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Clinical manifestation and genetic analysis of familial rare disease genodermatosis xeroderma pigmentosum**Renni Yuniati¹, Nydia Rena Benita Sihombing², Donny Nauphar³, Budi Tiawarman⁴, Diah Shinta Kartikasari¹, Meira Dewi⁵, Sultana MH Faradz^{2,*}**

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SUMMARY Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by hypersensitivity of the skin to ultraviolet radiation and other carcinogenic agents. This ailment is characterized by increased photosensitivity, skin xerosis, early skin aging, actinic keratosis, erythematous lesions, and hyperpigmentation macules. In this serial case report, we presented four cases with XP from two families in Indonesia. Both families were referred from rural referral health centers, and each family has two affected siblings. They had freckle-like pigmentation on the face, trunk, and extremities, which progressed since childhood. One patient of family 2 died because of an infectious disease. Histopathological examination using cytokeratine (CK), CD10, and Ber-EP4 staining from available tissue biopsy of one affected case of family 1 identified basal cell carcinoma (BCC) on the cheek and melanoma on the right eye. Mutation analysis found *ERCC2*, c2047C>T and *XPC*, c1941T>A in the first and second families, respectively. We suppose that this is the first case report of XP in Indonesia that incorporates clinical examination, genetic analysis, and extensive histopathological examination, including immunohistochemistry staining, and a novel pathogenic variant of *XPC* was found in the second family.

Keywords xeroderma pigmentosum, familial, autosomal recessive, photosensitivity, XPC, mutation

1. Introduction

Xeroderma pigmentosum (XP) is characterized by increased photosensitivity, skin xerosis, early skin aging, actinic keratosis, erythematous lesions, and hyperpigmentation macules (1,2). Another feature is abnormal lentiginosis (freckle-like pigmentation due to increased numbers of melanocytes) on sun-exposed areas. This is followed by areas of increased or decreased pigmentation, skin aging, and multiple skin cancers if the individuals are not protected from sunlight (3). These manifestations are due to cellular hypersensitivity to ultraviolet (UV) radiation resulting from a defect in DNA repair. The mutation that causes XP affects one of eight XP-related genes, including *XPA*, *XPB*, *XPC*, *XPD*, *XPE*, *XPF*, *XPG*, and *XPV* (XP variant), which encodes the nucleotide excision repair (NER) mechanism (4,5).

XP cases can be found in almost every place in the

world with variable prevalence (6,7). In the United States, this condition affects one person per one million population (6,8). In Europe, this case affects up to 2.3 persons per one million live births. In the Middle East, the prevalence of XP is around 15-20 persons per one million population (6-8). Consanguinity itself is highly related to the incidence of XP. Therefore, XP cases are higher in areas where consanguinity is common, including North Africa and the Middle East. Consanguinity is an important factor in autosomal recessive disorders (8). Up to 92.8% of XP patients in Libya had consanguinity history (7).

XP is a rare autosomal recessive inherited genodermatosis with only a few cases worldwide. Most people are not aware of this condition, which is why XP patients are often neglected and do not receive medical assistance. Seven different genes (labeled A to G), which have deficient excision repair of ultraviolet radiation-

induced DNA damage, are involved. The genes *XPA*, *XPC*, and *XPE* are required for DNA lesion recognition. The *XPB* and *XPD* gene products are helicases mediating local strand unwinding, and *XPF* and *XPG* specify structure-specific endonucleases performing strand incision on either side of the lesion. There exists an additional relatively mild "variant" form of XP caused by a defective ability to convert newly synthesized DNA after UV irradiation.

Advanced molecular techniques using next-generation sequencing (NGS) might help in the diagnosis of XP because of its ability to test multiple XP genes in a single analysis. Here we present two Indonesian families with several children affected by XP in Indonesia.

2. Case Report

2.1. Patients' description

We received four patients from referral physicians from two areas: Salatiga, Central Java, and Tasikmalaya, West Java. These patients were from two unrelated families and had XP. The first family had one son and two daughters, and both of the latter (IV:3 and IV:4) were affected by XP (Figure 1A). The second family had three daughters and two sons, and the third daughter (III:3) and first son (III:5) were affected by XP (Figure 1B). Both families had no history of consanguinity, but they came from an isolated rural area, and none of the parents or other siblings was affected by this disease. The second family had a history of miscarriage, but we did not know whether the miscarriage was due to XP or not. The study was approved by the local IRB (Health Research Ethics Committee, Faculty of Medicine, Diponegoro University, no. 456/EC/KEPK/FK UNDIP/X/2019). Written informed consent was obtained from all parents.

