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.,

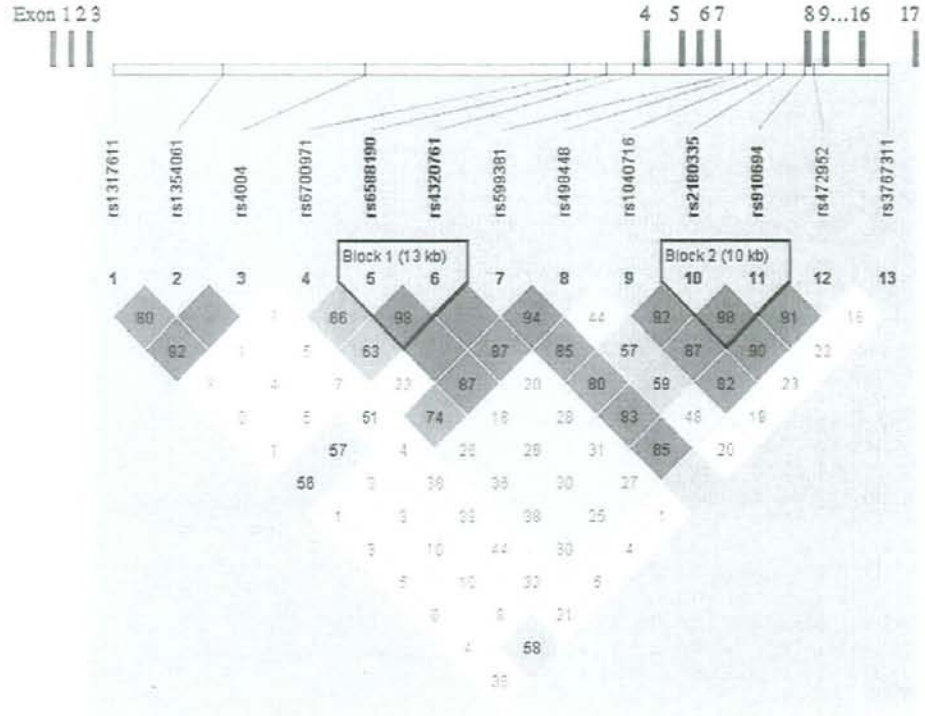

Fig. 1. Haplotype block structure of the PDE4B gene Haplotype block structure was determined using the HAPLOVIEW program (Barrett et al., 2005). Blocks were defined according to the criteria of Gabriel et al. (2002). There were two LD blocks in PDE4B. rs6588190 and rs4320761 reside in the block 1and 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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FKBP5, *SERT* and *COMT* mRNA expressions in the peripheral leukocytes during menstruation cycle in healthy reproductive females

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Abstract

There have been several evidences that the mRNA expressions in the peripheral leukocytes may indicate not only physical but also psychological states. The purpose of this study is whether the mRNA expressional changes in the leukocytes are related to the mental states across the menstrual cycle in reproductive healthy female subjects. Thirty-eight female subjects (22.4 ± 1.4 year-old) were participated in this study at three menstruation cycle periods (menstrual, follicular and luteal phase). The *FKBP5* (FK506-binding protein gene), *SERT* (serotonin transporter gene) and *COMT* (catechol-*o*-methyltransferase gene) mRNA expressions in the leukocytes were determined with hormonal data. The psychological changes were assessed with self-rating hospital anxiety and depression scale (HADS). Only one thirds of subjects ($n = 12$) had regular menstrual cycles during the experiment. So we analyzed the data from these 12 subjects. The anxiety score of each subject was changed across the menstrual cycle (Friedman test: $P < 0.05$). The *FKBP5* mRNA expression was significantly lower in the follicular phase than in the other phases but no changes were seen in either *SERT* or *COMT* mRNA expressions among the phases. In conclusion, there are differences of HADS anxiety score and *FKBP5* mRNA expression in the leukocytes across the menstrual cycle but there is no correlation between anxiety scores and FKBP5 mRNA.

Keywords: Menstrual cycle; HADS; mRNA expression; Leukocytes; Real time-PCR method

Approximately 80% of reproductive women experience physical and psychological symptoms during menstrual period [13]. The cases with severe symptoms seen only in the late luteal phase are diagnosed as premenstrual syndrome (PMS) and a psychiatric disorder related to PMS is called premenstrual dysphoric disorder (PMDD), which are prevalent disorders among women of reproductive age [10]. According to the DSM-IV criteria [1,2], 3–8% of women meet the strict criteria for PMDD [10]. Those disorders have multi-dimensional symptoms and may include diverse physiologic systems although their etiology is still unknown.

Previous studies including our own have been reported that altered mRNA expressions in the peripheral leukocytes might indicate the pathophysiology of the neuronal changes in mental disorders [14,15,18,19,21]. For example, the serotonin transporter gene mRNA expression in the leukocytes of depressive

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patients is higher than that in healthy control subjects [14]. So it is useful to study the changes of the peripheral leukocytes not only in the immune and blood diseases but also in the central nervous system disorders.

