JOMH

Journal of Men's Health

Chromosomal aneuploidies and associated rare genetic syndromes involved in male infertility

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Abstract

Background and objectives: Recent investigations have reported more than 70 genetic syndromes involved in male infertility; however, the majority of these syndromes are extremely rare. We aimed to report the most common chromosomal abnormalities and associated rare genetic syndromes in the context of human male infertility.

Materials and Methods: We performed a review of published articles considering the most common chromosomal aneuploidies and rare genetic syndromes associated with male infertility on PubMed, Web of Science, and Scopus.

Results: Chromosomal abnormalities are frequently found in infertile men, with an incidence rate of 2-15%. The chromosomal aberrations include the sex and autosomal chromosome abnormalities, as well as numerical and structural defects in chromosomes. There are various rare genetic syndromes involved in male infertility that are caused by structural and numerical abnormalities in chromosomes. Klinefelter syndrome is the most common type of sex chromosome aneuploidy in infertile males. Besides, Y chromosome microdeletions, particularly in azoospermia factor regions, serve as the second most common genetic cause of impaired spermatogenetic in infertile men. These molecular genetic abnormalities not only can be inherited, but also they may transmit to the next generation through assisted reproductive techniques and result in the birth of boys with higher risk of congenital abnormalities and infertility. Despite the normal secondary male sexual characteristics, some patients are azoospermic or severe oligozoospermic men. Therefore, identification of these molecular genetic factors and rare genetic disorders is essential in men with unexplained infertility.

Discussion and conclusion: Since most of molecular genetic abnormalities can be transmitted to the next generation, identification of these rare genetic disorders is crucial for men with unexplained infertility. It is also essential for clinicians and physicians of reproductive medicine and andrologists to initiate genetic evaluation, aneuploidy screening and counseling prior to any therapeutic procedures.

Keywords

Assisted reproductive techniques; Chromosomal aneuploidies; Male infertility; Rare genetic syndromes; Y chromosome

1. Introduction

Infertility, which is defined as the inability to conceive within 1 year of unprotected intercourse, is now considered as a major global health problem. It affects ~10-15% of couples with equal distribution among male and female [1, 2]. A wide range of disorders from structural abnormalities of gonads to environmental factors are involved in male infertility [3]. Infertile men with normal semen analysis are recognized as unexplained infertile patients. Many factors such as oxidative stress, mutations and polymorphisms on specific genes, mi-

T A B L E 1. The incidence and phenotype of the most common genetic aneuploidies associated with male infertility.

Chromosome aneuploidies	Phenotype	Incidence (%)	Ref
Chromosome aberrations Numerical disorders	Azoospermia to normospermia	2-10%	[52]
Klinefelter's syndrome	Azoospermia to sever oligospermia	5-10% azoospermia 2-5% oligospermia	[52]
Other sex chromosomes Structural disorders	Azoospermia to normospermia	0.1-0.2%	[10]
Robertsonian translocations	Azoospermia to sever oligospermia	0.5-1%	[10]
Reciprocal translocations	Azoospermia to sever oligospermia	0.5-1%	[30]

crodeletions on Y chromosome, mutations on mitochondrial DNA, epigenetic modifications, and changes in expression pattern of various non-coding RNAs can be considered as the common causes of idiopathic or unexplained male infertility [3–5].

Genetic abnormalities caused by chromosomal aneuploidies are responsible for ~15 to 30% of infertile patients [6]. It is assume that most patients with unexplained infertility may have underlying genetic causes [7]. Recent evidence has found more than 70 genetic syndromes contributed to male infertility; however, the majority of these syndromes are extremely rare. Genetic disorders cause male infertility by interfering with several physiological processes such as sex hormones homeostasis, spermatogenesis and sperm quality [8]. Current studies have shown that genetic abnormalities are frequently found in male cases with spermatogenesis deficiency and those who are candidates for assisted reproductive techniques (ART) [6, 9]. Therefore, genetic abnormalities can be considered as a main factor for the etiology of male infertility.

While recent advances in ART make possible and practical condition for cases with severe infertility to have children, they also raised concerns about passing on genetic abnormalities to the offspring of these men [8]. In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are valuable methods for treatment of male factor infertility, but they may carry risk of transmitting both genetically determined diseases and genetically determined infertility [10]. This underlines the importance of genetic counseling because mutations or karyotype anomalies associated with male infertility can be transmitted to future generations. Therefore, the frequency of chromosomal abnormalities may be directly related to the severity of male infertility and identification of the molecular genetic basis of reproductive dysfunction is important for appropriate management of infertile couples. Furthermore, genetic test analysis, including karyotyping, Y chromosome microdeletions (YCMD) and whole-genome sequencing (WGS), is worthful for patients with unexplained or idiopathic infertility before ART because it may enable the clinician to provide the best treatment option to achieve a successful pregnancy. In this review, we will discuss about the most common genetic abnormalities and associated rare genetic syndromes leading to reproductive failure and male infertility.

2. Types of chromosomal abnormalities and male infertility

The incidence of the most common genetic aneuploidies responsible for male infertility is shown in Table 1. Although chromosome aneuploidies are rare in fertile men (~0.5% in normal population), their incidence in azoospermic individuals varies from 2% to 15% [10, 11]. Sex or autosomal chromosome defects, as well as numerical and structural defects are the most common type of chromosomal anomalies that can be seen in infertile subjects. Numerical disorders, either as polyploid or aneuploid forms, are associated with changes in the number of chromosomes in a cell. In polyploidy condition, the whole number of nuclear chromosomes is multiplied [12]. Sex chromosomes aneuploidy, especially Y chromosome, is predominating; however, various structural autosomal anomalies may be found [13]. Klinefelter's syndrome (47,XXY) is the most common and well-established type of numerical disorder in sex chromosome that causes infertility in men [14]. Structural disorders include chromosomal rearrangements and translocations, as well as deletions or duplications of chromosomes [6]. These abnormalities may affect autosomal and sex chromosomes and consequently cause male infertility [12]. Therefore, chromosomal defects play a key role in genetics of male infertility.

3. Structural abnormalities of chromosome and male infertility

Chromosomal translocations can be considered as an additional source of chromosome aneuploidy [15]. Since chromosome translocations cannot be repaired, these structural abnormalities may be associated with the loss of genetic materials and corruption of the genetic message [16]. The relationship between chromosome translocations and male infertility was suggested ~40 years ago [17]. Likewise, others suggested autosomal translocations may be associated with spermatogenesis derangement. The most common type of structural aberrations are robertsonian and reciprocal translocations; however, autosomal and sex chromosome abnormalities are frequently occur in infertile men. The incidence of autosomal translocations in infertile men is ~4-10 times higher than healthy males [18]. The frequency of robertsonian and reciprocal translocations is ~1/1000 of all newborns, approximately 7-9 times higher in infertile men [14]. Seminal analysis in most patients

with robertsonian translocations is abnormal, but males presenting with reciprocal translocations may have normal to azoospermic spermiogram [19].

