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Reply to Chappell et al.

To The Editor: We appreciate the efforts of Chappell and colleagues[1] to replicate our *SERPINE2* findings. We identified *SERPINE2* as a candidate gene for chronic obstructive pulmonary disease (COPD [MIM 606963]) on the basis of our gene-expression results (in both murine and human lung) and our genetic association analysis results in two study populations. Chappell et al. found no evidence for association of five *SERPINE2* SNPs with COPD in their case-control study. As in many complex-disease genetic association studies in general, and in previous COPD genetic association studies in particular,[2] the results are inconsistent.

There are many potential explanations for these inconsistent results, including population stratification, genetic heterogeneity, false-positive and/or false-negative results, differences in the number of SNPs genotyped, and phenotypic heterogeneity.[3] In comparing the results of our two research groups for association analysis of *SERPINE2* SNPs with COPD, phenotypic heterogeneity is of particular importance. COPD is a syndrome composed of both emphysema and airway disease, with variable contributions of these processes in different individuals with COPD. Review of chest CT scans of probands from the Boston Early-Onset COPD Study—the population in which we performed family-based association analysis of COPD-related phenotypes—revealed that the vast majority of these probands had emphysema.[4] Moreover, the COPD cases in our case-control replication population were clearly selected for emphysema as part of the National Emphysema Treatment Trial (NETT). In addition, the Boston Early-Onset COPD Study probands and the NETT cases had very severe COPD. Thus, our test and replication populations were severely affected with COPD, typically with a substantial degree of emphysema. As noted by Chappell et al., our cases represent "a severe subset of the disease spectrum,"[1(p185)] and their cases represent a broader spectrum of severity, including individuals with and without emphysema. The differences in disease severity and emphysema may be important contributors to their nonreplication of our association findings. Also of note, although Chappell et al. genotyped five SNPs in *SERPINE2,* they did not genotype several other SNPs for which we observed replicated associations and LOD score reduction in conditional linkage models.

Chappell et al. also comment about apparently inconsistent association results in our family-based and case-control association analyses among SNPs in tight linkage disequilibrium (LD). Modest differences in the statistical significance of the association analysis results were noted for several SNPs that are in strong but not complete LD in our study populations. There are reasonable explanations for these modest differences. (1) The SNP pairs mentioned are not in complete LD; in our combined case-control cohort, the r^2 values were 0.93 for *rs3795879* and *rs3795877* and 0.91 for *rs1438831* and *rs920251*. (2) Despite excellent genotype completion rates, there were slight differences in missing data between these SNP pairs. Of note, these were not the only *SERPINE2* SNPs significantly associated with COPD-related phenotypes in our study; we observed 18 significantly associated *SERPINE2* SNPs in the family-based association analysis and 7 significantly associated SNPs in the case-control analysis.

We fully agree with Chappell et al. that replication of significant associations is essential—which is why we included in our article the replication of our family-based association analysis results in a separate case-control study. This is also the reason why we provided early access to significantly associated SNPs to the Chappell and Kalsheker group.

Is *SERPINE2* a *confirmed* COPD susceptibility gene? Certainly not. Before the impact of *SERPINE2* on COPD susceptibility is fully known, more genetic association studies as well as functional studies will be needed. However, we contend that *SERPINE2* remains a valid COPD candidate gene. Finally, we agree with Chappell et al. that agreement on phenotypic definitions and collaboration between re-

search groups are crucial for the future of genetic studies of COPD and other complex diseases.

Web Resources

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for COPD)

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