

REVIEW

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Genes linked with early menopause and the pathogenesis of its associated diseases: a systematic review

Kamila Thasneem^{1†}, Iyshwarya Bhaskar Kalarani^{1†}, Prema Jayaprasad², Vajagathali Mohammed¹ and Ramakrishnan Veerabathiran^{1*}

Abstract

Background: Menopause is a biological process when a woman's reproductive capability is no longer functional. A naturally or artificially caused premenopausal is known as early menopause occurs between the ages 40–45, which substantially impacts fertility and disease influenced by genetic plus environmental factors and their interactions. Women in early menopause are at greater risk of cardiovascular disease, general mortality, neurological disorders, osteoporosis, mental illness, and other problems.

Main body: A PubMed search of the electronic literature database yielded articles on early menopause and disease etiology. Several unique genes were identified, such as *ESR1*, *ESR2*, *CYP11B1*, *BRSK1*, *HK3*, and *TMEM150B* are associated with early menopause, and research focused on case-control, cohort, and cross-sectional studies are finding novel predisposition loci for early menopause.

Conclusion: The current study's focus is to understand better the genetic aspects of early menopause. This knowledge will help researchers enhance EM etiology and identify biomarkers that may detect early development of the disease, allowing women at risk to begin family planning earlier.

Keywords: Early menopause, Genetics, Risk factors, Pathogenesis, Associated diseases

Background

Menopause is the permanent stop of ovulation and menstruation caused by ovarian failure, which occurs in women by the age of 51, but early menopause (MS) can occur in women as early as 40 [1]. Ovulation disorders cause early pathological depletion of the ovarian follicle, resulting in early menopause [2]. Ovulation before the age of 40 at the projected menopausal age began to focus on hereditary variables, resulting in primary ovarian failure (POI) or premature menopause [3]. As a result

of primary ovarian failure (POF), women suffer amenorrhea for 4 to 6 months, an increase in the serum level of the follicle-stimulating hormone (FSH) to more than 40 mIU/l and hypoestrogenism (low estrogen levels) [4]. In addition, POF is linked to an increased risk of osteoporosis, osteoarthritis, and heart disease due to its hypoestrogenism. These symptoms are comparable to natural menopause; however, they are associated with earlier fertility loss. Follicle loss, the inability of left-overfollicles to act on ovulatory indicators, and diminished ovarian reserve upon delivery all contribute to fertility loss [5, 6].

Infections, metabolic disorders, immunological disorders, and iatrogenic factors such as radiation treatment, chemotherapy, and ovarian damage may contribute to POF [7]. Smoking, excessive drinking, oral contraceptives, caffeine, depression, and anthropometry are

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all factors that lead to early menopause [8]. In some instances, the POF phenotype is associated with a particular condition, such as Turner’s syndrome or Blepharophimosis–ptosis–epicanthus inversus syndrome (BPES) type 1. Menopausal age heritability estimates vary from 44 to 66% for mother-daughter pairs. According to genome-wide association studies, the age at which women enter menopause is strongly linked to various genetic loci [9]. According to research on the genetics of POF patients, gene polymorphism, single-gene mutations, and many chromosomal abnormalities from a variety of biochemical pathways have been connected to the development of POF [10]. The World Health Organization has established a global strategy and action plan on aging and health to ensure that people live better lives and longer. According to demographics, menopause affects 25 million women worldwide each year [11]. The POI in women under 40 is estimated at 1%, while about 5% of women ages 40 to 45 have MS. Among Caucasian women (1.1%), African American women (1.4%), Hispanic women (0.5%), and Japanese women (0.1%) each had POIs (Fig. 1) [12].

Mechanism of early menopause

Premature menopausal women have many characteristics from ordinary postmenopausal women, but they also differ widely. The pituitary gland produces the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and influences the synthesis of testosterone and progesterone in the ovaries throughout normal menopause. Estradiol and progesterone levels decrease due

to depletion of the ovarian reserve, while FSH and LH levels increase [13]. In early menopause, gonadotropins and sex steroids can be the same as in postmenopausal women, although gonadotropin levels can also indicate follicular and ovulation. Prematurely menopausal women may have a variety of menstrual cycles, some of which are short, some of which are lengthy, and some of which are normal. The ovulatory cycle is not always present in the anovulatory cycle. Estradiol levels may be low, normal, or high, while FSH levels may fluctuate intermittently [14]. After menopause, FSH and luteinizing hormone levels rise to over 30 mIU/ml; this shows a pulsating synthesis of the hormones, and the level of estradiol and estrone in the blood are also significantly reduced [15]. Ovulatory cycles are uncommon, while anovulatory cycles are standard; the cycles may be shorter or longer due to a reduced follicular phase. Depending on the stage of the follicular phase, the amount of estradiol might range from high to normal [15]. Due to the hypothalamus’ aging, the gonadotropin-releasing hormone (GnRH) and the luteinizing hormone (LH) released from the pituitary are disturbed. In addition, the changes in the menstrual cycle increase the follicle-stimulating hormone (FSH), as shown in Fig. 2 [16].

