Menopause age shaped by genes that influence mutation risk

By mining large-population genetic data sets, researchers identify the key factors controlling menopause timing, and reveal a close connection between reproductive longevity, cancer risk and new mutations in offspring. See p.xxx

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Menopause is a major physiological transition in a woman's life that signals the natural end of the ability to reproduce. Writing in *Nature*, Stankovic *et al.*[1] pinpoint some of the genetic factors that determine the timing of menopause. They show that these factors also influence an individual's cancer risk and the genetic quality of the egg, which affects how many new (that is, not inherited) mutations are passed on to their children**.** These findings not only begin to decipher the complex mechanisms that control reproductive ageing in women, but they also have implications for the safety of future treatments that aim to extend female fertility.

Unlike sperm, which are produced daily, a finite number of eggs (the 'ovarian reserve') is present in the ovaries at birth. This reserve diminishes with age, and when it is exhausted, usually around the age of 50, menopause begins. The age at natural menopause (ANM) varies considerably among individuals and serves as a proxy measure of the ovarian reserve. Beyond fertility, ANM broadly correlates with longevity, and early menopause is associated with an increased susceptibility to health problems such as diabetes, cardiovascular disease and bone fractures[2]. Heritability studies estimate that genetic factors account for about 50% of variation in ANM between individuals[3] — yet how genetic factors, and their complex interactions with the environment, modulate reproductive ageing in women is not well understood.

[Does this paragraph as it stands get across your original intended meaning? From my perspective, it looks good YES]

Previous genetic analyses[4] of large populations have identified common genetic variants that are associated with natural differences in menopause timing, and have proposed a role for several biological processes, including the DNA-damage response (DDR) — a complex signalling pathway that senses the quality of an egg's genome and either repairs it, or, if the genome is damaged beyond repair, marks the cell for destruction. Despite these useful hints, however, association studies analysing common variants often do not have the resolution necessary to identify specific genes and establish the causal links to biological mechanisms involved in ovarian ageing.

Over the last few years, genetic studies have considerably improved in both scale and scope. It has become affordable to perform whole-genome sequencing of large populations to provide unbiased access to all of the genetic variations present in individuals[5,6]. Furthermore, large-scale 'biobanking' efforts have begun to catalogue and make available large amounts of biomedical data — for example, the UK Biobank has documented the health traits of around half a million individuals[7,8]. When combined, these approaches provide unparalleled opportunities to decipher the genetic underpinnings of complex traits, such as ANM.

In their analysis, Stankovic and colleagues characterized the influence of rare genetic variants on ANM in over 100,000 post-menopausal women from the UK Biobank study. Unlike common variants, rare variants occur at a low frequency in the population, typically in fewer than 1 in 1,000 individuals. However, rare variants often have a stronger influence on health traits than do common variants and directly implicate specific genes, providing a clear entry point to uncover the biological mechanisms at play.

The authors identified rare variants that disrupt the function of nine genes, three of which had also been reported by another group[9]. Among these, seven are part of the DDR machinery. Some genes (*HELB, CHEK2, BRCA2* and *HROB*) had been inferred as likely candidates in earlier studies of common variants[4], but others are novel players.

What makes the author's analysis particularly valuable is that rare variants that disrupt gene function point to a clear landing point in the genome and often have a large 'effect size', which enables causality to be established. For example, a few common variants located in a genomic region near to the *ZNF518A* gene were spotted in earlier studies[4] and women with these variants had an ANM that was about 2 to 4 months earlier than women without the variants. However, it was not clear which gene in the region was responsible for this small effect.

By contrast, a single rare variant (present in only 28 women in the UK Biobank cohort) that disrupts *ZNF518A* has an effect that is 20-fold greater than that of the common variants, equating to an ANM that is about 5.6 years earlier. *ZNF518A* is of particular interest, not only because of its large effect size but also because, unlike many of the other ANM-associated genes, which are involved in DDR, very little is known about its function or role in disease. Yet *ZNF518A* appears to be a key regulator of ovarian ageing, and further studies will probably reveal how and why loss of this gene shortens female reproductive lifespan.

Using the full breadth of data available from the UK Biobank and other smaller data sets, the authors then asked whether ANM-associated variants could also affect other health outcomes. They show that both men and women who carry rare ANM-associated variants are at an increased risk of cancer, which is consistent with the loss of activity of DDR components. Finally, using another large data set from the 100,000 Genomes Project[6,10], they found that children born to women susceptible to earlier ANM carried a slightly elevated number of new DNA mutations.

Although the effect was relatively small, and could not be reproduced in a smaller-population data set from Iceland[5,11], the author's observation provides some food for thought because new mutations are a primary contributor to disease and could substantially affect the health of children in future generations.

The overall picture emerging from these genetics findings is that the ability of the egg to maintain its genetic integrity, by detecting and repairing DNA damage, is a key protective mechanism against ovarian ageing. This makes sense from an evolutionary point of view, given that the egg, like sperm, must ensure the faithful transmission of genetic material across generations to avoid the catastrophic consequences of passing on damaged DNA. Therefore, the egg is likely to be exceptionally sensitive to factors that influence quality control. In this context, it will be important to determine if environmental factors such as smoking and pollutants, which also influence ANM, have additive mutagenetic effects.

