Article

Association Analysis of 14 Candidate Gene Polymorphism with Depression and Stress among Gestational Diabetes Mellitus

Kai Wei Lee 1, Siew Mooi Ching 1,2,*, Vasudevan Ramachandran 2, Maiza Tusimin 3, Noraihan Mohd Nordin 4, Seng Choi Chong 5 and Fan Kee Hoo 6

1 Department of Family Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia; lee_kai_wei@yahoo.com
2 Malaysian Research Institute on Ageing, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia; vasudevan@upm.edu.my
3 Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia; maiza@upm.edu.my
4 Department of Obstetrics and Gynaecology, Hospital Kuala Lumpur, 50586 Kuala Lumpur, Malaysia; dr.noraihan@moh.gov.my
5 Department of Psychiatry, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia; sengchoi@upm.edu.my
6 Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia; fan_kee@upm.edu.my

* Correspondence: sm_ching@upm.edu.my

Received: 18 October 2019; Accepted: 28 November 2019; Published: 30 November 2019

Abstract: The association of candidate genes and psychological symptoms of depression, anxiety, and stress among women with gestational diabetes mellitus (GDM) in Malaysia was determined in this study, followed by the determination of their odds of getting psychological symptoms, adjusted for socio-demographical background, maternal, and clinical characteristics. Single nucleotide polymorphisms (SNPs) recorded a significant association between SNP of EPHX2 (rs17466684) and depression symptoms (AOR = 7.854, 95% CI = 1.330–46.360) and stress symptoms (AOR = 7.664, 95% CI = 1.579–37.197). Associations were also observed between stress symptoms and SNP of OXTR (rs53576) and (AOR = 2.981, 95% CI = 1.058–8.402) and SNP of NRG1 (rs2919375) (AOR = 9.894, 95% CI = 1.159–84.427). The SNP of EPHX2 (rs17466684) gene polymorphism is associated with depression symptoms among Malaysian women with GDM. SNP of EPHX2 (rs17466684), OXTR (rs53576) and NRG1 (rs2919375) are also associated with stress symptoms.

Keywords: polymorphisms; genetic variation; depression; anxiety; stress; gestational diabetes

1. Introduction

Gestational diabetes mellitus (GDM) is one of the common complications in pregnancy. Its prevalence in Asia is 11.5% [1]. GDM is a known risk factor for neonatal adverse outcomes [2–4]. Additionally, a diagnosis of GDM is a stressful life event [5–8] which has an adverse impact on self-perception towards health and quality of life [6,9]; as well as increased odds of experiencing emotional distress. Previous studies reported that the prevalence of depression among women sufferers from GDM stood at 56.7%, while anxiety was 57.7%, and stress was even higher at 62.8% [10–12]. GDM and perinatal mental problems undeniably affect all members of the family [13]. This mental condition may reoccur or worsen to postpartum depression [14]. Multiple determinants such as socio-demographical background, maternal and clinical profiles have a reported positive association with psychological symptoms [15–19].
Genetic factors clearly play a substantial role in the etiology of psychological symptoms of depression, anxiety and/or stress, as evidenced by other studies, which indicate a heritability ranges from 45% to 50% for these disorders [20–22]. The genetic profile of the mother is particularly important if she wants to determine whether her child will be predispose to psychological disorders in the future. However, it is challenging to identify particular genetic variants underlying for symptoms of depression, anxiety and/or stress susceptibility because their psychological symptoms are not caused by single gene, but a complex interaction among multiple genes, socio-demographic background, clinical, and biological moderators [23]. The candidate gene-by-environment interaction hypothesis regarding psychological symptoms of depression, anxiety and/or stress has received widespread attention and acclaim; therefore, many studies to date have used this approach to underpin their findings for genetic effects on psychological symptoms of depression, anxiety, and/or stress [24].

Indeed, it is not difficult to find studies which have reported a significant association between candidate genes and these psychological symptoms, such as brain-derived neurotrophic factor (BDNF) [25,26] and oxytocin receptor genes (OXTR) [27,28]. These genes may be associated with depression or anxiety; however, there are ample studies which have failed to replicate the same results in the candidate gene literature [29–31]. One explanation for this lack of success in producing the replicable main effect of these genes is that the certain genetic variants are highly dependent on the gender, population, and disease-related outcomes [32]; even though these studies have recruited patients with major depressive disorder [27–41]; anxiety disorder [42–44]; and post-traumatic stress disorders [45] diagnosed according to Diagnostic and Statistical Manual of Mental Disorders and/or International Statistical Classification of Diseases. This has led to increasing skepticism about the true association or lack thereof between candidate genes and psychological symptoms of depression, anxiety and/or stress. Without testing the candidate genes in our population, it is difficult to conclude that the previous results are also applicable in our samples. One strategy that may aid in identifying the candidate genes in association with symptoms of depression, anxiety and/or stress is to interrogate several candidate genes thought to be associated with the underlying psychological symptoms of depression, anxiety and/or stress. To this end, we have constructed a custom of SNP array containing 18 genes that were chosen based on hypotheses regarding biological systems of relevance to depression [46–50]; anxiety [42,51,52] and stress [45,53]. These custom SNPs provide excellent coverage of many previously suggested and functionally important candidate genes for depression, anxiety and stress, including NPY5R [42,52]; ANO2 [42]; EPHX2 [42,51]; TPH2 [35]; NRG1 [34]; LHPP [38,39,54]; FKBP5 [41,45]; SDK2 [42]; RORA [33,55]; OXTR [27,28]; BDNF [56,57]; HTR2C [43]; TEX51 [42]; and PLEKHG1 [42]. Many of the genes represented on the array have also been reported to be involved in associated heritable phenotypes that are associated with symptoms of depression, anxiety and/or stress. Despite that, the putative susceptibility genes for depression, anxiety or stress have yet to be definitively identified among GDM women.

In light of the complications caused by GDM itself and the devastating consequences of depression and related psychological symptoms of anxiety and stress among women with GDM, we suggest performing a study of fourteen candidate genes to elucidate its genotypic effect on symptoms of depression, anxiety and/or stress among GDM women. The aim of the present study was to perform candidate gene analysis via mass array to evaluate the associations, if any, between phenotypes of threees psychological symptoms and fourteen candidate genes, as adjusted for socio-demographical background, maternal and clinical profile among GDM women.

2. Materials and Methods

2.1. Study Population

We performed a post-hoc exploratory sub-analysis of a cross-sectional study among GDM women (n = 343) to check which candidate SNPs may be associated with symptoms of depression, anxiety and/or stress in this particular population. We conducted a genetic association study using the
cross-sectional study from the previously described “Prevalence and factors associated with depressive, anxiety and stress symptoms among women with gestational diabetes mellitus in tertiary care centres: A cross-sectional study”, which was conducted between July 2018 and October 2018 in Malaysia [58]. The study participants were women enrolled in second or third trimester care and diagnosed with GDM at Hospital Kuala Lumpur or Hospital Serdang. All participants were native Malaysians and residents of surrounding areas. The detailed study protocol has been described previously [58]. In that study, 526 women agreed to participate. Upon completion of sample collection and analysis, data for depression, anxiety and stress score and polymorphisms of candidate genes were available for a total of 343 participants.

The general inclusion criteria were that the pregnant women were Malaysian, aged ≥18 years old, with a diagnosis of GDM. The diagnosis of GDM is defined as fasting plasma glucose ≥5.1 mmol/L or 75 g two-hours oral glucose tolerance test ≥ 7.8 mmol/L according to Malaysian Clinical Practice Guidelines [59,60]. The exclusion criteria were those with pre-existing diabetes.

Regarding patients and controls, patients with depression were defined as those with the DASS depression subscale score ≥10; otherwise, they were in control group if scoring <10 in the DASS depression subscale. Similarly, they were categorized as a patient for anxiety if they scored ≥8 in the DASS anxiety subscale; they were in control group if the score was <8. They were categorized as a patient for stress if they scored ≥15 in the DASS stress subscale, and placed in the control group if scoring <15 in the DASS stress subscale.

2.2. Socio-Demographic Background and Clinical Characteristics

Socio-demographic backgrounds and clinical characteristics were recorded at enrollment to obtain information related to maternal profile, past-obstetrics history, concurrent medical problems, and family history. These data were obtained from the self-administered questionnaire and medical records.

2.3. Measurement of Depression, Anxiety and Stress Symptoms

The detailed sampling and assessment of depression, anxiety, and stress symptoms have been previously described [58]. We used an English [61] and Malay [62] version of the validated questionnaire on Depression, Anxiety, and Stress-21 items (DASS-21). DASS-21 is a valid and reliable measure to screen for depression, anxiety, and stress symptoms among both non-clinical and clinical populations. The English version of the questionnaire (DASS-21) has strong validation, with Cronbach’s alpha values of 0.72 for depression; 0.77 for anxiety; and 0.70 for stress, and the overall Cronbach’s alpha for DASS-21 is 0.88 [61]. The translated Malay version of the DASS-21 questionnaire has good Cronbach’s alpha values, as well as among the Malaysian population (0.84 for depression; 0.74 for anxiety; and 0.79 for stress) [62] and among diabetic patients (0.75 for depression; 0.74 for anxiety; and 0.79 for stress) [63]. The participants rated on a 4-point severity scale their experiences over the preceding week. Scores for subscale for depression, anxiety, and stress were calculated. The depression symptoms defined to follow the depression subscale, ≥10; anxiety symptoms, ≥8; and stress symptoms, ≥15 [61].

2.4. Blood Sample Collection and DNA Extraction

Samples of 5 mL of blood were collected from the participants’ peripheral blood using a 21-gauge needle with a 5.0 mL syringe by a qualified phlebotomist into EDTA tubes (Becton Dickinson, East Rutherford, NJ, USA). The samples were kept in portable icebox at 4 °C during the transportation and there were stored at −20 °C in laboratory for further analysis. Genomic DNA was isolated by using the QIAamp Blood DNA Mini Kit (QIAGEN, Hilden, Germany). The quantity and purity of extracted DNA were checked using a Biophotometer (Eppendorf, Hamburg, Germany). First, readings of a blank using distilled water against A260 and A280 of the genomic DNA were obtained. The DNA absorbed UV light with a maximum absorbance of 260 nm, while the protein absorbed UV light with a maximum absorbance of 280 nm. By dividing the amount of UV absorption at 260 nm by the absorption at 280 nm, the standard measure of the purity of the genomic DNA could be calculated. The genomic DNA
was measured to be relatively free of protein impurity when the ratio of optical density was between 1.7 and 2.0.

2.5. Mass Array Genotyping

Genes candidates were selected based on previous data implicating an association with the studies SNPs and clinical syndrome of depression [27–41]; anxiety [42–44] or stress [45] diagnosed according to Diagnostic and Statistical Manual of Mental Disorders and/or International Statistical Classification of Diseases. The genotyping analysis of candidate genes polymorphism was analyzed using Agene® MassARRAY platform. SNP analysis was analyzed by Typer Analyzer. Details of candidate genes (location and sequence of SNP) were shown in Table A1.