Robertsonian translocations (RT) or centric fusions are the most common type of structural abnormalities in human chromosomes that affect fertility in ~1/1000 men [20]. The incidence rate of robertsonian translocations in infertile males is 0.9, approximately 9 times higher than the general population [21]. It usually involves acrocentric chromosomes from pairs 13, 14, 15, 21 and 22 [22]. However, robertsonian translocations are frequently occur between chromosomes 13 and 14 (73%) or chromosomes 14 and 21 (10% of all robertsonian translocations) [14]. This type of structural abnormality may change gene expression pattern of spermatozoa in different stages and subsequently influence male fertility and pregnancy [23]. It is frequently found in infertile males with oligozoospermia (1.6%) and azoospermia (0.09%) [24]. Although carriers of RT may have a normal phenotype, they could be infertile due to possibility of impaired spermatogenesis or lack of sperm production [8]. Breakpoint diversity may be a main mechanism for impaired spermatogenesis [25]. In addition to the severe spermatogenetic failure, higher percentage of immaturity, apoptosis and necrosis have also been reported in RT carriers [26]. Other studies have shown a predominant proportion of higher rate of DNA fragmentation (26.3%), apoptosis (24.5%) and immaturity of spermatozoa (28%) in oligoasthenozoospermic patients carrying robertsonian translocation than in healthy donors [27]. This data suggests higher risk of impaired spermatogenesis or spermiogenesis in these patients. However, studies of the meiotic segregation process in robertsonian carriers revealed a predominance of alternate segregation resulting in the production of normal spermatozoa (mean 85.42%; range 60-96.60%), with a percentage of abnormal spermatozoa varying from 3.4% to 40% (mean 14.57%) [28]. Therefore, chromosomal constitution analysis in spermatozoa of RT carriers is essential for identifying the risk of unbalanced forms and adapting genetic counseling.

Reciprocal translocations are the other forms of chromosome rearrangement in which the exchange of chromosome segments are not belong to the same pair of chromosomes [14]. Previous studies reported that the incidence rate of reciprocal translocations in infertile patients is higher than healthy men [29]. These chromosomal abnormalities can be found in ~1% of infertile males [7]. The incidence rate of autosomal reciprocal translocations in men presenting with azoospermia (0.9%) is higher than those with severe oligozoospermia (0.6%) [30]. Because of the production of spermatozoa with chromosomal imbalances, carriers of reciprocal translocation may have a risk of abnormal pregnancy outcome even with normal sperm counts [31]. The mechanism by which reciprocal translocations affect male fertility is not well-understood. However, the involved chromosomes, the size of the translocated segments, and the presence/absence of recombination foci are likely correlated to the behaviour of reciprocal translocations. Impaired spermatogenesis may be another mechanism of these translocations [32]. The presence of reciprocal translocations alters the spermatogenic process [33].

Although all chromosomes can be contributed in reciprocal translocations, chromosomes 13 and 14, 13 and 21, and 21 and 22 are the typical targets for this translocation [34]. There are many cases of male infertility due to balanced reciprocal translocation between chromosomes 10 and 15 (q26; q12) [35], 6 and 12 (q23; q24) [36], 8 and 13 (q22; q11.2) [11], 18 and 21 (p11; q21) [37], 9 and 20 (q21.2; p13.3) [38]. In all carriers, these translocations impact on spermatogenesis and consequently cause poor quality of sperm, severe azoospermia and infertility. The first case of an autosomal reciprocal translocation t(7;16) with break-points at 7q21.2 and 16p13.3 was described by Mikelsaar *et al.*, [39] in an infertile man. The 16p13.3 breakpoint may affect *PRM1*, *PRM2*, or *TNP2* genes which are responsible for histones replacement and subsequently DNA packaging into the sperm head. This haploinsufficiency may be associated with sperm head defects and male infertility. This finding supports the idea that alterations in expression of protamines may be a main reason of male factor infertility [39].

Translocations may occur in autosome, Y or X chromosomes, either in a balanced or unbalanced form; however, the incidence is rare (~1 in 2000). It can be translocated onto an autosome [40]. While non-acrocentric chromosomes involvement is often associated with male infertility, involvement of acrocentric chromosomes is usually familial disorder with mild effect on fertility. A novel *de novo* translocation (Yp/13p) characterized by loss of the 13p and Yp telomeres had been reported previously [40]. Although most sperm had a normal chromosomal arrangement (85%), meiotic studies using FISH demonstrated meiosis I chromosome un-pairing, abnormal segregation abnormality and abnormality of the most of secondary spermatocytes (56.8%) due to the translocated chromosome justifies the severe oligozoospermia in these patients [40]. Pinho *et al.*, [41] characterized a *de novo* t(Y;1)(q12; q12) balanced reciprocal translocation with loss of the heterochromatic region of chromosome 1. This translocation was associated with un-pairing of sex chromosomes, meiosis I arrest, apoptotic degeneration of germ cells and azoospermia. Furthermore, reciprocal translation between Y chromosome and 6 (Yp6p; Yq6q) and 1 (Yq11.2; 1p34.3) had been reported [42]. Carriers were found in a phenotypically normal, but spermatogenesis arrest along with significant desquamation of the germinal epithelium was observed at the first metaphase stage of the meiosis. Besides, sex vesicle abnormalities at the pachytene stage and chain tetravalent formation at the diakinesis-metaphase I stage were found [42].

The incidence rate of translocations between autosomes and X chromosome is rare in genetic disorders that cause male infertility [33]. A novel reciprocal translocation was reported in an infertile male with t(X;14)(p11.4; p12) [33]. Although the patient showed normal phenotype without any familial history of congenital abnormalities, cytogenetic analysis and testis biopsies indicated an X-autosomal translocation and arrest of spermatogenesis. Another new
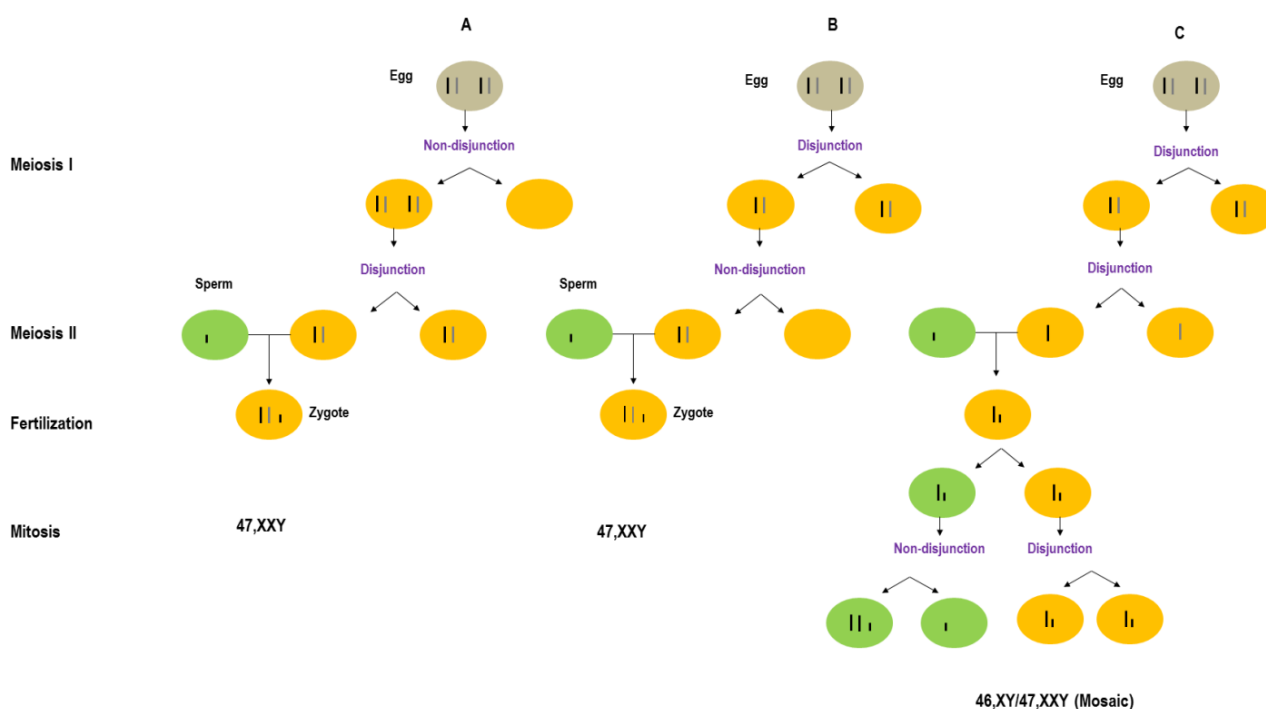
F I G . 1. The underlying mechanisms for occuring KS karyotype during spermatogenesisaa. The 47,XXY karyotype arises spontaneously when paired X chromosome fail to disjunction in the first (A) or second (B) stage of meiosis, either during oogenesis (40%) or spermatogenesis (50%). A similar failure occurring in the fertilized egg during mitosis (10%) results in a mosaic karyotype (C). The most common form of mosaicism is 46,XY/47XXY, but many other forms have been reported. The severity of this syndrome depends on the proportion of normal and abnormal cells.

