Association of Polygenic Score for Schizophrenia and HLA Antigen and Inflammation Genes With Response to Lithium in Bipolar Affective Disorder
A Genome-Wide Association Study

International Consortium on Lithium Genetics (ConLi’Gen)

**IMPORTANCE** Lithium is a first-line mood stabilizer for the treatment of bipolar affective disorder (BPAD). However, the efficacy of lithium varies widely, with a nonresponse rate of up to 30%. Biological response markers are lacking. Genetic factors are thought to mediate treatment response to lithium, and there is a previously reported genetic overlap between BPAD and schizophrenia (SCZ).

**OBJECTIVES** To test whether a polygenic score for SCZ is associated with treatment response to lithium in BPAD and to explore the potential molecular underpinnings of this association.

**DESIGN, SETTING, AND PARTICIPANTS** A total of 2586 patients with BPAD who had undergone lithium treatment were genotyped and assessed for long-term response to treatment between 2008 and 2013. Weighted SCZ polygenic scores were computed at different P value thresholds using summary statistics from an international multicenter genome-wide association study (GWAS) of 36,989 individuals with SCZ and genotype data from patients with BPAD from the Consortium on Lithium Genetics. For functional exploration, a cross-trait meta-GWAS and pathway analysis was performed, combining GWAS summary statistics on SCZ and response to treatment with lithium. Data analysis was performed from September 2016 to February 2017.

**MAIN OUTCOMES AND MEASURES** Treatment response to lithium was defined on both the categorical and continuous scales using the Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder score. The effect measures include odds ratios and the proportion of variance explained.

**RESULTS** Of the 2586 patients in the study (mean [SD] age, 47.2 [13.9] years), 1478 were women and 1108 were men. The polygenic score for SCZ was inversely associated with lithium treatment response in the categorical outcome, at a threshold $P < 5 \times 10^{-2}$. Patients with BPAD who had a low polygenic load for SCZ responded better to lithium, with odds ratios for lithium response ranging from 3.46 (95% CI, 1.42-8.41) at the first decile to 2.03 (95% CI, 0.86-4.81) at the ninth decile, compared with the patients in the 10th decile of SCZ risk. In the cross-trait meta-GWAS, 15 genetic loci that may have overlapping effects on lithium treatment response and susceptibility to SCZ were identified. Functional pathway and network analysis of these loci point to the HLA antigen complex and inflammatory cytokines.

**CONCLUSIONS AND RELEVANCE** This study provides evidence for a negative association between high genetic loading for SCZ and poor response to lithium in patients with BPAD. These results suggest the potential for translational research aimed at personalized prescribing of lithium.
Bipolar affective disorder (BPAD) is a severe and often disabling psychiatric condition characterized by recurrent dysregulation of mood, with episodes of mania and depression. With an early onset and an estimated lifetime prevalence of 1% to 4.4%, BPAD is associated with high levels of personal impairment and high societal costs, accounting for 9.9 million years of life lived with disability worldwide, increased all-cause mortality, and risk of suicide. The possible causes of BPAD are complex, and both genetic and environmental factors contribute to its pathogenesis. The estimated heritability of BPAD ranges from 60% to 85%, and candidate gene and genome-wide association studies (GWASs) have successfully identified genetic loci implicated in the illness.

Lithium’s mood-stabilizing properties were discovered in 1949. This has retained a status as the criterion standard mood stabilizer. Possessing unique protective effects against both manic and depressive episodes, as well as for suicide prevention. Consequently, lithium is recommended as first-line maintenance treatment for BPAD by several clinical practice guidelines. However, there is significant interindividual variation between those who do and who do not respond to treatment with lithium. About 30% of patients are only partially responsive, and more than one-fourth show no clinical response. Although clinical studies report a combination of demographic and clinical characteristics as potential factors determining response to lithium treatment, genetic factors also appear to be highly involved. So far, 3 GWAs have successfully identified single-nucleotide polymorphisms (SNPs) associated with treatment response to lithium in BPAD pointing to different genetic loci.

