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Gene expression in the peripheral leukocytes and association analysis of PDLIM5 gene in schizophrenia

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Abstract

PDLIM5 modulates neuronal calcium signaling, co-localizes with synaptic vesicles of neurotransmitters and positive association between its gene and schizophrenia was reported but its relation is still ambiguous. The differential expression of the PDLIM5 gene both in the brain and in the lymphoblasts has been found in schizophrenia compared to control subjects. In this study, we measured the expression level of the PDLIM5 gene transcripts in the peripheral leukocytes from 19 medication-free and 21 chronically medicated schizophrenic patients as well as age- and sex-matched control subjects using a quantitative real-time PCR method. The mRNA levels of the PDLIM5 gene in the leukocytes of medication-free schizophrenic patients were significantly higher than those of control subjects. On the other hand, our group has previously shown that its mRNA expression in the leukocytes of medication-free major depressive patients was significantly lower compared with controls. There was no difference in the PDLIM5 mRNA levels between chronic schizophrenic patients with antipsychotic medication and their controls. Further, we failed to find any genetic association between the PDLIM5 gene and schizophrenia with six single nucleotide polymorphics (SNPs) of the PDLIM5 gene in Japanese subjects (279 subjects each) and there was no significant relation between PDLIM5 gene and schizophrenia with the haplotype analysis ($P = 0.48$), either. We suggest that the higher expression levels of the PDLIM5 mRNA in the peripheral leukocytes may be a candidate marker for medication-free schizophrenic patients.

Keywords: PDLIM5; Gene expression; Leukocytes; Association analysis; Schizophrenia

PDLIM5 is an intermediate protein that has been shown to regulate intracellular calcium levels by linking calcium channel and protein kinase C (PKC) [2,3,16]. PDLIM5 is ubiquitously expressed and its cellular localization in the brain is identical to Synapsin which is known to be involved in the neurotransmitter release [16]. The PDLIM5 gene lies on chromosome 4q22, a locus previously reported to be linked with schizophrenia [13,19]. While Kato et al. failed to find any association between the PDLIM5 gene and schizophrenia [15], Horiuchi et al. found a significant association between them [6]. It was reported that the expression level of PDLIM5 mRNA was significantly increased in the postmortem brain tissues of patients with schizophrenia, bipolar disorder and major depression, but was decreased in the immortalized lymphoblastoid cell lines derived from patients with schizophrenia and bipolar disorder [10,11]. Our group has recently shown that levels of mRNA expression in the peripheral leukocytes of the PDLIM5 gene were significantly lower in medication-free major depressive patients compared with controls [8].

The expressional alterations of genes in the peripheral blood lymphocytes and leukocytes have been reported to indicate the changes of the central nervous systems in schizophrenia and

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Table 1a
Demographic data for medication-free schizophrenic patients studied in PDLIM5 mRNA expression analysis ($N = 19$)

	Age (y.o)	Gender	Age at onset (years)	BPRS score	Family history of schizophrenia in first-degree relative
S1	25	M	22	64	+
S2	24	M	24	42	−
S3	24	M	24	31	−
S4	27	M	24	37	−
S5	36	M	36	34	−
S6	39	M	38	59	−
S7	27	M	26	58	−
S8	20	F	19	46	−
S9	23	F	23	48	−
S10	34	F	31	36	−
S11	47	F	47	30	−
S12	15	F	13	30	+
S13	26	F	21	100	−
S14	23	M	23	31	−
S15	28	M	25	63	−
S16	47	F	47	37	−
S17	37	F	21	36	−
S18	30	F	25	41	−
S19	45	F	43	36	+

The age (years old: y.o) represents the age of the subject when the leukocytes were drawn. M: male, F: female, '+' indicates that at least one of the first-degree relatives has schizophrenia.

major depressive disorder [7,8,9,17,21]. In this study, we measured the PDLIM5 mRNA expression levels in the peripheral leukocytes in unmedicated and medicated schizophrenic patients as well as in control subjects, using a quantitative real-time PCR method. In addition, we examined the genetic case-control study of the PDLIM5 gene with schizophrenia in Japanese subjects comprising of 279 patients with schizophrenia and 279 controls.

All patients and controls were biologically unrelated Japanese. The diagnosis of schizophrenia was made by at least two experienced psychiatrists according to DSM-IV criteria [1]. Clinical symptoms were evaluated by the Brief Psychiatric Rating Scale scores (BPRS) [20] when blood samples were taken. Age- and sex-matched controls were in good physical health without a history of any psychiatric or serious somatic diseases and taking any medication during the sample collection period. Probands who had first-degree relatives with psychiatric disorders were excluded from the control subjects.

