

## REVIEW

# Origin and mechanisms of non-disjunction in human autosomal trisomies

Peter Nicolaidis<sup>1</sup> and Michael B.Petersen<sup>2,3</sup>

<sup>1</sup>Mitera Maternity Hospital and <sup>2</sup>Department of Genetics, Institute of Child Health, 'Aghia Sophia' Children's Hospital, GR-11527 Athens, Greece

<sup>3</sup>To whom correspondence should be addressed

**Chromosomal aneuploidy is one of the major causes of pregnancy wastage. In this review we summarize the knowledge about the origin and mechanisms of non-disjunction in human autosomal trisomies 8, 13, 15, 16, 18, and 21, accumulated during the last decade by using DNA polymorphism analysis. Maternal meiosis I non-disjunction is the most important single class, but chromosome-specific patterns exist. For the acrocentric chromosomes 15 and 21, meiosis I errors predominate among the maternal errors, in contrast to trisomy 18 where meiosis II errors predominate. For trisomy 16, virtually all cases are due to maternal meiosis I non-disjunction. Postzygotic (mitotic) non-disjunction constitutes 5–15% of cases of trisomies 15, 18, and 21, whereas for trisomy 8 and trisomy 8 mosaicism the majority of cases are due to mitotic non-disjunction. For paternal non-disjunction of chromosomes 18 and 21, meiosis II or mitotic errors predominate. There is aberrant meiotic recombination associated with maternal meiotic non-disjunction in all trisomies studied in detail so far. Advanced maternal age remains the only well documented risk factor for maternal meiotic non-disjunction, but there is, however, still a surprising lack of understanding of the basic mechanism(s) behind the maternal age effect.**

**Key words:** autosomal trisomy/chromosomal non-disjunction/meiosis/meiotic recombination/mitosis

## Introduction

Chromosome abnormality is the most common recognized cause of fetal death in our species. Around 50% of spontaneous abortions before 15 weeks of gestation are chromosomally aneuploid, with trisomies accounting for 50% of the abnormal abortions (Hassold *et al.*, 1980). Because of their high incidence in newborns, autosomal trisomies 21, 18, and 13 have large individual and socio-economic consequences (Hassold and Jacobs, 1984). Our knowledge about the mechanisms underlying chromosomal non-disjunction in man is, however, surprisingly poor. Advanced maternal age remains the only well-documented risk factor in non-disjunction (Penrose, 1933), but the biological mechanisms of this phenomenon are not well

understood. A basic prerequisite for elucidating the mechanisms of non-disjunction is the precise determination of parental origin and meiotic division error of the extra chromosome in the most common autosomal trisomies. In the present review, we summarize the progress in knowledge about the origin and mechanisms of the most extensively studied autosomal trisomies due to the use of DNA polymorphism analysis during the last decade.

## Historical background

Most of our knowledge about chromosomal non-disjunction in man comes from studies in trisomy 21, the most frequent of the autosomal trisomies in liveborns. With an incidence of 1–2:1000 in human populations (Hook, 1981), trisomy 21 is the most common chromosomal abnormality among children. The clinical entity known as Down's syndrome was described more than a century ago (Down, 1866), but it was not until 1959 that the aetiology was discovered to be an extra chromosome 21 in all cell nuclei (Lejeune *et al.*, 1959). The condition is usually the result of malsegregation (non-disjunction) of chromosome 21 in meiosis in either oogenesis or spermatogenesis. A big effort has been directed towards the identification of the biological mechanisms underlying chromosomal non-disjunction. Since the early 1970s, the origin of non-disjunction in trisomy 21 was studied using chromosomal short arm heteromorphisms (Grouchy, 1970; Juberg and Jones, 1970), which by different staining techniques were informative in as many as 75% of the cases (Mikkelsen *et al.*, 1980). The results of the major cytogenetic studies indicated that the origin of the extra chromosome was maternal in about 80% of the informative cases and paternal in about 20% (Juberg and Mowrey, 1983; Hassold and Jacobs, 1984).

With the recombinant DNA technology a new set of tools became available to the study of origin and mechanisms of chromosomal abnormalities using DNA polymorphism analysis. In the beginning this kind of analysis used chromosome 21-specific DNA probes to detect restriction fragment length polymorphisms (Davies *et al.*, 1984). The development of the polymerase chain reaction (PCR) amplification technique (Saiki *et al.*, 1988) enabled the identification of novel and highly informative classes of DNA polymorphisms in the human genome, the so called microsatellites or simple sequence repeat (SSR) polymorphisms (Weber and May, 1989; Litt and Luty, 1989; Economou *et al.*, 1990). Especially the multi-allelic and easily typified microsatellites have contributed to mapping of the human genome (NIH/CEPH Collaborative Mapping Group

**Table I.** Origin of non-disjunction in human autosomal trisomies by DNA polymorphism analysis

Trisomy	Origin	Number of cases (%)	Meiotic recombination
8 <sup>a</sup>	<b>Maternal</b>	10 (66.7)	
	MI/MII	5 (33.3)	
	Mit	5 (33.3)	
	<b>Paternal</b>	5 (33.3)	
	Mit	5 (33.3)	
13 <sup>b</sup>	Maternal	37 (88.1)	
	Paternal	5 (11.9)	
15 <sup>c</sup>	Maternal MI/MII	15 (88.2)	
	Paternal MI/MII	2 (11.8)	
	<b>mUPD15</b>		
	MI	88 (73.3)	Reduced
	MII	14 (11.7)	
	Mit	18 (15.0)	
16 <sup>d</sup>	<b>Maternal</b>	62 (100)	
	MI	56 (100)	Reduced
18 <sup>e</sup>	<b>Maternal</b>	161 (91.5)	
	MI	27 (29.0)	Reduced
	MII	52 (55.9)	
	Mit	7 (7.5)	
	<b>Paternal</b>	15 (8.5)	
	MI/MII	2 (2.1)	
21 <sup>f</sup>	<b>Maternal</b>	805 (91.5)	
	MI	556 (68.9)	Reduced
	MII	176 (21.8)	Increased
	Mit	17 (2.1)	
	<b>Paternal</b>	75 (8.5)	
	MI	17 (2.1)	
	MII	27 (3.3)	
	Mit	14 (1.7)	

MI = meiosis I, MII = meiosis II, Mit = mitosis, mUPD15 = maternal uniparental disomy of chromosome 15. The number of cases for which parental origin has been determined is usually bigger than the number of cases for which meiotic/mitotic origin has been determined.

