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Genetic Linkage and Heterogeneity in Type I Charcot-Marie-Tooth Disease (Hereditary Motor and Sensory Neuropathy Type I)

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Summary

The segregation patterns of DNA markers from the pericentromeric regions of chromosomes 1 and 17 were studied in seven pedigrees segregating an autosomal dominant gene for Charcot-Marie-Tooth neuropathy type I (CMT I; hereditary motor and sensory neuropathy I). A multilocus analysis with four markers (pMCR-3, pMUC10, FY, and pMLAJ1) spanning the pericentromeric region of chromosome 1 excluded the CMT I gene from this region in six pedigrees but gave some evidence for linkage to the region of Duffy in one pedigree. Linkage of the CMT I gene to markers in the pericentromeric region of chromosome 17 (markers pA10–41, pEW301, p3.6, and pTH17.19) was established; however, in these seven pedigrees homogeneity analysis with chromosome 17 markers detected significant genetic heterogeneity. This analysis suggested that three of the seven pedigrees are not linked to this same region. Overall, two of the seven CMT I pedigrees were not linked to markers tested from chromosomes 1 or 17. These results confirm genetic heterogeneity in CMT I and implicate the existence of a third autosomal locus, in addition to a locus on chromosome 17, and a probable locus on chromosome 1. This evidence of etiological heterogeneity, supported by statistical tests, will have to be taken into consideration when fine-structure genetic maps of the regions around CMT I are constructed.

Introduction

Charcot-Marie-Tooth disease type I (CMT I; hereditary motor and sensory neuropathy type I), a common form of genetic neuropathy (Dyck 1984), is clinically characterized by slowly progressive distal muscle weakness and atrophy with loss of deep tendon reflexes. The onset of this condition is usually in late childhood or adolescence. While autosomal recessive and X-linked forms have been reported, most CMT is inherited in an autosomal dominant manner (Skre 1974). Early studies in two CMT I families suggested linkage to the Duffy locus on chromosome 1 (Bird et al. 1980, 1982). Linkage to the Duffy locus was later confirmed in a large Indiana pedigree (Stebbins and Conneally 1982). In this same Indiana pedigree, close linkage to the FC gamma RII gene, which maps to chromosome 1 in the region of the Duffy locus, has recently been detected (Lebo et al. 1989). Many studies have identified CMT I families which failed to show linkage to the Duffy locus (Guiloff et al. 1982; Bird et al. 1983; Dyck et al. 1983; Marazita et al. 1985; Rossi et al. 1985; Ionasescu et al. 1987; Griffiths et al. 1988). Both a survey of the published data linking CMT I with the Duffy marker and a test of homogeneity of linkage confirmed that some CMT I families have a high posterior probability of linkage to the Duffy locus while others do not (Chance and Bird 1989). Recently, in two separate studies, linkage of CMT I to two anonymous DNA markers (pEW301 and pA10–41) on the proximal short arm of chromosome 17 was reported (Raeymaekers et

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al. 1989; Vance et al. 1989). The present paper documents linkage studies with multiple DNA markers from the pericentromeric regions of chromosomes 1 and 17 in seven CMT I families and reveals that this disorder is heterogeneous, with loci mapping to chromosome 17 and to another autosome(s).

Material and Methods

Pedigrees

Seven pedigrees meeting widely accepted criteria (Dyck 1984; Dyck et al. 1989) for CMT I were ascertained. The pedigrees are depicted in the Appendix (fig. A1). Pedigrees K1519–K1521 have been reported elsewhere (Bird et al. 1980, 1982) in linkage studies with the Duffy locus. Two hundred five subjects, including 106 affected individuals and 60 individuals at risk, were investigated. All subjects either with a presumption of CMT I or at genetic risk were examined by a neurologist (in most instances, T.D.B. or P.F.C.) to confirm CMT I and exclude other causes of peripheral neuropathy. Male-to-male transmission excluded X-linked inheritance in all pedigrees. Probands in all families demonstrated motor-nerve conduction velocities of less than 38 m/s, a finding compatible with CMT I (Harding and Thomas 1980). Nerve conduction velocities were also measured in at-risk family members whose clinical examinations were equivocal. In two pedigrees (K1520 and K1521), a sural nerve biopsy demonstrated the presence of hypertrophic demyelinating neuropathy. After informed consent was obtained, 30–50 ml of blood was obtained, by venipuncture, from each participant, for DNA isolation and for the constitution of transformed cell lines. Analysis of inheritance patterns at VNTR (variable-number tandem repeat) loci including CMM101, EFD126.3, and YNZ22 (Nakamura et al. 1987) detected no instances of either false paternity or errors of sample collection and processing (data not shown).

