Evaluation of The Association Between Lithium Treatment and GSK3β Polymorphism in Bipolar Disorder Patients

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SUMMARY

Objective: There is a lack of evidence regarding clinical predictors for the treatment response to lithium, which is the corner stone treatment option for bipolar disorder. Studies that examined the mechanistic action of lithium revealed that glycogen synthase kinase 3β (GSK-3β) enzyme-inhibition was important in regard to treatment responses. Based on this background, we aimed to investigate the association between responses to lithium treatment and five different polymorphisms of GSK-3β.

Method: Lithium treatment response scale (LTRS) scores for 100 patients diagnosed with bipolar disorders type I were calculated according to the hospital records. Blood samples were collected and genomic DNA was obtained using the MagNA Pure Compact automatic isolation method. The GSK-3β: rs17183904, rs17183897, rs34009575, rs34002644, and rs17183890 polymorphisms were analyzed by real time PCR.

Results: In this cohort, the mean age of patients was 41.1±10.3 years, the mean age of disease onset was 24.5±8.2, and the mean LTRS score was 4.9±1.8. There was no statistically significant difference for LTRS scores between groups in terms of gender, marital status, level of education, and the type of first episode. LTRS was significantly higher in only the patients harbouring GSK-3β rs17183890 AG genotype (p=0.008, t:2.71). Interestingly, no differences were found for the remaining polymorphisms.

Conclusion: The specific GSK-3β polymorphism that associated with lithium-response in our study may help to predict lithium responses and to develop individualized treatment. We presume that our pharmacogenomic findings may also provide important contributions to the clinical practice in regard to future evaluation of the treatment adherence and side effects. To obtain these goals, further genome-wide scanning studies conducted on larger sample cohorts are required.

Keywords: Bipolar disorders, lithium response, GSK-3β polymorphism

INTRODUCTION

Lithium, with its antimanic and antidepressive features, is the only mood stabilizer approved for longitudinal protection in bipolar disorder. On the other hand, a significant proportion of bipolar patients are poor responders to the treatment. Therefore, finding a suitable mood stabilizer for patients has been a major challenge for clinicians. Studies that assessed clinical response to lithium revealed predictive factors for those that respond well and and poor to lithium treatment. The predictive factors for response are as follows: for a good response: disease course manifested with manic-depressive-euthymic periods, presence of manic episode with euphoria, lesser frequency of disease episodes, a positive family history, and a good lithium-response of family members with bipolar disorder; for a poor response: presence of mixed episodes or psychotic features, a disease course manifested with depressive-manic-euthymic periods, drug and alcohol misuse, and

Received: 20.01.2017 - **Accepted:** 19.06.2017

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doi: 10.5080/u20582

accompanying anxiety or personality disorders (Mendlewicz et al. 1973, Taylor and Abrams 1975, Garfinkel et al. 1980, Maj et al. 1984, Maj et al. 1989, O'Connell et al. 1991, Keller et al. 1993, Maj et al. 1996, Swann et al. 1997, Swann et al. 1999).

The fact that a good lithium-response has been shown to be shared among family members indicates that the lithium response may be of genetic origin. When the current literature on the pharmacogenetics of lithium-response was reviewed, it became obvious that overlapping gene polymorphisms exist that involve both the lithium response and the etiopathogenesis of the bipolar disorder. These include the promoter region of the serotonin transponster gene (5-HTTLPR), Brain Derived Neurotrophic Factor (BDNF), Inositol Polifosfate 1-fosfatase (IPPase), Inositol Monofosfatase (IMPase), Bifosfate Nucleotidase (BPNase), Fructose 1,6-bisfosfatase (FBPase), Phosfoglucomutase (PGM), GSK-3β, mitochondrial DNA, serotonin receptors (5HT2A and 5HT2C) and X-box-binding protein-1 (XBP1) (Rybakowski et al. 2005, Seretti et al.2009, Smith et al. 2010). It has been thought that the IMPase, IPPase, and GSK-3β polymorphisms may be able to shed light on the genetic basis of the lithium response. In particular, they were found to both associate with bipolar disorder in genetic studies investigating the bipolar disorder-etiopathogenesis and with the action mechanisms of lithium (Li et al. 2002, Gould and Manji 2005, Gould 2006, Rowe et al. 2007, Seretti et al. 2009).

