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LEADING ARTICLE

Genetic Influences on Response to Mood Stabilizers in Bipolar Disorder

Current Status of Knowledge

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Abstract Mood stabilizers form a cornerstone in the long-term treatment of bipolar disorder. The first representative of their family was lithium, still considered a prototype drug for the prevention of manic and depressive recurrences in bipolar disorder. Along with carbamazepine and valproates, lithium belongs to the first generation of mood stabilizers, which appeared in psychiatric treatment in the 1960s. Atypical antipsychotics with mood-stabilizing properties and lamotrigine, which were introduced in the mid-1990s, form the second generation of such drugs. The response of patients with bipolar disorder to mood stabilizers has different levels of magnitude. About one-third of lithium-treated patients are excellent responders, showing total prevention of the episodes, and these patients are clinically characterized by an episodic clinical course, complete remission, a bipolar family history, low psychiatric co-morbidity and a hyperthymic temperament. It has been suggested that responders to carbamazepine or lamotrigine may differ clinically from responders to lithium. The main phenotype of the response to mood stabilizers is a degree of prevention against recurrences of manic and depressive episodes during long-term treatment. The most specific scale in this respect is the so-called Alda scale, where retrospective assessment of lithium response is scored on a 0–10 scale. The vast majority of data on genetic influences on the response to mood stabilizers has been gathered in relation to lithium. The studies on the mechanisms of action of lithium and on the neurobiology of bipolar disorder have led to the identification of a number of candidate genes. The genes studied for their association with lithium response have been those connected with neurotransmitters (serotonin, dopamine and glutamate), second messengers (phosphatidyl inositol [PI], cyclic adenosine-monophosphate [cAMP] and protein kinase C [PKC] pathways), substances involved in neuroprotection (brain-derived neurotrophic factor [BDNF] and glycogen synthase kinase 3-β [GSK-3β]) and a number of other miscellaneous genes. There are no published pharmacogenomic studies of mood stabilizers other than lithium, except for one study of the X-box binding protein 1 (*XBP1*) gene in relation to the efficacy of valproate. In recent years, a number of genome-wide association studies (GWAS) in bipolar disorders have been performed and some of those have also focused on lithium response. They suggest roles for the glutamatergic receptor AMPA (*GRIA2*) gene and the amiloride-sensitive cation channel 1 neuronal (*ACCN1*) gene in long-term lithium response. A promise for better elucidating the genetics of lithium response has been created by the formation of the Consortium on Lithium Genetics (ConLiGen) to establish the largest sample, to date, for the GWAS of lithium response in bipolar disorder. The sample currently comprises more than 1,200 patients, characterized by their response to lithium treatment according to the Alda scale. Preliminary results from this international study suggest a possible involvement of the sodium bicarbonate transporter (*SLC4A10*) gene in lithium response. It is concluded that the pharmacogenetics of response to mood stabilizers has recently become a growing field of research, especially so far as the pharmacogenetics of the response to lithium is concerned. Clearly, the ConLiGen project is a highly significant step in this research. Although the results of pharmacogenetic studies are of significant scientific value, their possible practical implications are yet to be seen.

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1 The Concept of a Mood Stabilizer

Bipolar disorder is a serious mental illness, with a worldwide prevalence of 2–5 % of the population [1]. The main symptoms are recurrent manic and depressive episodes. The disorder imposes a great burden on both patients and their families, and approximately 10–20 % of patients commit suicide over the course of their illness [2]. There are two important features of the illness. First, that a genetic predisposition is one of the highest among psychiatric disorders and the heritability index is estimated to be 0.85 [3]. Second, that adequate treatment may allow for long-term remission and good functioning in a majority of patients.

For the treatment of bipolar disorder, drugs, collectively known as mood stabilizers, play the most important role. A mood stabilizer can be defined as a drug that, if used as monotherapy it (1) acts therapeutically in mania and/or in depression; (2) acts prophylactically against manic and/or depressive episodes, as demonstrated in a trial of at least 1 year's duration; and (3) does not worsen any therapeutic or prophylactic aspect of the illness outlined above. A classification of mood stabilizers based on the chronology of their introduction for the treatment of bipolar disorder has been proposed by the author of this article [4].

The introduction of the first generation of mood stabilizers fulfilling the criteria mentioned above occurred nearly half a century ago. The mood-stabilizing property of lithium was first suggested in the early 1960s [5], for valproates at the turn of the 1960/1970s [6] and for carbamazepine in the early 1970s [7]. The first suggestion that the atypical antipsychotic drug, clozapine, had a mood-stabilizing action was advanced in the mid-1990s [8], and in the following years, mood-stabilizing properties have been confirmed for such atypical antipsychotic drugs such as olanzapine, quetiapine, aripiprazole and risperidone [4, 9, 10]. A suggestion for lamotrigine to be a mood-stabilizing drug was made in the early 2000s [11]. It has therefore been proposed to name lithium, carbamazepine and valproate as first-generation mood stabilizers, and atypical antipsychotics and lamotrigine as second-generation mood stabilizers [4].