DNA Isolation

Permanent cell lines were established by Epstein-Barr transformation (Neitzel 1986). High-molecular-weight DNA was isolated from lymphoblasts or leukocytes by standard procedures (Maniatis et al. 1982) and resuspended at a concentration of 0.15 μg/ml.

Enzyme Digestion and Southern Transfer

Restriction-enzyme digestions were carried out overnight according to the manufacturer's specifications (Molecular Biology Resources, Inc); enzyme digestions included 4 mM spermidine. DNA fragments were separated by 0.7%–1.2% agarose-gel electrophoresis. After electrophoresis, gels were soaked in 0.4 N NaOH for 30 min prior to overnight transfer to membranes (Gene Screen Plus; Dupont) by standard methods (Southern 1975). After the transfer, membranes were rinsed in 5 × SSC and exposed to UV light (1,200 μJ) in the presence of a Stratagene cross-linker.

Probes and Hybridization

DNA probes used in the present study are listed in table 1. Probes were denatured and labeled with α-dCTP^{32} to high specific activity (typically 5 × 10^8–5

Table 1

Polymorphic Markers

Probe	Locus Symbol	Chromosome Location	Enzyme	Alleles (kb)	Heterozygosity	Reference
pMCR3	NRAS	1p11	*Eco*RI	6.0/4.8	.36	O'Connell et al. 1989*a*
pMUC10	MUC 1	1q21-q25	*Hin*fI	VNTR (>10 alleles)	.79	O'Connell et al. 1989*a*
Duffy	Fy	1cen-q22	–	Fy^a/Fy^b	.48	O'Connell et al. 1989*a*
FcγRII	FCG2	1q22-q24	*Taq*I	7.7/7.3		
				/6.7/6.4	.65	Grundy et al. 1989
pMLAJ1	D1S61	1q22	*Hin*fI	VNTR (>8 alleles)	.68	O'Connell et al. 1989*b*
pA10-41	D17S71	17p11-q11	*Msp*I	2.4/1.9	.50	O'Connell et al. 1989*b*
			*Pvu*II	3.2/3.0	.26	
pEW301	D17S58	17p11	*Bgl*II	10.0/8.0	.39	Golgar et al. 1989
			*Taq*I	4.5/3.1	.54	
p3.6	D17Z1	17cen	*Eco*RI	2.0/1.1,0.9	.45	O'Connell et al. 1989*b*
pHHH202.....	D17S33	17q11.2	*Rsa*I	2.1/1.8	.49	O'Connell et al. 1989*b*
pTH17.19.....	D17S82	17q11.2	*Bgl*II	16.0/12.0	.52	O'Connell et al. 1989*b*

$\times 10^9$ cpm/μg DNA) by the random-hexamer priming method of Feinberg and Vogelstein (1984). Hybridizations were carried out overnight at 42°C in a solution containing 50% formamide, 4 × SSC, 1 × Denhardt's solution, 20 MM $NaPO_4$, 5% dextran sulfate, 0.5% SDS, and human placental DNA (200 mg/ml). After hybridization, filters were washed with 0.1 × SSC containing 0.1% SDS at 65°C for 30 s–10 min, depending on the probe. Filters were placed against X-ray film (Kodak X-OMat AR) with intensifying screens for 1–2 d at −70°C for autoradiography.

Linkage Analysis

LOD score (Z) values, under the assumption of single-gene autosomal dominant inheritance, were calculated with the computer program LINKAGE (Lathrop et al. 1985). In a retrospective study the CMT I gene was estimated to be 97% penetrant by age 27 years, when clinical features or nerve conduction velocity findings were examined (Bird and Kraft 1978). However, reliable age-dependent risk of affection curves have not been established for CMT I. Nerve conduction velocity can be used to identify individuals who have inherited the CMT I gene but who have no clinical symptoms of CMT I (distal muscle weakness, atrophy, diminished/absent deep tendon reflexes, etc.) (Vanasse and Dubowitz 1981). Therefore, all individuals below age 21 years who had normal clinical examinations yet were unavailable for confirmation by nerve conduction velocity testing were excluded from the linkage analysis. In view of the low prevalence and high penetrance of this condition (Bird and Kraft 1978), a gene frequency of .0001 was assumed for the CMT I allele, and penetrance was taken as .95. Male and female recombination fractions were assumed to be equal.

