Common Type 2 Diabetes Risk Gene Variants Associate with Gestational Diabetes

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Objective: We aimed to examine the association between gestational diabetes mellitus (GDM) and 11 recently identified type 2 diabetes susceptibility loci.

Research Design and Methods: Type 2 diabetes risk variants in TCF7L2, CDKAL1, SLC30A8, HHEX/IDE, CDKN2A/2B, IGF2BP2, FTO, TCF2, PPARG, KCNJ11, and WFS1 loci were genotyped in a cohort of women with a history of GDM (n = 283) and glucose-tolerant women of the population-based Inter99 cohort (n = 2446).

Results: All the risk alleles in the 11 examined type 2 diabetes risk variants showed an odds ratio (OR) greater than 1 for the GDM group compared with the control group ranging from 1.13 [95% confidence interval (CI) 0.88–1.46] to 1.44 (95% CI 1.19–1.74) except for the WFS1 rs10010131 variant with OR 0.87 (95% CI 0.73–1.05). Combined analysis of all 11 variants showed a highly significant additive effect of multiple risk alleles on risk of GDM [OR 1.18 (95% CI 1.10–1.27)] per risk allele, $P = 3.2 \times 10^{-6}$). Applying receiver-operating characteristic showed an area under the receiver-operating characteristic curve of 0.62 for the genetic test alone and 0.73 when combining information on age, body mass index, and genotypes of the 11 gene variants.

Conclusions: The prevalence in a prior GDM group of several previously proven type 2 diabetes risk alleles equals the findings from association studies on type 2 diabetes. This supports the hypothesis that GDM and type 2 diabetes are two of the same entity. **(*J Clin Endocrinol Metab* 94: 145–150, 2009)**

Gestational diabetes mellitus (GDM) is defined as an abnormal glucose tolerance diagnosed for the first time in pregnancy (1) and complicates 2–3% of Danish pregnancies (2). GDM is an important predictor for later development of type 2 diabetes (3), and we have previously found that 40% of a Nordic Caucasian cohort of women with prior diet-treated GDM had developed overt diabetes (89% type 2 diabetes) at a median of 10 yr after pregnancy (4). The majority of women with prior GDM is obese and insulin resistant and has a relatively impaired insulin secretion thereby resembling the pathogenesis of type 2 diabetes (5).

The epidemic increase in type 2 diabetes has called for extensive scientific exploration in the pathogenesis for type 2 diabetes. Recently candidate gene studies and genome-wide association studies have successfully identified several variants in previously unknown genomic regions to be associated with type 2 diabetes, impaired insulin response, and obesity (6–17). The type 2 diabetes risk variants are located both in biological candidate and noncandidate genes. The pathophysiologic role of some of the risk alleles is through the WNT signaling pathway involved in cell proliferation and normal embryogenesis including the development of the pancreas (18). Impaired β-cell func-

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Abbreviations: AUC, Area under the curve; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; OR, odds ratio; ROC, receiver-operating characteristic.

tion (*KCNJ11*, *WFS1*, *CDKAL1*, *SLC30A8*, *HHEX/IDE*, *CDKN2A/B*, *IGF2BP2*), insulin resistance (*PPARG*), and obesity (*FTO*) are major pathophysiological traits associated with variants in type 2 diabetes susceptibility loci (11, 19–22). These traits are also found in women with current or prior GDM (5, 23). The strongest known type 2 diabetes association is found with variants in *TCF7L2* (14), and two variants in *TCF7L2*, rs7903146 and rs12255372, associate with GDM (24, 25). In one study, the rs12255372 variant was found to interact with percentage of body fat to alter insulin secretion (25).

