

Association of Attention-Deficit/Hyperactivity Disorder and Depression Polygenic Scores with Lithium Response: A Consortium for Lithium Genetics Study

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Keywords

Bipolar disorder · Lithium response · Polygenic risk scores · Attention-deficit/hyperactivity disorder · Adherence

Abstract

Response to lithium varies widely between individuals with bipolar disorder (BD). Polygenic risk scores (PRSs) can uncover pharmacogenomics effects and may help predict drug response. Patients ($N = 2,510$) with BD were assessed for long-term lithium response in the Consortium on Lithium Genetics using the Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder score. PRSs for attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), and schizophrenia (SCZ) were computed using *lassosum* and in a model including all three PRSs and other covariates, and the PRS of ADHD ($\beta = -0.14$; 95% confidence interval [CI]: -0.24 to -0.03 ; p value = 0.010) and MDD ($\beta = -0.16$; 95% CI: -0.27 to -0.04 ; p value = 0.005) predicted worse quantitative lithium response. A higher SCZ PRS was associated with higher rates of medication nonadherence (OR = 1.61 ; 95% CI: 1.34 – 1.93 ; p value = $2e-7$). This study indicates that genetic risk for ADHD and depression may influence lithium treatment response. Interestingly, a higher SCZ PRS was associated with poor adherence, which can negatively impact treatment response. Incorporating genetic risk of ADHD, depression, and SCZ in combination with clinical risk may lead to better clinical care for patients with BD.

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Introduction

Bipolar disorder (BD) is a severe psychiatric disorder characterized by episodes of mania and depressive mood states. The main BD subtypes, type I and II, each have an estimated lifetime prevalence of approximately 1% [1, 2]. As a lifelong and recurrent illness, BD is associated with a high level of comorbidity and reduced quality of life and often results in recurrent suicidality.

Lithium, antiepileptic drug mood stabilizers (e.g., valproate/divalproex and lamotrigine), antipsychotics, and antidepressants are commonly prescribed treatments for BD. However, treatment response varies widely between individuals, and many patients cycle through different medications before they find an effective treatment with minimal side effects. Lithium is currently regarded as the first-line treatment due to its effectiveness in preventing both manic and depressive episodes [3], suicide [4], and

hospitalization [5]. However, only about 30% of patients show full response to the drug [4, 6], and currently, there are few clinical predictors such as episodic course, later age-of-onset, and absence of rapid cycling that may predict lithium response [7, 8].

Pharmacogenomic studies use genetics to better understand the biological mechanisms of treatment response and aim to develop biomarkers for response. Recent genome-wide association studies (GWAS) have shown that genetic variation could play an important role in mood-stabilization in response to pharmacotherapy for BD [6, 9–12]. The largest of these GWAS was performed by the International Consortium on Lithium Genetics (ConLiGen) [6] and included over 2,500 patients that have been treated with lithium. By creating polygenic risk scores (PRSs) in this sample, it was recently shown that higher genetic loading for schizophrenia (SCZ) and major depressive disorder (MDD) is associated with poorer response to lithium [13, 14]. Thus, while pharmacogenomic GWAS sample sizes still remain too small to have power to robustly detect individual variants associated with treatment response, PRSs derived from large, well-powered GWAS of psychiatric disorders and other traits have begun to provide insight into the genetic factors that contribute to treatment response.

MDD and SCZ PRSs were important early study targets, BD being closely related with these 2 disorders and lithium response being associated with some clinical features specific to them (e.g., psychotic symptoms) [13–15]. However, the symptomatic, syndromic, and genetic overlap in BD and attention-deficit/hyperactivity disorder (ADHD) [16–18] and the association of a history of ADHD with reduced lithium response [19] motivate the targeted investigation of the ADHD PRS as a potential predictor of lithium treatment response.

Here, we aimed to use PRS analyses to assess whether higher genetic loading for ADHD is associated with improved or poorer response to lithium. Additionally, we incorporate the joint effect of the ADHD PRS with the previously identified PRS already shown to be associated with lithium response (SCZ and MDD). Finally, we explore how these PRSs are associated with confounders of treatment response measurements.

