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Association of *SDF1β* (G801A) and *GNB3* (C825T) polymorphisms with the incidence and severity of coronary artery disease

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Coronary artery disease (CAD), manifesting as angina and myocardial infarction, is a common cause of death and disability worldwide. In addition to major aetiologic determinants such as lifestyle and environmental factors, there is considerable familial clustering of CAD indicating a causative genetic component [1]. Whilst cholesterol-laden plaque deposits in the blood vessel wall are a key characteristic, chemokines and inflammatory mediators may also have a role in the progression of atherosclerosis and the development of CAD [2,3].

Increased plasma levels of stromal cell derived factor (SDF)-1 (also known as CXCL-12), a chemokine expressed in a number of tissues and which regulates haematopoiesis, inflammation, embryonic development, organ homeostasis and tumorigenesis, are present in ST-elevation myocardial infarction [4]. The *SDF-1β* G801A (rs1801157) single nucleotide polymorphism (SNP) is located at the 3′ untranslated region: its recessive (mutated) allele induces the overexpression of *SDF-1β* and is linked to coronary heart disease in East Asians [5]. Alterations in this SNP have also been reported in type 2 diabetes mellitus, lung cancer and heart failure [6–8]. The beta 3 subunit of heterotrimeric G-proteins are encoded by *GNB3* and regulate intracellular signalling. The C825T SNP of *GNB3* is located on exon 9 and enhances G-protein activation, and is linked to hypertension, body mass index, hyperlipidaemia, type 2 diabetes and atherosclerosis, all well known risk factors for CAD [9,10]. However, few studies have considered the interaction of *SDF1β* G801A (rs1801157) and *GNB3* C825T (rs5443) with CAD. Therefore, we hypothesised an association of these SNPs with the incidence and severity of CAD.

To test our hypothesis, we recruited 155 CAD patients (defined by at least one significant stenosis on angiography) and 185 healthy controls with similar ethnicity and who were free of a history of chronic, cardiovascular or autoimmune disease. All subjects were recruited from the Department of Medicine, Era's Lucknow Medical College and Hospital, Lucknow, India. The study protocol was approved by Institutional Ethics Committee and written informed consent was obtained from all subjects before blood collection. Total cholesterol was measured by standard methods by the routine service of the hospital. Genomic DNA was extracted from whole blood in EDTA using a standard salting out method with a slight modification. The *SDF1β* G801A (rs1801157) and *GNB3* C825T (rs5443) SNPs were detected by using PCR-restriction fragment length polymorphism with specific primers F-5′CAGTCAACCTGGGCAAAGCC-3′ and R-5′CCTGAG AGTCCTTTTGCGGG-3′; F-5′TGACCCACTTGCCACCCGT GC-3′ and R-5′GCAGCAGCCAGGGCTGGC-3′ for *SDF1β* G801A and *GNB3* C825T, respectively. The digests of the PCR products were performed using two units of restriction enzymes (*MspI* and *BsaJI*, respectively) at 37°C for 16 h. Products were checked by ethidium bromide stained agarose gel. All data were analysed by SPSS (Version 21.0).

The cases and controls were matched for age (mean/SD 52.9 [5.5] and 51.9 [5.4] years, respectively, *t* test $P = 0.072$) but not for sex (119 men and 36 women, 88 men and 97 women, respectively, chi-squared $P < 0.01$) or BMI (24.8 [4.6] and 23.7 [1.2] kg/m^2, respectively, $P < 0.01$). Total cholesterol was 12.0 [1.7] and 8.6 [1.2] mmol/L, respectively ($P < 0.01$). Genotype patterns of *SDF-1β* G801A (rs1801157) and *GNB3* C825T (rs5443) SNPs are shown in Figure 1. Data on genotypes and alleles frequency distribution among cases and controls are shown in Table 1. The risk of CAD was significantly decreased with the GA and GA+ AA genotypes, and the A allele of *SDF-1β* G801A showed significant protection against CAD. Similarly, the *GNB3* C825T TT genotype and T allele were more frequent in the cases. The CAD severity was determined by the number of vessels with significant stenosis; 94 patients had 1 or 2 vessel disease, 61 patients had 3 vessel disease. Analysis according to these criteria failed to find any significant difference in the distributions of the variant SNPs (Table 2).

Molecular genetics is having an increasingly important role in our understanding of the aetiology, diagnosis and management of cardiovascular disease [11].

