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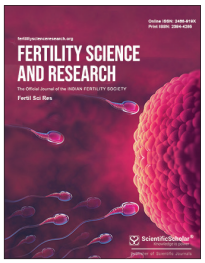

Review Article

Genetics of Premature Ovarian Insufficiency

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ABSTRACT

Premature ovarian insufficiency (POI) due to early depletion of ovarian follicles leads to primary amenorrhea or premature menopause. The causes can be genetic or secondary to infection, metabolic disease, autoimmune disorders, radiation, chemotherapy or physical damage to the ovary. Here in this paper we discuss the genetic causes of POI. The causes could be chromosomal disorders such as Turner syndrome (45, X) or structural X chromosomal abnormalities such as deletions/duplications/ring chromosome/X:autosome translocations. The causes could be single gene disorders with various inheritance patterns being possible such as autosomal dominant, autosomal recessive, X-linked dominant or X linked recessive We describe a panel of 157 genes which can be analysed on next generation sequencing panel and FMR1 gene which can be analysed on triple primer polymerase chain reaction method.

Keywords: Ovarian failure, Genetics, whole exome sequencing

GENETICS OF PREMATURE OVARIAN INSUFFICIENCY

Menopause signifies the end of the reproductive lifespan of a woman caused by an exhaustion of ovarian reserve. The average age is around 50–52 years. Early depletion of ovarian follicles leads to premature menopause. This phenomenon, also called premature ovarian failure or premature ovarian insufficiency (POI), is defined by the onset of menopause before 40 years, characterised by more than four months of amenorrhea, follicle-stimulating hormone (FSH) levels of more than 40 mIU/L and low estrogen levels.[1] It affects 1% of all women and 0.1% of women below 30 years of age in Western studies.[1] In the Indian National Family Health Survey 2019–2021, the prevalence of premature menopause (less than 40 years) was 2.2%, and that of early menopause (between 40 and 44 years) was 16.2%.[2] As a result, there is infertility, risk of osteoporosis and risk of cardiovascular disease. The causes can be genetic (50–90% cases) or secondary to infection, metabolic disease, autoimmune disorders, radiation, chemotherapy or physical damage to the ovary.[1] Here, in this paper, we discuss the genetic causes of POI.

Chromosomal causes: X chromosome abnormalities account for 12% of POI cases. These abnormalities include monosomy, trisomy, deletions, duplications and X-autosome translocations.[3] Turner syndrome (TS) occurs at an incidence of one in 2500 live births. TS can be caused by monosomy X (50% cases), partial X chromosome deletions (15% cases), isochromosome Xq (15% cases) (duplication of the q arm of X chromosome with deletion of p arm), ring chromosome (5% cases) and mosaicism (20% cases). The retained X chromosome

is maternally derived in two-thirds of cases. In non-mosaic TS, the oocytes degenerate by birth. The TS ovaries show immature follicles manifest by the arrest of oogenesis in the diplotene stage leading to foetal follicular atresia. In one study, the mechanism has been shown to accelerate apoptosis or programmed cell death.[4] In another study, elevated levels of reactive oxygen species producing oxidative stress were thought to be the mechanism.[5] In mosaic ovaries, however, this may not be the case, and spontaneous fertility and, in some cases, ovarian cryopreservation leading to later fertility can be possible. The other stigmata of TS are short stature, webbed neck, multiple skin nevi, cardiac anomalies (coarctation of aorta), susceptibility to hypothyroidism and hypertension. Cytogenetic studies have identified the critical regions on the X chromosome which can correlate with POI. Deletions affecting Xq21.3–q27 or X-autosome translocations in the region of Xq13.3–q21.1 have been associated with POI.[6,7] Deletion of the p arm of the X chromosome has also been shown to be associated with POI.[8] Y chromosome mosaicism can predispose to gonadoblastoma and has been found to occur in 18% of cases of TS in one study.[9] Genes mapped for POI on X chromosome after the discovery of breakpoints in X: autosome translocations include COL4A6 (collagen alpha 6), DACH2 (Dachschund transcription factor 2), DIAPH2 (diaphanous related formin 2), NXF5 (nuclear RNA export factor 5), PGRMC1 (progesterone receptor membrane component 1), POF1B (actin-binding protein), and XPNPEP2 (prolyl aminopeptidase) (Franca and Mendonca). Trisomy X usually does not lead to any significant clinical abnormalities, but occasionally has been described to lead to POI.[10]

Single gene causes: The Online Mendelian Inheritance in Man (OMIM) (www.omim.org) identifies and classifies 22 chromosomal loci for POI.

POI type 1 locus includes the FMR1 gene. This encodes the protein Fragile X mental retardation protein (FMRP). The 5'untranslated region of the gene contains the CGG repeat region. Normal individuals have up to 54 repeats. Premutation carrier females have 55–199 repeats. Fragile X-affected males and females have more than 200 CGG repeats (full mutation), which leads to loss of FMR1 protein production. Affected males or females have physical dysmorphism and mental retardation. Premutation females can transmit full mutation (expansion of CGG repeats) to their progeny. A significant proportion of FMR1 premutation carriers have POI. There are two hypotheses: first, the FMR1 protein, which is RNA-binding protein having a suppressive effect on the translation of a subset of mRNAs, may be overexpressed, leading to oocyte development abnormality, and second, by the toxic accumulation of FMR1 mRNA may lead to follicle atresia. FMR1 premutation accounts for 6% of POI cases overall.[11] In some studies from India, it was found to be an uncommon cause in Indian females, especially in those without a family history of X-linked mental retardation.[12,13] In yet another Indian study, 4% of POI cases were found to bear premutation allele.[14] Genetic association studies have also shown the association of POI with a length of the Cytosine, Adenine, and Guanine (CAG) repeat region in exon 1 of the AR (androgen receptor) gene. Chatterjee *et al.* (2009) showed the biallelic mean CAG ranged from 11 to 30 in control women compared to 16 to 30 in POI patients.[15] However, Panda *et al.* did not find any association with CAG repeat length rather an association was found with the GGN repeat in AR gene.[16] However, mutations in the AR gene are an accepted cause of androgen insensitivity syndrome (complete or partial) in 46 XY males and AR gene CAG repeat length analysis is not presently considered for diagnosis of POI in females, neither is included as one of POI loci in the OMIM database.

