Proposal for New CPIC Guideline on *KCNE1* D85N and Drug-Induced QT Prolongation

Jasmine Luzum, PharmD, PhD, FHFSA, FAHA
University of Michigan

Outline

- Background
  - QT Prolongation
  - Drug-induced QT prolongation (diQTP)
- Pharmacogenetics (PGx) of diQTP: KCNE1 D85N
  - Positive studies
    - in vitro
    - clinical
  - “Negative” studies
- Other groups’ reports/recs on KCNE1 D85N PGx
- Potential CPIC recommendation for KCNE1 D85N
- Summary

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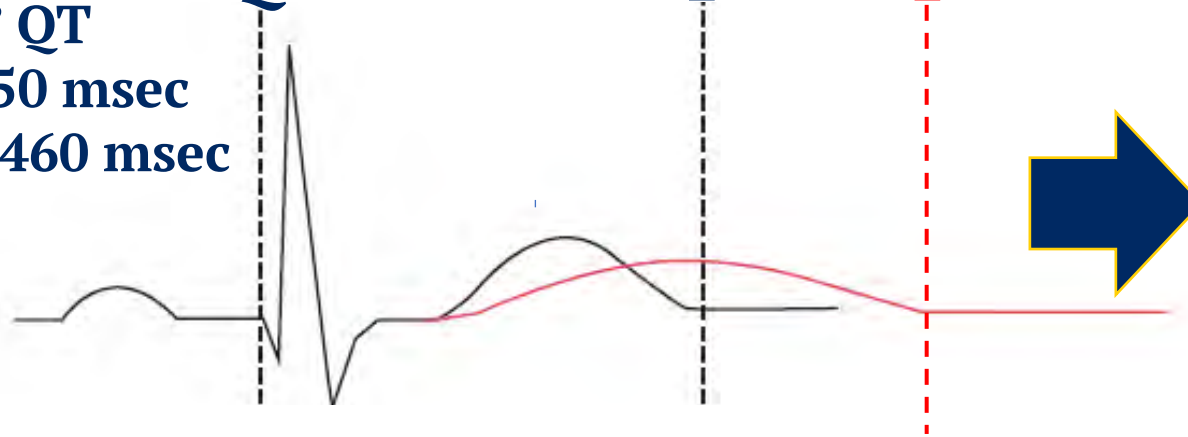
QT prolongation

Every 10 ms increase in the QT interval is associated with a 5 to 7% exponential increase in the risk of TdP.

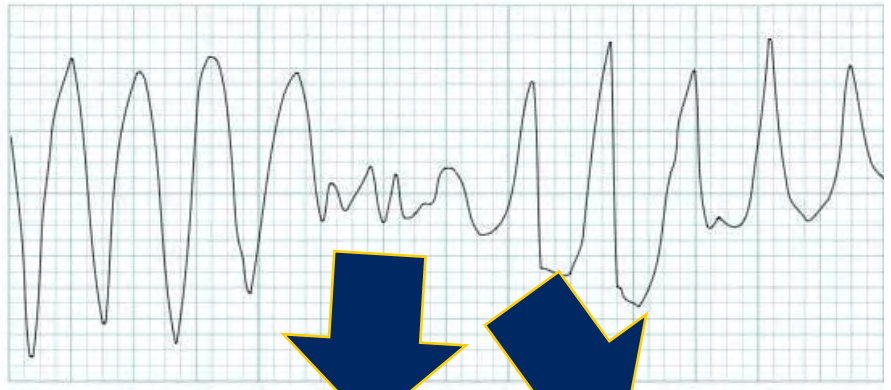
EKG

Q ⟷ T → T

"Normal" QT
Men = 350-450 msec
Women = 360-460 msec



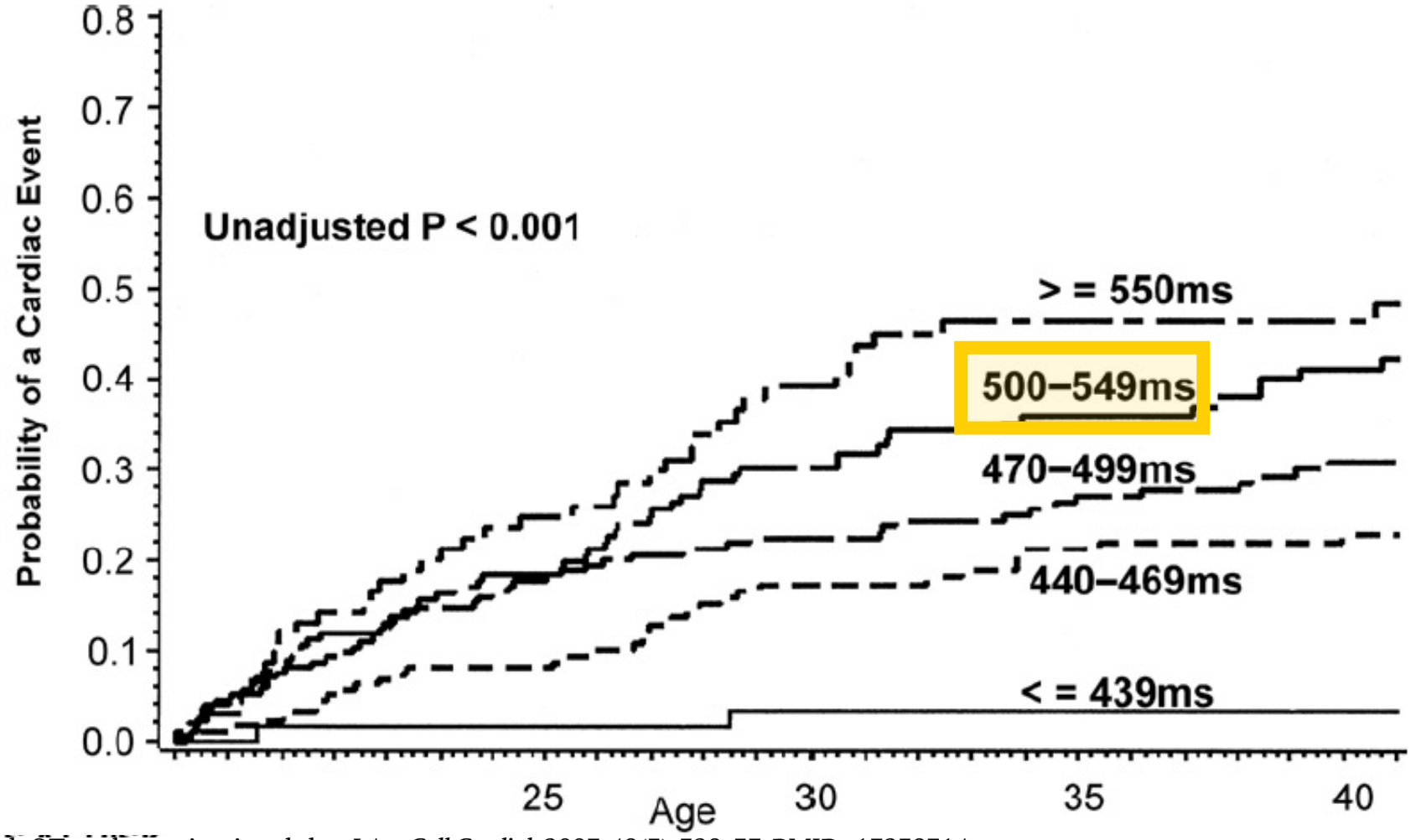
Torsades de pointes (TdP)



https://crediblemeds.org/
Lopez Medina AI, Chahal CAA, Luzum JA. The genetics of drug-induced QT prolongation: evaluating the evidence for pharmacodynamic variants. *Pharmacogenomics*. 2022 Jun;23(9):543-557. PMID: 35698903.

QT prolongation

QT prolongation significantly increases risk of major adverse cardiac events

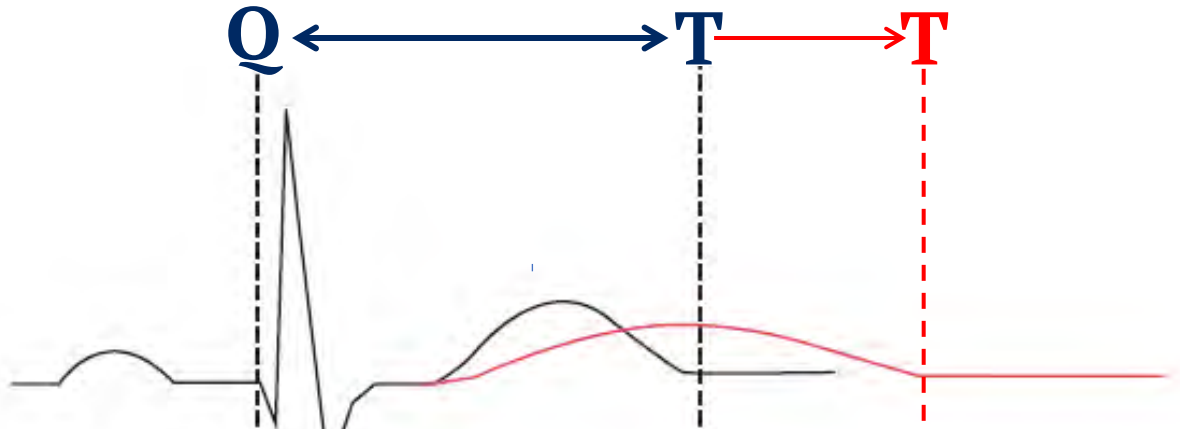


>500 ms typical high-risk cutoff

Sauer AJ, et al. QT prolongation in adults. *J Am Coll Cardiol*. 2007;49(3):329-37. PMID: 17239714.