Before studying the menstruation-related disorder patients, we tried to measure the changes with mental status across the menstruation cycle in healthy female subjects. Both biological and psychological changes across the menstrual cycle were studied simultaneously. We selected three gene expressions in the peripheral leukocytes as biological markers: *FKBP5* (FK506-binding protein; the FKBP51 gene which may be induced by glucocorticoids and its polymorphism is reported to be associated with antidepressant effects [6], *SERT* (5HTT; SLC6A4, the serotonin transporter gene) which codes a target protein of antidepressants used in PMS or PMDD treatment [9], *COMT* (catechol-*o*-methyltransferase gene) which codes COMT protein that degrades catecholamines and its soluble isoform is reported to be inhibited transcriptionally by estrogen [16,26]. The mRNAs of three genes are expressed in the leukocytes as suggested by the expression profile of analysis of EST counts in UNIGENE in NCBI home page (http://www.ncbi.nlm.nih.gov/UniGene/ESTProfileViewer) or our previous study [14], and quantitationally measured by real time-PCR method. For assessing the psychological state during menstruation, we used a self-rating scale, hospital anxiety and depression scale (HADS) score [27].

Thirty-eight female volunteers (mean age: 22.4 ± 1.4 year-old) were recruited from the university students of midwifery course. All subjects were in good health without a history of either psychiatric or serious somatic diseases. They were un-medicated during this study. Complete blood cell counts, liver function and hormone levels (LH: luteinizing hormone; FSH: follicle-stimulating hormone; TSH: thyroid-stimulating hormone; PRL: prolactin, free T3, free T4; E1: estrone; E2: estradiol and progesterone) were measured (SRL, Tokyo, Japan) before this study and there were no abnormal findings. They signed written informed consent approved by the Ethical Committee of The University of Tokushima School of Medicine.

Basal body temperature with menstrual memory scale was measured by each subject every morning. They recorded the period of menstruation and premenstrual symptoms in the table if there were. The dates of psychological assessment and blood drawing in each phase of menstrual cycle were determined by themselves. Before starting this study, the subjects checked their own menstruation cycles for about 6 months at least. The day in the menstruation phase was 2.7 ± 0.5 days after the onset of menstruation and the day in follicular phase was 9.8 ± 1.8 days after the onset of menstruation. In luteal phase, the day chosen was eighth day after the body temperature raised high phase period (6.8 ± 3.4 days prior to onset of menstruation).

Hospital anxiety and depression scale (HADS) [27], which consists of seven questions about anxiety and depression each, were performed to evaluate anxiety and depressive state in the menstrual phase. The score of each question ranges from 0 to 3 (higher score shows more serious symptom). Cut off point is eight in both anxiety and depression scales [7].

For the hormone assays and the quantitation of the mRNAs in the leukocytes, the subjects underwent venous blood drawing in the morning of the same day they performed self-rating HADS scores in each phase.

The blood samples were placed in the refrigerator just after sampling and the maximum time between taking the sample and centrifugation was 6 h. LH, FSH, PRL, E1, E2 and progesterone were determined each phase by ELISA by a third party (SRL, Tokyo, Japan).

The expressional profiles of the mRNA levels are determined with quantitative real time-PCR method [14]. Total RNA was extracted from the leukocytes of whole blood samples using PAXgene Blood RNA kit (Qiagen, Tokyo, Japan) according to the manufacturer's recommendations. Residual genomic DNA was digested with RNase-free DNase I. One to five micrograms of total RNA was used for cDNA synthesis by oligo (dT) primers and Powerscript Reverse Transcriptase (BD Biosciences, Tokyo, Japan). Primer and probe sequences were selected at exon-intron boundary of *FKBP5*, *SERT* and *COMT* and optimized melting temperatures (Nihon Gene Research Lab's Inc., Sendai, Japan). Primers and Hybridization probes were as followed: 5′-AGAAAGTGCTGGAAGTA-3′ and 5′-CCTTTTTCATTAGTGACC-3′ primers; 5′-TTCAAGAAGTT-TGCAGAGCAGGATGCCA-3′Fluorescein and 5′-LCRed640-GGAAGAGGCCAATAAAGCAATGGGCAAG-3′ for *FKBP5*; 5′-TCTATGGCATCACTCAGTT-3′ and 5′-TGGAAAAGTCG-TAGTTGTG-3′-primers, 5′-AACAGGAGAAACAGAGGGC-TGATGGC-3′Fluorescein and 5′-LCRed640-ACCCAGCAGA-TCCTCCAGAACCACC-3′ for *SERT*; 5′-TCGGCTGGAAC-GAGTTCA-3′ and 5′-CGTCCACGATCTTGCCTT-3′ primers, 5′-GGTTCAGGATGCGCTGCTCCTTGGT-Fluorescein and 5′-LCRed640-TCACCCATGAGCAGGTTGTGGATGG-3′ for *COMT*. Quantitative real time-PCR was performed with Light-Cycler (Roche Diagnostics, Tokyo, Japan). Two housekeeping genes were used for normalization (glucose-6-phosphate dehydrogenase; *G6PD* and hypoxanthine guanine phosphoribosyltransferase; *HPRT*, Qiagen, Tokyo, Japan). There was no expressional difference in either house keeping gene, so we used *G6PD* as an internal standard. Measurement of each gene expression was held in triplicates. Amplification of the product in the real time-PCR method was confirmed by agarose gel electrophoresis.

