Sex-Dependent Phenotypic Variability of an *SCN5A* Mutation: Brugada Syndrome and Sick Sinus Syndrome

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Background—Brugada syndrome (BS) is known to be 9 times more prevalent in males than females. However, little is known about the development of sick sinus syndrome in female members with familial BS.

Methods and Results—Familial BS patients and family members, both from our institutions and collaborating sites that specialize in clinical care of BS, participated in this study. We collected information on their clinical and genetic background, along with the inheritance patterns of BS. Detailed information on each case with familial BS is described. A total of 7 families, including 25 BS patients (12 females and 13 males), were included. Seven were probands and 18 were family members. Ten out of the 12 female patients and none of the 13 male patients developed sick sinus syndrome. Sudden death or spontaneous ventricular fibrillation occurred in 7 out of 13 male patients and 2 out of 12 female patients.

Conclusions—Familial BS existed in which female patients developed sick sinus syndrome but male patients did not. Some of those female patients with sick sinus syndrome had unrecognized BS. Information should be collected not only regarding a family history of sudden death or BS, but also whether a pacemaker was implanted in female members. (***J Am Heart Assoc***. 2018;7: e009387. DOI: 10.1161/JAHA.118.009387.)

B rugada syndrome (BS) is an inherited arrhythmic syndrome generally lacking structural abnormalities.[1,2] BS is diagnosed in patients with a coved-type ST-segment elevation occurring either spontaneously or after a provocative drug test with the intravenous administration of Class I antiarrhythmic drugs. Its prevalence is much higher in Asian and Southeast Asian countries, reaching 0.5 to 1 per 1000 in Japan. The incidence of BS is about 9 times more prevalent in males than females. *SCN5A* is the most common gene responsible for BS and is also linked to familial sick sinus

syndrome (SSS).[3–5] Mutations in the *SCN5A* gene have been linked to multiple arrhythmia syndromes, including long-QT syndrome type 3, BS, conduction defects, and SSS. A family history of BS or sudden death (SD) is present in some patients with BS. Therefore, history taking is emphasized, especially if there are any other patients with BS with any male family members that had SD. However, little is known about the development of SSS, especially in female members with familial BS. Moreover, history taking of pacemaker implantations is often ignored. We found a unique pattern of the phenotypic distribution in familial BS with *SCN5A* mutations. In females, not only was there a family history of SD or BS in male members, but also there a pacemaker implantation because SSS was present in female members. To further clarify this unique pattern, we collected similar patterns of inheritance from multicenters and provided the clinical and molecular characteristics.

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Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. We had 3 families (Families A, B, and C, mentioned below) in which

Clinical Perspective

What Is New?

- Brugada syndrome is more prevalent in males than females, but little is known about the development of sick sinus syndrome in females with familial Brugada syndrome.
- We present a series of 7 Brugada syndrome families in which female patients developed sick sinus syndrome.

What Are the Clinical Implications?

- Information regarding sick sinus syndrome and pacemaker implantation should be collected from females in families with Brugada syndrome.

female patients with SSS required a pacemaker implantation within the members with familial BS at Keio University Hospital. We queried our collaborators, who specialized in the clinical care of BS, for similar cases and collected the clinical data, ECG characteristics, and genetic information. Familial BS in which female patients developed SSS was the inclusion criterion of this study. The pedigree nomenclature was written by the standardized human pedigree nomenclature proposed by the National Society of Genetic Counselors.[6] The study was approved by the institutional review committee of Keio University School of Medicine. The patients provided written informed consent before the invasive studies and genetic analysis.

Definitions

The definition of a Brugada type ECG pattern was based on the Report of the Second Consensus Conference.[7] A type 1 Brugada syndrome ECG was characterized by a coved ST-segment elevation of ≥2 mm (0.2 mV) followed by a negative T wave.

Genetic Analysis

A comprehensive genetic analysis was performed using the TruSight One (Agilent Technologies, Santa Clara, CA) sequencing panel, which targets 4813 genes known to be associated with clinical phenotypes. To identify disease-causing mutations, we excluded variants found in dbSNP, from the 1000 Genomes Project (http://www.1000genomes.org/), Japanese SNP data set of 1208 normal individuals (www.hgvd.genome.med.kyoto-u.ac.jp/), and Exome Aggregation Consortium (http://exac.broadinstitute.org/). The identified mutations were validated by direct capillary sequencing. Genetic screening was performed at another institute for family E by denaturing high-performance liquid chromatography using a WAVE System Model 3500 (Transgenomic, Omaha, NE), and the exons that displayed abnormal denature patterns were reanalyzed by direct capillary sequencing to confirm the mutation.

Results

We collected data on 7 families from 6 institutes. A total of 25 BS patients (12 females and 13 males) were included in this study. Seven were probands and 18 were family members (Figure 1, Table).

Family A

A 25-year-old asymptomatic male (III-1) was referred to our hospital because of a type 1 BS ECG (Figure 2A). His maternal grandfather (I-1) died suddenly in his 40s. His uncle (II-3) was implanted with an implantable cardioverter defibrillator (ICD) after a cardiac arrest caused by BS. A missense mutation in SCN5A (M764K) was detected in family members (Figure 3A). Since the patient had refused an electrophysiology study (EPS) and ICD implantation, he had been under careful observation at an outpatient clinic. He developed syncope in the morning at the age of 25 years and was implanted with an ICD. His mother (II-2) with a type 1 ECG (Figure 2A) developed SSS with syncope and was implanted with a dual-chamber ICD during a follow-up at the age of 54 years. Periodic pacemaker checks revealed that atrial pacing, but no ventricular tachyarrhythmia/VF episodes, had been detected thus far in this mother. The ECG phenotypes of BS, such as ST elevation, QRS fragmentation, QRS widening, and early repolarization patterns, were more severe in the son than in the mother in this family (Figure 2A); however, SSS developed only in the mother.

