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A Genetic Linkage Map of Human Chromosome 21: Analysis of Recombination as a Function of Sex and Age

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Summary

A genetic linkage map of human chromosome 21 has been constructed using 22 anonymous DNA markers and five complementary DNAs (cDNAs) encoding the amyloid β protein precursor (*APP*), superoxide dismutase 1 (*SOD1*), the *ets*-2 proto-oncogene (*ETS2*), the estrogen inducible breast cancer locus ((*BCEI*), and the leukocyte antigen, CD18 (*CD18*). Segregation of RFLPs detected by these DNA markers was traced in the Venezuelan Reference Pedigree (VRP). A comprehensive genetic linkage map consisting of the 27 DNA markers spans 102 cM on the long arm of chromosome 21. We have confirmed our initial findings of a dramatically increased rate of recombination at the telomere in both females and males and of significantly higher recombination in females in the pericentromeric region. By comparing patterns of recombination in specific regions of chromosome 21 with regard to both parental sex and age, we have now identified a statistically significant downward trend in the frequency of crossovers in the most telomeric portion of chromosome 21 with increasing maternal age. A less significant decrease in recombination with increasing maternal age was observed in the pericentromeric region of the chromosome. These results may help in ultimately understanding the physical relationship between recombination and nondisjunction in the occurrence of trisomy 21.

Introduction

Chromosome 21 has become one of the major focal points of molecular human genetics, both because of its small size, making it amenable to complete mapping, and because of its apparent role in familial Alzheimer disease (FAD; St George-Hyslop et al. 1987, 1990), Down syndrome (DS), amyotrophic lateral sclerosis (ALS; Siddique et al. 1991), and Finnish progressive myoclonus epilepsy (PME; Lehesjoki et al. 1991). A gene defect responsible for FAD has been localized to chromosome 21 on the basis of genetic linkage to three pericentromeric loci, *D21S1/S11*, *D21S52*, and *D21S13/S16* (St George-Hyslop et al. 1987, 1990). The gene encoding the precursor of the Alzheimer-associated amyloid β protein (*APP*), the principle component of the senile plaques and cerebrovascular amyloid deposits of Alzheimer disease (AD), has also been mapped to chromosome 21, approximately 7 cM distal to *D21S1/S11* (Tanzi et al. 1987*a*). The *APP* gene physically maps at the border of bands 21q21 and 21q22, close to if not within the so-called obligate DS region in band 21q22 (Patterson et al. 1988). While the primary defect in FAD has been shown not to be tightly linked to *APP* (Tanzi et al. 1987*b*; Van Broeckhoven et al. 1987) in most FAD kindreds, one form of inherited dementia of the Alzheimer type appears to be caused by a mutation in exon 17 of the *APP* gene (Goate et al. 1991). The observation of obligate recombinants between *APP* and FAD in families demonstrating genetic linkage to

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pericentromeric markers on chromosome 21 suggests the possible existence of a second FAD gene defect on this autosome. However, this may also be attributed either to intragenic recombination within the *APP* gene or to the presence of more than one FAD gene defect in these pedigrees (Tanzi et al. 1987*b*, 1991*a*; Tanzi 1991*b*).

To more precisely localize the genes responsible for FAD, DS, ALS, PME, and other inherited disorders residing on chromosome 21, we have constructed a detailed genetic linkage map of the long arm of chromosome 21, consisting of 22 anonymous DNA markers and five genes (*APP, SOD1, ETS2, BCEI,* and *CD18;* table 1). We have previously reported a dramatically increased rate of recombination for both male and female meioses near the telomere, particularly in the distal portion of band 21q22.3 (Tanzi et al. 1988). In addition, we have reported that the frequency of crossovers in the pericentromeric region of 21q between the markers *D21S1/S11* and *D21S13/S16* is statistically higher in females. We have constructed a more detailed genetic linkage map in order to confirm these previous observations and to examine the effects that both parental sex and parental age have on recombination.

