Am. J. Hum. Genet. 44:639–645, 1989

The Probability of Detecting the Origin of Nondisjunction of Autosomal Trisomies

Aravinda Chakravarti

Human Genetics Program, University of Pittsburgh, Pittsburgh

Summary

For studying the biology of autosomal trisomies it is necessary to establish the parental origin and meiotic stage of nondisjunction by using genetic markers. Theoretical formulas are obtained for calculating the probability of establishing (1) parental origin and meiotic stage of nondisjunction by using a centromeric marker, (2) parental origin of nondisjunction by using a noncentromeric marker, and (3) meiotic stage, given parental origin of nondisjunction. These theoretical calculations demonstrate that parental origin of nondisjunction can be identified with virtual certainty by utilizing multiple genetic markers along a chromosome arm. Centromeric markers are by themselves inefficient for determining meiotic stage of the error, but the efficiency can be considerably increased if parental origin is known with certainty. Even then, multiple centromeric markers may be necessary.

Introduction

The vast majority of autosomal trisomies result from primary meiotic nondisjunction (NDJ) in germ cells (Therman 1986). The NDJ events leading to trisomy can occur in either the male or female parent and at either meiosis I (MI) or meiosis II (MII). For several autosomal trisomies, studied among spontaneous abortuses or live births, cytogenetic heteromorphisms have been used to establish the parental origin and meiotic stage of NDJ of the extra chromosome (Hassold et al. 1984). However, chromosomal heteromorphisms are informative in only 30%–60% of cases. These data have nevertheless been useful for estimating the probabilities of the four types of meiotic errors and for studying the natural history of NDJ (Jacobs and Morton 1977; Hassold and Jacobs 1984). For determining the origin of NDJ, chromosomal heteromorphisms located either at the centromere or in the pericentromeric region of the short or long arm of the relevant autosome are needed. In principle, any genetic marker completely linked to the centromere is useful for determining both parental origin and the meiotic stage of NDJ. However, only the parental origin of NDJ may be detected with a marker locus that recombines with the centromere.

It is clear that parental alleles at the marker locus studied must be distinguishable to detect the origin of NDJ. Thus, the efficiency of a marker locus in these studies is related to its degree of polymorphism, with efficiency increasing as a function of increasing heterozygosity. For these studies, DNA polymorphisms are the most useful markers for two reasons: first, highly RFLPs have been identified on each human chromosome (Willard et al. 1985) and, second, unlike biochemical or serological markers, the duplication of a specific parental allele in the trisomy can be uniquely identified even for a two-allele polymorphism (Davies et al. 1984; Stewart 1984; Antonarakis et al. 1985; Stewart et al. 1985). For centromeric markers, one may use cytogenetic variants (Jacobs 1977), unique-sequence probes to the pericentromeric regions (Stewart et al. 1988), or chromosome-specific alpha-satellite DNA probes (Willard et al. 1986). For noncentromeric markers, any DNA polymorphism is useful, but the highly polymorphic variable-number-of-tandem-repeat (VNTR) polymorphisms (Nakamura et al. 1987) are the most informative.

In the present paper I provide theoretical formulas

Received November 11, 1988; revision received December 27, 1988.

Address for correspondence and reprints: Dr. Aravinda Chakravarti, Room A310, Crabtree Hall, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261.

0002-9297/89/4405-0003$02.00

for predicting the informativeness of a genetic marker for detecting the origin of NDJ. Specifically, I calculate both the probability P(cen) of establishing parental origin and meiotic stage of NDJ by using a centromeric marker and the probability P(par) of establishing parental origin by using a noncentromeric marker. I also study the increase in efficiency obtained in identifying meiotic stage of NDJ, given parental origin, by using the probability P(cen|par). Langenbeck et al. (1976) were the first to provide formulas for P(cen) separately for MI and MII errors. These authors demonstrated the bias in favor of detecting MII errors, but they assumed that all gametic products from meiosis errors are equally likely. Current data (Hassold and Jacobs 1984) do not lend support to such an assumption. More recently, Stewart (1984) and Rudd et al. (1988) have provided approximate formulas for P(par) for a two-allele genetic marker.

