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Autosomal aberrations associated with testicular dysgenesis or spermatogenic arrest in Chinese patients

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Abstract **Aim:** To analyze the relationship between autosomal aberrations and testicular dysgenesis or spermatogenic arrest in Chinese patients and to map the corresponding regions on each autosome in regard to the recorded aberrations accompanying these distubances. **Methods:** One hundred and nineteen cases of aberrant karyotypes with testicular dysgenesis, azoospermia or oligozoospermia reported in five Chinese journals and one monograph were analyzed. For each autosome, the type and frequency of chromosomal aberrations were counted and the regions corresponding to the disturbances were mapped out. **Results:** Chromosomes 13, 14, 9, 21 exhibited a high frequency of aberration and bands 14q11 and 13p11 were the two regions showing the highest linkage to testicular dysgenesis or infertility. The frequency of chromosomal aberrations was higher in bands 9p11 and 22q than in others. **Conclusion:** Autosomes 13, 14, 9 and 21 in the order of importance play a critical role in testicular development and spermatogenesis and other autosomes may also contribute; the following regions, 14q11, 13p11,9p11, and 22q, are of high significance. *(Asian J Androl 2002 Mar; 4: 3-7)*

1 Introduction

There is a close relationship between chromosome aberrations and testicular dysgenesis or spermatogenic arrest. Chromosomal aberration impairs the normal inactivation process of the X chromosome [1] or damages the structure of functional genes, which would lead to male infertility as a result of testicular dysgenesis or spermatogenic arrest.

Testicular development and spermatogenesis are very complicated processes and a large number of genes are involved. Many genes related to gonad development and spermatogenesis have been cloned and characterized, such as *SRY, AZF, RBM, DAZ, USP9Y, TSPY, DFFRY, CREM, MIS, UTY*, etc., most of which are located on the male-specific Y chromosome. However, some of them are located on the autosomes, such as WT1 on 11, SOX9 on 17, DAZLA on 3 and FSHR on 2 [2,3]. Y chromosome is the smallest one in human and only a few genes have been found therein. Genes on the Y chromosome have been studied in detail and methods have been developed to diagnose the defects of DAZ and other genes [4-6]. However, genes on the autosomes have not been investigated systematically. Hence, study on the correlation between autosomal aberrations and relevant disturbances is helpful for cloning functional genes related to gonad, testis development and spermatogenesis, and for revealing the mechanisms of these processes both at the chromosome and the gene levels. The present review analyzed 119 cases of aberrant karyotypes with testicular dysgenesis, azoospermia or oligozoospermia reported

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in Chinese literature in order to help clarifying the relationship between autosomal aberrations and these disturbances.

2 Materials and methods

Articles related to male reproductive defect with aberrant karyotypes published in the Chinese Journal of Medical Genetics (from 1990 to 2000), the Chinese Journal of Birth Health & Heredity (1993 to 2000), the National Medical Journal of China (1977 to 1999), the Chinese Medical Journal (1980 to 1999), the Journal of Improving Birth Outcome and Child Development of China (1994 to 1999), and the Chromosomal atlas of the first reported aberrant karyotypes in the world among Chinese (Xia JH, Li LY, Ed., Zhengzhou, Henan Science And Technology Publishing House, 1993) were collected. Patients quoted in these literatures were from various parts of China, including Beijing, Tianjin, Xinjiang, Guangdong, Hebei, Fujian, Hunan, Jiangsu, Chongqing,

Table 1. Sixty-three cases employed in constructing the map of " hot " regions on autosomes.

