Clinical, genetic, and epigenetic markers associated with lithium response in bipolar disorder

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SUMMARY

Bipolar disorder is a chronic and common psychiatric disease that causes poor quality of life and loss of functionality. Although lithium remains in the first place in the acute mania and maintenance treatment of bipolar disorder, its mechanism of action is still unclear. In addition, the response to lithium varies widely among patients. Up to 30-55% of patients with bipolar disorder do not benefit from lithium treatment or experience side effects that cause them to discontinue the treatment. As a result of the studies carried out to date, some clinical variables that predict the difference in lithium response among individuals have been identified, but consistent results have not been obtained. Difficulties in detecting lithium response over clinical variables, lack of consistent peripheral and neuroimaging markers, and familial clustering of the disease and treatment response led researchers to conduct genetic studies. Researchers have primarily focused on candidate gene studies. However, whole genome association studies have begun to be performed due to the inadequacy of candidate gene studies in detecting the lithium response, which is estimated to be polygenic. Data on lithium response and some single nucleotide polymorphisms, noncoding RNAs, and polygenic risk score associations were acquired from these studies. Recently, researchers have been working to elucidate the epigenetic mechanisms involved in gene-environment interaction. In this article, both clinical features and both prominent genetic and epigenetic markers associated with lithium response are reviewed and critical points that should be considered in future research are emphasized.

Key Words: Lithium, bipolar disorder, genetic, epigenetic, biomarker

INTRODUCTION

Bipolar disorder is a chronic disorder characterized by recurrences of depression and mania/hypomania, with patients being almost completely functional between episodes. Although the lifetime prevalence is approximately 1%, this rate has been found to be between 5-7%, especially after the disease was considered as a spectrum in studies conducted since the 2000s. Bipolar disorder has a recurrence rate of up to 90%, more than half of the patients experience a new episode of illness within the first 2 years and the disease has a high heritability rate of around 70% (1).

Following the discovery of the effects of lithium on psychiatric disorders by psychiatrist John Cade in 1949, lithium was approved in the USA for use in manic episodes in 1970 and for maintenance treatment four years later. Today, although the mechanisms of action are not clearly known, glycogen synthase kinase 3, inositol monophosphatase, adenylyl cyclase and G proteins have been identified as the 4 main targets of lithium. In addition, lithium shows indirect effects through many pathways such as antioxidant pathways, DNA methylation processes, production of stress proteins, inhibition of proinflammatory cytokines, lipid peroxidation, mitochondrial functions, remyelination, neuronal differentiation, apoptosis and circadian rhythm. An increasing number of publications have found that bipolar disorder is not only caused by alterations in neurotransmitter levels, but also by

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genetic disruptions affecting synapses and neuronal cycles. Therefore, lithium, which is thought to be effective on intracellular pathways that may control neuronal plasticity and the continuity of cellular life, still maintains its place as the gold standard treatment (2). However, lithium response in bipolar disorder shows significant differences and familial clustering. In this review, it was aimed to review the clinical features related with lithium response and current results related with genetic and epigenetic markers.

Clinical evaluation of lithium response

In lithium treatment, patients are divided into 3 groups: those who have no mood episodes during treatment with lithium (excellent responders), those who have a 50% or more decrease in the number of mood episodes compared to the period before lithium use (partial responders) and those who have less than 50% decrease in the number of mood episodes compared to the period before lithium use, those who have no change in the disease course or those who worsen (non-responders/poor responders) (3). Although lithium is among the first-line drug therapies in the treatment of bipolar disorder, only 30% of patients respond well to lithium and 40% of patients are nonresponsive to treatment and discontinuation of the drug due to side effects. These well-responsive patients are generally patients with a classic pattern of manic-depressive disorder in whom periods of complete remission are observed between periods of illness, who do not have a history of psychiatric comorbidity, who have a family history of frequent bipolar disorder and good response to lithium (2). In addition, in studies conducted to determine the clinical factors that may predict lithium response, predominance of manic episodes, late age of onset, hyperthymic personality characteristics were found to be associated with good response to lithium, whereas predominance of depressive episodes, rapid cyclicity, diagnosis of additional psychiatric illness, history of multiple hospitalizations, cyclothymia, depressive and anxious personality characteristics, cognitive impairment, severity of psychotic symptoms and family history of schizophrenia were found to be associated with poor response to lithium (3).

To date, the ALDA Scale has been used in the majority of studies conducted to evaluate lithium treatment response. This scale includes criterion A, in which the relationship between clinical improvement and treatment is scored between 0-10, and criterion B, in which the number and frequency of disease episodes in the treatment-free period, duration of treatment, compliance and additional treatments are evaluated. The total score is obtained by subtracting the score of criterion B from the score of criterion A. Scores of 7 and above are considered as lithium responders and scores below 7 are considered as lithium non-responders. However, recent studies have yielded results suggesting that the evaluation made especially with criterion B is prone to error (4). It should be kept in mind that possible errors in phenotypic classification may affect the reliability and validity of the findings obtained in genetic studies.

