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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

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

with an N-terminal extracellular domain, three extracellular and three intracellular loops. The extracellular domains and/or transmembrane domains are involved in the formation of the ligand-binding pocket (Kim et al., 2010; Millar et al., 2004). The *GNRHR* protein is a G-protein coupled receptor (GPCR) expressed on the cell surface of pituitary gonadotropes (Fan et al., 1995). This GPCR interacts with pulsatile GnRH to initiate the secretion of FSH and LH which stimulate the testes or ovaries to produce sex steroids and gametes (Kim et al., 2010).

At least 19 different mutations have been identified in this GPCR, which consist mostly of missense mutations. Most affected patients have compound heterozygous *GNRHR* mutations that may cause either complete IHH (no evidence of puberty) or incomplete IHH (partial evidence of puberty) (Kim et al., 2010). The first *GNRHR* mutations was identified by de Roux et al. (1997) in a 22-year-old male with delayed puberty at 18, decreased libido, small testes and a small penis. He was found to harbor compound heterozygous *GNRHR* mutations Gln106Arg/Arg262Gln. The first mutation, affecting the first extracellular loop of the receptor, dramatically decreased the binding of GnRH to its receptor, and the second, affecting the third intracellular loop, did not modify the binding of the hormone but decreased the activation of phospholipase C. The patient's older sister, who had thelarche at age 14 years and menarche at age 18 (with only one period), exhibited also compound heterozygosity for these two mutations. His unaffected younger sister and their unaffected parents were heterozygous for either of the two mutations, indicating autosomal recessive inheritance. Other compound heterozygous *GNRHR* mutations (Arg262Gln/Tyr284Cys) were later identified in one family with four severely affected IHH patients, but not in unaffected sibs (Layman et al., 1998). More later, Meysing et al. (2004) revealed two heterozygous mutations in the coding sequence of *GNRHR* in a woman with IHH: On one allele, two nucleotide substitutions at position 30 and 31 in exon 1, resulting in a two-amino acid substitution (N10K + Q11K) in the N terminal extracellular domain, and on the other allele, a nucleotide substitution at position 959 in exon 3, resulting in P320L substitution in the seventh transmembrane domain of the GnRHR. The mother of the patient was found heterozygous for only the (N10K + Q11K) mutation. These revealed mutations highlight the differential sensitivity of LH and FSH to GnRH. More recently, a homozygous missense-mutation in exon 1 of the *GNRHR* gene (g. G7167A; p. Arg139His) was detected in a female patient with normosmic IHH (Zernov et al., 2016). Among the identified mutations, Gln106Arg and the Arg262Gln have been determined to represent the most common alleles in all reported cases of human *GNRHR* mutations (Bhagavath et al., 2005).

2.6. MTHFR gene and spermatogenesis arrest

The *MTHFR* (methylenetetrahydrofolate reductase) gene, located on the short arm of chromosome 1 (Maglott et al., 2005), codes for an enzyme involved in folate metabolism, a critical factor in DNA methylation and the spermatogenetic process (Nuti et Krausz, 2008). The *MTHFR* enzyme deficiency and hypomethylation may inhibit gene expression, cause absence of germinal cells and spermatogenesis arrest (Marques et al., 2008). Mutations in *MTHFR* gene have a negative effect on male infertility (O'Flynn O'Brien et al., 2010; Tahmasbpour et al., 2014). The 677C/T genomic change, leading to the substitution of an alanine for a valine in the *MTHFR* protein, is the most common in infertile men with *MTHFR* deficiency (Frosst et al., 1995; Tahmasbpour et al., 2014). This mutation, by decreasing the activity of the *MTHFR* enzyme, leads to the dysregulation of folic acid metabolism, causing errors in the methylation of genomic DNA and subsequent implications in spermatogenesis (Frosst et al., 1995; Nuti and

Krausz, 2008; O'Flynn O'Brien et al., 2010). A second common mutation in the same gene was described (Van der Put et al., 1998; Weisberg et al., 1998). In this mutation, an A to C transition at nucleotide 1298 (A1298C) leads to a glutamate to alanine substitution in the *MTHFR* protein. The A1298C mutation, like the C677T mutation, results in a decrease in *MTHFR* activity that is more pronounced in the homozygous (CC) than in the heterozygous (AC) or normal (AA) states (Friedman et al., 1999). The homozygosity for both C677T and A1298C mutations in the *MTHFR* gene was shown to be a risk factor for idiopathic male infertility in Indian population (Singh et al., 2010, 2005).

