

MDR1 polymorphisms effect cyclosporine AUC0-4 values in Behçet's disease patients

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Abstract: Cyclosporine (CYA) is used to preventing ocular attacks in Behçet's disease patients. Yet there are inter-individual variations in efficacy. In order to analyze the relationship between CYA fluctuation with treatment effectiveness and genetic factors, an association of area under the plasma concentration time at 0–4 hours (AUC0-4) values and polymorphism for multidrug resistance 1 (MDR1) and cytochrome3A5 (*CYP3A5*) genes was investigated. Genomic DNA was collected from 17 Japanese patients with Behçet's disease. *MDR1* polymorphisms were determined by direct sequencing from amplified products for promoter and two exons regions and *CYP3A5* polymorphisms were analyzed using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) method. AUC0-4 value was determined by the trapezoidal rule from the data of 5 times blood sampling at 0–4 hours. The haplotype 2 in the promoter region of *MDR1* influenced significantly lower AUC0-4 values, implying absorption decline of CYA. The *CYP3A5* polymorphisms had no direct influence on the effectiveness for CYA treatment. In the relation of CYA and AUC0-4 in the patients, 7 cases were grouped effective and 4 ineffective. Though there was no difference in dosage, the trough values for AUC0-4 were higher in the effective group compared to the ineffective group.

Keywords: cyclosporine, MDR1 gene, Behçet's disease, AUC0-4value

Introduction

The four main symptoms of Behçet's disease are recurrent oral aphthosis, skin lesions such as erythema nodosum, uveoretinitis, and genital ulcers. 20,000 patients have been diagnosed with Behçet's disease in Japan; however, including the latent, the actual number is estimated higher. It is thought to be a multifactorial disease strongly associated with a certain genetic background and triggered by the involvement of an environmental factor. Studies show strong association of the gene HLA-B51 with the disease as a genetic factor (Mizuki et al 2000). Behçet's disease, also known as "Silk Road disease," being common in Mongoloids along the Silk Road, and rare in Caucasians, is thought to have environmental exposures to something around the Silk Road as a factor. Cyclosporine (CYA) is effective in preventing ocular attacks in Behçet's disease patients, usually administered at the dosage of 5.0 mg/kg per day. Yet there are inter-individual variations in efficacy (Fujino et al 1999). In blood level monitoring of CYA, the trough level is most commonly used for its convenience, although AUC is considered most efficacious. However in organ transplantation, with the development of cyclosporine micro emulsion preparation, a new monitoring parameter is being evaluated as a possible alternative to trough level monitoring. The inter-individual variations of CYA is the most significant at 1–3 hours after administration; furthermore, the T-cell calcineurin inhibitor effect of CYA correlates with the CYA blood level at 2 to 3 hours from administration, suggesting the clinical significance of AUC0-4 (Keown 1999; Mahalati et al 1999; Johnston et al 2000; Levy et al 2002). On the other hand, CYA has been reported to be the substrate of P-glycoprotein (Saeki

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et al 1993). MDR1 protein has been reported to functionally express P-glycoprotein widely in normal tissue such as gastrointestinal epithelial cells, renal proximal tubules, luminal capillary bile ducts of the liver, cerebral capillary endothelial cells, choroid plexus epithelial cells (Thiebaut et al 1987; Sugawara et al 1988). In the gastrointestinal tract, P-glycoprotein is expressed in the brush border side, and CYA, digoxin, saquinavir which are good substrates of P-glycoprotein, are discharged from the gastrointestinal epithelial cells into the lumen of the gastrointestinal tract, resulting in reduced drug absorption (Fromm 2000). The MDR1 gene which codes P-glycoprotein is reported to have more than 20 SNPs, including intron and promoter region (Hoffmeyer et al 2000; Tanabe et al 2001; Marzolini et al 2004). Allele difference influences quantity in protein expression, suggesting the difference in drug absorption. MDR1 expression is especially small in homozygotes with cytosine to thymine mutation and homozygotes with guanine to thymine or guanine to adenine mutations in 2677th base of the exon 21, accelerating the absorption of CYA (Balram et al 2003; Chowbay et al 2003), however another report that in a healthy subject, C3435T mutation in exon 26 has no effect in the drug conductor of CYA (Min and Ellingrod 2002). Also, studies show the polymorphism of CYP3A5 affects the clearance of CYA significantly (Yates et al 2003; Min et al 2004). Therefore in order to analyze the relationship between CYA interindividual fluctuation and genetic factors in Behçet's disease patients, AUC0-4 values, polymorphisms for MDR1 and CYP3A5 retrieved, and relationship with treatment effectiveness was investigated.

