Genetic mutation inherited from father's side linked to early puberty

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Reaching puberty at an unusually early age can have adverse effects on social behavior and psychological development, as well as physical effects, including short stature, and lifelong health risks, such as diabetes, breast cancer and heart disease. Researchers at Brigham and Women's Hospital (BWH), in a multi-institutional collaboration with Boston Children's Hospital, the Broad Institute, and the University of Sao Paulo, Brazil, have identified that a genetic mutation leads to a type of premature puberty, known as central precocious puberty. Central precocious puberty is defined by the development of secondary sexual characteristics before eight years in girls and nine years in boys.

The study appears online June 5, 2013 in *The New England Journal of Medicine*. The results will also be presented at The Endocrine Society's 95th Annual Meeting & Expo in San Francisco on June 17, 2013.

"These findings will open the door for a new understanding of what controls the timing of puberty," said Ursula Kaiser, MD, chief of the BWH Division of Endocrinology, Diabetes and Hypertension, co-senior study author. "It also will allow doctors to diagnose the cause of precocious puberty in a subset of patients, or to identify patients at risk for developing precocious puberty, especially if others in their family are affected. By better understanding the role of this gene in the timing of puberty, we may be able to gain insights into how other factors, such as environmental factors, may influence pubertal timing."

The researchers performed whole exome sequencing analysis of forty individuals from fifteen families with central precocious puberty. In five of the fifteen families, the researchers identified four mutations in the MKRN3 gene. The MKRN3 gene is responsible for coding a protein called makorin ring finger protein 3, which is thought to help tag other proteins for degradation. The genetic mutations resulted in truncated MKRN3 proteins and disruption of MKRN3 protein function. A mutation in the MKRN3 gene can lead to premature activation of reproductive hormones in the body, thereby initiating early puberty.

The researchers also found that all affected individuals inherited the mutations from their fathers. Moreover, the MKRN3 gene is located on the same chromosome as genes for Prader-Willi syndrome, a rare condition that results in short stature, incomplete sexual development, cognitive disabilities, insatiable appetite and severe obesity, among other abnormalities; although, despite being on the same chromosome, MKRN3 is not thought to contribute to the clinical features of Prader-Willi syndrome.

Provided by Brigham and Women's Hospital