Chapter 5
Epidemiological Study of Xeroderma Pigmentosum in Japan: Genotype-Phenotype Relationship

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Abstract Xeroderma pigmentosum (XP) is a rare autosomal recessive hereditary disease caused by the deficiency of repairing DNA damage caused by ultraviolet radiation and some other compounds. Patients with XP display pigmentary change and numerous skin cancers in sun-exposed body sites, and some patients show exaggerated severe sunburn upon minimum sun exposure and neurological symptoms. We have conducted the nationwide survey for XP since 1980 as a research project supported for the intractable disease initiated by the Japanese Ministry of Health, Labour and Welfare. The frequency of each complementation group in Japan is considerably different from that in Western countries; in Japan, XP complementation group A is the most frequent, followed by variant type. Regarding skin cancers in XP, basal cell carcinoma was the most frequent cancer that patients with XP developed, followed by squamous cell carcinoma and malignant melanoma. The frequency of these skin cancers in patients with XP-A has decreased in these 20 years, and ages of onset of developing skin cancers are much older than those previously observed, which is greatly attributed to the education of sun protection for the patients with XP and their parents and guardians for these 20 years. In order to encourage the patients and their parents to perform appropriate sun protection for the prevention from skin cancers, definite diagnosis but not possible diagnosis is crucial. In addition, diagnosing at younger ages is important. On the other hand, the effective therapy for neurologic XP has not been established yet, and this needs to be done urgently.

5.1 Introduction

Xeroderma pigmentosum (XP) is an autosomal recessive hereditary photosensitive disease, in which patients display extreme hypersensitivity to ultraviolet radiation (UV) because of congenital defect of repair ability for UV-induced DNA damage. If

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these patients do not take appropriate protection from sunlight, they will develop serious photoaging skin symptoms, xerosis of the skin, progressive development of freckle-like pigmentation, and multiple skin cancers at sun-exposed area regardless of young age. XP is classified into eight subtypes; A–G genetic complementation groups of nucleotide excision repair deficient type and variant type. Responsible gene for each subtype has been identified, and each displays characteristic clinical features (Table 5.1). In Japan, the frequency of XP is higher than other countries, and furthermore genetic complementation group A (XP-A), of which patients develop progressive neurological symptoms and its severity impacts their prognosis, accounts for about half of XP patients. Therefore, XP has been assigned as an "intractable disease" which is supported by the *Research Grant Initiative on Overcoming Intractable Skin Diseases* by the Japanese Ministry of Health, Labour and Welfare (MHLW) since the 1980s. In July of 2015, XP has been assigned to the status of intractable diseases, making patients eligible for support from the government. In this chapter, we briefly discuss about the clinical aspects of XP, especially focusing on the status in the present Japan in comparison with that 25 years previously, and describe how we have coped with XP and what remains to be resolved in the future.

Table 5.1 Clinical and cytological characteristics of XP complementation groups

	Responsible gene	Number of patients and frequency (%)[a] Japan	UDS (%)	UV sensitivity (D_0) (J/m^2)	Skin symptom		Neurological symptom
					Sunburn	Age of onset of BCC (year)[b]	
A	*XPA* 9q34.1 (31kD)	63 (67.7)	<5	0.4	+++	9.3	++
B	*XPB/ERCC3* 2q21 (89kD)	0	3–7		++		− ~ ++
C	*XPC* 3q25 (106kD)	2 (2.2)	10–20	1.0	++	14.8	−
D	*XPD/ERCC2* 19q13.2 (87kD)	5 (5.4)	20–50	0.77	++	31	− ~ ++
E	*DDB2* 11q12-p11.2 (48kD)	Rare	40–60	2.2–2.4	+	43.5	−
F	*XPF* 16p13.13 (126kD)	1 (1.1)	10–20	1.7–2.2	+	45.5	−
G	*ERCC5* 13q33 (133kD)	Rare	<5	0.6	+	32	+
V	*POLH* 6p21.1-6p12 (83kD)	22 (23.7)	75–100	2.4–4.5	+	40.8	−

XP is subdivided into nucleotide excision repair (NER) deficient groups A through G and variant type. In Japan, half of the patients belong to the XP complementation group A, the severest type with the lowest DNA repair capacity, and 25% of the patients are assigned to the variant type, which has an almost normal level of nucleotide excision repair but is deficient in POLH, that is involved in translesional replication (TLR)

[a]Nakano et al [5]

[b]Sato and Nishigori [3]

5.2 Epidemiology

In Japan, the frequency of XP in newborn babies had been believed to be approximately 1/100,000 or less [1], and now it is estimated that XP occurs in 1 of 22,000 people [2]. This figure means that XP is not so extremely rare as compared with the incidence in Western countries, where the frequency is one of one million people, still it is a rare disease. In the old literature of the early twentieth century written in Japanese, we can find the description of siblings of XP which seems to be similar to cases of XP-A. In the late1980s, epidemiological survey for XP has been conducted. At that time, the DNA repair test had just become available for clinical use to diagnose XP in a certain laboratory, and big effort has been made to diagnose patients with possible or probable XP by DNA repair tests or genetic complementation tests, and these cytological data and clinical information from all patients who have once visited the hospitals were compiled by the nationwide survey in 1988 [3]. After a quarter of a century, nationwide XP survey was conducted again by the Research Committee for Intractable Diseases supported by the Japanese MHLW; in 2012, patients with probable XP who visited the medical institution during 2010–2012 were enrolled. For the first survey, questionnaires were distributed to 616 hospitals requesting for the number of patients who visited the hospital between 2010 and 2012. We received replies from 403 institutions and then the second survey questionnaires were sent to the dermatologists who attended to patients with XP and asked for more detailed clinical information [4]. In the survey_1988, as many patients with XP as possible were enrolled and analyzed in order to grasp the whole picture and natural history of Japanese patients with XP, who had hardly received any treatment or care for the disease, because at that time, clinical methodology on how to care and educate the patients with XP had not been established, while the results of the survey–2012 represent the status of Japanese patients with XP who needed medical care during 2010-2012, and it is useful to search for the present problem to be resolved. Table 5.2 shows the frequencies of each clinical form enrolled in the two surveys. In both surveys, XP-A, in which both cutaneous

