ている。臨床データベースを作成することにより、クロザピン療法非反応群という「真の」治療抵抗性統合失調症の治療戦略の基礎資料を得ることができる。

本研究の目的は、クロザピンによる治療患者のデータベースを構築し、治療反応性（効果、副作用）と関連する遺伝子、遺伝子発現マーカーを同定することを目的とする。それによって、効率的で薬害の少ないオーダーメイド医療が必現することが期待される。

B．研究方法

予定している対象は、国立精神・神経医療研究センター病院にて加療中で、年齢 15 歳～80 歳の治療抵抗性統合失調症患者約 30 名で、クロザピン投与を予定しており、本研究への参加に同意を得られた者である。主治医が治療上不適切であると判断される患者は、対象から除外する。初年度の研究にあたっては、既にクロザピン投与中の患者も対象とする。統合失調症の発症年齢は思春期後半以降であり、特に初発の未成年例では長年の抗精神病薬による影響を受けていない点で、研究上、特に重要性が高いため対象に含む。

血液検体は連結可能匿名化しトランスレーショナル・メディカル・センター（TMC）にて DNA, RNA を抽出し、管理・保存を行う。匿名化された検体の遺伝子解析は、神経研究所疾病研究第三部で行う。また、上述の目的を果たすためには、より大規模な共同研究が必要である。そこで、全国約 30 か所の研究分担、協力施設で採取され、各施設で連結可能匿名化された総計約 1000 例の血液についても同様に TMC で受入れ、神経研究所疾病研究第三部で遺伝子の解析を行う予定である。

解析の方法：症状の評価尺度として、Positive and Negative Syndrome Scale(PANSS)、神経認知の指標として、Brief Assessment of Cognition in Schizophrenia (BACS)日本語版、Quality of lifeの指標として、Global Assessment of Function（GAF）及び Quality of Life Scale (QLS)日本語版、副作用の指標としてUKU副作用評価尺度を用い評価を行う。評価の時期はクロザピン開始前、開始後4週を基本とし、副作用が生じた場合、症状に大きな変化を認めた場合等にも行う。血液は、初回に15ml、それ以降（4週間後、副作用・症状変化時）は10ml程度採取する。副作用、合併症、症状悪化、その他の理由により研究継続が困難になった場合には、速やかに研究を中断する。

遺伝子の解析：センター病院および、各施設より当センターTMC に送られてき

た匿名化済みの検体より DNA を抽出し遺伝子多型を解析する。解析する遺伝子はクロザピンの結合するドーパミンD3受容体、セロトニン 5HT2 受容体、ムスカリン作動性レセプター、α1-アドレナリンレセプター、ヒスタミン-H2 レセプターなどのほか、代謝する酵素遺伝子に関する多型、及び遺伝子チップを用いたゲノムワイド解析も行う予定である。

（倫理面への配慮）

本研究の主要部分は、精神疾患患者、健常対照群を対象とした遺伝子解析研究や臨床研究である。遺伝子解析研究では、試料提供者およびその血縁者の遺伝的素因を研究するため、その取り扱いによっては、さまざまな倫理的、社会的問題を招く可能性がある。したがって、文部科学省、厚生労働省、経済産業省による「ヒトゲノム・遺伝子解析研究に関する倫理指針」を遵守した研究計画書を作成し、倫理審査委員会において承認を受けた上で研究を行う。試料提供者への説明とインフォームド・コンセント、個人情報の厳重な管理（匿名化）などを徹底する。

C．D．研究結果、考察

今年度は上記の研究を遂行する上で必要な倫理申請を国立精神・神経医療研究センター倫理委員会に提出した。別紙資料のような計画書、説明文書、同意書を作成して、現在審理中である。

E．結論

今年度は、2 回の班会議を通じて、プロトコールについて話し合われ、倫理申請を行い、23 年度からゲノム DNA 収集が開始されることが見込まれる。

F．健康危険情報

なし。

G．研究発表

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H．知的財産権の出願・登録状況

なし

Ⅲ．　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ．　研究成果の刊行物・別刷

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Quality of life and cognitive dysfunction in people with schizophrenia

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ABSTRACT

The main purpose of the present study was to examine the relationship between quality of life (QOL) and cognitive dysfunction in schizophrenia. Subjects were 61 stabilized outpatients. Quality of life and cognitive function were assessed using the Quality of Life Scale (QLS) and the Brief Assessment of Cognition in Schizophrenia (BACS), respectively. Clinical symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS). The BACS composite score and the BACS Verbal memory score were positively correlated with the QLS total score and two subscales. The BACS Attention and speed of information processing score had positive correlation with the QLS total and all the subscales scores. The PANSS Positive and Negative syndrome scores also had significant correlations with the QLS total score and all of the subscales. In addition, the CDSS score was negatively correlated with the QLS total score and some of the subscales. Stepwise regression analysis showed that the BACS Attention and speed of information processing score was an independent predictor of the QLS total score but it was less associated with the QLS than the PANSS Negative syndrome score and the CDSS score. The results suggest that negative and depressive symptoms are important factors on patients' QOL and also support the view that cognitive performance provides a determinant of QOL in patients with schizophrenia.

1. Introduction

Quality of life (QOL) is thought to be one of the key outcome variables in the treatment of schizophrenia (Matsui et al., 2008), and the importance of evaluating it has been increasing in patient care and clinical research. Previous studies have revealed that several clinical factors such as negative and positive symptoms, depressive symptoms, and extrapyramidal adverse effect are associated with lowered QOL (Browne et al., 1996; Dickerson et al., 1998; Smith et al., 1999; Norman et al., 2000; Fitzgerald et al., 2001; Rocca et al., 2005; Strejilevich et al., 2005; Bozikas et al., 2006; Hofer et al., 2006; Tomotake et al., 2006; Aki et al., 2008; Yamauchi et al., 2008). Moreover,Yamauchi et al. (2008) reported that QOL correlated with dose of antipsychotics, and Xiang et al. (2007) and Browne et al. (1996) demonstrated that number of hospitalizations and duration of illness were associated with QOL.

Recently, cognitive dysfunction has been paid much more attention because they may lead to poor social functioning. Cognitive dysfunction is thought to be a core feature of schizophrenia (Kraus and Keefe, 2007), and it has been reported that cognitive functions of schizophrenia patients are of the order of one to two standard deviations below the mean of healthy controls in several cognitive dimensions, particularly memory, attention, verbal fluency, and executive function (Heinrichs

Abbreviations: BACS, the Brief Assessment of Cognition in Schizophrenia; CDSS, the Calgary Depression Scale for Schizophrenia; DIEPSS, the Drug-Induced Extrapyramidal Symptoms Scale; PANSS, the Positive and Negative Syndrome Scale; QLS, the Quality of Life Scale; QOL, quality of life.

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and Zakzanis, 1998; Gold, 2004; Kraus and Keefe, 2007; Savilla et al., 2008).