POI type 2A locus includes the DIAPH2 gene (chromosome locus Xq21.33) which encodes diaphanous related formin 2. This gene was identified in a family with mother and daughter having X;12 translocation which disrupted this gene. The daughter had secondary amenorrhea at 17 years, and the mother had premature menopause at 32 years. No mechanism is known. The inheritance is X-linked dominant (XLD).[17] **POI type 2B** locus includes the POF1B gene (chromosome locus Xq21.1) which was mapped by Bione *et al*. in a patient with X autosome translocation and a breakpoint in distal 4 kilobase of third intron of the gene.[18] The POF1B gene plays a role in the organisation of epithelial monolayers by regulating the actin cytoskeleton. This gene escapes X inactivation and is critical for early ovary development. Later, in another consanguineous Lebanese family having five affected sisters, the homozygous mutation p.R329Q was identified, which affects the protein kinase C domain, diminishing the function of POF1B to bind nonmuscle actin filaments. This suggested a role in germ cell division.[19] The inheritance of this disease was X-linked recessive (XLR). **POI type 3** locus includes the FOXL2 gene (chromosome locus 3q22), which encodes fork head box protein L2, a transcriptional regulator. FOXL2 is a critical factor essential for ovary maintenance and differentiation and prevents transdifferentiation of ovary to testis through repression of the Sertoli cell promoting gene (SOX9). Mutations in the FOXL2 gene are known to cause BPES syndrome (blepharophimosis [small palpebral fissures], ptosis [drooping eyelids], epicanthus inversus [epicanthic skin fold running inward and upward from lower lid]). Type I BPES includes eyelid anomalies and ovarian failure, while type II BPES only includes eyelid anomalies. Genotype phenotype correlation showed that before or within the fork head domain of the protein led to BPES type I, and truncating mutations distal to the fork head domain led to BPES type I or BPES type

II (mostly).[20] Harris *et al.* found a heterozygous 30 basepair deletion in the polyalanine tract (minus 10 alanine repeats) in a Slovenian patient with isolated POI (primary amenorrhea at 17 years) and a heterozygous p.Y258N mutation in a patient from New Zealand (menarche at 14 years, menopause at 36 years).[21] Laissue *et al.* found mutation p.G187D in a patient with isolated POI. The inheritance of BPES was autosomal dominant (AD).[22] Chatterjee *et al.* screened 80 Indian cases of POI for variants in the FOXL2 gene and did not find any pathogenic variants.[23]

Mutation in the BMP15 gene (locus Xp11), a transcription factor, causes **POI type 4.** DiPasquale *et al.* identified heterozygous mutation p.Y235C (tyrosine to cysteine) in two sisters with POI (ovarian dysgenesis [ODG] and primary amenorrhea) inherited from normal hemozygous father. In sheep, heterozygous ewes had higher ovulation numbers, whereas homozygous ewes had infertility due to the absence of primary follicles in the ovary. The inheritance in humans is thus XLD (limited to females) and in sheep, its XLR.[24] Dixit *et al.* sequenced the BMP15 gene in 133 women with POI, 60 women with primary amenorrhea, 9 women with secondary amenorrhea and 197 control women. They identified the following variants of uncertain significance p.Arg76His, p.Arg61Glu, p.Asn196Lys, p.Arg206His and the following pathogenic mutation p.Gln211Ter in patients with POI.[25] Heterozygous mutation in NOBOX gene (chromosome locus 7q35) encoding homeobox protein NOBOX leads to **POI type 5**. Both primary amenorrhea and secondary amenorrhea are reported. The p.R355H (arginine to histidine) mutation acted in dominant negative fashion (disrupted binding of normal protein to DNA), whereas the mutation p.R303X (arginine to nonsense mutation) led to haploinsufficiency (50% reduction in transcriptional activity). In a study by Bouilly *et al.*, NOBOX mutations were found in a significant 12 of 213 women with POI (5.6%).[26,27] Heterozygous or homozygous mutations in the FIGLA gene (chromosome locus 2p13) (factor in germline alpha) lead to **POI type 6**. Mutations identified include heterozygous 22 basepair deletion, heterozygous p.140delN (asparagine deletion) and homozygous M1T (initiation codon mutation). Hence, both AD and autosomal recessive (AR) phenotypes are possible. Both primary and secondary amenorrhea are reported.[28–30] Tosh *et al.* reported two heterozygous variants, p.Arg83Cys and Ser141Thr, in theFIGLA gene in two unrelated patients from a cohort of 219 Indian women with POI.[31] Mutation in the NR5A1 (chromosome locus 9q33), which encodes steroidogenic factor 1, a key transcription factor essential for sexual differentiation and formation of steroidogenic tissues, leads to **POI type 7**. Other phenotypes reported with this gene include sex reversal (male to female as well as female to male) and adrenal insufficiency. Heterozygosity for mutation c.666delC was identified in a mother with secondary amenorrhea at 35 years old and her child at 17 years old with 46, XY complete gonadal dysgenesis (phenotype female with primary amenorrhea). This showed variable expressivity for the mutation. Homozygosity for p.D293N (aspartic acid to asparagine) was seen in two sibs, one with 46, XY, complete gonadal dysgenesis, and another with 46, XX, primary amenorrhea. Hence, both AD and AR phenotypes are possible.[32]

