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

Background: Myosin heavy chain 11 (MYH11) and transforming growth factor-β (TGF-β) signaling-related genes as the regulation of the structure and function of vascular smooth muscle cells (VSMCs) play a key role in the pathogenesis of aortic dissection (AD). This study aims to investigate the association of MYH11 and TGF-β signaling-related gene polymorphisms with the susceptibility of DeBakey type III AD and its clinical outcomes.

Methods: A total of 159 patients with DeBakey Ⅲ AD and 305 healthy subjects were enrolled in this study. 4 SNPs (MYH11 rs115364997, rs117593370, TGFB1 rs1800469 and TGFBR1 rs1626340) were selected and analyzed. GMDR was used to evaluate gene-gene and gene-environment interactions. Patients were followed up for a median of 55.7 months.

Results: MYH11 rs115364997 G carriers (OR = 1.629; 95%CI: 1.077-2.462, *P* = 0.020) or TGFBR1 rs1626340 A carriers (OR = 1.500; 95CI: 1.032-2.181, *P* = 0.033) had a higher risk of DeBakey type Ⅲ AD. MYH11, TGFB1, TGFBR1, and environment interactions are contribute to DeBakey type Ⅲ AD risk (CVC=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 a higher risk of mortality in DeBakey type III AD. TGFB1 rs1800469 dominant model AG+GG genotype was associated with a higher risk of recurrence of chest pain in DeBakey type III AD (HR = 1.566; 95%CI: 1.018-2.378, *P* = 0.041).

Conclusions: This study indicated that variations of MYH11 rs115364997 and TGFBR1 rs1626340 are associated with genetic predisposition of DeBakey type III AD. 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 [1]. In the natural course, the mortality rate is as high as 50% within 48 hours [2]. The main pathological basis of AD is the degenerative change in the medial layer of the aorta [3]. The abnormal phenotypic transformation and systolic dysfunction of vascular smooth muscle cells (VSMC) in the medial layer of the aorta driven by multiple gene mutation are the main pathogenesis of AD [4,5].

Myosin heavy chain protein 11 (MYH11) gene encodes smooth muscle myosin heavy chain [6]. Myosin, as a specific contractile protein of SMCs, links with adhesion spot protein and constitutes the main component of elastin-contractile unit of SMC. Elastin-contractile unit conducts the mechanical force between elastin fiber and VSMCs, and it is also the micro-unit of pressure sensing device of aortic wall [7]. The elastin-contractile unit in the SMC plays a role in connecting the elastic fibers outside the cell and the contraction skeleton inside the cell. Mutations in genes encoding structural or functional proteins in this

elastic-contractile unit can cause aortic aneurysm or dissection. Previous studies suggested that MYH11 genetic mutation causes familial thoracic aortic aneurysm and dissection (FTAAD) [8]. MYH11[9] (IVS32+1G>A) mutation affected the classical splicing site sequence causing the conformational change of α-helix domain of myosin heavy chain, and damaging the movement function of myosin. The destruction of elastin-contractile unit structure of smooth muscle leads to the abnormal contraction function of smooth muscle or the pressure sensing function of aorta, which can induce aortic diseases. However, there are few studies on MYH11 genetic and sporadic aortic dissection.

Transforming growth factor-β (TGF-β) is a multi-functional cytokine that is crucial for vascular development, and regulates VSMC plasticity in mature and to maintain the stability of arterial walls [10]. The SMCs are in a static non-migration state in normal, with the contractile phenotype dominant, and TGF-β signaling induces differentiation in VSMC and regulates the interaction of cells with extracellular matrix [11]. However, excessive TGF-β signaling affects the structure of the smooth muscle in the medial layer of the aorta, then promotes aortic aneurysm/dissection, including Marfan syndrome and Loeys-Dietz syndrome. The paradoxical upregulation of TGF-β signaling induces the phenotypic transformation of VSMCs from contractile type to syncytial type by regulating the expression of differentiation markers of VSMCs [12,13]. This leads to the proliferation and migration of SMC, a large amount of extracellular matrix secretion and synthesis, and the elastic fiber ruptured [14]. Previous studies suggested that mutations in genes encoding various components of the TGF-β signaling cascade leads to TGF-β vasculopathies of aortic diseases [15,16]. Yang P et al. [17] used an inducible Cre-loxP system driven by a MYH11 promoter to delete TGF-β type I receptor (*Tgfbr1)* in SMCs, the mice rapidly formed serious aortic dissection. Therefore, the importance of TGF-β signaling in vascular diseases is mainly reflected in smooth muscle contraction pathway.

