Am. J. Hum. Genet. 53:1279–1288, 1993

An Index Marker Map of Chromosome 9 Provides Strong Evidence for Positive Interference

David J. Kwiatkowski,* Colette Dib,‡ Susan A. Slaugenhaupt,† Sue Povey,§ James F. Gusella,† and Jonathan L. Haines†

*Division of Experimental Medicine and Hematology-Oncology, Brigham and Women's Hospital, Harvard Medical School, and †Neurogenetics Laboratory, Massachusetts General Hospital, Boston; ‡Genethon, Evry, France; and §Medical Research Council Human Biochemical Genetics Unit, The Galton Laboratory, University College, London

Summary

An index marker map of chromosome 9 has been constructed using the Centre d'Étude du Polymorphisme Humain reference pedigrees. The map comprises 26 markers, with a maximum intermarker interval of 13.1 cM and only two intervals >10 cM. Placement of all but one marker into the map was achieved with >10,000:1 odds. The sex-equal length is 151 cM, with male length of 121 cM and female length of 185 cM. The map extends to within 2%–3% of physical length at the telomeres, and its coverage therefore is expected to be within 20–30 cM of full map length. The markers are all of the GT/CA repeat type and have average heterozygosity .77, with a range of .60–.89. The map shows both marked contraction of genetic distance relative to physical distance in the pericentromeric region and expansion in the telomeric regions. Genotypic data were carefully examined for errors by using the crossover routine of the program DATAMAN. Five new mutations were observed among 17,316 meiotic events examined. There were two double-crossover events occurring within an interval of 0–10 cM, and another eight were observed within an interval of 10–20 cM. Many of these could be due to additional mutational events in which one parental allele converted to the other by either gene conversion or random strand slippage. When there was no correction for these possible mutational events, the number of crossovers displayed by the maternal and paternal chromosomes was significantly different ($P<.001$) from that predicted by the Poisson distribution, which would be expected in the absence of interference. In addition, the observed crossover distribution for paternally derived chromosomes was similar to that predicted from cytogenetic chiasma frequency observations. In all, the data strongly support the occurrence of strong positive interference on human chromosome 9 and suggest that flanking markers at an interval of ≤20 cM are generally sufficient for disease gene inheritance predictions in presymptomatic genetic counseling by linkage analysis.

Introduction

Index marker (heterozygosity >.70) maps are a current goal of the NIH National Center for Human Genome Research and other human genome-mapping efforts. Although several maps of human chromosome 9 have been published (Donis-Keller et al. 1987; Lathrop et al. 1988; Fountain et al. 1992; Kwiatkowski et al. 1992; Ozelius et al. 1992*a*; Weissenbach et al. 1992), they have numerous limitations, in that markers are often poorly informative, the maps are limited in extent and/or contain large gaps, or the maps and the markers that are provided lack tie points to previously identified anchor markers and genes. Here we present an index marker map of human chromosome 9 and relate it to previous maps, including the recently published "second generation" map of the human genome (Weissenbach et al. 1992).

Errors are well recognized as a major problem in the construction of genetic linkage maps (Buetow 1991; Lincoln and Lander 1992). For example, if the true length of a genetic map is 150 cM, and if there are 25 markers on the map with average intermarker interval of 6 cM, then an error rate of 1% increases the length to

Received June 10, 1993; revision received August 2, 1993.

Address for correspondence and reprints: David J. Kwiatkowski, Division of Experimental Medicine, LMRC, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115.

0002-9297/93/5306-0015$02.00

200 cM, or by 33%. Accordingly, we have utilized extensive error-checking procedures to reduce the number of errors to a minimum. The density of the markers and the careful error checking permit assessment of the frequency of recombination events along the length of chromosome 9, in a manner not previously possible.

Evidence for positive meiotic crossover interference in humans has largely been limited to chiasma observations made on spermatocytes (Hulten 1974; Laurie and Hulten 1985). For chromosome 9, a particularly detailed study of 366 spermatocytes from 10 normal human males has shown that a single chiasma is always seen on the short arm and that one or two are always seen on the long arm, giving an overall genetic length of 116 cM (Povey et al. 1992). Moreover, three areas of full interference, where only a single recombination event may be seen, have been defined: 9pter-9cen, 9cen-9q32, and 9q32-9qter. These cytological observations are subject to potential artifact, however, including (*a*) the question of how small a double-recombination event might be when visualized by the staining methodology and (*b*) the possibility of chiasma migration during meiosis.

