HHS Public Access

Author manuscript

J Affect Disord. Author manuscript; available in PMC 2020 June 12.

Published in final edited form as:

J Affect Disord. 2019 April 01; 248: 175–179. doi:10.1016/j.jad.2019.01.010.

Study of 45 candidate genes suggests *CACNG2* may be associated with lithium response in bipolar disorder

Alannah Miranda[a], **Tatyana Shekhtman**[a,b], **Michael McCarthy**[a,b], **Anna DeModena**[a,b], **Susan G. Leckband**[b], **John R. Kelsoe**[a,b,c,*]

[a]Department of Psychiatry, University of California San Diego, La Jolla 92093 CA, USA

[b]Department of Psychiatry, VA San Diego Healthcare System, La Jolla, CA, USA

[c]Institute for Genomic Medicine, University of California San Diego, La Jolla, CA, USA

Abstract

Background: Bipolar disorder is a neuropsychiatric disorder that is characterized by fluctuations between manic and depressive phases. Lithium is the original and best mood stabilizing treatment for bipolar disorder. While its mechanism is not well understood, it is believed to have a strong genetic component, as several studies suggest that lithium responsiveness, in bipolar disorder, is heritable. In this study we aimed to identify genetic variants that are associated with lithium responsiveness in bipolar disorder.

Methods: Here we present two cohorts; a retrospective cohort in which patients were surveyed about their response to lithium, and a prospective cohort, in which patients were placed on a lithium monotherapy and monitored for their response to lithium. In both cohorts, patients were stratified into two categories in terms of lithium response; good responders and poor responders. 45 genes were selected based on previous associations with lithium pathways or bipolar disorder and 684 SNPs within these genes were selected to test for association with lithium response.

Results: While no single SNP was significant after correcting for multiple comparisons, there were several that were nominally significant ($p < 0.05$). Of these nominally significant SNPs, the most highly significant SNP in both the prospective and retrospective cohorts were found to be in *CACNG2*, or *Stargazin*. The second best association with lithium response was several SNPs in *NRG1*, a gene that has previously been associated with schizophrenia.

*Corresponding author at: Department of Psychiatry, University of California San Diego, La Jolla 92093 CA, USA, jkelsoe@ucsd.edu (J.R. Kelsoe).

Contributors

Alannah Miranda: Analysis of data and writing of manuscript.
Tatyana Shekhtman: Genotyping and data analysis.
Michael McCarthy: Assessment of human subjects.
Anna DeModena: Collection and assessment of human subjects.
Susan G. Leckband: Selection of genes and writing of manuscript
John Kelsoe: Overall design of experiment and writing of manuscript.

Conflict of interest

The authors have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.01.010.

Conclusions: Evidence for the association of lithium response with SNPs in *CACNG2* is consistent with previous findings that have identified *CACNG2* as associated with both bipolar disorder and lithium responsiveness.

1. Introduction

Bipolar Disorder (BD) is a major neuropsychiatric disorder affecting 1–3% of the population (Sher, 2008). Patients with BD are afflicted with shifts in mood between manic and depressive states, psychosis affects about half of patients and if untreated up to 17% suicide. BD has no cure, however 80–90% of individuals can achieve stabilization of their symptoms with proper treatment. While there are many frequently used mood stabilizers, lithium remains the original and best mood stabilizing treatment (BALANCE investigators and collaborators, 2010).

Despite the success in treating BD with lithium, its mechanism of action is still not well understood. Lithium is a cation that has wide ranging effects on many cellular processes. For example, lithium can increase or decrease neurotransmission by modulating neurotransmitters such as glutamine, dopamine and *GABA*. Lithium also alters second messenger systems in neurons; three theories currently predominate (Malhi et al., 2013). Lithium inhibits inositol turnover by inhibiting the enzymes that dephosphorylate inositol triphosphate (IP3), this is felt to dampen signaling in those systems. Lithium also inhibits glycogen synthase kinase 3 (GSK3), which is a central intracellular signaling molecule that regulates cell activity and survival. Lithium also stimulates the release of Brain-Derived Neurotrophic Factor (BDNF), which modulates cell growth and survival through its receptor, tyrosine kinase receptor B (TrkB). Bipolar disorder is often associated with irregularities in the circadian clock, most notably its effects on the sleep-wake patterns of affected individuals. Lithium has been shown to alter aspects of the sleep-wake patterns, including improvements of day-to-day rhythmicity. Lithium has also been shown to act directly on the circadian clock, by altering the gene expression patterns of many circadian clock genes (Moreira and Geoffroy, 2016). Since lithium affects such a wide range of processes, it can be difficult to determine precisely how it stabilizes mood in BD. However, on a macroscopic level, in addition to mood stabilization, lithium has been shown to specifically combat suicidality in bipolar patients, protect cells, improve survival and increase neurogenesis (Chen et al., 2002; Lewitzka et al., 2015).

