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Human Aneuploidy: Incidence, Origin, and Etiology

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INTRODUCTION

Chromosome abnormalities occur with astonishing frequency in humans, being present in an estimated 10–30% of all fertilized eggs. Of the different classes of chromosome abnormality, aneuploidy (trisomy and monosomy) is by far the most common and, clinically, the most important. For example, over 25% of all miscarriages are monosomic or trisomic, making aneuploidy the leading known cause of pregnancy loss. Furthermore, among those conceptions that survive to term, aneuploidy is the leading genetic cause of mental retardation.

Over the past 25 years, a considerable body of information has accrued on the incidence of aneuploidy in human gametes, fetuses, and newborns. More recently, the application of molecular biological techniques to the study of aneuploidy has begun to uncover some of the underlying causes of human aneuploidy. In this review, we first summarize the cytogenetic data on the incidence of aneuploidy in humans, and then discuss recent molecular data on the mechanism of origin of different aneuploid conditions, the basis of the maternal age effect on aneuploidy, and the importance of aberrant genetic recombination to the genesis of aneuploidy.

INCIDENCE OF ANEUPLOIDY IN HUMANS

The incidence of aneuploidy at a specific developmental time point depends on two factors: the incidence at the time of conception (or shortly thereafter) and the amount of postnatal selection occurring between conception and the time point being studied. In humans, it is not possible to assay all developmental stages and, therefore, the incidence of aneuploidy at the time of conception can only be estimated. These estimates rely primarily on cytogenetic data gathered from clinically recognized human pregnancies and from studies of human gametes (Fig. 1).

Clinically Recognized Pregnancies

Of the three types of naturally terminating, clinically recognized pregnancies (Fig. 1), livebirths are the most easily accessible population, and, therefore, they have been the most extensively studied. During the 1960s and 1970s, several cytogenetic studies of consecutive series of livebirths were conducted, and results on about 60,000 newborns were obtained (Table I). These results indicate that approximately 0.3% of liveborns are aneuploid, with the single most common abnormality being trisomy 21. Other autosomal trisomies and monosomies are virtually nonexistent, with most of the remaining aneuploidies involving an additional or missing sex chromosome.

Little information is available from stillbirths (i.e., fetal deaths occurring between about 20 weeks gestation and term), due to the relative infrequency of late fetal wastage in humans. Nevertheless, cytogenetic studies of several hundred stillborn infants were conducted in the 1970s and 1980s, and these are summarized in Table I. The overall frequency of aneuploidy among stillbirths is approximately 4.0%, over 10-fold that for livebirths. However, the distribution of specific aneuploid conditions is similar to that observed for livebirths, with the most common abnormalities being sex chromosome trisomies or trisomies 13, 18, and 21.

Many cytogenetic surveys of spontaneous abortions (i.e., fetal deaths occurring between about 6–8 weeks of gestation and 20 weeks) have now been reported, with results being available on several thousand cases (Table I). These studies indicate an extremely high frequency of aneuploidy in early clinically recognized fetal wastage; that is, over 35% of all karyotyped fetuses have been aneuploid, representing a 100-fold increase over that observed in liveborns. Furthermore, the distribution of specific aneuploid conditions differs remarkably from that seen in liveborns. For example, trisomies for most chro-

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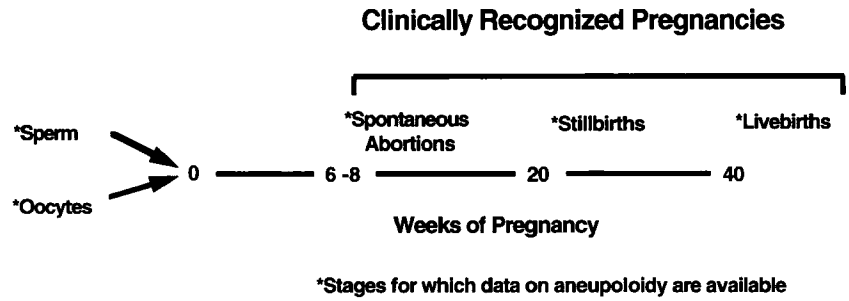

Fig. 1. Time course of human pregnancy, showing the types of conceptions that have been studied cytogenetically. Information on the incidence of aneuploidy is now available from the three different categories of naturally terminating, clinically recognized human pregnancies (spontaneous abortions, stillbirths, and livebirths), and from sperm and oocytes. These data have been used to estimate the incidence of aneuploidy among early pregnancy losses and at conception, time points for which little cytogenetic data are available.

mosomes have now been identified in spontaneous abortions, despite being absent in livebirths, with the most common of these being trisomy 16, which accounts for nearly one third of all trisomies in spontaneous abortions. Other aneuploid conditions common in spontaneous abortions, but rare or nonexistent in livebirths, include sex chromosome monosomy and trisomies 2, 14, 15, and 22.

