Chromosomic Causes of Infertility

8

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8.1 Definition and Epidemiology

The main genetic factors involved in male infertility are chromosomal abnormalities. These abnormalities can be structural (e.g., deletions, duplications, translocations, inversions, etc.) or numerical (e.g., trisomy, tetrasomy, aneuploidy, etc.) [1, 2] and involve sex chromosomes (e.g., Klinefelter syndrome, 47,XXY) or autosomes (reciprocal translocations and Robertsonian translocations). The incidence of chromosomal aberrations in the general population is approximately 0.5–0.6 % [3–6]. About 1 in 150 babies is born with a chromosomal abnormality [7, 8]. Chromosomal abnormalities account for about 5 % of infertility in males, and the prevalence reaches approximately 15–20 % of the azoospermic males [9, 10] and 5–10 % of the oligozoospermic males [11]. Karyotype abnormalities are reported in 2–14 % of males presenting with infertility [12]. Klinefelter syndrome and Y-chromosomal microdeletions are the most frequent genetic cause of male infertility.

8.2 Etiology

Chromosomal abnormalities are caused by *errors in the number or structure of chromosomes*. It is still unknown why these errors occur.

The *errors in the number of chromosomes* occur during cell division (mitosis and meiosis).

A chromosomal abnormality can also occur before fertilization.

Meiosis is the process of division of reproductive cells (with half the number of chromosomes, 23, haploid cell): eggs and sperms.

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If this process does not occur properly, the chromosomes do not segregate properly, and gametes, eggs, or sperms may end up with too few (monosomy) [13] or too many chromosomes (trisomy) [14].

Errors can also occur during mitosis, after fertilization, when the chromosomes are being duplicated during fetal development resulting in mosaicism: some cells with a typical number of chromosomes and some with an incorrect number of chromosomes.

The *errors in structure of chromosomes* can occur, usually before fertilization, and change the structure of one or more chromosomes. Usually, individuals with structural chromosomal abnormalities have a normal number of chromosomes, but a portion of a chromosome is missing, deleted or inverted, duplicated, misplaced, or exchanged with another part of another chromosome.

Chromosome abnormalities can be inherited from a parent, such as the translocation, or may also occur for the first time in an individual [15].

An important causal factor of chromosomal abnormalities is the *maternal age* (over 35 years) as the primary risk factor for nondisjunction during meiosis, which leads to the occurrence of trisomy 21 (Down syndrome) [16], trisomy 18 (Edward syndrome) [17], and trisomy 13 (Patau syndrome) [18].

The *paternal age* is less important as a causal factor of chromosomal abnormalities [19–21].

Environmental factors can cause chromosomal aberrations although there are few demonstrations [22–25].

8.3 Pathology, Diagnosis, Therapy, and Prognosis

The majority of human chromosomal abnormalities occur in the autosomes. The most common autosomal abnormalities are trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome), partial deletion of the short arm of chromosome 4 (Wolf–Hirschhorn syndrome), and deletion of the short arm of chromosome 5 (cri du chat syndrome). Individuals with these autosomal abnormalities usually have multiple physical malformations, mental retardation, and relatively short lives. The most common sex chromosome abnormalities are Klinefelter syndrome, monosomy X (Turner syndrome), and fragile X syndrome. These sex chromosome abnormalities are slightly less common than autosomal abnormalities, and they are generally much less severe in their effects, and the first two are not associated with mental retardation.

However, for the purposes of this chapter the author has chosen to focus mainly on the most common chromosomic causes of infertility [26]:

- Numerical sex chromosome abnormality = 54 %
- Structural chromosomal aberrations: chromosomal translocations (autosomal translocation, 15 %; Robertsonian translocation, 8 %; sex chromosome translocation, 4 %), Y-chromosomal microdeletions, and CFTR gene deletions or duplications
- Others = 19 %

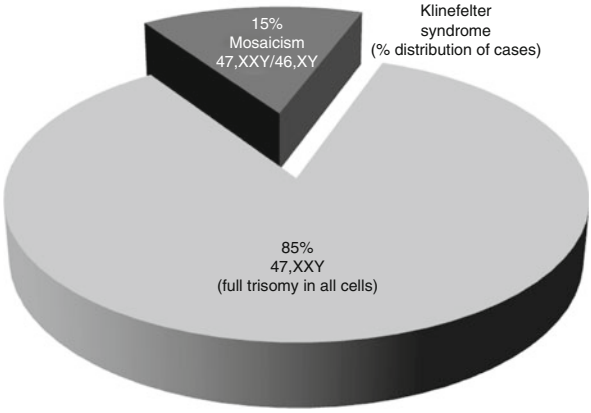

Fig. 8.1 The Klinefelter' s distribution

Table 8.1 Klinefelter syndrome

Common clinical signs
Infertility (azoospermia or oligospermia)
Small testes
Hypergonadotropic hypogonadism
Gynecomastia
Tall height
Learning difficulties (children)
Long arms and legs
Shorter torso
Decreased facial and pubic hair (adults)
Psychosocial or behavioral problems