To date, different results have been obtained in studies in terms of clinical characteristics used in the evaluation of response to lithium. The difficulties in determining lithium response based on clinical variables, the lack of consistent peripheral and neuroimaging markers, and the familial clustering of the disease itself and the response to lithium treatment have pushed researchers to conduct genetic studies to evaluate lithium response.

Genetic and epigenetic markers of lithium response

1. Candidate Gene Studies

The first genetic studies for the evaluation of lithium response were conducted on candidate genes affecting neuronal transmission, intracellular signaling, neuroprotection and circadian rhythm, which are thought to be involved in the neurobiology of bipolar disorder and lithium mechanisms of action. There are many candidate genes that have been examined to date for this purpose and the most frequently emphasized genes are presented in Table 1.

The serotonin transporter is a key determinant involved in serotonin inactivation after release at synapses and is involved in the mechanism of action

of many antidepressants. Polymorphisms in the serotonin transporter-linked promoter region (*5-HTTLPR*) activity regulator gene have been associated with both bipolar disorder and major depression. Therefore, evaluations in terms of polymorphisms of this gene were thought to be important in predicting lithium response in bipolar disorder. *5-HTTLPR* contains a deletion/insertion variant leading to a 'short (s)' or 'long (l)' allele. In a clinical study, it was observed that in bipolar patients with prophylactic lithium use for more than 3 years, patients with the l/l variant tended to develop more mood episodes. In the study, it was found that the group with the l/l genotype had an earlier age of onset of disease and higher doses of lithium use in this group, but no statistically significant relationship was found between the difference in genotypes and lithium response (5). In another study, it was found that bipolar patients with s/s genotype showed worse lithium response (6).

In bipolar disorder, dopamine hypoactivity during periods of depression and dopamine hyperactivity during periods of mania are known. The dopaminergic system consists of dopamine receptors, dopamine transporter and destructive enzymes. Within this system, dopamine receptor 1 (*DRD1*) has an important role in prefrontal cortex activity. In a study in which lithium response and *DRD1* gene -48A/G polymorphism were evaluated in

Table 1. Candidate genes frequently studied in lithium treatment response, pathways and findings

Candidate Gen	Effective Pathway	Findings
5HTTLPR	Serotonin transport	Having the L/L genotype is associated with worse response (5), Having S/S genotype was found to be associated with worse response (6).
DRD1	The most common dopamine receptor in the central nervous system, neuronal development and emotional-behavioral processes	In genotyping for -48A/G polymorphism, G/G genotype was observed more frequently in partial and poor responders (7).
DRD2, DRD3, DRD4	Inhibitory-acting dopamine receptors	No relation was found with lithium response (8,9).
COMT	Catecholamine metabolism	Carrying the Val allele instead of the Met allele is associated with better lithium response (10). No association with lithium response (11).
GSK3	Energy metabolism, neuronal development, oxidative stress	Having the T allele was associated with poor response (12,13).
TPH1	Serotonin synthesis	Gene variants are weakly associated with lithium response (5).
INPP1	Phosphoinositol signaling pathway	C973A polymorphism is associated with better response to lithium (15).
BDNF	Neuronal proliferation, synaptic plasticity	Presence of Met allele in Val66Met polymorphism is associated with better response (16). However, there are studies that found no association (17).
XBP1	Regulation of MHC genes and endoplasmic reticulum stress response	Being a carrier of the C allele (-116C/G) is associated with a better response to lithium (49).
CREB1	cAMP pathway	CREB1-1H and CREB1-7H polymorphisms are associated with lithium response (12).
FYN	Cell growth control, ion transport	rs3730353 polymorphism is associated with lithium protective response (49).
TIM CLOCK PER3 ARNTL	Regulating circadian rhythm, cell survival, metabolism and behavior	6 single nucleotide polymorphisms in ARNTL and 3 haplotypes in TIM were associated with better lithium response (19).
MMP9	Endopeptidase acting outside the cell	No association with lithium response (16).
CACNG2	Calcium transport, synaptic response, neuroplasticity	rs22884017, rs2284018, rs5750285 polymorphisms are associated with lithium response (22).
COMT	Catecholamine metabolism	Carrying the Val allele rather than the Met allele is associated with better lithium response (10). No association with lithium response (11).
BCR	Neuronal development	Ser976 allele frequency is higher in lithium non-responders than in responders (50).
REV-ERB-Alfa	Circadian rhythm	Having an allele T for rs2314339 is associated with poor response to lithium (20). Rs2071427 and rs8192440 are associated with better response to lithium treatment (21).
GADL1	Coding of proteins involved in decarboxylation	rs17026688 and rs17026651 polymorphisms are associated with good response to lithium (23).
PDLIM5	Protein kinase C-related neurosignaling	No association was found between PDLIM5 polymorphisms and lithium response (51).

