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Comment on "Evaluation of a Gene–Environment Interaction of *PON1* and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case–Control Study Drawn from the U.S. Military Health Survey's National Population Sample"

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In a case–control study of Gulf War illness (GWI), Haley et al. report an association of GWI with a gene–environment (G × E) interaction of the *paraoxonase-1* (*PON1*) Q192R polymorphism and low-level nerve agent exposure.[1] The frequency of the allele coding for the 192 arginine (R) isoenzyme, which metabolizes sarin less well than the glutamine (Q) isoenzyme, was higher in cases than in controls, and the fact that a G × E interaction was detected was taken to support the hypothesis that sarin exposure exerted a causal effect on susceptibility to GWI.

An important concern is that the frequency of the R allele is known to vary considerably between ancestries. For example, in subjects of European, African, and South Asian ancestries, the allele frequencies are reported to be 0.286, 0.646, and 0.379, respectively.[2] This means that if cases and controls tend to have different ancestries, then one will expect to observe differences in allele frequencies and genotype frequencies even if the variant in fact has no effect at all on the outcome. The study reported an allele frequency of 0.327 in controls and 0.470 in cases, both values being intermediate between those expected for subjects having European or African ancestry.

To avoid this sort of bias entering into genetic association studies, it is standard practice to ensure that case and control samples are ethnically homogeneous and well-matched for ancestry. In the study by Haley et al.,[1] the only matching was done on the basis of "non-Hispanic White" vs. "other," but this is clearly inadequate. The "other" category could include Hispanic White subjects with largely European ancestry, as well as subjects with African or Asian ancestry. Different proportions in cases and controls of such subjects could easily have produced the reported allele frequencies. In addition, the genotype frequencies in the cases were reported to depart from the Hardy–Weinberg equilibrium; again, this is an expected consequence of ancestral heterogeneity.

Although a difference in ancestries between cases and controls would not necessarily lead to a G × E interaction, such an interaction could occur if there were also an association between ethnicity and exposure. It seems entirely plausible that sociodemographic factors relating to deployment might have resulted in such an association, and the possibility certainly cannot be eliminated.

To conclude, there is an obvious source of bias to account for the association between *PON1* genotypes and GWI. The results reported cannot be taken as evidence of a causal effect of low-level nerve agent exposure on risk of GWI.

References

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The author declares he has nothing to disclose.

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