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Review

Aetiological coding sequence variants in non-syndromic premature ovarian failure: From genetic linkage analysis to next generation sequencing

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ABSTRACT

Premature ovarian failure (POF) is a frequent pathology affecting 1–1.5% of women under 40 years old. Despite advances in diagnosing and treating human infertility, POF is still classified as being idiopathic in 50–80% of cases, strongly suggesting a genetic origin for the disease. Different types of autosomal and X-linked genetic anomalies can originate the phenotype in syndromic and non-syndromic POF cases. Particular interest has been focused on research into non-syndromic POF causative coding variants during the past two decades. This has been based on the assumption that amino acid substitutions might modify the intrinsic physicochemical properties of functional proteins, thereby inducing pathological phenotypes. In this case, a restricted number of mutations might originate the disease. However, like other complex pathologies, POF might result from synergistic/compensatory effects caused by several low-to-mildly drastic mutations which have frequently been classified as non-functional SNPs. Indeed, reproductive phenotypes can be considered as quantitative traits resulting from the subtle interaction of many genes. Although numerous sequencing projects have involved candidate genes, only a few coding mutations explaining a low percentage of cases have been described. Such apparent failure to identify aetiological coding sequence variations might have been due to the inherent molecular complexity of mammalian reproduction and to the difficulty of simultaneously analysing large genomic regions by Sanger sequencing.

The purpose of this review is to present the molecular and cellular effects caused by non-synonymous mutations which have been formally associated, by functional tests, with the aetiology of hypergonadotropic non-syndromic POF. Considerations have also been included regarding the polygenic nature of reproduction and POF, as well as future approaches for identifying novel aetiological genes based on next generation sequencing (NGS).

Contents

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1. Introduction

Human infertility can be considered a public health concern since it affects ~15% of couples worldwide. Up to 30% of cases are caused by exclusive female factors, such as endometriosis, tubal disease and ovulation dysfunction (Smith et al., 2003). At least 14% of women show signs of hypofertility related to a decrease in ovarian reserve which, in some cases, evolves to early menopause (Santoro, 2011). Premature ovarian failure (POF) affects 1–1.5% of women under 40 years old and ~0.1% under the age of 30 (Conway, 2000; Coulam et al., 1986; Luborsky et al., 2003). In most cases, POF can be considered as the final stage of primary ovarian insufficiency (POI), a heterogeneous disease involving ovarian function impairment and irregular ovulation (Cox and Liu, 2014; Nelson, 2009). Although POI has been proposed recently as conditions describing ovarian dysfunction leading to infertility, the more classic term POF will be used in the present review. From a clinical point of view, POF has been defined as 4–6 months of amenorrhoea before the age of 40 related to high follicle stimulating hormone (FSH) plasma levels (>40UI/l) (Coulam, 1982). Hypergonadotropic hypogonadism in such patients results from an ovarian inability to close (via hormone signalling) a negative feedback loop on the synthesis of pituitary-secreted gonadotropins. POF women suffer primary (PA) or secondary amenorrhoea (SA), depending on the occurrence (SA) or not (PA) of menarche (Timmreck and Reindollar, 2003). In both cases, ovarian dysfunction can be found as an isolated phenotype (non-syndromic) or accompanying concomitant medical conditions (e.g. Turner's, BPES X syndromes). Distinct mechanisms (which might be deregulated at multistep levels) have been proposed for explaining the POF phenotype. This pathology might result from the development of a few follicles during embryogenesis, as well as from their abnormal recruitment. Enhanced follicular atresia could also lead to an early depletion of follicular stock (Goswami and Conway, 2005; Persani et al., 2011).

