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DNA Repair Characteristics and Skin Cancers of Xeroderma Pigmentosum Patients in Japan[1]

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SUMMARY

Fifty xeroderma pigmentosum patients in Japan were examined for clinical characteristics and DNA repair of their cells. Skin cancers developed in 22 patients. Most of the patients without skin cancers were children, except for 5 older patients who had intermediate or nearly normal levels of DNA repair in their cells. All patients younger than 10 years old had no or very low activity of unscheduled DNA synthesis after ultraviolet light irradiation. Three genetic complementation groups, A, D, and E, and variants were found. Many Group A patients and no Group C patients characterized Japanese patients, compared with those in Europe and the United States, where Group C patients were most frequent. The high frequency of patients with low DNA repair capacities in their cells may account for the apparent high frequency of xeroderma pigmentosum patients in Japan. Age distribution of the cancer-bearing patients and their DNA repair characteristics suggest that almost all xeroderma pigmentosum patients will develop skin cancers unless their cells have nearly normal levels of DNA repair.

INTRODUCTION

XP[5] is a rare hereditary disease attributed to an autosomal recessive gene. Most of the patients develop skin cancers in the areas of skin exposed to sunlight. Classification of XP in terms of different levels of DNA repair and genetic complementation groups has been reported on patients in Europe and the United States (7, 8, 17, 18, 21). When the clinical and repair characteristics of Japanese XP patients were compared with those of patients in other countries, they were generally similar, but a few significant differences were noticed. This report presents a survey of Japanese XP patients with emphasis on DNA repair characteristics and skin cancers, and discusses the characteristics unique to them.

MATERIALS AND METHODS

Cells and Culture Media. A list of patients whose cells were examined is presented in Table 1, which shows clinical characteristics and the results of repair tests. Skin biopsies were usually taken from the undamaged area of mildly suffering patients and from the damaged area of the carcinomatous skin lesions of severely suffering patients. Fibroblast cells grown from the biopsy specimens were used for all repair tests. Cells from skin of a normal person were used as a control for each experiment. Culture medium was one of the following formulae; essentially no significant differences for growth were noticed in any of these media. They were: Eagle's MEM (Research Foundation for Microbial Diseases of Osaka University, Suita-shi) supplemented with 20% fetal bovine serum (Flow Laboratories, Rockville, Md.); Medium 199 (Research Foundation for Microbial Diseases of Osaka University) supplemented with 20% fetal bovine serum; Dulbecco's modification of Eagle's MEM (Flow Laboratories) supplemented with 10% fetal bovine serum; and Eagle's MEM supplemented with amino acids and vitamins (both from Flow Laboratories) to twice the original formula and 15% fetal bovine serum.

Autoradiography. Immediately after cells were irradiated by UV, culture medium with 10 μCi/ml of [*methyl*-^{3}H]thymidine (15 to 30 Ci/mmole; Radiochemical Centre, Amersham, England) was added and cells were incubated for 3 hr. After that, cells were washed with buffer solution (NaCl, 8.0 g; KCl, 0.2 g; Na_2HPO_4, 1.15 g; KH_2PO_4, 0.2 g; and water, 1000 ml) and were further incubated in the culture medium supplemented with thymidine, 5 μg/ml, for 1 hr. Cells were fixed in methanol and were treated by iced trichloroacetic acid (5%) to remove acid-soluble substances. Cell plates were dipped in Kodak NTB-3 (in some cases, NTB-2) nuclear track emulsion, dried, and exposed for 1 to 4 weeks at 4°.

After development by standard photographic procedure, cells were stained by Giemsa solution (Merck, Darmstadt, Germany).

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[5] The abbreviations used are: XP, xeroderma pigmentosum; MEM, minimum essential medium; UDS, unscheduled DNA synthesis.

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Genetic Complementation Tests. All tests were performed against cell strains belonging to each complementation group obtained from American Type Culture Collection, Rockville, Md. Detailed procedures are to be published elsewhere (K. Tanaka, H. Akiba, and H. Takebe, in preparation).

