An exclusion map for Von Recklinghausen neurofibromatosis

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SUMMARY By using all the genetic linkage data available between Von Recklinghausen neurofibromatosis (VRNF) and various loci on the autosomes, a graphical display of all the non-excluded areas is presented. The probability of VRNF being on any of the 22 autosomes is also shown. The exclusion map presented is for 90 markers that have been localised relatively accurately. Data are also presented for a further 24 markers that have not yet been adequately localised. This exclusion map shows that most of the genome has been excluded as a likely location of any locus responsible for this disorder in the majority of families. Chromosomes 5, 10, 17, and 18 remain largely unexcluded. Concentration on these parts of the genome should help in the identification of the site of the VRNF gene.

The mapping of the gene for Von Recklinghausen neurofibromatosis (VRNF) is of paramount importance to our eventual understanding of the disease pathogenesis. It is one of the commonest autosomal dominant disorders in man and the very varied disease complications cause significant morbidity and mortality.¹ In 1986, we presented a preliminary exclusion map for VRNF using the computer programme EXCLUDE, based on the results of the Cardiff group and published linkage reports up to that time.²

More recently (February 1987), all groups involved in linkage analysis of VRNF were invited to attend the first European Symposium on Neurofibromatosis sponsored by the British neurofibromatosis patients' association, LINK. At the meeting it was agreed that a significant advance towards the mapping of the gene would be made by the pooling of all linkage data for VRNF to date. In particular, this would avoid unnecessary reduplication of negative results and highlight those areas of the genome not yet studied.

As a result of this meeting a consortium of those involved with VRNF linkage was formed. We are privileged to present in this paper a more detailed

exclusion map for VRNF based on previously published reports, and on the data provided by other members of the consortium; the individual data sets are given in full in the subsequent papers in this issue of the Journal.

Description of programme 'EXCLUDE'

The programme EXCLUDE is written in Pascal (Turbo version) and is designed to calculate the likelihood distribution of an unplaced locus around a series of previously mapped loci,³ following the general principle of Cook *et al*,⁴ who first used the term 'exclusion mapping'. The likelihood distribution at various recombination fractions or map distances gives the relative chance that the locus is in that position. In the pairwise analysis when the counts of recombinants and non-recombinants are available, the peak and position of the likelihood distribution are uniquely defined by these counts. However, when the direct counts are not available, an approximation may be obtained by defining the 'equivalent observations'⁵ after the data have been analysed by the likelihood method of Morton.⁶ This is achieved by defining the number of recombinants and non-recombinants which would give the same height and position of the likelihood distribution. For a given value of recombination fraction (θ) and

the corresponding value of lod score (Z), the equivalent number of informative meioses (s) is defined as:

$$s = Z[\theta * \log(2\theta) + (1-\theta) * \log(2(1-\theta))]$$

and the equivalent number of recombinants will be:

$$r = \theta * s$$

By knowing r and s , the likelihood for each position is then computed directly from these equivalents. For codominants and close loci, almost all the data can be extracted by counting.

The distribution of recombinant events varies by sex, age, chromosome number, and by position on that chromosome. In linkage data relating to a disease, only part of the information is usually available in the form of recombinants and non-recombinants, and the rest of the data has to be extracted in the form of lod score distributions for various values of θ . The direct count of recombinants and non-recombinants provides the optimal way of estimating the maximum likelihood. This also has the advantages of simplicity, additivity, and directness of meaning.

As the relationship between the recombination fraction (θ) and the map distance (w) is not linear, this leads to some problems in the positional likelihood distribution. By definition, θ and w are equal when $\theta=0.01$, and approximately linear up to $\theta=0.05$; however, w progressively exceeds θ at higher values. It is simplest to use Haldane's function, although it assumes two strand meiosis and an equal chance of recombination at any point unrelated to any nearby recombination. It is also possible to use Kosambi's mapping function in the EXCLUDE programme.³

The EXCLUDE programme finds the peak likelihood distribution by parabolic interpolation when presented with Z scores. When the information cannot be extracted efficiently by counting, the approximation is usually close, as is easily demonstrated by defining these 'equivalent observations' and then computing the lod score from θ . All likelihood data can be converted into these equivalents. The overall positional likelihoods are combined by multiplication and standardised either to display a unit area or to 'fill' the diagram.

The programme accepts pairwise data and is inefficient for close linkage, but the information loss is small when no linkage is established.

