

# Association of Single Nucleotide Polymorphisms With Insulin Secretion, Insulin Sensitivity, and Diabetes in Women With a History of Gestational Diabetes Mellitus

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## Research Article

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# Abstract

**Aims:** This study investigated whether single nucleotide polymorphisms (SNPs) reported by previous genome-wide association studies (GWAS) to be associated with impaired insulin secretion, insulin resistance, and/or type 2 diabetes are associated with disposition index, the homeostasis model assessment of insulin resistance (HOMA-IR), and/or development of diabetes following a pregnancy complicated by gestational diabetes mellitus (GDM).

**Methods:** Seventy-two SNPs were genotyped in 374 women with previous GDM from Southern Sweden. An oral glucose tolerance test was performed 1–2 years postpartum, although data on the diagnosis of diabetes were accessible up to 5 years postpartum. HOMA-IR and disposition index were used to measure insulin resistance and secretion, respectively.

**Results:** The risk A-allele in the rs11708067 polymorphism of the adenylate cyclase 5 gene (*ADCY5*) was associated with decreased disposition index (beta = -0.90, SE 0.38, p = 0.019). This polymorphism was an expression quantitative trait loci (eQTL) in islets for both *ADCY5* and its antisense transcript. The risk C-allele in the rs2943641 polymorphism, near the insulin receptor substrate 1 gene (*IRS1*), was associated with increased HOMA-IR (beta = 0.36, SE 0.18, p = 0.050), and the T-allele of the rs4607103 polymorphism, near the ADAM metalloproteinase with thrombospondin type 1 motif 9 gene (*ADAMTS9*), was associated with postpartum diabetes (OR = 2.12, SE 0.22, p = 0.00055). All analyses were adjusted for age, body mass index, and ethnicity.

**Conclusions:** This study demonstrated the genetic susceptibility of women with a history of GDM to impaired insulin secretion and sensitivity and, ultimately, to diabetes development.

## Introduction

During pregnancy, insulin sensitivity progressively decreases, while associated insulin response increases by late gestation [1]. Gestational diabetes mellitus (GDM) develops when beta-cells cannot compensate for increased insulin resistance, despite the physiological changes related to glucose homeostasis during gestation [1]. Women with a history of GDM have a higher risk of developing type 2 diabetes [2] and metabolic syndrome [3] than those who were normoglycemic during pregnancy. Genetic risk factors related to progression to type 2 diabetes in women with a history of GDM have been previously studied by many research groups, including ours. Two polymorphisms (*TCF7L2* rs7903146 and *FTO* rs8050136) and a weighted risk score of type 2 diabetes risk alleles predict diabetes following GDM [4]. Other research groups have shown an association of the genetic risk score (GRS) with eventual progression to diabetes after GDM [5]. However, GRS could not predict the progression to diabetes in women with a history of GDM from the Diabetes Prevention Program (DPP) [6].

Type 2 diabetes is a growing global health concern and is caused by insulin resistance and beta-cell dysfunction [7]. Recent evidence suggests that both insulin secretion and resistance are heritable traits [8] and studies have also demonstrated a genetic contribution to defective insulin secretion and resistance in individuals with type 2 diabetes [9, 10].

Genome-wide association studies (GWAS) have revealed many genetic susceptibility loci for type 2 diabetes and related traits, such as insulin resistance and beta-cell dysfunction [10–15]. In addition, we have recently shown an association of the rs11708067 polymorphism in the *ADCY5* (adenylate cyclase 5) gene with increased 2-h glucose levels and decreased homeostasis model assessment of beta-cell function (HOMA2-B) in Swedish women with GDM [16].

Only a few studies have examined the genetic susceptibility to postpartum diabetes in women with previous GDM [4, 17]. In addition, the genetic architecture of postpartum diabetes and its related traits could differ between ethnicities. Thus, we sought to validate the association of single nucleotide polymorphisms (SNPs) from previous GWAS [10–15] with indices

of beta-cell function, insulin resistance, and eventual progression to diabetes in a cohort of women from Southern Sweden with a history of GDM.