QT prolongation

What controls the duration of the QT interval?



Cardiac ion channels (gene)

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QT prolongation

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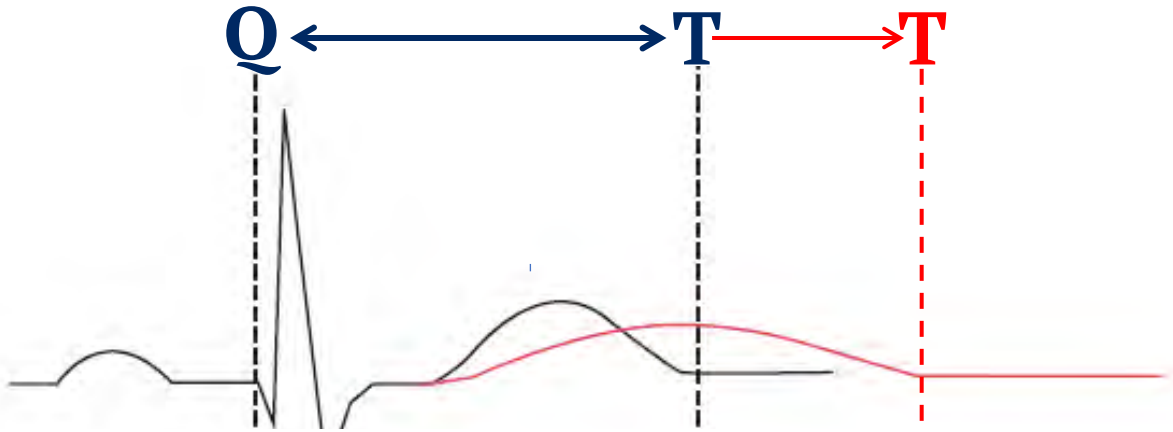

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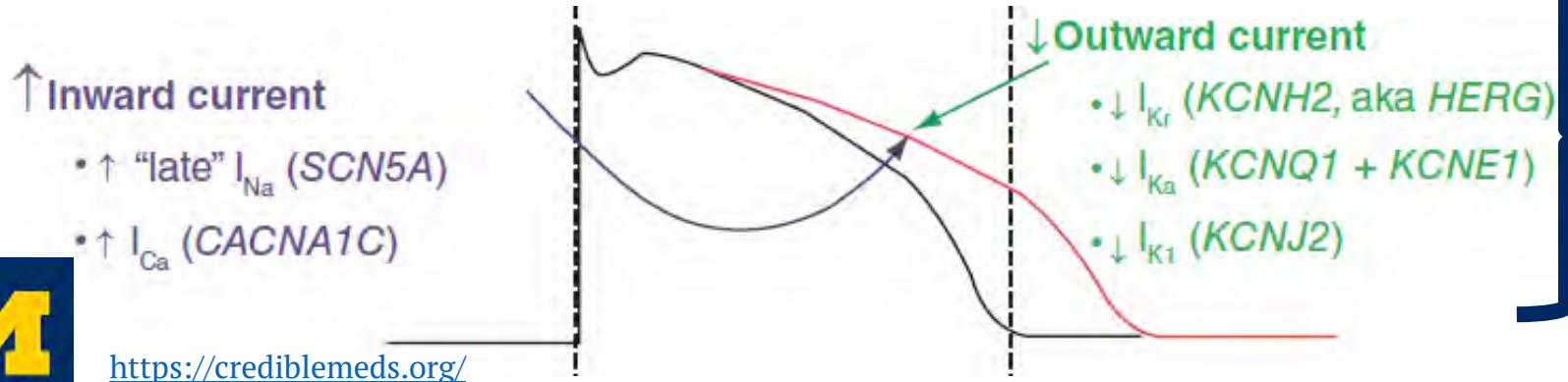

K+ channels inhibited by:

(congenital long QT)

(acquired long QT)

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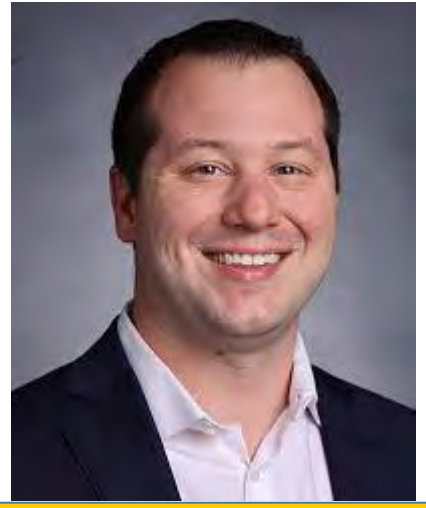
Lopez Medina AI, Chahal CAA, Luzum JA. The genetics of drug-induced QT prolongation: evaluating the evidence for pharmacodynamic variants. *Pharmacogenomics*. 2022 Jun;23(9):543-557. PMID: 35698903.

QT prolongation



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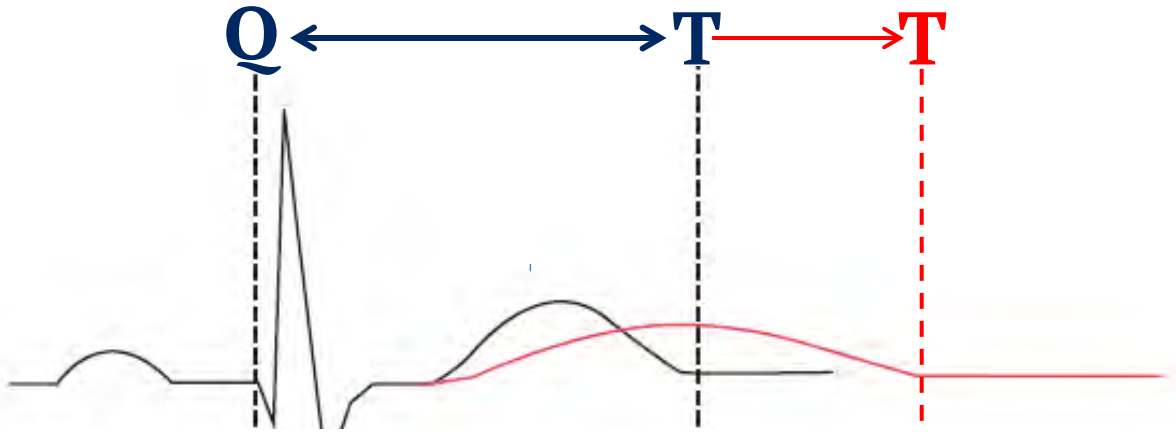
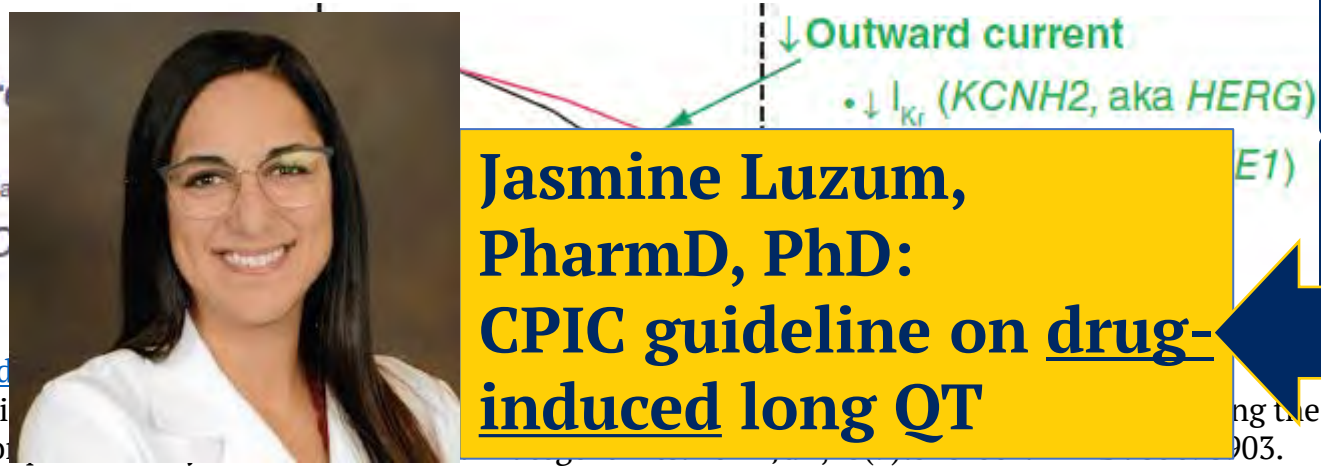


Cardiac ion channels (gene)



Josiah Allen, PharmD: Future CPIC guideline on med recs in congenital long QT

K+ channels inhibited by: (congenital long QT)

(acquired long QT)

Jasmine Luzum, PharmD, PhD: CPIC guideline on drug-induced long QT

https://cred

Lopez Medi ng the evidence fo 903.

