Association of BDNF polymorphism with gestational diabetes mellitus risk: a novel insight into genetic predisposition

Danyel Chermon and Ruth Birk*

Abstract

Objectives: Gestational diabetes mellitus (GDM) is a prevalent metabolic disorder during pregnancy with potential long-term health implications for the mother and child. The interplay between genetics and GDM susceptibility remains an area of active research. Recently, brain-derived neurotrophic factor (BDNF) was investigated in relation to obesity and impaired glucose metabolism and pathogenesis. We aimed to investigate the association of common BDNF polymorphisms, with GDM risk in Israeli females.

Methods: A cohort of 4,025 Israeli women data for polymorphisms, with GDM risk in Israeli females. Common SNPs was analyzed for potential association with GDM using binary logistic regressions analysis (SPSS 29.0 and R) adjusted for confounding variables (age, T1DM, T2DM, PCOS) under different genetic models.

Results: The GDM and Non-GDM genetic frequencies for the BDNF rs925946 Tag-SNP were significantly different. The genetic frequencies were 54.16 %, and 66.91 % for the wild type (GG), 38.88 and 29.64 % for the heterozygotes (TC), and 6.94 and 3.48 % for the risk allele homozygotes (TT) for the GDM non-GDM populations, respectively. Carriers of BDNF rs925946 were significantly associated with higher risk for GDM, following the dominant genetic model (OR=1.7, 95 % CI 1.21–2.39, p=0.002), the recessive genetic model (OR=2.05, 95 % CI 1.04–4.03, p=0.03), and the additive genetic model (OR=1.62, 95 % CI 1.13–2.3, p=0.008). This association persisted after adjusting for age, T1DM, T2DM, and polycystic ovary syndrome (PCOS).

Conclusions: Carrying BDNF rs925946 polymorphism predisposes to a higher risk of GDM pathogenesis. Its role and implications warrant further investigation, especially when considering preventive measures for GDM development.

Keywords: brain-derived neurotrophic factor; gestational diabetes mellitus; genetic susceptibility; single nucleotide polymorphism

Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, is the most common form of hyperglycemia during pregnancy and stands prominently as a significant public health challenge, influencing an estimated 15 % of pregnancies worldwide [1]. Globally, GDM has risen dramatically over the past several decades, echoing the ascendant trajectories of obesity and type 2 diabetes (T2D). Such prevalence is of paramount concern, given the negative health consequences of GDM for both the mother and child [2, 3]. GDM is characterized by hyperglycemia first identified during pregnancy [4]. Its prevalence is higher in pregnant women with maternal age≥30 years, in the third trimester of pregnancy, and in women with obesity and overweight compared to those with normal weight. While hyperglycemia can manifest at any stage of pregnancy, it is most commonly diagnosed post the 24th week of gestation [5, 6]. The increasing prevalence of GDM is closely linked to the global obesity rise, attributed to genetic predisposition expression following changes in lifestyle and dietary habits, including the adoption of a sedentary lifestyle and high-calorie processed foods consumption, and advancing maternal age [7–9]. The management of GDM typically involves dietary modifications and physical activity to control blood glucose levels [10], complemented by medical interventions when necessary. Insulin therapy remains the standard treatment, especially when dietary measures are insufficient to maintain glycemic control [11]. In some cases, oral hypoglycemic agents like glyburide and metformin are considered [12]. The treatment approach for GDM is highly individualized, balancing the need for glycemic control with the overall health and preferences of the patient [13]. Recent scientific research acknowledges the role of genetic predisposition to GDM [14]. Specifically, risk variants traditionally linked with T2D were studied for association with GDM, reinforcing their genetic commonality [15, 16]. It is imperative to note that genetic
predisposition associated with obesity risk and GDM can differ among diverse populations [17, 18].

