Received: 1 July 2021 | Revised: 20 December 2021 | Accepted: 2 January 2022

DOI: 10.1111/apha.13781

ACTA PHYSIOLOGICA

REVIEW ARTICLE

Celebrities in the heart, strangers in the pancreatic beta cell: Voltage-gated potassium channels K_v7.1 and K_v11.1 bridge long QT syndrome with hyperinsulinaemia as well as type 2 diabetes

Anniek F. Lubberding | **Christian R. Juhl** | **Emil Z. Skovhøj** | **Jørgen K. Kanters** | **Thomas Mandrup-Poulsen** | **Signe S. Torekov**

Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Correspondence
Signe S. Torekov, Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, DK-2200, Copenhagen, Denmark.
Email: torekov@sund.ku.dk

Funding information
Det Frie Forskningsråd, Grant/Award Number: 8020-00247B; Lundbeckfonden, Grant/Award Number: R252-2017-1570; Novo Nordisk Fonden, Grant/Award Number: NNF19OC0057507; Danish Heart Association

Abstract

Voltage-gated potassium (K_v) channels play an important role in the repolarization of a variety of excitable tissues, including in the cardiomyocyte and the pancreatic beta cell. Recently, individuals carrying loss-of-function (LoF) mutations in *KCNQ1*, encoding K_v7.1, and *KCNH2* (hERG), encoding K_v11.1, were found to exhibit post-prandial hyperinsulinaemia and episodes of hypoglycaemia. These LoF mutations also cause the cardiac disorder long QT syndrome (LQTS), which can be aggravated by hypoglycaemia. Interestingly, patients with LQTS also have a higher burden of diabetes compared to the background population, an apparent paradox in relation to the hyperinsulinaemic phenotype, and *KCNQ1* has been identified as a type 2 diabetes risk gene. This review article summarizes the involvement of delayed rectifier K^+ channels in pancreatic beta cell function, with emphasis on K_v7.1 and K_v11.1, using the cardiomyocyte for context. The functional and clinical consequences of LoF mutations and polymorphisms in these channels on blood glucose homeostasis are explored using evidence from pre-clinical, clinical and genome-wide association studies, thereby evaluating the link between LQTS, hyperinsulinaemia and type 2 diabetes.

KEYWORDS

cardiac, delayed rectifier, glucose homeostasis, insulin, KCNH2, KCNQ1, K_v, pancreatic islet

1 | INTRODUCTION

Voltage-gated K^+ (K_v) channels are important mediators of the repolarization phase of the action potential in a variety of different electrically excitable tissues[1,2]. Upon opening of the K_v channels, K^+ efflux out of the cell drives the membrane potential to more negative potentials, opposing depolarizing currents, thereby repolarizing or hyperpolarizing the membrane.[3] Overlap of expression and function of delayed rectifier K^+ channels occurs across tissues. One such example is the expression of *KCNQ1*, encoding K_v7.1, and *KCNH2*, encoding K_v11.1, in both the ventricular cardiomyocyte and the pancreatic beta cell.

This suggests the possibility of overlapping cardiac and metabolic phenotypes in patients with altered function of these channels.

In the heart, K_v7.1 and K_v11.1 are well-established to be responsible for the delayed repolarizing current. Their role in the pancreatic beta cell is more elusive, although data on their physiological role in the secretion of insulin are now accumulating. Importantly, in recent years, it was found that patients with loss-of-function (LoF) mutations in either *KCNQ1* or *KCNH2* not only present with long QT syndrome (LQTS), a cardiac disorder characterized by delayed repolarization of the ventricular myocardium, increased risk of cardiac arrhythmia and sudden cardiac death, but also post-prandial hyperinsulinaemia and symptomatic hypoglycaemia, potentially worsening the cardiac phenotype.[4,5]

Interestingly, patients with LQTS also show a higher burden of diabetes compared to the background population,[6] seemingly paradoxical given the post-prandial hyperinsulinaemia. Furthermore, in a large number of genome-wide association studies (GWAS), *KCNQ1* has been consistently identified as a type 2 diabetes susceptibility locus.[7-9] This review article will summarize the role of delayed rectifier K^+ channels in pancreatic beta cell function, with emphasis on K_v7.1 and K_v11.1, combining this with their cardiac impact, thereby reconciling the phenotypic traits of LQTS, hyperinsulinaemia and type 2 diabetes and how one may influence the other.

2 | THE PANCREATIC BETA CELL AND ITS ELECTROPHYSIOLOGY

The beta cell is responsible for the secretion of insulin in response to glucose and is situated in the islets of Langerhans of the pancreas in the company of a variety of different endocrine cells. The exact composition of the endocrine cells within the islet is species-dependent, but a human islet of Langerhans consists mostly of insulin-secreting beta cells (≈60%), in combination with glucagon-releasing alpha cells (≈30%), somatostatin-releasing delta cells (≈5%-10%), polypeptide-producing (PP) cells (≈5%) and ghrelin-producing epsilon cells (<1%).[10,11] Insulin is secreted mainly in response to rises in blood glucose after meal intake, and functions to mediate nutrient utilization and deposition in peripheral tissues, including glucose, thereby regulating circulating levels of substrates. Glucagon produced by the pancreatic alpha cells, on the other hand, functions to increase blood glucose when it is low. Together they are the main hormonal effectors involved in balancing blood glucose homeostasis. Fine-tuning of their release is mediated by neural innervation, a variety of humoral factors, including incretin hormones, amino acids, and metabolites, as well as by cell-cell communication within the islet, occurring both through paracrine signalling[12] and through electrical communication between the cell types.[13]

Insulin release is mediated by electrical activity dictated by glucose concentrations (Figure 1). The electrophysiology of the beta cell has been meticulously reviewed recently by Rorsman and Ashcroft,[14] and will only be summarized here. At low blood glucose concentrations (<3-5 mM), the beta cell is in an electrically quiescent, hyperpolarized state, with a resting membrane potential of ~−70 mV.[15] In the event of a rise in blood glucose after meal intake, glucose readily enters the human beta cell through the GLUT1 transporters,[16] where it is metabolized to form ATP. This increase in the intracellular ATP/ADP ratio closes ATP-sensitive K^+ (K_{ATP}) channels (K_{ir}6.2 and SUR1)[17] which are otherwise open, maintaining the negative resting membrane potential. This leads to a subsequent depolarization which triggers short, frequent action potentials. These phases of action potential firing are separated by silent interburst phases: the relative amount of action potential firing vs silent interburst phases increases with increasing concentrations of glucose, with firing becoming continuous >11 mM glucose.[14] The initial small depolarization initiated by the closure of the K_{ATP} channels triggers a cascade of voltage-gated ion channels to open.[15,18] First, transient T-type Ca^{2+} channels open,[19] followed by voltage-gated Na^+ channels (primarily Na_v1.6 and Na_v1.7)[14,20,21] and L-type Ca^{2+} channels.[19] Further Ca^{2+} influx occurs through P/Q-type Ca^{2+} channels when membrane potentials reach above −20 mV.[19] It is the accumulation of intracellular Ca^{2+} that directly triggers the fusion of readily available secretory granules with the plasma membrane, leading to insulin exocytosis (Figure 1).[22] Repolarization occurs through rapid inactivation of the Na_v channels, as well as the opening of large-conductance Ca^{2+}-activated (BK) channels[23] and delayed rectifier K^+ channels.[24] Additionally, small-conductance Ca^{2+}-activated (SK) channels open in response to the accumulation of intracellular Ca^{2+}, gradually increasing their current during action potential bursts, leading to hyperpolarization and the characteristic oscillatory electrical activity of the beta cell.[25]

3 | THE ROLE OF DELAYED RECTIFIER K^+ CHANNELS IN THE PANCREATIC BETA CELL

The K_v channels are a large family encompassing 12 known subfamilies of K^+ channels (K_v1-K_v12).[26] Each functional K_v channel is tetrameric, composed of four transmembrane alpha subunits surrounding a

