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Linkage of Cutaneous Malignant Melanoma/Dysplastic Nevi to Chromosome 9p, and Evidence for Genetic Heterogeneity

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Summary

We examined the relationship between cutaneous malignant melanoma/dysplastic nevi (CMM/DN) and chromosome 9p in 13 pedigrees with two or more living cases of invasive melanoma. We used two highly informative $(CA)_n$ repeats, D9S126 and IFNA, previously implicated in familial malignant melanoma (MLM), to conduct linkage analysis. Three analyses were performed: (1) CMM alone—all individuals without either confirmed melanoma or borderline lesions were considered unaffected (model A); (2) CMM/DN with both variable age at onset and sporadics (model B); and (3) CMM affecteds only—all individuals either without confirmed melanoma or with borderline lesions were designated "unknown" (model C). There was significant evidence for linkage to IFNA in all three models. For CMM alone, the maximum lod score (Z_{max}) was 4.36 at $\theta = .10$ for model A and 3.39 at $\theta = .10$ for model C. For CMM/DN (model B), $Z_{max} = 3.05$ at $\theta = .20$. There was no significant evidence for linkage between CMM alone or CMM/DN and chromosome 9p marker D9S126. In addition, there was significant evidence for heterogeneity when a homogeneity test allowing for linkage to chromosome 9p or chromosome 1p or neither region was used. These results suggest that there is an MLM susceptibility locus on chromosome 9p but that familial melanoma is heterogeneous and not all families with CMM/DN are linked to a locus in this region.

Introduction

Cutaneous malignant melanoma (CMM) is a potentially fatal form of skin cancer whose incidence is rising in many regions of the world (Osterlind et al. 1988; MacKie et al. 1992; MacLennan et al. 1992; Miller et al. 1993). Approximately 8%–12% of cases of CMM occur in persons with a familial predisposition (Greene and Fraumeni 1979), often in association with clinically dysplastic nevi (DN) (or clinically atypical nevi), a major precursor lesion of melanoma (Tucker 1988; Tucker et al. 1993).

To examine familial melanoma, we selected chromosome 9p, a region of the genome that has previously been proposed as a candidate region for melanoma on the basis of positive results from cytogenetic studies (Cowan et al. 1988; Petty et al. 1993), loss-of-heterozygosity studies (Dracopoli et al. 1987), and tumor-deletion studies showing homozygous deletion in malignant melanoma (Fountain et al. 1992*a*). Subsequently, Cannon-Albright et al. (1992) found significant evidence for a familial malignant melanoma (MLM) locus on chromosome 9p, and a second group has recently confirmed these findings by using multipoint linkage analysis (Nancarrow et al. 1993).

To further examine the relationship between CMM and chromosome 9p, we conducted linkage analysis on 13 families previously investigated for linkage to chromosome 1p (Bale et al. 1989; Goldstein et al. 1993). We

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Table 1

Description of National Cancer Institute Pedigrees

Family	No. of Melanoma Cases	Median Age at Diagnosis (years)	No. Diagnosed		No. of Borderline Lesions	No. of DN Cases	No. of Family Members Sampled
			At <20	20–29			
1016	7	39	2	1	0	2	16
342	7	34	0	2	1	3	22
928	7	31	2	1	0	5	23
255	6	39	0	3	0	6	25
481	3	33	0	1	0	3	8
2482	7	23	2	3	0	3	25
2884	3	31	0	1	0	1	6
2851	2	43	0	0	0	4	11
373	3	27	0	2	1	5	20
1017	4	28	0	3	1	4	9
873	5	31	0	2	0	3	13
2905	6	30	0	2	0	1	11
479	4	38	0	1	1	1	15

present data on two highly informative $(CA)_n$ repeats, D9S126 and IFNA, which map approximately 4.5 cM apart (Fountain et al. 1992*b*). Cannon-Albright et al. (1992) conducted linkage analysis using these two markers and found significant evidence for an MLM locus linked to these markers. In addition, D9S126 maps to 9p21, the chromosome 9p region where frequent homozygous deletions in malignant melanomas occur (Fountain et al. 1992*a*).

Subjects and Methods

Subjects

Families with at least two living cases of melanoma were recruited for study. Table 1 shows the distribution of melanoma cases, median age at diagnosis for invasive melanoma, and number of individuals with DN (clinically atypical nevi) in the 13 pedigrees. The average age at diagnosis of invasive melanoma, across all 13 families, was 35 years. The families were all Caucasian and unrelated; they resided in various regions of the United States.

