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ARTICLE

Association of polygenic score for major depression with response to lithium in patients with bipolar disorder

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Abstract

Lithium is a first-line medication for bipolar disorder (BD), but only one in three patients respond optimally to the drug. Since evidence shows a strong clinical and genetic overlap between depression and bipolar disorder, we investigated whether a polygenic susceptibility to major depression is associated with response to lithium treatment in patients with BD. Weighted polygenic scores (PGSs) were computed for major depression (MD) at different GWAS *p* value thresholds using genetic data obtained from 2586 bipolar patients who received lithium treatment and took part in the Consortium on Lithium Genetics (ConLi^{+}Gen) study. Summary statistics from genome-wide association studies in MD (135,458 cases and 344,901 controls) from the Psychiatric Genomics Consortium (PGC) were used for PGS weighting. Response to lithium treatment was defined by continuous scores and categorical outcome (responders versus non-responders) using measurements on the *Alda* scale. Associations between PGSs of MD and lithium treatment response were assessed using a linear and binary logistic regression modeling for the continuous and categorical outcomes, respectively. The analysis was performed for the entire cohort, and for European and Asian sub-samples. The PGSs for MD were significantly associated with lithium treatment response in multi-ethnic, European or Asian populations, at various *p* value thresholds. Bipolar patients with a low polygenic load for MD were more likely to respond well to lithium, compared to those patients with high polygenic load [lowest vs highest PGS quartiles, multi-ethnic sample: OR = 1.54 (95% CI: 1.18–2.01) and European sample: OR = 1.75 (95% CI: 1.30–2.36)]. While our analysis in the Asian sample found equivalent effect size in the same direction: OR = 1.71 (95% CI: 0.61–4.90), this was not statistically significant. Using PGS decile comparison, we found a similar trend of association between a high genetic loading for MD and lower response to lithium. Our findings underscore the genetic contribution to lithium response in BD and support the emerging concept of a lithium-responsive biotype in BD.

Introduction

Bipolar disorder (BD) is a chronic and severe psychiatric illness characterized by episodic, abnormal manic and depressive mood states. An estimated 48.8 million people are affected by BD globally [1]. The disorder accounts for 9.9 million years of life lived with disability worldwide, and substantially increases all-cause mortality and risk of suicide [1, 2].

Amongst available treatment options, lithium is regarded as a gold standard by several clinical guidelines [3, 4]. Lithium uniquely protects against both manic and depressive illness phases, has demonstrated protective effects against suicide [5–7], and is particularly effective in preventing rehospitalization [8]. However, not all patients with BD fully benefit from lithium and only about 30% show full response to the drug [5–7]. In current psychiatric practice, no biological or clinical markers exist that could reliably predict responsiveness to lithium [9], and prescribing cannot be targeted to patients who benefit most while avoiding side effects and sub-optimal treatment for poor responders [10–13].

In order to develop objective response markers and to move forward towards personalized prescribing of lithium

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for BD patients, a better understanding of the biological mechanisms underlying lithium response is urgently required. Recent genome-wide association studies (GWAS) carried out by our International Consortium on Lithium Genetics (ConLi^{+}Gen) [5] and others [14, 15] have indicated that genetic variation could be an important mediator of response to long-term lithium treatment response in BD patients. In addition, we have recently demonstrated that high genetic loading for schizophrenia (SCZ) risk variants in people with BD decreases the likelihood of favorable response to lithium [16], suggesting that polygenic score (PGS) analysis of mental and physical traits could yield important information on the genetic architecture of BD phenotypes [17–19].

BD and MD show 47% genetic overlap [20–22], and shared risk genes and biological pathways have been described [21, 23, 24]. Lithium can be effective as an augmentation strategy in MD patients who have experienced an insufficient response to first-line antidepressants [25, 26] and is protective against further MD episodes after symptom remission has been achieved [27]. Moreover, a large observational study based on the Finnish registry showed that lithium is the most effective agent preventing rehospitalization in MD [27].

