بسم الله الرحمن الرحيم

شبكة المعلومـــــات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الالكتروني والميكروفيلم

﴿ قـــسـم ﴾

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15 – 25c and relative humidity 20-40 %

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بالرسالة صفحات

لم ترد بالأصـــل

The Clinical Use of Cytogentics in Hematological Malignancies and Related Disorders

THESIS

Submitted for Partial Fulfillment of Master Degree in Internal Medicine

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INTRODUCTION

CHROMOSOME ABNORMALITIES (Mueller and young,1998)

Chromosme abnormalities can be divided into numerical and structural, with a third category consisting of different chromosome constitutions in two or more cell lines ***(Table 1)***

Table 1 Types of chromosome abnormality	
Numerical	
Aneuploidy	-Monosomy -Trisomy -Tetrasomy
Polyploidy	-Triploidy -Tetraploidy
Structural	
Translocations	-Reciprocal -Robertsonian
Deletions	
Insertions	
Inversions	-Paracentric -Pericentric
Rings	
Isochromosomes	
Different cell lines (mixoploidy)	
Mosaicism	
Chimaerism	

NUMERICAL ABNORMALITES

Numerical abnormalities involve the gain or loss of one or more chromosomes or what is known as aneuploidy or the addition of one or more complete haploid complements or polyploidy.Loss of a single chromosome results in monosomy.Gain of one or two homologous chromosomes is referred to as trisomy and tetrasomy respectively.

Trisomy

The presence of an extra chromosome is referred to as trisomy.Most cases of Down's syndrome are due to the presence of an additional number 21 chromosome,hence Down's syndrome is often known as trisomy 21.Other autosomal trisomies which are compatible with survival to term are Patau's syndrome (trisomy 13) and Edwards' syndrome (trisomy 18) .Most other autosomal trisomies result in early

pregnancy loss with trisomy 16 being a particularly common finding in first trimester spontaneous miscarriages.The presence of an additional sex chromosome (X or Y) has only mild phenotypic effects .

Trisomy 21 is usually caused by failure of separation of one of the pairs of homologous chromosomes during anaphase of maternal meiosis I.This failure of the bivalent to separate is called non-disjunction.Less often,trisomy can be caused by non-disjunction occurring during meiosis II when a pair of sister chromatids fail to separate.Either way the gamete receives two homologous chromosomes (disomy), and if subsequent fertilization occurs a trisomic conceptus results .

The origin of non-disjunction

The consequences of non-disjunction in meiosis I and meiosis II differ in the chromosomes found in the gamete.An error in meiosis I leads to the gamete containing both homologues of one chromosome pair.In contrast,non-disjunction in meiosis II results in the gamete receiving two copies of one of the homologues of the chromosome pair.Studies using centromeric DNA markers have shown that most children with an autosomal trisomy have inherited their additional chromosome as a result of non-disjunction occurring during one of the maternal meiotic divisions (Table 2).Centromeric markers have to be used for these studies as the use of markers on either chromosome arm can give misleading results due to recombination.

Non-dijunction can also occur during an early mitotic division in the developing zygote.This would,however,result in the presence of two or more different cell lines,a phenomenon known as mosaicism .

Table 2 Parental origin of meiotic error leading to aneuploidy		
Chromosome abnormality	*Paternal (%)*	*Maternal (%)*
Trisomy 13	15	85
Trisomy 18	10	90
Trisomy 21	5	95
45,X	80	20
47XXX	5	95
47XXY	45	55
47XYY	100	0

The cause of non-disjunction

The cause of non-disjunction is uncertain.The most favoured explanation is that of an ageing effect on the primary oocyte which can remain in a state of suspended inactivity for up to 50 years .There is a well-documented association between advancing maternal age and increased incidence of Down's syndrome .A maternal age effect has been noted for trisomies 13 and 18.

It is not known how or why advancing maternal age predisposes to non-disjunction.Research has shown that absence of recombination in prophase of meiosis I predisposes to subsequent non-disjunction.This is not surprising as the chiasmata which are formed after recombination are responsible for holding each pair of homologous chromosomes together until subsequent separation occurs in diakinesis.However in the female recombination occurs before birth whereas the non-dijunctional event occurs any time between 15 and 50 years later.This suggests that at least two factors can be involved in causing non-disjunction,the first being an absence of recombination between homologous chromosomes in the fetal ovary and the second an abnormality in spindle formation many years later.An alternative explanation for the association of advancing maternal age with increased risk of autosomal trisomy is that survival of trisomic embryos could be the result of an age-related reduction in

immunological completence.Firm evidence for this theory is limited.Other factors which have been implicated in causing non-disjunction include radiation and delayed fertilization after ovulation.In animals it has been shown that an increased incidence of aneuploid embryos can result from lengthening of the interval between ovulation and fertilization.It has been suggested that this could account for the relationship between maternal age and the incidence of Down's syndrome,as with increasing age intercourse is likely to occur less frequently,with delayed fertilization therefore being more likely.The story is further complicated by the fact that in some species such as Drosophila,non-dijunction is under genetic control.This could account for those occasional families which seem to be prone to recurrent non-disjunction.