Previous research groups have studied the relationship between QOL and cognitive function in people with schizophrenia, and reported the significant correlations between QOL and some domains of cognitive function such as verbal memory, vocabulary, fluency performance, attention, social knowledge, and executive function (Dickerson et al., 1998; Addington and Addington, 2000; Bozikas et al., 2006; Ritsner, 2007; Matsui et al., 2008; Savilla et al., 2008). Although, considering the results of previous studies, it is clear that cognitive dysfunctions and some clinical symptoms are significantly correlated with lowered QOL in schizophrenia patients, it seems to remain unclear how much impact these factors have on patients' QOL. Some studies demonstrated that cognitive dysfunction has a greater influence on patients' QOL than do positive symptoms (Breier et al., 1991; Green, 1996; Ho et al., 1998). On the other hand, some reported that neuropsychological function had a little impact on patients' QOL in the presence of some clinical symptoms (Wegener et al., 2005; Matsui et al., 2008). The discrepancy among these studies might have been caused by differences of sample population, sample size, cognitive tests, and QOL scales (Breier et al., 1991; Green, 1996; Wegener et al., 2005; Matsui et al., 2008).

The purpose of the present study was to elucidate clinical determinants of QOL in schizophrenia patients with a special reference to cognitive dysfunction. Using a schizophrenia disease-specific QOL measure, we have already studied and reported significant correlations between QOL and negative factor, cognitive factor, and emotional discomfort factor which derived from the Positive and Negative Syndrome Scale (PANSS). But we did not assess cognitive function with a real neuropsychological battery in the study (Yamauchi et al., 2008). Hofer et al. (2007) demonstrated that clinical assessment of cognitive deficits on PANSS is not a viable alternative to neuropsychological testing to obtain information about cognitive functioning in schizophrenia. Therefore, in the present study, we assessed cognitive function using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004; Kaneda et al., 2007) that is a newly developed neuropsychological battery for assessing cognitive function of schizophrenia patient.

2. Methods

2.1. Subjects

Clinical data were collected at Department of Psychiatry, Tokushima University Hospital from 1 October 2007 to 31 March 2009. Treating psychiatrists consecutively asked 77 stabilized outpatients with a DSM-IV diagnosis of schizophrenia to participate in this study every weekday for the first 6 months and a particular day of the week for another 12 months. Subjects were excluded if they presented with any organic central nervous system disorder, epilepsy, mental retardation, severe somatic disorder, drug dependence, or alcohol dependence. Of 77 patients, 62 gave us written informed consent to participate in this study. As one subject did not complete all the assessments, data from 61 were used for analysis. This study was approved by the Ethics Committee of University of Tokushima.

All subjects had been regularly receiving outpatient treatment. The information on patients was obtained from both patients and family members living with them by treating psychiatrists. Their mean age was 40.1 years (SD = 12.2), ranging from 20 to 60 years old. The subjects had never been hospitalized during the previous 6 months, including 13 who had never had inpatient treatment. 45 had followed the same antipsychotic regimen for at least 6 months before recruitment. Although 16 subjects had slight changes in regimen during the previous six months, the 16 were judged as clinically stabilized by the treating psychiatrists.

2.2. Procedure

To assess QOL, we used the Quality of Life Scale (QLS) (Heinrichs et al., 1984, 2001). Cognitive function was evaluated using the BACS. Clinical symptoms were evaluated using the PANSS, the Calgary Depression Scale for Schizophrenia (CDSS), and the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS).

The QLS is a rating scale to assess QOL by means of semistructured interview. The ratings are based upon patients' self-report and observers' judgment about the functioning and life circumstances. This instrument includes four subscales measured by a total of 21 items, and each item is rated from 0 to 6. The four subscales are Interpersonal relations, Instrumental role, Intrapsychic foundation, and Common objects and activities. Higher scores indicate higher levels of QOL. Experienced psychiatrists who have been treating the patients for a long term and understood the patients' living conditions conducted the interviews according to the Evaluation Manual for the QLS (Heinrichs et al., 2001). They got information about the patients from family members and psychiatric social workers when it was necessary.

The BACS has been developed for clinical trials with a brief battery of tests for measuring cognition. It assesses the aspects of cognition that were found to be most impaired and most strongly correlated with outcome in patients with schizophrenia. The domains of cognitive function that are evaluated by the BACS are Verbal memory (List learning), Working memory (Digit sequencing task), Motor speed (Token motor task), Verbal fluency (Category instances and Controlled oral word association test), Attention and speed of information processing (Symbol coding), and Executive function (Tower of London). The BACS is fully portable, and is designed to be easily administered by a variety of testers, including nurses, clinicians, psychiatrists, neurologists, social workers, and other mental staff (Keefe et al., 2004; Kaneda et al., 2007). It was reported that the Japanese version of it was a reliable and practical scale to evaluate cognitive function in schizophrenia (Kaneda et al., 2007). In the present study, we used the Japanese version of the BACS and the BACS data were collected by clinical psychologists who were very experienced and well trained for the use of it.

The PANSS was originally designed as a rating scale that represents Positive, Negative and General psychopathology (Kay et al., 1987, 1991). The score ranges from 30 to 210 for the global score, and higher score indicates a greater level of symptom severity. Some of the authors who were all experienced psychiatrists conducted the interviews according to the Evaluation Manual for the PANSS (Kay et al., 1991).

The CDSS was specifically developed to distinguish depressive symptoms from positive and negative symptoms or antipsychotic-induced side effects. This scale is a 9-item questionnaire (depression, hopelessness, self-deprecation, guilty ideas of reference, pathological guilt, morning depression, early awakening, suicidality, and observed depression), and higher score indicates a greater level of depression. The reliability and validity of the scale have been verified (Addington et al., 1993; Kaneda et al., 2000).

The DIEPSS is composed of eight individual parameters (gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, and dyskinesia) and one global assessment constructed to assess extrapyramidal adverse effects, using 5-point scale that ranges from 0 to 4. Higher score indicates greater level of extrapyramidal adverse effects. In this study, the sum of eight individual parameters was considered the extrapyramidal symptoms score. Some of the authors assessed the drug-induced extrapyramidal symptoms according to the Rater's Manual for the DIEPSS (Inada, 1996).

2.3. Statistical analysis

Spearman rank correlation coefficients were calculated to study the relationship between the QLS and other clinical variables including the BACS scores, the PANSS Positive syndrome score, the

Table 1
Demographic characteristics of subjects (mean ± SD).

N (MW)		61(33/28)
Age (years)		40.1 ± 12.2
Duration of illness (yrs)		15.5 ± 9.3
Number of hospitalization		2.1 ± 2.3
Dose of antipsychotics (mg/day)*		642.3 ± 5011
Type of schizophrenia (n) Paranoid		38
	Residual	13
	Disorganized	5
	Catatonic	4
	Undifferentiated	1
Marital state (n)	Married	6
	Never married	52
	Divorced	2
	Widowed	1
Social state (n) Full time	14	
	Part time	8
	No employment	39
PANSS	Total	61.3 ± 164
	Positive	13.4 ± 4.8
	Negative	18.0 ± 6.6
DIEPSS (Total)		1.6 ± 2.4
	CDSS (total)	3.2 ± 3.1
BACS	Verbal memory	33.6 ± 18.1
	Working memory	17,1 ± 6.4
	Motor speed	66.9 ± 18.5
	Attention and speed of information processing	50.8 ± 12.9
	Verbal fluency	37.3 ± 10.6
	Executive function	14.9 ± 5.3
QLS	Total	62.8
	Interpersonal relations	22.7 ± 12.7
	Instrumental role	10.3 ± 6.9
	Intrapsychic foundations	22.5 ± 9.4
	Common objects and activities	7.4 ± 2.9

* Chlorpromazine equivalent.
PANF, Positive and Negative Syndrome Sale; DIEP, Drug Induced Extrapyramidal Symptoms Scale; CDSS, Calgary Depression Scale for Schizophrenia BACS, Brief Assessment of Cognition in Schizophrenia QLS, Quality of Li Scale.

