The middle of 2007 saw what may, with time, turn out to be the single most important discovery in the genetics of cardiovascular diseases. Within a few weeks, 4 independent genomewide association studies reported the association of the same locus on chromosome 9p21 with coronary artery disease (CAD) and myocardial infarction (MI). In fact, of the hundreds of thousands single-nucleotide polymorphisms studied across the genome the same locus showed the strongest association with CAD in all 4 studies, as illustrated by a direct comparison of the data from the Wellcome Trust Case Control Consortium and the Cardiogenics Consortium. The finding has led to a plethora of further studies that have largely confirmed the association of the 9p21 locus with CAD and MI in both case–control and cohort studies and in multiple ethnic groups. Second, the association signal for CAD maps to a segment with no known protein coding genes. Indeed, the most strongly associated single-nucleotide polymorphisms lie almost a 100 kb from the nearest such genes—those for the hereditary forms of cutaneous malignant melanoma. Second, the association signal for CAD maps to a segment with no known protein coding genes. Indeed, the most strongly associated single-nucleotide polymorphisms lie almost a 100 kb from the nearest such genes—those for the 2 cyclin-dependent kinase inhibitors, CDKN2A (encoding p16INK4a) and CDKN2B (p15INK4b), p14ARF, which is encoded by alternative exons of the CDKN2A gene, and the MTAP gene (encoding methylthioadenosine phosphorylase; see the Figure). A number of expression sequence tags have been mapped to the segment and recently a gene for a noncoding RNA (ANRIL) that spans the entire region of association with CAD (see the Figure) has been identified, raising the fascinating possibility that a noncoding RNA has a causal role in the pathogenesis of CAD. ANRIL expression has been detected in vascular tissues and in cell types such as monocytes and smooth muscle cells relevant to atherosclerosis. Third, genomewide association studies have also identified 2 loci for type 2 diabetes mellitus that map to the same region on chromosome 9p21. Interestingly, however, these lie on either side of the segment associated with CAD, with no overlap at all in the association signal (see the Figure). Finally, homology mapping shows that although the ~100-kb segment associated with CAD is conserved in higher primates, the homology breaks down quite rapidly and the region is not strongly conserved evolutionarily.

CAD is a chronic multistage inflammatory disease with MI representing an acute complication. In most instances MI occurs as a consequence of plaque rupture or erosion followed by superadded thrombosis. It is therefore possible that genetic factors can affect the risk of CAD by acting at different stages in its clinical evolution. Specifically, one can envisage that genetic factors that affect either the risk of plaque rupture or the subsequent thrombotic response are likely to more strongly (or exclusively) associate with the risk of MI rather than the presence of CAD itself, whereas those that affect the development of coronary atheroma would be anticipated to be associated with the presence of CAD however this is defined. Because CAD provides the substrate for most MI events, one would expect the latter genetic factors to also be associated with MI, although this association could be weaker. Although the distinctions between these phenotypes are not perfect, either clinically or biologically, exploring whether any novel genetic association shows specificity with respect to CAD or MI has merit as it may provide important clues as to how it affects risk.

In this issue, Horne et al explore this with regard to the 9p21 locus. Using data from a large registry with >14 000 individuals assembled from those who underwent coronary angiography within the Utah-based Intermountain Healthcare system between 1994 and 2007, they investigated whether genotype at the 9p21 locus was associated with incident coronary plaque events (nonfatal MI or death) in those with CAD during longitudinal follow-up after discharge. In 2 nested case-control samples from their cohort
they found no association of genotype at the locus with occurrence of nonfatal MI or death. In a second analysis, they also investigated whether, in their angiography subjects, it was the presence of CAD or a history of MI at baseline that was associated with the 9p21 locus by comparing the genotype distributions of subjects selected on these phenotypes with those in a random population sample. Here, they found that the association of 9p21 genotype was stronger for the CAD phenotype rather than history of MI. However, they found no association of the 9p21 genotype with either the severity or extent of CAD assessed angiographically. Horne et al conclude that their findings suggest that the 9p21 locus acts at an early stage (as an "initiator") of coronary atherosclerosis. They also make a plea for better phenotyping in CAD and in particular the advantages of angiography-based phenotypes.

The article by Horne et al16 adds valuable information to our understanding of the association of the 9p21 locus with CAD. However, in any retrospective analysis of this type, the possibility of unrecognized confounders impacting on the findings cannot be ruled out. It is possible, for example, that in their longitudinal study, the treatments received by their CAD patients for secondary prevention masked the association of 9p21 genotype with risk of nonfatal MI and death. Indeed, as coronary atherosclerosis is the strongest risk factor for MI, under the paradigm discussed earlier, it is difficult to understand the lack of association with MI when an association with CAD was found and may simply reflect issues of power to detect an effect in the specific context of the study population. Furthermore, although we agree with Horne et al16 about the importance of high quality and more precise phenotyping in genetic association studies of CAD, the limitations of coronary angiography-based phenotypes also need to be recognized. Although classification of CAD on the basis of the number of coronary arteries with a significant (>50%) obstruction has clinical utility, ultrasound coronary studies have shown that the correlation of this phenotype with the extent (quantity) of coronary atheroma, the biologically important phenotype, is poor. Hence, the interpretation by Horne et al that the lack of association of genotype at the 9p21 locus with the number of coronary arteries with significant obstructions in their study indicates that the locus is involved in the "initiation" of coronary atherosclerosis rather than its "progression" may be rather simplistic. Furthermore, it conflicts with findings in some other studies that have shown an association with atheroma burden measured more precisely by assessment of coronary artery calcification score.11

Having said this, the findings by Horne et al16 provide support for the view that the 9p21 locus affects risk of CAD by influencing primary processes within the vessel wall rather than by affecting plaque rupture or thrombosis. This was indeed apparent even in the initial genomewide association studies where the association of the 9p21 locus was as strong with the CAD phenotype as with MI.1,4 Subsequent studies with noncoronary cardiovascular phenotypes provide additional evidence that the locus influences vascular structure. Hence, the locus is associated with the presence of abdominal aortic aneurysms.9,17 However, genotype at the locus does not appear to affect carotid


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