Linkage maps to date have provided relatively little evidence for interference, presumably because of error problems and insufficient marker density. The map presented here provides sufficient resolution that clear evidence for interference is seen. From a theoretical standpoint, the observations raise mechanistic questions as to how interference occurs. Moreover, the interference seen in this linkage map has considerable importance both in the mapping of disease genes in human populations and in the reliability of genetic counseling in situations where disease status assignment is dependent on family linkage analysis.

Material and Methods

Polymorphism Analysis

PCR analysis of all markers was carried out on 5–20 ng of genomic DNA in a reaction volume of 7.5 μl, with conditions of 94°C for 1 min 30 s and then 30 cycles of 94°C for 30 s, 45°C–55°C for 30 s, and 72°C for 40 s, followed by 72°C for 4 min 30 s, on an MJ Research machine in 96-well polypropylene plates (Falcon 3911). The annealing temperature was varied to provide optimal amplification without background (for details, see table 1). dNTPs were present at 200 μM for A, C, and T and at 10 μM for dGTP; 0.2 μCi of α^{32}P dGTP was included in each reaction mix. PCR products were analyzed by denaturing 8 M urea PAGE followed by autoradiography.

Data Management and Analysis

All loci were typed on every member of the original 40 Centre d'Étude du Polymorphisme Humain families comprising 413 individuals, except for genotypic data for three different markers in one individual (1345-08), which were missing because of a lack of DNA.

Allele data were entered onto a VAX 3400 computer using the program DATAMAN (D. J. Kwiatkowski, unpublished data), which incorporates some features of LIPIN (Trofatter et al. 1986) and CHROMLOOK (Haines 1992). DATAMAN accepts allele designations of three characters (which permits direct entry of observed allele sizes for short-tandem-repeat [STR] markers without coding), allows facile identification of gaps and noninheritances in the data, determines likely parental phase and identifies crossover events in the children (when given an arbitrary marker order), determines marker heterozygosity and allele frequency, and generates allele data output for direct input to MAPMAKER (Lander et al. 1987) and CRIMAP (Donis-Keller et al. 1987). The DATAMAN source code, examples of genotypic data files, and documentation are available on request.

Construction of Linkage Map

The map was constructed sequentially over time as new markers were identified or became available. Marker order was initially inferred from our previous work (Kwiatkowski et al. 1992), physical mapping information (Graw et al. 1992), or published partial maps of chromosome 9 (Fountain et al. 1992; Weissenbach et al. 1992). When genotypic data for new markers became complete, the data were analyzed using MAPMAKER to construct a tentative map and order. With this tentative order, crossovers were identified using the CROSSOVER option of DATAMAN. DATAMAN produces robust crossover analyses, except for the initial informative marker when that marker occurs as an AB × AB cross. Accordingly, in every pedigree the first three informative markers were manually examined to determine the minimal number of crossover events required to explain the observed data. Double-recombination events involving nearby markers were then identified and rechecked for all three of the involved markers, until such events were minimized to the maximum extent possible. Several cycles of this procedure were performed, with particularly careful review in cases where only a single marker provided support for the double-recombination event.

When this procedure was complete, the map was rebuilt, beginning with eight well-spaced and order-confirmed markers (Kwiatkowski et al. 1992)—IFN,

Table 1

DNA Markers

Locus	Sequence[a]	Clone	Heterozygosity	Size Range	CEPH 10201 Genotype	Annealing Temperature (°C)	Reference
D9S129		MS47	.66	133–143	137,139	55	Hudson et al. 1992
D9S132		G115	.68	148–166	156,158	55	Hudson et al. 1992
D9S199		SG/C101	.80	144–164	152,154	55	Graw and Kwiatkowski 1993
D9S168		AFM158xf12	.78	227–245	229,243	51	Weissenbach et al. 1992
D9S156		AFM051xd6	.76	132–154	137,148	51	Weissenbach et al. 1992
IFN		b1b	.67	138–152	142,150	55	Kwiatkowski and Diaz 1992
D9S104		mfd121	.80	181–199	189,191	48	Wilkie et al. 1992
D9S200		SG/C80	.81	107–127	123,123	55	Graw and Kwiatkowski 1993
D9S55	GAGAAAATTCCAGGCAGCAG, GGTTGAGTCGTTCTTAACCA	ICRFc102F0621	.79	165–197	185,187	55	Sharma et al. 1991
D9S15		mct112	.72	195–207	203,207	55	Wallis et al. 1990
D9S175		AFM224zh10	.85	204–232	204,206	55	Weissenbach et al. 1992
D9S153		AFM025yb2	.74	143–155	149,149	55	Weissenbach et al. 1992
D9S167		AFM157xb12	.87	260–286	272,272	55	Weissenbach et al. 1992
D9S201		SG/C123	.60	123–135	127,131	55	Graw and Kwiatkowski 1993
D9S12	CCTCCTCACACCTCATGTG, AAGGGGAGGGAATCAGGTGT	1AE1	.66	101–117	101,107	55	Kwiatkowski et al. 1992
D9S53		mfd135	.84	116–148	128,134	48	Wilkie et al. 1992
D9S58		1AC3	.89	105–137	125,125	55	Kwiatkowski et al. 1992
D9S131		MS202	.84	92–106	92,102	55	Hudson et al. 1992
HXB		p31	.73	107–117	111,113	55	Ozelius et al. 1992*b*
GSN		D3d	.73	111–147	125,137	55	Kwiatkowski and Perman 1991
D9S60		1AD2	.82	136–154	142,148	55	Kwiatkowski et al. 1992
D9S65		4AB7	.74	131–161	157,157	55	Kwiatkowski et al. 1992
ASS		ASSg1	.84	113–129	115,115	55	Kwiatkowski et al. 1991
DBH	AAAGTCAGGCACATGCACC, CGAGATGGGGAGGTGGA	cDBH14	.78	245–268	249,266	55	Nahmias et al. 1992
D9S66		4AF10	.74	109–135	111,119	55	Kwiatkowski et al. 1992
D9S67		3AE11	.76	71–113	105,105	55	Kwiatkowski et al. 1992

