



# Autopsy findings and clinical features of a mild-type xeroderma pigmentosum complementation group A siblings: 40 years of follow-up

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**Key words:** autopsy; forty years of follow-up; mild-type XP-A.

## INTRODUCTION

Xeroderma pigmentosum (XP) is an autosomal recessive disease characterized by abnormally accelerated photoaging skin symptoms for the patient's age caused by failure to repair DNA lesions damaged by ultraviolet radiation.<sup>1</sup> Two sibling cases of Japanese XP-A patients display milder symptoms in those who harbor compound heterozygous mutation of IVS3-1G>C and c.682C>T, (p.R228X). We present a follow-up report on two patients, XP4KO and XP5KO, after a brief report from 25 years ago.<sup>2</sup>

## CASE REPORTS

XP4KO was diagnosed with possible XP at 4 years of age.<sup>2</sup> Her initial onset of skin cancer was at 13 years old. Neurologically, although she had early ataxia, such as a tendency toward stumbling, at around 12 years old, and marked dementia from age 15, she managed to perform daily activities such as eating and dressing by herself. Magnetic resonance imaging at age 21 found remarkable atrophy of the cerebral cortex and ventricular dilation, whereas auditory brainstem response at 23 years was normal. She underwent tracheotomy for paralysis of the vocal cords at 31 years. At 35 years, she

### Abbreviation used:

XP: xeroderma pigmentosum

gradually had difficulty walking and swallowing, grew emaciated, had ischuria caused by neurologic bladder, and became bedridden and her general condition deteriorated over several months. She then died of multiple organ failure at 35 years.

An autopsy of XP4KO was performed immediately after death with written informed consent from her parents. The autopsy found emaciation, and her constitution was small: 147 cm tall and weighing 21 kg. Malignant skin tumors were not observed. Lung abscesses were seen. The left lung weighed 160 g, and the right was 240 g. Atrophy of generalized adipose tissue was noticeable. The ovaries, heart muscle, and mucosa of the stomach were also atrophic. Additionally, osteosclerosis and hypoplastic marrow were present.

The brain was small, with a proportional configuration of the cerebrum, brain stem, and cerebellum, weighing 510 g. The cerebral cortex and white matter were atrophic, and enlargement of the lateral

