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A Study on the Chromosomal Syndromes and Genetic Disease

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Abstract – With the discovery in 1956 that the correct chromosome number in humans is 46, the new era of clinical cytogenetics began its rapid growth. During the next few years, several major chromosomal syndromes with altered numbers of chromosomes were reported, i.e. Down syndrome (trisomy 21), Turner syndrome (45,X) and Klinefelter syndrome (47,XXY). Since then it has been well established that chromosome abnormalities contribute significantly to genetic disease resulting in reproductive loss, infertility, stillbirths, congenital anomalies, abnormal sexual development, mental retardation and pathogenesis of malignancy.

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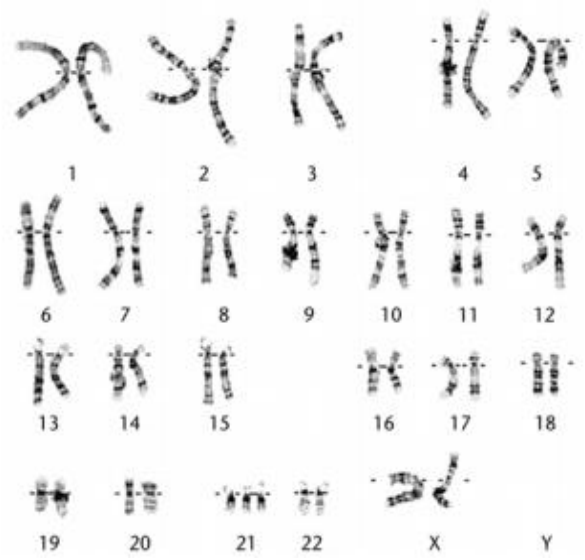
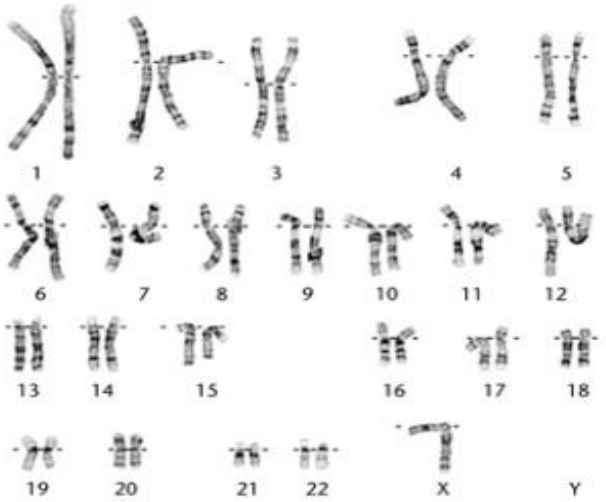
INTRODUCTION

Specific chromosome abnormalities have been associated with over 60 identifiable syndromes. They are present in at least 50% of spontaneous abortions, 6% of stillbirths, about 5% of couples with two or more miscarriages and approximately 0.5% of newborns. In women aged 35 or over, chromosome abnormalities are detected in about 2% of all pregnancies.

Chromosome abnormalities are classified as either numerical or structural and may involve more than one chromosome. In discussing numerical abnormalities, certain terms need to be clarified. The normal human chromosome complement consists of 46 chromosomes (diploid) which is double the euploid (haploid) or gamete complement of 23. Exact multiples of euploid chromosome sets are either diploid or polyploid, i.e. triploid or tetraploid consisting of three or four euploid sets, respectively. Aneuploidy refers to the presence of an extra copy of a specific chromosome, or trisomy, as seen in Figure 1 (Down syndrome karyotype with trisomy 21), or to the absence of a single chromosome, or monosomy, as seen in Figure 2 (Turner syndrome karyotype with 45,X). The most common clinically significant chromosome abnormalities involving aneuploidy are frequently detected in newborns. Although autosomal and sex chromosome trisomies result in clinical abnormalities they are more viable than monosomies, with the exception of monosomy X (45,X Turner syndrome). However, fewer than 5% of 45,X conceptions actually survive to birth. Aneuploidy is frequently associated with maternal age and constitutes a significant portion of chromosome abnormalities observed in spontaneous abortions (Table 2) and detected prenatally in fetuses (Table 3). Polyploidy resulting from triploidy (69 chromosomes) or tetraploidy (92 chromosomes) are lethal conditions most frequently seen in spontaneous abortions and very





rarely in newborns with a short survival time. Triploidy is more common and is related to abnormal events prior to or during fertilization: most often triploidy results from two haploid sperm fertilizing a single haploid egg. Aneuploid and normal diploid cells can occasionally exist simultaneously in an individual. This condition is known as mosaicism and involves two or more distinct cell populations derived from a single zygote or fertilized egg. Mosaicism can involve either autosomal or sex chromosomes but most frequently involves sex chromosomes. Mosaicism is seen in approximately 0.2% of fetuses prenatally, 1% of Down syndrome patients, 10% of Klinefelter syndrome patients and over 30% of patients with Turner syndrome. The clinical significance of mosaicism depends upon the proportion and tissue distribution of the aneuploid cells. Chimaerism, in contrast, is distinguished from mosaicism in that the different cell lines are derived from more than one zygote.

