

KIF6 719Arg Genetic Variant and Risk for Thoracic Aortic Dissection

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Abstract

Background: Carriers of the 719Arg variant in *KIF6*, compared with noncarriers, have been reported to be at greater risk for coronary heart disease (CHD) in six prospective studies. Because CHD, thoracic aortic dissection, and nondissection thoracic aortic aneurysm share some risk factors and aspects of pathophysiology, we investigated whether carriers of the 719Arg variant also have greater odds of thoracic aortic dissection or non-dissected thoracic aortic aneurysm than noncarriers.

Methods: We genotyped 140 thoracic aortic dissection cases, 497 nondissection thoracic aortic aneurysm cases, and 275 disease-free controls collected in the United States, Hungary, and Greece and investigated the association between *KIF6* 719Arg carrier status and thoracic aortic dissection, and between *KIF6* 719Arg carrier status and nondissection thoracic aortic aneurysm, using logistic regression models adjusted for age, sex, hypertension, smoking, and country.

Results: The odds of aortic dissection were two-fold greater in *KIF6* 719Arg carriers compared with noncarriers (odds ratio (OR) 2.14, 95% confidence interval (CI) 1.18-3.9). To account for the potential of concomitant CHD to confound the association between the *KIF6* 719Arg and thoracic aortic dissection, we repeated the analysis after removing subjects with concomitant CHD; the estimates for association of *KIF6* 719Arg carrier status remained essentially the same (OR 2.04, 95% CI 1.11-3.77). In contrast, *KIF6* 719Arg carrier status was not associated with risk for nondissection thoracic aortic aneurysm.

Conclusions: We observed an association of the *KIF6* 719Arg genetic variant with thoracic aortic dissection

in this multicenter case-control study. This association may enhance our management of patients with thoracic aortic disease.

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Key Words

Aneurysm • Aorta • Dissection • KIF6 • Biomarker

Introduction

Without surgical treatment, thoracic aortic dissection and thoracic aortic aneurysm can be lethal diseases [1, 2]; however, with elective surgical treatment, aneurysm patients have a near-normal prognosis [3]. Thus, early diagnosis and frequent monitoring with advanced imaging are the keys to survival via timely elective surgery for patients with thoracic aortic aneurysm. Because thoracic aortic aneurysm is asymptomatic until aortic dissection or aneurysm rupture occurs, detection methods, including advanced imaging, must be applied to asymptomatic individuals. Acute aortic dissection sometimes occurs without substantial aorta enlargement [4]. Even when it has occurred clinically, aortic dissection can be initially overlooked in up to 40% of cases and can be very deadly in such scenarios [5]. The mortality rate of untreated dissections of the ascending aorta approaches 1% per hour during the first 48 hours [6]. Thus, a noninvasive marker that can



identify individuals at greater risk for thoracic aortic dissection or nondissection aneurysm before clinical manifestations of the disease would represent a substantial advance in clinical care.

Because coronary heart disease (CHD), thoracic aortic dissection, and thoracic aortic aneurysm share risk factors and some aspects of underlying pathophysiology (vessel wall inflammation, common risk factors of hypertension, familial clustering, and smoking) [7, 8], a genetic variant associated with risk for CHD could be also associated with risk for thoracic aortic dissection or aneurysm.

It has recently been reported that carriers of the 719Arg variant in the kinesin-like protein 6 (encoded by *KIF6*), compared with noncarriers, were at greater risk for CHD in six prospective studies [9–15]. These studies included two large population-based studies (ARIC, Atherosclerosis Risk in Communities [9] and CHS, Cardiovascular Health Study [10]) and placebo arms of four landmark randomized clinical trials (CARE, Cholesterol and Recurrent Events [11]; WOSCOPS, West of Scotland Coronary Prevention Study [11]; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk [12]; and WHS, Women's Health Study [13]). In contrast to these earlier trials, the association of *KIF6* 719Arg with CHD failed to replicate in the placebo arms of the two more recent randomized clinical trials such as JUPITER (Intervention Trial Evaluating Rosuvastatin) [14] and HPS (Heart Protection Study) [15]. However, some important differences between the earlier and more recent trials may account for inconsistency in the observed association in these studies. For example, patients enrolled in the latter trials had lower low-density lipoprotein-cholesterol (LDL-C) at the time of randomization (in JUPITER, due to enrollment criteria; in HPS, due to the run-in period, which included treatment of placebo arm patients with high-dose simvastatin therapy). The lower LDL-C values in these studies could have ameliorated the risk associated with the deleterious *KIF6* 719Arg variant [16]. This thesis is supported by a recent meta-regression analysis of 88,535 participants by Ference, which included *KIF6* negative studies such as case-control studies of angiographically defined coronary artery disease [17] in the HPS and JUPITER trials. This meta-regression analysis concluded that

the *KIF6* 719Arg variant significantly increases vulnerability of patients to the harmful effect of high LDL-C levels on the risk of CHD.

