Genome-wide association study identifies SESTD1 as a novel risk gene for lithium-responsive bipolar disorder

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Lithium is the mainstay prophylactic treatment for bipolar disorder (BD), but treatment response varies considerably across individuals. Patients who respond well to lithium treatment might represent a relatively homogeneous subtype of this genetically and phenotypically diverse disorder. Here, we performed genome-wide association studies (GWAS) to identify (i) specific genetic variations influencing lithium response and (ii) genetic variants associated with risk for lithium-responsive BD. Patients with BD and controls were recruited from Sweden and the United Kingdom. GWAS were performed on 2698 patients with subjectively defined (self-reported) lithium response and 1176 patients with objectively defined (clinically documented) lithium response. We next conducted GWAS comparing lithium responders with healthy controls (1639 subjective responders and 8899 controls; 323 objective responders and 6684 controls). Meta-analyses of Swedish and UK results revealed no significant associations with lithium response within the bipolar subjects. However, when comparing lithium-responsive patients with controls, two imputed markers attained genome-wide significant associations, among which one was validated in confirmatory genotyping (rs116323614, \( P = 2.74 \times 10^{-8} \)). It is an intronic single-nucleotide polymorphism (SNP) on chromosome 2q31.2 in the gene SEC14 and spectrin domains 1 (SESTD1), which encodes a protein involved in regulation of phospholipids. Phospholipids have been strongly implicated as lithium treatment targets. Furthermore, we estimated the proportion of variance for lithium-responsive BD explained by common variants (SNP heritability) as 0.25 and 0.29 using two definitions of lithium response. Our results revealed a genetic variant in SESTD1 associated with risk for lithium-responsive BD, suggesting that the understanding of BD etiology could be furthered by focusing on this subtype of BD.

*ORIGINAL ARTICLE*

Genome-wide association study identifies *SESTD1* as a novel risk gene for lithium-responsive bipolar disorder

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INTRODUCTION

Bipolar disorder (BD) is a serious psychiatric illness characterized by recurrent episodes of depression and mania. The mood stabilizer lithium effectively reduces episode recurrences and remains a first-line option for maintenance treatment of BD. However, treatment responses vary considerably across individuals and a number of persons with BD show only partial or no response. Genetic factors may mediate variation in response to lithium, and several genetic association studies have been performed to assess this possibility. Most have been candidate gene studies based on putative pharmacological mechanisms of lithium or the pathophysiology of BD. Studies of single-nucleotide polymorphisms (SNPs) in the brain-derived neurotrophic factor (*BDNF*) gene have reported different findings between ethnicities. Also, two Japanese groups have examined the X-box binding protein 1 gene and found that -116C allele carriers seem to have better lithium response, but each was in a small number of patients (\( N < 70 \)). Small sample sizes in conjunction with the limited understanding of not only the pathophysiology of BD but also lithium’s pharmacodynamics to guide candidate gene selection are likely reasons for these equivocal findings.

Hypothesis-free genome-wide association studies (GWAS) of larger samples therefore offer a promising approach. One GWAS of lithium response performed in a Han Chinese population showed a strong association with variants in the gene *GAD1* (glutamate decarboxylase-like protein 1), but not only are the susceptibility alleles rare in European populations, the findings were not replicated in other Asian samples. Other GWAS of

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lithium response found no SNPs that reached genome-wide significance, but reported suggestive findings for the gene DGKH (diacylglycerol kinase eta)\(^{18}\) the GRIA2 gene coding for the glutamate receptor\(^{19}\), the gene ACCN1 (amiloride-sensitive cation channel 1 neuronal)\(^{20}\) and clock genes.\(^{21}\)

Another impetus to explore the genetic variability underlying lithium response is the possibility for new insights into the genetic basis of BD. The pathophysiology of BD is likely to be heterogeneous with multiple genetic mechanisms related to distinct biochemical pathway abnormalities giving rise to illnesses with similar clinical manifestations.\(^{22}\) The group of patients responding to lithium could suffer from a more etiologically homogeneous illness subtype caused by abnormal pathways that are direct or indirect targets of lithium.\(^{23,24}\) Lithium response in Swedish participants was assessed through both interviews (subjective assessment) and register data (objective assessment). The extent to which subjective assessment and objective assessment were in line with each other is shown in Supplementary Table S2. For participants from United Kingdom, lithium response information was collected by interviews and reviews of clinical notes. The inter-rater reliability is not applicable in Swedish samples but has been assessed in UK samples, with a kappa score of 0.76 calculated from a random selection of cases.\(^{10}\) We treat lithium response as a dichotomous trait based on the subjective and objective measurements, to maximize the sample size and to arrive at a narrower phenotype definition, respectively.

