High genetic heterogeneity of Premature Ovarian Insufficiency

From DNA replication and repair to hormonal regulation

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Abstract

Primary ovarian insufficiency greatly influences a woman's fertility potential and her overall health. The condition affects about 1–2 % of women and in most cases, the cause is undefined. Primary ovarian insufficiency (POI) may be caused by any process that results in dysfunction or depletion of ovarian follicles, reducing the number of oocytes within the ovary. The tendency for POI to run in families implies a strong genetic component underlying the condition. The most common single gene mutation to cause POI is the premutation of the fragile-X mental retardation gene 1 (FMR1), located on Xq27.3. Many other candidate genes have been suggested to play a role in the POI etiology, with mutations identified in genes involving follicle function and oogenesis, such as FOXL2, BMP15, NR5A1, Inhibin A, LHR, FSHR and the phenotype. In addition, variations in genes involved in meiosis and DNA repair have been hypothesized to affect the normal process of follicle formation and diminish ovarian reserve resulting in infertility. An alternative approach to identify novel POI candidate genes is the genome-wide analysis and we also report on a few studies that might have identified novel susceptibility genes for POI.

Introduction

A woman's ovary has several million potential oocytes at around five months of gestational age. These are held in a quiescent state until required for ovulation, years later. Most of these potential oocytes are destroyed by the body before birth presumably as part of a quality control mechanism. Between infancy and the age of 40 years, the potential oocytes are gradually reduced from approximately one million to 10,000 in each ovary and around the age of 40, the process of egg destruction accelerates with normal aging. Unfortunately, some women can experience irregular menstrual cycles and stop producing oocytes in their early 30's leading to the condition called Premature Ovarian Insufficiency (POI). Genetic analysis has identified aberrations in several biological pathways that can result in this condition. This review summarizes the evidence for involvement of multiple developmental genes, as well as highlights the role of known oncogenes in POI.

Disease Definition

A woman, through her reproductive life, uses fewer than 500 eggs, a tiny proportion of the original millions (Hsueh 1994, Tilly 2001). Primary Ovarian Insufficiency (POI) or Premature Ovarian Failure (POF) may be caused by any process that results in dysfunction or depletion of ovarian follicles, reducing the number of oocytes within the ovary. It is defined as early menopause with elevated levels of serum gonadotrophins before the age of 40 (Coulam 1982). Various terms have been used to describe this deviation from healthy ovarian function, including 'premature menopause'. Albright (1942) coined the term 'primary ovarian insufficiency' to emphasise that the primary defect was within, rather than outside the ovary. Other conditions involving endocrine disturbances outside the ovary can also result in abnormal ovulation including pituitary disorders, adrenal dysfunction, or polycystic ovary syndrome. The term 'ovarian insufficiency' is regarded as more scientifically accurate than 'ovarian failure' (De Vos 2010) as insufficiency indicates impaired ovarian function suggesting that follicular activity of the ovary might intermittently recover, years after diagnosis leading to pregnancy in some women (Nelson 2005).

Disease Diagnosis

Primary ovarian insufficiency (POI) affects about 1–2 % of women (Vegetti 2000) and in most cases, the cause is undefined. Destruction of primordial follicles by toxic agents, autoimmune response, activation of proapoptotic pathways, or accelerated follicular recruitment might result in premature depletion of the pool of primordial follicles. Accurate and timely diagnosis of POI poses challenges as hormonal and biochemical tests do not show the monthly follicle loss and thus do not indicate the true biological age of ovaries. Direct evidence of depletion of the resting pool of follicles can be reliably provided only through assessment of the total number of follicles in whole ovaries. Testing of biopsy samples of ovaries has been suggested as a diagnostic method to measure ovarian follicular reserve (Massin 2008), with other investigators concluding that analysis of laparoscopic biopsy samples cannot be used to predict follicular distribution in ovarian cortex (Lambalk 2004).

Genetics of POI

Chromosomal abnormalities account for 12% of cases (Jiao 2012), and the familial aggregation often associated with POI indicating a significant genetic contribution. Incidence of familial cases among women with POI has been reported to be as low as 4% (Conway, 1996), but it might be an underestimation and epidemiological studies have indicated incidence of familial POI as high as 30% (Cramer 1995, Torgerson 1997). In a large Italian study, Vegetti et al. (1998) found that the condition was inherited in one-third of the idiopathic POI patients. Pedigree studies on affected families showed a mode of inheritance suggestive of autosomal dominant sex-limited transmission or X-linked inheritance with incomplete penetrance (van Kasteren 1999). Using family history can help distinguish between familial or sporadic primary ovarian insufficiency as the risk of female relatives developing this condition may be as high as 100% in familial primary ovarian insufficiency, or as low as 1% in sporadic cases (van Kasteren 1999).