To improve our understanding of the molecular mechanisms underlying the therapeutic effects of lithium, alternative genomic approaches that can complement GWASs deserve consideration. One such approach is polygenic analysis, which quantifies the combined effects of genetic variants across the whole genome on a given clinical outcome, computed as a weighted summation of effect sizes of multiple independent polymorphisms. An accurate and successful polygenic model may assist early screening for disease risk, clinical diagnosis, and the determination of treatment response and prognosis. In the present study, we aimed to investigate whether patients with BPAD who had a high genetic susceptibility for schizophrenia (SCZ) expressed by their SCZ polygenic score (PGS), would respond better or more poorly to lithium compared with patients with BPAD who had a low PGS for SCZ. In addition, we set out to explore the genetic and molecular underpinnings of any identified association between SCZ and treatment response to lithium.

Several previous observations motivated this approach. First, there is increasing evidence for a substantial genetic overlap between BPAD and SCZ. The Psychiatric Genomics Consortium (PGC; http://www.med.unc.edu/pgc) estimated a shared genetic variation between BPAD and SCZ of approximately 68%, which is the highest among all pairs of psychiatric diagnoses, and several shared risk genes and shared biological pathways associated with both disorders have been identified. Second, despite these genetic and molecular commonalities, lithium is not an effective medication for people with SCZ, and increased SCZ trait loading in those with BPAD might be expected to be associated with poor treatment response to lithium. An earlier family study found an association between family history of SCZ and poor response to lithium. Third, during acute episodes of illness, BPAD and SCZ are often difficult to distinguish clinically because of overlapping psychotic symptoms such as hallucinations, delusions, and disorganization, as well as some common behavioral disturbances such as irritability or anger. Aiming to determine response to lithium, which could potentially confer advantages for patients and their treating physicians, we sought to evaluate the aggregated outcome of genome-wide SNPs for SCZ on treatment response to lithium in patients with BPAD using a PGS approach that was based on the results of the largest SCZ GWAS to date. Furthermore, to explore potential genetic and molecular drivers of any detected association, we carried out a cross-trait GWAS meta-analysis, combining the summary statistics from the largest available GWAS for both SCZ and response to lithium.

**Key Points**

**Questions** Is a polygenic score for schizophrenia associated with response to lithium in patients with bipolar affective disorder, and, if so, what are the molecular drivers of this association?

**Findings** This genome-wide association study found an inverse association between genetic loading for schizophrenia risk variants and response to lithium in patients with bipolar affective disorder. Genetic variants in the HLA antigen region and the antigen presentation pathway point to the molecular underpinnings of schizophrenia and lithium treatment response.

**Meaning** For patients with bipolar affective disorder, assessment of a polygenic load for schizophrenia risk variants, in conjunction with clinical data, may assist in determining whether they would respond to lithium treatment.

**Methods**

In the present study, conducted from 2008 to 2013, we first tested whether a PGS for SCZ is associated with treatment response to lithium in patients with BPAD; 2043 patients (79.0%) had BPAD type I and 543 (21.0%) had BPAD type II. In a second step, we applied a cross-trait GWAS meta-analysis approach to identify individual genetic variants shared between SCZ and treatment response to lithium. In a third step, we characterized the genetic variants identified in the second step and explored the shared biological pathways underlying genetic susceptibility to SCZ and treatment response in BPAD. We built the PGS using the discovery GWAS outcome estimates of odds ratio (OR) of 36 989 patients with SCZ and the targeted genetic data of 2586 patients from the International Consortium on Lithium Genetics (CONLi’Gen). The cross-trait meta-analysis and pathway analysis were based on GWAS summary statistics from GWASs of SCZ and treatment response to lithium from CONLi’Gen. Overlapping SNPs...
that met genome-wide significance in the meta-GWAS were subsequently analyzed for biological context using the Ingenuity Pathway Analysis platform (IPA; QIAGEN [http://www.ingenuity.com]). This study used consortium data through an international collaboration. The University of Heidelberg Ethics Committee provided central ethics approval for the consortium. Written consent was obtained from each patient according to the study protocols of the participating cohorts.

