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Serotonin transporter gene polymorphism and its association with bipolar disorder across different ethnic groups in Malaysia

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Abstract

Objectives: The risk variants have been shown to vary substantially across populations and a genetic study in a heterogeneous population might shed a new light in the disease mechanism. This preliminary study aims to determine the frequency of the serotonin transporter gene polymorphism (5-HTTLPR) in the three main ethnic groups in Malaysia and its association with bipolar disorder.

Methods: This is a candidate gene association study of randomly selected forty five unrelated bipolar disorder probands and sixty six controls. Diagnosis was evaluated using the Mini International Neuropsychiatric Interview (M.I.N.I). The control group consisted of healthy volunteers without personal psychiatric history and family history of mood disorder. Patients' whole blood was collected for genotyping.

Results: This study revealed that the frequency of the short variant of 5-HTTLPR in healthy control group was highest in Indians (42.9%) followed by Malays (23.5%) and was absent in Chinese. The association between the homozygous ss genotype of the 5-HTTLPR polymorphism with bipolar disorder was not found in the pooled subjects ($\chi^2 = 1.52$, d.f. = 1, p = 0.218, OR = 4.67, 95% C.I. = 0.69–7.58) and after stratification into Malays (p = 0.315, OR = 2.03, 95% CI = 0.50–8.17), Indians (p = 0.310; OR = 0.44, 95% CI = 0.21–0.92) and Chinese.

Conclusion: The differences in the frequency of the short allele of 5-HTTLPR across the three main ethnic groups in Malaysia were noteworthy. The present study showed no significant association between the homozygous short variant of the 5-HTTLPR and bipolar disorder in the pooled subject and after stratification into the three main ethnic groups in Malaysia.

1. Introduction

Bipolar disorder is a debilitating illness with strong genetic components. The relative risk of bipolar disorder for first-degree relatives of individuals with bipolar I disorder is seven times higher than the general population risk of ~1% [1]. In a twin study, the risk for bipolar I disorder in a monozygotic twin of an individual with bipolar disorder is 60 times higher than that of the general population, and concordance rates for bipolar disorder range between 60% and 90% in monozygotic twins and ~8% for dizygotic twins [1].

Several lines of evidence have demonstrate the association between polymorphism of serotonin transporter gene (5-HTT) which is located on chromosome 17q11.1-17q12 at the SLC6A4 locus [2] with bipolar disorder [3,4]. The insertion/deletion polymorphism in the promoter region (5-HTTLPR) is most commonly composed of either 14 (short or s allele) or 16 (long or l allele) repeating elements of 44-base-pairs (bp) [5].

The short allele of the 5-HTT gene results in reduced transcription of the serotonin transporter, and reduced serotonin (5-HT) uptake in lymphoblasts compared with the long version, leading to speculation that it may be a functional polymorphism for bipolar disorder [6]. Two independent groups using large samples have reported an association between the s allele of the 5-HTTLPR and bipolar disorder [3,4]. However, the absence of association has also been reported [7–11].

The results of the meta-analysis carried out by Furlong et al. (1998) [12], suggested the existence of an association

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between bipolar disorder and the 5-HTTLPR s allele [7,8]. The polymorphisms of the serotonin transporter gene are associated with different subgroups of the bipolar disease [3,4]. The association reported between the 5-HTTLPR s allele and early onset bipolar disorder with psychotic features also supports the existence of heterogeneity in the phenotype–genotype relationship in bipolar disorder [13], as does the association between the s allele and bipolar disorder with violent suicidal behaviour [4].

The 5-HTTLPR homozygous short variant polymorphism could be a useful contributor, among other clinical variables, to predict the risk for antidepressant induced mania [14] and negative response to lithium treatment [15].

Malaysia is a multicultural society made up of various races and religion. About 50.4% of its population is Malay, 23.7% Chinese, 7.1% Indian, 11% Indigenous and 7.8% others [16]. They were believed to have distinct genetic pool owing to different ancestry. The genetic heterogeneity in a culturally mixed country such as Malaysia may lead to different susceptibility to disease, different response to pharmacological agents and complex interaction of genetic and environmental factors in producing phenotypes [17]. These elucidate why a genetic study is important in this region.

In this preliminary study, we aim to determine the association of homozygous short variant of 5-HTTLPR with bipolar disorder in three major ethnic subgroups in Malaysia, namely Malays, Chinese and Indians.

