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KCNH2 pharmacogenomics summary

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Keywords

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Overview

The *KCNH2* gene, or human ether-a-go-go related gene (hERG), codes for a potassium voltage-gated ion channel [1,2]. The current through the channel is termed the rapid component of the cardiac delayed rectifier (I_{Kr}). The *KCNH2* gene is located on chromosome 7 and has 15 exons. Mutations and variants of *KCNH2* are one cause of congenital long QT syndrome (LQTS), a rare syndrome that carries an increased risk of cardiac arrhythmias, including the polymorphic ventricular tachycardia termed torsades de pointes (TdP), which can be fatal [3,4]. There has also been an association between *KCNH2* variants and sudden infant death syndrome [5]. Variants in many other genes, including *KCNQ1, KCNE2*, and *SCN5A* can cause congenital LQTS. However, the syndrome of drug-induced LQTS is most often caused by the block of the hERG channels encoded by the *KCNH2* gene [2–4,6,7]. Other rarer mechanisms for drug-associated QT prolongation and TdP have been reported [6,8]. In addition, other conditions, such as heart block or severe electrolyte abnormalities, can also cause QT prolongation and TdP; collectively, the drug-induced and other forms are termed ‘acquired LQTS’ (aLQTS). For the remainder of this summary, the gene *KCNH2* and the encoded protein, hERG, will be used interchangeably.

The hERG channel consists of six helical transmembrane domains, S1–S6 [4]. The structural determinants responsible for channel block have been identified by alanine scanning experiments and homology modeling [9–11]. These studies found that amino acids Y652 and F656 in the pore region of the channel on helix S6 are important for the binding of drugs and inhibitors [9–11].

There are more than 100 reported mutations in the *KCNH2* gene related to congenital LQTS. Information on these mutations can be found on several online websites, including: the Online Mendelian Inheritance in Man database webpage for *KCNH2* (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=152427), connections for heart hERG polymorphisms (*http://www.fsm.it/cardmoc/hergpoly.htm*), connections for heart

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hERG mutations (*http://www.fsm.it/cardmoc/hergmut.htm*), and LQTS db hERG mutations (*http://www.ssi.dk/graphics/html/lqtsdb/herg.htm*). In addition, gene deletions and duplications have been observed in patients with congenital LQTS [12,13].

However, there are very few variants and amino acid changes that have been clearly associated with drug-induced hERG-related LQTS. A number of studies have strongly supported the idea that variation, not only in *KCNH2* but also in other cardiac ion channels and associated genes, may predispose individuals to aLQTS [14,15]. In addition, several population studies have reported that *KCNH2* haplotypes modulate variability in the QT interval [16–18]. A more detailed discussion of two *KCNH2* variants related to drug response can be found later in this summary.

hERG/I_{Kr} inhibitors

Virtually all drugs that cause drug-induced QT prolongation are *KCNH2*/I_{Kr} blockers [4,7]. Eight drugs (astemizole, sertindole, terfenadine, cisapride, grepafloxacin, terodiline, lidoflazine, levomethadyl) have been removed from the market because of the risk of aLQTS and fatal TdP [1,19]; and a ninth, droperidol, has received highly restrictive labeling [1].

As a result of these events, testing for hERG blocking activity and subsequent evaluations for QT interval prolonging potential are routine in the pharmaceutical industry and such screening has resulted in halting the drug development of compounds that exhibit these potentially undesirable effects [4,20].

Inhibitors of hERG/I_{Kr} include amiodarone [14], astemizole [1,19,21–23] and its metabolite desmethylastemizole [22], cisapride [1,9,19,21,23,24], disopyramide [25], dofetilide [26,27], erythromycin [28,29], fluoxetine [30], grepafloxacin [1,19,21,23], haloperidol half maximal inhibitory concentration (IC_{50}) approximately 63 nmol/l [31], hydroxyzine [32], ibutilide [25]; levomethadyl [1,23], lidoflazine IC_{50} less than 37 nmol/l [1,31], methadone [33]; mibefradil [23], moxifloxacin [28], perhexiline [29], pimozide IC_{50} approximately 18 nmol/l [34], prenylamine IC_{50} approximately 590 nmol/l [31], probucol [35], quinidine [25,29]; risperidone IC_{50} 167 nmol/l [34], sertindole IC_{50} approximately 3 nmol/l [34], IC_{50} approximately 210 nmol/l [31], sotalol [25,29], telithromycin [28], terfenadine IC_{50} less than 52 nmol/l [31], [1,9,21,23], terodiline [1,19,21], thioridazine IC_{50} approximately 191 nmol/l [34], IC_{50} approximately 224 nmol/l [36], ziprasidone IC_{50} approximately 169 nmol/l [34].