Target Outcome
Lithium treatment outcome was assessed using the Retrospective Criteria of Long-term Treatment Response in Research Subjects With Bipolar Disorder scale, also known as the ALDA scale.\textsuperscript{38,39} The ALDA scale quantifies symptom improvement over the course of treatment (A score; range, 0-10), which is then weighted against 5 criteria (B score) that assess confounding factors, each scored 0, 1, or 2. The total score is calculated by subtracting the total B score from the A score, with negative scores set to zero.\textsuperscript{22} We employed a categorical and a continuous outcome for response to lithium. The categorical (ie, good vs poor) response to lithium was defined based on the total score as a cutoff score of 7, in which patients with a total score of 7 or higher were categorized as responders. The ALDA score on subscale A was used as a continuous outcome after excluding individuals with a total B score greater than 4 or who had missing data on the totals of ALDA subscale A or B.\textsuperscript{22}

Polygenic Scoring
Quality-controlled SNPs were clumped for linkage disequilibrium based on GWAS association P value-informed clumping using $r^2 = 0.1$ within a 250-kilobase (kb) window to create an SNP set in linkage equilibrium using PLINK software\textsuperscript{40} run on Linux (\texttt{plink–clump-p1 1–clump-p2 1–clump-r2 0.1–clump-kb 250}). Then, the SNPs up to 10 P value thresholds ($< 1 \times 10^{-4}$, $<1 \times 10^{-5}$, <0.01, <0.05, <1, <20, <30, <40, <50, and <1) were selected to compute the SCZ PGSs in the ConLi$^+$Gen sample. A genome-wide weighted SCZ PGS for each participant was calculated at each P value threshold as the sum of independent SNPs genotype dosage (from 0 to 2) of the reference allele in the ConLi$^+$Gen genotype data, multiplied by effect sizes on the SCZ GWAS for the reference allele, estimated as log (OR) divided by the total number of SNPs in each threshold.

Statistical Analyses
Statistical analysis was performed from September 2016 to February 2017. We applied PGS association analyses, cross-trait meta-GWAS, and IPA of the cross-trait findings.

PGS Association Analysis
Once the PGSs were constructed, the association of the PGSs at each threshold P value with treatment response to lithium was evaluated using regression models. While a binary logistic regression was implemented for the categorical outcome (response vs nonresponse), a linear regression was applied to treatment response to lithium on the continuous scale. Using the PGS at the most significant threshold ($P < 5 \times 10^{-3}$), we divided the study samples into 10 deciles, ranging from the lowest polygenic load (first decile) to the highest polygenic load (10th decile). We then compared patients with BPAD with a lower polygenic load (first to ninth deciles) for SCZ with patients with the highest polygenic load (10th decile) to quantify the association of SCZ polygenic load with lithium treatment outcomes.

To control for confounding factors, the PGS association analyses were adjusted for the covariates of age, sex, genotyping platforms, and 7 principal components. The analyses were performed using R (R Foundation for Statistical Computing) and PLINK, version 1.9, for Linux.\textsuperscript{40} The accuracy of determining factors and the percentage of variance in lithium response accounted for by the PGS at each P value threshold were estimated as the variance explained by the full model including each PGS and covariates minus the variance explained by the model including only covariates. Statistical significance was determined at $P < .05$ after adjusting for covariates.

