Polymorphisms Associated with Asthma Are Inversely Related to Glioblastoma Multiforme

To the Editor:

While searching for a recent article on asthma genetics, I came across the study by Schwartzbaum et al. (1). As the article carried a bold title I read on, but was somewhat disappointed by the content. Three years ago, asthma had already been associated with 64 genes, and 33 of these associations had been successfully replicated (ref. 2; these figures are at probably doubled now). The reasons the authors chose only three of these genes (and thus ignored broad categories of candidates) are not explained.

If the intention was purely to study the two genes for which plausible mechanisms in tumor development existed (IL-4RA and IL-13), it seems odd both to include ADAM33 and to select its T1 single nucleotide polymorphism (SNP). As a definitive causative SNP in ADAM33 remains elusive, selection of a single SNP to represent the gene would be contrary to most guidelines (e.g., ref. 3). Furthermore, the authors state the T1 polymorphism “was found to be associated with asthma in three different populations” in line with their selection criteria of SNPs “consistently associated with asthma.” In the first of three references, T1 was only associated with asthma in one of two study populations and not when the results were pooled (4). In the second reference (5), T1 was not associated with asthma in either a case-control nor a family-based analysis. The third paper describes T1 to “show borderline significance in the U.S. white subjects,” but is cautious as no association was seen in three other groups (and may have been a result of multiple testing; ref. 6). T1 was also not associated with asthma in a meta-analysis of new and existing data involving over 7,500 individuals (7).

In discussing their findings, it is surprising that the authors feel they are “confirming previous literature” then give an odds ratio whose confidence intervals comfortably include one (odds ratio, 0.64; 95% confidence interval, 0.33-1.25). Similarly, three of the SNPs tested are said to show association, although only one of these has a \( P \) value of \(<0.05\) in Table 2. The authors also do not mention important aspects of genetic association studies, such as linkage disequilibrium patterns across the genes, Hardy-Weinberg equilibrium testing, or the high false-positive rate in such studies with small populations.

Schwartzbaum et al. have highlighted a fascinating observation in clinical medicine and create a platform for further research in this area. However, they have succumbed to the increasing trend of using an attention-grabbing title that implies a greater scope or rationale genes as-...
gene because this gene is a member of a family involved in GBM invasion (2). In retrospect, based on our negative findings, we did not select the correct polymorphism and perhaps not even the correct gene for this particular analysis.

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References
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