

Letters to the Editor

The association of complement C3 genotype with coronary artery disease, markers of the metabolic syndrome and C3 plasma levels

Dear Sir,

It is well established that inflammation has a role in the pathogenesis of atherothrombosis and accumulating evidence suggests that the complement system is activated in patients with atherosclerotic disease (1). In particular, complement C3 has been shown to be predictive of future MI (2) and we have recently shown that C3 is associated with coronary artery disease independently of C-reactive protein (3). A common polymorphism in exon 3 of the C3 gene, Gly102Arg, was originally identified due to differential separation of the variants on gel electrophoresis: C3 fast (C3F, Gly102) and C3 slow (C3S, Arg102) (4). A previous study has shown an increase in Gly102 allele frequency in patients with a history of MI (5), but the frequency of this allele in patients with symptoms of coronary artery disease (CAD) and abnormal coronary angiography has not been determined.

In the present work, we investigated the association of the C3 Arg102Gly polymorphism with C3 plasma levels and CAD in 371 patients undergoing coronary angiography for typical symptoms of CAD and 211 healthy controls. This study was approved by the Leeds Teaching Hospitals Local Research Ethics Committee. Genotype was determined as previously described (4), and plasma C3 levels were analysed using an in-house ELISA, as previously described (3).

There was no significant difference in the Arg102Gly genotype distributions of patients with CAD (RR=223, RG=132, GG=16) and controls (RR=128, RG=74, GG=9, $p=0.9$).

In the patient group, initial analysis suggested an association between genotype and disease severity, assessed according to the number of vessels with >50% stenosis (Table 1), however, pairwise analysis with adjustment for multiple comparisons did not indicate any two groups which differed significantly ($p>0.1$). There was no association between genotype and previous history of MI. Patients with diabetes mellitus or impaired fasting glucose had a similar C3 allele distribution compared with controls (Table 1). Levels of C3 were higher in patients homozygous for the Arg102 allele (1.15 [1.13, 1.17] g/l) compared with those

possessing the Gly102 allele (1.11 [1.08, 1.14] g/l, $p=0.046$) and a similar trend was observed in the controls (RR: 0.93 [0.90, 1.17] g/l; RG+GG=0.89 [0.86, 0.92] g/l, $p=0.082$).

Previous work on C3 genotypes and atherothrombotic disease has been both limited and conflicting with some studies showing an association between the Gly102 (C3F) allele and atherosclerosis, while others demonstrated no association (5–8). In the present work, we found no association of the Arg102Gly polymorphism with CAD, extent of CAD or previous history of MI. It is worth noting that this work is a cross-sectional retrospective study, thereby excluding individuals who had a coronary event resulting in death, which may have underestimated the role of Arg102Gly genotype in predisposition to CAD. However, our data demonstrated that individuals homozygous for the Arg102 allele had higher plasma C3 levels than those possessing the Gly102 allele (3). Previous studies have shown that plasma C3 level is a marker of atherosclerosis and can predict future myocardial infarction and stroke (2, 3, 8, 9) and C3 levels were independently associated with CAD in the subjects included in the present study (3). Therefore, the lower levels of C3 associated with the Gly102 allele suggests that this allelic variant may have a protective role in patients predisposed to atherosclerosis. It is therefore possible that the studies demonstrating an increased incidence of the Gly102 allele in survivors of MI support a protective role for Gly102 following acute thrombosis. The failure to show an association between C3 genotype and CAD in this study may be related to the sample size, and therefore a large prospective study is warranted to fully investigate the role of C3 variants in the atherosclerotic process.

In summary, this work has shown that plasma C3 levels are elevated in individuals homozygous for the Arg102 allele. Des-

Table 1: C3 genotype distributions of patients classified according to number of vessels with >50% stenosis, history of myocardial infarction (MI), diabetes or impaired fasting glucose (IFG).

	Arg102Gly genotype			p
	RR	RG	GG	
Number of vessels with >50% stenosis				0.025
0	65 (0.63)	35 (0.34)	4 (0.04)	
1	45 (0.75)	13 (0.22)	2 (0.03)	
2	38 (0.53)	27 (0.35)	7 (0.09)	
3	67 (0.55)	52 (0.43)	3 (0.02)	
History of MI				0.43
No	157 (0.61)	88 (0.34)	13 (0.05)	
Yes	65 (0.58)	44 (0.39)	3 (0.03)	
Diabetes				0.71
No	154 (0.61)	89 (0.35)	10 (0.04)	
Yes	21 (0.58)	12 (0.33)	3 (0.09)	
IFG	41 (0.59)	27 (0.39)	2 (0.02)	

Data presented as number (frequency)

Correspondence to:

Professor PJ Grant
Academic Unit of Molecular Vascular Medicine, The LIGHT Laboratories
Clarendon Way
University of Leeds
Leeds, LS2 9JT
United Kingdom
Tel.: +44-113-343 7721, Fax: +44-113-343 7738
E-mail: p.j.grant@leeds.ac.uk

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pite higher C3 levels in CAD patients compared with controls, we did not find an association of C3 genotype with CAD, extent of disease or previous MI. Given the modest influence of Arg102Gly on C3 levels, a prospective study is required to clarify the role of this polymorphism in the pathogenesis of cardiovascular disease.