Notwithstanding the relatively unknown mechanism of action, lithium continues to provide a robust response in a large subset of BD patients. About a third of patients enjoy a virtual cure, and it has been argued that they represent a mechanistically distinct subform of illness affecting pathways modulated by lithium. Support for this comes from studies which show several clinical features such as strong family history and euphoric mania to be associated with good lithium response (Duffy et al., 2007). Further support, comes from studies using induced pluripotent stem cell (iPSC) derived neurons of BD patients, and showed that the BD neurons had a higher spontaneous firing rate of action potentials. This was then rescued by lithium only in those neurons derived from patients that had a positive clinical response to lithium (Mertens et al., 2015). Therefore, studying lithium response may not only inform regarding lithium’s mechanism, but also dissect BD into mechanistically distinct illnesses.

Identifying genetic variants associated with lithium response, can help to distinguish subsets of patients that are more likely to respond to lithium. Currently, clinical treatment consists of a trial and error process of multiple medication trials over several years. There is a great need to identify lithium responsive patients to ensure that they receive a trial of lithium that might change the course of their lives. Previous studies have determined several genes and SNPs as significantly associated with lithium response. One study with two separate cohorts (n = 470 and 170 subjects), identified a SNP in *CACNG2* as significantly associated with lithium response (Silberberg et al., 2008). However, simultaneous treatments and other drugs were frequent in these cohorts and treatment response measures were divided into 4–5 different categories. Additionally, a recent review points out that similar lithium responder versus non-responder association studies have yet to replicate a single lithium responsive marker in multiple cohorts of large sample size (n > 200) (Alda, 2015). These studies also struggle with the notable problems of retrospective assessment.

This current study identifies genetic markers that are associated with a positive lithium response, in a retrospective study, using an expert-selected subset of genes and SNPs that have been associated with bipolar disorder or lithium pathways. To distinguish from previous studies, we are able to validate the retrospective assessment of lithium response by using also using a prospective cohort. We then endeavored to replicate the significant genetic markers in an independent prospective study of lithium response in bipolar patients placed on a lithium monotherapy. It is clear in recent studies and reviews that there has been no conclusive evidence for a single marker as associated with positive lithium response. There is still a great need to be met in identifying putative markers for lithium response.

2. Methods

2.1. Subjects

All subjects provided written informed consent according to the Institutional Review Board (IRB) approved protocol. Subjects came from two independent studies of lithium response, one with retrospective assessment of lithium response, the other was a prospective trial with a relapse prevention design. Subjects in the retrospective sample were ascertained as part of a family based linkage study or a case control study of bipolar disorder genetics. From each family only the proband was included. Each subject underwent diagnostic assessment using the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). Only subjects with a Bipolar Disorder Type I (BDI) diagnosis were included. Demographic information on both the retrospective and prospective cohorts can be found in Table 1. The cohorts were not significantly different in terms of age, lithium response (good or poor), or family history. The two cohorts were significantly different in gender.

2.2. Assessment of lithium response

Retrospective sample—As part of the assessment, subjects were queried regarding all their past medication trials. Subjects were included if they had a past history of lithium treatment. Patients who had taken lithium, were then queried on whether the lithium reduced their symptoms by 50% or more. All clinical information, including the DIGS interview, review of medical history, medical records and family informants was reviewed by a panel

of experienced clinicians who were blind to genotype. The subject's response over their lifetime was assessed. Those who were rated as positive lithium responders (>50% reduction in symptoms) were classified as good responders, and those with a self-reported negative lithium response (< 50% reduction in symptoms) were classified as non, or poor, responders. We have validated this retrospective assessment method, by comparing blind retrospective scoring of prospective subjects to their prospective outcome (Supplemental Methods; Supplemental Table 1; Supplemental Fig. 1).

