

# Aneuploidy in Humans

A.V.H. McPhail

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## Introduction

Phenotypically normal humans have a diploid chromosome complement of forty-six, twenty-three chromosomes inherited maternally, and twenty-three paternally. Aneuploidy, changes in the number of whole or partial chromosomes through addition or subtraction, has been causally linked to various phenotypes, the most severe of which are incompatible with life. Cytogenetic studies have provided explanations for the mechanisms leading to aneuploidy but the mode(s) of action leading to the observed syndromes are still the subject of much inquiry.

Currently, two hypotheses have been proposed to account for the phenotypic abnormalities. The additive hypothesis predicts that aneuploid phenotypes are a result of differences in gene dosage and that combinations of different aneuploidies will result in a combination of the phenotypic effects (Epstein, 1988; Epstein, 1990). In contrast, the interactive hypothesis describes the downstream effects as a result of increased susceptibility of the organism to environmental, including intra-organismal, perturbation (Wilson, 1990). Unfortunately, the debate appears to have succumbed to occasional injections of anti-reductionist and anti-holist rhetoric. In fact, it appears that the crux of the former hypothesis, gene dosage, can be used as the underlying mechanism which powers the latter hypothesis.

The occurrence of aneuploidy has been shown to be much higher in humans than in other mammals (Gearhart, Oster-Granite, Reeves and Coyle, 1987). Thus, understanding the factors leading to the aneuploid condition will aid in providing substantively useful guidelines to both clinicians and genetic counsellors. Also, given that the stuff of inheritance is physically packaged as a chromosome and chromosome rearrangements are indicative of phylogenetic status, understanding the mechanisms, if any, by which chromosomes or their parts may or may not be modified will add to the current appreciation of fundamental genetic mechanisms (Wilson, 1990).

## Phenotype

The karyotype of an aneuploid individual can be identified by abnormal chromosome number or morphology. In the case of whole chromosome aneuploidy, in which an entire chromosome is extra, trisomic, or lacking, monosomic, the identification is relatively straightforward. On the other hand, partial monosomy, a loss of part of a chromosome arm, and partial trisomy, duplication of a chromosome section, are sometimes difficult to identify and may rely on predictable banding patterns or molecular techniques. There can also occur more complex aneuploidies derived from combinations of the above cases, one example being tetrasomy, in which there are two extra copies of one chromosome.

The only case of complete monosomy which results in liveborn progeny is that of 45,X0 (Turner syndrome, TS). Although trisomy 16 is the most prevalent chromosome imbalance in humans, accounting for 1% of clinically recognised pregnancies, all cases are spontaneously aborted. There have been no reported cases of trisomies 1 or 19, and of the autosomal trisomies only cases of 9, 13, 18, 21, and 22 have survived past the 28th week of term, and no individuals with trisomies 9 or 22 have survived to full term. Thus, the only liveborn trisomic aneuploids are those with an extra chromosome 13, 18, or 21. However, most cases of these three trisomies are aborted, with trisomy 21 having the greatest chance of survival to term (21%). Aneuploidies involving the sex chromosomes — 47,XXY, 47,XXX, 47,XYY, 48,XXXX and rare cases of individuals with higher numbers of sex chromosomes have a much greater chance of survival. Partial monosomy and trisomy are much more compatible with life, the likelihood of survival being dependent upon the size and chromosomal origin of the deleted or duplicated chromosomal matter. All together, it has been estimated that aneuploidy is accountable for ~50% of all unsuccessful conceptions (Hassold and Jacobs, 1984; Jacobs and Hassold, 1995).

