Association of a Polymorphism in the Lipin 1 Gene With Systolic Blood Pressure in Men

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BACKGROUND

Lipin 1 plays a role in abdominal obesity, insulin resistance, and hypertriglyceridemia. The gene is located at 2p25.1, a susceptibility locus for hypertension. We studied the association of tagging single-nucleotide polymorphisms (SNPs) in the lipin 1 (*LPIN1*) gene with hypertension and blood pressure.

METHODS

Twelve tagging SNPs from the HapMap database were genotyped using Sequenom MassArray in 268 hypertensive subjects and 407 normotensive controls, of whom 268 matched the cases in age and sex.

RESULTS

None of the tagging SNPs were found to be associated with hypertension after correcting for multiple testing, although carriers of the minor allele of rs10520097 had nominally lower odds for hypertension ($P = 0.014$). After excluding subjects who were on antihypertensive medications, the minor allele of rs10495584 was nominally associated with lower mean systolic and diastolic blood pressures in men (121.1 ± 14.2 and 76.3 ± 10.2 mm Hg vs. 127.4 ± 15.2 and 80.1 ± 10.5 mm Hg, $P = 0.002$ and 0.007, respectively), but not in women ($P > 0.05$). The association of rs10495584 with systolic blood pressure in men remained significant after correcting for multiple testing and adjustment for age, waist circumference, insulin resistance, triglyceride, and high-density lipoprotein (HDL) cholesterol ($\beta = -0.158$, $P = 0.005$). An analysis of statistically similar SNPs (ssSNPs) in the regions surrounding rs10495584 suggested that its effect may be caused by its high linkage disequilibrium (LD) with the SNP, rs11524, in which the major allele forms an exonic splicing silencer sequence.

CONCLUSION

Our study provides further evidence that lipin 1 may play a role in blood pressure regulation, especially in men.

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Hypertension is a common disease with a complex etiology. Genome-wide scans for hypertension have yielded inconsistent or even negative results, making the identification of genetic variants for hypertension a daunting challenge.[1–3] A recent high-resolution mapping for essential hypertension, using microsatellite markers, has revealed a significant association between the microsatellite D2S0949i at chromosome 2p25.1 and hypertension in a Japanese population with an odds ratio of 1.54 (95% confidential interval: 1.08–2.21).[3] A previous study also demonstrated suggestive evidence linking hypertension with microsatellite markers at the same chromosomal locus, 2p25.1, in African Americans.[4]

The microsatellite marker D2S0949i is located within the gene *LPIN1*, encoding lipin 1.[3] Lipin 1 is expressed in adipose tissue and plays a role in adipogenesis.[5] In mice, mutation in *LPIN1* causes lipin 1 deficiency and lipodystrophy, which is characterized by loss of body fat, fatty liver, hypertriglyceridemia, and insulin resistance.[6] Genetic polymorphisms in *LPIN1* are associated with serum insulin level and body mass index (BMI).[7] Because lipin 1 is associated with obesity, insulin resistance, and hypertriglyceridemia, all of which are components of the metabolic syndrome, lipin 1 may play a role in hypertension or blood pressure regulation. Therefore, in this study, we investigated the associations of tagging single-nucleotide polymorphisms (SNPs) in *LPIN1* with blood pressure and hypertension in a case–control study in Hong Kong Chinese subjects.

METHODS

Subjects. The study included 675 unrelated Hong Kong Chinese subjects from a cohort of adults originally randomly recruited from the general population in Hong Kong.[8] The sample consisted of 268 hypertensive subjects and 407 normotensive controls, of whom 268 matched the cases in age and sex. The 268 hypertensive subjects and 139 unmatched normotensive subjects were randomly selected from the cohort. Hypertension was defined as blood pressure ≥140/90 mm Hg or the use of antihypertensive medications. The study protocol was approved by the Faculty Ethics Committee, and written informed consent was obtained from all participants before blood samples were taken.

