



# Chromosome karyotype abnormality in peripheral blood lymphocytes and reproductive system diseases: an overview

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**Abstract:** With improvements in living standards and the medical environment, people are increasingly concerned about the causes and treatment of reproductive system diseases such as infertility and adverse pregnancy outcome. Karyotype abnormalities in peripheral blood lymphocytes are responsible for azoospermia, oligospermia, amenorrhea and abnormal gonad development in adults. It is important to focus on chromosome screening when evaluating infertility and people with a history of adverse pregnancy outcome to improve early intervention and the effective treatment of chromosomal abnormalities related to reproductive system diseases.

**Keywords:** Chromosome karyotype abnormality; peripheral blood lymphocytes; infertility; reproductive system diseases

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In the past, people thought that reproductive system diseases were due to changes in environmental, physical and chemical factors; hormone disorders; or pathogen infection. With the development of medical technology, people have begun to pay more attention to reproductive system diseases caused by chromosome abnormalities. In this paper, we will integrate current cutting edge research findings to discuss the association between chromosome karyotype abnormalities in peripheral blood lymphocytes and azoospermia, oligospermia, amenorrhea, abnormal gonad development and adverse pregnancy outcome.

## Azoospermia or oligospermia and chromosome karyotype abnormalities

Sexual chromosome abnormalities are the most important contributor to azoospermia or oligospermia. This phenotype is more common in patients with Klinefelter syndrome, which has the chromosomal karyotype 47,

XXY. Patients have basically normal or slightly lower intelligence. They are tall with slender limbs, a short penis, poorly developed testicles and no sperm. Furthermore, they have developed male breasts and less beard, armpit hair and pubic hair. Zhang *et al.* (1) reported that 10.55% of individuals with Klinefelter syndrome were azoospermic. Infertility in these patients is a consequence of the direct harmful effect of an extra X chromosome, which causes a lethal gene dosage effect in testicular cells that results in azoospermia (2).

Recent studies have shown that the absence of azoospermia factor (AZF) on the long arm of the Y chromosome can also lead to azoospermia or severe oligozoospermia, which is closely related to male infertility. AZF is a set of genes or gene clusters associated with spermatogenesis. Previous studies revealed that Y chromosome microdeletions occurred in 1% to 55% of infertile men with azoospermia or severe oligozoospermia (3-6). In another study, the prevalence of AZF microdeletions was 10.80%. The frequency of

AZF microdeletions was 11.75% among patients with azoospermia. Deletions of the different AZF regions occur at different frequencies. Previous data (3,7,8) were confirmed by more recent findings that classical AZFc deletions were the most frequent finding (54.17% of deletions in our cases), followed by those in the AZFbc region (18.75%), AZFb (10.42%) and AZFa (9.03%) regions (9).

Studies have shown that DAZL gene methylation is closely related to male infertility. Navarro-Costa *et al.* performed a comparative analysis of semen from normal men and men with oligospermia or asthenospermia. They evaluated CpG methylation in the promoter of the reproductive regulatory gene DAZL and found it be statistically higher in semen from patients with oligospermia or asthenospermia. These data indicate that hypermethylation of the DAZL gene is associated with abnormal spermatogenesis. Perhaps hypermethylation inhibits the expression of certain functional sperm proteins during spermatogenesis, leading to male infertility (10).

### Amenorrhea and chromosome karyotype abnormalities

Female amenorrhea is a common complication in gynecological clinical treatment that is classified as primary amenorrhea (PA), which is the failure of menses to occur by the age of 16, or secondary amenorrhea (SA), in which menses begins at puberty but is subsequently ceases (11). The prevalence of PA and SA in the United States is less than 1% and 5–7%, respectively. No evidence indicates that the occurrence of amenorrhea varies according to national origin or ethnicity (12), PA is primarily caused by pituitary/hypothalamic disorders (27.8%), gonadal dysfunction (50.4%), or outflow tract abnormalities (21.8%) (12,13). Thus, gonadal/ovarian disorders make up half of the all PA cases. This category of etiology often stems from abnormal sex chromosomes (13). In addition to gonadal dysplasia, patients tend to have a short stature, webbed neck, cubitus valgus, shield chest, immature vulva, breast dysplasia and other symptoms and signs of Turner syndrome (TS).

