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Association of hypertension with single nucleotide polymorphisms in the quantitative trait locus for abdominal obesity-metabolic syndrome on chromosome 17

Short title: SNP at 17p12 and blood pressure

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Abstract:

Background: Genome scan in Chinese revealed an association of blood pressure with the microsatellite marker D17S1303, which lies in a quantitative trait locus for the abdominal obesity-metabolic syndrome (AOMS2) at 17p12 on chromosome 17. We previously reported that D17S1303 was associated with hypertension and obesity. Therefore, we studied 10 single nucleotide polymorphisms (SNP) within 3kb of D17S1303.

Methods: 180 hypertensive subjects (91 men, 89 women, age 53 ± 12) and 180 normotensive matched controls (91 men, 89 women, age 52 ± 11) were genotyped using the Sequenom genotyping platform.

Results: Allelic frequencies in these Chinese subjects differed from those reported for Caucasians. Three SNPs (rs11656507, rs1357926, rs852319) were homozygous in our subjects. The genotype frequencies of rs852320, rs852321 and rs852322 did not differ between hypertensive and normotensive subjects. However, there were significant differences for rs1525402 ($p=0.048$), rs2692343 ($p=0.022$), rs2692344 ($p=0.017$) and rs2321313 ($p=0.028$). A 4-locus haplotype comprising G at rs1525402, C at rs2692343, C at rs2692344 and G at rs2321313 was associated with lower systolic blood pressure ($p=0.023$) and normotension ($p=0.048$).

Conclusion: Our results provide further evidence that there is a gene, as yet unidentified, influencing blood pressure in the vicinity of D17S1303 in a quantitative trait locus for

abdominal obesity-metabolic syndrome at 17p12.

[197 words]

Key words: hypertension, metabolic syndrome, single nucleotide polymorphism, blood pressure, genotype, haplotype

Introduction:

Patients with hypertension usually do not have a secondary cause. Primary or essential hypertension is likely to result from the interaction between genetic predisposition and environmental factors.¹ The environmental factors that lead to hypertension are well worked out. Of these, overweight or obesity is undoubtedly one of the most important.² The search for causative genes for hypertension has been ongoing for at least a decade. Many promising candidate genes have been examined. Thus, a gene that causes hypertension may also be associated with obesity and other components of the metabolic syndrome.

A genome scan of blood pressure-regulating genes done in Chinese sib pairs undertaken in Anhui in collaboration with Harvard University showed that the microsatellite marker D17S1303, which consists of GATA repeats, had a high LOD score.³ This marker lies close to a quantitative trait locus for abdominal obesity-metabolic syndrome (AOMS2) at 17p12 on chromosome 17.⁴ Recently, we have reported that D17S1303 was associated with hypertension.⁵ The number of GATA repeats correlated inversely with diastolic blood pressure and BMI. Nine GATA repeats were associated with hypertension whilst 14 GATA repeats were associated with normotension.

Chromosome 17 has been studied in genome scans,^{6,7} but the region around D17S1303 has not been intensively studied and there is a lack of reports of single nucleotide polymorphisms or genes in its close proximity. In case-control studies, single nucleotide polymorphisms are preferable to microsatellite markers, which are highly polymorphic. Therefore, we set out to study SNPs around D17S1303 and investigate their association with hypertension.

Methods:

Subjects

The study protocol was approved by the Faculty Ethics Committee. We studied 360 subjects, 180 hypertensive patients and 180 normotensive controls with their informed consent. Hypertensive subjects were recruited from the Hypertension Clinic of a teaching hospital. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg on at least 3 separate occasions. Patients on antihypertensive treatment and had been diagnosed as hypertensive by the above criteria were also eligible. Patients with secondary hypertension (e.g. Cushing's syndrome, Conn's syndrome, pheochromocytoma, acromegaly, renal artery stenosis, coarctation, glomerulonephritis and pyelonephritis) were excluded. Subjects who received drug treatment for diabetes mellitus were also excluded. Normotensive controls, matched for age and sex, were recruited from the Hong Kong Cardiovascular Risk Factor Prevalence Survey-2 (CRISPS2) cohort. These

subjects had been randomly chosen from the general population.^{8,9}

Physical examination (including measurement of height, weight, body fat, waist and hip circumference), urinalysis and electrocardiography were performed and a full medical history (including past medical history, drug history, family history, smoking status, alcohol intake and exercise habit) was obtained. Waist circumference was measured half way between the xiphisternum and the umbilicus while hip circumference was measured at the level of the greater trochanters.¹⁰ Percentage body fat was estimated by measuring the bioelectrical impedance (Tanita TBF300, Tanita Corporation, Tokyo, Japan).¹¹

Subjects were studied in the morning after fasting overnight. The blood pressure of each patient was measured by a trained nurse manually after at least 5 minutes of rest. Blood pressure was measured thrice at 5 minute intervals. The first measurement was to familiarise the patient with the procedure. The 2 subsequent systolic and phase V diastolic blood pressure readings were recorded to the nearest 2 mmHg, the mean of which was used for data analysis.

