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SHORT REPORT

Matrix Metalloproteinase-2 Gene Variants and Abdominal Aortic Aneurysm

L. Smallwood [a], N. Warrington [b], R. Allcock [c], F. van Bockxmeer [c], L.J. Palmer [b], B. Iacopetta [a], J. Golledge [d], P.E. Norman [a,*]

[a] *School of Surgery, University of Western Australia, Fremantle Hospital, PO Box 480, Fremantle, WA 6959, Australia*
[b] *Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Australia*
[c] *School of Pathology and Laboratory Medicine, University of Western Australia, Australia*
[d] *The Vascular Biology Unit, School of Medicine, James Cook University, Townsville, Queensland, Australia*

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Abstract *Objective:* To investigate associations between two polymorphisms of the matrix metalloproteinase-2 gene (*MMP2*) and the incidence and progression of abdominal aortic aneurysm (AAA).
Methods: Cases and controls were recruited from a trial of screening for AAAs. The association between two variants of *MMP2* ($-1360C > T$, and $+649C > T$) in men with AAA ($n = 678$) and in controls ($n = 659$) was examined using multivariate analyses. The association with AAA expansion ($n = 638$) was also assessed.
Results: In multivariate analyses with adjustments for multiple testing, no association between either SNP and AAA presence or expansion was detected.
Conclusion: MMP2 $-1360C > T$ and $+649C > T$ variants are not risk factors for AAA.

Introduction

Animal models and human aortic wall studies suggest a role for matrix metalloproteinase-2 (MMP-2) in the pathogenesis of AAAs.[1] However, studies of circulating MMP-2 levels have failed to find any association with aneurysm diameter or rate of expansion. Another approach to assessing the role of MMP-2 in the cause of AAA is to examine for associations between functional variants of *MMP2* that may influence life-long levels of circulating MMP-2. In the present study we investigated a case control series for associations between two common polymorphisms in *MMP2* and the incidence and progression of AAA.

Report

Details of the Western Australian AAA cohort are described elsewhere.[2] Two *MMP2* single nucleotide polymorphisms

* Corresponding author. Tel.: +61 894313333; fax: +61 894312623.
E-mail address: paul.norman@uwa.edu.au (P.E. Norman).

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Table 1 Genotyping success rate and distribution of *MMP2* genotypes and alleles

SNP		Success rate	*n* (%)					*p*-value[a]
			CC	CT	TT	C	T	
MMP2 −1306C > T	Cases	96.5%	385 (57.7)	243 (36.4)	39 (5.8)	1013 (75.9)	321 (24.1)	0.230
	Controls	98.9%	372 (56.9)	228 (34.9)	54 (8.3)	972 (74.3)	336 (25.7)	
			CC	CT	TT	C	T	
MMP2 +649C > T	Cases	96.3%	600 (90.0)	61 (9.2)	5 (0.8)	1261 (94.7)	71 (5.3)	0.004
	Controls	98.0%	554 (85.1)	95 (14.6)	2 (0.3)	1203 (92.4)	99 (7.6)	

[a] Cases vs controls using Fisher's test.

(SNPs) were chosen for this study; the first (−1306C > T, rs243865) lies within the gene promoter region and the second (+649C > T, rs1053605) within the coding region. The −1306C > T polymorphism has been shown to disrupt an SP-1 regulatory element which results in the minor (T) allele displaying significantly lower promoter activity. To date the functional effects of the +649C > T coding region polymorphism, have not been investigated. Both SNPs are found at >10% frequency in the Caucasian population (dbSNP; http://www.ncbi.nlm.nih.gov/SNP). The genotyping and statistical methods were as previously reported.[2]

Data were available from 1337 subjects: 659 were controls (aortic diameter <30 mm), 535 with AAAs between 30 and 39 mm, 118 with AAAs between 40 and 49 mm and 25 with AAAs of ≥50 mm. The baseline characteristics of the cases and controls are as previously reported.[2] Annual rates of expansion were available for 638 men with a median follow-up duration of 5 years. Of these men, 550 were classified as 'AAAs with slow expansion' (<3 mm expansion pa) and 88 as 'AAAs with definite expansion' (≥3 mm expansion pa).