Methods

Search strategy and extraction of literature

Researchers used the following approaches to identify potential genes connected to early menopause. To begin, researchers used the key terms “early menopause” and “natural menopause” to search the PubMed database and

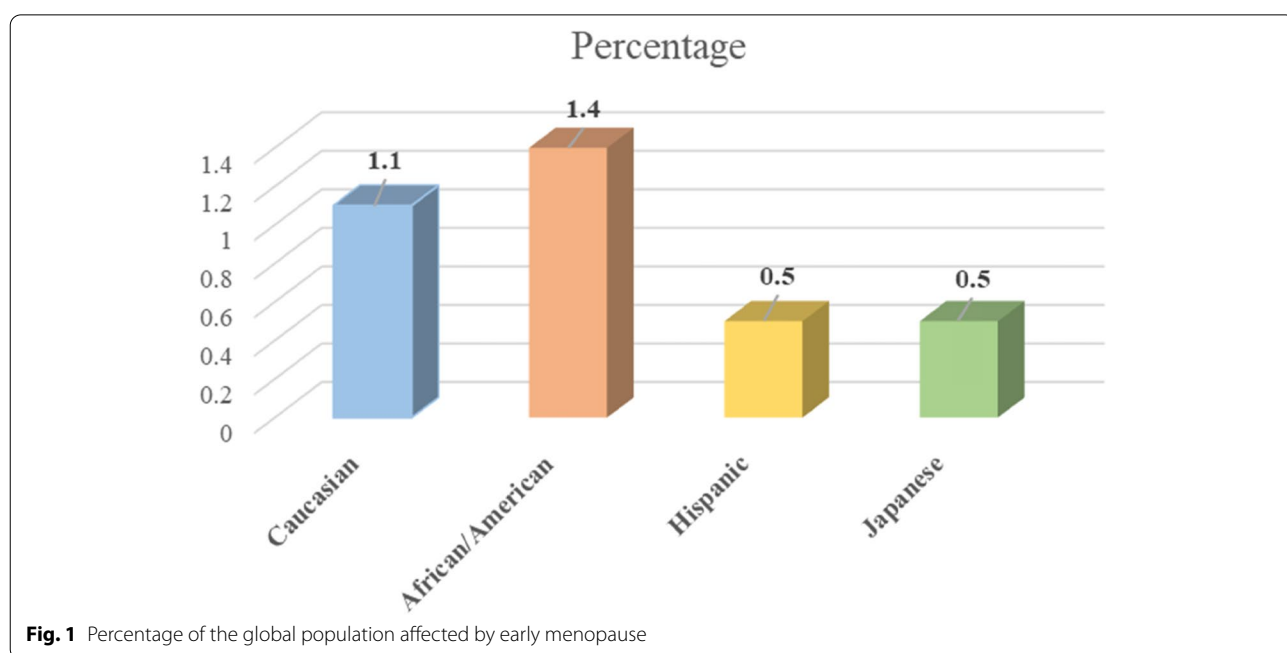
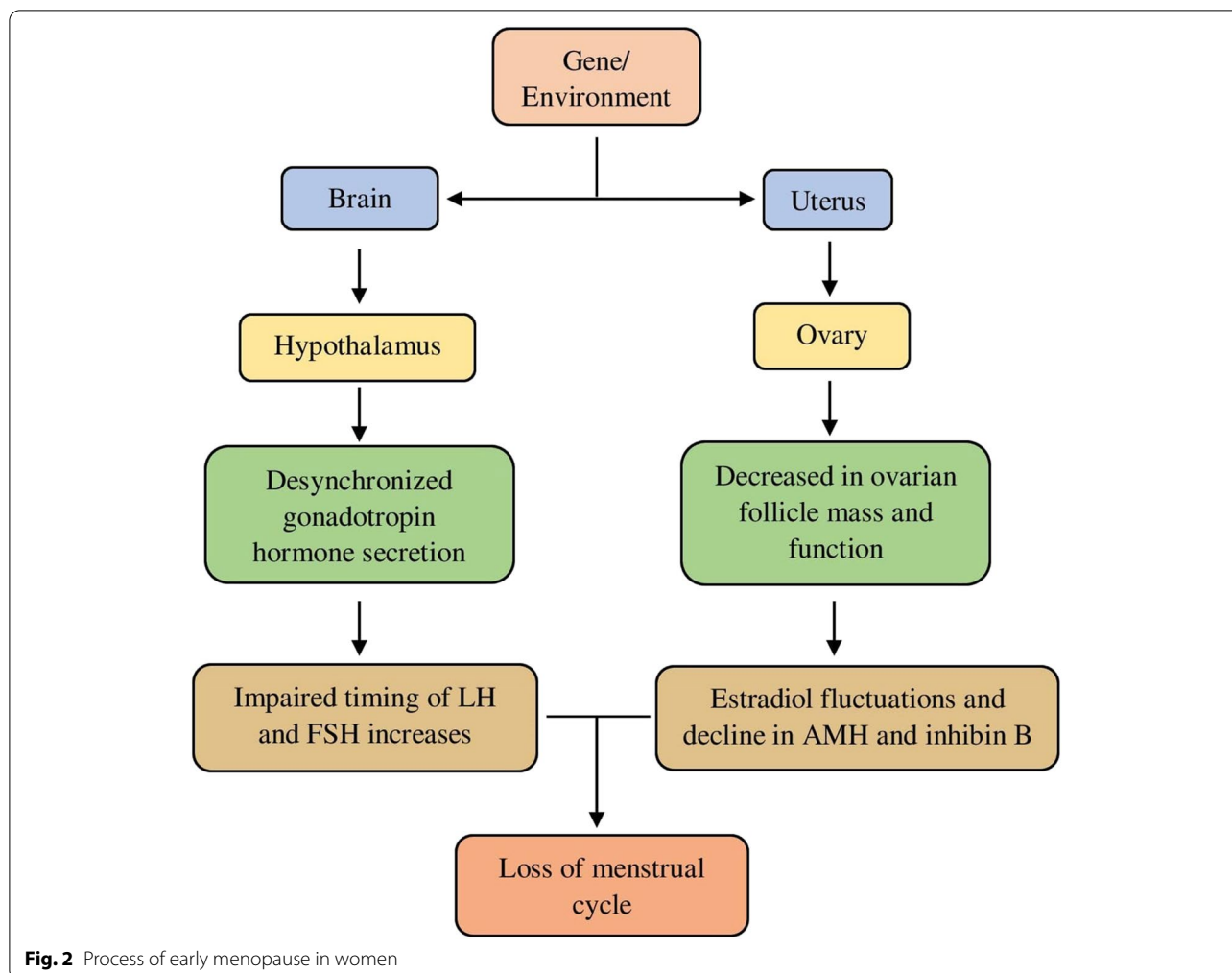


