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Genetic variations in the *CYP17A1* and *NT5C2* genes are associated with a reduction in visceral and subcutaneous fat areas in Japanese women

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ABSTRACT

Visceral fat accumulation plays an important role in increasing the morbidity and mortality rates, by increasing the risk of developing several metabolic disorders, such as type 2 diabetes, dyslipidemia, and hypertension. New genetic loci that are associated with increased systolic and diastolic blood pressures have been identified by genome-wide association studies in Caucasian populations. This study investigates whether single nucleotide polymorphisms (SNPs) that confer susceptibility to high blood pressure are also associated with visceral fat obesity. We genotyped 1279 Japanese subjects (556 men and 723 women) who underwent computed tomography (CT) for measuring the visceral fat area (VFA) and subcutaneous fat area (SFA) at the following SNPs: *FGF5* rs16998073, *CACNB2* rs11014166, *C10orf107* rs1530440, *CYP17A1* rs1004467, *NT5C2* rs11191548, *PLEKHA7* rs381815, *ATP2B1* rs2681472 and rs2681492, *ARID3B* rs6495112, *CSK* rs1378942, *PLCD3* rs12946454,and *ZNF652* rs16948048. In an additive model, risk alleles of the *CYP17A1* rs1004467 and *NT5C2* rs11191548 were found to be significantly associated with reduced SFA (P = 0.00011 and 0.0016, respectively). When the analysis was performed separately in men and women, significant associations of rs1004467 (additive model) and rs11191548 (recessive model) with reduced VFA (P = 0.0018 and 0.0022, respectively) and SFA (P = 0.00039 and 0.00059, respectively) were observed in women, but not in men. Our results suggest that polymorphisms in the *CYP17A1* and *NT5C2*

genes influence a reduction in both visceral and subcutaneous fat mass in Japanese women.

Key words: *CYP17A1*, *NT5C2*, visceral fat area, subcutaneous fat area, computed tomography, Japanese subjects, sexual dimorphism

INTRODUCTION

Metabolic syndrome is a combination of multiple risk factors, including central obesity, impaired glucose tolerance, dyslipidemia, and hypertension, which increases cardiovascular disease morbidity and mortality.[1] Several studies have indicated that the intra-abdominal adipose tissue plays a central role in metabolic syndrome, since the accumulated visceral adipose tissue leads to alterations in the plasma levels of adipocytokines, resulting in the development of dyslipidemia, hypertension, and insulin resistance.[2, 3] Intra-abdominal fat accumulation (central adiposity) is determined by waist circumference, waist-hip ratio, biological impedance, or the visceral fat area (VFA) measured using computed tomography (CT).[1, 4, 5] There is abundant evidence that body fat distribution is influenced by genetic loci.[6-8] Individual variation in waist-hip ratio is heritable, with heritability estimates ranging from 22% to 61%. Recent genome-wide association studies (GWAS) showed that genetic loci were associated with waist circumference and waist-hip ratio in the Caucasian population.[9, 10] We previously reported that the rs1558902 and rs1421085 genotypes of the fat mass- and obesity-associated gene (*FTO*) were significantly associated with VFA, as well as with the subcutaneous fat area (SFA) and body mass index (BMI) in the Japanese population.[11]

Recent progress in GWAS has increased the number of known genetic susceptibility loci for obesity.[12-16] We investigated the association between the single nucleotide

polymorphisms (SNPs) underlying susceptibility to obesity and fat distribution (as determined by CT), and found that rs7498665 in the SH2B adaptor protein 1 (*SH2B1*) gene was associated with VFA, uncovering the genetic background of central obesity.[17]

GWAS, and meta-analysis of GWAS, have identified various disease-associated genetic variations.[18] Hypertension is one of the risk factors of metabolic syndrome, and considerably related to central obesity. Obesity-associated allele of rs1558902 and rs1421085 in the *FTO* gene were associated with hypertension, but not that of rs7498665 in the *SH2B1* gene in the Japanese population.[19] The genetic variations associated with hypertension have been identified by GWAS.[20, 21] In this study, we investigate whether the recently reported hypertension-related loci are also associated with VFA, which is another important factor responsible for metabolic syndrome.

MATERIALS AND METHODS

Study subjects

We enrolled 1279 Japanese subjects from outpatient clinics; these patients agreed to undergo CT testing (in the supine position) to determine VFA and SFA values at the umbilical level (L4–L5), as previously reported.[17] Both VFA and SFA values were calculated using the FatScan software program (N2system, Osaka, Japan).[22] The patients visited the hospitals to undergo

treatment for obesity and/or metabolic abnormalities such as hypertension, dyslipidemia, and type 2 diabetes. Patients with secondary obesity and obesity-related hereditary disorders were excluded from this study. Patients with disease (such as cancer, and renal, heart and hepatic failure), or under treatment (such as corticosteroid and chemotherapy) that strongly affects body weight, were also excluded. Athletes were also excluded from this study. Clinical data were recorded at the first visit to the hospital. The clinical characteristics of the subjects are summarized in Table 1. Metabolic syndrome and metabolic abnormalities were diagnosed according to the criteria released by the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome in April 2005.[4, 5] Written informed consent was obtained from each subject, and the protocol was approved by the ethics committee of each institution and by that of Kyoto University.