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The clinical characteristics, including lipid profile, fasting glucose, insulin, and homeostasis model assessment of insulin resistance index (HOMA-IR), were measured in each subject as described earlier.[8] A physical examination was performed and a full medical history was obtained using a standard questionnaire. Blood pressure was measured using a mercury sphygmomanometer by a trained nurse as described earlier.[8]

Genotyping. Blood samples were taken and genomic DNA was extracted from the buffy coat using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). Tagging SNPs with $r^2 \geq 0.85$ and minor allele frequency ≥0.10 were selected from the database on Han Chinese in HapMap. There were 13 tagging SNPs that captured all the 40 known SNPs in the *LPIN1* gene in HapMap (Phase II data, release 22), from 3 kb upstream to 1 kb downstream of the gene (position 11801191–11885986, GenBank accession number NC_000002) (**Figure 1**). One tagging SNP, rs11524, could not be incorporated into the multiplex assay design, and therefore 12 tagging SNPs were chosen for genotyping. This does not constitute a problem because rs11524 and rs10495584 (which was genotyped) are in high linkage disequilibrium (LD) (r^2 = 0.837) in Han Chinese, according to HapMap. Genotyping was performed using the Sequenom MassArray platform (Sequenom, San Diego, CA). The iPLEX assay was performed in accordance with the manufacturer's instructions.

Statistically similar SNPs (ssSNPs) and prediction of functional effect. The program ssSNPer (http://gump.qimr.edu.au/general/daleN/ssSNPer/) was used for finding SNPs in the surrounding 1 Mb region of *LPIN1* (in the HapMap database for Han Chinese) that were in high LD ($r^2 > 0.80$) to the SNPs genotyped in this study. The PupaSuite program (http://pupasuite.bioinfo.cipf.es/) was used for predicting possible functional effects of the SNPs.

Statistical analysis. Statistical analysis was performed using SPSS 13.0 for Windows (SPSS, Chicago, IL). The data are reported as mean values ± s.d., except for fasting glucose, insulin, HOMA-IR, and triglyceride for which median values are given because of their skewed distributions. Clinical characteristics were compared using unpaired Student's *t*-test or Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. Haploview version 3.32 was used for testing each SNP for Hardy–Weinberg equilibrium and for assessing LD.[9] In all the analyses, subjects who were homozygous for the minor allele were grouped along with heterozygotes and compared with those who were homozygous for the major allele, so as to increase the overall sample size for comparison. The false discovery rate was set at 0.05 to correct for multiple testing.[10] Multiple regression was used for assessing the independent association of SNPs with dependent variables after adjusting for confounding factors. Haplotype analysis was performed using the program PLINK in a sliding window mode with two, three, four, and five consecutive markers across all the 11 SNPs.[11] Variables with skewed distribution were log-transformed in the regression models. A two-tailed *P* value <0.05 was considered statistically significant.

Using Genetic Power Calculator[12] and assuming a disease prevalence of 25%, our study of 268 hypertensive subjects and 268 controls had 80% power to detect an odds ratio of 1.86 for allele frequency of 0.10 at the 5% significance level under a dominant inheritance model.

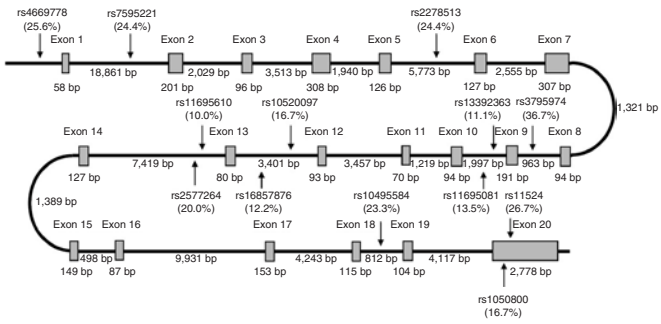

Figure 1 | A schematic diagram of the *LPIN1* gene, encoding lipin 1. Exons and introns are represented by gray boxes and thin lines, respectively, with their sizes indicated below. The minor allele frequencies of the 13 tagging SNPs in Han Chinese population from the HapMap database are indicated in brackets.