The information from these three types of pregnancy can be used to derive a minimal estimate of aneuploidy in our species. That is, by using the incidence figures in Table I and by assuming that approximately 15% of all clinically recognized pregnancies result in spontaneous abortion, approximately 1% in stillbirth, and the remainder in livebirth, we can estimate the (a) frequency of different aneuploid conditions among all clinically recognized pregnancies and (b) the likelihood of survival to term for the different conditions. These estimates are provided in Table I. They clearly underestimate the real incidence of aneuploidy in our species, since they do not take into account abnormalities that are eliminated before the time of clinical recognition of pregnancy; for example, autosomal monosomies, which should be the reciprocal nondisjunctional product of autosomal trisomies, but which are almost never identified in spontaneous abortions. Nevertheless, the estimates are useful in indicating that at least 5% of all human conceptions have an additional or missing chromosome.

Studies of Human Oocytes

Difficulty in obtaining suitable study material has limited cytogenetic investigations of human oocytes. However, the introduction of in vitro fertilization (IVF) has provided a means of obtaining oocytes for research purposes, and over the past decade several thousand human oocytes obtained in IVF clinics have been examined cytogenetically. The frequency of aneuploidy varies among the studies [reviewed in Jacobs, 1992], but in the largest ones rates of aneuploidy of approximately 20–25% have been reported (see Table II for summary). Presumably these values are underestimates, since the oocytes in these studies are arrested at meiosis II, so that only abnormalities occurring at meiosis I can be identified.

However, the relevance of these observations to the in vivo situation is uncertain. That is, the patients from whom the oocytes are obtained are unrepresentative of the general population of women of reproductive age; the oocytes are obtained from ovaries that have been hyperstimulated in association with the IVF procedure; and the oocytes studied are unrepresentative of all oocytes retrieved in IVF settings, since the vast majority studied are those remaining unfertilized after insemination with sperm. Furthermore, in a recent review of the oocyte data, Jacobs [1992] compared the types and overall frequency of chromosome abnormality with expected frequencies based on data from clinically recognized pregnancies. She found no correlation between the two data sets and concluded that the results of the studies of nondisjunction in IVF-retrieved oocytes are unlikely to reflect the in vivo situation.

Because of these concerns, the results of the IVF-associated cytogenetic studies must be viewed with caution. Nevertheless, the studies indicate that, at least under experimental conditions, abnormalities in chromosome segregation occur with very high frequency in human oocytes. Furthermore, one recent set of studies of human oocytes by Angell and colleagues [Angell et al., 1994; Angell, 1995] is notable in providing insight into a possible important mechanism of human nondisjunction. In analyses of 179 meiosis II oocytes, Angell and coworkers observed 64 with an abnormal haploid complement. Surprisingly, none of the abnormalities involved a whole extra chromosome, as would be predicted by the classical model of nondisjunction. Instead, they observed cells with 22 whole chromosomes and an additional chromatid, cells with 22 chromosomes and 2 chromatids, and cells with 23

TABLE I. Incidence of Sex Chromosome Monosomy and Individual Trisomies in Different Populations of Clinically Recognizable Human Pregnancies, and Estimated Proportion Surviving to Term

Chromosome constitution	Population			All clinically recognized pregnancies (%)	Liveborn (%)
	Spontaneous abortions (n = 4,088) (%)	Stillbirths (n = 624) (%)	Livebirths (n = 56,952) (%)		
Sex chromosome monosomy (45, X)	8.6	0.3	0.005	1.3	0.3
Total trisomy	26.1	4.0	0.3	4.1	c.6.0
47, +2	1.1	—	—	0.16	0.0
3	0.3	—	—	0.04	0.0
4	0.8	—	—	0.12	0.0
5	0.1	—	—	0.02	0.0
6	0.3	—	—	0.04	0.0
7	0.9	—	—	0.14	0.0
8	0.8	—	—	0.12	0.0
9	0.7	0.2	—	0.10	0.0
10	0.5	—	—	0.07	0.0
11	0.1	—	—	0.07	0.0
12	0.2	—	—	0.02	0.0
13	1.1	0.3	0.005	0.18	2.8
14	1.0	—	—	0.14	0.0
15	1.7	—	—	0.26	0.0
16	7.5	—	—	1.13	0.0
17	0.1	—	—	0.02	0.0
18	1.1	1.1	0.01	0.18	5.4
20	0.6	—	—	0.09	0.0
21	2.3	1.3	0.13	0.45	23.8
22	2.7	0.2	—	0.40	0.0
XXY	0.2	0.2	0.05	0.08	53.0
XXX	0.1	0.2	0.05	0.05	94.4
XYY	—	—	0.05	0.04	100.0
Mosaic trisomy	1.1	0.5	0.02	0.18	9.0
Double trisomy	0.8	—	—	0.12	0.0

Adapted from Hassold and Jacobs [1984].

whole chromosomes and an additional chromatid. These observations suggest that, contrary to conventional thinking, premature division of the centromere at meiosis I may be the most important source of human trisomy. However, as these abnormalities have been observed only in IVF-retrieved oocytes, it is important that they be confirmed in studies of unstimulated oocytes.

