

REVIEW

Genes involved in human premature ovarian failure

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Abstract

Premature ovarian failure (POF) is an ovarian defect characterized by the premature depletion of ovarian follicles before the age of 40 years, representing one major cause of female infertility. POF relevance is continuously growing because women tend to conceive ever more frequently in their thirties and forties. POF can present very early with a pubertal defect. More frequently, it is the end stage of an occult process (primary ovarian insufficiency, POI) affecting ~1–2% of under-40 women. POI is a heterogeneous disease caused by a variety of mechanisms. Though the underlying cause remains unexplained in the majority of cases, various data indicate that POI has a strong genetic component. These data include the existence of several causal genetic defects in humans, experimental and natural models, as well as the frequent familiarity. The variable expressivity of POI defect in women of the same family may indicate that, in addition to some monogenic forms, POI may frequently be considered as a multifactorial defect resulting from the contribution of several predisposing alleles. The X chromosome-linked defects play a major role among the presently known causal defects. Here, we review the principal X-linked and autosomal genes involved in syndromic and nonsyndromic forms of POI with the wish that this list will soon become upgraded because of the discovery of novel contributing mechanisms. A better understanding of POI pathogenesis will indeed allow the construction of tests able to predict the age of menopause in women at higher risk of POI.

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Introduction

The median age of natural menopause in Caucasian women is 50 ± 1 years (Morabia & Costanza 1998); however, ~1% of women under the age of 40 years and 0.1% under the age of 30 years experience premature menopause (Coulam *et al.* 1986). Premature ovarian failure (POF) is classically defined as 4–6 months of amenorrhea in women under the age of 40 years associated with menopausal level of serum gonadotropins (FSH >30 U/l) and hypoestrogenism and is also referred as hypergonadotropic hypogonadism. Depending on the age of onset, the disorder can manifest as primary amenorrhea (PA), without menarche, or secondary amenorrhea (SA) after the pubertal development (Timmreck & Reindollar 2003). Based on evidence that POF has a long and variable clinical course, it has been recently proposed the term of primary ovarian insufficiency (POI), as a more scientifically accurate definition, to better describe the

progression toward the cessation of ovarian function (Welt 2008, Nelson 2009). POI generates two types of consequence. One is premature hypoestrogenism, which in turn causes the premature aging of several tissues, targets of estrogen action, and thus increasing the risk of osteoporosis, cardiovascular diseases, or neurodegenerative diseases. The second consequence is infertility. Hypoestrogenism can nowadays be satisfactorily treated by hormone replacement therapy to be generally given until the age of physiological menopause. In contrast, fertility cannot be recovered when the diagnosis of POF (or end-stage POI) is generally reached, and is often compromised in the early phases of the disease when the clinical manifestations are absent. For this reason, research in this field aims at the identification of markers able to predict the premature cessation of menses, thus allowing women at risk of POF to plan an early conception. Biochemical markers (FSH, estradiol (E_2), inhibin B, or anti-Müllerian hormone (AMH))

are nowadays mainly useful to confirm a diagnosis indicated by menstrual irregularity. Prediction of POI therefore relies on a better understanding of its pathogenesis.

Mechanisms leading to a premature impairment of the ovarian reserve

Around 7 million primordial follicles are present in the developing ovary during embryogenesis (Fig. 1A). The large majority of these follicles are lost during fetal and postnatal life by atresia, and only 400–500 of them are generally ovulated before physiological menopause. Instead, as shown in Fig. 1B, the possible mechanisms at the origin of POI can be a) an initial decrease in the primordial follicle pool; b) an accelerated follicular atresia; or c) an altered maturation/recruitment of primordial follicles. However, in most of the cases, including a subset associated with PA and gonadal dysgenesis (Reynaud *et al.* 2004, Fechner *et al.* 2006), ovarian insufficiency occurs because of an anticipated depletion of the primordial follicular pool. The etiological causes that may activate such mechanisms are highly heterogeneous and include chromosomal, genetic, autoimmune, metabolic, infectious, and iatrogenic factors (Goswami & Conway 2005). At present,

about 25% of all forms of POF can be classified as iatrogenic and are related to cancer treatment, but more than 50% of the cases remain idiopathic, so that the origin of POI is still largely unknown.

Is genetic origin prevalent in POI?

Several observations support a prevalent role of genetic mechanisms in the pathogenesis of idiopathic POI.

First, the ovarian defect of patients with Turner's syndrome (TS) or related X chromosome abnormalities indicates the essential role played by X-linked genes in ovarian function. Furthermore, the genetic origin of POI is supported by the existence of monogenic forms in humans and animal models indicating also the relevance of non-X genetic loci for POI pathogenesis. Another clue is the important role of familiarity in the determination of menopausal age. Epidemiological evidences support the heritability of menopausal age between mothers and daughters (Cramer *et al.* 1995, Torgerson *et al.* 1997, Murabito *et al.* 2005), and recent genome-wide studies found loci on chromosomes 5, 6, 13, 19, and 20, which were significantly associated with age at natural menopause (He *et al.* 2009, Perry *et al.* 2009). Interestingly, POI has also a frequent familial incidence. In large series of POF women, the incidence of familial forms ranges from 4 to 31%, depending on the population

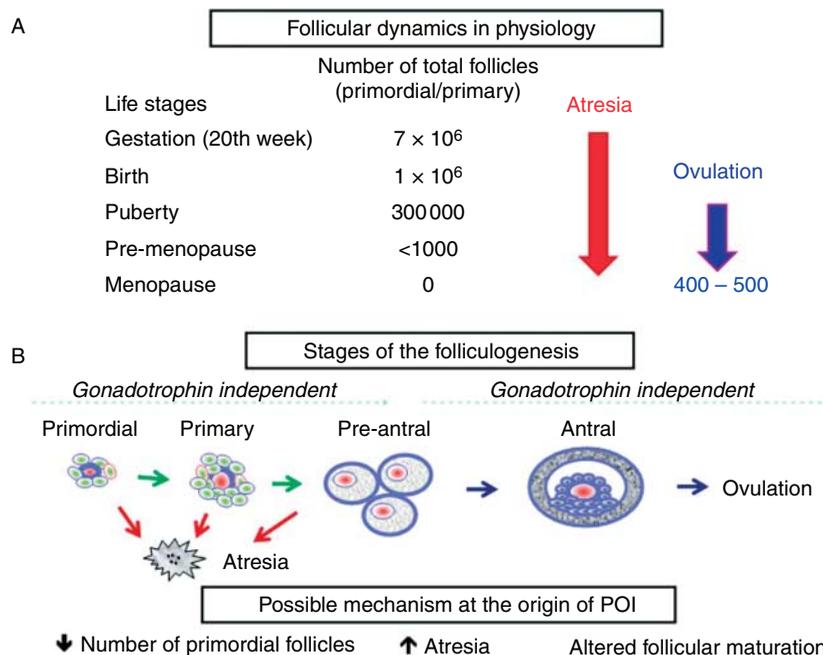


Figure 1 (A) Follicular dynamics and illustration of the folliculogenesis process in physiology. (B) The possible mechanisms generating POI may affect different stages of folliculogenesis.

Table 1 List of genetic defects associated with primary ovarian insufficiency (POI)

	Frequency in POI	Principal references
X chromosome defects		
Turner's syndrome and related defects	4–5%	Zinn & Ross (1998)
Fragile X syndrome (<i>FMR1</i> premutation)	3–15%	Marozzi <i>et al.</i> (2000) and Wittenberger <i>et al.</i> (2007)
<i>DIAPH2</i> disruption (translocation)	Unknown	Bione <i>et al.</i> (1998)
<i>BMP15</i> variants	1.5–12%	Di Pasquale <i>et al.</i> (2004), Dixit <i>et al.</i> (2006a), Laissue <i>et al.</i> (2006), Rossetti <i>et al.</i> (2009), Wang <i>et al.</i> (2010) and Tiotiu <i>et al.</i> (2010)
<i>PGRMC1</i> variants	1.5%	Mansouri <i>et al.</i> (2008)
Autosomal defects		
Complex diseases		
Galactosemia (<i>GALT</i>), BPES (<i>FOXL2</i>), APECED (<i>AIRE</i>), mitochondrial (<i>POLG</i>), Demirhan syndrome (<i>BMPR1B</i>), PHP1a (<i>GNAS</i>), ovarian leukodystrophy (<i>EIF2B</i>), ataxia telangiectasia (<i>ATM</i>)	Rare	Sedgwick & Boder (1991), Perheentupa (1996), Weinstein <i>et al.</i> (2004), Fogli <i>et al.</i> (2003, 2004), Beysen <i>et al.</i> (2009), Luoma <i>et al.</i> (2004), Demirhan <i>et al.</i> (2005), Pagnamenta <i>et al.</i> (2006) and Calderon <i>et al.</i> (2007)
Isolated diseases		
FSH/LH resistance (<i>FSHR</i> and <i>LHR</i>)	<1%	Aittomaki <i>et al.</i> (1995), Latronico <i>et al.</i> (1996), Beau <i>et al.</i> (1998) and Touraine <i>et al.</i> (1999)
<i>INHA</i> variants	Unknown	Shelling <i>et al.</i> (2000), Marozzi <i>et al.</i> (2002), Dixit <i>et al.</i> (2004, 2006b) and Corre <i>et al.</i> (2009)
<i>GDF9</i> variants	1.4%	Dixit <i>et al.</i> (2005), Laissue <i>et al.</i> (2006), Kovanci <i>et al.</i> (2007) and Zhao <i>et al.</i> (2007)
<i>NOBOX</i> variants	0% in Asians; 1% in North Americans	Zhao <i>et al.</i> (2005) and Qin <i>et al.</i> (2007, 2009)
<i>NR5A1</i> variants	8% in 25 Europeans	Lourenço <i>et al.</i> (2009)
Meiotic gene variants	Rare	Mandon-Pépin <i>et al.</i> (2008)
<i>FIGLA</i> mutations	2% (in 100 Chinese)	Zhao <i>et al.</i> (2008a,b)

