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CLINICAL STUDY

Association of risk variants for type 2 diabetes and hyperglycemia with gestational diabetes

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Abstract

Objective: The aim of this study was to investigate the association of risk variants for type 2 diabetes (T2D) and hyperglycemia with gestational diabetes (GDM).

Design and methods: Five hundred and thirty-three Finnish women who were diagnosed with GDM and 407 controls with normal glucose tolerance during the pregnancy were genotyped for 69 single-nucleotide polymorphisms (SNPs) which have been previously verified as susceptibility risk variants for T2D and hyperglycemia. All participants underwent an oral glucose tolerance test at the follow-up study after the index pregnancy.

Results: Risk variants rs10830963 and rs1387153 of *MTNR1B* were significantly associated with GDM (odds ratio (OR)=1.62 (95% CI 1.34–1.96), $P=4.5\times10^{-7}$ and 1.38 (1.14–1.66), $P=7.6\times10^{-4}$ respectively). Both SNPs of *MTNR1B* were also significantly associated with elevated fasting glucose level and reduced insulin secretion at follow-up. Additionally, risk variants rs9939609 of *FTO*, rs2796441 of *TLE1*, rs560887 of *G6PC2*, rs780094 of *GCKR*, rs7903146 of *TCF7L2* and rs11708067 of *ADCY5* showed nominally significant associations with GDM (OR range from 1.25 to 1.30).

Conclusions: Our study suggests that GDM and T2D share a similar genetic background. Our findings also provide further evidence that risk variants of *MTNR1B* are associated with GDM by increasing fasting plasma glucose and decreasing insulin secretion.

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Introduction

Gestational diabetes (GDM) is defined as abnormal glucose tolerance during pregnancy resolving after delivery. Previously published studies suggest that the prevalence of GDM is increasing, and currently affects 2–14% of all pregnancies depending on the diagnostic criteria (1, 2). GDM increases the risk of adverse neonatal outcomes and predicts the development of type 2 diabetes (T2D) in both the mother and the offspring (3, 4).

GDM and T2D share similar pathophysiology. During pregnancy, insulin resistance increases and when accompanied by impaired beta cell function, the risk of GDM increases. Similarly, peripheral insulin resistance accompanied by an insulin secretion defect leads to abnormal glucose tolerance and T2D (5) in the nonpregnant individual. In addition, GDM and T2D share several risk factors including overweight and family history of diabetes. A previous study has demonstrated that compared with women without a family history of diabetes, women with a maternal, paternal or sibling history of diabetes had greater risk of GDM (odds ratios (ORs) 3.0, 3.3 and 7.1 respectively) (6). Therefore, GDM could serve as a window to the subsequent metabolic health in women, and reflect a predisposition to developing T2D (7).

T2D has a strong genetic component. Previous studies have demonstrated that T2D is associated with genetic variation in several genes, each conferring a small increase in the risk of T2D by interacting with other diabetes-susceptibility genes, the metabolic environment of the body and lifestyle factors (8). Similarly, there is accumulating evidence that genetic factors contribute to abnormal glucose tolerance and GDM during pregnancy (9). However, knowledge regarding the genetic risk loci for GDM is still limited. The only genome-wide association study (GWAS) of GDM has been performed among Korean women and showed a strong association between risk alleles of rs10830962 *MTNR1B* and rs7754840 *CDKAL1* and

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GDM (10). The effects sizes of the known T2D risk variants in GDM and in T2D were of similar magnitude, giving evidence that GDM and T2D share a similar genetic background (10). In a recent meta-analysis of 22 studies including 10 336 GDM cases and 17 445 controls, eight single-nucleotide polymorphisms (SNPs) were significantly associated with GDM (rs7903146 *TCF7L2*, rs10830963 *MTNR1B*, rs4402960 *IGF2BP2*, rs5219 *KCNJ11*, rs7754840 *CDKAL1*, rs2237892 and rs2237895 *KCNQ1* and rs4607517 *GCK*) (11).

GWAS have so far identified ~70 genetic variants (SNPs) in different genes contributing to the risk of T2D or hyperglycemia (12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24). To give further evidence for the hypothesis that GDM and T2D share a common genetic basis we investigated the association of these SNPs with GDM in a case–control setting of 940 Finnish women.

