Brief Genetics Report

Genetic Variation of the GLUT10 Glucose Transporter (*SLC2A10*) and Relationships to Type 2 Diabetes and Intermediary Traits

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The *SLC2A10* gene encodes the GLUT10 facilitative glucose transporter, which is expressed in high amounts in liver and pancreas. The gene is mapped to chromosome 20q12-q13.1, a region that has been shown to be linked to type 2 diabetes. The gene was examined in 61 Danish type 2 diabetic patients, and a total of six variants (−27C→T, Ala206Thr, Ala272Ala, IVS2 + 10G→A, IVS4 + 18T→G, and IVS4 + 26G→A) were identified and investigated in an association study, which included 503 type 2 diabetic patients and 510 glucose-tolerant control subjects. None of the variants were associated with type 2 diabetes. Interestingly, carriers of the codon 206 Thr allele had 18% lower fasting serum insulin levels ($P = 0.002$) and 20% lower insulinogenic index ($P = 0.03$) than homozygous carriers of the Ala allele. These results suggest that variation in the coding region of *SLC2A10* does not contribute substantially to the pathogenesis of type 2 diabetes in the examined study population. However, the codon 206 polymorphism may be related to the interindividual variation in fasting and oral glucose–induced serum insulin levels. *Diabetes* 52:2445–2448, 2003

The recently cloned *SLC2A10* gene encodes a 541 amino acid putative facilitative glucose transporter (GLUT10) of the GLUT family class III with between 30 and 34% amino acid homology with the known GLUT proteins (1,2). The *SLC2A10* gene contains five exons and spans a genomic region of at least 28 kb. Northern hybridization analysis indicates highest levels of expression in liver and pancreas (2). When expressed in Xenopus oocytes, human GLUT10 exhibited 2-deoxy-D-glucose transport with an apparent K_m of ~0.3 mmol/l (3). Given the function of GLUT10 as a member of the GLUT family of facilitative glucose transporters, the tissue distribution, and the fact that *SLC2A10* is mapped to a chromosomal region 20q12-q13.1 (spanned by markers D20S119 and D20S197), which in several studies (4–8) has shown linkage to type 2 diabetes (logarithm of odds score peak is located at D20S195 within *SLC2A10*), we hypothesized that variation in *SLC2A10* may confer increased susceptibility to type 2 diabetes or altered circulating insulin levels. Thus, this study reports the results of a mutation analysis of the coding region of the *SLC2A10* gene and the identification of six novel single nucleotide polymorphisms. The mutation screening covered the coding (translated) region of *SLC2A10* and an additional 128 bp upstream from the translation initiation site (ATG). In the 61 diabetic patients, we identified a total of six different nucleotide variants: −27C→T (relative to the ATG site, identified in 2 of 61 patients), Ala206Thr (nucleotide position 616: GCC→ACC, 2 patients), Ala272Ala (816: GCC→GCG, 1 patient), IVS2 + 10G→A (5 patients), IVS4 + 18T→G (37 patients), and IVS4 + 26G→A (1 patient). These variants were further examined in a case-control study comprising 503 type 2 diabetic patients and 510 (or 231, see "Subjects") glucose-tolerant subjects. The allele frequencies and genotype distributions of the variants did not differ significantly between diabetic and nondiabetic subjects (Table 1). The degree of linkage disequilibrium between pairs of the variants was estimated; however, there was no evidence of linkage between these single nucleotide polymorphisms (R^2 values between 0 and 0.03). The distance between −27C→T and Ala206Thr is ~15 kb, and the IVS2 + 10G→A variant is located 682 base pairs further downstream. The distance from IVS2 + 10G→A to IVS4 + 18T→G is ~3 kb. The lack of linkage disequilibrium between the variants is unexpected. However, given the relatively long distance between these markers, this may be due to the presence of a hotspot recombination site. Furthermore, the low frequency of the mutant alleles makes it likely that they are located in separate haplotype blocks. The Ala272Ala and the IVS4 + 26G→A variants were each identified in only one diabetic patient participating in the initial mutation

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AUC, area under the curve; HNF, hepatic nuclear factor; OGTT, oral glucose tolerance test; PTP-1B, protein tyrosine phosphatase-1B; RG, restriction-site generating.

