are changed in the depressive state (6). The measurement of these hormones or cytokines has been used to objectively assess levels of mental conditions. However, their usefulness as biological markers is limited because of the unsatisfactory sensitivity and/or specificity.

One of the emerging approaches for assessing mental conditions is measuring the leukocyte mRNA expressions by using new technologies, such as DNA microarrays and quantitative real-time polymerase chain reaction (RT-PCR) methods (Figure 1). DNA microarray allows us to measure the thousands of mRNA transcripts simultaneously, while RT-PCR allows us to measure the mRNA transcripts of candidate gene promptly and precisely. Both methods are now recognized as useful clinical tools for making diagnostic, therapeutic, or prognostic decisions for patients with physical illness (7–13).

The peripheral blood leukocytes produce various cytokines, as well as proinflammatory cytokines, particularly gp130 family members which directly stimulate the HPA axis (14). At the same time, leukocytes express receptors for stress mediators, such as neurotransmitters, hormones, growth factors, and cytokines (15). Many studies showed similarities between receptor expression and mechanisms of transduction processes of cells in the central nervous system and lymphocytes (for review see (16)). Thus, investigating gene expression in the leukocytes may be a potential tool for evaluating psychological distress and depression. We review recent studies on the leukocyte gene expression to assess depression.

Molecular assessment of psychological distress with microarray

The neuroendocrine response, activated by psychological stress, makes stress into changes in mononuclear cell functions (17) and stimulates the production of tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, interleukin (IL)-6, IL-10, and IL-1 receptor antagonists (18). It is reported that the mRNA levels of several genes, including receptors for cytokines and associated molecules, were significantly upregulated in graduate school students in the defense of their Ph.D. degree, with DNA microarrays (19). The altered genes included the IL-1 receptor (*IL1R1* and *IL1R2*), the TNF receptor homologue (*TNFRSF10C*), the TNF-alpha-induced protein (*TNFAIP6*), the IFN-receptor 2 (*IFNGR2*), the IFN-induced cellular resistance mediator protein (*MX2*), the IFN-regulatory factor-2 (*IRF2*), and IFN inducible proteins (*IFITM1* and *IFITM3*). However, in posttraumatic stress disorder (PTSD), it is reported that the production of those metabolic parameters (TNF-alpha, IL-1beta, IL-6, etc.) was not changed but that the mRNA expressions of *TXR1* (thioredoxin reductase 1), *IL-16*, *IL-18*, *SOD1* (superoxide reductase 1), and *EDG1*

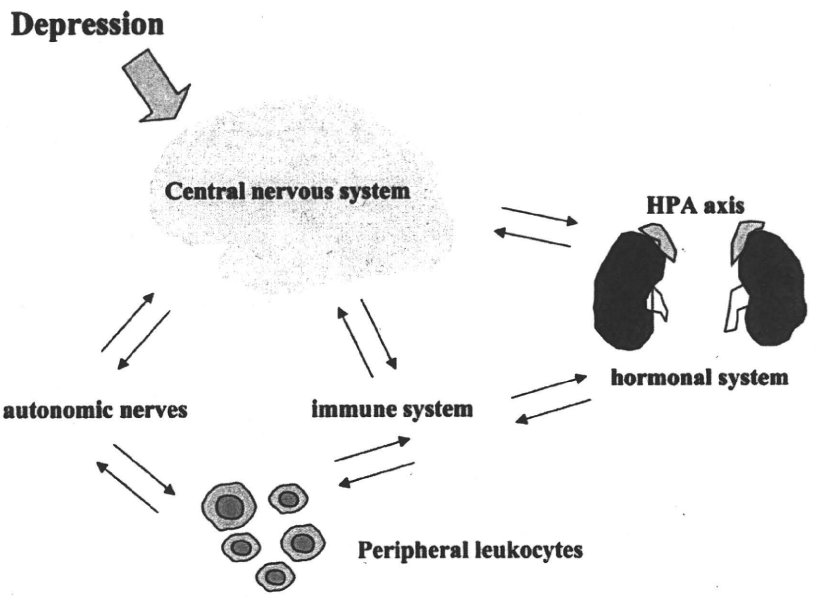

Figure 1. Depression is a mental disorder that affects the central nervous system. However, its dysfunction includes autonomic nerves, immune, and hormonal systems. Gene expressions in the peripheral leukocytes are under influence of these systemic dysfunctions and can be biological markers for depression. HPA = hypothalamus-pituitary-adrenal.

(endothelial differentiation sphingolipid G-protein-coupled receptor 1) were significantly reduced in the peripheral blood leukocytes using DNA microarray (20). It is suggested that reactive oxygen species (ROS) and/or different mechanisms are included in long-term stress reactions (21,22).

Molecular assessment of depression with quantitative real-time PCR

A large number of studies with laboratory examinations have been conducted to establish diagnostic markers for depression. Dexamethasone suppression test (DST) and its modified test, a dexamethasone-corticotrophin releasing hormone (DEX/CRH) test, have been extensively studied to detect hyperactivity of the HPA axis (23). Measurement of neurotransmitter receptors and transporters located in blood cells has also been vigorously studied with the assumption that they may reflect their counterparts in the CNS. For example, decreased serotonin transporter binding has been reported in the platelets of depressed patients (24,25), although some studies have reported no change (26–28). More recently, with the progress of experimental procedures, altered mRNA levels in leukocytes of major depression have been reported, such as dopamine D4 receptor mRNA levels (29) and cyclic adenosine monophosphate (AMP) response element-binding protein 1 (CREB) mRNA levels (30). We briefly summarize mRNA expression studies for depression using RT-PCR methods (Table I). Among them, we focused on serotonin transporter, calcium signaling, and trophic factors.

Table I. Molecular markers reported from peripheral blood leukocyte research.

Genes	Change	Authors (references)
Serotonin transporter	Increase	Iga 2005 (31), Tsao 2006 (32)
	Decrease	Lima 2005 (33)
cAMP response element-binding protein 1	Increase	Iga 2007 (34)
	No change	Lai 2003 (30)
Glucocorticoid receptor	Decrease	Matsubara 2006 (35)
Histone deacetylase 5	Increase	Iga 2007 (34)
Noradrenaline transporter	Decrease	Mata 2005 (36)
Dopamine receptor D4	Decrease	Rocc 2002 (29)
Vascular endothelial growth factor	Increase	Iga 2007 (37)
PDLIM5	Decrease	Iga 2006 (46)
Beta-arrestin1	Decrease	Matuzany-Ruban 2005 (38), Avissar 2006 (39)

cAMP, cyclic AMP or 3′-5′-cyclic adenosine monophosphate; ENH, Enigma homolog

Serotonin transporter

A serotonin transporter (5HTT) is the initial target for many classes of antidepressants, especially selective serotonin reuptake inhibitors (SSRI). 5HTT plays a key role in the regulation of serotonergic neurotransmission (40) and is one of the potential loci affecting the vulnerability to depression (41). The measurement of *5HTT* gene products in the peripheral leukocytes has been vigorously studied on the assumption that they reflect, to some extent, their counterparts in the CNS. We established the procedure for a precise measurement of *5HTT* mRNA levels in the leukocytes and measured the levels in the leukocytes of major depression before and after treatment with antidepressants (31). Baseline *5HTT* mRNA levels (before medication) were significantly higher in depressed patients than those in control subjects, and *5HTT* mRNA levels after 8 weeks of antidepressant treatment decreased significantly. Although some studies reported controversial results, our results have been reconfirmed by another group (32). Further studies will be needed to investigate the mechanism of these changes in depression.