Subjects

Pedigrees

We traced the segregation of 27 anonymous DNA markers and genes through the Venezuelan Reference Pedigree (VRP; table 1; Tanzi et al. 1988). For this analysis, we examined 21 interrelated sibships. The VRP has recently been expanded to contain 47 very large interrelated sibships representing over 888 po-

Table 1

Loci and Polymorphisms Used for Mapping on Chromosome 21

Locus	Probe	Polymorphism(s)	Reference
D21S110	p21-4U	*Msp*I	Stewart et al. 1986
D21S13	pGSM21	*Taq*I	Tanzi et al. 1988
D21S59	pPW552-3H	*Taq*I	Watkins et al. 1987
D21S4	pPW233F	*Pst*I	Tanzi et al. 1988
D21S52	pPW511-1H	*Bgl*III and *Hin*dIII	Watkins et al. 1987
D21S1	pPW228C	*Msp*I and *Bam*HI	Tanzi et al. 1988
D21S11	pPW236B	*Taq*I	Tanzi et al. 1988
D21S8	pPW245D	*Hin*dIII	Tanzi et al. 1988
APP	HL124	*Eco*RI and *Ban*I	Tanzi et al. 1988
D21S111	pCW21pcq	*Sst*I	Tanzi et al. 1988
S0D1	4A	*Msp*I	Tanzi et al. 1988
D21S58	pPW524-5P	*Pst*I	Tanzi et al. 1988
D21S16	pGSE9	*Nci*I and *Xba*I	Tanzi et al. 1988
D21S23	pPW244D	*Eco*RI and *Msp*I	Tanzi et al. 1988
D21S65	pPW525-5H	*Msp*I	Watkins et al. 1987
D21S17	pGSH8	*Bgl*II	Tanzi et al. 1988
D21S24	p21.3	*Pst*I	Millington-Ward et al. 1985
D21S3	pPW231F	*Taq*I and *Pst*I	Tanzi et al. 1988
ETS2	pH33	*Taq*I	Tanzi et al. 1988
D21S15	pGSE8	*Msp*I	Tanzi et al. 1988
D21S19	pGSB3	PstI and *Pst*I	Tanzi et al. 1988
	pPW526-1R	*Eco*RI	Watkins et al. 1987
D21S54	pPW513-5H	*Msp*I	Watkins et al. 1987
BCEI	pS2	*Bam*HI	Cohen-Haguenauer et al. 1985
D21S55	pPW518-1R	*Xba*I	Watkins et al. 1987
D21S56	pPW520-10R	*Apa*I	Watkins et al. 1987
	pPW520-5B	*Eco*RI	Watkins et al. 1987
D21S53	pPW512-16P	*Bcl*I	Watkins et al. 1987
	pPW512-18P	*Apa*I	Watkins et al. 1987
	pPW512-6B	*Sac*I	Watkins et al. 1987
CD18	p3.1.1	*Pst*I and *Stu*I	Stewart et al. 1988

tentially informative meioses. This pedigree has previously been demonstrated to display alleles and gene frequencies that, for most markers, are comparable to those of the North American population, and it represents a useful complement to the CEPH panel of mostly unrelated nuclear pedigrees (Tanzi et al. 1988). Permanent lymphoblastoid cell lines have been established for each family member by using standard techniques (Anderson and Gusella 1984). Genomic DNA for RFLP typing was extracted from the cultured lymphoblasts according to a method described elsewhere (Tanzi et al. 1988).

DNA Probes and RFLP Typing

The 27 DNA probes used consisted of five cDNAs encoding *APP* (Tanzi et al. 1987*a*), *SOD1* (Hallewell et al. 1985), *ETS2* (Sacchi et al. 1986), *BCEI* (Masiakowski et al. 1982), and *CD18* (Marlin et al. 1986) and 22 anonymous DNA markers cloned into either pBR322, pBR328, or pUC9. These probes and the RFLPs detected by each are presented in table 1. For RFLP typing, genomic DNA (5 μg) was digested with the indicated restriction enzyme as suggested by the supplier. Agarose gel electrophoresis, DNA transfer, hybridization, and autoradiography were performed according to methods described by Tanzi et al. (1988). Probes were labeled by the oligonucleotide priming method of Feinberg and Vogelstein (1983). All data were checked for consistency of inheritance, and all markers indicating double (or greater) recombinant chromosomes were rechecked for accuracy, including retyping of the individuals in question.