Data from <sup>a</sup>DeBrasi *et al.* (1995), Robinson *et al.* (1995), James and Jacobs (1996), Seghezzi *et al.* (1996); <sup>b</sup>Zaragoza *et al.* (1994), Robinson *et al.* (1996a); <sup>c</sup>Zaragoza *et al.* (1994), Robinson *et al.* (1993, 1996b); <sup>d</sup>Hassold *et al.* (1995); <sup>e</sup>Kondoh *et al.* (1988), Kupke and Müller (1989), Ya-gang *et al.* (1993), Fisher *et al.* (1995), Eggermann *et al.* (1996); <sup>f</sup>Antonarakis *et al.* (1993), Lamb *et al.* (1996).

1992; Weissenbach *et al.*, 1992) and to non-disjunction studies in recent years (Petersen *et al.*, 1991).

### Trisomy 21

Two large collaborative studies used multiple DNA polymorphisms spanning the long arm of human chromosome 21 to determine the parental origin of non-disjunction in trisomy 21 (Antonarakis *et al.*, 1991; Sherman *et al.*, 1991). These studies estimated that only 5% of the cases (of a total of 304 families studied) had paternal origin and attributed the difference from the cytogenetic studies to an increased accuracy of the DNA polymorphism analysis, as demonstrated by erroneous cytogenetic determinations in a subgroup of families (Antonarakis *et al.*, 1991; Sherman *et al.*, 1991). More recent population-based molecular studies show 8–9% paternal errors (Mikkelsen *et al.*, 1995; Yoon *et al.*, 1996). The latest results of the two major groups studying non-disjunction in trisomy 21 are summarized in Table I.

The study of meiotic stage of non-disjunction (meiosis I or II) in trisomy 21 by DNA polymorphism analysis has been hampered by the lack of centromeric markers. Alphoid DNA polymorphisms specific for the human chromosome 21 centromere had been described (Jabs *et al.*, 1991), but the incidence of these markers being informative was low, and they were not useful for routine non-disjunction studies. The alphoid DNA polymorphisms were, however, localized on the genetic linkage map of human chromosome 21 (Jabs *et al.*, 1991), giving an estimate of the genetic distance between the centromere and the closest markers on the long arm of chromosome 21. The meiotic division error has been inferred on the basis of non-reduction/reduction to homozygosity at the pericentromeric DNA polymorphic markers (Chakravarti and Slaugenhaupt, 1987). Among the maternal errors, approximately 75% are attributed to errors in meiosis I and 25% to errors in meiosis II (Antonarakis *et al.*, 1992; Mikkelsen *et al.*, 1995; Yoon *et al.*, 1996). Both maternal meiosis I and II errors are associated with increased maternal age (Antonarakis *et al.*, 1992; Mikkelsen *et al.*, 1995; Yoon *et al.*, 1996). Two comparative studies of cytogenetic short arm heteromorphisms and microsatellite DNA polymorphisms showed discrepancies regarding meiotic stage of non-disjunction and suggested an increased pericentromeric recombination rate associated with non-disjunction (Lorber *et al.*, 1992; Petersen *et al.*, 1992).

About 5% of cases of trisomy 21 are probably due to mitotic (postzygotic) non-disjunction of a chromosome 21 in the early embryo, as determined by pericentromeric DNA markers and the lack of observed recombination along the entire long arm of chromosome 21 (Antonarakis *et al.*, 1993; Mikkelsen *et al.*, 1995; Yoon *et al.*, 1996). The mitotic errors are not associated with advanced maternal age and show no preference in the parental origin of the duplicated chromosome 21 (Antonarakis *et al.*, 1993).

Non-disjunction in maternal meiosis I is associated with reduced recombination between the non-disjoined chromosomes 21 (Warren *et al.*, 1987; Sherman *et al.*, 1991), suggesting an important role for pairing/recombination failure or reduced recombination in the aetiology of trisomy 21. Recent results showed that the reduced recombination is not due to absence of recombination in a proportion of cases, but to an overall reduction in recombination (Sherman *et al.*, 1994). Interestingly, there was increased recombination in the most distal region of 21q studied. Based upon those data and analogous findings in the fruit fly (*Drosophila melanogaster*), a model has been proposed of age-dependent deterioration of some cellular reagent required for proper spindle function (Hawley *et al.*, 1994). Unexpectedly, non-disjunction in meiosis II is associated with increased recombination occurring in meiosis I, suggesting that all errors originate in meiosis I (Lamb *et al.*, 1996). The rate of recombination remains constant with advancing maternal age, but some chiasmata of chromosome 21 seem more susceptible to non-disjunction in aged oocytes compared to young oocytes (Lamb *et al.*, 1996). Analysis of the chiasma distribution showed that whereas absence of a proximal recombination predisposes to non-disjunction in meiosis I, the presence of a proximal exchange appears to predispose to non-disjunction in meiosis II (Lamb

*et al.*, 1996). These findings profoundly affect our understanding of the aetiology of trisomy 21 and may explain why both maternal meiosis I and II errors are associated with increased maternal age. A two-hit model of non-disjunction was proposed, in which the first hit is the establishment of a susceptible meiotic configuration, and the second hit is disruption of a meiotic process that increases the risk of non-disjunction of the susceptible configuration (Lamb *et al.*, 1996). The second hit might involve any number of meiotic structures and may be the source of the maternal age effect. This model has not yet been verified for other chromosomes. Recent data from direct observation of oocytes have failed to confirm all the predictions of the model, since second meiotic metaphase oocytes from in-vitro fertilization patients failed to show an additional whole chromosome (Angell, 1997). It can be argued, of course, that oocytes which failed in in-vitro fertilization do not represent an optimal sample, and further studies are obviously needed (Warburton, 1997).

