Genetics of premature ovarian insufficiency and the association with X-autosome translocations

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Abstract

Premature ovarian insufficiency (POI) is the cessation of menstruation before the age of 40 and can result from different etiologies, including genetic, autoimmune, and iatrogenic. Of the genetic causes, single-gene mutations and cytogenetic alterations, such as X-chromosome aneuploidies and chromosome rearrangements, can be associated with POI. In this review, we summarize the genetic factors linked to POI and list the main candidate genes. We discuss the association of these genes with the ovarian development, the functional consequences of different mutational mechanisms and biological processes that are frequently disrupted during POI pathogenesis. Additionally, we focus on the high prevalence of X-autosome translocations involving the critical regions in Xq, known as POI1 and POI2, and discuss in depth the main hypotheses proposed to explain this association. Although the incorrect pairing of chromosomes during meiosis could lead to oocyte apoptosis, the reason for the prevalence of X-chromosome breakpoints at specific regions remains unclear. In most cases, studies on genes disrupted by balanced structural rearrangements cannot explain the ovarian failure. Thus, the position effect has emerged as a putative explanation for genetic mechanisms as translocations possibly result in changes in overall chromatin topology due to chromosome repositioning. Given the tremendous impact of POI on women's quality of life, we highlight the value of investigations in to the interplay between ovarian function and gene regulation to deepen our understanding of the molecular mechanisms related to this disease, with the ultimate goal of improving patients' care and assistance.

Reproduction (2020) **160** R55–R64

Premature ovarian insufficiency

Premature ovarian failure (POF), or premature ovarian insufficiency (POI) in the updated nomenclature (Welt 2008), is a condition generated by the early depletion or non-functionality of the ovarian reserve (Fortuno & Labarta 2014). It affects 1–2% of women younger than 40 years of age and 0.1% of women younger than 30 years (Coulam *et al.* 1986), leading to defects in the reproductive system and infertility in those patients.

POI manifestation may vary among individuals, presenting either with severe forms, such as absent pubertal development and primary amenorrhea, or milder forms with early post-pubertal onset with the disappearance of menstrual cycles (secondary amenorrhea) and defective folliculogenesis (Genesio *et al.* 2015). It is generally characterized by elevated gonadotropin levels, hypoestrogenism, and amenorrhea, showing menopausal levels of follicle-stimulating hormone (FSH), estradiol, and anti-müllerian hormone (AMH) (Visser *et al.* 2012). The symptoms may include menopausal experience, with hot flashes, night sweats, and vaginal dryness, associated with the loss of fertility and an increased risk of osteoporosis (Nelson *et al.* 2009).

For many women with POI, the treatment is based on symptom relief using exogenous steroids, with estrogen and progestin replacement therapy, starting as soon as diagnosed (De Vos *et al.* 2010). Some measures to protect against osteoporosis should be recommended for patients with estrogen deficient levels, including the increase of physical exercises and calcium and vitamin D rich diet, as well as avoiding risk factors, such as smoking and high alcohol intake (Drillich & Davis 2007).

POI etiology

Among the main causes of POI are (1) iatrogenic factors, for example, pelvic surgery and chemotherapy, (2) environmental factors, for example, viral infections and toxins, (3) autoimmune diseases with anti-ovarian antibodies resulting in ovarian damage, and (4) genetic alterations, including point mutations and chromosome imbalances involving X chromosome or autosomes (Goswami & Conway 2007). Despite clinical advances, more than 50% of POI cases remain idiopathic (Persani *et al.* 2010), and can present with sporadic or familial forms (van Kasteren & Schoemaker 1999). Genetic factors may be the cause, or simply predispose

the individual to the disease. Regarding POI, those factors can be identified in approximately 20–25% of cases (Qin *et al.* 2015).

Genetic studies and candidate genes

The identification of causal genes related to POI in non-syndromic families can be challenging, since infertility is the main phenotype, usually resulting in absent informative family histories (Woad *et al.* 2006). Nonetheless, ~10–15% of the cases have an affected first-degree relative, indicating significant genetic etiology (van Kasteren & Schoemaker 1999), and population genetic studies have revealed pathogenic variants all over the genome (Fig. 1A and Table 1).