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Drug-Induced QT Prolongation (diQTP)

Seldane Should Be Taken Off Market, Fda Says Antihistamine Blamed For Deaths When Combined With Other Drugs

Tue., Jan. 14, 1997

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Washington Post

The popular antihistamine Seldane is unsafe and should be taken off the market, the Food and Drug Administration announced Monday.

Since its introduction in 1985, the drug has been blamed for perhaps hundreds of deaths from unstable heart rhythms when taken with the common antibiotic erythromycin or with the antifungal drug ketoconozole, the FDA said. Patients with liver disease have also reported abnormal heart rhythms when taking Seldane alone.

The agency suggested that users talk with their doctors about switching from Seldane, also known as terfenadine, to another prescription antihistamine approved in July 1996, Allegra (fexofenadine). Allegra has the same beneficial effects as Seldane without any of the harmful side effects, said Robert J. Temple, director of the FDA's Office of Drug Evaluation. Both drugs are manufactured by Hoechst Marion Roussel.

https://www.washingtonpost.com/archive/politics/1997/01/14/fda-wants-drug-seldane-off-market/8f7d42b9-2e91-42fd-9576-49882c60f600/

Drug-Induced QT Prolongation (diQTP)

Los Angeles Times

WORLD & NATION

PROPULSID: A Heartburn Drug, Now Linked to Children's Deaths

BY DAVID WILLMAN

DEC. 20, 2000 12 AM PT

TIMES STAFF WRITER

In mid-1993, FDA officials prepared to approve Propulsid, a drug that eased nighttime heartburn. But a sign of danger loomed.

FDA medical officer Andre Dubois noted that 48 of 1,993, or 2.4%, of the patients who took Propulsid in U.S. studies experienced "heart rate and rhythm disorders." In addition, eight children age 6 or younger who were given Propulsid had died.

Dubois found that the drug's chemical makeup could disturb cardiac function. But he agreed with drug maker Janssen Pharmaceutica, a Johnson & Johnson Co. subsidiary, that the deaths in the studies were attributable to other causes.

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https://www.latimes.com/nation/la-122001propulsid-story.html

Drug-Induced QT Prolongation (diQTP)

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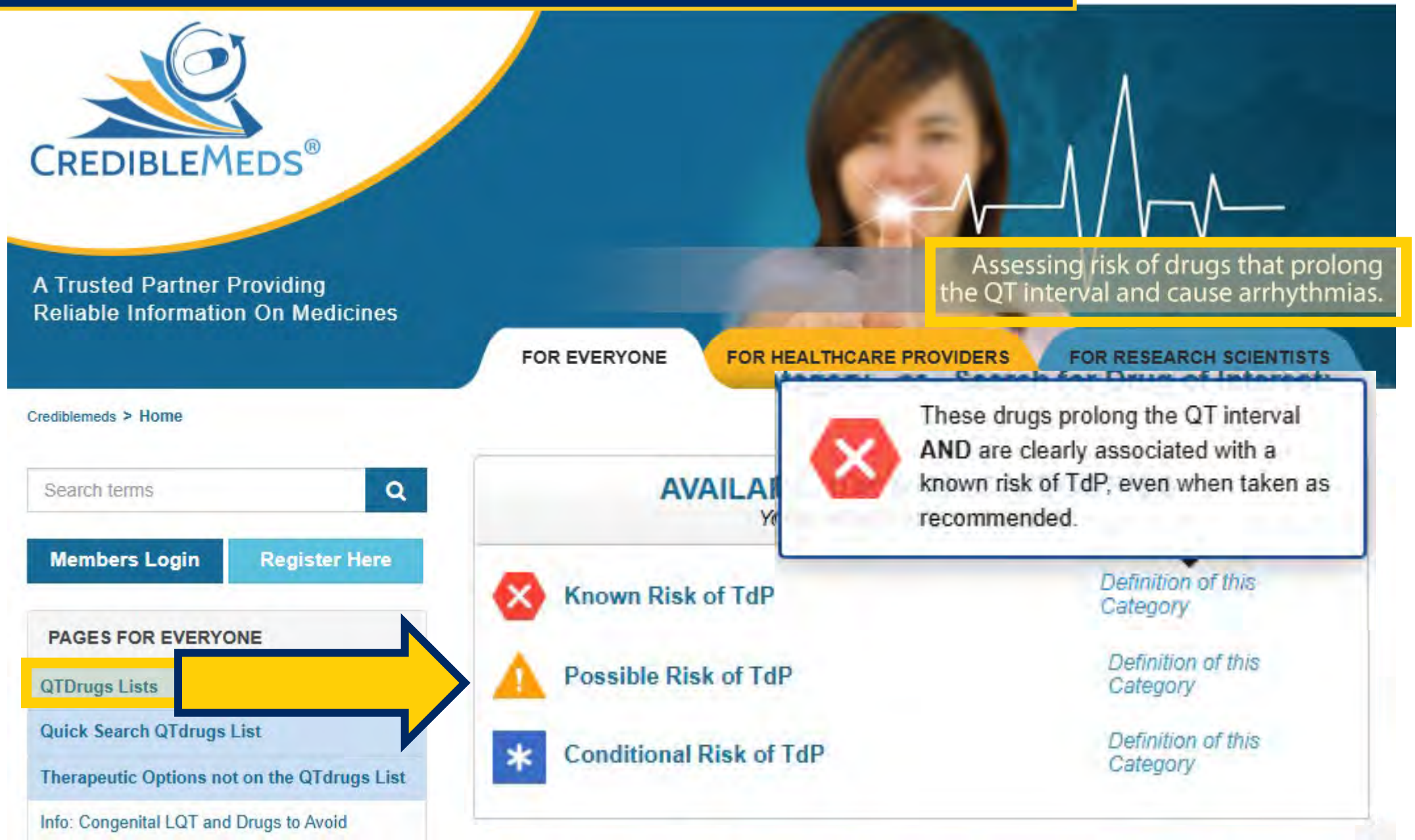

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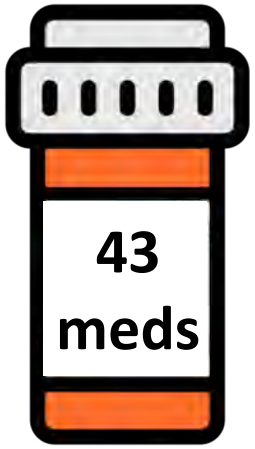
Drug-Induced QT Prolongation (diQTP)



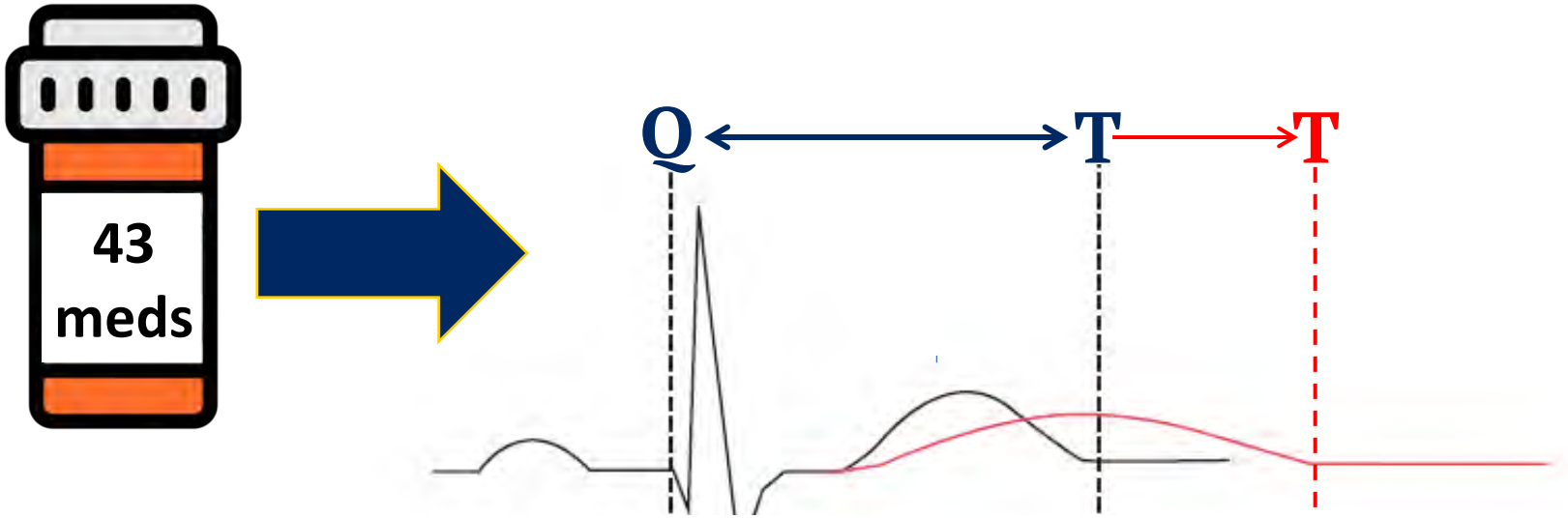
43 commonly prescribed medications are still currently on the market in the U.S. categorized as known risk for TdP

Antiarrhythmics Amiodarone Disopyramide Dofetilide Dronedarone Flecainide Ibutilide Procainamide Quinidine Sotalol	**Antibiotics** Azithromycin Ciprofloxacin Clarithromycin Erythromycin Levofloxacin Moxifloxacin	**Antipsychotics** Chlorpromazine Droperidol Haloperidol Pimozide Thioridazine **Antidepressants** Citalopram Escitalopram	**Antifungals** Fluconazole Pentamidine **Cholinesterase inhibitor** Donepezil **Opioid agonist** Methadone
Phosphodiesterase inhibitor Anagrelide Cilostazol **Anti-anginal** Ivabradine	**Antimalarial** Chloroquine Hydroxychloroquine **Anesthetic** Cocaine Propofol Sevoflurane	**Anti-cancer** Arsenic trioxide Cesium Chloride Mobocertinib Oxaliplatin Quizartinib Vandetanib	**Antiemetics** Ondansetron **Vasoconstrictor** Terlipressin **Vasodilator** Papaverine

https://crediblemeds.org/

Drug-Induced QT Prolongation (diQTP)

Why do so many different drugs prolong the QT interval?