After resting for at least 5 minutes, 20 ml venous blood was taken from a forearm vein for a full blood count (haemoglobin, haematocrit, differential white count and platelet count), renal

and liver function tests (sodium, potassium, urea, creatinine, glucose, bilirubin, albumin, ALT and alkaline phosphatase), plasma insulin and lipid profile. Insulin resistance was measured using the homeostasis model assessment of insulin resistance index (HOMA-IR), which is the product of the fasting plasma insulin (FPI) concentration in mU/L and fasting plasma glucose (FPG) in mmol/L divided by 22.5.¹² Pancreatic β -cell function was estimated using HOMA- β %, which equals $(20 \times \text{FPI})/(\text{FPG} - 3.5)$.

Genetic analysis

Genomic DNA was extracted from the buffy coat using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Candidate SNPs within 3kb of D17S1303 were selected from an SNP database (Fig. 1).¹³ High-throughput genotyping of the SNPs was performed using the Sequenom MassARRAY system (Sequenom, San Diego CA) which utilises Matrix Assisted Laser Desorption Ionization-Time Of Flight (MALDI-TOF) technology. Primers for SNP detection were designed using MassARRAY AssayDesign software (Sequenom).

Statistical analysis

Data were analysed using a statistical software programme (SPSS for Windows, ver. 11.0, SPSS Inc., Chicago, USA). Comparison of clinical characteristics in the hypertensive and

normotensive groups or in groups with different genotypes were performed using unpaired t test or Mann-Whitney U test and Chi-square test for continuous and categorical variables respectively. Genotype frequencies for each SNP were tested for Hardy-Weinberg equilibrium. We used the programme Haploview (ver. 3.2) to calculate the r^2 among all possible SNP pairs in order to assess the degree of linkage disequilibrium.¹⁴ The parameter r^2 is independent of allele frequency and is appropriate for modest sample sizes.^{15, 16} Haplotypes were predicted using the programme PHASE (version 2.1), which implements a Bayesian method for estimating haplotypes from population genotype data.¹⁷⁻¹⁹ A 2-tailed p-value less than 0.05 was considered statistically significant. With the study sample size, there was 95% power to detect an odds ratio of 2.5 for a minor allele with a frequency greater than 0.1.

Results

Baseline characteristics

Table 1 shows the characteristics of the 180 hypertensive subjects and 180 normotensive controls studied. There were no significant differences in the male:female ratio, age and alcohol consumption between the normotensive and hypertensive groups, but there were as expected, significant differences in blood pressure, weight, BMI, percentage body fat, HDL-cholesterol, plasma insulin and HOMA-IR. In the hypertensive group, 45 subjects (25%) were on antihypertensive drug treatment.

SNP genotyping

Table 2 shows the pairwise r^2 among genotyped SNPs. Three SNPs (rs11656507, rs1357926, rs852319) were homozygous in our subjects and therefore not shown. The average r^2 value across all SNP pairs was 0.46. The SNP pairs, rs852321 and rs852322, and the three SNPs, rs2692343, rs2692344 and rs2321313, exhibit a high degree of linkage disequilibrium. The results of Sequenom genotyping are shown in Table 3. Genotype frequencies in these Chinese subjects differed from those reported for Caucasians.¹³ There were no significant deviations of the observed genotype frequencies from Hardy-Weinberg equilibrium. The genotype frequencies of rs852320, rs852321 and rs852322 did not differ significantly between hypertensive and normotensive subjects ($p=0.171$, $p=0.464$ and $p=0.196$ respectively). However, the genotype frequencies of rs1525402, rs2692343, rs2692344 and rs2321313 differed between hypertensive and normotensive subjects ($p=0.048$, $p=0.022$, $p=0.017$ and $p=0.028$ respectively) (Table 3).

Table 4 shows the systolic and diastolic blood pressure in subjects with different genotypes. The AA genotype at rs1525402 was associated with higher systolic blood pressure ($p=0.02$). There was a small difference in systolic blood pressure between subjects with or without the CC genotype at rs2692344 ($p=0.049$).

