Letter to the Editor

Association of *PPARγ* and *AGTR1* Polymorphisms with Hypertriglyceridemia in Chinese Population*

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Hypertriglyceridemia (HTG) is an important metabolic disease and strongly associated with the development of hypertension, atherosclerosis, coronary artery disease, and type 2 diabetes mellitus (T2DM). HTG risk is affected by various factors and might occur owing to the complex synergistic interaction between the genetic background and environmental factors[1].

Among peroxisome proliferator-activated receptors (*PPARs*), *PPARγ* is an isotype that was recognized to play a major role in the regulation of fatty acid metabolism, probably in the adipose tissue storage and free fatty acids reduction. Several studies suggested that the single nucleotide polymorphisms (SNPs) in *PPARγ* including rs10865710, rs1805192, and rs709158 are associated with HTG related diseases. However, the results obtained from these studies remain controversial.

Angiotensin II type I receptor (*AGTR1*) is a G-protein-coupled receptor of angiotensin II that is a peptide hormone and plays a fundamental role as a vasoconstrictor in the regulation of cardiovascular function, renal homeostasis, oxidative stress, and lipid and cholesterol metabolism[2]. During the past decades, several studies reported the association between the *AGTR1* polymorphisms and risk of HTG-related diseases. HTG risk is affected by several gene polymorphisms or interactions among several genes and *PPARγ* as well as *AGTR1* are risk factors of HTG-associated diseases; however, to date, merely a few studies focused on the effects of *PPARγ-AGTR1* interaction on HTG risk. Therefore, in this study, we aimed to investigate the effect of *PPARγ* and *AGTR1* polymorphisms and synergistic interaction between these two genes on the HTG risk.

In this study, we included a total of 1,591 participants who were selected from a prospective cohort study of '135' in Soochow, China, that was performed during the period from August, 2012 to March, 2013 and designed to investigate the prevention strategy for chronic diseases[3]. In the current study, the age range of subjects was 53.95 ± 9.61 and the protocol was approved by the independent ethics committee of Suzhou Industrial Park (Soochow, China) in accordance with the Declaration of Helsinki (1975). A written informed consent was obtained from each participant.

The body weight, height, and waist circumference (WC) were measured by following the standardized procedures. Blood pressure (BP) was measured thrice in a seated position with 1 min interval between measurements using a mercury sphygmomanometer. Blood samples were collected in the morning after fasting for at least 8 h. All the plasma and serum samples were frozen at -80 °C until their use in the laboratory experiments. Plasma glucose was measured using oxidase enzymatic method.

The triglyceride (TG) levels were quantified and HTG was established according to the criteria defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) that is TG ≥ 1.7 mmol/L.

In this study, all the SNPs were selected based on the criteria of minor allele frequency (MAF) ≥ 0.05 and r^2 ≥ 0.8 according to the linkage disequilibrium (LD) values obtained using haploview

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version 4.2 software. The functional SNPs were analyzed by using the websites of selection tool for SNPs and SNPs with predictive biological effects were retuned as tag-SNPs (Supplementary Table S1, available in www.besjournal.com).

The DNA extraction and genotyping were performed by following the previously described method[3]. (Supplementary Table S2, available in www.besjournal.com)

Linear regression was applied to analyze the association between the gene polymorphisms and HTG risk. The association between the tag-SNPs and HTG risk was analyzed using SNPAssoc package of R. The potential gene-gene interactions among the selected polymorphisms were validated using model-based multifactor dimensionality reduction (MB-MDR) method[20]. All the statistical analyses were performed using R (X64 3.2.5) and SAS 9.4. $P \leq 0.05$ was considered to be statistically significant.

In this study, among the 1,591 participants 29.4% were identified as HTG patients and 44.4% of these HTG patients were males. The HTG group exhibited a higher systolic BP (SBP) and diastolic BP (DBP), body mass index (BMI), WC, TG, total cholesterol (TC), low-density lipoprotein cholesterol LDL-C, and fast blood glucose (FBG) levels as well as propensity for smoking and drinking than those in the normal-TG group. Contradictorily, the high-density lipoprotein cholesterol (HDL-C) levels in the HTG group were lower than those in the normal-TG group (Table 1).