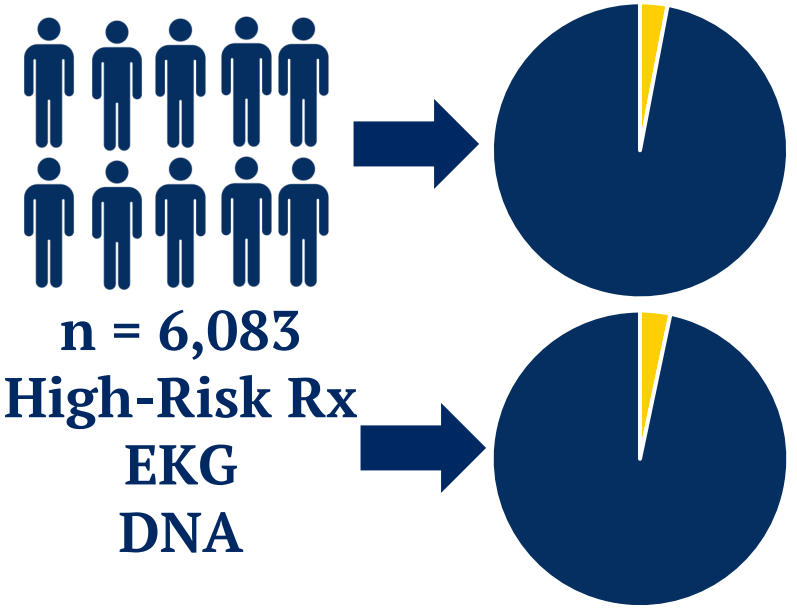
HERG channel is particularly susceptible to drug binding

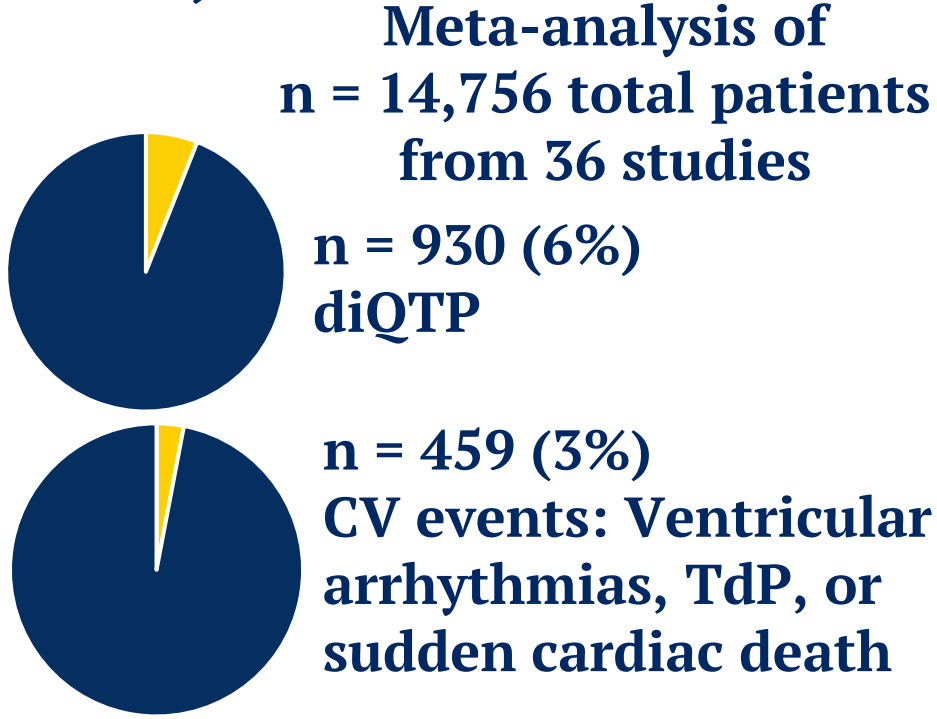
- Large inner cavity
- Inner cavity contains 2 aromatic residues and hydrophobic pockets that binds a variety of drug structures

Lopez Medina AI, Chahal CAA, Luzum JA. The genetics of drug-induced QT prolongation: evaluating the evidence for pharmacodynamic variants. *Pharmacogenomics*. 2022 Jun;23(9):543-557. PMID: 35698903.

Drug-Induced QT Prolongation (diQTP)

- diQTP is a common adverse drug effect (6-12%)
- diTdP is a rare adverse drug effect (0.3%)

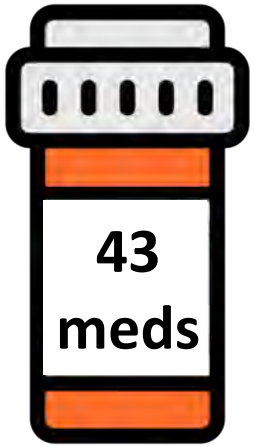




Arunachalam K, et al. Impact of Drug Induced QT prolongation: A Systematic Review. J Clin Med Res. 2018;10(5):384-390. PMID: 29581800.

Lopez-Medina AI, et al. Polygenic risk score for drug-induced QT prolongation: independent validation in a real-world patient cohort. Pharmacogenet Genomics. 2025;35(1):45-56. PMCID: PMC11543509.

Drug-Induced QT Prolongation (diQTP)



Not every patient treated with one of the 43 high-risk drugs has exaggerated QT prolongation.

What are the clinical risk factors for diQTP?

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Clinical Factors Associated with Prolonged QTc and/or TdP

CredibleMeds® maintains the following list of clinical factors that have been associated in the medical literature with prolonged QTc and/or Torsades de Pointes (TdP). Factors are placed in this list based on a systematic review and analysis of all available evidence. The quality of the evidence and the strength of associations are assessed using a modified GRADE scale (For definition, click *here*). We value your feedback and suggestions.

Filters:

Clinical Association with Increased QT ☐

Clinical Association with TdP ☐

Quality of Evidence ☐ **High** ☐ **Moderate** ☐ **Low** ☐ **Very Low**

Search clinical factors **Search**

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AUTONOMIC NERVOUS SYSTEM

Clinical Factor	Clinical Association with Increased QT	Quality of Evidence for Assoc. with Increased QT (more info)	Clinical Association with TdP	Quality of Evidence for Assoc. with TdP	Pubmed Search Link
Pheochromocytoma	Yes	High	Yes	High	link
Alpha adrenergic stimulation	Yes	Moderate	Yes	Low	link
Emotion (Arousal)	Yes	Moderate	Yes	Moderate	link