TS is the most common chromosomal aneuploidy; it affects 1 in every 2,000 girls and is characterized by a short stature and gonadal dysgenesis in females who lack all or part of one X chromosome (14). Approximately 50% of patients with TS have complete loss of one X chromosome, whereas the remaining of patients with TS display mosaicism or structural abnormalities of the X

chromosome, for example, 46,X,i(Xq); 46,X,del(X); or 46,X,r(X) (15). Similar to complete monosomy X, partial deletions of either the short or long arm can cause features of TS. Many studies have been conducted to verify and delineate the proposed loci for genes pertaining to the TS phenotype; some have indicated that the genes for physical and cognitive features lie on Xp, whereas the genes for ovarian function are present on both Xp and Xq (16,17). Approximately one-third of girls with TS may enter spontaneous puberty, but only half them completed menarche (18). The prevalence of spontaneous puberty is higher among patients with mosaic TS. In addition, there have been a few rare cases of TS with precocious puberty (18–22).

### Gonadal dysplasia and chromosome karyotype abnormalities

Disorders of sex development (DSD) are congenitally conditions with atypical chromosomal, gonadal or anatomical sex development. Sexually differentiated diseases are clinically diverse. External genital abnormalities can present as completely male or female, but more often the phenotype is intermediate. Chromosomal abnormalities can cause various deformities, especially when chromosome number or structure is affected, leading to cause genital malformations, gonadal dysplasia and poor development of secondary sex characteristics. Based on chromosomal classification, DSD is divided into sex chromosome abnormalities, 46,XY DSD and 46,XX DSD (23).

Sex chromosome abnormalities DSD include Klinefelter syndrome, Turner's syndrome, super-male syndrome, and ultra-female syndrome. The XYY karyotype has an incidence of one in 1,000 male newborns and may result from a nondisjunction in paternal meiosis II or postzygotic mitotic nondisjunction (24–26). The 48,XXXY syndrome has an incidence of 1:50,000, and patients present as male with external genital dysplasia (27,28). The pathogenesis may involve the dissociation and inactivation of the excess X chromosome; however, the inactivation of the genes on the chromosome is not complete, and the inactivated gene expression leads to gonadal dysplasia (29).

46,XY DSD and 46,XX DSD include additional marker chromosomes (mar), autosomal balanced translocations, Robertsonian translocation, and sex reversal. Mar chromosomes are a structural abnormal, and patients have the karyotype 48,XY,+mar1,+mar2. Although the source

of the chromosome cannot be determined, it is thought that it may carry decisive development-related genes, thus affecting the development of the reproductive system. Sex reversal includes 46,XY testicular feminization syndrome and 46,XX male syndrome. The first phenotype is typical of women, who present with good breast development, a blind vagina, and PA before and after adolescence. The second phenotype is male with testicular dysplasia, and the pathogenesis is associated with deletion, mutation, or translocation of the sex-determining region Y gene (SRY) on the Y chromosome (30).

### **History of adverse pregnancy outcome and chromosome karyotype abnormalities**

Chromosomal abnormalities are more common in spontaneous abortion, patients with congenital malformations or dysplasia, advanced maternal age pregnancy and infertile couples, leading to spontaneous abortion, infertility, congenital malformations and low intellect, which have a considerable societal impact. Balanced chromosomal translocation accounts for most cases; it has been observed in 0.6% of infertile couples and in as many as 9.2% of couples with recurrent miscarriages (31). Reciprocal translocation is defined as the exchange of chromosomal material between the arms of 2 heterologous chromosomes, thus changing the order but typically not the amount of genetic material. Carriers of balanced chromosomal translocations may have all of the necessary genetic information for normal development. Balanced translocations can be transmitted through generations; it is assumed that most familial cases are phenotypically normal, resulting from balanced rearrangements (32). However, when one member of a couple carries a balanced chromosome translocation, the risk of miscarriage is approximately doubled (33). Individuals with balanced reciprocal translocations are known to have high rates of unbalanced gametes, exhibit impaired or reduced gametogenesis, produce large numbers of unbalanced embryos and have a greater chance of being infertile and/or a high risk of conceiving chromosomally abnormal pregnancies that lead to recurrent spontaneous abortions or children with congenital anomalies (34-36). The Robertsonian translocation is also referred to as a “centric fusion” translocation of the entire long arms of two acrocentric chromosomes (chromosomes 13, 14, and 15 of the D group, and chromosomes 21 and 22 of the