Materials and Methods*Studies*

Ascertainment and diagnostic assessment for the ConLiGen study have been described previously [6, 20]. Briefly, data on gender, lithium response, and genotypes for patients with a DSM-III

or DSM-IV diagnosis of BD were collected in two waves from 23 sites in 15 countries. The dataset, which contained individuals of European (EUR) and East Asian (EAS) ancestry (Japan and Taiwan), was grouped by wave and ancestry: EUR1, EUR2, JPT1, and TAI2. Phenotyping, genotyping, quality control (QC), and imputation are fully described below and the sample sizes for all studies through QC steps in the analysis are shown in online supplementary Table 1 (see www.karger.com/doi/10.1159/000519707 for all online suppl. material).

Treatment Response Measures

The Alda scale was used to evaluate long-term treatment response to lithium for all participants. This scale is a retrospective assessment and is the most widely used clinical measure of lithium response phenotypes [21]. The Alda scale quantifies symptom improvement in the course of treatment (A score, range 0–10) and 5 criteria (B score) to assess possible confounding factors, each scored 0, 1, or 2 (more description in Statistical Analyses section). Alda scores showed a moderate to substantial inter-rater reliability in this sample [21, 22]. Patients with incomplete information on B score ($N = 37$) were removed from the analysis. Patients were considered lithium responders if they had a total Alda score (A score – B score) of 7 or greater, consistent with prior studies [6, 22].

Genotyping, Quality Control, and Imputation

Genotyping was performed in eleven different batches. For each genotyping batch, a standard QC pipeline was used to remove SNPs with a low call rate ($<95\%$) or showing departure from Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$) and to remove subjects with low call rate ($<95\%$), outlier heterozygosity, or mismatched sex. A total of 2,587 participants with phenotype data were genotyped, and 2,554 remained after the first QC step. After QC of each batch, the batches were combined to check for relatedness (kinship coefficient [23] threshold = 0.2) in the entire study. From each related pair ($N = 4$), we removed the subject with the highest B score (i.e., lowest confidence in A score), leaving 2,550 samples to be imputed. Further details can be found in online supplementary Table 1.

Each genotyping batch was imputed using the Human Reference Consortium [24] reference population on the Michigan Impute Server [25]. The Wrayner pre-imputation tool was used to remove SNPs with allele frequency differences compared to the Human Reference Consortium >0.2 using all samples (including Asian ancestry). A total of 5,896,308 well-imputed variants across all batches (dosage $R^2 > 0.7$ and MAF > 0.01) were used for the subsequent analyses. Because of updated QC and imputation (see online suppl. Table 1), the resulting dataset differs from that reported in Hou et al. [6] with fewer samples and more SNPs used in the current analyses.

Polygenic Risk Scores

PRSs for ADHD [26], MDD [27], and SCZ [28] were constructed using *lassosum* [29], a penalized regression approach which uses a lasso-penalty term (λ) to perform a “pruning-like” procedure for variants in linkage disequilibrium and a thresholding parameter (s) that ranges from soft-thresholding ($s = 0$), similar to p value thresholding, to hard thresholding. We used a grid of values for the two parameters: ($\lambda = 0.001, 0.003, \text{ and } 0.01$) and ($s = 0.2, 0.5, 0.9, \text{ and } 1$) as recommended [29]. Within each cohort (EUR1, EUR2, JPT, and TAI), each PRS was then standardized to have

mean equal to 0 and standard deviation equal to 1. Finally, within each cohort, we performed a principal component analysis on each set of PRS across different parameter settings (grid of λ and s) and kept the first PC. This PRS-principal component analysis approach avoids optimizing a given PRS to the outcome and thus avoids correcting for the resulting inflated type-I error [30].

Statistical Analyses

As a primary analysis, we assessed the association of treatment response with PRS using two different outcomes: (1) responder/nonresponder or (2) Alda A score. The binary response was modeled using logistic regression. For the quantitative response, we used a generalized least-squares model (using the *nlme* R package) to adjust for B score and to estimate study-specific error variances because the variance of A score differed between the studies (online suppl. Fig. 1). Within each cohort, we first regressed the ADHD PRS as well as the known associated PRS (MDD and SCZ) one at a time in our models. For EUR1 and EUR2 cohorts, the models were also adjusted for the first four genomic PCs to account for variation in European ancestries. We then used a fixed-effect meta-analysis to combine the PRS results across cohorts. We estimated the average variance explained by each PRS using R^2 (Nagelkerke’s pseudo- R^2 for binary outcomes using the *rsq* R package) within each cohort and using a weighted average R^2 for each meta-analysis. Next, to assess the joint effect of ADHD with the other two PRSs (MDD and SCZ), we included all three PRSs in a multivariate model to test the association of each trait’s PRS with lithium response after adjusting for the other trait PRS. We examined the heterogeneity of the PRS associations among the sites. We used a Bonferroni correction to adjust the significance threshold in our primary analysis to control for testing the ADHD PRS with the two different outcomes in the analysis ($p = 0.05/2 = 0.025$). We do not adjust our significance threshold for multiple PRSs because the SCZ and MDD PRSs were already known to be individually associated with treatment response.