2.2.1. Prospective sample: In the prospective study, patients with BDI were placed on lithium monotherapy and their progress was noted over the course of 2 years. This study consisted of 3 phases, the first stage being stabilization, during which patients were tapered off other medications and titrated up to a therapeutic lithium level. They were then judged to either be stabilized and a responder or a non-responder. Stabilization phase lasted for 4 months, and was followed by the observation phase, where subjects were observed on lithium monotherapy for 1 month in order to document response. Subjects then entered the maintenance phase which lasted over 2 years. During this time, they were monitored every 2 months for relapse. The physician rated Clinical Global Impression Scale (CGI) was used as the primary measure of response. Subjects rated as having only mild symptoms were considered responders and allowed to advance to maintenance. Subjects were also assessed with the Hamilton Rating Scale for Depression, the Young Mania Rating Scale, the Internal State Scale and the Beck Depression Inventory. Two different outcome measures were used: (1) for acute response. Patients were classified as either responders or non-responders based on their ability to stabilize on lithium monotherapy and enter maintenance; (2) for survival analysis, time to event was used as a measure, where the event is either failure to remit or relapse once remitted. The prospective study was designed for replication of results in the retrospective study. It is the gold standard for assessing response, but allowed only a small sample size.

2.3. Selection of genes and SNPs

45 genes were selected based on several criteria: (1) genes were included if they had previously been reported associated with lithium response; (2) genes involved in lithium's mechanism of action; and (3) genes associated with risk for bipolar disorder. Supplementary Table 2 groups the genes into each of the three categories and provides citations when necessary. Genes were targeted based upon their association with bipolar disorder based upon findings that suggest there is overlap between bipolar risk alleles and lithium responsive alleles. 684 SNPs were selected within these genes. SNPs were selected that optimally tagged the gene or had known functional effect. Data cleaning was performed via PLINK, limiting the analysis to SNPs with a genotype missingness rate of less than 10%, excluding subjects with missingness greater than 10% and eliminating SNPs with a minor allele frequency of less than 5%. Hardy Weinberg equilibrium was tested and SNPs excluded if not in equilibrium.

In order to reduce the number of multiple comparisons, we performed LD clumping following the association analysis. All SNPs were included in the LD clumping analysis by setting the index SNP and subsequent clumped SNPs to $p < 1$, and LD was then determined

by the following parameters: $r^2 > 0.1$ and within 250 kb windows. SNPs were grouped together as a single distinct signal with a single index SNP identified as being the association signal. The number of clumps determined in PLINK for each analysis was used as the number of independent tests to set the multiple comparisons threshold.

3. Genotyping

SNPs were directly genotyped in the retrospective study, using either the SNPlex multiplex method or Taqman genotyping (Life Technologies, San Diego) as previously described and according to the manufacturer's directions. (Nissen et al., 2012) In the prospective study, genotyping data from the prospective study was completed on the PsychArray Chip (Illumina, San Diego).

3.1. Statistical analysis

Phenotype and demographic differences between the retrospective and prospective cohorts, as well as between responders and non-responders within each cohort, were tested in SPSS using either the independent *T*-test or Chi-square test. *P*-values for these analyses, as well as other phenotype information can be found in Table 1 and in the supplemental information (Supplemental Tables 3 and 4).

Association analyses were completed using logistic regression in PLINK version 1.9. Principal components were computed in plink using the population stratification functions in PLINK version 1.9. For both the retrospective and prospective study, principal components were calculated based on pairwise identity by state (IBS) clustering. Principal components were calculated for the Caucasian population of each study, and as well the entire subject population.

In the retrospective study, the analysis was completed on 684 directly genotyped SNPs within the 45 selected genes (Table 2). This analysis included Caucasian subjects only, comparing lithium responders to non-responders, using age, sex and 3 principal components (within the Caucasian subject population) as covariates in the logistic regression.