With the improvement of next-generation sequencing techniques, whole-exome sequencing (WES) aggregation studies have explored the role of rare damaging coding variants on the ovarian development and related phenotypes. Those studies have confirmed the involvement of a handful of long-standing POI candidate genes and pointed to novel variants in their coding sequence (Yatsenko & Rajkovic 2019), with higher reliability. The rising of those unbiased approaches have also enabled the application of WES in non-syndromic POI, pinpointing several genes not previously associated (Qin *et al.* 2015). Jolly *et al.* performed WES in 42 affected females with POI from 36 unrelated families

and identified likely damaging variants in eight known genes and predicted deleterious variants in four genes not previously associated with POI (Jolly *et al.* 2019). Recently, additional studies performed WES in single POI pedigrees and identified variants in genes known to be associated with POI, such as *SALL4*, *EIF4ENIF1*, and *HFM1*, corroborating the relevance of this method as a powerful diagnostic tool (Wang *et al.* 2019, Zhao *et al.* 2019, Zhe *et al.* 2019).

Another useful method, genome-wide association study (GWAS) provides an agnostic search, with no *a priori* expectations, in which hundreds of thousands of common genetic variants are screened to assess their association with a trait. The variability of menopausal age has been evaluated by GWAS, providing additional information on the combined impact of identified variants to this specific trait (Stolk *et al.* 2012, Perry *et al.* 2013). In addition, even though most GWAS on cohorts of POI patients were conducted in small sample sizes, those efforts were able to pinpoint association or susceptibility of POI phenotype with eight genes and also regulatory regions (Corre *et al.* 2009, Qin *et al.* 2015).

The genetic architecture of POI is composed of rare damaging variants as well as common variants with smaller effect. In Table 1, it is possible to observe that these different mutational mechanisms can impact genes within similar biological pathways, leading to POI through diverse cellular processes that are related

Figure 1 Schematic view of most relevant POI-associated genomic regions with candidate genes (further described in Table 1). (A) Genomic localization (red arrow) of autosomal candidate genes driven by point mutations. (B) Genomic localization (red arrow) of candidate genes in the chromosome X, driven by point mutations. (C) Genomic localization of POI1 and POI2, the X-linked genomic regions commonly affected by POI-associated structural variants. On the right, the green and orange blocks schematically represent the approximate disruption frequency among POI-associated translocations and deletions, respectively, according to genomic location (Mumm *et al.* 2001, Portnoi *et al.* 2006, Rizzolio *et al.* 2006, Baronchelli *et al.* 2011).

Table 1 Main biological pathways implicated in POI-associated genetic variants and most relevant candidate genes.

Biological pathways/gene	Study type	References
Transcription factor involved in sexual development		
<i>NR5A1</i>	WES	Eggers <i>et al.</i> (2015)
<i>WT1</i>	CGES	Wang <i>et al.</i> (2015)
<i>FOXL2</i>	WES	Yang <i>et al.</i> (2017)
<i>BMP15</i>	WES	Kumar <i>et al.</i> (2017)
<i>GDF9</i>	CGES	Kumar <i>et al.</i> (2017)
<i>FIGLA</i>	WES	Tosh <i>et al.</i> (2015)
<i>NOBOX</i>	WES	França <i>et al.</i> (2017)
<i>SALL4</i>	WES	Wang <i>et al.</i> (2019)
Homologous recombination repair during meiosis		
<i>SYCE1</i>	WES	de Vries <i>et al.</i> (2014)
<i>SPIDR</i>	WES	Smirin-Yosef <i>et al.</i> (2017)
<i>PSMC3IP</i>	WES	Zangen <i>et al.</i> (2011)
DNA mismatch repair		
<i>MSH4</i>	WES	Carlosama <i>et al.</i> (2017)
<i>MSH5</i>	WES	Guo <i>et al.</i> (2017)
<i>ERCC6</i>	WES	Qin <i>et al.</i> (2015)
<i>EXO1</i>	GWAS	Stolk <i>et al.</i> (2012)
<i>UIMC1</i>	GWAS	Stolk <i>et al.</i> (2012)
Double strand break repair		
<i>MCM8</i>	WES	AlAsiri <i>et al.</i> (2015)
<i>MCM9</i>	WES	Wood-Trageser <i>et al.</i> (2014)
<i>FANCI</i>	GWAS	Stolk <i>et al.</i> (2012)
<i>HELQ</i>	GWAS	Stolk <i>et al.</i> (2012)
DNA replication		
<i>PRIM1</i>	GWAS	Stolk <i>et al.</i> (2012)
<i>TLK1</i>	GWAS	Stolk <i>et al.</i> (2012)
<i>POLG</i>	GWAS	Stolk <i>et al.</i> (2012)
<i>HFM1</i>	WES	Zhe <i>et al.</i> (2019)
mRNA transport and translation		
<i>FMR1</i>	CGS	Dean <i>et al.</i> (2018)
<i>STAG3</i>	WES	Caburet <i>et al.</i> (2014)
<i>KHDRBS1</i>	WES	Wang <i>et al.</i> (2017)
<i>NUP107</i>	WES	Weinberg-Shukron <i>et al.</i> (2015)
Germ cell development		
<i>NANOS3</i>	CGES	Santos <i>et al.</i> (2014)
<i>eIF4ENIF1</i>	WES	Zhao <i>et al.</i> (2019)
<i>SOHLH1</i>	WES	Jolly <i>et al.</i> (2019)
Sexual hormone pathway		
<i>PGRMC1</i>	CGES	Mansouri <i>et al.</i> (2008)
<i>AMH</i>	WES	Qin <i>et al.</i> (2014a)
<i>AMHR2</i>	WES	Qin <i>et al.</i> (2014a)
<i>FSHR</i>	WES	Bramble <i>et al.</i> (2016)
Immune pathway		
<i>IL11</i>	GWAS	Stolk <i>et al.</i> (2012)
<i>NLRP11</i>	GWAS	Stolk <i>et al.</i> (2012)
<i>PRRC2A</i>	GWAS	Stolk <i>et al.</i> (2012)