Other DNA Repair Tests. Tests for inactivation of colony-forming ability and host-cell reactivation of UV-irradiated herpes simplex virus were done as described previously (25).

RESULTS

Clinical information of the XP patients and the DNA repair characteristics of their cells are listed in Table 1. Additional information concerning the table is as follows.

Age. Ages in the table are those at the time of biopsy followed by the repair tests of the cells. XP had previously been diagnosed in most of the older patients.

Skin Cancer. Most of the skin cancers were confirmed by histological examination by pathologists. Cancers appearing after the time of biospy are not included in the table, except for 1 case, XP1KO.

Consanguinity. The consanguinous marriages in the table are within 2 generations ago (parents and grandparents of the patients). Some cases, for instance, XP6OS, had complex consanguinity involving several generations. The data are based only on results of inquiry of the patients or their relatives, and therefore, they may not be accurate. Among parents of 45 sibships, 14 were first-cousin marriages, 8 were consanguineous marriages of the degree other than first cousin, 22 were not related, and no information was available for 1 sibship.

Mental Retardation. Since mental retardation in children under 6 years of age is generally not clear clinically, the column was left undecided for such patients unless further information was available later. For example, the mental retardation of XP3OS was confirmed at the age of 7, although the biopsy and the repair tests were made at the age of 5. Intelligence quotient tests were performed in several cases, as shown in the table. In all other positive cases, the retardation was unquestionably confirmed by the physicians (mostly by neurologists). The negative (normal) cases were determined by oral questioning or by other supporting factors, such as occupational records or school records.

Gait Disturbance. All positive cases were confirmed by orthopedists. Three cases (XP2OS, XP3OS, and XP9OS) underwent Achilles tendon surgeries.

UDS. UDS was measured by autoradiography. When number of silver grains per nucleus was indistinguishable from the background level, it was described as less than 2% or less than 5% of the normal level, depending on the number of grains in normal (control) cell nuclei. All data represent measurements of UDS after exposure to a germicidal (254-nm) lamp, except for 1 case, XP6SE cells, which were exposed to a near-UV lamp (FL 20SE) with a peak around 310 nm, with control of normal cells against the same lamp.

UV Sensitivity. Two methods were used to test the UV sensitivity of the cells: (*a*) colony-forming ability: ++, 10 to 20 times more sensitive to UV than normal cells; +, 2 to 8 times more sensitive to UV than normal cells; (*b*) host-cell reactivation of UV-irradiated herpes symplex virus; ++, 5 to 10 times more sensitive than normal cells; +, 1.5 to 3 times more sensitive than normal cells. Details of the host-cell reactivation tests will be published elsewhere (H. Takebe, in preparation).

Development of XP Symptoms in Relation to DNA Repair. Table 2 shows the age distribution of the patients and their clinical and repair characteristics. Apparently, age and time of onset of XP symptoms were related. Cells of all patients 0 to 9 years old (1 patient not tested) had very low UDS levels, suggesting that the early development of skin lesions may be due to the loss of or severe reduction in DNA repair activity. Also, neurologically normal patients were not found in this age group, although most of them were too young to be tested mentally. On the other hand, only 1 of 10 patients 30 years old or older showed neurological abnormalities, and all of their cells had intermediate or nearly normal levels of UDS. There was only 1 patient (XP1KO) who had a very low UDS level (5 to 10%), but did not show neurological abnormalities.

All 10 patients with gait disturbance, 6 of them with hearing difficulties, had UDS levels of 10% or less. Although 17 patients under 6 years old were not extensively examined neurologically, slight retardedness in mental and physical activities was noted by physicians in many cases. Therefore, it was assumed that most of the 23 patients in the 0 to 9 age group and 8 older patients with UDS levels of 10% or less, all having neurological abnormalities (excluding XP1KO), were to be classified as De Sanctis-Cacchione syndrome patients.

