GeneViSTA

Genetics of Premature Ovarian Failure

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Introduction

The term premature ovarian failure (POF) refers to the cessation of menses in a woman prior to the age of forty years. It is characterized by amenorrhea (either primary or secondary) and hypergonadotropic hypogonadism (level of serum follicle stimulating hormone (FSH) >40mIU/ml) (Coulam et al.,1982). The general prevalence of POF is approximately 1% (Coulam et al., 1986). It is an etiologically heterogeneous disorder with autoimmune, infectious, iatrogenic, environmental and genetic causes being implicated. Yet, in nearly half of these cases, the cause remains unknown and is proposed to be multifactorial. Nevertheless, approximately 10%–15% of these idiopathic cases have an affected first-degree relative suggesting a strong genetic component (Van Kasteren et al., 1999). Overall, cytogenetic, cyto-genomic and whole genome approaches have shown that approximately 20 to 25% cases of premature ovarian insufficiency are of genetic etiology (Qin et al., 2015).

The term primary ovarian insufficiency (POI) has been suggested as a more appropriate term to encompass the biochemical abnormalities, menstrual and fertility issues, thus representing a disease continuum from insufficiency to failure (Welt et al., 2005). Online Mendelian inheritance in man (OMIM) uses the term POF to denote the causative genes/loci .

Pathophysiology of Premature Ovarian Failure

In POF, the lack of ovarian function is a result of either a primary ovarian defect due to streak gonads or dysgenetic gonads, or a normal ovary with depleted follicles or impaired function such as steroidogenesis or a receptor defect. Premature depletion of the ovarian reserve is attributed to either a low initial primordial follicle pool or to accelerated follicular atresia. Altered maturation/recruitment of primordial follicles are other factors causing ovarian dysfunction (Persani et al., 2010). Several important prenatal and postnatal events impact the overall function of the ovary and its endowment with primordial follicles. Therefore, understanding the key processes involved in ovarian development and function and their regulation provides insight into the pathophysiology of premature ovarian failure (Fig.1).

Genetic Causes of POF

The genetic causes of POF may be broadly classified as cytogenetic and single gene causes which are further subdivided into syndromic or non syndromic POF.

Cytogenetic abnormalities implicated in POF

Chromosomal abnormalities are a frequent cause of POF, with an estimated prevalence of 10 –13% from large population studies (Lakhal et al., 2010; Dalpr et al., 2011; Jiao et al., 2012; Kalantari et al., 2013). In ovarian failure presenting as primary amenorrhea, approximately 21% will be associated with an abnormal karyotype compared to approximately 13% of women with secondary amenorrhea (Jiao et al., 2012; Kalantari et al., 2013). A 'critical region' for normal ovarian function is defined on the long arm of the X chromosome, corresponding to the Xq13-q26 interval (Thermen et al., 1990). Epigenetic down-regulation of oocyte-expressed autosomal genes are proposed to be controlled by this region (Toniolo et al., 2007). Multiple POF genes (*POF1B, DIAPH2*, *DACH2*, *DACH2*, *CHM, PGRMC1, COL4A6, NXF5* etc.) have been identified by X- autosomal translocations studies. Cytogenetic abnormalities of the X chromosome account for 5-10% of cases of POF (Goswami et al.,2005). Table 1 lists the various X chromosome abnormalities and their key characteristics. These include numerical X chromosome defects