Table 5.2 Number of patients with each genetic complementation groups of XP patients

	A	B	C	D	E	F	G	V	Unknown	Total
Survey _1988[a]	117 (43.0)[c]		5 (1.8)[c]	5 (1.8)[c]	6 (2.2)[c]	12 (4.4)[c]	1	89[b] (32.7)[c]	37[d]	272 (100)
Survey _2012[e]	63 (67.7)[f]		2 (2.2)[f]	5 (5.4)[f]		1 (1.1)[f]		22 (23.7)[f]	77[g]	170

[a]Sato and Nishigori [3]

[b]Patients with clinically definite XP with the UDS level over >60%

[c]Number in parentheses: frequency(%)of each complementation group; the number of patients were divided by the total number of the patients

[d]Patients with reduced UDS but complementation groups has not been assigned

[e]Modified from the data from Nakano [5]

[f]Number in parentheses indicate the frequency out of the total numbers of patients excluded "unknown"

[g]Clinically the patient satisfies the criteria of XP, but the complementation group was not identified yet

symptoms and neurological symptoms are the most severe, accounts for about half of XP patients in Japan, followed by XP-V in which patients develop only cutaneous symptoms, accounts for about 25%. In the 1988 survey, all patients who were suspected of XP were subjected for the DNA repair tests for UDS and cell survival assay, but the responsible gene for XP has not been identified yet, and the diagnosis of XP has been done by genetic complementation tests using fusion technique or by the combination of clinical information, where patients manifesting typical severe exaggerated sunburn with UDS lower than 5% were diagnosed as "probable XP-A" and patients manifesting typical pigmented freckles with multiple skin cancer at younger ages with UDS higher than 60% were diagnosed as "probable XP-V." However in the 2012 survey, responsible genes for all XP clinical subtypes have been identified, and genetic analysis-based diagnosis has been made for most cases, which apparently increased the frequency of XP-A higher and decreased the frequency of XP-V slightly lower, since, in Japan, diagnosis of XP-A is very feasible because of its founder mutation, whereas diagnosis of XP-V needs several cumbersome examinations including UDS, POLH immunoblotting, and *POLH* gene sequencing, and not all patients cannot be genetically diagnosed. All the same, these frequency patterns are similar between the two surveys and differ substantially from that observed in Western countries, where XP-C and XP-D are the most common clinical subtypes. Patients with XP-E are rare, and there is no case report of patients with XP-B in Japan.

5.3 Cutaneous Symptoms of XP

XP Displaying Exaggerated Sunburn Reaction Followed by Pigmentary Change In patients with XP-A, XP-B, XP-D, XP-F, and XP-G, severe and exaggerated sunburn reaction occurs at the sun-exposed area upon a minimum sun exposure (e.g., face, nape, ear auricle, dorsum of the hand, and upper and lower limbs) (Fig. 5.1). Unlike normal sunburn, this exaggerated sunburn reaction is often associated with remarkable erythema, swelling, blister, and erosion and is exacerbated for 3–4 days after exposure and persists for at least 1 week. After having repeated such severe sunburn-like reaction, freckle-like small pigmented maculae are found at the sun-exposed area. Freckle-like pigmented maculae increase whenever sun exposure episode is repeated. In comparison with normal freckle, the sizes of freckle-like pigmented maculae in XP are various, and its color tone is heterogeneous, from pale-brown to brown or black-brown color. Small pigmented maculae can be found not only in the face but also in the nape, the dorsum of the hand, and the upper chest (Fig. 5.2). Sun-exposed area of the skin tends to be xerotic easily, and multiple malignant skin tumors (actinic keratosis, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, etc.) will be found in the face and others at young age. If such patients do not perform strict protection from sunlight, malignant skin tumors may occur at ages of 30–60 years younger than healthy people, and the frequency is considered as 1000 times or more as much as healthy generation.

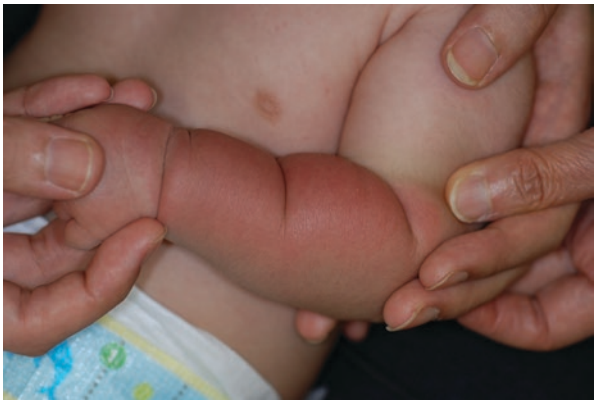

Fig. 5.1 XP-A patients (2 months old). Clearly demarcated edematous erythema was observed limited on the sun-exposed body site. This was her first sun exposure after birth

Fig. 5.2 XP-A patients (3 years old). Freckle-like pigmented maculae limited on the sun-exposed area. Whenever the patient experiences repeated severe exaggerated sunburn, freckle-like pigmented maculae develop in patients with XP

