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J. B. Lichter

S. M. Hackleman

B. A. J. Ponder

D. Easton

S. A. Narod

See next page for additional authors

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A Preliminary Analysis of Consortium Data for Markers Tightly Linked to Multiple Endocrine Neoplasia Type 2A

J. B. Lichter,* S. M. Hackleman,* B. A. J. Ponder,† D. Easton,† S. A. Narod,‡ G. M. Lenoir,‡ R. F. Gagel,§ N. E. Simpson,‖ E. Gardner,† P. J. Goodfellow,¶ S. Takai,# A. J. Pakstis,* and K. K. Kidd*

We have analyzed DNA marker typing data contributed by six independent groups to estimate the pairwise genetic distances between these markers and the locus for multiple endocrine neoplasia type 2A (MEN 2A). We used LIPED to calculate these distances for female, male, and sex-average linkage maps and to determine the corresponding LOD scores. The preliminary analyses of this large data set (89 MEN 2A families and five non-MEN 2A references families, with 1,934 total individuals) are reported here. These refined estimates of the genetic map in this region will aid in the assignment of presymptomatic diagnoses. This study clearly points out the limitation of pairwise linkage analysis in further refining the position of MEN2A in this small region of chromosome 10. Further refinement of the genetic map position of MEN2A will be best accomplished by finding, verifying, and accurately mapping crossovers in specific families. (Henry Ford Hosp Med J 1992;40:205-9)

The search for the gene for multiple endocrine neoplasia type 2A (MEN 2A) has relied heavily on the use of linkage analysis of genotype data in affected kindreds (1-3). These studies clearly place MEN2A into the pericentromeric region of chromosome 10 between D10S34 on the proximal short arm and RBP3 on the proximal long arm (1,3,4). Each of the groups involved in this analysis has independently confirmed the localization of MEN2A to the region between D10S34 and RBP3. Furthermore, each group has estimated the genetic distance of the region using their individual data sets and all of the groups largely agree. In an effort to localize the MEN 2A gene more precisely within the pericentromeric region, we have assembled all of our data for six loci and initiated an integrated analysis.

The analysis of these data represent the largest integrated investigation of this region of the genome. The preliminary results reported here clearly show that MEN2A is very likely to be near the centromere, confirming all previous observations, with pairwise LOD scores for MEN2A ranging from about 19 to over 64 with the pericentromeric markers FNRB, D10S34, D10Z1, D10S94, RBP3, and D10S15. We can further confirm the dramatic reduction in male recombination in this region. However, there does appear to be some male recombination across the region in both the long and short arms. This analysis reduces the confidence intervals associated with the genetic distance estimates thereby strengthening the presymptomatic diagnostic potential using these flanking and tightly linked markers. Finally, the analyses show that a complete statistical analysis of new markers will not increase the genetic resolution of MEN2A at a statistical level; on the contrary, only multipoint mapping or the mapping of specific crossovers in specific pedigrees will allow more precise mapping of the MEN2A locus.

Methods

Loci and polymorphic systems

Marker typing data from six loci were incorporated into the analysis. Three of the loci had more than one probe-enzyme combination. FNRB was typed with up to three probe-enzyme systems: pGEM32/BanII, HinfI, and KpnI. RBP3 was also typed with up to three probe-enzyme systems: H4IRBP/MspI, Bg1II, and cTBIRBP9/TaqI. D10Z1 was typed with pαRP8/HinfI and PstI. D10S34 was typed with cTB14.34/TaqI. Two loci were typed with only one probe-enzyme combination: D10S94 was typed with pCL1/A1-6-c23/PvuII, and D10S15 was typed with pMCK2/PvuII or RsaI (not both). All of these loci are cited in HGM10 and are available for noncommercial diagnostic purposes from the groups that originally isolated the probes. All affected individuals had MEN 2A, familial medullary thyroid carcinoma, pheochromocytoma, and/or parathyroid tumors. Some individuals in pedigrees from Dr. Gagel also had cutaneous lichen amyloidosis.