Besides the studies of *TCF7L2* and studies regarding monogenic forms of diabetes such as maturity-onset diabetes of the young, little is known about the genetic background of GDM. Because GDM often progresses to type 2 diabetes, we aimed at testing association of variants in 11 genomic regions recently shown to be associated with type 2 diabetes (*PPARG*, *KCNJ11*, *TCF7L2*, *CDKAL1*, *SLC30A8*, *CDKN2A/2B*, *HHEX/IDE*, *IGF2BP2*, *TCF2*, *WFS1*, and *FTO*) with GDM and incident post-GDM type 2 diabetes. Furthermore, we tested the combined additive effect of all type 2 diabetes susceptibility alleles on risk of GDM and performed receiver-operating characteristic (ROC) curves to assess the discriminative accuracy of these genetic variants.

Subjects and Methods

Subjects

The study population consisted of 283 women with previous GDM who were admitted to the Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, Denmark, during 1978–1996 and who had participated in a follow-up study during 2000–2002.

Women selected for the present study were Danish Caucasians by self-identification and were not diagnosed with type 1 diabetes or maturity-onset diabetes of the young (n = 32). Mean age was 43.1 yr [95% confidence interval (CI) 42.3–44.0] and body mass index (BMI) 28.9 kg/m^2 (95% CI 28.1–29.7). Women with GDM in the years 1978–1985 were diagnosed by a 3-h, 50-g oral glucose tolerance test (OGTT) (26), whereas women with GDM in 1987–1996 were diagnosed by a 3-h, 75-g OGTT (27). Women with GDM were routinely offered an OGTT 2 months postpartum and subsequently with 1- to 2-yr intervals, unless diabetes was diagnosed. At inclusion in the study, women without known diabetes (n = 236) underwent a 75-g OGTT after an overnight fast (10 h) with measurements of venous plasma glucose. Women reporting known diabetes (n = 47) had measurements of fasting levels of plasma glucose only. The OGTT was evaluated in accordance with the World Health Organization criteria from 1999 (28): normal glucose tolerance was found in 106 (37.4%), 75 (26.5%) had impaired fasting glucose or impaired glucose tolerance, 55 (19.5%) had diabetes diagnosed at follow-up, and 47 (16.6%) had known diabetes at enrollment.

The control group consisted of 2446 middle-aged glucose-tolerant Danish women from the population-based Inter99 cohort (clinicaltrials.gov, ID no. NCT00289237) (29, 30). Mean age was 45.2 yr (95% CI 44.9–45.5) and BMI 25.0 kg/m^2 (95% CI 24.8–25.2). All women in the control group were examined during 1999–2000 at the Research Centre for Prevention and Health, Copenhagen County, with a 75-g OGTT. No information considering previous pregnancies was available.

Before participation informed and written consent was obtained from all subjects. The study was approved by the Ethical Committee of Copenhagen and was in accordance with the principles of the Declaration of Helsinki II.

Genotyping

Genotyping of the *TCF7L2* rs7903146, *CDKAL1* rs7756992, *SLC30A8* rs13266634, *CDKN2A/2B* rs10811661, *HHEX/IDE* rs1111875, *IGF2BP2* rs4402960, *TCF2* rs7501939, *WFS1* rs10010131, *PPARG* rs1801282, *KCNJ11* rs5219, and *FTO* rs9939609 variants was performed using Taqman allelic discrimination (KBioscience, Herts, UK). Genotype data were obtained in 95–98% of the DNA samples with a genotype error rate of less than 0.5% for all variants estimated from 1464 duplicate samples genotyped simultaneously in the same assay. All genotype groups obeyed Hardy-Weinberg equilibrium except for the *CDKN2A/2B* rs10811661 variant ($P = 0.032$). That one of 11 single-nucleotide polymorphisms did not obey Hardy-Weinberg equilibrium is expected by chance. Also, the genotyping success rate and error rate for rs10811661 was 98 and 0.14%, respectively. Thus, this single-nucleotide polymorphism was included in the analysis.

Statistical power

We estimated statistical power in the case-control study including 283 GDM patients and 2446 glucose-tolerant women assuming an additive model. Assuming minor allele frequencies of 20 and 40%, we had 67 and 79% statistical power to detect an allelic relative risk of 1.3. Similarly, we had 87 and 93% power to detect a relative risk of 1.4.