For a prophylactic effect of existing mood-stabilizing drugs a concept of 'predominant polarity' (manic or depressive) can be adopted [12]. Clozapine, which exerts strong antipsychotic and antimanic effects, may be placed at one end of the continuum, being 'a mood stabilizer from above' where the drug has the best effect when administered during a severe manic episode of the illness, especially one with psychotic features. Other atypical antipsychotics, such as olanzapine, aripiprazole and risperidone, belong to a similar category. Lithium, carbamazepine and valproate also have stronger antimanic than antidepressant activity although, of these three first-generation mood stabilizers, lithium exerts the most pronounced antidepressant action. Quetiapine has turned out to be the most balanced mood stabilizer, being equally effective against both psychopathological poles [13]. Finally, lamotrigine may be placed on the opposite pole of this continuum, as it exerts a predominantly antidepressant effect, being 'a mood stabilizer from below' and its administration typically starts during a depressive episode [14].

2 Clinical Features of Responders to Mood Stabilizers

2.1 Excellent Lithium Responders

Fifty years after John Cade's original paper [15] that introduced lithium into the modern psychiatric armamentarium, the Canadian psychiatrist, Paul Grof [16] proposed the term "excellent lithium responders" for patients in whom lithium monotherapy has dramatically changed their lives by the total prevention of further episodes. In our subsequent study we demonstrated that patients on lithium therapy who do not experience affective episodes for 10 or more years (excellent lithium responders) make up one-third of lithium-treated patients [17]. Recently, Grof [18] has concluded that the best response to lithium is associated with clinical features of an episodic clinical course, complete remission, bipolar family history and low psychiatric co-morbidity similar to those described by Kraepelin [19] as *manisch-depressives Irresein*. By using the Temperament Scale of Memphis, Pisa, Paris and San Diego – Autoquestionnaire (TEMPS-A) in longitudinally lithium-treated patients we have also demonstrated that the response to lithium correlated significantly positively with a hyperthymic temperament score and negatively with anxiety cyclothymic and depressive temperaments scores [20].

2.2 Comparison of Lithium Responders with Responders to other Mood Stabilizers

The studies on excellent lithium responders indicate that monotherapy with a mood stabilizer (lithium) can yield optimal results (total prevention of recurrences) in about one-third of bipolar disorder patients. It is probable that similar efficacy can be obtained by monotherapy with other mood stabilizers, although the clinical characteristics of such patients may differ from those of excellent lithium responders. However, the data in this respect are scarce.

The German MAP (Multicenter Study of Long-Term Treatment of Affective and Schizoaffective Psychoses) compared the differential efficacy of lithium and carbamazepine in a randomized clinical trial with an observation

period of 2.5 years. It was found that in patients with the classical form of the illness (bipolar I without mood-incongruent delusions and without co-morbidity) the prophylactic efficacy of lithium was superior to that of carbamazepine, while the opposite was true for patients with the non-classical form of the illness [21]. Therefore, it may be suggested that carbamazepine responders may have an atypical bipolar disorder, characterized by mood-incongruent delusions and co-morbidity. Older studies had suggested a good response to carbamazepine in bipolar disorder patients with concomitant structural brain abnormalities and pathologies revealed by EEG recording [22]. It is not known whether the clinical features of responders to carbamazepine are similar to those with another mood-stabilizing anticonvulsant drug, valproate.

Canadian authors attempted to delineate clinical and family history features of responders to lamotrigine in contrast to those of lithium. Clinically, the course of illness in lamotrigine responders was rapid cycling or chronic, while episodic in responders to lithium, and lamotrigine responders had higher co-morbidity of panic disorder and substance abuse compared with lithium responders. The relatives of lithium responders had a significantly higher risk of bipolar disorder, while relatives of lamotrigine responders had a higher prevalence of schizoaffective disorder, major disorder and panic attacks [23].

The clinical features of bipolar disorder patients responding to long-term treatment with atypical antipsychotics have not been sufficiently established. In the case of clozapine, it is suggested that the best prophylactic effect may be associated with greater severity of psychosis during an acute manic episode [24].

3 Measurement of Response to Mood Stabilizers

The main phenotype of response to mood stabilizers is a degree of prevention against recurrences of manic and depressive episodes during long-term treatment. As such, excellent lithium responders may constitute a genetically distinct phenotype that could be used in pharmacogenetic studies. Establishing the degree of response to a mood stabilizer in an individual patient requires a relatively long period of follow-up. This can be assessed either retrospectively or prospectively and the response can be expressed in either categorical or dimensional terms.

The lithium-treated patients in the Department of Adult Psychiatry, Poznan University of Medical Sciences who were involved in our pharmacogenetic studies had a duration of lithium prophylaxis of at least 5 years (5–27 years, mean 15 years) allowing us to retrospectively assess the degree of lithium response accurately. In our studies, excellent lithium responders were contrasted with patients showing only a partial response, i.e. a 50 % reduction in the episode index (number of episodes per year, compared with the pre-lithium period) and with those showing no response (a $>$ 50 % reduction, no change or a worsening in the episode index)[25]. In the majority of other papers the response to lithium has also been assessed retrospectively, although the criteria for response have been defined in various ways. Usually, two categories of patients (responders and non-responders) are compared. In some papers, the response to lithium has been established prospectively, by comparing patients in whom recurrence occurred within a period of prospective observation (usually 2–3 years) with those without such a recurrence [26].