On the other hand, in BD, lithium is more effective in preventing manic than depressive episodes [28, 29], leading to the notion that better lithium responders might be more likely to experience manic predominant polarity, as opposed to depressive predominant polarity [30]. In support of this view, one study found that excellent lithium responders were characterized by a manic but not depressive polarity of the index episode [31]. Another study described an episodic illness pattern of 'mania-depression-interval' as a predictor for a good response, whereas a 'depression-mania-interval' predicted poorer outcomes [32]. Inter-episode residual mood symptoms, as opposed to full remission [6, 7, 33], a rapid cycling pattern [32, 33], and a history of mixed episodes [34, 35] have also been described as predictors of poor response.

On the background of these complex interactions between BD, MD, and lithium treatment, we asked whether BD patients with a high genetic susceptibility for major depression, expressed by their PGS, would respond better or worse to lithium than BD patients with a low genetic loading [36].

Methods and materials

Discovery GWAS summary dataset

The polygenic score for this study was computed using individual genetic data from the International Consortium on Lithium Genetics (ConLi^{+}Gen) [5], and GWAS summary statistics for MD from the Psychiatric Genomics Consortium (PGC) [36].

The summary GWAS for MD was produced from a meta-analysis of 9.6 million SNPs (PGC; http://www.med.unc.edu/pgc/), obtained from 7 cohorts (deCODE, Generation Scotland, GERA, iPSYCH, UK Biobank, PGC29 and 23andMe) containing 135,458 MD cases and 344,901 healthy controls [36].

Target study sample

For the PGS analysis, clinical data on lithium treatment response and genetic information were obtained from the International Consortium on Lithium Genetics (ConLi^{+}Gen; www.ConLiGen.org) for $n = 2586$ patients, including 23 patients in the replication sample [3, 5, 16]. A series of quality control procedures were implemented on the genotype data before and after imputation as described below.

Target outcome

Lithium treatment response was assessed using the validated "Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder" scale, also known as the *Alda* scale [7, 37, 38]. This scale quantifies symptom improvement over the course of treatment (A score, range 0–10), which is then weighted against five criteria (B score) that assess the quality of evidence for the response score [5], to arrive at a total Alda score. For dichotomized assessment of treatment response, patients with a total score of 7 or higher were categorized as "good responders", and the remainder were categorized as poor responders [5, 38]. For continuous assessment of treatment response, *Alda* A scores were used [39]. In addition to the *Alda* scale scores, information on covariates such as age and gender was collected, as described in detail elsewhere [5].

Genotyping and quality control

The genome-wide genotypes, as well as clinical and demographic data, were collected by 22 participating sites. Quality control (QC) procedures were implemented on the genotype data using PLINK, version 1.09 prior to imputation [40]. Samples with low genotype rates <95%, sex inconsistencies (based on X-chromosome heterozygosity), and one of a pair of genetically related individuals were excluded. SNPs were excluded based on the following criteria: a poor genotyping rate (<95%), strand ambiguity (A/T and C/G SNPs), a low minor allele frequency (MAF < 1%), or those deviated from genotype frequency expectations under the Hardy–Weinberg Equilibrium ($p < 10^{-6}$).

Imputation

The genotype data passing QC were imputed on the Michigan server [41] (https://imputationserver.sph.umich.edu) separately for each genotype platform using reference data from the 1000 Genomes Project Phase 3 (Version 5). The European reference panel was used for all the samples except for those from Japan and Taiwan, for which an East Asian reference population data was used. After excluding low-frequency SNPs (MAF < 10%); low-quality variants (imputation INFO < 0.9); and indels, the imputed dosages were converted to best-guess genotypes. The subsequent polygenic analyses were performed using these best-guess genotypes.

