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Gender, Body Mass Index, and *PPARγ* Polymorphism Are Good Indicators in Hyperuricemia Prediction for Han Chinese

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Hyperuricemia is closely associated with obesity and metabolic abnormalities, which is also an independent risk factor for cardiovascular diseases. The PPARγ gene, which is linked to obesity and metabolic abnormalities in Han Chinese, might be considered a top candidate gene that is involved in hyperuricemia. This study recruited 457 participants, aged 20–40 years old, to investigate the associations of the PPARγ gene and metabolic parameters with hyperuricemia. Three tag-single nucleotide polymorphisms, rs2292101, rs4684846, and rs1822825, of the PPARγ gene were selected to explore their association with hyperuricemia. Risk genotypes on rs1822825 of the PPARγ gene exhibited statistical significance with hyperuricemia (odds ratio: 1.9; 95% confidence interval: 1.05–3.57). Although gender, body mass index (BMI), serum total cholesterol concentration, or protein intake per day were statistically associated with hyperuricemia, the combination of BMI, gender, and rs1822825, rather than that of age, serum lipid profile, blood pressure, and protein intake per day, satisfied the predictability for hyperuricemia (sensitivity: 69.3%; specificity: 83.7%) in Taiwan-born obese Han Chinese. BMI, gender, and the rs1822825 polymorphism in the PPARγ gene appeared good biomarkers in hyperuricemia; therefore, these powerful indicators may be included in the prediction of hyperuricemia to increase the accuracy of the analysis.

Introduction

Recently, it has been reported that hyperuricemia is an independent predictor for all-cause cardiovascular risk (Fessel, 1980; Chen *et al.*, 2009b), which is also associated with high in-hospital mortality and poor long-term survival in acute myocardial infarction patients (Car and Trkulja, 2009). Several studies indicated that hyperuricemia was closely associated with obesity and obesity-related metabolic disorders, including hyperglycemia/insulin resistance (Rathmann *et al.*, 1998; Lin *et al.*, 2008), hyperlipidemia (Roux *et al.*, 1972; Barats and Smolenskaia, 1990; Nakamura, 1996), and hypertension (Hollister *et al.*, 1967; Oyama *et al.*, 2006; Cho *et al.*, 2008; Basen-Engquist and Chang, 2011; Hsu *et al.*, 2011). Higher odds ratios (ORs) for hyperuricemia were observed in Taiwan-born Han Chinese than in U.S. individuals within the same body mass index (BMI) range (Pan *et al.*, 2004). The prevalence of obesity/overweight in Taiwan has been increasing alarmingly (Page *et al.*, 2004; Ho and Tsai, 2007); therefore, an understanding of the fundamental mechanism of hyperuricemia becomes critical to prevent hyperuricemia in Han Chinese in Taiwan.

Previous studies indicated that hyperuricemia was associated with a long list of candidate genes such as solute carrier family 2, member 9 (SLC2A9) (Rule *et al.*, 2011), solute carrier family 22, member 12 (SLC22A12) (Jang *et al.*, 2008), and solute carrier family 17, member 3 (SLC17A3) (Polasek *et al.*, 2010). Additional candidates include the genes encoding ATP-binding cassette, sub-family G, member 2 (ABCG2) (Yamagishi *et al.*, 2010), klotho (KL) (Shimoyama *et al.*, 2009), guanine nucleotide binding protein, beta polypeptide 3 (GNB3) (Suwazono *et al.*, 2006), methylenetetrahydrofolate reductase (MTHFR) (Zuo *et al.*, 2000), nitric oxide synthase 3 (NOS3) (Wang *et al.*, 2007), adrenoceptor beta 2 (ADRB2)

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(Masuo *et al.*, 2005), and adrenoceptor beta 3 (ADRB3) (Wang *et al.*, 2002). However, considerable heterogeneity on the putative hyperuricemia loci was observed among different ethnic groups.

