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Genetic Analysis of Eight Loci Tightly Linked to Neurofibromatosis I

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Summary

The genetic locus for neurofibromatosis 1 (NF1) has recently been mapped to the pericentromeric region of chromosome 17. We have genotyped eight previously identified RFLP probes on 50 NF1 families to determine the placement of the NF1 locus relative to the RFLP loci. Thirty-eight recombination events in the pericentromeric region were identified, eight involving crossovers between NF1 and loci on either chromosomal arm. Multipoint linkage analysis resulted in the unique placement of six loci at odds >100:1 in the order of pter–A10-41–EW301–NF1–EW207–CRI-L581–CRI-L946–qter. Owing to insufficient crossovers, three loci—D17Z1, EW206, and EW203—could not be uniquely localized. In this region female recombination rates were significantly higher than those of males. These data were part of a joint study aimed at the localization of both NF1 and tightly linked pericentromeric markers for chromosome 17.

Introduction

von Recklinghausen neurofibromatosis (NF1) has recently been localized by genetic linkage to loci in the pericentromeric region of chromosome 17 (Barker et al. 1987*b;* Seizinger et al. 1987*b*). Subsequently, rapid progress has been made in identifying additional probes that detect linked RFLP (Fain et al. 1987; Stephens et al. 1987; White et al. 1987) and in demonstrating linkage of NF1 to chromosome 17 markers in a large number of affected families (Diehl et al. 1987; Fain et al. 1987; Pericak-Vance et al. 1987; Seizinger et al. 1987*a;* Stephens et al. 1987; Upadhyaya et al. 1987; White et al. 1987).

In the present paper we report the results of genotyping 50 NF1-affected families with eight tightly linked probes from the pericentromeric region of chromosome 17. We also describe the recombinant chromosomes identified and present a multipoint map of the NF1 region of chromosome 17, on the basis of our data set. These data represent our contribution to a joint study conducted under the auspices of the National Neurofibromatosis Foundation (NNFF). Linked probes were shared among consortium members for genotyping on NF1-affected families, and the pooled genotypic data were submitted for multipoint analysis. Analysis of the joint data set should result in localizing the tightly linked probes relative both to each other and to the NF1 gene and in reducing the confidence intervals to yield more precise distances between loci in the NF1 region. On the basis of these results, it will be determined whether the probes are sufficient for a diagnostic test for NF1. In addition, critical recombinants would be identified and shared among laboratories to aid future NF1 research. The multipoint analysis resulting from genotypic data submitted to the NNFF Consortium is published in this issue (Goldgar et al. 1989).

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Material and Methods

Family Resources

Forty-two families segregating NF-1 were diagnosed

and collected by V.M.R. through the Baylor Neurofibromatosis Program and are identified by the prefix BAY. Eight additional NF1-affected families were diagnosed and collected by F.S.C. at the University of Michigan and are identified by the prefix UMI. The criteria for diagnosis of NF1 are outlined in Riccardi and Eichner (1986, pp. 1–36) and Riccardi and Carey (1987). Lymphoblastoid cell lines were established for all family members by transformation with Epstein-Barr virus (Neitzel 1986). Forty-five of these families have been used in previously published NF1 linkage studies (Stephens et al. 1987).

DNA Probes

The RFLP probes, CRI-L581 and CRI-L946, identify the loci D17S37 and D17S36, respectively. Elsewhere we have described their isolation and mapping to chromosome 17 (Donis-Keller et al. 1987) and linkage to NF1 (Stephens et al. 1987; Upadhyaya et al. 1987). Data on properties of both RFLP probes have been submitted to the Howard Hughes Medical Institute Human Gene Mapping Library, and genotypic data have been submitted to the Centre d'Etude de Polymorphisme Humain (CEPH) data base. During this study we identified a second RFLP detected by CRI-L946, in addition to the previously described *Msp*I polymorphism. The second RFLP is revealed by the enzyme *Bgl*II and has two alleles, one 7.5 and one 6.5 kb in size. The combined heterozygosity of the *Msp*I and *Bgl*II polymorphisms for the probe CRI-L946 is .67. In this study we genotyped the *Taq*I RFLP revealed by the CRI-L581 probe and both the *Msp*I and *Bgl*II RFLPs revealed by CRI-L946.

