SHORT REPORT

A common SCN5A polymorphism attenuates a severe cardiac phenotype caused by a nonsense SCN5A mutation in a Chinese family with an inherited cardiac conduction defect

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The SCN5A mutations have been associated with a variety of arrhythmic disorders, including type 3 long QT syndrome (LQT3), Brugada syndrome and inherited cardiac conduction defects. The relationship between genotype and phenotype in SCN5A mutations is complex. Some SCN5A mutations may cause death or severe manifestations in some people and may not cause any symptoms or arrhythmias in others. The causes of these unpredictable clinical manifestations remain incompletely understood. The molecular basis of a four-generation family with cardiac conduction abnormalities was studied and whether variants in the SCN5A gene could account for the cardiac phenotypic variability observed in this family was determined. A novel mutation (W1421X) of SCN5A was identified in a four-generation family with cardiac conduction abnormalities and several cases of sudden death. Most family members who carry this W1421X mutation have developed major clinical manifestations or electrocardiographic abnormalities, both of which became more prominent as the patients grew older. However, the 73-year-old grandfather, who carried both the W1421X and R1193Q mutations, had thus far remained healthy and presented with only subtle electrocardiographic abnormalities, whereas most of his offspring, who carried a single mutation (W1421X), had died early or had major disease manifestations. This observation suggests that the R1193Q mutation has a complementary role in alleviating the deleterious effects conferred by W1421X in the function of the SCN5A gene. This report provides a good model to explain the mechanism of penetrance of genetic disorders.

The SCN5A gene encoding a voltage-gated sodium channel is predominately expressed in the heart, where it has a key role in the generation and propagation of the cardiac impulse.¹ SCN5A mutations have been associated with a variety of arrhythmic disorders, including type 3 long QT syndrome (LQT3), Brugada syndrome and inherited cardiac conduction defects.^{2–5} In general, the mutations that cause LQT3 result in a gain, whereas mutations that cause Brugada syndrome result in a loss of the sodium channel function.^{6,7} The pathophysiological sequence of inherited cardiac conduction defects remains unclear, although it most likely results from a loss of sodium ion channel function, as in the Brugada syndrome, perhaps with a different net effect on sodium ion current, after balancing with other modifying factors.^{5,8,9}

The relationship between genotype and phenotype in SCN5A mutations is intricate and complex. Some SCN5A mutations may cause death or severe disease manifestations in some people, and not cause any symptom of arrhythmias in others.^{10–11} Some SCN5A mutations can cause two or even three distinct phenotypes of arrhythmias in the same family.^{12–17} Furthermore, various clinical manifestations have also been observed among different ethnic populations. For example, a Brugada¹⁸ and a long QT¹⁹ mutation (R1193Q) found in Japanese and Caucasian populations, respectively, is a common polymorphism in Han Chinese.²⁰ The molecular basis of these various clinical manifestations and interethnic differences in the channelopathy related to the SCN5A is not completely understood.

We report a four-generation kindred with apparently autosomal dominant, however variable, expression of cardiac conduction abnormalities and sudden death. We studied

1. the molecular basis of this inherited conduction defect and
2. whether variants in the SCN5A gene could account for the cardiac phenotypic variability observed in this family.

METHODS

Clinical investigation

A four-generation Han Chinese family with apparent autosomal dominant inheritance of cardiac arrhythmias and sudden death was identified at the Taipei Veterans General Hospital (Taipei, Taiwan). We enrolled 17 members of this family in this study (fig 1), which was approved by our institutional review board. Informed consent was obtained from all those who participated in the study, or from the parents of the minors (generation IV, fig 1). The investigation included a review of the medical history, complete physical examination, echocardiography, a standard 12-lead electrocardiogram (ECG) measured at rest and, in some patients, a 24-h ambulatory ECG. PR, QRS interval, QT, QTc duration and QRS axis were measured. The normal range of the ECG measurements was based on the age of each person.²¹ For adults, a QRS interval >100 ms, and a PR interval >210 ms were considered prolonged.²²

