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Studies on candidate genes for lithium prophylactic efficacy performed at the Poznan University of Medical Sciences

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Summary

Lithium is a drug of choice as a mood-stabilizer for the maintenance treatment of bipolar disorder (BD). The prophylactic efficacy of lithium can be determined by genetic factors, partially related to a predisposition to bipolar disorder. In the field of psychiatric genetics, the first decade of the 21st century was dominated by the "candidate gene" research. In this paper, the studies on candidate genes associated with lithium prophylaxis performed at the Poznan University of Medical Sciences in 2005–2018 are presented. During this time, the polymorphisms of multiple genes have been investigated, many of which are also associated with a predisposition to bipolar disorder. The associations with lithium prophylactic efficacy were found for the polymorphisms in *5HTT*, *ACP1*, *ARNTL*, *BDNF*, *COMT*, *DRD1*, *FKBP5*, *FYN*, *GLCC*, *NR3C1*, and *TIM* genes, but not those in *5HT2A*, *5HT2C*, *DRD2*, *DRD3*, *DRD4*, *GRIN2B*, *GSK-3β*, *MMP-9*, and *NTRK2* genes. The polymorphism of the *GSK-3β* gene was found to be associated with the kidney side-effects occurring during lithium therapy. Possible roles for these genes in both the mechanism of lithium prophylactic efficacy and pathogenesis of bipolar disorder were discussed.

Key words: bipolar disorder, lithium prophylaxis, candidate genes

Introduction

Currently, lithium is a drug of choice as a mood-stabilizer for the maintenance treatment of bipolar disorder. Lithium is also therapeutically effective in episodes of mania and depression, as well as is used for the augmentation of antidepressants in

treatment-resistant depression. In addition to its antimanic, antidepressant and mood-stabilizing properties, lithium exerts anti-suicidal, immunomodulatory and neuroprotective action. The drug may protect against dementia and some promising effects of lithium in neurodegenerative disorders have been observed [1].

The term *excellent lithium responders* (ELR) was introduced by the Canadian psychiatrist, Paul Grof, for patients who on long-term monotherapy with lithium experienced a dramatic change in their life as their mood episodes were totally prevented [2]. We followed-up for ten years 60 patients who started lithium prophylaxis in the 1970s, and 49 patients beginning this procedure in the 1980s. Those without mood episodes during this period made 35% of the first group and 27% of the second one, roughly one-third of bipolar subjects treated longitudinally with lithium [3]. According to Grof [4], patients with good response to lithium have their episodes separated by euthymic remission periods, frequently have a family history of mood disorders, and do not have comorbid psychiatric disturbances. Such picture can recall a condition of *manisch-depressives Irresein* described by Emil Kraepelin [5]. In recent two decades, many other clinical factors and biomarkers associated with lithium prophylactic efficacy have been identified [6].

A degree of lithium prophylactic response provided a suitable area for molecular-genetic research. Such research up to the second decade of the 21st century has been dominated by the strategy of the *candidate gene*. In this approach, a specific gene based on its function is tested for possible involvement in the pathogenesis of disease or mechanism of pharmacological treatment. Genetic markers of known function or located in potentially important regions of the genome are analyzed in case-control studies to determine if the variant is involved in disease or pharmacological treatment of it. Such strategy makes it possible to identify genes relevant for pathogenesis and treatment of a given disorder. Whereas the procedure is constricted to limited number of indicated genes and does not have a potential to find unexpected novices. A multitude of research on lithium prophylactic efficacy in bipolar disorder using the candidate gene method has been performed so far.

In 2013, the current knowledge of candidate genes of lithium prophylactic efficacy was presented [7]. The genes included mostly neurotransmission (serotonin, dopamine and glutamate), intracellular signaling: phosphatidylinositol (PI), cyclic adenosine monophosphate (cAMP) and protein kinase C (PKC) pathways, the enzyme glycogen synthase kinase 3-β (GSK-3β), neuroprotective factors (e.g., brain-derived neurotrophic factor – BDNF), genes of biological rhythms, and several heterogenous ones (e.g., genes of chromosome 22q11-13).

A considerable amount of studies on candidate genes of lithium prophylactic efficacy had been performed at the Poznan University of Medical Sciences in the years 2005–2018. In this article, they will be presented and discussed.

