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Screening study for genetic polymorphisms affecting pharmacokinetics of pioglitazone

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Pioglitazone is known to have antidiabetic effects through decreasing peripheral, hepatic and vascular insulin resistance by the stimulation of PPAR gamma. To address the possible genetic factors affecting the pharmacokinetics (PK) of pioglitazone, 27 male Korean volunteers were enrolled from two separate bioequivalence studies. Each subject was administered 15 mg pioglitazone and reference drug PK parameters were used. We used Illumina Human610 Quad v1.0 DNA Analysis BeadChip for whole genome SNPs analysis and whole genome genotyping data was processed by linear regression analysis for PK parameters. We found 35 significant SNPs ($P < 0.0001$) in C_{max}, 1,118 significant SNPs ($P < 0.0001$) in T_{max} and 1,259 significant SNPs ($P < 0.0001$) in AUC_{inf} from whole genome analysis. For clinical pharmacological purpose, we selected SNPs from several phase I and II drug metabolizing enzyme and analyzed PK parameters with genotypes. Four SNPs (rs7761731 and rs3799872 from CYP39A1; rs156697 from GSTO2; rs1558139 from CYP4F2) showed significant associations with pioglitazone C_{max}. In the T_{max} group, seven SNPs from 3 genes (rs3766198 from CYP4B1; rs2270422 from GSTZ1; rs2054675, rs10500282, rs3745274, rs8192719, and rs11673270 from CYP2B6) had significant associations. In the AUC_{inf} group, seven SNPs from 4 genes (rs11572204 from CYP2J2; rs4148280 from UGT2A1, rs4646422 from CYP1A1; rs3745274, rs8192719, rs11673270, and rs707265 from CYP2B6) showed significant associations with pioglitazone absorption. These results showed that genetic makeup could affect the PK parameters and these informations could be provide information for personalized pioglitazone therapy.

Introduction

Genetic factors are known to be associated with pharmacokinetic (PK) and pharmacodynamics (PD) properties of drug.[1] Many factors, such as age, sex, weight, and environment factors also have effects on drug's action. The response to drugs differ from individual to individual, and single nucleotide polymorphisms (SNPs) of drug-metabolizing enzymes,[1,2] drug transporters,[3] and other molecules are known to play important roles in these differences between individuals. Genetic differences in the sequence of these genes alter drug absorption, distribution, biotransformation, and excretion. SNPs in every process of PK determine the individual characteristics of drug response.[4]

These individual variations have been explained by genetic polymorphisms. The SNP is the most common source of genetic differences, and SNPs are frequently used as predictive markers of pharmacokinetics. After a common dose, variations in drug toxicity and inefficacy can be observed depending on the polymorphism.[4,5] The genotyping of drug transporter and drug-metabolizing enzymes prior to drug administration would help to predict individual effects to drugs and possible adverse reactions that may occur, which is essential to realize tailored therapy for individual patients.[6]

Recent advances in molecular research have revealed that many of the genes that encode molecules involved in drug absorption, distribution, metabolism, and excretion have genetic polymorphism. Pioglitazone, oral antidiabetic drug, is an insulin-sensitizing agent that activates the peroxisome proliferator-activated receptor (PPAR) and influences the expression of multiple genes

involved in carbohydrate and lipid metabolism.[7]

The purpose of this study is to identify possible candidate genes affecting PK of pioglitazone. A total of 27 male Korean volunteers were recruited from two bioequivalence studies after approval by the Institutional Review Board (IRB) of Kyung Hee University Hospital. In this study, DNA from each subject was analyzed using Illumina Human610Quad v1.0 DNA Analysis BeadChip. Linear regression analysis was performed for significant SNPs against the PK parameters, such as maximum measured plasma concentration (C_{max}), time of the maximum measured plasma concentration (T_{max}) and area under the plasma concentration-time curve from zero to infinity (AUC_{inf}).[8] For clinical pharmacological purpose, several genes of phase I and II were selected from each PK parameter and analyzed to screen candidate gene for pioglitazone PK.

