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COMMENTARY

# The enteroinsular axis may mediate the diabetogenic effects of *TCF7L2* polymorphisms

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**Keywords** Beta cell function · Beta cell mass · Diabetes genes · Enteroinsular axis · Glucagon-like peptide-1 · Gut hormones · Incretins · Insulin secretion

**Abbreviations**

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| GIP | gastric inhibitory polypeptide |
| GLP-1 | glucagon-like peptide-1 |

In an article in this issue of *Diabetologia*, Schäfer et al. report that the acute insulin response to glucagon-like peptide-1 (GLP-1) is reduced in individuals with normal or impaired oral glucose tolerance undergoing a hyperglycaemic clamp experiment [1]. This effect was specific for individuals with the polymorphisms rs7903146 or rs12255372 in the gene sequence coding for transcription factor 7-like-2 (*TCF7L2*), polymorphisms associated with an increased risk of type 2 diabetes [2–4], and reduced insulin secretion [3, 5–11]. TCF7L2 plays a role in the WNT signalling pathway [12], which (among other things) influences the synthesis (and possibly secretion) of GLP-1 [13], and the embryological development of the endocrine pancreas [14]. It was therefore of interest to characterise the effect of GLP-1 upon insulin secretion in individuals with these polymorphisms.

Schäfer et al. started with the hypothesis that GLP-1 secretion, as tested following stimulation with oral glucose, would differ in those who carried diabetogenic *TCF7L2* polymorphisms [3, 12]. This was not the case: *TCF7L2* polymorphisms did not alter the pattern of GLP-1 secretion in response to oral glucose in any way. Although contrary to the expectations of the authors, this observation was nonetheless consistent with preliminary findings from another study [15].

The authors then went on to examine the influence of these polymorphisms on insulin secretion, using a standardised test that sequentially tested the insulin secretory responses to hyperglycaemia, exogenous GLP-1, and arginine, whilst separating the responses into early and second phases [1]. They found that carriers and controls produced identical responses to glucose and arginine, but the carriers had a reduced ability to secrete insulin in response to exogenous GLP-1.

This confirmed that diabetes-associated *TCF7L2* polymorphisms are associated with a lower incretin-mediated insulin secretory response. Contrary to the original hypothesis, however, this was mediated by under-responsiveness of endocrine pancreatic beta cells rather than an impairment in nutrient-stimulated GLP-1 secretion. This reduction in response appears to be specific to the insulinotropic action of GLP-1. Glucose and arginine apart, additional stimuli (e.g. β-adrenergic mimetics, sulfonylureas, leucine, gastric inhibitory polypeptide [GIP]) have yet to be studied. Such studies would help to separate specific defects in the response to GLP-1 from a more generalised beta cell secretory failure.

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*TCF7L2* polymorphisms are considered to make a greater contribution to the development of type 2 diabetes than any other genetic marker [16], and this study, taken together with preliminary data from a Danish research group [15] and another recent publication using different methods to demonstrate the involvement of incretins [17], suggests a mechanism by which these polymorphisms could lead to a higher risk of diabetes.

But are these results conclusive? Some aspects of the study may need to be supplemented with additional investigations. Some of the data characterising insulin secretory responses to oral and intravenous glucose administration appear to have been collected according to a study protocol not specifically designed to test the influence of *TCF7L2* polymorphisms on GLP-1 secretion and action. In contrast, the hyperglycaemic clamp test specifically tested the insulinotropic actions of GLP-1. More frequent sampling times would be needed to adequately define the pattern of GLP-1 secretion following oral glucose or a meal before definite conclusions could be drawn regarding minor differences in the secretion of GLP-1. The differences between patients with type 2 diabetes, individuals with impaired glucose tolerance and healthy controls also require more careful definition, with adequate power to detect such differences. We need to know how specific the differences were for the second to third hour after meal ingestion [18].

Further, and before conclusions can be drawn regarding the pathogenesis of diabetes, the effects of GLP-1 should be studied under near-physiological conditions; e.g. at a dose of GLP-1 that mimics physiological concentrations (approximately 0.3 pmol $l^{-1}$ $min^{-1}$ [19]), and at glucose concentrations that are closer to physiological postprandial levels of glycaemia. It would also be of interest to determine whether the incretin effect (i.e. the difference in insulin secretory responses between oral glucose administration and 'isoglycaemic' glucose infusions [20]) is different when subjects are categorised according to *TCF7L2* polymorphisms. If the observed reduction in signalling through GLP-1 receptors is functionally relevant, one might anticipate that the incretin effect should be reduced in those with the risk genotypes, as suggested by Lyssenko et al. [17]. Next, it can be noted that a specific defect in response to GLP-1 does not mimic the pathophysiology of the enteroinsular axis in type 2 diabetes. A profound hypo-responsiveness to GIP would be more typical [21, 22], together with a relatively well-preserved insulinotropic activity of GLP-1 [21–23]. Stimulation of insulin secretion by exogenous GIP should therefore be studied in relation to genetic polymorphisms of *TCF7L2*. Preliminary results suggest that GIP activity is not impaired in carriers of these risk polymorphisms [15]. Finally, the hyperglycaemic clamp test with sequential administration of GLP-1 and arginine has been used to characterise insulin secretory responses in subjects with impaired glucose tolerance and healthy controls by the same group from Tübingen [24], and in this study impaired glucose tolerance alone was associated with a reduced insulinotropic effect of GLP-1, quite independently from the genetic background. Since a higher percentage of subjects with *TCF7L2* polymorphisms had impaired glucose tolerance (29% vs 14%, as expected for a genotype conferring an increased risk of developing type 2 diabetes), this alone may have biased the results in the direction of a reduced responsiveness to GLP-1. Adjustment for oral glucose tolerance status is not mentioned in the statistical analysis. The authors have however stated that an adjustment for oral glucose tolerance status would not weaken the association (personal communication).