CGES, candidate gene exon sequencing; CGS, candidate gene sequencing.

to ovarian development and oogenesis. Since oogenesis is a process that involves a complex interaction between the oocyte and somatic surrounding cells, it calls for a fine orchestration of multiple transcriptional regulators (Pangas *et al.* 2006). The combination of the most relevant and consistent results leveraged by genetic studies pointed to several causative mutations in transcription factors, which are currently considered as the most reliable candidate genes for POI (Qin *et al.* 2014b).

In this scenario, genetic screenings have proven to be useful to identify potentially causative genes based on their role in folliculogenesis and ovarian function (Qin *et al.* 2012). A number of studies have used *in vitro* cellular modeling to demonstrate that some of the rare genomic variants associated with POI indeed cause functional impairments in their correspondent mutated proteins, as shown for *WT1*, *NR5A1*, *FSHR*, *NANOS3*, and *BMP15* (Santos *et al.* 2014, Wang *et al.* 2015, Liu *et al.* 2017, Robevska *et al.* 2018). An interesting example is a study performed by Wang *et al.* which assayed *in vitro* two *WT1* missense variants and showed that they modulated the expression of downstream genes required for granular cells proliferation, differentiation and interaction with oocytes, suggesting *WT1* gene variants as plausible causes for POI (Wang *et al.* 2015).

However, few studies have directly accessed the association between POI-associated genes and the ovarian function and/or development. Transcription and growth factors were preferentially screened (*NOBOX*, *FIGLA*, *WT1*, and *FOXL2*) in functional studies, which are represented in Fig. 2A. These studies were performed mainly two types of experiments: (1) gene suppression (by knockout or knockdown) in animal models and (2) patients' gene variants knockin in animal models or gonadal *in vitro* cellular systems, in which the impact in ovarian development was assessed (Dong *et al.* 1996, Lechowska *et al.* 2011, Gao *et al.* 2014, Qin *et al.* 2018).

The epistasis interaction between different transcription factors associated with POI has also been investigated (Fig. 2B). Some studies have demonstrated that variants found in *NOBOX* in POI patients had an impact in the expression of *GDF9*, a growth differentiation factor gene, whose role in oocyte differentiation is well established. Similarly, an indel mutation identified in *FOXL2* impaired its function, preventing it to activate *StAR* promoter, a steroidogenic regulatory protein essential for follicle development. (Bouilly *et al.* 2011, Chai *et al.* 2017, Li *et al.* 2017, Men *et al.* 2017). In early functional studies, *StAR* was demonstrated to be restricted to most steroidogenic compartments of the human ovary, thecal and luteinized granulosa cells, which was shown to be particularly relevant for the production of large amounts of progesterone (Kiriakidou *et al.* 1996).

Functional studies have provided significant advances in the understanding of ovarian development and follicle maturation, especially related to their gene regulatory pathways, emphasized by the frequent involvement of transcription factors. Further research will be crucial to address the significance of these findings in human POI pathogenesis, assessing the fine regulation of physiological functioning in the reproductive system. POI-associated genes from other functional classes, for example, DNA replication and repair, remain to be investigated in functional assays of the ovarian development and will require further attention in future studies in the field.