In rare cases, sufficient ovarian follicles are present but they do not function i.e. oocytes do not mature in regular cycles. However, in a large proportion of cases no cause is found and they are classified as idiopathic or karyotypically normal spontaneous ovarian failure (Laml 2000).

Unraveling the genetic causes of POI

Several methods have been used to elucidate the role of genetic contributors in the pathogenesis of POI — transgenic 'knockout' animals, mutation screening in affected women, analysing pedigree data in linkage analysis. Genetic association studies aim to identify candidate genes or genome regions that contribute to a specific trait or disease by identifying a correlation between disease status and genetic variation (Cordell 2005) and we report on several candidate genes that are believed to contribute to POI.

POI genes on the X-chromosome

Premature ovarian senescence is many times associated with abnormalities in the X chromosome. Women with structural and numerical abnormalities in the X chromosome make up the largest subgroup with POI. During early embryonic development, one of the X chromosomes is randomly inactivated by methylation in female somatic cells (Sato 2004). In some women with X chromosome structural abnormalities, such as large deletions and unbalanced translocations, skewed patterns of X chromosome inactivation (SXCI) may result with the abnormal inactive X chromosome in most of the cells. Other women may inherit only one X chromosome (45,X) leading to congenital Turner's syndrome (Sybert 2004). Although one X chromosome is sufficient to allow the normal development of most organs and initial differentiation of ovaries, oocytes need two active X chromosomes. Defective X chromosome leads to insufficient gene dosage of many genes, and haploinsufficiency of the X chromosome results in depletion of the oocyte pool in the first 10 years of life.

Link between Fragile X and POI

Mutations in the FMR1 gene can also lead to the expansion of a CGG trinucleotide repeat located at the 5' UTR region of the gene. Long repeats of 200 CGG trineucleotides lead to reduced gene expression and Fragile X mental retardation syndrome. Repeat lengths between 59 and 199 of the CGG repeat confer an unstable premutation state. Women with the premutation allele have a substantially increased risk of POI. Besides Turner's syndrome, premutation in the FMR1 gene is the most common known congenital cause of POI. Cryptic deletions in FMR2 gene, located near the FMR1, have also been suggested as an X chromosome-linked cause of primary ovarian insufficiency (Murray 1999).

Multiple rare mutations in oocyte development and hormone regulation genes contribute to the risk of POI

FOXL2 is a member of the forkhead /hepatocyte nuclear factor 3 gene family of transcription factors that plays a role in sex determination. Mutations in FOXL2 cause congenital blepharophimosis–ptosis–epicanthus inversus syndrome (BPES) that is characterized by premature death of egg cells (Crisponi 2001). Foxl2 knockout mice were shown to replicate the findings in humans (Schmidt 2004). Reduced Foxl2 expression resulted in the characteristic cranio-facial alterations and infertility with folliculogenesis being blocked at the early stages. A functional study supporting the role of FOXL2 mutations in nonsyndromic POI was reported by 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 functional activity was significantly lower than that of normal FOXL2 protein.

NR5A1

NR5A1 gene, also called steroidogenic factor 1, plays a key role in ovarian development and function. Mutations in the gene were detected in members of four families with a history of POI but not in the 700 control alleles (Lourenco 2009). Mutations were associated with a range of ovarian anomalies, with functional analysis revealing that mutant proteins had altered transcriptional activity that is important for follicle growth and maturation.

Members of the TGF superfamily

Hetrozygous mutations in BMP15 (Bone Morphogenetic Protein 15), an oocyte-specific growth/differentiation factor that stimulates folliculogenesis and is expressed in oocytes during early folliculogenesis, has been implicated in POI (Di Pasquale 2004). It is presumably expressed from both X chromosomes in oocytes, and could potentially show a gene dosage effect. BMP15 maps to a locus on the short arm of X chromosome (Xp11.2), within a 'POI critical region' (Persani 2009). In humans, mutations in BMP15 gene have been found in POI cohorts. Rossetti et. al. (2009) demonstrated that BMP15 protein coding variations resulted in reduced production of bioactive BMP15 proteins in comparison with wild type, thus functional effects of these mutation is consistent with a mechanism of haploinsufficiency. Mature BMP15 proteins with missense variations also showed significant reduction in their biological effects in human cell-lines (Rossetti 2009).

Besides BMP15, other TGFβ family members have a relevant role in the progression of folliculogenesis. GDF9 is also expressed in the oocyte. Several studies reported that variations in GDF9 gene (p.K67E; p.V216M; p.S186Y; p.P103S; and p.T238A) were found in women with POI but were not detected in the control samples (Laissue 2006, Kovanci 2007).