MYH11 and TGF-β pathway-related gene variations are involved in the occurrence of aortic diseases by affecting the structure and function of aortic SMC. 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 TGFBR1 genetic polymorphisms, gene-gene and gene-environment interaction with susceptibility and clinical outcome of Debakey type Ⅲ AD.

Material And Methods

Subjects

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

All subjects 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 case group. All these patients received thoracic endovascular aortic repair (TEVAR) and continued treatment after surgery. 335 normal subjects from health examination center of the same hospital as control group. The

information of all subjects was counted about age, gender, history of hypertension, diabetes, coronary heart disease, cerebrovascular disease, heart valve disease, BMI (body mass index), history of smoking and drinking. Then, we measured their white blood cell, blood urea nitrogen, creatinine, uric acid, glycosylated serum protein, triglyceride, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol.

SNP selection

Tag SNPs were screened according to Haploview 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 $R^2 \geq 0.8$, referencing data on the Han Chinese population in Beijing, China. Four tag SNPs were selected, rs115364997 and rs117593370 of MYH11, rs1800469 of TGFB1, and rs1626340 of TGFBR1.

DNA extraction and Genotyping

Blood samples were collected using the standard venipuncture technique. DNA was extracted from peripheral blood leukocytes using a whole blood genome DNA extraction kit (Beijing BiotekeCo. Ltd. Beijing, China). 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 (47.6-7.9) months. The study was terminated in December 2019. The information was obtained from their inpatient or outpatient records or by telephone calls. The primary end point was death due to recurrence of aortic dissection, and the secondary end point was hospitalization for chest pain recurrence.

Statistics

Measurement data were shown as means ± standard deviation, and the differences between case and control subjects were evaluated by independent-sample t-test. Hardy-Weinberg equilibrium, frequency distribution of genotype and allele was tested by $\chi 2$ test. The risks were expressed by odds ratio (OR) and 95% confidence interval (CI). The association of gene polymorphisms with survival outcomes and chest pain recurrence were performed by the Kaplan-Meier method, the log-rank test, univariate or multivariate Cox proportional hazards regression models. The risks were expressed by 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 was analysis by generalized multifactor dimensionality reduction (GMDR), as described previously [18]. The best model is defined as the model with the maximum values of cross validation consistency (CVC) and the sign test, and $P < 0.05$.

Results

1 Characteristics of participants

The General characteristics of study participants were shown in Table 1. A total of 173 patients with DeBakey type III AD and 335 normal subjects were enrolled in the study. There were 144 males and 29 females in case group, with an average age of 51.54 ± 11.53 years. In control group, there were 193 males and 142 females, with an average age of 57.12 ± 11.39 years. There were significant differences between the case and control groups: systolic blood pressure (SBP, $P < 0.001$)，diastolic blood pressure (DBP, $P < 0.001$), body mass index (BMI, $P < 0.001$), white blood cell (WBC, $P < 0.001$), blood urea nitrogen ($P = 0.053$), creatinine ($P = 0.003$), uric acid ($P = 0.005$), glucose ($P < 0.001$), glycosylated serum protein (GSP, $P < 0.001$), high density lipoprotein cholesterol ($P < 0.001$), hypertension ($P < 0.001$), diabetes ($P = 0.035$), smoking ($P < 0.001$) and drinking ($P < 0.001$). There were not significantly different between case and control groups including triglyceride ($P = 0.854$), total cholesterol ($P = 0.935$), low density lipoprotein cholesterol ($P = 0.692$).