All of these patients were referred to us by rural referral physicians from primary health-care centers with the typical characteristic appearance of XP, including freckle-like pigmentation on the face, trunk, and extremities, which progressed since childhood. Owing to generalized skin lesions and photosensitivity, all patients had dropped out of elementary school. They did not seek

medical treatment at the first occurrence of skin lesions, but all of them came to primary health-care centers when they had already developed further abnormalities such as ocular, hearing, and neurological problems.

2.2. Physical examination

In the first family, the oldest daughter (IV:3; 25 years old) was presented to us with freckle-like pigmentation. These pigmentations occurred during childhood and continued to occur on areas that have been more extensively exposed to sunlight, including the face, neck, upper part of the trunk, and extremities. She and her family initially did not seek medical treatment until she developed ocular abnormality and cheek tumor. We have been notified by the physician from the primary health-care center regarding this case and invited them to come to Dr. Kariadi referral hospital. We found uneven, localized brown spots in sun-exposed areas along with cancerous patches on the cheek. The patient also has a prolapsed right eyeball and cataract on the left eye. We found gait disturbance and hearing loss on both ears. After further pathological examination and tests, we confirmed that the ocular abnormality was malignant melanoma, which affects the ocular region, and the tumor on her cheek was confirmed as basal cell carcinoma (BCC). On the basis of the pedigree, we then screened the other siblings of IV:3 and found that her sister (IV:4; 23 years old) had the same uneven, localized brown spots in sun exposed areas. There was a cancerous patch on the cheek similar to patient IV:3, however, now it remains only as a black scar on her right cheek due to previous surgery. The clinical conditions of these patients are shown in Figure 2.

In the second family, the first son (III:5; 25 years old) and the third daughter (III:3; 21 years old) both sought medical attention from the primary health-care center because of a palpebral mass growth. They were referred to our clinic at Diponegoro National University Hospital, Semarang, because of the characteristic freckle-like pigmentation found on these patients. Similar to the first two patients, we found black generalized spots on the face, upper part of the trunk (of individual III:5), and extremities, all of which are directly exposed to

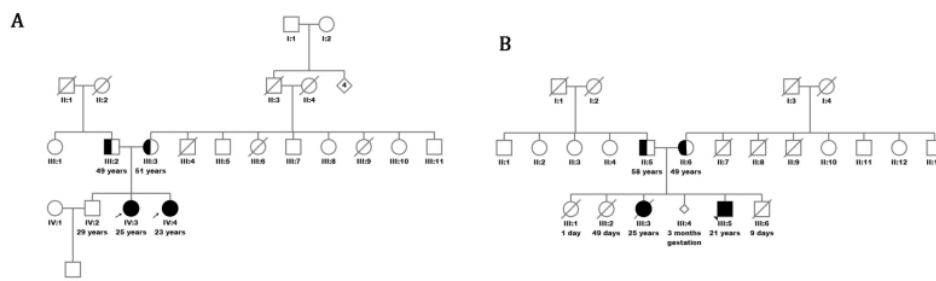


Figure 1. (A) Pedigree of the first family. The last two daughters (IV:3 and IV:4) were affected with XP. (B) Pedigree of the second family. Individuals III:3 and III:5 (marked in black) were affected with xeroderma pigmentosum.



Figure 2. The two daughters of the first family. (A) The first daughter (IV:3), which has the characteristic appearance of XP, with an ocular abnormality confirmed as malignant melanoma and a lesion on the cheek confirmed as basal cell carcinoma. (B) The second daughter (IV:4) showed freckle-like pigmentation and cancerous patch on the cheek.



Figure 3. The children of the second family who are affected by XP. (A & B) Note the freckle-like pigmentation and ocular abnormality on both patients. (C & D) Close-up of the freckles around the extremities area.

the sun in their daily activities. We found a cancerous patch on the lips and palpebrae of both patients. Both of the patients also had dry eyes and cataract in their eyes, and the daughter (III:3) has blepharitis on her eye. We diagnosed both patients as having XP (Figure 3). However, during the follow-up period, individual III:3 passed away because of an infectious disease. We did not know whether the death was related to the malignancy or not.