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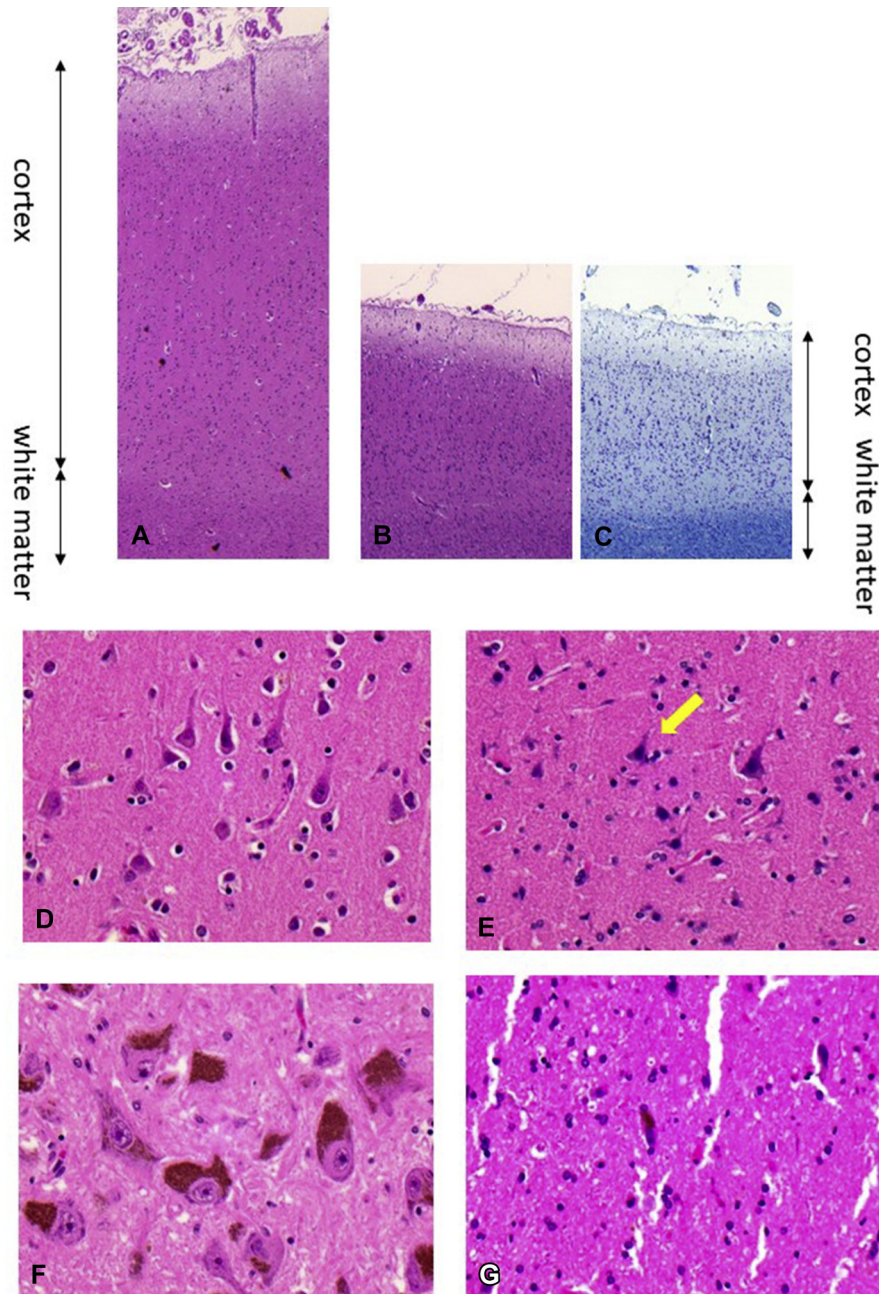
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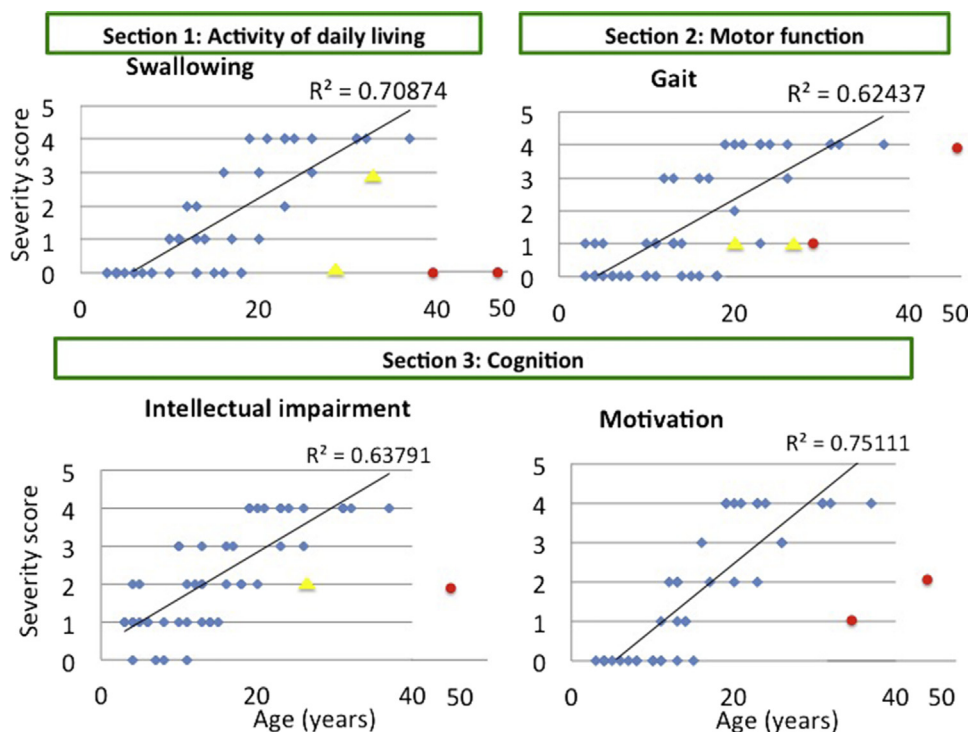
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**Fig 1.** Microscopic features of the cerebral cortex (**B, C, E**) and substantia nigra (**G**) of the patient (XP4KO), with reference to those of an age-matched control (**A, D, F**). The thickness of the cerebral cortex is apparently thin (**B, C**), and individual neurons (*yellow arrow*) are small (**E**). In the substantia nigra pars compacta, neurons are small in size with poor accumulation of melanin pigments (**G**). (**A, B, D-G**, Hematoxylin-eosin stain; **C**, Klüver–Barrera stain; original magnifications: **A-C**,  $\times 10$ ; **F** and **G**,  $\times 400$ ; **D** and **E**,  $\times 200$ .)