Data management and haplotyping

All data were collected electronically from the contributing groups. The data were integrated into a single data file in the

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*Department of Genetics, Yale University, New Haven, CT.
†Department of Pathology, University of Cambridge, Cambridge, UK.
‡The Montreal General Hospital, Montreal, Canada.
§Endocrinology Section, VA Medical Center, Houston, TX.
‖Department of Paediatrics, Queen's University, Kingston, Ontario, Canada.
¶Department of Medical Genetics, University of British Columbia, Vancouver, BC.
#Department of Medical Genetics, Osaka University Medical School, Biomedical Research Center, Osaka, Japan.
Address correspondence to Dr. Kidd, Department of Genetics, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

Table 1
Consortium Analysis for MEN2A

Interval	$\Theta_{m=f}$	$Z_{m=f}$	Θ_m	Θ_f	$Z_{m\neq f}$	Confidence Interval$_m$	Confidence Interval$_f$	Number of Families
FNRB-MEN2A	0.045	22.6	0.000	0.078	24.0	0.00-0.034	0.013-0.129	54
D10S34-MEN2A	0.070	25.2	0.114	0.045	25.2	0.042-0.183	0.005-0.061	75
D10Z1-MEN2A	0.001	21.6	0.000	0.013	21.7	0.00-0.053	0.00-0.070	57
D10S94-MEN2A	0.000	19.7	0.000	0.000	19.7	0.00-0.065	0.00-0.036	50
RBP3-MEN2A	0.048	41.2	0.001	0.074	43.5	0.00-0.015	0.015-0.118	85
D10S15-MEN2A	0.030	64.4	0.028	0.046	64.4	0.015-0.075	0.004-0.063	77
FNRB-D10S34	0.023	35.9	0.028	0.003	36.6	0.001-0.100	0.00-0.050	42
D10S34-D10Z1	0.030	18.0	0.000	0.090	18.0	0.00-0.050	0.010-0.300	55
D10Z1-D10S94	0.000	9.3	0.000	0.000	9.3	0.00-0.100	0.00-0.100	38
D10S94-RBP3	0.068	12.1	0.042	0.083	12.1	0.001-0.200	0.010-0.200	47
RBP3-D10S15	0.023	80.6	0.026	0.007	81.0	0.001-0.050	0.001-0.010	77
FNRB-D10Z1	0.056	21.8	0.000	0.133	23.1	0.00-0.050	0.050-0.200	43
FNRB-D10S94	0.072	9.7	0.048	0.094	9.7	0.00-0.200	0.001-0.200	44
FNRB-RBP3	0.123	35.5	0.024	0.216	41.5	0.001-0.050	0.100-0.300	60
FNRB-D10S15	0.099	31.3	0.021	0.194	36.4	0.00-0.050	0.100-0.300	54
D10S34-D10S94	0.028	9.4	0.000	0.080	9.4	0.00-0.100	0.001-0.200	39
D10S34-RBP3	0.129	17.4	0.072	0.161	17.5	0.010-0.100	0.050-0.200	71
D10S34-D10S15	0.136	20.3	0.047	0.200	21.6	0.001-0.100	0.100-0.300	69
D10Z1-RBP3	0.066	26.4	0.041	0.088	26.4	0.001-0.100	0.001-0.200	57
D10Z1-D10S15	0.065	19.8	0.010	0.127	20.3	0.00-0.100	0.050-0.200	57
D10S94-D10S15	0.051	16.9	0.000	0.069	17.4	0.00-0.100	0.001-0.200	47

Summary of the MEN2A consortium pairwise analysis. Each interval is listed in the first column with MEN2A intervals first, followed by adjacent intervals and then all other intervals. Columns 2 and 3 are the sex-average values for recombination frequency (θ) and the max LOD score (Z). Columns 4 and 5 are the sex-specific (male and female) genetic distance estimates, and column 6 is the corresponding maximum LOD score. Columns 7 and 8 are the 1 LOD unit support interval for each pairwise calculation. The MEN2A confidence intervals were determined by linear interpolation of adjacent data points (rows 1-6), while all other intervals are estimates based on the next closest data point and are in some cases severe overestimates (rows 7-21).