RESULTS

Baseline characteristics of study subjects

The baseline characteristics of the subjects are shown in **Table 1**. Hypertensive subjects had significantly higher mean blood pressures, BMI, waist circumference, plasma triglycerides, fasting insulin, and HOMA-IR, but lower mean high-density lipoprotein (HDL) cholesterol and current smoking percentage, in comparison with the age- and sex-matched normotensive control subjects. Among these hypertensive subjects, 146 (54.5%) were receiving anti-hypertensive drug treatment. When compared with the age- and sex-matched controls, the other 139 normotensive controls were younger and had significantly lower blood pressure, fasting glucose, prevalence of diabetes, and former smoking percentage, and a lower proportion of men.

Genotyping and LD pattern

The genotyping completion rate was ≥97.8% in all the SNPs except SNP rs16857876, which was genotyped in 80.4% of the subjects. This SNP showed significant deviation from Hardy–Weinberg equilibrium ($P < 0.001$) and was therefore not analyzed. The remaining 11 SNPs captured 38 (95%) out of 40 SNPs with $r^2 \geq 0.85$ and minor allele frequency ≥0.10 genotyped in the HapMap Han Chinese population. The average r^2 value across all SNP pairs in *LPIN1* gene was 0.27. Moderate-to-high LD was found in three SNP pairs, rs4669778 and rs7595221 ($r^2 = 0.70$), rs7595221 and rs2278513 ($r^2 = 0.89$), and rs11695081 and rs10520097 ($r^2 = 0.91$) (**Figure 2**). The pairwise LD pattern in our sample was similar to that in the HapMap Han Chinese population, except that three SNP pairs, rs10520097 and rs10495584, rs11695081 and rs10520097, and rs11695081 and rs11695610 showed significant differences in LD between our sample and the HapMap Han Chinese

Table 1 | Baseline characteristics of the subjects

	Hypertensive cases ($n = 268$)	Normotensive controls ($n = 268$)	Unmatched controls ($n = 139$)
Age (years)	57.8 ± 10.5	57.7 ± 10.5	43.8*
Men (%)	53.7	53.7	42.4†
Systolic blood pressure (mm Hg)	144.3 ± 17.4*	118.7 ± 10.7	112.1 ± 12.0*
Diastolic blood pressure (mm Hg)	86.5 ± 10.9*	73.5 ± 7.7	71.3 ± 8.2*
BMI (kg/m^2)	25.5 ± 3.3*	23.6 ± 3.5	23.2 ± 3.3
Waist circumference (cm)			
Men	87.8 ± 8.3*	83.4 ± 10.0	80.9 ± 8.1
Women	82.0 ± 8.6*	76.6 ± 8.5	74.0 ± 8.3
LDL cholesterol (mmol/l)	3.38 ± 0.88	3.30 ± 0.88	3.17 ± 0.67
HDL cholesterol (mmol/l)			
Men	1.22 ± 0.29‡	1.33 ± 0.38	1.29 ± 0.32
Women	1.42 ± 0.40‡	1.59 ± 0.43	1.51 ± 0.38†
Triglyceride (mmol/l)	1.4 (1.0–2.2)*	1.1 (0.8–1.6)	1.0 (0.7–1.5)
Fasting glucose (mmol/l)	5.4 (4.9–6.1)	5.3 (4.8–5.9)	5.0 (4.7–5.5)*
Fasting insulin (pmol/l)	57.6 (37.8–84.0)*	41.4 (28.8–58.8)	44.4 (30.6–60.0)
HOMA-IR	2.49 (1.48–3.62)*	1.70 (1.12–2.74)	1.64 (1.11–2.40)
Smoking (%)			
Former	20.9	16.0	8.6†
Current	13.1†	20.9	18.0
Diabetes (%)	33.2	26.1	12.2‡

Data are expressed as mean ± s.d. or median (inter-quartile range) unless otherwise stated.
BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance index; LDL, low-density lipoprotein.
*$P < 0.001$, †$P < 0.05$, ‡$P < 0.01$, compared to matched control subjects.

population after correcting for multiple testing ($r^2 = 0.002$ vs. 0.15, $P = 0.001$; $r^2 = 0.91$ vs. 0.73, $P < 0.001$, and $r^2 = 0.49$ vs. 0.21, $P = 0.001$, respectively).

