

Variance of the SGK1 Gene Is Associated with Insulin Secretion in Different European Populations: Results from the TUEF, EUGENE2, and METSIM Studies

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Abstract

Hypothesis: Serum- and Glucocorticoid-inducible Kinase 1 (SGK1) is involved in the regulation of insulin secretion and may represent a candidate gene for the development of type 2 diabetes mellitus in humans.

Methods: Three independent European populations were analyzed for the association of SGK1 gene (*SGK*) variations and insulin secretion traits. The German TUEF project provided the screening population (N=725), and four tagging SNPs (rs1763527, rs1743966, rs1057293, rs9402571) were investigated. EUGENE2 (N=827) served as a replication cohort for the detected associations. Finally, the detected associations were validated in the METSIM study, providing 3798 non-diabetic and 659 diabetic (type 2) individuals.

Results: Carriers of the minor G allele in rs9402571 had significantly higher C-peptide levels in the 2 h OGTT (+10.8%, $p=0.04$; dominant model) and higher $AUC_{C-peptide}/AUC_{Glc}$ ratios (+7.5%, $p=0.04$) compared to homozygous wild type TT carriers in the screening population. As interaction analysis for BMI \times rs9402571 was significant ($p=0.04$) for the endpoint insulin secretion, we stratified the TUEF cohort for BMI, using a cut off point of BMI = 25. The effect on insulin secretion only remained significant in lean TUEF participants (BMI \leq 25). This finding was replicated in lean EUGENE2 rs9402571 minor allele carriers, who had a significantly higher AUC_{Ins}/AUC_{Glc} (TT: 226 ± 7 , XG: 246 ± 9 ; $p=0.019$). Accordingly, the METSIM trial revealed a lower prevalence of type 2 diabetes (OR: 0.85; 95%CI: 0.71–1.01; $p=0.065$, dominant model) in rs9402571 minor allele carriers.

Conclusions: The rs9402571 *SGK* genotype associates with increased insulin secretion in lean non-diabetic TUEF/EUGENE2 participants and with lower diabetes prevalence in METSIM. Our study in three independent European populations supports the conclusion that *SGK* variability affects diabetes risk.

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Introduction

Type 2 diabetes arises when insulin resistance cannot be compensated for with increased insulin secretion owing to a gradual loss of pancreatic beta-cell function [1]. Recently, genome-wide association studies have been undertaken to further investigate the genetic background of type 2 diabetes, revealing that many high risk alleles are located within genes that are linked

to beta cell function, including TCF7L2 [2,3,4], CDKAL1 [5,6,7,8], SLC30A8 [5,9,10], IGF2BP2 [5], HHEX/IDE [6,9,11,12], and CDKN2A/B [13]. Our study therefore focuses on genes that play a role in insulin secretion, using a classical candidate-gene approach.

One interesting candidate for the regulation of insulin secretory function is the serum and glucocorticoid inducible kinase SGK1, which is a ubiquitously expressed serine-threonine kinase in