for these populations, we think that it is wiser to admit that the hypothesis of direct contact has not been adequately tested. Why is the B-lineage clade, a clade most common on the western coast of the Americas, not found in Beringia? Why does the B-lineage clade have lower sequence diversity and a different mismatch distribution than do the major A, C, and D clades (as well as others recently documented by T. Schurr and colleagues) in Amerindians? Why are other lineages, not just in the B group, found in Pacific and Amerindian populations? Finally, how do we account for the prehistoric distribution of the sweet potato in Oceania (Yen 1974)?

Just as current mtDNA data alone may be insufficient to answer the question of "Neanderthal" gene continuity with modern European populations, the question of whether there was limited gene flow between Native Americans and Oceanic populations is unresolved. Rather than make dogmatic statements, we feel that it is better to encourage the open exploration of this debate, with more genetic markers and the use of data already in the literature.

R. L. CANN[1] AND J. K. LUM[2]
[1]*Department of Genetics and Molecular Biology, University of Hawaii at Manoa, Honolulu; and*
[2]*Department of Human Genetics, University of Utah Health Science Center, Salt Lake City*

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Address for correspondence and reprints: Dr. Rebecca L. Cann, Department of Genetics and Molecular Biology, Biomedical Sciences Building, 1960 East-West Road, Honolulu, HI 96822. E-mail: rcann@hawaii.edu

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Misclassification and Linkage of Hereditary Sensory and Autonomic Neuropathy Type 1 as Charcot-Marie-Tooth Disease, Type 2B

To the Editor:

Recently Kwon et al. (1995) published in the *Journal* their work describing linkage of a single large family with an inherited axonal neuropathy to chromosome 3, which they suggest is a second locus for Charcot-Marie-Tooth (CMT) type 2 and subsequently named "CMT2B." We think that the diagnostic classification of this family as CMT2 is incorrect, since the subjects have a severe sensory neuropathy that fits within the hereditary sensory and autonomic neuropathy (HSAN) type 1 classification of Dyck (1993).

Abnormal sensory findings in CMT2 separate it from distal spinal muscular atrophy but are a *minor* component of clinical symptoms in most CMT patients, as CMT is primarily a *motor neuropathy*. When Kwon et al. (1995, p. 854) state that "all [patients] had characteristic findings on their physical examinations, including . . . evidence of foot sores that were slow to heal, or amputated limbs related to the poorly healing foot ulcers," it suggests that a different diagnosis is more appropriate. In our experience collecting data on >950 individuals in >60 CMT1 (Vance et al. 1989, 1991), CMT2 (Loprest et al. 1992; Ben Othmane et al. 1993*b*), CMTX (Rozear et al. 1987; Fischbeck et al. 1986) and CMT4 (Ben Othmane 1990; Ben Othmane et al. 1993*a*) families, we have not seen foot ulcers, osteomyelitis, or amputations. Ulcerations leading to osteomyelitis and amputations are usually associated with severe sensory neuropathies (Adams and Victor 1989).

HSAN type I follows an autosomal dominant pattern of inheritance, with an early adult onset associated with ulcerations, and often with lancinating pains and osteomyelitis, which may lead to amputations (Adams and Victor 1989; Dyck 1993). Peripheral sensory symptoms are much more common than autonomic complications. Muscle weakness is usually present with atrophy and is

Table 1

Two-Point LOD Scores for Chromosome 3 Markers versus CMT2

	LOD Score at θ =					
Family	.050	.100	.150	.200	.300	.400
	D3S1769					
1118	−2.172	−1.313	−.852	−.562	−.235	−.079
235	−1.099	−.615	−.374	−.231	−.081	−.018
1280	−4.163	−2.724	−1.916	−1.370	−.671	−.258
1730	−4.053	−2.883	−2.194	−1.695	−.964	−.424
1766	−1.839	−.764	−.236	.054	.261	.175
Total	−13.326	−8.299	−5.572	−3.804	−1.690	−.604
	D3S1290					
1118	−.772	−.330	−.116	−.001	.079	.060
235	−1.493	−.742	−.372	−.161	.023	.045
1280	−5.664	−3.294	−2.041	−1.261	−.422	−.117
1730	−2.436	−1.566	−1.079	−.752	−.342	−.113
1766	−5.323	−3.427	−2.343	−1.615	−.710	−.228
Total	−15.688	−9.359	−5.951	−3.790	−1.372	−.353
	D3S1744					
1118	−1.548	−.945	−.608	−.391	−.151	−.051
235	−2.015	−1.343	−.945	−.668	−.308	−.101
1280	−3.876	−2.085	−1.179	−.646	−.137	.001
1730	−.773	−.485	−.317	−.202	−.066	−.009
1766	−7.199	−4.696	−3.232	−2.232	−.969	−.299
Total	−15.405	−9.554	−6.281	−4.139	−1.631	−.459