The outcome of Poznan studies

Methodology

The prophylactic efficacy of lithium is defined as a disappearance or reduction of manic and depressive episodes in the course of longitudinal administration of the drug. In the lithium-treated patients of the Department of Adult Psychiatry, Poznan University of Medical Sciences included in our molecular-genetic studies of lithium prophylaxis, the administration of the drug lasted for at least 5 years, which made it possible to precisely estimate a magnitude of lithium efficacy. In most of research, excellent lithium responders (having no recurrences) were compared with partial responders, i.e., those with recurrences reduced by half or more per year in comparison with the course before lithium, and with non-responders, i.e., those with recurrences reduced by less than half per year, no change or with illness exacerbation.

In 2002, the Canadian researchers introduced a scale allowing quantitative retrospective assessment of the quality of lithium prophylactic efficacy. Since Martin Alda was instrumental in its creating, the tool is frequently named *the Alda scale*. In this research device, the magnitude of response, i.e., the activity of the illness when a patient receives appropriate lithium treatment is expressed by criterion A on a 10-point scale. According to the criteria B1–B5, a relationship between the amelioration and the treatment should be assessed. Criterion B1 gives the number of episodes and B2 – frequency of episodes when not treated. B3 estimates the treatment duration, B4 – adherence during stable mood, and B5 – the use of other drugs during the stable periods. Subtracting B from A gives the total score which ranges between 0 and 10. The Alda scale enables either a categorical estimation (when a cut-off point for the improvement is defined) or a dimensional determination of lithium prophylactic efficacy [8]. The scale has been employed in the Consortium of Lithium Genetics (ConLiGen) aiming to perform the genome-wide association study (GWAS) in a great number of patients receiving prophylactic lithium as well as in our recent candidate gene studies. A multicenter study using this scale identified two definitions of lithium efficacy, one dichotomous, and the other continuous. Good agreement and reliability of the Alda scale have also been demonstrated [9].

Brain-derived neurotrophic factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is essential for the function and survival of neurons and modulates the activity of such neurotransmitters like glutamate, gamma-aminobutyric acid, dopamine, and serotonin. The Val66Met polymorphism of the *BDNF* gene (rs6265) is linked to a predisposition to bipolar disorder in the European population [10]. Research conducted in Poznan has found that the Val allele of the Val66Met polymorphism in patients with bipolar disorder determines better cognitive functions associated with prefrontal cortex activity. This relationship is specific for bipolar disorder and does not occur in schizophrenic patients or healthy people [11].

Experimental studies have shown that lithium increases the expression of BDNF in the rat brain. One of the mechanisms is an activation by lithium of the cAMP response element-binding protein (CREB), which stimulates the transcription of the *BDNF* gene [12]. In clinical studies, the BDNF serum concentrations were reduced during episodes of both mania and depression and increased after successful pharmacological treatment, including the use of lithium. A low concentration of BDNF is considered a marker of late-stage bipolar affective disorder [13]. However, we showed that excellent lithium responders even with a very long duration of bipolar disorder had normal serum BDNF levels [14].

Our group was the first to demonstrate that the prophylactic effect of lithium is associated with the Val66Met polymorphism of the *BDNF* gene. In the study of 88 patients with bipolar disorder receiving lithium for 5–27 years (mean 16 years), it was found that the Val/Met genotype and Met allele occurred more frequently in lithium responders ($n = 27$) than in lithium non-responders ($n = 16$) [15].

BDNF acts by tyrosine receptor kinase B (Trk), making the signal transduction BDNF/TrkB pathway which may be involved in the pathogenesis of bipolar disorder [16]. The main gene related to Trk is the neurotrophic tyrosine receptor kinase type 2 (*NTRK2*) gene, mapped to 9q22.1. Our subsequent study involved 108 patients with bipolar disorder receiving lithium for 5–27 years (mean 15 years), with 23% classified as excellent lithium responders, 51% as partial responders and 26% as non-responders to lithium. We analyzed four single nucleotide polymorphisms (SNPs) of the *BDNF* gene and three of the *NTRK2* gene. We confirmed an association of the Val/Met polymorphism of the *BDNF* gene, and also the C/G polymorphism (rs988748) of this gene with the lithium prophylactic effect. However, no association with the efficacy of lithium prophylaxis was observed with the polymorphisms of the *NTRK2* gene, neither with the interaction of the *BDNF* and *NTRK2* genes [17].

