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Searching for the 'X' factor: investigating the genetics of primary ovarian insufficiency

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Abstract

Primary ovarian insufficiency (POI) is the cessation of ovarian function before the age of 40. The causes of POI are heterogeneous, but substantial evidence exists to support a genetic basis of POI, particularly in the critical involvement of genes on the X chromosome. Recent studies have revealed novel candidate genes through the identification of copy number variations associated with POI. This review summarizes the genes located on the X chromosome with variants shown to be associated with POI in humans and/or in mice. Additionally, we present evidence to support the potential involvement of these candidate genes in the etiology of POI. We conducted a literature search in PubMed to identify case studies and screenings for the genetic causes of POI. We then performed systematic searches for the proposed candidate genes to investigate their potential reproductive roles. Of the X-linked candidate genes investigated, 10 were found to have variants associated with cases of POI in humans. An additional 10 genes were found to play a supportive role in POI. Other genes were not implicated in any cases of POI but were associated with various roles in reproduction. In the majority of cases where variants were identified through whole-exome sequencing, rather than targeted screening of candidate genes, more than one genetic variant was identified. Overall, this review supports past findings that the X chromosome plays a critical role in ovarian function, as demonstrated by a link between POI and various disruptions to genes on the X chromosome. Current genetic screening for POI, which includes only *FMR1*, is inadequate to capture the majority of cases with a genetic origin. An expanded genetic testing may improve health outcomes for individuals with POI as it could lead to better early interventions and education about these health risks.

Keywords Primary ovarian insufficiency, X chromosome inactivation, Gene dosage, Folliculogenesis, Oogenesis, Ovarian phenotype, Genetic models, Early menopause

Introduction

Primary ovarian insufficiency (POI), often referred to as premature ovarian failure, is characterized by cessation of normal ovarian function before the age of 40. POI is diagnosed based on the presence of amenorrhea or oligomenorrhea for over 4 months, accompanied by a level of serum follicle-stimulating hormone (FSH) over 25 IU/I measured at two occasions separated by a 4-week time interval [1]. The causes of POI are heterogenous, and include iatrogenic, autoimmune, as well as genetic factors. In the general population, POI affects approximately 1–2% of women, and approximately 50% of those cases

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are considered idiopathic [2]. However, POI has a strong heritable component, evidenced by clustering of this condition in affected families. A recent study suggested that there is a 3-fold increased risk of POI for individuals with a first-degree relative with POI [3].

Further support for the genetic basis of POI comes from association with rearrangements on the X chromosome. Based on early studies of women with POI, 3 critical regions for ovarian function and reproductive lifespan have been identified on the X: Xq26qter (POF1), Xq13.3q21.1 (POF2), and Xp11p11.2 (POF3) (Fig. 1A) [4]. Within these regions, several genes have been demonstrated or proposed to play a critical role in ovarian function. Apart from the X chromosome, several autosomal genes have also been linked to POI, but these will not be discussed herein. In this review, we have summarized the current knowledge of genes and their variants shown to be associated with POI in humans and/or in genetic mouse models.

X chromosome inactivation and gene dosage

Genetically female mammalian cells evolved complex epigenetic mechanisms to preclude activity of all but one X-chromosome per diploid set, called X-chromosome inactivation (XCI). Overall, XCI is believed to occur shortly after lineage allocation during early stages of

