

## The Gas6 gene rs8191974 and Ap3s2 gene rs2028299 are associated with type 2 diabetes in the northern Chinese Han population

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Previous studies in other countries have shown that single nucleotide polymorphisms (SNPs) in the growth arrest-specific gene 6 (Gas6; rs8191974) and adapter-related protein complex 3 subunit sigma-2 (Ap3s2; rs2028299) were associated with an increased risk for type 2 diabetes mellitus (T2DM). However, the association of these loci with T2DM has not been examined in Chinese populations. We performed a replication study to investigate the association of these susceptibility loci with T2DM in the Chinese population. We genotyped 1968 Chinese participants (996 with T2DM and 972 controls) for rs8191974 in Gas6 and rs2028299 near Ap3s2, and examined their association with T2DM using a logistic regression analysis. We also analyzed the correlation of genotypes and clinical phenotypes. The distribution of the T allele of SNP rs8191974 in the Gas6 gene was significantly different between T2DM cases and controls when compared with the C allele ( $P < 0.05$ , OR: 0.80, 95% CI: 0.69–0.94). The occurrence of the CT genotype and the dominant model was also significantly less frequent in the T2DM cases vs. controls when compared with the CC genotype (CT vs. CC:  $P < 0.05$ , OR: 0.75, 95% CI: 0.62–0.90; TT+CT vs. CC:  $P < 0.05$ , OR: 0.75, 95% CI: 0.63–0.90). In SNP rs2028299, the allele C showed no statistically significant difference in distribution between the control and T2DM groups when compared with allele A. However, in male populations, the dominant model was statistically more frequent when compared with genotype AA (CC+CA vs. AA:  $P < 0.05$ , OR: 1.29, 95% CI: 1.02–1.64), and in obesity-stratified analysis, we also observed a significant difference in the distribution of the dominant model between the T2DM cases and controls in subjects with BMI  $\geq 24$  kg/m<sup>2</sup> and BMI  $< 28$  kg/m<sup>2</sup> (CC+CA vs. AA:  $P < 0.05$ , OR: 6.33, 95% CI: 4.17–9.61). In conclusion, our study shows that SNPs rs8191974 and rs2028299 are significantly associated with T2DM in the Chinese population.

**Key words:** Type 2 diabetes mellitus; Gas6 gene; Ap3s2 gene; single nucleotide polymorphisms; epidermal growth factor (EGF)-like

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**Abbreviations:** BMI, body mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HOMA- $\beta$ , homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance

### INTRODUCTION

Diabetes mellitus affects more than 300 million individuals worldwide, with increasing prevalence particularly in the developing countries (Whiting *et al.*, 2011). In fact, the prevalence of type 2 diabetes mellitus (T2DM) in China is among the highest in the world. The combination of insulin resistance in peripheral tissues and impaired insulin secretion from pancreatic  $\beta$ -cells is believed to contribute to the development and progression of T2DM. Both, the genetic and environmental factors confer susceptibility to T2DM. In recent years, studies of gene polymorphisms have helped identify a number of T2DM-susceptibility genes.

The growth arrest-specific gene 6 (Gas6) is located on human chromosome 13q34. Plasma Gas6 is a vitamin K-dependent protein very similar to plasma anticoagulant protein S and is comprised of the Gla domain ( $\gamma$ -carboxylated glutamic acid-rich region) and four EGF-like domains (Bellido-Martin *et al.*, 2008). Gas6 protein interacts with receptor tyrosine kinases of the Tyro-3, Axl, Mer (TAM) family (Hafizi *et al.*, 2006). The Gas6/TAM system has a number of diverse functions, including the regulation of cell survival and proliferation, cell adhesion and migration, and others (Godowski *et al.*, 1995; Nagata *et al.*, 1996; Bellosta *et al.*, 1997; Collett *et al.*, 2003). In recent years, several studies have explored the relationship between Gas6 polymorphisms and T2DM. Chien-Hsing Lee in Taiwan found that the Gas6 gene single nucleotide polymorphism (SNP) rs8191974 was associated with T2DM in the local population (Lee *et al.*, 2012).