2.3. Histopathological investigations

We analyzed a 0.5 cm skin sample taken from the upper right arm of the first daughter of the first family (individual IV:3). On microscopic analysis with HE staining, the tissue is lined with keratinized squamous

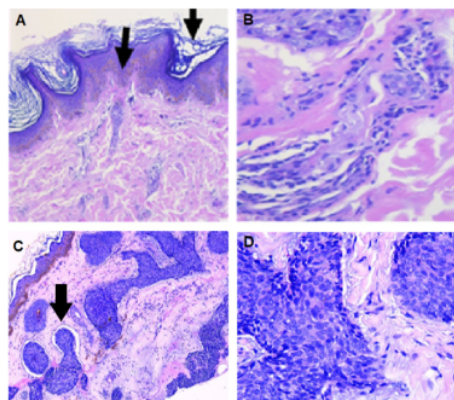


Figure 4. (A) Histopathological image of the macules in HE staining and 100× magnification showing keratinized layered squamous epithelial cells on the edge, epidermal hyperkeratosis and follicular plugging (see short arrow), and increased numbers of melanin pigment (see long arrow). (B) The macules showing lymphocytes and perivascular histiocytes (HE 400×). (C) Histopathological image of the cheek biopsy sample showing groups of tumor mass with cleft between the tumor mass and adjacent tissue (arrow) HE, 100×. (D) Closed-up image of the cells showing round oval nuclei, pleomorphic, hyperchromatic, coarse chromatin, and several prominent nucleoli (400× magnification).

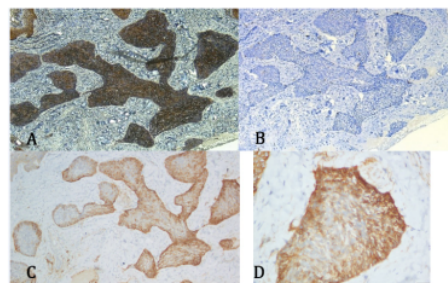


Figure 5. (A) IHC images showing positive pancytokeratin stain on tumor cells (100× magnification). (B) Negative HMB45 stain on tumor cells (100×). (C) Positive CD10 staining on palisading tumor cells (100×). (D) Positive BER-EP4 on tumor cells (400×).

epithelium, with follicular plugging, spongiosis, and increased melanin pigmentation on some areas of the tissue (Figure 4A). Some of the rete ridges were elongated. The dermal layer consists of fibrocollagenous stroma with scattered lymphocytes and perivascular histiocytes (Figure 4B). Hair follicles, eccrine glands, and sebaceous glands are visible. There were no signs of malignancy in the tissue. On the basis of the pathological anatomy examination, these findings confirmed the XP diagnosis.

Additionally, we analyzed a biopsy sample taken from the patient's right cheek. We found a layered keratinized squamous epithelium with follicular plugging, on microscopic analysis. The dermis layer consists of edematous fibro-collagen connective tissue stroma, with histiocytes and lymphocytes scattered in

the tissue. Skin adnexa and groups of cells with oval round nuclei, pleomorphic, hyperchromatic, coarse chromatin, and several prominent nucleoli were also found (Figure 4C and 4D). These cells are arranged in a palisading pattern on the edge, with a cleft between the tumor mass and adjacent connective tissue stroma, with scattered melanin pigmentation. These descriptions are suggestive of BCC metastasis. Furthermore, analysis of immunohistochemistry (IHC) markers on the sample found positive cytokeratin (CK) on the tumor cells (Figure 5A), negative HMB45 marker on the tumor cells (Figure 5B), positive CD10 (Figure 5C) on the palisading tumor cells, and positive Ber-EP4 stain (Figure 5D) on the tumor cells. These descriptions confirm the diagnosis of BCC.

We found that the lesion in her cheek was a metastasized BCC based on the histopathology examination. Because she also had a similar looking lesion on her palpebra, the BCC most likely metastasized from that region. Her right eye was also surgically resected because of malignancy. Frozen section taken from her right eye and histopathology examination using IHC showed groups of round, oval, and polygonal cells, pleomorphic, hyperchromatic with coarse chromatin, prominent nucleoli and wide eosinophilic cytoplasm. It also demonstrated clear cell boundaries and was scattered with brownish pigment, neutrophils, lymphocytes and histiocytes in fibrous connective tissue and necrotic regions. There were no malignancies found in the optic nerve. These findings confirm the diagnosis of malignant melanoma of the eye. The histopathology examination shows that the cheek lesion is a BCC that metastasized from another site. Because the patient also had a similar looking lesion on her palpebra, the BCC most likely metastasized from that region. The right eye of patient IV:3 was surgically removed because of malignancy. A frozen section taken on her right eye confirmed that the eye lesion is malignant melanoma.