Haplotypes were constructed for markers pA10–41 and pEW301. For these two markers there was significant linkage disequilibrium within the observed haplotypes determined from 33 unrelated persons ($\chi^2 = 50.1$, $P < .001$ for pA10–41; $\chi^2 = 22.5$, $P < .001$ for pEW301). Z values for haplotyped markers were calculated using the disequilibrium haplotype frequencies. Location scores were computed with the LINKAGE program, by using map information provided in published reports (Golgar et al. 1989; O'Connell et al. 1989*a*). Tests of homogeneity were carried out with the computer program HOMOG (Ott 1985).

Results

Chromosome 1 Markers

The results of pairwise linkage analyses in seven CMT I pedigrees, with DNA markers which span the pericentromeric regions of chromosomes 1 and 17, are presented as total Z ($\hat{Z}$) values in table 2 and for individual pedigrees in the Appendix. The Z values from all seven pedigrees did not implicate a CMT I locus on chromosome 1. A multilocus analysis for each pedigree by using markers pMCR-3, pMUC10, FY, and pMLAJ1 as fixed points gave no evidence for the localization of a CMT I locus to this region in any pedigree except K1521, which gave a location score of 2.0 in the immediate vicinity of FY (Duffy). The summed location scores on chromosome 1 and the individual analyses for pedigrees K1521, K1550, and K1551 are shown

Table 2

Cumulative LOD Scores with Chromosome 1 and 17 Markers in Seven CMT Type I Pedigrees

		θ							
MARKER	(Chromosome)	.001	.05	.10	.20	.30	.40	$\hat{Z}$	$\hat{\theta}$
pMCR3	(1)	−25.60	−11.23	−7.08	−3.02	−1.12	−.26	0	.50
pMUC10	(1)	−42.20	−18.40	−11.69	−4.94	−1.74	−.42	0	.50
Fy	(1)	−12.35	−3.60	−1.30	.37	.66	.45	.66	.30
FCγRII	(1)	−26.67	−8.01	−3.25	.22	.08	.05	.22	.20
pMLAJ	(1)	−37.08	−15.57	−10.14	−4.65	−1.96	−.72	0	.50
pA10-41	(17)	−2.20	3.21	4.10	3.94	2.87	1.44	4.19	.15
pEW301	(17)	−4.22	3.31	5.35	5.90	4.64	2.49	5.97	.15
p3.6	(17)	−.78	3.11	4.08	3.90	2.68	1.18	4.20	.15
pHHH202	(17)	−4.90	1.17	1.83	1.68	1.05	.32	1.89	.13
pTH17.19	(17)	−1.10	5.15	6.03	5.52	3.83	1.65	6.09	.12

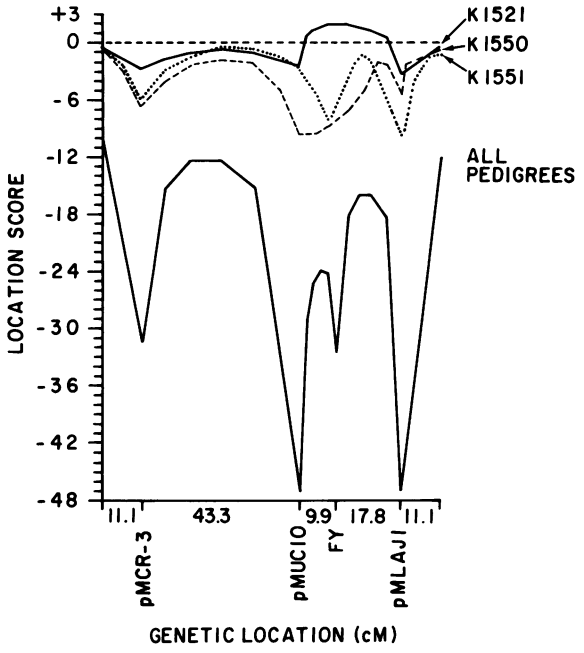

Figure 1 Multipoint linkage analysis of CMT I gene in seven pedigrees, with markers pMCR-3, pMUC10, Fy (Duffy), and pMLAJ1. The program LINKMAP from the LINKAGE package was used to calculate location scores of the CMT I locus relative to known position of the DNA markers. Location scores ($\log_{10}$) are shown on the vertical axis. Locations of the markers and genetic distances (cM) are shown on the horizontal axis. Also shown is a graph of the location scores for pedigrees K1521, K1550, and K1551.