Ten years ago, the Canadian researchers (Alda et al.) introduced a scale allowing quantitative retrospective assessment of the quality of prophylactic lithium response [27]. This scale is referred to as 'the Alda scale'. In this scale, criterion A rates the degree of response (activity of the illness while on adequate lithium treatment) on a 10-point scale. Criteria B1-B5 establish whether there is a causal relationship between the improvement and the treatment. Criterion B involves B1: the number of episodes off the treatment, B2: frequency of episode off the treatment, B3: the duration of treatment, B4: compliance during period(s) of stability, and B5: the use of additional medications during the periods of stability. The total score is obtained by subtracting B from A and is in the range of 0–10. Therefore, this scale allows for either a categorical assessment (i.e. below or above some cut-off point) or a dimensional assessment of lithium response. It has therefore been used in the Consortium of Lithium Genetics (ConLiGen) project aimed at performing a genome-wide association study (GWAS) in a large population of lithium-treated patients (preliminary results are discussed in Sect. 4.4), as well as in some other GWAS, and recent candidate gene studies.

4 Pharmacogenetics of Response to Lithium

The pharmacogenetic response to lithium was the topic of four excellent review papers published in the past 3 years [28–31]. These reviews mostly focused on candidate gene studies where candidate genes were selected, either on the basis of the mechanisms of action of lithium and/or the neurobiology of bipolar disorder. In one review [28], the results of susceptibility loci studies were also mentioned, and in another [29], gene expression studies in man and model organisms were described and discussed.

The following review of candidate genes will cover the reviews above, adding the results of some novel studies published in 2010–2012. While this issue is broad and may involve a great number of possible genes, attention has

been focused specifically on the genes on which some studies were performed. Also, GWAS carried out in recent years will be covered and discussed.

4.1 Studies on Candidate Genes of Lithium Response

4.1.1 Neurotransmitters

4.1.1.1 Serotonin The serotonergic system has long been implicated in the neurobiology of bipolar disorder and the mechanism of action of lithium [32]. A subject of special interest has been a functional promoter polymorphism of the serotonin transporter gene (*5-HTTLPR*) located on chromosome 17q12 where a short (s) allele is connected with lower activity of the gene. An s allele of *5-HTTLPR* has been associated with a predisposition to affective disorder, both bipolar and unipolar [33], and with a poor response to antidepressants in a Caucasian population [34]. That the s allele may be connected with prophylactic lithium non-response was demonstrated in several studies, including ours [35–37] but was not confirmed in two subsequent papers [38, 39].

Studies on an association between lithium response and the genes of the serotonergic receptors 5-HT_1, 5-$HT2_A$ and 5-$HT2_C$ have yielded negative results [40, 41]. On the other hand, one study on a polymorphism on the gene for tryptophan hydroxylase, the enzyme of serotonin synthesis, found a marginal association [42].

4.1.1.2 Catecholamines Severino et al. [43]. showed an association between bipolar illness and an A48G polymorphism of the dopaminergic receptor D_1 (*DRD1*) gene located on chromosome 5q35, and we have demonstrated an association of this polymorphism with lithium response [44]. Earlier studies on other dopaminergic system genes (*DRD2*, *DRD3* and *DRD4*) brought negative results [45, 46]. Also negative were results of studies on an association between lithium response and polymorphisms of genes coding enzymes of catecholamine metabolism such as monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT)[26, 47].

4.1.1.3 Glutamate Interest in the role of the glutamatergic system in the pathogenesis of bipolar illness and the mechanisms of action of lithium has been kindled recently, with special emphasis on such glutamate receptors as NMDA and AMPA. However, our study appears to be the only one to date [48]. We did not demonstrate any association between three polymorphisms in the NMDA receptor 2B subunit (*GRIN2B)* gene and lithium response.

The Src family, tyrosine kinase FYN, plays a key role in the interaction between brain-derived neurotrophic factor (BDNF) and the glutamatergic receptor NMDA. The *FYN* gene is located on chromosome 6q21. Our group showed an association between two polymorphisms of the *FYN* gene and bipolar disorder [49] but only a marginal association between the T/C polymorphism of this gene and lithium response [50].

4.1.2 Intracellular Second Messengers

4.1.2.1 Phosphatidyl Inositol Pathway The effect on the PI pathway has long been considered the most important mechanism of therapeutic action of lithium in bipolar disorder. A significant association with lithium response was obtained with a polymorphism of the inositol polyphosphate 1-phosphatase (*INPP1*) gene located on chromosome 2q32 [51]. Such an association with lithium response was also obtained in patients with co-morbid post-traumatic stress disorder [52], but this was not replicated in a study by Brazilian investigators [38].

Studies on the polymorphisms of other genes connected with the PI system, such as inositol monophosphatase2 (*IMPA2*) and diacylglycerol kinase eta (*DGKH*) genes, did not find any associations with lithium response [53, 54].

4.1.2.2 Cyclic Adenosine Monophosphate Pathway Lithium also exerts an effect on the cAMP pathway. Mamdani et al. [55] performed an association study with genes for cAMP-response binding protein (CREB) and found an association between bipolar disorder and lithium response and two polymorphisms of *CREB1* gene located at chromosome 2q32-34.

4.1.2.3 Protein Kinase C Pathway Lithium interacts with the PKC pathway, a mediator of intracellular responses to neurotransmitter signalling, and PDLIM5 is an adaptor protein that selectively binds the isozyme PKC epsilon to N-type calcium channels in neurons. Squassina et al. [56] did not find an association between the *PDLIM5* gene polymorphisms and lithium response.

4.1.3 Substances Involved in Neuroprotection

4.1.3.1 Brain-Derived Neurotrophic Factor BDNF is a neurotrophic factor involved in neuronal proliferation and synaptic plasticity. An association of Val66Met functional polymorphism of the *BDNF* gene, located on chromosome 11p13, with bipolar disorder has been suggested [57]. Our group was the first to demonstrate an association of this polymorphism with lithium response [25, 58]. Furthermore, we have found a significant interaction of this polymorphism with that of the serotonin transporter where, in subjects with the s allele of *5-HTTLPR* having a Val/Val genotype of BDNF, there is a 70 % probability of lithium non-response [59]. However, an association of lithium

response with a Val66Met polymorphism of the *BDNF* gene was not confirmed in populations other than Caucasian [38, 60].

