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Original Research Article

Comparison of the prevalence of four coding polymorphisms of *KCNH2* in healthy Kurds and Malays

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Abstract

***KCNH2* polymorphisms appear to be associated with arrhythmia susceptibility, drug-associated acquired long-QT syndrome and variability in drug responses. To date, little is known about the prevalence of *KCNH2* polymorphisms among Kurds and Malays. As such, there is clearly a need to explore the genetic polymorphisms of *KCNH2* among Kurds and Malays in order to understand the ethnic variation in *KCNH2* polymorphisms. DNA was extracted from whole blood and then subjected to genotyping for *KCNH2* polymorphisms, including 1539C>T (rs1805120), 1956T>C (rs1137617), 2350C>T (rs12720441) and 2690A>C (rs1805123) using nested allele-specific PCR. The *2350T* allele for the 2350C>T polymorphism was absent in 487 unrelated healthy Kurds and 117 Malays. The most frequent mutant allele in Kurds was *1956C* (63.9%), followed by *1539T* (26.6%) and *2690C* (22.4%). Frequencies of the *1956C*, *1539T* and *2690C* alleles in Malays were 80.8%, 52.6% and 8.1%, respectively. The relative commonness of mutant alleles of *KCNH2* polymorphisms in our study calls attention to *KCNH2* polymorphisms, which should be incorporated into future association studies in Kurds and Malays for the development of effective QT-prolonging medications.**

Keywords: Genetic polymorphisms; nested allele-specific PCR; *KCNH2*; Kurds; Malays

List of Abbreviations

LQTS: Long QT syndrome; **ECG:** electrocardiogram; **hERG:** human ether-a-go-go-related gene; **IKr:** potassium channel; ***KCNH2*:** potassium voltage-gated channel subfamily H member 2; **bp:** base pairs; **AF:** atrial fibrillation; **ATS:** Andersen-Tawil syndrome; **CCBs:** calcium channel blockers; **ADR:** adrenergic receptor; **aLQTS:** acquired long-QT syndrome; **PCR:** polymerase chain reaction; **HWE:** Hardy–Weinberg equilibrium; **SNPs:** single nucleotide polymorphisms; **MMT:** methadone maintenance therapy; **TdP VT:** torsade de pointes ventricular tachycardia; **NCBI:** National Center for Biotechnology Information; **LQT2:** congenital type 2 LQTS

INTRODUCTION

Long QT syndrome (LQTS) is characterized by an inherited or acquired prolonged QT interval on electrocardiogram (ECG). Inherited LQTS occurs as a result of mutations in the potassium voltage-gated