Materials and methods

Subjects

The subjects were 17 patients who had been diagnosed Behçet's disease, and had been administered CYA at either Yokohama City University Hospital Department of Ophthalmology or Hokkaido University Hospital Department of Ophthalmology (Table 1). Judgment of effectiveness was possible in 11 cases. When the number of attacks during six months after the initial administration was half or less the number of attacks during six months before the initial administration, the case was evaluated effective. All patients and control subjects agreed to a blood examination conducted according to the guidelines of the Declaration of Helsinki.

CYA blood level

5 times blood sampling, at before, 1, 2, 3 and 4 hours after administration of CYA, and levels were measured using

Table 1 Background characteristics of patients

Gender	
Male	14
Female	3
CYA Dose	4.3 ± 1.2 mg/kg
Effective	7
Ineffective	4
Nonjudgment	6

Abbreviations: CYA, cyclosporine.

AxSYM-Cyclosporine- II · Dynapack (Abbott Japan). AUC0-4 value was determined by the trapezoidal rule from the 5 time blood sampling data at 0–4 hours.

MDR1 typing

In examination of *MDR1* polymorphisms, variants in position 2677 of exon 21 (G2677A/T), variants in position 3435 of exon 26 (G3435T), and promoter region were tested. In examination of MDR1 gene promoter region polymorphisms, in accordance with reports by Takane and colleagues (2004), PCR was carried out using the primer pair 5'-GGAGCAAAGAAATGGAATACAATA-3', 5'-TTCTCCCGTGAAGACCAAGTTC-3' and in addition to the two previous 5'-CTTATGAACATAGAGGAAATAGG-3' and 5'-TGTAGCTCACGCCTGTAATCC-3' were used as sequence primers in sequence reaction using BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). Using Applied Biosystems 3130 Genetic Analyzer or ABI® 377 Genetic Analyzer, base sequence of the amplified genes were determined to assume the haplotype of the promoter region.

G2677A/T and G3435T were typed in accordance with reports by Tanabe and colleagues (2002).

CYP3A5

CYP3A5 typing was carried out in accordance with report by Fukuen and colleagues (2002) for CYP3A5*1, CYP3A5*3, CYP3A5*6 using the PCR-RFLP method.

Statistical analysis

Effective and ineffective groups of CYA, AUC0-4 value, the correlation of AUC0-4 with each polymorphism were evaluated by Student's t-test.

Results

AUC0-4 monitoring

As with transplantation patients, the AUC0-4 level showed higher correlation with C2 level ($r^2 = 0.80$, $p < 0.001$) than

Table 2 Cyclosporine dosage and pharmacokinetics parameters of each patient group

	Dosage (mg/kg/day)	C0 (ng/ml)	C2 (ng/ml)	AUC0-4 (ng · hr/ml)	AUC0-4/ dose
Effective	4.3 ± 1.3	110 ± 42	900 ± 490	2474 ± 1090	605 ± 336
Ineffective	4.3 ± 1.4	56 ± 16	579 ± 251	1857 ± 650	515 ± 360
	p = 0.986	p = 0.037	p = 0.259	p = 0.335	p = 0.622

trough level ($r^2 = 0.44$, $p = 0.035$). The trough values were significantly higher, but AUC0-4 and C2 values were not for effective groups of CYA (Table 2).

CYP3A5 polymorphisms

2 out of 17 subjects had homozygous CYP3A5*3/*3, and 15 had heterozygous CYP3A5*1/*3. AUC0-4 values were 2486 ± 952 ng · hr/ml in those with CYP3A5*3/*3, 1390 ± 349 ng · hr/ml in those with CYP3A5*1/*3. AUC0-4 values standardized by dosage values were 614 ± 233 ng · hr/ml and 354 ± 38 ng · hr/ml ($p = 0.146$). CYP3A5*1/*3 tended to have lower AUC0-4. However this was thought to have no direct influence on the effectiveness because of majority of patients being CYP3A5*3/*3 (Table 3).