Karyotype	Number of cases	Disturbance	Reference
46,XY,t(2;7)(p21;q11)	1	Testicular dysgenesis	8
46,XY,t(7;8)(p11;q21)	1	Testicular dysgenesis	8
46,XY,t(13;16)(q14;q22)	1	Infertility	11
46,XY,inv(9)(p11;p12)	2	Infertility	11
46,XY,inv(9)(p11;q13)	3	Infertility	11
45,XY,t(13;14)(p11;q11)	2	Infertility	11
45,XY,t(14;21)(p11;q11)	1	Infertility	11
45,XY,t(13;15)(q11;p11)	1	Infertility	15
45,XY,t(15;21)(p11;q11)	1	Infertility	15
45,XY,t(13;14)(p11;q11)	2	Infertility	15
46,XY,t(1;8)(p22;q21)	1	Infertility	15
46,XY,inv(5)(p13;q15)	1	Infertility	15
46,XY,t(1;14)(p11;q11)	1	Infertility	15
46,XY,t(5;22)(q35;q11)	1	Infertility	15
46,XY,inv(9)(p11;q21)	1	Infertility	15
46,XY,t(6;9)(q21;p24)	1	Infertility	15
45,XY,t(14;15)(p11;q11)	1	Infertility	15
45,XY,t(5;22)(5p->5q15::22q11->22qter)	1	Low sperm motility	16
46,XY,inv(1),t(1;6)(1qter->1q25::1p13->1q25::1p13->1p22::6q23->6qter;6pter->6q23::1p22->1pter)	1	Azoospermia	17
45,XY,rob(13;14)(p11;q11)	8	Infertility	18
45,XY,rob(14;15)(p11;q11)	1	Infertility	18
45,XY,rob(14;21)(p11;q11)	1	Infertility	18
45,XY,rob(21;22)(p11;q11)	1	Infertility	18
46,XY,t(1;4)(p21;q35)	1	Infertility	18
46,XY,t(2;3)(q23;q27)	1	Infertility	18
46,XY,t(2;18)(p13;q21)	1	Infertility	18
46,XY,t(3;13)(q27;q21)	1	Infertility	18
46,XY,t(4;13)(q35;q22)	1	Infertility	18
46,XY,inv(1)(p36;q21)	1	Infertility	18
47,XY,inv(3)(p21;q21)	1	Infertility	18
46,XY,t(14:20)(14pter->14q11::20q13->20qter,20pter->20q13::14q11->14qter)	1	Azoospermia	20
46,XY,t(1;4)(p31;q35)	1	Cryptorchidism	22
46,XY,t(1;7)(p32;q35),inv(12)(q15q24)	1	Cryptorchidism	22
46,XY,t(1;11)(p36;q13)	1	Azoospermia	22
46,XY,inv(2)(p11q31)	1	Teratospermia	22
46,XY,t(6;13)(p25;q12)	1	Azoospermia	22
46,XY,del(7)(q11q22)	1	Microphallus & cryptorchidism	22
46,XY,inv(10)(q11q22)	1	Oligozospermia	22
45,XY,ter rea(14;22)(q32.2;p13)	1	Testicular dysgenesis	22
46,XY,del(19)(q12)	1	Azoospermia	22
46,XY,t(6;7)(6pter->6p21; 7qter->7p22::6p21->6pter)	1	Azoospermia	23
46,XY,t(6;10)(6pter->6q22;10qter->10p15::6q22->6qter)	1	Azoospermia	23
46,XY,del(6)(6qter->6p12)	1	Azoospermia	23
46,XY,inv(9)(p21->p24::p13::q21->qter)	1	Azoospermia	23
46,XY,t(8;13)(8qter->8p12::13q12->13qter);del(8)(p12->pter);del(13)(pter->q12)	1	Azoospermia	23
46,XY,t(4;11)(4pter->4q31::11q23->11qter;11pter->11q23::4q31->4qter)	1	Azoospermia	25
46,XY,t(6;9)(q13;p24)pat	1	Teratospermia	27
46,XY,del(22)(q13->qter)	4	Azoospermia	27

Sichuan, Liaoning, Gansu and Shandong. Some karyotypes were reported the first time in the world. Chromosomal aberrations in these cases included deletion, inversion, insertion, translocation, etc. The clinical manifestations were also manifold, such as cryptorchidism, testicular dysgenesis, malformed sperm, low motility sperm, oligozoospermia, azoospermia and infertility of unidentified cause. In 63 cases (Table 1) the aberrant autosome regions were described in detail so that they could be employed to construct the autosome regional map, reflecting the correlation between the chromosomal regions and the disturbances. In the remaining 56 cases, although the aberrant chromosomes were indicated, the regions were not. In the 119 patients, the frequency of aberrations in each autosome was analyzed in cases showing identical karyotypes. As indicated above, 63 cases were employed to construct the regional map.

3 Results

From Figure 1, it can be seen that in Chinese patients aberrations leading to testicular dysgenesis, spermatogenic arrest and infertility were distributed almost over all the autosomes, with chromosome 13, followed by 14 showing the highest incidence. Chromosomes 9, 21, 22, and 1, in the order of incidence also displayed a high occurrence of aberrations, while chromosomes 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 15, 16, 17, 18, 19 and 20 had relatively low aberration rates (Fugire 1).