DNA extraction and SNP genotyping

Genomic DNA was extracted from the blood samples collected from each subject using the Genomix kit (Talent Srl, Trieste, Italy). We selected 12 SNPs that were previously identified as susceptibility loci for hypertension by GWAS in Caucasian populations,[20, 21] and constructed Invader probes (Third Wave Technologies, Madison, WI, USA) for each. The 12 selected SNPs were as follows: rs16998073 in the fibroblast growth factor 5 (*FGF5*) gene; rs11014166 in the calcium channel, voltage-dependent, β-2 subunit (*CACNB2*) gene; rs1530440 in the

chromosome 10 open reading frame 107 (*C10orf107*) gene; rs1004467 in the cytochrome P450, family 17, subfamily A, polypeptide 1 (*CYP17A1*) gene; rs11191548 in the 5'-nucleotidase, cytosolic II (*NT5C2*) gene; rs381815 in the pleckstrin homology domain containing, family A member 7 (*PLEKHA7*) gene; rs2681472 and rs2681492 in the ATPase, Ca^{2+} transporting, plasma membrane 1 (*ATP2B1*) gene; rs6495112 in the AT-rich interactive domain 3B (BRIGHT-like) (*ARID3B*) gene; rs1378942 in the c-src tyrosine kinase (*CSK*) gene; rs12946454 in the phospholipase C, delta 3 (*PLCD3*) gene; and rs16948048 in the zinc finger protein 652 (*ZNF652*) gene. The SNPs were genotyped using Invader assays, as previously described.[23] The success rate of these assays was >99.0%.

Statistical analysis

For the additive model, we coded the genotypes as 0, 1, or 2 depending on the number of copies of the risk alleles. For the recessive model, homozygosity with the risk allele was coded as 1 and the others were coded as 0. Risk alleles refer to the hypertension-associated alleles, according to previous reports.[20, 21] Multiple linear regression analyses were performed to test the independent effect of the risk alleles on BMI, VFA, and SFA, by taking into account the effects of other variables (i.e., age and gender) that were assumed to be independent of the effect of each SNP. The values of BMI, VFA, and SFA were logarithmically transformed before performing the multiple linear regression analysis. Differences in the quantities of

anthropometric parameters among the different genotypes were assessed by the analysis of covariance (ANCOVA), by taking into account the effects of other variables (i.e., age and/or institute). Hardy–Weinberg equilibrium was assessed using the χ^2-test.[24] To test SNP × SNP epistasis, we used a linear regression model for each SNP1 and SNP2, and fit the model in the form of $Y = \beta_0 + \beta_1 \times SNP1 + \beta_2 \times SNP2 + \beta_3 \times SNP1 \times SNP2 + \beta_4 \times age + \beta_5 \times gender$. Although we collected the samples at the region of Hondo (Kanto, Kinki, Chugoku, and Kyushu; Supplementary Table 1), we performed Wright's F-statistics[25] to evaluate the difference in the population structures of our sample using randomly selected 31 SNPs. We divided our samples into 2 groups (SFA >208 cm^2 and ≤208 cm^2). Median of SFA (208 cm^2) was used as a cut-off value. The results indicated that the population structure of 2 groups were almost the same in view of a very small F_{ST} value between the both groups (mean F_{ST} = 0.00023). Statistical analysis was performed using R software (http://www.r-project.org/). *P* values were assessed with a Bonferroni correction, and $P < 0.0042$ (0.05/12) was considered statistically significant.

RESULTS

The clinical characteristics and genotypes of the subjects are shown in Tables 1 and 2, respectively. All the SNPs were in Hardy–Weinberg equilibrium, and the minor allele

frequencies did not diverge from those reported in the HapMap database. The BMI, VFA, and SFA values for each SNP genotype are reported in Table 3. Multiple linear regression analyses of the anthropometric parameters with respect to the 12 analyzed SNPs are shown in Table 4. The A-allele of rs1004467 in the *CYP17A1* gene was significantly associated with reduced BMI (P = 0.0018). The other SNPs were not significantly associated with BMI. No SNP was significantly associated with VFA. The A-allele of rs1004467 in the *CYP17A1* and the T-allele of rs11191548 in the *NT5C2* gene were significantly associated with reduced SFA. These SNPs are in linkage disequilibrium (LD), as reported in the HapMap database ($D' = 0.98$, $r^2 = 0.71$), and the A-allele of rs1004467 and T-allele of rs11191548 are reported to be risk alleles for increased blood pressure.[20, 21]

