

## 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 stringency of research than the paper comprises.

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### In Response:

Wacholder et al.'s (1) discussion of false-positive findings in the genetic literature guided our selection of polymorphisms (2). These authors clearly show that a strong prior belief in the scientific hypothesis greatly reduces the role of statistical power in producing false-positive findings. Therefore, we selected polymorphisms on the *interleukin (IL)-4R $\alpha$*  and *IL-13* genes associated with asthma because *IL-4* and *IL-13* also inhibit glioma growth (2). Had we examined all known genetic variants associated with asthma, as Blakey et al. suggest in their letter, we would have increased our risk of producing false-positive findings. Looking at associations without sound *a priori* rationale has not proven to be a fruitful way to conduct genetic variant analyses.

Statistical hypothesis testing can also produce false negative results and therefore must be interpreted in the context of previous evidence. Thus, we state that the nonsignificant association between asthma and glioblastoma multiforme (GBM) (odds ratio, 0.64; 95% confidence interval, 0.33-1.25) is consistent with previous research because it is. Of five previous studies, the mean and median odds ratio characterizing the association between asthma and glioma is 0.63 (3). Furthermore, contrary to Blakey et al.'s statement, the three single-nucleotide polymorphisms that we conclude are associated with GBM are statistically significantly associated with GBM ( $P \leq 0.05$ ) when data are dichotomized using homozygotes for the most prevalent alleles as the reference category (see column 3, Table 2, ref. 2). It is only when we conduct trend tests by genotype (column 4, Table 2, ref. 2), where the sample size for the less common genotypes is small, that we observe only two *P* values  $\leq 0.05$ . However, more important than the statistical significance of our results are the inverse associations between asthma and GBM odds ratios predicted by our hypothesis. Additional supporting evidence for this negative relationship is found in Fig. 1 (2), which shows that an interaction between two polymorphisms has opposite effects on asthma and GBM risk.

The paradox of the inverse association between asthma, an inflammatory lung condition, and GBM is that asthma, in its later stages, is associated with genes that participate in GBM growth and tissue invasion (e.g., the gene for vascular endothelial growth factor; refs. 4, 5). We therefore evaluated a polymorphism on the *ADAM33*

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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