Table 1: Genotype and allele frequencies of *HTR2A*, *HTR3A* and *HTR4* polymorphisms in TRS and NON-TRS

	Genotype			P value	Allele frequency (%)		P value	Global P-value
HTR2A								
rs6313	C/C	C/T	T/T		C	T		
TRS	19	58	23	0.500	48	52	0.777	
NON-TRS	48	123	68		46	54		
HTR3A								
rs1062613	C/C	C/T	T/T		C	T		
TRS	75	21	5	0.117	85	15	0.400	
NON-TRS	189	47	3		89	11		0.576
rs1176713	A/A	A/G	G/G		A	G		
TRS	49	38	14	0.744	67	33	0.648	
NON-TRS	124	86	27		70	30		
HTR4								
rs2278392	G/G	G/A	A/A		G	A		
TRS	59	36	7	0.867	76	24	0.868	
NON-TRS	148	80	15		77	23		0.863
rs3734119	T/T	T/C	C/C		T	C		
TRS	59	36	8	0.891	75	25	0.869	
NON-TRS	148	80	19		76	24		

Table 2: Characteristics of NLP treatment among three subgroups showing *HTR2A*, *HTR3A* and *HTR4* polymorphisms

	Genotype		
HTR2A			
rs6313	C/C	C/T	T/T
Daily NLP	575 (2-4042)	603 (4-12893)	372 (3-6283)
HTR3A			
rs1062613	C/C	C/T	T/T
Daily NLP	496 (2-12893)	568 (5-12850)	1179 (281-3048)[a]
rs1176713	A/A	A/G	G/G
Daily NLP	559 (3-8337)	417 (2-12893)	710 (42-4226)
HTR4			
rs2278392	G/G	G/A	A/A
Daily NLP	491 (2-12893)	600 (4-6283)	460 (50-2262)
rs3734119	T/T	T/C	C/C
Daily NLP	491 (2-12893)	605 (4-6283)	439 (30-2262)

Data are expressed as median (Min-Max).

[a] **P=0.041** when compared to the (C/C+C/T) subgroup.

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BRIEF REPORT

CINP

Genetic polymorphisms in the 5-hydroxytryptamine type 3B receptor gene and paroxetine-induced nausea

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Abstract

Selective serotonin reuptake inhibitor (SSRI)-induced nausea can be severe enough to lead to early treatment discontinuation. However, it is currently not possible to predict the occurrence of nausea before the initiation of SSRI treatment. In this study, we investigated the effect of genetic polymorphisms in the 5-hydroxytryptamine type 2A, 3A, and 3B (*5-HT$_{3B}$*) receptors, 5-HT transporter, and *CYP2D6* genes on the incidence of paroxetine-induced nausea. A consecutive series of 72 Japanese patients with depressive or anxiety disorders were treated with paroxetine. Paroxetine-induced nausea was assessed by a pharmacist and was observed in 29.2% of the patients. A significant (nominal $p=0.00286$) association was found between the incidence of nausea and the -100_-102AAG insertion/deletion polymorphism of the *5-HT$_{3B}$* receptor gene. No significant associations were observed between the other genetic polymorphisms and the incidence of nausea. The -100_-102AAG deletion variant of the *5-HT$_{3B}$* receptor gene may affect paroxetine-induced nausea.

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Key words: Genetic polymorphism, nausea, paroxetine, selective serotonin reuptake inhibitor, 5-hydroxytryptamine type 3B receptor.

Introduction

Paroxetine, a selective serotonin reuptake inhibitor (SSRI), has been widely and successfully used in the treatment of major depressive disorder, panic disorder, obsessive–compulsive disorder, generalized anxiety disorder and social phobia (Wagstaff et al., 2002). SSRIs, including paroxetine, have now become the first-line treatment for depression, especially in elderly patients, replacing the well-established tricyclic antidepressants, probably because of their better adverse-effect profile and safety. However, SSRIs induce adverse effects such as gastrointestinal symptoms, headache, anxiety, and sexual dysfunction. Of the gastrointestinal side-effects, nausea is the most problematic. It has been reported to be the most frequent adverse effect induced by SSRIs, occurring in about 15–30% of treated patients (Ottevanger, 1994; Takahashi et al., 2002; Wagner et al., 1992), and the nausea can often be severe enough to lead to early discontinuation of treatment (Murphy et al., 2003;

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Ottevanger, 1994; Wagner et al., 1992). The four main SSRIs (sertraline, fluvoxamine, fluoxetine and paroxetine) have been shown to be similar in this regard (Ottevanger, 1994). Therefore, it would be of great benefit to be able to predict the occurrence of nausea before SSRI treatment is started.

Bergeron and Blier (1994) reported that a low dose of cisapride, which is not available now because of its cardiotoxic effects, with the 5-hydroxytryptamine type 3 (5-HT_3) antagonistic and 5-HT_4 agonistic property produced rapid relief from nausea elicited by SSRIs. Bailey et al. (1995) showed in a double-blind, placebo-controlled study that the co-administration of ondansetron, a selective 5-HT_3 receptor antagonist, significantly attenuated the nausea induced by fluvoxamine in healthy volunteers. Thus, nausea induced by SSRIs seems to be elicited by serotonin release and the consecutive activation of the 5-HT_3 receptors on peripheral vagal afferent terminals in the gastrointestinal mucosa and central structures such as the area postrema and nucleus tractus solitarii (Miller and Leslie, 1994; Tyers and Freeman, 1992). A few studies using the whole-cell patch-clamp technique have shown that fluoxetine inhibited the 5-HT_3 receptor-mediated currents (Choi et al., 2003; Fan, 1994) and indicate that the 5-HT_3 receptor may contribute to the pharmacological actions of SSRIs.

Tremblay et al. (2003) reported an interesting and notable study that investigated the efficacy of 5-HT_3 receptor antagonists for chemotherapy-induced nausea and vomiting in cancer patients and showed that patients who underwent anti-emetic treatment and who were homozygous for the -100_-102AAG deletion allele of the *5-HT_{3B}* receptor gene had the highest nausea and vomiting score, whereas patients homozygous for the -100_-102AAG insertion allele had the lowest nausea and vomiting score.

Based on the reports described above, we hypothesized that polymorphisms of the *5-HT_3* receptor gene might be also associated with the incidence of paroxetine-induced nausea.

Paroxetine is metabolized extensively by cytochrome P450 2D6 (CYP2D6) (Sindrup et al., 1992), and CYP2D6 is known to have genetic polymorphisms that affect enzymatic activity (Zanger et al., 2004). These observations suggest that the *CYP2D6* gene polymorphism may influence paroxetine-induced nausea.

Although, several studies have investigated the relationship between serotonergic genetic polymorphisms such as *5-HT_{2A}* receptor and 5-HT transporter (*5-HTT*) genes and SSRI-induced nausea (Murphy et al., 2003, 2004; Sugai et al., 2006; Suzuki et al., 2006; Takahashi et al., 2002), the association of the variants with individual differences in the occurrence of SSRI-induced nausea remains controversial. At present, it is not possible to predict the occurrence of nausea before the initiation of SSRI treatment.

The present study was done to elucidate the effects of genetic polymorphisms in the serotonergic receptors, *5-HTT* and *CYP2D6* genes of Japanese patients on the incidence of paroxetine-induced nausea.

Methods

Subjects

The subjects were a series of 81 consecutive Japanese outpatients who were treated with paroxetine and who provided written informed consent after the procedure was fully explained. All of the patients had DSM-IV diagnoses (APA, 1994) of depressive disorders or anxiety disorders, and were treated at the Department of Psychosomatic Medicine, Kyushu University Hospital. Patients with severe physical illness were excluded from the study. No patients were being treated with anti-emetic medication during the present study. The patients visited the hospital once each week during the first 2 wk of treatment, and then visited every 2 wk for the treatment and assessment of adverse effects, including nausea. The paroxetine dose was increased from 10 mg/d to 20, 30, or 40 mg/d in response to clinical symptoms. Patients taking benzodiazepines, zolpidem or tandospirone were included. No other psychotropic drugs were administered during the study. The study was approved by the Ethics Committee of the Kyushu University Hospital.

