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Report

A Locus for Hereditary Sensory Neuropathy with Cough and Gastroesophageal Reflux on Chromosome 3p22-p24

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Hereditary sensory neuropathy type I (HSN I) is a group of dominantly inherited degenerative disorders of peripheral nerve in which sensory features are more prominent than motor involvement. We have described a new form of HSN I that is associated with cough and gastroesophageal reflux. To map the chromosomal location of the gene causing the disorder, a 10-cM genome screen was undertaken in a large Australian family. Two-point analysis showed linkage to chromosome 3p22-p24 (Z_{max} = 3.51 at recombination fraction (θ) 0.0 for marker D3S2338). A second family with a similar phenotype shares a different disease haplotype but segregates at the same locus. Extended haplotype analysis has refined the region to a 3.42-cM interval, flanked by markers D3S2336 and D3S1266.

The hereditary motor and sensory neuropathies are a genetically heterogeneous group of disorders, caused by a number of different gene mutations. Neuropathies with predominantly sensory features are classified as hereditary sensory neuropathies (HSNs). The autosomal dominant form of HSN is classified as hereditary sensory neuropathy type I (HSN I) (Thomas 1993). HSN has an adult onset, generally between the 2nd and 4th decade, with sensory loss first affecting the feet and legs, leading to painless injuries. Later, foot ulcers, lancinating pains, and motor involvement can occur (Hicks 1922; Thomas 1993; Nicholson et al. 1996).

Mutations in subunit 1 (SPTLC1) of the enzyme serine palmitoyltransferase (SPT), the rate-limiting enzyme of the sphingolipid pathway, have been identified as the cause of HSN1 on chromosome 9q22.1-q22.3 (MIM #162400) (Dawkins et al. 2001). Bejaoui et al. (2001) have shown that SPTLC1 mutations result in reduced SPT activity and sphingolipid synthesis but do not alter the levels of SPTLC1 or SPT subunit 2; this result indicates that the mutations have a predominantly negative effect on the SPT enzyme. Another neuropathy, classified as hereditary motor and sensory neuropathy type IIB (HMSN IIB), involves severe sensory impairment and foot ulcers and could therefore be regarded as a form of HSN (Vance et al. 1996). HMSN IIB has been mapped to chromosome 3q13-q22 (Kwon et al. 1995). Two missense mutations in the RAB7 gene have been identified for the HMSN IIB phenotype (Verhoeven et al. 2003).

Approximately 25% of the general population experiences gastroesophageal reflux (GER) (Nebel et al. 1976). In some cases, it is an inherited trait (Crabb et al. 1985), but, for the most part, it is attributed to the effects of diet, obesity, or hiatus hernia. Two forms of dominantly inherited GER have been identified. A form of severe GER in children was mapped to chromosome 13q14 (Hu et al. 2000), and an inherited form of GER with autosomal dominant spastic paraparesis was mapped to chromosome 10q (Seri et al. 1999).

As many as 25% of patients with GER symptoms have associated respiratory manifestations, including cough (Poe et al. 1989; Irwin et al. 1990, 1993). In many of these individuals, cough may be the only manifestation of GER (Irwin et al. 1989).

HSN I with cough and GER was recently identified by two authors of the present report (J.D.P. and P.J.S.), and detailed clinical and neurophysiological studies of this family have been described elsewhere (Spring et al. 2002). The first symptoms of HSN I with cough and GER can be an unexplained chronic cough, which can

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progress to cough syncope. Monitoring of esophageal pH for 24 h shows that cough is temporally associated with GER and impaired laryngeal sensation. The disorder usually presents in adult life, with either cough or GER symptoms. The cough may occur between the 2nd and the 4th decade. Sensory loss commences in the feet and legs, between the 3rd and 5th decade. The Achilles tendon reflexes are decreased in some individuals, and nerve-conduction–velocity studies show an axonal neuropathy with absent or reduced sensory nerve action potentials. Nerve biopsy shows loss of unmyelinated and myelinated axons.

We have identified two families with HSN I with cough and GER. One, a three-generation Australian family (HSN32), was large enough for linkage studies. Male-to-male transmissions indicated autosomal dominant inheritance. A total of 20 at-risk individuals in this family and 7 spouses were recruited for clinical, electrophysiological, and genetic studies, after obtaining informed consent according to guidelines of the Concord Hospital medical ethics review committee. A second, unrelated family (HSN35) with nine at-risk family members and two spouses was large enough for haplotype studies.