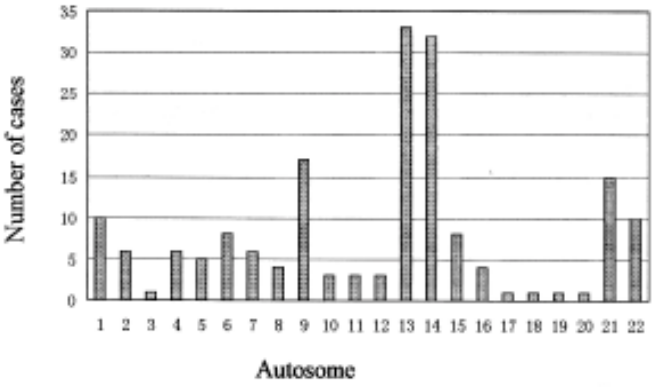

Figure 1. Number of aberration cases on each autosome.

Figure 2 shows the "hot" regions on the 22 autosomes. Aberrations in these regions could result in testicular dysgenesis, oligozoospermia, azoospermia or male infertility of unidentified cause. Small rectangles at the side of the regions indicated the number of cases showing the particular aberration. Bands 14q11 and 13p11 were the two regions exhibiting the highest rate of aberration, followed by 9p11, 22q and a few others, whereas in the majority of regions of many other chromosomes the aberration rate was low. Figure 1 indicated that chromosome 17 had certain relationship with testicular dysgenesis or spermatogenic arrest, but Figure 2 did not display any region on chromosome 17 that was related to these disturbances. This discrepancy is due to the fact that in many cases, the regions of aberration were not reported.

4 Discussion

Chromosome Y is the smallest one in human chromosome set, in which there are *SRY, DAZ, DFFRY* and a few other genes related to testicular development and spermatogenesis. In addition to the genes on the Y chromosome, many autosomal genes are also involved in testicular development and spermatogenesis. Luciani LM et al. [1] pointed out that translocations between some autosomes such as 13q or 14q could impair the inactivation of X chromosome, which would result in spermatogenic arrest. Similarly, there are 8 cases in Table 1 showing karyotypes of translocation between 13p11 and 14q11. Based on the proposal of Luciani, we think that the high translocation occurrence between 13p11 and 14 q11 could also disturb meiotic or postmeiotic development of germ cells.

Chromosomal aberrations, such as deletion, fusion and translocation, may cause structural alterations of the nucleic acid at the broken points and lead to gene defects and impede many important life processes. One of the famous examples is that the Ph chromosome caused by the translocation between 9 and 22 would generate a special protein BCR-ABL leading to leukaemia [29]. We believe that chromosomal aberrations, especially those on 14q11, 13p11, 9p11 and 22q, could affect testicular development and spermatogenesis. In the present review the sex chromosomes (X and Y) were not included as they have been explored extensively and detailed deletion maps of Y related to spermatogenesis have been constructed [22]. In the present review it was indicated that there exist many latent aberrant autosomal regions which may be regarded as significant genetic sources that may be of help to the study of novel gene cloning and their functions. For example, 4 azoospermic cases with the same karyotype of 46,XY,del(22)(q13->qter) were two pairs of twins from the same parents [23]. This information is highly valuable for screening relevant functional genes on chromosome 22. Furthermore, chromosome variation database for various diseases could also be built up in a similar manner.The web site (http://www.ncbi.nlm.nih.gov/omim/) is an example of this kind of bank. The more these banks be constructed, the more helpful will be to gene cloning and the study of their function.