TABLE 1
Genotype and allele frequencies of the examined variants in *SLC2A10* among type 2 diabetic patients and glucose-tolerant subjects

	Type 2 diabetic patients	Glucose-tolerant subjects	P_{AF}	P_{GD}
−27C→T				
C/C	466 (97)	488 (98)		
C/T	13 (3)	12 (2)		
T/T	0 (0)	0 (0)		
Allele frequency	1.4 (0.6–2.1)	1.2 (0.5–1.9)	0.8	0.8
Ala206Thr				
Ala/Ala	455 (91)	469 (92)		
Ala/Thr	42 (8)	36 (7)		
Thr/Thr	2 (0)	2 (0)		
Allele frequency	4.6 (3.3–5.9)	3.9 (2.7–5.1)	0.5	0.8
IVS2 + 10G→A				
G/G	450 (96)	474 (97)		
G/A	20 (4)	15 (3)		
A/A	1 (0)	1 (0)		
Allele frequency	2.3 (1.4–3.3)	1.7 (0.9–2.6)	0.4	0.7
IVS4 + 18T→G				
T/T	162 (33)	174 (40)		
T/G	248 (50)	190 (43)		
G/G	85 (17)	73 (17)		
Allele frequency	42.2 (39.1–45.3)	38.4 (35.2–41.7)	0.1	0.07

Data are number of subjects with each genotype (% of each group) and allele frequencies of minor allele in % (95% CI). The *P* values compare allele frequencies (P_{AF}) and genotype distributions (P_{GD}) between type 2 diabetic patients and glucose-tolerant subjects. All genotype groups obeyed Hardy-Weinberg equilibrium.

screening. Genotyping of these variants in a total of 734 (503 diabetic and 231 normal glucose-tolerant) subjects revealed no additional carriers. Since one mutation is silent and the other is located in an intronic region, we consider them to be insignificant in the present context. None of the two mutation carriers had anthropometrical or biochemical variables different from the values of the noncarriers.

In a preliminary phenotype-genotype association study ($n = 231$) the −27C→T variant was associated with higher concentrations of plasma glucose among carriers of the T-allele ($P = 0.03$ for fasting and 60-min values, data not shown). However, these findings were not replicated in an additional study sample ($n = 279$, data not shown), therefore we regard them as chance findings. Furthermore, we observed that T-allele carriers tended to have higher fasting serum insulin in each sample of normal glucose-tolerant subjects and when combining the two study groups ($P = 0.03$, data not shown). Also in the initial study, the A-allele of the IVS2 + 10G→A variant was associated with lower serum insulin concentrations ($P = 0.03$, 0.02, and 0.03 for fasting, 30-min, and 60-min values, respectively, as well as for the area under the insulin curve [AUC] [$P = 0.02$]) both with and without adjustment for corresponding plasma glucose concentrations. None of these findings were replicated in the subsequent phenotype study or when combining the two groups of unrelated subjects (data not shown). The IVS4 + 18T→G variant was not associated with any of the measured diabetes-related phenotypes. The Thr allele of the Ala206Thr polymorphism was associated with lower fasting serum insulin concentrations both with and without adjustment for fasting plasma glucose levels and also with lower insulinogenic index (Table 2). This was also the case for the post–oral glucose tolerance test (OGTT) levels, and after adjustment for corresponding glucose concentrations, the *P* values ranged from between 0.004 (fasting serum insulin) and 0.06 (60-min serum insulin). No differences in plasma glucose values were observed in the three genotype groups.

