Insertion and deletion polymorphism in the alpha-2B adrenoceptor gene in pregnant women ripens gestational diabetes mellitus

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Abstract There are no earlier studies that reported the association of the 12Glu9 polymorphism in the alpha-2B adrenoceptor (ADRA2B) gene with gestational diabetes mellitus (GDM). We examined the potential association between the ADRA2B gene insertion/deletion (I/D) polymorphism in the Saudi population with GDM. Pregnant women with GDM have been reported to exhibit the same susceptibility as that observed in type 2 diabetes mellitus (T2DM). We have selected I/D polymorphism of the ADRA2B gene located in chromosome 2q11.1 that has been extensively related to T2DM and cardiovascular diseases. This case–control study was conducted with 200 GDM and 300 non-GDM pregnant women. Genotyping of I/D polymorphism was performed by conventional PCR method. Biochemical analyses were found to be significantly different between GDM and non-GDM subjects (p < 0.05). Genotype (ID + DD vs II, p = 0.0002) and allele (D vs I, p = 0.0002) frequencies of the 12Glu9 polymorphism were found to be statistically significant. However, a significant difference was found between allele and genotypes of I/D polymorphism of the ADRA2B gene or the clinical characteristics of the subjects. Our results obtained in this study indicate the ADRA2B gene in the Saudi women was associated with the development of GDM.

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1. Introduction

Gestational diabetes mellitus (GDM) remains one of the most common clinical issues that obstetrician’s face (Hiraoka et al., 2011). The clinical characteristics of pregnant women that are associated with a high risk for GDM include obesity, increased Body Mass Index (BMI), family history of type 2 diabetes
mellitus (T2DM)/GDM, advanced maternal age, and glycosuria (Chon et al., 2013). GDM is a common pregnancy complication and a strong predictor for T2DM (Hederson et al., 2013). Epidemiological studies have confirmed that GDM is associated with increased feto-maternal morbidity and long-term complications in both the mothers and offspring. The pathogenesis of GDM is largely unknown. Women with a history of GDM are at an increased risk of developing T2DM later in their lives, and women with a family history of diabetes may be predisposed to an increased risk of GDM (Wang et al., 2012). GDM and T2DM share common pathophysiological features, including β-cell dysfunction and insulin resistance. The prevalence of GDM and T2DM continue to increase in many racial/ethnic populations. In the Kingdom of Saudi Arabia, the overall prevalence of GDM and T2DM is 22% (Wahabi et al., 2013) and T2DM has 23.1% respectively (Al-Daghri et al., 2012).

A common nonsynonymous variant (12Glu9) of the human α2β-adrenergic gene (ADRA2B) encodes a receptor protein leading to the insertion/deletion (I/D) of three consecutive glutamate residues at amino acid positions 301–303, and it has been associated with hypertension/T2DM (Vasudevan et al., 2008) and acute coronary events (Heinonen et al., 2002; Snapir et al., 2001). Vasudevan and coworkers (2008) found that the ADAR2B I/D polymorphism was associated with T2DM in Malaysian subjects. However, the exon 1 region of the ADAR2B I/D polymorphism has not been reported in GDM. Therefore, the goal of the present study was to determine whether the ADAR2B I/D polymorphism plays an important role in Saudi pregnant women who develop GDM.

2. Materials and methods

2.1. Study design

In this case–control study, we selected 500 pregnant women from the Department of Obstetrics and Gynecology, King Khalid University Hospital (KKUH), King Saud University, Riyadh, Saudi Arabia. The study included 200 GDM women who developed diabetes during pregnancy and 300 non-GDM women. We excluded 132 antenatal patients who were prediagnosed with type 1 or type 2 diabetes. Non-GDM women had normal glucose levels and demonstrated normal glucose tolerance (NGT). Samples of 5 mL of venous blood were collected from all pregnant women; 3 mL of each serum sample was used for biochemical analysis to confirm the disease, and 2 mL of each ethylenediaminetetraacetic acid (EDTA) sample was used for molecular analysis. The study protocol was approved by the Institutional Review Board at the Faculty of Medicine, King Saud University, and all pregnant women who participated in the study provided written informed consent. GDM and non-GDM samples were obtained by senior physician at KKUH.