Statistical calculations were carried out using the SPSS Statistical Software Package 11.5 (Tokyo, Japan). Menstrual cycle effects on HADS score in each subject were analyzed by Friedman test. The changes during menstruation cycles were analyzed by two-way analysis of variance (ANOVA) ("three menstruation cycles"×" subjects") with repeated measures followed by Bonferroni post hoc test. P values less than 0.05 were considered to be statistically significant in all tests. Data are presented as mean ± standard deviation.

All subjects showed no abnormal findings in laboratory examination. A gynecologist (T.K.) assessed the phase of menstrual cycles from the graphical data of basal body temperature and gonadal steroid levels. The critical decision points were body temperature (the length of high-temperature period), the data of E2 and progesterone levels. Twenty four subjects were diag-

Table 1
Endocrine examination in each menstrual phase

	Menstruation	Follicular	Luteal
LH (mIU/ml)	2.70 ± 1.78	5.69 ± 2.74	2.63 ± 3.22
FSH (mIU/ml)	4.81 ± 1.78	5.57 ± 1.41	2.15 ± 1.10
PRL (ng/ml)	14.2 ± 12.1	12.1 ± 10.1	14.4 ± 11.6
E1 (pg/ml)	25.6 ± 12.8	44.4 ± 18.5	75.8 ± 24.0
E2 (pg/ml)	28.3 ± 10.4	48.8 ± 18.2	131.2 ± 52.1
Progesterone (ng/ml)	0.66 ± 0.23	0.63 ± 0.26	9.54 ± 2.47

mean ± S.D. $n = 12$.

Table 2
Hospital anxiety and depression scale

	Menstruation	Follicular	Luteal
HADS-A	4.3 ± 3.2 (11)	3.8 ± 4.7	4.8 ± 3.5
HADS-D	5.3 ± 2.5	4.2 ± 3.0	5.3 ± 3.1 (11)
HADS-total	9.6 ± 5.2 (11)	8.0 ± 6.6	10.3 ± 4.9 (11)

The cut-off point is eight in anxiety and depression score. mean ± S.D. $n = 12$ (parenthesis: numbers tested) There was a significant difference among control subjects in HADS-A (Friedman test: $P < 0.05$).

nosed as luteal insufficiency or anovulatory cycle in that period. Two subjects showed amenorrhea during this study. They were excluded from data analyses. Finally, we analyzed 12 subjects with regular menstrual cycles and they did not meet criteria for PMDD according to DSM-IV [1]. The values of LH, FSH, PRL, E1, E2 and progesterone across the menstruation cycle were shown in Table 1.

The scores of HADS-A score (anxiety), HADS-D score (depression) and HADS-total score in each phase were shown in Table 2. When menstrual cycle effects on HADS score in each subject were analyzed by Friedman test, only HADS-A score significantly changed among the phases ($P = 0.048$). Comparison of HADS-A, HADS-D or total HADS scores using two-way ANOVA showed no significant differences across the menstrual cycle.

Fig. 1 shows mRNA expression of *FKBP5*, *SERT* and *COMT* in three phases calculated as a percentage of the mean values in each subject. The post hoc analysis by Bonferroni test revealed that the FKBP5 mRNA expression was significantly lower in the follicular phase than those in either menstruation or luteal phase ($P = 0.040$ and 0.029, respectively). But there was no significant difference in *SERT* or *COMT* mRNA levels among the phases. We could not find any correlation between three HADS scores and these three gene expressions.

Although 38 women participated in this study, 26 subjects showed luteal insufficiency or anovulatory cycle or amenorrhea. Then, we utilized only 12 subjects (about one thirds of participants) who were appropriate for this study. A study reported that 72% of 19-year-old women and 67% of 24-year-old women experienced problem with menstruation [22] but it was unexpected that more than two thirds of subjects have menstrual disturbances in that period. This fact may be due to their youth (22.0 ± 1.2 year-old) or their irregular daily schedule even in healthy controls without any symptoms or signs. This shows that the exact assessment of menstrual cycles and the appropriate selection of subjects are important for studies across the menstrual cycle.

We chose self- rating questionnaire, HADS, for the assessment of psychological changes in these three menstruation phases. HADS is a short but useful self-rating test that measures both anxiety and depressive score simultaneously. Bjelland et al reviewed that HADS is a suitable tool in assessing anxiety and depression in the general population [7]. We found significant fluctuation of anxiety over the menstrual cycles. It is expected that HADS is also useful for evaluating the psychological changes in the PMS or PMDD patients.

For the purpose of studying the mRNA changes across the menstruation cycle, we select *FKBP5* as a hormonal marker. Because Glucocorticoid induces *FKBP5* mRNA expression [4] and its response may be a suitable marker to assess individual glucocorticoid sensitivity [25]. Single-nucleotide polymorphisms in FKBP5 were reported to associate with response to antidepressants, the recurrence of depressive episodes and increased intracellular FKBP51 protein [6]. It is interesting that the *FKBP5* mRNA expression was significantly lower only in the follicular phase in this study. Kester et al. demonstrated that progestin regulates FKBP51 [17] and overexpression of *FKBP5* might attenuate progestin responsiveness [12]. It can be postulated that the increased progesterone level may induce *FKBP5* mRNA in the luteal phase. In the menstrual phase, the *FKBP5* expression was also high compared to the follicular phase. It is suggested that even the level of progesterone in the serum is low in that phase but that its effect continues in several days after the menstruation started because the maximum induction of *FKBP5* mRNA with progestin R5020 remained elevated for at least 24 h