Calcium signaling

LIM (PDLIM5) is a small protein that interacts with the protein kinase C-epsilon and the N-type calcium channel alpha-1B subunit and modulates neuronal calcium signaling (42,43). Recently, Iwamoto et al. reported that *PDLIM5* mRNA expression in postmortem brains and immortalized lymphoblastoid cells from mood disorder patients was different from that of healthy controls and seemed to be involved in the pathophysiology of mood disorder (44,45). Thus, we hypothesized that the *PDLIM5* mRNA level in the peripheral blood leukocytes might be a good candidate as a biological marker for mood disorders (46). The *PDLIM5* mRNA levels in the leukocytes of drug-free depressed patients were significantly lower than those of the controls and increased to almost the same level as the controls after recovery. These results indicate that the expression levels of *PDLIM5* mRNA in leukocytes are associated with the depressive state.

Recently, chromatin remodeling has attracted attention as an important factor in the treatment of depression because modifying histone acetylation alters depression-related behaviors in animal models of depression (47,48). One particularly interesting

target is histone deacetylase 5 (HDAC5) which is decreased by chronic antidepressant treatments (49). HDAC5 is known to be involved in calcium/calcium-dependent protein kinase signaling in the lymphocytes (49). On the other hand, hyperacetylation of histones catalyzed by histone acetyltransferases (HATs) is believed to facilitate gene transcription; this action is opposed by HDACs. CREB, a type of HAT, is one of the most important targets for antidepressants (50) and is related to calcium signaling (51). Because CREB is located downstream of HDAC5 in the lymphocyte calcium signaling (52), we have determined the expression levels of *HDAC5* and *CREB* mRNA in the leukocytes of depressed patients. Both *HDAC5* and *CREB* mRNA levels in the leukocytes of the untreated depressed patients are significantly higher than those of the control subjects and decreased to almost normal levels after antidepressant treatments (34). There is a positive correlation between *HDAC5* and *CREB* mRNA levels. Our results suggest that the alteration of *HDAC5* and *CREB* gene expression may represent the abnormal calcium signaling in major depression.

Trophic factors

A neurotrophic hypothesis of depression has been intensively studied. In particular, brain-derived neurotrophic factor (BDNF) has been demonstrated in the pathogenesis of major depressive disorder (MDD) (for review see (53,54)). Serum BDNF is consistently decreased not only in depressive patients (55,56) but also in other neuropsychiatic patients such as those with eating disorder (57), autism (58), and Huntington's disease (59). However, there is no report on the *BDNF* mRNA levels in the leukocytes of major depression because of its low revels in the leukocytes.

Increased reductive or oxidative stress to the cell or activation of numerous protein kinase pathways are thought to induce growth factor expression, among which the most important is vascular endothelial growth factor (VEGF). Elevated VEGF production in the serum has been detected in myocardial infarction (60,61), diabetic retinopathy (62), hyperlipidemia (63), and hypertension (64). Since VEGF has also been implicated in neuronal survival, neuroprotection, regeneration, growth, differentiation, and axonal outgrowth (65), we hypothesized that the expression of the *VEGF* mRNA in the leukocytes might be a good candidate as a biological marker for major depressive disorder (MDD) (37). The *VEGF* mRNA levels in the leukocytes of untreated depressive patients were significantly higher and decreased after antidepressant treatments. Its reduction is significantly correlated with clinical improvement. Our result may be related to previous reports showing an increased expression level of *VEGF* mRNA in the peripheral monocytes from diabetic patients with coronary artery disease (66). The relationship between major depression and cardiovascular disease is well known (67). Although there was no patient afflicted by cardiovascular disease in our study, the elevated *VEGF* mRNA expression in the leukocytes of depressed patients may reflect systemic oxidative stress, and the risk of cardiovascular events and the reduction of systemic stresses decrease the *VEGF* mRNA expression.

Molecular assessment of depression with microarray

An altered expression of one gene may be a useful biomarker of depression, but it may be more useful to use some of the altered expressions of genes in combination to create a more sensitive and reliable biomarker. For this purpose, DNA microarray or DNA tip seems suitable and intriguing. A preliminary study has been conducted to establish new biological markers for depression by a microarray specifically designed to measure the mRNA levels of stress-related genes in the leukocytes (68). The microarray analyses reveal that the expression of a dozen genes shows significant changes in the total group of depressed patients, compared to the controls (data not shown). These preliminary results reveal sets of gene expressions that could distinguish depressed patients from healthy controls, volunteers after psychological and physical stress, and from those in preliminary samples of patients with schizophrenia. Although mechanisms of alteration remain unclear, neurotransmitter, endocrinological, and immunological abnormalities are thought to have contributed to the alteration of expression to some extent. Some alteration may directly reflect intracellular abnormalities of depression that might be present in the leukocytes.

Limitations and future perspectives

According to the current hypotheses of major depression, most reports were focused on the mRNA expression of neurotransmitter transporter, second messengers, and trophic factors (Table I). Some findings were replicated; however, contradictory results were also reported. Possible reasons for these contradictions may come from the heterogeneous

etiology and pathophysiology of depression. Most studies use Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for the diagnosis of depression. However, the major depressive disorder described symptomatologically by DSM-IV may include depressive episodes of different pathophysiology. Genetic polymorphisms which affect the gene expression may also contribute to these contradictions. For example, it is known that serotonin transporter has two major allelic variants (5HTTLPR at promoter and 5HTTVNTR at intron 2) which affect gene expression, and there are racial differences in the distribution of these gene polymorphisms (41). In the interpretation of the results of gene expression levels, careful consideration should be given to genetic and racial differences of samples.

With new technologies, such as microarray and RT-PCR, we must pay attention to technical confounding factors. The ability for intra- and inter-laboratory reproduction of results must be determined, and the standardization of methodology must be established. The results may be influenced by tissue acquisition methods as well as sample handling. Particularly, the method for RNA isolation has a significant impact on gene expression profiles obtained from human whole blood or circulating blood leukocytes and needs to be considered as a critical variable in the design of the experiment (69). The relative amount of each gene mRNA should be standardized with at least two housekeeping mRNAs (70).

