Original Article

Risk of Major Depressive Disorder in Adult Diabetics

Association of rs6295 with Risk of Development of Major Depressive Disorder in Adult Diabetic Population in Context of Family History of Major Depressive Disorder

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ABSTRACT

Objective: To determine whether the presence of family history of Major Depressive Disorder (MDD) is associated with the risk of development of the disease in adult diabetic population on the basis of genetic association with single nucleotide polymorphism (SNP) rs6295.

Study Design: Case control study

Place and Duration of Study: This study was conducted at the Department of Biochemistry, Islamic International Medical College Rawalpindi in collaboration with Railway General Hospital Rawalpindi, Armed Forces Institute of Pathology (AFIP) Rawalpindi and Institute of Biomedical and Genetic Engineering (IB&GE) Islamabad. Duration of study was 1 year from September 2020 to September 2021.

Materials and Methods: A total of 400 subjects were included in the study, out of which 200 were cases and 200 were age, gender and ethnicity matched healthy controls. Out of 200 cases, 100 cases had diabetes mellitus (DM) only and 100 cases had DM with MDD. Both males and females were included in the study having ages 25 years and above. Cases of both type I and type II DM were included in the study. Blood samples were collected and DNA was extracted by Chelax method. Real-time PCR was carried out to determine respective allelic frequencies of rs6295 genotype using TaqMan SNP genotyping assays and master mix.

Results: According to our results no significant association was found between rs6295 genotype and risk of development of MDD in Pakistani diabetic population in context of family history of MDD.

Conclusion: There is no significant association of SNP rs6295 of 5-Hydroxytryptamine 1A receptor gene with MDD in Pakistani diabetics having family history of MDD.

Key Words: Diabetes mellitus, major depressive disorder, 5-hydroxytryptamine 1A receptor gene, single nucleotide polymorphism, polymerase chain reaction.

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INTRODUCTION

Diabetes Mellitus (DM) and Major Depressive Disorder (MDD) are two closely associated diseases which are increasing throughout the world resulting in an increase in complications associated with diabetes. Especially this has increased the expenditure on treatment of these patients up to five-fold. MDD is because of many factors with genetic predisposition being of great importance [(1)]. The exact mechanism of development of MDD is still not completely understood. However, many theories have been hypothesized in this regard. When considering MDD in context of DM there is activation of the Hypothalamic Pituitary Adrenal (HPA) axis and the sympathetic nervous system because of chronic stress [(2,3)]. This results in increase secretion of cortisol from adrenal cortex and epinephrine and norepinephrine from adrenal medulla[(4)]. DM type 2 and metabolic syndrome ultimately result because of insulin resistance and visceral obesity resulting from chronic hypercholesterolemia and activation of the sympathetic nervous system for long period of time[(5,6)]. Hippocampus is a part of brain which is involved in both type 2 DM and depression and excessive cortisol secretion results in disturbance of the neurogenesis of

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this part of the brain [7,8]. Here also there is dysfunction of the immune system of the body resulting in an increase in the synthesis of inflammatory cytokines[9]. Ultimately there is development of type 2 DM because of the increase amounts of inflammatory cytokines which interfere with the normal functions of the β-cells of the pancreas causing insulin resistance[10].

Serotonin is a neurotransmitter involved in the pathogenesis of depression. Serotonin receptors have 14 subtypes. A single nucleotide polymorphism C(-1019)G rs6295 exists in the promoter region of the gene which encodes for one of the serotonin receptors i.e. 5-Hydroxotryptamine 1A (5-HT1A) receptor[11]. The location of this polymorphism is on chromosome number 5[12]. According to initial researches on association of rs6295 with MDD, Taro Kishi et al. found that this polymorphism is associated with MDD in Asian population but not associated with MDD in Caucasians [13].

According to Haixia Zheng et al. rs6295 allele carries a high susceptibility for MDD[14].

There is a gap in literature in this context since there is no data available about association of this specific SNP with MDD in any group of Pakistani Population[15–17].

MATERIALS AND METHODS

The study was done at the Department of Biochemistry, Islamic International Medical College Rawalpindi in collaboration with Railway General Hospital Rawalpindi, Armed Forces Institute of Pathology (AFIP), Rawalpindi and Institute of Biomedical and Genetic Engineering (IB&GE), Islamabad. It was a case control study. The research protocol was approved from the Ethics Review Committee of Islamic International Medical College, Rawalpindi. Duration of study was 1 year from September 2020 to September 2021.

In our current we have taken 200 cases (100 males and 100 females) and 200 controls (100 males and 100 females). The cases were further divided into two groups. Group 1 consisted of cases of both type 1 and type 2 DM and group 2 consisted of cases of both type 1 and type 2 DM with MDD. All the subjects were adults having ages 25 years and above. Cases of all other chronic illness and other metabolic disorders were excluded. Blood samples were collected after taking informed consent from all the subjects, following the standard techniques and then stored in EDTA bottles at 6 to 8 °C. The sampling technique was nonprobability convenient sampling. DNA was then extracted from whole blood using Chelax method and was stored at -80°C until PCR amplification. PCR was performed using original TaqMan assay (Catalog # 4351379) and master mix (Catalog # 4371353) using real time PCR following the instructions of the manufacturer.

