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5-Hydroxy tryptamine transporter (5HTT) gene promoter region polymorphism in anxiety and depressive disorders

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Abstract

Background: 5HTTLPR polymorphism (5- Hydroxy tryptamine transporter linked promoter region polymorphism) is the most widely studied genetic variant in psychiatry. The present study is a modest effort at ascertaining the role of 5HT transporter linked promoter region polymorphism (5HTTLPR) in anxiety and depressive disorders in Kashmir (India).The aim of this study was to examine 5-Hydroxy tryptamine transporter (5HTT) gene promoter region polymorphism in anxiety and depressive disorders.

Methods: Thirty patients with unipolar depressive disorders, 30 patients with anxiety disorders and 40 healthy volunteers (controls) were studied on a case control design, using polymerase chain reaction (PCR) and agarose gel electrophoresis after digestion with endonuclease enzyme. Genotypes and allele frequencies were compared using chi square tests, and p value of < 0.05 was considered as statistically significant.

Results: The mean (±sd) HAM-A (Hamilton rating scale for anxiety) scores for anxiety and depressive groups were 28.2±5.14 and 17±5.61, respectively ($P < 0.001$). The mean (±sd) HAM-D (Hamilton rating scale for depression) scores for depressive and anxiety groups were 25±5.58 and 15±6.13, respectively. ($p< 0.001$). The frequency of S allele was significantly high (83.3% vs 60%) in the group with anxiety ($p< 0.05$) compared to the control group ($p> 0.05$).

Conclusion: The genetic studies are still evolving as pathogenesis of anxiety and depressive disorders and involve the interaction of environmental factors with various genes. Genetic variation in different populations and hence different environments is important for elucidation of the mechanisms of these disorders. However, the study concludes that the locus under study is not shared between the two disorders.

Keywords: 5HTTLPR, Anxiety disorder, Depressive Disorder.

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Introduction

Depression and anxiety disorders are the most prevalent psychiatric disorders. Depressive disorders are characterized by sustained and persistent low mood with loss of interest, easy fatigability, disturbed sleep, decreased concentration and suicidal thoughts. Anxiety disorders have sustained feeling of impending threat with disturbed autonomic system (ANS) functions. According to National Comorbidity Survey Replication (NCS-R) done in the U.S., the life time prevalence of major depressive disorders is 16.6% and of anxiety disorders is 28.8%, respectively (1,2). Panic disorder, post traumatic disorder (PTSD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD) and phobic anxiety disorders are the various subtypes of anxiety disorders (1). A variety of genetic, biological, psychological and social factors are postulated to be the causal factors, leading to emergence of anxiety and depressive disorders (1). The human 5- Hydroxy tryptamine transporter (5 HTT) gene also called SLC6A4 has been cloned and

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mapped on to chromosome 17q11.1-q12 (3). A polymorphism has also been identified in the promoter region of SLC6A4, called 5HT transporter linked promoter region (5HTTLPR) polymorphism. 5HTTLPR consists of different lengths of repetitive sequences which contains GC-rich 20-23 base pairs long repeat elements. A deletion/insertion in the promoter region creates a short (S) allele and a long (L) allele (14 and 16 repeat alleles), which alters the promoter activity (1,4,5). The 5HTTLPR polymorphism has been studied in both depressive and anxiety disorders (5). Individuals carrying 1 or 2 copies of the S allele were noted to exhibit elevated neuroticism, a personality trait involved in the propensity to depression(6). Further, it was reported that S carriers exhibited elevated depressive symptoms, depressive disorders and suicidality after experiencing stressful life events and childhood maltreatment (7). Short allele of serotonin transporter gene has been found to be associated with the risk of anxiety disorders in one race (Caucasians); however in another race (Asians), long allele was found to be associated with the risk of anxiety disorders (8). Killpatrick et al. (9) found that S-genotype was associated with increased risk of post- traumatic stress disorder, a type of anxiety disorder, but only under high environmental stress. Margoob et al. (3) in a study of 57 subjects having major depression found that L-type homozygotes responded much better to antidepressant treatment. Similar findings have also been reported in earlier studies (10). There are studies showing genetic variation in depressive disorders related to 5HTLPR gene responding to antidepressant treatment. In studies conducted on mongoloid races it has been reported that better response to treatment occurs in those persons with S-allele (11). L-homozygotes are reported to be more in Caucasian individuals while S genotypes are more frequent in mongoloid individuals. The contradictory results of 5HTTLPR polymorphism studies among different ethnic groups in both depressive and anxiety disorders and their treatment responses appear to be intriguing. It has been observed that allele frequency in the Indian population differed from other populations (10-12). This perhaps can be understood from the fact that India has been a melting pot for millennia: Caucasoid, Mongoloids, Australoid races intermingled and intermarried and inhabited the land for eons (13). In view of this, a study was conducted to make a modest effort to study 5HTT polymorphisms in anxiety and depressive disorders of Kashmiri (Indian) population.