For the measurement of expression levels of the PDLIM5 mRNA, the subjects consisted of 19 medication-free patients with schizophrenia (subject number S1–S19, Tables 1a and 1b) (14 first-episode and drug-naïve schizophrenic patients, 5 schizophrenic patients without antipsychotic treatment for at least 2 months; 9 males and 10 females, mean age: 30.4 ± 9.3), 19 age- and sex-matched controls (9 males and 10 females, mean age: 30.6 ± 8.6), 21 chronically treated patients with schizophrenia who were stably controlled under the same amount dosage of antipsychotics for at least 3 months (subject number S20–S40, Tables 2a and 2b) (13 males and 8 females, mean age: 47.7 ± 11.3) and 21 age- and sex-matched controls (mean age: 47.7 ± 11.1).

For the genetic association study, we used DNA samples from 279 in patients (189 male and 90 female; mean age: 51.3 ± 13.7 years) with schizophrenia from 13 psychiatric hospitals in the neighboring area of Tokushima Prefecture in Japan (population: about 820,000). Age- and sex-matched controls were selected from volunteers after assessing the psychiatric problems (189 male and 90 female; mean age: 51.4 ± 12.0) for the association and haplotype-based case-control study.

All subjects signed written informed consent to participate in the expression and genetic association studies approved by the institutional ethics committees.

Table 1b
PDLIM5 mRNA expression in medication-free schizophrenic ($N = 19$) and control subjects ($N = 19$)

	Male ($N = 9$)	Female ($N = 10$)	Total ($N = 19$)
Schizophrenia (S1–S19)			
Age	28.1 ± 5.6	32.4 ± 11.5	30.4 ± 9.3
The PDLIM5 mRNA expression before treatment	1.13 ± 0.3	1.29 ± 0.3	1.21 ± 0.3*
Control			
Age	27.6 ± 4.8	33.4 ± 10.4	30.6 ± 8.6
The PD1IM5 mRNA expression	0.95 ± 0.2	1.03 ± 0.4	1.00 ± 0.3

The mean PDLIM5 mRNA levels in the peripheral leukocytes from medication-free schizophrenia patients were significantly higher than those of age- and sex-matched controls (Mann–Whitney U test: $P = 0.023$); $^{*}P < 0.05$. No correlation between PDLIM5 mRNA levels and baseline BPRS scores were observed (Spearman's correlation efficient: $P = 0.38$).

Table 2a
Demographic data for chronic schizophrenic patients studied in PDLIM5 mRNA expression analysis ($N = 21$)

	Age (y.o)	Gender	Medication	BPRS Score
S20	57	M	QTP 75 mg, LP 150 mg, CP 300 mg	55
S21	56	M	Ris 6 mg	29
S22	56	M	Ris 5 mg, QTP 200 mg, sulpiride 150 mg	44
S23	60	M	Ris 8 mg, LP 20 mg	67
S24	57	M	HPD 9 mg, BPD 9 mg propericyazine 60 mg	52
S25	40	M	Ris 12 mg	33
S26	46	M	Ris 6 mg, HPD 9 mg, sultopride 900 mg	49
S27	45	M	BPD 9 mg, clocaprarmine 75 mg	59
S28	31	M	BPD 2 mg, HPD 1 mg, LP 15 mg Perospirone 24 mg	49
S29	49	F	Ris 6 mg, HPD 6 mg, CP 20 mg, HPD decanoate 150 mg	33
S30	53	F	HPD 2.25 mg, sulpride 150 mg	33
S31	65	F	HPD 4.5 mg, CP 37.5 mg	47
S32	51	F	Olz 10 mg	23
S33	43	F	Ris 6 mg, zotepine 50 mg	45
S34	54	F	Olz 20 mg, LP 50 mg	38
S35	54	M	Ris 12 mg, zotepine 150 mg timiperone 6 mg	42
Sc36	25	M	Ris 9 mg, perospirone 16 mg	39
Sc37	49	M	Ris 12 mg, LP 150 mg	54
Sc38	23	M	Ris 12 mg, LP 150 mg	38
Sc39	35	F	Olz 20 mg	33
Sc40	53	F	QTP 400 mg	27

The age (years old: y.o) represent the age of the subject when the leukocytes were drawn. M: male, F: female, Olz: olanzapine, Ris: risperidone, HPD: hapoperidol, BPD: bromperidol, LP; levom epromazine.