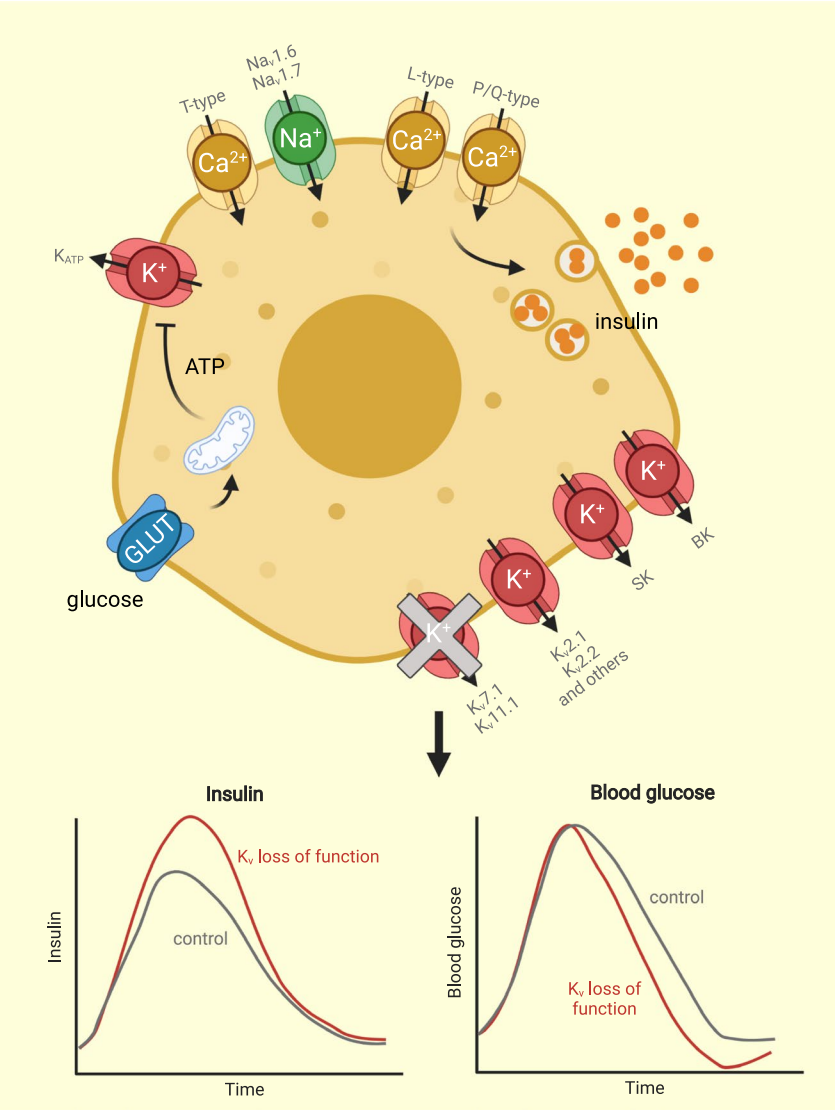

FIGURE 1 Ion channels involved in pancreatic beta cell electrophysiology and the effect of functional loss of the delayed rectifier K^+ channels $K_v7.1$ and $K_v11.1$. Glucose-induced insulin secretion is mediated by electrical activity. Upon an increase in the ATP/ADP ratio due to glucose metabolism, ATP-sensitive K^+ channels close. This initiates a cascade of ion channels to open, including Na^+ (green), Ca^{2+} (yellow) and K^+ (red) channels, leading to release of insulin (see text for details). Individuals with functional loss of delayed rectifier K^+ channel $K_v7.1$ or $K_v11.1$ show hyperinsulinaemia and subsequent hypoglycaemia after an oral glucose load (graphically depicted in figure based on[4,5]). Created with Biorender.com. Abbreviations: BK, large-conductance Ca^{2+}-activated K^+ channel; K_{ATP}, ATP-sensitive K^+ channel; K_v, voltage-gated K^+ channel; Na_v, voltage-gated Na^+ channel; SK, small-conductance Ca^{2+}-activated K^+ channel

central ion-conducting pore. Each alpha subunit consists of six transmembrane alpha helices (S1-S6; Figure 1).[27,28] Segments S1-S4 form a voltage-sensing domain positioned on the outside of the channel; specifically, the S4 domain contains multiple positively charged residues that act as the primary voltage sensor.[28-30] Segments S5-S6 from each alpha subunit form the ion-conducting pore.[28-30] Upon depolarization of the membrane, an outward displacement of S4 leads to a structural rearrangement that moves the pore domain into its open state.[31] The wide range of subfamilies encompasses a diversity in biophysical properties and gating kinetics of the channels, subdividing them into two general groups: delayed rectifier K^+ channels and transient A-type K^+ channels.[32] The delayed rectifier K^+ channels are named after their delay in activation, while the transient A-type K^+ channels inactivate rapidly in a time-dependent manner[32] and, thus, only open shortly after a depolarizing voltage change.

A wide variety of delayed rectifier K^+ channels are expressed in the human beta cell, although for many their role remains elusive.[14,33-35] The involvement of $K_v2.1$ and $K_v2.2$ in the secretion of insulin has been a main focus of study. In mice, $K_v2.1$ is the main channel accounting for the delayed outward current in the beta cell,[36] and $K_v2.1$ antagonism produces increased glucose-induced insulin secretion.[37,38] $K_v2.2$ may act as a suppressor of the outward current produced by $K_v2.1$, as overexpression of $K_v2.1$ alone in INS-1 832/13 rat insulinoma cells increases outward K^+ current, while co-overexpression with $K_v2.1$ and $K_v2.2$ reduced this increase by half.[39] This may be via direct physical interaction, as co-immunoprecipitation experiments showed an interaction between the two channels, possibly suggesting the formation of a heteromultimeric channel also in the pancreatic beta cell.[39] Inhibition by guangxitoxin, an inhibitor of $K_v2.1/K_v2.2$ channels, increases glucose-induced insulin secretion.[40] In human islets, the contribution of $K_v2.1$ and/or $K_v2.2$ to the outward K^+ current appears smaller. In one study, the $K_v2.1/2.2$ blocker stromatoxin only affected action potential height in one out of seven human beta cells studied,

in comparison to all beta cells studied during blockade with the non-selective K^+ inhibitor tetraethylammonium (TEA).[41] Furthermore, the evidence of the role of these channels on insulin secretion is inconsistent, with one study showing enhancement of glucose-induced insulin secretion with $K_v2.x$ inhibition in human islets,[42] while another reported no effect.[43] It appears that both $K_v2.1$ and $K_v2.2$ do contribute to the delayed outward K^+ current found in human islets,[43] but that this current may not be substantially involved in glucose-induced insulin secretion. Interestingly, $K_v2.1$ appears to affect insulin exocytosis outside of its current-carrying properties. The protein clusters at the plasma membrane where it is involved in the recruitment of new insulin granules to replenish the pool of readily available secretory granules.[43,44]

Human beta cells also express *KCNA5*,[14,33] encoding $K_v1.5$, and *KCNA6*,[14,35] encoding $K_v1.6$, although it remains unclear whether these participate in the repolarizing currents of the pancreatic beta cell. Some evidence suggests that $K_v1.5$ is involved in prosurvival signalling. Overexpression of *KCNA5* in the INS1 rat beta cell line resulted in increased endoplasmic reticulum (ER)-stress-induced apoptosis.[45] ER stress was simulated by incubation with thapsigargin, an inhibitor of the sarco/endoplasmic reticulum Ca^{2+} ATPase, with subsequent evaluation of apoptosis. *KCNA5* overexpression increased the induced apoptosis.[45] This could be prevented by *KCNA5* knockdown with RNAi or incubation with the incretins glucose-dependent insulinotropic polypeptide (GIP) or glucagon-like peptide 1 (GLP-1).[46]