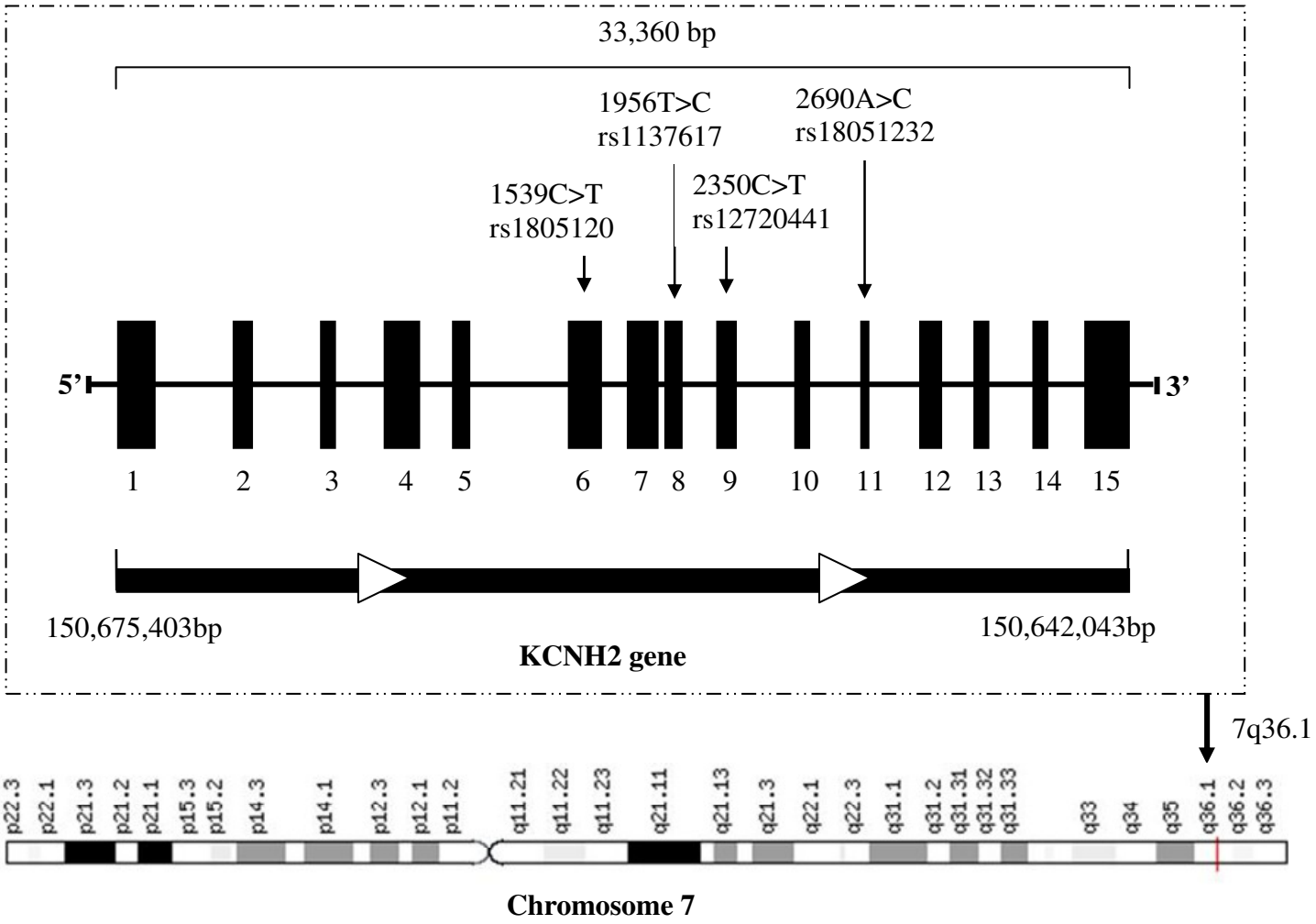

Figure 1. *KCNH2* gene structure and polymorphisms studied. Boxes represent exons; horizontal lines connecting boxes represent introns, promoters and untranslated regions; arrows indicate relative locations of the polymorphisms. This figure is based on the AceView genes, which are available at http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly.

channel *KCNE1* and *KCNQ1* genes (Baig et al., 2011). The acquired types of LQTS are generally caused by various drugs (Chugh et al., 2008), electrolyte imbalances (Gordon et al., 2008), marked bradycardia (Tsuji et al., 2006), cocaine (Wood et al., 2009), organophosphorus compounds (Vijayakumar et al., 2011), severe haemorrhage (Frangiskakis et al., 2009), myocardial ischaemia (Denney et al., 2005), protein sparing fasting, autonomic neuropathy (Khan, 2002) and human immunodeficiency virus disease (Bai et al., 2011).

The mechanism for most medications used to treat QT is inhibition of the potassium voltage-gated channel subfamily H member 2 *(*KCNH2*)*-encoded by human ether-a-go-go-related gene (*hERG*). The hERG channel mediates a rapid activation-delayed rectifier potassium channel current (IKr) that is important for phase 3 of the cardiac action potential repolarization. Inhibition of this results in prolonging the action of the potential duration and the QT interval. Interestingly, mutations in the *KCNH2*-encoded channel are also responsible for congenital type 2 LQTS (LQT2) (Ayad et al., 2010; Eldstrom and Fedida, 2011).