The PPARγ gene is associated with xanthine oxidase/reductase activity (Cheung *et al.*, 2007), glucose (Ylonen *et al.*, 2008; Ruchat *et al.*, 2010), blood pressure (Halabi *et al.*, 2008), and lipid metabolism (Iwata *et al.*, 2001; Ylonen *et al.*, 2008; Johansson *et al.*, 2009). We also have previously reported that polymorphisms of the PPARγ gene were strongly associated with obesity in Han Chinese (Chen *et al.*, 2009a). Furthermore, we reanalyzed the data retrieved from a human genome-wide gene study (Chung *et al.*, 2011) and found that the correlation coefficients among serum uric acid level, PPARγ gene, and xanthine oxidase/reductase (XDH) gene expression were -0.1 for serum uric acid and *PPARγ* expression ($p = 0.08$), -0.15 for *PPARγ* and *XDH* expression ($p = 3 \times 10^{-4}$), and -0.1 for serum uric acid and *XDH* expression ($p = 0.03$), respectively, using a new RNA expression analyzing platform (Human OneArray® v5 platform; Phalanx Biotech) (Appendix Table A1).

In sum, the PPARγ gene may play an important role in hyperuricemia for Han Chinese. Therefore, we conducted this study using tag-single nucleotide polymorphisms (SNPs) of the PPARγ gene to explore the association of the *PPARγ* polymorphism with hyperuricemia. Moreover, we tried to examine which factors, including age, gender, blood pressure, blood lipid profiles, blood creatinine, and blood urea nitrogen levels, exhibited potential predictability in hyperuricemia for Han Chinese, and how they were combined to exert their effects.

Materials and Methods

A total of 457 Han Chinese with normal renal function, aged 20–40 years old, were recruited in the outpatient clinic for health examination at Taipei Medical University Hospital between May 2008 and April 2009. All anthropometric and laboratory measurements were performed by the standard procedures. A 3-day, 24-h recall was conducted by a registered dietician at the beginning of the study. The quantification of three macronutrients was converted according to Food Nutrition Database from Taiwan Food and Drug Administration (http://doh.gov.tw/FoodAnalysis/ingredients.htm). The study protocol was approved by the ethics committees at both hospitals, and the informed consent forms were collected from all participants before the commencement of the study. All patients were checked for normal renal function by evaluating their blood creatinine and blood urea nitrogen levels.

Study design

Subjects were assigned to either the hyperuricemia (HUA) or non-hyperuricemia (NHUA) group according to their serum uric acid levels. Hyperuricemia was diagnosed based on a serum uric acid level greater than or equal to 7.0 mg/dL in men and 6.0 mg/dL in women (Dincer *et al.*, 2002; Chizynski and Rozycka, 2005). Any participant with hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), lowering serum uric acid agents, or type 2 diabetes in the last 6 months was excluded. The serum blood urea nitrogen, serum creatinine, and urine protein of all patients were within the normal range as evaluated by physicians. The associations between hyperuricemia and three tag-SNPs (rs2292101, rs4684846, and rs1822825) of the PPARγ gene were assessed by allelic association analysis; the significant SNP was identified for subsequent analysis, and the synergistic effect of the three tag-SNPs was also evaluated. Next, we conducted a series of analyses to investigate which indicators, including genetic elements, metabolic factors, and anthropometry parameters, could predict hyperuricemia, and whether these indicators exerted synergistic effects.

Genomic DNA extraction, SNPs selection, and genotyping

Genomic DNA was extracted from cells in the buffy coat layer using a modified phenol-chloroform method (Chomczynski and Sacchi, 1987, 2006; Puissant and Houdebine 1990). The quality of the DNA samples was confirmed, and the samples were diluted to 2.5–3.0 ng/μL for multiplex polymerase chain reaction. Three tag-SNPs, rs2292101, rs4684846, and rs1822825, of the PPARγ gene were selected from the dbSNP database (http://ncbi.nlm.nih.gov/SNP) and used for genotyping by the SNP stream genotyping system (Beckman Coulter, Inc.). To ensure unbiased selection, one tag-SNP was chosen from each linkage disequilibrium (LD) block as defined in the CHB (Han Chinese individuals from Beijing, China) database (www.hapmap.org).

