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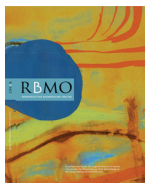

REVIEW

Progress in genome-wide association studies of age at natural menopause

BIOGRAPHY

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KEY MESSAGE

Menopause is not only the end of reproductive life, it is also associated with many diseases. Genome-wide association studies show that menopause age is inherited by multiple genes, and defects in the DNA damage repair pathway are the main genetic pathological mechanism of the age at natural menopause.

ABSTRACT

Menopause is not only the end of reproductive life, it is also related to diseases such as hyperlipidaemia, atherosclerotic cardiovascular disease, osteoporosis and breast cancer. Traditional epidemiological studies have found that heredity is the main determinant of age at natural menopause (ANM). Early studies on genetic factors were limited to candidate gene studies. Menopause age is not inherited by a single gene, but is the result of multiple gene effects. With the development of genomic technology, the Reproductive Genetics Consortium conducted several genome-wide association studies on ANM in people of European descent, and found that defects in DNA damage repair pathways were the main genetic mechanism. In recent years, due to the ethnic heterogeneity of ANM, there has been further development of global studies into multi-ethnic and trans-ethnic genome-wide association studies. Further genetic and epidemiological studies, including polygenetic score and genetic mechanism research, should be conducted to investigate the pathogenesis and mechanism with respect to menopause and its related diseases.

INTRODUCTION

Menopause not only represents the end of a woman's reproductive lifespan, but is also closely related to her health. Traditional epidemiological data show that early menopause can increase the risk of abnormal lipid metabolism, fractures, atherosclerotic cardiovascular disease, osteoporosis and other diseases, and can increase female all-cause mortality (*Huan et al., 2021*). Studies on age at natural menopause (ANM) are helpful for women to understand their fertility potential and disease risk, to plan their reproductive life and actively prevent related diseases, and to improve their quality of life. Heredity is an important factor affecting ANM. With the rapid development of genetic epidemiology over the last 10 years, genome technology combined with epidemiology has been widely applied in ANM and related diseases. This review collates the historical progress of genome-wide association studies (GWAS) on ANM and explores the impact and significance of ANM-related gene changes on women's health.

RELATED CONCEPTS OF MENOPAUSE AND EARLY AETIOLOGICAL RESEARCH ON ANM

Menopause is defined by the World Health Organization (WHO) as the cessation of

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KEYWORDS

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Genome-wide association study
Menopause
Trans-ethnic

menstruation for more than 12 months (*McKinlay, 1996*; *World Health Organization Scientific Group, 1981*). Normal menstruation is the result of ovulation from the dominant follicle. During the embryonic stage, the oocyte in the fetal ovary stops mitosis, enters the meiosis stage and stops at the prophase of meiosis I (*Channing et al., 1980*). There is essentially a continuous process of oocyte depletion during a female's life. The American Society for Reproductive Medicine (ASRM) defines the quantity and quality of remaining oocytes as the ovarian reserve (*Practice Committee of the American Society for Reproductive Medicine, 2020*). The decline in ovarian reserve is positively correlated with age. If the rate of decline is in the age-specific range, it is called normal physiologic ovarian ageing (NOA). Compared with same-age women, decreased fertility associated with ovarian function but regular menstruation is suggestive of diminished ovarian reserve (DOR). In the event of further amenorrhoea and a rise in FSH, early menopause can be considered if it occurs earlier than 45 years of age, while premature ovarian insufficiency (POI) or premature ovarian failure (POF) can be considered if it occurs earlier than 40 years of age. Age at menopause is crucial for assessing the decline in ovarian reserve and determining the diagnosis (*Pastore et al., 2018*). Spontaneous POI/POF is considered to be a special condition of ANM, which is the extreme of earlier menopause age and is defined to be a disease with abnormal menopause age. Patients with POF commonly experience POI before their ovaries fail entirely. In 2015, the ESHRE defined POI as oligo/amenorrhoea for more than 4 months before the age of 40 and FSH above 25 IU/l twice within 4 weeks, a diagnostic threshold lower than the 40 IU/l that defines POF (*Webber et al., 2016*).

The oldest and most cited classic study of the incidence of POF was the ANM study of 1858 women in Rochester, Minnesota, USA, in 1986. The survey found that the annual incidence of natural menopause between the ages of 15 and 29 years old was 10/100,000 person-years. For those aged 30–39 years old, it was 76/100,000 person-years. In the population aged 40–44 years old, it was 881/100,000 person-years. Consequently, the prevalence of POF was about 1% (*Coulam et al., 1986*). In subsequent studies, it came to be recognized that there were racial differences in ANM. A prospective multiracial study of 11,652 women indicated significant racial differences in the prevalence of POF, as low as 0.1% in Japanese, 0.5% in Chinese, about 1% in European, and about 1.4% in African-American and Hispanic-American populations (*Luborsky et al., 2003*). As early as 1997, some scholars proposed that the odds ratio (OR) of premature menopause in daughters was 6.02 (95%CI: 3.39–10.66) if the mother had a premature menopause (*Torgerson et al., 1997*). In 2007, a study investigated the prevalence of POF in 832 female twin-pairs from Australian and UK twin research databases and revealed a stronger ANM association in monozygotic twins than in dizygotic twins (*Gosden et al., 2007*). These studies suggested a significant genetic effect of ANM. In 2011, the Breakthrough Generations Study in Britain used logistic regression, a variance component model and other statistical methods to study the heritability of ANM in 2060 people. The results showed that among the factors causing a difference in menopause age, genetic effects accounted for about 42% and shared environmental factors accounted for about 14% (*Morris et al., 2011*). These studies tell us that heredity is a major determinant of ANM.

THE TRADITIONAL CANDIDATE GENE STUDIES AND THE EMERGENCE OF GWAS

The traditional indicators of ovarian reserve can only indicate abnormalities when approaching menopause, which has some limitations. With the development of genetic research, genetic technology has promoted research into ANM. In 1999, a study of 900 post-menopausal women aged 55–80 years old showed that the *Pvu II* polymorphism in the oestrogen α receptor (*ESR1*) gene was associated with menopausal age (*Weel et al., 1999*). Subsequent studies focused on candidate genes for the oestrogen pathway. In 2003, a study involving 317 menopausal women over 46 years of age showed that the *ESR1 Pvu II* polymorphism did not cause differences in menopausal age or reproductive lifespan, and the *CYP17* gene involved in oestrogen metabolism was only found to be related to age of menarche (*Gorai et al., 2003*). In 2005, a study of ANM in 385 people of European descent showed that neither the *ESR1 Pvu II* polymorphism nor the *CYP17* gene was significantly associated with ANM (*Kok et al., 2005*). Studies on the correlation between candidate genes and ANM yielded contradictory results. Some scholars proposed that the reason for this dilemma was that the genetic variation of ANM was not caused by single-gene mutation, and such complex clinical phenotypes had multi-gene effects (*Purcell et al., 2007*).