The neurotrophin BDNF binds to the TrkB receptor, transcribed from the *NTRK2* gene. The San Diego group of investigators has suggested an association of this polymorphism with lithium response in patients with higher suicidality [61] and euphoric mania [61]; however, we were not able to find such an association [58].

4.1.3.2 Glycogen Synthase Kinase 3-β Lithium inhibits GSK3β, the enzyme involved in synaptic plasticity, apoptosis and the circadian cycle. Italian investigators demonstrated an association between the functional -50 T/C polymorphism of the *GSK3β* gene located on chromosome 3q13 and lithium response [62] but this was not confirmed in two other studies, including ours [38, 63]. In a network coordinating circadian rhythms, GSK3β interacts with a number of proteins including Rev-Erbα, and a variant of the *Rev-Erbα* gene has been shown, in two recent studies, to be associated with prophylactic lithium response [64, 65].

4.1.4 Miscellaneous Genes

Matrix metalloproteinase-9 (MMP-9) is an extracellularly acting endopeptidase implicated in a number of pathological conditions including cancer, cardiovascular and neuropsychiatric diseases. Our group demonstrated an association between functional polymorphism of the *MMP-9* gene, located on chromosome 20q11-13, and bipolar disorder [66]. However, we were unable to find such an association with lithium response [67]. On the other hand, we did find an association with polymorphism of two other genes implicated in the pathogenesis of bipolar disorder, namely the glucocorticoid receptor *(NR3C1)* gene located on chromosome 5q31-32 [68], and the Disrupted-in-Schizophrenia (*DISC-1)* gene located on chromosome 1q42 [69].

Positive results have been obtained concerning associations of three genes located on chromosome 22q11-13 with lithium response. Japanese authors found a significant association between lithium response and genetic variations in the breakpoint cluster region (*BCR)* gene located on chromosome 22q11 [70] and with the X-box binding protein 1 (*XBP1*) gene located on chromosome 22q12 [71]. An association of both these genes with a predisposition to bipolar disorder had been previously reported [72, 73]. Silberberg et al. [74] described an association with lithium response and the calcium channel gamma-2 subunit *(CACNG2)* gene, also known as stargazin, located on chromosome 22q13.

Canadian investigators studied the prolyl endopeptidase *(PREP)* gene, located on chromosome 6q22, the region that has been linked to bipolar disorder in several studies, but did not find an association with lithium response [75]. On the other hand, in considering postulated abnormalities of mitochondrial DNA (mDNA) in bipolar disorder [76], Japanese researchers demonstrated an association between the 10398A mDNA polymorphism and the quality of lithium prophylaxis [77].

In our recent study [78] we investigated an association between the polymorphism of 14 common genes with the quality of prophylactic lithium response, in relation to the putative role of these genes in the pathogenesis of bipolar disorder and found some association with five of them; namely, *5-HTT*, *DRD1*, *COMT*, *BDNF* and *FYN*.

4.2 Studies on Candidate Genes of Response to other Mood Stabilizers

There is a paucity of pharmacogenetic studies of mood stabilizers other than lithium. One exception is that of Korean researchers studying functional -116C/G polymorphism of the *XBP1* gene in relation to the efficacy of valproate [79]. Interestingly, they found an association with a positive prophylactic effect for valproate with the C allele of this polymorphism, while with lithium it was with the G allele [71]. This may suggest that the response to different mood stabilizers may be connected with a different genetic make-up.

4.3 Limitations of Candidate Gene Studies

Candidate gene studies have yielded a number of associations between the polymorphism of a given gene and a prophylactic response to mood stabilizers, mostly lithium. However, only a minority of them has been consistently replicated in subsequent studies. Concerning lithium, each of the single nucleotide polymorphisms of a given gene accounts for a small portion of the total variance in lithium response (1–2 % at best). Therefore, lithium response is apparently polygenic and only by simultaneously examining multiple genes and multiple variants within these genes would it be possible to provide some guidelines for predicting the response. This may also apply to other mood stabilizers.

4.4 Genome-Wide Association Studies of Lithium Response

In recent years, a number of GWAS in bipolar disorders have been performed, some of which also focused on lithium response. Prior to this, there had been some linkage studies of susceptibility loci specifically analyzing those

connected with lithium response. Danish investigators [80] performed a haplotype-based study in lithium-responding patients with bipolar disorder on the Faroe Islands and found chromosomal region 18q23 to possibly be connected with lithium response. Canadian researchers [81] after having performed a genome scan of 31 families ascertained, through probands with an excellent lithium response, that the locus on chromosome 7q11 may be implicated. However, in spite of the susceptibility regions found in these studies, no specific genes have been identified.

Perlis et al. [82] carried out a family-based association study of lithium-related and other candidate genes in bipolar disorder. Lithium genes were selected as related primarily to inositol 1,4,5-triphosphate (17 genes), to GSK3β/Wnt signalling (39 genes) and to those implicated by messenger RNA expression data and related approaches (35 genes). Although some promising genes thought to be connected with bipolar disorder were postulated (including the *DISC1* gene previously associated with schizophrenia), no association with bipolar disorder was found in relation to genes specifically connected with lithium mechanisms. However, about the same time a paper appeared describing the results of GWAS in bipolar disorder, where the highest signal was obtained with the *DGKH* gene, which encodes a key protein in the lithium-sensitive PI pathway [83].

