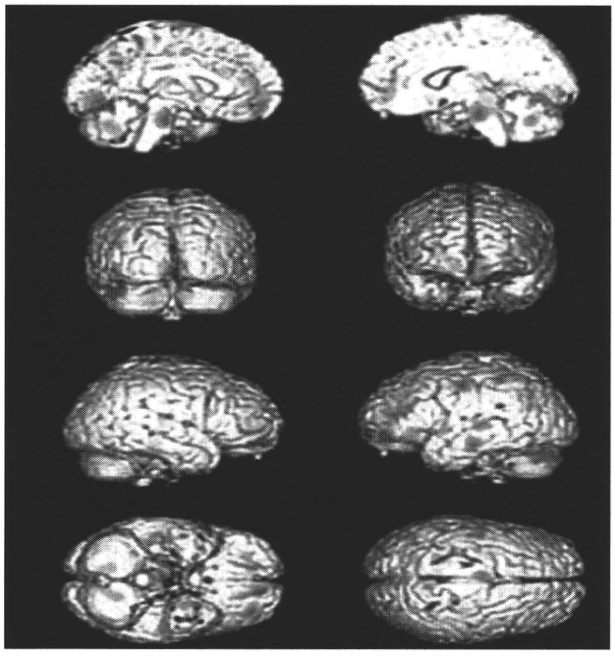
C. 研究結果

リチウム有効群は55%（N=5、男３名、年齢52.1歳±12.5歳）でリチウム無効群は45%（N=4、男２名、年齢 43.5±13.0 歳）であった。投与前のハミルトンうつ病評価尺度17項目は有効群22±6.0点、無効群21.0±6.2点で重症度に有意な差はなかった。

有効群と無効群での投与前のSPECT所見の差異では、有効群の方が眼窩前頭皮質、前部帯状回、背外側前頭前野などの左側前頭前野、左側頭葉皮質、脳幹の血流が高く（p<0.05）、特に左前頭前野では著明な差を認めた（P<0.01）【図３】。

【図 3】リチウム有効群のほうが投与前の脳血流が高い部位



D. 考察

SPECT 検査の問題は、絶対値での評価が困難であることや、疾患特異的な所見か状態特異的な所見か評価できないことから、世界各施設での報告が一致しにくいことである。しかしながら、うつ病の脳血流 SPECT 所見に関する報告を検討すると、前頭葉、側頭葉の血流低下については概ね一致している。

前頭葉については、頭部MRIにおいて患者での体積低下（約 7%）（Coffey, 1992）、重症度と相関する体積低下（Kumar, 1998）等の報告がある。脳血流では、前頭葉の血流低下、特に右と比較し左の前頭葉での低下が著しいという報告があり、これは我々が検証した左優位な前頭葉血流低下に一致する。特に注目すべきは、ドーパミン系関連部位で、うつ病の精神運動抑制や抑うつ気分に関与している可能性のある前頭前野背外側部である。うつ病患者における同部位の血流低下（Daniel J, 2005）の報告があり、また病理学的にうつ病で同部位の神経細胞、グリア細胞の減少（Rajkowska, 2001）が報告されている。今回の結果でも、同部位の血流低下を認めており、うつ状態を反映している可能性が高い。

今回の研究結果からは治療抵抗性うつ病において左前頭前野の血流低下所見が軽いほどリチウムで寛解しやすく、上記所見がリチウムの効果予測の指標となる可能性があることが示された。

E. 結論

リチウム投与前のSPECTにおいて有効群と無効群にわけて群間比較したところ、有効群の方が無効群より、眼窩前頭皮質、前部帯状回、背外側前頭前野などの左側前頭前野、左側頭葉皮質、脳幹の血流が高く、特に左前頭前野でその差が顕著であることが示された。これらの部位は我々が従来うつ病で健常群より低下すると報告した部位と一致し、特に左前頭前野の血流低下の度合いがリチウムの効果予測指標となる可能性が示唆された。

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G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得　該当なし。
2. 実用新案登録　該当なし。
3. その他　該当なし。

研究成果の刊行に関する一覧表

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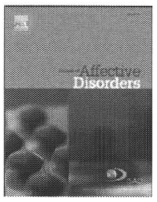

Research report

Difference in Temperament and Character Inventory scores between depressed patients with bipolar II and unipolar major depressive disorders