The *KCNH2* gene has been mapped to chromosome 7q36.1. This gene has 33,360 base pairs (bp) and 15 coding exons that are separated by 14 introns (GenBank accession number: NC_000007.13), as illustrated in Figure 1 (Atalar et al., 2010). Previous evidence has indicated that patients with a *KCNH2* polymorphism present with a higher incidence of atrial fibrillation (AF). Wang et al. (2009) observed an association between the rs1805120 (1539C>T, F513F) polymorphism and the risk of acquired AF in a Chinese population. The rs1805120 is a synonymous variation located in the coding sequence of exon 6 of *KCNH2* and exchanges the nucleic acid C with T at position 1539 of the cDNA (c.1539C>T). Another polymorphism, rs1805123 (2690A>C, K897T), is a non-synonymous variation located in the coding

sequence of exon 11 and exchanges nucleic acid A with C at position 2690 of the cDNA (c.2690A>C) and the amino acid lysine with threonine at position 897 of the protein (p.K897T). Sinner et al. (2008) observed an association of the rs1805123 with AF in Germans. Recently, Krych et al. (2017) examined the characteristics of 11 unrelated families with Andersen-Tawil syndrome (ATS) and suggested that rs1805123 may contribute to the occurrence of syncope.

A significant association was identified between rs1137617 (1956T>C, Y652Y) and the efficacy of antihypertensive drugs, such as calcium channel blockers (CCBs) and adrenergic receptor (ADR) blockers in a Chinese population (He et al., 2013). The rs1137617 is a synonymous variation located in the coding sequence of exon 8 and exchanges the nucleic acid T with C at position 1956 of the coding DNA (c.1956T>C). Another important polymorphism, rs12720441 (2350C>T, R784W), is a non-synonymous variation located in the coding sequence of exon 9 and exchanges the nucleic acid C with T at position 2350 of the coding DNA (c.2350C>T) and the amino acid arginine with tryptophan at position 784 of the protein (p.R784W). An *in vitro* study showed that the rs12720441 mutation reduced K^+ currents, consistent with the idea that they augment risk for the acquired long-QT syndrome (aLQTS) (Yang et al., 2002). Identifying the polymorphisms of *KCNH2* may be useful in preventing associated diseases, re-estimating drug safety, and individualizing treatment (Shimizu and Horie, 2011; Zhang et al., 2012). Unfortunately, the prevalence of these *KCNH2* polymorphisms has not yet being reported among Kurds and Malays. In this study, we aimed to investigate the frequencies of four polymorphisms of *KCNH2* in Kurds and Malays in order to understand better the ethnic variation in KCNH2 polymorphisms. The results of this study will generate a pharmacogenetics resource database for identifying the polymorphisms of *KCNH2* that may be useful in the drug development for individualizing treatment and choice of medications.

MATERIALS AND METHODS

Participants

The study that explored *KCNH2* polymorphisms in healthy Malays in Malaysia was part of our studies on the genetic polymorphism of drug-metabolizing enzymes that began in 2003 (Musa et al., 2012). The studied subject of healthy individuals was used for the preliminary stage of the study, to explore the type and frequencies of *KCNH2* polymorphisms, before the studies using patient populations could be conducted. An approval was obtained from the local institutional ethics committee and the study was conducted based on the protocols that are in accordance with the Helsinki Declaration of 1975 and 1983. All blood donors were unrelated healthy individuals enrolled from January to December 2003 at our blood bank. Written informed consent was obtained from all participants. All the subjects were screened against the following inclusion criteria:(i) Understood the aim of the study and study procedures, (ii) Willing to provide written informed consent, (iii) Ethnic origin could be determined up to three generations, and (iv) No family relationship with other subjects that were enrolled in this project. Subjects were excluded if their parents or grandparents up to three generations were of a different ethnic origin or the origin could not be determined.

Similar ethical and methodological considerations were used for the sample collections from unrelated healthy Kurds in Iraq for the second part of the study. Subjects were invited from several villages in Iraq over a period of three months in 2015. They were given an explanation about the study and were invited to participate if they were willing to sign a written informed consent form. They were administered standard questionnaires to obtain demographic data. All individuals participating in this study were required to know their ethnic origin up to three generations.

Genotyping of KCNH2 polymorphisms

Venous blood (5 ml) samples were obtained from healthy Malays in Malaysia and healthy Kurds in Iraq for KCNH2 genotyping. Sample collection was carried out using sodium citrate-containing tubes and was stored at –20°C until further processing. Genomic DNA was extracted from peripheral leucocytes using the method that was previously described (Ismail and Teh, 2001). The quantity and quality of the extracted DNA were determined on the spectrophotometer with measurements at 260 and 280 nm. Genotyping of *KCNH2* polymorphisms, including 1539C>T (rs1805120), 1956T>C (rs1137617), 2350C>T (rs12720441), and 2690A>C (rs1805123), were performed using a duplex nested allele-specific polymerase chain reaction (PCR). Briefly, the method involved the use of the primers listed in Table 1 for the first PCR to isolate regions of interest in the *KCNH2* gene. This was followed by a second parallel PCR using the primers listed in Table 1 that were designed to have specific 3'-ends, which were manipulated to differentiate single nucleotide changes at specific loci during PCR amplification. PCR was performed using Veriti 96-well thermal cycler (Applied Biosystem, Foster City, CA).