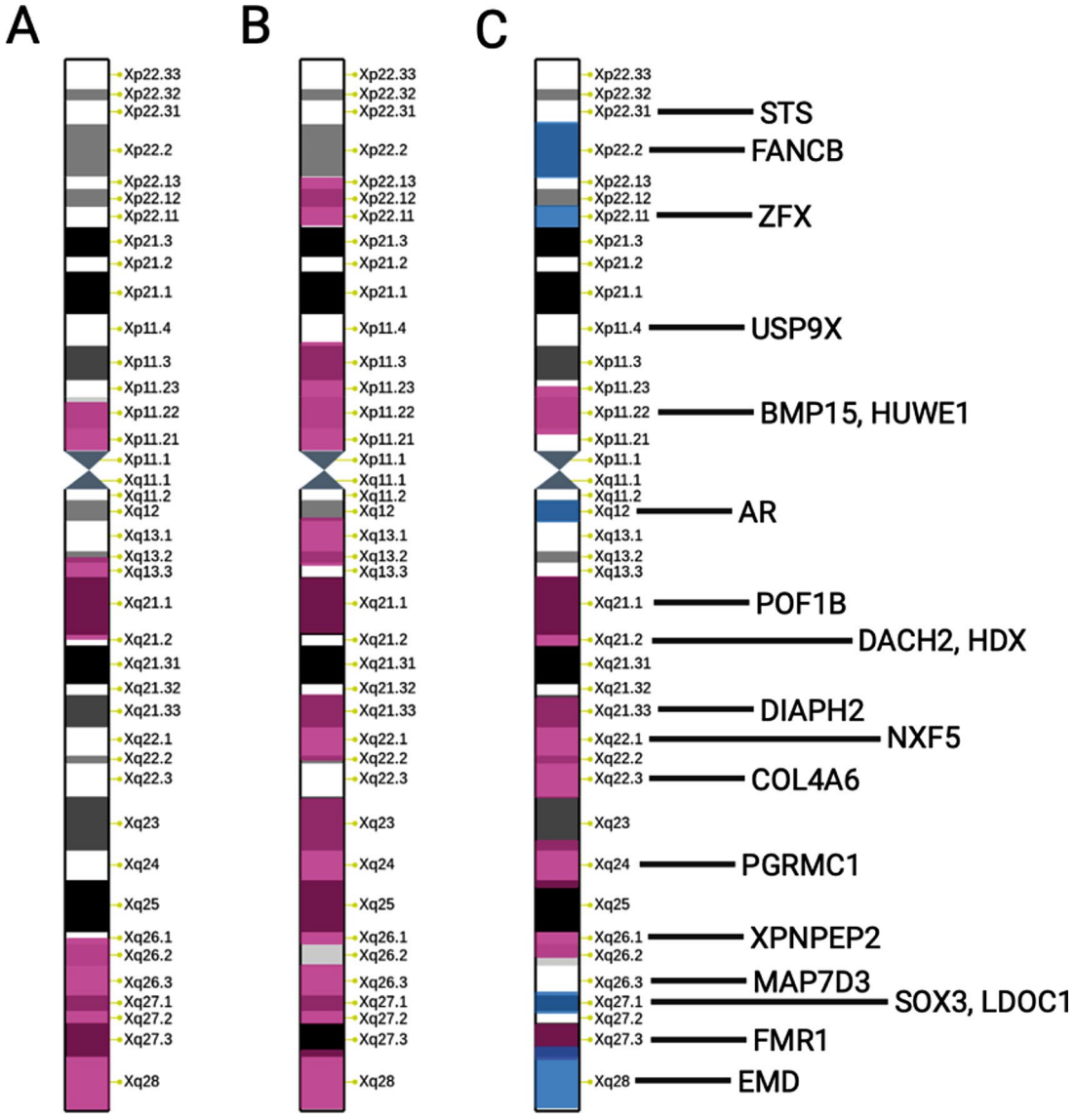

Fig. 1 Visual representation of proposed primary ovarian insufficiency (POI)-linked regions on the X chromosome. Black and grey regions represent heterochromatin and white regions represent euchromatin. Pink overlay represents regions identified as being liked to POI in humans, while blue overlay represents genes identified through mouse studies. (**A**) Critical regions proposed based on early studies of chromosomal rearrangements. (**B**) Locations of candidate genes proposed by X chromosome copy number variation analysis by Yatsenko et al. 2019 [5]. (**C**) Locations of genes found to have variants associated with cases of POI, and genes found to cause POI in knockout mouse models. Figure created with BioRender

embryo development with inactive X-chromosome being stably marked and transmitted through cell divisions. The silencing is initiated by the XCI centre containing the *XIST* locus. *XIST* encodes a long-non-coding RNA, which upon expression, accumulates to coat the X chromosome, recruiting protein complexes that enable the epigenetic and structural chromatin changes required for gene silencing. For a full review of the mechanism of XCI, see Mattimoe & Payer, 2023. However, some genes can escape X inactivation and are therefore transcribed from both the active and the inactive X chromosomes. RNA expression study of human tissues established that up to 25% of genes on the X chromosome escape inactivation in various somatic cells [6, 7]. Notably, in humans it has also been demonstrated that there is heterogeneity in XCI at the level of the individual, the tissue, and even the cell [7].

The timing of XCI has been characterized in several animal models, but the timing in humans remains somewhat elusive. Although it was initially suggested that XCI begins in human preimplantation embryos [8], some studies have demonstrated that despite the earlier upregulation of *XIST*, XCI in human cells begins by the late blastocyst stage, specifically, by embryonic day 7 [9]. Different patterns in the timing of XCI have been observed in trophectoderm, primitive endoderm, and epiblast cells using in vitro model of human implantation [10]. In contrast to somatic lineages, during primordial germ cell (PGC) development, both X chromosomes are reactivated [11, 12]. Specifically, germ cell-competent epiblast cells display moderate XCI characterized by inconsistent silencing of many X-linked genes followed up by stepwise X-reactivation [13]. This process is finalized during meiotic prophase I with both X chromosomes remaining active during oocyte development controlling gene dosage by transcriptional output regulation [14]. However, the status of X silencing and reactivation in human PGCs during the 2nd week of development when their specification is occurring is still unknown.

XCI requires epigenetic memory to determine whether the maternal or the paternal X chromosome will be silenced. While different mechanisms exist among mammals to accomplish this task, in humans, it is generally a random process. During early development, *XIST* is expressed from both X chromosomes in females, and intriguingly, it is also expressed from the X chromosome in male embryos [9]. Therefore, in humans, the determination of which X chromosome is inactivated appears to depend on the repression of *XIST* transcription in one of the X chromosomes [15]. Random XCI would suggest that both the maternally and paternally inherited X chromosomes would be inactivated at the same frequency in somatic cells. However, skewed XCI, where one of the X chromosomes is preferentially inactivated over the other, is observed in a large part of the general population. This may be explained by the fact that X inactivation is initiated at a time when cell number is limited, meaning that stochastic skewing is statistically likely [16]. That said, it has also been proposed that skewed inactivation may be a result of primary and secondary skewing, in which the X chromosomes are differentially inactivated due to the presence of variants within the genes involved in X inactivation, or due to the differential survival of cells based on which X chromosome is expressed. Importantly, skewed X inactivation in some studies has been associated with POI [17–19], suggesting that aberrations of the X chromosome may be responsible, at least in part, for the POI in these individuals. In line with this, a recent study comparing X chromosome copy number variations (CNVs) in fertile females versus females with POI found that CNVs in the latter were enriched in genes associated with X chromosome inactivation [5]. Surprisingly, compensatory gene-by-gene mechanisms have evolved for transcriptional gene dosage regulation [20]. Yet it is unclear at what point during development and what tissues, or cell types could be responsible for the POI outcome caused by skewed XCI.

Genes that require a specific concentration of protein product to preserve normal function are said to be dose sensitive with some genes being more sensitive to dosage than others. Haploinsufficiency is the state that ensues when one allele is mutated, deleted, or inactivated, resulting in a loss of function from that gene copy, while the other intact allele is insufficient to preserve normal function. The phenomenon of X inactivation in females would suggest that haploinsufficiency is not as relevant to genes on the X chromosome. However, genes escaping XCI may do so as they are sensitive to gene dosage [21]. Thus, through extrapolation, a loss of function mutation in genes escaping X inactivation in a subset of somatic lineages, or genes whose function is critical for early oocyte development when both X chromosomes are in an active state, could therefore result in impaired ovarian function.

Turner syndrome

Turner syndrome (TS) is a genetic disorder caused by the loss of one X chromosome in some cells (mosaicism, e.g. 45,X/46,XX or 45,X/46,XX/47,XXX) or in all cells (45,X). More generally, individuals with TS can be referred to as XO. The estimated prevalence of TS is approximately 1 in every 2,200 live born females, based on meta-analysis [22]. Although the rate of live born females with TS is low, it is estimated that only 1-1.5% of TS conceptuses make it to term [22]. Thus, the predominant phenotype of a 45,X karyotype is embryonic lethality. In a study comparing gene expression in XO and XX human embryonic stem cells, authors found that the only tissue in which many genes were upregulated in XX versus XO

was the placenta. This suggests that abnormal placental differentiation due to the haploinsufficiency of genes on the X chromosome may be, at least in part, responsible for the loss of XO fetuses [23]. Therefore, some have proposed that in a high proportion of 45,X fetuses, the 45,X cell lineage line is derived after fertilization, and this karyotype is only survivable due to some level of mosaicism [22].

