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Hereditary motor and sensory neuropathy with proximal dominancy in the lower extremities, urinary disturbance, and paroxysmal dry cough

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ABSTRACT

We studied a four-generation pedigree of a Japanese family with hereditary neuropathy to elucidate the genetic basis of this disease. Twelve members of the family were enrolled in this study. The clinical features were neurogenic muscle weakness with proximal dominancy in the lower extremities, sensory involvement, areflexia, fine postural tremors, painful muscle cramps, elevated creatine kinase levels, recurrent paroxysmal dry cough, and neurogenic bladder.

We performed a genome-wide search using genetic loci spaced at about 13 Mb intervals. Although nine chromosomes (1, 3, 4, 5, 6, 10, 17, 19, and 22) had at least one region in which the logarithm of odds (LOD) score was over 1.0, no loci fulfilled the criteria for significant evidence of linkage. Moreover, we analyzed an extra 14 markers on 3p12–q13 (the locus of hereditary motor and sensory neuropathy, proximal dominant form) and an extra five markers on 3p22–p24 (the locus of hereditary sensory neuropathy with chronic cough) and observed LOD scores of <-3 on both 3p12–q13 and 3p22–p24. Mutation scanning of the entire coding regions of the *MPZ* and *PMP22* genes revealed no mutations. We conclude that the disorder described here is a newly classified hereditary motor and sensory neuropathy with autosomal dominant inheritance.

1. Introduction

Hereditary motor and sensory neuropathy (HMSN) includes a heterogeneous group of neurodegenerative disorders characterized by progressive neuropathy [1]. Most HMSN patients show muscular weakness with distal predominance, while muscular weakness with proximal dominancy is quite rare. Causative mutations have been identified in over 20 types of HMSN with distal predominance. Two overlapping genetic loci (3q13.1 and 3p12–q13) for hereditary motor and sensory neuropathy (proximal dominant form) (HMSN-P) have been identified [2–4]. However, no causative gene for HMSN-P has yet been elucidated. We have identified a four-generation Japanese family with hereditary motor and sensory neuropathy with proximal dominancy in the lower extremities. The atypical features present in this family, when compared to previously reported HMSN-P cases, were urinary dysfunction and recurrent paroxysmal dry cough. We performed clinical, electrophysiological, and genetic analyses of this family. We propose here the existence of a new type of HMSN-P based on results of these analyses.

2. Subjects and methods

2.1. Subjects

We studied a four-generation Japanese pedigree originating from Kumamoto prefecture, a southern province of Japan. Fig. 1 shows an extract from this pedigree. After informed consent was obtained, nine available family members and three spouses underwent a neurological examination and were blood-sampled in 2006. This study was approved by the Ethics Committees of Kurume University School of Medicine and Kyushu University, Faculty of Medicine.

2.2. Genotype analysis

We performed a genome-wide scan using 292 fluorescent-labeled microsatellite markers covering 22 autosomes; markers were chosen from the ABI-PRISM Linkage Mapping Set version 2.5 (Applied Biosystems, Foster City, CA) and the NCBI database (Build 36.2) and spaced at intervals of approximately 13 Mb. Moreover, we analyzed an extra 14 markers on 3p12–q13 and an extra 5 markers on 3p22–p24 according to previous studies [3–5]. Polymerase chain reactions were performed as recommended by the supplier (Applied Biosystems) or three step methods. Amplified fragments with internal-size standards

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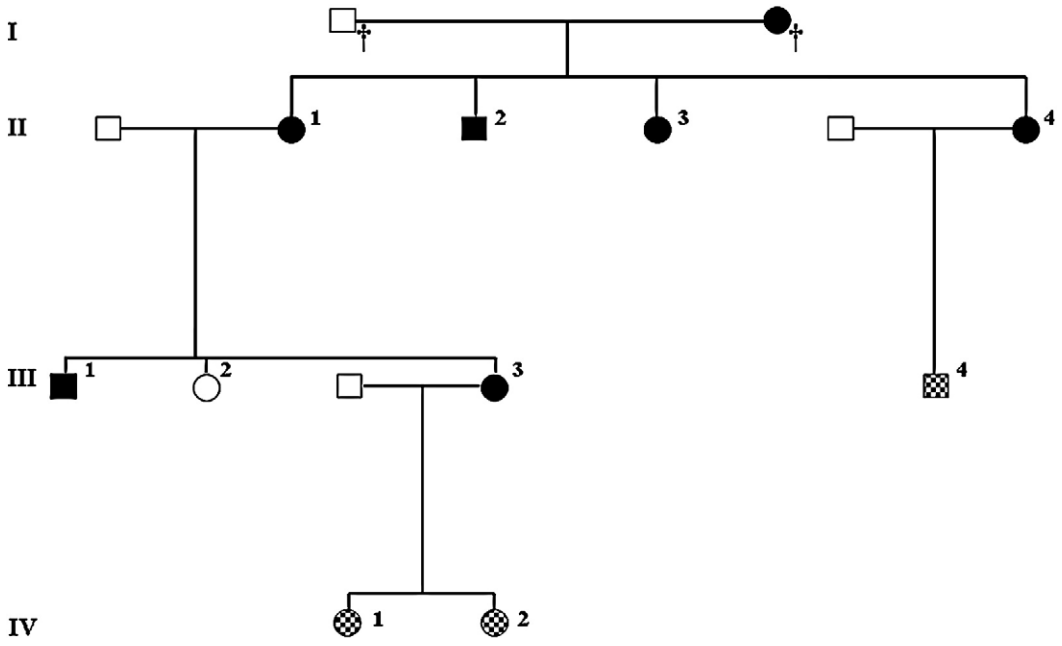

