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Review Article

Genetics of coronary artery disease – A clinician's perspective

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ABSTRACT

Coronary artery disease (CAD) is the major cause of fatality and disability among all cardiovascular diseases (CVD). Intricate interactions of genes and environment dictate the outcomes of CAD. Technological advances in the different fields of genetics including linkage studies (LS), candidate gene studies (CGS) and genome-wide association studies (GWA studies) have augmented the knowledge of pathogenesis of CAD. LS were more successful in identifying genetic variants among monogenic disease. GWA studies were relatively popular in identification of variation in polygenic disease. Until now, GWA studies recognized about 50 loci determining around 6% of the heritability in CAD. Clinical utility of the above knowledge would result in better CAD management, but validation of the variants in native population is warranted for active adoption into the clinic. The major aim of this review is to provide an adequate perspective of our current understanding and advances of genetics in CAD.

1. Introduction

Coronary artery disease (CAD) has reached epidemic proportions and is the significant cause of death among Cardiovascular Diseases (CVD).[1,2] Around three and half million Indians, both men and women had became victim to death due to CAD.[3–5] Further, CAD occurs ten years earlier in Indians when compared to the western population with 50% occurring in individuals below 50 years and 25% in individuals below the age of 40 years.[5,6] Moreover, 40–50% of subjects with CAD do not have any associated risk factors.[6] It is now universally accepted that CAD has a significant hereditary component, especially in the younger generation, and is widely reported in published studies, including familial, twin-concordance, pedigree, and adoption studies.[7–12]

Delineation of genetic factors associated with CAD is best studied in a phased manner. The primary phase entails recognition of the inheritable component/s of CAD. The secondary phase involves teasing the genetic framework of CAD, i.e., identification of exclusive loci, and the transmissible

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variants within the loci that lead to CAD susceptibility. The incidental phase is the most complicated aspect of the whole genetic characterization of CAD.

Basing on the apparent patterns of inheritance, genetic diseases are classified into two broad categories i.e. monogenic and polygenic forms. In the monogenic form of disease, familial variation in one gene is responsible for all or the major part of the disease incidence. Polygenic diseases, group gene variants are responsible for the intricate patterns of inheritance. Their interplay with each other often results in negligible effect and their interplay with a number of environmental factors leading to the outcome.

2. Historical and current understanding of CAD genetics

Our apprehension about the genetic framework of CAD has pronouncedly increased since 2007, when the first GWA studies in CAD were reported and a brief overview of the historical milestones in CAD genetics is documented in Table 1. A whole scale of intricate differences was identified in human genome. These differences range from single nucleotide polymorphisms (SNPs) to large variations such as deletions, insertions, translocations, and copy number variations. The original approach of research before 2000 was through analysis of inheritance patterns in susceptible families, through genetic LS. Positive results were obtained in identification of genetic variants in single gene disorders. For complicated diseases, the aforementioned approach was not so beneficial. This paved the way for introduction of GWA studies, used to catechize common genetic variants in diverse individuals associated with a particular trait. Two preliminary GWA studies in CAD were published concurrently in 2007, which documented the role of 9p21 loci in myocardial infarction (MI) and CAD; a third study later reproduced the above findings.[13–15] Our understanding of the genetic framework of CAD has significantly improved from the above studies.

Table 1 – Historical milestones in genetics and CAD genetic studies.

1953	J.D Watson and F.H Crick delineated the molecular structure of nucleic acid
1968	Deciphering of the genetic code
1975	DNA sequencing
1977	Development of electrophoretic methods for DNA sequencing
1983	Polymerase chain reaction
1987	First human genetics map using restriction enzyme digestion
2001	Initial sequencing and analysis of Human Genome.
2005	Detailed map of SNP variants by International HAP MAP project
2006	First computerized microarray assembled. Preliminary report of gene interrelation with an attribute using GWA studies
2007	Two SNPs at 9p21 associated with MI and CAD by GWA studies
2010	GWA studies described CVD risk factors (95 loci related with lipids, 30 loci with BMI and obesity)
2011	GWA studies reported >30 gene loci associated with CAD

In early 2013, a meta-analysis study listed 50 genetic variants associated with CAD. These variants explain more or less 6% of the inheritance effect transmitted in CAD. Most of these variants are associated with triglyceride-metabolism, hypertension, and inflammation, suggesting their role in the pathogenesis of CAD. Interestingly, the above study found no overlap between the CAD loci, and those affiliated with Type-2diabetes.[16,17] Moreover, most of these CAD loci are located in intragenic regions of the genome with unknown functions.

