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TO THE EDITOR

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The identification of robust biomarkers of medication response is key to precision medicine and offers the potential to improve treatment outcomes, especially in psychiatry.[1] The claim by Chen and colleagues that the response of patients with bipolar I disorder to lithium therapy is strongly associated with genetic markers in *GADL1* prompted us to undertake a replication study in 218 samples from patients collected by the Consortium on Lithium Genetics.[2] The alleles reported by Chen et al. are common in Asians but rare in whites, so we studied only the Asian samples obtained from the consortium. We tested 218 samples obtained from patients of Han Chinese or Japanese ancestry by means of genotyping on Illumina Omni 2.5M or OmniExpress arrays and evaluated the patients using the same Alda scale[3] that was used by Chen et al. The statistical power exceeded 99% at the lower end of all 95% confidence intervals reported by the authors.

We found no association between the variants and a response to lithium therapy at any threshold on the Alda scale (Table 1). Oddly, the two most significant markers in the study by Chen et al. trended in the opposite direction in our samples. Although small effects cannot be ruled out, we can find no support for the existence of a major gene affecting the response to lithium therapy among Asian patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The Consortium on Lithium Genetics

The members of the writing committee of the Consortium on Lithium Genetics (Liping Hou, Ph.D., Urs Heilbronner, Ph.D., Marcella Rietschel, M.D., Tadafumi Kato, M.D., Ph.D., Po-Hsiu Kuo, Ph.D., Francis J. McMahon, M.D., and Thomas G. Schulze, M.D.) take responsibility for the content of this letter.

No potential conflict of interest relevant to this letter was reported.

Members of the Consortium on Lithium Genetics are listed in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

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Table 1.

Association between *GADL1* SNP rs17026688 and the Response to Lithium Therapy in Samples Obtained from 218 Patients of Asian Ancestry.[*]

Origin of Sample and Alda Score[†]	No. of Patients with No Response: No. of Patients with Response	Frequency of T Allele		Odds Ratio (95% CI)[‡]	P Value	
		No Response	Response		Trend	Fisher's Exact Test
		%				
Japan						
>5	88:39	23.3	15.4	0.52 (0.23–1.21)	0.18	0.18
>6	97:30	22.2	16.7	0.59 (0.24–1.46)	0.39	0.47
>7	102:25	22.1	16.0	0.51 (0.19–1.39)	0.37	0.44
Taiwan						
>5	72:19	30.0	23.7	0.58 (0.21–1.61)	0.40	0.55
>6	78:13	30.9	15.4	0.34 (0.10–1.21)	0.07	0.16
>7	80:11	30.8	13.6	0.29 (0.07–1.18)	0.07	0.13
Meta-analysis[§]						
>5	160:58	NA	NA	0.54 (0.28–1.04)	0.11	0.15
>6	175:43	NA	NA	0.49 (0.23–1.02)	0.08	0.16
>7	182:36	NA	NA	0.42 (0.19–0.95)	0.07	0.13

[*] All samples were obtained from the Consortium on Lithium Genetics. NA denotes not applicable.

[†] Three thresholds for response were tested on the Alda scale. For each item, patients whose total score exceeded the threshold were considered to have a good response; the rest of the patients were considered to have a poor response.

[‡] Odds ratios are for the association between the T allele of the SNP (dominant model) and a response to lithium therapy. The SNP rs17026688 was imputed with the use of the MACH program (r^2>0.9).[4] All genotype distributions are consistent with Hardy–Weinberg equilibrium. Subsequent direct genotyping with the use of Taqman probes produced no discrepant genotypes.

[§] In the meta-analysis, odds ratios and P values were estimated by means of a fixed-effects model. We also tested the association between the response to lithium therapy and another SNP (rs17026651) that was identified by Chen et al. as being significant, and the results were very similar as those shown here (data not shown). The frequency of the T allele was not calculated in the meta-analysis, since allele frequencies differed among samples owing to population differences.