**Genotyping, QC, imputation and validation**

DNA from Swedish subjects was extracted from whole blood samples at the Karolinska Institutet Biobank. Genotyping was performed by the Broad Institute of Harvard and MIT using Affymetrix 6.0 (wave 1) (Affymetrix, Santa Clara, CA, USA) and Illumina OmniExpress and Illumina ComboChip. UK control samples were genotyped using Illumina 1.2M Custom Chip (Illumina), as described in the WTCCC GWAS.\(^{33}\) The detailed genotyping QC for Swedish and UK samples is described in Supplementary Methods.

Following all QC steps, the final analysis data set consisted of 896 bipolar cases, 2215 controls with 744 932 genotyped SNPs in Swedish wave 1, 1415 bipolar cases, 1271 controls with 598 894 genotyped SNPs in Swedish wave 2, and 2577 bipolar cases, 5413 controls with 393 635 SNPs genotyped in UK sample.

Data sets were then pre-phased using SHAPEIT\(^{34}\) and imputed with the full 1000 Genomes Project integrated variant set (Phase 1 integrated data version 3, released March 2012) as the reference panel\(^{35}\) using IMPUTE2.\(^{36}\) After imputation, the three waves shared more than 8 million SNPs.

To confirm the accuracy of imputed SNPs with GWAS significance, DNA from Swedish subjects putatively carrying the minor alleles for rs116323614 and rs146727601 and additional non-carriers were sent for confirmatory genotyping (N = 85). TaqMan assays (Applied Biosystems, Foster City, CA, USA) were used for genotyping and were performed by LGC Genomics (Teddington, Middlesex, UK).

**Association analyses**

Association analyses were conducted using imputed SNP dosages and logistic regression in PLINK version 1.07.\(^{37}\) Multidimensional scaling (MDS) was performed on each collection wave and MDS components were included as covariates (first six MDS components for Swedish wave 2 and first four MDS components for others) to control for population substructure. We retained only SNP dosages imputed with high confidence.
(Info > 0.6) and with minor allele frequency > 1%. The genome-wide significance threshold was set at \( P < 5 \times 10^{-8} \).

We first compared lithium responders with non-responders. Both subjective and objective assessments were used for association analysis separately for each wave, except for Sweden wave 1 due to an inadequate number of subjects with information regarding objective lithium measures. Results were then combined by meta-analysis using a fixed-effects model in PLINK for each measure of lithium response, respectively. Second, we conducted a GWAS comparing lithium responders, subjectively and objectively defined, respectively, with controls without history of schizophrenia and BD. Multiple testing correction was not attempted since the samples and phenotype definition were not independent (Supplementary Table S2). To define regions of association, we conducted PLINK linkage disequilibrium (LD) based ‘clumping’ to group SNPs with association \( P < 0.0001 \) and near-by SNPs with nominal associations \( P < 0.05 \) and LD \( r^2 > 0.1 \) within 500-kb windows. We also identified genes in these and the 20-kb flanking regions.

**Figure 1.** Sample ascertainment flow chart. (a) Subjectively defined lithium assessment. (b) Objectively defined lithium assessment.
SNP-heritability estimation

Furthermore, we estimated the heritability of lithium-responsive BD using the GCTA (genome-wide complex trait analysis) method.38 We first merged Sweden wave 2 and UK data sets, which were used for both subjective assessment and objective assessment of phenotype. We then used GCTA version 1.24 to calculate the pair-wise genetic relationship between individuals and created the genetic relationship matrix.38 SNP heritability of lithium-responsive BD phenotype was then estimated using the restricted maximum likelihood method in GCTA, with sex, different batches and the first four eigenvectors calculated from principal component analysis included as covariates to control for population structure. Details about the analysis procedure are provided in the Supplementary Methods.