The adapter-related protein complex 3 subunit sigma-2 gene (Ap3s2) is located on human chromosome 15q26, and was first found in muscle tissue of rats. Ap3s2 protein is composed of 193 amino acids and its physiological function involves protein transport. Two studies have reported that Ap3s2 gene SNP rs2028299 was associated with T2DM. A genome-wide association study (GWAS) in people of South Asian ancestry identified rs2028299 as a susceptibility locus for T2DM (Kooner *et al.*, 2011). A replication study investigating the association of SNP rs2028299 with T2DM in the Japanese population (Fukuda *et al.*, 2012). Found that SNP rs2028299 had a significant effect on the susceptibility of Japanese people to T2DM (Fukuda *et al.*, 2012).

To our knowledge, the role of the Gas6 and Ap3s2 genes in T2DM in the Han population has not been previously assessed. Given the apparent association between SNP rs8191974 and SNP rs2028299 with T2DM, we further investigated whether SNP rs8191974 and SNP rs2028299 are related to T2DM in Chinese people.

**Table 1. Clinical characteristics in patients and controls.**

	NGT	T2DM	P value
Sex (M/F)	568/404	612/384	0.1731
Age (years)	42.87±11.67	46.11±12.55	<0.0001
Height	1.69±0.08	1.68±0.08	0.0801
Weight	66.55±12.37	73.13±13.45	<0.0001
BMI	23.31±3.34	25.78±3.58	<0.0001
Waistline	81.25±10.84	93.49±10.44	<0.0001
Hipline	95.77±7.2	99.48±7.44	<0.0001
Waist-to-hip ratio	0.85±0.07	0.94±0.06	<0.0001
Systolic	121.24±15.08	130.17±17.5	<0.0001
Diastolic	79.21±9.64	84.64±11.17	<0.0001
Fasting glucose	4.82±0.33	10.03±3.41	<0.0001
TC	4.88±1.05	5±1.29	0.0289
TG	1.42±0.96	2.38±2.25	<0.0001
HDL	1.48±0.37	1.21±0.32	<0.0001
LDL	1.92±0.87	2.91±1.26	<0.0001
HOMA-IR	1.51±1.15	4.81±3.91	<0.0001
HOMA-β	104.78±74.62	38.42±37.51	<0.0001

## MATERIALS AND METHODS

**Study population.** All subjects were recruited from outpatient clinics of the Second Affiliated Hospital, Harbin Medical University, Heilongjiang, China. Basic parameters were collected from each subject, including name, age, gender, height, weight, waist circumference, hip circumference, blood pressure, plasma lipids, fasting

**Table 2. Correlation analysis of Gas6 rs8191974 and Ap3s2 rs2028299 alleles with T2DM.**

Gene	Allele	controls(972)	T2DM(996)	P <sup>a</sup>	OR <sup>a</sup> (95%CI)
Ap3s2	A	1573(80.92%)	1566(78.61%)	0.0725	1.1534(0.9870-1.3478)
	C	371(19.08%)	426(21.39%)		
Gas6	C	1465(75.36%)	1577(79.17%)	0.0044	0.8049(0.6931-0.9364)
	T	479(24.64%)	415(20.83%)		