Abbreviations: 5HTTLPR: serotonin transporter-associated promoter region, DRD: dopamine receptor, GSK: glycogen synthase kinase, TPH: tryptophan hydroxylase, INPP: inositol polyphosphate 1 phosphatase, BDNF: Brain-derived neurotrophic factor, XBP: X-Box binding protein, CREB: cAMP-responsive element-binding protein, ARNTL: aryl-hydrocarbon receptor core tranclocator-like protein, MMP: matrix metalloproteinaze, CACNG: calcium channel voltage-dependent gamma subunit, COMT: catechol-o-methyltransferase, BCR: breakpoint cluster protein, GADL: glutamate decarboxylase-like.

bipolar disorder, G/G genotype was found at a lower rate in excellent responders compared to partial responders and non-responders (7). Dopamine receptor 2 (*DRD2*) agonists show antidepressant and antagonists show antimanic effects. Dopamine receptor 4 (*DRD4*) also has similar activities. Therefore, *DRD2* and *DRD4* gene variants were also examined to evaluate lithium response in bipolar disorder, but no significant relationship was found between them and lithium response (8). Dopamine receptor 3 (*DRD3*) acts as both an autoreceptor and a postsynaptic receptor. This receptor is frequently located in the mesolimbic area, shows high affinity for dopamine and regulates the monoamine cycle. Therefore, *DRD3* polymorphisms thought to be related with lithium response were examined, but no relation was found with lithium response (9). Catechol-o-methyltransferase (COMT) enzyme is an enzyme that plays a role in the metabolism of catecholamines. Although there are studies in which no relation was found between COMT polymorphisms and the development of bipolar disorder, the presence of met allele was associated with susceptibility to the disease and rapid cyclicity in some studies. COMT enzyme activity is affected by Val158Met polymorphism. Val/Val genotype is associated with high, Val/Met genotype with moderate and Met/Met genotype with low enzyme activity. In bipolar disorder, Met/Met genotype resulting in low enzyme activity was found more frequently in the lithium non-responsive group (10). However, unlike these data, there are also studies in which no significant relationship was found between lithium response and COMT genotype (11).

Glycogen synthase kinase 3β (GSK-3β) regulates many pathways such as energy metabolism, oxidative stress, neuroplasticity, protein synthesis etc. by inactivating glycogen synthase enzyme. GSK-3β inhibition is one of the main pathways in the mechanism of action of lithium. In studies, having TT genotype in rs334558 and rs6438552 polymorphisms associated with transcriptional power for GSK-3β was associated with worse lithium response than having CC genotype. After statistical adjustments, it was found that this effect persisted only for the rs334558 polymorphism. Having the C allele was found to be associated with lower enzyme activity and having the T allele was found to be associated with stronger transcription of GSK-3β, stronger enzyme activity as a result of hyperphosphorylation and neurodegeneration (12,13). In the first clinical study evaluating the relationship between lithium response and genetic markers in our country, the relationship between 5 different polymorphisms for GSK-3β and lithium response in patients with bipolar disorder was examined and it was observed that only patients with rs17183839 AG genotype had higher lithium response scores determined by ALDA Scale (14).

The other main pathway of action of lithium is the changes it induces through the second messenger system. The enzyme inositol-polyphosphate 1-phosphatase, which is part of the phospholipase C system and involved in dephosphorylation, is encoded by INPP-1. The frequency of having a C to A transversion in this gene region and having the 973A allele is higher in the lithium-responsive group in bipolar disorder compared to the lithium non-responsive group and healthy controls. However, similar results could not be obtained when this study conducted among 23 bipolar disorder patients and 20 healthy controls was repeated in a larger sample (15).

Brain-derived neurotrophic factor *(BDNF*) has important roles in neuronal proliferation and synaptic plasticity processes. It is known that BDNF levels decrease during manic or depressive episodes of bipolar disorder and are similar to healthy controls outside of the episode periods. Having the Val allele for *BDNF* has been associated with many outcomes such as development of bipolar disorder, rapid cycling and better cognitive functions. The presence of Met allele in Val66Met polymorphism in bipolar disorder was found to be associated with better lithium response (16), but there are also studies in which no association was found (17). One of the most striking results of these studies is that simultaneous presence of the s allele for the serotonin transporter *5HTTLPR* and the Val/Val genotype for BDNF was found to be associated with a 70% rate of lithium non-response (18). This seems to point to the geneXgen interaction and the importance of molecular level studies in revealing more mechanisms.

