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REPRODUCTIVE ENDOCRINOLOGY

Novel mutations linked to central precocious puberty

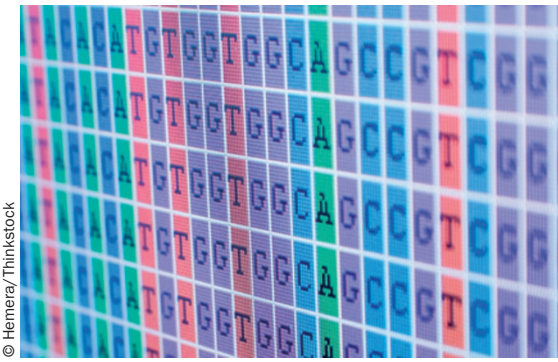
A genetic mutation in *MKRN3*, which encodes makorin ring finger protein 3, can initiate early puberty, according to a new study published in the *New England Journal of Medicine*.

The onset of puberty is influenced by complex interactions between genetic, nutritional, environmental and socio-economic factors. Reaching puberty at an unusually early age, before 8 years in girls and 9 years in boys, is known as central precocious puberty, which is associated with increased health risks such as type 2 diabetes mellitus, obesity, breast cancer and cardiovascular disease. To provide new insights into the mechanisms involved in the initiation and timing of puberty, Abreu *et al.* aimed to identify genetic changes associated with precocious puberty.

Abreu and co-workers completed whole-exome sequencing for 40 members of 15 families with central precocious puberty (32 individuals with central precocious puberty and eight with normal puberty). "This approach allows the identification of mutations in genes not previously implicated in pubertal onset or timing," says co-senior investigator Ursula Kaiser (Brigham and Women's Hospital, Boston).

The researchers identified four novel mutations in *MKRN3* in 15 patients from five of the families. The identified mutations include three frameshift mutations, predicted to encode truncated proteins, and one missense mutation, predicted to disrupt protein function. *MKRN3* is an imprinted gene, and the affected individuals inherited the mutated allele from their fathers.

"This gene seems to normally act as a 'brake' to prevent puberty from occurring too early. A mutation in *MKRN3* can, in a sense, cause this brake to malfunction, leading to premature activation of reproductive hormones and thereby initiating early puberty," explains Kaiser. The exact function of the MKRN3 protein is yet unknown, and the gene is only conserved in marsupial and placental mammals.



"The discovery of this new genetic link to early puberty will allow doctors to diagnose the cause of precocious puberty in a subset of patients, or identify children at risk of developing precocious puberty, especially if others in their family are affected. Treatment can then be initiated earlier," Kaiser concludes.

Elisabeth Kugelberg

Original article Abreu, P. A. *et al.* Central precocious puberty caused by mutations in the imprinted gene *MKRN3*. *N. Engl. J. Med.* doi:10.1056/NEJMoa1302160