Assessment of nausea induced by paroxetine

The severity of adverse effects after the administration of paroxetine was assessed according to the Udvalg for Kliniske Undersogelser (UKU) side-effects rating scale (Lingjaerde et al., 1987). For the assessment, a pharmacist interviewed the patient before and 1, 2, 4, 8, and 12 wk after the start of treatment. Because nausea and vomiting are not only adverse effects of paroxetine treatment but also symptoms of depressive disorders, subjects who had nausea before treatment were excluded.

DNA analysis

Genomic DNA was isolated from peripheral blood using the QIAamp DNA Blood Mini kit (Qiagen, Hilden, Germany). For the identification of polymorphisms in the protein coding exons including the

exon–intron junctions and the 5'-flanking region of the *5-HT$_{3B}$* receptor gene, polymerase chain reaction–single strand conformational polymorphism (PCR–SSCP) analysis was performed with genomic DNA obtained from 81 unrelated patients. The primer design was based on published sequences (GenBank accession number NM006028). The primer sequences are presented in Supplementary Table S1 (available in the online version of the paper). PCR products were sequenced either directly or after subcloning on an ABI 310 automatic sequencer (Applied Biosystems, Foster City, CA, USA). For genotyping of the *5-HT$_{3A}$* receptor gene, PCR–restriction fragment length polymorphism assays were developed; *Hpy*188III for C-42T (dbSNP database identification number, rs1062613), *Dra*I for G2423A (rs1176722), and *Bfa*I for A14371G (rs1176713). The other gene polymorphisms were genotyped according to the previously described methods for T102C (rs6313) of the *5-HT$_{2A}$* receptor gene (Ozaki et al., 1996), *5-HTT* gene-linked polymorphic region (5-HTTLPR) (Takahashi et al., 2002), and *CYP2D6* (Zanger et al., 2004).

Determination of plasma concentration of paroxetine

Blood samples were obtained after at least 2 wk of the same daily dose of paroxetine was administered to ensure that patients had a steady-state plasma concentration of paroxetine. Blood was collected into a heparinized tube approximately 15.7 ± 2.4 h (0.5–20.2) after the last dose of paroxetine. The plasma level of paroxetine was determined using a gas chromatography–mass spectrometry method described by Eap et al. (1998).

Statistical analysis

The significance of frequency differences of the different genotypes was assessed by Fisher's exact test. The scores of nausea and vomiting of the genotype groups were compared by the Mann–Whitney *U* test. The limit of significance was set to 0.05. Bonferroni correction was performed for multiple comparisons and the nominal *p* value was considered significant at <0.00294 (0.05 divided by 17 genetic polymorphisms). The plasma level of paroxetine was compared by one-way ANOVA.

Results

Of the 81 patients, nine who had nausea before the administration of paroxetine were excluded, leaving 35 male and 37 female patients (57 depressive disorder, 15 anxiety disorder; age range 17–78 yr; mean age ± S.D. 47.0 ± 17.5 yr; mean body weight ± S.D. 62.2 ± 11.4 kg) for analysis of the effect of genetic polymorphisms on nausea induced by paroxetine. Of these 72 patients, 21 (29.2%) experienced nausea within the first week after administration of paroxetine, and two (2.8%) discontinued the treatment with paroxetine due to severe paroxetine-induced nausea.

Among the 81 unrelated patients, eleven polymorphisms were detected in the *5-HT$_{3B}$* receptor gene by SSCP analysis and identified by subsequent sequencing (Table 1). In the coding region, A27373G was detected with an amino-acid substitution from Tyr to Ser at codon 129 (Tyr129Ser). G27449A (Ala154Ala) was observed as a synonymous polymorphism and G26943A, A26946G, and A28232G were found as intronic polymorphisms. In the 5'-flanking region, six polymorphisms were identified: C-1710T, T-833C, G-761A, T-381C, C-206T and an AAG deletion at -100 to -102. The genotype distributions of these 11 variants were in Hardy–Weinberg equilibrium. A screening of the dbSNP database showed T-833C, C-206T and G26943A to be novel variants.

As shown in Table 2, a significant (nominal $p=0.00286$, Fisher's exact test) difference in genotypic distribution associated with the -100_-102AAG insertion/deletion polymorphism of the *5-HT$_{3B}$* receptor gene was found between patients with and without nausea, and the -100_-102AAG deletion allele carriers (i.e. patients with either insertion/deletion or deletion/deletion) showed a significantly higher incidence of nausea than patients who were homozygous for the -100_-102AAG insertion allele. The Tyr129Ser polymorphism of the *5-HT$_{3B}$* receptor gene had no significant effect on the incidence of paroxetine-induced nausea (nominal $p=0.0680$, Fisher's exact test) nor did the other polymorphisms of the *5-HT$_{3B}$* receptor gene [data are presented in Supplementary Table S2 (available online)].

No significant differences between patients with and without nausea were found in the genotype distribution of C-42T, G2423A, and A14371G of the *5-HT$_{3A}$* receptor gene, T102C of the *5-HT$_{2A}$* receptor gene, 5-HTTLPR of the *5-HTT* gene and *CYP2D6* gene polymorphisms (Supplementary Table S2).

The nausea score was significantly higher in the -100_-102AAG deletion allele carriers than in patients homozygous for the -100_-102AAG insertion allele [median (25%, 75%): 1 (0, 1) vs. 0 (0, 0), nominal $p=0.0028$, Mann–Whitney *U* test). No significant associations were observed between the other genetic polymorphisms and the nausea score (data not shown).

Table 1. Genetic polymorphisms of the *5-HT$_{3B}$* receptor gene in 81 Japanese patients (36 males and 45 females)

Location	Position[a]	Reference allele[b]	Variant allele	Amino acid substitution	rs number[c]	Genotype[d]			Frequency of variant allele
						R/R	R/V	V/V	
5'-flanking region	-1710	gccaCtgtc	gccaTtgtc	–	rs10789970	11	39	31	0.623 (0.544–0.702)
	-833	ggggTgtct	ggggCgtct	–	–	76	5	0	0.031 (0.003–0.059)
	-761	atgcGtatt	atgcAtatt	–	rs11214763	61	20	0	0.123 (0.070–0.176)
	-381	agagTactg	agagCactg	–	rs3758987	41	33	7	0.290 (0.216–0.364)
	-206	atgaCggca	atgaTggca	–	–	77	4	0	0.025 (0.000–0.050)
	-100_-102	ggagAAGgagg	ggag—gagg	–	rs3831455[e] rs35312182	51	28	2	0.196 (0.132–0.260)
Intron 4	26943	gtgtGccag	gtgtAccag	–	–	78	3	0	0.019 (0.000–0.041)
	26946	tgccAgtgt	tgccGgtgt	–	rs1176746	6	29	46	0.747 (0.676–0.818)
Exon 5	27373	agatAccct	agatGccct	Tyr129Ser	rs1176744	44	31	6	0.265 (0.193–0.337)
	27449	ctgcGtgca	ctgcAtgca	Ala154Ala	rs2276305	56	25	0	0.154 (0.095–0.213)
Intron 6	28232	aggaAtttc	aggaGtttc	–	rs2276307	44	32	5	0.259 (0.188–0.330)

Values in parentheses indicate 95% confidence intervals.
[a] Position is in respect to the translation start site of the *5-HT$_{3B}$* receptor gene; the A in the ATG is +1 and the base immediately 5' is -1.
[b] Reference allele: GenBank accession no. NM006028.
[c] NCBI dbSNP database identification number.
[d] R, reference allele; V, variant allele.
[e] -104_-106GGA deletion (rs3831455) is identical to -100_-102AAG deletion when A-102G (rs35312182) is the variant allele.