Individuals were classified as affected, for the purpose of the linkage study, if they had a neuropathy and either a chronic cough or GER or both. The cough must have no other cause and be present at least 1 year. Initially, the cough may appear if the patient is repeatedly clearing the throat. The features of the neuropathy are sensory loss, painless injuries, or lancinating pains, with or without abnormal results of nerve-conduction studies that are consistent with an axonal neuropathy. GER is indicated by the occurrence of heartburn, regurgitation, or acid brash at least once a week. When clinically indicated, some individuals underwent a dual-probe 24-h ambulatory esophageal pH monitoring with a subject-triggered cough sensor (as described by Ing et al. [1994]). Episodes of reflux are detected by a reduction in pH to <4 in the distal or proximal esophagus, and these may be correlated with episodes of cough. Obligate carriers, defined as those family members who had affected offspring, were assigned to the affected group. Individuals with a chronic cough or GER without neuropathy were classified as having an unknown clinical phenotype. Individuals with no relevant symptoms and with normal results on clinical examination were assigned to the unaffected group. Eight members of family HSN32 were classified as affected. Of these, one individual did not have all three phenotypes. Six individuals were classified as unaffected, and six were classified as having unknown clinical status. Two of the individuals with unknown clinical status were obligate carriers. In family HSN35, two individuals were classified as affected. Both had all three phenotypes. Five individuals were classified as unaffected, and two individuals had an unknown clinical status. One of the individuals with unknown clinical status was an obligate carrier.

Genomic DNA was extracted from whole blood, using standard techniques. Known loci for HSN I (HSN1 [Nicholson et al. 1996]), HMSN I (HMSN IA [Valentijn et al.1992] and HMSN IB [Bird et al. 1983]), HMSN II (HMSN IIA [Ben Othmane et al. 1993], HMSN IIB [Kwon et al. 1995], HMSN IID [Ionasescu et al. 1996], HMSN IIE [Mersiyanova et al. 2000], and HMSN IIF [Ismailov et al. 2001]) were excluded by either linkage analysis or mutation screening. The pediatric GER locus and the hereditary spastic paraplegia locus were also excluded (data not shown) (Seri et al. 1999; Hu et al. 2000). A genomewide screen using 383 microsatellite markers at 10-cM intervals was undertaken at the Australian Genome Research Facility. Autosomal dominant inheritance was assumed, with 95% penetrance by the age of 35 years. A disease allele frequency of 0.001 and a phenocopy rate of 0.001 were assumed (Seri et al. 1999). Male and female recombination rates were considered equal. Marker allele frequencies were obtained from the Genome Database. DNA samples were amplified by PCR, as described by Nicholson et al. (1996).

The computer program MLINK was used to perform two-point linkage analysis (Lathrop et al. 1984). Haplotypes were assigned on the basis of the minimization of intermarker recombination.

The genome screen showed linkage to chromosome 3p22-p24. Marker D3S2338 gave a LOD score of 3.51 at recombination fraction (θ) 0.0. Elsewhere in the genome, no other significantly positive LOD score peaks were detected. Linkage studies, in which individuals expressing two of the three phenotypes were assigned a different affection status, showed no significant change in the LOD scores and no other significantly positive LOD score peaks elsewhere in the genome. Nine additional markers within this region were then tested in both families. The results of the two-point linkage analysis are shown in table 1. Extended haplotypes were constructed according to the order of the Marshfield genetic map (fig. 1). The disease haplotypes segregating in families HSN32 and HSN35 are shown in figure 2.

