The genetic origin of Klinefelter syndrome and its effect on spermatogenesis

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Klinefelter syndrome is the most prevalent chromosome abnormality and genetic cause of azoospermia in males. The availability of assisted reproductive technology (ART) has allowed men with Klinefelter syndrome to father their own genetic offspring. When providing ART to men with Klinefelter syndrome, it is important to be able to counsel them properly on both the chance of finding sperm and the potential effects on their offspring. The aim of this review is twofold: [1] to describe the genetic etiology of Klinefelter syndrome and [2] to describe how spermatogenesis occurs in men with Klinefelter syndrome and the consequences this has for children born from men with Klinefelter syndrome. (Fertil Steril® 2012;98:253–60. ©2012 by American Society for Reproductive Medicine.)

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The phenotype of what was later named "Klinefelter syndrome" was first described in 1942 by Harry Klinefelter (1). He reported nine men with gynecomastia, small testes, and azoospermia. In 1959, it was first demonstrated that men with Klinefelter syndrome have an additional X chromosome, resulting in a 47,XXY karyotype (2). Nowadays, it is known that a 47,XXY karyotype is found in 80%–90% of men with Klinefelter syndrome, whereas the remaining cases show a mosaic karyotype (46,XY/47,XXY), additional X chromosomes (e.g., 48,XXXYor 48,XXYY), or structurally abnormal X chromosomes (e.g., 47,X,iXq,Y) (3, 4). Klinefelter syndrome is the most prevalent chromosomal disorder in humans, with an estimated frequency of 1:500 to 1:1,000 men (3). It is also the most frequent genetic cause of azoospermia (5, 6). Most men with Klinefelter syndrome are diagnosed when they have failed to achieve a pregnancy and are diagnosed with azoospermia. However, a significant proportion of men with Klinefelter syndrome remain undiagnosed, probably because of the wide phenotypic variability and lack of knowledge of the syndrome among health professionals (3, 7).

Since the introduction of intracytoplasmic sperm injection (ICSI) (8) and testicular sperm extraction (TESE) (9), a considerable number of men with Klinefelter syndrome have been able to father genetically own offspring. In light of this possibility for paternity, a review of the genetic etiology of the syndrome as well as its effects on spermatogenesis is useful in order to allow discussion of the potential risks of this treatment. This review has two main objectives. First, we describe the genetic etiology of Klinefelter syndrome. In this section we address normal meiosis and focus on paternal and maternal causes of nondisjunction. Second, we describe how spermatogenesis occurs in men with Klinefelter syndrome and discuss the possible consequences for offspring from men with Klinefelter syndrome.

GENETIC ORIGIN OF KLINEFELTER SYNDROME

Normal Meiosis

Before the first meiotic division, the amount of DNA is doubled (replication), resulting in 46 chromosomes, each consisting of two chromatids (2n,4c). The first meiotic division (reduction division) involves segregation of homologous chromosomes (2n,4c) and gives rise to haploid (23 chromosomes; 1n,2c) germ cells: two secondary spermatocytes (male meiosis) or one secondary oocyte and one polar body (female meiosis). In male meiosis, the second meiotic division (segregation of sister chromatids; 2c → c) gives

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rise to spermatids that subsequently mature into spermatozoa. In female meiosis, the second meiotic division is finished only after fertilization, giving rise to a mature (fertilized) oocyte and a second polar body. Thus, each male germ cell entering meiosis eventually gives rise to four spermatozoa, whereas one complete round of female meiosis eventually produces one mature oocyte (10, 11).

During prophase of meiosis I, homologous chromosomes pair and form connections called chiasmata. In male meiosis, the (largely nonhomologous) X and Y chromosome pair at the tips of their short and long arms, the pseudoautosomal regions 1 and 2 (PAR1 and PAR2). Paired homologous chromosomes exchange random DNA segments at the chiasmata, a process called crossing over, which results in a recombination of these segments. Crossing over takes place during prophase of meiosis I and is nonrandomly distributed along the chromosomes, with at least one exchange per chromosome arm (except for the short arms of acrocentric chromosomes). Genomewide recombination rates in female meioses are approximately 1.6- to 1.7-fold greater than in male meioses (12). The PAR1 region (2.6 Mb) contains one obligatory crossover (13). Pairing and crossing over at the smaller (320-kb) pseudoautosomal region (PAR2) at the tip of the long arms of the X and Y chromosomes is not essential for completing meiosis (14, 15). The purpose of crossing over is twofold: [1] to generate diversity within a population and [2] to ensure accurate segregation of chromosomes during meiosis I (16). The latter will be discussed below.