American researchers utilized GWAS data, obtained from the STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) study, to examine association with risk for recurrence among patients treated with lithium, and subsequently examined the regions that showed the greatest evidence of association in a second cohort of bipolar disorder patients drawn from a clinical population at University College London. A phenotype definition was that of achieving euthymia for at least 8 weeks during a prospective follow-up. It turned out that of the regions with a p-value of $<5 \times 10^{-4}$ in the STEP-BD cohort, five (8q22, 3p22, 11q14, 4q32 and 15q26) showed consistent evidence of association in a second cohort. The authors found a region of special interest on chromosome 4q32 spanning a *GRIA2* gene, coding for the glutamate AMPA receptor [84].

Recently, a GWAS was performed by Squassina et al. [85] on lithium-treated Sardinian patients with bipolar disorder. A phenotypic assessment of lithium response was made, using the retrospective criteria of a long-term treatment response scale. The strongest association, also supported by the quantitative trait analysis, was shown for a single nucleotide polymorphism (SNP) of the amiloride-sensitive cation channel 1 neuronal (*ACCN1*) gene, located on chromosome 17q12, encoding a cation channel with high affinity for sodium, and permeable to lithium.

However, the main promise for elucidating the genetics of lithium response was provided in recent years, following an initiative by the International Group for the Study of Lithium-Treated Patient and the Unit on the Genetic Basis of Mood and Anxiety Disorders at the National Institute of Mental Health. Lithium researchers from around the world have formed the ConLiGen in order to establish the largest sample to date for genome-wide studies of lithium response in bipolar disorder. This sample currently comprises more than 1,200 patients characterized for response to lithium treatment. Such an endophenotype has been defined retrospectively by means of the Alda scale [86].

The first results of the ConLiGen initiative were presented during a CINP meeting in Stockholm in 2012. Inter-rater reliability of lithium response was good, with kappa values >0.7. The GWAS top hit ($p = 1.52 \times 10^{-6}$) was found for the *SLC4A10* gene coding solute carrier family 4, sodium bicarbonate transporter, member 10, which belongs to a family of sodium-coupled bicarbonate transporters [87]. This gene is located on chromosome 2q24 and is highly expressed in the hippocampus and cerebral cortex. It has been implicated in complex partial epilepsy and mental retardation [88] as well as being a subject of interest in recurrent major depression [89]. The bicarbonate sensitive pathway is the most important mechanism for active lithium influx into the cell [90]. A replication analysis is planned before the official publication of these results.

Recently, McCarthy et al. [91] analysed GWAS performed in bipolar disorder, comparing the rates of genetic associations of circadian clock genes in bipolar disorder with control subjects in relation to possible lithium-responsive genes, using a multi-level approach. They suggest that, despite the negative data obtained so far in GWAS, further studies on possible associations between clock genes, bipolar disorder and lithium response are warranted.

It should be also mentioned that another prospective, multicentre trial named PGBD (Pharmacogenomics of Mood Stabilizer Response in Bipolar Disorder) with John Kelsoe as a principal investigator is underway where lithium is an important part. An abstract describing the study is available on the web: http://pgrn.org/display/pgrnwevsite/PGBD+Profile.

5 Conclusions

The pharmacogenetics of response to mood stabilizers has recently become a growing field of research, especially in relation to the pharmacogenetics of lithium prophylaxis of bipolar disorder. Obviously, the ConLiGen project makes an important step in this research. It may be assumed that the response to any mood stabilizer is connected with the

interaction of multiple genes, as demonstrated in relation to lithium response. Possible practical implications of these pharmacogenetic studies have yet to be seen. However, we hope that clinicians will eventually be assisted by a panel of genetic tests that may successfully predict which bipolar disorder patient is the most likely to respond to lithium or to other mood stabilizers.