Fig. 1 Percentage of the global population affected by early menopause



Google Scholar from 2000 to 2020 for genetic studies of early menopause. People of various nationalities took part in the study. The study’s reference lists were then analyzed to determine if further research may be helpful. Only single nucleotide polymorphisms (SNPs) or genes that occurred in many studies were extracted and summarised in this study. Finally, based on the source of our selection criteria, the research articles were examined for further procedures. The study includes the following components: (1) a case-control, cohort, systematic review, and meta-analysis study design for assessing risk links between genetic polymorphism and early menopause; (2) data on subject size, allelic and genotypic scattering; and (3) investigations on case reports and up-to-date assessment reports. There are no articles in this review that are not written in English. The papers were separated into two categories. The first collection of publications focused on early menopause situations, whereas the second group focused on connection genes.

Main text

Genetics of early menopause

Early menopause and premature ovarian failure are linked to several genes, including estrogen receptor 1 gene (*ESR1*), estrogen receptor 2 gene (*ESR2*), cytochrome P450 1B1 gene (*CYP1B1*), BR serine/threonine kinase 1 gene (*BRSK1*), hexokinase 3 gene (*HK3*), and transmembrane protein 150B gene (*TMEM150B*) in Table 1 [19]. In terms of early menopause’s molecular etiology, this is the most common approach, based on informed predictions concerning pathways involved, such as the estrogen pathway with molecular abnormalities linked to hereditary illnesses like POI. However, this approach cannot find connective genes for early menopause due to a lack of extensive pedigrees. The crucial function of estrogens in female reproduction and specific genes involved in their synthesis, mechanism of action, and degradation have been studied and postulated as early menopause prediction variables.

Table 1 Candidate genes associated with early menopause

Gene Symbol	Gene name	Location	Exon	Amino acid	Functions	SNP	References
ESR1	Estrogen receptor 1	6q25.1	23	595	Nuclear hormone receptors are involved in regulating eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues.	PvuII (-397 T/C,rs2234693) XbaI (-351 A/G,rs9340799)	[17]
ESR2	Estrogen receptor 2	14q23.2	17	530	Nuclear hormone receptor binds estrogens with an affinity similar to that of ESR1/ER-alpha and activates the expression of reporter genes containing estrogen response elements (ERE) in an estrogen-dependent manner.	RsaI (G1082A/rs4986938) AluI (A+1730G/rs1256049)	[18]
CYP11B1	Cytochrome P450 11B1	2q21-22	3	543	Act as a major enzyme for all-trans retinoic acid biosynthesis in extrahepatic tissues. Catalyzes two successive oxidative transformations of all-trans-retinol to all-trans-retinal and then to the active form all-trans retinoic acid	(Arg48Gly, Ala119Ser, Leu432Val, Asn453Ser/rs1056836)	[19]
BRSK1	BR serine/threonine kinase 1	19	21	778	It plays a vital role in the polarization of neurons and centrosome duplication.	rs1172822, rs12611091	[20]
HK3	Hexokinase3	5	22	923	Catalyzes the phosphorylation of hexoses, such as D-glucose and D-fructose, to hexose 6-phosphate	rs2278493, rs691141	[21]
TMEM150B	Transmembrane protein 150B	19	12	233	Plays a role in extracellular matrix engulfment or growth factor receptor recycling, both of which can modulate cell survival	rs7246479, rs2384687, rs11668344, rs897798	[22]

