Dr. Gorelick is affiliated with the Department of Psychiatry, University of Maryland School of Medicine, Baltimore.

The author reports no financial relationships with commercial interests.

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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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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.

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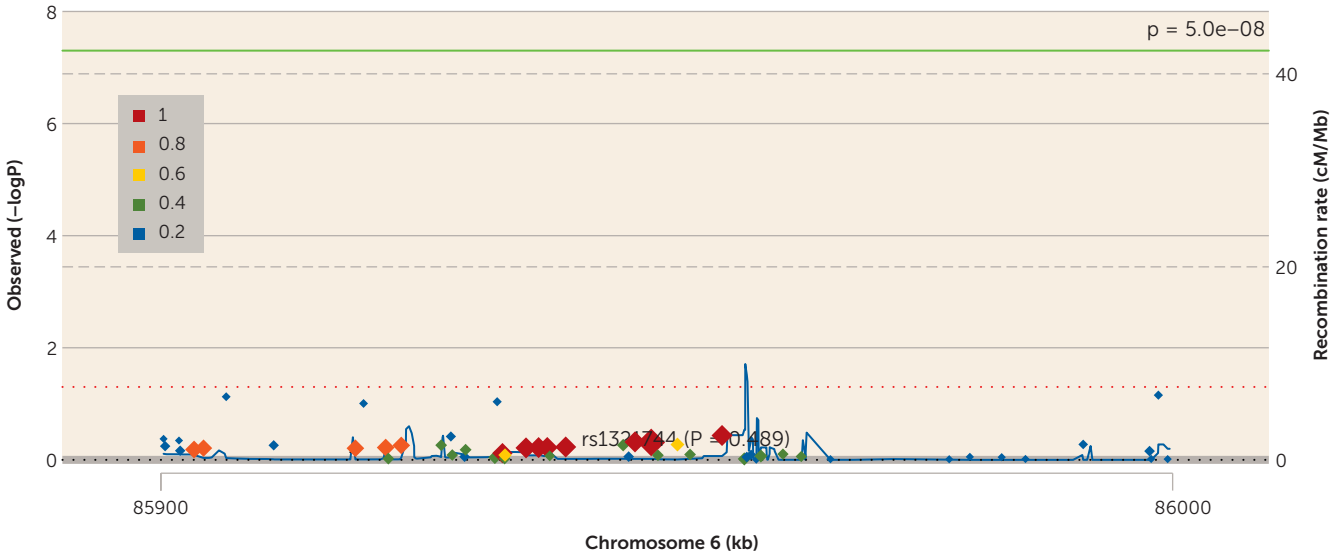
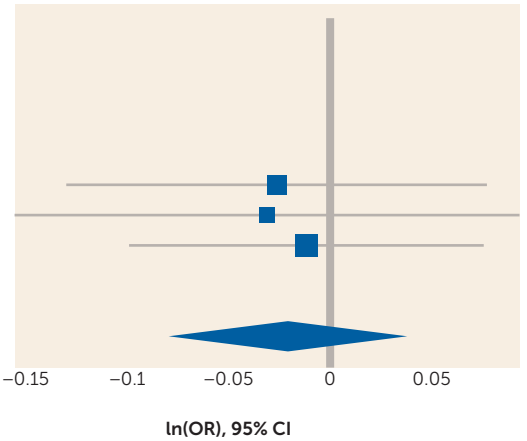
FIGURE 1. Lack of Association of rs1321744 and Nearby Common Polymorphisms With Depression Symptom Improvement During Antidepressant Treatment[a]



rs1321744		T/C		6:85948463			
		–––		het_P:	0.96	het_I:	0.0
	ngt	info	p_value	f_ca(n)	f_co(n)	ln(OR)	STDerr
gendep_mdperc12_all.txt.	–	1.02	0.618	0.510(672)	0.522(672)	−0.0264	0.0529
marsquan12_zscores.	–	0.97	0.624	0.544(604)	0.561(604)	−0.0311	0.0635
stard_eur	1	0.98	0.794	0.538()	0.538(1274)	−0.0117	0.0446
PCG3_0311c_quan12_0711	**1**	**0.99**	**0.489**	**0.722(1376)**	**0.539(2550)**	**−0.0208**	**0.03**