Another important factor that might affect the result of studies is whether one extracts mRNAs from whole blood cells or from particular cell populations of blood cells. mRNAs from a particular cell population such as lymphocyte may have the advantage to detect more sensitively the systemic dysfunction of depression, but the complicated extraction procedures may change gene expression patterns significantly. With a kit, such as a PAXgene Blood RNA kit (Qiagen), one can extract mRNAs directly from a small amount of whole blood without complicated procedures which might influence gene expressions (71). However, with this method, mRNAs come from total leukocytes that consist of neutrophils, lymphocytes, monocytes, etc., and which cell compartment contributes to the results remains unknown. Differences in the cell populations used for mRNA extraction might contribute to the discrepancy of the results. The gene expression profiles among different cell populations should be studied further.

Studying gene expression in leukocytes is an interesting tool for assessing the role of target genes in stress-related disorders. In clinical research for psychiatric diseases, the peripheral leukocyte is a very useful tissue because of its accessibility. We can compare gene expressions at several points of the clinical course. When gene expressions in the leukocytes are used as a marker for the changes in the CNS, the assumption is that gene expressions in the leukocyte and the CNS are correlated with each other. This assumption may not be always true, since preclinical studies show tissue-specific differences in glucocorticoid receptors among cells and tissues of the immune systems (6). One can examine the expression levels of genes in the leukocytes which have important roles in psychiatric diseases; however, the function of these genes in leukocytes is not yet well known, and the interpretation of changes should be treated with caution. Although molecular assessment of depression with peripheral leukocytes is still in the early stages, it is worthwhile studying further. It is necessary to examine if these markers discriminate major depression from bipolar depression, euthymic from depressed, drug-naive from drug-treated.

Molecular assessment with peripheral leukocytes may lead us to a paradigm shift in the discovery process of the pathophysiology of depression. The initial targets can be discovered from the microarray and real-time PCR analysis of clinical samples. This new approach is intriguing because it will likely lead us to possible and even unexpected targets that are relevant for depression.

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Regular Article

Predictors of subjective and objective quality of life in outpatients with schizophrenia

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Aim: In recent years, greater attention has been given to quality of life (QOL) in schizophrenia and several studies reported that negative and depressive symptoms and cognitive dysfunction are related to patient QOL. But because a variety of QOL measures have been used in the previous studies, there seems to be no unanimous predictors for subjective and objective QOL. The purpose of the present study was to elucidate the relationship between clinical variables and subjective and objective QOL in outpatients with schizophrenia, using schizophrenia disease-specific QOL measures. Particular attention was paid to cognitive function as a predictor of QOL.

Methods: Schizophrenia symptoms of the Positive and Negative Syndrome Scale (PANSS) were divided into five factors: positive factor, negative factor, cognitive factor, emotional discomfort, and hostility. The study sample consisted of 84 schizophrenia outpatients. Subjective and objective QOL were assessed with Schizophrenia Quality of Life Scale (SQLS) and the Quality of Life Scale (QLS), respectively.

Results: Subjective QOL correlated significantly with emotional discomfort, positive factor, negative factor, extrapyramidal symptoms and cognitive factor, while objective QOL correlated with negative factor, cognitive factor, emotional discomfort, extrapyramidal symptoms, and dose of antipsychotics. Total score and three of four subscales in the QLS correlated significantly with cognitive factor, while cognitive factor had a significant correlation with only one of three scales of SQLS. Stepwise regression showed that subjective QOL was significantly predicted by emotional discomfort and extrapyramidal symptoms, while negative factor was the most important predictor of objective QOL.

Conclusion: Cognitive dysfunction had a greater influence on objective QOL than subjective QOL. Treating depressive and negative symptoms and extrapyramidal symptoms might contribute to enhanced subjective and objective QOL.

Key words: cognitive dysfunction, depressive and negative symptoms, objective quality of life, schizophrenia, subjective quality of life.

OVER THE PAST two decades, the concept of quality of life (QOL) has become an important attribute in patient care and clinical research.[1,2] Although there seems to be no unanimous definition of QOL, QOL is generally thought to include life satisfaction, social functioning, daily living activities, and physical health, and it has been recognized as an important indicator of how well patients with schizophrenia can function.[2–4] QOL has been measured from two different viewpoints. One is subjective

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QOL, rated by patients themselves, and the other is objective QOL, rated by observers. Objective measures of QOL include indicators of health and living conditions, sociodemographic items and role functioning, whereas subjective indicators of QOL measure life satisfaction in general and within different life domains. Because patients with schizophrenia were thought to be unable to assess their QOL themselves because of their cognitive deficit function, objective QOL have been frequently used in many studies and the evaluation of treatments for schizophrenia was mainly based on objective assessment of the psychotic symptoms. But now there is general agreement that symptomatically stabilized patients are able to evaluate their QOL themselves.[5]

The clinical factors related to levels of QOL have been variously reported. Several studies including our own have suggested that depressive mood may be the most important determinant for subjective QOL.[6–11] Other studies reported that positive symptoms[12] or akathisia symptoms as well as the total severity of psychopathology[1] predicted subjective QOL.

In some studies, the severity of negative symptoms[7,10,11,13] or the presence of tardive dyskinesia[14] was reported to be associated with a poor objective QOL. Levels of insight into the illness showed no significant relationship with QOL levels.[15] In addition to clinical symptoms, sociodemographic factors also influence objective QOL of patients with schizophrenia.[16]

In recent years, greater attention has been given to the cognitive dimension in schizophrenia. One of the reasons is that atypical antipsychotics improve cognitive function while conventional antipsychotics produce minimal cognitive improvement.[17,18] Several studies strongly indicate that cognitive function has a greater impact on QOL in patients with schizophrenia than do positive symptoms.[19–21] Executive functioning and verbal learning appear to be especially valid predictors of work status.[19,22–24] Other studies reported that unemployed patients with schizophrenia were impaired on measures of memory and problem solving, even when IQ was within an average range.[25,26]

The purpose of the present study was to further elucidate clinical determinants of both subjective and objective QOL. In the present study, subjective and objective QOL were assessed on the Schizophrenia Quality of Life Scale (SQLS)[27,28] and the Quality of Life Scale (QLS),[29,30] respectively. Schizophrenia symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS).[31] Evidence from recent factor analysis studies conducted with PANSS has suggested that a five-dimensional structure appears to be a better representation of the psychopathological data. Analysis for the present study is based on five orthogonal dimensions according to Bell *et al.*:[32] positive factor, negative factor, cognitive factor, emotional discomfort, and hostility. Contribution of these five symptom factors as well as duration of illness, number of hospitalizations, dose of antipsychotics and extrapyramidal symptoms to the levels of QOL was investigated. Few studies have investigated the relationship between subjective and objective QOL and the five PANSS factors. Particular interest was paid to the PANSS cognitive factor as a predictor of subjective or objective QOL.

METHODS

Subjects

Clinical data were collected at Department of Psychiatry, Tokushima University Hospital from 18 May to 5 August 2005. After obtaining written consent from all subjects, we investigated a sample of 105 outpatients whose diagnosis was confirmed by at least two psychiatrists according to the DSM-IV.[33]

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 105 patients, 84 completed the questionnaire.