Given the common aspects of pathogenesis between CHD and thoracic aortic dissection and nondissection thoracic aortic aneurysm, in this case-control study we investigated whether carriers of the CHD risk variant *KIF6* 719Arg have greater odds for thoracic aortic dissection or nondissection thoracic aortic aneurysm compared with noncarriers.

Methods

Study Subjects

Study subjects included 140 patients with thoracic aortic dissection, 497 patients with nondissecting thoracic aortic aneurysm, and 275 disease-free control subjects collected in the United States (Yale University), Hungary (Sемmelweis University), and Greece (Athens Medical Center and Evangelismos Hospital). Characteristics of cases and controls are presented in Table 1. Controls included randomly selected unaffected individuals from Greek and Hungarian study centers (nonpatient visitors and staff) ($n = 206$) and unaffected spouses of patients with thoracic aortic aneurysm or dissection recruited at Yale University ($n = 69$). The patients from the United States, Hungary, and Greece (and the respective controls) were analyzed together to increase statistical power, despite the possibility for inherent differences between geographic and ethnic regions. To account for geographic differences, risk estimates were adjusted for the participating center (country). Controls generally shared the same ethnic background, geographic location, and environmental milieu as cases. The physicians caring for the patients verified the aneurysm and/or dissection phenotype from their own radiographic and surgical records, and provided the demographic and clinical data on the patients and controls.

None of the patients had Marfan's disease or Ehlers-Danlos syndrome. In the dissection group ($n = 140$), 77 (55%) were ascending dissection patients, and 63 (45%) descending. Among the aneurysms ($n = 497$), 97 (19.5%) were familial, and 58 (11.7%) had a bicuspid aortic valve. Among the dissections, 25 (17.9%) were familial, and 3 (2.1%) had bicuspid aortic valve. Among the aneurysms, 369 (74.2%) were in the aortic root or ascending aorta, 104 (20.9%) were in the descending aorta, and 24 (4.8%) patients had an aneurysm in both locations.

All subjects provided written informed consent to participate in the study. Both the study and informed consent procedure were approved by the institutional review boards of the participating centers: the Yale University Human Investigation Committee, the Semmelweis University (Budapest, Hungary) Institutional Review Board, the Athens Hospital Center (Athens, Greece) Institutional Review Board, and the Evangelismos General Hospital (Athens, Greece) Institutional Review Board.

Table 1. Characteristics of subjects with dissection and nondissection aneurysm and controls.

Characteristic	Dissection (n = 140)	Nondissection Aneurysm (n = 497)	Control (n = 275)	p Value*	p Value#
Age, y	63 ± 13.1	64 ± 13.8	57 ± 15.2	0.001	<0.0001
Male, n (%)	85 (60.7)	344 (69.2)	107 (39.2)	<0.0001	<0.0001
Smoking status, n (%)	69 (49.3)	185 (37.3)	91 (35.7)	0.01	0.69
Hypertension, n (%)	113 (81.3)	352 (71.0)	98 (38.0)	<0.0001	<0.0001
Center, n (%)				<0.0001	<0.0001
United States (Yale)	100 (71.4)	347 (69.8)	69 (25.1)		
Hungary	28 (20.0)	86 (17.3)	111 (40.4)		
Greece	12 (8.6)	64 (12.9)	95 (34.5)		

* Dissection cases vs. controls, # Nondissection aneurysm cases vs. controls

Data presented as mean ± standard deviation for age and as a number (%) of subjects for other variables.

P values are from Fisher exact tests, except those for age, which are from Wilcoxon rank sum tests.

Dissection and Aortic Aneurysm Assessment

Patient demographics and phenotypes were ascertained from clinical records available at each enrolling site. Aneurysm and dissection were documented conclusively by echocardiography, computerized tomography (CT), magnetic resonance imaging, or operative findings.

Genotyping and Laboratory Measurements

Genotypes for individual DNA samples were determined by real-time kinetic polymerase chain reaction as described previously [11].