PANSS Negative syndrome score, the CDSS score, the DIEPSS score, duration of illness, number of hospitalization, and dose of antipsychotics. As several data were non-normal distribution, we used non-parametric test for correlation analysis. Statistical significance was adjusted for multiple comparisons (Bonferroni correction). Then, the QLS total and the subscale scores were chosen as dependent variables. Using the clinical variables that showed significant correlations with each dependent variable, forward stepwise regression analyses were performed to assess which clinical variables were the best predictor of each dependent variable. Statistical analyses were done with the Statistical Package for the Social Sciences, version 14.0 J.

3. Results

Demographic characteristics and means and standard deviations of the clinical indices are presented in Table 1. All subjects were Japanese. 33 were males and 28 females. We used the chlorpromazine conversion chart to determine the dosage of antipsychotic medication (Inagaki and Inada, 2006).

The performance of subjects on each test of the BACS was standardized by creating z-scores whereby the healthy control mean was set to zero and the standard deviation set to one. The control data used to compare the performance of our subjects with that of healthy controls were collected by Kaneda et al. (2008). The mean age of the healthy control subjects ($n = 76$) was 38.3 years (SD = 14.2). Z-score for Verbal memory is −1.68 (SD = 1.28), that for Working memory −1.23 (SD = 1.78), that for Motor speed −1.81 (SD = 1.64), that for Attention and speed of information processing −1.66 (SD = 1.19), that for Verbal fluency −0.82 (SD = 1.11), and that for Executive function −1.20 (SD = 1.95).

3.1. QOL and cognitive function

The correlations between the QLS scores and the BACS scores are shown in Table 2. The BACS composite score, Attention and speed of information processing score, and Verbal memory score showed significant and positive correlations with the QLS total and all or some subscale scores. The individual data points from the correlation between the QLS and the BACS composite score is presented in Fig. 1.

Table 2
Correlation between QLS and BACS and clinical indices.

	QLS				
	Total	Interpersonal relations	Instrumental role	Intrapsychic f oundation	Common objects and activities
BACS					
Verbal memory	0.419**	0.415**	0.311	0.422**	0.295
Working memory	0.281	0.283	0.142	0.290	0.259
Motor speed	0.196	0.175	0.126	0.222	0.228
Attention and speed of information processing	0.51	0.495**	0.372*	0.541**	0.418**
Verbal fluency	0.203	0.200	0.154	0.206	0.170
Executive function	0.168	0.174	0.103	0.131	0.175
Composite score[a]	0.341*	0.346*	0.205	0.341*	0.305
PANSS					
Positive	−0.478**	−0.475**	0.400**	−0.441**	0.394*
Negative	−0.640**	−0.632**	−0.363*	0.685	−0.650
CDSS	−0.381*	0.360*	0.440**	0.342*	−0.249
DIEPSS	−0.317	−0.290	−0.221	−0.346*	−0.463**
Duration of illness	−0.279	−0.294	−0.212	−0.298	−0.300
Number of hospitalization	0.088	0.133	−0.025	0.001	0.027
Dose of antipsychotics	−0.215	−0.192	−0.191	−0.259	−0.227

*P < 005; **P < 0.01. Spearman rank correlations (Bonferroni correction).
BACS, Brief Assessment of Cognition in Schizophrenia. QLS, Quality of Life Scale.

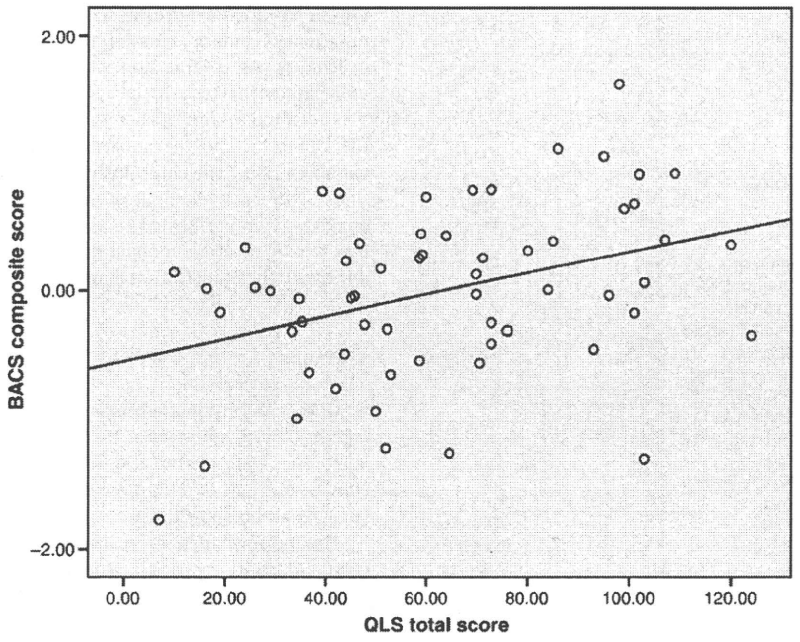

Fig. 1. Relationship between QLS total score and BACS composite score ($r = 0.341$, $p < 0.05$).

3.2. QOL and other clinical variables

The correlations between the QLS scores and clinical variables are shown in Table 2. The PANSS Positive syndrome scale score, the PANSS Negative syndrome scale score, the CDSS score, and the DIEPSS score had significant and negative correlations with the QLS total and all or some subscale score. However, there was no significant correlation between the QLS and duration of illness, number of hospitalization, and dose of antipsychotics. Figs. 2–4 show the individual data points from the correlations between the QLS total score and the PANSS Positive syndrome scale score, the PANSS Negative syndrome scale score, and the CDSS score, respectively.

3.3. Predictors of QOL

Table 3 shows the results of stepwise regression analyses. The QLS total score was significantly predicted by the PANSS Negative syndrome scale score, the CDSS score, and the BACS Attention and speed of information processing score. Interpersonal relations subscale score was significantly predicted by the PANSS Negative

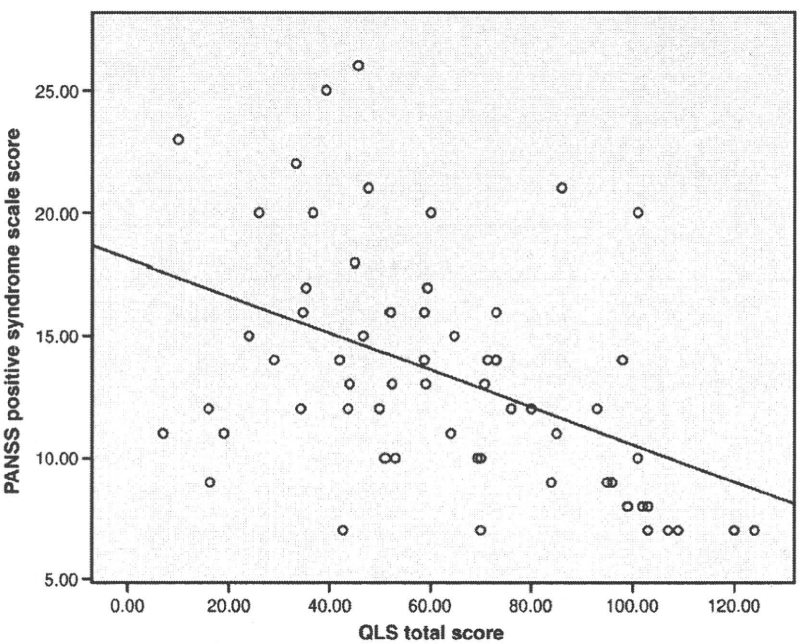

Fig. 2. Relationship between QLS total score and PANSS positive syndrome scale score ($r = -0.478$, $p < 0.01$).