Outline of Chromosome Syndromes Common autosomal trisomies Trisomy 21 (Down syndrome) is one of the best-recognized and most common chromosome disorders. It is the single most common genetic cause for mental retardation. The incidence of Down syndrome is approximately 1/800 newborns. The risk for having a child with trisomy. Down syndrome increases with maternal age.

RESEARCH STUDY

Postnatal survival is poor and more than 90% die within the first 6 months. About 80% are female. The incidence of trisomy 18 increases with maternal age. Very few cases of trisomy 18 mosaicism have been reported. Many features characteristic of trisomy 18 have also been reported in patients with unbalanced translocations involving all or most of chromosome 18 long arm. Based upon limited data, the recurrence risk for trisomy 18 is approximately 1%. Trisomy 13 (Patau syndrome) is the least common of the major autosomal trisomies with an estimated incidence of 1 in 20 000 live births. Owing to severe clinical abnormalities including central nervous system malformations, heart defects, growth retardation and numerous other congenital anomalies, trisomy 13 patients rarely survive the newborn period. Trisomy 13 is associated with advanced maternal age. The extra 13 usually results from a maternal meiotic nondisjunctional error. About 20% of cases have an unbalanced Robertsonian translocation involving chromosome 13. Balanced 13/14 Robertsonian translocation carriers have less than 2% risk of having an unbalanced trisomy 13 offspring. Trisomy 13 mosaicism is rare and may be associated with less severe clinical anomalies.

There are several rare inherited syndromes characterized by increased rates of spontaneous or induced chromosomal breakage and predisposition to leukaemia and solid cancers. The most extensively studied of these syndromes, each caused by a different autosomal recessive gene, are Bloom syndrome, Fanconi anaemia, ataxia telangiectasia and xeroderma pigmentosum. These syndromes have distinctive chromosome aberrations. Bloom syndrome is characterized by quadriradial formations, which is the exchange of chromatid segments between two chromosomes, and a high rate of sister chromatid exchange (SCE) or exchanges between homologous chromosome segments. Fanconi anaemia patients exhibit a high frequency of chromosome breakage and nonhomologous chromosome interchange following exposure to alkylating agents or ultraviolet radiation. Their SCE rate is normal. Individuals with ataxia telangiectasia show an increased level of chromosome breaks and rearrangements and may have abnormalities involving chromosome. These patients have a normal SCE level. Patients with xeroderma pigmentosum do not exhibit spontaneous chromosome breakage; however, rearrangement, breaks, and increased SCE rate are observed after exposure to ultraviolet radiation.

DATA ANALYSIS

Approximately 94% of Down syndrome patients have trisomy resulting from meiotic nondisjunction, the failure of homologous chromosomes or sister chromatids to separate during cell division. In about 95% of cases the extra chromosome 21 is of maternal origin, and of these cases approximately 80% are due to an error during meiosis I. About 4% of Down syndrome patients have an unbalanced Robertsonian translocation involving chromosome 21. Approximately 60% of these translocations involve the long arm of chromosome 13, 14, or 15 (most frequently chromosome 14). About half of these translocations are de novo and half are inherited from a balanced carrier parent (usually the mother). Nearly 40% of unbalanced Robertsonian translocations involve only chromosomes 21 and 22. Most of these (90%) involve 21/21 long-arm fusions or iso-chromosomes and nearly all are de novo. The rare parent who is a balanced 21/21 isochromosome carrier has a 100% risk for having a viable offspring with Down syndrome. Female carriers of balanced 14/21 or 21/22 Robertsonian translocations have a 10–15% risk for an unbalanced Down syndrome child.

Male carriers have a risk of less than 5%. Mosaicism involving a mixture of normal diploid cells and trisomy 21 cells is present in about 2% of Down syndrome patients. Trisomy 18 (Edwards syndrome) is the second most common autosomal trisomy syndrome. It has a frequency of about 1 in 8000 live births. Clinical features include failure to thrive, cardiac and kidney problems and other congenital abnormalities.

CONCLUSION

Chromosome abnormalities contribute significantly to genetic disease. This impact is seen in various human populations in the effect on the fetus or individual directly or in the ability to produce healthy offspring. Autosomal abnormalities are generally more detrimental than sex chromosome abnormalities. Abnormalities involving entire chromosomes or subtle microdeletions can result in clinically abnormal syndromes.

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