https://crediblemeds.org/ndfa_list

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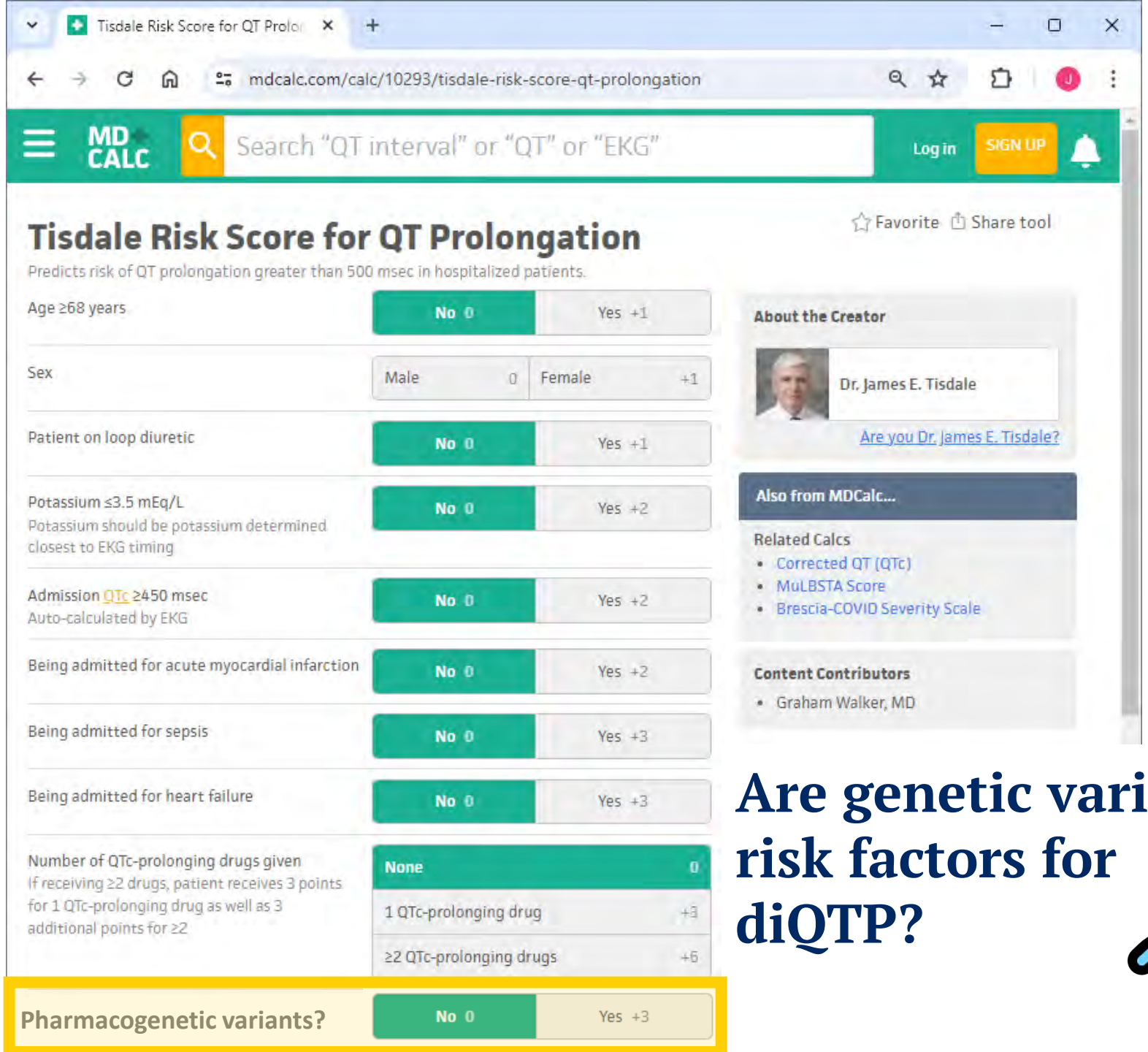

CPIC®
Clinical Pharmacogenetics Implementation Consortium

Are genetic variants risk factors for diQTP?

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Pharmacogenetics of diQTP: *KCNE1* D85N

Review

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Pharmacogenomics

The genetics of drug-induced QT prolongation: evaluating the evidence for pharmacodynamic variants

Ana I Lopez-Medina[1], Choudhary Anwar A Chahal[2,3,4,5] & Jasmine A Luzum*,[1]

[1]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI 48109, USA
[2]Division of Cardiovascular Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, USA
[3]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905, USA
[4]Barts Heart Centre, St. Bartholomew's Hospital, West Smithfield, London, EC1A 7BE, UK
[5]WellSpan Health, Lancaster, PA 17607, USA
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Ana I. Lopez Medina, PharmD, PhD graduate

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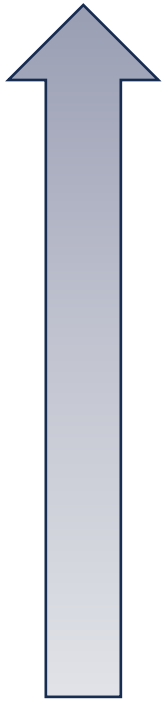
Lopez Medina AI, Chahal CAA, Luzum JA. The genetics of drug-induced QT prolongation: evaluating the evidence for pharmacodynamic variants. *Pharmacogenomics*. 2022 Jun;23(9):543-557. PMID: 35698903.

Pharmacogenetics of diQTP: *KCNE1* D85N

Strength of the evidence for 112 genetic variants associated with diQTP



Rating	Variants
Definitive	*KCNE1* D85N (rs1805128)
Strong	*KCNE2* T8A (rs2234916)
Moderate	*KCNE1* D76N (rs74315445) *KCNE2* I57T (rs74315448) *SCN5A* G615E (rs12720452) *SCN5A* L1825P (rs79299226)
Limited	106 variants

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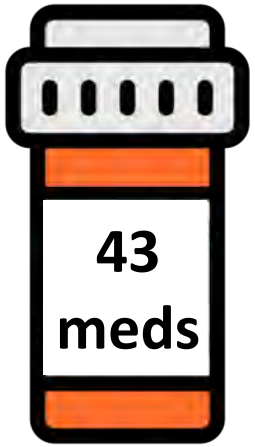
Lopez Medina AI, Chahal CAA, Luzum JA. The genetics of drug-induced QT prolongation: evaluating the evidence for pharmacodynamic variants. *Pharmacogenomics*. 2022 Jun;23(9):543-557. PMID: 35698903.

Pharmacogenetics of diQTP: *KCNE1* D85N

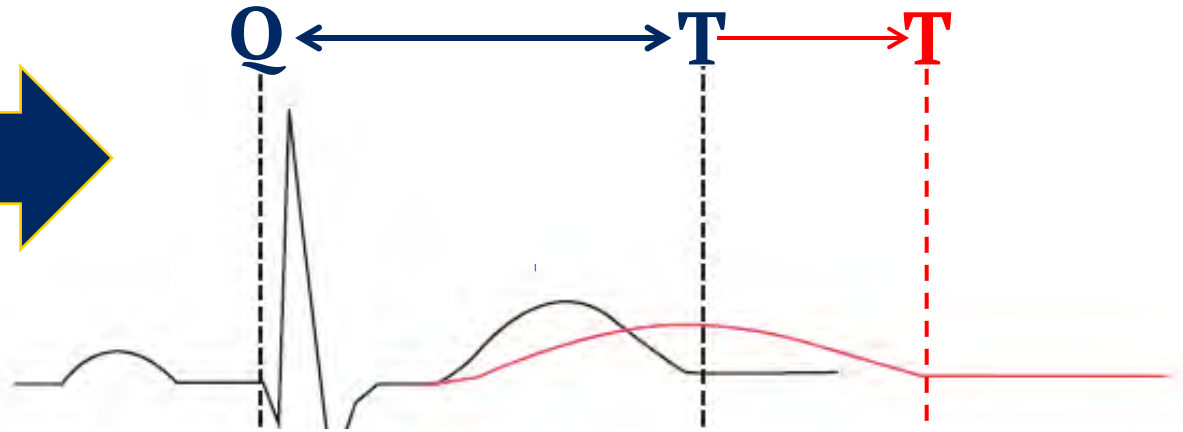
KCNE1 D85N minor allele frequency Global (dbSNP) = 1.2%

Ancestry Group	MAF (gnomad)
Ashkenazi Jewish	2.5%
European (Finnish)	1.7%
European (Non-Finnish)	1.2%
East Asian	0.5%
Admixed American	0.2%
African/African American	0.2%
South Asian	0.1%

Pharmacogenetics of diQTP: *KCNE1* D85N



What is the PGx mechanism of *KCNE1* D85N in diQTP?



***KCNE1* D85N does <u>NOT</u> cause congenital QT prolongation on its own, i.e., this is a pharmacogenetic**

***KCNE1* D85N = ↓ "<u>repolarization reserve</u>"**

Pharmacogenetics of diQTP: *KCNE1* D85N

- ***In vitro* studies demonstrate that *KCNE1* D85N significantly reduces currents through cardiac ion channels (in the absence of drug exposure).**

Citation	Model	Drug	Summary of Findings
Westenskow P, et al. 2004. PMID: 15051636	*Xenopus* oocytes	None	-*KCNE1 D85N* reduced IKs by about half compared to wild-type.
Nishio Y, et al. 2009. PMID: 19695459.	Chinese Hamster Ovary (CHO) cells	None	-*KCNE1* D85N induced loss of function on both *KCNQ1* and *KCNH2* channel currents.
Nof E, et al. 2011. PMID: 21712262	Human kidney, epithelial-like (TSA201) cells	None	-Homozygous *KCNE1*-D85N reduced *IKr* by 85%, whereas heterozygous reduced the current by 52%. -*KCNE1*-D85N produced no change in IKs.