3. Autosomal dominant single-gene disorders

3.1. SYCP3 gene and non-obstructive azoospermia

The human *SYCP3* (Synaptonemal complex protein 3) gene is composed of nine exons and is located on chromosome 12. Its expression is specific to the testis. It encodes a 236 amino acid protein with two coiled-coil-forming regions (Miyamoto et al., 2012, 2003). *SYCP3*, a DNA-binding protein mediating homologous chromosome mating and synapsis, is a structural element of the synaptonemal complex (Gurkan et al., 2013; Martinez et al., 2007; Miyamoto et al., 2003). Most *SYCP3* mutations are heterozygous mutations with dominant-negative effect on the region encoding the C-terminal coiled coil of the protein (Geisinger and Benavente, 2016).

In Miyamoto et al. (2003), *SYCP3* gene was identified for the first time as an azoospermia culprit gene: a heterozygous 1 bp deletion (643delA) was found in two azoospermic patients with maturation arrest (non-obstructive azoospermia). The deletion results in a premature stop codon and truncation of the C-terminal, coiled-coil-forming region of the *SYCP3* protein. The examination of testis biopsy samples from the patients with the 643delA mutation showed a profoundly abnormal spermatogenic process due to complete early meiotic arrest, suggesting that *SYCP3* has an essential meiotic function in human spermatogenesis that is compromised by the 643delA mutation via the dominant negative effect on the wild allele function during meiosis.

Recently, a heterozygous T657C genetic change in the *SYCP3* gene was identified in Iranian women presenting recurrent pregnancy losses of unknown causes. This polymorphism was investigated in the genome of 100 affected women as well as 100 normal fertile women having at least one healthy child, and the frequency of the heterozygous genotype was significantly higher in affected women, suggesting that the T657C mutation of the *SYCP3* gene is possibly associated with recurrent pregnancy loss of unknown cause in human (Sazegari et al., 2014).

By cons, in Martinez et al. (2007), no mutations were observed in the coding region of SYCP3 gene in a sample of azoospermic or severe oligozoospermic infertile male patients without Y chromosome deletions and having Caucasian-Spanish or Maghribian origins. In this study, the authors reported that *SYCP3* mutations were not correlated with the genetic susceptibility to meiotic arrest found mostly in European individuals and predicted that genetic background might explain the differences in the frequency of *SYCP3* mutations and/or polymorphisms in various populations (Gurkan et al., 2013; Martinez et al., 2007).

3.2. NR5A1 gene, gonadal dysgenesis and primary ovarian insufficiency (POI)

Human *NR5A1* (nuclear receptor subfamily 5 group A member 1) gene is located on the long arm of chromosome 9 (9q33) and consists of 7 exons spanning approximately 30 kb of genomic

DNA (Lin and Achermann, 2008; Oba et al., 1996; Taketo et al., 1995; Wong et al., 1996). It encodes for a 461 amino acid protein (NR5A1) (Lin and Achermann, 2008), which is a member of the nuclear receptor superfamily and is a key transcriptional regulator of genes involved in the hypothalamic-pituitary-steroidogenic axis (Bashamboo et al., 2010; Luo et al., 1994; Morohashi et al., 1992). NR5A1, also called steroidogenic factor-1 (SF-1), consists of a DNA-binding domain (DBD) including two zinc fingers, a flexible hinge region, a ligand-binding domain (LBD), and two activation function domains: AF-1 and AF-2 (Hoivik et al., 2010; Krylova et al., 2005; Sablin et al., 2009). NR5A1 has a key role in gonadal development, it is expressed in Sertoli and Leydig cells of the developing testis and in Sertoli cells of the prepubertal and adult testis, as well as in multiple cell types in the fetal, postnatal, prepubertal, and mature ovary (Bashamboo et al., 2010; Hanley et al., 1999; Ikeda et al., 1994; Morohashi et al., 1994). NR5A1 mutations are associated with a wide spectrum of phenotypes, including 46,XY partial and complete gonadal dysgenesis with or without adrenal failure, penoscrotal hypospadias, micropenis with anorchidia, and 46,XX POI (Bashamboo et al., 2010; Lin and Achermann, 2008; Lourenço et al., 2009).

In Lourenço et al. (2009) different mutations was identified in the NR5A1 gene to be associated with a 46,XY disorders of sex development and a range of ovarian anomalies, including 46,XX gonadal dysgenesis and 46,XX POI. Among these mutations, we can cite a missense heterozygous mutation (c.3G → A transition in the first codon of NR5A1), that predicts a p.Met1Ile change, and two heterozygous frameshift mutations (c.666delC and c.390delG), which are predicted to alter the protein sequence and create a premature termination codon in the messenger RNA (mRNA), both at codon 295, truncating the normal protein from 461 to 295 amino acids.