BMI, VFA, and SFA are known to be affected by gender; therefore, we compared rs1004467 and rs11191548 alleles with anthropometric parameters (BMI, VFA, and SFA) in men and women independently (Table 5). Association of both SNPs with VFA (P = 0.0018 and P = 0.0043) and SFA (P = 0.00039 and P = 0.0021) in women were significant except the association of T-allele of rs11191548 with VFA. The VFA and SFA values of the rs11191548 genotype suggest that the recessive model would be the best-fitted model both in men and women. By using the recessive model, results revealed significant associations of the rs11191548 genotype with VFA (P = 0.0022) and SFA in women (P = 0.00059). These SNPs

did not show any association with VFA or SFA in men, suggesting that they exhibit sexual dimorphism, as has been suggested in a recent report.[26] As both rs1004467 and rs11191548 were associated with a reduction in both VFA and SFA, we examined the association of these SNPs with total fat area (TFA). The SNPs were significantly associated with TFA (P = 0.00012 at rs1004467, P = 0.00052 at rs11191548 in additive model) in women, but not in men, suggesting that risk allele for high blood pressure of these SNPs are associated with reduced adiposity in women. The very small mean F_{ST} value (0.00023) indicated no population structure in our subjects. Since we collected the samples from 9 institutes in 4 regions in Japan (Supplementary Table 1), we tested multiple linear regression analysis with age and institute as explanatory variables in men and women. The very similar results were observed. In additive model, significant associations of the rs1004467 and rs11191548 genotype with VFA (P = 0.0015 and 0.0011, respectively) and SFA (P = 0.00021 and 0.00062, respectively) were observed in women (Supplementary Table 2). Statistical analysis using ANCOVA indicated significant associations of the rs1004467 and rs11191548 genotype with VFA (P = 0.0020 and 0.0015, respectively) and SFA (P = 0.00033 and 0.00042, respectively) in women (Supplementary Table 2). Since some diabetes medications effect on adiposity,[27] we performed the analysis excluding 147 type 2 diabetic patients treated with sulfonylureas, biguanides and thiazolidinediones We found that the similar significant associations of the

rs1004467 and rs11191548 genotype with VFA and SFA in women (Supplementary Table 3).

We have reported that rs1558902 in the *FTO* gene is associated with both VFA and SFA,[11] and that rs7498665 in the *SH2B1* gene is associated with VFA.[17] Thus, we examined SNP × SNP epistasis in men, women, and all subjects. The combination of rs1004467 and rs7498665 exhibited no epistatic effect on VFA in men (P = 0.43), women (P = 0.86), or all subjects (P = 0.76). The combination of rs1004467 and rs1558902 did not show epistatic effect on VFA in men (P = 0.99), women (P = 0.53), or all subjects (P = 0.60), or on SFA in men (P = 0.63), women (P = 0.83), or all subjects (P = 0.89).

Among the SNPs tested in this study, rs16998073 in the *FGF5* gene and rs11191548 in the *NT5C2* gene were associated with increased systolic blood pressure (P <0.05). Rs11191548 in the *NT5C2* gene were also associated with hypertension (P <0.05). We could replicate the association between blood pressure and the above 2 SNPs that were reported to be strongly associated with blood pressure in the Japanese population (Supplementary Table 4).[28]

DISCUSSION

In this study, we showed that the A-allele of rs1004467 in the *CYP17A1* and the T-allele of rs11191548 in the *NT5C2* gene were significantly associated with reduced VFA, SFA, and TFA in women. Association of T-allele of rs11191548 in the *NT5C2* gene with increased systolic

blood pressure and hypertension was replicated in our sample, as reported previously.[28] Our hypothesis was that these risk alleles would be associated with increased VFA and/or SFA since increased adiposity is a risk for hypertension;[4,5] however, these alleles affected decreased adiposity. The associations between SNPs and increased blood pressure/hypertension were evaluated after adjusted for BMI, age and gender. Thus, the SNPs associated with visceral fat obesity related and gender dependent hypertension would be excluded in the screening stage. Indeed, recent analysis has shown that genetic variation near insulin receptor substrate 1 (*IRS1*) is associated with reduced adiposity and an impaired metabolic profile.[29] Thus, it is likely that rs1004467 and rs11191548 are associated with reduced VFA and SFA, as well as with hypertension in women.

