Response to Liu et al.

To the Editor: The findings of Liu and colleagues seem to contradict our recent findings of an association of primary open-angle glaucoma (MIM 137760) with rare *NTF4* (MIM 162662) variants, one of which was shown to reduce TRKB signaling in vitro.[1] The authors have now investigated a similar patient group with comparable phenotypic characteristics and indeed also found rare *NTF4* variants in this group. Interestingly, they found an even higher number of variants in the control group (12/533). This is in marked contrast to our findings because we found only 1 variant in 895 control individuals. This difference is statistically significant ($p < 0.001$, χ^2 test). We noticed that the control group use by Liu and coworkers is significantly younger than ours (64.7 ± 14.2 years versus 73.9 ± 6.4 years). Also, the control group seems to be a hospital-derived control group, similar to our first control group. Although they have the advantage of being ophthalmologically investigated to exclude any sign of glaucoma, such control groups have the inherent potential for undetected bias because probands were identified when they sought ophthalmological care. Our second control group was population based, which should be free of this bias, although we expect this group to contain undiagnosed or unrecognized patients at the population frequency of glaucoma. Nevertheless, this is unlikely given the average age of 75.5 ± 7.4 years in this subgroup.

We cannot exclude, though, that some of the variants identified either in the original study or in this one are benign variants; we showed a functional impairment only for R206W. This situation is similar to that of the association of rare variants in *CYP1B1* (MIM 601771) and primary open-angle glaucoma. Only when variants were systematically classified as either benign or functionally impairing did a significant association become evident.[2] Furthermore, it is not unusual that other, similarly sized studies fail to replicate a true association finding, especially when the study involves rare variants, probably because of sampling effects. It may also be possible that the magnitude of effect in our study was overestimated as a result of such an effect. Finally, only a meta-analysis of different studies in glaucoma patients as well as population-based control individuals will eventually clarify the role of *NTF4* in glaucoma.

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Web Resources

The URL for data presented herein is as follows:

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

References

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