Total RNA was extracted from the peripheral leukocytes using the PAX gene Blood RNA kit (Qiagen, Tokyo, Japan) according to the manufacturer's recommendations. One microgram of total RNA was used for cDNA synthesis by QuantiTect Reverse Transcription Kit (Qiagen) after assessing RNA quality and quantity with NanoDrop (NanoDrop Technologies, DE, USA). Expression of the PDLIM5 gene transcript was quantified by real-time PCR with the TaqMan Gene Expression Assay (Applied Biosystems, CA, USA). Primers and probes (Hs00179051_m1) were purchased from Applied Biosystems as well as Horiuchi's group [6]. GAPDH gene expression was used as an internal control and measurement of threshold cycle (Ct) was performed in triplicate. Data were collected and analyzed with Sequence Detector Software version 2.1 (Applied Biosystems) and the standard curve method. Relative gene expression was calculated as the ratio of PDLIM5 to GAPDH gene and the mean of the three replicate measures was assigned to each individual. Almost all of blood samples were taken in the morning before lunch. The expression of the PDLIM5 mRNA was not changed among blood samples collected at several points during the day time or over several weeks in the same control subjects.

Genotyping was performed using commercially available TaqMan probes (C_2095059_10, C_16015055_20, C_3226622_10, C_16015313_10, C_1569781_10, C_11567561_10) with Applied Biosystems 7500 Fast Real Time PCR System according to the protocol recommended by the manufacturer (Applied Biosystems). We selected six single nucleotide polymorphic (SNP) markers for genotyping according to linkage disequilibrium (LD) and haplotype blocks in the PDLIM5 gene region [6]. Two SNPs (rs10008257, rs2433320) in the 5′-flanking region and four SNPs left in the genomic region are covered about 169-kb in the whole 214-kb of the PDLIM5 gene. The heterozygocities of four of these six SNPs, rs10008257, rs2433320, rs2433327 and rs2452600 in Japanese population are reported as 0.39, 0.18, 0.26 and

Table 2b
PDLIM5 mRNA expression in chronic treated schizophrenic ($N = 21$) and control subjects ($N = 21$)

	Male ($N = 13$)	Female ($N = 8$)	Total ($N = 21$)
Schizophirenia (S20–S40)			
Age	46.1 ± 12.7	50.4 ± 8.7	47.7 ± 11.3
The PDLIM5 mRNA expression	0.78 ± 0.2	0.93 ± 0.2	0.83 ± 0.2
Control			
Age	46.2 ± 12.3	50.1 ± 9.0	47.7 ± 11.1
The PD1IM5 mRNA expression	0.90 ± 0.3	1.14 ± 0.4	1.00 ± 0.3

The mean PDLIM5 mRNA levels in the peripheral leukocytes from schizophrenia patients who has been treated with antipsychotic drugs for many years were not different from controls' (Mann–Whitney U test: $P = 0.16$). No correlation between PDLIM5 mRNA levels and baseline BPRS scores were observed (Spearman's correlation efficient: $P = 0.82$).

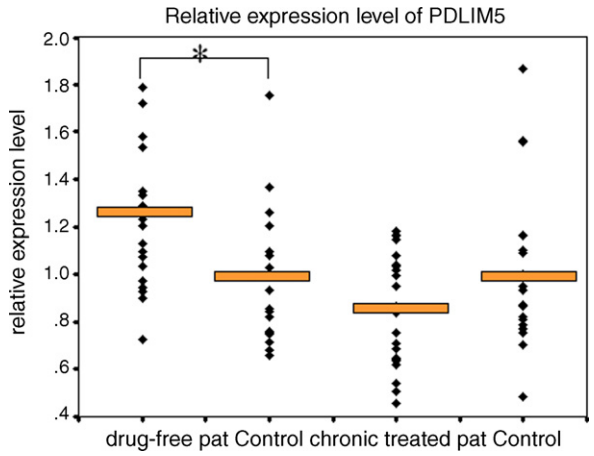

Fig. 1. Relative expression levels of PDLIM5 in the peripheral leukocytes in schizophrenic patients and control subjects. Compared with the normal control group, the mean PDLIM5 mRNA level in the leukocytes of medication-free schizophrenic patients ($N = 19$) was significantly higher (patients: 1.21 ± 0.29, controls: 1.00 ± 0.29, Mann–Whitney U test: $P = 0.023$). The mean PDLIM5 mRNA level in the leukocytes of chronic schizophrenic patients ($N = 21$) showed no significant difference compared with controls (patients: 0.83 ± 0.23, controls: 1.00 ± 0.32, Mann–Whitney U test: $P = 0.16$).

0.34, respectively. The heterozygocities of the other two SNPs, rs12641023 and rs14082, are not reported.