For the determination of the plasma levels of paroxetine, 63 blood samples from 50 patients who met the blood sampling conditions were tested. The mean plasma levels of paroxetine were 76.3±77.2 and 60.0±48.9 ng/ml in patients with and without nausea, respectively, and there was no significant difference ($p=0.4009$, one-way ANOVA).

Discussion

SSRIs frequently induce nausea as an adverse effect. In the present study, nausea was observed in approximately 30% of patients within the first week after the administration of paroxetine. These results are in keeping with previous reports in which the percentage of patients treated with SSRIs who experienced nausea ranged from 14% to 30% (Ottevanger, 1994; Takahashi et al., 2002). Nausea is also the most common reason for early discontinuation of SSRI treatment (Murphy et al., 2003; Ottevanger, 1994; Wagner et al., 1992).

In the present study, we showed that patients who had the -100_-102AAG deletion allele of the *5-HT$_{3B}$* receptor gene experienced paroxetine-induced nausea more frequently than other patients. In other words, patients homozygous for the -100_-102AAG insertion allele had a lower risk of developing nausea than did other patients.

The way in which SSRIs cause nausea has not been fully elucidated. Bergeron and Blier (1994) reported in an open study that the non selective 5-HT$_3$ antagonist cisapride reduced SSRI-induced nausea in most patients. Bailey et al. (1995) showed that co-administration of the 5-HT$_3$ antagonist ondansetron significantly reduced nausea induced by fluvoxamine

Table 2. The genotype distribution of -100_-102AAG insertion/deletion polymorphism of the *5-HT$_{3B}$* receptor gene in 72 patients with and without paroxetine-induced nausea

	Genotype distribution, *n* (%)				
	Ins/Ins	Ins/Del	Del/Del	Ins/Del + Del/Del	*p* value[a]
Nausea (+)	8 (38.1)	12 (57.1)	1 (4.8)	13 (61.9)	0.00286*
Nausea (−)	39 (76.5)	11 (21.6)	1 (2.0)	12 (23.5)	

Ins, Insertion; Del, deletion.
The severity of nausea and vomiting was scored as follows: Degree 0, no or doubtful nausea; Degree 1, slight nausea; Degree 2, disturbing nausea but without vomiting; Degree 3, nausea with vomiting. Subjects with a score of 1, 2, or 3 were defined as patients with nausea, whereas those with a score of 0 were defined as patients without nausea.
[a] Nominal *p* value by Fisher's exact test.
*5% statistical significant with Bonferroni correction for multiple comparison.

in volunteers in a double-blind, placebo-controlled study. The above studies strongly suggest that nausea induced by SSRIs might be mediated by the activation of 5-HT$_3$ receptors.

On the other hand, it has been shown that 5-HT$_3$ receptor antagonists can prevent chemotherapy-induced nausea in cancer patients (Kris et al., 2006). However, there are individual differences in the efficacy of anti-emetic treatment with 5-HT$_3$ receptor antagonists in cancer patients suffering from chemotherapy-induced nausea. Tremblay et al. (2003) reported that genetic polymorphism of the *5-HT$_{3B}$* receptor gene might be a pharmacogenetic predictor of the effect of anti-emetic treatment with 5-HT$_3$ receptor antagonists in cancer patients receiving chemotherapy. Interestingly, they showed that patients who were homozygous for the -100_-102AAG deletion allele of the *5-HT$_{3B}$* receptor gene, which is the same allele of the *5-HT$_{3B}$* receptor gene found in our study in relation to paroxetine-induced nausea, experienced vomiting more frequently than did other patients. Frank et al. (2004) also reported that the prevalence of the -100_-102AAG deletion of the *5-HT$_{3B}$* receptor gene was much lower in patients with bipolar affective disorder compared with controls and that the -100_-102AAG deletion variant may alter the structure of the 5'-untranslational region of mRNA, leading to changes in the translational efficiency of the 5-HT$_{3B}$ receptor.

To our knowledge, there are no in-vitro studies with regard to the functional effects of the -100_-102AAG deletion variant of the *5-HT$_{3B}$* receptor gene. We speculate that the -100_-102AAG deletion variant might regulate the mRNA and protein expression levels of the 5-HT$_{3B}$ receptor, because this variant is located in the 5'-flanking region of the *5-HT$_{3B}$* receptor gene. Otherwise, the possibility that the -100_-102AAG deletion variant is linked with other, yet unknown variants which change the 5-HT$_3$ receptor function could not be excluded. Barrera et al. (2005) showed that the subunit stoichiometry of the heteromeric 5-HT$_{3A}$ and 5-HT$_{3B}$ receptors is 2A:3B and that the subunit arrangement is B-B-A-B-A. The 5-HT$_{3B}$ subunit is thought to modify the 5-HT$_{3A}$ receptor and seems to be a major determinant of 5-HT$_3$ receptor function (Davies et al., 1999; Dubin et al., 1999). However, a functional explanation of the relationship between the -100_-102AAG deletion variant of the *5-HT$_{3B}$* receptor gene and nausea remains unaccounted for.

Sugai et al. (2006) reported that the 129Tyr/Tyr genotype of the *5-HT$_{3B}$* receptor gene had a significant effect on paroxetine-induced nausea. In the present study, we screened for genomic DNA polymorphisms in the protein coding exons, including the exon–intron junctions and the 5'-flanking region of the *5-HT$_{3B}$* receptor gene, and did not find a significant association between Tyr129Ser polymorphism and paroxetine-induced nausea. To resolve this discrepancy, we determined haplotypes for the -100_-102AAG insertion/deletion and Tyr129Ser polymorphisms, and three major haplotypes were identified: AAG(insertion)-Tyr, AAG(insertion)-Ser, and AAG(deletion)-Tyr. Because the Tyr129 allele was in linkage disequilibrium with the -100_-102AAG insertion and deletion alleles, there may be differences in the results of the two studies. Because Sugai et al. (2006) investigated only one variant of the *5-HT$_{3B}$* receptor gene and did not

examine the -100_-102AAG insertion/deletion polymorphism, the association between this polymorphism and paroxetine-induced nausea in the same subjects of their study remains unclear. The functional effects of the Tyr129Ser variant have not been clarified, thus further in-vivo and in-vitro studies with regard to haplotypic considerations are needed to elucidate the functional properties of these polymorphisms of the *5-HT$_{3B}$* receptor gene.

The sample size in the present study was too small. Therefore, in order to elucidate the associations between paroxetine-induced nausea and polymorphisms of the *5-HT$_{2A}$* receptor, *5-HT$_{3A}$* receptor, *5-HTT* and *CYP2D6* genes, further studies with larger sample sizes are warranted.

In conclusion, the -100_-102AAG insertion/deletion polymorphism of the *5-HT$_{3B}$* receptor gene may affect the incidence of paroxetine-induced nausea in Japanese patients with depressive and anxiety disorders. If our findings are replicated in further studies with larger sample sizes, genotyping of the *5-HT$_{3B}$* receptor gene before the initiation of treatment with paroxetine might provide a substantial improvement in paroxetine treatment of patients with depressive and anxiety disorders.

Note

Supplementary information accompanies this paper on the Journal's website (http://journals.cambridge.org).

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None.

Statement of Interest

None.

