

## ANTICIPATION IN A FAMILY WITH AUTOSOMAL DOMINANT SPINOCEREBELLAR ATAXIA

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The autosomal dominant spinocerebellar ataxias (SCA) are a heterogeneous clinical and genetic group of hereditary late-onset neurodegenerative disorders characterized by cerebellar and brainstem dysfunction that are caused by neuronal degeneration in the cerebellum and cranial nerve nuclei.<sup>1-3</sup> Anticipation, an increase in clinical severity and a younger age of onset of the disease in subsequent generations, is a typical feature of autosomal dominant SCA, and is due to the expansion of the trinucleotide repeats.<sup>3-5</sup> We report a family of three generations exhibiting this phenomenon.

### Case Report

The index case is an 11-year-old girl who presented at the age of eight years with a rapidly progressive ataxia. Currently, she is wheelchair-bound, unable to stand but can transfer objects with help. She has constant titubation and rhythmic jerking of her entire upper and lower extremities, obvious eye nystagmus and difficulty in initiating ocular saccades. Her speech is dysarthric with spastic and ataxic components. Motor examination has revealed mild generalized muscle atrophy with essentially normal strength. However, the deep tendon reflexes are exaggerated with bilaterally upgoing plantar responses. Loss of cerebellar functions is indicated by severe impaired performance of finger-to-nose test, and heel-to-chin maneuver, as well as dysmetria, intention tremor, and dysdiadochokinesia. The other systemic and neurological examinations are normal (Figure 1). Her brain CT scan documented advanced olivopontocerebellar atrophy (Figure 2). She has two other siblings, an 18-year-old male and a 10-year-old female, who are severely and mildly affected with the same disease. Both demonstrate similar neuro-radiological abnormalities. Three female cousins had the same disease, manifesting between 12 and 20 years of age. The mother (43 years old) and her sister (40 years old)

became symptomatic with similar clinical findings at 40 and 35 years of age, respectively. It is of interest to find that the grandmother was also symptomatic only three years before her death at the age of 73 years (Figure 3). Detailed genetic study of different family members is in progress.

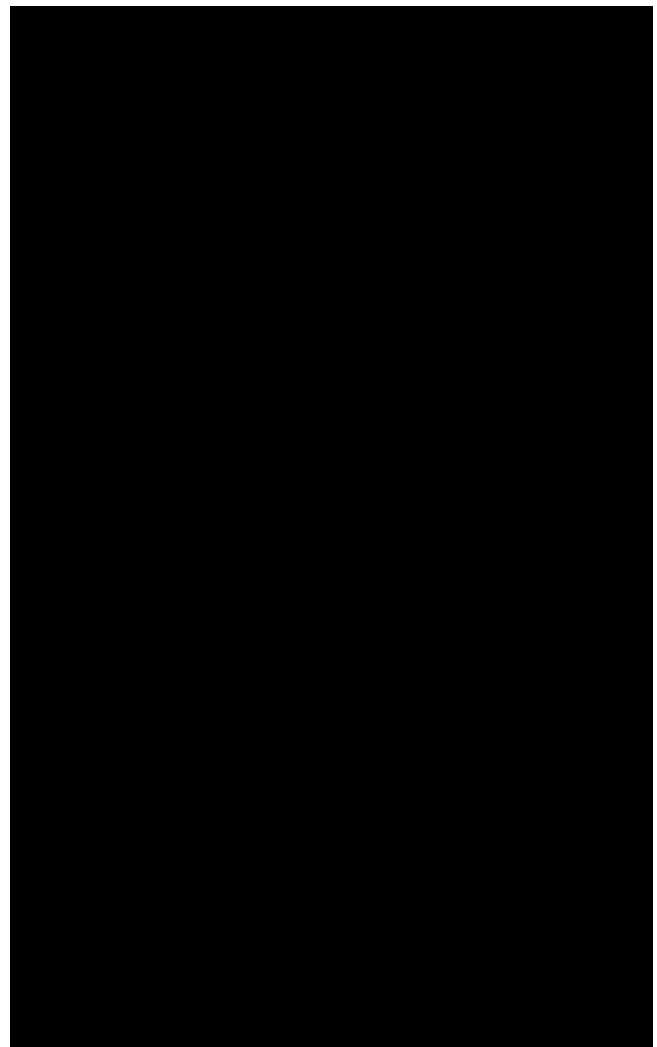


FIGURE 1. The index case (middle) who is unable to stand, is supported by her brother (left) and her sister (right). The brother is severely affected and the sister is mildly affected by the disease.