MDR1 polymorphisms

The polymorphisms of *MDR1* promoter region were examined to find neither the deletion at -1423a and -1132a nor mutation at -824a and -755a in the 17 subjects. In conformity with reports by Takane and colleagues (2004), haplotype was estimated from SNP types -1517a, -1459a, -1017a, -41a, -145, -129. Of the estimated haplotypes 9 cases were found to be 1/1, 3 cases 1/2, 2 cases 1/4, and 1 case each 1/5, 1/6, 2/4 (Table 4). Of the mutations in the 2677th base of exon 21 of *MDR1*, 8 cases were found to be G/G wild-type, 5 cases G/T heterozygote, 3 cases T/T mutant, and one case A/A mutant. Of the polymorphisms found in the 3435th base of exon 26, 7 cases were G/G wild-type, 7 cases G/T heterozygote, 3 cases T/T mutants (Table 5).

MDR1 polymorphisms and AUC0-4 values

The effect of *MDR1* polymorphisms on AUC0-4 standardized by dosage was examined. AUC0-4 values were 449 ± 195 ng · hr/ml in those with C/C wild-type in the G3435T, 666 ± 256 ng · hr/ml in those with C/T heterozygote, 704 ± 142 ng · hr/ml in those with T/T homozygote. C homozygotes tended to have lower AUC0-4 than other types ($p = 0.101$, $p = 0.079$) (Figure 1).

In terms of the G2677A/T, AUC0-4 values were 485 ± 206 ng · hr/ml in G/G homozygotes, 523 ± 189 ng · hr/ml

in G/T heterozygotes, 856 ± 122 ng · hr/ml in T/T, A/A homozygotes. T/T and A/A which are mutant homozygotes had higher AUC0-4 than G/G which is a wild-type (Figure 2). This does not disagree with previous reports.

In terms of promoter region polymorphisms, types 1/1, 1/4, 1/6 had relatively high AUC0-4, while types 1/2, 1/5, 2/4 had relatively low AUC0-4. Heterozygotes of haplotype 1/2 had significantly lower AUC0-4 values compared to types 1/1 and 1/4 ($p = 0.007$, 0.049) (Figure 3). Also, all four subjects possessing haplotype 1/2 or 2/4 showed wild-type homozygotes at 3435th and 2677th.

Discussion

Although there was no significant difference between the two groups in dosage at 4.3 ± 1.3 mg/kg/day and 4.3 ± 1.4 mg/kg/day, trough levels, AUC0-4, C2 tended to be higher in those of the effective group than those of the ineffective group (Table 2). The fact that T-cell calcineurin inhibitor effect correlates well with the CYA blood levels 2–3 hours post-dose CYA indicates that AUC0-4 is clinically significant³⁻⁶. The correlation coefficient (r^2) of AUC0-4 to trough and C2 were 0.44 ($p = 0.035$) and 0.80 ($p < 0.001$). C2 showed a higher positive

Table 3 CYP3A5 genotype and the effectiveness in each patient

Patient no	Evaluation	AUC0-4/dose	CYP3A5
1	Effective	846	*3/*3
2	Effective	732	*3/*3
3	Effective	840	*3/*3
4	Effective	327	*1/*3
5	Effective	492	*3/*3
6	Effective	716	*3/*3
7	Effective	286	*3/*3
8	Ineffective	1024	*3/*3
9	Ineffective	222	*3/*3
10	Ineffective	506	*3/*3
11	Ineffective	308	NT
12	Nonjudgement	551	*3/*3
13	Nonjudgement	730	*3/*3
14	Nonjudgement	636	*3/*3
15	Nonjudgement	831	*3/*3
16	Nonjudgement	490	*3/*3
17	Nonjudgement	381	*1/*3

Abbreviation: NT; not tested.

Table 4 Promoter haplotype of MDR1 gene in 17 Japanese Behçet's disease patients

Patient no	-129	-145	-41a	-1017a	-1459a	-1517a	Haplotype
1	T	C	A	T	G/A	T	1/4
2	T	C	A	T	G	T	1/1
3	T	C	A	T	G	T	1/1
4	C/T	C	A/G	C/T	G/A	C/T	2/4
5	T	C	A	T	G	T	1/1
6	T	C	A	T	G	T	1/1
7	C/T	C	A/G	C/T	G	C/T	1/2
8	T	C	A	T	G	T	1/1
9	T	C	A/G	T	G/A	T	1/5
10	T	C	A	T	G	T	1/1
11	C/T	C	A/G	C/T	G	C/T	1/2
12	T	C	A	T	G/A	T	1/4
13	T	C	A	T	G	T	1/1
14	T	C	A	T	G	T	1/1
15	T	C/G	A	T	G/A	T	1/6
16	T	C	A	T	G	T	1/1
17	C/T	C	A/G	C/T	G	C/T	1/2

correlation with AUC0-4, suggesting C2 to be a possible efficacy alternative to AUC0-4 in Behçet's disease patients. However in this study, although the AUC0-4 of the effective group tended to be higher than AUC0-4 of the ineffective group, the significance of this difference is questionable. One patient with high AUC0-4 4231 ng · hr/ml later developed a side effect in the central nervous system presumably owing to CYA. Additional cases must be evaluated in order to reveal effective AUC0-4 and C2 levels.