study has reported an azoospermic male with t(X;1)(p22.3; q25) translocation [43]. Therefore, carriers of X-autosome translocations are perpetually infertile, regardless of the break-point position in the X chromosome.

4. Numerical chromosome abnormalities and male infertility

4.1 Klinefelter's syndrome (KS)

Klinefelter syndrome (47,XXY) is the most common type of sex chromosome aneuploidy in infertile men, occurring in ~0.1-0.2% of all newborn males [14]. This syndrome is described by several findings such as testicular dysgenesis, eunuchoidism, small testicles, endocrine complications, tubular sclerosis, azoospermia, hypogonadism, and gynecomastia [44]. Enhanced levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and decreased level of testosterone have been reported in these cases [45]. The incidence of gynecomastia in KS varies from 56% to 88% [46]. Common phenotypic features include increased height, reduced facial and body hair, lower extremities varicosities, decreased intelligence, problems in speech and language abilities, autoimmune diseases, diabetes mellitus, obesity, decreased bone density, higher incidence of leukemia, germ cell tumors, infertility and breast cancer risk in patients who have gynecomastia [10].

The incidence of KS in infertile men with severe oligozoospermia and azoospermia 5% and 10%, respectively [14]. This karyotype occurs randomly when paired X

chromosomes fail to disjoin in the first or second phase of meiosis during oogenesis or spermatogenesis (Fig. 1). Approximately, 90% of men carry an extra X chromosome (47,XXY) and 10-15% are mosaic (46,XY/47,XXY) [47, 48]. However other sex chromosomal aneuploidies are much less frequent with 47,XXXY/46,XY mosaicism, 48,XXYY, 48,XXXY (1 per 17,000 to 50,000) and 49,XXXXY (1 per 85,000 to 100,000) being present in male births. Cases of 46 XX males have also been reported [49]. Rare case of a mosaic 47,XXY/46,XX is also reported in KS patients which is associated with impaired spermatogenesis, testicular atrophy, absence of germ cells and male infertility [50].

Patients with mosaic KS may have milder signs or symptoms, which depends on the number of cells with an additional X chromosome. Additional copies of genes on the X chromosome adversely affect the development of male sexual organs, prevent normal function of the testes and reduce the levels of testosterone which is associated with impaired spermatogenesis in these cases [2]. Although this abnormality is not inherited, it may occur as a random event during gonads (eggs and sperm) formation. More recently, Franik *et al.*, [51] have found different abnormalities in spermatogenesis process such as maturation arrest or hypospermatogenesis in ~54% of KS patients. This result suggests that the presence of spermatogenesis in KS patients is not always associated with production of mature spermatozoa. Only a small number of KS patients, especially mosaic cases, have normal fertilization ability without assisted reproductive technology [52]. Focal areas of spermatogenesis can be found within the testis of

azoospermic men with KS, and sperm can be retrieved in in about 30%-50% of KS patients through the use of micro dissection testicular sperm extraction (TESE) technique [51]. Therefore, ICSI can be performed in these cases with an a success rate of 30% to 50% [2]. Thus, TESE and ICSI can be used in men with KS and azoospermia.

4.2 47,XYY syndrome

47,XYY syndrome is the most common type of sex chromosomal aneuploidy after Klinefelter syndrome, occurring in one of 1,000 live male births in the general population [53]. The additional Y chromosome can be generated because of a random event from paternal post-zygotic mitotic non-disjunction or meiosis II non-disjunction [54]. Although the majority of cases have normal phenotypic features, they may have decreased fertility potential. A growing number of studies have demonstrated a relationship between 47,XYY syndrome and male infertility [55]. Some studies found low to normal testosterone level and high to normal contents of LH and FSH in patients with 47,XYY syndrome [56]. The sperm count in these patients varying from normal to oligospermia or azoospermia [57]. The exact mechanism of abnormal semen analysis in these patients is not well-understood; however, Y chromosome microdeletions and *CFTR* gene mutations may be a main reason for poor sperm quality in these cases [3]. Milazzo *et al.,* [58] indicated that the presence of the extra Y chromosome can result in spermatogenesis impairment during meiosis, which is consequently associated with increased number of immature sperm and decreased sperm counts. Since sperm cells with an additional copy of the Y chromosome can be transmitted to the next generations through ART, genetic consulting is necessary for these patients.

4.3 46,XX male syndrome

XX male syndrome is a rare chromosome aneuploidy with an incidence rate of 1 in 20,000 live births [59]. It causes a wide range of clinical manifestations from ambiguous genitalia in the newborn to normal male phenotype [60]. All men with 46,XX syndrome are azoospermic because of the absence of Y chromosome long arm containing *azoospermia factor* (*AZF*) gene, which is crucial for normal spermatogenesis [3]. Increased gonadotropin levels, impaired steroidogenesis and hypogonadism are typical laboratory findings in these patients [61].

Previous studies illustrated that Y chromosome translocation containing the *testes determining factor* (*SRY* gene) on X chromosome, mutation or overexpression of X-linked genes which are responsible for differentiation of testis, and mutation or overexpression of autosomal genes in *SRY* negative XX males are the major proposed mechanisms for the etiology of 46,XX syndrome [59]. These patients can be divided into two groups of positive (90% of the cases) and negative (10% of the cases) *SRY* gene [62]. Given the critical role of *SRY* gene in male reproductive organ differentiation and development, the external genitalia and masculinization are phenotypically normal in 46,XX SRY-positive males [61].

Moreover, small testis size can be seen in these patients. For this reason, these cases are usually diagnosed in late adolescence during chromosome analyses performed for infertility or small testis [62, 63]. The majority of 46,XX SRY-negative men have incomplete virilization of the external genital organs. Nevertheless, normal appearance of genitals and complete masculinization can be seen in these cases [64].

4.4 45,X male syndrome

Men with 45,X karyotype normally display a female phenotype. They are infertile and display azoospermia [65]. The underlying mechanism for this abnormality is related to the absence of the genes on the long arm of the Y chromosome which are responsible for spermatogenesis. Since the distal part of the euchromatic long Y arm (Yq11) is lost, these patients have an unbalanced karyotype [52]. Multiple studies showed normal secondary sexual characteristics and normal reproductive hormone levels, but small testes, azoospermia, and germinal aplasia in patients with a 45x Karyotype [65].