RESULTS

Demographic characteristics for the Swedish and UK samples can be found in Supplementary Table S1.

Lithium responders vs non-responders

For each genome-wide association analysis, and for meta-analyses combining each GWAS with comparable assessments of lithium response, the genomic inflation factor \( \lambda \) showed little or no evidence for inflation (\( \lambda = 0.97–1.02 \), Supplementary Table S3). The regions of association with the lowest \( P \)-values for each analysis can be found in Supplementary Table S4, while the top results for each meta-analysis are summarized in Table 2 (corresponding results for analyses of each sample separately are in Supplementary Table S7). The quantile-quantile and Manhattan plots for all analyses are shown in Supplementary Figure S1.

No SNP reached genome-wide significance in any sample separately, except for one imputed SNP in GWAS for Sweden wave 2 comparing lithium responders and non-responders with subjective assessment (588 responders vs 338 non-responders, \( r^2 = 2.03 \times 10^{-9} \), OR = 2.14, Supplementary Table S4). However, this marker failed to meet the threshold for genome-wide significance following meta-analysis (1639 responders vs 1059 non-responders, \( P = 1.81 \times 10^{-4} \), OR = 1.31).

No SNP achieved genome-wide significance in meta-analyses of association with lithium response. In the analyses of objective lithium response, the SNPs with the greatest evidence for association were located in an intron of the NOTCH4 gene and all in high LD (\( r^2 > 0.8 \)).

Lithium responders vs controls

For these GWAS and meta-analyses, the resulting genomic inflation factors again showed little evidence of inflation (\( \lambda = 1.01–1.05 \), Supplementary Table S5). The regions of association with the lowest \( P \)-values for each analysis are shown in Supplementary Table S6, while the top results for each meta-analysis are shown in Table 2 (corresponding results for analyses of each sample separately are in Supplementary Table S7). The quantile-quantile and Manhattan plots for all analyses are in Supplementary Figure S2.

In GWAS for each sample comparing lithium responders (subjective assessment and controls), one imputed SNP achieved genome-wide significance in Sweden wave 1 (149 responders vs 2215 controls, \( r_1 = 1.08 \times 10^{-8} \), OR = 0.20), and one imputed SNP approached genome-wide significance in Sweden wave 2 (588 responders vs 1271 controls, \( r_1 = 5.19 \times 10^{-8} \), OR = 1.55) (Supplementary Table S6). However, the meta-analysis combining Swedish and UK samples together showed no genome-wide significant associations for these SNPs.

In the subsequent meta-analyses comparing lithium responders (objective assessment) with controls, two imputed variants reached genome-wide significance (323 responders vs

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6684 controls, rs146727601, \( P = 1.33 \times 10^{-6} \), OR = 3.98; and rs116323614, \( P = 2.74 \times 10^{-6} \), OR = 3.14; Table 2). Rs146727601 is a two-base deletion on chromosome 11q22.4 in the gene PTS (6-pyruvoyl-tetrahydropterin synthase) and also about 500 base pair (bp) downstream of the gene placenta expressed transcript 1 (PLET1). Rs116323614 is an intronic marker on chromosome 2q31.2 in the gene SEC14 and spectrin domains 1 (SESTD1). Direct genotyping was successful in 82 Swedish samples confirming the imputed rs116323614 alleles (Pearson correlation coefficient = 0.92). However, three distinct primer designs failed to genotype rs146727601. The region plots depicting association signals surrounding rs116323614 and rs146727601 are in Supplementary Figure S3.

We calculated the predicted genotype frequencies for imputed rs116323614 and performed the exact test of Hardy–Weinberg Equilibrium (details are provided in the Supplementary Methods). There was no evidence of departure from Hardy–Weinberg Equilibrium for this variant in either Swedish or the UK population (Supplementary Table S8).

Noticing the sex differences in the ratio of responders to non-responders in the UK sample (Supplementary Table S1), we performed association tests and meta-analysis for male and female samples separately. The ORs for rs116323614 by sex were not significantly different (\( P = 0.55 \)) and including sex as a covariate in the association analyses did not alter the significance (\( P = 3.93 \times 10^{-9} \)) (Supplementary Table S9).