For the prospective analysis, again only Caucasian subjects were analyzed in a single SNP association analysis, using age, sex and 3 principal components (within the Caucasian subject population). Analyses were conducted using the acute response (entered maintenance) with covariates in PLINK.

In order to increase statistical power, a gene-based set analysis was also performed in PLINK. SNPs and subjects were similarly filtered in both cohorts for minor allele frequency, missingness and genotyping rate, as described for the SNP by SNP analysis. Only Caucasian subjects were analyzed for both cohorts, again similar to the SNP by SNP analysis. The number of permutations for this analysis is set to 10,000 and the empirical p-value result is the number of times the permuted test statistic exceeds the original test statistic. This p-value has been corrected for the multiple SNPs within a set.

4. Results

4.1. Retrospective analysis

Of the 45 selected candidate genes, 9 contained SNPs that showed nominal significance ($p > 0.05$) in a Caucasian only ($n = 286$), retrospective analysis. After accounting for SNPs in LD, a total of 174 distinct clusters of SNPs were determined. Using this to correct for multiple comparisons, no SNPs were found to be significant. The SNP with the highest significance was found in the *CACNG2* gene (rs140040; $p = 0.002632$, OR = 1.728) (Table 3).

A gene-based set analysis in PLINK showed that 10 genes had at least one SNP which had a p-value <0.05. The top hit in the retrospective gene based analysis was *CACNG2* ($p = 0.07249$). The empirical p-values for all 10 genes are reported in the Supplementary Table 6. No gene was nominally significant in this analysis.

4.2. Prospective analysis

11 genes showed nominal significance in the single SNP association analysis of the Caucasian prospective subjects ($n = 68$). After accounting for LD, there were a total of 146 distinct clusters of SNPs. In using this number to correct for multiple comparisons, no SNPs reached significance (Table 4). The most highly associated SNP in the prospective study (rs1347441; $p = 0.00993$, OR = 3.417) was found to be in PDE11A. Another SNP in *CACNG2* was also found to be nominally significant (rs2283967; $p = 0.0136$, OR = 0.2596). Upon further examination of the clumping groups for the retrospective and prospective studies, the SNPs, rs140040 and rs2283967, were found to be clumped together in both the retrospective and prospective studies. LD calculations done in PLINK using the retrospective dataset, report an r^2 of 0.194451 and a D' of 0.678938 for these SNPs. The most significant SNP in PDE11A from the retrospective analysis (rs7585543; $p = 0.0157$, OR = 1.801) and the most significant SNP in PDE11A in the prospective study (rs1347441; $p = 0.00993$, OR = 3.417) were not clumped together by PLINK.

In a secondary analysis only the nominally significant SNPs from the retrospective analysis were tested in the prospective cohort, in order to reduce the number of comparisons necessary to reach significance. However, this strategy resulted in no SNPs reaching even nominal significance (Supplementary Table 5). Additionally, the most significant SNP from the retrospective analysis was excluded in this secondary analysis due to a missingness rate higher than 10%.

A gene-based set analysis in PLINK showed that 8 genes had at least one SNP which had a p-value <0.05. The top hit in the retrospective gene based analysis was *CACNG2* ($p = 0.008799$). The empirical p-values for all 8 genes are reported in the Supplementary Table 7. *CACNG2* was also the top hit in this analysis and was nominally significant, however it was short of reaching significance after multiple comparisons. The analysis was repeated using only the 10 genes which returned an empirical p-value in the retrospective analysis. These results can be found in Supplementary Table 8. *CACNG2* was the top hit once again, and nominally significant (p = 0.008199). However, it failed to pass the multiple comparisons threshold ($p = 0.005$).

After determining that the gene with the highest significance in both the retrospective and prospective studies appeared to be *CACNG2*, the top SNP from the Silberberg study, rs2284017, that was found to be significant in both Silberberg cohorts, was directly genotyped in the prospective cohort (Silberberg et al., 2008). However, a Kaplan-Meier survival analysis showed no significant difference in genotype between the responders and non-responders. (Supplemental Fig. 2)

A meta-analysis using the program METAL did not result in any statistically significant SNPs when looking at the combined prospective and retrospective studies (Supplemental Table 9) (Wilier et al., 2010).