The SNPs rs1004467 and rs11191548 were not associated with BMI in men or women, as reported for rs2943650 near *IRS1*.[29] Since BMI represents both fat and lean body mass, our observation suggests that these SNPs influence a reduction in VFA and SFA, or influence an increased percentage of lean body mass. The significant associations of rs1004467 and rs1191548 with reduced VFA and SFA were observed in women, but not in men. The rs1004467 SNP located in the intron of the *CYP17A1* gene. CYP17A1 is involved in the biosynthesis of glucocorticoids, mineral corticoids, androgens, and estrogens.[30] The rs1004467 risk allele may reflect differences in *CYP17A1* gene expression that alter the

biosynthesis of steroid hormones, leading to hypertension and reduced adiposity in women. The region of LD that includes rs1004467 and rs11191548 contains a couple of genes in addition to *CYP17A1*: *NT5C2*, arsenic (+3 oxidation state) methyltransferase (*AS3MT*) and cyclin M2 (*CNNM2*). NT5C2 is a cytosolic IMP/GMP selective 5′-nucleotidase and involved in nucleic acids or DNA synthesis.[31] CNNM2 (ancient conserved domain protein, ACDP2) is a transporter of magnesium which is required for the catalytic activity of numerous metalloenzymes.[32] Thus, these genes would be important for metabolism in adipocyte hyperplasia and hypertrophy. Further investigation is warranted to elucidate the functional SNPs and susceptibility genes.

We have previously reported that *FTO* rs1558902 is associated with VFA and SFA, and that *SH2B1* rs7498665 is associated with VFA.[11, 17] Epistasis, or gene–gene interaction, has recently received much attention in human genetics.[33] In this study, the effect of these SNPs on VFA and SFA was additive, and an epistatic effect was not observed.

In summary, we showed that *CYP17A1* rs1004467 and *NT5C2* rs11191548 SNPs are significantly associated with both reduced VFA and SFA in women. Our results suggest that the region encompassing *CYP17A1* to *NT5C2* plays a role in reducing visceral and subcutaneous fat mass. However, these results require confirmation in other populations.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Table 1 Clinical characteristics of the subjects

	Men	Women	Total
n	556	723	1279
Age (years)	49.4 ± 12.2	52.2 ± 11.3	51.0 ± 11.8
BMI (kg m^{-2})	30.2 ± 6.1	28.1 ± 5.3	29.0 ± 5.8
VFA (cm^2)	155.3 ± 67.7	99.8 ± 53.6	123.9 ± 66.1
SFA (cm^2)	206.7 ± 108.6	241.6 ± 97.2	226.5 ± 103.7
Waist circumference (cm)	97.5 ± 11.3	91.8 ± 10.3	94.2 ± 11.1
Prevalence of metabolic disease			
Dyslipidemia	293 (53%)	244 (34%)	537 (42%)
Hypertension	379 (68%)	452 (63%)	831 (65%)
Impaired fasting glucose	177 (32%)	176 (24%)	353 (28%)
Metabolic syndrome	248 (45%)	162 (22%)	410 (32%)

Data are represented as mean ± SD.

Table 2 Genotypic characteristics of the subjects

SNP ID	CHR	Position (Build 36.3)	Nearby gene	Allele 1/2	BP-associated allele	Genotype	HWE *P*-value
rs16998073	4	81,403,365	*FGF5*	T/A	T	120/514/644	0.24
rs11014166	10	18,748,804	*CACNB2*	T/A	A	4/124/1151	0.73
rs1530440	10	63,194,597	*C10orf107*	T/C	C	30/296/953	0.22
rs1004467	10	104,584,497	*CYP17A1*	A/G	A	559/567/153	0.62
rs11191548	10	104,836,168	*NT5C2*	T/C	T	675/504/100	0.66
rs381815	11	16,858,844	*PLEKHA7*	C/T	T	842/381/56	0.13
rs2681472	12	88,533,090	*ATP2B1*	A/G	A	546/562/171	0.17
rs2681492	12	88,537,220	*ATP2B1*	C/T	T	168/561/549	0.19
rs6495112	15	72,619,851	*ARID3B*	A/C	A	530/575/173	0.39
rs1378942	15	72,864,420	*CSK*	A/C	C	49/410/817	0.78
rs12946454	17	40,563,647	*PLCD3*	T/A	T	34/343/901	0.84
rs16948048	17	44,795,465	*ZNF652*	G/A	G	18/326/935	0.08

BP, blood pressure; CHR, chromosome; HWE, Hardy–Weinberg equilibrium.

