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REVIEW

Genetic variants affecting incretin sensitivity and incretin secretion

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Abstract Recent genome-wide association studies identified several novel risk genes for type 2 diabetes. The majority of these type 2 diabetes risk variants confer impaired pancreatic beta cell function. Though the molecular mechanisms by which common genetic variation within these loci affects beta cell function are not completely understood, risk variants may alter glucose-stimulated insulin secretion, proinsulin conversion, and incretin signals. In humans, the incretin effect is mediated by the secretion and insulinotropic action of two peptide hormones, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1. This review article aims to give an overview of the type 2 diabetes risk loci that were found to associate with incretin secretion or incretin action, paying special attention to the potential underlying mechanisms.

Keywords Diabetes mellitus type 2 · *GIPR* · Glucagon-like peptide-1 · Glucose-dependent insulinotropic peptide · Insulin secretion · *KCNQ1* · Pancreatic beta cell · Review · *TCF7L2* · *WFS1*

Abbreviations

GIP	Glucose-dependent insulinotropic peptide
GIPR	GIP receptor
GLP-1	Glucagon-like peptide-1
GLP-1R	GLP-1 receptor
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1
MTNR1B	Melatonin receptor 1B
TCF7L2	Transcription factor 7-like 2
WFS	Wolfram syndrome
WNT	Wingless-type MMTV integration site family member 2
ZnT-8	Zinc transporter 8

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Introduction

As a result of the dramatic increase in the incidence of type 2 diabetes mellitus worldwide, this chronic and progressive disease has reached epidemic proportions with major health consequences at an individual as well as a public health level [1]. Impaired pancreatic beta cell function as well as central and peripheral insulin resistance are key features in the pathophysiology of type 2 diabetes mellitus [2]. The most relevant environmental factors in the development of type 2 diabetes comprise excessive energy intake and reduced physical activity on the background of a genetic predisposition [3].

Recent genome-wide association studies identified a series of novel type 2 diabetes risk loci [4–15]. The majority of these type 2 diabetes risk variants confer an impaired pancreatic beta cell function [8, 14–37]. Though the underlying mechanisms by which common genetic variation within these loci affects beta cell function are not completely understood, risk variants may alter glucose-stimulated insulin secretion [16, 17, 19, 24, 25, 30, 32], proinsulin conversion [21, 38–40] and incretin secretion or incretin action.

Effects of type 2 diabetes risk variants on incretin secretion and incretin action

The two major incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), for-

merly known as gastric inhibitory peptide, which account for up to 60% of postprandial insulin release in healthy people, are secreted in response to meals by the L cells of the distal ileum and colon and the K cells of the duodenum and jejunum, respectively (for review, see Holst et al. [41]). The biologically active forms of GLP-1, i.e. GLP-$1_{(7–36)}$ amide and GLP-$1_{(7–37)}$, and GIP are derived from post-translational processing of their precursors pro-GIP and proglucagon, respectively. As a result of rapid inactivation by the ubiquitously produced enzyme dipeptidyl peptidase-4, circulating incretins have a short duration of action. Both incretins act via specific receptors, i.e. the GLP-1 receptor (GLP-1R) and the GIP receptor (GIPR), respectively, both of which are members of the seven-transmembrane spanning, heterotrimeric G-protein-coupled receptor superfamily. The GLP-1R is produced in pancreatic alpha and beta cells as well as in heart, central nervous system, kidney, lung and gastrointestinal tract, whereas the GIPR is mainly found in pancreatic beta cells and, to a lesser extent, in the central nervous system, adipose tissue and osteoblasts. Metabolic actions of incretins comprise glucose-dependent insulin secretion, pancreatic beta cell proliferation, inhibition of beta cell apoptosis, and deceleration of gastric emptying. In addition, GLP-1 suppresses glucose-dependent glucagon secretion, appetite and food intake. In pancreatic beta cells, activation of the GLP-1R causes, through a stimulatory G-protein, production of the second messenger cyclic AMP, which mediates most of the GLP-1-dependent actions, including regulation of ion channel activity, intracellular calcium increase, insulin granule release, and insulin gene expression. Protein kinase A (PKA), the cyclic AMP-regulated guanine nucleotide exchange factor II (cAMP-GEFII, also known as EPAC2), as well as the cross-talk between PKA and the wingless-type MMTV integration site family member 2 (WNT) signalling pathway are involved in the aforementioned cyclic AMP-stimulated events (Fig. 1).