The characteristics and physical localizations of the RFLP probes A10-41, EW203, EW206, EW207, and EW301 have been described elsewhere (Fain et al. 1987). In addition to the two alleles described for the *Bgl*II RFLP for probe EW203 (Fain et al. 1987), we detected a rare third allele segregating in eight families; these three alleles are clustered between 2.8 and 3.1 kb. For this study we typed the following probe/enzyme systems. A10-41 *Msp*I and *Pvu*II, EW203 *Bgl*II and *Taq*I; EW206 *Msp*I, EW207 *Bgl*II and *Hin*dIII, and EW301 *Bgl*II and *Taq*I.

The probe p17H8 recognizes the D17Z1 locus which comprises >1 million bp of alpha satellite DNA located at the centromere of chromosome 17 (Willard et al. 1986, 1987). We conservatively typed the complex *Eco*RI polymorphic repetitive fragments by requiring that the different parental haplotypes be observed in the offspring before a parent was scored as a heterozygote (Willard et al. 1986, 1987).

DNA Isolation and RFLP Typing

High-molecular-weight DNA from lymphoblastoid cells are isolated either manually or automatically with a DNA extractor (Model 340A, Applied Biosystems, Inc., Foster City, CA) as described elsewhere (Stephens et al. 1987). Methods for restriction-endonuclease digestion, electrophoresis, Southern blotting, and hybridization with labeled DNA probes were as described elsewhere (Donis-Keller et al. 1987).

Linkage Analyses

Multipoint and two-point analyses were performed with the program CRI-MAP (Barker et al. 1987*a;* Donis-Keller et al. 1987), which has recently been extended to handle general pedigrees (P. G., unpublished data). Complete penetrance at the neurofibromatosis locus was assumed in all analyses. The multipoint map was constructed by sequential addition of loci, as described elsewhere (Barker et al. 1987*a;* Donis-Keller et al. 1987).

Data Checking

All autoradiographs were independently scored by at least two individuals, and computer data entry was checked against the original data sheets. The CHROMPICS option of the program CRI-MAP (Barker et al. 1987*b;* Donis-Keller et al. 1987) was used to check for more subtle errors. CHROMPICS displays the maximum likelihood phase choice for loci on the two chromosomes of each offspring in a particular family in the locus order assigned by the multipoint analysis. Loci involved in recombination events can be easily identified, and the data can be easily checked for consistency. In addition, all families showing recombinations between NF1 and RFLP loci – and a few families with crossovers between RFLP loci – were examined for possible nonpaternity and/or sample mixup with one of two probes that detect highly polymorphic DNA sequences, 3′HVR (Jarman et al. 1986) or CRI-L1065 (Kazazian et al. 1986; Donis-Keller et al. 1987). The possibility of sample mixup between parents or among siblings was examined by probing the recombinant families with a Y chromosome–specific probe, pDP105 (Disteche et al. 1986).

Results

Pairwise Marker Analysis

The pairwise lod scores for NF1 and eight RFLP loci are shown in table 1. The tight linkage between the DNA markers and NF1 is consistent with linkages observed for other NF1 family studies (Barker et al. 1987*b;* Fain