All melanoma diagnoses were confirmed using histologic review, local pathology reports, medical records, or death certificates. Only confirmed invasive cutaneous melanomas were counted as melanoma. Lesions that had histologic characteristics of melanoma but were not invasive (i.e., melanoma in situ) were designated as borderline lesions.

Clinical and histologic criteria for the diagnosis of DN have been described elsewhere (MacKie et al. 1989; Clark et al. 1990). These lesions have also been called "B-K moles," "clinically atypical moles," and "nevi with architectural disorder and moderate atypia." The combined trait of melanoma and atypical moles has been identified as "BK-mole syndrome," "familial atypical moles and melanoma syndrome" (FAMMM), "dysplastic nevus syndrome" (DNS), "CMM/DN," and "atypical mole syndrome" (AMS). For review of this literature, see Clark (1991), Clark et al. (1990), and National Institutes of Health (1992). We will use the term "CMM/DN" to describe the combined trait of familial melanoma and atypical moles, to better differentiate CMM alone, CMM/DN, and DN alone.

For purposes of this study, individuals were classified as having DN if they had clinical evidence of DN (clinically atypical nevi) with or without histologic evidence of DN. If an individual was deceased prior to onset of the study and had histologic evidence of DN, he or she was considered as having DN. All clinical diagnoses were made by one of us (M.A.T.), who was blinded to the genetic marker typings on all individuals. The clinical criteria used to diagnose DN were the same for all 13 pedigrees. All pathology was reviewed by one dermatopathologist (W.H.C., Jr.), who was blinded to the clinical diagnoses on all individuals. For purposes of analysis, prepubertal subjects (<16 years of age) were classified as indeterminate unless they had definite clinical and/or histologic evidence of DN, because clinically DN often do not develop before the onset of puberty (Tucker et al. 1983).

Genetic Analyses

Three genetic analyses were performed: two for CMM alone (models A and C) and one for the combined CMM/DN phenotype (model B) (Goldstein et al. 1993). In the first analysis of CMM alone (model A), all individuals without either confirmed melanoma or with borderline lesions were considered unaffected, with five liability classes. The liability classes for models A and B were selected using a life-table analysis by Bale et al. (1986) that was based on 14 CMM/DN families seen at the National Cancer Institute. The five classes were constructed to produce a generally linear age-at-onset model and to incorporate the age distribution of the families into the model. Autosomal dominant inheritance was assumed. The penetrances for gene carriers in the five liability classes based on age were as follows: 0–9 years, .01; 10–24 years, .25; 25–46 years, .50; 47–57 years, .71; and ⩾58 years, .92. Sporadics were incorporated into the CMM-alone model at a penetrance of .01 for individuals ⩾47 years of age. For model B (CMM/DN), the penetrances for sporadics in the five age classes were as follows: 0–9 years, .0; 10–24 years, .0; 25–46 years, .01; 47–57 years, .02; and ⩾58 years, .038. The second analysis for CMM alone (model C) was an affecteds-only analysis. All individuals without invasive melanoma or with borderline lesions were classified as unknown, and the trait was analyzed as fully penetrant. For all analyses, the disease gene frequency was set to .001.

The computer program LINKAGE (Lathrop et al. 1985) was used for both pairwise (MLINK) and multipoint (LINKMAP) linkage analyses assuming equal rates of recombination between males and females. All analyses were performed on a Gateway 2000/486. We tested for homogeneity of the estimated recombination fraction (θ) by using an admixture test (Smith 1963; Ott 1991, pp. 194–216) that allows for a set of families to be linked to one chromosomal region, a second set of families to be linked to a different chromosomal region, and a third set of families to be unlinked (HOMOG3R) (Ott 1992). The three types of families have respective sample proportions α_1, α_2, and $\alpha_3 = 1 - \alpha_1 - \alpha_2$. Thus, for this analysis, four parameters were estimated: α_1; α_2; θ_1, θ between disease locus 1 and the marker linked with it; and θ_2, θ between disease locus 2 and its linked marker (Ott 1991, pp. 194–216; 1992).