Given the growing tendency to delay pregnancies in many countries[2,12], the ability to predict female reproductive longevity ahead of time would be highly desirable. Based on current progress, personalized 'genetic risk scores' will probably become available soon, at least for some ethnic groups. Those at risk of early ANM might be advised to start their family earlier and monitor their own health more closely. It is worth noting that only women of European ancestry (the largest group in the UK Biobank cohort) were considered in the authors' analysis. Ongoing studies will determine whether genetic influences on ovarian ageing are shared with other ethnic groups[13,14], who have different genetic underpinnings and are shaped by different environmental inputs.

Stankovic and colleagues' findings could also provide avenues to develop treatments to delay ovarian ageing. For example, the discovery of three genes in which rare disrupting variants delay ANM could pave the way to therapeutic strategies to increase egg survival. However, it will be prudent

to balance the benefits of extending ANM with the potential risks, given that these genes also affect several health outcomes. Perhaps most importantly, the consequences of such treatments on the genetic health of the next generations must be evaluated carefully. This work provides the foundation on which to build a better understanding of the genetic liability of ANM on health, and to develop safe and effective strategies to prevent disease and extend fertility in ageing women.

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Figure

Thank you so much for your comments on the figure, they were extremely useful! Sounds like we have nailed down panel A, but some changes need to be made to panel B. Would the changes to the figure below address your points?

For the DNA damage, we could perhaps depict the DNA like this, in a similar way to what we have done previously for a News & Views figure. I'm struggling to come up with how we can show defective DNA-damage repair and defective DNA-damage detection in a way that is distinguishable and easy to interpret. I will have a chat with our art editors tomorrow and see if we can come up with a good way to show this.]

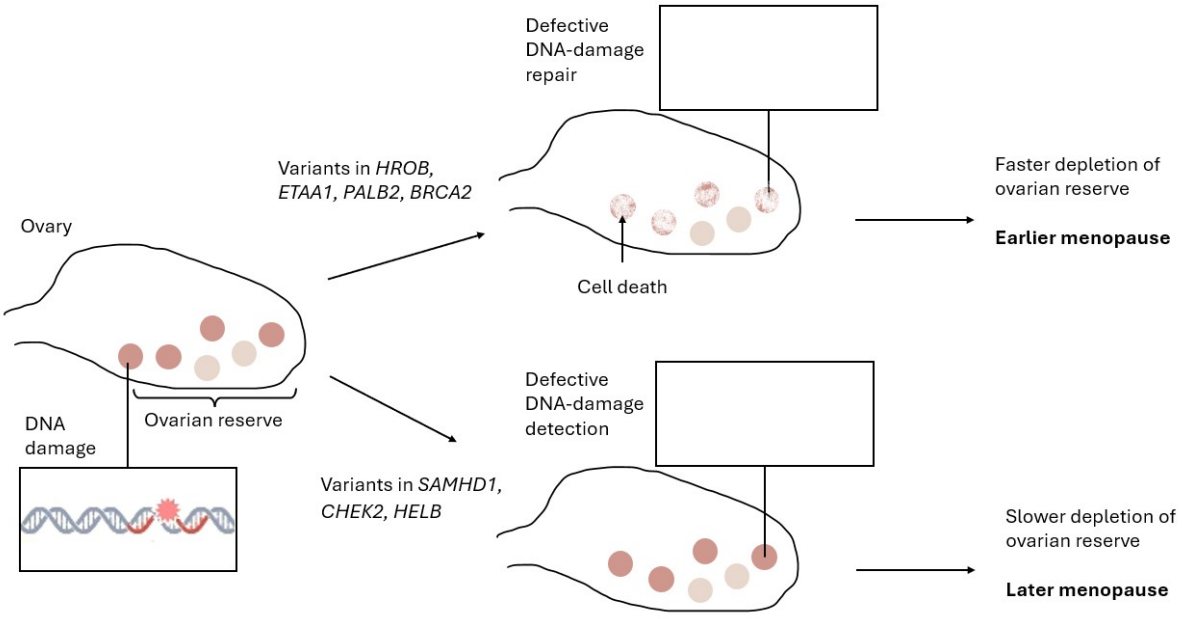

Figure 1 | Genetic influences on ovarian ageing. a, By analysing large-population genetic and health data sets, Stankovic *et al.*[1] identify rare disrupting variants in genes that have a strong effect on the age at natural menopause (ANM) in women. The *x* axis shows the effect on ANM in women with the gene variant compared to ANM in women without the variant. Most of the identified genes encode proteins that are part of the DNA-damage response (DDR) pathway. (Adapted from Fig. 2 of ref. 1) **b**, Eggs in ovaries constitute the 'ovarian reserve'. The DDR machinery repairs DNA damage in these cells. If DNA cannot be repaired, the cell is destroyed/elimitated, resulting in faster depletion of the reserve and earlier menopause. If DNA damage cannot be detected, DNA is not repaired but the cell is not targeted for destruction, resulting in slower depletion of the reserve and later menopause