All liveborn aneuploid progeny suffer predictable deficiencies. It has been found that phenotypic abnormalities associated with loss or gain of a whole chromosome can be mapped to certain critical regions which, when altered through partial-chromosome abnormalities, produce concordant effects, as is the case with Turner and Down's syndromes. TS is characterised by mild mental retardation, failure to develop secondary sexual characteristics or mature sex organs and certain morphogenic abnormalities, including short stature and a webbed neck. The most well documented syndrome is that of Down's syndrome (DS), which is characterised by mongoloid facial features, increased prevalence of congenital heart malformation, and mild to severe mental retardation, although most DS individuals are capable of producing phenotypically normal offspring. Angelman syndrome (AS) is caused by the deletion of a region of the maternally inherited chromosome 15 (15q11-15q13) and is characterised by lack of speech, seizures, and spon-

taneous laughter (Russell, 1992; Stalker and Williams, 1998). In general, liveborn aneuploid individuals in almost all cases suffer from major developmental problems which result in morphological abnormalities and mental retardation.

## Ætiology

Aneuploidy, in most instances, is the result of a *de novo* mutational event during gametogenesis. Partial aneuploidy results from deletions, as in Angelman's syndrome, and duplications, or from more complex events such as those which occur subsequent to a reciprocal translocation (in which imbalanced gametes fuse with normal gametes) as in the inherited form of Down's syndrome. In the case of whole chromosome aneuploidy, the cause is non-disjunction of chromatids during the transition from metaphase to anaphase in both divisions of meiosis (MI and MII) or, occasionally, during an early post-zygotic mitosis (PZM). The failure of the chromosomes to separate to opposite poles during cell division results in imbalanced daughter cells. While each daughter cell carrying an extra chromosome, in theory, should be balanced by a cell lacking a chromosome, those lacking a chromosome are lost, either during gametogenesis, oogenesis, or through cell selection in the early zygote and are not equally represented in conceptuses or zygotes, respectively. A non-disjunction occurring in PZM can sometimes give rise to mosaic trisomies, in which the affected individual has both normal and aneuploid cell lines (Hassold and Jacobs, 1984; Jacobs and Hassold, 1995).

The relative contributions of non-disjunctive events during MI, MII, and PZM and the parental origin of aneuploid complements have been estimated through the examination of centromeric and molecular polymorphisms. Non-disjunction of the X and Y chromosomes is the only case in which paternal origin is greater than maternal. In all cases of maternal non-disjunction except trisomy 18, MI errors account for the majority of imbalanced divisions. MII errors account for most non-disjunctions leading to trisomy 18. In all cases meiotic non-disjunction far outweighs PZM non-disjunction as the cause of aneuploidy (Jacobs and Hassold, 1995).

Workers have attempted to account for increased aneuploid incidence through a number of mechanisms, including oral contraception, irradiation, increased levels of environmental toxins, and parental age. Although paternal age provides ambiguous results depending upon the study reviewed, maternal age definitely correlates with increased incidence of trisomic conceptuses for all but two trisomies. Two mechanisms have been posited in order to explain this phenomenon. The production-line hypothesis holds that germ cells enter meiosis sequentially and are released in that order, and that those entering meiosis later (in foetal life) have fewer chiasmata (see below). The depleted oocyte hypothesis postulates that later in life

there is an increased likelihood of sub-optimal oocyte release because of the smaller number of antral-stage follicles (Jacobs and Hassold, 1995).

Recombinatorial marker analysis has shown that non-disjunction can be associated with varying degrees of chiasma formation. Jacobs and Hassold (1995) have classed chiasma formation as normal (NR), perturbed (PR), reduced (RR), and absent (AR) recombination. It was found that different chiasmata profiles accompanied trisomies of different chromosomes. Also, non-disjunction accompanied by NR, RR, and AR chiasmata in MI and NR chiasmata in MII increased with maternal age, whereas non-disjunction due to PR chiasmata during both MI and MII, and PZM errors did not correlate with maternal age (Jacobs and Hassold, 1995).