SNP-heritability estimates
SNP heritability \( (h^2) \) for lithium-responsive BD was 29% for the subjective definition (95% CI 23–36, \( P < 0.0001 \)) and 25% for the objective definition (95% CI 0–51, \( P = 0.03 \) for the null hypothesis of being non-heritable) (Supplementary Table S10).

DISCUSSION
By using two large samples of persons with BD treated with lithium and healthy controls, we found that (i) no markers met the threshold for genome-wide association with lithium response; (ii) variation in SESTD1 demonstrated association in the case–control analysis, where we used lithium response to define a BD subtype, with the proportion of variance explained by common genetic variants (SNP heritability) estimated at 0.25–0.29.

Interestingly, SESTD1 encodes a protein involved in the regulation of phospholipids. Inositol phospholipids have been implicated not only in the pathophysiology of BD but also are among the most studied molecular targets of lithium. These results suggest that using pharmacoresponse to define subgroups within complex disorders might be a complementary approach for identifying disease risk loci in case–control association studies.

Lithium-responsive BD
Lithium response has been suggested to be a distinct phenotype of BD for decades. A number of studies have identified specific clinical features in patients responsive to lithium, such as fewer hospitalizations preceding treatment, later age of onset and an episodic pattern of mania followed by depression. In addition, lithium response is suggested to have a genetic basis, based on evidence such as longitudinal stability and familial clustering. Moreover, both clinical observational and neurobiological studies show that lithium responders differ from responders to other mood stabilizers. Therefore, the present study utilizes this distinct subtype of BD to investigate the mechanisms behind it.

Lithium responders vs non-responders
GWAS for each sample separately yielded one SNP (Sweden wave 2) showing genome-wide significant association (Supplementary Figure S1-II, Supplementary Table S4), but it failed to remain significant in the ensuing meta-analysis. The variants ranking highly in prior GWAS also showed little evidence of association in our results, and although the alleles previously reported to be strongly associated with lithium response in GAD1 did not exist in our sample, other common variants in GAD1 did not support an association.

Our findings with strong, but not significant, associations might nevertheless be informative for future genetic and protein-level studies. For example, the SNPs with the lowest \( P \)-values for objectively defined lithium response are located in the NOTCH4 and the gene within the major histocompatibility complex. Several studies have associated NOTCH4 with schizophrenia and BD, and it was found to be upregulated in BD. The mechanisms might be related to neurodevelopment and inflammation. Thus, our results are in line with the evidence implicating NOTCH4 in the pathophysiology of BD and potentially lithium response.

Lithium responders vs controls
By comparing the subgroup of BD patients who were lithium responders with healthy controls, we identified two variants, rs146727601 and rs116323614, reaching genome-wide significance. When we performed GWAS comparing all patients with BD with healthy controls, the results for rs146727601 and rs116323614 were \( OR = 1.28, P = 0.05 \) and \( OR = 1.31, P = 0.003 \), respectively, which supports the contention of an association in a subset of BD cases. Moreover, the minor allele frequencies in these two variants in lithium responders were markedly higher than that in non-responders (with objective response definition meta-analysis, rs146727601, \( OR = 2.18, P = 0.04 \); rs116323614, \( OR = 2.25, P = 0.01 \)). The different allele distributions suggest that these variants are unlikely to be general BD-associated markers, but specifically associated with lithium-responsive BD. Furthermore, the estimate of SNP heritability in our sample showed that lithium-responsive BD is modestly heritable. Although the largest published GWAS for BD did not include the significant markers in our study, we hope that future studies incorporating them will offer the possibility of replication.

For rs146727601, it is noteworthy that this variant is located in the gene PTS, a catalyst involved in the regulation of serotonin biosynthesis and nitric oxide synthase activity. These processes are suggested to be potential therapeutic targets for lithium. However, validation attempts failed, and no reasonable proxy marker exists.