Association with hypertension

Table 2 shows the genotype distribution in three groups of subjects. There were no significant differences in genotype frequency between matched controls and the remaining controls for any of the 11 SNPs ($P > 0.05$). In case–control analysis of 268 hypertensive subjects and 268 matched controls, carriers of the minor allele of rs10520097 (odds ratio = 0.590; $P = 0.014$) had nominally lower odds for hypertension. However, this was no longer significant after correcting for multiple testing of 11 SNPs.

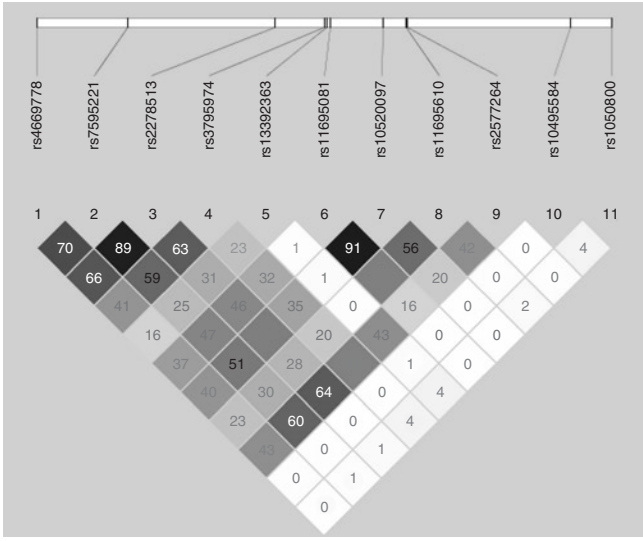

Figure 2 | Pairwise linkage disequilibrium pattern (r^2) in all 675 subjects.

Association with blood pressure

In order to examine the association of genotype with blood pressure as a continuous trait, we included all the normotensive subjects and excluded 146 hypertensive subjects who were on anti-hypertensive drug treatment. Overall, carriers of the minor alleles of rs11695610 and rs10495584 had nominally lower mean systolic blood pressure than the non-carriers (120.3 ± 13.2 mm Hg vs. 124.1 ± 18.3 mm Hg, $P = 0.033$ and 120.8 ± 15.5 mm Hg vs. 124.4 ± 18.4 mm Hg, $P = 0.025$, respectively) (Table 3). However, such associations were no longer significant after correcting for multiple testing of 11 SNPs for the two blood pressure phenotypes.

In sex-specific analysis (Table 3), the minor allele carriers of rs10495584 were nominally associated with lower mean systolic and diastolic blood pressures than non-carriers in men ($n = 78$, 121.1 ± 14.2 and 76.3 ± 10.2 mm Hg vs. $n = 199$, 127.4 ± 15.2 and 80.1 ± 10.5 mm Hg, $P = 0.002$ and 0.007, respectively), but not in women ($P > 0.05$). The association of rs10495584 with systolic (but not diastolic) blood pressure in men remained significant after correcting for multiple testing of 11 SNPs for the two blood pressure phenotypes. In men, carriers of the minor allele of rs10495584 had significantly lower BMI (23.1 ± 3.5 kg/m^2 vs. 24.5 ± 3.3 kg/m^2, $P = 0.001$), lower waist circumference (81.6 ± 9.8 vs. 84.7 ± 9.0 cm, $P = 0.001$), and lower plasma triglyceride (1.1 (0.8–1.6) vs. 1.3 (0.9–1.9) mmol/l, $P = 0.026$) than non-carriers, but there were no significant differences in any of the other baseline characteristics, as shown in Table 1. The association of rs10495584 with systolic blood pressure as determined using multiple linear regression remained significant ($\beta = -0.159$, $P = 0.005$) after adjusting for age, waist circumference, HOMA-IR (log-transformed), triglyceride (log-transformed), HDL cholesterol, current smoking, and former smoking. Replacement of waist circumference with BMI in the regression analysis did not result in any significant change ($\beta = -0.153$, $P = 0.007$). Multiple regression analysis, in which rs10495584 and all the