2.6. Statistical Analysis

We used IBM SPSS Statistics version 21.0 to perform the data analysis. A chi-square goodness-of-fit test was performed to assess the agreement of the genotype distribution among candidate genes using Hardy–Weinberg equilibrium, if the \( p \)-value for chi-square goodness-of-fit tests is significant \( (p < 0.05) \), the population is not in Hardy–Weinberg equilibrium. If the genotype distribution of candidate genes is not fit to Hardy–Weinberg equilibrium based on equal distribution, expected values for genotype distribution will be adjusted according to the global population. Univariate analysis was used to analyze the association between candidate genes and the presence of depression, anxiety, or stress symptoms among GDM women. The significant difference was set to \( p \)-value < 0.05. In addition, we tested the candidate gene polymorphism associations with depression phenotypes and any polymorphism adjusted for socio-demographical and clinical moderator effects. Variables with a \( p \)-value of less than 0.25 in univariate analysis underwent multiple logistic regression [64], because a \( p \)-value set at <0.05 may miss any variables known to be important [65,66]. A backward stepwise regression method was used [67]. All analyses were made with a 95% CI, and the level of significance was set at \( p < 0.05 \).

2.7. Ethical Consideration

The study was conducted after written informed consent was obtained from all participants. The Medical Research Ethics Committee (MREC), Ministry of Health Malaysia approved the study protocol (NMRR-17-2264-37814).

3. Results

Overall, we found that almost 50% of women with GDM suffered from anxiety symptoms, which was notably higher than symptoms of either depression (13.4%) or stress (11.7%). We also found a significant association between a specific SNP of gene \textit{EPHX2} and depression, as well as SNPs of \textit{EPHX2}, \textit{OXTR}, \textit{NRG1} with stress symptoms.

Analyses of the socio-demographic background and clinical characteristics of the final 343 participants were stratified by psychological problem, as shown in Table 1. Among the various backgrounds and clinical characteristics evaluated, significant differences were observed only in terms of self-monitoring with a glucometer, ethnicity, religion, marital status, underlying with allergy and family history of depression and anxiety \( (p < 0.05) \) in between those with and without depression symptoms. After a Bonferroni adjustment in the context of family-wise error, these variables (ethnicity, religion, marital status, underlying with allergy and family history of depression and anxiety) still had an adjusted \( p \)-value < 0.05, except self-monitoring with glucometer \( (p \)-value = 0.08). Likewise, there were significant differences among ethnicity, religion, smoking habit, and underlying asthma among those with and without anxiety symptoms \( (p < 0.05) \). After a Bonferroni adjustment in the context of family-wise error for anxiety symptoms among GDM women, variables with adjusted \( p \)-value < 0.05 included ethnicity and smoking habit, while adjust \( p \)-value for religion was 0.066 and underlying asthma \( (p \)-value = 0.058). Further, significant differences were observed in terms of religion, past...
history of GDM and underlying allergy among those with and without stress symptoms \((p < 0.05)\). After a Bonferroni adjustment in the context of family-wise error for stress symptoms among GDM women, the adjusted \(p\)-value for religion was 0.073, with past history of GDM \((p\text{-value} = 0.048)\) and underlying allergy history \((p\text{-value} < 0.0001)\). Bonferroni correction was used to reduce risk of multiple testing error. Even though some of the variables (self-monitoring with glucometer in depression, religion, and underlying asthma in anxiety symptoms) showed significant results with \(p\)-values \(< 0.05\) after Bonferroni correction, we still proceeded with multiple logistic regression as we did not want to miss any variables known to be important as one of the predictors in our study.

The distribution of candidate gene genotypes satisfied the Hardy–Weinberg equilibrium \((p > 0.05)\) (Table A2). Analyses of the genotypes in SNPs of genes \(EPHX2, NPY5R, ANO2, NRG1, FKBP5, RORA, OXTR\) and \(BDNF\) among women with GDM were stratified by psychological symptoms and for candidate genotypes with \(p\text{-value} > 0.25\) using univariate analysis is shown in Table 2. The analyses of the genotypes in SNPs of genes \(LHPP, SDK2, HTR2C, TEX51, PLEKHG1\) and \(TPH2\) genotype among women with GDM stratified by presence of psychological symptoms with \(p\text{-value} > 0.25\) using univariate analysis are shown in (Table A3).

Notably, the proportion of the TT or TC genotypes was higher than that of the CC genotype in SNP of \(NRG1\) \((T > C\) in rs17466684) among GDM women with stress symptoms \((13.2\% \text{ versus } 2.2\%; p = 0.031)\). Similarly, the proportion of the TT genotype was higher compared with TG or GG genotypes in the SNP of \(FKBP5\) \((T > G\) in rs3800373) among GDM women with stress symptoms \((57.5\% \text{ versus } 42.5\%; p = 0.047)\) as shown in Table 2. On the other hand, there was no significant association between SNPs for candidate genes: \([EPHX2, NPY5R, ANO2, FKBP5 \text{(rs947008)}, RORA, OXTR \text{ and } BDNF]\) and stress symptoms \((p > 0.05)\). There was also no association between candidate genes and depression or anxiety symptoms \((p > 0.05)\).

The association between specific SNPs’ genotype of candidate genes and psychological symptoms of depression, anxiety and/or stress adjusted for socio-demographical and clinical moderators is shown in Table 3. GDM women with the AA genotype in specific SNP of \(EPHX2\) \((G > A\) in rs17466684) are 7.9 times more likely to suffer from depression symptoms compared to those who carry G allele in the SNP, when adjusted for ethnicity, religion, practice of home glucose monitoring, planned pregnancy, marital status, past obstetric history of abortion, underlying with allergy, a family history of depression and anxiety and GDM. Likewise, GDM women with the AA genotype in specific SNP of \(EPHX2\) \((G > A\) in rs17466684) is at 7.7 times odds more likely of getting stress symptoms compared to those who carry G allele in the SNP adjusted for ethnicity, religion, marital status, treatment regimens, past obstetric history of GDM, underlying with allergy and asthma and a family history of depression and anxiety. Not only that, we also found that GDM women with the either AA or AG genotypes in specific SNP of \(OXTR\) \((A > G\) in rs53576) are 3.0 times more likely to suffer from stress symptoms compared to those who carry GG genotype in the SNP, as well as to those who carry either TT or TC genotypes in SNP of \(NRG1\) \((T > C\) in rs2919375), is at 9.9 times odds to experience stress symptoms compared to those who carry CC genotype in the SNP.

After a Bonferroni adjustment in the context of family-wise error for depression symptoms among GDM women, the adjusted \(p\)-value for self-monitoring with glucometer was 0.083, ethnicity \((p\text{-value} = 0.003)\), religion \((p\text{-value} = 0.004)\), marital status \((p\text{-value} = 0.012)\), allergy history \((p\text{-value} = 0.031)\) and family history of depression and/or anxiety \((p\text{-value} = 0.002)\).

After a Bonferroni adjustment in the context of family-wise error for anxiety symptoms among GDM women, the adjusted \(p\)-value for ethnicity with was 0.004, religion \((p\text{-value} = 0.066)\), smoking habit \((p\text{-value} = 0.007)\), and asthma \((p\text{-value} = 0.058)\).

After a Bonferroni adjustment in the context of family-wise error for stress symptoms among GDM women, the adjusted \(p\)-value for religion was 0.073, history of GDM \((p\text{-value} = 0.048)\), and allergy \((p\text{-value} < 0.0001)\).

After a Bonferroni adjustment in the context of family-wise error for stress symptoms among GDM women, the adjusted \(p\)-value for \(NRG1\) \((\text{rs2919375})\) was 0.066.
Table 1. Univariate analysis on the socio-demographic background and clinical characteristics of the participants with stratification by presence of psychological symptoms (n = 343).

| Parameters | Depression | | Anxiety | | Stress |
|------------|------------|-----|---------|-----|---------|
| | Without Symptoms | With Symptoms | p-Value | Without Symptoms | With Symptoms | p-Value | Without Symptoms | With Symptoms | p-Value |
| **Treatment Profile** | | | | | | | | | |
| Treatments | OAD and/or diet modification | 212 (87.6) | 30 (12.4) | 0.393 | 142 (58.7) | 101 (41.3) | 0.471 | 217 (89.7) | 25 (10.3) | 0.234 |
| | Without OAD and/or diet modification | 85 (84.2) | 16 (15.8) | | 55 (54.5) | 46 (45.5) | | 86 (85.1) | 15 (14.9) | |
| Self-Monitoring with | | | | | | | | | |
| Glucometer | No | 46 (80.7) | 11 (19.3) | 0.041 | 33 (57.9) | 24 (42.1) | 0.841 | 30 (87.7) | 7 (12.3) | 0.624 |
| | Yes | 198 (90.4) | 21 (9.6) | | 130 (59.4) | 89 (40.6) | | 197 (90.0) | 22 (10.0) | |
| **Socio-Demographic Factors** | | | | | | | | | |
| Age | | 32.17 ± 5.08 | 31.80 ± 4.65 | 0.645 | 31.73 ± 4.97 | 0.259 | 32.20 ± 5.00 | 31.53 ± 5.13 | 0.424 |
| Ethnicity | Malay | 247 (89.3) | 29 (10.3) | 0.001 | 167 (60.5) | 109 (39.5) | 0.019 | 248 (89.9) | 28 (10.1) | 0.076 |
| | Non-Malay | 50 (74.6) | 17 (25.4) | | 30 (44.8) | 37 (55.2) | | 55 (82.1) | 12 (17.9) | |
| BMI, kg/m² | | 29.23 ± 6.30 | 29.12 ± 5.84 | 0.912 | 29.53 ± 7.00 | 0.439 | 29.16 ± 5.96 | 29.59 ± 7.98 | 0.695 |
| Religion | Muslim | 252 (89.7) | 29 (10.3) | 0.000 | 169 (60.1) | 112 (39.9) | 0.031 | 253 (90.0) | 28 (10.0) | 0.037 |
| | Non-Muslim | 45 (72.6) | 17 (27.4) | | 28 (45.2) | 34 (54.8) | | 50 (80.6) | 12 (19.4) | |
| Education | Secondary and below | 151 (84.8) | 27 (15.2) | 0.321 | 102 (57.3) | 76 (42.7) | 0.959 | 155 (87.1) | 23 (12.9) | 0.450 |
| | Tertiary | 146 (88.5) | 19 (11.5) | | 95 (57.6) | 70 (42.4) | | 148 (89.7) | 17 (10.3) | |
| Employment | Unemployed | 115 (85.8) | 19 (14.2) | 0.738 | 79 (59.0) | 55 (41.0) | 0.648 | 116 (86.6) | 18 (13.4) | 0.413 |
| | Employed | 182 (87.1) | 27 (12.9) | | 118 (57.6) | 70 (42.4) | | 187 (89.3) | 22 (10.5) | |
| Family Income, Ringgit Malaysia | | 3714.90 ± 2400.77 | 3763.41 ± 3427.06 | 0.910 | 3628.01 ± 2490.53 | 2829.04 ± 2635.63 | 0.513 | 3690.32 ± 2397.41 | 3915.38 ± 3531.63 | 0.665 |
| Pregnancy Planned | No | 212 (88.7) | 27 (11.3) | 0.002 | 142 (59.4) | 97 (40.6) | 0.261 | 214 (89.5) | 25 (10.5) | 0.293 |
| | Yes | 85 (81.7) | 19 (18.3) | | 55 (52.9) | 49 (47.1) | | 89 (85.6) | 15 (14.4) | |
| Marital Status | Without husband | 9 (64.3) | 5 (35.7) | 0.927 | 8 (57.1) | 6 (42.9) | 0.982 | 10 (71.4) | 4 (28.6) | 0.400 |
| | With husband | 289 (87.5) | 41 (12.5) | | 189 (57.4) | 140 (42.6) | | 148 (89.7) | 17 (10.3) | |
| Parity | Nulliparous-Primiparous | 161 (86.5) | 27 (13.5) | 0.569 | 100 (55.2) | 86 (44.8) | 0.080 | 165 (97.5) | 4 (2.5) | 0.716 |
| | Multiparous ≥ 2 | 136 (86.7) | 19 (12.3) | | 87 (62.6) | 54 (37.4) | | 129 (89.9) | 17 (10.1) | |
| Smoking habit | No | 291 (86.4) | 46 (13.6) | 1.000 | 191 (56.7) | 146 (43.3) | 0.040 | 297 (88.1) | 40 (11.9) | 1.000 |
| | Yes | 6 (100.0) | 0 (0.0) | | 6 (100.0) | 0 (0.0) | | 6 (100.0) | 0 (0.0) | |
| Drink alcohol | No | 291 (86.6) | 45 (13.4) | 1.000 | 193 (57.4) | 143 (42.6) | 1.000 | 297 (88.4) | 39 (11.6) | 0.584 |
| | Yes | 6 (85.7) | 1 (13.3) | | 4 (57.1) | 3 (42.9) | | 6 (85.7) | 1 (14.3) | |
| Past Obstetric History | | | | | | | | | |
| Abortion | No | 225 (88.2) | 30 (11.8) | 0.128 | 150 (58.8) | 105 (41.2) | 0.376 | 226 (88.6) | 29 (11.4) | 0.776 |
| | Yes | 72 (81.8) | 16 (18.2) | | 47 (53.4) | 41 (46.6) | | 77 (87.5) | 11 (12.5) | |
| Macrosomia | No | 290 (96.3) | 46 (13.7) | 0.600 | 192 (57.1) | 144 (42.9) | 0.703 | 296 (88.1) | 41 (11.9) | 1.000 |
| | Yes | 7 (100.0) | 0 (0.0) | | 5 (71.4) | 2 (28.6) | | 7 (100.0) | 0 (0.0) | |
| Gestational hypertension | No | 283 (86.5) | 44 (13.5) | 1.000 | 188 (57.6) | 139 (42.5) | 0.922 | 289 (88.4) | 38 (11.6) | 1.000 |
| | Yes | 14 (87.5) | 2 (12.5) | | 9 (56.3) | 7 (43.8) | | 14 (97.5) | 2 (12.5) | |
| Stillbirth | No | 284 (86.6) | 44 (13.4) | 1.000 | 187 (57.0) | 141 (43.0) | 0.460 | 289 (88.1) | 39 (11.9) | 1.000 |
| | Yes | 13 (86.7) | 2 (13.3) | | 10 (66.7) | 5 (33.3) | | 14 (93.3) | 1 (6.7) | |
Table 1. Cont.

