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ORIGINAL ARTICLE

Implication of *SH2B1* gene polymorphism studies in gestational diabetes mellitus in Saudi pregnant women

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Abstract Genome-wide association studies have identified loci that are firmly associated with obesity. The Src-homology-2 B adaptor protein 1 (*SH2B1*) loci is abundantly expressed in the brain, liver, heart, muscle, and fat tissues. Gestational diabetes mellitus (GDM) is a growing health concern that usually appears during the latter half of pregnancy, and it is characterized by carbohydrate intolerance of variable severity. The *SH2B1* gene polymorphism has been linked with an increased risk of weight gain in several but not all population studies. This study aimed to investigate the genetic association of rs4788102 variants in the *SH2B1* gene with GDM in Saudi pregnant women. Genomic DNA samples from 200 women with GDM and 300 women without GDM were genotyped using the TaqMan method. The distribution of the GG, GA, and AA genotypes was significantly different between GDM and non-GDM women ($p < 0.05$). Thus, we identified rs4788102 variants as additional risk factors for GDM in Saudi women, and we suggest that these variants may have a prognostic value.

1. Introduction

Gestational diabetes mellitus (GDM), defined as any glucose intolerance detected during pregnancy, is a clinical condition associated with higher risks for maternal and perinatal morbidity (Khan et al., 2013). GDM is observed in approximately 22% of pregnancies and is associated with pregnancy complications and long-term risk of diabetes in both mother and fetus/offspring as well as predisposition to obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM) (Bassols et al., 2013; Wahabi et al., 2013). Well-documented risk factors for GDM include pre-pregnancy overweight, obesity, family history of GDM and T2DM, and advanced maternal age; history of subfertility or infertility may also be related to elevated risk of GDM (Reyes-Munoz et al., 2012; Jaques et al., 2010). Polycystic ovarian syndrome, a contributor to ovulatory fertility disorders, has been repeatedly linked to increased GDM risk (Boomsma et al., 2006; Bals-Pratsch

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et al., 2011; Zhang et al., 2013). Previous studies have indicated that poor diet and low physical activity before or during pregnancy may also be risk factors for GDM (Zhang and Ning, 2011). Current genome-wide association studies (GWASs) have identified 32 loci that are firmly associated with obesity, and among them, the Src-homology-2 B adaptor protein 1 (*SH2B1*) loci at 16p1 is abundantly expressed in the brain, liver, heart, muscle, and fat tissues (Prudente et al., 2011). Genome-wide association study-derived frequent variations (Ren et al., 2007; Li et al., 2007; Doria et al., 2008; Soccio et al., 2006), rare deletions (Sharma et al., 2011), and rare non-synonymous mutations (Jamshidi et al., 2007), at the *SH2B1* locus are pathogenic for obesity. Further studies have suggested that *SH2B1* is a physiological enhancer of insulin receptor and downstream signaling (Gorfien et al., 1993; Federici et al., 2004). Being pathogenic for both obesity and insulin resistance, *SH2B1* is a strong candidate for involvement in T2DM risk (Prudente et al., 2011).

Genetic and epidemiological studies have suggested an association between GDM and T2DM, whereas the prevalence of GDM is increasing parallel with the increased prevalence of T2DM (Shaat et al., 2007). No studies have examined the association between GDM and rs4788102 polymorphism in the *SH2B1*. Therefore, TaqMan assay was used to investigate the distribution of allele and genotype frequencies of rs4788102 polymorphism in Saudi women who developed GDM.

2. Materials and methods

2.1. Subjects

This cross-sectional study comprised 500 pregnant women: 200 with GDM and 300 without GDM. All of the women in the study were recruited from the Department of Obstetrics and Gynecology, outpatient clinic at the King Khalid University hospital (KKUH) in Riyadh, Kingdom of Saudi Arabia.

Pregnant women were selected based on the glucose challenge test (GCT) and oral glucose tolerance test (OGTT) results and were advised to fast overnight after three days of consuming an unrestricted diet. Fasting plasma samples were drawn 1, 2, and 3 h after the administration of glucose to perform the 100-g OGTT test. If two or more values were abnormal, the patient was considered GDM positive, whereas GDM-negative women were considered non-GDM/healthy controls or normal controls. GDM women were treated with diet alone, insulin, or both. In this study, insulin therapy was required for 10% of the subjects with GDM, and 90% of the GDM subjects followed a prescribed diet.

2.2. Ethical approval

The study protocol was approved by the institutional review board of the College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia (E-12-675). Informed consent was obtained from each patient involved in the study.

