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Apolipoprotein E genotype is associated with serum C-reactive protein but not abdominal aortic aneurysm

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Abstract

Objective—Apolipoprotein E (*ApoE*) genotype has been associated with systemic inflammation and athero-thrombosis however the association with abdominal aortic aneurysm (AAA) has not been previously examined. We assessed the association between *ApoE* genotype with AAA presence and growth, and serum C-reactive protein (CRP).

Methods—Serum concentrations of CRP (in 1358 men) and 6 single nucleotide polymorphisms (SNPs) for *ApoE* (in 1711 men) were examined in subjects from the Health In Men Study. 640 men with small AAAs were followed by ultrasound surveillance for a mean of 4.1 years.

Results—There was no association between *ApoE* genotype and AAA presence. Men heterozygote for the ApoE p.Arg176Cys polymorphism had slower AAA growth, odds ratio for AAA progression ≥ median 0.41, 95% confidence intervals 0.21-0.80, p=0.01. Men heterozygote for the ApoE g. 50093756A>G polymorphism had slightly more rapid AAA growth, odds ratio for AAA progression ≥ median 1.48, 95% confidence intervals 1.02-2.14, p=0.04. None of the *ApoE* SNPs were associated with AAA growth however taking into account multiple testing. Two SNPs in *ApoE* were associated with serum CRP under a co-dominant model, ApoE p.Cys130Arg (SNP ID rs429358), p=0.00003 and ApoE g.50114786A>G (SNP ID rs4420638), p=0.00013. Adjusting for other risk factors plus serum creatinine the ε4 allele was associated with lower serum CRP under a dominant model, coefficient 0.089, p=0.002.

Conclusion—We found no consistent association between *ApoE* genotype and AAA. We confirmed an association between *ApoE* genotype and serum CRP.

Keywords

Apolipoprotein E; abdominal aortic aneurysm; genotype

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1. Introduction

Apolipoprotein E (ApoE) is a component of circulating lipoproteins and controls their uptake within the liver and peripheral sites [1]. ApoE appears to play an important role in the development and progression of atherosclerosis. Deficiency of ApoE markedly promotes atherosclerosis development in mice and has become the most commonly used model of artery disease [1,2]. Circulating lipoprotein concentrations are influenced by ApoE genotype [3]. ApoE genotype has been also been associated with circulating markers of inflammation, such as C-reactive protein (CRP) and interleukin-10 [4-8]. Furthermore ApoE genotype has been found to predict the likelihood of coronary events in a number of studies [9,10].

The pathogenesis of atherosclerosis and abdominal aortic aneurysm (AAA) are believed to be distinct, due to differences in risk factors and pathological findings [11]. Diabetes is an important risk factor for athero-thrombosis but maybe negatively associated with AAA for example [11]. In mice however deficiency of ApoE predisposes to AAA formation as well as atherosclerotic changes [12]. In one small (n=57) study AAA progression was related to the common variation in exon 4 of the *ApoE* gene due to the single nucleotide polymorphisms (SNPs) ApoE p.Cys130Arg (SNP ID rs429358) and ApoE p.Arg176Cys (SNP ID rs7412) [10,13]. Three major ApoE isoforms are determined by these SNPs which translate into common (epsilon) protein isoforms ε2 (130Cys/176Cys), ε3 (130Cys/176Arg), and ε4 (130Arg/176Arg). While ε3 (wild type) and ε4 isoforms are recognized by their LDL receptors, the ε2 isoform displays extremely low binding affinity and is associated with type III hyperlipidemia [14]. The ε4 isoform has been implicated in atherosclerosis [9,10,15]. To our knowledge the association of *ApoE* genotype with AAA presence has not been previously examined in a large cohort. The aims of this study were to assess the association of *ApoE* genotype with AAA presence and growth in a large cohort of men screened for AAA. We also examined the association of *ApoE* genotype with circulating CRP concentrations.

