Ⅱ．研究成果の刊行に関する一覧表

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書籍

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Ⅲ. 研究成果の刊行物・別刷り

Common Sodium Channel Promoter Haplotype in Asian Subjects Underlies Variability in Cardiac Conduction

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Background—Reduced cardiac sodium current slows conduction and renders the heart susceptible to ventricular fibrillation. Loss of function mutations in *SCN5A*, encoding the cardiac sodium channel, are one cause of the Brugada syndrome, associated with slow conduction and a high incidence of ventricular fibrillation, especially in Asians. In this study, we tested the hypothesis that an *SCN5A* promoter polymorphism common in Asians modulates variability in cardiac conduction.

Methods and Results—Resequencing 2.8 kb of *SCN5A* promoter identified a haplotype variant consisting of 6 polymorphisms in near-complete linkage disequilibrium that occurred at an allele frequency of 22% in Asian subjects and was absent in whites and blacks. Reporter activity of this variant haplotype, designated HapB, in cardiomyocytes was reduced 62% compared with wild-type haplotype ($P=0.006$). The relationship between *SCN5A* promoter haplotype and PR and QRS durations, indexes of conduction velocity, was then analyzed in a cohort of 71 Japanese Brugada syndrome subjects without *SCN5A* mutations and in 102 Japanese control subjects. In both groups, PR and QRS durations were significantly longer in HapB individuals ($P\leq0.002$) with a gene-dose effect. In addition, up to 28% and 48% of variability in PR and QRS durations, respectively, were attributable to this haplotype. The extent of QRS widening during challenge with sodium channel blockers, known to be arrhythmogenic in Brugada syndrome and other settings, was also genotype dependent ($P=0.002$).

Conclusions—These data demonstrate that genetically determined variable sodium channel transcription occurs in the human heart and is associated with variable conduction velocity, an important contributor to arrhythmia susceptibility. **(*Circulation*. 2006;113:338-344.)**

Key Words: arrhythmia ■ conduction ■ death, sudden ■ genetics ■ ion channels

Sudden cardiac death (SCD) accounts for 20% of all mortality in Western countries.[1] One key determinant of normal excitation and conduction of the cardiac impulse is the cardiac sodium channel, responsible for rapid depolarization in most cardiomyocytes. Reduced sodium current predisposes to SCD. For example, although sodium channel blockers have been used for antiarrhythmic therapy, the Cardiac Arrhythmia Suppression Trial (CAST) showed that these agents increase the incidence of SCD.[2] Loss of function mutations in *SCN5A*, the cardiac sodium channel gene, causes ≈20% of cases of the Brugada syndrome, which is associated with a high risk of SCD.[3] Furthermore, there is evidence that such sodium channel mutations also may lead to enhanced fibrosis in myocardial tissue.[4,5]

Editorial 330
Clinical Perspective p 344

The overall hypothesis underlying the work presented here is that variability in regulation of sodium channel expression contributes to interindividual variability in cardiac conduction and consequently can be considered a candidate modulator of arrhythmia susceptibility, especially in the presence of other stressors such as drugs or acute myocardial ischemia.[6] As a first step in testing this hypothesis, we cloned and characterized the proximal promoter region of *SCN5A* and identified multiple cis-acting elements regulating gene expression.[7] We report here identification of an ethnic-specific, common *SCN5A* promoter variant that modulates PR and QRS durations, indexes of cardiac conduction.

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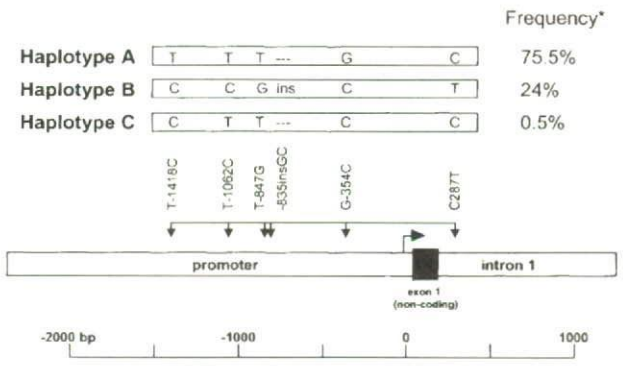

Figure 1. Haplotypes identified in the cardiac sodium channel gene (*SCN5A*) promoter. Nucleotide variations are indicated by their position relative to the major transcription initiation site (+1),[7] with the most frequent nucleotide given below and the least frequent nucleotide given above the position. *Frequency in the Japanese (control) population.