It has been assumed that lithium controls the intracellular signal transduction through second messenger molecules and that the effects of lithium occur by lowering the inositol levels in the cerebral tissue (Can et al. 2014). The GSK-3 enzyme has been shown to inactivate glycogen synthase, which converts glucose to glycogen and is involved in many metabolic and signal-transduction pathways including protein synthesis, proliferation, neural plasticity, and programmed cell death in the brain. Initial research investigating the role of lithium on this enzyme began with the demonstration that lithium directly inactivated GSK-3 in cell cultures (Stambolic et al., 1996). The GSK-3 enzyme exists in its active form in the cell and its deactivation has been shown to promote intracellular signaling. In addition, it has been reported that an indirect inhibition occurs via phosphorylation of the GSK-3β, which is one of the isoforms of the GSK-3. Phosphorylation of GSK-3β has been reported to play an important role in the regulation of oxidative stress, neuroinflammation, neurogenesis pathways, and the emergence of bipolar disorder through alteration of the enzyme activity (Gould et al. 2004; Can et al. 2014; Luca et al 2016)

Indeed, it has been shown that in animal models of mania, lithium prevents dopaminergic stimulant-induced increase in locomotion by inhibiting the GSK-3β enzyme activity directly. In the same manner, lithium has been shown to control psychomotor activity observed clinically during the manic episode (Gould and Einat. 2007; Urs ve ark. 2012). In addition, data exist, albeit limited, that has demonstrated the lithium effects on depression also occur via the GSK-3 enzyme (Zhang et al. 2012). The gene encoding the GSK-3β enzyme resides at chromosomal region 3q21.1. Over the years, studies have steadily increased and have investigated the pharmacogenetical interactions between its specific single nucleotide polymorphisms (SNPs) (Smith et al. 2010, Can et al. 2014, Alda 2015). In the light of these findings, we aimed to investigate the association between lithium responses of bipolar disorder patients receiving lithium and specific SNPs (rs17183904, rs17183897, rs34009575, rs17183904) of the GSK-3β isoform in this study.

METHODS

Ethical Approval and Sample Population

Before the study, the ethics committee approvals were sought from the Ethics Committee of "İstanbul Bakırköy Ord. Professor Dr. Mazhar Osman Mental and Neurological Diseases Education and Research Hospital" (dated 05.06.2012 and numbered B.10.4.İSM.04.34.26.08-213) and from the Directorate of Clinical Research Ethics Committee of "Çanakkale Onsekiz Mart University" (dated 21.01.2015 with decision number 2015- 02). One hundred patients aged 18 and older and diagnosed as "type I bipolar disorder" according to DSM IV-TR were included in the study. Other inclusion parameters were willingness to participate in follow up studies, treatment at "İstanbul Bakırköy Ord. Professor Dr. Mazhar Osman Psychiatric and Neurological Diseases Training and Research Hospital at Raşit Tahsin Duygudurum Center," and willing to undergo treatment for at least one year with lithium alone or lithium combined with either antipsychotics, antidepressants, and other mood stabilizers. Patients with concomitant psychiatric disorders other than bipolar disorder were excluded from the study because they may affect the assessment of treatment responses. Additionally, patients were asked to fill out the Sociodemographic Data Forms (SVF) developed by the researchers that supervised the study. The treatment registries were also examined and the treatment responses were calculated with the Lithium Response Scale.

Materials Used

The SVF was developed for this study in order to evaluate the sociodemographic and clinical characteristics of the patients. The form was composed of queries, which question age, level of education, marital status, household companions, status of employment, general family history, alcohol or substance misuse, psychiatric disease history in family members, duration of alcohol use, periods of remission, number of hospitalizations,

and treatment anamnesis. The Lithium Response Scale consisted of two parts, A and B, which evaluate the lithium treatment response. The 'A' criterion was used to determine the relationship between clinical healing and treatment. The rating should correspond to adequate treatment duration in terms of dose and duration. Disease activity was assessed by frequency, severity, and duration of episodes. The 'B' Criterion was used to determine if there was a causal relationship between clinical recovery and treatment. Each item was calculated as 0,1, or 2 points. The total scale score was calculated by subtracting A from B. Approximation of the total score to 10 full points was clinically indicative of a good response to lithium. Since the scale items were calculated on universally accepted clinical variables, the calculations were performed in different countries according to the specified criteria without studying validity and reliability (Grof et al., 2002).

