

Autosomal dominant distal hereditary motor neuropathy type II: a Korean family without sequence variation in HSPB1 and HSPB8

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Abstract

Distal hereditary motor neuropathy (dHMN) is a heterogeneous group of disorders characterized by weakness and wasting of distal limb muscles without overt sensory abnormalities. Recently, autosomal dominant dHMN has been mapped to chromosome 12q24 and 7q11-q21. We present a family with autosomal dominant adult onset dHMN type II consisting of five affected individuals spanning three generations. They developed mild symmetrical distal lower limb weakness, muscle wasting, and severe foot deformity after the third decade. Genetic analysis showed no support for linkage to chromosome 12q24 and 7q11-q21 in our family. These findings further demonstrate a genetic heterogeneity within dHMN type II.

INTRODUCTION

Distal hereditary motor neuropathy (dHMN), also called the spinal type of Charcot-Marie-Tooth disease or distal spinal muscular atrophy, represents a rare and exclusive motor neuropathy of clinically and genetically heterogeneous conditions caused by degeneration of motor neurons leading to distal muscle weakness and muscle wasting. A classification in seven types based upon mode of inheritance, age at onset, and prevalent involvement of upper or lower limbs has been made.¹ Out of seven types, dHMN type IIA is caused by mutation in the gene encoding heat-shock 22-kD protein-8 (HSPB8) on chromosome 12q24 and type IIB is caused by mutation in the gene encoding heat-shock 27-kD protein-1 (HSPB1) on chromosome 7q11-q21.²⁻⁵

We report a Korean family with autosomal dominant dHMN type II in which the disease started after the age of 20 years. Gene testing had excluded mutation in HSPB1, HSPB8 and superoxide dismutase genes.

CASE REPORT

A 46-year-old man (proband) visited our clinic because of frequent stumbling along the street. Neurological symptoms started around his early thirties. He denied diabetes, chronic alcoholism, or drug exposure history. There was no cranial

nerve involvement and no cerebellar or pyramidal signs. The weakness and atrophy only affected distal lower limbs. The weakness of ankle dorsiflexion was modest, but the pes cavus was prominent. Sensory and autonomic symptoms were absent and deep tendon reflexes were normal. Nerve conduction studies showed normal motor and sensory conduction with slightly decreased amplitudes of compound muscle action potentials. The amplitudes of sensory action potentials were normal. Electromyography in the tibialis anterior, gastrocnemius, and extensor digitorum brevis muscles disclosed high amplitude, long duration, and polyphasic motor unit potentials without active spontaneous activities, which are indicative of longstanding neuropathy. Serum creatine kinase was not elevated. We found 5 affected members in his family, where the phenotype segregates as an autosomal dominant trait (Figure 1). The sister of the proband also showed prominent pes cavus and leg muscle atrophy without upper limb involvement. The son of the proband had only minimal distal limb weakness without atrophy and electromyography showed mild neurogenic changes. A sural nerve specimen for histological analysis was not taken because of normal sensory nerve action potentials and conduction velocities. DNA was isolated from the peripheral blood of the two affected patients and unaffected members using standard methods. The HSPB1 gene for

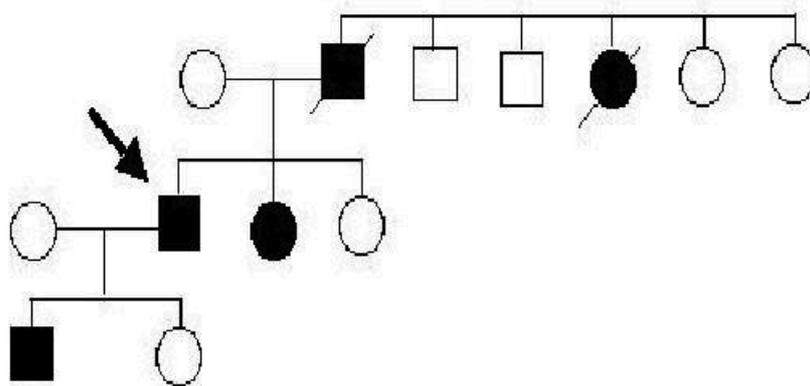


Figure 1. Pedigree of a Korean family with distal hereditary motor neuropathy type II. Symbols: squares, males; circles, females; filled, affected; white, normal; slashes, deceased; arrow, proband.