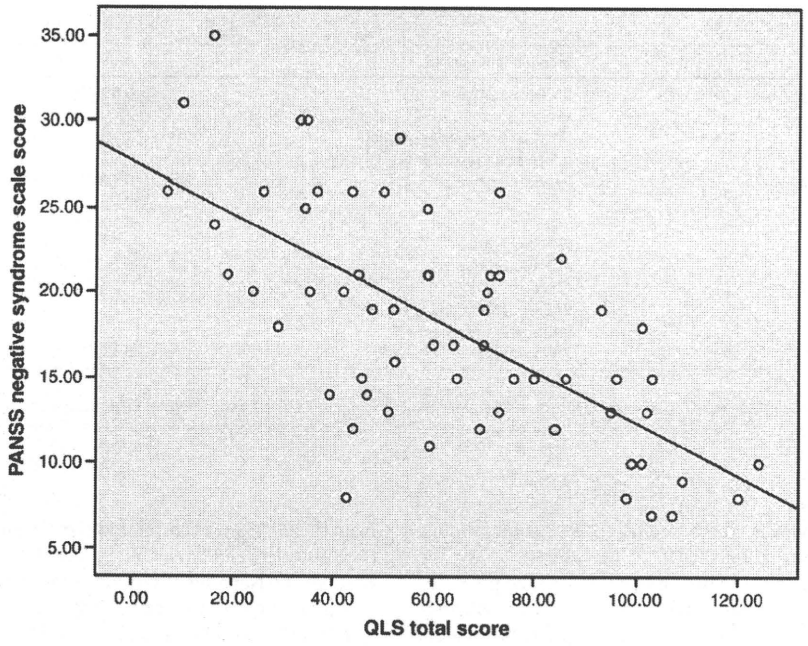

Fig. 3. Relationship between QLS total score and PANSS negative syndrome scale score ($r = -0.640$, $p < 0.01$).

syndrome scale score and the CDSS score. The CDSS score and the PANSS Negative syndrome scale score significantly predicted Instrumental role subscale score. Moreover, the Intrapsychic foundation subscale score was significantly predicted by the PANSS Negative syndrome scale score, the CDSS score, and the BACS Attention and speed of information processing score. The only significant predictor of the Common objects and activities subscale score was the PANSS Negative syndrome scale score.

4. Discussion

As QOL is considered a very important outcome in the treatment of schizophrenia, greater attention has been paid to it in recent years. QOL is generally thought to include life satisfaction, social functioning, daily living activities, and physical health (Aki et al., 2008; Yamauchi et al., 2008). Some studies have demonstrated that QOL has significant correlations with cognitive dysfunctions, psychotic symptoms, and

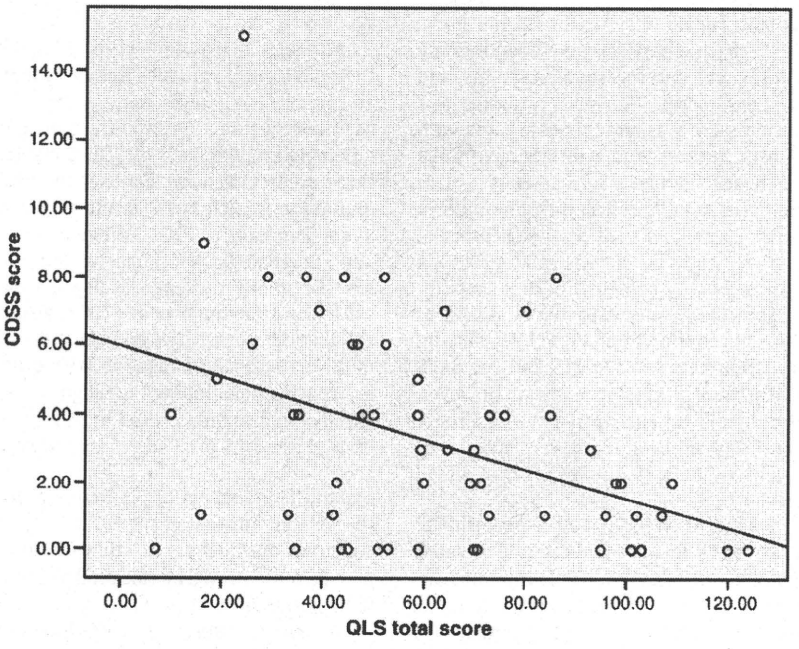

Fig. 4. Relationship between QLS total score and CDSS score ($r = -0.381$, $p < 0.01$).

Table 3
Results of stepwise regression analyses on QLS.

Dependent variable	Independent variable	Adjusted R^2	B
Total	PANSS-negative	0.585***	−0.551***
	CDSS		−0.340***
	BACS-attention and speed of information processing		0.192*
Interpersonal relations	PANSS-negative	0.490***	−0.619***
	CDSS		−0.299**
Instrumental role	CDSS	0.302***	−0.429***
	PANSS-negative		−0.339**
Intrapsychic foundation	PANSS-negative	0.647***	0.625***
	CDSS		−0.304***
	BACS-attention and speed of information processing		0.176*
Common objects and activities	PANSS-negative	0.432***	−0.664***

*P<0.05; **P<0.01; ***p<0.001.
PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; BACS, Brief Assessment of Cognition in Schizophrenia; QLS, Quality of Life Scale. PANSS-negative, The PANSS negative symdrom scal score;BACS-attention and speed of information processing, Attention and speed of information processing score of BACS.

other clinical factors. However, there seems to be no unanimous predictors of schizophrenia patients' QOL. In the present study, we tried to elucidate the predictors and how much impact each predictor has on patients' QOL measured by the QLS. The QLS is schizophrenia disease-specific QOL scale and widely used in schizophrenia research, and it was originally designed to assess deficit symptoms and the dysfunctions related to them outside institutions (Heinrichs et al., 1984).

Cognitive impairments in schizophrenia have been reported repeatedly. Keefe et al. (2006) reported that the BACS composite score was significantly correlated with functional capacity and real-world functional outcome in schizophrenia. In the current study, the performance of subjects on each of the primary measures of the BACS demonstrated about one to two standard deviations below the healthy control mean. The degree of cognitive dysfunctions in the present sample was consistent with that of the previous studies (Keefe et al., 2004; Kaneda et al., 2008).