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ABSTRACT

Background: Although some core personality variables are known to be characteristic of unipolar or bipolar depression, few studies have compared the personality profile between these two disorders.
Methods: Temperament and Character Inventory (TCI) was employed to assess the personality of 36 depressed patients with bipolar II disorder (BPII), 90 patients with unipolar major depressive disorder (UP), and 306 healthy controls. The TCI was administered during the depressive episode in BPII and UP patients so that the results can be applied in a clinical setting.
Results: Significantly higher scores in harm avoidance ($p<0.0001$) and lower scores in self-directedness ($p<0.0001$) and cooperativeness ($p<0.05$) were observed in both BPII and UP patients compared to controls. Lower novelty seeking in UP patients compared to BPII patients and controls was observed in females ($p<0.0001$, $p<0.01$, respectively). A significant difference in self-transcendence score was observed between BPII and UP patients in females ($p<0.0005$), with higher scores in BPII ($p=0.009$) and lower scores in UP ($p=0.046$) patients compared to controls. A logistic regression model predicted BPII in depressed females based on novelty seeking and self-transcendence scores with a sensitivity of 89% and a specificity of 73%, but did not accurately predict BPII in males.
Limitations: Patients in our study were limited to those receiving outpatient treatments, and bipolar patients were limited to those with BPII.
Conclusions: Novelty seeking and self-transcendence scores of TCI might be useful in the differentiation of UP and BPII in female patients.

1. Introduction

Differentiating unipolar and bipolar depression is of great clinical importance since the treatment of the two disorders differs substantially. However, the differentiation may be difficult due to the similar depressive symptomatology in these two disorders. One study reported that 69% of bipolar disorder (BP) had been misdiagnosed, with the most frequent

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misdiagnosis being unipolar depression (Hirschfeld et al., 2003). Some clinical characteristics such as hypersomnia and psychotic features have been suggested to be more common in bipolar depression than in unipolar depression (Forty et al., 2008; Mitchell et al., 2001). However, there are no clear-cut clinical features that distinguish the two disorders, and clinicians must use all available information to predict the possibility of bipolarity in depressed patients.

A few studies have attempted to examine differences in personality between unipolar and bipolar depression. Two studies (Mendlowicz et al., 2005; Nowakowska et al., 2005) used the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-Autoquestionnaire (TEMPS-A) and found that cyclothymic subscale score was significantly elevated in BP patients. Another study (Lovdahl et al., 2010), which used Temperament and Character Inventory (TCI) (Cloninger et al., 1993) to compare bipolar II disorder (BPII) with recurrent brief depression (RBD; defined as intermittent depressive episodes fulfilling the diagnostic criteria for major depressive episodes except for duration, which is less than 14 days), failed to find definitive difference between the two disorders. Evans, et al. (Evans et al., 2005) used both TEMPS-A and TCI to find higher dysthymic, cyclothymic, irritable, anxious, and novelty seeking temperaments and lower self-directedness and cooperativeness characters in BP patients. A study using a battery including 17 conventional personality scales has reported sanguine in patients with bipolar I disorder, labile or cyclothymic in patients with BPII, and subanxious and subdepressive in patients with unipolar depression (Akiskal et al., 2006).

Although above studies report a number of findings showing different personality in UP and BP patients, few have assessed the personality of the two disorders during depressive state (Mendlowicz et al., 2005). Since the severity of depressive symptoms impact on how the subject describes their personality (Spittlehouse et al., 2010), it is important that the mood state at the time of assessment is taken into account. If the personality assessment is to be used as an aid for differentiating unipolar and bipolar depression in the real world setting, studies are required to compare personality measures during depressed mood.

In the present study, TCI was used to assess the personality difference between depressed BPII and UP patients. TCI is a 240 item true/false questionnaire measuring four dimensions of temperament (novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P)) and three dimensions of character (self-directedness (SD), cooperativeness (C), and self-transcendence (ST)), developed on the basis of a psychobiological model of personality. Although TCI has been frequently used in the studies of mood disorders (Akiskal et al., 2005; Celikel et al., 2009; de Winter et al., 2007; Engstrom et al., 2004; Farmer et al., 2003; Hansenne et al., 1999; Hirano et al., 2002; Kimura et al., 2000; Loftus et al., 2008; Marijnissen et al., 2002; Matsudaira and Kitamura, 2006; Naito et al., 2000; Richter et al., 2000; Smith et al., 2005), no studies to date have compared TCI score profiles of patients with unipolar and bipolar depression during their depressed states. We aimed to identify personality profiles specific to either unipolar or bipolar depression, which could aid in the differentiation of the two disorders.