Methods

Subjects

Volunteers were healthy Korean males who participated in two pioglitazone bioequivalence tests (1st beginning January 12, 2007; 2nd beginning June 16, 2007) at Kyung Hee Clinical Medical Research Institute of Kyung Hee University Hospital. The clinical protocol was approved by the IRB of Kyung Hee University Hospital and volunteers were recruited by direct call. Twenty-seven out of 48 subjects in two pioglitazone bioequiva-

Table 1. Demographic characteristics and reference pioglitazone pharmacokinetics parameters of volunteers

Subject No.	Age (year)	Sex (M/F)	Weight (kg)	Height (cm)	Actos 15 mg (one tablets of 15 mg pioglitazone, Lilly Korea Co., Ltd.)			
					C_{max} (ng/ml)	T_{max} (h)	AUC_t (ng·h/ml)	AUC_{inf} (ng·h/ml)
1	22	M	71.5	185	946.3	1	8353.6	8915.2
2	33	M	60.7	166	579.7	4	14337.8	24413
3	26	M	77.8	175	539.1	1	4514.7	4741
4	24	M	69.5	178	847.6	1	6968.6	7360.5
5	24	M	87.7	172	584.4	1.5	6204.2	6522
6	37	M	64.5	177	522.6	2	5644.3	6095.7
7	33	M	68.3	157	608.8	1.5	6293.9	6910.6
8	28	M	70.7	177	642.7	1.5	7797.1	8477.2
9	24	M	59.3	177	1178.3	1	8077.5	8558.4
10	27	M	79	178	383.8	2	3827	4760.4
11	23	M	64	173	841.9	2	10027.2	11904.2
12	21	M	74.7	179	850.4	1	9603.6	10345.9
13	21	M	70.3	170	634.8	1	6384.8	7482
14	21	M	53.8	166	1331.1	1.5	12342.1	13660
15	26	M	63.8	171	738.2	1	5724.9	6332.5
16	25	M	68.7	169.7	990	1.5	7362.2	7519.1
17	25	M	64	177	1082.2	2	8973.5	9527.2
18	25	M	84.5	171	729.4	1	6275.4	6865.8
19	23	M	65.8	164.4	1044.4	2	8086.1	8325.9
20	25	M	87.9	187	644.9	2	9384.3	10432.5
21	25	M	82.5	178.4	851.7	2	7476.6	7615
22	28	M	72.8	177	816.4	1	4608.1	4912.1
23	24	M	67.5	169.1	665.7	2	6620.2	8263.3
24	23	M	75.5	178.3	797.1	2	8242.1	9705.8
25	36	M	66.3	166	332.2	2.5	3186.6	3444.9
26	25	M	63	174	745.6	2	5313	5415.7
27	23	M	63.4	176	792.3	1	8065.5	9249.6
Mean ± SD	26 ± 4.3		70.3 ± 8.6	173.7 ± 6.5	767.5 ± 230.2	1.6 ± 0.67	7396.1 ± 2453.5	8435.4 ± 3929.8

Abbreviation: M, male; F, female; C_{max}, maximum measured plasma concentration; T_{max}, time of the maximum measured plasma concentration; AUC_t, area under the plasma concentration-time curve from time zero to time of last measurable concentration; AUC_{inf}, area under the plasma concentration-time curve from zero to infinity; SD, standard deviation.

lence studies participated in this pharmacogenetics study after giving written informed consent. The demographic characteristics of the volunteers are summarized in Table 1. They ranged in age from 21 to 37 years (26 ± 4.3 years), in weight from 53.8 to 87.9 kg (70.3 ± 8.6 kg) and in height from 157.0 to 187.0 cm (173.7 ± 6.5 cm) (Table 1).