Studies of Human Sperm

Most studies of nondisjunction in male germ cells have used the "humster" technique. This approach involves cross-species fertilization of golden hamster oocytes with human sperm, and allows visualization of the chromosome complements of both species. To date, over 20,000 sperm chromosome complements have been examined (Table II), with the overall rate of aneuploidy (calculated as twice the hyperhaploidy rate) being approximately 1–2%. Disomy for most chromosomes has been identified, but there is also evidence for significant variation in disomy among chromosomes; that is, chromosomes 1, 9, 16, and 21 and the sex chromosomes are over-represented and cumulatively account for almost 60% of the hyperhaploid sperm that have been identified. Some of this excess may be artifactual [e.g., Jacobs, 1992], but it is also possible that the variation represents chromosome-specific differences in structures affecting pairing and/or recombination or chromosome separation.

However, it is unlikely that reliable chromosome-specific rates of disomy ever will be obtained using the humster assay, since it has taken several laboratories over a decade to identify fewer than 200 hyperploid sperm [Jacobs, 1992]. Fortunately, the recent introduction of fluorescence in situ hybridization (FISH) may provide a suitable alternative. Using chromosome-specific probes to score the numbers of signals in the sperm head, an extremely large number of sperm can be scored quickly, and all sperm in an ejaculate can be evaluated, not just those capable of fertilization in an in vitro situation. Furthermore, the use of multicolor FISH protocols makes it possible to study several chromosomes simultaneously, to distinguish between diploidy and disomy, and, for the sex chromosomes, to distinguish between meiosis I and meiosis II nondisjunction [Williams et al., 1993].

TABLE II. Summary of Chromosome Studies of Human Oocytes and Sperm

Cell type	Total no. studied	No. hypoploid (%)	No. hyperploid (%)	2× hyperploidy (%)
Oocytes	1024	189 (17.8)	70 (6.6)	140 (13.2)
Sperm	20895	448 (2.1)	146 (0.7)	292 (1.4)

Adapted from Jacobs [1992].

TABLE III. Summary of Chromosome-Specific Rates of Disomy (%) From Two-Color and Multicolor FISH Sperm Studies

Study	No. of Donors	Chromosome 1	3	4	6	7	8	10	12	15	16	17	18	XY	XX	YY
Han et al. [1993]														0.28	0.21	0.21
Wyrobek et al. [1993]							0.07							0.04	0.04	0.09
Williams et al. [1993]	9										0.13		0.08	0.04	0.06	0.09
Bischoff et al. [1994]	2		0.38	0.28	0.11	0.06	0.09	0.22	0.30	0.20	0.39	0.13	0.25	0.38	0.08	0.13
Spriggs et al. [1995]	5	0.10							0.16	0.11			0.11	0.07	0.21	0.15
Griffin et al. [1995]	24												0.04	0.02	0.03	0.13

Adapted from Spriggs et al. [1995].

The results of several recent two-color and multicolor FISH sperm studies are summarized in Table III. To date, only a relatively small number of donors have been studied. Nevertheless, the results are consistent with the hamster studies in two respects. First, the results suggest that, for individual autosomes, the likelihood of meiotic nondisjunction is probably about 0.1%, suggesting a total frequency of autosomal disomy of approximately 2%. Second, in each of the studies in which both autosomes and sex chromosomes have been investigated, sex chromosome disomy is at least twice as common as disomy for individual autosomes. Thus, it may be that the sex chromosomes are particularly susceptible to nondisjunction in male meiosis.

Summary: Incidence of Trisomy at Conception

Taken together, the studies of clinically recognized pregnancies and human gametes suggest a high level of aneuploidy at the time of conception. The studies of clinically recognized pregnancies make it clear that at least 5% of all human conceptions are aneuploid, and the studies of human gametes suggest that the actual value is much higher, possibly 20–25%.

Recent cytogenetic studies of human pre-implanation embryos suggest that the latter estimates may be more accurate. That is, Jamieson et al. [1994] recently analyzed 178 "spare" diploid embryos obtained in association with IVF or GIFT (gamete intra-fallopian transfer) procedures, and found 34 (19.1%) to be aneuploid. As would be expected from studies of clinically recognized pregnancies, trisomy 16 and trisomies involving the acrocentric chromosomes were the most common abnormalities; thus, the results may well reflect the in vivo situation. Furthermore, their results are similar to those of Angell and colleagues [1988], who identified aneuploidy in 6 of 30 early embryos. Additional studies will be necessary to confirm these initial impressions; nevertheless, on the basis of the present data it seems reasonable to suggest that at least one in five of all human conceptions is aneuploid.

ORIGIN OF ANEUPLOIDY

Despite its incidence and clinical importance, until recently we knew relatively little about the parent or meiotic stage of origin of most human trisomies or monosomies. In large part, this was due to the inability to distinguish between paternally and maternally derived chromosomes in the aneuploid conceptus; that is, polymorphisms were not available to distinguish between chromosomes that came from the father and those that came from the mother.