[a] Primer sequences are shown if different from the reference sequence.

D9S15, D9S12, D9S58, D9S60, ASS, D9S66, and D9S67—by using MAPMAKER. Individual markers were then added sequentially to the map; placement of all but D9S132 was favored by odds of >10,000:1. Placement of D9S132 telomeric to D9S199 was favored by odds of 160:1 only. Then a ripple analysis was performed in which the order of all quintuplets in the map was permuted. Again, the order of the map was favored by odds of >10,000:1 over all other orders, apart from inversion of D9S129 with D9S199, which again was favored by only 160:1. The identical order was generated using the Build option of CRIMAP, with similar odds of placement including D9S132 relative to D9S199. For purposes of female:male comparison of map distances, a subset of the markers at approximately 10-cM (sex-equal) intervals was used: D9S129, D9S199, D9S168, D9S156, IFN, D9S104, D9S55, D9S175, D9S153, D9S201, D9S12, D9S53, D9S58, HXB, GSN, D9S65, D9S66, and D9S67.

Chiasma Frequency-Distribution Calculations

The cytogenetic chiasma observations of Laurie and Hulten (1985) permit a direct calculation of the frequency distribution of crossover events per inherited paternal chromosome 9. A total of 17.6% of chromosomes are predicted to have zero crossover events; 42.6% are predicted to have one crossover event; 32.4% are predicted to have two crossover events; and 7.4% are predicted to have three crossover events. When this distribution is applied to the 333 meiotic events observed in this reference population, these chiasma observations predict that there will be 58 chromosomes with zero crossover events, 142 with one crossover event, 108 with two crossover events, and 25 with three crossover events. However, for comparison with the observed number of crossovers determined by genetic linkage analysis, one must correct the chiasma distribution to account for those crossovers that either do not involve any of the current markers (i.e., occur in the telomeric regions) or involve the current markers but that are not detected because the distal marker(s) is uninformative. This correction was made by assuming that 10 cM of distance (male) is not covered by the current marker set at each telomere and by using the observed heterozygosities for the distal p and q markers to calculate that approximately one-quarter of all crossover events on the p arm are undetected, approximately one-fifth of all single-crossover events on the q arm are undetected, and approximately one-third of all double-crossover events on the q arm are detected as a single crossover. This calculation results in the data presented in table 2.

Results

Polymorphic Markers

Markers used in this study are presented in table 1. They are all of the GT/CA repeat (i.e., STR) type and have a heterozygosity range of .60–.89, with an average of .77. All have been used by two or more laboratories and are relatively robust.

Error Detection and Linkage Map Construction

The process of creation of the map occurred simultaneously with the process of error detection. Initial marker order for a set of 10 markers was based upon previous studies (Kwiatkowski et al. 1992). Placement of an additional marker into the map was initially based upon available genetic linkage and/or physical map information. When genotypic data were nearly complete, analysis with MAPMAKER (Lander et al. 1987) permitted firmer positioning of the marker relative to the existing map. Then genotypic data were analyzed for double-crossover events in a standardized manner until all were removed or confirmed. Addition of markers in groups of three to five resulted in several iterative steps in the map-extension/error-detection/correction process.

