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Genetic prediction of postpartum diabetes in women with gestational diabetes mellitus

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ABSTRACT

Aims: To examine whether genetic variants that predispose individuals to type 2 diabetes (T2D) could predict the development of diabetes after gestational diabetes mellitus (GDM).

Methods: 13 SNPs (*FTO* rs8050136, *CDKAL1* rs7754840 and rs7756992, *CDKN2A/2B* rs10811661, *HHEX* rs1111875, *IGF2BP2* rs1470579 and rs4402960, *SLC30A8* rs13266634, *TCF7L2* rs7903146, *PPARG* rs1801282, *GCK* rs1799884, *HNF1A* rs1169288, and *KCNJ11* rs5219) were genotyped in 793 women with GDM after a median follow-up of 57 months.

Results: After adjustment for age and ethnicity, the *TCF7L2* rs7903146 and the *FTO* rs8050136 variants significantly predicted postpartum diabetes; hazard ratio (95% confidence interval 1.29 (1.01–1.66) and 1.36 (1.06–1.74) respectively (additive model) versus 1.45 (1.01–2.08) and 1.56 (1.06–2.29) (dominant model). Adjusting for BMI attenuated the effect of the *FTO* variant, suggesting that the effect was mediated through its effect on BMI. Combining all risk alleles to a weighted risk score was significantly associated with the risk of postpartum diabetes (hazard ratio 1.11, 95% confidence interval 1.05–1.18, p=0.00016 after adjustment for age and ethnicity).

Conclusions: The *TCF7L2* rs7903146 and *FTO* rs8050136 polymorphisms, and particularly a weighted risk score of T2D risk alleles, predict diabetes after GDM. Further studies in other populations are needed to confirm our results.

KEY WORDS

FTO, GDM, Gestational diabetes mellitus, postpartum diabetes, risk prediction, risk score, *TCF7L2*

MAIN TEXT

Introduction

Gestational diabetes mellitus (GDM), affects about 2% of pregnant women in Sweden (1). About 50% of the women develop diabetes, mostly type 2 diabetes (T2D), within five to ten years after pregnancy (2, 3). Studies have consistently shown that women with a family history of diabetes have an increased risk of GDM (4, 5). In addition, we and others have demonstrated that GDM shares some genetic risk factors with T2D (6-9). To our knowledge, only one study has evaluated whether genetic variants can predict postpartum diabetes in women with GDM (10). Given the very high rate of progression to overt diabetes after GDM, genetic factors, which show modest effects for prediction of T2D, might show stronger effects in women with GDM. We therefore investigated whether 13 SNPs in 11 genes that have been reproducibly associated with modest effects for prediction of T2D might predict the development of diabetes after GDM. These genes include the *CDKAL1*, *CDKN2A*/2B, *HHEX*, *IGF2BP2*, *SLC30A8*, *TCF7L2*, *KCNJ11*, *GCK*, *HNF1A*, *PPARG* and *FTO* (11-13).

Materials and methods

A 75 g oral glucose tolerance test (OGTT) was offered to all women at the 28th week of gestation and also at gestational week 12 if they had a first degree relative with diabetes or a history of GDM during previous pregnancies. The diagnostic criteria for GDM were those recommended by the World Health Organization (WHO) in 1999, defining GDM as the joint category of diabetes and impaired glucose tolerance (IGT) in non-pregnant adults. A 2-h capillary blood glucose concentration $\geq$ 7.8 mmol/L (or plasma glucose $\geq$ 8.6 mmol/L) was regarded as diagnostic for GDM, while a glucose concentration below that limit was considered as normal glucose tolerance during pregnancy (14, 15). HemoCue blood glucose meters (HemoCue, Ängelholm, Sweden) were used to obtain immediate analyses of glucose

concentrations. The screening programme has previously been described in detail (1). The study population consisted of 838 women with GDM participating in two previous studies (2, 16). A 75 g OGTT was offered to all women 1, 2 and 5 years after delivery and the WHO criteria for the diagnosis of diabetes were used (14). In all, 793 women (75% Europeans and 25% non-Europeans) underwent an OGTT postpartum. Women of non-European origin were immigrants from different countries in South America, Africa, Asia and the Middle East. All participants gave written informed consent and the Ethics Committee of Lund University approved the study protocol.