In paternal non-disjunction of chromosome 21 meiosis II errors predominate in contrast to maternal non-disjunction, where meiosis I errors predominate, as indicated by DNA polymorphisms (Table I). The mechanisms associated with paternal non-disjunction are therefore likely to differ from those associated with maternal non-disjunction. There was some indication of an association between increased paternal age and paternal meiosis I non-disjunction among seven cases in a molecular study (Petersen *et al.*, 1993). Additional cases are needed to determine whether such an effect actually applies to trisomy 21, which had been a matter of big controversy before the DNA studies (Hook and Cross, 1982; Stene *et al.*, 1987; Stene and Stene, 1989; Hook *et al.*, 1990). The issue of a paternal age effect was recently raised again by a study showing an effect of donor (paternal) age on the incidence of trisomy 21 after artificial insemination with frozen donor spermatozoa, independently of maternal age (Thépot *et al.*, 1996). The study involved 11 535 pregnancies where the influences of paternal and maternal ages could be completely separated, in contrast to natural reproduction, but the parental origin of trisomy 21 was not determined (Thépot *et al.*, 1996). A significant increase in mean maternal age was found between cases of maternal origin and those of paternal origin in a molecular study (Petersen *et al.*, 1993). This indicates that the maternal age effect in Down's syndrome is confined to maternal non-disjunction, and does not provide evidence for a relaxed selection against trisomic fetuses in older women, as suggested on the basis of the cytogenetic studies where there was no evidence for a difference in mean maternal age between trisomy 21 cases of maternal and paternal origin (Aymé and Lippman-Hand, 1982; Stein *et al.*, 1986). It therefore seems reasonable to conclude that a factor associated with ageing of the oocyte is responsible for the maternal age effect in Down's syndrome.

There is a well known increased sex ratio (around 1.15) in liveborns with Down's syndrome (Hug, 1951; Huether *et al.*, 1996). This effect is restricted to free trisomy 21 and does not extend to translocations, suggesting that the increased sex ratio is associated with free trisomy 21 *per se* and not with differential selection based on sex (Hassold *et al.*, 1983). A

molecular study demonstrated a highly increased sex ratio (3.50) among paternal meiotic errors in contrast to paternal mitotic errors and maternal errors (Petersen *et al.*, 1993). This suggested that there may be mechanisms of paternal non-disjunction in which the extra chromosome 21 preferentially segregates with the Y chromosome, as already hypothesized from cytogenetic studies (Hassold *et al.*, 1984). Finally, an excess of Y-bearing spermatozoa disomic for chromosome 21 was observed in semen samples from healthy volunteers, providing conclusive evidence that the excess of males in trisomy 21 is attributable at least in part to paternal non-disjunction (Griffin *et al.*, 1996). The cytologic basis for such a non-disjunctional mechanism may be the close association between the Y-heterochromatin and the acrocentric short arms in meiotic prophase (Stahl *et al.*, 1984; Speed and Chandley, 1990).

Mosaicism with a normal cell line occurs in about 2–4% of Down's syndrome newborns (Hook, 1981). DNA polymorphism analysis in 17 families with mosaic trisomy 21 probands showed that the majority of cases resulted from a trisomic zygote with mitotic loss of one chromosome (Pangalos *et al.*, 1994).

### Trisomy 18

Trisomy 18 (Edwards' syndrome) is the second most common autosomal trisomy in newborns, with a prevalence at birth of about 1:7000 (Goldstein and Nielsen, 1988). Studies of the parental origin of the extra chromosome in trisomy 18 have been limited in the past due to the lack of routine cytogenetic heteromorphisms of chromosome 18 (Babu and Verma, 1986). The description of chromosome 18-specific DNA markers, the development of detailed maps of chromosome 18, and more recently the isolation and mapping of microsatellite DNA markers on human chromosome 18 (Straub *et al.*, 1993) have enabled the study of non-disjunction in trisomy 18 by DNA polymorphism analysis. Seven studies have been published so far using a variable number of DNA markers (Kondoh *et al.*, 1988; Kupke and Müller, 1989; Fisher *et al.*, 1993, 1995; Nöthen *et al.*, 1993; Ya-gang *et al.*, 1993; Eggermann *et al.*, 1996). Summarizing these studies the parental origin was determined in 176 families and was maternal in 91% and paternal in 9% of cases (Table I). Among 86 maternal cases studied with multiple markers along the chromosome and by using markers flanking the centromere for the determination of the meiotic stage of non-disjunction, 31% were attributable to an error at the first meiotic division, 60% to an error at the second meiotic division, and about 8% were due to mitotic errors (Fisher *et al.*, 1995; Eggermann *et al.*, 1996) (Table I). This is in contrast to trisomy 21, where meiosis I errors predominate. Among the paternal cases, the majority were the result of a postzygotic, mitotic error and only two meiotic errors have been identified (Fisher *et al.*, 1995; Eggermann *et al.*, 1996) (Table I). Maternal meiosis I non-disjunction is associated with reduced recombination between the non-disjoined chromosomes 18 (Fisher *et al.*, 1995). There is increased maternal age in cases of maternal meiotic origin compared to cases of paternal or mitotic origin, but after

exclusion of prenatal cases ascertained because of advanced maternal age the maternal age is significantly elevated only in maternal meiosis II errors, probably due to the small number of meiosis I errors in the individual studies (Ya-gang *et al.*, 1993; Fisher *et al.*, 1995; Eggermann *et al.*, 1996). The preponderance of females with trisomy 18 in liveborns (sex ratio 0.63) compared to fetuses diagnosed prenatally (sex ratio 0.90) indicates a prenatal selection against trisomy 18 males after the time of amniocentesis (Huether *et al.*, 1996).