GLP-1 and GIP are the two major incretins accounting for up to 60% of postprandial insulin release in healthy people

As suggested by the production of GLP-1R and GIPR in multiple organs outside the pancreas, incretin actions are not limited to pancreatic islet cells, but they play regulatory roles in distinct tissues. While GLP-1 appears to promote beneficial effects on the cardiovascular system and central nervous system, the extrapancreatic actions of GIP comprise adipocyte function and fat storage as well as bone formation through stimulation of osteoblast proliferation and inhibition of apoptosis.

In type 2 diabetes, the incretin effect is impaired, with the insulinotropic action of GLP-1 being significantly more conserved than that of GIP. Though in some studies, postprandial concentrations of GLP-1 and GIP were diminished, the contribution of the potentially altered incretin secretion to the development of type 2 diabetes remains obscure [42]. In light of the described incretin actions in health and disease, genes encoding for proteins with impact on incretin production and secretion or on incretin signalling pathways appear to be potential type 2 diabetes candidate genes. In accordance with this assumption, some of the recently identified type 2 diabetes risk alleles appear to affect incretin secretion and incretin action (Table 1).

Genetic variants of *TCF7L2* are associated most consistently with alterations in the incretin function. *TCF7L2* encodes the transcription factor 7-like 2 (TCF7L2), which mediates the WNT signalling pathway [43]. The latter has been reported to be involved in the neonatal regulation of normal and regenerative growth of pancreatic beta cells [44]. Heterodimerisation of TCF7L2 with β-catenin results in transcription of numerous genes, such as that for proglucagon, which is processed to GLP-1 in the intestinal L cells [45]. GLP-1, which exhibits a wide range of glucose-lowering actions [43], stimulates pancreatic beta cell proliferation through activation of the WNT signalling pathway [46]. Positive feedback between GLP-1 and WNT signalling enhances the beneficial effects of GLP-1 on pancreatic beta cell function [47]. Also the insulin gene appears to be a direct target of TCF7L2, given that the expression of the insulin gene was reported to correlate strongly with *TCF7L2* expression and to be diminished after targeted silencing of the *TCF7L2* gene [48, 49]. In patients with type 2 diabetes, as well as in animal models of type 2 diabetes, *TCF7L2* mRNA levels were found to be increased several-fold, whereas protein levels were decreased [49, 50]. Experimental knockdown of *TCF7L2* by RNA interference in human and murine islets resulted in an increase in beta cell apoptosis as well as in a decrease in beta cell proliferation and glucose-stimulated insulin secretion [51]. The impairment of glucose-stimulated and incretin-stimulated insulin secretion after *TCF7L2* gene silencing was accompanied by a decrease in production of the GLP-1R and the GIPR as well as by an attenuation of the GLP-1-stimulated and GIP-stimulated AKT phosphorylation, and AKT-mediated forkhead box O1 (FOXO-1) phosphorylation and nuclear exclusion. A comparable reduction in GLP-1R and GIPR levels was also detected in islets from patients with type 2 diabetes [49]. Furthermore, reducing TCF7L2 levels by RNA interference decreased expression of beta cell genes regulating secretory granule fusion, such as *Munc18-1* (also known as *STXBP1*) and *ZnT-8* (also known as *SLC30A8*), resulting in defective insulin exocytosis [52]. In contrast, overexpression