Family B

A 65-year-old female (II-2) implanted with a pacemaker because of SSS gave a history of multiple SD episodes in her family (her brother: II-3, at 21 years old and her son: III-1, at 41 years old) during the follow-up at the pacemaker clinic. Her ECG revealed a type 1 BS ECG (Figure 2B), and an SCN5A splice site mutation (c.3840+1G>A) was detected in this patient, leading to a diagnosis of familial BS. After the pacemaker implantation, she did not complain of any further syncopal episodes and no ventricular arrhythmias have been detected to date.

Family C

A 43-year-old male (II-1) was referred to our hospital for consideration of an ICD implantation. He did not have any syncopal episodes or a family history of SD. He had been informed he had complete right bundle branch block during
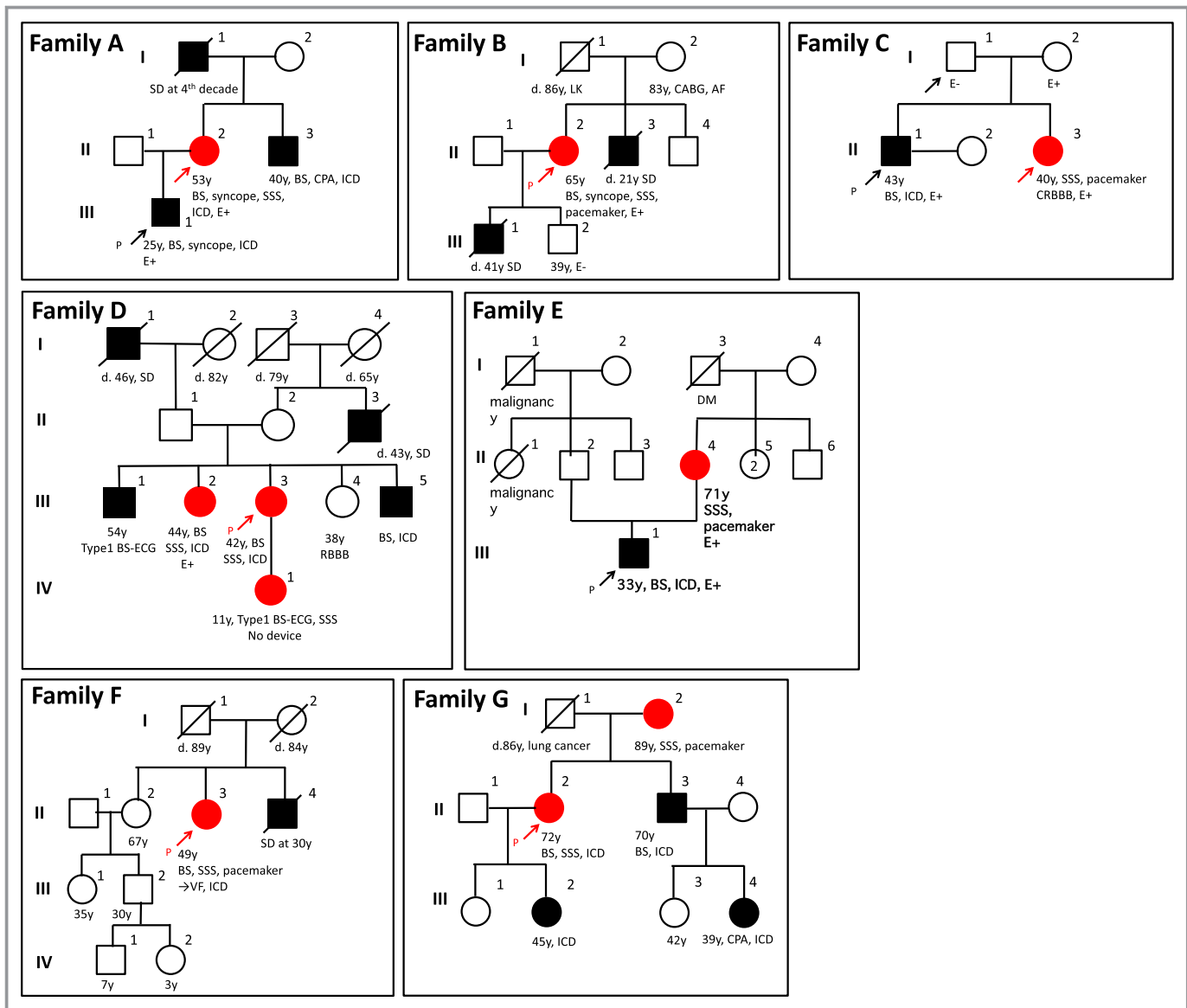
Figure 1. Pedigree of the familial BS collected in this study. The affected individuals are shown by the filled symbols. The female members shown by red circles indicate SSS with BS. The arrow indicates evaluated in the hospital; BS, Brugada syndrome; CABG, coronary artery bypass grafting; CPA, cardiopulmonary arrest; DM, diabetes mellitus; E, positive genetic testing; ICD, implantable cardioverter defibrillator; P, proband; SD, sudden death; SSS, sick sinus syndrome; VF, ventricular fibrillation.

junior high school and that he had a Brugada-type ECG 5 years prior (Figure 2C). Programmed electrical stimulation during his EPS could not induce any ventricular tachyarrhythmia or VF, but spontaneous VF was induced after a pilsicainide challenge test. QRS fragmentation was noted in his ECG, and late potentials were positive. He refused an implantation of a transvenous ICD but was implanted with a subcutaneous ICD at the age of 45 years. A genetic analysis revealed an *SCN5A* mutation (Gly1433Typ) in this patient, and in his mother and sister (Figure 3B). A Holter ECG recording in his sister (II-3) recorded paroxysmal atrial fibrillation and a sinus arrest of 9.5 s following the termination of atrial fibrillation.