After this iterative process, the map was reconstructed by sequential addition of markers by using MAPMAKER, beginning with the initial set: IFN, D9S15, D9S12, D9S58, D9S60, ASS, D9S66, and D9S67. Sequential addition of all markers was favored by odds of >10,000:1, except in the case of D9S132; placement of D9S132 telomeric to D9S199 was favored by odds of 160:1 only. The sex-specific map is shown in figure 1. Physical mapping correlates are available for several of these markers and are shown to the right (Kwiatkowski et al. 1993; M. Leversha, personal communication). The map extends to within about 2%–3% of the physical length of each arm at the telomeres, so that its coverage is expected to be within 10–15 cM of full map length on each arm.

Comparison of the sex-specific maps provided evidence for significant differences in several intervals ($\chi^2 > 6.64$ for 2 df corresponds to $P<.01$): D9S168–D9S156, IFN–D9S104, D9S104–D9S55, D9S55–DS175, D9S175–D9S153, and D9S53–D9S58. These intervals represent much of the p arm and bands q13-31 on the long arm. Several other intervals showed differences that approached significance as well.

New Mutations

Five new mutations were observed among 17,316 meiotic events. These represented shifts in length of

Table 2

Observed and Possible Mutational Events

Marker	Base Shift	Parental Chromosome	Individual	Double-Crossover Interval (cM)
Observed mutational events:				
D9S53	−2	fa	45-6	
D9S104	+6	mo	1344-11	
D9S175	+2	fa	1413-8	
D9S168	+2	mo	1423-3	
D9S131	+4	?	1424-10	
Tight double recombinations/ possible mutational events:				
D9S55	+4	fa	21-3	1.6
D9S12	+2	fa	21-3	17.5
D9S167	−18	mo	37-9	29.2[a,c]
D9S175	−4	mo	37-9	29.2[c]
D9S15	−2	mo	1332-17	9.7
D9S55	−4	fa	1340-6	16.4[a]
D9S199	−4	fa	1349-8	17.8
...[b]		fa	1350-4	15.4
D9S167	−8	mo	1418-3	12.6
D9S104	−2	fa	13291-7	16.6
DBH	−2	mo	13294-3	13.2[c]
D9S67	+2	mo	13294-3	13.2[c]

[a] Triple-recombination event observed.
[b] Double recombination confirmed by second marker.
[c] More than one mutational event can explain a double-recombination event; both are listed.

alleles of −2, +6, +2, +2, and +4, occurred on maternal chromosomes in two cases and on paternal chromosomes in two cases, and could have occurred on either parental chromosome in the last case (table 2). They are presumed to represent a loss of one dinucleotide repeat in the first case and a gain of three, one, one, and two repeats, respectively, in the latter four cases.

Positive Interference

Using the derived map-distance information, we examined the phase data carefully for double-recombination events occurring within small intervals. When flanking informative markers were used to define the size of the interval in which a double-recombination event occurred, there were two double-recombination events in an interval of 0–10 cM, and another eight were observed within an interval of 10–20 cM (table 2). Two of the latter represented triple-recombination events, one occurring in an interval of 16.4 and the other occurring in an interval of 29.2 cM. One of the double-recombination events was supported by two independent markers, both of which indicated the alternate phase. Many of the remainder could be due to mutational events in which one parental allele converted to the other by either gene conversion or random strand slippage. On the basis of the observed frequency of new mutations, one can predict that one to three additional mutations due to strand-slippage events would occur and be undetected because they result in conversion from one parental allele to the other. Estimates for the frequency of gene-conversion events in humans are not available, and it is unknown what fraction of the remaining double-recombination events might be due to gene conversion. Even when there is no correction for these mutational events, in light of the density of markers on the map this overall number of close double-recombination events (10 in an interval <20 cM) suggests that positive interference was being observed.

To explore further the occurrence of interference in this data set, we determined the frequency distribution of recombinations per chromosome. These data were then compared with the distribution of recombination events per chromosome that were predicted by the Poisson distribution, as would be appropriate if there were no effect from interference. As shown in the Appendix, for both paternal and maternal chromosomes the frequency distribution was significantly different

