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Common Genetic Variation Influences the Heterogeneity of Response to Oral Glucose

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Trial

Saxena R, Hivert MF, Langenberg C, et al.: Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge.

Rating

Of importance

Introduction

Type 2 diabetes is a disease that arises out of a complex interaction between genes and the environment. At present, most of the loci reproducibly associated with the disease have weak to moderate effects on disease predisposition (odds ratio ≤ 1.4). Although genome-wide association scans (GWAS) allow undirected scientific inquiry and have implicated unsuspected pathways in diabetes pathogenesis, they have required large case-control cohorts to reliably and reproducibly make these associations [1]. In addition to examination of discrete traits (diabetes vs no diabetes), analysis of quantitative traits such as fasting insulin may help elucidate variants that affect insulin secretion and action in response to standardized challenges such as a 75-g glucose drink. Pooling of large GWAS datasets with corresponding data from oral glucose tolerance testing should allow identification of novel loci that impact response to oral glucose [2].

Aims

The MAGIC (Meta-Analysis of Glucose and Insulin-Related Traits Consortium) has enabled pooling and combined analysis of large numbers of subjects with GWAS data to elucidate the contribution of common genetic variation to quantitative traits such as fasting glucose concentrations, 2-h glucose, and insulin concentrations irrespective of whether such loci are associated with type 2 diabetes.

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Methods

Nine GWAS were combined to give a cohort of 15,234 used as a discovery cohort to identify potential candidate single nucleotide polymorphisms (SNPs) for replication in a separate cohort of 17 GWAS ($n=30,620$). The discovery cohort identified 29 SNPs with a minor allele frequency ≥ 0.10 associated with 2-h glucose values with a P value below a prespecified threshold. These associations were subsequently tested independently in the replication cohort to allow independent validation.

Results

When adjusted for fasting glucose concentrations, variants in the *GIPR* locus were associated with a 0.11 ± 0.01 -mmol/L increase in 2-h glucose concentrations. Also of note, the same allele (A) at rs10423928 was associated with decreased postchallenge insulin concentrations whether expressed as an insulinogenic index, area under the curve of insulin concentrations divided by area under the curve of glucose concentrations, or 2-h insulin concentrations adjusted for 2-h glucose concentrations. In addition to *GIPR*, two other novel loci *VPS13C* and *ADCY5* were associated with 120-min insulin concentrations as well as glucose concentrations. *ADCY5* also affected fasting glucose concentrations and is also associated with type 2 diabetes. As expected from the known physiologic effects of *GIPR*, this variant did not alter response to intravenous glucose. Furthermore, in 804 nondiabetic individuals, an estimate of the incretin effect produced by comparing the responses to oral and intravenous glucose was also associated with rs10423928.

Discussion

Glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide (GIP) is secreted by the enteroendocrine K cells in the upper gastrointestinal tract and is part of the incretin system. At supraphysiologic concentrations it inhibits gastric acid secretion. However, it also stimulates insulin secretion in a glucose-dependent manner and is a mediator of the incretin effect. This refers to the increase in insulin secretion observed in response to oral glucose compared to that observed in response to intravenous glucose [3].

GIP is part of the hormonal component of the incretin system, although it has been thought to be of secondary importance compared with glucagon-like peptide-1 (GLP-1), which is secreted by L cells. Both hormones have short circulating half-lives due to their rapid degradation by dipeptidyl peptidase-4, an enzyme with wide distribution. A significant proportion of active hormone is degraded prior to entering the portal circulation and reaching the islets. For this reason, vagal and other neurohumoral interfaces are thought to be important in mediating the integrated incretin signal [4]. Intriguingly, type 2 diabetes is characterized by loss of β -cell responsiveness to GIP but not GLP-1, although differences in incretin secretion have not been reliably implicated in the pathogenesis of type 2 diabetes [3].

The current data is the first to suggest that decreased responsiveness to an endogenous incretin may be important in characterizing response to an oral glucose challenge. The variation in *GIPR* that altered response to oral glucose, however, was not associated with predisposition to type 2 diabetes. Impaired glucose tolerance (IGT) is strongly associated with progression to type 2 diabetes [5]. Nevertheless, not all subjects with IGT will develop type 2 diabetes—and this association may exemplify the genetic heterogeneity of IGT and type 2 diabetes. Also of note is the fact that other type 2 diabetes-associated genes such as *TCF7L2* may mediate their effects via the incretin pathway, with some suggestion that diabetes-associated genetic variation in *TCF7L2* alters responsiveness to GLP-1 and may mediate downregulation of incretin receptors on the β cell [6,7].

There are a few caveats to note with the current data. Insulin concentrations are decreased by the A allele of rs10423928, but this does not necessarily imply that insulin secretion was decreased. Peripheral concentrations of insulin reflect secretion, distribution through multiple compartments, and hepatic clearance. The insulinogenic index and other such qualitative measures of insulin secretion correlate poorly with acute insulin response. The other caveat is that differences in insulin response to an oral versus intravenous glucose challenge are a very crude estimate of incretin effect and do not account for potential differences in gastric volume and emptying mediated by incretin hormones that would be of relevance with a solid as opposed to a liquid meal challenge. Moreover, the correlation of this estimated incretin effect with *GIPR* was not consistent in all the cohorts in which this data was available.

Comments

The report that variations in an incretin receptor alter response to an oral glucose challenge is an important first step in using genetics to characterize the contribution of this system to the pathogenesis of type 2 diabetes. Although incretin-based therapy is available for the treatment of type 2 diabetes, better understanding of the physiology and variability of incretin responses is likely to lead to improved therapy for the disease.

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