Haplotypes

Four-locus haplotypes made up of rs1525402, rs2692343, rs2692344 and rs2321313 were analysed. Table 5 shows the frequencies of ACCG, AAGA and GCCG haplotypes. ACCG and AAGA were common and had a frequency of 0.445 and 0.443, respectively. ACCG was not associated with hypertension ($p=0.908$) but AAGA was more common among hypertensive subjects ($p=0.022$). GCCG had a frequency of 0.109 and was less common among hypertensive patients ($p=0.048$). The GCCG haplotype was associated with lower systolic blood pressure ($p=0.023$) (Table 6).

Stepwise regression with hypertension as the dependent variable and the various SNPs and haplotypes as independent variables showed that rs2692343 was the best predictor of hypertension ($\beta=0.058$, $p=0.021$). Neither rs2692343, other SNPs or any of the haplotypes are related significantly to body mass index, waist circumference and percentage body fat.

Discussion

The most important finding of this study was the association of several SNPs at 17p12 with hypertension. The haplotype comprising G at rs1525402, C at rs2692343 and rs2692344, and G at rs2321313 was associated with lower systolic blood pressure and was less frequent

among hypertensive patients. These new findings confirm and extend previous reports of the association of 17p12 with hypertension.³⁻⁵

Our findings should be interpreted with a degree of caution. SNPs that are close to each other would be expected to show linkage disequilibrium and similar associations with a particular trait. Therefore, the association of several SNPs or a haplotype with hypertension may be more a single SNP effect. Moreover, there might be other as yet unidentified SNPs in the region that are more strongly associated with hypertension. Conversely, our study did not have the power to detect weak associations between SNPs and hypertension. Thus, there is a need for replication of our study in an independent and larger data set.

In our population, blood pressure is related to indices of obesity and sodium intake.^{2, 20-22}

The relationship between obesity and raised blood pressure is expected because both are components of the metabolic syndrome, which is a clustering of abdominal obesity, elevated blood pressure, blood glucose and triglycerides, and low levels of high density lipoprotein cholesterol (HDL).²³ Insulin resistance is believed to be a key underlying metabolic abnormality in the syndrome.^{24, 25} Our hypertensive and age and sex matched normotensive subjects differed not just in blood pressure, but also in the other aspects of the metabolic syndrome. We believe that obesity, particularly central obesity, is an early abnormality in

the cardiovascular continuum.^{10, 26} Increased abdominal adiposity leads to a state of chronic low grade inflammation, insulin resistance and endothelial dysfunction.²⁷⁻²⁹ Adipocytes in adipose tissues secrete adipokines such as leptin, adiponectin and acylation-stimulating protein (ASP) that regulate obesity.³⁰ Leptin suppresses appetite, whilst adiponectin increases insulin sensitivity. ASP, a cleavage product of complement C3, stimulates triacylglycerol synthesis and its storage in adipocytes. Genome scan revealed two loci, 3q27 and 17p12, associated with the metabolic syndrome.⁴ The former is near the adiponectin gene. The latter, AOMS2, is related to plasma levels of leptin⁴ and ASP.³¹ Neither the gene coding for leptin nor ASP (C3) is on chromosome 17, so there is an unidentified gene in this locus that determines abdominal obesity. The polymorphisms we investigated all lie within this quantitative trait locus. This locus is associated with hypertension, as shown in the genome scan in Chinese sib-pairs in Anhui.³ We previously reported that D17S1303 was associated with hypertension and obesity.⁵ We now found four SNPs that are a few kilobases from D17S1303 and within the AOMS2 quantitative trait locus are associated with hypertension. These consistent findings in different populations using diverse genetic approaches collectively suggest a high probability of a disease susceptibility gene in the locus.

In conclusion, our study showed that SNPs at 17p12 in Hong Kong Chinese are associated

with hypertension. This is further evidence that a gene influencing blood pressure is in the vicinity of D17S1303, in a quantitative trait locus for abdominal obesity-metabolic syndrome. Our results should prompt the fine mapping of this part of chromosome 17, so as to identify the gene linked to hypertension and the metabolic syndrome, although final proof would require study of the function and dysfunction of the gene.³²

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Conflict of interest

None

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Table 1 Subjects characteristics

Table 2 Pairwise r^2 among the genotyped SNPs

Table 3 Genotype and allele frequencies of SNPs in normotensive and hypertensive subjects

Table 4 Blood pressure and genotypes

Table 5 Haplotype frequencies in normotensive and hypertensive subjects

Table 6 Blood pressure and haplotypes

Figure 1 The locations of the SNPs investigated and the microsatellite marker D17S1303 on chromosome 17.