Fig. 1. Family pedigree (partial omissions are to protect the identities of other family members). Filled square: affected male; open square: unaffected male; checked square: unknown status male; filled circle: affected female; open circle: unaffected female; checked circle: unknown status female; dagger: deceased.

were resolved using an automated ABI Prism 3100 DNA sequencer and analyzed using GENESCAN version 3.7 software (Applied Biosystems).

2.3. Linkage analysis

Scores of multi-point logarithm of odds (LOD) were calculated using the GENEHUNTER program (version 2.1_v2 beta), and scores of two-point LOD were calculated using the MLINK program of the computer package FASTLINK (version 4.1) under the assumptions of autosomal dominant inheritance, a disease frequency of 1 per 100,000, a penetrance of 0.90, and equal frequencies of all alleles of each marker.

2.4. Mutation analysis

We designed primers to examine the entire exonic sequences of the *MPZ* (MIM: 159440) and *PMP22* (MIM: 601097) genes by direct sequencing. We sequenced both strands of PCR products using the BigDye Terminator v3.1 Sequencing Standard Kit (Applied Biosystems) on an automated ABI 3100 DNA sequencer. Additionally, we screened single copy number variants (CNV) using Human CNV370–2 v 1.0 in patient III-3 according to the manufacturer's protocol (Illumina, http://www.illumina.com).

3. Results

3.1. Phenotypic features

Autosomal dominant transmission was the most likely mode of inheritance, although male-to-male transmission was absent in the pedigree (Fig. 1). In this pedigree, five members (two men and three women) were affected, and the disease statuses of three members (III-4, IV-1, and IV-2) were undefined because of the current difficulty in evaluating symptoms. The clinical and laboratory findings in the five afflicted patients are summarized in Table 1. In the affected individuals, the age at onset was 21.2±5.02 (SD) years and ranged from 18 to 30 years. Anticipation was not apparent in this family. The age at examination was 56.2±15.2 (SD) years and ranged from 38 to 70 years. The disease duration spanned 18 to 51 years. The initial symptom was lower limb muscle cramping in four members (II-1, II-2, III-1, and III-3) and paroxysmal dry cough in one (II-4). The progression was relatively slow. All affected individuals experienced urinary dysfunction and paroxysmal recurrent dry cough triggered by inhalation of strong odors. Fine postural hand tremor, muscle cramping, and an absence of deep tendon reflexes were also seen. Serum creatine kinase (CK) levels were elevated in four of the five affected individuals (II-1, II-4, III-1, and III-3) (80%).

Table 1
Clinical and laboratory findings in 5 patients with hereditary motor and sensory neuropathy with paroxymal dry cough

Patient	Age/ sex	Age at onset	Initial symptom	Paroxysmal dry cough	Urinary dysfunction	Postural tremor	Muscle cramp	Reflexes	Distribution of muscle weakness	Hand grip (right/left)	Sensory disturbance	Serum CK level (U/l)	Brain MRI	Transfer
II-1	70/F	20	Muscle cramp of lower limbs	(+)	+	+	(+)	Absence	Proximal lower dominant	9 kg/6 kg	+	55 (296 at age 63)	Binswanger like	Wheelchair
II-2	69/M	18	Muscle cramp of lower limbs	(+)	+	+	(+)	Absence	Proximal lower dominant	8 kg/5 kg	+	146	ND	Wheelchair
II-4	62/F	30	Paroxysmal dry cough	(+)	+	+	(+)	Absence	Proximal lower dominant	19 kg/ 17 kg	+	851	Lacunar infarction	Independent
III-1	42/M	18	Muscle cramp of lower limbs	+	+	+	+	Absence	Proximal lower dominant	40 kg/ 40 kg	−	1218	ND	Independent
III-3	38/F	20	Muscle cramp of lower limbs	+	+	+	+	Absence	Proximal lower dominant	22 kg/ 20 kg	+	1140	normal	Independent

M, male; F, female; (+), experienced; ND, not done; normal range of serum CK=45–163 U/l.