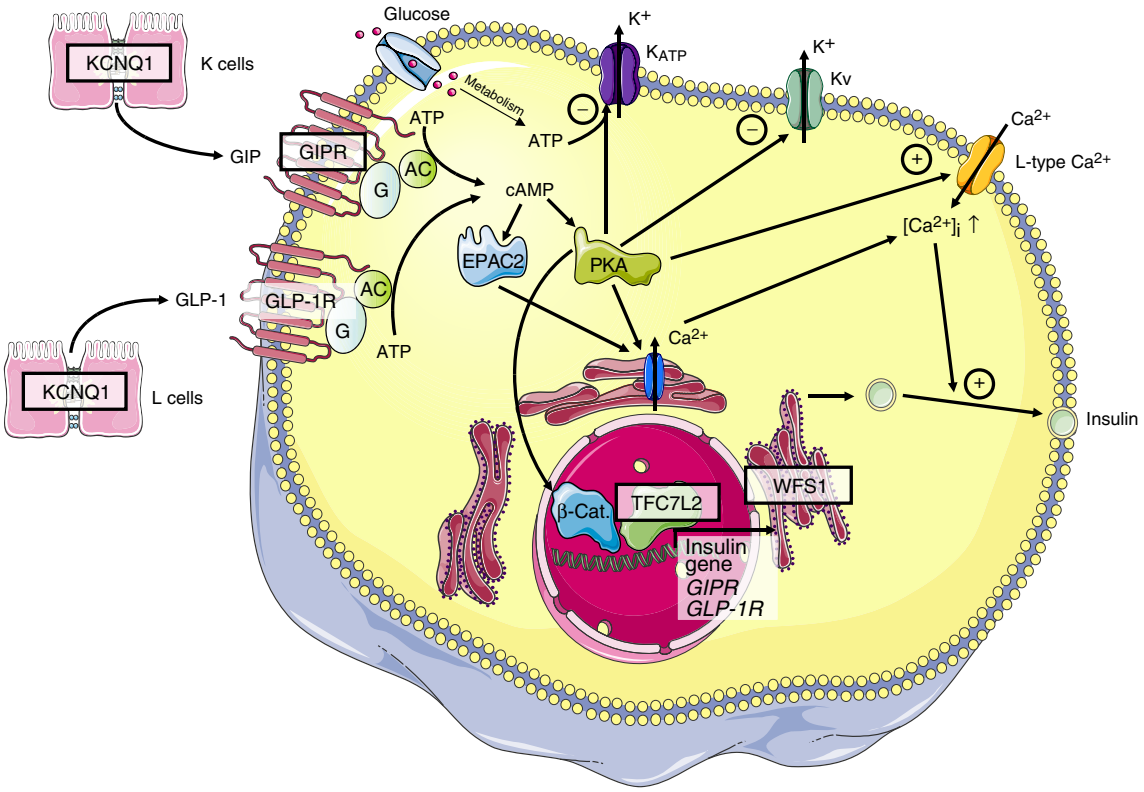

Fig. 1 Insulinotropic actions of GLP-1 and GIP in pancreatic beta cells. Binding of GLP-1 and GIP to their specific receptors, i.e. GLP-1R and GIPR, causes, through a stimulatory G-protein (G), activation of adenylyl cyclase (AC), which converts ATP into the second messenger cyclic AMP (cAMP). Increase of intracellular cAMP levels results in activation of protein kinase A (PKA) and the cAMP-regulated guanine nucleotide exchange factor II (cAMP-GEFII, also known as EPAC2), which mediate most of the incretin-dependent actions. Synergistically with an increase in intracellular ATP levels, PKA-mediated phosphorylation of the ATP-sensitive potassium (K_{ATP}) channel leads to closure of the K_{ATP} channel, causing depolarisation of the membrane potential. Inhibition of the voltage-gated potassium (Kv) channel through a PKA-dependent phosphorylation leads to prolongation of the action potential duration. On depolarisation, the voltage-dependent L-type calcium channel (L-type Ca^{2+}) opens and calcium flows into the cells. The PKA-dependent phosphorylation also activates the L-type calcium channel. This calcium influx into the cell causes calcium mobilisation from the endoplasmic reticulum through PKA- and EPAC2-dependent mechanisms, which serves as a significant source for increasing intracellular calcium concentration ($[Ca^{2+}]_i$). The increase in intracellular calcium levels finally causes release of preformed insulin granules into the circulation. Furthermore, PKA mediates expression of the insulin gene as well as of *GLP-1R* and *GIPR* by activation of the WNT signalling pathway via phosphorylation of β-catenin (β-cat.) and subsequent interaction of β-catenin with transcription factors, such as TCF7L2. WFS1 (Wolframin) has recently been identified as a component of the unfolded protein response in the endoplasmic reticulum [79], whereas *KCNQ1* is ubiquitously expressed in epithelial cells, including the small intestine [86] and appears to be involved in hormone and electrolyte transport processes [88]. Proteins encoded by recently identified type 2 diabetes risk loci with a potential impact on incretin secretion and action are highlighted by the boxes surrounded by solid black lines

of *TCF7L2* attenuated glucose-induced and cytokine-induced islet apoptosis and impaired function, confirming the important role of TCF7L2 in beta cell survival and beta cell proliferation as well as in glucose-stimulated and incretin-stimulated insulin secretion [51]. Together, these studies point towards a role for TCF7L2 as the major effector of the canonical WNT signalling pathway in the pathogenesis of type 2 diabetes.