## Participants And Methods

### Participants

Women delivering between 2003–2005 were invited to participate in the study in the County of Skane in Southern Sweden, as described previously [18]. GDM was diagnosed by a 75-g oral glucose tolerance test (OGTT) at the 28th and/or the 12th week of gestation for those with a first-degree relative with diabetes or previous GDM. Study participants were followed-up for development of diabetes using OGTT up to 5 years postpartum or until a diagnosis of diabetes; data were accessible through the primary care journals. GDM and diabetes were diagnosed according to the diagnostic criteria recommended by the WHO in 1999 [19]. Based on these criteria and the availability of stored DNA, a cohort of 374 women with previous GDM (57 of whom developed diabetes) were included in the present study.

### Glycaemic trait measurements

Women underwent OGTT with measurements of both glucose and insulin concentrations at 0, 30, and 120 min to calculate indices of beta-cell function and insulin resistance, at 1–2 years postpartum, as reported previously [20]. Homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate insulin resistance (fasting serum insulin  $\times$  fasting plasma glucose)/22.5 [21]. Insulin secretion capacity was estimated using the disposition index  $([\text{insulinogenic index (insulin}_{30 \text{ min}} - \text{insulin}_{0 \text{ min}})]/(\text{glucose}_{30 \text{ min}} - \text{glucose}_{0 \text{ min}})]/\text{HOMA-IR})$  [22].

### Genotyping

DNA was extracted from whole blood using the MaxiPrep Kit (QIAGEN, Sollentuna, Sweden). SNPs were genotyped using a Sequenom massARRAY platform or TaqMan allelic discrimination assay with an ABI Prism 7900 sequence detection system (Applied Biosystems, Foster City, CA, USA). The success rate of genotyping was > 90%. Replication genotyping of 6% of the samples showed > 98% concordance. All SNPs were in Hardy-Weinberg equilibrium (HWE), except for rs11920090 and rs6467136, which significantly deviated in women who did not develop diabetes postpartum ( $p < 0.01$ ), and were eventually excluded from the analysis. We analysed 12 SNPs previously shown to be associated with measures of insulin secretion [11, 12, 14], and 4 SNPs previously shown to be associated with measures of insulin resistance in GWAS [10, 11, 13], for association with disposition index and HOMA-IR, respectively, in women with previous GDM. We also analysed 70 (2 out of 72 were excluded for not being in HWE) SNPs, previously associated with diabetes in GWAS [11, 15, 23], for association with diabetes postpartum.

### Exploration of expression quantitative trait loci (eQTLs)

Polymorphisms associated with disposition index, HOMA-IR, or T2D were assessed for association with gene expression in human pancreatic islets in RNA-Seq data of 191 donors [24]. The data are uploaded to EGA (<https://ega-archive.org/>) with the following accession numbers: RNAseq: EGAS00001004042, GWAS: EGAS00001004044, and Phenotype: EGAS00001004056.

### Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY) and PLINK (version 1.07, <http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml>). Generalized linear models with maximum likelihood estimates were used for estimating SNP associations with disposition index and HOMA-IR. Age, ethnicity, and body mass index (BMI) were used as covariates/confounders, and data are presented as beta estimates and standard errors (SE). Correction for multiple testing was performed using permutations. We applied a false discovery rate (FDR) for

the association analysis of postpartum diabetes. Since it was a validation of previous associations, we considered  $p \leq 0.05$  as significant.

## Results

### Clinical characteristics

Clinical characteristics of the study subjects were detailed previously [25]. Mean (SE) age of the participants was 32.9 (0.25) years and mean BMI was 25.2 (5.2) kg/m<sup>2</sup>. The study participants were of European (n) 286 [76.5%] or non-European (n) 77 [20.6%] origin, and 11 [2.9%] were unclassifiable.

### Association of SNPs with disposition index

The risk A-allele of SNP rs11708067 in the *ADCY5* locus was associated with decreased disposition index (beta = -0.90, SE 0.38,  $p = 0.019$ ) after adjustment for age, BMI, and ethnicity (Table 1). Interestingly, the rs11708067 polymorphism was an eQTL for both *ADCY5* and the antisense transcript for *ADCY5* (Table 2). The *ADCY5* rs11708067 genotype was also associated with 2-h glucose level, though only in the additive model (AG vs. GG: beta = 0.62, SE 0.33,  $p = 0.06$ ; AA vs. GG: beta = 0.71, SE 0.32,  $p = 0.027$ ).