Previous bioequivalence studies

Previous studies were based on two pioglitazone bioequivalence tests. Each bioequivalence study of two 15 mg pioglitazone formulation (reference drug, Actos 15 mg, Lilly Korea Co., Ltd.) was conducted in healthy male Korean volunteers after a single dose administration in a randomized cross-over study with a washout period of at least one week. The subjects were hospitalized (Kyung Hee University Hospital, Seoul, Korea) and fasted overnight (10 h) and until 4 h after each drug administration. The doses were administered at 8.00 a.m. of each dosing day along with 240 ml of tap water. No food was allowed until 4 h after dose administration. Approximately 7 ml of blood for pioglitazone and active metabolite assays were drawn into heparinized tubes through indwelling cannula before (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 36 h after dosing. Blood samples were centrifuged at 3000 rpm for 10 min; plasma was separated and kept frozen at -70°C until assayed. Plasma was analyzed for pioglitazone concentration using a validated high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Pharmacokinetics analysis

PK parameters (C_{max}, T_{max}, AUC_t and AUC_{inf}) were calculated by noncompartmental models in WinNonlin v5.2 (Table 1).

DNA extraction

From May to August 2008, blood samples were obtained from 27 participants. After obtaining informed consent, approximately 10 ml of whole blood was collected from each participant. Blood samples were drawn into sterile tubes containing ethylenediaminetetraacetic acid (EDTA) and stored at -70°C until the isolation of genomic DNA. Genomic DNA was isolated from the blood sample by a standard phenol chloroform extraction method.

Genotyping

SNPs of 27 healthy male volunteers were analyzed by Standard Illumina procedures using Illumina BeadStation 500G (Illumina Human610Quad v1.0 DNA Analysis BeadChip) as previously described.[9] Intensity files (*.idat) were processed by BeadStudio GT module 3.3.4 with default analysis settings. Each SNP was analyzed independently to cluster and identify genotypes. Genotype calls were generated by comparing experimental data with those in the supplied cluster file (*.egt). The SNP set was filtered on the basis of genotype call rates (≥ 95%), and minor allele frequency (MAF ≥ 0.05).

Statistical analysis & data analysis

Hardy Weinberg equilibrium (HWE) was calculated for individual SNPs using an exact test. All of the SNPs reported in this manuscript have HWE *P*-values > 0.001. To calculate the degree (Beta), 95% confidence intervals (CI) and *P*-value while controlling for age, height and weight as covariants in a linear regression analysis with significant SNPs on individual PK parameters of pioglitazone, unadjusted genotypic association with additive, dominant and recessive models were tested by calculating the Beta and *P*-value using PLINK version 1.06 (Shaun Purcell, USA). When the additive model was used, each genotype was independently coded as 0, 1, or 2. In the dominant model, a homozygote major allele and another two genotypes were coded as 0 and 1. In the recessive model, a homozygote minor allele and another two genotypes were coded as 0 and 1. After filtering, SNPs were analyzed on chromosome 1 through chromosome 22 for each group.

Significant SNPs were identified from each PK parameter (C_{max}, T_{max} and AUC_{inf}). Among these, SNPs of phase I and II enzymes selected from the further analysis in each PK parameters (four SNPs in C_{max}, seven SNPs in T_{max} seven SNPs in AUC_{inf}).

Results

Pharmacokinetics analysis

The PK parameters of pioglitazone are shown in Table 1. These data were used for linear regression analysis.

SNPs analysis

PK parameters of C_{max}, T_{max} and AUC_{inf} were analyzed by linear regression analysis. A total of 35 SNPs from Cmax group, 1,118 SNPs from Tmax group and 1,259 SNPs from AUCinf group were significantly associated with each parameters (Table 2, P <0.0001). All data were adjusted for age, height, and weight. For clinical pharmacological purposes, significant SNPs encoding phase I and II drug metabolizing enzymes were selected for fur-

Table 2. Summary of regression analysis

		N
C_{max}	P <0.0001	35
	0.0001 ~ <0.001	468
	<0.01	5,089
T_{max}	P <0.0001	1,118
	0.0001 ~ <0.001	527
	0.001 ~ <0.01	4,541
AUC_{inf}	P <0.0001	1,259
	0.0001 ~ <0.001	1,140
	0.001 ~ <0.01	5,098

N=number

Table 3. Selected SNPs of Phase I and II drug metabolizing enzymes in C_{max} group from linear regression analysis

