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RESEARCHERS DISCOVER ABNORMAL BONE LENGTHENING, BONE MASS IN MALES WITH ESTROGEN-RELATED DEFICIENCY

DALLAS — January 12, 1996 — The next time you're at a professional basketball game, take a closer look at the almost 8-footer charging the basket. He may not be as strong as you think — he may not have enough estrogen, said Dr. Evan Simpson, a biochemist at UT Southwestern Medical Center at Dallas.

Simpson is one of the authors of the first patient study linking abnormalities in male bone growth and mineralization to lack of the female hormone estrogen. "Aromatase Deficiency in Male and Female Siblings Caused by a Novel Mutation and the Physiological Role of Estrogens" appeared in the December 1995 issue of the *Journal of Clinical Endocrinology and Metabolism*. Researchers from the Columbia University College of Physicians and Surgeons and the University of California, San Francisco, School of Medicine, also participated in the research.

While there have been previous reports of the effect of aromatase deficiency on females, including recent work by Simpson, this article reported on the first deficiency in a male and its implications for growth and development. Simpson is a professor of biochemistry and obstetrics and gynecology at UT Southwestern and a researcher in the Cecil H. and Ida Green Center for Reproductive Biology Sciences.

Simpson and his colleagues explained how a mutation in the CYP19 gene results in a major malfunction of estrogen metabolism. The normal gene encodes an enzyme called aromatase, which converts the male hormone androgen into estrogen in gonads, bones and other body areas. Simpson, who originally cloned and characterized the gene with his associates at UT Southwestern, explained that lack of aromatase causes uncontrolled bone lengthening and a lack of bone mineralization, which results in weak bones. He said the effect of the deficiency on male development was unknown until now.

In women, this deficiency leads to female gender-related problems, failure to go

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through puberty, lack of breast development, failure to menstruate and cystic ovaries. Most of these conditions, however, can be treated with estrogen. If left untreated, females also may experience uncontrolled bone lengthening.

Dr. Akira Morishima of Columbia University, one of the paper's authors, first diagnosed the female patient in the journal article as having gender problems when she was 22 months old. Eventually she was recognized as the first recorded case of aromatase deficiency, a project in which Simpson also was involved. Morishima has treated the patient throughout her formative years and continues to be her physician.

The researchers later determined that her brother also carried the defective gene that causes the production of estrogen to go awry. At the time he was first examined, the boy was 14 years old and was of normal stature; however, 10 years later he was 6 feet 8 inches tall and was still growing. "Moreover, his bones were markedly undermineralized," Simpson said.

"The report of the male sibling without a functional aromatase enzyme shows that estrogen has a role in bone formation in males as well as females," Simpson said. "In the past we had assumed that androgens played the same role in the development of male bones as estrogen does in women. Clearly this is not the case."

Researchers have uncovered no problems associated with the male patient's gender development, with the possible exception of a low libido.

Another important point to emerge from this work is the fact that two siblings with aromatase deficiency have reached adulthood and are otherwise normal. This indicates that estrogen may not have an essential role in human embryonic development as was previously thought, Simpson said. Meanwhile his lab continues this research with familial DNA studies related to aromatase deficiency in both men and women.

Other participants in the study were UT Southwestern obstetrics and gynecology researchers Dr. Ke-nan Qin, a research fellow, and Carolyn Fisher, a senior research associate; and UCSF researcher Dr. Melvin Grumbach.

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