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Pharmacogenetics of diQTP: *KCNE1* D85N

- ***KCNE1* D85N significantly associates with QT prolongation in epidemiologic studies (in the absence of drug exposure).**

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Pharmacogenetics of diQTP: *KCNE1* D85N

ARTICLES

nature genetics

VOLUME 46 | NUMBER 8 | AUGUST 2014 NATURE GENETICS

Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization

The QT interval, an electrocardiographic measure reflecting myocardial repolarization, is a heritable trait. QT prolongation is a risk factor for ventricular arrhythmias and sud[illegible] presence of the potentially lethal mendelian long-QT syndrome (LQTS). Using [illegible] genome-wide association and replication study [illegible] up to 100,000 individuals, we identified 35 common variant loci associated with QT interval that collectively explain ~8–10% of QT-interval variation and hi[illegible] lo[illegible] re[illegible] p[illegible] n[illegible]

103,331 European ancestry individuals:
+7.4 ms per *KCNE1* D85N allele ($p = 2 \times 10^{-18}$)

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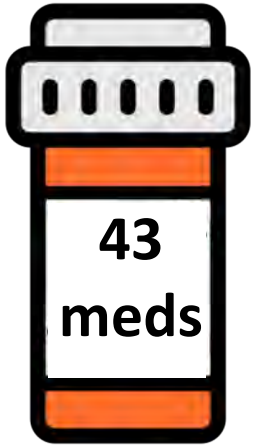
Pharmacogenetics of diQTP: *KCNE1* D85N

- Central hypothesis for KCNE1 D85N pharmacogenetic effects

↓ "repolarization reserve" + slight QT prolongation

high-risk QT-prolonging drugs

KCNE1 D85N



diQTP risk

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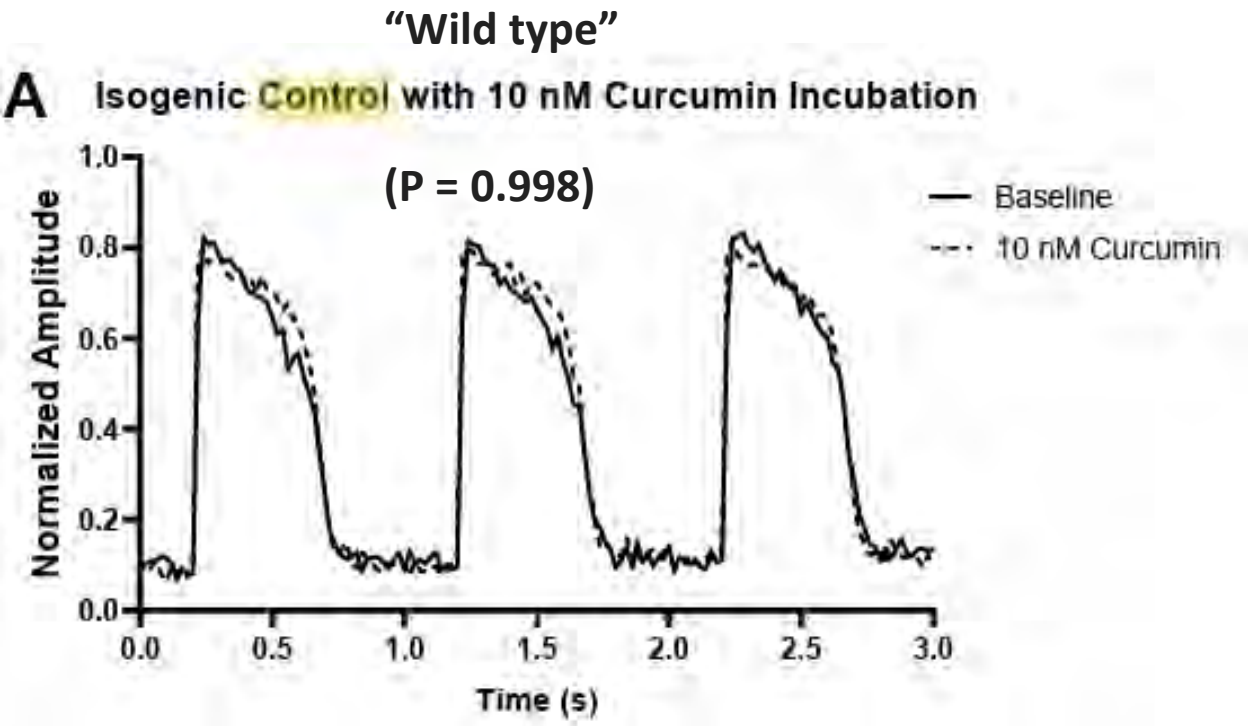
Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – *in vitro* studies + drugs

Citation	Model	Drug	Summary of Findings
Du C, et al. 2013. PMID: 24400172	Human embryonic kidney (HEK 293) cells	quinidine cisapride clarithromycin	-*KCNE1* D85N reduced the amplitude of HERG currents compared to wild-type and enhanced the inhibitory effects of clarithromycin and cisapride (but not quinidine).
Sakata S, et al. 2014. PMID: 24499369.	African green monkey kidney fibroblast-like (COS7) cells	verapamil amiodarone	-The protein level of *KCNE1* D85N was lower than that of the wild-type. -IKs was much smaller in D85N than in wild-type. -Verapamil increased the protein level of D85N, decreased its ubiquitination, slowed its degradation, and enhanced *KCNQ1/KCNE1* D85N channel currents. -Pretreatment with amiodarone abolished the effects of verapamil.
Martinez K, et al. 2023. PMID: 36586707.	Human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs)	curcumin	-*KCNE1*-D85N-derived iPSC-CMs demonstrated significant prolongation of action potential duration with curcumin.

Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – *in vitro* studies + drugs

In vitro study of *KCNE1*-D85N-derived human-induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) vs. isogenic controls ± curcumin.



Martinez K, et al. Curcumin, a dietary natural supplement, prolongs the action potential duration of KCNE1-D85N-induced pluripotent stem cell-derived cardiomyocytes. Heart Rhythm. 2023;20(4):580-586. PMID: 36586707.

Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – Clinical

Citation	Outcome	Design	Genetic Analyses	n	Drug(s)	*KCNE1* D85N Result Summary
Paulussen AD, et al. 2004. PMID: 14760488.	TdP	case/control	Sequenced *KCNH2, KCNQ1, SCN5A, KCNE1, KCNE2*	32/32	sotalol quinidine	2 cases had D85N; 0 controls
Kääb S, et al. 2012. PMID: 22100668.	TdP	case/control	Genotyped 1,386 tag SNPs + 38 non-synonymous SNPs in 18 candidate genes	176/207/837 57/211	antiarrhythmics antipsychotics antibiotics	Discovery: OR (95% CI) = 9.9 (2.4-41.8) p = 0.002 Validation: 1.5 (0.4-6.6) p = 0.058
Lin L, et al. 2012. PMID: 22999324.	TdP + QTc ⩾ 580ms	case report	"genetic test for LQTS candidate genes"	1	procainamide disopyramide	Patient is heterozygous for KCNE1 D85N
Weeke P, et al. 2014. PMID: 24561134.	TdP + QTc ⩾ 600ms	case/control	WES + 20 candidate genes	65/148/515	quinidine sotalol dofetilide amiodarone procainamide "other cardiac" "non-cardiac"	Overall OR = 13.6 (p=0.019); Non-overlapping subjects p = 0.008
Marstrand P, et al. 2018. PMID: 31020182.	TdP + QTc 600 ms	case report	Not stated	1	citalopram	Patient is heterozygous for *KCNE1* D85N
Martinez-Matilla, M., et al. 2019. PMID: 31376648	TdP, borderline & long QTc interval, Brugada Syndrome and SCD	cases only	Sequenced 96 candidate genes	32	"proarrhythmic/QT prolonging drugs"	D85N identified in 1 patient
Lopez-Medina AI, et al. 2024. PMID: 38506312	ΔQTc > 60 ms or QTc ⩾ 600ms	cohort	3 candidate non-synonymous SNPs	6,083	27 different drugs with known risk of TdP from	Clinical covariate adjusted odds ratio: 2.24 [95% CI: 1.35-3.58]; p = 0.001)

Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – Clinical

A 54-year-old woman was brought to the emergency department after a syncope at home. The patient had been cleaning the barbecue in the garden when she felt ‘hard heart beats’ and passed out without further warning.

Genetic testing revealed she was a **carrier of *KCNE1* D85N.**

Time	Event
Hospitalization, Day 0	

Marstrand P, et al. Citalopram and the KCNE1 D8
a case report on the implications of a genetic modifi
Heart J Case Rep. 2018;2(4):yty106. PMID: 31020182.

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Genetic testing revealed she w **carrier of *KCNE1* D85N.**

Could this all have been prevented if a non-QT prolonging alternative was prescribed to a known KCNE1 D85N carrier? Or if there was increased caution with citalopram use?

Time	Event
10 months prior	Started citalopram 20 mg/day for depression
	Hospitalised due to dizziness and head-ache. An MRI identified an ischaemic lesion i psule. No se
	Q erval = 18 orsade d tes. Patien out ren the episode
	Antidepressant was switched from cita-lopram to the non-QT-prolonging antidepressant sertraline
	Normalization of QT-interval, QTc = 450 ms
In hospital, +9 days	Implantation of implantable cardi-overter-defibrillator

Marstrand P, et al. Citalopram and the KCNE1 D8 a case report on the implications of a genetic modifie Heart J Case Rep. 2018;2(4):yty106. PMID: 31020182.

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Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – Clinical

- Inclusion & exclusion criteria:

n = 7,843

Adult patients in MGI and had a QT interval measured during a prescription for one of the 41 high-risk meds.

- Congenital QT prolongation
- Left bundle branch block
- Pacemaker use
- 1st or 2nd degree family members

n = 6,083

Analysis limited to self-reported white patients because none of the non-white MGI patients carried D85N.