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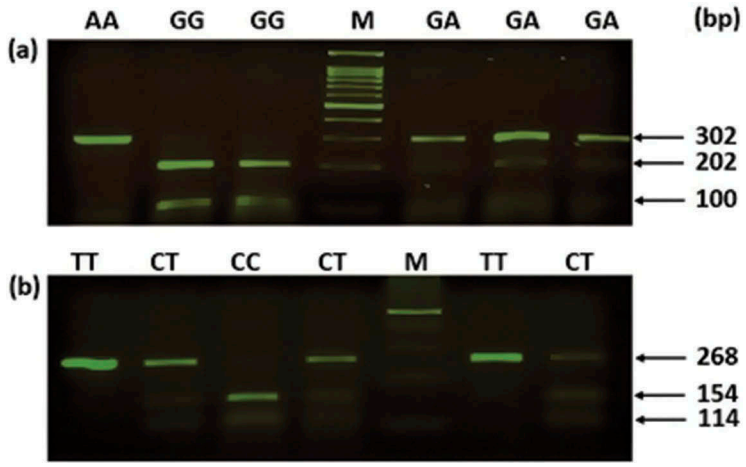

Figure 1. Agarose gels showing different genotypes of *SDF1β* G801A and *GNB3* C825T polymorphisms. (a) SNP (*SDF-1β* G801A) showing GG (Wild): 202, 100 bp; GA (Heterozygous): 302, 202, 100 bp; AA (Mutant): 302 bp (b) SNP (*GNB3* C825T) showing CC (Wild): 154, 114 bp; CT (Heterozygous): 268, 154, 114 bp; TT (Mutant): 268 bp; M: 100 bp ladder.

Table 1. Genotype and allele frequencies of *SDF1β* G801A and *GNB3* C825T SNPs.

	Cases controls		OR (95%CI)	
Genotypes	*N* (%)	*N* (%)		*P* value
***SDF1β* 801A**				
GG	79 (51)	48 (25.9)	1(Ref)	
GA	62 (40)	131 (70.8)	0.29 (0.18–0.46)	<0.0001
AA	14 (9)	6 (3.2)	1.42 (0.51–3.94)	0.503
GA+ AA	76 (49)	137 (74.1)	0.34 (0.21–0.53)	<0.0001
Allele				
G*	220 (71)	227 (61.4)	1(Ref)	
A*	90 (29)	143 (38.6)	0.65 (0.47–0.90)	0.009
***GNB3* C825T**				
CC	68 (43.9)	91 (49.2)	1(Ref)	
CT	51 (32.9)	82 (44.3)	0.83 (0.52–1.33)	0.444
TT	36 (23.2)	12 (6.5)	4.02 (1.95–8.29)	<0.0001
CT+ TT	87 (56.1)	94 (50.8)	1.24 (0.81–1.90)	0.328
Allele				
C*	187 (60.3)	264 (71.4)	1(Ref)	
T*	123 (39.7)	106 (28.6)	1.64 (1.19–2.25)	0.002

CI: confidence interval; OR: odds ratio; Alleles*: total number of chromosomes in cases: 310 and controls: 370. *N*: number. Ref: reference

Our first contribution to this literature is the finding is that the frequency of the A allele of *SDF-1* G801A (rs1801157) is lower in the cases as compared to the controls, bringing a reduction in the odds ratio of some 35%, and so extends the work of Luan et al. in their Chinese cohort [12]. However, this contradicts the findings of Apostalakis et al. in a Greek cohort, where no link was found [13], possible because of differences in the demographics and clinical history of the participants. Our second is that *GNB3* (rs5443) is linked with CAD: the T allele was more frequent in cases than controls, and brought a 1.64 times increase in the odds ratio for CAD. This is in accordance with long-term survival studies where the TT genotype brought increased risk of myocardial infarction [14], and of coronary heart disease and stroke [15]. Despite these differences, our third finding was that neither of the SNPs were linked to the severity of the CAD, as defined by the number of diseased vessels. It follows that other features, such as dyslipidaemia and obesity, are likely to play a part in disease progression, as are other SNPs. These questions can only be answered by larger studies, a limitation of the current work being that the sample size is modest.

Table 2. Association between *SDF1β*G801A and *GNB3* C825T SNPs and CAD severity.

		Number of vessels			
Genotypes/ Alleles		1 or 2 (*N*, %)	3 (*N*, %)	OR (95%CI)	*P* value
***SDF1β* G801A**					
	GG	47 (50.0)	32 (52.5)	1 (Ref)	
	GA	41 (43.6)	21 (34.4)	0.75 (0.38–1.50)	0.42
	AA	6 (6.4)	8 (13.1)	1.96 (0.62–6.18)	0.252
Allele	G	135 (71.8)	85 (69.7)	1 (Ref)	
	A	53 (28.2)	37 (30.3)	1.11 (0.67–1.83)	0.686
***GNB3* C825T**					
	CC	43 (45.7)	25 (41.0)	1 (Ref)	
	CT	30 (31.9)	21 (34.4)	1.20 (0.57–2.53)	0.625
	TT	21 (22.4)	15 (24.6)	1.23 (0.54–2.81)	0.625
Allele	C	116 (61.7)	71 (58.2)	1 (Ref)	
	T	72 (38.3)	57 (41.8)	1.30 (0.82–2.04)	0.269

See Table 1 for abbreviations.

This report represents and advance in biomedical science because it points to the A allele of rs1801157 (*SDF1β* G801A) being protective for CAD, whilst the presence of the T allele of rs5443 (*GNB3* C825T) might be a risk factor for this disease.

Disclosure statement

No potential conflict of interest was reported by the authors.

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