The present subjects were all clinically stable and received outpatient treatment regularly. Seventy-two had never been hospitalized during the previous 1 year including 28 who had never had inpatient treatment, while 12 had inpatient treatment during the previous 1 year. The antipsychotic regimen of 75 subjects had been unchanged for at least 6 months before the recruitment, and only nine subjects had a little change in regimen during the previous 6 months, but the nine were judged as clinically stabilized by the treating psychiatrists.

Procedure

To assess subjective QOL, we used the SQLS.[27,28] Objective QOL was evaluated using the QLS.[29,30] Psychotic symptoms were evaluated using the PANSS.[31] Drug-induced extrapyramidal symptoms were

assessed using the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS).[34]

The SQLS is a self-reported, 30-item questionnaire for measuring QOL specific to patients with schizophrenia with good reliability and validity.[27,28] It is composed of three scales: psychosocial, motivation/energy and symptoms/side-effects. Lower scores indicate higher levels of subjective QOL.

The QLS assesses objective QOL by means of a semistructured interview. The reliability and validity of the scale has been verified.[29,30] The ratings are based upon patient self-report and observer judgment about patient functioning and life circumstances. This instrument has four subscales: interpersonal relations, instrumental role, intrapsychic foundation, and common objects and activities. Higher scores indicate higher levels of objective QOL. Some of the authors, who are all experienced psychiatrists, conducted the interviews according to the Evaluation Manual for the QLS.[30]

The PANSS was originally designed as a rating scale that represents positive, negative and general psychopathology.[31] The score ranges are 30–210 for the global score; 7–49 for the positive score; 7–49 for the negative score; and 16–112 for the general psychopathology score. A breakdown into five factors was used according to Bell *et al.*:[32] positive factor (score range 6–42; items: delusions, hallucinations, grandiosity, suspiciousness, somatic concern, unusual thought content); negative factor (score range 8–56; items: blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, lack of spontaneity, motor retardation, disturbance of volition, preoccupation); cognitive factor (score range 7–49; items: difficulty in abstract thinking, stereotyped thinking, conceptual disorganization, lack of judgment and insight, poor attention, tension, mannerisms and posturing); emotional discomfort factor (score range 4–28; items: depression, anxiety, guilt feeling, active social avoidance); and hostility factor (score range 4–28; items: excitement, hostility, poor impulse control, uncooperativeness).

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 a 5-point scale that ranges from 0 to 4 (0, none; 4, severe). The reliability and validity of the scale have been verified.[34]

All the scales except the SQLS were applied by the authors, who were experienced psychiatrists. Inter-rater consistencies of all the scales in our group have been shown to be satisfactory.[35]

Statistical analysis

Pearson's correlation coefficients were calculated to study the relationship between subjective and objective QOL and clinical variables (duration of illness, number of hospitalizations, dose of antipsychotics, PANSS positive symptoms score, PANSS negative symptoms score, PANSS cognitive score, PANSS emotional discomfort score, PANSS hostility score and the DIEPSS score). Because data were normal continuous variables except for the PANSS positive symptoms score, duration of illness and dose of antipsychotics, and because the sample size was large, we used parametric test. Then, using clinical variables that showed significant correlation, stepwise regression was done to determine which clinical variables were the best predictors for each dependent variable. The SQLS score and the QLS total score and subscales were chosen as dependent variables. Statistical analysis was done using SPSS version 11.5J (SPSS, Chicago, IL, USA).

RESULTS

Demographic characteristics and means and standard deviations of the clinical indices are presented in Table 1. All subjects were Japanese, and 42 were male and 42 were female. We used the chlorpromazine conversion chart[36] to determine the dosage of antipsychotic medication.

The correlations between the SQLS scores and clinical variables are shown in Table 2. Only positive factor and emotional discomfort were correlated significantly with the score of psychosocial scale. The score of the motivation and energy scale correlated significantly with positive factor, negative factor and emotional discomfort. Positive factor, cognitive factor, and extrapyramidal symptoms were correlated significantly with the score of the symptoms and side-effects scale.

The correlations between the scores of the QLS total and subscales and clinical variables are shown in Table 3. Negative factor was correlated with total and all subscales. Total score and three subscales of four correlated with cognitive factor.

Table 4 shows the results of stepwise regression on the SQLS and the QLS.

Table 1. Subject characteristics (mean ± SD)

n (M/F)		84 (42/42)
Age (years)		40.7 ± 12.6
Duration of illness (years)		14.6 ± 10.4
No. hospitalizations		1.4 ± 1.6
Dose of antipsychotics (mg/day)†		534 ± 542
Type of schizophrenia (*n*)	Paranoid	65
	Residual	13
	Disorganized	1
	Catatonic	4
	Undifferentiated	1
Marital state (*n*)	Married	19
	Never married	63
	Divorced	2
PANSS	Total	61.7 ± 11.7
	Positive factor	12.1 ± 4.9
	Negative factor	21.1 ± 6.9
	Cognitive factor	14.4 ± 5.5
	Emotional discomfort	5.6 ± 2.1
	Hostility	8.3 ± 2.5
DIEPSS (Overall)		1.3 ± 2.3
SQLS	Psychosocial	24.3 ± 10.7
	Motivation/energy	14.3 ± 4.6
	Symptoms/side-effects	7.9 ± 4.7
QLS	Total	65.4 ± 22.9
	Interpersonal Relations	21.2 ± 10.6
	Instrumental Role	13.2 ± 5.0
	Intrapsychic Foundations	23.6 ± 8.0
	Common Objects and Activities	7.3 ± 2.0

†Chlorpromazine equivalent.
DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; PANSS, Positive and Negative Syndrome Scale; QLS, Quality of Life Scale; SQLS, Schizophrenia Quality of Life Scale.

The psychosocial scale score and the motivation/energy scale score were significantly predicted only by emotional discomfort. The symptoms/side-effects scale score was significantly predicted only by extrapyramidal symptoms.

The QLS total score was predicted independently by negative factor and dose of antipsychotics. Four subscales were predicted independently by negative factor.

DISCUSSION

In recent years, greater attention has been given to QOL in schizophrenia and several symptoms have been reported to be related to patient QOL. But in the < previous studies, because a variety of QOL measures have been used, there seems to be no unanimous predictors for subjective and objective QOL. The purpose of the present study was to elucidate the relationship between clinical variables and subjective and objective QOL, using PANSS five-factor analysis and schizophrenia disease-specific QOL measures. Several recent studies strongly indicate that cognitive function has a greater impact on QOL in patients with schizophrenia than do positive symptoms.[19–21] Therefore we paid particular attention to the PANSS cognitive factor and explored the relationship between cognitive dysfunction and patient QOL.

