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Autosomal single-gene disorders involved in human infertility

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ABSTRACT

Human infertility, defined as the inability to conceive after 1 year of unprotected intercourse, is a health-care problem that has a worldwide impact. Genetic causes of human infertility are manifold. In addition to the chromosomal aneuploidies and rearrangements, single-gene defects can interfere with human fertility. This paper provides a review of the most common autosomal recessive and autosomal dominant single-gene disorders involved in human infertility. The genes reviewed are *CFTR*, *SPATA16*, *AURKC*, *CATSPER1*, *GNRHR*, *MTHFR*, *SYCP3*, *SOX9*, *WT1* and *NR5A1* genes. These genes may be expressed throughout the hypothalamic-pituitary–gonadal-outflow tract axis, and the phenotype of affected individuals varies considerably from varying degrees of spermatogenic dysfunction leading to various degrees of reduced sperm parameters, through hypogonadotropic hypogonadism reslting in pubertal deficiencies, until gonadal dysgenesis and XY and XX sex reversal. Furthermore, congenital bilateral absence of the vas deferens, as well as premature ovarian failure, have been reported to be associated with some single-gene defects.

1. Introduction

Infertility is a disease of the reproductive system characterized by inability of a couple to conceive after 1 year of unprotected intercourse (Venkatesh et al., 2014), and it affects approximately 15% of the reproductive-age population (Di Spiezio Sardo et al., 2016).

Genetic causes of human infertility include numerical and structural chromosomal abberations and single-gene disorders (Zorrilla and Yatsenko, 2013). Among abnormalities in chromosome number, Turner syndrome (45, X) in women and Klinefelter syndrome (47, XXY) in men, resulting from a meiotic non-disjunction of gametogenesis, are the most frequent (Bojesen and Gravholt, 2007; Uematsu et al., 2002). Robertsonian translocations, resulting in a derivative chromosome composed of 2 long arms from 2 acrocentric chromosomes (13, 14, 15, 21, and 22), are recognized among the most common structural chromosomal abnormalities in humans. The most frequent robertsonian translocations are der(13;14) and der(14;21) (Engels et al., 2008; Harton and Tempest, 2012; Martin, 2008; O'Flynn O'Brien et al., 2010; Roux et al., 2005). Furthermore, human puberty and fertility are ensured and controlled by a multitude of single-genes (Matzuk and Lamb, 2008). These genes are expressed in 4 different locations or compartments: hypothalamus, pituitary, gonads and outflow tract (Layman, 2003), and mutations in these genes may cause pubertal and reproductive deficiencies in humans (Layman, 2002). Single-gene disorders causing human infertility may affect only men, only women or both sexes. The inheritance patterns depends on the chromosomal location of the concerned gene (X, Y or 1–22 autosomes) and if one or two mutated copies of the gene are needed for the expression of the mutation (dominant or recessive) (Chial, 2008).

In this review, we will focus on the most common autosomal recessive (i) and autosomal dominant (ii) single-genes defects that have been clearly shown to be involved in human infertility.

2. Autosomal recessive single-gene disorders

2.1. CFTR gene and congenital bilateral absence of the vas deferens

The *CFTR* (cystic fibrosis transmembrane conductance regulator) gene is located on the long arm of chromosome 7q31.2 and

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contains 27 coding exons that spread over 230 kb. Its normal allele produces a 6.5-kb mRNA that encodes a 1480-amino acid integral membrane protein that functions as a regulated chloride channel in a variety of epithelial cells (Hwang et al., 2010; Moskowitz et al., 2005). *CFTR*-related disorders are inherited in an autosomal recessive manner (Hwang et al., 2010; Layman, 2003).

Cystic fibrosis (CF) is a heterogeneous genetic disease caused by mutations in *CFTR* gene. There is a positive correlation between CF and congenital bilateral absence of the vas deferens (CBAVD), a form of obstructive azoospermia caused by the disconnection between the epididymis and the ejaculatory duct (O'Flynn O'Brien et al., 2010; Tahmasbpour et al., 2014). 60–90% of patients with CBAVD present mutations in *CFTR* gene (Ferlin et al., 2007; Georgiou et al., 2006; O'Flynn O'Brien et al., 2010).

The genetics of CBAVD caused by *CFTR* mutations is extremely complex (Layman, 2003), because men with CBAVD usually either have two mild mutations in the *CFTR* gene or the combination of a severe mutation and a mild mutation (O'Flynn O'Brien et al., 2010). The most common severe mutation is a 3-bp deletion, resulting in loss of a phenylalanine at amino acid position 508 of the *CFTR* polypeptide (F508del). It is found in 60–70% of patients with CBAVD (Georgiou et al., 2006; Hwang et al., 2010; Moskowitz et al., 2005; O'Flynn O'Brien et al., 2010). Additionally, a 5 T polymorphism within intron 8 in the *CFTR* gene was found in 21% of the subjects and is considered a mild mutation (Sertić et al., 2001; Tahmasbpour et al., 2014; von Eckardstein et al., 2000). The 7 T polymorphism within intron 8 and the missense R117H mutation within exon 4 in the *CFTR* gene were also reported (Chillón et al., 1995; Dada et al., 2011). Other common mutations including G542X, G551D, R553X, W1282X and N1303K occur with a frequency of 1–2% (Tahmasbpour et al., 2014).

