Drugs (sertindole, cisapride, etc.):**
 - uniquely bind to Y (tyrosine) and F (phenylalanine) in HERG pore region**
 - long inner pore favors drug trapping**
- 2. Bound drug blocks repolarizing I_{Kr} current in HERG channel resulting in QT prolongation**

DRUGS and TdP: Multiple-Hit Hypothesis

Life-threatening arrhythmias may occur with drugs that prolong QTc in association with one or more of the following:

- Bradycardia
- Hypokalemia
- Heart disease
- Liver or renal disease
- Dose of drug
- LQTS mutation/polymorphism
- Age
- Female gender
- Drug interactions