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References

1. Merinkangas KR, Tohen M. Epidemiology of bipolar disorder in adults and children. In: Tsuang MT, Tohen MT, Jones PB, editors. Textbook in psychiatric epidemiology. Chichester: John Wiley and Sons; 2011. p. 329–42.
2. Rihmer Z, Kiss K. Bipolar disorders and suicidal behavior. Bipolar Disord. 2002;4(Suppl. 1):21–5.
3. McGuffin P, Rijsdijk F, Andrew M, et al. The heritability of bipolar affective disorder and the genetic relationship to bipolar depression. Arch Gen Psychiatry. 2003;60:497–502.
4. Rybakowski JK. Two generations of mood stabilizers. Int J Neuropsychopharmacol. 2007;10:709–11.
5. Hartigan G. The use of lithium salts in affective disorders. Br J Psychiatry. 1963;109:810–4.
6. Lambert PA, Borselli S, Marcou G, et al. Long-term thymoregulative action of Depamide in manic-depressive psychoses [in French]. Ann Med Psychol. 1971;2:442–7.
7. Okuma T, Kishimoto A, Inue K. Anti-manic and prophylactic effect of carbamazepine (Tegretol) on manic depressive psychosis. Folia Psychiatr Neurol Japan. 1973;27:283–97.
8. Zarate CA. Is clozapine a mood stabilizer? J Clin Psychiatry. 1995;56:108–12.
9. Rybakowski JK. Aripiprazole joins the family of second-generation mood stabilizers. J Clin Psychiatry. 2008;69:862–3.
10. Quiroz JA, Yatham LN, Palumbo JM, et al. Risperidone long-acting injectable monotherapy in the maintenence treatment of bipolar disorder. Biol Psychiatry. 2010;68:156–62.
11. Ketter T, Calabrese JR. Stabilization of mood from below versus above baseline in bipolar disorder: a new nomenclature. J Clin Psychiatry. 2002;63:146–51.
12. Colom F, Vieta E, Daban C, et al. Clinical and therapeutic implications of predominant polarity in bipolar disorder. J Affect Disord. 2006;93:13–7.
13. Severus E, Schaaff N, Möller HJ. State of the art: treatment of bipolar disorders. CNS Neurosci Ther. 2012;18:214–8.
14. Popovic D, Reinares M, Goikolea JM, et al. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. Eur Neuropharmacol. 2012;22:339–46.
15. Cade J. Lithium salts in the treatment of psychotic excitement. Med J Aust. 1949;2:349–52.
16. Grof P. Excellent lithium responders: people whose lives have been changed by lithium prophylaxis. In: Birch NJ, Gallicchio VS, Becker RW, editors. Lithium: 50 years of psychopharmacology, new perspectives in biomedical and clinical research. Cheshire (CT): Weidner Publishing Group; 1999. p. 36–51.
17. Rybakowski JK, Chłopocka-Woźniak M, Suwalska A. The prophylactic effect of long-term lithium administration in bipolar patients entering lithium treatment in the 1970s and 1980s. Bipolar Disord. 2001;3:63–7.
18. Grof P. Sixty years of lithium responders. Neuropsychobiology. 2010;62:27–35.
19. Kraepelin E. Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. Barth, Leipzig: 6 Auflage, 1899.
20. Rybakowski JK, Dembinska D, Kliwicki S, et al. TEMPS-A and long-term lithium response: positive correlation with hyperthymic temperament. J Affect Disord. Epub 28 Aug 2012.
21. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. Neuropsychobiology. 2000;42(Suppl. 1):2–10.
22. Kessler AJ, Barklage NE, Jefferson JW. Mood disorders in the psychoneurologic borderland: three cases of responsiveness to carbamazepine. Am J Psychiatry. 1989;146:81–3.
23. Passmore MJ, Garnham J, Duffy A, et al. Phenotypic spectra of bipolar disorder in responders to lithium versus lamotrigine. Bipolar Disord. 2003;5:110–4.
24. Zarate CA, Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. J Clin Psychiatry. 1995;56:411–7.
25. Rybakowski JK, Suwalska A, Skibinska M, et al. Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. Pharmacopsychiatry. 2005;38:166–70.
26. Serretti A, Lorenzi C, Lilli R, et al. Pharmacogenetics of lithium prophylaxis in mood disorders: analysis of COMT, MAO-A, and Gß3 variants. Am J Med Genet Part B Neuropsychiatr Genet. 2002;144:370–9.
27. Grof P, Duffy A, Cavazzoni P, et al. Is response to prophylactic lithium a familial trait? J Clin Psychiatry. 2002;63:942–7.
28. Cruceanu C, Alda M, Turecki G. Lithium: a key to the genetics of bipolar disorder. Genome Med. 2009;1:79.1–7.
29. McCarthy MJ, Leckband SG, Kelsoe JR. Pharmacogenetics of lithium response in bipolar disorder. Pharmacogenomics. 2010;11:1439–65.
30. Smith DJ, Evans R, Craddock N. Predicting response to lithium in bipolar disorder: a critical review of pharmacogenetic studies. J Ment Health. 2010;19:142–56.
31. Serretti A, Drago A. Pharmacogenetics of lithium long-term treatment: focus on initiation and adaptation mechanisms. Neuropsychobiology. 2010;62:61–71.
32. Müller-Oerlinghausen B. Lithium long-term treatment: does it act via serotonin? Pharmacopsychiatry. 1985;18:214–7.
33. Hauser J, Leszczynska A, Samochowiec J, et al. Association analysis of the insertion/deletion polymorphism in serotonin transporter gene in patients with affective disorder. Eur Psychiatry. 2003;18:129–32.
34. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol. 2012;22:239–58.
35. Serretti A, Lilli R, Mandelli L, et al. Serotonin transporter gene associated with lithium prophylaxis in mood disorders. Pharmacogenomics J. 2001;1:71–7.
36. Serretti A, Malitas PN, Mandelli L. Further evidence for a possible association between serotonin transporter gene and lithium prophylaxis in mood disorders. Pharmacogenomics J. 2004;4:267–73.
37. Rybakowski JK, Suwalska A, Czerski PM, et al. Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. Pharmacol Rep. 2005;57:124–7.
38. Michelon L, Meira-Lima I, Cordeiro Q, et al. Association study of the INPP1, 5HTT, BDNF, AP-2beta and GSK-3beta gene