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A possible association between missense polymorphism of the breakpoint cluster region gene and lithium prophylaxis in bipolar disorder

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Abstract

Lithium is one of the most commonly used drugs for the treatment of bipolar disorder. To prescribe lithium appropriately to patients, predictors of response to this drug were explored, and several genetic markers are considered to be good candidates. We previously reported a significant association between genetic variations in the breakpoint cluster region (BCR) gene and bipolar disorder. In this study, we examined a possible relationship between response to maintenance treatment of lithium and Asn796Ser single-nucleotide polymorphism in the BCR gene. Genotyping was performed in 161 bipolar patients who had been taking lithium for at least 1 year, and they were classified into responders for lithium monotherapy and non-responders. We found that the allele frequency of Ser796 was significantly higher in non-responders than in responders. Further investigation is warranted to confirm our findings.

Keywords: BCR (breakpoint cluster region); Bipolar disorder; Lithium; SNP (single-nucleotide polymorphism)

1. Introduction

Bipolar disorder (BPD) is one of the most distinct syndromes in psychiatry, which is characterized by recurrent episodes of mania and depression. Three representative mood stabilizers, lithium, valproate and carbamazepine, are used worldwide for its treatment, and American Psychiatric Association guideline listed lithium as a first line agent (American Psychiatric Association, 2002). However, these treatments are associated with variable rates of efficacy and often with intolerable side effects. Therefore, many researchers explored psychopathological and biological markers for good response to lithium treatment (Gelenberg and Pies, 2003; Ikeda and Kato, 2003). To date, several studies investigated possible molecular predictors of lithium efficacy. The functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR) has been associated with lithium efficacy in two independent studies (Serretti et al., 2001;

Abbreviations: ANOVA, analysis of variance; BCR, breakpoint cluster region; BDNF, brain-derived neurotrophic factor; BPD, bipolar disorder; BP I, bipolar I disorder; BP II, bipolar II disorder; PH domain, pleckstrin homology domain; SNP, single-nucleotide polymorphism.

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Del Zompo et al., 1999), although the polymorphism associated with better lithium response was opposite. Other numerous genetic variants including catechol-*O*-methyltransferase were not associated with lithium response (Serretti et al., 2002). The association between prophylactic lithium response and the polymorphism of the brain-derived neurotrophic factor (BDNF) gene was reported (Rybakowski et al., 2005); however, this association was not replicated in subsequent studies (Masui et al., 2006; Michelon et al., 2006).

We previously reported a significant association between genetic variants in the breakpoint cluster region gene (*BCR*), which is located on chromosome 22q11, and BPD (Hashimoto et al., 2005). The *BCR* is highly expressed in hippocampal pyramidal cell layer and dentate gyrus (Fioretos et al., 1995), and encodes a Rho GTPase-activating protein (GAP), which inactivate the Rho GTPase playing an important role in neuronal development (Diekmann et al., 1991; Negishi and Katoh, 2002). The A2387G single-nucleotide polymorphism (SNP) in the *BCR* gene [National Center for Biotechnology Information (NCBI) SNP ID: rs140504] is the non-conservative SNP giving rise to an amino acid change of asparagine to serine at codon 796 (Asn796Ser; NCBI Protein ID: NP_004318). Ser796 allele showed a significant association with BPD and stronger evidence for an association with bipolar II disorder (BPII) than bipolar I disorder (BPI) (Hashimoto et al., 2005). It has been reported that patients with BPII have greater number of abnormal mood episodes and comorbidity of other psychiatric illnesses than patients with BPI (Ayuso-Gutierrez and Ramos-Brieva, 1982; Berk and Dodd, 2005). These clinical features of BPII have been also considered as markers for poor response to lithium treatment (Ikeda and Kato, 2003). Therefore, Ser796 allele of the *BCR* gene may contribute to poorer response to lithium therapy in BPD.

In this study, we examined the possible association between prophylactic effect of lithium and Asn796Ser SNP of the *BCR* gene in Japanese patients with BPD.

2. Methods

2.1. Subjects

Subjects were 161 patients with BPD (83 patients were BPI, and 78 patients were BPII). Consensus diagnosis was made for each patient by at least two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria. The presence of concomitant diagnoses of mental retardation, drug dependence, or other Axis I disorder, together with somatic or neurological illnesses that impaired psychiatric evaluation, represented exclusion criteria. They were composed of 76 males and 85 females with mean age of 48.2± 12.8 years (mean±S.D.). All the subjects were biologically unrelated Japanese. Patients had been treated with lithium carbonate and its serum concentration was maintained between 0.4 and 1.2 mEq/L at least for one year, in a completely naturalistic setting.

Response to lithium treatment was retrospectively determined for each patient from all available information including clinical interview and medical records, by at least two psychiatrists, and the patients were classified into lithium responders and non-responders. The phenotype definition of lithium prophylaxis is a very difficult issue. Lithium responders were defined as those patients without any affective episodes during the maintenance period of lithium mono-therapy. During the maintenance period, the addition of antidepressants, antipsychotics, or anticonvulsants was regarded as a relapse, and excluded from the responder group. However, coadministration of hypnotics for sleep disturbance was allowed, and was not regarded as a relapse when subsequent affective episode did not appear.

Our definition of response to lithium treatment is full response without any affective episode during lithium treatment. This definition is similar to "excellent lithium responders" used as clinical endophenotypic marker of BPD in some molecular-genetic research (Rybakowski et al., 2005; Mamdani et al., 2007). On the other hand, recurrence index [number of episodes/duration of illness (years)] before and during lithium treatment is a better method to measure the response to lithium including partial response (Gasperini et al., 1993; Serretti et al., 2002). However, more clinical information is necessary to calculate the recurrence index. We investigated the association between the change of recurrence index and clinical variables in parts of total subjects (24 patients) whose recurrence pattern were clearly established during more than 1 year [mean 5.8±5.0 (range 1.3–21.0) years] before lithium treatment. They were composed of 9 BPI and 15 BPII patients, whose age of onset was 35.4± 9.5 years old, duration from onset of illness to lithium treatment was 9.5±7.0 (range 1.3–22.0) years, number of episodes which could be clearly identified before lithium treatment was 16.3± 30.3 (range 3.0–150.0), duration of lithium treatment was 6.0± 4.3 (range 1.0–14.3) years, number of episodes during lithium treatment was 6.8±6.0 (range 0.0–26.0) and recurrence index before and during lithium were 2.7±2.8 (range 0.6–14.2) and 1.8±1.5 (range 0.0–5.3), respectively.

After complete description of the study, written informed consent was obtained from every subject. The study protocol was approved by institutional ethics committees.

Table 1
Clinical characteristics of subjects, sorted by response to lithium treatment

	Response to lithium treatment		
	Responders (N=43)	Non-responders (N=118)	
Subtype			χ^2test
BPI	29 (34.9%)	54 (65.1%)	$p<0.05$
BPII	14 (18.0%)	64 (82.0%)	
Gender			
Male	25 (32.9%)	51 (67.1%)	NS
Female	18 (21.2%)	67 (78.8%)	
			t-test
Age at last observation	54.4±11.8	46.1±12.4	$p<0.01$
Age of onset	41.5±13.6	32.9±10.7	$p<0.01$
Duration of illness	12.9±9.0	13.2±9.9	NS

Continuous values were represented as the mean±SD.
BPI=bipolar I disorder, BPII=bipolar II disorder,
NS=not significant.

Table 2
Allele frequencies and genotype of the Asn796Ser polymorphism of the BCR gene and response to lithium treatment

Response to lithium treatment	Allele frequency		χ^2test	Genotype		χ^2test
	Asn	Ser	p value (OR)	Asn/Asn Asn/Ser	Ser/Ser	p value
Responders (n=43)	49 (57.0%)	37 (43.0%)		35 (81.4%)	8 (18.6%)	
Non-responders (n=118)	101 (42.8%)	135 (57.2%)		77 (65.3%)	41 (34.7%)	
			0.024 (1.77)			0.049
Total patients (n=161)	150 (46.6%)	172 (53.4%)		112 (69.6%)	49 (30.4%)	

OR: Odds ratio.

