INTRODUCTION

Voltage-gated K⁺ (Kᵥ) channels are important mediators of the repolarization phase of the action potential in a variety of different electrically excitable tissues. Upon opening of the Kᵥ channels, K⁺ efflux out of the cell drives the membrane potential to more negative potentials, opposing depolarizing currents, thereby repolarizing or hyperpolarizing the membrane. Overlap of expression and function of delayed rectifier K⁺ channels occurs across tissues. One such example is the expression of KCNQ1, encoding Kᵥ7.1, and KCNH2, encoding Kᵥ11.1, 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, $K_C7.1$ and $K_C11.1$ 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 $K_C7.1$ and $K_C11.1$, 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 ($\approx 60\%$), in combination with glucagon-secreting alpha cells ($\approx 30\%$), somatostatin-secreting delta cells ($\approx 5\%-10\%$), polypeptide-producing (PP) cells ($\approx 5\%$) and ghrelin-producing epsilon cells ($\approx 1\%$).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 signalling12 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 ($K_C6.2$ 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.15,16 First, transient T-type $Ca^{2+}$ channels open,19 followed by voltage-gated $Na^+$ channels (primarily $Na_C1.6$ and $Na_C1.7$)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 $Na^+$ channels, as well as the opening of large-conductance $Ca^{2+}$-activated (BK) channels23 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 $K_C$ channels are a large family encompassing 12 known subfamilies of $K^+$ channels ($K_C1$-12).26 Each functional $K_C$ channel is tetrameric, composed of four transmembrane alpha subunits surrounding a
central ion-conducting pore. Each alpha subunit consists of six transmembrane alpha helices (S1-S6; Figure 1). 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. Segments S5-S6 from each alpha subunit form the ion-conducting pore. Upon depolarization of the membrane, an outward displacement of S4 leads to a structural rearrangement that moves the pore domain into its open state. The wide range of sub-families 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. 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 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. The involvement of K⁺,2.1 and K⁺,2.2 in the secretion of insulin has been a main focus of study. In mice, K⁺,2.1 is the main channel accounting for the delayed outward current in the beta cell, and K⁺,2.1 antagonism produces increased glucose-induced insulin secretion. K⁺,2.2 may act as a suppressor of the outward current produced by K⁺,2.1, as overexpression of K⁺,2.1 alone in INS-1 832/13 rat insulinoma cells increases outward K⁺ current, while co-overexpression with K⁺,2.1 and K⁺,2.2 reduced this increase by half. 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. Inhibition by guangxitoxin, an inhibitor of K⁺,2.1/K⁺,2.2 channels, increases glucose-induced insulin secretion. In human islets, the contribution of K⁺,2.1 and/or K⁺,2.2 to the outward K⁺ current appears smaller. In one study, the K⁺,2.1/2.2 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). It appears that both Kᵥ2.1 and Kᵥ2.2 do contribute to the delayed outward K⁺ current found in human islets, but that this current may not be substantially involved in glucose-induced insulin secretion. Interestingly, Kᵥ2.1 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.

Human beta cells also express Kᵥ1.5, Kᵥ1.6, and Kᵥ6, encoding Kᵥ1,5, and Kᵥ6, although it remains unclear whether these participate in the repolarizing currents of the pancreatic beta cell. Some evidence suggests that Kᵥ1,5 is involved in prosurvival signalling. Overexpression of Kᵥ1,5 in the INS1 rat beta cell line resulted in increased endoplasmic reticulum (ER) stress-induced apoptosis. ER stress was simulated by incubation with thapsigargin, an inhibitor of the sarco/endoplasmic reticulum Ca²⁺ ATPase, with subsequent evaluation of apoptosis. Kᵥ1,5 overexpression increased the induced apoptosis. This could be prevented by Kᵥ1,5 knockdown with RNAi or incubation with the incretins glucose-dependent insulinotropic polypeptide (GIP) or glucagon-like peptide 1 (GLP-1).

### 3.1 Kᵥ7.1 in the pancreatic beta cell

The involvement of Kᵥ7.1, encoded by KᵥNQ1, well known for its function in the heart, has been debated because of the low expression of KᵥNQ1 in beta cells in comparison to other Kᵥ channels. However, functional data have suggested an involvement of Kᵥ7.1 in insulin secretion. The MIN6 mouse beta cell line was found to have an outward current sensitive to chromanol 293B, a selective Kᵥ7.1 inhibitor, which was increased when overexpressing the Kcnq1 gene. Additionally, this overexpression resulted in decreased glucose-induced insulin secretion, as well decreased insulin secretion induced by tolbutamide, a blocker of the beta cell K­sATP channel. Chromanol 293B also reduced outward currents in the INS-1 rat beta cell line and increased tolbutamide-induced insulin secretion. 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). Chromanol 293B also inhibits the cystic fibrosis transmembrane conductance regulator (CFTR) channel, 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. Recent functional data in patients with LQTS with a LoF mutation in KᵥNQ1, named LQT1, confirm the involvement of Kᵥ7.1 in insulin response to glucose as well. During an OGTT patients with LQT1 showed hypersecretion of insulin which resulted in 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. This suggests that the hypersecretion of insulin found in the setting of KᵥNQ1/ 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 KᵥNQ1 revealed hypoinsulinemia after an oral glucose load, further confirming Kᵥ7,1’s function in insulin secretion.

### 3.2 Kᵥ11.1 in the pancreatic beta cell

Expression of Kᵥ11.1, encoded by the KᵥN2H2 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. Just like LoF mutations in KᵥNQ1, LoF in KᵥN2H2 also creates a dual cardiac and metabolic phenotype in patients. Patients with LQTS because of a LoF mutation in KᵥN2H2, named LQT2, showed hypersecretion of insulin during an OGTT, resulting in hypoglycaemia, similar to the patients with LQT1. This same pattern was confirmed in rats during pharmacological blockade of the Kᵥ11.1 channel with the selective inhibitor dofetilide, and in the MIN6 mouse beta cell line with siRNA knockdown of the channel. KᵥN2H2 is strongly expressed in the pancreatic beta cell. 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. Additionally, WAY-123 398 increased insulin secretion. In another study, using the Kᵥ11.1 selective
inhibitor BeKm-1, intracellular Ca\(^{2+}\) was increased in murine and human islets.\(^5\) 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 \(K_{\text{v}}11.1\) block on insulin secretion.\(^5\) Further investigations are required to understand how these data relate to \(K_{\text{v}}11.1\) LoF in beta cell function.