variants and retrospectively scored response to lithium prophylaxis in bipolar disorder. Neurosci Lett. 2006;403:288–93.
39. Manchia M, Congiu D, Squassina A, et al. No association between lithium full responders and the DRD1, DRD2, DRD3, DAT1, 5-HTTLPR and HTR2A genes in a Sardinian sample. Psychiatry Res. 2009;169:164–6.
40. Serretti A, Lorenzi C, Lill R, et al. Serotonin receptor 2A, 2C, 1A genes and response to lithium prophylaxis in mood disorders. J Psychiatr Res. 2000;34:89–98.
41. Dmitrzak-Weglarz M, Rybakowski JK, Suwalska A, et al. Association studies of 5-HT2A and 5-HT2C serotonin receptor gene polymorphisms with prophylactic lithium response in bipolar patients. Pharmacol Rep. 2005;57:761–5.
42. Serretti A, Lilli R, Lorenzi C, et al. Tryptophan hydroxylase gene and response to lithium prophylaxis in mood disorders. J Psychiatr Res. 1999;33:371–7.
43. Severino G, Congiu D, Serreli C, et al. A48G polymorphism in the D1 receptor genes associated with bipolar I disorder. Am J Med Genet B Neuropsychiatr Genet. 2005;134B:37–8.
44. Rybakowski JK, Dmitrzak-Weglarz M, Suwalska A. Dopamine D1 receptor gene polymorphism is associated with prophylactic lithium response in bipolar disorder. Pharmacopsychiatry. 2009; 42:20–2.
45. Serretti A, Lilli R, Lorenzi C, et al. Dopamine receptor D3 gene and response to lithium prophylaxis in mood disorders. Int J Neuropsychopharmacol. 1998;1:125–9.
46. Serretti A, Lilli R, Lorenzi C, et al. Dopamine receptor D2 and D4 genes, GABAA alpha-1 subunit genes and response to lithium prophylaxis in mood disorders. Psychiatry Res. 1999;87:7–19.
47. Turecki G, Grof P, Cavazzoni P, et al. MAOA: association and linkage studies with lithium responsive bipolar disorder. Psychiatr Genet. 1999;9:13–6.
48. Szczepankiewicz A, Skibinska M, Suwalska A, et al. No association of three GRIN2B polymorphisms with lithium response in bipolar patients. Pharmacol Rep. 2009;61:448–52.
49. Szczepankiewicz A, Rybakowski JK, Skibinska M, et al. FYN kinase gene: another glutamatergic gene associated with bipolar disorder? Neuropsychobiology. 2009;59:178–83.
50. Szczepankiewicz A, Skibinska M, Suwalska A, et al. The association study of three FYN polymorphisms with prophylactic lithium response in bipolar patients. Hum Psychopharmacol. 2009;24:287–91.
51. Steen VM, Løvlie R, Osher Y, et al. The polymorphic inositol polyphosphate 1-phosphatase gene as a candidate for pharmacogenetic prediction of lithium-responsive manic-depressive illness. Pharmacogenetics. 1998;8:259–68.
52. Bremer T, Diamond C, McKinney R, et al. The pharmacogenetics of lithium response depends upon clinical co-morbidity. Mol Diagn Ther. 2007;11:161–70.
53. Dimitrova A, Milanova V, Krastev S, et al. Association study of myo-inositol monophosphatase 2 (IMPA2) polymorphisms with bipolar affective disorder and response to lithium treatment. Pharmacogenomics J. 2005;5:35–41.
54. Manchia M, Squassina A, Congiu D, et al. Interacting genes in lithium prophylaxis: preliminary results of an exploratory analysis on the role of DGKH and NR1D1 gene polymorphisms in 199 Sardinian bipolar patients. Neurosci Lett. 2009;467:67–71.
55. Mamdani F, Alda M, Grof P, et al. Lithium response and genetic variation in the CREB family of genes. Am J Med Genet B Neuropsychiatr Genet. 2008;147B:500–4.
56. Squassina A, Congiu D, Manconi F, et al. The PDLIM5 gene and lithium prophylaxis: an association and gene expression analysis in Sardinian patients with bipolar disorder. Pharmacol Res. 2008; 57:369–73.
57. Sears C, Markie D, Olds R, et al. Evidence of associations between bipolar disorder and the brain-derived neurotrophic factor (BDNF) gene. Bipolar Disord. 2011;13:630–7.
58. Dmitrzak-Weglarz M, Rybakowski JK, Suwalska A, et al. Association studies of the BDNF and the NTRK2 gene polymorphisms with prophylactic lithium response in bipolar patients. Pharmacogenomics. 2008;9:1595–603.
59. Rybakowski JK, Suwalska A, Skibinska M, et al. Response to lithium prophylaxis: interaction between serotonin transporter and BDNF genes. Am J Med Genet Part B Neuropsychiatr Genet. 2007;144B:820–3.
60. Masui T, Hashimoto R, Kusumi I, et al. Lithium response and Val66Met polymorphism of the brain derived neurotrophic factor gene in Japanese patients with bipolar disorder. Psychiatr Genet. 2006;16:49–50.
61. Leckband SG, DeModena A, McKinney R, et al. Lithium response is associated with the NTRK2 gene in a prospective study. Presented at 17th Annual Molecular Psychiatry Conference; 31 Jan–2 Feb 2010; Park City (UT).
62. Benedetti F, Serretti A, Pontigia A, et al. Long-term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3-beta-50T/C SNP. Neurosci Lett. 2005;376: 51–5.
63. Szczepankiewicz A, Rybakowski JK, Suwalska A, et al. Association study of the glycogen synthase kinase-3beta gene polymorphism with prophylactic lithium response in bipolar patients. World J Biol Psychiatry. 2006;7:158–61.
64. Campos-de-Sousa S, Guindalini C, Tondo L, et al. Nuclear receptor rev-erb-(alpha) circadian gene variants and lithium carbonate prophylaxis in bipolar affective disorder. J Biol Phythms. 2010;25:132–7.
65. McCarthy MJ, Nievergelt CM, Shenkhtman T, et al. Functional genetic variation in the Rev-Erbα pathway and lithium response in the treatment of bipolar disorder. Genes Brain Behav. 2011;10:852–61.
66. Rybakowski JK, Skibinska M, Leszczynska-Rodziewicz A, et al. Matrix metalloproteinase-9 (MMP-9) gene and bipolar mood disorder. Neuromolecular Med. 2009;11:128–32.
67. Rybakowski JK, Skibinska M, Suwalska A, et al. Functional polymorphism of matrix metalloproteinase-9 (MMP-9) gene and response to lithium prophylaxis in bipolar patients. Hum Psychopharmacol. 2011;26:168–71.
68. Szczepankiewicz A, Rybakowski JK, Suwalska A, et al. Glucocorticoid receptor polymorphism is associated with lithium response in bipolar patients. Neuro Endocrinol Lett. 2011;32: 545–51.
69. Czerski PM, Kliwicki S, Maciukiewicz M, et al. Multiple single nucleotide polymorphisms of schizophrenia-related DISC1 gene in lithium-treated patients with bipolar affective disorder. Eur Neuropsychopharmacol. 2011;21(Suppl. 1):S4–5.
70. Masui T, Hashimoto R, Kusumi I, et al. A possible association between missense polymorphism of the breakpoint cluster region gene and lithium prophylaxis in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:204–8.
71. Masui T, Hashimoto R, Kusumi I, et al. A possible association between the −116C/G single nucleotide polymorphism of the XBP1 gene and lithium prophylaxis in bipolar disorder. Int J Neuropsychopharmacol. 2006;9:83–8.
72. Hashimoto R, Okada T, Kato T, et al. The breakpoint cluster region gene on chromosome 22q11 is associated with bipolar disorder. Biol Psychiatry. 2005;57:1097–102.
73. Kakiuchi C, Iwamoto K, Ishiwata M, et al. Impaired feedback regulation of XBP1 as a genetic risk factor for bipolar disorder. Nature Genet. 2003;35:171–5.