Genome-wide association studies (GWAS) found a plethora of single nucleotide polymorphisms (SNPs) across diverse genes intertwined with susceptibility to obesity and a suite of metabolic disorders. Brain-derived neurotrophic factor (BDNF) common genes’ SNPs have been linked to obesity in GWAS. BDNF, a neurotrophin, plays an essential role in neuronal survival, growth, and differentiation, appears to play a role in glucose metabolism, and may be involved in type 2 diabetes. Low levels of BDNF have been shown to impair glucose metabolism [19, 20]. Additionally, BDNF triggers multiple signaling pathways, some of which are also stimulated by insulin, such as the phosphatidylinositol-3 kinase/Akt pathway [21]. BDNF has recently garnered attention in the context of GDM. Emerging evidence suggests a potential link between BDNF levels and the pathogenesis of GDM, although the exact mechanisms remain to be elucidated [22, 23].

Given BDNF emerging role in T2D, and the predisposition to obesity and T2D, we aimed to study the association of BDNF common SNPs with GDM within the Israeli female population.

Subjects and methods

Participants

A total of 4,025 Israeli women, aged 56.53 ± 14.27 years, were included in this research. The primary dataset was extracted from the Israeli registry database (#700068969) managed by Lev Hai Genetics LTD – MyGenes. The study was approved by the Ethical Committee of Ariel University (#AU-HEA-RB-20220214). Only anonymous genetic data were accessed and utilized for this investigation. Participants younger than 18 years, having a genetic disorder, or with incomplete information were not considered for this analysis. While most data, including demographic, anthropometric, and medical history, were contemporaneous with the time of completing the online questionnaire, the information regarding the diagnosis of GDM was collected retrospectively. Participants completed an online questionnaire regarding their demographic, anthropometric, and medical history, including inquiries about diagnose of GDM, T1DM, T2DM, polycystic ovarian syndrome (PCOS), prediabetes, hypertension and cardiovascular disease.

SNP selection and Hardy–Weinberg equilibrium (HWE)

SNPs that were previously shown to be significantly associated with obesity were selected. These SNPs were prioritized based on their minor allele frequency (MAF) (>0.01) in at least two GWAS populations [24, 25] and based on the validated catalog of published genome-wide association studies [26]. The SNPs included: BDNF rs925946, rs10767664, rs2030323, rs4074134, rs4923461. Except for the rs925946 SNP, the SNP’s were in strong linkage disequilibrium (LD; D=0.999–1). Using Tag-SNPs analysis the following SNPs rs925946 and rs4923461 were tagged. The Hardy–Weinberg equilibrium (HWE) was confirmed for all SNPs using a 1 degree of freedom χ²-test, ensuring that the SNP’s distribution was in line with genetic equilibrium expectations.

Statistical analyses

Descriptive statistics, and allele frequencies, were generated for BDNF studied SNPs among adult females, and further stratified based on GDM status. For continuous variables such as age, weight, height, and BMI, means and standard deviations (SD) were calculated. The differences between the GDM and non-GDM groups were evaluated using independent sample t-tests for normally distributed variables and Mann-Whitney for non-normally distributed variables. For categorical variables frequencies and percentages were computed. The associations between categorical variables and GDM status were assessed using chi-squared tests or Fisher’s exact tests, as appropriate. To probe the association between the BDNF variants and GDM risk, binary logistic regression was performed. The model evaluated the relative likelihood of developing GDM based on the BDNF genotypes while adjusting for confounding factors such as age, T1DM, and T2DM.

Furthermore, various genetic models, namely dominant, recessive, and additive, were assessed to pinpoint the pattern of genetic inheritance that best explained the variant’s association with GDM. The results were expressed in terms of odds ratios (ORs) and their corresponding p-values. All statistical computations were executed using SPSS 29.0 software and R software. Results were considered significant at an α=0.05.

Results

Participants

This cross-sectional study involved 4,025 participants of which 144 have been diagnosed with GDM. Participants descriptive characteristics are presented in Table 1. Participants diagnosed with GDM had an average age of 47.99 ± 11.37 years, which was significantly younger than those without GDM diagnostic (56.85 ± 14.26 years, p<0.001). No significant differences were observed in weight, height, and BMI values for GDM participants compared to those without GDM.

