The Second Kindred With Autosomal Dominant Distal Myopathy Linked to Chromosome 14q

Genetic and Clinical Analysis

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Background: Distal myopathies (MPDs) are genetically heterogeneous. Genetic causes within this subgroup of muscle disorders remain largely unknown. An MPD linked to chromosome 14q11-q13 (MPD1) is rare, and to our knowledge, only one family with definitive linkage has been described. Objective: To describe the results of clinical and genetic analysis of the second kindred with MPD1. Patients and Methods: We have identified a family with an MPD segregating in an autosomal dominant fashion. We tested linkage to previously identified genetic loci on chromosomes 2p, 2q, and 14q. The coding sequence of PABP2 (the polyadenylate-binding protein 2 gene) was analyzed. Results: Every affected individual had selective weakness of foot extensors, with the average age of symptom onset at 20 years. Some patients also had proximal weakness, but none had signs of finger or hand extensor muscle involvement, even in advanced stages of the disease. Two typically affected individuals had signs of idiopathic dilated cardiomyopathy. Genetic analysis detected a tight linkage to chromosome 14q11-q13. Recombination at the telomeric end of the 14q11-q13 locus was found in an unaffected individual who was not considered to be at risk, potentially reducing the locus interval by 2 centimorgans. No mutations in the PABP2 gene were identified. Conclusions: To our knowledge, our described family is only the second known kindred with a chromosome 14-linked MPD in whom the linkage has unequivocally established. We did not detect signs of involvement of hand or finger extensors and neck muscles, seen in the original family with MPD1. The degree and frequency of proximal weakness seem to be more prominent than in other patients with MPD1. Haplotype analysis suggests that the gene is located between polymorphic microsatellite markers D14S283 and D14S1034 on chromosome 14q11-q13. The presence of cardiomyopathy in some affected individuals may help in the identification of candidate genes. Arch Neurol. 2003;60:1321-1325

DISTAL MYOPATHIES (MPDs) are a genetically heterogeneous group of muscle disorders that are considerably less common than limb-girdle myopathies (Table 1).1-6 Weakness of distal limb muscle groups is a clinical hallmark of MPDs, even though some patients may also experience weakness of proximal muscles. The molecular basis of most MPDs is still unknown.

The first genetic locus for autosomal dominant (AD) MPD was discovered in an Australian family, in which affected individuals developed selective weakness of foot and toe extensors between the ages of 4 and 25 years, followed by progressive weakness of finger extensors and neck muscles.5 Linkage analysis identified the locus for this type of MPD, designated as MPD1, on chromosome 14q11-q13.5,7 To our knowledge, no additional kindreds with an MPD and definitive linkage to chromosome 14q11-q13 have been described. However, few small families with an early onset of an MPD and finger and neck extensor involvement have been described.8-10 We describe a large Italian American family with AD MPD linked to chromosome 14q11-q13, making it only the second kindred with definitive linkage to this region, to our knowledge. This family further expands the phenotype of MPD1, because we did not detect involvement of finger extensors or neck muscles, even in elderly affected individuals. Furthermore, idiopathic cardiomyopathy was diagnosed in 2 affected individuals.

METHODS

CLINICAL AND LABORATORY STUDIES

Eighteen individuals, including 12 affected subjects, 4 unaffected subjects, and 2 unrelated spouses, from a large American Italian kin-
subjects III:I, IV:1, IV:2, and IV:5. In addition, electrocardiography was performed on cardiologic examinations were available for subjects III:1, III:7, and IV:11. In addition, electrocardiography was performed on subjects III:4, III:6, IV:1, IV:2, IV:4, IV:5, and VI:1. The results of cardiologic examinations were available for subjects III:1, III:7, and IV:11. In addition, electrocardiography was performed on subjects III:4, IV:1, IV:2, and IV:5.

MUSCLE BIOPY

Subject III:7 underwent a diagnostic muscle biopsy from the vastus lateralis muscle, performed at an outside institution at the age of 65 years. The muscle was stained with hematoxylin-eosin, Gomori trichrome, cytochrome-c oxidase, nicotinamide adenine dinucleotide dehydrogenase, succinate cytochrome-c oxidase, oil red O, periodic acid–Schiff, and adenosine triphosphatase at pH levels of 9.4, 4.6, and 4.2. The slides were reviewed at the University of Michigan Medical Center by a neuropathologist (M.B.).

