Research challenges current thinking on the genetic causes of very early menopause

June 22 2023

Credit: Unsplash/CC0 Public Domain

The genetic causes of very early menopause will have to be reconsidered after researchers found that nearly all women who carried variations thought to cause the condition in fact had their menopause at an older

age.

Until now, variants in any one of more than 100 genes were thought to cause premature ovarian insufficiency (POI), which results in menopause before the age of 40 and affects around 1% of women, making it a leading cause of infertility. Under current guidance, a variation in one of these genes is cause for clinicians to consider a genetic diagnosis of POI.

Now, in the largest study to date, a team led by the University of Exeter and the University of Cambridge analyzed genetic data from more than 104,733 women in UK Biobank, of whom 2,231 reported experiencing menopause before the age of 40. The study, entitled: "Penetrance of pathogenic genetic variants associated with Premature Ovarian Insufficiency," is published in *Nature Medicine*,

The study found evidence that 98% of women carrying variations in the genes that were previously considered to be causes of premature menopause in fact had menopause over 40, therefore ruling out a diagnosis of POI in these women.

Anna Murray, Professor of Human Genetics at the University of Exeter Medical School and senior author on the study, said, "Our research means rethinking what causes very early menopause. The presence of specific genetic variants in multiple women who experience premature menopause has led to the assumption that they are causing the condition—but we have shown that these gene variations are also found in women with a normal age of menopause and therefore in many cases the link could just be coincidence. It now seems likely that premature menopause is caused by a combination of variants in many genes, as well as non-genetic factors. As genomic medicine evolves, we need to apply this standard of evidence to other conditions, so we can tailor diagnosis, treatment and support."

Dr. Julia Prague, Consultant Endocrinologist and Clinical Academic at the University of Exeter, and an author on the paper, said, "Having a very early menopause is often extremely distressing because it means losing fertility and treatment with hormone replacement is required to prevent negative health consequences. Clinicians need to understand the reasons why premature menopause occurs so that they do not miss the true underlying cause and can counsel patients appropriately. Misinterpreting genetic tests could have negative implications for women, such as suggesting that their relatives may also be at risk of very early menopause due to their genes, when in fact they may not be."

Stasa Stankovic, of the University of Cambridge's MRC Epidemiology Unit, and co-lead analyst of the study, said, "Each woman's unique genetic combination shifts menopause timing, either earlier or later. Although genetic variation in the studied genes were not sufficient to cause very early menopause, we did identify genetic drivers that had a much more subtle impact on reproductive longevity."

"For example, women carrying genetic variation in TWNK and SOHLH2 genes experienced menopause up to three years earlier than the general population. Our future studies will continue using the power of human genomics to better understand the underlying biology of reproductive aging in women and key genetic drivers of its extreme forms, including very early menopause. With this knowledge, we are also paving the path towards development of next-generation treatments for reproductive disorders."

More information: Penetrance of pathogenic genetic variants associated with Premature Ovarian Insufficiency, *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02405-5

Provided by University of Exeter