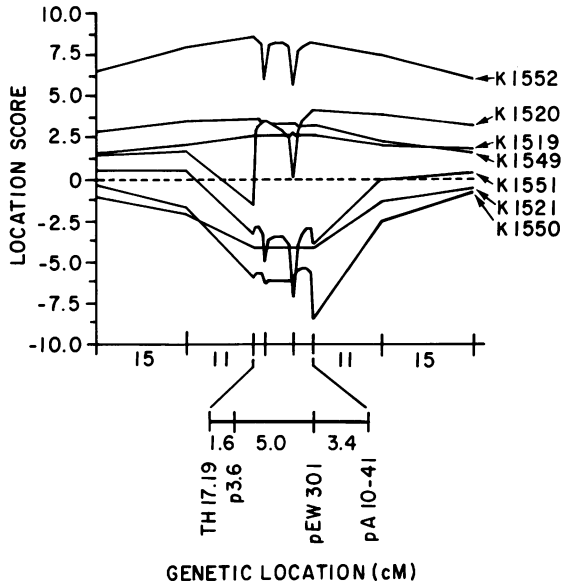

Figure 2 Multipoint linkage analysis of the CMT I gene in seven pedigrees, with markers pA10–41, pEW301, p3.6, and pTH17.19. The program LINKMAP from the LINKAGE package was used to calculate location scores of the CMT I locus relative to known position of the DNA markers. Location scores ($\log_{10}$) are shown on the vertical axis. Locations of the markers and genetic distances (cM) are shown on the horizontal axis.

in figure 1. The pairwise results of an analysis with FC gamma RII in all seven pedigrees are shown in the Appendix (table A1). FC gamma RII was not selected as a locus for multipoint analysis, since its precise map position was unknown. While pedigree K1550 gave a positive yet nonsignificant Z with FC gamma RII ($\hat{Z}$ = 1.34, recombination fraction [θ] = .15), no pedigree gave significant evidence for linkage to this marker, known to map near the Duffy locus.

Chromosome 17 Markers

The summed $\hat{Z}$ values from all seven families indicated strong evidence for linkage to markers pTH17.19 ($\hat{Z}$ = 6.09, θ = .12), p 3.6 ($\hat{Z}$ = 4.20, θ = .15), pEW301 ($\hat{Z}$ = 5.97, θ = .15), and pA10–41 ($\hat{Z}$ = 4.19, θ = .15). However, closer inspection of the individual pairwise Z values suggested that not all of the pedigrees supported linkage to this region of chromosome 17 (see Appendix). Location scores for the CMT I gene on a map of markers pA10–41, pEW301, p3.6, and pTH17.19, as shown in figure 2, were calculated for each of the seven CMT I pedigrees. Four pedigrees (K1519, K1520, K1549, and K1552) demonstrated positive location scores for this region on chromosome 17, and three pedigrees (K1521, K1550, and K1551) had negative location scores within this same region. While pedigree K1551 gave weakly positive yet nonsignificant Z values with three markers (pA10–41, pEW301, and p3.6) from this region, close inspection of this pedigree with all three marker genotypes detected numerous independent recombinational events involving one or more of the markers and the disease locus. All individuals (in most instances affected persons) in pedigrees K1521, K1550, and K1551 who exhibited apparent recombination were rechecked for both genotype error (pA10–41, and pEW301) and affected status, to confirm initial assignment.

Homogeneity Analysis

Evidence of genetic heterogeneity was confirmed by formal tests (Ott 1985), in which the general hypothesis assumes that sampling units can be either linked or unlinked to the marker loci. The location scores ($\log_{10}$) from the seven pedigrees were examined for evidence of genetic heterogeneity on chromosomes 1 and 17, by

Table 3

Testing Homogeneity of Linkage in Seven CMT I Pedigrees

Chromosome and Interval	θ^a	χ^2_1	P
1:			
Duffy–pMUC10	.02 .04 .06 .08	4.03	<.05
Duffy–pMLAJ-1	.03 .06 .08 .12	4.03	<.05
17:			
pA10-41–pter	.1 .2 .3 .4	18.93	<.001
pEW301–pA10-41	.007 .013 .02 .026	49.29	<.001
p3.6–pEW301	.01 .02 .03 .04	53.75	<.001
pTH17.19–qter	.1 .2 .3 .4	10.07	<.001

NOTE.—For testing homogeneity of linkage, location scores were examined by means of the computer program HOMOG (Ott 1985, pp. 200–203).