Cross-trait Meta-analysis of GWASs
Biologically, a significantly associated PGS implies that genetic factors influencing the 2 traits are overlapping. Thus, further analyses were performed to identify genetic polymorphisms that are likely to increase the susceptibility to SCZ and also influence treatment response to lithium in patients with BPAD. We performed cross-trait meta-analyses by combining the summary statistics for GWAS on lithium response from the ConLi$^+$Gen\textsuperscript{28} and GWAS on SCZ from the PGC.\textsuperscript{36} We applied both the O’Brien method and the direct linear combination of dependent test statistics approach,\textsuperscript{41,42} which are implemented in the C\textsuperscript{2+} eLX package (https://sites.google.com/site/multivariateyihsianghsu/). In brief, the O’Brien method and the direct linear combination of dependent test statistics approach combine univariate meta-GWAS summary statistics ($\beta$ coefficients or z scores) at each SNP.\textsuperscript{41,42} Further details are available elsewhere.\textsuperscript{41,42}

Ingenuity Pathway Analysis
To characterize the potential biological significance of the SNPs discovered from the cross-trait meta-analyses, we performed analyses using IPA (eAppendix in the Supplement).

Results
Sample Characteristics
A total of 3193 patients with BPAD who had undergone lithium treatment and had available genotype and clinical data participated in the study. After quality control, 2586 patients remained for analysis, of whom 2366 were of European ancestry and the rest Asian. The mean (SD) age of all the patients combined was 47.2 (13.9) years and 1478 (57.2%) were female. A total of 704 patients (27.2%) had a good response to lithium treatment (ALDA scale score $\geq 7$). The mean (SD) ALDA scale score for all participants was 4.1 (3.2) (Table 1).

Association of SCZ PGS With Treatment Response to Lithium in Patients With BPAD
At the most significantly associated P value threshold ($P < 5 \times 10^{-5}$), the PGS for SCZ was strongly associated with
Cross-trait Meta-analysis of GWAS for Lithium Treatment Response in BPAD and of GWAS for SCZ

Subsequent to the PGS analysis, we performed an SNP-based cross-trait meta-analysis by combining the summary statistics for the GWASs on SCZ and treatment response to lithium in the categorical outcome and on SCZ and treatment response to lithium in the continuous outcome. This meta-analysis yielded 15 loci with P values below the genome-wide significance level ($P < 5 \times 10^{-8}$). The top 6 loci and closest genes were rs1611255 (HCG4 [OMIM 124800]), rs66486766 (ADAMTS3 [OMIM 609199]), rs7405404 (ERCC4 [OMIM 133520]), rs1611259 (HCG4), rs3919583 (CCNH [OMIM 601953]), and rs59724122 (EPHX2 [OMIM 132811]) (Table 3 and Figure 2A and B in the Supplement). To characterize the functional implications of these loci, we undertook IPA using query gene inputs generated from the results of the cross-trait and expression quantitative trait loci analyses (http://www.brainiac.org/; eTable 1 in the Supplement). The IPA found significantly represented canonical pathways, with the top 5 being antigen presentation pathway, OX40 signaling pathway, autoimmune thyroid disease signaling, Cdc42 signaling, and B-cell development (eTable 2 in the Supplement). These pathways were predominantly identified on the basis of several HLA antigen genes: HLA-A (OMIM 124800), HLA-DM (OMIM 124855), HLA-DMB (OMIM 124856), HLA-DOB (OMIM 600629), HLA-DPB1 (OMIM 124858), HLA-F (OMIM 143110), HLA-G (OMIM 124871), PSMB9 (OMIM 177045), and TAP2 (OMIM 170261).

The IPA revealed 2 relevant functional networks (eTable 3 in the Supplement). As shown in eFigure 3A and B in the Supplement, the top 2 networks indicate that tumor necrosis factor (TNF), interleukin 4 (IL-4), and interferon-gamma (IFNγ) might represent important functional molecular nodes in the interaction between response to lithium and SCZ.

