Genetics of Coronary Artery Disease and Its Association with Dyslipidemia in Diabetes Mellitus in India

Ishaan Siwach1, Chiranjeev Singh Sethi2, Amit Kumar Yadav3

Abstract

Coronary artery disease is amongst the commonest diseases seen in India. Increasingly it has been realized that Indians are very prone to get this disease. The genetic basis of this predisposition and its relation to dyslipidemia is discussed in detail.

Keywords: Coronary artery disease, Genetics, Dyslipidemia

Introduction

Coronary artery disease (CAD) has emerged as a major cause of morbidity and mortality 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 2020.1 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.2 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.3

Recent findings on the role of genetic factors in the etiopathology 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 Indians.4 Numerous studies have shown that patients with diabetes mellitus have accelerated atherosclerotic vascular disease, and major advances in understanding its pathogenesis have been made.

Lipid Metabolism

Atherogenic dyslipidemia, 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 Indians and has been identified as one of the well-established risk factors of CAD.5 Further, metabolic syndrome is an antecedent to both dyslipidemia 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.6

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Although several genes have been associated with dyslipidemia, hypertriglyceridermia in particular and subsequent risk of CAD, the frequency of allele distribution vary in Asian Indians as compared to the Caucasians. Studies conducted on Indians from the subcontinent include the apolipoprotein-C ApoC3 Sst1 variant associated with hypertriglyceridermia in a healthy population from northern India, the apolipoprotein-A5 (APOA5) gene variants from an adult cohort from western India and the lipoprotein lipase (LPL) gene variants in the Chennai Urban Rural Epidemiology Study (CURES). 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. Polymorphisms in the APOE and APOA1 genes can function in a synergistic manner and modulate CAD risk. These genes have also been implicated in studies on Asian Indians living in Singapore and South Africa. 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. Similar observations have been independently reported in patients from the subcontinent. 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.

Comorbidities of Coronary Artery Disease

Insulin resistance, which is closely related to obesity, is an important comorbidity of CAD, particularly among Asian Indians. 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. 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 etiology of these traits in this population. The peroxisome proliferator activator receptor (PPAR) gene, a transcription factor involved in adipogenesis is an important locus that regulates glucose metabolism. 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.

Based on the above discussion, major factors involved in the etiopathogenesis of CAD are summarized in Table 1 and presented in Fig.1.

Conclusion

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. 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. Exhaustive information on various clinical and other phenotypic aspects as well as ethnicity of the study participants should be given due consideration while analyzing 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 in this population.
Table 1. Summary of Major Pathways, Genes, Genetic Variation and Plasma Biomarkers Associated with CAD as Reported in Indians

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

CAD, coronary artery disease; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; TC, total cholesterol; TNF-α, tumor necrosis factor alpha
Figure 1. Summary of Major Pathways, Genes, Genetic Variation and Plasma Biomarkers Associated with CAD as Reported in Indians

Conflict of Interest: None

References

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