Spontaneous POI/POF and ANM have different genetic factors. Studies of POI/POF need to be conducted in women under 40 years old with amenorrhoea, not in the general population with natural menopause (*Ruth et al., 2021*). According to statistics, genetic factors account for 20–25% of all causes of POI, including chromosomal defects and gene defects (*Qin et al., 2015*). In 2012, Jiao et al. reported the results of karyotype analysis of chromosome G bands in 531 patients with POF recruited from four medical centres in China. Of the 64 (12.1%) POF patients with abnormal karyotypes, 93.7% were characterized by X chromosome abnormalities, including number abnormalities, structural abnormalities and chromosome translocations (*Jiao et al., 2012*). In the study of gene defects, the number of candidate genes of POI/POF was higher than that of ANM. These mutant genes are located in X chromosomes, autosomal and mitochondrial. The X chromosome contains the most POI genes, including *BMP15*, *FMR1*, *PGRMC1*, *AR*, *FOXO4*, *DACH2*, etc. Candidate genes located in autosomes include *FSHR*, *GDF9*, *NOBOX*, *PTEN*, *AMHR2*, etc. (*Qin et al., 2015*; *Tapanainen et al., 1997*; *Venturella et al., 2019*; *Wang et al., 2016*). Although single-gene techniques explored some genetic causes of POI, these candidate genes explain only a small fraction of the cause.

As the traditional candidate gene studies first adopted the hypothesis and then verified the method, this led to limitations in the studies of complex clinical phenotypes such as ANM, and the research methods on polygenic effects arose at that historic moment. With the emergence and rapid development of whole genome sequencing and exon sequencing, *Nature* published the second generation of the human genome haplotype map (HapMap) on 18 October 2007 (*Frazer et al., 2007*). It provided more sophisticated single nucleotide polymorphism (SNP) data for genome studies, and offered a way to compare large numbers of genes simultaneously and to verify genome-wide disease-causing

associations. GWAS are a direct comparison of high-throughput genetic data between the population with clinical phenotypes and the control population, to reveal the genetic mechanism of clinical phenotypes. Unlike candidate gene research, this method does not need to put forward hypotheses in advance, but can directly find multiple different molecules, which greatly improves the research efficiency. The application of GWAS in research into the reproductive lifespan has become a new hotspot in the study of ovarian reserve.

A SERIES OF STUDIES ON ANM BY THE REPRODUCTIVE GENETICS CONSORTIUM

In 2009, a GWAS combined data from the Rotterdam Study and the Twins UK Study on 2979 European women. The results suggested that six SNP on human chromosomes 19q13.4, 20p12.3 and 13q34 might be related to ANM, and the minor allele frequency (MAF) ranged from 0.12 to 0.48. *BRSK1* (MAF = 0.39, $P = 6.3 \times 10^{-11}$) might affect ovarian function by regulating AMPK-related kinase, which was associated with ANM advance. *TMEM150B* might be related to FGF receptor activation. *MCM8* might be involved in DNA replication damage at the hypothalamic–pituitary and ovarian levels, thus regulating ovarian ageing (*Stolk et al., 2009*). In the same year, another large GWAS analysed the Nurses' Health Study (NHS) and the Women's Genome Health Study (WGHS). This study identified 13 SNP clustered in five genes: 19q13.42/*BRSK1*, 20p12.3/*MCM8*, 5q35.2/*RAP80* and *HK3*, and 6p24.2/*SYCP2L* (*He et al., 2009*). In these two large GWAS in 2009, *BRSK1* and *MCM8* were replicated, but SNP on 13q34 was not.

The GWAS of ANM identified new loci by comparing SNP in a large sample population. The number of associated loci that GWAS can identify is related to the size of the sample. When the sample size of GWAS was increased to the threshold value, the number of new loci detected would increase significantly (*Visscher et al., 2012*). Therefore, the data sharing of multiple large cohorts can increase the number of gene loci detected by increasing the sample size. Based on this principle, public data from some large cohort studies were summarized and analysed. The Reproductive Genetics Consortium (ReproGen) is an international website that shares reproductive genetic data (https://reprogen.org/). In 2012, Stolk et al. laid the foundation for ReproGen's ANM dataset by conducting a large GWAS that meta-reviewed 22 studies of mostly women of European descent. The studies included AGES (Age, Gene/Environment Susceptibility Study), ARIC (Atherosclerosis Risk in Communities), CHS (Cardiovascular Health Study), deCODE (a commercial company from Iceland), EGCUT (Estonian Genome Centre University of Tartu), ERF (Erasmus Rucphen Family study), FHS (Framingham Heart Study), HAPI (Heredity and Phenotype Intervention) Heart Study, InChianti (Invecchiare in Chianti), NHS, QIMR (Queensland Institute of Medical Research), the Rotterdam Study, SardiNIA (GWAS of the Ogliastra region of Sardinia, Italy), SHIP (Study of Health in Pomerania), TwinsUK and WGHS. The total sample size reached 38,968, and the number of identified new loci increased to 17 (*Stolk et al., 2012*).

This GWAS, which combined multiple studies, also found that the effect of each allele ranged from 8.7 weeks to 50.5 weeks, explaining 2.5–4.1% of the variation in menopausal age. The associations in four of the 17 genes replicated the two 2009 GWAS, but the SNP on 13q34 were still unreplicated. Of the 13 newly discovered regions, eight genes (*HELQ* and *FAM175A* on chromosome 4, *PRIM1* on chromosome 12, *POLG* and *FANCI* on chromosome 15, *EXO1* on chromosome 1, *UIMC1* on chromosome 5, *TLK1* on chromosome 2) were involved in DNA repair. Three genes (*IL11* and *NLRP11* on chromosome 19 and *BAT2* on chromosome 6) were associated with immune function. *ASH2L* on chromosome 8 was associated with X chromosome inactivation. There were four main functional networks within the ingenuity pathway analysis (IPA). One was the *HNF4A* centred network on 'lipid metabolism, molecular transport and small molecule biochemistry', which contained 14 genes and was suggested to be involved in diabetes. The second was *ESR1*, centred on the 'cell cycle, cell death and tumour' network, involving 12 genes that might be affected by oestrogen signalling. The third was the TNF and NF-κB related 'cell death' network. The fourth involved networks of 'infection, DNA replication, recombination, repair and gene expression'. Gene-set enrichment pathway analyses (GSEA) suggested that ANM was associated with biological processes such as exodeoxyribonuclease ($P = 0.0005$), the NF-κB pathway ($P = 0.0006$) and mitochondrial dysfunction ($P = 0.0001$). The false discovery rate (FDR) of multiple hypothesis testing was <0.05. This study showed that ANM genes were mainly related to DNA damage response (DDR), and defects in the DNA repair mechanism resulted in decreased oocyte quality accumulated with age and increased follicle loss, which was an important cause of ovarian function decline. In addition, this study also emphasized that genes associated with autoimmune diseases could also affect ANM, such as *BAT2* associated with type I diabetes and rheumatoid arthritis, whose missense mutation could cause inflammation in oocytes (*Stolk et al., 2012*).