In agreement with these in vitro data, genetic variants in *TCF7L2* were identified to associate with an increased risk of type 2 diabetes in humans [53–55], with impaired insulin secretion as a potential link [29, 54, 56, 57]. Two recent studies investigating the underlying mechanisms of altered insulin secretion in *TCF7L2* risk allele carriers provided evidence for an involvement of *TCF7L2* genetic variants (rs7903146 and rs12255372) in incretin-induced insulin secretion by comparison of OGTT and IVGTT data [50, 58] as well as by hyperglycaemic clamp combined with GLP-1 infusion, without affecting plasma GLP-1 levels [50, 58]. The lower incretin effect on insulin secretion despite similar GIP and GLP-1 responses to oral glucose in risk allele carriers was also confirmed by two recent studies [59, 60]. In agreement with these findings, knockdown of *TCF7L2* in human and murine islets have demonstrated a role for the transcription factor in incretin signalling [51]. Pilgaard et al. found elevated endogenous glucose production at fasting

Table 1 Effects of single nucleotide polymorphisms in confirmed type 2 diabetes genes on incretin action and incretin secretion

Gene	Chr.	Relevant tissue expression	Variants (approximate RAF)	Risk allele effects
TCF7L2	10	Pancreas	rs7903146 (30%), rs12255372 (30%), rs7901695 (30%)	Incretin (GLP-1)-stimulated insulin secretion ↓
GIPR	19	Pancreas	rs10423928 (20%)	Incretin (GIP)-stimulated insulin secretion ↓
WFS1	4	Pancreas	rs10010131 (60%)	Incretin (GLP-1)-stimulated insulin secretion ↓
KCNQ1	11	Pancreas, intestine	rs2237892 (90%), rs151290 (80%)	Incretin secretion ↓

Chr., chromosome; RAF, risk allele frequency

conditions and during a euglycaemic–hyperinsulinaemic clamp despite diminished plasma glucagon levels in participants carrying the risk allele [60]. The authors interpreted these conflicting results as either a more direct role of TCF7L2 in the regulation of hepatic glucose homeostasis, such as modulation of expression of the gene encoding glucagon in pancreatic alpha cells [45], or as an indirect influence on hepatic glucose balance via the central nervous system. The latter assumption would be in agreement with a previous study showing that in the presence of hyperglycaemia intracerebroventricular application of the GLP-1 agonist exendin-4 resulted not only in a fourfold rise in insulin secretion, but also in increased liver glycogen storage [61].

TCF7L2 variants affect incretin actions, with alterations of the WNT signalling pathway as a potential underlying mechanism

Very recently the variant rs10423928 in the *GIPR* (gastric inhibitory polypeptide receptor; OMIM entry no. 137241) locus was found to associate with increased 2 h glucose levels during an OGTT, decreased insulin secretion, and diminished incretin effect [62]. Activation of the seven-transmembrane GIPR by GIP requires interaction of the N-terminal moiety of GIP with determinant residues within the transmembrane helices of GIPR [63]. GIPR is produced widely, but in particular is found on pancreatic beta cells. The physiological and pharmacological regulation of GIPR production is modulated by peroxisome proliferator-activated receptor gamma signalling [64]. In different animal models, functional knockout of the *Gipr* gene resulted in impaired glucose tolerance with altered early insulin response after oral glucose load, whereas glucose tolerance and pancreatic beta cell function were normal following an intraperitoneal or intravenous glucose challenge [65, 66]. In line with these findings, in different rat models of diabetes, GIPR agonist treatment exhibited beta cell anti-apoptotic actions leading to improvement of beta cell function and glycaemic control [67].

At present, the function of the intron-located *GIPR* variant rs10423928, which associated with indices of glucose intolerance and impaired beta cell function, remains elusive. However, it is worth noting that this single nucleotide polymorphism (SNP) is in strong linkage disequilibrium with the *GIPR* variant rs1800437, a missense mutation that results in substitution of glutamic acid by glutamine at codon 354 (E354Q). In glucose-tolerant patients homozygous for the Gln354 variant, serum C-peptide concentrations in fasting conditions and 30 min after an oral glucose challenge were significantly diminished compared with concentrations in wild-type carriers [68]. However, while neither in the study by Almind et al. [68] nor in two other small case–control studies of type 2 diabetes [69, 70], was an association between genetic variation in *GIPR* and risk for type 2 diabetes observed, in a recent meta-analysis comprising about 19,000 individuals with diabetes and more than 38,000 individuals without diabetes, the rs10423928 A allele was nominally associated with a moderate type 2 diabetes risk (OR 1.07, 95% CI 1.03–1.12) [62].