Laboratory Method For SNP Analysis of GSK3β

For DNA isolation, peripheral blood samples were collected in tubes containing EDTA. Genomic DNA was obtained using the Magna Pure Compact (Roche) automatic isolation method. A total of 100 patients were analyzed for GSK3β: rs17183904, rs17183897, rs34009575, rs34002644, and rs17183890 polymorphisms using a real time PCR technique (LightCycler 2.0, Roche). In the genotyping of GSK-3β gene polymorphisms, the reaction mixture for one reaction was prepared with 12.4 µl solvent, 1.6 µl Mg^{+2} solution, 1 µl oligotool (containing primers), and 2 µl Roche Fast Start Master mix. The final reaction volume (20 µl) was obtained by adding 3 µl of template DNA. The protocol was defined as follows: denaturation 10 minutes at 95°C, quantification 45 cycles of 10 seconds at 95°C, 10 seconds at 60°C and 15 seconds at 72°C, melting 20 seconds at 95°C, 20 seconds at 40°C and 0.2 continuous mode at 85°C, cooling at 40°C for 30 seconds. Tm (melting point) values for GSK3β specific polymorphisms; 47.1°C in A/A 530 channel for wild type (normal allele) for rs17183904 polymorphism, 55.7°C for the corresponding mutant allele G/G; 63.1°C in the C/C 530 channel for the normal allele for rs17183897 polymorphism, 55.2°C for the corresponding mutant allele T/T; 60.6°C in A/A 530 channel normal allele for rs34009575 polymorphism, 55.2°C for the corresponding mutant allele T/T; 51.6 °C in the A/A 530 channel for normal allele for rs34002644 polymorphism; 56.9°C for the corresponding mutant allele T/T; 63.9°C in the A/A 530 channel for the normal allele for rs17183890 polymorphism and 59.3°C for the corresponding mutant allele G/G.

Statistical Method

SPSS 18.0 statistical program was used in the analysis. Numerical variables are shown as minimum-maximum values, mean and standard deviation, and categorical variables as % (percent). The Kolmogorov-Smirnov test and Histograms were used to assess whether the data fit the normal distribution. A student t test was used for comparison of two independent groups in normal distributions. Hypotheses were bidirectional and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Sociodemographical, Clinical, and Genotypic Characteristics of the Sample Population

When the sociodemographic characteristics of the 100 patients were examined, it was revealed that 69 (69%) were women, approximately half was married (51%, n = 51), and primary school graduates (43%, n=43). All of the patients had bipolar disorder type-1 diagnosis. The mean age of the patients was 41.1 ± 10.3 years and the mean age of disease onset was 24.5 ± 8.2 years. Thirty four percent of the patients were using an antipsychotic drug combined with lithium, while 27% were using lithium, antipsychotics, and mood stabilizers. Fifteen percent of the patients were using lithium combined with mood stabilizers without antipsychotics, and only 11% were on lithium monotherapy. The mean Lithium Treatment Response Scale scores were 4.9±1.8 points (Table 1 and Table 2).

When the heterozygosity rates of the GSK-3β polymorphisms of the sample were evaluated, rates were determined as 2% (n=2, AG) for rs17183904, 9% for rs17183890 (n=9, AG), 9% for rs34009575 (n=9, AT), 1% for rs17183897 (n=1,

Table 1. Sociodemographical Characteristics of the Sample

Variable	n	%
Gender		
Female	69	69
Male	31	31
Marital Status		
Married	51	51
Single	37	37
Widowed	12	12
Level of Education		
Primary School	23	23
Elementary School	20	20
High School	38	38
University or Higher Education	12	12

Table 2. Clinical Features of the Sample

Variable	Min-Max.	Mean	Standart Deviation
Age (years)	22-76	41.1	10.3
Age of Disease Onset (years)	14-49	24.5	8.2
Duration of Disease (years)	4-36	17.3	7.1
Lithium Response Scale Score	1-9	4.9	1.8

CT), and 34% for rs34002644 (n=34, AT). No homozygous mutant allele was detected in the sample. The allele frequencies of GSK-3β single nucleotide polymorphisms were calculated as 1% for rs17183904, 4.5% for rs17183890 and rs34009575, 0.5% for rs17183897, and 17% for rs34002644.