Serotonergic system

The promoter polymorphism in the regulatory region of the serotonin transporter (*5-HTT*) gene is the main element of the serotonergic system studied in molecular-genetic research in psychiatry. This polymorphism (5-HTTLPR) has two allelic variants: a long variant (l) and a short one (s), functionally associated with transcriptional efficiency and expression of the 5-HTT protein. The s allele acts in a nearly dominant way, thus subjects with s/s and s/l genotype may be classified as S individuals and subjects with l/l genotype as L individuals. In the Poznan study, we confirmed the previous reports showing that the occurrence of the s allele of 5-HTTLPR can increase the risk for both bipolar and unipolar mood disorders [18]. In other studies, the s allele was also associated with a greater influence of life stress on depression [19] as well as a worse therapeutic response of depression to selective serotonin reuptake inhibitors (SSRIs) [20]

We studied 67 patients receiving lithium prophylaxis for a minimum of 5 years (mean 15 years), including 18 excellent, 35 partial and 14 poor responders. Non-

responders to lithium prophylaxis had the s/s genotype and the s allele significantly more frequent than excellent and partial responders [21]. In this respect, we confirmed previous findings obtained by Italian investigators [22].

In subsequent research, we investigated an interaction between the Val/Met polymorphism of the *BDNF* gene and the 5HTTLPR polymorphism of the *5-HTT* gene as far as the prophylactic effect of lithium is concerned. The study included 111 patients with bipolar disorders receiving lithium for 5–27 years (mean 15 years). Thirty-one patients were excellent responders, 54 – partial responders and 26 – non-responders to prophylactic lithium administration. A significant interaction between the Val/Met polymorphism of the *BDNF* gene and 5HTTLPR polymorphism and lithium effect was demonstrated. Patients with s/s or s/l genotype (S individuals) with Val/Val genotype were overrepresented in non-responders group. These individuals showed large differences in lithium prophylactic effect, according to either Val/Val genotype or Met allele of the *BDNF* gene polymorphism. Those with Val/Val genotype constituted 19% of lithium responders and 37% of lithium non-responders, while those with Met allele accounted for 40% of lithium responders and only 3% of lithium non-responders. These results may indicate an important epistatic interaction between 5-HTTLPR, *BDNF* gene polymorphism and the effect of lithium prophylaxis [23].

In a separate study, we investigated possible associations of prophylactic effect of lithium and the polymorphisms of serotonergic receptors *5-HT2A* and *5-HT2C* genes. No association regarding these genes was obtained [24].

Dopaminergic system

The most important study of the dopaminergic system concerning lithium prophylaxis was performed in Poznan with the dopamine D1 receptor *(DRD1)* gene. DRD1 plays an important role in prefrontal cortex activity and optimal cognitive performance associated with this structure [25]. This topic had been prompted by our previous case-control research where the association between the – 48A/G (rs4532) polymorphism of this gene and bipolar disorder was demonstrated [26]. A similar finding was previously obtained by Italian investigators studying patients in Sardinia [27]. For the lithium study, we included 92 patients (39 males, 53 females) receiving lithium for 5–27 years (mean 15 years), including 24 excellent, 48 partial and 20 poor responders. It turned out that the frequency of G/G genotype of the -48A/G polymorphism of the *DRD1* gene, which had been associated with a predisposition to bipolar disorder, was significantly more often in poor than excellent responders to lithium (60 vs. 21%) [28].

Recently, Iranian investigators in a search of lithium responsiveness-associated genes performed the gene set enrichment analysis (GSEA). Among their findings, they showed that the chromosomal region 5q34, to which *DRD1* gene maps, is strongly associated with response to lithium [29].

We also investigated possible associations of the prophylactic effect of lithium and the polymorphisms of dopaminergic receptors *DRD2, DRD3* and *DRD4* genes. However, no association regarding these genes with lithium efficacy was obtained [24].