Table 2 | Genotype distributions in three groups of subjects

Tag SNPs	Position (NC_000002)	Genotyping rate (%)	Genotype	Frequency (%) (*N*)			
				Normotensive controls	Hypertensive cases	Unmatched controls	*P* (odds ratio)[a]
rs4669778	11801431	99.3	TT	58.3 (155)	59.4 (158)	66.9 (91)	0.860 (0.954)
			TC	35.7 (95)	35.0 (93)	29.4 (40)	
			CC	6.0 (16)	5.6 (15)	3.7 (5)	
rs7595221	11814426	100	GG	61.2 (164)	64.6 (173)	70.3 (97)	0.475 (0.866)
			GA	35.1 (94)	31.3 (84)	28.3 (39)	
			AA	3.7 (10)	4.1 (11)	1.4 (2)	
rs2278513	11835356	98.1	TT	59.1 (156)	64.9 (170)	67.6 (92)	0.179 (0.782)
			TC	36.0 (95)	30.2 (79)	30.1 (41)	
			CC	4.9 (13)	5.0 (13)	2.2 (3)	
rs3795974	11842401	100	TT	50.7 (136)	57.5 (154)	56.1 (78)	0.141 (0.763)
			TC	42.2 (113)	35.4 (95)	40.3 (56)	
			CC	7.1 (19)	7.1 (19)	3.6 (5)	
rs13392363	11842786	100	AA	85.1 (228)	83.2 (223)	88.4 (122)	0.636 (1.150)
			AG	13.8 (37)	15.7 (42)	11.6 (16)	
			GG	1.1 (3)	1.1 (3)	0.0 (0)	
rs11695081	11843233	100	CC	75.0 (201)	81.7 (219)	79.9 (111)	0.074 (0.671)
			CT	23.1 (62)	16.4 (44)	20.1 (28)	
			TT	1.9 (5)	1.9 (5)	0.0 (0)	
rs10520097	11850837	100	AA	72.0 (193)	81.3 (218)	77.7 (108)	0.014 (0.590)
			AG	26.1 (70)	16.4 (44)	22.3 (31)	
			GG	1.9 (5)	2.2 (6)	0.0 (0)	
rs11695610	11854042	97.8	CC	82.8 (216)	87.1 (229)	88.7 (118)	0.181 (0.713)
			CG	16.5 (43)	12.5 (33)	11.3 (15)	
			GG	0.8 (2)	0.4 (1)	0.0 (0)	
rs2577264	11854249	99.6	AA	68.7 (184)	70.7 (188)	77.0 (107)	0.638 (0.909)
			AG	28.0 (75)	27.1 (72)	22.3 (31)	
			GG	3.4 (9)	2.3 (6)	0.7 (1)	
rs10495584	11877434	99.8	AA	70.4 (188)	76.1 (204)	74.6 (103)	0.144 (0.747)
			AG	27.3 (73)	22.8 (61)	23.9 (33)	
			GG	2.2 (6)	1.1 (3)	1.4 (2)	
rs1050800	11883265	97.9	CC	62.7 (165)	59.9 (157)	62.7 (84)	0.531 (1.126)
			CT	32.7 (86)	35.1 (92)	31.3 (42)	
			TT	4.6 (12)	5.0 (13)	6.0 (8)	

SNP, single-nucleotide polymorphism.
[a]Comparisons were performed between hypertensive cases and matched normotensive controls. Subjects homozygous for the minor allele were grouped with heterozygotes for comparison with those homozygous for the major allele.

variables shown in Table 1 (except blood pressure) were entered stepwise, showed that rs10495584 ($\beta = -0.149$, $P = 0.009$), age ($\beta = 0.292$, $P < 0.001$), BMI ($\beta = 0.158$, $P = 0.012$), HDL cholesterol ($\beta = 0.139$, $P = 0.047$), triglyceride (log-transformed, $\beta = 0.212$, $P = 0.001$), and former smoking ($\beta = 0.142$, $P = 0.013$) were the significant independent predictors of systolic blood pressure ($r^2 = 0.191$). Haplotype analysis revealed a more significant association of the haplotype GC (comprising SNPs rs10495584 and rs1050800 and present in 14.4% of the subjects) with lower systolic blood pressure in men (regression coefficient = −6.716, $P = 0.0004$).