## Effect

When examining the phenotypic effects of aneuploidy, it must be remembered that there are not necessarily any gene mutations *per se*. Although aneuploid segments may cause either ectopic expression of unwanted genes by interrupting their regulatory regions or silencing of required genes by interrupting their coding regions and these effects can be significant, they are ignored henceforth. The appeal of studying aneuploid effects is that the important factor is the difference in specific gene copy number. Even though the clinical assessment of human aneuploids has shown that the same chromosome imbalance can lead to variable phenotypic expression, there is a high degree of accuracy in predicting the specific aneuploidy from patterns of abnormality. In other words, while there are features common to different trisomies, the various aneuploidies all have characteristic patterns of phenotypic deficiency (Gearhart et al., 1987; Epstein, 1990; Wilson, 1990).

Epstein (1988) suggests that the phenotype of aneuploid individuals is a result of the effects of a 50% change in gene products from genes on the aneuploid segment. While enzymes are unlikely to be affected by this dosage change, other gene product classes may have severe effects. The relative cellular concentrations of *trans*-regulatory elements, cell-cell interaction molecules, multimeric protein components, and signal transduction pathway members, may well be critical in many finely tuned systems. In addition, this additive hypothesis predicts that there will be critical regions in which there are loci of major, determinant effect (Gearhart et al., 1987; Epstein, 1988; Epstein, 1990).

Another explanation for the effects seen in trisomic individuals is that the chromosomal imbalance affects the cellular environment in general, disrupting the overall homeostasis of the cell. While early forms of the interactive argument cited such effects as retarded cellular division due to imbalanced chromosome number as major causative factors in the observed development abnormalities (Epstein, 1988), later versions emphasised the notion

that many gene systems and their effects converge on limited canalised pathways. This more recent version of the interactive hypothesis argues that the observed phenotype will not bear a one-to-one relationship with each of the genes present or absent as a result of the aneuploid state, and that the aneuploid region will not have discrete boundaries (Gearhart et al., 1987; Wilson, 1990).

As evidence that the opposing additive hypothesis is incorrect, the fact that many trisomies share common phenotypic abnormalities is put forward. Also, the fact that the phenotypes of two aneuploid segments do not exhibit a completely additive phenotype when found together is supposed to discount the additive hypothesis. Finally, Wilson (1990) attempts to dismiss the additive hypothesis by claiming that the epitome of experimental design would be to study the effects of each gene on the aneuploid segment in isolation. This last criticism is indicative of a runaway anti-reductionist argument.

Work with aneuploid mice has shown that trisomy 16 (murine homolog of human chromosome 21) individuals exhibited features such as abnormal neuronal membrane potentials, neurochemical abnormalities, and growth retardation (Gearhart et al., 1987). The neurobiological features can certainly be explained by the differences in relative levels of gene products. One group of patients, representing ~20% of all AS individuals, clinically diagnosed as having AS but lacking any cytogenetic feature commonly associated with AS, were found to all have a mutation at a common locus, the gene product of which is possibly involved in protein turnover in the brain. Thus providing evidence of a major, determinant gene (Stalker and Williams, 1998).

The major criticism of the additive hypothesis is that it ignores the (possibly complex) interactions of the genes on the aneuploid segment and the major criticism of the interactive hypothesis is that it lacks a concrete grounding in molecular mechanisms. It appears as if the two opposing hypotheses agree in fact and are merely discordant in form. What the interactive hypothesis lacks is a molecular mechanism by which various gene effects are canalised and homeostatic mechanisms are disrupted, whereas the additive hypothesis is strong on molecular mechanism, but weak on epistatic interaction. Is it not the case that gene dosage effects are the proximate cause and their interplay provides the interactive cause for the observed aneuploid phenotype?

## Conclusion

While the fundamental causes of aneuploidy remain unknown, the general mechanisms by which chromosome anomalies arise have been uncovered. Further unravelling of the mechanisms leading to the phenotypic abnormalities found in aneuploid individuals will reinforce current understanding of

genetic mechanisms. It will aid in the understanding of the physical organisation of genes and allow for improved clinical diagnosis and prognosis. Future research should be directed towards understanding agents, genetic and environmental, which cause non-disjunction at meiosis and dosage effects, alone and combined, which lead to phenotypic abnormality.

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