The expanded GWAS substantially increased the sample size, but the average age of menopause in these studies ranged from 48.20 to 50.78 years. Most women experienced menopause at a normal age. In the same period as the ReproGen study, *Qin et al. (2012)* conducted another GWAS in 371 patients with POF and 800 control women in China. The mean age of secondary amenorrhoea in POF patients was 24.87 years. ESR1, BRSK1 and HK3 were found to be associated with POF. SNP associated with ANM might promote the occurrence of POF, but do not play a major role in it (*Qin et al., 2012*). In addition, it is important to note that POF/POI and early menopause were defined as two diseases with different clinical traits, although both have early menopausal age. Studies have shown that FSH might rise more rapidly in patients with POI than early menopause, and patients with POI might have menarche earlier than early menopause (*Bompoula et al., 2020*). A meta-analysis showed that the relative risks (RR) of all-cause death and ischaemic heart disease (IHD) in women with POI were 1.39 and 1.48, which were higher than those in women of normal menopausal age. The RR of IHD in early menopause women was 1.09, which was slightly higher than that in women with normal menopausal age, while all-cause mortality was not significantly different (*Tao et al., 2016*). There might be differences in genetic variants among women with unexplained different menopause ages. In 2013, ReproGen continued to compare GWAS data from 3493 post-menopausal women under 45 years of age (early menopause and POI) with 13,598 post-menopausal women between 50 and 60 years of age (controls). This study calculated the OR values of the 17 ANM genes that were known to predict early menopause and POI. The OR value of early menopause ranged from 1.09 to 1.55, and the OR value of POI ranged from 1.04

to 1.17. All 17 genes of ANM were correlated with early menopause or POI, and early menopause and POI might be associated with the additive effect of different gene variants (*Perry et al., 2013*).

Menopausal age and reproductive lifespan have different meanings. Menopausal age represents the end of reproductive life, while reproductive lifespan is the period from menarche to menopause. The reproductive lifetime in women with earlier ANM might not be changed due to earlier age at menarche, but might have left shift in reproductive lifespan. In 2014, through bivariate GWAS meta-analysis of age at menarche and natural menopause, ReproGen found that 6q21.32/*PRRC2A* and 2p16.3/*MSH6* might cause left shift in reproductive lifespan, and each allele of *MSH6* could reduce ANM by 1.3 months (MAF = 0.83). It was the 18th gene identified by the ReproGen Consortium to be associated with ANM advance, and its function was also associated with DNA repair defects (*Perry et al., 2014*).

ReproGen expanded the sample size to 69,360 in 2015 and further identified 44 ANM-related genes with MAF ranging from 0.07 to 0.49 and effect size of each allele ranging from 0.07 to 0.88 years using a large-scale genetic analysis in women of European descent (*Day et al., 2015*). Three low-frequency variants associated with ANM were identified by exon array meta-analysis, including the organic anionic transporter gene 20q13.33/*SLCO4A1* (MAF = 0.008) and two SNP (MAF = 0.036 and 0.025) on the DNA helicase gene 12q14.3/*HELB*. Pathway enrichment analysis revealed 29 genes in or near DDR regions. *HELQ*, *MCM8*, *RAD51*, *MSH5*, *BRE*, *UIMC1*, *FANCI*, *RAS54L*, *DMC1*, *BRCA1*, *FAM175A* and *FBXO18* were most involved in homologous recombination after double strand break. *UIMC1* and *BRCA1* participated in DDR through the oestrogen α receptor. Other DDR mechanisms included DNA damage sensors *BRSK1*, DNA damage transducers and effectors *CHEK2*, mismatch repair genes *MSH5* and *MSH6*, base excision genes *APEX1* and *PARP2*, etc.

More ANM-associated genes were discovered, which may help reveal the genetic causes of ANM-associated diseases. In the expanded ReproGen GWAS in 2015, a partial genetic mechanism of some ANM-associated diseases such as breast cancer was identified using bioinformatics methods. STRING signalling pathway analysis showed that breast cancer gene *BRCA1* is associated with 15 ANM genes, such as *BRE*, *MSH6*, *POLR2H*, *FAM175A*, *UIMC1*, *RAD51*, *CHEK2*, etc. The gene effect of ANM was positively correlated with the gene effect of breast cancer. In women with a menopausal age ≥55 years old, the breast cancer OR value was 1.06 (95%CI: 1.04–1.10) with $P = 2.23 \times 10^{-7}$, while the OR value was 1.00 (95%CI: 0.97–1.05) with $P = 0.95$ in women with menopausal age ≤45 years. This explained why the younger the age at menopause, the lower the risk of breast cancer from the perspective of genetic epidemiology. Disease association analysis of POI also showed that recessive mutation of *MCM8* was associated with primary amenorrhoea, pituitary amenorrhoea and hypothyroidism. Recessive mutation of *EIF2B4* was associated with ovarioleukodystrophy and vanishing white matter syndrome. *POLG* mutation was associated with POI and neurological conditions. *MSH5* was not only associated with POI, but also with many other diseases. *TDRD3* was related to POI caused by pre-mutation of *FMR1* (*Day et al., 2015*). The ReproGen Consortium study provided a wealth of genetic data for GWAS of reproductive longevity and sets the stage for the following research.

ASIAN GWAS OF ANM AND MULTI-ETHNIC STUDIES

The studies performed by the ReproGen Consortium were a landmark in ANM research, but they were based on women of European descent. Whether these genetic loci can be replicated in other populations needed to be confirmed in different populations. In 2016, a study of reproductive lifespan in East Asia included 16,395 women from Shanghai in China and South Korea, and replicated part of the ANM genes identified in European descent. In view of the correlation between ANM and breast cancer, endometrial cancer and type II diabetes, the Shanghai Genome-wide Association Studies (SGWAS), including multiple related diseases genomic data of 8073 patients, were used to correlate ANM genes with diseases in the first phase of the project. A total of 1638 women aged 50 to 70 in the Nutrition and Health of Ageing Population in China (NHAPC), 2164 new breast cancer patients and 2051 control women in the Seoul Breast Cancer Study (SeBCS), as well as 2877 healthy control women in the Shanghai Women's Health Study (SWHS) were added in the second phase. 22q12.2/*SFI1* was found in SGWAS as a novel ANM gene locus, and each allele could advance the age of menopause by 0.454 ± 0.089 years. *SFI1* was found to regulate the dynamic structure of centrosome-related fibres by encoding a spindle assembly related *sfi1* homolog. Five ANM genes of East Asian descent were copied among 20 ANM genes of European descent, namely *TMEM150B*, *RHBDL2*, *UIMC1*, *NLRP11* and *POLG* (*Shi et al., 2016*). *TMEM150B* was located on chromosome 19, near *BRSK1*, encoding transmembrane protein and participating in autophagy regulation. *RHBDL2* was located on chromosome 1 encoding a serine kinase associated with epidermal growth factor receptor activation.