Comparison of Lithium Treatment Response Scores with Sociodemographic, Clinical and Genotype Characteristics of the Cohort

No statistically significant associations were found between treatment response scores and gender (p = 0.41), marital status (p = 0.32), education level (p = 0.47), and the type of the first episode (p= 0.75) (Table 3). There was no association between the lithium-response scale scores and age (p = 0.78) and age of disease onset (p = 0.77) in the correlation analysis. When the homozygous and heterozygous genotypes of GSK-3β-specific SNPs were compared with lithium treatment response scores, the lithium treatment response score was found to be higher only in the patients harbouring the AG genotype in the rs17183890 polymorphism (p = 0.008, t: 2.71). For other polymorphisms (rs17183904, rs17183897, rs34009575, and rs34002644), there were no statistically significant differences in response to lithium treatment (Table 4).

Table 3. Comparison of Lithium Treatment Response Scores According to Sociodemographic and Clinical Features of the Patients

	Lithium Response Score Mean±S.D.	t/z	p
Gender			
Male	4.6±1.7	-0.8	0.41
Female	4.9±1.9		
Marital Status			
Married	5.1±1.9		
Single	4.8±1.7	1.2	0.32
Widowed	4.1±1.7		
Level of Education			
Primary School	4.7±1.3		
Elementary School	5.3±2.4	0.9	0.47
High School	4.6±1.8		
University or Higher Education	5.2±1.7		
Type of the First Episode			
Depression	4.8±1.9		
Mania/hipomania	5.1±1.9	-0.7	0.49

p<0.05 statistically significant

Table 4. Comparison of GSK-3β Specific Polymorphisms and Lithium Response Scale Scores

Polymorphism	Lithium Response Score Mean±S.D.	t/z	p
rs17183904			
AG	2.5±0.7	-1.9	0.06
AA	4.9±1.8		
rs17183897			
CT	6.0±1.8		
CC	5.0±1.8	0.55	0.59
rs34009575			
AT	5.5±1.5		
AA	4.9±1.9	0.9	0.36
rs34002644			
AT	5.1±1.9		
TT	4.5±1.6	1.2	0.23
rs17183890			
AG	6.6±1.9		
AA	4.5±1.7	2.7	0.008*

*p<0.05 statistically significant

DISCUSSION and CONCLUSIONS

In our current investigation conducted on patients with bipolar disorder and treated with lithium, we aimed to determine the association of lithium-treatment responses with 5 specific polymorphisms of GSK-3β, which are thought to be important in the pathogenesis of the disease and in the mechanism of action for lithium. We revealed that the lithium treatment response scores were higher in patients harbouring the GSK-3β rs17183890 AG genotype.

Since earlier times, genetic factors were assumed to be important in predicting lithium responses, but the first data was obtained from clinical parameters. Among the major clinical parameters thought to be important in lithium response; the presence of disease episodes with complete remission, euphoric mania, presence of bipolar disorder, and good lithium response in family members were defined as features predicting good clinical response. On the other hand, accompanying drug or alcohol-misuse and presence of mixed episodes or rapid cycling episodes were found to associate with poor response (Smith et al., 2010, Kessing et al., 2011, Sportiche et al., 2016). In our study, no statistically significant difference was found between the sociodemographic and clinical characteristics of the patients and their lithium response. This may be related to the facts that the sensitivity of the each of these clinical variables alone was not strong enough to predict lithium-response and also that the study population was not large enough to detect significant associations.

In recent years, studies on predicting the response to lithium have focused on pharmacogenetic mechanisms and revealed significant data. The first information on the lithium response was obtained from family and twin studies and reported by Mendlewicz et al. (1978), who demonstrated similar clinical efficacy of lithium in twins. In addition, Grof et al. (2002) also found that patient's lithium response was similar to the lithium response or unresponsiveness of the patients' relatives. In linkage analysis studies, data were gained in regard to 15q, 10p15, phospholipase C-G1 (PLCG1), and serotonin transporter genes (Oedegaard et al., 2016). Many of these studies were supported on the molecular level through the examination of the action mechanisms of lithium. Indeed, research

on lithium efficacy has focused on two main pathways, including phosphoinositol (PI) and GSK-3 cascades in recent years (Adli et al., 2007, Mitjans et al., 2015). In particular, the neuroprotective actions of lithium were reported to occur via inhibition of GSK-3β (Malhi and Outhred 2016).