Weak inhibitors of hERG/I_{Kr} (IC_{50} >1 μmol/l) include arsenic trioxide I_{Kr} approximately 300 μmol/l [31], chlorpheniramine IC_{50} approximately 13 μmol/l [31], cimetidine IC_{50} greater than 10 μmol/l [31], doxepin IC_{50} approximately 4 μmol/l [37], loratadine IC_{50} approximately 4 μmol/l [31], lovastatin IC_{50} approximately 7 μmol/l [31], olanzapine IC_{50} approximately 6013 nmol/l [34], pentamidine Iherg approximately 1 mmol/l [31], procainamide IC_{50} approximately 139 μmol/l [38], pyrilamine IC_{50} approximately 6 μmol/l [31], quetiapine IC_{50} approximately 5765 nmol/l [34], sparfloxacin (fluoroquinolone) IC_{50} approximately 18 μmol/l [34,39].

Drugs that prolong QT interval by reducing cell surface *KCNH2* expression include pentamidine [40], arsenic trioxide [41].

KCNH2 variants and their functional consequences

The discussion below focuses on two well-studied variants related to drug-induced LQTS: *KCNH2*: K897T (Lys897Thr); rs1805123; *KCNH2:1670A > C* and *KCNH2*: R1047L (Arg1047Leu); rs36210421; *KCNH2:2120G > T*.

Minor allele frequencies for both variants are reported in Table 1 at end of the summary.

KCNH2: K897T (Lys897Thr); rs1805123; *KCNH2:1670A > C*

K897T (rs1805123) has been shown, in several studies, to be associated with longer [17,44], or shorter QT intervals [45–47]. K897T was also shown to create a phosphorylation site that inhibited channel activity, independent of drug binding [48]. But, in another small study, the impact of common *KCNH2* polymorphisms, including K897T as well as P967L, R1047L (rs36210421) and Q1068R were found to have no significant differences in cisapride IC_{50} values or Hill coefficients (compared with wild type) [42]. The K897 allele has been associated with higher incidence of atrial fibrillation, in a study conducted without drugs [49].

KCNH2: R1047L (Arg1047Leu); rs36210421; *KCNH2:2120G > T*

This variant has been implicated in sensitivity to the I_{Kr} blocker dofetilide [26]. However, in *in vitro* studies using variant protein, sensitivity to another blocker, cisapride, was similar to wild-type protein [42]. Another study showed that the R1047L mutation impaired K + current density [50]. Additional information is available at http://www.pharmgkb.org/search/annotatedGene/kcnh2/

