REVIEW ARTICLE

Genetic epidemiology of coronary artery disease: an Asian Indian perspective

SHANKER JAYASHREE[1]*, MAITRA ARINDAM[2] and KAKKAR V. VIJAY[1]

[1]*Functional Genomics Thrombosis Research Institute, Bengaluru 560 099, India*
[2]*National Institute of Biomedical Genomics, Kalyani 741 251, India*

Abstract

Coronary artery disease (CAD) has emerged as a major cause of morbidity and mortality worldwide. Recent findings on the role of genetic factors in the aetiopathology of CAD have implicated novel genes and variants in addition to those involved in lipid and lipoprotein metabolism. However, our present knowledge is limited due to lack of clarity on their exact identity and the quantum of impact on disease susceptibility, and incident risk. It is a matter of great interest to understand the role of genetic factors in ethnic populations that have a strong underlying predisposition to CAD such as the South Asian populations, particularly among Asian Indians living in India and abroad. Although, a number of isolated studies do implicate certain gene polymorphisms towards enhanced disease susceptibility, the available data remains scanty and inconclusive as they have not been validated in large, prospective cohorts. The present review aims to consolidate the available literature on the genetics of CAD in Asian Indians and seeks to provide insights on the concerns that need to be addressed in future studies to generate information having clinical value.

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Introduction

Our present understanding on the genetic epidemiology of complex disease traits is limited; nevertheless, some remarkable advances in recent times in age-related macular degeneration (AMD) and inflammatory bowel disease (IBD) have led to renewed expectations of similar breakthrough in others (Klein *et al*. 2005; Ng *et al*. 2012). Given the high impact of coronary artery disease (CAD) on the public health burden, substantial efforts are being invested to unravel the genetic epidemiology of CAD across major populations of the world. CAD is polygenic and multifactorial in nature. Hence, large, population-based genome initiatives should be undertaken to derive clinically meaningful outcomes. Asian Indians living in India carry a heavy burden of CAD. Further, Indians living abroad exhibit a predominantly higher disease burden than the native Caucasian populations (Dodani 2008; Liem *et al.* 2009). Presence of premature disease onset and strong family history highlights genetic predisposition as one of the major contributing factors (Nadeem *et al.* 2013). Studies pertaining to Asian Indians include diverse group of subjects ranging from those living overseas such as the descendents of Asian Indian migrants in Netherlands (Liem *et al.* 2009) and USA (Dodani 2008) as well as adults (Fang *et al.* 2005) or neonates (Rao *et al.* 2010) dwelling in their home country. Of the studies that involved the resident Indian population, some hailed from Chennai, Tamil Nadu in southern India (Radha and Mohan 2007; Angeline *et al.* 2011) or from Pune, Maharashtra in western India, which were compared to the UK Caucasians (Chandak *et al.* 2006; Radha *et al.* 2006b), from northern India (Chhabra *et al.* 2002; Agrawal *et al.* 2004; Banerjee *et al.* 2009; Ahmad *et al.* 2012; Gupta *et al.* 2012) and the Punjabis from Punjab in western India and the US who were participating in the Sikh Diabetes Study (Braun *et al.* 2012). The present review attempts to bring together the key findings from various studies on candidate genes and their variants associated with CAD and its comorbidities hitherto reported on Asian Indians.

CAD in Asian Indians: an epidemic?

Over the past few decades, CAD has emerged as one of the leading causes of death and disability worldwide. The annual death rates in India due to cardiovascular disease are predicted to rise from 2.26 million in 1990 to 4.77 million by

*For correspondence. E-mail: jayashreeshanker@triindia.org.in.