After adjustment based on the gender, age, BMI, and drinking and smoking propensity, the homozygous wild type A allele (AA, recessive model) of rs13433696 was associated with a decreased HTG risk compared to the carriers of (GA+AA) genotype (difference = -0.186, 95% *CI* = -0.362 to -0.011, *P* = 0.038). However, the homozygous wild type C allele (CC, recessive model) of rs5182 was associated with an increased HTG risk compared to the carriers of (TT+TC) genotype (difference = 0.208, 95% *CI* = 0.001 - 0.415, *P* = 0.049) (Table 2). However, the remaining ten SNPs did not exhibit any association with HTG after the covariates adjustment (Supplementary Tables S3-S4, available in www.besjournal.com). The results of Hardy-Weinberg equilibrium (HWE) test to identify candidate SNPs was presented in Supplementary Table S5 (available in www.besjournal. com).

We observed that 2 to 9-locus models were significantly associated with HTG by quantitative trait that indicated a potential gene-gene interaction among rs5182, rs1492100, rs2972164, rs9817428, rs1175543, rs3856806, rs2920502, rs2638360, and rs12631819 after adjustment for gender, age, drinking and smoking status (Table 3). As rs13433696 in *PPARγ* as well as rs5182 in *AGTR1* were potentially associated with HTG risk, we further analyzed the gene-gene interactions among the remaining ten SNPs using MB-MDR method (Supplementary Table S6, available in www.besjournal.com).

In the present study, our results demonstrated that the AA genotype individuals with rs13433696 in *PPARγ* exhibited a decreased HTG risk, while the CC genotype individuals with rs5182 in *ATGR1* exhibited an increased HTG risk. Furthermore, we observed that the gene-gene interactions existed in the HTG-associated SNPs as well as HTG-non-associated SNPs of *PPARγ* and *AGTR1*.

Table 1. Baseline Characteristics of the Participants in This Study

Variables	Group	HTG (*n* = 482)	Normal-TG (*n* = 1,109)	t/χ^2	*P*
Gender	Male	214 (44.4)	468 (42.2)	0.66	0.421
	Female	268 (55.6)	641 (57.8)		
Age (year)		56.10 ± 9.95	53.90 ± 9.59	0.38	0.886
Blood pressure (mmHg)	SBP	127.51 ± 16.32	123.81 ± 16.41	4.13	< 0.001
	DBP	80.72 ± 11.76	78.42 ± 11.20	3.71	< 0.001
TC (mmol/L)		5.23 ± 1.03	4.70 ± 0.82	9.95	< 0.001
TG (mmol/L)		2.97 ± 1.40	1.03 ± 0.34	29.92	< 0.001
HDL-C (mmol/L)		1.31 ± 0.33	1.43 ± 0.28	6.53	< 0.001
LDL-C (mmol/L)		2.74 ± 0.85	2.58 ± 0.61	3.70	< 0.001
FBG (mmol/L)		5.81 ± 1.04	5.57 ± 0.79	4.47	< 0.001
BMI (kg/m^2)		24.63 ± 2.87	23.07 ± 2.95	9.78	< 0.001
WC (cm)		83.16 ± 8.06	79.32 ± 8.11	6.76	< 0.001
Smoking	Yes	156 (32.4)	300 (27.1)	4.64	0.032
	No	326 (67.6)	809 (72.9)		
Drinking	Yes	100 (20.7)	183 (16.5)	4.14	0.041
	No	382 (79.3)	926 (83.5)		