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References

1. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004; 350:1013–1022. [PubMed: 14999113]
2. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I_{Kr} potassium channel. Cell. 1995; 81:299–307. [PubMed: 7736582]
3. Kannankeril PJ, Roden DM. Drug-induced long QT and torsade de pointes: recent advances. Curr Opin Cardiol. 2007; 22:39–43. [PubMed: 17143043]
4. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. Nature. 2006; 440:463–469. [PubMed: 16554806]
5. Maron BJ, Clark CE, Goldstein RE, Epstein SE. Potential role of QT interval prolongation in sudden infant death syndrome. Circulation. 1976; 54:423–430. [PubMed: 947572]
6. Mitcheson JS. hERG potassium channels and the structural basis of drug-induced arrhythmias. Chem Res Toxicol. 2008; 21:1005–1010. [PubMed: 18447395]
7. Pearlstein R, Vaz R, Rampe D. Understanding the structure-activity relationship of the human ether-a-go-go-related gene cardiac K+ channel. A model for bad behavior. J Med Chem. 2003; 46:2017–2022. [PubMed: 12747773]
8. Roden DM, Lazzara R, Rosen M, Schwartz PJ, Towbin J, Vincent GM. Multiple mechanisms in the long-QT syndrome. Current knowledge, gaps, and future directions. The SADS Foundation Task Force on LQTS. Circulation. 1996; 94:1996–2012. [PubMed: 8873679]
9. Kamiya K, Niwa R, Morishima M, Honjo H, Sanguinetti MC. Molecular determinants of hERG channel block by terfenadine and cisapride. J Pharmacol Sci. 2008; 108:301–307. [PubMed: 18987434]
10. Perry M, de Groot MJ, Helliwell R, Leishman D, Tristani-Firouzi M, Sanguinetti MC, Mitcheson J. Structural determinants of HERG channel block by clofilium and ibutilide. Mol Pharmacol. 2004; 66:240–249. [PubMed: 15266014]
11. Mitcheson JS, Chen J, Lin M, Culberson C, Sanguinetti MC. A structural basis for drug-induced long QT syndrome. Proc Natl Acad Sci U S A. 2000; 97:12329–12333. [PubMed: 11005845]

12. Eddy CA, MacCormick JM, Chung SK, Crawford JR, Love DR, Rees MI, et al. Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. Heart Rhythm. 2008; 5:1275–1281. [PubMed: 18774102]
13. Koopmann TT, Alders M, Jongbloed RJ, Guerrero S, Mannens MM, Wilde AA, Bezzina CR. Long QT syndrome caused by a large duplication in the KCNH2 (HERG) gene undetectable by current polymerase chain reaction-based exon-scanning methodologies. Heart Rhythm. 2006; 3:52–55. [PubMed: 16399053]
14. Yang P, Kanki H, Drolet B, Yang T, Wei J, Viswanathan PC, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation. 2002; 105:1943–1948. [PubMed: 11997281]
15. Kannankeril PJ, Roden DM, Norris KJ, Whalen SP, George AL Jr, Murray KT. Genetic susceptibility to acquired long QT syndrome: pharmacologic challenge in first-degree relatives. Heart Rhythm. 2005; 2:134–140. [PubMed: 15851285]
16. Pfeufer A, Sanna S, Arking DE, Muller M, Gateva V, Fuchsberger C, et al. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. Nat Genet. 2009; 41:407–414. [PubMed: 19305409]
17. Pfeufer A, Jalilzadeh S, Perz S, Mueller JC, Hinterseer M, Illig T, et al. Common variants in myocardial ion channel genes modify the QT interval in the general population: results from the KORA study. Circ Res. 2005; 96:693–701. [PubMed: 15746444]
18. Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, et al. Common variants at ten loci influence QT interval duration in the QTGEN Study. Nat Genet. 2009; 41:399–406. [PubMed: 19305408]
19. Aronov AM. Predictive in silico modeling for hERG channel blockers. Drug Discov Today. 2005; 10:149–155. [PubMed: 15718164]
20. Netzer R, Ebneth A, Bischoff U, Pongs O. Screening lead compounds for QT interval prolongation. Drug Discov Today. 2001; 6:78–84. [PubMed: 11166255]
21. Fenichel RR, Malik M, Antzelevitch C, Sanguinetti M, Roden DM, Priori SG, et al. Drug-induced torsades de pointes and implications for drug development. J Cardiovasc Electrophysiol. 2004; 15:475–495. [PubMed: 15090000]
22. Zhou Z, Vorperian VR, Gong Q, Zhang S, January CT. Block of HERG potassium channels by the antihistamine astemizole and its metabolites desmethylastemizole and norastemizole. J Cardiovasc Electrophysiol. 1999; 10:836–843. [PubMed: 10376921]
23. Fitzgerald PT, Ackerman MJ. Drug-induced torsades de pointes: the evolving role of pharmacogenetics. Heart Rhythm. 2005; 2:S30–S37. [PubMed: 16253929]
24. Mohammad S, Zhou Z, Gong Q, January CT. Blockage of the HERG human cardiac K+ channel by the gastrointestinal prokinetic agent cisapride. Am J Physiol. 1997; 273:H2534–H2538. [PubMed: 9374794]
25. Cubeddu LX. QT prolongation and fatal arrhythmias: a review of clinical implications and effects of drugs. Am J Ther. 2003; 10:452–457. [PubMed: 14624285]
26. Sun Z, Milos PM, Thompson JF, Lloyd DB, Mank-Seymour A, Richmond J, et al. Role of a KCNH2 polymorphism (R1047 L) in dofetilide-induced Torsades de Pointes. J Mol Cell Cardiol. 2004; 37:1031–1039. [PubMed: 15522280]
27. Finlayson K, Turnbull L, January CT, Sharkey J, Kelly JS. [3H]dofetilide binding to HERG transfected membranes: a potential high throughput preclinical screen. Eur J Pharmacol. 2001; 430:147–148. [PubMed: 11698075]
28. Wisialowski T, Crimin K, Engtrakul J, O'Donnell J, Fermini B, Fossa AA. Differentiation of arrhythmia risk of the antibacterials moxifloxacin, erythromycin, and telithromycin based on analysis of monophasic action potential duration alternans and cardiac instability. J Pharmacol Exp Ther. 2006; 318:352–359. [PubMed: 16614168]
29. Perrin MJ, Kuchel PW, Campbell TJ, Vandenberg JI. Drug binding to the inactivated state is necessary but not sufficient for high-affinity binding to human ether-a-go-go-related gene channels. Mol Pharmacol. 2008; 74:1443–1452. [PubMed: 18701618]