The first PCR was expected to yield four products of sizes ranging from 430 to 741 base pairs. The reactions were carried out in 25 µl volume reaction mixtures each contained 2 µl genomic DNA, 12.5 µl MyTaq master mix and primers at appropriate concentrations. The products were analysed on 2.5% agarose gels (Promega Corporation, Madison, USA) in 1×Tris-Borate-EDTA (TBE) buffer. In the second PCR, 2 sets of parallel allele-

Table 1. *KCNH2* primers used for nested allele-specific PCR. The primers are rs1805120 (1539C>T, F513F), rs1137617 (1956T>C, Y652Y), rs12720441 (2350C>T, R784W), and rs1805123 (2690A>C, K897T).

PCR	Primer	Sequence (5'–3')	Fragment size (bp)	[Primer] (µM)
First PCR	HERG EX6 FW	TGC TGT GGT CGC TTG GCT GAG G	741	0.20
	HERG EX6 RV	CAG CTG CCT TGC CAC CAT GTC TC		0.20
	HERG EX8 FW	CAT CGT GAC ATG GTT TGC GGG CT	670	0.20
	HERG EX8 RV	TAG AGA CCA TTC CCG CCC TGG G		0.20
	HERG EX9 FW	TGA CAT GGA GGG GTC GGA TGG T	578	0.20
	HERG EX9 RV	TGG CGG ATC CTG AAG GGA AGG		0.20
	HERG EX11 FW	TGG GGC GCC CAG CCC TAC TTT T	430	0.25
	HERG EX11 RV	TAG GCT TGC CCT GGA GGG TGG A		0.25
Second PCR Set 1				
Common primer	HERG EX8 RV	TAG AGA CCA TTC CCG CCC TGG G		0.15
Wild-type primers	HERG Y652Y wt FW	CAC GCC CCC AGC CCT CAT GTA T	478	0.15
Mutant-type primers	HERG Y652Y mt FW	CAC GCC CCC AGC CCT CAT GTA C		0.15
Common primer	HERG EX11 RV	TAG GCT TGC CCT GGA GGG TGG A		0.15
Wild-type primers	HERG K897T wt FW	CTT CCG CAG GCG CAC GGA CAA	248	0.15
Mutant-type primers	HERG K897T mt FW	CTT CCG CAG GCG CAC GGA CAC		0.15
Second PCR Set 2				
Common primer	HERG EX6 FW	TGC TGT GGT CGC TTG GCT GAG G		0.15
Wild-type primers	HERG F513F wt RV	ACC TCC TCA GAG CCA GAG CCG	584	0.15
Mutant-type primers	HERG F513F mt RV	ACC TCC TCA GAG CCA GAG CCA		0.15
Common primer	HERG EX9 RV	TGG CGG ATC CTG AAG GGA AGG		0.25
Wild-type primers	HERG R784W wt FW	ACC GCC CTG TAC TTC ATC TCC C	308	0.25
Mutant-type primers	HERG R784W mt FW	ACC GCC CTG TAC TTC ATC TCC T		0.25

specific PCR were performed: set 1 for rs1137617 (1956T>C, Y652Y) and rs1805123 (2690A>C, K897T), and set 2 for rs1805120 (1539C>T, F513F) and rs12720441 (2350C>T, R784W). For all the sets, 2 µl of the first PCR product (diluted 25×) was used as a template for the second PCR in a 25 µl reaction mixture that contained 1× PCR buffer,1.0 mM $MgCl_2$, 0.2 mM dNTPs, 0.5 U DNA Taq Polymerase and the appropriate amounts of the primers. The cycling conditions were again optimized for the different sets of PCR, and the products were analysed on 3% agarose gels in 1× TBE buffer.