Table 2. Association of the Selected SNP Genotypes with HTG

SNP	Model	Genotype	*n* (%)	Me	Se	dif	95% *CI*	*P*	AIC
rs13433696	Codominant	G/G	658 (41.6)	1.639	0.048	0.000	1	0.112	5,099
		G/A	714 (45.1)	1.650	0.047	0.016	-0.112, 0.145		
		A/A	210 (13.3)	1.461	0.067	-0.178	-0.366, 0.010		
	Dominant	G/G	658 (41.6)	1.639	0.048	0.000	1	0.652	5,101
		G/A-A/A	924 (58.4)	1.607	0.040	-0.028	-0.149, 0.093		
	Recessive	G/G-G/A	1,372 (86.7)	1.645	0.034	0.000	1	0.038	5,097
		A/A	210 (13.3)	1.461	0.067	-0.186	-0.362, -0.011		
	Overdominant	G/G-A/A	868 (54.9)	1.596	0.040	0.000	1	0.332	5,100
		G/A	714 (45.1)	1.650	0.047	0.059	-0.061, 0.179		
rs5182	Codominant	T/T	754 (47.4)	1.638	0.045	0.000	1	0.069	5,121
		T/C	692 (43.5)	1.563	0.044	-0.077	-0.202, 0.048		
		C/C	144 (9.1)	1.811	0.108	0.171	-0.044, 0.387		
	Dominant	T/T	754 (47.4)	1.638	0.045	0.000	1	0.577	5,124
		T/C-C/C	836 (52.6)	1.606	0.041	-0.034	-0.153, 0.085		
	Recessive	T/T-T/C	1,446 (91.9)	1.602	0.032	0.000	1	0.049	5,120
		C/C	144 (9.1)	1.811	0.108	0.208	0.001, 0.415		
	Overdominant	T/T-C/C	898 (76.7)	1.666	0.042	0.000	1	0.657	5,124
		T/C	692 (43.5)	1.563	0.044	-0.105	-0.225, 0.016		

Note. Adjusted for age, sex, BMI, drinking and smoking propensities. Dif, difference. AIC, Akake information criterion.

Table 3. Best Gene-gene Interaction Models Identified Using Model-based Multifactor Dimensionality Reduction Method

Locus No.	Best Model	NH[a]	βH[b]	WH[c]	NL[d]	WL[e]	βL[f]	Wmax[g]	Risk[h]	Perm[i]
2	rs9817428, rs1175543	1	3.76	19.54	0	NA	NA	19.54	H	0.003
3	rs9817428, rs13433696, rs2638360	2	2.81	27.38	1	3.57	-0.19	27.38	H	0.015
4	rs2972164, rs13433696, rs6817428, rs2638360	3	4.39	54.37	2	5.41	-0.23	54.37	H	0.004
5	rs5182, rs1175543, rs13433696, rs3856806, rs2920502	14	1.18	85.75	3	8.93	-0.51	85.75	H	0.014
6	rs2972164, rs5182, rs9817428, rs1175543, rs3856806, rs2920502	17	1.87	144.20	3	12.22	-0.57	144.20	H	0.012
7	rs2972164, rs5182, rs9817428, rs1175543, rs3856806, rs2920502, rs2638360	25	2.27	216.70	2	6.43	6.43	216.70	H	0.004
8	rs275646, rs5182, rs9817428, rs1175543, rs13433696, rs3856806, rs2920502, rs2638360	32	2.31	262.00	1	3.41	-0.67	262.00	H	0.037
9	rs5182, rs1492100, rs2972164, rs9817428, rs1175543, rs3856806, rs2920502, rs2638360, rs12631819	33	2.58	291.60	1	4.11	-0.74	291.60	H	0.030
10	rs275646, rs5182, rs1492100, rs9817428, rs1175543, rs13433696, rs3856806, rs2920502, rs2638360, rs12631819	47	2.13	342.40	2	6.59	-0.77	342.40	H	0.139

Note. [a]The merged number of cells of high-risk categories. [b]The regression coefficient of high-risk categories. [c]The Wald test value of high-risk categories. [d]The merged number of cells of low-risk categories. [e]The regression coefficient of low-risk categories. [f]The Wald test value of low-risk categories. [g]Wmax = max(WH,WL). [h]The categories of combinatorial model tested using Perm. P (H: high-risk; L: low-risk). [i]Adjusted for age, sex, BMI, TC, TG, HDL-C, LDL-C, FBG, smoking, and drinking with 1,000 times replacement.

Although the studies that analyzed the association between *AGTR1* polymorphisms and risk of HTG are rare, the association between rs5182 SNP and BP was extensively discussed[4-6]. Additionally, in a case-control study, screening the exon 5 and 3´-untranslated region of *ATGR1* demonstrated that solely the +1166 SNP in the 3´-untranslated region was significantly associated with hypertension among the five polymorphisms that are +573 (rs5182), +1062, +1166, +1517, and +1878. Therefore, although our results from the present study suggest that rs5182 in C allele is a risk factor for HTG, further studies are necessary to investigate the functions of *ATGR1* polymorphisms.