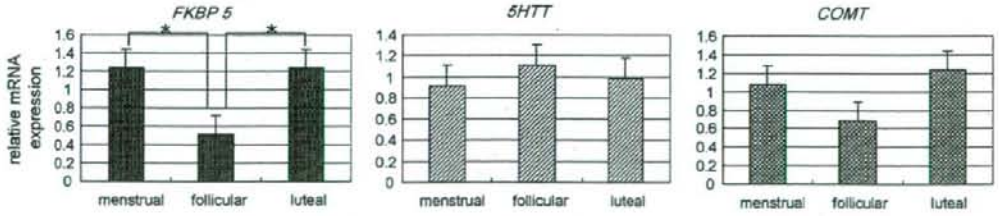

Fig. 1. Effects of each menstrual cycle on mRNA expression of *FKBP5*, *SERT* and *COMT* in the peripheral leukocytes. Relative mRNA expression of three genes was shown in the vertical axis (the bars indicate S.D.). *FKBP5* mRNA expression was significantly lower in the follicular phase compared with the other phases (two-way ANOVA and Bonferroni test: menstruation vs. follicular; $P = 0.040$, follicular vs. luteal; $P = 0.029$). There was no significant difference in 5-HTT or COMT mRNA levels during the phases.

after treatment in vitro [12]. Another possibility is that the other factors may be related to its elevation, for example, glucocorticoid level. The concentration of progesterone is reported to be not related to PMS directly [11] and the relation between the elevation of the *FKBP5* mRNA and the psychological symptoms are not known yet.

On the other hand, serotonergic system also plays an important role in the pathogenesis of premenstrual symptoms because selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of PMS and PMDD [8,9]. Previous studies have indicated that whole blood serotonin levels [20], platelet uptake and content of serotonin in the luteal phase are lower in patients with PMS compared to control [3]. We have reported that *SERT* mRNA is expressed in the peripheral leukocytes and that its expression in depressive state is higher than that in control subjects and decreased after SSRI treatment [14]. In this study, we found no significant changes of *SERT* mRNA level in the leukocytes across the menstrual cycle in healthy female subjects. This result suggests that serotonergic system may not be involved primarily in the mood change during menstruation cycles. Although *SERT* mRNA in the leukocytes was not changed transcriptionally in normal females, there is a possibility that SERT expression may be posttranscriptionally modified and that the expression of *SERT* mRNA in the brain may be affected during menstrual cycles.

We also measured *COMT* mRNA expression levels in the leukocytes. Several studies have shown that *COMT* mRNA expression in the frontal cortex is related to the level of cognitive function [5,24]. Total *COMT* mRNA expression in the leukocyte was not changed during the menstrual cycles. However, we analyzed the mRNA expressions of *COMT* soluble and membrane-bound type together. Further studies to analyze each type of *COMT* mRNA are required because estrogen is reported to modify soluble type of *COMT* transcript while the membrane-bound type of *COMT* mRNA expression is higher in the brain [23].

In conclusion, our study suggests that the *FKBP5* mRNA but not either *SERT* or *COMT* mRNA expression changes across the menstrual cycle in the peripheral leucocytes of healthy female subjects. They showed a fluctuation of anxiety across the menstruation cycle but there were no correlation between anxiety and *FKBP5* mRNA expression. Since the sample sizes were small and this study was done only with healthy controls, further studies to analyze the psychological and biological effect of the menstrual cycle in patients with menstruation-related disorders are required.

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Subjective and objective quality of life, levels of life skills, and their clinical determinants in outpatients with schizophrenia

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Abstract

The purpose of the present study is to investigate the relationships among subjective and objective quality of life (QOL), and levels of life skills, and their clinical determinants in outpatients with schizophrenia by using schizophrenia disease-specific QOL measures. Data collected from 64 outpatients were analyzed. Subjective QOL was measured with the Schizophrenia Quality of Life Scale (SQLS) and objective QOL with the Quality of Life Scale (QLS). Patients' family members completed the Life Skills Profile (LSP). Clinical symptoms were also assessed with several scales including the Brief Psychiatric Rating Scale (BPRS) and the Calgary Depression Scale for Schizophrenia (CDSS). Only the motivation/energy scale, but not the other scales of the SQLS, correlated with the QLS. The LSP rated by the family showed significant correlations with both the SQLS and the QLS. The CDSS score predicted each scale of the SQLS, and the BPRS negative symptoms score predicted the QLS. The LSP was predicted by the BPRS negative symptoms score and the CDSS score independently. These results indicate that the patient's QOL could be predicted by the life skills measured by a family member and suggest that active treatment for depressive and negative symptoms might be recommended to improve the patient's QOL and life skills.

Keywords: Quality of life; Life skill; Schizophrenia

1. Introduction

Although there seems to be no unanimous definition of quality of life (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 (Lehman, 1998; Meltzer, 1992, 1999). QOL has been measured from two different viewpoints. One is subjective QOL rated by patients themselves, and another is objective QOL rated by observers. Although patients with schizophrenia were thought to be unable to assess their QOL by themselves because of their cognitive deficit function, it would be reasonable to assume that symptomatically

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stabilized patients are able to evaluate their QOL by themselves (Voruganti et al., 1998). To date, several assessment scales have been developed to assess subjective and objective QOL (Heinrichs et al., 1984; Wilkinson et al., 2000). However, the relationship between these two QOL perspectives is not clear. Fitzgerald et al. (2001) reported that some significant correlations were found between subjective and objective QOL measures in schizophrenia.

