ALK7 Gene Polymorphism is Associated with Metabolic Syndrome Risk and Cardiovascular Remodeling

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Abstract

Background: Activin receptor-like kinase 7 (ALK7) is a type I receptor for the TGF-β superfamily and has recently been demonstrated to play an important role in the maintenance of metabolic homeostasis.

Objective: To investigate the association of the ALK7 gene polymorphism with metabolic syndrome (MetS) and cardiovascular remodeling in MetS patients.

Methods: The single nucleotide polymorphism rs13010956 in the ALK7 gene was genotyped in 351 Chinese subjects undergoing carotid and cardiac ultrasonography. The associations of the ALK7 gene polymorphism with the MetS phenotype, MetS parameters, and cardiovascular ultrasonic features were analyzed.

Results: The rs13010956 polymorphism in the ALK7 gene was found to be significantly associated with the MetS phenotype in females ($p < 0.05$) and was also significantly associated with blood pressure in the total ($p < 0.05$) and female populations ($p < 0.01$). Further analysis revealed that rs13010956 was associated with mean intima-media thickness of the carotid arteries in females ($p < 0.05$). After control for body mass index, blood pressure, fasting blood glucose, and triglycerides, rs13010956 was also found to be significantly associated with left ventricular mass index in the total ($p < 0.05$) and female populations ($p < 0.05$).

Conclusion: Our findings suggested that the ALK7 gene polymorphism rs13010956 was significantly associated with MetS risk in females and may be involved in cardiovascular remodeling in MetS patients. (Arq Bras Cardiol. 2013;101(2):134-140)

Keywords: Polymorphism, Genetic; Metabolic Syndrome; Ventricular Remodeling.

Introduction

Activin receptor-like kinase 7 (ALK7) is a type I receptor for a selected group of ligands in the transforming growth factor beta (TGF-β) superfamily, which includes Nodal, G-patch domain protein (GDP)-1, GDP-3, activin B, and activin AB[1-4]. Two classes of receptors are involved in the signaling cascades of the TGF-β superfamily, namely type I and type II receptors. Binding of ligands to type II receptors recruits and phosphorylates type I receptors at their glycine- and serine-rich domain[5] and subsequently induces an intracellular downstream signaling cascade[6]. To date, a total of seven type I receptors (ALK1–7) have been cloned from mammals[7]. ALK7, which was initially cloned from the rat brain[8,9], has been mapped to the gene locus 2q24.1-q3 in humans. Up to now, four ALK7 transcripts generated from alternative splicing of the ALK7 gene have been described[10,11].

Recently, several studies have focused on ALK7 function and suggested a role for ALK7 in the maintenance of metabolic homeostasis. ALK7 is expressed in several organs involved in metabolic regulation, including the pancreas and adipose tissue[8,9,12]. Reportedly, ALK7 induces apoptosis of pancreatic β-cells and β-cell lines via the activation of downstream pathways[13], and negatively regulates glucose-stimulated insulin release by β-cells[14]. Mutant mice lacking ALK7 developed an age-dependent syndrome involving progressive hyperinsulinemia, reduced insulin sensitivity, liver steatosis, impaired glucose tolerance, and islet enlargement[14]. Meanwhile, ALK7 was found to be a novel marker of adipocyte differentiation[15] and was involved in obesity[16]. Mutant mice lacking ALK7 showed reduced fat accumulation and partial resistance to diet-induced obesity[3]. In humans, ALK7 expression in adipose tissue was correlated with several measures of body fat, carbohydrate metabolism, and lipids, all of which are risk factors implicated in metabolic syndrome (MetS)[17].

MetS, which strongly contributes to the development of cardiovascular disease and type 2 diabetes mellitus,

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is a multifactorial disorder characterized by insulin resistance, obesity, hypertension, dyslipidemia, and glucose intolerance[18]. Given its function in metabolic homeostasis, ALK7 may also play an influential role in MetS pathogenesis. In this study, however, we investigated the association of ALK7 with MetS and related cardiovascular features at the genetic level and evaluated whether the ALK7 gene polymorphism contributed to MetS risk and cardiovascular remodeling.

Methods

Study population

The study population consisted of 351 unrelated Chinese subjects (182 with MetS and 169 control subjects without abnormalities), aged 24–85 years, who were recruited from Qilu Hospital of Shandong University (Shandong, China). MetS was defined according to the 2005 International Diabetes Federation (IDF) consensus worldwide definition[19]. Peripheral blood samples were collected in the morning after subjects had fasted for 12–14 h. Written, informed consents were obtained from all subjects before enrollment and the study protocol was approved by the institutional ethics committee of Shandong University.