The clinical factors related to levels of QOL have been variously reported. For the clinical factors associated with subjective QOL, Dickerson *et al.* found that patients' subjective QOL measured by the Quality of Life interview was related to the depression factor in PANSS.[6] Huppert *et al.* reported that more severe depression as rated on the brief Psychiatric Rating Scale (BPRS) was associated with lower subjective QOL measured by the Quality of Life interview.[8] Fitzgerald *et al.* reported that subjectively reported life satisfaction was more influenced by depressive symptom on the Montgomery–Asberg Depression Rating Scale (MADRS) than positive symptom or negative symptom.[7] Other similar studies including our own also support the association of depressive symptom with subjective QOL.[9–11] In the present study, emotional discomfort and positive factor were correlated with psychosocial scale scores of SQLS, and stepwise regression showed that emotional discomfort predicted the psychosocial score. Emotional discomfort, negative factor and positive factor were correlated with motivation/energy scores of SQLS, and stepwise regression showed that emotional discomfort predicted the motivation/energy scale score. The present results are consistent with those reported by Tomotake *et al.* and Aki *et al.*, who assessed subjective QOL and depressive symptoms with SQLS and the Calgary Depression Scale for Schizophrenia, respectively.[10,11]

In the current study, drug-induced extrapyramidal symptoms, cognitive factor, and positive factor were correlated with symptoms/side-effects scale scores of SQLS, and stepwise regression showed that drug-induced extrapyramidal symptoms predicted the symptoms/side-effects scale score. The present result suggests that the extrapyramidal symptom is a factor negatively influencing subjective QOL. The influence

Table 2. SQLS scores and clinical variables

	SQLS		
	Psychosocial	Motivation/energy	Symptoms/side-effects
PANSS			
Positive factor	0.274*	0.227*	0.260*
Negative factor	0.184	0.293**	0.056
Cognitive factor	0.19	0.176	0.266*
Emotional discomfort	0.449***	0.408***	0.195
Hostility	0.152	0.141	0.120
DIEPSS	0.204	0.179	0.279*
Duration of illness	0.170	−0.111	0.140
Number of hospitalization	0.149	−0.016	0.151
Dose of antipsychotics	0.210	0.011	0.047

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, Pearson correlations.
DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; PANSS, Positive and Negative Syndrome Scale; SQLS, Schizophrenia Quality of Life Scale.

of extrapyramidal adverse effects has already been documented. Ritsner *et al.*, using the MADRS, the Talbieh Brief Distress Inventory (TBDI), the Abnormal Involuntary Movement Scale (AIMS) and the Quality of Life Enjoyment and Satisfaction Questionnaire in schizophrenia patients, reported that the depression score on the TBDI and the score at the AIMS were predictors of poor QOL.[37] Awad *et al.* reported that, using PANSS, Hillside Akathisia scale and the Drug Attitude Inventory, subjective QOL is greatly influenced by psychopathology, akathisia and patients' subjective tolerance of medications, and concluded that effort should be directed towards effective control of psychotic symptoms and minimizing the side-effects of antipsychotic drugs in order to improve the QOL of schizophrenia patients.[1] These two studies, however, used subjective QOL measures, which, unlike SQLS, did not have a subscale focused on symptoms/side-effects. The current study suggests that patients with drug-induced extrapyramidal symptoms have subjective discomfort with respect to their symptoms and side-effects.

Table 3. QLS total and subscale scores and clinical variables

	QLS				
	Total	Interpersonal relations	Instrumental role	Intrapsychic foundation	Common objects and activities
PANSS					
Positive factor	−0.098	−0.059	−0.143	−0.110	−0.002
Negative factor	−0.535***	−0.487***	−0.340**	−0.584***	−0.337**
Cognitive factor	−0.303**	−0.228*	−0.267*	−0.350**	−0.177
Emotional discomfort	−0.272*	−0.263*	−0.208	−0.269*	−0.121
Hostility	−0.022	−0.039	−0.022	−0.025	0.108
DIEPSS	−0.252*	−0.241*	−0.206	−0.207	−0.248*
Duration of illness	−0.043	−0.053	0.137	−0.128	−0.038
Number of hospitalization	0.003	−0.046	0.013	0.023	0.149
Dose of antipsychotics	−0.272*	−0.258*	−0.253*	−0.222*	−0.210

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, Pearson correlations.
DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; PANSS, Positive and Negative Syndrome Scale; QLS, Quality of Life Scale.

Table 4. Stepwise regression for SQLS and QLS

	Dependent variable	Independent variable	Adjusted R^2	β
SQLS	Psychosocial	Emotional discomfort	0.191***	0.449***
	Motivation/energy	Emotional discomfort	0.156***	0.408***
	Symptoms/side-effects	DIEPSS	0.067**	0.279**
QLS	Total	Negative factor	0.334***	−0.504***
		Dose of antipsychotics		−0.190*
	Interpersonal Relations	Negative factor	0.228***	−0.487***
	Instrumental Role	Negative factor	0.105**	−0.340**
	Intrapsychic Foundations	Negative factor	0.333***	−0.584***
	Common Objects and Activities	Negative factor	0.180***	−0.337**

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; QLS, Quality of Life Scale; SQLS, Schizophrenia Quality of Life Scale.

The present study suggests that negative symptoms predict objective QOL (QLS total and all the subscales). The present results are consistent with those reported by Tomotake *et al.* and Aki *et al.*, who assessed objective QOL and negative symptoms using QLS and BPRS, respectively.[10,11] Considering that QLS was originally designed to assess deficit symptoms and the dysfunctions related to them,[29] the correlation between negative symptoms and QLS scores seems to be reasonable.

The influence of negative symptoms on objective QOL has already been documented. Fitzgerald *et al.*, using QLS, PANSS and MADRAS, indicated a significant positive relationship between all of the four QLS subscales and PANSS negative scores, but none of the QLS subscales was related significantly to PANSS positive scores and MADRAS scores.[7] Norman *et al.*, using QLS, Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms (SANS), reported that negative symptom, level of functioning and positive symptom related to the scores on QLS and that QLS was most strongly related to negative symptom.[12] Browne *et al.* also investigated the relationship between objective QOL assessed with QLS and clinical variables, and reported that total QLS score correlated significantly with negative symptom rated with SANS.[14]

Greater attention has been given to the cognitive dimension in schizophrenia in recent years. Several studies strongly indicate that cognitive function has a greater impact on QOL in patients with schizophrenia than do positive symptoms.[19–21] Bell *et al.* found that higher scores on PANSS cognitive component were significantly correlated with poorer performance on neuropsychological tests.[32,38] Hofer *et al.* reported that, using the cognition subscale of the PANSS, poorer cognition scores reduced the competitive employment and that PANSS cognition subscale as well as negative symptom and positive symptom were found to contribute significantly to the Global Assessment of Functioning score.[39] Consistent with these previous studies, the QLS total score and all the subscale scores of QLS except common objects and activities subscale correlated significantly with PANSS cognitive score in the present study. Although stepwise regression showed that negative factor alone significantly predicted objective QOL, cognitive function also had an apparent influence on it. But Hofer *et al.* found that clinical assessment of cognitive deficits on PANSS is not a viable alternative to neuropsychological testing to obtain information about cognitive functioning in schizophrenia.[40] Their finding limits the interpretation of the present results. To elucidate influence of the cognitive dysfunction on QOL, further studies using neuropsychological tests such as Brief Assessment of Cognition in Schizophrenia[41] are necessary.