One of the first studies on the relationship between lithium and GSK3β was reported by Beneddetti et al. (2005), which revealed a strong association between T-50C polymorphism and a good response to lithium. Interestingly, different studies demonstrated inconsistent findings on this relationship (Szczepankiewicz et al 2006, Adli et al 2007). In subsequent years, studies that investigated the association of different SNPs of GSK-3β with lithium responses were found to have a relationship between rs2199503 and rs6438552 and the response to treatment (Can et al., 2014). As a matter of fact, Mitjans et al. (2015) reported that GSK-3β rs1732170, rs11921360, and rs334558 polymorphisms were significantly associated with lithium treatment responses in their study. When we investigated the relationship between specific SNPs of GSK-3β and the response to lithium treatment in our study, we found that patients harbouring GSK-3β rs17183890 AG genotype had higher lithium treatment response scores. On the other hand, we did not find a significant association between other polymorphisms (rs17183904, rs17183897, rs34009575, and rs34002644) and lithium treatment response.

We think that our current study is valuable since it is the first in this field in our country to evaluate a bipolar disorder cohort treated with lithium. Thus, genetic test panels evaluating the therapeutic response to this particular polymorphism will improve the functioning of patients in terms of morbidity and treatment compliance by providing prediction of response to lithium in bipolar patients (Gao and Calabrese 2016, Pisanu et al., 2016). Although it is important to be the first study to evaluate the response of lithium treatment in regard to genetic configuration in our country sample, there are some limitations. For example, the sample consists of 100 patients and makes the generalization of the findings difficult. Furthermore, the sample consisted only of patients that had been using lithium for the last 1 year. In addition, the fact that patients who previously used lithium and left lithium treatment for different reasons were not included in the study can be regarded as another limitation. Some of these patients may have not responded to lithium therapy in the past and may be currently being treated with additional drugs. The inability to retrospectively determine the causes of lithium cessation in all patients makes it difficult to make further comments. Furthermore, the fact that only 5 polymorphisms associated with GSK-3β were evaluated is another drawback that makes it difficult for us to respond to all questions about the mechanism of action of lithium. For this reason, we believe that stronger findings can be found to determine the response to lithium therapy with genome-wide screening trials conducted in larger sample cohorts.

REFERENCES

Adli M, Hollinde DL, Stamm T et al (2007) Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta -50T/C single nucleotide polymorphism. Biol Psychiatry 62:1295-302.

Alda M (2015) Lithium in the treatment of bipolar disorder: pharmacology and pharmacogenetics. Mol Psychiatry 20:661-70.

Benedetti F (2005) Long-term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3-beta-50 T/C SNP. Neurosci Lett 376:51-5.

Can A, Schulze TG, Gould TD (2014) Molecular actions and clinical pharmacogenetics of lithium therapy. Pharmacol Biochem Behav 123:3-16.

Gao K, Calabrese JR (2016) Pharmacogenetics of lithium response: close to clinical practice? Lancet 387:1034-6.

Garfinkel PE, Stancer HC, Persad E (1980) A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. J Affect Disord 2:279–88.

Goodwin FK, Jamison KR (2007) Maintenance Medical Treatment. Manic Depressive Illness, 2.Baskı, IGoodwin FK, Jamison KR(Ed), New York. Oxford University Press, s. 797-843.

Gould TD (2006) Targeting glycogen synthase kinase-3 as an approach to develop novel mood-stabilising medications. Expert Opin. Ther Targets 10:377-92.

Gould TD, Manji HK (2005) Glycogen synthase kinase-3: a putative molecular target for lithium mimetic drugs. Neuropsychopharmacology 30:1223-37.

Gould TD, Chen G, Manji HK (2004) In vivo evidence in the brain for lithium inhibition of glycogen synthase kinase-3. Neuropsychopharmacology 29:32-8

Gould TD, Einat H (2007) Animal models of bipolar disorder and mood stabilizer efficacy: a critical need for improvement. Neurosci Biobehav Rev 31:825-31.

Grof P, Duffy A, Cavazzoni P et al (2002) Is response to prophylactic lithium a familial trait? J Clin Psychiatry 63:942–7.

Keller MB, Lavori PW, Coryell W ve ark. (1993) Bipolar I: a five-year prospective follow-up. J Nerv Ment Dis 181:238–45.

Kessing LV, Hellmund G, Andersen PK (2011) Predictors of excellent response to lithium: results from a nationwide register-based study. Int Clin Psychopharmacol 26:323-28.

Li X, Bijur GN, Jope RS (2002) Glycogen synthase kinase-3beta, mood stabilizers, and neuroprotection. Bipolar Disord 4:137-44.