\(K_{\text{v}}11.2\), 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.\(^5\) A recent study revealed that a mutation in the \(KCNH6\) gene co-separated with multigenerational early-onset diabetes.\(^5\) 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 multi-generational 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 \(K_{\text{v}}\) currents, increased action potential duration and increased intracellular Ca\(^{2+}\), indicating a direct involvement of \(K_{\text{v}}11.2\) in beta cell insulin secretion.\(^5\) This hyperinsulinaemic phenotype developed 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.\(^5\) 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.\(^5\)

4 | CAN KNOWLEDGE OF THE CARDIAC FUNCTION OF \(K_{\text{v}}7.1\) AND \(K_{\text{v}}11.1\) INFORM THEIR ROLE IN THE PANCREATIC BETA CELL?

As indicated, pre-clinical and clinical data are accumulating to suggest that \(KCNQ1/K_{\text{v}}7.1\) and \(KCNH2/K_{\text{v}}11.1\) 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 \(K_{\text{v}}7.1\) and \(K_{\text{v}}11.1\) 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 \(I_{\text{K1}}\) current mediated by the \(K_{\text{v}}2.1\) channels.\(^6\) Upon arrival of an electrical stimulus, \(Na_{\text{v}}1.5\) 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).\(^6\) These channels inactivate rapidly in a time-dependent manner. What follows is a short-lived transient outward K\(^{+}\) current (\(I_{\text{to}}\)), conducted by \(K_{\text{v}}4.2\) and \(K_{\text{v}}4.3\) (fast component), and \(K_{\text{v}}1.4\) (slow component) leading to a transient repolarization.\(^6\) In the atria, an additional ultra-rapid outward K\(^{+}\) current (\(I_{\text{kur}}\)) is present, conducted through \(K_{\text{v}}1.5\) channels,\(^6\) 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\(^{2+}\).\(^6\) 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 \(K_{\text{v}}7.1\) and \(K_{\text{v}}11.1\).

Functional loss of either \(K_{\text{v}}7.1\) or \(K_{\text{v}}11.1\) 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\(^6\) (Figure 2). Loss-of-function (LoF) mutations in \(KCNQ1\) occur in ~30%-35% of all patients with LQTS (LQT1),\(^6\) while LoF mutations in \(KCNH2\) (LQT2) cover a further 25%-40%.\(^6\)
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 ($I_{Ks}$). 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). 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. 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, 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. K_\text{r}.7.1 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_\text{r}.7.1-mediated current I_{Ks}. For this reason, K_\text{r}.7.1 is responsible for the shortening of the repolarization phase during high heart rates. When this mechanism is not present in the cardiomyocyte because of functional loss of K_\text{r}.7.1, 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_\text{r}.7.1'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. 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. This K^+ current does not appear to involve K_\text{ATP} channels and both adrenaline-induced insulin inhibition and adrenaline-induced hyperpolarization is present in islets without functional K_\text{ATP} channels.

The K_\text{r}.7.1 current is, however, unlikely to be involved in this K^+ current, since the adrenaline-induced hyperpolarization was not abolished by administration of chromanol 293B, an inhibitor of K_\text{r}.7.1. Similarly, the K_\text{r}.11.1 blocker E-4031 also did not affect the adrenaline-induced hyperpolarization.

K_\text{r}.11.1 gives rise to the rapid delayed rectifier K^+ current (I_{Kr}) in the heart. The channel activates and deactivates slowly, yet its voltage-dependent inactivation and recovery from inactivation are much faster. 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. Because of slow channel closure, K_\text{r}.11.1 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_\text{r}.11.1-mediated K^+ current. It is of interest to note that the cardiac K_\text{r}.11.1 is likely a heteromeric channel composed of two different isoforms K_\text{r}.11.1a and K_\text{r}.11.1b, the relative abundance of which may impact K_\text{r}.11.1 current dynamics (reviewed in 82). Whether the different isoforms have an impact on K_\text{r}.11.1's role in pancreatic beta cell insulin secretion is to our knowledge unknown, although both transcripts of K_\text{r}.11.1a and K_\text{r}.11.1b have been found in rat pancreatic islets and the INS-1 rat beta cell line.

In relation to K_\text{r}.11.1, acquired LQTS can also occur by means of drug-induced block of this channel. Not just anti-arrhythmic drugs targeting K_\text{r}.11.1 block the channel. Many pharmacological compounds used in the clinic inadvertently block K_\text{r}.11.1, including drug classes that are widely used by the general public. This hazard has resulted in the requirement of screening for K_\text{r}.11.1 inhibition during pre-clinical and clinical testing of new pharmaceuticals. K_\text{r}.11.1'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_\text{v} channels (reviewed in 31.87 and more recently in 88). Thus, since many pharmaceuticals affect K_\text{r}.11.1 conduction 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_\text{r}.7.1 and K_\text{r}.11.1, 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 × 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 × 10⁻⁴²). Unoki et al.⁷ at the same time studied rs2283228 and rs2074196, but not rs231362 which were indeed associated with T2DM (Figure 3A) covering 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 1.49 (P = 7 × 10⁻¹³), also identified by Yasuda et al.⁸ and rs2237897 (odds ratio: 1.41, P = 6.8 × 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,⁹²,⁹₃,¹₀₁,₁₁₉ and South Asian⁹₀,⁹₂,⁹₃,¹₀₁,₁₁₂ 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 Kv7.1 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
higher fasting glucose levels and decreased insulin secretion. 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.

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. Of note, the hyperinsulinaemic LQT1 patients with LoF mutations in KCNQ1 have comparable GLP-1 and GIP responses to control during an OGTT. 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. For instance, KCNQ1 is expressed maternally during early embryogenesis, but becomes biallelic later on in gestation or post-natally. 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. Additionally, SNP rs2299620 in KCNQ1 was associated with T2DM when derived maternally, but not paternally.

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).\textsuperscript{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\textsuperscript{311}). 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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% \( P = .011 \)).\textsuperscript{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.\textsuperscript{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%, \( P = .10 \)).\textsuperscript{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.\textsuperscript{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.\textsuperscript{115,136} K⁺ current density has also been shown to decrease with age in murine beta cells.\textsuperscript{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.\textsuperscript{53} This transition from hyper- to hyposecretion of insulin is reminiscent of the phenotype described in Kcnh6/Kcenh6 LoF in humans and mice\textsuperscript{58} and may explain the combination of hyperinsulinaemia\textsuperscript{\textsuperscript{55}} and diabetes\textsuperscript{\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 Kᵥ7.1/KCNQ1 and Kᵥ11.1/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). This may be in part related to concomitant high plasma insulin levels. Insulin leads to increased K⁺ uptake in peripheral tissues, resulting in hypokalaemia, which subsequently may prolong the QT interval. However, in patients with diabetes, hypoglycaemia-associated QT interval prolongation has been both observed in the presence and absence of concomitant hypokalaemia. Additionally, despite the presence of hypokalaemia, the change in plasma potassium was not correlated with the increase in QT duration. 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, as well as the depression of the Kᵥ11.1 current. Hypoglycaemia-induced depression of the Kᵥ11.1 is related to the reduction of intracellular ATP in the setting of low glucose, which is normally required for phosphorylation of the channel. Suppression of the Kᵥ11.1 current may be of particular significance in patients with LoF in Kᵥ7.1, with an already reduced repolarization reserve. Acute hypoglycaemia has not just been associated with a prolonged QT interval, but also with cardiac arrhythmia. Hypoglycaemic events increase both the QTc interval and the incidence of ventricular premature beats, both in individuals with and without diabetes. 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.