2.2. Glucose test

Pregnant women without a previous diagnosis of glucose intolerance were routinely screened for GDM by two methods between 24 and 28 weeks of gestation. Initially, a 50 g glucose challenge test (GCT) was used as a preliminary screen. The GCT was considered positive if the plasma glucose values surpassed 7.8 mmol/L. Pregnant women with positive GCTs were evaluated with the second method, i.e., a 100 g oral glucose tolerance test (OGTT). Diagnosis of GDM was based on criteria set by the American Diabetes Association (Swan et al., 2007). After an overnight fast that followed for three days of unrestricted diet, fasting plasma samples were drawn after one, two, and three hours of glucose administration. The glucose threshold values are shown in Table 1. A diagnosis of GDM was made if two or more of the glucose values met or exceeded the threshold value. NGT was diagnosed when all plasma glucose values were below the threshold values. Based on the above criteria, 200 subjects with GDM and 300 with NGT were recruited into the study. The NGT patients were considered as controls, or non-GDM, for this study.

2.3. Anthropometric measurement

Anthropometric measurements were obtained by trained personnel at the health care centers. Height and body weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Body Mass Index (BMI) was calculated as weight/height² (kg/m²). Subjects with BMI > 30 kg/m² were categorized as obese. Waist circumference was measured to the nearest 0.5 cm at the level of the midpoints of the lowest rib, and the hip circumference was measured to the nearest 0.5 cm at the maximum extension of the buttocks.

2.4. Biochemical analysis

Fasting and postprandial blood and lipid profile biochemical parameters were assessed. High-density lipoprotein-cholesterol (HDLC), triglycerides (TG), total cholesterol (TC), and plasma glucose were measured with an automated clinical chemistry analyzer (Kit provided by KoneLab, Espoo, Finland) using commercially available kits. Dyslipidemia (low levels of HDLC) was defined as HDLC levels < 1.03 mmol/L. It was measured to the nearest 0.5 cm at the level of the midpoints of the lowest rib, and the hip circumference was measured to the nearest 0.5 cm at the maximum extension of the buttocks.

2.5. Genetic analysis

DNA was extracted from peripheral leukocytes using the standard AccuVis Bio DNA extraction kit (AccuVis Bio, UAE). DNA samples were stored at −80 °C. The concentration of genomic DNA was quantitatively determined by optical density measurements using a NanoDrop 2000 (Thermo Fisher Scientific, MA, and USA). The purity was determined by calculating the ratio of absorbance at 260 nm to absorbance at 280 nm (A260/A280). Non-anealed DNA should have an A260/A280 ratio of 1.7–1.9. For the 12Glu9 I > D polymorphism, the primers 5’-AGGGTGTTTGTGGGGCATCT-3’

| Table 1 Diagnosis of GDM with a 100 g oral glucose tolerance test. |
|-----------------|--------|---|
|                  | mmol/L | mg/dL** |
| Fasting          | 5.3    | 95      |
| First hour       | 10.0   | 180     |
| Second hour      | 8.6    | 155     |
| Third hour       | 7.8    | 140     |

** mg/dL – milligram/deciliter. * mmol/L – milli molar/liter.
primer, 6 of 20

tion of the I/D polymorphism was performed in a total volume
the insertion and deletion alleles, respectively.

designated the insertion, and the smaller allele of
12Glu9 allele of
by electrophoresis on a 12% polyacrylamide gel. The larger
(Bhyderabad, India). The amplified products were analyzed
DNA. Primers were synthesized by Bioserve Biotechnologies
included MgCl2
reaction mixture composed of 2 μL (10 pmol) of each
primer, 6 μL of sterile water, and 10 μL of a 2x master mix that included MgCl2, 10x Taq buffer, 10 unit of Taq DNA poly-
merase (Norgen Biotek corp, Canada), and 2 μL template
daNA. Primers were synthesized by Bioserve Biotechnologies
(Hyderabad, India). The amplified products were analyzed
electrophoresis on a 12% polyacrylamide gel. The larger
allele of 12Glu9 contained 3 tandem, 9 bp repeats and it was
designated the insertion, and the smaller allele of 12Glu9 con-
tained no tandem repeats, being designated as the deletion.
The sizes of the PCR products were 112 bp and 103 bp for
the insertion and deletion alleles, respectively.