Statistical Analysis

Differences in traditional risk factors between thoracic aortic dissection cases and controls or between nondissection thoracic aortic aneurysm cases and controls were assessed by the Fisher exact test or Wilcoxon rank sum test for discrete and continuous characteristics, respectively. An exact test was used to assess deviation of genotype frequencies from Hardy-Weinberg expectations. The associations of *KIF6* Trp719Arg genotype with dissection or nondissection aneurysm were assessed using logistic regression models without or with adjusting for traditional risk factors including age (at the index aneurysm diagnosis or dissection event for cases, at enrollment for controls), sex, current smoker (versus not) status, hypertension (defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, a physician's diagnosis of hypertension, or the use of antihypertensive medications), and participating center. The difference in frequency of *KIF6* 719Arg carrier status among participating centers, while controlling for thoracic aortic disease, was tested for

statistical significance with the Cochran-Mantel-Haenszel statistic. Information on concomitant CHD for thoracic aortic dissection cases was available for samples collected in the United States (Yale University). All other probability values are two-sided, and 95% confidence intervals (CIs) are presented. All statistical tests were two-sided and performed using SAS version 9 (SAS Institute Inc., Cary, NC, USA).

Results

Subject Characteristics and Allele Frequencies

The characteristics of cases and controls are presented in Table 1. Traditional risk factors such as older age, hypertension, and male sex were significantly more prevalent among cases. The smoking status differed between thoracic aortic dissection cases and controls but not between nondissection thoracic aortic aneurysm cases and controls.

Among controls, the genotype frequencies were 14.5% for ArgArg, 41.8% for ArgTrp, and 43.6% for TrpTrp; overall, 56.4% of controls carried at least one copy of the *KIF6* 719Arg variant. The carrier frequency in controls in this genetic study did not differ from that in other large Caucasian populations such as ARIC (52.6%, $p = 0.24$ for difference between studies). Since the majority of cases were from the United States (Yale University) and the majority of controls were from Hungary and Greece, there was a potential for confounding in this study if the Hungarian and Greek

controls had lower *KIF6* 719Arg carrier frequency than the controls from the United States. Therefore, we compared *KIF6* 719Arg carrier frequency in Hungarian and Greek controls with that in the controls from the United States; we found that the carrier frequency in Hungarian (56.8%) and Greek (58.9%) controls was not lower than in U.S. controls (52.2%). *KIF6* 719Arg carrier frequency did not differ by participating center ($p > 0.5$) after controlling for disease status (Table 2). In addition, we adjusted association results for participating centers. The genotype distribution of the *KIF6* 719Arg variant among controls did not deviate from Hardy-Weinberg equilibrium expectations ($p = 0.15$).

Association of *KIF6* 719Arg with Dissection and Nondissection Aneurysm

Carriers of the *KIF6* 719Arg variant, compared with noncarriers, had greater odds of thoracic aortic dissection (odds ratio (OR) 2.14, 95% CI 1.18-3.90) after adjusting for age, sex, hypertension, smoking status, and participating center (Table 3).

Because concomitant CHD could potentially confound the observed association between the *KIF6* 719Arg variant and thoracic aortic dissection, we re-analyzed the data after excluding cases with known CHD. The magnitude of association between carrier status and thoracic aortic dissection remained largely unchanged after excluding those with CHD (adjusted OR 2.04, 95% CI 1.11-3.77; Table 3).

In contrast to thoracic aortic dissection, nondissection thoracic aortic aneurysm was *not* significantly associated with *KIF6* 719Arg carrier status, compared with noncarriers: adjusted OR for *KIF6* 719Arg carriers was 0.94, 95% CI 0.64-1.38 (Table 4). Although *KIF6* 719Arg carriers, compared with noncarriers, were at greater risk for descending nondissection aneurysm (unadjusted OR 2.07, 95% CI 1.26-3.40), the association was no longer significant after adjusting for potential confounders (OR 1.73, 95% CI 0.91-3.29; Table 5).

Discussion

We found that the *KIF6* 719Arg variant, which has previously been associated with CHD in six prospective studies, is also associated with thoracic aortic

Table 2. Genotype proportion according to case control status and participating centers.