There are numerous reports on type 2 diabetes linkage peaks to a 20-cM region of chromosome 20q12-q13.1 (4–8), which harbors the genes encoding hepatic nuclear factor *(HNF)-4α* (EMBL#NM_000457) and protein tyrosine phos-

TABLE 2
Anthropometric and metabolic characteristics of 510 glucose-tolerant Danish white subjects stratified according to *SLC2A10* Ala206Thr genotype

Ala206Thr	Ala/Ala	Ala/Thr + Thr/Thr	*P*
n (men/women)	469 (217/252)	38 (20/18)	
Age (years)	56 ± 10	58 ± 9	
BMI (kg/m^2)	25.7 ± 3.7	26.0 ± 3.4	0.8
Plasma glucose			
Fasting (mmol/l)	5.1 ± 0.4	5.0 ± 0.4	0.2
30-min post-OGTT (mmol/l)	7.7 ± 1.4	7.8 ± 1.4	1.0
60-min post-OGTT (mmol/l)	7.5 ± 1.9	7.4 ± 2.1	0.6
120-min post-OGTT (mmol/l)	5.4 ± 1.2	5.5 ± 1.2	0.7
Post-OGTT AUC (min · mmol/l)	195 ± 119	206 ± 131	0.8
Serum insulin			
Fasting (pmol/l)	39 ± 19	32 ± 17	0.002
30-min post-OGTT (pmol/l)	261 ± 148	217 ± 122	0.03
60-min post-OGTT (pmol/l)	310 ± 194	276 ± 217	0.05
120-min post-OGTT (pmol/l)	183 ± 123	163 ± 117	0.2
Post-OGTT AUC (min · pmol/l)	23,021 ± 12,933	20,397 ± 14,358	0.04
Insulinogenic index	29.0 ± 17.9	23.2 ± 11.8	0.03

Data are means ± SD. Values of insulin or values derived from insulin were logarithmically transformed before statistical analysis. Calculated *P* values were adjusted for age, sex, and BMI and were calculated assuming a dominant model for the penetrance of the Thr allele. The insulinogenic index was calculated as fasting serum insulin (pmol/l) subtracted from 30-min post-OGTT serum insulin (pmol/l) and divided by 30-min post-OGTT plasma glucose (mmol/l).

TABLE 3
Primer sequences and PCR conditions for mutation analysis of *SLC2A10*

Primer	Sequence, 5′→3′	Location	T_{anneal} (°C)	$MgCl_2$ (mmol/l)
G10F1.1*	AGG GCA GGA GGG ACA GAG	exon 1	55	1
G10R1.1*	CAC CCG AGA GGC GGT ATC			
G10F2.1	GGA TGG TAT GAC AAG GAA CCA	exon 2	55	2
G10R2.1	CAA GTT GCT CCC GAG GAT G			
G10F2.2	GGT GGC TTC CTC ATT GAC TG	exon 2	55	3
G10R2.2	ATC CCC AGG GGG TAC CAG			
G10F2.3	TGC TCT CCT ATG CCC TCA AC	exon 2	55	2
G10R2.3	GCT GCC CTG TTA GTT GCT G			
G10F2.4	CAG GGC ACG CGA TAA CAT	exon 2	55	2
G10R2.4	CAC GGC AAA GCT GAC GAG			
G10F2.5	TCT GTT GCT AGC TGG CTG TG	exon 2	55	2
G10R2.5	GGC TGA GGG GTC TCC AGA T			
G10F2.6	AGC CAA TCT TGT CCA CTG CT	exon 2	55	2
G10R2.6	ACC CTG CCA GGT CAT CAG			
G10F3.1	GAA AAT CCC ATT GTT GAG AGG	exon 3	55	1
G10R3.1	TGC TTT AGA GTA GGG AGC TTG G			
G10F4.1	TCC ATG CCT GAC CTA GAA CC	exon 4	55	2
G10R4.1	AAA ATC CTG AAG CTG TGT GC			
G10F5.1	GAA CCC CAG TGG AAG GTC	exon 5	55	2
G10R5.1	CAG CAA AAG CAG ACC ACC T			

*When amplifying exon 1 (using primers G10F1.1 and G10R1.1), 7.5% DMSO was included in the reaction mix.