XP Displaying Abnormal Pigmentary Change Without Exaggerated Sunburn In patients with XP-C, XP-E, and XP-V, freckle-like pigmented maculae gradually progresses without the history of exaggerated sunburn at the sun-exposed skin sites. This pigmented maculae varies in size from miliary to rice grain size, and its color tone is heterogeneous, and its border is indistinct. Patients present with photoaging skin which is unsuitable for their age and symptoms are progressive. In some cases, depigmented maculae are also observed. Multiple skin malignant tumors occur at the sun-exposed body sites at younger age [6]. In patients with XP presenting with only pigmentary change, lifelong cumulative UV dose to which patients exposed, develop their skin symptoms. It often happens that patients become to know that they have XP for the first time when they visit the dermatologist to refer the skin cancers (Fig. 5.3). At that time, they have already received a substantial amount of UV. Recently, parents who experienced their children's exag-

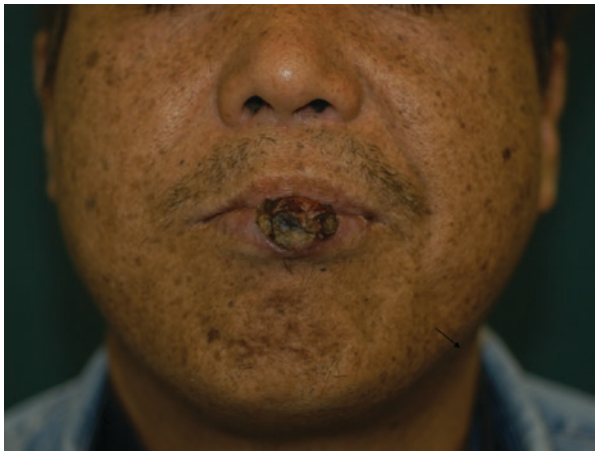

Fig. 5.3 XP-V (55 years old). He visited a hospital consulting the tumor on the lower lip and was referred to us to examine the genetic diagnosis for XP. He has grown up in the island, and he never protected himself from sunlight

gerated sunburn tend to protect their children from sun exposure, while parents whose children display only pigmentary change, but not exaggerated sunburn, easily overlooked the presence of the disease. Therefore, frequency of skin cancer tends to be greater in XP patients with only pigmented freckles, especially XP-C and XP-V, rather than the patients with XP who present with exaggerated sunburn, especially XP-A and XP-D. We will discuss this matter in the latter paragraph.

5.4 Neurological Symptom of XP

In Japan, progressive central and peripheral neurodegeneration occurs in approximately 100% of XP-A patients. For typical development in children patients with XP-A in which the most severe symptoms are found, in their childhood, they can acquire approximately age-appropriate functions, although they show slight delay in their development. The head is held up at an average of 3.5-month-old; rolling over, sitting position, pulling up to standing, and walking are achieved at an average of 6-month-old, 7-month-old, 12-month-old, and 15-month-old, respectively. The peak of physical performance is achieved at about 6 years old, gait disturbance occurs at about 12 years old, and wheelchairs are required at about 15 years old [7]. Deformity in the foot such as contracture in pes equinovarus and pes cavus can be found approximately around 6 years of age [8]. In some cases, it may be complicated with callosity, skin ulcer, contact dermatitis, and tinea pedis due to foot deformity and the use of prostheses. Regarding auditory function, hearing loss occurs at mostly around 4–7 years old [9], and wearing of hearing aid devices is required in the second half of school age. At about 15 years old, auditory function almost nonexistent. Regarding speech function, the peak is achieved at 5–6 years old. The language that they acquired once is maintained in spite of the progressive deafness during the elementary school period. However, they show dysarthria with decline of

intellectual ability and advanced deafness, and their speech function disappears at about 15 years old. Involuntary movement, such as tremor and myoclonus, may be also found in older children. Deep tendon reflexes in the extremities gradually disappear. Progressive sensory-dominant axonal neuropathy is found by peripheral nerve conduction studies. This finding goes along well with our experience that XP patients with progressive neurodegenerative symptoms scarcely express their pain sensation during biopsy procedures. Brain CT and MRI reveal atrophy of all the cerebrum, brainstem, and cerebellum with ventricular dilatation [10, 11]. Currently, we are following up 35 patients with XP-A (0–48 years old), and among them, choke occurs in 18–20 years old, dysphagia may occur between 15 and 19 years old, and they frequently cause aspiration pneumonia. In some cases, tracheotomy may be required because of vocal cord paralysis and larynx dystonia at about 20 years (17–24 years old). Afterward, their general status becomes deteriorated and dies because of pneumonia or sudden death. Figure 5.4 shows the age distribution of patients with XP-A, indicating that in the 1987 survey, patients older than 20 years old were extremely rare, meaning that most patients died before 20 years old. In fact, previously we reported that patients with XP-A mostly die around the age of 20 years, because of aspiration pneumonia and sudden death [9]. However now, life expectancy of patient with XP-A became strikingly longer than that of 25 years