Table 3 Mean BMI, VFA, and SFA for 12 blood pressure risk variants

		Mean ± SD								
		BMI (kg m^{-2})			VFA (cm^2)			SFA (cm^2)		
	Nearby	Genotype			Genotype			Genotype		
SNP ID	Gene	11	12	22	11	12	22	11	12	22
rs16998073	*FGF5*	28.8 ± 4.7	29.0 ± 5.8	29.0 ± 6.0	126.2 ± 66.1	121.6 ± 66.5	125.3 ± 65.9	227.4 ± 98.3	224.5 ± 111.0	227.7 ± 98.7
rs11014166	*CACNB2*	27.0 ± 2.7	29.6 ± 6.1	28.9 ± 5.8	123.4 ± 82.2	136.7 ± 68.2	122.5 ± 65.8	178.6 ± 35.8	233.7 ± 106.4	225.8 ± 103.6
rs1530440	*C10orf107*	30.8 ± 6.5	28.6 ± 5.4	29.1 ± 5.9	129.8 ± 63.1	120.2 ± 66.4	124.9 ± 66.2	236.4 ± 119.2	223.0 ± 91.4	227.2 ± 106.9
rs1004467	*CYP17A1*	28.4 ± 5.6	29.5 ± 6.1	29.4 ± 5.2	117.5 ± 64.9	130.6 ± 68.5	122.5 ± 59.3	215.5 ± 92.7	231.4 ± 111.5	247.9 ± 107.9
rs11191548	*NT5C2*	28.6 ± 5.8	29.5 ± 5.9	28.9 ± 5.1	119.2 ± 65.3	130.9 ± 68.6	120.5 ± 55.7	217.2 ± 96.0	238.5 ± 113.2	228.1 ± 98.8
rs381815	*PLEKHA7*	29.2 ± 5.9	28.7 ± 5.7	27.8 ± 4.3	124.1 ± 64.2	124.3 ± 71.5	117.9 ± 55.9	229.4 ± 105.9	221.5 ± 101.6	215.3 ± 83.1
rs2681472	*ATP2B1*	29.2 ± 5.8	28.8 ± 5.4	29.0 ± 7.0	127.1 ± 67.5	121.5 ± 64.8	121.8 ± 65.8	227.4 ± 100.4	223.5 ± 100.3	233.1 ± 123.6
rs2681492	*ATP2B1*	29.0 ± 7.1	28.7 ± 5.2	29.3 ± 5.9	121.9 ± 66.3	121.4 ± 64.8	127.0 ± 67.4	234.6 ± 123.9	221.9 ± 98.3	228.7 ± 102.3
rs6495112	*ARID3B*	28.9 ± 5.8	29.0 ± 5.7	29.3 ± 6.2	122.5 ± 63.4	125.0 ± 69.2	124.9 ± 64.3	223.7 ± 106.5	229.5 ± 102.6	225.1 ± 99.2
rs1378942	*CSK*	28.0 ± 4.2	28.9 ± 6.1	29.1 ± 5.7	110.0 ± 63.3	121.8 ± 62.4	125.6 ± 67.6	222.9 ± 84.5	225.9 ± 104.3	227.0 ± 104.7
rs12946454	*PLCD3*	30.1 ± 8.2	28.6 ± 5.0	29.1 ± 5.9	137.2 ± 80.0	123.0 ± 67.4	123.7 ± 65.1	254.4 ± 105.0	216.4 ± 93.7	229.2 ± 107.0
rs16948048	*ZNF652*	28.1 ± 2.8	29.4 ± 5.9	28.9 ± 5.8	128.6 ± 73.7	124.8 ± 65.9	123.5 ± 66.1	215.0 ± 60.6	227.0 ± 96.3	226.5 ± 106.9

11, allele1/allele1; 12, allele1/allele2; 22, allele2/allele2. Allele 1 and allele 2 of each SNP is indicated in Table 2.

Table 4 Relationship between blood pressure-associated loci and adiposity measures

	Nearby	BMI			VFA			SFA		
SNP ID	gene	β	SE	*P*-value	β	SE	*P*-value	β	SE	*P*-value
rs16998073	*FGF5*	-0.002	0.003	0.55	-0.003	0.010	0.78	-0.010	0.008	0.22
rs11014166	*CACNB2*	-0.005	0.007	0.48	-0.043	0.021	0.043	-0.008	0.017	0.63
rs1530440	*C10orf107*	-0.002	0.004	0.71	0.010	0.014	0.48	-0.005	0.011	0.64
rs1004467	*CYP17A1*	-0.010	0.003	**0.0018**	-0.022	0.010	0.027	-0.030	0.008	**0.00011**
rs11191548	*NT5C2*	-0.008	0.003	0.015	-0.019	0.011	0.078	-0.026	0.008	**0.0016**
rs381815	*PLEKHA7*	-0.007	0.004	0.046	-0.004	0.012	0.76	-0.015	0.009	0.10
rs2681472	*ATP2B1*	0.002	0.003	0.43	0.006	0.010	0.52	0.005	0.008	0.49
rs2681492	*ATP2B1*	0.003	0.003	0.34	0.006	0.010	0.54	0.006	0.008	0.40
rs6495112	*ARID3B*	-0.002	0.003	0.45	-0.004	0.010	0.65	-0.007	0.008	0.36
rs1378942	*CSK*	0.005	0.004	0.20	0.010	0.012	0.40	0.005	0.009	0.61
rs12946454	*PLCD3*	-0.003	0.004	0.39	0.009	0.013	0.50	-0.011	0.010	0.28
rs16948048	*ZNF652*	0.005	0.004	0.30	0.008	0.014	0.57	0.005	0.011	0.67

Data were derived from a linear regression analysis. The values of BMI, VFA, and SFA were logarithmically transformed. Logarithmically transformed BMI, VFA, and SFA were adjusted for age and gender. Tested alleles are risk alleles of increased blood pressure.