The clinical factors related to levels of QOL have been variously reported. Several studies have suggested depressive mood may be the most important determinant for subjective QOL (Dickerson et al., 1998; Fitzgerald et al., 2001; Huppert et al., 2001; Reine et al., 2003). Of these studies, only Reine et al. used the Calgary Depression Scale for Schizophrenia (CDSS), which specifically measures depressive rather than positive or negative symptoms or antipsychotic-induced side effects (Rocca et al., 2005). Other studies reported that positive symptoms (Norman et al., 2000) or akathisia symptoms as well as the total severity of psychopathology (Awad et al., 1997) predicted subjective QOL. In some studies, the severity of negative symptoms (Fitzgerald et al., 2001; Strejilevich et al., 2005) or the presence of tardive dyskinesia (Browne et al., 1996) was reported to be associated with a poor objective QOL. Levels of insight into the illness showed no significant relationship with QOL levels (Browne et al., 1998). In addition to clinical symptoms, socio-demographic factors also influence objective QOL of patients with schizophrenia (Caron et al., 2005). The variance in previous findings might derive from the difference of the QOL measures used and the difference of the subjects investigated. Further research is needed to clarify clinical factors influencing subjective and objective QOL using appropriate measures.

Another approach to measuring QOL of patients with schizophrenia is to use the assessment by family members of patients. We used the Life Skills Profile (LSP) for this purpose. The LSP developed by Rosen et al. (1989) is a suitable measure of function and disability associated with schizophrenia. The LSP can be used by family members of patients as well as by community housing managers or professional staff (Rosen et al., 1989; Parker et al., 1991), and it shows good internal consistencies and validity (Trauer et al., 1995). Up to now, there have been few reports concerning the influence of psychiatric symptoms or of, the dosage and side effects of drugs, on the scores of the LSP.

In this study, we investigated relationships among patient-rated subjective QOL, observer-rated objective QOL, and family-rated LSP in patients with schizophrenia. This study is the first trial to utilize patient-rated, observer-rated, and family-rated measures simultaneously. We also investigated their clinical determinants with multivariate analysis.

2. Material and methods

2.1. Subjects

Clinical data were collected at the Department of Psychiatry, Tokushima University Hospital, from April 26 to June 18, 2004. After getting written consent from all subjects, we selected 105 outpatients whose diagnoses had been confirmed by at least two psychiatrists according to the DSM-IV.

Subjects were excluded if they presented with any organic central nervous system disorder, epilepsy, mental retardation, severe somatic disorder, drug dependence, or alcohol dependence. We also asked their family members to complete the LSP. Of 105 family members, 64 gave us written consent and completed the questionnaire. Of 64, 46 were their parents, 6 their spouses, 6 their siblings, and 5 their children. Only one did not specify the relationship to the patient. Data from 64 family members and 64 corresponding outpatients were used for the statistical analysis.

The subjects in the present study were all stabilized and had been able to receive outpatient treatment regularly. Fifty had never been hospitalized during the previous 1 year, including 13 who had never had inpatient treatment, while 14 had inpatient treatment during the previous 1 year. Sixty-one subjects had followed the same antipsychotic regimen for at least 6 months before recruitment, while three subjects had slight changes in regimen during the previous 6 months; however, the three were judged as clinically stabilized by the treating psychiatrists.

2.2. Procedure

To assess subjective QOL, we used the Schizophrenia Quality of Life Scale (SQLS) (Wilkinson et al., 2000; Kaneda et al., 2002). Objective QOL was evaluated using the Quality of Life Scale (QLS) (Heinrichs et al., 1984, 2001). Psychotic symptoms, including positive and negative symptoms, were evaluated using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962; Miyata et al., 1995). Depressive symptoms were assessed using the CDSS (Addington et al., 1993; Kaneda et al., 2000). Drug-induced extrapyramidal symptoms were assessed using the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) (Inada, 1996). Life skills were assessed by family members living with the subjects using the LSP (Rosen et al., 1989; Hasegawa and Ogawa, 1997).

The SQLS is a self-reported, 30-item questionnaire for measuring QOL specific to patients with schizophrenia with good reliability and validity (Wilkinson et al., 2000; Kaneda et al., 2002). It is composed of three scales:

psychosocial, motivation/energy and symptoms/side effects. Lower scores indicate higher levels of subjective QOL.

The QLS is a measure to assess objective QOL by means of a semistructured interview. The reliability and validity of the scale have been verified (Heinrichs et al., 1984, 2001). The ratings are based upon patients' self-report and observers' judgment about the patients' functioning and life circumstances. This instrument has the following 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 were all experienced psychiatrists, conducted the interviews according to the Evaluation Manual for the QLS (Heinrichs et al., 2001).