Mechanisms Leading to Aneuploidy

Nondisjunction is the failure of chromosomes to separate (disjoin) at anaphase during meiosis I (paired homologs), meiosis II (sister chromatids), or mitosis (sister chromatids) (11), giving rise to daughter cells with an aberrant number of chromosomes. The proper formation and resolution of chiasmata is necessary to keep the homologs in the right position during meiosis for their accurate separation into their daughter cells. "Classical" nondisjunction in meiosis I can result from failure to resolve chiasmata ("true nondisjunction"), premature resolution of chiasmata or failure to establish chiasmata ("achiasmate nondisjunction"). Another mechanism, premature separation of sister chromatids, can result in one complete chromosome and a single chromatid segregating together in meiosis I (17). Nondisjunction has long been regarded as the main mechanism leading to aneuploidy. Interestingly, however, using array comparative genomic hybridization (array-CGH) on first polar bodies, it has recently been shown that chromatid errors (premature separation; 3:2 ratio of sample vs. control DNA) were 11.5 times more common than whole chromosome errors (nondisjunction; 2:1 ratio) (18). Handyside et al. (19), who studied both polar bodies and the corresponding zygote by array-CGH, also conclude that almost all meiosis I errors are caused by premature division of sister chromatids.

Finally, anaphase lagging is the failure of a chromosome or chromatid to be incorporated into a daughter cell following cell division (11). Chromosomes or chromatids not entering a daughter cell are lost, resulting in aneuploidy (monosomy) for that chromosome.

Origin of XXY Aneuploidy

It has always been assumed that most human trisomies originate from nondisjunction at maternal meiosis I (20). Indeed, paternal meiotic errors account for only 10% of autosomal trisomies. However, this is very different for sex chromosomal aneuploidies, including Klinefelter syndrome that results from a nondisjunction event in the father in nearly half of the cases (20, 21). In cases of Klinefelter syndrome with an additional maternal X, nondisjunction in either the first or second meiotic division is most likely to have occurred. In paternal cases, the additional X chromosome can only be the result of nondisjunction in the first meiotic division, because a meiosis II error will result in either XX or YY gametes (and therefore XXX or XYY zygotes) (20). As mentioned previously, premature separation of sister chromatids in meiosis I might be a more common cause of aneuploidy than originally thought (18). This mechanism could also underlie the origin of nonmosaic XXY cases of either paternal or maternal origin.

Aberrant meiotic recombination has been shown to play an important role in the etiology of nondisjunction in Klinefelter syndrome (20, 22). The vast majority of Klinefelter cases of paternal origin result from a "nullitransitional" meiosis I nondisjunction, that is, a meiotic division with complete absence of recombination of the PAR regions, but "transitional" (with occurrence of crossing over) paternally derived cases also occur. Maternal cases with either absent or normal recombination have also been described (20, 23). In addition to studies using DNA markers in Klinefelter men (or fetuses) and their parents to assess recombination, direct analysis of 24,XY disomic sperm of a normal 46,XY male showed a significantly lower recombination frequency compared with 23,X or 23,Y sperm (24). Not only the number of crossing overs but also the localization of chiasmata seems to be important for meiosis to occur accurately. Crossing overs occurring too near or too far from the centromere have been described in autosomal trisomies: for example, trisomy 21 and trisomy 16. However, the position of recombination was normal in cases with Klinefelter syndrome as reviewed by Lamb et al. (25).

Maternal age is a well-known risk factor for meiotic nondisjunction, especially in Down syndrome. Bojesen et al. found a 4-fold increase in the prevalence of Klinefelter cases with maternal age greater than 40 years compared with those with maternal age below 24 years (3). A maternal age effect was also shown in Klinefelter cases with a normal recombination pattern and in cases with postzygotic mitotic nondisjunction (resulting from a mitotic error early in the developing zygote) (20). The latter could be explained by the fact that in humans the first three mitotic divisions are solely controlled by maternal protein and RNA (26); with increasing maternal age, the chance of mitotic errors in the first cell divisions increases and therefore perhaps also the chance of Klinefelter syndrome of postzygotic origin. In a recent review of both epidemiologic studies and direct fluorescence in situ hybridization (FISH) studies, Fonseka et al. conclude that there is very little or no evidence for a correlation between paternal age and autosomal aneuploidy and some—albeit debatable—evidence for a relation with sex chromosomal trisomies and paternal age (27).