Researchers look for ways to start puberty 'on time'

March 9 2023, by Albert McKeon

Credit: Unsplash/CC0 Public Domain

Children who experience early puberty or delayed puberty may be at risk of having shortened height as adults. They may also feel emotionally unprepared for the changes of puberty, and may feel self-conscious or

experience social anxieties as a result.

To address this challenge, Boston Children's researchers are trying to further the study of an important genetic player in pubertal timing: Makorin Ring Finger Protein 3 (MKRN3). A recent study in the brains of mice led by Stephanie Roberts, MD, of the Division of Endocrinology, found that adding more copies of Mkrn3 in the brain during a time when this protein is typically low could delay puberty. It's a promising finding that could someday lead to future treatment options for children experiencing puberty too soon or too late.

The study opened the door to another possibility: genetic variants in MKRN3 could be an unrecognized cause of delayed puberty in children. Further research on that end is now being conducted with Yee-Ming Chan, MD, Ph.D., of the Division of Endocrinology.

Overexpressing a protein could delay puberty

Roberts and her colleagues, including Ursula Kaiser, MD, of Brigham and Women's Hospital, built their research off a previous study by Kaiser in 2013. That research showed loss-of-function mutations in MKRN3 are connected to the premature activation of the hormonal system in the brain involved in pubertal onset, known as the hypothalamic-pituitary-gonadal (HPG) axis. Roberts and the team wanted to flip that finding and see if an increase in Mkrn3—a process known as overexpressing—could stop the HPG axis from releasing gonadotropin-releasing hormone (GnRH) and delay puberty.

As explained in their article, published in *Endocrinology*, they injected mice with an adeno-associated virus expressing either Mkrn3 or a control virus. Female mice injected with Mkrn3 had a significantly delayed vaginal opening and first ovulation—both signs of puberty—compared with the control group. Ovulation cycling and

fertility were normal in the mice that received Mkrn3 after the start of puberty. Puberty wasn't delayed in male mice.

Possible answers for the late start of puberty

Aside from potentially creating a path toward future treatment options for pubertal disorders that manipulate MKRN3 expression, the study could also inform future research on how unknown genetic variations in MKRN3 might play a role in suppressing puberty. That's because while Roberts and her fellow researchers studied the mice, they observed Mkrn3 impeding a neuron that controls the release of GnRH and the activity of the HPG axis.

Finding a way to initiate puberty when it hasn't started by an expected age could ease the social anxieties of some teenagers who aren't maturing at the same pace as their peers, Roberts says.

More information: Stephanie A Roberts et al, Hypothalamic Overexpression of Makorin Ring Finger Protein 3 Results in Delayed Puberty in Female Mice, *Endocrinology* (2022). DOI: 10.1210/endocr/bqac132

Provided by Children's Hospital Boston