2.6. Statistical analysis

Clinical characteristics of all the subjects were expressed as the
mean ± SD. Alleles and genotype frequency differences
between GDM patients and non-GDM subjects were tested
using a chi-square test. Odds ratios (ORs) and 95% confidence
intervals are calculated by binomial logistic regression for the
allele, genotype, and haplotype frequencies, and the chi-square
test was used to identify departures from the Hardy–Weinberg
equilibrium. Statistical analyses were performed with SPSS
version 19.0 software. A p-value of < 0.05 was considered
statistically significant.

3. Results

3.1. Clinical characteristics

Clinical, biochemical, and anthropometric data are shown in
Table 2 for GDM and non-GDM subjects. The results show
that GDM subjects were significantly older than controls, but
anthropometric measurements, including weight, height, BMI and LDL-C were not significantly different (p > 0.05).
The biochemical profile, consisting of FBS, PPBG, GCT,
OGTT, TC, TG, and HDL-C was significantly higher in
GDM patients compared with non-GDM subjects
(p < 0.05). Family histories of T2DM and GDM patients were
significantly different between the groups (p < 0.05). Women
diagnosed with GDM were given dietary instructions by a
dietician as soon as possible after diagnosis. Ninety percent
of the GDM women were on diet, and 10% of them were using
insulin because they were unable to maintain normal blood
glucose levels by the diet.

3.2. Genotype and allele distribution

The genotype and allele distribution of 12Glu9 variants are summarized in Table 3. Distribution of genotypes and allele
frequencies of the 12Glu9 polymorphism in GDM and
non-GDM women satisfy the Hardy–Weinberg equilibrium.
The genotype and allele frequencies for the 12Glu9 polymor-
phism were significantly different between GDM and non-
GDM subjects. The results from this study show a high
prevalence of the DD genotype in GDM women (6.5%) com-
pared to non-GDM (2.3%). The frequency of the D allele was
15.2% in the GDM group and 7% in the non-GDM group.
Notably, a significant association was observed between I/D
polymorphism and genotypes/allele frequencies, i.e., between
the ID + DD genotype and the D allele [OR-2.3 (1.48, 3.8),
p = 0.0002; OR-2.3 (1.57, 3.6), p = 0.0002].

3.3. Association of the ADRA2B gene variants with clinical and
biochemical parameters

The prevalence of different components of the ADRA2B gene
was analyzed based on the 12Glu9 polymorphisms and geno-
types. Results showed that the DD and ID genotypes were sig-
nificantly associated only with TC (p = 0.03), whereas the II
genotype was found to have high values of weight, height,
BMI, FBS, PPBG, GCT, and HDL-C (p > 0.05). Family his-

tory of T2DM and GDM was found to be high among individ-
uals with the II genotype. More than 88% of the pregnant
women were on a diet, and 11.8% of the pregnant women were
on insulin (Table 4).

4. Discussion

There are many factors, such as obesity, family history of
T2DM, and other complications, that have been reported to
influence the pathogenesis of GDM, thought to be a multifac-
torial disease similar to essential hypertension, T2DM, and
chronic heart disease (CHD). The association of gene poly-
morphisms with GDM has been a major focus of recent
research. Our team genotyped a target SNP, rs4426564,
located at the 5’-end of exon 1 of the ADRA2B gene. We stud-
ied I/D (12Glu9) polymorphism in Saudi women, grouped
according to those who do and do not develop GDM.

It is understood that the etiology of GDM is similar to
T2DM, where genetic and environmental factors affect disease
onset and progression during pregnancy. The hyperglycemia
associated with GDM is detected at one point in a women’s
life. If glucose levels are already in the diabetic range, GDM
could represent glucose intolerance that is limited to preg-
nancy, where it is chronic but stable, or the detected GDM
could indicate progression to diabetes (Buchanan and Xiang,
2005). The 12Glu9 or I/D polymorphism is linked to the auto-

donomic dysfunction and increased sympathetic nervous system
activity (Papanas et al., 2007). These characteristics have been
associated with adverse metabolic and vascular effects, includ-
ing reduced basal metabolic rate (Heinonen et al., 1999), obesity
(Siitonen et al., 2004), and earlier onset of diabetes
(Papazoglou et al., 2006), acute coronary ischemia (Snipir
et al., 2001), T2DM with neuropathy (Papanas et al., 2007), sudden
cardiac death (Laukkanen et al., 2009), spontaneous
abortions (Galazios et al., 2011), migraine (Ni et al., 2010),
glucose 6 phosphate dehydrogenase (Alharbi et al., 2013), sui-
cide (Fukutake et al., 2008), and hypertension with and with-
out T2DM (Vasudevan et al., 2008). Several studies of
subjects from different ethnic backgrounds have reported a
positive or negative association between the ADRA2B gene
Table 2  Clinical details.