8.3.1 Klinefelter Syndrome (47,XXY)

Klinefelter syndrome (KS) is the most common numerical sex chromosome disorder in males caused by aneuploidy, affecting one in 660 newborn males [27]. This disease was described for the first time in 1942 [28].

KS is usually associated with the karyotype 47,XXY which may be in all cells (full trisomy) or in mosaic form (15 % of the cases, see Fig. 8.1) [29]. In KS mosaicism some of the cells only have an extra X chromosome (47,XXY/46,XY).

The extra X chromosome derives from nondisjunction during meiosis and may have a paternal (>50 %) or maternal (40–50 %) origin [29]; for the rest of the cases, the X chromosome is originated post-zygotically [30]. The only way to confirm the presence of an extra X chromosome is by a karyotype analysis of peripheral blood or on amniocytes or chorionic villi from prenatal specimens. Common signs and symptoms are small testes (bi-testicular volume <6 ml) [31], hypergonadotropic hypogonadism, gynecomastia, learning difficulties (children), azoospermia and decreased facial and pubic hair (adults), long arms and legs, and tall height (see Table 8.1). Most, but not all, patients affected by KS, are infertile with small

testicles, increased numbers of Leydig cells, tubular sclerosis, and interstitial fibrosis of varying degrees [32]. The physical manifestations of KS are often variable.

This syndrome generally causes spermatogenesis arrest at the primary spermatocyte stage, but occasionally later stages of sperm maturation are observed [33]. It has been estimated that 25 % of non-mosaic KS patients have sperm in their ejaculate [9]. Paduch (2008) reported that over 50 % of KS patients were not sterile [34]. Some recent studies have reported a reduction of life expectancy for KS patients by 1.5–2 years, with increased mortality due to different disorders: diabetes, lung cancer, breast cancer, non-Hodgkin lymphoma, cerebrovascular disease, vascular insufficiency of the intestine, and epilepsy [35, 36]. Klinefelter syndrome should first be suspected whenever a patient consults the doctor because of infertility. In this case these following tests should always be performed: karyotype analysis, semen count, and blood test to check hormone levels of follicle-stimulating hormone, luteinizing hormone, testosterone, and estradiol. Differential diagnoses for KS may include the following conditions: fragile X syndrome, Marfan syndrome, and Kallmann syndrome. With the introduction of the procedure intracytoplasmic sperm injection (ICSI), which consists of the use of sperm extraction from deep within the testicles of KS patients (non-mosaic), some 47,XXY men will have an increased chance of fathering a child [37–39]. Androgen replacement therapy in KS patients should begin in puberty to promote linear growth and secondary sexual characteristics and to permit the normal accrual of muscle mass, bone mineral content, and the adult regional distribution of body fat [40]. However, this treatment is ineffective for treating infertility, gynecomastia, and small testes. Treatment options include different routes of administration: transdermal, oral, and intramuscular injections. A gradual increase of dosage sufficient to maintain age-appropriate serum concentrations of testosterone, estradiol, FSH, and LH is recommended.

8.3.2 Structural Chromosomal Aberrations

- *Chromosomal translocations*
- *Y-chromosomal microdeletions*
- *CFTR gene deletions or duplications*

8.3.2.1 Chromosomal Translocations

Chromosomal translocations are caused by the rearrangement of parts between non-homologous chromosomes.

There are two types of chromosomal translocations: reciprocal or Robertsonian translocations.

Reciprocal translocations occur when there is an exchange of chromosomal material between two different chromosomes. When translocations affect the non-sex chromosomes, they are called autosomal translocations. These translocations occur in 1 in 500 newborns and are the most commonly observed structural chromosomal anomalies in infertile men [26]. Reciprocal translocations can be inherited

from a parent, or they can appear de novo. Translocations are "balanced" when the chromosome material has been rearranged but no genetic material has been lost or gained. Balanced translocations do not usually impact on the growth or development of the individual involved. Nevertheless, carriers (parents) of balanced translocations (who are normal phenotypes) produce both balanced and unbalanced gametes with deletions and duplications of large pieces of the chromosomes involved. The child conceived by an unbalanced gamete inherits a rearrangement of the chromosomes with deletion and/or duplication of chromosome; this condition is known as an unbalanced translocation. Although carriers of balanced chromosomal translocations are phenotypically normal, they may experience reduced fertility, spontaneous abortions, or birth defects [41, 42].

