A Family With X-linked Dystonia-Deafness Syndrome With a Novel Mutation of the DDP Gene

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Background: X-linked dystonia-deafness syndrome (DDS) is characterized by early-onset deafness followed by progressive dystonia in adulthood. Only 4 families with the syndrome have been reported, and all were white.

Objective: To describe the first nonwhite family with X-linked DDS, involving 5 affected males in 4 generations.

Results: Clinical features of the family members, who were Japanese, were mostly consistent with reports of DDS in whites except for a lack of visual disturbances. Whereas microdeletions in the deafness-dystonia peptide (DDP) gene were found in 2 white DDS families, our patients showed a novel mutation (arg80ter) in exon 2 of the DDP gene.

Conclusion: The existence of a DDS family of Japanese origin with a new kind of mutation in the DDP gene provides additional evidence that the DDP gene is a causative gene for X-linked DDS.

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X-LINKED dystonia-deafness syndrome (DDS) was originally reported as X-linked deafness in a Norwegian family by Mohr and Mage-roy1 in 1960, and designated as DFN-1. The family was later studied by Tranebjaerg et al,2 who found that the patients had not only deafness but also several other symptoms, including progressive dystonia. They named the syndrome the Mohr-Tranebjaerg syndrome. X-linked DDS is characterized by postlingual progressive sensorineural deafness as the initial symptom occurring in early childhood followed by progressive dystonia, mental deterioration, cortical blindness, spasticity, and psychiatric manifestations. To date, 4 families with X-linked DDS have been reported, and were all white. We report the first nonwhite family (Japanese) with X-linked DDS, affecting 5 males from 4 generations.

PROBAND

Proband III-6 (Figure 1), a 39-year-old Japanese man, was born by normal delivery and was of average birth weight, but found to be deaf at age 6 months. He had shown no developmental delay or any other neurological symptoms except for deafness. He graduated from a high school for the deaf and mute, worked in a timber plant, and lived alone. He obtained a driver’s license and drove a car. He first noticed stiffness in the upper limbs and difficulty holding a cup and using chopsticks at the age of 30 years, and this gradually progressed. At the age of 34 he was examined by neurologists, who found sensorineural deafness, dystonia in the upper limbs, brisk deep tendon reflexes in all 4 limbs, and clonus in the lower limbs that decreased 5 to 10 seconds after induction. There were no visual or sensory disturbances, ataxia, autonomic symptoms, or pathological reflexes. Mental deterioration was found, but it was mild. Electroencephalography showed excess theta waves of 6 to 7 Hz with a diffuse distribution. Brain magnetic resonance imaging revealed moderate cortical atrophy, especially in the frontal cortex, and moderately dilated third and fourth ventricles. An electroretinogram was normal. Electromyography showed normal motor and sensory nerve conduction velocity. At the age of 35, the dystonia had extended to the lower limbs and blepharospasm was also evident. He began to need a cane for walking and standing. The dystonia did not respond to levodopa, carbamazepine, or trihexyphenidyl hydrochloride therapy. In recent years, the pa-
tient showed personality changes, becoming unstable and of uneven temperament.

CASE 2
Individual III-5 (Figure 1), the 41-year-old brother of the propositus, was born by normal delivery and found to be deaf at 4 years of age. He did well in regular primary and junior high school and graduated. At the age of 16, he noticed mild dystonia in his neck, trunk, and upper limbs. This gradually progressed, and by age 27, it had extended to his lower limbs, resulting in clumsiness while walking. By age 29, he frequently fell and needed assistance for daily activities such as bathing and eating. By age 31, he needed a cane for walking, and at 33, blepharospasm was evident. He showed mild mental deterioration but no personality changes or psychiatric symptoms. There was no visual disturbance.

CASE 3
Individual I-1 (Figure 1), the grandfather of the propositus, died when he was 89 years old. Exact information was not available, but it appeared that he was deaf and had slight dystonia in the lower limbs.

CASE 4
Individual III-7 (Figure 1), a 35-year-old maternal male cousin, was born by normal delivery and was found to be deaf at 3 to 4 years of age. The deafness was not severe, because he had no difficulty hearing when wearing a hearing aid. He showed mild dystonia in all 4 limbs. His use of chopsticks and writing became clumsy when under stress, and his walking was slow with a tendency to stumble, although he did not need any assistance for daily activities. He graduated from high school and was a successful farmer. There was no mental deterioration.

CASE 5
Individual IV-4 (Figure 1), a 15-year-old maternal nephew, was born by normal delivery. He was found to be deaf in a lower grade of primary school at 8 or 9 years of age. His deafness was compensated for fully.
RESULTS

Sequence analysis of case 1 revealed that CGA codon 80 of exon 2 was replaced by TGA, resulting in substitution of arginine by a stop codon (Figure 2). The mother of case 1 was shown to be a heterozygote of the normal and nonsense mutated alleles. This mutation breaks a cognate site of the restriction enzyme TaqI. Restriction fragment length polymorphism analysis using TaqI revealed that the affected males (cases 1, 2, and 4) had a single band of 859 base pairs that was not cleaved by TaqI (Figure 3). However, the father of case 1 (II-4), who had no symptoms of DDS, showed 2 bands of 676 bp and 189 bp that were cleaved by TaqI. The mother of case 1 (II-3) and the mother of case 4 (II-5) showed 3 bands, a single uncleaved band and 2 cleaved bands, that indicated that they were carriers. These obligate carriers did not show any symptoms of DDP. The maternal aunt of case 1 (II-1), who had only 1 healthy grandson as a male descendant, was also found to be a carrier. The mutation in exon 2 was screened for using TaqI in 50 healthy volunteers (25 males, 25 females) and was found to be absent in normal subjects.