Table 1

Pairwise Lod Scores for NF1 and Chromosome 17 Markers

Markers	Lod Score at $\hat{\theta}$ of								$\hat{z}$	$\hat{\theta}$
	.001	.01	.05	.10	.20	.30	.40	.50		
A10-41	4.64	7.51	9.01	9.15	8.52	7.55	6.66	6.13	9.17	.09
	8.15	9.10	9.07	8.55	7.14	5.58	4.11	3.04		.03
	3.62	7.35	8.91	8.53	6.48	3.96	1.59	.00	8.92	.06
EW301	7.86	9.73	10.55	10.41	9.50	8.37	7.32	6.67	10.56	.06
	9.62	10.45	10.37	9.69	7.98	6.20	4.63	3.63		.02
	6.92	9.62	10.36	9.54	6.96	4.10	1.56	.00	10.41	.04
D17Z1	7.22	7.18	7.01	6.78	6.34	5.93	5.60	5.42	7.22	.00
	7.21	7.11	6.65	6.06	4.83	3.59	2.47	1.81		.00
	7.21	7.07	6.43	5.62	3.95	2.30	.84	.00	7.22	.00
EW203	3.75	6.62	8.14	8.30	7.70	6.75	5.81	5.24	8.31	.09
	7.28	8.14	8.22	7.73	6.42	5.00	3.74	3.07		.03
	2.72	6.45	8.05	7.72	5.80	3.43	1.24	.00	8.07	.06
EW206	9.63	9.58	9.37	9.10	8.53	7.95	7.40	6.92	9.63	.00
	9.62	9.48	8.84	8.02	6.33	4.64	3.13	2.11		.00
	9.61	9.42	8.58	7.50	5.32	3.20	1.32	.00	9.63	.00
EW207	8.24	9.12	9.31	8.96	7.94	6.83	5.84	5.23	9.35	.03
	6.83	8.67	9.35	9.04	7.81	6.38	5.07	4.12		.05
	5.72	8.45	9.31	8.65	6.40	3.86	1.56	.00	9.33	.04
CRI-L581	2.89	5.76	7.24	7.35	6.64	5.60	4.65	4.21	7.38	.08
	4.68	6.55	7.37	7.22	6.30	5.15	4.03	3.17		.06
	.20	4.93	7.23	7.20	5.57	3.37	1.31	.00	7.35	.07
CRI-L946	12.09	11.96	11.36	10.60	9.07	7.60	6.39	5.79	12.11	.00
	9.63	11.47	12.10	11.74	10.36	8.77	7.32	6.32		.05
	9.62	11.32	11.36	10.23	7.32	4.26	1.60	0.00	11.61	.03

NOTE.—Lod scores at varying recombination fractions for each pairwise analysis are shown in three lines, in the order female, male, and sex averaged. The sex-specific $\hat{z}$ ($= \log_{10} [L(\hat{\theta}_{females}, \hat{\theta}_{males})/L(.5, .5)]$, where L is the sex-specific likelihood function), is given in the first line with the female data. The sex-averaged $\hat{z}$ is shown in the third line. $\hat{z}$ = maximum lod score. $\hat{\theta}$ = recombination fraction at $\hat{z}$.

et al. 1987; Upadhyaya et al. 1987). Table 2 shows the pairwise lod scores of the eight pericentromeric RFLP loci. Significant differences in female and male recombination fractions were observed between several pairs of loci: A10-41 and EW203 ($\chi^2_{(1)} = 6.67$, $P < .01$), EW301 and EW206 ($\chi^2_{(1)} = 4.69$, $P < .05$), and EW301 and CRI-L946 ($\chi^2_{(1)} = 8.33$, $P < .005$) (table 2).

Multipoint Analysis

Six loci were uniquely ordered at odds 100:1 by multipoint analysis. These six loci, including NF1, span a distance of 16 cM on the sex-averaged linkage map (fig. 1). The placement of the three other loci—D17Z1, EW206, and EW203—could not be resolved at odds >100:1. The possible positions of these loci, along with their relative odds, are shown in figure 1. This order of loci is consistent with the reported physical localizations of A10-41 and EW301 to the p proximal arm of chromosome 17 (Fain et al. 1987) and of EW203, EW206, EW207, CRI-L581, and CRI-L946 to the q proximal arm (Fain et al. 1987, 1989; Fountain et al. 1989).

