OBSERVATIONS

Variation in the *CDKAL1* Gene Is Associated With the Titer of Antibodies to GAD

Genome-wide association studies have described new diabetes susceptibility genes including *TCF7L2*, *CDKAL1*, *HHEX*, *SLC30A8*, *CDKN2A/B*, and *IGF2BP2* (1). Most of these novel risk loci are associated with impaired β-cell function (2). Impaired β-cell function due to autoimmune processes plays a role in the pathogenesis of type 1A diabetes and latent autoimmune diabetes in adults. Therefore, it is conceivable that some of the susceptibility genes may be related to autoimmunity and inflammation leading to β-cell dysfunction. This hypothesis was recently excluded for the variation in the *TCF7L2* gene, which was not found to be associated with type 1 diabetes.

We investigated whether there is a relationship between the GAD antibody (GADA) titers, risk markers for autoimmune diabetes, and the above-mentioned susceptibility genes using data obtained from a nondiabetic German population with increased risk of type 2 diabetes. In total, 1,362 subjects (aged 39 ± 1 year, 464 male and 898 female, BMI 28.4 ± 0.2 kg/m^2, 120-min glucose 6.2 ± 0.1, 1,118 normal glucose tolerant and 244 impaired glucose tolerant) were genotyped as previously described (2), and GADA titers for each subject were measured with a radio-immunoassay (MEDIPAN, Berlin, Germany). A GADA titer >0.8 units/ml was considered to be positive according to the specifications of the manufacturer.

We found no effects of *TCF7L2*, *HHEX*, *SLC30A8*, *CDKN2A/B*, and *IGF2BP* on GADA titers in the nonparametric test (all $P > 0.05$). However, the homo- and heterozygous risk allele carriers of *CDKAL1* rs7754840 had higher GADA titers (range <0.1–18.8 units/ml, GG 0.20 ± 0.01 units/ml [$n = 618$], GC 0.31 ± 0.04 units/ml [$n = 596$], CC 0.33 ± 0.08 units/ml [$n = 148$], $P = 0.014$). A contingency analysis showed that C-allele carriers more frequently had GADA titers >0.8 units/ml (GG 0.5%, GC 3.5%, and CC 4.1% GADA positive, $P = 0.0004$). Exclusion of subjects with impaired glucose tolerance did not alter the results. We calculated first-phase insulin secretion from plasma glucose and insulin during the oral glucose tolerance test using a validated index and confirmed the decreased insulin secretion on the risk allele carriers of the *CDKAL1* allele in the present population ($P = 0.0057$).

The function of the *CDKAL1* gene is unknown; its protein product shares protein domain and amino acid sequence homology with CDK5 regulatory subunit–associated-protein-1, a neuronal protein that inhibits activation of Cyclin-dependent kinase-5 (3). *CDKAL1* is expressed in human pancreatic islets. It is known that variation in the *CDKAL1* gene is associated with immune-mediated disorders (4). Thus, *CDKAL1* may play an important role in inflammation and immune processes.

The underlying mechanisms linking *CDKAL1*, GADA, and insulin secretion are at present unclear. A recent case-control study found no association of variation in *CDKAL1* with type 1 diabetes (5). However, this does not exclude the possibility that variation in *CDKAL1* is associated with the presence of low-level β-cell autoimmunity leading to limited insulin-secretory capacity in type 2 diabetes or latent autoimmune diabetes in adults.

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