| Parameters                        | Depression       | Anxiety           | Stress            |
|-----------------------------------|------------------|-------------------|-------------------|
|                                   | Without Symptoms | With Symptoms     | p-Value           |
|                                   | n = 297 (86.6%)  | n = 46 (13.4%)    |                   |
| Preterm Delivery                  |                  |                   |                   |
| No                                | 284 (86.6)       | 44 (13.4)         | 1.00              |
| Yes                               | 13 (86.7)        | 2 (13.3)          |                   |
| Gestational Diabetes Mellitus     |                  |                   |                   |
| No                                | 230 (87.1)       | 34 (12.9)         | 0.597             |
| Yes                               | 67 (84.8)        | 12 (15.2)         |                   |
| Current Medical Problems          |                  |                   |                   |
| Hypertension                      |                  |                   |                   |
| No                                | 284 (86.6)       | 44 (13.4)         | 1.00              |
| Yes                               | 13 (86.7)        | 2 (13.3)          |                   |
| Allergy                           |                  |                   |                   |
| No                                | 294 (87.5)       | 42 (12.5)         | 0.007             |
| Yes                               | 3 (42.5)         | 4 (57.1)          |                   |
| Asthma                            |                  |                   |                   |
| No                                | 273 (86.9)       | 41 (13.1)         | 0.567             |
| Yes                               | 24 (82.8)        | 5 (17.2)          |                   |
| Heart Disease                     |                  |                   |                   |
| No                                | 291 (86.4)       | 46 (13.6)         | 1.00              |
| Yes                               | 6 (100.0)        | 0 (0.0)           |                   |
| Anaemia                           |                  |                   |                   |
| No                                | 278 (86.8)       | 43 (13.4)         | 1.00              |
| Yes                               | 19 (86.4)        | 3 (13.6)          |                   |
| Thalasemia                        |                  |                   |                   |
| No                                | 294 (86.5)       | 46 (13.5)         | 1.00              |
| Yes                               | 3 (100.0)        | 0 (0.0)           |                   |
| Family History                    |                  |                   |                   |
| Diabetes mellitus                 |                  |                   |                   |
| No                                | 133 (88.1)       | 18 (11.9)         | 0.473             |
| Yes                               | 164 (85.4)       | 28 (14.6)         |                   |
| Heart Disease                     |                  |                   |                   |
| No                                | 250 (86.5)       | 39 (13.5)         | 0.916             |
| Yes                               | 47 (87.0)        | 7 (13.0)          |                   |
| Hypertension and Anxiety          |                  |                   |                   |
| No                                | 138 (85.7)       | 23 (14.3)         | 0.655             |
| Yes                               | 159 (87.4)       | 23 (12.6)         |                   |
| Gestational Diabetes Mellitus     |                  |                   |                   |
| No                                | 194 (88.6)       | 25 (11.4)         | 0.149             |
| Yes                               | 103 (83.1)       | 21 (16.9)         |                   |

Data are presented as either n (%) or mean ± SD. * Pearson Chi-Square at p < 0.25 entered multivariate logistic regression; b Fisher’s Exact Test at p < 0.25 entered multivariate logistic regression.
Table 2. Analyses of the EPHX2, NPY5R, ANO2, NRG1, FKBP5, RORA, OXTR and BDNF genotype among women with GDM were stratified by psychological symptoms.

| Candidate Genes | SNP       | Genotype | Normal Presence of Depression Symptoms | p-Value | Normal Presence of Anxiety Symptoms | p-Value | Normal Presence of Stress Symptoms | p-Value |
|-----------------|-----------|----------|-----------------------------------------|---------|-------------------------------------|---------|------------------------------------|---------|
| EPHX2 rs17466684 | GG       | 223 (75.1) | 36 (78.3) | 0.122 | 155 (78.7) | 0.267 | 228 (75.2) | 0.078 |
|                 | GA       | 68 (22.9)  | 7 (15.2)  |        | 38 (19.3)  |        | 69 (22.8)  |        |
|                 | AA       | 6 (2.0)    | 3 (6.5)   |        | 4 (2.0)    |        | 6 (2.0)   |        |
| G genotype      |          |           |           |        |           |        |           |        |
|                 | A carrier | 223 (75.1) | 36 (78.3) | 0.641 | 155 (78.7) | 0.113 | 228 (75.2) | 0.756 |
|                 | AA carrier| 74 (24.9)  | 10 (21.7) |        | 42 (21.3)  |        | 75 (24.8)  |        |
| NPY5R rs12501691 | TT       | 202 (68.0) | 32 (69.5) |        | 137 (69.6) |        | 202 (66.7) | 0.519 |
|                 | TA       | 89 (30.0)  | 13 (28.3) | 0.972 | 55 (27.9)  | 0.590 | 95 (31.3)  | 0.197 |
|                 | AA       | 6 (2.0)    | 1 (2.2)   |        | 2 (1.4)    |        | 6 (2.0)   |        |
| T genotype      |          |           |           |        |           |        |           |        |
|                 | A carrier | 202 (68.0) | 32 (69.6) | 0.833 | 137 (69.5) | 0.541 | 202 (66.7) | 0.089 |
|                 | AA carrier| 95 (32.0)  | 14 (30.4) |        | 60 (30.5)  |        | 101 (33.3) |        |
| ANO2 rs12579350 | GG       | 261 (87.9) | 36 (78.3) |        | 168 (85.3) |        | 263 (86.8) | 0.730 |
|                 | GA       | 33 (11.3)  | 10 (21.7) | 0.107 | 27 (13.7)  | 0.704 | 37 (12.2)  | 0.748 |
|                 | AA       | 3 (1.0)    | 0 (0.0)   |        | 2 (1.0)    |        | 3 (1.0)   |        |
| G genotype      |          |           |           |        |           |        |           |        |
|                 | A carrier | 261 (87.9) | 36 (78.3) | 0.075 | 168 (85.3) | 0.408 | 263 (86.8) | 0.754 |
|                 | AA carrier| 95 (32.0)  | 14 (30.4) |        | 60 (30.5)  |        | 101 (33.3) |        |
| FKBP5 rs3880373 | GG       | 261 (87.9) | 36 (78.3) |        | 168 (85.3) |        | 263 (86.8) | 0.730 |
|                 | TA       | 33 (11.3)  | 10 (21.7) | 0.107 | 27 (13.7)  | 0.704 | 37 (12.2)  | 0.748 |
|                 | AA       | 3 (1.0)    | 0 (0.0)   |        | 2 (1.0)    |        | 3 (1.0)   |        |
| G genotype      |          |           |           |        |           |        |           |        |
|                 | A carrier | 261 (87.9) | 36 (78.3) | 0.075 | 168 (85.3) | 0.408 | 263 (86.8) | 0.754 |
|                 | AA carrier| 95 (32.0)  | 14 (30.4) |        | 60 (30.5)  |        | 101 (33.3) |        |
| BDNF rs2919375 | TT       | 119 (40.2) | 18 (39.1) | 0.812 | 79 (39.8)  | 0.981 | 119 (39.4) | 0.097 |
|                 | TC       | 136 (45.9) | 23 (50.0) |        | 92 (46.9)  |        | 138 (45.7) |        |
|                 | CC       | 41 (13.9)  | 5 (10.9)  |        | 26 (13.3)  | 0.945 | 45 (14.9)  |        |
| T genotype      |          |           |           |        |           |        |           |        |
|                 | A carrier | 119 (40.2) | 18 (39.1) | 1.000 | 79 (39.8)  | 1.000 | 119 (39.4) | 1.000 |
|                 | AA carrier| 95 (32.0)  | 14 (30.4) |        | 60 (30.5)  |        | 101 (33.3) |        |
| OXTR rs17466684 | TT       | 122 (41.8) | 23 (50.0) | 0.097 | 82 (42.5)  | 0.982 | 122 (41.9) | 0.013 |
|                 | TG       | 146 (50.0) | 16 (34.8) |        | 93 (48.2)  |        | 149 (50.0) |        |
|                 | GG       | 24 (8.2)   | 7 (15.2)  |        | 18 (9.3)   |        | 27 (9.1)  |        |
| T genotype      |          |           |           |        |           |        |           |        |
|                 | A carrier | 122 (41.8) | 23 (50.0) | 0.295 | 82 (42.5)  | 0.86  | 122 (41.9) | 0.047 |
|                 | AA carrier| 170 (58.2) | 53 (50.0) |        | 111 (57.5) |        | 176 (59.1) |        |
| RORA rs17466684 | TT       | 268 (81.8) | 39 (84.8) | 0.164 | 175 (90.7) | 0.909 | 271 (90.9) | 0.774 |
|                 | TG       | 24 (8.2)   | 7 (15.2)  |        | 18 (9.3)   |        | 27 (9.1)  |        |
|                 | GG       | 24 (8.2)   | 7 (15.2)  |        | 18 (9.3)   |        | 27 (9.1)  |        |
| Candidate Genes | SNP    | Genotype | Normal | Presence of Depression Symptoms | p-Value | Normal | Presence of Anxiety Symptoms | p-Value | Normal | Presence of Stress Symptoms | p-Value |
|-----------------|--------|----------|--------|----------------------------------|---------|--------|-------------------------------|---------|--------|-----------------------------|---------|
| **RORA**        | rs4775340 | GG       | 31 (67.4) | 0.775 | 127 (64.5) | 0.818 | 188 (62.3) | 0.449 | 18 (72.5) | 10 (25.0) | 0.026 |
|                 | GG     | GA       | 14 (30.4) | 65 (32.5) | 6 (4.3) | 103 (34.1) | 11 (3.6) | 29 (72.5) | 1 (2.5) | 988 9 of 20 |
|                 | AA     | A carrier | 1 (2.2) | 6 (3.0) | 49 (33.8) | 0.649 | 118 (62.3) | 11 (2.5) | 114 (72.5) | 0.000 |
| **OXTR**        | rs35376 | AA       | 16 (34.8) | 0.137 | 9 (24.9) | 0.611 | 81 (24.9) | 0.337 | 11 (27.5) | 23 (57.5) | 0.889 |
|                 | AG     | G carrier | 24 (52.2) | 69 (47.6) | 33 (22.8) | 145 (48.0) | 6 (35.0) | 11 (27.5) | 29 (72.5) | 0.000 |
|                 | GG     | A carrier | 6 (13.0) | 49 (32.9) | 57 (34.1) | 148 (48.0) | 22 (72.5) | 11 (27.5) | 29 (72.5) | 0.000 |
| **BDNF**        | rs6265     | GG       | 19 (42.2) | 0.059 | 96 (41.3) | 0.370 | 81 (31.9) | 0.157 | 76 (25.2) | 6 (13.0) | 1.000 |
|                 | GA     | A carrier | 20 (44.4) | 66 (45.8) | 36 (21.8) | 148 (48.2) | 112 (31.9) | 0.200 | 66 (25.2) | 6 (13.0) | 1.000 |
|                 | AA     | GG genotype | 56 (18.9) | 0.062 | 62 (31.5) | 0.646 | 96 (31.9) | 0.230 | 112 (31.9) | 0.099 | 0.099 |
| **FKBP5**       | rs9470080 | CC       | 22 (47.0) | 0.810 | 127 (41.6) | 0.953 | 127 (41.6) | 0.953 | 23 (57.5) | 12 (30.5) | 0.321 |
|                 | CT     | T carrier | 18 (39.2) | 65 (44.5) | 36 (18.3) | 142 (46.4) | 33 (11.0) | 13 (30.5) | 4 (10.0) | 0.160 |
|                 | TT     | C carrier | 33 (11.0) | 0.618 | 85 (42.9) | 0.453 | 127 (41.6) | 0.769 | 11 (2.5) | 17 (42.5) | 0.059 |
|                 |       | TT genotype | 33 (11.0) | 118 (38.1) | 112 (31.9) | 118 (38.1) | 35 (11.5) | 35 (11.5) | 36 (90.0) | 4 (10.0) | 1.000 |

