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ORIGINAL RESEARCH

HTR1A Gene Polymorphism in Type 2 Diabetes Mellitus Comorbid with Major Depressive Disorder in a Chinese Population

Dilixia Simayi[1,2], Yaqun Guan[1]

[1]State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia, Xinjiang Key Laboratory of Molecular Biology for Endemic Diseases, Department of Biochemistry and Molecular Biology, School of Basic Medical Sciences, Xinjiang Medical University, Urumqi, Xinjiang, People's Republic of China; [2]Department of Oncology, the First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, People's Republic of China

Correspondence: Yaqun Guan, State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia, Xinjiang Key Laboratory of Molecular Biology for Endemic Diseases, Department of Biochemistry and Molecular Biology, School of Basic Medical Sciences, Xinjiang Medical University, Urumqi, Xinjiang, People's Republic of China, Email yaqunguan557@xjmu.edu.cn

Background: Major depressive disorder is a frequent mental illness, which is common in patients with type 2 diabetes. Type 2 diabetes comorbid with depression has a worse prognosis. There are multiple risk factors for depression, and genetic studies have shown that gene polymorphism may play an important role in the pathogenesis of depression.

Methods: A total of 874 patients with type 2 diabetes were recruited for this study and divided into two groups: depressive group (DDM group, n = 234) and non-depressive group (NDDM group, n = 640). HTR1A gene polymorphisms (rs6295, rs878567, rs1800044) genotyping work was performed using a custom by design 48-Plex SNPscan^{TM} Kit.

Results: The rs6295, rs878567, and rs1800044 SNPs were not associated with type 2 diabetes comorbid with depression. Female sex, age, and FBG level increased the risk of depression in patients with type 2 diabetes.

Conclusion: HTR1A rs6295, rs878567, and rs1800044 SNPs polymorphism is not associated with type 2 diabetes comorbid with depression. Rather, female sex, age, and FBG level are risk factors for depression among patients with type 2 diabetes. Larger studies are needed to further confirm our findings.

Keywords: type 2 diabetes mellitus, major depressive disorder, HTR1A, polymorphism

Introduction

Diabetes is a chronic metabolic disease characterized by elevated plasma glucose levels due to insulin deficiency and/or insulin function disorders.[1] The worldwide prevalence of diabetes among the adult population in 2017 was 8.8%, meaning that approximately 425 million patients had diabetes; there were 4 million deaths related to diabetes, and the medical expenses due to diabetes were estimated to be 727 billion US dollars.[2] According to the International Diabetes Federation (IDF), by 2045, the global prevalence of diabetes will increase to 9.9%, the number of patients with diabetes will reach 628.6 million, and the medical expenditures will rise to 776 billion US dollars.[3] Diabetes has become a major threat to human health in the 21st century. In 1980, the prevalence of diabetes in China was 0.67%,[4] while in 2013 the overall standardized prevalence of diabetes in Chinese adults reached 10.9% (95% CI, 10.4%–11.5%).[5] T2DM accounts for about 95% of cases of diabetes.[6] Given that most T2DM patients do not have obvious symptoms, they often receive a diagnosis of T2DM only when they seek medical attention due to complications.

Multiple studies have suggested that the prevalence of major depressive disorder (MDD) is higher in patients with diabetes than in those without diabetes. The prevalence of depression in T1DM and T2DM is three times and two times higher than that in the normal population, respectively. Epidemiological studies have shown that approximately 26%–30% T2DM patients have different degrees of depressive symptoms or depression.[7,8] There is evidence that depression

Received: 25 February 2022
Accepted: 11 May 2022
Published: 25 May 2022

may accelerate the progression of T2DM and increase the risk of hyperglycemia, insulin resistance, and microvascular and macrovascular complications. When patients receive the diagnosis of T2DM, the risk of depression increases. Hence, there seems to be a bidirectional relationship between MDD and T2DM. Patients with newly diagnosed T2DM are more likely to have had depression in the past 3 years.[9] Prospective studies have shown that patients with depression have an increased risk (65%) of T2DM.[10–12] A logistic regression analysis by Eaton showed that the relative risk of onset of diabetes in MDD patients was 2.23 (95% CI, 0.90–5.55),[13] and Campayo found that MDD patients had an increased risk (65%) of T2DM than controls.[10] A meta-analysis has indicated a 24% increased risk of having MDD among T2DM patients.[14]