Mutation screening of the NR5A1 gene in 315 mixed ancestry patients with unexplained spermatogenic failure (azoospermia or oligozoospermia) revealed 6 heterozygous mutations in 7 infertile men. Four among them, p.Pro311Leu, p.Arg191Cys, p.Gly121Ser and p.Asp238Asn, were identified in single patients. The other 2 mutations were present in the same allele in three men of African origin (p.Gly123Ala/p.Pro129Leu) (Bashamboo et al., 2010). This same change was previously described in a West African girl with POI, suggesting that this mutation may be present at low levels in the general population (Lourenço et al., 2009). These reported NR5A1 mutations were all missense mutations in the hinge region or proximal LBD of the protein. Functional studies indicated that these mutations impaired NR5A1 transactivational activity (Bashamboo et al., 2010).

Recently, a novel heterozygous mutation (c.195G > A) in NR5A1 gene was identified in three Brazilian 46,XY siblings with normal testosterone levels and their mother with primary ovarian insufficiency (Fabbri et al., 2014). The nucleotide change c.195G > A is predicted to cause the substitution of a cysteine residue in position 65, which is located at the second zinc finger of the DBD and is highly conserved across mammalian species (Little et al., 2006), by a tyrosine amino acid (p.Cys65Tyr) in the NR5A1 protein (Fabbri et al., 2014).

3.3. WT1 gene, gonadal malformations, spermatogenic impairment and premature ovarian failure (POF)

The WT1 (Wilms' tumor 1) gene, located at 11p13, spans approximately 50 kb and contains 10 coding exons (Sakamoto et al., 2001). It encodes a protein with a C-terminal zinc finger domain that is involved in DNA and RNA binding. WT1 acts as a transcription factor through the interaction of WT1 activation and repression domains with its targets (Discenza and Pelletier, 2004; Scharnhorst et al., 2001; Seabra et al., 2015). WT1 was first

identified as the gene responsible for Wilms' tumor. It was later associated with a plethora of clinical phenotypes often accompanied by urogenital defects and male infertility (Seabra et al., 2015).

Phenotypic expression of WT1 mutations varies and depends on the affected protein domains (Seabra et al., 2015): Missense or nonsense mutations affecting the WT1 protein C-terminus typically have severe impacts, gonadal dysgenesis and/or nephropathy, resulting from a dominant negative action of heterozygous WT1 missense mutations or from haploinsufficiency (Huff, 2011; Little and Wells, 1997; Royer-Pokora et al., 2004). However, patients with N-terminal missense mutations are expected to show milder gonadal malformations since the DNA binding domain should remain intact (Köhler et al., 2004).

A heterozygous point mutation at intron 7 (+2,T → G) of WT1 gene in a patient with Wilms' tumor and congenital male genitourinary malformation was described in 2001. The position of the mutation is at a splice donor site of intron 7, which causes the splicing out of exon 7, generating the truncation of the protein in the C-terminal zinc finger domain (Sakamoto et al., 2001). This study suggested that WT1 may function in gonadogenesis, in addition to its nephrogenesis and Wilms' tumor tumorigenesis fonctions.

R362Q and K386R WT1 missense mutations, both affecting the zinc finger domain and causing WT1 protein loss of function, were recently found associated with non-obstructive azoospermia without major gonadal malformation in a Chinese population, suggesting that WT1 is also important for human spermatogenesis (Wang et al., 2013).

Motivated by the results of the previous study, Seabra et al. evaluated the impact of WT1 mutations in isolated severe spermatogenic impairment, in a Portuguese population of non-obstructive azoospermic and severe oligozoospermic patients. They found two WT1 missense substitutions at higher frequency in patients than in controls: the first was a novel variant in exon 1 (p.Pro130Leu) disrupting a mammalian-specific polyproline stretch within the self-association domain and it was more frequent in azoospermic patients, and the second was a rare variant in a conserved residue in close proximity to the first zinc finger (pCys350Arg) and it was more frequent in severe oligozoospermic patients. These results suggested a role for WT1 defects in severe spermatogenic failure in European ancestry populations (Seabra et al., 2015).

Recently, WT1 protein was shown to have novel roles linked to female fertility: an ovarian follicle development function by regulating granulosa cell differentiation (Gao et al., 2014) and an oviductal proteostasis regulation function (Nathan et al., 2017). Due to the first role, two novel heterozygous missense mutations (p. Pro126Ser in exon1 and p. Arg370His in exon7 of the WT1 gene) were identified to be involved in POF in Han Chinese women (Wang et al., 2015); in fact, both mutant p. Pro126Ser and p. Arg370His repressed the expression of AMH, FSHR, CYP19 and CDH1 genes, which are required for granular cells (GCs) differentiation and oocyte-GCs interaction, resulting in loss of follicles prematurely and then POF.