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2020 (Murray and Lopez 1997). There was an estimated 17.5 million deaths in 2005 due to CAD alone which is expected to increase by 120% in women and 137% in men by 2020 in the developing countries (World Health Organization 2005; Gupta *et al.* 2008). The estimated prevalence of cardiovascular disease in India is about 10.5% which extrapolates to a burden of about 32 million affected individuals, and amounts to a loss of 15 million disease adjusted life years (Sharma and Ganguly 2005; Goyal and Yusuf 2006). Cross-sectional analysis of epidemiological studies over the past 50 years have shown that CAD prevalence rates have increased from 2% in 1970 to 4.5% in 2000 in the rural areas and from 2% in 1960 to 10.5% in 2000 in the urban areas (Gupta 2008; Gupta *et al.* 2008). The risk of CAD in Asian Indians is nearly three to four times higher than Caucasians, six times higher than Chinese and about 20 times higher than the Japanese populations (Enas and Senthilkumar 2001). As opposed to 22% of CAD related deaths in patients younger than 70 years of age in the Western countries, and 26% in developing countries, it is 52% in India (Bahl *et al.* 2001). Analysis of age-standardized CAD mortality in Canada over a 15-year period has revealed that South Asia, which includes people from India, Pakistan, Sri Lanka, Nepal and Bangladesh, have a higher mortality as compared to individuals of Chinese and European descent (Sheth *et al.* 1999). The coronary artery disease in Indians (CADI) study showed 10% CAD prevalence among the first generation South Asian immigrants to the US as compared to 2.5% in the general population in the Framingham study (Enas *et al.* 1996). Further, high CAD mortality rates have been reported in migrant Indian populations in England and Wales, Canada, Singapore, Mauritius, South Africa and Trinidad (Tan *et al.* 2014). In essence, there is a higher rate of prevalence (Jayasinghe and Jayasinghe 2009), incidence, hospitalization (Enas *et al.* 1998; Klatsky and Tekawa 2005) and mortality rates due to CAD in India as compared to other developed countries like Europe and USA (Tan *et al.* 2014). Further, a strong family history, distinctive disease pattern, smaller coronary artery diameter, higher prevalence of comorbidities like diabetes and hypertension at a much younger age and lower thresholds of comorbidity alongside elevated baseline plasma levels of inflammatory markers like interleukin-6 (IL6) and C-reactive protein (CRP) have been some of the noteworthy features of CAD in this population (Tillin *et al.* 2007; Rao *et al.* 2010; Lee *et al.* 2011). These findings suggest that substantial efforts need to be undertaken within as well as beyond the framework of the classical risk factors with special emphasis on the interplay between the genetic and environmental factors to elucidate the driving forces and the underlying genetic factors which are catalyzing this ongoing epidemic of CAD in the Indian subcontinent.

Genetic epidemiology of CAD

The heritability of CAD is estimated to exceed 50% based on twin studies and family studies (Lusis 2000). Family-based studies suggest five- to seven-fold higher risk of death for the first degree relatives of patients compared to those with no family history (Slack and Evans 1966). With the virtual explosion of genomic information over the last decade from genomewide linkage and association studies assisted by automated technologies, a large number of novel genetic markers have been identified; however, their function, and diagnostic and prognostic implications are yet to be realized (Consortium 2007; Samani *et al.* 2007; Connelly *et al.* 2008; Shah *et al.* 2009; de las Fuentes *et al.* 2012). Some studies have implicated novel candidate genes/loci associated with CAD in their respective cohorts (Kathiresan 2008; Kathiresan *et al.* 2008; Erdmann *et al.* 2009; Tregouet *et al.* 2009). Nonetheless, the quantum of effect of the individual genetic markers on CAD risk appears to be small. Further, the identity of other plausible contributing genetic factors, complex gene–gene and gene–environmental interactions and the magnitude of their collective effect on the onset and progression of CAD remain elusive. In addition, the findings across different ethnic populations generally lack replicability or portability which can be ascribed partly to factors such as clinical heterogeneity, varying genetic landscapes, different environmental effects and confounding effect of the comorbidities (Li *et al.* 2010).