The mosaic karyotype 45X/46XY is another chromosomal aneuploidy which is associated with infertility in men. The incidence rate of this syndrome in infertile men is 4%. The 45X/46XY karyotype is associated with a wide range of phenotypes, including male with mixed gonadal dysgenesis, female with Turner syndrome, pseudohermaphroditism, and male with normal apparent (~33%) [66]. Increased levels of serum FSH and normal values of serum testosterone were reported in these cases [67].

5. Syndromes caused by mutations or deletions

While some of genetic syndromes associated with male infertility are caused by chromosomal aneuploidies, the others are resulted by mutations or deletions on multiple genes involved in spermatogenesis and steroidogenesis. Kallmann syndrome, Sertoli cell-only syndrome, deafness-infertility syndrome, Noonan syndrome, immotile-cilia syndrome and Myotonic dystrophy 1 are examples of these abnormalities.

5.1 Kallmann syndrome

Kallmann syndrome (KS) is a rare genetic disorder which is characterized by anosmia and hypogonadotropic hypogonadism due to abnormal migration of gonadotropin-releasing hormone (GnRH)-producing neurons [68]. This is because of mutations in several genes such as *KAL1*, *FGFR1*, and *PROKR2* genes which are mainly inherited in an autosomal dominant manner [3]. The prevalence of KS is 1 in 8000 to 1 in 10,000 in men [69]. X-linked (X p 22.3) recessive disorder is the most common type of KS occurring in 1 in every 30,000 males at birth [70]. However, its inheritance may be autosomal. Small penis, erectile dysfunction, delayed puberty, prepubertal external genitalia and absent secondary sexual characters can be seen in these cases [71]. Treatments with testosterone and gonadotropins are usually used to induce virilization and spermatogenesis

in these cases [72].

5.2 Sertoli cell-only syndrome

Sertoli cell-only (SCO) syndrome is a rare cause of male infertility which is associated with seminiferous tubules damage and complete absence of germ cells. SCOS incidence in azoospermic cases varies from 26.3% to 57.8% [73]. The exact mechanism of SCO is still unclear. Y chromosome microdeletions, especially on the AZF region (AZF-a-c), hypogonadotropic hypogonadism, and cryptorchidism are considered as significant causes of SCOS syndrome [3, 6, 74]. Klinefelter syndrome is the most frequent cause of nonobstructive azoospermia with SCO. Although many of patients with SCO have normal secondary male sexual characteristics and karyotype, they are azoospermic or severe oligozoospermic men [75]. Reduced testicular size and high FSH levels can be also found in these patients. ICSI and Micro-TESE are useful in retrieving spermatozoa from these patients [76].

5.3 Deafness-infertility syndrome

Deafness-infertility syndrome (DIS) is a very rare syndrome (~1 in 1,000,000 births) which is caused by a large contiguous deletion of *STRC* and *CATSPER2* and genes at chromosome 15q15.3 [77]. This is an autosomal recessive syndrome which is characterized by moderate to severe hearing loss and male infertility. Although men with DIS syndrome produce sperm, increased number of sperm with abnormal morphology and sperm dysmotility negatively affect their fertility potency [77]. Azoospermia and abnormal spermatogenesis are also reported in these cases [78].

5.4 Noonan syndrome

Noonan syndrome (NS) is another rare genetic disorder (~1 : 1000 to ~1 : 2500 in newborns) which can be associated with male infertility [79]. Mutations in several genes such as *PTPN11*, *SOS1*, *KRAS* and *RAF1* genes may be involved in the etiology of this syndrome. NS is inherited in an autosomal dominant pattern. Undescended testes may be seen in boys with Noonan syndrome [80]. Delayed puberty, azoospermia or oligozoospermia may occasionally found in these cases [81].

5.5 Immotile-cilia syndrome

Immotile-cilia syndrome, also known as primary ciliary dyskinesia (PCD), is an inherited autosomal recessive disease. The incidence rate of this syndrome is approximately one in 10,000 to 30,000 individuals [82]. This syndrome is resulted by the defects in several genes such as *DNAH5*, *DNAI2*, and *DNAH9*, which are responsible in formation of several kinds of proteins composed of a ciliary microstructure [83]. It is also associated with aplasia, ciliary dysplasia, and sperm motility disorder. Sometimes, these cases are diagnosed with Kartagener's syndrome. Since immotile sperm are unable to participate in fertilization process naturally or via conventional IVF, the ICSI technique is useful for these cases. Micro-TESE-ICSI is effective for patients with azoospermia [83].

5.6 Myotonic dystrophy 1

Myotonic dystrophy 1 (DM1) is another inherited and autosomal dominant disorder which can be associated with reproductive abnormalities and male infertility. The expansion of CTG repeats in the myotonic dystrophy protein kinase (*DMPK*) gene on chromosome 19q13.3 is the underlying mechanism for this genetic defect [84]. Progressive testicular atrophy, increased FSH levels, fibrosis of seminiferous tubules, and decreased number of spermatozoa can be found in these patients [85]. Oligospermia and azoospermia can be observed in ~73% of DM1 patients [86].

5.7 Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a rare genetic disorder with an incidence rate of ~1/15,000 to ~1/30,000 births [87]. PWS is paternally inherited and caused by the lack of expression of one or more genes on chromosome 15q11-q13 [88]. Men with PWS are usually infertile. It is characterized by different signs and symptoms such as small testicular size, testicular failure, delayed pubertal, hypothalamic dysfunction, hypogonadism and cryptorchidism (found in ~93% of cases) [89]. Azoospermia can be seen in most cases [89]. Some studies showed high FSH levels and defect in the Sertoli cells [88].

5.8 Bardet–Biedl syndrome

Bardet–Biedl syndrome (BBS) is another rare genetic syndrome that causes various abnormalities. The incidence rate of the disease ranges from ~1/125,000 to ~1/175,000 births [90]. Several case reports have demonstrated testicular atrophy, hypogonadotrophic hypogonadism, spermatogenic arrest, low plasma levels of LH and testosterone, hypothalamic–pituitary dysfunction, and degeneration of seminiferous tubules in these cases [91].

5.9 Autosomal and X linked genes mutations

Numerous autosomal or X linked genes are essential for male reproductive development and function, spermatogenesis and fertility in men. Therefore, mutations, translocations, deletions or inversions in these genetic materials can result in severe male infertility and azoospermia. The human X chromosome includes many testis-specific genes which are essential for normal spermatogenesis and successful fertility. The frequency of mutations in autosomal genes such as *INSL3-RXFP2*, *CFTR*, *KAL-1*, *c-kit receptor* (c-kitR), and X-linked *androgen receptor* (*AR*) genes is high and can cause infertility due to defects in germ cell proliferation or urogenital system.