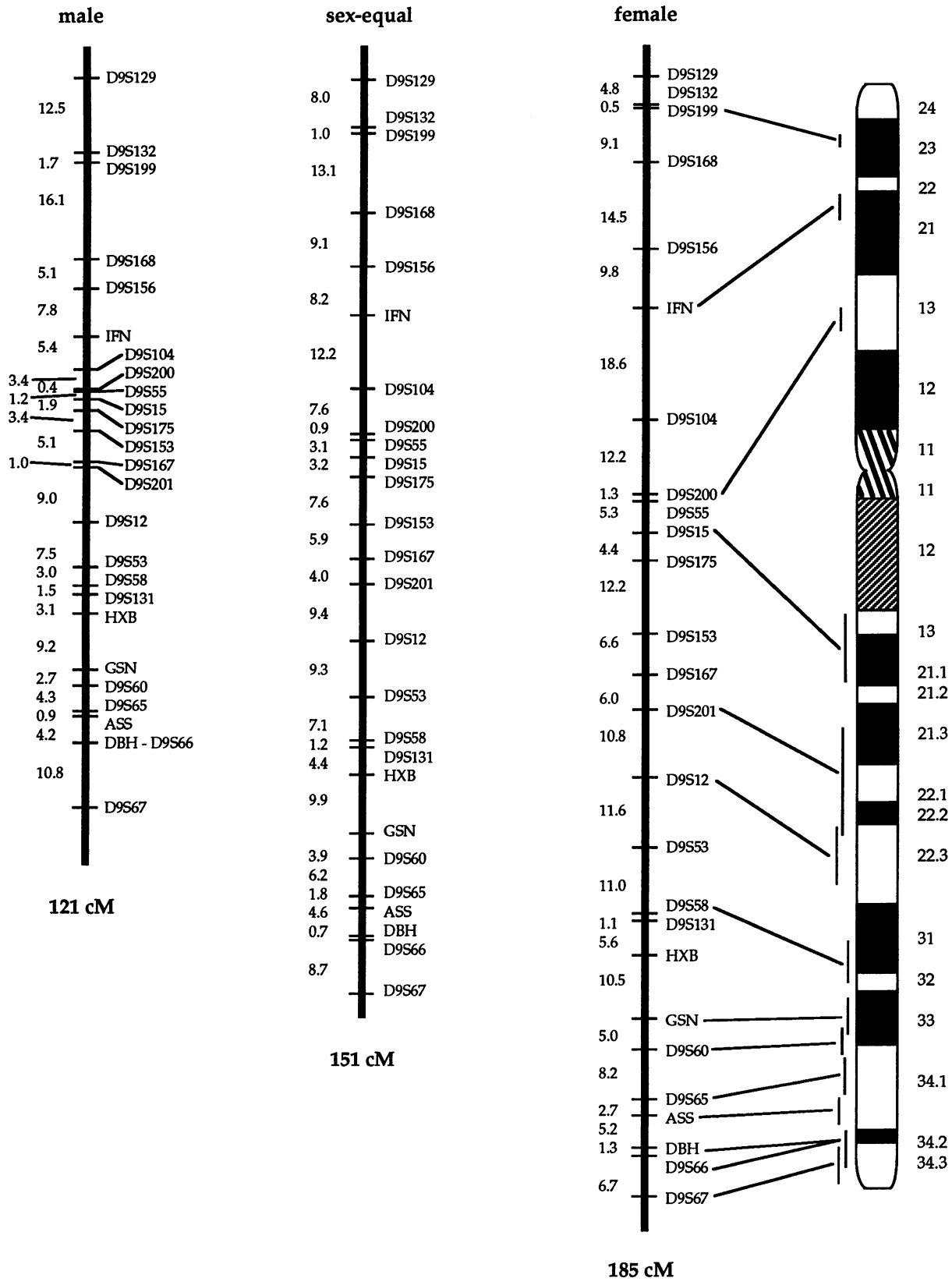

Figure 1 Index marker map of human chromosome 9. Male, sex-equal, and female maps are shown, with physical localization of markers (where known) shown on the ideogram on the right. The numbers are intermarker distances in cM.

from that predicted ($P<.001$ in each case). For paternal chromosomes, there were fewer chromosomes showing zero, three, four, or five recombination events than were predicted, and there were more chromosomes with one or two recombination events than were predicted. For maternal chromosomes, there were fewer chromosomes with zero, four, or five recombination events than were predicted, and there were more chromosomes with one, two, or three recombination events than were predicted. The paternal crossover distributions were also compared with those predicted by the chiasma frequency distribution observed by Hulten (Laurie and Hulten 1985). This chiasma distribution frequency was modified (see Material and Methods) to account for the lack of informative telomeric markers. The observed recombination-frequency distribution was not significantly different ($P>.10$) from that predicted by the data of Hulten. The occurrence of three chromosomes with four, four, and six recombinations, respectively, is in contrast to the Hulten distribution but likely is due to mutational events/residual errors.

Integration of Other STR Markers into the Map

Recently several new STR markers have been described that provide additional highly informative markers for linkage analysis on chromosome 9 (Weissenbach et al. 1992). These markers have been integrated into the current data set, but without error-checking review. Fifteen of these 24 additional markers map uniquely into the current map, as shown in figure 2.