Luca A, Calandra C, Luca M (2016) Gsk3 Signalling and Redox Status in Bipolar Disorder: Evidence from Lithium Efficacy. Oxid Med Cell Longev 2016:3030-547.

Maj M, Del Vecchio M, Starace F et al (1984) Prediction of affective psychoses response to lithium prophylaxis. The role of socio-demographic, clinical, psychological and bioloical variables. Acta Psychiatr Scand 69:37–44.

Maj M, Pirozzi R, Starace F (1989) Previous pattern of course of the illness as a predictor of response to lithium prophylaxis in bipolar patients. J Affect Disord 17:237–41.

Maj M, Pirozzi R, Magliano L (1996) Late non-response to lithium prophylaxis in bipolar patients: Prevalence and predictors. J Affect Disord 39:39–42.

Malhi GS, Outhred T (2016) Therapeutic Mechanisms of Lithium in Bipolar Disorder: Recent Advances and Current Understanding. CNS Drugs 30:931-49.

Mendlewicz J, Verbanck P, Linkowski P et al (1978) Lithium accumulation in erythrocytes of manic- depressive patients: an in vivo twin study. Br J Psychiatry 133:436-44.

Mendlewicz J, Fieve RR, Stallone F (1973) Relationship between the effectiveness of lithium therapy and family history. Am J Psychiatry 130:1011-3.

Mitjans M, Arias B, Jiménez E et al (2015) Exploring Genetic Variability at PI, GSK3, HPA, and Glutamatergic Pathways in Lithium Response: Association With IMPA2, INPP1, and GSK3B Genes. J Clin Psychopharmacol 35:600-4.

O'Connell RA, Mayo JA, Flatow L et al (1991) Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry 159:123-9.

Oedegaard KJ, Alda M, Anand A et al (2016) The Pharmacogenomics of Bipolar Disorder study (PGBD): identification of genes for lithium response in a prospective sample. BMC Psychiatry 5;16:129.

Pisanu C, Melis C, Squassina A (2016) Lithium Pharmacogenetics: Where Do We Stand? Drug Dev Res 77:368-73.

Rowe MK, Wiest C, Chuang DM (2007) GSK-3 is a viable potential target for therapeutic intervention in bipolar disorder. Neurosci Biobehav Rev 31:920-31.

Rybakowski JK, Suwalska A, Czerski PM et al (2005) Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. Pharmacological Reports 57:124–7.

Seretti A, Drago A, De Ronchi D (2009) Lithium Pharmacodynamics and Pharmacogenetics: Focus on Inositol Mono Phosphatase (IMPase), Inositol Poliphosphatase (IPPase) and Glycogen Sinthase Kinase 3 Beta (GSK-3 Beta). Current Medicinal Chemistry 16:1917-48.

Smith DJ, Evans R, Craddock N (2010) Predicting response to lithium in bipolar disorder: a critical review of pharmacogenetic studies. J Ment Health 19:142-56.

Sportiche S, Geoffroy PA, Brichant-Petitjean C et al (2016) Clinical factors associated with lithium response in bipolar disorders. Aust N Z J Psychiatry pii: 0004867416664794.

Stambolic V, Ruel L, Woodgett JR (1996) Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signalling in intactcells. Curr Biol 1;6:1664-8.

Swann AC, Bowden CL, Calabrese JR et al (1999) Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry 156:1264-6.

Swann AC, Bowden CL, Morris D et al (1997) Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry 54:37-42.

Szczepankiewicz A, Rybakowski JK, Suwalska A et al (2006) Association study of the glycogen synthase kinase-3beta gene polymorphism with prophylactic lithium response in bipolar patients. World J Biol Psychiatry 7:158-61.

Taylor MA, Abrams R (1975) Acute mania. Clinical and genetic study of responders and nonresponders to treatments. Arch Gen Psychiatry 32:863-5.

Urs NM, Snyder JC, Jacobsen JPR et al (2012). Deletion of GSK3β in D2R-expressing neurons reveals distinct roles for β-arrestin signaling in antipsychotic and lithium action. Proc Natl Acad Sci 109:20732-7.

Zhang K, Song X, Xu Y et al (2012) Continuous GSK-3β overexpression in the hippocampal dentate gyrus induces prodepressant-like effects and increases sensitivity to chronic mild stress in mice. J Affect Disord 146:45–52