For 45,X and mosaic females that do survive to term, the phenotypic characteristics of TS are heterogeneous, and include shortened stature, anatomic differences, congenital heart defects, cognitive deficits, and POI. As such, TS presents a rather extreme case of POI linked to the X chromosome. POI in TS is generally characterized by insufficient pubertal development, primary amenorrhea, and infertility due to premature loss of oocytes. Yet there have been spontaneous pregnancies reported at low rates within this population [24]. The TS mosaic karyotype has been associated with milder ovarian dysfunction, marked by the occurrence of spontaneous menarche and the presence of ovarian follicles in some of these patients [25]. The ovaries of young girls with mosaic TS appear relatively morphologically normal, while 45,X girls present with bilateral streak ovaries [25]. Importantly, in individuals with TS mosaicism, the proportion of 45,X cells in somatic cells is not necessarily predictive of the proportion of 45,X cells in germ cells. Therefore, it has been proposed that in the rare cases of pregnancy in 45,X females, rather than being truly monosomic, these individuals may show cryptic mosaicism in the ovary [25, 26].

The findings of a recent study suggested that in TS, the loss of germ cells in early gestation may be caused, at least in part, by increased apoptosis and impaired folliculogenesis. These early features of TS appear to be less severe in cases of TS mosaicism [27]. Although the mechanisms underlying this loss of oogonia remain unclear, the predominant theories suggest that apoptosis is induced due to the haploinsufficiency of genes localized to the X chromosome, or due to the meiotic failure caused by monosomy. Given that in somatic cells, up to 30% of genes on the X chromosome can escape inactivation, the haploinsufficiency of specific genes on the X chromosome may be responsible for the various phenotypic features observed in TS [28–30]. Thus, a possible explanation for the early loss of germ cells observed in TS is the haploinsufficiency of genes involved in oocyte development, a time when both X chromosomes are maintained in an active state. Alternatively, the early loss of germ cells may occur as a result of meiotic failure. As meiosis involves the pairing and crossing-over of homologous chromosomes, the failure of the chromosomes to form bivalents can result in meiotic arrest followed by death. In cases of aneuploidy, pairing failure is inevitable, and indeed, infertility is a common feature of aneuploidies. It has been proposed that a surveillance mechanism exists to eliminate aneuploid germ cells during meiosis, a mechanism that then prevents aneuploidies in offspring. In support of this, a study of an XO mouse model found that asynapsis of the X chromosome caused oocyte elimination during prophase I. However, it was found that this was not explained by asynapsis alone, but also by altered gene dosage [31]. This suggests that both asynapsis and haploinsufficiency may be involved in germ cell loss in TS.

The curious rare cases of X chromosome multisomies

X trisomy, or 47,XXX, is a rare aneuploidy with an occurrence of about 1 in every 10,000 female births [32]. It has been related to oligomenorrhea and POI as well as an array of autoimmune diseases [33, 34]. Interestingly, there have also been reported cases of greater X chromosome multisomies, including X tetrasomies (47, XXXX) and X pentasomies (47, XXXXX), yet POI does not seem to be an observed phenotype in these individuals. It is also not clear if some tissues in these patients could be mosaic. These X chromosome multiplicities are mostly characterized by intellectual developmental disorders [34]. Curiously, based on the few cases studied to date, it seems as though the presence of too many X chromosomes does not hinder reproductive function in female individuals, suggesting that increased X chromosome gene dosage may not be implicated in ovarian dysfunction.

X chromosome genes associated with POI

Since several X chromosomal rearrangements in POI patients implicated the same critical regions, genes that were affected by breakpoints in these rearrangements were considered to be POI gene candidates and were subsequently screened for in cohorts of women with idiopathic POI. Since then, more elegant tools for screening have evolved and have been used to elucidate critical variants and rearrangements in both autosomes and sex chromosomes. Recently, a high-resolution CNV map was performed to compare a cohort of women with POI to a cohort of fertile women, ultimately leading to the pool of 50 new POI candidate genes (Fig. 1) [5]. Along with these candidates, we considered other genes from case reports of X chromosome rearrangements, as well as additional CNV studies, and genes implicated in POI through whole-exome sequencing. Here, we describe candidate genes with variants associated with POI in humans, candidate genes associated with a POI-like phenotype in mice, chromosomal regions implicated in POI through X chromosomal disruptions, and other candidates associated with reproductive phenotypes.

Genes with established link to POI

FMR1

FMR1, located at Xq27.3, is arguably the most well-established causative single-gene linked to fragile X-associated premature ovarian insufficiency (FXPOI). The *FMR1* gene contains a polymorphic CGG repeat within the 5' UTR of its first exon and it typically contains 24 to 40 repeats. Conditions where repeat number exceeded this range have been described. These pathological states are referred to as the *FMR1* premutation (PM), consisting of 55 to 200 repeats, or the full mutation (FM), containing over 200 repeats. Like other known repeat expansion disorders, the number of triplet repeats have the potential to expand [35]. *FMR1* gene encodes the Fragile X Retardation Protein (FMRP), a multifunctional RNA-binding protein, highly expressed in the brain. If the *FMR1* FM allele is present, the gene is silenced via hypermethylation, thus preventing the transcription of FMRP, resulting in the accumulation of RNAs leading to the cognitive deficits associated with fragile X syndrome (FXS) [36]. Conversely, the *FMR1* PM results in increased *FMR1* mRNA levels, resulting in toxicity [37]. Therefore, although the *FMR1* PM is not causative of FXS, it has been linked to neurodegenerative disorders such as ataxia, psychiatric disorders, and POI [38].