The Indian Atherosclerosis Research Study (IARS) aims to unravel the predisposing factors of CAD in Asian Indians living in their home country (Shanker *et al.* 2010). Large, well-designed multinational studies such as the SABRE (Southall and Brent Revisited) (Forouhi *et al.* 2006) and LOLIPOP (London Life Sciences Prospective Population) (Tan *et al.* 2014) study on Indians and Europeans in UK, the INTERHEART study, a case–control study on primary MI cases and healthy individuals from 52 countries (Yusuf *et al.* 2004) have provided valuable insights on the common and unique predisposing factors leading to premature CAD in Indians (figure 1). The Indian genome variation consortium is a government of India initiative managed by the council of scientific and industrial research that aims to determine the extent of genetic diversity and heterogeneity of the Indian population (2005).

Certain pathways and genes have been implicated in the aetiopathology of CAD. Most of these reports are based on the Hap Map populations that are not as yet replicated or validated in Asian Indians. Table 1 provides the summary of the major pathways implicated in CAD, the associated genes, polymorphisms and plasma biomarkers reported on Asian Indians. Details of candidate genes and their variants implicated till date in this highly predisposed population are summarized below.

Genetic markers associated with CAD

Inflammation

Inflammation plays a significant role in the onset and progression of atherosclerosis (Libby *et al.* 2002; Shishehbor

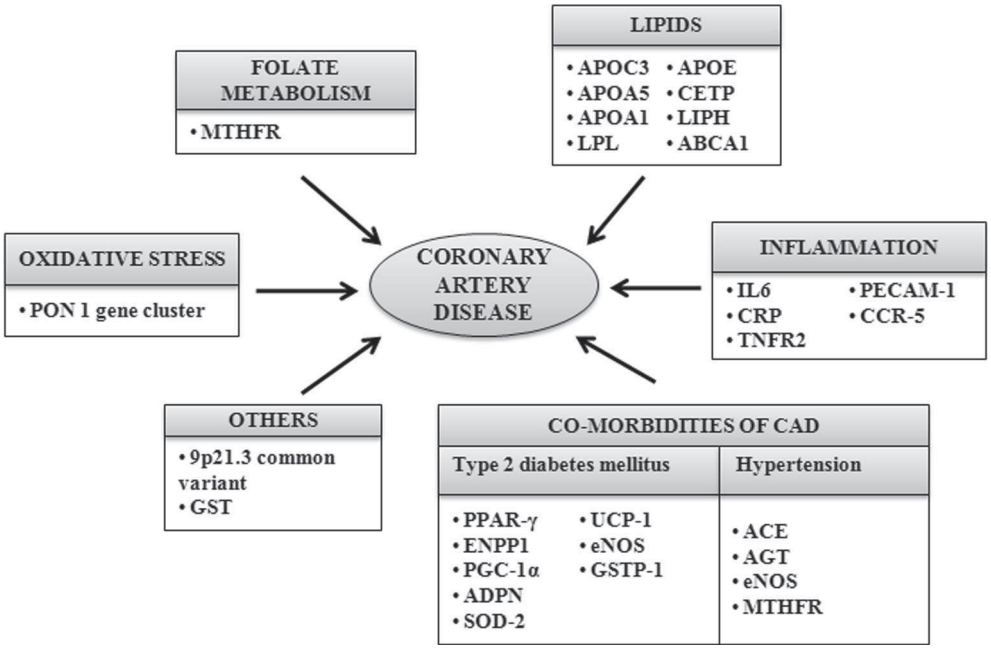

Figure 1. Overview of genes and genetic variants associated with CAD pathways investigated in Asian Indians.

and Bhatt 2004; Golia *et al.* 2014). The importance of various inflammatory markers like IL6, CRP, fibrinogen and tumour necrosis factor-α (TNF-α) have been highlighted at various stages of the disease process (Tuomisto *et al.* 2006). Several conflicting reports have been published on the putative association of *IL6* gene polymorphisms with CAD (Jang *et al.* 2008; Bhanushali and Das 2013; Yin *et al.* 2013). These variants are located mainly in the promoter region and regulate the expression of IL6 and its acute phase response markers such as CRP and fibrinogen (Vickers *et al.* 2002). A risk haplotype, GGAAG was reported in the promoter region of IL6 gene in a subset of patients with age at onset under 45 years and that was shown to modulate plasma CRP and fibrinogen levels (Maitra *et al.* 2008). Patel *et al.* (2008) have commented that as there in general consenses on early CAD onset in Asian Indian based on earlier reports, the findings Maitra *et al*. (2008) could further contribute to a better understanding of the genetic basis of premature CAD, at least in Asian Indian. In fact, susceptibility to premature disease may be ascribed to an inherent genetic predisposition to a chronic proinflammatory state.