Another gene associated with the dopaminergic system studied by us was the catechol-O-methyltransferase *(COMT)* gene. COMT is involved in the enzymatic inactivation of dopamine. The *COMT* gene has the Val158Met (rs4680) functional polymorphism which is associated with the predisposition to bipolar disorder where susceptibility to the illness is mostly conferred by the Met allele [30]. In our study of 101 patients receiving lithium for 5–27 years (mean 15 years), including 24 excellent, 51 partial and 26 poor responders, we found that excellent responders were significantly less likely to have the Met/Met genotype and Met allele of this polymorphism. Similar as in the case of the *BDNF, 5-HTT* and *DRD1* genes, the functional genotype of the *COMT* gene, predisposing to bipolar disorder, was associated with poorer lithium prophylactic efficacy [24].

Glutamatergic system

FYN is a protein kinase functionally related to the glutamatergic NMDA receptors and preferentially phosphorylates subunit GRIN2B of the NMDA receptor. FYN is also involved in mediating signal transduction in the BDNF/TrkB pathway. The study of the *FYN* gene polymorphisms in relation to lithium prophylactic effect became aftermath of our previous case-control research where the association between some polymorphisms of this gene and bipolar disorder was demonstrated [31]. he study group consisted of 100 bipolar patients receiving lithium for 5–27 years (mean 15 years). Among them, 24 patients were excellent lithium responders, 51 – partial responders and 26 – non-responders. We did not find any significant differences in genotype distribution and allele frequencies between T/G and A/G *FYN* gene polymorphisms and the efficacy of lithium prophylaxis. On the other hand, a trend toward an association of TT genotype and T allele of T/C polymorphism (rs3730353) with poorer lithium response was observed [32]. Interestingly, in our previous study, such association was found with a predisposition to bipolar disorder [31].

We also investigated a possible association of the prophylactic effect of lithium with two polymorphisms (rs73013328 and rs890) of the glutamatergic receptor *GRIN2B* gene. However, we did not find any relationship with lithium efficacy [24].

Glycogen synthase kinase-3 beta (GSK-3β)

GSK-3β is a serine/threonine kinase which regulates gene transcription, influences synaptic plasticity, apoptosis, cell structure, resistance to stress, and biological rhythms. Lithium inhibition of GSK-3β may be important for the therapeutic effect in mood disorders [33]. Since GSK-3β is also a major enzyme for the metabolism of amyloid precursor protein and tau protein phosphorylation, which play a major pathogenetic role

in Alzheimer's disease, the inhibitory effect of lithium on the enzyme may determine a potential therapeutic effect of lithium in neurodegenerative diseases [34]. The effects of lithium on GSK-3β may be also significant in causing lithium-induced side effects, e.g., in the kidneys and thyroid gland, as well as may be related to the anti-suicidal properties of this ion [35].

In 2005, Italian investigators reported that the efficacy of long-term lithium prophylaxis is influenced by the – 50C/T polymorphism in the *GSK-3β* gene (rs334558). In their sample, a better efficacy of lithium was observed in the carriers of the mutant C allele of this polymorphism [36]. In our study, a relationship between the lithium prophylactic efficacy and – 50C/T polymorphism of the *GSK-3β* gene was investigated in 89 bipolar patients receiving lithium for 5–27 years (mean 15 years), including 23 excellent responders, 47 partial responders and 19 non-responders to lithium [37]. Our findings did not confirm those of Benedetti et al. [36].

In 2013, we studied this functional – 50C/T polymorphism of the *GSK-3β* gene in a group of long-term lithium-treated patients and assessed its association with various parameters of kidney function. The study group consisted of 78 patients with bipolar mood disorder receiving lithium for 5–38 years (mean 16 years). Thirty-four patients had the T/T genotype, 37 patients had the T/C genotype and 7 patients had the C/C genotype. Patients homozygous for the C allele had significantly higher urine specific gravities compared to the remaining genotypes [38]. It can be reminded that in the Italian research C allele was associated with better lithium prophylactic efficacy [36]. The results of our study indicate that the GSK-3β genotype may be associated with lithium-induced impairment of renal concentrating ability in long-term lithium-treated bipolar patients

Biological rhythms

In the regulation of biological rhythms, several genes, termed *clock* genes, take part. At the molecular-genetic level, candidate gene studies showed that some clock genes, such as *ARNTL*, *CLOCK, PER3*, and *TIM*, have been associated with a predisposition to bipolar disorder [39, 40]. Our study of these genes was performed on 115 patients with bipolar disorder receiving lithium prophylaxis for 6–39 years (mean 22 years). In this study, we used the Alda scale for the retrospective estimation of lithium response. We genotyped nine single nucleotide polymorphisms (SNPs) of the *CLOCK* gene, 18 SNPs of the *ARNTL* gene, six SNPs of the *TIM* gene, and nine SNPs of the *PER3* gene. The association with the efficacy of lithium prophylaxis was demonstrated for six SNPs and three haplotype blocks of the *ARNTL* gene, and two SNPs and one haplotype block of the *TIM* gene. We did not find any connection with SNPs or haplotypes of the *CLOCK* and *PER3* genes [41].

Hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis is the primary hormonal stress response-regulating mechanism in humans. Genetic variations in the main genes involved in the HPA axis function may determine the differences among individuals in the HPA axis response to stress. These genes include (1) corticotropin-releasing hormone (*CRH*) gene; (2) corticotropin-releasing hormone-binding protein (*CRHBP*) gene, (3) corticotropin-releasing hormone receptor 1 and 2 (*CRHR1* and *CRHR2*) genes, (4) glucocorticoid receptor (*NR3C1*) gene; (5) mineralocorticoid receptor (*NR3C2*) gene, and (6) FK506 binding protein 5 (*FKBP5*) gene. There have been several studies, including those of Poznan center, showing an association of these genes with bipolar disorder and some features of the illness [42–44].

In Poznan, we tried to assess the association of the polymorphisms of these genes with lithium prophylactic actions. In our first study, 115 bipolar patients receiving lithium for 5–27 years (mean 15 years) were included. The criteria of excellent lithium responders were met by 30 patients, of partial responders by 58 patients, and of non-responders by 27 patients. We genotyped eight polymorphisms of the glucocorticoid receptor *(NR3C1*) gene (rs10052957, rs6196, rs6198, rs6191, rs258813, rs33388, rs6195, rs41423247) by Taq-Man SNP Genotyping Assays. Linkage disequilibrium analysis was performed in Haploview v. 4.1. Significant differences in allele frequencies for rs41423247 polymorphism between patients with different lithium responses were demonstrated, and the C allele was associated with excellent lithium response. For the remaining studied *NR3C1* gene polymorphisms, no association with lithium prophylactic effect was observed. We found a strong linkage disequilibrium of five *NR3C1* gene polymorphisms (rs6198, rs6191, rs6196, rs258813, rs33388). The TAAGA haplotype was less prevalent in excellent lithium responders [45].

The second study included 93 patients with bipolar disorder receiving lithium carbonate for 5–27 years (mean 16 years). The degree of the prophylactic lithium efficacy was estimated by means of the Alda scale. We genotyped 28 polymorphisms in the genes encoding the following proteins involved in HPA axis regulation: CRHR1, AVPR1b, FKBP 5, FKBP4, BAG1, STIP1, GLCC1, DUSP1, SRSF 3, SRSF9, SRSF5, and ACP1. A correlation between stressful life events at the first episode and poorer response to lithium was observed. Also, a significant association between three *FKBP5* polymorphisms (rs1360780, rs7748266, and rs9296158), one *ACP1* variant (rs300774), one *GLCC1* variant (rs37972) and the degree of lithium response was demonstrated. Five out of seven *FKBP5* polymorphisms showed a linkage with a haplotype associated with lithium efficacy. Concerning the remaining analyzed SNPs, no connection was found with lithium prophylactic efficacy [46].

Matrix metaloproteinase-9 (MMP-9)

Matrix metalloproteinases are extracellular endopeptidases that act on extracellular matrix proteins and adhesion proteins. Matrix metalloproteinase 9 (MMP-9) has been implicated in many pathological conditions, including cancer and heart diseases, as well as in various aspects of brain functions (e.g., neuroplasticity). The Poznan group was the first to show a possible role of the *MMP-9* gene in the pathogenesis of bipolar disorder. In 416 patients with bipolar disorder and 558 healthy controls, we genotyped a functional – 1562C/T polymorphism of the *MMP-9* gene (rs3918242). Patients with bipolar disorder had a significant preponderance of T allele versus C allele of 1562C/T polymorphism of the *MMP-9* gene, compared to healthy controls. Our results obtained for this polymorphism in schizophrenia showed a preponderance of C allele. Therefore we put forward a hypothesis that the *MMP-9* gene may be a susceptibility gene to both bipolar disorder and schizophrenia, however, with different allelic variants occurring in these two illnesses [47].