Statistical analyses

Polygenic score (PGS) association analysis

PGSs were calculated using the approach previously described by the International Schizophrenia Consortium [42]. Prior to the PGS computation, independent SNPs were identified through a clumping procedure. Quality-controlled SNPs were clumped for linkage disequilibrium based on GWAS association p value informed clumping at $r^2 = 0.1$ within a 250-kilobase window to create an SNP-set in linkage equilibrium using PLINK software, version 1.09 run on Linux (*plink --clump-p1 1 --clump-p2 1 --clump-r2 0.1 --clump-kb 250*). PGSs of MD were calculated for each patient in the ConLi$^+$Gen sample at ten p value thresholds ($<1 \times 10^{-4}$, $<1 \times 10^{-3}$, <0.01, <0.05, <0.1, <0.2, <0.3, <0.4, <0.5, <1). For a patient, a PGS was calculated at each p value threshold (P_T) as the sum of allelic counts (from 0 to 2) for the reference alleles across independent SNPs on a genome-wide scale weighted by their effect sizes estimated as beta or log10 (odds ratio), obtained from previously published GWASs of MD [36].

Once the PGSs were constructed, a binary logistic regression model was applied for the binary outcome (lithium response versus non-response) and a linear regression modeling was implemented for the continuous outcome (*Alda* score on subscale A) to evaluate the association of the PGSs for MD with lithium treatment response at each P_T. Using the PGS at the most optimal thresholds, we divided the study samples into quartiles and deciles, ranging from the lowest polygenic load (1st quartile or 1st decile) to the highest polygenic load (4th quartile or 10th decile). Then, we compared BP patients in the lower polygenic load quartiles (1st–3rd quartiles or 1st–9th deciles) with patients in the highest polygenic load quartile (4th quartile or 10th decile), to quantify the effect of MD polygenic load on lithium treatment response. The analysis was performed for the European sample ($N = 2366$), Asian sample ($N = 220$) and all the sample combined ($N = 2586$). Associations were considered significant at $p < 0.05$ after adjusting for covariates.

The PGS association analyses were adjusted for the covariates age, gender, genotyping platform, a polygenic score for schizophrenia [16], a polygenic score for bipolar disorder [43], and seven principal components (PCs) in the combined sample or five PCs in the European sample or four PCs in the Asian sample. The PCs were computed using a --pca command in PLINK and then the top PCs with an eigenvalue of >2.0 were extracted and used as covariates to correct for population stratification. The analyses were performed using R for Statistical Computing and PLINK, version 1.09 for Linux [40]. Prediction accuracy, the percentage of variance in lithium response accounted for by the PGS at each P_T, was estimated as the variance explained by the full model including each PGS and covariates minus the variance explained by the model including only covariates.

Sensitivity analysis

To evaluate the robustness of our findings, we ran sensitivity analyses using GWAS summary data from bone traits [lumbar spine bone mineral density, femoral neck mineral density and forearm bone mineral density] [44] that have previously shown nonsignificant genetic correlations with psychiatric disorders [45]. Once we compute polygenic scores for lumbar spine bone mineral density, femoral neck mineral density and forearm bone mineral density, we evaluated its association with lithium treatment response, both continuous and categorical outcomes, in the combined sample ($N = 2586$). Each analysis was adjusted for covariates age, gender, genotyping platform, polygenic score for schizophrenia [16], polygenic score for bipolar disorder [43] and seven PCs.

Results

Sample characteristics and lithium treatment response rate

After QC, 2586 patients (3193 before QC) remained for analysis. While $n = 2366$ were of European ancestry, the remaining ($n = 220$) were of Asian ancestry. In all, 704 patients (27.2%) responded optimally to lithium treatment (total *Alda* score ≥7). Detailed sample and demographics details have been described previously [16]. Analysis of the correlation between the PGSs for MD and the self-reported number of depressive episodes available for a

subset of the ConLi^{+}Gen sample ($N = 1140$) showed a statistically significant positive correlation, with estimates ranging from 0.08 to 0.12, suggesting that the PGS for MD may be an approximation to a more severe depressive phenotype in BD (Supplementary Fig. 1).

The polygenic score for MD is inversely associated with lithium treatment response in BD

Statistically significant associations were found at various p value thresholds between the PGSs for MD and lithium treatment response. In the combined multi-ethnic sample, the strongest association were found at $P_T < 5 \times 10^{-2}$; $p < 0.001$, $R^2 = 0.8\%$ with the continuous outcome (*Alda* A score) and $p < 0.001$, $R^2 = 0.7\%$ with the categorical outcome (total *Alda* score ≥7) (Fig. 1a).