The 5-HT1A receptor (5-HT_{1A}) is the most important inhibitory receptor in the 5-Hydroxytryptamine (5-HT) system and has been extensively studied in the context of depression.[17] In vivo animal experiments and postmortem studies have shown that 5-HT_{1A} autoreceptor expression levels are elevated and heteroreceptor expression levels are reduced in depression.[18] Moreover, 5-HT system was related to hampered insulin signaling controls, glycogen synthase kinase 3 and hypothalamic–pituitary–adrenal (HPA) activity during diabetic progression.[19] The *HTR1A* gene, which encodes 5-HT_{1A}, is located on human chromosome 5q12.3. Researchers claimed that impaired HTR1A function can increase the risk of MDD[20] and inhibit insulin secretion.[21] Furthermore, it is reported that HTR1A polymorphisms were associated with MDD[22] and diabetes.[23] However, there was no attempt to investigate the *HTR1A* genetic overlap between T2DM and MDD.

Therefore, the present study examined the involvement of HTR1A gene polymorphisms (rs6295, rs878567, rs1800044) in T2DM patients with and without MDD. And all the polymorphisms were functional polymorphisms (rs1800044) and tagSNP from the HapMap (rs6295 and rs878567).

Materials and Methods

Study Subjects

A total of 874 northwest Han Chinese patients with T2DM were recruited from the 5th Affiliated Hospital of Xinjiang Medical University (Urumqi, Xinjiang, China) between January 2016 and January 2017. T2DM was diagnosed in accordance with the 1999 WHO criteria. All of the T2DM patients were divided into two groups: depressive group (DDM group, n = 234) and non-depressive group (NDDM group, n = 640).

This study was a non-interventional study, and all participants only need to participate in a questionnaire survey, all blood samples used in this study for SNP scan were collected from the leftover blood routine examination samples, which was meant to dispose as medical waste after the blood routine examination is finished, we did not take any blood samples or any kinds of samples from the patients directly, in this study there are no any kinds of potential risk or harm to the participants, and we keep participants information confidential. The Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University reviewed this study method before the study started, and all procedures carried out were in line with the ethical standards and the Declaration of Helsinki and granted this study for ethical approval. All the subjects were taken a one-on-one interview and provided a written informed consent to explain the purpose and method of this study, after the participants fully understood the purpose of this study and agreed then we recruit them into this study.

Depression Assessment

Zung self-rating depression scale (SDS) was used for screening of depression in patients diagnosed with T2DM in this study. The SDS scale has been widely used for depression screening for over half a century. It shows good reliability and accuracy, and it is easy to use. The scale contains 20 items, where each item represents a symptom; patients select one of the four options to indicate the symptoms based on their actual feelings in the past week. The score ranges from 25 to 100. The score indicates the severity of the depressive symptoms as follows: <53, no depressive symptoms; 53–62, mild depression; 63–72, moderate depression; >72, severe depression.

In this study, a one-on-one interview was conducted by a senior psychiatrist with each of the subjects. The subjects first understood the meaning of completing the scale and gave their consent, and then completed the scale according to their actual feeling in the past week independently. None of the subjects took any antidepressant medication.

DNA Extraction

Blood samples were collected from the leftover blood routine examination samples, which were meant to dispose of as medical waste after the blood routine examination was finished and were transferred to tubes lined with ethylenediamine tetra-acetic acid (EDTA). Genomic DNA was isolated from whole blood using the QIAamp DNA Blood Mini Kit (Qiagen, Berlin, Germany).