GENETIC LINKAGE ANALYSIS

We examined candidate loci on chromosomes 2q31, 2p13, and 14q11-q13. The phenotype was determined as definitely affected or unaffected before genetic analysis. DNA was available from every subject enrolled in the study; unaffected at-risk individuals were excluded. Genetic linkage analysis was performed as previously described.11

A 2-point linkage analysis was performed with computer software (the MLINK subroutine of the LINKAGE program) using an AD mode of disease inheritance and a disease allele frequency of 0.001.11 We assigned a genetic penetrance of 0.90 for logarithm of odds (LOD) score calculations. Allele frequencies were not calculated from this family, but instead were considered to be equal.

ANALYSIS OF THE PABP2 GENE

Intronic primers were designed for all 7 exons based on the published PABP2 (polyadenylate-binding protein 2 gene) sequence (available at: http://www.ncbi.nlm.nih.gov/) using computer software (Lasergene; DNASTAR, Inc, Boston, Mass). The PABP2 exons were amplified from 4 affected and 2 unaffected subjects. Each exon was sequenced in both directions, and the DNA sequence was analyzed using computer software (SeqMan; DNASTAR).

Table 1. Distal Myopathies (MPDs)

<table>
<thead>
<tr>
<th>Type of MPD</th>
<th>Genomic Localization</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Characteristic Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laing type (MPD1)</td>
<td>14q11-q13</td>
<td>Unknown</td>
<td>AD</td>
<td>Lower and upper extremity extensor weakness and neck weakness</td>
</tr>
<tr>
<td>Welander type</td>
<td>2p13</td>
<td>Unknown</td>
<td>AD</td>
<td>Finger and wrist extensor weakness</td>
</tr>
<tr>
<td>Tibial muscular dystrophy</td>
<td>2q31</td>
<td>Titin</td>
<td>AD</td>
<td>Anterior tibial muscle weakness</td>
</tr>
<tr>
<td>MPD2</td>
<td>4q31</td>
<td>Unknown</td>
<td>AD</td>
<td>Upper extremity extensor weakness and vocal cord and pharyngeal muscle weakness</td>
</tr>
<tr>
<td>Nonaka type (rimmed vacuole–related type)</td>
<td>9p13</td>
<td>GNE</td>
<td>AR</td>
<td>Anterior tibial muscle weakness, allelic to hereditary inclusion body myopathy</td>
</tr>
<tr>
<td>Miyoshi type</td>
<td>2p12-p14</td>
<td>Dysferlin</td>
<td>AR</td>
<td>Weakness of foot flexor muscles</td>
</tr>
<tr>
<td>Desmin-related type</td>
<td>2q35</td>
<td>Desmin</td>
<td>AD</td>
<td>Proximal and distal muscle weakness</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; GNE, UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase.

RESULTS

The phenotypic features of our kindred with MPD1 are summarized in Table 2. Every affected individual had weakness of the foot and toe extensors, and some patients also had proximal limb weakness. However, none had distal weakness of the upper extremities or neck muscles, even in advanced stages of the disease. Serum creatine kinase levels were normal in subjects III:1, IV:1, IV:2, and IV:5; subject III:7 had persistent elevation of creatine kinase levels in the range of 300 to 400 IU/L (normal, 0-70 IU/L).

CARDIOLOGIC ABNORMALITIES

A review of the family history did not reveal the presence of sudden death or morbidity attributed to the cardiac causes in subjects younger than 65 years. The results of routine electrocardiography, performed on subjects III:1, IV:1, IV:2, and IV:5, were within normal limits. The result of surface echocardiography, performed on subject III:1, who complained of mild shortness of breath, was unremarkable, without any signs of cardiomyopathy or structural changes. Other affected family members denied any history of chest pain or shortness of breath.

Subject IV:11, whose neurologic examination at the age of 35 years showed only mild distal weakness, developed shortness of breath within a few weeks at the age of 32 years. His 2-dimensional echocardiogram at that time revealed a cardiomegaly with an ejection fraction of approximately 35%. He was diagnosed as having viral myocarditis, but a cardiac biopsy was not performed. The patient experienced worsening of his cardiac status, and his ejection fraction was estimated at about 25% 3 years later. The patient’s father (subject III:7) had a history of a mild heart attack at the age of 56 years. A coronary angiogram, obtained 2 years later, demonstrated only mild diffuse atherosclerotic changes, without any significant stenosis. A surface 2-dimensional echocardiogram dem-
Kindred with a distal myopathy linked to chromosome 14q11-q13. Genotypes are shown (in descending order) for microsatellite markers D14S50, D14S1003, D14S548, D14S283, D14S1458, D14S1459, D14S990, D14S596, D14S580, D14S1034, D14S64, D14S69, and D14S49. The haplotype segregating with the disease is boxed. Squares indicate males; circles, females; filled symbols, affected individuals; open symbols, unaffected individuals; slash marks, deceased individuals; and arrows, obligatory recombinations.

