18. Observations over distances greater than 2 m were difficult because of the rapid flight speed, small size, and dark coloration of the insects.
19. Most recently championed by Bradshaw, Baker, and Lisk (*7*) and P. E. Howse, J. C. Lisk, and J. W. S. Bradshaw [in *Mechanisms in Insect Olfaction*, T. L. Payne, M. C. Birch, C. E. J. Kennedy, Eds. (Oxford Univ. Press, Oxford, 1986), pp. 157–162].
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Evidence for Reduced Recombination on the Nondisjoined Chromosomes 21 in Down Syndrome

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Trisomy 21 usually results from nondisjunction during meiosis I. In order to determine whether nondisjunction results from failure of normal chromosome pairing or premature unpairing, recombination frequencies were estimated between DNA polymorphic markers on the long arm of chromosome 21 in families containing one individual with trisomy 21. The recombination frequencies on chromosomes 21 that had undergone nondisjunction were then compared to those on chromosomes 21 that had disjoined normally. The data indicate that recombination is reduced between DNA markers on nondisjoined chromosomes 21. These results are consistent with the hypothesis that reduced chiasma formation predisposes to nondisjunction, resulting in trisomy 21 in humans.

TRISOMY 21 RESULTS FROM CHROMOSOME nondisjunction, which occurs most frequently in maternal meiosis I (*1*). Studies in other species, most notably *Drosophila*, have demonstrated reduced recombination frequencies on chromosomes undergoing nondisjunction during meiosis (*2*). We have estimated the frequency of recombination between loci identified by DNA polymorphisms on human chromosomes 21 that have undergone nondisjunction. These frequencies were compared with the estimated frequencies of recombination between the same DNA loci (i) on chromosomes 21 from normal control families and (ii) on chromosomes 21 that disjoin normally in the families containing one individual with trisomy 21. These comparisons demonstrate that recombination is significantly reduced on chromosomes 21 that have undergone nondisjunction.

Nondisjunction of chromosomes occurs commonly during meiosis, and the resultant aneuploidies cause significant human morbidity and mortality. Trisomies occur in approximately 4% of clinically recognized pregnancies and trisomy 21 occurs in approximately 0.1% of live births and 0.5% of all conceptions (*3*). Trisomy 21 (Down syndrome) is the commonest known genetic cause of mental retardation (*3*). Nondisjunction of chromosome 21 is strongly influenced by maternal age (*3, 4*).

The following hypotheses have been proposed (*5*) to account for the abnormal segregation of chromosome 21 leading to Down syndrome in humans: nondisjunction results from (i) asynapsis (failure of normal pairing of the homologous chromosomes at meiosis I) or (ii) desynapsis (premature unpairing of the homologous chromosomes after normal pairing). Theoretically, asynapsis during meiosis will lead to absence of recombination, whereas desynapsis will lead to normal recombination on the homologous chromosomes undergoing nondisjunction. In this study, we tested these hypotheses by comparing linkage maps of chromosomes 21 that had disjoined normally and chromosomes 21 that had undergone nondisjunction.

A linkage map of human chromosome 21 was constructed with DNA polymorphisms adjacent to several single-copy DNA fragments derived from human chromosome 21. The recombination values obtained between pairs of DNA markers are shown in Table 1.

The DNA markers D21S1 and D21S11 are closely linked; no recombinants were observed in over 135 meioses (*6, 7*). These two markers were thus treated as a single locus in subsequent analyses. Similarly, the DNA markers D21S3 and D21S23 are closely linked; one recombinant has been observed in 23 meioses [this study and (*7*)]. The estimated recombination value is $\hat{\theta} = 0.04$ (LOD score $\hat{Z} = 5.14$). Thus, D21S3 and D21S23 were also treated as one locus in subsequent analyses.

Multilocus linkage analysis by the computer program package Linkage reveals that the most probable location of CW21pc is proximal to D21S13 (Table 2). The locus CW21pc thus appears to be close to the centromere, as D21S13 maps proximal to a breakpoint in band q21 (*8*). The linkage map of chromosome 21q in control families is illustrated in Fig. 1.