CRP

CRP is a marker of systemic inflammation and a predictor of cardiovascular events (Wang *et al.* 2014). High sensitive CRP (hsCRP) has been associated with risk of CAD in Asian Indians (Mohan *et al.* 2005) and acts as a predictor of metabolic syndrome risk independent of insulin resistance and obesity (Mahajan *et al.* 2012). Although genetic determinants modulating CRP expression have been recently identified, their associations with CAD remain to be confirmed in this population (Reiner *et al.* 2008; Ridker *et al.* 2008). Another important candidate is the proinflammatory cytokine TNF-α which has been implicated in the formation and progression of the atheromatous plaque (Battes *et al.* 2014). A study based on a small sample size has reported the association of genetic polymorphisms located in the gene coding for one of the receptors of TNF-α (TNFR2) with CAD (Sankar *et al.* 2005). Platelet endothelial cell adhesion molecule-1 (PECAM-1) is known to play an important role in vascular inflammation and mediates the transendothelial migration of circulating leucocytes which in turn might lead to the development of atheroma (Elrayess and Talmud 2005). In a study conducted on Asian Indians based in Singapore, L125V polymorphisms in the PECAM-1 gene and plasma level of soluble PECAM-1 was found to be associated with CAD (Fang *et al.* 2005). A few reports on the genes coding for other modulators of inflammation, namely Chemokine receptor-5 (*CCR5*) are also available in this population (Sharda *et al.* 2008). Given the emerging importance of inflammation in atherosclerosis, exhaustive and organized investigative efforts are required to further delineate the contribution of inflammatory genes to the enhanced risk of incident and recurrent events.

Common genetic variants in the 9p21 locus

Recent studies have reported the association of common variants in the 9p21 genomic region with premature CAD, abdominal aortic and intracranial aneurism as well as stroke in Caucasian and other populations Helgadottir *et al*. 2007, 2008. Previously, Koreans and Japanese were the only Asian populations to have been tested for these variants (Hinohara *et al.* 2008; Shen *et al.* 2008). We were the first group from India to report the association of rs10757278

Table 1. Summary of major pathways, genes, genetic variation and plasma biomarkers associated with CAD as reported in Asian Indians.

Pathways	Gene involved	Genetic variation	Associated disease-related traits
Inflammation	*IL6*	(rs1800797, rs1800796, rs7802307, rs7802308, rs1800795) constituting promoter haplotype (GGAAG)	CAD, plasma levels of hsCRP and fibrinogen
	TNFR2	MM genotype at 196 position	CAD, progression of atherosclerosis and TNF-α levels
	PECAM-1	L125V	CAD, atherosclerosis, soluble PECAM-1 in plasma, P-selectin and lipid levels
	CCR5	Delta32 deletion	CAD
Lipid metabolism	*ABCA1*	−14C/T	Premature CAD, plasma levels of HDL-c, triglycerides and cholesterol
	LIPH	−514C/T	CAD, plasma levels of triglyceride and HDL-c
	CETP	TaqIB and −629C/A	CVD, CETP activity, plasma levels of triglycerides and HDL-c
	APOE	apoE3/E4	Premature CAD and MI, hypertension, stroke, dyslipidaemia and accelerated atherosclerosis, plasma levels of triglycerides and lipoprotein (a), serum apoE levels
	APOA1	−75G/A	CAD, plasma lipid and apoA-I levels
	APOA5	−1131T/C	Premature CAD, serum triglycerides, pancreatitis, diabetes
	APOC3	APOC3-Sac1 and ApoC3-/SstI (S2 allele)	CAD, hypertension, plasma triglycerides, TC, HDL-c and ApoB levels
	LPA	−93T/G	CVD, obesity, carotid stenosis, serum homocysteine, uric acid, plasma lipoprotein (a) and CRP levels
	LPL	Hind III (T–G) and Ser447Ter constituting (H+ Ser) haplotype	Serum HDL-c and triglyceride levels
Folate metabolism	*MTHFR*	MTHFR 677 CT and MTHFR 1298 CC	CAD, hypertension, plasma homocysteine and folate levels
Oxidative stress	*PON1*	Cys311Ser and Gln192Arg	CAD, MI, hypercholesterolaemia-plasma levels of lipids, plasma PON1 activity
DNA damage	*GST*	GSTT1 (null)	CAD
Renin–angiotensin pathway	*ACE*	Alu ACE insertion/deletion polymorphism	CAD with triple vessel defect and associated with diabetes
	9p21	rs10757278, rs10757274, rs2383206, rs1333049, rs4977574	CAD

