

GENES THAT DETERMINE THE ONSET OF MENOPAUSE

An international consortium found an association of 290 genomic loci and the age of natural menopause. The results are published in Nature, August 4, 2021 ([K.S. Ruth et al. 2021](#)).

About 7 million oocytes are present in a 24 weeks-old fetus, of which about 5 million will have been lost at birth. At the beginning of puberty, this non-renewable ovarian reserve is less than half a million and some 1000 oocytes are lost during every menstrual cycle. The cycles stop at an average age of 50-52 but in women with POF (Premature Ovarian Failure) this happens in their-mid-thirties. Oocyte loss is determined by environmental factors such as diet, alcohol, smoking and exposure to radiation, but there are also genetic determinants. A well-known genetic determinant is the *FMR1* pre-mutation.

The genome-wide association study involved ~200,000 women of European descent. A total of 290 statistically significant signals were identified. A high number of genes at or around these loci have a life-long function in DNA damage response (DDR) with functions in relieving replication stress, DNA-protein crosslink repair, and meiotic recombination. Also 58 genes that function in the regulation of apoptosis were found. Experimental manipulation in mice of two genes, *Chek1* and *Chek2*, each extended female reproductive lifespan. Specifically, an extra copy of *Chek1* increased ovarian reserve during life and caused a higher number of ovulated meiosis II oocytes after gonadotropin stimulation. The resulting embryos were normally healthy and fertile.

This study greatly increases the number of genes that affect female fertility, and the authors expect that their findings will instigate further work to develop therapies for preserving female fertility.