The linkage map of chromosomes 21 from normal families was compared with the linkage map of human chromosomes 21 that have nondisjoined. Nondisjoined chromosomes were identified in informative fam-

Table 1. Values for recombination between polymorphic DNA markers on chromosome 21 presented with LOD scores. Tests of linkage in the control families were performed with the maximum likelihood LOD score method of Morton (*23*) and the computer program Liped (*24*). For each LOD table, the maximum likelihood estimate $\hat{\theta}$ and the maximum LOD score $\hat{Z}$ were computed with the interpolation formulas of Rao *et al.* (*25*). The 95% confidence limits on the recombination value were computed by the method of Buetow *et al.* (*26*).

Locus pair	$\hat{\theta}$	$\hat{Z}$	95% confidence limits
CW21pc-D21S13	0.14	2.05	0.01–0.27
CW21pc-D21S1/D21S11	0.17	3.87	0.09–0.25
D21S13-D21S1/D21S11	0.17	2.51	0.07–0.27
D21S1/D21S11-SOD1	0.08	4.96	0.00–0.19

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ilies by studying the inheritance of the parents' DNA polymorphism markers by the child with Down syndrome. Any marker on chromosome 21 may identify the parent of origin of nondisjunction. A pericentromeric marker, such as CW21pc, may in addition identify the stage of meiosis at which nondisjunction occurred. Thirty-four Greek families, each containing one offspring with trisomy 21 and at least one other normal sibling, were examined with the polymorphic DNA markers on chromosome 21. We were able to identify the parent of origin or the stage of the meiotic error (or both) in all but 9 of the 34 families. The meiotic error occurred in 22 mothers and 3 fathers. Using the pericentromeric marker CW21pc, we identified nine errors of maternal meiosis I and one error of maternal meiosis II.

To determine the frequency of recombination on chromosomes 21 that have undergone nondisjunction, we estimated the parameter y, which is a measure of the probability of heterozygosity of a marker in the disomic gamete transmitted to the child with Down syndrome. The parameter y is dependent on the stage of meiotic error and can be related to the recombination value (θ) between the centromere and the marker locus. For complete linkage of a marker to the centromere ($\theta = 0$) $y = 0$, and for no linkage to the centromere ($\theta = 0.5$) $y = 0.67$ (*9–12*). For chromosome 21 the assumption of complete interference is appropriate as there is on average only 1.06 chiasmata per chromosome 21 per meiosis (*13*); then, $y = 2\theta$ (*10, 11*). The parameter y was estimated for each marker on chromosomes undergoing nondisjunction in the 34 families (*10*). Table 3 shows the maximum likelihood estimate of y for each marker together with the corresponding LOD score for linkage between the marker and the centromere; the LOD score was calculated with the null hypothesis of no linkage to the centromere ($y = 0.67$). Initially, we estimated y as zero at the maximum LOD score ($\hat{Z} = 1.35$) for the marker CW21pc, representing a significant linkage ($\chi^2 = 6.23$, 1 df, $P = 0.013$). Thus CW21pc may be used as a pericentromeric marker. The CW21pc genotypes were therefore used to calculate the probability of paternal, maternal, meiosis I, and meiosis II errors in each family (*10*). The parameter y was then estimated for each marker locus in the 34 families and separately for the 9 families with maternal meiosis I nondisjunction (Table 3).

The data suggest that crossing-over is reduced on chromosomes 21 that have nondisjoined. For the markers D21S13, D21S1/D21S11, and D21S3/D21S23, the estimated values of y were 0.00, 0.00, and 0.05, respectively, whereas from the normal map these values would be expected to be approximately 0.28, 0.34, and 0.67, respectively. The latter values were calculated by using $y = 2\theta$ from the θ values obtained from the normal map (Table 1).

In the families with an offspring with trisomy 21, values for the frequency of recombination between the centromere and the marker loci can also be directly compared for chromosomes 21 that underwent nondisjunction (θ_T) and chromosomes 21 that segregated normally (θ_c) (Table 4). The latter chromosomes include chromosomes 21 in normal children as well as the single chromosome 21 in the children with trisomy 21 that was inherited from the parent in whom nondisjunction did not occur. The data suggest that recombination is reduced only on the nondisjoined chromosomes 21 in these families, as the $\hat{\theta}_c$ values were not