FMR1 is expressed in a variety of tissues including the fetal ovary and has been suggested to escape inactivation in the granulosa cells (GCs) [39]. Interestingly, some studies have suggested that the normal range of CGG repeats is more constricted in terms of ovarian function and is between 26 and 34 [40]. Correspondingly, relative to this range, *FMR1* alleles can have a low, high, or normal number of CGG repeats, and thus different genotypes have been associated with variations in ovarian reserve [40, 41]. This suggests that the distinction of typical, PM, and FM may not fully capture the relevance of *FMR1* triplet repeats as they apply to ovarian function. In a mouse model carrying a human *FMR1* PM, FMRP was expressed predominantly in GCs and oocytes, and *FMR1* transcript levels were associated with a reduction in follicle numbers, resulting in reduced fertility [42]. Impaired fertility accompanying the *FMR1* PM has been proposed to be explained by its effects on FSH-dependent signalling in GCs, dysregulation of anti-Mullerian hormone expression, alterations to AKT/mTOR signalling [39], and the accumulation of FMR polyG, a protein whose translation is triggered by CGG repeats that has been implicated in various disorders [43, 44]. Since the original study, published by Conway et al. in 1995, screening of various patients' cohorts has consistently suggested that *FMR1* PMs are present in women with POI at higher rates than expected in the general population, ranging from approximately 2–9% [18, 45–48]. More recently, screening for *FMR1* PMs has become an important initiator for early cryopreservation of oocytes in affected patients [49].

BMP15

Bone morphogenic protein 15 *(BMP15)*, located at Xp11.22, encodes a member of the TGF-β superfamily and was first identified in 1998 [50, 51]. This member of TGF-β family can act as a homodimer or can partner with GDF9 and form a cumulin heterodimer. Heterozygous *BMP15* variants in the precursor or mature peptide have been associated with POI. Both *BMP15* and *GDF-9* are oocyte-produced growth factors that modulate the development of GCs via stimulation of DNA replication and proliferation [52]. Variations in *BMP15* gene dosage have been proposed to significantly influence female ovarian function (for a recent review, see Liu et al., 2021) [53]. Studies of mutant or knockout mice first demonstrated that Bmp15 is implicated in oocyte development, in a dose-dependent manner [54, 55]. Subsequently, BMP15 has been shown to regulate GC and oocyte response to growth factors, thus promoting proper maturation of the cumulus-oocyte complex [56–58]. Recent findings have also suggested that BMP15 induces FSH receptor (FSHR) expression, leading to increased follicle growth [59, 60].

The first documented mutation in *BMP15* in humans was linked to two cases of POI in sisters who inherited a mutation from their father [61]. Mutations of *BMP15* have been extensively documented across POI cohorts throughout Europe and in parts of Asia. For a list of documented variants, see Supplementary Table S1 [62–72]. A review of literature screening for variants of *BMP15* across various study populations found that nonsynonymous variants were 10-fold more prevalent in women with POI compared to controls [73]. More recently, *BMP15* mutations have been linked to poor ovarian response during oocyte retrieval in young patients. This is likely due to BMP15's association with ovarian responsiveness to hormonal stimulation for follicular development, and as such, can lead to POI resulting from failed folliculogenesis [74]. The association between *BMP15* variants and ovarian response was also recently reported – the p.N103K and p.M184T variants both being associated with POI in a cohort of Iranian women. Interestingly, mutations in these variants were both found in the pro-domain region of *BMP15* – a region critical for proper protein folding and reconfiguration during a protein's transition from its active to inactive state, and vice versa. Additionally, despite there being other *BMP15* variants reported, p.N103K and p.M184T seem to be the only ones significantly sterically changing the protein conformation [75].

Genes with variants identified in POI patients

POF1B

Premature ovarian failure 1B (*POF1B)*, located at Xq21.1, was first considered a POI candidate gene as it was found to be in a critical region for ovarian function. It escapes XCI and has no Y homolog. The mouse homolog, *Pof1b* is expressed in the mouse ovary from embryonic day 16.5 to postnatal day 5, suggesting a possible role in gonadal development [76]. In vitro studies have demonstrated that POF1B binds non-muscle actin filaments, and that its mutation reduces its binding affinity to actin [77]. Otherwise, *POF1B* has been implicated in tight junctions involved with epithelial polarization, as well as ciliogenesis, and cystogenesis via interaction with F-actin [77]. The altered actin-binding capacity of *POF1B* variants may be causative of POI due to a critical role in chromosomal alignment, or in anti-apoptosis mechanisms in germ cells.

POF1B was first identified as being disrupted by the breakpoint of a balanced X;1 translocation in a patient presenting with secondary amenorrhea at the age of 17 [78]. Subsequently, screening for variants in this gene has yielded mixed results. In a cohort of 223 Italian women with POI, 5 variants in POF1B were identified, but none were associated with POI when considering their prevalence in the control population [76]. In a Lebanese family, all sisters with POI had a homozygous mutation, c.986G > A:p.R329Q in POF1B, while unaffected sisters were heterozygous for this variant. Moreover, the variant had a frequency of 2.2% in a cohort of unaffected Lebanese women and was only present in a heterozygous state [79]. An additional POI patient with a balanced X;3 translocation was found to be heterozygous for the c.986G > A:R329Q variant, which authors proposed to be causative of POI phenotype due to skewed XCI [4]. However, XCI was not evaluated in the ovary itself, and screening was only conducted for POF1B and DIAPH2. Hence, it is possible that in this patient XCI is not skewed in the ovary, or that other genes contributed to POI. This variant and others have been identified through genetic screening of different study populations with POI (refer to Table 1).