On the laboratory examination of family 2, we found that patient III:5 had serum vitamin D25OH < 4 ng/mL, which is indicative of vitamin D deficiency. Pathological examination of the skin tissues from the second family was not performed because the samples cannot be collected from the inaccessible very rural village.

2.4. Mutation analysis

Exome sequencing was performed for patients from two families at the Genome Diagnostics Laboratory of the Department of Human Genetics, Radboud University Medical Centre, Nijmegen, Netherlands. A pathogenic variant of the *ERCC2* gene (Chr19(GRCh37):g.45855610G>A; NM_000400.3: c.2047C>T, p.(Arg683Trp)) was discovered in the two daughters of the first family, and a nonsense pathogenic variant of the *XPC* gene (NM_004628.4), c.1941T>A, p.(Tyr647^{*}) was identified in patient III:5 of the second

family. The variant of the *ERCC2* gene was reported elsewhere (9). Meanwhile, the pathogenic variant of *XPC* has not been reported previously, but it is considered a pathogenic variant because it is a nonsense variant. All patients showed homozygous mutation with normal parents. Therefore, we assumed that the inheritance pattern in our patients was autosomal recessive. We summarized the clinical findings, histopathology, and genetic analysis of all patients in Table 1.

2.5. Clinical treatment

We applied sunblock lotion and administered vitamin D3 supplementations to all of the patients. The sunblock lotion, smeared thinly on skin areas exposed to sunlight, is applied twice a day. Sunblock lotion can protect the skin from damage due to sun exposure, thus preventing the appearance and progression of XP lesions. However, supplementation with vitamin D3 is needed to overcome the lack of endogenous vitamin D3 production caused by the sunblock lotion (2,10). The progress of their condition was not much better than before treatment because of late treatment and management.

3. Discussion

The genetic mutation that occurs in XP patients causes a defect in the NER mechanism, and UV radiation from sun exposure will cause DNA damage due to the defective repair mechanism, changes in skin cells, and formation of carcinogenic photoproducts, which eventually leads to the formation of malignancies in the skin.

The patients from unrelated families in this serial case report exhibited freckle-like pigmentation on the face, trunk, and extremities since childhood. Patient IV:3, the older sister from the first family, started to show pigmentation of the skin during childhood, which worsened as time progressed. She developed ocular abnormality and malignancy on the cheek. The pigmentation was also worse in areas more frequently exposed to sunlight, such as the face, neck, upper part of the trunk, and extremities. Patient IV:4, the younger sister, also showed similar pigmentation in similar areas as her sister's that started during childhood. Her pigmentation, however, seemed milder, and she had yet to develop more severe complications like her sister. Both patients III:3 and III:5 of the second family exhibited similar symptoms of darker freckle-like pigmentation on the face, neck, upper trunk, and extremities, and complaints of palpebral mass growth.

As XP is a disease caused by the accumulation of damage over time, the milder phenotype of the younger sister may be attributed to several factors, such as age, amount of UV exposure, and the extent of the defect of the DNA repair mechanism. The amount of DNA damage accumulated due to increased photosensitivity is

Table 1. Summary of clinical findings, histopathology, and genetic analysis of all patients

Case/Family	Clinical features				Histopathological Examination	Gene mutation
	Freckle-like pigmentation	Cutaneous malignancy	Ophthalmologic abnormalities	Neurological abnormalities		
Case 1/1 (Patient IV:3)	Uneven brown spots (Localized) in sun-exposed area	Cancerous lumps (patches) on the cheek	Prolapse right eyeball, ectropion. Cataract left eye	Gait disturbance, Hearing loss	Frozen section from right eye and palpebra: melanoma maligna. Biopsy sample from right cheek: suggestive of BCC metastasis. Immunohistochemistry of right cheek sample: Cytokeratine positive, Negative HMB45, Positive CD10 on the palisading tumor cells, and Positive Ber-EP4 stain. Skin tissue: Suggestive of Xeroderma Pigmentosum	Pathogenic variant of the <i>ERCC2</i> gene (Chr19(GRCh37):g.45855610G>A; NM_000400.3: c.2047C>T, p.(Arg683Trp))
Case 2/1 (Patient IV:4)	Uneven brown spots (Localized) in sun-exposed area	Cancerous lumps (patches) on the cheek	Dry eye	N/A	Skin tissue: Suggestive of Xeroderma Pigmentosum	Pathogenic variant of the <i>ERCC2</i> gene (Chr19(GRCh37):g.45855610G>A; NM_000400.3: c.2047C>T, p.(Arg683Trp))
Case 1/2 (Patient III:V)	Black spots evenly (Generalized)	Cancerous patch on the lips and palpebrae	Dry eye, cataract	N/A	N/A Passed away	N/A
Case 2/2 (Patient III:3)	Black spots evenly (Generalized)	Cancerous patch on the lips and palpebrae	Cataract, blepharitis	N/A	Skin tissue: Suggestive of Xeroderma Pigmentosum	Nonsense pathogenic variant of the <i>XPC</i> gene (NM_004628.4): c.1941T>A, p.(Tyr647*)

