Researchers discover new gene that regulates body weight

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Abraham Kovoor was studying a brain protein, called RGS9 2, that he had previously related to the involuntary, random and repetitive body movements that are side effects of drugs used to treat Parkinson's disease and schizophrenia.

While studying these side effects, which are called dyskinesia, Kovoor, an assistant professor in the University of Rhode Island's College of Pharmacy, discovered that RGS9 2 also plays a role in regulating body weight.

Results of his study were published in the November issue of PLoS One, an interactive open-access, peer-reviewed scientific and medical research journal.

Kovoor and his collaborators found that humans with a gene variation that could reduce RGS9 2 levels had a significantly higher body mass index.

Similarly, when they examined a strain of mice in which the RGS9 2 gene was deleted, so that these mice do not make RGS9 2 protein, they found that these weighed more than the wild-type strain and the percentage of body fat was much greater. Conversely, when RGS9-2 protein is over-expressed in rats, they found that the rats lost weight.

Because RGS9-2 is normally expressed in the brain's striatum, a section of the brain involved in both motor control and reward responses, Kovoor and his fellow researchers thought that the weight gain could be a result of an increased reward response triggered during eating.

"You would expect more eating from the mice without RGS9-2 (because they were the ones that gained weight), but that was not the case," Kovoor said. "Studies with humans, rats and mice implicate RGS9-2 as a factor in regulating body weight. But we had to look at another factor other than feeding behavior".

"Our research shows that the striatum, through RGS9-2, has a role in regulating body weight that is independent of the motivation, movement and reward responses," Kovoor said. "We have identified a new gene that likely regulates weight gain through metabolism."

Surprised by the discovery, Kovoor said he and his team have been studying RGS9-2 and its role in the movement side effects of drug therapy for Parkinson's disease and schizophrenia for almost a decade.

In fact, a company he established, Kovogen LLC, now based in Mystic, Conn., is developing methods for predicting which individuals are more likely to get these irreversible and debilitating side effects so that drug treatment can be optimized and tailored for individual patients.

"When you see Michael J. Fox continuously weaving and shaking, his movements are actually dyskinesia, a reaction to the medication used to treat his Parkinson's. Many people mistakenly assume that the shaking is a result of his Parkinson's disease, but the disease itself causes rigidity. Anti-psychotic drugs, which are used to treat schizophrenia, also cause similar involuntary movements that are irreversible.

"When we began looking at RGS9-2, nobody had an inkling as to why these drugs cause dyskinesias. We showed very early on that RGS9-2 modulates the function of the dopamine receptors, and dopamine receptors are the major targets of Parkinson's and anti-psychotic drugs," Kovoor said.

"We treated RGS9-2 knockout mice (those without the RGS9-2 gene) with anti-psychotic drugs or with L-DOPA, a drug used to treat Parkinson's disease, and the mice all rapidly developed dyskinetic movement disorders when being treated.

"RSG9-2 provided a springboard for investigating

how drugs produce these disorders," Kovoor said.

In fact, prompted by Kovoor's discovery, one of his collaborators, Stephen Gold, and his colleagues at the University of Texas, were able to show that gene therapy with RGS9-2 could suppress drug-induced dyskinesias in monkeys.

"Separately, we were looking to see if we could predict the risk susceptibility for these (movement) disorders by searching for variations in the RGS9-2 gene in humans."

Kovoor and his fellow researchers at the University of California in San Francisco also monitored the body mass index of patients in their study. "We noticed that study subjects with a variation in the RGS9-2 gene, which could weaken expression of the gene, had a higher body mass index."

Parallel experiments in mice and rats confirmed these findings implicating RGS9-2 in weight regulation.

Provided by University of Rhode Island