2. Methods

2.1. Samples

2.1.1. Bipolar disorder probands

Forty five unrelated patients diagnosed with bipolar I and bipolar II disorder according to DSM-IV criteria were recruited from psychiatric inpatient, and outpatient clinics of the Universiti Kebangsaan Malaysia Medical Centre. They were all Malaysian. They were selected randomly and interviewed by a trainee psychiatrist who was trained using Mini International Neuropsychiatric Interview 5.0. (M.I.N.I) [18], case notes were reviewed and the diagnosis was made on the basis of all available information. Those with comorbid substance abuse or mental retardation were excluded.

2.1.2. Control

Sixty six control subjects were derived from hospital personnel, students and relative of patients from departments other than the psychiatric department. Those with personal or family history of mood disorders in first and second degree relatives were excluded. Written consent was obtained from the participants. The study was approved by the institutional ethics committee.

All subjects gave informed consent.

2.1.3. Genotyping

About 3 to 5 ml of whole blood was collected in EDTA bottle. Genomic DNA was isolated from leucocytes (EDTA-anticoagulated blood) using a DNA-extraction kit (Qiagen). Amplification of the 5HTTLPR was performed by PCR method using Top Taq Master Mix, 2×, in a final volume of 25 μl containing diluted primer mix — primer A (forward) 0.2 μl; primer B (reverse), coral load concentrate 10 × 2.5 μl, RNAse free water 4.6 μl and template DNA 5 μl. Polymerase chain reaction (PCR) products were separated on agarose gel electrophoresis stained with ethidium bromide [19].

The long 'l' and short 's' alleles are represented by 419 bp and 375 bp PCR products respectively (Fig. 1). The following primers are used: forward 5′-ATG CCA GCA CCT AAC CCC TAA TGT-3′; reverse 5′-GGA CCG CAA GGT GGG CGG GA-3 [18].

2.2. Statistical analysis

Hardy–Weinberg equilibrium (HWE) for the distributions of genotypes was estimated by the χ^2 tests. Allele and genotype frequencies were compared between groups using the χ^2 tests with Yates correction. Odds ratio (OR) with 95% confidence interval (CI) was calculated using Statistical Package for Social Science (SPSS) program version 19. A p-value of <0.05 was considered as significant.

3. Results

The demographic and clinical data of the bipolar disorder probands and control group are shown in Table 1. 68.9% (n = 31) of the bipolar probands had family history of mood disorder. The mean age at onset of illness for the bipolar disorder probands was 28.4 ± 10.42 (s.d.) years.

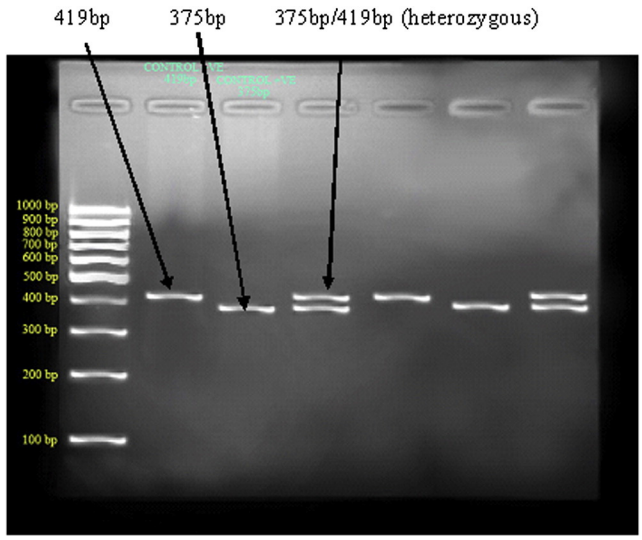

Fig. 1. Polymerase Chain Reaction analysis of 5-HTTLPR polymorphism.

Table 1
Sociodemographic data of bipolar disorder probands and control.