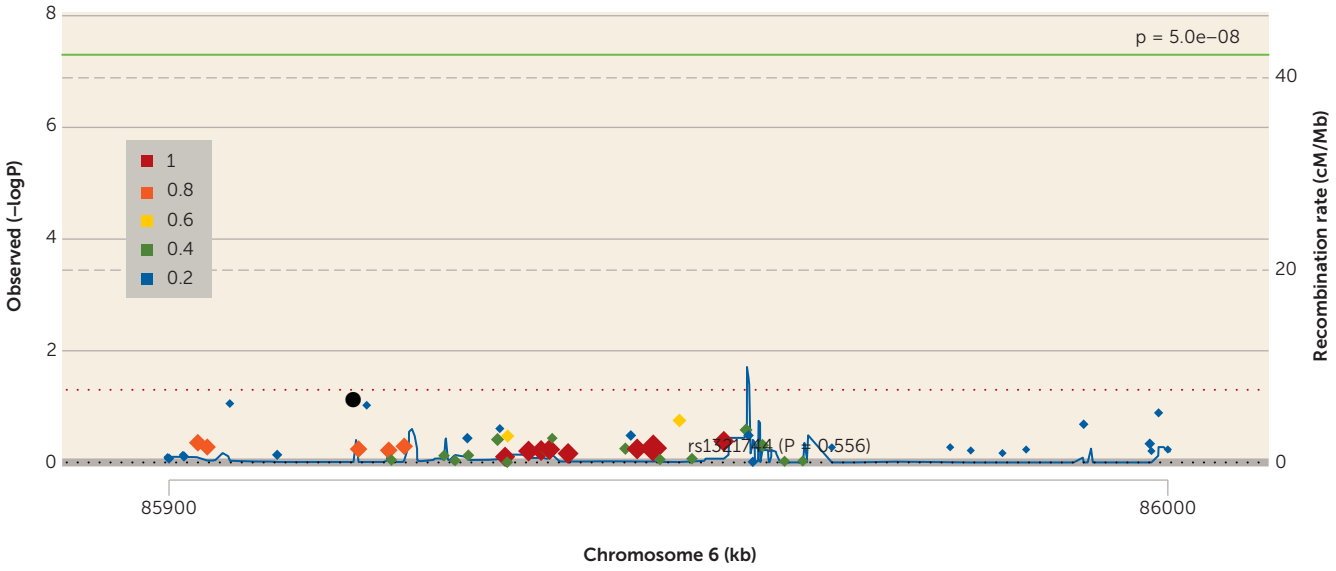


[a] The top panel (obtained from the publically available source [http://www.broadinstitute.org/mpg/ricopili/]) shows lack of any significant association in the region surrounding rs1321744. The bottom panel is a forest plot, showing no association in GENDEP, MARS, and STAR*D or in the meta-analysis of the three studies.

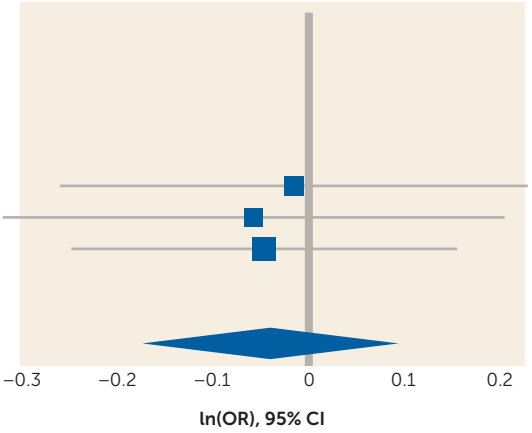
Response to Uher et al.