CAD, coronary artery disease; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; TC, total cholesterol; TNF-α, tumour necrosis factor alpha.

variant with young CAD (Maitra *et al.* 2009) and this has been further supported by functional studies (Shanker *et al.* 2014). Kumar *et al.* (2011). have reported the association of six variants with CAD in a representative cohort from north India (Kumar *et al.* 2011). This region does not harbour any known gene. However, the implicated variants are located in the vicinity of the *CDKN2A* and *CDKN2B* genes, which are known to have a regulatory role in cell proliferation, ageing and apoptosis, processes that are important in the aetiopathology of CAD and atherosclerosis (Helgadottir *et al.* 2007). Additionally, exons 13 to 19 in antisense noncoding RNA in the INK4 locus (ANRIL), an antisense RNA that might be a part of the cellular transcriptional regulation machinery and expressed by multiple cell types involved in atherosclerosis overlap with this genomic region (Broadbent *et al.* 2008). Studies including our recent publication (Shanker *et al.* 2014) demonstrate that the impact of the 9p21.3 locus on CAD is independent of the classical risk factors and is primarily mediated through the association of ANRIL with the CDKN2A/2B genes which together control cellular proliferation (Jarinova *et al.* 2009; Congrains *et al.* 2012). Given the strong implication of this genomic region in CAD, elucidation of the underlying molecular mechanism is under progress and could hold tremendous value as a potential genetic marker of clinical utility.

Lipid metabolism

Atherogenic dyslipidaemia, defined by high triglycerides, low high-density lipoprotein cholesterol (HDL-c) levels and elevated levels of small, dense, low-density lipoprotein-cholesterol (LDL-c) particles, is predominant among Asian Indians and has been identified as one of the well-established risk factors of CAD (Guptha *et al.* 2014). Further, metabolic syndrome is an antecedent to both dyslipidaemia and CAD, and has been previously shown to be present in 56% of CAD patients in a predisposed Asian Indian cohort having a strong family history (Kanjilal *et al.* 2008). Although several

genes have been associated with dyslipidaemia, hypertriglyceridaemia in particular and subsequent risk of CAD, the frequency of allele distribution vary in Asian Indians as compared to the Caucasian population (Chandak *et al.* 2006). Most of the knowledge gained on the role of genetic variants in dyslipidaemia and associated morbidities till date have been primarily based on reports on Asian Indians living in India, on minority ethnic communities in Singapore (Heng *et al.* 2001) and South Africa (Ranjith *et al.* 2004). Studies conducted on Indians from the subcontinent include the apolipoprotein-C *ApoC3 SSt1* variant associated with hypertriglyceridaemia in a healthy population from northern India (Chhabra *et al.* 2002), the apolipoprotein-A5 (*APOA5*) gene variants from an adult cohort from western India (Chandak *et al.* 2006) and the lipoprotein lipase (*LPL*) gene variants in the Chennai Urban Rural Epidemiology Study (CURES) (Radha *et al.* 2006a). A report on the *APOA1-C3-A5* gene cluster has shown that the *APOC3-Sac1* polymorphism and the *APOA1 –75G>A* variant accounted for over 60% of the variability in CAD status in a cohort of 190 affected sibling pairs (Shanker *et al.* 2008). Variants in this locus have been shown to modulate the response to lipid-lowering therapy by fenofibrates (Liu *et al.* 2009). Replication of lipid genes/SNPs derived from GWAS has reiterated the contribution of SNPs in the 11p23.3 region to the regulation of plasma triglycerides (Braun *et al.* 2012). Investigations are on to clarify the pharmacogenomic implications of this locus.