As for the relationship between QOL and cognitive function, the results of the present study were rather consistent with those of previous researches in terms of that cognitive dysfunction was on the whole related to lowered QOL (George et al., 1996; Bozikas et al., 2006; Savilla et al., 2008; Yamauchi et al., 2008). In the current study, the BACS composite score and Verbal memory score were significantly correlated with the QLS total and Interpersonal relations and Intrapsychic foundation subscales scores. The BACS Attention and speed of information processing score was strongly associated with the QLS total and all the subscale scores. These results have some different points from the previous findings (Bozikas et al., 2006; Savilla et al., 2008). The differences seem to reflect the differences in which types of cognitive tests researchers used and what types of subjects they investigated. In the study by Bozikas et al. (2006), a different neuropsychological test battery consisted of nine tests for the putative neurocognitive domains was used. Savilla et al. (2008) investigated the relationship between the QLS and the BACS, and did not find the significant correlation between the QLS and the BACS Attention and speed of information processing domain. However, their subjects included schizophrenia patients with abuse of alcohol (25.8%) or other substances (29%). Moreover, there were differences of the patient's average ages and psychotic symptoms severity, which might cause the different results.

Regarding the associations between QOL and other clinical variables, our results showed that QOL was significantly correlated with positive, negative, depressive and extrapyramidal symptoms. On the other hand, no significant correlation was found between QOL and duration of illness, number of hospitalization, or dose of antipsychotics. Yamauchi et al. (2008) demonstrated that Negative factor derived from the PANSS was correlated significantly with the QLS total and all the subscales, and Savilla et al. (2008) reported that both the PANSS Positive and Negative symptoms scores were strongly associated with them. Moreover, Rocca et al. (2005) showed that the CDSS score was significantly correlated with the QLS scores. Our results seem to support these previous findings. However, the results may be affected by measurement overlap because the QLS and the PANSS have some similar items. Besides, there is a possibility that some significant correlation might be caused by the fact that some items of the PANSS are not scored simply on symptom severity but on the degree of functional disturbance the symptom causes. For example, score of 4 or more on the item of delusion of the PANSS positive syndrome scale is judged on both the symptom severity and the functional impairment the symptom causes, and score of 3 or more on the item of passive/apathetic social withdrawal of the PANSS negative syndrome scale is judged mainly on the impairment of social functioning. That may partly explain the significant correlation between the QLS and the PANSS. Therefore, in further study, it may be necessary to consider use of other scales such as the Scale for Assessment of Positive Symptoms (Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (Andreasen, 1983) that hardly conflate functioning with symptoms.

Although there were several significant correlations between QOL and clinical variables in the present study, stepwise regression analyses clearly showed that negative and depressive symptoms and cognitive dysfunction in certain of domains were significant and independent predictors of QOL. Considering the beta coefficients of these predictors, it is clear that the negative symptom is the most important predictor of QOL and cognitive dysfunction also provides a determinant of QOL. Wegener et al. (2005) reported that neuropsychological variables were no longer significant predictors for QOL in the presence of psychiatric symptoms. Narvaez et al. (2008) and Yamauchi et al. (2008) also demonstrated that cognitive variable did not predict the QLS scores independently when doing multivariate analysis together with other clinical variables. However, we got a new finding that cognitive dysfunction in attention and speed of information processing domain is an independent predictor of QOL (the QLS total score) in people with schizophrenia. Ritsner (2007) reported a similar result that visual sustained attention was one of the independent predictors of Instrumental role subscale of the QLS but not that of the QLS total score. Our results suggest that cognitive dysfunction in attention and processing speed domain may be most strongly associated with lowered QOL in patients with schizophrenia.

The current study has some limitations. Considering the PANSS scores, our subjects seem to have rather mild psychotic symptoms,

which would cause the possibility that they did not represent the whole patients with schizophrenia. In addition, as the sample size was relatively small, we did not have an opportunity to assess subgroups of patients.

5. Conclusion

We investigated the independent predictors of QOL in people with schizophrenia, and found that not only negative and depressive symptoms but also cognitive dysfunction in attention and speed of information processing domain influenced patients' QOL. Our results support the view that cognitive performance provides a determinant of QOL in patients with schizophrenia. However, cognitive dysfunction had less association with the QLS than negative and depressive symptoms. Therefore, it is also suggested that treatment effort should be mainly paid to negative and depressive symptoms in order to improve patients' QOL.

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Gene expression and association analysis of the epithelial membrane protein 1 gene in major depressive disorder in the Japanese population

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ABSTRACT

The epithelial membrane protein 1 (*EMP1*) plays a role in neuronal differentiation and neurite outgrowth, which are involved in the pathogenesis of major depressive disorder (MDD). We sought to determine whether the *EMP1* gene is implicated in MDD. We determined the mRNA expression levels of the *EMP1* gene in peripheral-blood leukocytes of patients and control subjects ($n = 27$ each). Next, we performed case–control association analyses (MDD, $n = 182$; controls, $n = 350$) in the Japanese population. The level of expression of the *EMP1* mRNA was significantly lower in medication-free patients compared with control subjects ($P < 0.001$). The association analysis revealed an absence of association between the polymorphisms studied and MDD, whereas a gender-specific association was observed between male controls and male patients for marker rs7315725 (permutation $P = 0.039$). Our results suggest that the *EMP1* gene may be implicated in the pathophysiology of MDD in the Japanese population.

The lifetime population prevalence of major depressive disorder (MDD) is 5–10%. The heritability of MDD, as assessed based on twin studies, is 40–50%, and adoption studies provide some support for a role for genetic factors in this disease [20]. Recently, it has been proposed that a deficit in neurogenesis is involved in MDD and that the mechanism of action of antidepressant medications may involve the promotion of neurogenesis [10]. The epithelial membrane protein 1 (*EMP1*) is a tetraspan transmembrane protein that plays a role in cell–cell adhesion and in interactions with the extracellular membrane [6], and is a biomarker of tumor resistance [15]. Earlier research found that *EMP1* is expressed in the immature mouse brain, but is lost in adult animals [32]. In human tissues, the *EMP1* mRNA was not detected in the adult brain or peripheral leukocytes, as assessed by Northern blot analysis [8]. However, recent reports using microarray or quantitative reverse transcriptase polymerase chain reaction (RT-PCR) analyses revealed that the *EMP1* gene is expressed in the adult brain [3,21] and peripheral leukocytes [25]. Thus, *EMP1* may be an important molecule for neuronal migration and neurite outgrowth [21,32].

Previously, we reported an association between the phosphodiesterase 4B (*PDE4B*) gene and MDD [24]. *PDE4B* plays an important role in the regulation of cyclic adenosine monophosphate (cAMP) signaling, which is a second messenger that is implicated in learning, memory, and mood [5,9,17]. Millar et al. [23] reported that disrupted-in-schizophrenia 1 (DISC1), which is an important genetic risk factor for MDD [14], interacts with *PDE4B* and that elevation of cellular cAMP levels leads to dissociation of *PDE4B* from DISC1 and an increase in *PDE4B* activity [23]. A recent report showed that the level of expression of the *PDE4B* mRNA was significantly elevated in the monocytes of bipolar depression patients compared with healthy controls and correlated with the level of the *EMP1* mRNA [25].