Since any prolongation of the QTc is particularly precarious in the setting of an already prolonged QT interval, 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. Beta-blockers inhibit the beta-adrenergic-mediated glycogenolysis and hepatic gluconeogenesis, lowering blood glucose. Thus, beta-blocker treatment can further enhance the likelihood and severity of hypoglycaemia, as observed both in paediatric patients with LQTS, as well as non-critically ill hospitalized patients.

6.2 | Hyperglycaemia and the QT interval

Hyperglycaemia, on the other hand, can also cause prolongation of the QT interval. After an oral glucose load, QT interval prolongs in healthy controls, as well as in patients with LQT1 and LQT2, 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. 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. 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. 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.

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. Additionally, hyperglycaemia has been associated with an increased risk of ventricular tachycardia after an acute myocardial infarction and, in critically ill patients, hyperglycaemia not only associates with QTc prolongation but also increased mortality. 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\textsuperscript{160} and high HbA1c levels\textsuperscript{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.\textsuperscript{162} Increased QTc has also been reported in patients with type 1 diabetes\textsuperscript{163,164}, and glycaemic variability alone has been shown to increase the incidence of cardiac arrhythmia in individuals with T2DM,\textsuperscript{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.\textsuperscript{166} Hyperglycaemia alone could induce pro-arrhythmic electrophysiological changes, but in combination with K\textsubscript{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.\textsuperscript{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\textsuperscript{+} channels K\textsubscript{v}7.1 and K\textsubscript{v}11.1 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\textsubscript{v}7.1 or K\textsubscript{v}11.1 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\textsubscript{v}7.1 or K\textsubscript{v}11.1 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\textsubscript{v}2.1.\textsuperscript{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.\textsuperscript{43,44} Additionally, a variety of factors influence insulin secretion from the pancreatic beta cell. LQT2 patients with LoF mutations in \textit{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.\textsuperscript{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 \textit{KCNH2} have been associated with altered circulating GIP and glucagon levels.\textsuperscript{167} On top of this, GLP-1 secretion has also been implicated in the altered insulin response associated with a number of \textit{KCNQ1} SNPs,\textsuperscript{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\textsubscript{v}7.1/\textit{KCNQ1} and K\textsubscript{v}11.1/\textit{KCNH2} in insulin secretion is the link between hyperinsulinaemia found in LQT1 and LQT2 patients during an OGGT 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 \textit{KCNH6/Kcnh6} (encoding K\textsubscript{v}11.2), as described in detail earlier.\textsuperscript{57-59} Loss-of-function of K\textsubscript{v}11.2 leads to increased intracellular Ca\textsuperscript{2+}, as was also found when inhibiting K\textsubscript{v}11.1 in human beta cells,\textsuperscript{56} as well as beta cell ER stress and beta cell apoptosis.\textsuperscript{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 \textit{Ins2} gene in these mice leads to misfolding of pro-insulin, leading to ER stress, beta cell apoptosis and subsequent severe insulin deficiency.\textsuperscript{168} Similar mechanisms may be instigated by the hypersecretion in \textit{KCNQ1} and \textit{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 comorbidities compared to the background population, which may represent an increased burden of depression and anxiety, potentially related to living with a cardiac diagnosis.\textsuperscript{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,\(^\text{169}\) which may lead to patients refraining from regular exercise. Exercise is known to improve insulin sensitivity,\(^\text{170}\) thus promoting glucose uptake in peripheral tissues. Therefore, regular exercise is an excellent tool in combatting insulin resistance,\(^\text{170,171}\) an important contributor to the development of T2DM. Such lifestyle effects must be taken into consideration when evaluating the link between hyperinsulinemia and diabetes in this patient population.

8 | CONCLUSION

Evidence of the involvement of Kv7.1/KCNQ1 and Kv11.1/KNHC2 in the secretion of insulin from the pancreatic beta cell is accumulating. Interestingly, the genes, and the channels they encode, not only associate with hyperinsulinemia, 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 Kv7.1 and Kv11.1 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.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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REFERENCES