Note: * p-value based on fisher’s exact test.
Table 3. Multiple regression analysis between genotypes of candidate genes and the presence of psychological symptoms adjusted for the confounding factors (n = 343).

| Candidate Genes SNP | Geno-Types | Depression Symptoms | | Anxiety Symptoms | | Stress Symptoms |
|---------------------|------------|---------------------| |--------------------| |--------------------|
|                     |            | Crude OR (95% CI, p-Value) | Adjusted OR (95% CI, p-Value) | Crude OR (95% CI, p-Value) | Adjusted OR (95% CI, p-Value) | Crude OR (95% CI, p-Value) | Adjusted OR (95% CI, p-Value) |
| EPHX2 rs17466684    | GG/GA      | 3.846 (0.852-17.353), 0.080 | 7.854 (1.330-46.360), 0.023 | 1.490 (0.909-2.444), 0.114 | 1.580 (0.943-2.659), 0.083 | 4.622 (0.964-22.158), 0.056 | 7.664 (1.579-37.197), 0.012 |
|                     | AA/GA      | 2.037 (0.907-4.573), 0.085 | 1.880 (0.655-5.393), 0.240 | - | - | - | - |
| ANO2 rs12579350     | GG/GA      | 1.879 (0.729-4.841), 0.192 | 2.497 (0.746-8.359), 0.138 | - | - | - | - |
|                     | AA/GA      | 1.498 (0.778-2.885), 0.227 | 1.045 (0.429-2.548), 0.922 | - | - | - | - |
| FKBP5 rs3800373     | GG/GA      | 2.490 (0.988-6.274), 0.053 | 2.114 (0.704-6.348), 0.182 | - | - | - | - |
|                     | AA/GA      | 1.797 (0.729-4.841), 0.192 | 2.497 (0.746-8.359), 0.138 | - | - | - | - |
| OXTR rs53576        | GG/GA      | 1.879 (0.729-4.841), 0.192 | 2.497 (0.746-8.359), 0.138 | - | - | - | - |
| BDNF rs6265         | GG/GA      | 1.879 (0.729-4.841), 0.192 | 2.497 (0.746-8.359), 0.138 | - | - | - | - |
| NPY5R rs13051691    | GG/GA      | 1.879 (0.729-4.841), 0.192 | 2.497 (0.746-8.359), 0.138 | - | - | - | - |
| NRG1 rs2919375      | GG/GA      | 1.879 (0.729-4.841), 0.192 | 2.497 (0.746-8.359), 0.138 | - | - | - | - |
| FKBP5 rs9470680     | GG/GA      | 1.879 (0.729-4.841), 0.192 | 2.497 (0.746-8.359), 0.138 | - | - | - | - |
| RORA rs4773340      | GG/GA      | 1.879 (0.729-4.841), 0.192 | 2.497 (0.746-8.359), 0.138 | - | - | - | - |

Note: Adjusted OR was determined by adjusting for socio-demographical and clinical moderators with p-value < 0.25 in univariate analysis.
4. Discussions

Over the years, an increasing number of polymorphisms in candidate genes related to the psychological problems have been discovered. Even so, most candidate gene association studies have been either overpowered or underpowered to detect the odds of genotypic heterogeneity for psychological symptoms. In this study, we performed simple logistic regression for every candidate gene, followed by multiple logistic regressions to elucidate the actual effect size of genotypes on the presence of depression, anxiety and/or stress symptoms. To our knowledge, this is the first study to examine the symptoms of depression, anxiety and/or stress among GDM women in Malaysia, and is also the first study to use the gene-environmental interaction hypothesis.

It is noteworthy that anxiety symptoms were the most commonly reported symptoms among the population of pregnant women with GDM (57.4% vs. 42.6%), whereas depressive symptoms (86.6% vs. 13.4%) and stress (88.3% vs. 11.7%) were much lower.

Based on logistic regression in this study, we reported that there is significant between SNP (rs17466684) of Epoxide Hydrolase 2 gene \((EPHX2)\) with depression symptoms \((AOR = 7.854, 95\% CI = 1.330–46.360)\) and stress symptoms \((AOR = 7.664, 95\% CI = 1.579–37.197)\). This is different finding compared with a study done in Japan where the carrier of AA genotype in SNP \((rs17466684)\) of \(EPHX2\) was found to be a risk variant of anxiety particularly panic disorder \([42,68]\). However, according to our genotypic analysis, this candidate gene was not associated with anxiety symptoms among Malaysian women. Polymorphism in \(EPHX2\) contributes to the odds of suffering from depression, anxiety, and stress symptoms in the Japanese and Malaysian population. A possible explanation for these findings is that \(EPHX2\) encodes for a key gate-keeper enzyme (soluble epoxide hydrolase) which functions in the catabolism of epoxy-fatty acids to their corresponding diols \([69–71]\). Soluble epoxide hydrolase is localized in neurons of central amygdala and this enzyme plays a vital role in neuronal firing \([72]\) and it is hence believed that polymorphism in \(EPHX2\) reduce the potency of anti-inflammatory activity of epoxy-fatty acids in brain \([73]\), thus affecting the release of functional neurotransmitters that influence neuropsychiatric disorders \([74]\).

Neuregulin 1 \((NRG1)\) is an important gene signaling numerous neurodevelopment processes such as neurotransmitter receptor expression regulation and synaptic plasticity \([75]\). In our study, there was a significant association between SNP \((rs2919375)\) of \(NRG1\) and stress symptoms \((AOR = 9.894, 95\% CI = 1.159–84.427)\). To date, the C allele in SNP of \(NRG1\) \((T > C\) in \(rs2919375)\) is a minor allele and also a risk allele for major depression disorder among the Han Chinese population \([34]\) was not found in our study. The reason for this difference is unknown. Apart from the population factor, the possible reason might be due to minor allele frequency in this study was 0.366, compared to 0.410 among Han Chinese population \([34]\), therefore the effect of risk allele or genotype might be underestimated in our study. The minor allele frequency has influence on the power to detect genetic effects, SNPs with minor allele frequency ranges from 25% to 50% might give a false-positive rate ranging from 69.2% to 70.8% \([76]\). Therefore, the analysis for genes \(NRG1\) \((T > C\) in \(rs2919375)\) indicates that either TT or TC genotypes are determinants for stress symptoms, which might inflate false positive concerns.

Oxytocin receptor genes \((OXTR)\) were found to have an association with neuropsychiatric disorders \([27,28]\); a possible explanation is that \(OXTR\) regulates the expression of \(OXTR\) p53, a potent transcription factor for the oxytocinergic pathway in neurons \([77–79]\). Emerging evidence also shows that \(OXTR\) rs53576 was associated with the structural coupling of the hypothalamus and amygdala, alteration to this structure is potentially to inflict neuropsychiatric disorders \([80–82]\). In our study, we found a positive association between \(OXTR\) rs53576 and stress symptoms among GDM women. Our finding contradicts with previous studies among the Japanese population \([27]\) and Caucasian in Italy \([28]\). In a Japanese study, the G allele is the minor allele and presence of either AA or AG genotypes in SNP \(rs53576\) were associated with panic disorders among the Japanese population \([27]\). In comparison to the finding done among Caucasians in Italy, a allele is a minor allele among Caucasians in Italy and the presence of either AA or AG genotypes is the protective factor for depression \((OR = 0.67, 95\% CI = 0.45–0.99)\) \([28]\). The findings of this study are of potential clinical and scientific importance as the identification of a significant association between particular candidate genes polymorphism with depression and stress...
among GDM women in Malaysia have certainly helped in the understanding of genetic aetiology among GDM women in local settings. Future studies should be conducted to validate the value of these candidate genes polymorphism in terms of genetic screening, so that the clinicians can send those GDM women at risk of having depression and stress for a genetic study.

Study Strength and Limitations

The present study contains multiple logistic regression analysis, adjusted for all socio-demographic backgrounds, and maternal and clinical profiles that potentially modulate the presentation of psychological symptoms. Therefore, the results shown on significant genotype related to depression and stress symptoms are clinically relevant despite this is an unmatched comparative case-control study, a sub-analysis from a cross-sectional study. The study demonstrates an association between candidate genes and the presence of depression, anxiety, or stress symptoms among GDM women. The interpretation of these association is limited by the screening nature of the psychometric tools used in measuring for these psychological symptoms, and not the diagnoses per se. Thus, the results should be interpreted cautiously. Future studies should be conducted with the inclusion of more SNP numbers per candidate gene to confirm the epigenetics-environmental moderator effects.