Clinical measurements

Clinical and biochemical characteristics of the subjects were obtained. Height, weight, and waist and hip circumferences were measured by trained personnel, from which body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Systolic and diastolic blood pressures (SBP and DBP) were measured and laboratory measurements, including triglycerides (TG), fasting blood glucose (FBG) and others, were determined. Insulin resistance was assessed using the homeostasis model assessment equation[20]. Ultrasonography of the carotid arteries and the heart was performed by a trained clinical technician. Intima-media thickness (IMT) and left ventricular mass index (LVMI) were determined as previously described[21,22]. The early (E) and late (atrial - A) ventricular filling velocity ratio (E/A) determined by pulsed Doppler echocardiography, the E-A ratio (E'/A') determined by tissue velocity imaging, and the ratio of E velocity (E/E') determined by pulsed Doppler echocardiography to that by tissue velocity imaging were then calculated.

Single nucleotide polymorphism (SNP) selection and genotyping

The SNP rs13010956 in the ALK7 gene was selected for comparison. Genomic DNA was extracted from peripheral blood leukocytes according to a standard procedure and stored at -80°C until analyzed. Fragments containing rs13010956 were replicated by polymerase chain reaction (PCR). PCR products were visualized in GelRed-stained 2% agarose gel in 1× Tris-acetate-ethylenediaminetetraacetic acid buffer and then sent to the Sequencing Department of Shandong Academy of Agriculture Sciences (Shandong, China) for direct sequencing.

Statistical analyses

Statistical analyses were performed using SPSS ver. 17.0 statistical software (SPSS, Inc., Chicago, IL, USA). Normal distribution was tested using the Kolmogorov–Smirnov test. Comparisons of the clinical and biochemical characteristics between case and control groups were conducted using the *t*-test. The Hardy–Weinberg equilibrium and genotype distribution in case and control subjects were analyzed using the χ^2 test. Binary logistic regression analysis was performed, while adjusting for sex, age, and smoking, and presented as odds ratios (ORs; 95% confidence intervals [CIs]). The association between genotypes and continuous variables was assessed using the *t*-test. Ultrasound data between different genotypes were further compared by one-way analysis of covariance (ANCOVA). A p-value < 0.05 was considered statistically significant.

Results

Characteristics of the subjects

The clinical and biochemical characteristics of the study subjects are shown in Table 1. Except sex, age and smoking, there were significant differences in all variables between case and control subjects ($p < 0.001$ for all). We then separately studied these variables in male and female groups and found significant differences between cases and controls as well (data not shown).

Genotypic distribution of the ALK7 gene polymorphism

No departure from the Hardy–Weinberg equilibrium was observed for rs13010956. The genotypic distribution of rs13010956 is shown in Table 2, which was analyzed using the χ^2 test in the total, male, and female groups, respectively. As shown, the genotypic distribution was significantly different between cases and controls in the female group ($p = 0.009$).

Association of the ALK7 gene polymorphism with MetS risk

Next, we explored the association of rs13010956 with the MetS phenotype using binary logistic regression analysis adjusting for sex, age, and smoking. We found that rs13010956 significantly contributed to the MetS phenotype in females (Table 2). Females with the GG genotype had an increased risk for MetS compared to those with the AA and AG genotypes ($p = 0.015$). No association was observed in the total and male populations.

Then, we divided the population into subgroups by BMI (BMI < 25 for group 1, $25 \leq$ BMI < 30 for group 2, and BMI ≥ 30 for group 3) and WHR (group1, WHR ≤ 0.90 for males and WHR ≤ 0.85 for females; group 2, WHR > 0.90 for males and WHR > 0.85 for females), according to the World Health Organization recommendations. We evaluated the association of the ALK7 gene polymorphism with the MetS phenotype in each group, but found none ($p > 0.05$ for all).