Methods

Identification of Polymorphisms

Resequencing 2.8 kb of the *SCN5A* promoter region in a single individual of Asian origin identified him as a homozygote for 6 DNA polymorphisms in the region: T-1418C, T-1062C, T-847G, −835insGC, G-354C, and C287T (Figure 1). The resequenced region encompassed positions −2190 to 613, relative to the major transcription initiation site[7] of the *SCN5A* promoter, including 2.2 kb upstream of exon 1, exon 1 (which is 173 bp and noncoding), and the proximal 439 bp of intron 1. The fragment was amplified by long and accurate polymerase chain reaction (PCR; TaKaRa kit) with primers F1 and R1 (Data Supplement Table I; see http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.580811/DC1). Further studies described below established that these polymorphisms were common and in near-total linkage disequilibrium, thereby identifying 2 common haplotype blocks, designated HapA and HapB. We also detected a third combination of polymorphisms, designated HapC, in <1% of subjects. In addition to the study populations, 150 white and 100 black individuals were tested for these haplotypes.

Functional Analysis

Generation of Constructs

The 2.8-kb fragment described above was amplified from genomic DNA of HapA- and HapB-homozygous individuals. These fragments were cloned into the pGEM-T Easy vector (Promega), and inserts were subsequently subcloned into the pGL3-basic vector (Promega), which contains the firefly luciferase coding sequence, to generate *SCN5A* promoter–luciferase fusion constructs for reporter assays. These constructs were designated pGL3-Hap A and pGL3-Hap B.

Reporter Activity

Reporter activity was assayed in neonatal mouse cardiomyocytes and in Chinese hamster ovary cells as described in detail previously.[7] In brief, 1 μg pGL3-Hap A or pGL3-Hap B was transfected into neonatal mouse cardiomyocytes or Chinese hamster ovary cells. In each experiment, 0.05 μg pRL-TK plasmid (Promega) encoding Renilla luciferase was cotransfected to normalize for experimental variability caused by differences in cell viability or transfection efficiency. Luminescence was measured 48 hours after transfection with the Dual-Luciferase Reporter Assay System (Promega). The pGL3-basic (promoterless) plasmid was tested in each experiment; its activity level served as the baseline.

Study Participants

Participants in the clinical study were ascertained at the National Cardiovascular Center (Osaka, Japan). All protocols (including molecular screening) were reviewed and approved by the Ethical Review Committee of the National Cardiovascular Center, and informed consent was obtained from all individuals.

The control population consisted of 102 subjects drawn from mutation-negative relatives in congenital long-QT syndrome families in which the causative mutation had been identified. Only 1 person was drawn from each family. There were 67 male and 35 female subjects ranging from 9 to 69 years of age; mean age was 40±14 years (mean±SD).

The Brugada syndrome population included 80 patients diagnosed with Brugada syndrome, defined as type 1 "coved" ST-segment elevation in V_1 through V_3 (spontaneous in 70 patients, induced by sodium channel blocker in 10 patients).[8] In all patients, physical examination, chest roentgenogram, laboratory values, echocardiography with wall motion analysis, and Doppler screening excluded structural heart disease. Aborted cardiac arrest or ventricular fibrillation (VF) was documented in 30 patients, syncope was identified in 20, and 30 were asymptomatic. All patients had previously been screened for *SCN5A* coding region mutations, and a mutation had been identified in 9 patients. The patient group included 76 male and 4 female subjects ranging from 1 to 76 years of age (mean±SD, 47±16 years).

ECG Phenotypes

ECGs were assessed by an investigator (W.S.) who was blinded to age, gender, and genetic and clinical information. Phenotypes assessed included RR interval, PR interval measured in lead II (PR_{II}), QRS interval measured in leads V_1 (QRS_{V1}) and V_6 (QRS_{V6}), ST amplitude at J point (ST_J), and ST amplitude at 80 ms after the end of the QRS (ST_{80}).

The effects of intravenous administration of sodium channel blockers on these ECG parameters were examined in 49 of 80 Brugada syndrome patients. Pilsicainide (maximum 1 mg/kg at a rate of 0.1 mg · kg^{-1} · min^{-1}) was used in 37 patients, flecainide (maximum 2 mg/kg at a rate of 0.2 mg · kg^{-1} · min^{-1}) was used in 9 patients, and disopyramide (maximum 2 mg/kg at a rate of 0.2 mg · kg^{-1} · min^{-1}) was used in 3 patients.