*Remarks: Not all examinations are available for all patients (eg. For Vitamin D measurement) due to socioeconomic limitations which hinders the patient to take all laboratory examinations

less at a younger age than at a more advanced age (11). The amount of UV exposure also plays an important role in the severity of XP as UV light induces the formation of thymine dimers from covalent linkages between consecutive pyrimidine bases along the nucleotide chain. The amount of thymine dimers increases with increased exposure to UV and coupled with defective DNA damage repair may result in a more severe clinical presentation compared with patients exposed to less UV. The extent of the defect in the NER mechanism may also affect clinical severity.

Mutations affecting the promoter regulatory elements may affect the transcription rate and may have a less severe impact in the defect of the NER mechanism when compared to mutations affecting RNA translation, such as mutations at the initiation codon, mutations causing frameshift, and mutations causing nonsense codons. Meanwhile, in a missense mutation such as that of family 1, nucleotide substitution occurred on the putative nuclear location signal of the *ERCC2* protein, thus limiting the amount of functional protein, which makes it insufficient for DNA repair (9). Malignancy of the skin of the palpebral and cheek, as seen in patient IV-3 of family 1 in this case report, might be the result of the defect in repairing genetic changes. In advanced cases, XP may cause malignancies such as BCC, squamous cell carcinoma, and malignant melanoma (12).

Approximately 40% to 80% of patients with XP will have ocular problems, which is caused by UV-induced DNA changes on conjunctival, corneal, and palpebral epithelial cells (13). One of the early signs of ocular involvement in XP patients is photophobia, and the most frequently found ocular abnormalities caused by XP are conjunctivitis, corneal neovascularization, and dry eyes, up to loss of sight (14). Long-term sun exposure can cause neoplasm of eyes and its supporting structures, including epithelioma, squamous cell carcinoma, and melanoma (15). Patient IV:3 developed ocular disorders due to XP with histopathological findings of malignant changes of palpebral and periocular skin, malignant melanoma of the eyeball, and ocular manifestations that arise from neurological degenerations. The skin around the eye formed cicatricial changes or skin malignancies that need to be excised. All of the patients in the case series developed ocular abnormality with varying degrees of severity, with one confirmed melanoma both clinically and microscopically.

Around 30% of all patients with XP will experience neurological deficits (2,3,16). The neurological deficits and problems that might occur in patients with XP include isolated hyperreflexia, progressive mental retardation, sensorineural deafness, and seizures (17). Neurological degeneration may manifest in the eye as a small pupillary size, nystagmus, and strabismus (2,18). Neurological deficit in patients with XP mostly occurs in XP-A, XP-B, XP-D, and XP-G patients (19). Our patient with XPD from the first family also suffered from

hearing and vision loss.

Besides ocular malignancies, patient IV:3 also developed dermal malignancies in the form of BCC. This is a common occurrence in XP patients, due to the high predisposition for developing malignancies. Patients with XP have 10,000-fold risk of developing BCC and 2,000-fold risk of developing melanoma compared to normal people (18). Dermatological malignancies in XP patients are difficult to prevent, especially in regions with abundant amounts of sun rays such as in the Middle East and in Asia (20).