His sister (II-3) was diagnosed with SSS and was implanted with a pacemaker at the age of 40 years. The ECG revealed a complete right bundle branch block with ST elevation in lead V1 during intrinsic and pacing rhythms (Figure 2C). His mother (I-2) carried the *SCN5A* mutation but she was asymptomatic and no Brugada-type ECG pattern was observed in upper intercostal recordings.

Family D

A 42-year-old female (III-3) was referred to our hospital to evaluate SSS with dizziness. Her ECG showed a type 2

Table. Clinical Characteristics of Patients With BS in This Study

Family	Patient No.	Sex	Age (y)	ECG	Phenotype	Device Implantation	Genetic Analysis
A	I-1	M	40s	na	SD	...	na
	II-2	F	53	Type 1	Syncope, SSS	ICD	*SCN5A* c.2291T>A, p.Met764Lys
	II-3	M	40	Type 1	CA	ICD	Negative
	III-1	M	25	Type 1	Syncope	ICD	*SCN5A* c.2291T>A, p.Met764Lys
B	II-2	F	65	Type 1	Syncope, SSS	Pacemaker	*SCN5A* Intron 3840+1G>A
	II-3	M	21	na	SD	...	na
	III-1	M	41	IVCD	SD	...	na
C	II-1	M	43	Type 1	VF at EPS	S-ICD	*SCN5A* c.4297G>T, p.Gly1433Trp
	II-3	F	40	Type 1, CRBBB	Syncope, SSS	Pacemaker	*SCN5A* c.4297G>T, p.Gly1433Trp
D	I-1	M	46	na	SD	...	na
	II-3	M	43	na	SD	...	na
	III-1	M	54	Type 1	na	ICD	na
	III-2	F	44	Type 1	Dizziness, SSS	ICD	*SCN5A* c.2677C>T, p.Arg893Cys
	III-3	F	54	Type 1	SSS	ICD	na
	III-5	M	Na	Na	na	ICD	na
	IV-1	F	11	Type 1	SSS	...	na
E	II-4	F	71	Type 1	SSS	Pacemaker	*SCN5A* c.560C>T, p.T187I,
	III-1	M	33	Type 1	Syncope, VF	ICD	*SCN5A* c.560C>T, p.T187I
F	II-3	F	49	Type 1	Syncope, VF, SSS, VF	Pacemaker→ICD	na
	II-4	M	30	na	SD	...	na
G	I-2	F	89	na	Syncope, SSS	Pacemaker	na
	II-2	F	72	Type 1	Dizziness, SSS	ICD	na
	II-3	M	70	Type 1	VF at EPS	ICD	na
	III-2	F	45	Type 1	na	ICD	na
	III-4	F	39	Type 1	CA	ICD	na

BS indicates Brugada syndrome; CA, cardiac arrest; CRBBB, complete bundle branch block; EPS, electrophysiology study; F, female; ICD, implantable cardioverter defibrillator; IVCD, interventricular conduction disturbance; M, male; na, not available; SD, sudden death; S-ICD, subcutaneous implantable cardioverter defibrillator; SSS, sick sinus syndrome; VF, ventricular fibrillation.

Brugada ECG. She had a family history of sudden cardiac death (grandfather: 1-1, 46 years old, and uncle: II-3, 43 years old). The EPS revealed that the sinus node recovery time was 6.2 s and the Wenckebach rate was 120 beats per minute. She was implanted with a DDD pacemaker and then was followed up at our outpatient clinic. Her usual rhythm was atrial pacing with ventricular sensing and the ECG showed a type 1 Brugada ECG during the follow-up (Figure 2D). An EPS was performed again, in which VF was reproducibly induced. Therefore, we implanted an ICD for primary prevention. After that, there have been no fatal arrhythmias documented on her ICD. Her elder brother (III-1) also had a type 1 Brugada ECG and her younger sister (III-4) had complete right bundle branch block on the ECG. Her 11-year-old daughter (IV-1) was also diagnosed with mild SSS without symptoms, and an EPS

