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Dopamine Transporter Gene (SLC6A3) 3'UTR VNTR Genotype as a Marker for Subtypes of Bipolar Affective Disorder I in an Egyptian Sample

Nisrin M El-Saadouni[1] , Karim Abdel Aziz[2]*, Wafaa El-Bahaey[1], Zeinab Abu Elfotouh[1], Farha El-Shenawy[1], Ahmed Alboraie[1], Haytham Shabayek[2], Dina Aly El-Gabry[3], Hamdy F Moselhy[2]

1. Psychiatry Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.
2. Department of Psychiatry, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates.
3. Institute of Psychiatry, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

ABSTRACT

We aimed to investigate the distribution of alleles and genotypes of the 3'UTR VNTR polymorphism of *SLC6A3* between a sample of patients with bipolar I disorder and healthy controls. We used a cross-sectional, case-control study which was carried out on 100 subjects with bipolar disorder and 50 healthy controls. The bipolar group was divided into three subgroups: 40 with bipolar disorder without psychotic features, 31 with bipolar disorder with mood-congruent psychotic features and 29 with bipolar disorder with mood-incongruent psychotic features. All participants provided a blood specimen for analysis and genomic DNA extraction. The genotypic distribution of DAT 3´UTR (*SLC6A3*) for both patients and controls was within the Hardy–Weinberg equilibrium. For the genotypes of DAT 3 intron VNTR, the gene frequency estimates for the whole sample indicated a significant departure from the Hardy–Weinberg equilibrium. Genotype frequencies showed a significant difference between the bipolar I and the control groups. There was a marginally significant higher frequency of *7/8* 3 intron VNTR genotypes in the bipolar I disorder with mood-incongruent psychotic features. Among patients with a positive family history of psychosis in the three bipolar subtypes, the frequency of 3 intron DAT VNTR showed a statistically significant difference in the mood-incongruent group and 7/8 genotype was statistically significant. This study suggests that the 7/8 genotype may predispose a subtype of bipolar disorder characterized by mood-incongruent psychotic features in cases with a positive family history of psychotic disorder.

Keywords: Bipolar, Genetics, DAT, SLC6A3, VNTR.

*Corresponding Author Email: kabdelaziz@uaeu.ac.ae
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INTRODUCTION

Dopamine (DA) is the predominant catecholamine neurotransmitter involved in cognition and mood. In addition, the dopaminergic system has been implicated in the etiology of bipolar disorder (Missale et al., 1998)[1]. The function of dopamine depends on multiple elements, such as the dopamine transporter (DAT), dopamine receptors, the enzymes metabolizing dopamine, such as monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (Zhao et al., 2015)[2]. Among them, several specific genes have been associated with bipolar disorder in independent samples: dopamine transporter (SLC6A3), brain-derived neurotrophic factor (BDNF), the N methyl- D-aspartate glutamate receptor subunit 2B (GRIN2B), the serotonin transporter (SLC6A4), tryptophan hydroxylase–2 (TPH2) and COMT (Craddock and Forty, 2006)[3]. Multiple studies and meta-analyses of association studies have supported a role for SLC6A4, BDNF (Kremeyer et al., 2006)[4], DAOA (d-amino acid oxidase activator) (Detera-Wadleigh and McMahon, 2006)[5] and the gene encoding 5, 10-methylenetetrahydrofolate reductase (MTHFR) (Gilbody et al., 2007)[6]. However, to date, no gene has been established as a bipolar disorder susceptibility gene. The dopamine transporter (DAT) plays an important role in the modulating dopaminergic neurotransmission via high-affinity reuptake of dopamine into presynaptic terminals. DAT is a target for stimulant medications used to treat ADHD symptoms, and stimulant drugs of abuse, such as cocaine, inhibit DAT dopamine reuptake and increase dopamine activity in the synapse. Genetic variants in the DAT gene (also known as SLC6A3) have been implicated in ADHD (Ouellet-Morin et al., 2008; Feng et al., 2005)[7,8], schizophrenia (Saiz et al., 2010)[9], bipolar disorder (Mick et al., 2008)[10], posttraumatic stress disorder (Segman et al., 2002)[11] and cocaine abuse (Guindalini et al., 2006)[12]. Most studies considered only one variant: a functional variable number tandem repeat polymorphism (VNTR) in the 3´UTR. However, there were inconsistent results (Talkowski et al., 2007)[13]. Vandenbergh et al. (1992)[14] investigated 3'UTR VNTR polymorphism in patients (n = 336) screened for bipolar affective disorder according to DSM-IV criteria and in control subjects. They did not observe any statistically significant difference between patients with bipolar affective disorder and the healthy controls. A weak association with the A9 allele was present in the early-onset subgroup (P = 0.047). Although the 3´UTR variant, located in the 3'-untranslated region of the *SLC6A3* gene, does not change the structure of the DAT1 protein, it may affect the level of expression of the DAT1 gene (Michelhaugh et al., 2001)[15], resulting in variable dopamine transporter phenotypes. However, the issue remains controversial. In the present study, we investigated two

