Author Response: Stronger Association of CDKN2B-AS1 Variants in Female Normal-Tension Glaucoma Patients in a Japanese Population

We read with great interest the letter to the editor by Mori et al. titled “Stronger Association of CDKN2B-AS1 Variants in Female Normal-Tension Glaucoma Patients in a Japanese Population.” As pointed out in our original publication, the robust replication of genetic findings in independent populations is vital in understanding the significance of any reported association. Mori et al. have provided strong additional evidence for a sex-biased association with primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG) at this locus. This finding vastly improves confidence in the results in our original report.

Due to differences in the genotyping methods in the underlying studies, Mori et al. present data at variants that were not dissected in detail in our original study, although a nominal association with POAG in the full Australian dataset was reported at the same variants. There are clear population-specific allele frequency differences between Europeans and Asians at this locus; however, Mori et al. show a very similar finding of stronger association in females and in particular in females with NTG. To reach the same conclusion in a population of different ethnicity adds significant further weight to the findings, indicating similar biology and mechanisms between the groups, despite different genetic architecture at this locus.

Since conducting our work looking at just the 9p21 region, we have looked genome-wide to see if there are differences in the genetic contribution to POAG risk in males and females. We found that the genetic correlation estimated from markers genome-wide was substantially less than 1 (correlation 0.33, with standard error 0.24). Our findings on POAG are in contrast to findings across other complex traits, where the genome-wide genetic correlation between males and females is typically close to 1. For example, in age-related macular degeneration, the genetic correlation is not significantly different to 1 (estimated to be 0.71, with standard error 0.23). It should be emphasized that a higher prevalence in one sex does not prohibit there being a very high genetic correlation; for example, in oesophageal cancer there are eight times as many male as female cases, and yet the genetic correlation is estimated to be 1. A low genetic correlation between the sexes implies that a proportion of the genetic variants that influence POAG risk in one sex have little or no effect in the opposite sex. Such a finding means that future studies should consider routinely stratifying genetic association analysis by sex. It is also likely that some of the difference in POAG prevalence between sexes is due to heritable factors. However, as for our finding at 9p21 we have only estimated the genome-wide genetic correlation in one population (Australians of European ancestry). It would be interesting to investigate sex differences genome-wide in other populations.

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References

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