The identification of DNA polymorphisms has eliminated this problem. Highly informative polymorphisms are now available for all human chromosomes, making it

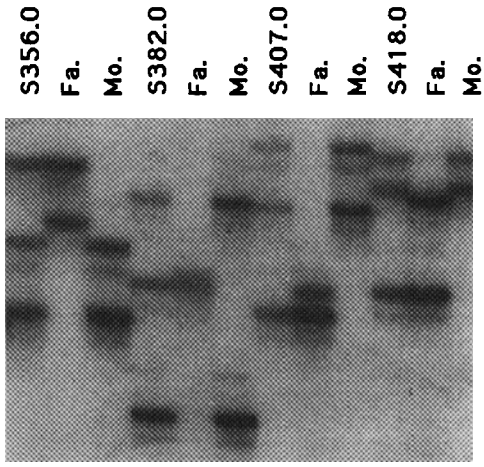

Fig. 2. Studies of the origin of the additional chromosome 16 in four fetuses with trisomy 16, using the chromosome 16 polymorphic marker SPN. In each case, the fetus had three alleles, two of which were maternally derived; because SPN is closely linked to the centromere of chromosome 16, this suggests that each case originated from a maternal meiosis I error.

possible to determine the parent and meiotic origin of any chromosome abnormality. An example of this technique is provided in Figure 2, and the results of analyses of several hundred aneuploid fetuses and liveborns are summarized in Tables IV and V. The results of these studies demonstrate that sex chromosome monosomy usually results from loss of the paternal sex chromosome (Table IV). This is the case regardless of whether the conception is liveborn or spontaneously aborted, indicating that the parental origin of the abnormality does not affect its likelihood of surviving to term.

Trisomies show remarkable variation in parental origin (Table V). For example, paternal nondisjunction is responsible for nearly 50% of 47, XXYs, but only 5–10% of cases of trisomies 13, 14, 15, 21, and 22, and is rarely—if ever—the source of the additional chromosome in trisomy 16. Similarly, there is considerable variability in the meiotic stage of origin. For example, among maternally derived trisomies, all cases of trisomy 16 may be due to meiosis I errors, while for trisomy 21 one third of cases are associated with meiosis II errors, and for trisomy 18 the majority of cases are apparently due to meiosis II nondisjunction. Nevertheless, irrespective of this variation in parental and meiotic origin, nondisjunction at maternal meiosis I appears to be the most common source of human trisomy.

ETIOLOGY OF HUMAN ANEUPLOIDY

Despite years of intensive study, we still know little about factors that influence the frequency of trisomy in humans. For example, efforts to identify important environmental or genetic components to trisomy have met with little success. However, recent molecular studies have identified an important correlate of human trisomy, aberrant meiotic recombination, and have begun to shed light on the only etiological factor incontrovertably linked to trisomy, increasing age of the mother.

TABLE IV. Parental Origin of the Single X Chromosome in Presumed Nonmosaic 45, X Livebirths and Spontaneous Abortions

	Parental origin of the single X chromosome	
Population	Paternal	Maternal
Livebirths	19 (23%)	65 (77%)
Spontaneous abortions	8 (17%)	39 (83%)

Adapted from Hassold et al. [1992].

Recombination and Human Nondisjunction

In yeast and Drosophila, mutants that reduce meiotic recombination typically have increased frequencies of nondisjunction [e.g., Hawley et al., 1993; Rockmill and Roeder, 1994]. In humans, the first evidence of an association between aberrant recombination and trisomy came in 1987, when Warren et al. reported reduced levels of chromosome 21 recombination in meioses leading to Down syndrome. Subsequently, several laboratories have extended these observations. Using centromere mapping techniques, Sherman and colleagues [1991, 1994] constructed genetic maps of chromosome 21 based on trisomies of maternal meiosis I and maternal meiosis II origin and compared them with the normal female map of chromosome 21. The length of the meiosis I map was approximately one-half that of the normal map, demonstrating the importance of reduced recombination in the genesis of trisomy 21. One explanation for this might be that, in a proportion of trisomy-generating meioses, the chromosome 21 bivalent failed to pair and/or recombine. However, other evidence suggests that this is not the case. That is, Sherman et al. [1994] observed an altered distribution of exchanges between the trisomy-generating and normal meioses, indicating that placement, as well as number, of chiasmata is important in segregating the chromosomes 21.

Abnormalities in the frequency or location of meiotic exchanges have been implicated in several other human trisomies. In studies of paternally derived 47, XXY, the overwhelming majority of cases show no evidence of crossing over in the short arm pseudoautosomal region [Hassold et al., 1991]. This is in sharp contrast to normal male meioses, in which a single chiasma ordinarily joins Xp and Yp [Schmitt et al., 1994], and suggests that failure of recombination in the region is an important component of paternal sex chromosome nondisjunction. Studies of maternal sex chromosome trisomies also suggest an effect

TABLE V. Molecular Studies of Parental and Meiotic Stage of Origin in Autosomal and Sex Chromosome Trisomies

		Paternal			Maternal			
Trisomy	No. informative cases	I	II	I or II	I	II	I or II	Percent maternal
2–12	16			3			13	81
13–15	54	1	4	2	12	8	27	87
16	62				51	1	10	100
18	73			3	16	35	19	96
21[a]	436	5	24		306	101		93
22	11			2	6		11	89
XXY	133	58			40	13	22	56
XXX	47		2		24	10	10	94

[a] For trisomy 21, we have presented only those cases having information on both parent and meiotic stage of origin of trisomy.
Adapted from Abruzzo and Hassold [1995].

of aberrant recombination. Thus, MacDonald et al. [1994] constructed a trisomy-based genetic map of the X chromosome from analyses of 47, XXY and 47, XXX conceptuses of maternal origin, and found it to be significantly shorter than the normal female map. However, unlike maternal trisomy 21, some proportion appeared to be due to failure of recombination between the X chromosomes. Another proportion appeared attributable to altered placement of exchanges, but, surprisingly, the effect was associated with increased rather than decreased recombination. That is, pericentromeric recombination was elevated in the trisomy-generating cases, suggesting that proximally located exchanges might lead to "chromosome entanglement" [Bridges, 1916] and failure of the X chromosomes to nondisjoin.