Autosomal translocations negatively affect spermatogenesis due to disrupted meiotic pairing and segregation [43–45]. While translocations have no effect on other tissues, these aberrations can seriously impair spermatogenesis causing severe oligozoospermia or azoospermia [45, 46].

In the same way that occurs in other chromosomal translocations, any part of the sex chromosome may translocate to autosomes. Translocations affecting sex chromosomes have direct consequences on genes involved in spermatogenesis. Translocations between the Y chromosome and autosomes are rare and often cause abnormal spermatogenesis and infertility [47, 48]. The possible mechanisms for reduced fertility due to sex chromosome translocation are the altered gene loci or altered formation of sex vesicle during meiosis.

Translocations involving a sex chromosome and an autosome cause infertility more easily than translocations involving autosomes.

When translocations involve acrocentric chromosomes, these aberrations are called Robertsonian translocations.

Robertsonian translocations involve only these chromosomes and specifically chromosomes 13, 14, 15, 21, and 22. This type of translocation originates from a centric fusion of two acrocentric chromosomes.

When two chromosomes fuse at the centromere (centric fusion), the result is a Robertsonian translocation. Robertsonian translocation is the most frequent structural chromosomal abnormality in humans, and it occurs in around 1 in 1,000 live births [49]. Balanced Robertsonian translocations do not usually impact on the growth or development of the individual involved. Nevertheless, carriers (parents) of Robertsonian translocations, as with reciprocal translocations, can have reproductive effects, when the child receives the translocation in an unbalanced form. Robertsonian translocations can cause various degrees of sperm alteration (oligospermia or azoospermia) [50, 51]. Robertsonian translocations are more common in oligozoospermic and azoospermic men, with rates of 1.6 and 0.09 %, respectively [52].

Robertsonian translocations involving chromosome 21 are found in 5 % of patients with Down syndrome [53].

Preimplantation genetic diagnosis (PGD) by fluorescence in situ hybridization (FISH) is recommended for a Robertsonian translocation and may be useful for couples who opt for assisted reproductive techniques [26].

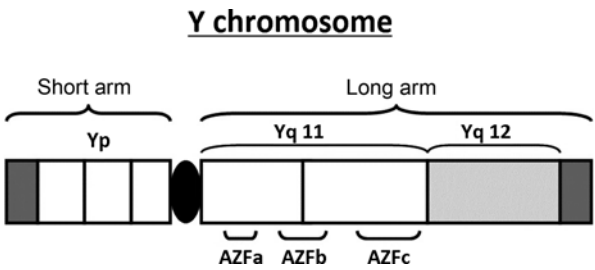

Fig. 8.2 Schematic representation of human Y chromosome

8.3.2.2 Y-Chromosomal Microdeletions (Y Chromosome-Related Azoospermia)

The Y chromosome is the smallest human chromosome and contains many of the genes that are necessary for spermatogenesis and the development of testes. Y-chromosomal microdeletions, which span several genes and remove one or more of them, are able to cause various spermatogenic defects. Y-chromosomal microdeletions are determined by submicroscopic deletions on the Y chromosome (Yq11 region) (see Fig. 8.2), and these alterations are not large and visible by conventional cytogenetic methods. After the Klinefelter syndrome, Y-chromosomal microdeletions are the most frequent genetic cause of male infertility [54, 55]. These gene deletions have been attributed to intrachromosomal homologous recombination within unstable amplicons clustered within the AZF region (azoospermia factor region) [56]. Y chromosome-related azoospermia is the most frequent structural chromosomal anomaly associated with failure in sperm production. The incidence of this anomaly is 15–20 % in men with idiopathic azoospermia and 7–10 % in men with idiopathic severe oligozoospermia [57]. Y-chromosomal microdeletions are extremely rare in infertile males with a sperm concentration >5 million/ml. Generally, Y-chromosomal microdeletions are "de novo" events and are estimated to occur in one in 2,000–3,000 males [58–61]. Infertile men with Y-chromosomal microdeletions usually have no visible symptoms, although some have small testicles and/or cryptorchidism. The first association between azoospermia and deletions of the long arm of the Y chromosome was demonstrated by Tiepolo (1976) [62].