then revealed a sinus node recovery time of 5.5 s. She refused to receive a pacemaker implantation (Figure 2D). Her older sister (III-2) was a 44-year-old female who had developed dizziness at the age of 39 years and was diagnosed with SSS at the age of 40 years. A pilsicainide challenge test unmasked a coved-type ST elevation, and VF followed by frequent premature ventricular contractions developed spontaneously. Atrial flutter was observed after the termination of the VF by a direct-current cardioversion (DC). An ICD was implanted in this patient after a cavotricuspid isthmus ablation. Coronary angiography revealed no significant findings. Her clinical course was uneventful after the ICD implantation. An *SCN5A* mutation, c.2677C>T, p.Arg893Cys, was detected in this patient. So far only a genetic analysis has been performed in this patient.
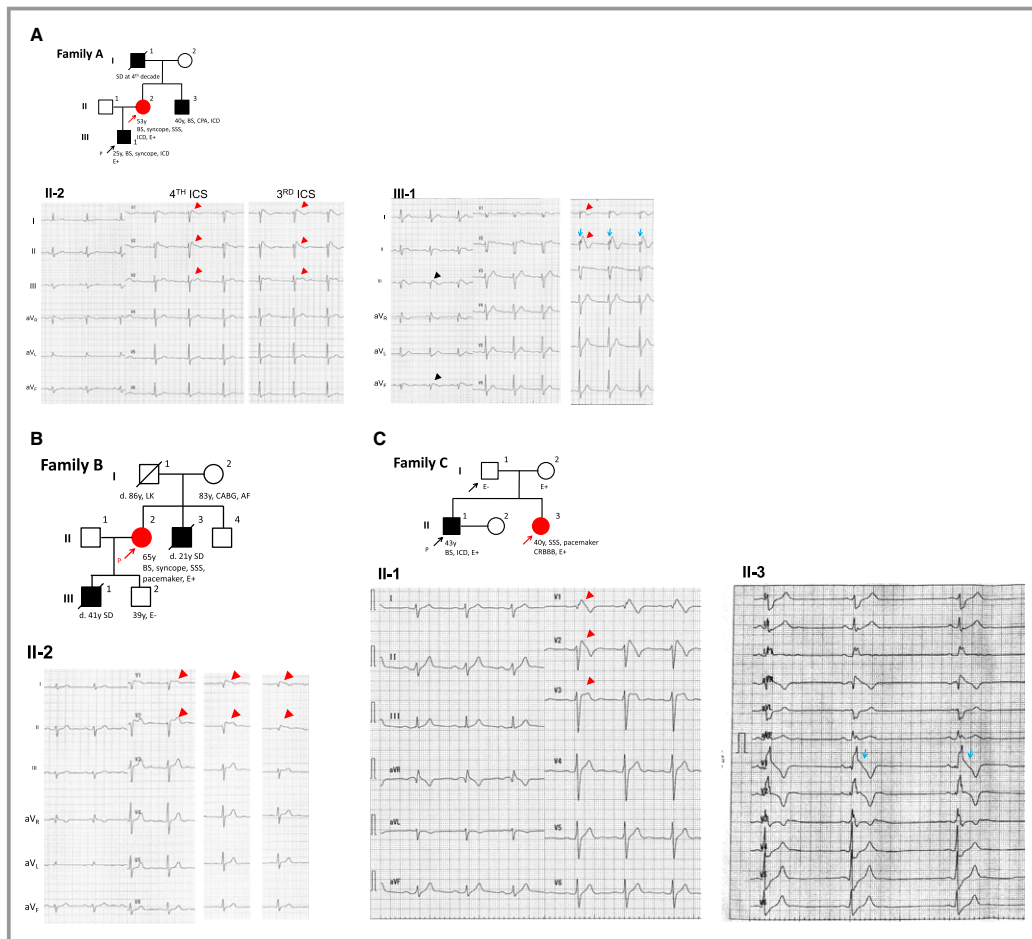
Figure 2. Twelve-lead ECGs obtained from family members of Families A through G. A, An ECG from a 53-year-old female (II-2, family A) showed a coved-type ST elevation. An ECG from a 25-year-old male (III-1, family A) also showed a coved-type ST elevation recorded from the higher intercostal spaces (red arrow), and QRS fragmentation (blue arrow), QRS widening, and an early repolarization pattern (black arrow). Note that the degree of the ST elevation of the mother was milder than that of her son. E+ signifies that genetic evaluation was performed and positive *SCN5A* mutation (M764K) was found. B, An ECG of 65-year-old female (II-2) implanted