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Short communication

Frequency and association of disabled homolog 2-interacting protein (DAB2IP) variant rs7025486 G>A with coronary artery disease risk in Indian population

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ABSTRACT

Genome wide association study has identified rs7025486 G>A polymorphism within DAB2IP (Disabled homolog 2-interacting protein) gene with increased risk of coronary heart disease (CAD). In this study we have determined the frequency and association of rs7025486 with CAD in Indians. The study was performed on 214 patients with CAD and 125 controls. The 'AA' genotype was associated with an increased risk in the CAD age group <50 yrs as compared to CAD age group>50 yrs (OR 3.149; P 0.034) and controls >50 yrs (OR 3.430; P 0.080). The risk allele (A) was significantly associated with premature CAD.

1. Introduction

In 2010, a Genome wide association study (GWAS) identified a sequence variant rs7025486 (G/A) within Disabled homolog 2-interacting protein (DAB2IP) to have a strong association with increased risk of vascular diseases like abdominal aortic aneurysm (AAA), pulmonary embolism, myocardial infarction (MI) and peripheral arterial disease (PAD) [1]. DAB2IP is a novel member of the Ras-GTPase activating protein family and acts as a tumor suppressor gene.

The minor allele (A) of rs7025486, present within intron-1 of DAB2IP gene on chromosome 9q33 was also found to be associated with 1.08–1.34 higher risk of coronary artery disease (CAD) [1,2]. CAD is a complex, multifactorial disease causing 3 million deaths per year in India alone [3,4].

Till date there is no information available on the frequency and association of DAB2IP

rs7025486 G>A variant with CAD in Indians. The current study aims to address this lacunae by determining the frequency of this variant and its association with CAD/non-fatal MI in the Indian population.

2. Methods

The study population included a total of 339 unrelated individuals which consisted of 214 patients with CAD confirmed by coronary angiography: >50% stenosis in one or more arteries and stable or unstable angina and 125 controls: examined clinically and investigated by electrocardiography and tread mill test to exclude CAD. The study was approved by the local ethical committee and is performed in accordance with the Helsinki declaration. Blood specimens were collected using the vacutainer system from Becton Dickinson (Franklin Lakes, NJ USA).

Serum total cholesterol (TC) triglyceride (TG) and High Density Lipoprotein- cholesterol (HDL-C) levels, were determined by routine enzymatic endpoint methods (X Imola; Randox Laboratories Ltd, UK). Low density Lipoprotein- cholesterol (LDL-C) and VLDL cholesterol were calculated according to Friedwald's formula. Genomic DNA was extracted from EDTA whole blood using QIAamp® DNA extraction kit (Qiagen, Germany).

DAB2IP (G/A) genotypes were determined by real-time PCR Taqman genotyping assay (Applied Biosystems).

Allele frequency were calculated, deviation of the genotype frequencies from the Hardy - Weinberg equilibrium (HWE) was assessed by Fischers exact test. Chi-square tests were used for comparison of binary variables across groups. Routine statistical analysis were carried out with the SPSS v 15 software (SPSS Inc., Chicago, IL). Under the significance level of P = 0.05, minor allele frequency between 0.25 and 0.40, assuming population disease

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Table 1
General Characteristics of Cases and Controls.

General Characteristics	¥Cases (n = 214)	Controls (n = 125)
Age (years)	55 ± 11	49 ± 12
Sex (male)	89%	85%
€Smoker (%)	40.5*	24.3
£ Alcohol (%)	20	22
Hypertension (%)	50Ψ	19
Diabetes (%)	36Ψ	14
Family History (%)	49$	38
TC (mg/dl)	165.5 ± 52.5	192.7 ± 36.3
HDL-C (mg/dl)	38.9 ± 13.4	39.4 ± 7.8
LDL-C (mg/dl)	98.5 ± 45.9	125.1 ± 30.1
VLDL-C (mg/dl)	30.5 ± 19.4	31.4 ± 18.4
TG (mg/dl)	152.6 ± 96.8	156.5 ± 91.4
SVD (%)	27	NA
DVD (%)	8	NA
TVD (%)	41	NA
MVD (%)	24	NA
MI (%)	40	NA

Mean ± SD for continuous variables. SD, standard deviation; NA, not applicable; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; TG, triglycerides; SVD, single-vessel disease; DVD, double-vessel disease; TVD, triple-vessel disease; MVD, multiple-vessel disease; MI, myocardial infarction. *p < 0.001; **p < 0.0001. ¥Includes individuals on lipid lowering medications. €Smokers includes ex smokers for more than 5 years. £ Alcohol consumption indicates individuals with > 5–7 pegs/week. $P < 0.1, *P < 0.005, ΨP < 0.001.

prevalence between 5% and 10% and main genetic effect between 1.5 and 1.2, our study design can reach >85% power when the relative risk (RR) is 1.5 and 50% when it is 1.2.

3. Results

Table 1 displays means and standard deviations for the study subjects for relevant biochemical characteristics as well as risk factors. Statistically significant differences were seen in the smoking status (P < 0.005), presence of family history (P < 0.1), diabetes (P < 0.001) as well as hypertension (P < 0.001) in cases vs controls.

The difference in the frequency of the rs7025486 (A) allele between cases and controls (0.31 vs 0.28), was not significant; OR = 1.157, CI- 0.808–1.659, p-value-0.433 in the univariate analysis as well as in the multivariate analysis; OR = 1.42, CI = 0.85–2.35, p = 0.18 (Table 2a). However when the cases were sub-grouped based on age i.e > 50 years and < 50 years, almost 2-fold higher OR (OR 3.149 95% CI 1.181–8.389) with AA genotype was seen with CAD age group <50 yrs as compared to CAD age group >50 yrs along with statistically significant p-value (0.034) (Table 2b).