Genotyping success rates and frequencies are shown in Table 1. Amongst controls *MMP2* + 649C > T was in HWE, but *MMP2* −1306C > T was not (*p*-value = 0.031). A significant difference was found in the frequency of the *MMP2* +649C > T but not *MMP2* −1306C > T (Table 1). In the multivariate modelling (Table 2) the CT genotype of *MMP2* +649C > T was associated with a reduced risk of AAA (OR 0.59, 95% CI 0.40, 0.88). As the TT homozygote was very rare, the polymorphism was modelled under a dominant genetic model which increased the Odds Ratio to 0.62 (95% CI: 0.42, 0.92). Following adjustment for multiple testing for the current SNPs and the results of 5 other SNPs examined in this case control series,[2] the finding with *MMP2* +649C > T became non-significant (*q*-value = 0.10). No association was detected between either of the SNPs and the rate of expansion (data not shown).

Discussion

There have been two previous genetic association studies of *MMP2* and AAA: one examined a single SNP (nt-955) in 387 cases and 425 controls[3] and the other examined 18 SNPs in only 51 cases and 48 controls.[4] Neither study found any association between genetic variants and AAA. Although

Table 2 Results of the multiple logistic regression modelling for the *MMP2* +649C > T variant

Variable	OR (95% CI)	*p*-value
Age (yrs)	1.08 (1.05, 1.12)	<0.001
Waist Hip Ratio (≥1.00)	1.45 (1.08, 1.94)	0.01
Diastolic BP (mmHg)	1.02 (1.01, 1.03)	0.005
History of/treatment for hypertension	1.65 (1.26, 2.15)	<0.001
Past history of stroke	1.78 (1.05, 2.99)	0.03
Past history of myocardial infarction	2.91 (1.94, 4.36)	<0.001
Past history of coronary surgery	2.27 (1.44, 3.58)	<0.001
Vigorous exercise	0.53 (0.39, 0.72)	<0.001
Non-vigorous exercise	0.75 (0.57, 0.99)	0.04
Never smoked (Baseline)		
Ex-smoker	3.46 (2.50, 4.79)	<0.001
Current smoker < 25/day	6.30 (3.59, 11.05)	<0.001
Current smoker ≥ 25/day	6.07 (3.19, 11.53)	<0.001
MMP2 +649C > T CT	0.59 (0.40, 0.88)	0.009
MMP2 +649 C > T TT	2.04 (0.31, 13.44)	0.46

the present study suggests a protective effect of the *MMP2* +649C > T polymorphism for the presence of AAA, following adjustment for multiple testing the finding was non-significant. Furthermore, there was no association with the expansion of AAAs, and no association between the functional *MMP2* −1306C > T polymorphism and either AAA presence or expansion. Different results may have been obtained with the inclusion of more cases of large AAAs, however genetic associations with smaller AAAs are more likely to be informative about factors involved with the initiation of aneurysm formation.

Our findings are consistent with results from the UK Small Aneurysm Trial which found no association between *MMP2* −1306C > T and the rate of AAA expansion.[5] There was a minor deviation from HWE in the control subjects for this SNP in the present study. The cause for this was unclear, however there is no reason to suspect this was responsible for the negative result.

Despite human data and animal model studies implicating MMP-2 in the pathogenesis of AAA,[1] no obvious association between AAA and circulating levels of MMP-2 or *MMP2* variants have been detected.[5] This does not exclude a role for MMP-2 at the level of the aortic wall but it suggests that systemically elevated activity or circulating levels are not involved in the initiation of AAA formation.

Conflict of Interest statement

The authors declare no conflict of interests.

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