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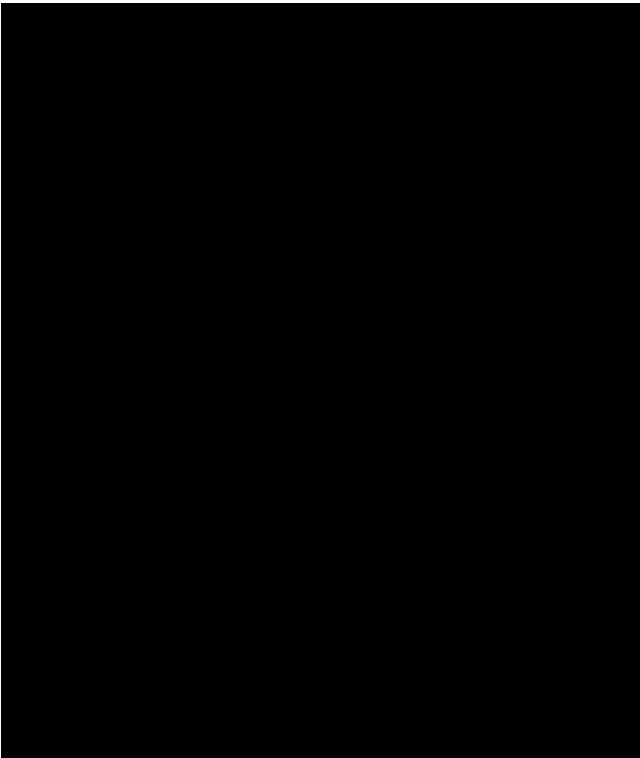


FIGURE 2A. Different cuts of CT scan of the brain of the index case at 11 years of age show atrophy of the cerebellar folia (A-C). These neuroradiological features are typical of olivopontocerebellar atrophy.

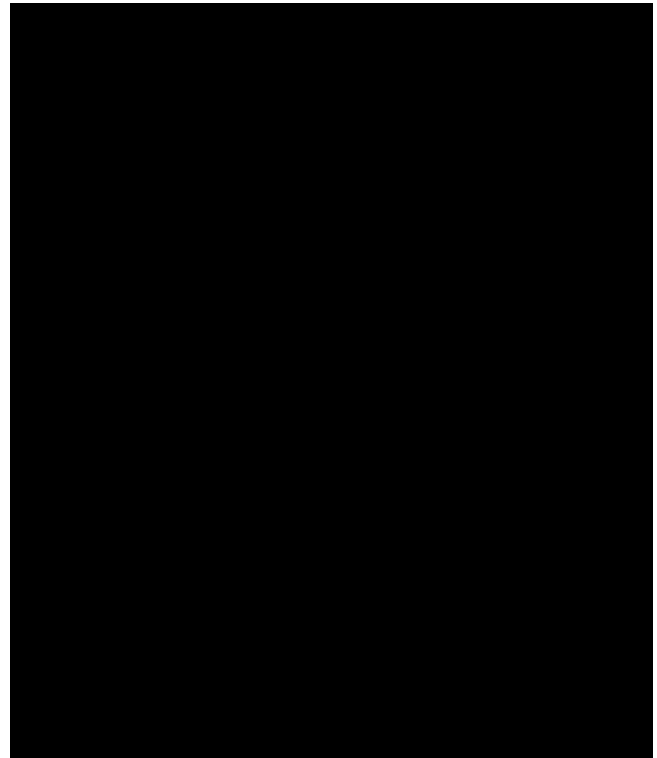


FIGURE 2B. This CT scan of the same patient shows scalloping of the medial portion of the medulla oblongata bilaterally in symmetric fashion due to olivary atrophy. All the neuroradiological features shown in Figures A-C are typical of olivopontocerebellar atrophy.

### Discussion

Spinocerebellar ataxias include at least seven subtypes, and usually have the onset of ataxia, cranial nerve palsies, and abnormal sensory findings in the second or third decade. However, some cases have been described in children, with rapidly progressive ataxia, nystagmus, dysarthria, and seizures.

Linkage studies have identified seven different loci associated with SCA. SCA type 1 (SCA1) maps to chromosome 6p, and SCA type 3 maps to chromosome 14q24.3-qter,<sup>6,7</sup> both showing common mutational mechanism.<sup>4,8</sup> Recently, three reports described the isolation of the gene mutated in SCA type 2 (SCA2), which maps to chromosome 12q22-24.<sup>9-11</sup> The SCA1, SCA2 and SCA3 contain a CAG repeat in their coding region that is expanded in affected subjects. The SCA2 gene encodes a novel protein of unknown function termed *ataxin-2*. Expansion of a CAG repeat in the *ataxin-2* gene is a common cause of dominant SCA, accounting for about 15% of all autosomal dominant SCA.<sup>3,9-12</sup> Lately, SCA type 6 (SCA6) has been associated with the expansion of a CAG repeat contained in the coding region of a voltage-gated calcium channel that maps to chromosome 19p13.<sup>13</sup> An inverse correlation between the age of onset and the number of CAG repeats has been clearly demonstrated in

