Association of gene polymorphisms in MYH11 and TGF-β signaling with the susceptibility and clinical outcomes of DeBakey type III aortic dissection

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Abstract
To investigate the association of myosin heavy chain protein 11 (MYH11) and transforming growth factor β signaling-related gene polymorphisms with the susceptibility of DeBakey type III aortic dissection (AD) and its clinical outcomes. Four single-nucleotide polymorphism (SNPs) (MYH11 rs115364997, rs117593370, TGFB1 rs1800469, and TGFBR1 rs1626340) were analyzed in patients with DeBakey III AD (173) and healthy participants (335). Gene–gene and gene–environment interactions were evaluated using generalized multifactor dimensionality reduction. The patients were followed up for a median of 55.7 months. MYH11 rs115364997 G or TGFBR1 rs1626340 A carriers had an increased risk of DeBakey type III AD. MYH11, TGFB1, TGFBR1, and environment interactions contributed to the risk of DeBakey type III AD (cross-validation consistency = 10/10, \(P = 0.001\)). Dominant models of MYH11 rs115364997 AG + GG genotype (HR = 2.443; 95%CI: 1.096–5.445, \(P = 0.029\)), TGFB1 rs1800469 AG + GG (HR = 2.303; 95%CI: 1.069–4.96, \(P = 0.033\)) were associated with an increased risk of mortality in DeBakey type III AD. The dominant model of TGFB1 rs1800469 AG + GG genotype was associated with an increased risk of recurrence of chest pain in DeBakey type III AD (HR = 1.566; 95%CI: 1.018–2.378, \(P = 0.041\)). In conclusions, G carriers of MYH11 rs115364997 or TGFB1 rs1800469 may be the poor prognostic indicators of mortality and recurrent chest pain in DeBakey type III AD. The interactions of gene–gene and gene–environment are associated with the risk of DeBakey type III AD.

Introduction
Aortic dissection (AD) is an acute disease with rapid progress and high mortality rates (Evangelista et al. 2018). Of all patients with acute AD, those with DeBakey type III AD and endovascular management had a better cumulative survival rate and lower in-hospital mortality (Booher et al. 2013). Medial degeneration of the aorta is the main pathological substrate for DeBakey type III AD (Piechota-Polanczyk et al. 2015). Medial (smooth muscle cells) SMCs phenotypic switching and systolic dysfunction driven by multiple gene mutations are the major pathogenesis (Takeda and Komuro 2019).

Myosin heavy chain protein 11 (MYH11) gene encodes smooth muscle myosin heavy chain (Utako et al. 2018). Myosin, as a specific contractile protein of SMCs, links with adhesion spot protein and constitutes the main component of the elastin-contractile unit of SMC. The elastin-contractile unit conducts the mechanical force between elastin fiber and SMCs, also the pressure-sensing device of the aortic wall (Karimi and Milewicz 2016). The aortic medial layer confers...
elastin and strength to the aortic wall and is composed of alternating layers of SMCs and elastic fibers. The SMC elastin-contractile unit is a structural unit that links the elastin fibers to the SMCs. Gene mutations in encoding proteins in this elastic-contractile unit result in aortic aneurysm or dissection. Previous studies have suggested that MYH11 genetic mutation causes familial thoracic aortic aneurysm and dissection (FTAAD) (Harakalova et al. 2013). MYH11 (IVS32 + 1G > A) mutation changes the structure of α-helix domain of the myosin heavy chain, which may destroy the elastin-contractile unit (Renard et al. 2013). The destroyed structure of the elastin-contractile unit leads to the dysfunction of smooth muscle contraction or the aortic pressure sensing, which can induce aortic diseases. However, only a few studies exist on the association between the association between MYH11 and sporadic AD.