2. Methods

2.1. Subjects

Subjects were 36 patients with BPII (18 men, 18 women; age ± S.D. (standard deviation) = 36.3 ± 11.1 years), 90 patients with UP (45 men, 45 women; age ± S.D. = 36.7 ± 10.2 years), and 306 healthy volunteers (153 men, 153 women; age ± S.D. = 36.4 ± 11.0 years), matched for age distribution in each gender group, recruited from the outpatient clinic of the National Center of Neurology and Psychiatry Hospital, Tokyo, Japan or through advertisements in local free magazines, website announcement, notices posted in the hospital, flyers, and word of mouth. Consensus diagnoses by at least two research psychiatrists were made according to the DSM-IV criteria (American Psychiatric Association, 1994) for BPII or UP for enrollment in the study. Those recruited from the outpatient clinic (BPII: 24 patients (67%); UP: 66 patients (73%)) were also assessed with the Structured Clinical Interview for DSM-IV by a trained psychiatrist to confirm the diagnosis. BPII and UP patients with Hamilton Rating Scale for Depression (17-item version) score greater than 7 were enrolled in the study. Healthy participants were interviewed using the Japanese version of the Mini-International Neuropsychiatric Interview (Otsubo et al., 2005; Sheehan et al., 1998) by a research psychiatrist, and only those who demonstrated no history of psychiatric illness or contact to psychiatric services were enrolled as healthy controls. Participants were excluded from both the patient and control groups if they had a prior medical history of central nervous system disease or severe head injury, or if they met DSM-IV criteria for mental retardation, substance dependence, or substance abuse. All subjects were biologically unrelated Japanese who resided in the Western part of Tokyo. Written informed consent was obtained from all subjects prior to their inclusion in the study and the study was approved by the ethics committee of the National Center of Neurology and Psychiatry, Japan.

2.2. Measures

All participants were administered the TCI (Cloninger et al., 1993), a 240 item true/false self-report questionnaire measuring four dimensions of temperament and three dimensions of character. The Japanese version of the TCI (Kijima et al., 1996; Kijima et al., 2000) was used in the present study. Each subject was allowed to take as much time as needed to complete the questionnaire. Depressive symptoms were assessed by an experienced research psychiatrist using the Japanese version of the GRID Hamilton Rating Scale for Depression, 17-item version (HDRS) (Hamilton, 1967), which has been demonstrated to show excellent inter-rater reliability (Tabuse et al., 2007).

2.3. Statistical analyses

Gender differences concerning the temperament and the character dimensions have been reported previously (Gutierrez-Zotes et al., 2004; Hansenne et al., 2005; Pelissolo and Lepine, 2000), and thus is one of the major potential confounding factors

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in TCI studies. Therefore, the data for male and female subjects were analyzed separately to avoid gender-dependent influence.

Statistical differences of demographic data among groups were evaluated by the chi-squared test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Student t-test was used for comparisons of clinical variables between BPII and UP patients. The scores of the dimensions of TCI were compared among the three diagnostic groups using Kruskal–Wallis test, and thereafter, pairwise comparisons between each group were done using Mann–Whitney tests. Bonferroni method was used to correct for multiple comparisons among the three diagnostic groups. However, since the scale scores of each TCI dimension are intercorrelated and thus are not completely independent measures, we did not apply Bonferroni method for the number of TCI dimensions. Correlations between TCI scores and HDRS scores were assessed using Spearman's rank correlation coefficients. A stepwise logistic regression analysis was used in patients with BPII and UP to determine the optimal model for the prediction of BPII in depressive patients. Prediction models were developed separately for males, females, and both genders combined. The stepwise analysis was conducted as a forward stepping procedure based on a likelihood ratio test, with $p<0.05$ for variable inclusion and $p>0.2$ for exclusion from the model. Variables used as potential predictor variables were age, gender, HDRS score, and scores of 7 dimensions of TCI. Nagelkerke's R^2 was used to approximate the percent of variance explained by the model (Nagelkerke, 1991). The area under the receiver-operating characteristic (ROC) curve (AUC) was also used to determine the predictive power of the logistic model. The predicted probability with the highest Youden index was selected as the optimal cut-off point. Statistical significance was set at two-tailed $p<0.05$. Analyses were performed using the SPSS version 11.0 (SPSS Japan, Tokyo).