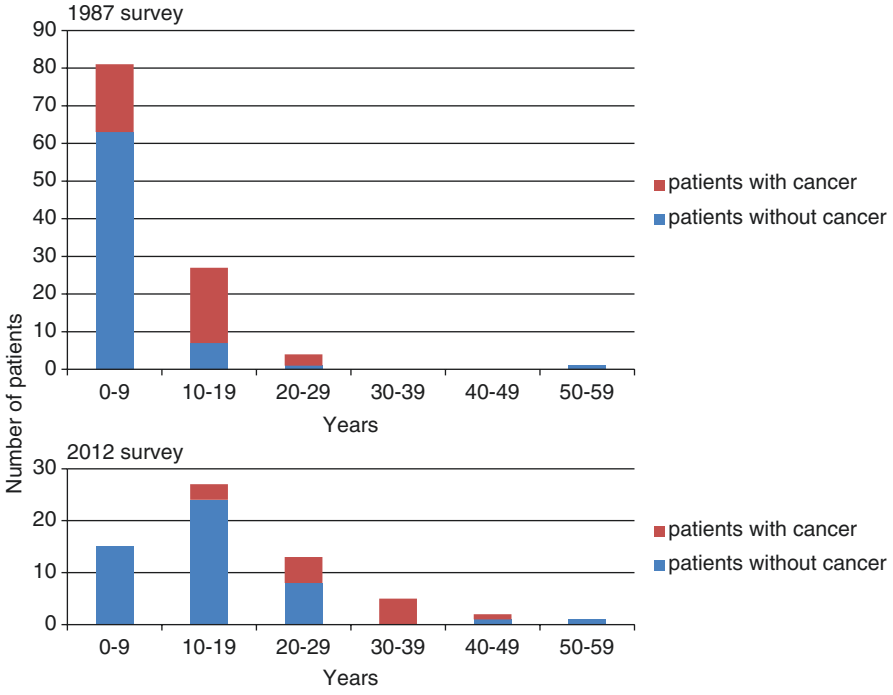

Fig. 5.4 Difference of age distribution of patients with XP-A between 1987 survey and 2012 survey. Life expectancy of patients with XP-A prolonged strikingly

before, and the number of patients with XP-A older than 20 years remarkably increased. The reason for this striking difference is not known. Advances in medical practice may be one reason. Whether strict sun protection contributes this elongation of life expectancy remains to be elucidated. XP-D patients in Western countries develop neurological symptoms frequently. Meanwhile XP-D patients in Japan commonly do not develop neurological symptom, and most of them can do normal work, if any. We speculated this difference because of the difference in the ability of ATP binding due to the difference in the mutation sites [4]. Rarely, some XP-F patients showed neurological symptoms [12].

5.5 Eye Manifestation of XP

In XP patients, the eye tissues exposed to UV are also involved. Therefore, they have lesions in the anterior ocular segment such as conjunctival xerosis and corneal drying, conjunctivitis, keratitis, evagination, corneal ulcer, and decrease of lacrimation. Since most of UVB spectrum does not reach the retina, no morbid change due to direct exposure to UV occurs, and conjunctivitis, corneal neovascularization (pannus), corneal drying, corneal cicatrization, ectropion, blepharitis, pigmentation of the conjunctiva, and cataract may occur. Abnormalities in the optic nerve as neurological symptom of XP may occur, including visual field disturbance and optic neuropathy. There are some reports of malignant tumors as well.

5.6 Genotype-Phenotype Relationship in XP

At least in some complementation groups, genotype-phenotype correlation has been noticed depending on the mutated site in the same responsible gene [4, 9, 13], and it explains the heterogeneity of clinical symptoms within the same complementation groups. In Japanese XP-A, three frequent mutation sites has been known, two nonsense mutation, c. 348 T>A, p.Y116X, and c. 682 C>T, p. R228X, and splicing mutation, IVS3-1G>C. This IVS3-1G>C mutation of *XPA* gene was reported to be the founder mutation among Japanese patients with XP-A, where 86% (25/29) of the patients harbored the homozygous IVS3-1G>C mutation and 14% (4/29) were the compound heterozygote of the founder mutation and the other mutation in *XPA* gene [9]. Consequently, the allele frequency of the founder mutation among Japanese XP-A patients was calculated as 93.1% ($25 \times 2 + 4/29 \times 2$). Later on, using the haplotype analysis, this founder mutation has been shown to originate 120 generation previously, 2400 years before, assuming a 20-year generation interval [14]. In the XP survey in 2012 as well, we could also detect frequency of the homozygous IVS3-G>C mutation as high as 88.7% (49/55) among genetically diagnosed XP-A patients who visited the medical institution during 2010–2012, and