5. Conclusions

A significant association was observed between SNP (rs17466684) of EPHX2 and depression symptoms when adjusted for ethnicity, religion, the practice of home glucose monitoring, planned pregnancy, marital status, past obstetric history of abortion, underlying with allergy, a family history of depression, and anxiety with GDM. SNPs in EPHX2 (rs17466684), OXTR (rs53576) and NRG1 (rs2919375) are also associated with stress symptoms adjusted for ethnicity, religion, marital status, treatment regimens, past obstetric history of GDM, underlying with allergy and asthma and a family history of depression and anxiety.

Author Contributions: Conceived and designed the experiments: K.W.L. and S.M.C. Data collection: K.W.L., S.M.C., M.T. and N.M.N. Analysed the data: K.W.L., S.M.C., V.R., F.K.H., M.T. and S.C.C. Wrote the paper: K.W.L., S.M.C., F.K.H., V.R., S.C.C., M.T. and N.M.N. All authors have read and approved the manuscript.

Funding: This research received its funding from the Universiti Putra Malaysia under Putra Graduate Initiative (UPM/700-2/1/GP-IPS/2018/9593800), High Impact Grant (UPM/800-3/3/1/GPB/2018/9659600) and Graduate Research Fellowship (UPM/SPS/GS48750). The article processing charge was funded by Universiti Putra Malaysia. The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Acknowledgments: The authors would like to thank all the participants in the study, including the obstetricians and psychiatrists for their contributions in the diagnosis of psychological symptoms and all the GDM patients. This work was supported by the Universiti Putra Malaysia under Putra Graduate Initiative (UPM/700-2/1/GP-IPS/2018/9593800), High Impact Grant (UPM/800-3/3/1/GPB/2018/9659600) and Graduate Research Fellowship (UPM/SPS/GS48750). The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflicts of Interest: The authors declare that they have no competing interests.

Appendix A

| Candidate Genes | SNP | Chromosome: Location | Sequence of SNP (60 upstream, 60 downstream) |
|-----------------|-----|----------------------|--------------------------------------------|
| Epoxide Hydrolase 2 | rs17466684 | 8:27595330 | CCGTGGAGAC CCAAGTCCCT TTTCTGATGTGCT CTTAGAAGCT CTCGTCCAAT CTCTTGGGTTT |
|                  |     |                      | GCACTATCC ATTTTCTAGT GGGGCCCTGT GATCCCCAGA GACAGACCCG TGTGTTCATC |
| Neuropeptide Y   | rs12501691 | 4:163346876 | GTAATATAT ATCTTCAGTT TAGTTCGATG TGCTGATGTG CATAGCAGTT ATTAAGTCAAG TAT |
|                  |     |                      | TATCCAAATT TAAAGTGCCT AACTCTTCTT ATGTCTGATG TAGTAATCTC CTCTCATAAG |
| Candidate Genes                     | SNP    | Chromosome: Location | Sequence of SNP (60 upstream, 60 downstream) |
|------------------------------------|--------|-----------------------|---------------------------------------------|
| Anoctamin 2                        | rs12579350 | 12:5687935            | AAAACACACCA GGAAGGTCAGG TTCAAGTCTCC          |
|                                    |         |                       | CACATCCTGT GCTCCCTCCTG ACTTGTGCTF            |
|                                    |         |                       | AGG                             |
|                                    |         |                       | ACCCTGTTGAGAAATAGTTTCAAAAGCATTAAGG         |
|                                    |         |                       | AAAAATTAATG TTTAAGGACCTGTT            |
| Neuregulin 1                       | rs2919375 | 8:32719327            | AAAAACACTCAT GAACTGCTGAG TACACATCTCC       |
|                                    |         |                       | CTTTCTCTCACGAGGATGACCAGG                 |
|                                    |         |                       | C/AG                             |
|                                    |         |                       | TTGTATTTTAC AGGTTTTTAA TATGCATGTT         |
|                                    |         |                       | TAAATGGATA TTTATATGGTTAA                |
| FK506 binding protein 5            | rs3800373 | 6:3557469             | AAAACAAAACT GATAACGGCT GAAGTGGGTG           |
|                                    |         |                       | ATGGCTACAT GGAGATTCAT TACACAATCC       |
|                                    |         |                       | C/AG                             |
|                                    |         |                       | TTGTATTTTAC AGGTTTTTAA TATGCATGTT         |
|                                    |         |                       | TAAATGGATA TTTATATGGTTAA                |
| retinoid-related orphan receptor   | rs4775340 | 15:6097553            | AAAACAGTAAG AAAATTGGAT CCTAGAATCTC         |
| alpha                              |         |                       | ACTCTGGAGA ACACTGAAAT GAACATGTGG         |
|                                    |         |                       | A/ G                             |
|                                    |         |                       | GTCCTATTCA GAACTGTGGT GCCGTACTG           |
|                                    |         |                       | TATGGAACTTGG CACCTACCTT CACTGAAGC        |
|oxytocin receptor genes             | rs53576 | 3:8786265             | TCCCCCACCT CGGCGGACC CATCCAGTGGG          |
|                                    |         |                       | AAAAGGAAAGG TGTACGGGAC ATGCCCGAGG         |
|                                    |         |                       | AGG                             |
|                                    |         |                       | TCCCTACTA CACAAAGAAG GGGGGCGGCT       |
|                                    |         |                       | GGGAGGCTCA TTCTACAGGT GGGGGGACAG       |
| Brain-derived neurotrophic factor  | rs6265 | 11:27658369           | GTGAATGGGC CCAAGGCAGG TTCAAGGAGGC        |
|                                    |         |                       | TGGACTCATG TTGGCTGAC TTTGCAAGG       |
|                                    |         |                       | AGG                             |
|                                    |         |                       | TGAATAGAGA GCACAGCATG GAGGAGCACGA       |
|                                    |         |                       | AAGGCTCCGGCA AAAGTGAAGA AAACATAAGG |
| FK506 binding protein 5            | rs9470080 | 6:35678588            | ATTTGACAAAA AGCAGCTAAA GACAAAAGAA         |
|                                    |         |                       | ATGGCAAAATT AAGGACTTAA CAAAGATCAGA       |
|                                    |         |                       | C/AG                             |
|                                    |         |                       | TTCTGACCTA ACAAACAGT GTTTTATTGT         |
|                                    |         |                       | TCTCTACT ATATAACAAAT TCCGGGAAAA       |
| Tryptophan hydroxylase 2           | rs1843809 | 12:71954918           | TAGTATTTGCA AATCCCATCT ATICCTGCTG        |
|                                    |         |                       | AAAAAAGAGCC TGGACTCTCA CTTTATATAT         |
|                                    |         |                       | C/AG                             |
|                                    |         |                       | CCATCTTGATGCTTAAAT GGATTGAGAA TATTATGTT |
|                                    |         |                       | ATGATGTTAT ATGATGTTAT       |
| Catenin Alpha 3                    | rs1099724 | 10:6657637            | CCCACCCACC TCCCCCAATGA AGCAGITCCGC       |
|                                    |         |                       | AGAAGCTTTCAT TTGGCTGAC ATGTGCTCATT      |
|                                    |         |                       | C/AT                             |
|                                    |         |                       | ATATCCAGCT TGGACTCTCC AATTAAGCACG       |
|                                    |         |                       | GAAAACATG TGAAGATGTC TGGCTGCTCC         |
| Phospholysine Phosphohistidine     | rs35936514 | 10:124556401          | CACCTGCTAC TCTCGGGGCG CAGGGTTTCA           |
| Inorganic Pyrophosphate Phosphatase|         |                       | ATGGCTGAC CACTGGTGGCC GCGTGGGACG        |
|                                    |         |                       | C/AG                             |
|                                    |         |                       | ATCTCGTAAC GACAAAGAAG GGGGGCGGCT       |
|                                    |         |                       | GGGAGGCTCA TTCTACAGGT GGGGGGACAG       |
| Calcium Voltage-Gated Channel Subunit Alpha1 C | rs10186737 | 12:2236129           | ACTTGGGCTG TATCAAGATGG TCTGCTCAAA CTTAACAGT |
|                                    |         |                       | TCCATCTCC ATCAAGCGGA TCCAGCTGGC          |
|                                    |         |                       | TGCAAGCA CTACCCCTGTT GGGTGTTAAG          |
|                                    |         |                       | AGG                             |
| Apolipoprotein L3                  | rs132617 | 22:3637373            | AGCAGAAGA GAGAGTCTTC TTTGCTGGTTA       |
|                                    |         |                       | TTGGAAAGAG ACTGCGTTGG CAGTACAAAG        |
|                                    |         |                       | C/AG                             |
|                                    |         |                       | GATGATTCTG ATACAGTACG CCAAAACTCA       |
|                                    |         |                       | GGGCTCTTG TTGGCAAGG CTTGCCTATTA         |
| Testis Expressed 51                | rs6733840 | 2:126902405           | GTGATACGTG TGGCCAGGCT GGGCGCTGGC       |
|                                    |         |                       | GGCCCGGGAA CAGCGCCCGG CAGCACGCATC       |
|                                    |         |                       | C/AG                             |
|                                    |         |                       | TTGGCAGTAT TTGGCAGTGC CATGCTGGGA        |
|                                    |         |                       | CAGCGGGCAGG CTTCCCTTCC CTTCCCTCCT      |
| Pleckstrin Homology And RhoGEF     | rs9372078 | 6:150592825           | AAGGACGGTG GGCTGGACCT CAGGAACTGG          |
| Domain Containing G1               |         |                       | ACACAAGCTC CTTGTTGGA CTTGGCGCTA         |
|                                    |         |                       | A/ T                             |
|                                    |         |                       | TTTTGGTTG GTAATACTC CCAACAGCCTG        |
|                                    |         |                       | GATCCACA CCACAATG GATGTCAGT            |
| 5-Hydroxytryptamine receptor 2     | rs6318 | X:114731326           | GATTTGGTTT TTTTCTTCA ATITTTAGCGG TACCACTAAT |
|                                    |         |                       | TGCCCTCATT GGGGAACATG                  |
|                                    |         |                       | CGG                             |
|                                    |         |                       | TGATATTCT GGGGACCCAC TGGACCTGAT       |
|                                    |         |                       | AGTAACTGAC ATTTCAACTA CTTGCCAGAGG   |
| Sidekick Cell Adhesion Molecule 2  | rs3816995 | 17:73339121           | ACTGTCGGCC TCCCCAGCGG CTCCACCTGGG        |
|                                    |         |                       | AGGGCTCGTTT CCGGCCCTGG GAGGAGACCCG   |
|                                    |         |                       | AAGGAATCTG TATGGGTTGG CCCCGACTG        |
Table A2. Genotype and allelic information for candidate genes and its chi-squared goodness-of-fit based global distribution (n = 343).

