Genetic variants influencing human fertility identified by new research

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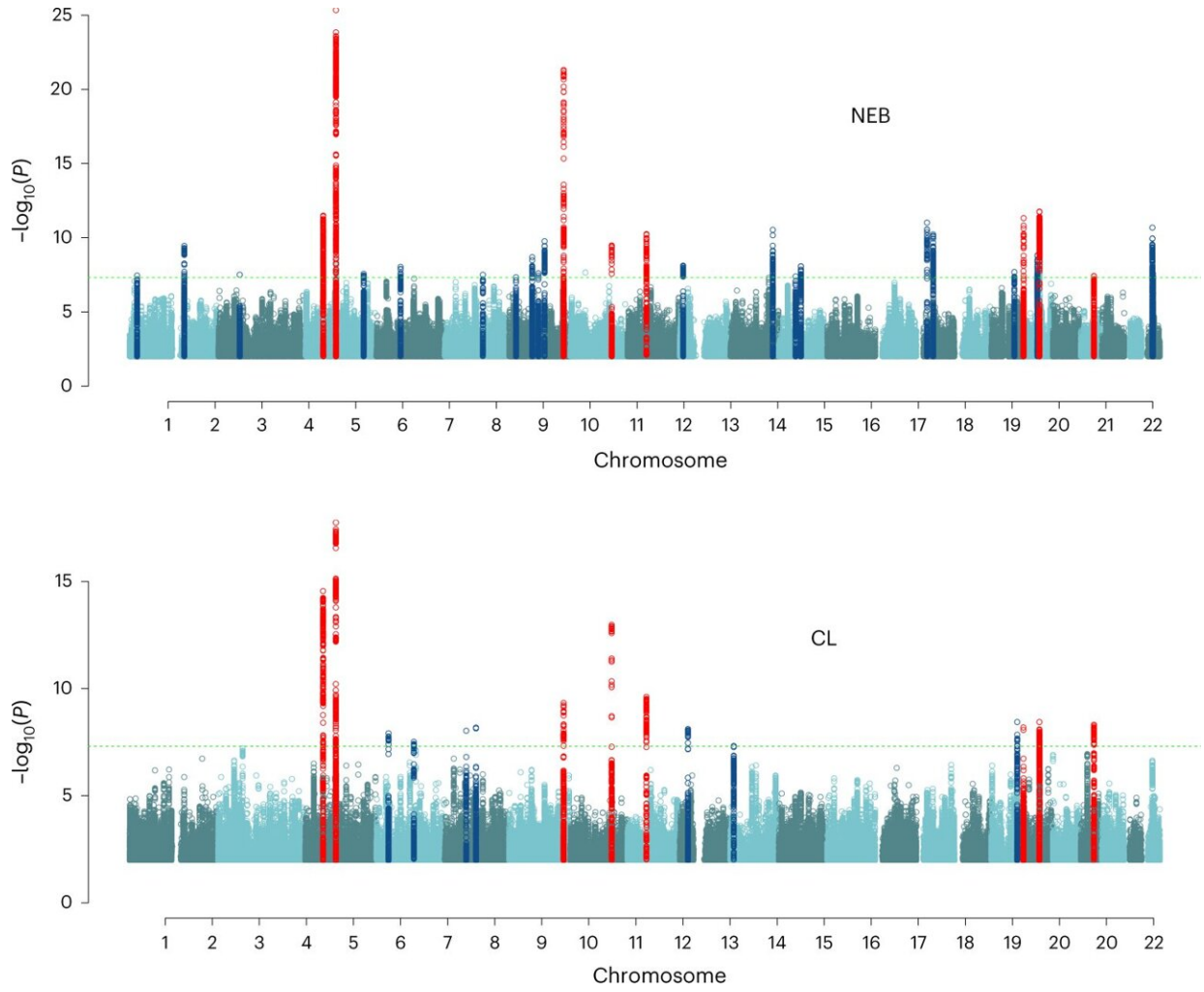

Manhattan plots for genome-wide association analyses of NEB and CL. Credit: *Nature Human Behaviour* (2023). DOI: 10.1038/s41562-023-01528-6

How many children an individual may have is influenced by reproductive biology and human behavior, according to the largest study to date, which identifies genetic determinants. The study, led by researchers at the Universities of Cambridge, Oxford and Pennsylvania, also identified that the human genome has been influenced by natural selection for thousands of years and continues to affect fertility today.

The findings demonstrate that fertility is affected by diverse biological mechanisms, which contribute to variations in fertility, and directly affect puberty timing, sex hormone levels (such as testosterone), endometriosis and age at menopause. There were also links to behaviors such as risk taking.

Professor Melinda Mills, Director of Oxford's Leverhulme Centre for Demographic Science, comments, "This study is of interest to understanding changes in human reproduction over longer periods of time, reproductive biology and potential links to infertility."

"It also empirically tests one of the most gripping and fundamental questions asked by scientists across many disciplines and decades: Is there evidence of ongoing natural selection in humans and, if so, what is it and how does it operate?"

The major study, published today in *Nature Human Behaviour*, used data from 785,604 individuals of European ancestry, including individuals in the UK Biobank study, to identify 43 regions of the genome containing genetic variants associated with reproductive success, defined as the number of children ever born to an individual.

Some findings highlight trade-offs across the life-course, for example, the researchers found variations in the gene ARHGAP27 that were associated with having more children, but also with a shorter lifetime window of fertility. The analysis also suggested a novel role for the red

hair color gene, melanocortin 1 receptor (MC1R) in reproductive biology. But the genetic evidence suggests the influence on number of children is not related to the same genetic mechanisms that affect pigmentation.

Professor John Perry, MRC Epidemiology Unit, University of Cambridge notes, "This study is the largest of its kind and has highlighted new biology that we anticipate will help identify novel therapeutic targets for reproductive diseases such as infertility. It will also help us better understand the biological mechanisms that link reproductive health to broader health outcomes in men and women."

By integrating their findings from modern genomes with ancient genome data, the researchers were able to identify a region of the genome that has been under selection for thousands of years, and remains under selection today.

The genes in this region—FADS1 and FADS2—are involved in synthesizing specific fats that are important for health and seem to have been important in helping people in Europe to adapt to an agricultural diet. The observation that these genes still affect fertility today suggests that this adaptation may be ongoing.

Dr. Iain Mathieson, Department of Genetics, University of Pennsylvania, points out, "Independent evidence shows the FADS region has been under selection in Europe for thousands of years. It represents the clearest example of a genetic variant with evidence of both historical and ongoing natural selection, though the reason for selection remains unclear."

More information: Iain Mathieson, Genome-wide analysis identifies genetic effects on reproductive success and ongoing natural selection at the FADS locus, *Nature Human Behaviour* (2023). DOI:

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