5. Discussion

Single SNP association analyses of both the retrospective cohort and the prospective cohort did not result in significant SNPs that met the multiple comparisons threshold. Additional analyses, such as the meta-analysis and gene-based set test, also failed to reach significance after multiple comparisons. However, this study was limited in sample size, particularly in the prospective study, which was restricted due to the nature of the experiment. Placing patients on a lithium monotherapy is challenging as many patients may already be on medications before coming into the study. Additionally, there can be errors in assessing lithium response. In the prospective study, there are many variables, such as prescription history that could have an effect on assessment of lithium monotherapy. Alternatively, in the retrospective study, assessment of lithium response is largely based on patient recollections during interviews, therefore accuracy of responses can vary greatly. Differences in the study design between the retrospective and prospective cohort ultimately results in a difference of outcome measures. Wherein the retrospective cohort the outcome measured is lithium response after stabilization, whereas in the prospective cohort, the response measured is an acute response to lithium. Although we have validated the retrospective assessment, using the prospective cohort, it is nonetheless challenging to determine an outcome measure that is highly comparable between these two studies designs. The differences in design introduce other confounding variables, including probable different lithium plasma levels between the cohorts, that are difficult to account for.

Despite the limitations and lack of significant SNPs, a number of nominally significant SNPs suggested several interesting genes that maybe linked with positive lithium response. In particular, the presence of SNPs in *CACNG2* associated with lithium response is confirmatory of a previous study identifying *CACNG2* as associated with lithium response in bipolar disorder (Silberberg et al., 2008). The most significant SNP in the retrospective study was found to be in *CACNG2* and the third most significant SNP in the prospective study was also in *CACNG2*. Furthermore, when using plink clumping, both *CACNG2* SNPs, rs2283967and rs140040, were found to be clumped together using PLINK LD clumping. rs2283967and rs140040 are both located in an intronic region of *CACNG2.* Thus far there is no report in the literature that suggests how either SNP may impact lithium efficacy. However, in a study of pharmacogenetics of antipsychotic response, rs2283967 was also shown as a top hit associated with discontinuation of risperidone due to inefficacy, although it also failed to meet the multiple comparisons threshold (Need et al., 2009).

We have previously reported genome-wide significant linkage to *CACNG2* in a set of 20 families and 164 subjects using 443 microsatellite markers. This study showed that chromosome 22 yielded the highest LOD score of 3.8 at 22q12 near *CACNG2* (Kelsoe et al., 2001). Further study of this region using fine mapping association analysis identified significant association in a region very near *CACNG2* (Nissen et al., 2012). *CACNG2*, or Stargazin, has also previously been reported to be overexpressed in the dorsolateral prefrontal cortex of patients with bipolar disorder, compared to expression levels in both schizophrenia patients and controls (Silberberg et al., 2008). This same study also identified three SNPs in Stargazin that were associated with lithium response in bipolar patients. While, none of these three previously identified SNPs were included in the retrospective direct genotyping phase of this study, the top SNP from that study, rs2284017, was directly genotyped in the prospective cohort. This SNP was not significantly associated with lithium response in the prospective cohort. The SNP was also determined to not be in LD with either the top retrospective SNP (rs140040) or the top prospective *CACNG2* SNP (rs2283967) using the prospective genotyping data and LD calculations performed in PLINK.

Stargazin is believed to be similar in structure to gamma subunit to neuronal skeletal muscle voltage-gated calcium channels, however it has been demonstrated to act as an AMPA receptor auxiliary subunit (Letts et al., 1998; Vandenberghe et al., 2005). Previous studies have established that stargazin plays a key role in trafficking AMPA receptors to the cell surface, thereby regulating the amount of AMPA receptors present at neuronal synapses (Chen et al., 2000). Stargazin has also been shown to effect ion flow, specifically playing a role in channel gating, in conjunction with GluA subunits, and in the reduction in channel blocking of calcium-permeable AMPA receptors (Soto et al., 2007; Vandenberghe et al., 2005). When coexpressed with GluA subunits, stargazin increases glutamate-evoked currents and slowing channel closing (Tomita et al., 2005; Turetsky et al., 2005). Polyamine channel blocking of calcium-permeable AMPA receptors (CP-AMPARs) has been found to be modulated by stargazin, wherein stargazin reduces the polyamine blockage and increases Ca^{2+} flux (Soto et al., 2007). AMPA receptors and glutamate signaling have been targeted as playing putative roles in the pathophysiology of mood disorders due to their roles in synaptic plasticity and mood neural networks (Du et al., 2004). It is possible that lithium also interacts with some of these pathways, and thus these mutations in stargazin may work in conjunction with lithium to provide a particularly beneficial response to the remedial effects of lithium.