Methods and Results

The probability with which the origin of NDJ can be established depends on the parental mating types at a genetic marker locus. Consider an autosomal locus with n codominant alleles $A_1, A_2, \ldots, A_n$ and allele frequencies $x_1, x_2, \ldots, x_n$ ($\sum_{i=1}^{n} x_i = 1$), respectively. When four or more alleles ($n \geq 4$) can be distinguished, the parental mating types can be classified into seven different classes as given in table 1. This classification results from each parent in the mating being homozygous or heterozygous and from each mating segregating for one, two, three, or four distinct alleles. Each of the seven mating types represents a prototypic class of matings of similar but not identical genotypes, and they are represented by allele indexes i, j, k, l, where $i, j, k, l = 1, 2, \ldots, n$ with the constraint $i \neq j \neq k \neq l$. The population frequency of a specific mating type within each of the seven classes is calculated under random mating and is presented in the column termed "typical" in table 1. For obtaining the frequency of all matings within each of the seven classes, the typical frequency is summed over the indexes i or $i \neq j$ or $i \neq j \neq k$ or $i \neq j \neq k \neq l$ as relevant and is presented in table 1 in the column termed "total." For example, mating type 3 ($A_iA_i \times A_iA_j$) represents all matings, between a homozygote and a heterozygote, in which the heterozygote has one allele in common with the homozygote; thus $i \neq j$ is the only restriction. The typical frequency of this mating, given specific values of $i \neq j$, is clearly $4x_i^3x_j$, since the four matings $A_iA_i \times A_iA_j$, $A_iA_i \times A_jA_i$, $A_iA_j \times A_iA_i$, and $A_jA_i \times A_iA_i$ are to be considered. The total frequency is obtained by summing $4x_i^3x_j$ under the condition $i \neq j = 1, 2, \ldots, n$. To simplify later results, the seven mating-type total frequencies ($f_1, f_2, \ldots, f_7$) have been expressed in terms of gene frequency moments $a_r = \sum_{i=1}^{n} x_i^r$, where $r = 1, 2, 3, 4$. Comparison of the typical frequencies shows that $f_5 = 2f_2$ and that $f_6 = 2f_4$. Also, as expected, $f_1 + f_2 + \ldots + f_7 = 1$.

Each parental mating type can produce a variety of genotypes of the trisomic offspring, depending on whether NDJ occurred at MI or at MII; whether NDJ occurred in the male or female parent; and whether the marker locus is centromeric or not. In table 2 I

Table 1

Mating Types and Their Frequencies at an Autosomal Codominant Locus

Mating Type[a]	Frequency	
	Typical	Total
$A_iA_i \times A_iA_i$	x_i^4	$f_1 = a_4$
$A_iA_i \times A_jA_j$	$x_i^2x_j^2$	$f_2 = a_2^2 - a_4$
$A_iA_i \times A_iA_j$	$4x_i^3x_j$	$f_3 = 4(a_3 - a_4)$
$A_iA_i \times A_jA_k$	$2x_i^2x_j$-	
	x_k	$f_4 = 2[a_2(1-a_2) - 2(a_3 - a_4)]$
$A_iA_j \times A_iA_j$	$2x_i^2x_j^2$	$f_5 = 2f_2$
$A_iA_j \times A_iA_k$	$4x_i^2x_j$-	
	x_k	$f_6 = 2f_4$
$A_iA_j \times A_kA_l$	$x_ix_jx_kx_l$	$f_7 = 1 - 6a_2 + 8a_3 - 6a_4 + 3a_2^2$

[a] A_i is the ith allele ($i = 1,2,\ldots,n$) with frequency x_i; $a_r = \sum_{i=1}^{n} x_i^r$ ($r = 1,2,3,4$); i, j, k, l are labels for distinct alleles, where $i, j, k, l = 1, 2, \ldots, n$ and where $i \neq j \neq k \neq l$.