PCOS was more prevalent in the GDM group, with 15.28 % having the condition, as opposed to only 5.10 % in the non-GDM group (p=0.001). Smoking habits were somewhat higher in the GDM group at 12.5 % compared to 9.73 % in the non-GDM group, and the incidence of T2DM was slightly elevated in the GDM group at 7.64 % in contrast to 6.42 % in the non-GDM group, yet these differences were not statistically significant (p=0.18 and p=0.53, respectively).
BDNF SNPs association with GDM risk

Table 2 shows all BDNF studied SNPs genotype frequencies and GDM risk in acceptable genetic models. Genotype frequency among GDM for BDNF rs925946 was 54.16 % for the wild type (GG), followed by 38.88 % for the heterozygotes (TC), and 6.94 % for the risk allele homozygotes (TT). In contrast, within the non-GDM population, 66.91 % were genotypes as wild type (GG), 29.64 % were heterozygotes (TC), and 3.48 % were risk allele homozygotes (TT).

GDM risk was significantly elevated for BDNF rs925946 risk allele carriers in the dominant genetic model, recessive genetic model, and additive genetic model (OR=1.7, 95 % CI 1.21–2.39, p=0.002, OR=2.05, 95 % CI 1.04–4.03, p=0.03 and OR=1.62, 95 % CI 1.13–2.3, p=0.008, respectively).

Further adjustment for PCOS risk has slightly changed the GDM risk which was significantly elevated for BDNF rs925946 risk allele carriers in the dominant genetic model, recessive genetic model, and additive genetic model (OR=1.66, 95 % CI 1.18–2.33, p=0.003, OR=2.06, 95 % CI 1–3.86, p=0.03 and OR=1.57, 95 % CI 1.18–2.05, p=0.001, respectively), but remained significant (Table 3).

All other SNPs did not show statistical differences in genotype frequency between GDM and Non-GDM populations.

Discussion

Our study findings demonstrate that BDNF rs925946 SNP, previously associated with obesity, is also significantly

### Table 1: Descriptive characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=4,025)</th>
<th>GDM (n=144)</th>
<th>Non-GDM (n=3,881)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>56.53 ± 14.27</td>
<td>47.99 ± 11.37</td>
<td>56.85 ± 14.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (mean ± SD)</td>
<td>82.02 ± 16.98</td>
<td>83.76 ± 16.95</td>
<td>81.96 ± 16.98</td>
<td>0.15</td>
</tr>
<tr>
<td>Height, cm (mean ± SD)</td>
<td>162.69 ± 6.28</td>
<td>162.66 ± 5.61</td>
<td>162.691 ± 6.30</td>
<td>0.92</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>30.98 ± 6.11</td>
<td>31.68 ± 6.21</td>
<td>30.95 ± 6.10</td>
<td>0.1</td>
</tr>
<tr>
<td>PCOS</td>
<td>220 (5.47 %)</td>
<td>22 (15.28 %)</td>
<td>198 (5.10 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T2DM</td>
<td>262 (6.5 %)</td>
<td>11 (7.64 %)</td>
<td>249 (6.42 %)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

SD, standard deviation. Values in bold represent significance at α<0.05.