Molecular Genetic Analyses

Analyses of the D9S126 (Fountain et al. 1993) and IFNA (Kwiatkowski and Diaz 1992) $(CA)_n$ repeats were performed in one laboratory (that of N.C.D.), in which the molecular geneticists and technicians were blinded to the diagnostic status of all individuals. PCR analysis was carried out using a single [γ-^{32}P] ATP end-labeled primer. Allele frequencies were estimated from the observed or completely implied genotypes of founders in the 13 pedigrees. For D9S126, five alleles were observed, but the frequencies of the two smallest alleles (frequencies .01 and .02) were combined for purposes of analysis; the allele frequencies were .43, .33, .20, and .03. For IFNA, four alleles were observed, with frequencies .29, .42, .20, and .09. Since not all marker typings were standardized across pedigrees, the results derived from estimated frequencies were compared with results derived by assuming equifrequent estimates for each marker. There were essentially no differences in results between these two approaches, and therefore the estimated allele frequencies were used in all analyses.

Results

Tables 2 and 3 present the two-point lod score (Z) values for linkage between D9S126 and IFNA, for the three analysis models. IFNA showed significant evidence for linkage, with all three analysis models. For CMM alone, the maximum Z (Z_{max}) was 4.36 at $\theta = .10$ for model A and 3.39 at $\theta = .10$ for model C. For CMM/DN (model B), $Z_{max} = 3.05$ at $\theta = .20$. There was no significant evidence for linkage between CMM alone or CMM/DN and chromosome 9p marker D9S126, and very tight linkage could be excluded at $\theta < .01$ for model A. For model A, $Z_{max} = 0.96$ at $\theta = .20$; for model C, $Z_{max} = 1.08$ at $\theta = .20$. For CMM/DN (model B), $Z_{max} = 0.49$ at $\theta = .30$, and linkage could be excluded for $\theta < .08$.

Because of previous evidence for linkage of a CMM locus to chromosome 1p in several of these pedigrees, we tested for homogeneity, using an admixture test that allows for some families to be linked to one chromosomal region, a second set of families to be linked to a different chromosomal region, and a third set of families to be unlinked (Ott 1992). We used marker typings for IFNA as one locus and for D1S47 from chromosome 1p as the second locus (Goldstein et al. 1993). Table 4 shows the Z values between CMM alone and D1S47. Table 5 presents the results and the conditional probabilities that each pedigree is linked to either chromosome 9p or chromosome 1p. When a critical level likelihood ratio of 50 was used, there was significant evidence for heterogeneity; the difference in natural log likelihood was 4.49, corresponding to a likelihood ratio of 89. The estimated proportion of families linked to

Table 2

Z Values between CMM/DN and IFNA, for Three Analyses

Model and Family	Z at θ = .0	.01	.05	.10	.20	.30	.40
Model A—CMM alone:							
1016	1.41	1.38	1.28	1.14	.87	.59	.30
342	−5.36	−3.03	−1.57	−.83	−.23	−.01	.05
928	.12	.12	.09	.07	.02	−.02	−.02
255	1.34	1.32	1.23	1.10	.79	.44	.13
481	.00	.00	.00	.00	.00	.00	.00
2482	1.65	1.61	1.48	1.32	.96	.59	.25
2884	.52	.51	.48	.45	.36	.26	.14
2851	−1.00	−.90	−.64	−.45	−.23	−.11	−.04
373	−.34	−.32	−.24	−.16	−.06	.00	.02
1017	1.24	1.22	1.12	1.0	.73	.44	.15
873	−.03	−.02	−.01	−.00	.00	−.00	−.00
2905	−1.92	−.88	−.29	−.08	.03	.03	.01
479	1.03	1.01	.93	.83	.60	.36	.14
Total	−1.34	2.02	3.88[a]	4.36[a]	3.84	2.58[a]	1.12[a]
Model B—CMM/DN:							
1016	−1.56	−.30	.28	.44	.47	.36	.20
342	−5.23	−3.67	−2.37	−1.50	−.58	−.18	−.03
928	−1.61	−.90	−.36	−.18	−.06	−.03	−.01
255	−3.30	−1.71	−.74	−.31	.02	.07	.03
481	.00	.00	.00	.00	.00	.00	.00
2482	1.78	1.74	1.60	1.41	1.02	.62	.25
2884	.96	.95	.89	.81	.64	.44	.23
2851	.04	.04	.04	.03	.03	.02	.01
373	1.80	1.77	1.65	1.50	1.16	.78	.38
1017	−1.48	−1.39	−.94	−.59	−.23	−.08	−.02
873	−1.09	−.92	−.56	−.35	−.15	−.06	−.02
2905	−.25	−.11	.14	.24	.23	.14	.04
479	1.03	1.00	.90	.78	.52	.27	.08
Total	−8.92[a]	−3.49[a]	.53	2.30[a]	3.05[a]	2.34[a]	1.13[a]
Model C—CMM affecteds only:							
Total	1.35	2.61	3.29	3.39	2.80	1.79	0.76

