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The author reports no financial relationships with commercial interests.

This letter was accepted for publication in January 2015.

Am J Psychiatry 2015; 172:394–395; doi: 10.1176/appi.ajp.2015.14111429

Response to Gorelick

TO THE EDITOR: Dr. Gorelick raises a reasonable question as to whether the sex-by-treatment interaction reported in our article on combined varenicline/bupropion sustained-release treatment could have been due in part to a lower efficacy of varenicline alone in men compared with women. Although we, along with the editorialist, highlight this possibility, two factors argue against it being a major contributor to the interaction effect. First, the previous literature has not reported sex differences in varenicline treatment. Second, the statistical argument advanced in Dr. Gorelick's comment is imprecise. Error-bar overlap is not a reliable criterion for assessing statistical significance. Using the information presented in Table 2 of our article, a chi-square calculation yields a p value of 0.27 for the difference between varenicline plus placebo treatment in men compared with women. Thus, although the possibility remains that there is an effect that contributed to the overall interaction effect, there is no compelling data in support of that interpretation at the present time.

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The authors' disclosures accompany the original article.

This reply was accepted for publication in January 2015.

Am J Psychiatry 2015; 172:395; doi: 10.1176/appi.ajp.2015.14111429r

Association of a Brain Methylation Site With Clinical Outcomes in Depression Does Not Replicate Across Populations

TO THE EDITOR: In the December 2014 issue of the *Journal*, Ma-Li Wong, M.D., et al. (1) reported a strong association between the genetic variant rs1321744 and outcome of treatment with the antidepressants fluoxetine and desipramine in a small sample of Mexican Americans with major depressive disorder. They further reported that a predictive model based on this genetic variant, in addition to several other variants, predicts remission with a high accuracy (area under the receiver operating characteristic curve equal to 0.95). Such prediction would be highly clinically significant and applicable in practice. However, it is based on an analysis of only 65 genotyped individuals, which raises the question whether this might be a false positive or a highly population-specific finding.

The clinical applicability of the reported finding fully depends on whether it is replicable. Wong et al. reported no replication attempt. However, results from much larger samples are available. We previously reported a meta-analysis of three genome-wide pharmacogenetic studies of antidepressants with data on 2,256 individuals (2), and the results, summarized in Figures 1 and 2, are publicly available (http://www.broadinstitute.org/mpg/ricopili/) (3). We queried these data to test whether the finding reported by Wong et al. is replicable. Since the genetic association was reported to apply across the two antidepressant drugs from different classes, we used the whole combined sample analysis of 2,256 individuals from the United States and Europe with major depressive disorder treated with all types of antidepressants. In this large, combined sample, rs1321744 was not significantly associated with either reduction in depressive symptoms ($p=0.489$, uncorrected) or with remission ($p=0.556$, uncorrected).

This completely negative result in a large, combined sample suggests that the reported finding is extremely unlikely to replicate across populations. Because we have no access to results on other Mexican American samples, the currently available data do not allow us to distinguish between highly population-specific association and false positive findings. The comparison between the reported results and the publicly available meta-analysis cautions against accepting results from intensive analyses of small samples without replication. Future reports should take advantage of publicly available data to estimate the robustness of results in context.

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Dr. Müller-Myhsok is a consultant with HMNC and an inventor on several patents in the subject area of pharmacogenetics. Dr. Lewis has received consultant fees from Eli Lilly. Dr. Perlis has served on scientific advisory boards or received consulting fees from Genomind LLC, Healthrageous, Perfect Health, Pfizer, Proteus Biomedical, Psybrain, and RID Ventures, and he receives royalties through Massachusetts General Hospital from Concordant Rater Systems (now UBC). Drs. Uher and Ripke report no financial relationships with commercial interests.

This letter was accepted for publication in January 2015.

Am J Psychiatry 2015; 172:395–397; doi: 10.1176/appi.ajp.2015.14101348