Recombination Events Identified

We have identified a total of 38 chromosomes with recombination events in the pericentromeric region of chromosome 17. Twenty-nine of these, including all those informative for NF1, are depicted in table 3. On the basis of the order of loci shown in table 3, nine chromosomes have recombination events between NF1 and the nearest informative locus; eight of these recombinants are NF1-affected individuals. One double recombination event was observed (table 3, BAY34, individual 3) involving the loci EW301–D17Z1–EW207. This appears to be a true double crossover and not an error in the order of loci, since physical mapping has shown

Table 2

Sex-specific Lod Scores from Pairwise Linkage Analysis of Eight Markers in the Pericentromeric Region of Chromosome 17

Markers	$\hat{z}$	$\hat{\theta}_f$	$\hat{\theta}_m$
A10-41 vs. EW301	7.71	.09	.03
A10-41 vs. EW203[a] ...	4.17	.29	.00
A10-41 vs. EW206	6.61	.04	.00
A10-41 vs. EW207	10.73	.08	.00
A10-41 vs. CRI-L581 ..	4.49	.20	.07
A10-41 vs. CRI-L946 ..	3.47	.23	.08
A10-41 vs. D17Z1	8.43	.00	.00
EW301 vs. EW203	3.64	.21	.08
EW301 vs EW206[a]	5.97	.15	.00
EW301 vs. EW207	10.38	.07	.00
EW301 vs. CRI-L581 ..	6.25	.13	.09
EW301 vs. CRI-L946[a] .	6.41	.21	.00
EW301 vs. D17Z1	4.78	.00	.08
EW203 vs. EW206	9.53	.07	.00
EW203 vs. EW207	10.07	.05	.00
EW203 vs. CRI-L581 ..	14.13	.01	.01
EW203 vs. CRI-L946 ..	10.41	.06	.00
EW203 vs. D17Z1	4.71	.05	.06
EW206 vs. EW207	6.62	.00	.00
EW206 vs. CRI-L581 ..	8.23	.00	.03
EW206 vs. CRI-L946 ..	3.67	.13	.05
EW206 vs. D17Z1	3.61	.00	.00
EW207 vs. CRI-L581 ..	7.29	.05	.06
EW207 vs. CRI-L946 ..	4.84	.10	.07
EW207 vs. D17Z1	4.43	.04	.07
CRI-L581 vs. CRI-L946	13.58	.05	.00
CRI-L581 vs. D17Z1 ..	4.99	.03	.03
CRI-L946 vs. D17Z1 ..	2.88	.09	.12

NOTE.—$\hat{z}$ = maximum sex-specific lod score; $\hat{\theta}_f$ = recombination fraction for females at $\hat{z}$; $\hat{\theta}_m$ = recombination fraction of males at $\hat{z}$.

[a] Significant differences in female and male recombination fractions ($P < .05$).

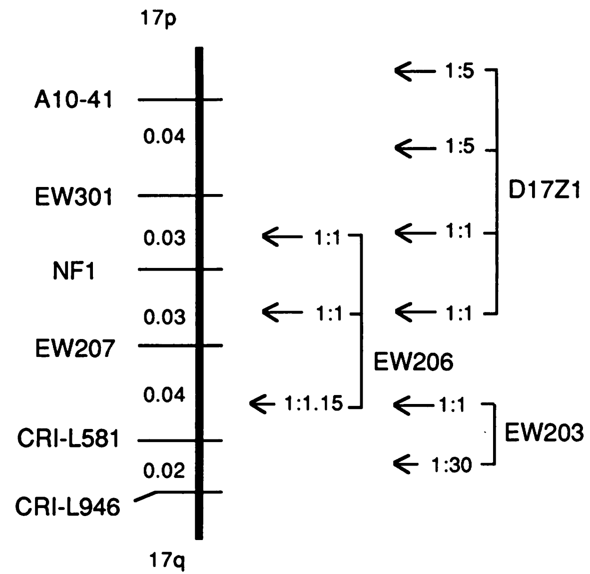

Figure 1 Linkage map of loci in pericentromeric region of chromosome 17. The given order of loci identified by the RFLP probes is favored over alternate orders by odds >100:1. Distances between loci are given as sex-averaged recombination fractions. Subchromosomal localization of RFLP probes permitted orientation of the genetic linkage map relative to the physical chromosome (see Results; Fain et al. 1987). Three loci could not be uniquely ordered with respect to the others; the arrows indicate the possible placements, along with their odds relative to the most likely placement.

the centromere (D17Z1) is flanked by EW301 and (EW206, EW207, and CRI-L946) (Fain et al. 1987, 1989).