Ramzi A. Ajjan, Peter J. Grant, Timothy S. Futers, Jane M. Brown, Angela M. Carter
Academic Unit of Molecular Vascular Medicine, Leeds Institute of Genetics Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, United Kingdom

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A case of thrombosis : Possible sickle cell?

Dear Sir,

I read about the patient reported by Schreijer et al. which appeared in the last issue of the journal with great interest. They reported a heterozygous Factor V Leiden carrier woman with unknown ethnic background who experienced recurrent thrombosis attacks which appeared following long sedentary travel and high altitude. During her first ascent to 4450 m, she developed a painful and warm left leg; and aspirin was prescribed by the local physician (1).

A 41-year-old Nigerian, apparently in good health with an unexpected sudden death and a 7-year old Ghanese boy with repeated bone pain were reported previously and both were linked to long duration flights. Autopsy of the former case revealed that the immediate cause of death was pulmonary thromboembolism originating from calf vein thrombosis. Electrophoresis confirmed that both patients had Hb S/C disease (2, 3).

As it is well known, sickling can occur under certain situations such as prolonged hypobaric hypoxia, dehydration and also aspirin medication. The patient reported by Schreijer et al. also had these three risk factors which are also risk factors for sickling.

Although there is no doubt in the diagnosis of deep vein thrombosis in this 33 year old woman, I wonder whether she may have a sickle cell disease.

Correspondence to:
Prof. Nejat Akar, MD
Pediatric Molecular Genetics Department of Ankara University
Cebeci
06100 Ankara, Turkey
Tel.: +903123623030, Fax: +903123201433
E-mail: akar@medicine.ankara.edu.tr

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Nejat Akar
Pediatric Molecular Genetics Department of Ankara University,
Ankara, Turkey

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A case of thrombosis: Not sickle cell

Dear Sir,

We thank Dr. Akar for his letter regarding our case report on a young woman who suffered from recurrent episodes of venous thrombosis after air travel and exposure to high altitude (1). She is of Caucasian origin and was therefore not suspected of sickle cell disease (or trait). We have now confirmed this by High Performance Liquid Chromatography demonstrating the presence of the normal homozygous HbA/A phenotype.

The rationale behind Akar's question is interesting: Does sickle cell disease or trait increase the risk of venous thrombosis under certain conditions such as hypobaric hypoxia and air travel? This is relevant since about 8% of African-Americans have sickle cell trait (HbA/S) and 0.15% are homozygous and have sickle cell disease (HbS/S) (2).

HbS/C disease in particular, a combination of the sickle cell gene with haemoglobin C gene from which the patients mentioned in Akar's letter suffered, has an incidence of about 1:833 live births in African-Americans, with a much higher prevalence of up to 25% in some West African regions (3).

Neither sickle cell disease nor sickle cell trait are established risk factors for venous thrombosis. It has been speculated that HbS/C patients are at risk for venous thrombosis as a result of an elevation in blood viscosity in combination with crystal

formation of HbC (4). In one autopsy study with 72 sickle cell patients (including at least 12 HbS/C patients) and 72 age, sex and race matched control subjects, evidence of venous thrombosis in 18 sickle cell patients vs in 11 control subjects was found (5). Furthermore, low levels of protein C and S, elevated levels of thrombin-antithrombin complexes and D-dimer, as well as increased activation of tissue factor have been observed in patients with sickle cell disease (2). This hypercoagulable state could increase the risk of venous thrombosis in this group.

As mentioned by Akar, sickling crisis [due to blocking of small vessels by sickling red cells commonly resulting in infarctions of organs such as bone or spleen (4)] can occur in several situations including hypoxia and dehydration (6), which may both be present during air travel (7). Atmospheric altitudes above 3000 m are believed to be associated with an increased risk of splenic infarction in individuals with sickle cell trait (6, 8). Although sickling has been associated with air travel in several case reports (9–11), the cabin altitude in aircrafts (2400 m) (7) is considered too low to be a risk factor for sickling. The only group that has been described to be at risk for flight related splenic infarction are HbS/C patients (6). Ware et al. reported a frequency of bone pain of 1 in 73 sickle cell patients who had flown 24 hours before the event (6). To our knowledge, no controlled studies have been done in this field.

We conclude that it is not clear from the literature whether sickle cell patients (and especially HbS/C patients) are at risk for venous thrombosis, let alone under specific circumstances such as high altitude and air travel.

Anja J. M. Schreijer¹, Suzanne C. Cannegieter¹, Piero C. Giordano², Frits R. Rosendaal^{1,3}, Frans M. Helmerhorst¹
¹Clinical Epidemiology, ²Hemoglobinopathies Laboratory, Human and Clinical Genetics, ³Department of Haematology, Leiden University Medical Center Leiden, The Netherlands

Correspondence to:

Prof. Frits R. Rosendaal
 Leiden University Medical Center
 Department of Clinical Epidemiology
 C9-P, P.O. Box 9600
 2300 RC Leiden
 The Netherlands
 Tel.: +31 71 5264037, Fax: +31 71 5266994
 E-mail: f.r.rosendaal@lumc.nl

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