Inhibin A, NOBOX

Inhibin A plays an important role in regulating ovarian function either as a negative modulator of pituitary FSH synthesis. Inhibin A (INHA) gene knockout mice have raised FSH levels, are infertile and develop tumors in the gonads at an early age with nearly 100% penetrance (Matzuk 1992). Therefore, Inhibin A was regarded as a candidate gene for mutational studies. One missense variation of INHA gene (p.A257T) was found to be associated with POI in several populations: the INHA variant was identified in Indian, New Zealand and Slovenian patients (Shelling 2000, Dixit 2004). An Italian study also reported a significant association between the p.A257T allele in INHA and sporadic (4.5%) and familial (7.7%) POI cases (Marozzi 2002). However, other studies have found no differences in variant frequency between POI cases and controls (Corre 2009).

NOBOX and FIGLA are oocyte-specific transcription factors, and deletion of either of these genes could accelerate post-natal oocyte loss. Mutations in NOBOX seem to occur more frequently in the Caucasian POI population. The NOBOX missense variant, p.R355H, first identified in 1 of 96 Caucasian POI subjects, could disrupt the binding of the NOBOX homeodomain to DNA (Qin 2007). Bouilly et al. (2011) subsequently demonstrated that loss-of-function NOBOX mutations accounted for 6.2% of POI cases in a Caucasian cohort of 178 participants.

Gonadotropin Receptors

FSHR and LHR are glycoprotein hormone receptors which together with their binding hormones, LH and FSH, are essential for normal reproductive function. A linkage analysis in a Finnish population revealed a significant association between a locus containing both FSHR and LHR genes and ovarian developmental disorder. Sequencing of the entire FSHR gene revealed a homozygous missense mutation, p.A189V (Aittomaki 1995) that has been observed only in the Finnish population suggesting a founder effect. From in vitro studies it was observed that the p.A189V mutation had altered receptor folding and it failed to reach the plasma membrane, causing complete FSH resistance.

STAG3

Using a combination of genome wide linkage analysis and exome sequencing in a consanguineous (people descended from the same ancestor) family with POI, Caburet et al. (2014) identified a homozygous 1-bp deletion in the gene encoding stromal antigen 3 (STAG3). All affected family members analyzed were homozygous for the mutation. This finding was supported by the phenotype of female mice with a homozygous disruption in Stag3. These mice were sterile and their fetal oocytes were arrested at early prophase I, leading to oocyte depletion at one week of age.

Genes involved in meiosis and DNA repair

It has been proposed that genetic defects in meiotic genes are involved in POI as several meiotic-gene knockout mice have phenotypes resembling human POI. Wang et al (2014) identified a heterozygous mutation in a meiotic gene, HFM1, which encodes a protein necessary for homologous recombination of chromosomes, in two sisters suffering from POI. Variants in genes that affect the normal processes of primordial germ-cell proliferation, oocyte meiosis, and follicle formation are plausible candidates in the pathogenesis of POI. Also, Hfm1-deficient mice are infertile (Guiraldelli 2013).

BRCA1 mutations, fertility treatments and POI

As infertility is associated with breast and ovarian cancer risks, Oktay et al (2010) hypothesized that mutations in the BRCA1 and BRCA2 genes may be associated with low response to fertility treatments. Low response to ovarian stimulation is a strong indication of diminished ovarian reserve and infertility. As DNA repair is deficient in patients with BRCA mutations, their oocytes may be more prone to DNA damage, and when DNA damage cannot be repaired, apoptotic pathways are activated. Thus, oocytes with deficient BRCA function may be prematurely eliminated, resulting in early depletion of oocyte pool and, as a consequence, POI. Oktay et al (2010) found that in BRCA mutation-positive patients, the incidence of low ovarian response was significantly higher compared to BRCA mutation-negative patients. Of note, all BRCA mutation-positive low responders to fertility treatment had BRCA1 mutations, but not BRCA2 mutations. These finding can explain, in part, the link between infertility and breast/ovarian cancer risks.

Genome Wide Association Studies in POI

Genes mentioned above were chosen as candidates in the context of POI because they are known to be associated with folliculogenesis or other related biological pathways. Genome Wide Association Studies (GWAS), on the other hand, is unbiased and discovery-driven, providing a comprehensive approach that is based on a case-control design.

PTHB1 and ADAMTS19

In a two-stage association study in a Korean population (101 cases and 87 controls), Kang et al. (2008) showed a strong association of POI with the PTHB1 gene. PTHB1 was first identified in osteoblastic cells and then in other tissues, but not the ovary, and its physiological function remains unknown. PTHB1 variants have been described in a subset of patients with Bardet–Biedl syndrome who sometimes exhibit POI. It is possible that the study has identified PTHB1 as a novel susceptibility gene for POI.