Based on the above-described findings, the *EMP1* gene appears to be a good candidate for a genetic study of MDD. To our knowledge, however, there are no reports on the association between the *EMP1* gene and MDD.

In this study, we determined the mRNA expression levels of the *EMP1* gene in the peripheral blood leukocytes of patients with MDD and in control subjects ($n = 27$ each). Next, we performed case–control association analyses (MDD, $n = 182$; controls, $n = 350$) in the Japanese population to determine whether the *EMP1* gene was implicated in MDD.

For the gene expression study, we enrolled 27 medication-free MDD patients (eight males (mean age, 40.9 ± 11.5 years) and 19 females (mean age, 42.4 ± 15.2 years)) from four psychiatric hospitals in the Tokushima Prefecture of Japan. Twenty-four patients were in their first depressive episode and were drug-naïve, and another three patients were having a recurrent episode

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and had been without antidepressant treatment for at least two months. The diagnosis of MDD was established according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [1] by at least two experienced psychiatrists. We excluded patients who had organic disorders or alcohol or substance abuse. Blood samples were obtained from MDD patients before and 8 weeks after antidepressant treatment. Physicians were allowed to choose the antidepressants and to assign doses of medication according to clinical assessment. Clinical symptoms were evaluated using the 17-item Hamilton depressive rating scale (HAM-D) at the time blood samples were collected. Twenty-seven sex- and age-matched healthy controls were selected from a pool of volunteers (eight males (mean age, 41.9 ± 12.7 years) and 19 females (mean age, 40.2 ± 11.4 years)) who had no history of either psychiatric or serious somatic disease, and were not taking any medication. Clinical assessment was performed by an experienced psychiatrist before blood collection. Almost all samples are collected in the morning. Besides, we found no apparent fluctuation in the expression levels in blood samples from the same healthy person taken at 9:00, 14:00 and 19:00 in a day.

Total RNA was extracted from the peripheral leukocytes of whole blood samples using the PAXgene Blood RNA kit (Qiagen, Tokyo, Japan) according to the protocol recommended by the manufacturer. Two micrograms of total RNA was used for cDNA synthesis using random (N6) primers and Quantiscript Reverse Transcriptase (Qiagen, Tokyo, Japan) after assessing RNA quality and quantity using NanoDrop (NanoDrop Technologies, Wilmington, DE). Real-time quantitative RT-PCR analysis was performed on an ABI 7500 Fast Real Time PCR System (Applied Biosystems, Foster City, CA). Taqman primer/probes for the *EMP1* (Hs00608055_m1) gene were purchased from Applied Biosystems. Two housekeeping genes were used for normalization (beta-actin gene (ACTB) and glyceraldehyde-3-phosphate dehydrogenase gene (GAPDH)). All reactions were performed in triplicate. A validation experiment using the comparative threshold cycle (C_t) method was performed as described previously [24]. The amounts of *EMP1* mRNA were normalized to the endogenous reference and were expressed relative to the calibrator as $2^{-\Delta\Delta C_t}$ (comparative C_t method).

For the genetic association study, we enrolled 182 MDD patients (76 males, median age, 46.5 years (interquartile range, 17.5 years); 106 females, median age, 44.5 years (interquartile range, 29.3 years)) from four psychiatric hospitals in the neighboring area of the Tokushima Prefecture and from the Ehime University Hospital in Japan. We also selected 350 controls from a pool of volunteers (147 males, median age, 47 years (interquartile range, 16 years); 203 females, median age, 45 years (interquartile range, 19 years)). All subjects were genotyped. The diagnosis of MDD was established according to DSM-IV criteria [1] by at least two experienced psychiatrists. Control subjects were healthy volunteers who had no current or past contact with psychiatric services.

Genotyping was performed using commercially available TaqMan probes for the *EMP1* gene on an ABI 7500 Fast Real Time PCR System, according to the protocol recommended by the manufacturer. We selected four single-nucleotide polymorphic (SNP) markers at an average density of 5 kb across the *EMP1* gene, based on information from the International HapMap Project (Fig. 2). The reference SNP ID numbers and the location of these four SNPs were as follows: SNP1 (rs7315725, 5′ untranslated region (UTR)), SNP2 (rs4763327, intron 1), SNP3 (rs2291060, intron 2), and SNP4 (rs8885, 3′ UTR).

All subjects were biologically unrelated Japanese. All subjects signed written informed consent, which was approved by the Ethical Committee of the University of Tokushima or the Graduate School of Ehime University.

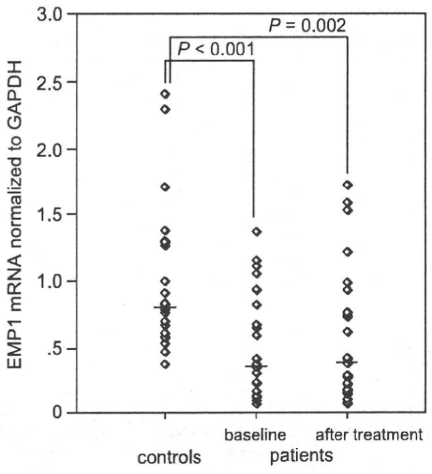

Fig. 1. Epithelial membrane protein 1 (*EMP1*) mRNA expression levels. Bars indicate the median of the values for each subject ($n = 27$). The *EMP1* mRNA levels of patients were significantly lower than those of controls, regardless of the absence (controls, 0.81 (0.70); patients at baseline, 0.36 (0.66); Mann–Whitney *U*-test, $P < 0.001$) or presence (after treatment, 0.39 (0.59); Mann–Whitney *U*-test, $P = 0.002$) of treatment. The *EMP1* mRNA levels did not vary significantly during the treatment period (Wilcoxon signed-rank test, $P = 0.068$).

Statistical calculations were performed using SPSS 17 (SPSS Inc., Chicago, USA). Data were expressed as mean ± standard deviation or as median (interquartile range) values for normally or not normally distributed continuous variables, respectively. The Fisher exact test was used for categorical data. The Student's *t*-test was used for normally distributed data, and the Mann–Whitney *U*-test and the Wilcoxon signed-rank test were used for data that was not normally distributed. Spearman's rho or Pearson's correlation coefficients were calculated to assess the correlations between parameters, depending on the distribution of the data. A multiple linear regression analysis was performed to evaluate the independent relationship of the variables under study.

In the case–control association study, the HAPLOVIEW program [4] was used to estimate haplotype frequencies, linkage disequilibrium (LD), permutation *P* values (50,000 permutations), and deviation from the Hardy–Weinberg distribution of alleles. Pairwise LD indices (D') were calculated for the control subjects. Power calculations for sample size were performed using the G*Power program [11].

All tests were two sided and $P < 0.05$ were considered significant. To account for multiple testing, Bonferroni criterion ($\alpha = 0.05$ divided by the number of tests) was used to interpret findings and determine significance.

HAM-D scores improved significantly after eight weeks of antidepressant treatment ($n = 27$; at baseline median, 21 (interquartile range, 8); after treatment, 6 (12); Wilcoxon signed-rank test, $P < 0.0001$). The following antidepressant drugs were administered: paroxetine ($n = 18$), sertraline ($n = 4$), fluvoxamine ($n = 3$), milnacipran ($n = 2$), amitriptyline ($n = 1$), and maprotiline ($n = 1$). The dose of antidepressants was 37.5–300 mg/day of the imipramine equivalent.

