Genetic analysis can provide better dosage of antipsychotic drugs

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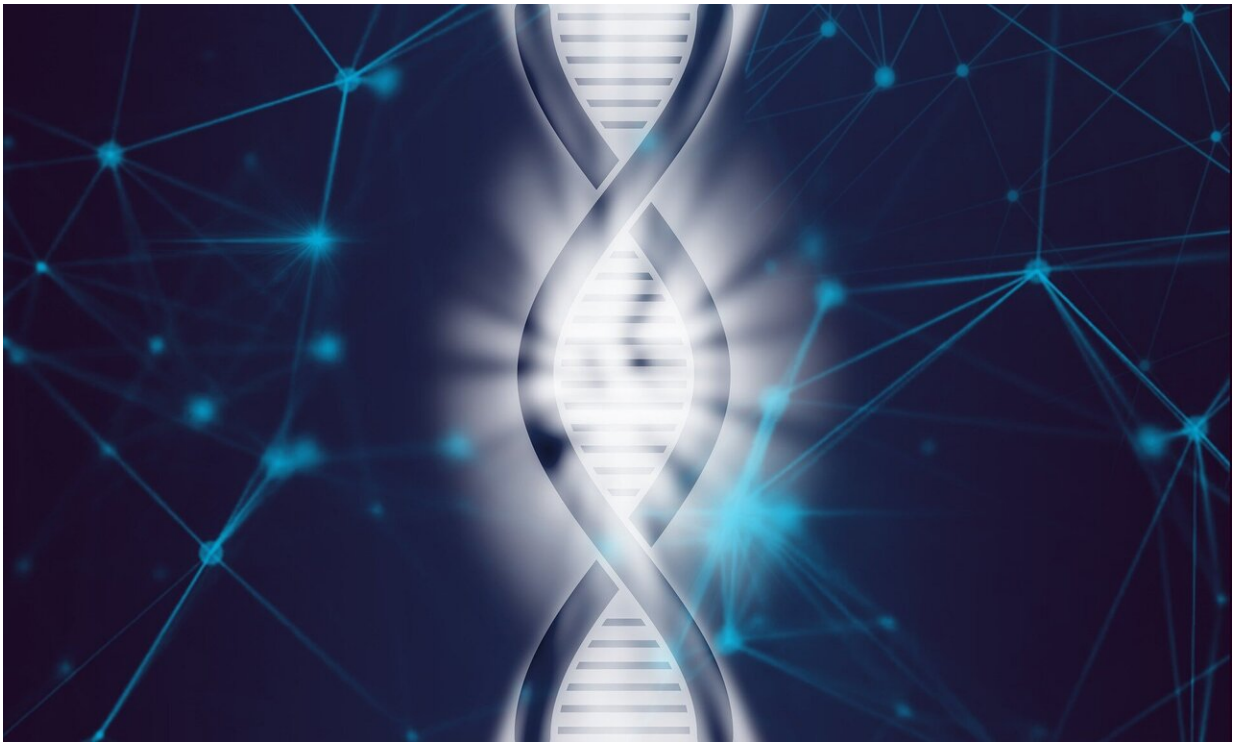

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An initial gene analysis may yield better outcomes when patients are treated with the antipsychotic drugs risperidone and aripiprazole. A novel study shows how the activity of a specific enzyme, which metabolises the two drugs, affects the individual dose that should be given for optimal treatment. The study is published in *The Lancet*

Psychiatry and has been conducted by researchers at Karolinska Institutet, Sweden, in collaboration with the Diakonhjemmet Hospital in Oslo, Norway.

The enzyme CYP2D6 metabolises many different drugs in the body, including the antipsychotic drugs risperidone and aripiprazole. The activity of the enzyme differs widely in the population due to variations in the CYP2D6 gene.

In collaboration with Espen Molden's group at the Diakonhjemmet Hospital in Oslo, researchers at Karolinska Institutet have studied how CYP2D6 gene variants affect the treatment result in 2,622 patients with psychosis or schizophrenia receiving either risperidone or aripiprazole.

The results show that patients with low CYP2D6 enzyme activity were given the drugs at too high a dose, while patients with high enzyme activity were given the drugs at too low a dose. As a consequence, many of them switched medication.

"In patients with too low or too high activity of the CYP2D6 enzyme, treatment failed to a larger extent, most likely due to side effects and lack of efficacy, respectively," says Marin Jukic, a postdoctoral researcher at the Department of Physiology and Pharmacology at Karolinska Institutet and the study's first author.

"Interestingly, we found that without knowing which gene variant the patient had, the psychiatrists had in the main altered the dose based on the clinical outcome, and this correlated with the anticipated effects of the patient's specific CYP2D6 genotype," says Magnus Ingelman-Sundberg, Senior Professor at the same department at Karolinska Institutet and the study's last author. "However, the dose changes were insufficient to avoid side effects or lack of effect. This is the first time we have been able to retrospectively compare dose changes during

routine clinical treatment with the patient's specific genotype."

The researchers believe that genotyping, i.e. the identification of the specific gene variant the patient carries, before initiation of risperidone or aripiprazole treatment, would result in much more effective treatment for millions of patients globally.

"Further studies are now needed to test other psychoactive drugs in order to generate additional scientific evidence to support new recommendations in psychiatry," says Magnus Ingelman-Sundberg. "Psychiatrists also need more education in this area."

In the early 1990s, Magnus Ingelman-Sundberg's research group was the first in the world to show the presence of several variants of the CYP2D6 gene explaining why some people, the so-called ultra-rapid metabolisers, require higher drug doses than others.

More information: Marin M Jukic et al. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study, *The Lancet Psychiatry* (2019). DOI: 10.1016/S2215-0366(19)30088-4

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