It has been reported that certain CYP3A5 alleles express different CYA metabolic activity, consequently possibly

effecting CYA blood levels greatly enough to alter the curative effect of CYA (Yates et al 2003; Min et al 2004). In the present study when efficient group and inefficient group were investigated for CYP3A5 polymorphisms, one case in the efficient group had CYP3A5*1/*3 heterozygote, others in the efficient group had CYP3A5*3 homozygote with no protein expression. Low AUC0-4 values were shown in CYP3A5*1/*3 group. However it was hard to obtain genotypic influence of CYP3A5 to AUC0-4 values, because all 15 patients except for two were CYP3A5*3/*3.

No significant differentiation was shown between the two groups indicating the low possibility that CYP3A5 gene directly affects the efficacy of CYA.

Concerning the effect of MDR1 polymorphism, Hoffmeyer and colleagues (2000) have investigated Caucasian MDR1 polymorphisms in which the 3435th base mutate from C to T, revealing that the P-glycoprotein expression in the intestine of patients with CC genotype is less than half of those with TT genotype, that alimentary tract MDR1 expression is low and digoxin AUC high in TT subjects.

The clearance of CYA is significantly greater in patients with allele mutations to T than in patients with wild-type homozygotes (Yates et al 2003). On the other hand, it has been reported that MDR1 gene expression is limited and CYA absorption is accelerated in homozygote mutations from C to T and homozygote mutations of base 2677 of exon 21 (Hoffmeyer et al 2000; Tanabe et al 2001) and that mutation in the 3435th base of exon 26 in healthy subjects has no effect on the dynamics of CYA (Marzolini et al 2004). Also, Anglicheau and colleagues (2004) reported that effect vary between race,

Table 5 Dose normalized cyclosporine AUC(0-4) and MDR1 polymorphism in each patient

Patient no	AUC0-4/ dose	Promoter haplotype	G2677 (AT)	C3435T
1	846	1/4	G/G	C/C
2	732	1/1	G/G	C/T
3	840	1/1	T/T	C/T
4	327	2/4	G/G	C/C
5	492	1/1	G/T	C/C
6	716	1/1	G/T	C/T
7	286	1/2	G/G	C/C
8	1024	1/1	A/A	C/T
9	222	1/5	G/T	C/T
10	506	1/1	G/G	C/C
11	308	1/2	G/G	C/C
12	551	1/4	G/T	T/T
13	730	1/1	T/T	T/T
14	636	1/1	G/T	C/T
15	831	1/6	T/T	T/T
16	490	1/1	G/G	C/T
17	381	1/2	G/G	C/C