Skin Cancer. Twenty-two patients had had skin cancers in various stages of development. These were basal cell carcinoma, squamous cell carcinoma, or both, for all the histologically examined cases. No malignant melanoma was encountered in this series of XP. No internal cancers were found either, although the latter were not extensively searched for.

In the 0 to 9 age group, 20 of 23 patients did not have skin cancers, probably because they were too young to develop skin cancers. There were 6 patients of age 20 or over without skin cancers, all of them having UDS levels of 60% or over. Basal cell carcinomas were the skin cancers that appeared earliest; these were observed in XP2OS, XP3OS, and XP1NA at the age of 5, all of them having very low UDS levels, while that in the patients with intermediate or nearly normal levels of UDS was 9 years of age in XP9SE.

Repair Tests. Repair tests of the following patients were published previously: XP1SE-XP9SE (2), XP6TO (22), XP1OS (24), XP2OS (25), and XP1KO (11). Among 10 cell lines from the patients in Tables 2 with UDS levels of 70 to 100%, 8 cases were found to be defective, at least partially, in repair other than UDS. They were XP5SE, XP1OSE, ZP8TO, XP9TO, XP13OS, and XP3KO, determined by decreased host-cell reactivation of UV-irradiated herpes simplex virus (H. Takebe, manuscript in preparation), and XP5TO, XP5OS, and XP3KO, determined by deficiency in postreplication repair (12). Therefore, except for XP4TO and XP20OS, which have not been tested for repair other

Table 1

Clinical and DNA repair characteristics of XP patients[a] in Japan

Patient[b]	Sex	Age[c] (yr)	Skin cancers[d]	Consanguineous marriage[e]	Mental retardation (IQ)[f]	UDS[g] (% of normal)	UV sensitivity[h]	Complementation group[i]	Physician[j]
XP1SE	F	38	+ (20)	1st cousin	–	50			Akiba
XP2SE	F	1	–	–	ND	<2		A	Akiba
XP3SE	M	28	+ (20)	1st cousin	+ (30)	40			Akiba
XP4SE	M	31	+ (13)		+	40			Akiba
XP5SE	M	33	+ (20)	Uncle-niece	–	70	+ b	E	Akiba
XP6SE	M	29	+ (20)	1st cousin	–	25			Akiba
XP7SE	M	3	–	1st cousin	ND	<2		A	Akiba
XP8SE	F	16	+	1st cousin	+ (15–20)	3		A	Akiba
XP9SE	F	45	+ (9)	–	–	40			Akiba
XP10SE	F	54	+	1st cousin	–	100	+ b		Akiba
XP11SE	F	12	–	–	+	<2			Akiba
XP12SE	M	1	–	1st cousin	ND	<5			Akiba
XP13SE	M	3	–	–	ND	<2			Akiba
XP14SE	M	13	+	1st cousin	+	<2	++ b	A	Akiba and Nagao
XP15SE	M	6	–	–	+	<2	++ b	A	Akiba and Kato
XP4TO	F	19	–	1st cousin	–	100			Komiya
XP5TO	F	23	+		–	100		Variant	Komiya
XP6TO	F	7	–	–	+ (55)	5–10	++ b	A	Toda
XP7TO	F	17	+ (7)	–	+	<2		A	Toda
XP8TO	F	75	+	–	–	80	+ b		Utsunomiya
XP9TO	M	60	–	1st cousin	–	100	+ b		Toda
XP10TO	M	51	+	1st cousin	–	25		D	Toda
XP1NA	F	5	+	+	ND	<5		A	Ohno
XP2NA	M	2	–	–	ND	<2		A	Hoshino
XP3NA	F	3	–	1st cousin	ND	<2			Ohno
XP4NA	F	1	–	1st cousin	ND	<2			Ohno
XP1OS	F	12	+ (10)	–	+ (37)	<2	++ a		Miki
XP2OS	F	7	+ (5)	+	+	<2	++ a, b	A	Kozuka
XP3OS	F	5	+ (5)		+	<2		A	Kozuka
XP4OS	M	2	–		ND	<2		A	Kozuka
XP5OS	M	30	–	–	–	100	Normal a	Variant	Aoki
XP6OS	M	7	–	+	+ (71)	ND			Taniguchi
XP7OS	F	12	+ (10)	ND	+	<2			Miki
XP8OS	F	5 mo.	–	–	ND	<2	++ b	A	Nishioka
XP9OS	M	10	–	1st cousin	+	<2	++ b	A	Ueeda
XP10OS	M	9	–	–	+ (30–54)	<2	++ b	A	Shimasaki
XP11OS	F	1	–	–	ND	<5		A	Akimoto
XP12OS	F	24	+ (12)	–	+	<5		A	Sato
XP13OS	M	28	–	–	–	70	+ b		Kawatsu
XP14OS	M	1	–	–	ND	<2		A	Okumura
XP15OS	F	2	–	+	ND	<2	++ b	A	Kozuka
XP16OS	F	4	–	–	ND	<2		A	Aoki
XP17OS	F	18	+ (18)	1st cousin	–	40	+ b		Tashiro
XP18OS	F	6 mo.	–	–	ND	<2			Kozuka
XP19OS	M	1	–	+	ND	<2			Kozuka
XP20OS	M	21	–	–	–	100			Okumura
XP21OS	M	42	–	–	–	60			Endo
XP1KO	F	16	+ (17)	+	–	5–10	++ a		Sano
XP3KO	M	29	+ (27)	+	–	100	+ a	Variant	Sano
XP1YO	M	5	–	–	ND	<2		A	Sasaki, H.