Table 5 Relationship between rs1004467 and rs11191548, and adiposity in men and women

SNP ID			Values at each genotype			Additive model		Recessive model	
(gene)	Phenotype	Gender	11	12	22	β (SE)	*P*-value	β (SE)	*P*-value
rs1004467	n	Men	233	259	64				
(*CYP17A1*)		Women	326	308	89				
	BMI (kg m^{-2})	Men	29.7 ± 6.6	30.6 ± 5.9	30.1 ± 5.1	-0.011 (0.005)	0.029	-0.017 (0.006)	0.0085
		Women	27.6 ± 4.6	28.5 ± 6.0	28.9 ± 5.3	-0.010 (0.004)	0..017	-0.013 (0.006)	0.019
	VFA (cm^2)	Men	152.9 ± 67.7	160.6 ± 69.2	142.8 ± 59.9	0.004 (0.014)	0.78	-0.012 (0.019)	0.52
		Women	92.3 ± 49.2	105.4 ± 56.8	107.8 ± 54.7	-0.044 (0.014)	**0.0018**	-0.061 (0.019)	**0.0014**
	SFA (cm^2)	Men	198.6 ± 103.0	211.9 ± 113.8	215.4 ± 106.7	-0.028 (0.013)	0.037	-0.036 (0.018)	0.047
		Women	227.6 ± 82.7	248.0 ± 106.9	271.2 ± 103.3	-0.033 (0.009)	**0.00039**	-0.040 (0.013)	**0.0020**
rs11191548	n	Men	289	220	47				
(*NT5C2*)		Women	386	284	53				
	BMI (kg m^{-2})	Men	30.0 ± 6.8	30.6 ± 5.4	29.4 ± 5.4	-0.007 (0.005)	0.19	-0.013 (0.006)	0.049
		Women	27.6 ± 4.7	28.7 ± 6.1	28.5 ± 4.8	-0.010 (0.004)	0.021	-0.015 (0.006)	0.0080
	VFA (cm^2)	Men	153.8 ± 68.0	161.3 ± 69.3	137.2 ± 54.8	0.007 (0.014)	0.65	-0.008 (0.018)	0.65
		Women	93.3 ± 49.3	107.4 ± 58.1	105.8 ± 52.8	-0.043 (0.015)	0.0043	-0.059 (0.019)	**0.0022**
	SFA (cm^2)	Men	202.1 ± 107.5	214.3 ± 111.3	199.9 ± 102.5	-0.023 (0.014)	0.10	-0.035 (0.018)	0.048
		Women	228.5 ± 84.9	257.4 ± 111.1	253.0 ± 89.0	-0.031 (0.010)	**0.0021**	-0.044 (0.013)	**0.00059**

Values are shown as the mean ± SD. Data were derived from a linear regression analysis. The values of BMI, VFA, and SFA were logarithmically transformed. Logarithmically transformed BMI, VFA, and SFA were adjusted for age. Tested alleles (allele1 at both SNPs) are risk alleles of increased blood pressure.

Supplementary Table 1　Clinical characteristics of the subjects in 4 regions

	Regions			
	Kanto	Kansai	Chugoku	Kyushu
Number of institutes	3	2	2	1
n	1080	126	64	9
Men/Women	463/617	62/64	31/33	0/9
Age (years)	51.1 ± 11.1	50.0 ± 14.2	51.4 ± 15.1	41.9 ± 17.5
BMI (kg m^{-2})	28.0 ± 4.8	35.9 ± 7.1	30.7 ± 5.6	41.8 ± 8.1
VFA (cm^2)	118.2 ± 64.2	165.6 ± 68.4	129.8 ± 60.9	187.3 ± 61.5
SFA (cm^2)	215.1 ± 90.7	322.0 ± 134.8	204.3 ± 105.1	474.9 ± 158.2
Genotype				
rs16998073	102/427/551	12/53/60	5/31/28	1/3/5
rs11014166	4/101/975	0/14/112	0/8/56	0/1/8
rs1530440	25/246/809	3/33/90	1/17/46	1/0/8
rs1004467	481/463/136	50/63/13	27/34/3	1/7/1
rs11191548	568/422/90	63/56/7	42/20/2	2/6/1
rs381815	700/332/48	93/29/4	42/18/4	7/2/0
rs2681472	467/471/142	55/55/16	21/30/13	3/6/0
rs2681492	139/471/469	16/55/55	13/29/22	0/6/3
rs6495112	447/490/142	50/58/18	29/23/12	4/4/1
rs1378942	45/335/698	3/47/75	1/27/36	0/1/8
rs12946454	26/291/763	2/34/89	4/17/43	2/1/6
rs16948048	16/262/802	2/36/88	0/27/37	0/1/8

Data are represented as mean ± SD.