Table 1. Subjects Characteristics

	Normotensive	Hypertensive	<i>P</i>
	Controls		
	N = 180	N = 180	
Age (years)	51.9 ± 10.8	53.1 ± 11.9	0.29
Gender (M: F)	91: 89	91: 89	1.0
Regular smoking (%)	26	12	0.004
Regular drinking (%)	12	10	0.58
Systolic blood pressure (mmHg)	115.5 ± 12.1	144.9 ± 16.4	< 0.001
Diastolic blood pressure (mmHg)	72.9 ± 8.0	90.8 ± 10.6	< 0.001
Body weight (kg)	60.2 ± 10.2	65.2 ± 11.7	< 0.001
Body mass index (kg/m ²)	23.2 ± 3.0	25.5 ± 4.0	< 0.001
Waist circumference (cm)	77.8 ± 8.8	84.4 ± 9.8	< 0.001
Body fat (%)	27.4 ± 7.7	31.4 ± 9.0	< 0.001
Fasting glucose (mmol/L)	5.1 ± 0.7	5.2 ± 0.9	0.16
Plasma insulin (mIU/L)	6.8 (4.6-9.2)	7.4 (5.4-11.0)	0.009
HOMA-IR	1.4 (1.0-2.2)	1.9 (1.2-2.7)	0.005
HOMA-β%	91.0 (64.0-119.6)	93.8 (67.3-150.0)	0.10

Total cholesterol (mmol/L)	5.1 ± 0.7	5.4 ± 1.0	0.008
LDL-cholesterol (mmol/L)	3.1 ± 0.7	3.3 ± 0.9	0.03
HDL-cholesterol (mmol/L)	1.5 ± 0.4	1.4 ± 0.4	0.03
Triglycerides (mmol/L)	1.2 ± 0.7	1.6 ± 1.1	< 0.001

Unless otherwise specified, data are expressed as mean ± SD, or median (interquartile range).

Table 2

Pairwise r^2 among the genotyped SNPs

rs852320						
0.098	rs852321					
0.098	0.994	rs852322				
0.762	0.076	0.075	rs1525402			
0.128	0.641	0.648	0.099	rs2692343		
0.126	0.644	0.651	0.098	0.994	rs2692344	
0.129	0.639	0.646	0.099	0.989	0.994	rs2321313

The r^2 values that are 0.9 or higher are shown in bold type.

Table 3

Genotype and allele frequencies of SNPs in normotensive and hypertensive subjects

SNP	Genotype	Normotensive	Hypertensive	p-value (odds ratio)
rs852320	TT	70.8%	76.2%	0.171(0.759)
	TG	27.7%	20.1%	
	GG	1.5%	3.7%	
rs852321	CC	42.4%	39.3%	0.464(1.141)
	CT	42.8%	46.1%	
	TT	14.8%	14.6%	
rs852322	GG	43.3%	36.1%	0.196(1.353)
	GA	40.6%	48.9%	
	AA	16.1%	15.0%	
rs1525402	AA	75.6%	84.4%	0.048(0.569)
	AG	22.8%	13.3%	
	GG	1.7%	2.2%	
rs2692343	CC	36.7%	25.0%	0.022(1.737)
	CA	43.9%	55.0%	
	AA	19.4%	20.0%	
rs2692344	CC	36.9%	25.0%	0.017(1.752)
	CG	43.6%	55.6%	
	GG	19.6%	19.4%	
rs2321313	GG	35.8%	24.9%	0.028(1.685)
	GA	44.3%	55.9%	
	AA	19.9%	19.2%	

Subjects carrying one or both minor alleles were grouped together

Table 4

Blood pressure and genotypes

SNP		Genotype	N	Mean (mmHg)	p-value
rs1525402	Systolic BP	AA	288	131.45±1.219	0.020
		AG+GG	72	125.17±2.319	
	Diastolic BP	AA	288	81.84±0.768	0.963
		AG+GG	72	81.76±1.493	
rs2692343	Systolic BP	CC	111	127.26±1.660	0.071
		CA+AA	249	131.50±1.380	
	Diastolic BP	CC	111	82.04±1.162	0.839
		CA+AA	249	81.73±0.841	
rs2692344	Systolic BP	CC	111	127.26±1.660	0.049
		CG+GG	248	131.53±1.385	
	Diastolic BP	CC	111	82.04±1.162	0.088
		CG+GG	248	81.82±0.840	
rs2321313	Systolic BP	GG	107	127.48±1.715	0.066
		GA+AA	246	131.55±1.395	
	Diastolic BP	GG	107	82.23±1.184	0.693
		GA+AA	246	81.64±0.851	

