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## Case report

### **Unusual retinal phenotypes in an SCA7 family**

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ataxia, ADCA II

## **Abstract**

We report the cases of a father and his son with spinocerebellar ataxia type 7 (SCA7), a disorder rarely reported in Japan. The father had noticed dysarthria at age 38, and gait instability at age 46. Visual disturbance was noted 3 years later. Neurological examination at age 54 revealed visual disturbance, dysarthria, and cerebellar ataxia in all four extremities and the trunk. Cranial MRI showed moderate atrophy of the brain stem and cerebellar hemispheres. However, no retinal degeneration was found. The son was 16 years old at our first examination. Since age 6, his visual acuity began to decrease; at age 10, he noticed clumsiness in his hands. Six years later he began to experience gait instability. Neurological examination revealed visual disturbance and cerebellar ataxia. He was diagnosed with SCA7 by genetic analysis. His ophthalmologic examination showed retinal degeneration without pigmented spots, which is different from those of retinal phenotypes previously described in SCA7.

## 1. Introduction

Spinocerebellar ataxia (SCA) with retinal degeneration has been known since it was reported by Havener in 1951 [1]. Harding classified autosomal dominant cerebellar ataxia (ADCA) into four types. According to this classification, ADCA II is characterized as spinocerebellar ataxia with retinal degeneration [2]. In 1995, Benomar et al [3], Guow et al [4], and Holmberg et al [5] reported that ADCA II is linked to 33cM of chromosome 3p12-p21.1, and ADCA II was renamed spinocerebellar ataxia type 7 (SCA7). In 1997, a study by David et al reported that SCA7 is the disease which occurs with abnormal extension of CAG in the open-reading frame of the responsible gene, “*ataxin-7*” [6]. After these reports, many genetic analyses have been performed in Japan. However, SCA7 is rare in Japan, and only three families with SCA7 have been identified to date [7,8]. In this paper, we report the cases of the fourth Japanese family with SCA7 and unique retinal degeneration.

## **2. Case report**

The pedigree of our present family is shown in Figure 1.

Patient 1: A 54-year old male, his past medical history included a gastric ulcer at age 45.

His chief complaint was gait instability. He had been inarticulate since age 38. At age 45,

he noticed gradually deteriorating unsteadiness when walking. At age 46, he noticed

decreased visual acuity. His symptoms continued to worsen. At age 49, he visited our

department for the first time. At the time, his physical examination showed no

remarkable abnormalities in head, cervical area, heart, lungs, or abdomen. Visual acuity

was 0.5 in the right eye and 0.6 in the left eye. Dysarthria, dysphagia, spasticity and

hyperreflexia in all four extremities, muscular atrophy of the lower legs, cerebellar

ataxia, and dystonia of the head and face were also observed. His brain MRI (FLAIR

TR/TE 8002/104.5) at his first visit showed moderate atrophy of the brain stem and

cerebellar vermis (Fig. 2A). His brain MRI T2 view did not show any alteration of

signal intensity. The subject's ophthalmological examination at age 49 did not show

any abnormalities either in the optic fundi (Fig. 3A), visual evoked potential test or

electroretinogram (data not shown). Based on these results, he was diagnosed with

spinocerebellar ataxia, type unknown. The symptoms have progressed since his first visit; at the present time, he is unable to walk, and his best-corrected visual acuity has deteriorated (0.09 right eye, 0.09 left eye). Significant pathological findings still have not been detected in the optic fundi. Genetic analysis was not done, since he did not agree to genetic testing.

Patient 2: A 17-year old man, his past medical history included bronchial asthma at age 1, atopic dermatitis at age 2, and allergic rhinitis at age 4. His chief complaints were visual deterioration, clumsiness in hands, and gait instability. At age 6, his visual disturbance was identified at a routine health examination, and his visual acuity worsened gradually. At age 10, he noticed that he could not use his hands well. At age 12, his best-corrected visual acuity was 0.2 in the right eye and 0.2 in the left eye. He was diagnosed with bilateral depigmentary degeneration of the retina at age 15. By age 16, he noticed that he walked unsteadily, his symptoms progressed, and he first visited our department. At the time, we found no remarkable abnormalities of the head, cervical area, heart, lungs, or abdomen. His neurological examination showed slight dysarthria,

visual disturbance, hyperreflexia in all four extremities, and cerebellar ataxia of all four extremities and the trunk. His brain MRI (T1 TR/TE 550/11) showed moderate atrophy in the cerebellar vermis and caudal portion of the pons (Fig. 2B). His brain MRI T2 view did not show any alteration of signal intensity. SPECT imaging showed decreased blood flow in the brain stem and cerebellum. Fundoscopic examination revealed depigmentary degeneration of the retina on both eyes (Fig. 3B). His electroretinogram showed flat wave forms and decreased retinal function. At age 17, his best-corrected visual acuity was 0.01 in the right eye and 0.01 in the left eye. After informed consent was obtained from both the patient and his mother, genetic analysis was performed; he was diagnosed with SCA7 (normal allele/expanded allele = 12/59 repeat).