Mutation analysis

As the dominant inheritance and clinical presentations suggested that SCN5A was a candidate gene, we directly sequenced all the coding regions and exon–intron junctions of SCN5A in this family. Genomic DNA was extracted directly

Abbreviations: ECG, electrocardiogram; LQTS, long QT Syndrome

Figure 1 Pedigree of the family with genotypes listed below the individual numbers. #, W1421X mutation; &, R1193Q mutation; NA, DNA sample not available.

from whole blood, using a PUREGENE purification kit (Gentra systems, Minneapolis, Minnesota, USA). Genomic DNA samples were amplified by polymerase chain reaction, using primers designed to amplify the coding region and intron–exon junctions of the SCN5A gene.²³ DNA sequencing was carried out using an ABI 3700 sequencer and BigDye Terminator sequencing kit (Applied Biosystems, Foster, California, USA). DNA samples from 95 healthy subjects randomly selected from a biobank in a nationwide population study, in which 3312 Han Chinese descendants were recruited based on the geographical distribution across Taiwan, were used as controls. The Han Chinese, representing roughly 98% of the population, is the largest ethnic group in Taiwan. None of the participants were aboriginal Taiwanese, who account for the remaining 2% of Taiwan's population. Mutation screening in normal subjects was carried out using the MassARRAY system (Sequenom, San Diego, California, USA) and confirmed by direct sequencing.

RESULTS

Clinical description

The severity of disease manifestations and age at the time of sudden death varied among family members. I-2 died suddenly in her 30s and II-2 died as a teenager (fig 1). However, II-4, at the age of 73 years, had never experienced syncope or chest tightness and remained healthy. He had a normal heart rate (60 bpm), normal QRS (64 ms) and QTc (0.313 ms) durations, a normal QRS axis and a mildly prolonged PR interval (240 ms) for his age (fig 2, table 1). III-1 had occasional syncope from about the age of 10 years, at which time he was found to have a patent arteriosus and underwent a ligation operation. However, the frequency of syncope increased gradually thereafter. He was diagnosed with sick sinus syndrome at 32 years of age and underwent implantation of a permanent pacemaker. He died suddenly in the absence of pacemaker malfunction or other apparent cause, 14 years after device implantation. III-3 died from measles infection at about 12 months of age. III-4 died suddenly, when about 2 years old, during a crying spell witnessed by the parents. III-5 was informed of having a minor cardiac conduction defect at a health examination for the military service. He began developing frequent syncopal episodes at about 30 years of age. A high-grade conduction defect with sinus bradycardia was diagnosed, and he underwent pacemaker implantation. III-7 experienced occasional bradycardia and chest tightness from the age of about 20 years, although he never underwent medical investigations for these symptoms. Sinus bradycardia and first-degree atrioventricular block were observed on the ECG recorded for this study. III-9 also had occasional heart rate slowing and chest tightness beginning in his early 20s. Sinus bradycardia

Figure 2 Lead II tracing of the electrocardiogram (ECG) obtained from participants II-4, III-5, III-7, IV-6, IV-7, IV-9, IV-10 and IV-12, and 24-h ambulatory ECG lead in patient III-9. The ECG was recorded at a 25 mm/s paper speed and 10 mm/mV signal amplitude. The ECG of III-9 was from a 24-h ambulatory tracing recorded 3 years before he died. III-5 was permanently paced. All the offspring had a wider QRS than patient II-4.

with first-degree atrioventricular block, incomplete right bundle-branch block and low P wave voltage were diagnosed at the age of 30 years. Three years after this diagnosis, he died suddenly while eating breakfast.