Table 1  
Single nucleotide polymorphisms with disposition index at 1–2 years postpartum in women with a history of gestational diabetes mellitus.

SNP	Locus	Location	CHR	EA	B (SE)	P-value
rs11708067	<i>ADCY5</i>	Intron	3	A	-0.90 (0.38)	0.019
rs340874	<i>PROX1</i>	Intergenic	1	C	0.09 (0.15)	0.56
rs560887	<i>G6PC2/ABCB11</i>	Intron	2	C	0.027 (0.13)	0.83
rs10885122	<i>ADRA2A</i>	Intergenic	10	G	-0.075 (0.37)	0.84
rs4607517	<i>GCK</i>	Intergenic	7	A	-0.005 (0.17)	0.98
rs2191349	<i>DGKB/TMEM195</i>	Intergenic	7	T	-0.07 (0.20)	0.72
rs7034200	<i>GLIS3</i>	Intron	9	A	-0.04 (0.19)	0.82
rs7944584	<i>MADD</i>	Intron	11	A	-0.24 (0.28)	0.40
rs174550	<i>FADS1</i>	Intron	11	T	-0.001 (0.13)	0.99
rs10830963	<i>MTNR1B</i>	Intron	11	G	0.12 (0.18)	0.49
rs11605924	<i>CRY2</i>	Intron	11	A	-0.60 (0.32)	0.064
rs7756992	<i>CDKAL1</i>	Intron	6	G	-0.25 (0.20)	0.21

CHR = chromosome, EA = effect allele, B = beta/effect size, SE = standard error; significant p-values ( $\leq 0.05$ )

Table 2

The rs11708067 as an expression quantitative trait loci (eQTL) for both adenylate cyclase 5 (*ADCY5*) and the antisense transcript of *ADCY5* in islets (n = 191).

SNP	Gene	Gencode ID	Beta	t_STAT	P-value
rs11708067	ADCY5_ANTISENSE TRANSCRIPT	ENSG00000272678	0.70	5.91	1.56e-08
rs11708067	ADCY5	ENSG00000173175	0.45	3.63	0.00037

SNP = single nucleotide polymorphism; p-values ( $\leq 0.05$ )

### Association of SNPs with HOMA-IR

The risk C-allele of the insulin receptor substrate-1 (*IRS1*) rs2943641 polymorphism was associated with increased HOMA-IR (beta = 0.36, SE 0.18, p = 0.050) after adjustment for age, BMI, and ethnicity (Table 3). This SNP was an eQTL for the *IRS1* gene in adipose tissue (from public data [<https://gtexportal.org/>]) (Table 4) [26].

Table 3

Association of single nucleotide polymorphisms (SNPs) with the homeostasis model assessment of insulin resistance (HOMA-IR) at 1–2 years postpartum in women with a history of gestational diabetes mellitus.

SNP	Locus	Location	CHR	EA	B (SE)	p-value
rs2943641	IRS1	Intergenic	2	C	0.36 (0.18)	0.050
rs4675095	IRS1	Intron	2	A	-0.11 (0.55)	0.83
rs1801282	PPARG	Coding – missense	3	C	0.29 (0.41)	0.48
rs35767	IGF1	Near Gene-5	12	G	0.02 (0.31)	0.94

CHR = chromosome, EA = effect allele, B = beta/effect size, SE = standard error; significant p-values ( $\leq 0.05$ ). HOMA-IR was normalized using rank normal transformation.

Table 4

The rs2943641 as an expression quantitative trait loci (eQTL) for the insulin receptor substrate 1 (*IRS1*) gene in adipose tissue [from The Genotype-Tissue Expression (GTEx) project].

