Neuroscience Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Minireviews

Lithium response in bipolar disorder: Genetics, genomics, and beyond

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ARTICLE INFO

Keywords:
Genome-wide association studies
Polygenic risk score
iPSC
Mood-stabilizer

ABSTRACT

Lithium is an effective mood stabilizer in bipolar disorder (BD). There is, however, high variability in treatment response to lithium and only 20–30% of individuals with BD are excellent responders. This subgroup has been shown to have specific phenotypic characteristics, and family studies have implicated genetics as an important factor. However, candidate gene studies did not find evidence for major effect genes. Genome-wide association studies (GWAS) have emphasized that lithium response is a polygenic trait. GWAS based on larger sample sizes and non-European ancestries are likely to shed light on the genomic architecture of this trait. Furthermore, induced pluripotent stem cells, transcriptomics, epigenetics, the integration of multiple omics data, and their combination with advanced machine learning techniques hold promise for the understanding of the complex biological underpinnings of lithium treatment response.

1. Introduction

Lithium, first introduced in 1949 as a pharmacological option in psychiatry, remains the most prescribed mood stabilizer for long-term maintenance treatment in bipolar disorder (BD) patients [1], although its exact mode of action is only partially understood [2]. Besides its well-documented effect on reducing risk of relapse, particularly effective for the prevention of manic episodes, lithium has also proven to be effective for the reduction of the risk of suicide attempt [3–7]. Moreover, lithium can be used to treat acute episodes of mania in BD [8,9].

Regarding its mood stabilizing properties, unfortunately, not all patients treated with lithium salts have the same clinical response. The studies that have evaluated such heterogeneity have consistently reported that 20% to 30% of patients have a sustained improvement in the course of the disease, with a remarkable reduction or even absence of affective episodes [10]. These subjects are considered as excellent lithium responders. However, about 30% of patients are only partially responsive and more than 40% have no clinical response to lithium at all [11–13].

The lack of a well-established mode of action of lithium also complicates the search for the molecular targets underlying the differential response to it. Since relevant targets of lithium are incompletely understood, hypotheses-driven research into these mechanisms has had limited success so far (see below). Furthermore, since lithium is not metabolized in the liver, knowledge on the large effects of genetic variation in the Cytochrome-P450 enzyme family on drug clearance (e.g., [14,15]) cannot be applied.

Considering such inter-individual variability in lithium response, the identification a priori of who will likely respond/not respond would represent a major reduction of duration of untreated illness in these patients. In this vein, several studies have shown that the course and clinical characteristics of a patient are able to explain, at least, part of the variability on lithium response. Earlier studies had already established that lithium-responders correspond to the 'classic' subtype of BD, presenting with euphoric mania and melancholic depression, low comorbidities, frequently having a family background of psychiatric disorders [16,17]. Moreover, a recent study has shown that late age of onset, completely episodic clinical course, lack of rapid cycling, absence of psychosis, and few psychiatric comorbidities are characteristics usually found in patients with a good lithium response [18]. Conversely, another study described that the presence of suicidal behavior, a chronic course of the disease, current anxiety symptoms, functional impairments, negative life events, presence of mixed episodes, and a comorbid personality disorder were associated with a poor lithium response [19]. However, prediction based exclusively on clinical data has not been, so far, able to generate predictive models of clinical utility due to their

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https://doi.org/10.1016/j.neulet.2022.136786
Received 1 April 2022; Received in revised form 1 July 2022; Accepted 6 July 2022
Available online 8 July 2022

limited combined power. However, machine-learning models may do so in the future [20].

Biological markers hold promise as factors able to fill this gap and contribute to current and future clinical predictive models. Among them, genetic factors have gained interest over the last years due to the advances in the technical and statistical methods for their analysis [21].

2. Genetics and genomics of lithium response

According to current evidence, and like BD itself, clinical response to lithium treatment is a complex phenotype, result of the interplay between multiple factors. The first evidence of the role of genes in lithium response was based on family studies. These early studies made the interesting observation that patients with a good lithium response frequently belong to lithium-responsive families [22,23]. Also, youths with BD whose BD parents were good responders to lithium showed a similar, classical pattern of mood disorder with an episodic course, while offspring of poor lithium responders showed a more chronic course [24]. These results suggested that genetic factors participate in the lithium response phenotype although family studies did not have the ability, due to their design, to identify specific candidate regions in our DNA.