LIPED format. We have a utility that allows us to analyze many pedigrees with LIPED in a single integrated data file. We formed haplotypes at three loci. Both FNRB and RBP3 were typed at up to three sites. Several families, however, were not typed with all three probe-enzyme combinations. In that event, to integrate the analysis we built the haplotype definitions to code for partial data. All possible genotypes at the specific untyped system(s) were allowed for in the phenotype/genotype table. Similarly, haplotypes and partial haplotypes were built for D10Z1. The two enzyme systems for D10S15 appear to recognize the same polymorphism and as such no haplotypes were built; in fact, no collaborator contributed both PvuII and RsaI data.

Computer analyses and data summaries

The integrated analysis was accomplished on a VAX 8820 in the Biomedical Computer Center at Yale. Pairwise LOD scores were calculated at eight recombination frequencies; 0.00, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, and 0.4. These recombination frequencies were used separately for male and female recombination resulting in an 8 × 8 matrix of sex-specific recombination frequencies or 64 data points for each pairwise calculation in each family. Pairwise LOD scores were calculated for all combinations of FNRB, D10S34, D10Z1, D10S94, RBP3, D10S15, and MEN2A where applicable. This modified version of LIPED produced a single LODSUM data file, containing the 64-point data matrix of LOD scores for each possible pair of loci in each family. These unanalyzed files of intermediate results (about 10 megabytes) are freely available to all interested researchers. LOD scores were summed across families for each pairwise analysis into a report format which includes interpolated maximum values using the utility, ZMATRIX, designed and implemented by A. J. Pakstis.

Results

The LOD scores, genetic distances, and 1 LOD unit confidence intervals are summarized for all 21 pairwise combinations in Table 1. The confidence intervals for the MEN2A pairs were determined by linear interpolation of neighboring points. The confidence intervals for the other pairwise intervals were estimated to the next closest data point in the 8 × 8 matrix. The largest LOD score for MEN2A with any of the markers was with D10S15 at 64.4 with recombination rates of 2.8% in males and 4.6% in females.

The estimation of the genetic distance across the interval from FNRB to D10S15 is 2% recombination in males and 19.4% in females (Z_{max} = 36.4). This confirms the previous ob-

Table 2
Crossover Summary of the Consortium Analysis

Interval	# Families with at least One Male Crossover	# Families with at least One Female Crossover	# of Families with at least One Crossover of undetermined Sex	Total # of Families
FNRB-D10S15	2	13	5	20
FNRB-D10Z1	1	8	0	9
D10Z1-RBP3	2	8	2	12
Total Observations	5	29	7	41

Summary of families in the consortium data set that contain crossovers. Column 1 is the interval. If a crossover occurred between D10Z1 or D10S94 and either flanking marker set (FNRB/D10S34 on the short arm and RBP3/D10S94 on the long arm), then the crossover was sublocalized. When D10Z1 and D10S94 were not informative, the crossover was only placed in the larger region. Columns 2-4 are the number of families with at least one crossover of the given sex of the meiotic donor. This was determined by inspection of the LIPED summary tables for each family. A LOD score of $-\infty$ at $\theta = 0.00$ was evidence for an obligate recombinant in the particular family. In most cases, the sex of the recombinant donor could be determined by finding a non $-\infty$ LOD score at a male or female $\theta = 0.00$. In some cases this could not be determined, and that is the source of data in column 4. Column 5 is the total across the table of all of the obligate recombinant containing families.

servations that there is a drastic reduction in male recombination across the centromere (1,2). Table 2 summarizes the obligate crossovers detected from this data set. This was determined by counting the number of families with $Z = -\infty$ at $\theta = 0.00$, which implied that a particular family had at least one obligate recombinant. We have observed five families with at least one male recombinant in this region with no apparent bias towards either the short or long arm subregions.