Linkage Analysis

Framework map.—Our procedure for framework-map generation has been described elsewhere (Haines et al. 1990) and will be described briefly here. The VRP was analyzed as 21 separate nuclear families (including grandparents, where available), to speed analyses. Little loss of information was found when these data were compared with those from analyses of the pedigree as a single entity (data not shown). We initially typed parents of large sibships to identify informative matings. If either or both of the parents were heterozygous for a specific marker, all of the children were subsequently typed.

To construct the framework map, all possible pairwise two-points were generated using MAPMAKER (version 1.0; Lander et al. 1987) and were examined to determine a set of four highly informative, well spaced (about 10-cM) markers. All possible orders were tested, and, if one had odds of 1,000:1 better than any other order, it was chosen as the "backbone" onto which other markers were mapped. Additional markers were then tested in every possible position and were added to the map if one placement was favored by odds of at least 100:1 over all other positions. The process was then repeated until all possible markers were added. Final recombination-fraction estimates were obtained using the LINKAGE package (version 4.9; Lathrop et al. 1984), since it includes all data in the analyses.

Comprehensive map.—A comprehensive map contains all typed markers, regardless of whether they can be placed significantly into a single interval. For each marker not already placed in the framework map, all possible positions with odds of no more than 100:1 against the most likely position were noted. Each marker was placed in its most likely position. If two or more markers were placed into a single interval, all possible orders of those markers were tested, and the most likely order was chosen.

Significance Tests

Sex-specific recombination was tested for significance by using the likelihood-ratio test according to a method described elsewhere (Tanzi et al. 1988). Tests of recombination on the basis of age of parent were obtained using a χ^2 statistic.

Recombination as a Function of Parental Age

The effect of parental age on recombination was assessed by comparing recombination rates in four subregions of chromosome 21 (*D21S13-D21S52, D21S52-APP, APP-ETS2,* and *ETS2-CD18*) in three groups defined by age of the parent at conception of the progeny (<20 years, 20–30 years, and 31–61 years). The data were considered both as a whole and also separately as maternal and paternal events. Recombination events occurring within each of the four intervals were assessed both visually and with the program CHROMLOOK (J. L. Haines, unpublished data). Intervals on specific chromosomes for which no markers were informative and for which recombination could not be assessed were not used in the analysis.

Results

To construct the genetic linkage map, two separate approaches used used. First, a framework map was constructed in which only those markers which could

be ordered relative to each other with odds greater than 100:1 were included (fig. 1*A*). Although several markers not included on the framework map were highly informative in the sibships tested (*D21S59, D21S55, D21S110, D21S53,* and *D21S65*), they could not be ordered with greater than 100:1 odds relative to the other loci, because of their close proximity to another marker. Consequently, the framework map includes 13 of the anonymous DNA markers and four of the cDNAS. The total length of the sex-averaged framework map spans 85 cM from *D21S13* near the centromere to *CD18* near the telomere. The map was oriented on the chromosome according to the physical mapping of these markers (Gardiner et al. 1988). Four of the markers—*APP, D21S8, D21S54,* and *D21S111*—exhibited no crossovers with each other, creating a potentially powerful marker locus at the proximal end of the obligate DS region. The occurrence of increased recombination relative to physical distance at the telomere within band 21q22.3 agrees both with our original linkage map (Tanzi et al. 1988) and with direct counts of male chiasmata which are observed most frequently at the telomeres of virtually all the autosomes (Laurie and Hulten 1985).

A comprehensive genetic linkage map of chromosome 21, incorporating available physical mapping data, was constructed next and is shown in figure 2*A*. Markers that could not be ordered with odds of greater than 100:1 in the multipoint linkage analyses were incorporated into the the map by utilizing both the limited linkage and available physical mapping data (Gardiner et al. 1988). The total length of the sex-averaged comprehensive map is 102 cM, with *D21S16* and *CD18* representing the proximal and distal endpoints, respectively.