Homozygous or compound heterozygous mutations in the STAG3 gene (AR) (locus 7q22) (encoding stromal antigen 3) can lead to **POI type 8** in females and spermatogenic failure type 61 in males. This is an important component of the cohesin complex, which keeps the sister chromatids together after DNA replication during meiosis. Mutations described in females include c.968delC, c.1947_1948dupCT, c.1573+5G>A, c.dup291C and p.Y650X and those described in males include c.dup1762G, c.2394+1G>A, p.R438X and p.L421R. The R321H was described in a 35-year-old female with delayed puberty, elevated gonadotropins and having developed one ovary with some follicles, and her brother with azoospermia.[33–40] Homozygous or compound heterozygous mutations in the HFM1 gene (AR) (locus 1p22.2) (helicase for meiosis 1 protein), which is required for crossover formation and complete synapsis of homologous chromosomes during meiosis, lead to **POI type 9**. It is exclusively expressed in the ovary and testis. Mutations described are loss of function (LOF) type p.I884S, c.1686-1G>C, p.G736S and c.3929_3930delCCinsG. Mutations in the HFM1 gene have recently been described in males with non-obstructive azoospermia.[41] Homozygous mutations in MCM8 gene (minichromosome maintenance) (AR) (locus 20p12.3) lead to primary gonadal failure (**POI type 10** in females and small testes and azoospermia in males). MCM8 knockout mice are sterile. Association with cancer is also known. One patient with Lynch syndrome and fertility problems and two patients with breast cancer were identified with biallelic mutations in the MCM8 gene. MCM8 gene knockout cells have been shown to have DNA damage, microsatellite instability and DNA mismatch repair (MMR) deficiency. Mutations identified for POI include p.P149R, c.1954-1G>A and c.1469_1470insTA.[42–44] Heterozygous loss of function (LOF) mutations in ERCC6 gene (AD) (chromosome locus 10q11.23) have been identified in females with secondary amenorrhea (**POI type 11**). Mutations identified include p.G746D, p.E215X and p.V1056I. Homozygous LOF mutations in the ERCC6 gene have been known to lead to Cockayne syndrome, ultraviolet (UV) sensitive syndrome type 1 and Cerebro-oculo-facio-skeletal syndrome type 1. Risk for lung cancer has also been reported in heterozygous carriers.[45] Homozygous mutations in SYCE1 gene (AR)