According to the previous study, the sum of the scores for four symptoms (suspiciousness, hallucinatory behavior, conceptual disorganization, and unusual thought content) of the BPRS was considered to be a positive symptom score (McCreadie et al., 1990; Arango et al., 2003; Josiassen et al., 2005), and the sum of the scores for four other symptoms (emotional withdrawal, motor retardation, blunted affect, and disorientation) of the scale was considered to be a negative symptom score (Meltzer et al., 1990; Poulin et al., 2003; Kaneda and Ohmori, 2005).

The CDSS was specifically developed to distinguish depressive symptoms from positive or negative symptoms or antipsychotic-induced side effects in schizophrenia. A 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 nine items using a 5-point scale that ranges from 0 to 4. In this study, we used the rating of overall severity, which is one of the items of the DIEPSS. The reliability and validity of the scale have been verified (Inada, 1996).

Life skills were assessed using the LSP. The LSP was designed by Rosen et al. (1989) to assess survival and adaptation in the community by individuals with severe mental illness (Norman et al., 2000). The reliability and validity of the scale have been verified (Rosen et al., 1989; Hasegawa and Ogawa, 1997). The LSP has the following five subscales: self-care, non-turbulence, socialization, communication, and responsibility.

All the scales except for the SQLS and the LSP were carried out by the authors, all of whom were experienced psychiatrists. Inter-rater consistencies of the CDSS and the BPRS in our group have been shown to be satisfactory (Kaneda et al., 2000; Numata et al., 2006).

2.3. Statistical analysis

Pearson's correlation coefficients were calculated to study the relationships among the SQLS, the QLS and the LSP. Statistical significance was adjusted for multiple comparisons (Bonferroni correction). The SQLS scale score, the QLS total score and the LSP total score were chosen as dependent variables. Stepwise regression analyses were done to assess the independent contribution of other clinical variables (duration of illness, number of hospitalization, dose of antipsychotic medication, the BPRS positive symptoms score, the BPRS negative symptoms score, the DIEPSS score, and the CDSS score) to each dependent variable. Statistical analyses were done with the Statistical Package for the Social Sciences, version 11.5J. A P-value <0.05 was taken to indicate statistical significance.

3. Results

Demographic characteristics and means and standard deviations of the clinical indices are presented in Table 1.

Table 1
Demographic characteristics of subjects

N (M/W)		64(29/35)
Age (years)		41.8(12.7)
Duration of illness (years)		12.5(9.2)
Number of hospitalizations		1.4(1.5)
Dose of antipsychotics (mg/day)*		535.4(463.5)
Type of schizophrenia (n)	Residual	8
	Paranoid	49
	Catatonic	1
	Disorganized	6
Marital state (n)	Married	10
	Never married	48
	Divorced	5
	Widowed	1
Social state (n)	Full time	7
	Part time	5
	No employment	52
BPRS	Total	31.7(8.4)
	Positive	8.3 (3.8)
	Negative	9.1(3.3)
DIEPSS (Overall)		0.4(0.7)
CDSS (Total)		2.8(3.4)
SQLS	Psychosocial	39.9(18.7)
	Motivation/energy	49.3(19.9)
	Symptoms/side effects	25.5(17.7)
QLS (Total)		64.8(29.7)
LSP (Total)		133.7(13.1)

Results are means with S.D.; *Chlorpromazine equivalent; BPRS, Brief Psychiatric Rating Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; CDSS, Calgary Depression Scale for Schizophrenia; SQLS, Schizophrenia Quality of Life Scale; QLS, Quality of Life Scale; LSP, Life Skills Profile.

Table 2
Correlation coefficients among SQLS, QLS and LSP

	SQLS			QLS				
	Psychosocial	Motivation/ energy	Symptoms/side effects	Total	Interpersonal relations	Instrumental role	Intrapsychic foundation	Common objects and activities
QLS								
Total	−0.29	−0.49**	−0.28					
Interpersonal relations	−0.22	−0.43**	−0.20					
Instrumental role	−0.37*	−0.47**	−0.32					
Intrapsychic foundation	−0.29	−0.45**	−0.26					
Common objects and activities	−0.17	−0.40*	−0.34					
LSP								
Total	−0.47**	−0.41*	−0.46**	0.55**	0.48**	0.56**	0.49**	0.47**
Self-care	−0.40*	−0.32	−0.43**	0.52**	0.46**	0.54**	0.45**	0.49**
Non-turbulence	−0.44*	−0.25	−0.43**	0.16	0.08	0.24	0.17	0.13
Socialization	−0.36	−0.44**	−0.28	0.63**	0.57**	0.57**	0.57**	0.50**
Communication	−0.33	−0.31	−0.37*	0.37	0.32	0.39*	0.33	0.27
Responsibility	−0.24	−0.17	−0.25	0.26	0.22	0.29	0.23	0.26

SQLS, Schizophrenia Quality of Life Scale; QLS, Quality of Life Scale; LSP, Life Skills Profile; *$P<0.05$, **$P<0.01$ (Bonferroni correction).

All subjects were Japanese, with 29 males and 35 females. The average age was 41.8 years (S.D.=12.7). Subtype diagnoses included 49 paranoid type, 8 residual type, 6 disorganized type, and 1 catatonic type. Ten of the subjects were married, 48 had never been married, five had been divorced, and one was widowed. We used the chlorpromazine conversion chart (Inagaki et al., 1998, 2001a,b,c) to determine the dosage of antipsychotic medication.