Discussion

The present study reports 2 main findings. First, using PGS, we demonstrate that there is an inverse association between genetic loading for SCZ risk variants and long-term therapeutic response to lithium in patients with BPAD on the categorical outcome of the ALDA scale. Second, we show in the cross-trait meta-GWAS and IPA that genetic variants in the HLA antigen region, the antigen presentation pathway, and inflammatory cytokines such as TNF, IL-4, and IFNγ could play a biological role in treatment response to lithium in BPAD.

These findings are consistent with previous clinical and epidemiologic studies of response to lithium. Lithium is not an effective medication for people with SCZ spectrum disorders. Moreover, lithium may be deleterious for patients with SCZ because of their greater liability to developing lithium-induced neurotoxic effects even at modest doses and blood levels. The severity of psychotic symptoms in patients with BPAD was found to be inversely associated with treatment response to lithium. Similarly, slow resolution of psychosis in response to lithium treatment during acute manic episodes has been shown to be associated with poorer overall response to the drug. Among patients with BPAD, those with a family history of SCZ show poorer response to lithium compared with those with a family history of BPAD. Our findings may provide insight into the genetic architecture underlying these clinical observations.

Table 1. Characteristics of Patients With BPAD and Outcomes With Lithium Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Categorical Outcomea (Good vs Poor Response) (n = 2586)</th>
<th>Continuous Scaleb (ALDA Score on Subscale A) (n = 2244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders, No. (%)</td>
<td>704 (27.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Age at interview, mean (SD), y</td>
<td>47.2 (13.9)</td>
<td>47.4 (13.9)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>1478 (57.2)</td>
<td>1291 (57.5)</td>
</tr>
<tr>
<td>ALDA scale A score, mean (SD)</td>
<td>6.2 (3.0)</td>
<td>6.3 (3.0)</td>
</tr>
<tr>
<td>ALDA scale total B, mean (SD)</td>
<td>2.5 (1.7)</td>
<td>2.1 (1.2)</td>
</tr>
<tr>
<td>ALDA scale total, mean (SD)</td>
<td>4.1 (3.2)</td>
<td>4.5 (3.1)</td>
</tr>
</tbody>
</table>

Abbreviations: ALDA, Retrospective Criteria of Long-term Treatment Response in Research Subjects With Bipolar Disorder; BPAD, bipolar affective disorder; NA, not applicable.

a Total ALDA scale score of 7 or higher was defined as good response.

b Participants with total B score higher than 4 or who had missing data on the total scores on ALDA subscale A or B were excluded.
In the SCZ to lithium response cross-trait GWAS meta-analyses, 15 genetic loci located within protein-coding genes that appear to have overlapping outcomes on SCZ risk and treatment response to lithium in BPAD were identified. Only 1 of these genes, type I adenyl cyclase (ADCY1 [OMIM 103072]), had previously been directly implicated in genetic studies of both SCZ and treatment response to lithium.26

Both the most significant finding of the cross-trait GWAS and the SNPs from the post-GWAS functional analyses suggest that the HLA antigen system could be implicated in genetic susceptibility to SCZ and treatment response to lithium. The HLA antigen region is the most robust genetic finding in SCZ49 and could be marking a SCZ-type pathogenesis that is compromised the biological precision of our pathway analysis, fact that non-HLA antigen genes are embedded with it, could compromise the biological precision of our pathway analysis, some previous studies have linked HLA antigen surface protein composition to responsiveness to lithium in patients with BPAD.50-52 Lithium exposure of human monocytes and mouse
microglia in vitro resulted in an increased expression of complement component 3, an HLA antigen protein, which in turn was driven by the inhibition of glycogen synthase kinase-3. Inhibition of glycogen synthase kinase-3 is, to date, the most comprehensively documented molecular effect of lithium in neurons, glia, and peripheral immune cells. Whether these outcomes are in some way compromised by the decreased neuronal complement component 3 expression that is associated with SCZ risk variants in the HLA antigen region, and whether such mechanisms play a role in the clinical efficacy of lithium, needs to be explored in future studies.