74. Silberberg G, Levit A, Collier D, et al. Stargazin involvement with bipolar disorder and response to lithium treatment. Pharmacogenet Genomics. 2008;18:403–12.
75. Mamdani F, Sequeira A, Alda M, et al. No association between the PREP gene and lithium responsive bipolar disorder. BMC Psychiatry. 2007;7:9.
76. Kato T, Kunugi H, Nanko S, et al. Mitochondrial DNA polymorphism in bipolar disorder. J Affect Disord. 2001;62:151–64.
77. Washizuka S, Ikeda A, Kato N, et al. Possible relationship between mitochondrial DNA polymorphisms and lithium response in bipolar disorder. Int J Neuropsychopharmacol. 2003; 6:421–4.
78. Rybakowski JK, Czerski P, Dmitrzak-Weglarz M, et al. Clinical and pathogenic aspects of candidate genes for lithium prophylactic efficacy. J Psychopharmacol. 2012;26:368–73.
79. Kim B, Kim CY, Lee MJ, et al. Preliminary evidence on the association between XBP1-116C/G polymorphism and response to prophylactic treatment with valproate in bipolar disorders. Psychiatry Res. 2009;168:209–12.
80. Ewald H, Wang AG, Vang M, et al. A haplotype-based study of lithium responding patients with bipolar affective disorder on the Faroe Islands. Psychiatr Genet. 1999;9:23–34.
81. Turecki G, Grof P, Grof E, et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry. 2001;6:570–8.
82. Perlis RH, Purcell S, Fagerness J, et al. Family-based association study of lithium-related and other candidate genes in bipolar disorder. Arch Gen Psychiatry. 2008;65:53–61.
83. Baum AE, Akula N, Cabanero M, et al. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. Mol Psychiatry. 2008;13:197–207.
84. Perlis RH, Smoller JW, Ferreira MAR, et al. A genome wide association study of response to lithium for prevention of recurrence in bipolar disorder. Am J Psychiatry. 2009;166:718–25.
85. Squassina A, Manchia M, Borg J, et al. Evidence for association of an ACCN1 gene variant with response to lithium treatment in Sardinian patients with bipolar disorder. Pharmacogenomics. 2011;12:1559–69.
86. Schulze TG, Alda M, Adli M, et al. The International Consortium on Lithium Genetics (ConLiGen): an initiative by the NIMH and IGSLI to study the genetic basis of response to lithium treatment. Neuropsychobiology. 2010;62:72–8.
87. Schulze T. The Consortium on Lithium Genetics (ConLiGen) genome-wide association studies of lithium response phenotypes in bipolar disorder [abstract book]. CINP Congress; 3–7 June 2012; Stockholm: 36.
88. Gurnett CA, Veile R, Zempel J, et al. Disruption of sodium bicarbonate transporter SLC4A10 in a patient with complex partial epilepsy and mental retardation. Arch Neurol. 2008;65:550–3.
89. Schosser A, Gaysina D, Cohen-Woods S, et al. A follow-up case-control association study of tractable (druggable) genes in recurrent major depression. Am J Med Genet B Neuropsychiatr Genet. 2011;156B:640–50.
90. Ehrlich BE, Diamond JM. Lithium fluxes in human erythrocytes. Am J Physiol. 1979;237:102–10.
91. McCarthy MJ, Nievergelt CM, Kelsoe JR, et al. A survey of genomic studies supports association of circadian clock genes with bipolar disorder spectrum illnesses and lithium response. PLoS ONE. 2012;7:e32091.