Table 1 - Clinical and biochemical characteristics of the study population

Characteristics	Control (n=169)	Case (n=182)	p
Sex (male/female)	67/102	81/101	0.357
Smoking (Yes/No)	63/105	66/116	0.811
Age (years)	51.42 ± 9.29	53.31 ± 8.64	0.052
BMI (kg/m^2)	24.32 ± 2.88	29.08 ± 4.13	< 0.001
WC (cm)	84.09 ± 8.44	98.14 ± 10.10	< 0.001
WHR	0.86 ± 0.06	0.93 ± 0.06	< 0.001
SBP (mmHg)	115.37 ± 10.25	150.77 ± 22.34	< 0.001
DBP (mmHg)	75.45 ± 6.92	94.34 ± 13.84	< 0.001
TG (mmol/L)	1.04 ± 0.41	2.28 ± 1.32	< 0.001
TC (mmol/L)	4.58 ± 0.81	5.32 ± 1.10	< 0.001
HDL-C (mmol/L)	1.53 ± 0.35	1.23 ± 0.35	< 0.001
LDL-C (mmol/L)	2.87 ± 0.71	3.55 ± 0.93	< 0.001
FBG (mmol/L)	4.87 ± 0.57	6.59 ± 2.44	< 0.001
Insulin (uU/mL)	10.63 ± 4.77	20.58 ± 10.77	< 0.001
HOMA_IR	2.36 ± 1.24	6.12 ± 4.33	< 0.001
Maximum IMT (mm)	0.81 ± 0.81	1.19 ± 0.86	< 0.001
Mean IMT (mm)	0.54 ± 0.15	0.76 ± 0.16	< 0.001
LVMI (g/m^2)	78.18 ± 14.52	95.27 ± 21.50	< 0.001
E/A	1.21 ± 0.30	0.94 ± 0.23	< 0.001
E'/A'	1.53 ± 0.84	0.97 ± 0.39	< 0.001
E/ E'	9.38 ± 2.82	12.20 ± 4.96	< 0.001

Data are presented as means ±SD unless otherwise indicated. BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio ; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; FBG: fasting blood glucose; HOMA-IR: homeostasis model assessment for insulin resistance; IMT: intima-media thickness; LVMI: left ventricular mass index; E/A: E-A ratio determined by pulsed Doppler echocardiography; E'/A': E-A ratio determined by tissue velocity imaging; and E/E': the ratio of E velocity determined by pulsed Doppler echocardiography to that by tissue velocity imaging.

Table 2 - Genotypic Distribution of rs13010956 and its association with MetS risk

	Genotypic Distribution			Risk of MetS	
	Control (n)	Case (n)	p	OR (95%CI)	p
Total					
AA+AG	163	169		1	
GG	6	13	0.137	2.289 (0.843 - 6.218)	0.104
Male					
AA+AG	63	79		1	
GG	4	2	0.410	0.468 (0.082 - 2.661)	0.392
Female					
AA+AG	100	90		1	
GG	2	11	0.009#	6.949 (1.451 - 33.286)	0.015*

** p < 0.05, # p < 0.01; OR: odds ratio; CI: confidence interval.*

Association of the ALK7 gene polymorphism with MetS parameters

The association of rs13010956 with the MetS parameters was further analyzed in the total, male, and female populations, respectively. As shown in Table 3, rs13010956 was significantly associated with SBP in the total population ($p = 0.021$) and with SBP and DBP in the female population ($p < 0.001$ for both). In these groups, the GG genotype was significantly associated with increased blood pressure levels.

Association of the ALK7 gene polymorphism with cardiovascular remodeling

Next, we explored the association of rs13010956 with cardiovascular remodeling (Table 4) and found that rs13010956 was significantly associated with mean IMT in the female population ($p = 0.036$). On average, females with the GG genotype had a relatively larger IMT than those with AA and AG genotypes.

Furthermore, we performed one-way ANCOVA to control possible effects of confounding factors. After control for BMI, SBP, DBP, FBG, and TG, rs13010956 was found to be significantly associated with LVMI in the total and female populations ($p = 0.043$ and 0.045), respectively. None of the other ultrasound variables revealed a significant association with rs13010956.

Discussion

To our knowledge, the present study is the first to establish an association between the ALK7 gene polymorphism and MetS. We revealed that the ALK7 gene polymorphism rs13010956 was a risk factor for MetS in females and also significantly associated with cardiovascular remodeling in MetS patients.

Recently, ALK7 was shown to be involved in both insulin resistance and obesity in humans[17]. Reportedly, the loss of islet β-cells through apoptosis can lead to the onset of types 1 and 2 diabetes[23]. ALK7 can induce β-cell apoptosis via both small mothers against decapentaplegic (Smad)-dependent and Smad-independent downstream pathways[13]. Moreover, ALK7 also played an important role in the regulation of insulin secretion[4,14]. On the other hand, it was reported that ALK7 was also involved in obesity[16]. Mice lacking ALK7 were partially resistant to diet-induced obesity, had smaller adipocytes, and smaller epididymal fat pads[3]. We hypothesized that genetic variations at this locus could be associated with MetS and related cardiovascular features.