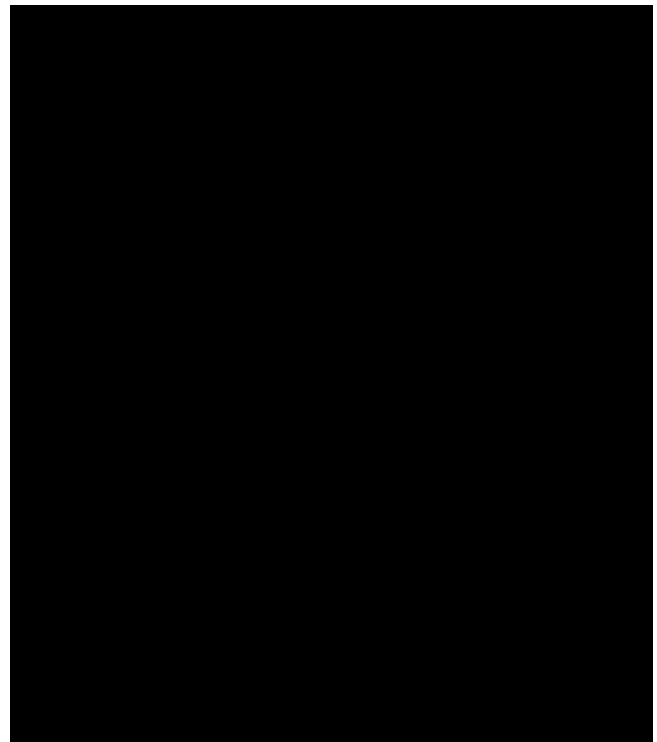


FIGURE 2C. CT scan of the brain of the index case at 11 years of age shows that the pons is flattened.

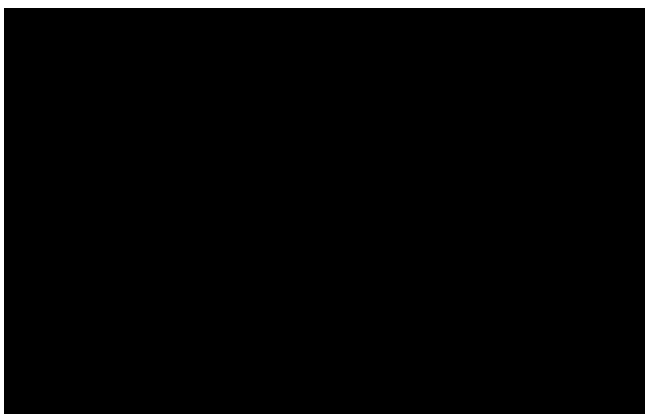


FIGURE 3. The family pedigree showing the three generations. The age when the disease's symptoms started/current age is shown for each affected member in the family. Note the younger age of onset of the disease in subsequent generations.

SCA1 and SCA3.<sup>14,15</sup> Other mapped SCA loci include types 4, 5, and 7, which have been localized to chromosome 16q22.1 (SCA4),<sup>16</sup> chromosome 11cen (SCA5),<sup>17</sup> and chromosome 3p (SCA7).<sup>18</sup> A founder effect may account for the different frequencies of autosomal dominant SCA mutations observed.

The overlapping phenotypes and the variability of the clinical manifestations, even in individuals from the same kindred, have hampered attempts to define the different subtypes of this group of diseases. However, the recent identification of the SCA1, SCA2, SCA3, SCA4, SCA5, SCA6 and SCA7 mutations has greatly facilitated the accurate diagnosis and classification of these disorders, and has allowed proper genetic counseling.<sup>3,6-11,13,16-18</sup>

The SCA1, SCA2, SCA3, and SCA6 genes have presumably different cellular functions but, nevertheless, their expanded counterparts lead to almost identical clinical and neuropathological phenotypes. Similarly, the remaining autosomal dominant SCAs of unknown etiology are likely to be caused by a CAG repeat expansion in novel but unrelated genes mapping either to one of the three known autosomal dominant SCA loci (SCA4, SCA5, and SCA7), or to other chromosomal locations yet unidentified. The grandmother of the index case, representing the first generation of the family, had milder clinical findings of SCA at the age of 70 years. The mother and her sister, representing the second generation of the family, had moderate findings of SCA manifesting at the third and fourth decade of life. The index case (11 years old and wheelchair-bound) and her brother (18 years old), representing the third generation of the family, had severe features of the disease, including extreme dysarthria, axial and limb ataxia, titubation, and decreased saccadic movements (a common clinical finding of the disease). In this third generation, the symptoms started earlier, in the first and second decade of life. This pattern of increased

clinical severity and affection of a younger age in subsequent generations is a typical feature of autosomal dominant SCA and is due to the expansion of the trinucleotide repeats.<sup>3</sup>

We believe that this family is an additional report to the existing literature of this rare hereditary entity.

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