In European ancestry patients, the PGS at most of the tested p value thresholds showed significant associations of MD PGS with lithium response across continuous and dichotomized outcomes. Strongest associations were found at $P_T < 5 \times 10^{-2}$; $p < 0.001$, $R^2 = 0.7\%$ with the continuous outcome and $p < 0.001$, $R^2 = 0.9\%$ with the categorical outcome (Fig. 1b). However, in the Asian subsample, the association of the PGS for MD and lithium treatment response was less robust and marginal associations were found only with the continuous outcome at $P_T < 1 \times 10^{-2}$ ($p = 0.034$, $R^2 = 0.85\%$) and $P_T < 5 \times 10^{-2}$ ($p = 0.042$, $R^2 = 0.75\%$) (Fig. 1c). Using PRSice2 software, we found consistent results of association between the PGSs for MD and lithium treatment response [46] (Supplementary Fig. 2A–C). After adjusting for multiple testing using the Bonferroni method [47], associations remained statistically significant in the muti-ethnic and European sample, but not in the Asian sample (Supplementary Table 1). Beta coefficients for all associations were negative, indicating that high genetic loadings for MD are associated with poorer response to lithium in BD.

To further evaluate the impact of MD PGS on lithium treatment response, we divided the study population into quartiles and deciles based on their polygenic loading for MD. As shown in Fig. 2 and Table 1, BD patients who carry a lower polygenic load (1st quartile or 1st decile) for MD have higher odds of favorable lithium treatment response, compared to patients carrying a high polygenic load (4th quartile or 10th decile). In the combined sample, the odds ratio (OR) of favorable response for patients in the 1st quartile compared with those in the 4th quartile was 1.54 (95% CI: 1.18–2.01) and the OR of patients in 1st decile compared to the 10th decile was 1.49 (95% CI: 0.97–2.31). Stratified analysis by ethnicity found a stronger association in the European sample than the Asian sample (Table 1, Fig. 2 & Supplementary Fig. 3).

Sensitivity analysis

To ensure the robustness of our findings, we performed a sensitivity analysis and found no significant association between the polygenic scores for lumbar spine bone mineral density, femoral neck mineral density or forearm bone mineral density and lithium treatment response in bipolar patients, $p > 0.05$ for all polygenic score association tests at different p value thresholds (Supplementary Fig. 4A–C).

Discussion

Our study represents the first direct molecular evidence of an association between a genetic predisposition for major depression and poorer response to lithium treatment in patients with BD. Using PGS analyses of genetic variants related to MD, we found that BD patients with *low* genetic loading for these variants were about 1.5 times *more* likely to have favorable long-term outcomes following lithium treatment compared to BD patients with high MD genetic loading. Higher MD PGSs were associated with a higher number of reported life-time depressive episodes. Analyses following stratification of our sample into European and Asian ancestries indicated that these associations were particularly robust in the European subsample. Adjustment for the potential effects of psychiatric traits that show genetic overlap with MD (SCZ, BD), and sensitivity analyses with medical traits that are unrelated to psychiatric disorders [44] underscored the overall robustness of our findings.

Our findings could form part of a genetic explanation for the previously described clinical observations in relation to mania, depression and lithium response in BD [6, 7, 28–35] and supports the notion that better lithium responsiveness could be associated with a 'core' bipolar phenotype in the *Kraepelinian* form of manic depression [35, 48], characterized by a predominant mania-depression-interval (MDI) sequence pattern [49, 50]. The fact that such a phenotype is complex and difficult to clinically identify is exemplified by the lack of meta-analytic evidence for a more straightforward association between lithium response and mania over depression dominance in BD [50]. Similarly, previous family studies found no association between a family psychiatric history of MD and poorer lithium response in BD [51].

Together with the previously reported inverse association of lithium response and schizophrenia PGS [16], in the same cohort, our finding suggests that the presence of psychiatric co-morbid genetic traits in BD diminishes the likelihood of optimal treatment response to lithium. Given the substantial overlap between schizophrenia- and MD risk alleles [43], the possibility that these effects are driven by similar molecular mechanisms warrants further clarification in future studies.

