Familial sick sinus syndrome possibly associated with novel *SCN5A* mutation diagnosed in pregnancy

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Introduction

Sick sinus syndrome (SSS) denotes a collection of cardiac arrhythmias associated with dysfunction of the sinoatrial node that commonly lead to disorders in cardiac rhythm and conduction.[1] Mechanisms underlying the pathogenesis for sinus node dysfunction in SSS patients are still not clear. It could occur in healthy people without any evident structural heart disease. Recent studies have identified several gene mutations, including the *SCN5A* gene, in congenital SSS patients.[2,3] *SCN5A* is the cardiac Na channel gene responsible for the generation and rapid propagation of action potentials in the heart. Mutations in *SCN5A* have been linked to a wide range of inherited lethal arrhythmias, referred to as cardiac Na channelopathy, including long QT syndrome type 3,[4] Brugada syndrome,[5] progressive cardiac conduction defect,[6] and SSS. In the present report, we describe a proband (and her family members) with a novel *SCN5A* mutation, who displayed SSS, which was diagnosed during pregnancy.

KEY TEACHING POINTS

- This case highlights a proband with familial sick sinus syndrome (SSS) diagnosed during pregnancy.
- The genetic analysis identified a novel missense mutation in *SCN5A* (M1838V), which was electrophysiologically characterized using patch clamp experiments.
- This is the first report in which heart rate changes during pregnancy with threatened premature labor were precisely evaluated in an SSS patient carrying an *SCN5A* mutation.

Case report

In April 2019, a 30-year-old woman presented to a local hospital with severe nausea and anorexia at 9 weeks of pregnancy. She had a past medical history of pregnancy after in vitro fertilization and had a family medical history of permanent pacemaker implantation for SSS in her maternal grandmother. She had never complained of syncope, dizziness, or other brain ischemic episodes. When she was diagnosed as having severe hyperemesis gravidarum and admitted to the hospital, the 12-lead electrocardiogram (ECG) showed sinus bradycardia with a heart rate of 37 beats per minute (bpm), and the P waves exhibited low voltage and wandering (Figure 1A). The Holter ECG revealed a total of 56,315 beats per day (mean heart rate: 42 bpm), with a minimum heart rate of 25 bpm (Figure 1B). Escape rhythm and atrial tachycardia were also observed (Figure 1B). To examine whether the cause of nausea was hyperemesis gravidarum or bradycardia, she was transferred to our hospital and admitted (first admission).

The heart rate change during pregnancy is shown in Figure 1A and 2B. Following her first admission, on physical examination, the pulses were equally palpable bilaterally. Lung fields were clear, and precordial auscultation noted a normal first heart sound and a single second heart sound without murmur. The Holter ECG showed 51,846 beats per day of total beats (mean heart rate: 36 bpm), with a minimum rate of 22 bpm. Echocardiography showed that the left ventricle ejection fraction measured by the biplane Simpson method was 64% with no structural abnormalities. Although exercise test including treadmill test could not be done because of her pregnancy, there were no apparent symptoms on low-level activity. Her physical status was NYHA functional class