Origin of the linkage data

Up to now, more than 10 groups have undertaken genetic linkage studies to map the locus of the

VRNF gene, but none of these has detected significant linkage between a marker and the disorder. A total of 114 markers on the various autosomes has been tested for a possible linkage to VRNF. Out of these, 90 have been localised firmly with various degrees of precision, 18 are known to be on a specific chromosome, and the remaining six have not been assigned to any chromosome.

All the linkage data from previously published work and from those participating in this consortium were pooled to be used with the programme EXCLUDE. When the lod score was uniformly negative for all values of θ , the lod at 0.10 was used. For $Z > 0$ the value of $Z_{\max}$ and the value of θ at which it occurred were used. The overall linkage data available on VRNF are summarised in tables 1 and 2. The chromosomal position in table 1 is denoted by chromosome number, a period, and the location of the marker on that chromosome expressed as % of pter to qter. For example, the value of 1.36 for PGM1 means that this marker is on chromosome 1 at an approximate position of 36% from the top of that chromosome. When the localisation of a marker on the chromosome is expanded over a region of that chromosome, the location of that marker is taken to be in the middle of that region. For those markers with no regional localisation, the data were excluded and are shown in the first part of table 2. All the unassigned markers were also excluded from the data set and are shown in the lower part of table 2.

Input to programme EXCLUDE consists of chromosomal position, locus name, a number defining the types of data (1 for this data set), followed by the linkage data given in the form of θ and Z (first five columns of table 1). Each of these fields is separated by a few spaces. As the programme starts to read each of the data sets on a separate line, it calculates the equivalent number of informative meioses (s), number of recombinants (r), and the ratio r/s as described previously (table 1). The programme then accesses an internal file (HUMAN.CHR) which contains the approximate length of each of the human chromosomes given in centimorgans for both male and female chromosomes, which is assumed proportional to length as a rough approximation. The programme then calculates the positional likelihood of the disease locus on each chromosome, and also the percentage probability of any locus being on any of the 22 autosomes (table 3). The last two columns of table 3 give the maximum values of likelihood and probability of VRNF being on that chromosome. The figure is the graphical representation of these values.

TABLE 1 Overall linkage data used to obtain the VRNF exclusion map. The first five columns of data were used as input to the programme.