[a] Because of rounding error, the total does not exactly equal the sum of the individual family Z values.

chromosome 9p was .50 (θ = .0), and the estimated proportion linked to chromosome 1p also was .50 (θ = .05). Three of 11 informative pedigrees had conditional probabilities of >90% of being linked to chromosome 9p, and 2 of 11 had conditional probabilities >90% of being linked to chromosome 1p.

Figure 1 shows the multipoint results for models A and B, for all 13 families. For CMM alone, there was significant evidence for linkage. For CMM/DN, the results were no longer significant, and it was possible to exclude linkage in the interval between IFNA and D9S126. For CMM affecteds only (model C), Z_{max} = 4.16 at 11 cM distal to IFNA, and the odds in favor of that location were only four times more likely than those in favor of a location approximately halfway between D9S126 and IFNA (data not shown).

Discussion

We examined the relationship between CMM/DN and chromosome 9p markers IFNA and D9S126, utilizing the same analysis models previously employed to examine evidence for linkage to chromosome 1p (Goldstein et al. 1993). The results showed significant evidence for linkage between CMM alone (model A), CMM/DN (model B), and CMM affecteds only (model C), and IFNA. Multipoint analyses also showed significant evidence for linkage to CMM alone. In ad-

Table 3

Z Values between CMM/DN and D9S126, for Three Analyses

Model and Family	Z at θ = .0	.01	.05	.10	.20	.30	.40
Model A—CMM alone:							
1016	.34	.33	.29	.24	.15	.08	.03
342	−2.50	−2.47	−1.85	−1.12	−.41	−.09	.02
928	.95	.93	.84	.73	.51	.31	.13
255	1.34	1.32	1.23	1.10	.79	.44	.13
481	−.07	−.06	−.05	−.04	−.02	−.01	−.00
2482	−2.45	−1.00	−.37	−.15	−.01	.02	.01
2884	.03	.03	.03	.03	.02	.01	.01
2851	.19	.19	.17	.14	.08	.04	.01
373	.05	.06	.10	.13	.13	.09	.04
1017	−2.65	−1.38	−.72	−.44	−.19	−.08	−.02
873	.10	.1	.08	.06	.03	.01	.00
2905	.00	.00	.00	.00	.00	.00	.00
479	−.44	−.41	−.32	−.24	−.13	−.06	−.02
Total	−5.09[a]	−2.37[a]	−.58[a]	.43[a]	.96[a]	.76	.34
Model B—CMM/DN:							
1016	−2.60	−1.26	−.62	−.37	−.17	−.08	−.04
342	−4.48	−3.16	−2.00	−1.24	−.49	−.17	−.04
928	−3.47	−2.86	−1.81	−1.11	−.44	−.14	−.01
255	−3.30	−1.71	−.74	−.31	.02	.07	.03
481	.29	.28	.25	.21	.13	.06	.02
2482	−2.17	−1.20	−.59	−.35	−.16	−.07	−.02
2884	−.07	−.07	−.06	−.05	−.04	−.03	−.01
2851	.01	.00	−.00	−.01	−.02	−.03	−.03
373	2.17	2.13	1.99	1.79	1.37	.91	.42
1017	−.98	−.85	−.56	−.37	−.17	−.07	−.02
873	.33	.31	.27	.22	.13	.06	.01
2905	.00	.00	.00	.00	.00	.00	.00
479	.08	.08	.05	.02	−.01	−.01	−.01
Total	−14.20[a]	−8.32[a]	−3.84[a]	−1.58[a]	.14[a]	.49[a]	.31
Model C—CMM affecteds only:							
Total	−1.68	−.62	.35	.86	1.08	.77	.33

[a] Because of rounding error, the total does not exactly equal the sum of the individual family Z values.

dition, there was significant evidence for heterogeneity, with only a subset of families showing linkage to chromosome 9p. Results from this homogeneity test that allowed for linkage to either chromosome 9p or chromosome 1p or neither revealed that 3 of 11 pedigrees had conditional probabilities of >90% of being linked to 9p marker IFNA, versus 2 of 11 pedigrees being linked to 1p marker D1S47. These findings suggest that there is a susceptibility locus on chromosome 9p but that not all families with CMM/DN are linked to this region.