studied, but this percentage can increase further if a familial history of early menopause (EM) between 40 and 45 years of age is considered (Conway *et al.* 1996, Vegetti *et al.* 1998). Pedigree analysis demonstrates different modes of inheritance, including dominant or recessive forms either through maternal or paternal transmission (Vegetti *et al.* 1998). The more frequent maternal transmission would be consistent with an X-linked inheritance with incomplete penetrance (Davis *et al.* 2000, Toniolo 2006, Persani *et al.* 2009). However, the presence in the same pedigree of women with PA, POF, or EM indicates that POI may be a genetic disease with a highly variable expressivity (Tibiletti *et al.* 1999), thus supporting the view of POI as a complex multifactorial disease probably involving the contribution of several alleles (Toniolo 2006). The purpose of this review is to illustrate the principal genes involved in the pathogenesis of POI (Table 1 and Fig. 2), either when ovarian failure arises apparently isolated in a woman before 40 years of age (nonsyndromic forms) or when this defect is part of a complex phenotype involving other organs and tissues (syndromic forms). Researches are focused in the past years on the candidate gene approach, mostly based on animal models of the pathology, which permitted to identify several genetic variations

associated with POI. Very recently, genome-wide studies are beginning to emerge as a novel and alternative approach for finding novel candidate genes and chromosomal loci.

Syndromic POI

Turner's syndrome

Many forms of familial as well as sporadic POI implicate X chromosome aberrations that range from numerical defects, such as the X monosomy (TS) and trisomy X, to structural defects, such as deletions, isochromosomes, and balanced X-autosomal translocations (Zinn 2001). TS is the consequence of complete or partial absence of one X chromosome in a phenotypic female usually associated with short stature and infertility (Sybert & McCauley 2004). In about 50% of the cases, there is complete loss of one X chromosome, whereas the remaining TS patients harbor mosaicism or structural abnormalities of the X chromosome resulting in a milder phenotype (Bharath *et al.* 2010). The prevalence of the disorder is about 1:2500 live female births (Sybert & McCauley 2004). In women with 45,X karyotype, oocyte loss occurs in the early stages of meiotic prophase, resulting in gonadal dysgenesis and PA with

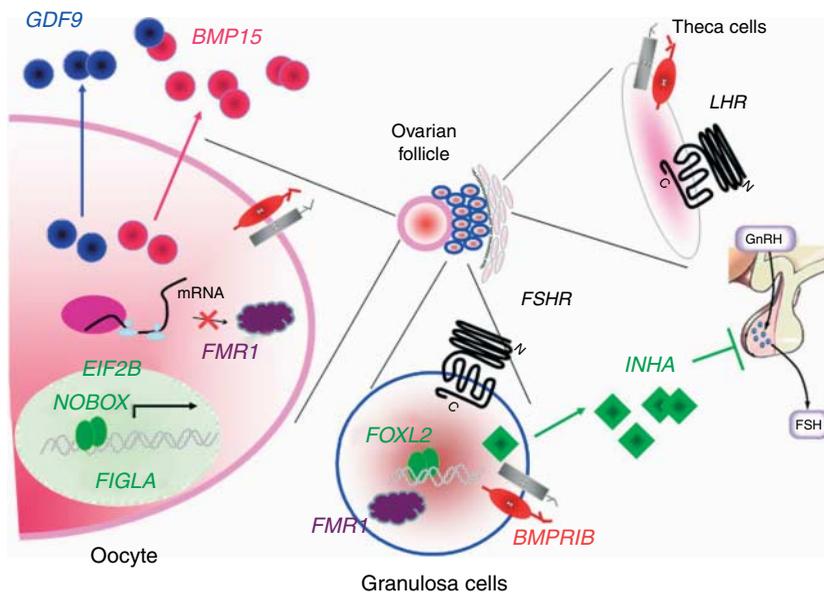


Figure 2 Schematic illustration of the principal genes known to be involved in POI pathogenesis and their site of expression in the ovary.

elevated FSH levels since early childhood (Reynaud *et al.* 2004, Fechner *et al.* 2006). However, spontaneous menarche and pregnancy have been reported not only in patients with mosaic karyotype, but also in few nonmosaic 45,X women (Pasquino *et al.* 1997, Cools *et al.* 2004, Livadas *et al.* 2005). The TS phenotype may be explained by several mechanisms, including the defective pairing of X chromosomes at meiosis (Ogata & Matsuo 1995), but the most substantiated one is the haploinsufficiency of X-linked genes (such as *SHOX*) that physiologically escape X chromosome inactivation and are needed in two copies for ovarian function (Zinn & Ross 1998). The requirement for a double dosage of certain X-linked genes is supported by the observation that complete spontaneous puberty can be reached in 30–40% of mosaic Turner patients (Pasquino *et al.* 1997). Consistently, 45,X subjects have FSH levels already in the postmenopausal range during infancy, whereas FSH levels are frequently low in mosaic Turner patients of the same age (Fechner *et al.* 2006). The mechanism supporting pubertal development in a small subset of 45,X Turner patients is presently unexplained, but low mosaic percentages undetected at standard karyotyping might be a possible explanation.

Cytogenetic and molecular analyses of POI women carrying a balanced X-autosome translocation allowed the identification of a ‘critical region’ for ovarian development and function on the long arm of the X chromosome from Xq13.3 to q27. This region could be split into two functionally different portions: Xq13–21 and Xq23–27 (Therman *et al.* 1990, Rizzolio *et al.* 2006). In balanced translocations, most breakpoints involve

the region Xq13–q21, while only interstitial deletions in Xq23–q27 were found associated with POI. Alternative mechanisms proposed for the explanation of the ovarian defect account for the size of the critical Xq region (Toniole 2006). They include the direct disruption of relevant loci or a ‘position effect’ caused by the rearrangements on contiguous genes. The ‘position effect’ is a mechanism involving the deletion or translocation of regulatory domains to different position on the genome that might cause changes in gene transcription. Transcriptional characterization of breakpoint regions in >40 balanced translocations led to the identification of five genes interrupted by translocations: the *XPNEP2* (MIM *300145) gene in Xq25 (Prueitt *et al.* 2000), the *POF1B* (MIM *300603) gene in Xq21.2, the *DACH2* (MIM *300608) gene in Xq21.3 (Bione *et al.* 2004), the *CHM* (MIM *300390) gene in Xq21.2 (van Bokhoven *et al.* 1994), and the *DIAPH2* (MIM *300108) gene in Xq22 (Bione *et al.* 1998). Only the *DIAPH2* gene, a human homolog of the *Drosophila melanogaster* diaphanous gene affecting spermatogenesis and oogenesis, was found disrupted by a breakpoint in a family with POI, but no mutation demonstrated its role in ovarian function nor that of the others candidates. However, most breakpoints described in POI patients were frequently mapped in Xq21, outside of genic regions, consistent with models for POI associated with X to autosome translocations that involve extra X chromosome effects (Mumm *et al.* 2001, Prueitt *et al.* 2002). These observations suggest the hypothesis that chromosomal rearrangements due to an epigenetic effect of the active X chromosome may

account for a position effect on promoters of autosomal genes when involved in balanced translocations (Rizzolio *et al.* 2007). Recently, heterochromatin rearrangements of the Xq13–q21 region were reported to downregulate oocyte-expressed genes during oocyte and follicle maturation indicating that X-linked POI may be an epigenetic disorder (Rizzolio *et al.* 2009). Another model suggests that some translocations adversely affect X chromosome structure leading to defective meiotic pairing that might increase apoptosis of germ cells at meiotic checkpoints (Schlessinger *et al.* 2002), thereby leading to POI.

Carbohydrate-deficient glycoprotein syndromes and galactosemia

Genetic defects of enzymes providing glycosylation of proteins (carbohydrate-deficient glycoprotein syndromes) are rare and complex diseases are generally characterized by severe systemic disorders. The clinical presentation and course are highly variable, ranging from death in infancy to mildly involved adults (Sparks & Krasnewich 2009). In these cases, ovarian defects may be seen indicating that a defective glycosylation of ovarian glycoproteins is critical for ovarian function.