The other members of this family who carry a W1421X mutation are all quite young (generation IV, all <17 years of age) and have had no major clinical manifestation or sign of cardiac arrhythmia. On ECG, IV-6 had first-degree atrioventricular block with right bundle-branch block; IV-7 and IV-9 had first-degree atrioventricular block with non-specific intraventricular conduction delay (low voltage of the P wave was also present in IV-7); and IV-10 and IV-12 had non-specific intraventricular conduction delays. Table 1 summarises the QRS axis, longest PR, QRS interval and QTc durations of the affected members carrying a W1421X mutation. The remainder of the family members who did not have a W1421X mutation including II-1, II-5, III-2, III-8, III-10, IV-1, IV-2, IV-3, IV-8 and IV-11, had a normal ECG and no major clinical manifestation or sign of cardiac arrhythmia.

Mutation analysis

A G→A base substitution in exon 24, resulting in a premature stop codon (W1421X, fig 3), was found in all affected people in this kindred. In addition, a W1421X mutation was not found in any of the 95 normal subjects, suggesting that it is a disease-specific mutation, not a polymorphism.

Table 1 Demographic and electrocardiographic characteristics of W1421X mutation carriers

	Sex	Age (years)	ECG intervals (ms)			
			QRS axis	PR	QRS	QTc
II-4	M	73	12 (−30 to 105)	240 (210)	64 (100)	0.31 (0.44)*
III-7	M	42	191 (−30 to 105)	260 (210)	80 (100)	0.32 (0.44)*
III-9†	M	33	-	240 (210)	120 (100)	0.42 (0.44)*
IV-6	F	13	214 (20 to 120)	208 (180)	120 (100)	0.43 (0.44)*
IV-7	F	17	133 (20 to 120)	208 (180)	104 (100)	0.42 (0.44)*
IV-9	F	13	172 (20 to 120)	204 (180)	108 (100)	0.44 (0.44)*
IV-10	M	12	94 (20 to 120)	180 (170)	104 (90)	0.44 (0.44)*
IV-12	F	9	87 (20 to 120)	164 (170)	104 (90)	0.44 (0.44)*

Values in parentheses indicate normal QRS axis range and upper normal limits of PR, QRS and QTc intervals for age.
 *Indicate abnormal values for age.
 †The PR, QRS and QTc intervals in patient III-9 were measured on a 24-h ambulatory electrocardiograph (ECG) recorded 3 years before he died.
 A distinct ECG pattern of Brugada consisting of right bundle-branch block with ST-segment elevation in the right precordial leads (V1, V2 and V3) and normal QT interval.
 A QTc $\geq$ 480 ms in females or $\geq$ 470 ms in males, in the absence of drugs, electrolyte disturbance or other conditions that might independently lengthen the QT interval, is a sign for QT syndrome.

We also identified a G→A transition in exon 20, causing the substitution of arginine by glutamine (R1193Q) in patient II-4 but not in his children (III-5 and III-7), indicating that W1421X and R1193Q in II-4 were located on different chromosomes. However, the 1193Q mutation was observed in his daughter-in-law (III-2) and two of her children (IV-1 and IV-3), who had normal ECGs and no manifestations of heart disease, an observation consistent with our previous finding that R1193Q is a normal polymorphism in our population, present in 12% of normal Han Chinese.²⁰

To further confirm the parental origins of the R1193Q in participants IV-1 and IV-3, we established haplotypes of SCN5A in selected family members (II-4, III-2, IV-1 and IV-3) with intragenic single-nucleotide polymorphisms identified in sequencing. Participants IV-1 and IV-3 had identical haplotypes and shared one common allele with their mother (III-2). The two alleles of participant II-4 were not present in participants IV-1 and IV-3 (data not shown). This suggests that participants IV-1 and IV-3 inherited the sequence variant (R1193Q) from their mother, not from their father or grandfather.