Genotyping

Genomic DNA was prepared from blood leukocytes. Genotyping for the T-1418C and T-1062C single nucleotide polymorphisms (SNPs) was performed by restriction fragment length polymorphism analysis after PCR amplification with *Ear*I and *Hae*III, respectively. PCR primers used to amplify the 161-bp fragment encompassing the T-1418C SNP were F2 and R2, and those used to amplify the 123-bp fragment encompassing the T-1062C SNP were F3 and R3 (Data Supplement Table II). Genotyping for the other 4 polymorphisms (T-847G, 835insGC, G-354C, and C287T) was done by DNA resequencing of both strands. PCR primers used to amplify the 638-bp fragment encompassing the T-847G, 835insGC, and G-354C polymorphisms were F4 and R4; those used to amplify the 599-bp fragment encompassing the C287T polymorphism were F5 and R5.

Statistical Analysis

Using the individual genotypes for the 6 polymorphisms, we estimated haplotype frequencies using an E-M algorithm.[9] The haplotype frequencies were used to calculate the probabilities of the haplotype pairs compatible with the genotype combinations of the multiple heterozygous patients using Bayes' theorem. Observed haplotype pair frequencies were compared with those expected under Hardy-Weinberg equilibrium in the Brugada syndrome population and control population separately with a χ^2 test. To compare haplotype pair frequencies among Brugada syndrome patients and control subjects, Fisher's exact test was used.

All quantitative phenotypes were normally distributed, and data are expressed as mean±SD. Continuous ECG phenotypes were compared between *SCN5A* mutation–negative Brugada syndrome patients, *SCN5A* mutation–positive Brugada syndrome patients, and control subjects by ANOVA adjusted for age and gender, followed by a post hoc test for pairwise comparisons. Student *t* tests were used

to compare the after-drug-challenge continuous ECG phenotypes between *SCN5A* mutation–negative and –positive Brugada syndrome patients. Correlations between quantitative phenotypes before and after sodium channel blockade are expressed as Pearson correlation coefficients (r). For comparison of the proportion of male subjects, Fisher's exact test was used.

The effect of haplotype pairs on the continuous ECG phenotypes was tested in the Brugada syndrome patients and control subjects separately by ANOVA with adjustment for age and gender. The 9 *SCN5A* mutation–positive Brugada syndrome patients were treated as a separate category (7 HapA/HapA homozygotes, 2 HapA/HapB heterozygotes, pooled). The 2 individuals with the rare HapC variant (1 patient from each group) were excluded from analyses. In all analyses, the proportion of variance attributable to the haplotype pair (R^2) was calculated and corrected for the effects of age and gender.

Differences in reporter gene expression activity between HapA and HapB were examined for statistical significance with Student's t test. Throughout, values of $P<0.05$ were interpreted as being significant. All statistical analyses were done with SAS software (version 9, SAS Institute).

Multiple Testing

When a Bonferroni correction for the 24 statistical models is used to compare the continuous ECG phenotypes, the significance level for the overall probability values is 0.002. Similarly, the Bonferroni-corrected significance levels for the pairwise comparisons between 3 and 4 groups is 0.017 and 0.008, respectively.

Results

Haplotypes

The 6 polymorphisms were in near-complete linkage disequilibrium, with only 2 (similar) discordant haplotypes (of 364; <1%), each occurring in 1 subject from each population. We designated HapA as containing all common alleles and HapB as containing all minor alleles (Figure 1). The discordant haplotype was designated HapC. The estimated frequencies of HapA, HapB, and HapC were 0.755, 0.240, and 0.005 in the control subjects and 0.782, 0.211, and 0.007 in the *SCN5A* mutation–negative Brugada syndrome patients, respectively. Haplotype distributions were in Hardy-Weinberg equilibrium ($P>0.05$) in both populations. No significant difference in haplotype frequencies was observed between the Brugada syndrome group and the control subjects. The haplotypes were absent in white and black samples.

Functional Analysis

In cardiomyocytes, reporter activity of HapB was markedly reduced, by 62%, compared with HapA: 5.5±0.4 (mean±SE) versus 14.5±2.8 (normalized activity units; n=9 each; $P=0.006$; Figure 2). A similar trend was seen in the noncardiac cells: 2.7±0.3 versus 3.6±0.3 (n=13 each; $P=0.04$; Figure 2).

