its small size and the negative data for the three RFLPs reported here, two of which have been localised to 20p and one to 20q. Negative linkage between VRNF and the IGLC locus on the long arm of chromosome 22 is interesting in view of the recent work of Seizinger *et al*[6] which suggests that the locus for bilateral acoustic neurofibromatosis (BANF) may be in this region.

Our negative results, taken with the previously published negative results of linkage analysis between VRNF and the locus SIS (22q12→13), suggest that VRNF and BANF are genetically as well as phenotypically distinct.

The negative linkage between VRNF and the chromosome 16 DNA markers, α globin and APRT, is in agreement with the previously published data[8] on protein markers PGP (16pter→p12) and Hp (16q22).

Although the VRNF gene has not been localised, the combined data have already excluded significant areas of the genome and illustrate the value of collaborative studies to maximise information. In future, one needs to concentrate on the genomic regions which have not been studied. Pooling of data will also allow the detection of possible genetic heterogeneity in VRNF.

Localisation of the VRNF gene to a specific chromosome will be a significant advance towards isolation of the gene. Closely linked markers will not only be useful for assessing the status of the subject at risk for the disease but will also be able to provide prenatal diagnosis for at least a proportion of those families who request this.

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A genomic search for linkage of neurofibromatosis to RFLPs

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SUMMARY Our initial attempt to map NF was directed towards chromosomes 4 and 19, both of which had provided positive evidence for linkage in previous reports. This analysis showed no evidence in support of either hypothesis. Our second attempt at mapping NF was a general search of the genome, analysing a set of markers selected according to

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their degree of polymorphism, chromosomal location, ease of use, and availability. Data for linkage analysis were obtained from 17 multiplex families which are segregating a gene for NF. Linkage analyses were performed using PAP. Of note is the lod score of +1·17 at a recombination fraction of 0·1 between NF and the centromere of chromosome 17.

Our initial attempt to map NF genetically was directed towards examining the hypotheses that genes segregating for NF were located on either chromosomes 4 or 19 or both. Initial evidence of linkage to Gc on chromosome 4 was found by Spence *et al.*[1] Linkage of NF to chromosome 19 was considered because of the reported cosegregation of NF with myotonic dystrophy.[2] Our analysis showed no evidence to support either of these hypotheses.

TABLE 1 *Number of meioses in NF families by generation.*

Sibship type	*Sibship size*	*No of meioses*
Grandchildren		28
Children	2	8
	3	21
	4	24
	5	15