GWAS on the pharmacogenetics of lithium have since been performed after the a priori selection of the candidate genes in this study. The authors are active collaborators in the ConLiGen Consortium and have contributed samples to this analysis as well. Nonetheless, the retrospective and prospective studies both represent distinctly different study designs and subject sets that adds valuable information to the understanding of the pharmacogenetics of lithium in bipolar disorder. *CACNG2* was repeatedly identified as nominally significant in both studies. *CACNG2* is an exceptionally noteworthy association, considering two SNPs in LD with one another were found to be amongst the top significant hits in both studies. The identification of *CACNG2* in this study also acts as a confirmatory result for several other studies associating lithium response and *CACNG2*. While not a true replication, the prevalent number nominally significant *CACNG2* SNPs in both studies, and the close

proximity of these two top SNPs, indicates that *CACNG2* could play a substantial role in lithium response. While more research must be done to evaluate the role *CACNG2* may play in lithium response, it is nonetheless a promising candidate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Role of Funding Source

Provided financial support; no other role.

UCSD Genetics Training Grant (T32 GM008666)

Department of Veterans Affairs (I01CX000363).

References

Alda M, 2015 Lithium in the treatment of bipolar disorder: pharmacology and pharmacogenetics. Mol. Psychiatry 20, 661–670. https://doi.Org/10.1038/mp.2015.4. [PubMed: 25687772]

Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK, 2002 Enhancement of hippocampal neurogenesis by lithium. J. Neurochem. 75, 1729–1734. 10.1046/j.1471-4159.2000.0751729.x.

Chen L, Chetkovich DM, Petralia RS, Sweeney NT, Kawasaki Y, Wenthold RJ, Bredt DS, Nicoll RA, 2000 Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. Nature 408, 936–943. 10.1038/35050030. [PubMed: 11140673]

Du J, Quiroz J, Yuan P, Zarate C, Manji HK, 2004 Bipolar disorder: involvement of signaling cascades and AMPA receptor trafficking at synapses. Neuron Glia Biol. 1, 231–243. 10.1017/S1740925X05000098. [PubMed: 18634600]

Duffy A, Alda M, Milin R, Grof P, 2007 A consecutive series of treated affected offspring of parents with bipolar disorder: is response associated with the clinical profile? Can. J. Psychiatry 52, 369–376. 10.1177/070674370705200606. [PubMed: 17696023]

Kelsoe JR, Spence MA, Loetscher E, Foguet M, Sadovnick AD, Remick RA, Flodman P, Khristich J, Mroczkowski-Parker Z, Brown JL, Masser D, Ungerleider S, Rapaport MH, Wishart WL, Luebbert H, 2001 A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. Proc. Natl. Acad. Sci 98, 585–590. https://doi.Org/10.1073/pnas.98.2.585. [PubMed: 11149935]

Letts VA, Felix R, Biddlecome GH, Arikkath J, Mahaffey CL, Valenzuela A, Bartlett FS, Mori Y, Campbell KP, Frankel WN, 1998 The mouse stargazer gene encodes a neuronal Ca2 +-channel γ subunit. Nat. Genet 19, 340–347. 10.1038/1228. [PubMed: 9697694]

Lewitzka U, Severus E, Bauer R, Ritter P, Müller-Oerlinghausen B, Bauer M, 2015 The suicide prevention effect of lithium: more than 20 years of evidence—a narrative review. Int. J. Bipolar Disord 3, 15 10.1186/s40345-015-0032-2.