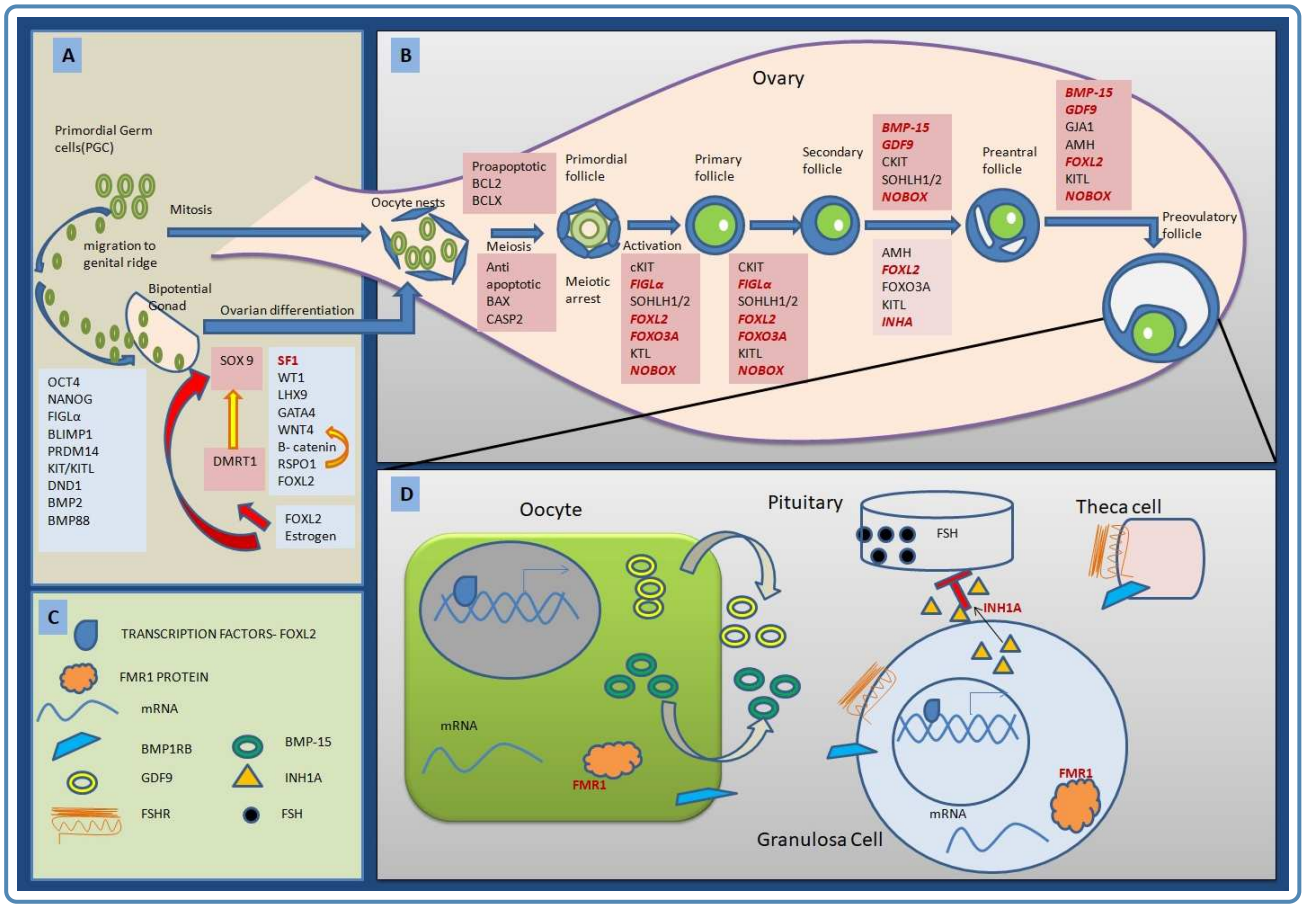

Figure 1 Schematic representation of the genes and signalling factors involved in the genetic control of ovarian function. Panel A depicts migration of the primordial germ cell (PGC) to the bipotential gonad specified by the BMP pathway. Gonadal differentiation into the ovary occurs in the absence of SRY together with the antagonistic effects of FOXL2 and estrogen on SOX9 and DMRT1 and the agonistic effects of the Wnt signalling molecules such as Rspo1 and Wnt4 and various other factors. The yellow arrows depicted in the figure represent an agonistic effect and the red arrows indicate an antagonistic effect. Panel B shows the morphogenesis of follicles from the arrival of primordial germ cells (PGC) in the nascent ovary to secondary follicles along with the genes and signalling factors involved in each transition. Some of the known single gene defects have been highlighted in red and bold. Panel D illustrates the site of expression of some of the genes involved in the pathogenesis of POF. Panel C lists the key to the depictions in Panel D.

(monosomy X; X chromosomal mosaicism; 47,XXX), structural rearrangements (X-autosome translocations, X-isochromosomes and others), X-deletions and other abnormalities such as 46,XY.