Galactosemia (MIM #230400) is a hereditary disorder of galactose metabolism caused by the deficiency of GALT (MIM *606999) enzyme (galactose-1-phosphatase uridyltransferase). The incidence of this disease in Europe and North America is about 1:30 000–1:50 000 (Rubio-Gozalbo *et al.* 2010). Galactosemia presents with the worst complications in organs with high GALT expression, such as liver, kidney, ovary, and heart. More than 220 mutations have been described in *GALT* gene (Calderon *et al.* 2007); however, two common mutations (Q188R and K285N) account for more than 70% of cases associated with impaired GALT function (Tyfield *et al.* 1999). POI occurs in almost all women homozygous for mutations in the *GALT* gene that partially or completely abolishes GALT activity and is associated with a severe phenotype (Waggoner *et al.* 1990). FSH levels can be increased from birth to puberty (Steinmann *et al.* 1981, Schwarz *et al.* 1984, Rubio-Gozalbo *et al.* 2006), and the timing of the damage to the ovary is quite different. More frequently, streak ovaries or few primordial follicles failing to mature have been reported (Robinson *et al.* 1984, Fraser *et al.* 1986, Sauer *et al.* 1991). Pathogenetic mechanisms at the origin of galactosemia are not well understood, but several hypotheses have been proposed. Ovarian damage can be induced by toxic accumulation of galactose metabolites that cause oocyte apoptosis (Liu *et al.* 2000) or by deficiency of galactose-containing glycoproteins and/or glycolipids involving FSH and its receptor, causing in turn a decreased ovarian stimulation and an increased follicle

atresia (Tedesco & Miller 1979, Jaeken *et al.* 1992, Ornstein *et al.* 1992). As a word of caution, it should be kept in mind that spontaneous pregnancies have been reported in a few women with galactosemia, even when biochemical markers (undetectable AMH, E₂, and high gonadotropins) were indicative of ovarian failure (Gubbels *et al.* 2008).

Pseudohypoparathyroidism type 1a

The first intracellular element downstream gonadotropin receptors is G α , the G protein whose activation couples the stimulation of FSH and LH receptors (FSHR and LHR) to their enzymatic effector, adenylyl cyclase. This protein is encoded by a gene locus (*GNAS1*; MIM +139320) on chromosome 20q13 that is subject to parental imprinting (Weinstein *et al.* 2004, Mantovani & Spada 2006). *GNAS1* loss-of-function variants inherited from the mother are known to cause a generalized form of hormone resistance named pseudohypoparathyroidism type 1a (Patten & Levine 1990), which is the first syndrome of hormone resistance, which was described by Albright *et al.* (1942) and also named as Albright's hereditary osteodystrophy. The presence of gonadotropin resistance and POI in these patients is justified by the preferential expression of a mutant maternal allele in gonads as in other target tissues of peptide hormones acting through the same G-protein-coupled receptor (GPCR)–G α –cAMP pathway, such as kidney (parathyroid hormone, PTH), thyroid (TSH), and pituitary (GHRH; Mantovani *et al.* 2002). The mechanism leading to POI should be identical to that seen in FSH resistance.

Progressive external ophthalmoplegia

POLG gene (MIM *174763) encodes the DNA polymerase γ , the enzyme that replicates the human mitochondrial DNA. Mutations in this gene are causative of the autosomal dominant (MIM #157640) or recessive (MIM #258450) progressive external ophthalmoplegia (PEO), a disease characterized by weakness of the ocular muscles and fatigue secondary to mitochondrial tissue depletion. It is a genetically heterogeneous disease; dominant *POLG* mutations cluster in the polymerase (*pol*) domain, while the recessive ones affect the proofreading (exonuclease, *exo*) domain. Luoma *et al.* (2004) described co-segregation of POI and parkinsonism with *POLG* *pol* domain mutations in three families with PEO. The POI manifestations were variable from PA to SA at 44 years of age, frequently anticipating the other manifestations. Two of these families carried the p.Y955C mutation in the highly conserved catalytic polymerase domain, and POI was documented in the extended family.

The affected men of these families presented with testicular atrophy, suggesting a defect in steroidogenesis, in which the mitochondria have a gatekeeper role. In the third family, the authors reported the POI case of a compound heterozygote for p.N468D in the *exo* domain and p.A1105T in *pol* domain mutations. Pagnamenta *et al.* (2006) described dominantly maternal inherited POI in a three-generation pedigree in association with PEO and parkinsonism carrying the p.Y955C mutation. This site might be a hotspot for mutations and can lead to mitochondrial DNA depletion, as demonstrated by Southern blot in fibroblasts. On the basis of the early age of onset in comparison with neurological defects, these authors suggested that POLG mutations might also be searched in cases of isolated POI.

Autoimmune polyglandular syndrome type I

Autoimmune polyglandular syndrome type I (APS1; MIM #240300) or autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an autosomal recessive disorder characterized by the presence of 2/3 major clinical symptoms, including Addison's disease, hypoparathyroidism, and chronic mucocutaneous candidiasis. The onset of manifestations frequently occurs during childhood. Patients with APECED also routinely exhibit a variable number of other autoimmune manifestations, including thyroiditis, type 1 diabetes, ovarian failure, and hepatitis (Paterson & Peltonen 2005). It was generally considered to be a monogenic disorder; however, more recent analyses have revealed influences of additional genetic loci, in particular the human leukocyte antigen (HLA) complex, on certain disease parameters (Mathis & Benoist 2007). The autoimmune regulator (*AIRE*) gene (MIM *607358) was identified as the locus underlying susceptibility to APECED (Finnish-German APECED Consortium 1997, Nagamine *et al.* 1997), and to date more than 60 variants, including several nonsense and missense variations as well as frameshift ones, were found. Disruption of *AIRE* protein results in the loss of central tolerance, a process by which developing T cells with potential reactivity for self-antigens are eliminated during early differentiation in the thymus (Michels & Gottlieb 2010). APS1 is a rare disorder, but a particular prevalence is seen in Finns, Iranian Jews, and Sardinians (Cervato *et al.* 2009). In a Finnish survey of 72 patients, hypogonadism was present in 60% of female patients aged >12 years; half of the females with ovarian atrophy failed in pubertal development (Perheentupa 1996). Steroid cell and steroid side-chain cleavage enzyme auto-antibodies in female patients are good predictors of ovarian failure (Falorni *et al.* 2002).

Ovarian leukodystrophy

Ovarian leukodystrophy is the name used by Schiffmann *et al.* (1997) to describe unusual association of POI with vanishing white matter (VWM) disease observed in four patients on magnetic resonance imaging. VWM disease (MIM #603896) is characterized by slowly progressive neurological deterioration, but the onset is extremely variable including prenatal period until adult age (van der Knaap *et al.* 2006). In addition, the ovarian insufficiency onset is different among affected females, and it could result in PA or SA. Moreover, the age at onset of neurological degeneration correlated positively with the severity of ovarian dysfunction (Boltshauser *et al.* 2002). The basic defect of VWM disease is associated with variations in any of the five subunits of eukaryotic translation initiation factor EIF2B. This factor has an important role in protein synthesis and its regulation under different stress conditions, in particular, prevents accumulation of denaturated proteins during cellular stress. Therefore, its dysfunction could be responsible for increased apoptosis of ovarian follicles. In seven patients who presented with POI and ovarian leukodystrophy, eight variants were found in EIF2B2, 4, and 5 (Fogli *et al.* 2003). To further test the involvement of known mutations in *EIF2B* genes in POI, 93 patients with POI not associated with leukodystrophy or neurological symptoms have been investigated. None of the known mutations in *EIF2B* genes, either homozygous or heterozygous, were detected in patients with isolated 46,XX POI (Fogli *et al.* 2004).

Ataxia telangiectasia

Ataxia telangiectasia mutated (*ATM*) gene (MIM *607585) encodes a protein kinase that is involved in cell cycle regulation (Shiloh 2003, Kastan & Bartek 2004) and is also required for processing the DNA strand breaks that occur during meiosis and immune system maturation, and for maintaining telomere. Mutations in *ATM* gene generally result in the total loss of the protein (Lakin *et al.* 1996) and are the underlying causes of ataxia telangiectasia (AT; MIM #208900), an autosomal recessive neurodegenerative disorder characterized by uncoordinated movements and ocular telangiectases (Savitsky *et al.* 1995), chromosome instability, radiosensitivity, immunodeficiency, and a predisposition for cancer. Some patients with AT present ovarian insufficiency due to gonadal hypoplasia with a complete absence of mature gametes (Miller & Chatten 1967, Boder 1975, Sedgwick & Boder 1991). The mouse phenotype closely resembles the human phenotype. *Atm* deficiency in mutant female mice causes lack of primordial and mature follicles and oocytes in extremely small ovaries. Primordial follicles

seem to degenerate at the time of prophase of meiosis I in gametogenesis, demonstrating a total disruption of meiosis during early stages (Barlow *et al.* 1996). Several case–control mutation screening studies on the gene have been performed in order to assess the association of *ATM* mutations and risk of breast cancer (Tavtigian *et al.* 2009). On the contrary, studies of this gene in 46,XX POI cohorts have not yet been performed.