(locus 10q26), a component of the synaptonemal complex which mediates homologous chromosome synapsis and crossover formation, have been identified in males with spermatogenic failure type 15 and females with **POI type 12**. Mutations are LOF type such as p.Q205X, c.197-2A>G and c,375-2A>G.[46] Homozygous mutations in MSH5 gene (AR) (locus 6p21.33), a component of DNA MMR mechanism and meiotic recombination process, have been identified in **POI type 13** and azoospermia (spermatogenic failure type 74). Mutations have been LOF type such as p.D487Y in females and c,75dup, c.1857del and p.R322C in males.[47,48] Homozygous mutation in GDF9 (AR), growth differentiation factor 9 (locus 5q31.1) leads to **POI type 14**. Mutations are LOF type c.783delC. GDF9 is essential for ovarian folliculogenesis and is expressed only in the oocyte. Heterozygous tandem duplication in the GDF9 gene promoter region has also been reported in a lady with secondary amenorrhea. Hence, both AD and AR phenotypes are possible.[49,50] Homozygous LOF mutations in FANCM (AR), a DNA-dependent ATPase component of the Fanconi anaemia core complex (locus 14q21.2), lead to **POI type 15** in females and spermatogenic failure type 28 in males. POI type 15 presents as secondary amenorrhea in the third decade of life. The protein is related to the Fanconi anaemia associated genes but does not lead to Fanconi anaemia. However, they show a risk for breast cancer and chemotherapy toxicity and may display chromosomal fragility. Mutations described include p.Q1701X (in female and male) and p.R1931X and c.1946_1958del in males.[51,52] Heterozygous LOF mutations in the BNC1 gene (AD) which encodes basonuclin 1, a transcriptional regulator (locus 15q25.2), were found in females with **POI type 16**. POI 16 affects females in the fourth decade, ovaries are smaller than normal and show a solid echo pattern with no follicle. Mutation described in large families with affected females and unaffected carrier males is c.1065_1069del. Analysis of 82 Chinese women with POI showed heterozygosity for p.L532P in four unrelated women, indicating the possible pathogenic nature of this variant.[53] Homozygous mutations in XRCC2 gene (AR) (locus 7q36.1), a protein involved in the homologous recombination repair pathway of double-stranded DNA, have been identified in females with **POI type 17,** which present as secondary amenorrhea and in males as spermatogenic failure type 50. Mutation in the XRCC2 gene has also been described in cases with Fanconi anaemia. Mutations in the XRCC2 gene have also been found to increase susceptibility to breast cancer.[54] Homozygous LOF mutation c.204_205del in C14orf39 (AR) (locus 14q23.1) has been found in a female with **POI type 18** and her two brothers with spermatogenic failure type 52. The protein localises to central element of the synaptonemal complex and is required for chromosome synapsis during meiotic recombination.[55] Homozygous LOF mutation in HSF2BP (AR) (chromosome locus 21q22.3), a heat shock transcription factor, leads to **POI type 19**. Knockout mice show infertility in males and normal fertility in females. In the three sisters from an Arab family with secondary amenorrhea in the third decade, the p.S167L mutation was identified. Male and female mice homozygous for p.S167L were able to reproduce, but females showed reduced litter size.[56] Homozygous mutation in MSH4 gene (AR) (mutS protein homolog 4) (locus 1p13.1), a protein involved in meiotic recombination and proper segregation of chromosomes at meiosis, leads to **POI type 20** in females and spermatogenic failure type 2 in males. Mutations identified are c.2355+1G>A (females), p.Q518X, p.S754L, c.805_812del, p.W650X, c,2179del, c.2220_2223del and c.S733X (males).[48,57,58] Heterozygous LOF mutation in the TP63 gene (AD) (locus 3q28) leads to **POI type 21** in females. Mutations occur at the distal end of the protein. Mutations identified include p.R594X, p.RW598X (in last exon 14), mutations p.R97P and p.R647C (last exon) which disrupt TP63 dimerisation Functional analysis suggested that the variants in the C terminal transactivation inhibitory domain disrupts the inactive TP63 conformation, generating constitutively active Tp63 that increases expression of target genes and induces apoptosis leading to exhaustion of oocytes leading to POI. Mutations in the TP63 gene have also been described to lead to other phenotypes: ADULT syndrome, ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome, Hay-Wells syndrome, limb-mammary syndrome, Rapp-Hodgkin syndrome and split hand-foot malformation.[59,60] Homozygous mutations in KASH5 gene (CCDC155 gene) (AR) (chromosome locus 19q33.33) have been identified in females with **POI type 22** and in males with spermatogenic failure type 88. Females had secondary amenorrhea in the third decade. Mutations identified include p.L535Q, p.L197P, c.979_980delAG, exon2-exon9 del, p.Ala249Ala and c.1270_1273del. The c.1270_1283del mutation was also reported to lead to recurrent pregnancy loss phenotype in the three sisters and POI in two sisters. The KASH5 protein is a component of the linker of the nucleoskeleton and cytoskeleton complex and is required for homolog pairing during meiotic prophase in spermatocytes and oocytes.[61,62]

OMIM classifies a second group that presents as hypergonadotrophic ovarian failure, ovarian dysgenesis (ODG), which accounts for half the number of primary amenorrhea cases. Ovarian dysgenesisODG manifests as delayed puberty, primary amenorrhea, streak/ hypoplastic ovaries, and an underdeveloped uterus. As per OMIM, ten identified loci for ODG exist.

Homozygous LOF mutations in the FSHR gene (AR) (locus 2p16.3) (follicle stimulating hormone receptor) (locus chromosome 2p16) lead to **ODG type 1**. The p.A189V is a founder mutation in Finnish women with ODG who present

with hypoplastic ovaries (low number of follicles) due to residual FSHR activity. Males homozygous for FSHR gene mutation had variable degrees of spermatogenic failure but did not show azoospermia or infertility demonstrating that FSH is more important for female than for male infertility. Other mutations identified include p.I160T, p.A419T and p.R573C. Achrekar *et al.* identified a novel homozygous variant p.A575V in an Indian woman with primary amenorrhea out of a cohort of 86 women with primary/secondary amenorrhea. Heterozygous gain of function mutation in FSHR gene is known to lead to ovarian hyperstimulation syndrome.[63–67] Achrekar *et al.* showed that Indian females with homozygous p.T307A polymorphic variant require lower amounts of FSH for ovarian stimulation in assisted reproductive cycles and are at increased risk of ovarian hyperstimulation syndrome.[68] Achrekar *et al.* also showed that the AA genotype at position -29 in the 5 untranslated region of the FSH receptor gene is associated with impaired transcriptional activity and may be associated with poor ovarian response to FSH during the assisted reproductive cycle.[69] Heterozygous mutation in the BMP15 gene (AD) leads to **ODG type 2**, already discussed in POI type 4. Homozygous mutations in PSMC3IP gene (HOP2 gene) (chromosome locus 17q21.2) (AR) lead to **ODG type 3**. This protein has a role in meiotic recombination and also in the nuclear hormone receptor-mediated transcription process. In a large Arab family, p.Glu201del mutation was identified, which abolished PSMC3IP activation of estrogen-driven transcription.[70] Homozygous mutation in the MCM9 gene (AR) (locus 6q22.31) leads to **ODG type 4.** Minichromosome maintenance proteins such as MCM9 have a role in eukaryotic DNA replication initiation and the early stage of elongation. Mutations identified include p.R132X (Kurdish family) and p.E495X (Arab family).[71,72] Homozygous mutation in SOHLH1 gene (AR) (chromosome locus 9q34.3) leads to **ODG type 5** in females whereas heterozygous mutation in SOHLH1 gene can lead to spermatogenic failure type 32 in males. SOHLH1 is involved in early folliculogenesis and also in early testis development. Mutations identified for ODG5 phenotype include c.705delT and p.Y9X, whereas, for spermatogenic failure, it is c.346-1G>A.[73,74] Homozygous mutation in NUP107 gene (AR) (chromosome locus 12q15) leads to **ODG type 6** phenotype. Mutations in this gene are also reported to cause unrelated phenotypes: Galloway Mowat syndrome and nephrotic syndrome type 11. Mutations for the ODG 6 phenotype include p.D447N and p.R355C. The nucleoporin 107 protein is a component of the nuclear pore complex, which mediates nucleocytoplasmic transport.[75,76] Homozygous mutation in MRPS22 gene (AR) (chromosome locus 3q23) leads to **ODG type 7** phenotype. The gene encodes chromosome 3 open reading frame protein (C3orf5). Mutation in this gene has also been associated with another phenotype combined with mitochondrial oxidative phosphorylation deficiency type 5. Mutations identified for ODG7 phenotype include p.R202H (Arab) and p.R135Q (Turkey). Primordial germ cell dependence on high levels of oxidative phosphorylation for its metabolism could be the possible mechanism behind the oocyte-specific phenotype, whereas the mutation spares other tissues.[77] Heterozygous mutation in the ESR2 gene (AD) (estrogen receptor beta) (a nuclear receptor for transducing estrogen signals into the transcriptional response) (locus 14q23.2-q23.3) can lead to **ODG type 8** phenotype. The mutation identified was p.K314R, which acts via a dominant negative mechanism. Heterozygous mutations in the ESR2 gene have also been identified in 46 XY disorder of sex development cases (phenotype female with no visible gonads).[78] Homozygous mutation in the SPIDR gene (locus 8q11.21) (AR) leads to **ODG type 9**. SPIDR is a nuclear scaffolding protein that functions in the DNA repair pathway via homologous recombination. Patient cells show chromosome instability. Hence, cancer susceptibility is a possibility. Mutations identified include p.W280X (Arab) and p.R272X (Indian).[79,80] Homozygous LOF mutations in ZSWIM7 (AR) (locus 17p12) have been identified in females with **ODG type 10** and males with spermatogenic failure type 71. ZSWIM7 functions in DNA repair via homologous recombination. Mutations identified include p.S58X (Turkey) in females, c.201+1G>T and c.231_232del (Arab) in males. Genomic instability leads to chromosome instability.[81–83]

