

Association of Common Genetic Variation in the *FOXO1* Gene with β -Cell Dysfunction, Impaired Glucose Tolerance, and Type 2 Diabetes

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Context: The transcription factor forkhead box protein (FOX) O1A plays a crucial role in regulation of β -cell function and metabolic effects of insulin in the liver.

Objective: The objective of the study was to investigate whether common genetic variation within the *FOXO1* gene encoding FOXO1A contributes to prediabetic phenotypes, such as insulin resistance or β -cell dysfunction, and to risk of type 2 diabetes.

Design and Settings: Study I was a study enrolling thoroughly phenotyped subjects from Germany at increased risk for type 2 diabetes. Study II was a population-based study of Finnish men for the assessment of the prevalence of type 2 diabetes and metabolic syndrome.

Participants: Study I included 941 nondiabetic subjects (353 males, 588 females, aged 39 ± 1 yr, body mass index 29.2 ± 0.3 kg/m²). Study II included 5957 middle-aged men (870 type 2 diabetic and 5087 nondiabetic subjects).

Interventions: Genotyping for 10 single-nucleotide polymorphisms (SNPs) covering 100% of common genetic variation (minor allele frequency $\geq 10\%$) within the *FOXO1* gene ($r^2 \geq 0.8$) based on HapMap data, oral glucose tolerance test, and in a subset additionally a hyperinsulinemic-euglycemic clamp.

Main Outcome Measurements: Parameters of insulin secretion, insulin resistance, and glucose tolerance status were measured.

Results: In the German subjects at increased risk for type 2 diabetes, SNPs rs2721068 and rs17446614 were significantly ($P = 0.0045$ and $P = 0.0018$, respectively) and SNPs rs17446593 and rs2297627 were nominally ($P = 0.0091$ and $P = 0.0387$, respectively) associated with β -cell dysfunction. rs2721068, rs17446614, and rs2297627 were also nominally associated with impaired glucose tolerance ($P = 0.0264$, $P = 0.0162$, and $P = 0.0221$, respectively). Minor allele carriers showed reduced insulin secretion and elevated glucose levels during an oral glucose tolerance test. Investigating the relevance of our findings in a separate cohort, we found that SNP rs2721068 was significantly associated with type 2 diabetes in the additive ($P = 0.002$) and dominant model ($P = 0.009$) in Finnish men.

Conclusions: Common genetic variation within the *FOXO1* gene affects insulin secretion and glucose tolerance and associates with an increased risk of type 2 diabetes. (*J Clin Endocrinol Metab* 94: 1353–1360, 2009)