Demirhan syndrome

Demirhan *et al.* (2005) reported the case of a 16-year-old girl with acromesomelic chondrodysplasia, genital anomalies, amenorrhea, and hypergonadotropic hypogonadism due to a homozygous variant in the gene coding for bone morphogenetic protein receptor 1B (*BMPR1B*; MIM *603248). Acromesomelic chondrodysplasias are hereditary skeletal disorders characterized by short stature, very short limbs, and hand/foot malformations. They are caused by homozygous mutations in growth differentiation factor 5 (*GDF5*), a BMP belonging to the transforming growth factor β (*TGF β*) superfamily, which binds to *BMPR1B* with high affinity, and plays an essential role in chondrocyte differentiation (Kornak & Mundlos 2003). The skeletal phenotype of the patient with *BMPR1B* mutation is similar to that observed in patients with homozygous variations of *GDF5* gene, who instead do not have gonadal defects. Mutation analysis of *BMPR1B* revealed a homozygous 8 bp deletion (del359–366). This mutation is expected to result in a loss-of-function and is thus different from the heterozygous missense mutations in *BMPR1B* recently shown to cause brachydactyly type A2 through a dominant negative effect (DNE; Lehmann *et al.* 2003). *BMPR1B* variants can occur naturally also in animals and are found associated with the hyperproliferic Booroola phenotype in sheep (Wilson *et al.* 2001), while female knockout mice present with brachydactyly and infertility (Yi *et al.* 2001). These findings highlight the dual function of *BMPR1B*: on one hand in skeletal development as the predominant receptor for *GDF5*, and on the other and, its role in genital development and ovarian function.

Blepharophimosis–ptosis–epicanthus inversus syndrome

Blepharophimosis–ptosis–epicanthus inversus syndrome (BPES; MIM #110100) is an autosomal dominant eyelid malformation characterized by BPES and telecanthus associated (type I) or not associated (type II) with POF. Forkhead transcription factor L2 (*FOXL2*; MIM *605597) is the only gene currently known to be associated with BPES (Crisponi *et al.* 2001). These authors pointed out that polled/intersex syndrome in

the goat was an animal model of human BPES. Subsequently, the *Foxl2* knockout mice were shown to replicate the findings in humans (Schmidt *et al.* 2004, Uda *et al.* 2004). The invalidation of *Foxl2* expression indeed produced the characteristic cranio-facial alterations, absent upper eyelid, and female-limited infertility with folliculogenesis being blocked at the early stages. Extensive histological studies showed that *FOXL2* can be implicated in the squamous to cuboidal transformation of granulosa cells (GCs) and also in the oocyte activation process (Schmidt *et al.* 2004, Uda *et al.* 2004). *FOXL2* gene encodes a nuclear protein that contains a highly conserved DNA-binding domain and a poly-alanine tract of 14 residues, the role of which has not been elucidated yet. More than 125 *FOXL2* variants have been described in individuals with BPES types I and II, demonstrating that phenotypic features are caused by the pleiotropic effect of a single gene, rather than by a contiguous gene syndrome. Beysen *et al.* (2009) recently reviewed a total of 106 unique intragenic *FOXL2* mutations identified in 206 unrelated families with BPES of different ethnic origins. Detailed information on most *FOXL2* mutations and on affected individuals or families with BPES was made available in the *FOXL2* mutation database (<http://users.ugent.be/~dbeysen/foxl2>). Intragenic mutations represent about 80% of all genetic defects found in BPES cohorts (De Baere *et al.* 2003). They include missense changes, frameshift and nonsense mutations, in-frame deletions, and duplications that are distributed along the single exon gene. Genomic rearrangements, comprising deletions encompassing *FOXL2* entire gene or located outside its transcription unit, represent 12 and 5% of all genetic defects respectively (Beysen *et al.* 2005).

A genotype–phenotype correlation for intragenic mutations was proposed: mutations predicted to result in proteins with truncation before the poly-Ala tract might be associated with BPES type I, whereas poly-Ala expansions might rather lead to BPES type II. These correlations were based on the classification of intragenic mutations into seven groups according to their effect on the predicted protein that is likely to be produced (De Baere *et al.* 2003). A recent model of *FOXL2* protein proposed that mutants can be sorted into two classes: those that potentially alter protein–protein interactions and those that might disrupt the interactions with DNA (Nallathambi *et al.* 2008).

It was also shown that the steroidogenic acute regulatory (*STAR*) gene, whose protein is a marker of GC differentiation, is a direct target of *FOXL2*, acting as a repressor of *STAR*. Two disease-associated truncating variations of *FOXL2* (truncation of 93 and 218 amino acids) did not result in complete loss of repressor activity. In addition, these *FOXL2* truncated proteins were shown to exhibit a DNE, whereas several mutants led to a loss-of-function protein. It was concluded that

the entire alanine/proline-rich carboxyl terminus is important for the repressor activity of FOXL2, and that truncating mutations may preferentially lead to BPES and ovarian dysfunction by accelerated differentiation of GCs and secondary depletion of the primordial follicle pool (Pisarska *et al.* 2004).

Poly-Ala expansions preferentially lead to BPES type II; however, this view has been challenged by several reports. Raile *et al.* (2005) described a 16-year-old girl who was thought to have BPES type I with the poly-Ala expansion c.667_702dup (p.A221_A234dup) and had an extremely large corpus luteum cyst that caused transient ovarian dysfunction. Although it was postulated that this transient ovarian insufficiency might be caused by malfunction of the FOXL2 protein, this possibility may be unlikely, as the ovarian dysfunction seen in BPES type I is generally irreversible. Nallathambi *et al.* (2007) reported the first case with a positive correlation between the size of the poly-Ala expansion, its dosage, and the penetrance of the BPES phenotype in a consanguineous Indian family, within which a novel homozygous expansion of 19 Ala residues in FOXL2 was associated with a recessive form of BPES with ovarian dysfunction. Méduri *et al.* (2010) recently described two patients carrying two different heterozygous poly-Ala expansions of the FOXL2 protein associated with the typical eyelid defects and variable degrees of ovarian dysfunction (from PA to SA). The cases described here emphasize the importance of long-term clinical follow-up of ovarian function also in patients with a poly-Ala expansion.

FOXL2 was also suggested as a possible candidate gene also for nonsyndromic POI (Crisponi *et al.* 2001, Prueitt & Zinn 2001). Recently, the first functional study supporting a role of FOXL2 mutations in nonsyndromic POI was reported (Laissue *et al.* 2009). A novel FOXL2 missense mutation p.G187N was found in a case of POI without BPES. The subcellular localization of the mutant protein was normal, but its transactivation capacity tested on two reporter promoters, specific for the ovary, was significantly lower than that of normal FOXL2. However, the mutant protein was found to strongly activate a reporter construct driven by the *Osr2* promoter, a gene assumed to be a craniofacial target of FOXL2, compatibly with the absence of BPES in the patient. Other studies rarely found or failed to find FOXL2 sequence variants in POI cases without BPES (De Baere *et al.* 2001, 2002, Harris *et al.* 2002, Bodega *et al.* 2004, Gersak *et al.* 2004, Laissue *et al.* 2009).

Nonsyndromic POI

Genetic forms of isolated POI can be suspected in women with 46,XX karyotype (Simpson 2008). They can have different modes of inheritance mainly depending

on the location of the gene involved. In general, defects in autosomal genes follow a recessive mode of inheritance, whereas the inheritance of the defects in X-linked genes may be dominant through maternal lineage or may be transmitted by a male carrier.

Fragile X mental retardation 1

The fragile X mental retardation 1 (*FMRI*; MIM *309550) gene is located at Xq27.3 and is responsible for the fragile X syndrome, a form of X-linked mental retardation, when the CGG trinucleotide in the 5'-untranslated region of the gene is expanded over 200 repeats (full mutation). The premutated allele contains expansions between 55 and 199 repeats that can further expand to full mutation in one generation (Allen *et al.* 2007). Women with *FMRI* premutations, but not full mutations, have an increased likelihood of developing POI (Allen *et al.* 2007). The prevalence of POI in women with premutated alleles is estimated around 16%, with a relative risk of 16% (Wittenberger *et al.* 2007). Premutation carriers have been identified in 0.8–7.5% of women with sporadic form of POI and in up to 13% of women with familial forms. Interestingly, the association of repeat size with POI risk is nonlinear, as the risk appears to be higher between 79 and 99 repeats, and the risk appears to be much reduced for women with repeat sizes between 55 and 78 and over 100 (Allen *et al.* 2007, Wittenberger *et al.* 2007). Large repeat size between normal (<40 repeats) and premutation repeats that is termed intermediate or 'gray zone' (41–54 repeats) exists. Two studies have also reported an increased risk of POI for women with a 'gray zone' size repeats (Bretherick *et al.* 2005, Bodega *et al.* 2006). However, a recent English study failed to replicate these previous studies, despite a significantly larger sample size (Bennett *et al.* 2010). A possible explanation of the association between ovarian insufficiency and the premutation state of *FMRI* gene is that the transcription from premutated alleles is significantly increased (Loesch *et al.* 2007). Repeats between 55 and 79 may, on one hand, lead to an increased production of fragile X mental retardation protein (FMRP), an RNA-binding protein regulating the translation of a subset of mRNAs through a suppression mechanism (Jin & Warren 2000). Since FMRP is highly expressed in germ cells of the fetal ovary (Rifé *et al.* 2004), the accumulation of FMRP may impair the expression of genes required for oocyte development. Longer repeats may instead be translated less efficiently. Since *FMRI* expression was also seen in GCs of maturing follicles (Hergersberg *et al.* 1995), accumulation of abnormal *FMRI* mRNAs may alternatively have long-term toxic effect favoring follicle atresia (Tassone *et al.* 2000). This mechanism is well supported for the other known premutation-associated disorder, FXTAS

(Oostra & Willemsen 2003). Screening for fragile X premutations is recommended for the routine work-up for any woman presenting with POF. The reason for this is that women with POF have an ~5% chance of conceiving, and this possibility may be even higher in the premutation subgroup. Women need to be informed if they are at risk of having a child with fragile X syndrome. In addition, the identification of a family in which the fragile X repeat site is expanded can lead to the identification of other female family members at risk either of transmitting fragile X syndrome or of POI. The identification of an index case should therefore trigger genetic counseling throughout the pedigree (Conway *et al.* 1996).