Statistical analysis

Logistic regression analyses with adjustment for age and BMI and Fisher's exact test were applied to test for differences in genotype distribution or allele frequencies. To assess the combined effect of multiple risk alleles, we applied a linear model assuming equal effects of each risk allele at the 11 loci and compared this with a model lacking the risk allele parameter. However, to make such assumptions, we first tested whether the effect size of each allele was equal. Because we examined only the association with GDM for alleles previously found to be associated with type 2 diabetes and because an additive effect of the alleles has been found in other studies, we included all 11 variants in the analysis of an additive effect. We used logistic regression to construct ROC curves and estimate area under the curves (AUC). Genetic data were entered numerically to assume an additive model for each locus. The statistical analyses were performed using RGui version 2.6.2 (http://www.r-project.org). A $P < 0.05$ was considered significant.

Results

In the present study, we examined the frequency of 11 validated type 2 diabetes susceptibility alleles in 283 women with a history of GDM compared with 2446 glucose-tolerant women in the control group. The individual allele odds ratios (ORs) are presented in Table 1 and were all above 1.0, ranging from 1.13 (95% CI 0.88–1.46) to 1.44 (95% CI 1.19–1.74) except for the *WFS1* rs10010131 variant with OR 0.87 (95% CI 0.73–1.05). For three of the risk alleles, the *TCF7L2* rs7903146, *CDKAL1* rs7756992, and *TCF2* rs7501939, the age- and BMI-adjusted additive model was nominal statistically significant ($P = 0.00017$, 0.049, and 0.039 respectively).

Subsequently we tested the additive effect of multiple alleles on risk of GDM by combined analysis of all 11 variants. Each individual could therefore harbor between 0 and 22 possible risk alleles. Figure 1 shows the distribution of risk alleles in patients with GDM and in glucose-tolerant control subjects. No subjects with less than five or more than 19 risk alleles were observed. We found a highly statistically significant additive effect of multiple alleles on risk of GDM with an OR of 1.18 per allele (95% CI

TABLE 1. Studies of association of variants in 11 type 2 diabetes risk genes with GDM in 283 women with prior GDM and 2446 glucose-tolerant control women