Discussion

Features of the Map

The current map represents a "best attempt" at an error-free map of chromosome 9. In contrast to other published maps (Donis-Keller et al. 1987; Lathrop et al. 1988; Ozelius et al. 1992*a*), it predicts a male map of length close to that predicted by chiasma observations. The sex-equal length of the map is 151 cM, with potentially another 20–30 cM uncovered by relatively small physical gaps at the telomeres. The map consists of 26 markers, with average intermarker interval of 6.0 cM and no gaps >13.1 cM. All oligonucleotide primer pairs/markers are relatively robust, having been used in more than one laboratory. Markers were chosen for their ease of use, informativeness, and map location, to provide a map of maximal utility. As such, these markers provide a useful set for linkage analysis on chromosome 9, and the narrow physical localization of many markers permits rapid progress from linkage to physical cloning of a region of the chromosome in positional cloning projects.

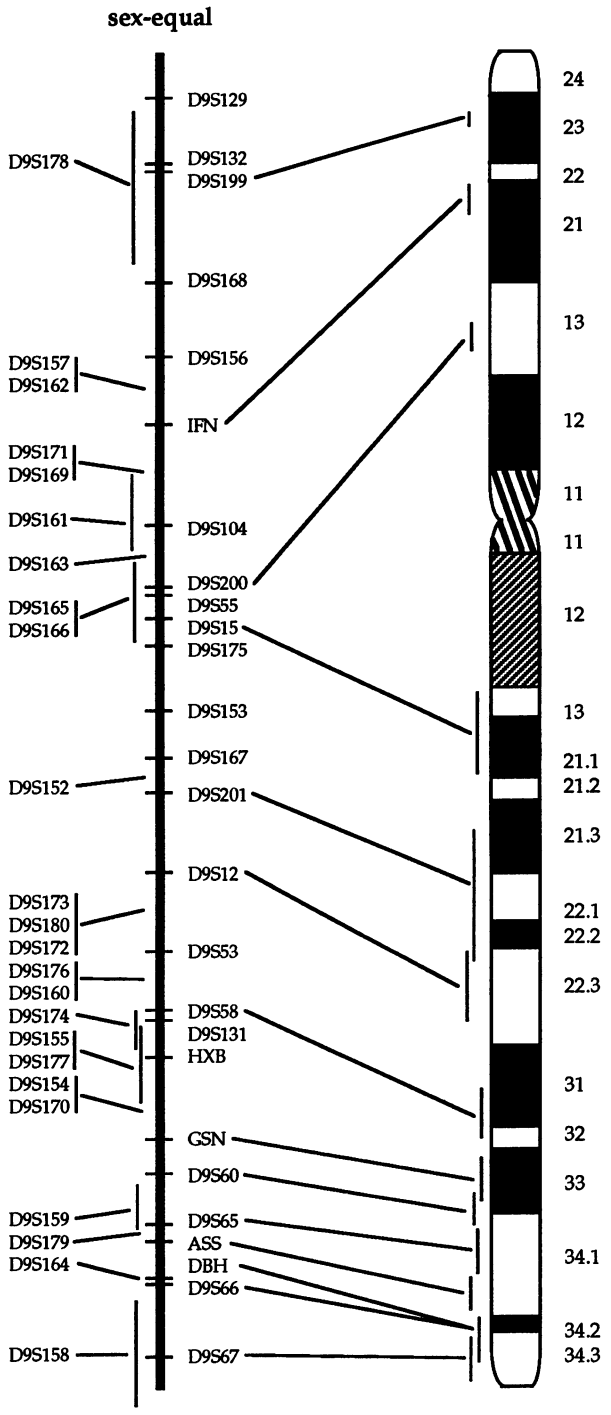

Figure 2 Relative localization of 24 Genethon markers. Fifteen markers (e.g., D9S157, D9S162, and D9S171) mapped uniquely, and nine markers (e.g., D9S178, D9S161, D9S165, and D9S166) did not.

The map is most remarkable for the wide variation in the ratio between genetic and physical distance. The distance from p13 to q13-21.2 has a physical distance of approximately 45 Mb (estimated from ideogram measurements and data of Morton 1991; the distance is 30 Mb if the heterochromatin region of 9q is excluded) yet has a genetic distance of 1.6 cM in men and 6.6 cM in women. This translates to a physical/genetic ratio of 28 Mb/cM in men and 6.8 Mb/cM in women, in this pericentromeric region. The subtelomeric regions, on the other hand, have increased genetic distance relative to physical distance, such that the ratio is <1 Mb/cM.

Error Detection and Residual Errors

We carefully examined marker allelotypes for potential errors, and, in particular, we reanalyzed all allelotypes that resulted in double-recombination events. Other errors that we might have missed could result in small balancing changes in intermarker distances but would not result in significant lengthening or shortening of the map or in marker order inversion, apart from the D9S129–D9S199 ordering. All other marker orderings were supported by at least two crossover events.