Methods

Data

This study was conducted in the post Graduate Department of Psychiatry, Government Medical College Srinagar, India. Thirty unrelated persons suffering from unipolar major depression and anxiety disorders were selected for this study. Bipolarity was excluded on the basis of history and current mental status examination. Diagnoses were confirmed by two experienced psychiatrists independently; 40 unrelated healthy volunteers (controls) belonging to the same state were selected after excluding mental disorders by comprehensive clinical interview by two experienced psychiatrists.

The inclusion criteria included persons suffering from depressive disorders and anxiety disorders, conforming to DSM IV TR criteria, all patients above 18 years of age and patients willing to participate in the study by means of informed consent. The exclusion criteria included persons below 18 years of age, all those with depressive disorders and anxiety disorders due to general medical conditions and psychoactive substances use and patients not willing to participate.

All patients were subjected to detailed physical and mental status examination clinically. All diagnoses were made as per DSM IV TR criteria. Data were meticulously recorded on a specially designed proforma. An observer rating scale such as

HAM –A and HAM-D was used to assess the severity of anxiety and depression in these disorders.

For genotyping gene, DNA was extracted from a portion of whole blood using GENEI Genomic Extraction Kit supplied by the Messers Bangalore Genei, India. Polymerase chain reaction was carried out with primers 5' GGCGTTGCCGCTCTCAATG C-3' (stpi-5-2) and 5' GAGGGACTGAG CTGGACAACCCAC 3' (stpi3-2). PCR was performed in 20 ul mixture containing about 50ng genome DNA, 10pmol of each primer, Tris-HCL, ph 8, 100uM dNTP's, 1U of Taq Polymerase using Tech-gene – Thermal cycle (UK). The amplification was carried out after an initial incubation at 95 degree Celsius for ten minutes, 30 cycles of a denaturation at 94 degree Celsius for one minute and an annealing step at 65 degree Celsius for one minute followed by an extension step at 72 degree Celsius for one minute, and final incubation at 72 degree Celsius was done for ten minutes. After a 1.5 agarose gel electrophoresis, the PCR products were stained with ethidium bromide and then bands were observed under a UV light. Allelic size was determined by the comparison of bands with size standards after electrophoresis in Polyacramide gel, using Psi X 174 hae III endonuclease enzyme followed by silver staining, and 3 genotypes i.e., LL, LS, SS were observed (Fig. 1) . Short allele(s) consisted of 448 base pair and long allele (l) of 528 base pair.

Statistical Analysis

Hardy-Weinberg equation was applied to the genotypes of the patients and controls.