6. Male infertility caused by Y chromosome microdeletions

Human Y chromosome, one of the smallest in the genome, contains ~60 million DNA base sequences [92]. It is a degen-
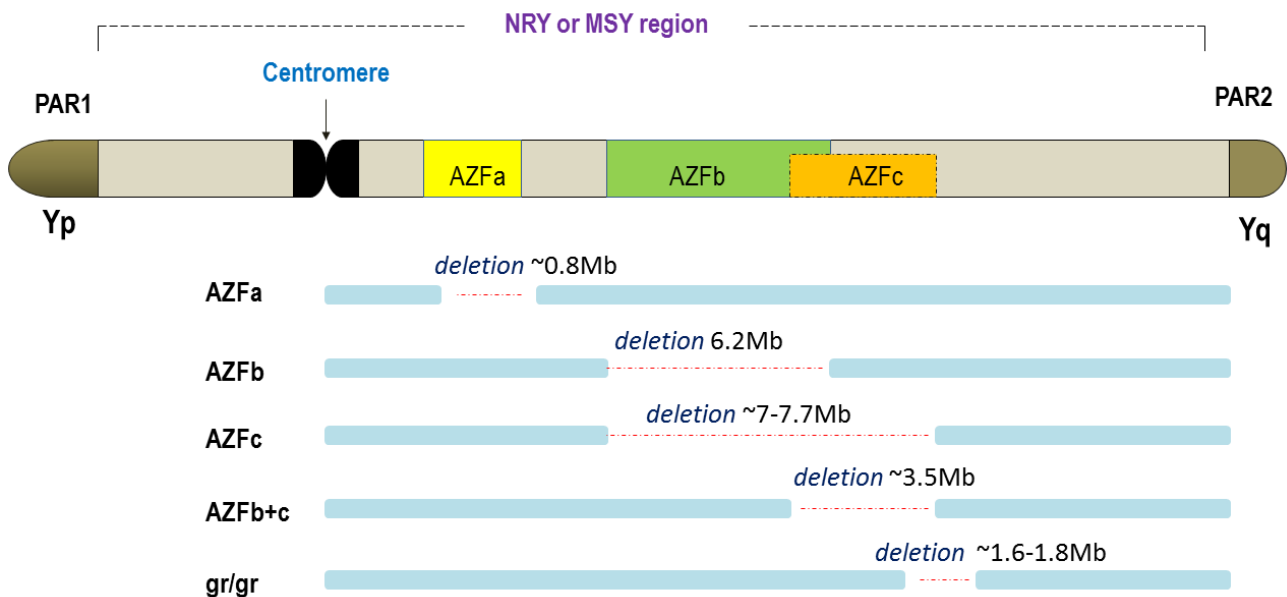
F I G . 2. A schematic of Y chromosome including AZF regions (AZFa-c) and associated microdeletions. Deletion in AZFa is associated with azoospermia and SCOS, AZFb deletion is associated with impaired spermatogenesis and azoospermia, deletions in AZFb + c cause spermatogenesis arrest and azoospermia, deletion in AZFc is associated with oligozoospermia and azoospermia, gr/gr deletion is associated with oligozoospermia and azoospermia.

erated X chromosome which has lost several housekeeping genes becoming specialized in male sex determination. Approximately 95% of its sequence, known as the male specific region (MSY) of the Y or non-recombining region (NRY), is present only in men and does not undergo sexual recombination [93]. It is divided into euchromatic (Yq11; 24 Mb), centromeric and heterochromatic (Yq12; 30 Mb) regions [94]. There are two pseudoautosomal regions (PAR1 and PAR2) on the long (Yq) and short (Yp) arms of Y chromosome that recombine with their homologues on the X chromosome (Fig. 2).

Recent evidences have indicated that Y chromosome microdeletions are associated with severe male infertility because it carries various regions and genes that are essential for normal spermatogenesis and male gonads development. Human Y chromosome microdeletions (Yq11.2) serve as the main genetic cause of infertility in men with idiopathic severe oligozoospermia and azoospermia [52]. Furthermore, it is considered as the second most common genetic cause of impaired spermatogenesis in infertile men after Klinefelter's syndrome [9]. The incidence rate of Y microdeletions in infertile men ranged from ~1% to ~55% [95]. They are extremely rare in cases with normal spermatozoa (0.7%), but the highest frequency is found in azoospermic (8-12%) and oligozoospermic men (3-7%) [96]. In addition to Y chromosome microdeletions, other abnormalities such as variations in repeat sequences in multi copy gene families, or polymorphisms or mutations in Y chromosome genes, and duplications or rearrangements can also involve in male infertility [97].

Molecular genetics analysis of the Y chromosome has identified three main regions known as AZF in proximal, middle, and distal Yq11, designed as AZFa, AZFb and AZFc, respectively (Fig. 2). Additionally, a fourth AZF region has

been also suggested to exist in the area where AZFb and AZFc overlap, and is termed as AZFd [98]. These regions carry several genes and transcriptional units, which are particularly expressed in male gonads. Many studies reported azoospermia or severe oligozoospermia caused by gene deletions in these regions [99]. Therefore, the loss of this genetic information can lead to poor sperm production and male infertility.

AZFa, P5/proximal-P1 (previously termed AZFb), AZFc (b2/b4), P5/distal-P1 (AZFb + c), b1/b3, b2/b3 and gr/gr deletions are the most described recurrent deletions in Yq [100] (Fig. 2). The b1/b3, b2/b3 and gr/gr deletions are considered as partial deletions of AZFc. The AZFb deletions are extend from palindrome P5 to proximal arm of palindrome P1, 1.5 Mb within AZFc. The deletions involving AZFb + c extend from P5 to distal arm of P1 sparing distal AZFc, and encompass 7.7Mb removing 42 genes and transcripts. It has been uniformly associated with azoospermia [3]. Compared to the AZFb region (~15%) and the AZFa region (~5%), multiple gene deletions in the AZFc region (~60-70%) are the most common aberrations that occur in the AZF region [96]. These deletions can produce a wide range of infertile phenotypes. Although ART such as IVF, ICSI and TESE permit cases with Y chromosome microdeletions to achieve pregnancy, it increases concerns about the fact that some pregnancies may generate male offspring with similar microdeletions and subsequently infertility problems [3]. Therefore, it is essential to consider these critical genes, regions and deletions when considering ART because microdeletions are always transmitted to the male offspring.

7. Conclusions

Chromosomal aneuploidies and associated rare genetic syndromes are the main reasons for impaired spermatogenesis and male infertility. These aneuploidies can be either numerical or structural. Developmental failure in reproductive organs, delayed puberty, testicular atrophy and dysfunction, hypothalamic-pituitary dysfunction, hypogonadism, declined levels of sex hormones, impaired spermatogenesis, and poor sperm quality are the major findings in men with rare genetic syndromes associated with infertility. Although the incidence of these genetic syndromes is rare, they may diminish the likelihood of a successful outcome from ART. Since most of rare syndromes are paternally inherited, these genetic abnormalities can be transmitted to the offspring via ICSI, TESE, IVF and consequently cause male offspring with similar abnormalities and infertility. Therefore, it is essential to perform routine karyotyping prior to ART in infertile males with idiopathic or unexplained spermatogenic failure. Furthermore, it is necessary to consider detailed medical history, critical genes, regions and deletions when considering ART because microdeletions are always transmitted to the male offspring.

Abbreviations

AR, androgen receptor; ART, assisted reproductive techniques; AZF, azoospermia factor; BBS, Bardet-Biedl syndrome; CFTR, Cystic fibrosis transmembrane conductance regulator; DIS, Deafness-infertility syndrome; DM1, Myotonic dystrophy 1; DMPK, myotonic dystrophy protein kinase; FSH, Follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; ICSI, intracytoplasmic sperm injection; IVF, In vitro fertilization; KS, Klinefelter syndrome; LH, Luteinizing hormone; MSY, male specific region; NRY, non-recombining region; NS, Noonan syndrome; PCD, primary ciliary dyskinesia; PWS, Prader-Willi syndrome; RT, Robertsonian translocations; SCO, Sertoli cell-only; SRY, Sex-determining Region Y; TESE, testicular sperm extraction.

Author contributions

ETM is contributed in study design, manuscript writing and revision, and figure design; ABH is contributed in manuscript writing and data collecting; IL is contributed in study design, manuscript writing, and submission.