Ligands of TGF β (TGF β superfamily)

Several members of TGF β superfamily are expressed in the ovarian follicle, either by the oocyte or by GCs (Shimasaki *et al.* 2004). These factors are known to promote growth and differentiations (GDFs) in the tissues where they are expressed and include either GDFs, BMPs, as well as inhibins, activins, or AMH. TGF β s are commonly translated as pre-pro-proteins. The pro-region typically regulates posttranslational processing and dimerization of mature peptide forming either hetero- or homo-dimeric proteins that finally exert the biological activity at the target cell. The follicular paracrine action of several of these factors has been shown to be required for correct folliculogenesis, and the encoding genes have been investigated in the case of POI.

Bone morphogenetic protein 15

BMP15 gene (MIM *300247) encodes an oocyte-derived growth and differentiation factor, which is involved in follicular development as a critical regulator of many GC processes (Dube *et al.* 1998, Chang *et al.* 2002, McNatty *et al.* 2004, Shimasaki *et al.* 2004).

As other TGF β s, *BMP15* gene encodes a pre-pro-protein consisting of a signal peptide, a pro-region and a mature domain that can form homo- or hetero-dimers with related factors, such as GDF9 (Chang *et al.* 2002; Fig. 2). The main roles of *BMP15* include a) the promotion of follicle maturation since the primordial gonadotropin-independent phases of folliculogenesis; b) regulation of follicular GC sensitivity to FSH action; c) prevention of GC apoptosis; d) promotion of oocyte developmental competence; and e) regulation of ovulation quota (Shimasaki *et al.* 2004, Hashimoto *et al.* 2005, Hussein *et al.* 2005, 2006, Fabre *et al.* 2006). The relevance of *BMP15* action in ovarian folliculogenesis was initially shown by experimental and natural models. All together, the data so far collected in different mammalian species indicate that the role of *BMP15* may be more critical in mono-ovulating species (such as sheep and human) than in the poly-ovulating ones (mice). Experimental disruption of *Bmp15* gene in mice causes a mild fertility defect limited to females (Yan *et al.* 2001), whereas natural missense mutations in several strains of ewes cause a hyperprolificacy phenotype in the heterozygous state (increased litter size to three to five lambs per litter against one in wild type) and a female infertility with complete block of folliculogenesis in the homozygous state (FecX factors; Galloway *et al.* 2000, Davis 2004, Hanrahan *et al.* 2004, McNatty *et al.* 2005, Bodin *et al.* 2007). *BMP15* maps to a locus on the short arm of X chromosome (Xp11.2) within a 'POF critical region' where several of the TS traits are located including ovarian failure (Zinn *et al.* 1998, Persani *et al.* 2009). In humans, mutations in *BMP15* gene have been found in association with both PA and SA in several worldwide POI cohorts with a variable prevalence between 1.5 and 12% (Table 2). The first heterozygous mutation in *BMP15* gene (p.Y235C) was reported by us in two Italian sisters with hypergonadotropic ovarian failure characterized by PA and ovarian dysgenesis, who inherited the genetic alteration from the unaffected father (Di Pasquale *et al.* 2004). This mutation was

Table 2 Frequency of *BMP15* gene variants in patients with primary ovarian insufficiency (POI) and controls of different ethnicity

Origin	Size of POI cohort	Patients with nonsynonymous variations (%)	Size of control population	References
Japan	15	0	–	Takebayashi <i>et al.</i> (2000)
New Zealand	38	0	51	Chand <i>et al.</i> (2006)
Europe and USA (Caucasian)	166	4.2 ^a	211 (0%) ^a	Di Pasquale <i>et al.</i> (2006)
Europe and North Africa	203	1.5 ^a	54 (0%) ^a	Laissue <i>et al.</i> (2006)
India	202	8.9 ^a	197 (0%) ^a	Dixit <i>et al.</i> (2006a)
Italy and USA (Caucasian)	300	4.3 ^a	216 (0%) ^a	Rossetti <i>et al.</i> (2009)
China	100	6 ^a	100 (1%) ^a	Wang <i>et al.</i> (2010)
Europe, North Africa and Asia	50	12 ^a	214 ^a (1.9%)	Tiotiu <i>et al.</i> (2010)

^aAfter exclusion of p.ins263L, p.N103S found in 3–12% of POI patients and controls.

located in a residue highly conserved among species and generated aberrant high-molecular weight products *in vitro* as observed by western blot performed in nonreducing conditions, a likely consequence of the additional Cys in the pro-region. A bioassay on primary cultures of human GCs showed an impairment of the growth stimulatory activity of recombinant mutant BMP15 in comparison with wild-type protein. Co-incubation experiments of wild-type and p.Y235C proteins were consistent with a DNE exerted by mutant on the stimulatory activity of wild-type protein on GCs (Di Pasquale *et al.* 2004; Fig. 3). Afterward, other variants were identified with variable frequency in patients from Europe, USA, North Africa, India, China, and Asia (Di Pasquale *et al.* 2006, Dixit *et al.* 2006a, Laissue *et al.* 2006, Rossetti *et al.* 2009, Tiotiu *et al.* 2010, Wang *et al.* 2010; Fig. 4 and Table 2). Almost all of these are missense variations found in the heterozygous state. These variations are also located in the gene sequence encoding the pro-region of the protein. More recently, we studied the recombinant products of several of these missense variations and showed an impaired amount of mature BMP15 protein produced by variant vectors in comparison with wild type, suggesting a hampered

processing. Consistently, we showed a significant reduction in their biological effects by using a novel BMP-responsive luciferase-reporter assay on a human GC line (Rossetti *et al.* 2009). Co-transfection of equal amounts of wild-type plasmids failed to completely restore the normal transcriptional activity. Since a reduced production of bioactive proteins was observed by western blot, we interpreted these results as consistent with a mechanism of haploinsufficiency similar to that described for the mutations found in sheep. Among all the identified variations, only one was found to cause a premature truncation. This truncated variant created a premature stop in the pro-region (p.E211X), resulting in the complete lack of mature BMP15 peptide, and was found in an Indian woman with PA and ovarian dysgenesis (Dixit *et al.* 2006a). Very recently, a Chinese group has reported the first missense substitution (p.R329C) located in the region of the mature peptide that, involving an Arg to Cys amino acid change, could alter the structure of BMP15 by impairing the correct folding of the protein (Wang *et al.* 2010). This variant co-segregated with POF phenotype in mother and daughter. To date, only two studies failed to find an association between BMP15 mutations and

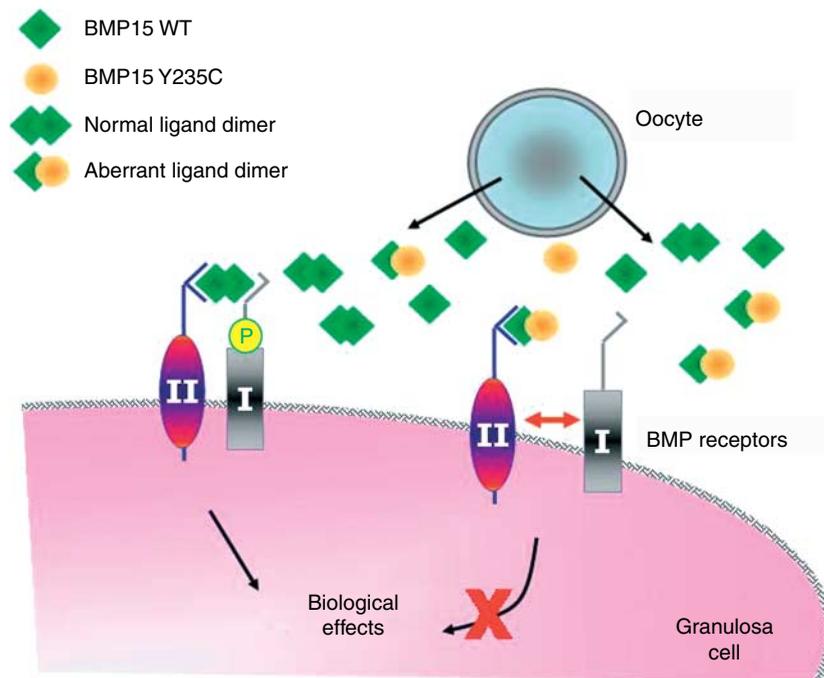


Figure 3 Hypothetical scheme of the dominant negative mechanism generated by the original BMP15 mutations described in the two heterozygous sisters affected with ovarian dysgenesis. The recombinant p.Y235C variant was shown to produce aberrant products of high molecular weight by western blot performed in nonreducing conditions. These aberrant products secreted in the follicular fluid microenvironment may impair the paracrine signal of wild-type bioactive dimers by receptor sequestration, thus hampering the formation of dimers between types I and II BMP receptors and consequent generation of intracellular signal leading to the biological effects in target cells, i.e. granulosa cell growth and differentiation.