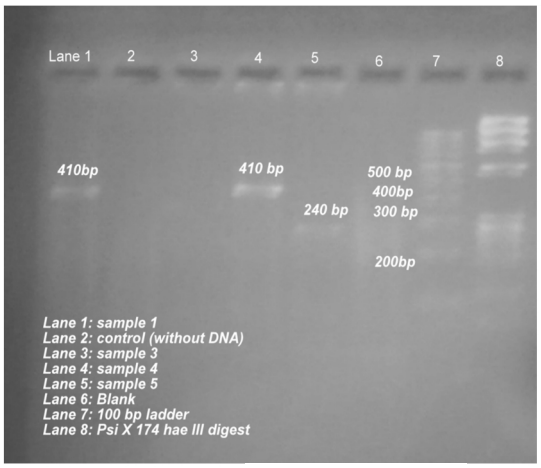

Fig. 1. Electrophoresis of 5 HTTLPPR Gene using polyacramide gel and Endonuclease Enzyme

Genotypes and allele frequencies were compared using chi square tests. Fisher's test was employed where chi square test could not be employed. Continuous data were analyzed using t tests and one way ANOVA. All statistical analyses were performed using SPSS software version 16.0 for Windows, and the differences were taken as significant when P-value was less than 0.05.

Results

The mean (±sd) age of the control, anxiety and depressive groups were found to be 29.75 ± 10.94, 32.7 ± 10.99 and 32.5 ± 9.93, respectively. The differences were not statistically significant (p> 0.05) (Table 1). Males constituted 65% (n= 26) of the controls while they formed 57% (n= 17) and 50% (n= 15) of the depressive and anxiety groups of patients. Gender differences were not statistically significant (p>0.05) (Table 2). In the depressed group, 53% (n = 16) had severe depression. Panic disorder patients constituted the majority in

Table 1. Age Distribution in the Study and Control Groups

Groups	Mean Age(years)	S.D	ANOVA	D.F	p
Control	29.75	10.94			
Depression	32.5	9.93	1.02	2	P: > 0.05
Anxiety	32.7	10.99			

Table 2. Sex Distribution in the Study and Control Groups

Group	Male	Female	X^2	DF	p
Control	26	14			
			1.43	2	P: > 0.05

Table 3. Diagnosis of the Study and Control Groups

Depression Group (N=30)	
Depression Severe	16 (53%)
Depression Mild/Moderate	14 (47%)
Anxiety Group (N = 30)	
Generalised Anxiety Disorder	8 (26.67%)
Panic Disorder	17(56.67%)
Obsessive Compulsive Disorder	3 (10%)
Specific Phobia	2 (6.67%)

Table 4. Hamilton Anxiety Scale (HAM-A) Scores and Hamilton Depression Scale (HAM-D) in the Study and Control Groups

Group	Anxiety		Depression		t Value	D.F	p
	Mean	S.D	Mean	S.D			
Ham-A	28.2	5.14	16.7	5.61	8.33	58	<0.001*
Ham-D	15	6.13	25.1	5.58	6.43	58	<0.001*

Table 5. 5HTT LPR Genotype and Allele Frequency in the Study and Control Groups

	Genotype					Allele			
Group	Ll	Ls	Ss	X^2	P Value	L	S	X^2	p
Control	5	22	13			16(40%)	24(60%)		
Depression	2	6	22	4.44	$> 0.05^{a}$	5(16.7%)	25(83.3%)	1.54	$> 0.05^{a}$
Anxiety	10	13	7	10.29	$<0.01^{b*}$	16.5(55%)	13.5(45%)	4.38	$< 0.05^{*B}$

Superscript a Denotes Comparison of Control vs. Depression, Superscript b Denotes Comparison of Control vs. Anxiety
* Significance at $p < 0.05$

the anxiety group 56.67% (n= 17). Patients with generalized anxiety disorder formed 27% of the group (Table 3).

The mean (±sd) HAM-A scores for the anxiety and depressive group were 28.2 ± 5.14 and 16.7 ± 5.61, respectively. Difference in the mean scores was found to be statistically significant ($p< 0.001$). However, 12 out of the 30 (40%) depressed patients had HAM-A scores of mild to moderate anxiety (18 to 30) (Table 4).