Statistical analysis was carried out using commercial statistical software package, SPSS 26 software for Microsoft Windows. Possible association of SNP rs6295 with MDD in Pakistani diabetics was determined by computing odds ratio (OR) and 95% confidence intervals (CIs). Frequencies and percentages were determined for descriptive statistics. *p*-value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

There were 200 cases and 200 healthy age, sex and ethnicity matched controls. Out of 200 cases, 100 cases had DM and 100 cases had DM with MDD. In the group having positive family history of MDD, among 100 cases of DM 4 (1.0%) none had CC, CG or GG genotype. Among 100 cases of DM with MDD 7 (1.8%) had CC genotype, 5 (2.2%) had CG genotype and 0(1.3%) had GG genotype. In Controls, out of 200 subjects 2(10.0%) subjects had CC genotype, 11(16.9%) subjects had CG genotype and 3 (7.7%) subjects had GG Genotype.

Table No.1: Association of 5-HT1A receptor gene SNP rs6295 Genotype with family history of MDD in cases and controls

Parameter	N=400			OR (95% CI) P
	Cases n=200		Controls n=200	
Family History of MDD	DM n=100	DM with MDD n=100		(*P ≤ 0.05)
Present				
CC	0(0.00%)	7(1.75%)	2(0.50%)	Ref I -[a] -[a]
CG	0(0.00%)	5(1.25%)	11(2.75%)	Ref I -[b] -[b]
GG	0(0.00%)	0(0.00%)	3(0.75%)	Ref I 0.13 (0.02-0.86) -[c] -[c]
Absent				
CC	28(7.00%)	30(7.50%)	61(15.25%)	Ref I 1.73 (0.89-3.38) 0.106[a]
CG	55(13.75%)	34(8.50%)	92(23.00%)	0.75 (0.33-1.72) 0.478[a]
GG	17(4.25%)	14(3.50%)	31(7.75%)	Ref I 1.30 (0.74-2.28) 0.354[b] 0.92 (0.46-1.81) 0.806[b] Ref I 0.75 (0.42-1.35) 0.340[c] 1.22 (0.58-2.57) 0.597[c]

[a] – Association of genotype of group DM and group DM with MDD
[b] – Association of genotype of group DM and Controls
[c] – Association of genotype of group DM with MDD and Controls

In group having no family history of MDD, among 100 cases of DM 28 (6.0%) had CC genotype, 55 (10.7%) had CG genotype and 17 (4.3%) had GG genotype. Among 100 cases of DM with MDD 30 (7.5%) had CC genotype, 34 (10.0%) had CG genotype and 14 (2.2%)

had GG genotype. In Controls, out of 200 subjects 61 (5.8%) subjects had CC genotype, 92 (8.8%) subjects had CG genotype and 31 (0.8%) subjects had GG Genotype.

DISCUSSION

DM and depression have common pathological pathways[18]. Presence of DM ultimately results in MDD and presence of depression ultimately causes DM[18]. The presence of one causes another[19]. The presence of depression with DM worsens the compliance and patient's glycemic control resulting in serious complications of DM including cataract, retinopathy, nephropathy and neuropathy etc.[20,21]. Therefore, in order to keep DM under check it is very necessary to evaluate all the suspected patients for MDD. Timely referral to psychiatrist and early start of treatment of MDD can work miracles when it comes to treatment of diabetes, as it is true for the treatment of many other chronic diseases.

To the best of our knowledge this is the first study to be conducted in Pakistan using this SNP rs6295. This SNP is known for causing MDD[22]. As we already know that genetic studies are the most advanced field of research in medical and health sciences and give details of a disease at the molecular level so findings of such studies are very reliable if genotyping is performed on modern techniques. For this purpose, work has been done using original TaqMan genotyping assay and original TaqMan genotyping master mix using real-time PCR technique.

According to literature so far very limited work has been done in Pakistan when it comes to genetic studies regarding depression. Here we have taken both type 1 and type 2 diabetic patients who were all adults having ages 25 years and above. We have tried to find the genetic association of this SNP with the family history of major depressive disorder. No significant association of rs6295 genotype and risk of development of MDD has been determined with respect to family history of MDD in our diabetic population. In the context of genetic diseases not finding a significant association is also important. This means that the population under consideration is less likely to develop the disease which in this case is MDD. However according to M. Dijk et al, who conducted a study on the population of United States there is an increased risk of development of MDD in children whose parents are affected with the disease[23].

CONCLUSION

No significant association was found between rs6295 genotype and risk of development of MDD in context of family history of MDD.

Recommendations: In our current study we have taken into consideration SNP rs6295 and we have tried to determine its genetic association with risk of development of MDD in context of family history of MDD. In future, other similar SNPs can be taken into consideration and combination of two or more SNPs can be taken into consideration for more elaborated results.

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Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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