HTR1A Polymorphism Analyses

The genotyping work of genotypes of *HTR1A* gene polymorphism rs6295, rs878567, and rs1800044 SNPs was performed using a custom by design 48-Plex SNPscan^{TM} Kit (Genesky Biotechnologies Inc., Shanghai, China). This kit was developed according to patented SNP genotyping technology by Genesky Biotechnologies Inc., which was based on double ligation and multiplex fluorescence PCR. For quality control, repeated analyses were done for 4% of randomly selected samples with high DNA quality. Furthermore, three samples with different genotypes for each SNP were randomly selected to confirm the genotyping results by direct sequencing.

Statistical Analyses

Differences in the distributions of demographic characteristics, selected variables, and genotypes of the *HTR1A* rs6295, rs878567, and rs1800044 SNPs variants between the cases and controls were evaluated using the χ^2 test. The associations of *HTR1A* rs6295, rs878567, and rs1800044 SNPs genotypes with the risk of depression were estimated by computing the odds ratios (ORs) and their 95% confidence intervals (CIs) using logistic regression analyses. We calculated both the crude ORs and the adjusted ORs (adjusted for age, sex, smoking, and drinking status). The Hardy–Weinberg equilibrium (HWE) was tested by a goodness-of-fit χ^2 test to compare the observed genotype frequencies to the expected ones among the control subjects. All statistical analyses were performed using Microsoft Excel and SPSS software (version 22.0, IBM Inc, USA).

Results

The Demographic Characteristics of the Subjects

Of the 874 T2DM patients, 234 had depression (DDM group, 106 men and 128 women), while 640 did not (NDDM group), meaning that the prevalence of depression in this sample was 27.12%. In DDM group, mild depression was found in 48 (20.51%) patients, moderate depression in 108 (46.15%) patients, and severe depression in 78 (33.33%) patients. In DDM group, the proportion of women was higher than that of men (128, 54.7% vs 106, 45.3%; $p<0.05$). The mean age of DDM group was higher than that of NDDM group (62 ± 11.62 vs 58 ± 12.34, $p<0.05$), but there was no significant difference in age between men and women in DDM group (Table 1).

According to the marital status, we divided the subjects into four groups: single, married, divorced, and widowed. The proportion of depression was higher in the divorced group than in the married group (8/13, 61.5% vs 197/806, 24.4%; $\chi^2=9.38$, $p=0.002$). There were no significant differences between the other groups.

Of the subjects, 150 had received primary school education, 515 had received middle school education, while 170 individuals had received college education. The rate of T2DM comorbid with depression was higher in the primary school group than in the college group (54/150, 36% vs 39/209, 18.7%; $\chi^2=13.68$, $p=0.0002$), but there were no significant differences between the other groups.

The Clinical Characteristics of T2DM Patients Comorbid with Depression

The DDM group had a higher HbA1c% (7.79 ± 1.02 vs 7.35 ± 2.57; $p=0.01$) and FBG level than the NDDM group (9.5 ± 0.2 vs 7.9 ± 0.2; $p = 3.075\times10^{-9}$). The number of patients with HbA1c ≥7 in the DDM group was also higher than that in the NDDM group (123/234, 52.6% vs 265/640, 41.4%; $\chi^2=16.45$, $p = 0.002$) (Table 2).

The DDM group had a longer duration of diabetes than the NDDM group (9.30 ± 7.15 vs 7.86 ± 6.73; $p = 0.006$).

There was no significant difference in the presence of diabetic complications between the DDM and NDDM groups ($\chi^2=0.08$, $p = 0.803$). However, the DDM group showed a higher number of diabetic complications than the NDDM group (2.45 ±

Table 1 The Demographic Characteristics of T2DM Patients

Variables	Group	NDDM	DDM	χ^2	*p*
ALL		640 (73.2%)	234 (26.8%)		
Gender	Male	430 (80.2%)	106 (19.8%)		**4.02×10^{-9}**
	Female	210 (62.1%)	128 (37.9%)		
Age		58±12.34	62±11.62		**0.017**
	Male	56	63		0.09
	Female	62	60		
Education level	Primary school	96 (64%)	54 (36%)	13.63	**0.001**
	Middle school	374 (72.6%)	141 (27.4%)		
	College	170 (81.3%)	39 (18.7%)		
Marital status	Single	16 (59.3%)	11 (40.7%)	18.56	**0.0003**
	Married	609 (75.6%)	197 (24.4%)		
	Divorced	5 (38.5%)	8 (61.5%)		
	Widowed	15 (53.6%)	13 (46.4%)		

Note: Bold figures indicates p-value less than 0.05.

