Decreased inward rectification of Kir2.1 channels is a novel mechanism underlying the short QT syndrome

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This editorial refers to ‘A novel gain-of-function KCNJ2 mutation associated with short-QT syndrome impairs inward rectification of Kir2.1 currents’ by T. Hattori et al., pp. 666–673, this issue.

The short QT syndrome (SQTS) is a recently recognized cardiac channelopathy characterized by a shortened QT interval in the electrocardiogram (ECG). It is associated with a high incidence of atrial fibrillation (AF), syncope, and sudden death in the absence of structural cardiac abnormalities. Gussak et al. first described the syndrome in 2000 within the context of an isolated case of sudden cardiac death in a young female and the presence of early-onset AF in a separate family.¹ Cardiac workup demonstrated a structurally normal heart in affected individuals, but a remarkable short QTc interval on the ECG ranging between 248 and 300 ms. These first studies led to the emerging recognition of SQTS as a distinct clinical entity and were followed by reports on similar cases (reviewed in Gollob et al.²). The diagnosis of SQTS is somewhat complicated as QT intervals overlap between affected cases and apparently healthy subjects. The presence of a short QT interval by itself is not always predictive of an increased arrhythmic risk and therefore should not invariably lead to a diagnosis of SQTS.³ To address this, Gollob et al.² recently proposed a set of formal diagnostic criteria based on the review of all reported SQTS cases to date.

SQTS is a genetically heterogeneous disease, with three ion channel genes identified as causative (SQT1–3, OMIM #609620, #609621, #609622). SQT1 is associated with mutations in KCNH2⁴ and SQT2 with mutations in KCNQ1.⁵ Mutations in KCNJ2, the gene encoding the Kir2.1 channels underlying the inward rectifier potassium current I_K1, are linked to SQT3.⁶ Overall, in only 30% (18/62) of the published SQTS cases can a causative mutation be identified,² indicating that additional genes likely play a role in the pathogenesis of SQTS.

Kir2.1 is part of a large family of inwardly rectifying potassium channels, and it is widely expressed with particularly high levels in the heart, brain, placenta, lung, and skeletal muscle.⁷ This family of potassium channels is unique, in that the channels conduct potassium ions better in the inward direction than in the outward direction (inward rectification).⁸ The inward rectification is thought to be due to a voltage dependence pore blockade induced by intracellular magnesium and/or polyamines that interact with negatively charged amino acids. Analysis of the crystal structure of Kir2.1 channels identified an additional rectification mechanism, namely a flexible cytoplasmic pore-facing loop, effectively forming a restraint around the central pore axis, termed the G loop.⁹ In the heart, I_K1 plays an important role both in membrane potential stabilization (Phase 4) and in the final repolarization phase of the action potential (Phase 3), thereby modulating cardiac excitability.⁸

Mutations in the KCNJ2 gene have been identified in patients affected by Andersen–Tawil cardiomyopathic periodic paralysis (ATS OMIM #170390),¹⁰ an autosomal dominant multisystem channelopathy characterized by periodic paralysis, ventricular arrhythmias, and distinctive dysmorphic features. Patients have a variable prolongation of the QT interval and short runs of bidirectional ventricular tachycardia. More than 40 KCNJ2 mutations are known to date causing ATS, all of them resulting in a loss of function. In contrast, a gain-of-function mutation in KCNJ2 was shown to underlie the SQTS.⁶ A small family presented with presyncopeal events, palpitations, and a short QT interval (<320 ms QTc). Mutational analysis revealed a co-segregating mutation, D172N. The D172N mutation alters one of the negatively charged amino acids involved in rectification. Nonetheless, mutant D172N channels had normal rectification properties but did demonstrate a significantly increased outward current.

In this issue, Hattori et al.¹¹ report the findings of a novel KCNJ2 gain-of-function mutation. In an elegant study, they detail the findings of a small family in which the proband suffered from an extremely short QT interval (QTc 194 ms) and also exhibited paroxysmal AF. The Kir2.1 channels underlying the inward rectifier potassium current I_K1, are linked to SQT3. Overall, in only 30% (18/62) of the published SQTS cases can a causative mutation be identified, indicating that additional genes likely play a role in the pathogenesis of SQTS.

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positive potentials. This represents a novel mechanism causing the
which results in a significantly larger outward potassium current at
M301K and wild-type channels shows a weak inward rectification,
mutation mentioned above. However, co-expression of both
channel is expressed alone, in contrast to the results of the D172N
I\text{\textsubscript{K1}} when the M301K mutant
responsible for the short QTc interval. The M301K proband. Ulti-
mately, to further address these issues, the use of knock-in mice or
induced pluripotent stem cells would be instrumental, not only in
vestigating the patients’ extra-cardiac phenotypes and the role of the
genetic background but also to further explore Kir2.1 inward
rectification.

Conflict of interest: none declared.

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