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Genetic influences on response to mood stabilizers in bipolar disorder: current status of knowledge.

Rybakowski JK[1].

Author information

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-1990 s, 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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