... demonstrate an ejection fraction of 30% without any additional structural changes; however, the degree of cardiac dysfunction could not be entirely explained by his coronary artery disease.

EMG AND NERVE CONDUCTION STUDIES

The results of EMG studies showed no fibrillations or signs of myotonia. Motor unit action potentials from the quadriceps muscle were present in subjects IV:1 and IV:2; other muscle groups, including the extensor carpi radialis longus, had normal motor unit action potentials. The results of nerve conduction studies were normal in every studied subject. Subject IV:4, whose clinical examination result was normal, underwent EMG 1 year before his participation in this study because of lower back pain; his EMG result was normal, without any myopathic or neurogenic changes.

MUSCLE BIOPSY

The muscle biopsy specimen obtained from the vastus lateralis muscle showed only minimal fiber size variability, with infrequent, small, rounded fibers. Necrotic regenerative fibers and rimmed vacuoles were not seen. The results of staining for mitochondria and the results of adenosine triphosphatase and periodic acid–Schiff stains were normal.

GENETIC ANALYSIS

We tested 3 candidate loci that were previously identified in individuals with AD MPD: microsatellite markers on chromosomes 2q31 and 2p13 gave significantly negative 2-point LOD scores, excluding the linkage to these regions (data not shown).3,33 Linkage to a group of microsatellite markers on chromosome 14q11-q13 was detected with the maximum 2-point LOD score of 3.99 at the marker D14S1459 (Table 3). Haplotype analysis (Fig-
Table 2. Summary of Clinical Features of the Affected Individuals*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, y</th>
<th>At Onset</th>
<th>Present</th>
<th>E</th>
<th>F</th>
<th>E</th>
<th>F</th>
<th>E</th>
<th>F</th>
<th>E</th>
<th>F</th>
<th>AB</th>
<th>AD</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
</table>
| III:1    | 21    | 71       | 3       | 5  | 3  | 5  | 4  | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 4  | 5  
| III:6    | 27    | 73       | 3       | 5  | 3  | 5  | 4  | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  |
| III:7    | 26    | 69       | 1†      | 5  | 3  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 4  | 5  |
| III:8    | 25    | 77       | 3       | 5  | 3  | 5  | 4  | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  |
| III:9    | 58    | 122      | 4       | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| IV:1     | 17    | 38       | 3       | 5  | 3  | 5  | 4  | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  |
| IV:2     | 18    | 40       | 3       | 5  | 3  | 5  | 4  | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  |
| IV:3     | 19    | 37       | 1       | 5  | 1  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| IV:4     | 34    | 54       | 4       | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| IV:5     | 23    | 50       | 4       | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| IV:6     | 18    | 35       | 4       | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| V:1      | 18    | 49       | 4       | 5  | 4  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| V:2      | 15    | 32       | 3       | 5  | 3  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |

Abbreviations: AB, abductors; AD, adductors; E, extensors; F, flexors; INT, intrinsic muscles; NA, data not applicable.

Adamite: This subject did not report any subjective problems, but his examination demonstrated mild distal weakness.

†This subject had an asymmetric weakness, with toe/ankle extensor strength one fifth on the left side and three fifths on the right side.

‡This subject did not report any subjective problems, but his examination demonstrated mild distal weakness.

We present a kindred with an AD MPD whose clinical features are similar to persons with MPD1 (Laing type). We unequivocally established linkage to chromosome 14q11-q13, and to our knowledge, this is only the second family with definitive linkage to the previously identified MPD1 locus. Analysis of this family further expands the clinical phenotype of MPD1 and tentatively refines its genetic locus. The average age of symptom onset in our family was slightly older than in the original family with MPD1 (20 years vs early childhood), but others have also found some individuals who developed symptoms later in their 20s. However, it is still considerably earlier than the average age of symptom onset in persons with tibial muscular dystrophy or Welander type; these affected individuals develop the first symptoms of distal weakness after the age of 35 years. More significant phenotypic differences between our kindred and an original Australian family with MPD1 are lack of involvement of finger and hand extensors and preserved neck strength, even in older affected individuals. Furthermore, proximal weakness was more frequent in our patients, even though there was significant intrafamilial variability. This suggests that the diagnosis of MPD1 needs to also be considered in patients who have only selective distal weakness of foot dorsiflexion or who have distal and proximal weakness without involvement of the finger and hand extensors.

The gene causing MPD1 was previously mapped to a 24-centimorgan region of chromosome 14q11-q13 that is flanked by microsatellite markers D14S283 and D14S49, as it was refined by Mastaglia et al. However, unaffected subject IV-4, whose EMG result at the age of 47 years was normal and who was older by more than 2 SDs from the average age of onset, inherited 4 telomeric markers, segregating with the disease with an obligatory recombination at D14S1034.