Supplementary Table 2 Relationship between rs1004467 and rs11191548, and adiposity in men and women adjusted for age and institute

SNP ID			Values at each genotype			ANCOVA *P*-value		Additive model		Recessive model	
(gene)	Phenotype	Gender	11	12	22	adjusted with age	adjusted with age and institute	β (SE)	*P*-value	β (SE)	*P*-value
rs1004467	n	Men	233	259	64	–	–				
(*CYP17A1*)		Women	326	308	89	–	–				
	BMI	Men	29.7 ± 6.6	30.6 ± 5.9	30.1 ± 5.1	0.082	0.23	-0.009 (0.004)	0.044	-0.013 (0.006)	0.028
	(kg m^{-2})	Women	27.6 ± 4.6	28.5 ± 6.0	28.9 ± 5.3	0.033	0.015	-0.009 (0.003)	0.0049	-0.011 (0.005)	0.016
	VFA	Men	152.9 ± 67.7	160.6 ± 69.2	142.8 ± 59.9	0.13	0.13	0.007 (0.013)	0.59	-0.007 (0.018)	0.69
	(cm^2)	Women	92.3 ± 49.2	105.4 ± 56.8	107.8 ± 54.7	**0.0020**	**0.0026**	-0.042 (0.013)	**0.0015**	-0.054 (0.018)	**0.0029**
	SFA	Men	198.6 ± 103.0	211.9 ± 113.8	215.4 ± 106.7	0.10	0.21	-0.024 (0.013)	0.066	-0.027 (0.017)	0.12
	(cm^2)	Women	227.6 ± 82.7	248.0 ± 106.9	271.2 ± 103.3	**0.00033**	**0.00013**	-0.032 (0.009)	**0.00021**	-0.036 (0.012)	**0.0027**
rs11191548	n	Men	289	220	47						
(*NT5C2*)		Women	386	284	53						
	BMI	Men	30.0 ± 6.8	30.6 ± 5.4	29.4 ± 5.4	0.20	0.60	-0.004 (0.005)	0.35	-0.008 (0.006)	0.16
	(kg m^{-2})	Women	27.6 ± 4.7	28.7 ± 6.1	28.5 ± 4.8	0.017	**0.0032**	-0.012 (0.004)	**0.0015**	-0.015 (0.005)	**0.00090**
	VFA	Men	153.8 ± 68.0	161.3 ± 69.3	137.2 ± 54.8	0.072	0.046	0.010 (0.014)	0.48	-0.005 (0.018)	0.77
	(cm^2)	Women	93.3 ± 49.3	107.4 ± 58.1	105.8 ± 52.8	**0.0015**	**0.00044**	-0.047 (0.014)	**0.0011**	-0.060 (0.018)	**0.0010**
	SFA	Men	202.1 ± 107.5	214.3 ± 111.3	199.9 ± 102.5	0.13	0.43	-0.016 (0.013)	0.22	-0.025 (0.017)	0.14
	(cm^2)	Women	228.5 ± 84.9	257.4 ± 111.1	253.0 ± 89.0	**0.00042**	**0.00045**	-0.033 (0.009)	**0.00062**	-0.042 (0.012)	**0.00048**

Data are shown as the mean ± SD. Differences in the quantities of anthropometric data among the different genotypes were assessed by the ANCOVA, adjusted with age and/or institute. Data of additive and recessive model were derived from a linear regression analysis. BMI, VFA, and SFA were adjusted for age and institute after the values of BMI, VFA, and SFA were logarithmically transformed. Tested alleles (allele1 at both SNPs) are risk alleles of increased blood pressure.

Supplementary Table 3 Relationship between rs1004467 and rs11191548, and adiposity in men and women without 147 type 2 diabetic subjects