with a pacemaker because of SSS revealed a type 1 BS ECG. E+ signifies that genetic evaluation was performed and positive *SCN5A* mutation (Intron 3840+1G>A) was found. C, An ECG from a 43-year-old male (II-1, family C). A coved-type ST elevation (red arrow) in leads V1-3 is evident. His younger sister (II-3) had sinus bradycardia and CRBBB with ST elevation (blue arrow). E+ signifies that genetic evaluation was performed and positive *SCN5A* mutation (Gly1433Trp) was found. D, An ECG from a 42-year-old female (III-3) after an implantation of a DDD pacemaker exhibiting a type 1 BS ECG. Her 11-year-old daughter (IV-1) who was also diagnosed with SSS had a type 1 ECG recorded from the higher intercostal spaces. Her older sister (III-2) also was diagnosed with SSS at the age of 40 years. An ECG recorded from the higher intercostal spaces unmasked a coved-type ST elevation. E+ signifies that genetic evaluation was performed and positive *SCN5A* mutation (Arg893Cys) was found. E, An ECG of a 33-year-old male (III-1) who was resuscitated from VF in a febrile state. His ECG shows ST-elevation in leads V1-3 and polymorphic VT was induced during the EPS. His mother (II-4) was implanted with a pacemaker but no ECG was available. E+ signifies that genetic evaluation was performed and positive *SCN5A* mutation (Thr187Ile) was found. F, A 49-year-old woman (II-3) developed multifocal PVCs followed by VF after the implantation of a pacemaker for SSS with recurrent syncope. ST elevation was relieved after an isoproterenol