Pak Heart J

ROLE OF GENETICS IN CORONARY ARTERY DISEASE (CAD) - MANAGEMENT AND PREVENTION

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This article may be cited as: Hafizullah M. Role of genetics in coronary artery disease (cad) - management and prevention. Pak Heart J 2016;49(04): 133-8.

The incidence of Coronary artery disease (CAD) decreased significantly following implementation of primary and secondary prevention strategies like promotion of healthy life style, cessation of smoking, positive changes in nutrition and more emphasis on physical activity besides effective medical treatment like platelet inhibitors and Statins in the later part of last century. [1,2] Improved application of established primary prevention strategies undoubtedly has the potential to further reduce the incidence of CAD. Collectively, these strategies are able to reduce the incidence of CAD by almost 50% in high-risk populations.[3,4] However, many individuals with significant risk, either do not take medications or are unable to introduce the necessary lifestyle changes that are necessary to substantially reduce risk.[5–8] Recent substantial progress in genomic medicine, guided by great breakthroughs in laboratory technology and computing power, provides us with a golden opportunity to understand the genetic basis of CAD. This knowledge should be used to improve our ability to identify subjects who are at high risk and we should try to develop special protocols for them.

Family studies prove that common presentations of CAD are heritable. Recent epidemiological studies involving unrelated individuals provided the first clues that non Mendelian common presentations of CAD in middle to late adulthood were heritable.[9] Studies have documented 2.5- to 4-fold higher rates of CAD among individuals with a family history compared with those with no family history when adjusting only for age and sex. When traditional risk factors are controlled, the excess risk of CAD is reduced to about 1.5- to 2.5 folds. This supports that some part of this excess risk is a consequence of familial aggregation of traditional risk factors. Familial aggregation studies prove that a stronger family history or an earlier age of onset of disease in a family member further increases the risk for close relatives.[9-11] The twin studies have observed higher heritability, similar to the familial aggregation studies, especially when disease occurs at a younger age and a reduction in estimates when traditional risk factors are taken into account.[12–14]

Employing the genome-wide association studies (GWAS) approach, three groups in Europe in 2007 independently reported the first region of the genome to be linked to CAD. The susceptibility locus is located on the short arm (p) of chromosome 9 at band 2.1, and thus is commonly referred to as 9p21. The locus has 60 strongly correlated SNPs over 53,000 base pairs and is 100,000 to 150,000 base pairs upstream of the genes encoding 2 cyclin-dependent kinase

(CDK) inhibitors and known tumor suppressors, CDKN2B and CDKN2A. The locus overlaps the last section of a long noncoding ribonucleic acid and is transcribed antisense to CDKN2B (CDKN2BAS or ANRIL).[15-17] The lead variants at 9p21 are common, with a minor allele frequency of about 50% in Europeans, resulting in about 75% of individuals of European ancestry carrying at least 1 allele that increases risk. The increase in risk for CAD was approximately 25% for 1 copy and about 50% for 2 copies, with somewhat higher risks per allele observed among those with early-onset CAD. The risk mediated by 9p21 seemed to be completely independent of all known risk factors, proving that other unknown factors contribute substantially to the pathogenesis of CAD.[15-17]

The exact mechanism linking genetic variation at 9p21 to the risk of CAD remains uncertain, although several sets of observations at the population level and in the laboratory have helped to point to the possibilities. Firstly, exactly same variants have been linked to extra cardiac atherosclerosis like carotid plaque, ischemic stroke, and peripheral arterial disease, suggesting that the locus predisposes to atherosclerosis in all vascular beds. Secondly, same variants have been linked to both abdominal aortic and intracranial arterial aneurysms, implying that the cells that are affected are in the vessel wall of the artery.[19] Thirdly, evidence suggests that the SNPs in the high-risk region disrupt or create transcription factor binding sites that alter the expression levels, or the relative abundance of different transcripts of the noncoding ribonucleic acid, ANRIL, which in turn affects the expression levels of CDKN2B and/or 2A. The protein products of these 2 genes, p15INK4a and p16 INK4a, then alter the function of macrophages and/or vascular smooth muscle cells, facilitating the formation of atherosclerotic plaque. Fourthly, animal model studies suggest that these effects could involve increased proliferation and reduced apoptosis of resident macrophages and/or vascular smooth muscle cells.[19]

Eleven other loci for CAD were identified within a very short interval of the discovery of 9p21 by three groups that included the Welcome Trust Case-Control Consortium, Cardiogenics Consortium and Myocardial Infarction Genetics Consortium.[20-24] The result of these initial genome-wide association studies (GWAS) confirmed that common susceptibility variants for CAD carried minimal incremental risk hence it would require a very large sample size - in tens of thousands to hundreds of thousands to be uncovered. Therefore larger national and international consortia were formed to tackle this challenge like Coronary Artery Disease Genome Wide Replication and Meta-analysis (CARDIoGRAM) and the Coronary Artery Disease (C4D) Genetics consortia that confirmed selected SNPs are genotyped in an independent cohort or case-control set in 2011. Almost all of the previously reported loci and uncovered 17 new loci through meta-analysis.[25,26] Through further collaboration between these 2 consortia, and the testing of a larger fraction of SNPs with a minor allele frequency >1% using advanced imputation algorithms, CARDIoGRAM plus C4D reported an additional 15 novel loci in 2013 and 8 loci in 2015, after the examination of >60,000 cases and >120,000 control subjects. These studies brought the total loci to 58 in largely European and to a lesser extent in South Asian populations.[27,28] East Asians represent the next most studied ethnic group. A total of 12 loci were recognized and reached genome-wide significance for CAD in studies involving either Han Chinese, Korean and Japanese subjects, with at least 6 of these loci overlapping with loci uncovered in Europeans.[30-34] Well-powered studies using this array firmly established associations between CAD and genetic variants in LPA, the gene encoding lipoprotein(a), and confirmed several early GWAS discoveries for CAD.[35,36]

