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Genetics of coronary artery disease.

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Editorial

Coronary artery disease (CAD) and its major complication myocardial infarction (MI) are the leading causes of death worldwide, which often occurs with the accumulation of atherosclerotic plaques in the walls of the coronary arteries. The heritability of CAD has been estimated between 40% and 60%, indicating genetic factor holds an equal or more important contribution to risk of CAD with the other traditional risk factors (i.e., lipid abnormalities, smoking, hypertension, diabetes, and obesity) [1]. In the genetics studies of CAD, the primary goal is to identify causative variants, genes or genetic loci that contribute to the risk of CAD. Given the fact that many risk factors are also strongly are modulated by genetic factors, Mendelian Randomization studies have been designed to estimate causative effects of risk factors on CAD, single-nucleotide polymorphisms (SNPs) servers as instruments [2]. Due to the clinical heterogeneity of CAD, the genetic architecture of CAD is not fully elucidated yet.

In the past years, the progress in the genetics of CAD lies in a large amount of genome-wide association study (GWAS), which employs a case-control design to detect common risk variants (minor allele frequency, MAF>0.05) among population samples [3]. The more samples are recruited, the more powerful the GWAS exhibits. The first and the most robust CAD susceptibility locus was 9p21.3 was initially identified by 4 GWASs in 2007 and successfully replicated in populations with multiple races [4]. Thanks to SNP imputation methods based on the HapMap project (https://www.hapmap.org/) and the 1000 Genome project (http://www.internationalgenome.org/), meta-GWAS is becoming a more popular strategy for CAD as well as other complex diseases. The largest meta-GWAS recently analyzed 9.4 million imputed SNPs among >185,000 samples and identified 10 novel CAD loci. The majority of GWAS for CAD focused on European-ancestry populations, and several GWAS were also reported in Africans, East Asians, and South Asians. To date, there are 65 independent CAD susceptibility loci reported at genome-wide significant level [5]. However, the major disadvantage of GWAS is that its discovering power is limited to common variants with relatively low risk (odds ratio or OR of 1.2 on average or lower), and most GWAS variants are not causative variants [6]. Moreover, recent studies strongly indicate that GWAS risk variants may aggregately explain 10–20% of the heritability of CAD.

Genome-wide linkage analysis (GWLA) is a powerful and classic approach to detect genetic loci for CAD and to search for evidence of major genetic effects [7]. The first GWLA for CAD dated back to the year of 2000 and joint analysis of 156 affected sibling pairs identified two genetic loci at 2q21.1–22 and Xq23–26 for premature CAD. Subsequent GWLAs have revealed over 20 additional genetic loci for CAD/MI [8]. The majority of GWLAs for CAD was conducted in either single large pedigree or hundreds of nuclear families, joint-linkage analysis of multiple large pedigrees has been not reported so far. In general, linkage study is limited to a low density of microsatellite markers with an average bin of 10 cm. Follow-up fine mapping may introduce additional microsatellite markers or apply SNP microarray to increase marker density. Single SNP is not feasible for linkage analysis due to bi-allelic status; haplotypes constructed using multiple SNPs may be considered as multi-allelic markers. In contrast to aforementioned GWASs, family samples are much less than sample size required for GWAS, Increasing the number of family members within families can achieve a comparable power of GWAS using population samples and outperformed in detecting variants with large effect. The number of genetic loci identified by GWLA was much less and independent, suggesting that many linkage loci remain to be identified in new CAD or MI families.

Searching Missing heritability for CAD remains a hot topic in the genetics of CAD. Based on recent studies, it is postulated that the remaining heritability for CAD may include rare variants, structural variants such as copy number variants, epigenetics, and gene-environment interactions. Rare variants constitute the major variation sites in human populations, and the hypothesis "**Common Disease and Rare Variants**" has been supported by a growing number of reports. With the wide application of exome-centric and whole-genome next generation sequencing (NGS) technology, many rare variants association methods have been developed to identify rare variants in genes or functional regions in unrelated samples or family samples. Massive public databases are being integrated to detect pathogenic variants. Identification and analysis of rare variants, which are assumed to have large effects, is a key to capturing some missing heritability of CAD [9]. Indeed, the field of genetics of common complex diseases is shifting toward this direction. Examples include rare *PCSK9* variants for LDL-C levels and CAD, rare *ABCA1/APOA1/LCAT* variants for HDL-C levels and rare *NPC1L1* variants for

triglyceride levels [10]. The finding that rare loss of function variants in *PCSK9* reduce LDL-C levels and CAD risk has led to the development of anti-PCSK9 therapy for CAD, which exemplifies the extremely important value of research on identification of rare variants for CAD. Nevertheless, high experiment and data analysis cost, comprehensive variants annotation, and follow-up functional studies for CAD risk variants or genes still pose challenges to prevent the rapid applications of NGS. In a summary, GWAS and GWLA are two unbiased and powerful methods to identify risk genes and genetic loci for CAD, and NGS is becoming a popular way to identify rare variants in genetic of CAD. Integrative analysis of GWAS, GWLA, and deep sequencing analysis is a promising way to capture missing CAD risk variants and to illustrate the rare variants with pathogenic roles during atherosclerosis progress of CAD. The above findings can provide a new framework to discover novel molecular pathways and eventually lead to developing effective treatments for CAD.

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