A recombinant individual in family HSN32 (individual III:9) defines marker D3S1266 as the proximal flanking marker. The distal flanking marker is defined by a recombination event in family HSN35 (individual III:5), occurring between markers D3S2336 and D3S2466. Both of these individuals have the full disease syndrome. On the basis of these two informative recombination events, HSN with cough and GER has been localized to a 3.42-cM region that is flanked by the markers D3S2336 and D3S1266 and corresponds to a physical distance of 3 Mb. The two families do not share a common disease

Table 1

Pedigrees HSN32 and HSN35 Combined: Two-Point LOD Scores between the Locus for HSN with Cough and GER and the Microsatellite on Chromosome 3p

Marker and Pedigree	LOD Score at $\theta_{(m=f)}$ = 0	.01	.05	.1	.2	.3	.4
D3S1259:							
HSN32	2.21	2.23	2.22	2.09	1.66	1.09	.88
HSN35	−2.58	−1.72	−.91	−.50	−.14	.01	.02
HSN32/35	−.37	.51	1.31	1.59	1.52	1.10	.90
D3S3610:							
HSN32	−.86	−.76	−.46	−.24	−.01	.07	.08
HSN35	−1.88	−1.14	−.55	−.31	−.12	−.04	−.01
HSN32/35	−2.74	−1.90	−1.01	−.55	−.13	.03	.07
D3S2403:							
HSN32	2.37	2.33	2.15	1.92	1.42	.87	.74
HSN35	−.51	−.44	−.26	−.12	.02	.07	.08
HSN32/35	1.86	1.89	1.89	1.80	1.40	.08	.82
D3S1585:							
HSN32	2.65	2.61	2.43	2.20	1.70	1.13	1.02
HSN35	−1.34	−1.18	−.77	−.46	−.13	.01	.02
HSN32/35	1.31	1.43	1.66	1.74	1.57	1.14	1.04
D3S2338:							
HSN32	3.51	3.45	3.21	2.88	2.19	1.42	1.32
HSN35	−1.46	−1.28	−.78	−.44	−.11	.02	.02
HSN32/35	2.05	2.17	2.43	2.44	2.08	1.44	1.34
D3S1293:							
HSN32	1.46	1.50	1.57	1.54	1.30	.91	.81
HSN35	−2.03	−1.05	−.38	−.09	.12	.17	.18
HSN32/35	−.43	.45	1.19	1.45	1.42	1.08	1.18
D3S2336:							
HSN32	3.34	3.28	3.04	2.73	2.08	1.36	1.27
HSN35	−1.52	−.75	−.16	.06	.20	.20	.19
HSN32/35	2.82	2.53	2.88	2.79	2.28	1.56	1.46
D3S2466:							
HSN32	3.23	3.18	2.95	2.65	2.00	1.29	1.15
HSN35	.63	.63	.61	.58	.50	.38	.31
HSN32/35	3.86	3.81	3.56	3.23	2.50	1.67	1.46
D3S2337:							
HSN32	1.56	1.52	1.36	1.16	.76	.40	.32
HSN35	1.36	1.33	1.23	1.11	.84	.55	.41
HSN32/35	2.92	2.85	2.59	2.27	1.50	.95	.73
D3S2335:							
HSN32	3.23	3.18	2.95	2.65	2.00	1.29	1.18
HSN35	−.04	−.04	−.03	−.02	−.01	.00	.00
HSN32/35	3.19	3.14	2.92	2.63	1.99	1.29	1.18
D3S21266:							
HSN32	.53	1.50	1.94	1.93	1.59	1.06	.94
HSN35	−.97	−.34	.21	.41	.49	.40	.33
HSN32/35	−.44	1.16	1.73	1.52	1.10	.66	.61

haplotype, suggesting that different mutations in a single gene might occur.

We have demonstrated a significant linkage score of 3.51 at $\theta = 0.0$ in one family with cough and GER and in a second family with a similar phenotype, in which all affected individuals share a haplotype in the same region. It could be argued that there are two separate syndromes affecting these families (GER with chronic cough and hereditary sensory neuropathy) and that they occurred together by chance. Because there are no instances of the neuropathy without GER and cough, the two disorders could be closely linked on the same chromosome or they could be allelic at the same locus. The natural history of the disease is consistent with all these features being part of a single disorder, because neuropathy is the last feature of the disease to develop. Given that cough or GER always precedes sensory loss by many years, the natural history of the disease explains the presence of cough or GER without neuropathy in younger individuals. The oldest individual with cough and GER but minimal signs of neuropathy was 52 years old at the time of investigation.

