# Long-term follow-up of permanent atrial standstill in a German family with mutation in the *SCN5A* gene

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## Introduction

Mutation in the cardiac sodium channel gene *SCN5A* has been reported in patients with Brugada syndrome, long QT syndrome 3,[1] familial progressive cardiac conduction disease (Lenègre disease),[2] familial atrial fibrillation, sinus node disease, and familial atrial standstill (AS).[3–6]

AS is a rare condition that is usually characterized by bradycardia, lacking P waves, a junctional or ventricular escape rhythm in the electrocardiogram (ECG), and progressive atrial degeneration.[7] Only a few cases that follow a hereditary pattern have been reported in the past.[8–11] In some families with AS, mutations in the cardiac sodium channel gene *SCN5A* have been characterized.[5,6] In 1 large Dutch family, mutation in *SCN5A* required an additional connexin-40 polymorphism for phenotypical penetrance into AS.[5] We report the rare case of a German family with autosomal-dominant permanent atrial standstill (PAS) in which a previously undescribed *SCN5A* mutation was identified.

## Case report

### Clinical history and presentation

A partial pedigree of the described family is depicted in Figure 1. Family members II-3, III-2, and III-3 were affected by PAS. Family member I-2 was affected by history, but the patient's diagnosis could not be clinically confirmed, and the patient did not undergo genetic testing.

A 55-year-old father presented his 2 sons, 18 and 16 years old, to our hospital because the teenagers had suffered from lightheadedness and multiple syncopal spells. The father of 3 sons was born with presumed atrioventricular block with a heart rate of about 50 beats per minute (bpm) and a junctional escape rhythm (Figure 2). Because of normal and asymptomatic development during childhood and adolescence, no ECGs had been obtained; even athletic sport performance during his college education was possible. At the age of 30 years the patient was first seen at the university hospital by 1 of the authors (H.U.K.) because of a noted, but asymptomatic, bradycardia during routine check-up. At that time the patient's ECG revealed a junctional rhythm, no P waves, and a right bundle branch block QRS configuration with a heart rate of 35–40 bpm. The electrophysiologic study (EPS) revealed AS in both atria with no atrial signals, a prolonged HV interval (HV 100 ms), and no retrograde ventriculoatrial conduction. Even with very high-stimulation energy (maximum set at 10 mA, 2 ms), all right atrial (RA) areas were completely inexcitable. Because of the asymptomatic clinical situation, pacemaker implantation was deferred at that time. However, a few years later a VVI pacemaker was implanted after an episode of syncope, as the patient had become symptomatic. Ten years later the patient experienced transient ischemic attack episodes along with an arterial embolism in his right arm. Subsequently, a left atrial (LA) thrombus was found on transthoracic echocardiography, leading to lifelong anticoagulation therapy with warfarin (target INR 2–3). Within the following 20 years, right ventricular (RV) pacing mildly reduced left ventricular and RV ejection fraction to 50%–55% (from normal baseline of 60%–65%).

At the first medical visit the 18-year-old and 16-year-old sons demonstrated the same ECG abnormalities with absent P waves, junctional rhythm of 40 bpm, and right bundle branch block QRS configuration. Holter ECG recordings showed a few episodes of 10–15 seconds of ventricular asystole. Review of their outside hospital records indicated that they were both born with normal sinus rhythm. However, both patients became symptomatic, with several episodes of syncope during adolescence. During these years, 12-lead ECGs revealed loss of P wave deflections. EPS showed complete AS with no atrial signals and atrial inexcitability. The HV interval was prolonged (90–100 ms), QRS duration was 110–120 ms, and no retrograde VA conduction was present. Echocardiography examination showed normal ventricular dimensions and function, no valvular abnormalities, and normal RA and LA dimensions. Both patients received VVI pacemakers and anticoagulation therapy with warfarin (target INR 2–3). Long-term follow-up of the

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**KEY TEACHING POINTS**

- Atrial standstill with sick sinus syndrome can have a variety of etiologies, which include genetic causes.
- Among common mutations are mutations of the *SCN5A* gene.
- Besides treatment of symptomatic bradycardia, anticoagulation is pertinent—even in the absence of other risk factors.