The correlations among the SQLS, the QLS and the LSP are shown in Table 2. The SQLS motivation/energy scale significantly and negatively correlated with the QLS total ($r=-0.49$, $P<0.01$), interpersonal relations subscale ($r=-0.43$, $P<0.01$), instrumental role subscale ($r=-0.47$, $P<0.01$), intrapsychic foundation subscale ($r=-0.45$, $P<0.01$), and common objects and activities subscale ($r=-0.40$, $P<0.05$). The SQLS psychosocial scale significantly and negatively correlated with the LSP total ($r=-0.47$, $P<0.01$), self-care subscale ($r=-0.40$, $P<0.05$), and non-turbulence subscale ($r=-0.44$, $P<0.05$). The SQLS symptoms/side effects scale also had significant and negative correlations with the LSP total ($r=-0.46$, $P<0.01$), self-care subscale ($r=-0.43$, $P<0.01$) and non-turbulence subscale ($r=-0.43$, $P<0.01$). The SQLS motivation/energy scale had significant and negative correlations with the LSP total ($r=-0.41$, $P<0.05$) and socialization subscale ($r=-0.44$, $P<0.01$). The LSP total score significantly and positively correlated with the QLS total ($r=0.55$, $P<0.01$), interpersonal relations ($r=0.48$, $P<0.01$), instrumental role ($r=0.56$, $P<0.01$), intrapsychic foundation ($r=0.49$, $P<0.01$), and common objects and activities ($r=0.47$, $P<0.01$). The LSP self-care subscale correlated significantly and positively with the QLS total ($r=0.52$, $P<0.01$), interpersonal relations ($r=0.46$, $P<0.01$), instrumental role ($r=0.54$, $P<0.01$), intrapsychic foundation ($r=0.45$, $P<0.01$), and common objects and activities ($r=0.49$, $P<0.01$). The LSP socialization subscale score also had significant and positive correlation with the QLS total ($r=0.63$, $P<0.01$), interpersonal relations ($r=0.57$, $P<0.01$), instrumental role ($r=0.57$, $P<0.01$), intrapsychic foundation ($r=0.57$, $P<0.01$), and common objects and activities ($r=0.50$, $P<0.01$).

Table 3
Results of multiple regression analysis on SQLS, QLS Total and LSP Total

Dependent variable	Independent variable	R^2	β^*
SQLS			
Psychosocial	CDSS	0.405***	0.636***
Motivation/energy	CDSS	0.264***	0.514***
Symptoms/side effects	CDSS	0.197***	0.444***
QLS total	BPRS-negative	0.329***	−0.573***
LSP total	BPRS-negative	0.276***	−0.335**
	CDSS		−0.324**

SQLS, Schizophrenia Quality of Life Scale; QLS, Quality of Life Scale; LSP, Life Skills Profile; CDSS, Calgary Depression Scale for Schizophrenia; BPRS, Brief Psychiatric Rating Scale; *Standardized regression coefficient; **$P<0.01$, ***$P<0.001$.

Table 3 shows the results of stepwise regression analyses. The psychosocial scale score was significantly predicted only by the CDSS total score (β=0.636 P<0.001). The only significant predictor of the motivation/energy scale score was the CDSS total score (β=0.514 P<0.001). The symptoms/side effects scale score was also significantly predicted only by the CDSS total score (β=0.444 P<0.001). The QLS total score was significantly predicted only by the BPRS negative symptoms score (β=−0.573 P<0.001). The LSP total score was significantly and independently predicted by the BPRS negative symptoms score (β=−0.335 P<0.01) and the CDSS total score (β=−0.324 P<0.01).

4. Discussion

The primary goal of the present study was to examine how clinical factors influence patients' QOL and life skills. In addition, we investigated relationships among patient-rated subjective QOL, observer-rated objective QOL, and family-rated level of life skills. There were several important findings in this study. The results suggest what symptoms we should focus on in order to improve patients' QOL and life skills.

4.1. Relationship between subjective and objective QOL

Fitzgerald et al. (2001) reported some significant correlations between subscales of objective and subjective QOL measures in 174 outpatients. They used the QLS, a schizophrenia disease-specific objective QOL measure, and the self-report life satisfaction scale from the Schizophrenia Care and Assessment Program as a subjective QOL scale. We used a newly developed schizophrenia disease-specific subjective QOL measure, the SQLS, to investigate the relationship. It is of note that the motivation/energy score of the SQLS correlated with the QLS total and all subscales while the scores of the psychosocial scale of the SQLS correlated with only the instrumental role subscale but not other subscales of the QLS. The symptoms/side effects subscale of the SQLS did not significantly correlate with the total score or any subscale of the QLS. The motivation/energy subscale addresses various problems of motivation and activity, such as lacking the will to do things or engage in positive aspects of life (Wilkinson et al., 2000). It has been suggested that subjective assessment of motivation and activity might predict objective QOL. The absence of strong correlations between psychosocial or symptom/side effects scores of the SQLS and the QLS scores, however, suggests that these two QOL measures reflect different aspects of QOL.