The Japanese pedigree presented here, consisting of 5 affected males in 4 generations, showed X-linked recessive inheritance. Their main symptoms were neural deafness in early childhood and progressive dystonia in adulthood. Mild mental deterioration and character changes were also seen, but visual disability was absent. Visual disability, like cortical blindness, was seen only in the original Norwegian family but not in the Japanese cases. In comparison with previously reported X-linked DDS in 4 white families, the symptoms and clinical course of these Japanese cases were comparable, but generally milder (Table). The onset of dystonia was later in the Japanese cases, appearing at around 15 to 30 years of age, as opposed to less than 10 years of age in the white subjects in the other studies. All of our patients were able to walk and stand with or without a cane, but most of the white subjects became confined to a wheelchair between the ages of 9 and 22 years. Regarding mental status, the present cases showed only mild mental deterioration and few or no psychiatric problems. However, in the previously reported cases, mental deterioration was common, and personality changes, such as restlessness, irritability, anxiety, and aggressive outbursts, were seen in at least half of the patients. Symptoms of paranoia were also evident in these patients.

Tranebjaerg et al reported that the Norwegian pedigree showed a significant linkage disequilibrium to Xq21.3-q22. The Bruton gammaglobulinemia tyrosine kinase (BTK) gene, which is involved in immunodeficiency X-linked agammaglobulinemia, is located in this region. Jin et al analyzed the X-linked agammaglobulinemia patients who had deafness and dystonia, and found that deletion of the BTK gene extended to the next gene in the 3’ location of the BTK gene. They designated this gene as DDP (deafness-dystonia peptide) and cloned the transcript lying in that region. The DDP gene has 2 exons and a single intron of about 2 kb and encodes a small peptide consisting of 97 amino acids. Jin et al found 2 kinds of microdeletion in the coding region of the DDP gene in a Norwegian patient and an American patient. In the Norwegian patient, a 1-bp deletion (151delT) in exon 1 produced a consequent frame shift resulting in an incorporation of 25 amino acids after glutamic acid at codon 38, followed by early termination. In the American patient (pedigree K8190), a 10-bp deletion (183del10) in exon 2 of the DDP gene produced a frame shift resulting in the addition of 12 novel amino acids after the methionine residue at codon 48, followed by early termination. In our cases, arginine at codon 80 was substituted by a stop codon. Therefore, this nonsense mutation produced a truncated DDP gene of 79 amino acids. However, this was longer than the normal

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Affected Individuals/No. of Generations</th>
<th>Deafness</th>
<th>Dystonia</th>
<th>Psychiatric Problems</th>
<th>Visual Loss</th>
<th>Mutation in DDP Gene</th>
</tr>
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<td>Scribanu and Kennedy, 1976</td>
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<td>2-6</td>
<td>7</td>
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<td>1.5-5</td>
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<td>Teens (?)</td>
<td>Mid-30s</td>
<td>151delT</td>
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<td>5/2</td>
<td>Unknown</td>
<td>&lt;10</td>
<td>Teens (?)</td>
<td>None</td>
<td>183del10</td>
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<tr>
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<td>2</td>
<td>6-12</td>
<td>12-16</td>
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<tr>
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<td>5/4</td>
<td>2</td>
<td>16-30</td>
<td>38</td>
<td>None</td>
<td>arg80ter</td>
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</tbody>
</table>

*NE indicates not encoded.
†All males.
amino acid sequence of those peptides produced by the microdeletions (151delT and 183del10) of the DDP gene found by Jin et al; normal sequences of these have only 38 and 48 amino acids, respectively. It is possible that the truncated peptide produced by the nonsense mutation with a longer normal amino acid sequence could be related to the milder clinical symptoms and slower progression of the disease seen in the Japanese patients with X-linked DDS. The physiological function of the DDP gene is unknown. Although it is expressed at the highest concentration in the fetal brain, it is expressed ubiquitously in other tissues, such as the liver, heart, kidney, and lung. Recently, DDP was shown to strongly resemble Tim8p, a zinc-binding yeast protein that is implicated in the import of a class of transmembrane carrier proteins from the cytoplasm to the mitochondrial inner membrane. It was also found that DDP protein is located in the mitochondrial intermembrane space. Therefore, mutated DDP may disrupt the mitochondrial import system and energy production, inducing dystonia and deafness.

The finding that patients of a particular race with a different kind of mutation (arg80ter) of the DDP gene had clinical symptoms consistent with those of white patients with DDS strongly indicates that the DDP gene must be a causative gene for X-linked DDS.

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REFERENCES