Replication validity of genetic association studies of smoking behavior: What can meta-analytic techniques offer?

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To the Editor:

A recent issue of Nicotine & Tobacco Research devoted considerable attention to a failure to replicate the previously reported association between smoking status and the human dopamine transporter variable number of tandem repeats (VNTR) polymorphism (Vandenbergh et al., 2002a), with editorial comment from Lerman and Swan (2002) and a corresponding response from the study authors (Vandenbergh et al., 2002b). A number of very valuable suggestions were made in both editorials regarding the design of future association studies, but more may be said. In particular, the contribution that meta-analytic procedures can make to the debate was largely overlooked.

Ioannidis, Ntzani, Trikalinos, and Contopoulos-Ioannidis (2001) conducted a meta-analysis of 370 studies addressing 36 genetic associations with various disease and behavioral phenotypes. In particular, they compared the strength of the postulated genetic association determined in the first study against that determined in the subsequent studies. They concluded that significant between-study heterogeneity is frequent, and the results of the first study often correlate only modestly with subsequent research on the same association. In particular, Ioannidis et al. (2001) noted that the first study will often suggest a stronger genetic effect than subsequent studies, and typically a very strong association suggested by the first study becomes less prominent (or even disappears) as data accumulate.

A comparable situation can be seen to exist in the case of genetic association studies of smoking behavior. In the example of the association of the A1 allele of the dopamine D2 receptor (DRD2) gene and smoking behavior, for example, the first study (Noble et al., 1994) suggested a strong association that has not been consistently supported by subsequent studies (Lerman & Swan, 2002). The simple process of comparing the number of studies reporting positive results against those failing to do so may singularly fail to provide a definitive answer to the question of whether the putative genetic effect is real. However, a meta-analysis of nine independent studies of Whites showed a strong association of the DRD2 A1 allele with smoking behavior (Noble, 2003).

Meta-analysis is a potentially powerful tool for assessing population-wide effects of candidate genes on complex behavioral phenotypes such as smoking and also may provide evidence for previously undiscovered diversity, for example, by revealing heterogeneity in studies of apparently similar populations (Ioannidis et al., 2001), which may suggest the presence of important moderating factors that have not been measured by existing studies. Further uses to which meta-analytic datasets can be put include testing for the presence of publication bias or for whether the data in fact derive from two (or more) distinct populations, such as might be expected if the genetic effect was stratified by sex or ethnicity. Methods such as the normal quantile plot (Wang & Bushman, 1998) allow for the data to be tested in these ways, and this approach, in turn, can guide the design of future studies.
Although efforts to develop increasingly refined smoking phenotypes, to focus on functional genetic polymorphisms, and to examine interaction effects will enhance future association studies (Lerman & Swan, 2002), more information may be gleaned from the corpus of data that already exists that also will serve to guide the design of future studies.

References
Vandenbergh, D. J., Kozlowski, L. T., Bennett, C. J., Grant, M. D., Strasser, A. A., O’Connor, R., Stauffer, R. L., & Vogler, G. P. (2002b). DAT’s not all, but it may be more than we realize Nicotine & Tobacco Research, 4, 251–252.