Table 2

Parental Mating Types, Their Trisomic Offspring, and the Probability of Detecting the Origin of NDJ

Genotypes of					
Father	Mother	Trisomy	P (cen)	P (par)	P (cen|par)
A_iA_i	A_iA_i	$A_iA_iA_i$	0	0	0
A_iA_i	A_jA_j	$A_iA_iA_j$	0	u_1+u_2	0
		$A_iA_jA_j$	0	u_3+u_4	0
A_iA_j	A_iA_j	$A_iA_iA_i, A_jA_jA_j$	0	0	$(u_2+u_4)/2$
		$A_iA_iA_j, A_iA_jA_j$	0	0	0
A_iA_j	A_iA_i	$A_iA_iA_i$	0	0	$u_2/2$
		$A_iA_iA_j$	0	0	u_1
		$A_iA_jA_j$	$u_2/2$	$(1-\alpha)(u_1+u_2)/2$	$u_2/2$
A_iA_i	A_iA_j	$A_iA_iA_i$	0	0	$u_4/2$
		$A_iA_iA_j$	0	0	u_3
		$A_iA_jA_j$	$u_4/2$	$(1-\beta)(u_3+u_4)/2$	$u_4/2$
A_jA_k	A_iA_i	$A_iA_jA_j, A_iA_kA_k$	u_2	$(1-\alpha)(u_1+u_2)$	u_2
		$A_iA_iA_j, A_iA_iA_k$	0	u_3+u_4	0
		$A_iA_jA_k$	u_1	$\alpha(u_1+u_2)$	u_1
A_iA_i	A_jA_k	$A_iA_jA_j, A_iA_kA_k$	u_4	$(1-\beta)(u_3+u_4)$	u_4
		$A_iA_iA_j, A_iA_iA_k$	0	u_1+u_2	0
		$A_iA_jA_k$	u_3	$\beta(u_3+u_4)$	u_3
A_iA_j	A_iA_k	$A_iA_iA_j$	0	0	$u_1/2+u_4/4$
		$A_iA_jA_j, A_jA_jA_k$	$u_2/2$	$(1-\alpha)(u_1+u_2)/2$	$u_2/2$
		$A_iA_jA_k$	0	0	$(u_1+u_3)/2$
		$A_iA_kA_k, A_jA_kA_k$	$u_4/2$	$(1-\beta)(u_3+u_4)/2$	$u_4/2$
		$A_iA_iA_i$	0	0	$(u_2+u_4)/4$
		$A_iA_iA_k$	0	0	$u_2/4+u_3/2$
A_iA_j	A_kA_l	$A_iA_jA_k, A_iA_jA_l$	u_1	$\alpha(u_1+u_2)$	u_1
		$A_iA_kA_l, A_jA_kA_l$	u_3	$\beta(u_3+u_4)$	u_3
		A_iA_i-, A_jA_j-	u_2	$(1-\alpha)(u_1+u_2)$	u_2
		$-A_kA_k, -A_lA_l$	u_4	$(1-\beta)(u_3+u_4)$	u_4

NOTE.—$A_1, A_2, \ldots, A_n$ are alleles at an autosomal codominant locus; $i \neq j \neq k \neq l$; u_1, u_2, u_3 and u_4 are probabilities of paternal MI, paternal MII, maternal MI, and maternal MII NDJ, respectively; α and β are as defined in eq. (4) in the text.

enumerate all such trisomic offspring genotypes. Let u_1, u_2, u_3, and u_4 denote the probability of paternal MI, paternal MII, maternal MI, and maternal MII NDJ events, respectively, where $u_1 + u_2 + u_3 + u_4 = 1$. Thus, the probabilities of paternal and maternal NDJ events are $u_1 + u_2$ and $u_3 + u_4$, respectively; the probabilities of MI and MII NDJ events are $u_1 + u_3$ and $u_2 + u_4$, respectively. Maximum likelihood estimates of u_i ($i = 1, \ldots, 4$) for some autosomal trisomies, as estimated using centromeric cytogenetic heteromorphisms, are given by Hassold and Jacobs (1984).

In the following I calculate the following three types of probabilities of detecting the origin of NDJ: (1) P(cen), (2) P(par), and (3) P(cen|par). Each of these three probabilities is different for each mating type, so that the overall probability is calculated as

$$P = \sum_{i=1}^{9} f_i P_i , \qquad (1)$$

where $P_i = P$(cen), P(par), or P(cen|par) for the ith mating type and where f_i is the total frequency of the ith mating type. The number of mating types in equation (1) and table 2 is nine, rather than the seven listed in table 1, since two matings have been split into their reciprocal types. This is necessary since the genotypes of the father and mother need to be distinguished.