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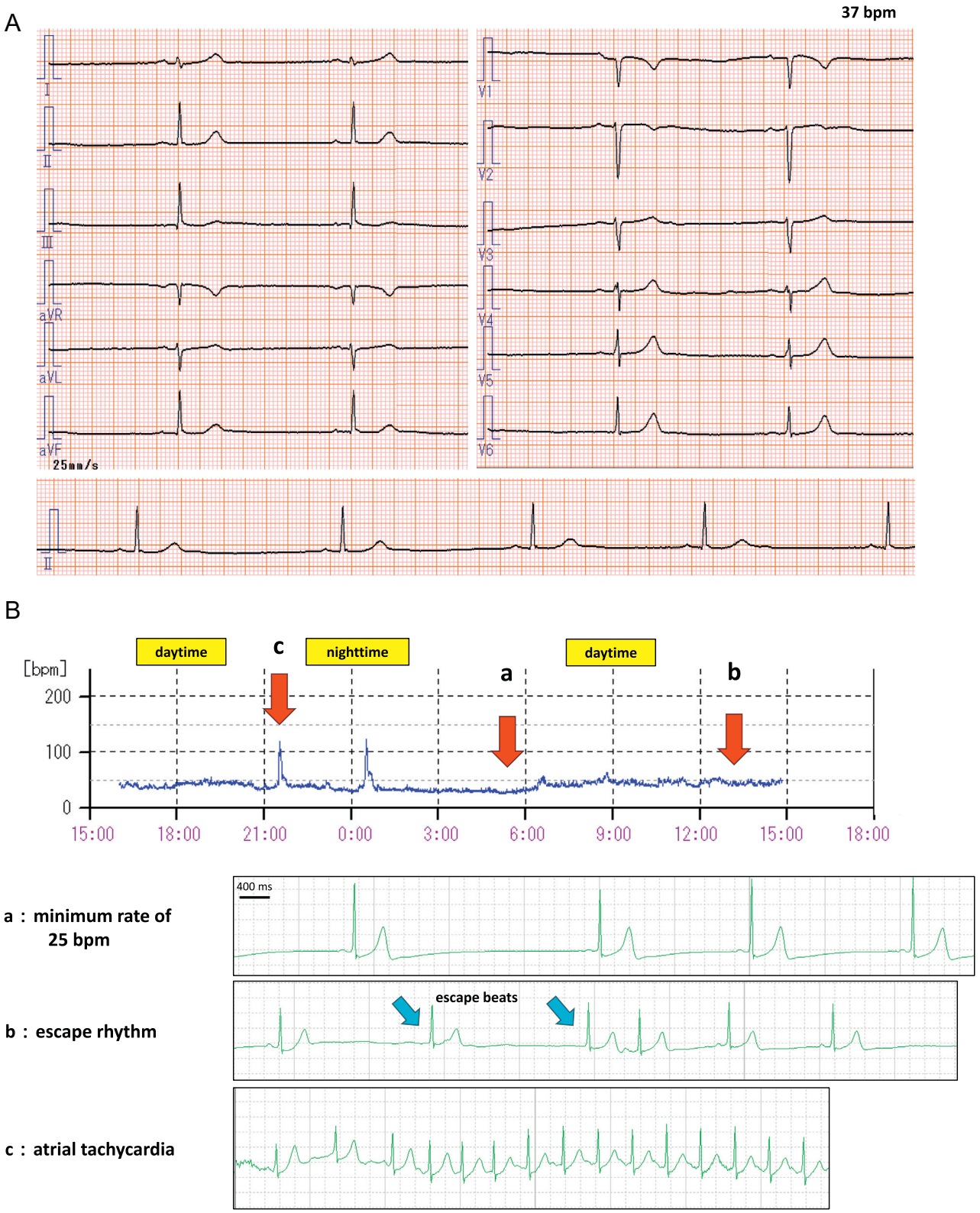
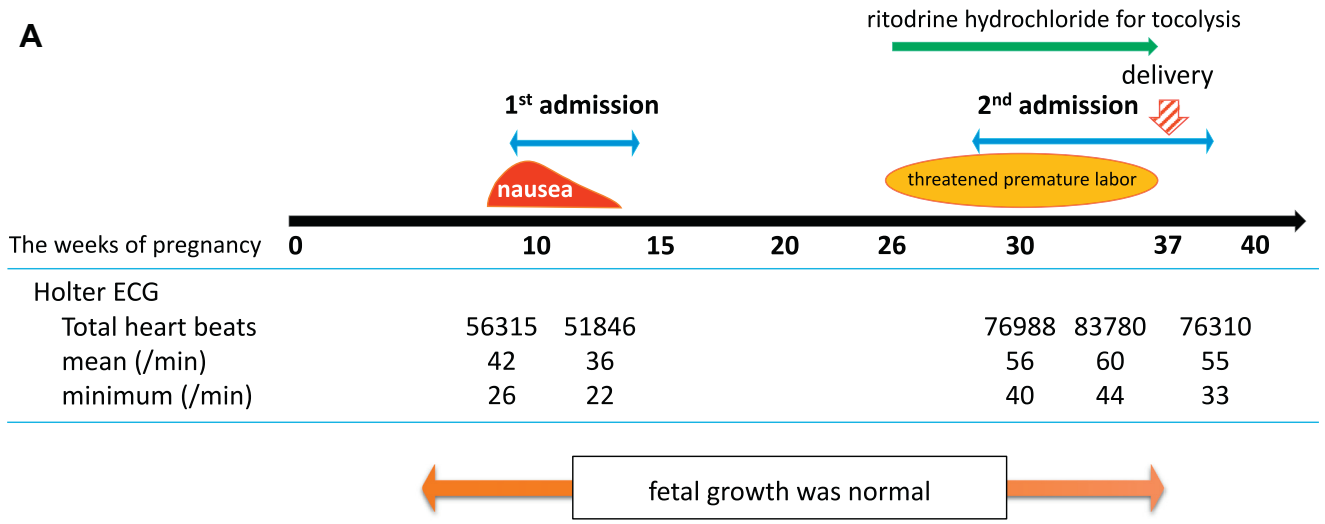