TABLE 2 *Lod scores for linkage between RFLPs and neurofibromatosis.*

Gene symbol	*Clone name*	*Location*	*Enzyme*	*r=0·0*	*r=0·1*	*r=0·2*	*r=0·3*	*r=0·4*
D1S2	L1·22	1	*Bgl*II	−7·88	−1·04	−0·34	−0·08	−0·01
POMC	Lamb P2	2p23	*Sst*I	−17·15	−2·09	−0·85	−0·36	−0·08
D3S3	pMS1-37	3	*Msp*I	−9·49	−2·01	−0·87	−0·34	−0·08
D3S2	p12-32	3p14→p21	*Msp*I	−18·35	−2·12	−0·75	−0·17	+0·04
MT2P1	pHM6	4p11→q21	*Eco*RI	−22·87	−1·37	−0·29	+0·00	+0·02
	YNH24	4	*Msp*I	−19·78	−2·35	−0·70	−0·17	−0·068
D5S4	L1·4	5	*Msp*I	−2·93	+0·15	+0·21	+0·14	+0·04
D5S4	L1·4	5	*Eco*RI	−1·09	+0·55	+0·47	+0·26	+0·07
D6S3	L2·56	6	*Hind*III	−0·29	−0·17	−0·09	−0·04	−0·01
COL1A2	NJ3·5	7q21·3→q22·1	*Eco*RI	−14·50	−1·85	−0·77	−0·29	−0·06
PLAT	ptPA-21	8p21→q11·2	*Eco*RI	−4·87	−0·77	−0·30	−0·10	−0·02
	PTHH5	8	*Hind*III	−15·28	−2·74	−0·97	−0·29	−0·07
D9S1	p12-8	9pter→q11	*Taq*I	−9·86	−1·55	−0·67	−0·26	−0·06
D11S12	ADJ762	11p15	*Taq*I	−5·28	−0·76	−0·30	−0·11	−0·02
D11S12	ADJ762	11p15	*Msp*I	−2·23	−0·57	−0·53	−0·39	−0·18
INS	pHI-214	11p15	*Sst*I	−18·70	−2·35	−1·49	−0·81	−0·36
PTH	pPTHm122	11p15	*Pst*I	−2·76	−0·36	−0·15	−0·06	−0·01
CALC1	ptt42	11	*Taq*I	−23·12	−1·93	−0·73	−0·42	−0·27
CAT	pHC19-1	11p13	*Hae*III	−5·39	−1·03	−0·40	−0·14	−0·03
CAT	pHC16-2	11p13	*Hae*III	−6·09	−0·77	−0·26	−0·08	−0·02
HRAS1	pec	11p15	*Msp*I	−7·42	−1·65	−0·70	−0·27	−0·08
D12S6	p11-1-7	12cen→q13	*Msp*I	−4·57	−1·90	−0·98	−0·42	−0·13
D12S6	p11-2-2	12	*Msp*I	−4·18	+0·15	+0·25	+0·22	+0·12
D13S5	pHUB8	13q12→q22	*Eco*RI	−8·72	−1·06	−0·46	−0·18	−0·04
D15S2	pDP151	15q15→q22	*Eco*RI	−12·86	−1·08	−0·37	−0·15	−0·07
D15S1	pMS1-14	15q14→q21	*Msp*I	−17·46	−1·81	−0·46	−0·06	−0·00
HBA	pJW101	16p12→pter	*Bgl*II	−6·00	−0·05	+0·12	+0·09	+0·02
HBA	pJW101(1)	16p12→pter	*Sst*I	+0·01	+0·01	+0·00	+0·00	+0·00
HBA	pJW101(2)	16p12→pter	*Sst*I	−9·41	−0·15	+0·10	+0·11	+0·08
D17S1	12-2	17p13→pter	*Msp*I	−1·46	+0·21	+0·23	+0·15	+0·06
D17S1	12-2	17p13→pter	*Sst*I	−5·38	−0·43	−0·10	−0·01	+0·00
D17S3	L2·7	17	*Pst*I	−5·26	−0·56	−0·22	−0·08	−0·02
MYH2	p10-5	17p12→pter	*Msp*I	−4·73	−0·51	−0·16	−0·04	−0·01
MYH2	p10-5	17p12→pter	*Hind*III	−6·87	−0·59	−0·22	−0·09	−0·02
D17Z1	p3-6	17cen	*Hind*III	−0·73	+1·17	+0·79	+0·20	+0·11
D17S2	L1·31	17	*Bgl*II	−15·91	−2·40	−1·04	−0·40	−0·09
	PTHH59	17	*Taq*I	−18·90	−3·01	−1·15	−0·40	−0·11
	YNZ22	17	*Taq*I	−14·57	−1·36	−0·43	−0·10	+0·03
D18S1	12-62	18	*Taq*I	−13·85	−2·08	−0·83	−0·31	−0·07
D20S4	pMS1-27	20	*Msp*I	−15·48	−1·44	−0·44	−0·08	+0·00
D21S17	pGSH8	21	*Bgl*II	−4·49	−0·20	+0·01	+0·02	+0·06
D22S1	pMS3-18	22q11·2→q13	*Bgl*II	+0·54	+0·38	+0·23	+0·11	+0·03
	PTH162	?	*Bgl*II	−14·20	−2·13	−0·96	−0·42	−0·14
	PTHH39	?	*Pst*I	−11·86	−0·76	+0·16	−0·01	+0·04
	YNZ132	?	*Taq*I	−10·48	−0·87	−0·29	−0·07	−0·01

In this paper we present the results of our second attempt at mapping neurofibromatosis (NF). In this study we began a general search of the genome, analysing a battery of markers for linkage to NF that were generously made available to us by a large number of investigators (see acknowledgements). Markers were selected according to a number of criteria: their degree of polymorphism, chromosomal location, ease of use, and availability. As part of this effort, we emphasised analysis of a set of highly polymorphic markers developed in R White's laboratory.[3]

Materials and methods

Data for linkage analysis were obtained from 17 multiplex families in which a gene for NF is segregating. Information on family structure is shown in table 1. RFLP analysis for one or more of the markers listed in table 2 were available from 136 sampled family members. Diagnostic criteria used in this study have been described by Carey *et al.*[4] Linkage analyses were performed using PAP.[5] The DNA markers were assayed using standard techniques as previously described for this study.[6]

Results and discussion

The lod scores for the RFLPs analysed are presented in table 2. Of note is the lod score of +1·17 at a recombination fraction of 0·1 between NF and the centromere of chromosome 17.[7] This lod score represents our initial reading of a complex polymorphism which is still under investigation.

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Note added in proof (Seizinger *et al*, p 529)

We have recently provided conclusive evidence that the gene causing VRNF is genetically linked to the locus encoding the nerve growth factor receptor on chromosome 17q12–q22 (Seizinger BR, *et al.* Genetic linkage of von Recklinghausen neurofibromatosis to the nerve growth factor receptor gene. *Cell* 1987;**49**:589–94).