The sex-specific versions of both the framework map (fig. 1*B*) and the comprehensive map (fig. 2*B*) are different in length. The female framework map at 96 cM is 1.5 times longer than the male map of 64 cM and represents a statistically significant difference (χ^2 (11) = 22.81, P = .02). Likewise, the comprehensive female map (118 cM) is 1.4 times longer than the male map (86 cM), but this difference does not reach statistical significance (χ^2 (15) = 14.95, $P < .50$). Although there is a greater frequency of recombination in females, over the entire chromosome, the most striking difference is in the subcentromeric region. In the proximal long arm, the genetic distance between *D21S52* and *D21S1/D21S11* on the framework map is 11 cM in females and 0.0 cM in males. Similarly, on the comprehensive map, recombination is 3.7 times greater in females than in males (22 cM vs. 6 cM). The distance between *D21S1/S11* and *D21S13* is 3 times greater in females than in males, according to the framework map (24 cM vs. 8 cM) but is only 1.7 times longer in the comprehensive map (31 cM vs. 18 cM).

Trends in recombination were next analyzed as a function of both parental sex and parental age. For this purpose, recombination rates in four subregions of chromosome 21 (*D21S13-D21S52, D21S52-APP, APP-ETS2,* and *ETS2-CD18*) were compared in three groups defined by age of the parent at conception of

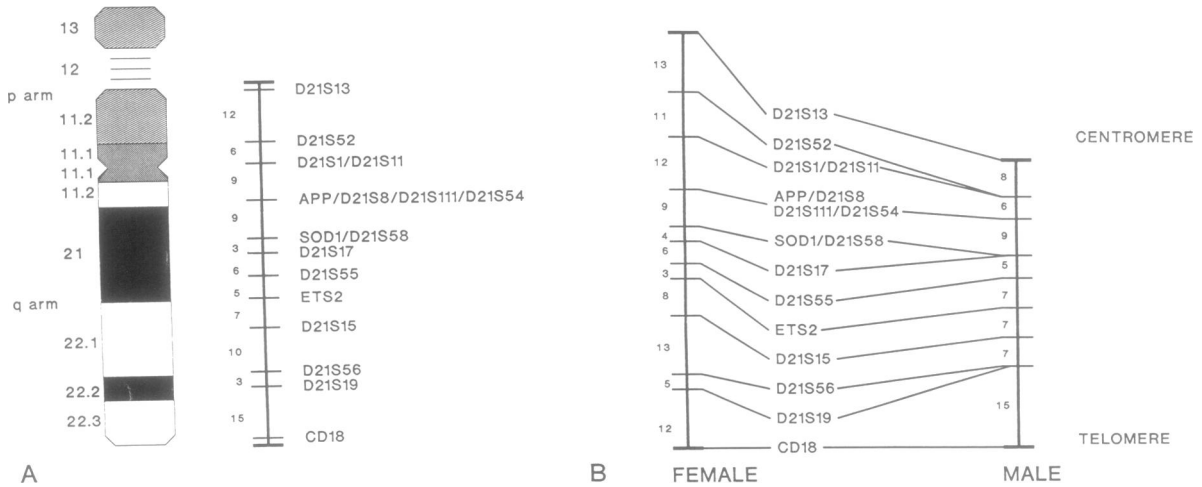

Figure 1 Framework genetic linkage map of chromosome 21. *A*, Sex-averaged map. Values to the left indicate genetic distance in centimorgans (Kosambi). *B*, Female-specific and male-specific maps.