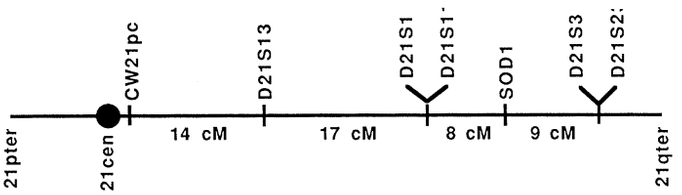

Fig. 1. Linkage map of chromosome 21q. Linkage analysis was performed on a total of 50 Caucasian control families from different ethnic backgrounds (two or three generations). The following cloned Eco RI genomic DNA fragments were used as probes: pPW228C (1.5 kb, detecting locus D21S1), pPW236B (1.85 kb, detecting locus D21S11), pPW231C (2.1 kb, detecting locus D21S3), pPW244D (0.95 kb, detecting locus D21S23); [all cloned in pBR328 (*30*)]; and D21K9 (9 kb, detecting locus D21S13) cloned in phage λ (*31*). These DNA fragments map to the long arm of chromosome 21 and are present in single copy. More specifically, D21S1 and D21S11 map to 21q11.2-21q21 (*32*), D21S13 maps to 21q proximal to a breakpoint in band 21q21 (*8*), and D21S3 maps to 21q22.3 (*33*). We also used as probes genomic and complementary DNA (cDNA) fragments of the superoxide dismutase gene (*SOD1*) (*34*) which map to 21q22.1 (*35*), and a genomic Pvu II–Sph I fragment CW21pc (0.65 kb) cloned in M13. Locus CW21pc is present in single copy in humans and was cloned from the junction fragment of a ring chromosome 21; the long arm breakpoint of this ring chromosome 21 has been assigned to DNA fragment DS21S3 at 21q22.3, and the proximal breakpoint to the pericentromeric region of the long arm of chromosome 21 (*36*). The polymorphic DNA fragments produced by digestion with restriction enzymes and detected by these probes are described elsewhere (*22, 36*). Digestion with restriction endonucleases, electrophoresis of DNA fragments, transfer of the fragments to nitrocellulose filters, hybridization, washing, and autoradiography of filters were performed as described (*37*).

Table 2. Multilocus mapping of CW21pc relative to D21S13, D21S1/D21S11, SOD1, and D21S3/D21S23. Multilocus linkage analysis was performed with the computer program package Linkage (*27*). For this analysis the positions of several loci were assigned on a map distance (centimorgan) scale by means of the Haldane mapping function (no interference) (*28*). By varying the location of one locus at a time and by computing the likelihood of the joint segregation of multiple markers, the relative odds for various gene orders were computed by comparing the likelihoods (location scores) directly. The maximum likelihood locations from the most likely gene order were then transformed into recombination values with Haldane's map function. For the three-point analysis (data from 45 families), the recombination value between D21S13 and D21S1/D21S11 was fixed at $\hat{\theta} = 0.17$ and the most probable location of CW21pc was estimated to be proximal to D21S13. For the four-point analyses (data from 28 families), the recombination fraction between D21S1/D21S11 and SOD1 in the first four-point analysis was fixed at $\hat{\theta} = 0.08$, and that between D21S3/D21S23 and SOD1 in the second four-point analysis was fixed at $\hat{\theta} = 0.09$. The most probable location of CW21pc is proximal to D21S1/D21S11.

Presumed locus order	Location score	Relative odds	LOD score
Three-point analysis			
CW21pc-D21S13-D21S1/D21S11	18.50	12.7	4.02
D21S13-CW21pc-D21S1/D21S11	13.42	1.0	2.91
D21S13-D21S1/D21S11-CW21pc	17.58	8.0	3.82
Four-point analysis			
CW21pc-D21S13-D21S1/D21S11-SOD1	16.31	1085.7	3.54
D21S13-CW21pc-D21S1/D21S11-SOD1	13.33	301.0	2.89
D21S13-D21S1/D21S11-CW21pc-SOD1	2.66	1.0	0.58
D21S13-D21S1/D21S11-SOD1-CW21pc	14.46	495.0	3.13
Four-point analysis			
CW21pc-D21S1/D21S11-SOD1-D21S3/D21S23	16.95	1124.0	3.68
D21S1/D21S11-CW21pc-SOD1-D21S3/D21S23	2.90	1.0	0.63
D21S1/D21S11-SOD1-CW21pc-D21S3/D21S23	8.63	17.6	1.87
D21S1/D21S11-SOD1-D21S3/D21S23-CW21pc	5.24	5.0	1.14