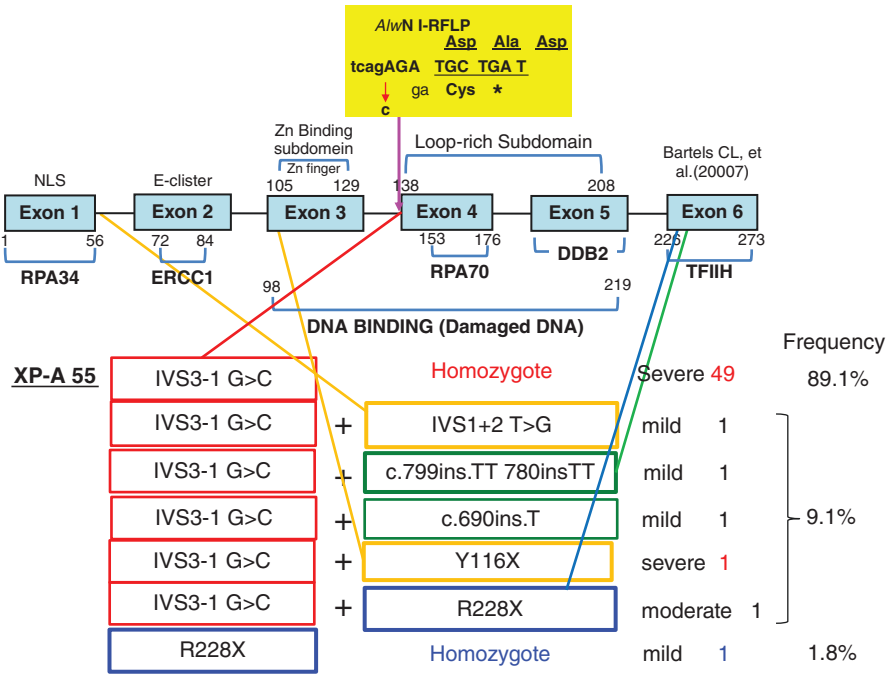

Fig. 5.5 Mutation sites detected in the 2012 survey were indicated with the scheme of XPA protein and its functional sites. Patients having homozygous IVS3-1G>C mutation are most frequently detected (89.1%), and patients having compound heterozygous mutation of IVS3-1G>C and other mutation account for 9.1%

9.1% of the patients (5/55) have compound heterozygote of the founder mutation and other mutations (Fig. 5.5). In this assay, the allele frequency of IVS3-1G>C among Japanese XP-A patients was 93.6% (49 × 2 + 5/55 × 2), almost the same as that of the previous study. This founder mutation at the 3′ splice acceptor site of intron 3 (IVS3-1G>C) induce alternative splicing, creating a stop codon at the second codon of exon 4, which results in no detectable protein production due to nonsense mediated decay and then markedly reduced DNA repair [15]. It goes along with the fact that typical Japanese patients with XP-A present with severe cutaneous symptoms and neurologic symptoms as described above. In the survey of 2012, we evaluated the severity scoring scale regarding neurologic and cutaneous symptoms for the 49 XP-A patients with IVS3-1G>C founder mutation. Among them we found that the patients' age and severity score were well correlated on "swallowing," "gait," "intellectual impairment," and "motivation," being the $R^2 = 0.70874$, 0.62437, 0.63781, and 0.75111, respectively [5]. The natural history of these XP-A patients with founder mutations coincides well with aforementioned typical clinical symptoms of XP-A. To date, several patients with XP-A have been reported in the literature who manifested milder symptoms among Japanese XP-A patients, including XP39OS [16]; two siblings XP3KR and XP4KR [9]; two

siblings XP4KO and XP5KO [17]; XP2NI [18]; XP17HM, XP21HM, XP42HM, and XP43HM [19]; and XP113KO [20]. Among them all patients but XP39OS harbored IVS3-1G>C mutation, the known founder mutation, in one allele and the other mutations in the other allele. XP2NI, who manifested mild skin symptoms with slight sun sensitivity without skin cancer development or hearing loss at the age of 11 years, harbored G to C one base change at the last nucleotide of exon 5 in addition to the founder mutation, and the former mutation produced three types of aberrant mRNA, lacking 7 nucleotides at the end of exon 5, lacking entire exon 5, and lacking exons 3, 4, and 5. Western blot of XP2NI cells indicated that small but significant amount of a truncated protein was produced and the size of the protein coincides the protein lacking the seven nucleotides in exon 5 [18]. XP17HM, XP21HM, XP24HM, XP42HM, and XP43HM were newly diagnosed as XP-A at the age of 35 years old, 30 years old, 40 years old, and 45 years old, respectively. They presented with mild neurological symptoms and a history of moderate sun sensitivity. In addition to the IVS3-1G>C founder mutation in one allele, XP17HM had c.690insT in the exon 6 of the other allele and the rest of the three had 779insTT 780insTT in the exon6 of the other allele [19]. On the other hand, XP3KR, XP4KR, XP4KO, and XP5KO, having the founder mutation, IVS3-1G>C, in one allele and R228X in exon 6 in the other allele, manifested milder symptoms than typical IVS3-1G>C homozygotes [9, 17, 21], but they exhibited sun sensitivity since their childhood, and their fist consultation to the dermatologists was under 5 years old, and XP4KO developed BCC at the age of 13 years old, indicating these cases' severity was moderate. Note that the severity score of the XP5KO is far apart from the average score of the XP-A patients with founder mutation (Red circle in Fig. 5.6). XP39OS, who showed no neurological abnormalities at the age of 7 years, but areflexia of the patellar tendons at 11 years old, was diagnosed as XP-A by means of cell fusion technique before the discovery of *XPA* gene. In addition, fibroblasts form XP39OS revealed sensitivity to UVR but two times resistance as those of typical XP-A, XP3OS, homozygous IVS3-1G>C [16]. Genetic diagnosis indicated that XP39OS harbored homozygous R228X, which is the second frequent gene mutation identified among Japanese patients with XP-A and the only common mutation found in and outside Japan [22]. Previously, we reported that homozygous mutation of R228X is the most common type of mutation in Tunisian patients with XP-A, and they rather manifested milder cutaneous and neurologic symptoms despite their living environment was not so protective from UVR. Comparison of the genotype-phenotype correlation in patients with XP-A has suggested that those with mutations closer to the C-terminal coding region of the *XPA* have milder neurological and cutaneous symptoms. Figure 5.5 shows the putative function of its each domain of XPA protein and the mutation sites and their clinical severity of the XP-A patients enrolled in the survey of 2012. Cells from patients with milder symptoms in the literature, XP2NI, XP17HM, XP21HM, XP42HM, and XP43HM, showed a very small but traceable amount of XPA protein lacking a part of exon 5 or exon 6, which explains the residual repair functions observed in these patients. Furthermore recently, cases of XP-A having homozygous IVS4 + 8A>G manifesting unusually

