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Single-Nucleotide Polymorphisms and Glaucoma Severity

To the Editor:

A recent publication in the *Journal* (Copin et al. 2002) reported that SNPs in the promoter of apolipoprotein E (APOE [MIM 107741]) modify the phenotype of primary open-angle glaucoma, result in increased optic-nerve damage, and interact at a highly significant level with an SNP in the promoter of myocilin (MYOC [MIM 601652]), a known glaucoma-causing gene. If correct, this would be of considerable importance for providing novel insight into the pathogenesis of a leading cause of worldwide blindness (Quigley et al. 1993), which is characterized by visual-field loss and progressive excavation (cupping) of the optic disc.

That study's conclusions are entirely dependent on the observation of differing disease severity in the genotypic subgroups. Glaucoma severity was graded by use of ordinal scales, and it is important to relate statistical analysis back to these scales. If we consider a simple example of patients with a bacterial infection that is scored (1, 2, or 3) according to whether they "got better," "stayed the same," or "got worse," if equal numbers got better and got worse, it would be meaningless to state that, on average, patients stayed the same (Campbell 2001). It would be equally invalid to present fractional differences in the data (e.g., 1.3). Unfortunately, Copin et al. (2002) employed this approach with both parameters used to gauge glaucoma severity.

The first parameter, cup-to-disc ratio (CDR), estimates in 10% (0.1) increments the proportion of the optic nerve that has been damaged. CDR is only an approximate guide because of high interindividual (normal range 0.0 to almost 0.9) and interobserver variability (>0.2) among specialists assessing optic discs (Lichter 1976; Jonas et al. 1988; Tielsch et al. 1988). Although CDR is a form of ordinal data with a fixed scale (0.1, 0.2, 0.3, etc.), Copin and coworkers (2002) report fractional differences (0.03 or 0.06), smaller than the scale increments, as evidence of increased disease severity with particular genotypes. The second parameter, visual-field loss, has been similarly evaluated. Recorded with an unspecified number of different techniques, the data were reanalyzed with a version

of the authors' semiquantitative five-point scale that differs from the one cited (Brézin et al. 1997) and that does not appear to have been prospectively evaluated relative to more widely used grading systems (Advanced Glaucoma Intervention Study 1994). Again, it is unclear how a fractional difference (mean 0.6) in a narrow, whole-integer scale (2 = early defect; 3 = moderate [arcuate] defect; 4 = advanced defect) can be interpreted.

Without supportive clinical data, evidence is lacking that APOE SNPs either are associated with a more severe phenotype or interact at a highly significant level with an SNP in the MYOC promoter. Since a large prospective study (Alward et al. 2002) failed to replicate the authors' report of an association between the MYOC promoter SNP and glaucoma severity (Colomb et al. 2001), the hypotheses that either APOE or MYOC promoter SNPs affect the severity of glaucoma (Copin et al. 2002), for now, remain to be proven.

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Electronic-Database Information

The URL for data presented herein is as follows:

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

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Reply to Bunce et al.

To the Editor:

Bunce et al. (2003 [in this issue]) did not question the validity of the statistical method, nonparametric, that was used for testing an explanatory potential of apolipoprotein E (APOE) genotypes relative to glaucoma phenotype variation. Nor did they criticize the second part of our study, which was relative to an influence of APOE polymorphism on intraocular pressure.

Their comment regarding an ordinal nature of the cup-to-disk ratio is unexpected, as the cup-to-disk ratio—the ratio of the diameters of the excavation and of the optic disc—is fractional by definition.

This measure of the optic-nerve status remains commonly used by clinicians and researchers, especially in the area of glaucoma genetics (Alward et al. 2002). It is reassuring to read a recent article contributed by three of the authors of this letter (Aung et al 2003) that uses it, with values taken between the increments (table 2 of the article).

Contrary to the statement of Bunce et al., the scale that we used for grading the visual-field loss was similar to that described elsewhere (Brézin et al. 1997). Critical for the consistency of our data set, cup/disc ratios and visual-field evaluations were tightly correlated (nonparametric correlations: Spearman R 0.596, $P < 1 \times 10^{-17}$; Kendall τ 0.496, $P < 1 \times 10^{-8}$; γ 0.625, $P < 1 \times 10^{-8}$).

The interesting study of Alward et al. (2002) was clearly not prospective, and it did not investigate a role of APOE. A detailed discussion of the reasons for the discordance