2. Methods

Patients

In order to assess the association of *ApoE* genotype with AAA and CRP we utilised subjects from the Health In Men Study (HIMS). HIMS is a prospective follow-up study of men who originally participated in a trial of screening for AAA [16,17]. Between 1996 and 1999, 12,203 (out of 17,432 invited) community-dwelling men aged 65-83 years from Perth, Western Australia, attended for screening and AAAs were diagnosed in 875. Details of the characteristics of these 12,203 men are shown in a previous publication [16,17]. 686 men subsequently attended for surveillance of their small AAA. Men underwent repeat ultrasound scans at intervals of 6 months if the initial aortic diameter was ≥40 mm and 12 months if the initial diameter was 30 to 39 mm. Between 2001 and 2004, 4,263 of the original cohort of 12,203 men completed a follow-up visit during which time fasting blood samples were collected including serum and DNA [18,19]. Genotyping was undertaken in all men with an AAA for whom DNA was available (n=640). In addition 1071 age-matched men without an AAA, who had provided DNA, were randomly selected as controls. Of these 1771 men serum CRP was measured in 312 men with and 1046 without AAAs. All subjects included had undergone abdominal ultrasound. AAA was defined as maximum infrarenal aortic diameter ≥30mm. Ultrasound reproducibility was assessed during subject recruitment and 95% confidence intervals were <3mm [20]. The definitions of clinical risk factors such as hypertension, dyslipidaemia, diabetes and coronary heart disease (CHD) were as previously described [18]. Ethics approval was granted from the relevant committee and all men gave written informed consent to their involvement in the study.

Genotyping

Using Haploview, tagging SNPs for *ApoE* (n=6) were identified from HapMap Phase II data utilising a pairwise approach (minor allele frequency >5% and r^2 >0.8). Regions analysed included the entire gene, plus additional sequences 10 kb upstream and downstream of the gene. With this approach 100% of the variation in the genes (minor allele frequency >5%) was captured. Genotyping on the HIMS subjects was carried out using the Illumina Golden Gate® assay on an Illumina BeadLab System at University of Western Australia. Genotype calls were made using Bead Studio Genotyping Module software package Version 3.1 (Illumina, Inc., San Diego, CA). SNPs with genotyping efficiency <15% were excluded. As a result findings for one SNP (APOE g.50106541C>T, SNP ID rs 439401) was excluded since genotyping failed in 91%. Genotyping efficiency for the other SNPs was between 91 and 99%.

Serum CRP

Serum C-reactive protein (CRP) concentration was measured by immunophelometry using the BNII analyzer as reported previously (Dade Behring, Milton Keynes, UK) [20].

Analysis

The dichotomous and quantitative characteristics of patients with AAA and controls were compared with non-parametric tests (chi squared, Mann Whitney U and Kruskal Wallis test). Hardy-Weinberg equilibrium of genotypes was tested on a contingency table of observed versus predicted phenotype frequencies using a modified Markov-chain random-walk algorithm. The association between *ApoE* genotypes and AAA presence was assessed using logistic regression. Analyses were adjusted for other risk factors, including age, smoking, hypertension, diabetes, CHD, dyslipidemia and waist to hip ratio as previously described [21]. The relationship between *ApoE* genotype and CRP was assessed using linear regression adjusting for age, smoking, hypertension, diabetes, CHD, dyslipidemia, waist to hip ratio and serum creatinine. CRP was log transformed for inclusion in these analyses. The annual growth rates of AAAs were assessed by taking into account all diameters measured during follow-up and calculating time-weighted average growth rates for each patient. Median yearly AAA growth rates for the whole cohort were calculated and expansion ≥ or < median noted. The relationship between *ApoE* genotypes and weighted average growth was examined using logistic regression analysis adjusting for variables known to influence AAA growth rate (initial aortic diameter and diabetes). The biallelic SNPs were initially analysed under co-dominant models and if significant associations were identified dominant and recessive models were also assessed. ε haplotypes were identified using the results of ApoE p.Cys130Arg (SNP ID rs429358) and ApoE p.Arg176Cys (SNP ID rs7412). To reduce the possibility of false positive findings we required a Bonferroni corrected P value of <0.003 to assume significance for genotypic associations, based on the 6 SNPs assessed in three associations.

3. Results

Patients and genotyping

The risk factors for the subjects genotyped and in whom serum CRP was measured are shown in relation to the presence of AAA in Table 1. The 5 SNPs successfully genotyped were all demonstrated to be in Hardy Weinberg equilibrium in controls.

Association of CRP and polymorphisms in ApoE with AAA

CRP concentrations were higher in patients with AAA (Table 1). None of the 5 SNPs assessed were associated with AAA presence (Table 2). ε2, ε3 and ε4 allele frequencies were similar in patients and controls (Table 3).