2.3. Assessment

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Subjects with BMIs >30 kg/m^2 were categorized as obese. Fasting and postprandial blood biochemical parameters included high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC). GCT and OGTT were measured with a commercially available clinical chemistry kit purchased from Konelab (Espoo, Finland). Plasma glucose standards that exceeded 7.8 mmol/L were considered GCT positive. Five milliliters of venous blood was collected from all subjects; 3 mL of the serum was used for biochemical analysis, and 2 mL was used for genetic analysis.

2.4. Genetic analysis

Genomic DNA was extracted from whole peripheral blood collected in an Ethylenediaminetetraacetic acid tube using an AccuVis kit (AccuVis Bio, UAE). DNA samples were stored at -80 °C. Allelic discrimination was performed using the TaqMan single-nucleotide polymorphism genotyping assays (rs4788102 and C_26672045_10) on an Applied Biosystems Prism 7300 real-time polymerase chain reaction apparatus (Applied Biosystems, Foster City, CA, USA) using the default cycling conditions. TaqMan fluorogenic probes bearing a suitable reporter dye on the 5′ end and a quencher dye on the 3′ end were designed and produced by Applied Biosystems. Both the VIC and the FAM probes were labeled from the 3′ to the 5′ end, and serial dilutions were run to determine the optimal working concentration.

2.5. Statistical analysis

Categorical variables were analyzed with the χ^2 test and used to compare genotype frequencies between GDM and non-GDM subjects. Univariate and multivariate logistic regression analyses were used to compute odds ratio (OR) and 95% confidence interval (95% CI) with the SPSS software version 19 (SPSS, Inc., Chicago, IL, USA). Descriptive results of continuous variables are expressed as means ± standard error of the mean. Bonferroni tests were carried out to correct the effect of age on these relationships. Agreement with the Hardy–Weinberg equilibrium was tested using the χ^2 goodness-of-fit test. Comparison of the means between the two groups was analyzed with Student's *t*-test. The χ^2 test was used to compare the proportion of genotypes or alleles. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Clinical particulars

The anthropometric and biochemical parameters of the GDM and non-GDM subjects are highlighted in Table 1. The GDM and non-GDM subjects were similar, and anthropometric measurements including age, weight, height, and BMI were the same ($p > 0.05$). The values of coagulated serum parameters such as fasting blood sugar, postprandial blood glucose, GCT, and OGTT and lipid profile tests consisting of TC, TG, HDL-C, and LDL-C were higher in the GDM subjects ($p < 0.05$). Family history of GDM and T2DM was more frequent in women with GDM ($p < 0.05$). Women with recognized GDM (90%) were prescribed a diet to maintain normal

Table 1 Demographic characteristics of the pregnant women.

S. No.	Aspects	GDM cases (n = 200)	Non-GDM (n = 300)	Statistical significance
1	Age (years)	32.43 ± 5.79	31.36 ± 6.02	$p = 0.55$
2	Weight (kg)	77.1 ± 13.34	74.85 ± 12.09	$p = 0.12$
3	Height (m^2)	158.51 ± 5.92	157.81 ± 5.31	$p = 0.08$
4	BMI (kg/m^2)	33.43 ± 4.68	33.36 ± 4.28	$p = 0.16$
5	Mean gestational age	30.27 ± 5.77	NA	NA
6	FBS (mmol/L)	5.0 ± 0.93	4.5 ± 0.87	$p < 0.0001$
7	PPBG (mmol/L)	6.8 ± 2.0	4.9 ± 1.8	$p = 0.0001$
8	GCT (mmol/L)	9.5 ± 1.8	6.3 ± 1.5	$p < 0.0001$
9	OGTT (Fasting hour)	5.2 ± 1.18	4.5 ± 0.87	$p < 0.0001$
10	OGTT (1st hour)	10.7 ± 1.8	8.0 ± 1.7	$p < 0.0001$
11	OGTT (2nd hour)	9.2 ± 1.8	6.7 ± 1.6	$p < 0.0001$
12	OGTT (3rd hour)	5.6 ± 1.7	4.5 ± 1.3	$p < 0.0001$
13	TG (mmol/L)	2.3 ± 1.8	1.7 ± 0.98	$p < 0.0001$
14	TC (mmol/L)	5.7 ± 1.2	5.2 ± 1.0	$p < 0.0001$
15	HDL-C (mmol/L)	0.92 ± 0.38	0.64 ± 0.24	$p < 0.0001$
16	LDL-C (mmol/L)	3.7 ± 0.93	3.7 ± 1.0	$p = 0.82$
17	Family history of T2DM (n%)	120 (60%)	55 (18.3%)	$p < 0.0001$
18	Family history of GDM (n%)	46 (23%)	13 (4.3%)	$p < 0.0001$
19	R_x (diet/insulin)	180 (90%)/20 (10%)	NA	NA

glucose values, whereas 10% of these women were using 4–8 units of insulin owing to diet failure.