Mean (±sd) depression scores for the depressed and anxiety group of patients were 25.15 ± 5.58 and 15 ± 6.13, respectively. The difference was found to be statistically significant ($p< 0.001$). However, 16 out of the 30 patients with anxiety (53%) had moderate to severe depression. An additional 12 patients (40%) had depression in the mild range of 8 to 17, showing considerable overlap of symptoms between the two groups (Table 4).

5HTTLPR genotype and allele frequencies were not distributed uniformly between the control and patient groups ($p<0.001$); and this may be due to the significant differences in the genotype frequencies between the anxiety group and controls ($p< 0.001$). The frequency of S allele was significantly high (83.3% vs. 60%) in the group with anxiety when compared to controls ($p< 0.05$). No significant

Table 6. 5 HTTLPR Genotype relation to HAM-A and HAM-D in Groups with Anxiety and Depression

HAM-A*		HAM-D**	
SS	LS/LL	SS	LS/LL
22 31	29	37	27 26
28 24	29	24	28 28
34 30	20	31	35 28
27 30	29	28	28 30
35 13	28	29	24 26
25 32	28	30	27 26
34 32	24	20	19 21
31 33	34	..	22 21
34 23	..	..	20 19
31 34	..	..	17 11
23 24	..	..	29 28
			28..

SS: Mean 28.6, LS/LL: Mean 27.62, SS: Mean 28.4, LS/LL: Mean 24.5
*t: 0.48, Df: 28, $p >0.05$, **t: 1.62, Df: 28, $p > 0.05$
*HAM D Scores on the Depressed Group, ** HAM A Scores on the Anxiety Group

Table 7. Severity of anxiety @: 5 HTTLPR

	LL	LS	SS
Severe	0	1	13
Less Severe	2	5	9

@ HAM-A Score of 30 and above is taken as severe anxiety, 5HTTLPR FISHER'S EXACT TEST: p= 0.0205*

differences were observed in the genotype or allele frequencies between controls and depressed group (p> 0.05) (Table 5).

HAM-A scores in persons carrying SS and LS/LL genotypes of 5HTTLPR were compared within the anxiety group, but no significant differences were found in HAM-A scores between SS and LS/LL genotypes (p> 0.05). HAM-D scores of SS genotype persons were not significantly different from that of LS/LL genotypes (Table 6).

Scores of 30 and above on HAM-A is considered as severe anxiety. There was more number of severe anxiety cases in SS genotype than in LS/LL genotypes (13 0ut of 14 versus 9 out of 16). The difference was statistically significant (p= 0.020). 5HTTLPR genotypes were not related to the severity of anxiety (p= 0.107) (Table 7).

Discussion

5HTTLPR polymorphism is the most widely studied genetic variant in psychiatry (14). A few studies have been carried out on 5HTTLPR polymorphisms in India (14). The present study is a modest effort at ascertaining the role of polymorphisms in genes of 5HT transporter (5HTTLPR) in anxiety and depressive disorders of Kashmiri (Indian) population. Though there was no deliberate effort to match the control and patient groups for age, both groups were found to be matched for age. Excluding social anxiety disorder, anxiety disorders are known to be more common in women (1). Depression is also known to be more common in women (1). In the present study, gender distribution in anxiety and depressive groups of patients was found to be the same as that of controls. Panic disorder and severe depression appeared to be disproportionally represented in the sample, but perhaps could be understood from the fact that this was a hospital based study.

The mean anxiety score in the anxiety and depression groups was 28.2 and 19.47, respectively. A score of 18 and above was considered as mild anxiety (Ham-A). Though the difference was highly significant, the fact that a substantial number (40%) of depressive patients have at least mild levels of anxiety lends credibility to the contention that depression and anxiety are two facets of the same disorder (15,16). This argument can be further advanced by the fact that 53% of the anxiety patients in this study had moderate to severe levels of depression and an additional 40% had mild levels of depression. It appears that phenotype anxiety cannot readily be distinguished from phenotype depression.