3. Results

Table 1 shows demographic and clinical characteristics of the subjects. Age distribution did not differ across the three diagnostic groups. Although the average years of education were significantly higher in the male controls, there was no significant difference between BPII and UP patients. Patients with BPII and UP did not differ significantly in age at onset or in HDRS scores.

The mean scores for the 7 dimensions of TCI are presented in Table 2. Three-group comparisons of BPII, UP patients, and controls revealed differences in all dimensions except for RD in both genders, P in females, and ST in males. Significantly higher HA and lower SD and C scores in BPII and UP patients compared with control subjects were observed in both males and females. Significantly higher P scores in BPII and UP patients were detected only in females. Lower NS in UP patients compared to BPII patients and healthy controls was observed only in females. ST scores in female subjects showed the opposite directions between BPII and UP patients, i.e. BPII patients scored higher and UP patients scored lower in ST compared to controls. The comparison of ST scores in female subjects between the UP patients and controls nearly reached the Bonferroni-corrected significance of $p<0.017$, and the comparisons of BPII patients with control subjects and with UP patients remained significant after Bonferroni correction.

The HDRS scores of UP patients were significantly correlated positively with P in female patients ($rho=0.327$, $p<0.05$) and negatively with SD in male patients ($rho=-0.407$, $p<0.01$). The HDRS in male BPII patient group was significantly correlated positively with C score ($rho=0.497$, $p<0.05$). No other significant correlations were found between TCI and HDRS scores.

Results of the stepwise logistic regression analysis are shown in Table 3. The Nagelkerke R^2 values show that 8.7%, 40.3%, and 24.1% of the variance are explained by the models for males, females, and both genders combined, respectively. The total AUC was significantly greater than 0.5 in models for females and for both genders combined but not for the model for males. These results indicate that the logistic regression model for female patients and for both genders combined appropriately fit the data while the model for male patients does not accurately predict BPII and UP. The following prediction model for female patients was derived:

$$Predicted\ Probability = 1/\{1 + \exp(-5.8143 + 0.129601 \times (NS\ score) + 0.20554 \times (ST\ score))\}$$

At the optimal cut-off point of 0.782 determined by the Youden index, the sensitivity and the specificity of differentiating BPII from UP were 89% and 73%, respectively.

4. Discussion

The main findings of the present study could be summarized as follows. Higher HA, lower SD, and lower C scores were observed in both BPII and UP patients when compared with controls. In females, ST scores significantly

Table 1
Demographic and clinical characteristics.

	Male				Female			
	Controls (n=153)	BPII (n=18)	UP (n=45)	Statistical difference	Controls (n=153)	BPII (n=18)	UP (n=45)	Statistical difference
Demographics								
Age, years: mean (S.D.)	35.6 (12.0)	36.1 (8.4)	34.5 (10.8)	F=0.20, p=0.82	37.3 (9.9)	36.5 (13.6)	39.0 (12.3)	F=0.52, p=0.60
Education, years: mean (S.D.)	16.7 (2.9)	16.1 (2.5)	15.5 (2.4)	F=3.5, p=0.032	15.0 (1.8)	14.7 (2.6)	14.5 (2.1)	F=1.6, p=0.21
Clinical features								
Age at onset, years: mean (S.D.)	–	28.5 (8.2)	28.1 (7.1)	t=0.19, p=0.85	–	28.0 (11.7)	30.5 (13.2)	t=0.70, p=0.49
HDRS score: mean (S.D.)	–	15.4 (4.7)	15.8 (5.9)	t=0.20, p=0.84	–	16.6 (5.4)	16.2 (5.8)	t=0.25, p=0.80

BPII: patients with bipolar disorder, UP: patients with unipolar major depressive disorder, S.D.: standard deviation, HDRS: Hamilton Depression Rating Scale.

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Table 2
Comparisons of TCI scores across diagnostic groups.