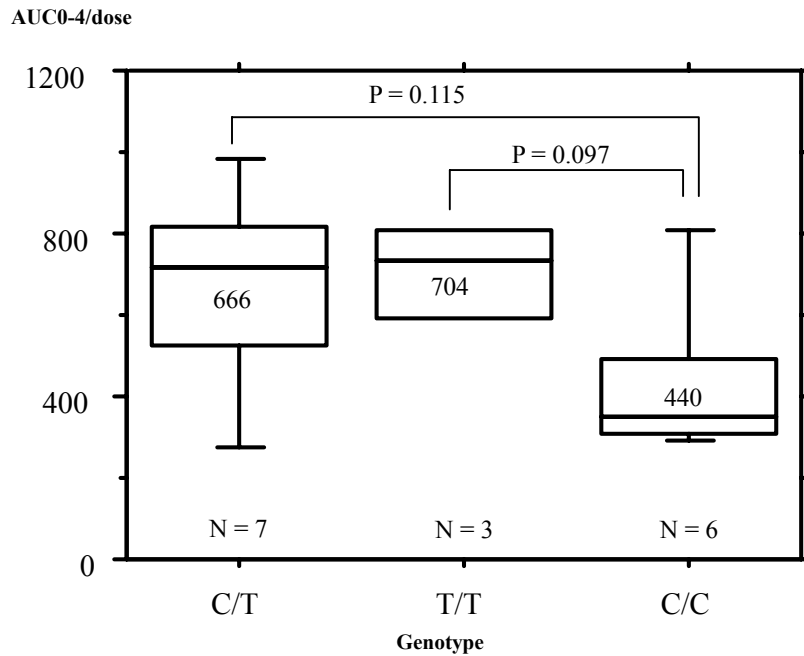


Figure 1 Correlation of the MDR1 exon 26 SNP with dose normalized cyclosporine AUC0-4. AUC0-4 values were 449 ± 195 ng · hr/ml in those with C/C in the C3435T, 666 ± 256 ng · hr/ml in those with C/T, 704 ± 142 ng · hr/ml in those with T/T genotype. C homozygotes tended to have lower AUC0-4 than other types. ($p = 0.101$, $p = 0.079$).

furthermore, SNPs T-129C, C1236T, G2677AT, and C3435T of MDR1 have no great impact on pharmacokinetics of CYA. In Asian heart transplantation patients, Chowbay investigated SNPs C1236T, G2677TA, and C3435T for effect on CYA pharmacokinetics, and suggested that not genotypes but haplotypes of each should be examined (Chowbay et al 2003). Concerning polymorphisms of the promoter region in Japanese and Caucasian subjects, there were greater MDR1 mRNA expressions in the placenta and liver of Japanese heterozygous haplotypes 1/2, 1/3 (Takane et al 2004).

In the present study, MDR1 polymorphisms in Japanese Behçet's disease patients were investigated to reveal that in genetic region SNP patients possessing alleles with replacement from C to T in base 3435 in exon 26 tended to have a high AUC(0-4) level but no significant difference. Also, MDR1 mutations in base 2677 of exon 21 which possess G (G/G, G/T) compared to those which do not possess G (A/A, A/T) had significantly higher AUC(0-4) levels. (Figure 2)

Concerning promoter region polymorphisms, types 1/1, 1/4 and 1/6 had high AUC0-4 levels, types 1/2, 1/5, 2/4 had low AUC0-4 levels, and heterozygote of haplotype 1/2, compared to 1/1 and 1/4 had significantly lower AUC0-4 levels ($p = 0.007$, 0.049) (Figure 3). Out of the five patients who showed low AUC0-4 levels, 4 patients had promoter region haplotypes which possess 2 and bases of 3435 and 2677 were

wild-type homozygote. Thereupon, 10 C3435T homozygote subjects were investigated (Table 6). Out of 7 who possessed CC, 4 patients had promoter haplotype which possesses 2 and 3 patients did not. The promoter haplotype of three out of three patients whose C3435T genotype was T/T did not possess 2. Out of those who do not possess promoter haplotype 2, the three CC patients showed AUC0-4 value of 615 ± 200 ng · hr/ml, and the three T/T patients showed AUC0-4 value of 704 ± 142 ng · hr/ml. It can be said that there was no significant difference between C3435T genotypes when there is no promoter haplotype 2 possession ($p = 0.56$). On the other hand, the four promoter haplotype 2 possessors whose C3435T genotype was CC showed AUC0-4 value of 326 ± 41 ng · hr/ml. This was significantly lower in comparison to the AUC0-4 values of promoter haplotype 2 nonpossessors whose C3435T genotype is CC and promoter haplotype 2 nonpossessors whose C3435T genotype is T/T ($p = 0.034$, 0.003).

These findings suggested the necessity of investigation of MDR1 gene polymorphisms, including promoter region haplotypes.