DIAPH2

DIAPH2, located at Xq21.33, is a human homolog of the diaphanous (dia) gene, the mutation of which results in impaired oogenesis and spermatogenesis, and sterility in D. melanogaster. DIAPH2 has been implicated in stable

Table 1 Genetic variants identified through screening of POI cohorts

Gene (location on human X chromosome)	Expression in human fetal ovary	Mutation	State	Rate in women with POI (study population size)	Rate in controls (study population size)	PA or SA (age at menarche)	Reference
POF1B (Xq21.1)	No	c.439–2 A > G	Het.	1.2% (1/86)	N/A	Not reported	[165]
		c. 932 A > C: p.K311T	Hom	Case report (1)	N/A	SA (21)	[166]
		c.986G > A: p.R329Q	Het.	Case report (1)	N/A	SA (23)	[4]
			Hom.	Case report (5)	0% (0/92)	PA	[79]
				Case report (1)	N/A	PA	[167]
COL4A6 (Xq22.3)	Unknown	c.2371G > A: p.G791S	Het.	2% (1/50)	N/A	SA (not reported)	[100]
NXF5 (Xq22.1)	Unknown	c.958 C > T:p.R320	Het.	2% (1/50)	N/A	SA (not reported)	[100]
		c.959G > A:p.R320Q	Hom.	2% (1/50)	N/A	PA (NA)	[100]
		c.145 A > G:p.I49V	Hom.	2% (1/50)	N/A	PA (NA)	[100]
XPNPEP2 (Xq26.1)	Unknown	c.644 C > T:p.T215I	Het.	2% (1/50)	N/A	SA (not reported)	[100]
PGRMC1 (Xq24)	Yes	c.494 A > G:p.H165R	Het.	1.49% (1 of 67)	N/A	Not reported	[94]
		c.533 C > T:p.T178I	Het.	14.2% (2 of 14)	N/A	SA (17, 18)	[76, 168]
DACH2 (Xq21.2)	Unknown	c.C271T: p.P36L	Het.	1.17% (3/257)	0.54% (6/1110)	SA (17, 37, 39)	[76]
		c.G274T: p.R37L	Het.	0.39% (1/257)	0% (0/1110)	SA (35)	[76]
		c.G340A: p.G59D	Het.	0.39% (1/257)	0.09% (1/1110)	SA (24)	[76]
		c.G1399A: p.R412K	Het.	0.39% (1/257)	0.09% (1/1110)	SA (22)	[76]
DIAPH2 (Xq21.33)	Yes	c.733-2_733-1del	Het.	2.78% (1/36)	N/A	SA (37)	[88]

Het. = heterozygous; Hom. = homozygous; PA = primary amenorrhea; SA = secondary amenorrhea

kinetochore and microtubule attachment, and proper metaphase chromosome alignment in HeLa cells, associating with the kinetochore [80, 81]. Mutated DIAPH2 has also been implicated in a shift from cell proliferation to increased cell motility in laryngeal squamous cell carcinoma [82].

DIAPH2 is expressed in the mouse and the human ovary during early development [83]. In sheep ovaries, expression of DIAPH2 was found to be highest at a time point that corresponds with oogonia proliferation [84]. DIAPH2 was first proposed to be necessary for human ovarian development in 1998, when it was demonstrated to be disrupted by the breakpoint of a balanced X;12 translocation in a patient with POI, likely resulting in a truncated or fused protein [85]. Other chromosomal rearrangements with breakpoints disrupting DIAPH2 have been documented as well [48]. For example, DIAPH2 was found to be overexpressed in a POI patient with a balanced X;1 translocation [86]. However, as a result of the translocation, FMR1 was also overexpressed in this patient without a repeat expansion being detected; therefore, it is unclear which gene is responsible for the observed POI [86]. A high-resolution CNV analysis also supported DIAPH2 as one of the top candidate genes for POI [87]. However, only one variant has been documented in a POI patient so far (Table 1) [88, 89].

PGRMC1

PGRMC1, located at Xq24, encodes the progesterone receptor membrane component 1, first cloned in human cells in 1998, when it was identified as the human homolog for a porcine progesterone receptor [89]. It has been shown to modulate the effects of progesterone in various tissues including uterus, liver and kidney. In relevance to the ovary, it was shown to supress oocyte meiotic progression and primordial follicle formation [90], as well as to provide anti-apoptotic mechanisms in human granulosa cells [91]. PGRMC1 has also been shown to associate with beta-tubulin and has thus been implicated in mitotic events [92], including cytokinesis [93]. PGRMC1 was implicated in a human case of POI in a mother and daughter who both had an X;11 translocation, resulting in a reduced expression of PGRMC1 [94]. A duplication encompassing PGRMC1 and disrupting the NXF gene cluster, which encodes nuclear RNA export factors, has also been identified in a POI patient with intellectual disabilities [95]. Furthermore, POI screenings in a cohort of predominantly Swedish, Italian and a cohort of Chinese POI patients, have identified 2 mutations in PGRMC1 (Table 1). In a Pgrmc1/2 knockout mouse, primordial follicles were severely (~80%) depleted by 6 months of age, demonstrating that this receptor may play a critical role in the survivability of adult primordial follicles [96]. Apart from its relevance to reproduction, PGRMC1 expression has been linked to several malignancies [97].

XPNPEP2

XPNPEP2, located at Xq26.1, encodes X-prolyl aminopeptidase P, a hydrolase with a diverse array of functions. In rats, it has been implicated in germ cell nest breakdown, a necessary step in the formation of primordial follicles, likely by regulating the hydrolysis of collagens [98]. The gene was first implicated in POI as it was disrupted by the breakpoint in a X;11 translocation in a POI patient [99]. Otherwise, one heterozygous point mutation in XPNPEP2 was discovered in a different POI patient (Table 1), but potentially deleterious point mutations were detected in some of their other genes [100].

NXF5

NXF5, located at Xq22.1, encodes nuclear RNA export 5, involved in the export of mRNAs from the nucleus [101]. NXF5 is suggested to play a role in RNA metabolism in the brain and has been associated with intellectual disabilities [102, 103]. NXF5 was first associated with POI as it was disrupted by the breakpoint of a X;15 translocation in a POI patient with primary amenorrhea [104]. A case report of a patient with intellectual disability and amenorrhea at age 19 reported a deletion encompassing NFX5 [95]. Through screening of a Brazilian POI cohort, homozygous and heterozygous point mutations were discovered within NXF5 (Table 1), but other potentially pathogenic point mutations were also identified in many of these individuals [100]. Deletion of Nxf2, mouse orthologue of NXF5, causes male subfertility due to impaired spermiogenesis and age-dependent depletion of spermatogonia [105]. This phenotype, however, depends on a genetic background and thus variants of NXF5 would likely have variable phenotypic outcomes in human patients of various ethnicities.