For any given mating type the probability of detection is simply the proportion of trisomic offspring whose genotypes allow unambiguous detection of the origin of NDJ. For calculating P(cen) these probabilities, for a centromeric marker, are derived from the results of either Jacobs and Morton (1977) or Chakravarti and Slaugenhaupt (1987) and are listed in table 2, column 4. These probabilities in Table 2 are provided for each trisomic genotype and are to be added for all trisomic genotypes arising from a specific mating type. Then, using tables 1 and 2, and equation (1), I obtain

$$P(\text{cen}) = (f_4/2+f_7) + (f_3/4+f_6/2)(u_2+u_4)$$
$$= (1-5a_2+2a_2^2+6a_3-4a_4) + [2a_2(1-a_2) - 3(a_3-a_4)](u_2+u_4) . \quad (2)$$

This probability is a maximum when all alleles are equally frequent, $x_i = 1/n$ $(i = 1, 2, \ldots, n)$, when

$$P_{\max}(\text{cen}) = (n - 1)[(n - 2)^2 + (2n - 3)(u_2 + u_4)]/n^3 . \quad (3)$$

Note that $u_2 + u_4$ is the probability of an MII NDJ, which is approximately .2 for trisomy 21 (Hassold and Jacobs 1984). When this value is assumed, $P_{\max}(\text{cen})$ = .025, .119, .234, .333, and .607 for n = 2, 3, 4, 5, and 10 alleles, respectively. Thus, very highly polymorphic marker systems are necessary to establish the meiotic stage of NDJ, since even for a locus with 10 equifrequent alleles this probability is only 61%.

Any centromeric or noncentromeric marker may be used to detect the parental origin of NDJ. Once again, the probabilities of each trisomic genotype are necessary. These probabilities, for a noncentromeric marker locus, were earlier derived by Chakravarti and Slaugenhaupt (1987) and are dependent not only on the NDJ probabilities u_i($i = 1, \ldots, 4$) but also on the location of the marker locus on the chromosome. The location of a marker locus is considered relative to the centromere and in terms of the probability of nonreduction, which is defined as the probability of producing a heterozygous disomic gamete by a heterozygous host. For MI and MII NDJ the probabilities of nonreduction are $\phi = 1 - y/2$ and $\chi = y$, respectively, where y is the tetratype frequency and is related to the gene-centromere map distance w (Chakravarti and Slaugenhaupt 1987). Under complete interference $y = 2w$, and under no interference $y = (2/3)(1 - e^{-3w})$; relationships under various other assumptions regarding interference are summarized by Chakravarti and Slaugenhaupt (1987) and Halloran and Chakravarti (1987). For a noncentromeric marker, the meiotic stage of NDJ cannot be known, and thus the probabilities of nonreduction (heterozygosity) conditional on paternal or maternal NDJ are necessary. These are

$$\alpha = (\phi u_1 + \chi u_2)/(u_1 + u_2) ,$$

and (4)

$$\beta = (\phi u_3 + \chi u_4)/(u_3 + u_4) .$$

These probabilities define the probability of detecting parental origin for each trisomic genotype and are presented in table 2, column 5. Thus, for a given level of interference and a gene-centromere distance of w Morgans, y and subsequently ϕ and χ may be calculated; then α and β and the probabilities in table 2, column 5, may be calculated using equation (4). Once again, using tables 1 and 2 and equation (1), I obtain

$$P(\text{par}) = (f_2 + f_4 + f_7) + (f_3/4 + f_6/2)[(1 - \alpha)(u_1 + u_2) + (1 - \beta)(u_3 + u_4)] ,$$

which reduces to

$$P(\text{par}) = (1 - 4a_2 + 4a_3 - 3a_4 + 2a_2^2) + [2a_2(1 - a_2) - 3(a_3 - a_4)][y + (u_2 + u_4)(2 - 3y)]/2 , \quad (5)$$

where $u_2 + u_4$ is the probability of MII NDJ and where y is the teratype frequency. As discussed by Chakravarti and Slaugenhaupt (1987), y is a linkage parameter and a measure of the gene-centromere distance.