Center	Dissection (n, %)			Nondissection aneurysm (n, %)			Control (n, %)			
	Arg/Arg	Arg/Trp	Trp/Trp	Arg/Arg	Arg/Trp	Trp/Trp	Arg/Arg	Arg/Trp	Trp/Trp	Arg/Arg + Arg/Trp
United States	14 (14.0)	54 (54.0)	32 (32.0)	61 (17.6)	157 (45.2)	129 (37.2)	12 (17.4)	24 (34.8)	33 (47.8)	36 (52.2)
Hungary	5 (17.9)	15 (53.6)	8 (28.6)	14 (16.5)	37 (43.5)	34 (40.0)	10 (9.0)	53 (47.7)	48 (43.3)	63 (56.8)
Greece	1 (8.3)	8 (66.7)	3 (25.0)	6 (9.4)	23 (35.9)	35 (54.7)	18 (18.9)	38 (40.0)	39 (41.1)	56 (58.9)

Table 3. Association of *KIF6* Trp719Arg with thoracic aortic dissection.

Genotype	Case	Control	Unadjusted			Adjusted*		
			OR	95% CI	p Value	OR	95% CI	p Value
Including CHD								
Arg/Arg+Arg/Trp Arg/Trp Arg/Trp	97	155	1.75	1.14–2.69	0.0112	2.14	1.18–3.90	0.013
Arg/Trp	77	115	1.87	1.19–2.94	0.0068	2.39	1.27–4.48	0.0066
Arg/Arg	20	40	1.40	0.74–2.65	0.3077	1.40	0.56–3.50	0.4692
Trp/Trp	43	120	ref			ref		
Without CHD								
Arg/Arg + Arg/Trp	81	155	1.70	1.07–2.67	0.0234	2.04	1.11–3.77	0.0224
Arg/Trp	63	115	1.78	1.10–2.87	0.0189	2.23	1.17–4.23	0.0144
Arg/Arg	18	40	1.46	0.75–2.84	0.2670	1.49	0.59–3.72	0.3985
Trp/Trp	37	120	ref			ref		

*Adjusted for sex, age, smoking (current versus noncurrent), country, and hypertension.
CHD = congestive heart disease; CI = confidence interval; OR = odds ratio; ref = reference.

Table 4. Association of *KIF6* Trp719Arg with nondissection aneurysm.

Genotype	Case	Control	Unadjusted			Adjusted*		
			OR	95% CI	p Value	OR	95% CI	p Value
Arg/Arg + Arg/Trp	298	155	1.17	0.87–1.57	0.3154	0.94	0.64–1.38	0.7622
Arg/Trp	217	115	1.14	0.83–1.58	0.4114	0.96	0.64–1.44	0.8267
Arg/Arg	81	40	1.23	0.79–1.91	0.3632	0.90	0.51–1.61	0.7296
Trp/Trp	198	120	ref			ref		

*Adjusted for sex, age, smoking (current versus noncurrent), hypertension, and participating center.
CI = confidence interval; OR = odds ratio; ref = reference.

Table 5. Association of *KIF6* Trp719Arg with descending and ascending nondissection aneurysm.

Genotype	Case	Control	Unadjusted			Adjusted*		
			OR	95% CI	p Value	OR	95% CI	p Value
Descending								
Arg/Arg+Arg/Trp Arg/Trp Arg/Trp	75	155	2.07	1.26–3.40	0.0039	1.73	0.91–3.29	0.0965
Arg/Trp	53	115	1.98	1.17–3.34	0.0110	1.71	0.87–3.37	0.1215
Arg/Arg	22	40	2.36	1.21–4.58	0.0113	1.78	0.73–4.33	0.2057
Trp/Trp	28	120	ref			ref		
Ascending								
Arg/Arg + Arg/Trp	207	155	1.00	0.73–1.37	0.9920	0.86	0.57–1.28	0.4491
Arg/Trp	153	115	1.00	0.71–1.40	1.0	0.89	0.58–1.36	0.5755
Arg/Arg	54	40	1.01	0.63–1.62	1.0	0.77	0.41–1.43	0.4065
Trp/Trp	160	120	ref			ref		

*Adjusted for sex, age, smoking (current versus noncurrent), hypertension and participating center.
CI = confidence interval; OR = odds ratio; ref = reference.

dissection. The ORs approaching 2.00 are quite substantial for association of a single genetic polymorphism with a complex clinical disease. The effect size for this association remained essentially unchanged after adjusting for sex, age, smoking, participating country, and hypertension. This association of the *KIF6* 719Arg variant with thoracic aortic dissection was not confounded by concomitant CHD, since the effect size was not attenuated and remained statistically significant after removing cases of the thoracic aortic dissection with CHD from the analysis.