[a] Previous descriptions of the patients or their cells. XP1SE-XP9SE (2); XP6TO (22, 27); XP10S (24), and as XP1 in Ref. 11; XP2OS (25); XP1KO, as XP3 in Ref. 11; XP8OS and XP10OS (27). Siblings: XP3SE and XP4SE; XP7SE and XP12SE; XP4TO and XP5TO; XP2OS, XP3OS, and XP4OS. Age is in years unless otherwise indicated.

[b] SE, Sendai; TO, Tokyo; NA, Nagoya; OS, Osaka; KO, Kobe; YO, Yonago.

[c] Age at biopsy.

[d] Skin cancers: +, present; –, not present. Numbers in parentheses, age of onset, if known.

[e] Consanguineous marriage: +, of the degree other than 1st cousin, except for XP5SE (uncle-niece); –, parents were not consanguineous. ND, no information was available.

Table 1—*Continued*

[f] +, mentally retarded; −, not mentally retarded; numbers in parentheses, IQ, if examined; ND, not determined. In most cases, patients were too young to be tested. Neurological abnormalities other than mental retardation: gait disturbance, XP8SE, XP11SE, XP14SE, XP15SE, XP7TO, XP2OS, XP3OS, XP10OS, and XP12OS; hearing difficulty, XP8SE, XP11SE, XP7TO, XP2OS, XP3OS, and XP4OS.

[g] ND, not tested.

[h] ++, extremely sensitive; +, slightly more sensitive than normal cells; a determined by colony-forming ability; b, determined by host-cell reactivation of UV-irradiated herpes simplex virus; blank spaces, not tested.

[i] Blank spaces, not tested.

[j] Physicians who diagnosed and referred the patients as XP or XP suspects.

Table 2

Age distribution, clinical characteristics, and DNA repair of XP patients in Japan

Age (yr)	No. of patients	Skin cancers		Mental retardation (gait disturbance)			UDS (% of normal)[b]		
		Yes	No	Yes[a]	No	Unknown	≦10	25–50	60≦
0–9	23	3	20	6 (4)	0	17	22 (3)	0	0
10–19	10	7	3	7 (5)	3	0	8 (6)	1 (1)	1
20–29	7	5	2	2 (1)	5	0	1 (1)	2 (2)	4 (2)
30–39	4	3	1	1	3	0	0	2 (2)	2 (1)
≦40	6	4	2	0	6	0	0	2 (2)	4 (2)
Total	50	22	28	16 (10)	17	17	31 (10)	7 (7)	11 (5)

[a] Numbers in parentheses, number of patients with gait disturbance.

