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Genotype–phenotype associations in a robust cohort of 69 patients with xeroderma pigmentosum across Türkiye: a multicentre study

Defne Baskurt,[1] Şule Altıner,[2] Tuğba Atcı,[3] Bengü Nisa Akay,[4] Nilay Duman,[5] Burhan Engin,[6] Ayşenur Botsalı,[7] Serkan Yazıcı,[8] Mehmet Bugrahan Duz,[9] Esra Adışen,[10] İrem Özdemir,[10] Deniz Aksu Arıca,[11] Leyla Baykal Selçuk,[11] Pınar Kaderi,[6] Ayça Aykut,[12] Zeynep Topkarcı,[13] Asude Durmaz,[12] Yıldız Gürsel Ürün,[14] Vefa Aslı Erdemir,[15] Ferhan Bulut Demir,[16] Işıl Karaarslan,[5] Deniz Yücelten,[16] Sibel Ersoy Evans[17] and Seçil Vural[18]

[1]School of Medicine, Koç University, Istanbul, Türkiye
[18]Department of Dermatology and Venereology, Koç University Hospital, İstanbul, Türkiye

Correspondence: Seçil Vural. Email: secilsaral@gmail.com

The current affiliation for D.B. is Department of Dermatology, University of California, San Francisco, CA, USA.

The current affiliation for M.B.D. is Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.

D.B. and S.A. contributed equally as co-first authors.

See Appendix 1 for the complete list of author affiliations.

Abstract

Background Xeroderma pigmentosum (XP) is a rare DNA damage repair disorder. Seven distinct complementation groups and an XP variant form have been identified; however, limited literature exists on the genotype–phenotype correlation in XP.

Objectives To explore the manifestations of XP variants in patients from Türkiye.

Methods Our multicentric investigation involved 69 patients with XP from 52 unrelated families across 12 centres in Türkiye. Clinical examinations and genetic tests were conducted to assess the correlation between variants and disease characteristics.

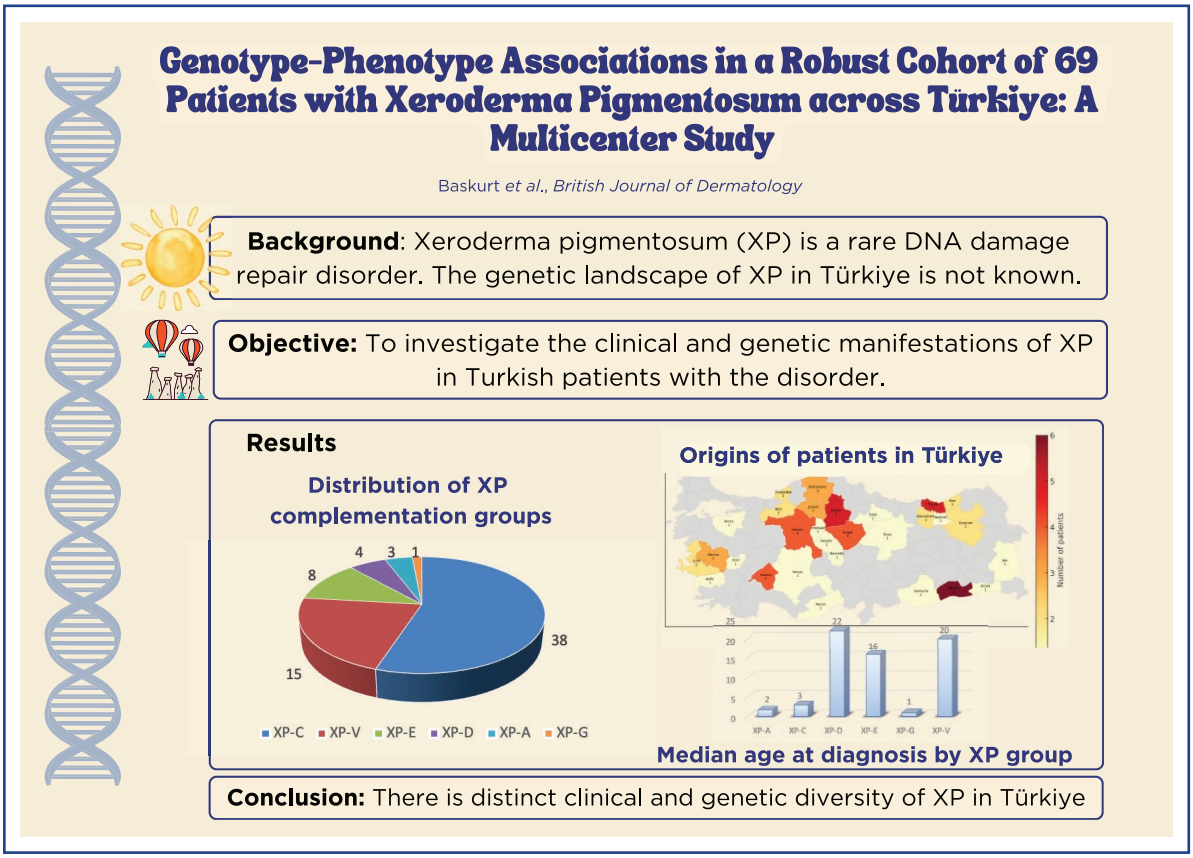
Results Of the XP groups, XP-C was the most prevalent (n=38; 55%), followed by XP-variant (n=15; 22%), XP-E (n=8; 12%), XP-D (n=4; 6%), XP-A (n=3; 4%) and XP-G (n=1; 1%). XP-B and XP-F were not identified. Median patient age at diagnosis was 9 years (interquartile range 2–19), although this varied significantly according to complementation group, with XP-D and XP-V diagnoses occurring later. Genetic analyses revealed 30 novel variants, including one in a patient with XP/Cockayne syndrome complex. Despite the link of XP-D to neurological degeneration, none of the patients showed neuropathy, while three patients with XP-E had neurological involvement. Notably, 26% (n=18) of patients reported no consanguinity, yet a significant proportion (n=11/18) had distant family members with XP.