2.1. Linkage and segregation studies

Molecular genetics approaches have been performed to identify genes and genetic variants associated with lithium response since the early 1980s. The results of these studies have been extensively reviewed by Pisanu et al. [25,26] and Senner et al [27]. Linkage and segregation studies have been extremely successful for the identification of genes involved in mono- / oligogenic mendelian human disorders [28,29]. Several loci with a LOD score > 3 (evidence for linkage) for lithium response have been identified in linkage studies: 20p11.2–q11.2, 15q14, and 14q11.2 [30–32]. However, the lack of replicability of these results across the studies suggests that it is unlikely that this phenotype can be explained by a major gene with large effect size. Conversely, it provides additional evidence of the polygenic nature of this trait, with many genetic variants of modest effect contributing to an individual profile of better/worse response to lithium, in a similar fashion as other psychiatric traits [33,34].

2.2. Candidate-gene association studies

Genetic association studies, better powered for the identification of genetic risk variants of milder effect [35], have also analyzed this phenotype. Approximately 70 different candidate-gene association studies, normally exploring genetic variation in a gene (or several genes) that has been selected a priori, have tested the association of specific genetic variants with lithium response in almost 60 different genes [27]. Taken together, the results of these studies suggest that genes that code for GSK3β, BDNF, and the serotonin transporter are robust candidates to be associated with lithium response in BD, despite inconsistent results [25]. Recently, an association study based on the imputation of classical HLA alleles found that HLA-DRB1 and HLA-DQB1 were associated with lithium response, although results need to be replicated in independent samples [36].

Candidate-gene association studies have been useful to uncover suggestive associations with this trait in our DNA. However, their hypothesis-driven design focus on a specific region of our DNA, missing the global (genomic) perspective. Technical and methodological advances have catalyzed the development of genome-wide association studies (GWAS) in the last decades.

2.3. Genome-wide association studies

GWAS, a hypothesis-free extension of candidate gene studies, aim to reveal genotype-phenotype associations with specific genetic loci by testing the association between millions of common genetic variants distributed across the human genome with the phenotype of interest. This genome-wide approach, applied to large samples of individuals to ensure adequate statistical power, has remarkably improved our understanding of the genetic architecture of complex traits, including psychiatric disorders [37,38]. Several GWAS of lithium response have been published to date. Some of them were not able to find genome-wide associations (association with a P-value $< 5 \times 10^{-8}$) with a formal definition of lithium response: the STEP-BD study (discovery sample: n = 458 Caucasian individuals; phenotype: time to reoccurrence of mood episode; replication sample: University College London, n = 359 lithium-treated European individuals, phenotype: classification of clinical records by research psychiatrist into “good”, “intermediate” and “poor” lithium responders), a combined Swedish-UK sample (n = 2698 individuals with self-reported, and n = 1176 individuals with clinically documented response to lithium, both of European ancestry), and a sample from Sardinia (n = 204, using the so-called Alda scale, formally named “Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder” [22,39–41]. Chen et al. reported in a sample of BD patients of Han Chinese descent a genome-wide association of lithium response with intronic variants in the *GADL1* gene (n = 294 in the discovery sample, n = 100 in the first replication sample and n = 24 in the second replication sample, phenotype: Alda scale) [42]. Unfortunately, this association could not be replicated in independent samples (n = 218, phenotype: Alda scale), raising questions about the generalizability of this result [43]. Taken together, the results of these GWAS suggested that two factors needed to be improved to find meaningful associations between genetic variants and lithium response: sample size to be able to detect moderate effect size effects, and a standardized assessment of lithium response.

With the aim to tackle the limitations mentioned above, the ConLiGen consortium was founded in 2008 to carry out a genome-wide association study of lithium response using a standardized lithium response definition whose psychometric properties are well-defined (www.conligen.org) [44,45]. A GWAS was performed using combined data from 22 centers around the world, with a total of 2563 genotyped subjects (post-QC, dichotomous phenotype: n = 2343 European and n = 220 East Asian individuals, continuous phenotype: 2039 European and 194 East Asian individuals) evaluated for lithium response using the Alda scale [46]. A genomic locus on chromosome 21 that contains two long non-coding RNAs (AL157359.4 and AL157359.3) yielded genome-wide significant associations with a continuous definition of lithium response. An independent prospective sample of patients treated with lithium for 2 years showed that those patients who were carriers of good-response genetic variants in the chromosome 21 locus had a significantly lower rate of relapse than non-carriers patients in the same study, reinforcing the interest of these genetic variants. While this finding is encouraging, its practical value is limited, even if confirmed in further studies, as the low frequency of the allele limits the utility for genetic testing. Further GWAS studies using larger samples, including those with non-European ancestries, are needed to find additional response-associated alleles.

