Noninvasive Phenotypes of Atherosclerosis

To the Editor:

The otherwise excellent review by Manolio et al1 seems to have misinterpreted some points in our recent article about noninvasive phenotypes of atherosclerosis.2 We showed that 2 different ultrasound traits, specifically carotid plaque area and percent carotid stenosis, were only modestly correlated with each other and had different associations with risk factors, including genetic determinants.3 By focusing on intima-media thickness (IMT), Manolio et al have overlooked the looming impact of new ultrasound traits, such as carotid plaque area and volume and percent stenosis. Furthermore, by treating IMT as synonymous with “atherosclerosis,” these authors perpetuate the outmoded idea that IMT, which is widely used mainly because of convention and practicality, bears some unique relationship with atherogenesis. In reality, newer quantitative ultrasound measures, including plaque area or volume, percent stenosis, degree of plaque calcification, and other manifestations each, like IMT, says something fundamental, and distinctive, about the process of “atherosclerosis.”

From a genetic perspective, quantitative ultrasound phenotypes are biologically distinct with different determinants and different meanings. For instance, among patients in whom various ultrasound determinations were made concurrently, IMT and percent stenosis were each poorly correlated with traditional risk factors, whereas carotid plaque area was more strongly correlated.2–6 Furthermore, IMT and plaque volume are only modestly correlated with each other (r=0.6).6 From a genetic perspective, it follows that different ultrasound phenotypes will also have different genetic associations, such as the disparate PPARα allelic associations with either carotid IMT or plaque volume.6 IMT and plaque measurements each represent end-organ disease in the arterial wall but reflect different disease attributes or stages. Both IMT and plaque measures can predict clinical outcomes. For instance, patients in the top quartile of plaque area had 3.4× the risk of stroke, death, or myocardial infarction during follow-up, compared with patients in the lowest quartile.7 But the association of IMT with coronary atherosclerosis is less strong than its association with left ventricular mass and less strong than the association between carotid plaque and coronary atherosclerosis.8–11 Finally, when they did discuss “carotid plaque” as a phenotype for genetic studies, Manolio et al mainly cited studies of categorical plaque scores, overlooking those that used the more powerful approach of treating carotid plaque area and/or volume as continuous traits.4–7,12–14

As a continuous ultrasound trait, IMT is also a relatively insensitive measure of plaque evolution: plaque grows along the carotid axis of flow 2.4× faster than it thickens.15 Serial plaque measurements would therefore be expected to detect changes in atherosclerosis more readily than serial IMT measurements. Indeed, serial changes in plaque area are another predictor of vascular outcomes3 and another phenotype that has distinct genetic determinants.2 Evaluating new ultrasound phenotypes based on plaque progression may thus be important for future genetic research. The strongest predictor of baseline plaque is age, which accounts for nearly half the explained variance of plaque area in multiple regression analysis.4 Because age is neither genetic nor treatable, traits based on progression of plaque from baseline, adjusted for traditional risk factors in multiple regression, may be a more sensitive way to find new determinants of atherosclerosis, including genes.4

J. David Spence
Stroke Prevention and Atherosclerosis Research Centre
Robarts Research Institute
London, Canada

Robert A. Hegele
Blackburn Cardiovascular Genetics Laboratory
Robarts Research Institute
London, Canada


In response:

We appreciate the comments of Drs Spence and Hegele regarding the value of carotid plaque area as a noninvasive phenotype of atherosclerosis. We agree that plaque area may have different genetic determinants from other ultrasound-defined measures of carotid atherosclerosis, and we included a statement to this effect with a citation of their work in our discussion of carotid phenotypes.1 Whereas one would anticipate that genes influencing plaque overlap with those influencing intima-media thickness (IMT), there are likely to be unique sets of genes related to both.2–3 Our focus on carotid IMT was largely because of the bulk of the published literature focusing on this trait for genetic research. As noted in our review, there is clear evidence that carotid IMT is both inheritable and associated with risk for atherosclerotic myocardial infarction and stroke independent of other atherosclerotic risk factors. We included several articles of Spence et al on genetics of carotid plaque in our review and supplementary material. We appreciate Drs Spence and Hegele making us aware of their article on the peroxisome proliferator-activated receptor γ, which was published after our review. The other articles mentioned by Spence et al did not deal directly with associations of genetic variants to carotid atherosclerosis and were thus not eligible for inclusion in this review.
We agree that evaluating a breadth of noninvasive phenotypes may be important in identifying the genetic and nongenetic contributions to carotid atherosclerosis.

Teri Manolio  
National Heart, Lung, and Blood Institute  
Bethesda, Maryland

Eric Boerwinkle  
University of Texas Health Science Center at Houston  
Houston, Texas

Christopher O’Donnell  
National Heart, Lung, and Blood Institute  
Framingham, Massachusetts

Alexander F. Wilson  
National Human Genome Research Institute  
Baltimore, Maryland