TCI dimension	Number of items	Gender	Mean score (S.D.)			Kruskal–Wallis test p values	Mann–Whitney test (uncorrected P values)		
			Ctrl (n=153)	BPII (n=18)	UP (n=45)		BPII vs Ctrl	UP vs Ctrl	BPII vs UP
NS	40	Male	20.8 (4.5)	19.5 (5.0)	17.7 (4.3)	<0.001	n.s.	<0.0005	n.s.
		Female	21.0 (4.5)	22.4 (6.3)	17.2 (5.0)	<0.0001	n.s.	<0.0001	0.007
HA	35	Male	17.8 (6.3)	25.4 (6.0)	28.1 (4.0)	<0.0001	<0.0001	<0.0001	n.s.
		Female	18.8 (6.0)	26.6 (4.2)	27.6 (4.9)	<0.0001	<0.0001	<0.0001	n.s.
RD	24	Male	14.7 (3.8)	14.0 (2.6)	14.5 (3.3)	n.s.	n.s.	n.s.	n.s.
		Female	15.8 (3.3)	16.6 (3.2)	15.2 (3.2)	n.s.	n.s.	n.s.	n.s.
P	8	Male	4.8 (1.8)	4.9 (1.7)	4.7 (1.8)	n.s.	n.s.	n.s.	n.s.
		Female	4.1 (1.8)	5.6 (1.7)	5.2 (1.9)	<0.0001	0.001	<0.0005	n
SD	44	Male	28.3 (6.5)	18.7 (8.6)	18.8 (7.2)	<0.0001	<0.0001	<0.0001	n.s.
		Female	28.8 (6.7)	17.3 (7.1)	20.2 (7.6)	<0.0001	<0.0001	<0.0001	n.s.
C	42	Male	28.2 (5.6)	24.4 (6.3)	24.3 (5.7)	<0.0001	0.016	<0.0001	n.s.
		Female	28.9 (4.7)	24.3 (7.5)	26.0 (6.3)	0.002	0.011	0.005	n.s.
ST	42	Male	10.2 (5.0)	11.4 (6.3)	8.7 (4.1)	n.s.	n.s.	n.s.	n.s.
		Female	11.2 (5.6)	14.9 (5.8)	9.1 (4.4)	0.002	0.009	0.046	<0.0005

Ctrl: control subjects, BPII: patients with bipolar II disorder, UP: patients with unipolar major depressive disorder, S.D.: standard deviation, NS: novelty seeking, HA: harm avoidance, RD: reward dependence, P: persistence, SD: self-directedness, C: cooperativeness, ST: self-transcendence.

differed between BPII and UP patients, with higher scores in BPII patients and lower scores in UP patients compared to controls. Patients with UP showed lower NS scores compared to controls in both genders and also to BP patients in females. BPII in depressed females could be predicted using the NS and ST scores.

Consistent with our results, several previous studies have shown higher scores on HA and lower scores on SD and C in patients with UP (Farmer et al., 2003; Hansenne et al., 1999) or in those with BP (Engstrom et al., 2004; Evans et al., 2005) compared to healthy controls. Higher NS (Evans et al., 2005; Nowakowska et al., 2005) and ST (Evans et al., 2005; Loftus et al., 2008; Nowakowska et al., 2005) have also been reported in BP patients compared to controls, though most studies comparing UP patients and controls have shown no significant difference in these two dimensions (Celikel et al., 2009; Evans et al., 2005; Farmer et al., 2003; Hansenne et al., 1999; Kimura et al., 2000; Marijnissen et al., 2002; Nowakowska et al., 2005; Smith et al., 2005). Although the comparison between BPII and UP patients showed similar trends in both genders (i.e., higher NS and ST in BPII), statistical significance between these two disorders was reached only in females. This suggests that, despite the similar tendency in both genders, the differences between diagnostic groups in TCI profiles are more evident in women than in men.

The mood state affects how the subjects describe their personality. Therefore, most previous studies on mood

Table 3
Stepwise logistic regression analyses in patients with BPII and those with UP.