The extension of a genetic association from CHD to thoracic aortic disease perhaps is not surprising given that both diseases share risk factors and some aspects of underlying pathophysiology. Another example of such extension is the genetic variant on chromosome 9p21 that has been reported to be associated with both CHD and abdominal aortic aneurysms, as well as intracranial aneurysms [18]. In contrast to the 9p21 genetic variant, *KIF6* 719Arg was associated with thoracic aortic dissection but not with nondissection thoracic aortic aneurysm. Although we have observed an association with descending, but not ascending, aortic aneurysm in the unadjusted model, effect size was attenuated and became insignificant after adjustment for sex, age, smoking, participating center, and hypertension. Interestingly, in a recent study by LeMaire, investigators observed larger effect size for the association of the genetic polymorphisms in the *FBN1* gene with thoracic aortic dissection than for association with nondissection thoracic aortic aneurysm [19].

The *KIF6* protein is a member of the kinesin superfamily of proteins that mediate the intracellular transport of organelles, protein complexes, and messenger ribonucleic acids [20]. Typical kinesins are homodimeric molecules consisting of two N-terminal domains ("heads") that move along microtubules and C-terminal domains ("tails") that directly interact with the transported cargos or indirectly through adapter molecules. The *KIF6* polymorphism replaces a non-polar residue (Trp) with a basic residue (Arg) near the putative cargo-binding tail domain; thus, it has the potential to alter the affinity for the cargo molecules or possibly to modulate motor activity of the *KIF6* protein. These cargos, which have yet to be identified, may play a role in modulating cardiovascular risk and the statin response. In addition, *KIF9*, the closest

homolog of *KIF6*, interacts with a member of the small guanosine triphosphatase family that promotes endothelial cell sprouting and cytoskeleton reorganization. A similar role for *KIF6* in endothelial cell growth and function could provide a link between *KIF6* and CHD pathogenesis. *KIF6* ribonucleic acid has been shown to be expressed in coronary arteries (see data deposited by King et al [21]), and *KIF6* expression is reportedly higher in healthy homozygous carriers of the chromosome 9p21 CHD and aortic dissection risk allele than in noncarriers of the 9p21 risk allele. In terms of any potential mechanisms for predisposition to aortic dissection, these are currently unknown.

This study had some limitations. This genetic study had a case-control design and therefore the deaths from thoracic aortic dissection or nondissection aneurysm rupture were not included in the analysis. The impact of absent lethal cases on the analysis can be substantial [16]; for example, a presumptive preferential mortality of Arg/Arg homozygotes in addition to insufficient power might explain the smaller effect size for association of Arg/Arg genotype with nonlethal thoracic aortic dissection than the association of Arg/Trp heterozygotes. Because there were only a few non-Caucasian participants in this study, we analyzed only Caucasians; therefore, the association of the *KIF6* 719Arg with thoracic aortic dissection should be further investigated in large replication studies that would include additional ethnic groups. Also, due to the use of spousal controls in the U.S. cohorts, males and females predominated the patient and control groups, respectively. This was addressed by taking potential confounders into account in the adjusted analysis.

Also, there are differences in the underlying characteristics of the aortic aneurysm, aortic dissection, and control groups. While male sex, smoking, and hypertension (Table 1) can fairly be expected to predominate in cardiovascular disease, we do not have detailed information on other risk factors for our control group patients. Differences in underlying group characteristics may have introduced bias in our findings. Also, while inclusion of three geographic patient sources (United States, Hungary, Greece) enhances the generalizability of our findings, an imbalance between origin of patients and controls (most patients from United States, most controls from abroad) may introduce its own bias, although we adjusted the risk estimates for geographic location of the participating clinical center

(country).

We feel this study raises the possibility that *KIF6* variant status may serve as a predictor for likelihood of aortic dissection. However, there are several methodologic shortcomings of this initial examination of this topic. Additional work is clearly needed, with more ideal group matching, deeper background information on controls, and greater patient numbers. If our findings are borne out in subsequent prospective studies, assessing *KIF6* status could reasonably be added to our armamentarium for predicting aortic dissection risk in patients with thoracic aortic aneurysm.

Conclusion

In this multicenter case-control study, the *KIF6* 719Arg genetic variant was associated with thoracic aortic dissection but not thoracic aortic aneurysm. If the association of the *KIF6* 719Arg variant with thoracic aortic dissection is further confirmed, this variant could be useful in assessing thoracic aortic dissection risk.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

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