G group) after breakage at the centromeres (37). During meiosis, these rearrangements form trivalent, which upon segregation, may result in nullisomic or disomic gametes for one of the chromosomes involved in the rearrangement and, consequently, a zygote with trisomy or monosomy for one of the involved chromosomes. In humans, an individual with a “balanced” Robertsonian translocation has a karyotype of 45 chromosomes, with the translocation chromosome containing the two complete long arms of the two acrocentric chromosomes involved. The short arms of the two translocated chromosomes are lost. The most common Robertsonian translocation is between chromosomes 13 and 14. Translocation between the D and G groups is responsible for approximately 75% of all Robertsonian translocations, and the potential live-born chromosomally unbalanced outcome of this translocation is trisomy 13; there is also potential for uniparental disomy of chromosome 14 following trisomy rescues. The second most common Robertsonian translocation is between the D and G groups (14 and 21), and the potential live-born unbalanced outcome of this is trisomy 21, resulting in Down syndrome (38).

Chromosome inversion is also more common, and the main clinical manifestations are infertility, abortion and stillbirth. Chromosome inversion is divided into pericentric inversion and paracentric inversion. The mechanism underlying adverse pregnancy outcome is the matching of homologous chromosome fragments in germ cells during meiosis. In theory, this will create four kinds of gametes: one is a normal individual, one is an inverted carrier, and the other two harbor partial duplication and partial deletion. Pericentric inversion of chromosome 9 [(9)(p11q13)] is a frequently seen chromosomal alteration in humans due to its structural organization, which makes it more prone to breakage. The incidence is estimated at 1–3% of the general population, with the lowest rate among Asians at approximately 0.25% (39,40). There are several conflicting assessments of its clinical impact; some studies claim it to be a normal variant, while others have associated it with several diseases, such as infertility and poor obstetric history. Among the various types, *inv(9)(p11q12)* and *inv(9)(p11q13)* are the most common. Variable clinical manifestations have been observed from normal to multiple malformations among babies born to carriers of such structurally balanced chromosomal aberrations (41).

There are no definite conclusions about the relationship between chromosomal polymorphisms and reproductive

abnormalities. The conventional view is that the alterations do not cause phenotypic effects, but an increasing number of studies have found that such polymorphisms have clinical consequences. Chromosomal polymorphisms refer to the constant, small but non-pathological difference in the structure and tinctorial strength of chromosomes between different individuals. It usually refers to variation in the satellite zone of the D/G group chromosomes, insertion or deletion of the secondary constriction of chromosome 1, 9, 16 and Y chromosome; and inversion of chromosome 9 and Y (42,43). When the homologous chromosomes with polymorphisms pair, the polymorphic section cause difficulties in homologous chromosome pairing, which affects cell division, leading to embryonic developmental disorders that result in abortion, embryonic death or chromosomal abnormalities (43).

Currently, the primary treatments for chromosomal diseases are symptomatic treatment and correction of organ deformity. Gene therapy, cellular therapy and alternative therapy are under development. However, chromosome abnormalities are difficult to treat, and the curative effect is not satisfactory. There is no effective medicine for congenital mental retardation. Patients can try Chinese medicine or rehabilitation training. The prognoses of different types of chromosome dysplasia are not the same, most are undesirable. Therefore, prevention is particularly important. Preventive measures include the implementation of chromosome counseling and chromosome detection. The best preventative measure is third-generation of IVF (genetic screening) to prevent the birth of fetuses with chromosomal abnormalities. Pregnant women should attend regular prenatal checkups to identify fetal problems as soon as possible.

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### Footnote

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jlpm.2018.06.02>). The authors have no

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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