As a secondary analysis, we examined the PRS associations with the Alda B score as well as the individual components of the B score: number of episodes off treatment (4 or more episodes vs. less than 4), frequency of episodes off treatment (average to high vs. low or only one episode), length of use of lithium (2 or more years vs. less than 2 years), medication adherence (poor vs. good/excellent), and lithium monotherapy (lithium-only vs. lithium + sleep/antidepressant/antipsychotic medications). All statistical analyses were performed in R 3.5.2.

Results

Sample Characteristics and Lithium Response

After QC and imputation, a total of 2,510 patients were included in the analysis including 2,299 of European ancestries (1,057 from the EUR1 sample and 1,242 from EUR2) and 211 of Asian ancestries (126 from JPT1 and 85 from TAI2). Of the 2,510 patients in the study (mean [standard deviation] age, 47.1 [13.9] years), 1,434 were women, and 1,076 were men. Patients’ response to lithium varied widely (online suppl. Fig. 1). The average Alda

Table 1. Summary of Alda scores distributions in the full sample and by ancestry (European or East Asian)

	All (N = 2,510), n (%)	EUR1 + EUR2 (N = 2,299), n (%)	JPT1 + TAI2 (N = 211), n (%)
Lithium responder			
No	1,822 (72.6)	1,653 (71.9)	169 (80.1)
Yes	688 (27.4)	646 (28.1)	42 (19.9)
A score: clinical improvement in symptoms			
0: none	171 (6.8)	131 (5.7)	40 (19.0)
1: minimal	90 (3.6)	82 (3.6)	8 (3.8)
2: mild	84 (3.4)	73 (3.2)	11 (5.2)
3: mild	162 (6.5)	150 (6.5)	12 (5.7)
4: moderate	196 (7.8)	188 (8.2)	8 (3.8)
5: moderate	246 (9.8)	228 (9.9)	18 (8.5)
6: good	282 (11.2)	255 (11.1)	27 (12.8)
7: good	235 (9.4)	218 (9.5)	17 (8.1)
8: very good	314 (12.5)	294 (12.8)	20 (9.5)
9: very good	365 (14.5)	345 (15.0)	20 (9.5)
10: complete	365 (14.5)	335 (14.6)	30 (14.2)
B score			
B1: episodes off the treatment, n			
4 or more	1,843 (73.7)	1,694 (74.0)	149 (70.6)
2 or 3	501 (20.0)	459 (20.0)	42 (19.9)
1	157 (6.3)	137 (6.0)	20 (9.48)
B2: frequency of episodes off the treatment			
Average to high	1,807 (72.3)	1,637 (71.5)	170 (80.6)
Low	558 (22.3)	536 (23.4)	22 (10.4)
1 episode only	136 (5.4)	117 (5.1)	19 (9.0)
B3: duration of treatment			
2 or more years	1,937 (77.5)	1,761 (76.9)	176 (83.4)
1–2 years	268 (10.7)	244 (10.7)	24 (11.37)
Less than 1 year	296 (11.8)	285 (12.4)	11 (5.21)
B4: adherence			
Excellent	1,719 (68.7)	1,570 (68.6)	149 (70.6)
Good	616 (24.6)	577 (25.2)	39 (18.5)
Poor	166 (6.6)	143 (6.2)	23 (10.9)
B5: use of additional medication			
None	767 (30.7)	713 (31.1)	54 (25.6)
Others as “insurance”	639 (25.6)	559 (24.4)	80 (37.9)
Systematic use of others	1,094 (43.7)	1,017 (44.4)	77 (36.5)
Missing	9	9	0

total score was 6.2 [3.0] with patients of European ancestries responding better on average than those of Asian ancestries (6.3 [2.9] vs. 5.3 [3.5], respectively; p value = 0.0009). Furthermore, 688 patients (27.4%) were classified as responding well to lithium (Alda score ≥ 7) with patients of European ancestries having a better response rate than patients of Asian ancestries (28.1% vs. 19.9%, respectively; p value = 0.01). Table 1 shows the distribution of each individual component in the Alda score.