Subjects and methods

The study population was collected from an existing clinical pregnancy registry at the Kuopio University Hospital, Kuopio, Finland. A total of 533 previously nondiabetic women were identified who were diagnosed with GDM between the years 1989 and 2009, and 407 women with normal glucose tolerance in an oral glucose tolerance test (OGTT, 75 g glucose dose after overnight fasting) during pregnancy served as controls. The diagnosis of GDM was based on the following criteria: until September 2001 fasting plasma blood glucose >4.8 mmol/l, 1-h blood glucose >10.0 mmol/l and 2-h blood glucose >8.7 mmol/l, and since September 2001 fasting plasma glucose >4.8 mmol/l, 1-h plasma glucose >11.2 mmol/l and 2-h plasma glucose >9.9 mmol/l. One or more elevated values during an OGTT resulted in the diagnosis of GDM. To study the glucose tolerance after the pregnancy an OGTT was performed in all women (mean follow-up 7.2, S.D. 6.2 years). T2D at follow-up was defined as fasting plasma glucose ≥7.0 mmol/l or 2-h plasma glucose >11.0 mmol/l, or antidiabetic medication started between index pregnancy and the follow-up study. Seventeen women were started on antidiabetic medication between the index pregnancy and follow-up and 15 were diagnosed with incident T2D at the follow-up.

At the follow-up study plasma glucose during OGTT was measured by enzymatic hexokinase photometric assay (Konelab Systems reagents; Thermo Fischer Scientific, Vantaa, Finland). Insulin was determined by immunoassay (ADVIA Centaur Insulin IRI no. 02230141; Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). HbA1c was measured using the HPLC assay (TOSOH G7 glycohemoglobin analyzer; Tosoh Bioscience, Inc., San Francisco, CA, USA), calibrated to Diabetes Control and Complications Trial (DCCT) standard. The trapezoidal method was used to calculate glucose area under the curve (AUC) and insulin AUC during the OGTT. Insulin sensitivity was evaluated using the Matsuda Insulin Sensitivity Index (ISI) and insulin secretion was evaluated by dividing insulin AUC during the first 30 min of an OGTT by the corresponding glucose AUC, as previously described (25).

Genotyping was performed using the Sequenom iPlex (Sequenom, Inc., San Diego, CA, USA) or the TaqMan Allelic Discrimination Assays (Applied Biosystems) for rs1111875 of *HHEX*, rs5219 of *KCNJ11*, rs231362 and rs2283228 of *KCNQ1*, rs10830963 of *MTNR1B*, and rs7578597 of *THADA* at the University of Eastern Finland. All SNPs were consistent with Hardy–Weinberg equilibrium at the significance level of $P>0.05$ except for rs4607517 of *GCK* ($P=0.000006$), rs10811661 of *CDKN2B* ($P=0.0135$) and rs10885122 of *ADRA2A* (0.0263). Genotyping call rate was 99.5% and error rate 0% in 5.0% of SNPs re-genotyped.

All statistical analyses were performed using SPSS 19 statistical software (SPSS). Anthropometric and biochemical variables were log-transformed to correct for their skewed distribution, when appropriate. Comparisons between the women with GDM and corresponding controls (mean, S.D.) were done using *t*-test, using log-transformed variables for *P* values when appropriate. Allele frequencies were compared between cases and controls using Fisher's exact test. Association of SNPs with GDM was evaluated by logistic regression analysis adjusted for maternal age at index pregnancy, and results are given as ORs with their 95% CI. $P<7.2\times10^{-4}$ (0.05/69) was considered as statistically significant, given the 69 SNP analyzed. OR and 95% CI for incident T2D at follow-up were calculated using logistic regression. The SNPs significantly associated with the risk of GDM were evaluated for their effects on fasting and postprandial glycemia, insulin sensitivity (Matsuda ISI), and insulin secretion (adjusted for Matsuda ISI) at the follow-up study using linear regression (effect size B, S.E.), adjusting for maternal age and BMI at follow-up, using log-transformed variables when appropriate. Participants with T2D and taking antidiabetic medication were excluded, leaving 923 for the follow-up analysis. At follow-up, $P<1.8\times10^{-4}$ ($P=0.05$ divided by 276) was considered as statistically significant, given the 276 tests performed (69 SNPs and four traits). The required relative risk to achieve ≥80% statistical power was 1.45 to 1.3 for allele frequencies between 0.1 and 0.4.

Ethical considerations: the study was approved by the local ethics committee in Kuopio University Hospital, and it was conducted in accordance with the Helsinki Declaration.