Marker	Chr.	Location	Gene	Genotype	N	Mean	Stdev.	P
rs7761731	6	missense	CYP39A1	AA	9	636.091	190.301	0.005**
				TA	13	775.532	181.510	
				TT	5	982.968	275.762	
rs3799872	6	intron	CYP39A1	CC	8	639.504	203.146	0.004**
				TC	13	746.211	174.641	
				TT	6	984.135	246.665	
rs156697	10	missense	GSTO2	CC	2	987.680	269.563	0.009**
				TC	7	910.693	251.258	
				TT	18	687.298	183.096	
rs1558139	19	intron	CYP4F2	AA	2	483.500	213.999	0.007**
				AG	16	725.477	171.676	
				GG	9	905.217	257.265	

Chr, chromosome; N, number; Stdev, standard deviation. *p<0.05, **p<0.01, ***p<0.001

Table 4. Selected SNPs of Phase I and II drug metabolizing enzymes in T_{max} group from linear regression analysis

Marker	Chr.	Location	Gene	Genotype	N	Mean	Stdev.	P
rs3766198	1	intron	CYP4B1	GG	11	2.045	0.757	0.006**
				TG	11	1.409	0.437	
				TT	5	1.200	0.447	
rs2270422	14	intron	GSTZ1	CC	7	2.143	0.900	0.004**
				CG	12	1.625	0.528	
				GG	8	1.188	0.259	
rs2054675	19	flanking_5UTR	CYP2B6	CC	2	3.000	1.414	0.002**
				TC	9	1.722	0.441	
				TT	16	1.406	0.491	
rs10500282	19	intron	CYP2B6	CC	2	3.000	1.414	0.002**
				TC	9	1.722	0.441	
				TT	16	1.406	0.491	
rs3745274	19	missense	CYP2B6	GG	17	1.441	0.496	0.004**
				TG	8	1.688	0.458	
				TT	2	3.000	1.414	
rs8192719	19	intron	CYP2B6	CC	17	1.441	0.496	0.004**
				TC	8	1.688	0.458	
				TT	2	3.000	1.414	
rs11673270	19	intron	CYP2B6	AA	17	1.441	0.496	0.004**
				AC	8	1.688	0.458	
				CC	2	3.000	1.414	

Chr, chromosome; N, number; Stdev, standard deviation. *p<0.05, **p<0.01, ***p<0.001

Table 5. Selected SNPs of Phase I and II drug metabolizing enzymes in AUC_{inf} group from linear regression analysis

Marker	Chr.	Location	Gene	Genotype	N	Mean	Stdev.	P
rs11572204	1	intron	CYP2J2	CC	22	7526.019	2303.326	0.006**
				CG	2	10804.994	1554.542	
				GG	3	13524.397	9502.091	
rs4148280	4	intron	UGT2A1	CC	16	7184.061	1870.072	0.003**
				TC	7	8063.100	2900.045	
				TT	4	14092.233	6942.204	
rs4646422	15	missense	CYP1A1	AA	2	17422.783	9885.719	0.009**
				AG	8	7954.883	2328.169	
				GG	17	7604.174	2381.115	
rs3745274	19	missense	CYP2B6	GG	17	7521.493	1970.203	0.004**
				TG	8	7946.620	2828.162	
				TT	2	18158.632	8845.072	
rs8192719	19	intron	CYP2B6	CC	17	7521.493	1970.203	0.004**
				TC	8	7946.620	2828.162	
				TT	2	18158.632	8845.072	
rs11673270	19	intron	CYP2B6	AA	17	7521.493	1970.203	0.004**
				AC	8	7946.620	2828.162	
				CC	2	18158.632	8845.072	
rs707265	19	flanking_3UTR	CYP2B6	AA	4	6697.185	1682.872	0.010*
				AG	12	6631.089	1792.361	
				GG	11	11035.799	4818.251	

Chr, chromosome; N, number; Stdev, standard deviation. *p value<0.05, **p value<0.01, ***p value<0.001