After adjusting for site differences, 4 of the 5 individual components of the B score were associated with poorer treatment response. The A score of patients with an average to high frequency of episodes off lithium was on average

0.52 points less than those with low frequency (SE = 0.14; $p = 0.0003$). Patients taking lithium for over 2 years had an A score 1.24 points higher (SE = 0.15; $p < 2e-16$). Patients with poor adherence had an A score 1.29 points lower (SE = 0.23; $p < 0.0001$). Finally, patients taking lithium-only had an A score 1.56 points higher (SE = 0.13; $p < 0.0001$). The associations of these individual B score components with the A score remained significant in a multivariate model including all B components. This suggests that rather than including B score directly in a lithium response measure (e.g., Alda total score or dichotomized Alda total score), the B score can be included as a covariate in the model to account for potential confounding.

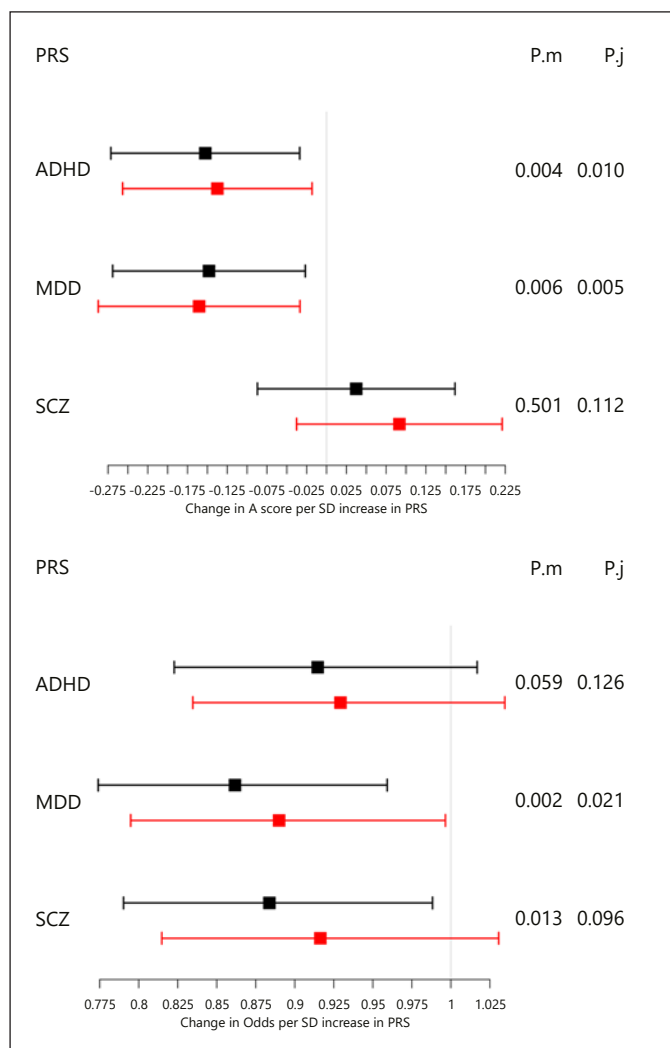


Fig. 1. PRS effect sizes with each outcome (A score) (top) or non-responder (bottom) meta-analysis in either a model with each PRS included by itself (black) or in a joint model with all PRSs (red). CIs shown are Bonferroni corrected. *p* values are shown on the right from either the model with each PRS by itself (P.m) or in the joint model (P.j). CI, confidence interval; PRS, polygenic risk score; ADHD, attention-deficit/hyperactivity disorder; MDD, major depressive disorder; SCZ, schizophrenia.