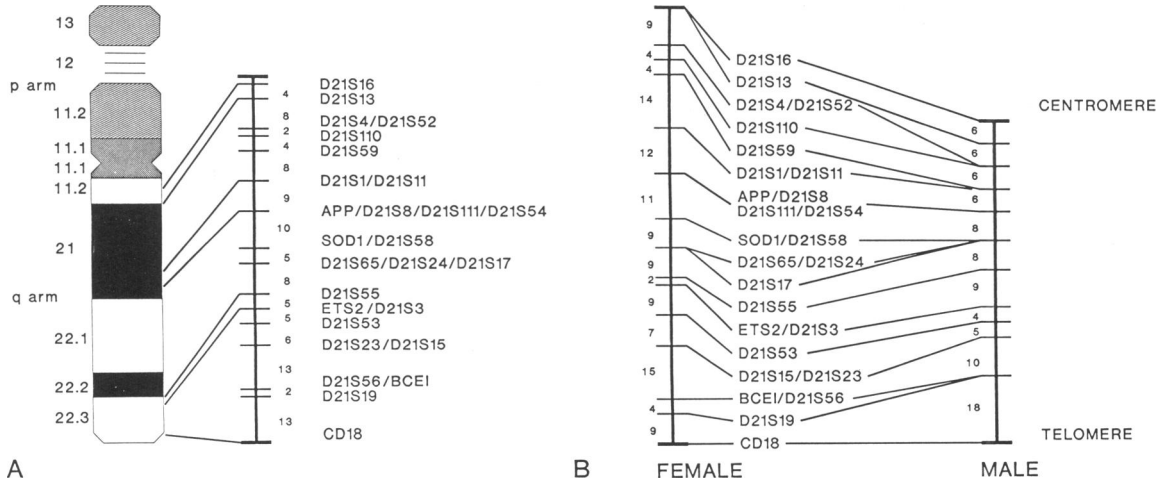

Figure 2 Comprehensive genetic linkage map of human chromosome 21. *A*, Sex-averaged map. Values to the left indicate genetic distance in centimorgans (Kosambi). *B*, Female-specific and male-specific maps.

the progeny (<20 years, 20–30 years, and 31–61 years). The results are presented in table 2. In the most telomeric subregion, *ETS2-CD18*, a significant decrease in recombination was observed with parental age ($P < .001$). Sex-specific analysis showed this to be primarily a maternal effect ($P = .006$). A less significant change in recombination was seen in the subcentromeric region, *D21S13-D21S52* ($P = .06$). In this case, recombination was more frequent in the 20–30-year-old age group than in either the younger or the older groups. Once again, this effect was primarily of maternal origin.

The occurrence of double recombinants was also examined in the various age groups. Only one double recombinant was observed in the entire male data set, whereas females displayed a total of 13 double crosses.

Table 2

Observed Recombination Events, by Age and Sex of Parent

Sex and Segment[a]	Observed Recombination Frequency (no. of informative events) at Age			
	<20 Years	20–30 Years	31–61 Years	*P*
Female:				
A	.08 (12)	.22 (40)	.00 (21)	<.16
B	.19 (36)	.16 (79)	.13 (37)	>.50
C	.07 (28)	.23 (64)	.15 (39)	>.50
D	.47 (30)	.20 (72)	.06 (35)	<.01[b]
Male:				
A	.12 (8)	.03 (33)	.02 (47)	>.50
B	.18 (11)	.04 (57)	.13 (61)	>.50
C	.12 (8)	.21 (47)	.20 (55)	>.50
D	.10 (10)	.04 (46)	.07 (72)	>.50
Both:				
A	.05 (20)	.14 (73)	.02 (68)	<.10
B	.19 (47)	.11 (136)	.13 (98)	>.50
C	.08 (36)	.23 (111)	.18 (94)	>.30
D	.38 (40)	.18 (118)	.06 (107)	<.001[b]

[a] A = D21S13/D21S16 to D21S52; B = D21S52 to APP/D21S8/D21S111/D21S54; C = APP/D21S8/D21S111/D21S54 to ETS2; and D = ETS2 to CD18.

[b] Statistically significant.

An overall downward trend in double recombinants was observed with increasing maternal age but did not reach statistical significance ($P = .06$). It is interesting that no double recombinants were observed in the entire 31–61-year-old age group, in either males or females ($N = 94$). The frequency of double recombinants did not differ between the two younger age groups (<20 years and 20–30 years).

Discussion

We have analyzed the linkage relationships of 27 DNA markers on chromosome 21. The resulting genetic linkage map can be compared with those previously published (Donis-Keller et al. 1987; Tanzi et al. 1988; Warren et al. 1989; Peterson et al. 1991). The present map includes all 15 loci constituting our previous map (Tanzi et al. 1988), 12 loci in common with the map reported by Warren et al. (1989) and 4 loci in common with the map reported by Donis-Keller et al. (1987). The order established in the present map is entirely consistent with that of the three previously published versions, but, because of the addition both of extra loci (detecting additional recombination events) and of additional sibships, there are small differences in estimates of genetic distances between loci.