NOTE.—The markers D3S1769 and D3S1744, which are reported to flank the region of interest by Kwon et al. (1995), and D3S1290, which is located within the region of interest, were genotyped in all family members by using standard techniques (Ben Othmane et al. 1992). The frequency of the disease allele was assumed to be .0001, and the frequencies for the marker alleles were estimated from a series of ≥78 unrelated Caucasian chromosomes. Two-point and multipoint LOD scores were calculated using the MLINK and LINKMAP modules of the FASTLINK program (v2.2) (Cottingham et al. 1993; Schaffer et al. 1994). The genetic map used in the multipoint linkage analysis was extracted from Kwon et al. (1995). In addition to analyses utilizing the entire pedigree, "low-penetrance" analyses, in which the phenotypes of unaffected individuals are eliminated from the linkage analysis while retaining the marker genotyping data to maximize inferences of missing parental data, were performed.

variable, often leading to its association with peroneal atrophy. Dyck reported a HSAN I family with findings similar to those in Kwon et al.'s (1995) family. These findings led Dyck to the conclusion that classification between HSAN I and CMT2 could be "problematic" in some families (Dyck 1993). But certainly the lack of ulcerations and amputations as primary manifestations of CMT, and the rarity of severe pain, all common in HSAN type I, distinguish these two forms of inherited peripheral neuropathy in most families.

Furthermore, we would like to point out some difficulties with respect to the statistical analysis of the linkage data in Kwon et al. (1995). First, and potentially most troublesome, is the use of equal allele frequencies for the marker loci in the analysis. This practice should not be encouraged, as it has been shown to significantly inflate LOD scores (Ott 1991; Knowles et al. 1992) and can lead to type 1 errors in linkage results. This issue is of concern in this study, as the peak LOD score reported by Kwon et al. (1995) has only marginal significance ($z = 3.462$ at $\theta = .0$). Additional analysis such as a multipoint linkage results may have been useful in determining the robustness of their analysis. Unfortunately, Kwon et al. (1995) do not present such an analysis. Minor considerations regarding the linkage analysis include the authors' failure to specify clearly the penetrance of the disease allele for the analysis (they term it "highly penetrant") and the fact that the crossover defining the distal flanking marker occurs in an unaffected family member. The probability that this marker repre-

sents a true distal crossover is entirely dependent on the assumed penetrance of the disease allele.

We have investigated a series of five American Caucasian CMT2 families (39 affected individuals, 85 asymptomatic, at-risk individuals, and 21 spouses) previously reported to be excluded from the CMT2A locus on chromosome 1 (Ben Othmane et al. 1993*b*). Diagnostic criteria include unequivocal distal muscle weakness and atrophy in lower extremities, depressed deep tendon reflexes, pes cavus, and an abnormal sensory exam or obligate heterozygote status (Ben Othmane et al. 1993*b*). The penetrance of the disease allele is dependent on age at examination (Loprest et al. 1992). No affecteds had ulcerations, amputations, or suffered severe pain in their distal extremities. None of the families show evidence of linkage to this region, using single marker (table 1) or multipoint linkage analysis (data not shown).

Genetic linkage studies have shown that the CMT phenotype has extensive genetic heterogeneity. However, "genetic heterogeneity," as defined, implies clinical homogeneity. Thus, if diagnostic criteria are not consistent, the meaning of genetic heterogeneity is misleading to the clinician, geneticist, and neurologist.

We congratulate Kwon et al. (1995) on their report of linkage for this family to chromosome 3. But we suggest that instead of CMT2B, their report describes HSAN type 1. We believe that it is these families that should be screened for possible confirmation of their chromosome location, rather than those of CMT2.

JEFFERY M. VANCE, MARCY C. SPEER, JEFFREY M. STAJICH, SANDRA WEST, CHANTELLE WOLPERT, PETE GASKELL, FELICIA LENNON, RICHARD M. TIM, MARVIN ROZEAR, KAMEL BEN OTHMANE, AND MARGARET A. PERICAK-VANCE

Division of Neurology, Duke University Medical Center, Durham

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Address for correspondence and reprints: Dr. Jeffery M. Vance, Box 2900 DUMC, Durham, NC 27710. E-mail: jeff@dnadoc.mc.duke.edu

0002-9297/96/5901-0035$02.00

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Reply to Vance et al.

To the Editor:

In our report of a family with a motor and sensory polyneuropathy that was linked to chromosome 3q