Table 2 The Clinical Characteristics of DDM and NDDM Groups

Variables	NDDM	DDM	χ2	p
All	640	234		
Diabetes Duration (year)	7.86 ± 6.73	9.30 ± 7.15		**0.006**
HbA1c (%)	7.35 ± 2.57	7.79 ± 1.02		**0.01**
HbA1c <7%	378 (59.1%)	111 (47.4%)	9.40	**0.002**
HbA1c ≥7%	262 (40.9%)	123 (52.6%)		
FBG (mmol/L)	7.9 ± 0.2	9.5 ± 0.2		**3.075×10-9**
BMI (kg/m2)	26.09 ± 3.47	25.58 ± 3.73		0.6
BMI (kg/m2)				
<24	176 (27.5%)	72 (30.8%)	0.901	0.342
≥24	464 (72.5%)	162 (69.2%)		
Hypertension	374/640 (58.4%)	158/234 (67.5%)	5.936	**0.015**
Diabetic complications	449/640 (70.2%)	167/234 (71.4%)	0.121	0.728
Neuropathy	433/640 (67.7%)	157/234 (67.1%)	0.025	0.875
Retinopathy	89/640 (13.9%)	195/234 (83.3%)	376.526	**7.102×10-84**
Nephropathy	82/640 (12.8%)	49/234 (20.9%)	8.883	**0.003**
Diabetic foot	9/640 (1.4%)	5/234 (1.6%)	0.580	0.446
Number of complications	2.23±1.38	2.45±1.35		**0.042**

Note: Bold figures indicates p-value less than 0.05.

1.35 vs 2.23 ± 1.38; p=0.042). By analyzing various diabetic complications, we found that the proportions of patients with retinopathy (195/234, 83.3% vs 89/640, 13.9%) and diabetic nephropathy (49/234, 20.9% vs 82/640, 12.8%) in the DDM group were higher than those in the NDDM group (χ^2= 376.526, p=7.102×10^{-84}; χ^2= 8.883, p = 0.003; respectively). There were no significant differences in neuropathy and diabetic foot between the groups (Table 2).

There was no significant difference in BMI between the DDM group and the NDDM group, and there was no significant difference in the proportion of patients with BMI higher than 24 between the two groups (Table 2).

The DDM group showed a higher rate of comorbid hypertension than the NDDM group (158/234, 67.5% vs 374/640, 58.4%; χ^2=5.936, p=0.015).

Association of HTR1A Polymorphism with T2DM and Depression

The primary information of the three *HTR1A* SNPs is shown in Table 3. In all 874 samples, the genotyping success rate was 100%. Minor allele frequency (MAF) of all the three SNPs in this study was similar to MAF for CHB in 1000 Genomes database. The genotype distribution of the three *HTR 1A* SNPs followed the Hardy–Weinberg equilibrium.

The genotype distribution of *HTR1A* rs6295, rs878567, and rs1800044 in the two groups is shown in Table 4. In the single locus analyses, the genotype frequencies of *HTR1A* rs878567 were GG (0.607), GA (0.350), and AA (0.043) in the NDDM group; and GG (0.579), GA (0.346), and AA (0.075) in the DDM group. The allele frequencies were G (0.782) and A (0.218) in the NDDM group, and G (0.752) and A (0.248) in the DDM group. The intergroup differences in genotype frequencies and allele frequencies were not statistically significant (p = 0.150, p = 0.177). In rs1800044, there were only two genotypes in this locus: CC and CA. The genotype frequencies of *HTR1A* rs1800044 in the NDDM group were CC (0.988), CA (0.003), and CC (1) in the DDM group; the allele frequencies were C (0.998) and A (0.002) in the NDDM group, and C (1) in the DDM group. The differences in genotype frequencies and allele frequencies between the two groups were not statistically significant (p = 0.384, p = 0.384, respectively). The *HTR1A* rs6295 has three genotypes: GG, GC, and CC. The genotype frequencies were GG (0.539), GC (0.396), and CC (0.065) in the NDDM group, and GG (0.513), GC (0.375), and AA (0.113) in the DDM group. The allele frequencies were G (0.737) and C (0.263) in the NDDM group, and G (0.7) and C (0.3) in the DDM group. The differences in genotype frequencies and allele frequencies of rs6295 between the two groups were not statistically significant (p=0.062, p=0.117, respectively).