	Bipolar disorder n=45	Control n=66
Age Median (IQR)	37.0 (16.0)	28.0 (12.8)
Gender, n (%)		
Male	19 (42.2)	11 (16.7)
Female	19 (42.2)	11 (16.7)
Ethnic group, n (%)		
Malays	31 (68.9)	49 (74.2)
Chinese	5 (20.0)	8 (12.1)
Indians	9 (11.1)	7 (10.6)
Others	0 (0.0)	2 (3.0)
Marital status, n (%)		
Married	20 (44.4)	32 (48.5)
Never married	21 (46.7)	33 (50.0)
Divorced/widowed/Separated	4 (8.9)	1 (1.5)
Educational level, n (%)		
No formal school	0 (0.0)	1 (1.5)
Primary school	9 (18.9)	12 (18.2)
Secondary school	10 (21.9)	14 (21.2)
Tertiary education	26 (58.6)	39 (59.1)
Employment status, n (%)		
Employed	32 (58.2)	23 (51.1)
Unemployed	17 (30.9)	17 (37.8)
Student	6 (10.9)	5 (11.1)
Family history of mood disorders, n (%)	31 (68.9)	
Age at onset of illness, mean±s.d. (years)	28.4±10.42	

s.d.=standard deviation.

3.1. Ethnic differences in the distribution of genotypes and alleles

We found substantial differences in the distribution of short variants of 5-HTTLPR in bipolar disorder and control subjects in the three main subethnic groups in Malaysia (Table 2). In the healthy control group, the frequency of the homozygous short variant of the 5-HTTLPR was highest among Indians (42.9%), followed by Malays (18.4%) and was absent in Chinese. Indian ethnic group constitutes the highest frequency of the short allele of 5-HTTLPR (42.9%) followed by Malays (23.5%) and Chinese (0.0%). In the bipolar probands, the ss genotype was highest among Malays (12.9%) and absent in Chinese and Indians. Malays constitute the highest frequency of the short allele of 5-HTTLPR (21%), followed by Indians (10.0%) and absent in Chinese.

Table 2
Genotypes and alleles distribution on different ethnic groups.

	Genotypes						Alleles			
	ss		sl		ll		s		l	
	n	%	n	%	n	%	n	%	n	%
Bipolar disorder										
Malay	4	12.9	5	16.1	22	71.0	13	21.0	49	79.0
Chinese	0	0.0	0	0.0	9	100	0	0.0	18	100.0
Indian	0	0.0	1	20.0	4	80.0	1	10.0	9	90.0
Others	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Control										
Malay	9	18.4	5	10.2	35	71.4	23	23.5	75	76.5
Chinese	0	0.0	0	0.0	8	16.3	0	0.0	16	100.0
Indian	3	42.9	0	0.0	4	57.1	6	42.9	8	57.1
Others	0	0.0	0	0.0	2	100	0	0.0	4	100.0

Table 3 shows no significant association between the 5-HTTLPR homozygous ss genotype and bipolar disorder in the pooled subjects (p=0.220, OR=4.67, 95% C.I.=0.69–7.58) as well as after stratification into ethnic subgroups, the Malays (p=0.315, OR=2.03, 95% C.I.=0.50–8.17) and Indians (p=0.310; OR=0.44, 95% C.I.=0.21–0.92).

Similarly, comparison across all three ethnic subgroups and pooled subjects of the 5-HTTLPR s allele between bipolar disorder and controls yielded no significant differences (Table 4).

4. Discussion

This study represents the preliminary research in Malaysia that examines the association between serotonin transporter gene polymorphism in bipolar disorder.

We found that 68.9% of bipolar probands had first and second degree relatives with mood disorders. This result is consistent with studies that link genetic to bipolar disorder [1]. The mean age at onset for bipolar disorder occurs at younger age ranging from the age of 18 to 29 [20]. This present study also found younger mean age at onset in bipolar disorder, 28.4±10.42 (s.d.) years.

Contrary to the positive meta-analysis finding by Furlong et al. (1998) [12] and Jessica et al. (2004) [21], this study failed to detect the association between serotonin transporter gene and bipolar disorder pooled subjects and also after stratification into 3 major subethnic groups, the Malays, Chinese and Indians. Nonetheless, this finding is consistent with studies done in a group of 50 Indian bipolar patients when compared with 50 ethnically matched control [22] and in a sample of 137 Han Chinese patients compared with 362 ethnically matched control [23] or in several independent samples of Caucasians [24,25].