phatase-1B (PTP-1B) (EMBL#AY029236). Mutations in HNF-4α are responsible for the rare maturity-onset diabetes of the young subtype 1 (9); however, among late-onset type 2 diabetic patients, variability in the coding region of *HNF-4α* is rare and no mutations in this gene have been reproducibly associated with the common forms of type 2 diabetes (10,11). Recently, a Pro387Leu substitution was identified in PTP-1B and was associated with type 2 diabetes in the Danish population (12). Even though the Pro387Leu variant is associated with a genotype relative risk of 3.7, it is rare (allele frequency 1.4% among diabetic patients). Therefore, additional genetic variability in this chromosomal region might well account for most of the observed linkage to type 2 diabetes. The *SLC2A10* gene encoding the facilitative glucose transporter protein GLUT10 at chromosome 20q13.1 was chosen as a diabetes candidate gene due to its genomic position, the abundant expression in pancreas and liver, and the demonstration of the function of GLUT10 as a transporter of 2-deoxy-D-glucose transport in vitro (3). The present mutation analysis of *SLC2A10* resulted in the identification of a total of six novel genetic variants, of which one predicted an amino acid substitution in the GLUT10 protein. None of the identified variants were associated with type 2 diabetes in studies of allele frequency differences or genotype distributions. Even though this may be due to the low frequency of most of the identified variants and the resulting relatively low power to detect differences, we conclude that variation of *SLC2A10* is not a major contributor to the etiology of type 2 diabetes in the examined population. For two of the identified variants (−27C→T and IVS2 + 10G→A) we observed some inconsistent phenotype associations, which could not be replicated in our additional genotype-phenotype studies. Intriguingly, we found that the Thr allele of the codon 206 polymorphism was associated with 18% lower fasting serum insulin levels and 20% lower insulinogenic index. GLUT10 is abundantly expressed in pancreas, and the observed decrease in fasting and post-OGTT serum insulin may be due to a mild β-cell defect, resulting in impaired insulin secretion. Furthermore, we examined the effect of the Thr allele on insulin resistance estimated by the homeostasis model assessment and observed no differences between the genotype groups. The lack of association with the diabetes phenotype per se can most likely be ascribed to the low allelic frequency and to type 2 diabetes being a heterogeneous disease resulting from multiple defects other than low insulin secretion.

GLUT10 contains 12 transmembrane helices with a hydrophilic intracellular loop between the predicted helices 6 and 7 (2), which has a surprising lack of a PESPR (proline, glutamate, serine, and arganine) motif otherwise present in not only all other members of the GLUT family but also in the organic cation transport facilitators (1). The Ala206Thr substitution is located within this intracellular loop, and its functional significance is not clear. Threonine is generally regarded as much more reactive than alanine, and this amino acid substitution therefore might be of importance to the function of the GLUT10 protein. If the present finding can be replicated in independent studies, functional in vitro studies are needed to clarify whether this variant itself is functional or if it should be considered a marker for an unknown causative variant with which it is in linkage disequilibrium. In summary, even though none of the GLUT10 variants identified in the present study point toward a substantial relationship between *SLC2A10* and type 2 diabetes, the Ala206Thr substitution or a linked, as-yet-unidentified causal genetic variant may contribute to a lower serum insulin level.

RESEARCH DESIGN AND METHODS

Subjects. Mutation analysis was performed in 61 type 2 diabetic patients (36 men and 25 women) recruited from the outpatient clinic at Steno Diabetes

Center. The patients were aged 62 ± 11 years (mean ± SD), age of diagnosis 54 ± 10 years, BMI 29.9 ± 4.8 kg/m^2, and HbA_{1c} 8.1 ± 1.7%. The case-control study was performed in unrelated type 2 diabetic patients recruited from Steno Diabetes Center and in unrelated normal glucose-tolerant subjects sampled at random during 1994–1997 at Steno Diabetes Center (231 subjects) and Copenhagen County Center of Preventive Medicine (279 subjects) (13). In the group of diabetic patients (n = 503, 292 men and 211 women) mean age was 61 ± 11 years, age of diagnosis 55 ± 11 years, BMI 29.0 ± 5.2 kg/m^2, and HbA_{1c} 8.0 ± 1.6%. The patients were treated with diet alone (27%), with oral hypoglycemic agent (58%), or with insulin alone or in combination with oral hypoglycemic agent (15%). In the group of glucose-tolerant subjects (n = 510, 238 men and 272 women) mean age was 57 ± 10 years and BMI 25.7 ± 3.7 kg/m^2. Two variants (Ala272Ala and IVS4 + 26G→A) were genotyped in only one subgroup (n = 231) of the glucose-tolerant control subjects due to low allelic frequencies. Diabetes was diagnosed according to 1999 World Health Organization criteria (14). All control subjects underwent a standard 75-g OGTT. All participants were Danish white subjects by self-report. Informed written consent was obtained from all subjects before participation. The study was approved by the Ethical Committee of Copenhagen and was in accordance with the principles of the Declaration of Helsinki.

