

Letter to the Editor

Response to Dr. Kopke's Comments on Haplotypes at the OPRM1 Locus

To the Editor:

The letter from Dr. Kopke brings up interesting and important issues in a constructive way. We maintain that correction of the significance level is necessary in the context of multiple statistical tests. Although the Bonferroni correction may be overly conservative, we believe that the procedure used by Hoehe et al. [2000] is not strictly correct in that the significance level was checked via simulation only at certain branch points. Under these circumstances, we believe it would have been preferable to keep track of the minimal *P*-value throughout the branch merges, with an a priori definition of statistical significance. Without an a priori definition, there is the risk that once a nominally significant *P*-value is reached, the analysis would be terminated prematurely.

The allele frequency of "1222 + 2222" in African-American (AA) cases in the study by Hoehe et al. [2000] is 0.088, which is close to the frequency of 0.073 in AA cases in our study [Luo et al., 2003] and the frequency of 0.089 ~ 0.096 in AA cases reported in the newly published study by Crowley et al. [2003]. There are no significant differences in these allele frequencies among the cases in these three studies and the controls both in the Luo et al. study ($f = 0.082$) and the Crowley et al. study ($f = 0.097 \sim 0.099$). Based on this, we argued that the allele frequency of 0.014 in the AA controls in the Hoehe et al. study might be the outlying value. That is lower than 0.082 [95% confidence intervals (CI): 0.028 ~ 0.135] in AA controls in the study by Luo et al. (2003) and 0.097 ~ 0.099 (95%CI: 0.053 ~ 0.143) in AA controls in the study by Crowley et al. [2003]. The allele frequency of 0.014 in the Hoehe et al. study is outside the 95% CI of the allele frequencies in both the Luo et al. and Crowley et al. studies. The probability that the population represented by the control sample in the Hoehe et al. study overlaps with the population represented by the control sample in the Luo et al. study is 0.091 [Luo et al., 2003]; the probability that the population represented by the control sample in the Hoehe et al. study overlaps with the population represented by the sample in the Crowley et al. study is $0.031 < 0.05$, suggesting that the controls in the Hoehe et al. study are sampled from a population different from those of Luo et al. and Crowley et al. Given the similarity in allele

frequencies across the studies by Luo et al. and Crowley et al., and their comparatively large sample sizes, we would argue that these control samples are more representative of the general healthy African-American population than the control sample in the Hoehe et al. study.

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Received 12 December 2003; Accepted 3 March 2004

DOI 10.1002/ajmg.b.30060