When error checking was complete, there remained a total of two double-recombination events in an interval of <10 cM, and there were another eight in a 10–20-cM interval. Some of these may represent genuine close recombination events, but new mutations due to either strand-slippage events or gene conversion could also explain the observations. Improved map resolution will be required for clarification these possibilities. Nonetheless, few close double-recombination events were seen, and this impression is quantitatively supported by the comparisons presented in table 2.

Interference

These observations therefore strongly support the occurrence of positive interference on human chromosome 9, both in males and in females. This positive interference means that, under optimal conditions, using multipoint analysis, one could perform an initial linkage analysis of chromosome 9 for an unknown disease gene by using only five informative markers, with positions at 9pter, 9p13-21, 9q21, 9q31-32, and 9qter. This assumes that the family or families under study are of sufficient size for detection of linkage and that there are no errors in either the family disease assignments or DNA collection process. Four markers could be used if males are predominantly affected in the family at hand. Since diagnostic, DNA sample identification, and other errors are difficult to avoid in linkage studies, and since few markers will be informative in all families, the use of a slightly expanded panel of markers—perhaps seven or eight spanning the chromosome—is advisable in initial linkage analyses.

Although it is possible that significant numbers of crossovers were missed because of insufficient density of informative markers, the average intermarker interval of 6 cM (5 cM in males and 7 cM in females) makes this unlikely. It is possible that there are localized small regions where double-recombination events are particularly common. However, our data on the distribution of apparent tight double-recombination events (see table 2) provide no evidence for such clustering. Improved map resolution will be required for examination of this possibility in greater detail.

The value of the approach that we have taken to error detection and correction—i.e., the approach of minimization of crossovers and reanalysis of double-crossover events—is indicated by our conclusions regarding interference. This minimization strategy has been described elsewhere (CROSSMAP [M. Polymeropoulos, personal communication] and CHROMLOOK [Haines 1992]) and may be usefully applied to other chromosomes and mammalian species, for construction of linkage maps.

Our work also serves to validate the pioneering efforts made by Hulten and co-workers in analyzing interference, by cytogenetic means, in humans. The fit between the number of observed crossovers and those predicted by Hulten is remarkably good (see Appendix). Comparison of highly error-corrected male maps for other chromosomes with the data of Hulten will be of considerable interest. We predict that the cytogenetic data will again be confirmed. It is unfortunate that cytogenetic chiasma analysis is not available for comparison with female-specific linkage maps in humans.

Finally, the work presented here suggests that high confidence can be placed in the use of flanking informative markers to predict disease gene inheritance in presymptomatic genetic counseling, when the markers are separated by ≤20 cM. As noted above, this requires careful family diagnostic ascertainment, DNA sample preparation, and analysis to avoid errors. The use of closer flanking markers, where available, is always preferable.

Acknowledgments

This work was supported by NIH grants HG00169, HG00324, and HG00598. D.J.K. is an Established Investigator of the American Heart Association.

Appendix

Comparison of Observed with Expected Recombination Distributions for Paternal and Maternal Chromosomes

Paternal:								
Recombinations per chromosome	0	1	2	3	4	5	6	
Observed	79	161	83	7	2	0	1	
Expected (Poisson) (χ^2 = 40.52, 4 df, P<.001)	107	122	69	26	7	2	0	
Expected (Hulten) (χ^2 = 2.33, 3 df, P>.10)	87	150	83	13	0	0	0	
Maternal:								
Recombinations per chromosome	0	1	2	3	4	5	6	7
Observed	37	111	103	69	9	2	2	0
Expected (Poisson) (χ^2 = 29.68, 5 df, P< .001)	58	101	88	52	23	8	2	1
Totals:								
Recombinations per chromosome	0	1	2	3	4	⩾5		
Observed	116	272	186	76	11	5		
Expected (Poisson) (χ^2 = 47.53, 5 df, P< .001)	165	223	157	78	30	13		

References

Buetow KH (1991) Influence of aberrant observations on high-resolution linkage analysis outcomes. Am J Hum Genet 49:985–994

Donis-Keller H, Green P, Helms C, Cartinhour S, Weiffenbach B, Stephens K, Keith TP, et al (1987) A genetic linkage map of the human genome. Cell 51:319–337

Fountain JW, Karayiorgou M, Taruscio D, Graw SL, Buckler AJ, Ward DC, Dracopoli NC, et al (1992) Genetic and physical map of the interferon region on chromosome 9p. Genomics 14:105–112