VNTRs, the frequently studied 3´UTR variant (Vandenbergh et al., 1992)[14] and a novel VNTR in intron 3 (Miyajima et al., 2006)[16] of the *SLC6A3* gene, in a sample of Egyptian patients with bipolar I disorder and healthy controls.

MATERIALS AND METHOD

Participants

Inclusion criteria for this study were: aged 18–65 years; met DSM-IV TR (American Psychiatric Association, 2000)[31], diagnostic criteria for one of the bipolar disorders I (bipolar disorder depressive episode, bipolar disorder manic episode, or bipolar disorder mixed episode); a mean baseline Young Mania Rating Scale (Young et al., 1978)[21] score of ≥ 20. Exclusion criteria were: other or co-morbid psychiatric disorder; evidence of an organic brain disorder; evidence of a substance misuse disorder; subjects with learning difficulties; subjects with bipolar affective disorder in remission; and subjects who refused to give written consent. A total of 100 bipolar disorder I subjects were recruited for this study (55 males, 45 females), from the outpatient clinic at Mansoura University Hospital, Mansoura, Egypt. The participants were divided into three groups. Group 1: patients diagnosed as bipolar disorder without psychotic features (40 subjects); Group 2: patients diagnosed as bipolar disorder with mood-congruent psychotic features (31 subjects); and Group 3: patients diagnosed as bipolar disorder with mood-incongruent psychotic features (29 subjects). The control group consisted of 50 subjects who were recruited from pre-employment testing programs. A psychological testing profile was performed to confirm they did not have any psychiatric disorder. The control and patient groups were age and gender-matched. The nature and scope of the study was discussed with each participant and written informed consent was obtained from all participants before each interview. Ethical approval was obtained from the ethical and research committee of the Department of Psychiatry and Neurology, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt.

Tools

A pro forma data collection sheet was used to record socio-demographic information and to detail each participant's clinical and family genetic history. The data form included the following measures:Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990)[17], the Positive and Negative Symptoms Scale (PANSS) (Lindenmayer et al., 2004)[18], Global Assessment of Function scale (GAF) (American Psychiatric Association, 1994)[19], the Structured Clinical Interview for DSM-IV (SCID II) for personality assessment (First et al., 1997)[20], Young Mania Rating Scale (YMRS) (Young et al., 1978)[21], Hamilton Rating Scale for Depression

(HRSD) (Hamilton, 1980)[22] and the Arabic form of Family Interview Genetic Study (FIGS) (Maxwell, 1992)[23].

Genotyping of the dopamine transporter gene (DAT)

Blood samples from 150 subjects were collected in EDTA-containing tubes and stored at −70°C until use. All participants were then subjected to a blood analysis for genomic DNA extraction. Genomic DNA was obtained from participants' venous blood samples. Two representative functional polymorphisms from DAT (dopamine transporter gene), DAT 3 intronic VNTR (variable number of tandem repeats) and 3 untranslated regions VNTR of dopamine transporter gene were investigated. Genomic DNA was extracted using a DNA isolation kit. For the polymorphism, the primer sequence used was: Intron 3 VNTR-Forward: 5' CCA GAG TCC CCC TTA CCA AGA-3 and Intron 3 VNTR- Reverse: 5' GGT GAA GTT GGC TGG TTG GTG-3. The primer sequence of 3 UTR-Forward: 5-TGTGGTGTAGGGAAGGGCCTCAG-3 and 3 UTR-Reverse: 5-CTTCCTGGAGGTCACGGCTCAAGG-3. Amplification reactions were carried out in a total volume of 20 µl containing 1X PCR Buffer, 3.75 mM $MgCl_2$, 0.25 mMdNTP, 0.5 µM primers, 0.5 U TaqDNA polymerase (AmpliTaq Gold, ABI), 20 ng genomic DNA and 5% DMSO. Incubation was at 95ºC for 10 minutes, followed by 35 cycles at 95°C for 45 seconds, 65°C for 45 seconds and 72°C for 1 minute and an extra 10 minutes at 72°C.