Discussion

We have demonstrated both tight linkage between the NF1 locus segregating in our collection of 50 disease families and eight RFLP loci located in the pericentromeric region of chromosome 17 (tables 1, 2). Multipoint analysis resulted in a unique order for five RFLP loci and the NF1 locus spanning 16 cM on the sex-averaged map (fig. 1). The order of these loci is consistent with the genetic mapping data of Fain et al. (1987), who described the most likely order of four of the loci as being A10-41–EW301–NF1–EW207. Our order of loci is also consistent with physical mapping data that show A10-41 and EW301 to be on the p proximal arm and EW203, EW206, and EW207 to be on the q proximal arm (Fain et al. 1987). Three RFLP probes—EW206, EW203, and D17Z1—could not be uniquely positioned on the map because of an insufficient number of crossovers involving these loci in our data set. We could not place the NF1 locus on either chromosomal arm, since the exact position of the centromeric locus D17Z1 remains unclear. However, pooling our genotypic data with those generated by other consortium members using these same probes will increase the chances for unambiguously placing all the loci (Goldgar et al. 1989).

In three intervals in the pericentromeric region, female recombination frequencies were significantly higher than those observed for males (table 2). This difference is reflected in the length of the female genetic linkage map at 25 cM compared with the male map at 9 cM (data not shown). NF1 was localized between

Table 3

Summary of Recombination Events between Chromosome 17 Pericentromeric Loci

Kindred, Individual	NF1 Status	Loci								
		A10-41	EW301	D17Z1	NF1	EW206	EW207	EW203	L581	L946
BAY 10, 6	A	0	1	–	1	–	1	1	1	1
UMI 5, 504	A	0	1	–	1	1	–	1	1	1
BAY 17, 3	A	0	–	–	1	1	–	–	1	1
BAY 14, 5	A	0	–	–	–	–	1	1	1	1
BAY 21, 3	A	0	–	–	–	–	–	1	1	–
BAY 34, 3	U	–	0	1	–	–	0	0	–	0
BAY 43, 4	A	–	0	1	–	–	1	1	1	1
UMI 4, 408	A	–	0	1	1	1	–	1	–	–
BAY 15, 8	A	1	1	–	0	–	–	0	–	–
UMI 5, 507	A	0	0	–	1	1	–	1	1	1
BAY 17, 4	U	0	0	–	–	–	1	1	1	–
BAY 35, 2	A	–	0	–	–	–	1	1	1	1
UMI 16, 701	U	0	0	0	–	–	1	1	–	1
BAY 28, 2	A	0	0	–	0	–	–	1	1	–
BAY 77, 4	A	–	–	–	1	–	0	0	–	–
BAY 77, 12	U	–	–	–	0	–	1	–	–	–
BAY 28, 3	A	0	0	–	0	–	–	1	1	–
BAY 77, 9	A	–	1	–	1	–	–	0	–	–
BAY 45, 3	A	–	–	–	1	–	–	–	0	–
BAY 8, 2	A	0	–	–	–	0	–	1	–	1
BAY 25, 3	A	0	0	–	0	–	0	1	1	1
BAY 31, 4	U	0	0	–	–	0	0	1	1	1
BAY 13, 6	A	0	0	0	0	–	0	–	1	1
BAY 21, 4	A	1	–	–	1	1	1	–	0	–
BAY 40, 4	A	0	–	–	0	0	0	–	–	1
BAY 58, 3	A	–	–	–	–	–	–	0	1	1
BAY 14, 4	A	0	–	–	–	–	0	0	0	1
BAY 25, 4	A	0	0	–	–	–	–	–	0	1
BAY 78, 9	U	0	0	–	–	0	0	0	0	1

Note.—Loci are listed in their most probable order as determined by cri-map. The loci D17Z1, NF1, and EW206 are bracketed to indicate that these loci are unseparated by crossovers. The most probable phase is shown for each recombinant chromosome as determined by the chrompics option of the cri-map program; alleles designated 0 were inherited from one grandparent, while those designated 1 were derived from the other grandparent, and a minus sign (–) designates a noninformative locus. For brevity's sake, nine additional recombinant chromosomes were omitted: four with crossovers between A10-41 and EW301, four with crossovers between EW301 and informative markers on the q arm, and one with a crossover between D17Z1 and EW207. A = affected; U = unaffected.

