Chromosomal break gives scientists a break in finding new puberty gene

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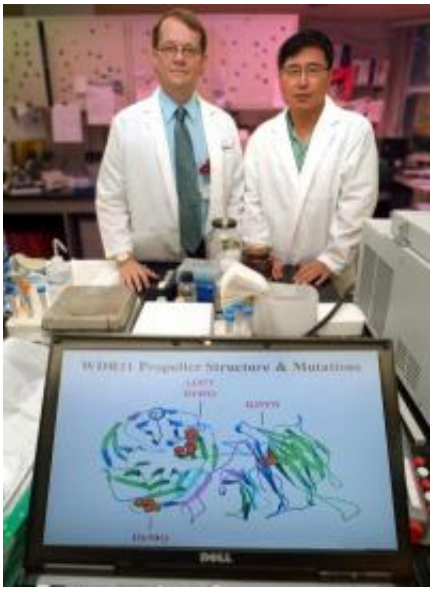

Drs. Lawrence C. Layman (left) and Hyung-Goo Kim have identified a new puberty gene. Credit: Phil Jones, Campus Photographer

A break in the two chromosomes has given scientists a break in finding a new gene involved in puberty, Medical College of Georgia researchers report.

It's also helped clear up why some patients with delayed puberty have no sense of smell, said Dr. Lawrence C. Layman, chief of the MCG Section of Reproductive Endocrinology, Infertility and Genetics.

The WRD11 gene interacts with a transcription factor that appears to be involved in development of gonadotropin releasing hormones that enable sexual maturation as well as olfactory neurons in the brain, according to a study published in The American Journal of Human Genetics and funded by the National Institutes of Health. A genetic mutation can diminish or eliminate this important interaction, impairing puberty and the sense of smell.

This was first found in a patient with Kallmann syndrome - delayed puberty coupled with the inability to smell. Next, a variety of WRD11mutations were identified in five other patients with delayed puberty, some of whom also had no sense of smell.

The findings provide insight into normal puberty as well as rare situations in which children don't sexually mature. "Even something that causes a rare disease can have an extremely important function in normal physiology," Layman said. A longer-term goal is finding better therapies for delayed puberty and perhaps alternative birth control methods.

Girls normally develop breasts by age 13 and menstruate by 15. Boys' testicles generally develop by age 14. Sex hormones can be prescribed to prompt puberty when it is delayed but more complex and expensive therapy is required to enable fertility. The therapy can lead to multiple births and related problems such as prematurity.

Layman, who receives blood samples of children and young adults with delayed puberty from across the globe, said the misplacement of portions of two chromosomes in the Kallmann patient worked like a global positioning system to help narrow down the gene search.

The patient had pieces of chromosome 10 on chromosome 12 and vice versa; such recombinations are fairly common and not necessarily bad. But knowing that a recombination can disrupt a gene's function, the

researchers analyzed a handful of genes in the immediate vicinity of the break before finding WRD11.

They still have to determine whether the chromosomal swapping had anything to do with the gene dysfunction in this case but the five other patients who had WRD11 mutations did not have the translocation. "Either way, it helped point us in the right direction," said Layman, a corresponding author on the study along with lead author Dr. Hyung-Goo Kim, molecular geneticist in Layman's lab.

"Performing genetic analysis in rare individuals harboring balanced chromosomal locations opens an important portal in the hunt for disease genes," noted Kim, who established the Developmental Gene Discovery Project at MCG to identify genes involved in a wide variety of human genetic disorders.

Layman recently received a $1.5 million grant from the NIH's Eunice Kennedy Shriver National Institute of Child Health and Human Development to learn more about how several of these puberty genes work.

The scientists will be looking further at WRD11, but also CHD7, a gene Kim and Layman identified in 2008, as well as the NELF gene, for fundamentals such as function and frequency. They will also look at more patients and their families to see if they have the same or different genetic variations.

"We have to know, for example, if they are transcription factors, which we think both CHD7 and NELF are. This means that they go into the cell nucleus and turn on expression of other genes," Layman said. "We also have to know what they bind to. It may be that some of these genes work in the same pathway."

Counting WRD11, there are now at least 17 known puberty genes and evidence suggests multiple genetic mutations are involved in some patients. Layman suspects that plenty of those genes are still unknown.

Provided by Medical College of Georgia