Knauff et al. (2009) conducted a GWAS involving 309 158 SNPs in 99 unrelated idiopathic Caucasian POI patients and 235 unrelated controls, focusing on chromosomal areas and candidate genes previously implicated in POI. A genome-wide significant association was observed for a SNP (rs246246) which maps to an intron of ADAMTS19, a gene encoding a zinc-dependent metalloprotease, known to be up-regulated in the female mouse gonads during sexual differentiation. Although limited by sample size, this proof-of-principle study's findings did reveal ADAMTS19 as a biologically plausible candidate gene for POI.

Early Menopause and Primary Ovarian Insufficiency

Early menopause (EM) affects up to 10% of the female population. Perry et al (2013) undertook a meta-analysis of GWAS in 3493 EM cases and 13 598 controls from 10 independent studies. Although no novel genetic variants were discovered, 17 variants previously associated with normal age at natural menopause as a quantitative trait (QT), were found to be associated with both EM and POI. This included genes implicated in DNA repair (EXO1, HELQ, UIMC1, FAM175A, FANCI, TLK1, POLG, PRIM1) and immune function (IL11, NLRP11, BAT2) suggesting common biological and genetic mechanism for these two related phenotypes. The 17 alleles associated with younger menopause age were also associated with increased risk of EM and POI. Their data supported the hypothesis that EM and POI have overlapping polygenic aetiology, with individuals who carry more risk variants for lower-age-at-menopause having an increased risk of EM and POI.

In GWAS, genetic variations are investigated in unrelated affected individuals compared to matched controls by means of single nucleotide polymorphisms (SNPs). The drawback is that the SNPs are not chosen on the basis of their possible functional effect. The approach follows the common disease-common variant hypothesis and would fail to identify rare and novel variations in genes involved in oocyte development and maturation.

A rapid decline in the cost of sequencing is enabling effective mutational analysis for rare and common variations along with chromosomal deletions and copy number analysis. Application of genome or exome sequencing to identify variants can confirm and validate the role of candidate genes described in this overview and reveal the function of new genes which have a role in the etiology of POI.

Genetic heterogeneity

The genetic studies described above demonstrate the high genetic heterogeneity of POI. It is likely that most severe familial cases of early onset (before age of 30) are caused by rare, highly penetrant mutations, while POI of later onset are caused by a large number of less penetrant alleles. It is also possible that different genes play a role in the development of familial and sporadic POI. The condition should be regarded as a complex genetic disease and as with other complex genetic disorders; it is characterized by familial clustering without an obvious Mendelian pattern of inheritance because several genes, their mutations and environmental factors contribute to the etiology of the disease.

Can genetic testing impact on POI management?

Considering that 1% of women suffer from primary ovarian insufficiency, the underlying mechanism is unknown in 90% of the cases, and that an even a larger fraction of infertile women may be suffering from occult primary ovarian insufficiency, discovery of susceptibility genes for POI will have positive implications for understanding the link between infertility and the pathogenic mechanism. However, as the pathogenic mechanism remains unknown in most cases of POI, should women with idiopathic POI be screened for genetic alterations?

Screening for the most prevalent alterations i.e. X chromosome abnormalities, FMR1 premutations and the BRCA1 alleles would not only identify the cause of disease but also help affected women make more informed reproductive decisions. Also, when a genetic alteration is observed in one of the POI candidate genes in a woman suffering from idiopathic POI, it can be useful for family counselling, and to help predict other female relatives who might be at higher risk for POI and fertility loss at a young age. This information is particularly important now, as many women choose to conceive in their late thirties and early forties, when the risk of POI is highest. Women who experience irregular menstrual cycles should be concerned and consider not deferring child bearing to a later age due to an increasing risk of POI.

Genome sequencing can identify potential cause of both female and male infertility, as well as carrier status for multiple genetic disorders, helping couples make more informed reproductive decisions. Important limitations of genomic sequencing to predict disease risk include its potential use in genetic selection. While for a condition such as POI, information gathered from genetic screening may allow those at risk to start trying to conceive at a younger age, and increase chances of a healthy pregnancy; screening for genetic diseases may influence the decision to carry pregnancies to term. For example, there is robust data indicating that well over 50% of Down's syndrome pregnancies detected by antenatal screening are selectively terminated (Natoli 2012, Wu 2013). For healthcare providers, the ethical consequences of applying genetic screening should be evaluated on a case-by-case basis. ■

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