Much awaited clinical application for genetic risk variants predisposing to CAD is to be able to improve ability to risk-stratify individuals[37,38] Large room for improvement exists although current clinical risk prediction scores for CAD perform relatively well compared to scores for other chronic diseases. A large pool of individuals with incident events carries either only 1 modifiable risk factor or only borderline risk factor.[39-41] Improving our ability to better predict a particular set of women with similar risk factors will experience an event through the addition of a novel biomarker, such as one's genetic susceptibility to CAD, would be expected to improve outcomes through more efficient application of established primary prevention therapies. The most practical way to currently integrate genetics into risk prediction models, such as the Framingham Risk Score or the ACC/AHA pooled cohorts calculator, is through the calculation of a genetic risk score (GRS) for individuals.[42] A GRS is a single variable that summarizes one's exposure to variants that increase risk for CAD.[43] A GRS is typically calculated by summing the product of the number of high-risk variants inherited by each individual for each susceptibility variant and the log of the odds ratio previously determined in a GWAS for the same variant.[42] The use of GRS in clinical practice has been slow to materialize for several reasons, including the high cost of genotyping, the more modest effects of genetic variants on the risk of CAD than originally anticipated, and the challenge of improving a clinical risk score, such as the Framingham or ACC/AHA risk score, that already performs quite well.[38,42,44] Consequently, it has been difficult to demonstrate substantial improvements to standard model performance metrics with the addition of a GRS, even though ample evidence now exists that a GRS of known CAD loci predicts incident CAD events independent of all other traditional risk factors.[42,45-50] Though family history serves as a substitute for genetic risk, yet individual variants, as well as GRS of CAD, have been shown to predict clinical complications of CAD independent of family history.[49]

Recent studies emphasize the potential for a GRS of CAD to improve primary and secondary prevention outcomes.[46] GRS involving 27 variants previously proven to be associated with CAD was constructed after genotyping DNA biobanked at baseline from participants in 1 community-based cohort study (the Malmo Diet and Cancer Study), 2 primary prevention trials of statins (JUPITER and ASCOT), and 2 secondary prevention trials assessing the efficacy of statin therapy (CARE and PROVE ITTIMI 22).[46] Among the 48,421 individuals and 3,477 events included in this study, investigators showed that the GRS not only predicted incident CAD events, but also predicted recurrent CAD events, independent of all traditional risk factors including family history.[46] The absolute risk reduction estimated a roughly 3-fold decrease in the number needed to treat (NNT) to prevent 1 CAD event in the primary prevention trials.[46] In primary prevention trials number needed to treat (NNT) to prevent 1 such event in 10 years was 66 in people at low genetic risk, 42 in those at intermediate genetic risk and 25 in those at high genetic risk in JUPITER, and 57, 47, and 20, respectively, in ASCOT. GRS served as a prognostic marker and also as a marker to predict response to single most important primary and secondary therapy already available.[51] Using GRS, one can target large populations at high risk like premenopausal women with high genetic risk and optimal response to statin therapy, for primary prevention. The incremental predictive ability of GRS is expected to improve over time. [38]

Recent advances have made it possible to perform high-throughput genetic profiling in a cost-efficient manner and allowed research groups around the world to share data and collaborate. These collaborations have resulted in identifying over 60 susceptibility loci which underline the importance of established mechanisms of disease like cholesterol metabolism. These genetic studies help us to understand relationship between established or emerging risk factors and CAD and shall improve our ability to identify individuals who are at high risk of CAD through addition of genetic risk into clinical risk scores. This has thrown newer challenges like identification of remaining susceptibility loci for CAD and exploring clinical utility of genetic data in prevention of CAD. This knowledge shall be used to develop newer therapeutic agents. Considering the distribution of effect sizes observed to date for both common and rare variants very large sample sizes are needed for additional discoveries. In the coming times this need will be fulfilled by mega-biobanks involving at least one-half million participants, including, but not limited to UK Biobank, China Kadoorie Biobank, Million Veteran Program and soon-to-be-established National Institutes of Health Precision Medicine Initiative cohort.[52-55] These new resources and techniques have already provided important mechanistic insights for several novel susceptibility loci for CAD, including those regions harboring the genes CDKN2B, SORT1, TCF21, ADAMTS7, SMAD3, and other loci.[56-63] This knowledge has yet to be applied to therapeutic agents to target these loci. The rapid translation for loci such as PCSCK9 offer some optimism that such developments are possible. This is likely to provide us with innovative opportunities to further reduce and possibly eliminate CAD in times to come.

To conclude, we are entering a new exciting era as we can use genetic risk variants for the prevention and management of coronary artery disease (CAD). Current knowledge pertaining to 60 susceptibility loci identified for CAD confirms the importance of established risk factors and many novel causal pathways. This will surely improve our understanding of genetic basis of CAD and hopefully open the door to development of new therapeutic agents in the future. Mendelian randomization studies have enhanced our understanding of causal relationship between CAD-related traits. This has further highlighted the potential benefits of long-term modifications of risk factors. Genetic risk scores of CAD are important both as prognostic and predictive markers. This may also change the approach to delivery of established prevention strategies.

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