[a] For each interval, location scores were computed at equidistant recombination fractions between markers. The genetic distances between markers were based on the known genetic map of the regions on chromosomes 1 and 17.

means of the HOMOG computer program test (Ott 1985). The results of this analysis for chromosomes 1 and 17 are shown in table 3. For chromosome 1, heterogeneity was detected only in the region of the Duffy locus, and pedigree K1521 gave a posterior probability of .95 for mapping to this region. Significant heterogeneity was observed for all chromosome 17 markers tested. The posterior probabilities of linkage (for pA10–41 and pEW301) were greater than .99 for pedigrees K1519, K1520, K1549, and K1552 and were zero for pedigrees K1521, K1550, and K1551.

As pedigrees K1519, K1520, K1549, and K1552 consistently gave high posterior probabilities for linkage to this region of chromosome 17, the location scores of these four pedigrees were combined for an overall location of the CMT I gene on this chromosome. As shown in figure 3, the results clearly assign the CMT I gene segregating in these pedigrees to this region, yet they do not localize the gene to a specific interval of the map.

Discussion

Since the first reported suggestion of linkage of CMT I to the Duffy locus (Bird et al. 1980, 1982), attempts have been made to confirm this relationship and to explore the possibility of genetic heterogeneity within this disorder. To date, the Indiana kindred reported by Stebbins and Conneally (1982) remains the only pedigree which individually can support linkage to the Duffy locus at a $\hat{Z}$ in excess of 3.0. Recently, close linkage to the FC gamma RII gene, which maps to 1q21.2→q23, was reported in this same Indiana pedigree (Lebo et al. 1989). None of the pedigrees in the present report gave evidence confirming linkage of CMT I to FC gamma RII. Unfortunately, the FC gamma RII marker was uninformative in pedigree K1521, the only pedigree with a location score suggesting linkage to the region of the Duffy locus. Numerous other studies with either the Duffy locus or other chromosome 1 pericentromeric loci have remained inconclusive (Lebo et al.

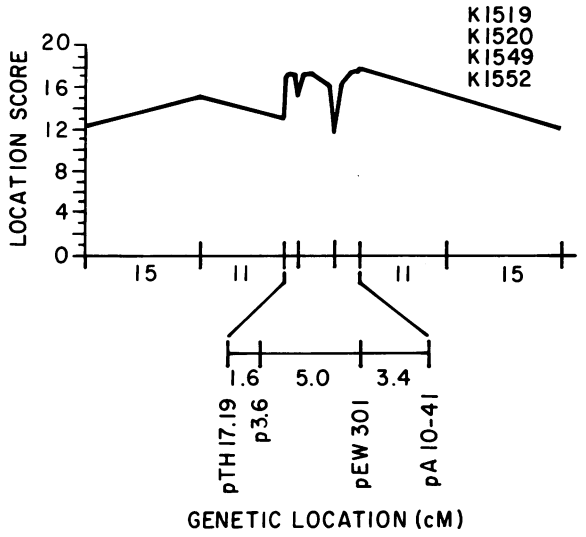

Figure 3 Combined location scores from a multipoint analysis of CMT I pedigrees (K1519, K1520, K1549, and K1552) with markers pA10–41, pEW301, p3.6, and pTH17.19 as fixed positions in the pericentromeric region of chromosome 17.