3.4. SOX9 gene, campomelic dysplasia and sex reversal

SOX9 (SRY-box 9) gene, located in the 17q24.3-q25.1 chromosome region, belongs to the family of SRY-related box (SOX) genes (Foster et al., 1994; Kwok et al., 1995). SOX9 gene encodes for a 509 residue SOX9 protein. This protein contains a 80 amino acid HMG domain, a DNA-binding motif that characterizes, besides the SOX proteins, a whole class of transcription factors (Grosschedl et al., 1994). This DNA-binding domain presents 60% or more of similarity to the amino acid sequence of the SRY HMG box (Goodfellow and Lovell-Badge, 1993). In addition to the HMG box, SOX9 con-

tains a stretch of 41 amino acid residues composed solely of proline, glutamine and alanine (PQA motif) ranging from 339 to 379 residues, and a C-terminal transcription activation domain rich in serine, proline and glutamine, ranging from residues 402–509 (Meyer et al., 1997; Sudbeck et al., 1996).

In humans, *SOX9* gene is involved in bone formation and control of testis development (Foster et al., 1994), that's why mutations in *SOX9* result in both campomelic dysplasia (CD), a skeletal malformation syndrome, and XY sex reversal (Foster et al., 1994; McDowall et al., 1999; Wagner et al., 1994). *SOX9* mutations may be amino acid substitutions in the HMG domain, truncations or frameshifts that alter the C terminus of *SOX9*, mutations at splice junctions or chromosomal translocations. Almost all these mutations affect a single allele, indicating a dominant mode of inheritance (Foster, 1996; Hsiao et al., 2006; Kwok et al., 1995; McDowall et al., 1999; Wagner et al., 1994).

Among the *SOX9* mutations causing both campomelic dysplasia and XY sex reversal, five mutations were identified by Wanger et al. in four patients presenting both syndromes: 1: a heterozygous nonsense mutation within the HMG box, generating a stop codon (GAG-TAG, E148X) and eliminating the fast 70% of the protein. 2: a heterozygous mutation in the 5′ splice donor site of intron 2, changing the invariant GT dinucleotide to AT and abolishing splicing. 3: another heterozygous nonsense mutation, generating a stop codon (TAC-TAG; Y44OX) and resulting in a truncated protein missing 70 amino acid residues at its C-terminus. 4: an insertion of a G residue, after nucleotide 1357, creating an altered C-terminal reading frame and leading to a mutant *SOX9* protein. 5: an in-frame deletion of 9 bp between nucleotides 1432 and 1442, removing three amino acids from the 41 amino acid glutamine-proline-alanine motif. The last two mutations, both found in the same patient, reside on different alleles of *SOX9* gene (Wagner et al., 1994).

In a more recent study, another *SOX9* gene frameshift mutation (at nucleotide position 1095G → AT) in the open reading frame, resulting in a frameshift with 211 new amino acids, was found in a 46,XY female neonate with CD and sex reversal (Hsiao et al., 2006).

A case of autosomal XX sex reversal was reported to be caused by a duplication of *SOX9* gene. The patient was a newborn infant who was referred for genetic evaluation because of abnormal male external genitalia. Cytogenetic analysis demonstrated a de novo mosaic 46,XX,dup(17)(q23.1q24.3)/46,XX karyotype. Due to the role that play *SOX9* gene in male sex determination and differentiation, this study suggests that extra dose of *SOX9* is sufficient to initiate testis differentiation in the absence of the Y-located SRY gene (Huang et al., 1999).

4. Conclusion

This review provides an evaluation of the most common autosomal single-genes disorders involved in human infertility. An increasing number of autosomic genes were reported to be expressed throughout the hypothalamic-pituitary–gonadal-outflow tract axis and to have critical roles in pubertal and reproductive deficiencies in humans. Mutations in these genes may be transmitted to the offspring by a dominant or a recessive inheritance. Although a large number of these genetic disorders can be treated by administering hormones such as pulsatile GnRH or exogenous gonadotrophins or by following different artificial procedures like ICSI, several other genetic defects may cause an untreatable infertility. In addition these artificial procedures do not avoid the transmission of these genetic abnormalities to the offspring who manifest with higher risk of infertility s/and congenital abnormalities. Consequently, the human infertility should be

evaluated by using a multidisciplinary approach involving genetics, epigenetics and at molecular levels to develop appropriate screens for abnormal phenotypes and to discover more effective solutions for an infertile couple's problems. Generally, as more genes involved are discovered and the causes of infertility disorders become better understood, the more infertility management and treatment will be improved.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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