		Genotype distribution		Risk allele frequencies		Unadjusted[a]	Adjusted[b]
Variant/nearest gene	Allele	GDM, n (%)	Control, n (%)	GDM, % (95% CI)	Control, % (95% CI)	Allele frequency model OR (95% CI)	Additive model OR (95% CI)
rs7903146/*TCF7L2*	CC	118 (42.8)	1292 (54.9)	34.6	26.8	1.45 (1.19–1.75)	1.44 (1.19–1.74)
	C**T**	125 (45.3)	863 (36.7)	(30.6–38.7)	(25.5–28.1)	p_{freq} = **0.00013**	p_{add} = **0.00017**
	TT	33 (12)	198 (8.4)				
rs7756992/*CDKAL1*	AA	124 (45.1)	1229 (52.5)	31.8	27.6	1.22 (1.01–1.49)	1.22 (1–1.49)
	A**G**	127 (46.2)	929 (39.7)	(27.9–35.9)	(26.3–28.9)	p_{freq} = **0.04**	p_{add} = **0.049**
	GG	24 (8.7)	181 (7.7)				
rs13266634/*SLC30A8*	TT	22 (7.9)	266 (11.3)	70.8	67.4	1.17 (0.97–1.43)	1.19 (0.97–1.44)
	T**C**	119 (42.7)	998 (42.6)	(66.8–74.5)	(66–68.7)	p_{freq} = 0.1	p_{add} = 0.092
	CC	138 (49.5)	1080 (46.1)				
rs10811661/*CDKN2A/2B*	CC	11 (4)	68 (2.9)	84.9	83.4	1.12 (0.87–1.45)	1.13 (0.88–1.46)
	C**T**	61 (22.2)	647 (27.5)	81.6–87.8	(82.3–84.4)	p_{freq} = 0.39	p_{add} = 0.34
	TT	203 (73.8)	1640 (69.6)				
rs1111875/*HHEX/IDE*	TT	35 (12.8)	412 (17.7)	62.4	58.9	1.16 (0.96–1.4)	1.18 (0.98–1.43)
	T**C**	136 (49.6)	1090 (46.8)	(58.2–66.5)	(57.5–60.3)	p_{freq} = 0.12	p_{add} = 0.082
	CC	103 (37.6)	827 (35.5)				
rs4402960/*IGF2BP2*	GG	115 (42)	1138 (48.8)	33.9	30.4	1.18 (0.97–1.42)	1.16 (0.95–1.41)
	G**T**	132 (48.2)	972 (41.6)	(30–38.1)	(29.1–31.8)	p_{freq} = 0.096	p_{add} = 0.13
	TT	27 (9.9)	224 (9.6)				
rs7501939/*TCF2*	CC	84 (31.1)	832 (35.6)	44.8	39.9	1.22 (1.02–1.47)	1.22 (1.01–1.48)
	C**T**	130 (48.1)	1144 (49)	(40.6–49.1)	(38.5–41.3)	p_{freq} = **0.029**	p_{add} = **0.039**
	TT	56 (20.7)	360 (15.4)				
rs10010131/*WFS1*	AA	62 (22.9)	409 (18.3)	54.2	57.6	0.87 (0.73–1.05)	0.87 (0.73–1.05)
	A**G**	124 (45.8)	1080 (48.3)	49.9–58.5	56.1–59.0	p_{freq} = 0.14	p_{add} = 0.14
	GG	85 (31.4)	749 (33.5)				
rs1801282/*PPARG*	GG	4 (1.5)	51 (2.1)	87.2	86.5	1.06 (0.81–1.41)	1.16 (0.82–1.52)
	G**C**	60 (22.6)	542 (22.7)	(84.0–89.9)	(85.5–87.4)	p_{freq} = 0.74	p_{add} = 0.30
	CC	201 (75.8)	1790 (75.1)				
rs5219/*KCNJ11*	CC	91 (35.7)	985 (40.9)	40.0	27.6	1.17 (0.97–1.41)	1.20 (0.99–1.45)
	C**T**	124 (48.6)	1101 (45.7)	(35.7–44.4)	(35.0–37.7)	p_{freq} = 0.10	p_{add} = 0.070
	TT	40 (15.7)	325 (13.5)				
rs9939609/*FTO*	TT	82 (29.7)	833 (35.8)	46.2	40.6	1.26 (1.05–1.51)	1.15 (0.95–1.38)
	T**A**	133 (48.2)	1101 (47.3)	(42–50.5)	(39.2–42)	p_{freq} = **0.012**	p_{add} = 0.15
	AA	61 (22.1)	395 (17)				

Data are number of subjects with each genotype (percent of each group), risk allele frequencies in percent (95% CI), and OR (95% CI). All variants are shown according to published diabetes risk allele, which is shown in *bold*.

[a] Differences in allele frequencies (p_{freq}) not adjusted for age and BMI were calculated using Fisher's exact test.

[b] The *P* values compare genotype distributions between women with a history of GDM and glucose-tolerant control subjects, applying an additive (p_{add}) logistic regression model and adjusting for age and BMI.

1.10–1.27, $P = 3.2 \times 10^{-6}$) in a logistic regression model adjusting for age and BMI. Comparing the extremes of the distribution showed a 3.30-fold increased risk (95% CI 1.69–6.39) of GDM for women carrying 15 or more risk alleles [n_{cases} = 21 (7.4% of population), $n_{controls}$ = 99 (4.0%)] compared with women with nine or fewer risk alleles [n_{cases} = 26 (9.2%), $n_{controls}$ = 406 (16.6%)] ($P = 2.8 \times 10^{-4}$).

We evaluated the discriminative power of a genetic test based on 11 gene variants in combination with information on age and BMI by calculating the area under the ROC curve. The area under the ROC curve was 0.62 for the genetic test alone, 0.68 when including age and BMI but not the genetic test, and 0.73 when all three parameters were included (Fig. 2).