Biochemical assays. Blood samples for measurement of concentrations of serum insulin and plasma glucose were drawn after a 12-h overnight fast. The plasma glucose and serum-specific insulin levels and HbA_{1c} were measured as described elsewhere (15).

Mutation analysis and genotyping. The coding region of *SLC2A10* (EMBL#AL031055/AF321240), including intron-exon boundaries (2,385 bp in total), was divided into 10 segments (sized 262–300 nucleotides) for combined single-strand conformational polymorphism and heteroduplex analysis performed as described elsewhere (16). PCR amplification was carried out as described (15) with primer sequences, $MgCl_2$ concentration, and annealing temperatures as listed in Table 3. Aberrantly migrating samples were sequenced using fluorescent chemistry (MWG-Biotech AG, Ebersberg, Germany). The −27C→T variant was genotyped by restriction fragment–length polymorphism-PCR (1 mmol/l $MgCl_2$, T_{anneal} 60°C, and 7.5% DMSO) with primers G10F1.1 and G10R1.1 (Table 3) followed by digestion with *Dde*I. The Ala206Thr variant was genotyped (1 mmol/l $MgCl_2$, T_{anneal} 52°C, and 7.5% DMSO) with forward primer 5′-GGG CAT CCT GCT CTC CTA T-3′ and reverse primer 5′-CCG GGC CCA GCT TGG GGG-3′ followed by digestion with *Hae*III. The Ala272Ala variant was genotyped using restriction-site generating (RG) PCR (2 mmol/l $MgCl_2$, T_{anneal} 68°C, and 7.5% DMSO) with upstream primer 5′-GAG CAA CTT GGT GCT GCT G-3′ and downstream RG primer 5′-CTG CGC CAA GCC CCA CAG *G*-3′ (mismatched nucleotide is italicized) followed by digestion with *Hha*I. The IVS2 + 10G→A variant was genotyped (3 mmol/l $MgCl_2$ and T_{anneal} 65°C) with primers 5′-TGT CTG GCT GTG CCC AAT T-3′ and 5′-ACC CTG CCA GGT CAT CAG-3′ followed by digestion with *Tsp*509I. The IVS4 + 18T→G variant was genotyped using single-strand conformational polymorphism with conditions as described (Table 3). The IVS4 + 26G→A variant was genotyped (2 mmol/l $MgCl_2$ and T_{anneal} 55°C) using primers G10F4.1 and G10R4.1 followed by digestion with *Mnl*I. All restriction enzyme digests were separated on 4% agarose gels and visualized by ethidium-bromide staining.

Statistical analysis. Fisher's exact test was applied to examine differences in allele frequencies and genotype distributions between diabetic and nondiabetic subjects. A general linear model was used to test variables (or transformed variables) for differences between genotype groups in the two samples of unrelated subjects. Genotype and sex were considered as fixed factors and age and BMI as covariates. All phenotype analyses were performed using SPSS version 11.0 (Chicago, IL). $P < 0.05$ was considered significant. Protein and nucleotide sequence alignments were performed using ClustalW, EMBL-EBI, 2002. Linkage disequilibrium was estimated as R^2, where $R^2 = 1$ in the case of complete linkage and $R^2 = 0$ in the case of no linkage. R^2 was calculated as described at www.biostat.ku.dk/~ce/programs.html.

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