Sodium channelopathies do we really understand what's going on?

Journal of Cardiovascular Electrophysiology
2010; in press

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ABSTRACT

We describe a family harboring two SCN5A mutations: the SCN5A ∆KPQ mutation, the ‘classical’ gain-of-function mutation associated with Long-QT syndrome, and the SCN5A I1660V mutation, a loss-of-function mutation associated with Brugada syndrome. With the knowledge of the association of these mutations, we were surprised by the result of genetic testing in this family. One son who carried the ∆KPQ mutation but did not carry the I1660V mutation did not show the expected Long-QT phenotype but, unexpectedly, showed a conduction disease/Brugada phenotype.
INTRODUCTION

The importance of mutations in the cardiac sodium channel gene (SCN5A) in inheritable arrhythmia syndromes has been known since the mid 1990s.\(^1\) Subsequently mutations were described which caused either Long-QT syndrome (type 3),\(^2\) Brugada syndrome,\(^3\) or progressive cardiac conduction defects (also known as Lev-Lenegre’s disease).\(^4\) The pathophysiological mechanism explaining these different phenotypic expression originate from either gain-of-function (Long-QT syndrome) or loss-of-function characteristics (Brugada syndrome, progressive cardiac conduction defects) of the mutant sodium channels.\(^5\) The gain-of-function mutations result in persistent inward sodium current during the plateau phase of the cardiac action potential causing action potential prolongation. The loss-of-function mutations result in decreased sodium inward current, causing a decrease of sodium current available for activation. Hence, conduction slowing ensues. In addition, structural derangements initiated by the mutant channels may play a role in the latter.\(^6\) Therefore, from the electrocardiographic phenotype one can already presume either a gain- or a loss-of-function defect. Interestingly, in 1999 a SCN5A mutation (1795insD) was described which caused both Long-QT syndrome, Brugada syndrome and progressive cardiac conduction defects, referred to as an overlap syndrome.\(^7\),\(^8\) Not surprisingly it was discovered that the mutant channels exhibited both gain- and loss-of-function characteristics.\(^9\)

In the past years it became increasingly clear that variable phenotypic expression (also known as incomplete penetrance) is often present. While about 50% of a family carries the mutation, there are often only a few who actually experience symptoms and the electrocardiographic signature of the mutation is present in very variable degrees. Apart from the influence of environmental factors, genetic modifiers may play a pivotal role in this issue.\(^10\) However, sometimes we are even more puzzled by the result of genetic testing. In the present report we describe a family harboring two SCN5A mutations: the SCN5A ΔKPQ mutation, the ‘classical’ gain-of-function mutation associated with Long-QT syndrome,\(^1\) and the SCN5A I1660V mutation, a loss-of-function mutation associated with Brugada syndrome.\(^11\) With the knowledge of the association of these mutations, we were surprised by the result of genetic testing in this family.

METHODS AND RESULTS

All patients provided written informed consent.

Case report: After the successful resuscitation of a 69 year old female (the proband), laboratory investigation revealed a low serum potassium (3 mmol/l) which was restored. The ECG is depicted in figure 1. There is sinus rhythm, 73 bpm, with normal conduction intervals and
a prolonged QTc of 480 ms with a stretched ST segment and a late onset T-wave. Holter recordings showed severe QT prolongation upon bradycardia. Additional cardiological investigation, including exercise testing, echo and coronary angiography, was without abnormalities. As the inheritable arrhythmia syndrome Long-QT syndrome was suspected, she was referred to our cardiogenetics outpatient clinic together with her two sons. ECGs of her two sons (46 and 43 years old) were obtained. The ECG of the oldest son (46 years of age, figure 2A) shows sinus bradycardia, 59 bpm, with slightly prolonged conduction intervals (PQ 220 ms, QRS 105 ms). The T-wave morphology is abnormal with a biphasic T-wave in V4 and low amplitude late onset T-wave in other lateral leads. QTc is prolonged (500 ms) and there is some ST-elevation in the right precordial leads followed by negative a T-wave suggestive of Brugada syndrome. The ECG of the younger son (43 years of age, figure 3) shows sinus bradycardia, 50 bpm, high to normal PQ interval (197 ms) and wide QRS (130 ms). The ST-segment is somewhat elevated in the right precordial leads and the QTc-interval is normal (427 ms). Although the father of the family was deceased (due to a malignancy at the age of 73 years) an ECG performed several years before his death showed a high PQ interval (215 ms) and a normal QRS and QTc interval duration (not shown).