Results

The clinical and laboratory characteristics of the study groups are presented in Table 1. Participants with GDM

Table 1 Clinical characteristics of individuals with GDM and controls in index pregnancy and at the follow-up study.

Variable	GDM patients Mean (S.D.)	Controls Mean (S.D.)	*P*
Number of women	448–533	358–407	
Index pregnancy			
Age at index pregnancy (years)	32.6 (5.9)	29.9 (5.3)	<0.001
Duration of pregnancy (weeks)	39.2 (1.5)	39.5 (1.6)	0.033
BMI in the first trimester (kg/m^2)	26.3 (4.7)	24.1 (3.8)	<0.001
Birth weight of the child (g)	3380 (560)	3480 (590)	0.059
Follow-up study			
Age at follow-up study (years)	38.1 (7.1)	38.9 (7.0)	0.117
Family history of diabetes (%)	79.9	71.1	0.004
Current smoker (%)	18.2	13.9	0.082
BMI (kg/m^2)	28.3 (5.5)	26.8 (5.0)	<0.001
HbA1c (%), (mmol/mol)	5.5 (0.5), (37 (5.5))	5.4 (0.3), (36 (3.3))	<0.001
Fasting plasma glucose (mmol/l)	5.7 (0.9)	5.3 (0.4)	<0.001
30-min plasma glucose (mmol/l)	8.0 (1.7)	7.1 (1.5)	<0.001
2-h plasma glucose (mmol/l)	6.1 (1.7)	5.5 (1.3)	<0.001
Fasting plasma insulin (pmol/l)	71.7 (51.0)	54.2 (36.6)	<0.001
30-min plasma insulin (pmol/l)	440.5 (308.7)	382.9 (240.2)	0.008
2-h plasma insulin (pmol/l)	311.9 (295.3)	239.5 (206.2)	<0.001
Matsuda ISI	5.7 (3.2)	7.2 (3.7)	<0.001
$InsAUC_{0–30}/GluAUC_{0–30}$ (pmol/mmol)	37.2 (23.3)	35.0 (19.0)	0.402

were older than the controls (mean age at index pregnancy 32.6 years (S.D. 5.9, range 17–47) and 29.9 years (S.D. 5.3, range 16–45 years), for GDM and control groups respectively. In the follow-up study after the pregnancy they had higher HbA1c, glucose and insulin levels during an OGTT and were more insulin resistant than control subjects. No difference in insulin secretion was observed.

Table 2 reports association of 69 SNPs studied with GDM. SNP rs10830963 of *MTNR1B* was significantly associated with GDM (OR 1.62 (95% CI 1.34–1.96), $P=1.3\times10^{-7}$) adjusted for age at GDM pregnancy. In addition, rs1387153 of *MTNR1B* was significantly associated with GDM (1.38 (1.14–1.66), $P=3.6\times10^{-4}$). Furthermore, rs4737009 ($P=0.002$) and rs516946 ($P=0.0499$) of *ANK1*, rs9939609 of *FTO* ($P=0.006$), rs2796441 of *TLE1* ($P=0.014$), rs12571751 of *ZMIZ1* ($P=0.007$), rs560887 of *G6PC2* ($P=0.026$), rs780094 of *GCKR* ($P=0.028$), rs7903146 of *TCF7L2* ($P=0.016$) and rs11708067 of *ADCY5* ($P=0.029$) showed nominally significant associations with GDM (ORs between 0.74 and 1.38) even after the adjustment for maternal age at index pregnancy. Mean risk allele frequencies for GDM and control groups are given in Supplementary Table 1, see section on supplementary data given at the end of this article.