[b] Numbers in parentheses, number of patients with skin cancers; XP6OS is omitted since UDS was not measured.

than UDS, 8 patients in this group were shown to be partially defective in DNA repair, thus supporting the diagnosis of XP made by physicians.

Genetic Complementation Groups of XP Cells. The results of genetic complementation tests are summarized in Table 3, in comparison with those in Europe and the United States (6). Details of the experimental data will be published elsewhere (K. Tanaka, H. Akiba, and H. Takebe, manuscript in preparation).

Three distinct characteristics were noted. There were many Group A patients, but no Group C patients, and no new complementation group was found in Japan so far in addition to the existing 5 groups reported in other countries. There were 3 "variants," as identified by the tests of postreplication repair (12).

It has been reported that each complementation group corresponds to a certain amount of UV-induced UDS (21), but some discrepancy was observed between the data of the Rotterdam and NIH groups (18), making the temporal assignment of the cell strains to complementation groups only by UDS levels difficult. Moreover, the recent finding of a Group A strain XP8LO with 30% of UDS instead of less than 2 or 5% (9) strongly suggested that the classification based on UDS levels might be misleading. It may be reasonable to say, however, that if the levels of UDS are very low (less than 5% of normal), the chance of being assigned to Group A is very high, especially in Japan where no Group B and Group C patients are found. We may then estimate the frequency of Group A patients in Japanese XP patients as 59% (29 of 49), in which 21 were assigned by the complementation test. This ratio is approximately twice the ratio in Europe and the United States (9 of 31 = 29%).

Table 3

Genetic group of XP patients

Area	No. in complementation group						
	A	B	C	D	E	Variant	Total no.
Japan	21	0	0	1	1	3	26
Europe and United States[a]	9	1	12	3	2	4	31

[a] Ref. 6.

DISCUSSION

It has been known that there are at least 5 complementation groups and 1 variant group in XP (7, 8, 17, 18, 21). We found complementation Groups A, D, E, and variants in Japan, but no patient belonging to Groups B and C was found. There was no new complementation group found in Japan, suggesting that the present 5 groups may represent the complete set to be expected, although the total number of the cell strains tested for complementation, 50 (excluding variants), may not be enough to so conclude. The Group E patient in Japan, XP5SE, is the 2nd family of this group found in the world. This made Group B the only complementation group represented by a sole patient who had both XP and Cockayne's syndrome; the presence of the latter disease may have influenced the complementation tests to constitute a peculiar group. Lack of patients belonging to Group C, which is the most frequent in other countries, was the most unique to XP in Japan. Such difference of gene distribution among different races might be regarded as a general phenomenon in human genetics, considering that there have been many examples of nonuniform gene distributions known, such as ABO blood groups or cystic fibrosis, the latter seldom found in Japan.

Table 4 gives a comparative view of age distribution of XP patients in Europe, the United States, and Egypt. Although the ages of the patients at the time of the first visit to University clinics may not reflect their clinical characteristics, the presence of very young patients may indicate that the symptoms appeared early in their lives, and if the pa-

Table 4

Age distribution and DNA repair of XP patients in Europe, the United States, and Egypt

Patient numbers, shown in brackets or in footnotes, are abbrev ated by omitting "XP" for the patients bearing city initials. Unless otherwise indicated in parentheses in footnotes, reference for all Bethesda (BE) patients is Ref. 21, and that for other patients is Ref. 15. Additional information on XP13BE can be found in Ref. 5. No repair data were available for the patients in Egypt (10).

