Genetic difference predicts antidepressant response

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Researchers have identified subtle genetic variations that predict the efficacy of two widely used antidepressant drugs. They found that certain variants in the gene for a protective transporter protein that pumps drugs and other substances out of the brain compromise the effectiveness of the antidepressants citalopram (trade name Celexa) and venlafaxine (Effexor).

The researchers said their findings indicate that genetic testing could help predict the responses of patients to particular antidepressants. More broadly, they said, such tests could help predict the efficacy of any drugs used to treat neurological disease.

Manfred Uhr and colleagues published their findings in the January 24, 2008, issue of the journal *Neuron*, published by Cell Press.

“Antidepressants are the first-line treatment for major depression, but their overall clinical efficacy is unsatisfactory, as remission … occurs in only one-third of the patients after a trial with an adequately dosed single drug, and remission rates further decline following successive treatment failures,” wrote the researchers. “This situation is particularly alarming in view of the fact that major depression constitutes one of the greatest disease burdens worldwide and is anticipated to be the second leading global disease burden by the year 2020, trailing only cardiovascular disease.”

One reason for such poor response rates, said the researchers, is that

protective transporter proteins pump such substances as drugs and some hormones back into the bloodstream, preventing them from crossing the blood-brain barrier.

In their studies, the researchers explored the function of one such transporter protein, called P-gp, in preventing the entry of antidepressants into the brain. They first knocked out genes for the transporter protein in mice and administered the antidepressants to the animals. The researchers found that brain concentrations of citalopram and venlafaxine were regulated by P-gp—that the antidepressants were thus "substrates" of the transporter.

Studying 443 patients on the antidepressants, they next searched for variants in the human gene that correlated with reduced efficacy of the drugs. Their genetic analysis identified 11 such variants.

"To our knowledge, our results provide for the first time evidence that genetic variants in the [gene for P-gp] account for differences in the clinical efficacy of antidepressants, most likely by influencing their access to the brain," they wrote.

"The general conclusion to be drawn is that any drug administered to treat CNS diseases should be analyzed for its P-gp substrate status, which can be determined by using …knockout mice. From a clinical point of view, the findings warrant that patients receiving a drug that is a P-gp substrate for the treatment of brain diseases are genotyped to exclude the possibility that a patient receives a drug that fails to enter the CNS to an extent required for efficacy."

The researchers also suggested that development of future antidepressants should take into account whether the candidate drugs are transported by P-gp. And, clinical trials of antidepressants should be designed to take into account the P-gp genetic status of patients in the

trial.

Source: Cell Press