A total of 32 women had T2D at the follow-up study, of whom 30 were from the GDM and two were from the control group. GDM was strongly associated with the development of T2D after the pregnancy (OR 12.2, 95% CI 2.9–51.2). We subsequently studied the association of SNPs having significant or nominally significant association with GDM with fasting and 2-h glucose levels, insulin sensitivity and insulin secretion in an OGTT performed after the pregnancy (Table 3). Risk alleles of rs10830963 and rs1387153 of *MTNR1B* ($P=9.5\times10^{-12}$ and $P=4.1\times10^{-5}$ respectively), and rs560887 of *G6PC2* ($P=0.001$) were associated with elevated fasting glucose level and the risk allele of rs11708067 of *ADCY5* with elevated 2-h glucose level ($P=0.008$, all after the adjustment for age and BMI at follow-up). The glucose-increasing minor alleles of rs10830963 and rs1387153 of *MTNR1B* were associated with impaired first-phase insulin secretion at follow-up after the adjustment for age and BMI and Matsuda ISI ($P=3.9\times10^{-6}$ and $P=2.0\times10^{-5}$ respectively). The SNPs associated with the risk of GDM were not associated with insulin sensitivity at follow-up. Additional adjustment for the diabetes status during the index pregnancy (belonging to GDM or control group) somewhat attenuated, but did not abolish the associations of *MTNR1B* rs10830963 and rs1387153 with FPG ($P=1.1\times10^{-8}$ and $P=0.001$ respectively) and insulin secretion at follow-up ($P=2.7\times10^{-4}$ and $P=3.8\times10^{-4}$ respectively).

Discussion

Previous prospective population-based studies have shown that a history of GDM considerably increases the risk of T2D. This is not unexpected since these two conditions share similar environmental and lifestyle risk factors (such as obesity, unhealthy diet and physical inactivity), and pathophysiology, including increased insulin resistance and impaired insulin secretion (7). There is limited but increasing evidence suggesting that similar genetic risk variants which predispose to T2D

Table 2 Association of known risk gene variants for T2D and hyperglycemia with GDM.

