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Linkage Analysis of Chromosome 17 Markers in British and South African Families with Neurofibromatosis Type 1

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Summary

Nine markers from the pericentromeric region of chromosome 17 were typed in 16 British and five South African families with neurofibromatosis type 1 (NF1). The markers—p17H8, pHHH202, and EW204—were linked to NF1 at recombination fractions <1%. No evidence of locus heterogeneity was detected. Inspection of recombinant events in families informative for several markers suggests that the NF1 gene is located between the markers EW301 (cen-p11.2) and EW206 (cen-q12) and possibly distal to pHHH202 (q11.2-q12).

Introduction

The gene for neurofibromatosis type 1 (NF1; von Recklinghausen NF) has recently been mapped to the pericentromeric region of chromosome 17 (Barker et al. 1987; Seizinger et al. 1987*b*). Further linkage studies established flanking markers (Fain et al. 1987) and a tightly linked marker (White et al. 1987) for the gene. We now report an analysis of nine chromosome 17 markers in British and South African families with NF1.

Material and Methods

Our sample set contained 144 informative meioses and consisted of 16 British NF1 families (ICR 05–20) who were ascertained through the United Kingdom neurofibromatosis association LINK, four South African families of Indian descent ascertained through the Department of Human Genetics at the University of Cape Town (ICR 01–04), and an Afrikaner family from the MRC Cytogenetics Unit at the University of Stellenbosch (ICR 21). Diagnostic criteria and clinical descriptions have been documented elsewhere (Mathew et al. 1987; Wallis and Slater 1987).

DNA isolation, restriction digestion, electrophoresis, blotting, and hybridization with radioactively labeled probes were carried out by standard methods (Wong et al. 1987). The following chromosome 17 markers were typed in the NF1 families: pA10–41 (Barker et al. 1987); EW301, EW204, EW206, and EW207 (Fain et al. 1987); p17H8 (Willard et al. 1986); pHHH202 (White et al. 1987); erbA1 (Rider et al. 1987); and COS H17.3 (Moore et al., in press).

Likelihood computations were carried out using a modification of the LINKAGE program (Lathrop et al. 1985) and assuming a population frequency of 2×10^{-4} for the NF1 gene and a penetrance of 95%.

Results and Discussion

LOD scores for pairwise analysis of the nine markers and NF1 in the families is given in table 1. The data suggest that the most closely linked markers are the α-satellite centromere probe, p17H8, and the proximal long arm markers pHHH202 and EW204. This correlates well with the findings of Barker et al. (1987), which placed the NF1 gene in the pericentromeric region of chromosome 17. A recombinant between the erbA1 on-

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Table 1

LOD Scores for Pairwise Analysis of Nine Chromosome 17 Markers and NF1

Marker	Z ($\theta_m = \theta_f$)	$\theta_m = \theta_f$[a]	Regional Assignment[b]
pA10-41	.90	.20	p11.2-p12
EW301	1.80	.10	cen-p11.2
p17H8	4.73	.01	cen
pHHH202	8.63	.00	q11.2-q12
EW204	5.51	.00	cen-q12
EW206	3.77	.05	cen-q12
EW207	2.60	.05	cen-q12
erbA1	1.14	.10	q11.2-q21.1
COS H17.3	1.36	.15	q11.2-q12

[a] Eight of nine recombinations in the data set are female, but insufficient data are available for separate calculations of θ_m and θ_f.

[b] Skolnick et al. (1987); vanTuinen et al. (1987).

cogene and NF1 was detected, which supports the results of Seizinger et al. (1987*a*) that exclude erbA1 as a candidate gene for NF1. Of the nine recombinant events observed in the families, eight were from a female parent, which suggests that significant sex differences exist for recombination in this region of chromosome 17.

Four of the families included in the present study were South Africans of Indian descent. They were phenotypically somewhat unusual in that (*a*) macromelanosomes were absent in skin biopsies of cafe-au-lait macules and (*b*) no Lisch nodules were observed on slit-lamp examination (Wallis and Slater 1987). All four families were informative for either p17H8 or pHHH202, and all showed linkage of the NF1 phenotype to these markers (table 1). This provides further evidence that NF1 is caused by mutation at a single locus.

The data from this sample set are being pooled with those of other groups participating in the neurofibromatosis linkage consortium, to construct a high-resolution multipoint linkage map of the NF1 locus (Goldgar et al. 1988). However, some preliminary observations on the position of the NF1 gene relative to the markers tested can be made by inspection of recombinant events in families informative for three or more of these markers (table 2). These events suggest that the NF1 gene lies proximal to EW301, which is located on the proximal short arm of the chromosome, and proximal both to the probe COS H17.3 from the vicinity of the breakpoint in acute promyelocytic leukemia (Moore et al., submitted) and to the markers EW206 and 207 on the proximal long arm. We have also detected an individual who is recombinant with both pHHH202 and EW301 (ICR 01; table 2). Since other analyses have indicated that NF1 is unlikely to be distal to EW301 on the short

Table 2

NF1 Recombinant Events

Family	Parent Sex	NF1 Phenotype	Haplotype
ICR 01	F	U	EW301, pHHH202 —X—
ICR 50	F	A	EW301 —X— p17H8,EW204,erbA1
ICR 80	F	U	pA10-41 —X— pHHH202 —X— EW207
ICR 11	F	U	pA10-41,EW301 —X— EW206
ICR 15	F	A	EW301,pHHH202 —X— COS H17.3
ICR 21	M	A	pHHH202,EW204 —X— EW206

NOTE.—Summary of recombinant events in families informative for three or more markers. Markers underlined are recombinant with NF1. A = affected; U = unaffected.

arm (Fain et al. 1987), this suggests that NF1 is located distal to pHHH202 on the long arm, although this family was not informative with markers distal to pHHH202. However, the apparently recombinant individual is young (aged 11 years at her last examination) and unaffected, with one cafe-au-lait macule, and may be an example of partial expression of the NF1 gene.

The existence of markers that are tightly linked to the NF1 gene, as well as the lack of evidence for locus heterogeneity in the large number of families analyzed thus far (table 1; Skolnick at al. 1987), raise the possibility of providing a prenatal or presymptomatic diagnostic test for those families who require it.

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