The estimation of genetic distance between D10S34 and D10S15 is 4.7% in males and 20% in females ($Z_{max} = 21.6$). This shows a greater genetic distance in this interval than in the FNRB and D10S15 interval, superficially discordant with previously reported results suggesting that D10S34 is proximal to FNRB (4-6). However, the confidence intervals for both of these pairwise calculations do not exclude D10S34 being proximal to FNRB.

The greatest genetic distance between a short arm flanking marker and MEN2A is 11.4% in males (D10S34, see Discussion) and 7.8% in females (FNRB). On the long arm, the distances are 2.8% in males (D10S15) and 7.4% in females (RBP3). These distances should allow for presymptomatic genetic diagnoses of MEN 2A in affected families with accuracies of greater than 99% in both male and female donors assuming that flanking markers are informative and no crossover occurred in the interval. Closer tightly linked markers will increase the informativeness of the region in more patients and further increase the diagnostic capabilities of DNA-based testing (7).

Summary tables from the ZMATRIX pairwise linkage analysis of loci with MEN2A include Tables 3 through 8. The complete tables of all pairwise combination data are freely available upon request.

Discussion

The original goal of this analysis was to refine the position of MEN2A with respect to the flanking and most commonly studied loci; FNRB, D10S34, D10Z1, D10S94, RBP3, and D10S15. We have initiated this analysis by generating a linkage map based on pairwise distance estimates. The male, female, and sex average maps are shown in the Figure. Under each map is the estimated location of MEN2A based on the pairwise distance from each marker. Clearly, this analysis does not add any new location information to refine the position of MEN2A.

We did not detect any obligate recombinants between MEN2A and the known markers using this pairwise analysis. This lack of detection is caused by three factors. First, we used a linear age-of-onset curve with incomplete penetrance; therefore any recombinant recipients who are unaffected would not produce an obligate recombinant statistic using LIPED. Second, we incorporated a small allowance for phenocopies; any recombinant recipients that are affected would also not produce an obligate recombinant statistic using LIPED. Third, many of our MEN2A recombinant chromosomes are inferred from deceased donors with few offspring. Multipoint analysis should detect these recombinants. LIPED, however, does estimate a non-zero theta for Z_{max}, acknowledging the possibility of an obligate recombinant. A multipoint may be better suited for the detection of these crossovers by allowing for the unambiguous determination of linkage phase in the deceased meiotic recombinant donor.

The D10S34 distance in males appears to be aberrant. We interpret these D10S34 data as potentially erroneous for three reasons. First, of the 74 families that were typed for D10S34, only five estimate a genetic distance between D10S34 and MEN2A at significantly greater than 0% in males. If we remove these families from the data set and re-sum the LOD scores for D10S34 only, the estimates of genetic distances are more consistent (Table 9) with other data presented here (Figure, gray bars) and elsewhere (3-6). Second, although genetic heterogeneity is a possibility for this result, this is not supported by other loci typed in these families. Third, the recombination frequencies between D10S34 and both D10Z1 and D10S94 are 0.0 in males; the recombination frequencies between MEN2A and D10Z1 and D10S94 are also 0.0. Even allowing for the confi-