Estrogen receptor 1 (ESR1) gene

The *ESR1* gene controls cyclic gonadotropin release in the hypothalamus-hypophysis-ovarian axis (HHOA) on chromosome 6 (6q25.1). It promotes the expression of the follicle-stimulating hormone (FSH) receptor and stimulates cell proliferation. A potential gene for *ESR1* might be necessary for sexual development and reproduction. *ESR1* gene with two noticeable SNPs of PvuII (397T/C, rs2234693) and XbaI (351 A/G, rs9340799) have been linked to reproductive patterns in women [17]. There are two essential mechanisms implicated in early menopause: sex steroid hormone (SSH) metabolism and biosynthesis (Fig. 3). Several studies have linked increased reproductive function to SSH, particularly estrogen. Since its interaction determines a hormone's effect with its receptor, variation in *ESR1* may induce differences in susceptibility to premature ovarian failure

or reduced ovarian function [23]. The age of menopause affects the level of initial follicular reserve and the rate of follicular depletion, and genetic variations in genes for sex hormone receptors can affect the risk of FOP. Estrogen regulates folliculogenesis by stimulating gonadotropin synthesis through the ER in the hypothalamic-pituitary-ovarian axis [24].

Estrogen receptor 2 (ESR2) gene

Estrogen receptor 2 genes are located on chromosome 14q23.2 and the SNPs 'rs4986938/G1082A (RsaI)' and 'rs1256049/A+1730G (AluI)' responds to estrogens. The estrogen receptor beta (ER-β), expressed in the ovary to stimulate follicular development, is encoded by *ESR-2*. Estrogen increases the expression of the FSH receptor by stimulating the proliferation of granulosa cells (GCs) [18]. The hypothalamus-pituitary-gonadal