In this study, we found that the ALK7 gene polymorphism rs13010956 was significantly associated with the MetS phenotype. Logistic regression analysis showed that females with the GG genotype had almost a 7-fold higher risk for MetS compared to those with AA and AG genotypes. The interaction with sex was not pre-specified and the association of this polymorphism with MetS only in females remains unknown. In fact, some of our other results seem to be slightly opposite when comparing females to males, which seems particularly true when evaluating blood pressures and LVMI. Data have shown that adipose tissue and adipocytes display the highest ALK7 expression levels and that in obesity, ALK7 expression is decreased[17]. Women generally have a higher percentage of body fat than men and women store more fat in the gluteal-femoral region, whereas men store more fat in the visceral (abdominal) depot[24]. The IDF definition of MetS[19] emphasized the importance of abdominal obesity and Costa et al[25] reinforced the constant presence of abdominal

Table 3 - Association of rs13010956 with MetS parameters

	Total			Male			Female		
	AA+AG (n=332)	GG (n=19)	p	AA+AG (n=142)	GG (n=6)	p	AA+AG (n=190)	GG (n=13)	p
Age (years)	52.35 ± 9.08	53.05 ± 7.74	0.743	50.39 ± 9.78	51.00 ± 9.53	0.882	53.77 ± 8.27	54.00 ± 7.00	0.922
BMI (kg/m^2)	26.71 ± 4.35	27.49 ± 3.12	0.444	27.78 ± 4.69	26.95 ± 4.27	0.670	25.97 ± 3.95	27.74 ± 2.61	0.114
WC (cm)	91.21 ± 11.82	91.68 ± 9.14	0.864	96.63 ± 11.12	94.33 ± 13.54	0.624	87.50 ± 10.83	90.46 ± 6.62	0.333
WHR	0.89 ± 0.07	0.89 ± 0.06	0.675	0.93 ± 0.06	0.91 ± 0.06	0.421	0.87 ± 0.07	0.87 ± 0.05	0.673
SBP (mmHg)	132.78 ± 24.12	146.37 ± 33.98	0.021*	135.15 ± 24.53	125.00 ± 22.01	0.322	131.13 ± 23.75	156.23 ± 34.59	<0.001#
DBP (mmHg)	84.81 ± 14.27	90.89 ± 17.66	0.076	88.89 ± 14.67	82.50 ± 12.36	0.296	81.98 ± 13.30	94.77 ± 18.78	0.001#
TG (mmol/L)	1.66 ± 1.17	1.82 ± 1.13	0.568	1.83 ± 1.12	1.10 ± 0.35	0.115	1.55 ± 1.18	2.15 ± 1.22	0.076
TC (mmol/L)	4.96 ± 1.03	4.94 ± 1.22	0.931	4.88 ± 1.02	4.40 ± 0.83	0.263	5.02 ± 1.03	5.19 ± 1.32	0.578
HDL-C (mmol/L)	1.38 ± 0.37	1.32 ± 0.43	0.448	1.27 ± 0.34	1.34 ± 0.47	0.633	1.47 ± 0.38	1.31 ± 0.43	0.144
LDL-C (mmol/L)	3.21 ± 0.88	3.27 ± 1.07	0.780	3.15 ± 0.86	2.91 ± 0.82	0.498	3.26 ± 0.90	3.44 ± 1.16	0.488
FBG (mmol/L)	5.74 ± 1.97	5.87 ± 2.28	0.789	5.75 ± 1.74	4.93 ± 0.79	0.255	5.74 ± 2.13	6.30 ± 2.62	0.364
Insulin (uU/mL)	15.99 ± 9.98	14.60 ± 7.10	0.570	16.96 ± 11.94	13.54 ± 8.00	0.527	15.29 ± 8.25	15.04 ± 7.02	0.917
HOMA_IR	4.38 ± 3.82	3.84 ± 2.56	0.567	4.62 ± 4.32	3.09 ± 2.23	0.432	4.21 ± 3.42	4.16 ± 2.71	0.961

*Data are presented as means ± SD. * P < 0.05, # P < 0.01; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; FBG: fasting blood glucose; and HOMA-IR: homeostasis model assessment for insulin resistance.*