The SMC phenotypic conversion from a contractile to a synthetic phenotype depends on transforming growth factor-β (TGF-β), which leads to the attenuation of smooth muscle-specific contractile signals (MYH11, ACTA2, etc.), thus promoting AD. TGF-β, a multifunctional cytokine, is necessary for vascular development that modulates the plasticity of SMC and maintaining the stability of vascular walls (Frismantiene et al. 2018). The medial SMCs of mature vessels keep quiescent and contractile, which is regulated by TGF-β signaling-induced differentiation of SMCs to maintain the elasticity and contractile function, and the interaction with extracellular matrix (Haize et al. 2018). However, the paradoxical activation of TGF-β signaling modulates the phenotype of SMCs from contractile to synthetic by regulating the expression of de-differentiation markers; promoting the proliferation and migration of SMCs, and rupture of elastic fibers. (Goumans and Dijke 2018; Gao et al. 2014; Li et al. 2014). Fujiwara et al. focused on a novel splice donor site variant in the TFGBR1 gene (IVS5 + 1G > A) causing a familial case of LDS (Fujiwara et al. 2018). Missense and truncating variants in the serine/threonine kinase domain induce LDS through the dominant negative effect. The deficiency of TGF-β signaling deteriorates the aorta causing aortic aneurysm/dissection (Hu et al. 2015), including Marfan syndrome and Loey-Dietz syndrome (Mizuguchi et al. 2004; Loey et al. 2005), by destroying the structure of the SMCs or extracellular matrix (Takeda and Komuro 2019). However, the suppression of the TGF-β signaling pathway also deteriorates the aorta. Yang P et al. (Yang et al. 2016) delete TGF-β type I receptor (Tgfr1) in SMCs of mice using an inducible Cre-loxP system, which rapidly resulted in their severe aortic aneurysm. Studies have demonstrated that the TGF-β signaling-related gene mutations lead to TGF-β vasculopathy of aortic diseases (Cario et al. 2018; Isselbacher et al. 2016). Therefore, the importance of TGF-β signaling is mainly associated with the smooth muscle contraction pathway of vascular diseases.

MYH11 and TGF-β pathway-related gene variations are involved in the occurrence of aortic diseases by affecting the structure and function of aortic SMCs. However, the interaction between MYH11 and TGF-β pathway-related genetic polymorphisms in DeBakey type III AD is controversial. Therefore, this study aims to explore the association of MYH11, TGFB1, and TGFB1R1 genetic polymorphisms, gene–gene, and gene–environment interaction with susceptibility and clinical outcome of DeBakey type III AD.

Material and methods

Participants

This study was approved by the ethics committee of the First Affiliated Hospital of Xinjiang Medical University and implemented following the Helsinki declaration. All participants provided informed consent.

All participants were from the First Affiliated Hospital of Xinjiang Medical University from January 2013 to December 2016. In this study, 173 patients with DeBakey type III AD were recruited as the case group. All these patients underwent thoracic endovascular aortic repair (TEVAR). From the health examination center of the same hospital, 335 normal participants without aortic disease by aortography or aortic CTA were included in the control group. Participants with coronary heart disease, cardiomyopathy, heart valve disease, congenital heart disease were excluded.

The information on their age, gender, history of hypertension, diabetes, BMI (body mass index), history of smoking, and drinking was collected. Then, we measured the levels of their blood urea nitrogen, creatinine, uric acid, glycosylated serum protein, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol.

SNP selection

Tag single-nucleotide polymorphism (SNPs) were screened according to Haplovie software version 4.2 and National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/SNP). The standard is minimum allele frequency ≥ 0.05 and R² ≥ 0.8, referencing data on the Han Chinese population in Beijing, China. The four tag SNPs selected were as follows: rs115364997 and rs117593370 of MYH11, rs1800469 of TGFB1, and rs1626340 of TGFB1R1.

DNA extraction and genotyping

The blood samples were collected using the standard venipuncture technique. The DNA was extracted from peripheral blood leukocytes using a whole-blood genome DNA
The SNPs genotyping was performed using chain reaction-restriction fragment length polymorphism analysis as described previously.