Our previous studies suggested that *PPARγ* polymorphisms such as rs3856806 allele are significantly associated with the apoA-I/apoB ratio in the Chinese Han population[7]. Additionally, Chan et al. found a borderline significant association between the Pro12Ala (rs1801282) variant in *PPARγ* and risk of T2DM in women's health initiative-observational study (WHI-OS)[8]. Moreover, the results of a study in Kazakh population suggested that *PPARγ* polymorphism rs1175543 is significantly associated with metabolic syndromes[9]. In this study, we reported that a novel variant of AA genotype with rs13433696 in *PPARγ* is significantly associated with HTG susceptibility indicating that the polymorphisms of *PPARγ* might play a critical role in dyslipidemia associated diseases.

PPARγ inactivation leads to familial partial lipodystrophy (FPLD) syndrome associated with early-onset severe hypertension[10]. Considering that *PPARγ* and *AGTR1* are located on the chromosome 3, it is not surprising that the gene-gene interactions exist not only in HTG-associated SNPs but also in HTG-non-associated SNPs.

In conclusion, the present study suggested that the polymorphisms of *PPARγ* and *AGTRI* contribute to the HTG risk either independently or in an interactive manner in the Chinese population. Further multiple comprehensive studies must be performed to confirm this genetic association using large sample size and to analyze the probable interactions of these SNPs with other gene variants.

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Supplementary Table S1. Biological Information about Candidate SNPs of *PPARG* Gene and *AGTR1* Gene

Gene	tagSNPs	HGVS Nomenclature	Chromosome	Alleles[a]	Region	Biological Effect	Transcription Factor Binding Site	MAF[b,c]
PPARG	rs12631819	NC_000003.12: g.12301362G > T	3	G/T	12301362	intron variant	cap	0.378/0.402
	rs2920502	NC_000003.12: g.12287696G > C	3	G/C	12287696	upstream variant 2KB	cap	0.273/0.244
	rs3856806	NC_000003.12: g.12434058C >	3	C/T	12434058	intron variant,synonymous codon, utr variant 3 prime	-	0.268/0.250
	rs13433696	NC_000003.12: g.12316993G > A	3	G/A	12316993	intron variant	Skn-1, cap	0.378/0.390
	rs1175543	NC_000003.12: g.12424934A > G	3	A/G	12424934	intron variant	CdxA	0.450/0.484
	rs9817428	NC_000003.12: g.12298768C > A	3	A/C	12298768	intron variant	HSF, SRY	0.435/0.402
	rs2972164	NC_000003.12: g.12292917T > C	3	C/T	12292917	intron variant	CdxA, Abd-B	0.090/0.073
AGTR1	rs2638360	NC_000003.12: g.148710569G > A	3	T/C	148710569	intron variant	CdxA, Dfd, Oct-1, Skn-1, cap, STATx, C/EBPa	0.077/0.156
	rs1492100	NC_000003.12: g.148719640T > A	3	A/T	148719640	intron variant	Hb	0.122/0.098
	rs5182	NC_000003.12: g.148741608C > T	3	T/C	148741608	synonymous codon	-	0.306/0.433
	rs2933249	NC_000003.12: g.148698733G > A	3	C/T	148698733	intron variant	HSF	0.128/0.098
	rs275646	NC_000003.12: g.148745735T > C	3	C/T	148745735	-	-	0.120/0.110

Note. [a]Major/minor allele. [b]MAF in the control. [c]MAF in CHB.