For a simple two-allele polymorphism with minor-allele frequency x, equation (5) reduces to

$$P(\text{par}) = 2x^2(1 - x)^2 + x(1 - x)[1 - 2x(1 - x)][y + (u_2 + u_4)(2 - 3y)]/2 . \quad (6)$$

Recently, Rudd et al. (1988) have calculated P(par) by using the first term only. Also, Stewart (1984) calculated P(par) on the assumption $y = 0$, i.e., by assuming the marker locus is centromeric.

The numerical value of P(par) is a maximum when all alleles are equally frequent, $x_i = 1/n$ $(i = 1, \ldots, n)$, in which case

$$P_{\max}(\text{par}) = (n - 1)\{(n^2 - 3n + 3) + (2n - 3)[y + (u_2 + u_4)(2 - 3y)]/2\}/n^3 . \quad (7)$$

Note that in equations (5) and (7) the location of the marker locus on the chromosome arm is crucial in determining P(par). Also, note that the term $y + (u_2 + u_4)(2 - 3y)$ can be rewritten as $2(u_2 + u_4) + y[1 - 3(u_2 + u_4)]$. Since $u_2 + u_4$ is the probability of an MII error, this implies that (1) if $u_2 + u_4 < 1/3$, then, for any set of gene frequencies at the marker locus, P(par) increases, while (2) if $u_2 + u_4 > 1/3$, then P(par) decreases as the marker locus becomes more telomeric. In order to study the effect of location and polymor-

phism, I present in figure 1 the values of P_{max} (par) for n = 2, 3, 4, and 10 and for marker genes located at varying distances ($\leq$50 cM) from the centromere. We have assumed that the probability of an MII error is .2. Figure 1 also presents the values obtained under no interference (solid lines) and under complete interference (broken lines).

Figure 1 makes it clear that the map location for a marker, as well as chiasma interference, does affect P(par) values but that the effect is not large. However, increasing interference increases P(par) values, as does increasing the distance between the locus and the centromere. Thus, for two marker loci having identical gene frequencies, the more distal marker is more useful for establishing parental origin. Figure 1 also emphasizes the effect of polymorphism. Thus, an equifrequent three-allele polymorphism is 78% more useful than an equifrequent two-allele polymorphism; also, an equifrequent four-allele marker locus is 41% more efficient than an equifrequent three-allele marker locus.

The feature that detection of parental origin depends on the location of the marker locus relative to the centromere is not intuitively clear but may be explained in the following manner: Note that, in table 2, the only situations in which some but not all offspring give evidence for parental origin are mating types $A_iA_i \times A_iA_j$ and $A_iA_j \times A_iA_k$. Since in both mating types parents share one allele in common, parental origin can only be detected when the offspring is homozygous for the unshared marker allele. Since the majority of NDJ events occur at MI, homozygosity will only arise owing to recombination, the probability of which increases as the marker locus becomes more telomeric. However, the opposite will happen if MII errors are common. As discussed above, the critical value which determines whether P(par) increases or decreases is an MII error probability of 1/3. The effect of interference, higher interference giving higher P(par) values, is due to the tetratype frequency being greater under higher interference levels for a fixed map distance. Conversely, if $u_2 + u_4 > 1/3$, then higher interference will give lower P(par) values.

Finally, I consider the problem of establishing the meiotic stage of NDJ by using a centromeric marker when the parental origin is already known from a noncentromeric marker. The calculations are similar to those given above; using tables 1 and 2 (col. 6) and equation (1), I obtain

$$P(\text{cen}|\text{par}) = (1 - a_2 - 2a_2^2 + 2a_4) + (a_2^2 - a_4)(u_2 + u_4), \quad (8)$$

which takes the maximum value when $x_i = 1/n$ (i=1, . . . , n) and is then expressed as

$$P_{max}(\text{cen}|\text{par}) = (n - 1)[(n^2 - 2) + (u_2 + u_4)]/n^3. \quad (9)$$

If, as above, it is assumed that $u_2 + u_4 = .2$, then this maximum value is .275, .533, .666, .742, and .884 for n = 2, 3, 4, 5 and 10, respectively. These values are considerably higher than those obtained using a centromeric marker alone. The values of P_{max}(cen) and P_{max}(cen|par) are graphically compared in figure 2, and clearly demonstrates the increase in efficiency.