Ethics approval and consent to participate

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee. This article does not contain any studies with human and animal subjects performed by the any of the authors.

Conflict of interest

All the authors have read and approved the final version of the manuscript. The authors declare that there are no conflicts of interests.

References

[1] Beigi Harchegani A, Shafaghatian H, Tahmasbpour E, Shahriary A. Regulatory functions of microRNAs in male reproductive health: a new approach to understanding male infertility. Reproduction Science. 2018; 1: 1-11.

[2] Dada R. Genetic Testing in male infertility. The Open Reproductive Science Journal. 2011; 3: 42-56.

[3] Tahmasbpour E, Balasubramanian D, Agarwal A. A multi-faceted approach to understanding male infertility: gene mutations, molecular defects and assisted reproductive techniques (ART). Journal of Assisted Reproduction and Genetics. 2014; 31: 1115-1137.

[4] Tüttelmann F, Simoni M. Current recommendations for genetic testing in male infertility. European Urological Review. 2008; 3: 88-92.

[5] Hosseinzadeh Colagar A, Tahmasbpour Marzony E, Chaichi MJ. Zinc levels in seminal plasma are associated with sperm quality in fertile and infertile men. Nutrition research. 2009; 29: 82-88.

[6] Krausz C, Riera-Escamilla A. Genetics of male infertility. Nature Reviews Urology. 2018; 15: 369-384.

[7] Walsh T, Pera R, Turek P. The genetics of male infertility. Seminars in Reproductive Medicine. 2009; 27: 124-136.

[8] O'Flynn O'Brien KL, Varghese AC, Agarwal A. The genetic causes of male factor infertility: a review. Fertility and Sterility. 2010; 93: 1-12.

[9] Asero P, La Vignera S, Lanzafame F. Genetic aspects of male infertility. Journal of Andrological Sciences. 2010; 17: 1-16.

[10] Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C. Male infertility: role of genetic background. Reproductive Biomedicine Online. 2007; 14: 734-745.

[11] Goel H, Phadke SR. Reciprocal balanced translocation: infertility and recurrent spontaneous abortions in a family. Andrologia. 2009; 43: 75-77.

[12] Maduro MR, Lamb DJ. Understanding the new genetics of male infertility. The Journal of Urology. 2002; 168: 2197–2205.

[13] Carrell DT, De Jonge C, Lamb DJ. The genetics of male infertility: a field of study whose time is now. Archives of Andrology. 2006; 52: 269-274.

[14] Ferlin A, Arredi B, Foresta C. Genetic causes of male infertility. Reproductive Toxicology. 2006; 22: 133-141.

[15] Gianaroli L. Possible interchromosomal effect in embryos generated by gametes from translocation carriers. Human Reproduction. 2002; 17: 3201-3207.

[16] Carrell DT. Contributions of spermatozoa to embryogenesis: assays to evaluate their genetic and epigenetic fitness. Reproductive BioMedicine Online. 2008; 16: 474-484.

[17] Chandley AC, Edmond P, Christie S, Gowans L, Fletcher J, Frackiewicz A, *et al*. Cytogenetics and infertility in man. I. Karyotype and seminal analysis: results of a five-year survey of men attending a subfertility clinic. Annals of Human Genetics. 1975; 39: 231-254.

[18] Krausz C, Giachini C. Genetic risk factors in male infertility. Archives of Andrology. 2007; 53: 125-133.

[19] Antonelli A, Gandini L, Petrinelli P, Marcucci L, Elli R, Lombardo F, *et al.* Chromosomal alterations and male infertility. Journal of Endocrinological Investigation. 2000; 23: 677-683.

[20] Therman E, Susman B, Denniston C. The nonrandom participation of human acrocentric chromosomes in Robertsonian translocations. Annals of Human Genetics. 1989; 53: 49-65.

[21] Ananthapur V, Avvari S, Tella S, Nallari P, Akka J. A robertsonian translocation rob (14;15) (q10:q10) in a patient with recurrent abortions: a case report. Journal of Reproduction & Infertility. 2010; 11: 197-200.

[22] Van Assche E, Bonduelle M, Tournaye H, Joris H, Verheyen G, Devroey P, *et al.* Cytogenetics of infertile men. Human Reproduction. 1996; 11: 1-24.

[23] Keymolen K, Van Berkel K, Vorsselmans A, Staessen C, Liebaers I. Pregnancy outcome in carriers of Robertsonian translocations. American Journal of Medical Genetics Part A. 2011; 155: 2381-2385.

[24] Johnson MD. Genetic risks of intracytoplasmic sperm injection in the treatment of male infertility: recommendations for genetic counseling and screening. Fertility and Sterility. 1998; 70: 397-411.

[25] Moradkhani K, Puechberty J, Bhatt S, Vago P, Janny L, Lefort G, *et al.* Meiotic segregation of rare Robertsonian translocations: sperm analysis of three t(14q;22q) cases. Human Reproduction. 2006; 21: 1166-1171.

[26] Baccetti B, Collodel G, Marzella R, Moretti E, Piomboni P, Scapigliati G, *et al.* Ultrastructural studies of spermatozoa from infertile males with Robertsonian translocations and 18, X, Y aneuploidies. Human Reproduction. 2005; 20: 2295-2300.

[27] Brugnon F, Janny L, Communal Y, Darcha C, Szczepaniak C, Pellestor F, *et al.* Apoptosis and meiotic segregation in ejaculated sperm from Robertsonian translocation carrier patients. Human Reproduction. 2011; 4: 1-12.

[28] Anahory T, Hamamah S, Andréo B, Hédon B, Claustres M, Sarda P, *et al.* Sperm segregation analysis of a (13;22) Robertsonian translocation carrier by FISH: a comparison of locus-specific probe and whole chromosome painting. Human Reproduction. 2005; 20: 1850-1854.

[29] Shi Q, Martin RH. Aneuploidy in human spermatozoa: FISH analysis in men with constitutional chromosomal abnormalities, and in infertile men. Reproduction. 2001; 121: 655-666.

[30] Gunel M, Cavkaytar S, Ceylaner G, Batioglu S. Azoospermia and cryptorchidism in a male with a de novo reciprocal t(Y;16) translocation. Genetic Counseling. 2008; 19: 277-280.

[31] Morel F, Douet-Guilbert N, Le Bris M, Herry A, Amice V, Amice J, *et al.* Meiotic segregation of translocations during male gametogenesis. International Journal of Andrology. 2004; 27: 200-212.

[32] Oliver-Bonet M, Benet J, Sun F, Navarro J, Abad C, Liehr T, *et al.* Meiotic studies in two human reciprocal translocations and their association with spermatogenic failure. Human Reproduction. 2005; 20: 683-688.

[33] Hwang SH, Lee SM, Seo EJ, Choi KU, Park HJ, Park NC, *et al.* A case of male infertility with a reciprocal translocation t(X;14)(p11.4;p12). The Korean Journal of Laboratory Medicine. 2007; 27: 139-142. (In Korean)

[34] Hsu LYF. Phenotype/Karyotype correlations of Y chromosome aneuploidy with emphasis on structural aberrations in postnatally diagnosed cases. American Journal of Medical Genetics. 1994; 53: 108-140.

[35] Baccetti B, Bruni E, Collodel G, Gambera L, Moretti E, Marzella R, *et al.* 10, 15 reciprocal translocation in an infertile man: ultrastructural and fluorescence in-situ hybridization sperm study: case report. Human Reproduction. 2003; 18: 2302-2308.