2 The genotype and allele frequencies

The genotype and allele distribution characteristics of SNPs in case and control group were shown in Table 2. The genotype distributions of 4 SNPs for both case and control participants were in accordance with 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 difference between case and control group. The genotype frequencies of MYH11 rs117593370, TGFB1 rs1800469, allele frequencies of MYH11 rs117593370, TGFB1 rs1800469 and TGFBR1 rs1626340 did not differ between the case and control groups ($P > 0.05$).

3 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; 95CI: 1.032-2.181, $P = 0.033$) were found to be the risk factors for AD. But there was no difference on genotypes of MYH11rs117593370, TGFB1rs1800469 ($P > 0.05$) (Table 3).

4 Gene-gene interaction

GMDR was used to analyze the interaction of the four SNPs (Table 4). The best model is 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), $P = 0.0010$.

5 Gene-environment interaction

GMDR was used to analyze the association between gene-environment interaction and AD risk (Table 5). Possible risk factors including the four SNPs, smoking, drinking, hypertension, type 2 diabetes, BMI ≥ 24kg/m^2 and dyslipidemia were considered in the model. The best model is the seven-factor interaction model of MYH11rs115364997, TGFB1rs1800469, TGFBR1rs1626340, smoking, drinking, hypertension, BMI ≥ 24kg/m^2 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 ≥ 24kg/m^2 on 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) and maximum cross-validation consistency (10/10). However, compared with the seven-factor model, these models have lower values of test balance accuracy.

5 Associations of 4 SNPs with clinical outcomes in Debakey type Ⅲ aortic dissection patients

At the end of the study, a total of 28 patients died of recurrence of aortic dissection, and 94 patients had recurrent chest pain. The association of Tag SNPs and clinical outcomes in Debakey type Ⅲ aortic dissection patients were assessed by Kaplan-Meier method, the log-rank test (Figure 1). Patients with these genotypes are associated with a higher 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 differences were found between mortality risk and genetic models of MYH11 rs117593370, TGFBR1 rs1626340 (P > 0.05) (Table 6).

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

Discussion

Aortic dissection is a complex multifactorial disease influenced by genetic and environmental factors [19,20]. Single gene mutation is not the determinant of AD, while interaction of multiple genes and environment may result in a higher risk of AD [21]. Therefore, MYH11 and TGF-β pathway-related gene about structure and function of SMCs were discussed in this study to assessing whether genetic variation, environmental factors and their interaction are associated with the risk of Debakey type III AD and poor prognosis.

The present study indicates that gene variations of MYH11 was associated with risk of Debakey type Ⅲ AD and high mortality. The mutation site of MYH11 rs115364997 located in the intron region. Recent studies [22] indicate that mutations in some intron regions are mainly involved in expression regulation and selective splicing, mutations in different splicing sites cause mRNA shearing Cleavage leads to the

change of protein sequence and function. Previous studies suggested that mutations in MYH11 are identified in patients with aortic aneurysm/dissection [9]. This mutation result in a defective contractile apparatus and the proliferation of SMCs that do not produce contractile proteins in the aortic media. Then, it further leads to the contraction dysfunction of SMCs and lower the reduction of aortic compliance and elasticity. In addition, Larson et al. [23] found that MYH11 gene mutation is also associated with patent ductus arteriosus and intracranial artery disease，which shown that MYH11 plays a key role in maintaining the stability of blood vessel walls. Mutations in the MYH11 gene results in abnormal structure or function of myosin, which in turn leads to smooth muscle contraction dysfunction and impaired vascular stability.