ssSNPs and prediction of functional effects

The SNP rs10495584 has four ssSNPs, rs1370547, rs2716610, rs2716609, and rs11524, all located in the *LPIN1* gene (Table 4). The results of an analysis of these SNPs using the PupaSuite program suggested that the major allele of rs11524 (T) may form an exonic splicing silencer sequence (TGTTAG), and all of them,

Table 3 | Association of genotypes with blood pressures in all subjects without taking anti-hypertensive drug medications

			P					
			Systolic blood pressure (mm Hg)			Diastolic blood pressure (mm Hg)		
Genotypes		*n*	Overall (*n* = 529)	Men (*n* = 278)	Women (*n* = 251)	Overall (*n* = 529)	Men (*n* = 278)	Women (*n* = 251)
rs4669778	TT	314	0.410	0.849	0.428	0.995	0.943	0.853
	TC + CC	208						
rs7595221	GG	341	0.937	0.368	0.434	0.627	0.352	0.897
	GA + AA	187						
rs2278513	TT	326	0.835	0.478	0.916	0.735	0.515	0.842
	TC + CC	192						
rs3795974	TT	286	0.892	0.428	0.673	0.357	0.379	0.604
	TC + CC	243						
rs13392363	AA	450	0.088	0.252	0.181	0.535	0.729	0.591
	AG + GG	78						
rs11695081	CC	416	0.102	0.056	0.476	0.546	0.160	0.967
	CT + TT	113						
rs10520097	AA	404	0.056	0.074	0.223	0.296	0.229	0.547
	AG + GG	125						
rs11695610	CC	445	0.033	0.206	0.143	0.411	0.440	0.806
	CG + GG	70						
rs2577264	AA	378	0.667	0.833	0.446	0.815	0.779	0.495
	AG + GG	149						
rs10495584	AA	386	0.025	0.002	0.786	0.138	0.007	0.744
	AG + GG	141						
rs1050800	CC	318	0.313	0.070	0.690	0.403	0.058	0.248
	CT + TT	197						

Table 4 | ssSNPs of the SNP rs10495584

ssSNP	r^2	Position (NC_000002)	Gene (location)
rs10495584	1.000	11877434	*LPIN1* (intron 18)
rs1370547	1.000	11879141	*LPIN1* (intron 19)
rs2716610	0.941	11876833	*LPIN1* (intron 17)
rs2716609	0.941	11877356	*LPIN1* (intron 18)
rs11524	0.837	11883768	*LPIN1* (exon 20, 3′ UTR)

LPIN1, lipin 1 gene; *r*, correlation coefficient; ssSNP, statistically similar single-nucleotide polymorphism; UTR, untranslated region.

except rs2716610 and rs1370547, are located in conserved regions common to humans and mice.

DISCUSSION

This is the first report of the association of genetic polymorphisms in the *LPIN1* gene with systolic blood pressure in men. The present results confirm and extend the results of a recent genome scan in Japan that suggested *LPIN1* as a candidate gene for hypertension.[3] The association of rs10495584 with hypertension did not reach statistical significance, which could be because of insufficient power in the study design, the involvement of multiple genes in the etiology of hypertension, and misclassification of hypertension status. Moreover, blood pressure is a continuous variable whereas hypertension is a discrete variable. Thus, an SNP associated with a 6.3 mm Hg change in systolic blood pressure may be insufficient to cause hypertension in someone whose blood pressure is in the normal range. Certainly, the use of tagging SNPs did not result in any loss of power.[13] An analysis of ssSNPs in the surrounding regions suggested that the causative variants for systolic blood pressure are located in *LPIN1*. SNPs in *LPIN1* are associated not only with blood pressure but also with serum insulin level and BMI,[7] and therefore functional studies are needed for unraveling the direct functional consequences of genetic variants in *LPIN1*.