[36] Bianco B, Christofolini D, Gava M, Mafra F, Moraes E, Barbosa C. Severe oligospermia associated with a unique balanced reciprocal translocation t(6;12)(q23;q24.3): male infertility related to t(6;12). Andrologia. 2009; 43: 145-148.

[37] Gu L, Zhang H, Zhu G. Impact of reciprocal translocation t(18; 21) on male infertility and embryo development: lessons from an oocyte-donating ICSI cycle. Journal of Assisted Reproduction and Genetics.

[38] Chandley AC, Speed RM, McBeath S, Hargreave TB. A human 9;20 reciprocal translocation associated with male infertility analyzed at prophase and metaphase I of meiosis. Cytogenetics and Cell Genetics. 1986; 41: 145-153.

[39] Mikelsaar R, Pauklin M, Lissitsina J, Punab M. Reciprocal translocation t(7;16)(q21.2;p13.3) in an infertile man. Fertility and Sterility. 2006; 86: 719.e9-719.11.

[40] Alves C, Carvalho F, Cremades N, Sousa M, Barros A. Unique (Y;13) translocation in a male with oligozoospermia: cytogenetic and molecular studies. European Journal of Human Genetics. 2002; 10: 467-474.

[41] Pinho MJ, Neves R, Costa P, Ferrás C, Sousa M, Alves C, *et al.* Unique t(Y;1)(q12;q12) reciprocal translocation with loss of the heterochromatic region of chromosome 1 in a male with azoospermia due to meiotic arrest: a case report. Human Reproduction. 2005; 20: 689-696.

[42] Pabst B, Glaubitz R, Schalk T, Schneider U, Schulze W, Miller K. Reciprocal translocation between Y chromosome long arm euchromatin and the short arm of chromosome 1. Annales De Genetique. 2002; 45: 5-8.

[43] Karaer K, Ergun MA, Weise A, Ewers E, Liehr T, Kosyakova N, *et al.* The case of an infertile male with an uncommon reciprocal X-autosomal translocation: how does this affect male fertility? Genetic Counseling. 2010; 21: 397-404.

[44] Klinefelter HF, Reifenstein EC, F A. Syndrome character-ized by gynecomastia aspermatogenes without A-Leydigism and increased excretion of follicle stimulating hormone. Journal of Clinical Endocrinology & Metabolism. 1942; 2: 615-627.

[45] Karimi H, Sabbaghian M, Haratian K, Vaziri Nasab H, Farrahi F, Moradi SZ, *et al.* A rare case of klinefelter syndrome patient with quintuple mosaic karyotype, diagnosed by GTG-banding and FISH. International Journal of Fertility &Amp; Sterility. 2014; 8: 221-224.

[46] Smyth CM, Bremner WJ. Klinefelter syndrome. Archives of Internal Medicine. 1998; 158: 1309-1314.

[47] Walsh T, Pera R, Turek P. The genetics of male infertility. Seminars in Reproductive Medicine. 2009; 27: 124-136.

[48] Foresta C, Garolla A, Bartoloni L, Bettella A, Ferlin A. Genetic abnormalities among severely oligospermic men who are candidates for intracytoplasmic sperm injection. The Journal of Clinical Endocrinology and Metabolism. 2005; 90: 152-156.

[49] Bielanska M, Tan SL, Ao A. Fluorescence in-situ hybridization of sex chromosomes in spermatozoa and spare preimplantation embryos of a Klinefelter 46,XY/47,XXY male. Human Reproduction. 2000; 15: 440-444.

[50] Velissariou V, Christopoulou S, Karadimas C, Pihos I, Kanaka-Gantenbein C, Kapranos N, *et al.* Rare XXY/XX mosaicism in a phenotypic male with Klinefelter syndrome: case report. European Journal of Medical Genetics. 2006; 49: 331-337.

[51] Franik S, Smeets D, van de Zande G, Gomes I, D'Hauwers K, Braat DDM, *et al.* Klinefelter syndrome and fertility-Impact of X-chromosomal inheritance on spermatogenesis. Andrologia. 2018; 50: e13004.

[52] Vogt P. Molecular genetic of human male infertility: from genes to new therapeutic perspectives. Current Pharmaceutical Design. 2004; 10: 471-500.

[53] Kim I, Khadilkar A, Ko E, Sabanegh Jr E. 47,XYY syndrome and male infertility. Reviews in Urology. 2013; 15: 188-196.

[54] Robinson DO, Jacobs PA. The origin of the extra Y chromosome in males with a 47,XYY karyotype. Human Molecular Genetics. 1999; 8: 2205-2209.

[55] Blanco J, Rubio C, Simon C, Egozcue J, Vidal F. Increased incidence of disomic sperm nuclei in a 47,XYY male assessed by fluorescent in situ hybridization (FISH). Human Genetics. 1997; 99: 413-416.

[56] El-Dahtory F, Elsheikha HM. Male infertility related to an aberrant karyotype, 47,XYY: four case reports. Cases Journal. 2009; 2: 28.

[57] Abdel-Razic MM, Abdel-Hamid IA, ElSobky ES. Nonmosaic 47,XYY syndrome presenting with male infertility: case series. Andrologia.

2011; 28: 603-605.

2012; 44: 200-204.

[58] Milazzo JP, Rives N, Mousset-Siméon N, Macé B. Chromosome constitution and apoptosis of immature germ cells present in sperm of two 47,XYY infertile males. Human Reproduction. 2006; 21: 1749-1758.

[59] Zenteno-Ruiz JC, Kofman-Alfaro S, Méndez JP. 46,XX sex reversal. Archives of Medical Research. 2001; 32: 559-566.

[60] Pepene CE, Coman I, Mihu D, Militaru M, Duncea I. Infertility in a new 46, XX male with positive SRY confirmed by fluorescence in situ hybridization: a case report. Clinical and Experimental Obstetrics & Gynecology. 2008; 35: 299-300.

[61] Ergun-Longmire B, Vinci G, Alonso L, Matthew S, Tansil S, Lin-Su K, et al. Clinical, hormonal and cytogenetic evaluation of 46,XX males and review of the literature. Journal of Pediatric Endocrinology & Metabolism. 2005; 18: 739-748.

[62] Anık A, Çatlı G, Abacı A, Böber E. 46,XX male disorder of sexual development:a case report. Journal of Clinical Research in Pediatric Endocrinology. 2013; 5: 258-260.

[63] Wang T, Liu JH, Yang J, Chen J, Ye ZQ. 46, XX male sex reversal syndrome: a case report and review of the genetic basis. Andrologia. 2009; 41: 59-62.

[64] Rajender S, Rajani V, Gupta NJ, Chakravarty B, Singh L, Thangaraj K. SRY-negative 46,XX male with normal genitals, complete masculin-ization and infertility. Molecular Human Reproduction. 2006; 12: 341-346.

[65] Peng D, Zhang Y, Zhang X, Hu C, Liu M, Liu R. An infertile 45,X male with a SRY-bearing chromosome 13: a clinical case report and literature review. Journal of Assisted Reproduction and Genetics. 2015; 32: 107-109.

[66] Papadimas J, Goulis DG, Giannouli C, Papanicolaou A, Tarlatzis B, Bontis JN. Ambiguous genitalia, 45,X/46,XY mosaic karyotype, and Y chromosome microdeletions in a 17-year-old man. Fertility and Sterility. 2001; 76: 1261-1263.

[67] Gassó-Matoses M, Picó-Alfonso A, Fernández-García J, Lobato-Encinas J, Mira-Llinares A. 45,X/46,XY gonadal dysgenesis in an infertile adult male. Urologia Internationalis. 1992; 48: 239-241.