EW301 and EW207 (fig. 1), and the distance between these two loci was 10 cM in females and 3 cM in males. Increased female recombination frequencies between loci in the NF1 region have been documented elsewhere (Barker et al. 1987*b;* Fain et al. 1987; Stephens et al. 1987). These data indicate that sex-based differences in recombination rates will need to be considered in risk assessment for prenatal and presymptomatic diagnostic tests based on genetic linkage.

In the present study we identified 38 recombination events in the pericentromeric regions of chromosome 17 (table 3). Nine recombination events involved the NF1 locus, with three crossovers between NF1 and loci on the p arm and six crossovers between NF1 and loci on the q arm (table 3). These recombinant chromosomes should prove valuable for the rapid localization of newly isolated polymorphic loci in the pericentromeric region of chromosome 17.

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References

Barker, D., P. Green, R. Knowlton, J. Schumm, E. Lander, A. Oliphant, H. Willard, G. Akots, V. Brown, T. Gravius, C. Helms, C. Nelson, C. Parker, K. Rediker, M. Rising, D. Watt, B. Weiffenbach, and H. Donis-Keller. 1987*a*. Genetic linkage map of human chromosome 7 with 63 DNA markers. Proc. Natl. Acad. Sci. USA **84**:8006–8010.

Barker, D., E. Wright, K. Nguyen, L. Cannon, P. Fain, D. Goldgar, D. T. Bishop, J. Carey, B. Baty, J. Kivlin, H. Willard, J. S. Waye, G. Greig, L. Leinwand, Y. Nakamura, P. O'Connell, M. Leppert, J.-M. Lalouel, R. White, and M. Skolnick. 1987*b*. Gene for von Recklinghausen neurofibromatosis is in the pericentric region of chromosome 17. Science **236**:1100–1102.

Diehl, S. R., M. Boehnke, R. P. Erickson, A. B. Baxter, M. A. Bruce, J. L. Lieberman, D. J. Platt, L. M. Ploughman, K. A. Seiler, A. M. Sweet, and F. S. Collins. 1987. Linkage analysis of von Recklinghausen neurofibromatosis to DNA markers on chromosome 17. Genomics **1**:361–363.

Disteche, C. M., L. Brown, H. Sall, C. Friedman, H. C. Thuline, D. I. Hoar, R. A. Pagon, and D. C. Page. 1986. Molecular detection of a translocation (Y:15) in a 45,X male. Hum. Genet. **74**:372–377.

Donis-Keller, H., and 32 coauthors. 1987. A genetic linkage map of the human genome. Cell **51**:319–337.

Fain, P. R., D. F. Barker, D. E. Goldgar, E. Wright, K. Nguyen, J. Carey, J. Johnson, J. Kivlin, H. Willard, C. Mathew, B. Ponder, and M. Skolnick. 1987. Genetic analysis of NF1. Identification of close flanking markers on chromosome 17. Genomics **1**:340–345.

Fain, P. R., E. Wright, H. F. Willard, K. Stephens, and D. F. Barker. 1989. The order of loci in the pericentric region of chromosome 17, based on evidence from physical and genetic breakpoints. Am. J. Hum. Genet. **44**:68–72.

Fountain, J. W., M. R. Wallace, A. M. Brereton, P. O'Connell, R. L. White, D. C. Rich, D. H. Ledbetter, R. J. Leach, R. E. K. Fournier, A. G. Menon, J. F. Gusella, D. Barker, K. Stephens, and F. S. Collins. 1989. Physical mapping of the von Recklinghausen neurofibromatosis region on chromosome 17. Am. J. Hum. Genet. **44**:58–67.

