Coronary artery disease genetics: bigger is better

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This editorial refers to "Genetic risk and gene–environment interaction in coronary artery spasm in Japanese men and women" by Y. Murase et al. on page 970.

The complexity of coronary artery disease genetics arises from the diversity of clinical phenotypes and from the many biological pathways that contribute to atherosclerotic plaque biology, including lipid metabolism, inflammation, endothelial function, oxidative stress and thrombosis. In addition to environmental factors, inter-individual variation in disease susceptibility or outcome may arise from common polymorphic variation in the genes encoding the proteins that participate in these and other biological pathways. Twin studies suggest that the total genetic contribution to coronary artery disease risk is substantial, but dissecting out the nature of these effects in a complex polygenic trait with multiple sub-phenotypes remains a major challenge.

In this issue, Murase et al. have investigated possible associations between the presence of coronary artery spasm and 35 single nucleotide polymorphisms (SNPs) in 29 candidate genes. In comparing these SNPs in approximately 600 patients with coronary artery spasm and 1600 controls, they observed a significant association between coronary artery spasm in men and an SNP in the NAD(P)H oxidase p22phox gene, and in women with polymorphisms in the stromelysin-1 and interleukin-6 genes. These findings add weight to smaller case-control studies that have found associations between these and other gender group) will not be the norm. In all genetic studies, greater power is achieved not only by greater sample sizes but also by stringent selection of severe phenotypes to enrich for genetic load – studies in 'average' patients are much less informative.

Additionally, the findings of candidate gene case-control studies, even large-scale ones, are potentially limited by phenotyping errors and by selection bias. For example, defining genetic associations with coronary spasm relies upon the validity of detecting and defining coronary spasm in cases and excluding coronary spasm in controls, whilst ensuring that both groups are derived from a similar population. Furthermore, the findings will necessarily be limited to genes that have been chosen, a priori, as known or plausible biological candidates. Accordingly, such studies are usually justified on the basis...
of 'predicting genetic risk', whereas in reality even a strong association with one SNP is unlikely to contribute to clinical risk management in an individual patient. In contrast, the more exciting potential of systematic, genome-wide, genetic studies in coronary artery disease is to identify genetic variants in genes that encode proteins not previously implicated in coronary artery disease pathogenesis. Even a small genetic risk may identify a gene with an important biological role that could reveal new mechanistic insights and provide novel therapeutic targets.

Genome-wide linkage studies use families with two or more affected members to map genetic variants using anonymous DNA markers that are distributed across the genome without prior bias towards 'plausible' candidate genes. Broeckel et al. undertook genome-wide scanning with 394 markers in 1406 individuals from 513 families with at least 2 members who had sustained MI at age 59 or less. Linkage analysis revealed several promising chromosomal regions (loci) that were linked with either MI, or with other quantitative intermediate phenotypes such as Lp(a), lipid levels, diabetes or hypertension, but identification of possible causative genetic variants within these regions will require much further work. Genome-wide association studies that would type several hundred thousand SNPs across the whole genome in case-control collections are theoretically powerful but are daunting in scale and cost. In a first approximation of such a genome-wide association study, Ozaki et al. typed more than 65,000 SNPs across the genome in 94 patients with MI and in 658 controls. Following initial analysis, 1% of the potentially associated SNPs were typed in 1133 patients with MI and 1006 controls. Narrowing down the strongest associations with MI identified a group of SNPs (a haplotype) in a region of chromosome 6 containing several genes related to inflammation. Of these, the SNPs in the gene encoding lymphotoxin-alpha resulted in changes in both protein structure and in the activity of the gene in mediating downstream signalling effects such as adhesion molecule expression in endothelial cells. The study concluded that lymphotoxin-alpha may be a novel susceptibility gene in coronary artery disease that merits greater biological focus than more 'established', related candidates. Importantly, these findings in the Japanese population are supported by recent data from a European population in the large-scale family study of premature MI, PROCARDIS. This study also illustrates that 'trio' families (i.e., including parents of an affected case) can be collected even in a 'late-onset' disease such as MI and that such a study design, by investigating transmission of a susceptibility allele in families, is free from the concerns of genetic mismatching in case-control studies.

The implication of inflammatory pathways in atherosclerosis is further supported by a large-scale family study in the Icelandic population. A genome-wide linkage scan in 713 individuals with MI from 296 families found linkage with a haplotype of SNPs in the ALOX5AP gene encoding 5-lipoxygenase activating protein. A possible functional effect of these genetic variants was suggested by the observation of increased leukotriene B4 production by neutrophils taken from MI cases that was related to ALOX5AP haplotype. Furthermore, the association between ALOX5AP haplotype and MI was reproduced in a separate case-control British cohort.

These recent studies have begun to illustrate the power of complex trait genetics to make important contributions to understanding coronary artery disease pathogenesis and risk. Large-scale studies can detect the modest, but biologically important, effects of individual susceptibility genes and so can overcome the problems of poor reproducibility; systematic genome-wide linkage and association studies have the potential to go beyond the incremental step-wise approach of biological studies in providing entirely novel targets for diagnosis and treatment in coronary artery disease.

References