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), syncpe, 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.\textsuperscript{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.).\textsuperscript{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.\textsuperscript{3} To address this, Gollob et al.\textsuperscript{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 KCNH2\textsuperscript{4} and SQT2 with mutations in KCNJ1.\textsuperscript{5} Mutations in KCNJ2, the gene encoding the Kir2.1 channels underlying the inward rectifier potassium current \(I_{K1}\), are linked to SQT3.\textsuperscript{5} Overall, in only 30% (18/62) of the published SQTS cases a causative mutation can be identified,\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{8}

Mutations in the KCNJ2 gene have been identified in patients affected by Andersen–Tawil cardiodyrhythmic periodic paralysis (ATS OMIM #170390),\textsuperscript{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.\textsuperscript{6} A small family presented with presyncopal 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.\textsuperscript{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. In addition, she presented with severe mental retardation, Kawasaki disease, and proliferation of oesophageal blood vessels. Mutational analysis demonstrated a novel heterozygous KCNJ2 mutation, M301K. This mutation results in the substitution of a neutrally charged amino acid for a positively charged one. The mutation is...
located in the G-loop, which is crucial to inward rectification.\(^9\) Functional assays demonstrated an absence of \(I_{K1}\) when the M301K mutant channel is expressed alone, in contrast to the results of the D172N mutation mentioned above. However, co-expression of both M301K and wild-type channels shows a weak inward rectification, which results in a significantly larger outward potassium current at positive potentials. This represents a novel mechanism causing the SQTS. Hattori et al. went on to probe the importance of the charge at this position by introducing a variety of charges and firmly demonstrate that the nature of the charge at position 301 plays a crucial role in Kir2.1 channel inward rectification. Lastly, they demonstrate that co-expression of the wild-type and the M301K mutant channel in neonatal rat ventricular myocytes results in action potentials lacking the plateau phase.

While the end result is similar (QT interval shortening), the functional consequences of these two KCNJ2 short QT mutations are quite different. Mixed wild-type/D172N channels show a larger outward current between \(-75\) mV and \(-50\) mV, while at more positive voltages, \(I_{K1}\) rectifies normally in the inward direction and inactivates completely around \(-30\) mV. In contrast, the wild-type/M301K channels show a significantly increased outward current at positive voltages to \(-30\) mV due to a diminished inward rectification. These different gain-of-function mechanisms may impact differently on the action potential and could explain the diverse clinical manifestations observed in the two probands. Indeed, the D172N mutation resulted in the shortening of the terminal phase of the action potential, whereas the M301K mutation led to the loss of the action potential plateau phase which probably caused the extremely short QTc observed in the M301K proband.

The extra-cardiac phenotype of the M301K proband is in contrast to carriers of the aforementioned D172N mutation. It is likely that the diminished inward rectification of the M301K also creates problems in other tissues, as Kir2.1 channels are ubiquitously expressed. Therefore, it would be prudent to investigate the KCNJ2 gene for mutations in syndromic cases mimicking the M301K proband. Ultimately, to further address these issues, the use of knock-in mice or induced pluripotent stem cells would be instrumental, not only in investigating 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.

**References**