**End points**

Patients were followed up clinically for a median of 55.7 (47.6–57.9) months. The study was terminated in December 2019. The information was obtained from their inpatient or outpatient records or by telephone calls. The primary endpoint was death due to the recurrence of AD, and the secondary endpoint was hospitalization for chest pain recurrence.

**Statistical analysis**

Measurement data were shown as means ± standard deviation, and the differences between case and control participants were evaluated using an independent-sample t-test. The Hardy–Weinberg equilibrium and the frequency distribution of genotype and allele was tested using χ² test. The risks were expressed as odds ratio (OR) and 95% confidence interval (CI). The association of gene polymorphisms with survival outcomes and chest pain recurrence was performed by the Kaplan–Meier method, the log-rank test, and the Cox proportional hazards regression models. The risks were expressed as hazard ratio (HR) and 95%CI. SPSS software version 22.0 (SPSS Inc., USA.) was used for this analysis. The figures were made using GraphPad Prism 9.0 (GraphPad Software Inc., San Diego, CA, USA). Gene–gene and gene–environment interactions were analyzed using generalized multifactor dimensionality reduction (GMDR), as described previously (Xu et al. 2016). The best model was the one with the maximum values of cross-validation consistency (CVC) and the sign test, and P < 0.05.

**Results**

**Characteristic of participants**

The general characteristics of study participants are shown in Table 1. A total of 173 patients with DeBakey type III AD and 335 normal participants were enrolled in the study. The case group comprised 144 males and 29 females, with an average age of 51.54 ± 11.53 years. The control group comprised 193 males and 142 females, with an average age of 57.12 ± 11.39 years. Significant differences existed between the case and control groups in terms of systolic blood pressure (P < 0.001), diastolic blood pressure (DBP, P < 0.001), BMI (P < 0.001), white blood cell (P < 0.001) count, blood urea nitrogen level (P = 0.053), creatinine level (P = 0.003), uric acid level (P = 0.005), glucose level (P < 0.001), glycosylated serum protein level (P < 0.001), high-density lipoprotein cholesterol level (P < 0.001), hypertension (P < 0.001), diabetes (P = 0.035), smoking (P < 0.001), and drinking (P < 0.001). No significant difference existed between the case and control groups in terms of triglyceride (P = 0.854), total cholesterol (P = 0.935), and low-density lipoprotein cholesterol (P = 0.692).

| Table 1 | General characteristics between case and control subjects |
|-----------------|-----------------|-----------------|-----------------|
| Characteristics | Case (n = 173) | Control (n = 335) | P              |
| Age (years)     | 51.54 ± 11.53   | 57.12 ± 11.39   | < 0.001         |
| Male (male, %)  | 144 (83.2)      | 193 (57.6)      | < 0.001         |
| SBP (mmHg)      | 154.04 ± 30.37  | 126.23 ± 17.94  | < 0.001         |
| DBP (mmHg)      | 87.89 ± 18.31   | 77.19 ± 12.04   | < 0.001         |
| BMI (kg/m²)     | 27.0 ± 4.23     | 25.3 ± 3.33     | < 0.001         |
| WBC (10⁹/L)     | 11.59 ± 4.17    | 6.35 ± 1.87     | < 0.001         |
| BUN (mmol/L)    | 6.23 ± 3.56     | 5.42 ± 4.82     | 0.053           |
| Creatinine (μmol/L) | 92.1 ± 94.81  | 70.43 ± 19.69   | 0.003           |
| Uric acid (μmol/L) | 336.52 ± 108.16 | 309.45 ± 89.77  | 0.005           |
| Glucose (mmol/L)| 7.20 ± 2.40     | 5.52 ± 1.78     | < 0.001         |
| GSP (mmol/L)    | 2.01 ± 0.36     | 2.26 ± 0.51     | < 0.001         |
| Triglyceride (mmol/L) | 1.56 ± 0.88 | 1.54 ± 0.72     | 0.854           |
| Total cholesterol (mmol/L) | 4.21 ± 1.01 | 4.22 ± 1.07     | 0.935           |
| HDL-C (mmol/L)  | 1.05 ± 0.49     | 1.16 ± 0.45     | 0.015           |
| LDL-C (mmol/L)  | 2.62 ± 0.77     | 2.66 ± 1.19     | 0.692           |
| Hypertension (n, %) | 136 (78.61) | 143 (42.69)     | < 0.001         |
| Diabetes (n, %) | 10 (5.78)       | 27 (8.06)       | 0.035           |
| Smoking (n, %)  | 102 (58.96)     | 79 (23.58)      | < 0.001         |
| Drinking (n, %) | 89 (51.45)      | 56 (16.72)      | < 0.001         |