3. Coronary atherosclerosis and atherothrombosis

The various genetic markers associated with CAD discovered through studies can be grouped into four major biological pathways. These pathways are responsible for the pathogenesis of lipid disorders, endothelial dysfunction, arterial inflammation, and thrombosis.[18,19]

i. Familial Hypercholesterolemia (FH): High levels of LDL in the blood characterize FH, which is often present as tendon and joint xanthomas. Numerous studies have demonstrated the role of lipid irregularities, mainly altered levels of LDL–C as a risk factor for CAD. Although FH is often diagnosed by evidence of high LDL levels and family history of premature heart disease, the unequivocal diagnosis of FH is done through genetic testing. FH is most usually transmitted as an autosomal co-dominant trait.[20]
   a. Autosomal Dominant – Loss-of-function deviation in the LDL–receptor gene results in autosomal dominant form of FH. Overall, there have been more than 800 different documented mutations involving the LDL–R gene. This receptor is found on the surface of all nucleated cells, but mainly in the liver. LDL receptors facilitate the uptake and degradation of LDL from the circulation. As such, mutations to the LDL receptor lead to higher plasma levels of LDL.[21] There are two forms of FH – homozygous and heterozygous. The homozygous form is rare with a frequency of less than $1/10^6$, is associated with a complete absence of the LDL receptor, and can lead to four times the normal LDL value. About 40% of FH, homozygotes may develop CAD before the age of 20. They generally do not respond to dietary or drug treatment. The heterozygous form with a frequency of about 1 in 500 in most populations can cause an elevation in LDL levels of about twice the normal value. The heterozygous forms do respond to dietary and drug treatment.

Apogene: ApoB that encodes Apo lipoprotein (ApoB) is also involved in autosomal dominant transmission of FH. It is by the recognition and binding of ApoB on the surface of LDL particles that the LDL receptor is able to mediate the endocytosis of LDL from circulation. Unlike the over 800 LDL-R mutations that were documented, there have been only two variants found on ApoB. The prevalence of mutation in this gene is 1 in 100. Clinically, a phenotype caused by an ApoB mutation cannot be distinguished from that caused by LDL–R mutation, although the former tends to be less severe as the defective ApoB allele exhibits incomplete penetrance. It should be noted that some

sources refer to the disease caused by an ApoB gene mutation as familial defective ApoB 100 (FDB) rather than FH.[22]

PCSK-9 gene: PCSK–9 is the most recent entry found to be responsible for the autosomal dominant transmission of FH. Although the mechanism is not completely understood it is thought that PCSK – 9 is a serine protease that is involved in the regulation of blood cholesterol levels by breaking down the LDL receptors within the liver cells before they are able to reach the surface. Mutations in this gene are relatively rare with a prevalence of less than one in 2500.[22]

b. Autosomal Recessive – *LDLRAP1 An* autosomal recessive form of hypercholesterolemia referred to as autosomal recessive hypercholesterolemia (ARH), has also been found in a small number of patients with hypercholesterolemia. Only one gene LDLRAP1 has been implicated in ARH. LDLRAP1 encodes LDL receptor adaptor protein 1 which is required for endocytosis of LDL particles by liver cells.[21]

Cholesterol 7a-hydroxylase deficiency is also a rare autosomal recessive disease that causes high cholesterol and triglyceride levels.[22]

4. Landscape of genetic studies in CAD

Interplay of many factors is relevant in the manifestation of disease including lifespan, gender, gene pool, and environment. There is considerable variability in susceptibility and expression of disease even with the same degree of exposure/time of environmental risk factors. This considerable variability is due the individual's unique genetic make-up, or some other potentiating risk factor or the interplay of factors among them. Genetic landscape studies in CAD are generally conducted by two most popular approaches, i.e. linkage studies (LS) and association studies (AS).

i. Linkage studies (LS) – LS involves identification of genetic variants among individuals of affected families for many generations. LS usually commence by recognizing genetic markers, leading to either a gene or gene variant (SNP) of interest. LS are exemplary studies for pin-pointing disease risk site across the genome, and can be used to study different genetic markers concurrently.[17] The major drawback of LS is that researchers need to pool a large number of afflicted families in generation. In addition, LS hold good for study of single genes only and not when multiple genes are involved.