PRS Association with Treatment Response

We estimated the association of the ADHD PRS and the 2 previously established PRSs (MDD and SCZ) individually with treatment response (Fig. 1). Higher ADHD PRS was associated with poorer quantitative response (change in Alda A score per 1SD increase in PRS = -0.15 ; $R^2 = 0.18\%$; p value = 0.004) and no association with lithium nonresponse (OR per 1SD increase in PRS = 0.92; $R^2 = 0.14\%$; p value = 0.059). The ADHD PRS association with quantitative response was driven by the EUR sample ($\beta = -0.16$;

$R^2 = 0.19\%$; p value = 0.003) with no evidence of association in the EAS sample ($\beta = -0.02$; $R^2 = 0\%$; p value = 0.95). As has been previously shown [14], higher genetic loading for MDD was associated with lithium nonresponse (OR = 0.86; $R^2 = 0.76\%$; p value = 0.002) and worse quantitative response ($\beta = -0.15$; $R^2 = 0.12\%$; p value = 0.006) in the full sample. Unlike previous analyses in the ConLiGen sample [13], higher PRS for SCZ showed only weak evidence of association with lithium nonresponse (OR = 0.88; $R^2 = 0.57\%$; p value = 0.013) and showed no effect on quantitative response ($\beta = 0.04$; $R^2 = 0.12\%$; p value = 0.5). There was low heterogeneity of the ADHD or MDD PRS associations between sites with no site-specific outlier effects driving our findings (online suppl. Fig. 2, 3).

We next estimated the association of each PRS with lithium treatment response in a multivariate model including all 3 PRSs. Prior to fitting the multivariate model, we evaluated the correlations among the PRSs. PRS correlations were highest between MDD and SCZ ($r = 0.30$) and lowest between SCZ and ADHD ($r = 0.05$). After adjusting for the other PRSs, the effects of ADHD ($\beta = -0.14$; p value = 0.010) and MDD ($\beta = -0.16$; p value = 0.005) remained significant predictors of worse quantitative response. MDD (OR = 0.89; p value = 0.021) was the only PRS associated with lithium nonresponse after adjusting for the other PRSs. The PRS for SCZ showed no evidence of association with treatment response after accounting for the genetic contributions of ADHD and MDD PRS.

PRS Association with B Score

As a secondary analysis, we assessed each PRS's association with the B score, a measure of uncertainty in treatment response ascertainment, and its components (Fig. 2). The B score is used in the calculation of the total Alda score (A – B) and thus is used in assignment to responder/non-responder groups. In the full sample, higher genetic load for SCZ was associated with a higher total B score ($\beta = 0.120$; p value = 0.0002). This association was driven by a higher SCZ PRS being associated with higher rates of medication nonadherence (OR = 1.61; p value = $2e-7$); this association of the SCZ PRS with medication nonadherence was observed both in the EUR (OR = 1.59; p value = $3e-6$) and EAS (OR = 1.73; p value = 0.035) samples.

Discussion

This is the first study to assess whether genetic risk for ADHD is associated with lithium response. We found that higher genetic loading for ADHD was associated with less