Malhi GS, Tanious M, Das P, Coulston CM, Berk M, 2013 Potential mechanisms of action of lithium in bipolar disorder. CNS Drugs 27, 135–153. 10.1007/s40263-013-0039-0. [PubMed: 23371914]

M.D.Sher L, 2008 Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression In: Goodwin FK, Jamison KR (Eds.), second ed. Oxford University Press, New York, pp. 1288 10.1176/appi.ajp.2007.07121846. M.D. Ph.D.2007Am. J. Psychiatry 165, 541–542.

Mertens J, Wang Q-W, Kim Y, Yu DX, Pham S, Yang B, Zheng Y, Diffenderfer KE, Zhang J, Soltani S, Eames T, Schafer ST, Boyer L, Marchetto MC, Nurnberger JI, Calabrese JR, Oedegaard KJ, McCarthy MJ, Zandi PP, Alda M, Nievergelt CM, Mi S, Brennand KJ, Kelsoe JR, Gage FH, Yao J, Yao J, 2015 Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. Nature 527, 95–99. 10.1038/naturel5526. [PubMed: 26524527]

Moreira J, Geoffroy PA, 2016 Lithium and bipolar disorder: impacts from molecular to behavioural circadian rhythms. Chronobiol. Int 33, 351–373. 10.3109/07420528.2016.1151026. [PubMed: 27003509]

Need AC, Keefe RSE, Ge D, Grossman I, Dickson S, McEvoy JP, Goldstein DB, 2009 Pharmacogenetics of antipsychotic response in the CATIE trial: a candidate gene analysis. Eur. J. Hum. Genet 17, 946–957. 10.1038/ejhg.2008.264. [PubMed: 19156168]

Nissen S, Liang S, Shehktman T, Kelsoe JR, Bipolar Genome Study (BiGS),Greenwood TA, Nievergelt CM, McKinney R, Shilling PD, Smith EN, Schork NJ, Bloss CS, Nurnberger JI, Edenberg HJ, Foroud T, Roller DL, Gershon ES, Liu C, Badner JA, Scheftner WA, Lawson WB, Nwulia EA, Hipolito M, Coryell W, Rice J, Byerley W, McMahon FJ, Berrettini WH, Potash JB, Zandi PP, Mahon PB, Mclnnis MG, Zollner S, Zhang P, Craig DW, Szelinger S, Barrett TB, Schulze TG, 2012 Evidence for association of bipolar disorder to haplotypes in the 22ql2.3 region near the genes stargazin, ift27 and parvalbumin. Am. J. Med. Genet. Part B Neuropsychiatr. Genet 159B, 941–950. 10.1002/ajmg-b.32099.

Nurnberger JI, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T, 1994 Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch. Gen. Psychiatry 51, 849–859 discussion 863–4. [PubMed: 7944874]

Silberberg G, Levit A, Collier D, St. Clair D, Munro J, Kerwin RW, Tondo L, Floris G, Breen G, Navon R, 2008 Stargazin involvement with bipolar disorder and response to lithium treatment. Pharmacogenet. Genom 18, 403–412. 10.1097/FPC.0b013e3282f974ca.

Soto D, Coombs ID, Kelly L, Farrant M, Cull-Candy SG, 2007 Stargazin attenuates intracellular polyamine block of calcium-permeable AMPA receptors. Nat. Neurosci 10, 1260–1267. 10.1038/nnl966. [PubMed: 17873873]

The BALANCE investigators and collaborators, 2010 Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 375, 385–395. 10.1016/S0140-6736(09)61828-6. [PubMed: 20092882]

Tomita S, Adesnik H, Sekiguchi M, Zhang W, Wada K, Howe JR, Nicoll RA, Bredt DS, 2005 Stargazin modulates AMPA receptor gating and trafficking by distinct domains. Nature 435, 1052–1058. 10.1038/nature03624. [PubMed: 15858532]

Turetsky D, Garringer E, Patneau DK, 2005. Stargazin modulates native AMPA receptor functional properties by two distinct mechanisms. J. Neurosci 25, 7438–7448. 10.1523/JNEUROSCI.1108-05.2005. [PubMed: 16093395]

Vandenberghe W, Nicoll RA, Bredt DS, 2005 Stargazin is an AMPA receptor auxiliary subunit. Proc. Natl. Acad. Sci. U.S.A 102, 485–490. 10.1073/pnas.0408269102. [PubMed: 15630087]

Wilier CJ, Li Y, Abecasis GR, 2010 METAL: fast and efficient meta-analysis of genomewide association scans. Bioinforma. Appl. NOTE 26, 2190–219110. 10.1093/bioinformatics/btq340.