EXCLUSION OF THE PABP2 GENE

An analysis of the coding sequence of all 7 exons and splice sites of the PABP2 gene was normal, without any mutations. An analysis of alanine repeats in the first exon did not identify expansion of GCG repeats.

We present a kindred with an AD MPD whose clinical features are similar to persons with MPD1 (Laing type). We unequivocally established linkage to chromosome 14q11-q13, and to our knowledge, this is only the second family with definitive linkage to the previously identified MPD1 locus. Analysis of this family further expands the clinical phenotype of MPD1 and tentatively refines its genetic locus. The average age of symptom onset in our family was slightly older than in the original family with MPD1 (20 years vs early childhood), but others have also found some individuals who developed symptoms later in their 20s. However, it is still considerably earlier than the average age of symptom onset in persons with tibial muscular dystrophy or Welander type; these affected individuals develop the first symptoms of distal weakness after the age of 35 years. More significant phenotypic differences between our kindred and an original Australian family with MPD1 are lack of involvement of finger and hand extensors and preserved neck strength, even in older affected individuals. Furthermore, proximal weakness was more frequent in our patients, even though there was significant intrafamilial variability. This suggests that the diagnosis of MPD1 needs to also be considered in patients who have only selective distal weakness of foot dorsiflexion or who have distal and proximal weakness without involvement of the finger and hand extensors.

The gene causing MPD1 was previously mapped to a 24-centimorgan region of chromosome 14q11-q13 that is flanked by microsatellite markers D14S283 and D14S49. Haplotype analysis of affected individuals in our family did not identify obligatory recombinants that would further reduce the size of the MPD1 locus. However, we identified a crossover event in an unaffected man who had a normal EMG result and who was not considered at risk because
of his age. The caveat in analysis of a recombination event in an unaffected subject is unknown genetic penetrance; however, the review of published MPD1 cases did not suggest an incomplete penetrance. Thus, our data suggest that the gene causing MPD1 lies in the region flanked by markers D14S283 and D14S1034, potentially reducing the locus by 2 centimorgans.

The MPD1 locus contains PABP2. A small expansion of the polyalanine tract (GCG) is a cause of oculopharyngeal muscular dystrophy. The mechanism of the disease is presumed gain of function. One possibility is that MPD1 is allelic with oculopharyngeal muscular dystrophy, with a different disease mechanism, such as loss of function due to a point mutation. While this article was in preparation, Mastaglia et al7 reported exclusion of the PABP2 gene in their family with MPD1. Our results are similarly negative, because we also did not identify a coding change in this gene and, thus, are excluding it as the cause of MPD1.

Another important candidate gene within the MPD1 locus is MYH7 (heavy chain cardiac β-myosin 7). Mutations in this gene cause familial hypertrophic cardiomyopathy, and these patients do not have signs of clinical myopathy. Similarly, mutations in a giant skeletal muscle protein, titin, localized on chromosome 2q31, cause a diluted form of cardiomyopathy, and these patients do not have clinical signs of MPD. However, different mutations in the same gene have been recently identified in patients with tubular muscular dystrophy who do not have any signs of cardiomyopathy. The MYH7 gene is also expressed in skeletal muscles. Different splice forms of heavy chain myosin are expressed in the cardiac and skeletal muscles; skeletal muscles with a predominance of type 1 fibers, such as the soleus muscle, have particularly high levels of expression. Histochemical analysis of the skeletal muscle (soleus muscle) from 25 patients with hypertrophic cardiomyopathy due to 4 different MYH7 point mutations demonstrated histological signs of central core disease in 17 individuals; however, this was clinically silent, because only 2 patients had mild proximal weakness and none had signs of distal weakness. Histological features of central core disease were not detected in published cases in which a muscle biopsy was performed and MPD1 was confirmed or presumed, or in the muscle biopsy specimen from one individual in the presented kindred. It is intriguing that 2 patients from our family had idiopathic cardiomyopathy, even though it was the dilated and not the hypertrophic type. A mutation affecting only the skeletal muscle tissue–specific form of MYH7 is a possible cause of this type of MPD.

In summary, we describe the second family with early-onset MPD that has definitive linkage to chromosome 14q11-q13. Our results suggest that the gene causing MPD1 lies between markers D14S283 and D14S1034. The phenotype of this type of MPD may be without clinical signs of finger extensor weakness, and the history of idiopathic cardiomyopathy in some affected individuals may provide an important clue for candidate genes.

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