In this study, we found that the TGFBR1 and TGFB1 gene variants were associated with the risk of Debakey type Ⅲ AD and poor prognostic risks, respectively. Previous studies suggested that FTAAD and Marfan syndrome patients with TGFBR1 mutation have low expression of smooth muscle contractile protein [24,25]; TGFBR1 deficiency mice rapidly formed serious aortic dissection [17]. In an UK cohort study, the TGFBR1 rs1626340 AA genotype was found to have a higher proportion of abdominal aortic aneurysms [26]. And genetic variations in TGFBR1 rs1626340 are also associate with abdominal aortic aneurysm in a Dutch population[27] and intracranial aneurysm [28]. According to our results, that carriers of the TGFBR1 rs1626340 A allele, but not TGFB1 rs1800469 alleles or genotypes, were likely to a higher risk of DeBakey type III aortic dissection. On the contrary, Zuo et al [29] have demonstrated that the recessive model and additive model of TGFB1 rs1800469 are related to abdominal aortic aneurysm, but not TGFBR1 rs1626340 genotypes or genetic models. Therefore, the dysfunction of TGF-β signaling transduction may lead to aortic aneurysm/dissection through different molecular processes. Furthermore, Kaplan-Meier analysis from present study indicate that carriers of the AG genotype of the dominant model of TGFB1rs1800469 have a higher risk of death and chest pain recurrence, which may be related to the aortic dilation and the continuous progression of aortic dissection. A meta-analysis demonstrated a significant association of the latent TGF-β binding protein 4 (LTBP4) 21011 A > T genotype and abdominal aortic aneurysms growth [26]. A multicenter from around the world study found that patients with a TGFBR1 mutations have 80% survival rate at 60 years, and 23% aortic dissection risk [30]. However, there has been no study other than ours on the association between TGF-β signaling-related genetic polymorphism and aortic dissection outcomes after surgery.

In addition, GMDR analysis shown that there were interactions between MYH11rs115364997, TGF-β related-gene polymorphism and environmental factors, affecting AD. The results of Zuo et al. [29] about TGFB1 gene polymorphism and environmental factors interactions worked together in abdominal aortic aneurysm risk, which are similar in this study. TGF-β signaling is found in non-syndromic aortic disease caused by MYH11 mutations and undefined etiology[31].TGF-β causes the contraction of smooth muscle cells that is shown by continuously increasing the level of related contractile proteins (including MYH11). In turn, mutations of the MYH11 may also be associated with upregulation of TGF-β signaling, which is implicated in Marfan syndrome and TAA formation. MYH11 is regulated by Smads, a downstream signal of TGFBRs. Mutations in MYH11 will lead to abnormalities in myosin, leading to defects in the assembly of fibronectin fibrils on the cell surface. This in turn causes fibrin-1 to assemble into microfibrils making

TGF-β signaling easier to activate and leading to an increase in the number of nuclear phosphorylated Smad2[15]. In addition, studies have shown that smoking, drinking, obesity, and hyperlipidemia are the risk factors of AD [32-34]. Nicotine in tobacco stimulates blood vessels, causing abnormal proliferation of smooth muscle cells to produce inflammatory reactions and other effects, leading to the formation of aortic dissection [35]. Ethanol consumption may reduce the vasodilation caused by Adrenomedullin, leading to vascular dysfunction and hypertension [36].

Limitations of this study: aortic dissection is a polygenic genetic disease regulated by multiple signaling pathway, more genes on other signaling pathways should be discussed. Secondly, it is necessary to study the mechanism of protein or cells aspects in AD patients. Third, the subjects in this study come from the same hospital, and may have selection bias, which could not better represent the general population.

Conclusions

According to our results, MYH11 rs115364997 and TGFBR1 rs1626340 SNPs are associated with genetic predisposition of DeBakey type III AD. MYH11 rs115364997 and TGFB1 rs1800469 genetic polymorphisms maybe a prognostic indicator, especially in motility and recurrence of chest pain for DeBakey type III aortic dissection. The interaction between MYH11, TGF-β pathway-related genetic polymorphisms and environmental factors may associated with DeBakey type III aortic dissection.

