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SHORT COMMUNICATION

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Twenty single nucleotide polymorphisms (SNPs) and their allelic frequencies in four genes that are responsible for familial long QT syndrome in the Japanese population

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Abstract We report here 20 single nucleotide polymorphisms (SNPs), including 10 novel ones, and their allelic frequencies detected in four genes that are known to be responsible for familial long QT syndrome in the Japanese population; 7 polymorphisms are in the *KCNQ1* gene, 6 in the *KCNH2* gene, 5 in the *SCN5A* gene, and 2 in the *KCNE1* gene. These data will be of use for genetic association studies of acquired cardiac arrhythmias.

Key words Long QT syndrome · Single nucleotide polymorphism · Japanese population · Acquired arrhythmia · Proarrhythmia

Introduction

Long QT syndrome (LQTS), an arrhythmogenic disorder characterized by prolongation of the QT interval on electrocardiograms (ECGs), often causes syncope or cardiac sudden death as the result of a recurrent and lethal arrhythmia, such as ventricular tachycardia, torsades de pointes, and ventricular fibrillation. Five genes responsible for this syndrome (*KCNQ1* (also known as *KVLQT1*), *KCNH2* (also known as *HERG*), *KCNE1*, *KCNE2*, and *SCN5A*) have been identified until now (Curran et al. 1995; Wang et al. 1996a; Wang et al. 1996b; Splawski et al. 1997; Abbott et al. 1999). Previous studies have suggested that some mild LQTS mutations may cause drug-induced LQTS (Donger et al. 1997; Abbott et al. 1999), leading to the expectation that polymorphisms of LQTS-related genes will potentially provide useful information on acquired cardiac arrhythmias. Until now, 17 SNPs in these genes have been reported (Abbott et al. 1999; Akimoto et al. 1998; Itoh et al. 1998a; Lai et al. 1994; Larsen et al. 1999; Tesson et al. 1996; Wang et al. 1995).

Here we report single nucleotide polymorphisms in genes responsible for familial long QT syndrome in the Japanese population, along with their allelic frequencies.

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Subjects and methods

In the course of our screening of mutations in Japanese patients with long QT syndrome, we have identified 20 polymorphisms in both LQTS patients and normal individuals. The screening method was as described previously (Itoh et al. 1998a). In brief, genomic DNA was prepared from blood samples according to the standard protocols. All exons of each gene (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2*) and their flanking intronic sequences were amplified by polymerase chain reaction (PCR) primers described previously (Itoh et al. 1998a; Itoh et al. 1998b; Wang et al. 1996a), and analyzed by single-strand conformation polymorphism (SSCP) analysis. Fragments presenting an aberrant conformer were sequenced using ABI 377 sequencers.

To further investigate the allelic frequencies in a normal control population, hybridization of allele-specific oligonucleotides was performed in 50 or 100 normal independent individuals as described previously (Saiki et al. 1986). Oligonucleotides specific for both alleles were synthesized and used to discriminate the two alleles.

Results and discussion

In total, we have confirmed 20 SNPs (7 in the *KCNQ1* gene, 6 in the *KCNH2* gene, 5 in the *SCN5A* gene, and 2 in the *KCNE1* gene) and examined their allelic frequencies in

Table 1. Polymorphism of LQTS genes in Japanese population

Gene	Nucleotide change[a]	Amino acid change	Frequency of minor allele	Region	Number of chromosomes examined	Previous report (if any)
KCNQ1	435C > T	I145I	0.06	Exon 3	100	Itoh et al. 1998a
	1110G > A	A370A	0.04	Exon 10	100	
	1394 − 12C > T	Intronic variant	0.04	Intron 12	100	
	1638G > A	S546S	0.28	Exon 15	100	Lee et al. 1997
	1685 + 23G > A	Intronic variant	0.04	Intron 15	100	
	1732 + 43T > C	Intronic variant	0.23	Intron 16	100	
	1927G > A	G643S	0.09	Exon 18	100	Itoh et al. 1998a
KCNH2	1467T > C	I489I	0.33	Exon 6	100	Akimoto et al. 1998
	1539T > C	F513F	0.28	Exon 6	100	Akimoto et al. 1998
	1692A > G	L564L	0.06	Exon 7	100	Akimoto et al. 1998
	1956T > C	Y652Y	0.12	Exon 8	98	Larsen et al. 1999
	2690A > C	K897T	0.02	Exon 11	100	
	2965 + 22A > G	Intronic variant	0.22	Intron 12	100	
SCN5A	1673A > G	H558R	0.08	Exon 12	100	
	3269C > T	P1090L	0.04	Exon 18	100	
	4299 + 53T > C	Intronic variant	0.27	Intron 24	100	
	5457C > T	D1819D	0.46	Exon 28	100	Wang et al. 1995
	5851G > T	V1951L	0.005	Exon 28	200	
KCNE1	112A > G	S38G	0.19	Exon 1	98	Lai et al. 1994
	253G > A	D85N	0.02	Exon 1	100	Tesson et al. 1996

[a] Nucleotide numbering starts from ATG start codon (GenBank accession numbers AF000571 [*KCNQ1*], U04270 [*KCNH2*], NM000335 [*SCN5A*], M26685 [*KCNE1*], and NM005136 [*KCNE2*])

Japanese population. We were unable to detect any polymorphism in the *KCNE2* gene. Table 1 shows a summary of SNPs detected in our samples.

Among 17 SNPs reported previously, 7 could not be detected in this study. Although the sensitivity of the PCR-SSCP analysis could be one of the reasons for this non-detection, there must be differences in SNP distribution and/or allelic frequencies among ethnic groups. As we could not obtain information on the allelic frequencies of the 10 other SNPs that overlapped with those in the previous studies, we could not directly compare our results in the Japanese population with those in Caucasian populations.

We believe these data will provide useful information for the identification of genes related to secondary arrhythmia, for the classification of patients at high risk of proarrhythmia, and, eventually, for the selection of antiarrhythmic agents with possible proarrhythmic effects for these patients.

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