**Abbreviations:** CI, confidence interval; OR, odds ratio. <sup>a</sup>Adjusted for age, gender and BMI.

**Table 3. Correlation analysis of Gas6 rs8191974 and Ap3s2 rs2028299 genotypes with T2DM.**

Gene	Genotype	Controls	T2DM	P <sup>a</sup>	OR <sup>a</sup> (95%CI)
Ap3s2	AA	637 (65.53%)	613 (61.55%)	0.1809	1.18 (0.98-1.43)
	CA	299 (30.76%)	340 (34.14%)		
	CC	36 (3.7%)	43 (4.32%)		
Ap3s2	AA	637 (65.53%)	613 (61.55%)	0.0661	1.19 (0.99-1.43)
	CC+CA	335 (34.47%)	383 (38.45%)		
	CC	550 (56.58%)	632 (63.45%)		
Ap3s2	CT	365 (37.55%)	313 (31.43%)	0.0078	0.75 (0.62-0.90)
	CC	550 (56.58%)	632 (63.45%)		
	TT	57 (5.86%)	51 (5.12%)		
Gas6	CC	550 (56.58%)	632 (63.45%)	0.0019	0.75 (0.63-0.90)
	TT+CT	422 (43.42%)	364 (36.55%)		

<sup>a</sup>Adjusted for age, gender and BMI.

blood glucose, homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA of beta-cell function (HOMA-β). We used the case control study methods to analyze the association between Gas6 gene rs8191974, Ap3s2 gene rs2028299 and T2DM. The case group included 1000 patients with T2DM, and the control group included 1000 healthy human subjects. Inclusion criteria for the control subjects were as follows: 1) Hemoglobin A1c level <6.0%; 2) fasting plasma glucose level <5.1 mmol/L; 3) no history of diabetes; 4) no family history of T2DM; 5) not taking drugs that affect lipid and carbohydrate exchange; and 6) no systemic diseases. Exclusion criteria for this study were as follows: 1) renal and hepatic failure; 2) cardiovascular disease; 3) acute diabetic complications; 4) malignant tumors, severe injury, infections, or other endocrine diseases; or 5) other types of diabetes.

**DNA extraction and genotype analysis.** DNA was obtained from blood samples using the TIANGEN whole blood DNA extraction kit and following the manufacturer's instructions. The quality of isolated genomic DNA was checked using agarose gel electrophoresis and quantitation was determined using spectrophotometry. The Gas6 gene SNP rs8191974 and Ap3s2 gene SNP rs2028299 genotyping was performed using commercial SNPscan Genotyping assays from Applied Biosystems Inc.

**Statistical methods.** Descriptive results of continuous variables are expressed as means ± standard error of the mean. Before statistical analysis was performed, normal distribution and homogeneity of variables was evaluated by using the Levene's test, and if necessary, a base logarithmic transformation was applied. The  $\chi^2$ -test was used to determine the genotype distributions for Hardy-Weinberg equilibrium and to compare the observed allele and genotype frequencies in patients with those in control subjects. Statistical significance was considered to be  $P < 0.05$ . Logistic regression analyses were performed with SPSS (Chicago, Illinois, USA; version 13.0) and the odds ratio (OR) and 95% confidence interval (CI) were calculated for each variant genotype compared to the homozygous wild-type genotype.

## RESULTS

### Subject Characteristics

There were four cases in the T2DM group and 28 cases in the control group without genotypes, so the final study included 996 T2DM patients and 972 control subjects.

Characteristics of the subjects are shown in Table 1. A slightly higher proportion of older subjects were observed among T2DM patients compared to controls, which may be due to a participation bias. In the T2DM group, BMI, waistline, hipline, waist-hip ratio, systolic and diastolic blood pressure, fasting glucose, total