Position on the chromosome	Locus	Data type	Theta (cM)	Lod score	Localisation	r	s	Reference
1-05	PGD	1	0-10	-0.44	1p36-2→p36-13	0.99	1.98	9
1-09	RH	1	0-10	-10.71	1p36-2→p34	24.14	48.28	9, 11, 16
1-24	D1	1	0-10	-3.02	1p	6.80	13.61	20
1-36	PGM1	1	0-10	-3.74	1p22-1	8.43	16.86	9, 11, 16
1-36	NGFB	1	0-10	-5.98	1p22-1	13.48	26.96	12, 19
1-39	AMY1	1	0-10	0.74	1p21	0.46	4.63	10
1-53	FY	1	0-10	-11.31	1p21→q23	25.49	50.98	9, 11, 16
1-72	F13B	1	0-10	-1.83	1q	4.12	8.25	18
1-72	D1	1	0-10	-2.20	1q	4.96	9.92	20
1-75	AT3	1	0-20	0.57	1q23→q25	1.36	6.81	17, 18
2-06	ACPI	1	0-10	-4.59	2p25 or 2p23	10.35	20.69	10, 11, 16
2-08	POMC	1	0-10	-2.09	2p23	4.71	9.42	22
2-29	TGFA	1	0-10	-1.47	2p13	3.31	6.63	18
3-07	RAF1	1	0-10	-3.18	3p25→p24	7.17	14.33	19
3-23	D1S1	1	0-10	-4.07	3p21	9.17	18.35	18
3-25	D3S2	1	0-10	-2.12	3p14→p21	4.78	9.56	22
3-26	D3S3	1	0-10	-2.01	3q	4.53	9.06	22
3-74	TF	1	0-10	-0.21	3q21→q26-1	0.47	0.95	16
4-08	RAF2	1	0-10	-2.49	4p15→pter	5.61	11.22	19
4-20	D4S1	1	0-10	-0.27	4p15-1→q11	0.61	1.22	19
4-22	D4S35	1	0-10	-11.27	4p15-1→q12	25.40	50.80	18, 19
4-32	GC	1	0-10	-14.43	4q12→q13	32.52	65.04	7, 9, 11, 14, 16, 18
4-33	ALB	1	0-10	-1.42	4q11→q13	3.20	6.40	18, 19
4-35	MT2P1	1	0-10	-1.37	4p11→q21	3.09	6.18	22
4-48	ADH3	1	0-30	0.21	4q21→q25	1.76	5.88	18
4-61	EGF	1	0-10	-1.36	4q25→q27	3.07	6.13	18
4-66	FG	1	0-10	-0.25	4q26→q28	0.56	1.13	18
4-73	GIFN	1	0-10	-1.15	4q	2.59	5.18	18
4-75	MNSs	1	0-10	-10.63	4q28→q31	23.96	47.92	9, 11, 14, 16
5-35	GRL	1	0-20	0.29	5q11→q13	0.69	3.46	18
6-20	HLA	1	0-10	-6.65	6p21-3	14.99	29.98	8, 10
6-21	BF	1	0-10	-1.30	6p21-3	2.93	5.86	10
6-23	GLO1	1	0-10	-3.78	6p21-31→p21-1	8.52	17.04	9, 10, 16
6-53	F13A	1	0-10	-2.57	6p23→qter	5.79	11.58	18
6-93	PLG	1	0-10	-5.90	6q25→qter	13.30	26.59	18
7-30	EGFR	1	0-10	-0.47	7p13→p11	1.06	2.12	18
7-34	NJ33-2	1	0-10	-0.63	7pter→q22	1.42	2.84	7
7-34	D7	1	0-10	-4.86	7pter→q22	10.95	21.91	20
7-62	COL1A2	1	0-10	-1.85	7q21-3→q22-1	4.17	8.34	22
7-72	MetD	1	0-10	-0.58	7q21→q31	1.31	2.61	7
8-29	PLAT	1	0-10	-1.65	8p12	3.72	7.44	22, 23
8-93	TG	1	0-10	-6.21	8q24	14.00	27.99	7, 23
8-93	MYC	1	0-10	-1.48	8q24	3.34	6.67	17
9-17	D9S1	1	0-10	-1.55	9pter→q11	3.49	6.99	22
9-34	ORM	1	0-10	-1.32	9q	2.98	5.95	18
9-94	ABL	1	0-10	-0.59	9q34	1.33	2.66	19
9-94	ABO	1	0-10	-7.97	9q34	17.96	35.93	9, 10, 16
9-94	AK1	1	0-10	0.49	9q34	0.31	3.07	9
11-02	HRAS1	1	0-10	-10.77	11p15-5→pter	24.27	48.55	7, 19, 22
11-03	INS	1	0-10	-5.43	11p15-5	12.24	24.48	18, 22
11-07	HbG1	1	0-10	-0.74	11p15	1.67	3.34	17
11-09	CALC1	1	0-10	-1.93	11p15-4→p15-1	4.35	8.70	22
11-09	PTH	1	0-10	-0.67	11p15-4→p15-1	1.51	3.02	17, 22
11-21	D11S21	1	0-10	-1.07	11p14→p13	2.41	4.82	21
11-23	D11S12	1	0-10	-1.33	11p15-5	3.00	6.00	22
11-27	CAT	1	0-10	-1.80	11p13	4.06	8.11	22
11-57	D11	1	0-10	-2.45	11p14→qter	5.52	11.04	20
11-74	APOA4	1	0-10	-1.17	11q13→qter	2.64	5.27	18
11-85	ETSI	1	0-10	-4.07	11q23→q24	9.17	18.35	7, 17
12-19	KRAS2	1	0-10	-3.18	12p12-1	7.17	14.33	19
12-31	D12S6	1	0-10	-2.05	12cen→q13	4.62	9.24	22
12-76	IGF1	1	0-10	-2.01	12q22→q24-1	4.53	9.06	17, 19
12-81	PAH	1	0-10	-1.64	12q22→q24-2	3.70	7.39	7
13-28	ESD	1	0-10	-3.34	13q14-1	7.53	15.06	9, 10
13-41	D13S5	1	0-10	-1.06	13q12→q22	2.39	4.78	22

TABLE 1 Continued.