Statistical calculations were carried out using the SPSS Statistical Software Package 11.5 (SPSS, Tokyo, Japan). Expressional differences between patients and control subjects were calculated using the Mann–Whitney U test. Spearman correlation coefficients were used to evaluate the correlations between PDLIM5 mRNA levels and BPRS scores. Two-way ANOVA was performed to determine the independent and combined effects of age and the expression of PDLIM5 between groups. Allele and genotype frequencies of patients and control subjects were compared using Fisher's exact test. The SNPAlyze 3.2 Pro software (DYNACOM, Japan) was used to estimate haplotype frequencies, LD, and permutation P-values. Pair-wise linkage disequilibrium indices, D' and r2, were calculated in the control subjects. The criterion for significance was set at $P < 0.05$ for all tests. Data are presented as mean ± standard deviation.

Relative expression levels of PDLIM5 mRNA in 19 medication-free patients (S1–S19) were 1.21 ± 0.29 in the range of 0.73–1.79, while 1.00 ± 0.29 (range: 0.66–1.75) in healthy volunteers, showing a statistical difference (Mann–Whitney U test: $P = 0.023$, Fig. 1). Mean BPRS scores was 45.2 ± 17.4. No correlation between PDLIM5 mRNA levels and baseline BPRS scores were observed (Spearman's correlation efficient: $P = 0.38$). There was no significant expressional difference of PDLIM5 mRNA levels either between males and females or between genotypes of the single nucleotide polymorphism (rs2433320) both in patients with schizophrenia and in control subjects.

Relative PDLIM5 mRNA level was 0.83 ± 0.23 (0.46–1.18) in 21 chronically treated patients (S20–S40), while 1.00 ± 0.32 (0.49–1.87) in healthy volunteers, showing no significant statistical difference (Mann–Whitney U test: $P = 0.16$; Fig. 1). Mean chlorpromazine-equivalent doses were 932.1 ± 510.5 mg/day and mean duration of treatment was 23.5 ± 10.7 years and mean BPRS scores was 43.1 ± 10.8. No significant relationship between PDLIM5 mRNA levels and BPRS scores was observed (Spearman correlation efficient: $P = 0.71$). There was no significant expressional difference of PDLIM5 mRNA levels either between males and females or between genotypes of the single nucleotide polymorphism (rs2433320) both in patients with schizophrenia and in control subjects.

There were no significant deviations in all six SNPs from Hardy-Weinberg equilibrium in either patients or control subjects. Allele and genotype frequencies of the six SNPs are shown in Table 3. There were no associations between these SNPs and schizophrenia neither in the allelic frequency nor in the genotypic distributions. Although both rs2433320-rs2443327 and rs12641023-rs14082 were in a tight LD ($D' = 0.936$, 0.968, each), permutation test showed no significant difference in estimated frequencies of these haplotypes between the controls and patients (global permutation $P = 0.58$, 0.45, each, Table 4). Haplotypes of six SNPs were evaluated, but no significant difference was observed in frequencies of any estimated haplotype or in distributions of all estimated haplotypes between the controls and patients (global permutation $P = 0.48$).

The present study is the first report on the PDLIM5 gene expression in the peripheral leukocytes in schizophrenia. The mean PDLIM5 mRNA levels in the peripheral leukocytes from medication-free schizophrenia patients were significantly higher than those of age- and sex-matched controls. Altered mRNA expression in the peripheral lymphocytes could reflect the altered metabolism of brain cells [4]. Our result is consistent with the result of higher expression in the postmortem brains from schizophrenic patient but not with the result of lower expression in the lymphoblastoid cells derived from schizophrenic patients [10,11]. The differences of the mRNA expression between studies may be partly attributed to the difference in the materials. When using lymphoblastoid cells, the effect of virus infection or chromosomal alterations during culture must be taken into account [12]. On the other hand, the mRNA expression level of PDLIM5 gene was not significantly higher in chronically treated schizophrenics compared with that of controls. This finding in the chronic patients may be a consequence of pharmacological effects of antipsychotics or clinical improvement. This result suggests that expression of PDLIM5 mRNA may not be trait-oriented but state-related change. To confirm whether the expression of this gene is a state marker, a follow-up investigation is needed in the same patients before and after treatment.