4.2. Relationship between LSP and either subjective or objective QOL

Parker et al. (2002) reported no significant correlation between the LSP and subjective QOL. In contrast, we found the LSP total score, the LSP self-care subscale score, and the LSP non-turbulence subscale score correlated with psychosocial and symptoms/side effects scales of the SQLS. The LSP total score and socialization subscale score correlated with the motivation/energy scale. The LSP communication subscale score correlated with the symptoms/side effects score. However, the LSP responsibility subscale score did not correlate with any scale of the SQLS. The difference in results between the two studies may reflect the differences of subjects and QOL measures. Our subjects were composed of patients with schizophrenia, while their subjects included patients with schizophrenia, schizoaffective disorder, schizophreniform disorder, and bipolar disorder. We used the schizophrenia disease-specific subjective QOL measure, while they used the Quality of Life Index for Mental Health, which is not a measure specific to schizophrenia. Alternatively, the difference in the rater might contribute to the difference. The rater was the family member in our study but the community staff in theirs.

As for the relationship between objective QOL measure and the LSP, Norman et al. (2000) reported that the LSP assessed by psychiatrists was associated with objective QOL measured with the QLS. In agreement with their report, the LSP total, self-care and socialization subscales significantly correlated with the QLS total and the subscales. The LSP assessed by family members correlated with objective QOL. These results indicate that the LSP rated by the family is associated with both patient-rated subjective and observer-rated objective QOL in patients with schizophrenia. Assessment of patient life skill with the LSP by the family member may conveniently and accurately predict subjective and objective QOL.

4.3. The factors influencing subjective and objective QOL

Previous studies have found depressive symptoms predict subjective QOL (Dickerson et al., 1998; Fitzgerald et al., 2001; Sim et al., 2004). However, depressive symptoms in schizophrenia are difficult to distinguish from negative and drug-induced extrapyramidal symptoms (Addington et al., 1993). Recently, Reine et al. (2003) measured depressive symptoms with the CDSS, a scale specifically developed to measure depressive symptoms in schizophrenia, and replicated the previous finding. In the present study, using the CDSS and the SQLS, disease-specific measures of depressive

symptoms and subjective QOL, respectively, an association between depressive symptoms and subjective QOL was further confirmed. Objective QOL has been reported to be predicted by negative (Fitzgerald et al., 2001; Strejilevich et al., 2005) and extrapyramidal symptoms (Browne et al., 1996; Strejilevich et al., 2005). Our results also suggest negative symptoms predict objective QOL. Considering that the QLS was originally designed to evaluate deficit symptoms and the dysfunctions related to them (Heinrichs et al., 1984), the correlation between negative symptoms and the QLS scores seems to be reasonable. We did not find a significant correlation between objective QOL and extrapyramidal symptoms, probably because of relatively low levels of extrapyramidal symptoms in the present subjects. Positive symptoms have been reported to predict neither subjective (Dickerson et al., 1998; Fitzgerald et al., 2001; Sim et al., 2004) nor objective QOL (Fitzgerald et al., 2001; Browne et al., 1996; Strejilevich et al., 2005). Consistent with these previous studies, the present study suggests that positive symptoms do not predict subjective or objective QOL in stabilized outpatients with schizophrenia. In contrast, Norman et al. (2000) reported that positive symptoms were related to subjective QOL and that both positive and negative symptoms were related to objective QOL. Differences in the method and/or the subject population may account for the different findings.

4.4. The factors influencing the LSP

Parker et al. (2002) reported that the LSP correlated strongly with the Health of the Nation Outcome Scale, which assesses behavior (aggression, self-harm, substance abuse), impairment (memory, orientation, physical health), symptoms (mood disturbance, hallucinations, delusions), and social functioning (social relations, housing, activities). Their results suggest a good consistency between the two scales as measures of the functioning of patients with schizophrenia. Norman et al. (1999) reported that positive but not negative symptoms correlated with the LSP total and three subscales: social contact, communication, and self-care. They did not measure depressive symptoms. In contrast to their results, this study found that the BPRS negative symptom score and the CDSS total score predicted the LSP total independently, but positive symptoms did not predict it. One reason for the discrepancy may be different methods of analysis. We analyzed several clinical factors together using stepwise regression analyses, while they simply studied correlations between them. Another explanation may involve difference in the rater who completed the LSP. The patient's family members rated the LSP in our study while care managers did in their study. Although untrained, family members have a great advantage as the rater for the LSP because they know the patients' life skills thoroughly. Alternatively, the difference may be related to the difference in patient populations. Compared with their patients, our patients were older (41.8 vs. 30.9 years), with longer durations of illness (12.5 vs. 5.2 years) and with higher doses of antipsychotic medication (535.4 vs. 308.1 mg/day). Our results suggest that general levels of function and disability as assessed by family members using the LSP in outpatients with schizophrenia are associated with two types of symptomatology: depressive and negative symptoms.

In summery, we examined the relationship among patient-rated subjective QOL, observer-rated objective QOL, family-rated life skills, and their clinical determinants in outpatients with schizophrenia using schizophrenia disease-specific QOL measures as well as the LSP. The results indicate that depressive symptoms predict subjective QOL, negative symptoms predict objective QOL, and each of them predicts the level of social skills. Only the motivation/energy aspect, but no other aspect of subjective QOL, correlated with objective QOL. Family-rated life skills showed significant correlations with both subjective and objective QOL. These results suggest that the patient's QOL could be predicted by life skills assessed by a family member and also imply the importance of active treatment for depressive and negative symptoms in improving QOL and life skills of outpatients with schizophrenia.

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