COL4A6

COL4A6, located at Xq22.3, encodes collagen type IV alpha-6, a component of basement membranes. Deletions encompassing both COL4A6 and COL4A5 have been associated with Alport syndrome, a nephropathy characterized by an altered glomerular basement membrane [106]. It was first associated with POI in a patient with a translocation that was found to disrupt COL4A6 while leaving COL4A5 intact [107]. Since the intact X chromosome was inactivated in this individual, the study posited that POI may be related to a loss of COL4A6 function as a consequence of the breakpoint [107]. Additionally, in a screening of a Brazilian POI cohort, a heterozygous point mutation in COL4A6 was identified in one participant (Table 1), but other mutations were present in this individual as well [100]. Moreover, COL4A6

surrounds primordial as well as growing follicles and its deposition changes with age in humans [108]. In addition, in mice, Col4a6 expression was found to decrease upon the induction of follicles due to ovotoxicity, yet its direct role in folliculogenesis remains unknown [109].

DACH2

DACH2, located at Xq21.2, encodes dachshund family transcription factor 2. In mice, although Dach2 homozygous and Dach1 heterozygous knockouts are fertile, Dach1/Dach2 double knockouts are infertile with abnormal Mullerian duct development, suggesting the two function redundantly to support the development of the female reproductive tract [110, 111]. Although Dach2 appears to have a role in the reproductive tract, a potential role in the ovaries has not yet been demonstrated. In humans, DACH2 was first suggested to be a POI candidate as it was disrupted by a translocation in a POI patient [112]. Upon screening for this gene in a cohort of over 200 Italian women, missense variants were found in POI patients at a higher rate than in controls (Table 1) [76]. However, no further studies linking DACH2 to POI have since been published.

FANCB

FANCB, located at Xp22.2, encodes a Fanconi anemia-associated polypeptide which was first identified in 2003 as part of a Fanconi anemia multiprotein complex [113]. Fanconi anemia is an X-linked disorder characterized by bone marrow failure, increased risk of cancer, as well as reduced fertility [114]. Functionally, FANCB has been implicated in DNA damage repair [5]. Although RNA sequencing data revealed that it is not expressed in the fetal ovary [5], its functional role in females was determined by its disruption and the subsequent depletion of primordial follicles by 6 weeks of age [115]. Moreover, in males, Fancb disruption has been shown to impact primordial germ cell expansion [116], albeit alongside the influence of genetic background. FANCB has also been proposed as a candidate gene for nonobstructive azoospermia (Table 2) [117]. That said, the mechanism by which FANCB influences germ cell loss has not yet been elucidated and genetic background will likely influence penetrance of phenotype for various variants in different populations.

Table 2 Genes associated with a POI phenotype in mice

Gene (location on human X chromosome)	Mouse model	Reproductive phenotype (compared to wild type)	Reference
Sox3 (Xq27.1)	KO	Excess follicular atresia, more dead or malformed oocytes, subfertility	[123]
Fancb (Xp22.2)	KO	Reduced PGCs, primordial follicles depleted by 6 weeks	[115]
Huwe1 (Xp11.22)	Primary oocyte-specific KO	Infertile. Fewer GV oocytes, oocytes fail to mature and are morphologically abnormal	[155]
	Primordial oocyte-specific KO	Depletion of primordial follicles due to increased death	[155]
Zfx (Xp22.11)	KO	Reduced PGCs in embryo, dramatically reduced oocytes at all ages, with negligible counts at 18 weeks	[151]
	Het	Modest reduction in number of oocytes	[151]
Bmp15 (Xp11.22)	KO	Subfertility, reduced ovulation, development of cystic ovaries that reduce oocyte number	[55]
Fmr1 (Xq27.3)	PM (90 CGG repeats)	Subfertile, reduction in mature follicles at 35 days and 9 weeks, increased follicle atresia at 35 days, 16 weeks, 22 weeks	[42]
	Hom PM (130 GCC repeats)	Significant increase in atretic antral follicles, fewer corpora lutea, smaller litter size	[169]
	Het PM (130 CGG repeats)	Fewer corpora lutea	[169]
	KO	Earlier reduction in fertility, earlier decline in primordial follicles, higher proportion of antral and pre-antral follicles	[170]
Abcd1 (Xq28)	KO	Reduced fertility, increased interstitial cells, and needle-like lipid inclusions in ovary at 6 months	[171]
Ar (Xq12)	KO	Longer estrous cycle and subfertility. Reduced number of corpora lutea. Loss of follicles by 40 weeks due to GC apoptosis	[130]
	KO	Fewer follicles at 8 weeks and smaller litter size. Loss of follicles by 40 weeks	[131]
Emr (Xq28)	KO	Reduced ovarian reserve	[135]

Hom. = homozygous; Het. = heterozygous; KO = knockout; PM = premutation; PGCs = primordial germ cells; GV = germinal vesicles

Other candidate genes with evidence to support a role in POI

SOX3

SOX3, located at Xq27.1, encodes SRY-box transcription factor 3. Overexpression of SOX3 has been associated with sex reversal in humans and mice [118, 119], as well as hypopituitarism in humans [120]. Expression patterns in mice testes have demonstrated that Sox3 is implicated in the transition from stem cells to committed spermatogonia [121]. Furthermore, analysis of gene expression patterns throughout mouse ovarian folliculogenesis suggested that Sox3 is one of the major transcription factors regulating folliculogenesis [122]. While no variants have been documented in human cases of POI, both male and female Sox3 knockout mice have been shown to have reduced fertility (Table 2) [123].

AR

AR, located at Xq12, encodes an androgen receptor of the activated class I steroid receptors. As such, AR recognizes androgen response elements, and expression levels in tissues determine the response to hormones [124, 125]. AR has been linked to androgen insensitivity syndrome and X-linked spinal and bulbar dystrophy syndrome in males [125, 126]. AR contains a polymorphic tandem CAG repeat in the coding region, and increased size of the repeat is associated with X-linked spinal and bulbar dystrophy syndrome [125]. Androgen insensitivity syndrome has been linked to several variants of AR [126]. Otherwise, AR action has been shown to stimulate GC proliferation and modulate folliculogenesis [127, 128]. However, androgens can also have negative effects on follicle development and a balance in androgen action is required for female reproduction [129]. In mice, AR knockouts are sub-fertile and by 40 weeks of age, have a complete loss of ovarian function (Table 2) [130–132]. Despite these findings, in humans, variants in AR have not yet been detected through screening for POI. Specifically, in a cohort of 46 POI patients, CAG repeat length of AR was not associated with POI [18].