Table 1

Demographics for subjects included in the retrospective (n = 286) and prospective (n = 68) study including Caucasian subjects only.

	Retrospective	**Prospective**	***p*-value**
Gender (M/F)	148/138	60/8	
	<0.0001		
Mean age (Range)	44.8 (15–76)	45.75 (23–70)	0.611
Lithium response (Good/Poor)	135/151	40/28	
	0.085		
Family history (Positive/Negative)	152/134	43/25	0.133

Table 2

Genes and # of SNPs selected for analysis in the retrospective study. Genes and SNPs were selected based on prior association with lithium pathways or bipolar disorder.

Gene	SNP count	Gene	SNP count
ADCY1	21	*MAPK1*	7
AKT1	5	*MAPK3*	1
AKT3	24	*MARCKS*	5
BAD	8	*NRG1*	51
BCL2	17	*NTRK1*	49
BDNF	9	*NTRK2*	32
CACNG2	41	*NTRK3*	49
CLOCK	10	*P2RX7*	17
CREB1	2	*PDE11A*	34
CREM	10	*PDE4B*	34
CSNK1E	4	*PER3*	13
CTNNB1	20	*PIK3C2A*	6
DAOA	9	*PIK3C2B*	9
DGKH	37	*PIK3CA*	8
FAIM	5	*PIK3CB*	3
FKBP5	6	*PIK3CG*	32
GSK3A	3	*PLCG1*	5
GSK3B	5	*PPP1R1B*	2
HTR2A	21	*SLC10A5*	1
IMPA1	5	*SOS1*	11
IMPA2	14	*SOS2*	15
INPP1	7	*YWHAG*	4
KCNMB3	13		
Total	**684**		

Table 3

SNPs and genes associated with a positive response to lithium in the retrospective analysis ($p < 0.05$) after LD clumping (N = number of SNPs in LD with index SNP, $r^2 = 0.1$).

SNP	OR	*P*	*N*	Gene
rs140040	1.728	0.00263	9	*CACNG2*
rs2975498	0.516	0.00532	7	*NRG1*
rs11208844	2.019	0.00557	3	*PDE4B*
rs10908523	3.509	0.00693	2	*NTRK1*
rs42154	1.661	0.0132	1	*PIK3CG*
rs7585543	1.801	0.0157	12	*PDE11A*
rs1211166	1.784	0.0201	13	*NTRK2*
rs9638987	1.68	0.0244	5	*ADCY1*
rs11208816	0.6781	0.027	5	*PDE4B*
rs2466061	1.976	0.029	4	*NRG1*
rs17664708	1.897	0.036	6	*NRG1*
rs2150906	0.4587	0.0396	7	*NTRK1*
rs10149742	1.811	0.046	2	*SOS2*
rs868362	0.5793	0.0462	1	*ADCY1*

Table 4

SNPs and genes associated with a positive response to lithium in the prospective analysis ($p < 0.05$) after LD clumping (N = number of SNPs in LD with index SNP, $r^2 = 0.1$), using directly genotyped SNPs.

SNP	OR	*P*	*N*	Gene
rs1347441	3.417	0.00993	11	*PDE11A*
rs1491851	0.2705	0.01306	2	*BDNF*
rs2283967	0.2596	0.0136	8	*CACNG2*
rs2076148	3.398	0.01371	5	*PLCG1*
rs12741937	0.1863	0.01661	6	*PER3*
rs5755694	0.3556	0.01742	7	*MAPK1*
rs484698	2.877	0.01911	6	*FAIM*
rs13329385	0.2859	0.02618	14	*NTRK3*
rs16879922	3.579	0.02901	8	*NRG1*
rs13003683	3.842	0.03077	8	*PDE11A*
rs6339	0.2184	0.04543	4	*NTRK1*
rs2070062	2.856	0.04883	8	*CLOCK*