LS in CAD yielded mixed results among diverse population studies. Genomic regions/loci from published LS is largely non-overlapping, implicating genetic and or phenotypic diversity. The original fine mapping LS yielded two genes, i.e. ALOX5AP and MEF2A. Different Haplotypes of the ALOX5AP gene in the Icelandic locus corresponded with CAD in the population-based studies of Iceland/England. The same Icelandic haplotype was linked to stroke in Iceland and Scotland.[23] Another transcription factor expressed in coronary artery endothelium Myocyte enhancer factor 2A (MEF2A) was identified by LS in a pedigree analysis in which 13 individuals had CAD, nine had MI.[23]

ii. Association studies (AS) – These studies assess the correlation between genetic variants, either single nucleotide polymorphisms (SNPs)/copy number variations (CNVs).[17] The most common and significant limitations of these studies are defining the phenotype to be studied and reduplication of the findings among different populations. In addition, to recognize genetic variants with minor effects, large population sizes are required. This is obtained by pooling different samples and populations. There are several types of AS, which are outlined below:
   a. Candidate gene studies (CGS) – CGSare generally used for study of complicated diseases with transitional traits. This approach is based on an a-priori postulation generated from knowledge of disease pathogenesis and or leads from preceding studies. Many CGS analyzing the correlation between genetic variants and phenotypes were published. The major limitation of these studies is the reproduction and reduplication of the results.
   b. Genome-Wide Association Study (GWA study) – The major objective of GWA studies is to recognize hereditary variants correlating with complex phenotypes, without the prior selection of candidate loci or genes. GWA studies rely majorly on two presumptions: primarily, a greater part of variation in the genome can be explained by a relatively smaller number of genetic variants and second; complex diseases are predominantly generated by close interaction of common genetic variants.[17] GWA studies became accomplishable through technological breakthroughs allowing large numbers of SNPs to be genotyped simultaneously. Moreover, overwhelming and robust association analysis algorithms have also been developed to encompass and interpret the above information in a structured manner.[12]

Simultaneously, international collaborations and consortia in the field of GWAS research in CAD have provided new impetus in CVD pathogenesis. While, the total number of research studies that use GWA studies in CAD has expanded expeditiously in recent years, significant challenges still exist using the GWAS. The major challenges includes defining case – control groups, controls for multiple testing and population stratification issues and the large number of statistical tests involved, which may lead to false positives. However, these studies have constantly identified significant loci in scores of clinically important CAD phenotypes.[24]

5. International Genome-Wide Association Studies of CAD

9p21 was uncovered in two diverse populations, in the Wellcome Trust namely the British Case Control Consortium (WTCCC) and the German MI Family Study (GerMIFS).[25] Around the same time it was reported that this particular locus on chromosome 9 was consistently associated with CAD.[13] This CAD association with 9p21.3 represents one of the

most reliable and strong SNP disease associations in the GWA studies strata. This result has been duplicated in several independent samples and ethnic populations including the European, Korean, and Japanese. In addition, studies have shown that 9p21.3 locus is also associated with a variety of vascular phenotypes such as abdominal aortic aneurysms, intracranial aneurysms, and peripheral arterial disease.[15]

Soon it was realized that to identify the modest effects of risk variants in CAD, a larger population sample size is needed. For example, detecting a variant that bestows a risk of 10%, existing in15% of the population, necessitates a representative sample size of 20,000 to contribute a 80% statistical power and almost a similar sample size would be needed for replication studies.[26] These huge requirements favored the formation of international groups to pool resources and form consortia.[11]

The two major consortia formed are the CARDIoGRAM (Coronary Artery Disease Genome-wide Replication and Meta-analysis) in 2010 & Coronary Artery Disease (C4D) Genetics Consortium in 2011.[16] These consortia reported 13 novel susceptibility loci correlating with CAD and MI. Cardiogram & C4D identified four additional novel loci in individuals with European and South Asian ancestry.[18] Together, these consortia having evaluated more than 200,000 individuals have identified and replicated more than 30 novel loci for CAD.[26]