1986; Chance et al. 1987, 1988; Ionasescu et al. 1987, 1988; Griffiths et al. 1988; Middleton-Price et al. 1989). In six CMT I pedigrees linkage was found to markers from the very proximal short arm of chromosome 17 (Vance et al. 1989). In two of the six pedigrees the Z values with marker pEW301 were greater than 3.0, and no genetic heterogeneity was detected. Subsequently, in an additional large pedigree, the CMT I gene was entirely excluded from chromosome 1 and also was found to be linked to chromosome 17 (Raeymaekers et al. 1989). The present report confirms this assignment of a form of CMT I to the pericentromeric region of chromosome 17 in four pedigrees. Furthermore, it also demonstrates genetic heterogeneity within this group of hereditary neuropathies. Three of the seven pedigrees in the present report do not appear to have the CMT I mutation in the pericentromeric region of chromosome 17. This study has also provided evidence that some pedigrees fulfilling the clinical criteria for CMT I may have a locus which maps neither to chromosome 1 nor to chromosome 17 (see figs. 1 and 2 for pedigrees K1550 and K1551). The existence of CMT I loci on chromosome 17 and on the X chromosome (Gal et al. 1985; Fischbeck et al. 1986) now appears firm. It is also likely that other CMT I loci are located on chromosome 1 and another autosome(s). The present study has shown that the CMT I gene in pedigree K1520 (family B of Bird et al. 1982), which had demonstrated a weakly positive $\hat{Z}$ value with the Duffy locus ($Z = 0.64, \theta = .15$), is actually linked to markers on chromosome 17. The CMT I gene in pedigree K1521 (family A in Bird et al. 1982), which has a positive Z value with the Duffy locus ($\hat{Z} = 2.0, \theta = 0$), is not linked to chromosome 17 markers. The study of additional markers more closely linked to the Duffy locus is warranted in pedigree K1521 in order to confirm or reject linkage to chromosome 1.

Genetic heterogeneity characterizes conditions which are phenotypically similar yet arise from mutations at different loci. For multilocus analyses and fine genetic mapping of a given disorder, it is crucial that the data be collected from a set of families which have mutations at the same locus. Huntington disease (Conneally et al. 1989), neurofibromatosis I (Collins et al. 1989), and Friedreich ataxia (Chamberlain et al. 1989) are disorders for which no genetic heterogeneity has been observed, whereas X-linked spastic paraplegia can be caused by mutation at either of two distinct loci on the X chromosome (Keppen et al. 1987). Further refinement of the location of the CMT I locus on chromosome 17 will require demonstrating the absence of genetic heterogeneity within the collection of pedigrees under study. Furthermore, the establishment of genetic heterogeneity in CMT I predicts that the universal clinical application of chromosome 17 probes for presymptomatic and prenatal diagnosis is premature at this time.

Note added in proof.—Additional evidence supporting genetic heterogeneity in CMT I can be found in the recent report by Defesche et al. (1990), who described five CMT I pedigrees, one of which was not linked to markers tested from chromosome 17 and gave evidence for linkage to chromosome 1.

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Table A1

Two-Point LOD Scores for CMT 1 and Chromosome 1 Markers

Marker and Pedigree	θ						$\hat{Z}$	$\hat{\theta}$
	.001	.05	.10	.20	.30	.40		
Duffy:								
K1519	−1.25	−.76	−.52	−.26	−.12	−.04	0	.50
K1520	−3.11	.20	.58	.57	.31	.10	.64	.15
K1521	2.09	1.94	1.78	1.42	1.02	.55	2.09	.001
K1549	−.74	−.48	−.33	−.15	−.06	−.01	0	.50
K1550	−6.67	−3.08	−2.01	−.96	−.43	−.15	0	.50
K1551	−2.68	−1.43	−.79	−.25	−.05	−.01	0	.50
K1552[a]	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
pMCR-3:								
K1519	−1.75	−.14	.06	.16	.13	.06	.16	.20
K1520	−6.73	−2.52	−1.51	−.63	−.27	−.01	0	.50
K1521	−3.32	−1.44	−.89	−.39	−.15	−.04	0	.50
K1549	−2.82	−1.13	−.79	−.37	−.11	0	0	.50
K1550	−6.12	−3.65	−2.41	−1.1	−.45	−.11	0	.50
K1551	−4.73	−2.24	−1.45	−.64	−.25	−.07	0	.50
K1552	−.16	−.12	−.01	0	0	0	0	.50
pMUC-10:								
K1519	−4.49	−3.47	−2.34	−1.1	−.51	−.17	0	.50
K1520	−1.05	−6.06	−4.88	−3.0	−1.63	−.70	0	.50
K1521	−2.92	−1.45	−.93	−.46	−.23	−.09	0	.50
K1549	−8.85	−4.90	−3.31	−1.59	−.68	−.20	0	.50
K1550	−1.68	−.18	.09	.24	.20	.14	.24	.20
K1551	−5.34	−.02	.78	1.13	.90	.40	1.13	.20
K1552	−8.40	−2.31	−1.11	−.18	.21	.22	.22	.40
pMLAJ-1:								
K1519	−4.13	−2.32	−1.71	−1.0	−.53	−.21	0	.50
K1520	−12.32	−6.26	−5.14	−3.30	−1.83	−.80	0	.50
K1521	−3.29	−.89	−.39	.01	.13	.12	.13	.20
K1549	−3.76	−1.03	−.27	.29	.30	.10	.34	.25
K1550	−7.68	−3.41	−2.15	−.92	−.35	−.08	0	.50
K1551	−4.11	−1.67	−.77	.07	.11	.08	.11	.30
K1552	−1.8	.02	.03	.35	.20	.06	.36	.15
FC gamma RII:								
K1519	−4.62	−1.41	−.79	−.29	−.11	−.03	0	.50
K1520	−8.85	−4.16	−2.56	−1.25	−.80	−.48	0	.50
K1521[b]	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
K1549	−.64	.03	.32	.43	.26	.05	.43	.20
K1550	−.97	.96	1.26	1.30	1.03	.59	1.34	.15
K1551	−5.13	−1.83	−.96	−.21	.05	.08	.08	.40
K1552	−6.47	−1.59	−.53	.24	.38	.25	.25	.40