X chromosome abnormalities

Among the genetic causes of POI, X chromosome numerical and structural alterations are the commonest imbalances, representing about 13% of the cases (Cordts *et al.* 2011). POI involving X chromosomal abnormalities includes X monosomy or trisomy, X

chromosome partial deletions, isochromosomes, inversions, and balanced X-autosomal translocations (Sala *et al.* 1997, Sherman 2000, Goswami & Conway 2005, Moyses-Oliveira *et al.* 2015), showing the importance of karyotype and cytogenomic evaluation in patients with ovarian dysgenesis.

Figure 2 Functional studies indicate the importance of transcription factors for ovarian development. (A) Ovarian histological analysis of *GDF9* and *NOBOX* mutant mice showed defects in follicle development, leading to infertility (Dong *et al.* 1996, Lechowska *et al.* 2011). While *WT1* homozygous mice were not viable, heterozygous female mice presented with decreased follicle number and altered expression of *WT1* gene targets, resulting in a subfertility of ~15% (Gao *et al.* 2014). *FIGLA* knockout in zebrafish resulted in 'all-male' development, in which an estrogen treatment failed to rescue the phenotype. Transcriptome-wide analysis demonstrated an altered regulation of pathways related to oocyte development (Qin *et al.* 2018). (B) Mutations in *NOBOX* and *FOXL2* impact their transcription factor activity, preventing them to bind at target genes, essential for follicle development (Bouilly *et al.* 2011, Chai *et al.* 2017, Li *et al.* 2017). Steroidogenesis is regulated by H19/*let-7* axis by activating *StAR* expression (Men *et al.* 2017).

Among the aneuploidies, Turner syndrome (X monosomy) has an incidence of 1:2500 and is associated with short stature, gonadal dysgenesis, and primary amenorrhea (Hook & Warburton 2014). Even though most women with Turner syndrome are infertile due to gonadal dysgenesis, a minority of these patients reach menarche, most of them with the monosomy in mosaic (45,X/46,XX), which can present ovaries with a relatively low number of follicles (Abir *et al.* 2001).

Another frequently observed X chromosome aneuploidy is the trisomy X (47,XXX), which occurs in approximately 1:1000 females, but only 10% of the cases are diagnosed (Cordts *et al.* 2011). In trisomy X, pubertal onset and sexual development usually follow the typical trajectory; however, there are several reports of patients presenting with POI characterized by endocrine findings of hypergonadotropic hypogonadism (Villanueva & Rebar 1983).

Regarding the structural rearrangements involving the X chromosome, the isochromosome (46,X,i(X)(q10)) is frequently observed, with most patients presenting with Turner syndrome phenotype, indistinct of the 45,X patients. Deletions and translocations have also been described in POI, and show enrichment for breakpoints within the long arm of the X chromosome (Rizzolio *et al.* 2006). Deletions usually present breakpoints in the Xq24–Xq27 region (Powell *et al.* 1994, Eggermann *et al.* 2005), while translocation breakpoints occur predominantly from Xq13 to Xq21 (Powell *et al.* 1994, Davison *et al.* 2000). Based on these observations, the Xq24–q27 and Xq13.1–q21.33 regions became known as POI critical regions 1 and 2, respectively (Summitt *et al.* 1978) (Fig. 1C).

POI and X-autosome translocations

POI patients represent an important group among X-autosome translocation carriers, independently of which autosome is involved in the rearrangement. POI is observed in approximately 50% of translocations affecting the X chromosome (Therman *et al.* 1990). It is important to mention that the breakpoints usually fall in one of the two POI critical regions, while breakpoints outside these regions rarely result in ovarian development impairment (Mumm *et al.* 2001).

Encompassed by POI2 region, the chromosome band Xq21 concentrates around 80% of the breakpoints (Portnoi *et al.* 2006, Rizzolio *et al.* 2006) (Fig. 1C). Interestingly, interstitial deletions of this region do not seem to affect ovarian function (Cremers *et al.* 1989, Aboura *et al.* 2009), suggesting that this phenotype might not be related to the loss of the Xq21 region. In addition to the fact that Xq21 monosomy is not associated with ovarian phenotypes, this chromosomal segment is identified as a gene-poor region (Rizzolio *et al.* 2006). Thus, the main hypotheses proposed to explain the relationship between balanced X-autosome

translocations and POI are related to gene disruption, meiosis error, and/or position effect.