In addition, several genes are known for syndromic POI (ovarian sufficiency with additional system involvement). Examples are AIRE gene (Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, APECED), BLM (Bloom syndrome), ATM (ataxia telangiectasia), WRN (Werner syndrome) and RECQL4 (Rothmund Thomson syndrome). Bloom syndrome is a chromosomal breakage leading to early onset of ageing, short stature and elevated rates of most cancers. Ataxia telangiectasia is characterised by progressive cerebellar degeneration, telangiectasias, immunodeficiency, recurrent infections, insulin-resistant diabetes, premature ageing, radiosensitivity, and high risk for epithelial cancers in surviving adults. Werner syndrome is characterised by premature ageing of the skin, vasculature and bone and elevated rates of certain cancers, particularly sarcomas. Rothmund Thomson syndrome is characterised by skin rash, sparse hair, small stature, skeletal and dental abnormalities, cataracts, premature ageing and an increased risk for cancer, especially malignancies originating from bone and skin tissue.[84-87] Another example of syndromic POI is ovario leukodystrophy caused due to mutations in EIF2B1, EIF2B2, EIF2B3, EIF2B4 and EIF2B5 (eukaryotic initiation factor 2B complex) genes; leukoencephalopathy can occur at variable age and patients and carrier females are at risk of POI.[88] Ciliopathies such as DNAH6 can lead

to recurrent respiratory tract infections, situs inversus and azoospermia in males and POI in females.[89] Perrault syndrome is characterised by deafness in both males and females and POI in females (males are fertile). Causative genes for this syndrome are HSD17B4 (Hydroxysteroid [17-beta] dehydrogenase 4), HARS2 (histidyl-tRNA synthetase 2), CLPP (caseinolytic matrix peptidase proteolytic subunit), LARS2 (leucyl-tRNA synthetase), TWNK (Twinkle mtDNA helicase) and ERAL1 (ERA G-protein-like 1) (corresponding to Perrault syndrome loci 1–6, respectively).[90] In a similar syndrome, progressive leukoencephalopathy with ovarian failure linked to the AARS2 gene, POI was observed in females along with neurologic dysfunction. Patients may also have mental retardation, neuropathy, cerebellar dysfunction and spasticity. In surviving females with Leigh syndrome (French Canadian variety), linked to mutations in gene LRPPRC (leucine rich protein), a mitochondrial disease, POI was observed.[91] Classical galactosaemia is an inherited inborn error of the major galactose assimilation pathway caused by galactose-1-phosphate uridyltransferase (GALT) deficiency leading to liver failure. Newborns present with a life-threatening, acute toxic syndrome that rapidly regresses under a galactose-restricted diet. However, long-term complications, particularly cognitive and motor abnormalities, as well as hypergonadotrophic hypogonadism/ovarian failure in female patients, are still unavoidable.[92] Kumar *et al.* sequenced the GALT gene in Indian females with premature ovarian failure (n = 108), primary amenorrhoea (n = 37) and secondary amenorrhoea (n = 9) and could not find any significant variant.[93] Ataxia with oculomotor apraxia type 2 (AOA2) is an AR disorder associated with mutations in the Senataxin (SETX) gene. Clinical manifestations (ataxia, peripheral neuropathy, oculomotor apraxia) of this disease have previously been limited to the nervous system. Lynch *et al.* described a patient homozygous for a novel mutation of SETX who manifested not only ataxia but also ovarian failure.[94] Kinkar *et al.* identified an Indian patient with a heterozygous deletion in exon 6 of the SETX gene causing ataxia with oculomotor apraxia type 2 (AOA-2) with ovarian failure.[95]

Homozygous inactivating/LOF (AR) mutations in the LHCGR gene lead to luteinising hormone resistance and ovarian failure in females and Leydig cell hypoplasia in males. Female patients have oligomenorrhea/amenorrhea and structurally normal ovaries, whereas males have pseudohermaphroditism. Heterozygous-activating mutations (AD) in the LHCGR gene lead to limited male precocious puberty.[96]

Beyond these OMIM database-reported phenotypes, several new genes have been identified in recent publications.