infusion. G, An ECG from a 72-year-old-female (II-2) who was implanted with a dual-chamber ICD because of symptomatic SSS and a family history of sudden death. ST elevation in leads V1-2 that was more evident after a pilsicainide challenge test was observed. Although this patient had a family history of multiple pacemaker or ICD implantations, the ECGs of those members were not available. BS indicates Brugada syndrome; CRBBB, complete right bundle branch block; EPS, electrophysiology study; ICD, implantable cardioverter defibrillator; PVCs, premature ventricular contractions; SD, sudden death; SSS, sick sinus syndrome; VF, ventricular fibrillation; VT, ventricular tachyarrhythmias.
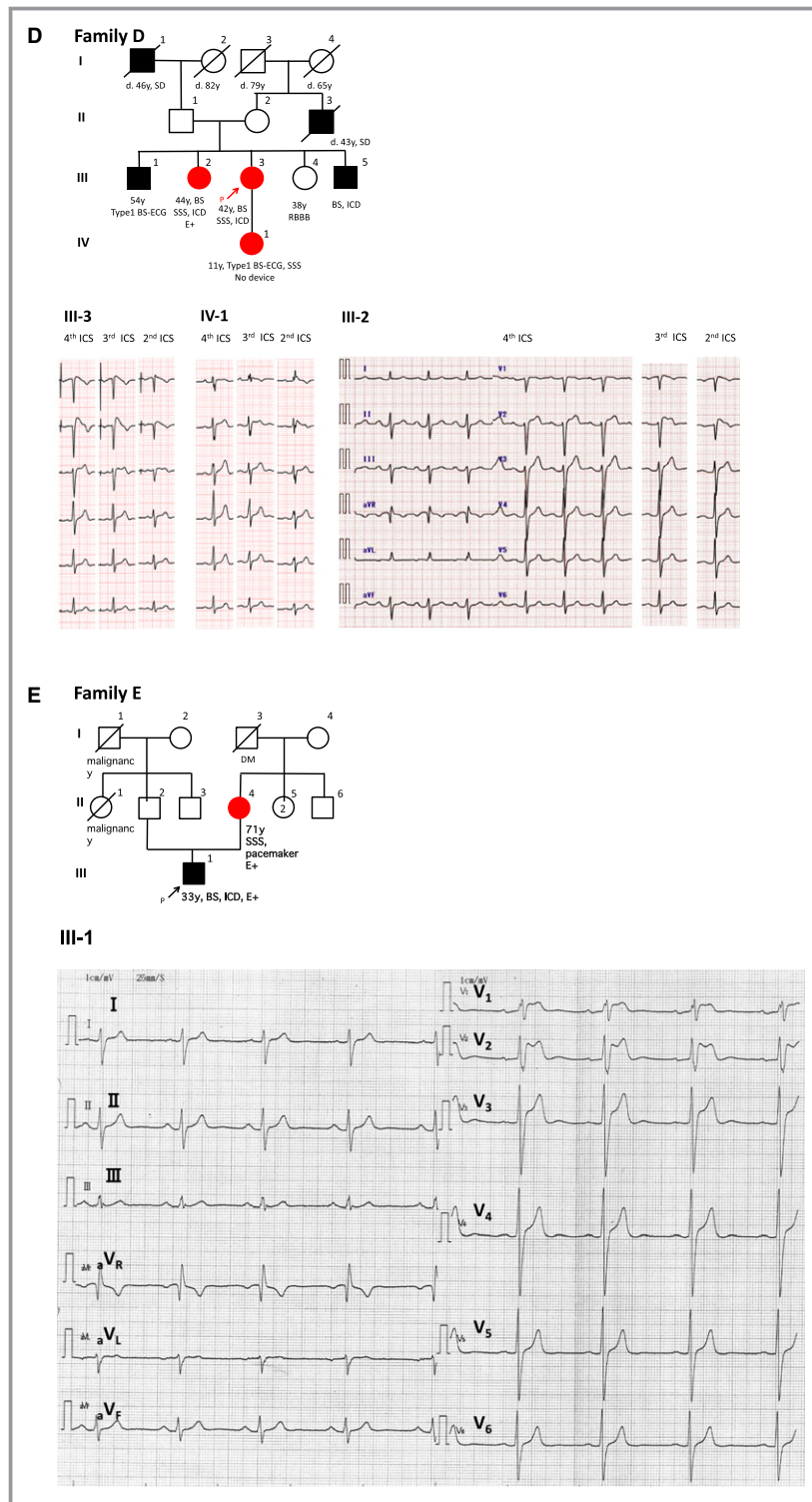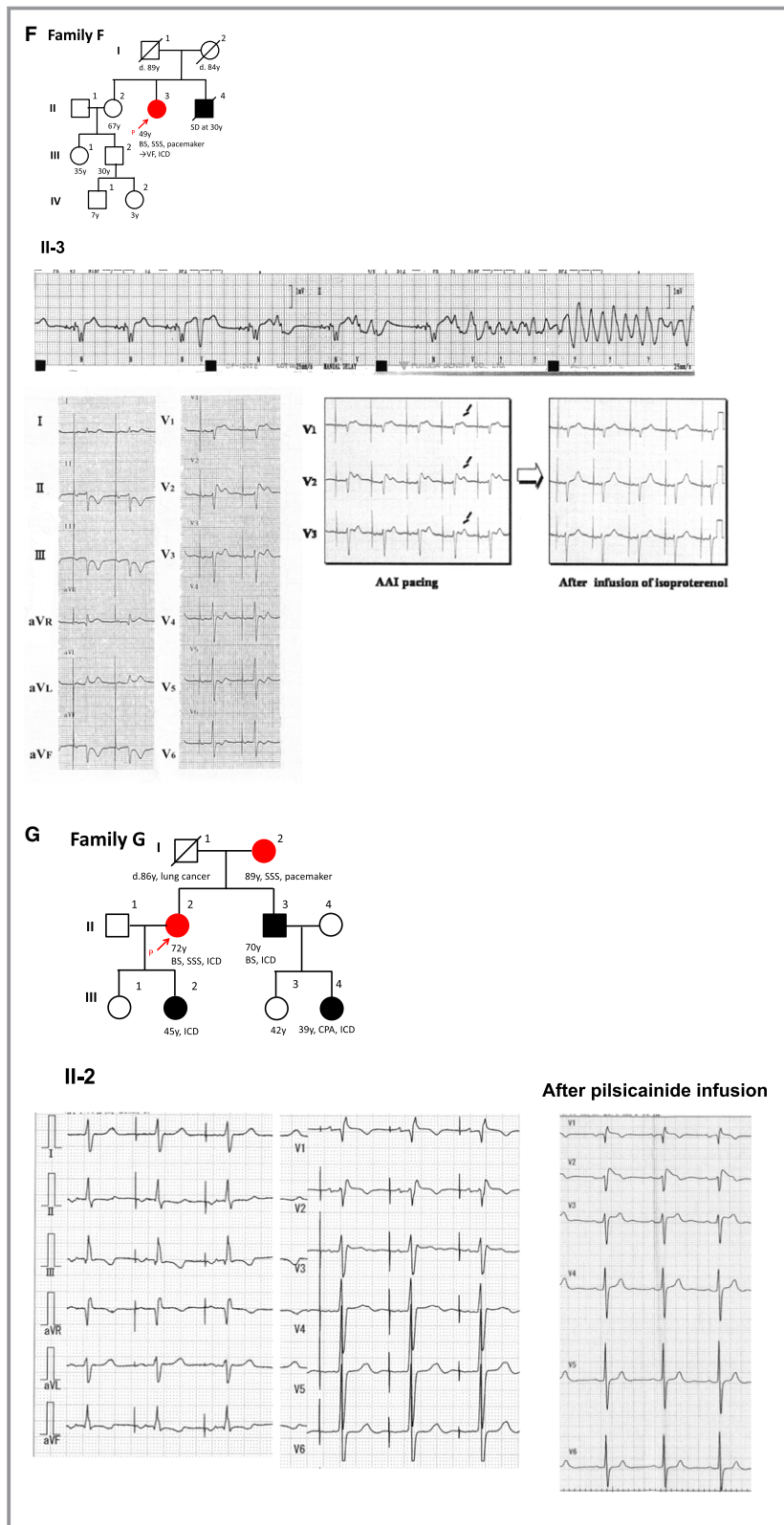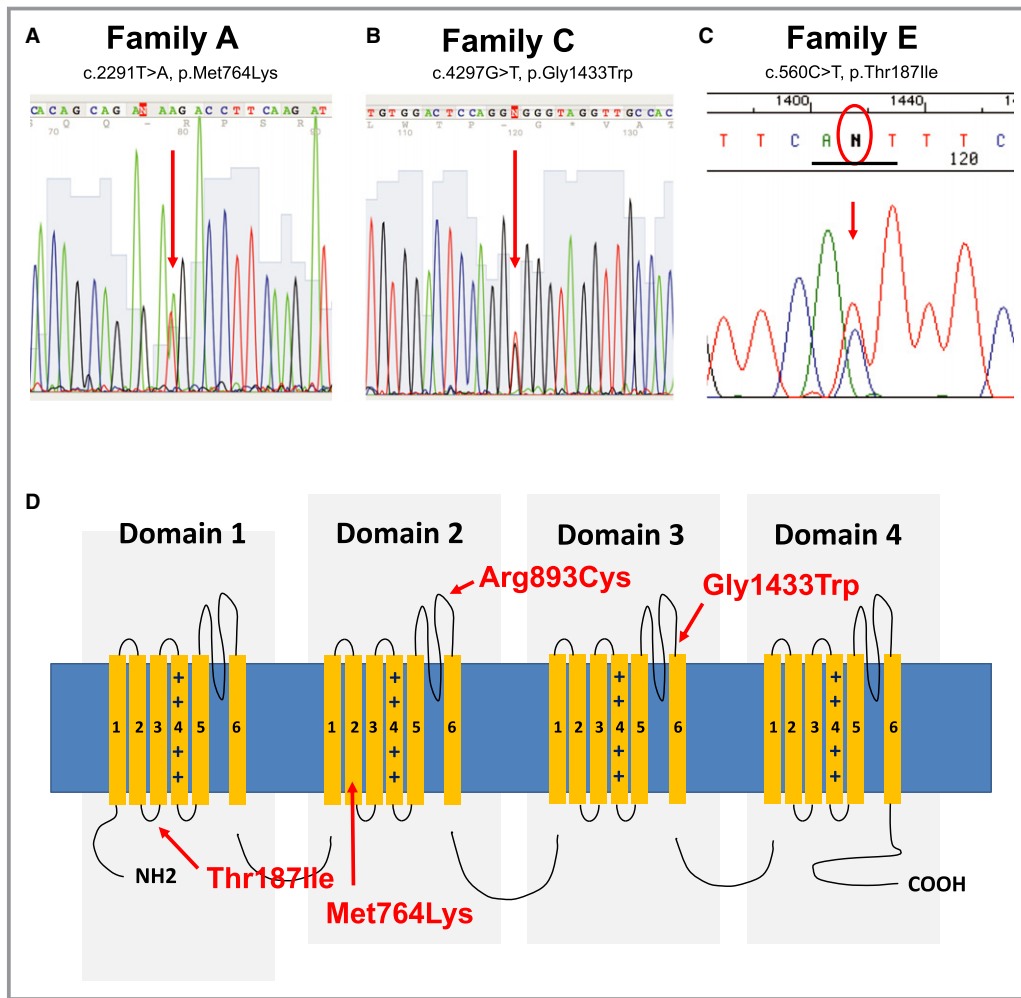
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Figure 3. A, Results of the DNA sequencing in family A demonstrating a heterozygous single T to A nucleotide substitution at position 2291 of the *SCN5A* gene leading to a Met764Lys missense mutation. B, The results of DNA sequencing in family C demonstrating a heterozygous single G to T nucleotide substitution at position 4297 of the *SCN5A* gene leading to a Gly1433Trp missense mutation. C, Genetic screening for *SCN5A* was performed by denaturing high-performance liquid chromatography and a Thr187Ile (560C>T) mutation was detected in family E. D, Schematic topology of *SCN5A* displaying the putative localization of the mutations detected in this study (red arrow).