### Trisomy 16

Trisomy 16 is the most common trisomy in our species with a well known relationship with increasing maternal age (Hassold and Jacobs, 1984). It is estimated to occur in 1.5% of all recognized pregnancies (Wolstenholme, 1995) and found in 5.1% of spontaneous abortions (Hassold *et al.*, 1980). Trisomy 16 is incompatible with postnatal survival, but a few liveborn infants with trisomy 16 mosaicism have been described with an extremely variable clinical expression (Devi *et al.*, 1993; Greally *et al.*, 1996). Non-disjunction studies on spontaneous abortions ( $n = 62$ ) show maternal meiotic origin of all cases (Hassold *et al.*, 1995) (Table I). Using a centromeric marker, which detects polymorphic fragments in the alpha satellite sequences of the centromere of chromosome 16, the meiotic stage of non-disjunction was determined as meiosis I in all informative cases (Hassold *et al.*, 1995) (Table I). In studies of genetic recombination, a highly significant reduction in recombination was observed in comparison with the normal female genetic map. The crossover distribution indicated a striking reduction in recombination in the proximal short and long arms of the chromosome, therefore reduced rather than absent recombination is the predisposing factor to non-disjunction of chromosome 16 (Hassold *et al.*, 1995).

### Trisomy 16 and confined placental mosaicism

Chromosomal mosaicism originates during early embryonic development and may be generalized or confined to the placenta or the embryo. About 1–2% of prenatal chorionic villus samplings (CVS) show chromosomal mosaicism, most often between a numerical aberration and a normal diploid cell line (Veijerslev and Mikkelsen, 1989). In most cases the mosaicism is confined to the placenta (CPM) and does not involve the fetus proper (Kalousek and Dill, 1983). CPM for trisomy 16 (CPM16) occurs with an overall incidence of 34:100 000 samples based on a large series of prenatal CVS (Wolstenholme, 1995). Molecular studies show maternal meiosis I origin of the trisomic cell line in almost all (17/18) studied cases of CPM16, and the diploid fetus therefore resulted from postzygotic loss of one of the three chromosomes 16 in a trisomic conceptus (Robinson *et al.*, 1997). This mechanism of trisomy rescue may be regarded as a prerequisite for intrauterine survival of an otherwise lethal trisomy. Theoretically in one third of such cases, the consequence in the fetus will be uniparental disomy (UPD) in which both chromosomes 16 originate from the mother (Engel, 1980). CPM may be associated with a spectrum of fetal manifestations ranging from

normal pregnancy outcome, intrauterine growth retardation (IUGR) to fetal death (Kalousek and Vekemans, 1996). Abnormal pregnancy outcome (usually IUGR) has been correlated to the presence of fetal UPD (Kalousek *et al.*, 1993; Robinson *et al.*, 1997). It is difficult to distinguish whether an abnormal outcome associated with UPD is due to the UPD itself or to the presence of high levels of trisomic cells in the placenta (Kalousek *et al.*, 1993; Robinson *et al.*, 1997). The adverse effect that UPD of certain chromosomes has on fetal development is caused by imprinting (Hall, 1990). Both maternal and paternal copies of some chromosomes are required for normal development. It has been suggested that imprinting may exist for chromosome 16 and that the effect is limited to the placental tissues affecting prenatal growth (Schneider *et al.*, 1996; Robinson *et al.*, 1997).

### Trisomy 15 and uniparental disomy 15

UPD is defined as the presence of both homologues of a chromosomal pair derived from the same parent in a diploid offspring (Engel, 1980). The concept was first described by Engel in 1980 on the basis of the high frequency of aneuploidy in human gametes. One of the theoretical mechanisms, and probably the most important, resulting in UPD is trisomy rescue (the zygote starts trisomic but loses one of the homologues, resulting in two remaining homologues from only one parent in one third of cases). This has been demonstrated in several cases of CPM15, normal karyotype of amniocytes, and the birth of a child with Prader–Willi syndrome due to maternal UPD15 (Cassidy *et al.*, 1992). UPD can result in human genetic disorders as a result of homozygosity of recessive phenotypes (isodisomy) or as a result of genomic imprinting (differential phenotypic expression of the same genetic material depending on the sex of the transmitting parent) (Hall, 1990). It was not until 1989 with the discovery of UPD15 in some Prader–Willi syndrome patients, that the importance of UPD and genomic imprinting in human biology was realized (Nicholls *et al.*, 1989).

Trisomy 15 occurs in 1.4% of spontaneous abortions (Hassold *et al.*, 1980). In one molecular study of 17 spontaneous abortions with trisomy 15, 15 cases were of maternal meiotic origin and two of paternal meiotic origin (Zaragoza *et al.*, 1994) (Table I). Another way to study maternal non-disjunction of chromosome 15 has been undertaken in studies of Prader–Willi syndrome patients ( $n = 120$ ) with maternal UPD15 (Robinson *et al.*, 1996b). Maternal non-disjunction of chromosome 15 took place in 73% of cases in meiosis I, 12% in meiosis II, and 15% in postzygotic mitosis (Robinson *et al.*, 1996b) (Table I). There is increased maternal age and reduced recombination associated with maternal meiotic non-disjunction of chromosome 15 (Robinson *et al.*, 1993, 1996b).

### Trisomy 13

Trisomy 13 (Patau's syndrome) is the third most common autosomal trisomy in newborns, with a prevalence at birth of about 1:29 000 (Goldstein and Nielsen, 1988). The parental origin was determined in a total of 42 cases from two molecular

studies (Table I), showing 88% maternal errors and 12% paternal errors (Zaragoza *et al.*, 1994; Robinson *et al.*, 1996a). The number of cases studied is still very small, meiotic division error has not been established with certainty due to the lack of a useful centromere polymorphism and with considerable distance from the centromere to the most proximal long arm marker, and the issue of altered recombination has not been addressed.