Figure 1 Twelve-lead and Holter electrocardiogram (ECG). **A:** Twelve-lead ECG, which showed sinus bradycardia with a heart rate of 34 beats/min and low P-wave voltage. **B:** Holter ECG, which showed a minimum rate of 25 beats/min (a), escape rhythm (b), and atrial tachycardia (c).

I. The serum value of her N-terminal pro-brain natriuretic peptide was 162.8 pg/mL. The serum thyroid stimulating hormone was 0.257 μIU/mL, and serum free thyroxine was 2.01 ng/dL without any change in the thyroid-related antibodies, indicative of transient nonimmune hyperthyroidism of early pregnancy. The arterial blood gas analysis showed no remarkable change,



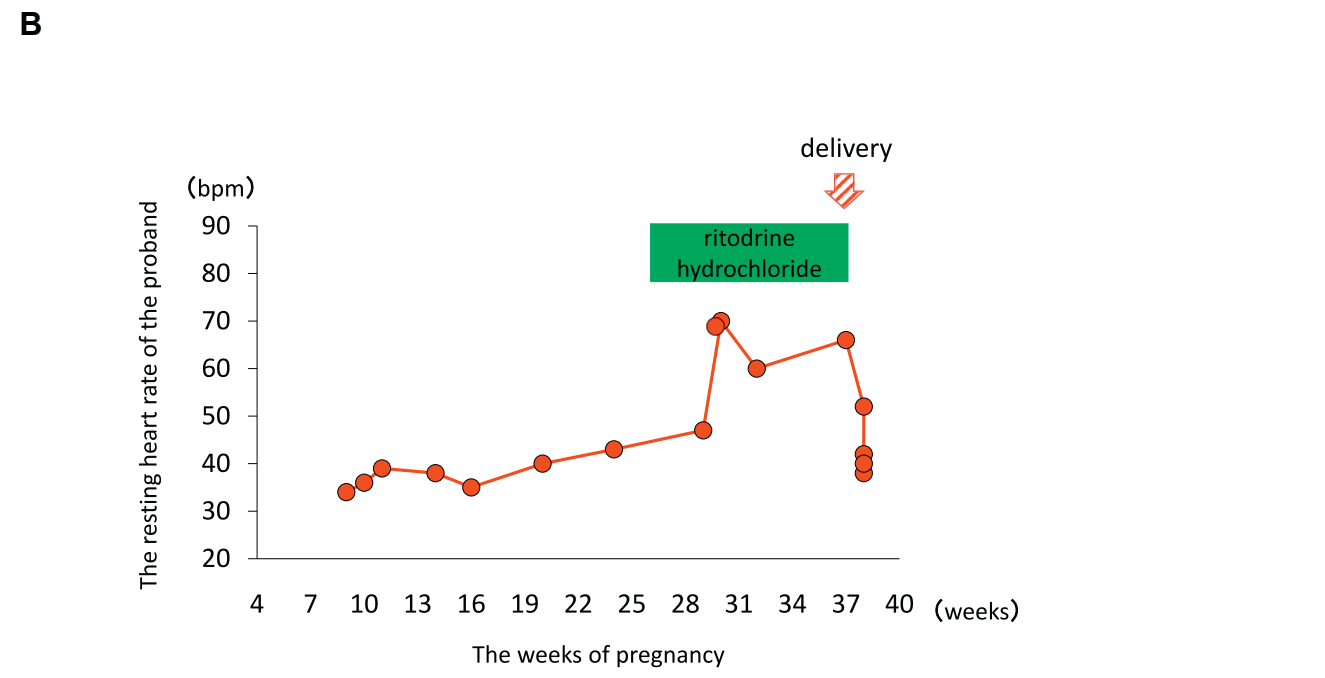


Figure 2 Graphical abstract of the process. **A:** The summary of the process from first to second admission. **B:** The resting heart rate change of the proband during pregnancy.

including lactate 1.1 mmol/L. Following 3 weeks of inpatient observation, neither apparent symptoms consistent with bradycardia and with low-level activity nor heart failure signs on physical examination were observed. In addition, fetal growth on ultrasound was normal, and nausea and anorexia improved by 13 weeks of pregnancy. We concluded that nausea was caused by hyperemesis gravidarum, not by bradycardia-induced cardiac low output, and it was decided that a permanent pacemaker was not indicated at that time. The patient was discharged at 13 weeks of pregnancy and was followed up as an outpatient at our department.