Watkins *et al.* (2006) reported FOXO1A and FOXO3A gene variants in patients with POI; however, follow-up studies are lacking. These two genes are transcription factors related to the FOXL2 gene.[97] Mansouri *et al.* (2008) identified t(X;11)(q24;q13) in a mother and daughter with POI with a breakpoint in the progesterone receptor membrane component-1 gene (PGRMC1). The missense variant p.H165R was found in another case with POI. Haploinsufficiency of PGRMC1 was shown to lead to impaired activation of microsomal cytochrome P450 and increased apoptosis of ovarian cells.[98] Qin *et al.* (2012) reported variants in ESR1 (estrogen receptor 1), HK3 (hexokinase 3) and BRSK1 gene (serine-threonine kinase) in patients with POI, but definitive studies are lacking.[99] In a family with AD-inherited POI, Kasippillai *et al.* (2013) identified a heterozygous stop codon (Ser429X) (AD) in the eukaryotic translation initiation factor 4E nuclear import factor 1 (eIF4ENIF1), which highlights the importance of translation initiation factors and their regulators in ovarian function.[100] Santos *et al.* (2013) identified homozygous LOF variant p.Glu120Lys in the NANOS3 gene in two sisters with POI. Functional analysis showed that this variant prevented the NANOS3 protein (RNA-binding protein) function of repressing apoptosis.[101] Qin *et al.* (2014) identified AMHR2 (anti-mullerian hormone receptor 2) gene missense variants in patients with POI.[102] Wang *et al.* (2015) identified WT1 gene (transcription factor) heterozygous missense variants in patients with POI.[103] Hyon *et al.* (2016) identified a heterozygous microdeletion at 15q25.2 locus disrupting the CPEB1 gene in three unrelated patients with POI. CPEB1 is an RNA-binding protein important for oocyte maturation.[104] In a patient with POI, Faridi *et al.* (2017) identified a homozygous variant p.Glu485Lysfs*5 in the SGO2 gene encoding shugoshin 2, which is necessary during meiosis in both sexes to maintain the integrity of the cohesin complex that tethers sister chromatids.[105] Moriwaki *et al.* (2017) identified a heterozygous nonsense mutation in the POLR2C gene (RNA polymerase II) in a family with four generations of women affected with POI.[106] Wang *et al.* (2017) showed that heterozygous mutations in the KHDRBS1 gene can lead to POI by affecting the mRNA alternative splicing mechanism.[107] Patino *et al.* (2017) identified 55 coding variants in 49 genes in 48% of patients after WES. They identified new genes for POI: GREM1 gene (TGF beta signalling pathway) p.R169T, HK3 (hexokinase family) p.G97E, NOTCH2 (cell-cell signaling) p.Q1811H, p.L2408H and p.S1804L, GATA4 (transcription factor) p.D425N, INHBC (TGF beta signalling) p.L170Q, MLH3 (MMR) p.T145A, PCSK5 (anterior-posterior patterning in embryo) p.Y679H, ATG7 (autophagy) p.F403L, UMODL1 (uromodulin) p.I1330N, HTRA3 (serine peptidase) p.R336C, NBL1 (transcription factor) p.L38F, UBR2 (N-end rule pathway) p.P215L, PCSK1 (serine endoprotease) p.T608M, BMP6 (TGF beta pathway) p.R385H, CXCR4 (chemokine receptor) p.V139I, FGFR2

