Letter by Patel et al Regarding Article “Chromosome 9p21 Haplotypes and Prognosis in White and Black Patients With Coronary Artery Disease”

To the Editor:

We read with great interest the article by Gong et al1 in a recent issue of Circulation: Cardiovascular Genetics. We first would like to congratulate the authors on presenting these results, which although do not fit neatly into the chromosome 9p21 story, are robust and merit open discussion to further our understanding of this risk locus and its effects on adverse outcomes.

In fact, we have observed similar findings in our cohort of consecutive patients undergoing elective or emergent cardiac catheterization. The Emory Biobank includes a subset of >2400 white patients (mean age, 65 years; men, 67%) genotyped for the 9p21 locus (rs10757278) of whom 20% had angiographically normal coronary arteries and 40% reported prior myocardial infarction (MI).2 In this heterogeneous group, we too did not observe significant associations with major adverse events (all-cause death, cardiac death, nonfatal MI) over a median follow-up of 2.8 years. Hazard ratios generally were <1 for homozygotes with the G allele, suggesting, if anything, a protective effect. Similar nonsignificant findings were observed in a subset of 450 black patients.

We have considered the reason for our findings given such robust cross-sectional and prospective associations in population cohorts. One possibility is that our cohort and that of Gong et al consist of older individuals and that results are affected by selective survival. It is well established that genetic effects are greatest for premature disease and are attenuated by age, which is confirmed for 9p21 in a recent meta-analysis, whereas others have demonstrated no association with adverse events in a population study of elderly individuals.3,4 Furthermore, it is now generally accepted that the phenotype of 9p21 is likely to be atherosclerotic rather than thrombotic. In a coronary artery disease-enriched cohort, it is therefore likely that the genetic effect has already manifested and that further risk of more coronary artery disease or its consequences becomes more difficult to demonstrate clinically, especially over short follow-up times. Finally, there also may be a survival bias with perhaps greater numbers of 9p21 risk carriers not surviving their first event to enter a secondary prevention cohort.

Another intriguing finding is a tendency toward a protective effect. Gong et al quite rightly discuss the possibility of errors in genotype calling, but despite this, the results are robust. One possible answer is that those with prior MI (who are more likely to carry risk variants) are aggressively treated, and statins, for example, have an especially powerful effect on reducing risk. Some support for this hypothesis comes from our data where stratification based on the presence of previous MI shows that the hazard ratio trends toward protection and toward risk for homozygotes if there was no previous MI. This also may explain why in population samples, when most subjects are not receiving prognostically beneficial therapies, we observe a 9p21 risk effect.

Thus, we would be necessary to identify detailed drug/treatment patterns in future large-scale studies and examine these potential gene-environment interactions to try to understand this observation. Such findings could have significant implications for understanding mechanisms of risk and how to prevent future clinical events, perhaps even with currently available therapies.

Disclosures

None.

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References