EMD

Emerin (EMD), is an inner nuclear envelope protein located in Xq28, and is mostly known for its role in cardiac and skeletal muscle function. Mutations in EMD have been linked to X-linked Emery-Dreifuss muscular dystrophy, characterized by muscle wasting with nuclear laminopathies [133]. On a molecular level, this nuclear lamina tethered protein interacts with several transcription factors, orchestrating gene expression and chromatin architecture [134, 135]. EMD also interacts with inner nuclear envelope protein, NEMP1, which regulates the size of ovarian reserve and oocyte developmental competence. Both proteins are highly expressed in oocytes of primordial follicles, and while Emd deficient female mice breed, their ovarian reserve is severely reduced [135].

LDOC1

LDOC1, located at Xq27.1, was first described in 1999, when its protein product was found to be localized to the nucleus, and was downregulated in certain cancer cell lines [136]. Protein product of this leucine zipper, belonging to LTR retrotransposon family is thought to regulate NFKB and STAT3 signaling [137]. Through analysis of cancer cells and other disease states, LDOC1 has been demonstrated to influence cell proliferation, apoptosis, cell cycle, and migration ability [137–140]. Through analysis of RNA sequencing data, LDOC1 was found to be expressed in the fetal ovary [5]. Single cell RNA sequencing of adult ovaries attributed expression of LDOC1 to a subset of primordial oocytes and granulosa cells (refer to https://eovary.ki.se/). As of now, LDOC1 has only been implicated in one case of POI, where a patient with secondary amenorrhea was found to have an X;3 translocation and a deletion spanning SPANX genes and LDOC1 on the intact chromosome. However, once again, it is possible that position effects may be responsible for POI in this patient, and their gene expression was not profiled [141].

HDX

HDX (highly divergent homebox), located at Xq21.2, was first proposed as a POI candidate gene as it was disrupted in a 17-year-old patient with secondary amenorrhea, who was discovered to have a X;15 translocation with a breakpoint disrupting HDX [142]. Although no variants of HDX have been directly documented in patients with POI, recent CNV analysis of the X chromosome in POI patients confirmed that region containing HDX [5]. RNA sequencing data of adult ovaries revealed that its expression is restricted to a subset of thecal cells as well as progenitor granulosa cells (refer to https://eovary.ki.se/).

MAP7D3

MAP7D3, located at Xq26.3, is a microtubule-binding protein that regulates microtubule assembly and stability and regulates spindle dynamics [143, 144]. Male Map7d3 knockout mice were fertile but had reduced spermatogonial stem cell population [145]. Other studies have also suggested that MAP7D3 is involved in sperm motility [146]. In humans, variants in MAP7D3 have been associated with non-obstructive azoospermia [53, 145]. Given its potential role in cell division, and its effect on spermatogonial stem cells in mice, this may suggest a potential role in female fertility. Although it is expressed in the fetal ovary, the only evidence of its potential impact on female reproduction is in the case of a 16-year-old girl presenting with psychological disorders and polycystic

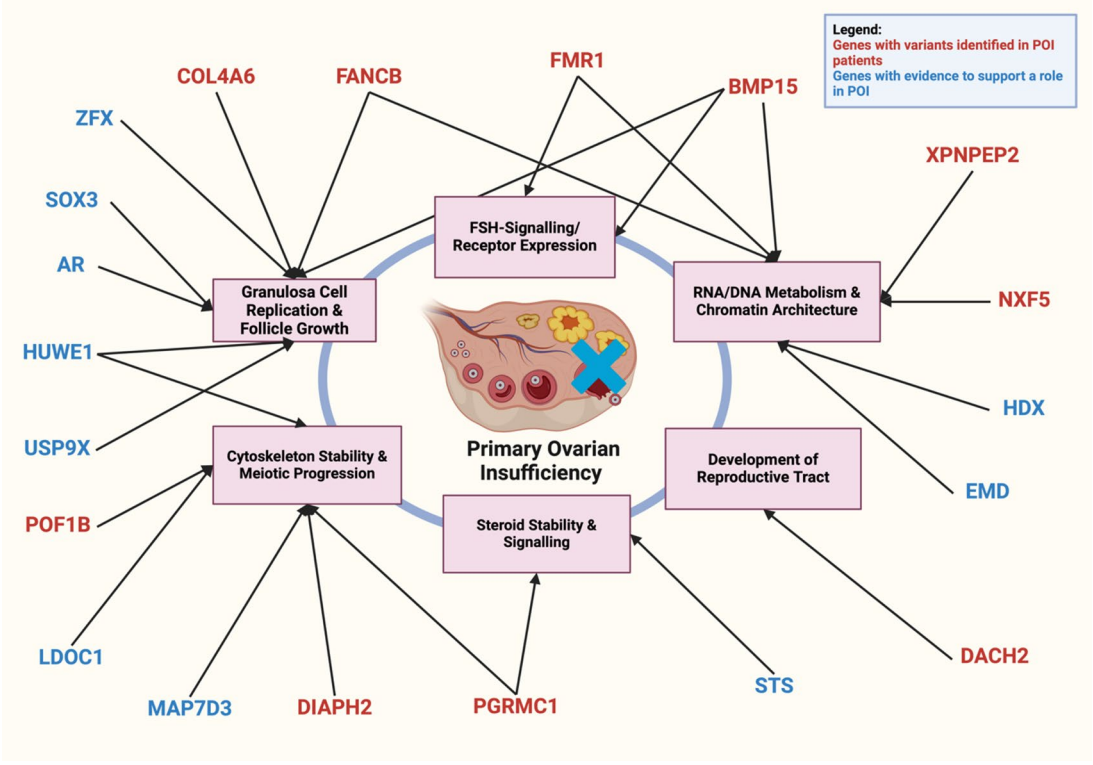

Fig. 2 Summary of X chromosomal genes linked to POI. Overview of the genes described within this review and their functions in relation to primary ovarian insufficiency. Arrows connecting gene names and functions describe the main functions described within the literature – suggested functions were not included herein. Figure created using BioRender

ovaries having a microduplication encompassing the MAP7D3 gene [147]. Transcripts for MAP7D3 are present in primordial oocytes, albeit at a low copy number. More abundant expression was observed in subset of GC and atretic theca (refer to https://eovary.ki.se/).

