Longitudinal Differences in Familial Combined Hyperlipidemia Quantitative Trait Loci

In response:

Previously in Arteriosclerosis, Thrombosis, and Vascular Biology we commented on genome-wide linkage analysis of quantitative trait loci (QTL) as a strategy to solve the genetics of complex traits, such as familial combined hyperlipidemia (FCHL).1 We noted that although this approach has yielded numerous linkage peaks, only rarely have these peaks led to defined molecular genetic determinants. We suggested that replication of QTL analysis is an important filtering process to increase confidence in preliminary observations by reducing false-positive leads.1 The usual replication strategy involves repeating the analysis in independent samples and identifying shared peaks. In their letter, Brouwers et al report the use of an alternate replication strategy, namely repeating QTL analysis for FCHL in the same cohort after an elapsed time period of 5 years.2 On first glance, this strategy would appear quite likely to yield replicable results, considering that the same subjects should be stable for both their genotype (definitely) and for their quantitative phenotypes (essentially) over time.

In the baseline study performed using phenotypes collected in 1999,3 Cantor et al identified 4 peaks, using the threshold of \( P<0.001 \) to report significant linkage. These peaks were located at chromosome 1p21-31 and 17p11-q23 for apoB, 12p13 for cholesterol, and 4p15-16 for triglycerides. Each QTL was re-examined in their follow-up study of the same subjects using phenotypes collected in 2004.2 First, the unambiguous good news: the peak at 1p21-31 for apoB is significant positive signal given the prespecified criteria in the original report. The peak for cholesterol at 12p13 flattened from a Z-score of 3.7 to <1, and the peak for apoB dropped from a Z-score of 4.3 to 1.7, both of which now fall below the threshold for significance. The peak for triglycerides at 4p15-16 had shifted position, and although it was somewhat less eroded, the observed probability value of 0.003 would not have been accepted as a significant positive signal given the prespecified criteria in the original report.

Thus, repeating the analysis produced 1 replicable QTL of 4 that were initially identified as being significant. The glass is thus either one-quarter full or three-quarters empty, depending on one’s perspective and temperament. Although the peak at 1p21-31 for apoB is worth pursuing, it is also probably appropriate that resources are not expended to pursue the other 3 peaks. Such disparities within the same study sample followed longitudinally show that quantitative traits are a moving target.

Typically, replication implies the study of independently ascertained samples; it has somehow been assumed that replication of significant results internally within the same sample would be a foregone conclusion. This longitudinal study provides a glimpse of the apparently tenuous nature of replication in QTL analysis even within the same sample. The need for replication cannot be stressed enough; it must be considered as an essential element of these investigations, perhaps beginning with replication in the same sample studied at different points in time.

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