TO THE EDITOR: Dr. Uher et al. attempted to replicate the results of our study on pharmacogenetics of antidepressants in Mexican Americans, using "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 genetics, the phenotype is diagnosis; therefore, it is highly feasible to replicate from Mexican Americans to other populations, as we have previously done (1). In contrast, in pharmacogenetics, the phenotype studied is drug response, which is a defined clinical pharmacological outcome. Consequently, a valid replication would consist of a study in which the same drugs were administered under the same conditions to the same population: in our study, this was a prospective, placebo lead-in pharmacogenetic double-blind trial of fluoxetine versus desipramine for the treatment of major depression in U.S.-based Mexican Americans, who were meticulously assessed by us to exclude confounding variables, such as other drugs or diagnoses. Those conditions were not met in the work conducted by Uher et al.; therefore, their results do not represent replication. They appeared to have used a retrospective, convenience sample, consisting of subjects with depression who took any antidepressants. That does not by any means replicate our study design. Clinically, patients respond specifically to some antidepressants and not to others (2); therefore, responses to specific drugs need to be individually assessed. Moreover, as we showed previously, at least for the Mexican American population, variations in allele frequency across this and other ethnic groups are higher in many studies than statistically significant differences between case and control subjects (2–4). It is highly likely that this was the case in relation to the results

FIGURE 2. Lack of Association of rs1321744 and Nearby Common Polymorphisms With Remission During Antidepressant Treatment[a]



rs1321744		T/C		6:85948463			
		–––		het_P:	0.97	het_I:	0.0
	ngt	**info**	**p_value**	**f_ca(n)**	**f_co(n)**	**ln(OR)**	**STDerr**
gendep_mdremit12_covar_	–	1.03	0.9	0.515(270)	0.522(321)	−0.0157	0.125
marsdich12_locf.	–	0.97	0.667	0.535(198)	0.567(340)	−0.0578	0.134
stard_eur	1	0.99	0.65	0.523(330)	0.541(613)	−0.0467	0.103
PCG3_0311c_dich12_0711	**1**	**0.99**	**0.556**	**0.523(798)**	**0.543(1274)**	**−0.0403**	**0.0684**



[a] The top panel (obtained from the publically available source [http://www.broadinstitute.org/mpg/ricopili/]) shows lack of any significant association in the region surrounding rs1321744. The bottom panel is a forest plot, showing no association in GENDEP, MARS, and STAR*D or in the meta-analysis of the three studies.

now reported by Uher et al. Because, to our knowledge, no other study has obtained the same phenotype of response to the same drugs in a prospective manner in the same population, our results cannot be, at this point, subjected to a true replication effort.

We strongly disagree with Uher et al. that "the comparison between the reported results and the publicly available meta-analysis cautions against accepting results from intensive analyses of small samples without replication." Mexican Americans are the most rapidly growing ethnic group in the United States. Several large areas of the United States now have minority majority populations (i.e., their populations predominantly consist of minority ethnic groups). Those areas include the two most populous states: California (with 38,802,500 people [6.6% black or African American, 14.1% Asian, 38.4% Hispanic, and 39.0% white/not Hispanic or Latino]) and Texas (with 26,956,958 people [12.4% black or African American, 4.3% Asian, 38.4% Hispanic, and 44.0% white/not Hispanic or Latino]) (5). Medical research has been typically conducted in large, white non-Hispanic populations, and the results may eventually trickle down much later to ethnic minority groups in repetitive replication studies, when those are conducted at all. Our approach represents a paradigm shift in which health and medical research disparities are addressed through innovative discovery studies in minority populations. It is inappropriate to suggest that intensive, focused studies cannot be conducted and published on ethnic minority populations because in the context of interethnic variations in allele frequencies, other groups cannot immediately obtain the same results when their convenience stock of frozen samples from Caucasian subjects is queried.

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