| S. No | Aspects                        | GDM cases (n = 200) | Controls (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 (m²)                    | 158.51 ± 5.92       | 157.81 ± 5.31      | p = 0.08                 |
| 4     | BMI (kg/m²)                    | 34.43 ± 4.68        | 33.36 ± 4.28       | p = 0.16                 |
| 5     | Hypertension (%)               | 76 (38%)            | 14 (4.6%)          | p < 0.0001               |
| 6     | Mean gestational age           | 30.27 ± 5.77        | NA                 | NA                       |
| 7     | FBS (mmol/L)                   | 5.0 ± 0.93          | 4.5 ± 0.87         | p < 0.0001               |
| 8     | PPBG (mmol/L)                  | 6.8 ± 2.0           | 4.9 ± 1.8          | p = 0.0001               |
| 9     | GCT (mmol/L)                   | 9.5 ± 1.8           | 6.3 ± 1.5          | p < 0.0001               |
| 10    | OGTT (Fasting hour)            | 5.2 ± 1.5           | 4.5 ± 0.87         | p < 0.0001               |
| 11    | OGTT (1st hour)                | 10.7 ± 1.8          | 8.0 ± 1.7          | p < 0.0001               |
| 12    | OGTT (2nd hour)                | 9.2 ± 1.8           | 6.7 ± 1.6          | p < 0.0001               |
| 13    | OGTT (3rd hour)                | 5.6 ± 1.7           | 4.5 ± 1.3          | p < 0.0001               |
| 14    | TG (mmol/L)                    | 2.3 ± 1.8           | 1.7 ± 0.98         | p < 0.0001               |
| 15    | TC (mmol/L)                    | 5.7 ± 1.2           | 5.2 ± 1.0          | p < 0.0001               |
| 16    | HDL-C (mmol/L)                 | 0.92 ± 0.38         | 0.64 ± 0.24        | p < 0.0001               |
| 17    | LDL-C (mmol/L)                 | 3.7 ± 0.93          | 3.7 ± 1.0          | p = 0.82                 |
| 18    | Family History of T2DM (%)     | 120 (60%)           | 55 (18.3%)         | p < 0.0001               |
| 19    | Family History of GDM (%)      | 46 (23%)            | 13 (4.3%)          | p < 0.0001               |
| 20    | Rx (Diet/Insulin)              | 180 (90%)/20 (10%)  | NA                 | NA                       |

NA = not applicable/not analyzed.

Table 3  Genotype distribution of 12Glu9 polymorphism in the individuals enrolled in the study.

| Genotypes | Non-GDM N (%) | GDM N (%) | Odds ratio (95% CI) | p Value |
|-----------|---------------|-----------|---------------------|---------|
| N         | 300           | 200       | Reference           | –       |
| II        | 265 (88.4)    | 152 (76)  | 2.1 (1.27, 3.74)    | 0.003   |
| ID        | 28 (9.3)      | 35 (17.5) | 1.5 (0.52, 4.2)     | 0.45    |
| DD        | 7 (2.3)       | 13 (6.5)  | 2.3 (1.48, 3.8)     | < 0.0001* |
| ID + DD   | 35 (11.6)     | 48 (24)   | 2.3 (1.57, 3.6)     | 0.0002  |
| I         | 558 (93.0)    | 339 (84.8)| Reference           | –       |
| D         | 42 (7)        | 61 (15.2) | 2.3 (1.57, 3.6)     | 0.0002  |

* After continuity correction.