Table 4 - Association of rs13010956 with cardiovascular remodeling

	Total			Male			Female		
	AA+AG (n=332)	GG (n=19)	p	AA+AG (n=142)	GG (n=6)	p	AA+AG (n=190)	GG (n=13)	p
Maximum IMT (mm)	1.01 ± 0.87	0.98 ± 0.65	0.882	1.09 ± 0.94	0.85 ± 0.82	0.537	0.95 ± 0.81	1.05 ± 0.57	0.703
Mean IMT (mm)	0.65 ± 0.19	0.69 ± 0.21	0.345	0.69 ± 0.22	0.63 ± 0.32	0.552	0.62 ± 0.16	0.73 ± 0.12	0.036*
LVMI (g/m^2)	86.58 ± 20.26	82.01 ± 16.32	0.377	90.94 ± 21.61	76.25 ± 12.79	0.136	83.73 ± 18.86	84.63 ± 17.61	0.878
E/A	1.08 ± 0.30	1.00 ± 0.33	0.288	1.07 ± 0.28	1.00 ± 0.43	0.567	1.08 ± 0.31	0.99 ± 0.29	0.371
E'/A'	1.24 ± 0.69	1.31 ± 0.97	0.794	1.15 ± 0.50	1.43 ± 1.05	0.539	1.31 ± 0.79	1.24 ± 0.97	0.781
E/ E'	10.73 ± 4.26	11.46 ± 4.23	0.511	10.36 ± 4.37	8.95 ± 1.87	0.434	10.98 ± 4.19	12.96 ± 4.60	0.152
LVMI (g/m^2)†	86.46 ± 20.25	82.01 ± 16.32	0.043*	91.09 ± 21.66	76.25 ± 12.79	0.293	83.42 ± 18.72	84.63 ± 17.61	0.045*

*Data are presented as means ± SD. * P < 0.05; †LVMI value from ANCOVA, adjusted for BMI, SBP, DBP, FBG, and TG; IMT, intima-media thickness; LVMI, left ventricular mass index; E/A, E-A ratio determined by pulsed Doppler echocardiography; E'/A', E-A ratio determined by tissue velocity imaging; and E/E', the ratio of E velocity determined by pulsed Doppler echocardiography to that by tissue velocity imaging.*

obesity in the MetS phenotype. To further explore whether obesity can affect the ALK7-MetS association, we studied the association of the ALK7 gene polymorphism with MetS in subgroups divided by BMI and WHR, respectively, and found no association in any group. These results suggested that neither the amount nor the distribution of adipose tissue contributed to the diverse findings between the total, male, and female populations in our study. However, elucidation of the underlying mechanisms of these sexual differences will require further research.

Further analysis in our study revealed that the ALK7 gene polymorphism rs13010956 was also associated with MetS parameters. We found that the ALK7 gene polymorphism was primarily correlated with blood pressure, as little association was observed with body fat and carbohydrate and lipid metabolism. These results suggested that the GG genotype of rs13010956 might contribute to MetS risk for females mainly by affecting blood pressure levels, since no other MetS parameter seemed to be affected.

Furthermore, we also studied the association of the ALK7 gene polymorphism with echocardiographic parameters. Females with the GG genotype of rs13010956 had a higher mean IMT value than those with AA and AG genotypes. However, this association disappeared after controlling for BMI, SBP, DBP, FBG, and TG. This result suggested that rs13010956 might exert its effect on mean IMT only through these parameters. LVMI, on the other hand, was significantly correlated with rs13010956 in the ANCOVA analysis, suggesting that rs13010956 could affect LVMI independent of BMI, SBP, DBP, FBG, and TG. This finding was of particular significance. Assessment of left ventricular hypertrophy showed that LVMI was a predictor of myocardial and ventricular remodeling[26]. Our results showed that both blood pressure and LVMI were associated with rs13010956, suggesting a potential role of the ALK7 gene polymorphism in the early stages of diastolic heart failure. Previous studies have revealed the significance of ALK7 in cell apoptosis and proliferation[13,27,28]. However, whether the ALK7 gene polymorphism contributes to cardiac remodeling and heart dysfunction by playing a role in myocardial apoptosis and fibrosis needs to be determined in the future.

Conclusion

The current findings indicated that the ALK7 gene polymorphism was significantly associated with MetS in females and closely correlated with cardiovascular remodeling.

Author contributions

Conception and design of the research: Zhang W, Wang ZH, Zhong M, Tang MX; Acquisition of data: Zhang WC, Wang H; Analysis and interpretation of the data: Zhang WC, Lv RJ; Statistical analysis: Zhang WC, Shang YY; Obtaining funding: Zhang W, Zhong M, Tang MX; Writing of the manuscript: Zhang WC; Critical revision of the manuscript for intellectual content: Wang ZH, Zhang Y, Chen YG.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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