Statistical analysis

All data analysis was performed with SAS 9.3 software. An analysis of covariance model was applied to adjust for age, gender, and BMI in all health-related indicators. The allele frequency analysis and Hardy–Weinberg equilibrium were performed by the PROC ALLELE procedure. The genetic loci that showed significant LD ($p < 0.05$) were subsequently analyzed for the association between genotype and disease status. The association between candidate loci and hyperuricemia was tested by logistic regression models, and the *p*-values were calculated based on 1000 random permutations. A *p*-value < 0.05 denotes significant difference between the groups. Moreover, variables significantly associated with hyperuricemia (Table 1) were selected to perform the stepwise-discriminant analysis by the STEPDISC procedure for model selection in order to find the variables with powerful potency in hyperuricemia. The pooled within-class standardized canonical coefficient was further calculated to show the relative influence in hyperuricemia among the identified variables. Subsequently, the Mahalanobis' distance analysis was applied to show the sensitivity and specificity of the hyperuricemia prediction using the powerful factors, derived from the stepwise-discriminant analysis, related to hyperuricemia.

The multiple-variable linear regression analysis was performed to search for high impact factors in serum uric acid level prediction. Statistical significant variables in both stepwise-discriminant and linear regression analyses were considered as the influential factors in uric acid metabolism for Han Chinese. The Mahalanobis' distance method was applied to hyperuricemia prediction using variables with great influence in uric acid metabolism for Han Chinese.

Results

As shown in Table 1, individuals with HUA exhibited less favorable profiles of the anthropometric and biochemical

Table 1. Comparison of the Selective Anthropometric and Biochemical Indicators in Individuals with Hyperuricemia or Non-Hyperuricemia

	NHUA (n = *343*)	*HUA* (n = *114*)	p-*Value*
Male/female	108/142	120/85	0.003[a]
Age (years)	31.4 ± 5.9	29.0 ± 5.7	0.078[b]
BMI (kg/m^2)	21.0 ± 3.0	25.9 ± 6.9	< 0.001[b]
Serum triglyceride (mg/dL)	158.6 ± 132.9	195.5 ± 164.4	0.683
Serum cholesterol (mg/dL)	172.7 ± 32.9	188.2 ± 37.9	0.038
Serum HDL-cholesterol (mg/dL)	55.3 ± 12.6	50.7 ± 13.2	0.368
HbA1c (%)	5.0 ± 0.4	5.2 ± 0.9	0.193
Blood pressure (mmHg)			
Systolic	110.6 ± 13.4	120.4 ± 16.3	0.044
Diastolic	71.2 ± 10.7	77.0 ± 12.0	0.246
Serum uric acid (mg/dL)	4.7 ± 0.9	7.6 ± 1.3	< 0.001
Serum creatinine (mg/dL)	0.7 ± 0.4	0.8 ± 0.3	0.586
Blood urine urea nitrogen (mg/dL)	16.3 ± 4.9	16.1 ± 4.1	0.671
Protein intake (g/day)	88.4 ± 18.9	76.0 ± 14.0	0.038

An analysis of covariance model was performed to adjust for age, sex distribution, and BMI among all indicators.
[a]Chi-square analysis was performed.
[b]Student *t*-test was performed.
HUA, hyperuricemia; NHUA; non-hyperuricemia; BMI, body mass index; HDL, high density cholesterol.

indicators, including gender distribution, BMI, total serum cholesterol concentration, serum uric acid level, blood pressure, and protein intake per day as compared with the NHUA group. Notably, relative low protein intake per day was observed in the HUA group as compared with the NHUA group (HUA: 76.0 g/day vs. NHUA: 84.4 g/day, $p = 0.038$). The allelic distributions of the three selected tag-SNPs, rs2292101, rs4684846, and rs1822825, of the PPARγ gene from the dbSNP database met the Hardy–Weinberg principle (data not shown). The allelic association between the three selected SNPs and hyperuricemia was analyzed. The result showed that the allelic distributions of rs1822825 and rs4684846 were significantly associated with hyperuricemia (A allele on rs1822825: 45% in HUA group and 37% in NHUA group, $p < 0.001$; G allele on rs4684846: 55% in HUA group and 49% in NHUA group, $p = 0.048$) (Appendix Table A2).