Table 3. Map distance from the centromere of the displayed DNA markers on chromosomes 21 participating in nondisjunction in 34 Greek families containing an offspring with trisomy 21. In each family, DNA samples from father, mother, trisomy 21 offspring, and at least one unaffected sibling were examined. All samples were collected in the cytogenetics division of the Agia Sophia Children's Hospital of Athens Medical School. Each sample was digested with the appropriate enzyme that detects a DNA polymorphism with each particular probe. In the individual with trisomy 21, the differences in the intensity of the hybridizing allelic fragments on autoradiographs permitted the identification of the three chromosome 21 alleles per locus. In this manner, the DNA polymorphisms at CW21pc, D21S13, D21S1/D21S11, and D21S3/D21S23 were analyzed (*22*). The parameter y was estimated by the method of maximum likelihood. When the origin of nondisjunction is known one can calculate the likelihood of the genotype of a trisomy 21 offspring given the parental genotypes by using the probabilities of each type of meiotic error. When the origin of nondisjunction is not known, the likelihood is calculated as a weighted average, weighted by the probabilities of each meiotic error. These probabilities, as estimated by Hassold and Jacobs (*3*), are paternal I, 0.13; paternal II, 0.07; maternal I, 0.67; and maternal II, 0.13. We present our results as a LOD score, $Z(y) = \log_{10}[L(y)/L(0.67)]$ where $L(y)$ is the likelihood function for all families. A detailed description of these new methods is provided (*10*). The LOD score calculations are performed by the computer program Cenmap (*10*).

Loci	Trisomy 21 (n = 34 families)		Meiosis I error (n = 9 families)	
	$\hat{y}$	$\hat{Z}$	$\hat{y}$	$\hat{Z}$
21cen to CW21pc	0.00	1.352		
21cen to D21S13	0.00	0.935	0.00	0.432
21cen to D21S1/D21S11	0.00	1.873	0.00	0.687
21cen to D21S3/D21S23	0.05	1.709	0.00	1.215

Table 4. Estimation of the recombination fraction between DNA markers on chromosomes 21 that undergo nondisjunction ($\hat{\theta}_T$) and those that disjoin normally ($\hat{\theta}_c$). The method described in Table 3 to calculate values of y on chromosomes 21 that participate in nondisjunction was extended to calculate θ on chromosomes 21 that did not participate in nondisjunction in these families. These include chromosomes inherited by the normal children and the one chromosome inherited by the child with Down syndrome that did not undergo nondisjunction. The LOD score is $Z(\theta,y) = \log_{10}[L(\theta,y)/L(0.5,0.67)]$. The calculations are performed by the computer program Dslink (*29*). The χ^2 test was performed to test $\theta_T = \theta_c$ versus $\theta_T < \theta_c$.

Marker locus	$\hat{\theta}_T$	$\hat{\theta}_c$	$\hat{Z}$ (θ_T, θ_c)	χ^2	P-value
CW21pc-D21S13	0.00	0.30	1.23	0.61	0.22
CW21pc-D21S1/D21S11	0.00	0.20	2.67	3.01	0.04
CW21pc-D21S3/D21S23	0.00	0.25	1.95	2.92	0.04

significantly different from those obtained in control families.

These results suggest that asynapsis of the parental homologous chromosomes, rather than premature or delayed desynapsis, is an etiologic factor in nondisjunction, resulting in trisomy 21 in humans. Similar findings have been reported in aneuploid conditions in other species, such as *Drosophila* (*14*) and mice (*15*).

It is unclear whether frequencies of nondisjunction, chiasmata formation, or recombination are genetically determined in humans as they are in *Drosophila* (*2*) and other organisms (*16*). In *Drosophila*, mutations at 24 loci have been described that disrupt recombination or segregation of all chromosome pairs during meiosis; these mutations may therefore affect a general control of recombination or disjunction. Mutants deficient in recombination have increased frequencies of nondisjunction of all chromosome pairs (*2*). There is only suggestive evidence for such genetic control of recombination or disjunction in mammals. For example, strain-specific differences in the age dependency of nondisjunction have been described in mice (*17*). In humans, trisomic spontaneous abortions tend to recur in some women (*18*), and relatives of a proband with trisomy 21 appear to have a slightly increased risk of having a child with Down syndrome (*19*). Similarly, several different trisomic conditions sometimes occur in related family members (*20*). Individuals with Down syndrome may have an increased prevalence of other aneuploid conditions, such as Klinefelter syndrome (XXY) (*21*). Finally, a haplotype of DNA polymorphisms on chromosome 21 has been described that may occur more frequently in individuals with Down syndrome (*22*).

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