| Candidate Genes | SNP | Genotype | Expected Genotype Frequency | Expected N | Frequency | N | Allele Frequency | Call Rate, % | p-Value |
|-----------------|-----|----------|----------------------------|------------|----------|---|-----------------|-------------|---------|
| **BDNF**        |     | GG       | 0.466                      | 160        | 0.334    | 114| G               | 0.576       | 98.9    | 0.69    |
|                 |     | GA       | 0.333                      | 114        | 0.484    | 165| A               | 0.424       |         |         |
|                 |     | AA       | 0.201                      | 69         | 0.182    | 62 |                 |             |         |         |
| **OXTR**        |     | AA       | 0.389                      | 134        | 0.269    | 92 | A               | 0.515       | 98.9    | 0.68    |
|                 |     | AG       | 0.333                      | 114        | 0.491    | 168| G               | 0.485       |         |         |
|                 |     | GG       | 0.278                      | 95         | 0.240    | 82 |                 |             |         |         |
| **RORA**        |     | GC       | 0.450                      | 155        | 0.635    | 217| G               | 0.800       | 99.2    | 0.43    |
|                 |     | GA       | 0.333                      | 114        | 0.330    | 113| A               | 0.200       |         |         |
|                 |     | AA       | 0.217                      | 74         | 0.035    | 12 |                 |             |         |         |
| **NRG1**        | rs2919375 | TT       | 0.388                      | 133        | 0.401    | 137| T               | 0.634       | 99.2    | 0.86    |
|                 |     | TC       | 0.333                      | 114        | 0.465    | 159| C               | 0.366       |         |         |
|                 |     | CC       | 0.279                      | 96         | 0.135    | 46 |                 |             |         |         |
| **TPH2**        | rs1843809 | TT       | 0.514                      | 177        | 0.915    | 312| T               | 0.958       | 99.2    | 0.43    |
|                 |     | TG       | 0.333                      | 114        | 0.085    | 29 | G               | 0.042       |         |         |
|                 |     | GG       | 0.153                      | 52         | 0.000    | 0  |                 |             |         |         |
| **LHPP**        | rs33936314 | CC       | 0.593                      | 204        | 0.474    | 162| C               | 0.683       | 99.2    | 0.45    |
|                 |     | CT       | 0.333                      | 114        | 0.418    | 143| T               | 0.317       |         |         |
|                 |     | TT       | 0.074                      | 25         | 0.108    | 37 |                 |             |         |         |
| **FBKP5**       | rs8470080 | CC       | 0.363                      | 125        | 0.436    | 155| T               | 0.662       | 100     | 0.73    |
|                 |     | CT       | 0.333                      | 114        | 0.451    | 155| T               | 0.338       |         |         |
|                 |     | TT       | 0.304                      | 104        | 0.113    | 39 |                 |             |         |         |
| **FBKP5**       | rs3800373 | TT       | 0.425                      | 146        | 0.429    | 145| T               | 0.669       | 98.4    | 0.17    |
|                 |     | TG       | 0.333                      | 114        | 0.479    | 162| T               | 0.331       |         |         |
|                 |     | GG       | 0.242                      | 83         | 0.092    | 31 |                 |             |         |         |
| **TEX51**       | rs6733840 | TT       | 0.488                      | 168        | 0.638    | 219| C               | 0.796       | 99.7    | 0.68    |
|                 |     | TC       | 0.333                      | 114        | 0.315    | 108| T               | 0.204       |         |         |
|                 |     | CC       | 0.179                      | 61         | 0.047    | 16 |                 |             |         |         |
| **PLEKH1**      | rs9572078 | AA       | 0.384                      | 131        | 0.388    | 132| A               | 0.624       | 98.4    | 0.78    |
|                 |     | AT       | 0.333                      | 114        | 0.471    | 160| T               | 0.376       |         |         |
|                 |     | TT       | 0.283                      | 97         | 0.141    | 48 |                 |             |         |         |
| **HTR2C**       | rs6318 | GG       | 0.571                      | 196        | 0.944    | 323| G               | 0.971       | 99.5    | 0.63    |
|                 |     | GC       | 0.333                      | 114        | 0.053    | 18 | C               | 0.029       |         |         |
|                 |     | CC       | 0.095                      | 33         | 0.003    | 1  |                 |             |         |         |
| **EPHX2**       | rs17466684 | GG       | 0.536                      | 184        | 0.755    | 259| G               | 0.864       | 99.7    | 0.19    |
|                 |     | GA       | 0.333                      | 114        | 0.219    | 75 | C               | 0.136       |         |         |
|                 |     | AA       | 0.131                      | 45         | 0.026    | 9  |                 |             |         |         |
| **ANO2**        | rs12579350 | GG       | 0.541                      | 186        | 0.860    | 297| G               | 0.923       | 101.0   | 0.28    |
|                 |     | GA       | 0.333                      | 114        | 0.125    | 43 | C               | 0.077       |         |         |
|                 |     | AA       | 0.126                      | 43         | 0.009    | 3  |                 |             |         |         |
| **NPSYR**       | rs12501691 | TT       | 0.613                      | 210        | 0.682    | 274| T               | 0.831       | 99.5    | 0.18    |
|                 |     | TA       | 0.333                      | 114        | 0.297    | 102| T               | 0.169       |         |         |
|                 |     | AA       | 0.054                      | 19         | 0.020    | 7  |                 |             |         |         |
| **SOD2**        | rs3816995 | GG       | 0.466                      | 140        | 0.617    | 211| G               | 0.779       | 99.2    | 0.39    |
|                 |     | GA       | 0.333                      | 114        | 0.325    | 111| T               | 0.221       |         |         |
|                 |     | AA       | 0.260                      | 89         | 0.058    | 20 |                 |             |         |         |
Table A3. Analyses of the genotype of LHPP, SDK2, HTR2C, TEX51, PLEKHG1 and TPH2 among women with GDM were stratified by presence of psychological symptoms. *p-value based on fisher’s exact test.

| Candidate Genes | SNP     | Genotype | Normal Presence of Depression Symptoms | p-Value | Normal Presence of Anxiety Symptoms | p-Value | Normal Presence of Stress Symptoms | p-Value |
|-----------------|---------|----------|-----------------------------------------|---------|--------------------------------------|---------|-------------------------------------|---------|
| **LHPP**        | rs3936514 | CC       | 139 (85.8) 23 (14.2)                    | 0.600   | 97 (59.9) 65 (40.1)                  | 0.262   | 144 (88.9) 18 (11.1)               | 0.909   |
|                 |         | CT       | 123 (86.0) 20 (14.0)                    |         | 75 (52.4) 68 (47.6)                  | 0.262   | 123 (87.4) 18 (12.6)               | 0.864   |
|                 |         | TT       | 34 (91.9) 3 (8.1)                       |         | 24 (94.9) 3 (5.1)                    | 0.262   | 33 (89.2) 4 (10.8)                 | 0.864   |
|                 |         | C carrier| 157 (87.2) 23 (12.8)                    | 0.701   | 97 (59.9) 81 (40.1)                  | 0.363   | 144 (88.9) 18 (12.2)               | 0.750   |
|                 |         | TT genotype| 262 (85.9) 43 (14.1)                  | 0.445 * | 172 (56.4) 24 (43.6)                 | 0.325   | 269 (88.2) 33 (11.8)               | 4.108   |
| **SDK2**        | rs3816995 | GG       | 183 (86.7) 28 (13.3)                    | 0.910   | 119 (56.4) 92 (43.6)                  | 0.262   | 187 (88.6) 24 (11.4)               | 0.921   |
|                 |         | GA       | 96 (86.5) 15 (13.5)                     |         | 65 (58.8) 46 (41.4)                  | 0.735   | 97 (87.4) 14 (12.6)                | 1.000   |
|                 |         | AA       | 18 (90.0) 2 (10.0)                      |         | 13 (65.0) 7 (35.0)                   |         | 18 (90.0) 2 (10.0)                 |         |
| **HTR2C**       | rs6318  | GG       | 279 (86.4) 44 (13.6)                    | 0.883   | 187 (57.9) 136 (42.1)                | 0.496 * | 286 (88.5) 37 (11.5)               | 0.748   |
|                 |         | GC       | 16 (88.9) 2 (11.1)                      |         | 10 (55.6) 8 (44.4)                   |         | 15 (83.3) 3 (16.7)                 |         |
|                 |         | CC       | 1 (100.0) 0 (0.0)                       |         | 0 (0.0) 1 (100.0)                    |         | 1 (100.0) 0 (0.0)                  |         |
| **TEX51**       | rs6733840 | GG       | 189 (86.3) 30 (13.7)                    | 0.977   | 125 (57.1) 94 (42.9)                  | 0.914   | 191 (87.2) 28 (12.8)               | 0.643   |
|                 |         | TC       | 14 (87.5) 2 (12.5)                      |         | 10 (62.5) 6 (37.5)                   |         | 98 (90.7) 10 (9.3)                 |         |
|                 |         | CC       | 1 (100.0) 0 (0.0)                       |         | 0 (0.0) 1 (100.0)                    |         | 1 (100.0) 0 (0.0)                  |         |
| **PLEKHG1**     | rs9372078 | GG       | 115 (87.1) 17 (12.9)                    | 0.865   | 75 (56.8) 57 (43.2)                   | 0.738   | 118 (89.4) 14 (10.6)               | 0.597   |
|                 |         | AT       | 138 (86.5) 22 (13.8)                    | 0.951   | 75 (56.8) 57 (43.2)                   | 0.878   | 139 (86.9) 21 (13.1)               | 0.763   |
|                 |         | TT       | 41 (84.5) 7 (14.6)                      |         | 27 (56.3) 21 (43.8)                  |         | 43 (89.6) 5 (10.4)                 |         |
| **TPH2**        | rs1843909 | GG       | 115 (87.1) 17 (12.9)                    | 0.780   | 75 (56.8) 57 (43.2)                   | 0.738   | 118 (89.4) 14 (10.6)               | 0.597   |
|                 |         | T carrier| 179 (86.1) 29 (13.9)                    |         | 122 (58.7) 86 (41.3)                 |         | 182 (87.5) 26 (12.5)               |         |
|                 |         | TT genotype| 253 (86.6) 39 (13.4)                  | 0.818   | 170 (58.2) 122 (41.8)                 | 0.798   | 257 (88.0) 35 (12.0)               | 0.754   |
|                 |         | TG       | 27 (93.1) 2 (6.9)                       |         | 17 (58.6) 12 (41.4)                  |         | 27 (93.1) 2 (6.9)                  |         |
|                 |         | GG       | 0 (0.0) 0 (0.0)                         |         | 0 (0.0) 0 (0.0)                      |         | 0 (0.0) 0 (0.0)                    |         |
Genes 2019, 10, 988

References

1. Lee, K.W.; Ching, S.M.; Ramachandran, V.; Yee, A.; Hoo, F.K.; Chia, Y.C.; Sulaiman, W.A.W.; Suppiah, S.; Mohamed, M.H.; Veettil, S.K. Prevalence and risk factors of gestational diabetes mellitus in Asia: A systematic review and meta-analysis. *BMC Pregnancy Childbirth* **2018**, *18*, 494. [CrossRef]

2. Hilden, K.; Hanson, U.; Persson, M.; Fadl, H. Overweight and obesity: A remaining problem in women treated for severe gestational diabetes. *Diabet Med.* **2016**, *33*, 1045–1051. [CrossRef] [PubMed]

3. Domanski, G.; Lange, A.E.; Ittermann, T.; Allenberg, H.; Spoo, R.A.; Zygmunt, M.; Heckmann, M. Evaluation of neonatal and maternal morbidity in mothers with gestational diabetes: A population-based study. *BMC Pregnancy Childbirth* **2018**, *18*, 367. [CrossRef] [PubMed]

4. Menticoglou, S. Shoulder dystocia: Incidence, mechanisms, and management strategies. *Int. J. Women's Health* **2018**, *10*, 723–732. [CrossRef] [PubMed]