Approximately 10% of the heritability of CAD is explained by the 50 genetic loci discovered so far. It has been shown that eight of the 50 loci belong to lipid metabolism and blood pressure regulation pathways. An overview of the major GWAS studies are compiled in Table 2. Further the additional identified loci do not correlate with any of the present known risk factors in CAD.[17] This aspect is very essential to know; as it indicates that there are other pathways and unknown pathophysiological, mechanisms are yet to be elucidated further.[27] New genetic analysis tools can shed light on the identified loci and their role in the susceptibility, progression, and or development of CAD. The following prototypes demonstrate the promise and potential, as well as the challenges this field presents.

i. 9p21 Locus and CAD – Correlation of 9p21 locus with CAD and MI has been evident in almost all major GWA studies published including a meta-analysis, which implies at least, that this correlation is widely distributed and evident in the pathogenesis of CAD. 9p21 lies in the intragenic region, near to the group of cell-cycle regulating tumor suppressor genes (CDKN2A and CDKN2B).[28] The above genes have been shown to be involved in progression of atherosclerosis, their role in secretion of transforming growth factor. The 9p21 risk is not connected with known cardiac risk factors, implicating a novel mechanism for CAD pathogenesis and the many more to be discovered subsequently.[28] This risk allele is seen in European, Chinese, Korean, Japanese, Indian, and Pakistani ethnic groups,[11] and its presence is correlates with a two-fold increase in early CAD onset. It is observed that 9p21.2 dosage is also responsible for the severity of CAD.[29] Left main coronary and multiple coronary arterial diseases were also shown associated with a high dosage of 9p21.3 risk allele.[6]

The ADAMTS7 risk allele has an action on the vascular wall and is involved in the pathogenesis of coronary atherosclerosis.[30] It is also shown that ABO blood group locus as a risk factor for MI in the same study. The study was done on 4372 patients with angiographic evidence of MI compared with angiogram-documented CAD without MI. A genetic marker at 9q34.2 showed correlation with MI but not with CAD.[11] The blood group AB and O have a single locus at 9q34.2. It is well accepted that blood group O has some protection from MI as compared with other blood groups. The A and B gene transcribesa protein which transfers carbohydrate molecules on to the von Willebrand factor making them susceptible to coronary thrombosis, whereas the O group gene, encodes a protein which is abnormal and thereby decreases the risk of MI.[30]

ii. Association of known risk factors with GWA studies – While, the molecular pathways/genes through which these genetic variants intervene and their risk remains to be discovered, the positive results from the above GWAstudies have clearly indicated that the novel genetic variants do exist and waiting to be characterized. Conduction of GWAS studies provided the incentive in the form of recognition of brand new molecular pathways through which the risk is expressed. All the 50CAD loci discovered until now do not work through known mechanisms and new pathways are waiting to be discovered. The usage of these pathways to discover new targets for drug therapy should be a worthwhile pursuit. These findings also underline the prerequisite of identifying genetic risk factors to provide exhaustive data useful in the prevention and treatment of CAD.

iii. Salient features of GWA studies in CAD – The following are the main features of the GWA studies in CAD

- *In early onset CAD, genetics association exhibits higher risk than for those with late onset CAD.*
- *Genetic association is consistent across various ethnicities and for both genders. However, the South Asian population group data are inadequate.*
- *Vascular phenotype (defined by angiography >50% obstruction) and MI have been shown to have different loci, namely 9p21.3 for vascular phenotype and 9q34.2 with MI.*
- *Only eight loci are associated with known risk factors like lipids and hypertension.*
- *Role of novel loci in risk prediction and for therapeutic and preventive intervention needs further study.*
- *Presently, routine genetic testing for primary prevention of CAD is not recommended.*

6. Indian CAD studies

The majority of Indian studies are conducted in urban areas. Prevalence of CAD in urban adults has increased four-fold in

Table 2 – Summary of major international GWA studies.