Besides the interest of GWAS for the identification of single genetic variants that participate in lithium response, the results of these studies also allow to estimate the proportion of variance in lithium response explained by common, i.e. frequent variants, the so-called SNP-heritability (SNP-h^2). The only GWAS on lithium response that reported this parameter in lithium response, Song et al., observed a SNP-h^2 for self-reported lithium response of 29% and a SNP-h^2 for a clinically documented lithium of 25% [40].

2.4. Polygenicity and lithium response

GWAS studies on complex traits have provided compelling evidence of their polygenicity. This means that hundreds to thousands of genetic variants jointly determine the genomic risk associated with a given trait.

Such a joint contribution en masse of genetic variants can be quantified nowadays using polygenic scores (PGS, also known as PRS). PGS are calculated as a sum of an individual's phenotype-associated alleles weighted by the effect size of each variant as estimated in discovery GWAS [47]. Taken together, PGS provide a quantitative measure of the individual genetic burden of a phenotype.

To the best of our knowledge, current GWAS on lithium response have not achieved the statistical power required to generate good estimates of the effect size of each genetic variant yet. As a consequence, lithium response-PGS are not suitable to predict lithium response in independent samples. Ongoing efforts based on larger samples of lithium treated patients may achieve the desired statistical power and therefore provide the required information for the calculation of lithium response-PGS of clinical utility regarding both prevention and patient stratification.

Interestingly, PGS for other psychiatric traits have been associated with lithium response in the ConLiGen sample [46]. The first study, published on 2018, found an association of polygenic risk of schizophrenia (PGS-SCZ) with a worse lithium response in bipolar patients [48]. Very similar results were obtained for the polygenic risk of major depressive disorder (PGS-MDD) in another study, showing that individual genetic burden for depression is associated with a poor lithium response [49]. Likewise, combining PGS-SCZ and PGS-MDD was found to improve the performance of predictive models aiming to differentiate lithium responders from non-responders [50]. The exact nature of the relationship between mental illness and treatment response remains to be established, although these results strongly suggest that an extensive genetic overlap exists between them. Using a different approach, a machine-learning study has tried to predict response to lithium directly from genomic data, although with limited success [51]. However, further harmonization of lithium response assessment, and larger datasets, may improve this interesting approach in the future.

2.5. Whole exome sequencing studies

Whole Exome Sequencing (WES) analysis has also been carried out in a discrete number of studies in lithium response. WES allows to identify variants (common and rare) that are likely to modify the structure and/or function of the proteins that are coded by the sequenced exomes. A WES study based on pedigrees of European lithium-responsive BD patients (phenotype: combination of a. primary episodic BD according to the Schedule for Affective Disorders and Schizophrenia, lifetime version, b. high risk of recurrence, and c. unequivocal lithium response) reported several rare variants in the exomes of affected subjects: *DNAH14*, *ARV1*, *SLK*, *TTC40*, *CARD16*, *ZNF259*, *SLU7*, *WWC1*, *TAB2*, *MTOR*, *CASP1*, *SLC25A21*, *ID1*, *CDV3*, and *ODZ2* [52]. A study that combined linkage and exome sequencing in a lithium-responsive (phenotype: absence of psychiatric symptoms interfering with daily and social activities for more than 1 year) pedigree of Japanese BD patients narrowed down their findings to the *DOCK5* (Dedicator Of Cytokinesis 5) gene and a rare heterozygous mutation in exon 31 [53]. Finally, another study performed WES in a European family with monozygotic twins discordant for lithium response (phenotype: clinical course under lithium therapy) and found suggestive evidence for Neurofibromin type 1 (*NF1*), Biorientation of chromosomes in cell division 1 (*BOD1*), Golgi-associated gamma adaptin ear-containing ARF binding protein 3 (*GGA3*), Disrupted in schizophrenia 1 (*DISC1*), Neuromedin U receptor 2 (*NMUR2*), and Huntingtin interacting protein 1-related (*HIP1R*) [54].

3. Different avenues to the genomics of lithium response

3.1. Induced pluripotent stem cells

Advances in the methodologies for obtaining induced pluripotent stem cells (iPSCs) from somatic cells and the subsequent reprogramming into different cell types of the central nervous system could represent a game changer for the understanding of how genomic background influences cellular phenotypes relevant for lithium response. The big advantage of this approach with respect to other cellular or animal models is that it retains the full individual genomic risk background. Such a possibility paves the way for the in vitro experiments that could shed light in the role of the individual genomic risk background on the mechanism of action of lithium with unprecedented resolution.