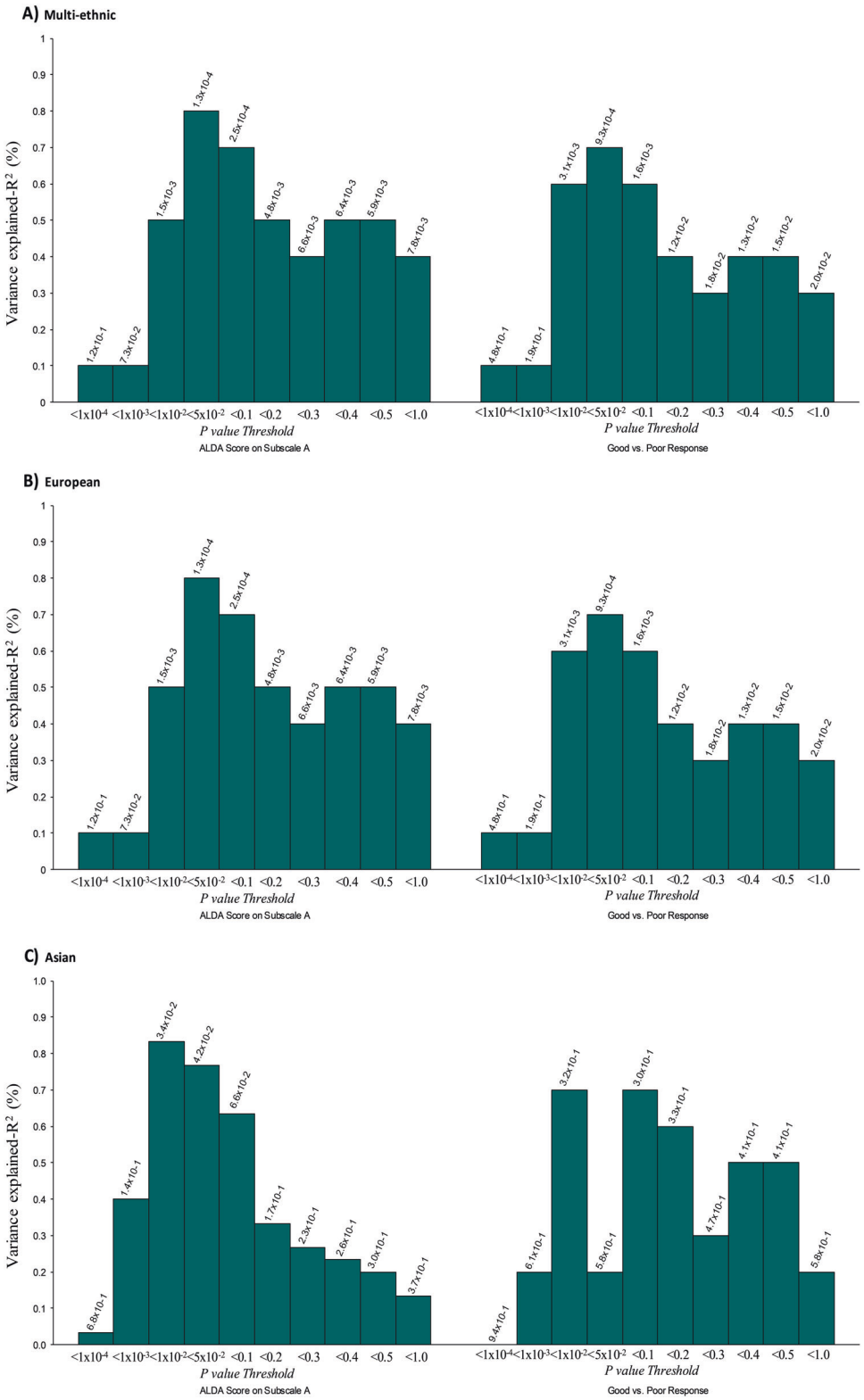

Fig. 1 The association of PGS for major depression (MD) and lithium treatment response at different GWAS *p* value thresholds. The *y*-axis refers to the percentage of variance in treatment response to lithium accounted for by the PGSs for MD at particular *p* value thresholds. On the *x*-axis, are the GWAS *p* value thresholds used to select single-nucleotide polymorphisms for the PGSs. On the top of each bar are the *p* values for the association between the PGSs for MD and lithium treatment response. Beta coefficients (not shown) were negative for all associations, indicating an inverse effect of MD PGS on lithium response.