In 2018, the GWAS results of the BioBank Japan Project (BBJ), which included 67,029 women of Japanese descent, identified 16 ANM genes, of which eight were novel loci and different from those of European descent, suggesting widespread genetic differences in allele frequencies between Japanese and European populations. The eight novel gene loci were 10q24.1/*CCNJ*, 3q21.3/*H1FX*, 4p11/*ZAR1*, 8p21.2/*GNRH1*, 18q21.33/*ZCCHC2*, 8q24.11/*RAD21*, 4q23/*EIF4E* and 14q24.2/*DCAF4*. In terms of the analysis of cell and tissue type enrichment, significant enrichment was also found in the hypothalamic–pituitary–ovarian (HPO) axis involved by *GNRH1* in addition to the DDR mechanism (*Horikoshi et al., 2018*).

Studies in women of Japanese descent showed ethnic heterogeneity of ANM genes, so further trans-ethnic studies need to be developed. However, genetic heterogeneity was also one of the difficulties in multi-population genome-wide meta-analyses, and so the GWAS meta-analysis method should be developed to increase detection ability. On the other hand, it was necessary to continue conducting larger sample GWAS in multiple regions and ethnic groups (*Zakharov et al., 2015*). In November 2012, *Nature* published the '1000 Genomes Project Consortium' data involving 1092 people from 14 ethnic groups, which formed a large international scientific collaboration in Europe, America, Asia and Africa. The establishment of gene databases could help to find trans-ethnic gene variations and analyse the general applicability of the association between diseases and genomes.

TRANS-ETHNIC GWAS OF ANM AND USE OF THE NATIONAL BIOBANK

The Population Architecture using Genomics and Epidemiology (PAGE) project reported the results of a multi-ethnic study of reproductive age in 2013. The study involved 42,251 women from American Indian, African, Asian, European, Hispanic/Latino and Native Hawaiian populations. Three ANM genes, 6p24.2/*SYCP2L*, 5q35/*UIMC1* and 20p12.3/*MCM8*, were replicated in non-European populations. However, 19q13/*BRSK1* was not replicated significantly in other populations (*Carty et al., 2013*). In 2018, PAGE used a variety of meta-analysis techniques to revalidate ANM genes of European descent in multiple populations. After excluding smaller sample sizes of American Indian/Alaska Native populations, 23 ANM studies were included from three large groups of Asian, African and Hispanic/Latino women. Trans-ethnic analysis showed that *BRSK1* and *MCM8* genes were associated with ANM and could be applied to non-European populations. The modified random effect association showed that *FRMD5* and *GPRC5B* were associated with ANM genes in Asian and African populations, but there was heterogeneity in Hispanic/Latino populations (*Fernández-Rhodes et al., 2018*). *FRMD5* is related to triglyceride metabolism, while *GPRC5B* has DNA enzyme activity in the ovary and is, for example, related to obesity and age at menarche.

The high-test efficiency of multi-ethnic GWAS needs to include a larger biological sample size. In the process of the development of GWAS, the national biological bank provides extensive data. The UK Biobank (UKBB) is based on a large prospective cohort study, which recruited about 500,000 participants aged 40–69 years old from 2006 to 2010 and recorded detailed health information, disease phenotypes and genomic data. The interim UKBB release in May 2015 contained data from 150,000 participants. In the full UKBB release database, 88.26% were of British background. The rest included genetic data from other ethnic groups, such as Asians and Africans (*Bycroft et al., 2018*). In 2019, a new GWAS method, functionally informed novel discovery of risk loci (FINDOR), was reported. This method used multi-gene functional enrichment for association analysis of UKBB. Among the traits of ANM, about 44,000 participants of the interim UKBB release and 143,000 participants of the full UKBB release were included, and 53 new ANM-associated gene loci were detected (*Kichaev et al., 2019*). Biobanks and advancing technologies of bioinformatics have improved the power of GWAS.

In 2021, the genetic data of 225,200 people were combined with the ReproGen, UKBB and BBJ. ReproGen and UKBB were derived from the European genetic data, while BBJ studied an East Asian population. The study reported 49 novel loci associated with ANM. Bioinformatics assessment was carried out and candidate genes were prioritized based on functional annotation. The trans-ethnic meta-analysis identified 127 loci, of which 43 were novel loci. Most ANM genes of European and East Asian populations were not found to be heterogeneous. In molecular network analysis, *TP53BP1* had the most contact with other genes, which was related to breast cancer and ovarian cancer. *FANCM* was followed, which was associated with breast cancer risk. In addition, this GWAS also correlated genetic data with some clinical characteristics, such as 'ever used hormone replace therapy' and 'age started hormone replacement', adding evidence of ANM gene association (*Zhang et al., 2021*).

RECENT GWAS STUDIES OF ANM AND FUTURE RESEARCH AGENDA

Polygenic score (PGS) is the weighted sum of the effect sizes of the associated alleles. In recent years, PGS was used to assess the genetic risks of different menopause ages. In 2021, *Ruth et al. (2021)* further explored the genetic risks of POI, early menopause and ANM by calculating PGS in a large GWAS. This study identified 209 SNP associated with ANM in 201,323 women of European ancestry and were replicated in women of East Asian ancestry (the China Kadoorie Biobank study and BBJ), although with different effect sizes. The effects of each allele ranged from 3.5 weeks to 74 weeks. This study calculated the PGS of 108,840 women aged 34–61 years in the UKBB and used it to assess the association between POI and common ANM variants. The results showed that the PGS of common ANM genes had a low ability to predict early menopause and POI; the area under the receiver operating characteristic curve (ROC-AUC) was 0.65 and 0.64. Nevertheless, PGS of common ANM were still able to identify individuals at high risk of POI. ANM genes with higher PGS could predict the risks of POI and early menopause. The identified genes are mainly enriched in functions related to DNA damage repair, meiosis recombination and apoptosis across the life course (*Ruth et al., 2021*).

Although GWAS discovered more new related gene loci, its clinical predictive value is still limited. Because neighbour SNP are highly associated, it is often difficult to assess the validity of the new gene loci (*Tam et al., 2019*). In recent years, in addition to improving the research methods and expanding the sample size to find new ANM loci, more in-depth studies combined with clinical trials have been carried out to target the identified genes. For example, a candidate genome for ANM was established based on GWAS results. Targeted sequencing of genes associated with DDR, hormone regulation, mitochondrial function, etc., was conducted in POI patients to explore the internal relationship between the causes and clinical manifestations of diseases from the perspective of gene regulation (*Yang et al., 2021*). Post-menopausal women may have different clinical characteristics. The ANM gene might be associated with menopausal symptoms or disease experience. The ANM gene may be involved in menopausal symptoms or enduring diseases. Mendelian randomization, linkage disequilibrium score regression (LDSC) and other methods were used to demonstrate the disease-associated genetic mechanism between ANM and coronary atherosclerotic heart disease (*Dam et al., 2022*), rheumatoid arthritis (*Zhu et al., 2021*), chronic kidney disease (*Qian et al., 2022*) and other diseases, but the conclusion was still controversial. In addition, there might be variations in laboratory indicators among women with different ANM, especially some important tested molecules that could indicate ovarian reserve. Genes associated with these molecules might affect ANM or ANM-associated genes. For example, recently reported age-stratified GWAS studies further found age specificity in four loci (*MCM8* and in or near *AMH*, *TEX41* and *CDCA7*) associated with anti-Müllerian hormone (*Verdiesen et al., 2022*). These studies not only explored the genetic mechanism of natural menopause age, but also provided new ideas and directions for research on the pathogenesis and genetic epidemiology of menopause-related diseases. Although GWAS have