2 men over 10 years after pacemaker implantation showed gradual enlargement of RA and LA dimensions without change in biventricular function. One of the men reported an episode of a short self-terminating tachycardia, but performed EPS could not identify the origin of the tachycardia. The third, completely asymptomatic man (III-4) was routinely examined as well; his ECG showed normal sinus rhythm with morphologically normal P waves, a small QRS complex, and a completely normal echocardiogram.

### Mutation in the *SCN5A* gene

The clinical phenotype of PAS in all 3 men prompted us to screen for mutations in the gene of the α-subunit of the cardiac sodium channel *SCN5A*, in patients II-3, III-2, III-3, and III-4. A mutation in the position of nucleic acid 664 (C > G, exon 6) was detected in patients II-3, III-2, and III-3. The asymptomatic brother (III-4) of patients III-2 and III-3 was screened negative. On the amino acid level the mutation resulted in a substitution of arginine to glycine in position 222 (R222G).

## Discussion

In the presented case history, we describe a previously unreported *SCN5A* mutation in a German family with PAS. We could identify 3 carriers of the mutation, with all of them being phenotypically affected. Interestingly, the hearts of 2 young patients were structurally normal at the time of initial presentation to our hospital, but showed progressive RA as well as LA dilatation in the following years, without change in ventricular function or development of heart failure.

In the past, *SCN5A* mutations have been closely linked to cases of dilated cardiomyopathy.[12] We do not know if the structural degeneration of atrial myocardium that we describe here is a direct consequence of the PAS[13] or part of an additional underlying atrial cardiomyopathy process.

AS is a very rare condition and was previously described as a consequence of multiple systemic diseases, such as amyloidosis or muscular dystrophy. The voltage-gated cardiac sodium channel plays a decisive role for the excitation and action potential propagation through the cardiac muscle. Hence, the gene that encodes the α-subunit of the cardiac sodium channel, *SCN5A* (located on chromosome 3 p 21),[14] has been described to be mutated in several cardiac electrical disorders, as for instance in long QT syndrome 3, Brugada syndrome, and progressive conduction disorder (Lenègre disease). Recently, a phenotype of a sodium channelopathy, leading to an overlap syndrome of familial sick sinus syndrome with Brugada syndrome, male predominance, and early onset in adolescence, has been described.[12] Interestingly, cases in this family are in line with this described syndrome with regard to time of symptom onset and also male predominance. *SCN5A* mutation has been shown to result in reduced current density with alteration of biophysical tissue properties.[14] In an animal model, this subsequently led to sick sinus syndrome, because of loss-of-function properties with exit block to the surrounding tissue, providing likely biophysiological underpinnings for the clinical presentation of this family.

Even though overlap with syndromes in which patients are susceptible for development of ventricular tachycardia, such as Brugada syndrome, have been described, no ajmaline or