ventricle was evident. The substantia nigra showed marked paleness. Histologically, the thickness of the cerebral cortex was evidently thin, wherein individual neurons were small (Fig 1). Loss of neurons in the caudate nucleus, putamen, and substantia nigra (Fig 1, G) and loss of Purkinje cells, were evident. In the cerebral white matter, myelin pallor was

unremarkable. In the substantia nigra pars compacta, there was little melanin pigment in the remaining neurons (Fig 1, G). No neurofibrillary tangles or senile plaques were seen. Myelin pallor in the posterior funiculus of the upper cervical cord was evident. The features are consistent with those of previous reports.<sup>3,4</sup>



**Fig 2.** Severity indices of the current cases are plotted in comparison with those of patients with XP-A with homozygous Japanese XPA founder mutation, IVS3-1G>C. Horizontal axis indicate years and vertical axis indicates severity scores. Scores in swallowing are: 0, normal; 1, infrequent choking; 2, occasional choking; 3, require soft food; 4, requires nasogastric or gastrostomy tube. Scores in walking are: 0, normal; 1, mild difficulty; 2, moderate difficulty, but require little or no assistance; 3, severely disturbed walking, requiring assistance; 4, cannot walk at all, even with assistance. Scores in intellectual impairment are: 0, normal; 1, mild (consistent impairment with partial recollection of events, but with no other difficulties); 2, moderate difficulty handling complex problems; 3, severe impairment with problems; 4, unable to make judgments or solve problems. Scores in motivation are: 0, normal; 1, lacking energy, does not restrict activities; 2, lacking energy, restricts hobbies and interests; 3, lacking energy, restricts routine activities; 4, unable to perform any task. Yellow triangle indicates XP4KO, red circle indicates XP5KO.

XP5KO is the younger sister of XP4KO by 2 years, and is now 48 years old. She began strict sun protection measures at age 2. She finished her compulsory education by age 15. Skin cancer developed at age 23. At 29 years, she began having difficulty walking, which increased to moderate difficulty at 35 years. When she was 41, her magnetic resonance imaging findings showed remarkable atrophy of the cerebrum and cerebellum. Despite mental retardation, hearing impairment has not been evident. She can perform daily activities such as eating and dressing by herself and has been followed up 3 times a year at our hospital.

## DISCUSSION

The genotype–phenotype correlation has been reported in XP-A patients<sup>5</sup> and patients with homozygous IVS3-1G>C who have severe cutaneous and

neurologic symptoms and skin cancers before age 10 if they do not use appropriate sun protection. These patients die at around 20 years, whereas patients with homozygous R228X are known to manifest milder clinical features.<sup>5,6</sup> We compared the progress of our cases' symptoms with that of patients with homozygous IVS3-1G>C by using the XP severity classification scale, wherein the patients' neurologic status in daily living activities, motor function, and cognition are assessed.<sup>7,8</sup> Previously, we found the severity score is well correlated with patients' ages in 49 patients with homozygous IVS3-1G>C mutation of XPA. Swallowing and motivation had an especially strong correlation with age, at R<sup>2</sup> 0.7089, and 0.7511. When we plotted the severity score of our cases, it was apparent their progress in neurologic symptoms was about 15 years slower than that of patients with homozygous IVS3-1G>C (Fig 2). For

example, XP4KO could perform daily activities such as eating and dressing by herself until age 34, lived to age 35, and could communicate before her death. XP5KO is now 48 years old and can eat with some assistance and without a gastrostomy tube, which is quite different from patients with homozygous IVS3-1G>C, who have a gastrostomy tube placed and tracheostomy around age 20. Although hearing impairment is believed to be the earliest symptom XP-A patients have,<sup>9</sup> and most Japanese XP-A patients with homozygous founder mutations have accompanying hearing impairments before age 10, neither XP4KO nor XP5KO manifested a hearing disability. At least for our cases, easily stumbling was the earliest symptom, starting at age 11, and difficulty walking started at 29 years.

Interestingly, XP5KO outlived her sister, and both cutaneous and neurologic manifestations are progressing more slowly than in her sister. They have the same mutation in *XPA* and were brought up in the same environment. The main difference was the age they began strict sun protection: at 4 years for XP4KO and 2 years for XP5KO. However, this earlier start affecting the slower progress of symptoms in XP5KO remains to be elucidated in future studies.

Noticeable findings in our study were that macroscopically, the substantia nigra lost its black color, and microscopically, the number of neurons containing melanin were markedly reduced and melanin deposits were pale. This provided insight, as melanin is assumed to be a radical scavenger, and some investigators have hypothesized that patients with XP are deficient at repairing DNA damage caused by free radicals produced in the brain, which might damage neuronal cells.<sup>10</sup> Further accumulation of

autopsies of XP patients will shed light on the mechanism of neurodegeneration with XP.

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