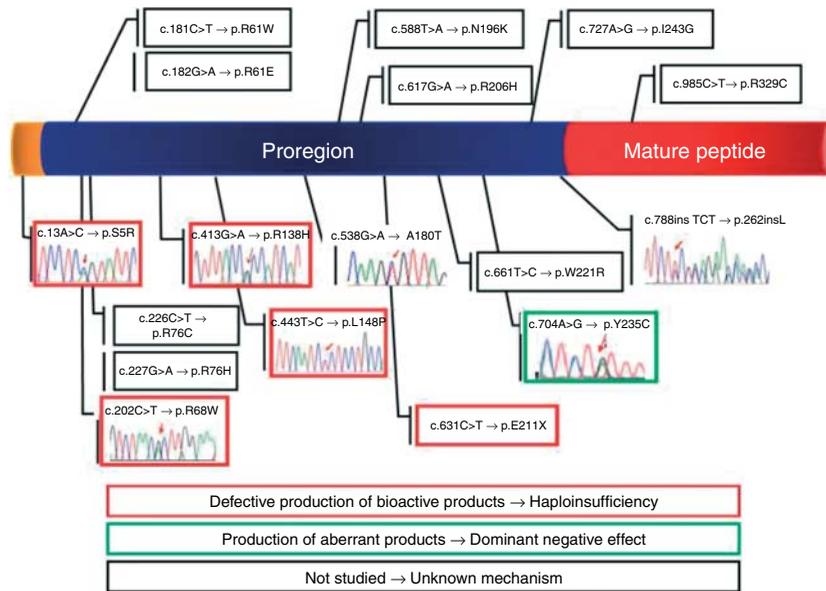


Figure 4 Schematic illustration of the known BMP15 variants that have been detected in POI patients. The specific electropherograms of the variations identified by our group are reported. The different colored boxes show the potential biological mechanisms involved by the variants tested *in vitro* by Di Pasquale *et al.* (2004) and Rossetti *et al.* (2009). The two variants not enclosed in a box did not display any functional defect *in vitro* and should probably be considered missense variations with modest or no biological effect (Rossetti *et al.* 2009). The biological impact of the first variation in the mature peptide is presently unknown.

POI: a Japanese group (Takebayashi *et al.* 2000) and a group from New Zealand (Chand *et al.* 2006), which reported the absence of BMP15 mutations in a series of women with SA. One possible explanation for these negative results may be the small size of the cohorts studied (15 and 38 POF patients respectively). Importantly, some of the missense variations in *BMP15* gene have also been found at low percentages in the control populations (see Table 2 for details), a finding that may question or diminish their pathogenic role. In light of these findings, one could hypothesize that BMP15 variations might play a predisposing role in a context of POI considered as a complex multifactorial disorder, in contrast to the view of POI as a monogenic disorder. However, before drawing conclusions, it must be emphasized that the correct control population of these studies should be represented by women of the same ethnicity and with proven physiological menopause beyond the age of 50 years. Unfortunately, both these conditions were not met in most of the studies reporting BMP15 variants, as opposed to the studies designed by our group (Di Pasquale *et al.* 2006, Rossetti *et al.* 2009).

The functional mechanism by which BMP15 variants with a proven biological impact may disturb ovarian folliculogenesis is presently unknown. We may envisage that a diminished BMP15 paracrine signal in the follicle

would involve an impairment of the anti-apoptotic effects on GCs, a mechanism then favoring follicle atresia. Alternatively, BMP15 variants may finally result in an altered recruitment of pre-antral follicles by gonadotropins. For this reason, *BMP15* gene has also been investigated in patients with opposite alterations of ovulation mechanism, and no linkage was found either in patients with polycystic ovaries or in mothers with spontaneous dizygotic twinning (Zhao *et al.* 2008a,b). Indeed, further studies are needed to understand the exact role of BMP15 variants in POI pathogenesis. Interestingly, all the findings described here for several human variants might also suggest *BMP15* as the first X-linked gene whose haploinsufficiency may play a determinant role for the generation of ovarian dysgenesis in TS, as hypothesized earlier by others (Layman 2006).

Growth differentiation factor 9

Besides BMP15, other TGF β family members have a relevant role in the progression of folliculogenesis. Among them, *GDF9* (MIM *601918) is the homologous gene of *BMP15* (also named *GDF9b*). GDF9 is also expressed in the oocyte and its products can form noncovalent heterodimers acting in a synergistic manner on the function of surrounding follicular GCs (Yan *et al.* 2001). From experimental animals, it was

observed that GDF9 function is more critical in poly-ovulating species such as mice where GDF9 is required for folliculogenesis (Dong *et al.* 1996). Natural GDF9 gene mutations with ovarian effects similar to those seen in BMP15 mutants were also detected in Cambridge and Belclare sheeps (Hanrahan *et al.* 2004). GDF9 was shown *in vitro* to stimulate cumulus expansion, with the induction of hyaluronan synthase 2, cyclooxygenase 2, and STAR protein (Elvin *et al.* 1999). GDF9 can therefore be considered a candidate gene for human POI. The first mutational screening of the GDF9 gene was reported in 15 Japanese women with premature ovarian insufficiency, but no mutations were found (Takebayashi *et al.* 2000). Following this first study, a more extensive number of POI patients ($n=629$) have been screened for mutations in the coding region of the GDF9 gene. GDF9 gene variations in humans described so far in different ethnicity (p.K67E; p.V216M; p.S186Y; p.P103S; and p.T238A) are all heterozygous, affect exclusively the pro-region with a prevalence of 1.4%, and are not detected in the control samples (Dixit *et al.* 2005, Laissue *et al.* 2006, Kovanci *et al.* 2007, Zhao *et al.* 2007). Some studies, however, failed to identify possible deleterious variants suggesting a rare contribution of GDF9 gene variations in those populations (Chand *et al.* 2006, Wang *et al.* 2010). Some rare insertion/deletion and missense variations in GDF9 gene have also been associated with spontaneous dizygotic twinning; the reported frequency of these variants is around 4% confirming a possible role of this factor in the determination of ovulation quota also in humans (Montgomery *et al.* 2004, Palmer *et al.* 2006).

Inhibin A

Inhibin is another candidate gene for mutational studies in humans, given its important role in regulating ovarian function either as a negative modulator of pituitary FSH synthesis or as a paracrine factor. Inhibin A (INHA) gene knockout mice lack the bioactive inhibin dimers thus resulting in raised FSH levels, infertility, and sex chord stromal tumors at an early age with nearly 100% penetrance, demonstrating that inhibin functions *in vivo* as a tumor suppressor in the gonads of mice (Matzuk *et al.* 1992). In a subsequent work, Matzuk *et al.* (1994) showed that INHA-KO mice eventually developed adrenal cortical sex steroidogenic tumors with nearly 100% penetrance, demonstrating that inhibin is also a tumor suppressor for the adrenal gland. The first evidence of a genetic association between inhibin and POI came forth from a POI patient with the translocation 46,XX,t(2;15)(q32.3;q13.3). The translocation breakpoint on chromosome 2 paved interest in the INHA (MIM *147380) subunit locus (2q33–36), therefore further investigations are required

for the mutational screening of this gene (Burton *et al.* 2000). One missense variation of INHA gene (p.A257T) has been associated with POI in several populations (Shelling *et al.* 2000, Marozzi *et al.* 2002, Dixit *et al.* 2004), with a prevalence of 0–11% depending on the ethnicity of the population studied. In fact, the highest frequency of INHA variant was found in the Indian population (Dixit *et al.* 2004, 2006a, Prakash *et al.* 2010) and in the New Zealand study, including Slovenian patients (Shelling *et al.* 2000). An Italian study reported a significant association between the INHA p.A257T variant and sporadic (4.5%) and familial POI cases (7.7%; Marozzi *et al.* 2002). However, the study has been recently replicated in a larger cohort of Italian and German subjects, and no differences in variant frequency were detected between POI cases and controls (Corre *et al.* 2009). The INHA variation is also rare in populations from Argentina (Sundblad *et al.* 2006) and Korea (Jeong *et al.* 2004). Nevertheless, a recent meta-analysis of the random effects on the risk of POI in carriers of the INHA variant from the most relevant studies revealed a combined risk difference of 0.04 (–0.03 to 0.11) with 95% confidence interval (Chand *et al.* 2010). Based on these, it is plausible that the INHA variant allele might confer a susceptibility to develop POI. This view may also be confirmed by the functional study demonstrating a reduced bioactivity of INHA variant in the inhibition of a inhibin-reporter in mouse LβT2 pituitary gonadotrope cells, while variable results were obtained when the reporter was expressed in COV434 GCs line; interestingly, dimerization with β-subunits was unaffected by the variation (Chand *et al.* 2007). Moreover, two promoter variations (c.–16C>T and c.–124A>G) were also reported as additional mechanisms potentially affecting the transcriptional regulation of INHA gene and predisposing to POI. However, the association with POI never reached the statistical significance in all the populations studied (Marozzi *et al.* 2002, Harris *et al.* 2005, Corre *et al.* 2009, Woad *et al.* 2009). In humans, no variations were ever found in the inhibin βA or βB subunit.