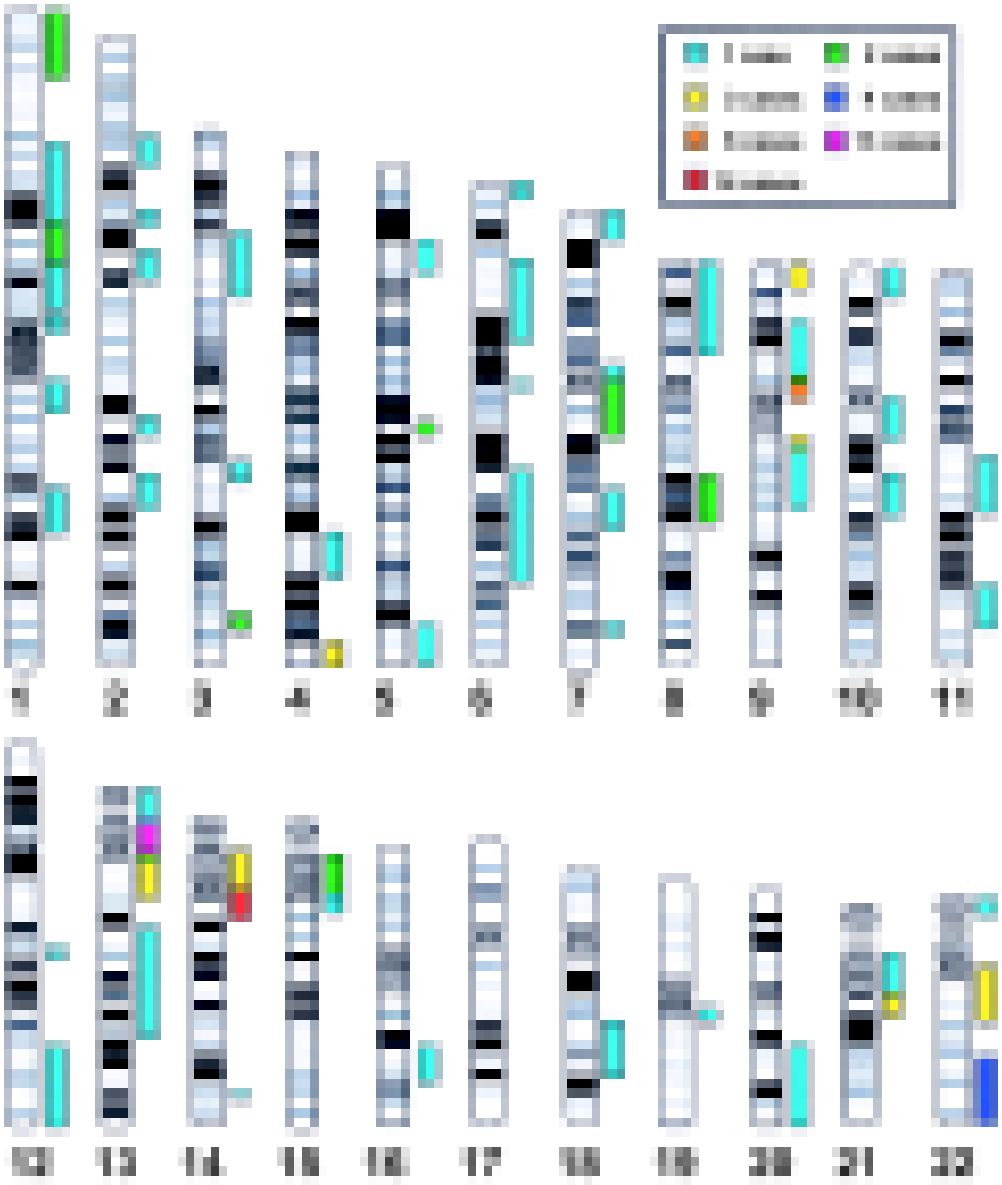

Figure 2. Regional map indicating the regions related to testicular dysgenesis/spermatogenic arrest, attached rectangles specifying the case number.

With the progress of the Human Genome Project (HGP), a large number of databases, including the GenBank, relevant to the Expressed Sequence Tag (EST), UniGene and genomic DNA sequence, become more and more abundant and valuable. UniGene (http://www.ncbi.nlm.nih.gov/UniGene/) is an experimental system for the automatic categorization of the GenBank ESTs into a non-redundant set of gene-oriented clusters. Each UniGene cluster contains sequences that represent a single gene, as well as related information such as the tissue types in which the gene expressed [31]. Although the relationship between certain chromosome aberrations and diseases should be further confirmed, these data could be of help to find novel functions for some cloned genes through analyzing the reported patients and their chromosomal variations.

A practicable strategy is first to ascertain the aberrant regions, then to search all the Unigenes locating at these regions and finally to find out all Unigenes containing ESTs expressed in the testis. Thus one can restrict the study of these genes in the target organ. Therefore the Unigenes obtained would be the crucial candidate genes for further study. Another traditional strategy is to label painting probes from the variation region or the library (probe pool), and then screen the relevant cDNA library employing the probe to get the candidate genes [32]. In the views of Collins [33] and He [34], positional cloning strategy will play a major role in the future.

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