Clustering of Chromosomal Aneuploidy and Tracing of Nondisjunction in Man

by I. Hansmann*

Chromosomal aneuploidy is the most frequent genetic damage observed in newborn children and originates as a rule from nondisjunction during maternal or paternal germ cell development. The error of chromosome segregation could be allocated in the past — at least in cases of 47,XXY — to maternal meiosis I (50%) or meiosis II (10%) and to paternal meiosis I (40%). Recent cytological improvements with various banding techniques enabled a further study on the origin of nondisjunction. Summarizing the published data one can argue that errors in Down's syndrome are most often due to cleavage errors during maternal meiosis I. Approximately 70% of errors occur in oogenesis and only 30% in spermatogenesis. Maternal meiosis I seems also to be involved in most cases of fetal trisomy 16.

Such a preferential missegregation of chromosomes offers the possibility of studying more closely the very mechanisms of nondisjunction in mammalian meiosis and early cleavages.

Tracing of Nondisjunction in Man

Most of abnormal karyotypes in human abortions (1, 2) and newborns (3) are due to chromosomal aneuploidy. Trisomy originates as a rule from nondisjunction during male and female germ cell development, whereas the 45,X0-syndrome is said to originate predominantly from post-meiotic events (4). A better understanding of the mechanisms leading to nondisjunction necessarily require knowledge of the origin, whether paternal or maternal, of the supernumerary chromosomes.

Earlier studies took advantage of X-linked marker red-green blindness and were able to allocate the additional X chromosome in Klinefelter's syndrome and in 47,XXX females to oogenesis or spermatogenesis (5). Much more families could be studied after the discovery of the X-linked Xg blood group (6). The suggestion was made from these studies that in Klinefelter's syndrome nondisjunction of the X chromosome in 50% of all patients occurred during maternal meiosis I, in 10% during maternal meiosis II, and in 40% the missegregation occurred during paternal meiosis I (7). It was possible to trace nondisjunction of autosomes only after the introduction of chromosome banding techniques (8), although one could assume that some cases of Down's syndrome should be due to meiotic failures during oogenesis, because of the known dependency of this trisomy on maternal age (9). With the aid of such chromosomal polymorphism, e.g. the brilliant fluorescence of satellites, the supernumerary chromosome could be allocated to maternal or paternal meiosis (10) and to first or second meiotic division (11).

In our review of the literature on this subject (12) we summarized 62 cases which were informative with respect to the allocation of nondisjunction. In 43 patients with Down's syndrome the odd-numbered chromosome 21 originated from oogenesis (~70%) and in 19 cases (~30%) from spermatogenesis. After we considered a serious bias in tracing nondisjunction involved with the use of chromosomal polymorphism it was concluded that first meiotic cleavage errors contribute at least 10 times more often to Down's syndrome than second meiotic cleavage errors (12). The same conclusion was drawn from another method of analysis (13) and from studies of abortions (14). It can be concluded, therefore, that at least in those families where a polymorphism is segregating with chromosome 21 nondisjunction occurs preferably during the first meiotic division of the oocyte. It seems to be very unlikely that this pattern is created by a selectively acting elimination during prenatal and/or postnatal development.

Such a preferential malsegregation of chromosomes offers the possibility to study more closely the mechanisms involved in meiotic nondisjunction.

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*Institut für Humangenetik, Universität Göttingen, Germany.
Experiments in mutagenesis should consider the fact, however, that both meiotic divisions in oogenesis and spermatogenesis potentially contribute to the incidence of aneuploidy in human abortions and in newborns.

Clustering of Aneuploidy

Several mutations are known from plants and Drosophila to cause meiotic irregularities (15). The genetic control of meiosis, and hence also of meiotic divisions in mammals is, however, only poorly understood. According to results obtained from biochemical studies in, e.g., mouse oocytes (16), and based on the information from those plants and Drosophila mentioned above, one should accept that also a genetically mediated susceptibility, or predisposition, for nondisjunction may exist in mammals and in man. One further evidence for this suggestion is the apparent strain difference in the age-dependency of nondisjunction in oocytes of mice (17, 18). Some kind of clustering of chromosomal aneuploidy in different races or even within a human race seems therefore not to be irrational. Although, such a cluster effect must not be caused exclusively by a different incidence of aneuploidy at conception, but may also be caused by a different sensitivity for the tolerance of chromosomally imbalanced fetuses.

Several studies dealing with this problem of a possible clustering have been reviewed recently (19), and it is these authors’ belief that there is still no definite evidence in the literature for consistent differences between races in the prevalence at birth of Down’s syndrome. Differences in the incidence of sex-chromosome anomalies at birth have been reported, and it was suggested that one studied race has a lower incidence of XXY karyotypes at birth than the second race (15).

It was proposed that chromosomal polymorphisms of constitutive heterochromatin may predispose to nondisjunction in man (20). The authors found in this study that one of the parents from a child with trisomy 21 carried significantly more often an increased amount of C-heterochromatin on chromosome 9 than did control individuals. The suggestion of a predisposition has not been confirmed yet, and also the method of ascertaining polymorphism in controls and parents of trisomy 21 children may be a matter of criticism. Nevertheless, it is interesting to note that these chromosome regions showing polymorphism have been found in close contact with micronucleoli (21, 22) and therefore may have a specific transcriptional activity during meiosis. It would be very interesting to know whether “house keeping” (23) genes for meiosis, or cell divisions generally are located within those chromosome regions and whether they do show a gene-dosage effect.

Further studies are required to gain some information on the mechanisms of meiotic divisions, and such data will provide us with more information for a better understanding of those irregularities leading to such a high incidence of aneuploidy in our human species.

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