3.1 | $K_v7.1$ in the pancreatic beta cell

The involvement of $K_v7.1$, encoded by *KCNQ1*, well known for its function in the heart, has been debated because of the low expression of *KCNQ1* in beta cells in comparison to other K_v channels.[14] However, functional data have suggested an involvement of $K_v7.1$ in insulin secretion. The MIN6 mouse beta cell line was found to have an outward current sensitive to chromanol 293B, a selective $K_v7.1$ inhibitor, which was increased when overexpressing the *Kcnq1* gene.[47] Additionally, this overexpression resulted in decreased glucose-induced insulin secretion, as well decreased insulin secretion induced by tolbutamide, a blocker of the beta cell K_{ATP} channel.[47] Chromanol 293B also reduced outward currents in the INS-1 rat beta cell line and increased tolbutamide-induced insulin secretion.[48] In mice, chromanol 293B increased glucose-induced secretion of insulin both in isolated pancreatic islets, and *in vivo* in response to an oral glucose tolerance test (OGTT).[49] Chromanol 293B also inhibits the cystic fibrosis transmembrane conductance regulator (CFTR) channel,[50] although this is unlikely to contribute to the chromanol 293B-mediated increase in insulin secretion in these studies, since the decreased function of the CFTR channel leads to a reduction rather than an increase in glucose-induced insulin secretion, if any effect exists at all.[51,52] Recent functional data in patients with LQTS with a LoF mutation in *KCNQ1*, named LQT1, confirm the involvement of $K_v7.1$ in insulin response to glucose in humans as well.[4] During an OGTT patients with LQT1 showed hypersecretion of insulin which resulted in symptomatic hypoglycaemia ~3-5 hours after the glucose load. Follow-up studies in mice with a clinically relevant LoF mutation in *Kcnq1* showed that the hypersecretory phenotype was also present *ex vivo*.[53] This suggests that the hypersecretion of insulin found in the setting of *KCNQ1/Kcnq1* LoF is because of an effect in the beta cell itself and/or in the other endocrine cells of the pancreatic islet, but not from effects occurring outside of the pancreas. Additionally, a case study of a patient with a gain of function mutation in *KCNQ1* revealed hypoinsulinaemia after an oral glucose load, further confirming $K_v7.1$'s function in insulin secretion.[54]

$K_v7.2$, encoded by *KCNQ2*, not expressed in the cardiomyocyte, is also expressed in the pancreatic beta cell, with findings of a high mRNA expression profile in the human adult beta cell population compared to the alpha cell population within the islet,[35] however, to our knowledge, its function in beta cell physiology has yet to be defined.

3.2 | $K_v11.1$ in the pancreatic beta cell

Expression of $K_v11.1$, encoded by the *KCNH2* gene or human ether-a-go-go related gene (hERG), is shared between a variety of tissues, including the ventricular cardiomyocyte and pancreatic beta cell.[14] Just like LoF mutations in *KCNQ1,* LoF in *KCNH2* also creates a dual cardiac and metabolic phenotype in patients. Patients with LQTS because of a LoF mutation in *KCNH2*, named LQT2, showed hypersecretion of insulin during an OGTT, resulting in hypoglycaemia,[5] similar to the patients with LQT1. This same pattern was confirmed in rats during pharmacological blockage of the $K_v11.1$ channel with the selective inhibitor dofetilide, and in the MIN6 mouse beta cell line with siRNA knockdown of the channel.[5] *KCNH2* is strongly expressed in the pancreatic beta cell.[14] In human islets blockade of the delayed rectifier current by WAY-123 398 resulted in increased glucose-induced action potential firing, as well as increased action potential firing induced by the amino acid arginine, known to stimulate insulin secretion.[55] Additionally, WAY-123 398 increased insulin secretion.[55] In another study, using the $K_v11.1$ selective

inhibitor BeKm-1, intracellular Ca^{2+} was increased in murine and human islets.[56] However, when assessing insulin secretion after 90 minutes of incubation at high glucose (11.1 and 20 mM), hERG inhibitors E4031 and BeKm-1 did not affect glucose-induced insulin secretion, an interesting finding since increased intracellular Ca^{2+} directly stimulates the exocytosis of insulin. During further scrutiny of insulin secretion over time, with measurements taken every minute, BeKm-1 was found to increase insulin secretion, but only temporarily for about 5 minutes, suggesting only a transient effect of K_v11.1 block on insulin secretion.[56] Further investigations are required to understand how these data relate to K_v11.1 LoF in beta cell function.

K_v11.2, encoded by *KCNH6*, is also expressed in the pancreatic beta cell (although not in the cardiomyocyte), and has been implicated as a causative gene in congenital hyperinsulinism.[57] A recent study revealed that a mutation in the *KCNH6* gene co-separated with multigenerational early-onset diabetes.[58] Interestingly, they found that a newborn that carried one of the identified mutations presented with neonatal hypoglycaemia that required glucose treatment. A further two genotype-positive children within the studied families with multigenerational diabetes had high blood insulin and low blood glucose levels. Knockout of *Kcnh6* or knock-in of a LoF mutation in *Kcnh6* showed increased insulin secretion in neonatal mice, with reduced K_v currents, increased action potential duration and increased intracellular Ca^{2+}, indicating a direct involvement of K_v11.2 in beta cell insulin secretion.[58] This hyperinsulinaemic phenotype devolved into a hypoinsulinaemic, diabetic phenotype at a later age in both the knockouts and the LoF knock-in mice, which was associated with beta cell apoptosis.[58] To further investigate the mechanisms behind the transition from hyper- to hypoinsulinaemia and diabetes, ER stress and apoptosis was induced by exposing isolated murine islets to thapsigargin, an inhibitor of the sarco/endoplasmic reticulum Ca^{2+} ATPase, or palmitic acid. In islets overexpressing *Kcnh6* ER stress and apoptosis were attenuated in these conditions, suggesting an involvement of *Kcnh6* in mitigating ER stress and apoptosis, possibly in relation to ER Ca^{2+} depletion.[59]

4 | CAN KNOWLEDGE OF THE CARDIAC FUNCTION OF K_v7.1 AND K_v11.1 INFORM THEIR ROLE IN THE PANCREATIC BETA CELL?

As indicated, pre-clinical and clinical data are accumulating to suggest that *KCNQ1*/K_v7.1 and *KCNH2*/K_v11.1 are involved in the secretion of insulin from the pancreatic beta cell, although many questions remain. Both of these channels are well-known for their function in the heart and have been studied extensively in this setting (reviewed in 31,60-62). Although a thorough review on the function of K_v7.1 and K_v11.1 in the cardiomyocyte is not within the scope of this review, characteristics of their cardiac function may inform on their role in the pancreatic beta cell.

4.1 | The electrophysiology of the cardiomyocyte

As in all electrically excitable tissues, the cardiac action potential is orchestrated by a symphony of ion channels opening and closing (Figure 2). In the ventricular cardiomyocyte, the resting membrane potential is maintained by the inward rectifying I_{K1} current mediated by the K_{ir}2.1 channels.[63] Upon arrival of an electrical stimulus, Na_v1.5 channels open, leading to a rapid influx of Na^+ ions and depolarization of the membrane potential, as represented by the upstroke of the action potential (Figure 2).[64] These channels inactivate rapidly in a time-dependent manner. What follows is a short-lived transient outward K^+ current (I_{to}), conducted by K_v4.2 and K_v4.3 (fast component), and K_v1.4 (slow component) leading to a transient repolarization.[65] In the atria, an additional ultra-rapid outward K^+ current (I_{Kur}) is present, conducted through K_v1.5 channels,[63] producing additional early repolarization and a more triangular action potential compared to the ventricular action potential shown in Figure 2. The plateau phase of the action potential is carried by the opening of voltage-gated L-type Ca^{2+} channels allowing influx of Ca^{2+}.[64] This leads to Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum (SR), producing the necessary intracellular Ca^{2+} concentration required for contraction. In comparison to the pancreatic beta cell, where extracellular Ca^{2+} influx is primarily responsible for the glucose-induced insulin secretion, contraction of the cardiomyocyte is dependent on the release of Ca^{2+} from intracellular stores.[14] Repolarization of the membrane potential is orchestrated by the opening of delayed rectifier K^+ channels K_v7.1 and K_v11.1.