Graw SL, Buckler AJ, Britt DE, Jackson CL, Taruscio D, Baldini A, Ward DC, et al (1992) Generation and characterization of a human chromosome 9 cosmid library. Somat Cell Mol Genet 18:269–284

Graw SL, Kwiatkowski DJ (1993) Three dinucleotide repeat polymorphisms on chromosome 9. Hum Mol Genet 2:614

Haines J (1992) CHROMLOOK: an interactive program for error detection in reference linkage data. Genomics 14:517–519

Hudson TJ, Engelstein M, Lee MK, Ho EC, Rubenfield MJ, Adams CP, Housman DE, et al (1992) Isolation and chromosomal assignment of 100 highly informative human simple sequence repeat polymorphisms. Genomics 13:622–629

Hulten M (1974) Chiasma distribution at diakinesis in the normal human male. Hereditas 76:55–78

Kwiatkowski DJ, Armour J, Bale AE, Fountain JW, Goudie D, Haines JL, Knowles MA, et al (1993) Report on the Second International Workshop on Human Chromosome 9. Cytogenet Cell Genet 64:93–121

Kwiatkowski DJ, Diaz MO (1992) Dinucleotide repeat polymorphism at the IFNA locus (9p22). Hum Mol Genet 1:658

Kwiatkowski DJ, Henske EP, Weimer K, Ozelius L, Gusella JF, Haines J (1992) Construction of a GT polymorphism map of human 9q. Genomics 12:229–240

Kwiatkowski DJ, Nygaard TG, Schuback DE, Perman S, Trugman JM, Bressman SB, Burke RE, et al (1991) Identification of a highly polymorphic microsatellite VNTR within the argininosuccinate synthetase locus: exclusion of the dystonia gene on 9q32-34 as the cause of dopa-responsive dystonia in a large kindred. Am J Hum Genet 48:121–128

Kwiatkowski D, Perman S (1991) A GTn dinucleotide repeat polymorphisms within the GSN locus. Nucleic Acids Res 19:967

Lander ES, Green P, Abrahamson J, Barlow A, Daly MJ, Lincoln FE, Newberg L (1987) Mapmaker: an interactive computer package for constructing primary genetic linkage map of experimental and natural populations. Genomics 1:174–181

Lathrop M, Nakamura Y, O'Connell P, Leppert M, Woodward S, Lalouel J-M, White R (1988) A mapped set of genetic markers for human chromosome 9. Genomics 3:361–366

Laurie DA, Hulten MA (1985) Further studies on bivalent chiasma frequency in human males with normal karyotypes. Ann Hum Genet 49:189–201

Lincoln SE, Lander ES (1992) Systematic detection of errors in genetic linkage data. Genomics 14:604–610

Morton N (1991) Parameters of the human genome. Proc Natl Acad Sci USA 88:7474–7476

Nahmias J, Burley MW, Povey S, Porter C, Craig I, Wolfe J (1992) A 19 bp deletion polymorphism adjacent to a dinucleotide repeat polymorphism at the human dopamine beta-hydroxylase locus. Hum Mol Genet 1:286

Ozelius L, Kwiatkowski D, Schuback D, Breakefield X, Wexler N, Gusella J, Haines J (1992*a*) A genetic linkage map of human chromosome 9q. Genomics 14:715–720

Ozelius L, Schuback DE, Stefansson K, Slaugenhaupt S, Gusella JF, Breakefield XO (1992*b*) Dinucleotide repeat polymorphism for the hexabrachion gene (HXB) on chromosome 9q32-34. Hum Mol Genet 1:141

Povey S, Smith M, Haines J, Kwiatkowski D, Fountain J, Bale A, Abbott C, et al (1992) Report and abstracts of the First International Workshop on Chromosome 9. Ann Hum Genet 56:167–221

Sharma V, Brown D, Smith L, Magenis RE, Litt M (1991) Dinucleotide repeat polymorphism at the D9S55 locus. Nucleic Acids Res 19:4023

Trofatter JA, Haines JL, Conneally PM (1986) LIPIN: an interactive data entry and management program for LIPED. Am J Hum Genet 39:147–148

Wallis J, Williamson R, Chamberlain S (1990) Identification of a hypervariable microsatellite polymorphism within D9S15 tightly linked to Friedreich's ataxia. Hum Genet 85:98–100

Weissenbach J, Gyapay G, Dib C, Vignal A, Morissette J, Millasseau P, Vaysseix G, et al (1992) A second-generation linkage map of the human genome. Nature 359:794–801

Wilkie PJ, Krizman DB, Weber JL (1992) Linkage map of human chromosome 9 microsatellite polymorphisms. Genomics 12:607–609