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, WBC: white blood cell, BUN: blood urea nitrogen, GSP: Glycosylated serum protein, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.

**Genotype and allele frequencies**

The genotype and allele distribution characteristics of SNPs in the case and control group are shown in Table 2. The genotype distributions of 4 SNPs for both case and control participants followed the Hardy–Weinberg equilibrium. The genotype frequencies of MYH11 rs115364997 (P = 0.044), TGFBR1 rs1626340 (P = 0.030) and the allele frequencies of MYH11 rs115364997 (P = 0.011) were different between the case and control groups. The genotype frequencies of MYH11 rs117593370, TGFBR1 rs1800469 and allele frequencies of MYH11 rs117593370, TGFBR1 rs1800469 and TGFBR1 rs1626340 did not differ between the case and control groups (P > 0.05).
Analysis of the association between genetic models and aortic dissection risk

We further assessed the association between genetic models and the risk of DeBakey type III AD. MYH11 rs115364997 dominant model AG + GG genotype (OR = 1.629; 95%CI: 1.077–2.462, \( P = 0.020 \)) and TGFBR1 rs1626340 dominant model GA + AA genotype (OR = 1.500; 95%CI: 1.032–2.181, \( P = 0.033 \)) were found to be the risk factors for AD. However, no difference between the case and control groups in genotypes of MYH11 rs117593370 (\( P > 0.05 \)), similar results in TGFB1 rs1800469 (\( P > 0.05 \)) (Table 3).

Gene–gene interaction

GMDR was used to analyze the interaction of the four SNPs (Table 4). The best model was the two-factor interaction model of MYH11 rs115364997 and TGFBR1 rs1626340 with the maximum CVC (10/10) after 1000 permutation tests, and the maximum values of sign test (10) and testing balance accuracy (0.5600), \( P = 0.0010 \).

Gene–environment interaction

GMDR was used to evaluate the association between gene–environment interaction and risk of AD (Table 5). The possible risk factors including the four SNPs, smoking, drinking, hypertension, type 2 diabetes, BMI ≥ 24 kg/m², and dyslipidemia were considered in the model.
The best model was the seven-factor interaction model of MYH11rs115364997, TGFB1rs1800469, TGFB1rs1626340, smoking, drinking, hypertension, and BMI ≥ 24 kg/m² with the maximum CVC (10/10) after 1000 permutation tests, and the maximum values of sign test (10) and testing balance accuracy (0.7673), \( P = 0.0010 \). The potential interaction of drinking and BMI ≥ 24 kg/m² with type III AD risk was discovered (CVC = 10/10; \( P = 0.0010 \)). In addition, we found that the two-factor, six-factor, and eight-factor models are also statistically significant (\( P = 0.0010 \)) with the maximum CVC (10/10). However, compared with the seven-factor model, these models had lower values of test balance accuracy.

