Largest ever genetic study of age of puberty in girls shows links with weight gain

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Genes can indirectly influence the age at which girls have their first period by accelerating weight gain in childhood, a known risk factor for early puberty, a Cambridge-led study has found. Other genes can directly affect age of puberty, some with profound effects.

In the largest study of its kind to date, an international team led by researchers at the Medical Research Council (MRC) Epidemiology Unit, University of Cambridge, studied the DNA of around 800,000 women from Europe, North America, China, Japan, and Korea.

Published in *Nature Genetics*, the researchers found more than 1,000 variants—small changes in DNA—that influence the age of first menstrual period. Around 600 of these variants were observed for the first time.

The age at which girls hit puberty and start having periods normally occurs between ages 10 to 15, though this has been getting earlier and earlier in recent decades. The reasons for this are not fully understood. Early puberty is linked with increased risk of a number of diseases in later life, including type 2 diabetes, cardiovascular disease, and certain cancers. Later puberty on the other hand, has been linked to improved health in adulthood and a longer lifespan.

Just under half (45%) of the discovered genetic variants affected puberty indirectly, by increasing weight gain in early childhood.

Corresponding author Professor John Perry said, "Many of the genes we've found influence early puberty by first accelerating weight gain in infants and young children. This can then lead to potentially serious health problems in later life, as having earlier puberty leads to higher rates of overweight and obesity in adulthood."

Previous work by the team—together with researchers at Cambridge's MRC Metabolic Diseases Unit—showed that a receptor in the brain, known as MC3R, detects the nutritional state of the body and regulates the timing of puberty and rate of growth in children, providing a mechanism by which this occurs. Other identified genes appeared to be acting in the brain to control the release of reproductive hormones.

The scientists also analyzed rare genetic variants that are carried by very few people, but which can have large effects on puberty. For example, they found that one in 3,800 women carry variants in the gene ZNF483, which caused these women to experience puberty on average, 1.3 years later.

Dr. Katherine Kentistou, lead study investigator, added, "This is the first time we've ever been able to analyze rare genetic variants at this scale."

"We have identified six genes which all profoundly affect the timing of puberty. While these genes were discovered in girls, they often have the same impact on the timing of puberty in boys. The new mechanisms we describe could form the basis of interventions for individuals at risk of early puberty and obesity."

The researchers also generated a genetic score that predicted whether a girl was likely to hit puberty very early or very late. Girls with the highest 1% of this genetic score were 11 times more likely to have extremely delayed puberty—that is, after age 15 years. On the other hand, girls with the lowest 1% genetic score were 14 times more likely to have extremely early puberty—before age 10.

Senior author and pediatrician Professor Ken Ong said, "In the future, we may be able to use these genetic scores in the clinic to identify those girls whose puberty will come very early or very late. The NHS is already trialing whole genome sequencing at birth, and this would give us the genetic information we need to make this possible.

"Children who present in the NHS with very early puberty—at age seven or eight—are offered puberty blockers to delay it. But age of puberty is a continuum, and if they miss this threshold, there's currently nothing we have to offer. We need other interventions, whether that's oral medication or a behavioral approach, to help. This could be important

for their health when they grow up."

More information: Kentistou, KA & Kaisinger, LR, et al. Understanding the genetic complexity of puberty timing across the allele frequency spectrum, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01798-4

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