Functional loss of either K_v7.1 or K_v11.1 results in LQTS, characterized by a delay of the repolarization of the cardiomyocyte, which can be measured on the electrocardiogram as a prolonged QT interval. This delay in repolarization increases the risk for ventricular arrhythmia, including the characteristic *torsades de pointes* tachyarrhythmia, and sudden cardiac death[66] (Figure 2). Loss-of-function (LoF) mutations in *KCNQ1* occur in ~30%-35% of all patients with LQTS (LQT1),[67] while LoF mutations in *KCNH2* (LQT2) cover a further 25%-40%.[68]

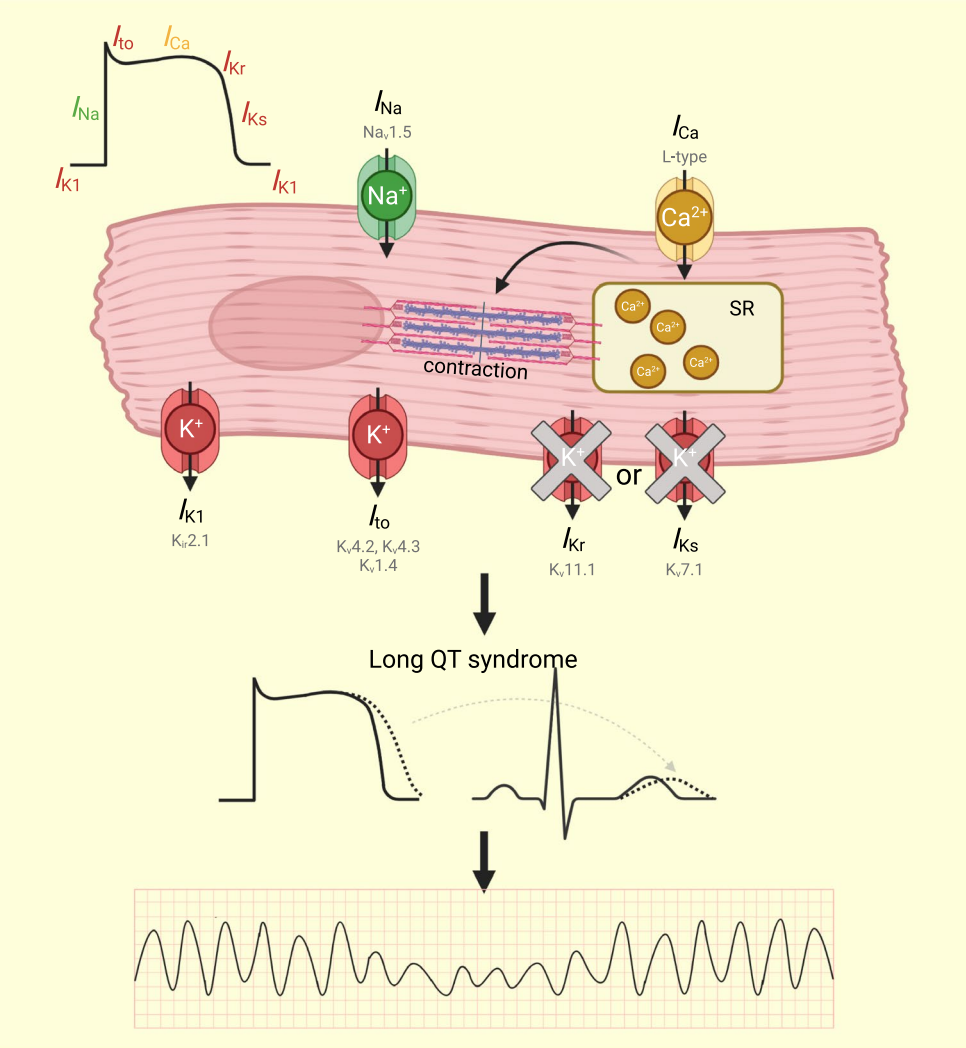

FIGURE 2 Ion channels involved in the cardiac action potential of the ventricular cardiomyocyte and the effect of functional loss of the delayed rectifier K^+ channels $K_v7.1$ and $K_v11.1$. The cardiac action potential is mediated by Na^+ (green), Ca^{2+} (yellow) and K^+ (red) channels leading to contraction of the cardiomyocyte (see text for details). Loss of delayed rectifier K^+ channels $K_v7.1$ or $K_v11.1$ leads to a reduction in repolarizing currents, and prolongation of the action potential duration. This can be seen on the electrocardiogram as a prolonged QT interval and is termed long QT syndrome (LQTS). Individuals with a prolonged QT interval are at an increased risk of cardiac arrhythmia, specifically the polymorphic tachycardia *torsades de pointes* (graphically depicted in the figure), and sudden cardiac death. Created with Biorender.com. Abbreviations: *I*, current; I_{Kr}, rapid delayed rectifier K^+ current; I_{Ks}, slow delayed rectifier K^+ current; I_{to}, transient outward K^+ current; K_{ir}, inward rectifier K^+ channel; K_v, voltage-gated K^+ channel; Na_v, voltage-gated Na^+ channel

4.2 | $K_v7.1$ and $K_v11.1$ in the cardiomyocyte vs the pancreatic beta cell

In the heart, $K_v7.1$ is a co-assembly of alpha subunits KCNQ1 and auxiliary KCNE1 subunits. The channel progressively opens with increasing depolarization of the membrane potential, giving rise to a current that is slowly activated and deactivated, known as the slow delayed rectifier K^+ current (I_{Ks}).[60] Assembly of KCNQ1 with the KCNE family (KCNE1-5) of beta subunits affects channel function. Co-assembly with KCNE1, as in the heart, increases channel conductance compared to KCNQ1 alone, slows activation and deactivation and nearly completely eliminates inactivation.[60,69] Co-assembly with the other KCNEs either results in a constitutively open channel (KCNE2 and KCNE3) or in inhibition of the current (KCNE4 and KCNE5).[60] In comparison to the heart, KCNE1 does not appear to be expressed in the human pancreatic beta cell,[14] and in a case report of a patient with a KCNE1 LoF mutation no changes in insulin secretion were observed.[54] It remains unclear which KCNE(s) may be co-assembling with KCNQ1 in the pancreatic beta cell. An option may be KCNE2, as deletion of *Kcne2* in a mouse model resulted in reduced *ex vivo* insulin secretion and diabetes *in vivo*.[70] This was, however, also accompanied by

insulin resistance and reduced peripheral insulin receptor expression, indicating the possibility of other factors outside of the pancreatic islet contributing to the observations.[70] Human KCNE2 LoF mutations are linked to LQTS (LQT6), but to our knowledge, there is no evidence of a metabolic phenotype in these patients. Another possibility is KCNE4, which is expressed in the human pancreatic beta cell,[14] although its function remains unclear.

The occurrence of ventricular arrhythmia in LQTS is gene-specific, occurring under different circumstances in LQT1 than in LQT2. The majority of patients with LQT1 that experience a major cardiac event do so during exercise.[71] $K_v7.1$ is sensitive to beta-adrenergic stimulation: beta-adrenergic stimulation increases cAMP levels, leading to protein kinase A-mediated phosphorylation of KCNQ1, thus enhancing the $K_v7.1$-mediated current I_{Ks}.[62] For this reason, $K_v7.1$ is responsible for the shortening of the repolarization phase during high heart rates.[72] When this mechanism is not present in the cardiomyocyte because of functional loss of $K_v7.1$, repolarization does not shorten appropriately at higher heart rates, evidenced by a relatively longer corrected QT (QTc) interval at high heart rates compared to at rest. This poses an even stronger trigger for cardiac events, explaining the exercise-related cardiac events in LQT1. It is largely uninvestigated whether $K_v7.1$'s beta-adrenergic sensitivity has an effect in the pancreatic beta cell. It is well-established that adrenaline has a dual effect on the pancreatic beta cell: it increases insulin secretion through beta-adrenoceptor activation, while it decreases insulin secretion through alpha-adrenoceptor stimulation, the latter being the dominant effect.[73] In addition, noradrenaline also decreases insulin secretion through alpha-adrenoceptor stimulation. Alpha-adrenoceptor stimulation hyperpolarizes the cell membrane through activation of a K^+ current, thus, inhibiting insulin secretion.[74-76] This K^+ current does not appear to involve K_{ATP} channels[76] and both adrenaline-induced insulin inhibition and adrenaline-induced hyperpolarization is present in islets without functional K_{ATP} channels.[77,78] The $K_v7.1$ current is, however, unlikely to be involved in this K^+ current, since the adrenaline-induced hyperpolarization was not abolished by administration of chromanol 293B,[78] an inhibitor of $K_v7.1$. Similarly, the $K_v11.1$ blocker E-4031 also did not affect the adrenaline-induced hyperpolarization.[78]