At 29 weeks of pregnancy, she had emergency admission to our hospital because of threatened premature labor (second admission). For the management of the threatened premature labor, ritodrine hydrochloride, a β_2-adrenoceptor agonist widely used to treat tocolysis, was orally (15 mg/day) and intravenously (50–150 μg/min) administered every day. Following her second admission, the heart rate was gradually increased according to the use of ritodrine hydrochloride. Indeed, the Holter ECG showed 76,988 beats per day of total beats (mean heart rate: 56 bpm), with a minimum rate of 40 bpm, at 30 weeks of pregnancy; and 83,780 beats per day of total beats (mean heart rate: 60 bpm), with a minimum rate of 44 bpm, at 35 weeks of pregnancy. The option of spontaneous labor or cesarean delivery was discussed with the patient, her family, cardiologists, gynecologists, and anesthesiologists. As a result, a planned cesarean delivery was eventually performed. A 2516 g healthy female infant was born

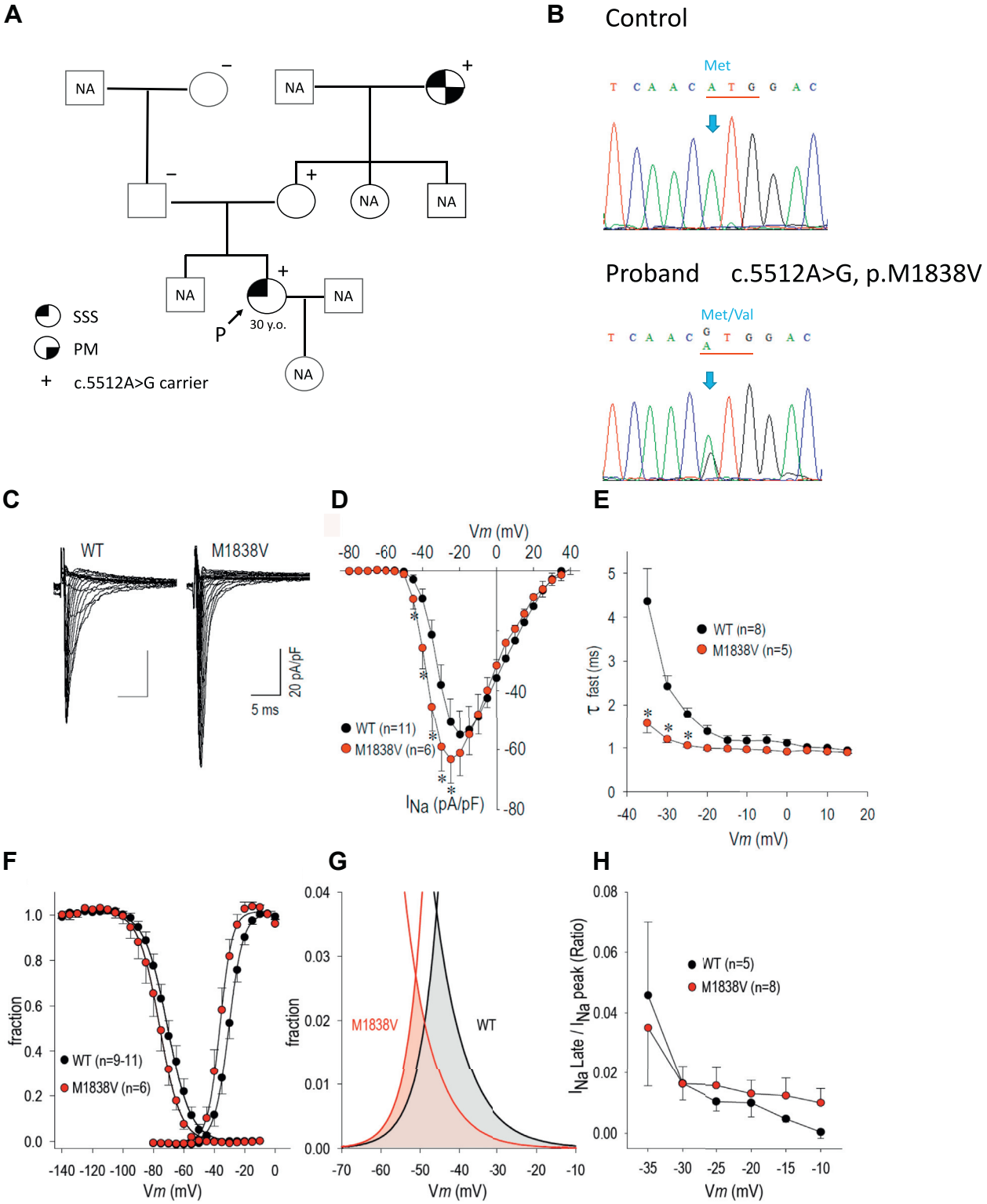


Figure 3 Genetic and functional analysis of the novel *SCN5A* mutation. **A:** Pedigree of the family. Phenotypic traits are designated with pedigree symbols. NA = not available for genetic information; P = proband; PM = pacemaker; SSS = sick sinus syndrome. **B:** Electropherograms of *SCN5A* gene showing a mutation, c.5512A>G, p.M1838V, in the proband and her family members. **C:** Representative I_{Na} current trace family obtained from HEK293 cells transfected with wild-type (WT) or mutant Na^+ channel Nav1.5. **D:** Current-voltage relationship of WT-I_{Na} and M1838V-I_{Na}. **E:** Time constant for fast inactivation of WT-I_{Na} and M1838V-I_{Na}. The decay of I_{Na} was fitted by a single exponential curve, yielding inactivation time constants (tau, τ) at the respective test potentials (abscissa). *$P < .05$ vs WT-I_{Na}. **F:** Steady-state inactivation and conduction-voltage relationship of WT-I_{Na} and M1838V-I_{Na}. **G:** Bolzmann fitting curves of activation and steady-state inactivation current data, indicating window current of WT-I_{Na} (*red*) and M1838V-I_{Na} (*gray*), and their voltage dependency. **H:** Relative amplitude of late or persistent I_{Na} ($I_{Na.Late}$) as a ratio to the peak current I_{Na}.