In contrast, in the present study, cognitive dysfunction did not predict subjective QOL, although the symptoms/side-effects scale score of SQLS was significantly correlated with cognitive dysfunction. Consistent with the present result, Reine *et al.* reported that only one of eight subscales in the short version

of the Lehman quality of life scale correlated with PANSS cognitive factor, while five subscales correlated with PANSS depression factor.[9] Karow *et al.* reported that on longitudinal study, only one subscale of five in the short form of the subjective Well-being under Neuroleptics Scale (SWN) correlated with PANSS cognitive factor in the acute and mid-term phase, while PANSS depression factor correlated with total scores of SWN in the acute, mid-term, and long-term phase.[42] These reports, including our own, suggest that cognitive dysfunction has little association with subjective QOL. It seems that cognitive dysfunction has apparent influence on objective but not subjective QOL.

Considering the results of previous studies as well as the present study, active treatment for depressive and negative symptoms and extrapyramidal symptoms is recommended to improve patient QOL. From this point, atypical antipsychotics are perceived to be more effective and have fewer adverse effects than typical antipsychotics.[17,18] The influence of atypical antipsychotics on QOL has already been documented. Using QLS, SQLS, BPRS and DIEPSS, Taniguchi *et al.* reported that the replacement of previous drugs including both typical and atypical antipsychotics with quetiapine improved patients' subjective and objective QOL, clinical symptoms and extrapyramidal symptoms, although they did not comment on the improvement of depressive symptoms.[43] In contrast, a randomized controlled trial provided evidence that typical antipsychotics showed an improvement in QLS score and PANSS total and positive, negative and general symptoms, and concluded that there is no disadvantage across 1 year in terms of QOL and symptoms in using typical antipsychotics rather than atypical antipsychotics.[44] Further well-controlled studies are necessary to elucidate the influence of antipsychotics on QOL.

In summary, we have examined the relationship between clinical factors and QOL in schizophrenia outpatients in the chronic phase with schizophrenia disease-specific subjective and objective QOL measures. Consistent with past report, the results indicate that depressive symptoms and extrapyramidal symptoms predict subjective QOL and that negative symptoms predict objective QOL. The present results also showed that cognitive dysfunction had an apparent influence on objective but not subjective QOL. Active treatment for depressive and negative symptoms and extrapyramidal symptoms is recommended to improve patient QOL.

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Positive association of the PDE4B (phosphodiesterase 4B) gene with schizophrenia in the Japanese population

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Abstract

The phosphodiesterase 4B (PDE4B) gene is located at 1p31, a susceptibility region for schizophrenia (SZ). Moreover, PDE4B interacts with DISC1, which is a known genetic risk factor for SZ. Recently, it was reported that the PDE4B gene is associated with SZ in Caucasian and African American populations. In this study, case-controlled association analyses were performed in the Japanese population to determine if the PDE4B gene is implicated in SZ. Thirteen single nucleotide polymorphisms (SNPs) were analyzed in 444 schizophrenic patients and 452 control subjects. Three SNPs (rs2180335, rs910694 and rs472952) were significantly associated with SZ after applying multiple test correction ($p = 0.039$, 0.004 and 0.028). In addition, a significant association was found between specific haplotypes (rs2180335 and rs910694) and SZ (permutation $p = 0.001$). Our result suggests that variations at the PDE4B locus may play a significant role in the etiology of SZ in the Japanese population.

Keywords: PDE4B; DISC1; Association analysis; Schizophrenia

1. Introduction

Schizophrenia (SZ) is a complex psychiatric disorder that afflicts approximately 1% of the population throughout the world and has high heritability (Craddock et al., 2005). The phosphodiesterase 4B (PDE4B) gene is located at 1p31, a susceptibility region for SZ (Faraone et al., 2006). PDE4B belongs to the PDE4 family of phosphodiesterases, which are orthologous to the Drosophila learning and memory gene dunce (Davis et al., 1995). The PDE4B gene has been found to be disrupted by a translocation breakpoint in two related individuals with psychosis in Scotland (Millar et al., 2005). Moreover, disrupted-in-schizophrenia 1 (DISC1), which is an important genetic risk factor for mental disorders such as SZ (Hennah et al., 2006; Ishizuka et al., 2006), has been shown to interact dynamically in a cyclic adenosine monophosphate (cAMP) dependent manner with PDE4B. DISC1 interacts with the UCR2 domain of PDE4B and elevation of cellular cAMP caused by protein kinase A (PKA) leads to dissociation of PDE4B from DISC1 and an increase in PDE4B

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activity (Millar et al., 2005). Long PDE4 isoforms are activated upon phosphorylation of UCR1 by PKA and are transiently inhibited by phosphorylation of their catalytic domains by extra cellular signal regulated kinase (ERK) (Houslay and Adams, 2003; Houslay et al., 2005). Moreover, Hashimoto et al. showed that genetic variation of the DISC1 gene is associated with lower biological activity on ERK signaling (Hashimoto et al., 2006). This implies that the DISC1–PDE4B interaction is important in the regulation of cAMP signaling. It was reported that patients with schizophrenia have decreased levels of intracellular cAMP (Muly, 2002) and that antipsychotic medications raise intracellular cAMP levels in the brain after blocking D2 receptors (Kelly et al., 2007). Recently, King et al. reported that variation in the PDE4B gene is associated with SZ in Caucasian and African American populations (King et al., 2006).

Taken together, the findings mentioned above suggest that the PDE4B gene may be a susceptibility one to SZ. In this study, we attempted to confirm the association of the PDE4B gene with SZ in Japanese subjects.

2. Materials and methods

2.1. Subjects for analysis

All patients and control subjects were biologically unrelated and Japanese. The diagnosis of SZ was made by at least two experienced psychiatrists according to DSM-IV criteria (American Psychiatric Association, 1994). For the genetic studies, we used genomic DNA samples from 444 SZ patients (265 male [mean age: 48.4 ± 13.9 years] and 179 female [mean age: 48.4 ± 15.0 years]) from thirteen psychiatric hospitals in the neighboring area of Tokushima Prefecture and the Ehime University Hospital in Japan. Controls (452) were selected from volunteers (271 male [mean age: 48.7 ± 12.1 years] and 181 female [mean age: 47.5 ± 12.7]) who were genetically unrelated residents living in Japan without either mental past histories or family histories of at least first degree relatives. All subjects signed written informed consent to participate in the genetic association studies approved by the institutional ethics committees.