### Table 2: BDNF SNPs genotype frequency and associated risk for GDM.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Allele</th>
<th>Overall population (n=4,025)</th>
<th>GDM (n=144)</th>
<th>Non-GDM (n=3,881)</th>
<th>p-Value OR ± 95 % (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Allele Genotype frequency (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GDM (n=144)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs925946</td>
<td>G&gt;T</td>
<td>GG 2,673 (66.4 %) 78 (54.2 %)</td>
<td>2,595 (66.9 %)</td>
<td>0.002</td>
<td>1.7 (1.21–2.39) 2.05 (1.04–4.03) 1.62 (1.13–2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TC 1,206 (30 %) 56 (38.9 %)</td>
<td>1,150 (29.6 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT 145 (3.6 %) 10 (6.9 %)</td>
<td>135 (3.5 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2030323</td>
<td>C&gt;A</td>
<td>AA 2,112 (52.5 %) 86 (59.7 %)</td>
<td>2,026 (52.2 %)</td>
<td>0.07</td>
<td>0.7 (0.52–1.04) 0.9 (0.46–1.83) 0.8 (0.6–1.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC 1,637 (40.7 %) 49 (34 %)</td>
<td>1,588 (40.9 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC 276 (6.9 %) 9 (6.3 %)</td>
<td>267 (6.9 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs4074134</td>
<td>C&gt;T</td>
<td>CC 2,223 (55.2 %) 89 (61.8 %)</td>
<td>2,134 (55.5 %)</td>
<td>0.1</td>
<td>0.1 (0.53–1.06) 1.06 (0.53–2.12) 0.83 (0.62–1.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TC 1,562 (38.8 %) 46 (31.9 %)</td>
<td>1,516 (49.1 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT 240 (6 %) 9 (6.3 %)</td>
<td>231 (6 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs4923461</td>
<td>A&gt;G</td>
<td>AA 2,228 (55.4 %) 90 (62.5 %)</td>
<td>2,138 (55.1 %)</td>
<td>0.08</td>
<td>0.8 (0.53–1.02) 0.89 (0.53–2.12) 0.16 (0.6–1.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AG 1,555 (38.8 %) 45 (31.3 %)</td>
<td>1,510 (38.9 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 242 (6 %) 9 (6.3 %)</td>
<td>233 (6 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10501087</td>
<td>T&gt;C</td>
<td>TT 2,233 (55.5 %) 89 (61.8 %)</td>
<td>2,144 (55.2 %)</td>
<td>0.1</td>
<td>0.1 (0.53–1.07) 0.87 (0.06–2.79) 0.2 (0.54–2.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TC 1,544 (38.4 %) 46 (31.9 %)</td>
<td>1,498 (38.6 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC 248 (6 %) 9 (6.3 %)</td>
<td>239 (6.2 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs10767664</td>
<td>A&gt;T</td>
<td>AA 2,120 (52.2 %) 85 (59 %)</td>
<td>2,017 (52%)</td>
<td>0.1</td>
<td>0.1 (0.53–1.07) 0.87 (0.06–2.79) 0.2 (0.54–2.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT 1,635 (40.6 %) 50 (34.7 %)</td>
<td>1,585 (40.8 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT 279 (6.9 %) 9 (6.3 %)</td>
<td>270 (7 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, T1DM, T2DM and PCOS.

### Table 3: BDNF rs925946 further adjusted risk for GDM.

<table>
<thead>
<tr>
<th>SNP</th>
<th>p-Value OR ± 95 % (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dominant model</td>
</tr>
<tr>
<td>rs925946</td>
<td>0.003</td>
</tr>
</tbody>
</table>

1.66 (1.18–2.33) 2.06 (1–3.86) 1.57 (1.18–2.05)
associated with an elevated risk of GDM. BDNF rs925946 exhibited an elevated risk for GDM across multiple genetic models, with the most pronounced association observed in the recessive model (OR=2.05, 95% CI 1.04–4.03, p=0.03). This association persisted after adjusting for confounding factors such as age, T1DM, T2DM, and PCOS. The BDNF rs925946 variant has been relatively underexplored. Notably, this variant has been linked to an increased risk of early-onset psoriasis related to obesity [27]. The obesity risk associated with this variant appears to be age-dependent, with the risk being twice as pronounced in children and adolescents compared to adults [28]. One study identified a significant association between rs925945 and neurocognitive performance in patients with major depressive disorder, a relationship mediated by methylation values at specific promoter regions.