The results obtained in patients with bipolar disorder prompted us to assess a possible association of this – 1562C/T *MMP-9* gene polymorphism (rs3918242) with lithium prophylactic effect. One hundred and nine bipolar patients treated with lithium for 5–27 years (mean 15 years), including 23 excellent responders, 47 partial responders, and 19 non-responders to lithium were studied. However, in our research, no association was found between the studied polymorphism and the lithium prophylactic efficacy [48].

Discussion

The studies using the *candidate gene* approach have several limitations, which were mentioned earlier. However, given all methodological restrictions, it can be said that the candidate gene studies of lithium prophylactic efficacy performed at the Poznan University of Medical Sciences in 2005–2018 corroborated a role of several biological systems in lithium prophylactic activity as well as a connection between lithium mechanisms and pathogenesis of bipolar disorder. These systems include BDNF, serotonergic, dopaminergic and glutamatergic neurotransmission, GSK-3β, biological rhythms, and the HPA axis.

An interesting picture emerges when the functional polymorphism of the gene associated with better response to lithium is considered in the framework of the predisposition to bipolar disorder. In most of our studies, a polymorphism associated with a predisposition to bipolar disorder determined a poorer prophylactic lithium efficacy. This was the case with the Val/Met *BDNF*, l/s *5-HTTLPR*, – 48A/G *DRD1*, Val/Met *COMT*, and T/C *FYN* genes polymorphisms. The association of s allele of the *5-HTT* gene polymorphism with poorer lithium prophylactic efficacy is similar to the association with the poorer antidepressant effect of SSRIs [20]. It looks like the better effect of lithium in these instances could be associated with a compensatory action of

this ion on a gene-related deficit in bipolar disorder. On the other hand, in our study of the association between lithium effects on kidney and the – 50C/T polymorphism of the *GSK-3β* gene, the C allele of this polymorphism implied to a predisposition to bipolar disorder was associated with resistance to lithium-induced decrease of renal concentrating ability [38].

In the second decade of the 21st century, the most important molecular genetic studies have been performed using the genome-wide association study (GWAS) method. In 2009, on the initiative of the IGSLI (International Group for The Study of Lithium Treated Patients) and the American National Institute of Mental Health (NIMH), the International Consortium on Lithium Genetics (ConLiGen) was established during a meeting in Bethesda. It aimed to gather a large number of patients with bipolar disorder receiving lithium for prophylactic purposes in order to carry out a GWAS of lithium prophylactic efficacy. The prime mover of this undertaking was Thomas Schulze, German psychiatrist, at the time a NIMH fellow, currently working at the University of Munich. Apart from Schulze, the founding group consisted of such lithium researchers as Martin Alda (Canada), Michael Bauer (Germany), Maria Del Zompo (Italy), Gonzalo Laje (USA), Francis McMahon (USA), Mirko Manchia (Italy), Roy Perlis (USA), Johannes Schumacher (USA), and Janusz Rybakowski (Poland). The description of the ConLiGen initiative was featured in a special edition of the *Neuropsychobiology* journal on the 60thanniversary of the introduction of lithium into treatment [49], while the work on the clinical assessment methods used in the ConLiGen study has already been mentioned [9].

The Poznan group contributed to the first GWAS concerning the prophylactic effects of lithium conducted as part of the ConLiGen project showing a significant association of lithium efficacy with the locus on chromosome 21, which contains two genes of long non-coding RNA (lncRNAs) – an important regulator of gene expression in the central nervous system [50]. Following this first study, the Poznan center has been a part of further publications of the ConLiGen group. In one of them, it was found that in bipolar patients, the polygenic risk score for schizophrenia was associated with poorer lithium prophylactic efficacy [51]. In another research paper, 15 microRNAs showed an association with both the dichotomous and continuous phenotype concerning lithium prophylactic efficacy according to the Alda scale [52]. Several new studies are underway.

In conclusion, the candidate gene studies, including those performed in Poznan, have provided a creditable service to the pharmacogenomics of lithium prophylaxis, setting the stage for the next generation of molecular genetic research of this issue.

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