Family E

A 33-year-old male (III-1) lost consciousness when he visited a clinic because of a high fever. VF was recorded on the ECG monitor, and sinus rhythm was recovered by a direct-current cardioversion shock. Since his ECG showed ST-elevation in V1-3 (Figure 2E), an EPS was performed. Polymorphic ventricular tachyarrhythmia was induced, and an ICD was implanted. The proband did not have any family history of SD. However, his mother (II-4) was implanted with a pacemaker because of SSS. A genetic analysis revealed an *SCN5A*-Thr187Ile mutation that was confirmed by DNA sequencing in the proband and his mother (Figure 3C).[8]

Family F

A 49-year-old woman (II-3) was admitted to the hospital because of recurrent syncope. Her younger brother (II-4) died suddenly at the age of 30 years old. The ECG in the proband revealed atrial flutter with an incomplete right bundle branch block pattern. At the time of the EPS, persistent atrial flutter (AFL) with a cycle length of 280 ms was noted. Rapid right atrial pacing with a cycle length of 260 ms terminated the AFL, but sinus arrest with junctional escape beats followed. The maximum sinus node recovery time was prolonged by more than 5 s at a rate of 180 beats per minute even with an atropine sulfate administration. The H-V interval prolonged to

75 ms. No ventricular tachyarrhythmias were induced despite programmed ventricular stimulation. With the diagnosis of SSS and an infra-Hisian conduction delay, a DDD pacemaker was implanted. Ten months after the pacemaker implantation, she experienced a syncope recurrence and was transferred to our emergency department for an evaluation. New ST elevation in leads V1 to V3 was noted compared with the patient's previous ECG. The patient suddenly lost consciousness while she was conversing with a nurse. The monitored ECG revealed multifocal premature ventricular contractions followed by VF (Figure 2F). After an immediate direct-current cardioversion, a saddle-back–type ST elevation was confirmed by changing the pacing mode from DDD to AAI (Figure 2F). A saddleback–type ST elevation was observed in leads V1 to V3. The ST elevation was alleviated after an isoproterenol infusion (Figure 2F). Subsequent administration of cilostazol 200 mg/d also improved the ST elevation. The coronary angiography and left ventriculography were normal and a left ventricular myocardial biopsy did not demonstrate any specific findings. A diagnosis of BS was made. The DDD pacemaker and lead system were removed, and a dual-chamber ICD was implanted.
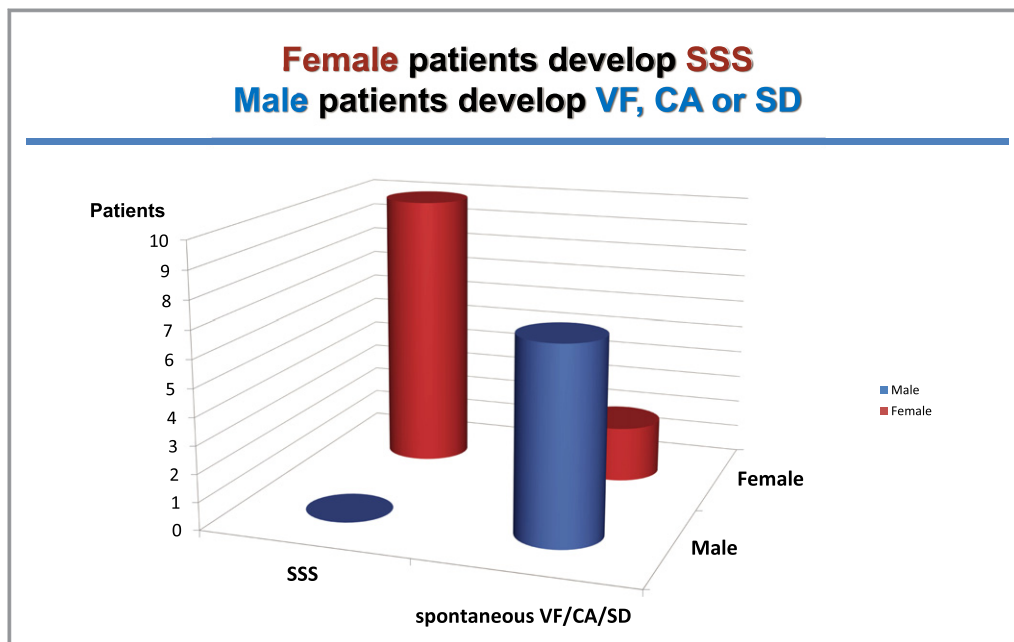
Family G

The proband was a 72 year-old-female (II-2) who developed dizziness at the age of 64 years. An EPS was performed, revealing a normal atrioventricular conduction and sinus node recovery time of 3 s at 140 beats per minute, and an atrial

tachycardia was induced at 220 beats per minute. No ventricular arrhythmias were induced by programmed ventricular stimulation. A coved-type ST elevation was unmasked by a pilsicainide infusion and was normalized by an isoproterenol infusion (Figure 2G). Coronary angiography did not detect any significant stenosis. Her younger brother (II-3) had a type 1 BS ECG and was implanted with an ICD since the EPS was positive. Her niece (III-4) was resuscitated from a cardiopulmonary arrest and was diagnosed with BS. Her mother (I-2) was diagnosed with SSS and was implanted with a pacemaker. The proband was implanted with an ICD at the age of 64 years. Atrial fibrillation developed in this patient and bepridil, bisoprolol, and apixaban were prescribed. A genetic analysis could not be performed in this family member.