We found a captivating result that the 5-HTTLPR homozygous ss genotype and short allele were absent in both Chinese healthy control and bipolar proband group. This was contrary to the finding in the East Asian population which shows that 70%–80% of individuals are s carriers compared to 40%–45% in the European population [26,27]. This outlier could be due to the impact of migration and genetic admixture. Albeit Malaysian Chinese share some similarities with other Orientals, they also seemed to have some notable differences. Gene frequencies tend to remain constant from generation to generation when disturbing factors are not present. Factors that disturbed the genetic equilibrium include mutations, natural selection, non-random mating, genetic drift and gene flow [28]. Pertaining to the

Table 3
Association tests on 5-HTTLPR ss genotype and bipolar disorder in 3 major subethnic groups, the Malays, Chinese and Indians and pooled subjects.

	ss genotype frequency		χ^2	df	p value	OR	95% CI
	Bipolar	Control					
Malays	0.13	0.18	0.47	1	0.315	2.03	0.50–8.17
Chinese[a]	0	0					
Indians	0	0.43	2.86	1	0.310	0.44	0.21–0.92
Overall (Malays+Chinese+Indians)	0.88	0.18	1.52	1	0.220	4.67	0.69–7.58

OR=odds ratio.
CI=confidence interval.
[a] No statistic can be computed because both groups are constant.

Malaysian Chinese, their genetic evolution could be modulated by migration, intermarriage and integration with the local customs. Evolution may have latched onto a gene linked to optimism and adventurousness. Historically, the first wave of 15th century Chinese settlers came during the Malacca Empire for diplomatic relations between China and Malacca. A much larger wave came during the 19th century and early 20th century to work in tin mines and businesses [29]. The long allele which predominates among Chinese in this study could actually be innate survival traits that were selected during their migration out of mainland China. The homozygous long variant of the serotonin transporter gene has shown positive association with emotional resilience [30] and biased attention of positive emotional stimuli which suggest that those having the alleles may tend to be more optimistic and have less risk to develop psychiatric illnesses [31].

Meanwhile, Indians had the highest frequency of the short allele of 5-HTTLPR (42.9%) in this study. Nevertheless, this frequency is slightly lower compared to their counterparts in Indian subcontinents (50.0%–60.0%) [32,33] and American Indians (64.0%–66.0%) [34], respectively. Malaysian Indians are largely descended from those who migrated from southern India during the British colonization of Malaya [35]. The frequency of the short allele of 5-HTTLPR in Malays (23.5%) was intermediate between Chinese and Indians. This possibly reflects the unique mixed blood nature of Malays [19,36]. The present-day Malays (Deutero-Malays) originally migrated from Southern China over 1500 years ago. Their intermarriages with traders from Java, Sumatra, India, Siam, Arab and China resulted in the diverse Deutero-Malays population [37,38].

The substantial disparity in the frequency of homozygous short variant of the 5-HTTLPR across three ethnic groups in this preliminary study could lead to a different treatment response for bipolar disorder and clinical expression of the disease such as significantly higher rate of homozygous short variant for 5-HTTLPR among patients with a history of antidepressant-induced mania [14] and negative prophylactic lithium response [15].

We acknowledged the main limitation in this study was the lack of statistical power. The lack of statistical power may lead to inability to detect a small effect size in a complex disease like bipolar disorder particularly in heterogenous population like Malaysia. Hardy–Weinberg equilibrium (HWE) was not met in the present study. In Malaysian context, it is difficult to assume that there is no violation of the basic assumption of the HWE because of the history of migration and interracial marriage [19]. Other possible explanation of the deviation from HWE is that the sample size of the present study may not be sufficiently large [19]. Future study with a larger sample size is recommended to confirm the finding.

5. Conclusion

This preliminary study failed to demonstrate the association between homozygous short variant of the 5-HTTLPR with bipolar disorder in the pooled subjects and after stratification into three ethnic subgroups in Malaysia. The difference in the frequency of the short allele of 5-HTTLPR across the three main ethnic groups in Malaysia was notable. Migration and mixed marriage may explain the differences in

Table 4
Association tests on 5-HTTLPR s allele and bipolar disorder in 3 major subethnic groups, the Malays, Chinese and Indians and pooled subjects.

	s allele frequency		χ^2	df	p value	OR	95% CI
	Bipolar	Control					
Malays	0.21	0.24	0.29	1	0.780	0.76	0.27–2.09
Chinese[a]	0	0					
Indians	0.10	0.43	0.04	1	0.836	0.33	0.02–4.74
Overall (Malays+Chinese+Indians)	0.16	0.22	0.18	1	0.670	0.82	0.34–2.01

OR=odds ratio.
CI=confidence interval.
[a] No statistic can be computed because both groups are constant.

the s allele and ss genotype frequency of Indians and Chinese Malaysian from their counterparts in the Indian subcontinents and other Orientals.

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