2.2. Genotyping

We genotyped thirteen SNPs of the PDE4B gene. Genotyping was performed using commercially available TaqMan probes for the PDE4B gene with the Applied Biosystems 7500 Fast Real Time PCR System, according to the protocol recommended by the manufacturer (Applied Biosystems, California, USA.). We selected thirteen single nucleotide polymorphic (SNP) markers (rs1317611 (C/G), rs1354061 (A/G), rs4004 (G/T), rs6700971 (C/T), rs6588190 (C/T) and rs4320761 (C/T), rs599381 (A/G), rs498448 (C/T), rs1040716 (A/T), rs2180335 (A/G), rs910694 C/T), rs472952 (A/G), rs3767311 (A/G)) for genotyping from the public databases (dbSNP Home page) as reference for International Hap Map Project and the Applied Biosystems software SNPbrowser 3.5. Considering King's report that showed highly significant association between SNPs in introns 7 and 8 and SZ (King et al., 2006), we selected six SNPs that locate at the region from intron 7 to intron 8 and show high linkage disequilibrium (LD) between each pair of these SNPs. Haplotype block structure was determined using the HAPLOVIEW program (Barrett et al., 2005). Blocks were defined according to the criteria of Gabriel et al. (Gabriel et al., 2002).

2.3. Statistical analysis

Allelic and genotypic frequencies of patients and control subjects were compared using Fisher's exact test. Deviation from Hardy–Weinberg (HW) distribution of alleles was determined using the Haploview program. The SNPAlyze 3.2Pro software (DYNACOM, Japan) was used to estimate haplotype frequencies, LD, and permutation p values (10,000 replications). Pair-wise LD indices, D′ and r^2, were calculated for the control subjects. Power calculations for our sample size performed using the G*Power program (Erdfelder et al., 1996). The criterion for significance was set at $p < 0.05$ for all tests.

3. Results

We genotyped thirteen SNPs in the PDE4B gene in 444 SZ patients and 452 controls. Genotypic and allelic frequencies of thirteen SNPs on PDE4B are shown in Table 1. There were two LD blocks (Gabriel et al., 2002) in PDE4B (Fig. 1) with rs6588190 and rs4320761 residing in block 1 and rs2180335 and rs910694 residing in block 2. Significant differences in allelic frequencies were observed between SZ patients and controls for four SNPs in introns 7 and 8, but not for the remaining nine SNPs. The T allele of rs1040716, the G allele of rs2180335, the T allele of rs910694 and the G allele of rs472952 occurred more frequently in the SZ patient' group than in control subjects ($p = 0.013$, 0.003, 0.0003, 0.002, respectively). After applying the Bonferroni correction test, these three SNPs (rs2180335, rs910694 and rs472952) still had significant allelic associations with schizophrenia ($p = 0.039$, 0.004, 0.028, respectively). Genotypic distributions of all SNPs were in Hardy–Weinberg equilibrium in control subjects, however, rs1040716 and rs2180335 showed deviations from Hardy–Weinberg equilibrium in SZ subjects ($p < 0.01$). In addition, we performed haplotype analyses for block 1 and block 2. The two marker haplotypes of block 2, containing SNPs (rs2180335 and rs910694), were associated with SZ (permutation $p = 0.001$, Table 2), while the two marker haplotypes of block 1 were not associated with SZ (permutation $p = 0.283$).

In power calculations using the G*Power program, we found that the sample size had >0.84 power for detecting

Table 1
Allele frequencies of thirteen SNPs in the PDE4B gene in patients with schizophrenia and control

SNP	Diagnosis	HWE	*n*	Allele		*p*-Value	Genotype			*p*-Value	Frequency
				C	G		C/C	C/G	G/G		
rs1317611	SZ	0.934	444	490	398	0.601	136	218	90	0.837	0.448
	CT	0.597	452	510	394		147	216	89		0.436
				A	G		A/A	A/G	G/G		
rs1354061	SZ	1	443	310	576	0.302	54	202	187	0.5	0.35
	CT	0.49	452	338	566		67	204	181		0.374
				G	T		G/G	G/T	T/T		
rs4004	SZ	0.64	444	709	179	1	285	139	20	0.32	0.202
	CT	0.116	451	721	181		283	155	13		0.201
				C	T		C/C	C/T	T/T		
rs6700971	SZ	0.47	444	332	556	1	66	200	178	0.912	0.374
	CT	0.93	452	338	566		64	210	178		0.374
				C	T		C/C	C/T	T/T		
rs6588190	SZ	0.799	443	638	248	0.232	228	182	33	0.462	0.28
	CT	0.858	452	627	277		216	195	41		0.306
				C	T		C/C	C/T	T/T		
rs4320761	SZ	1	443	637	249	0.178	229	179	35	0.398	0.281
	CT	1	452	623	281		215	193	44		0.311
				A	G		A/A	A/G	G/G		
rs599381	SZ	1	444	81	807	0.74	4	73	367	0.922	0.091
	CT	0.865	451	78	824		4	70	377		0.086
				C	T		C/C	C/T	T/T		
rs498448	SZ	0.159	444	522	366	0.316	161	200	83	0.58	0.412
	CT	0.362	452	510	394		149	212	91		0.436
				A	T		A/A	A/T	T/T		
rs1040716	SZ	0.001	444	183	705	0.013	31	121	292	0.012	0.206
	CT	0.305	449	230	668		34	162	253		0.256
				A	G		A/A	A/G	G/G		
rs2180335	SZ	0.005	444	160	728	0.003	24	112	308	0.0014	0.18
	CT	0.986	452	215	689		26	163	263		0.238
				C	T		C/C	C/T	T/T		
rs910694	SZ	0.018	444	158	730	0.0003	22	114	308	0.00013	0.178
	CT	0.623	451	223	679		25	173	253		0.247
				A	G		A/A	A/G	G/G		
rs472952	SZ	0.03	444	161	727	0.002	22	117	305	0.0037	0.181
	CT	0.729	452	218	686		28	162	262		0.241
				A	G		A/A	A/G	G/G		
rs3767311	SZ	0.906	444	98	790	0.354	6	86	352	0.528	0.11
	CT	0.693	452	89	815		3	83	366		0.098

a significant association (alpha < 0.05) when an effect size index of 0.2 was used.