Monosomy

The absence of a single chromosome is referred to as *monosomy*.Monosomy for an autosome is almost always incompatible with survival to term,with the possible exception of a few very rare reported cases of monosomy 21.Absence of an X or a Y chromosome results in a 45X karyotype which causes a condition known as Turner's syndrome .

As with trisomy,monosomy can also result from non-disjunction in meiosis.If one gamete receives two copies of a homologous chromosome (disomy), the other corresponding daughter gamete will have no copy of the same chromosome (nullisomy).Monosomy can also be caused by loss of a chromosome as it moves to the pole of the cell during anaphase,an event known as *anaphase lag*.

Polypoidy

Polyploid cells contain multiples of the haploid number of chromosomes such as 69,*triploidy*,or 92,*tetraploidy*.In humans triploidy is found relatively often in material grown from spontaneous miscarriages but survival beyond mid-pregnancy is rare.Only a few

triploid live births have been described and all have died soon after birth.

Triploidy can be caused by failure of a maturation meiotic divison in ovum or sperm,leading,for example ,to retention of a polar body or to the formation of a diploid sperm.Alternatively it can be caused by fertilization of an ovum by two sperm: this is known as *dispermy*.When triploidy results from the presence of an additional set of paternal chromosomes,the placenta is usually swollen with what are known as *hydatidiform* changes. In contrast when tripliody results from an additional set of maternal chromosomes, the placenta is usually small.Triploidy usually results in early spontaneous miscarriage .

STRUCTURAl ABNORMALITIES

Structural chromosome rearrangements result from chromosome breakage with 2 subsequent reunion in a different configuration.They can be balanced or unbalanced.In balanced rearrangements the chromosome complement is complete with no loss or gain of genetic material.Consequently,balanced rearrangements are generally harmless with the exception of rare cases in which one of the breakpoints damages an important functional gene.However,carriers of balanced rearrangements are often at risk of producing children with an unbalanced chromosomal complement.

When a chromosome rearrangement is unbalanced the chromosomal complement contains an incorrect amount of chromosome material and the clinical effects are usually very severe.

Translocations

A translocation refers to the transfer of genetic material from one chromosome to another.A reciprocal translocation is formed when a break occurs in each of two chromosomes with the segments being exchanged to form two new derivative chromosomes.A Robertsonian translocation is a particular type of recipocal translocation in which

the breakpoints are located at or close to the centromeres of two acrocentric chromosomes .

Reciprocal translocations

A reciprocal translocation involves breakage of at least two non-homologous chromosomes with exchange of the fragments.Usually the chromosome number remains at 46,and if the exchanged fragments are of roughly equal size, a reciprocal translocation can often only be identified with detailed chromosomal banding studies or FISH.In general reciprocal translocations are unique to a particular family,although,for reasons which are unknown,balanced reciprocal translocations involving the long arms of chromosomes 11 and 22 are relatively common.The overall incidence of reciprocal translocations in the general population is approximately 1 in 500.

Risks in reciprocal translocations

When counselling a carrier of a balanced translocation it is necessary to consider the particular rearrangement to determine whether it could result in the birth of an abnormal baby.Usually this risk will lie somewhere between 1% and 10% .For carriers of the 11;22 translocation discussed,the risk has been shown to be 5%

Robertsonian translocations

A Robertsonian translocation results from breakage of two acrocentric chromosomes (numbers 13,14,15,21 and 22) at or close to their centromeres,with subsequent fusion of their long arms.s This is also referred to as *centric fusion*.The short arms of each chromosome are lost,this being of no clinical importance as they contain only genes for ribosomal RNA for which there are multiple copies on the various other acrocentric chromosomes.The total chromosome number is reduced to 45.Since there is no loss or gain of important genetic material this is a functionally balanced rerrangement.The overall incidence of Robertsonian translocations in the general population is