5. Daniells, S.; Grenyer, B.F.; Davis, W.S.; Coleman, K.J.; Burgess, J.-A.P.; Moses, R.G. Gestational diabetes mellitus: Is a diagnosis associated with an increase in maternal anxiety and stress in the short and intermediate term? *Diabetes Care* **2003**, *26*, 385–389. [CrossRef] [PubMed]

6. Rumbold, A.R.; Crowther, C.A. Women’s experiences of being screened for gestational diabetes mellitus. *Aust. New Zealand J. Obstet. Gynaecol.* **2002**, *42*, 131–137. [CrossRef] [PubMed]

7. Hjelm, K.; Berntorp, K.; Frid, A.; Åberg, A.; Apelqvist, J. Beliefs about health and illness in women managed for gestational diabetes in two organisations. *Midwifery* **2008**, *24*, 168–182. [CrossRef]

8. Hirst, J.E.; Tran, T.S.; Do, M.A.T.; Rowena, F.; Morris, J.M.; Jeffery, H.E. Women with gestational diabetes in Vietnam: A qualitative study to determine attitudes and health behaviours. *BMC Pregnancy Childbirth* **2012**, *12*, 81. [CrossRef]

9. Greenhalgh, T.; Clinch, M.; Afsar, N.; Choudhury, Y.; Sudra, R.; Campbell-Richards, D.; Claydon, A.; Hitman, G.A.; Hanson, P.; Finer, S. Socio-cultural influences on the behaviour of South Asian women with diabetes in pregnancy: Qualitative study using a multi-level theoretical approach. *BMC Med.* **2015**, *13*, 120. [CrossRef]

10. Pace, R.; Rahme, E.; Da Costa, D.; Dasgupta, K. Association between gestational diabetes mellitus and depression in parents: A retrospective cohort study. *Clin. Epidemiol.* **2018**, *10*, 1827–1838. [CrossRef]

11. Gemeay, E.M.; Moawed, S.A.; Mansour, E.A.; Ebrahiem, N.E.; Moussa, I.M.; Nadrah, W.O. The association between diabetes and depression. *Saudi Med. J.* **2015**, *36*, 1210. [CrossRef] [PubMed]

12. Egan, A.; Dunne, F.; Lydon, K.; Conneely, S.; Sarma, K.; McGuire, B. Diabetes in pregnancy: Worse medical outcomes in type 1 diabetes but worse psychological outcomes in gestational diabetes. *QJM Int. J. Med.* **2017**, *110*, 721–727. [CrossRef] [PubMed]

13. Goodman, J.H. Perinatal depression and infant mental health. *Arch. Psychiatr. Nurs.* **2019**, *33*, 217–224. [CrossRef] [PubMed]

14. Robertson, E.; Grace, S.; Wallington, T.; Stewart, D.E. Antenatal risk factors for postpartum depression: A synthesis of recent literature. *Gen. Hosp. Psychiatry* **2004**, *26*, 289–295. [CrossRef] [PubMed]

15. Martini, J.; Petzoldt, J.; Einsle, F.; Beesdo-Baum, K.; Höfler, M.; Wittchen, H.-U. Risk factors and course patterns of anxiety and depressive disorders during pregnancy and after delivery: A prospective-longitudinal study. *J. Affect. Disord.* **2015**, *175*, 385–395. [CrossRef]

16. Lydsdottir, L.B.; Howard, L.M.; Olafsdottir, H.; Thome, M.; Tyringsson, P.; Sigurdsson, J.F. The mental health characteristics of pregnant women with depressive symptoms identified by the Edinburgh Postnatal Depression Scale. *J. Clin. Psychiatry* **2014**, *75*, 393–398. [CrossRef]

17. Brittain, K.; Myer, L.; Koen, N.; Koopowitz, S.; Donald, K.A.; Barnett, W.; Zar, H.J.; Stein, D.J. Risk Factors for Antenatal Depression and Associations with Infant Birth Outcomes: Results From a South African Birth Cohort Study. *Paediatr. Perinat. Epidemiol.* **2015**, *29*, 505–514. [CrossRef]

18. Bayrampour, H.; McDonald, S.; Tough, S. Risk factors of transient and persistent anxiety during pregnancy. *Midwifery* **2015**, *31*, 582–589. [CrossRef]

19. Gournouli, K.; Anagnostopoulos, F.; Lykeridou, K. Coping strategies as psychological risk factor for antenatal anxiety, worries, and depression among Greek women. *Arch. Women's Ment. Health* **2013**, *16*, 353–361. [CrossRef]

20. Sullivan, P.F.; Neale, M.C.; Kendler, K.S. Genetic epidemiology of major depression: Review and meta-analysis. *Am. J. Psychiatry* **2000**, *157*, 1552–1562. [CrossRef]
21. Stein, M.B.; Jang, K.L.; Livesley, W.J. Heritability of anxiety sensitivity: A twin study. *Am. J. Psychiatry* 1999, 156, 246–251. [PubMed]

22. Federenko, I.S.; Schlotz, W.; Kirschbaum, C.; Bartels, M.; Hellhammer, D.H.; Wüst, S. The heritability of perceived stress. *Psychol. Med.* 2006, 36, 375–385. [CrossRef] [PubMed]

23. Border, R.; Johnson, E.C.; Evans, L.M.; Smolen, A.; Berley, N.; Sullivan, P.F.; Keller, M.C. No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. *Am. J. Psychiatry* 2019, 176, 376–387. [CrossRef] [PubMed]

24. Duncan, L.E.; Keller, M.C. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am. J. Psychiatry* 2011, 168, 1041–1049. [CrossRef]

25. Fan, M.; Li, R.H.; Hu, M.S.; Xiao, L.Y.; Zhou, X.D.; Ran, M.S.; Fang, D.Z. Association of Val66Met polymorphism at brain derived neurotrophic factor gene with depression among Chinese adolescents after Wenchuan earthquake: An 18 months longitudinal study. *Physiol. Behav.* 2017, 179, 16–22. [CrossRef]

26. Tsang, R.S.; Mather, K.A.; Sachdev, P.S.; Reppermund, S. Systematic review and meta-analysis of genetic studies of late-life depression. *Neurosci. Biobehav. Rev.* 2017, 75, 129–139. [CrossRef]

27. Onodera, M.; Ishitobi, Y.; Tanaka, Y.; Aizawa, S.; Masuda, K.; Inoue, A.; Oshita, H.; Okamoto, K.; Kawashima, C.; Nakaniishi, M. Genetic association of the oxytocin receptor genes with panic, major depressive disorder, and social anxiety disorder. *Psychiatr. Genet.* 2015, 25, 212. [CrossRef]

28. Costa, B.; Pini, S.; Baldwin, D.S.; Silove, D.; Silvano, V.; Abelli, M.; Coppede, F.; Martini, C. Oxytocin receptor and G-protein polymorphisms in patients with depression and separation anxiety. *J. Affect. Disord.* 2017, 218, 365–373. [CrossRef]

29. Verhagen, M.; Van Der Meij, A.; Van Deurzen, P.; Janzing, J.; Arias-Vasquez, A.; Buitelaar, J.; Franke, B. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: Effects of gender and ethnicity. *Mol. Psychiatry* 2010, 15, 260. [CrossRef]

30. Skibinska, M.; Groszew ska, A.; Kapelski, P.; Rajewska-Rager, A.; Pawlak, J.; Dmitrzak-Weglarz, M.; Szczepankiewicz, A.; Twarowska-Hauser, J. Val66Met functional polymorphism and serum protein level of brain-derived neurotrophic factor (BDNF) in acute episode of schizophrenia and depression. *Pharmacol. Rep.* 2018, 70, 58–59. [CrossRef]

31. Wasilewska, K.; Pawlak, A.; Kostrzewa, G.; Sobczyk-Kopciol, A.; Kaczorowska, A.; Badowski, J.; Brzozowska, M.; Drygas, W.; Piwowarska, I.; Bielecki, W. OXTR polymorphism in depression and completed suicide—A study on a large population sample. *Psychoneuroendocrinology* 2017, 77, 84–89. [CrossRef] [PubMed]

32. Colhoun, H.M.; McKeigue, P.M.; Smith, G.D. Problems of reporting genetic associations with complex outcomes. *Lancet* 2003, 361, 865–872. [CrossRef]

33. Ming, Q.; Wang, X.; Chai, Q.; Yi, J.; Yao, S. Retinoid-related orphan receptor alpha (RORA) gene variation is associated with trait depression. *Psychiatry Res.* 2015, 229, 629–630. [CrossRef]

34. Wen, Z.; Chen, J.; Khan, R.A.W.; Song, Z.; Wang, M.; Li, Z.; Shen, J.; Li, W.; Shi, Y. Genetic association between NRG1 and schizophrenia, major depressive disorder, bipolar disorder in Han Chinese population. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* 2016, 218, 468–478. [CrossRef] [PubMed]

35. Zill, P.; Baghai, T.; Zwanzger, P.; Schüle, C.; Eser, D.; Rupprecht, R.; Möller, H.; Bondy, B.; Ackenheil, M. SNP and haplotype analysis of a novel tryptophan hydroxylase isoform (TPH2) gene provide evidence for association with major depression. *Mol. Psychiatry* 2004, 9, 1030–1036. [CrossRef]

36. Cocchi, E.; Fabbri, C.; Han, C.; Lee, S.-J.; Patkar, A.A.; Masand, P.S.; Pae, C.-U.; Serretti, A. Genome-wide association study of antidepressant response: Involvement of the inorganic cation transmembrane transporter activity pathway. *BMC Psychiatry* 2016, 16, 106. [CrossRef]

37. Rigaud, A.-S.; Traykov, L.; Caputo, L.; Coste, J.; Latour, F.; Couderc, R.; Moulin, F.; Boller, F.; Forette, F. Association of the apolipoprotein E ε4 allele with late-onset depression. *Neuropyschopharmacology* 2001, 20, 268–272. [CrossRef]

38. Neff, C.; Abkevich, V.; Packer, J.; Chen, Y.; Potter, J.; Riley, R.; Davenport, C.; Warren, J.D.; Jammalapati, S.; Bhathena, A. Evidence for HTR1A and LHPP as interacting genetic risk factors in major depression. *Mol. Psychiatry* 2009, 14, 621–630. [CrossRef]

39. Cai, N.; Bigdell, T.B.; Kretzschmar, W.; Li, Y.; Liang, J.; Song, L.; Hu, J.; Li, Q.; Jin, W.; Hu, Z. Sparse whole-genome sequencing identifies two loci for major depressive disorder. *Nature* 2015, 523, 588–591.
40. Fabbri, C.; Corponi, F.; Albanì, D.; Raimondi, I.; Forloni, G.; Schruers, K.; Kasper, S.; Kautzky, A.; Zohar, J.; Souery, D. Pleiotropic genes in psychiatry: Calcium channels and the stress-related FKBP5 gene in antidepressant resistance. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2018, 81, 203–210. [CrossRef]

41. Szczepankiewicz, A.; Leszczyńska-Rodziewicz, A.; Pawlak, J.; Narożna, B.; Rajewska-Rager, A.; Wilkos, M.; Zaremba, D.; Maciukiewicz, M.; Twarowska-Hauser, J. FKBP5 polymorphism is associated with major depression but not with bipolar disorder. J. Affect. Disord. 2014, 164, 33–37. [CrossRef] [PubMed]

42. Otowa, T.; Yoshida, E.; Sugaya, N.; Yasuda, S.; Nishimura, Y.; Inoue, K.; Tochigi, M.; Umekage, T.; Miyagawa, T.; Nishida, N. Genome-wide association study of panic disorder in the Japanese population. J. Hum. Genet. 2009, 54, 122–126. [CrossRef] [PubMed]