In addition to studies of sex chromosome trisomies and trisomy 21, reductions in recombination have been observed for uniparental disomy 15 [Mascari et al., 1993; Robinson et al., 1993] and trisomy 16 [Hassold et al., in press]. Further, for each of these conditions the placement of exchanges appears different between the trisomy-generating and normal meioses because the majority of exchanges in the nondisjunctional meioses occur distally. This is illustrated in Figure 3 for trisomy 16. The distribution and frequency of exchanges in normal and trisomy 16–generating meioses appears similar over distal 16p and distal 16q; however, in the proximal regions the difference between the two maps is remarkable—an interval measuring approximately 80 cM in the normal is reduced to 4 cM in the trisomic map. Possibly, proximally located chiasmata are important in properly segregating the chromosome 16 bivalent at meiosis I.

Thus, aberrant genetic recombination is an important contributor to all human trisomies that have been appropriately studied. However, the relative importance of failure to recombine, as opposed to alterations in chiasma distribution, needs to be determined, as does the relation-

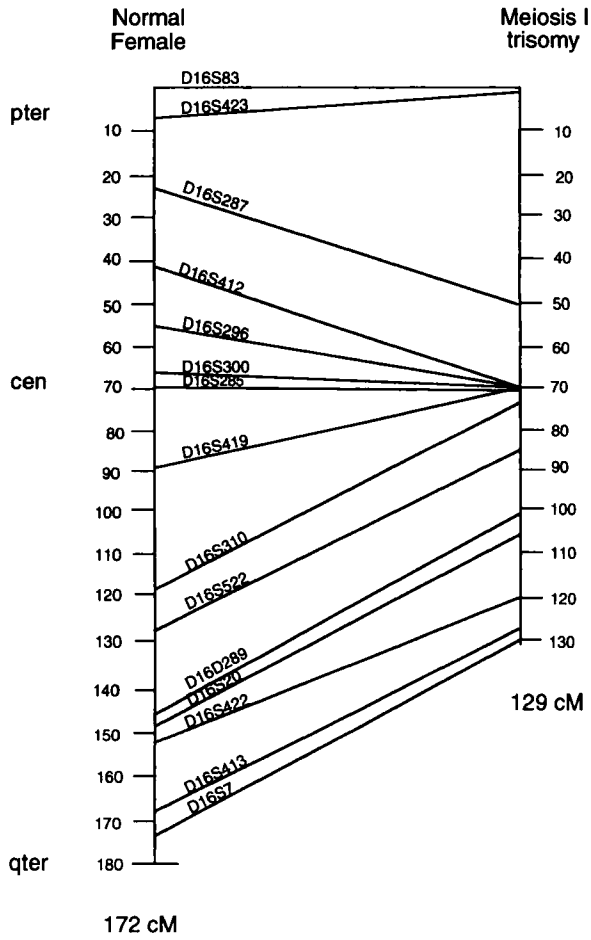

Fig. 3. Comparison of chromosome 16 genetic maps of normal female meioses (using genotyping information from CEPH families) and trisomy 16–generating meioses. Most loci on the map are short sequence repeat polymorphisms, detectable by standard PCR methodology. The trisomy 16 map is significantly shorter than the normal map, due to a deficit of exchanges in the proximal long and short arms.