Polymorphisms in the *APOE* and *APOA1* genes can function in a synergistic manner and modulate CAD risk (Rai *et al.* 2008). These genes have also been implicated in studies on Asian Indians living in Singapore (Lai *et al.* 2003) and South Africa (Ranjith *et al.* 2004). In a comparative study on three different ethnic groups living in Singapore, namely Asian Indians, Chinese and Malays, it was observed that despite a high incidence of cardiovascular disease (CVD), the differential allele frequencies could not account for the presence of low HDL-c among these groups. This study also showed group-specific interaction between the dietary cholesterol intake, the *Taq1B* polymorphisms in the cholesteryl ester transfer protein (*CETP*) gene and HDL-c levels (Tai *et al.* 2003b). Similar observations have been independently reported in patients from the subcontinent (Mukherjee and Shetty 2004; Padmaja *et al.* 2009). In the Sikh Diabetics study, low CETP activity was associated with CAD risk. Although, there was no association between the *CETP* polymorphisms and CETP activity, their association was shown to affect HDL-c levels (Schierer *et al.* 2012).

In addition to these reports, investigations on the polymorphisms in the gene encoding hepatic lipase (*LIPH*) have also revealed association with CAD in Asian Indians (Tai *et al.* 2003a). The association of the polymorphisms of the ATP-binding cassette transporter-1 (*ABCA1*) gene with CAD and variations in the plasma lipid levels has been investigated in a cohort based on the Chinese, Malay and Indian populations located in Singapore and the association was shown to be influenced by ethnicity (Tan *et al.* 2003).

Folate metabolism

Elevated level of total homocysteine is shown to be an independent risk factor for CAD in certain populations, including Asian Indians (Vinukonda *et al.* 2009; Gupta *et al.* 2012). Oxidative damage, smooth muscle cell proliferation and modification of LDL are some of the adverse effects of homocysteine that may impact on the atherosclerotic disease progression. Homocysteine is released in the blood following the breakdown of methionine and elevated homocysteine levels can cause hardening of arteries and lead to heart attack and stroke (Varga *et al.* 2005). Deficiency of B vitamins and folate in the diet can cause an increase in blood homocysteine levels. Common genetic variants in the methylenetetrahydrofolate reductase (*MTHFR*) gene impair the ability to process folate, thus leading to higher homocysteine levels (Varga *et al.* 2005). To date, the most common variant studied is C677T, which is considered as a determinant of circulating homocysteine level (Bharatkumar *et al.* 2014). Nair *et al.* (2002) reported significant association between heterozygous C677T variant and hyperhomocysteinaemia (Nair *et al.* 2002), Mukherjee *et al.* (2002) showed low prevalence of this variant whereas Kumar *et al.* (2005) reported the association of another MTHFR variant, A1298C with plasma homocysteine levels. In contrast, Deepa *et al.* (2001) did not observe any significant association between serum homocysteine levels and CAD in a small south Indian male cohort. Significant positive correlation has been reported between elevated plasma homocysteine levels and increased DNA methylation in CAD patients (Sharma *et al.* 2008).