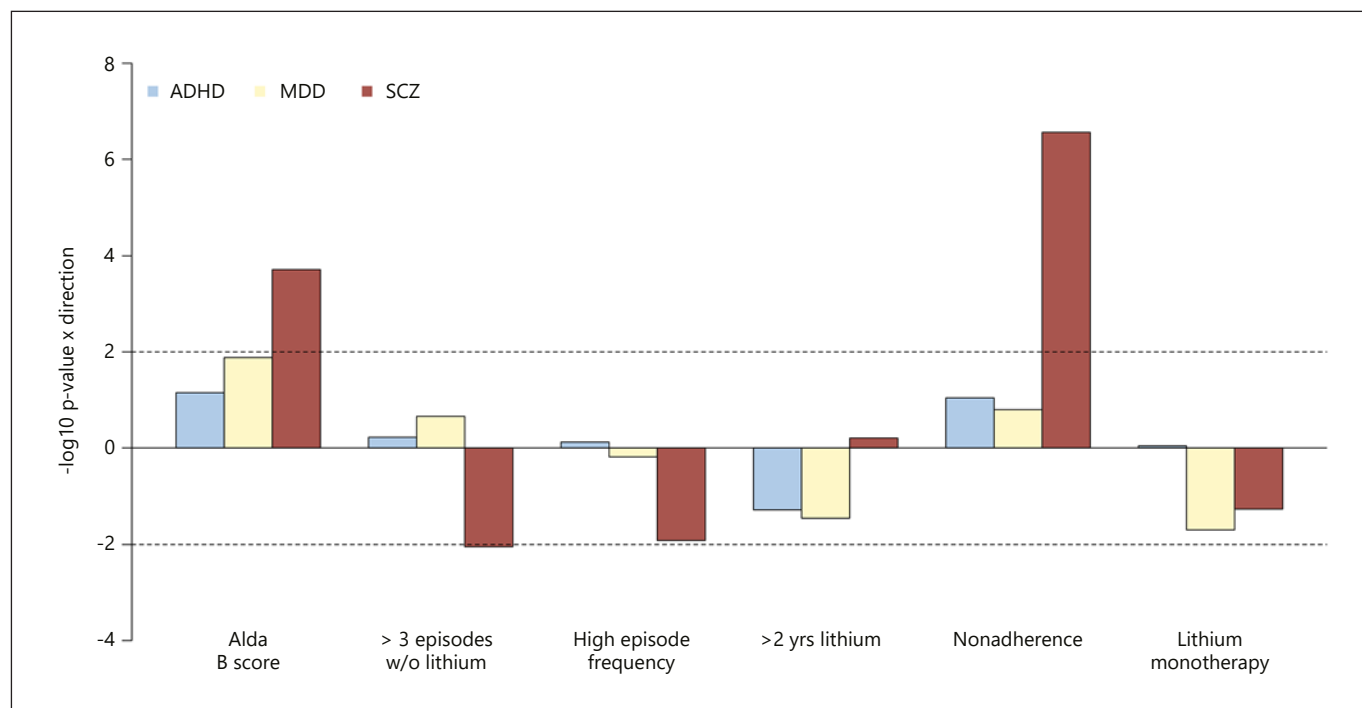


Fig. 2. Independent PRS associations with the Alda B score and each component for the full meta-analysis. Bars indicate $-\log_{10}(p \text{ value})$ and direction of association. Dashed lines are drawn at $p \text{ value} = 0.01$. PRS, polygenic risk score. ADHD, attention-deficit/hyperactivity disorder; MDD, major depressive disorder; SCZ, schizophrenia.

clinical improvement, while on lithium using a continuous measure of response. Importantly, our study is also the first to assess the joint impact of multiple PRSs on lithium response. We found that while the association of ADHD and MDD PRS remained significant after adjusting for other PRSs, the association of the SCZ PRS with response outcomes did not hold after adjusting for the association with ADHD and MDD PRSs. Furthermore, our study is the first to investigate the polygenic effects on the Alda B score and found that only the SCZ PRS was associated with the Alda B score, operating through a strong association with nonadherence to taking medication.

These findings are important in light of the clinical and genetic overlap between ADHD and BD. There is a substantial comorbidity of ADHD and BD in adulthood, with ADHD estimated to co-occur in around 9 to 35% of adult patients with BD [2, 31–33] and longitudinal studies showing that approximately 25% of individuals with childhood ADHD develop BD [34]. Furthermore, the symptomatic overlap between the two disorders (e.g., impulsivity, mood swings, sleep difficulties, talkativeness), as well as the similar profile of other psychiatric comorbidities, makes the differential diagnosis challenging [16,

35]. Finally, genetic studies have shown a small but significant genetic overlap and shared risk genes between BD and ADHD and suggested that the amount of overlap varies with the age-of-onset of BD [16–18, 36, 37]. Furthermore, prior history of ADHD during childhood and earlier age-of-onset of BD have been associated with worse response to lithium [15, 19]. Comorbidity with ADHD also led to lower response rates in children with mania [38]. In a predictive model for lithium response, ADHD was among the factors with the strongest effect size [39]. It was also recently shown that lithium was inferior to risperidone in treating prepubertal patients with BD and comorbid ADHD [40]. These results point toward the fact that the delineation between BD with and without ADHD might help define subgroups that respond differently to lithium. Our results show that genetic vulnerability to ADHD might influence lithium response and that ADHD PRS could therefore be used in future studies to stratify clinical populations. It is important to note that because ADHD history was not consistently collected as part of the clinical battery for inclusion in ConLiGen, we were not able to explicitly test for association between ADHD history and lithium response.