Table 4  Anthropometric and metabolic parameters according to genotype of 12Glu9 I > D polymorphism in GDM women.

| S. No | Aspects                        | ID + DD (n = 48) | II (n = 152) | p Value |
|-------|--------------------------------|------------------|--------------|---------|
| 1     | Age (Years)                    | 33.58 ± 6.51     | 32.07 ± 5.46 | p = 0.11 |
| 2     | Weight (kg)                    | 75.96 ± 14.99    | 77.46 ± 12.80| p = 0.15 |
| 3     | Height (m²)                    | 157.42 ± 6.30    | 158.86 ± 5.81| p = 0.46 |
| 4     | BMI (kg/m²)                    | 29.89 ± 4.89     | 30.48 ± 4.62 | p = 0.59 |
| 5     | Mean gestational age           | 31.12 ± 6.71     | 29.93 ± 5.54 | p = 0.08 |
| 6     | FBS (mmol/L)                   | 3.29 ± 2.38      | 3.55 ± 8.29  | p = 0.61 |
| 7     | PPBG (mmol/L)                  | 3.91 ± 3.31      | 4.04 ± 3.97  | p = 0.14 |
| 8     | GCT (mmol/L)                   | 1.39 ± 3.45      | 1.81 ± 3.84  | p = 0.39 |
| 9     | TG (mmol/L)                    | 1.81 ± 1.04      | 1.74 ± 0.96  | p = 0.46 |
| 10    | TC (mmol/L)                    | 5.41 ± 1.26      | 5.12 ± 1.00  | p = 0.03 |
| 11    | HDL-C (mmol/L)                 | 0.62 ± 0.25      | 0.64 ± 0.24  | p = 0.69 |
| 12    | LDL-C (mmol/L)                 | 3.95 ± 1.06      | 3.60 ± 0.87  | p = 0.07 |
| 13    | Family History of T2DM (%)     | 20 (41.6%)       | 100 (65.8%)  | NA      |
| 14    | Family History of GDM (%)      | 11 (22.9%)       | 35 (23%)     | NA      |
| 15    | Rx (Diet/Insulin)              | 46 (95.8%)/2 (4.2%) | 134 (88.2%)/18 (11.8%) | NA      |
| 16    | OGTT (Fasting hour)            | 4.26 ± 2.68      | 3.70 ± 2.54  | p = 0.61 |
| 17    | OGTT (1st hour)                | 8.41 ± 4.89      | 7.66 ± 5.07  | p = 0.79 |
| 18    | OGTT (2nd hour)                | 7.28 ± 4.20      | 6.47 ± 4.37  | p = 0.77 |
| 19    | OGTT (3rd hour)                | 3.76 ± 2.92      | 3.26 ± 3.14  | p = 0.57 |

NA = not applicable/not analyzed.
variants in different diseases. The 12Glu9 polymorphism was studied in relation to multiple diseases, and the reports are summarized in Table 5.

In this case-control study, we find significant differences in the distribution of the 12Glu9 or I/D polymorphism among GDM and non-GDM subjects. A significant association was found between the genotypes and the GDM status, obesity, or dyslipidemia, indicating that these polymorphisms may be important risk determinants of cardio or metabolic disease in Saudi women. Furthermore, our data suggest that I/D polymorphism contribute to variation in expression of the ADRA2B gene. In addition, no associations were noted between genotype and anthropometric parameters, including age and BMI, indicating that this polymorphism may not independently contribute to obesity and advanced maternal age as stated in the studied population. The results of this study also indicated that the frequency of the heterozygous carriers and homozygous variants of I/D polymorphism of ADRA2B was significantly higher in GDM women than in non-GDM women.

Papanas et al. (2007) studied T2DM with and without nephropathy. The results of their study indicate that D allele was significantly higher (p = 0.001) in group A (26.9%) as compared to group B (11.7%). Papanas et al. (2007) and co-authors concluded that patients with neuropathy exhibit a significantly higher frequency of the D allele. Essential hypertension in a Malaysian population with and without T2DM was studied earlier in three separate groups, controls, hypertension with T2DM, and hypertension without T2DM. There was a significant difference between the genotype and clinical data (p < 0.05), but there is no significant difference between the three genotypes and the clinical characteristics of the study subjects (p > 0.05). The results obtained in the Malaysian study indicated that the D allele in the ADRA2B gene was associated with essential hypertension with and without T2DM in Malaysian subjects (Vasudevan et al., 2008). In this present study, the genotype distribution of the 12Glu9 polymorphism was strongly associated with GDM. This consistency might be due to differences in genetic background and sample size (Table 6). No clinical effects of this