Statistical analysis

Analyses were performed using the Statistical Package for Social Sciences (SPSS, version 17). The analysis of the data was done to test statistically significant differences between groups. The one-way ANOVA test was used to compare more than two groups, followed by a *post hoc* LSD (least significant difference) test for inter-group comparisons. For quantitative data, the Student's t-test was used to compare between two groups and the paired sample t-test was used to compare one group at different time. The chi square test was used for qualitative data and the correlation coefficient determined to detect association between variables. Odds ratios and 95% confidence intervals were used to quantify any association between polymorphism and bipolar affective disorders. A P value of < 0.05 was considered statistically significant. The Hardy–Weinberg equilibrium was assessed for all genotypes in all available samples using a $\chi 2$ test. Only the most common alleles/genotypes were taken into account in the haplotype analysis and the tests of association with bipolar affective disorders.

RESULTS AND DISCUSSION

Sociodemographic Data of the Patients Groups

Table 1 reports the sociodemographic data of the entire patients groups. The age ranged from 18-55 years. There is no significant difference between the mean age of the non-psychotic bipolar I group and the two groups of psychotic bipolar disorder.

Table 1: The Sociodemographic Data of the Three Patients Groups

	Non-psychotic bipolar I		Mood congruent psychotic bipolar I		Mood incongruent psychotic bipolar I			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**P**
Age	29.5	9.1	30.4	8.9	33.3	10.6	1.404	0.251
	No.	%	No.	%	No.	%	Chi-square	P
Sex							0.243	0.885
Male	22	55%	18	58.1%	15	51.7%		
Female	18	45%	13	41.9%	14	48.3%		
Residence							3.274	0.774
Urban	18	45%	15	48%	14	48%		
Rural	22	55%	16	52%	15	52%		
Marital status							3.274	0.774
Married	16	40%	13	41.9%	12	41.4%		
Single	23	57.5%	16	51.6%	15	51.7%		
Divorced	1	2.5%	1	3.2%	2	6.9%		
Widow	0	0.0%	1	3.2%	0	0.0%		

Comparisons of Genotypes and Allele Frequencies between Groups

For the genotypes of DAT 3 intron VNTR, the results of frequencies in our sample of normal controls and patients, and of chi-squared analysis for Hardy–Weinberg proportions, are summarized in Tables 2 and 3.

Table 2: Observed Genotype Frequencies of 7/7, 7/8 and 8/8 of3 Intron VNTR of DAT (*SLC6A3*) among Healthy Controls and Patients Suffered Bipolar I Disorder with no Psychotic Symptoms (Group1), Bipolar I with Psychotic Symptoms Mood Congruent (Group 2), and Bipolar I with Psychotic Symptoms Mood Incongruent (Group 3).

	7/7	*7/8*	*8/8*
Controls	2/50	45/50	3/50
Group 1	19/40	17/40	1/40
Group 2	18/31	11/31	1/31
Group 3	9/29	19/29	1/29

Table 3: Allele Frequency Estimates and Results of χ^2 Analysis for Hardy-Weinberg Proportion in Healthy Controls and Patients Suffered Bipolar I Disorder with no Psychotic Symptoms (Group1), Bipolar I with Psychotic Symptoms Mood Congruent (Group 2), and Bipolar I with Psychotic Symptoms Mood Incongruent (Group 3).