$K_v11.1$ gives rise to the rapid delayed rectifier K^+ current (I_{Kr}) in the heart.[31,79] The channel activates and deactivates slowly, yet its voltage-dependent inactivation and recovery from inactivation are much faster.[31] Upon depolarization the channel opens but almost immediately inactivates. As repolarization begins, the channel recovers from inactivation faster than its speed of channel closure, giving rise to a large outward K^+ current contributing to the repolarization of the cardiomyocyte.[31] Because of slow channel closure, $K_v11.1$ channels remain open for a while as the membrane potential has returned to its resting potential. Although there is little current flow at this time, as the membrane potential is close to the K^+ reversal potential, it does protect the cardiomyocyte from premature depolarization, as this would instigate a large increase in $K_v11.1$-mediated K^+ current.[31] It is of interest to note that the cardiac $K_v11.1$ is likely a heteromeric channel composed of two different isoforms $K_v11.1a$ and $K_v11.1b$,[80,81] the relative abundance of which may impact $K_v11.1$ current dynamics (reviewed in 82). Whether the different isoforms have an impact on $K_v11.1$'s role in pancreatic beta cell insulin secretion is to our knowledge unknown, although both transcripts of $K_v11.1a$ and $K_v11.1b$ have been found in rat pancreatic islets and the INS-1 rat beta cell line.[83]

In relation to $K_v11.1$, acquired LQTS can also occur by means of drug-induced block of this channel. Not just anti-arrhythmic drugs targeting $K_v11.1$ block the channel. Many pharmacological compounds used in the clinic inadvertently block $K_v11.1$, including drug classes that are widely used by the general public.[84] This hazard has resulted in the requirement of screening for $K_v11.1$ inhibition during pre-clinical and clinical testing of new pharmaceuticals.[85] $K_v11.1$'s promiscuity in binding a large variety of compounds is largely dependent on the presence of specific aromatic residues on S6, which are not present on the majority of other K_v channels[86] (reviewed in 31,87 and more recently in[88]). Thus, since many pharmaceuticals affect $K_v11.1$ conduction,[89] investigating their effects on blood glucose in addition to their cardiac effect may be warranted. This is of specific cardiac relevance since both hypoglycaemia and hyperglycaemia may further prolong the QT interval and further increase the risk of cardiac arrhythmia (please refer to Section 6 for more information on glycaemic status and QT interval).

5 | *KCNQ1*, LONG QT SYNDROME, AND THE DEVELOPMENT OF DIABETES

While the pre-clinical studies involving acute pharmacological blockade of $K_v7.1$ and $K_v11.1$, as well as the OGTT studies in individuals with LQT1 and LQT2, indicate that blocking the currents of these channels leads to hypersecretion of insulin from the pancreatic beta cell, there have also been indications of links between *KCNQ1* and LQTS and the development of type

2 diabetes mellitus (T2DM). These data are outlined below.

5.1 | The association of *KCNQ1* and type 2 diabetes

In 2008 two simultaneously published articles in Nature Genetics each independently identified *KCNQ1* as a susceptibility locus for T2DM. Yasuda et al[8] conducted a GWAS study in a Japanese population containing 1612 T2DM cases and 1424 controls, using 100 000 single nucleotide polymorphisms (SNPs). They found that the most significant association was SNP rs2237892 in the *KCNQ1* locus with an odds ratio of 1.49 ($P = 7 \times 10^{-13}$). They replicated this same strong association in separate populations of Korean, Chinese, European and two more groups of Japanese descent covering a total of 9569 T2DM cases and 10 361 controls, finding an overall odds ratio of 1.4 ($P = 1.7 \times 10^{-42}$). Unoki et al[7] at the same time studied three independent Japanese populations with a total of 5118 T2DM cases and 4176 controls, starting with 207 097 SNPs. In each of these three populations SNP rs2283228, in the *KCNQ1* locus, was found to be associated with T2DM, finding an overall odds ratio of 1.26 ($P = 3.1 \times 10^{-12}$) when combining all three populations. Additionally, they found strong associations with SNPs rs2237892 (odds ratio: 1.32, $P = 7.3 \times 10^{-9}$), also identified by Yasuda et al,[8] and rs2237897 (odds ratio: 1.41, $P = 6.8 \times 10^{-13}$). These latter two associations were also replicated in a population of Singaporeans and a population of Danes.[7]

Since these early findings, over 25 more GWAS studies have been published identifying SNPs on the *KCNQ1* gene associated with T2DM (Figure 3A) covering populations of African,[90] African American,[91-93] American Indian,[94] East Asian,[90,92,93,95-108] European,[90,92,93,101,109-115] Latin American[92,93,101,116-119] and South Asian[90,92,93,101,112] ancestry, with high risk-allele frequency for a number of these SNPs (Table S1). A recent meta-analysis covering the seven most well-studied *KCNQ1* SNPs indicated that six out of these seven (rs151290, rs2237892, rs2237895, rs2237897, rs2283228 and rs2074196, but not rs231362) were indeed significantly associated with T2DM.[9] Figure 3A shows the SNPs in *KCNQ1* that have so far been associated with T2DM. What is important to note is that these SNPs are all found in intronic regions of the *KCNQ1* gene. However, although these regions are non-coding, they may affect gene expression nonetheless, e.g. by stimulating or repressing gene expression, affecting post-translational modifications, or affecting splicing of the coding region. For reference, Figure 3A includes SNPs in *KCNQ1* that have been linked to QT interval and Figure 3B shows the genomic structure of *KCNH2*, also indicating SNPs linked to QT interval (to date no SNPs associated with T2DM have been identified in *KCNH2*). All of these QT interval-linked SNPs are also found in intronic regions, with some of the T2DM-linked and QT interval-linked SNPs on *KCNQ1* in similar regions of the gene, indicating that intronic SNPs in *KCNQ1* may indeed affect the function or expression of the *KCNQ1*-encoded protein and thereby the function of the $K_v7.1$ channel. A few studies have investigated whether T2DM-associated SNPs in *KCNQ1* affect *KCNQ1* mRNA expression, but have made somewhat divergent observations. In one study, *KCNQ1* mRNA expression was compared between different SNP genotypes in pancreatic islets from 18 non-diabetic cadaver organ donors, and no differences were found, although the authors note that the low sample size could have affected these results.[120] In another study, the GTEx Portal database was used to evaluate the association between *KCNQ1* mRNA expression and SNPs rs2237892, rs2283228 (both in subcutaneous adipose) and rs231362 (in cultured fibroblasts).[9] The first two SNPs were associated with an increased *KCNQ1* expression, while the latter SNP was associated with a decreased *KCNQ1* expression.[9]

A number of studies have investigated the functional effect of a variety of the T2DM-associated SNPs in *KCNQ1* which have revealed associations with altered beta cell function. In one study, human islets from individuals with the rs2237895 risk allele in *KCNQ1* did not show altered insulin secretion, but showed reduced exocytosis, as demonstrated by a reduced depolarization-evoked increase in cell capacitance.[121] This was in comparison to siRNA knockdown of the *KCNQ1* gene, which increased exocytosis.[121] Additionally, the number of docked insulin granules at the plasma membrane was reduced in the islets carrying the rs2237895 risk allele. An independent SNP (rs231362) from the same study was not associated with differences in insulin secretion or exocytosis, yet had an increased number of docked insulin granules.[121] In another study, the effect of three risk SNPs was investigated using hyperglycaemic clamps, where the blood glucose level of study participants was clamped at 10 mM for at least 2 hours.[122] The risk variant rs151290 was associated with reduced first-phase insulin secretion (first 10 minutes of the hyperglycaemic clamp), while having the risk variant SNP rs2237892 was associated with reduced second-phase insulin secretion (last 40 minutes of the second hour of the clamp).[122] The third SNP investigated (rs2237895) did not affect insulin secretion.[122] In a third study, investigating the SNPs rs2283228, rs2237892, rs2237895 and rs2237897, having the risk-allele rs2237895 was associated with reduced insulin response to an oral glucose load *in vivo*.[123] Additionally, risk alleles rs2237897, rs2237892 and rs2283228 have been associated with