TABLE 1 LIST OF IDENTIFIED GENES ASSOCIATED WITH AGE AT MENOPAUSE

Chromosome band	Gene	Gene full name	Subcellular location	Function	Population[a]	First reference
1p33	UQCRH	Ubiquinol-cytochrome c reductase hinge protein	Mitochondrion inner membrane	Metabolic proteins	UKBB	*Kichaev et al., 2019*
1p34.1-p33	LRRC41	Leucine-rich repeat-containing 41	Cytosol	Transcription	European (ReproGen)	*Day et al., 2015*
1p34.2	CCDC30	Coiled-coil domain-containing 30	Intracellular	Protein coding	UKBB	*Kichaev et al., 2019*
1p34.3	RHBDL2	Rhomboid-like 2	Membrane	Enzymes	European (ReproGen); UKBB	*Stolk et al., 2012*
1p36.31	DNAJC11	DnaJ heat shock protein family (Hsp40) member C11	Mitochondrion	Protein binding	UKBB	*Kichaev et al., 2019*
1q21.2	H2BC19P	H2B clustered histone 19, pseudogene	Nucleus	Nucleic acid binding	UKBB	*Kichaev et al., 2019*
1q24.2	SELE	Selectin E	Membrane	Cell adhesion	UKBB	*Kichaev et al., 2019*
1q24.2	C1orf112	Chromosome 1 open reading frame 112	Mitochondrion	Transcription	UKBB	*Kichaev et al., 2019*
1q25.3	STX6	Syntaxin 6	Nucleoplasm, Golgi apparatus	Transporter, plasma proteins	European (ReproGen); UKBB	*Day et al., 2015*
1q43	EXO1	Exonuclease 1	Nucleoplasm, nuclear bodies	Enzyme	European (ReproGen); UKBB	*Stolk et al., 2012*
1q44	ADSS2	Adenylosuccinate synthase 2	Plasma membrane, cytosol	Ligase, DNA repair	UKBB	*Kichaev et al., 2019*
2p16.3	MSH6	mutS homolog 6	Nucleoplasm, Golgi apparatus, vesicles	DNA damage, DNA repair, host—virus interaction	European (ReproGen); UKBB	*Day et al., 2015*
2p16.3	FBXO11	F-box protein 11	Nucleoplasm, nucleoli	Ubl conjugation pathway	European (ReproGen)	*Day et al., 2015*
2p23.3	FNDC4	Fibronectin type III domain-containing 4	Nucleoplasm, aggresome, cytosol	Anti-inflammatory factor	European (ReproGen); UKBB	*Stolk et al., 2012*
2q21.3	CCNT2	Cyclin T2	Nucleoplasm, plasma membrane, cytosol	Cell cycle, cell division, host—virus interaction, transcription, transcription regulation	UKBB	*Kichaev et al., 2019*
2q23.3	RIF1	Replication timing regulatory factor 1	Nucleoplasm, nuclear bodies, plasma membrane	Cell cycle, DNA damage, DNA repair	UKBB	*Kichaev et al., 2019*
2q31.1	TLK1	Tousled-like kinase 1	Nucleoplasm	Cell cycle, DNA damage	European (ReproGen)	*Stolk et al., 2012*
2q31.1	METAP1D	Methionyl aminopeptidase type 1D, mitochondrial	Vesicles	Enzyme	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2012*
2q31.1	GORASP2	Golgi reassembly stacking protein 2	Golgi apparatus	Differentiation	UKBB	*Kichaev et al., 2019*
2q33.1-q33.2	BMPR2	Bone morphogenetic protein receptor type 2	Nucleoplasm, plasma membrane	Kinase	UKBB	*Kichaev et al., 2019*
3p21.31	SEMA3F-AS1	SEMA3F antisense RNA 1	Nucleus	lncRNA	UKBB	*Kichaev et al., 2019*
3q21.3	H1-10	H1.10 linker histone	Nucleus, cytosol	Nucleic acid binding	BBJ	*Horikoshi et al., 2018*
3q21.3	UROC1	Urocanate hydratase 1	Cytosol, peroxisome, mitochondrion	Histidine metabolism	UKBB	*Kichaev et al., 2019*
3q25.31	TIPARP	TCDD inducible poly (ADP-ribose) polymerase	Microtubules	Metabolic proteins	UKBB	*Kichaev et al., 2019*

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TABLE 1 (*Continued*)

Chromosome band	Gene	Gene full name	Subcellular location	Function	Population[a]	First reference
3q26.2	SLC7A14-AS1	SLC7A14 antisense RNA 1	No data	lncRNA	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2009*
3q27.1	CYP2AB1P	Cytochrome P450 family 2 subfamily AB member 1, pseudogene	No data	Pseudogene	European (ReproGen)	*Day et al., 2015*
3q27.1	PARL	Presenilin-associated rhomboid-like	Mitochondrion	Enzyme, control of apoptosis	UKBB	*Kichaev et al., 2019*
4p11	FRYL	FRY-like transcription coactivator	Microtubules, cytokinetic bridge, cytosol	Transcription, transcription regulation	BBJ	*Horikoshi et al., 2018*
4p11	OCIAD1	OCIA domain-containing 1	Mitochondria	Maintains stem cell potency	UKBB	*Kichaev et al., 2019*
4p15.33	BOD1L1	Biorientation of chromosomes in cell division 1-like 1	Nucleoplasm	DNA damage, DNA repair	UKBB	*Kichaev et al., 2019*
4q21.23	HELQ	Helicase, POLQ-like	Nucleoplasm, nuclear speckles	DNA damage, DNA repair	European (ReproGen); BBJ	*Stolk et al., 2012*
4q21.23	ABRAXAS1	Abraxas 1, BRCA1 A complex subunit	Nuclear bodies	DNA damage, DNA repair	UKBB	*Kichaev et al., 2019*
4q23	EIF4E	Eukaryotic translation initiation factor 4E	Nucleoplasm, cytosol, cytoplasmic bodies	Initiation factor, RNA binding	BBJ	*Horikoshi et al., 2018*
4q23	H2AZ1-DT	H2AZ1 divergent transcript	No data	lncRNA	UKBB	*Kichaev et al., 2019*
4q35.1	ACSL1	Acyl-CoA synthetase long chain family member 1	Vesicles	Lipid metabolism	UKBB	*Kichaev et al., 2019*
5p15.31	TENT4A	Terminal nucleotidyltransferase 4A	Nucleoplasm, nuclear membrane, Golgi apparatus	Enzyme	European (ReproGen); UKBB	*Day et al., 2015*
5q13.3	CERT1	Ceramide transporter 1	Nucleoplasm, Golgi apparatus	Lipid transporter	African-American (PAGE)	*Spencer et al., 2013*
5q35.2	UIMC1	Ubiquitin interaction motif-containing 1	Nucleoplasm, nuclear bodies	DNA damage, DNA repair, transcription, transcription regulation	US (NHS, WGHS); European (ReproGen); UKBB	*He et al., 2009*
5q35.2	RNF44	Ring finger protein 44	Nucleoplasm	Metal binding, zinc	European (ReproGen)	*Day et al., 2015*
5q35.2	ZNF346	Zinc finger protein 346	Nucleoplasm	RNA binding	BBJ	*Horikoshi et al., 2018*
5q35.2	C5orf47	Chromosome 5 open reading frame 47	Intracellular	Protein coding	UKBB	*Kichaev et al., 2019*
5q35.3	GRK6	G protein-coupled receptor kinase 6	Mitochondria	Kinase	UKBB	*Kichaev et al., 2019*
5q35.3	F12	Coagulation factor XII	Secreted to blood	Blood coagulation, fibrinolysis, haemostasis	UKBB	*Kichaev et al., 2019*
6p21.33	SLC44A4	Solute carrier family 44 member 4	Membrane	Transporter	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2009*
6p21.33	CYP21A2	Cytochrome P450 family 21 subfamily A member 2	Intracellular	Steroidogenesis	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2009*
6p21.33	PRRC2A	Proline-rich coiled-coil 2A	Nucleoplasm, plasma membrane, cytosol	Regulation of pre-mRNA splicing	European (ReproGen)	*Stolk et al., 2012*
6p21.33	NFKBIL1	NFKB inhibitor-like 1	Nucleoplasm	Immune response	European (ReproGen)	*Day et al., 2015*