An exploratory study of the potential effects of the individual variants on incident type 2 diabetes within the GDM group was performed for all the risk genes. We found that *CDKN2A/2B* rs10811661 T allele and the *WFS1* rs10010131 G allele were significantly associated with incident type 2 diabetes. The women who were homozygote carriers of the *CDKN2A/2B* rs10811661 T allele had a 2.5-fold (95% CI 1.31–4.79, p_{rec} = 0.0054), and women being a homozygote carrier of the *WFS1* rs10010131 G allele a 1.82-fold (1.03–3.22, p_{rec} = 0.039) risk of having type 2 diabetes after adjustment for age and BMI compared with the women without diabetes at follow-up.

Discussion

This is the first study evaluating the impact of the most recent identified type 2 diabetes risk variants in a GDM cohort. The study provides evidence of the strong genetic background for the development of GDM in a multigenetic manner. We have shown ORs above 1.0 for GDM with 10 of the 11 investigated known type 2 diabetes risk genes. Only the *WFS1* rs10010131 variant

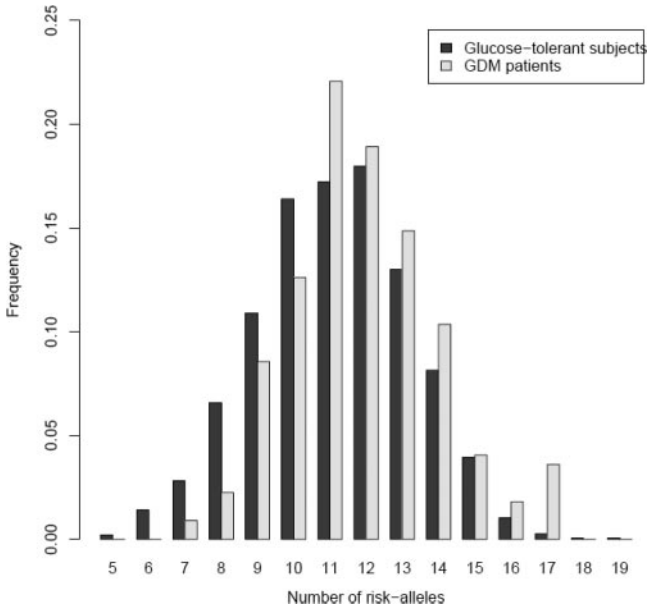

FIG. 1. Distribution of risk alleles of 11 type 2 diabetes risk variants in women with previous gestational diabetes (n = 244) and glucose-tolerant control women (n = 1883). Only women with available genotype information for all 11 loci were included in the analysis. No subjects with less than five or more than 19 risk alleles were found. *P* value for difference in risk allele distribution was 5×10^{-6}. Assuming an additive effect of multiple risk alleles, the increase in risk of GDM was an OR of 1.18 (95% CI 1.10–1.27), $P = 3.2 \times 10^{-6}$ per risk allele.

showed an OR less than 1.0. In general, the risk allele frequencies found in the present study in the control group resemble the frequencies found in the nondiabetic control groups in the genome-wide association studies with higher frequencies in the GDM group resembling the type 2 diabetes groups (6–17, 19, 31).