Association of polymorphisms in ApoE with AAA growth

The 640 patients with AAA were followed for a median (inter-quartile range) of 5.0 (2.5-6.0) years and underwent a median of 6 (4-7) scans. Median increase in AAA diameter was 1.2 (0.5-2.2) mm/year. Men who were heterozygote for the ApoE p.Arg176Cys (SNP ID rs7412) polymorphism (n=48 of 483, 9.9%, successfully genotyped for this SNP) had slower AAA growth, odds ratio for AAA progression ≥ median 0.41, 95% confidence intervals [CI] 0.21-0.80, p=0.01. Men who were heterozygote for the ApoE g.50093756A>G (SNP ID rs8106922) polymorphism (n=304 of 632, 48.1%, successfully genotyped for this SNP) had slightly more rapid AAA growth, odds ratio for AAA progression ≥ median 1.48, 95% CI 1.02-2.14, p=0.04. However no *ApoE* SNPs were associated with AAA growth after taking into account multiple testing (Table 2). ε haplotypes were not significantly associated with AAA growth (Table 3). We have previously found no association between CRP and AAA growth [20].

Association of polymorphisms in ApoE with serum CRP

Two SNPs in *ApoE* were associated with serum CRP under a co-dominant model, ApoE p.Cys130Arg (SNP ID rs429358) likelihood ratio p value 0.00003 and ApoE g.50114786A>G (SNP ID rs4420638) likelihood ratio p value 0.00013. Men with CC, CT and TT genotypes for the ApoE p.Cys130Arg (SNP ID rs429358) polymorphism had median serum CRP concentrations of 1.13 (0.51-1.98), 1.74 (0.99-3.67) and 2.14 (1.20-4.51) mg/l respectively. Men with AA, AG and GG genotypes for the ApoE p. g.50114786A>G (SNP ID rs4420638) polymorphism had median serum CRP concentrations of 2.12 (1.19-4.70), 1.89 (1.03-3.44) and 1.15 (0.53-2.77) mg/l respectively. Under dominant models ApoE p.Cys130Arg (SNP ID rs429358), coefficient 0.089, p=0.002, and ApoE g.50114786A>G (SNP ID rs4420638), coefficient 0.073, p=0.007, polymorphisms were associated with serum CRP. Only the association between ApoE p.Cys130Arg (SNP ID rs429358) and CRP was at a significance level required for multiple testing. The serum CRP concentrations were related to ε haplotype (Table 3). The ε4 allele was associated with lower serum CRP (Table 3). Adjusting for other risk factors plus serum creatinine the ε4 allele was associated with lower serum CRP under a dominant model, coefficient 0.089, p=0.002.

4. Discussion

The main finding of this large case control study is the lack of significant association between *ApoE* genotype and AAA presence. We are not aware of a previous publication where this association has been studied. One previous investigation assessed the association between *ApoE* ε and AAA growth in 57 men and reported faster AAA progression in men with ε2/ε4 haplotype [13]. In the current study we found no evidence to support the findings of this earlier study and examined the association of *ApoE* genotype with AAA growth in a much larger group of 640 men. ApoE p.Arg176Cys and ApoE g.50093756A>G were mildly associated with AAA growth but not significantly after adjusting for multiple testing. CRP concentrations were higher in patients with AAA but not associated with AAA expansion, as previously reported [20].

Studies in mice suggest ApoE is critical in protecting against atherosclerosis, although the exact relevance of these findings to human athero-thrombosis is not clear [1,2]. ApoE expressed and secreted by macrophages is believed to promote cholesterol efflux from the vessel wall and favour anti-inflammatory pathways [22,23]. The role of dyslipidemia in AAA is less well defined compared to its established role in athero-thrombosis [11]. A number of studies have suggested that *ApoE* genotype predicts the risk of developing atherosclerosis [9,10]. The lack of association between *ApoE* genotype and AAA fits with other data suggesting that the mechanisms involved in athero-thrombosis and AAA are distinct [11].

A number of previous studies have suggested an association between *ApoE* genotype and serum CRP, a generalised marker of inflammation [4-6,8]. In agreement with other studies we found that serum CRP was lower in subjects with ε4 haplotypes [25,28,29,30]. This association was present after adjusting for other risk factors, such as age, diabetes, CHD and hypertension. CRP has also been associated with loci related to *ApoE* in a whole genome analysis [26]. There is currently controversy regarding the role of CRP in atherosclerosis and it is possible that the association of CRP and cardiovascular events may just be due to confounding with other factors such as *ApoE* genotype [27]. ApoE ε4 allele has however been associated with increased risk of cardiovascular events despite its association with lower CRP concentrations.

In conclusion this study demonstrates no convincing evidence of an association between *ApoE* genotype and AAA but confirms an association between *ApoE* and CRP.