In bipolar disorder, there are irregularities in circadian rhythms, sleep/wake cycles and related hor-

monal systems. Biological rhythms are regulated by clock genes. Lithium is known to prolong the circadian period. Therefore, polymorphisms in circadian locomotor output cycle caput (*CLOCK*), aryl-hydrocarbon receptor core translocator-like (*ARNTL*), timeless circadian clock (*TIM*) and periodic circadian clock (*PER 3*) genes, which are among clock genes related with circadian rhythm, were examined and *ARNTL* and *TIM* polymorphisms were found to be related with lithium response (19).

In a study evaluating lithium response in bipolar disorder, carrying a homozygous C allele at rs 6438552 for GSK-3β and a homozygous A allele at rs2071427 for nuclear receptor subfamily 1 group D member 1 (*NR1D1*), which encodes Rev-Erbα involved in circadian rhythm regulation, was associated with being in the 75% lithium-responsive group. On the contrary, carrying homozygous T allele at rs6438552 and homozygous G allele at rs2071427 was associated with being in the 44% lithium-responsive group (20). Rev-Erbα, which is stable when phosphorylated under normal conditions, becomes dephosphorylated and disintegrates as a result of lithium inhibition of GSK-3β, which phosphorylates it. Having the rs2071427 variant in *NR1D1* results in structurally different Rev-Erbα production. This variant form lacks amino acids, proteins and additional sequences targeted for phosphorylation by GSK-3β. This makes variant Rev-Erbα a poor substrate for GSK-3β and the protein becomes more stable than the full-length form. Thus, this new configuration, which seems to be against the effects of lithium, provides regulatory results for circadian rhythm (21). However, the number of studies examining the relationship between lithium response and circadian rhythm genes in bipolar disorder is very limited.

Recently, the calcium channel γ2 subunit (*CACNG2*) gene has been associated with the development of both schizophrenia and bipolar disorder. The fact that this gene is involved not only in disease development but also in processes such as synaptic response and neuroplasticity has made this gene a candidate gene to be used in the evaluation of lithium response. In a study combining two cohort samples in which post-mortem prefrontal cortex samples of schizophrenia and bipolar disorder patients and control group were examined, it was reported that having C allele and CC genotype for rs2284017 for *CACNG2* in both cohorts, and for rs2284018 and rs5750285 polymorphisms in different cohort groups may be associated with better lithium response (22).

In addition to the candidate genes shown in Table 1, clinical studies have been conducted on many other genes and related polymorphisms. Candidate gene studies have revealed a number of associations between the polymorphism of a particular gene and lithium response. However, the number of candidate genes that have shown significance in more than two studies and whose results can be replicated is very low. With regard to lithium, single nucleotide polymorphisms of a particular gene can each explain a small proportion of the total variance in lithium response, at best around 1%.

2. Genome-Wide Association Studies (GWAS)

Researchers who think that simultaneous evaluation of multiple genes and multiple variants within these genes would be more effective in the examination of lithium response, which is thought to be polygenic, have turned to genome-wide association studies that allow whole genome examination (16). Polygenic analyses are computational methods that help quantify the effects of multiple independent genetic variants across the entire genome on a clinical outcome, especially in diseases with complex genetic features. A successful polygenic model can help detect disease risk at an early stage, confirm the diagnosis, and determine treatment response and disease course.

To date, there are a total of 5 genome-wide association studies on lithium response (23-27). These studies are summarized in Table 2. In GWASs, which were initially conducted in small samples, no single nucleotide polymorphism was able to pass the genome-wide association threshold ($P<5x10^{-8}$). To address this sampling problem, in 2008 a group at the US National Institute of Mental Health (NIMH) interested in the genetics of mood disorders established the International Consortium for Lithium Genetics (ConLiGen). The first results of ConLiGen were published in 2012 and in a sample of more than 1200 patients, the *SLC4A10*

Table 2. Results of genome-wide association studies of lithium response

Study	Sample	Findings	Recommendations
Perlis et al. (2009) (23)	N=458 patients with bipolar disorder type I and type II were included.	No polymorphism crossed the genome-wide association threshold.	Polymorphisms in the GRIA2 gene encoding the glutamate AMPA receptor on chromosome 4q32 have been thought to be associated with lithium response.
Squassina et al. (2011) (24)	N=52 patients with bipolar disorder were included.	No polymorphism crossed the genome-wide association threshold.	Polymorphisms in the ACCN1 gene on chromosome 17q12 have been thought to be associated with lithium response.
Chen et al. (2014) (25)	N=294 bipolar type I patients were included.	The rs17026688 and rs17026651 polymorphisms on the GADL1 gene on chromosome 3p24.1 were associated with good response to lithium.	
Song et al. (2016) (26)	N=3874 patients with bipolar disorder were included. Lithium response was assessed by self-report in 2698 patients and clinically documented in 1176 patients.	No polymorphism crossed the genome-wide association threshold.	The rs116323614 polymorphism in the SESTD1 gene on chromosome 2q31.2 is thought to be associated with lithium response.
Hou et al. (ConLiGen) (2016) (27)	N=2563 patients with bipolar disorder were included.	Four polymorphisms (rs74795342, rs75222709, rs79663003, rs78015114) in 2 lncRNA-encoding regions (AL157359.3 and AL157359.4) on chromosome 21q21.1 were associated with lithium response..	