2.2. Genotyping

Venous blood was drawn from the subjects and genomic DNA was extracted from whole blood according to the standard procedures. The genotype of the Asn796Ser SNP (rs140504) of the *BCR* gene was determined by TaqMan 5′-exonuclease allelic discrimination assay, described previously (Hashimoto et al., 2005). Briefly, probes and primers for detection of the polymorphism were: forward primer 5′-AGCTGGACGCTTTGAAGATCA-3′, reverse primer 5′-TGGTGTGCACCTTCTCTCTCT-3′, probe 1 5′-VIC-CCAGATCAAGAATGACAT-MGB-3′, and probe 2 5′-FAM-CCAGATCAAGAGTGACAT-MGB-3′. PCR cycling conditions were: at 95 °C for 10 min, 50 cycles of 92 °C for 15 s and 60 °C for 1 min.

2.3. Statistical analysis

Difference in clinical characteristics between responders and non-responders to lithium treatment was analyzed using the χ^2 tests for categorical variables and t tests for continuous variables. The presence of Hardy–Weinberg equilibrium was examined by using the χ^2 test for goodness of fit. Subsequently, multiple logistic regression analysis was performed to correct background difference between responders and non-responders for lithium treatment. Possible predictors (genotype of the *BCR* gene, subtype of bipolar disorder, age of onset, age at last observation, and gender) were included in the original model. Backward stepwise regression was performed, and p-value greater than 0.10 was used for variable removal. Pearson coefficient of correlation test was used for comparison between recurrence index and clinical variables. The effect of the Asn796Ser SNP on recurrence index was assessed by analysis of variance (ANOVA). All p-values reported are two-tailed. Statistical significance was defined at $p<0.05$.

3. Results

Among 161 patients with BPD, 43 patients were determined as responders and 118 patients as non-responders for the maintenance treatment of lithium. The clinical characteristics sorted by response to lithium treatment and genotype distribution were presented in Table 1. There were significant differences between responders and non-responders in subtype of bipolar disorder (BPI and BPII), age at last observation, and age of onset.

The genotype distributions for the total patients, responders, and non-responders were in Hardy–Weinberg equilibrium (total patients: $\chi^2=0.94$, $df=1$, $p=0.33$; responders: $\chi^2<0.001$, $df=1$, $p=0.98$; non-responders: $\chi^2=0.81$, $df=1$, $p=0.37$). Allele frequencies and genotype distributions of the Asn769Ser polymorphism of the *BCR* gene among responders and non-responders for lithium treatment are presented in Table 2. The Ser796 allele was in excess in the non-responders rather than responders ($\chi^2=5.09$, $df=1$, $p=0.024$; OR 1.77, 95% CI 1.08–2.92). Then, we examined patients homozygous for the Ser796 allele and the Asn796 allele carriers, separately. Patients homozygous for the Ser796 allele were significantly more common in the non-responders than the Asn796 carriers ($\chi^2=3.88$, $df=1$, $p=0.049$; OR 2.33, 95% CI 0.99–5.49). After backward stepwise regression, the final logistic regression model included subtype of bipolar ($p<0.01$), age of onset ($p<0.01$), and genotype which is separated to the Asn796 carrier and homozygous for the Ser796 ($P=0.04$).

We next investigated the association between lithium response using recurrence index and clinical variables in 24 subjects with BPD. The change of recurrence index before to during lithium treatment was not associated with subtype (t=0.79, $df=22$, $p=0.44$), age of onset (correlation coefficient=−0.29, $p=0.17$), duration from onset of illness to lithium treatment (correlation coefficient=0.12, $p=0.57$), duration during treatment (correlation coefficient=0.11, $p=0.60$), or the Asn796Ser SNP ($df=2$, $F=0.03$, $p=0.97$).

We also examined the association between age of onset and recurrence index before lithium treatment, which reflects severity of illness. There was a negative trend between age of onset and recurrence index (correlation coefficient=−0.37, $p=0.074$). Although difference among genotype of Asn796Ser SNP was not statistically significant, the number of Ser796 allele was associated with higher recurrence index before lithium treatment (Asn/Asn=1.63±1.19, Asn/Ser=2.89±0.84, and Ser/Ser=3.23±1.19. $df=2$, $F=0.53$, $p=0.60$). Therefore, the Ser796 allele might also be associated with both early onset and severity of illness, which could result in poorer lithium response.

4. Discussion

We investigated a possible association between the *BCR* gene and the prophylactic effect of lithium treatment in patients with BPD for the first time. As expected, our results suggested that lithium treatment might be less effective in patients homozygous for the Ser796 allele of the *BCR* gene than in patients with the Asn796 allele. In addition, allele frequencies of the Ser796 associated with poorer lithium response were 43.0%

in responders and 57.2% in non-responders. As allele frequency of the Ser796 in healthy subjects in our previous study was 48.1% (Hashimoto et al., 2005), allele frequency of the Ser796 of responders is similar to the general population.

Comparing clinical characteristics of responders and non-responders, there were more BPII patients in non-responder group. Clinical characteristics predicting poorer response to lithium therapy and that of BPII seem to overlap each other, but better lithium response in BPI is not universally accepted. We excluded any Axis I comorbidity in this study. This would leave in more typical bipolar II patients who would be more likely to respond to lithium, however, other clinical factors such as Axis II comorbidity might influence our results. The presence of positive family history of lithium responsive BPD has been reported as indicative of favorable response (Grof et al., 2002). However, it was not assumed that our sample size was enough to investigate this issue because only 8.7% of BPD had positive family history of the same disease in 1st degree relatives (Smoller and Finn, 2003). Therefore, information about family history of lithium response was not collected in this study.

Age at onset was also different between responders and non-responders, and early age of onset was associated with poorer response to lithium treatment in our subjects. This observation is consistent with recent meta-analysis (Kleindienst et al., 2005). As the objective of this study is to examine the association between response to lithium treatment and a SNP in the *BCR* gene, the differences in demographic parameters of responders and non-responders might not be preferable. Therefore, we conducted a multiple logistic regression analysis, and homozygous for the Ser796 allele of the *BCR* gene was still significantly associated with poorer response to lithium treatment.

The evaluation of lithium prophylaxis is considerably difficult because of complex clinical course of BPD, and each researcher has used different methodologies. Although our finding was based on the simple definition, in which lithium responders didn't have any affective recurrences during lithium, one of the limitation of this study is lack of detailed clinical information, e.g. duration from onset of illness to lithium treatment and number of episodes which could be clearly identified before lithium treatment in total subjects. To evaluate lithium efficacy including partial response, calculating recurrence index before and during lithium treatment is used in several researches. This would be a correct measure of lithium prophylaxis, but evaluating mood recurrence accurately before the first contact to mental professionals is difficult. We tried to evaluate lithium response with recurrence index; however, we could examine it in only 24 subjects out of 161 subjects due to the difficulty of collecting this clinical information. We did not found any association between the recurrence index and clinical variables and the SNP in the *BCR* gene, except for the trend between the recurrence index and age of onset. As these results were from subgroup analysis with smaller number, further investigation is needed in a larger sample size.