G-protein-coupled receptors

Gonadotropin receptors

FSHR and LHR are glycoprotein hormone receptors belonging to the GPCRs family (Themmen & Huhtaniemi 2000). Together with their binding hormones, LH and FSH, these receptors are essential for normal reproductive function in both sexes. Loss-of-function mutations affecting these receptors cause gonadotropin resistance with hypergonadotropic hypogonadism. However, such mutations are extremely rare. A linkage analysis in a Finnish population

revealed a significant association between a locus on 2p21 and ovarian dysgenesis. This locus contains both the genes encoding FSHR and LHR, and following the sequencing of the entire *FSHR* gene (MIM *136435) revealed a homozygous missense mutation that determines the p.A189V substitution in the extracellular domain of the receptor (Aittomaki *et al.* 1995). This type of POF follows a classic recessive transmission with homozygous female carriers affected by PA and ovarian dysgenesis. From *in vitro* studies, it was observed that this mutant receptor has an altered folding and is retained inside the cells failing to reach the plasma membrane, likely due to an impaired glycosylation, thus causing a complete FSH resistance (Aittomaki *et al.* 1995, Rannikko *et al.* 2002). The p.A189V mutation appears to be particularly frequent only in the Finnish population, and it was not found in most other populations, suggesting a founder effect (da Fonte Kohek *et al.* 1998, Jiang *et al.* 1998, Layman *et al.* 1998, Loutradis *et al.* 2006, Prakash *et al.* 2009). Ghadami *et al.* (2008, 2010) succeeded in restoring FSH responsiveness in various cell lines expressing the mutated FSHR through the transfection of the normal human *FSHR* gene carried by an adenovirus vector and, very recently, also in the *FSHR*^{-/-} mouse. These are the first attempts to develop a gene therapy approach for this type of ovarian failure. Other mutations in different regions of the *FSHR* gene have nowadays been reported in women with the classic biochemical phenotype of POI (FSH higher than LH levels). Complete FSH resistance is associated with absent pubertal development, and PA and partial forms are characterized by postpubertal POI and SA. All mutations in the extracellular domain generally impair the targeting of the receptor to the plasma membrane, thus affecting the ligand binding; in contrast, mutations in the transmembrane domain partially impair the transduction of the stimulatory hormone signal (Beau *et al.* 1998, Touraine *et al.* 1999, Doherty *et al.* 2002, Allen *et al.* 2003, Nakamura *et al.* 2008).

Biallelic inactivating variants of the *LHR* gene (MIM +152790) are a rare cause of POI in 46,XX women. They represent a particular form of the disease characterized by LH levels higher than those of FSH. Evidence for a particular phenotype of ovarian insufficiency in women with LH resistance was obtained by the pedigree studies of males affected with Leydig cell hypoplasia (Latronico *et al.* 1996, 1998). Differently from male patients, the degree of LH resistance must be severe to cause the POI phenotype, which is in general characterized by oligoamenorrhea or SA with evidence of multiple antral follicles by ultrasound. Ovarian biopsies reveal all stage of follicular development until the pre-ovulatory stage, but typically ovulation fails to occur.

G-protein-coupled receptor 3

The oocyte-specific *GPR3* (MIM *600241) gene is essential in maintaining meiotic arrest in mammalian oocytes (Mehlmann *et al.* 2004). Disruption of *GPR3* in the knockout mouse determines LH-independent resumption of meiosis resulting in early depletion of oocytes and thus premature ovarian aging (Ledent *et al.* 2005). To determine whether mutations in the *GPR3* gene were associated with POI, Kovanci *et al.* (2008) performed a mutational screening in 82 North American Caucasian women with POF, but none showed perturbations of significance. Recently, another study screened the coding region of *GPR3* in 100 Chinese POI patients for variants of the *GPR3* gene. As in the previous study, no perturbations were found in the coding region (Zhou *et al.* 2010). The results of these studies suggest that mutations in *GPR3* are not a common explanation for POI.

Nuclear proteins

NR5A1

NR5A1 (MIM +184757) gene, also termed steroidogenic factor 1 or fushi tarazu factor (*Drosophila*) homolog 1, encodes a nuclear receptor expressed in bipotential gonads since early human embryonic development. *NR5A1* is a key transcriptional regulator of genes involved in the hypothalamic–pituitary–steroidogenic axis (Luo *et al.* 1994), including *STAR*, *CYP11A1*, *CYP17A1*, *CYP19A1*, *LH/CGR*, and *INHA*. Until 2008, 18 mutations of *NR5A1* were described in cases of 46,XY disorders of sex development (DSD), with or without adrenal failure (Achermann *et al.* 1999, Lin *et al.* 2007). Recently, a key role for this factor in ovarian development and function as well has been evidenced. In fact, further 19 mutations in the gene, including in-frame deletions, missense, and frameshift mutations, were detected in members of four families with histories of both 46,XY DSD and 46,XX POI and also in 2/25 women with isolated ovarian insufficiency but in none of the 700 control alleles (Lourenço *et al.* 2009). Mutations were associated with a range of ovarian anomalies, including gonadal dysgenesis with PA or SA. Functional analysis revealed that each mutant protein had altered transactivational properties in gonadal promoters important for follicle growth and maturation. Such transcriptional disorder in the ovary would then lead to altered folliculogenesis and ovarian insufficiency (Bashamboo & McElreavey 2010).

Other transcription factors

The family of forkhead transcription factors comprises over 100 members involved in several developmental processes, including the mediation of TGFβ

superfamily signals by binding to members of the SMAD family proteins (Atisano *et al.* 2001). Similar to FOXL2, a small subfamily of forkhead transcription factors consisting of *FOXO3a* (MIM *602681), *FOXO1a* (MIM *136533), and *FOXO4* (MIM *300033) has been shown to have a key role in ovarian function. *Foxo3a* knockout female mice exhibit a marked age-dependent decline in reproductive fitness due to a premature follicular development leading to oocyte death and early depletion of follicles, which results in infertility (Castrillon *et al.* 2003). In contrast, the constitutive expression of *Foxo3a* in the oocytes of transgenic mice leads to a delayed follicular development and oocyte growth, in the end causing infertility. Furthermore, constitutive expression of *Foxo3a* determines a significant reduction in BMP15 expression, suggesting a regulatory action of FOXO3a on this factor (Liu *et al.* 2007). The ovarian phenotype of mouse models resembles the human POI phenotype, thus suggesting that *FOXO3a* could be a candidate gene for POI in women. The first mutation screening in POI patients revealed two potentially pathogenic variations that were absent in controls (p.S421L and p.R506H) in 2 out of 90 POI cases from New Zealand and Slovenia (2.2%; Watkins *et al.* 2006). A subsequent analysis on 50 patients of a French cohort identified only one amino acid substitution (p.Y593S) probably with no deleterious impact on protein function (Vinci *et al.* 2008). The sequencing of *FOXO1a* gene in 90 POI patients showed no association with the ovarian phenotype (Watkins *et al.* 2006), but it should be necessary to extend the study of this gene to a larger panel of POI patients. *FOXO4* gene maps at Xq13.1 (MIM *300033), and it has been demonstrated to be a potent regulator of cell cycle, but no linkage has been established so far with POI.

Since animal models affected by a disrupted expression of meiotic genes showed a rapid depletion of germ cells in the ovaries, a recent study investigated whether variations in such genes may be associated with POI (Mandon-Pépin *et al.* 2008). The authors analyzed genes involved in meiosis, such as *DMC1* (MIM *602721), *MSH4* (MIM *602105), *MSH5* (MIM *603382), and *SPO11* (MIM *605114). The sequencing of genomic DNA from 41 POI women led to the identification of a single heterozygous missense substitution (p.P29S in *MSH5*) in two Caucasian women. This variant was not found in 36 controls. Another POI patient of African origin showed a homozygous change in *DMC1* gene (p.M200V). This study needs further confirmation in larger cohorts of patients and controls and functional studies evaluating the functional activity of the variants. However, *MSH5* and *DMC1* variations may be an additional, and probably obvious, explanation for POI.