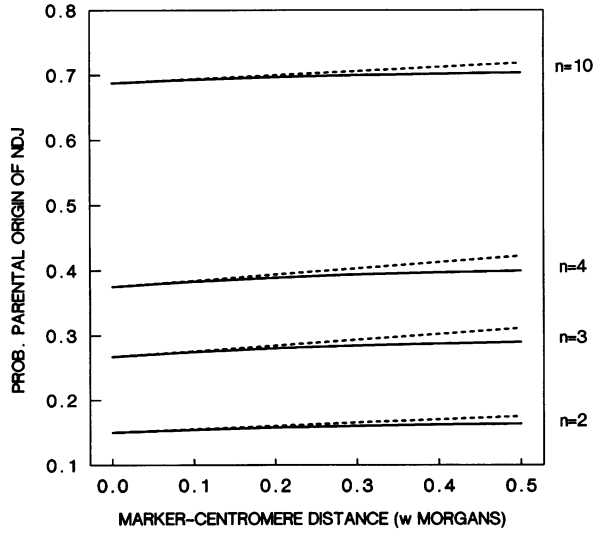

Figure 1 Probability of detecting parental origin of NDJ as a function of location of a marker locus that is w cM away from the centromere. The marker locus has n equally frequent alleles; the broken lines (— — —) and the solid lines (———) refer to calculations assuming complete and no interference, respectively.

Discussion

For any given genetic marker, these theoretical formulas are useful for calculating the probability of detecting the origin of NDJ. Given the availability of a large number of polymorphisms, equation (6) is useful for choosing a set of these markers which will give a high rate of detection. If m noncentromeric markers have been chosen for determination of parental origin, then the total probability of success is

$$P(\text{par}) = 1 - \prod_{j=1}^{m} [1 - P(\text{par } j)],$$

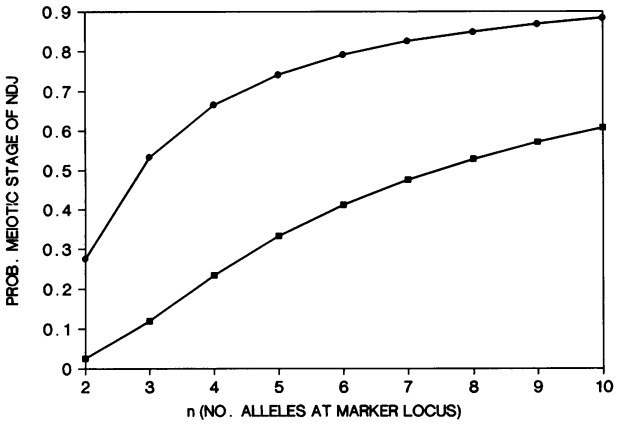

Figure 2 The maximum probability of detecting meiotic stage of NDJ without [P_{max} (cen); ■] and with [P_{max} (cen|par); ●] a noncentromeric marker locus as a function of the number of alleles at the marker locus. The probability of an MII NDJ is assumed to be .2.

where P(par j) is the probability for the jth marker. Stewart et al. (1988) use this formula to predict that approximately 50 DNA polymorphisms will be necessary to obtain ≥98% success, if each locus is successful with probability .073. The probability .073 is provided by a two-allele RFLP with a 20% minor-allele frequency. My calculations (see fig. 2) suggest that the judicious selection of a few RFLPs may lead to ≥98% success. In any case, multiple DNA polymorphisms can lead to detection of parental origin with virtual certainty. My results demonstrate that using centromeric markers to detect meiotic stage of NDJ has low efficiency, since even a equifrequent 10-allele locus is informative only 61% of the time. I have, however, shown that knowledge of parental origin can dramatically increase the efficiency of detecting meiotic stage of NDJ by using a centromeric marker, since the efficiency increases to 88% when an equifrequent 10-allele locus is used. To achieve a higher success rate, multiple centromeric polymorphisms will be necessary. Knowledge of both parental origin and meiotic stage of NDJ are necessary in order to study the biology of NDJ—e.g., the relationship between NDJ and genetic recombination on nondisjoined chromosomes (Hassold et al. 1987; Warren et al. 1987; Stewart et al. 1988).

Acknowledgments

I gratefully acknowledge the comments by Partha Majumder, Sue Slaugenhaupt, and the two referees on an earlier draft. This research was supported by funds from NIH grants GM33771 and RCDA HD00774.