Gencode ID	Gene Symbol	Variant ID	SNP ID	P-value	NES	Tissue
ENSG00000169047.5	IRS1	chr2_226229029_T_C_b38	rs2943641	1.4e-16	-0.30	Adipose - Subcutaneous
ENSG00000169047.5	IRS1	chr2_226229029_T_C_b38	rs2943641	6.1e-12	-0.23	Adipose - Visceral (Omentum)
ENSG00000272622.1	RP11-395N3.2	chr2_226229029_T_C_b38	rs2943641	3.5e-9	-0.23	Adipose - Subcutaneous
ENSG00000261379.1	RP11-395N3.1	chr2_226229029_T_C_b38	rs2943641	2.1e-7	-0.23	Adipose - Subcutaneous
ENSG00000272622.1	RP11-395N3.2	chr2_226229029_T_C_b38	rs2943641	0.0000023	-0.19	Adipose - Visceral (Omentum)

SNP = single nucleotide polymorphism, NES = normal effect size

## Association studies of diabetes postpartum

The T-allele of rs4607103, near the ADAM metallopeptidase with thrombospondin type 1 motif 9 (*ADAMTS9*) gene, was associated with an increased risk of diabetes postpartum (OR for the C-allele 0.47 (CI: 0.30–0.73),  $p = 0.00055$ ;  $pFDR = 0.039$ ) (Table 5). The CC carriers have more insulin resistance than TT carriers ( $\beta = -0.11$ ,  $SE = 0.05$ ,  $p = 0.036$ ). The women who developed diabetes postpartum had a lower disposition index (Mean = 3.01,  $SE = 0.88$  vs. 13.29,  $SE = 0.87$ ,  $p \leq 0.0001$ ), higher insulin resistance HOMA-IR (Mean = 3.20,  $SE = 0.26$  vs. 1.69,  $SE = 0.07$ ,  $p \leq 0.0001$ ), and higher BMI (Mean = 30.48,  $SE = 0.82$  vs. 24.29,  $SE = 0.25$ ,  $p \leq 0.001$ ) (Table 6).

Table 5

Single nucleotide polymorphisms (SNPs) with nominal p-values for association with diabetes up to 5 years after a pregnancy complicated by gestational diabetes mellitus.

SNP	Gene/nearest gene	Location	CHR	RA/OA	OR (CI)	P-value	P-value (FDR_BH)
rs4607103	ADAMTS9-AS2	Intron	3	C/T	0.47 (0.30–0.73)	0.00055	0.039
rs4607517	GCK	Intergenic	7	A/G	1.765 (1.09–2.85)	0.019	0.4902
rs1552224	CENTD2	Intergenic	11	A/C	2.22 (1.09–4.61)	0.024	0.4902
rs11634397	ZFAND6	Intergenic	15	G/A	1.58 (1.03–2.42)	0.037	0.4902
rs7578597	THADA	Coding - missense	2	T/C	3.29 (1.004–10.75)	0.037	0.4902
rs4457053	ZBED3	Intron of ZBED3-AS1	5	G/A	1.56 (1.02–2.38)	0.041	0.4902

CHR = chromosome, SNP = single nucleotide polymorphisms, RA/OA = risk allele/other allele, OR = estimated odds ratio (for risk), P = exact p-value for this test, FDR\_BH = Benjamini & Hochberg (1995) step-up FDR control

Table 6

Disposition index and homeostasis model assessment of insulin resistance in women who developed diabetes compared to that in women without diabetes postpartum.

Variable	Women with postpartum diabetes Mean (SE)	Women without postpartum diabetes Mean (SE)	p-value
Disposition index	3.01 (0.88) N (57)	13.29 (0.87) N (256)	< 0.0001
HOMA-IR	3.20 (0.26) N (54)	1.69 (0.07) N (277)	< 0.0001
BMI	30.48 (0.82) N (57)	24.29 (0.25) N (316)	< 0.001
N = number of women, SE = standard error; significant p-value ( $\leq 0.05$ )			

## Discussion

In this study, we found an association between the risk A-allele of *ADCY5* rs11708067 and decreased disposition index derived from OGTT at 1–2 years postpartum in women with previous GDM. This was concordant with previous findings of an association of rs11708067 with HOMA-B, a measure of insulin secretion [11], and the involvement of the *ADCY5* gene in regulation of insulin secretion in pancreatic islet  $\beta$ -cells [27]. Previous studies reported reduced *ADCY5* mRNA expression in islets due to risk alleles at rs11708067 [28] and suggested that *ADCY5* rs11708067 is essential for coupling glucose to insulin secretion in human islets [28]. Wagner et al. implicated the rs11708067 polymorphism in defective proinsulin-to-insulin conversion [29]. Furthermore, rs11708067 is an eQTL in islets for both *ADCY5* and the antisense transcript for *ADCY5* supports the role of this SNP in impairment of insulin secretion in women with previous GDM, thus increasing the risk of diabetes postpartum. We also found that the *ADCY5* rs11708067 genotype was associated with 2-h glucose level, consistent with the previous results from our group [16] as well as others [11, 29].