It has been observed that ethnicity plays an important role in gene related studies and has vital clinical applications. The risk for anxiety and depressive disorders is linked with short allele of serotonin-transporter gene in the Caucasian population; however, the association is still unclear in the Asian population. In a study done by Long H et al. in 2013 it was found that in the Chinese Han population, in contrast to the Caucasian population, the L-allele has susceptibility to anxiety or depression disorders (8). Most of the studies reported that polymorphisms in the population of controls and patients were in Hardy- Weinberg equilibrium (14,17). In the present study, controls and patients were in Hardy –Weinberg equilibrium. Widely varying 5HTTLPR genotype frequencies have been reported by various workers in their control populations (18-20). Mukherjee et al. commented on the different genotype frequencies in the psychiatric patients of our country (12). The LL, LS and SS

genotypes in the controls of the present study were 12.5%,55% and 32.5% while Billiviers et al. (18) reported 32.6%, 52.7% and14.7%; Lee et al. (19) reported 4%, 31% and 65% while Mann et al. (20) reported 28%, 57% and 15% in the same genotypes. Genotype frequencies of 33.3%, 43.3% and 23.3% in the mood disorder patients of the present study corresponds to those of Margoob et al. (14). The genotype frequencies of LL 6.6%, LS 20% and SS 73.3 % in the anxiety group of the present study correspond to those of Lee et al. (19). Lee et al. reported frequencies of 2%, 21% and 77% in their study of PTSD patients. The SS genotype was significantly high in the anxiety group, and the frequency of S allele was also high in the anxiety group. The finding of this study is similar to that of other studies (7, 19, 21, 22). There are many studies showing an association of the SS genotype and S allele with depression (19,20,22). No association of the genotypes or allele frequencies with depression was found in the present study. Risch et al. also reported no association of 5HTTLPR with depression (23); Margoob et al. in their review pointed to several studies which reported no association of depression with 5HTTLPR polymorphism (14). Few researchers believe that this disparity in the results is due to the fact that ethnic variation may play a part in it (24, 25).

The findings of this study which showed 5HTTLPR association with anxiety and not with depression is intriguing. As it has been observed, 93% of the patients in the anxiety group had a mild to moderate depression on the one hand and 40% of the depressive patients had significant anxiety on the other hand. The finding of this study seems to suggest that the biological underpinnings of the two conditions are different. Some studies have suggested that female gender plays a role in the effect of polymorphisms over the emergence or exacerbation of phenotype anxiety and depression (17, 26-29). In the present study, there were no statistically significant differences in genotype frequencies, HAM-D scores and HAM-A scores between the male and female population. Perhaps gender has no role to play in the effects of 5HTTLPR polymorphisms.

In the preliminary analysis, SS genotype was found to be significantly high in patients with anxiety. Further comparison of anxiety scores between the 5HTTLPR genotypes revealed no statistically significant differences in the anxiety scores between SS genotype and LL/LS genotypes. This finding is rather unexplainable, but one outlier score 13 in SS genotype patients (S.No. 10 of table 6) and outlier 34 in LL/LS genotypes may have something to do with it. The intriguing finding of this study was that SS genotype of 5HTTLPR was associated with anxiety disorders and not with their severity (Table 6). Further analysis was made considering the HAM-A cutoff score of 30 and above as indicative of severe anxiety. In this study, 13 out of 14 (92.8%) of the severely anxious patients carried the SS genotype whereas only 56% of the patients with mild/moderate anxiety carried SS genotype. The difference was found to be statistically significant. It appears that SS genotype of 5HTTLPR is associated with anxiety disorders. The sample size of this study was too small for an association study and therefore the findings can only be generalized with caution.

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