CORRESPONDENCE

R1193Q of SCN5A, a Brugada and long QT mutation, is a common polymorphism in Han Chinese

Recently, Wang *et al*¹ reported R1193Q mutation of SCN5A in one of the seven patients with acquired long QT syndrome (LQTS) and suggested that R1193Q is a functional mutation that can increase the susceptibility to this syndrome. The mutation destabilised channel inactivation and generated a persistent late current. The investigators found that 0.2% (4/2087) of the control subjects (of whom more than 90% were white and only 0.4% were Asian) also carried the mutation, and they suggested that it may be a risk factor for LQTS in the general population. The same mutation (listed as R1192Q using SCN5A RefSeq: NM_000335) has been reported in a Japanese infant with Brugada syndrome with frequent episodes of ventricular fibrillation.² They found that none of the 100 control subjects of Asian descent carried the variant.

We have identified the same R1193Q mutation by direct DNA sequencing of SCN5A in a four generation family of Chinese descent with cardiac conduction abnormalities and several instances of sudden death. However, the mutation is not associated with the disease or any ECG abnormalities in this family.

We then screened for the presence of R1193Q mutation in randomly selected control subjects consisting of Han Chinese by direct DNA sequencing and single nucleotide polymorphism (SNP) genotyping, using high throughput MALDI-TOF mass spectrometry. The R1193Q mutation was present in 12% (11/94) of the subjects, with an allele frequency of 6%. One of the carriers (subject 9) was homozygous for the mutation, and all the others were heterozygous. Clinical studies were available in nine of the 11 carriers (table 1). None of the carriers had electrocardiographic signs of Brugada syndrome; however, one had prolonged QTc (subject 7) and another had borderline QTc (subject 9, who is homozygous for R1193Q). In addition, subject 1 had frequent ventricular premature complexes of unknown aetiology. Her QTc was normal.

To investigate whether sequence variants other than R1193Q had any effects on the

clinical presentation, we sequenced all the coding regions of SCN5A in all the carriers and compared the sequences to four control subjects. Fifteen SNPs including six novel ones were identified (table 2). All novel SNPs were either located within the introns or showed synonymous amino acid changes, thus suggesting these SNPs are likely to be normal variants. There was no clear association of any particular SNPs in the carriers with abnormal ECG as compared with those with normal tracings (including H558R polymorphism which has been reported to modify the expression of the arrhythmia-causing mutation⁴).

Our identification of an R1193Q carrier with LQTS is consistent with the report by Wang *et al*¹ that R1193Q increases the risk for LQTS. We also noticed that the 76 year old male subject who is an R1193Q homozygote (subject 9) had a borderline QTc (437 ms). Incomplete penetrance in LQTS is a well characterised phenomenon, especially in males, who have a shorter QTc than females.⁵ Approximately 5–8% of LQTS patients had QTc values less than 440 ms.^{6–8} Two carriers in the report by Wang *et al* also had QTcs of

421 ms and 430 ms.¹ On the other hand, several of our carriers (subjects 1, 2, 5, and 6) had QTcs well below 410 ms, which is the shortest QTc reported for LQTS patients.⁶ This excluded these subjects with the diagnosis of LQTS.⁷ Challenging with drugs may induce LQTS in the asymptomatic individuals and could help to clarify the phenotypes; however, such tests are not without danger. For ethical reasons, these tests were not done.

R1193Q has also been reported to cause Brugada syndrome.² Both Vatta *et al* and Wang *et al* have shown that the mutant channel also inactivated faster than the wild type channel, which may cause Brugada syndrome.^{1,2} Nevertheless, none of our carriers had signs of this syndrome on their ECGs. The ECG hallmark of Brugada syndrome is dynamic³ and there are limitations in detecting it by single ECG assessment. A sodium channel blocker challenge test may help to establish the diagnosis, but again this raises ethical concerns.

In summary, R1193Q—a Brugada and long QT mutation found in patients with other ethnic background—is a common polymorphism in Han Chinese. R1193Q may increase the risk of LQTS; however, further studies will be needed to determine whether this variant indeed carries an increased risk for arrhythmia in the Chinese population.

Table 2 SCN5A single nucleotide polymorphisms identified in the R1193Q carriers and control subjects

No	Abbreviations	dbSNP ref number
1	42C→T (Arg14Arg)	Novel
2	87G→A (Ala29Ala)	Rs6599230
3	482+184G→A	Rs6781731
4	703+104C→T	Novel
5	1140+98G→A	Rs6599222
6	1673A→G (His558Arg)	Rs1805124
7	3183A→G (Glu1061Glu)	Rs7430407
8	3269C→T (Pro1090Leu)	Rs1805125
9	3621C→T (Phe1207Phe)	Novel
10	3840+17G→A	Novel
11	3840+73G→A	Novel
12	4245+82A→G	Rs6799868
13	4404C→T (V1468V)	Novel
14	4342+86A→G	Rs12715317
15	5457T→C (Asp1819Asp)	Rs1805126

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Table 1 Summary of clinical findings in the R1193Q carriers

	1	2	3	4	5	6	7	8	9
Genotype	R/Q	R/Q	R/Q	R/Q	R/Q	R/Q	R/Q	R/Q	Q/Q
Age/sex	35, F	32, M	45, F	40, F	71, M	26, M	75, F	46, M	76, M
History of syncope or arrhythmia	—*	—	—	—	—	—	—	—	—
Family history of sudden death or arrhythmia	—	—	—	—	—	—	—	—	—
ECG findings	—	—	—	—	—	—	—	—	—
Brugada sign†	—	—	—	—	—	—	—	—	—
QTc (ms)‡	367	395	427	422	367	364	472	418	437
Others	Frequent VPCs	—	—	—	—	—	—	—	—

*Indicated negative findings.

†Type 1–3 ST segment abnormalities in leads V1–V3.[3]

‡Normal <440 ms.

F, female; M, male; VPC, ventricular premature complex.

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