Monogenic defects

Syndromic monogenic defects

- Perrault syndrome: Perrault syndrome is characterized by 46,XX ovarian dysgenesis and bilateral prelingual onset sensorineural deafness in females. The spectrum of ovarian dysfunction extends across a continuum from mild to severe. Perrault syndrome is known to be caused by biallelic pathogenic variants in one of four genes: *HARS2, HSD17B4, LARS2,* or *CLPP* and in the majority of cases, the molecular basis is unknown. Mental retardation, ataxia, and cerebellar hypoplasia may be associated features. HSD17B4/D-bifunctional protein is a multifunctional peroxisomal enzyme involved in fatty acid β-oxidation and steroid metabolism, while *LARS2* which encodes a mitochondrial leucyl-tRNA synthetase and *HARS2* which codes for histidyl tRNA synthetase are mitochondrial genes.

- Galactosemia: Classical galactosemia is an inherited inborn error of galactose metabolism caused by galactose-1-phosphate uridyltransferase

Table 1 X Chromosome abnormalities in premature ovarian failure.

X chromosome abnormality	Phenotype	Genetic mechanism
Turner syndrome (Monosomy X)	Female with dysmorphism, structural cardiac defects (one third cases), skeletal abnormalities, hearing loss (50%), hypothyroidism (10%), short stature. Milder phenotype in mosaic Turner	Non-disjunction event (meiotic or post zygotic), haploinsufficiency of *SHOX* gene, accelerated prenatal oocyte apoptosis
47,XXX (Trisomy X)	Small proportion experience POF and may have genitourinary abnormalities.	Nondisjunction errors in meiosis I or II in oogenesis.
Xq deletions	Terminal deletions originating at Xq13 are associated with primary amenorrhea and absent secondary sexual development. Primary amenorrhoea is not a feature of terminal deletions arising at Xq25 or Xq26, and more distal deletions having a milder phenotype (Simpson et al.,1999).	
Xp deletions	Approximately 50% of delXp11 cases show primary amenorrhea and 45% show secondary amenorrhea (Ogata et al.,1995). Deletion of only the most telomeric portion of Xp (Xp22.3 → Xpter) does not result in amenorrhea (Thomas et al., 1999).	
X autosome translocations	Primary or secondary amenorrhoea. Turner stigmata if translocation occurs within the critical region of Xq13-q26	Haploinsufficiency or disruption of critical genes in these regions, positional effect on contiguous genes or non-specific defective meiotic pairing
46,XY gonadal dysgenesis	Female internal and external genitalia, minimal breast enlargement, propensity for malignant transformation of the gonads (20-30%,)	Mutations in *SRY* (15% of cases), *SOX9, GATA4, FOG2, NR5A1, WT1, DHH, CBX2, ATRX, MAP3K1* and *FGF9*. Deletions encompassing DMRT1 (9p) or EMX2 (10q) Duplication of Xp21 (DAX1/NROB1)

(GALT) deficiency and premature ovarian failure is the most common long-term complication experienced by girls and women with this condition, with more than 80% being affected despite neonatal diagnosis and careful lifelong dietary restriction of galactose. The presence of a homozygous Q188R mutation is associated with a 16-fold increased risk of POF.

- Others syndromic causes: A variety of genetic disorders (Table 2) have been described in which POF is a commonly occurring feature, and the genes implicated in these cases may therefore have a role in ovarian failure. In some of these conditions the onset of POF is related to gonadal insult or endocrine dysfunction resulting from the disease process, while in others the mechanism of ovarian failure remains unknown.

Non–syndromic Monogenic Defects

There are many X-linked genes and autosomal genes implicated in non-syndromic presentations of POF.

- Fragile X premutation: The *FMR1* premutation occurs in the critical gene for Fragile X mental retardation gene located at Xq27.3. In females with POF, the risk of having a premutation allele

is 3–4% when she is the only affected individual in the family, but 12–15% if a second female in the pedigree is affected with POF. The pathology is caused by expansion of the CGG repeat in the gene's 5' untranslated region to a premutation state of between 56 and 199 repeats which leads to an increased production of the fragile X mental retardation protein (FMRP), an RNA-binding protein which is highly expressed in germ cells of the foetal ovary Its accumulation is believed to impair the expression of genes required for oocyte development and have toxic effects leading to follicle atresia. The risk of having POF appears to increase with increasing premutation repeat size between 59 and 99. The risk plateaus or decreases for women with repeat sizes of 100. FMR1 premutations carried by women are unstable and can expand in the next generation to transmit fragile

Table 2 Syndromes with premature ovarian failure.