Aetiologically, POF has been linked to iatrogenic events (especially pelvic surgery and anti-cancer treatment), autoimmune conditions, infectious agents (viral oophoritis), metabolic disorders (galactosaemia) and environmental factors (Dragojević-Dikić et al., 2010; Goswami and Conway, 2005; Laissue et al., 2008; Persani et al., 2010). Unfortunately, despite advances in diagnosing and treating human infertility, POF is still classified as being idiopathic in 50–80% of cases, strongly suggesting a genetic origin for the disease. Differing types of autosomal and X-linked genetic anomalies, such as large chromosomal rearrangements and sequence point mutations, can originate the phenotype in syndromic and non-syndromic POF cases. Ovarian failure in Turner's syndrome (XO monosomy) might be caused by the haploinsufficiency of genes located on critical X chromosome regions which escape inactivation (Elsheikh et al., 2002; Zinn and Ross, 1998). X chromosome deletions and translocations have led to POF loci (POF-1, POF-2 and POF-3) being identified which might contain critical candidate genes (Davison et al., 2000; Lacombe et al., 2006; Marozzi et al., 2000; Powell et al., 1994; Tharapel et al., 1993). *FMR1* premutations displaying an intermediate number (between 55 and 200) of CGG repeats located on the 5′UTR region of the gene as well as *FMR2* microdeletions have been linked to an increased predisposition to POF (Allingham-Hawkins et al., 1999; Murray et al., 1998, 1999; Sherman, 2000). Sequence point mutations of a transcription factor (*FOXL2*) originate the ovarian phenotype in the BPES syndrome (Beysen et al., 2009; Crisponi et al., 2001).

Particular interest has been focused on research into non-syndromic POF causative coding variants during the past two decades. This has been based on the assumption that amino acid substitutions might modify the intrinsic physicochemical properties of functional proteins, thereby inducing pathological phenotypes. In this case, a restricted number of mutations might originate the disease. However, like other complex pathologies, POF might result from synergistic/compensatory effects caused by several low-to-mildly drastic mutations which have frequently been classified as non-functional SNPs (Gibson, 2012; Kryukov et al., 2007). Indeed, reproductive phenotypes can be considered quantitative traits resulting from the subtle interaction of many genes (L'Hôte et al., 2010).

Although numerous sequencing projects have involved candidate genes, only a few coding mutations explaining a low percentage of cases have been described. Mutations in *FSHR*, *LHCGR*, *NR5A1*, *NOBOX*, *FOXL2*, *FIGLA*, *BMP15*, *NANOS3* and *STAG3* have been formally validated as being causative of non-syndromic POF (Aittomäki et al., 1995; Beau et al., 1998; Caburet et al., 2014; Di Pasquale et al., 2004; Doherty et al., 2002; Laissue et al., 2008; Latronico et al., 1996; Lourenço et al., 2009; Qin et al., 2007; Rannikko et al., 2002; Rossetti et al., 2009; Santos et al., 2014; Touraine et al., 1999; Wu et al., 2013; Zhao et al., 2008). Such apparent failure to identify aetiological coding sequence variations might have been due to the inherent molecular complexity of mammalian reproduction and to the difficulty of simultaneously analysing large genomic regions by Sanger sequencing.

The purpose of this review is to present the molecular and cellular effects caused by non-synonymous mutations which have been formally associated by functional tests with the aetiology of hypergonadotropic non-syndromic POF. To present this data, the relevant POF genes have been classified into three distinct groups: genes encoding gonadotropins receptors, transcription factor (TF) genes and other types of gene. Considerations have also been included regarding the polygenic nature of reproduction and POF, as well as future approaches for identifying novel aetiological genes based on next generation sequencing (NGS).

2. Genes encoding gonadotropin receptors: follicle stimulating hormone receptor (*FSHR*) and luteinising hormone/choriogonadotropin receptor (*LHCGR*)

Subtle regulation of the hypothalamic-pituitary-gonadal (HHG) axis is crucial in humans for proper sexual development and gonad function. Gonadotropin-releasing hormone (GnRH) neurons migrate across the cribiform plate into the hypothalamus during embryo development to contact the hypophyseal-portal vascular system (Tobet and Schwarting, 2006). These cells secrete the GnRH peptide (in a pulsatile fashion) which in turn stimulates the pituitary synthesis and secretion of the follicle stimulating (FSH) and luteinising (LH) hormones. FSH and LH bind to specific gonadal transmembrane receptors named FSHR and LHCGR, respectively to regulate particular reproductive functions. The negative feedback loop in the pituitary synthesis of gonadotropins is closed by the secretion of steroid and non-steroid substances (e.g. oestradiol, progesterone, inhibins A and B, gonadotrophin surge-attenuating factor-GnSAF) (Messinis, 2006; Messinis et al., 2014; Plant, 2008). FSHR participates in regulating ovarian physiology in females by stimulating oestrogen synthesis and follicle development while LHCGR-related effects