SNP	Gene	Alleles	OR	95% CI	*P*	*P**
rs10830963	*MTNR1B*	C/G	1.62	1.34–1.96	**4.5×10^{-7}**	**1.3×10^{-7}**
rs1387153	*MTNR1B*	C/T	1.38	1.14–1.66	**7.6×10^{-4}**	**3.6×10^{-4}**
rs4737009	*Ank1*	G/A	0.74	0.61–0.91	**0.004**	**0.002**
rs9939609	*FTO*	T/A	1.28	1.06–1.54	**0.011**	**0.006**
rs12571751	*ZMIZ1*	A/G	0.80	0.67–0.96	**0.016**	**0.007**
rs2796441	*TLE1*	G/A	1.27	1.06–1.54	**0.011**	**0.014**
rs7903146	*TCF7L2*	C/T	1.30	1.03–1.64	**0.028**	**0.016**
rs560887	*G6PC2*	C/T	1.28	1.05–1.56	**0.017**	**0.026**
rs780094	*GCKR*	C/T	1.25	1.03–1.51	**0.027**	**0.028**
rs11708067	*ADCY5*	A/G	1.29	1.00–1.67	0.055	**0.029**
rs516946	*ANK1*	C/T	0.80	0.63–0.996	**0.047**	0.050
rs7578597	*THADA*	T/C	0.64	0.39–1.04	0.072	0.060
rs1111875	*HHEX*	C/T	0.86	0.71–1.03	0.107	0.067
rs7034200	*GLIS3*	C/A	1.11	0.92–1.35	0.274	0.09
rs13266634	*SLC30A8*	C/T	0.85	0.70–1.02	0.080	0.105
rs4457053	*ZBED3*	A/G	1.23	0.99–1.54	0.061	0.116
rs7578326	*IRS1*	A/G	1.13	0.94–1.37	0.201	0.12
rs896854	*TP53INP1*	C/T	1.12	0.93–1.34	0.226	0.133
rs5945326	*DUSP9*	A/G	1.12	0.92–1.38	0.262	0.159
rs282587	*ATP11A*	A/G	1.17	0.90–1.51	0.240	0.189
rs2191349	*DGKB*	G/T	1.15	0.96–1.39	0.139	0.196
rs552976	*ABCB11/G6PC2*	G/A	1.15	0.94–1.40	0.166	0.210
rs7754840	*CDKAL1*	G/C	1.14	0.94–1.38	0.179	0.210
rs972283	*KLF14*	G/A	1.04	0.87–1.25	0.674	0.220
rs340874	*PROX1*	T/C	1.10	0.91–1.33	0.327	0.229
rs7202877	*BCAR1*	T/G	1.15	0.90–1.48	0.287	0.242
rs231362	*KCNQ1*	G/A	1.12	0.93–1.35	0.229	0.274
rs7957197	*HNF1A*	T/A	0.92	0.74–1.15	0.471	0.302
rs243021	*BCL11A*	G/A	1.14	0.95–1.37	0.169	0.326
rs13389219	*GRB14*	C/T	1.12	0.92–1.36	0.267	0.343
rs12454712	*BCL2*	T/C	1.10	0.91–1.31	0.351	0.362
rs4402960	*IGF2BP2*	G/T	1.13	0.93–1.38	0.218	0.365
rs10923931	*NOTCH2*	G/T	1.17	0.89–1.52	0.261	0.375
rs10012946	*WFS1*	C/T	0.94	0.78–1.13	0.511	0.392
rs5219	*KCNJ11*	C/T	0.98	0.81–1.17	0.789	0.425
rs11634397	*ZFAND6*	G/A	0.89	0.74–1.07	0.22	0.431
rs16926246	*HK1*	C/T	1.26	0.86–1.84	0.239	0.462
rs459193	*ANKRD55*	G/A	1.02	0.84–1.24	0.856	0.469
rs1799884	*GCK*	C/T	1.14	0.85–1.53	0.387	0.525
rs10885122	*ADRA2A*	G/T	1.05	0.83–1.33	0.685	0.547
rs12970134	*MC4R*	G/A	0.94	0.74–1.19	0.586	0.563
rs10842994	*KLHDC5* (*KLHL42*)	C/T	0.96	0.75–1.22	0.714	0.578
rs2283228	*KCNQ1*	A/C	0.95	0.65–1.39	0.792	0.590
rs7961581	*TSPAN8*	T/C	0.93	0.74–1.16	0.495	0.591
rs10770141	*TH/INS*	G/A	1.07	0.88–1.31	0.484	0.599
rs11071657	*FAM148B* (*C2CD4B*)	A/G	1.07	0.88–1.30	0.515	0.602
rs7501939	*HNF1B*	C/T	0.95	0.78–1.17	0.639	0.607
rs1408272	*HFE*	T/G	0.85	0.54–1.33	0.477	0.657
rs4607517	*GCK*	G/A	1.1	0.80–1.51	0.572	0.678
rs3794991	*GATAD2A*	C/T	1.00	0.68–1.47	0.997	0.682
rs7177055	*HMG20A*	A/G	1.00	0.83–1.22	0.972	0.723
rs1801282	*PPARG*	C/G	0.93	0.73–1.20	0.578	0.731
rs10811661	*CDKN2B*	T/C	1.09	0.85–1.40	0.487	0.743
rs11605924	*CRY2*	A/C	0.99	0.82–1.18	0.881	0.747
rs174550	*FADS1*	T/C	1.04	0.87–1.26	0.652	0.780
rs4607103	*ADAMTS9*	C/T	1.00	0.82–1.23	0.967	0.784
rs7944584	*MADD*	A/T	1.00	0.79–1.28	0.972	0.803
rs10423928	*GIPR*	T/A	1.02	0.81–1.28	0.885	0.804
rs4925115	*SREBF1*	G/A	1.01	0.83–1.22	0.949	0.808
rs2612067	*HMGA2*	T/G	1.02	0.72–1.45	0.909	0.830
rs8042680	*PRC1*	C/A	1.05	0.87–1.28	0.614	0.863
rs11920090	*SLC2A2*	T/A	0.97	0.74–1.27	0.803	0.877
rs12779790	*CDC123*	A/G	0.97	0.77–1.22	0.786	0.885
rs1046896	*FN3K*	C/T	0.94	0.77–1.16	0.580	0.897
rs13292136	*CHCHD9* (*CHCHD2P9*)	C/T	0.91	0.70–1.19	0.484	0.900
rs17271305	*VPS13C*	G/A	1.02	0.85–1.23	0.813	0.904
rs864745	*JAZF1*	C/T	0.95	0.79–1.14	0.591	0.906
rs2779116	*SPTA1*	C/T	0.98	0.80–1.19	0.823	0.946
rs10401969	*SUGP1/CILP2*	T/C	1.07	0.72–1.59	0.746	0.981

Alleles major/minor, risk allele underlined. OR (95% CI) calculated as per risk allele using logistic regression. *P** adjusted for maternal age at the GDM pregnancy. Significant *P* values ($P<7.2\times10^{-4}$) after the Bonferroni adjustment for multiple testing (for 69 SNPs and one trait) are given in bold and underlined. Significant *P* values are given in bold.

Table 3 Association of known risk gene variants for T2D and hyperglycemia with postpregnancy glycemia, insulin sensitivity and insulin secretion.