Ten out of the 12 female patients and none of the 13 male patients developed SSS. SD or spontaneous VF occurred in 7 out of 13 male patients and 2 out of 12 female patients (Figure 4). Five out of 7 probands underwent a genetic analysis and *SCN5A* mutations were detected in those families (Figure 3).

Discussion

The main finding of our study was that a sex-dependent phenotypic distribution existed in familial BS. Also, although the female patients developed SSS, none of the male patients did, but instead they had VF/sudden cardiac death. The *SCN5A* mutations were detected in all the families who

Figure 4. The sex-dependent phenotypes of Brugada syndrome included in this study. A unique distribution of the phenotypes (SSS or VF/CA/SD) depending on the sex was noted in the family members included in this study. CA, cardiopulmonary arrest; SD, sudden death; SSS, sick sinus syndrome; VF, ventricular fibrillation.

underwent a genetic analysis. A sex-dependent phenotypic variability of the *SCN5A* mutation may exist.

For members with familial BS, the responsible gene is inherited by 50% of the offspring according to an autosomal dominant mode of transmission. Both males and females equally inherit the responsive gene. Di Diego et al studied epicardial myocytes isolated from male and female canine hearts and reported that the predominance of the Brugada phenotype in males is a result of the presence of a more prominent Ito in males versus females.[9] Shimizu et al reported that a higher testosterone level associated with a lower body mass index and body fat percentage plays a significant role in male predominance in BS.[10] Benito et al conducted a prospective study and found that men with BS present with a greater risk of sudden cardiac death or documented VF.[11] They also found that women with a greater risk demonstrated a longer PR interval. Sieira et al also reported that the clinical presentation is less severe in women than men, with a greater asymptomatic status, and less spontaneous type 1 ECGs and favorable outcomes.[12]

Hayashi et al examined patients with an indication for a pacemaker for SSS and found that a Brugada-type ECG was found in 2.87%, including 0.82% with type 1.[13] In that study, they presented 4 patients with a type 1 ECG and 1 was a female. On the contrary, Letsas et al examined spontaneous or drug-induced BS patients, and SSS was found in 6 symptomatic subjects (8.8%).[14] In that study, 3 out of the 6 patients with BS and SSS were females but 2 patients with a type 1 BS ECG were female. Both studies provided us important data but did not mention a detailed family tree as in our study. In our study, in 5 out of the 10 female patients implanted with a pacemaker because of SSS, BS was unrecognized at the time of the pacemaker implantation.

Variable phenotypic expressions and a reduced penetrance are observed in patients with *SCN5A* mutations. Therefore, the role of the environmental and genetic modifiers in the phenotypic manifestation is debatable. In our case, 1 family member with normal phenotypes (subjects II-2 in Family C) was found to carry this novel *SCN5A* mutation, suggesting an incomplete penetrance. Although more than 13 genotypes have been reported in BS, *SCN5A* accounts for <30% of clinically diagnosed BS. Inheritance of BS occurs via an autosomal dominant mode of transmission. We identified the responsible *SCN5A* mutations in 5 families (but it was not analyzed in 2 families). The *SCN5A* gene mutations were also associated with SSS. The cellular mechanism for the development of SSS in female members with BS should be determined by further experiments.

Some epigenetic modifications may have affected the expression of the mutant gene in the family, and further analysis is required to explain the various phenotypes and penetrance of this gene. In general, women are more likely to have SSS, atrioventricular nodal reentrant tachycardia, and long QT syndrome. On the other hand, men are more likely to have atrioventricular block, atrioventricular reentrant tachycardia, idiopathic ventricular fibrillation, and BS.[15,16] A family history of SD or a Brugada-type ECG is important for the management of BS. It is also important to take a family history of any pacemaker implantations in familial BS based on the existence of the unique pattern of inheritance presented in this study. A similar pattern presented in this report has been observed in published case reports.[5,17] This type of inheritance reflects the fact that BS is genetically transmitted to offspring without being selected. It would be of critical importance to study families with BS in which male patients developed SSS in a further study since there currently is no information regarding the phenotypic distribution of such families with BS.

Study Limitations

Although we present, for the first time, the unique phenotypic distribution from the largest number to date of unique families with BS, the true incidence of the development of SSS in familial BS remains unknown. We could not obtain the ECG and genetic information of the members who died at the time of the evaluation. A genetic analysis was not performed in all family members. Furthermore, the number of patients included in this study was too small to compare the ECG characteristics between females and males. We could not compare the clinical differences between these families and the ones without SSS in females.

Conclusion

We present 7 families with BS in which the female patients developed SSS. Most of the male members developed SD instead of SSS. These findings suggested that, in selected families with familial BS in which female members developed SSS, a sex-dependent phenotypic distribution may exist. Even though the female members developed SSS, none of the male patients developed SSS, but they may have a higher susceptibility to VF/SD. Some female members with familial BS were implanted with pacemakers because of SSS without recognizing BS. Not only a family history of SD or BS, but also a history of a pacemaker implantation should be collected.

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Disclosures

None.

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