Position on the chromosome	Locus	Data type	Theta (cM)	Lod score	Localisation	r	s	Reference
14-88	PI	1	0-10	-7.79	14q32-1	17.56	35.11	7, 16, 18
14-95	IGHV	1	0-10	-4.11	14q32.3	9.26	18.53	7
14-95	GM	1	0-10	-0.27	14q32.3	0.61	1.22	7
15-32	D15S1	1	0-10	-1.81	15q14→q21	4.08	8.16	22
15-46	D15S2	1	0-10	-1.08	15q15→q22	2.43	4.87	22
16-14	HBA	1	0-10	-1.35	16p12	3.04	6.09	7, 20, 22
16-19	PGP	1	0-10	-3.15	16p11→pter	7.10	14.20	9, 10, 16
16-77	APRT	1	0-10	-4.59	16q22	10.34	20.69	7, 21
16-79	HP	1	0-10	-1.65	16q22.1	3.72	7.44	9, 10, 16, 21
17-06	D17S1	1	0-10	-0.22	17p13→pter	0.50	0.99	22
17-06	MYH2	1	0-10	-1.10	17p13→pter	2.48	4.96	22
17-32	D17Z1	1	0-10	1.17	17cen	0.73	7.32	22
17-34	ERBA2	1	0-10	-0.38	17q11	0.86	1.71	20
19-08	D19S6	1	0-10	-1.75	19q13.3→qter	3.94	7.89	21
19-12	C3	1	0-10	-2.59	19p13.3→p13.2	5.84	11.67	9, 13, 16, 21
19-57	APOC2	1	0-10	-7.55	19cen→q13.2	17.02	34.03	9, 21
19-72	SE	1	0-10	-2.32	19q	5.23	10.46	9, 13
20-19	D20S5	1	0-10	-1.20	20p12	2.70	5.41	7
22-22	D20S6	1	0-10	-1.93	20p	4.35	8.70	7
20-86	D20S4	1	0-10	-4.47	20q13.2	10.07	20.15	7, 22
21-77	D21S17	1	0-10	-0.20	21q21.2→qter	0.45	0.90	22
22-37	D22S9	1	0-10	-3.59	22q11	8.09	16.18	19
22-37	IGLV	1	0-10	-4.13	22q11.1→q11.2	9.31	18.62	7
22-52	D22S1	1	0-10	-1.97	22q11.2→q13	4.44	8.88	19, 22
22-59	SIS	1	0-10	-3.73	22q12.3→q13.1	8.41	16.81	15, 19, 20

r=equivalent number of recombinants.

s=equivalent number of informative meioses.

TABLE 2 Linkage data between VRNF and those marker loci not accurately localised.

Chromosome No	Locus	Theta (cM)	Lod score	r	s	Reference
1	D1S2	0-10	-1.04	2.35	4.69	22
2	JK	0-10	-0.39	0.88	1.76	10, 16
3	A2HS	0-10	-2.59	5.83	11.67	18
4	YNH24	0-10	-2.35	5.29	10.59	22
5	D5	0-10	-5.20	11.72	23.44	20
5	D5S4	0-10	0.70	0.44	4.38	22
6	D6	0-10	-5.32	11.99	23.98	20
6	D6S3	0-10	-0.17	0.39	0.77	22
8	PTHH5	0-10	-2.74	6.17	12.35	22
12	D12	0-10	-4.86	10.96	21.91	20
17	LDR111	0-10	-3.01	6.79	13.57	21
17	LDR92	0-10	-0.71	1.60	3.20	21
17	D17S3	0-10	-0.56	1.26	2.52	22
17	D17S2	0-10	-2.40	5.41	10.82	22
17	PTHH59	0-10	-3.01	6.79	13.57	22
17	YNZ22	0-10	-1.36	3.06	6.13	22
18	D18S1	0-10	-2.08	4.69	9.38	22
22	D22S10	0-10	-0.23	0.52	1.04	20
?	GPT	0-10	-0.30	0.68	1.35	16
?	PTH162	0-10	-2.13	4.80	9.60	22
?	PTHH39	0-10	-0.76	1.72	3.43	22
?	YNZ132	0-10	-0.87	1.96	3.92	22
?	P	0-10	-0.07	0.16	0.32	16
?	C6	0-10	-2.38	5.37	10.73	7, 18

r=equivalent number of recombinants.

s=equivalent number of informative meioses.

TABLE 3 Results from programme EXCLUDE, indicating the most likely location of the VRNF gene.