### Trisomy 8

Trisomy 8 is a rare condition in man, comprising 0.7% of spontaneous abortions (Hassold *et al.*, 1980), and estimated to occur in about 0.1% of recognized pregnancies (Wolstenholme, 1996). In liveborns, trisomy 8 is almost always associated with mosaicism and more than 100 patients have been reported so far with Warkany syndrome (Warkany *et al.*, 1962; Riccardi, 1977). The exact incidence is not known but is certainly low. One incidence study detected one case among 34 910 newborns (Nielsen and Wohler, 1991). In trisomy 8 little is known about the origin of the additional chromosome, as very few cases have been studied so far (Table I). In one molecular study, four spontaneous abortions showing 100% trisomic cells were all of maternal meiotic origin, while one liveborn with apparent non-mosaic trisomy 8 was consistent with a mitotic gain of the extra chromosome (James and Jacobs, 1996). Studies of trisomy 8 mosaicism in liveborns have demonstrated 12 cases of mitotic duplication and only one case of probable meiotic origin (DeBrasi *et al.*, 1995; Robinson *et al.*, 1995; James and Jacobs, 1996; Seghezzi *et al.*, 1996). Three cases of CPM8 ascertained through mothers undergoing CVS for advanced maternal age also showed somatic (postmeiotic) origin of the trisomic cell line (Robinson *et al.*, 1997). Trisomy 8 of meiotic origin does not seem compatible with a continuing pregnancy. The aetiology of trisomy 8 therefore seems to differ from that of the common autosomal trisomies and makes a new addition to the expanding category of mitotically derived chromosome abnormalities, as previously described in some cases of homologous Robertsonian translocations and isochromosomes (Blouin *et al.*, 1994; Robinson *et al.*, 1994) and unbalanced de-novo translocations (Eggermann *et al.*, 1997; Sarri *et al.*, 1997).

### Future perspectives

The causative mechanisms in the genesis of aneuploidy need to be better understood, but a reduction in the rate of non-disjunction leading to trisomy is less likely to be achieved, as chromosomal non-disjunction is such a basic characteristic of our species (Epstein, 1997). Future research should try to answer these questions: why do different chromosomes have different potential for non-disjunction? What is the mechanism behind the maternal age effect? Do paternal age effect and genetic susceptibility factors exist for non-disjunction (Avramopoulos *et al.*, 1996)? What is the effect of environmental factors on cell division (Sperling *et al.*, 1994)? It will be interesting to examine whether the origin of non-disjunction

is related to different levels of maternal serum markers for aneuploidy (Brizot *et al.*, 1996).

### Conclusion

We have reviewed the molecular studies of the last decade regarding origin and underlying mechanisms of non-disjunction in human autosomal trisomies 8, 13, 15, 16, 18, and 21. Maternal meiosis I errors constitute the most important single class of non-disjunction in man, but chromosome-specific patterns exist. The mechanisms associated with paternal non-disjunction are likely to differ from those associated with maternal non-disjunction. There is aberrant meiotic recombination associated with maternal meiotic non-disjunction in all trisomies studied in detail (trisomies 15, 16, 18, and 21), and this is the only positive finding associated with non-disjunction identified so far (except the increased maternal age). There is some evidence that aberrant recombination is not the primary cause of non-disjunction, but that susceptible chiasmata are more prone to result in non-disjunction, when a meiotic process is disrupted. The second hit of this two-hit model could be the source of the maternal age effect on trisomy. There is, however, still a surprising lack of understanding of the basic mechanism(s) behind the maternal age effect, and chromosomal non-disjunction remains one of the unanswered questions of human genetics.

### Acknowledgements

The work of M.B.P. was supported by EC BIOMED grants GENE-CT93-0015 and BMH4-CT96-0554 to the European Chromosome 21 Consortium, Else og Mogens Wedell-Wedellsborgs Fond, Smedemester Niels Hansen og hustru Johanne f. Frederiksen's Legat, Brødrene Hartmanns Fond, Fru C. Hermansens Mindelegat, Direktør Jacob Madsens og Hustru Olga Madsens Fond, Kirstine Fonden, and Kong Christian den Tiendes Fond.

### References

- Angell, R. (1997) First-meiotic-division nondisjunction in human oocytes. *Am. J. Hum. Genet.*, **61**, 23–32.
- Antonarakis, S.E., Lewis, J.G., Adelsberger, P.A. *et al.* (1991) Parental origin of the extra chromosome in trisomy 21 as indicated by analysis of DNA polymorphisms. *N. Engl. J. Med.*, **324**, 872–876.
- Antonarakis, S.E., Petersen, M.B., McInnis, M.G. *et al.* (1992) The meiotic stage of nondisjunction in trisomy 21: determination by using DNA polymorphisms. *Am. J. Hum. Genet.*, **50**, 544–550.
- Antonarakis, S.E., Avramopoulos, D., Blouin, J.-L. *et al.* (1993) Mitotic errors in somatic cells cause trisomy 21 in about 4.5% of cases and are not associated with advanced maternal age. *Nat. Genet.*, **3**, 146–150.
- Avramopoulos, D., Mikkelsen, M., Vassilopoulos, D. *et al.* (1996) Apolipoprotein E allele distribution in parents of Down's syndrome children. *Lancet*, **347**, 862–865.
- Aymé, S. and Lippman-Hand, A. (1982) Maternal-age effect in aneuploidy: does altered embryonic selection play a role? *Am. J. Hum. Genet.*, **34**, 558–565.
- Babu, A. and Verma, R.S. (1986) The heteromorphic marker on chromosome 18 using restriction endonuclease AluI. *Am. J. Hum. Genet.*, **38**, 549–554.
- Blouin, J.-L., Binkert, F. and Antonarakis, S.E. (1994) Biparental inheritance of chromosome 21 polymorphic markers indicates that some Robertsonian translocations t(21;21) occur postzygotically. *Am. J. Med. Genet.*, **49**, 363–368.
- Brizot, M.L., Jauniaux, E., Mckie, A.T. *et al.* (1996) Placental mRNA expression of  $\alpha$  and  $\beta$  human chorionic gonadotropin in early trisomy 18 pregnancies. *Mol. Hum. Reprod.*, **2**, 463–465.
- Cassidy, S.B., Lai, L.-W., Erickson, R.P. *et al.* (1992) Trisomy 15 with loss of