Sporadic cases of GER are found in approximately one-third of the general population. In a large study in the British population, Jones and Lydeard (1989) confirmed this figure, showing that 38% of the population reported symptoms of GER. Therefore, cases of GER alone could be explained as being nonhereditary sporadic cases. Cough has been estimated to affect 10% of subjects with GER (i.e., 3% of the population) (Poe et al. 1989; Irwin et al. 1990, 1993). However, to eliminate these probabilities, for the linkage study, we assigned an unknown phenotype to all subjects with GER and/or cough without neuropathy.

The 3.42-cM interval containing the locus for HSN I with cough and GER on chromosome 3p22-24 has been almost completely sequenced and contains 28 mapped genes. Two positional candidate genes have been identified on the basis of their expression profiles in peripheral nerve and spinal cord through the Entrez Human

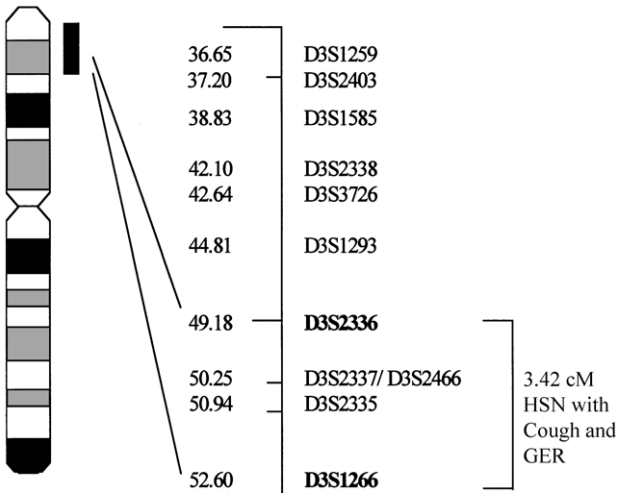

Figure 1 Genetic map (sex averaged) of chromosome 3 markers used in the present study. The marker-map positions are based on the sex-averaged maps from the Center for Medical Genetics, Marshfield Medical Research Foundation. Loci on the same line were mapped to the same genetic location. Markers flanking the HSN I with cough and GER genetic interval are shown in boldface.