30. Thomas D, Gut B, Wendt-Nordahl G, Kiehn J. The antidepressant drug fluoxetine is an inhibitor of human ether-a-go-go-related gene (HERG) potassium channels. J Pharmacol Exp Ther. 2002; 300:543–548. [PubMed: 11805215]

31. Katchman AN, Koerner J, Tosaka T, Woosley RL, Ebert SN. Comparative evaluation of HERG currents and QT intervals following challenge with suspected torsadogenic and nontorsadogenic drugs. J Pharmacol Exp Ther. 2006; 316:1098–1106. [PubMed: 16278312]

32. Sakaguchi T, Itoh H, Ding WG, Tsuji K, Nagaoka I, Oka Y, et al. Hydroxyzine, a first generation H(1)-receptor antagonist, inhibits human ether-a-gogo-related gene (HERG) current and causes syncope in a patient with the HERG mutation. J Pharmacol Sci. 2008; 108:462–471. [PubMed: 19057127]

33. Eap CB, Crettol S, Rougier JS, Schlapfer J, Sintra Grilo L, Deglon JJ, et al. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. Clin Pharmacol Ther. 2007; 81:719–728. [PubMed: 17329992]

34. Kongsamut S, Kang J, Chen XL, Roehr J, Rampe D. A comparison of the receptor binding and HERG channel affinities for a series of antipsychotic drugs. Eur J Pharmacol. 2002; 450:37–41. [PubMed: 12176106]

35. Hayashi K, Shimizu M, Ino H, Yamaguchi M, Terai H, Hoshi N, et al. Probucol aggravates long QT syndrome associated with a novel missense mutation M124T in the N-terminus of HERG. Clin Sci (Lond). 2004; 107:175–182. [PubMed: 15043509]

36. Kim KS, Kim EJ. The phenothiazine drugs inhibit hERG potassium channels. Drug Chem Toxicol. 2005; 28:303–313. [PubMed: 16051556]

37. Duncan RS, McPate MJ, Ridley JM, Gao Z, James AF, Leishman DJ, et al. Inhibition of the HERG potassium channel by the tricyclic antidepressant doxepin. Biochem Pharmacol. 2007; 74:425–437. [PubMed: 17560554]

38. Ridley JM, Milnes JT, Benest AV, Masters JD, Witchel HJ, Hancox JC. Characterisation of recombinant HERG K+ channel blockade by the Class Ia antiarrhythmic drug procainamide. Biochem Biophys Res Commun. 2003; 306:388–393. [PubMed: 12804575]