Summary Tables for Pairwise LOD Scores and Distances for Markers with MEN2A

Table 3
FNRB versus MEN2A

Θ(m\f)	.000	.001	.010	.050	.100	.200	.300	.400
.400	8.13	8.68	10.36	11.56	11.28	9.37	6.78	4.04
.300	11.46	12.02	13.74	14.99	14.72	12.78	10.13	7.26
.200	14.57	15.15	16.93	18.27	18.01	16.08	13.39	10.45
.100	17.28	17.88	19.79	21.24	21.01	19.09	16.37	13.39
.050	18.38	19.03	21.06	22.57	22.37	20.45	17.73	14.73
.010	19.00	19.74	21.96	23.54	23.35	21.44	18.71	15.72
.001	19.06	19.87	22.14	23.74	23.55	21.65	18.92	15.93
.000	19.06	19.88	22.16	23.76	23.58	21.67	18.95	15.95

Male genetic distances are shown vertically and female distances are shown horizontally. LOD scores at each male and female distance evaluated make up the 64 point matricies.

Table 4
D10S34 versus MEN2A

Θ(m\f)	.000	.001	.010	.050	.100	.200	.300	.400
.400	18.61	18.94	19.78	19.66	18.21	14.20	9.64	5.05
.300	20.90	21.22	22.07	21.99	20.55	16.55	11.92	7.19
.200	22.72	23.05	23.94	23.98	22.64	18.74	14.14	9.37
.100	23.24	23.59	24.62	25.03	23.93	20.29	15.82	11.08
.050	22.11	22.49	23.78	24.63	23.78	20.40	16.07	11.40
.010	17.63	18.19	20.38	22.33	21.96	19.07	15.00	10.47
.001	11.95	13.12	16.88	19.84	19.89	17.37	13.43	9.06
.000	9.17	11.08	15.62	18.96	19.18	16.73	12.84	8.57

Male genetic distances are shown vertically and female distances are shown horizontally. LOD scores at each male and female distance evaluated make up the 64 point matricies.

Table 5
D10Z1 versus MEN2A

Θ(m\f)	.000	.001	.010	.050	.100	.200	.300	.400
.400	12.43	12.45	12.50	11.99	10.90	8.17	5.18	2.42
.300	14.77	14.79	14.84	14.30	13.17	10.37	7.26	4.31
.200	17.26	17.28	17.33	16.79	15.65	12.81	9.64	6.57
.100	19.64	19.66	19.70	19.16	18.02	15.17	11.97	8.80
.050	20.70	20.72	20.77	20.24	19.09	16.24	13.02	9.82
.010	21.46	21.47	21.52	20.99	19.85	16.99	13.76	10.55
.001	21.60	21.61	21.67	21.14	20.00	17.14	13.91	10.67
.000	21.62	21.64	21.69	21.15	20.01	17.16	13.93	10.69

Male genetic distances are shown vertically and female distances are shown horizontally. LOD scores at each male and female distance evaluated make up the 64 point matricies.

Table 6
D10S94 versus MEN2A

Θ(m\f)	.000	.001	.010	.050	.100	.200	.300	.400
.400	12.24	12.22	12.00	11.02	9.77	7.23	4.72	2.47
.300	14.22	14.20	13.97	12.97	11.68	9.06	6.46	4.08
.200	16.20	16.18	15.95	14.93	13.62	10.95	8.31	5.87
.100	18.06	18.04	17.81	16.77	15.45	12.76	10.10	7.62
.050	18.91	18.88	18.65	17.61	16.28	13.59	10.92	8.43
.010	19.51	19.49	19.26	18.21	16.88	14.19	11.52	9.01
.001	19.64	19.61	19.38	18.33	17.00	14.31	11.65	9.13
.000	19.65	19.62	19.39	18.35	17.02	14.33	11.66	9.14

Male genetic distances are shown vertically and female distances are shown horizontally. LOD scores at each male and female distance evaluated make up the 64 point matricies.