Advances in molecular techniques such as NGS have massively helped in diagnosing XP faster and in having a higher throughput. For example, exome sequencing for dermatological conditions comprises 619 genes, five of which (*XPA*, *XPC*, *DDDB2*, *POLH*, and *ERCC2*) are relevant for XP diagnosis (2,5,19). Results from massively parallel sequencing for the XP gene panel revealed an *ERCC2* c.2047C>T mutation, which caused an amino acid change from arginine to tryptophan at position 683 in both daughters from the first family and a nonsense causing mutation at c.1941T>A of the *XPC* gene in the male patient of the second family. The *ERCC2* gene codes the XP group D (XPD) protein, an ATP-dependent DNA helicase that is important in the NER mechanism. A previous *ERCC2* mutation study in Vietnam with a missense mutation (c.2048G>A; p.Arg683Gln) and nonsense mutation (c.1354C>T; p.Gln452*) showed that patients experienced severe sunburn and irritation after unprotected sun exposure, hypopigmentation, dry skin, and skin peeling. Patients also experience ocular damage, photophobia, and dry eyes. The fibroblasts in the Vietnamese cohort showed a defect in the NER pathway (1). The defect affects the DNA repair mechanism that occurs in XP, which renders it more sensitive to UVA radiation (21). A study of Comorian and Pakistani cohorts revealed that the most common variant of mutation was in the *XPC* c.2251-1G>C mutation, with some patients showing the *POLH/XPV* variant (22). The Comorian cohort is unique because of its geographical and historical background. The Comorians live in an isolated area to avoid invasion from other populations, and their people are segregated into different villages based on social status, which leads to a high frequency of consanguineous marriages (22,23). Different founder variants are present in specific parts of the world. For *XPA* mutations, there are three different founder variants for India, Japan, and Tunisia. In the Indian population, the mutation that occurs related to the *XPA* gene is c.335_338delTTATinsCATAAGAAA (11,24). In Japan, the mutation that occurs in the *XPA* gene is c.390-1G>C, and in Tunisia, the mutation that occurs on the *XPA* gene is p.Arg228Ter (11). In North Africa, the mutation of *XPC* occurs in c.1643_1644delTG, and in an Iraqi Jewish population, the mutation of p.Arg683Gln can be found among xeroderma pigmentosum patients in that

region. *POLH* mutation can be found in a Tunisia/North African population, Japanese population, and Basque/Northern Spain population. *POLH* mutation in Tunisia occurs as the deletion of exon 10; in Japan, it occurs as c.490G>T (splice site variant); p.Ser242Ter; p.Glu306Ter and c.1661delA; and in Basque/Northern Spain, it occurs as c.764+1G>A (11). The pathogenic variant found on *XPC* in our patient has not been reported previously. Although mutation analysis of the parents have not been done, we have identified two families with two affected sibs and normal parents, suggesting autosomal recessive inheritance.

Management of XP is based on early diagnosis, follow-up, and minimization of unprotected sun exposure. These are important to reduce or prevent the occurrence of dermatological malignancies in patients with XP, which will improve their quality of life and increase their survival rate. Photoprotection can be achieved using UV-absorbent films on windows, UV-absorbent clothing, sunglasses, and sunscreens. However, all of the patients encountered in this report were not aware of their condition, hence the lack of a photoprotective effort. The rarity of the condition, lack of awareness, and knowledge regarding this condition played important roles in the progress of the disease for all patients. With a prevalence of 1 in 10,000 to 30,000, this condition is rarely seen, and information regarding XP is not widely available to medical care providers managing this disease. Owing to the nature of the cumulative damage, most patients do not have any serious complaints during early life and do not feel the need to check themselves until more complications are present, such as ocular, hearing, and neurological problems.

Another possible reason why the disease is often overlooked is that XP is passed down in an autosomal recessive manner, which sometimes skips generations, causing parents to be unaware of their carrier status and their affected children. Vitamin D supplementation given later during the course of the disease may not be very helpful. Genetic counseling regarding the progressivity of the diseases, pattern of inheritance, and risk of having more children with the same condition was given to the family. Because XP is inherited in an autosomal recessive manner and both families live in an isolated area, further analysis is warranted to evaluate the possibility of a founder mutation.

To the best of our knowledge, this is the first comprehensive clinical and genetic analysis report on patients with XP in Indonesia, with a novel pathogenic variant of *XPC* found in the second family. This case report highlights the importance of a rare disease that is manageable but often overlooked because of its rarity, inheritance pattern, and late onset of severe symptoms. New advances in molecular biology techniques can help diagnosis faster with a higher throughput, but they are still not available in low resource settings.

4. Conclusion

This is the first case report of XP in Indonesia that incorporates clinical examination, genetic analysis, and histopathological examination including immunohistochemistry staining, and a novel pathogenic variant of *XPC*, c.1941T>A was found in the second family. Diagnosis of XP has been made using history taking, physical examination, pedigree analysis, and histopathology and mutation analysis using advanced molecular techniques.

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