It is however important to keep in mind that causality cannot be inferred from associations with PRS and that these should therefore be interpreted with caution. Indeed, PRSs for ADHD, MDD, and SCZ have recently been associated with several subphenotypes in BD [41–43] and traits in the general population [44], which are in turn associated with lithium response [15, 45, 46]. For instance, PRSs for MDD and ADHD are associated with higher BMI [44], while lower BMI was associated with better lithium response [15]. Also, SCZ PRS is associated with psychotic features in BD, which have repeatedly been shown to be associated with worse lithium response [41, 46]. Finally, all three PRSs have shown associations with socioeconomic traits as well as general and mental health outcomes that might directly or indirectly impact treatment response [44]. These traits were not systematically collected as part of ConLiGen and thus were not included in analyses.

To address the question of whether the observed effect of PRSs on treatment response was mediated by important confounders for measuring treatment response, we assessed PRS associations with the B score and its components. Somewhat surprisingly, the PRS for ADHD was not associated with any of the components, while the PRS for SCZ showed a strong positive association with nonadherence. This is of particular importance as the association between the SCZ PRS and responder status (Alda Total >7) seems to be mainly mediated through this association and disappears when analyzing Alda A alone. Furthermore, this result underlines the importance of including potential confounders, in particular treatment adherence, in response scores to better understand causality. While the PRS for SCZ is being extensively studied as a potential predictor for treatment response in several disorders [13, 47–50], the nonadherence or other confounders are often not studied and could strongly impact the conclusions.

While our data suggest that the relationship between ADHD and lithium response is worth further investigation, these results have limited clinical utility as the variances explained by each PRS are small. This can partially be explained by the heterogeneity of lithium response in our large multicenter dataset but also points toward a limitation of current application of PRS. It is probable that treatment models will have to include multiple PRSs as well as other types of data (e.g., clinical subphenotypes) to have enough predictive power to be effectively used in clinical practice. This was unfortunately not possible in the current analyses as deeper phenotypic information is only currently being collected by the consortium. Inte-

gration of such data will not only strengthen predictions but also allow for a better understanding of causality. Indeed, complex relationships such as those between genetic loading for SCZ, psychotic events, adherence, and responsiveness can only be studied in an integrative way.

In summary, our study shows independent associations between PRS for ADHD and MDD with poorer lithium response, as well as an association between PRS for SCZ and nonadherence to treatment. While being based on the largest collection of lithium response currently available, it is important that these results are replicated in an independent dataset. With larger GWAS becoming available and PRS methods continuing to be refined, incorporating polygenic risk into predictive models may lead to an improved understanding of lithium treatment and, ultimately, to better clinical care.

Acknowledgments

Recruitment and genotyping for the Mayo Clinic Bipolar Disorder Biobank was supported by the Marriott Family Foundation and the Mayo Clinic Center for Individualized Medicine, supported in part by the Intramural Research Program of the National Institute of Mental Health. Recruitment and genotyping of the Romanian (Obregia) sample were supported by UEFISCDI (several grants, PN-III-P4-ID-PCE-2020-2269). E.V. thanks the support of the Spanish Ministry of Science and Innovation (PI15/00283, PI18/00805) integrated into the Plan Nacional de I+D+I and cofinanced by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365), the CERCA Programme, and the Departament de Salut de la Generalitat de Catalunya for the PERIS Grant SLT006/17/00357. A.T.A. has received a 2020–2022 NARSAD Young Investigator Grant from the Brain & Behaviour Research Foundation.

Statement of Ethics

Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Each site's institutional review board approved the study protocol and every participant provided written consent. Further information can be found in the seminal ConLiGen paper (Hou et al. [6]).

Conflict of Interest Statement

Eduard Vieta has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Daiippon Sumitomo Pharma, Farindustria, Ferrer, Forest Research Insti-