The pathophysiological mechanism remains unknown, but we speculate that the higher expression of PDLIM5 is related with putatively elevated Ca^{2+} signaling in schizophrenia. It has been suggested that abnormalities in Ca^{2+} signaling was associated with molecular etiology of schizophrenia. Regulator of G protein signaling-4 (RGS4) and B-cell limphoma/leukaemia-2 gene (Bcl-2) which reduce free Ca^{2+} in a cell have been found to be down regulated in the temporal cortex of schizophrenic patients [14,18]. It was reported that there was high levels of free intracellular Ca^{2+} in platelets of schizophrenic patients

Table 3
Genetic studies of PDLIM5 gene with schizophrenia in case-control samples

Group	Genotype			*n*	Hardy-Weinberg equilibrium	*P*-value	Allele		*P*-value
ra1 0008257	A/A	A/G	G/G				A	G	
sch	42	127	105	274	0.823	0.471	211	337	0.804
cont	34	140	102	276	0.229		208	344	
rs2433320									
sch	7	75	197	279	0.858	0.601	89	469	0.871
cont	11	70	198	279	0.205		92	466	
rs2433327	T/T	T/C	C/C				T	C	0.833
sch	169	88	16	273	0.414	0.917	426	120	
cont	164	92	15	271	0.788		420	122	
rs2452600	T/T	T/C	C/C				T	C	
sch	54	125	96	275	0.306	0.232	233	317	0.080
cont	68	130	81	279	0.325		266	292	
rsl2641023	A/A	A/G	G/G				A	G	
sch	51	126	93	270	0.555	0.497	228	312	0.295
cont	42	131	103	276	0.924		215	337	
rs14082	A/A	A/G	G/G				A	G	
sch	58	124	91	273	0.243	0.302	240	306	0.141
cont	45	125	103	273	0.582		215	331	

sch: Schizophrenia, cont: control subjects. *P*-values are calculated by Fisher s exact test.

[22]. PDLIM5 regulates intracellular calcium levels by linking calcium channel and protein kinase C [2,3,16]. The levels of PDLIM5 might be up-regulated both in the brain and in the peripheral leukocytes in patients with schizophrenia in response to increased intracellular calcium levels. It has been demonstrated that antipsychotic drugs block IP3-induced release of Ca^{2+} [23] and Ca^{2+} dependence of PKC is well known [5]. So antipsychotic medication might normalize the up-regulation of PDLIM5 expression in schizophrenia by reducing Ca^{2+} signaling.

PDLIM5 may be involved in other mental disorders. Iwamoto et al. reported that expression level of PDLIM5 was significantly and commonly increased in the postmortem brain tissues of patients with schizophrenia, major depression and bipolar disorder [11]. However, we have already shown that mean PDLIM5 mRNA level in the peripheral leukocytes of medication-free patients with major depression was significantly lower than in control subjects [8]. Therefore, the higher expression of this gene in the peripheral leukocytes of medication-free patients with schizophrenia may be disease-specific and not due to non-specific stress of psychiatric condition. Further investigations of other psychiatric diseases including bipolar disorder are needed.

Table 4
Linkage disequilibrium (LD) indices (lower left are r2, upper right are *D′*)

	rs10008257	rs2433320	rs2443327	rs2452600	rs12641023	rs14082
rs10008257		0.37227	0.44147	0.28294	0.12734	0.15919
rs2433320	0.01632		0.9364	0.50709	0.37209	0.40839
rs2443327	0.03427	0.57719		0.54423	0.43945	0.45693
rs2452600	0.0447	0.05573	0.09541		0.19114	0.18089
rs12641023	0.00626	0.04284	0.08854	0.02152		0.96845
rs14082	0.01002	0.05068	0.09508	0.01918	0.93062	

Horiuchi et al. reported that there were significant association between polymorphisms (rs2433320 and rs2433322) of PDLIM5 gene and schizophrenia. Their group also showed that the different alleles of the rs2433320 showed different DNA–protein complexes on electrophoreic mobility shift assay and GA heterozygotic genotype might have higher transcriptional activity in schizophrenia [6]. However, our result showed that there was not significant association between schizophrenia and six polymorphisms of PDLIM5 gene, including rs2433320, and this result is consistent with a previous study with a large number of subjects ($n = 562$) [15]. In addition, neither patients nor controls showed a significant difference of the PDLIM5 mRNA expression in the peripheral leukocytes between GG and GA genotypes of this SNP in our subjects although the typeII error was not denied.

In conclusion, our investigation revealed that the mean PDLIM5 mRNA levels in medication-free schizophrenic patients were significantly higher compared to those in controls and the chronic schizophrenic patients with antipsychotic treatment for many years showed almost the same expression levels as healthy control levels. There were no associations between schizophrenia and PDLIM5 gene. These results suggest that the higher expression levels of PDLIM5 mRNA in the leukocytes may be a candidate marker for medication-free schizophrenic patients. Further studies are necessary to confirm the present results.

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