Supplementary Table S2. The Informations about the Primers and Probes of the Candidate SNPs of *PPARG* Gene and *AGTR1* Gene

Gene	SNP	Primers and Probes	
PPARG	rs12631819	forward sequence	AAATGAGGCCAAAACTTGATAGTGT
		reverse sequence	AAGGTTTACAATAATGCCCAGTACAA
		probes 1	FAM-AAGTTTAAGAAGAGAACCAG-MGB
		probes 2	HEX-AGTTTAAGAAGAGAACAAGT-MGB
	rs2920502	forward sequence	GCACAGTAGGGCCCACG
		reverse sequence	GGATCCCTCCTCGGAAATG
		probes 1	FAM-CCACTCTCTGCCC-MGB
		probes 2	HEX-CCACTGTCTGCCC-MGB
	rs3856806	forward sequence	CGTCTTCTTGATCACCTGCAGTA
		reverse sequence	AAAATGACAGACCTCAGACAGATTGT
		probes 1	FAM-CTGCACGTGTTCC-MGB
		probes 2	HEX-CTGCACATGTTCC-MGB
	rs13433696	forward sequence	GAGGGAGAAAAGGGTTTAGATAAAAGA
		reverse sequence	TGCTCCATCCAGTACATCTATAATTGA
		probes 1	FAM-AACTTGTTTGGTCTCAGTG-MGB
		probes 2	VIC-ACTTGTTTGGTCTCAATGA-MGB
	rs1175543	forward sequence	ATGTGAAGCCTCTGGCACAAT
		reverse sequence	ATATAGGGCAAAAGGGAAAATTAGC
		probes 1	FAM-TTCAGCACACAGTAAA-MGB
		probes 2	VIC-TTCAGCACACAATAA-MGB
	rs9817428	forward sequence	AAAATAAAACGCATCAGTCTCAGTAGAT
		reverse sequence	GCCAAGACAAACTTCAGCTAACAA
		probes 1	FAM-ATCATCACATCGAGTTT-MGB
		probes 2	VIC-TATCATCACATCGAGGTT-MGB
	rs2972164	forward sequence	CTGGACTGGCAAGCCACTCT
		reverse sequence	GCATCCTTTTAGTGAAGTCCCTACTT
		probes 1	FAM-AGTGTGGAGCTATAAA-MGB
		probes 2	VIC-AGTGTGGAGCTACAAA-MGB
AGTR1	rs2638360	forward sequence	GCCAATATTTTCTTCCTTACTCATTACC
		reverse sequence	GTTTGGCTCTCCAACTGCTTAAA
		probes 1	FAM-TTTCTTTAGTTTTCCAGTAAT-MGB
		probes 2	HEX-TCTTTAGTTTTCCAATAAT-MGB
	rs1492100	forward sequence	CCTGTGCTGTTCTCAGGTTCTG
		reverse sequence	CACATGGAGTTTCCCTCTCATG
		probes 1	FAM-ATTGGATGGCTTTTT-MGB
		probes 2	VIC-ATTGGATGGCTATTTAG-MGB
	rs5182	forward sequence	TGCTTTCCATTATGAGTCCCAAA
		reverse sequence	GAAAAGGAAACAGGAAACCCAGTA
		probes 1	FAM-CAACCCTTCCGATAGG-MGB
		probes 2	VIC-TTCAACCCTCCCGATAG-MGB
	rs2933249	forward sequence	GGCTAAGGCTGTAGGGATTGG
		reverse sequence	TCCCAGATGTCCTTTGAATAATCA
		probes 1	FAM-TGCTTCTCCTTCTTCAGT-MGB
		probes 2	VIC-TGCTTCTCCTTCCTC-MGB
	rs275646	forward sequence	GGAAATTCATCTTTTTGGACATCA
		reverse sequence	CAACAAGAGTGAAACTCCATCTCAA
		probes 1	FAM-ATCATTTTTCAAGTATGGTGAG-MGB
		probes 2	VIC-CATCATTTTTCAAGTACGG-MGB

Supplementary Table S3. Associations of the Selected SNPs Genotypes in *PPARγ* Gene with HTG