Abbreviations: AMPA: Alfa amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, GRIA: glutamate ionotropic receptor AMPA type subunit, ACCN: amiloride-sensitive cation neuronal channel, GADL: glutamate decarboxylase-like, SESTD: containing SEC14 and spectrin field, SLC: solute carrier gene.

gene, which encodes solute carrier family 4 of the sodium bicarbonate transporter family, was found to be associated with lithium response. This gene is located on chromosome 2q24 and is highly expressed in the cortex and hippocampus. This bicarbonate-related pathway plays an active role in the intracellular uptake of lithium (28).

In GWASs, the results obtained in only two studies were able to pass the genome-wide association threshold. The first of these studies was conducted by Chen et al. in 2014. In the study, only rs1702688 ($p=5.50 \times 10^{-37}$) and rs17026651 ($p=2.52 \times 10^{-37}$) polymorphisms in glutamate decarboxylase-like protein 1 (*GADL1*) introns on chromosome 3p24.1 were found to be associated with better lithium response. These polymorphisms were found to predict lithium response with a sensitivity of 93% and 86%, respectively, and similar results were obtained in the replicates performed for control. Among these polymorphisms, carrying the T allele for rs1702688 was associated with better lithium response than a different allele. Since the polymorphisms were concentrated on *GADL1*, local variants that may affect *GADL1* gene expression were evaluated in the study and 1 base deletion in *GADL1* intron 8 (IVS8+48delG) was found to be nonrandomly associated with rs17026688 polymorphism. Although the physiological effects of *GADL1* protein are not clearly known, it is thought to have similar effects to glutamate decarboxylase, which plays a key role in the glutamate cycle and γ-aminobutyric acid (GABA) biosynthesis. It has been suggested that these genetic alterations found for *GADL1* associated with lithium response may have effects on both structural and functional changes in excitatory/inhibitory neurotransmitter balance (23). In the GWAS with the largest number of participants conducted by ConLiGen (n=2563), rs79663003 ($p=1.3 \times 10^{-8}$), rs78015114 ($p=1.31 \times 10^{-8}$), rs74795342 ($p=3.31 \times 10^{-9}$) and rs75222709 ($p=3.50 \times 10^{-9}$) polymorphisms were found to be associated with lithium response. These polymorphisms are located in two long non-coding RNA (lncRNA) regions (AL157359.3 and AL157359.4) on chromosome 21 and their effects are not yet known. In the continuation of the study, 73 bipolar disorder patients receiving lithium monotherapy were followed up for 2 years. Lower recurrence

rates were found in patients carrying the polymorphisms and alleles associated with lithium response (27).

Despite all these attempts, in order to detect the effects of genetic variants with small effects in genome-wide association studies, samples ranging from hundreds of thousands to millions of participants are needed. As observed in the study conducted by Chen et al. when the current population was grouped according to ethnicity, the effects of some polymorphisms could be sustained only in certain groups (25).

The largest genomic dataset evaluating lithium response in bipolar disorder, including 47.465 single nucleotide polymorphisms, was analyzed using machine learning methods. In this analysis, which included participants from different regions, overlapping genetic variants associated with lithium response were found in two regions. These variants were most frequently associated with increased expression of postsynaptic membrane genes ankyrin (*ANK3*), *DISC1*, Homer scaffold protein (*HOMER1*), various glutamate and adhesion molecule-related genes, etc.). These genes have important roles in cellular excitation and plasticity. However, lithium response in bipolar disorder could not be predicted as a result of the whole data set analysis (29).

In a recent study, it was found that the schizophrenia polygenic risk score was associated with poor response to lithium in bipolar disorder, as approximately 68% similar genetic variation was found between schizophrenia and bipolar disorder. After the polygenic risk score was calculated, a meta-analysis based on single nucleotide polymorphism was performed within the same study. In this meta-analysis, genome-wide differences exceeding the association threshold were identified in 15 genetic regions. The genetic regions with the highest association were clustered in various human leukocyte antigen (HLA) genes. Two related functional networks were also identified. In these networks, tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4) and interferon-γ (IFN-γ) play an important role in the association with schizophrenia risk and lithium response. This result is thought to explain the findings observed clinically in the past such as i) severity of psychotic symptoms in bipolar disorder being inversely proportional to lithium response, ii) delayed resolution of psychotic symptoms in acute mania being associated with poor lithium response and iii) poorer response to lithium in patients with a family history of schizophrenia rather than bipolar disorder (30).