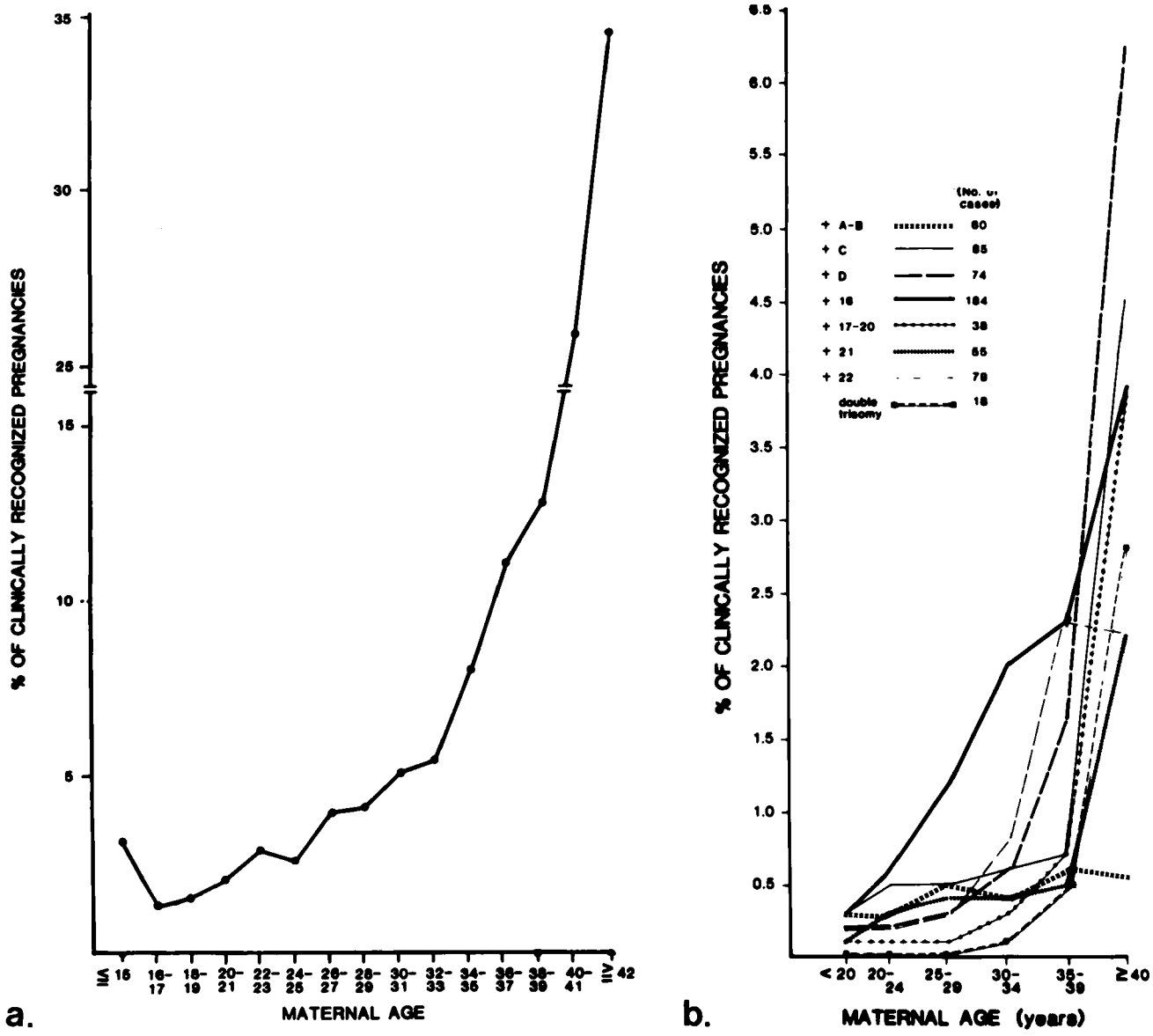

Fig. 4. Maternal age and trisomy. Estimated incidence of trisomy among all clinically recognized pregnancies, assuming a spontaneous abortion rate of 15%, for all trisomies (a) and for individual trisomies (b).

ship of aberrant recombination to maternal age-dependent trisomy.

Maternal Age Effect on Trisomy

The association between increasing maternal age and Down syndrome was recognized over 60 years ago [Penrose, 1933], long before it was determined that Down syndrome was caused by trisomy 21. Subsequently, studies of spontaneous abortions have shown that most, if not all, human trisomies are similarly affected (Fig. 4). Furthermore, these studies suggest that, by age 40–45 years, a majority of all ovulated oocytes may be aneuploid.

Despite the obvious clinical importance of the maternal age effect on trisomy, we still know very little about its basis. Several models have been proposed to explain the effect. These include prenatally determined differences in chiasma frequency among oocytes (the so-called production line hypothesis) [Henderson and Edwards, 1968], exposure to agents inducing double-strand breaks during the prolonged dictyotene stage of meiosis I [Hawley et al., 1994], a declining oocyte pool with age [Warburton, 1989], and changes in the follicular environment or in the meiotic cell cycle in the aging ovary [Crowley et al., 1979; Gaulden, 1992]. However, it remains unknown which, if any, of these models apply. Indeed, until recently it has not been possible even to exclude the idea that the age-dependent increase in trisomy is due to de-

creased likelihood of aborting a trisomic conception [e.g., Ayme and Lippman-Hand, 1982] rather than to an increase in trisomy frequency at conception.

Recently, molecular studies finally have put this last, "relaxed selection," model of the maternal age effect to rest; that is, the model predicts the presence of a maternal age effect in trisomy, regardless of the way in which the extra chromosome originates. However, studies of trisomy 21 [Sherman et al., 1994] and sex chromosome trisomy [MacDonald et al., 1994] indicate a maternal age effect in cases of maternal, but not paternal, origin. Furthermore, in trisomy 18 [Fisher et al., 1995] and trisomy 21 [Antonarakis et al., 1993], those cases consistent with a mitotic origin show no association with increasing maternal age, regardless of the parent of origin of the additional chromosome. Thus, it seems likely that the maternal age effect is restricted to cases involving maternal meiotic nondisjunction.