tute, Gedeon Richter, GlaxoSmithKline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), and the Stanley Medical Research Institute. Michael Bauer has received grants from the Deutsche Forschungsgemeinschaft and Bundesministeriums für Bildung und Forschung and served as consultant, advisor, or CME speaker for the following entities: Allergan, Aristo, Janssen, Lilly, Lundbeck, neuraxpharm, Otsuka, Sandoz, Servier, and Sunovion outside the submitted work. Sarah Kittel-Schneider has received grants and served as consultant, advisor, or speaker for the following entities: Medice Arzneimittel Pütter GmbH and Shire. Bernhard Baune has received grants and served as consultant, advisor, or CME speaker for the following entities: AstraZeneca, Bristol-Myers Squibb, Janssen, Lundbeck, Otsuka, Servier, the National Health and Medical Research Council, the Fay Fuller Foundation, and the James and Diana Ramsay Foundation. Tadafumi Kato received honoraria for lectures, manuscripts, and/or consultancy, from Kyowa Hakko Kirin Co., Ltd., Eli Lilly Japan K.K., Otsuka Pharmaceutical Co., Ltd., GlaxoSmithKline K.K., Taisho Toyama Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Meiji Seika Pharma Co., Ltd., Pfizer Japan Inc., Mochida Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Janssen Pharmaceutical K.K., Janssen Asia Pacific, Yoshitomiya, Astellas Pharma Inc., Wako Pure Chemical Industries, Ltd., Wiley Publishing Japan, Nippon Boehringer Ingelheim Co. Ltd., Kanoe Foundation for the Promotion of Medical Science, MSD K.K., Kyowa Pharmaceutical Industry Co., Ltd., and Takeda Pharmaceutical Co., Ltd. T.K. also received a research grant from Takeda Pharmaceutical Co., Ltd. Peter Falkai has received grants and served as consultant, advisor, or CME speaker for the following entities Abbott, GlaxoSmithKline, Janssen, Essex, Lundbeck, Otsuka, Gedeon Richter, Servier, and Takeda as well as the German Ministry of Science and the German Ministry of Health. Eva Reininghaus has received grants and served as consultant, advisor, or CME speaker for the following entities: Janssen and Institut Allergosan. Mikael Landén declares that, over the past 36 months, he has received lecture honoraria from Lundbeck and served as scientific consultant for EPID Research Oy; no other equity ownership, profit-sharing agree-

ments, royalties, or patent. Kazufumi Akiyama has received consulting honoraria from Taisho Toyama Pharmaceutical Co., Ltd. The other authors have no other conflict of interest to disclose.

Funding Sources

This pharmacogenomics analysis of the ConLiGen data was supported by a gift from Kent and Liz Dauten.

Author Contributions

B.J.C., A.B., and B.L. performed data analysis. B.J.C., L.H., S.P., U.H., M.A.-2, M.A.F., T.G.S., F.J.M., and J.M.B. conceived and/or designed work. S.P., M.A., K.A., N.A., A.T.A., R.A., B.A., J.-M.A., L.B., M.B., B.T.B., F.B., A.B.-2, S.B., A.B.-2, P.C., H.-C.C., C.C., S.C., S.R.C., F.C., C.C.-2, P.M.C., N.D., A.D., F.D., M.D., J.D., B.É., P.F., E.F.-R., A.J.F., L.F., S.G., J.S.G., F.S.G., M.G.-S., P.G., R.H., J.H., S.H., P.H., S.J., E.J., J.-P.K., L.K., T.K., J.R.K., S.K.-S., B.K., P.-H.K., I.K., G.L., M.L., C.L., M.L.-2, S.G.L., M.M., M.M.-2, L.M., M.J.M., S.L.M., P.B.M., M.M.-2, F.M.M., P.M., C.M.N., M.M.N., T.N., C.O., U.O., N.O., A.P., C.P., J.B.P., A.R., E.R., M.R., G.A.R., J.K.R., M.S., P.R.S., K.S., B.W.S., G.S., T.S., P.D.S., K.S.-2, C.S., C.M.S., A.S., T.S.-2, P.S., A.T., G.T., E.V., S.H.W., P.P.Z., J.M.F., M.A.-2, M.A.F., T.G.S., F.J.M., and J.M.B. acquired data. B.J.C., V.M., J.M.F., M.A.-2, M.A.F., T.G.S., F.J.M., and J.M.B. interpreted results. Drafting was performed by B.J.C., V.M., and J.M.B. All the authors have contributed to the critical revision of the paper and approved the final version. Despite extensive efforts, we were unable to reach authors B.L., A.B.-2, and L.K. for their approval of the final manuscript. The authors are aware of the article and have had the opportunity to review an earlier version of the manuscript.

Data Availability Statement

Data are available through a formal research proposal to the Consortium of Lithium Genetics (<http://www.conligen.org/>).

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