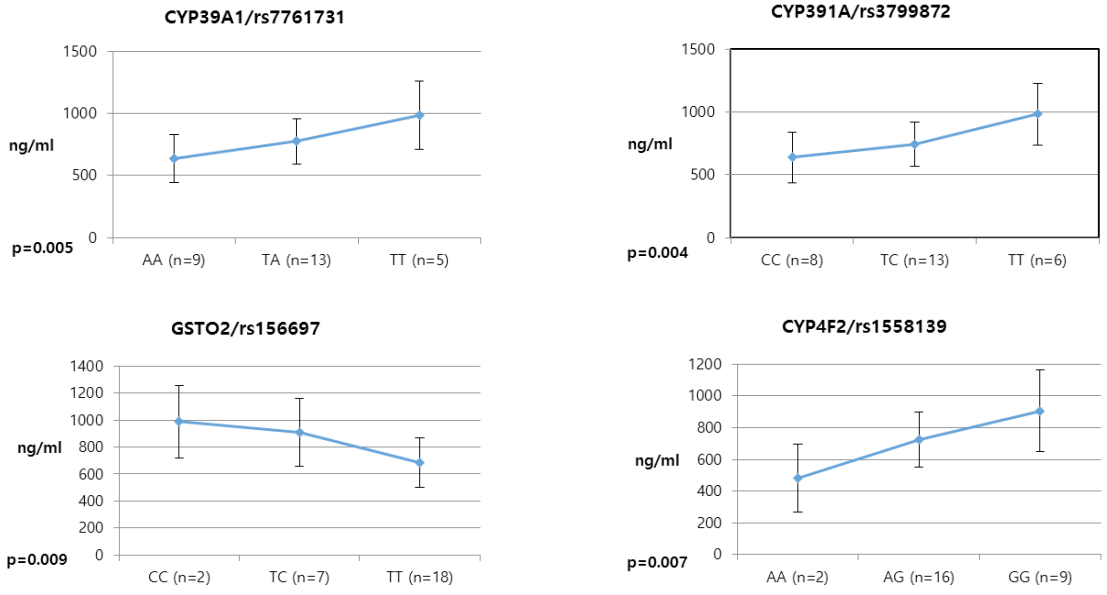