Syndrome	Gene	Prominent associated findings
Aromatase deficiency	*CYP19A1*	Maternal virilization during pregnancy due to absence of placental aromatase
Ataxia telangiectasia	*ATM*	Cerebellar ataxia, telangiectasias, immune defects, a predisposition to malignancy, premature aging, genome instability
Autoimmune polyendocrine syndrome, type 1/Autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy (APECED)	*AIRE*	Adrenal insufficiency, hypoparathyroidism, chronic mucocutaneous candidiasis <60% of patients have ovarian failure
Autoimmune polyendocrine syndrome, type 2	Unknown	Adrenal insufficiency, type 1 diabetes mellitus, autoimmune thyroid disease 3-10% of APS type II patients have POF
Bassoe syndrome	Unknown	Muscular dystrophy and infantile cataract
Blepharophimosis -ptosis- epicanthus inversus syndrome (BPES) Type I	*FOXL2*	Autosomal Dominant condition. Complex eyelid malformation.
Bloom syndrome	*BLM*	Premature aging, a predisposition to malignancy, genome instability
Cerebellar ataxia with hypergonadotropic hypogonadism	Unknown	Ataxia, sensorineural deafness with vestibular hypofunction, peripheral sensory impairment
Congenital adrenal hyperplasia due to 17-alpha hydroxylase deficiency	*CYP17A1*	Hypertension, hypokalemic alkalosis
Congenital disorder of glycosylation, type 1A	*PMM2*	Neonatal encephalopathy, hypotonia, psychomotor retardation, cerebellar hypoplasia, retinitis pigmentosa
Demirhan syndrome	*BMPR1B*	Severe limb malformation, genital anomalies
Fanconi anemia	*FANCA, FACA, FA1, FA, FAA*	Anemia, leucopenia, thrombocytopenia; cardiac, renal and limb malformations; dermal pigment changes
Fryns syndrome	*PIGN* & additional unknown loci	Intellectual disability, craniofacial dysmorphism
GAPO	*ANTRX1*	Growth retardation, alopecia, pseudoanodontia, and optic atrophy

Leukoencephalopathy with vanishing white matter	*EIF2B2, EIF2B4, EIF2B5*	Encephalopathy with leukodystrophy
Lipoid congenital adrenal hyperplasia	*STAR*	Congenital adrenal insufficiency, testis function is more severely affected than ovarian function
Malouf syndrome	Unknown	Cardiomyopathy
Marinesco-Sjogren syndrome	*SIL1*	Cerebellar ataxia, congenital cataracts, retarded somatic and mental maturation
Mental retardation, X linked	*FRAXE*	Intellectual disability
Progressive external ophthalmoplegia with mitochondrial DNA deletions	*POL G*	Adult onset weakness of external eye muscles and exercise intolerance
Proximal symphalangism (SYM1)	*NOG*	Symphalangism
Pseudohypoparathyroidism(PHP) type Ia	*GNAS*	Elevated parathyroid hormone (PTH) with low/normal calcium, high thyrotropin (TSH) with normal thyroid hormone levels, growth hormone deficiency and high gonadotropins in patient with delayed puberty and skeletal abnormalities (Albright osteodystrophy)
Rapp-Hodgkin syndrome	*TP73L*	Ectodermal dysplasia, cleft lip, cleft palate
Werner syndrome	*WRN*	Premature aging, a predisposition to malignancy, genome instability
Woodhouse-Sakati syndrome	*DCAF17*	Alopecia, diabetes mellitus, intellectual disability, extrapyramidal syndrome

X syndrome to male offspring, especially if women have more than 100 repeats. As women with POF have an 5% chance of conceiving, these women are at risk of having a child with fragile X syndrome. As per the American College of Medical Genetics (ACMG), carrier screening of *FMR1* premutation is recommended for women who are experiencing reproductive or fertility problems associated with elevated follicle stimulating hormone (FSH) levels, especially if they have: (a) a family history of premature ovarian failure, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation (Sherman et al., 2005).

