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.

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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

(Kwon et al. 1995), we classified this neuropathy as a form of hereditary motor and sensory neuropathy II (HMSN II, also known as "CMT2"). Doubts have been raised by Vance et al. as to whether this neuropathy should be classified as hereditary sensory autonomic neuropathy I (HSAN I) instead of HMSN II. While it is reasonable to raise such doubts, we believe that the neuropathy is best designated as HMSN II for the reasons described below.

The group of disorders described as HSAN are characterized by primary or predominant involvement of sensory and autonomic neurons that fail to develop or that undergo atrophy and degeneration. These disorders were extensively reviewed by Dyck and Ohta (Dyck and Ohta 1975; Dyck 1984, 1993), who initially described them as the hereditary sensory neuropathies (HSN). It was Dyck who subsequently suggested that these disorders be designated HSAN rather than HSN, because of the presence of autonomic involvement.

The diagnosis of HSAN I is made primarily on clinical grounds. The primary clinical features in HSAN I are autosomal dominant inheritance, severe sensory loss with foot complications, spontaneous lancinating or burning pain, and loss of sweating. Contrary to Vance et al.'s assertion, muscle weakness or wasting may not be present, and, if present, it is typically mild and not a presenting symptom (Dyck 1993).

In the family we studied, motor involvement is a major feature of the disorder. Indeed, muscle weakness of the feet, weak ankles, or foot drop were presenting symptoms in all affected members evaluated. Furthermore, electrodiagnostic studies showed complete loss of peroneal and tibial distal compound muscle action potentials (CMAPs) in all affected members studied, except in one in whom an extremely small tibial CMAP was present. These electrodiagnostic findings indicate very severe and, it is likely, complete distal loss of motor axons.

None of the affected members presented with or developed the type of lancinating, aching, or burning pain reported in patients with HSAN I. Although autonomic function was not evaluated with physiological testing, a survey of autonomic symptoms (Low 1993) in three affected members showed none with significant symptoms. No affected member questioned was aware of loss of or disordered sweating in the feet.

Foot ulceration occurred in about half the affected members, in association with distal sensory loss. We do not accept that the presence of foot ulceration inevitably leads to classification under HSAN, or that it excludes the diagnosis of HMSN. Contrary to Vance et al.'s assertion, HMSN patients may also develop foot ulceration and amputation, as reported in the large review of HMSN by Harding and Thomas (1980). In referring to apparent similarities between our family and the Virginia kindred reported by Dyck et al. (1965) in whom there was muscle weakness and atrophy with severe acral mutilation, Vance et al. did not quote in full Dyck's recent opinion of the classification of this Virginia kindred. Dr. Dyck admitted that "it is problematic whether they should be classified as HSAN I or as HMSN II. The prominent involvement of muscles in HSAN I raises the question whether the separation of some varieties of HSAN I from some varieties of HMSN II is real" (Dyck 1993, p. 1065).

We recognize this difficulty, so clearly stated by Dyck, but in consideration of the ubiquitous and prominent motor involvement and the absence of pain and autonomic symptoms in our kindred, we conclude that their neuropathy is best included under the rubric of HMSN II. We anticipate that further linkage studies with 3q markers of additional HMSN II families, HSAN I families and, if possible, the Virginia kindred, will eventually resolve remaining questions about classification.

The clinical description of the neuropathy in our original paper was very abbreviated, as the emphasis was on the genetic linkage studies. This may have led to misplaced emphasis or misperceptions regarding the clinical features in this family. We will be providing a detailed account of the clinical and the electrodiagnostic characteristics of this family in a separate paper, which we have submitted for publication.

Vance et al. also raise a number of important points regarding parameters used for the linkage analysis. While we agree with their concerns regarding the use of arbitrarily set allele frequencies, estimates of penetrance, etc., we maintain that the choice of parameters used in our analyses was appropriate. While it is true that the practice of setting equal allele frequencies might serve to inflate LOD scores, it is also possible that this practice might lead to an underestimation of the true magnitude of the linkage association. In a series of simulation studies for our data set, altering the allele frequencies for various markers did not significantly change the results of the linkage analysis. This is in part due to the fact that the majority of the linkage data came from one branch of the family in which all of the marker genotypes were determined directly or were easily deduced from the genotypes of the progeny.

We did not report multipoint analyses because we did not believe that they would provide any more data on the location of the disease gene locus than did the two-point LOD scores. We found significant evidence of linkage between the disease locus and two markers (GGAA8B03 and D3S1551) that are separated by ~3 cM. The genetic distances between many of the markers we investigated were not well established at the time of the submission of our manuscript. Therefore, the multipoint analysis, while confirming linkage, would have been unlikely to give more useful information. As

far as setting the penetrance for the disease allele in the kindred, we maintain that the disease allele is highly penetrant in this family. Until the disease gene is identified and all individuals are genotyped, it is not possible to estimate the penetrance more accurately. The concern regarding the definition of a distal flanking marker on the basis of recombination in an unaffected individual is legitimate. On the basis of our clinical assessment, however, we think it highly unlikely that the individual in which the recombination event occurred is a disease-allele carrier.

Note added in proof.—A gene for HSAN I was recently assigned to the 9q22.1-q22.3 region (Nicholson et al. 1996). Although we have not tested for linkage with the 9q markers in the family that we classified as having HMSN II and for which we mapped the disease locus to 3q, it is highly unlikely that the disease gene in our family is linked to 9q22.2-q22.3 sequences. The assignment of HSAN I to 9q adds further weight to our argument that the family we investigated has HMSN II and not HSAN I, as suggested by Vance et al.

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Elevated Total Plasma Homocysteine and 677C→T Mutation of the 5,10-Methylenetetrahydrofolate Reductase Gene in Thrombotic Vascular Disease

To the Editor:

Moderate elevation of total plasma homocysteine (tHcy) has been reported as an independent risk factor for thrombotic vascular disease, a well-known multifactorial disorder. Possible genetic causes of elevated tHcy include defects of the sulfur-containing amino acids metabolism due to deficiencies of cystathionine β-synthase, of 5,10-methylenetetrahydrofolate reductase (MTHFR), and of the enzymes of cobalamin metabolism. An impaired activity of MTHFR due to a thermolabile form of the enzyme has been observed in ≤28% of hyperhomocysteinemic patients with premature vascular disease (Engbersen et al. 1995). More recently, the molecular basis of such enzymatic thermolability has been related to a common mutation of the MTHFR gene, causing a C-to-T substitution at nt 677 (677C→T) (Frosst et al. 1995). This mutation was found in 38% of unselected chromosomes from 57 French Canadian individuals. The homozygous state for the mutation was present in 12% of these subjects and correlated with significantly elevated tHcy. Preliminary evidence indicates that the frequency of homozygotes for the 677C→T mutation may vary significantly in populations from different geographic areas (from 1.4% to 15%; Motulsky 1996).

We evaluated the frequency of the 677C→T mutation of the MTHFR gene in an Italian population of 64 unrelated patients with early-onset venous or arterial occlusive disease or with thrombosis occurring at unusual sites who were referred to a thrombosis research unit of