However, there is less certainty about the relative importance of advanced maternal age on errors at meiosis I and II. In maternally derived sex chromosome trisomy, the increase in maternal age is limited to cases of maternal meiosis I origin [MacDonald et al., 1994]. Similarly, in trisomy 16, a condition thought to be entirely maternal-age dependent [Risch et al., 1986], virtually all cases result from maternal meiosis I nondisjunction [Hassold et al., 1995]. Thus, these studies implicate an age-related effect on maternal meiosis I but not meiosis II. However, in studies of trisomies 18 [Fisher et al., 1995] and 21 [Sherman et al., 1994], there is no significant difference in mean maternal age in cases of maternal meiosis I and maternal meiosis II origin, suggesting that age affects chromosome segregation at both divisions.

Regardless of the relative importance of meiosis I and II errors in generating the age effect, recent studies have identified the first molecular correlate of maternal age-dependent trisomy, namely, reduced recombination. In sex chromosome trisomy [MacDonald et al., 1994] the effect of reduced recombination is most pronounced in the older maternal age categories. Further, in trisomy 16 [Hassold et al., 1995], thought to be entirely maternal age-dependent, reduction in recombination in the proximal regions appears to be an important predisposing factor. Taken together, these observations suggest that with increasing maternal age human oocytes are more likely to nondisjoin because they lack the appropriate number or placement of chiasmata or because the aging ovary is less able to process oocytes with reduced levels of recombination or altered location of exchanges.

SUMMARY AND PERSPECTIVE

Over the past 30 years a great deal of information has accumulated on the incidence of aneuploidy in different types of human pregnancies; on the contribution of aneuploidy to infertility, pregnancy loss, and malformation syndromes; and on the parental source and meiotic stage of origin of aneuploid gametes. However, surprisingly little has been learned about the underlying mechanisms that cause aneuploidy, or the possible effect of environmental insults on the incidence of aneuploidy. Advances in molecular and cytogenetic methodology now make it possible to address many of these issues, which, until recently, were considered intractable. The application of these techniques to the study of human gametes, human trisomic and monosomic conceptions, and mammalian model organisms is only now beginning; nevertheless, by the end of the century it seems likely that we will understand the molecular basis of human nondisjunction, as well as the reason for the well-known association between increasing maternal age and trisomy.

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REFERENCES

Abruzzo MA, Hassold TJ (1995): The etiology of nondisjunction in humans. Environ Mol Mutagen 25(Suppl. 2):38–47.

Angell RR (1995): Mechanisms of chromosome non-disjunction in human oocytes. In Epstein CJ (ed): "Etiology in Pathogenesis of Down Syndrome." New York: Wiley-Liss, pp 13–26.

Angell RR, Hillier SG, West JD, Glasier AF, Rodger MW, Baird DT (1988): Chromosome abnormalities in early human embryos. J Reprod Fertil 36(Suppl):73–81.

Angell RR, Xian J, Keith J, Ledger W, Baird DT (1994): First meiotic division abnormalities in human oocytes: Mechanism of trisomy formation. Cytogenet Cell Genet 65:194–202.

Antonarakis SE, Avramopoulos D, Blouin J-L, Talbot CC Jr, Schinzel AA (1993): Mitotic errors in somatic cells cause trisomy 21 in about 4.5% of cases and are not associated with advanced maternal age. Nature Genet 3:146–150.

Ayme S, Lippman-Hand A (1982): Maternal-age effect in aneuploidy: Does altered embryonic selection play a role? Am J Hum Genet 34:558–565.

Bischoff FZ, Nguyen DD, Burt KJ, Shaffer LG (1994): Estimates of aneuploidy using multicolor fluorescence in situ hybridization on human sperm. Cytogenet Cell Genet 66:237–243.

Bridges CB (1916): Nondisjunction as proof of the chromosome theory of heredity. Genetics 1:1–52, 107–163.

Crowley PH, Gulati DK, Hayden TL, Lopez P, Dyer R (1979): A chiasma-hormonal hypothesis relating Down's syndrome and maternal age. Nature 280:417–418.

Fisher JM, Harvey JF, Morton NE, Jacobs PA (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.

Gaulden ME (1992): Maternal age effect: The enigma of Down syndrome and other trisomic conditions. Mutat Res 296:69–88.

Griffin D, Abruzzo M, Millie E, Sheean L, Sherman S, Hassold T (1995): Non-disjunction studies of human sperm: Evidence for a paternal age effect on trisomy. Hum Mol Genet 4:2227–2232.

Han TL, Webb G, Flaherty S, Correll A, Matthews C, Ford J (1992):

Detection of chromosome 17- and X-bearing human spermatozoa using fluorescence in situ hybridization. Mol Reprod Dev 33: 189–194.

Hassold T (1986): Chromosome abnormalities in human reproductive wastage. Trends Genet 2:105–110.

Hassold T, Jacobs PA (1984): Trisomy in man. Annu Rev Genet 18:69–97.

Hassold T, Sherman SL, Pettay D, Page DC, Jacobs PA (1991): XY chromosome nondisjunction in man is associated with diminished recombination in the pseudoautosomal region. Am J Hum Genet 49:253–260.

Hassold T, Pettay D, Robinson A, Uchida I (1992): Molecular studies of parental origin and mosaicism in 45,X conceptases. Hum Genet 89:647–652.