The impact of polymorphisms in *GIPR* on type 2 diabetes risk and diminished incretin action is supported by its function in beta cell regulation

In light of the rather well-defined role of TCF7L2 and GIPR in the regulation of incretin actions, it appears plausible that genetic variants in these loci confer pancreatic beta cell dysfunction and increased risk for type 2 diabetes by alteration of incretin-dependent signalling pathways. In contrast, only limited data are available on the association of other type 2 diabetes risk loci, such as *WFS1* and *KCNQ1*, with impaired incretin secretion or action. Besides, the underlying pathophysiological mechanisms by which variants within these loci contribute to alterations in the incretin system are not understood.

In a recent hyperglycaemic clamp study combined with GLP-1 infusion, we found the variant rs10010131 in the confirmed diabetes risk gene *WFS1* (Wolfram syndrome 1 [wolframin]; OMIM entry no. 606201) to be associated with impaired insulin secretion after GLP-1 administration [71] in humans. A similarly powered study confirmed reduced GLP-1 induced insulin secretion in carriers of the diabetes risk alleles [72]. *WFS1* encodes an 890-amino-acid transmembrane polypeptide that is found ubiquitously, particularly in pancreatic islets and specific neurons, and is predominantly localised in the endoplasmic reticulum [73]. Mutations in the *WFS1* gene cause the rare autosomal recessive neurodegenerative disorder Wolfram syndrome. In light of its clinical presentation with diabetes insipidus, young-onset non-immune insulin-dependent diabetes mellitus, optic atrophy and deafness, Wolfram syndrome is also known by the acronym DIDMOAD. In a mouse model, *Wfs1* gene knockout resulted in glucose intolerance and overt diabetes as the result of enhanced beta cell endoplasmic reticulum stress, diminished beta cell proliferation, progressive apoptotic beta cell loss and, consequently, impaired insulin secretion [74–76]. Though the exact function of wolframin is unknown, a very recent study indicated its involvement in the development of the pancreas [77]. Furthermore, based on its localisation in the pancreatic endoplasmic reticulum, a key site for insulin biosynthesis and the folding of newly synthesised proinsulin [78], polymorphisms in the *WFS1* gene may alter the endoplasmic reticulum homeostasis and so impair beta cell function. This assumption would be in agreement with the recent identification of WFS1 as a component of the unfolded protein response [79]. The unfolded protein response has a key function in maintaining homeostasis of the pancreatic endoplasmic reticulum by modulating the capacity and quality of the endoplasmic reticulum protein-folding machinery to prevent the accumulation of unfolded or misfolded proteins [80]. However, impairment of the GLP-1 response may not only result in a diminished postprandial insulin secretion, but also in altered stimulation of beta cell growth and beta cell differentiation [41].

The association between *WFS1* variants and impaired incretin action may result from alterations of endoplasmic reticulum homeostasis and, consequently, beta cell dysfunction

Confirmed type 2 diabetes risk variants in *KCNQ1* (OMIM entry no. 607542) were found to associate with insulin secretion after an OGTT [81–84] but not after an IVGTT [82]. None of these SNPs affected GLP-1-induced insulin secretion. However, one variant, rs151290, was associated with glucose-stimulated GIP and GLP-1 increase [82] in our recent study. The *KCNQ1* gene encodes potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1), which plays an important role in controlling the ventricular repolarisation process. Mutations in *KCNQ1* have initially been associated with inherited cardiac disorders, such as long QT syndrome and familial atrial fibrillation. The long QT syndrome may occur in a recessive form, which is associated with deafness (Jervell and Lange-Nielsen syndrome) or in an autosomal dominant variant not associated with deafness (Romano–Ward syndrome) [85]. In addition to heart and cochlea, *KCNQ1* is ubiquitously expressed in epithelial cells, including the exocrine and endocrine pancreas as well as the small intestine [86]. *KCNQ1* was shown to be expressed in insulin-secreting INS-1 cells and inhibition of this potassium channel by the sulfonamide analogue 293B was found to enhance tolbutamide-induced insulin secretion [87]. In the gastrointestinal tract, KCNQ1 appears to be involved in hormone and electrolyte transport processes [88]. Though an involvement of KCNQ1 has not been shown for incretin secretion, in light of the ubiquitous expression of *KCNQ1* in epithelial cells, one could speculate that genetic variants in *KCNQ1* may alter the effectiveness of the incretin transport machinery in the gastrointestinal tract.