<i>Chromosome</i>		<i>No of loci</i>	<i>Relative probability of locus location (%)</i>	<i>Maximum probability (%)</i>	<i>Maximum likelihood</i>
<i>No</i>	<i>Length (cM)</i>				
1	250	10	8.67	2.64	1.27
2	225	3	7.80	10.55	1.00
3	200	5	6.93	4.71	1.00
4	180	11	6.24	0.00	0.99
5	180	1	6.24	29.66	1.95
6	170	5	5.89	0.00	0.94
7	160	5	5.55	0.90	0.99
8	150	3	5.20	0.95	0.95
9	150	5	5.20	0.31	0.98
11	140	11	4.85	0.00	0.90
12	140	4	4.85	0.05	0.93
13	100	2	3.47	0.99	0.65
14	100	3	3.47	0.88	0.59
15	100	2	3.47	1.29	0.76
16	90	4	3.12	0.00	0.87
17	80	4	2.77	20.04	6.88
19	70	4	2.43	0.00	0.73
20	70	3	2.43	0.00	0.74
21	50	1	1.73	3.38	0.90
22	50	4	1.73	0.00	0.07

FIGURE The exclusion map for VRNF. The shaded area of the chromosome shows the possible location of the disease gene and the white area the excluded zones.

Results and discussion

The additional data presented in this issue of the Journal provide the means of extending the exclusion map for the VRNF locus. Before this consortium, data on a total of 28 linkage markers on 13 chromosomes were available, including some of our own unpublished data set.⁷ This has now been expanded to 114 and at least one marker has been studied on all chromosomes except No 10 (table 4).

Although one RFLP has been studied on chromosome 18, it has no subchromosomal localisation and therefore could not be included in the exclusion map; taken together, these two chromosomes represent about 8% of the genome. The overall data show that the most likely location for the VRNF gene is on chromosome 17 with a likelihood of seven times more likely than being on any other chromosome. Another possible chromosome is No 5, with a likelihood of only 2. As this exclusion map clearly shows, the chance of the disease gene being on any other chromosome is very remote.

The strong indication from the exclusion map that the VRNF gene lies on one of the chromosomes 5, 10, 17, or 18 will give impetus to the use of markers on those chromosomes, and to the search for new informative polymorphisms in these areas of the genome. The possibility must also be considered, however, that genetic heterogeneity might mask a positive result. While the existence of a number of large individual kindreds in the various studies makes this unlikely, a careful analysis for heterogeneity would be required in the event of negative results for those chromosomes not currently excluded.

We would like to thank the British Neurofibromatosis Patients' Association, LINK, for organising the European Symposium on Neurofibromatosis, members of the consortium who provided us with their data for this analysis, and Professor Marcus Pembrey who chaired and coordinated the consortium.

TABLE 4 Comparison of available linkage data on VRNF before and after the collaborative work of this consortium.

Chromosome		Before consortium			After consortium		
No	Length (cM)	No of loci	Exclusion area		No of loci	Exclusion area	
			(cM)	(%)		(cM)	(%)
1	250	5	245.2	8.50	10	243.4	8.44
2	225	1	204.7	7.10	3	201.3	6.98
3	200	1	183.0	6.34	5	190.6	6.61
4	180	2	179.0	6.20	11	180.0	6.24
5	180	—	0.0	0.00	1	126.6	4.39
6	170	3	164.8	5.71	5	170.0	5.89
7	160	1	150.0	5.20	5	158.6	5.50
8	150	—	0.0	0.00	3	148.6	5.15
9	150	1	144.6	5.01	5	149.5	5.18
10	150	—	0.0	0.00	—	0.0	0.00
11	140	—	0.0	0.00	11	140.0	4.85
12	140	—	0.0	0.00	4	139.9	4.85
13	100	1	99.2	3.44	2	99.0	3.43
14	100	2	98.3	3.41	3	99.1	3.44
15	100	—	0.0	0.00	2	98.7	3.42
16	90	3	89.7	3.11	4	90.0	3.12
17	80	—	0.0	0.00	4	64.0	2.22
18	80	—	0.0	0.00	—	0.0	0.00
19	70	3	70.0	2.43	4	70.0	2.43
20	70	3	70.0	2.43	3	70.0	2.43
21	50	—	0.0	0.00	1	48.3	1.67
22	50	2	50.0	1.73	4	50.0	1.73
Total	2885	28	1748.4	60.60	90	2537.6	87.96