The treatment options for men with *CFTR* mutation causing obstructive azoospermia include both microsurgical epididymal sperm aspiration and testicular sperm extraction, in conjunction with intra cytoplasmic sperm injection (ICSI) (Hwang et al., 2010). This may be a useful method of treatment as long as the female does not also carry the *CFTR* mutation (Ferlin et al., 2007). Partners who both carry the mutation should be advised to have pre-implantation genetic diagnosis to avoid passing the abnormality to their offspring (Georgiou et al., 2006; O'Flynn O'Brien et al., 2010).

2.2. SPATA16 gene and globozoospermia

SPATA16 (spermatogenesis-associated 16, also known as *NYD-SP12*) is located on 3q26.32 and is composed of 11 exons encoding for a highly conserved protein of 569 amino acid protein. The most conserved domain of the protein is a tetratricopeptide repeat (TPR) domain, a protein–protein interaction domain commonly, but not exclusively, found in cochaperone proteins. The *SPATA16* protein is specifically expressed in human testis and localizes to the Golgi apparatus (Blatch and Lassle, 1999; El Inati et al., 2012; Miyamoto et al., 2012; Xu et al., 2003).

SPATA16 gene mutation was identified in a consanguineous Jewish family including three brothers suffering from globozoospermia; a same homozygous sequence variation in exon 4 (c. 848G → A) was revealed in all affected brothers. Since the two parents and two healthy brothers are heterozygous for the mutation and the third unaffected brother appeared to be homozygous for the wild-type sequence, an autosomal recessive inheritance of *SPATA16* gene mutation has been certified (Dam et al., 2007). The c.848G → A mutation is predicted to change an amino acid of a highly conserved residue (p.R283Q) located at the C-terminal end of the highly conserved TPR domain. In addition, this mutation affects the last nucleotide of exon 4 and disrupts the 5′ splice site of intron 4. Thus, it leads to an inappropriate splicing of exon 4, causing the disruption of the TPR domain since 36 amino acids are deleted (Dam et al., 2007; El Inati et al., 2012; Miyamoto et al., 2012).

2.3. AURKC gene and large-headed polyploidy spermatozoa

AURKC (aurora kinase C) gene is located on 19q13.3-qter. It has 7 exons and is highly expressed in testes. A homozygous deletion in exon 3 of *AURKC* gene (c.144delC) was detected in 10 infertile men with a large-headed polyploidy spermatozoa phenotype. This mutation introduces a frameshift, leading to a premature stop codon and resulting in a truncated protein that lacks the kinase domain. The absence of *AURKC* causes male infertility owing to the production of large headed multi flagellar polyploidy spermatozoa (Dieterich et al., 2007; El Inati et al., 2012; Miyamoto et al., 2012). Since all the spermatozoa of these patients are tetraploid, it was strongly suggested that *AURKC* is implicated in the segregation of chromosomes and/or meiotic cytokinesis, explaining the large size of the gametes (Dieterich et al., 2009). In the last study, the (c.144delC) mutation was further studied in a larger cohort of North African patients, and a frequency of heterozygotes of over 1 in 50 was established, implying an expected prevalence of 1/10,000 affected men. This high frequency makes *AURKC* infertility among the most frequent single-gene defect in this population. Interestingly, the authors identified two fertile homozygous females, excluding a fundamental role of *AURKC* in female meiosis and confirming the differences between male and female meiotic mechanisms (Dieterich et al., 2009; El Inati et al., 2012).

2.4. CATSPER1 gene and oligo-astheno-theratozoospermia

CATSPER1 (cation channel sperm associated 1) gene is located on chromosome 11q13.1 and it encodes for a *CATSPER1* protein (Avenarius et al., 2009). This protein consists of a single, six-transmembrane-spanning repeat with a P loop between transmembrane domains S5 and S6 that shows homology to four-repeat calcium (Ca_v) channels, and is required for the entry of Ca^{2+} into the flagellum and for the hyperactivation of the sperm once they enter the female reproductive tract (Ren et al., 2001).

The *CATSPER1* gene was selected for a homozygosity mapping in two consanguineous Iranian families with cases of non-syndromic male infertility. All affected males demonstrated an oligo-astheno-theratozoospermia compound semen abnormality. In both families, an insertion mutation was observed, segregating as a non-syndromic autosomal recessive pathology: In the first one, the mutation (c.539-540insT) introduces a premature stop codon that could eventually lead to the production of a truncated protein of 188 amino acids. In the second one, the mutation (c.948-949insATGGC) also introduces a premature stop codon with a resulting protein of 335 residues. In both cases, the truncated protein produced lacks all six transmembrane domains, abolishing the *CATSPER1* channel activity (Avenarius et al., 2009; El Inati et al., 2012). These results suggest that *CATSPER1* is essential for normal male fertility in humans.

2.5. GNRHR gene and normosmic idiopathic hypogonadotropic hypogonadism

The human *GNRHR* (gonadotropin-releasing hormone receptor) gene spans 18.7 kb of genomic sequence on chromosome 4q13.2 and consists of three exons (Fan et al., 1994; Kaiser et al., 1994; Kakar et al., 1992). *GNRHR* gene was the first gene found to cause autosomal recessive normosmic idiopathic hypogonadotropic hypogonadism (IHH) (de Roux et al., 1997; Kim et al., 2010; Layman et al., 1998). It encodes for a 328 amino acid protein, containing the characteristic seven transmembrane domains, along

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