Gene disruption hypothesis

In this first hypothesis regarding the association of POI with X-autosome translocation, it has been proposed that a group of genes at the critical regions would be involved in ovarian function, leading to gonadal dysgenesis (Davison *et al.* 2000). However, only a few X-linked genes were pointed as a candidate for POI (Fig. 1B), and in some patients, Mumm *et al.* found the breakpoints in the X-autosome translocations located in regions with no genes (Mumm *et al.* 2001).

Similarly, Moysés-Oliveira *et al.* determined the breakpoint of three patients with X-autosome translocations and POI, all of them with X chromosome breakpoint at POI2, but with no gene disruptions capable of explaining their ovarian dysgenesis (Moyses-Oliveira *et al.* 2015). Genesio *et al.* described one patient with a balanced translocation between Xq21 (POI2 region) and 1q41, presenting short stature and POI in whom no gene disruptions were identified but gene expression alterations of ovarian related genes were observed (Genesio *et al.* 2015).

Although most of the breakpoints in Xq21 have been mapped to gene-free genomic regions, two genes (*POF1B* and *DACH2*) were screened to mutations in over 200 patients with POI (Bione *et al.* 2004). Rare mutations were found for both genes; however, the genetic analysis failed to show association with *POF1B* and suggested that *DACH2* might be related to the POI phenotype, proposing that further investigation should be necessary to elucidate this association.

These findings, similar to others, reinforce that more complex mechanisms should be involved in POI associated with X-autosome translocations (Toniolo & Rizzolio 2007).

Meiosis error hypothesis

It has been shown that some X chromosomal imbalances result in increased oocyte atresia since, after meiosis initiation, both X chromosomes are active in germ cells. The loss of one X chromosome constitutes true monosomy in these cells, and indeed, ovarian dysgenesis is one of the main symptoms in Turner syndrome (Therman *et al.* 1990). During the development of Turner syndrome fetuses, normal ovaries development and primordial germ cells are observed up to the third month of gestation, followed by a cellular apoptosis process resulting in gonadal connective tissue devoid of follicles (Singh & Carr 1966). The absence of one chromosome in Turner syndrome could also result in perturbations in telomere length and/or function, contributing to the association with POI, since telomeres are essential for proper

chromosomal pairing, and other early steps in meiosis and oogenesis (Jackson-Cook 2019).

Similarly, this hypothesis suggests that translocations, disrupting genes or not, could influence the X chromosome dynamics during the formation and maintenance of ovarian follicles (Mumm *et al.* 2001). It has been proposed that the incorrect pairing of translocation-derived chromosomes could affect the checkpoints between meiosis phases in germ cells and lead to oocyte apoptosis (Schlessinger *et al.* 2002). It is important to consider the difficulty of properly addressing this matter, due to restriction of accessing target gonadal cells in the developing ovary, combined with the challenge of modeling cellular states with both X chromosomes in the active state, especially during gonadal development.

Additionally, such suggestions do not consider the enrichment for translocations in the POI critical regions. Although Xp and Xq deletion carriers can present both normal and deficient ovarian development, a higher percentage of Xq deletion carriers shows gonadal abnormalities, suggesting a more complex level of organization related to gonadal development in this chromosome.

Position effect hypothesis

The position effect hypothesis refers to changes in the overall chromatin topology due to chromosome repositioning after the translocation. Chromosome positioning during interphase is not random (Lanctot *et al.* 2007) and chromatin is organized in chromosome territories, or nuclear domains (Cremer *et al.* 2006). Genomic architecture is built upon physical interaction networks between different DNA segments (Miele & Dekker 2008), thought to be essential for the correct genome regulation and biological functions of cells, such as transcription, replication, and DNA repair (Bonev & Cavalli 2016).

The development of advanced chromatin conformation capture techniques, such as Hi-C (Lieberman-Aiden *et al.* 2009, Belton *et al.* 2012), allowed the identification of an even more complex and well-defined three-dimensional organization, as known as topological-associated domains (TADs) (Dixon *et al.* 2012). Thus, chromosome rearrangements can lead to TAD disruptions and three-dimensional disorganization that can modify the interactions among regulatory elements and their target genes, possibly perturbing gene expression profiles (Zepeda-Mendoza *et al.* 2017, Despang *et al.* 2019, Finn & Misteli 2019, Ghavi-Helm *et al.* 2019).