SNP	Model	Genotype	*n* (%)	me	se	dif	Lower, upper	*P*	AIC
rs12631819	Codominant	G/G	623 (39.3）	1.674	0.052	0.000	1	0.186	5104
		G/T	759 (47.9)	1.609	0.042	-0.006	-0.193, 0.064		
		T/T	202 (12.8)	1.505	0.070	-0.176	-0.368, 0.016		
	Dominant	G/G	623 (39.3)	1.674	0.000	0.000	1	0.156	5103
		G/T-T/T	961 (60.7)	1.587	0.037	-0.088	-0.211, 0.034		
	Recessive	G/G-G/T	1,382 (87.2)	1.638	0.033	0.000	1	0.123	5103
		T/T	202 (12.8)	1.505	0.070	-0.141	-0.320, -0.038		
	Overdominant	G/G-T/T	825 (52.1)	1.632	0.043	0.000	1	0.719	5105
		G/T	759 (47.9)	1.609	0.043	-0.022	-0.142, 0.098		
rs12920502	Codominant	G/G	817 (51.6)	1.603	0.040	0.000	1	0.713	5106
		G/C	659 (41.6)	1.632	0.048	0.032	-0.093, 0.156		
		C/C	107 (6.8)	1.701	0.149	0.094	-0.150, 0.338		
	Dominant	G/G	817 (51.6)	1.603	0.040	0.000	1	0.509	5104
		G/C-C/C	766 (48.4)	1.642	0.046	0.040	-0.079, 0.160		
	Recessive	G/G-G/C	1,476 (83.2)	1.616	0.031	0.000	1	0.511	5104
		C/C	107 (6.8)	1.701	0.149	0.080	-0.158, 0.317		
	Overdominant	G/G-T/T	924 (58.4)	1.614	0.039	0.000	1	0.738	5105
		G/T	659 (41.6)	1.609	0.048	0.021	-0.100, 0.142		
rs3656806	Codominant	C/C	882 (55.9)	1.654	0.042	0.000	1	0.391	5066
		C/T	588 (37.3)	1.583	0.048	-0.066	-0.192, 0.059		
		T/T	107 (6.8)	1.515	0.093	-0.135	-0.377, 0.106		
	Dominant	C/C	882 (55.9)	1.615	0.034	0.000	1	0.689	5126
		C/T-T/T	695 (44.1)	1.573	0.043	-0.077	-0.197, 0.043		
	Recessive	C/C-C/T	1,470 (93.2)	1.625	0.032	0.000	1	0.367	5065
		T/T	107 (6.8)	1.515	0.093	-0.109	-0.345, 0.127		
	Overdominant	C/C-T/T	989 (62.7)	1.639	0.039	0.000	1	0.411	5065
		C/T	588 (37.3)	1.583	0.048	-0.052	-0.174, 0.071		
rs1175543	Codominant	A/A	479 (30.2)	1.606	0.057	0.000	1	0.551	5114
		A/G	800 (50.4)	1.601	0.038	0.003	-0.134, 0.140		
		G/G	307 (19.4)	1.696	0.083	0.086	-0.088, 0.259		
	Dominant	A/A	479 (30.2)	1.606	0.057	0.000	1	0.692	5113
		A/G-G/G	1,107 (69.8)	1.627	0.036	0.026	-0.104, 0.156		
	Recessive	A/A-A/G	1,279 (80.6)	1.603	0.032	0.000	1	0.275	5112
		G/G	307 (19.4)	1.696	0.083	0.084	-0.067, 0.235		
	Overdominant	A/A-G/G	786 (49.6)	1.641	0.047	0.000	1	0.618	5113
		A/G	800 (50.4)	1.601	0.038	-0.030	-0.150, 0.089		
rs9817428	Codominant	A/A	477 (30.1)	1.617	0.059	0.000	1	0.259	5116
		A/C	786 (49.5)	1.585	0.038	0.003	-0.162, 0.114		
		C/C	324 (20.4)	1.720	0.078	0.086	-0.064, 0.277		
	Dominant	A/A	477 (30.1)	1.617	0.059	0.000	1	0.829	5117
		A/C-C/C	1,110 (69.9)	1.625	0.035	0.014	-0.116, 0.144		
	Recessive	A/A-A/C	1,263 (79.6)	1.597	0.033	0.000	1	0.108	5114
		C/C	324 (20.4)	1.720	0.077	0.121	-0.026, 0.269		
	Overdominant	A/A-C/C	801 (49.6)	1.659	0.047	0.000	1	0.271	5116
		A/C	786 (50.4)	1.585	0.038	-0.067	-0.186, 0.052		