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Table 1

Comparison of patients with and without AAA undergoing genotyping and CRP assessment in the HIMS

	APOE SNPs examined			Serum CRP measured		
Characteristic	**AAA**	**No AAA**	**P value**	**AAA**	**No AAA**	**P value**
Number	640		1071	312	1046	
Aortic diameter (mm)	34.0 (31.5-38.7)	21.6 (20.2-23.7)	<0.01	33.4 (31.5-38.4)	21.6 (20.2-23.4)	<0.01
Age (years)	73.1 (69.7-76.6)	72.8 (69.8-76.5)	0.68	71.8 (68.8-74.9)	72.8 (69.8-76.5)	<0.01
Hypertension	345 (53.9%)	444 (41.4%)	<0.01	158 (50.6%)	429 (41.0%)	<0.01
Diabetes mellitus	67 (10.5%)	80 (7.5%)	0.05	31 (9.9%)	78 (7.5%)	0.16
Dyslipidaemia	285 (44.5%)	375 (35.0%)	<0.01	150 (48.1%)	366 (35.0%)	<0.01
Ever smoker	551 (86.1%)	672 (62.7%)	<0.01	268 (85.9%)	650 (62.1%)	<0.01
CHD	257 (40.2%)	228 (21.3%)	<0.01	127 (40.7%)	225 (21.5%)	<0.01
WHR	0.97 (0.93-1.01)	0.95 (0.92-0.99)	<0.01	0.97 (0.93-1.01)	0.95 (0.91-0.99)	<0.01
CRP (mg/l)				2.55 (1.37-5.19)	1.90 (1.08-4.03)	<0.01
Creatinine (uM)				95.0 (83.0-114.5)	87.0 (77.0-100.0)	<0.01

Nominal variables are presented as numbers and compared with chi squared. Continuous variables are presented as median (inter-quartile range) and compared with Mann Whitney U test. CHD= Coronary heart disease; WHR=Waist to hip ratio.

Table 2

Association of tagging SNPs in APOE with AAA presence and growth

SNP	SNP ID	AAA presence		AAA growth	
		Association of Heterozygous genotype	Association of rare homozygote genotype	Association of Heterozygous genotype	Association of rare homozygote genotype
g.50100926A>C	rs405509	1.27 (0.96-1.68)	1.09 (0.78-1.51)	1.32 (0.82-2.11)	1.00 (0.57-1.77)
p.Cys130Arg	rs429358	1.15 (0.87-1.51)	0.88 (0.32-2.42)	1.03 (0.66-1.61)	7.16 (0.75-68.33)
g.50114786A>G	rs4420638	1.07 (0.85-1.36)	1.05 (0.57-1.93)	1.24 (0.86-1.79)	1.47 (0.58-3.73)
p.Arg176Cys	rs7412	0.70 (0.48-1.01)	2.04 (0.53-7.88)	0.41 (0.21-0.80)*	1.99 (0.32-12.24)
g.50093756A>G	rs8106922	1.08 (0.85-1.37)	0.91 (0.66-1.25)	1.48 (1.02-2.14)**	1.13 (0.66-1.91)

Shown are odds ratios and 95% confidence intervals for heterozygote and rare homozygote genotype association with AAA presence and growth. Analysis of association with AAA presence was adjusted for age, smoking, hypertension, diabetes, CHD, past history of or past treatment (diet or medication) for dyslipidemia and waist to hip ratio. Analysis of association with AAA growth ≥ median was adjusted for initial aortic diameter and diabetes.

all other p values were ≥0.05.

* p=0.01

** p=0.04

Table 3

Prevalence of ε2, ε3 and ε4 alleles of ApoE in men with and without AAAs and relationship to serum CRP

Haplotype	AAA	No AAA	AAA growth (mm/year)*	Number of men in which serum CRP was measured	Serum CRP (mg/l)*
Total with both SNPs genotyped	475	1028		1278	
ε2/ ε2	5 (1.0%)	5 (0.5%)	2.3 (1.0-3.3)	7	3.89 (0.96-4.69)
ε2/ ε3	39 (8.2%)	120 (11.7%)	0.7 (0.2-1.9)	141	2.39 (1.18-4.88)
ε2/ ε4	10 (2.1%)	26 (2.5%)	1.0 (0.1-1.7)	33	2.23 (1.17-4.11)
ε3/ ε3	303 (63.8%)	649 (63.1%)	1.2 (0.5-2.2)	805	2.12 (1.20-4.49)
ε3/ ε4	112 (23.6%)	208 (20.2%)	1.3 (0.6-2.5)	267	1.70 (0.99-3.45)
ε4/ ε4	6 (1.3%)	20 (1.9%)	1.8 (1.1-3.6)	25	1.13 (0.51-1.98)

* Median and inter-quartile range shown. Serum CRP (P=0.002) but not AAA growth (P=0.07) was associated with *ApoE* ε genotype.