Since tissue compatibility antigens and inflammatory markers are prominent in lithium response in bipolar disorder, two genome-wide association studies conducted by ConLiGen were reanalyzed in terms of HLA regions. As a result of this study, no HLA variant exceeded the association threshold as a result of Bonferroni corrections. However, in the first study, for *HLA-DRB1*, tyrosine or leucine at position 37, arginine at position 71 and phenylalanine at position 67 were associated with better lithium response. For *HLA-DQB1*, leucine at position 26 was associated with poor lithium response. However, none of these results were replicated in the second study group. Analyzing both studies together identified two signals that almost reached the threshold. *HLA-DQB1*02* heavy chain was associated with lithium unresponsiveness. For *HLA-DRB1*, carrying alanine or leucine at position 74 is associated with better lithium response, while carrying arginine or glutamic acid is associated with poorer lithium response. In the past period, in diseases such as inflammatory polyarthritis, multiple sclerosis, Graves' disease, hepatitis C with different complex genetic mechanisms, associations of changes in similar HLA regions with disease risk, disease course and treatment response have been shown (31).

As with schizophrenia, bipolar disorder is genetically correlated with major depression at a rate of approximately 47%. In a study examining the effect of major depression polygenic risk score on lithium response in bipolar disorder, increased polygenic loading for major depression was associated with poor treatment response in bipolar disorder. In this study, more significant results were obtained in a multi-ethnic and European population. In the Asian group, the association between polygenic risk score for depression and lithium response was closer to borderline significance. This difference is mainly due to the fact that the Asian group had almost 10 times fewer participants in the sample than the European group. However, the polygenic

risk score was previously determined by alleles from the ConLiGen cohort. However, in the present study, the genetic correlation for depression between the East Asian and European groups ranged between 0.33-0.41. Therefore, it has been suggested that the risk score may have underestimated the effect in the Asian group. This study supports the findings that i) patients with good lithium response show a manic episode-dominant disease course, ii) lithium is more successful in preventing manic episodes than depression, and iii) accompanying features of different genetic psychiatric diseases are associated with worse lithium response (32).

A combined polygenic risk score for major depressive disorder and schizophrenia was calculated to assess lithium response in bipolar disorder. The 10% group with the lowest combined score had approximately 2.5 times better lithium response than the 10% group with the highest combined score. In these combined risk score variants, genes associated with metabolic diseases such as histone biology and diabetes were found to be the most common. In addition, no association was found between bipolar disorder polygenic risk score and lithium response. The reason for this has been suggested that polygenic risk scores in schizophrenia and depression are calculated in larger samples (33). Although research on polygenic risk calculation is promising, the success of the polygenic score is related to the strength of initial genome-wide association studies, homogeneity of the population and sample size. The scarcity of previous genome-wide association studies in bipolar disorder, the heterogeneous nature of the disease and the small sample size make it difficult to conduct polygenic research and obtain new data.

3.Epigenetic Markers

Epigenetic alterations are heritable changes in gene expression or cellular phenotype caused by mechanisms independent of DNA nucleotide sequence. Histone modification, DNA methylation, genomic imprinting and regulation mediated by non-coding RNAs are the most important epigenetic mechanisms that cause changes in gene expression due to environmental effects during development. For this reason, studies related to lithium and epigenetic changes in bipolar disorder, which is thought to have polygenic multifactorial inheritance, have started to be conducted in the last 5 years.

Studies examining methylation changes in bipolar disorder patients using lithium have mostly focused on global DNA methylation changes. In a study evaluating global methylation changes, lower global methylation rates were found in bipolar disorder patients using antipsychotic drugs compared to patients treated with mood stabilizers. In another study evaluating global methylation, decreased methylation was found in patients using lithium monotherapy compared to patients using lithium-valproic acid combination and healthy controls. However, no relationship was found between lithium response and global methylation levels. Consistent and reproducible definitive results could not be obtained in studies conducted in small samples. There are single gene studies reporting methylation changes in BDNF promoter region, prodynorphin (*PDYN*) promoter region and two *ARNTL* CpG islands in bipolar disorder patients with lithium use. Generally, lower methylation rates were observed in BDNF and *PDYN* promoter regions in patients using lithium (34).

There are two genome-wide studies analyzing the relationship between lithium and methylation changes in bipolar disorder. In the first one, patients with bipolar disorder exposed to different psychotropic drugs were analyzed in terms of methylation changes. At the end of the study, it was found that valproic acid and quetiapine caused methylation changes, but no such effect was observed in lithium (35). The second study was the first genome-wide analysis of the relationship between lithium response and methylation changes in patients with bipolar disorder. In this study, 15 patients diagnosed with bipolar disorder type 1 with good lithium response and 11 patients diagnosed with bipolar disorder type 1 without lithium response were included. At the end of the study, 111 different methylation sites were found between the two groups, only 7 of which were statistically significant. 17% of these changes distributed on 14 different chromosomes were in the promoter region, 39% in the intergenic region, 11% in the exonic region, 27% in the intronic region and 6% in

the non-coding region. Three of these 7 regions with different methylation changes were found to be associated with defined genes such as eukaryotic translation initiation factor 2B epsilon subunit (*EIF2B5*) and Ral GTPase activating protein catalytic alpha 1 subunit (*RALGAPA1*) (36).