Risk-genotype analyses were carried out for rs1822825 and rs4684846 to explore any dominant or recessive effect on these two tag-SNPs (Table 2). A recessive effect was observed on rs1822825, where the "AA" genotype was associated with hyperuricemia with OR (95% confidence interval [CI]) at 1.9 (1.05–3.57). In contrast, a dominant effect was observed on rs4684846 where the "GG" and "AG" genotypes were not significantly associated with hyperuricemia with OR (95% CI) at 0.9 (0.48–1.40). The model selection was used in the stepwise-discriminant analysis in order to confirm that rs1822825 was significantly associated with hyperuricemia, as shown in Table 3. The *p*-value of the best selected multi-variable model was less than 0.0001. The selected variables included gender, BMI, and rs1822825 (*p*-value was < 0.001 for gender and BMI, and 0.047 for rs1822825), and the order of relative influence in hyperuricemia was BMI, gender, and rs1822825 (standardized canonical coefficients: 0.9, 0.3, and 0.15, respectively) (Table 3). For validating the results derived from the discriminant analysis, we performed a linear regression analysis with a forward selection model to search for the more influential factors in serum uric acid level for Han Chinese. The results showed that the combination of BMI, rs1822825 polymorphism, and gender was the best predictive model in serum uric acid level for Han Chinese, with a serum uric acid increment of 0.2, 1.05, and 0.95 mg/dL with 1 BMI unit, risk genotype (AA) on rs1822825 polymorphism, and being male ($p < 0.001$ for BMI, $p = 0.022$ for rs1822825 polymorphism, and $p < 0.001$ for gender) (Table 4). Moreover, a stratum analysis was performed in both men and women, where participants with the risk genotype rs1822825 had a greater serum uric acid level as compared with the non-risk genotype (1.42 mg/dL for men, $p < 0.001$; 0.50 mg/dL for women, $p < 0.002$) (Table 4).

The Mahalanobis' distance was applied for verifying the best selected model that was derived from the stepwise-discriminant analysis. The hyperuricemia prediction model, including gender, BMI, and rs1822825, showed 69.3% of sensitivity and 83.7% of specificity (Table 5). It should be noted that men had an almost twofold higher risk of hyperuricemia than did women (OR: 1.92; 95% CI: 1.45–2.53), after having adjusted the genetic effects of the *PPARγ* polymorphisms (data not shown).

Table 2. The Analysis of Genotypic Association Between Hyperuricemia and Three Selective tag-Single Nucleotide Polymorphisms of the PPARγ Gene

	NHUA, n	*HUA*, n	*OR (95% CI)*[a]
rs1822825			
AA	46	22	1.9 (1.05–3.57)
AG	182	49	0.70 (0.40–1.10)
GG	115	43	1
rs4684846			
GG	76	27	0.9 (0.48–1.40)
GA	177	51	0.64 (0.38–0.74)
AA	88	35	1

The *p*-values were calculated based on 1,000 random permutations.
Genotyping success rate was 100% and 99.3% for rs1822825 and rs4684846, respectively.
[a]Adjusted for gender, age group, and BMI group.
OR (95% CI), odds ratio (95% confidence interval).

Table 3. Selected Variable Significantly Associated with Hyperuricemia by Using Discriminant Analysis

	F-*Value*	p-*Value* (Pr > F)	p-*Value for Lambda*	*Pooled within-class standardized canonical coefficients*
Gender	15.68	< 0.001	< 0.001	0.30
BMI (kg/m^2)	210.63	< 0.001	< 0.001	0.90
rs1822825	13.56	0.047	< 0.001	0.15
Serum cholesterol (mg/dL)	0.86	0.354	—	—
Blood pressure (mmHg)			—	—
Systolic	0.10	0.939	—	—
Diastolic	0.10	0.966	—	—
Protein intake (g/day)	0.09	0.972	—	—

The *p*-value for Wilks' Lambda in multi-variable model (gender, BMI, and rs1822825) was less than 0.0001 (< 0.0001).
The stepwise method was performed.

Discussion

This is a pioneer study that explores hyperuricemia-associated candidate genes in Han Chinese. Our data indicate two main findings. First, hyperuricemic individuals exhibited abnormal, subclinical manifestations of cardiovascular diseases. Second, the tag-SNP rs1822825 of the PPARγ gene was associated with hyperuricemia, and the synergistic effect of rs1822825, gender, and BMI appeared a good prediction for hyperuricemia in Taiwan-born Han Chinese, rather than dietary protein intake per day (Table 1). Therefore, uric acid metabolism may be closely associated with genetic components, rather than dietary protein intake, for Han Chinese.

