Apolipoprotein E Genotyping and Concussion: Time To Fish or Cut Bait

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Biomarkers are hot. The National Institutes of Health awarded more than $2.5 billion for biomarker research in 2008 and 2009. Because clinicians and researchers are interested in concussion, we can easily appreciate their allure. What is not to like about apolipoprotein E (APOE)? Apolipoprotein E has established itself as a biomarker for Alzheimer disease, a condition that may have head trauma as one of its antecedents. However, the role of APOE within lesser severity brain injuries is less clear.

In this edition of the Clinical Journal of Sport Medicine, Tierney et al present evidence that carrying 3 rare APOE polymorphisms (present in 0.7% of their population) may be associated with an increased likelihood of reporting previous concussions and that carrying a minor allele of the APOE promoter (present in 49% of their nonconcussed population) may be associated with an increased likelihood of reporting multiple concussions (≥2) within a cross-sectional sample of collegiate male football and female soccer players. This research was hypothesis driven and biologically plausible, given the recognized modification of APOE with nervous system injury and recovery. Their reported associations (odds ratios) are sizeable.

But are these findings new or, in the language of genetic association studies, “hypothesis generating”? In a previous edition of the Clinical Journal of Sport Medicine, Terrell et al found the same APOE promoter G-219T to be potentially associated with an increased likelihood of reporting previous concussion within a similar cross-sectional sample of college male football and female soccer players. Both studies demonstrated an increasing likelihood of reporting concussion with sport exposure. Terrell et al identified a potential genotype–concussion interaction with the homozygous APOE promoter TT genotype association, with concussion appearing stronger for those with 5 or more sports-years of exposure and for those who were identified as African American.

So, now we have 2, small, significantly underpowered studies reporting modest to sizeable associations of the APOE promoter G-219T with concussion, where this genetic risk is present for a small proportion of 2 samples of experienced collegiate athletes. Where do we go next in this burgeoning era of genetic association studies? Not surprisingly, first there is work to be done by our clinical researchers.

If our genetics colleagues continue to use retrospective study designs (cross-sectional or case–control), we will continue to be hampered by the validity of self-reported concussion. The only study that I am aware of on the validity of self-reported concussion clearly sits on the fence. In that study, 62% of collegiate football players (N = 62) accurately self-reported concussion(s) that had been prospectively ascertained. The remainder of players were as likely to under as over report their number of concussions. This abstract can be used to either validate or denigrate the self-report of concussion. Misreporting of concussion numbers ultimately leads to significant misclassification bias and undoubtedly affects the measures of association. Several concussion researchers have extensive cohorts of athletes with prospectively ascertained concussion data; it is now time to find out whether these same athletes accurately self-report their concussion history within the period of observation.
Given the low incidence of concussion, genetic studies using a case–control study design will always have a considerable efficiency advantage over the counterpart, the cohort study design, albeit with potentially more room for recall bias. The control athletes should be selected so as to provide an estimate of the genotyping that would be expected to occur in the source population that produced the cases of concussion. Concussion is an injury and, without also considering an injured control group, genotype associations that are more appropriately attributed to injury have the potential to be reported as genotype–injury associations.

Clinicians involved in the management of concussed athletes are well aware of the considerable interindividual variation in the occurrence, manifestations, and prognosis of concussion. Teasdale et al., in an earlier article about APOE polymorphism, highlighted that “there may be genetically determined variation between individuals in the acute response to brain injury or in the capacity for repair and regeneration.” We need to consider the multicausality of concussion, where multiple pathways lead to a common phenotype. To understand what may prove to be a complex interplay of both genetic and environmental factors, we will need to continue to expand our understanding of “phenomics,” the systematic measurement and analysis of qualitative and quantitative traits of concussion. Thus, future genetic studies may need to examine genotype–multiple phenotype associations and their interactions.

Potential studies will need to be truly “multicentered.” Genetic studies often involve multiple comparisons, which, when coupled with statistical testing, increase the probability of type 1 error(s). Analyses will have to account for this multiple statistical testing. In conjunction with multivariate statistics and the investigation of gene–gene and gene–environment interactions, significant sample sizes will be necessary to control the possibility of both type 1 and type 2 errors. The sample size calculations need to be done a priori and reported with the methodology.

There are, in addition, design issues germane to genetic association studies. Genotype data require demonstration of validity through duplicate sample testing and must be done blind to the results of the phenotype. Population stratification, the systematic difference in allele frequencies between subpopulations related to different ancestry, needs to be considered because it may affect reported associations. Replication studies are required because of the likelihood of false-positive results. Reports of genetic association studies should be mindful of the recommendations of the STREGA (Strengthening the Reporting of Genetic Association studies) statement.

Unfortunately, the track record of genetic association studies has already been shown to be less than optimal. Nonreplication and inconsistency have become a “common feature” of this literature. Most reported associations are ultimately going to be shown to be false. This has already entered the rubric of genetic association studies, the so-called winner’s curse. The grim reality is that the results of many genetic studies will not be reproducible.

The studies of Tierney et al and Terrell et al from the pages of this journal are indeed “hypothesis generating.” Without validation, these promising findings remain tentative. It is time for a collaborative consortium to develop a large rigorously designed validation study to clarify these associations and the potential role of other genetic and epigenetic markers on the occurrence, manifestations, and prognosis of concussion.

It truly is “time to fish or cut bait.”

REFERENCES