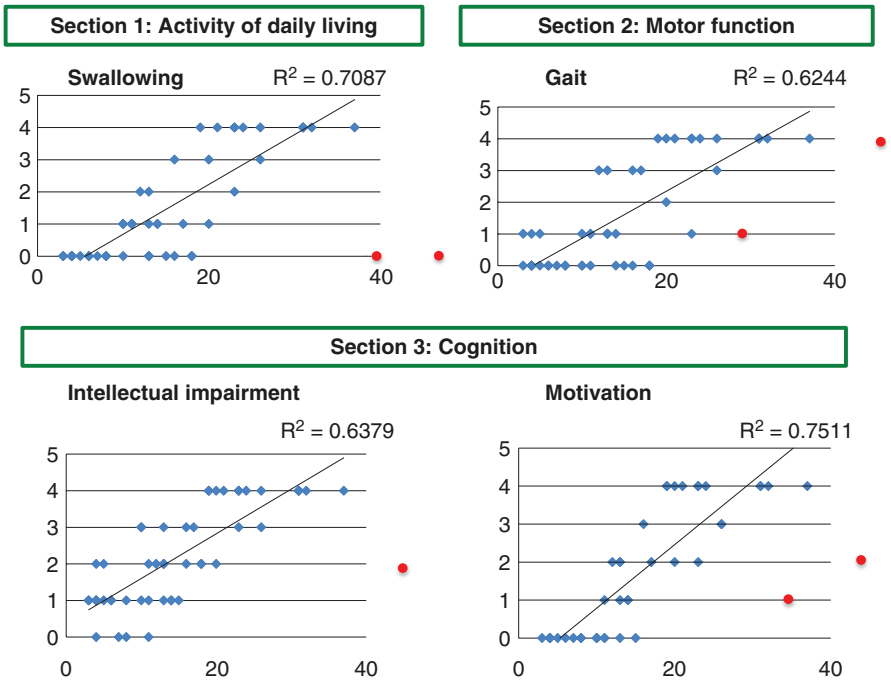

Fig. 5.6 Correlation of the severity index of patients with XP-A having homozygous Japanese XPA founder mutation, IVS3-1G>C, and patients' ages (Modified from the reference Masaki et al. [21]). The severity score of a milder case, a compound heterozygotes of the founder mutation, and R228X was plotted in red circle. Horizontal axis indicates years, and vertical axis indicates severity scores. Scores in swallowing stand for 0, normal; 1, rare choking; 2, occasional choking; 3, requires soft food; and 4, requires nasogastric or gastrostomy tube, respectively. Scores in walking stand for 0, normal; 1, mild difficulty; 2, moderate difficulty, but require little or no assistance; 3, severe disturbance of walking, requiring assistance; and 4, cannot walk at all, even with assistance. Scores in intellectual impairment stand for 0, normal; 1, mild (consistent impairment with partial recollection of events with no other difficulties); 2, moderate difficulty handling complex problems; 3, severe impairment with problems; and 4, unable to make judgments or solve problems. Scores in motivation stand for 0, normal; 1, lacking in energy, does not restrict activities; 2, lacking in energy, restricts hobbies, and interests; 3, lacking in energy, restricts routine activities; and 4, unable to carry out any task

mild symptoms have been reported [23]. Takahashi et al. [24] also reported an unusually mild XP-A patient having homozygous c.529G>A in exon 4, which creates a new cryptic donor site in exon 4, resulting in aberrant splicing. In both cases, the authors indicated that the patient's cells produce a very small amount of leaky normal XPA protein, although majority of the aberrant splicing product is nonfunctional truncated XPA protein. These findings indicate that even a very small amount of protein and even partially dysfunctional protein could ameliorate clinical symptoms. Analysis for those who manifested mild clinical symptoms gives us an important insight how we approach to treat XP-A patients.

Unlike the cases in Western countries, most Japanese patients with XP-D do not present with neurological symptom [4]. Before the identification of the responsible gene for XP-D, *ERCC*2, when genetic diagnosis for XP was not covered by health insurance, patients with XP-D without neurological abnormalities had failed to be diagnosed since we did not think of XP-D as a diagnosis for XP patients without neurologic abnormalities and often tentatively diagnosed as "possible XP-V" without detailed DNA repair test. However, after "genetic diagnosis for XP" became covered by health insurance, we were referred to many adult cases with possible XP, and among them several patients with XP-D were included. Thereafter, we gradually came to know that most Japanese patients with XP-D do not manifest neurologic abnormalities, which may increase the chance of diagnosis for XP-D greater than previously. To date, 11 Japanese patients with genetically diagnosed XP-D have been reported, and among them at least at present, few of them manifested neurologic abnormalities, and the onset age of skin cancer development was after 20 years [25]. Using molecular simulation, it has been hypothesized that the difference in the clinical symptoms between Japanese patients and patients from Western countries could be attributed to the difference in ATP binding ability of the mutated XPD proteins; R683W XPD cells, frequently observed in Western countries, do not bind with ATP, whereas R683Q, frequently observed in Japan and the Middle East, retain some, although reduced, binding ability with ATP [4]. Since XPD protein functions as ATP-dependent helicase, it may explain the heterogeneity within the same complementation group to a certain extent.