3.2. Occurrence of rs4788102 polymorphism in pregnant women

The genotypic distribution of rs4788102 polymorphism was consistent with the Hardy–Weinberg equilibrium ($p > 0.05$). Significant differences in the frequencies for the A allele and AA genotype in the rs4788102 polymorphism were found between the patients with GDM and the women with normoglycemic pregnancies, as shown in Table 2. Statistically significant difference was found in the genotypic distribution between GDM and non-GDM subjects [GA vs GG: $p = 0.02$, OR = 1.52 (95% CI, 1.05–2.26)]. Significant difference was observed in the frequency of the G and A alleles in GDM and non-GDM subjects [A vs G: $p = 0.01$, OR = 1.41 (95% CI, 1.05–1.89)] (Table 3). When we performed the dominant model for pregnant women, we found evidence for an association between rs4788102 and risk of GDM [for AA + GA vs GG, $p = 0.02$, OR = 1.52 (95% CI = 1.05–2.20)].

3.3. Distribution of genotype-based characteristics

To determine the consequence of rs4788102 polymorphism on anthropometric, biochemical, and clinical parameters, we analyzed the distribution of these variables in relation to the GG and GA + AA genotypes. The analysis revealed that BMI and TG have showed a significant association with the characteristics shown in Table 4 ($p < 0.05$). Other characteristics were found to be insignificant ($p > 0.05$).

Table 3 Genotype and allele distribution between GDM cases and non-GDM subjects.

Genotypes/alleles	Odds ratio + 95% class interval + p value
GA vs GG	OR-1.512; 95% CI (1.009–2.265); $p = 0.04$
AA vs GA	OR-1.034; 95% CI (0.5392–1.984); $p = 0.91$
AA vs GG	OR-1.564; 95% CI (0.8523–2.87); $p = 0.14$
AA + GA vs GG	OR-1.525; 95% CI (1.056–2.202); $p = 0.02$
GA vs GG + AA	OR-1.419; 95% CI (0.957–2.104); $p = 0.08$
AA vs GG + GA	OR-1.369; 95% CI (0.7576–2.475); $p = 0.29$
A vs G	OR-1.416; 95% CI (1.056–1.899); $p = 0.01$

4. Discussion

This cross-sectional study examined rs4788102 polymorphism in the *SH2B1* gene in Saudi pregnant women with and without GDM. Screening and identifying GDM is based on biochemical criteria, and serum samples are used, despite the progress of genetic screening methods. No genetic test is currently available to identify GDM (Alharbi et al., 2014). To the best of our

Table 2 Genotype and allele distribution of the *SH2B1* gene polymorphism for GDM and non-GDM subjects.

SH2B1 (rs4788102)	GDM N (%)	Non-GDM N (%)	Odds ratio (95% CI)	p value
N	200	300		
GG	112 (56)	198(66)	Reference	
GA	65 (32.5)	76 (25.3)	1.5(1.00–2.26)	0.04*
AA	23 (11.5)	26 (8.7)	1.0(0.53–1.98)	0.91
GA + AA	88 (44)	102 (34)	1.5(1.05, 2.20)	0.02*
G	289 (0.72)	472 (0.79)	Reference	
A	111 (0.28)	128 (0.21)	1.4(1.05, 1.89)	0.01

* After continuity correction.

Table 4 Anthropometric and metabolic parameters according to the *SH2B1* polymorphisms.

Aspects	GG (n = 112)	GA + AA (n = 88)	p value
Age (years)	32.9 ± 5.6	32.1 ± 5.8	0.31
Age of onset	30.5 ± 5.6	29.9 ± 6.0	0.52
BMI (kg/m^2)	30.5 ± 4.1	33.2 ± 5.3	0.01
FBS (mmol/L)	5.0 ± 1.2	4.9 ± 0.60	0.83
PPBG (mmol/L)	6.5 ± 1.9	7.0 ± 2.0	0.23
GCT (mmol/L)	9.8 ± 2.1	9.3 ± 1.6	0.41
OGTT (Fasting hour)	5.2 ± 1.4	5.2 ± 1.3	0.73
OGTT (1st hour)	10.9 ± 1.5	10.6 ± 1.9	0.38
OGTT (2nd hour)	9.3 ± 1.9	8.9 ± 1.9	0.24
OGTT (3rd hour)	4.9 ± 2.9	4.6 ± 2.4	0.54
TG (mmol/L)	1.6 ± 0.76	1.9 ± 1.06	0.0009
TC (mmol/L)	5.3 ± 1.0	5.1 ± 1.1	0.24
HDL-C (mmol/L)	0.63 ± 0.26	0.65 ± 0. 32	0.69
LDL-C (mmol/L)	3.8 ± 0.94	3.7 ± 0.91	0.13

knowledge, this study is the first to be conducted in pregnant women as well as in Saudi population. We explored the effects of rs4788102 variants of the *SH2B1* and found that the variant allele rs4788102 of *SH2B1* is significantly associated with GDM.