In addition to its effects in BD, lithium's effectiveness as an adjunct antidepressant treatment for people with treatment-resistant MD is well established [52–58], and lithium is a first-line treatment for BD type 2 that shows a substantial genetic overlap with MD [59]. Therefore, our finding raises the intriguing possibility that lithium possesses specific antidepressant mechanisms of action that are different from the mechanisms conferring long-term treatment response in BD.

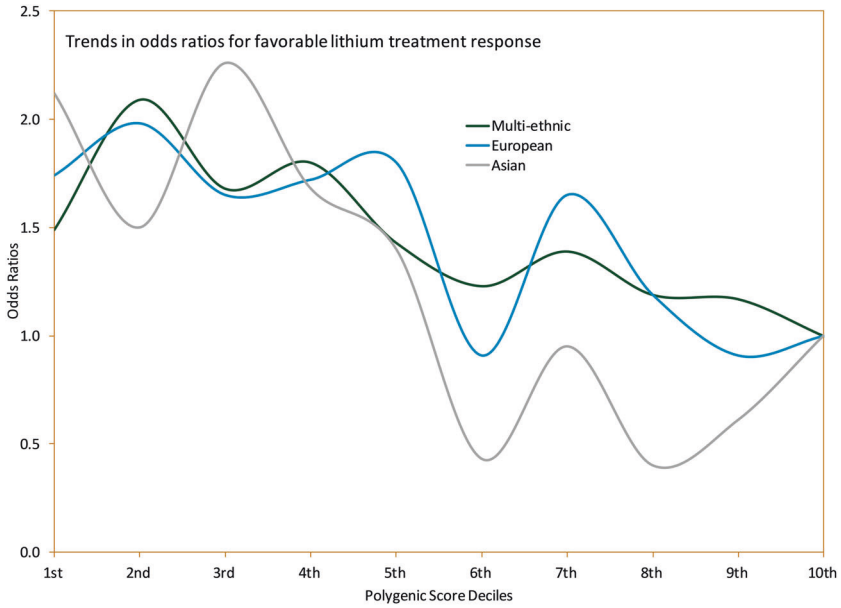

Fig. 2 Odds ratios (ORs) for favorable treatment response to lithium in patients with BD. ORs are derived by comparing BD patients with the low major depression (MD) polygenic load deciles (1st–9th) with patients with the highest MD polygenic load (10th decile), estimated at the most significant *p* value thresholds ($n = 2586$).

Table 1 Odds ratios of favorable lithium treatment response in patients with BD—comparing the response status of patients in the low polygenic score (PGS) quartile or decile for MD with patients with the highest polygenic load (4th quartile or 10th decile).