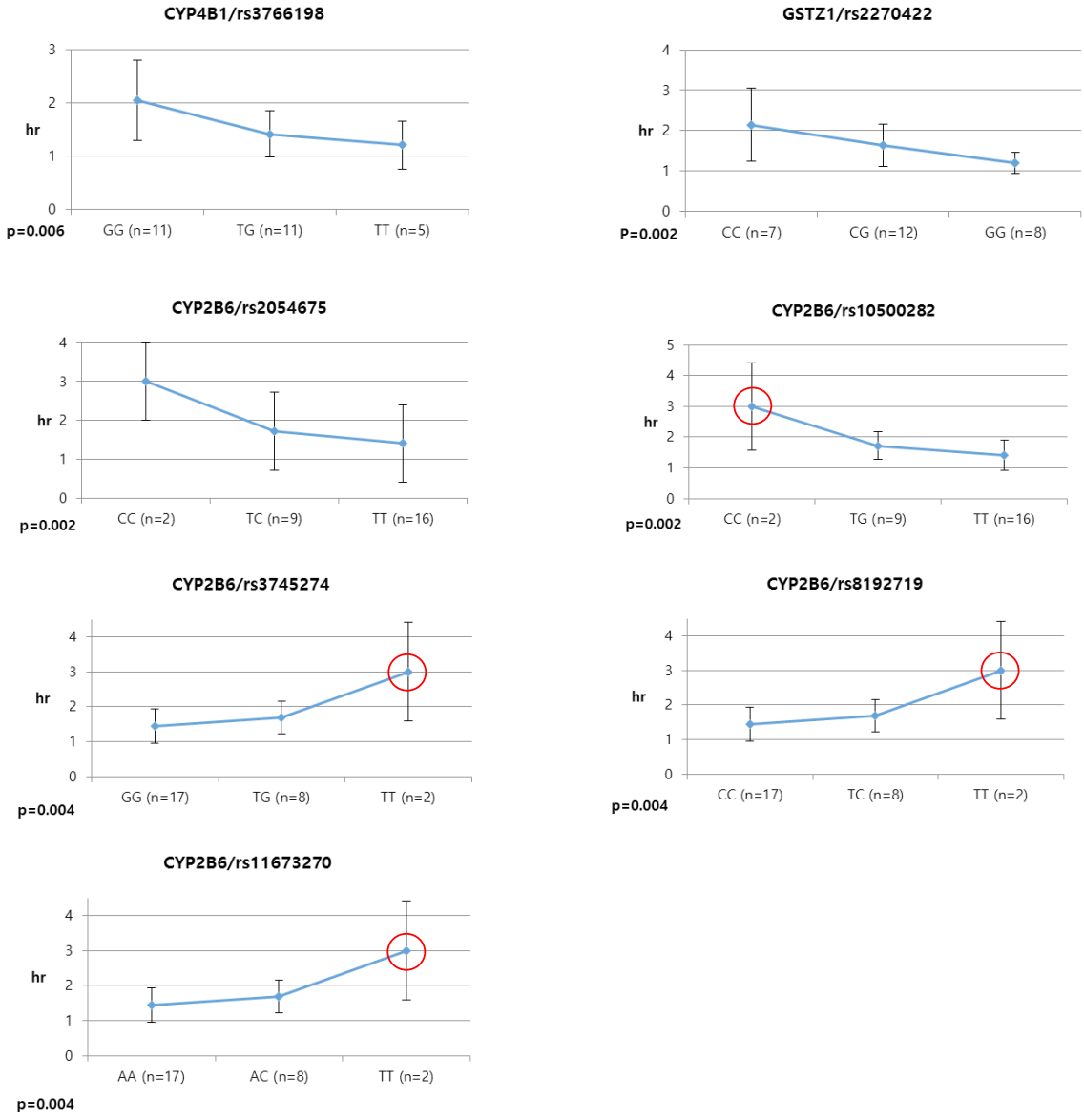