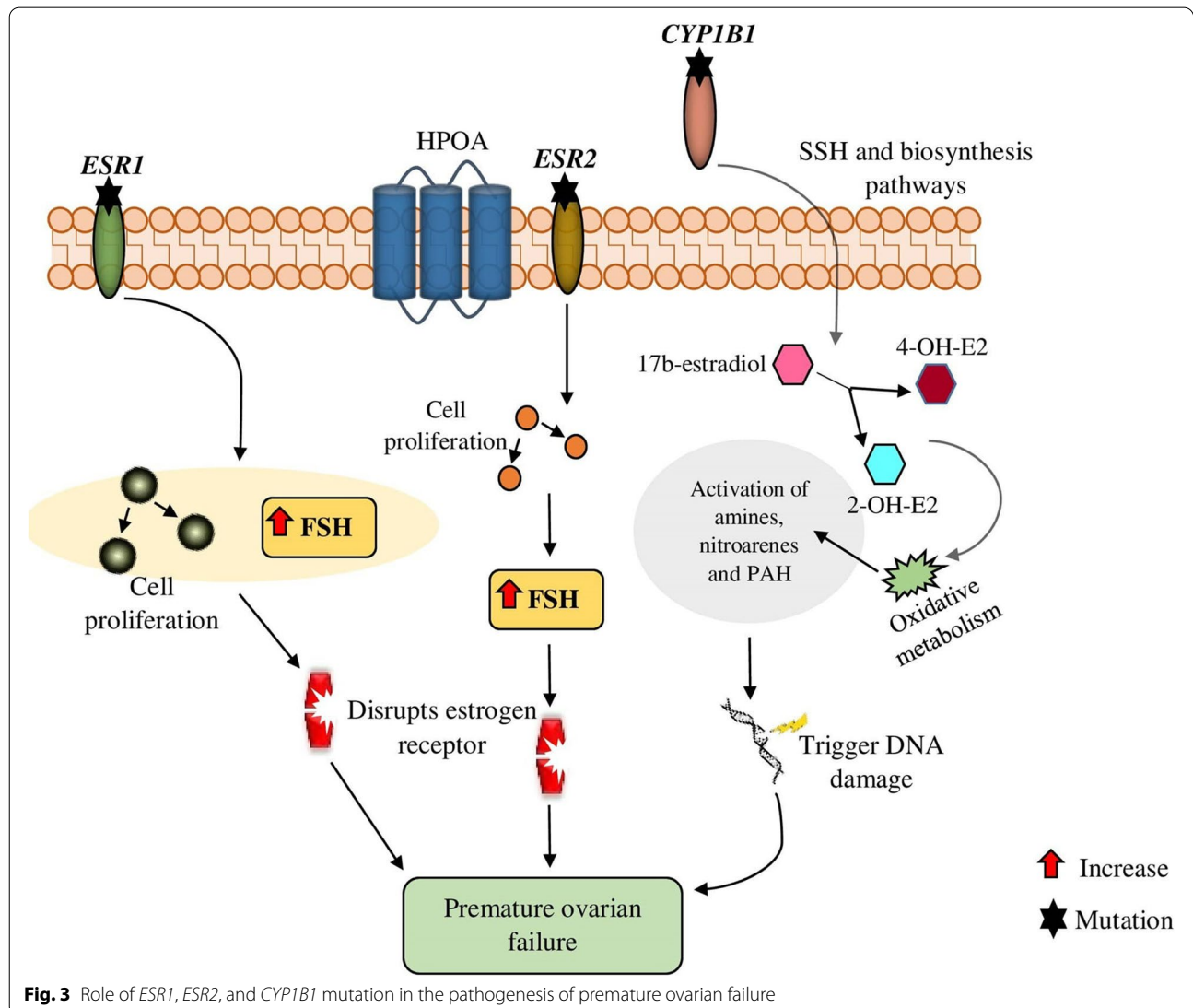


Fig. 3 Role of *ESR1*, *ESR2*, and *CYP1B1* mutation in the pathogenesis of premature ovarian failure

axis, a major concept in this association, controls, and responds to estrogen. Although estrogen-responsive pathways extend well beyond the hypothalamus to include the neocortex, hippocampus, and brainstem, the hypothalamus is the beginning site for neuroendocrine activity.

Furthermore, as endocrine and neuronal senescence overlap in time and are mechanistically linked in complex feedback loops, estradiol plays an essential role in the neurobiology of aging [25]. The change in the hormonal pattern is related to the SNPs in the genes. A specific gene maintains the development and promotion of the follicle. When a gene goes through a variation, it affects its function. The *ESR2* gene helps the follicle develop and support its activity, and their transcription factors are discovered in macrophages, fat cells, vascular smooth muscles, and vascular endothelial cells, among others [26]. *ESR2* is connected with early menopause that influences the estrogen signaling pathway (Fig. 3). Overexpression of *ESR2* in the ovary, granulosa cells, and endometrium implies that *ESR2* is crucial in estrogen metabolism. Natural menopause age has a significant role in assessing ovarian senescence; therefore, *ESR2* is believed to be one of the possible genes for menopause induction [27].

Cytochrome P450 1B1 (*CYP1B1*) gene

Cytochrome P450 1B1 (*CYP1B1*) is an enzyme that catalyzes 4-hydroxylation, which plays a significant role in menopause. This gene is found on chromosome 2p22.2. The amount of estrogen in the blood may be related to the onset of menarche and menopause. Hydroxylation is essential in eliminating estrogen, producing estrogen catechol through sex steroid hormone (SSH) and biosynthesis pathways [28]. The oxidative metabolism is mediated by the phase I enzyme *CYP1B1*, which converts 17 β -estradiol to 4-hydroxyestradiol (4-OH-E2) and 2-hydroxyestradiol (2-OH-E2) catechol estrogens that activate estrogen receptors. Polymorphisms cause changes in the catalytic properties of estradiol (E2) metabolic enzymes in the *CYP1B1* gene, leading to an increase or decrease in enzyme activity [29]. Nitroarenes, polycyclic aromatic hydrocarbons (PAH), and arylamines are activated by the human *CYP1B1* enzyme, resulting in reactive metabolites that trigger DNA damage [30]. Researchers have seen many SNPs in this gene; (Arg48Gly, Ala119Ser, Leu432Val, and Asn453Ser) are mutations that have been identified mainly in the change in estrogen function (Fig. 3). For example, the SNP mutation rs1056836 had menopause 0.9 years earlier, a shorter reproductive year of life than others [19].

