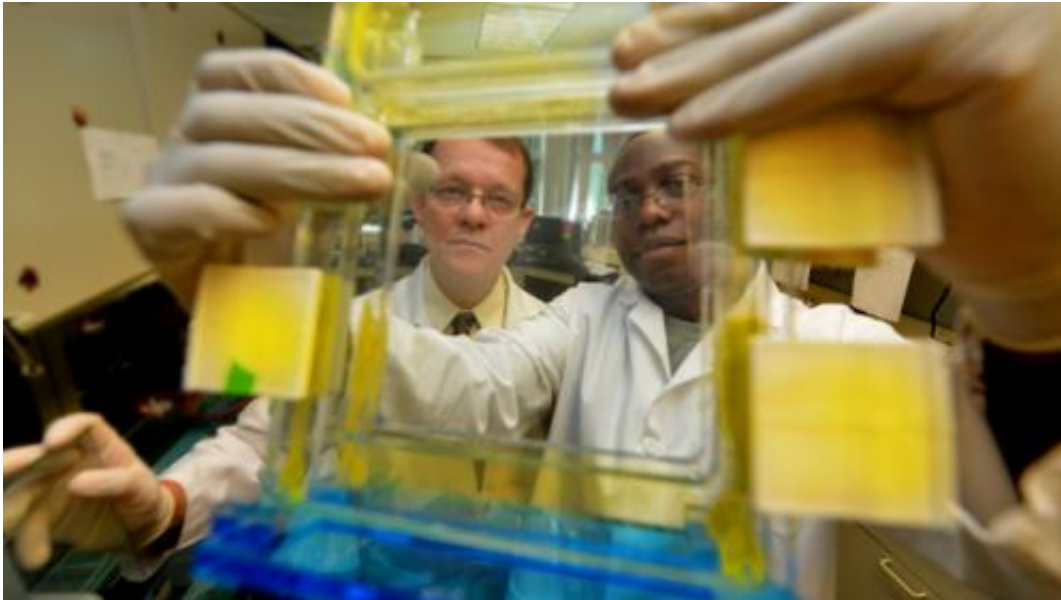


First estrogen receptor mutation found in a young woman

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This is Dr. Lawrence C. Layman, Chief of the Section of Reproductive Endocrinology, Infertility and Genetics at the Medical College of Georgia at Georgia Regents University. Credit: Phil Jones

A receptor mutation that essentially blocks estrogen's action has been identified for the first time in a female, researchers report.

The 18-year-old wasn't experiencing breast development or menstruation, classic symptoms of too little [estrogen](#), the usual cause of delayed puberty. Subsequent studies revealed instead sky-high levels of the sex hormone in her blood, said Dr. Lawrence C. Layman, Chief of

the Section of Reproductive Endocrinology, Infertility and Genetics at the Medical College of Georgia at Georgia Regents University.

"Her body totally ignores estrogen," Layman said. "Even at levels that are 10 to 15 times normal, it has no effect." In fact, in laboratory studies, 240 times the normal level was required to get a response out of the receptor.

There are two confirmed estrogen receptors, and genetic testing subsequently determined she had a mutation in estrogen receptor- α , which is essential to reproduction and bone health, researchers report in the *New England Journal of Medicine*. Estrogen levels in her blood were comparable to those of a mouse whose estrogen receptor- α gene has been deleted.

Interestingly the first mutation in this receptor was reported nearly 20 years earlier in the *NEJM* in a 28-year old man with knock-knees and signs of [insulin resistance](#). Studies showed his [testosterone levels](#) were normal and, although his estrogen and related hormone levels were high, he also had essentially no response to estrogen. The research team, led by Children's Hospital Medical Center in Cincinnati, found the estrogen receptor defect, concluding that estrogen is important to bone health in men as well as women.

The estrogen receptor- α mutation found in the female is slightly different but also results in profound estrogen resistance in women, said Layman, the new study's corresponding author. The major known impacts of estrogen in women are enabling reproduction, breast development, and bone health.

While generally healthy, the young woman sought medical help due to her lack of [breast development](#) and menstruation as well as lingering, lower-abdominal pain. Studies by Dr. Earl "Sandy" W. Stradtman Jr., a

reproductive endocrinologist in Birmingham, Ala., revealed the markedly high [estrogen levels](#) as well as multiple, large ovarian cysts. Stradtman referred her to Layman, an expert in delayed puberty.

Overwhelmingly, [delayed puberty](#) results from insufficient estrogen, but the bottom line is similar for this woman because estrogen's effect is missing, Layman said. Estrogen production normally begins with the brain telling the ovaries to make it, so most of his patients have a problem with brain signaling.

The receptor defect creates the slightly different problem of not being able to use the estrogen that is there, control how much is made, or control its result. For example, the woman had cystic ovaries because her body was constantly producing follicles rather than the usual one a month needed so an egg can descend and either be fertilized or shed along with blood, cervical mucus and endometrial tissue during menstruation.

It's estrogen's binding with its receptor that activates the negative feedback system that tells the brain there is plenty of the sex hormone. In this case, that didn't happen so estrogen built up in her blood, eventually dumping in her urine, said Samuel D. Quaynor, an M.D./Ph.D student at MCG and GRU and the study's first author.

Without estrogen, insulin levels also typically increase, putting the patient at risk for diabetes. However, unlike the mouse and the male with a receptor mutation, the woman's glucose and insulin levels were normal, Quaynor said. However, she did have an unusual response to an oral glucose test that indicated glucose and insulin problems could be in her future, They noted that the male's elevated levels might be related to obesity.

To fully understand the impact of the receptor mutation, they'd like to

do large-scale screening to see if other substances bind to its altered state.

Since the young woman is adopted, her biological family history was unavailable but she was just over five feet tall and had lower than expected bone mass for her age, although she was still growing. Abnormally high bone turnover was indicated as well.

Estrogen receptor- α was cloned in 1986 and estrogen receptor- β was cloned 10 years later. Eliminating estrogen receptor- α doesn't cause any significant problems in mice and eliminating [estrogen receptor- \$\beta\$](#) had the most impact in female mice.

Provided by Medical College of Georgia

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