Our analysis also identified an association of the risk C-allele of rs2943641 near the *IRS1* gene with HOMA-IR in our cohort. *IRS1* is a substrate of the insulin receptor tyrosine kinase, which plays a crucial role in the insulin signalling pathway and is expressed in insulin-sensitive tissues [30]. This finding agrees with an earlier study by Rung J et al., who reported an association of the C-allele of rs2943641 with measures of insulin resistance (HOMA-IR and ISI) and hyperinsulinemia in French, Danish, and Finnish participants from population-based cohorts [10]. Moreover, this SNP has been associated with type 2 diabetes in meta-analyses involving European [10] and Japanese participants [31]. Notably, rs2943641 is an eQTL for the *IRS1* gene in adipose tissue. Thus, genetic variation near *IRS1* may increase the risk of postpartum diabetes in women with previous GDM through increased insulin resistance.

Finally, we found that the T-allele of rs4607103, near the *ADAMTS9* gene, could predict development of diabetes in our cohort. However, the risk allele in this study was opposite to that reported for diabetes [15]. Graae et al. showed that the C-allele was associated with increased expression of secreted ADAMTS9 and decreased insulin sensitivity and signalling in human skeletal muscle [32]. Contrarily, in our data CC carriers seemed to have reduced insulin resistance compared to TT carriers, although there was no significant association. This phenomenon is not uncommon in genetics [33]; the actual functional variant in the *ADAMTS9* region is not yet known, and the rs4607103 polymorphism may be in a linkage disequilibrium with the functional variant in this region. Interestingly, the C-allele was associated with protection from type 2 diabetes in African Americans [34] but our study population was primarily European. Moreover, a potential gender effect

could not be excluded [35]. Women who developed Diabetes were more likely to have severe beta-cell dysfunction and were unable to meet the demands of increased insulin resistance compared to those who did not develop diabetes postpartum. Therefore, women who developed diabetes postpartum could represent a unique subtype with a more severe beta-cell dysfunction than those with previous GDM who did not develop diabetes during the study period, which might also explain the protective effect of the rs4607103 polymorphism. We do not have any data on the presence of antibodies in women who developed diabetes postpartum. Since approximately 1% of women with diabetes postpartum are diagnosed with type 1 diabetes postpartum in Sweden [36], the vast majority of women included in this study were expected to have been diagnosed with type 2 diabetes.

A strength of this study was the use of the disposition index, derived from OGTT, as a measure of beta-cell function adjusted for insulin resistance. The women in the study were followed up for development of diabetes up to 5 years postpartum. Our study provides novel insights into the genetic variants associated with postpartum diabetes and its related traits. A major weakness of the study was the failure to correct for multiple comparisons in the analyses, except for the analysis of development of diabetes after pregnancy. However, the analyses were adjusted for age, BMI, and ethnicity; permutations were performed to address the issue to a certain extent. The studied SNPs were previously shown to be associated with their respective traits, suggesting that this study could be considered a replication study. The study did not aim to detect small potential effects of the studied SNPs on insulin secretion and sensitivity.

In conclusion, we demonstrated the genetic susceptibility for impaired insulin secretion and sensitivity, as well as for the development of diabetes in women with a history of GDM. This finding could aid in the early identification of women at higher risk of developing diabetes postpartum.

## **Declarations**

### **Ethics approval and consent to participate**

The study was approved by the Ethics Committee of Lund University (LU 259-00) and written informed consent was obtained from all women included in the study.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that there is no conflict of interest associated with this manuscript.

### **Authors contribution statement**

RPB and NS designed the study. RPB and NS wrote the first draft, reviewed and edited the manuscript. NS supervised the study. RPB performed the statistical analysis. AK and KK reviewed and edited the manuscript. NS is the guarantor of this work.

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