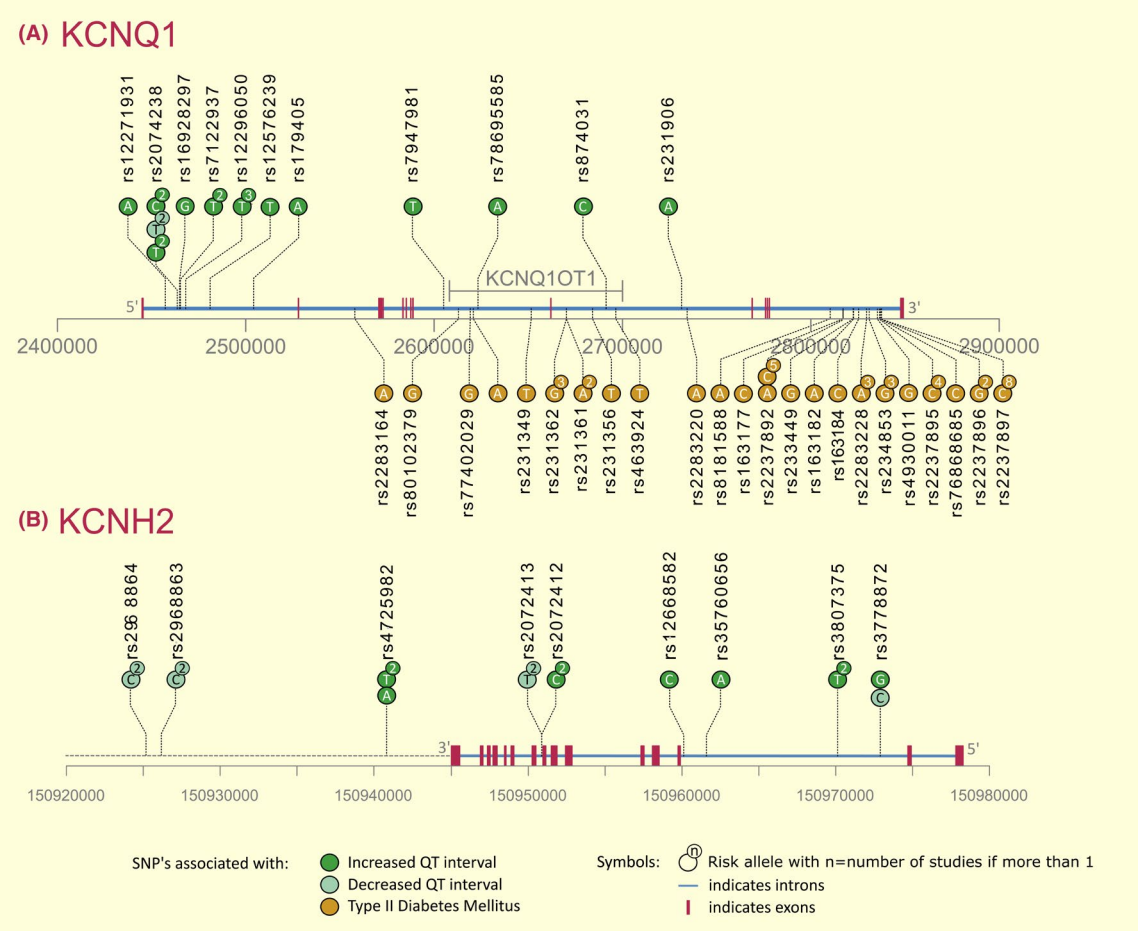

FIGURE 3 Genomic structure of *KCNQ1* and *KCNH2* indicating single nucleotide polymorphisms (SNPs) associated with diabetes and QT interval. Genomic structure of *KCNQ1* (A) and *KCNH2* (B). The *KCNQ1OT1* region is also highlighted in A. SNPs are indicated with coloured circles identifying the risk allele; those linked to QT interval are shown above the genomic structure, while those linked to type 2 diabetes mellitus (T2DM) are shown below it. When more than one study has identified the risk allele, the number above the risk allele indicates how many. The figure is created using R and the R package trackViewer based on the data from the NHGRI-EBI Catalog of human genome-wide association studies (www.ebi.ac.uk/gwas)

higher fasting glucose levels and decreased insulin secretion.[124] Similarly, an OGTT in a population of subjects with allelic differences at rs151290, rs2237892, rs2237895 and rs2237897 revealed altered insulin secretion, as measured by C-peptide plasma concentrations 30 minutes after the OGTT, associated with all SNPs. However, SNP rs151290, but not the others, was also associated with a significantly altered GLP-1 secretion.[125] In a subset of these subjects, intravenous glucose tolerance tests, rather than oral, revealed no associations with beta cell function with any of the studied SNPs, further suggesting possible involvement of incretin secretion.[125] Of note, the hyperinsulinaemic LQT1 patients with LoF mutations in *KCNQ1* have comparable GLP-1 and GIP responses to control during an OGTT.[4] To summarize, these data collectively identify a likely beta cell-related mechanism in the association of SNPs in *KCNQ1* and T2DM, although this may be both intrinsic or indirect.

Another interesting but complex aspect of *KCNQ1* SNPs and *KCNQ1* gene expression is the presence of imprinting of the *KCNQ1* gene. *KCNQ1* is part of a larger cluster of neighbouring genes, all on chromosome 11p15, that are imprinted, with their expression dependent on the parental origin of the allele.[126,127] For instance, *KCNQ1* is expressed maternally during early embryogenesis, but becomes biallelic later on in gestation or post-natally.[128,129] Although this suggests imprinting does not impact *KCNQ1* gene expression after birth, some T2DM-associated SNPs in *KCNQ1* indicate an effect of parental imprinting. For instance, the associations between SNPs rs2237892 and rs231362 in *KCNQ1* and T2DM have been shown to be linked to maternal transmission.[126] Additionally, SNP rs2299620 in *KCNQ1* was associated with T2DM when derived maternally, but not paternally.[130]

Other regions and genes involved in the cluster of imprinted genes on 11p15 are insulin-like growth factor

2 (*IGF2*), cell cycle inhibitor cyclin-dependent kinase inhibitor 1C (*CDKN1C*) and *KCNQ1* overlapping transcript 1 (*KCNQ1OT1*).[126,127] Epigenetic dysregulation of this region can lead to Beckwith-Wiedemann syndrome, an overgrowth syndrome that, amongst a wide clinical set of features, is characterized by neonatal, and sometimes longer lasting, hyperinsulinaemic hypoglycaemia (for detailed information on Beckwith-Wiedemann syndrome, see[131]). The aetiology of the hyperinsulinaemia remains unknown, but has been suggested to involve IGF2-mediated pancreatic islet overgrowth, as well as increased expression of *KCNQ1* in the pancreatic beta cell.[127,132]

As mentioned, the *KCNQ1OT1* region, situated within the *KCNQ1* gene, is also imprinted. It is a non-coding RNA that is paternally expressed.[126] It is of importance to note that some of the T2DM-associated SNPs identified in the *KCNQ1* gene lie in *KCNQ1OT1* (Figure 3A). This may influence the impact of these SNPs since *KCNQ1OT1* has been associated with controlling foetal and postnatal growth through its epigenetic effect on the expression of *CDKN1C*.[133] This has also been linked to pancreatic beta cell growth. One study in mice showed that heterozygous *Kcnq1* knockout mice had lower beta cell mass only when the knocked-out allele was inherited from the father.[134] This was associated with increased expression of *Cdkn1c*, which could explain the reduced proliferation of the beta cells. These data indicate that the parental origin of SNP inheritance may differentially affect gene expression of *KCNQ1* and/or that of neighbouring genes. Thus, analysis of these susceptibility variants should take into account this possibility when further establishing the links between SNPs in *KCNQ1* and the development of T2DM, especially for those that lie in the *KCNQ1OT1* region.