[68] Ach T, Marmouch H, Elguiche D, Achour A, Marzouk H, Sayadi H, et al. A case of Kallmann syndrome associated with a non-functional pituitary microadenoma. Endocrinology, Diabetes & Metabolism Case Reports. 2018; 2018: 18-0027.

[69] Dzemaili S, Tiemensma J, Quinton R, Pitteloud N, Morin D, Dwyer AA. Beyond hormone replacement: quality of life in women with congenital hypogonadotropic hypogonadism. Endocrine Connections. 2017; 6: 404-412.

[70] Sato N, Katsumata N, Kagami M, Hasegawa T, Hori N, Kawakita S, et al. Clinical assessment and mutation analysis of kallmann syndrome (KAL1) and fibroblast growth factor receptor 1 (FGFR1 or KAL2) in five families and 18 sporadic patients. Journal of Clinical Endocrinology & Metabolism. 2004; 89: 1079-1088.

[71] Pratap Singh R, Mahmood K, Garg A, Goel K, Gunjana K. Kallmann syndrome-a rare and treatable cause of male infertility with imaging findings. Journal of Evolution of Medical and Dental Sciences. 2016; 5: 6154-6156.

[72] Arkoncel MLCR, Arkoncel FRP, Lantion-Ang FL. A case of Kallmann syndrome. BMJ Case Reports. 2011; 2011: bcr0120113727.

[73] Paulis G, Paulis L, Romano G, Concas C, Di Sarno M, Pagano R, et al. Pregnancy and live birth after follicle-stimulating hormone treatment for an infertile couple including a male affected by Sertoli cell-only syndrome. Research and Reports in Urology. 2017; 9: 203-208.

[74] Stouffs K, Gheldof A, Tournaye H, Vandermaelen D, Bonduelle M, Lissens W, et al. Sertoli cell-only syndrome: behind the genetic scenes. BioMed Research International. 2016; 2016: 6191307.

[75] Hanmayyagari B, Guntaka M, Srinagesh. A rare case of male infertility: Sertoli only syndrome. CHRISMED. Journal of Health and Research. 2015; 2: 64.

[76] Seo JT, Ko WJ. Predictive factors of successful testicular sperm recov-ery in non-obstructive azoospermia patients. International Journal of Andrology. 2001; 24: 306-310.

[77] Zhang Y, Malekpour M, Al-Madani N, Kahrizi K, Zanganeh M,

Mohseni M, et al. Sensorineural deafness and male infertility: a contiguous gene deletion syndrome. Journal of Medical Genetics. 2007; 44: 233-240.

[78] Hoppman N, Aypar U, Brodersen P, Brown N, Wilson J, Babovic-Vuksanovic D. Genetic testing for hearing loss in the United States should include deletionduplication analysis for the deafness/infertility locus at 15q15.3. Molecular Cytogenetics. 2013; 6: 19.

[79] Digilio M, Marino B. Clinical manifestations of Noonan syndrome. Images in Paediatric Cardiology. 2011; 3: 19-30.

[80] Sharland M, Burch M, McKenna WM, Paton MA. A clinical study of Noonan syndrome. Archives of Disease in Childhood. 1992; 67: 178-183.

[81] Elsawi MM, Pryor JP, Klufio G, Barnes C, Patton MA. Genital tract function in men with Noonan syndrome. Journal of Medical Genetics. 1994; 31: 468-470.

[82] Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Pri-mary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. American Journal of Respiratory and Critical Care Medicine. 2013; 188: 913-922.

[83] Kawasaki A, Okamoto H, Wada A, Ainoya Y, Kita N, Maeyama T, et al. A case of primary ciliary dyskinesia treated with ICSI using testicular spermatozoa: case report and a review of the literature. Reproductive Medicine and Biology. 2015; 14: 195-200.

[84] Mahadevan M, Tsilfidis C, Sabourin L, Shutler G, Amemiya C, Jansen G, et al. Myotonic dystrophy mutation: an unstable CTG repeat in the 3' untranslated region of the gene. Science. 1992; 255: 1253-1255.

[85] Kim WB, Jeong JY, Doo SW, Yang WJ, Song YS, Lee SR, et al. Myotonic dystrophy type 1 presenting as male infertility. Korean Journal of Urology. 2012; 53: 134.

[86] Klesert TR, Otten AD, Bird TD, Tapscott SJ. Trinucleotide repeat expansion at the myotonic dystrophy locus reduces expression of DMAHP. Nature Genetics. 1997; 16: 402-406.

[87] Cassidy SB, Driscoll DJ. Prader-Willi syndrome. European Journal of Human Genetics. 2009; 17: 3-13.

[88] Siemensma EPC, de Lind van Wijngaarden RFA, Otten BJ, de Jong FH, Hokken-Koelega ACS. Testicular failure in boys with Prader-Willi syndrome: longitudinal studies of reproductive hormones. The Journal of Clinical Endocrinology & Metabolism. 2012; 97: E452-E459.

[89] Vogels A, Moerman P, Frijns J, Bogaert GA. Testicular histology in boys with Prader-Willi syndrome: fertile or infertile? The Journal of Urology. 2008; 180: 1800-1804.

[90] Garcia-Tizon Larroca S, Blagoeva Atanasova V, Orera Clemente M, Aluja Mendez A, Ortega Abad V, Perez Fernandez-Pacheco R, et al. Prenatal diagnosis of Bardet-Biedl syndrome in a case of hyperechogenic kidneys: clinical use of DNA sequencing. Clinical Case Reports. 2017; 5: 449-453.

[91] Desai A, Jha O, Iyer V, Dada R, Kumar R, Tandon N. Reversible hypogonadism in Bardet-Biedl syndrome. Fertility and Sterility. 2009; 92: 391.e13-391.e15.

[92] Fox MS, Reijo Pera RA. Male infertility, genetic analysis of the DAZ genes on the human Y chromosome and genetic analysis of DNA repair. Molecular and Cellular Endocrinology. 2002; 186: 231-239.

[93] Ali S, Hasnain SE. Molecular dissection of the human Y-chromosome. Gene. 2002; 283: 1-10.

[94] Singh AR, Vrtel R, Vodicka R, Dhaifalah I, Konvalinka D, Janikova M, et al. Y Chromosome and male infertility. International Journal of Human Genetics. 2005; 5: 225-235.

[95] Foresta C, Ferlin A, Garolla A, Moro E, Pistorello M, Barbaux S, et al. High frequency of well-defined Y-chromosome deletions in idiopathic Sertoli cell-only syndrome. Human Reproduction. 1998; 13: 302-307.

[96] Krausz C, Giachini C. Genetic risk factors in male infertility. Archives of Andrology. 2007; 53: 125-133.

[97] Krausz C, Forti G, McElreavey K. The Y chromosome and male fertility and infertility. International Journal of Andrology. 2003; 26: 70-75.

[98] Müslümanoglu MH, Turgut M, Cilingir O, Can C, Ozyürek Y, Artan S. Role of the AZFd locus in spermatogenesis. Fertility and Sterility.

2005; 84: 519-522.

[99] Sertic J, Cvitkovic P, Myers A, Saiki RK, Rukavina AS. Genetic markers of male infertility: Y chromosome microdeletions and cystic fibrosis transmembrane conductance gene mutations. Croatian Medical Journal. 2001; 42: 416-420.

[100] Krausz C, Riera-Escamilla A. Genetics of male infertility. Nature Reviews Urology. 2018; 15: 369-384.