Microdeletions most frequently occur on the long arm of the Y chromosome, Yq 11 region. An important area of interest on Yq is the AZF region that contains genes involved in germ cell development. This region contains three subregions: AZFa, AZFb, and AZFc [63] (see Fig. 8.2).

Gene deletions in this region cause various spermatogenic and infertility phenotypes [64]. Severe infertility or azoospermia is manifest when AZFa, AZFb, or AZFc is singly, or in combination, deleted from the genome. AZFc deletions are the most common form of Y-chromosomal microdeletions and account for approximately 58.3–69 % of reported microdeletions [65–67], followed by deletions of the AZFb region (14 %) and deletions of the AZFa region (6 %) [67]. Zhang et al. reported these incidence rates of several possible combinations of AZF region microdeletions [68]: AZFa = 1.7 %, AZFb = 12.5 %, AZFc = 64.2 %, AZFb + c = 20.0 %, and AZFa + b + c = 1.7 %.

AZFc deletions are usually associated with low levels of sperm in the ejaculate or azoospermia (about two-thirds of individuals) [69]. Transmission of Y-chromosomal AZFc microdeletions could potentially result in the development of sexual ambiguities and Turner stigmata (45,X0) [70, 71]. Microdeletions of AZFa are associated with the complete Sertoli-cell-only (SCO) syndrome and azoospermia, while microdeletions of AZFb or AZFc result in a variable clinical and histological phenotype, ranging from the SCO syndrome to oligozoospermia [72–74]. AZFb + c deletions usually produce no testicular sperm. When AZF-deleted sperms are used for *assisted reproductive techniques* (ART), fertility defects in male offspring are inevitable [65]. Classical Y-chromosomal microdeletions do not confer a risk for cryptorchidism or testicular cancer [74, 75]. If complete AZFa or AZFb microdeletions are detected, micro-testicular sperm extraction (TESE) is not indicated because this technique is very time consuming—it is extremely difficult to find sperm cells [74]. Microdeletion analysis using PCR helps determine the frequency and site of gene deletion and thus the testicular phenotype. Yq microdeletion analysis (AZF screening) is generally carried out by multiplex polymerase chain reaction (PCR) amplifying AZFa, AZFb, and AZFc loci in the q arm of the Y chromosome [76]. The analysis of Y-chromosomal microdeletions permits to establish a diagnosis and to formulate a prognosis, in men with idiopathic infertility presenting with azoospermia or severe oligospermia with sperm concentrations <5 million/ml [77]. AZF screening is important before varicocelectomy because infertile men carrying a Yq microdeletion will most likely not benefit from the surgical procedure [77]. In case of diagnosis of Y-chromosomal microdeletion, a genetic counseling is mandatory (especially for the ART candidates) to provide information about the risk of conceiving a son with impaired spermatogenesis.

8.3.2.3 Mutations in the CFTR Gene

Congenital bilateral absence of the vas deferens (CBAVD) is an important disorder characterized by agenesis of the vas deferens, and it affects about one in 1,000 male individuals [78]. It is an important cause of sterility in men, approximately 2 % of infertility cases [79], and it accounts for 6 % of cases of obstructive azoospermia (OAZ) [80].

Genetic mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) are responsible for CBAVD and cystic fibrosis (CF). The CFTR gene is located on the long (q) arm of human chromosome 7 at position 31.2 [81] (see Fig. 8.3).

CFTR gene mutations are responsible in about 95 % of men with CBAVD [82].

Cystic fibrosis is the most frequent severe autosomal recessive genetic disorder in the Caucasian population, affecting about 1 in 2,500 live births [83]. The most frequent clinical manifestations of CF are chronic obstruction and infection of the respiratory tract and often exocrine pancreatic insufficiency. About 98 % of male CF patients are infertile as a result of CBAVD [84, 85]. The CFTR gene encodes for a membrane protein that also influences the formation of the ejaculatory duct, seminal vesicle, vas deferens, and distal two-thirds of the epididymis.

Fig. 8.3 Location of the CFTR gene on human chromosome 7

Genetic mutations in the CFTR gene (deletions or duplications) lead to the low function of CFTR resulting in the production of viscous secretions (dehydration of mucus secretions) that obstruct the lumen of airways, sweat glands, gastrointestinal tract, pancreatobiliary ducts, sinuses, and reproductive tissues [86].