BR serine/threonine kinase 1 (*BRSK1*) gene

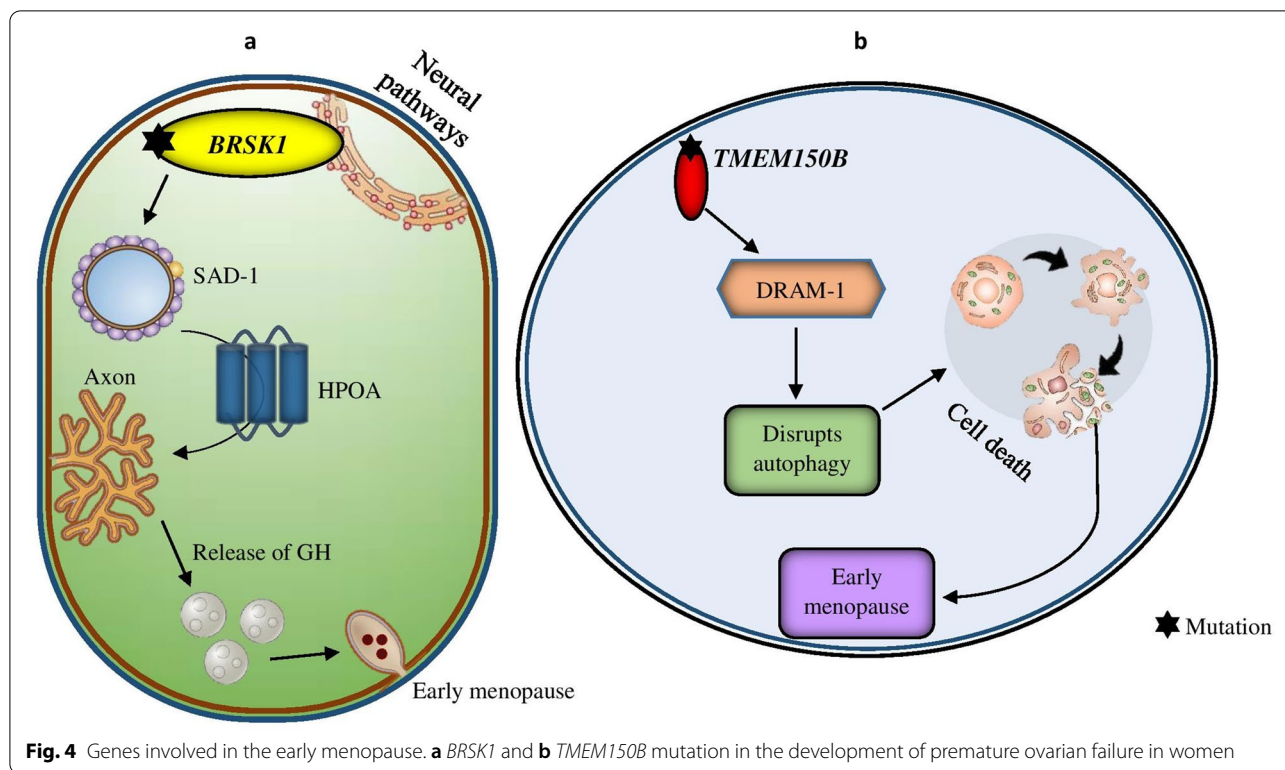
The *BRSK1* gene (also known as SAD kinase), which codes for an AMP-activated protein kinase (AMPK)-related kinase, contains rs12611091 in its intron region, located on chromosome 19 (19q13.42) and is primarily produced by the human brain. It controls the release of neurotransmitters at mature synapses with presynaptic cytomatrix and is involved in neuronal polarization, replication, regulating neurotransmitters, and expressing synapses. At the same time, the mammalian ovaries express it to a moderate extent; it is mutated or overexpressed, which leads to transport vesicle release (SAD-1 protein) causes axonal ends, which may affect the release of gonadotropin-hormone from the hypothalamus. Thus, a neural pathway is involved in this whole mechanism [20]. As a result, the mutation in *BRSK1* affects the release of the gonadotropin-releasing hormone from the hypothalamic-pituitary-ovarian axis (HPOA), resulting in the evidence that *BRSK1* is associated with early menopause (Fig. 4a) [6].

Hexokinase 3 (*HK3*) gene

Hexokinase 3 is a member of the hexokinase family found in chromosome 5q35.2, and the primary function is glycolysis. It actively takes part in the carbohydrate pathway to convert glucose into glucose-phosphate, which is observed in the uterus, placenta, lungs, and adipose tissue. Hexokinase 3 phosphorylates glucose and converts it into 'glucose-6-phosphate', a primary stage in all glucose metabolic pathways [31]. Previous studies on *HK3* showed that the observed association was not the case. The *HK3* gene variations must be thoroughly sequenced and functionally studied to understand the molecular process [32]. When there is a threat of follicular thyroid bulges, *HK3* is over-expressed and communicates in the uterus. According to Gene Atlas, the uterus, the placenta, lungs, and adipose tissue all contain the *HK3* gene [33]. There are two SNPs (rs2278493 and rs691141) associated with early menopause [21]. An examination of the literature for *HK3* revealed that no information could find from the empirical evidence regarding the association. Therefore, substantial sequence analysis and signaling pathways of the *HK3* gene variations are required to explain the exact underlying mechanisms.

Transmembrane protein 150B (*TMEM150B*) gene

TMEM150B is located in chromosome 19q13.42, encodes the DRAM-related/associated member 3 (DRAM-3) proteins, which increases cell survival by triggering autophagy when cells are in a stressful environment. Self-degradation within the cell, known as autophagy, is highly conserved throughout species. When autophagy is



disrupted, it contributes to various biological processes such as stress adaptation, cell death, and neurodegenerative diseases [34, 35]. According to Gawriluk et al., ovarian function similarly depends on autophagy homeostasis [36]. Thus, *TMEM150B* might be a potential gene for POI because of its role in autophagy (Fig. 4b). There are four SNPs in *TMEM150B* that have been highly linked to early menopause in GWAS studies: rs7246478, rs2384687, rs11668344, and the rs897798 [22].