[a] Marker not evaluated.
[b] Marker uninformative.

Table A2

Two-Point LOD Scores for CMT I and Chromosome 17 Markers

	θ							
Marker and Pedigree	.001	.05	.10	.20	.30	.40	$\hat{Z}$	$\hat{\theta}$
pA10-41:								
K1519	1.60	1.49	1.37	1.10	.79	.43	1.60	.001
K1520	.80	.73	.66	.52	.37	.20	.80	.001
K1521	−3.52	−2.17	−1.35	−.60	−.24	−.06	0	.50
K1549	1.49	1.33	1.18	.83	.48	.16	1.49	.001
K1550	−3.89	−.49	−.07	.45	.46	.29	.46	.30
K1551	−.27	.87	.92	.74	.46	.17	.93	.07
K1552	1.59	1.42	1.24	.89	.54	.23	1.59	.001
pEW301:								
K1519	1.34	1.25	1.15	.93	.67	.37	1.34	.001
K1520	1.35	3.10	3.22	2.83	2.05	1.01	3.22	.10
K1521	.18	.17	.15	.12	.01	0	.18	.001
K1549	.83	.76	.70	.56	.40	.21	.83	.001
K1550	−6.12	−4.62	−2.82	−1.11	−.37	−.01	0	.50
K1551	−3.78	−.65	−.27	−.10	−.11	−.11	0	.50
K1552	1.96	3.28	3.21	2.68	1.93	1.01	3.28	.05
p3.6:								
K1519[a]	...	...	...	...	...	...	...	...
K1520	−.17	−.16	−.14	−.12	−.10	−.06	0	.50
K1521	−4.70	−3.25	−2.20	−1.15	−.57	−.22	0	.50
K1549	.23	.38	.41	.33	.18	.05	.41	.10
K1550	−1.48	−1.07	−.71	−.33	−.12	−.03	0	.50
K1551	−.83	.65	.73	.55	.27	.06	.73	.09
K1552	5.45	6.40	5.93	4.59	3.02	1.37	6.47	.03
pHHH202:								
K1519[a]	...	...	...	...	...	...	...	...
K1520	−1.42	.13	.30	.34	.26	.15	.35	.17
K1521[a]	...	...	...	...	...	...	...	...
K1549	.55	.51	.47	.37	.26	.14	.55	.001
K1550	−6.27	−2.83	−2.01	−1.20	−.63	−.23	0	.50
K1551	.13	.12	.10	.06	.02	.00	.13	.001
K1552	2.11	3.24	2.97	2.11	1.12	.25	3.25	.04
pTH17.19:								
K1519	1.03	.93	.82	.59	.34	.11	1.03	.001
K1520	3.43	3.15	2.84	2.15	1.37	.54	3.43	.001
K1521	−3.95	−1.72	−1.14	−.59	−.30	−.11	0	.50
K1549	.49	2.07	2.14	1.81	1.21	.50	2.15	.09
K1550	−4.08	−2.35	−1.58	−.80	−.38	−.14	0	.50
K1551	−1.72	−.19	.00	.08	.05	.01	.08	.20
K1552	3.53	3.26	2.96	2.29	1.55	.75	3.53	.001

[a] Marker uninformative.