The relative amount of the *EMP1* mRNA in peripheral leukocytes was standardized to GAPDH mRNA, which was used as an internal standard. At baseline, patients showed significantly lower *EMP1* mRNA levels than did control subjects (controls, 0.81 (0.70); patients at baseline, 0.36 (0.66); Mann–Whitney *U*-test, $P < 0.001$). After antidepressant treatment, there remained a significant difference in the levels of *EMP1* mRNA normalized by the GAPDH between controls and patients (patients after treatment, 0.39 (0.59); Mann–Whitney *U*-test, $P = 0.002$) (Fig. 1). This difference

Table 1
Allele frequencies of the four *EMP1* SNPs in patients with MDD and in controls.

SNP	Marker	Position	Diagnosis	*n*	Genotype (%)			*P* value	HWE	Allele		*P* value	MAF
All subjects													
					A/A	A/G	G/G			A	G		
SNP1	rs7315725	13239012	MDD	182	16 (8.8)	77 (42.3)	89 (48.9)	0.261	0.910	109	255	0.146	0.299
		5′ upstream	control	346	23 (6.6)	132 (38.2)	191 (55.2)		0.976	178	514		0.257
					C/C	C/T	T/T			C	T		
SNP2	rs4763327	13246467	MDD	182	8 (4.4)	66 (36.3)	108 (59.3)	0.248	0.600	82	282	0.205	0.225
		intron1	control	350	29 (8.3)	125 (35.7)	196 (56.0)		0.160	183	517		0.261
					G/G	A/G	A/A			G	A		
SNP3	rs2291060	13256321	MDD	182	6 (3.3)	52 (28.6)	124 (68.1)	0.736	0.848	64	300	0.801	0.176
		intron2	control	347	10 (2.9)	108 (31.1)	229 (66.0)		0.520	128	566		0.184
					C/C	C/T	T/T			C	T		
SNP4	rs8885	13260463	MDD	182	35 (19.2)	101 (55.5)	46 (25.3)	0.500	0.124	171	193	1.000	0.470
		3′ UTR	control	350	77 (22.0)	175 (50.0)	98 (28.0)		0.946	329	371		0.470
Male subjects													
					A/A	A/G	G/G			A	G		
SNP1	rs7315725	13239012	MDD	76	10 (13.2)	37 (48.7)	29 (38.2)	**0.031**	0.737	57	95	**0.012**	0.375
		5′ upstream	control	145	9 (6.2)	56 (38.6)	80 (55.2)		0.847	74	216		0.255
					C/C	C/T	T/T			T	C		
SNP2	rs4763327	13246467	MDD	76	0 (0)	28 (36.8)	48 (63.2)	**0.008**	0.049	28	124	**0.028**	0.184
		intron1	control	147	14 (9.5)	54 (36.7)	79 (53.7)		0.293	82	212		0.279
					G/G	A/G	A/A			G	A		
SNP3	rs2291060	13256321	MDD	76	0 (0)	21 (27.6)	55 (72.4)	0.190	0.162	21	131	0.149	0.138
		intron2	control	145	5 (3.4)	47 (32.4)	93 (64.1)		0.752	57	233		0.197
					C/C	C/T	T/T			T	C		
SNP4	rs8885	13260463	MDD	76	14 (18.4)	46 (60.5)	16 (21.1)	0.233	0.065	74	78	0.842	0.487
		3′ UTR	control	147	34 (23.1)	71 (48.3)	42 (28.6)		0.706	139	155		0.473
Female subjects													
					A/A	A/G	G/G			A	G		
SNP1	rs7315725	13239012	MDD	106	6 (5.7)	40 (37.7)	60 (56.6)	0.944	0.843	72	140	0.929	0.340
		5′ upstream	control	201	14 (7.0)	76 (37.8)	111 (55.2)		0.840	139	263		0.346
					C/C	C/T	T/T			C	T		
SNP2	rs4763327	13246467	MDD	106	8 (7.5)	38 (35.8)	60 (56.6)	0.982	0.566	54	158	0.922	0.255
		intron1	control	203	15 (7.4)	71 (35.0)	117 (57.6)		0.360	101	305		0.249
					G/G	A/G	A/A			G	A		
SNP3	rs2291060	13256321	MDD	106	6 (5.7)	31 (29.2)	69 (65.1)	0.371	0.325	43	169	0.445	0.203
		intron2	control	202	5 (2.5)	61 (30.2)	136 (67.3)		0.547	71	333		0.176
					C/C	C/T	T/T			C	T		
SNP4	rs8885	13260463	MDD	106	21 (19.8)	55 (51.9)	30 (28.3)	0.974	0.641	97	115	0.865	0.458
		3′ UTR	control	203	43 (21.2)	104 (51.2)	56 (27.6)		0.681	190	216		0.468

Statistical differences in genotypic and allelic distributions were evaluated using the Fisher exact test. Values of $P < 0.05$ are shown in bold.

was also confirmed using normalization by the ACTB gene (controls, 1.10 (0.60); patients at baseline, 0.76 (0.82); Mann–Whitney *U*-test, $P = 0.018$: patients after treatment, 0.69 (0.94); Mann–Whitney *U*-test, $P < 0.001$). After eight weeks of treatment, the *EMP1* mRNA levels of patients showed a trend toward upregulation; however, this result was not significant (Wilcoxon signed-rank test, $P = 0.068$). There were no significant differences in the levels of the *EMP1* mRNA either before or after treatment according to gender, age and other demographic characteristics (number of episodes, age of onset, hereditary load, dose of antidepressants, and HAM-D scores before and after treatment).

The genotypic and allelic frequencies of the four SNPs located in the *EMP1* gene are shown in Table 1. There were no significant deviations from the Hardy–Weinberg equilibrium for all four SNPs, in either patients or control subjects.

There was no significant association between either the allelic frequencies or the genotypic distributions of these SNPs and MDD. To assess the presence of gender differences, we examined males and females separately. Significant differences were observed between male patients and male controls for the genotypes of two SNPs (rs7315725, $P = 0.031$; rs4763327, $P = 0.008$) and for their allelic frequencies (rs7315725, $P = 0.012$; rs4763327, $P = 0.028$). After application of the permutation test (50,000 permutations) to correct for multiple testing, rs7315725 retained significant allelic associations with MDD (permutation $P = 0.039$). Among females, there were no significant differences in either allele frequency or genotype distribution between patients and controls.

Next, we performed haplotype analyses. The values of absolute *D′* for the control subjects are presented in Fig. 2. There was one LD block in the *EMP1* gene (rs2291060 and rs8885), which resided in block 1. The permutation test of the two markers revealed no significant differences (permutation $P = 0.99$).

No correlations were detected between *EMP1* genotypes and clinical subtype (age, sex, age of onset, psychotic features, suicidal behavior, and family history).

Twenty four patients participated in both mRNA expression and genetic analysis. The expression level of the *EMP1* mRNA before and after treatment was investigated via multiple linear regression analysis with adjustment for cofounders (age, sex, number of episodes, age of onset, hereditary load, dose of antidepressants, HAM-D scores before and after treatment, and single SNP genotype). However, we did not observe any significant correlations between the level of the *EMP1* mRNA and these parameters.