Hassold T, Merrill M, Adkins K, Freeman S, Sherman S (1995): Recombination and maternal-age dependent non-disjunction: Molecular studies of trisomy 16. Am J Hum Genet 57:867–874.

Hawley RS, McKim K, Arbel T (1993): Meiotic segregation in *Drosophila melanogaster* females: Molecules, mechanisms and myths. Annu Rev Genet 27:281–317.

Hawley RS, Frazier J, Rasooly R (1994): Separation anxiety: The biology of non-disjunction in flies and people. Hum Mol Genet 3:1521–1528.

Henderson SA, Edwards RG (1968): Chiasma frequency and maternal age in mammals. Nature 218:22–28.

Jacobs PA (1992): The chromosome complement of human gametes. Oxford Rev Reprod Biol 14:48–72.

Jacobs PA, Hassold T, Harvey J, May K (1989): The origin of sex chromosome aneuploidy. In Hassold TJ, Epstein CJ (eds): "Molecular and Cytogenetic Studies of Non-Disjunction." New York: Alan R. Liss, pp 135–152.

Jamieson ME, Coutts J, Connor JM (1994): The chromosome constitution of human preimplantation embryos fertilized in vitro. Hum Reprod 9:709–715.

MacDonald M, Hassold T, Harvey J, Wang LH, Morton NE, Jacobs P (1994): The origin of 47, XXY and 47, XXX aneuploidy: Heterogeneous mechanisms and role of aberrant recombination. Hum Mol Genet 3:1365–1371.

Mascari MJ, Ladda RL, Woodage T, Trent RJ, Lai LW, Erickson RP, Cassidy SB, Petersen MB, Mikkelsen M, Driscoll DJ, Nicholls RD, Rogan PK (1993): Perturbed recombination of chromosome 15 in Prader-Willi patients with maternal disomy. Am J Hum Genet 53(Suppl):260.

Penrose LS (1933): The relative effects of paternal and maternal age in mongolism. J Genet 27:219–224.

Peterson MB, Antonarakis SE, Hassold TJ, Freeman SB, Sherman SL, Mikelsen M (1993): Paternal nondisjunction in trisomy 21. Hum Mol Genet 2:1691–1695.

Risch N, Stein Z, Kline J, Warburton D (1986): The relationship between maternal age and chromosome size in autosomal trisomy. Am J Hum Genet 39:68–78.

Robinson WP, Bernasconi F, Mutirangura A, Ledbetter DH, Langlois S, Malcolm S, Morris MA, Schinzel AA (1993): Nondisjunction of chromosome 15: Origin and recombination. Am J Hum Genet 53:740–751.

Rockmill B, Roeder GS (1994): The yeast *med 1* mutant undergoes both meiotic homolog nondisjunction and precocious separation of sister chromatids. Genetics 136:65–74.

Schmitt K, Lazzeroni LC, Foote S, Vollrath D, Fisher E, Goradia TM, Lange K, Page DC, Arnheim N (1994): Multipoint linkage map of the human pseudoautosomal region, based on single-sperm typing: Do double crossovers occur during male meiosis? Am J Hum Genet 55:423–430.

Sherman SL, Takaesu N, Freeman SB, Grantham M, Phillips C, Blackston RD, Jacobs PA, Cockwell AE, Freeman V, Uchida I, Mikkelsen M, Kurnit DM, Buraczynska M, Keats BJB, Hassold TJ (1991): Trisomy 21: Association between reduced recombination and non-disjunction. Am J Hum Genet 49:608–620.

Sherman SL, Petersen MB, Freeman SB, Hersey J, Pettay D, Taft L, Frantzen M, Mikkelsen M, Hassold TJ (1994): Nondisjunction of chromosome 21 in maternal meiosis I: Evidence for a maternal-age dependent mechanism involving reduced recombination. Hum Mol Genet 3:1529–1535.

Spriggs E, Rademaker A, Martin RH (1995): Aneuploidy in human sperm: Results of two- and three-colour fluorescence in situ hybridization using centromeric probes for chromosomes 1, 12, 15, 18, X, and Y. Cytogenet Cell Genet 71:47–53.

Warburton D (1989): The effect of maternal age on the frequency of trisomy: Change in meiosis or in utero selection? In Hassold TJ, Epstein CJ (eds): "Molecular and Cytogenetic Studies of Non-Disjunction." New York: Alan R. Liss, pp 165–181.

Warren AC, Chakravarti A, Wong C, Slaugenhaupt SA, Halloran SL, Watkins PC, Metaxotou C, et al. (1987): Evidence for reduced recombination on the nondisjoined chromosomes 21 in Down syndrome. Science 237:652–654.

Williams BJ, Ballenger CA, Malter HE, Bishop F, Tucker M, Zwingman TA, Hassold TJ (1993): Nondisjunction in human sperm: Results of fluorescence in situ hybridization studies using two and three probes. Hum Mol Genet 2:1929–1936.

Wyrobek AJ, Robbins WA, Tang C, Kobayashi A, Baulch J, Weier HU, Pinkel D (1993): Hierarchial organization of human sperm chromatin is a critical factor in the detection of chromosomal aneuploidy by fluorescence in situ hybridization. Am J Hum Genet 53(Suppl):130.

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