Genotyping was performed with the use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on the MassARRAY platform (Sequenom, San Diego, CA, USA) (17), with the exception of *KCNJ11* rs5219, which was genotyped using an allelic discrimination assay on the ABI7900 platform (Applied Biosystems, Foster City, Ca, USA). Average SNP genotyping success rates were 94.5%. All SNPs were in HWE ($p>0.05$).

Variables are presented as mean (standard deviation). X^2 tests were used to test for deviations from Hardy-Weinberg equilibrium. Cox proportional hazards regression was used to estimate the effect of genetic variants on the risk of developing postpartum diabetes and shown as Kaplan–Meier survival curves and hazard ratios (18). Data were treated as right censored with diabetes diagnosis as endpoint. Risk alleles/genotypes were defined as earlier described (12, 13). Both additive and dominant genetic models were analyzed. We also evaluated whether the combined risk alleles of the 13 SNPs could increase the predictive value. The effect of all SNPs in the risk score were weighted by their respective regression coefficients in a Cox regression model, with and without adjustment for age and non-European ethnicity (19). All statistical analyses were performed with the use of STATA software version 11.2.

Results

Out of the 793 women who were followed with OGTTs after pregnancy, postpartum diabetes was diagnosed in 134 (17%), while 503 (63%) had normal glucose tolerance. These were the glucose categories used when calculating risk estimates. The remaining 156 (20%) had IGT. The clinical characteristics are presented in Table 1. If more than one OGTT had been performed, the latest available data were used. Median time to follow-up was 57 months (interquartile range 14 to 61 months).

After adjustment for age and ethnicity, the *TCF7L2* rs7903146 variant predicted postpartum diabetes when applying an additive model (hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.01–1.66, p=0.039) as well as a dominant model (HR 1.45, 95% CI 1.01–2.08, p=0.044) (Table 2 as well as figure 1a and b). Furthermore, the *FTO* rs8050136 variant also predicted postpartum diabetes under an additive model (HR 1.36, 95% CI 1.06–1.74, p=0.015) as well as under a dominant model (HR 1.56, 95% CI 1.06–2.29, p=0.023) (Table 2 as well as figure 2a and b). As expected, the association of the *FTO* rs8050136 polymorphism disappeared after adjustment for postpartum BMI, suggesting that the effect was primarily mediated through the effect of *FTO* on BMI (additive model: HR 1.30, 95% CI 0.98–1.73, p=0.069 and dominant model: HR 1.39, 95% CI 0.91–2.12, p=0.128) (Table 2). The genotype frequencies of the FTO rs8050136 and TCF7L2 rs7903146 polymorphisms postpartum in women with GDM are presented in Table 3.

In addition, we calculated a genetic risk score as the weighted sum of the risk alleles from the 13 SNPs and observed that a score including all these SNPs was significantly associated with a higher risk of postpartum diabetes, HR 1.15 (95% CI 1.09–1.21), $p=1x10^{-6}$ as well as 1.11 (95% CI 1.05–1.18), p=0.00016 after adjustment for age and ethnicity for each risk-allele increase.

Discussion

We have previously shown that the *TCF7L2* rs7903146 polymorphism is associated with an increased risk of GDM (6, 7, 9) as well as with an increased susceptibility to T2D (20). In addition, we have shown that the risk T-allele of the *TCF7L2* rs7903146 polymorphism is associated with impaired insulin secretion, incretin effects, and enhanced rate of hepatic glucose production. Moreover, TCF7L2 expression in human islets was increased 5-fold in patients with T2D, particularly in carriers of the TT genotype (21). Furthermore, overexpression of TCF7L2 in human islets has been shown to reduce glucose-stimulated insulin secretion (21). Watanabe et al. found that variation in TCF7L2 is associated with GDM and interacts with adiposity to alter insulin secretion in Mexican Americans (8). These mechanisms could partly explain the association between *TCF7L2* rs7903146 polymorphism and the increased risk of postpartum diabetes in women with GDM in the present study.

In a study by Frayling et al. it was shown that the common *FTO* rs9939609 variant increases the risk of diabetes through an effect on BMI (22), and this finding has been confirmed by others (23). In the present study the *FTO* rs8050136 variant was associated with an increased risk of developing diabetes postpartum. Adjusting for BMI clearly attenuated the effect of the *FTO* variant, suggesting that most of its effect is mediated through its effect on BMI. The finding that the *FTO* rs8050136 variant increases the risk for postpartum diabetes is not surprising given its effect on BMI, since most women with GDM are obese. Furthermore, we show that a combined risk score of 13 SNPs that have been associated with T2D and related traits increases the risk for postpartum diabetes in women with GDM.