with Apgar scores of 6 and 9 at 1 and 5 minutes, respectively. Ritodrine hydrochloride was discontinued immediately before delivery. During 2 days after the cesarean delivery, the heart rate decreased to 76,310 beats per day of total beats (mean heart rate: 55 bpm), with a minimum rate of 33 bpm by Holter ECG, but there were no apparent symptoms consistent with bradycardia. After the careful follow-up, the patient was discharged 5 days postoperatively without any complications.

For further examination regarding SSS, she was admitted to our hospital with termination of breastfeeding, which was 1 month after the delivery (third admission). Coronary computed tomography angiography scan showed normal coronary function, and treadmill test showed gradual increase of the heart rate by exercise, reaching the target heart rate of 162 bpm. The electrophysiological test revealed that the sinus node recovery time was 2941 ms and HV interval was 37 ms. The atrioventricular nodal effective refractory period was 520 ms. In addition, pilsicainide provocation testing revealed that the sinus node recovery time was significantly prolonged to 8266 ms, while Brugada-type ECG was not observed. Based on these examinations, together with lack of symptoms consistent with bradycardia, we again judged that a permanent pacemaker was not indicated.

We performed genetic analysis after obtaining written informed consent (methods are detailed in Supplemental Appendix), and identified a novel missense mutation (c.5512A>G, p.M1838V) in *SCN5A* in the proband, her mother, and her maternal grandmother (Figure 3A and 3B, Supplemental Figure S1). The in vitro functional analysis revealed unexpected differences in both current amplitudes and kinetics between WT-I_{Na} and M1838V-I_{Na}. Currents generated by the M1838V channels were apparently larger than those of the WT channel in these traces (Figure 3C and 3D). The voltage dependency of time constants was even smaller or faster in the current decay in the M1838V channel (Figure 3E). As shown in Figure 3F, the steady-state half-inactivation potential of the M1838V channel was hyperpolarized by 5.2 mV compared to that of the WT channel. Taking this together with a shift of the activation curve toward the hyperpolarization direction, we postulate that a substantial window current of M1838V-I_{Na} is narrower and more hyperpolarized (Figure 3G). On the other hand, late component of I_{Na} or $I_{Na.late}$ was unchanged in the M1838V mutation (Figure 3H).