4. Discussion

In this study, we performed a genetic and haplotypic-based association of the PDE4B gene with SZ in the Japanese population. We observed significant differences in allele frequency for rs2180335 and rs910694 of intron 7, and rs472952 of intron 8 between SZ-cases and controls after applying the Bonferroni correction test ($p = 0.039$, 0.004, 0.028, respectively). Furthermore two marker haplotypes covering rs2180335 and rs910694 in the same block were significantly associated with SZ (permutation $p = 0.001$). The most common haplotype (GT) was present in 82% of SZ -cases and 75% of controls. Therefore, this haplotype might be a risk factor for SZ. The second most common haplotype (AC) was present in 18% of SZ – cases and 24% of controls, suggesting that this haplotype might be protective against SZ. King et al. also reported that several SNPs, in particular two SNPs in introns 7 and 8, and three marker haplotypes showed highly significant association with SZ in Caucasian and African American populations (King et al., 2006). During the preparation of this manuscript, another study, demonstrating that three – SNP haplotypes in intron 3 are significantly associated with SZ in a female Scottish population (110 subjects), was published (Pickard et al.,

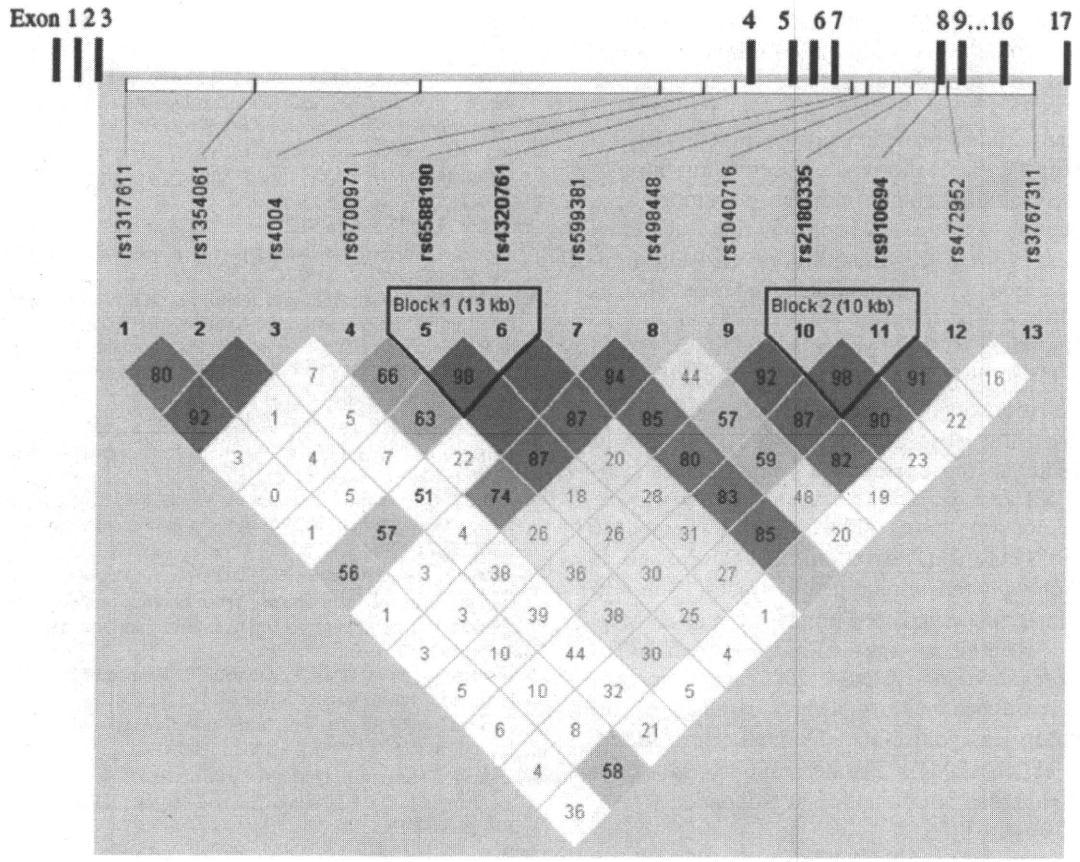

Fig. 1. Haplotype block structure of the PDE4B gene Haplotype block structure was determined using the HAPLOVIEW program (Barrett et al., 2005). Blocks were defined according to the criteria of Gabriel et al. (2002). There were two LD blocks in PDE4B. rs6588190 and rs4320761 reside in the block 1and rs2180335 and rs910694 reside in the block 2.

Table 2
Haplotype analysis among SZ and controls

Haplotype (rs2180335-rs910694)	Overall (%)	Schizophrenia	Control	Chi-Square	*p*-Value	Permutation *p*-value
(a) Schizophrenia						
GT	78.4	81.8	75.1	11.9	0.0006	0.0012
AC	20.6	17.6	23.6	9.99	0.0016	0.0021
Select locus	Chi-Square	*p*-Value		Permutation *p*-value		Replications
rs2180335/ rs910694	16.4	0.0009		0.0011		10000

Haplotypes were omitted from analysis if the estimated haplotype probabilities were less than 5%. The two marker haplotypes of the block 2 containing SNPs (rs2180335, rs910694) were associated with SZ (permutation $p = 0.0003$).

2007). In our study, when the data were subdivided on the basis of sex, no significant association was observed in single SNPs after the Bonferroni correction either in male and female samples. The two marker haplotypes of block 2, containing SNPs (rs2180335 and rs910694), were associated with SZ in male (permutation $p = 0.006$), while this two marker haplotypes were not associated with SZ in female (permutation $p = 0.208$). Three marker haplotypes (rs2180335-rs910694-rs472952, $D' > 0.9$ and $r^2 > 0.8$ in this region) were associated with SZ both in male and female (permutation $p = 0.009$, 0.039, respectively). Different results of gender effect and positive association regions between our study and Pickard's study may be caused by sample size, different SNPs examined and ethnic difference. However it is very interesting that all three reports including ours show positive association of the PDE4B gene with Schizophrenia. In our study, rs1040716 and rs2180335 showed deviations from HWE in SZ ($p < 0.01$), while all genotype frequencies in the PDE4B gene SNPs of control subjects were in HWE. This result

may reflect a SZ- specific mutation such as microdeletion of the region around rs1040716 and rs2180335, which causes the PDE4B expressional changes in our Japanese SZ samples.

Several recent studies provide evidence that PDE4 is a SZ susceptibility factor. Rolipram, a selective inhibitor of PDE4, reversed amphetamine (indirect dopamine agonist) – disrupted auditory sensory gating (Maxwell et al., 2004) and blocked the disruption of pre-pulse inhibition (PPI) caused by amphetamine in mice (Kanes et al., 2007). In rodents, rolipram suppressed conditioned avoidance responding (CAR), which is a commonly used test to screen for antipsychotic activity, at doses that did not produce response failures (Wadenberg and Hicks, 1999). Moreover, the dose-related effects of rolipram in CAR were similar to those seen with antipsychotics (Siuciak et al., 2006) and the same authors recently showed that PDE4B knockout mice exhibit a blunted response to rolipram in CAR (Siuciak et al., 2007). PDE4B is involved not only in the dopaminergic system, but also in the glutamatergic system. Rolipram attenuates MK-801 (NMDA receptor antagonist)-induced deficits in latent inhibition (Davis and Gould, 2005) and improves working -and reference-memory deficits induced by an NMDA receptor antagonist (O' Donnell and Zhang, 2004; Zhang et al., 2004). Furthermore, it has been reported that rolipram is efficacious in SZ patients (Pietzcker et al., 1979).

In conclusion, we here provide evidence that PDE4B is a genetic susceptibility factor for SZ. Larger studies are needed to confirm these associations by genotyping more PDE4B polymorphisms and haplotypes.

Conflict of interest

There are none.

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