The Danish study by Lauenborg et al. (10) found that of 11 established T2D susceptibility variants the *CDKN2A/2B* rs10811661 and the *WFS1* rs10010131 polymorphisms were associated with incident T2D in 283 women with GDM up to 2 years postpartum. They did

not observe any increased risk associated with the *TCF7L2* rs7903146 or *FTO* rs9939609 variants.

Although the present study to our knowledge is the largest study to evaluate the risk of genetic variants on postpartum diabetes it suffers like the Danish study from limited power. Another weakness of the study is that we have not corrected for multiple comparisons. Therefore the results should be considered preliminary. Larger studies in other populations are encouraged to confirm our results.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1

Clinical characteristics of women with GDM in relation to glucose category postpartum

Glucose category	**NGT**	**Diabetes**	**P-value**
Number of women	503	134	
Age at delivery (years)	32.2 ± 4.8	32.8 ± 5.3	0.25
BMI at follow up (kg/m²)	25.5 ± 4.8	30.8 ± 6.3	$6x10^{-22}$
Origin			
European	413 (82)	71 (53)	$1x10^{-11}$
Non-European	90 (18)	61 (46)	
Unknown	0 (0)	2 (1)	

Data are mean ± SD, n (%). Differences in means were tested by T-test. Frequency differences were tested by Pearson chi-square test. NGT = normal glucose tolerance.

Table 2

The effect of the studied variants on the risk for development of postpartum diabetes

SNP	Risk alleles	Additive model		Dominant model	
		HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
CDKAL1 rs7754840	**C**	0.93 (0.72-1.20)	0.554	0.90 (0.63-1.28)	0.550
CDKAL1 rs7756992	**G**	0.92 (0.71-1.18)	0.500	0.92 (0.65-1.31)	0.650
CDKN2A/2B rs10811661	**T**	1.29 (0.85-1.94)	0.228	1.37 (0.33-5.64)	0.664
HHEX rs1111875	**C**	1.21 (0.94-1.56)	0.146	1.05 (0.65-1.70)	0.850
IGF2BP2 rs1470579	**C**	1.22 (0.94-1.59)	0.140	1.14 (0.80-1.63)	0.476
IGF2BP2 rs4402960	**T**	1.16 (0.89-1.53)	0.272	1.06 (0.74-1.53)	0.733
TCF7L2 rs7903146	**T**	1.29 (1.01-1.66)	**0.039**	1.45 (1.01-2.08)	**0.044**
PPARG rs1801282	**C**	0.94 (0.63-1.40)	0.769	0.93 (0.23-3.78)	0.921
SLC30A8 rs13266634	**C**	1.16 (0.85-1.58)	0.344	0.69 (0.37-1.30)	0.251
GCK rs1799884	**A**	1.18 (0.88-1.59)	0.277	1.12 (0.77-1.62)	0.548
HNF1A rs1169288	**C**	1.05 (0.82-1.35)	0.692	1.05 (0.72-1.53)	0.790
KCNJ11 rs5219	**A**	1.15 (0.89-1.48)	0.293	1.02 (0.70-1.48)	0.918
FTO rs8050136	**A**	1.36 (1.06-1.74)	**0.015**	1.56 (1.06-2.29)	**0.023**
		1.30 (0.98-1.73)	0.069*****	1.39 (0.91-2.12)	0.128*****

Analyses were carried out with age and ethnicity-adjusted Cox proportional hazard regression model. *corrected for age, ethnicity and postpartum BMI

Table 3
The genotype frequencies of the *FTO* rs8050136 and *TCF7L2* rs7903146 polymorphisms in women with GDM in relation to glucose category postpartum

Polymorphism	Genotype	Glucose category postpartum		P-value
		NGT n (%)	Diabetes n (%)	
FTO rs8050136				
	CC	180 (37.5)	39 (31.0)	0.332
	CA	223 (46.5)	62 (49.2)	
	AA	77 (16.0)	25 (19.8)	
TCF7L2 rs7903146				
	CC	239 (50.2)	49 (39.2)	0.020
	CT	195 (41.0)	56 (44.8)	
	TT	42 (8.8)	20 (16.0)	

Frequency differences were tested by Pearson chi-square test. NGT = normal glucose tolerance.