Furthermore, network analyses of genes from our meta-GWAS findings implicated interferon-related genes as central functional nodes, suggesting that the negative interaction between response to lithium and genetic predisposition for SCZ could be mediated by mechanisms implicating these inflammatory cytokines; this finding is also supported by a growing body of evidence describing aberrant inflammatory processes in patients with a first episode of psychosis and SCZ. Previous studies have reported modulatory outcomes of lithium treatment on these cytokines and underscore the possibility that mechanisms involving inflammatory cytokines might play a role in mediating the therapeutic outcomes of lithium in patients with BPAD.

Our findings have important implications for the treatment of BPAD and for future research. We show for the first time, to our knowledge, that genetic characterization has the potential to aid the stratification of patients with BPAD into those who respond and those who do not respond to lithium, prior to initiation of treatment. Our study also supports the idea that responsiveness to lithium could represent a true psychiatric endophenotype beyond current nosologic descriptions. The findings underscore the importance of careful assessments of patients’ family psychiatric histories in the context of treatment selection. In schizoaffective disorder, which remains challenging clinically owing to a lack of specific effective treatments, determination of SCZ PGS might aid the choice of mood-stabilizing agents. To achieve full clinical translation, PGS analyses could be combined with other biological and clinical factors in prognostic algorithms.

Limitations
This study has some limitations. First, the polygenic load for SCZ accounted for only a modest percentage (approximately 1%) of the observed variation in lithium treatment response in patients with BPAD. Although this finding is in line with previous reports on the outcomes of PGSs on complex clinical phenotypes such as SCZ and BPAD, the significance of this finding at clinical and population levels needs to be further explored. Second, response to lithium in our study was assessed using the ALDA scale, which is a retrospective measure. To substantiate our findings further, prospective studies are required that can prospectively measure clinical responses to lithium. Third, while our strategy for exploring the biological context of our genetic findings can point toward avenues for future research, it is not designed to provide definitive mechanistic answers. Hypothesis-driven experiments are required to follow up on these leads.

Table 3. Loci Resulting From Cross-trait Meta-analysis of GWAS on Lithium Treatment Response in Patients With BPAD and GWAS on SCZ