- the paternal 15 as a cause of Prader-Willi syndrome due to maternal disomy. *Am. J. Hum. Genet.*, **51**, 701-708.
- Chakravarti, A. and Slaugenhaupt, S.A. (1987) Methods for studying recombination on chromosomes that undergo nondisjunction. *Genomics*, **1**, 35-42.
- Davies, K.E., Harper, K., Bonthron, D. *et al.* (1984) Use of a chromosome 21 cloned DNA probe for the analysis of non-disjunction in Down syndrome. *Hum. Genet.*, **66**, 54-56.
- DeBrasi, D., Genuardi, M., D'Agostino, A. *et al.* (1995) Double autosomal/gonosomal mosaic aneuploidy: study of nondisjunction in two cases with trisomy of chromosome 8. *Hum. Genet.*, **95**, 519-525.
- Devi, A.S., Velinov, M., Kamath, M.V. *et al.* (1993) Variable clinical expression of mosaic trisomy 16 in the newborn infant. *Am. J. Med. Genet.*, **47**, 294-298.
- Down, J.L.H. (1866) Observations on an ethnic classification of idiots. *London Hospital Clinical Lectures and Reports*, **3**, 259-262.
- Economou, E.P., Bergen, A.W., Warren, A.C. *et al.* (1990) The polydeoxyadenylate tract of Alu repetitive elements is polymorphic in the human genome. *Proc. Natl Acad. Sci. USA*, **87**, 2951-2954.
- Eggermann, T., Nöthen, M.M., Eiben, B. *et al.* (1996) Trisomy of human chromosome 18: molecular studies on parental origin and cell stage of nondisjunction. *Hum. Genet.*, **97**, 218-223.
- Eggermann, T., Engels, H., Heidrich-Kaul, C. *et al.* (1997) Molecular investigation of the parental origin of a de novo unbalanced translocation 13/18. *Hum. Genet.*, **99**, 521-522.
- Engel, E. (1980) A new genetic concept: uniparental disomy and its potential effect, isodisomy. *Am. J. Med. Genet.*, **6**, 137-143.
- Epstein, C.J. (1997) The future of research on Down syndrome. *Cytogenet. Cell Genet.*, **77**(S1), 33.
- Fisher, J.M., Harvey, J.F., Lindenbaum, R.H. *et al.* (1993) Molecular studies of trisomy 18. *Am. J. Hum. Genet.*, **52**, 1139-1144.
- Fisher, J.M., Harvey, J.F., Morton, N.E. *et al.* (1995) Trisomy 18: studies of the parent and cell division of origin and the effect of aberrant recombination on nondisjunction. *Am. J. Hum. Genet.*, **56**, 669-675.
- Goldstein, H. and Nielsen, K.G. (1988) Rates and survival of individuals with trisomy 13 and 18: data from a 10-year period in Denmark. *Clin. Genet.*, **34**, 366-372.
- Greally, J.M., Neiswanger, K., Cummins, J.H. *et al.* (1996) A molecular anatomical analysis of mosaic trisomy 16. *Hum. Genet.*, **98**, 86-90.
- Griffin, D.K., Abruzzo, M.A., Millie, E.A. *et al.* (1996) Sex ratio in normal and disomic sperm: evidence that the extra chromosome 21 preferentially segregates with the Y chromosome. *Am. J. Hum. Genet.*, **59**, 1108-1113.
- Grouchy, J. de (1970) 21p - maternel en double exemplaire chez un trisomique 21. *Ann. Génét.*, **13**, 52-55.
- Hall, J.G. (1990) Genomic imprinting: review and relevance to human diseases. *Am. J. Hum. Genet.*, **46**, 857-873.
- Hassold, T.J. and Jacobs, P.A. (1984) Trisomy in man. *Annu. Rev. Genet.*, **18**, 69-97.
- Hassold, T., Chen, N., Funkhouser, J. *et al.* (1980) A cytogenetic study of 1000 spontaneous abortions. *Ann. Hum. Genet.*, **44**, 151-178.
- Hassold, T., Quillen, S.D. and Yamane, J.A. (1983) Sex ratio in spontaneous abortions. *Ann. Hum. Genet.*, **47**, 39-47.
- Hassold, T., Chiu, D. and Yamane, J.A. (1984) Parental origin of autosomal trisomies. *Ann. Hum. Genet.*, **48**, 129-144.
- Hassold, T., Merrill, M., Adkins, K. *et al.* (1995) Recombination and maternal age-dependent nondisjunction: molecular studies of trisomy 16. *Am. J. Hum. Genet.*, **57**, 867-874.
- Hawley, R.S., Frazier, J.A. and Rasooly, R. (1994) Separation anxiety: the etiology of nondisjunction in flies and people. *Hum. Mol. Genet.*, **3**, 1521-1528.
- Hook, E.B. (1981) Down syndrome: frequency in human populations and factors pertinent to variation in rates. In de la Cruz, F.F. and Gerald, P.S. (eds), *Trisomy 21 (Down syndrome): Research Perspectives*. University Park Press, Baltimore, pp. 3-67.
- Hook, E.B. and Cross, P.K. (1982) Paternal age and Down's syndrome genotypes diagnosed prenatally: no association in New York State data. *Hum. Genet.*, **62**, 167-174.
- Hook, E.B., Cross, P.K. and Regal, R.R. (1990) Factual, statistical and logical issues in the search for a paternal age effect for Down syndrome. *Hum. Genet.*, **85**, 387-388.
- Huether, C.A., Martin, R.L.M., Stoppelman, S.M. *et al.* (1996) Sex ratios in fetuses and liveborn infants with autosomal aneuploidy. *Am. J. Med. Genet.*, **63**, 492-500.
- Hug, E. (1951) Das Geschlechtsverhältnis beim Mongolismus. *Ann. Paediatr.*, **177**, 31-54.