It is well known that PPARγ gene encodes a nuclear receptor involved in adipocyte differentiation, which functions as a lipid sensor in the regulation of energy storage and the metabolism of glucose and lipid (Rosen *et al.*, 1999; Picard and Auwerx, 2002; Carmen and Victor, 2006). Nakamura (1996) has indicated that both insulin resistance and abnormal lipid metabolism were associated with hyperuricemia. In addition, individuals with hyperuricemia had greater prevalence in metabolic abnormalities of lipid and glucose and had significantly higher blood pressure as compared with their normal counterparts (Nakamura, 1996). Thus, we hypothesized that hyperuricemia may partially result from metabolic abnormalities in the regulation pathway of the PPARγ gene.

Recent studies have shown that PPARγ gene expression is associated with uric acid metabolism such that PPARγ gene expression is related to monosodium urate monohydrate levels (Akahoshi *et al.*, 2003) and xanthine oxido/reductase activity (Cheung *et al.*, 2007). Since xanthine oxido/reductase plays an important role in uric acid metabolism (Fields *et al.*, 1996; Watts, 1966), the preliminary data indicated that PPARγ gene expression was substantially correlated with XDH gene and serum uric acid level (Appendix Table A1). Besides, we previously reported that *PPARγ* was associated with obesity in Han Chinese (Chen *et al.*, 2009a). The current findings also verified that the variables with the best discriminant capacity for hyperuricemia diagnosis included gender, BMI, and rs1822825 (Tables 3–5). We tried to predict the probability of hyperuricemia using gender and BMI only. The results displayed that the sensitivity decreased to 63.9% and the 1-specificity increased from 16.3% to 23.9% (data not shown). Accordingly, PPARγ gene owns potential capacity for the predisposition to hyperuricemia due to its association with xanthine oxidase/reductase activity (Cheung *et al.*, 2007), obesity (Chen *et al.*, 2009a), glucose (Ylonen *et al.*, 2008; Ruchat *et al.*, 2010), blood pressure (Halabi *et al.*, 2008), and lipid (Iwata *et al.*, 2001; Ylonen *et al.*, 2008; Johansson *et al.*, 2009) homeostasis. We supposed that PPARγ gene may play a foundational role in hyperuricemia etiology rather than metabolic abnormality, dietary protein intake, and obesity, which were downstream of the physiological pathway regulated by PPARγ gene.

Table 4. The Influential Factors in Serum Uric Acid Level Prediction for Han Chinese with a Linear Regression Analysis

	BMI	*rs1822825, R vs. NR*	*Gender, M vs. F*	*Adjusted-R^2*
Model 1				
β	0.20	1.05	0.95	0.9
p-Value	< 0.001	0.022	< 0.001	
Model 2				
β	0.16	1.42	—	0.83
p-Value	< 0.001	< 0.001	—	
Model 3				
β	0.18	0.50	—	0.84
p-Value	< 0.001	0.002	—	

Model 1: The forward-selection model was performed, where gender, BMI, and rs1822825 were selected; Model 2: Male participants involved in model 2; Model 3: Female participants involved in model 3.

M, male; F, female; R, risk genotype (AA) on rs1822825 polymorphism; NR, non-risk genotype (AG/GG) on rs1822825 polymorphism.

Table 5. The Prediction of Hyperuricemia using Gender, Body Mass Index, and rs1822825 Polymorphism on the PPARγ Gene

			Prediction	
	Hyperuricemia		*No*	*Yes*
Truth	No	*N*	287	56
		%	83.7%	16.3%
	Yes	*N*	35	79
		%	30.7%	69.3%

The Mahalanobis' distance was applied in this analysis.
The previous probability of hyperuricemia and non-hyperuricemia was 0.4 and 0.6, respectively.