4. Discussion

CAD is a substantial and growing problem which has reached almost epidemic proportions in India [4]. This population based cohort study of CAD, determines for the first time the frequency and association of rs7025486 G/A SNP the risk of CAD in select Indian population. This sequence variant is important because it been associated with increased risk of CAD as well as other vascular diseases like AAA, PAD and MI [1].

The minor allele frequency of DAB2IP (A) allele in our study is 0.28, on comparing the allelic frequency in our population with that of other populations obtained from GWAS and HapMap database, it was seen to be almost similar to other populations (European 0.286, Japanese 0.215) [1,5].The HapMap reposition also has data on Asian-Sindhi population and the minor allele frequency of this variant was found to be 0.28 which is similar to the reported frequency in our population.

In the current study, higher frequency of the risk allele A was seen in cases (0.31 vs 0.28) as compared to controls. Both in the univariate and multivariate analysis a trend towards increased CAD risk was seen with the minor allele, albeit not reaching significance.

These findings are in agreement with a recent study where genotyping of 1386 CHD cases and 3532 controls was done, as well as meta-analysis using data from several studies such as the WTCCC [6], CVHS GWAS, Northwick Park Heart Study II (NPHS II), Simon Broome Study, HIFMECH, CABG and UDACS was performed [2,7,8]. The meta-analysis obtained an OR of 1.16, 95% CI 1.05–1.29 indicating statistically significant association of the SNP rs7025486 (A) with CAD. The rare allele was associated with 1.08–1.34 higher risk of CAD and interestingly, it was seen that in

Table 2a
Genotypic and allelic frequency of DAB2IP rs7025486 G/A variant in controls and cases and association with CAD.

	Genotype Frequency n (%)			Allele Frequency		OR	95% CI	P value
DAB2IP rs7025486 G/A	GG	AG	AA	G	A			
Cases (n = 214)	102 (48%)	93 (43%)	19 (9%)	0.69	0.31	1.157	0.808-1.659	0.433
Controls (n = 125)	65 (52%)	51 (41%)	9 (7%)	0.72	0.28	[b]1.42	[b] 0.85-2.35	[b]0.18

OR: Odds ratio by univariate analysis, 95%CI: 95% confidence interval in univariate analysis, P value in univariate analysis. [b]OR, [b]95%CI, [b]P; indicates values by multivariate analysis after adjusting for covariates such as age, sex, presence of family history, diabetes and hypertension.

Table 2b
Genotype, allelic frequency and association of rs7025486 with premature CAD.

Outcome	Genotype Frequency (%)			Allele Frequency		OR AA vs GG	95% CI	P value
	AA	AG	GG	A	G			
CAD < 50 (n = 74)	11(15%)	32(43%)	31 (42%)	0.36	0.64	$3.149	1.181-8.389	0.034
CAD > 50 (n = 140)	8 (6%)	61(45%)	71 (51%)	0.28	0.72			
Controls >50 (n = 55)	3 (5%)	23(42%)	29 (52%)	0.21	0.74	#3.430	0.922-12.526	0.080

$OR CAD < 50 vs CAD > 50, # OR CAD < 50 vs Controls >50.

each of the study groups a trend towards increased risk was seen, whereas only in the CABG (Coronary Artery Bypass Graft) a statistically significant increased risk with OR 1.2, 95% CI 1.03–1.46, P = 0.021 was seen [2].

Most interestingly in our study, the risk allele (A) of SNP rs7025486 conferred a significantly higher OR in the subset of subjects with premature CAD (CAD < 50 years) compared with CAD > 50 years. So it can be suggested that DAB2IP SNP could be a genetic marker for detection of premature CAD.

Though our current study has the limitation of sample size, but the similar frequency of this SNP with respect to other populations and a trend towards increased risk indicates that this can be an important marker even in our population. Larger studies are thus warranted selecting a sub-set of premature CAD cases in the Indian population

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Conflict of interest

The authors have no potential conflicts of interest.

References

[1]. Gretarsdottir S, Baas AF, Thorleifsson G, et al. Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. *Nat. Genet.* 2010;42:692–697.

[2]. Harrison SC, Cooper JA, Li K, et al. Association of a sequence variant in DAB2IP with coronary heart disease. *Eur. Heart J.* 2012;30:1–8.

[3]. Gupta R. Burden of coronary heart disease in India. *Indian Heart J.* 2005;57 (6):632–638.

[4]. Liu H, Liu W, Lia Y, et al. CAD gene: a comprehensive database for coronary artery disease genes. *Nucleic Acids Res.* 2010;1–6.

[5]. http://www.hapmap.org.

[6]. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. The wellcome trust case control consortium. *Nature*. 2007;447:661–668.

[7]. Cooper JA, Miller GJ, Humphries SE, et al. A comparison of the PROCAM and framingham point-scoring systems for estimation of individual risk of coronary heart disease in the second northwick Park heart study. *Atherosclerosis*. 2005;181:93–100.

[8]. Wootton PT, Arora NL, Drenos F, et al. Tagging SNP haplotype analysis of the secretory PLA2-V gene, PLA2G5, shows strong association with LDL and oxLDL levels, suggesting functional distinction from sPLA2-IIA: results from the UDACS study. *Hum. Mol. Genet.* 2007;16:1437–1444.