In summary, Patient 1's cerebellar symptoms occurred first, followed 8 years later by visual symptoms, while Patient 2's visual symptoms occurred first, followed 3 years later by cerebellar symptoms. Unfortunately, we could not obtain clinical information from the other affected members in this family.

### **3. Discussion**

In Japan, SCA7 is a rare disease, and only three familial cases have been reported in the literature [7,8]. SCA7 is caused by abnormal CAG repeats expansion of ataxin-7 on 3p. The mean age at onset ranged from 40 to 50 years of age [9 – 11]. The clinical features of SCA7 include retinal degeneration and cerebellar ataxia. Generally, retinal degeneration and cerebellar ataxia occur at the same time, or retinal degeneration may be noted to precede cerebellar ataxia slightly, and both symptoms progress slowly [9 – 11]. The larger the expansion of CAG repeats, the faster the symptoms progress. Severe gait instability usually makes these patients wheelchair-bound within 10 to 20 years after onset. There is an inverse correlation between age at onset of SCA7 and the number of CAG repeats, and it has been reported that the age at onset ranges from 3 months to 70 years old. In SCA7, anticipation of onset is often seen in patients who have the expanded allele from their fathers in comparison with those from their mother.

Two clinical features are presented in this SCA7 family. First, the coexistence of cerebellar and ophthalmic symptoms is not always the first feature of this condition; the onset of cerebellar symptoms and ophthalmic symptoms are separate. Second, significant pathological retinal findings are not always found associated with visual disturbance. The father had visual disturbance without significant pathological retinal findings, while the son had a rare retinal finding of SCA7 - depigmentary degeneration of the retina. Although the number of CAG repeats of father was not analyzed, we can expect that it is smaller than that of the son because these variable retinal phenotypes are considered to depend on the difference in CAG repeat numbers [9-11]. Unfortunately, we could not explain why the father reported visual disturbance without retinal degeneration, other than possible subclinical retinal degeneration. In addition, Patient 2's clinical course progressed more rapidly than did those of previously reported patients with 59 or 60 CAG repeats [11]. The clinical features of Patient 2 suggest that there are some modification factors in SCA7.

Pigmentary degeneration of the retina is found in a group of genetic and progressive diseases which cause decreased retinal function and atrophy, with degeneration and loss

of neuroepithelial cells. Retinal degeneration is classified in macular degeneration, pigmentary degeneration of the retina, and depigmentary degeneration of the retina. The cardinal symptoms of pigmentary degeneration are nyctalopia, constriction of the visual field, and decreased vision. Hereditary types of autosomal dominant, autosomal recessive and X-chromosome recessive pigmentary degeneration are frequent, but there are dozens of responsible genes [12], and the mechanism behind retinal degeneration is still not clear. Degeneration of neuroepithelial cells extends to the sensory retina, but may also lead to atrophy of whole retina (including the retinal pigmentary epithelium). Due to this degeneration, changes in retinal tone, deposition of pigment-like ossicles, and narrowing of retinal blood vessels occur [12]. Depigmentary degeneration of the retina, in which the deposition of pigment is scarcely perceived or not identified at all, is a type of retinal pigmentary degeneration [12]. In past reports of SCA7, macular degeneration has been the main clinical feature [8], [13]. A few cases with similar clinical course and retinal degeneration have been reported [8]. Abe et al said that macular dysfunction generally occurs earlier in the younger generation of patients than in older patients [8]. However, pigmentary degeneration was also reported in SCA7 [13].

Since the depigmentary degeneration is also considered to be a phenotype of early stage of pigmentary retinal degeneration [14], our patient may progress to pigmentary retinal degeneration in the future. However, the mechanism for retinal degeneration by the mutation of ataxin-7 is still not understood.

In this paper, we report the cases of a family with SCA7. In this Japanese family, the father had no ocular disease finding (such as degeneration of the retina), while the son did have depigmentary degeneration of the retina. Accumulation of further data regarding the variation in physical and pathological presentation in SCA7 may aid in better defining the diagnostic characteristics of this inherited condition.

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## Legends

Figure 1: The pedigree of our cases

Black symbols indicate individuals affected with spinocerebellar ataxia, and white symbols indicate unaffected individuals. Square shows man. /; deceased.

Figure 2: Brain MRI findings

A: Father (at age 49): Sagittal brain MRI (FLAIR TR/TE 8002/104.5) shows moderate atrophy of the brain stem and cerebellar vermis.

B: Son (at age 16): Sagittal brain MRI (T1 TR/TE 550/11) shows moderate atrophy of the cerebellar vermis and caudal portion of the pons.

Figure 3: Funduscopy findings

A: Father (at age 49): Macular degeneration was not perceived.

B: Son (at age 16): The picture condition was dark due to the small pupil size of the patient, although mydriatics had been employed. He was diagnosed with bilateral depigmentary degeneration of the retina.