Six mRNA isoforms (*PPARγ*1, *PPARγ*2, *PPARγ*3, *PPARγ*4, *PPARγ*2ORF4, and *PPARγ*3ORF4) of the PPARγ gene, resulting from alternative splicing, were identified (Auwerx, 1999; Rosen and Spiegelman, 2001; Cecil *et al.*, 2006). The rs1822825 tag-SNP used in this study, spanning a genomic region from intron 3 to intron 5, was selected from an LD block that includes the stop codon of *PPARγ*3ORF4 (exon 4). Another tag-SNP, rs4684846, located in the promoter region between exon A1 and exon A2, was chosen from an LD block whose 5′ and 3′ ends are near the transcriptional start site of *PPARγ*3 (about 5 kb apart) and −681 C/G polymorphism (about 9 kb apart), respectively. The current study revealed that the tag-SNP, rs1822825, was strongly associated with hyperuricemia where the association was still significant after having adjusted for rs4684846, another tag-SNP. The rs1822825 SNP is a synonymous polymorphism such that both alleles produce the same polypeptide sequence. In general, synonymous polymorphisms are relatively unimportant genetic markers. Thus, further studies are necessary to clarify the role of rs1822825 and its corresponding LD blocks.

Hyperuricemia is one of the major indicators in cardiovascular diseases (Fessel, 1980; Lee *et al.*, 1995). Recently, it has even been reported that hyperuricemia is an independent risk indicator for all-cause cardiovascular disease and ischemic stroke mortality (Fessel, 1980; Chen *et al.*, 2009b), and it is associated with higher in-hospital mortality and poorer long-term survival in acute myocardial infarction patients (Car and Trkulja, 2009). However, the decreased prevalence of hyperuricemia was observed in elderly or women after the adjustment of genetic influence, which is similar to the findings derived from a Nutrition and Health Survey conducted in Taiwan (Chang *et al.*, 2001). This may contribute to the higher morbidity of myocardial infarction in the younger and male population.

A certain proportion of normal uricemic individuals carried hyperuricemia-risk genetic variants without exhibiting hyperuricemic phenotypes, further suggesting that a hyperuricemia-induced environment is a prerequisite of developing hyperuricemia. Lack of physical activity and purine intake data was one limitation of this study, as uric acid metabolism is affected by dietary purine and physical activity. However, some issues contingent on the original data collection and available funding support cannot be addressed directly in this study. We will incorporate physical activity data, purine intake, and more candidate genes into the follow-up study to confirm the biological mechanism of hyperuricemia.

The current results indicated that the genetic factors in our study showed a relatively smaller effect than that of gender and BMI. Thus, other candidate genetic markers of hyperuricemia remain to be found. The pooled genetic effect could play a pivotal role in the predisposition of hyperuricemia diagnosis. In addition, the sample size of this study was moderate; the power of this study only allowed for identifying genetic variants with large effects. Therefore, a larger sample size and more genetic variants are warranted to ensure significant association and profound interpretation.

Conclusion

The variants of rs1822825 on the *PPARγ* gene were associated with hyperuricemia. BMI, gender, and rs1822825 on the *PPARγ* gene, rather than blood lipid profiles, blood pressure, and protein intake per day, served as good indicators for hyperuricemia. This finding might be applicable to the Han Chinese in Taiwan to identify potential risk assessments for hyperuricemia.

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Author Disclosure Statement

This article is not currently being considered by other journals. All authors declare that they have no competing financial interests, agree to submit the paper to this journal, and transfer copyright to the publisher.

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Appendix

Appendix Table A1. The Correlation Among Serum Uric Acid Level, *PPARγ* RNA Expression, and XDH RNA Expression

	Serum uric acid level	*PPARγ gene expression*	*XDH gene expression*
Serum uric acid level			
Correlation coefficient	1	−0.1	−0.1
p-Value		0.08	0.03
PPARγ gene			
Correlation coefficient	−0.1	1	−0.15
p-Value	0.08		3×10^{-4}
XDH gene			
Correlation coefficient	−0.1	−0.15	1
p-Value	0.03	3×10^{-4}	

The Pearson's correlation was performed.

Appendix Table A2. The Allelic Association Between Hyperuricemia and Three Selected tag-Single Nucleotide Polymorphisms on the PPARγ Gene

	Allele frequency (%)		
	HUA	*NHUA*	p-*Value*
rs1822825	A/G	A/G	
	45/55	37/63	0.001
rs4684846	A/G	A/G	
	45/55	51/49	0.048
rs2292101	C/T	C/T	
	65/35	69/31	0.101