Micro RNAs (miRNAs) constitute a subclass of non-coding RNAs. These short RNA molecules function specifically as post-transcriptional regulators. Previous studies have found that miRNAs are associated with complex diseases such as cancer, psoriasis and treatment response. In addition, miRNAs are also involved in synaptic plasticity and brain development. In a genome-wide association study for bipolar disorder, 9 miRNAs were associated with the development of bipolar disorder. These 9 candidate miRNAs were also analyzed for their association with lithium response in bipolar disorder and only miR-499a was found to be associated with lithium response. In the same study, other genome-wide miRNAs were analyzed and 15 miRNAs were found to be associated with different phenotypes in terms of lithium response, but after multiple testing corrections, no significant association was observed in any of them, including miR-499a. Although not statistically significant, the strongest associations with lithium response were found between miR-633 and miR-607 (37). Recent studies have shown that miR-499 targets the voltage-dependent L-type calcium channel subunit beta-2 (*CACNB2*), which is thought to play an important role in the development of bipolar disorder. *CACNB2* is the regulatory subunit of these calcium channels and is involved in depolarization-related calcium entry into neurons. miR-499a deficiency was thought to be associated with increased *CACNB2* and increased intracellular calcium levels. In another study in which postmortem examinations were performed, expression changes were found for miR-499a in patients with bipolar disorder (38). miR-633 and miR-607 have more limited information in the literature. miR-633 deletion has been shown to play a role in the development of lupus by activating the AKT/mTOR pathway in lupus. The AKT family ranks high in candidate gene research for the development of bipolar disorder and schizophrenia. One of the proteins with a key role in this pathway is phosphotidylinositol-3-kinase (PI3K), which is involved in cell survival, proliferation, protein synthesis and vesicle transport. PI3K activates AKT, and activation of the pathway signals the release or inhibition of many molecules such as insulin, glucose, cytokines and growth factors. The AKT/mTOR-related risk locus has shown stronger overlaps in schizophrenia and bipolar disorder with psychosis (39). In chronic lymphocytic leukemia, if miR-607 accessibility is blocked, activation of the WNT/β-Catenin pathway was found and miR-607 was thought to suppress the progression of this cancer type. In the inactive WNT/β-Catenin pathway, β-Catenin is bound to a complex including GSK-3β, which has an important role in the mechanisms of action of lithium, and the intracellular stabilization of β-Catenin is regulated by this complex (40). Therefore, miR-607, which is thought to have an effect on this basic mechanism mediated by GSK-3β, may play an important role in predicting lithium response in bipolar disorder. In a recent study conducted in our country, the relationship of 13 miRNAs including miR-499, miR-607 and miR-633 with lithium response was examined in 66 euthymic bipolar disorder patients with lithium use and 66 healthy controls, but no statistically significant results were obtained. In the same study, a decrease in miR-155-5p levels was found in bipolar disorder patients compared to healthy controls (41).

In the first genome-wide association study using next-generation sequencing in lymphoblastoid cell lines, 12 lithium-responsive and 12 lithium non-responsive patient samples were analyzed. As a result of the examinations, changes in miR-320a and miR-155-3p expression were detected. A decrease in miR-320a expression, which is involved in neuronal differentiation, apoptosis and synaptic plasticity processes, and an increase in the expression of calpain small subunit 1 (CAPNS1) and ribosomal protein S16 (RSG16) genes involved in circadian rhythm were observed. CAPNS1 has regulatory functions for neuroprotective calpain-1 and neurodegenerative calpain-2. There is no research on CAPNS1 in bipolar disorder yet. RSG16 is involved in the circadian regulation of cyclic AMP (cAMP) in the suprachiasmatic nucleus (42). Circadian rhythm irregularities are known to predict relapses in bipolar disorder. There are different results regarding the role of miR-155 in the inflammatory response. Some studies suggest that miR-155 suppresses the inflammatory response through negative feedback (43), while others suggest that it has