1. Petersen OH, Findlay I. Electrophysiology of the pancreas. *Physiol Rev* 1987;67(3):1054-1116.
2. Sanguinetti MC, Curran ME, Zou A, et al. Coassembly of K(V) LQT1 and minK (IsK) proteins to form cardiac I(Ks) potassium channel. *Nature*. 1996;384(6604):80-83.
3. MacDonald PE, Wheeler MB. Voltage-dependent K(+) channels in pancreatic beta cells: role, regulation and potential as therapeutic targets. *Diabetologia*. 2003;46(8):1046-1062.
4. Torekov SS, Iepsen E, Christiansen M, et al. KCNQ1 long QT syndrome patients have hyperinsulinism and symptomatic hypoglycemia. *Diabetes*. 2014;63(4):1315-1325.
5. Hylten-Cavallius L, Iepsen EW, Wewer Albrechtsen NJ, et al. Patients with long-QT syndrome caused by impaired hERG-encoded Kv11.1 potassium channel have exaggerated endocrine pancreatic and incretin function associated with reactive hypoglycemia. *Circulation*. 2017;135(18):1705-1719.
6. Marstrand P, Theilade J, Andersson C, et al. Long QT syndrome is associated with an increased burden of diabetes, psychiatric and neurological comorbidities: a nationwide cohort study. *Open Heart*. 2019;6(2):e001161.
7. Unoki H, Takahashi A, Kawaguchi T, et al. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat Genet*. 2008;40(9):1098-1102.
8. Yasuda K, Miyake K, Horikawa Y, et al. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet*. 2008;40(9):1092.
9. Yu X-X, Liao M-Q, Zeng Y-F, et al. Associations of KCNQ1 polymorphisms with the risk of type 2 diabetes mellitus: an updated meta-analysis with trial sequential analysis. *J Diabetes Res*. 2020;2020:7145139.
10. Cabrera O, Berman DM, Kenyon NS, Ricordi C, Berggren P-O, Caicedo A. The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. *Proc Natl Acad Sci USA*. 2006;103(7):2334-2339.
11. Sakata N, Yoshimatsu G, Kodama S. Development and characteristics of pancreatic epsilon cells. *Int J Mol Sci*. 2019;20(8):1867.
12. Caicedo A. Paracrine and autocrine interactions in the human islet: more than meets the eye. *Semin Cell Dev Biol*. 2013;24(1):11-21.
13. Benninger RK, Piston DW. Cellular communication and heterogeneity in pancreatic islet insulin secretion dynamics. *Trends Endocrinol Metab*. 2014;25(8):399-406.
14. Rorsman P, Ashcroft FM. Pancreatic beta-cell electrical activity and insulin secretion: of mice and men. *Physiol Rev*. 2018;98(1):117-214.
15. Rorsman P, Braun M. Regulation of insulin secretion in human pancreatic islets. *Annu Rev Physiol*. 2013;75:155-179.
16. De Vos A, Heimberg H, Quartier E, et al. Human and rat beta cells differ in glucose transporter but not in glucokinase gene expression. *J Clin Invest*. 1995;96(5):2489-2495.
17. Aguilar-Bryan L, Clement IPT, Gonzalez G, Kunjilwar K, Babenko A, Bryan J. Toward understanding the assembly and structure of KATP channels. *Physiol Rev*. 1998;78(1):227-245.
18. Braun M, Ramacheya R, Bengtsson M, et al. Voltage-gated ion channels in human pancreatic β-cells: electrophysiologic characterization and role in insulin secretion. *Diabetes*. 2008;57(6):1618-1628.
19. Barnett DW, Pressel DM, Misler S. Voltage-dependent Na+ and Ca2+ currents in human pancreatic islet beta-cells: evidence for
roles in the generation of action potentials and insulin secretion. *Pflugers Arch.* 1995;431(2):272-282.
20. Zhang Q, Chihalina MV, Bengtsson M, et al. Na+ current properties in islet alpha- and beta-cells reflect cell-specific Scn3a and Scn9a expression. *J Physiol.* 2014;592(21):4677-4696.
21. Nica AC, Ongen H, Irminger JC, et al. Cell-type, allelic, and genetic signatures in the human pancreatic beta cell transcriptome. *Genome Res.* 2013;23(9):1554-1562.
22. Jahn R, Fasshauer D. Molecular machines governing exocytosis of synaptic vesicles. *Nature.* 2012;490(7419):201-208.
23. Houamed KM, Sweet IR, Satin LS. BK channels mediate a novel ionic mechanism that regulates glucose-dependent electrical activity and insulin secretion in mouse pancreatic beta-cells. *J Physiol.* 2010;588( Pt 18):3511-3523.
24. Jacobson DA, Philipson LH. Action potentials and insulin secretion: new insights into the role of Kv channels. *Diabetes Obes Metab.* 2007;9(Suppl 2):89-98.
25. Gopel SO, Kanno T, Barg S, et al. Activation of Ca(2+)-dependent Kv4.2 channels contributes to rhythmic firing of action potentials in mouse pancreatic beta cells. *J Gene Physiol.* 1999;114(6):759-770.
26. Gutman GA, Chandy KG, Grissmer S, et al. International union of pharmacology. LI. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol Rev.* 2005;57(4):473-508.
27. Christie MJ. Molecular and functional diversity of K+ channels. *Clin Exp Pharmacol Physiol.* 1995;22(12):944-951.
28. Yellen G. The voltage-gated potassium channels and their relatives. *Nature.* 2002;419(6902):35-42.
29. Long SB, Campbell EB, Mackinnon R. Crystal structure of a mammalian voltage-dependent Shaker family K+ channel. *Science.* 2005;309(5736):897-903.
30. Doyle DA, Morais Cabral J, Pfuetzner RA, et al. The structure of the potassium channel: molecular basis of K+ conduction and selectivity. *Science.* 1998;280(5360):69-77.
31. Vandenbergl JI, Perry MD, Perrin MJ, Mann SA, Ke Y, Hill AP. hERG K+ channels: structure, function, and clinical significance. *Physiol Rev.* 2012;92(3):1393-1478.
32. Yang S-B, Jan LY. Potassium channels: their physiological and molecular diversity. In: Roberts GCK, ed. *Encyclopedia of Biophysics.* Springer Berlin Heidelberg; 2013:1933-1941.
33. Camunas-Soler J, Dai X-Q, Hang Y, et al. Patch-Seq links single-cell transcriptomes to human islet dysfunction in diabetes. *Cell Metab.* 2020;31(5):1017-1031.e1014.
34. Yan L, Figueroa DJ, Austin CP, et al. Expression of voltage-gated potassium channels in human and rhesus pancreatic islets. *Diabetes.* 2004;53(3):597-607.
35. Blodgett DM, Nowosieleska A, Afik S, et al. Novel observations from next-generation RNA sequencing of highly purified human adult and fetal islet cell subsets. *Diabetes.* 2015;64(9):3172-3181.
36. Jacobson DA, Kuznetsov A, Lopez JP, Kash S, Ammala CE, Philipson LH. Kv2.1 ablation alters glucose-induced islet electrical activity, enhancing insulin secretion. *Cell Metab.* 2007;6(3):229-235.
37. MacDonald PE, Sewing S, Wang J, et al. Inhibition of Kv2.1 voltage-dependent K+ channels in pancreatic β-cells enhances glucose-dependent Insulin Secretion. *J Biol Chem.* 2002;277(47):44938-44945.
38. Tamarina NA, Kuznetsov A, Fridlyand LE, Philipson LH. Delayed-rectifier (Kv2.1) regulation of pancreatic β-cell calcium responses to glucose: inhibitor specificity and modeling. *Am J Physiol-Endocrinol Metab.* 2005;289(4):E578-E585.
39. Jensen MV, Haldeman JM, Zhang H, et al. Control of voltage-gated potassium channel Kv2.2 expression by pyruvate-isocitrate cycling regulates glucose-stimulated insulin secretion. *J Biol Chem.* 2013;288(32):23128-23140.
40. Herrington J, Zhou YP, Bugianski RM, et al. Blockers of the delayed-rectifier potassium current in pancreatic beta-cells enhance glucose-dependent insulin secretion. *Diabetes.* 2006;55(4):1034-1042.
41. Braun M, Ramracheya R, Bengtsson M, et al. Voltage-gated ion channels in human pancreatic beta-cells: electrophysiological characterization and role in insulin secretion. *Diabetes.* 2008;57(6):1618-1628.
42. Li X, Herrington J, Petrov A, et al. The role of voltage-gated potassium channels Kv2.1 and Kv2.2 in the regulation of insulin and somatostatin release from pancreatic islets. *J Pharmacol Exp Ther.* 2013;344(2):407-416.
43. Fu J, Dai X, Plummer G, et al. Kv2.1 clustering contributes to insulin exocytosis and rescues human β-cell dysfunction. *Diabetes.* 2017;66(7):1890-1900.
44. Gretzinger-Antes D, Xie L, Qin T, et al. Kv 2.1 clusters on & β-cell plasma membrane act as reservoirs that replenish pools of newcomer insulin granule through their interaction with syntxin-3. *J Biol Chem.* 2018;293(18):6893-6904.
45. Kim SJ, Widenaier SB, Choi WS, et al. Pancreatic β-cell prosurvival effects of the incretin hormones involve post-translational modification of Kv2.1 delayed rectifier channels. *Cell Death Differ.* 2012;19(2):333-344.
46. Kim S-J, Ao Z, Warnock G, McIntosh Christopher HS. Incretin-stimulated interaction between β-cell Kv1.5 and Kvβ2 channel proteins involves acetylation/deacetylation by CBP/Sirt1. *Biochem J.* 2013;451(2):227-234.
47. Yamagata K, Senokuchi T, Lu M, et al. Voltage-gated K+ channel KCNQ1 regulates insulin secretion in MIN6 beta-cell line. *Biochem Biophys Res Commun.* 2011;407(3):620-625.
48. Ullrich S, Su J, Ranta F, et al. Effects of I(Ks) channel inhibitors in insulin-secreting INS-1 cells. *Pflugers Arch.* 2005;451(3):428-436.
49. Liu L, Wang F, Lu H, Ren X, Zou J. Chromanol 293B, an inhibitor of KCNQ1 channels, enhances glucose-stimulated insulin secretion and increases glucagon-like peptide-1 level in mice. *Islets.* 2014;6(4):e962386.
50. Bachmann A, Quast U, Russ U. Chromanol 293B, a blocker of the slow delayed rectifier K+-current (IKs), inhibits the CFTR CI- current. *Naunyn Schmiedebergs Arch Pharmacol.* 2001;363(6):590-596.
51. Sun X, Yi Y, Xie W, et al. CFTR influences beta cell function and insulin secretion through non-cell autonomous exocrine-derived factors. *Endocrinology.* 2017;158(10):3325-3338.
52. Fontés G, Ghislain J, Benterki I, et al. The ΔF508 mutation in the cystic fibrosis transmembrane conductance regulator is associated with progressive insulin resistance and decreased functional β-cell mass in mice. *Diabetes.* 2015;64(12):4112-4122.
53. Lubberding AF, Zhang J, Lundh M, et al. Age-dependent transition from islet insulin hypersecretion to hyposecretion in mice with the long QT-syndrome loss-of-function mutation Kcnq1-A340V. *Sci Rep.* 2021;11(1):12253.
54. Zhang J, Juhl CR, Hytten-Cavallius L, et al. Gain-of-function mutation in the voltage-gated potassium channel gene KCNQ1
and glucose-stimulated hypoinsulinemia—case report. BMC Endor. Disord. 2020;20(1):38.