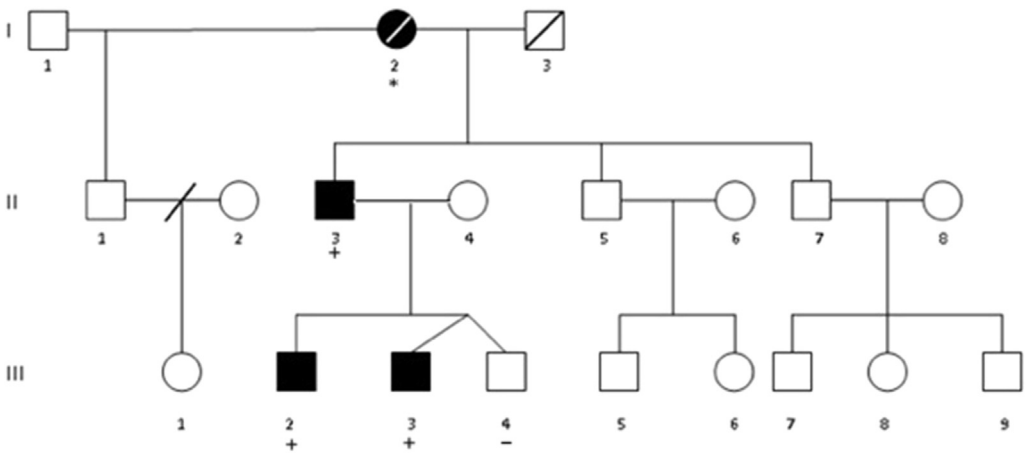


**Figure 1** Partial pedigree of the family. Empty symbols indicate phenotypically unaffected members (circles indicate females, squares indicate males), and filled symbols depict members with permanent atrial standstill. + indicates genotype positive; − indicates genotype negative; asterisk indicates no genotyping performed.

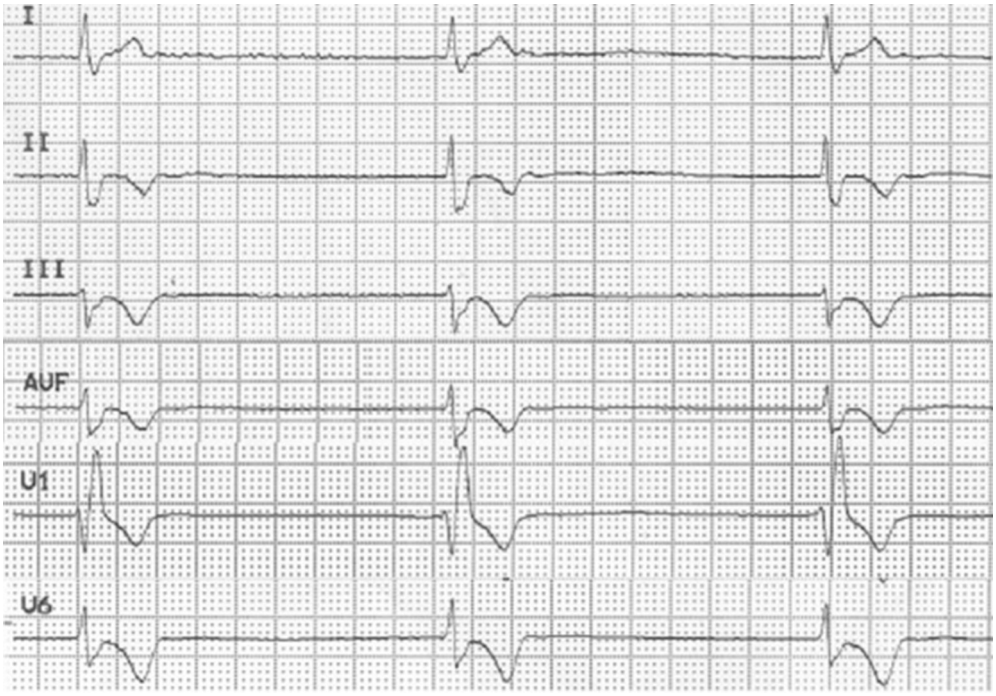


**Figure 2** Electrocardiogram of Patient III-2 (50 mm/s). No P waves could be detected—even in lead V1—consistent with complete persistent atrial standstill.

flecainide challenge was performed in these patients. However, family history was negative for sudden cardiac death and all patients received repetitive ECG monitoring without any evidence of ventricular arrhythmias.

## Conclusion

The PAS in the described family seems to be consequence of an *SCN5A* mutation (R222G) and is transmitted in an autosomal-dominant pattern. Long-term follow-up revealed progressive atrial dilatation without significant impairment of ventricular function, ventricular arrhythmias, or sudden cardiac death. Ventricular function over time slightly decreased from RV pacing in 1 individual. Lifelong anticoagulation in this situation was performed in all cases and appears pertinent even in the absence of any other cardiovascular risk factors.

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