			FPG at follow-up				2hPG at follow-up				Matsuda ISI at follow-up				InsulinAUC$_{0-30}$/glucoseAUC$_{0-30}$ adjusted for Matsuda ISI at follow-up			
SNP	**Gene**	**Alleles**	B	S.E.	*P*	*P**	B	S.E.	*P*	*P**	B	S.E.	*P*	*P**	B	S.E.	*P*	*P**
rs10830963	*MTNR1B*	C/G	0.15	0.02	**9.5×10^{-12}**	**1.1×10^{-8}**	0.11	0.07	0.074	0.285	−0.22	0.17	0.333	0.934	−3.04	0.72	**3.9×10^{-6}**	**2.7×10^{-4}**
rs1387153	*MTNR1B*	C/T	0.10	0.02	**4.1×10^{-5}**	**0.001**	0.05	0.07	0.388	0.735	−0.10	0.17	0.844	0.393	−2.55	0.73	**2.0×10^{-5}**	**3.8×10^{-4}**
rs560887	*G6PC2*	C/T	0.09	0.03	**0.001**	**0.003**	−0.03	0.08	0.785	0.557	0.00	0.19	0.669	0.471	0.79	0.79	0.354	0.181
rs7903146	*TCF7L2*	C/T	0.05	0.03	0.057	0.165	0.07	0.09	0.245	0.387	−0.03	0.22	0.764	0.940	−2.38	0.91	0.089	0.202
rs516946	*ANK1*	C/T	0.03	0.03	0.426	0.171	0.15	0.09	0.050	**0.022**	−0.20	0.22	0.640	0.348	−1.56	0.90	0.139	**0.033**
rs4737009	*ANK1*	G/A	0.02	0.03	0.534	0.174	0.04	0.08	0.482	0.276	0.08	0.20	0.474	0.789	−1.45	0.81	0.149	**0.041**
rs2796441	*TLE1*	G/A	−0.01	0.02	0.520	0.269	0.02	0.08	0.781	0.608	0.04	0.18	0.317	0.189	−0.40	0.74	0.278	0.492
rs780094	*GCKR*	C/T	0.00	0.02	0.698	0.332	−0.04	0.08	0.605	0.412	−0.14	0.19	0.796	0.897	−0.14	0.77	0.704	0.381
rs12571751	*ZMIZ1*	A/G	0.01	0.02	0.804	0.347	−0.04	0.07	0.212	0.370	−0.01	0.17	0.539	0.839	0.87	0.72	0.062	0.161
rs9939609	*FTO*	T/A	0.01	0.02	0.944	0.452	0.07	0.08	0.396	0.621	−0.13	0.18	0.750	0.890	−0.06	0.74	0.239	0.519
rs11708067	*ADCY5*	A/G	0.01	0.03	0.680	0.878	0.18	0.11	**0.008**	**0.018**	0.25	0.25	0.914	0.747	−0.49	1.02	0.121	0.305

Linear regression, *P* values per risk allele obtained by linear regression analysis were calculated using log-transformed variables where appropriate. *P* adjusted for age and BMI at follow-up study. *P** adjusted for age and BMI at follow-up study, and GDM or control group. Significant *P* values ($P<1.8\times10^{-4}$) after the Bonferroni adjustment for multiple testing (276 tests given 69 SNPs and four traits) are given in bold and underlined. Significant *P* values are given in bold. $n=923$, individuals with T2D diagnosed between pregnancy and follow-up study and taking antidiabetic medication are excluded. FPG, fasting plasma glucose; 2hPG, 2-h plasma glucose; Matsuda ISI, Matsuda insulin sensitivity index.

also contribute to the risk of GDM (8). In the present study we investigated the association of all 69 thus far published confirmed risk variants for T2D or hyperglycemia with GDM in Finns. Our study showed that several risk SNPs for T2D or hyperglycemia were also associated with GDM, giving further evidence that GDM and T2D share a similar genetic background.