Author/year	Study details	Results
Samani, et al, 2007[14]	This study Identifies correlation of specific genetic loci to CAD and MI susceptibility.	9p21.3 (SNP, rs1333049) loci have been identified in both WTCCC and German studies
McPherson R, et al, 2007[13]	GWA studies identifies associations in CHD	9p21 association was identified with CHD in the Caucasian population
Helgadottir A, et al, 2007[15]	GWA studies confirms association between MI and variant 9p21	CDKN2A and CDKN2B, tumor suppressor genes, adjacent to 9p21 variant were linked with MI
Kathiresan S, et al, 2009[27]	GWA studies testing associates SNPs and CNVs with early-onset myocardial infarction.	SNPs at nine loci reached significance: Three were newly identified 21q22 near *MRPS6-SLC5A3-KCNE2*, 6p24 in *PHACTR1*, 2q33 in *WDR12* and Six replicated prior observations 9p21, 1p13 near *CELSR2-PSRC1-SORT1*, 10q11 near *CXCL12*, 1q41 in *MIA3*, 19p13 near *LDLR* and 1p32 near *PCSK9*
Coronary Artery Disease (C4D) Genetics Consortium, 2011[16]	Meta-analysis of four large GWAS of CAD implicates new pathways for CAD susceptibility.	This study recognized five new loci associated with CAD ($p < 5 \times 10^{-8}$) *LIPA* on 10q23 *PDGFD* on 11q22 *ADAMTS7-MORF4L1* on 15q25, a gene rich locus on 7q22 and *KIAA1462* on 10p11.
SchunkertetH, et al, 2011[24]	Meta-analysis of 14 GWAS of CAD in European descent individuals.	This study identified 13 new loci ($p < 5 \times 10^{-8}$) associated with CAD.
Preus M, et al, 2010[38]	Genome-wide reproduction and meta-analysis (CARDIoGRAM) consortium formed, to improve the chance of finding novel predisposition loci for CAD and MI.	9p21 variant, rs1333049 was found in the meta-analysis and accorded a 29% increase in risk for MI per copy ($p = 2 \times 10^{-20}$).
Xiangfeng L, et al, 2012[39]	Meta-analysis of 2 GWA Studies of CAD presents new understanding into novel pathways, contributing to the susceptibility for CAD in the Chinese Han population.	Four new loci ($p < 5 \times 10^{-8}$) were recognized in CAD. These loci mapped in or near *TTC32-WDR35*, *GUCY1A3*, *C6orf10-BTNL2*, and *ATP2B1*.
The CARDIoGRAM plus C4D Consortium, Deloukas P, et al, 2012[40]	This study provides hereditary basis of CAD and identifies major biological pathways.	15 significant loci were recognized, increasing the number of CAD susceptible loci to 46. The above loci belong to the Lipid metabolism and inflammation networks.
ReillyM P, et al, 2011[30]	Study identifies that specific genetic predispositions promote the development of coronary atherosclerosis whereas others lead to MI.	Novel ADAMTS7 and ABO loci were recognized with independent roles in CAD pathogenesis.

the last 40 years, and even in rural areas, it has doubled.[2] The factors responsible for increased prevalence in CAD in India include adoption of unhealthy lifestyles, increased tobacco consumption, and socioeconomic transitions associated with urbanization and industrialization. With evidence of the increasing prevalence of CAD during the past two decades among Indians and Indian emigrants in other countries, a large number of GWA studies have been conducted.[5] Many of the candidate gene polymorphisms reported in Western studies have been replicated in Indians.

Despite intrinsic difficulties in the design and execution of GWA studies, two recent studies attempted sib pair analysis in order to determine the familial nature of CAD. The Indian Atherosclerotic Research Study (IARS), a genetic study exploring the molecular basis of CAD in Indian families with a strong familial history.[31] Another group from the National Institute of Biomedical Genomics (NIBMG), Kolkata, screened for 209 SNP markers in 31 genes for ten quantitative traits like Apo lipoprotein B (ApoB), C-reactive protein (CRP), fibrinogen (FBG), homocysteine (HCY), lipoprotein (a) (LPA), cholesterol-total (CHOL-T), cholesterol-HDL (CHOL-H), cholesterol-LDL (CHOL-L), cholesterol-VLDL (CHOL-V), and triglyceride (TG) in 144 nuclear families of a homogenous Marwari population from Kolkata.[32] Through Q-TDT analysis, nine SNPs were discovered in four genes – SELE, VEGFA, FBG, and NFKB1 have a meaningful impact on quantitative precursors of CAD. An overview of the major indian genetic studies in CAD with referenced genes is compiled in Table 3.