In this study, the same variant associated with the illness was also associated with poorer outcome. This situation is similar to that of the Val allele of the *BDNF* Val66Met polymorphism (Rybakowski et al., 2005), and it is possible that the *BCR* Ser796 and the *BDNF* Val66 alleles are associated with severer illness presentation. The trend between the recurrence index and age of onset in our subgroup analysis might imply this possibility. In case of the *BDNF* Val66Met SNP, the functional differences arisen from each allele were reported (Eagan et al., 2003). While biological functional of the *BCR* Asn796Ser SNP is still unknown, this SNP may produce functional difference in the brain, like the *BDNF* Val66Met SNP. To speculate this issue, it is noteworthy that this SNP is in the pleckstrin homology (PH) domain of the *BCR*. As PH domain is known for its ability to bind phosphatidylinositol and this binding regulates the activity of PH domain containing protein (Lemmon et al., 2002), signal transduction from inositol cycle to the *BCR* products might be affected by this SNP. As the *BCR* is RhoGAP, this change may influence on the activity of its downstream target, RhoGTPase, which activates many kind of effectors associated with constructing neuronal network, and subsequently influence on neuronal development. Additionally, as inositol cycle is considered as one of therapeutic targets of lithium (Harwood, 2005), this SNP could alter the clinical efficacy of lithium. To understand the mechanism of our findings, it is worth investigating whether the Asn796Ser SNP alters the binding ability of PH domain to inositol.

5. Conclusion

This is the first report demonstrating that long-term lithium treatment may be less effective in BPD patients homozygous for Ser796 allele of the *BCR* gene than in patients with the Asn796 allele. The limitations of this study are retrospective design without placebo control group, small sample size, and lack of clinical information such as presence of rapid cycling and/or psychotic symptoms, and detailed lithium levels. Further investigations are needed to confirm our findings.

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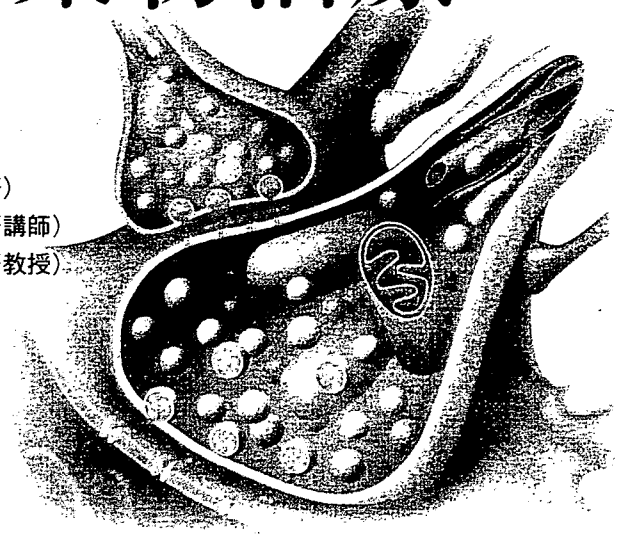
薬物動態および薬力学（臨床効果、副作用）の予測、オーダーメイド薬物治療



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Point

- 抗うつ薬の治療反応性や副作用発現には個人差があり、薬剤の選択基準および投与量についての科学的根拠は十分に得られていない。この問題に対処するために、ゲノムレベルから薬物の反応性や副作用の発現を予測しようとする薬理遺伝学的研究が行われている。
- その薬理遺伝学的研究は、抗うつ薬の代謝に関与すると考えられる遺伝子（薬物動態学的研究）を対象としたものと、抗うつ薬の作用に関与すると考えられる遺伝子（薬力学的研究）を対象としたものに大きくわけられる。
- 薬物動態学的研究としては、選択的セロトニン再取り込み阻害薬（SSRI）の代謝に関与する各種チトクロームP450（CYP）遺伝子が中心に研究されており、薬物動態を予測するさまざまなCYP遺伝子多型が同定されてきている。
- 薬力学的研究では、SSRIやセロトニン・ノルアドレナリン再取り込み阻害薬（SNRI）の作用に関連のあるセロトニントランスポーターや各種セロトニン受容体などが中心に研究され、SSRIやSNRIの効果・副作用を予測できる可能性が示されつつある。
- 各種遺伝子多型と効果・副作用の関係について追認されたものは決して多くない。その原因の一つに、サンプルサイズの問題があり、今後は多施設が共同で行なう大規模研究が望まれる。
- 同一用量であっても個体間で大きな血中濃度のばらつきが存在し、それが臨床効果・副作用の発現に影響を及ぼすため、研究対象となる薬剤の血中濃度および代謝に関与する薬物動態学的因子を、薬力学的因子と同時に解析することが望まれる。

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うつ病の生涯有病率は約10％と非常に高く、うつ病が原因となる社会機能低下や自殺は重大な社会問題となっている。うつ病治療は抗うつ薬による薬物療法が主体となっており、選択的セロトニン再取り込み阻害薬（selective serotonin reuptake inhibitor；SSRI）であるフルボキサミン、パロキセチン、セルトラリンやセロトニン・ノルアドレナリン再取り込み阻害薬（serotonin noradrenaline reuptake inhibitor；SNRI）であるミルナシプランなどの新規抗うつ薬がわが国でも登場し、第一選択薬として使用されている。しかしながら、抗うつ薬の治療反応性や副作用発現には個人差があり、薬剤の選択基準および投与量についての科学的根拠は十分に得られていないのが現状である。この問題に対処するために、ゲノムレベルから薬物の反応性や副作用の発現を予測しようとする薬理遺伝学的研究が行われており、抗うつ薬の代謝（薬物動態）や作用（薬力学）に関連のある遺伝子を対象とした研究がその中心となっている。さらに最近では、ゲノムを包括的に解析し、薬物の反応性や副作用の発現に関与する遺伝子を探索する方法も注目されているが、コストの問題や莫大な数の偽陽性を排除することの困難さなどが障害となり広く行われるに至っていない。

本稿では、うつ病治療の第一選択となっているSSRIおよびSNRIに関する薬理遺伝学的研究を中心に、当施設の検討結果を提示しながら、現在知られている代表的な知見を概説する。

遺伝子情報を用いた薬物動態の予測

SSRIは各種チトクロームP450（CYP）が代謝に関与しているとされており、各種CYPを対象とした薬理遺伝学的研究が行われている。例えば、フルボキサミン50mg単回投与を用いた研究では、CYP2D6代謝活性とフルボキサミン薬物動態との間に有意な関係を報告しており、フルボキサミン代謝にCYP2D6が関与することが示唆されている[1,2]。さらに、フルボキサミン50mg単回投与を用いた研究で、喫煙者が非喫煙者に比べてフルボキサミン血中濃度が有意に低くなることも報告されており[3]、喫煙によりCYP1A2が誘導されることからフルボキサミン代謝にCYP1A2が関与していることも示唆されている。一方で、フルボキサミン200mg/日を用いた研究では、CYP2D6および喫煙はフルボキサミン代謝に有意な影響を与えなかったと報告している[4]。

当施設では、フルボキサミン50、100、150および200mg/日の用量別に対象を分けて、CYP2D6遺伝子多型および喫煙がフルボキサミン代謝に与える影響を検討した。その際、CYP2D6遺伝子多型として、活性が正常な*1と活性が低下する*10および活性が消失する*5を同定し、変異アレル0個群（*1/*1）、変異アレル1個群（*1/*5、*1/*10）および変異アレル3個群（*5/*10、*10/*10）の3つの遺伝子型に分類した。その結果、50gm/日（**図1**）および100mg/日でCYP2D6遺伝子型のフルボキサミン血中濃度に対する強い影響を認め、150mg/日と200mg/日では有意な影響を認めるもののその程度は減弱していた。また、喫煙（20本/日以上）は50mg/日でのみフルボキサミン血中濃度に対する有意な影響を認めた（**図2**）。フルボキサミン用量増加により、CYP2D6遺伝子型およびCYP1A2を誘導する喫煙の影響が減弱するのは、CYP2D6とCYP1A2活性の飽和現象が関与していると考えられる。実際