Conclusions We found unique clinical patterns and diversity among complementation groups in Turkish patients with XP. Future investigations should focus on functional characterization of the novel variants, preferably through assays like unscheduled DNA synthesis, to determine their potential impact on DNA repair mechanisms and their implications for improved patient care.

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Graphical Abstract



Lay summary

Xeroderma pigmentosum is a rare genetic condition where the body does not properly repair the damage caused by sunlight. People with the condition often develop severe sunburns after a short time in the sun. Over time, they are much more likely to develop certain skin cancers at a young age. The condition can also cause other changes to the skin and cancers of different organs. In some cases, it can cause problems with the nervous system.

In this study, we looked at how different genetic changes affect the way the condition shows up in patients from Türkiye. We included 69 patients from hospitals in Türkiye. Dermatologists (skin doctors) examined the patients and genetic testing was done to find out which type of XP the patients had. Most patients examined had a type of the condition called 'XP-C'. The age at which patients were diagnosed with the condition varied greatly by the type of xeroderma pigmentosum they had. We also found new gene variants (what we used to call 'genetic mutations'). This means the condition can look very different depending on a person's specific genetics.

We need more research to better understand the effects of the new gene variants found and how this may help improve patient care.

What is already known about this topic?

- Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder characterized by defective DNA repair, photosensitivity, early-onset skin cancers and variable neurodegeneration.
- Seven complementation groups and an XP-variant form have been identified, with genotype influencing cancer risk and clinical severity; however, the genotype–phenotype correlations remain understudied.

What does this study add?

- This study identifies XP-C as the most common complementation group among Turkish patients with XP and reveals 30 novel variants, including one in a patient with XP/Cockayne syndrome complex.
- Our data reveal diverse clinical patterns, including unexpected neurological outcomes in patients with XP-D and XP-E and variability in age at diagnosis among complementation groups.

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Xeroderma pigmentosum (XP) is a rare autosomal recessive DNA damage repair disorder presenting with photosensitivity, pigmentary changes in sun-exposed skin and early-onset skin cancers, especially basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma.[1] XP prevalence varies globally, with incidences of 1 in 1 million reported in the USA, 45 in 1 million in Japan and 17.5 in 1 million in Middle Eastern countries, where consanguinity is higher.[1] Its prevalence in Türkiye remains uncertain.

Limited studies exist on the genotype–phenotype relationship in XP. To date, seven distinct complementation groups (XP-A, XP-B, XP-C, XP-D, XP-E, XP-F, XP-G) and an XP variant (XP-V) form have been identified. These forms are associated with biallelic pathogenic or likely pathogenic variants of *XPA*, *ERCC3*, *XPC*, *ERCC2*, *DDB2*, *ERCC4*, *ERCC5* and *POLH*.[1,2] XP-C is the most common subtype found in the USA, Europe and Africa, while XP-A is dominant in Japan and China. Clinical manifestations vary based on variant type and sun protection habits. Short ultraviolet (UV) exposure can cause severe sunburn in patients with XP-A, XP-B, XP-D, XP-F and XP-G, with erythema persisting for weeks in two-thirds of these patients. Patients with XP-C, XP-E and XP-V may have minimal photoinduced erythema and may tan normally.[1–3] Patients with XP are also at an increased risk of internal malignancies, most frequently involving the central nervous system, the haematological system, the thyroid gland and the sex organs, particularly in those with XP-C.[4,5] Neurodegeneration is mostly linked to XP-A and XP-D, while XP-C and XP-E rarely show neurological involvement.[1,6]

Several families and patients with XP have been reported from Türkiye, but in most cases the diagnosis was based solely on clinical features without genetic confirmation. Only a few case reports and series include proper genetic analyses, and, overall, the spectrum of XP types in Türkiye remains poorly characterized.[7–11] This multicentre study investigated the clinical and genetic features of patients with XP in Türkiye.