- Jabs, E.W., Warren, A.C., Taylor, E.W. *et al.* (1991) Alphoid DNA polymorphisms for chromosome 21 can be distinguished from those of chromosome 13 using probes homologous to both. *Genomics*, **9**, 141-146.
- James, R.S. and Jacobs, P.A. (1996) Molecular studies of the aetiology of trisomy 8 in spontaneous abortions and the liveborn population. *Hum. Genet.*, **97**, 283-286.
- Juberg, R.C. and Jones, B. (1970) The Christchurch chromosome (Gp-): mongolism, erythroleukemia and an inherited Gp- chromosome (Christchurch). *N. Engl. J. Med.*, **282**, 292-297.
- Juberg, R.C. and Mowrey, P.N. (1983) Origin of nondisjunction in trisomy 21 syndrome: all studies compiled, parental age analysis, and international comparisons. *Am. J. Med. Genet.*, **16**, 111-116.
- Kalousek, D.K. and Dill, F.J. (1983) Chromosomal mosaicism confined to the placenta in human conceptions. *Science*, **221**, 665-667.
- Kalousek, D.K. and Vekemans, M. (1996) Confined placental mosaicism. *J. Med. Genet.*, **33**, 529-533.
- Kalousek, D.K., Langlois, S., Barrett, I. *et al.* (1993) Uniparental disomy for chromosome 16 in humans. *Am. J. Hum. Genet.*, **52**, 8-16.
- Kondoh, T., Tonoki, H., Matsumoto, T. *et al.* (1988) Origin of the extra chromosome in trisomy 18: a study on five patients using a restriction fragment length polymorphism. *Hum. Genet.*, **79**, 377-378.
- Kupke, K.G. and Müller, U. (1989) Parental origin of the extra chromosome in trisomy 18. *Am. J. Hum. Genet.*, **45**, 599-605.
- Lamb, N.E., Freeman, S.B., Savage-Austin, A. *et al.* (1996) Susceptible chiasmate configurations of chromosome 21 predispose to non-disjunction in both maternal meiosis I and meiosis II errors. *Nat. Genet.*, **14**, 400-405.
- Lejeune, J., Gauthier, M. and Turpin, R. (1959) Les chromosomes humains en culture de tissus. *C. R. Acad. Sci. Paris*, **248**, 602-603.
- Litt, M. and Luty, J.A. (1989) A hypervariable microsatellite revealed by in vitro amplification of a dinucleotide repeat within the cardiac muscle actin gene. *Am. J. Hum. Genet.*, **44**, 397-401.
- Lorber, B.J., Grantham, M., Peters, J. *et al.* (1992) Nondisjunction of chromosome 21: comparisons of cytogenetic and molecular studies of the meiotic stage and parent of origin. *Am. J. Hum. Genet.*, **51**, 1265-1276.
- Mikkelsen, M., Poulsen, H., Grinstead, J. *et al.* (1980) Non-disjunction in trisomy 21: study of chromosomal heteromorphisms in 110 families. *Ann. Hum. Genet.*, **44**, 17-28.
- Mikkelsen, M., Hallberg, A., Poulsen, H. *et al.* (1995) Epidemiological study of Down's syndrome in Denmark, including family studies of chromosomes and DNA markers. *Dev. Brain Dysfunct.*, **8**, 4-12.
- Nicholls, R.D., Knoll, J.H.M., Butler, M.G. *et al.* (1989) Genetic imprinting suggested by maternal heterodisomy in non-deletion Prader-Willi syndrome. *Nature*, **342**, 281-285.
- Nielsen, J. and Wohler, M. (1991) Chromosome abnormalities found among 34 910 newborn children: results from a 13-year incidence study in Aarhus, Denmark. *Hum. Genet.*, **87**, 81-83.
- NIH/CEPH Collaborative Mapping Group (1992) A comprehensive genetic linkage map of the human genome. *Science*, **258**, 67-86.
- Nöthen, M.M., Eggermann, T., Erdmann, J. *et al.* (1993) Retrospective study of the parental origin of the extra chromosome in trisomy 18 (Edwards syndrome). *Hum. Genet.*, **92**, 347-349.
- Pangalos, C., Avramopoulos, D., Blouin, J.-L. *et al.* (1994) Understanding the mechanism(s) of mosaic trisomy 21 by using DNA polymorphism analysis. *Am. J. Hum. Genet.*, **54**, 473-481.
- Penrose, L.S. (1933) The relative effects of paternal and maternal age in mongolism. *J. Genet.*, **27**, 219-224.
- Petersen, M.B., Schinzel, A.A., Binkert, F. *et al.* (1991) Use of short sequence repeat DNA polymorphisms after PCR amplification to detect the parental origin of the additional chromosome 21 in Down syndrome. *Am. J. Hum. Genet.*, **48**, 65-71.
- Petersen, M.B., Frantzen, M., Antonarakis, S.E. *et al.* (1992) Comparative study of microsatellite and cytogenetic markers for detecting the origin of the nondisjoined chromosome 21 in Down syndrome. *Am. J. Hum. Genet.*, **51**, 516-525.
- Petersen, M.B., Antonarakis, S.E., Hassold, T.J. *et al.* (1993) Paternal nondisjunction in trisomy 21: excess of male patients. *Hum. Mol. Genet.*, **2**, 1691-1695.
- Riccardi, V.M. (1977) Trisomy 8: an international study of 70 patients. *Birth Defects Orig. Art. Ser.*, **XIII**, 171-184.
- Robinson, W.P., Bernasconi, F., Mutirangura, A. *et al.* (1993) Nondisjunction of chromosome 15: origin and recombination. *Am. J. Hum. Genet.*, **53**, 740-751.