55. Rosati B, Marchetti P, Crociani O, et al. Glucose- and arginine-induced insulin secretion by human pancreatic beta-cells: the role of HERG K(+ ) channels in firing and release. FASEB J. 2000;14(15):2601-2610.

56. Hardy AB, Fox JE, Giglou PR, et al. Characterization of Erg K+ channels in alpha- and beta-cells of mouse and human islets. J Biol Chem. 2009;284(44):30441-30452.

57. Proverbio MC, Mangano E, Gessi A, et al. Whole genome SNP genotyping and exome sequencing reveal novel genetic variants and putative causative genes in congenital hyperinsulinism. PLoS One. 2013;8(7):e68740.

58. Yang J-K, Lu J, Yuan S-S, et al. From hyper- to hypoinsulinemia and diabetes: effect of KCNH6 on insulin secretion. Cell Rep. 2018;25(13):3800-3810.e3806.

59. Lu J, Shen H, Li Q, et al. KCNH6 protects pancreatic β-cells from endoplasmic reticulum stress and apoptosis. FASEB J. 2020;34(11):15015-15028.

60. Jespersen T, Grunnet M, Olesen SP. The KCNQ1 potassium channel: from gene to physiological function. Physiology (Bethesda). 2005;20:408-416.

61. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome. Circ Arrhythm Electrophysiol. 2012;5(4):868-877.

62. Wang Y, Eldstrom J, Fedida D. Gating and regulation of KCNQ1 and KCNQ1 + KCNE1 channel complexes. Front Physiol. 2020;11:504.

63. Nerbonne JM. Molecular basis of functional voltage-gated K+ channel diversity in the mammalian myocardium. J Physiol. 2000;525(Pt 2):285-298.

64. Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. Physiol Rev. 2005;85(4):1205-1253.

65. Oudit GY, Kassiri Z, Sah R, Ramirez RJ, Zobel C, Backx PH. The molecular physiology of the cardiac transient outward potassium current (Ito) in normal and diseased myocardium. J Mol Cell Cardiol. 2001;33(5):851-872.

66. Attali B. Ion channels. A new wave for heart rhythms. Nature. 1996;384(6604):24-25.

67. Shimizu W, Horie M. Phenotypic manifestations of mutations in genes encoding subunits of cardiac potassium channels. Circ Res. 2011;109(1):97-109.

68. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the heart rhythm society (HRS) and the European Heart Rhythm Association (EHRA). EP Europace. 2011;13(8):1077-1109.

69. Splawski I, Tristani-Firouzi M, Lehmann MH, Sanguinetti MC, Keating MT. Mutations in the hminK gene cause long QT syndrome and suppress IKs function. Nat Genet. 1997;17(3):338-340.

70. Lee SM, Baik J, Nguyen D, et al. Kcnq2 deletion impairs insulin secretion and causes type 2 diabetes mellitus. FASEB J. 2017;31(6):2674-2685.

71. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103(1):89-95.

72. Marx SO, Kurokawa J, Reiken S, et al. Requirement of a macromolecular signaling complex for beta adrenergic receptor modulation of the KCNQ1-KCNE1 potassium channel. Science. 2002;295(5554):496-499.

73. Porte D Jr. A receptor mechanism for the inhibition of insulin release by epinephrine in man. J Clin Invest. 1967;46(1):86-94.