(tyrosine kinase) p.R22W, MEI1 (chromosome synapsis in meiosis) p.P41H, GJA4 (gap junction protein) p.R322H, IPO4 (nuclear import receptor signal activity) p.D1069H, ADAMTS16 (zinc dependent protease) p.R789C and p.R100W, PDE3A (phosphodiesterase) p.R459Q, TSC1 (hamartin) p.R651G, PTCH1 (transmembrane protein) p.V1131A, BMPR1B (serine threonine kinase) p.R254H and p.F272L, TSC2 (tuberin) p.R1796C, BMPR1A (serine threonine kinase) p.Y425C and p.R442H, LAMC1 (laminin gamma 1) p.P321S, PTX3 (pentraxin 3) p.P303R, FANCG (DNA repair) p.G59E, SEBOX (homeodomain protein) p.S116Afs*7, FANCL (DNA repair) p.T372Nfs*11, ZPI (protease inhibitor precursor) p.D107N, BMPER (BMP binding endothelial regulator) p.P222S, CYP26B1 (cytochrome P450 family) p.V181M, PRDM1 (transcription repressor) p.R679H, PADI6 (post-translational protein processing) p.L37F, KIT (tyrosine kinase receptor) p.W8S, THBS1 (thrombospondin) p.Q96R, MTHFR (folate metabolism) p.S605P, BRD2 (nuclear kinase) p,A2C, SOX15 (transcription factor) p.P45L, LEPR (leptin receptor) p.S292Y, PCSK6 (serine endoprotease) p.T964M, SAPCD1 (suppressor APC domain containing protein) p.Q76X, BMP5 (TGF beta pathway) p.P78X and C3orf77 (expressed only in testis and ovary) p.K117N and p.E118V.[108] Several of these novel gene associations need further functional characterisation for the definitive pathogenesis of POI. He *et al.* (2018) identified a homozygous mutation in the DMC1 gene, viz p.D36N, leading to spermatogenic failure and POI in the same family.[109] Caburet *et al.* (2019) reported homozygous LOF (truncating) mutation in the MEIOB gene, which is a chromatin-associated protein that is required for meiotic recombination and synapsis in a family with POI.[110] Franca *et al.* (2019) reported a novel biallelic missense mutation (c.149A>G:p.Asp50Gly) in POLR3H in two unrelated families with POI and generated two mouse lines using the CRISPR/Cas9 method to evaluate the intrinsic mechanisms of POLR3H-p.Asp50Gly mutation. Early embryonic lethality was observed in mice harbouring a loss-of-function Polr3h D50G mutation.[111] Bestetti *et al.* (2019) performed microarray analysis on 67 cases of POI and identified variants in novel and known genes for POI. They identified copy number variants in known genes (e.g. BMP15, DIAPH2, CPEB1, BNC1, TP63) and in new genes (VLDLR, gene involved in steroidogenesis).[112] Delcour *et al.* (2019) found heterozygous variants p.F403L (ATG7 gene) and p.R758C (ATG9A gene) in two unrelated patients with POI. Both genes are implicated in the autophagy pathway.[113] Oral *et al.* (2019) performed cytogenetic analysis followed by FMR1 repeat analysis, followed by sequencing test for 9 genes in 86 patients and found X chromosome abnormalities in four patients, two patients with FMR1 premutation alleles, and variants of uncertain significance in following genes FSHR, NR5A1, PDPK1 and POI1B. A novel finding was the postulation of the PDPK1 gene as a candidate gene for POI. The PDPK1 gene is important for PI3K/PTEN/Akt signalling which affects the developmental steps of the primordial follicles, including their activation, survival and death.[114] He *et al.* (2021) identified two homozygous variants in SYCP2L gene (synaptonemal complex gene involved in meiosis) in two unrelated families with POI.[115] Heddar *et al.* (2022) identified mutations in 29.3% cases in 70 families using a whole exome sequencing (WES) approach.[116] Mutations were identified in novel genes not known to previously be linked to Mendelian phenotypes: ELAVL2 (AR), NLRP11 (AR), CENPE (AD), SPATA33 (AR), CCDC150 (AR), CCDC185 (AR), C17ORF53 (AR), HELQ (AR) and SWI5 (AR). They also identified variants in BRCA2, FANCM, BNC1, ERCC6, MSH4, BMPR1A, BMPR1B, BMPR2, ESR2, CAV1, SPIDR, RCBTB1 and ATG7 genes. ELAVL2 encodes RNA-binding protein expressed in ovaries, testis and neurons. Mutations identified included p.R150C and p.L105F. NLRP11 or nod-like receptor protein 11 regulates immune response through NF-KB and type I interferon signalling pathway. A heterozygous p.Q675X variant in the CENPE gene, was identified in three sisters. This gene is important for correct chromosome segregation in meiosis and mitosis and is highly expressed in germ cells. A homozygous c.34dup variant was identified in an Algerian patient in the SPATA33 gene (AR), which is exclusively localised in the localised mitochondria of germ cells and is involved in mitophagy. Heterozygous variant c.63_94del was identified in the XPNPEP2 gene (AD) of a French patient; the XPNPEP2 gene regulates collagen formation. Two genes of the coiled-coiled family were identified in unrelated cases. Homozygous p.C97X in CCDC150 (Moroccan patient) and homozygous p.Q392X (Turkish patient) in CCDC185 were seen in unrelated cases. Both genes are highly expressed in the testes. A homozygous c.502delG variant in the C17ORF53 gene was found in the Turkish family, a homozygous c.3095delA variant was found in HELQ (DNA helicase) gene in a Moroccan patient, and a homozygous c.261-1G>C variant was found in SWI5 gene in a Moroccan patient. All three genes are involved in DNA repair pathways; hence patients showed chromosome instability in mitomycin-induced chromosome breakage studies as in Fanconi anaemia. One patient had homozygous GALT gene variant p.G188Q, which is associated with galactosemia, a metabolic disease associated with liver disease. However, the patient had POI and a cataract requiring surgery but no metabolic disease. Eight unrelated patients had variants in genes causing pulmonary arterial hypertension, namely CAV1, BMPR2, BMPR1B and BMPR2. Seven unrelated patients had variants in the POLG gene (DNA polymerase gene), which usually presents with neurological, ophthalmological, and myopathy features; however, the