Step and variable	Stepwise analysis							ROC	
	Beta	S.E.	Wald	p value	OR	95% CI	Nagelkerke R^2	AUC	95% CI
Male subjects									
Step 1									
HA	−0.12	0.06	3.8	0.05	0.89	0.79–1.00	0.09	0.61	0.45–0.78
Constant	2.18	1.60	1.8	0.18					
Female subjects									
Step 1									
ST	0.24	0.07	11.1	0.0009	1.27	1.10–1.45	0.32		
Constant	−3.70	0.93	15.7	<0.0001					
Step 2									
NS	0.13	0.06	4.4	0.04	1.14	1.01–1.29	0.40	0.83	0.72–0.95
ST	0.20	0.07	7.8	0.005	1.23	1.06–1.42			
Constant	−5.81	1.49	15.3	<0.0001					
All subjects									
Step 1									
ST	0.16	0.04	14.8	0.0001	1.17	1.09–1.28	0.19		
Constant	−2.70	0.53	26.0	<0.0001					
Step 2									
NS	0.10	0.04	5.3	0.02	1.11	1.02–1.20	0.24	0.74	0.64–0.83
ST	0.14	0.05	9.8	0.002	1.15	1.05–1.27			
Constant	−4.39	0.95	21.3	<0.0001					

S.E.: standard error, Wald: Wald statistic, OR: odds ratio, ROC: receiver-operating characteristic, AUC: area under the curve, CI: confidence interval, NS: novelty seeking, HA: harm avoidance, ST: self-transcendence.

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disorders assessed the personality in euthymic period. However, in order to be used as an aid for differentiating unipolar and bipolar depression in a real world clinical setting, it is required to evaluate TCI scores during depressed period. It has been reported that depressed individuals accurately portray their vulnerability to stress, their joylessness, and their lack of motivation, and that depression-caused changes in the assessed personality trait may reflect their current condition of the individual (Costa et al., 2005). Previous studies reported that severity of depression positively correlates with HA and negatively with SD scores (Farmer et al., 2003; Hansenne et al., 1999; Naito et al., 2000; Richter et al., 2000; Spittlehouse et al., 2010). In our study, however, correlation coefficients of HA and SD scores with HDRS scores did not reach statistical significance except for SD in male UP patients. This discrepancy might be due in part to the fact that we did not include patients with a HDRS score of 7 or less.

The fact that TCI scores are influenced by the severity of depression complicates the interpretation of the findings. However, the prediction model of BPII for female depressed patients in the present study is unlikely to be greatly biased by the severity of depression for several reasons. First, the mean HDRS scores were similar in BPII and UP patients. Secondly, HA and SD, which are previously reported to be influenced by depression severity, were not included in the prediction model for females. Thirdly, the correlation coefficients relating HDRS scores to each TCI score did not significantly differ between female patients with BPII and UP.

The present study is the first to use personality profiles to create a logistic regression model to predict BPII in depressed patients. Previously, Perlis, et al. (Perlis et al., 2006) made a logistic regression prediction model accurately distinguishing BP and UP by including age at onset, number of previous depressive episodes, family history, Montgomery Åsberg Depression Rating Scale (MADRS) scores, and Hamilton Anxiety Scale scores. Their model predicted bipolarity in depressed patients with a sensitivity of 69.0% and a specificity of 94.9%, with the total area under the ROC curve of 0.914. Combining their model with the present one may result in a more accurate prediction model with a wide clinical application.

A major strength of this study was that patients with BPII and UP were both in depressed state with similar severity of depressive symptoms. To our knowledge, this study is the first to compare the TCI score profiles in BPII and UP patients during depressed states. Knowing the differences in TCI profiles in their depressed states could help clinicians to predict bipolarity in depressed patients.

There are several limitations to this study. First, the cross-sectional design did not allow any definitive conclusions as to whether the TCI score profiles of the BPII and UP patients were premorbid or the results of illness onset. Whether the TCI profiles observed here can be generalized to recovered patients needs further investigation. Some UP subjects in this study may go on to experience a manic/hypomanic episode and be rediagnosed as BP, and thus follow-ups are necessary for accurate diagnosis. Secondly, the subjects were recruited through methods such as advertisements and notices, and therefore sampling biases may exist. Thirdly, bipolar patients in our study were limited to BPII. Larger studies are needed to compare the TCI scores between different subtypes of BP or UP. Fourthly, as the BPII and UP patients were limited to those receiving outpatient treatments, our subjects might have been overrepresented by milder forms of illness.