- Other isolated gene defects: Several of the isolated gene defects and their prevalence is listed below in Table 3.

Genomic aberrations, copy number variants (CNVs)

In rare cases, microdeletions and microduplications in known POF genes (*SYCE1, CPEB1*), genes involved in meiosis (*PLCB1, RB1CC1, MAP4K4, RBBP8, IMMP2L, FER1L6, MEIG1*) and possible candidate genes for POF and ovarian dysfunction involving DNA repair, or folliculogenesis have been identified.

Micro RNAs (MiRNAs)

MiRNAs are a class of small (18-22 nucleotides in length) noncoding RNAs which cause negative regulation of target genes by mediating post-translational gene silencing (He et al., 2004). Dicer, a pre-miRNAs processor is shown to be important for folliculogenesis, maturation of oocytes, and follicle recruitment (Murchison et al., 2007). Polymorphisms in *XPO5* (Exportin), a premiRNA transporter are associated with an increased risk of POI (Rah et al., 2013). Differentially expressed miRNAs are involved in various ovarian processes and have been associated with POI (Yang et al., 2012).

In many instances, candidates genes that have been found in experimental or natural animal models showing ovarian failure have shown no variants in the corresponding human orthologue.

Table 3 Isolated gene defects associated with premature ovarian failure.

Gene	Prevalence in POF cohorts
TGF-B family	
BMP 15	1.5-12%
GDF9	1.4%
INHA	0–11%
Gonadotropin receptors	
FSH/LH resistance (*FSHR* and *LHCGR*)	0–1%
Transcription factors	
Nuclear Proteins	
NR5A1(SF1)	1.6%
Oocyte specific transcription factors	
NOBOX	0–6%
FIGLA	1–2%
Forkhead like transcription factors	
FOXL2	Rare
FOXO3	2.2%
Progesterone receptor membrane component 1	
Progesterone receptor membrane component 1 *(PGRMC1)*	1.5%
LHX8	Rare
DNA replication/meiosis and DNA repair genes variants	
DMC1, *MSH4*, *MSH5*, *SPO11*, *STAG3*, *SMC1β*, *REC8*, *POF1B*, *HFM1*, *MCM8*, *MCM9*, *SYCE1*, *PSMC3IP*, *NUP107*, *FANCA*, *FANCC*, *FANCG*	Unknown

Clinical presentation

The lack of ovarian function leads to absence of production of ovarian hormones leading to low estradiol levels. The resulting effects represent the consequences of hypoestrogenism and also vary depending on the age at which the ovarian failure occurred. Failed development of the gonads, prenatal or prepubertal depletion of the ovarian follicles and ovarian dysfunction result in primary amenorrhoea with poor/absent secondary sexual development. The age limit for defining primary amenorrhea is 13 years of age in the absence of secondary sexual development or 15 years of age in the presence of normal secondary sexual characteristics. Secondary amenorrhea (as absence of menstruation for three normal menstrual cycle or four months period) and well developed secondary sexual characteristics are features of post-pubertal events. A preceding history of infertility, recurrent pregnancy loss or irregular cycles is usually elicitable in such cases. Other symptoms of POF are the typical manifestations of climacterium such as palpitations, heat intolerance, flushes, night sweats, irritability, anxiety, depression, sleep disturbance, decreased libido, hair coarseness, vaginal dryness, fatigue. These symptoms are uncommon among women with primary amenorrhea who never received estrogen. Over 75% of women with POI will have at least menopausal intermittent symptoms including hot flushes, night sweats, and emotional lability. Moderate hirsutism may be seen due to the action of androgens originating from the adrenal glands. In addition to these common manifestations, some have additional specific features associated with specific syndromes or etiologies (see Table 2).

