

EPILEPSY

Psychiatric adverse effects of levetiracetam linked to genetic variation in dopamine signalling

Levetiracetam (LEV) is an effective and generally well-tolerated antiepileptic drug (AED), but has been shown to provoke psychiatric adverse effects such as aggression and irritability in a subset of patients. Clinical observations and behavioural data have provided hints that patients with pre-existing impulsive and aggressive tendencies might be at risk of adverse events on LEV treatment. In a study published in *Epilepsia*, Christoph Helmstaedter and colleagues sought to understand the genetic basis of these complications, and they pinpointed genetic variants in dopamine-related genes as probable contributory factors.

“Up to now, genetic research regarding AED treatment was focused on the question of efficacy,” says Helmstaedter. “However, efficacy of AED treatment represents only one aspect of drug action; side effects—more often negative than positive—are common, and significantly determine compliance and the longer-term retention of the individual drug.”

The researchers conducted an initial discovery study in 290 patients with epilepsy, followed by an independent replication study in 100 such patients. They used a candidate gene approach, focusing on single nucleotide polymorphisms (SNPs) that were already known to be associated with impulsivity and aggression.

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The discovery study provided evidence for associations between the psychiatric adverse effects of LEV and SNPs in the dopaminergic genes *COMT*, *DBH* and *DRD2*. However, only one of the associations—involving rs1800497 in *DRD2*, which affects dopamine D2 receptor availability at the synapse—was confirmed in the replication study. The team also

examined aggression-associated SNPs in genes involved in serotonergic and noradrenergic signalling, but none of these seemed to be risk variants for aggression or impulsivity in patients receiving LEV.

“The data provide supportive evidence that a predisposition to impulsivity and aggression increases the risk of negative psychotropic side effects under treatment with LEV,” concludes Helmstaedter. “The results encourage us to further follow this promising pharmacogenetic approach to characterize the genetic underpinnings of behavioural profiles of AEDs, in order to optimize treatment choices and improve compliance, drug retention and—last but not least—quality of life.”

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Original article Helmstaedter, C. *et al.* Genetic variation in dopaminergic activity is associated with the risk for psychiatric side effects of levetiracetam. *Epilepsia* doi:10.1111/j.1528-1167.2012.03603.x