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TABLE 1 (*Continued*)

Chromosome band	Gene	Gene full name	Subcellular location	Function	Population[a]	First reference
6p21.33	MSH5	mutS homolog 5	Endoplasmic reticulum, vesicles	DNA damage, DNA repair, meiosis	European (ReproGen)	*Day et al., 2015*
6p21.33	MSH5-SAPCD1	MSH5-SAPCD1 read-through (NMD candidate)	No data	Transporter	European (ReproGen)	*Day et al., 2015*
6p22.3	CDKAL1	CDK5 regulatory subunit-associated protein 1-like 1	Intracellular, membrane	Transferase	African-American (PAGE)	*Spencer et al., 2013*
6p24.2	SYCP2L	Synaptonemal complex protein-2 like	Nucleoplasm	Regulates the survival of primordial oocytes	US (NHS, WGHS); European (ReproGen); BBJ	*He et al., 2009*
6q16.3-q21	LIN28B	lin-28 homolog B	Nucleoplasm, nucleoli, cytosol	RNA-mediated gene silencing	US (NHS, WGHS); BBJ	*He et al., 2009*
6q21	MFSD4B	Major facilitator superfamily domain-containing 4B	Membrane	Transporter	European (ReproGen)	*Day et al., 2015*
6q25.3	SOD2	Superoxide dismutase 2	Mitochondria	Oxidoreductase	UKBB	*Kichaev et al., 2019*
7p11.2	PSPH	Phosphoserine phosphatase	Cytosol	Hydrolase	UKBB	*Kichaev et al., 2019*
7p22.1	TNRC18	Trinucleotide repeat-containing 18	Nucleus, mitochondria, cytosol	Enable chromatin binding activity	UKBB	*Kichaev et al., 2019*
7p22.1	CCZ1	CCZ1 homolog, vacuolar protein trafficking and biogenesis-associated	Vesicles	Guanine-nucleotide releasing factor	UKBB	*Kichaev et al., 2019*
7q22.1	CASTOR3	CASTOR family member 3	Cytosol, mitochondrion, nucleus, extracellular, plasma membrane	Cellular response to L-arginine, negative regulation of TORC1 signalling	UKBB	*Kichaev et al., 2019*
7q31.1	NRCAM	Neuronal cell adhesion molecule	Nucleoplasm, vesicles, plasma membrane	Cell adhesion	US Caucasians; Chinese	*Ran et al., 2013*
7q32.1	TNPO3	Transportin 3	Vesicles	Transporter	UKBB	*Kichaev et al., 2019*
7q35	NOBOX	NOBOX oogenesis homeobox	Intracellular	Developmental protein, DNA binding	UKBB	*Kichaev et al., 2019*
7q36.3	ESYT2	Extended synaptotagmin 2	Plasma membrane, cytosol	Endocytosis, lipid transport, transport	UKBB	*Kichaev et al., 2019*
8p11.23	ADGRA2	Adhesion G protein-coupled receptor A2	Intracellular, membrane	G-protein coupled receptor	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2009*
8p11.23	ASH2L	ASH2-like, histone lysine methyltransferase complex subunit	Nucleoplasm, plasma membrane	Nucleoli	European (ReproGen)	*Stolk et al., 2012*
8p11.23	EIF4EBP1	Eukaryotic translation initiation factor 4E-binding protein 1	Nucleoplasm, cytosol	Protein synthesis inhibitor, translation regulation	BBJ	*Horikoshi et al., 2018*
8p21.2	GNRH1	Gonadotropin-releasing hormone 1	Secreted to blood	Hormone	BBJ	*Horikoshi et al., 2018*
8q12.2	CHD7	Chromodomain helicase DNA-binding protein 7	Nucleoplasm, nucleoli	Chromatin regulator, DNA binding, helicase, hydrolase	European (ReproGen)	*Day et al., 2015*
8q21.13	ZFHX4	Zinc finger homeobox 4	Nucleoplasm, nucleoli fibrillar centre	Transcription, transcription regulation	BBJ	*Horikoshi et al., 2018*

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TABLE 1 (*Continued*)

