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.
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 with lithium response (rs79663003: p=1.37×10^{-8}; rs78015114: p=1.31×10^{-8}; rs74795342: p=3.31×10^{-9}; rs75222709: p=3.50×10^{-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.

References

Сведения об авторах

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