However, the precise cognitive effects attributed to rs925946 were not delineated [29]. Furthermore, this risk variant demonstrated a significant correlation with endomorphic somatotype in a Spanish cohort [30]. It is plausible that rs925946 exhibits a distinct genetic behavior compared to the other SNPs, given that it was with a low r2 LD value (though with D=1), indicative of the genetic frequency of the risk allele that differs from the rest of LD SNPs, as was clearly shown in our research population. Previous studies have demonstrated BDNF role in T2DM. Specifically, BDNF enhances glucose metabolism and insulin responsiveness while decreasing food intake [31, 32]. BDNF may have a crucial role in developing obesity and T2DM as it regulates the release and functions of insulin, leptin, ghrelin, and pro-inflammatory cytokines related to energy balance [33].

BDNF was also found to be related to the total and abdominal subcutaneous fat mass and energy metabolism in newly diagnosed T2DM female patients [34].

Moreover, a pronounced link has been observed between depression and T2DM, suggesting that BDNF might serve as a bridge between the two conditions. This implies that BDNF could be a potential treatment target for patients with both disorders. The BDNF gene, known for its role in neuronal survival, growth, and differentiation, has recently been spotlighted in the context of GDM [23]. Our study adds to this growing body of evidence by highlighting the potential genetic predisposition of BDNF SNP in the pathogenesis of GDM. While not entirely elucidated, the mechanism underlying this association can be postulated based on the known functions of BDNF. BDNF is involved in energy homeostasis and appetite regulation [35], and its levels or function alterations could disrupt glucose metabolism, leading to conditions like insulin resistance and diabetes [36].

Furthermore, the relevance of BDNF in GDM can be contextualized by its connection to obesity. Obesity is a known risk factor for GDM [37], and given that certain BDNF SNPs have been linked to obesity [24], it is plausible that these SNPs could indirectly influence GDM risk through their impact on obesity-related metabolic pathways [38]. BDNF’s influence on the modulation of insulin, leptin, and other metabolic regulators may also suggest its potential involvement in glucose metabolism during pregnancy. BDNF was downregulated in fetuses exposed to GDM irrespective of their growth pattern, suggesting a potential mechanism linking maternal diabetes to subsequent neurodevelopmental disorders [31]. Our study, focusing on the Israeli female population, underscores the importance of understanding genetic variations in different populations, as genetic predispositions can vary based on ethnicity and geographical regions. In the context of our findings, it is important to discuss the broader implications of our retrospective analysis of genetic data. The primary objective of our study was to identify genetic markers that could predispose Israeli females to GDM. This retrospective approach is particularly valuable in the field of predictive medicine, where early identification of risk factors can lead to more effective prevention and management strategies. By uncovering associations between specific genetic markers and GDM, we could potentially identify women at an elevated risk for GDM, enabling healthcare providers to implement preventive measures and appropriate treatments early in the pregnancy. Such proactive management is crucial for mitigating the risks associated with GDM, which extend beyond the immediate health of the mother and child to include long-term societal and economic impacts. While our study provides novel insights into the genetic predisposition of GDM in Israeli females, it is essential to consider its limitations. The cross-sectional nature of our study design limits our ability to infer causality. A notable strength of this study lies in its pioneering exploration within the Israeli population, being the first to investigate the association of these specific BDNF SNPs with GDM. Additionally, the substantial cohort size of females enhances the validity and applicability of our results.

In conclusion, our study offers a novel perspective on the genetic underpinnings of GDM, emphasizing the potential role of BDNF rs925946 SNP. Understanding these genetic markers can pave the way for early identification of at-risk individuals, allowing for timely interventions and potentially reducing the burden of GDM. Future research is needed to examine the potential influence of SNPs, previously associated with obesity, on GDM pathogenesis.
Acknowledgments: We would like to acknowledge Lev Hai Genetics LTD – MyGenes for the data.

Research ethics: The Helsinki Committee of Ariel University (#AU-HEA-RB-20220214) in accordance with the Declaration of Helsinki.

Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.

Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: D.C. state no conflict of interest. R.B. is a scientific consultant of MyGenes.

Research funding: None declared

Data availability: Not applicable.

References