Declarations

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Not available

Authors' contributions

YM and XM designed the work and revised the manuscript; YC, QY, PJ and LS collected all clinical data and participated in conceiving the work; YC and QY drafted and revised the manuscript. The authors have approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University.

Consent for publication

All participants consented to the publication of their data.

Competing interests

All authors have declared no conflicts of interest.

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Tables

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/m^2)	27.0±4.23	25.3±3.33	<0.001
WBC (10^9/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 (umol/L)	92.1±94.81	70.43±19.69	0.003
Uric acid (umol/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.

Table 2 Description for genotype and allele frequencies in case and control group

SNP	Genotype/Allele	Case, n (%)	Control, n (%)	*P*
rs115364997	AA	119(68.8)	262(78.2)	**0.044**
	AG	47(27.2)	67(20.0)	
	GG	7(4.0)	6(1.8)	
	A	285(82.4)	591(88.2)	**0.011**
	G	61(17.6)	79(11.8)	
rs117593370	CC	159(91.9)	316(68.8)	0.577
	CT	11(6.4)	15(27.2)	
	TT	3(1.7)	4(4.0)	
	C	329(95.1)	647(96.6)	0.250
	T	17(4.9)	23(3.4)	
rs1800469	AA	61(35.3)	101(30.1)	0.466
	AG	78(45.1)	158(47.2)	
	GG	34(19.7)	76(22.7)	
	A	200(57.8)	360(53.7)	0.216
	G	146(42.2)	310(46.3)	
rs1626340	AA	23(13.3)	52(15.5)	**0.030**
	GA	84(48.6)	122(36.4)	
	GG	66(38.2)	161(48.1)	
	A	130(37.6)	226(33.7)	0.224
	G	216(62.4)	444(66.3)	

Table 3 Analysis of the association between genetic models and aortic dissection risk

SNP	Genetic Model	Genotype	OR	95%CI	*P*
rs115364997	Dominant	(AG+GG)/AA	1.629	1.077-2.462	**0.020**
	Recessive	GG/(AA+AG)	2.312	0.765-6.990	0.127
	Additive	AA	1.000		
		AG	1.544	1.003-2.377	**0.047**
		GG	2.569	0.845-7.808	0.086
rs117593370	Dominant	(CT+TT)/CC	1.464	0.716-2.997	0.294
	Recessive	TT/(CC+CT)	1.46	0.323-6.599	0.621
	Additive	CC	1.000		
		CT	1.457	0.654-3.247	0.354
		TT	1.491	0.330-6.741	0.602
rs1800469	Dominant	(AG+GG)/AA	0.792	0.537-1.170	0.241
	Recessive	GG/(AA+AG)	0.834	0.529-1.312	0.432
	Additive	AA	1.000		
		AG	0.817	0.538-1.241	0.344
		GG	0.741	0.443-1.239	0.252
rs1626340	Dominant	(GA+AA)/GG	1.500	1.032-2.181	**0.033**
	Recessive	AA/(GG+GA)	0.834	0.492-1.417	0.502
	Additive	GG	1.000		
		GA	1.68	1.127-2.503	**0.011**
		AA	1.079	0.611-1.905	0.793

Table 4 Generalized multifactor dimensionality reduction analysis of gene-gene interactions and aortic dissection risk.

Model	Training Bal. Acc	Testing Bal. Acc	Sign Test (p)	CV Consistency
TGFBR1rs1626340	0.5591	0.5134	6(0.3770)	7/10
MYH11rs115364997, TGFBR1rs1626340	0.5842	0.5600	9(0.0107)	10/10
MYH11rs115364997, TGFB1rs1800469, TGFBR1rs1626340	0.6604	0.5156	6(0.3770)	10/10
MYH11rs15364997, MYH11rs17593370, TGFB1rs1800469, TGFBR1rs1626340	0.6100	0.4845	5(0.6230)	10/10

Table 5 Generalized multifactor dimensionality reduction analysis of gene-environment interactions and aortic dissection risk.