74. Straub SG, Sharp GW. Evolving insights regarding mechanisms for the inhibition of insulin release by norepinephrine and heterotrimeric G proteins. Am J Physiol Cell Physiol. 2012;302(12):C1687-C1698.

75. Drews G, Debuyser A, Nenquin M, Henquin JC. Galanin and epinephrine act on distinct receptors to inhibit insulin release by the same mechanisms including an increase in K+ permeability of the B-cell membrane. Endocrinology. 1990;126(3):1646-1653.

76. Rorsman P, Bokvist K, Åmmälä C, et al. Activation by adrenergic agonists of an α3/β2 dopamine receptor in mouse pancreatic B cells. Nature. 1991;349(6304):77-79.

77. Szollosi A, Nenquin M, Henquin JC. Pharmacological stimulation of inhibition of insulin secretion in mouse islets lacking LAT-sensitive K+ channels. Br J Pharmacol. 2010;159(3):669-677.

78. Sieg A, Su J, Muñoz A, et al. Epinephrine-induced hyperpolarization of islet cells without CATP channels. Am J Physiol Endocrinol Metab. 2004;286(3):E463-E471.

79. Ravens U. Cardiac sympathetic innervation and control of potassium channel function. J Mol Cell Cardiol. 2003;35(2):137-139.

80. Jones EM, Roti EC, Wang J, Delfosse SA, Robertson GA. Cardiac IKr channels minimally comprise hERG 1a and 1b subunits. J Biol Chem. 2004;279(43):44690-44694.

81. Larsen AP, Olesen SP, Grunnet M, Jespersen T. Characterization of hERG1a and hERG1b potassium channels: a possible role for hERG1b in the 1 (Kr) current. Pflugers Arch. 2008;456(6):1137-1148.

82. Larsen AP. Role of ERG1 isoforms in modulation of ERG1 channel trafficking and function. Pflugers Arch. 2010;460(5):803-812.

83. Mühlbauer E, Bazwinsky I, Wolgast S, Klemenz A, Peschke E. Circadian changes of ether-a-go-go-related gene (ErA) potassium channel transcripts in the rat pancreas and beta-cell. Cell Mol Life Sci. 2007;64(6):768-780.

84. Kannankeril P, Roden DM, Darbar D. Drug-induced long QT syndrome. Pharmacol Rev. 2010;62(4):760-781.

85. Villoutreix BO, Taboureau O. Computational investigations of hERG channel blockers: new insights and current predictive models. Adv Drug Deliv Rev. 2015;86:72-82.

86. Mitcheson JS, Chen J, Lin M, Culberson C, Sanguinetti MC. A structural basis for drug-induced long QT syndrome. Proc Natl Acad Sci USA. 2000;97(22):12329-12333.

87. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. Nature. 2006;440(7083):463-469.

88. Butler A, Helliswell MV, Zhang Y, Hancock JC, Dempsey CE. An update on the structure of hERG. Front Pharmacol. 2020;10:1572.

89. Roden DM. Mechanisms and management of proarrhythmia. Am J Cardiol. 1998;82(4):491-571.

90. Wheeler E, Leong A, Liu C-T, et al. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. PLoS Medicine. 2017;14(9):e1002383.

91. Ng MCY, Shriner D, Chen BH, et al. Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes. PLoS Genet. 2014;10(8):e1004517.
92. Flannick J, Mercader JM, Fuchsberger C, et al. Exome sequencing of 20,791 cases of type 2 diabetes and 24,440 controls. *Nature*. 2019;570(7759):71-76.

93. Vujkovic M, Keaton JM, Lynch JA, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ethnic meta-analysis. *Nat Genet*. 2020;52(7):680-691.

94. Hanson RL, Muller YL, Kobes S, et al. A genome-wide association study in American Indians implicates DNER as a susceptibility locus for type 2 diabetes. *Diabetes*. 2014;63(1):369-376.

95. Ishigaki K, Akiyama M, Kanai M, et al. Large-scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases. *Nat Genet*. 2020;52(7):669-679.

96. Takeuchi F, Serizawa M, Yamamoto K, et al. Confirmation of multiple risk loci and genetic impacts by a genome-wide association study of type 2 diabetes in the Japanese population. *Diabetes*. 2009;58(7):1690-1699.

97. Tsai PJ, Yang CF, Chen CC, et al. A genome-wide association study identifies susceptibility variants for type 2 diabetes in Han Chinese. *PLoS Genet*. 2010;6(2):e1000847.

98. Cui B, Zhu X, Xu M, et al. A genome-wide association study confirms previously reported loci for type 2 diabetes in Han Chinese. *PLoS One*. 2011;6(7):e22353.

99. Li H, Gan W, Lu L, et al. A genome-wide association study identifies GRK5 and RASGRP1 as type 2 diabetes loci in Chinese Hans. *Diabetes*. 2013;62(1):291-298.

100. Hara K, Fujita H, Johnson TA, et al. Genome-wide association study identifies three novel loci for type 2 diabetes. *Hum Mol Genet*. 2014;23(1):239-246.

101. Mahajan A, Go MJ, Zhang W, et al. Genome-wide trans-ancestry meta-analysis provides insights into the genetic architecture of type 2 diabetes susceptibility. *Nat Genet*. 2014;46(3):234-244.

102. Wen W, Zheng W, Okada Y, et al. Meta-analysis of genome-wide association studies in East Asian-ancestry populations identifies four new loci for body mass index. *Hum Mol Genet*. 2014;23(20):5492-5504.

103. Imamura M, Takahashi A, Yamauchi T, et al. Genome-wide association studies in the Japanese population identify seven novel loci for type 2 diabetes. *Hum Mol Genet*. 2014;23(1):239-246.

104. Kim J, Kim MK, Jung S, et al. Interaction of iron status with single nucleotide polymorphisms on incidence of type 2 diabetes. *PLoS One*. 2017;12(4):e0175681.

105. Kanai M, Akiyama M, Takahashi A, et al. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. *Nat Genet*. 2018;50(3):390-400.

106. Suzuki K, Akiyama M, Ishigaki K, et al. Identification of 28 new susceptibility loci for type 2 diabetes in the Japanese population. *Nat Genet*. 2019;51(3):379-386.

107. Spracklen CN, Horikoshi M, Kim YJ, et al. Identification of type 2 diabetes loci in 433,540 East Asian individuals. *Nature*. 2020;582(7811):240-245.

108. Cho SB, Jiang JH, Chung MG, Kim SC. Exome chip analysis of 14,026 Koreans reveals known and newly discovered genetic loci associated with type 2 diabetes mellitus. *Diabetes Metab J*. 2021;45(2):231-240.