References

Antonarakis, S. E., S. D. Kittur, C. Metaxotou, P. C. Watkins, and A. S. Patel. 1985. Analysis of DNA haplotypes suggests a genetic predisposition to trisomy 21 associated with DNA sequences on chromosome 21. Proc. Natl. Acad. Sci. USA **82**:3360–3364.

Chakravarti, A., and S. A. Slaugenhaupt. 1987. Methods for studying recombination on chromosomes that undergo nondisjunction. Genomics **1**:35–42.

Davies, K. E., K. Harper, D. Bonthron, R. Krumlauf, A. Polkey, M. E. Pembrey, and R. Williamson. 1984. Use of a chromosome 21 cloned DNA probe for the analysis of nondisjunction in Down's syndrome. Hum. Genet. **66**: 54–56.

Halloran, S. L., and A. Chakravarti. 1987. DSLINK: a computer program for gene-centromere linkage analysis in families with a trisomic offspring. Am. J. Hum. Genet. **41**: 350–355.

Hassold, T. J., D. Chiu, and J. Yamane. 1984. Parental origin of autosomal trisomies. Ann. Hum. Genet. **48**:129–144.

Hassold, T. J., and P. A. Jacobs. 1984. Trisomy in man. Annu. Rev. Genet. **18**:69–97.

Hassold, T. J., P. A. Jacobs, M. Leppert, and M. Sheldon. 1987. Cytogenetic and molecular studies of trisomy 13. J. Med. Genet. **24**:725–732.

Jacobs, P. A. 1977. Human chromosome heteromorphisms (variants). Prog. Med. Genet. **2**:252–274.

Jacobs, P. A., and N. E. Morton. 1977. Origin of human trisomics and polyploids. Hum. Hered. **27**:59–72.

Langenbeck, U., I. Hansmann, B. Hinney, and V. Honig. 1976. On the origin of the supernumery chromosome in autosomal trisomies—with special reference to Down's syndrome. Hum. Genet. **33**:89–102.

Nakamura, Y., M. Leppert, P. O'Connell, R. Wolff, T. Holm, M. Culver, C. Martin, E. Fujimoto, M. Hoff, E. Kumlin, and R. White. 1987. Variable numer of tandem repeat (VNTR) markers for human gene mapping. Science **235**: 1616–1622.

Rudd, N. L., L. S. Dimnik, C. Greentree, K. Mendes-Crabb, and D. I. Hoar. 1988. The use of DNA probes to establish parental origin in Down syndrome. Hum. Genet. **78**: 175–178.

Stewart, G. D. 1984. The isolation and characterization of cloned DNA from a chromosome 21 enriched DNA library. Ph.D. thesis, University of Glasgow.

Stewart, G. D., P. Harris, J. Galt, and M. S. Ferguson-Smith. 1985. Cloned DNA probes regionally mapped to human chromosome 21 and their use in determining the origin of nondisjunction. Nucleic Acids Res. **3**:4125–4132.

Stewart, G. D., T. J. Hassold, A. Berg, P. Watkins, R. Tanzi, and D. M. Kurnit. 1988. Trisomy 21 (Down syndrome): studying nondisjunction and meiotic recombination by using cytogenetic and molecular polymorphisms that span chromosome 21. Am. J. Hum. Genet. **42**:227–236.

Therman, E. 1986. Human chromosomes: structure, behavior, effects. Springer, New York.

Warren, A. C., A. Chakravarti, C. Wong, S. A. Slaugenhaupt, S. L. Halloran, P. C. Watkins, C. Metaxotou, and S. E. Antonarakis. 1987. Evidence for reduced recombination on the nondisjoined chromosomes 21 in Down syndrome. Science **237**:652–654.

Willard, H. F., M. H. Skolnick, P. L. Pearson, and J.-L. Mandel. 1985. Human gene mapping by recombinant DNA techniques. Cytogenet. Cell Genet. **40**:360–489.

Willard, H. F., J. S. Waye, M. H. Skolnick, C. E. Schwartz, V. E. Powers, and S. B. England. 1986. Detection of restriction fragment length polymorphisms at the centromeres of human chromosomes by using chromosome-specific satellite DNA probes: implications for development of centromere-based genetic linkage maps. Proc. Natl. Acad. Sci. USA **83**:5611–5615.