| S. No | Disease                                      | Population     | p Value | Association | References         |
|-------|----------------------------------------------|----------------|---------|-------------|-------------------|
| 1     | Type 2 diabetes mellitus + Hypertension     | Malaysian      | p = 0.51| No          | Vasudevan et al. (2008) |
| 2     | Acute coronary events                        | Finland/Sweden | p = 0.03| Yes         | Heinonen et al. (1999, 2002) |
| 3     | Acute coronary events                        | Finland        | p = 0.02| Yes         | Snapir et al. (2001, 2003) |
| 4     | T2DM + Neuropathy                           | Greece         | p = 0.0008| Yes        | Papanas et al. (2007) |
| 5     | Insulin Secretion + T2DM                    | Finland        | p = 0.04| Yes         | Siitonen et al. (2004) |
| 6     | T2DM                                        | Greece         | p = 0.40| No          | Papazoglou et al. (2006) |
| 7     | Sudden cardiac death (SCD)                  | Finland        | p < 0.05| Yes         | Laukkanen et al. (2009) |
| 8     | Spontaneous recurrent abortions              | Greece         | p = 0.78| No          | Galazios et al. (2011) |
| 9     | Migraine                                    | Chinese        | p = 0.35| No          | Ni et al. (2010) |
| 10    | Glucose 6 phosphate dehydrogenase            | Saudi          | p = 0.68| No          | Alharbi et al. (2013) |
| 11    | Suicide                                     | Japanese       | p = 0.04| Yes         | Fukutake et al. (2008) |
| 12    | Artery compliance                           | Chinese        | p = 0.73| No          | Zhang et al. (2005) |
| 13    | Cardiac conduction                          | Russian        | p < 0.05| Yes         | Chernova et al. (2013) |
| 14    | Hypertension                                | Scandinavian   | p = 0.04| Yes         | Von Wopern et al. (2004) |
| 15    | Myocardial ischemia + T2DM                  | Chinese        | p < 0.05| Yes         | Chen et al. (2010) |
| 16    | Obesity                                     | Greek          | p > 0.05| No          | Sykiotis et al. (2003) |
| 17    | Myocardial infarction + SCD                 | Finland        | p = 0.01| Yes         | Snapir et al. (2001, 2003) |
| 18    | Gestational diabetes mellitus               | Saudi          | p = 0.0002| Yes        | Present study |

Table 5: Association of 12Glu9 polymorphism of ADRA2B gene in relation to different diseases and population of ethnicity.

Table 6: Genotype distribution of 12Glu9 polymorphism of ADRA2B gene in controls vs different forms of diabetes in relation to ethnicity.

| Genotype/allele | Saudi (n = 500) | Greece (n = 190) | Malaysia (n = 210) |
|-----------------|-----------------|------------------|-------------------|
|                 | GDM N (%)       | Non-GDM N (%)    | Controls N (%)     |
| II              | 152 (76)        | 265 (88.4)       | 6 (8.57)           |
| ID              | 35 (17.5)       | 28 (9.3)         | 34 (48.57)         |
| DD              | 13 (6.5)        | 7 (2.3)          | 30 (42.86)         |
| ID + DD         | 48 (24)         | 35 (11.6)        | 64 (91.43)         |
| I               | 339 (84.8)      | 558 (93)         | 46 (32.86)         |
| DD              | 61 (15.2)       | 42 (7)           | 94 (67.14)         |
| OR              | 2.3 (1.5–3.6)   | 2.789 (1.4–5.1)  | 0.545 (0.3–0.8)    |
| p-Value         | p = 0.0002      | p = 0.0008       | p = 0.012          |
polymorphism were observed in this prospective study. This is clearly a limitation of the study and indicates that the influence on obesity risk of I/D polymorphism may be of major importance in GDM women. However, the subjects in our study had a mean age greater than 30, which indicates the presence of obesity in both GDM and non-GDM subjects.

In conclusion, the present study shows that 12glu9 polymorphism of the ADRA2B gene is associated with the risk of GDM in a Saudi population. Further research is warranted to confirm the causality. The association of the DD genotype and the D allele with GDM should be examined in multiple, well-designed genetic epidemiological studies, and the physiological effects should be identified.

Conflict of interest

We confirm that all the authors have no actual or potential competing interests regarding the submitted article.

Authors’ contributions

AMM and AZ have helped to collect the samples and edited the manuscript. AKK was the PI of the project and design the study, helped us to finalize the manuscript. KIA had performed the experiment and written and finalized the manuscript. All the authors read and approved the final manuscript.

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