5.7 Cancer Frequency and Age Onset of Skin Cancer in Japanese Patients with XP: Results from the Survey for the XP Patients in 2012 vs 1988

Using the 1988 XP survey and the 2012 XP survey conducted in Japan with 25 years interval, we analyzed the cancer frequency and its onset age in Japanese patients with XP and compared the present results with those of 25 years ago. On the results of 1988 survey, we could exclude the effect of sun protection on the development of skin cancers, since most people at that time did not practice strict sun protection. And the survey 2012 may show the outcome of performance of strict sun protection. A survey for patients with XP was conducted by the Research Committee for Intractable Diseases supported by the Japanese Ministry of Health, Labour and Welfare. Finally, we could obtain clinical information of 170 patients from 57 institutions who visited the medical institutions, and they were analyzed and previously reported focusing on the neurologic symptoms [5]. Here using the same survey, we compared the cancer frequency and age onset of cancer development between the present results and those of 25 years ago [3]. In 1988, the frequency of skin cancer in XP patients was very high in all complementation groups and variant

Table 5.3 Frequency of skin cancer in xeroderma pigmentosum patients

		2012 [5]					1988 [3]				
		Total number of patients	Number of patients with cancer (%)	Numbers of patients with (%)			Total number of patients	Number of patients with cancer (%)	Numbers of patients with (%)		
				BCC	SCC	MM			BCC	SCC	MM
NER-deficit type	A	63	14 (22)	10 (16)	2 (3.2)	1 (1.8)	117	41 (34)	35 (85)	20 (49)	5 (12)
	C	2	0	0	0	0	5	7 (88)	5 (71)	4 (57)	3 (43)
	D	5	4 (80)	3 (60)	1 (20)	0	5	4 (67)	2 (50)	2 (50)	0
	F	1	1 (100)	1 (100)	0	0	12	3 (25)	2 (67)	1(33)	0
Variant type	V	22	19 (86)	10 (45)	7 (32)	8 (36)	87	40 (46)	29 (73)	14 (35)	9 (23)
Total		93	38 (41)	24 (26)	10 (11)	9 (10)					

(Table 5.3). In 1988, as high as 34% (41/117) of patients with XP-A developed skin cancers, and the onset was younger than 10 years old (Table 5.4), while the survey 2012 revealed that the frequency of skin cancer in XP-A strikingly decreased and age onset of developing skin cancer was later (Tables 5.3 and 5.4). This striking reduction of frequency of skin cancer in XP-A is largely attributed to the early detection and early diagnosis by dermatologists. Since the late 1980s, scientists and dermatologists have educated the patients and patients' families about sun protection, in addition to early diagnosis of the disease. Owing to these efforts, the frequency of skin cancer with XP-A has strikingly decreased.

Figure 5.4 represents the age distribution of patients with XP-A of the two surveys. It clearly shows that the cancer-developing age shifted toward the older age and the ratio of cancer-having patients reduced very much. Patients less than 5 years old in the 1988 survey are now patients in 20–29 in the present survey, and obviously the cancer frequency of these patients is lower than the patients in the 1988 survey, indicating the importance of educating sun protection. Also in patients with XP-D and variant, cancer-developing age is higher in the present results than that of 1988 results. In the survey 1988, the tendency can be observed that the higher frequency of melanoma in complementation group C and variant type. This tendency is more apparent in XP variant type in the present survey. The frequency of melanoma is strikingly high, reaching a level similar to or even more than squamous cell carcinoma (SCC), whereas in XP-A patients, the frequency of BCC is the highest, in both surveys, which frequency distribution is similar to that of normal control. Patients with XP-V do not manifest exaggerated sunburn, and in most cases, they

Table 5.4 Age of onset of skin cancer in xeroderma pigmentosum patients

		2010–2012					In 1988 [3]				
		Total number of patients	Number of patients with cancer (%)	Age of onset (year) and number of patients			Total number of patients	Number of patients with cancer (%)	Age of onset (year) and number of patients		
				BCC	SCC	MM			BCC	SCC	MM
NER-deficit type	A	63	14	16.8 (10)	17 (2)	22 (1)	117	41	9.3 (35)	8.2 (20)	7.5 (5)
	C	2	0	–	–	–	5	4	14.8 (5)	8.3 (4)	11.0 (3)
	D	5	4	40.3 (3)	55.0 (1)	–	5	3	31.0 (2)	42.5 (2)	–
	F	1	1	42.0 (1)	–	–	12	3	43.4 (2)	64 (1)	–
Variant type	V	22	19	46.9 (10)	56.2 (7)	54.2 (8)	89	41	40.8 (30)	42.0 (14)	46.8 (9)

are diagnosed as XP after adolescence, which may result in a high cumulative dose exposure to UV in the patients with XP-V. We should note that patients with XP-V have almost normal level of NER but are deficient in TLS.

5.8 Diagnosis, Treatment, and Patient Care

Early definite diagnosis by genetic analysis before skin cancers develop is crucial for the patient management, and performance of strict sun protection is essential. Brief summary of diagnostic procedure is shown in Fig. 5.7. Clinical symptoms are varied depending on the lifestyle that patients used to behave. Therefore, clinical inspection, history taking, and DNA repair test are important. Regarding DNA repair test, unscheduled DNA synthesis (UDS) has been used, and recently, UDS using non-RI such as bromodeoxyuridine (BrdU) or 5-ethynyl-2′-deoxyuridine (EdU) is also used. Recently flow cytometry-based quantification of removal of photolesions (6-4)PP was shown to correlate very well with UDS, and this method enables to measure cell cycle-specific NER, which is useful for the diagnosis of XP-V, since in XP-V cells, DNA repair is slower specifically in S-phase [26]. Phototesting is useful when the patient has possible "XP-D, or X′-F, and XP-G" to obtain objective sign of "exaggerated sunburn," since only history taking is not so reliable, but the highest dose for minumem erythema dose (MED) measurement for possible XP may be used below 100 mJ/cm^2. However, patients' clinical symptoms strongly suggest XP-A, the severest type, and we directly perform sequencing, without measuring MED. After the identification of the responsible gene for XP-A, and the presence of the founder mutation in Japanese patients with