The occurrence of a reciprocal translocation could shift the derived chromosomes from their usual positions, perturbing specific *cis*- and *trans*-acting DNA regulatory elements and modifying the DNA accessibility in large-scale (Harewood *et al.* 2010). It has been demonstrated

that chromosomal breaks or deletions in gene-poor regions, like Xq21, could interfere with the functioning of genes localized far away from the breakpoint region since they could contain regulatory sequences (Nobrega *et al.* 2004). Therefore, POI due to X-autosome translocation could be related to the expression dysregulation of ovarian genes and not necessarily to the direct disruption of their sequence.

In males and females across species, only one X chromosome is active, and a combination of upregulation and repression states was already observed during germline development, possibly to reach similar expression levels between X chromosome genes and autosomal genes (Cheng & Disteche 2006). This increased X-chromosome expression in female and male cells was confirmed by single-cell RNA-seq, which indicated that the X chromosome achieved upregulation by elevated burst frequencies (Larsson *et al.* 2019). However, during female gametogenesis, the POI2 critical region presents a diminished gene expression in oocytes, which is not found elsewhere along the X chromosome nor in the autosomes, downregulation probably due to an oocyte-specific regulation (Rizzolio *et al.* 2007). In oocytes, since both X chromosomes are active, the upregulated state would not be necessary. Thus, it has been suggested that, in balanced X-autosome translocations, these epigenetic mechanisms responsible for diminishing the expression of the Xq13–q22 region could be propagated to autosomal segments, conferring heterochromatic characteristics to this fragment (Rizzolio *et al.* 2009). Since there is no preferred autosomal partner in t(X;A) associated with ovarian phenotypes, this would implicate that many genes spread throughout the genome can be causative of POI, and until now, the position effect mechanism related to POI2 region is not well defined. Nevertheless, POI candidate genes (Table 1) do not seem to be clustered in any specific genomic regions or chromosomes.

Since POI2 is thought to be a region poor in genes, but rich in regulatory elements, it is plausible to hypothesize that this region is essential for the correct functioning of genes related to ovarian development. The regulation of this critical region could be related to its spatial genome organization, which would be directly affected by the translocation breakpoint. Then, ovarian dysfunction due to X-autosome translocations in POI would be the result of chromosomal segments shifting from their correct nuclear positioning regulatory alterations after a three-dimensional shifting (Rizzolio *et al.* 2009).

It is worth to mention that the previously discussed hypotheses are not necessarily mutually exclusive; for instance, different kinds of rearrangements, even between autosomes, can result in POI, pointing to meiosis error, or disruption of autosomal genes. In contrast, X-autosome translocations with breakpoints at the critical regions, that is, POI1 and POI2, are much more frequent, suggesting a high correlation of

regulatory elements in this region with the phenotype. Additionally, most candidate genes for POI are not found in the critical regions as previously described.

Conclusion

The genetic factors underlying POI etiology are still poorly understood and seem to compose a complex pathogenic molecular mechanism. A wide range of biological processes (i.e. DNA replication and repair, mRNA transport and translation, germ cell development, sexual hormone pathways, and immune pathways) are frequently disrupted by common and rare genetic variation. Although animal modeling of POI-associated transcription factors has been valuable for the field advancement, there is a vast list of genes with other biological roles that remain untouched by functional studies during the ovarian development. In a similar vein, chromosome rearrangements might disturb chromatin organization and result in consequences to phenotypic manifestations when this nuclear structure is perturbed. Since gene regulation is known to be causally linked to chromatin dynamics at interphasic nuclei, the investigation of the molecular pathways underlying the ovarian phenotype can represent a valuable resource to elucidate the regulatory control related to this precise organization.

We must consider that premature ovarian insufficiency is likely to be a multifactorial origin disorder that affects women's quality of life, which can often express depressive feelings, especially related to impaired fertility. For those women, infertility can be a significant issue, and although some of them might sporadically ovulate, this is not easily predictable. Considering the relatively high prevalence of X-autosome translocations related to POI, we propose that further investigations of this group of patients should be conducted in order to identify the interplay between this phenotype, genomic structural variants, and the specific X chromosome critical regions. This detailed screening can catalyze efforts to elucidate the disorder and possibly prevent some of the drawbacks for the patients, developing new diagnostic methods and better-targeted treatments.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work was supported by São Paulo Research Foundation (FAPESP) (grant 2014/11572-8 to M I M) and by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES).

Author contribution statement

Adriana Di-Battista performed the literature review and wrote the manuscript. Mariana Moysés-Oliveira and Maria Isabel Melaragno revised and edited the manuscript. Maria Isabel Melaragno was responsible for funding acquisition.

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Received 6 March 2020

First decision 11 May 2020

Revised manuscript received 17 June 2020

Accepted 3 August 2020