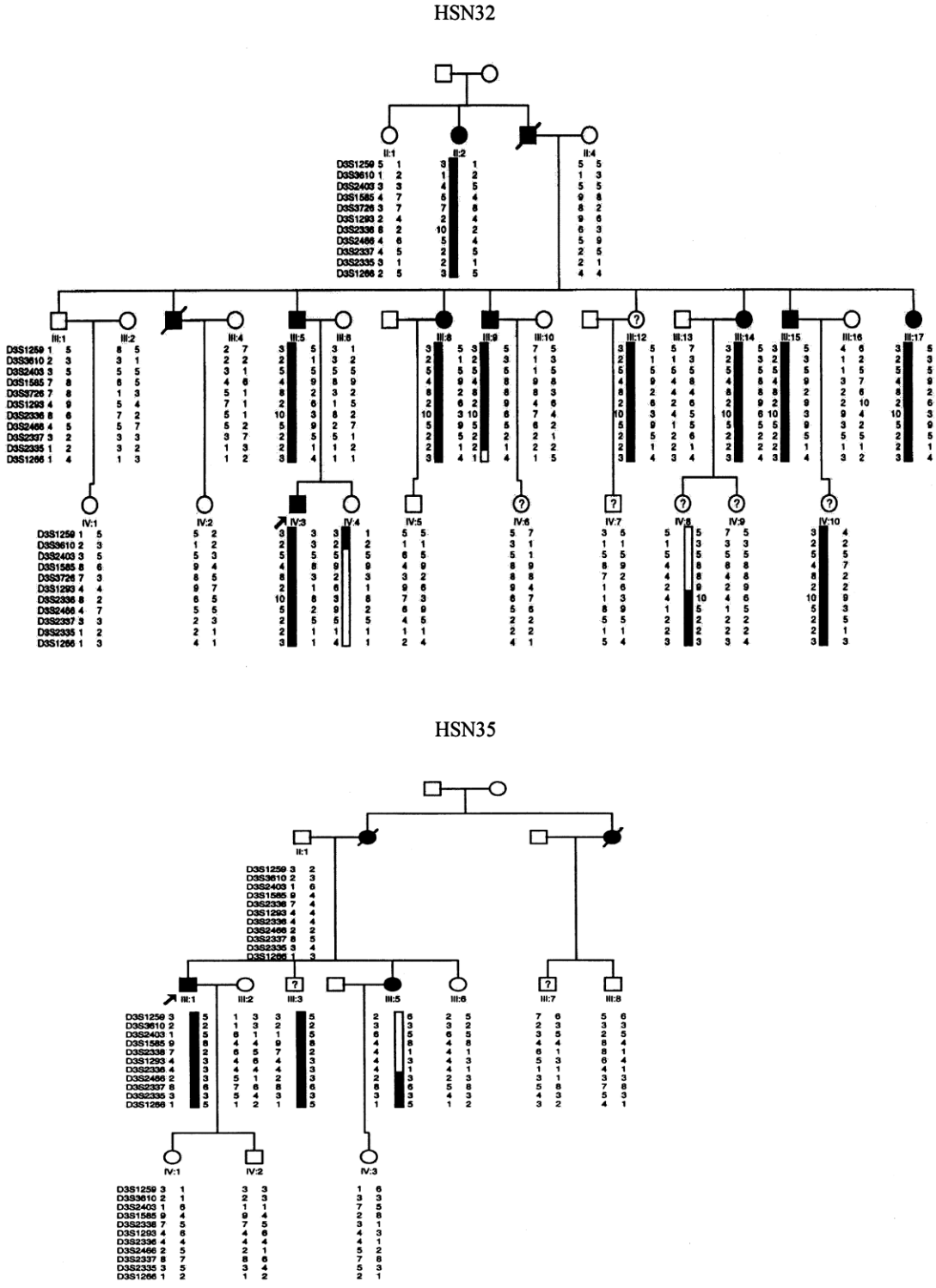

Figure 2 Haplotype analysis of markers from chromosome 3p22-p24 in families HSN32 and HSN35 with autosomal dominant HSN I with cough and GER. The haplotype segregating with the disease is indicated (*blackened bar*). The markers are presented in order from telomere (*top*) to centromere (*bottom*). Blackened symbols denote affected individuals; unblackened symbols denote unaffected individuals; individuals with unknown clinical status are denoted by a question mark. Individuals are numbered consecutively in each generation, from left to right. Individual III:5 in family HSN35 defines the telomeric boundary of the disease at D3S2336, whereas individual III:9 in family HSN32 defines the centromeric boundary at D3S1266.

Genome Map viewer. These genes include the topoisomerase II β (TOP2B) and the solute-carrier family 4 (SLC4A7). The TOP2B gene encodes a DNA topoisomerase, an enzyme that controls and alters the topologic states of DNA (Lang et al. 1998, Jenkins et al. 1992). Takashima et al. (2002) described the gene tyrosyl-DNA phosphodiesterase 1 (TDP1) as causing an autosomal recessive spinocerebellar ataxia with axonal neuropathy. TDP1 repairs covalently bound I–DNA complexes and has a function in the DNA repair pathway in humans. TDP1 dysfunction does not predispose to neoplasia, but it can cause progressive neuronal disease and death (Yang et al. 1996; Pouliot et al. 1999). Reduced activity of the enzyme may also play a role in ataxia-telangiectasia (Davies et al. 1989). SLC4A7 is a sodium bicarbonate cotransporter mainly expressed in the brain and spinal cord (Pushkin et al. 1999). These positional candidate genes are currently being screened for a possible role in the pathogenesis of HSN I with cough and GER.

Identification of the disease gene may lead to clues to an understanding of the cause of reflux at a molecular level. Functional studies will be required to determine whether the GER is secondary to a neuropathy affecting the gastroesophageal sphincter or whether the reflux has an unrelated etiology. The association between neuropathy and GER may be more common than previously recognized, because the neuropathy may occur late in life and may therefore be easily missed. Further studies are continuing, to refine the genetic interval and to screen candidate genes for mutations.

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Electronic-Database Information

URLs for data presented herein are as follows:

Center for Medical Genetics, Marshfield Medical Research Foundation, http://research.marshfieldclinic.org/genetics/

Entrez Genome View, National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?

Genome Database, http://www.gdb.org/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for HSN1)

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