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Genetic Predictors of Lithium Response

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Summary. Lithium remains a first-line pharmacological treatment of bipolar disorder (BD). However, treatment response is heterogeneous, with several lines of evidence implicating genetic factors. Unfortunately, neither hypothesis-driven approaches nor initial genome-wide association studies (GWAS) were successful in identifying genetic drivers of response heterogeneity, probably due to low statistical power and different phenotype measurements. Recently, a GWAS of the Consortium of Lithium Genetics (ConLiGen) has identified four single nucleotide polymorphisms (SNPs) mediating response to lithium, located in genes for two long non-coding RNAs. This success was only possible by international collaboration and the use of an established lithium response scale. The findings await further replication.

Key words: bipolar disorder; medication; GWAS; response; ALDA scale; long non-coding RNA.

Генетические предикторы терапевтического ответа на препараты лития

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Резюме. В настоящее время литий остается фармакологическим препаратом первой линии для лечения биполярного расстройства (БАР). Тем не менее, ответ на лечение неоднороден, что объясняется несколькими линиями доказательств вовлечения генетических факторов. К сожалению, ни исследования генов-кандидатов, основанные на гипотезах, ни первичные полногеномные исследования (GWAS) не были успешны в определении генетических факторов гетерогенности ответа. Вероятно, это связано с низкой статистической мощностью и различными подходами к оценке фенотипа. Недавно Международный консорциум по фармакогенетике препаратов лития (ConLiGen) провел GWAS и идентифицировал четыре однонуклеотидных полиморфизма (SNP), опосредующих ответ на литий и расположенных в генах двух длинных некодирующих РНК. Этот успех был возможен только благодаря международному сотрудничеству и использованию единой шкалы оценки ответа на терапию литием. Полученные данные нуждаются в дальнейшей репликации.

Ключевые слова: биполярное аффективное расстройство, терапия, GWAS, терапевтический ответ, шкала ALDA, длинная некодирующая РНК.

BD is a severe psychiatric condition, characterized by alternating episodes of mania and depression. Lithium remains a first-line pharmacological treatment of BD, and is effective in reducing affective episodes, suicide risk, and overall mortality (Papiol, Schulze, & Alda, 2018). However, individual response is heterogeneous, only about 30% of BD patient treated with lithium robustly respond to it (Garnham et al., 2007). Also, although having superior efficacy, serious side effects and interactions with other medication classes complicate its use (Alda & Manchia, 2018). Thus, there is a pressing need to identify predictors of lithium response that may eventually serve as biomarkers. As previous studies have also found evidence that lithium response is a familial trait (Grof et al., 2002), this implicates that there may be genetic factors mediating treatment response. Indeed, the heritability of lithium response estimated from SNPs is around 0.30, i.e. about 30% of the total variation in lithium response can be explained by SNPs (Song et al., 2017). In search of specific genetic underpinnings, hypothesis-driven studies have researched single genes associated with neurotransmitters, circadian signaling, the inositol pathway, brain-derived neurotrophic factor/tropomyosin receptor kinase B (BDNF/TrkB) signaling and other signaling pathways (Pisanu, Heilbronner, & Squassina, 2018). However, no molecular genetic markers have been reproducibly identified using this approach. Recently, hypothesis-free GWAS, simultaneously investigating millions of SNPs, have examined differences in lithium response phenotypes. A GWAS by Perlis et al. (2009) examined lithium response using the time to recurrent mood episodes as phenotype, however no SNP met the stringent statistical threshold for GWAS ($p=5\times10^{-8}$). Also, Squassina et al. (2011) compared extreme groups for lithium response in 204 Sardinian BD subjects, without finding GWAS-significant signals. Notably, the study used an established lithium response scale, the so-called Alda scale (Grof et al., 2002), which retrospectively evaluates long-term treatment response to lithium. Specifically, the Alda scale quantifies symptom improvement in the course of lithium treatment (A scale, range 0–10), which is then weighted against five criteria (B scale) that assess confounding factors, each scored 0,1, or 2. These confounding factors are the number and frequency of episodes without lithium treatment, duration and use of additional medication during lithium treatment, and compliance. The total score is then derived by subtracting the total B score from the A score. Negative scores are set to 0 by default so that the total score ranges from 0 to 10. In 2016, ConliGen (Schulze et al., 2010), reported a genome-wide significant find-

ing in the largest GWAS on lithium response to date (Hou et al., 2016, n = 2563). This study also used the Alda scale, and researched two different phenotypes, a continuous and a dichotomous one. The continuous phenotype used the subscale A of the Alda scale, while filtering out subjects with values on the B scale greater than 4. Using this phenotype, four SNPs on chromosome 21 (A single locus of four linked SNPs on chromosome 21 met genome-wide significance criteria for association with lithium response (rs79663003: $p=1.37\times10^{-8}$; rs78015114: $p=1.31\times10^{-8}$; rs74795342: $p=3.31\times10^{-9}$; rs75222709: $p=3.50\times10^{-9}$) were GWAS-significant, in genes for two long non-coding RNAs (AL157359.3 and AL157359.4), putatively regulating a variety of downstream processes. In an independent, prospective study of 73 patients treated with lithium monotherapy for a period of up to two years, carriers of the response-associated alleles had a significantly lower rate of relapse than carriers of the alternate alleles (p=0.03, hazard ratio = 3.8). The identified SNPs, while having moderate effects (about 1 point per allele on the 11-point Alda A subscale), do however have the drawback that the frequencies of the response-associated alleles are rather low, with most people carrying lithium-responsive alleles. No SNPs were associated with the dichotomous phenotype, that classified all individuals with a total score of 7 or greater as lithium responders. These results await further replication in independent samples. Also, further biological research is necessary to elucidate the functional role of these SNPs in lithium response.

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