- Robinson, W.P., Bernasconi, F., Basaran, S. *et al.* (1994) A somatic origin of homologous Robertsonian translocations and isochromosomes. *Am. J. Hum. Genet.*, **54**, 290–302.
- Robinson, W.P., Binkert, F., Bernasconi, F. *et al.* (1995) Molecular studies of chromosomal mosaicism: relative frequency of chromosome gain or loss and possible role of cell selection. *Am. J. Hum. Genet.*, **56**, 444–451.
- Robinson, W.P., Bernasconi, F., Dutly, F. *et al.* (1996a) Molecular studies of translocations and trisomy involving chromosome 13. *Am. J. Med. Genet.*, **61**, 158–163.
- Robinson, W.P., Langlois, S., Schuffenhauer, S. *et al.* (1996b) Cytogenetic and age-dependent risk factors associated with uniparental disomy 15. *Prenat. Diagn.*, **16**, 837–844.
- Robinson, W.P., Barrett, I.J., Bernard, L. *et al.* (1997) Meiotic origin of trisomy in confined placental mosaicism is correlated with presence of fetal uniparental disomy, high levels of trisomy in trophoblast, and increased risk of fetal intrauterine growth restriction. *Am. J. Hum. Genet.*, **60**, 917–927.
- Saiki, R.K., Gelfand, D.H., Stoffel, S. *et al.* (1988) Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science*, **239**, 487–491.
- Sarri, C., Gytodimou, J., Avramopoulos, D. *et al.* (1997) Partial trisomy 17q22-qter and partial monosomy Xq27-qter in a girl with a de novo unbalanced translocation due to a postzygotic error: case report and review of the literature on partial trisomy 17qter. *Am. J. Med. Genet.*, **70**, 87–94.
- Schneider, A.S., Bischoff, F.Z., McCaskill, C. *et al.* (1996) Comprehensive 4-year follow-up on a case of maternal heterodisomy for chromosome 16. *Am. J. Med. Genet.*, **66**, 204–208.
- Seghezzi, L., Maserati, E., Minelli, A. *et al.* (1996) Constitutional trisomy 8 as first mutation in multistep carcinogenesis: clinical, cytogenetic, and molecular data on three cases. *Genes Chromosom. Cancer*, **17**, 94–101.
- Sherman, S.L., Takaesu, N., Freeman, S.B. *et al.* (1991) Trisomy 21: association between reduced recombination and nondisjunction. *Am. J. Hum. Genet.*, **49**, 608–620.
- Sherman, S.L., Petersen, M.B., Freeman, S.B. *et al.* (1994) Non-disjunction of chromosome 21 in maternal meiosis I: evidence for a maternal age-dependent mechanism involving reduced recombination. *Hum. Mol. Genet.*, **3**, 1529–1535.
- Speed, R.M. and Chandley, A.C. (1990) Prophase of meiosis in human spermatocytes analysed by EM microspreading in infertile men and their controls and comparisons with human oocytes. *Hum. Genet.*, **84**, 547–554.
- Sperling, K., Pelz, J., Wegner, R-D. *et al.* (1994) Significant increase in trisomy 21 in Berlin nine months after the Chernobyl reactor accident: temporal correlation or causal relation? *Br. Med. J.*, **309**, 158–162.
- Stahl, A., Hartung, M., Devictor, M. *et al.* (1984) The association of the nucleolus and the short arm of acrocentric chromosomes with the XY pair in human spermatocytes: its possible role in facilitating sex-chromosome acrocentric translocations. *Hum. Genet.*, **68**, 173–180.
- Stein, Z., Stein, W. and Susser, M. (1986) Attrition of trisomies as a maternal screening device: an explanation of the association of trisomy 21 with maternal age. *Lancet*, **i**, 944–947.
- Stene, E. and Stene, J. (1989) Controversy concerning paternal age effect in 47, +21 Down's syndrome. *Hum. Genet.*, **81**, 300–301.
- Stene, E., Stene, J. and Stengel-Rutkowski, S. (1987) A reanalysis of the New York State prenatal diagnosis data on Down's syndrome and paternal age effects. *Hum. Genet.*, **77**, 299–302.
- Straub, R.E., Speer, M.C., Luo, Y. *et al.* (1993) A microsatellite genetic linkage map of human chromosome 18. *Genomics*, **15**, 48–56.
- Thépot, F., Mayaux, M.J., Czyglick, F. *et al.* (1996) Incidence of birth defects after artificial insemination with frozen donor spermatozoa: a collaborative study of the French CECOS Federation on 11 535 pregnancies. *Hum. Reprod.*, **11**, 2319–2323.
- Vejslev, L.O. and Mikkelsen, M. (1989) The European collaborative study on mosaicism in chorionic villus sampling: data from 1986–1987. *Prenat. Diagn.*, **9**, 575–588.
- Warburton, D. (1997) Invited editorial. Human female meiosis: new insights into an error-prone process. *Am. J. Hum. Genet.*, **61**, 1–4.
- Warkany, J., Rubinstein, J.H., Soukup, S.W. *et al.* (1962) Mental retardation, absence of patellae, other malformations with chromosomal mosaicism. *J. Pediatr.*, **61**, 803–812.
- Warren, A.C., Chakravarti, A., Wong, C. *et al.* (1987) Evidence for reduced recombination on the nondisjoined chromosomes 21 in Down syndrome. *Science*, **237**, 652–654.
- Weber, J.L. and May, P.E. (1989) Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. *Am. J. Hum. Genet.*, **44**, 388–396.
- Weissenbach, J., Gyapay, G., Dib, C. *et al.* (1992) A second-generation linkage map of the human genome. *Nature*, **359**, 794–801.
- Wolstenholme, J. (1995) An audit of trisomy 16 in man. *Prenat. Diagn.*, **15**, 109–121.
- Wolstenholme, J. (1996) Confined placental mosaicism for trisomies 2, 3, 7, 8, 9, 16, and 22: their incidence, likely origins, and mechanisms for cell lineage compartmentalization. *Prenat. Diagn.*, **16**, 511–524.
- Ya-gang, X., Robinson, W.P., Spiegel, R. *et al.* (1993) Parental origin of the supernumerary chromosome in trisomy 18. *Clin. Genet.*, **44**, 57–61.
- Yoon, P.W., Freeman, S.B., Sherman, S.L. *et al.* (1996) Advanced maternal age and the risk of Down syndrome characterized by the meiotic stage of the chromosomal error: a population-based study. *Am. J. Hum. Genet.*, **58**, 628–633.
- Zaragoza, M.V., Jacobs, P.A., James, R.S. *et al.* (1994) Nondisjunction of human acrocentric chromosomes: studies of 432 trisomic fetuses and liveborns. *Hum. Genet.*, **94**, 411–417.

Received on July 22, 1997; accepted on November 12, 1997