Pathogenesis of early menopause

A series of events determine the proper development of the ovaries; various factors can cause ovarian dysfunction. According to their pathophysiology, these defects can be divided into accelerated follicle depletion and primary hypogonadism without follicle depletion. The inheritance of menopause is probably between 30 and 85%. It is believed that 15 to 30% of POI cases are familial [37]. A greater degree of heritability was found between 40 and 45 early menopause family history women. According to the newest research, two X chromosomes are required for the proper function of the ovaries. The short arm of the X chromosome is often connected with ovarian failure if there is a terminal loss in the proximal region. In addition, the X chromosomes are terminal and induce primary amenorrhea [38]. People with Turner syndrome, which affects up

to 1.5% of conception, 10% of miscarriages, and 1 in 2500 live births, have a second X chromosome deficiency. The POI is a widespread problem [39] linked to Fragile X Syndrome, a dominant X-linked genetic disorder. Women with long repeats of the CGG trinucleotide sequence are mutated (55,199 repeats) or have the entire disease (> 200 repeats). Premenopausal women have a 23% chance of developing POI and reaching menopause 5 years earlier than average. It has been shown that POIs have frequencies of 3% to 15% [40]. The transforming growth factor-beta (TGFβ) superfamily comprises the bone morphogenetic protein 15, located on the X chromosome's short arm. It is believed that POI is caused by mutations in this gene that play critical roles in fertility and egg quality [41]. Autoimmunity was first postulated as a possible etiology of POI when it was observed that women with adrenal failure also had an ovarian failure. The symptoms of polyglandular autoimmune failure are associated with autoantibody against multiple endocrine and organ systems. According to some studies, POI and myasthenia gravis are linked [42]. Primary hypogonadism without follicle deficiency is mainly caused by endogenous mediators of gonadotropin receptor activation and steroidogenic enzyme defects that limit estradiol production. These modulators can be caused in the ovaries, either directly or through a decreased cellular

response to gonadotropins. However, ovarian failure has only been associated with polymorphisms in the alpha subunit of inhibiting [43].

Disease-associated with early menopause

There are several long-term health consequences of going through early menopause, including increased risk of cardiovascular disease, depression, neurological problems, sexual dysfunction, and osteoporosis.

Cardiovascular disease (CVD)

Cardiovascular disease has been connected to early menopause; women with untreated POI had a lower life expectancy due to cardiovascular illness and stroke. People with POI have already shown a strong link between endothelial dysfunction. Lower vascular endothelial function was observed in EM, an early indicator of atherosclerosis. Through catecholamine modulation, estrogen has a favorable effect on cholesterol metabolism, reducing atherosclerotic plaques and decreasing coronary constriction [44]. Menopause before the age of 40–45 years had double the risk of severe angina 1 year after a myocardial infarction than normal menopause, indicating an increased risk of CVD and death [45, 46]. After a successful estrogen therapy, women under the age of 40–45 years were suffering from bilateral oophorectomy, coronary heart diseases, and many other cardiovascular problems after surgery due to low-level estrogen [47, 48]. It is clearly stated that with a reduced estrogen level in the body, metabolic activities have been changed, increasing abdominal adiposity, abdominal circumference, and cholesterol. If estrogen levels are high in early menopausal

women are more prone to develop cardiovascular disease [49].

Mental disease

When people are diagnosed with EM, they often experience a traumatic event that leads to many psychiatric issues. Feeling exceedingly timid in front of society, low self-esteem, anxiety, and profound despair are some of the primary difficulties [49]. Although, usually, anxiety and depression start when a person is in their 40s, many studies understand that POI can cause many psychological issues in women. There is a link between mental anguish and depression, and they will constantly be depressed and have less social support throughout their lives. People who suffer from anxiety or depression have been engaged in long-term harmful behaviors [50]. A woman’s cognitive performance is negatively impacted by early menopause and can have a severe implication in life. While it is natural for anxiety to become focused or constantly remember difficulties, it tends to lose control over eyesight, memory, and processing speed. Depression can lead to insomnia, leading to problems with concentration and memory (Fig. 5) [51].