Table 7
RBP3 versus MEN2A

Θ(m\f)	.000	.001	.010	.050	.100	.200	.300	.400
.400	14.12	17.18	20.63	22.65	21.76	17.51	12.16	6.82
.300	19.47	22.53	25.95	27.91	26.99	22.72	17.35	11.88
.200	24.82	27.89	31.32	33.36	32.58	28.48	23.11	17.50
.100	29.42	32.51	36.12	38.67	38.14	34.18	28.78	23.01
.050	30.90	34.14	38.25	41.14	40.71	36.82	31.42	25.56
.010	30.55	35.00	39.57	42.75	42.49	38.76	33.36	27.44
.001	29.79	34.53	39.42	42.97	42.83	39.15	33.77	27.83
.000	29.08	34.06	39.32	42.99	42.87	39.20	33.81	27.87

Male genetic distances are shown vertically and female distances are shown horizontally. LOD scores at each male and female distance evaluated make up the 64 point matricies.

Table 8
D10S15 versus MEN2A

Θ(m\f)	.000	.001	.010	.050	.100	.200	.300	.400
.400	28.64	31.04	33.00	33.31	31.37	25.54	18.64	11.50
.300	36.92	39.48	41.92	42.50	40.58	34.69	27.66	20.26
.200	44.95	47.80	50.61	51.29	49.37	43.47	36.40	28.85
.100	52.45	55.41	58.34	59.07	57.18	51.31	44.23	36.58
.050	55.43	58.43	61.41	62.16	60.28	54.45	47.39	39.73
.010	56.11	59.15	62.16	62.95	61.12	55.41	48.48	40.90
.001	54.08	57.13	60.20	61.16	59.53	54.08	47.30	39.79
.000	50.83	54.76	58.75	60.27	58.81	53.47	46.73	39.22

Male genetic distances are shown vertically and female distances are shown horizontally. LOD scores at each male and female distance evaluated make up the 64 point matricies.

dence limits, these observations are not consistent with a pairwise estimate of the distance between D10S34 and MEN2A of 0.119. Collectively, we provisionally conclude that some of the D10S34 data in these five families is likely to be erroneous. Whether this can be confirmed as due to sample mixups, electronic data manipulation errors, or misdiagnoses is now being investigated. While genetic heterogeneity in recombination frequencies cannot be ruled out as an explanation, the uncertainty should have little impact on presymptomatic diagnosis.

Even without this possible aberration, these pairwise linkage analyses do not greatly refine the position of MEN2A. Although one might be tempted to define the MEN2A region using the smallest region of overlap in the long arm, the confidence limits associated with each pairwise estimate are not reliable enough to conclude the absolute location of MEN2A. Furthermore, the addition of new tightly linked markers (such as D10S97, RET, D10S102, D10S30, and others that have not been seen to recombine with MEN2A) will not help refine the position of MEN2A using a complete statistical analysis. Each of these markers would predict an estimated location for MEN2A with substantial confidence intervals that would preclude a definitive answer. We expect that a multipoint analysis would also produce

Table 9
Scores with Data from Five Potentially Erroneous Families Excluded

Interval	$\theta_{m=f}$	$Z_{m=f}$	θ_m	θ_f	$Z_{m\neq f}$	Confidence Interval$_m$	Confidence Interval$_f$	Number of Families
MEN2A-D10S34	0.029	30.23	0.060	0.008	30.23	0.008-0.127	0.00-0.048	69
FNRB-D10S34	0.024	49.89	0.029	0.001	51.03	0.010-0.100	0.00-0.050	43
D10S34-D10Z1	0.045	22.37	0.000	0.090	24.57	0.00-0.100	0.010-0.200	55
D10S34-D10S94	0.028	9.35	0.000	0.080	9.35	0.00-0.100	0.010-0.200	39
D10S34-RBP3	0.117	23.44	0.057	0.155	24.24	0.010-0.100	0.050-0.300	68
D10S34-D10S15	0.132	23.10	0.056	0.194	24.32	0.010-0.100	0.100-0.300	69