Four pedigrees presented here (255, 342, 928, and 1016) are updated versions of pedigrees that previously showed no evidence for linkage between a CMM/DN trait and chromosome 9p marker D9S3 (Bale and Dracopoli 1988), which is 1.6 cM proximal to D9S126 (Fountain et al. 1992*b*). Updated analysis of linkage between D9S3 and CMM alone was essentially informative in only two families (255 and 342). For family 255, $Z_{max} = 0.90$ at $\theta = .0$. Family 342, which showed strong evidence against linkage to both IFNA and D9S126, also showed evidence against linkage to D9S3 when CMM alone was considered as the trait. Reanalysis of a combined CMM/DN trait in these four pedigrees continued to show no evidence for linkage between CMM/DN and D9S3, as well as exclusion of tight linkage.

The results from the present linkage analysis were

Table 4

Z Values between CMM Alone and D1S47

	Z AT θ =[a]					
FAMILY	.0	.01	.05	.10	.20	.30
1016	−1.20	−.18	.39	.57	.61	.49
342	−2.01	−.42	.20	.40	.44	.31
928	.09	.09	.09	.09	.08	.05
255	−2.84	−1.45	−.80	−.53	−.25	−.10
2482	1.21	1.19	1.08	.95	.67	.40
2884	.01	.01	.00	.00	.00	.00
373	.43	.42	.40	.37	.30	.22
1017	−2.53	−1.32	−.66	−.38	−.14	−.04
873	.51	.49	.38	.27	.09	.01
2905	.61	.59	.53	.44	.28	.13
479	1.19	1.17	1.07	.95	.69	.43
Total	−4.53	.59	2.68	3.13	2.77	1.90

[a] Values for some families may differ from those of Goldstein et al. (1993) because of additional typed individuals and minor changes in marker allele frequency estimates.

compared with those of the previous chromosome 1p linkage analysis for the 13 CMM/DN pedigrees (Goldstein et al. 1993). Three pedigrees (255, 928, and 1017) that previously showed little or no evidence for CMM linkage to chromosome 1p showed evidence for linkage to at least one chromosome 9p marker. In addition, three other pedigrees (1016, 2482, and 479) that previously showed evidence for linkage to chromosome 1p also showed evidence for linkage to chromosome 9p. Finally, two pedigrees (342 and 2905) that showed linkage to 1p showed no evidence for linkage to chromosome 9p. In addition, in family 342, tight linkage to both IFNA and D9S126 could be rejected for both CMM alone and CMM/DN.

The above findings lead to the question, Is a susceptibility locus on chromosome 9p sufficient for the CMM and DN observed in these 13 pedigrees? First, the results for family 342 argue against this hypothesis. Second, if the 9p susceptibility locus were either a single CMM/DN locus or two tightly linked loci, one for CMM and the other for DN, then we would expect the Z values to increase when DN was included in the phenotype. For half the families showing evidence for CMM linkage to 9p, this phenomenon did occur. For the CMM/DN phenotype, families 2482, 373, 2884, and 479 showed the same or increased evidence for linkage to chromosome 9p. For family 373, $Z_{max} > 2.0$. Alternatively, families 255, 928, 1016, and 1017 all yielded negative Z values when a combined CMM/DN trait was analyzed. Three of these pedigrees (255, 928, and 1016) showed evidence for linkage to chromosome 1p, for the combined CMM/DN trait. The observations of linkage to chromosomes 9p and 1p in several of these pedigrees suggest that two loci may be responsible for CMM/DN in some of these pedigrees. Investigation of various two-locus models is currently underway.

We previously used two measures of clinical variation in the 13 pedigrees to search for differences in the estimated θ value. The first measure used the variation, across families, in the distribution of melanoma and DN, to divide families into two groups—those with predominantly melanoma and those with predominantly DN. The second homogeneity test compared pedigrees that had immune-related tumors—such as Hodgkin disease, non-Hodgkin lymphoma, sarcoma, and leukemia—with pedigrees that did not have these immune-related tumors. Both tests produced significant evidence for heterogeneity for the CMM/DN trait, with families having predominantly melanoma

Table 5

Results of Test of Homogeneity (HOMOG3R) for CMM Alone

	CONDITIONAL PROBABILITY THAT FAMILY IS LINKED TO[a]	
Family	Type 1 (CHR 9p:IFNA)	Type 2 (CHR 1p:D1S47)
342	.0	1.0
2905	.0	1.0
373	.15	.85
873	.28	.72
479	.48	.52
928	.52	.48
2884	.77	.23
2482	.79	.21
1016[b]	.91	.09
255	.99	.01
1017	.99	.01

NOTE.—Evidence for heterogeneity: difference in natural log likelihood = 4.49; and likelihood ratio for heterogeneity = 89.1.