SNP ID			Values at each genotype			ANCOVA	Additive model		Recessive model	
(gene)	Phenotype	Gender	11	12	22	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
rs1004467	n	Men	205	219	60					
(*CYP17A1*)		Women	294	273	81					
	BMI	Men	29.6 ± 6.8	30.3 ± 6.0	29.8 ± 4.9	0.21	-0.010 (0.005)	0.055	-0.015 (0.007)	0.028
	(kg m^{-2})	Women	27.1 ± 4.3	28.3 ± 5.9	28.7 ± 5.1	0.0066	-0.012 (0.004)	**0.0032**	-0.017 (0.006)	**0.0028**
	VFA	Men	153.9 ± 68.1	160.2 ± 69.2	139.8 ± 59.1	0.11	0.011 (0.015)	0.45	-0.004 (0.020)	0.83
	(cm^2)	Women	88.7 ± 47.4	101.4 ± 54.2	103.6 ± 53.5	**0.0030**	-0.044 (0.015)	**0.0027**	-0.064 (0.020)	**0.0018**
	SFA	Men	199.8 ± 104.0	209.9 ± 116.1	207.9 ± 102.0	0.21	-0.023 (0.014)	0.10	-0.030 (0.019)	0.13
	(cm^2)	Women	224.6 ± 79.1	248.9 ± 105.8	273.4 ± 103.8	**8.4×10^{-5}**	-0.037 (0.010)	**0.00013**	-0.045 (0.013)	**0.00073**
rs11191548	n	Men	255	182	47					
(*NT5C2*)		Women	347	253	48					
	BMI	Men	29.8 ± 7.0	30.1 ± 5.3	29.4 ± 5.4	0.49	-0.006 (0.005)	0.23	-0.011 (0.007)	0.12
	(kg m^{-2})	Women	27.2 ± 4.4	28.6 ± 6.0	28.2 ± 4.3	**0.0038**	-0.012 (0.005)	0.0066	-0.018 (0.006)	**0.0016**
	VFA	Men	153.8 ± 68.3	161.3 ± 69.4	137.2 ± 54.8	0.082	0.009 (0.015)	0.54	-0.006 (0.020)	0.78
	(cm^2)	Women	89.7 ± 47.3	103.3 ± 55.7	101.7 ± 52.6	**0.0027**	-0.043 (0.016)	0.0077	-0.059 (0.020)	**0.0037**
	SFA	Men	202.5 ± 108.6	210.9 ± 112.3	199.9 ± 102.5	0.26	-0.021 (0.015)	0.16	-0.031 (0.019)	0.11
	(cm^2)	Women	225.6 ± 81.7	259.2 ± 110.7	256.0 ± 86.1	**6.9×10^{-5}**	-0.037 (0.011)	**0.00039**	-0.052 (0.013)	**0.00011**

147 type 2 diabetic patients treated with sulfonylureas, biguanides and thiazolidinediones were excluded. Data are shown as the mean ± SD. Differences in the quantities of anthropometric data among the different genotypes were assessed by the ANCOVA, adjusted with age. Data of additive and recessive model were derived from a linear regression analysis. BMI, VFA, and SFA were adjusted for age after the values of BMI, VFA, and SFA were logarithmically transformed. Tested alleles (allele1 at both SNPs) are risk alleles of increased blood pressure.

Supplementary Table 4 Effect of risk alleles of blood pressure-associated loci on blood pressure and hypertension in this study

	Nearby	Systolic bold pressure			Diastolic blood pressure			Hypertension	
SNP ID	gene	β	SE	*P*-value	β	SE	*P*-value	OR (95%CI)	*P*-value
rs16998073	*FGF5*	2.181	0.810	**0.0072**	1.041	0.541	0.055	1.10 (0.91 – 1.32)	0.33
rs11014166	*CACNB2*	-0.874	1.695	0.61	-1.186	1.130	0.29	0.75 (0.50 – 1.12)	0.16
rs1530440	*C10orf107*	-0.253	1.073	0.81	-0.067	0.716	0.93	0.97 (0.76 – 1.25)	0.84
rs1004467	*CYP17A1*	1.215	0.788	0.12	0.527	0.526	0.32	1.20 (1.00 – 1.43)	0.053
rs11191548	*NT5C2*	1.712	0.837	**0.041**	0.668	0.559	0.23	1.28 (1.05 – 1.55)	**0.013**
rs381815	*PLEKHA7*	-1.068	0.933	0.25	-0.275	0.623	0.66	0.86 (0.69 – 1.06)	0.15
rs2681472	*ATP2B1*	0.771	0.772	0.32	0.251	0.515	0.63	1.12 (0.94 – 1.34)	0.21
rs2681492	*ATP2B1*	0.705	0.774	0.36	0.239	0.516	0.64	1.12 (0.94 – 1.34)	0.20
rs6495112	*ARID3B*	-0.512	0.781	0.51	0.293	0.521	0.57	1.07 (0.89 – 1.27)	0.48
rs1378942	*CSK*	1.816	0.942	0.054	0.776	0.629	0.22	1.09 (0.88 – 1.35)	0.43
rs12946454	*PLCD3*	-0.885	1.027	0.39	-0.259	0.685	0.71	1.00 (0.79 – 1.26)	1.00
rs16948048	*ZNF652*	1.425	1.113	0.20	0.106	0.743	0.89	1.04 (0.80 – 1.34)	0.78

Data were derived from a linear regression analysis or logistic regression analysis. Systolic and diastolic blood pressure, and hypertension were adjusted for age, age^2, gender, and BMI, according to Takeuchi et al.[28] In individuals receiving antihypertensive therapies, blood pressure was imputed by adding 15mmHg and 10mmHg for systolic and diastolic blood pressures, respectively. Tested alleles are risk alleles of increased blood pressure. OR, odds ratio; CI, confidential interval.