Statistical analysis

Allele frequencies were estimated from the genotype numbers observed in the sample by gene counting method. A possible deviation from Hardy–Weinberg equilibrium (HWE) was tested for statistical significance by a comparison of the observed and expected homozygote frequency using X^2-test with one degree of freedom.

RESULTS

Characteristics of study participants

This study investigated the prevalence of four known genetic polymorphisms of *KCNH2* among Malays in Malaysia and Kurds in Iraq. The sum of

Table 2. Genotype and allele distributions for the four polymorphisms of *KCNH2* among Kurds and Malays.

Polymorphism	Kurds					Malays				
	n (%)		95% CI		HWE *p* value*	n (%)		95% CI		HWE *p* value*
rs1805120 (1539C>T, F513F)										
1539 CC	272	(55.9)	51.5	- 60.3	0.921	25	(21.4)	14.0	- 28.8	0.965
1539 CT	171	(35.1)	30.9	- 39.3		61	(52.1)	43.0	- 61.2	
1539 TT	44	(9.0)	6.5	- 11.5		31	(26.5)	18.5	- 34.5	
1539C	715	(73.4)	70.6	- 76.2		111	(47.4)	41.0	- 53.8	
1539T	259	(26.6)	23.8	- 29.4		123	(52.6)	46.2	- 59.0	
rs1137617 (1956T>C, Y652Y)										
1956 TT	74	(15.3)	12.1	- 18.5	0.922	5	(4.3)	0.6	- 8.0	0.969
1956 TC	202	(41.6)	37.2	- 46.0		35	(29.9)	21.6	- 38.2	
1956 CC	209	(43.1)	38.7	- 47.5		77	(65.8)	57.2	- 74.4	
1956T	350	(36.1)	33.1	- 39.1		45	(19.2)	14.2	- 24.2	
1956C	620	(63.9)	60.9	- 66.9		189	(80.8)	75.8	- 85.8	
rs12720441 (2350C>T, R784W)										
2350 CC	487	(100.0)	-		-	117	(100.0)	-		-
2350 CT	0	(0.0)				0	(0.0)			
2350 TT	0	(0.0)				0	(0.0)			
2350C	974	(100.0)	-			234	(100.0)	-		
2350T	0	(0.0)				0	(0.0)			
rs1805123 (2690A>C, K897T)										
2690 AA	294	(60.4)	56.1	- 64.7	0.994	98	(83.8)	77.1	- 90.5	0.928
2690 AC	168	(34.5)	30.3	- 38.7		19	(16.2)	9.5	- 22.9	
2690 CC	25	(5.1)	3.1	- 7.1		0	(0.0)	-		
2690A	756	(77.6)	75.0	- 80.2		215	(91.9)	88.4	- 95.4	
2690C	218	(22.4)	19.8	- 25.0		19	(8.1)	4.6	- 11.6	

*A comparison of the observed and expected homozygote frequency using a X^2-test with one degree of freedom, - not present/available. n: number of participant/allele; CI: confidence interval; HWE: Hardy-Weinberg equilibrium

487 unrelated healthy Kurds (mean age = 30.0 ± 10.63 years) and 117 healthy Malays (mean age = 30.7± 8.56 years) were recruited. The majority of Malay participants were males (n = 78, 66.7%), while most of the Kurd's participants were females (n = 419, 86.0%).

Distributions of investigated KCNH2 polymorphisms

The genotype and allele frequencies of the investigated *KCNH2* polymorphisms are shown in Table 2. All genotypes of the Kurds and Malays were within HWE (p>0.921) except for the 2350C>T polymorphism for which HWE could not be determined because only one genotype was observed in the samples. Subjects from both the Kurd and Malay groups were assumed to be random and representative of their respective

Table 3. Allele frequencies for the four polymorphisms of *KCNH2*.