Neurological disorder

Women in the early stages of menopause are more likely to experience cognitive issues and dementia. Cognitive functioning is also reduced in those diagnosed with this illness and treated for 5–10 years with estrogen treatment. It positively impacts neuropathology when a person takes estrogen treatment for early menopausal symptoms. However, when the dose increases in older women and the therapy is continued, the patient

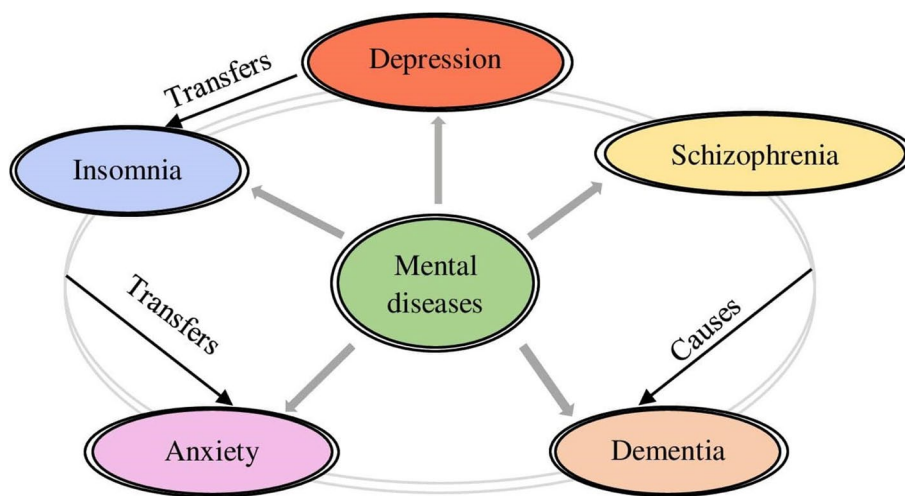


Fig. 5 Mental diseases involved in early menopause

is more likely to develop additional issues such as cognitive impairment and dementia. Cognitive impairment is currently being dealt with or treated by premature menopause and oophorectomy. Many scientists have conducted surveys and investigated the link between neurological issues and early menopause [37]. Estrogen therapy showed neurology in animal and rat models; it helped neurological development. After looking at the neuroimages, it was confirmed that estrogen treatment would upgrade the brain actions of memory processing in human beings [52].

Sexual dysfunction

Early menopause leads to ovarian problems, such as reduced estrogen due to hormonal loss, which causes dryness, loss of suppleness, pain, sexual pleasure, sexual dysfunction, insomnia, and mood swings [53]. Ovarian dysfunction is the major problem of early menopause, and it is purely connected with sex hormones like estrogens and androgens. Estrogen is essential for vaginal functioning and stimulation in women's reproductive organs. In normal ovarian dysfunction, androgen deficiency is seen, decreasing the quality of a person's life. Women with EM have always shown a positive connection with infertility [46].

Osteoporosis

Women who experience premature menopause have a higher risk of poor bone density, fractures, and osteoporosis. The pathogenesis of osteoporosis has been linked to maternal age and estrogen insufficiency due to decreased ovarian function. Previous research has found a link between estrogen insufficiency, menopause, and an increased risk of fractures in women [54]. According to numerous studies, bone loss accelerates after menopause. Oophorectomy before the age of 45 is a well-known osteoporosis risk factor. In women who have had bilateral oophorectomy, osteoporotic fracture risk may be more significant than those who have had intact ovaries [55]. When estrogen levels in the body decrease, it affects joints, muscles, skin, bone, wrinkles, and speeds up the aging process. People who use gonadotropin medicines to boost estrogen levels always have joint and muscle pain. In addition, estrogen can remodel bones, and when this occurs, bone formation is disrupted, resulting in bone loss. It is confirmed that women with EM will have reduced their bone density mass [56].

Conclusion

Early menopause is when a woman stops her menstrual cycle, typically occurring in the late 40s to early 50s; the reason can be genetic. The incidence rate of 5-10 % in the world at 40–45 years of age in women, if the

release of gonadotropins in the brain's hypothalamus at that time was changed, the sexual hormone deficiency began to initiate and lead to reproductive dysfunction. Over recent years, the genetic intention has been helped identify genes and their disease associated with early menopause and its metabolic pathways involved in primary ovarian failure, so in most cases, the pathogenic mechanism is still unknown. It is also claimed that women with premature or early menopause have developed diseases such as mental illness, cardiovascular disease, neurological disorders, reproductive disorders, and osteoporosis. In the future, these study mechanisms will provide early detection and identification of specific genomic level inadequacy that would be associated with EM can provide a better prospect for the early interruption and provide a focus on potential targets for therapeutic approach.

Abbreviations

EM: Early menopause; ESR1: Estrogen receptor 1 gene; ESR2: Estrogen receptor 2 gene; CYP11B1: Cytochrome P450 11B1 gene; BRSK1: BR serine/threonine kinase 1 gene; HK3: Hexokinase3 gene; TMEM150B: Transmembrane protein 150b gene; POI: Primary ovarian insufficiency; POF: Polycystic ovarian failure; FSH: Follicle stimulating hormone; FSHR: Follicle stimulating hormone receptor; CGH: Comparative genome hybridization; SNP: Single nucleotide polymorphism; LH: Luteinizing hormone; CVD: Cardiovascular disease.

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Code availability

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Authors' contributions

KT and IB have written the contents of this manuscript. VM edited the figures and tables. PJ revised the final version of the manuscript. RV designed the study and approved the manuscript for publication. All authors read and approved the final manuscript.

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Competing interests

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