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>BP</th>
<th>Allele</th>
<th>P Value Schizophrenia*</th>
<th>Lithium*</th>
<th>Cross-traitb</th>
<th>Effect Directionc</th>
<th>Nearby Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs324899</td>
<td>5</td>
<td>87915582</td>
<td>A  G</td>
<td>5.82 × 10−7</td>
<td>4.63 × 10−3d</td>
<td>2.28 × 10−8</td>
<td>to−</td>
<td>MEF2C</td>
</tr>
<tr>
<td>rs6942227</td>
<td>6</td>
<td>25177508</td>
<td>A  G</td>
<td>9.86 × 10−8</td>
<td>8.45 × 10−3d</td>
<td>2.53 × 10−8</td>
<td>to+</td>
<td>CMAHP</td>
</tr>
<tr>
<td>rs142425863</td>
<td>6</td>
<td>29751753</td>
<td>T  C</td>
<td>2.50 × 10−10</td>
<td>9.29 × 10−3d</td>
<td>5.13 × 10−11</td>
<td>to−</td>
<td>HCG4</td>
</tr>
<tr>
<td>rs9721422</td>
<td>8</td>
<td>27424696</td>
<td>T  C</td>
<td>2.22 × 10−8</td>
<td>7.21 × 10−3d</td>
<td>5.16 × 10−9</td>
<td>to+</td>
<td>EPHX2</td>
</tr>
<tr>
<td>rs61123830</td>
<td>11</td>
<td>123392846</td>
<td>A  G</td>
<td>2.85 × 10−6</td>
<td>2.60 × 10−3d</td>
<td>4.53 × 10−8</td>
<td>to−</td>
<td>GRAMD18</td>
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<tr>
<td>rs7959663</td>
<td>12</td>
<td>109884367</td>
<td>C  G</td>
<td>4.74 × 10−5</td>
<td>2.06 × 10−3d</td>
<td>2.79 × 10−8</td>
<td>to−</td>
<td>MYO1H</td>
</tr>
<tr>
<td>rs66486766</td>
<td>15</td>
<td>84806060</td>
<td>A  G</td>
<td>1.07 × 10−10</td>
<td>4.95 × 10−3d</td>
<td>1.38 × 10−11</td>
<td>to−</td>
<td>ADAM17SL3</td>
</tr>
<tr>
<td>rs74054040</td>
<td>16</td>
<td>13749859</td>
<td>T  C</td>
<td>3.93 × 10−10</td>
<td>5.27 × 10−3d</td>
<td>4.62 × 10−11</td>
<td>to+</td>
<td>ERCC4</td>
</tr>
<tr>
<td>rs6728642</td>
<td>2</td>
<td>97607071</td>
<td>A  G</td>
<td>1.10 × 10−4</td>
<td>1.34 × 10−8e</td>
<td>4.81 × 10−8</td>
<td>to−</td>
<td>FAM1788</td>
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<tr>
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<td>2</td>
<td>185750642</td>
<td>T  C</td>
<td>1.70 × 10−7</td>
<td>5.45 × 10−3e</td>
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<td>to+</td>
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<tr>
<td>rs7588746</td>
<td>2</td>
<td>200986345</td>
<td>A  G</td>
<td>2.08 × 10−7</td>
<td>6.33 × 10−3e</td>
<td>3.91 × 10−8</td>
<td>to+</td>
<td>MAIP1</td>
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<tr>
<td>rs39195858</td>
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<td>86947591</td>
<td>A  C</td>
<td>4.18 × 10−6</td>
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<td>4.54 × 10−9</td>
<td>to−</td>
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<td>rs144337463</td>
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<td>29751005</td>
<td>A  C</td>
<td>8.30 × 10−17</td>
<td>3.93 × 10−3e</td>
<td>1.28 × 10−17</td>
<td>to−</td>
<td>HCG4</td>
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<td>rs2094747</td>
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<td>32924584</td>
<td>A  G</td>
<td>7.49 × 10−7</td>
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<td>to−</td>
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<td>4564852</td>
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<td>2.41 × 10−6</td>
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<td>3.25 × 10−8</td>
<td>to+</td>
<td>ADCY1</td>
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<tr>
<td>rs7403677</td>
<td>14</td>
<td>3539131</td>
<td>T  G</td>
<td>2.91 × 10−7</td>
<td>2.04 × 10−3e</td>
<td>1.92 × 10−8</td>
<td>to+</td>
<td>FAM177A1</td>
</tr>
</tbody>
</table>

Abbreviations: A1, effect allele; A2, another allele; BPAD, bipolar affective disorder; BP, position in base pairs at Human Genome Assembly build 37; Chr, chromosome; GWAS, genome-wide association study; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; +, increased susceptibility to SCZ or positive effect on lithium response; −, decreased susceptibility to SCZ or negative effect on lithium response. P < 1 × 10−2.

a Continuous.

b Cross-trait P < 5 × 10−8.

c Effect direction is the effect of the SNPs on schizophrenia and treatment response to lithium oriented to the effect allele (A1). Nearest genes were based on The Reference Sequence genes (build 37).

d Categorical.

e Continuous.

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Conclusions

We demonstrated for the first time that lower SCZ loading is associated with better response to lithium in patients with BPAD. Follow-up functional analyses implicate genes that code for the immune system, including the HLA antigen complex and inflammatory cytokines. For future clinical translation, a high genetic loading for SCZ risk variants could be used in conjunction with clinical parameters to determine the likelihood of nonresponse to lithium treatment in BPAD.

**ARTICLE INFORMATION**

Accepted for Publication: August 26, 2017.
Published Online: November 9, 2017.