Figure 1. Results of regression analysis of in C_{max} group.



*Circles indicate significant changes by genotype

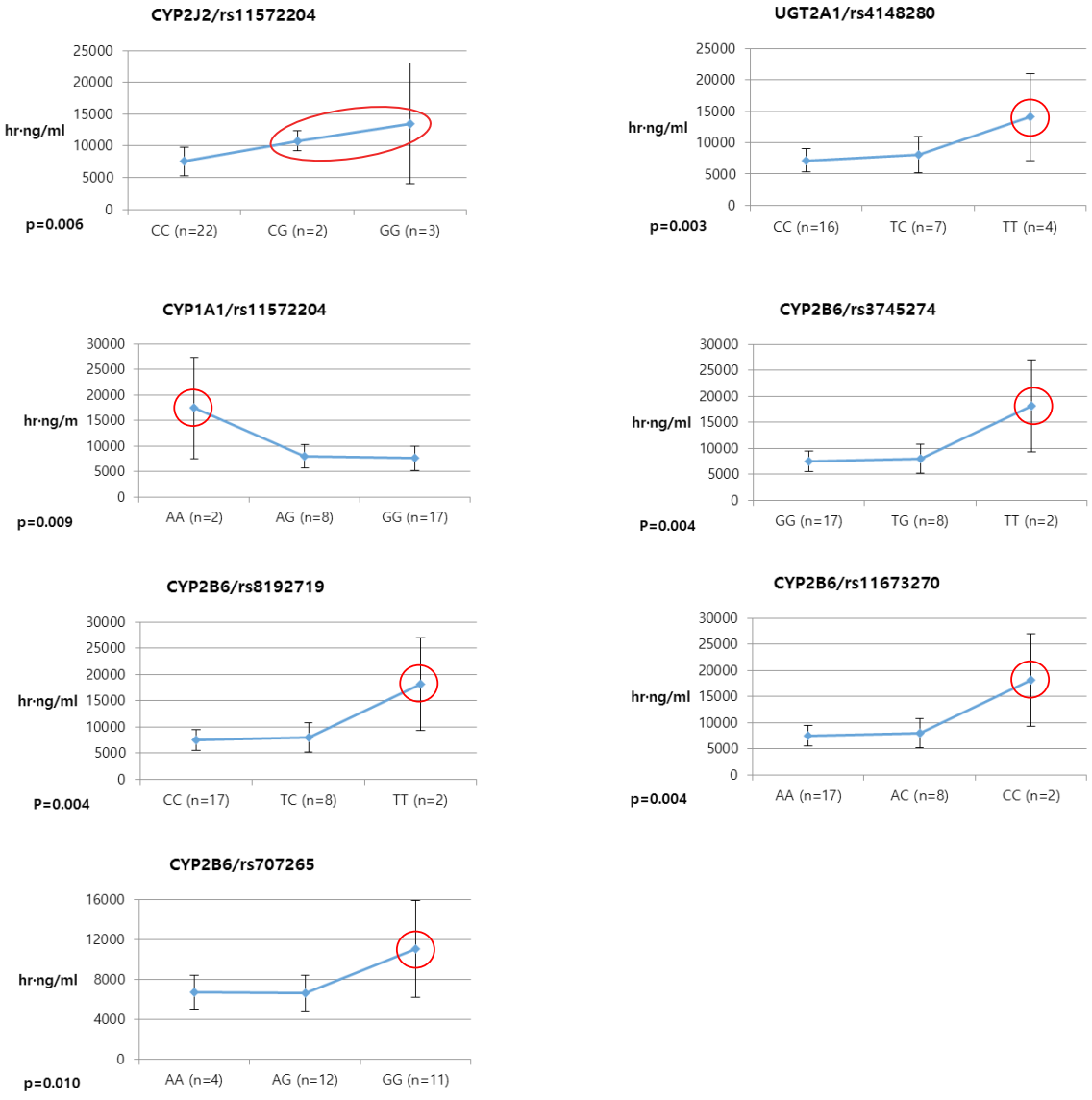
Figure 2. Results of regression analysis of in T_{max} group.

ther analysis.

In the C_{max} group, we selected four SNPs for further analyses (rs7761731 and rs3799872 from CYP39A1; rs156697 from GSTO2; rs1558139 from CYP4F2, Table 3). In the T_{max} group, we selected seven SNPs from 3 genes (rs3766198 from CYP4B1; rs2270422 from GSTZ1; rs2054675, rs10500282, rs3745274, rs8192719 and rs11673270 from CYP2B6, Table 4). In the AUC_{inf} group, we selected seven SNPs from four genes (rs11572204 from CYP2J2; rs4148280 from UGT2A1, rs4646422 from CYP1A1; rs3745274, rs8192719, rs11673270, and rs707265 from CYP2B6, Table 5).

Of the phase I and II enzymes, especially, CYP39A1 (rs7761731, $P = 0.005$; rs3799872, $P = 0.004$), CYP4F2 (rs1558139, $P = 0.006$), GSTO2 (rs156697, $P = 0.008$) showed statistically significant changes by genotype in C_{max} group (Table 3 and Fig. 1). In CYP39A1 rs7761731, TT genotype showed 1.5fold increase in C_{max} than AA genotype. In rs3799872, TT genotype showed 1.5 fold increase in C_{max} than CC genotype. CC genotype of rs156697 (GSTO2) showed twofold increase in C_{max}. AA genotype of rs1558139 (CYP4F2) showed twofold decrease in C_{max}.

In T_{max} group, CYP2B6 (rs2054675, $P = 0.002$; rs10500282, $P = 0.002$; rs3745274, $P = 0.004$; rs8192719, $P = 0.004$; rs11673270,



*Circles indicate significant changes by genotype

Figure 3. Results of regression analysis of in AUC_{inf} group.