Lopez-Medina AI, et al Luzum JA. Genetic risk factors for drug-induced QT prolongation: findings from a large real-world case-control study. Pharmacogenomics. 2024;25(3):117-131. PMID: 38506312

Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – Clinical

- Statistical analysis:
  - Primary outcome:
    - QTc prolongation (Bazett), defined as a change of >60 ms from the baseline QTc and/or an absolute QTc value ⩾500 ms
  - Logistic regression:
    - Model 1: Unadjusted, unmatched (n = 6,083)
    - Model 2: Propensity-matched 1:1 (n = 1,466)
    - Model 3: Propensity-adjusted (n = 6,083)

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Lopez-Medina AI, et al Luzum JA. Genetic risk factors for drug-induced QT prolongation: findings from a large real-world case-control study. Pharmacogenomics. 2024;25(3):117-131. PMID: 38506312

Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – Clinical

- Baseline clinical characteristics:

Characteristics	Unmatched cohort		p-value
	Normal QTc	Prolonged QTc	
Patients, n (%)	5,350 (88.0)	733 (12.0)	__
Aged 68 years or older, n (%)	2,967 (55.5)	403 (55.0)	0.838
Female, n (%)	2,985 (55.8)	385 (52.5)	0.103
Hypokalemia, n (%)	325 (6.1)	103 (14.1)	**<0.001**
Loop diuretic, n (%)	659 (12.3)	261 (35.6)	**<0.001**
Digoxin, n (%)	21 (0.4)	16 (2.2)	**<0.001**
Beta-blockers, n (%)	1,453 (27.2)	341 (46.5)	**<0.001**
Elixhauser comorbidity score (IQR)	7.0 (13.0)	11.0 (14.0)	**<0.001**
KCNE1 D85N	89 (1.7)	23 (3.1)	**<0.001**

PHARMACY

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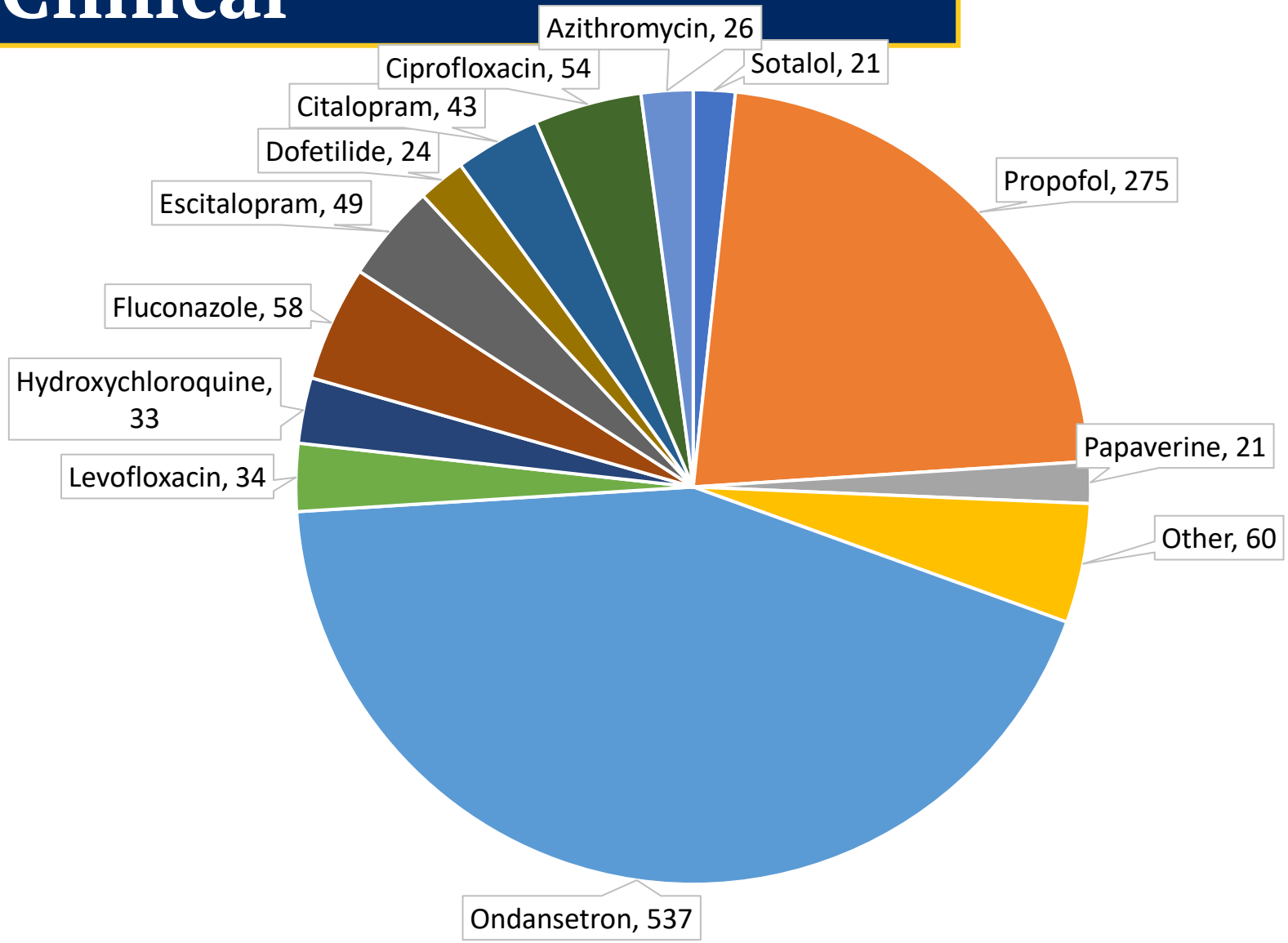
Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – Clinical

QT-Prolonging Drugs Prescribed to Cases, n



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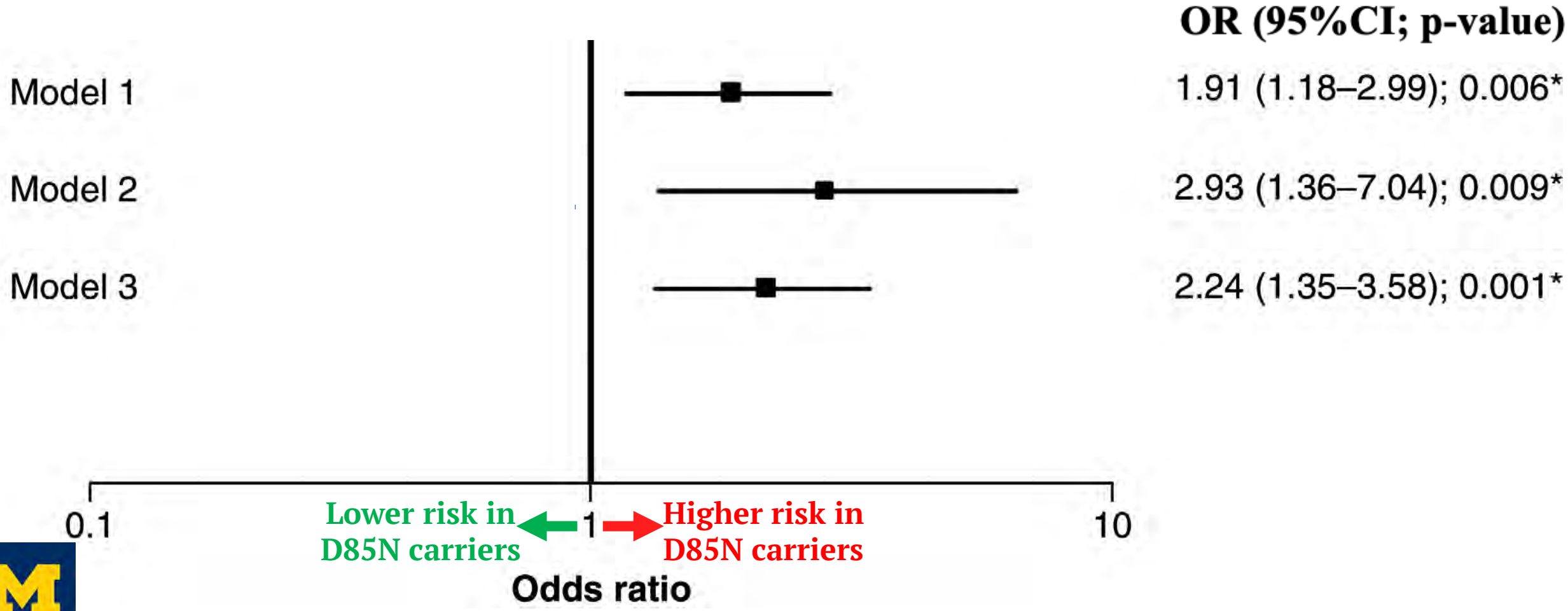
Pharmacogenetics of diQTP: *KCNE1* D85N Positive Studies – Clinical

- Association of *KCNE1* D85N with diQTP:



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Pharmacogenetics of diQTP: *KCNE1* D85N "Negative" Studies - Clinical

Citation by year	Outcome	Study Design	Genetic Analyses	n	Drug(s)
Chevalier P, et al. 2001. PMID: 11334843.	TdP + QTc >600 ms	Case/control	5 candidate genes-sequencing	16/100	sotalol, amiodarone
Makita N, et al. 2002. PMID: 12208804.	TdP + QT prolongation	Case report	*6 candidate genes-SSCP	1	cisapride
Itoh H, et al. 2009. PMID: 19843919.	TdP + QTc >600 ms	Case/control	*6 candidate genes-SSCP	20/220	disopyramide, pirmenol, aprindine, MDMA, cisapride, erythromycin, hydroxydine, probucol
Aberg K, et al. 2012. PMID: 20921969	ΔQTc	Cohort	*16 candidate genes & GWAS-custom genotyping array-no imputation	738	olanzapine, perphenazine, quetiapine, risperidone, ziprasidone
Ramirez AH, et al. 2013. PMID: 22584458.	TdP	Case/control	79 candidate genes-sequencing	31/1,411	16 different anti-arrhythmics, antibiotics, and others
Sanchez, et al. 2016. PMID: 27930701	diQTP COD	Cases only	55 candidate genes-sequencing	2	Not stated
Itoh, et al. 2016. PMID: 26715165	QTc ⩾ 480 ms	Case/control	5 candidate genes-"screening"	117/2379	46 different anti-arrhythmics, anti-depressants, anti-psychotics, antibiotics, and other classes
Corponi F, et al. 2019. PMID: 30544110.	ΔQTc	Cohort	8 candidate genes-genotyping array + imputation	77	"antidepressants and antipsychotics"

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Why could these be "negative"?