LOD scores and genetic distance estimates for the consortium data for D10S34 pairwise data with the five potentially erroneous families removed (see text). Each D10S34 interval is listed in the first column. Columns 2 and 3 are the sex-average values for recombination frequency (θ) and the maximum LOD score (Z). Columns 4 and 5 are the sex-specific (male and female) genetic distance estimates, and column 6 is the corresponding maximum LOD score. Columns 7 and 8 are the 1 LOD unit confidence interval for each pairwise calculation. The MEN2A confidence interval was determined by linear interpolation of adjacent data points (row 1), while all other intervals are estimates based on the next closest data point and are in some cases severe overestimates (rows 2-6).

similar results, placing MEN2A over a broad range of positions between D10S34 and RBP3. Only when additional markers help define the positions of the few crossovers in the region will a more precise localization result.

This analysis provides better estimates for the genetic size of the MEN2A region. The recombination frequencies between MEN2A and these markers will help determine more accurately a presymptomatic genetic diagnosis in families with MEN 2A. Furthermore, this provides a framework in which to place closer and better markers that will in turn help in diagnostic efforts. These flanking markers will continue to be valuable for confirmation of presymptomatic tests with closer markers and will help refine the positions of specific crossovers with respect to MEN2A.

Although we plan to continue analyses and interpretations of this data set as a consortium, it is freely available to any researcher in the field who wishes to join the consortium as a collaborator.

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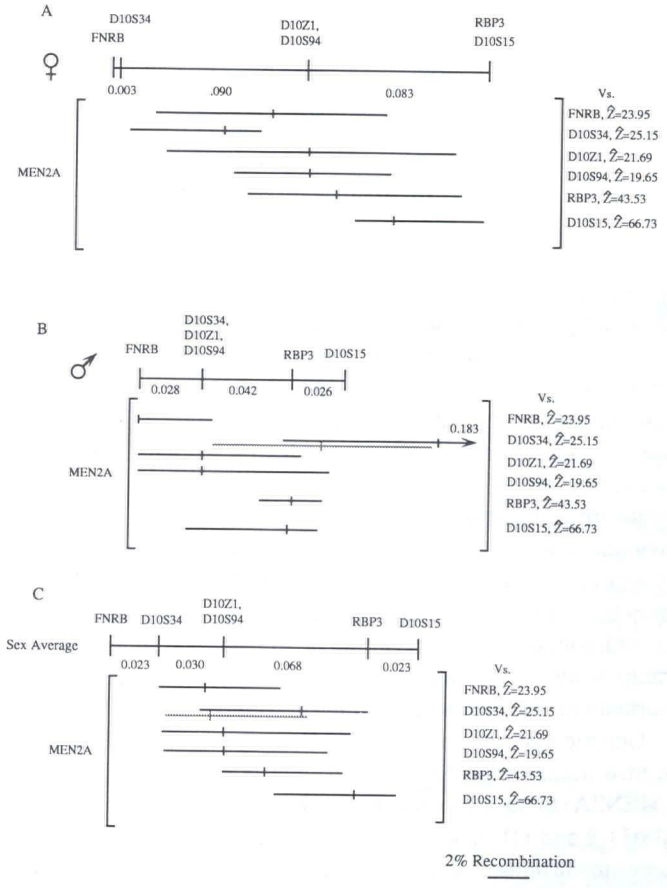

Figure—Genetic maps of human chromosome 10 pericentromeric region. These maps are drawn using data generated exclusively from this pairwise consortium analysis. Each map is drawn for the markers using the interval distance of adjacent markers, starting at FNRB. The vertical bars below each map are the location of MEN2A with the confidence intervals (horizontal bars) determined in Table 1. The gray bars are the D10S34 estimates based only on data in Table 9. The column on the right shows the peak LOD score for MEN2A and the specific marker. Panel A (top) is the female map; panel B (middle) is the male map; and panel C (bottom) is the sex-average map. The confidence intervals for the sex-average map are based on the arithmetic average of the male and female values. Quadratic interpolation of the sex-average data was not possible.