Ultimately, it remains unclear through which mechanisms SNPs in *KCNQ1* affect the development of T2DM. In summary, there are data suggesting that SNPs in *KCNQ1* can affect its protein expression, but also data suggesting that it may not. There are *ex vivo* and *in vivo* data supporting decreases in beta cell insulin secretion in relation to these SNPs, placing the mechanism inside the beta cell, but other factors that affect insulin secretion, such as the incretins, have also been implied. Finally, the effect of the different SNPs may be subject to imprinting and SNPs, especially those in the *KCNQ1OT1* region, may alter the expression of genes other than *KCNQ1* and thus affect the development of T2DM through mechanisms unrelated to the *KCNQ1*-encoded protein. Many questions remain, but with the overwhelming amount of GWAS data indicating *KCNQ1* as a susceptibility locus for T2DM it will be important to further investigate this link and the mechanisms that underlie it.

5.2 | The association of LQTS and type 2 diabetes

Not only *KCNQ1*, but also LQTS has been linked to the development of diabetes. A Danish retrospective cohort study on 463 patients with congenital LQTS and 2315 matched controls, with an average age of 36 years and 4-year follow-up, showed that patients with LQTS have a higher burden of diabetes compared to the background population (3.7% vs 1.8% $P = .011$).[6] Additionally, patients with LQTS were more often prescribed antidiabetic medication (5.2% vs 1.9%, $P < .001$). Although this study did not report the proportion of LQTS types of the population studied, ~30%-35% of all patients with LQTS have *KCNQ1*-linked LQT1.[67] This suggests that the association between congenital LQTS and a higher burden of diabetes may not be only through mutations in *KCNQ1* or may indicate that the association would be different if the study would have differentiated between LQTS subtypes. Further studies differentiating between LQTS-subtype will be required to elucidate this further.

Interestingly, the increased burden of diabetes was not statistically significant prior to LQTS diagnosis (2.2% vs 1.2%, $P = .10$).[6] This may be explained by increased blood sampling in patients diagnosed with LQTS compared to the background population, increasing the probability of catching T2DM, although authors note that 88% of patients on antidiabetic treatment started prior to LQTS diagnosis.[6] It may also indicate an age-component. Age is a known risk factor in the development of T2DM and is associated with deterioration of beta cell function.[135,136] K^+ current density has also been shown to decrease with age in murine beta cells.[70] This possible involvement of age is supported by our own study in mice with *Kcnq1* LoF. Islets carrying the LoF mutation on both alleles hypersecreted insulin in response to glucose *ex vivo* at a young age (12-14 weeks). Yet when performing the same experiments 10 weeks later, at 24 weeks of age, islets heterozygous and homozygous for the mutation now secreted less insulin in response to glucose compared to their littermate controls.[53] This transition from hyper- to hyposecretion of insulin is reminiscent of the phenotype described in *KCNH6*/*Kcnh6* LoF in humans and mice[58] and may explain the combination of hyperinsulinaemia[4,5] and diabetes[6] in patients with LQTS. In a number of prospective studies, a variety of *KCNQ1* SNPs have been associated with the development of future T2DM.[104,120,137-139] However, the average age of cases and controls of a large number of published GWAS studies is between 45 and 65, and many studies lack information on the age of T2DM onset, as noted by a recent meta-analysis.[9] This makes it difficult to assess the involvement of age on the effect of *KCNQ1* SNPs on

the development of T2DM. Thus, the mechanistic links between congenital LQTS and the higher burden of diabetes remains to be further elucidated.

6 | GLYCAEMIC STATUS AND QT INTERVAL: HOW IS THE HEART AFFECTED BY THE OVERLAP OF LQTS AND A METABOLIC PHENOTYPE?

The concurrence of cardiac and metabolic phenotypes due to the overlap of expression and functional significance of K_v7.1/*KCNQ1* and K_v11.1/*KCNH2* also poses the important clinical consideration of their interaction. Blood glucose levels, both increased and decreased, affect cardiac electrophysiology, including the QT interval. Such glucose-dependent changes in QT interval may be particularly paramount in individuals with an already increased QT interval.

6.1 | Hypoglycaemia and the QT interval

Hypoglycaemia is known to prolong the QT interval, also when the QT interval has been corrected for heart rate (QTc).[140-142] This may be in part related to concomitant high plasma insulin levels. Insulin leads to increased K^+ uptake in peripheral tissues,[143] resulting in hypokalaemia[144], which subsequently may prolong the QT interval. However, in patients with diabetes, hypoglycaemia-associated QT interval prolongation has both been observed in the presence[140,141] and absence[142] of concomitant hypokalaemia. Additionally, despite the presence of hypokalaemia, the change in plasma potassium was not correlated with the increase in QT duration.[141] This suggests that hypoglycaemia-induced QT prolongation is not only mediated through plasma K^+ levels, but also through other mechanisms. These mechanisms include the involvement of catecholamine release,[140,145] as well as the depression of the K_v11.1 current.[146] Hypoglycaemia-induced depression of the K_v11.1 is related to the reduction of intracellular ATP in the setting of low glucose, which is normally required for phosphorylation of the channel.[146] Suppression of the K_v11.1 current may be of particular significance in patients with LoF in K_v7.1, with an already reduced repolarization reserve. Acute hypoglycaemia has not just been associated with a prolonged QT interval, but also with cardiac arrhythmia.[145] Hypoglycaemic events increase both the QTc interval and the incidence of ventricular premature beats, both in individuals with and without diabetes.[147] Hypoglycaemia has also been implicated in the nocturnal 'dead-in-bed' syndrome in patients with diabetes, in particular in those with type 1 diabetes in the setting of intensive glycaemic control.[148]

Since any prolongation of the QTc is particularly precarious in the setting of an already prolonged QT interval,[149] blood glucose monitoring may be considered in the treatment of LQTS. This is of particular relevance in relation to beta-blocker treatment, a common treatment in patients with LQTS.[150] Beta-blockers inhibit the beta-adrenergic-mediated glycogenolysis and hepatic gluconeogenesis,[151] lowering blood glucose. Thus, beta-blocker treatment can further enhance the likelihood and severity of hypoglycaemia, as observed both in paediatric patients with LQTS,[152] as well as non-critically ill hospitalized patients.[153]

6.2 | Hyperglycaemia and the QT interval

Hyperglycaemia, on the other hand, can also cause prolongation of the QT interval.[154] After an oral glucose load, QT interval prolongs in healthy controls,[5,155] as well as in patients with LQT1[155] and LQT2[5] in whom the prolongation is even more pronounced. Additionally, the shape or morphology of the T wave is also altered in response to an oral glucose load.[5,155] In these studies, T-wave morphology was evaluated with a morphology combination score which evaluates the shape of the T wave by looking at T-wave flatness, T-wave asymmetry and the appearance of a notch or hump on the T wave (notching). This score has been shown to have independent prognostic information on mortality independently of heart rate and QT interval duration.[156] The T-wave morphology change during the OGTT was more pronounced in patients with LQTS than healthy controls, indicating larger changes in ventricular repolarization during the OGTT in the individuals with LQTS. This, along with the increased QT interval, may pose an increased risk of cardiac arrhythmia.[157] This is exemplified in mice with LoF in *Kcnq1* where refeeding after overnight fasting induced premature ventricular contractions that were not seen in wild-type littermate controls.[53]

The combination of increased QT and cardiac arrhythmia in the setting of hyperglycaemia has been reported in multiple settings. A case report described QT prolongation and subsequent *torsade de pointes* during hyperglycaemia in a patient being refed after severe malnourishment.[157] Additionally, hyperglycaemia has been associated with an increased risk of ventricular tachycardia after an acute myocardial infarction[158] and, in critically ill patients, hyperglycaemia not only associates with QTc prolongation but also increased mortality.[159] Thus, hyperglycaemia can pose an arrhythmic risk, especially in those with pre-existing co-morbidities or QT interval prolongation.