**Table 4. Gender stratification analysis of Ap3s2 rs2028299 alleles/genotypes with T2DM.**

Allele/Genotype	NGT	T2DM	P <sup>a</sup>	OR <sup>a</sup> (95%CI)
<b>Male</b>				
A	373 (67.70%)	365 (62.50%)		1
C	178 (32.30%)	219 (37.50%)	0.022	1.26 (1.03-1.54)
AA	373 (65.67%)	365 (59.64%)		1
CA	178 (31.34%)	219 (35.78%)	0.0680	1.26 (0.98-1.61)
CC	17 (2.99%)	28 (4.58%)		1.68 (0.91-3.13)
AA	373 (65.67%)	365 (59.64%)	0.0325	1.29 (1.02-1.64)
CC+CA	195 (34.33%)	247 (40.36%)		
<b>Female</b>				
A	264 (68.57%)	248 (67.21%)		1
C	121 (31.43%)	121 (32.79%)	0.993	1.00(0.78-1.28)
AA	264 (65.35%)	248 (64.58%)		1
CA	121 (29.95%)	121 (31.51%)	0.7932	1.06 (0.78-1.45)
CC	19 (4.7%)	15 (3.91%)		0.84 (0.42-1.69)
AA	264 (65.35%)	248 (64.58%)	0.8224	1.03 (0.77-1.39)
CC+CA	140 (34.65%)	136 (35.42%)		

<sup>a</sup>Adjusted for age, gender and BMI. Data are presented as means  $\pm$  S.D.

cholesterol, triglycerides, low density lipoprotein cholesterol, HOMA IR and HOMA- $\beta$  were significantly higher than in the control group.

#### Correlation analysis of SNP rs8191974 and rs2028299 with T2DM

As displayed in Table 2, rs8191974 showed an allelic difference between cases and controls in the Chinese population, with an OR of 0.80 (95% CI:0.69–0.94,  $P=0.004$ ); however, SNP rs2028299 showed no significant difference between the A and C alleles in the two groups.

We further analyzed the effect of the genotypes of the two SNPs under a dominant genetic model by logistic tests (Table 3). The CT genotype and the dominant model displayed significant differences between cases and controls when compared with the CC genotype (CT *vs.* CC:  $P<0.05$ , OR:0.75, 95% CI:0.62–0.90; TT+CT *vs.* CC:  $P<0.05$ , OR:0.75, 95% CI:0.63–0.90).

In the male populations, the dominant model was significantly different when compared with the AA genotype (CC +CA *vs.* AA;  $P<0.05$ , OR:1.29, 95% CI:1.02–1.64; Table 4). In the female subjects, there were no differences in any genotype between the two groups (Table 4).

**Table 5. BMI stratification analysis of Ap3s2 rs2028299 genotypes with T2DM.**

Gene	Genotype	Control	T2DM	P <sup>a</sup>	OR <sup>a</sup> (95%CI)
<b>24<math>\leq</math>BMI&lt;28</b>					
Ap3s2	AA	292 (90.40%)	256 (64.42%)		1
	CA	18 (5.58%)	150 (31.84%)	0.0001	9.50(5.67-15.94)
	CC	13 (4.02%)	22 (3.75%)		1.93 (0.95-3.91)
	AA	292 (90.40%)	256 (64.42%)		
	CC+CA	31 (9.60%)	172 (35.58%)	0.0001	6.33 (4.17-9.61)

<sup>a</sup>Adjusted for age, gender and BMI.

#### Associations between SNPs and T2DM Characteristics

Subjects were further divided into groups with different genotypes and the main clinical and biological characteristics are summarized in Table 6. We found that weight, waist, hip and fasting glucose were significantly different for every rs8191974 genotype by analyzing the association between the genotypes and clinical phenotypes ( $P<0.05$ ). The CA heterozygote of rs2028299 was significantly associated with increased weight ( $P<0.05$ ).

#### DISCUSSION

To date, more than 120 genetic loci have been suggested to be associated with T2DM, or with glucose and insulin levels in the European and multi-ethnic populations (Sladek *et al.*, 2007; Zeggini *et al.*, 2008; Dupuis *et al.*, 2010; Imamura *et al.*, 2011; Lyssenko *et al.*, 2015). Of these, several loci have been shown to be associated with T2DM in different ethnic groups, whereas the remaining loci have not shown any significant effects in the ethnic populations other than those in the original reports. Although the power of these studies may be insufficient in some cases, genetic heterogeneity among different ethnicities may exist for some particular loci. In this study, we examined the association of SNP rs8191974 and rs2028299 with susceptibility to T2DM in a Chinese population and showed that they were significantly associated.