Chromosome band	Gene	Gene full name	Subcellular location	Function	Population[a]	First reference
9p21.1	APTX	Aprataxin	Nucleoplasm, nucleoli	DNA damage, DNA repair	European (ReproGen); UKBB	*Day et al., 2015*
9q21.31	TLE4	TLE family member 4, transcriptional corepressor	Nucleoplasm	Transcription factor	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2009*
9q31.2	LINC01505	Long intergenic non-protein coding RNA 1505	No data	lncRNA	US (NHS, WGHS); BBJ	*He et al., 2009*
9q31.3	ZNF483	Zinc finger protein 483	Nucleoli	Transcription, transcription regulation	BBJ	*Horikoshi et al., 2018*
9q31.3	PTGR1	Prostaglandin reductase 1	Intracellular	Oxidoreductase	BBJ	*Horikoshi et al., 2018*
10p15.1	TASOR2	Transcription activation suppressor family member 2	Nucleoplasm, cytosol	Negative regulation of gene expression, epigenetic	European (ReproGen)	*Day et al., 2015*
10q21.3	DNA2	DNA replication helicase/nuclease 2	Mitochondria	DNA damage, DNA repair, DNA replication	UKBB	*Kichaev et al., 2019*
10q24.1	ENTPD1-AS1	ENTPD1 antisense RNA 1	Nucleus, plasma membrane	lncRNA	BBJ; UKBB	*Horikoshi et al., 2018*
10q24.1	CCNJ	Cyclin J	Nucleoplasm, Golgi apparatus	Enzyme modulator	BBJ	*Horikoshi et al., 2018*
10q24.31	CHUK	Component of inhibitor of nuclear factor kappa B kinase complex	Nucleoplasm, cytosol	Kinase	UKBB	*Kichaev et al., 2019*
10q26.13	ZRANB1	Zinc finger RANBP2-type containing 1	Nucleoplasm, cytosol	Enzyme	UKBB	*Kichaev et al., 2019*
10q26.3	LINC02666	Long intergenic non-protein coding RNA 2666	No data	lncRNA	UKBB	*Kichaev et al., 2019*
11p14.1	BDNF-AS	BDNF antisense RNA	Nucleus, cytoskeleton, cytosol	lncRNA	BBJ	*Horikoshi et al., 2018*
11p14.1	BDNF	Brain-derived neurotrophic factor	Nuclear speckles, mitochondria	Signalling	BBJ	*Horikoshi et al., 2018*
11p15.5-p15.4	KCNQ1	Potassium voltage-gated channel subfamily Q member 1	Endoplasmic reticulum, plasma membrane	Ion channel	African-American (PAGE)	*Spencer et al., 2013*
12q13.3	PRIM1	DNA primase subunit 1	Intracellular	DNA replication, transcription	European (ReproGen); UKBB; BBJ	*Stolk et al., 2012*
12q13.3	HSD17B6	Hydroxysteroid 17-beta dehydrogenase 6	Nucleoplasm, vesicles	Lipid metabolism, steroid metabolism	European (ReproGen); UKBB; BBJ	*Stolk et al., 2012*
12q14.3; 12q	HELB	DNA helicase B	Nucleoplasm, plasma membrane	DNA damage, DNA repair	European (ReproGen); UKBB	*Day et al., 2015*
12q24.31	PITPNM2	Phosphatidylinositol transfer protein membrane-associated 2	Vesicles	Transporter	European (ReproGen)	*Day et al., 2015*
12q24.31	SPPL3	Signal peptide peptidase-like 3	Vesicles, plasma membrane	Hydrolase, protease	European (ReproGen)	*Day et al., 2015*
12q24.31	TMEM120B	Transmembrane protein 120B	Nucleoli fibrillar centre, cytosol	Fat cell differentiation, protein hetero-oligomerization	UKBB	*Kichaev et al., 2019*
12q24.31	RILPL2	Rab-interacting lysosomal protein-like 2	Cytosol	Protein transport, transport	UKBB	*Kichaev et al., 2019*

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TABLE 1 (*Continued*)

Chromosome band	Gene	Gene full name	Subcellular location	Function	Population[a]	First reference
12q24.33	PIWIL1	piwi-like RNA-mediated gene silencing 1	Intracellular	Developmental protein, endonuclease, hydrolase, nuclease, RNA binding	UKBB	*Kichaev et al., 2019*
13q14.2	KPNA3	Karyopherin subunit alpha 3	Nucleoplasm, cytosol	Transporter	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2012*
13q21.2	TDRD3	Tudor domain-containing 3	Nucleoplasm, Golgi apparatus, cytosol	Chromatin regulator	European (ReproGen); UKBB	*Stolk et al., 2012*
14q11.2	PNP	Purine nucleoside phosphorylase	Cytosol	Enzyme	European (Rotterdam Study, Twins UK Study); UKBB	*Stolk et al., 2012*
15q15.1	NUSAP1	Nucleolar and spindle-associated protein 1	Nucleoplasm, nucleoli, nucleoli fibrillar centre	Cell cycle, cell division, mitosis	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2012*
15q15.1	INO80	INO80 complex ATPase subunit	Nucleoplasm, nuclear bodies, cytosol	Actin binding, DNA binding, hydrolase	European (ReproGen)	*Day et al., 2015*
15q15.1	MGA	MAX dimerization protein MGA	Nucleoplasm, cytosol	Transcription factor	UKBB	*Kichaev et al., 2019*
15q22.31	USP3	Ubiquitin-specific peptidase 3	Nucleoplasm, midbody ring	Cell cycle, DNA damage, Ubl conjugation pathway	UKBB	*Kichaev et al., 2019*
15q26.1	POLG	DNA polymerase gamma, catalytic subunit	Mitochondria	DNA replication	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2012*
16p13.13	GSPT1	G1 to S phase transition 1	Located in vesicles, cytosol	Plasma proteins	UKBB	*Kichaev et al., 2019*
16p13.2	C16orf72	Chromosome 16 open reading frame 72	Nucleoplasm, vesicles		European (ReproGen)	*Day et al., 2015*
16q12.2	FTO	FTO alpha-ketoglutarate-dependent dioxygenase	Vesicles, cytosol	Dioxygenase, oxidoreductase, transferase	UKBB	*Kichaev et al., 2019*
16q23.2	LINC01229	Long intergenic non-protein coding RNA 1229	No data	lncRNA	UKBB	*Kichaev et al., 2019*
16q23.2	MAFTRR	MAF transcriptional regulator RNA	No data	lncRNA	UKBB	*Kichaev et al., 2019*
16q24.2	BANP	BTG3-associated nuclear protein	Nucleoplasm, nuclear bodies	Cell cycle, transcription, transcription regulation	European (Rotterdam Study, Twins UK Study)	*Stolk et al., 2009*
16q24.2	ZFPM1	Zinc finger protein, FOG family member 1	Nucleoplasm, vesicles, cytosol	Transcription factor	UKBB	*Kichaev et al., 2019*
16q24.3	VPS9D1	VPS9 domain-containing 1	Nucleoplasm, cytosol	GTPase activation	UKBB	*Kichaev et al., 2019*
16q24.3	TCF25	Transcription factor 25	Intracellular	Transcriptional repressor	UKBB	*Kichaev et al., 2019*
17p13.2	RPAIN	RPA-interacting protein	Nucleoplasm, nucleoli fibrillar centre	RPA function in DNA metabolism	European (ReproGen); UKBB	*Day et al., 2015*
17q12	PGAP3	Post-GPI attachment to proteins phospholipase 3	Plasma membrane, cytosol	GPI-anchor biosynthesis	European (ReproGen); UKBB	*Day et al., 2015*
17q21.31	BRCA1	BRCA1 DNA repair-associated	Nucleoplasm, nuclear bodies	Activator, DNA binding, transferase	European (ReproGen); BBJ	*Day et al., 2015*
17q21.31	NBR2	Neighbour of BRCA1 lncRNA 2	Nucleus	Mediating the energy stress response	BBJ	*Horikoshi et al., 2018*

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TABLE 1 (*Continued*)