In conclusion, we assessed personality profiles in patients with BPII and UP during depressed period and confirmed that both UP and BPII patients have characteristic personality profiles in common: higher HA, lower SD, and lower C scores assessed with TCI when compared to controls. However, BPII and UP patients differ in some personality profiles, i.e., higher NS and ST in BPII than in UP patients particularly in female patients. Logistic regression analyses showed that BPII and UP could be predicted based on NS and ST scores in female patients. On the other hand, TCI scores were not very helpful for predicting BPII and UP in male patients. Our findings suggest that assessment of personality profiles using TCI in depressed female patients may serve as a useful tool to conveniently differentiate UP and BPII.

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Conflict of interest

The authors declare no conflicts of interest.

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Resequencing and Association Analysis of the *KALRN* and *EPHB1* Genes And Their Contribution to Schizophrenia Susceptibility

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Background: **Our genome-wide association study of schizophrenia found association signals at the Kalirin gene (*KALRN*) and EPH receptor B1 gene (*EPHB1*) in a Japanese population. The importance of these synaptogenic pathway genes in schizophrenia is gaining independent supports. Although there has been growing interest in rare (<1%) missense mutations as potential contributors to the unexplained heritability of schizophrenia, there are no population-based studies targeting rare (<1%) coding mutations with a larger effect size (eg, OR >1.5) in *KALRN* or *EPHB1*. *Methods and Results:*** **The present study design consisted of 3 phases. At the discovery phase, we conducted resequencing analyses for all exon regions of *KALRN* and *EPHB1* using a DNA microarray–based method. Seventeen rare (<1%) missense mutations were discovered in the first sample set (320 schizophrenic patients). After the prioritization phase based on frequencies in the second sample set (729 cases and 562 controls), we performed association analyses for each selected mutation using the third sample set (1511 cases and 1517 controls), along with a combined association analysis across all selected mutations. In *KALRN*, we detected a significant association between schizophrenia and P2255T (OR = 2.09, corrected *P* = .048, 1 tailed); this was supported in the combined association analysis (OR = 2.07, corrected *P* = .006, 1 tailed). We found no evidence of association of *EPHB1* with schizophrenia. *In silico* analysis indicated the functional relevance of these rare missense mutations.** ***Conclusion:*** **We provide evidence that multiple rare (<1%) missense mutations in *KALRN* may be genetic risk factors for schizophrenia.**

Key words: synaptogenic pathway/rare missense mutations/GWAS/Japanese population

Introduction

Schizophrenia is a genetically heterogeneous disorder with heritability estimated at up to 80%.[1] According to a recent simulation based on genome-wide association study (GWAS) datasets, a highly polygenic model involving a number of common variants of very small effect may explain more than one-third of the total variation in risk of schizophrenia.[2] On the other hand, interest has been growing in rare variants as potential contributors to the unexplained heritability of schizophrenia.[3] This is partly triggered by recent studies establishing an important role for rare genomic copy number variants (CNVs) in the etiology of schizophrenia.[4] Another potential genetic variation to explain the remaining heritability is rare missense mutations. Kryukov et al[5] reported that ~20% of new (de novo) missense mutations in humans result in a loss of function, whereas ~53% have mildly deleterious effects and ~27% are effectively neutral with respect to phenotype by a combined analysis of mutations causing human Mendelian diseases, mutations driving human-chimpanzee sequence divergence, and systematic data on human genetic variation. Their results were supported by an independent study.[6] Because the pressure of purifying selection acting on the mildly deleterious mutations is weak, their cumulative high frequency in the human population is being maintained

by "mutation-selection balance." This provides support to a speculation that the accumulation of mildly deleterious missense mutations in individual human genomes can be a genetic basis for complex diseases.[5] The importance of rare missense mutations in schizophrenia is demonstrated by a study of the *ABCA13* gene in which multiple rare (<1%) coding variants were associated with schizophrenia.[7]

We recently performed a GWAS for schizophrenia in a Japanese population.[8] Although single locus analysis did not reveal genome-wide support for any locus, a shared polygenic risk of schizophrenia between the Japanese and the Caucasian samples was confirmed. In our GWAS, association signals were detected at the regions of the Kalirin gene (*KALRN*) on 3q21.2 and the EPH receptor B1 gene (*EPHB1*) on 3q21-q23, both of which are in the same synaptogenic pathway[9] (supplementary figure S1). Associations of each gene with schizophrenia have recently received support from independent GWASs in different populations.[10,11] Furthermore, a rare de novo CNV overlapping with the *EPHB1* gene locus was detected in a patient with schizophrenia.[12]