Previous studies indicated that the Gas6/TAM system was involved in the pathogenic mechanism for renal and cardiovascular complications associated with diabetes (Nagai *et al.*, 2003; Cavet *et al.*, 2008). Recent studies in animal models have shown that Gas6/TAM signaling plays an important role in pathophysiological mechanisms underlying obesity-related inflammation and insulin resistance (IR) (Augustine *et al.*, 1999). Hsieh *et al.*, had suggested that the Gas6 gene variants were associated with IR, although their effects on subsequent progression to T2DM were minimal in this study (Hsieh *et al.*, 2015). It is also important to mention that the Gas6 polymorphism has been associated with stroke (Muñoz *et al.*, 2004; Muñoz *et al.*, 2007). The Hsieh study conducted in Taiwan had shown that the Gas6 gene rs8191974 mutations reduced the risk of T2DM (Lee *et al.*, 2012). Likewise, our study found that the SNP rs8191974 T allelic gene is a protective factor in T2DM, consistent with the Taiwanese study (Lee *et al.*, 2012). Northern and southern Chinese have obviously different living environments and lifestyles. However,



Table 6. Correlation analysis of rs8191974 and rs2028299 genotypes and phenotypes in the T2DM group.

	rs2028299									
	TT	CT	CC	F	P	AA	CA	CC	F	P
Age (years)	45.22±14.05	43.91±12.01	44.8±12.17	1.3291	0.265	44.44±12.12	44.72±12.53	43.92±11.64	0.2009	0.818
Height	1.67±0.07	1.68±0.08	1.68±0.08	2.2316	0.1076	1.68±0.08	1.69±0.08	1.67±0.07	2.3539	0.0953
Weight	67.23±12.67	69.3±13.69	70.45±13.16	3.8831	0.0207	69.48±13.34	70.89±13.45	67.95±11.84	3.214	0.0404
BMI	23.98±3.46	24.42±3.84	24.7±3.59	2.7221	0.066	24.45±3.69	24.8±3.68	24.34±3.41	2.011	0.1341
Waistline	84.81±12.96	86.77±12.67	88.08±11.93	5.102	0.0062	87.02±12.42	88.35±12.03	86.89±11.56	2.5591	0.0776
Hipline	96.14±7.81	97.11±7.88	98.1±7.3	5.9878	0.0026	97.44±7.56	98.12±7.59	97.13±6.97	1.893	0.1509
Waist-to-hip ratio	0.88±0.08	0.89±0.08	0.9±0.08	2.568	0.0769	0.89±0.08	0.9±0.08	0.89±0.08	2.0252	0.1322
Systolic	126.14±18.51	124.77±17.03	126.3±16.73	1.7919	0.1669	125.47±17.03	126.32±16.68	125.94±17.79	0.5359	0.5852
Diastolic	81.47±11.75	81.34±10.37	82.35±10.91	2.0216	0.1327	81.88±10.74	81.9±10.86	83.61±10.84	0.9656	0.3809
Fasting glucose	7.33±3.39	7.06±3.33	7.7±3.69	6.8704	0.0011	7.42±3.58	7.53±3.54	7.55±3.61	0.2246	0.7988
TC	5.04±1.05	4.91±1.16	4.94±1.2	0.627	0.5343	4.96±1.16	4.91±1.22	4.89±1.06	0.4962	0.6089
TG	1.83±1.78	1.89±1.74	1.93±1.84	0.1868	0.8296	1.9±1.79	1.9±1.77	2.09±2.27	0.4182	0.6583
HDL	1.4±0.36	1.35±0.37	1.33±0.37	1.9041	0.1492	1.36±0.37	1.31±0.36	1.39±0.47	2.6867	0.1252
LDL	2.91±0.88	2.89±0.88	2.93±0.94	0.4139	0.6611	2.93±0.92	2.9±0.92	2.87±0.79	0.2474	0.7809
HOMA-IR	2.46±1.38	2.52±1.37	2.51±1.44	1.3152	0.0616	2.49±1.26	2.54±1.23	2.52±1.31	1.3261	0.0725
HOMA-β	68.25±12.57	67.36±11.48	68.13±11.52	1.4729	0.4729	67.83±13.41	67.48±12.46	67.57±12.36	1.4627	0.4627