Among other obvious candidates, two additional transcription factors may be included. Newborn ovary homeobox (*NOBOX*; MIM *610934) and factor in germline alpha (*FIGLA*; MIM *608697) encode two oocyte-specific transcription factors that regulate genes unique to oocytes. *NOBOX* is a homeobox gene that is critical for specifying an oocyte-restricted gene expression pattern including *Mos*, *Oct4*, *Rfp14*, *Fgf8*, *Zar1*, *Dnmt1o*, *Gdf9*, *Bmp15*, and *H1oo* transcripts (Rajkovic *et al.* 2004). *Nobox* deletion in knockout mice accelerates postnatal oocyte loss with follicles replaced by fibrous tissue resulting in a phenotype similar to nonsyndromic ovarian failure in women. Causative mutations in this gene have been investigated recently in several populations. A novel missense variant (p.R355H), which disrupts the binding of the *NOBOX* homeodomain to DNA, has been reported in a small subset (1 of 96) of Caucasian POI patients from the United States (Qin *et al.* 2007); however, two other studies failed to find causative mutations in Japanese and Chinese series (Zhao *et al.* 2005, Qin *et al.* 2009), suggesting that mutations in the homeobox domain of *NOBOX* may be uncommon explanations for POI in Asiatic populations. *FIGLA* is a basic helix-loop-helix transcription factor that regulates the expression of zona pellucida genes. Female *Figla*^{-/-} mice show rapid oocytes loss after birth and no primordial follicles formation. The ovarian phenotype in knockout mice thus suggested that *FIGLA* variations might contribute to human POI. To date, the only mutational study evaluating *FIGLA* gene in women with POF identified two heterozygous deletions in two unrelated cases among 100 Chinese POI subjects. These variants were not detected among 304 ethnically matched controls. Molecular analyses showed that these variants may indeed have a pathogenic role. One deletion leads to a premature truncation of the peptide sequence lacking the functional domains (p.G6fsX66), and may thus contribute to the ovarian defect by a mechanism of haploinsufficiency. In contrast, the other deletion leads to the loss of one residue (p.140delN), and *in vitro* studies showed an altered heterodimerization of mutant *FIGLA* with other partner nuclear transcription factors, thus suggesting a potential DNE mechanism leading to POF (Zhao *et al.* 2008a,b).

Progesterone receptor membrane component 1

Progesterone receptor membrane component 1 (*PGRMC1*; MIM *300435) gene was recently described as a new candidate gene, thanks to the finding of an X/autosome translocation in a mother and daughter both diagnosed with POI that maps within the X 'critical region' for POF at Xq13–26. The subsequent screening of the entire gene has been performed on a cohort of 67 women with idiopathic POI and revealed

one sporadic patient who was heterozygous for a single missense substitution (p.H165R) located in the intracellular C-terminus, within a domain that is essential for the nontranscriptional regulation of cytochrome P450. The missense variation of *PGRMC1* would impair the anti-apoptotic action of progesterone in the developing ovary resulting in the premature loss of ovarian follicles and, ultimately, in ovarian insufficiency (Mansouri *et al.* 2008).

The genome-wide approach to POI

An alternative approach for novel *POI* candidate genes finding is the genome-wide analysis. This approach can be divided in analysis of linkage and in genome-wide association studies (GWAS). In linkage analysis, genetic loci that contribute to a trait can be identified using a set of genetic markers (microsatellites) in related individuals. The overall incidence of familial cases of POI is reported to range 4–31% (Cramer *et al.* 1995, Torgerson *et al.* 1997, Vegetti *et al.* 1998). However, due to the rarity of pedigrees with a large enough number of patients available for analysis, few linkage analyses have been performed so far. Oldenburg *et al.* (2008) performed a genome-wide linkage analysis on a relatively large Dutch family with POI, showing a dominant pattern of inheritance, with complete penetrance and possible anticipation, given that the subsequent generations developed POI at an earlier age. The authors identified a region on chromosome 5q14.1–q15, which revealed several genes expressed in the ovary with a possible role in pathways related to ovarian failure.

In contrast, GWAS investigate genetic variations in unrelated affected individuals compared to matched controls by means of 500k-1M single nucleotide polymorphisms (SNPs) not chosen on the basis of their possible functional effect. Since the publication of the International HapMap Consortium (2005), a public database containing frequent genetic variants ($\geq 1\%$), GWAS in population-based POI cases are beginning to emerge. In a two-stage association study in a Korean population (101 cases and 87 controls), Kang *et al.* (2008) showed for the first time a strong association of *PTH1B* gene (MIM #607968) with POI ($P < 0.001$). *PTH1B* was first identified in osteoblastic cells, where its expression is downregulated early in response to PTH exposure. It has been identified in other tissue, but not in the ovary, and its physiological function remains unknown. Interestingly, *PTH1B* variants have been described in a subset of patients with Bardet–Biedl syndrome (MIM #209900), a heterogeneous disease characterized by variable manifestations, including retina, kidney, liver abnormalities, mental retardation, polydactyly, obesity, and sometimes POI and genitourinary defects in females. This study may suggest *PTH1B* as a novel susceptibility gene for POI.

A genome-wide significant association was observed in another study on a small Caucasian POI population (99 unrelated cases and 235 controls) for the SNP rs246246 (allele frequency $P = 6 \times 10^{-7}$), which mapped to an intron of *ADAMTS19* (MIM #607513; Knauff *et al.* 2009). This gene encodes a zinc-dependent metalloprotease and is known to be upregulated in the female mouse gonads during sexual differentiation. However, replication in an independent Dutch cohort (60 POI cases and 90 controls) could not confirm a clear association ($P = 4.1 \times 10^{-5}$ in a joint analysis; Knauff *et al.* 2009). These authors did not observe strong evidence for any of the 74 selected *POF* candidate genes or linkage regions being previously associated with idiopathic POI in Caucasian females. Nevertheless, suggestive association ($P < 0.005$) was observed for SNPs that mapped in *BDNF*, *CXCL12*, *LHR*, *USP9X*, and *TAF4B*, all possible candidate genes on the basis of animal models showing POI or POI-like phenotype (Knauff *et al.* 2009). However, these GWAS have several limitations. Replications in independent cohorts are needed, as the presence of false positives resulting by chance is due to the general small size of these studies. GWAS would therefore require thousand cases and controls to be genotyped to obtain a significant statistical power. Moreover, there may be particular problems beyond mere statistical association to identify the functional basis of the link between a genetic variant and a complex trait, such as the onset of premature menopause.

Finally, in addition to linkage analysis and GWAS based on SNPs, there is increasing interest toward the association of structural variants (deletions, insertions, and copy number variations, CNVs) with complex traits.

An array comparative genomic hybridization (a-CGH) analysis for the research of CNVs has been recently performed for the first time on 99 Caucasian POI women, with PA ($n = 33$) or SA ($n = 66$) of sporadic or familial (20%) origin, and led to the identification of 31 CNVs spread over the genome. The authors reported eight statistically significantly different CNVs, and, among them, they identified two genes to be involved in reproductive disease (*DNAH5* and *NAIP*), two genes in reproductive endocrinology (*DUSP22* and *NUPRI*), and one gene in folliculogenesis (*AKT1*), which could represent new putative candidate gene associated with POI (Aboura *et al.* 2009). Very recently, Quilter *et al.* (2010) reported an a-CGH study on 42 idiopathic cytogenetically normal POF patients in order to detect cryptic CNVs of the X chromosome. The new data reported in this study might reveal further discrete X chromosome intervals that were not previously associated with the disease and were new clusters of X-linked candidate gene. These structural modifications of the genome may have a role in phenotypic variation exerting their influence by modifying the

expression of the genes varying in copy number or also of other genes mapping within or close to the rearranged region, affecting globally the transcriptome (Henrichsen *et al.* 2009). So far, the functional impact of most CNVs remains unknown; however, the collection of more a-CGH data from different cohorts may provide the basis for the identification of pathogenic CNVs and for the investigation on the contribution of individual genes to the genetic etiology of POF.

Moreover, epigenetics may help to elucidate genetic factors underlying common diseases, focusing not on DNA variations but on the regulation of gene expression by DNA methylation (Voorhuis *et al.* 2010). Epigenetic variations might indeed explain the quantitative nature of complex traits and the gene–environment interaction in the onset of the disease in the perspective of further understanding the causes affecting the timing of premature menopause.

Can genetic investigations in POI be useful for patients?

On the basis of the references quoted in Table 1, the prevalence of known genetic alterations in POI patients can nowadays be estimated as ranging 20–25% of the cases originally classified as idiopathic. Therefore, the pathogenic mechanism still remains unknown in most cases. However, when a genetic alteration is found in a woman, it can be useful for family counseling because it can predict the female relatives that are at higher risk for POI and fertility loss in young age. The female carriers will thus be able to plan their conception before ovarian failure occurs. This possibility is becoming more and more important in this century as women tend to conceive more frequently in their thirties and forties, when the risk of POI in the general population is about 1–2%. At present, a facility involved in the counseling of female infertility should consider screening women with idiopathic POI at least for the most prevalent genetic alterations, i.e. X chromosome abnormalities and *FMRI* premutation (see Table 1). The finding of these abnormalities has obvious implications for family counseling beyond female fertility, including the risk of X-linked male mental retardation associated with *FMRI* full mutation. More recent works may suggest the possibility of including the investigation of *BMP15* gene, and if the initial studies were confirmed *FIGLA* and *NR5A1* genes shall also be added to the study. The aim of several groups around the world, including ours, is to increase in the near future the sensitivity of genetic screening and possibly to develop a test for the prediction of menopausal age. This may indeed open the possibility of an efficient counseling service for female infertility and establish ‘ad hoc’ interventions for the prevention of the consequences of premature ovarian aging.

Declaration of interest

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

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