	P (7)	*P (8)*	χ^2	P
Controls	0.49	0.51	32.0	0.000
Group 1	0.74	0.26	1.537	0.215
Group 2	0.78	0.22	0.193	0.6605
Group 3	0.64	0.36	5.074	0.0243

Pooling all Table 1 data, the gene frequency estimates are: *P(7)* = 0.64, *P(8)* = 0.36 and χ^2 = 20.419 (P = 0.0001), indicating significant departure from the Hardy–Weinberg equilibrium. Genotype frequencies were compared among the different groups using chi-squared analysis. Table 4 shows significant difference between the bipolar I and control groups. Furthermore, genotype frequencies differ between groups when patients are divided into three subgroups (Table 5). Table 4 shows marginally significantly higher frequencies of *7/8* 3 intron VNTR genotypes in Group 3 (bipolar I disorder with psychotic symptoms and mood incongruent) (χ^2 = 5.97, P = 0.05). In studying the associations between the demographic data and clinical characteristics of *7/7*, *7/8*, and *8/8* of 3 intron VNTR DAT genotypes, there were no statistical differences. However, 7/8 genotype was reported to be more frequent in the group with an earlier age of onset, more frequent episodes, and lower scores on the YMRS.

Table 4: The Frequencies of Genotypes of DAT 3 Intron VNTR in Bipolar I and Matched Controls

Genotypes of DAT 3 intron VNTR	Bipolar I patients		Controls		Chi square	P value
	No	%	No	%		
6-7	2	2.0%	0	0%	1.01	0.314
6-8	2	2.0%	0	0%	1.01	0.314
7-7	46	46.0%	2	4.0%	27.02	0.000
7-8	47	47.0%	45	90%	25.99	0.000
8-8	3	3.0%	3	6.0%	0.78	0.376

Table 5: Frequencies of 3 Intron VNTR of DAT (*SLC6A3*) Genotypes among the Three Bipolar Subtypes

Genotypes 3 Intron VNTR of DAT	Non-psychotic bipolar		Mood congruent bipolar		Mood incongruent bipolar		Chi-Square test	P value
	NO	%	No	%	No	%		
6/7	1	2.5%	1	3.2%	0	0%	0.88	0.643
6/8	2	5.0%	0	0%	0	0%	3.06	0.216
7/7	19	47.5%	18	58.1	9	31.0%	2.07	0.354
7/8	17	42.5%	11	35.5	19	65.5%	5.97	0.05
8/8	1	2.5%	1	3.2%	1	3.4%	0.06	0.970

Table 6: Frequencies of DAT 3´UTR (*SLC6A3*) among Patients of the Three Bipolar Subtypes

Genotypes of DAT 3´UTR	Bipolar I patients		Controls		Chi square	P value
	No	%	No	%		
3-3	3	3.0%	0	0%	1.45	0.216
9-9	20	20.0%	3	6.0%	5.03	0.024
9-10	57	57.0%	24	48.0%	1.09	0.297
10-10	20	20%	23	46.0%	11.02**	----------

The genotypic distribution of DAT 3´UTR (*SLC6A3*) for both patients and controls was within the Hardy–Weinberg equilibrium (patients: $\chi^2 = 2.979$, P = 0.0843 and controls: $\chi^2 = 1.020$, P = 0.3124). Genotype frequencies were compared among the different groups using chi-squared analysis. Table 6 shows significant differences between bipolar I and control group. Where *9/9* was higher among patients ($\chi^2 = 5.03$, $P < 0.024$) and *10/10* genotype was higher among the control group ($\chi^2 = 11.02$, $P < 0.001$).

Family History of Psychiatric Disorders

The consanguinity in the three bipolar subtypes showed that in the non-psychotic group, positive consanguinity represented 27.5% (11 patients), in the psychotic groups it represented 38.7% (12 patients) and 34.5% (10 patients) in the mood-congruent and in mood-incongruent subtypes, respectively. There was no significant difference in consanguinity among the three groups.

Family history of bipolar probands in the three subtypes was positive in first degree relatives for any psychiatric disorder in 35%, 58.6% and 32.2% in the non-psychotic group, mood-congruent and mood-incongruent subtypes, respectively, with significant differences between them (χ^2 = 6.44, P = 0.04). Positive family history in other relatives was 12.5%, 13.7% and 12.9% in the non-psychotic, mood congruent and mood-incongruent subtypes, respectively, with no significant differences (χ^2 = 0.03, P =0.987). Among patients with positive family history of psychosis in the three bipolar subtypes, the frequency of 3 intron DAT VNTR showed that 1 patient was of 6/8, 6 patients were of 7/7 and 14 patients were of 7/8 genotypes with statistically significant differences between them (χ^2=18.4, P=0.0001). In the mood-incongruent group, 85.7% of those with a positive family history of psychosis were with 7/8 genotype, which was statistically significant (χ^2 = 13.29, P = 0.001). Among patients with a positive family history of mood disorders in the three bipolar subtypes the frequency of 3 intron DAT VNTR showed that 53.1% were of 7/8, 46.9% were of 7/7 genotypes and only 1 patient (3.1%) was of the rare 6/7 genotype. The differences were statistically significant (χ^2 = 20.73, P = 0.0001). In addition, there was a significant difference between the three subgroups where mood-congruent and non-psychotic groups were higher (χ^2 = 7.20, P = 0.027); (χ^2 = 7.82, P = 0.02).