The combination of the ECG features found in the mother and her two sons (bradycardia, conduction delay, QTc-prolongation and ST-elevation), closely resembled the electrocardiographic phenotype in the previously mentioned family with an overlap syndrome based on the SCN5A 1795insD mutation with both gain- and loss-of-function characteristics (figure 2B). This prompted us to screen SCN5A for this particular mutation first in the oldest son (patient II:1, figure 4) who had the most severe ECG abnormalities with a mixed phenotypic expression of Long-QT syndrome and Brugada syndrome. However, the SCN5A 1795insD mutation was not found. Instead, screening of SCN5A first revealed the SCN5A gain-of-function ΔKPQ mutation, and, actually not unexpectedly, also a loss-of-function SCN5A mutation, I1660V. In the mother (patient I:1) who had the Long-QT phenotype, the same ΔKPQ mutation was identified. However, in the youngest son (patient II:2) who had a
Brugada syndrome-like phenotype and no Long-QT phenotype, the SCN5A I1660V mutation was not identified, instead he carried the same SCN5A ΔKPQ mutation as his mother and brother. Further screening in the family did not reveal other mutation carriers. In addition, all family members were homozygous for H558. Ajmaline provocation testing was not performed.

**DISCUSSION**

The present family displays a complex SCN5A-related phenotype with features of both Long-QT syndrome and Brugada syndrome (figure 2A). Overlap syndromes with different electrocardiographic features of SCN5A-related syndromes at different cardiac levels have been recognized from single mutations. In general these features are reasonably well explained by functional biophysical studies of the mutant protein in heterologous expression systems. For the SCN5A ΔKPQ mutant the sentinel study of Bennett et al. clearly demonstrated the presence of persistent inward current during the plateau phase of the action potential, explaining the Long-QT phenotype. The SCN5A I1660V mutant channels show a trafficking defect leading to haploinsufficiency in the heterologous state as associated with Brugada syndrome.

Patient I:1, the mother, with the gain-of-function SCN5A ΔKPQ mutation has a ‘clean’ Long-QT (type 3) phenotype, as expected. Patient I:2, the father, from whom no DNA was available, might have harbored the SCN5A I1660V mutation which would explain the prolonged PQ interval. Patient II:1, the...
oldest son, with both the gain-of-function SCN5A ΔKPQ mutation and the loss-of-function SCN5A I1660V mutation had prolonged QT and displayed long conduction intervals at different cardiac levels and a (mild) Brugada-phenotype with suggestive J elevation in V1 and V2 (although without a type-1 or coved-type Brugada ECG) as compatible with these two (both gain-of-function and loss-of-function) mutations. The unexpected result, however, was observed in patient II:2, the youngest son. If anything, this patient demonstrates a ‘loss-of-function-phenotype’, with clear conduction disease, some right precordial ST elevation and no QT prolongation. Yet only the ‘classical’ gain-of-function Long-QT ΔKPQ mutation was found. Interestingly, slightly prolonged conduction intervals have been noted earlier in SCN5A ΔKPQ mutation carriers. The late onset of the T-wave in lead I, and especially during bradycardia, as seen in patients I:1 and II:1 is considered typical for SCN5A associated Long-QT syndrome (type 3). Prolonged conduction indices and elevated ST-segments resemble the Brugada and conduction disease phenotype associated with SCN5A mutations as seen in patients II:1 and II:2. A mixed phenotypic expression might be seen in mutations harboring both gain- and loss-of-function characteristics, and also compound heterozygous mutations have been described which may lead to overt (mixed) phenotypes. In addition, incomplete penetrance (different carriers of a single mutation who display a different severity of disease expression) is the rule.
rather than the exception. Furthermore, it has recently been noted that SCN5A mutations may not be directly causal to the occurrence of Brugada syndrome and that other factors including genetic background may play a powerful role in its pathophysiology. One of these modifiers might be the frequently occurring polymorphism SCN5A H558R which has been shown to modify the basic electrophysiological phenotype of loss-of-function SCN5A mutations associated with Brugada syndrome and sick sinus syndrome. In the present study, however, all subjects carried a similar H558 genotype precluding a modifying effect. Aging is another modifier of the clinical phenotype in SCN5A mutations, as has been shown both in human and mice studies. Because of the lack of earlier ECGs of this family, this potential modifier could not be studied.

Hence, the absence of a Long-QT phenotype while carrying the Long-QT mutation and the presence of a conduction disease/Brugada-like phenotype while not carrying the loss-of-function mutation was, and is, a surprise to us and remains unexplained so far. Unfortunately, other mutation carrying family members were not available to substantiate this observation. Most likely, genetic background including as yet unknown factors plays a substantial role in defining the ultimate phenotypic expression of the sodium channelopathy in this family.

REFERENCES

11 Cordeiro JM, Barajas-Martinez H, Hong K et al. Compound heterozygous mutations P336L and I1660V in the human cardiac sodium channel associated with the Brugada syndrome. Circulation.


