

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)

### References

- Advanced Glaucoma Intervention Study (1994) Visual field test scoring and reliability. *Ophthalmology* 101:1445–1455
- Alward WLM, Kwon YH, Khanna CL, Johnson T, Hayreh SS, Zimmerman MB, Narkiewicz J, Andorf JL, Moore PA, Fingert JH, Sheffield VC, Stone EM (2002) Variations in the myocilin gene in patients with open-angle glaucoma. *Arch Ophthalmol* 120:1189–1197
- Brézin AP, Bechettille A, Hamard P, Valtot F, Berkani M, Belmouden A, Adam MF, Dupont de Dinechin S, Bach JF, Garchon HJ (1997) Genetic heterogeneity of primary open angle glaucoma and ocular hypertension: linkage to GLC1A associated with an increased risk of severe glaucomatous optic neuropathy. *J Med Genet* 34:546–552
- Campbell MJ (2001) *Statistics at square two*. BMJ Publishing, London
- Colomb E, Nguyen TD, Béchetoille A, Dascotte J-C, Valtot F, Brézin AP, Berkani M, Copin B, Gomez L, Polansky JR, Garchon H-J (2001) Association of a single nucleotide polymorphism in the TIGR/MYOCILIN gene promoter with the severity of primary open-angle glaucoma. *Clin Genet* 60:220–225
- Copin B, Brézin AP, Valtot F, Dascotte J-C, Béchetoille A, Gar-

chon H-J (2002) Apolipoprotein E–promoter single-nucleotide polymorphisms affect the phenotype of primary open-angle glaucoma and demonstrate interaction with the myocilin gene. *Am J Hum Genet* 70:1575–1581

Jonas JB, Gusek GC, Naumann GO (1988) Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes. *Invest Ophthalmol Vis Sci* 29:1151–1158

Lichter PR (1976) Variability of expert observers in evaluating the optic disc. *Trans Am Ophthalmol Soc* 74:532–572

Quigley HA (1993) Open-angle glaucoma. *N Engl J Med* 328:1097–1106

Tielsch JM, Katz J, Quigley HA, Miller NR, Sommer A (1988) Intraobserver and interobserver agreement in measurement of optic disc characteristics. *Ophthalmology* 95:350–356

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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  $\tau$  0.496,  $P < 1 \times 10^{-8}$ ;  $\gamma$  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

between this study and that of Colomb et al. (2001) goes beyond the scope of this reply letter and will be given elsewhere. In brief, however, there were substantial differences between the patient samples, notably the age at diagnosis. Investigating these differences will provide insight into the significance of the SNPs for glaucoma phenotypes.

Although negative results may be most instructive, it is also essential to obtain data that are supportive of an initial finding. The readers of the *Journal* should be aware of two recent reports that are consistent with an involvement of APOE in glaucoma (Bayer et al. 2002; Vickers et al. 2002).

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## References

- Alward WL, Kwon YH, Khanna CL, Johnson AT, Hayreh SS, Zimmerman MB, Narkiewicz J, Andorf JL, Moore PA, Fingert JH, Sheffield VC, Stone EM (2002) Variations in the myocilin gene in patients with open-angle glaucoma. *Arch Ophthalmol* 120:1189–1197
- Aung T, Okada K, Poinosawmy D, Membrey L, Brice G, Child AH, Bhattacharya SS, Lehmann OJ, Garway-Heath DF, Hitchings RA (2003) The phenotype of normal tension glaucoma patients with and without OPA1 polymorphisms. *Br J Ophthalmol* 87:149–152
- Bayer AU, Keller ON, Ferrari F, Maag KP (2002) Association of glaucoma with neurodegenerative diseases with apoptotic cell death: Alzheimer's disease and Parkinson's disease. *Am J Ophthalmol* 133:135–137
- Brézin AP, Bechettoille A, Hamard P, Valtot F, Berkani M, Belmouden A, Adam MF, Dupont de Dinechin S, Bach JF, Garchon HJ (1997) Genetic heterogeneity of primary open angle glaucoma and ocular hypertension: linkage to GLC1A associated with an increased risk of severe glaucomatous optic neuropathy. *J Med Genet* 34:546–552
- Bunce C, Hitchings RA, Bhattacharya SS, Lehmann OJ (2003) Single-nucleotide polymorphisms and glaucoma severity. *Am J Hum Genet* 72:1593–1594 (in this issue)
- Colomb E, Nguyen TD, Béchettoille A, Dascotte J-C, Valtot F, Brézin AP, Berkani M, Copin B, Gomez L, Polansky JR, Garchon H-J (2001) Association of a single nucleotide polymorphism in the TIGR/MYOCILIN gene promoter with the severity of primary open-angle glaucoma. *Clin Genet* 60:220–225
- Vickers JC, Craig JE, Stankovich J, McCormack GH, West AK, Dickinson JL, McCartney PJ, Coote MA, Healey DL, MacKey DA (2002) The apolipoprotein epsilon4 gene is associated with elevated risk of normal tension glaucoma. *Mol Vis* 8:389–393

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