Categories	Multi-ethnic ($N = 2586$)		European ($N = 2366$)		Asian ($N = 220$)	
	Unadjusted OR (95% CI)	[a]Adjusted OR (95% CI)	Unadjusted OR (95% CI)	[a]Adjusted OR (95% CI)	Unadjusted OR (95% CI)	[a]Adjusted OR (95% CI)
Quartile						
1st: lowest score	1.50(1.17–1.92)	1.54(1.18–2.01)	1.86(1.41–2.47)	1.75(1.30–2.36)	1.43(0.55–3.79)	1.71(0.61–4.90)
2nd	1.45(1.13–1.86)	1.46(1.12–1.90)	1.81(1.37–2.40)	1.77(1.31–2.38)	1.54(0.60–4.04)	1.74(0.64–4.85)
3rd	1.16(0.90–1.49)	1.12(0.85–1.47)	1.25(0.94–1.66)	1.21(0.89–1.64)	0.63(0.21–1.81)	0.55(0.17–1.66)
4th: highest score	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Decile						
1st: lowest score	1.50(1.00–2.27)	1.49(0.97–2.31)	1.92(1.23–2.99)	1.74(1.08–2.81)	1.77(0.40–8.52)	2.12(0.41–12.13)
2nd	2.06(1.39–3.09)	2.09(1.38–3.20)	2.10(1.35–3.28)	1.98(1.24–3.18)	1.25(0.27–6.08)	1.50(0.28–8.61)
3rd	1.76(1.18–2.64)	1.68(1.10–2.59)	1.90(1.22–2.96)	1.65(1.03–2.66)	1.62(0.37–7.73)	2.26(0.46–12.55)
4th	1.84(1.23–2.75)	1.80(1.18–2.77)	1.77(1.14–2.77)	1.72(1.08–2.78)	1.25(0.27–6.08)	1.68(0.33–9.44)
5th	1.49(1.00–2.25)	1.43(0.93–2.20)	1.92(1.23–2.99)	1.80(1.13–2.90)	1.25(0.27–6.08)	1.40(0.28–7.49)
6th	1.38(0.92–2.10)	1.23(0.80–1.92)	1.00(0.63–1.59)	0.91(0.56–1.50)	0.41(0.05–2.43)	0.43(0.05–2.87)
7th	1.39(0.92–2.10)	1.39(0.90–2.15)	1.65(1.06–2.58)	1.65(1.03–2.66)	0.93(0.18–4.68)	0.95(0.17–5.46)
8th	1.30(0.86–1.97)	1.19(0.77–1.85)	1.36(0.87–2.14)	1.19(0.74–1.94)	0.41(0.05–2.43)	0.40(0.04–2.74)
9th	1.25(0.82–1.90)	1.17(0.75–1.81)	0.92(0.57–1.47)	0.91(0.56–1.50)	1.25(0.27–6.08)	0.61(0.12–3.34)
10th: highest score	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

The references (4th quartile and 10th decile) are the PGSs categories with the highest polygenic load for MD at the most significant threshold.
[a]Adjusted for the covariates age, gender, genotyping platform, PGS for schizophrenia [16], PGS for bipolar disorder [43], and seven principal components (PCs) in the combined sample or five PCs in the European sample or four PCs in the Asian sample. OR odds ratio.

Our finding of a more robust effect of the MD PGS association with lithium response in European compared to Asian patients is interesting but needs to be interpreted with caution. First, our Asian subsample was small ($n = 220$) and may not have been powered sufficiently to detect more consistent effects. Second, the polygenic basis of MD in East Asian and European populations is only partially shared with reported trans-ancestry genetic correlation of 0.33–0.41 [60]. The projection of MD risk alleles obtained from the global PGC study onto the Asian ConLi^{+}Gen cohort for PGS analysis may, therefore, be less precise and underestimate the true MD PGS effect. It

is notable that ethnic differences with regards to lithium response have not been studied extensively and are not supported by a smaller previous study [61].

The main limitation of our study is that PGSs for MD explain only a small proportion of the variance in lithium treatment response (<1%), and on their own have no utility as clinical tests. However, since we detected significant effects in our relatively small sample, it is likely that in the future increased sample sizes will further improve the predictive power of PGSs [62]. Further, the current version of the *Alda* scale assesses only overall lithium efficacy but not effects specific to predominant illness polarity or episode sequence pattern. Availability and incorporation of such information would have refined our results. While our findings, in isolation, are not yet ripe for clinical applications, they could serve as a component of multimodal prediction models incorporating clinical and other biological data. The development of such models and the demonstration of their potential clinical utility in prospective study designs are beyond the scope of the current investigation but need to be attempted to translate our research findings into actionable clinical applications.

In conclusion, we demonstrated that high genetic loadings for MD are predictive of unfavorable long-term response to lithium in patients with BD. Our study underscores the potential of PGS analysis to contribute to predictive models for medication response in psychiatry. The results of our study support clinical observations that have pointed to better lithium responsiveness in a BD subtype characterized by lower psychiatric co-morbidity and more dominant mania-related clinical features.

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