Not just acute hyperglycaemia, but also long-term hyperglycaemia[160] and high HbA1c levels[160,161] are associated with longer QTc. In accordance with this, glycaemic control in the form of daily insulin injections has been shown to shorten QTc in patients with T2DM.[162] Increased QTc has also been reported in patients with type 1 diabetes[163,164], and glycaemic variability alone has been shown to increase the incidence of cardiac arrhythmia in individuals with T2DM,[165] further supporting that long-term hyperglycaemia may affect cardiac electrophysiology as well.

As mentioned, these cardiac electrophysiological effects of blood glucose and its fluctuations may be particularly hazardous in the setting of LQTS. This is supported by a recent study in isolated rabbit ventricular myocytes.[166] Hyperglycaemia alone could induce pro-arrhythmic electrophysiological changes, but in combination with K_v channel block, or beta-adrenergic stimulation, the pro-arrhythmic changes were exacerbated, with further prolongation of the action potential duration, increased alternation in action potential shape (alternans), and increased variation in action potential firing.[166] These data together suggest that glycaemic control is important in relation to the electrophysiology of the heart and that a dual-hit of altered blood glucose and LQTS may be particularly detrimental.

7 | KNOWLEDGE GAPS AND FUTURE AREAS OF INTEREST

Our knowledge and understanding of the overlapping cardiac and metabolic phenotypes associated with functional loss of delayed rectifier K^+ channels K_v7.1 and K_v11.1 are undoubtedly still in their infancy. Many more questions remain unanswered. The following section outlines some of the key avenues that require exploration.

While the clinical studies in individuals with LQT1 and LQT2 showed hypersecretion of insulin followed by symptomatic hypoglycaemia, little remains known about the mechanisms involved. As outlined above, only a handful of studies have explored the role of K_v7.1 or K_v11.1 in the isolated beta cell or pancreatic islet, the majority of which were performed in beta cell lines or murine islets. Therefore, it remains unclear whether the K_v7.1 or K_v11.1 channel conducts a physiologically relevant current involved in insulin secretion in human beta cells, and whether it is disruption of channel conductance in the human beta cell that leads to the insulin hypersecretion seen in LQT1 and LQT2 patients. Other alternatives are possible. First of all, channels may influence insulin secretion by functions other than their current conducting properties. This possibility is exemplified by K_v2.1.[43,44] This channel affects exocytosis of insulin not (only) by its current-carrying properties, but by participating in recruiting new insulin granules through its position at the plasma membrane.[43,44] Additionally, a variety of factors influence insulin secretion from the pancreatic beta cell. LQT2 patients with LoF mutations in *KCNH2* showed reduced plasma glucagon levels at baseline compared to matched controls, as well as increased plasma GLP-1 and GIP levels after an oral glucose load.[5] Both GLP-1 and GIP directly stimulate insulin secretion from the pancreatic beta cell and, thus, may play a role in the hyperinsulinaemia seen in these patients. Additionally, two SNPs in *KCNH2* have been associated with altered circulating GIP and glucagon levels.[167] On top of this, GLP-1 secretion has also been implicated in the altered insulin response associated with a number of *KCNQ1* SNPs,[125] further underlining a possible involvement of other hormones in the hyperinsulinaemia of LQT1 and LQT2 patients.

Another important gap in our understanding of the involvement of K_v7.1/*KCNQ1* and K_v11.1/*KCNH2* in insulin secretion is the link between hyperinsulinaemia found in LQT1 and LQT2 patients during an OGTT and the higher burden of diabetes in patients with LQTS. It will be important to clarify whether the hypersecretion of insulin is the cause of diabetes later in life, and if so, by what mechanisms. The possibility of insulin hypersecretion leading to insulin hyposecretion later on is exemplified by the findings in both humans and mice of LoF mutations in *KCNH6*/*Kcnh6* (encoding K_v11.2), as described in detail earlier.[57-59] Loss-of-function of K_v11.2 leads to increased intracellular Ca^{2+}, as was also found when inhibiting K_v11.1 in human beta cells,[56] as well as beta cell ER stress and beta cell apoptosis.[58,59] Additionally, high insulin secretion in itself puts a high demand on insulin production and pro-insulin folding in the ER, an important step in the maturation of insulin. A high demand may lead to a higher degree of misfolding. An extreme example of how pro-insulin misfolding devastates the ER is the insulin-deficient Akita mouse model. A mutation in the *Ins2* gene in these mice leads to misfolding of pro-insulin, leading to ER stress, beta cell apoptosis and subsequent severe insulin deficiency.[168] Similar mechanisms may be instigated by the hypersecretion in *KCNQ1* and *KCNH2* LoF. However, it is also possible that the higher burden of diabetes in individuals with LQTS is unrelated to their insulin hypersecretion and develops as a co-morbidity because of other reasons. One of these reasons could be lifestyle. Individuals with LQTS have a higher burden of psychiatric comorbodities compared to the background population, which may represent an increased burden of depression and anxiety, potentially related to living with a cardiac diagnosis.[6] This may severely impact their lifestyle, including activity levels and dietary choices. Additionally, participation in intense sports is considered

a potential risk in patients with LQTS, especially in those with LQT1,[169] which may lead to patients refraining from regular exercise. Exercise is known to improve insulin sensitivity,[170] thus promoting glucose uptake in peripheral tissues. Therefore, regular exercise is an excellent tool in combatting insulin resistance,[170,171] an important contributor to the development of T2DM. Such lifestyle effects must be taken into consideration when evaluating the link between hyperinsulinaemia and diabetes in this patient population.

8 | CONCLUSION

Evidence of the involvement of K_v7.1/*KCNQ1* and K_v11.1/*KCNH2* in the secretion of insulin from the pancreatic beta cell is accumulating. Interestingly, the genes, and the channels they encode, not only associate with hyperinsulinaemia, but also associate with the development of diabetes. Although the mechanisms behind these seemingly paradoxical associations remain unclear, it has become apparent that the well-known cardiac phenotypes associated with functional loss of K_v7.1 and K_v11.1 coincide with metabolic alterations which may in turn detrimentally affect the cardiac phenotype. This vicious cycle may increase the risk of lethal cardiac arrhythmias and requires clinical awareness in the management of patients with LQTS. Further investigations into the involvement of *KCNQ1* in the development of diabetes, whether mediated through the *KCNQ1*-encoded protein or not, may reveal important beta cell-related mechanisms of vulnerability or dysfunction that can further our understanding of the complicated polygenic disease aetiology of T2DM.

ACKNOWLEDGEMENTS

The project was supported by the Danish Heart Association and the Lundbeck Foundation (SST). AFL was supported by a grant from the Novo Nordisk Foundation (NNF19OC0057507). CRJ was supported by a grant from the Independent Research Fund Denmark (to SST).

CONFLICT OF INTEREST

The authors report no conflict of interest.

ORCID

Anniek F. Lubberding https://orcid.org/0000-0002-6691-8581
Christian R. Juhl https://orcid.org/0000-0003-3024-4017
Jørgen K. Kanters https://orcid.org/0000-0002-3267-4910
Thomas Mandrup-Poulsen https://orcid.org/0000-0002-3215-9273
Signe S. Torekov https://orcid.org/0000-0001-6779-0252

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How to cite this article: Lubberding AF, Juhl CR, Skovhøj EZ, Kanters JK, Mandrup-Poulsen T, Torekov SS. Celebrities in the heart, strangers in the pancreatic beta cell: Voltage-gated potassium channels $K_v7.1$ and $K_v11.1$ bridge long QT syndrome with hyperinsulinaemia as well as type 2 diabetes. *Acta Physiol*. 2022;234:e13781. doi:10.1111/apha.13781