The only GWAS published so far on risk variants for GDM reported significant associations of rs10830962 of *MTNR1B* (OR 1.47, $P=5.02\times10^{-7}$) and rs7754840 of *CDKAL1* (OR 1.71, $P=2.15\times10^{-11}$) with GDM in Korean women (10). The effect of *MTNR1B* risk variants on glucose levels during pregnancy has also been found in Greek (26) and Chinese (27) women with GDM. We confirmed the association of *MTNR1B* with GDM in Finns as rs1083092 and rs1387153 of *MTNR1B* were significantly associated with GDM in our study ($P=1.3\times10^{-7}$ and $P=3.6\times10^{-4}$ respectively). Both of these SNPs of *MTNR1B* were significantly associated with fasting glucose levels, as previously reported also in patients with T2D (14). The glucose-increasing minor alleles of both SNPs of *MTNR1B* were also associated with impaired insulin secretion, with no effect on insulin sensitivity. Melatonin, which mediates its effects through melatonin receptors MTNR1A and MTNR1B, is best known as a regulator of seasonal and circadian rhythms (28). Carriers of the risk genotypes exhibit increased expression of MTNR1B in pancreatic β cells which leads to impaired insulin secretion. In a very recent meta-analysis including a total of 10 336 GDM cases and 17 445 controls, eight T2D risk SNPs were significantly associated with GDM (rs7903146 of *TCF7L2*, rs10830963 of *MTNR1B*, rs4402960 of *IGF2BP2*, rs5219 of *KCNJ11*, rs7754840 of *CDKAL1*, rs2237892 and rs2237895 of *KCNQ1* and rs4607517 of *GCK*) (11).

The other risk variant detected in a previous Korean GWAS, rs7754840 of *CDKAL1* (10), was not significantly associated with GDM in our study (OR 1.14, $P=0.210$ after adjustment for maternal age), although a trend was observed in the same direction. The lack of statistical significance is probably due to a limited number of subjects included in our study. Unexpectedly, the two T2D risk variants rs4737009 and rs516946 of *ANK1* gene and rs12571751 of *ZMIZ1* gene showed a nominally significant protective effect on GDM risk in our study, whereas in previous studies these two SNPs have increased the risk of T2D (23).

SNP rs7903146 of *TCF7L2*, the most significant risk variant for T2D reported to date (29), was nominally associated with GDM (OR 1.30, $P=0.016$) in our study. In previous studies rs7903146 of *TCF7L2* has increased the risk of GDM by 44–49% (30, 31). Furthermore, previous studies have indicated that SNPs of *TCF7L2* increase the risk of T2D by reducing insulin secretion (32).

FTO has been reported to be associated with obesity and therefore this gene indirectly contributes to the risk

of T2D (21). We also found that rs9939609 of *FTO* was associated with the risk of GDM (OR 1.28, $P=0.006$) which is expected as obesity is a well-known risk factor of GDM (33). Risk variants rs560887 of *TLE1*, rs560887 of *G6PC2* and rs780094 of *GCKR* have not been associated with GDM in previous studies, but in our study these variants were nominally associated with GDM (ORs 1.27, 1.28 and 1.25 respectively). *G6PC2* encodes glucose-6-phosphatase 2 (G6PC2) which is involved in the terminal step of the gluconeogenic and glycogenolytic pathways, and regulates fasting plasma glucose levels (34). In agreement with previous studies, rs560887 of *G6PC2* was nominally associated with fasting glucose in our follow-up study as well as with GDM. *GCKR* encodes the glucokinase regulatory protein, and SNPs at the *GCKR* locus have been associated with fasting glycemia and the risk of T2D (35, 36).

The limitation of our study is quite a small sample size. We had only modest statistical power to demonstrate statistically significant associations of gene variants with GDM. Furthermore, the diagnostic criteria of GDM vary worldwide which makes it difficult to compare results across different populations.

In conclusion, our study shows that several gene variants increasing the risk of T2D and hyperglycemia are also associated with GDM, suggesting a common genetic background for these two conditions. Risk variants of *MTNR1B* had the most significant associations with GDM in Finnish women. We also demonstrated that these variants increased fasting plasma glucose and decreased insulin secretion.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-13-0286.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

H Huopio designed the study, collected and researched the data and wrote the manuscript. H Cederberg researched the data and wrote the manuscript. J Vangipurapu researched the data and reviewed/edited the manuscript. H Hakkarainen contributed to discussion and reviewed/edited the manuscript. M Pääkkönen designed the study, collected the data and reviewed/edited the manuscript. T Kuulasmaa performed genotyping and reviewed/edited the manuscript. S Heinonen designed the study, collected the data and reviewed/edited the manuscript. M Laakso designed the study, contributed to discussion and reviewed/edited the manuscript, is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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