Many factors, including obesity, family history of T2DM, and other complications, reportedly influence the pathogenesis of GDM, which is thought to be a multifactorial disease similar to essential hypertension, T2DM, and chronic heart disease. The association of gene polymorphisms with GDM has been a major focus of recent research. Earlier publications have shown that the rs4788102 polymorphism has been associated with obesity, metabolic syndrome, BMI, TG level and T2DM (Takeuchi et al., 2011; Volckmar et al., 2012; Vastermark et al., 2012; Yang et al., 2013; Guo et al., 2013).

During pregnancy, the combination of increased maternal adiposity and the insulin-desensitizing hormonal products of the placenta results in insulin resistance. In this scenario, pancreatic β-cells enhance insulin secretion to compensate for the resistance. However, in women with GDM, the pancreatic β-cells are dysfunctional or the insulin supply becomes inadequate. This dysfunction is most likely where T2DM susceptibility genes play a role in the impairment of insulin secretion as well as in the pathogenesis of GDM, which may have the same genetic background as T2DM, given the evidence for the clustering of T2DM and impaired glucose tolerance in

Table 5 Earlier studies carried out in the *SH2B1* gene in different ethnicities.

S. No.	References	Disease	Significance
1	Zhoa et al. (2014)	Metabolic syndrome	No
2	Prudente et al. (2013)	Glucose homeostasis	No
3	Warrington et al. (2013)	Obesity in children	No
4	Volckmar et al. (2012)	Obesity	Yes
5	Yang et al. (2013)	Metabolic syndrome	Yes
6	Guo et al. (2013)	Body mass index	Yes
7	Vastermark et al. (2012)	Triglyceride levels	No
8	Beckers et al. (2011)	Obesity	Yes
9	Wang et al. (2012)	Overweight/obesity	No
10	Sandholtch et al. (2011)	T2DM	Yes
11	Prudente et al. (2011)	CAD/MI	No/Yes
12	Hotta et al. (2011)	Fat visceral obesity	Yes
13	Hotta et al. (2011)	Metabolic Syndrome	No
14	Gutierrez-Aguilar et al. (2012)	Obese rats	No
15	Hester et al. (2012)	Obesity	Yes
16	Takeuchi et al. (2011)	Obesity + T2DM	Yes
17	Perez-Lglesia et al. (2010)	Weight gain	No
18	Shi et al. (2010)	Obesity women	Yes
19	Holzapfel et al. (2010)	Obesity	Yes
20	Bochukova et al. (2010)	Obesity	Yes
21	Hotta et al. (2009)	Obesity	No
22	Bauerf et al. (2009)	Obesity	No
23	Willer et al. (2009)	Body mass index	No
24	IMSGC (2009)	Auto immune Disorder	No
25	Yamada et al. (2008)	Bone mineral density	Yes
26	Present study	GDM	Yes

families with women with GDM and the higher prevalence of T2DM in the mothers of women with GDM (Cho et al., 2009). Our results provided evidence that rs4788102 is a susceptibility gene locus for GDM in Saudi pregnant women [$p = 0.01$, OR = 1.41 (95% CI: 1.056–1.899)]. No other studies of this polymorphism have been carried out in GDM in any ethnicity.

No clinical effects of this polymorphism were observed in this prospective study. This absence is clearly a limitation of the study and indicates that the influence of rs4788102 polymorphism on obesity risk may be of major importance in women with GDM (see Table 4). However, the subjects in our study had only a mean age greater than 30, which indicates the presence of obesity in both GDM and non-GDM subjects. The *SH2B1* gene polymorphism has been associated with various diseases, primarily obesity, in many ethnicities (Table 5).

The *SH2B1* causes weight gain and encodes an adaptor molecule through which hormones such as leptin and insulin send signals from the bloodstream to target tissues such as the neurons in the brain. Defects in the *SH2B1* have been found in obese patients. In clinical studies, patients had an increased drive to eat and resistance to the effects of circulating insulin, and they were slightly shorter than expected. These studies have established that *SH2B1* may be important in weight problems and diabetes.

5. Conclusion

In conclusion, we propose that genetic polymorphism of the *SH2B1* could be of value in the prediction and diagnosis of GDM. Further research is warranted to confirm the causality. The association of the AA genotype and the A allele with GDM should be examined in multiple well-designed epidemiological genetic studies, and the physiological effects should be identified.

Conflict of Interest

The author declares that there is no conflict of interest.

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