43. Grzesiak, M.; Beszlę, J.A.; Waszczuk, E.; Szechowiński, M.; Szewczuk-Bogusławska, M.; Frydecka, D.; Dobosz, T.; Jonkisz, A.; Lebioda, A.; Malodobra, M. Serotonin-related gene variants in patients with irritable bowel syndrome and depressive or anxiety disorders. Gastroenterol. Res. Pract. 2017, 2017, 4290430. [CrossRef]

44. Otowa, T.; Kawamura, Y.; Nishida, N.; Sugaya, N.; Koike, A.; Yoshida, E.; Inoue, K.; Yasuda, S.; Nishimura, Y.; Liu, X. Meta-analysis of genome-wide association studies for panic disorder in the Japanese population. Transl. Psychiatry 2012, 2, e186. [CrossRef]

45. Wang, Q.; Shelton, R.C.; Dwivedi, Y. Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: A systematic review and meta-analysis. J. Affect. Disord. 2018, 225, 422–428. [CrossRef]

46. Bath, K.G.; Lee, F.S. Variant BDNF (Val66Met) impact on brain structure and function. Cogn. Affect. Behav. Neurosci. 2006, 6, 79–85. [CrossRef]

47. Nestler, E.J.; Carlezon, W.A., Jr. The mesolimbic dopamine reward circuit in depression. Biol. Psychiatry 2006, 59, 1151–1159. [CrossRef]

48. Kim, H.S.; Sherman, D.K.; Sasaki, J.Y.; Xu, J.; Chu, T.Q.; Ryu, C.; Suh, E.M.; Graham, K.; Taylor, S.E. Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking. Proc. Natl. Acad. Sci. USA 2010, 107, 15717–15721. [CrossRef]

49. Kirsch, P.; Esslinger, C.; Chen, Q.; Mier, D.; Liss, S.; Siddhanti, S.; Grzesiak, M.; Beszlę, J.A.; Waszczuk, E.; Szechiński, M.; Szewczuk-Bogusławska, M.; Frydecka, D.; Dobosz, T.; Jonkisz, A.; Lebioda, A.; Malodobra, M. Serotonin-related gene variants in patients with irritable bowel syndrome and depressive or anxiety disorders. Gastroenterol. Res. Pract. 2017, 2017, 4290430. [CrossRef]

50. Fitzpatrick, P.F. Tetrahydropterin-dependent amino acid hydroxylases. Annu. Rev. Biochem. 1999, 68, 355–381. [CrossRef]

51. Sato, K.; Emi, M.; Ezura, Y.; Fujita, Y.; Takada, D.; Ishigami, T.; Umemura, S.; Xin, Y.; Wu, L.L.; Larrinaga-Shum, S. Soluble epoxide hydrolase variant (Glu287Arg) modifies plasma total cholesterol and triglyceride phenotype in familial hypercholesterolemia: Intrafamilial association study in an eight-generation hyperlipidemic kindred. J. Hum. Genet. 2004, 49, 29–34. [CrossRef] [PubMed]

52. Dumont, Y.; Martel, J.-C.; Fournier, A.; St-Pierre, S.; Quirion, R. Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Prog. Neurobiol. 1992, 38, 125–167. [CrossRef]

53. Binder, E.B.; Salyakina, D.; Lichtner, P.; Wochnik, G.M.; Ising, M.; Pütz, B.; Papiol, S.; Seaman, S.; Siddhanti, S.; Kohli, M.A. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat. Genet. 2004, 36, 1319–1325. [CrossRef] [PubMed]

54. Cui, L.; Gong, X.; Tang, Y.; Kong, L.; Chang, M.; Geng, H.; Xu, K.; Wang, F. Relationship between the LHPP gene polymorphism and resting-state brain activity in major depressive disorder. Neuroplast. 2016, 2016, 9162590. [CrossRef]

55. Terraciano, A.; Tanaka, T.; Sutin, A.R.; Sanna, S.; Deiana, B.; Lai, S.; Uda, M.; Schlessinger, D.; Abecasis, G.R.; Ferrucci, L. Genome-wide association scan of trait depression. Biol. Psychiatry 2010, 68, 811–817. [CrossRef]

56. Říbeiro, L.; Busnello, J.V.; Cantor, R.M.; Whelan, F.; Wittaker, P.; Deloukas, P.; Wong, M.-L.; Licinio, J. The brain-derived neurotrophic factor rs6265 (Val66Met) polymorphism and depression in Mexican-Americans. Neuroreport 2007, 18, 1291–1293. [CrossRef]

57. You, J.; Yuan, Y.; Zhang, Z.; Zhang, X.; Li, H.; Qian, Y. A preliminary association study between brain-derived neurotrophic factor (BDNF) haplotype and late-onset depression in mainland Chinese. J. Affect. Disord. 2010, 120, 165–169. [CrossRef]
58. Lee, K.W.; Ching, S.M.; Hoo, F.K.; Ramachandran, V.; Chong, S.C.; Tusimin, M.; Mohd Nordin, N. Prevalence and factors associated with depressive, anxiety and stress symptoms among women with gestational diabetes mellitus in tertiary care centres: A cross-sectional study. *BMC Pregnancy Childbirth* **2019**, *19*, 367. [CrossRef]

59. Malaysia, M.O.H. *Clinical Practice Guidelines: Management of Diabetes in Pregnancy*; Malaysia Health Technology Assessment Section: Putrajaya, Malaysia, 2017.

60. Society, M.E.M.; Malaysia, M.O.H. *Management of Type 2 Diabetes Mellitus*, 5th ed.; Ministry of Health: Kuala Lumpur, Malaysia, 2015.

61. Lovibond, S.; Lovibond, P. *Manual for the Depression Anxiety Stress Scales*; Sydney: Psychology Foundation of Australia: Sydney, Australia, 1995; ISBN 7334-1423-0.

62. Ramli, M.; Fadzil, M.A.; Zain, Z. Translation, validation and psychometric properties of Bahasa Malaysia version of the Depression Anxiety and Stress Scales (DASS). *Asean J. Psychiatry* **2009**, *8*, 82–89.

63. Ramli, M.; Salmiah, M. Validation and psychometric properties of Bahasa Malaysia version of the Depression Anxiety and Stress Scales (DASS) among diabetic patients. *Malays. J. Psychiatry* **2009**, *18*.

64. Bursac, Z.; Gauss, C.H.; Williams, D.K.; Hosmer, D.W. Purposeful selection of variables in logistic regression. *Am. J. Epidemiol.* **1999**, *129*, 125–137. [CrossRef] [PubMed]

65. Mickey, R.M.; Greenland, S. The impact of confounder selection criteria on effect estimation. *Am. J. Epidemiol.* **1989**, *129*, 125–137. [CrossRef] [PubMed]

66. Lomax, R.G. *An Introduction to Statistical Concepts for Education And Behavioral Sciences*; Lawrence Erlbaum Associates: New York, NY, USA, 2001.

67. Shih, P.B.; Yang, J.; Morisseau, C.; German, J.B.; Scott-Van Zeeland, A.; Armando, A.M.; Quehenberger, O.; Koeners, M.P.; Wesseling, S.; Sepulveda, R.L.; Morisseau, C.; Braam, B.; Hammock, B.D.; Joles, J.A. Soluble epoxide hydrolase in the generation and maintenance of high blood pressure in spontaneously hypertensive rats. *Am. J. Physiol. -Endocrinol. Metab.* **2011**, *300*, E691–E698. [CrossRef]

68. Newman, J.W.; Morisseau, C.; Hammock, B.D. Epoxide hydrolases: Their roles and interactions with lipid metabolism. *Prog. Lipid Res.* **2005**, *44*, 1–51. [CrossRef]

69. Koners, M.P.; Wesseling, S.; Ulu, A.; Sepulveda, R.L.; Morisseau, C.; Braam, B.; Hammock, B.D.; Joles, J.A. Soluble epoxide hydrolase in the mouse brain and its contribution to cerebral epoxyeicosatrienoic acid metabolism. *Neuroscience* **2009**, *163*, 646–661. [CrossRef]

70. Sura, P.; Sura, R.; EnayetAllaha, A.E.; Grant, D.F. Distribution and expression of soluble epoxide hydrolase in human brain. *J. Histochem. Cytochem.* **2008**, *56*, 551–559. [CrossRef]

71. Otowa, T.; Tani, H.; Sugaya, N.; Yoshida, E.; Inoue, K.; Yasuda, S.; Shimada, T.; Kawamura, Y.; Tochigi, M.; Minato, T. Replication of a genome-wide association study of panic disorder in a Japanese population. *J. Hum. Genet.* **2010**, *55*, 91. [CrossRef] [PubMed]

72. Newman, J.W.; Morisseau, C.; Hammock, B.D. Epoxide hydrolases: Their roles and interactions with lipid metabolism. *Prog. Lipid Res.* **2005**, *44*, 1–51. [CrossRef]

73. Sura, P.; Sura, R.; EnayetAllaha, A.E.; Grant, D.F. Distribution and expression of soluble epoxide hydrolase in human brain. *J. Histochem. Cytochem.* **2008**, *56*, 551–559. [CrossRef]

74. Lomax, R.G. *An Introduction to Statistical Concepts for Education And Behavioral Sciences*; Lawrence Erlbaum Associates: New York, NY, USA, 2001.

75. Bergen, A.W.; Magistretti, P.; Berrettini, W. Dysregulation of soluble epoxide hydrolase and lipidomic profiles in anorexia nervosa. *Mol. Psychiatry* **2016**, *21*, 537. [CrossRef]

76. Li, B.; Sura, R.; Mei, L.; Malinow, R. The neuregulin-1 receptor erbB4 controls glutamatergic synapse maturation and plasticity. *Neuron* **2007**, *54*, 583–597. [CrossRef] [PubMed]

77. Lomax, R.G. *An Introduction to Statistical Concepts for Education And Behavioral Sciences*; Lawrence Erlbaum Associates: New York, NY, USA, 2001.

78. Toxich, M.; Kohlhoff, J.; Khan, F.; Radom, N.; Silove, D.M. Separation anxiety, attachment and inter-personal representations: Disentangling the role of oxytocin in the perinatal period. *PLoS ONE* **2014**, *9*, e107745. [CrossRef] [PubMed]

79. Buizza, L.; Prandelli, C.; Bonini, S.; Delbarba, A.; Cenini, G.; Lanni, C.; Buoso, E.; Racchi, M.; Govoni, S.; Memo, M. Conformational altered p53 affects neuronal function: Relevance for the response to toxic insult and growth-associated protein 43 expression. *Cell Death Dis.* **2013**, *4*, e484. [CrossRef] [PubMed]

80. Tolstonog, G.V.; Deppert, W. Metabolic sensing by p53: Keeping the balance between life and death. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 13193–13194. [CrossRef] [PubMed]
80. Gimpl, G.; Fahrenholz, F. The oxytocin receptor system: Structure, function, and regulation. *Physiol. Rev.* 2001, 81, 629–683. [CrossRef]

81. Carter, C.S. Oxytocin pathways and the evolution of human behavior. *Annu. Rev. Psychol.* 2014, 65, 17–39. [CrossRef]

82. Feldman, R.; Monakhov, M.; Pratt, M.; Ebstein, R.P. Oxytocin pathway genes: Evolutionary ancient system impacting on human affiliation, sociality, and psychopathology. *Biol. Psychiatry* 2016, 79, 174–184. [CrossRef]

© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).