Data are presented as means ±SD.

that SNP rs8191974 is associated with an increased risk of T2DM via these indicators. In recent years, increasing attention has been paid to the role of fattyacid toxicity in the pathogenesis of T2DM. We hypothesize that rs8191974 is likely to affect the risk of T2DM factors involving obesity and lipid metabolism in the pathogenesis of T2DM. This theory will require subsequent experimental verification.

The Ap3s2 protein is widely distributed in the islet and fat cells. A South Asian GWAS had shown that the Ap3s2 gene SNPrs2028299 had relatively strong links to T2DM (Kooner *et al.*, 2011). In addition, the association of rs2028299 and T2DM was examined in a Japanese population in which it was shown that the genetic risk score was significantly associated with T2DM (Fukuda *et al.*, 2012). Our study found that SNP rs2028299 allele C and dominant model CC+CA *vs.* AA were risk factors for T2DM in males, but we observed no association between SNP rs2028299 and T2DM in females. It may be that subject variation among male and female participants or differing levels of sex hormones caused false negative results.

In a subsequent analysis to determine the association of SNP rs2028299 with weight, we found that subjects with the CA genotype had greater weight among all T2DM patients. It has been previously reported that SNP rs2028299 was associated with increased patient BMI levels (Fukuda *et al.*, 2012), and studies have confirmed that excess weight or BMI can cause insulin resistance. Combining the results of our study and related literature reports (Kooner *et al.*, 2011; Fukuda *et al.*, 2012; van de Bunt *et al.*, 2013), we suggest that SNP rs2028299 may participate in the occurrence and development of T2DM in one of the following ways: 1) Disturbing the intracellular localization of the insulin receptor substrate to affect insulin function; 2) Altering the expression of microRNAs in islet cells to affect the secretion of insulin;

3) Since SNP rs2028299 is widely expressed in fat cells, its mutations may increase the BMI of T2DM patients, which can lower insulin sensitivity and indirectly cause insulin resistance; 4) SNP rs2028299 may affect nearby loci that are correlated with T2DM and thus indirectly influence the occurrence and development of T2DM.

## CONCLUSION

We have observed a significant association of Gas6 rs8191974 and Ap3s2 rs2028299 with type 2 diabetes in a Chinese population. Our results suggest that both SNPs are common T2DM susceptibility loci in differ-

the fact that both, our study and Lee *et al.* found that SNP rs8191974 was associated with T2DM, suggests that the contribution of genetic factors is greater than environmental factors in Chinese T2DM.

The molecular mechanisms by which the Gas6 gene participates in T2DM have not yet been elucidated. Lee *et al.* speculated that the Gas6 gene polymorphisms participated in the occurrence and development of T2DM by altering the function of the islet cells (Lee *et al.*, 2012). Among the T2DM group, we found that subjects with the rs8191974 CC genotype had higher glucose, weight, waistline and hipline values. It is well known that the three indicators of weight, waistline and hipline are commonly used measures of obesity, so it may be the case

ent ethnic groups. However, further functional studies will be required to elucidate the biological mechanisms underlying each locus which confer susceptibility to the disease.

### Ethical considerations

Ethical issues, including informed consent, plagiarism, misconduct, data fabrication and/or falsification, and double publication and/or submission, have been fully observed by the authors.

### Competing Interests

The authors have declared that no competing interests exist.

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