Discussion

We identified a novel, heterozygous nonsense *SCN5A* mutation in a family with SSS, which might have never been diagnosed if the proband did not have hyperemesis. In our case, as shown in Figure 2B, sinus bradycardia was observed the whole time during pregnancy, compared with the normal average heart rate in pregnant Japanese women.[7] The physiological increase of the heart rate according to the pregnancy course was observed. The heart rate was increased using ritodrine hydrochloride, a β_2-adrenoceptor agonist. This is the first report in which heart rate change during pregnancy with threatened premature labor was precisely evaluated in an SSS patient carrying the *SCN5A* mutation.

It has been reported that *SCN5A* is the most common gene responsible for Brugada syndrome and is also linked to familial SSS.[3,5] Aizawa and colleagues[8] indicated a sex-dependent phenotypic distribution, with female members developing SSS, in a family with *SCN5A* mutation. In our case, all those carrying the *SCN5A* mutation were female, and the proband did not show spontaneous and pilsicainide test–induced Brugada-type ECG. Although the fetal abnormality was not observed and the fetal heart rate was normal during pregnancy (mean fetal heart rate by cardiotocogram at 35 weeks gestation: 140 bpm), the female infant showed relatively sinus bradycardia after birth (Holter ECG at 1 week old: 165,518 beats/day of total beats, with a mean rate of 119 bpm and minimum rate of 78 bpm). In addition, there was an older brother of the proband who had no past medical history and apparent symptoms including syncope and fatigue. The genetic analyses for the infant and the older brother were discussed and we could not get an acceptance at this time. Furthermore, in the family members carrying *SCN5A* mutation, the proband and the maternal grandmother have shown sinus bradycardia, but the mother has not shown obvious sinus bradycardia (Supplemental Figure S1). These discrepancies suggest that not only genetic, but also epigenetic factors might contribute to the phenotype of this novel *SCN5A* mutation. The possibility that the *SCN5A* mutation is bystander for SSS cannot be denied.

Nevertheless, with respect to the phenotype of this family, it is logical to consider the function of the novel *SCN5A* mutation, M1838V-I_{Na}. Spontaneous electrical activity of the sinus node is generated by a complex interaction of multiple ionic currents, and the present case revealed a role of the voltage-gated Na^+ channel $Na_v1.5$. This novel mutation, M1838V-I_{Na}, showed a negatively shifted substantial window current. In general, the term "window current" is used to describe a small Na^+ current that may be seen in a "window" of potentials where the activation and steady-state inactivation curves overlap. The presence of the "Na^+ window current" contributes to the sustained inward current in the "Na^+ channel-positive" cells. The window peaked at -45.5 mV in the WT-I_{Na} and at -50.8 mV in the M1838V-I_{Na}, while the window current by itself was reduced in current density in M1838V-I_{Na}. If I_{Na}-window currents contribute to the generation potentials that underlie spontaneous firing in peripheral sinus node cells, it is highly probable that sustained currents in the window voltage ranges around -45 mV accelerate the slow diastolic potentials and that the I_{Na}-window current shift toward the negative potential direction may reduce the pacemaking ability of the cell, because the pacemaker cell take-off potentials are set at approximately -45 mV. Moreover, the fast inactivation gating of the M1838V-type Na^+ channel is faster than that of the WT-type Na^+ channel, which also indicates that the fast-activating and fast-inactivating properties of this channel are not lost in this mutation. Because of this, the M1838V mutation cannot be classified as a "loss-of-function" mutation. Previous studies have reported several

SCN5A mutations possibly related to familial SSS.[9,10] Although these mutations showed a reduction or no change in the maximum inward current of I_{Na} with various functional defects, the M1838V mutation verified the increase in the maximum inward current and reduction of the window current. Thus, the functional expression of the M1838V-Na^+ channel revealed a rare property of both gain- and loss-of-function gating responsible for the familial SSS.

Conclusion

This case report presents a proband with familial SSS possibly associated with a novel *SCN5A* mutation (M1838V) diagnosed during pregnancy.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2020.11.016.

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