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Funding/Support: Mr Amare received a Postgraduate Research Scholarship support from the University of Adelaide through the Adelaide Scholarship International (ASI) program. The primary sources of funding were grants RI 908/7/1, FOR207 and RI 908/11/1 from the Deutsche Forschungsgemeinschaft (Dr Rietschel) and grant 2 NO 246/10-1 (Dr Nöthen) and grant ZA 191/23/1 from the National Health and Medical Research Council (Dr Rietschel) and grant MH008431 from the Intramural Research Program of the National Institute of Mental Health (ClinicalTrials.gov identifier: NCT0001174). The genotyping was funded in part by the German Federal Ministry of Education and Research through the Integrated Network IntegrAment (Integrated Understanding of Gases and Mental Disorders), under the auspices of the eMed Programme (Drs Schulze, Rietschel, and Nöthen). This study was supported by National Institutes of Health grants P50CA83932 from the National Cancer Institute and SK02DA021237 from the National Institute of Drug Abuse. The Canadian part of the study was supported by grant 64410 from the Canadian Institutes of Health Research (Dr Alda). Collection and phenotyping of the Australian University of New South Wales sample was funded by program grant 1037196 from the Australian National Health and Medical Research Council (Mr Mitchell, Dr Schofield, Dr Fullerton, and Mr Wright). The collection of the Barcelona sample was supported by grants P10B08247, P110D00906, P110/00018, 2014SGR1636, 2014SGR398, and 2011F/00030 from the Centro de Investigación en Red de Salud Mental, Institut d’Investigacions Biomèdiques August Pi i Sunyer, the Centres de Recerca de Catalunya Programme/Generalitat de Catalunya, and the Miguel Servei II and Instituto de Salud Carlos III. The Swedish Research Council, the Stockholm County Council, Karolinska Institutet, and the Söderström-Königsska Foundation supported this research through grants awarded to Drs Backlund, Frisen, Lavevett, and Schalling. The collection of the Geneva sample was supported by grants Synapsy-The Synaptic Basis of Mental Disease SINIF40-158776 and 3203BS125469 from the Swiss National Foundation. The work by the French group was supported by INSERM (Institut National de la Santé et de la Recherche Médecale), AP-HP (Assistance Publique des Hôpitaux de Paris), the Fondation FondaMental (RTRS Santé Mentale), and the labex Bio-PSY (Investissements d'Avenir program managed by the ANR under reference ANR-11-IDEX-0004-02). The collection of the Romanian sample was supported by a grant from Unitatea Executiva pentru Finantarea Invatamantului Superior, a Cercetarii, Dezvoltarii si Inovarii (Dr Grigoriou-Serbanescu). The collection of the Greek sample was supported by the project II.11.11.02.01 and financial support from the MEYS under the NPI I program and by the Czech Science Foundation, grant Nr. 17-07072S.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank all the patients who participated in the study, and we appreciate the contributions of the clinicians, scientists, research assistants, and study staff who helped in the patient recruitment, data collection, and sample preparation of the studies. We are also indebted to the members of the ConLi+Gen Scientific Advisory Board (http://www.conli-gen.org) for critical input over the course of the project. The analysis of this study was carried out using the high-performance computational capabilities of the University of Adelaide, the Phoenix supercomputer (https://www.adelaide.edu.au/phoenix) and the Lisa Computer Cluster within the Dutch national e-infrastructure (https://www.surf.nl/en/). Some data and biomaterials were collected as part of 11 projects (Study 40) that participated in the National Institute of Mental Health Research Original Investigation Polygenic Score for Schizophrenia and Response to Lithium in Bipolar Affective Disorder JAMA Psychiatry January 2018 Volume 75, Number 1 jama.psychiatry © 2017 American Medical Association. All rights reserved.
Polygenic Score for Schizophrenia and Response to Lithium in Bipolar Affective Disorder

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