**Associations of the SNPs with clinical outcomes in patients with DeBakey type III aortic dissection**

At the end of the study, 28 patients died due to the recurrence of AD, and 94 patients had recurrent chest pain. The association of tag SNPs and clinical outcomes in patients with DeBakey type III AD were assessed by the Kaplan–Meier method and the log-rank test (Fig. 1). Patients with these genotypes were associated with an increased mortality risk: dominant models of MYH11 rs115364997 AG + GG genotype (HR = 2.443; 95%CI: 1.096–5.445, \( P = 0.029 \)), TGFB1 rs1800469 AG+GG (HR = 2.303; 95%CI: 1.069–4.96, \( P = 0.033 \)), and additive models of MYH11 rs115364997 (AG vs. AA) (HR = 2.754; 95%CI: 1.187–6.391, \( P = 0.018 \)), TGFB1 rs1800469 (AG vs. AA) (HR = 2.893; 95%CI: 1.241–6.448, \( P = 0.013 \)). No statistically significant differences were found between the association of mortality risk and genetic models of MYH11 rs117593370 (\( P > 0.05 \)), similar results in TGFBR1 rs1626340 (\( P > 0.05 \)) (Table 6).

The same statistical methods were used in analyzing the risk of recurrence of chest pain. As a result, the TGFB1 rs1800469 dominant model AG + GG genotype was found to be associated with an increased risk of recurrence of chest pain (HR = 1.566; 95%CI: 1.018–2.378, \( P = 0.041 \)). No statistically significant differences were found between the association of mortality risk and other genetic models (\( P > 0.05 \)) (Table 7).

**Discussion**

AD is a complex multifactorial disease influenced by genetic and environmental factors (Ito et al. 2008; Mussa et al. 2016). The single-gene mutation is not the determinant of...
AD, while the interaction between multiple genes and environment may result in an increased risk of AD (Adam et al. 2018). Therefore, our study investigated MYH11 gene and TGF-β signaling-related gene of SMCs, environmental factors in DeBakey type III AD. We found that the genetic variation in MYH11 and TGF-β signaling, and environmental factors were associated with DeBakey type III AD and poor prognosis.

The present study indicated that MYH11 gene variations were associated with an increased risk DeBakey type III AD and poor prognosis. At the time of the submission of this manuscript, no report about rs115364997 and the susceptibility of AD existed. Rs115364997 is locate in the intron region of the MYH11 gene. Intrinsic mutations affect gene function and protein sequence mainly through alternative splicing (Jacob and Smith 2017). Several studies confirmed that mutations in MYH11 are identified in patients with aortic aneurysm/dissection (Renard et al. 2013; Pucci et al. 2020). Pucci L et al. reported that a missense mutation in the MYH11 gene (c.4658C > T, p.Thr1553Met) is associated with an unusual familial form of thoracic aortic aneurysm (Pucci et al. 2020). MYH11 gene mutation results in the defect of the contractile structure of SMCs, which further led to the contraction dysfunction of SMCs and decreased aortic compliance and elasticity. In our study, MYH11 rs115364997 gene polymorphism was associated with the susceptibility

Table 6 Association between the SNPs and mortality risk in DeBakey type III aortic dissection patients