a proinflammatory role through activation of the interleukin-1 pathway (44). SP4 is a transcription factor and is involved in many complex neuronal processes such as dendritic development, hippocampal long-term potentiation, memory, etc. There are studies suggesting that SP4 gene has a role in both bipolar disorder and schizophrenia predisposition (45). SP4 degradation in neurons by calcium-activating proteases in response to glutamate-induced cytotoxicity has been demonstrated. Calcium-dependent regulation and recent post-translational modifications leading to ubiquitin-dependent degradation are key pathways for SP4 stabilization in neurons. Non-depolarization of the membrane and inhibition of N-methyl-D-aspartate receptor (NMDA)-related signaling increase SP4 phosphorylation and accelerate SP4 degradation. In a postmortem study of bipolar disorder patients and controls, most (80%) of whom died by suicide, decreased SP4 levels were found in the cerebellum and prefrontal cortex of bipolar disorder patients. In addition, a decrease in SP4 mRNA levels was observed in the prefrontal cortex, but not in the cerebellum. Therefore, when all results were analyzed, it was thought that decreased SP4 levels in the cerebellum may be related to posttranscriptional reasons. In the later part of the study, neurons were treated with lithium under non-depolarized conditions and it was shown that lithium prolonged SP4 half-life and partially stabilized SP4 which would be rapidly degraded by ubiquitin proteasome complex. No similar effect was observed when neurons were treated with 3 specific GSK-3 inhibitors other than lithium. This effect observed under in vitro conditions and at doses higher than therapeutic doses limits the generalizability of the results (46). Postmortem examinations showed that SP4 S770 phosphorylation increased in the cerebellum of patients with bipolar disorder and severe schizophrenia who died with suicide attempt. In addition, in this study, a decrease in SP4 levels and an increase in SP4 phosphorylation in the prefrontal cortex and cerebellum were found independent of the disease course. Increased phosphorylated SP4/SP4 ratio in the cerebellum was correlated with more severe negative symptoms in schizophrenia patients (47).

The results of the first study in which transcriptomic data sets obtained from lymphoblastoid cell lines were used to evaluate lithium response in bipolar disorder were published in 2023. This study included 9 lithium-responsive and 10 lithium non-responsive bipolar disorder patients and 10 healthy controls. The study was strengthened by adding the results of 12 lithium-responsive and 12 lithium non-responsive bipolar disorder patients from another cohort study. RNA sequencing and machine learning methods were used to identify differentially expressed genes. Increased expression of genes related to immunoglobulin light and heavy chain regions was observed in the lithium non-responsive group compared to the lithium-responsive group. Unlike immunoglobulin genes, the expression of HLA-U, zinc finger protein 300 (*ZNF300*) and T cell receptor-associated transmembrane adaptor 1 (*TRAT1*) genes decreased in the lithium-responsive group. These genes are associated with major histocompatibility complex (MHC) and neurodevelopment. In addition, interleukin-18 (IL-18) was suppressed in the lithium non-responsive group. Proinflammatory IL-18 is known to be involved in neuroinflammation processes. When the results obtained from this study were compared with the results of previous GWAS, it was seen that there were commonalities with a total of 5 studies in terms of one or two differently expressed gene regions. Regulator of synaptic membrane exocytosis 1 (*RIMS1*) and *BCL11B* were reported as the most common genes. Previous studies have shown changes in *RIMS1* expression in schizophrenia and autism. *BCL11B* is known to be involved in neuronal cycles and to have immunologic functions (48).

Working on lymphoblastoid cell lines is more economical than working with induced pluripotent stem cells and provides convenience in terms of standardization and sampling. However, the possibility that these changes detected in the periphery may not reflect the effects in the brain and the small sample size are the most important limitations of the studies (37). The miRNA analyses are still in their infancy because there is no miRNA database for all normal tissues, tissue-specific miRNAs cannot be studied, and perhaps miRNAs that are expressed at the onset of the disease but whose effect on drug response is still ongoing may be ignored. However, the results obtained so far suggest that miRNAs may have effects on the

development of bipolar disorder, the course of the disease and lithium treatment response.

The results of studies conducted to predict response to lithium, the gold standard treatment for bipolar disorder, are currently not very reproducible and generalizable. Differences in the methods used in the evaluation of clinical response to lithium in the studies, the absence of evaluations for subthreshold symptoms, whether the patients were under monotherapy for lithium, the relationship between lifetime lithium levels and lithium response, which mood episodes lithium inhibits more, ignoring the effect of life events on the process, not including patients whose lithium treatment was terminated in the past due to side effects but who had good lithium response, etc. It was thought that factors may be the reason for the inconsistencies in the results. However, the results obtained from the studies conducted to date make some pathways candidates for detailed investigations. Recently, multiomics approaches have been tried in pluripotent stem cell lines to evaluate lithium response in bipolar disorder. In order to better predict lithium response in the future and to create personalized treatment methods, genetic and epigenetic studies to be conducted in large samples, in well-defined bipolar disorder groups and with advanced techniques are needed. It is thought that the data to be obtained from such studies may help to better understand the etiology of bipolar disorder, which is a chronic disease, and to predict the treatment responses of patients more easily. Personalized treatments may increase the likelihood of patients recovering in a shorter period of time by experiencing fewer side effects with less amount and appropriate medication. Thus, patients' medication adherence may increase, and the ability to identify the drug that may be more effective in preventive treatment may reduce the frequency of attacks. It is thought that all these gains may contribute to alleviating the disease burden of bipolar disorder, which can lead to serious functional losses and death.

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