STS

STS, located at Xp22.31, encodes steroid sulfatase, a microsomal enzyme that hydrolyzes inactive steroid sulfates to form active steroids. STS activity has been demonstrated in GCs in vitro [148], and elevated expression has been linked to pathological states such as endometriosis (Yanaihara et al., 2005). In a CNV analysis, CNVs spanning Xp22.31 were found in both POI patients and controls, but interestingly, STS gene itself was only encompassed in CNVs in POI patients [149].

ZFX

ZFX, located at Xp22.11, encodes a zinc finger protein, a transcription factor which is the X-homolog for a previously described Y-encoded protein [150]. Though present in one of the described critical regions for POI, no variants have been identified in humans with POI. However, female Zfx knockout mice have reduced fertility (Table 2), and male knockouts have reduced sperm count [151]. Based on its expression patterns and localization in mouse oocytes, Zfx has been suggested to have a role in primordial follicle activation, specifically in oocyte-GC communication [152]. In addition to this suggested role in female fertility, ZFX has been identified as a candidate gene for non-obstructive azoospermia [153].

HUWE1

Mule in mice, or HUWE1 in humans, located at Xp11.22, encodes an E3 ubiquitin ligase involved in diverse cellular functions. Due to its role in neuronal development, synaptogenesis, and proliferation, HUWE1 has been associated with intellectual disabilities in both males and females [154]. Though not yet implicated in POI in humans, Mule is necessary for oocyte maturation in mice, as demonstrated by oocyte death and infertility in female Mule knockouts (Table 2). Interestingly, female mice that were heterozygous for Mule exclusively produced wildtype pups since all embryos lacking Mule arrested at the morula stage [155].

USP9X

Based on its gene location and known function, USP9X could be an excellent candidate responsible for POI. It is located at Xp11.4 within a critical chromosomal region involved in ovarian development and functions as a substrate-specific de-ubiquitin ligase. While it has a variety of protein targets, these must be regulated in a cell type and

a context specific fashion [156]. USP9X is highly expressed in primordial germ cells as well as developing oocytes [157]. Several studies identified increased CNV for region containing USP9X in POI patients [158, 159]. Amplification of USP9X gene in these cases could lead to an increased level of USP9X expression. In return, increased de-ubiquitin ligase activity could result in the stabilization of numerous protein targets, which could alter oocyte development. In addition, USP9X escapes inactivation, indicating that it may be sensitive to gene dosage (USP9X curation results for Dosage Sensitivity (clinicalgenome.org)). It is also intriguing that HUWE1 and USP9X share targets such as BRCA1 [160–162] and Mcl-1 [162], both of which have been implicated in the regulation of ovarian reserve [163, 164].

Conclusion

Altogether, this review highlights the critical role of several genes on the X chromosome in maintaining proper ovarian function (Fig. 2). However, only eight of the proposed gene candidates were found to have variants documented as being directly associated with POI. While some of these genes have established roles in ovarian biology, the potential role of many of the candidates remains speculative. Additionally, in mice, disruption of several proposed POI candidate genes was found to induce POI, their chromosomal position putting them within the previously identified critical regions for human folliculogenesis. Yet many of the genes identified in animal studies exceeded these boundaries (Fig. 1C), and their involvement in human ovarian functions remains to be established. Of the genetic variants associated with POI, some have been revealed through specific screening for candidate genes, while others were revealed through whole-exome sequencing of POI cohorts. As for variants discovered through the latter approach, the majority of POI patients were found to have multiple variants, often in multiple candidate genes. These findings support the notion that POI rarely has a monogenic cause and may rather be caused by the interplay between several different hypomorphic allelic states.

The heritability patterns support a genetic basis of POI. Due to need for both X chromosomes especially in germ cells biology, paternal family history of early menopause and POI should not be ignored. It may be as relevant in predicting the risk of developing POI as is maternal X chromosome lineage. Due to the substantial contribution of genetic factors in the etiology of POI, genetic screening could potentially be a valuable tool in assessing the risk of developing POI. The currently offered genetic screening is simply insufficient. Continued research and screening of POI cohorts will help to identify candidate alleles, which could be subsequently used for biological studies in humanized animal models. This is the only way we will be establish a causative link between human allelic variants and their impact on ovarian biology.

Abbreviations

AR	Androgen receptor
BMP15	Bone morphogenic protein 15
CNV	Copy number variations
COL4A6	Collagen type IV alpha–6
DACH2	Dachshund family transcription factor 2
DIAPH2	Diaphanous 2
EMD	Emerin
FANCB	Fanconi anemia–associated polypeptide
FM	Full mutation
FMRP	Fragile X retardation protein
FMR1	Fragile X messenger ribonucleoprotein 1
FSH	Follicle–stimulating hormone
FSHR	FSC receptor
FXS	Fragile X syndrome
FXPOI	Fragile X–associated premature ovarian insufficiency
GC	Granulosa cell
HDX	Highly divergent homebox
HUWE1	HECT, UBA, and WWE domain–containing 1, E3 ubiquitin
LDOC1	Leucine zipper down–regulated in cancer
MAP7D3	Microtubule–binding protein domain–containing 3
NXF5	Nuclear RNA export 5
PGC	Primordial germ cells
PGRMC1	Progesterone receptor membrane component 1
PM	Premutation
POF	Premature ovarian failure
POF1B	Premature ovarian failure 1B
POI	Primary ovarian insufficiency
SOX3	SRY–box transcription factor 3
STS	Steroid sulfatase
TS	Turner syndrome
USP9X	Ubiquitin specific peptidase 9 X–linked
XCI	X chromosome inactivation
XPNPEP2	X–prolyl aminopeptidase P
ZFX	Zinc finger protein X–linked

Supplementary Information

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Supplementary Material 1 [62–65, 67, 69–72]

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