39. Kang J, Wang L, Chen XL, Triggle DJ, Rampe D. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG. Mol Pharmacol. 2001; 59:122–126. [PubMed: 11125032]

40. Cordes JS, Sun Z, Lloyd DB, Bradley JA, Opsahl AC, Tengowski MW, et al. Pentamidine reduces hERG expression to prolong the QT interval. Br J Pharmacol. 2005; 145:15–23. [PubMed: 15711592]

41. Ficker E, Kuryshev YA, Dennis AT, Obejero-Paz C, Wang L, Hawryluk P, et al. Mechanisms of arsenic-induced prolongation of cardiac repolarization. Mol Pharmacol. 2004; 66:33–44. [PubMed: 15213294]

42. Anson BD, Ackerman MJ, Tester DJ, Will ML, Delisle BP, Anderson CL, January CT. Molecular and functional characterization of common polymorphisms in HERG (KCNH2) potassium channels. Am J Physiol Heart Circ Physiol. 2004; 286:H2434–H2441. [PubMed: 14975928]

43. Larsen LA, Andersen PS, Kanters J, Svendsen IH, Jacobsen JR, Vuust J, et al. Screening for mutations and polymorphisms in the genes KCNH2 and KCNE2 encoding the cardiac HERG/MiRP1 ion channel: implications for acquired and congenital long Q-T syndrome. Clin Chem. 2001; 47:1390–1395. [PubMed: 11468227]

44. Paavonen KJ, Chapman H, Laitinen PJ, Fodstad H, Piippo K, Swan H, et al. Functional characterization of the common amino acid 897 polymorphism of the cardiac potassium channel KCNH2 (HERG). Cardiovasc Res. 2003; 59:603–611. [PubMed: 14499861]

45. Laitinen P, Fodstad H, Piippo K, Swan H, Toivonen L, Viitasalo M, et al. Survey of the coding region of the HERG gene in long QT syndrome reveals six novel mutations and an amino acid polymorphism with possible phenotypic effects. Hum Mutat. 2000; 15:580–581. [PubMed: 10862094]

46. Bezzina CR, Verkerk AO, Busjahn A, Jeron A, Erdmann J, Koopmann TT, et al. A common polymorphism in KCNH2 (HERG) hastens cardiac repolarization. Cardiovasc Res. 2003; 59:27–36. [PubMed: 12829173]

47. Marjamaa A, Newton-Cheh C, Porthan K, Reunanen A, Lahermo P, Vaananen H, et al. Common candidate gene variants are associated with QT interval duration in the general population. J Intern Med. 2009; 265:448–458. [PubMed: 19019189]

48. Gentile S, Martin N, Scappini E, Williams J, Erxleben C, Armstrong DL. The human ERG1 channel polymorphism, K897T, creates a phosphorylation site that inhibits channel activity. Proc Natl Acad Sci U S A. 2008; 105:14704–14708. [PubMed: 18791070]

49. Sinner MF, Pfeufer A, Akyol M, Beckmann BM, Hinterseer M, Wacker A, et al. The non-synonymous coding IKr-channel variant KCNH2-K897T is associated with atrial fibrillation: results from a systematic candidate gene-based analysis of KCNH2 (HERG). Eur Heart J. 2008; 29:907–914. [PubMed: 18222980]

50. Chevalier P, Bellocq C, Millat G, Piqueras E, Potet F, Schott JJ, et al. Torsades de pointes complicating atrioventricular block: evidence for a genetic predisposition. Heart Rhythm. 2007; 4:170–174. [PubMed: 17275752]

Table 1

Table of minor allele frequencies for variants

	Those with aLQTS [14]	Those without aLQTS [14]	TN-control [14]	NHGRI-control [14]	African–American with SIDS [42]	African–American control [42]	Caucasian with SIDS [42]	Caucasian control [42]	Danish population [43]
K897T (%)	14	16	12	13	5.9	4	17.8	24	
R1047L (%)					0	0.5	4.2	1.5	4

aLQTS, acquired long QT syndrome; NHGRI, National Human Genome Research Institute; SIDS, sudden infant death syndrome; TN, Tennessee (population).