References

- Riccardi VM, Carey JC. Von Recklinghausen neurofibromatosis and genetic linkage studies: clinical considerations. *J Med Genet* 1987;24:521-2.
- Huson S, Upadhyaya M, Sarfarazi M, Edwards J, Harper PS. Peripheral neurofibromatosis: progress in mapping of the disease locus. *J Med Genet* 1987;24:246A.
- Edwards JH. Exclusion mapping. *J Med Genet* 1987;24:539-43.
- Cook PJJ, Noades JE, Lomas CG, Buckton KE, Robson EB. Exclusion mapping illustrated by the MNSs blood group. *Ann Hum Genet* 1980;44:61-73.
- Edwards JH. The analysis of X linkage. *Ann Hum Genet* 1971;34:229-50.
- Morton NE. Sequential tests for the detection of linkage. *Am J Hum Genet* 1955;7:277-318.
- Upadhyaya M, Sarfarazi M, Huson SM, Harper PS. Further exclusion data for the Von Recklinghausen neurofibromatosis gene: a genetic linkage study of 19 polymorphic markers. *J Med Genet* 1987;24:534-6.
- Lepage V, Tongio MM, Mayer S, et al. Neurofibromatosis (Von Recklinghausen disease). In: Terasaki PI, ed. *Histocompatibility testing* 1980. Los Angeles: UCLA Tissue Laboratory, 1981:719-21.
- Dunn BG, Ferrell R, Riccardi V. A genetic linkage study of 15 families with Von Recklinghausen neurofibromatosis. *Am J Med Genet* 1985;22:403-7.
- Spence MA, Bader JL, Parry DM, et al. Linkage analysis of neurofibromatosis (Von Recklinghausen disease). *J Med Genet* 1983;20:334-7.
- Spence MA, Parry DM, Bader JL, et al. Genetic linkage analysis of neurofibromatosis. *Ann NY Acad Sci* 1986;486:287-92.
- Darby JK, Goslin K, Riccardi VM, et al. Linkage analysis between B-nerve growth factor gene and other chromosome 1p markers and disseminated neurofibromatosis. *Ann NY Acad Sci* 1986;486:311-26.
- Huson SM, Meredith AL, Sarfarazi M, Shaw DJ, Compston DAS, Harper PS. Linkage analysis of peripheral neurofibromatosis (Von Recklinghausen disease) and chromosome 19 markers linked to myotonic dystrophy. *J Med Genet* 1986;23:567-7.
- Dietz JN, Robbins T, Cannon LA, et al. Linkage analysis of Von Recklinghausen neurofibromatosis: chromosome 4 and centromere. *Genet Epidemiol* 1986;3:313-21.
- Seizinger BR, Tanzi RE, Gilliam TC, et al. Genetic linkage analysis of neurofibromatosis with DNA markers. *Ann NY Acad Sci* 1986;486:304-10.
- Spence MA, Sparkes RS, Parry DM, Bale SR, Cortessis V, Mulvihill JJ. Genetic linkage studies with neurofibromatosis: the question of heterogeneity. *J Med Genet* 1987;24:527-9.
- Kittur S, Lubbs ML, Bauer M, Chakravarti A, Kazazian H. Linkage analysis of neurofibromatosis. *J Med Genet* 1987;24:526-7.
- Ferrell RE, Buclow KH, Darby JK, et al. Von Recklinghausen neurofibromatosis: a linkage study of candidate and random marker genes. *J Med Genet* 1987;24:522-4.
- Seizinger BR, Rouleau G, Lane AH, et al. DNA linkage analysis in Von Recklinghausen neurofibromatosis. *J Med Genet* 1987;24:529-30.
- Mathew CGP, Thorpe K, Easton DF, et al. Linkage analysis of British and Indian families with Von Recklinghausen neurofibromatosis. *J Med Genet* 1987;24:524-6.
- Pericak-Vance MA, Yamaoka LH, Vance JM, et al. Linkage studies in peripheral neurofibromatosis. *J Med Genet* 1987;24:530-2.
- Barker D, Wright E, Nguyen K, et al. A genomic search for linkage of neurofibromatosis to RFLPs. *J Med Genet* 1987;24:536-8.
- Diehl SR, Boehnke M, Collins FS, et al. Linkage analysis of peripheral neurofibromatosis to DNA markers on chromosome 8. *J Med Genet* 1987;24:532-4.

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