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-
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>
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</thead>
<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>DSS1995</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>DSS116</td>
<td>-7.13</td>
<td>-0.62</td>
<td>-0.20</td>
<td>-0.04</td>
<td>0.07</td>
<td>0.04</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 distal wasting and weakness and the disorder was therefore classified as HMSN IIC (CMT2C). Of note, symptoms compatible with respiratory compromise were noted in two subjects in the Young-Harper family, although there was no evidence of diaphragmatic weakness. In view of the additional features, it is possible that the HMSN IIC families are the result of mutation of a different gene from dSMA-VII. However, it is equally possible that HMSN IIC and dSMA VII are allelic, as has recently been described for HMSN IID (CMT2D) and dSMA-V. These latter disorders were independently mapped to the same region of chromosome 7p. Subsequently, a single pedigree was described in which both clinical phenotypes segregated with a common 7p15 haplotype of marker alleles.

Bolstshauser et al. presented a pedigree with distal muscular atrophy, vocal cord paralysis, and possible sensory symptoms in some cases. Affected subjects also had sensorineural hearing loss. Recently, a family with CMT and sensorineural deafness was reported to have a predisposing point mutation in PMP22. The proband had bilateral vocal cord palsy and her mother had a husky voice. PMP22 is thus a plausible candidate for the disease gene in the Bolstshauser 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.

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