Data are expressed as mean ± SE

Table 5

Haplotype frequencies in normotensive and hypertensive subjects

Haplotype	Haplotype frequency from PHASE	Genotype	Normotensive	Hypertensive	p-value (odds ratio)
ACCG	0.445	Non-carrier	30.2%	29.4%	0.908 (1.035)
		1 copy carrier	48.6%	53.9%	
		2 copies carrier	21.2%	16.7%	
AAGA	0.443	Non-carrier	36.3%	25.0%	0.022 (1.711)
		1 copy carrier	44.1%	55.6%	
		2 copies carrier	19.6%	19.4%	
GCCG	0.109	Non-carrier	76.0%	84.4%	0.048 (0.583)
		1 copy carrier	22.3%	13.3%	
		2 copies carrier	1.7%	2.2%	

The four-locus haplotypes consist of rs1525402, rs2692343, rs2692344 and rs2321313.

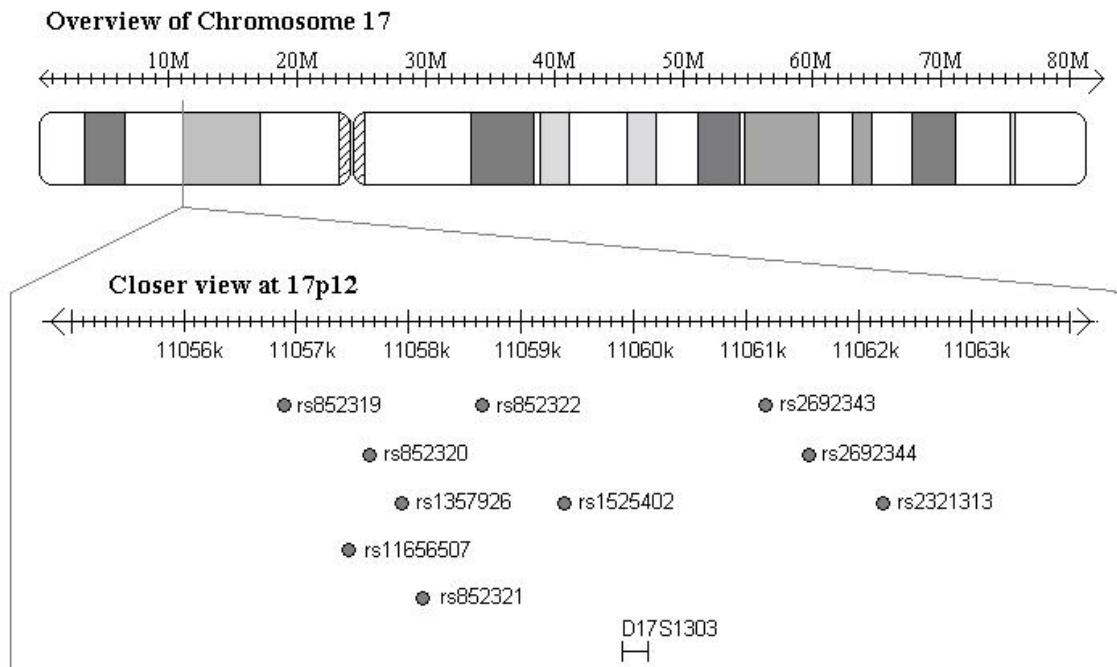
Table 6

Systolic blood pressure and haplotypes

Haplotype		N	Systolic blood pressure (mean±SE, mmHg)	p-value
ACCG	Non-carrier	107	130.0±2.1	0.908
	Carrier(1 or 2 copies)	252	130.3±1.3	
AAGA	Non-carrier	110	127.3±1.7	0.055
	Carrier (1 or 2 copies)	249	131.5±1.4	
GCCG	Non-carrier	288	131.5±1.2	0.023
	Carrier (1 or 2 copies)	71	125.2±2.4	

Figure 1

The locations of the SNPs investigated and the microsatellite marker D17S1303 on chromosome 17.



What is known on this topic

Hypertension is more common in obese people. There is a quantitative trait locus for the abdominal obesity-metabolic syndrome on chromosome 17. A microsatellite, D17S1303, that lies in this quantitative trait locus has previously been found to be associated with hypertension.

What this paper adds

Four single nucleotide polymorphisms within 3 kilobases of D17S1303 were found to be associated with hypertension in this case control study. This provides further evidence that a gene predisposing to hypertension in Chinese is in this region of chromosome 17.