

A Candidate Type 2 Diabetes Polymorphism Near the *HHEX* Locus Affects Acute Glucose-Stimulated Insulin Release in European Populations

Results from the EUGENE2 study

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OBJECTIVE—In recent genome-wide association studies, two single nucleotide polymorphisms (SNPs) near the *HHEX* locus were shown to be more frequent in type 2 diabetic patients than in control subjects. Based on *HHEX*'s function during embryonic development of the ventral pancreas in mice, we investigated whether these SNPs affect β -cell function in humans.

RESEARCH DESIGN AND METHODS—A total of 854 nondiabetic subjects, collected from five European clinical centers, were genotyped for the *HHEX* SNPs rs1111875 and rs7923837 and thoroughly characterized by an oral glucose tolerance test (OGTT). To assess glucose-stimulated insulin release, a subgroup of 758 subjects underwent an intravenous glucose tolerance test (IVGTT).

RESULTS—SNPs rs1111875 and rs7923837 were not associated with anthropometric data (age, weight, height, BMI, body fat, and waist and hip circumference). After adjustment for center, family relationship, sex, age, and BMI, both SNPs were also not associated with glucose and insulin concentrations in the fasting state and during the OGTT or with measures of insulin sensitivity. Furthermore, *HHEX* SNP rs1111875 was not associated with insulin release during the IVGTT. By contrast, the minor A-allele of *HHEX* SNP rs7923837 was significantly associated with higher IVGTT-derived first-phase insulin release before and after appropriate adjustment ($P = 0.013$ and $P = 0.014$, respectively).

CONCLUSIONS—A common genetic variation in the 3'-flanking region of the *HHEX* locus, i.e., SNP rs7923837, is associated with

altered glucose-stimulated insulin release. This SNP's major allele represents a risk allele for β -cell dysfunction and, thus, might confer increased susceptibility of β -cells toward adverse environmental factors. *Diabetes* 57:514–517, 2008

Type 2 diabetes is the most prevalent metabolic disease of the Western industrialized world. It is generally agreed that type 2 diabetes is caused by environmental factors, such as high-caloric diet and reduced physical activity, and a polygenic background that confers increased susceptibility toward these environmental challenges (1). To identify the genes involved in the pathogenesis of type 2 diabetes, genome-wide association studies in several cohorts based on large-scale single nucleotide polymorphism (SNP) analysis of genomic variation were recently published (2–7). These studies revealed 10 potential type 2 diabetes candidate genes. Three formerly characterized genes with known effects on insulin sensitivity or insulin secretion, respectively, i.e., *PPARG*, *KCNJ11*, and *TCF7L2*, could be confirmed. However, the role of the other seven candidate genes in the development of pre-diabetes phenotypes, such as insulin resistance and β -cell dysfunction, is not well established. Two of the type 2 diabetes candidate SNPs are located in the 3'-flanking region of the *HHEX* locus (2). *HHEX* encodes the transcription factor hematopoietically expressed homeobox protein (HHEX), which is expressed in the embryonic ventral-lateral foregut that gives rise to the ventral pancreas and the liver (8). Knockout of this gene was shown to impair proliferation of endodermal epithelial cells, positioning of ventral foregut endoderm cells relative to the mesoderm, and budding and morphogenesis of the ventral pancreas (8). This genetic manipulation finally provoked lethality during midgestation (8). Due to these developmental defects of the *HHEX* knockout, it was obvious to investigate whether the two reported type 2 diabetes candidate SNPs near the *HHEX* locus (2) affect β -cell function. This was therefore assessed in five nondiabetic European populations thoroughly characterized by an intravenous glucose tolerance test (IVGTT).

RESEARCH DESIGN AND METHODS

A total of 844 nondiabetic subjects were recruited from the five European clinical centers constituting the EUGENE2 consortium, i.e., the Lundberg Laboratory for Diabetes Research (Göteborg, Sweden), the Polyclinic Mater Domini of the University Magna Graecia (Catanzaro, Italy), the Steno Diabetes

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HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test; IVGTT, intravenous glucose tolerance test; SNP, single nucleotide polymorphism.

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