The presence of R1193Q in II-4 may explain the absence of clinical manifestations in this 73-year-old patient, who also carried the W1421X mutation. To determine whether III-5 and III-7, who had severe manifestations of the disease, had a second mutation other than W1421X, we sequenced all the coding regions and exon–intron junctions of SCN5A in the nucleus family members (II-4 and II-5, and their two affected children III-5 and III-7). We identified two intronic single

nucleotide polymorphisms (IVS21+73 G→A, IVS26+86 A→G) and one synonymous amino acid change (5663 T→C) segregating in this family. Haplotype analysis showed that both affected children had received the same disease allele from their father, but different normal alleles from the mother. Neither a clear association with a particular single nucleotide polymorphism, nor a second mutation (non-synonymous amino acid change or nonsense mutation) other than the W1412 mutation was found in III-5 and III-7.

DISCUSSION

The progressive familial cardiac conduction defect associated with SCN5A is characterised by an impaired conduction of the cardiac impulse through the His-Purkinje system, which worsens with ageing. In this study, we observed a new mutation (W1421X) in a four-generation kindred with apparently autosomal inheritance of the cardiac conduction defect and sudden death. Most of the family members who carried this W1421X mutation had major disease manifestations, died suddenly or had abnormal ECGs, manifestations that became more prominent with increasing age. Several members of this family died suddenly between 20 and 30 years of age. However, the 73-year-old grandfather (II-4), who carried a W1421X mutation, was asymptomatic, enjoyed an uneventful life, and had only subtle ECG abnormalities, whereas all his children (III-1, 4, 5, 7 and 9) who carried the mutation had died at a young age or had major disease manifestations.

The W1421X mutation, located in exon 24 of the SCN5A, causes an early-truncated polypeptide (with a loss of 595 amino acids), which includes the S6 segment of the DIV domain and the whole DIV domain of SCN5A. Although we did not carry out a biophysical study of this mutation, we believe that the W1421X mutation should result in complete loss of channel function, owing to the loss of such a large fragment of SCN5A. A mutation (IVS.22+2TC) associated with cardiac conduction defects was recently proved to cause a complete loss of function of SCN5A.²⁴ Therefore, the haplo-insufficiency (complete loss of channel function) of SCN5A, as observed in our patients, might be a cause of cardiac conduction defects.

It is particularly noteworthy that a missense mutation (R1193Q) that can cause a gain of the sodium ion channel function and cause LQT3¹⁹ was also identified in the other allele of SCN5A in the grandfather, but not in his offspring. It has been reported that the R1193Q mutation confers a risk of LQTS3 or Brugada syndrome in the general population,^{18 19}

Figure 3 Results of DNA sequencing from participants II-4 (exon 23) and III-2 (exon 19), showing the nucleotide change and the predicted codon change. GenBank sequence NP_000326 was used as a reference sequence in the numbering of amino acids.

although it seems to be a common polymorphism in the Han Chinese population. Electrophysiological studies showed that R1193Q destabilises inactivation gating and generates a persistent, non-inactivating current, which results in a gain of the sodium channel function, as in the LQT3 syndrome.¹⁹ Through an unknown compensatory mechanism, the combination of R1193Q and W1421X mutations could result in a smaller "net" decrease in sodium current in comparison with the W1421X mutation alone, thereby generating a less prominent phenotype in patient II-4. This is further supported by the observation made in the grandfather II-4, who was the only carrier of two SCN5A mutations (W1421X and R1193Q), and by the absence of other sequence variants or the second SCN5A mutation among the patients with major disease manifestations (III-5 and III-7). These observations suggest that R1193Q could have an important role in mitigating the adverse effects conferred by W1421X of SCN5A.

There are ample examples to show that if one mutation resulted in an affected phenotype, then two mutations would result in an even more severe phenotype,^{25–27} examples including some of the channelopathy.^{28–30} There are also examples that a second mutation in cis can ameliorate the phenotype caused by the first mutation.^{31–32} However, examples of a second mutation in trans ameliorates the phenotype seem to be very rare and, to our knowledge, our report is perhaps the first in vivo observation of mitigation of the severity of channelopathic disease caused by a double mutation. This is a good model to explain the mechanism of penetrance of autosomal dominant disorders.

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