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Researchers discover gene that leads to severe weight gain with antipsychotic treatment

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Antipsychotic medications are increasingly prescribed in the US, but they can cause serious side effects including rapid weight gain, especially in children. In the first study of its kind, researchers at Zucker Hillside Hospital and the Feinstein Institute for Medical Research identified a gene that increases weight gain in those treated with commonly-used antipsychotic drugs. These findings were published in the May issue of *Archives of General Psychiatry*.

Second-generation antipsychotics (SGAs) were used as the treatment in this study. SGAs are commonly used to treat many psychotic and nonpsychotic disorders. However, it is important to note that these SGAs are associated with substantial weight gain, including the development of obesity and other cardiovascular risk factors. The weight gain side effect of SGAs is significant because it often results in a reduced life expectancy of up to 30 years in those who suffer from chronic and severe mental illnesses. The weight gain also prompts some to stop taking the medication, adversely impacting their quality of life.

In this genome-wide association study (GWAS), researchers first evaluated a group of pediatric patients in the US being treated for the first time with antipsychotics. They then replicated the result in three independent groups of patients who were in psychiatric hospitals in the United States and Germany or participating in European antipsychotic drug trials. The gene that was identified to increase weight gain, MC4R or melanocortin 4 receptor, has been previously identified as being linked to obesity and type 2 diabetes. In the new study, it was found that

patients gained up to 20 pounds when on treatment.

"This study offers the prospect of being able to identify individuals who are at greatest risk for severe weight gain following antipsychotic treatment," said Anil Malhotra, MD, investigator at the Zucker Hillside Hospital Department of Psychiatry Research and Feinstein Institute for Medical Research. "We hope that those who are at risk could receive more intensive or alternative treatment that would reduce the potential for weight gain and we are currently conducting studies to identify such treatment."

Additional Details About the Study

Researchers conducted the first GWAS of SGA-induced weight gain in patients carefully monitored for medication adherence who were undergoing initial treatment with SGAs. To confirm results, they next assessed three independent replication cohorts: 1) a cohort of adult subjects undergoing their first treatment with a single SGA (clozapine), 2) a cohort of adult subjects treated with the same SGAs as in our discovery sample, and 3) a cohort of adult subjects in the first episode of schizophrenia and enrolled in a randomized clinical trial of antipsychotic drugs.

The discovery cohort consisted of 139 pediatric patients undergoing first exposure to SGAs. The 3 additional cohorts consisted of 73, 40, and 92 subjects. Patients in the discovery cohort were treated with SGAs for 12 weeks. Additional cohorts were treated for 6 and 12 weeks.

This GWAS yielded 20 single-nucleotide polymorphisms at a single locus exceeding a statistical threshold of P□10-5. This locus, near the melanocortin 4 receptor (MC4R) gene, overlaps a region previously identified by large-scale GWAS of obesity in the general population. Effects were recessive, with minor allele homozygotes gaining extreme

amounts of weight during the 12-week trial. These results were replicated in 3 additional cohorts, with rs489693 demonstrating consistent recessive effects; meta-analysis revealed a genome-wide significant effect. Moreover, consistent effects on related metabolic indices, including triglyceride, leptin, and insulin levels were observed.

Provided by North Shore-Long Island Jewish (LIJ) Health System

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