CBAVD may also occur as an isolated form of genital disorder without clinical CF symptoms (incomplete genital form of CF) [87]. Patients with this phenotype of CF, previously considered a distinct genetic entity, have an increased frequency of CFTR gene mutations [88, 89]. CFTR gene mutations were detected in some patients with congenital unilateral absence of the vas deferens (CUAVD); this condition could be an incomplete form of CBAVD [89]. CUAVD is a rare condition and has an incidence of 0.5–1 % in the male population [90]. CUAVD was found to occur twice as frequently on the left than on the right side [91]. Whereas in some of CUAVD patients the condition is associated with mutations in the CFTR gene, in other patients this congenital anomaly is probably caused by other factors [88]. Men with CUAVD may be normally fertile [88]; in these males there is a high incidence of ipsilateral renal agenesis [92]. CUAVD is interesting because of its association with renal anomalies and CFTR gene mutations [92]. Renal imaging and cystic fibrosis (CF) screening were recommended to all

patients with CUAVD or CBAVD. In fact unilateral renal agenesis is also possible in CABVD patients with an incidence of about 10 %, mostly seen in patients without CFTR gene aberrations [93].

Screening for CFTR mutations is recommended in the following conditions:

- Azoospermic male with a semen volume of < 1.5 ml and pH less than 7.0
- Individuals with a family history of CF or CFTR mutations
- Males with CBAVD or CUAVD
- Patients with chronic or idiopathic pancreatitis
- Reproductively active individuals or couples
- Couples who opt for ART (assisted reproductive techniques) for determining the risk of transmitting CFTR mutations to the offspring

8.3.3 Prader–Willi Syndrome

Prader–Willi syndrome (PWS) is a rare genetic disease which occurs equally in both sexes and all races.

PWS was first described in 1956 [94] and has a prevalence about of one in 50,000 newborns [95–98].

This syndrome is characterized by severe muscular hypotonia, hyperphagia, obesity, hypogonadism, mental retardation, and short stature. This condition is caused by the absence of paternal expression of imprinted genes localized in the 15q11-q13 region [94, 99]. However, the following are possible genetic subtypes [100]: paternal deletion of chromosome 15q11-q13 (type I or II), 75 %; maternal uniparental disomy (UPD), 24 %; imprinting center defects (ID), 1 %; and translocation <1 %.

Delayed and incomplete pubertal development is documented in almost all PWS patients. Manifestations of hypogonadism in infancy include micropenis and/or cryptorchidism (80 %) in males [101, 102]. Hypogonadism was generally considered to be of hypothalamic origin [102–105].

DNA methylation analysis is the only technique, which can both confirm and reject the diagnosis of this syndrome [86]. A prenatal diagnosis could be suspected in cases of reduced fetal movement and polyhydramnios [106]. In a family who previously had a child with PWS (with an imprinting defect), the man with a deletion has a 50 % chance of fathering a baby with PWS again [100]. At present there are no reports of paternity in PWS [100].

A possible therapeutic program should include:

- Obesity management with institution of a low-calorie, well-balanced diet, with regular exercise and rigorous supervision
- GH treatment in children to improve growth during childhood
- Hormonal treatment for induction, promotion, or maintenance of puberty
- Management of behavioral and psychiatric problems

8.3.4 Angelman Syndrome

Angelman syndrome (AS) is a rare condition caused by deletion on the mother's chromosome 15. The incidence is one in 12,000–20,000 births [107–109]. Angelman syndrome is a rare neurological disorder characterized by developmental delay, significant intellectual disability, difficulties with speech development, seizures, uncontrolled limb and body movements, motor impairment, spontaneous laughter, EEG abnormalities, and epilepsy [110]. Anomalies of the head and face are common, including microcephaly, macrostomia, maxillary hypoplasia, mandibular prognathism, deeply set eyes, and widely spaced teeth. Males and females with Angelman syndrome achieve puberty normally, with normal secondary sexual characteristics. However, there has been no documented case of reproduction in a male with Angelman syndrome [110]. A successful reproduction has been reported in only one case of female with Angelman syndrome [110].

DNA methylation analysis identifies approximately 80 % of individuals with AS. If the DNA methylation analysis is abnormal, the next step is FISH or array CGH analysis [111].

For completeness, other very rare forms of male infertility caused by genetic disorders [79] are listed at the end of this chapter:

- Myotonic dystrophy (DM)
- Kallmann syndrome
- Immotile cilia syndrome
- Noonan syndrome
- Denys–Drash syndrome (DDS) and Frasier syndrome
- Androgen insensitivity syndrome
- Polycystic kidney disease (with multiple cysts in the liver, kidneys, epididymis, and seminal vesicles)
- Usher's syndrome

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