Chromosome band	Gene	Gene full name	Subcellular location	Function	Population[a]	First reference
17q21.31	VAT1	Vesicle amine transport 1	Intracellular	Oxidoreductase	UKBB	*Kichaev et al., 2019*
17q22	MSI2	Musashi RNA-binding protein 2	Cytosol	RNA binding	UKBB	*Kichaev et al., 2019*
17q23.3	POLG2	DNA polymerase gamma 2, accessory subunit	Nuclear bodies, mitochondria	DNA replication	UKBB	*Kichaev et al., 2019*
18q21.33	ZCCHC2	Zinc finger CCHC-type-containing 2	Nucleoplasm, nucleoli, cytosol	Metal binding, zinc	BBJ	*Horikoshi et al., 2018*
19p13.2	SMARCA4	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4	Nucleoplasm, nucleoli fibrillar centre, nucleoli rim	Neurogenesis, transcription, transcription regulation	African-American (PAGE)	*Spencer et al., 2013*
19p13.3	ARID3A	AT-rich interaction domain 3A	Nucleoplasm, cytosol	Transcription, transcription regulation	European (ReproGen); UKBB	*Day et al., 2015*
19p13.3	NMRK2	Nicotinamide riboside kinase 2	Nucleoplasm, vesicles	Kinase	UKBB	*Kichaev et al., 2019*
19q13.32	PPP5C	Protein phosphatase 5 catalytic subunit	Vesicles, cytosol	DNA damage, DNA repair	UKBB	*Kichaev et al., 2019*
19q13.42	TMEM150B	Transmembrane protein 150B	Membrane	Autophagy	European (ReproGen); UKBB; African-American (PAGE)	*Stolk et al., 2009*
19q13.42	BRSK1	BR serine/threonine kinase 1	Nucleoplasm, cell junctions	Cell cycle, DNA damage, neurogenesis	European (Rotterdam Study, Twins UK Study); US (NHS, WGHS); African-American (PAGE)	*He et al., 2009*
19q13.42-q13.43	NLRP11	NLR family pyrin domain-containing 11	Cytosol	Inflammation	European (ReproGen); UKBB	*Stolk et al., 2012*
20p11.21	ABHD12	Abhydrolase domain-containing 12	Intracellular, membrane	Lipid metabolism	UKBB	*Kichaev et al., 2019*
20p12.3	MCM8	Minichromosome maintenance 8 homologous recombination repair factor	Nucleoplasm, cytosol	Cell cycle, DNA damage, DNA repair, DNA replication	European (ReproGen); US (NHS, WGHS); UKBB; BBJ	*He et al., 2009*
20q13.33	SLCO4A1	Solute carrier organic anion transporter family member 4A1	Cell junctions	Transporter	European (ReproGen); UKBB	*Day et al., 2015*
20q13.33	DIDO1	Death inducer-obliterator 1	Nucleoplasm, vesicles, cytosol	Apoptosis	European (ReproGen); UKBB	*Day et al., 2015*
22q12.1	TTC28	Tetratricopeptide repeat domain 28	Microtubules, cytokinetic bridge, mitotic spindle, cytosol	Cell cycle, cell division, mitosis	European (ReproGen)	*Day et al., 2015*
22q13.1	DDX17	DEAD-box helicase 17	Nuclear speckles	Helicase, hydrolase, RNA binding	European (ReproGen); UKBB	*Day et al., 2015*

The genetic information was obtained from the references and the website of DisGeNET (https://www.disgenet.org), NCBI (https://www.ncbi.nlm.nih.gov), UniProt (https://www.uniprot.org), the Human Protein Atlas (https://www.proteinatlas.org) and GeneCards (https://www.genecards.org).

BBJ = Biobank Japan Project; NHS = Nurses' Health Study; PAGE = Population Architecture using Genomics and Epidemiology; ReproGen = Reproductive Genetics Consortium; UKBB = UK Biobank; WGHS = Women's Genome Health Study

[a] The UKBB was composed mainly of British, but also includes Asians, Africans and other ethnic groups. BBJ was made up mainly of Japanese.

TABLE 2 LIST OF ABBREVIATIONS

Category	Abbreviation	Full name
Research projects and organizations	AGES	Age, Gene/Environment Susceptibility Study
	ARIC	Atherosclerosis Risk in Communities
	ASRM	American Society for Reproductive Medicine
	BBJ	BioBank Japan Project
	CHS	Cardiovascular Health Study
	EGCUT	Estonian Genome Center University of Tartu
	ERF	Erasmus Rucphen Family study
	FHS	Framingham Heart Study
	HAPI	Heredity and Phenotype Intervention
	InChianti	Invecchiare in Chianti
	NHANES	National Health and Nutrition Examination Survey
	NHAPC	Nutrition and Health of Aging Population in China
	NHGRI	National Human Genome Research Institute
	NHS	Nurses' Health Study
	PAGE	Population Architecture using Genomics and Epidemiology
	QIMR	Queensland Institute of Medical Research
	ReproGen	Reproductive Genetics Consortium
	SeBCS	Seoul Breast Cancer Study
	SGWAS	Shanghai Genome-wide Association Studies
	SHIP	Study of Health in Pomerania
	SWHS	Shanghai Women's Health Study
	UKBB	UK Biobank
	WGHS	Women's Genome Health Study
	WHO	World Health Organization
Vital terms	ANM	age at natural menopause
	DDR	DNA damage response
	DOR	diminished ovarian reserve
	FDR	false discovery rate
	FINDOR	functionally informed novel discovery of risk loci
	GSEA	gene-set enrichment pathway analyses
	GWAS	genome-wide association studies
	HapMap	haplotype map
	HPO	hypothalamic–pituitary–ovarian
	IHD	ischaemic heart disease
	IPA	ingenuity pathway analysis
	LDSC	linkage disequilibrium score regression
	MAF	minor allele frequency
	NOA	normal physiologic ovarian ageing
	PGS	polygenic score
	POF	premature ovarian failure
	POI	premature ovarian insufficiency
	ROC-AUC	area under receiver operating characteristic curve
	SNP	single nucleotide polymorphism

This abbreviation list includes the names of research projects and organizations, as well as vital terms, in alphabetical order.

established the association between genes and clinical phenotypes, the details of these molecular mechanisms are largely based on bioinformatics reasoning, so further laboratory studies, animal experiments and clinical data are needed for verification.

CONCLUSION

This paper has reviewed the history of the genetic epidemiology of ANM. Initially, genetic traits of ANM were discovered; the limitations of traditional candidate gene studies then promoted the emergence of GWAS. GWAS verified the association between ANM and cardiovascular diseases, abnormal lipid metabolism, osteoporosis, diabetes, breast cancer, ovarian cancer and other diseases from the perspective of genes and molecular functions, and speculated on the related molecular mechanisms (*Louwers and Visser, 2021*). Given the importance of related biological information, the following websites were consulted: DisGeNET (https://www.disgenet.org/), NCBI (https://www.ncbi.nlm.nih.gov/), UniProt (https://www.uniprot.org), the Human Protein Atlas (https://www.proteinatlas.org) and GeneCards (https://www.genecards.org), and the identified ANM genes detected in the important literature were summarized (TABLE 1). This list will help identify genes associated with menopause and provide clues for clinical prediction and scientific research. A summary of relevant abbreviations is provided as TABLE 2.

DATA AVAILABILITY

No data was used for the research described in the article.

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CONTRIBUTORS

Che Xu, MD, drafted the manuscript and revised it. Professor Xiangyan Ruan and Professor Alfred O Mueck reviewed the manuscript, contributed to the revision, and Professor Xiangyan Ruan approved the final version of this paper.

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