Risk Factors for Depression in T2DM

In order to understand the risk factors for depression in patients with T2DM, we performed a logistic regression analysis of the clinical features in all of the subjects. Our results showed that female sex (OR: 2.332, 95% CI: 1.69–3.22, p = 2.42×10^{-7}), age (OR: 1.02, 95% CI: 1.00–1.03, p = 0.037), and FBG level (OR: 1.06, 95% CI: 1.00–1.11, p=0.040) were significant predictors of depression in T2DM patients. The diabetes duration, presence of hypertension, presence and

Table 3 The Primary Information of HTR1A SNPs

SNP	Chr	Location	Alleles	MAF for CHB	MAF in Our Study	p value for HWE
rs878567	5	3'-UTR	A>C, G	0.173	0.218	0.793
rs1800044	5	nonsynon_exon1	C>A	0.000	0.001	1
rs6295	5	5'-flanking	C>G	0.216	0.261	0.678

Table 4 Allele and Genotype Association Analysis of the Three SNPs in HTR1A

SNP	Group	Allele		p	OR [95% CI]	Genotype			p
rs878567		G	A			G/G	G/A	A/A	
	NDDM	0.782	0.218	0.1771	0.844 (0.66–1.08)	0.607	0.350	0.043	0.150
	DDM	0.752	0.248			0.579	0.346	0.075	
rs1800044		C	A			C/C	C/A	A/A	
	NDDM	0.998	0.002	0.384	NA (NA–NA)	0.988	0.003	0	0.384
	DDM	1	0			1	0	0	
rs6295		G	C			G/G	G/C	C/C	
	NDDM	0.737	0.263	0.1174	0.831 (0.66–1.05)	0.539	0.396	0.065	0.062
	DDM	0.7	0.3			0.513	0.375	0.113	

Table 5 Logistic Regression Analysis of the Associations Between Clinical Factors and Risk of DDM

Variables	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Female sex	2.46 (1.81–3.42)	**9.6×10^{-9}**	2.332 (1.69–3.22)	**2.42×10^{-7}**
Age	1.03 (1.01–1.04)	**0.00006**	1.02 (1.00–1.03)	**0.037**
Duration of the disease	1.03 (1.00–1.05)	**0.006**	1.01 (0.98–1.04)	0.470
Hypertension	1.45 (1.06–2.00)	**0.021**	0.96 (0.60–1.53)	0.864
Presence of complications	1.06 (0.76–1.47)	**0.744**	0.566 (0.27–1.19)	0.132
Number of complications	1.12 (1.00–1.25)	**0.042**	1.28 (0.97–1.71)	0.087
FBG level	1.02 (0.98–1.06)	**0.256**	1.06 (1.00–1.11)	**0.040**
HbA1c level	1.00 (0.94–1.07)	**0.896**	0.96 (0.88–1.04)	0.312

Note: Bold figures indicates p-value less than 0.05.

number of diabetic complications, and level of HbA1c were not associated with the risk of depression in T2DM patients (Table 5).

Discussion

Given that the relationship between T2DM and MDD is bidirectional, this eventually leads to a vicious cycle.[15] It has been shown that the use of antidepressant medication (ADM) could improve the glycemic control without affecting the body weight.[16] Therefore, it is important to pay attention to the influence of MDD on T2DM.