| SNP         | Genetic Model | Genotype     | X²   | P      | HR    | 95%CI        |
|-------------|---------------|--------------|------|--------|-------|--------------|
| rs115364997 | Dominant      | (AG + GG)/AA | 4.770| 0.029  | 2.443 | 1.096–5.445  |
|             | Recessive     | GG/(AA + AG) | 0.036| 0.850  | 0.838 | 0.135–5.211  |
|             | Additive      | AA           | 1.000|        |       |              |
|             |               | AG           | 5.561| 0.018  | 2.754 | 1.187–6.391  |
|             |               | GG           | 0.029| 0.864  | 1.211 | 0.135–10.85  |
| rs117593370 | Dominant      | (CT + TT)/CC | 0.027| 0.869  | 0.891 | 0.227–3.505  |
|             | Recessive     | TT/(CC + CT) | 0.506| 0.477  | 0.361 | 0.022–5.986  |
|             | Additive      | CC           | 1.000|        |       |              |
|             |               | CT           | 0.031| 0.859  | 1.148 | 0.25–5.267   |
|             |               | TT           | 0.498| 0.481  | 0.361 | 0.212–6.133  |
| rs1800469   | Dominant      | (AG + GG)/AA | 4.544| 0.033  | 2.303 | 1.069–4.96   |
|             | Recessive     | GG/(AA + AG) | 0.134| 0.715  | 0.843 | 0.337–2.108  |
|             | Additive      | AA           | 1.000|        |       |              |
|             |               | AG           | 6.124| 0.013  | 2.893 | 1.241–6.448  |
|             |               | GG           | 0.812| 0.368  | 1.810 | 0.498–6.585  |
| rs1626340   | Dominant      | (GA + AA)/GG | 0.440| 0.507  | 0.771 | 0.358–1.662  |
|             | Recessive     | AA/(GG + GA) | 0.689| 0.406  | 1.603 | 0.526–4.888  |
|             | Additive      | GG           | 1.000|        |       |              |
|             |               | GA           | 0.895| 0.344  | 0.671 | 0.293–1.534  |
|             |               | AA           | /    | /      | /     | /             |
of DeBakey type III AD. In addition, Larson et al. (Larson et al. 2020) found that the MYH11 gene mutation was associated with patent ductus arteriosus and intracranial artery disease, indicating that MYH11 played a key role in maintaining the stability of vessel walls. In addition, Larson et al. (Norifumi et al. 2018) found that MYH11 gene mutation was associated with patent ductus arteriosus and intracranial artery disease, indicating that MYH11 played a key role in maintaining the stability of vessel walls. Mutations in the MYH11 gene resulted in abnormal structure or function of myosin, which, in turn, led to smooth muscle contraction dysfunction and impaired vascular stability.

In this study, we found that the TGFBR1 and TGFB1 gene variants were associated with DeBakey type III AD and poor prognostic risks. Previous studies suggested that patients with FTAAD and Marfan syndrome with TGFBR1 mutation have low expression of smooth muscle contractile protein (Norifumi et al. 2018; Franken et al. 2015); TGFBR1-deficient mice rapidly developed severe aneurysmal degeneration, with 100% penetrance of ascending thoracic aortas (Yang et al. 2016). In a UK cohort study, the TGFBR1 rs1626340 AA genotype was found to have a higher proportion of abdominal aortic aneurysm (Thompson et al. 2010). Genetic variations in TGFBR1 rs1626340 were also associated with abdominal aortic aneurysm (Baas et al. 2010) and intracranial aneurysm (Ruigrok et al. 2012) in the Dutch population. Our results showed that carriers of TGFBR1 rs1626340 A allele, but not TGFB1 rs1800469 alleles or genotypes, were likely to have a higher risk of DeBakey type III AD. Zuo et al. (Zuo et al. 2015) demonstrated that the recessive model and additive model of rs1800469, but not rs1626340 genotypes or genetic models, were related to abdominal aortic aneurysm. This might be due to the difference in people’s living environment. Furthermore, the Kaplan–Meier analysis showed that carriers of the AG genotype of the dominant model of TGFB1rs1800469 had an increased risk of death and chest pain recurrence, which might be related to the continuous progression of AD. A multicenter study found that patients with a TGFBR1 mutation have an 80% survival rate at 60 years and a 23% risk of AD (Jondeau et al. 2016). However, evidences for the association of these gene and the outcomes of patients with DeBakey type III AD undergoing TEVAR remain lacking before the submission of this manuscript.

In addition, as the results of GMDR analysis, the interactions between MYH11rs115364997, TGF-ß signaling-related genetic polymorphism, and environmental factors promoted type III AD. The study of Zuo et al. suggested (Franken et al. 2015) that interactions between TGFB1 gene polymorphism and environmental factors promoted abdominal aortic aneurysm, which was similar to the results of this study. TGF-ß combines with the TGF-ß receptor catalyzes the phosphorylation of the Smad2/3 molecule and its translocation to the nucleus, which drives the SMC gene (e.g., SMMHC) expression (Wang et al. 2015). MYH11 gene mutation will result in an incorrect assembly of the myosin filaments, leading to defects in the assembly of fibronectin fibrils, making TGF-ß signaling