Concerning the number of genes linked with CAD worldwide, the CGS conducted so far on Indian populations is insufficient to draw any conclusions. Nevertheless, the association of the prominent locus 9p21.3 found in international GWA studies is replicated for three SNPs, rs10116277, rs1333040 and rs2383206inNorth Indians and two SNPs, rs2383207 and rs10757278, in the South Indian population.[33] This 9p21 locus, which includes a large 53-kilobase region, has been hypothesized to regulate expression of genes controlling cell proliferation pathways, leading to atherosclerosis.[34] Hence, there is a need for an analysis of risk conferred by this region among different ethnic groups in India.

Apollo Hospitals has completed the first preliminary Indian GWA study to identify the genetic basis of MI in young Indians in collaboration with the National Institute of Biomedical Genomics (NIBMG) and the Institute of Genomics and Integrative Biology (IGIB). This unpublished study identified networks, canonical pathways derived from SNPs through a pathway based approach belonging to CAD. However, this study needs to be replicated in larger cohorts for validation.

7. Clinical implication and utility

Despite the success of the GWA studies in recognizing significant genetic associations, the translation of such findings into clinically adept tools for CAD prognosis has only now begun to yield fruits. Owing to the fact of the very recent and swift discovery of multiple genes and loci for MI, care should be taken for the use of cardiovascular genomics at the bedside. It should be noted that despite their very strong statistical associations with MI and the consistency of the associations in multiple populations, SNPs associated with MI in GWA studies have consistently shown small to modest relative risks and explain a fraction of the heritability estimates of CAD and only a very small proportion of the inter-individual variance in risk of CAD (1–5%); this suggests that large numbers of SNPs (including many rarer variants) will likely be required for clinical utility in risk prediction. The translation of genetic discovery into useful clinical biomarker for prediction, prevention, and treatment of patients still requires detailed studies to demonstrate these "causal" genetic variants, through sequencing of the concerned regions of the human genome. The discovery of 50 genetic risk variants for CAD and the augmented awareness of impediment have

Table 3 – Major Indian genetic studies in CAD with identified genes.

Author/year	Gene	Function of genes
Hebbagodi S, et al, 2008[32]	ApoA1-C3-A5	Regulation of lipids.
Siwach P, et al, 2010[41]	GHRd3	Significant association of deletion allele GHRd3 with CAD.
Kakkar VV, et al, 2010[42]	High levels of CRP	hsCRP appears to be an independent predictor of recurrent CAD events
Kakkar VV, et al, 2009[43]	Plasma factor 7 glu353 arg (RR, RQ, QQ)	Significant association of FVIIc activity with lipid markers, Concurrently, among those with RR and RQ genotype after covariate adjustment.
Gupta D, et al, 2011[2]	APoA5-1131T > C	Promoter polymorphism in APOA5 correlated with augmented serum triglycerides and that of HL with raised HDL2 levels.
Kumar P, et al, 2010[44]	ACEI/D	Risk factors for MI in a South Indian population.
Ghosh A, et al, 2008[45]	Apo E	ACE gene insertion/deletion polymorphism has been acknowledged as an important genetic risk factor for essential hypertension.
Jyothy A, et al, 2010	MMP3 5A/6A promoter gene polymorphism	Role of MMP3 5A/6A gene is clarified in MI.
Gill KD, et al, 2011[2]	PON1 Q192R	CAD patients have down regulated PONase and AREase enzyme activities as compared to the controls.
Renuka Nair R, et al, 2011[46]	PPARα Intron 7 G2528C	Impaired lipid metabolism in carriers of the PPARα Intron 7C risk allele is susceptible to CAD.
Nair KG, et al, 2006[47]	MTHFR (Hinf1) AA, AV, VV, MS (HaeII) (DD, DG, GG)	MS (A2756G) genotype was recognized. A significant association of HHcy with MTHFR (C677T).
Khan AS, et al, 2011[48]	ACEI/D	Metabolic syndrome was associated with ACE gene polymorphism.
Majumder PP, et al, 2011[32]	209 SNPs in 31 genes of 10 QTLS	9 SNPs from four genes SELE, VEGFA, FBG, and NFKB1 were reported.

catalyzed the search for improved treatments and the exploitation of their biology and pathophysiology.[11]

However, a number of issues remain unclear. Most of the genetic variants have been identified preponderantly in European populations, and such variants demand comprehensive validation in Indian population to substantiate their clinical utility. Second, the assessment of apparently significant (gene-environment and gene–gene) interactions has thus far been limited and will require adequately powered large-scale studies to delineate the role of such interactions and their impact on risk prediction.