Oxidative stress

Paraoxanase-1 (PON1) activity is considered to be atheroprotective based on its ability to prevent the formation and hydrolysis of lipid peroxides, notably LDL. Low serum PON-1 levels have been found to enhance oxidative stress and hence acts as an independent risk factor for CAD (Singh *et al.* 2007). Variations in *PON* gene cluster have been found to be associated with CAD in a population specific manner (Sanghera *et al.* 1998; Reddy *et al.* 2008; Agrawal *et al.* 2009; Ahmad *et al.* 2012). While Agrawal *et al*. (2009) demonstrated a significant association of PON1-192R allele and RR genotype to be associated with CAD in a north Indian cohort, Ahmad *et al*. (2012). showed the association of a 2-SNP and 3-SNP haplotypes involving variants in the coding and promoter regions of *PON1* gene with CAD whereas Sanghera *et al*. showed a synergistic effect of both *PON1* and *PON2* gene polymorphism contributing to CAD risk in Asian Indians.

DNA damage

DNA damage can lead to atherosclerosis (Kaya *et al.* 2012). The glutathione *S* transferase (GST) enzyme protects the

DNA from genotoxins and adduct formation. Polymorphisms in the *GST* gene have been widely investigated in relation to CAD (Wilson *et al.* 2003). A protective role of the GSTT1-null genotype in CAD has been reported on a small Indian cohort (Girisha *et al.* 2004).

Comorbidities of CAD

Insulin resistance, which is closely related to obesity, is an important comorbidity of CAD, particularly among Asian Indians (Misra and Vikram 2004). Epidemiological studies suggest that a high underlying genetic risk compounded by lower thresholds for acquired risk factors such as age, abdominal adiposity and increased body fat percentage, in spite of a normal body mass index, serve as an important link between obesity and insulin resistance in Indians (Chandalia *et al.* 1999; Ramachandran *et al.* 2004; Misra and Khurana 2009). Although environmental agents do influence this trait to some extent, evidence obtained from epidemiological observations, twin and family studies suggest a strong heritable component in type 2 diabetes (Ty2DM) (Radha and Mohan 2007). In a study involving 1250 sibling pairs from 508 Asian Indian families, living in Indian subcontinent and having a strong predisposition to CAD, significant concordance was observed for both diabetes and hypertension, implicating a predominant genetic component in the aetiology of these traits in this population (Shanker *et al.* 2007). The peroxisome proliferator activator receptor-γ (*PPAR-*γ) gene, a transcription factor involved in adipogenesis is an important locus that regulates glucose metabolism (Tonjes and Stumvoll 2007). A comparative study among Caucasians and south Asians from India has shown that a polymorphism in this gene, which is protective against Ty2DM in the former group, does not show a similar effect in Asian Indians (Radha *et al.* 2006b). On the other hand, the K121Q polymorphism on exon 4 of the ectonucleotide pyrophosphatase/phosphodiesterase-1 (*ENPP1*) gene was found to predict susceptibility to Ty2DM among both Asian Indian and Caucasian populations (Abate *et al.* 2005). A PPAR-γ coactivator-1 alpha (*PGC-1*α) gene polymorphism was found to confer 1.6 times greater risk of Ty2DM in a population from south India (Vimaleswaran *et al.* 2005). Similarly, the +10211T>G polymorphism of the adiponectin gene (*ADPN*) was found to be significantly associated with Ty2DM, obesity and hypoadiponectinaemia (Vimaleswaran *et al.* 2008). In a study involving 1100 normal glucose tolerant (NGT) and 1100 type 2 diabetic subjects selected from CURES, four out of eight adiponectin gene variants (+276 G/T (rs1501299), −4522 C/T (rs822393), −11365 C/G (rs266729) and +712 G/A (rs3774261)) and two 8-SNP haplotypes (GCCATGAAT and AGCGTGGGT) contributed to the risk of developing type 2 diabetes, obesity and hypoadiponectinaemia (Ramya *et al.* 2013). Additionally, genetic polymorphisms in the superoxide dismutase 2 (*SOD-2* Ala9Val), uncoupling protein 1 (*UCP-1* −112T>G and Ala64Thr), endothelial nitric oxide synthase, (*eNOS* Glu298Asp), glutathione *S* transferase P1 (*GSTP-1* Ile105 Val) and other nonconventional genes in the cytokine and dopaminergic pathways have also been implicated in Ty2DM, insulin secretion and resistance (Chandak *et al.* 2007; Prasad *et al.* 2008; Angeline *et al.* 2011) and appear to indirectly exert an impact on the onset and progression of CAD. Hypertension is yet another important risk factor for CAD. The prominent genes implicated till date in hypertension in the Indian population are angiotensin converting enzyme (*ACE*), angiotensinogen (*AGT*), *eNOS* and *MTHFR* (Markan *et al.* 2007; Das *et al.* 2008; Nejatizadeh *et al.* 2008; Periaswamy *et al.* 2008). Genetic variants include the common insertion/deletion polymorphism in the *ACE* gene (Das *et al.* 2013) which has shown a similar pattern of association across several ethnic groups.