109. Voight BF, Scott LJ, Steinthorsdottir V, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet*. 2010;42(7):579-589.

110. Morris AP, Voight BF, Teslovich TM, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet*. 2012;44(9):981-990.

111. Wood AR, Tyrrell J, Beaumont R, et al. Variants in the FTO and CDKAL1 loci have recessive effects on risk of obesity and type 2 diabetes, respectively. *Diabetologia*. 2016;59(6):1214-1221.

112. Zhao W, Rasheed A, Tikkanen E, et al. Identification of new susceptibility loci for type 2 diabetes and shared etiological pathways with coronary heart disease. *Nat Genet*. 2017;49(10):1450-1457.

113. Xue A, Wu Y, Zhu Z, et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. *Nat Commun*. 2018;9(1):2941.

114. Mahajan A, Talirn D, Thurmer M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet*. 2018;50(11):1505-1513.

115. Wu Y, Byrne EM, Zheng Z, et al. Genome-wide association study of medication-use and associated disease in the UK Biobank. *Nat Commun*. 2019;10(1):1891.

116. Parra EL, Below JE, Krithika S, et al. Genome-wide association study of type 2 diabetes in a sample from Mexico City and a meta-analysis of a Mexican-American sample from Starr County, Texas. *Diabetologia*. 2011;54(8):2038-2046.

117. Consortium STD, Williams AL, Jacobs SBR, et al. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. *Nature*. 2014;506(7486):97-101.

118. Palmer ND, Goodarzi MO, Langefeld CD, et al. Genetic variants associated with quantitative glucose homeostasis traits translate to type 2 diabetes in Mexican Americans: the GUARDIAN (Genetics Underlying Diabetes in Hispanics) consortium. *Diabetes*. 2015;64(5):1853-1866.

119. Qi Q, Stilp AM, Sofer T, et al. Genetics of type 2 diabetes in U.S. Hispanic/Latino individuals: results from the Hispanic community health study/study of Latinos (HCHS/SOL). *Diabetes*. 2017;66(5):1419-1425.

120. Jonsson A, Isomaa B, Tuomi T, et al. A variant in the KCNQ1 gene predicts future type 2 diabetes and mediates impaired insulin secretion. *Diabetes*. 2009;58(10):2409-2413.

121. Rosengren AH, Braun M, Mahdi T, et al. Reduced insulin exocytosis in human pancreatic beta-cells with gene variants linked to type 2 diabetes. *Diabetes*. 2012;61(7):1726-1733.

122. van Vliet-Ostaptchouk JV, van Haeften TW, Landman GW, et al. Common variants in the type 2 diabetes KCNQ1 gene are associated with impairments in insulin secretion during hyperglycaemic glucose clamp. *PLoS One*. 2012;7(3):e32148.

123. Holmquist J, Banasik K, Andersen G, et al. The type 2 diabetes associated minor allele of rs2237895 KCNQ1 associates with reduced insulin release following an oral glucose load. *PLoS One*. 2009;4(6):e5872.

124. Tan JT, Nurbaya S, Gardiner D, Ye S, Tai ES, Ng DP. Genetic variation in KCNQ1 associates with fasting glucose and beta-cell function: a study of 3,734 subjects comprising three ethnicities living in Singapore. *Diabetes*. 2009;58(6):1445-1449.

125. Mussig K, Stariger H, Machicao F, et al. Association of type 2 diabetes candidate polymorphisms in KCNQ1 with incretin and insulin secretion. *Diabetes*. 2009;58(7):1715-1720.

126. Kong A, Steinthorsdottir V, Masson G, et al. Parental origin of sequence variants associated with complex diseases. *Nature*. 2009;462(7275):868-874.

127. Kalish JM, Boodhansingh KE, Bhatti TR, et al. Congenital hyperinsulinism in children with paternal 11p uniparental...
128. Lee MP, Hu RJ, Johnson LA, Feinberg AP. Human KVLQT1 gene shows tissue-specific imprinting and encompasses Beckwith-Wiedemann syndrome chromosomal rearrangements. *Nat Genet.* 1997;15(2):181-185.

129. Korostowski L, Sedlak N, Engel N. The Kcnq1ot1 long non-coding RNA affects chromatin conformation and expression of Kcnq1, but does not regulate its imprinting in the developing heart. *PLoS Genet.* 2012;8(9):e1002956.

130. Hanson RL, Guo T, Muller YL, et al. Strong parent-of-origin effects in the association of KCNQ1 variants with type 2 diabetes in American Indians. *Diabetes.* 2013;62(8):2984-2991.

131. Brioude F, Kalish JM, Mussa A, et al. Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol.* 2018;14(4):229-249.

132. DeBaun MR, King AA, White N. Hypoglycemia in Beckwith-Wiedemann syndrome. *Semin Perinatol.* 2000;24(2):164-171.

133. Heide S, Chantot-Bastaraud S, Keren B, et al. Chromosomal rearrangements in the 11p15 imprinted region: 17 new 11p15.5 duplications with associated phenotypes and putative functional consequences. *J Med Genet.* 2018;55(3):205-213.

134. Asahara S, Etoh H, Inoue H, et al. Paternal allelic mutation at the Kcnq1 locus reduces pancreatic beta-cell mass by epigenetic modification of Cdkn1c. *Proc Natl Acad Sci USA.* 2015;112(27):8332-8337.

135. De Tata V. Age-related impairment of pancreatic Beta-cell function: pathophysiological and cellular mechanisms. *Front Endocrinol (Lausanne).* 2014;5:138.

136. Aguayo-Mazzucato C. Functional changes in beta cells during ageing and senescence. *Diabetologia.* 2020;63(10):2022-2029.

137. Park SE, Lee WY, Oh KW, et al. Impact of common type 2 diabetes risk gene variants on future type 2 diabetes in the non-diabetic population in Korea. *J Hum Genet.* 2012;57(4):265-268.

138. Zhao Q, Xiao J, He J, et al. Cross-sectional and longitudinal replication analyses of genome-wide association loci of type 2 diabetes in Han Chinese. *PLoS One.* 2014;9(3):e91790.

139. Tabara Y, Osawa H, Kawamoto R, et al. Genotype risk score of common susceptible variants for prediction of type 2 diabetes mellitus in Japanese: the Shimanami Health Promoting Program (J-SHIPP study). Development of type 2 diabetes mellitus and genotype risk score. *Metabolism.* 2011;60(11):1634-1640.