The actual implementation of the GWA studies results into clinical practice is highly challenging. Knowledge of the cardiac risk factors and genetic DNA variants together will definitely strengthen the prognosis of the disease. Risk variants can be determined and quantified using sophisticated and intricate algorithms already available. Well-designed randomized studies will be indispensible to demonstrate that the use of genetic information in risk predisposition, selection of targeted drug therapies, or personalized medicine leads to purposeful improvements in outcomes and is cost-effective. Several studies have begun to assess the prognostic power of the inclusion of single SNPs and multiple SNPs in predicting the genetic risk scores of MI.

An exciting new outcome of the genetic studies is thePCSK9 gene, a reliable target that can be translated as a new therapeutic treatment option for CAD. This gene was initially identified by LS and is later found to be linked with autosomal dominant FH for which causal mutations were recognized in 2003.[22] PCSK9 is responsible for the metabolism of LDL cholesterol through its role in recycling of the LDL receptor, such that down regulation of this protein could become a therapeutic target source for treatment of FH. New clinical trials in patients with FH have reported that a composite treatment with atorvastatin and evolocumab (REGN727/SAR236553), a human monoclonal antibody that blocks the PCSK9 protein, results in a greater reduction of LDL cholesterol than with atorvastatin alone.[35]

The GAUSS-Z, a randomized placebo-controlled phase III trial of evolocumab, reported a favorable efficacy along with an extremely beneficial toxicity profile for statin intolerant patients.[35] The MENDEL-Z randomized controlled phase III clinical trial showed that anti-PCSK monotherapy with evolocumab produced successive LDL-C down regulation compared with placebo or ezetimibe, and is well accepted in patients with hypercholesterolemia.[36]

Function mutations in APOC3 have been validated in CAD recently. Mutations that disorganizeAPOC3 function correlated with diminished plasma levels of triglycerides. Carriers hosting these mutations were found to have a decreased risk of coronary heart disease.[37]

In spite of substantial gaps in evidence of genetic testing, a large number of genomic companies have already commenced offering direct-to-consumer genetic testing for CAD. Clinicians faced with such information should carefully consider the above caveats and challenges. While, evidence keeps on evolving and adding, standard risk prediction algorithms such as the Framingham risk score and careful consideration of a familial history of premature CAD should continue to form the basis of cardiovascular risk assessment.[26] As new knowledge becomes available, a judicious blend of clinical risk assessment and proven interventions based on evolving genetic information will predict the much awaited outcomes of CAD in the future.

8. Conclusions and future considerations

GWA studies for CAD yielded some remarkably promising leads in discovering new familial variants associated with MI and CAD. Further, some potentially novel biologic pathways of atherogenesis and or thrombosis are also in place from these studies. With advances in genomic technologies, including low-cost and economical whole genome sequencing technologies, additional rare genomic variants will be discovered, allowing unprecedented insights into the biology of CAD. In spite of, the very rapid and early successes of GWA studies and the newly discovered MI risk variants, the role of genetic data in clinical medicine remains to be comprehensively established and validated. Genetic information may hold enormous potential for cardiovascular medicine, but much work is still in place to delineate the role of this information into clinical practice and rigorously evaluate its impact in terms of efficiency, results, and cost effectiveness.

Developing an appropriate targeted therapy for a novel pathway/mechanism does not take very long time. The time from discovery of the defective cholesterol receptor gene to development of first statin took almost 20 years.[21] The discovery of 50 genetic risk variants for CAD, and the increased knowledge of CAD prevention, has catalyzed the search for improved therapeutic treatments. The increased risk conferred by these variants is widespread and with advances in technology, the bench to bedside translation surely enhance at a rapid pace. Research on the use of genetic information to improve cardiovascular risk will continue to progress rapidly as we now know that genetic prediction through genetic testing will be a reality very soon.

Conflicts of interest

All authors have none to declare.

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