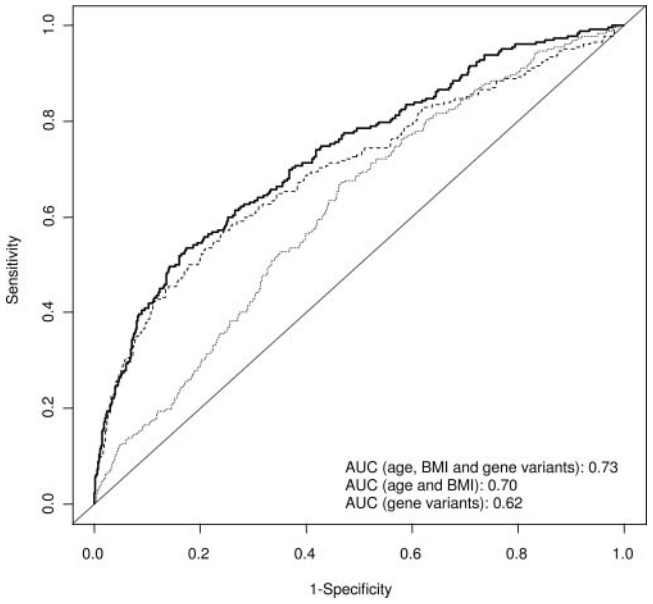

FIG. 2. ROC curves in 244 GDM patients and 1883 glucose-tolerant women with available genotype information for all 11 loci applying a model including age, BMI, and 11 confirmed type 2 diabetes risk variants (*solid line*); age and BMI (*dashed line*); or only genetic information (*dotted line*). AUCs were 0.73, 0.70, and 0.62, respectively.

The association with GDM for *TCF7L2* rs7903146 found in our study confirms a previous study in women with GDM (24) in which an OR of 1.49 per allele was found, which is similar to the OR found in the present study (1.44). Another study demonstrated a higher frequency of the minor T allele of *TCF7L2* rs7903146 in nonobese type 2 diabetes patients and a younger age at diagnosis (32). A younger age at diagnosis is also a characteristic of women with prior GDM.

Furthermore, we show that type 2 diabetes risk alleles additively increase the risk of GDM underlining the common genetic predisposition of type 2 diabetes and GDM. The impact of several risk alleles on risk of incident type 2 diabetes has recently been evaluated in a large cohort of subjects with different glycemic status at baseline followed for up to 9 yr (33). This study showed an additive effect of multiple risk alleles on both type 2 diabetes and impaired fasting glycemia. An additive effect of the variants was also found by Lango *et al.* (31). These results support our finding of an additive effect of the type 2 diabetes risk alleles on the risk for GDM.

The discriminative power of genetic testing with the 11 variants examined in the present study evaluated by the ROC curve showed an AUC of 0.73. This result is close to the level of 0.75 considered consistent with clinical utility. A recent study by Cauchi *et al.* (34) found an area under the ROC curve of 0.86 by testing 15 risk alleles, and in a study by Weedon *et al.* (35), the AUC was 0.58 when testing the combined effect of *PPARG*, *KCNJ11*, and *TCF7L2*. Other studies, however, found that adding the genetic risk variants to the effect of age, BMI, and gender only increased the AUC marginally (31, 36).

The small number of subjects in the GDM cohort obviously severely impedes statistical power to reach statistical significance for an association of the individual genotypes with GDM. The power analysis showed that we only had about 80% power to detect an allelic relative risk of 1.3, given a minor allele frequency of 40%. Because the majority of the ORs were below this, we could not expect the results to be statistically significant. However, the ORs equals what are found for type 2 diabetes. Therefore, we assume that the lack of statistical significance is due to lack of power. We are aware of the need for confirming our results in other GDM cohorts, keeping in mind that large-scale studies needed to replicate the results from association studies on type 2 diabetes (7).

We did not have exact data on the prevalence of GDM in the control group. However, more than 90% of the controls were parous, similar to the Danish background population. With a prevalence of GDM around 2%, approximately 44 women in the control group could have had GDM. We have previously shown that only one third of a GDM population have normal glucose tolerance at a median age of 43 yr. Because the control group consists of glucose-tolerant subjects only, less than 15 women could be expected to have had GDM.

In conclusion, several previously proven type 2 diabetes risk alleles were more frequent among women with a history of GDM. Women who carry 15 or more type 2 diabetes risk alleles have a more than 3-fold increased risk of having GDM compared with women with nine or fewer risk alleles. Knowledge about the biological function of the different type 2 diabetes risk genes may

throw light on the causal factors resulting in progression to type 2 diabetes in some but not all women with GDM.

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