KALRN is a large neuronal dual Rho guanine nucleotide exchange factor (GEF) that activates small guanosine triphosphate–binding proteins of the Rho family, including Rac1.[13] This activation enables KALRN to regulate neurite initiation, axonal growth, dendritic morphogenesis, and spine morphogenesis. Consistent with its biological function, KALRN is a key factor responsible for reduced densities of dendritic spines on pyramidal neurons in the dorsolateral prefrontal cortex (DLPFC)[14] observed in postmortem brains from schizophrenic patients. The messenger RNA expression level of *KALRN* is significantly reduced in DLPFC of patients with schizophrenia and strongly correlated with spine density.[15] In addition, *KALRN*-knockout mice not only exhibit spine loss and reduced glutamatergic transmission in the frontal cortex but also schizophrenia-like phenotypes including robust deficits in working memory, sociability, prepulse inhibition, and locomotor hyperactivity reversible by clozapine, an atypical antipsychotic.[16] These synaptic and behavioral dysfunctions are apparent during young adulthood in mice (12 weeks old), which coincides with the onset of schizophrenia in patients. Notably, Disrupted-in-Schizophrenia 1, a prominent schizophrenia risk factor, was shown to be involved in the maintenance of spine morphology and function by regulating access of KALRN to Rac1.[17] *EPHB1* belongs to a receptor tyrosine kinase family and controls multiple aspects of neuronal development, including synapse formation and maturation, as well as synaptic structural and functional plasticity. In neurons, activation of EphB receptors by its ligand B-type ephrins induces the rapid formation and enlargement of dendritic spines, as well as rapid synapse maturation. One of the downstream effectors of ephrinB/EphB signaling is KALRN. In young hippocampal neurons, KALRN is reported to play an important role in the maturation of synapses induced by trans-synaptic ephrinB/EphB signaling.[18]

According to the above-mentioned study,[5] most missense mutations with a frequency of <1% are mildly deleterious, indicating that a low frequency of missense mutation per se can serve as a strong predictor of a deleterious effect of variants. Therefore, the working hypothesis of the present study is that rare (<1%) missense or nonsense mutations with a larger effect size (eg, OR >1.5) in *KALRN* and *EPHB1* may be genetic risk factors for schizophrenia. Recently, a DNA microarray–based resequencing method has been developed to enable accurate and rapid resequencing analysis of candidate genes.[19] Using this system, we conducted resequencing analyses for all exon regions of *KALRN* and *EPHB1* in 320 schizophrenic patients and found evidence that rare (<1%) missense mutations in *KALRN* are significantly associated with schizophrenia using the 3-phase study design.

Methods and Materials

Subjects

Three sample sets were used in this study. The first sample set, comprising 320 schizophrenic patients (mean age, 54.2 ± 14.1 years, 49.1% male), with long-term hospitalization for severe symptoms, was used to search for rare missense or nonsense mutations. We used the first sample set for mutation screenings because patients with extreme phenotypes (severe symptoms) can be expected to carry more deleterious mutations.[20] The second sample set, including 729 cases (45.4 ± 15.1 years, 52.2% male) and 562 controls (44.0 ± 14.4 years, 49.8% male), was used to prioritize detected functional variants for subsequent association analyses. The third sample set, including 1511 cases (45.9 ± 14.0 years, 49.6% male) and 1517 controls (46.0 ± 14.6 years, 49.6% male), was used for association analyses. Age and gender were matched in the second and third sample sets, respectively. All patients were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria, and controls were evaluated using unstructured interviews to exclude individuals with history of mental disorders. Detailed information regarding diagnostic procedures is available elsewhere.[21] All subjects were ethnically Japanese and provided written informed consent. This study was approved by the ethics committees at each participating university.

Array Design for Resequencing Analyses

We used the Affymetrix GeneChip CustomSeq Resequencing Array (Affymetrix, Santa Clara, California) for exon sequencing in the first sample set. These arrays rely on allele-specific hybridization for determining DNA