Distal spinal muscular atrophy with vocal cord paralysis (dSMA-VII) is not linked to the MPD2 locus on chromosome 5q31

EDITOR—Hereditary distal limb weakness and atrophy is a heterogeneous condition that may be neurogenic or myopathic in origin. Hereditary motor and sensory neuropathy (HMSN) I and II (also known as Charcot-Marie-Tooth (CMT) 1 and 2), distal spinal muscular atrophy (dSMA), and the distal myopathies may all present with this clinical picture. Traditionally, these disorders were differentiated according to electrophysiological and histopathological characteristics, with subtypes of each group identified on the basis of inheritance pattern, age of onset, and associated clinical features. The localisation of several genes that confer susceptibility to these disorders has necessitated the re-evaluation of current classification systems, as conditions that were clinically classified as distinct are now known to be allelic at the genetic level.

Vocal cord weakness/paralysis is occasionally associated with distal muscular atrophy. This association was first described by Young and Harper in a Welsh family in which the disorder segregated in an autosomal dominant fashion. The presentation was one of progressive distal muscle wasting and weakness together with a dysphonic or hoarse voice. Motor and sensory nerve conduction was normal with the exception of one patient who showed mild motor slowing. Spontaneous fibrillation was detected on EMG. Unilateral or bilateral vocal cord palsy was present in all affected subjects. The findings were consistent with anterior horn cell disease and the condition was assumed to be a form of dSMA associated with vocal cord paralysis. In a subsequent classification of the proximal and distal spinal muscular atrophies the disorder was designated dSMA type VII.

Recently, a family with vocal cord and pharyngeal weakness associated with a distal myopathy was reported. This family has many clinical similarities with the pedigree presented by Young and Harper. Both families exhibit autosomal dominant inheritance; in both families distal wasting and weakness is observed, with particularly severe involvement of the abductor pollicis brevis; laryngeal involvement was present in the majority of subjects from both pedigrees and was the presenting symptom in some cases. In contrast to the Young-Harper family, the family presented by Feit et al showed both neurogenic and myopathic muscle potentials on EMG. Following evaluation of electrophysiology and histopathology data, the disorder was judged to be myopathic in origin and distinct from previously described distal myopathies. The condition was designated vocal cord and pharyngeal weakness with distal myopathy (VCPDM). Using genetic linkage analysis, the gene predisposing to VCPDM was localised to chromosome 5q31 and was called MPD2.

In view of the clinical similarities between VCPDM and dSMA-VII, it was suggested that the two conditions may be allelic and that the Young-Harper pedigree may also be the result of an MPD2 mutation. To evaluate this hypoth-

Figure 1 Pedigree of family affected with distal spinal muscular atrophy and vocal cord paralysis. Filled symbols denote affected subjects. Genotypes for markers spanning the MPD2 locus at chromosome 5q31 are depicted below the subjects.
We thank all the family members who participated in this study. The authors are grateful to Professor Mike Owen, Dr Pat Kelso, Iain Fenton, Dr Joanne Dixon, and other CMT and SMA disorder.

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Table 1 Two point lod scores between dSMA-VII and the MPD2 locus on chromosome 5q31

<table>
<thead>
<tr>
<th>Marker</th>
<th>0.00</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
</tr>
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<tbody>
<tr>
<td>DSS2002</td>
<td>-6.99</td>
<td>-0.85</td>
<td>-0.40</td>
<td>-0.09</td>
<td>-0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>DSS4995</td>
<td>-2.94</td>
<td>0.22</td>
<td>0.37</td>
<td>0.35</td>
<td>0.23</td>
<td>0.10</td>
</tr>
<tr>
<td>DSS458</td>
<td>-7.22</td>
<td>-0.92</td>
<td>-0.46</td>
<td>-0.13</td>
<td>-0.03</td>
<td>-0.00</td>
</tr>
<tr>
<td>DSS479</td>
<td>-2.93</td>
<td>-0.13</td>
<td>0.05</td>
<td>0.12</td>
<td>0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>DSS2116</td>
<td>-7.10</td>
<td>-0.20</td>
<td>0.04</td>
<td>0.07</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>DSS2017</td>
<td>-7.38</td>
<td>-0.85</td>
<td>-0.40</td>
<td>-0.09</td>
<td>-0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>DSS638</td>
<td>-2.68</td>
<td>-0.03</td>
<td>0.11</td>
<td>0.12</td>
<td>0.06</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Two further unrelated families with features of distal muscular atrophy, diaphragmatic weakness, and vocal cord paralysis have been published. The severely affected subjects in these families had limb weakness or a hoarse voice or both. Extensive clinical and patholo-gical details of this family have been previously published.1 ID-601 has become a multiplex family and distances between the markers is centromeric to chromosome 5q31.