In the present study, we performed an mRNA expression analysis of the *EMP1* gene in the peripheral blood leukocytes of MDD and control subjects. We also performed a case–control association analysis of the *EMP1* gene to clarify its implication in MDD.

First, we observed significantly decreased levels of expression of the *EMP1* mRNA in the peripheral blood leukocytes of medication-free MDD patients compared with control subjects. Recent reports revealed that the *EMP1* gene is expressed in the brain [3,21] and peripheral leukocytes [25]. *EMP1* has the single N-linked carbohydrate chain attached to the protein backbone, which carries the HNK-1/L2 carbohydrate epitope [22,29]. This special structure may

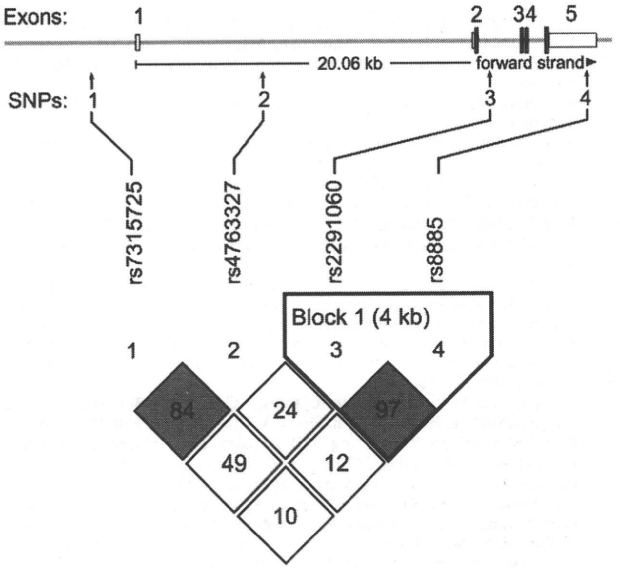

Fig. 2. Schematic representation of the *EMP1* gene. SNP locations and haplotype-block structure of *EMP1* gene. The horizontal line represents the genomic sequence; filled or empty boxes represent exons; and connected lines represent introns. Coding-region exons are shown as filled boxes; 5′ and 3′ UTRs are shown as empty boxes; and vertical arrows indicate the SNPs that were investigated in this study. Haplotype-block structure was determined using the Haploview program [4]. There was one linkage-disequilibrium block in the *EMP1* gene. Each box represents the *D′* values that correspond to each pairwise SNP.

not only contribute to cell–cell or cell–extracellular matrix recognition functions, but also affect differentiation, proliferation, and cell growth [27]. Thus, *EMP1* may be required during neurogenesis and the establishment of neural connectivity [32]. The observation that the *EMP1* mRNA level was decreased in leukocytes may provide a clue on the pathophysiology of MDD, as lymphocytes may reflect the metabolism of brain cells, and may be exploited as a neural and possible genetic probe in studies of psychiatric disorders [13,30]. Padmos et al. reported that the level of *EMP1* mRNA in monocytes was significantly elevated in bipolar depression patients compared with healthy controls [25]. Our results seem to contradict their findings. However, our findings were in line with recent reports that propose the neurotrophic hypothesis in which decreased expression of growth factors, notably brain-derived neurotrophic factor (BDNF) [7,18,26], contributes to depression, and upregulation of neurotrophic factors plays a role in the action of antidepressant treatment [10]. At the present time, we can only speculate on the reasons for this inconsistency, which may reflect differences such as cell type (monocytes vs. whole leukocytes) and disease subtype (bipolar depression vs. MDD). Though there is an overlap of core clinical features between bipolar depression and MDD, these diseases exhibit opposite differences regarding specific biological markers, e.g., BDNF [12,28].

Another possibility is that the *EMP1* mRNA change in leukocytes may reflect an activated inflammatory response system which is associated with MDD. Several studies have reported abnormalities in the immune system of patients with MDD [13,19]. Although the function of the *EMP1* gene is not entirely known, it is reported that *EMP1* mRNA in monocytes was correlated with the expression of the genes for proinflammatory cytokines mutually and strongly [25]. This suggests that *EMP1* may be involved in inflammation-related processes.

Second, although the *EMP1* mRNA levels of MDD patients after eight weeks of antidepressant treatment did not show significant changes from baseline levels, 70% of patients (19 out of 27) exhibited *EMP1* mRNA upregulation after treatment. Whether the upregulation of the *EMP1* mRNA after treatment is caused by pharmacological effects of the antidepressants or by clinical improvement remains to be elucidated. It is possible to assume that upregulation of the *EMP1* mRNA levels is more likely to be detectable after a period longer than a few weeks of treatment. Regarding the results of our study, though we did not examine whether the *EMP1* mRNA levels of patients were normal at the time of recovery, further studies (in particular a long-term study of a larger cohort of patients) are required to determine the clinical significance of *EMP1* mRNA expression in peripheral leukocytes.

Third, we investigated the genetic association between the *EMP1* gene and MDD in the Japanese population. We did not find any association of the four *EMP1* SNPs tested with the disease. However, rs7315725 exhibited significant allelic association with male MDD patients after subdivision of the subjects according to gender. To our knowledge, this is the first study of *EMP1* genetic variants in MDD. A potential explanation for this gender-specific effect is that MDD may involve different genetic factors in men and women. Several studies provide evidence of gender differences in the genotypic risk to develop MDD, such as the serotonin transporter [2], monoamine oxidase [16], and catechol-O-methyltransferase [31] genes. Our results suggest the existence of a gender-specific association between the *EMP1* genotype and MDD. Power calculations using the G*Power program [11] revealed that the size of our sample required an effect size of 0.16 (i.e., relatively weak) to archive a power of 80% (which is usually considered as sufficient power) at the 0.05 significance level (two tailed). Considering that the effect size of rs7315725 observed among male subjects was 0.177, our sample size may have been insufficient to reliably detect weak gene effects. Future studies using larger sample sizes may uncover additional associations between other *EMP1* polymorphisms and MDD.

Our study had several limitations. The size of the sample used in the expression analysis was small and the follow-up period was relatively short. It is possible that the MDD diagnosis will change into bipolar disorder with time in some MDD patients who participated in this study. The prognostic significance of *EMP1* mRNA levels warrants further investigation using additional studies with a larger number of patients and a longer follow-up period. The size of the sample used in the genetic association analysis was relatively small. Larger studies including participants of different ethnic backgrounds and meta-analyses are warranted to confirm the associations found here. Finally, we did not address how SNPs in the *EMP1* gene, which were significantly associated with MDD in our study, alter its function. Further investigations including intermediate phenotype approaches are needed to determine the effect of genetic variations in the *EMP1* gene on the etiology of MDD.

A significantly lower expression of the *EMP1* mRNA was observed in the leukocytes of MDD patients compared with control subjects. The *EMP1* genotype exhibited a significant association between male MDD patients and male controls. Our results suggest that *EMP1* may be implicated in the pathophysiology of MDD in the Japanese population.

Conflicts of interest

The authors declare that they have no conflict of interest.

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