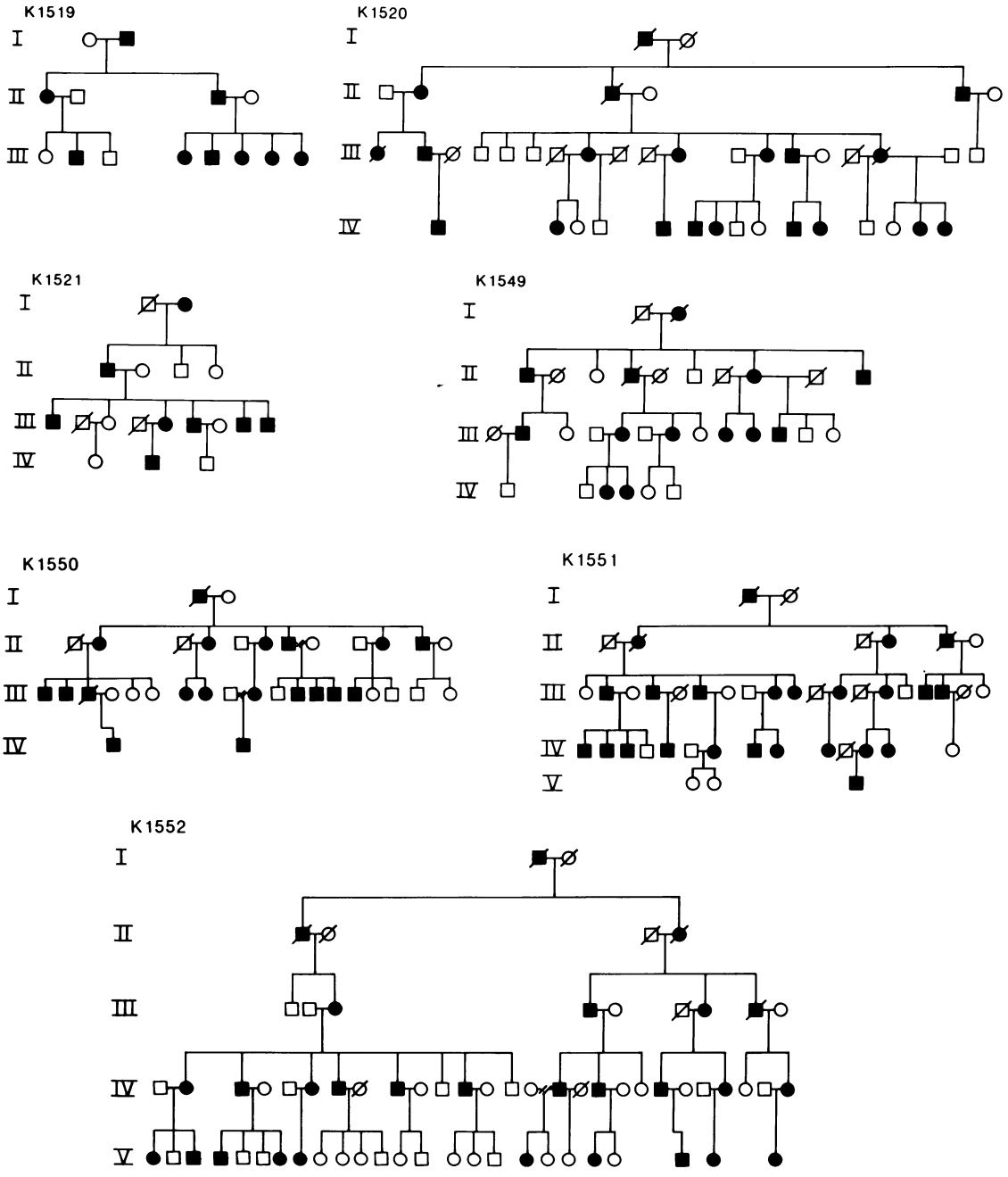

Figure A1 CMT I pedigrees K1519, K1520, K1521, K1549, K1550, K1551, and K1552. Darkened circles and squares denote affected females and affected males, respectively. Cross-slashed figures are deceased. The linkage analysis included all living individuals shown.

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