Tooth neuropathy type 2.5-6 The proband had bilateral vocal cord palsy and her mother had a husky voice.1 PMP22 is thus a plausible candidate for the disease gene in the Boltshauser family.

Our results indicate that despite clinical similarities between the two conditions, the MPD2 gene that predisposes to VCPDM is not causative in dSMA-VII. The clinical phenotype of other families with distal muscular atrophy and vocal cord weakness suggest that they are also unlikely to be the result of MPD2 mutations. We are hoping to localise the gene predisposing to dSMA-VII in the Young-Harper family. This should further the understanding of the genetic defects present in subjects with distal muscular atrophy and vocal cord weakness, and may allow clarification of the relationship between these conditions and other CMT and SMA disorders.

We have analysed the Young-Harper family for linkage to chromosome 5q31. Informed consent for participation in the study was obtained from eight affected subjects and three spouses, as shown in fig 1. All affected subjects had distal limb weakness or a hoarse voice or both. Extensive clinical and pathological details of this family have been previously published.1 ID-601 has become affected since the original report.

DNA was extracted from peripheral venous blood using standard protocols. Seven polymorphic fluorescently labelled microsatellite markers were PCR amplified and electrophoresed through 4.5% denaturing polyacrylamide gels on an ABI377 sequencer. Genotyping data were analysed with GENESCAN and GENOTYPER software. The order and distances between the markers is centromeric to chromosome 5q31.

DSS2002 -1.5 cm - DSS1995 - 1.5 cm - DSS458 - 2 cm - DSS479 - 1.5 cm - DSS2116 - 2.5 cm - DSS2017 - 3 cm - DSS638 - tel. These markers span the 12 cM interval that harbours MPD2.3 Two point lod scores were calculated using the MLINK program. The disorder was modelled as an autosomal dominant trait with a disease allele frequency of 0.0001. The penetrance was set at 90% and no sporadic cases were allowed. Marker alleles were assumed to be iso-frequent.

Two point lod scores at θ=0 were strongly negative at all markers (table 1). No haplotype of marker alleles was found to segregate with the disease (fig 1). These results exclude linkage of the dSMA-VII phenotype in the Young-Harper family to the MPD2 locus on chromosome 5q31.

Although there are clinical similarities between VCPDM and dSMA-VII, there are also several differences. The most striking is that myopathic changes are seen in VCPDM, whereas the disorder in the Young-Harper pedigree appears to be a disease of the anterior horn cells. Pharyngeal weakness is prominent in VCPDM, but has not been described in dSMA-VII. The age of onset is somewhat later in VCPDM (35-57 years) than in dSMA-VII (teenage years). Moreover, both families have been examined by one of the authors (CJ) who concluded that the clinical phenotypes are distinct. Our results indicate that VCPDM and dSMA-VII are also distinct at the molecular level.

The genetic defect in dSMA-VII is currently unknown. The common deletions of the SMN gene associated with proximal SMA at chromosome 5q13, and the 17p11 duplication associated with HMSN IA (CMT1A) have been excluded in the Young-Harper pedigree (data not shown).

Several other autosomal dominant families with vocal cord paralysis/weakness in association with distal wasting and weakness have been published. Pridmore et al reported a family from Wales with similar clinical features to those in the Young-Harper pedigree. Although there is no known relationship between the families, given the rarity of the condition, the similarity of the clinical features, and the Welsh ancestry, it is likely that a founder mutation within the same gene is responsible for the disease in both pedigrees.