Phenotypic Characteristics of the Control and Brugada Syndrome Patient Populations

The decreased reporter activity for HapB suggested that individuals carrying this promoter haplotype would display ECG-detectable conduction slowing. Accordingly, the relationships between genotype and ECG intervals were evaluated in the control and Brugada syndrome populations.

ECG data are shown in Table 1. As expected, Brugada syndrome patients had significantly longer conduction intervals (PR_{II}, QRS_{V1}, QRS_{V6}) and greater ST-segment elevation

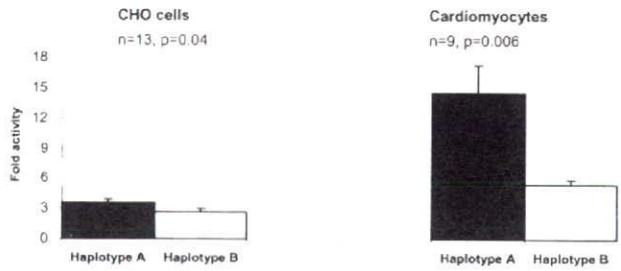

Figure 2. Reporter activity of *SCN5A* promoter haplotypes A and B. Firefly luciferase expression levels, which report the activities of the inserted *SCN5A* sequence, were divided by coexpressed Renilla luciferase activities and expressed as relative luciferase units.[7] Data are presented as mean±SE (vs empty vector). CHO indicates Chinese hamster ovary.

(ST_J, ST_{80}) compared with control subjects. Heart rate was not significantly different between the 2 populations. In addition, we found differences between *SCN5A* mutation–positive and *SCN5A* mutation–negative Brugada syndrome patients similar to those previously reported[10]: Mutation-positive subjects had significantly longer baseline PR and QRS intervals and longer RR intervals. Data on the subset of Brugada syndrome patients who underwent drug challenge are presented in Table 2. For all ECG parameters investigated, highly significant ($P<0.0001$) correlations were present between measures before and after drug challenge (Table 2). As previously reported, *SCN5A* mutation–positive patients displayed longer PR and QRS intervals after challenge with sodium channel blockers compared with *SCN5A* mutation–negative patients.[10]

Haplotype Pair Effects

PR and QRS durations were significantly longer in HapB individuals in both study populations (Brugada syndrome and control subjects: $P\leq0.002$ for PR_{II}; $P<0.0001$ for QRS_{V1} and QRS_{V6}; Figure 3). In the control population, PR_{II}, QRS_{V1}, and QRS_{V6} intervals showed a gene-dose effect, being longest in HapB homozygotes, intermediate in HapA/HapB heterozygotes, and shortest in HapA homozygotes. A similar pattern was observed in the *SCN5A* mutation–negative Brugada syndrome patient group. As discussed earlier, these analyses excluded data in the 2 individuals with HapC. PR_{II}, QRS_{V1}, and QRS_{V6} means (±SD) per haplotype group for the 2 populations are listed in the Data Supplement Table II. Both the overall and pairwise probability values were highly statistically significant even after correction for multiple testing.

The amount of variance (R^2) in PR and QRS intervals explained by the haplotype pair after correction for age and gender is shown in Table 3. As can be seen, a significant proportion of variance in PR and QRS intervals, both at baseline (both groups) and after drug challenge (Brugada syndrome group), was attributable to the haplotype. No significant association was found between haplotype and RR, ST_J, and ST_{80} in either population (data not shown).

Drug Challenge and Haplotype

The haplotype pairs were also highly associated with conduction intervals (PR_{II}, QRS_{V1}, QRS_{V6}) after sodium channel

TABLE 1. Baseline ECG Characteristics of the Control and Brugada Syndrome Patient Populations