rs2972164	Codominant	C/C	1,344 (84.5)	1.625	0.033	0.000	1	0.778	5126
		C/T	237 (14.9)	1.610	0.081	-0.017	-0.185, 0.150		
		T/T	9 (0.6)	1.324	0.156	-0.277	-1.071, 0.516		
	Dominant	C/C	1,344 (84.5)	1.625	0.033	0.000	1	0.749	5124
		C/T-T/T	246 (15.5)	1.600	0.078	-0.027	-0.191, 0.138		
	Recessive	C/C-C/T	1,581 (99.4)	1.623	0.031	0.000	1	0.497	5124
		T/T	9 (0.6)	1.324	0.156	-0.275	-1.068, 0.518		
	Overdominant	C/C-T/T	1,353 (85.1)	1.623	0.033	0.000	1	0.856	5124
		C/T	237 (14.9)	1.610	0.081	-0.016	-0.183, 0.152		

Note. Adjusted for age, sex, BMI, drinking and smoking.

Supplementary Table S4. Associations of the Selected SNPs Genotypes in *AGTR1* Gene with HTG

SNP	Model	Genotype	*n* (%)	me	se	dif	Lower, upper	*P*	AIC
rs2638360	Codominant	T/T	1,294 (81.3)	1.615	0.034	0.000	1	0.544	5127
		T/C	286 (18.0)	1.633	0.068	0.017	-0.138, 0.172		
		C/C	11 (0.7)	2.011	0.326	0.399	-0.319, 1.117		
	Dominant	T/T	1,294 (81.9)	1.615	0.034	0.000	1	0.689	5126
		T/C-C/C	297 (18.7)	1.647	0.067	-0.031	-0.121, 0.184		
	Recessive	T/T-T/C	1,580 (99.3)	1.618	0.030	0.000	1	0.279	5125
		C/C	11 (0.7)	2.011	0.326	0.396	-0.321, 1.113		
	Overdominant	T/T-C/C	1,305 (82.0)	1.618	0.034	0.000	1	0.863	5127
		T/C	286 (18.0)	1.633	0.068	0.014	-0.141, 0.168		
rs1492100	Codominant	A/A	1,200 (76.1)	1.651	0.035	0.000	1	0.148	5088
		A/T	347 (22.0)	1.515	0.063	-0.133	-0.278, 0.012		
		T/T	30 (1.9)	1.781	0.234	0.140	-0.299, 0.579		
	Dominant	A/A	1,200 (76.1)	1.651	0.035	0.000	1	0.120	5088
		A/T-T/T	377 (23.9)	1.536	0.061	-0.111	-0.252, 0.029		
	Recessive	A/A-A/T	1,547 (90.1)	1.620	0.031	0.000	1	0.448	5090
		T/T	30 (1.9)	1.781	0.233	0.170	-0.269, 0.608		
	Overdominant	A/A-T/T	1,230 (88.0)	1.654	0.035	0.000	1	0.064	5087
		A/T	347 (22.0)	1.515	0.063	-0.137	-0.281, 0.008		
rs293249	Codominant	C/C	1,198 (75.6)	1.608	0.035	0.000	1	0.458	5108
		C/T	356 (22.5)	1.651	0.065	0.044	-0.100, 0.187		
		T/T	30 (1.9)	1.851	0.212	0.255	-0.184, 0.694		
	Dominant	C/C	1,198 (75.6)	1.608	0.035	0.000	1	0.397	5106
		C/T-T/T	386 (24.4)	1.666	0.624	-0.060	-0.079, 0.199		
	Recessive	C/C-C/T	1,554 (98.1)	1.618	0.031	0.000	1	0.272	5106
		T/T	30 (1.9)	1.851	0.212	0.245	-0.192, 0.683		
	Overdominant	C/C-T/T	1,228 (77.5)	1.614	0.034	0.000	1	0.608	5107
		C/T	356 (22.5)	1.651	0.065	0.037	-0.105, 0.180		
rs275646	Codominant	C/C	1,212 (76.8)	1.619	0.034	0.000	1	0.290	5071
		C/T	344 (21.8)	1.647	0.069	0.032	-0.112, 0.176		
		T/T	23 (1.4)	1.267	0.150	-0.376	-0.872, 0.121		
	Dominant	C/C	1,212 (76.8)	1.619	0.034	0.000	1	0.930	5071
		C/T-T/T	367 (23.2)	1.623	0.066	0.006	-0.134, 0.147		
	Recessive	C/C-C/T	1,556 (98.6)	1.625	0.031	0.000	1	0.131	5069
		T/T	23 (1.4)	1.267	0.150	-0.382	-0.878, 0.113		
	Overdominant	C/C-T/T	1,235 (78.2)	1.613	0.034	0.000	1	0.597	5071
		C/T	344 (21.8)	1.647	0.069	0.039	-0.105, 0.183		