Several factors have been attributed to the occurrence of DDM in patients with T2DM, of which genetic and environmental are the essential factors. This study was the first to investigate a stratification effect of HTR1A variation on the correlation between T2DM and DDM in a human study.

First, we investigated the demographic and clinical characteristics of the DDM group and the NDDM group. There is evidence indicating that women are more likely to have depression than men.[24] Indeed, our study showed that the DDM group had a higher female-to-male ratio (37.9%/19.8%). The patients in the DDM group were older than those in the NDDM group (62 ± 11.62 years vs 58 ± 12.34 years), which is consistent with previous studies.[25] Several lines of evidence have shown that there is a bidirectional association between depression and T2DM; T2DM patients comorbid with depression usually have poor adherence, and depression also increases the risk of hyperglycemia, insulin resistance, and microvascular and macrovascular complications, eventually leading to a poor outcome.[26] By comparing the various clinical characteristics between the DDM and the NDDM groups, we found that the DDM group had a longer diabetes duration (9.30 ± 7.15 vs 7.86 ± 6.73), higher FBG level (9.5 ± 0.2 vs 7.9 ± 0.2), and higher HbA1c level (7.79 ± 1.02) than the NDDM group (7.35 ± 2.57). Diabetic complications, including microvascular and macrovascular complications, are important factors affecting the patient outcomes. In this study, we showed that the proportion of patients with retinopathy (83.3% vs 13.9%) and nephropathy (20.9% vs 12.8%) was higher in the DDM group; moreover, the number of diabetic complications (2.45 ± 1.35 vs 2.23 ± 1.38) was also significantly higher in the DDM than in the NDDM group. These results indicate that patients with T2DM comorbid with depression have a higher risk of diabetic complications. When patients have diabetic complications, they often have a poor glycemic control and poor adherence, which increases the disease burden and requires more treatment, including insulin. All of these factors may cause a greater stress in these patients, leading to depressive symptoms or depression. Moreover, the depressive symptoms or depression may further accelerate the progression of T2DM, leading to a vicious cycle.

Several meta-analyses have confirmed that rs6295 is associated with depression, bipolar disorder, schizophrenia, substance abuse, and the efficacy of antidepressants.[27–29] In vitro experiments have revealed that SNPs in the rs6295 locus affect the transcription of the HTR1A gene by altering its binding to transcription factors, thereby reducing the release of 5-HT and increasing the risk of depression.[30] However, we noted that the effect of rs6295 on T2DM comorbid with DDM risk was pronounced at genotype frequencies ($p = 0.062$), although there was only a borderline significant difference. Therefore, further prospective larger sample size and well-designed studies to solve this question are needed.

In addition, our logistic regression analysis showed that female sex, older age, and high FBG level were the risk factors for depression in T2DM patients. These results are consistent with a previous study that showed that women had

a higher risk of depression than men.[24] In our study, women with T2DM patients had a higher risk of depression than men (OR: 2.332, 95% CI: 1.69–3.22), and older patients had a higher risk than younger patients (OR: 1.02, 95% CI: 1.00–1.03). A recent study showed that elevated FBG was an independent predictor of depressive disorder in young patients with obesity.[31] And we further found that higher FBG level was associated with a higher risk of depression in T2DM patients (OR: 1.06, 95% CI: 1.00–1.11).

However, there were several limitations in our study. First, peripheral blood gene expression may not associate well with levels in the brain. Second, we only collected the Northwest Chinese Han population, and the negative associations may be due to a stratification effect or to chance. Future research should aim at other populations and ethnicities with large sample sizes, as well as the brain samples.

Conclusion

To sum up, HTR1A rs6295, rs878567, and rs1800044 polymorphisms are not associated with T2DM comorbid with DDM. Rather, female sex, age, and FBG level are risk factors for depression among patients with T2DM. The effect of HTR1A polymorphisms on T2DM comorbid with DDM needs to be confirmed by prospective studies with larger sample sizes.

Disclosure

The authors report no conflicts of interest in this work.

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