Lipin 1 is the phosphatidic acid phosphatase that produces diacylglycerol in adipocytes.[14] It has two isoforms (α and β) produced by alternative mRNA splicing.[15] Lipin 1α is predominantly localized to the nucleus, stimulates expression of genes involved in adipocyte differentiation, and thereby enhances the expression of PPAR-γ and adipocyte fatty acid–binding protein (aP2).[15] aP2 is an abundant protein in the cytosol of mature adipocytes. Its serum level correlates with carotid atherosclerosis and predicts the development of the metabolic syndrome and type 2 diabetes in long-term prospective studies in our population.[16–18] Lipin 1β is predominantly localized to the cytoplasm, stimulates the expression of genes involved in lipogenesis and

triglyceride synthesis, and enhances the expression of acetyl-CoA carboxylase 1 and fatty acid synthase.[15] Lipin 1β expression in the liver and adipose tissues is inversely correlated to fasting plasma insulin, insulin resistance, and BMI.[19] Lipin 1 expression is decreased in obesity and increases upon weight loss.[19] Thus, lipin 1 plays a role in adipogenesis in humans as well as in mouse models, in which alteration in the level of expression of lipin 1 can cause either lipodystrophy or obesity.[5,6] Lipin 1 plays a critical role in the maturation of adipocytes and promotes lipid accumulation in mature adipocytes. The expression of lipin 1 in adipose tissues leads to appropriate energy storage. Conversely, under-expression of lipin 1 in appropriate tissues, or expression of lipin 1 in inappropriate tissues could be key abnormalities in insulin resistance.

The latest evidence does indeed suggest a role for lipin 1 in insulin resistance.[19,20] Insulin stimulates the phosphorylation of lipin 1 through the mammalian target of the rapamycin pathway.[21] In contrast, epinephrine and oleic acid promote dephosphorylation of lipin 1.[22] These substances modulate the phosphatidic acid phosphatase activity of lipin 1 by changing its subcellular localization.

Chromosome 2p25 has also been linked to plasma levels of N-terminal proatrial natriuretic peptide.[23] Natriuretic peptides play a role in sodium homeostasis and blood pressure regulation.[24,25] Obese individuals in Framingham were found to have low circulating levels of natriuretic peptides.[26] The interaction between *LPIN1* and the natriuretic peptides warrants further investigation.

Like adiponectin, the expression of lipin 1 in subcutaneous adipose tissue is lower in subjects with obesity and the metabolic syndrome.[20] We have previously shown, in the Hong Kong Chinese population, that obesity and the metabolic syndrome precede and predict the development of hypertension.[27] Obesity can lead to hypertension through the activation of the renin–angiotensin and sympathetic nervous systems, sodium and water retention, expansion in extracellular fluid volume and increase in glomerular filtration rate.[28]

A recent study in Caucasians revealed a significant association between genetic variants in *LPIN1* and human metabolic traits, including blood pressure, BMI, waist circumference, and glycosylated hemoglobin level.[29] In our study, the association of rs10495584 with blood pressure in men, but not in women, is not surprising, and is consistent with other reports. For instance, the SNP rs11693809 in *LPIN1* was associated with serum insulin level in men only,[7] although we did not study this SNP because it has not been chosen for inclusion in the HapMap database. We found that men who were carriers of the minor allele of rs10495584 had significantly lower BMI, lower waist circumference, and lower plasma triglyceride than non-carriers. It is possible that lipin 1 plays a more important role in obesity in men than in women. Men and pre-menopausal women have different patterns of fat accumulation. Men are more prone to central obesity that is more associated with the metabolic syndrome and cardiovascular risk. Interestingly, physical activity, which reduces intra-abdominal adiposity effectively, increases the expression of *LPIN1*.[30]

In conclusion, our study demonstrated a significant association between rs10495584 and systolic blood pressure in men. Although this SNP is in high LD with rs11524, in which the major allele forms an exonic splicing silencer sequence, it remains to be established how these two SNPs affect blood pressure by alternative splicing.

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