patient had POI without syndromic features.[116] Gorsi *et al.* (2022) performed WES in a large cohort of POI patients and identified 7 new genes for POI, namely USP36 (ubiquitin-specific protease), VCP (valosin-containing protein), WDR33 (WD repeat-containing protein), PIWIL3 (argonaute family), NPM2 (nucleoplasmin family), LLGL1 (polarity complex component protein) and BOD1L1 (replication fork protection pathway component).[117] Ke *et al.* (2023) performed WES in 1030 POI cases and identified mutations in 59 known genes in 193 cases (18.7%). They further identified 20 novel genes indicating their involvement in ovarian development and function. These genes are involved in gonadogenesis – LGR4 (G protein coupled receptor) and PRDM1 (DNA binding transcriptional repressor), meiosis (CPEB1, KASH5, MCMDC2; minichromosome maintenance domain containing protein 2), MEIOSIN (meiosis initiator), NUP43 (nucleoporin 43), RFWD3 (Fanconi anaemia complementation group W protein), SHOC1 (shortage in chiasmata 1), SLX4 (Fanconi anemia complementation group P protein) and STRA8 (stimulated by transcription factor 8, a transcription factor) – and folliculogenesis and ovulation – ALOX12 (arachidonate oxidoreductase), BMP6 (bone morphogenetic protein), H1-8 (linker histone), HMMR (hyaluronan-mediated motility receptor), HSD17B1 (17-beta-hydroxysteroid dehydrogenase), MST1R (macrophage stimulating receptor), PPM1B (magnesium/manganese-dependent protein phosphatase), ZAR1 (zygote arrest 1) and ZP3 (zona pellucida glycoprotein).[118]

In addition to several MMR genes included above, some MMR genes such as MSH6, BRCA1 and BRCA2 are also reported to affect menopause, but definitive association is lacking.[119] Variants in Inhibin A (INHA) gene, which has a role in regulating the pituitary secretion of FSH (gonadal glycoprotein hormone) was reported to be associated with POI.[120] Prakash *et al.* sequenced the INHA gene in 100 Indian women with POI and identified c.769G>A missense variant and three novel variants, c.734C>A/ p.A245D, c.755C>A/p.P252H and c.777C>A/p.H259Q, which were absent in controls.[121] However, definitive evidence is lacking.

To summarise considering the above mechanisms, the following clinical features should be looked for in a patient with POI: short stature, wide carrying angle, shield chest, delayed secondary sexual characters, primary/secondary amenorrhea, susceptibility to hypothyroidism, hypertension (TS phenotype), history of X-linked mental retardation in males in family (Fragile X syndrome), blepharophimosis, ptosis, epicanthus inversus (BPES), skin hyperpigmentation, radial ray abnormalities, history of cancer or aplastic anaemia in self or family (Fanconi anaemia/Rothmund Thomson syndrome), ataxia (SETX, ATM gene abnormality), jaundice, cataracts (galactosemia), photosensitivity (Bloom syndrome), microcephaly (NUP107), endocrine disorders, ectodermal dystrophy (APECED), deafness (Perrault syndrome) and Leucoencephalopathy (neurological deterioration) (AARS2 gene, LRPPRC). The following panel of investigations can be considered for a patient with POI: karyotype, FMR1 gene triple primer polymerase chain reaction for CGG repeat analysis and next generation sequencing panel, including the following genes: AARS2, ADAMTS16, AIRE, ALOX12, AMHR2, ATG7, ATM, BLM, BMP5, BMP6, BMP15, BMPER, BMPR1A, BMPR1B, BMPR2, BNC1, BOD1L1, BRD2, BRSK1, C3ORF77, C17ORF53, CAV1, CCDC150, CCDC185, CENPE, CLPP, COL4A6, CPEB1, CXCR4, CYP26B1, DACH2, DIAPH2, DMC1, DNAH6, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, EIF4ENIF1, ELAVL2, ERAL1, ERCC6, ESR1, ESR2, FANCG, FANCL, FANCM, FGFR2, FIGLA, FOXL2, FOXO1A, FOXO3A, FSHR, GALT, GATA4, GDF9, GJA4, GREM1, H1-8, HARS2, HELQ, HFM1, HK3, HMMR, HSD17B1, HSD17B4, HSF2BP, HTRA3, INHBC, IPO4, KASH5, KHDRBS1, KIT, LAMC1, LARS2, LEPR, LGR4, LHCGR, LLGL1, LRPPRC, MCM8, MCM9, MCMDC2, MEI1, MEIOB, MEIOSIN, MLH3, MRPS22, MSH4, MSH5, MST1R, MTHFR, NANOS3, NBL1, NLRP11, NOBOX, NOTCH2, NPM2, NR5A1, NUP43, NUP107, NXF5, PADI6, PCSK1, PCSK5, PCSK6, PDE3A, PDPK1, PGRMC1, PIWIL3, POF1B, POLG, POLR2C, POLR3H, PPM1B, PRDM1, PSMC3IP, PTCH1, PTX3, RCBTB1, RECQL4, RFWD3, SAPCD1, SEBOX, SETX, SGO2, SHOC1, SLX4, SOHLH1, SOX15, SPATA33, SPIDR, STAG3, STRA8, SWI5, SYCE1, SYCP2L, THBS1, TP63, TSC1, TSC2, TWNK, UBR2, UMODL1, USP36, VCP, VLDLR, WDR33, WRN, WT1, XPNPEP2, XRCC2, ZAR1, ZP3, ZPI and ZSWIM7. Females who wish to conceive can avail of donor egg in vitro fertilisation, provided they do not have syndromic POI with multisystem involvement, particularly neurological affection.

CONCLUSION

Current research in patients with POI has revealed exciting novel pathways which will be helpful in planning diagnostic and therapeutic strategies for these patients. However, a diagnostic yield of 20–30% by whole exome in these patients suggests that several pathways and genes have yet to be identified and will require a combination of proteomic, genomic and cellular/animal modelling studies or approaches.

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Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of AI-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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