$P = 0.004$), GSTZ1 (rs2270422, $P = 0.003$), CYP4B1 (rs3766198, $P = 0.006$) showed statistically significant changes by genotype (Table 4 and Fig. 2). rs3766198 of CYP4B1 showed twofold changes according to genotypes (GG genotype showed twofold increase in T_{max} than TT genotypte). TT genotype of rs8192719 (CYP2B6) showed twofold increase in T_{max}. CC genotype of rs2054675 (CYP2B6) showed twofold increase in time to peak concentration. Other SNPs also showed similar results.

In AUC_{inf} group, CYP2J2 (rs11572204, $P = 0.006$), CYP1A1 (rs4646422, $P = 0.009$), UGT2A1 (rs4148280, $P = 0.003$), CYP2B6 (rs3745274, $P = 0.004$; rs8192719, $P = 0.004$; rs11673270, $P = 0.004$; rs707265, $P = 0.010$) showed statistically significant changes by genotype (Table 5 and Fig. 3). AA genotype of rs4646422 (CYP1A1) showed twofold increase in drug absorption. TT genotype of rs3745274 (CYP2B6) also showed twofold increase.

Discussion

Pioglitazone is an oral antidiabetic agent that has been shown to affect abnormal glucose and lipid metabolism associated with insulin resistance.[10] The genetic polymorphism which affect pioglitazone response had been studied by several researchers.[11-13] In their paper, PPAR gamma, adiponectin, ACE, and SLCO1B1 gene polymorphisms were studied. The PK studies

with pioglitazone were reported by Aquilante et al.,[14] Tornio et al.[15] and Kalliokoski et al.[16] In their studies, pioglitazone AUC_{inf} were significantly changed with polymorphisms of CYP2C8 and SLCO1B1. In our study, we performed the whole genome SNP analysis to screen the possible SNPs which affect the pioglitazone pharmacokinetics. This study was conducted using whole genome association study (WGAS) and regression analysis.

Our results implied that genotype differences of CYP39A1, GSTO2 and CYP4F2 could play important roles on pioglitazone C_{max}. The CYP39A1 expressed in the liver[18] is involved in the conversion of cholesterol to bile acid. Recently, Shafaati *et al.* reported that CYP39A1 genotype affected drug metabolism.[19]

GSTO2 polymorphism involving an A to G transition at nucleotide position 424 in exon 4 might be associated with lower activity of the variant enzyme in a substrate-dependent manner. This SNP may be one of the main causes to the different susceptibility between individuals to oxidative stress and inorganic arsenic metabolism[20,21] and showed significant associations in our studies.

CYP4F2 is a part of a cluster of cytochrome P450 genes on chromosome 19.[22,23] CYP4F2 is localized in the endoplasmic reticulum and is related with oxidation. Results from this study, CYP4F2 may affect metabolism of pioglitazone.

CYP2B6 is known to metabolize some xenobiotics, such as the anti-cancer drugs cyclophosphamide and ifosphamide.[24] Our results suggest that CYP2B6 has a clinically important effect on pioglitazone metabolism. By regression analysis, CYP2B6 gene has significant effect on T_{max} and AUC_{inf}. Moreover, significant SNPs of CYP2B6 have effects on T_{max} and AUC_{inf}, together. According to these facts and result of study suggest that CYP2B6 affected pioglitazone metabolism.

Approaches for elucidating polygenic determinants of drug response include genome-wide analysis to perform genome-wide searches for polymorphisms associated with drug effects, and candidate gene strategies based on existing knowledge of a medication's mechanism of action and pathway for metabolism and disposition.[25]

In this study, we screened several significant SNPs affecting pioglitazone PK using whole-genome analysis. Significant SNPs in this study might be related to metabolism of pioglitazone and also meaningful genes and SNPs could affect the pioglitazone PK. But our study has significant limitations. Because of small sample size, Bonferroni correction cannot be adjusted. Because all significant SNPs showed p value above 10^{-6}, SNPs from this study could be only used for candidate genes for further evaluation. So further studies for pioglitazone pharmacogenomics using these SNPs are needed. Also, from now on, it will require biological depth-research about meaningful genes and SNPs to confirm these data.

Conflict of interest

The authors declare no conflict of interest.

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