Goldgar, D. E., P. Green, D. M. Parry, and J. J. Mulvihill. 1989. Multipoint linkage analysis in neurofibromatosis type 1: an international collaboration. Am. J. Hum. Genet. **44**:6–12.

Jarman, A. P., R. D. Nickolls, D. J. Weatherall, J. B. Clegg, and D. R. Higgs. 1986. Molecular characterization of a hypervariable region downstream of the human alpha-globin gene cluster. EMBO J. **5**:1857–1863.

Kazazian, H. H., Jr., S. H. Orkin, C. D. Boehn, S. C. Goff, C. Wong, C. E. Dowling, P. E. Newburger, R. G. Knowlton, V. Brown, and H. Donis-Keller. 1986. Characterization of a spontaneous mutation to a beta-thalessemia allele. Am. J. Hum. Genet. **38**:960–967.

Neitzel, H. 1986. A routine method for the establishment of permanent growing lymphoblastoid cell lines. Hum. Genet. **73**:320–326.

Pericak-Vance, M. A., L. H. Yamaoka, J. M. Vance, K. Small, G. O. D. Rosenwasser, P. C. Gaskell, Jr., W.-Y. Hung, M. J. Alberts, C. S. Haynes, M. C. Speer, J. R. Gilbert, M. Herbstreith, A. S. Aylsworth, and A. D. Roses. 1987. Genetic linkage studies of chromosome 17 RFLPs in von Recklinghausen neurofibromatosis (NF1). Genomics **1**: 349–352.

Riccardi, V. M., and J. Carey. 1987. von Recklinghausen neurofibromatosis and genetic linkage studies: clinical considerations. J. Med. Genet. **24**:521–522.

Riccardi, V. M., and J. E. Eichner. 1986. Neurofibromatosis: phenotype, natural history, and pathogenesis. Johns Hopkins University Press, Baltimore.

Seizinger, B. R., G. A. Rouleau, A. H. Lane, G. Farmer, L. J. Ozelius, J. L. Haines, D. M. Parry, F. R. Korf, M. A. Pericak-Vance, A. G. Faryniarz, W. J. Hobbs, J. A. Iannazzi, J. C. Roy, A. Menon, J. L. Bader, M. A. Spence, M. V. Chao, J. J. Mulvihill, A. D. Roses, R. L. Martuza, X. O. Breakefield, P. M. Conneally, and J. F. Gusella. 1987*a*. Linkage analysis in von Recklinghausen neurofibromatosis (NF1) with DNA markers for chromosome 17. Genomics **1**:346–348.

Seizinger, B. R., and 32 coauthors. 1987*b*. Genetic linkage of von Recklinghausen neurofibromatosis to the nerve growth factor receptor gene. Cell **49**:589–594.

Stephens, K., V. M. Riccardi, M. Rising, S. Ng, P. Green, F. S. Collins, K. S. Rediker, J. A. Powers, C. Parker, and H. Donis-Keller. 1987. Linkage studies with chromosome 17 DNA markers in 45 neurofibromatosis 1 families. Genomics **1**:353–357.

Upadhyaya. M., M. Sarfarazi, S. M. Huson, K. Stephens, W. Broadhead, and P. S. Harper. 1987. Chromosome 17 markers and von Recklinghausen neurofibromatosis: a genetic linkage study in a British population. Genomics **1**:358–360.

White, R., Y. Nakamura, P. O'Connell, M. Leppert, J.-M. Lalouel, D. Barker, D. Goldgar, M. Skolnick, J. Carey, C. E. Wallis, C. P. Slater, C. Mathew, and B. Ponder. 1987. Tightly linked markers for the neurofibromatosis type 1 gene. Genomics **1**:364–367.

Willard, H. F., G. M. Greig, V. E. Powers, and J. S. Waye. 1987. Molecular organization and haplotype analysis of

centromeric DNA from human chromosome 17: implications for linkage in neurofibromatosis. Genomics **1**:368–373.

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