7q11 and the HSPB8 for 12q24 loci, that are associated with different type of dHMN, were screened by direct sequencing, but no mutation was found. All genes were sequenced on their all coding exons and exon-intron boundaries. A molecular analysis for mutation in the superoxide dismutase gene was also performed. There was no mutation in the tested genes.

DISCUSSION

The diagnosis of dHMN in this family is supported by the absence of sensory symptoms and of sensory involvement on nerve conduction studies. Additionally, a distal myopathic process was ruled out by the chronic neurogenic changes in the needle electromyography and the presence of pes cavus which is characteristic of Charcot-Marie-Tooth disease in the patients with full-blown symptoms. These findings are in keeping with the guidelines proposed by the 2nd Workshop of European Charcot-Marie-Tooth Consortium.⁶ Furthermore, these patients may be distinguished with certainty from Charcot-Marie-Tooth type I and II by normal sensory conduction velocities and normal sensory action potentials. Given the clinical features, electrophysiological findings, and inheritance pattern of the disease, these patients must have dHMN type II. However, establishing the onset of a very slowly progressive disease is often difficult. In this family, the youngest patient showed a slight difficulty with heel walking on clinical examination and mild neurogenic changes on electromyography. Regarding the onset of symptoms, we agree that the division into type I and II of autosomal dHMN with onset in the lower limbs is somewhat artificial.⁷

Several clinical features are unique in this

family. Taken together with available information, in all patients, the weakness and atrophy started in leg or foot muscles between 20 and early thirty years of age. The weakness was confined to the lower limbs in spite of the lapse of time. The proband of this family, who is 49 years old now, has neither symptom nor sign of upper limb involvement. The youngest patient showed only some difficulties in heel walking. They did not show any involvement of the CNS, including pyramidal tract signs or hyporeflexia even several years after symptom onset, while on the other hand the pes cavus deformities were prominent. However, there were no patients who became wheelchair dependent in the latest stage of the disease. Compared to our family, areflexia, involvement of upper limbs, and absence of pes cavus were not uncommon in the Belgian family, so called the prototype of dHMN type II.² The functional disabilities in our family are not more severe than in most CMT1A families nor the Belgian family. Affected patients in the Russian family, who were reported to have a mutation in the gene encoding 27-kDa small HSPB1 (also called HSP27), had depressed or absent reflexes and distal sensory abnormalities.³ Other Korean patients also showed upper limb involvement and areflexia, but on the other hand they did not have pes cavus at all.⁵ The phenotype in our family is strictly compatible with the original description of dHMN type II by Harding¹ and is similar to the phenotype reported in Japan as a sporadic case with HSP27 mutation.⁴ The only difference is younger age at onset in the Japanese patient.

It has now become evident that some dHMN subtypes have unusual features or associated symptoms. To what extent the involvement is always exclusively motor system is still a matter

of debate since some minor sensory abnormalities have been described. Although these features and signs often show intra-familial variability, they represent essential hallmarks of particular dHMN subtypes. Therefore, the study of additional patients in a family may be useful to clearly define the clinical dHMN subtype. Recent molecular genetic studies have confirmed the accuracy of this classification by showing that the clinical complexity has indeed a genetic basis. Even clinically homogenous dHMN subtypes turn out to be genetically heterogeneous. Although we did not find any mutations of alleged heat shock protein genes in this family, there is some genetic possibilities. A change in gene copy number, gene rearrangement such as large deletion/duplication, mutation in promoter gene or deep intronic mutation rather than a known sequence variation could be suggested. A direct sequencing of the coding exon cannot find these variations. Another possibility is that a gene of this family is not linked to 12q24 and 7q11-q21. It remains to be established how frequent these gene loci are in the total dHMN type II population. Additionally, despite the growing list of genes associated with motor neuron disorders, many families with clear dominant inheritance of an appropriate phenotype are not found to have mutations in any of the relevant gene or linkage to known loci. This heterogeneity leads to the conclusion that at a genetic level motor neuron degeneration could be a common final expression of disruptions in a number of cellular systems. This variation has proved to be extensive, illustrating in some cases the arbitrary nature of our diagnostic classifications.

In conclusion, gene testing in our dHMN type II family excluded mutation in HSPB1, HSPB8 and superoxide dismutase genes. This and previously reported studies reconfirm further locus heterogeneity for distal HMN^{7,8} and suggest that the phenotype in this family could be caused by other, yet unmapped, genes. This family could represent a restarting point towards a clinical-genetic classification of dHMN.

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