Variants in *KCNQ1* affect glucose-induced incretin hormone release, with altered incretin transport machinery in the gastrointestinal tract as a potential explanation

Gene variants in two additional diabetes risk loci, *THADA* and *MTNR1B*, were found to be associated with altered insulin response towards GLP-1 treatment [72]. SNPs within the *THADA* locus associated with diminished insulin secretion following GLP-1 treatment, whereas variants within the *MTNR1B* locus associated with increased insulin secretion after GLP-1 stimulation. However, the associations between *THADA* and *MTNR1B* gene variants and altered pancreatic beta cell function were not specific for GLP-1 treatment but were also observed following arginine stimulation. Furthermore, the association between the risk allele of the *MTNR1B* SNP rs10830963 and increased insulin responses towards GLP-1 and arginine stimulation, despite a diminished insulin response to oral glucose during an OGTT [72], was surprising because incretins such as GLP-1 are known to mediate, at least in part, the insulin secretion after oral intake of glucose. Therefore, confirmation in other cohorts is important to rule out false-positive findings, before drawing any further conclusions.

It is worth mentioning that additional known diabetes risk variants might affect incretin secretion and incretin function. Given that the effect sizes of diabetes risk alleles are often small [89], associations may have been missed by the recent studies of limited sample sizes and may be identified only by meta-analysis or large well-designed studies.

Conclusions

Recent genome-wide association studies identified several new type 2 diabetes risk loci. The majority of these risk loci appear to increase the risk of developing type 2 diabetes through alteration of pancreatic beta cell homeostasis. Though the molecular mechanisms by which the diabetes risk alleles contribute to beta cell dysfunction are not understood, in addition to glucose-induced insulin secretion and proinsulin conversion, incretin action or insulin secretion may be altered. Variants in *TCF7L2*, *GIPR*, and *WFS1* were found to be associated with incretin action and variants in *KCNQ1* were associated with incretin secretion. Although the known physiological actions of the transcription factor TCF7L2 and the seven-transmembrane GIPR clearly indicate a pathophysiological link between genetic variation in the *TCF7L2* and the *GIPR* loci and attenuation of incretin susceptibility, the potential underlying mechanisms by which variants in *WFS1* and *KCNQ1* contribute to impairments of incretin-dependent pathways still have to be identified.

In recent years, it has become evident that genetic variants in several diabetes risk genes may predict treatment outcome of glucose-lowering drugs. Response to thiazolidinedione therapy has been associated with *PPARG* (peroxisome proliferator-activated receptor-gamma) variation [90, 91], though not by all studies [92–94]. Literature on the impact of the *KCNJ11* risk variant E23K on treatment response to sulfonylureas is similarly controversial. Whereas E23K associated with an increased risk of secondary failure to sulfonylureas in patients with type 2 diabetes [95], a lack of protection by metformin [96], and diminished repaglinide efficacy [97], in another study, the *KCNJ11* risk variant did not affect response to sulfonylurea therapy [98]. Data on the association between SNPs in *TCF7L2* and treatment outcome appears to be more consistent. The *TCF7L2* variants have been reported to influence disease severity and therapeutic control [99], including lifestyle intervention [54], response to sulfonylureas [100] and repaglinide efficacy [97].

In light of the potential impact of a certain genetic background on treatment response towards glucose-lowering drugs, elucidation of the involvement of the type 2 diabetes risk genes with impact on incretin signals in alterations of the entero–insular axis appears to be highly relevant, as it could open novel treatment options. Though possible interactions between these type 2 diabetes risk loci with impact on incretin signals and insulin secretagogues, incretin mimetics, or dipeptidyl peptidase-4 inhibitors have, so far, not been studied, defective glucose-stimulated insulin secretion by pancreatic beta cells may be alleviated with GLP-1 analogues and dipeptidyl peptidase-4 inhibitors in risk allele carriers.

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