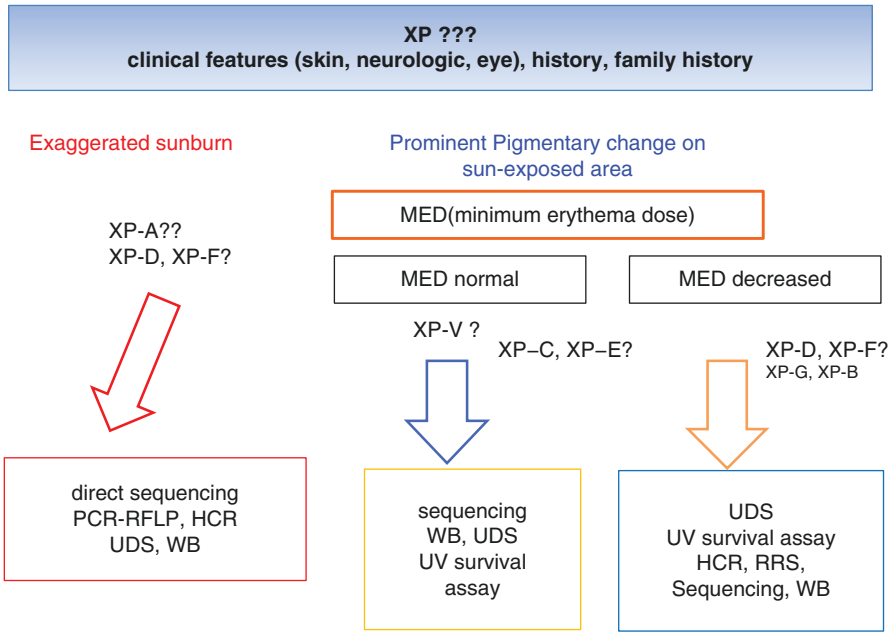

Fig. 5.7 Diagnostic procedures for each complementation groups of XP and variant type. When history of exaggerated sunburn exists, XP-A, XP-D, and XP-F are probable, and sunburn reaction is remarkable with blister formation, perform directly *XPA* sequencing, and otherwise perform measurement of MED and unscheduled DNA synthesis using fibroblasts derived from patients. If exaggerated sunburn is not obvious and freckle-like pigmentation is restricted on the sun-exposed area, then Western blot for POLH and POLH sequencing is required for the definite diagnosis

XP-A, the genetic diagnostic system for XP-A has been rapidly established. As for XP-V, patients do not manifest exaggerated sunburn but present only gradually increasing freckle-like pigmentation, and definite diagnosis before skin cancer develops is crucial. Diagnosis can be done by using immunoblot for POLH [27] and *POLH* direct sequencing because unscheduled DNA synthesis is within normal limit in XP-V cells. In Japan, genetic diagnosis for XP was approved as an advanced medical practice in 2008 based on its performance in our institution and eventually became covered by national health insurance starting from 2012. Accordingly, dermatologists became to refer to patients with possible XP for genetic diagnosis more easily, which increased the detection frequency of the disease for those that used to have overlooked 20 years ago. Previously, the frequency of the first-cousin marriage in parents of Japanese patients with XP was approximately 30% [31], while the frequency in the survey 2012 was only 11%, which reduced the frequency of XP slightly. However, the frequency of XP-A seems to remain at a certain level of frequency in Japan, because the frequency of the heterozygote carrier of XP-A founder mutation, IVS3-1G>C in *XPA*, is 1 out of 113 among the Japanese population [2].

5.8.1 Sun Protection

XP patients have to perform strict and complete protection from UV to prevent progression of dyschromatosis on the sun-exposed area and prevent the development of skin cancer. The eye and lips, especially lower lips, should be also protected from sun exposure. Specific protections are as follows:

1. Apply a sunscreen formulation with high sun protection factor and high protection grade of UV-A (PA) to the skin before going out; wear a cloth with long sleeves, trousers, protective clothing from UV, and glasses for UV protection.
2. Apply a film offering UV protection to windows and use a sunshade curtain to protect from light when the windows are opened.
3. When the patient is in school age, apply a film for UV protection to the windows in the school and be careful to avoid direct exposure to UV during outdoor activities and attending school.

Skin cancers, if developed, should be excised by like punch biopsy. Early case detection and early excision are principles. It has been also reported that imiquimod is useful for actinic keratosis and basal cell carcinoma and interferon are useful for melanoma [28]. Since there is also a report that delayed awakening from anesthesia occurs in XP patients, it is desirable to perform treatment early before general anesthesia is required. Probably because of the neurological dysfunction, patients in teen ages are mostly resistant to pain sensation, and local anesthesia using lidocaine can be used when excising small tumors.

For patients with XP, occasion in which chemotherapy is required seems to be infrequent, but sometimes patients need chemotherapy. Some investigators reported that cells derived from XP are sensitive to doxorubicin and other chemotherapeutic reagent [29]. Recently, side effect of cisplatin reportedly appeared to be severer in XP patients than non-XP patients [30].

5.8.2 Care for Neurological Symptoms

There is no useful evidence-based therapy since the pathogenesis for neurodegeneration of XP is still unknown. However, rehabilitation can be performed to deal with motor impairment and intellectual disability associated with neurodegeneration. Since patients' peak of neurologic development is achieved at about 5–6 years old, it is desirable to bring the peak of development to be higher by early rehabilitation. Since hearing loss often occurs around 4–7 years old, hearing test should be conducted at regular intervals to know an appropriate timing of wearing a hearing aid device.

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