Population/Sample	N	Frequency (%)	References
1539T allele			
Kurd (Iraq)	487	26.6	-
Malay (Malaysia)	117	52.6	-
Han Chinese (Beijing)	82	61.0	NCBI
Han Chinese (Beijing)	86	55.8	NCBI
Han Chinese (Beijing)	90	26.7	Chen, Xia, Li, Zhai, Yin, Liu, Zhang, Wang [23]
Han Chinese (Shanghai)	297	74.2	Wang, Wang, Chen, Yu, Wang, Sun, Lu, Shen, Lu, Li, Jin [14]
Japanese (Tokyo)	170	72.9	NCBI
Caucasian (German)	188	19.0	Aydin, Bähring, Dahm, Guenther, Uhlmann, Busjahn, Luft [30]
European	70	8.6	NCBI
European	226	20.4	NCBI
Sub-Saharan African (Yoruba in Ibadan)	226	25.7	NCBI
African American	52	9.6	NCBI
1956C allele			
Kurd (Iraq)	485	63.9	-
Malay (Malaysia)	117	80.8	-
Caucasian (German)	188	43.0	Aydin, Bähring, Dahm, Guenther, Uhlmann, Busjahn, Luft [30]
African American	86	82.6	NCBI
European	92	55.4	NCBI
2350T allele			
Kurd (Iraq)	487	0.0	-
Malay (Malaysia)	117	0.0	-
Han Chinese (Beijing)	86	0.0	NCBI
Japanese (Tokyo)	88	0.0	NCBI
European	116	0.0	NCBI
Sub-Saharan African (Yoruba in Ibadan)	116	0.0	NCBI
2690C allele			
Kurd (Iraq)	487	22.4	-
Malay (Malaysia)	117	8.1	-
Han Chinese (Beijing)	82	4.9	NCBI
Han Chinese (Beijing)	86	2.3	NCBI
Han Chinese (Guangzhou)	100	2.0	Liu, Zhao, Su, Tang, Lv, Liu, Quan, Cheng [32]
Japanese (Tokyo)	172	2.3	NCBI
Caucasian (German)	188	25.0	Aydin, Bähring, Dahm, Guenther, Uhlmann, Busjahn, Luft [30]
Caucasian(Finland)	81	15.4	Laitinen, Fodstad, Piippo, Swan, Toivonen, Viitasalo, Kaprio, Kontula [33]
Caucasian(Finland)	413	16.0	Pietila, Fodstad, Niskasaari, Laitinen, Swan, Savolainen, Kesaniemi, Kontula, Huikuri [24]
Caucasian (German)	2399	23.5	Sinner, Pfeufer, Akyol, Beckmann, Hinterseer, Wacker, Perz, Sauter, Illig, Nabauer, Schmitt, Wichmann, Schomig, Steinbeck, Meitinger, Kaab [15]
European	226	23.9	NCBI
Sub-Saharan African (Yoruba in Ibadan)	118	1.7	NCBI

"-" indicates the data from our present and previous studies

populations as the HWE did not reveal a significant deviation. The *1539C/T*, *2350C,* and *2690A/C* alleles were successfully amplified in all the 487 Kurdish participants, while the *1956T/C* alleles could not be amplified in two Kurds. Mutated alleles for all of the single nucleotide polymorphisms (SNPs) were observed except for the 2350C>T polymorphism (Table 3). Frequencies of mutated allele for 1539C>T, 1956T>C and 2690A>C polymorphisms were 26.6%, 63.9%, and 22.4%, respectively. The *1539C/T*, *1956T/C*, *2350C* and *2690A/C* alleles were also successfully amplified in 117 Malay participants, while the *2350T* allele for the 2350C>T polymorphism was absent. Frequencies of *1956C*, *1539T*, and *2690C* alleles in Malays were 80.8%, 52.6%, and 8.1%, respectively.

DISCUSSION

Until now, only a small number of studies on the prevalence of *KCNH2* polymorphisms have been reported. Among these are the studies from China, Germany and Finland that investigate *KCNH2* polymorphisms and their association with AF, as well as the duration of re-polarization (Chen et al., 2016; Pietila et al., 2002; Sinner et al., 2008). Unfortunately, *KCNH2* polymorphisms have not previously been investigated in Kurds and Malays. In our current study, we genotyped the healthy Kurds and Malays for four polymorphisms of *KCNH2*, namely 1539C>T (rs1805120), 1956T>C (rs1137617), 2350C>T (rs12720441) and 2690A>C (rs1805123).