Note. Adjusted for age, sex, BMI, drinking and smoking.

Supplementary Table S5. HWE Test for Candidate SNPs of *PPARG* Gene and *AGTR1* Gene for Both HTG and Normal-TG Group

Gene	SNP	WT/HT/MT	HTG	*P*	Normal-TG	*P*
PPARG	rs12631819	GG/GT/TT	191/233/56	0.235	432/526/146	0.476
	rs2920502	GG/GC/CC	246/200/33	0.371	541/459/74	0.154
	rs3856806	CC/CT/TT	271/174/33	0.572	611/414/75	0.669
	rs13433696	GG/GA/AA	205/220/53	0.599	493/494/157	0.235
	rs1175543	AA/AG/GG	141/246/92	0.406	338/554/215	0.655
	rs9817428	AA/AC/CC	210/225/103	0.100	267/531/221	0.157
	rs2972164	CC/CT/TT	416/64/2	0.782	928/173/7	0.729
AGTR1	rs2638360	TT/TC/CC	384/92/6	0.854	910/194/5	0.115
	rs1492100	AA/AT/TT	330/136/12	0.648	870/211/18	0.213
	rs5182	TT/TC/CC	221/205/56	0.423	533/487/88	0.109
	rs2933249	CC/CT/TT	353/111/15	0.092	845/245/15	0.560
	rs275646	CC/CT/TT	364/109/6	0.497	848/235/17	0.876

Note. WT wild type, HT heterozygote, MT mutant type.

Supplementary Table S6. Best Gene-gene Interaction Models Identified by the Model-based Multifactor Dimensionality Reduction Method

Locus No.	Best model	NH[a]	betaH[b]	WH[c]	NL[d]	WL[e]	betaL[f]	Wmax[g]	Risk[h]	Perm[i]
2	rs9817428, rs1175543	1	3.76	19.54	0	NA	NA	19.54	H	0.004
3	rs9817428, rs1175543, rs2638360	2	3.50	25.44	0	NA	NA	25.44	H	0.013
4	rs9817428, rs1175543, rs2920502, rs2638360	3	3.80	51.31	2	10.86	-0.33	51.31	H	0.005
5	rs2933249, rs9817428, rs1175543 rs3856806, rs2920502	10	1.36	71.60	3	8.26	-0.34	71.60	H	0.018
6	rs275646, rs9817428, rs1175543, rs2638360, rs3856806, rs2920502	16	1.65	116.10	2	6.90	-0.43	116.10	H	0.010
7	rs275646, rs9817428, rs1175543, rs2638360, rs3856806, rs2920502, rs12631819	20	2.02	140.60	2	6.66	-0.45	140.60	H	0.038
8	rs275646, rs2933249, rs1492100, rs2972164, rs1175543, rs3856806, rs2920502,rs2638360	25	1.59	147.30	1	2.72	-0.70	147.30	H	0.165

Note. [a]The merged number of cells of high-risk categories. [b]The regression coefficient of high-risk categories. [c]The Wald test value of high-risk categories. [d]The merged number of cells of low-risk categories. [e]The regression coefficient of low-risk categories. [f]The Wald test value of low-risk categories. [g]Wmax = max (WH, WL). [h]The categories of combinatorial model tested by Perm. P (H: high-risk; L: low-risk). [i]Adjusted for age, sex, BMI, TC, TG, HDL-C, LDL-C, FBG, smoking, and drinking with 1,000 times replacement.