Proof-of-concept studies have already shown that iPSCs of BD patients are hyperexcitable compared to healthy controls and that such hyperexcitability was normalized with lithium only in lithium responders (phenotype: Clinical Global Impressions Scale score after four months of lithium treatment) [55]. A subsequent study (phenotype: Alda scale) confirmed these findings [56]. More recent studies have observed that cell death of lymphoblastoid cell lines (LCLs) from BD patients could only be rescued by lithium in LCLs from lithium responders (phenotype: Alda scale) [57]. Likewise, circadian rhythms in neuronal precursor cells (NPCs) and reprogrammed glutamatergic neurons were more disturbed in samples derived from lithium non-responders with respect to lithium responders (phenotype: most and least lithium-responsive as defined by time to clinical relapse) [58]. The same study observed that lithium lengthened the period of neuronal rhythms in lithium responders and control neurons. Finally, a very recent study has observed that lithium treatment improves oxygen consumption rate levels only in NPCs derived from lithium-responders (phenotype: clinical course under lithium therapy), suggesting that the effect of lithium finally modifies mitochondrial function [59].

Despite the interest of these studies, their integration with the individual genomic burden of each patient regarding lithium response remains to be established. Therefore, further studies are warranted to find a relationship between the complex genetic architecture of lithium response and its cellular phenotypes.

3.2. Transcriptomics and epigenetics

Another approach to characterize the biology of lithium response is to research transcriptomic differences in whole blood between responders/non-responders. Two studies from the same laboratory pursued this strategy, and identified pathways related to regulation of anti-apoptosis [60] and to amino-acid transport [61] (phenotype in both studies: reduction in HAM-D score after lithium treatment). Although the small number of patients researched in these studies limits the generalizability of their results, the approach may bear fruit when larger patient samples are studied. A related approach to improve statistical power in transcriptomic studies is the use of techniques such as weighted gene co-expression network analysis (WGCNA), which identifies modules of co-regulated, and thus assumed to be functionally related, genes. Using this technique, Stacey et al. [62] (phenotype: Alda scale), identified a module whose main regulators were mitochondrially-encoded genes. Further, enrichment analysis showed that "genes involved in mitochondrial functioning were heavily overrepresented in this module, specifically highlighting the electron transport chain (ETC) and oxidative phosphorylation (OXPHOS) as affected processes." Mitochondrial function has long been implicated in lithium's mode of action [2], with further evidence provided by the latter WGCNA study. A different but related field of research is focusing on epigenetic mechanisms of lithium response. These heritable mechanisms of gene regulation independent of DNA sequence changes provide another window into the differential treatment response of lithium and have recently been comprehensively reviewed [26]. Although the results are promising, the limited number of both candidate gene and genome-wide studies in combination with their small sample sizes did not allow replicable results to emerge.

3.3. Integration of multiple omics data

A highly desirable goal is to integrate multiple levels of omics data using modern analytic strategies. In a preprint (https://doi.org/10.110

1/2022.01.10.21268493), Niemsiri et al. (2022) used a combination of lithium-response GWAS data (European ancestry; phenotype: stabilization on lithium monotherapy after 4 months, n = 256) and transcriptomic data from iPSCs derived from responders/non-responders to lithium (phenotype: Alda scale). These data were analyzed using a combination of sophisticated data science methods and implicate focal adhesion and the extracellular matrix in lithium response. Importantly, the study revealed large transcriptomic differences between iPSCs from responders and non-responders to lithium, emphasizing biological heterogeneity. Although the conclusions of the study are limited by their small sample size, such integration of multiple levels of omics data is a harbinger of future research.

4. Conclusion

Responders to lithium differ from non-responders both on the phenotype as well as on the genomic level. GWAS studies have shown that lithium response is best understood as a complex, polygenic trait, similar to BD and other severe mental disorders. Furthermore, there appears to be extensive overlap of the genomics of lithium response to those of psychiatric disorders. Further studies with larger samples of multiple ancestries will likely lead to robust response-associated alleles and PGS in the future. Furthermore, genome sequencing and methodological advances such as the integration of multiple omics data will further improve our understanding of this highly relevant phenotype. To this end, a well-defined lithium response phenotype is of crucial importance to any genetic study. In light of the large sample sizes necessary for modern genomics research, we suggest that the Alda scale, which retrospectively assesses response to lithium, to be used in future large-scale studies. Its psychometric properties are well-known [45], and there exist a questionnaire [63] to improve standardization. Furthermore, the systematic assessment of various confounders makes this instrument a valuable tool for future research.

5. Data availability

Data availability is not applicable to this article as no new data were created or analyzed in this review.

6. Funding Statement:

Thomas G. Schulze was supported by DFG grants SCHU 1603/4–1, 5–1, 7–1. Urs Heilbronner was supported by European Union's Horizon 2020 Research and Innovation Programme (PSY-PGx, grant agreement No 945151).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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