Our interest in *KCNH2* stemmed from the purported importance in the mechanism of action for most potential QT-prolonging medications, such as methadone. Methadone is used in methadone maintenance therapy (MMT) worldwide. It is known to be associated with a LQTS and the subsequent development of torsades de pointes (TdP) (Digby et al., 2011). QT prolongations, TdP ventricular tachycardia (TdP VT) and death have been reported to be associated with methadone use. Methadone's proarrhythmic toxicity is related to inhibition of the cardiac rapid component of the delayed rectifier IKr and prolongation of the action potential (Behr and Roden, 2013; Grilo et al., 2010). Although this study was not sufficiently powered to determine the ethnic differences, there was a trend suggesting that the Malays in Malaysia and Kurds in Iraq shared some similarities and some differences in terms of the investigated *KCNH2* polymorphisms. In both ethnic groups, the *2350T* allele was absent. Population-wide, this was not expected to confer phenotypic differences among the ethnic groups. Our study showed that the frequency of the*1539T* allele (52.6%) and the*1956C* allele (80.8%) of the 1539C>T and 1956T>C polymorphisms, respectively, in Malays were higher than those found among Kurdish samples (26.6% and 63.9%, respectively). However, the Malays (8.1%) had a lower frequency of the *2690C* allele of the 2690A>C polymorphism compared to Kurds (22.4%).

Polymorphisms in *KCNH2* were reported to be associated with common arrhythmias, such as AF (Chen et al., 2016; Sinner et al., 2008; Wang et al., 2009). The common *2690A* allele of the 2690A>C polymorphism was replicated in 536 independent AF cases and 1781 controls [overall odds ratio 1.25, 95% confidence interval 1.11–1.41, p=0.00033] (Sinner et al., 2008). This study showed that the *2690A* allele was associated with a higher incidence of AF. However, the consequences of the 2690A>C polymorphism at the atrial level require further functional investigations. The effects of drugs to treat or prevent arrhythmias are highly variable, and the reasons for this include a genetic component factor. Our study compared the allele frequencies of the SNPs that were detected in the Kurds and Malays and other populations in order to determine the potential differences between the populations of the allele distributions and the SNPs. Taken together, there were marked inter-ethnic differences in allele frequencies of *KCNH2* polymorphisms. Thus, the present data point to future work in unravelling both arrhythmia susceptibility and variability in response to drug therapy in different ethnic groups.

Polymorphisms in *KCNH2* were also reported to be associated with the efficacy of antihypertensive drugs, CCBs and ADR blockers (He et al., 2013) on a LQTS (Yang et al., 2002). The knowledge gained from these studies could be useful in planning drug therapies for the different groups, especially as they pertain to drugs associated with cardiac ion channel blockade and QTc prolongation (Ackerman et al., 2011; Paulussen et al., 2004). Individuals free from variations in a QT syndrome gene may develop prolongations in the QT interval as a response to medications or electrolyte imbalances. Nevertheless, genetic variations govern their tendency to have such developments (Aydin et al., 2005). Clinical toxicities that have occurred during treatment with methadone may be due to the genetic polymorphisms that are coupled with dose-dependent drugs. Because of the known ethnic variation in *KCNH2* polymorphisms, there is clearly a need to be careful in the selection of SNPs for association studies (Bush et al., 2009). To the best of our knowledge, this is the first study to determine the prevalence of *KCNH2* polymorphisms among Kurds and Malays. Thus, this study provides a basic and working understanding of population differences in the *KCNH2* polymorphisms that are necessary for conducting future association studies.

The *KCNH2* polymorphisms investigated in this study did not cover the entire *KCNH2* gene. The sample size was another limitation, and thus, further studies with larger sample sizes are encouraged. Even so, we feel that our study did reveal some important information about *KCNH2* polymorphisms and may contribute to the genetic variation across the global samples for the Single

Nucleotide Polymorphism Database of National Center for Biotechnology Information (NCBI).

CONCLUSIONS

We conclude the two ethnic groups shared some similarities and some differences in terms of the investigated KCNH2 polymorphisms. The KCNH2 polymorphisms that occur in Kurds and Malays are of importance since the SNPs are associated with arrhythmia susceptibility, variability in response to drug therapy and acquired long-QT syndrome. These data generated from the healthy individuals allow comparisons of pharmacogenetic variation between populations with different ethnicities. These findings also provide a rationale for follow-up research to better understand KCNH2 phenotypic associations with possible disease development and their advantages in delivering personalized medicine to different ethnic groups.

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