We were unable to detect any crossover events among the markers *APP, D21S8, D21S54,* and *D21S111*. Peterson et al. (1991), however, have reported the order of three of these loci as being centromere–*D21S8–APP–D21S111*–telomere. One possible explanation for this difference is that sampling variation has occurred, given that each group examined a separate set of families. Warren et al. (1989) found 105, 94, and 81 informative events with six, six, and four recombinants for the loci pairs *D21S8-APP, D21S8-D21S111,* and *APP-D21S111,* respectively. We have observed approximately one-half as many informative events (60, 50, and 48, respectively) with no recombinants, while the expectation (based on the map of Peterson et al. 1991) would be to see three, three, and two recombinants, respectively. To test the difference in the recombination fraction estimates, we obtained $\log_{10}$ likelihoods for two models: one with no recombination between the three loci and one with recombination fractions of .05 and .04 (*D21S8–APP–D21S111*). The odds favoring the former model were 230:1. Thus, it is highly likely that there is a true difference between the data sets and that sampling variation alone does not explain the difference.

The length of the present sex-averaged framework map from *D21S13* to *CD18* is 85 cM (fig. 1*A*). On the comprehensive map (fig. 2*A*), this distance is estimated to be 102 cM, with an additional 4 cM between *D21S13* and the more proximal marker *D21S16*. The sex-averaged genetic map of chromosome 21 recently reported by Peterson et al. (1991) covers 158 cM, with approximately 25 cM of the extra length accounted for by the addition of three markers found to be distal to *CD18* (*PFKL, D21S112,* and *Col6A1*). The estimated distance between *D21S13* and *CD18* on the comprehensive map presented here is 102 cM, compared with 133 cM in the map of Peterson et al. (1991). This large difference seems to arise from two specific areas. The inclusion of the markers *MX1, D21S42, CRYA1,* and *D21S113* between the *D21S15* and *CD18* in the map of Peterson et al. (1991) may have detected additional recombination events in the distal portion of the chromosome. As described above, the detection of recombination events between *APP, D21S8,* and *D21S111* in the analysis of Peterson et al. (1991) adds approximately 10 cM to the map. Whether these differences reflect true heterogeneity of recombination fraction or are the result of uncorrected and undetected laboratory errors remains to be determined.

A fundamental problem in the biology of DS is understanding the association between maternal age and nondisjunction (Smith and Berg 1976). The risk of giving birth to a baby with DS when maternal age is 20–34 years is approximately 1 in 2,000. After the age of 34 years, this value increases to 1 in 300. By the age of 45 years, the risk of a woman bearing a child with trisomy 21 rises to 1 in 45 (Smith and Warren 1985). Chiasma formation has been proposed to provide mechanical stability for first-meiotic-division spindle assembly, thereby promoting normal segregation (Darlington 1937). We have observed that the rate of recombination in both the pericentromeric and telomeric regions of chromosome 21 decreases with increasing maternal age. In females <20 years old, 47% of all recombination on chromosome 21 occurs in the most distal portion, toward the telomere. For the maternal age group of 31–61 years, this value diminishes to 6%. In the subcentromeric portion of the autosome, the frequency of crossover decreases, from 22% for females in their 20s to 0% in mothers >31 years of age. It is conceivable that the observed decrease in recombination in either or both of these regions of chromosome 21 in mothers >31 years of age may somehow either promote nondisjunction or be a

by-product of a mechanism which does so. Warren et al. (1987) have suggested, on the basis of observations of reduced recombination on the nondisjoined chromosome, that asynapsis of parental chromosomes is a primary etiological factor in the occurrence of nondisjunction. The data presented here would indicate that, if the above hypothesis is correct, then the effect that recombination has on this phenomenon is greatest in the most distal and proximal portions of chromosome 21, where crossover frequency appears to be diminished in mothers >30 years of age. Future studies employing additional telomeric markers and other populations (e.g., the CEPH panel of pedigrees) will be helpful in confirming these findings.

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