[a] Test of homogeneity with three types of families: type 1 linked to chromosome 9p, type 2 linked to chromosome 1p, and type 3 unlinked. For this test of homogeneity, all families had a probability of .0 of being type 3 families.

[b] Comparison of Z values for IFNA (on chromosome 9p) and D1S160 (on chromosome 1p) yielded conditional probabilities of approximately .50 for each marker. Therefore, there was essentially equal probability of family 1016 being linked to either chromosome 9p or chromosome 1p.

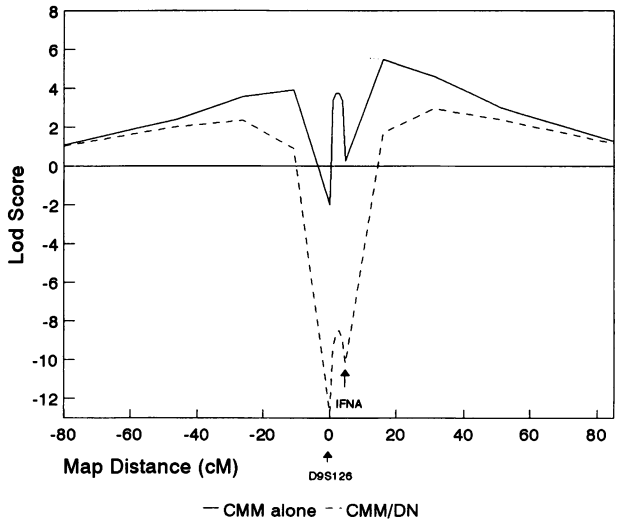

Figure 1 Multipoint Z values for a gene for MLM, in relation to chromosome 9p markers D9S126 and IFNA. The genetic distance between the markers was 4.5 cM. Multipoint linkage analyses were conducted assuming a fixed map of markers, no interference, and equal rates of recombination between males and females. Multipoint Z values are for all families analyzed, using either CMM alone (model A) or CMM/DN (model B). For CMM alone (model A), there was significant evidence for linkage, with a three-point Z_{max} of 5.48 at about 11 cM distal to IFNA. However, the odds in favor of that location vs. an alternative position 11 cM proximal to D9S126 were only 37:1. For CMM/DN (model B), Z_{max} = 2.94 at 26 cM distal to IFNA, although a Z value of 2.34 (relative odds of 1:4, vs. the position distal to IFNA) was observed 26 cM proximal to D9S126.

and those without immune-related tumors appearing linked to chromosome 1p (Goldstein et al. 1993). Examination of homogeneity by using these measures of clinical variation for markers on chromosome 9p no longer discriminated between linked and unlinked pedigrees. When these predivided sample tests were used, there was no evidence for heterogeneity for the combined CMM/DN trait or for CMM alone (Morton 1956) (data not shown).

Recently, Cannon-Albright et al. (1992) presented statistically significant evidence for linkage of familial MLM to chromosome 9p. The authors also reported no evidence for heterogeneity in the families that they studied and did not examine a combined CMM/DN trait. A second study of CMM alone showed significant evidence for linkage to chromosome 9p, on the basis of multipoint analysis (Nancarrow et al. 1993). Again, a combined CMM/DN trait was not investigated. We have presented linkage findings in 13 pedigrees with CMM/DN. Overall, there was statistically significant evidence for linkage to chromosome 9p marker IFNA, for all analysis models used. There was also significant evidence for linkage to CMM alone, on the basis of multipoint analysis. In addition to the positive evidence for linkage to chromosome 9p, there was significant evidence for heterogeneity when a homogeneity test (i.e., HOMOG3R) allowing for linkage to chromosome 9p or chromosome 1p or neither region was used. These results suggest that on chromosome 9p there is a susceptibility locus for familial MLM but that familial MLM is heterogeneous and that not all families with CMM/DN are linked to a locus in this region. More work needs to be done to find other loci for CMM, CMM/DN, and possibly DN alone and to better characterize the MLM locus on chromosome 9p.

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