140. Marques JL, George E, Peacey SR, et al. Altered ventricular repolarization during hypoglycaemia in patients with diabetes. *Diabet Med.* 1997;14(8):648-654.

141. Landstedt-Hallin L, Englund A, Adamson U, Lins PE. Increased QT dispersion during hypoglycaemia in patients with type 2 diabetes mellitus. *J Intern Med.* 1999;246(3):299-307.

142. Beom JW, Kim JM, Chung EL, et al. Corrected QT interval prolongation during severe hypoglycaemia without hypokalemia in patients with type 2 diabetes. *Diabetes Metab J.* 2013;37(3):190-195.

143. Nguyen TQ, Maalouf NM, Sakhaee K, Moe OW. Comparison of insulin action on glucose versus potassium uptake in humans. *Clin J Am Soc Nephrol.* 2011;6(7):1533-1539.

144. Liamas G, Liberopoulos E, Barkas F, Eliasf M. Diabetes mellitus and electrolyte disorders. *World J Clin Cases.* 2014;2(10):488-496.

145. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycaemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes.* 2014;63(5):1738-1747.

146. Zhang Y, Han H, Wang J, Wang H, Yang B, Wang Z. Impairment of human ether-a-go-go-related gene (HERG) K+ channel function by hypoglycaemia and hyperglycemia. Similar phenotypes but different mechanisms. *J Biol Chem.* 2003;278(12):10417-10426.

147. Andersen A, Bagger JJ, Baldassarre MP, et al. Acute hypoglycemia and risk of cardiac arrhythmias in insulin-treated type 2 diabetes and controls. *Eur J Endocrinol.* 2021;185(2):343–353.

148. Tanenberg RJ, Newton CA, Drake AJ. Confirmation of hypoglycemia in the “dead-in-bed” syndrome, as captured by a retrospective continuous glucose monitoring system. *Endocr Pract.* 2010;16(2):244-248.

149. Cha SA, Yun JS, Lim TS, et al. Baseline-corrected QT (QTc) interval is associated with prolongation of QTc during severe hypoglycemia in patients with type 2 diabetes mellitus. *Diabetes Metab J.* 2016;40(6):463-472.

150. Cho Y. Management of patients with long QT syndrome. *Korean Circ J.* 2016;46(6):747-752.

151. Vue MH, Setter SM. Drug-induced glucose alterations part 1: Drug-induced hypoglycemia. *Diabetes Spectrum.* 2011;24(3):171-177.

152. Poterucha JT, Bos JM, Cannon BC, Ackerman MJ. Frequency and severity of hypoglycemia in children with beta-blocker-treated long QT syndrome. *Heart Rhythm.* 2015;12(8):1815-1819.

153. Dungan K, Merrill J, Long C, Binkley P. Effect of beta blocker use and type on hypoglycemia risk among hospitalized insulin requiring patients. *Cardiovasc Diabetol.* 2019;18(1):163.

154. Marzelf RA, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D. The effect of acute hyperglycaemia on QTc duration in healthy man. *Diabetologia.* 2000;43(5):571-575.

155. Hylten-Cavallius L, Iepsen EW, Christiansen M, et al. Glucose ingestion causes cardiac repolarization disturbances in type 1 long QT syndrome patients and healthy subjects. *Heart Rhythm.* 2017;14(8):1165-1170.

156. Isaksen JL, Ghouse J, Graff C, et al. Electrocardiographic T-wave morphology and risk of mortality. *Int J Cardiol.* 2021;328:199-205.

157. Nakashima T, Kubota T, Takasugi N, et al. Hyperglycemia and subsequent torsades de pointes with marked QT prolongation during refeeding. *Nutrition.* 2017;33:145-148.

158. Tran HV, Gore JM, Darling CE, Ash AS, Kiefe CI, Goldberg RJ. Hyperglycemia and risk of ventricular tachycardia among patients hospitalized with acute myocardial infarction. *Cardiovasc Diabetol.* 2018;17(1):136.

159. Pickham D, Flowers E, Drew BJ. Hyperglycemia is associated with corrected QT prolongation and mortality in acutely ill patients. *J Cardiovasc Nurs.* 2014;29(3):264-270.

160. Su JB, Yang XH, Zhang XL, et al. The association of long-term glycaemic variability versus sustained chronic hyperglycaemia with heart rate-corrected QT interval in patients with type 2 diabetes. *PLoS One.* 2017;12(8):e0183055.

161. Stern K, Cho YH, Benitez-Aguirre P, et al. QT interval corrected for heart rate, is associated with HbA1c concentration and autonomic function in diabetes. *Diabet Med.* 2016;33(10):1415-1421.

162. Kobayashi S, Nagao M, Fukuda I, Okawa S, Sugihara H. Multiple daily insulin injections ameliorate QT interval by lowering blood glucose levels in patients with type 2 diabetes. *Ther Adv Endocrinol Metab.* 2021;12:2042018821010057.

163. Suyos BE, Huybrechts SJ, De Wolf D, et al. QTc interval prolongation and QTc dispersion in children and adolescents with type 1 diabetes. *J Pediatr.* 2002;141(1):59-63.
164. Lo SS, Sutton MS, Leslie RD. Information on type 1 diabetes mellitus and QT interval from identical twins. *Am J Cardiol*. 1993;72(3):305-309.

165. Zhang J, Yang J, Liu L, et al. Significant abnormal glycemic variability increased the risk for arrhythmias in elderly type 2 diabetic patients. *BMC Endocr Disord*. 2021;21(1):83.

166. Hegyi B, Ko CY, Bossuyt J, Bers DM. Two-hit mechanism of cardiac arrhythmias in diabetic hyperglycemia: reduced repolarization reserve, neurohormonal stimulation and heart failure exacerbate susceptibility. *Cardiovasc Res*. 2021;117(14):2781–2793.

167. Engelbrechtsen L, Mahendran Y, Jonsson A, et al. Common variants in the hERG (KCNH2) voltage-gated potassium channel are associated with altered fasting and glucose-stimulated plasma incretin and glucagon responses. *BMC Genet*. 2018;19(1):15.

168. Kong L-L, Wu H, Cui W-P, et al. Advances in murine models of diabetic nephropathy. *J Diabetes Res*. 2013;2013:797548.

169. Schnell F, Behar N, Carré F. Long-QT syndrome and competitive sports. *Arrhythm Electrophysiol Rev*. 2018;7(3):187-192.

170. Borghouts LB, Keizer HA. Exercise and insulin sensitivity: a review. *Int J Sports Med*. 2000;21(1):1-12.

171. Lundgren JR, Janus C, Jensen SBK, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. *N Engl J Med*. 2021;384(18):1719–1730.

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