Present limitations and future studies

At present, there is limited information available on the reported genetic factors of CAD in Asian Indians. Further, most of the studies conducted till date lack sufficient power to detect significant associations and are based on cohorts from divergent ethnic backgrounds thereby leading to contradictory findings (Mukherjee *et al.* 2002; Agrawal *et al.* 2004; Banerjee *et al.* 2009). Large scale prospective studies based on phenotypically well-characterized patients and controls that are matched for age, gender and ethnicity should be given priority while selecting the study population. In addition to the clinical data, information on anthropometrics, demographics, socio-economic conditions as well as food habits and lifestyle should be recorded at the time of enrollment of the study participants. This would permit an exhaustive analysis, which when considered together with the genetic and biomarker data as well as quantitative correlates of the disease might lead to the development of a robust risk prediction model of high clinical relevance. Promising developments in the field of noninvasive imaging indicate that information on arterial endothelial dysfunction and arterial compliance might provide novel information on the natural course of disease progression in both symptomatic as well as asymptomatic patients (Paul *et al.* 2005; Chang *et al.* 2006). Hence, analysis of genetic variations in the context of such background information might provide important breakthroughs in our understanding of the molecular basis of CAD.

An important aspect of any genetic epidemiological investigation is the strategy adopted for the selection of genomic variants for the study. In this regard, the haplotype tagging SNPs (tag SNPs) provide maximum information and simultaneously prevent the analysis of redundant markers. Exhaustive databases compiled on existing genomic variation can facilitate marker selection; however, such information is currently available only for the Caucasian, Yeruban,

Han Chinese and the Japanese populations in the HAPMAP database (Consortium 2005). Published studies suggest that the HapMap data should be carefully reviewed prior to extrapolation and application on other populations (Biswas *et al.* 2007). Recently reported population genetic studies conducted on Asian Indians have indicated that the genetic diversity of this population is distinct from those included in the HapMap (Consortium 2008). Further, the portability of tag SNPs across the various ethnic groups of India is low and hence resequencing of representative participants from such groups should be undertaken prior to the selection of markers for large-scale genotyping (Sarkar Roy *et al*. 2008). Recent advances in network biology and selection of genes based on topological parameters and complex computational algorithms can provide additional basis for gene prioritization. Such observation can have a profound impact on the design and outcome of future genetic epidemiological studies.

In conclusion, Asian Indians serve as a hotbed for conducting genetic epidemiological research due to the high propensity for developing premature heart disease and a strong familial predisposition. This provides unique opportunities to undertake systematic large-scale studies in order to understand the genetic epidemiology of CAD. Such studies should be designed with care, conform to the principles of statistical genetics and take into account the genetic diversity of the Indian population rather than rely solely on the data available in the HapMap database. Exhaustive information on various clinical and other phenotypic aspects as well as ethnicity of the study participants should be given due consideration while analysing genomic data of clinical relevance. Further, comparison of findings based on Asian Indians located in the Indian subcontinent and abroad might provide interesting information on the contribution of environmental factors and varied lifestyles that could modulate the genetic susceptibility of the disease. Such findings are expected to contribute significantly towards the elucidation of the genetic epidemiology of CAD in Asian Indians and thereby lead to the development of effective methods for detection and quantification of genetic risk.

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