In the current study, we evaluated two VNTRs: the frequently studied 3´UTR variant and a novel VNTR in intron 3 in patients with bipolar I disorder, compared with a healthy control group. The results suggest a significant association between the VNTR in intron 3 polymorphisms and bipolar affective disorder I: the *7/7* genotype increases the risk to develop bipolar affective disorder and 7/8 increases the risk for developing subtype of mood incongruent psychotic features. Our results are consistent with those of other researchers studying the VNTR in intron 3 polymorphisms in patients with bipolar I disorder (Pinsonneault et al., 2011)[24]. However, Krelling et al. (2008)[25] investigated the allelic and genotypic distributions of polymorphisms in 167 women (105 with psychosis and 62 controls). The results showed no significant association for such polymorphisms as risk factors for the investigated phenotype (Krelling et al., 2008)[25]. The difference between different studies may be due to significant variations in the allelic frequency when comparing different ethnicities (Aparecida da Silva et al., 2011)[26]. In addition, our results revealed that the *7/8* genotype of 3 intron DAT VNTR was statistically significant in bipolar affective disorder I patients with a family history of psychosis compared with other genotypes. Furthermore, *7/8* genotype was significantly higher among the group of patients with mood-incongruent psychotic symptoms. These finding indicating that *7/8* genotype can increase the risk of developing bipolar affective disorder I with mood-incongruent psychotic symptoms

among patients with a positive family history of psychotic symptoms. The results of the present study suggest no significant association between the3′ UTR DAT VNTR polymorphism and bipolar affective disorder I. These results are consistent with others where a repeat (9/10 repeat) polymorphism in the 3′ untranslated region (3′UTR) (rs28313670) of DAT has been studied extensively in association studies, but with inconsistent and even contradictory results (Das and Mukhopadhyay, 2007;Laucht et al., 2007;Feng et al., 2005;Todd et al., 2001)[27,28,8,29]. However, some studies have found positive associations between the VNTR 9/9 and 10/10 polymorphisms of DAT1 and risk for schizophrenia (Todd et al., 2001)[29]. However most of studies have not supported these findings (Stober et al., 2006)[30]. There were several limitations to this study. First, all patients were recruited from the outpatient clinic, therefore excluding the more severe patients who require hospitalization. In addition, the bipolar group did not include subjects who were in the euthymic phase of remission, which limited the generalizability of the findings. These limitations notwithstanding, our results corroborate previous research that suggests the dopamine transporter gene is associated with bipolar affective disorder I (Pinsonneault et al., 2011)[24].

CONCLUSION

In conclusion, the data presented here provide evidence for an association between DAT and bipolar disorder I. They also implicate the 3′ end of DAT as the region of interest and are thereby consistent with previous studies of the 3′ VNTR. These data suggest the presence of a functional variant of a 3′ non-coding sequence element that is involved in the susceptibility to bipolar disorder. Thus, further investigation of this region is needed to define any regulatory elements that may be present, and to evaluate their relevance with regard to bipolar disorder. It is important to conduct large-scale studies to explore the mood-incongruent psychotic bipolar on various relevant levels (age at onset, family history and outcome) to help solve the controversy of whether it should be considered a separate disease entity or whether it exists on a diagnostic continuum between bipolar disorder and schizophrenia. Another future direction to consider is to conduct further research on intermediate phenotypes and underlying genetics focusing on dimensions, like psychosis, mood symptoms, negative symptoms, impulsivity and rapid cycling instead of targeting categorical diagnosis. Identifying effective interventions and medications that foster a patient's emotional stability and its relationship with genotypes are also to be recommended.

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