| SNP          | Genetic Model | Genotype     | $X^2$ | $P$  | HR        | 95% CI       |
|--------------|--------------|--------------|-------|------|-----------|-------------|
| rs115364997  | Dominant     | (AG + GG)/AA | 0.056 | 0.813| 1.054     | 0.679–1.638 |
|              | Recessive    | GG/(AA + AG)| 0.016 | 0.901| 0.945     | 0.387–2.304 |
|              | Additive     | AA           | 0.000 | 1.000|           |             |
|              |              | AG           | 0.084 | 0.772| 1.072     | 0.671–1.714 |
|              |              | GG           | 0.013 | 0.910| 0.949     | 0.384–2.351 |
| rs117593370  | Dominant     | (CT + TT)/CC | 0.158 | 0.691| 1.201     | 0.488–2.953 |
|              | Recessive    | TT/(CC + CT)| 1.101 | 0.294| 0.360     | 0.054–2.425 |
|              | Additive     | CC           | 1.000 |      |           |             |
|              |              | CT           | 0.919 | 0.338| 1.627     | 0.601–4.418 |
|              |              | TT           | 1.100 | 0.294| 0.360     | 0.534–2.428 |
| rs1800469    | Dominant     | (AG + GG)/AA | 4.165 | 0.041| 1.566     | 1.018–2.378 |
|              | Recessive    | GG/(AA + AG)| 1.556 | 0.212| 0.731     | 0.447–1.196 |
|              | Additive     | AA           | 1.000 |      |           |             |
|              |              | AG           | 7.912 | 0.005| 1.949     | 1.226–3.100 |
|              |              | GG           | 0.005 | 0.943| 1.023     | 0.549–1.907 |
| rs1626340    | Dominant     | (GA + AA)/GG | 1.162 | 0.281| 0.790     | 0.514–1.213 |
|              | Recessive    | AA/(GG + GA)| 0.376 | 0.540| 1.220     | 0.647–2.300 |
|              | Additive     | GG           | 1.000 |      |           |             |
|              |              | GA           | 1.715 | 0.190| 0.739     | 0.470–1.612 |
|              |              | AA           | 0.035 | 0.852| 1.064     | 0.554–2.043 |
more prone to activation (Renard et al. 2013). In addition, studies have shown that uncontrolled hypertension (Howard et al. 2013; Bossone et al. 2018), smoking, drinking, obesity, and hyperlipidemia are the risk factors for AD (Feldo et al. 2015; Yoshiyama et al. 2014; Kim et al. 2015; Zhu et al. 2019). Our results showed that patients with a history of hypertension had a higher risk of DeBakey type III AD (OR = 3.557). Nicotine has already been reported to promote SMC transform from the contractile type to synthetic-like type (Yoshiyama et al. 2014), causing abnormal proliferation of SMCs to produce inflammatory reactions and other effects (Zhu et al. 2019). Ethanol consumption may reduce the vasodilation caused by adrenomedullin, leading to vascular dysfunction and hypertension (Hipólito et al. 2011).

Limitations of this study: First, the pathogenesis of AD is multifactorial, and hence more AD-related loci or other signaling pathways should be discussed. Second, mechanism underlying on protein expression or cell morphology of AD needs to be studied. Third, the sample size is small, and participants were selected from a single center. Therefore, large-scale population studies should be designed.

Conclusions

MYH11 rs115364997 and TGFB1 rs1800469 genetic polymorphisms are associated with the increased risks of DeBakey type III AD. The interaction between MYH11, TGF-β signaling-related genetic polymorphisms, and environmental factors may accelerate the progression of DeBakey type III AD. G allele in MYH11 rs115364997 or TGFB1 rs1800469 may be the prognostic indicators for DeBakey type III AD, especially in mortality and recurrence of chest pain.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest All authors have declared no conflict of interest.

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