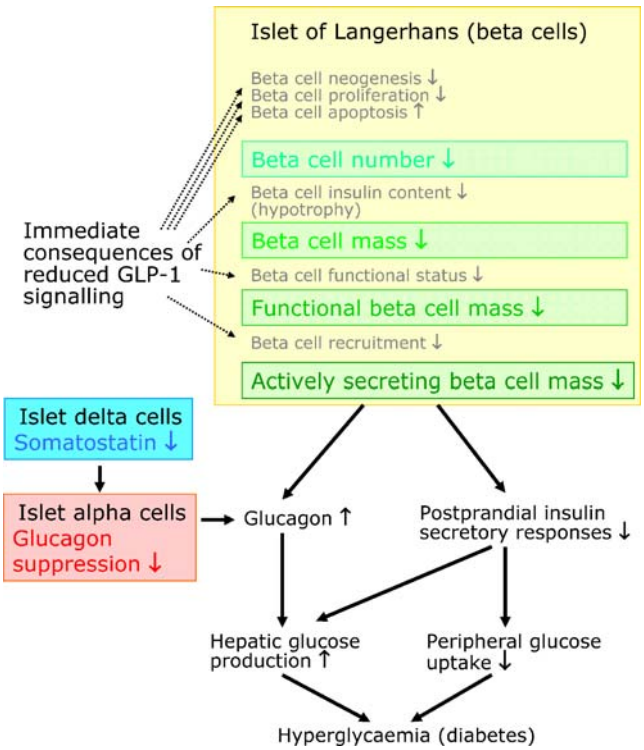


**Fig. 1** Potential consequences of reduced signalling through GLP-1 receptors. GLP-1 has been shown to modulate beta cells at all levels. GLP-1 is known to promote beta cell neogenesis [25] and proliferation [26], and to inhibit apoptosis induced by a toxic environment [27]. GLP-1 also increases the insulin content of beta cells [27, 28] and increases the functional performance of beta cells even in patients with type 2 diabetes [29, 30]. GLP-1 may have a profound influence on the number of cells that respond to hyperglycaemia ('glucose competence', beta cell recruitment [31]). In addition to effects determining actively secreting beta cell mass, GLP-1 reduces glucagon secretion [21], presumably through stimulation of delta cell somatostatin release [32]. If GLP-1 receptor signalling is reduced (e.g. by a *TCF7L2* polymorphism), this might lead to decreases in beta cell mass and functional status, which in turn result in reduced insulin secretory responses to nutritional stimuli, impaired glucagon suppression, and eventually, hyperglycaemia

What then is the picture that emerges from this important study? It would be tempting—yet premature—to conclude that *TCF7L2* polymorphisms result in reduced GLP-1-mediated ('incretin') stimulation of insulin secretion, with impaired insulin secretory responses to feeding, and that this might produce subtle disturbances in glucose tolerance which, via glucose toxicity or other mechanisms, would further decrease glycaemic control until diabetes develops. This interpretation would however appear incompatible with the observation that defective insulin secretion has been described in carriers of *TCF7L2* polymorphisms not only after oral glucose [3, 5–7], but also in the fasting state [8–10] or following intravenous glucose [11], circumstances in which incretin hormones play at most a minor role [33].

Instead, we would interpret the findings of Schäfer et al. [1] and other groups who have investigated the link between these polymorphisms and diabetes risk [15, 17] as indicating impaired signalling of GLP-1 via GLP-1 receptors at the level of endocrine pancreatic beta cells. Given the multiple effects of GLP-1 on several aspects of beta cell gene expression (e.g. insulin synthesis), neogenesis, proliferation, apoptosis and function (glucose competence, i.e. the ability to initiate insulin secretion at high glucose concentrations, recruitment of dormant beta cells) (Fig. 1), both during embryonic development and in adult islets, impaired GLP-1 signalling—as conferred by *TCF7L2* polymorphisms—could eventually lead to a reduced beta cell mass and a functional status compatible with our current view of the involvement of beta cells in the pathogenesis of type 2 diabetes (Fig. 1).

With this scheme in mind, it matters less that differences in insulin secretion between subjects with and without diabetogenic *TCF7L2* polymorphisms were sometimes detected after oral glucose stimulation [3, 5–7], and sometimes observed in fasting samples [8–10] or after intravenous glucose [11]. A possible sequence of events linking reduced GLP-1-receptor-mediated signalling to type 2 diabetes is depicted in Fig. 1.

In summary, this is the third [12, 16], but possibly not the last, commentary on *TCF7L2* polymorphisms to be published in *Diabetologia* this year. Schäfer et al. have made an important observation that will lead to further studies into the functional consequences of these polymorphisms. If their findings are confirmed, the incretins, and GLP-1 in particular, could be seen to play a central role in the pathophysiology of type 2 diabetes. Should this prove to be the case, we will need to view these molecules as a dog that not only barks, but bites.

**Duality of interest** The authors declare that there is no duality of interest associated with this manuscript.

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