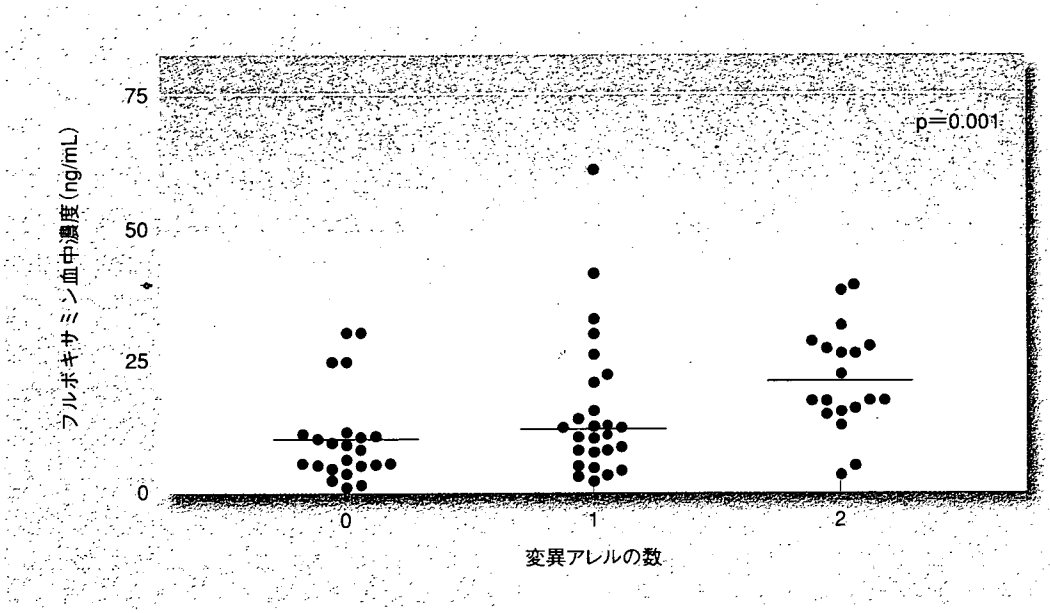

図1　フルボキサミン50mg/日投与におけるフルボキサミン血中濃度に対するCYP2D6遺伝子型の影響

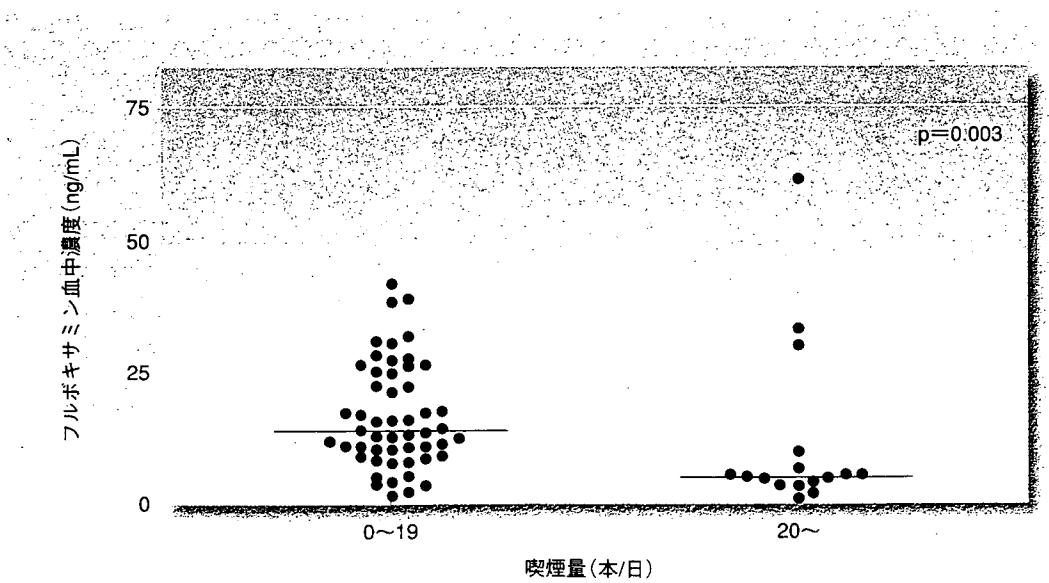

図2　フルボキサミン50mg/日投与におけるフルボキサミン血中濃度に対する喫煙の影響

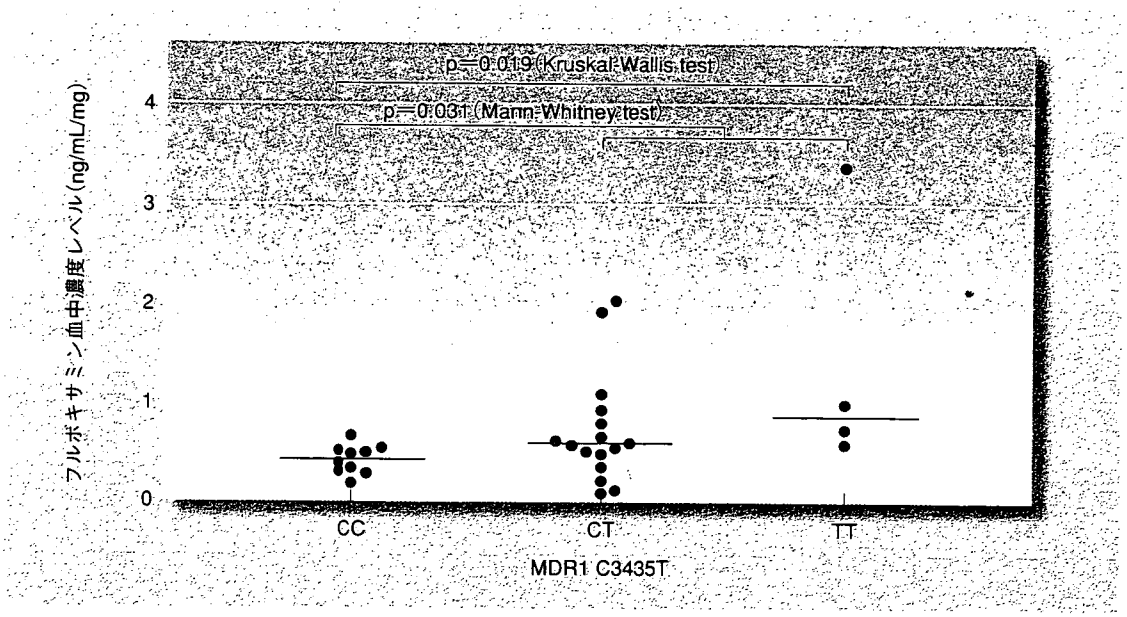

図3 フルボキサミン200mg/日投与におけるMDR1 C3435Tとフルボキサミン血中濃度との相関

に、フルボキサミン用量が増加すると血中濃度はnon-linearに増加するが、この現象にはCYP2D6およびCYP1A2活性の飽和現象が関与していると考えられている。

さらに当施設では、腸管からの薬剤吸収に関与するP-glycoproteinをコードするmultiple drug resistance 1 (MDR1) 遺伝子多型 (C3435T) とフルボキサミン血中濃度との関係を用量別に検討した。その結果、高用量の200mg/日のみでC3435T多型のフルボキサミン血中濃度に対する有意な影響を認めた(**図3**)。フルボキサミン高用量では、代謝活性が飽和するCYP2D6およびCYP1A2に代わり、P-glycoproteinがフルボキサミン血中濃度に大きな影響をもつ可能性が示唆された。しかし、フルボキサミンがP-glycoproteinの器質であることを示した報告はこれまでになく、今後のさらなる研究が必要である。