Model	Training Bal. Acc.	Testing Bal. Acc.	Sign Test (p)	CV Consistency
Smoking	0.6891	0.6772	10 (0.0010)	9/10
Drinking, BMI≥24kg/m^2	0.7567	0.7447	10 (0.0010)	10/10
Smoking, hypertension, BMI≥24kg/m^2	0.7712	0.7374	10 (0.0010)	7/10
Smoking, drinking, hypertension, BMI≥24kg/m^2	0.8010	0.7763	10 (0.0010)	9/10
TGFB1rs1800469, TGFBR1rs1626340, smoking, hypertension, BMI≥24kg/m^2	0.8261	0.7458	10 (0.0010)	8/10
TGFB1rs1800469, TGFBR1rs1626340, smoking, drinking, hypertension, BMI≥24kg/m^2	0.8649	0.7665	10 (0.0010)	10/10
MYH11rs115364997, TGFB1rs1800469, TGFBR1rs1626340, smoking, drinking, hypertension, BMI≥24kg/m^2	0.8940	0.7673	10 (0.0010)	10/10
MYH11rs115364997, TGFB1rs1800469, TGFBRlrs1626340, smoking, drinking, hypertension, BMI≥24kg/m^2, dyslipidemia	0.9212	0.7554	10 (0.0010)	10/10
MYH11rs115364997, MYH11rs117593370, TGFB1rs1800469, TGFBRlrs1626340, smoking, drinking, hypertension, BMI≥24kg/m^2, dyslipidemia	0.9251	0.7261	10 (0.0010)	7/10

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

SNPs	Genetic Model	Genotype	χ^2	*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	/	/	/	/

Table 7 Association between Tag SNPs and recurrent chest pain in DeBakey type Ⅲ aortic dissection patients

SNPs	Genetic Model	Genotype	χ^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			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

Figures

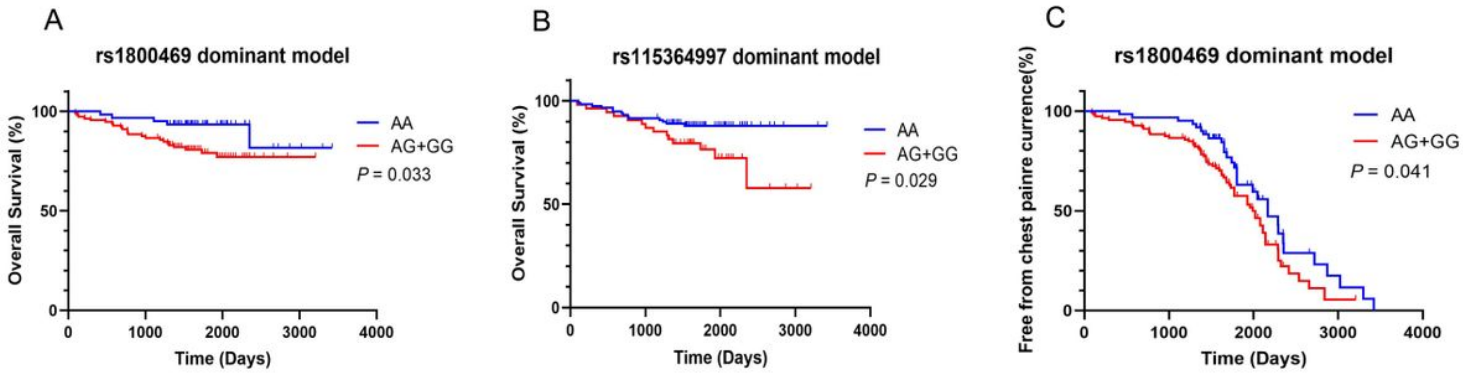

Figure 1

A. Kaplan-Meier analysis of overall survival based on MYH11 rs115364997 dominant model. B. Kaplan-Meier analysis of overall survival based on TGFB1 rs11800469 dominant model. C. Kaplan-Meier analysis of free from chest pain recurrence based on TGFB1 rs11800469 dominant model.