		Brugada Syndrome Patients			Pairwise Comparison *P*	
	Control Subjects	*SCN5A*$^{-ve}$	*SCN5A*$^{+ve}$	Overall *P*	*SCN5A*$^{-ve}$ vs *SCN5A*$^{+ve}$	*SCN5A*$^{-ve}$ vs Control Subjects
n	102	71	9			
Male, n (%)	67 (66)	67 (94)	9 (100)	<0.0001	1.000	<0.0001
Age, y	40.0±14.2	46.5±16.3	51.1±8.4	0.005	0.376	0.005
RR, ms	925.3±130.0	913.7±134.3	1055.6±154.2	0.012	0.003*	0.572
PR_{II}, ms	162.3±21.8	180.4±20.4	238.9±26.7	<0.0001*	<0.0001*	<0.0001*
QRS_{V1}, ms	93.8±11.8	104.9±19.3	142.2±19.1	<0.0001*	<0.0001*	<0.0001*
QRS_{V6}, ms	87.4±12.4	100.2±19.1	139.4±21.6	<0.0001*	<0.0001*	<0.0001*
ST_J, mV	0.10±0.05	0.30±0.14	0.34±0.18	<0.0001*	0.249	<0.0001*
ST_{80}, mV	0.18±0.10	0.25±0.12	0.24±0.13	0.001*	0.778	0.001*

Values are given as mean±SD.

*Below the Bonferroni-corrected overall or pairwise significance levels (see Multiple Testing).

blockade in 44 *SCN5A* mutation–negative Brugada syndrome patients who underwent drug challenge (for PR_{II}, QRS_{V1}, QRS_{V6}, $P<0.0001$; Figure 3). PR_{II}, QRS_{V1}, and QRS_{V6} means (±SD) per haplotype group are listed in the Data Supplement Table II. Here also, overall and pairwise probability values were highly statistically significant even after correction for multiple testing.

In addition, the extent of QRS widening (ΔQRS) after drug challenge was genotype dependent, and a gene-dose effect was also observed (ΔQRS_{V6}: HapB/HapB=30 ms [mean± SD]; HapA/HapB=24.2±7.9; HapA/HapA=17.8±7.2; $P=0.002$; Figure 4). A similar trend was seen for extent of PR widening (ΔPR) after drug challenge (ΔPR_{II}: HapB/HapB=40 ms; HapA/HapB=33.8±13.2; HapA/HapA−28.6±8.3; $P=0.05$).

Discussion

We demonstrate that a set of 6 *SCN5A* promoter polymorphisms found in Asian subjects are in near-complete linkage disequilibrium, have a significant impact on sodium channel expression in vitro, account for a large proportion of variance in ECG conduction parameters in 2 independent Japanese populations, and represent pharmacogenetic markers predicting variable drug response.

Twin studies have identified strong genetic effects for ECG parameters, including PR and QRS durations.[11–14] Indeed, associations have been reported between ECG parameters and single coding region nonsynonymous (amino acid–changing) SNPs in ion channel genes.[15,16] However, common functional variants in regulatory regions that strongly modulate basal ECG intervals have not previously been identified; 1 preliminary report has suggested an association between a potassium channel promoter polymorphism and QRS axis in women only.[17] Only recently has the concept of tightly linked polymorphisms (constituting a haplotype block) been applied to understanding variability in cardiac electrophysiology. In 1 study, a small degree of variance (<1%) in QT interval in a central European population could be attributed to single SNPs and haplotype blocks in 4 potassium channel genes.[18]

TABLE 2. Clinical Characteristics of the Brugada Syndrome Patients After Sodium Channel Blocker Challenge

	SCN5A^{-ve}	*SCN5A*$^{+ve}$	*P*	*r*, Before and After Sodium Channel Blockade
n	44	5		
Male, n (%)	42 (95)	5 (100)	1.000	
Age, y	46.3±14.8	52.0±5.4	0.397	
aRR, ms	892.3±113.1	956.0±99.4	0.234	0.94
aPR_{II}, ms	209.6±25.1	278.0±35.6	<0.0001*	0.95
$aQRS_{V1}$, ms	124.1±16.1	166.0±17.8	<0.0001*	0.92
$aQRS_{V6}$, ms	119.2±17.1	166.0±17.8	<0.0001*	0.92
aST_J, mV	0.51±0.21	0.78±0.25	0.013	0.84
aST_{80}, mV	0.41±0.17	0.70±0.31	0.109	0.63

Values are given as mean±SD. Pearson correlation coefficients (*r*) observed between measures before and after sodium channel blocker challenge ($P<0.0001$). Mean baseline ECG parameters for the 44 *SCN5A*$^{-ve}$ and 5 *SCN5A*$^{+ve}$ patients (not shown) were very similar to those for the total patient group given in Table 1.

*Below the Bonferroni-corrected overall significance levels (see Multiple Testing).