パロキセチンの代謝には少なくとも2つの経路が関与しており、1つはCYP2D6の関与する飽和型の代謝経路であり、もう一つはCYP2D6以外のCYPによる代謝経路であるとされている。

当施設では、パロキセチン血中濃度とCYP2D6遺伝子型との関係を検討したが、パロキセチン10mg/日内服時には変異アレルである*10の保有群が変異アレル非保有群よりも有意に血中濃度が高いという結果を得た(**図4**)[5]。しかし、パロキセチンを20mg/日以上内服時にはパロキセチン血中濃度とCYP2D6遺伝子型との間に関係を認めず、この現象にはCYP2D6活性の飽和が関与していると考えられた。

セルトラリンの代謝にはCYP2D6、2C19、2C9、2B6、3A4などのいくつかのCYPが関与するとさ

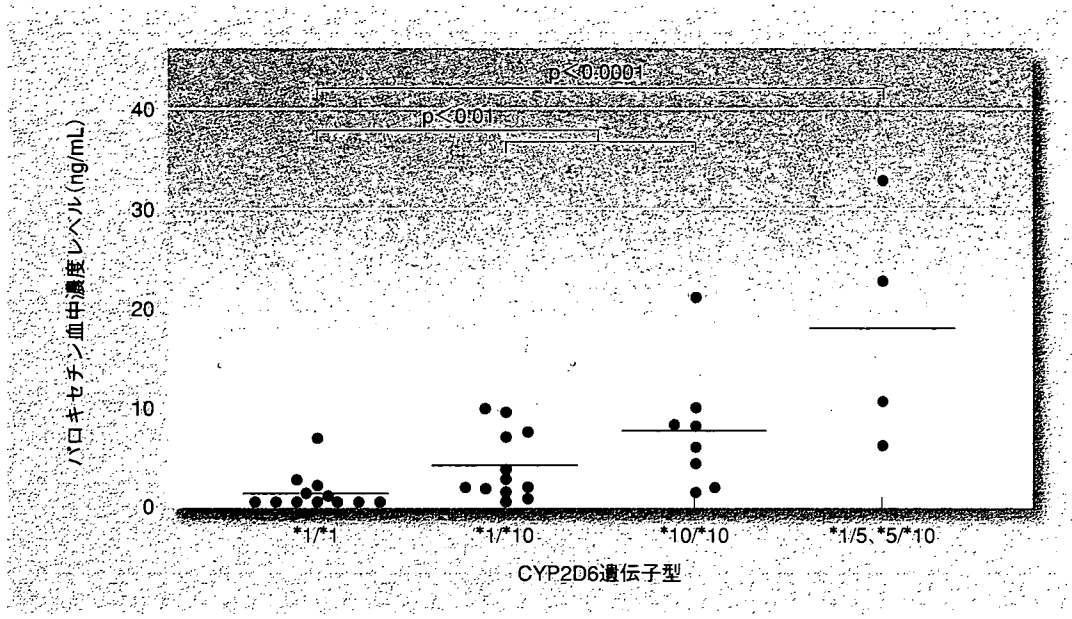

図4　パロキセチン10mg/日投与におけるCYP2D6遺伝子型とパロキセチン血中濃度との相関
(文献5より引用)

れている[6]。したがって、一つのCYPの活性変化は、セルトラリン代謝にそれほど大きな影響を与えないと考えられる。

遺伝子情報を用いた効果・副作用の予測

1．セロトニントランスポーター(5-HTT)遺伝子

SSRIおよびSNRIの作用部位である5-HTTに関する報告は多く、プロモーター領域における5HTT-linked polymorphic region (5-HTTLPR)が特に注目されている。5-HTTLPRは、20～23bpの繰り返しを14回もつshort type (S型)と、16回もつlong type (L型)が存在するとされている。Smeraldiらはうつ病患者を対象とした研究で、5-HTTLPRのL型がフルボキサミンに対する良好な反応性と関係していたと報告した[7]。同じSSRIであるパロキセチンについても、L型が良好な治療反応性と関係していたと報告された[8]。

一方、韓国人を対象にした研究では、S/S型を有する群で有意にパロキセチンの効果が優れていたとの報告があり[9]、わが国でもS型を有する個体でフルボキサミンの効果が良好であったと報告されている[10]。欧米と逆の結果になり注目を集めたが、アジア人種を対象としたその後の研究では見解が一定していない[11,12]。

5-HTTのsecond intronにおけるVNTRは、16～17bpの繰り返しが9回(STin2.9)、10回(STin2.10)、12回(STin2.12)のアレルが存在す

る。韓国の研究では、STin2.12型をホモで有している大うつ病患者ほど、フルボキサミンまたはパロキセチンに良好な反応が得られたと報告している[13]。しかし日本人を対象とした研究では、VNTR多型とフルボキサミンの反応性との関連は認められないと報告されており[14]、一定した結論に至っていない。

5-HTTと副作用に関しては、Takahashiらが5-HTTLPRおよび5-HTT-VNTRとフルボキサミンによる嘔気出現の関連を検討しているが、有意な関連は認めなかったと報告している[15]。Perlisらは5-HTTLPRとフルボキサミンによる不眠と焦燥感の発現の関連を調べ、S型が不眠と焦燥のリスクファクターとなると報告している[16]。

2. 5-HT2A受容体遺伝子

5-HT2A受容体遺伝子とSSRIの薬理遺伝学的研究についていくつかの報告が存在する。Minovらは、抗うつ治療（三環系抗うつ薬やSSRI、電気痙攣療法など）の反応性と102T/C多型の関係を調べたが、Cアレルを有する遺伝子型がT/T型よりも抗うつ治療の反応が良好であったと報告している[17]。日本人を対象としたSatoらの研究では、102T/C多型とほぼ完全な連鎖不平衡の関係にある－1438A/G多型がフルボキサミンの治療反応性に与える影響を検討したが、有意な相関は認めなかったと報告している[18]。一方、最近のKatoらの報告では、－1438A/G多型のG/G型とフルボキサミンおよびパロキセチンの良好な治療反応性との関連を報告しており[12]、一定の見解は得られていない。

5-HT2A受容体遺伝子多型と抗うつ薬の副作用については、Murphyらが102T/C多型とパロキセチンの副作用との関連について検討しているが、Cアレルを有する群で副作用による治療の中断が有意に多かったと報告している[19]。先程のKatoらの報告では、－1438 A/G多型のG/G型がパロキセチン誘発性の吐気との関連を報告している[12]。

当施設では、－1438A/G多型がフルボキサミンによる消化器系副作用の出現に与える影響を調べた。その結果、A/G、G/G遺伝子型はA/A型に比べてそれぞれ2.17、2.93倍副作用出現頻度が高かった[20]。

3. 5-HT1A受容体遺伝子

近年、シナプス細胞体における5-HT1A自己受容体がSSRIの治療効果発現の遅れと関係している可能性や[21]、pindololなどの5-HT1A受容体アンタゴニストの併用によりSSRIの臨床効果発現が早まる可能性が示唆されている[22]。当教室では、5-HT1A受容体遺伝子のGly272Asp多型とフルボキサミンの臨床効果について検討した。その結果、Aspアレルはうつ症状の改善の仕方に影響を与え、特に治療2週目においてAspアレルをもつ個体ではハミルトンうつ病評価尺度（Hamilton Depression Scale；HAM-D）の改善率が特に良好であった[23]。

最近、5-HT1A受容体遺伝子のプロモーター領域にある－1019C/G多型とSSRIの臨床効果との関連が報告されている[24-26]。アジア人種において、この－1019C/G多型はGly272Asp多型と強い連鎖不平衡あることを示した報告もあり[27]、今後は、両多型を含む5-HT1A受容体遺伝子多型を包括的に解析し、SSRIの臨床効果に及ぼす本遺伝子の影響を調べる必要がある。