	Europe and United States						
		UDS after UV (% of normal)					
Age (yr)	No. of patients	<7	10–25	25–55	50–75[a]	≦80	Egypt
0–9	13	9[b]	4[c]	0	0	0	15
10–19	11	1[12RO]	7[d]	3[e]	0	0	19
20–29	14	1[11BE]	5[f]	5[g]	1[3RO]	2 [4BE, 7TA]	
30–39	4	1[1LO]	0	0	1[2RO]	2 [30RO, 13BE]	8
<40	4	0	2 [16RO, 14BE]	0	1[1RO]	1[1RO]	4
							0
Total	46	12	18	8	3	5	46

[a] UDS level of 50 to 60% is assigned to this group.
[b] 25RO, 26RO, XP1 (1), 4LO, 12BE, KFSF (4), KMSF, 17SF, and PKSF.
[c] 9RO, 20RO, 2LO (20), and 3LO (20).
[d] 4RO, 21RO, 8BE, 9BE, 10BE, 19HO, and 12SF.
[e] 6RO, 7RO, and 7BE.
[f] XP6 (23), XP9 (23), 1BE, 2 BE, and 3BE.
[g] 5RO, 5BE, 6BE, XP1 (13), and XP2 (13) (last 2 could be assigned to 10 to 25% UDS level).

tients are old, the symptoms may be regarded as not so severe as to be lethal. The age distribution patterns in Tables 2 and 4 suggest that there are more young patients in Japan whose cells have a very low UDS level and belong to Complementation Group A. We may assume that the high frequency of the patients belonging to complementation Group A who develop XP symptoms early in life and are diagnosed decisively may account for, at least partially, the high incidence of XP patients in Japan. Additional factors such as different medical service systems in different countries, or other unknown factors such as nutrition, might also be involved in the high frequency of XP in Japan. Although it may be difficult to compare 1 from among 14,600 at birth in Japan (Ref. 26, based on Ref. 19) with 1 from among 250,000 births in general population in other countries (21), the true frequency in Japan could be higher than that in other countries, because even the most severe cases of XP usually are known to survive up to 30 years in Japan and, therefore, the frequency in general population in Japan may not be greatly different from the frequency at birth. The reason there were few Group A patients in their teens and 20's may be that the patients or family members of the patients, knowing that the disease is not curable, stop coming to the University hospitals (almost all of the patients listed in Table 1 were patients received at University hospitals) and may die at small hospitals or even at their residences.

Apparently, the levels of repair deficiency and the clinical development are related as suggested by Bootsma *et al.* (3), although Robbins *et al.* (21) denied such correlation. All of 22 patients in the 0 to 9 age group tested for UDS had low levels, suggesting that the lower the levels of repair, the earlier the symptoms appear. Similarly, the age distributions of patients with intermediate or nearly normal levels of UDS may indicate that the higher the levels of repair, the less likely the patient is to have severe symptoms, and the more likely it is that the patients are much older, at least in Japan.

If we assume that XP patients in Complementation Group A will not have children but that other patients will reproduce normally, and that the frequency of XP has not been changing for generations, we can estimate the mutation rate of new XP gene(s) as a whole from the normal allele, according to Komai's formula (16), $u \simeq sfq$, where u is the mutation rate, s is the adaptability of the mutant gene, f is the coefficient of inbreeding in the population, and q is a frequency of the recessive gene. The maximum estimate obtained is $u = 6 \times 10^{-6}$ based on $s = 0.4$ (20 of 49, frequency of patients other than Complementation Group A and those having UDS levels of 5% or less), $f = 0.00179$ (12), and $q = 0.0083$ ($= \sqrt{1/14600}$).

The fact that the patients who had not developed skin cancers at age 20 or over were those with high UDS levels suggests that the onset of carcinogenesis is also related to the levels of DNA repair. All other patients of age 20 or over, including 4 patients with high (70 to 100%) UDS levels, have developed skin cancers. Therefore, it may be reasonable to assume that all XP patients with UDS levels of 50% or less should develop skin cancers by the age of 20. It is very likely that all young patients now in the 0 to 9 age group who have not yet developed cancers will develop cancers later. The only XP patients who may be able to survive without developing cancers are some of those with nearly normal or normal levels of UDS. If these assumptions are correct, approximately 90% of the XP patients in Japan have already developed or are expected to develop skin cancers.

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