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***Cannot verify that *KCNE1* D85N was even tested in some studies**

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Some of the drugs are not high risk for TdP/QT prolongation

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Some of the studies did not have TdP or only a few patients/none with QTc > 500 msec

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Corponi PMID: 30				77	"antidepressants and antipsychotics"
Zerdazi E PMID: 30				154	methadone

All of these "negative" studies are underpowered.

Pharmacogenetics of diQTP: *KCNE1* D85N Overall Evidence Evaluation Needed

Does the evidence overall support *KCNE1* D85N as a significant risk factor for diQTP?

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Groups' Reports/Recs on *KCNE1* D85N and diQTP

CPIC	FDA	DPWG	AHA
Level 3	None	None	None

Groups' Reports/Recs on *KCNE1* D85N and diQTP

Circulation

ORIGINAL RESEARCH ARTICLE

An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome

Editorial, see 440

Arnon Adler, MD

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Adler A, et al. An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital QT prolongation. Circulation. 2020;141(6):418-428. PMID: 31983240.

Groups' Reports/Recs on *KCNE1* D85N and diQTP

"…the Working Group identified 2 genes, KCNE1 and KCNE2, as having numerous reports supporting their role in the etiology of drug or electrolyte-provoked LQTS, referred to as acquired LQTS (aLQTS)…both genes were classified as having strong evidence for specific risk alleles [D85N, D76N] in predisposing to aLQTS."

PHARMACY

Adler A, et al. An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital QT prolongation. Circulation. 2020;141(6):418-428. PMID: 31983240.

Groups' Reports/Recs on *KCNE1* D85N and diQTP

ESC European Society of Cardiology

Europace (2022) **24**, 1307–1367
https://doi.org/10.1093/europace/euac030

POSITION PAPER

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

Groups' Reports/Recs on *KCNE1* D85N and diQTP

"Variants which are <u>unequivocally associated with drug-induced LQTS (e.g. D85N in KCNE1)</u> should be reported as a relevant result. Active family screening for the presence of these variants should be considered when QT prolonging drugs are or could be prescribed (expert opinion)."

PHARMACY

Wilde AAM, et al. Expert Consensus Statement on the state of genetic testing for cardiac diseases. Europace. 2022;24(8):1307-1367. PMID: 35373836.

Groups' Reports/Recs on *KCNE1* D85N and diQTP

PHARMACOGENOMICS
2025, VOL. 26, NOS. 1–2, 53–72
https://doi.org/10.1080/14622416.2025.2481025

Taylor & Francis
Taylor & Francis Group

SYSTEMATIC REVIEW

Pharmacogenomic markers associated with drug-induced QT prolongation: a systematic review

Marlene Schouby Bentestuen [a,b], Christian Noe Weis[c], Caroline Bækmann Jeppesen [d], Liv Swea Thiele[e], Janne Pia Thirstrup[b,e,f], Juan Cordero-Solorzano [f,g,h], Henrik Kjærulf Jensen [b,i,j], Anna Starnawska [f,g,h], Alexander Sebastian Hauser [k] and Christiane Gasse [a,b,e]

[a]Psychosis Research Unit, Aarhus University Hospital Psychiatry, Aarhus, Denmark; [b]Department of Clinical Medicine, Health, Aarhus University, Aarhus, Denmark; [c]Department of Forensic Psychiatry, Aarhus University Hospital Psychiatry, Aarhus, Denmark; [d]Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark; [e]Department of Affective Disorders, Aarhus University Hospital Psychiatry, Aarhus, Denmark; [f]Department of Biomedicine, Health, Aarhus University, Aarhus, Denmark; [g]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark; [h]Center for Genomics and Personalized Medicine, CGPM, and Center for Integrative Sequencing, iSEQ, Aarhus, Denmark; [i]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [j]European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart: ERN GUARD-Heart, Aarhus, Denmark; [k]Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Groups' Reports/Recs on *KCNE1* D85N and diQTP

Results: Of 4,493 reports, 84 studies were included, identifying 213 unique variants across 42 drug classes, of which 10% were replicated. KCNE1-Asp85Asn was the most consistent variant. Most findings (82%) were

"…the consistent evidence supporting KCNE1-Asp85Asn as a risk factor for diQTP warrants consideration in clinical practice guidelines, which are currently lacking."

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Clinical Pharmacogenetics Implementation Consortium

M PHARMACY

Bentestuen MS, et al. Pharmacogenomic markers associated with drug-induced QT prolongation: a systematic review. Pharmacogenomics. 2025;26(1-2):53-72. PMID: 40116580.

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Potential Clinical Recommendation for *KCNE1* D85N and diQTP

CPIC GUIDELINE

Expanded Clinical Pharmacogenetics Implementation Consortium Guideline for Medication Use in the Context of *G6PD* Genotype

Roseann S. Gammal[1,2], Munir Pirmohamed[3], Andrew A. Somogyi[4], Sarah A. Morris[2,5], Christine M. Formea[6], Amanda L. Elchynski[7], Kazeem A. Oshikoya[8], Howard L. McLeod[9], Cyrine E. Haidar[2], Michelle Whirl-Carrillo[10], Teri E. Klein[10], Kelly E. Caudle[2] and Mary V. Relling[2,*]

PHARMACY

Gammal RS, et al. Expanded Clinical Pharmacogenetics Implementation Consortium Guideline for Medication Use in the Context of G6PD Genotype. Clin Pharmacol Ther. 2023;113(5):973-985. PMID: 36049896.

Potential Clinical Recommendation for *KCNE1* D85N and diQTP

Table 1: Assignment of predicted KCNE1 phenotype based on genotype

Predicted phenotype	Genotype (rs1805128 [C>T])	Examples of KCNE1 genotypes
Normal	*KCNE1* D85 homozygous (~99%)	C/C D85/D85 p.Asp85/Asp85
Reduced repolarization reserve	*KCNE1* N85 heterozygous or homozygous (~1%)	C/T or T/T N85/D85 or N85/N85 p.Asn85/Asp85 or p.Asn85/Asn85

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Potential Clinical Recommendation for *KCNE1* D85N and diQTP

Table 2: Drug- specific risk level and associated strength of recommendation for patients with KCNE1 D85N

Drug category (crediblemeds)	Classification of recommendation
Known risk of TdP	Moderate
Possible risk of TdP	No recommendation
Conditional risk of TdP	No recommendation

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Potential Clinical Recommendation for *KCNE1* D85N and diQTP

Table 3: Recommended therapeutic use of drugs categorized as known risk of TdP in relation to KCNE1 D85N genotype

Predicted phenotype based on KCNE1 D85N genotype	Implications for phenotypic measures	Therapeutic recommendations for known TdP risk drugs	Classification of recommendations	Considerations
Normal	Typical risk of drug-induced QT prolongation/TdP	Standard selection and dosing.	Strong	Clinical risk factors should also be considered, e.g., advanced age, female sex, electrolyte disturbances, comorbidities, and number of QT-prolonging drugs.[a,b]
Reduced repolarization reserve	Increased risk of drug-induced QT prolongation/TdP	Avoid or use with increased caution.	Moderate	

PHARMACY

a. "Clinical factors associated with prolonged QTc and/or TdP". https://crediblemeds.org/
b. "Tisdale Risk Score for QT Prolongation". https://www.mdcalc.com/calc/10293/tisdale-risk-score-qt-prolongation

Outline

- Background
  - QT Prolongation
  - Drug-induced QT prolongation (diQTP)
- Pharmacogenetics (PGx) of diQTP: KCNE1 D85N
  - Positive studies
    - in vitro
    - clinical
  - "Negative" studies
- Other groups' reports/recs on KCNE1 D85N PGx
- Potential CPIC recommendation for KCNE1 D85N
- Summary

Summary

- Prolongation of the QT interval on an EKG significantly increases risk for major adverse cardiovascular events.
- Many commonly prescribed drugs can significantly prolong the QT interval and have known risk for TdP.
- Evidence strongly supports that KCNE1 D85N reduces repolarization reserve and prolongs the QT interval in the general population.
- Several studies show significantly increased risk of drug-induced QT prolongation and TdP in KCNE1 D85N carriers.
- A formal evidence evaluation and clinical recommendations for KCNE1 D85N in diQTP by CPIC are now needed.

Proposal for New CPIC Guideline on *KCNE1* D85N and Drug-Induced QT Prolongation

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