By contrast, we successfully validated the rs116323614 association. This is an intronic SNP in the gene SESTD1, which shows relatively high expression in brain and is also significantly expressed in vascular cells. Importantly, SESTD1 Ca2+-dependent binds phospholipids (for example, phosphatidylinositol monophosphates (PIP) and diphosphates (PIP2)) that are involved in the phosphoinositide signaling pathway. This pathway is activated by G protein-coupled receptors, leads to the hydrolysis of PIP2 and produces inositol 1,4,5-trisphosphate (IP3) via the enzyme phospholipase C. IP3 regulates calcium signaling and is used to produce inositol, which is utilized to form PIP2, directing the initial step of this pathway. Decades of research into the therapeutic effects of lithium suggest that they are mediated through the inhibition of inositol monophosphatase and inositol polyphosphate 1-phosphatase. Both enzymes are important in the process of recycling inositol to PIP2 and PIP3 levels in vivo. Lithium thereby modulates the phosphoinositide pathway, and indirectly influences the actions of downstream neurotransmitter receptors. The fact that the phosphoinositide pathway is the most validated lithium target confers biological plausibility to our understanding of lithium's role in BD.

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finding of an association between SESTD1 and risk for lithium-responsive BD.5,66

Additionally, SESTD1 is proposed to be involved in phospholipid regulation of transient receptor potential channels TRPC4 and TRPC5.39,67 Both TRPC4 and TRPC5 are Ca2+ permeable channels and have an important role in functions of neurotransmitter release68 and in regulation of neurite growth.69,70 Interestingly, TRPC4 and TRPC5 are assumed to be activated by stimulation of phospholipase C, through IP3-induced intracellular Ca2+ store depletion.71 Moreover, recent GWAS for BD identified a novel variant located in the gene TRPC4 Associated Protein (TRPC4AP).72 The relationships between the TRPC families and the phospholipid signaling pathway further imply that SESTD1 is associated, possibly indirectly, with BD as well as lithium targets.

The A allele frequency for SNP rs116323614 is ~3% in European populations (1000Genome phase 1) with an odds ratio of 3.14 (95% confidence interval 2.10–4.70) in our study, suggesting that this variant alone is not well suited for clinical use. Moreover, it is likely that response to lithium is polygenically mediated, and only by examining multiple variants simultaneously will genetic screening be sufficiently powerful to guide decisions regarding mood stabilizers.5

Strengths and limitations

Our samples comprise two distinct populations, and the total number of patients with available assessment of lithium response in our study exceeds that of other reported studies to date. Nevertheless, the sample size is still small by GWAS standards, and results should be interpreted cautiously pending replication. To some extent, our results identifying associated variants in the responders/controls comparison but not in the responders/non-responders comparison could reflect reduced power rather than underlying biology.

The evaluation of genetic heterogeneity is important for meta-analyses, and our relatively homogeneous samples from Sweden and the United Kingdom offer greater power compared with studies involving populations that are more diverse. The markers demonstrating the greatest association in our results showed no evidence of heterogeneity using Q-tests (P = 0.73) and I2 heterogeneity index (I2 = 0.00).73

A key issue for pharmacogenetic studies is reliable assessment of treatment response. The irregular clinical course of BD74 and the difficulty in accurately measuring treatment adherence75 complicate the assessment of lithium response. Furthermore, whether a person is lithium responsive takes years to reliably establish. In this study, the harmonization of lithium response measures across sites is a potential concern as the assessments were conducted differently in Sweden and United Kingdom. Even though we carefully attempted to harmonize measures across sites, potential phenotypic misclassification cannot be excluded, and is a possible reason why significantly associated loci in the respective samples did not hold in the meta-analysis.

In addition to measuring the extent of clinical improvement, a refined evaluation could also consider additional factors (for example, the duration and severity of illness before and during lithium treatment, the duration and compliance of lithium treatment and additional medications) to determine whether the reduction of BD symptoms is actually due to the treatment.24 However, in the trade-off between certainty of response and sufficient sample size, the rate of missing data hampered inclusion of such variables. Hence, it cannot be excluded that a more elaborate measurement of lithium response might yield positive results.

CONCLUSION

In conclusion, the present study suggests that rs116323614, located in an intron of SESTD1, is associated with a lithium-responsive subtype of BD. This illustrates that defining homogeneous subgroups of complex genetic traits by response to treatment might be a productive strategy for identifying susceptibility alleles. Although the specific genetic variants identified in this study are not clinically applicable due to rare frequency, the findings provide new insights into the pathophysiology of BD and lithium's mechanism of action.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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