Fig. 1 The pedigree of our cases

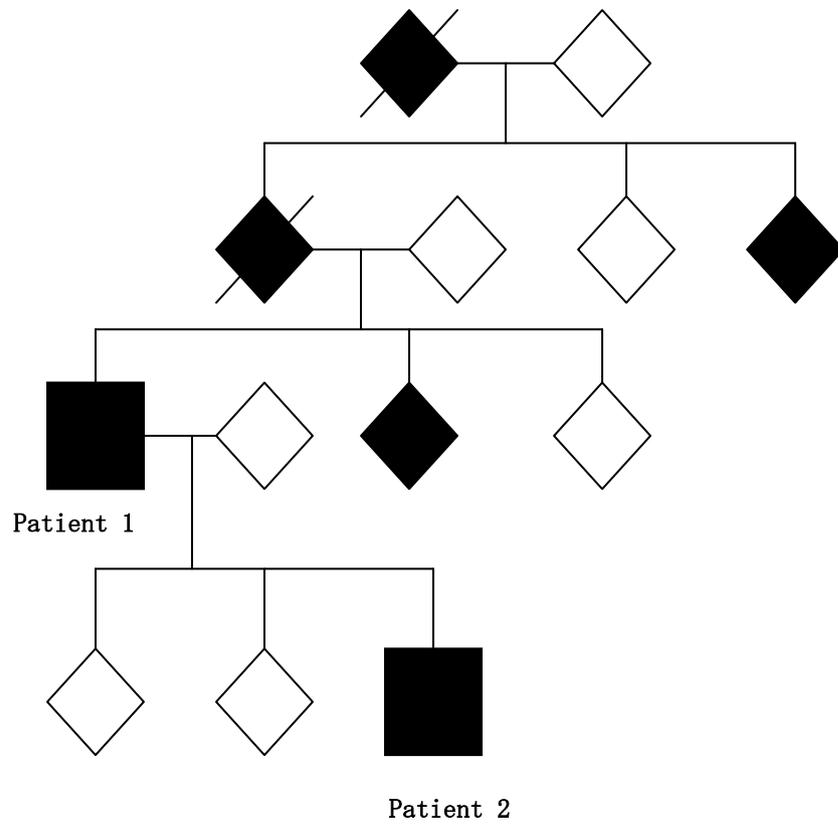


Fig. 2 Brain MRI findings

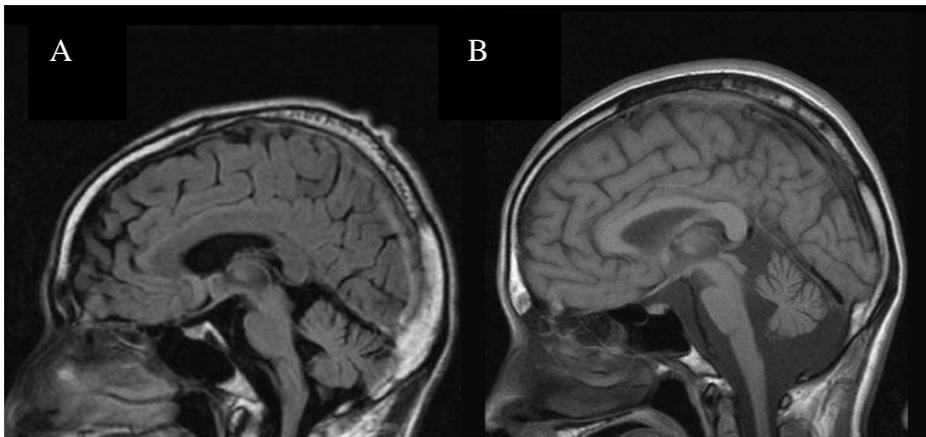
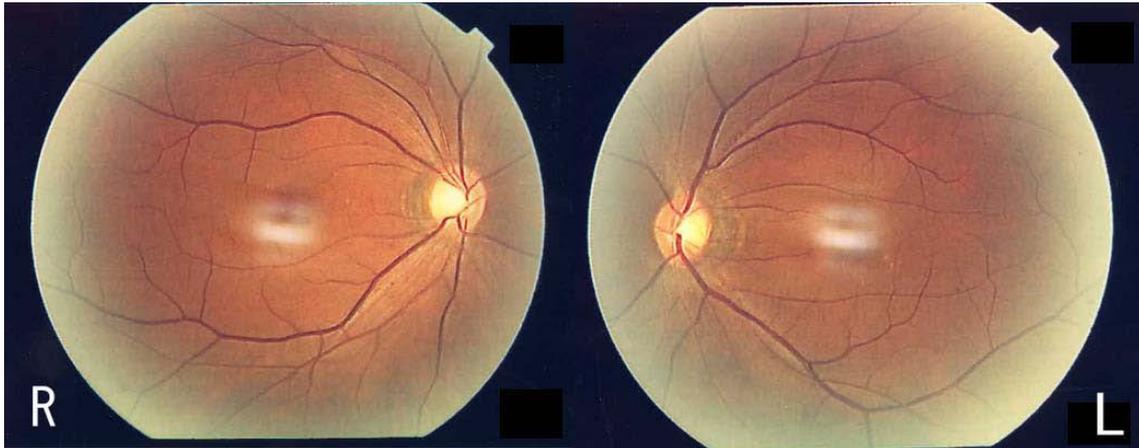


Fig. 3 Funduscopy findings

A)



B)