Clinical workup

The clinical assessment of a woman with premature ovarian failure is aimed at finding etiological clues. These include determining the age of onset of amenorrhea, the sexual maturity rating (SMR), anthropometry, dysmorphological assessment, systemic examination for associated features such as cardiac abnormalities or signs of endocrinological disturbances and examination of the external genitalia. A comprehensive three generation pedigree for history of familial POF and for members affected with Fragile X syndrome or ataxia, and maternal menarcheal and menopausal age may provide vital information. A sonographic evaluation of the pelvis helps to delineate the pelvic anatomy, presence of female internal genital organs, and uterine and ovarian morphology. Relevant imaging and laboratory tests may then be undertaken to further aid in establishing the diagnosis and optimize patient management. In every woman of reproductive age with amenorrhea pregnancy should be ruled out. Serum FSH levels of greater than 40 mIU/ml are diagnostic of POF and this is confirmed with a repeat value after four weeks. About half of the cases of primary amenorrhea are due to ovarian dysgenesis, which is revealed by the finding of streak ovaries accom-

panied by uterus hypoplasia at ultrasound. In the other patients, follicles (<10 mm) may be found on histological evaluation, such as in the case of *FSHR* gene mutations.

Genetic testing

A routine karyotype is performed in all cases with premature ovarian failure regardless of the age of onset. Besides detecting X chromosome abnormalities, a karyotype will help identify any Y chromosome material which necessitates gonadectomy due to the associated risk of gonadal tumors. The ACMG 2005 guidelines and the American College of Obstetrics and Gynaecology (ACOG) 2010 committee opinion recommend Fragile X premutation screening in women with unexplained premature ovarian insufficiency (Sherman et al.,2005; ACOG committee opinion., 2006). All identified premutation carriers should be counseled regarding the risk to their offspring of inheriting an expanded full-mutation Fragile X allele and also the importance of cascade screening of at-risk female relatives. Currently there are no recommendations for the routine testing of other candidate genes associated with POF in cases with a normal karyotype. Testing of specific disease-associated genes can be considered if a particular syndrome is suspected.

Role of Next Generation Sequencing

Strategies to identify POF candidate genes have included studies in animal models, study of X chromosome deletions and X-autosome translocations, linkage analysis, comparative genomic hybridization (CGH) array, genome-wide association studies (GWAS), and recently, next generation sequencing (NGS) based approaches. Of these, NGS has several advantages and is a powerful diagnostic tool. The mitochondrial gene linked to Perrault syndrome *LARS2*, which codes for a mitochondrial leucyl-tRNA synthetase, was identified by exome sequencing in two POF families (Pierce et al., 2013). Studies involving whole exome sequencing(WES) have identified pathogenic variants in genes implicated in DNA repair and genomic stability such as stromal antigen 3 (*STAG3*), synaptonemal complex central element 1 (*SYCE1*), minichromosome maintenance complex component 8 and 9 (*MCM8*, *MCM9*) and ATP-dependent DNA helicase homolog (*HFM1*) genes in consanguineous families with non-syndromic POF (Carburet et al., 2014; Wood-Trageser et al., 2014; Al Asiri et al., 2015; Wang et al., 2014; de Vries et al., 2014). A multigene panel study by Fonseca et al. in 12 unrelated women with POF identified two plausible candidate genes in POF, namely *ADAMTS19* and BMP receptor 2 (*BMPR2*) genes with POF pathogenesis (Fonseca et al., 2015). Candidate gene discoveries are important to enhance the knowledge of the underlying molecular mechanisms of POF and thereby increase the prospects of development of definitive treatment.

Emerging Concepts

Recently, the concept of POF being a purely monogenic disorder has been questioned with digenic findings in several cases and the synergistic effects of several mutations have been suggested to underlie the POI phenotype (Bouilly et al., 2016). Research in POF besides being directed towards identifying causative gene defects, involves exploring therapeutic options to restore ovarian function. In vitro activation of dormant primordial germ cells and grafting are being studied as a potential infertility therapy for POF patients who have residual follicles (Kawamura et al., 2013; Suzuki et al., 2015). The online Ovarian Kaleidoscope Database (http://ovary.stanford.edu) provides information regarding the biological function, expression pattern and regulation of genes expressed in the ovary. It also contains information on gene sequences and is a useful resource of knowledge on ovarian genetics.

Conclusion

Currently there are no proven predictive tests or biomarkers to identify women who will develop POF, unless a mutation known to be related to POI is detected, and there are no established POI preventing measures. The development of multigene predictive panels may enable the identification of women at risk for early menopause or premature ovarian failure. The availability of target therapies is the ultimate goal for the immense ongoing research in unravelling the intricacies of the ovarian function.

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