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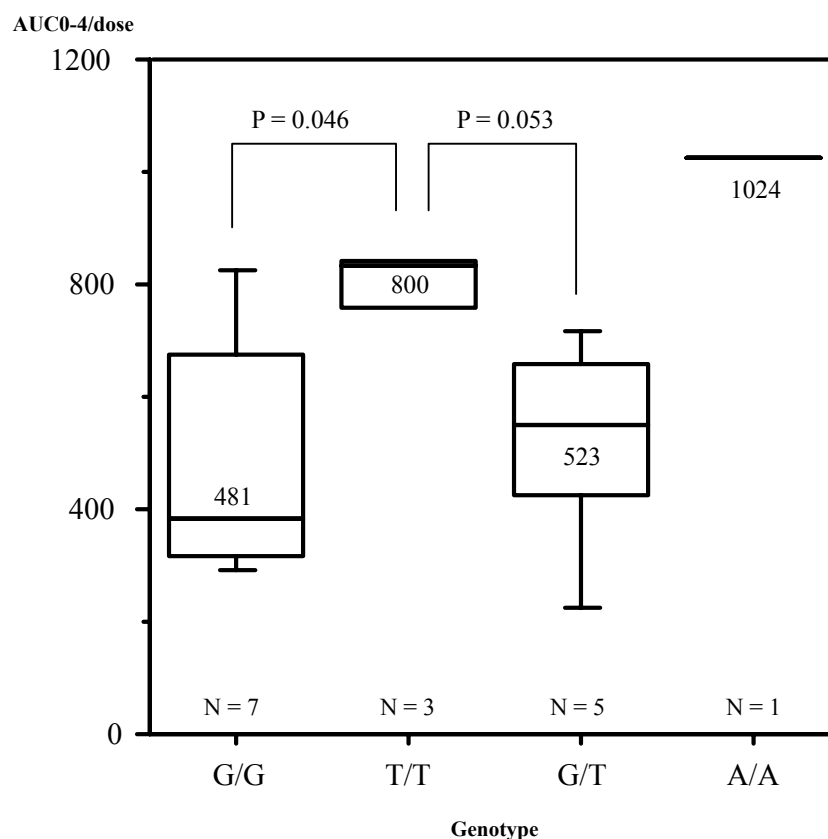


Figure 2 Correlation of the MDR1 exon 21 SNP with dose normalized cyclosporine AUC(0-4). AUC(0-4) values were 485 ± 206 ng · hr/ml in G/G genotype, 523 ± 189 ng · hr/ml in G/T genotype, 856 ± 122 ng · hr/ml in T/T, A/A genotype. T/T and A/A which are mutant homozygotes had higher AUC0-4 than G/G genotype. ($p = 0.008, 0.019$).

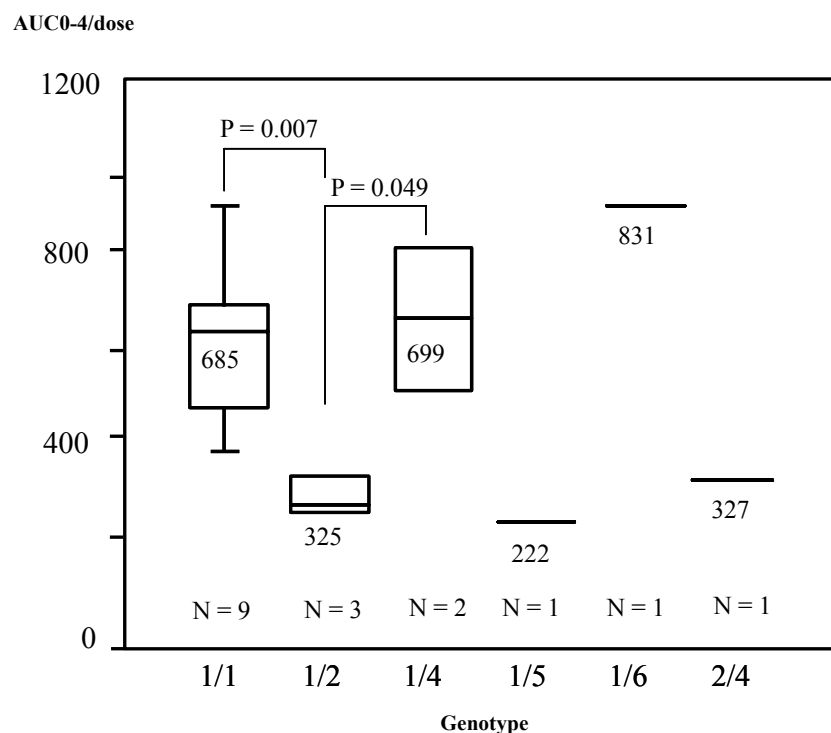


Figure 3 Correlation of the MDR1 promoter region polymorphisms with dose normalized cyclosporine AUC0-4. Promoter types 1/1, 1/4, and 1/6 had high AUC0-4 levels, types 1/2, 1/5, 2/4 had low AUC0-4 levels, and heterozygote of haplotype 1/2, compared to 1/1 and 1/4 had significantly lower AUC0-4 levels. ($p = 0.007$ and 0.049).

Table 6 Dose normalized cyclosporine AUC0-4 and MDR1 promoter haplotype polymorphism in C3435T homozygote patients

C3435T	Promoter haplotype	N	AUC0-4/ dose	P
CC	1/2 or 2/4	4	326 ± 41	p = 0.034
	1/1 or 1/4	3	615 ± 200	
TT	2/others	0		p = 0.563
	Others	3	704 ± 142	

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