Patients and methods

The Turkish Dermatological Society's Dermato-oncology and Pediatric Dermatology study groups were contacted, and 12 centres across Türkiye participated. Inclusion required genetically confirmed XP. Details of the genetic analyses can be found in Appendix S1 (see Supporting Information).[12,13]

During the study, all patients were examined by dermatologists, with additional consultations arranged as needed. At diagnosis, all had been evaluated by neurology and ophthalmology, and individuals continued follow-up in these departments as necessary.

Each patient underwent a full dermatological and dermoscopic examination, and completed a standardized questionnaire covering demographics, family history, initial symptoms, age at onset, sun-exposed skin changes, cancer history, disease course, treatments, surgeries and sun-protection behaviours. A systemic physical examination was also performed. Photosensitivity was assessed using the sunburn severity scale proposed by Sethi *et al.* (0 = normal, 1 = mild, 2 = moderate, 3 = severe),[14] applied here for standardization, despite Türkiye's higher UV exposure. Patients with a score > 0 were classified as being photosensitive. Neurological, ophthalmic and comorbidity data were retrieved retrospectively from medical records.

Results

The demographic data and clinical features of the 69 included patients are summarized in Table S1 (see Supporting Information), with selected patients shown in Figure S1 (see Supporting Information). Female participants accounted for 52% (n = 36) and male participants accounted 48% (n = 33) of the study cohort. Median patient age was 23 years [interquartile range (IQR) 16–33]. Patient age ranged from 2 to 54 years and 36% (n = 25) were ≤ 18 years old. Median age at clinical diagnosis was 9 years (IQR 2–19).

Consanguinity was reported for 51 patients (74%). XP was present in 64% (n = 44) of families, mainly in siblings (n = 34/44; 77%). three had affected cousins, five an aunt or uncle, and three more distant relatives. The geographical distribution of the participants is shown in Figure S2 (see Supporting Information).

The most common initial cancer was BCC (n = 28/69; 41%), followed by SCC [including SCC *in situ*; n = 25/69 (36%)]. Basosquamous cell carcinoma occurred in 3% (n = 2/69) of patients. Three patients (XP-C25.1, XP-D2.1, XP-V2.2) developed oral mucosal SCC. Melanoma was the first cancer in 17% (n = 12/69) of patients, including three with melanoma *in situ* (MIS). Ten patients (14%) had no skin cancer (median age 22 years; IQR 8–32). Median age at first nonmelanoma skin cancer (NMSC) was 12 years (IQR 8–22) and 14 years (IQR 12–28) at first melanoma.

Photosensitivity (score > 0) was present in 64% (n = 44/69) of patients, all of whom had early-onset pigmentary changes (see Table S1). Neurological involvement affected 14% (n = 10/69) of patients, including sensorineural hearing loss [SNHL; n = 6 (9%)], ataxia (n = 3; 4%) and incontinence (n = 1; 1%); 8 patients (12%) had neurodevelopmental delay. Ophthalmopathy occurred in 57% (n = 39/69) of patients, with ocular malignancies in 20% (n = 14/69). Solid organ cancers occurred in 4% (n = 3) of patients, including thyroid papillary carcinoma, vertebral angiosarcoma, and leiomyosarcoma. Autoimmune or metabolic comorbidities were present in 29% (n = 20) of patients. Group-specific characteristics are shown in Table 1.

Sun protection measures included sunscreen (n = 58), protective clothing (n = 33), hats or visors (n = 21) and sunglasses (n = 16). UV-filtered window films (n = 8) and home schooling (n = 2) were less frequently used.

Of the 69 patients enrolled, genetics revealed that 38 (55%) had XP-C, 15 (22%) had XP-V, 8 (12%) had XP-E, 4 (6%) had XP-D, 3 (4%) had XP-A and 1 (1%) had XP-G. No patients with XP-B or XP-F were identified. Variant schematics for *XPA*, *DDB2*, *XPC*, *ERCC5*, *ERCC2* and *POLH* are provided in Figure 1. Homozygosity was present in 96% (n = 66/69) of patients, consistent with high consanguinity; three patients were compound heterozygotes. Thirty novel variants were detected in 53 of 69 patients (77%). Of these variants, 27 (90%) were deemed likely to be pathogenic, 1 was a variant of unknown significance (VUS), 1 was unequivocally pathogenic and 1 deep intronic novel variant was considered likely to be benign but had clinical features of XP (Table 2).

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Table 1 Summary of patient characteristics according to xeroderma pigmentosum (XP) complementation group

Complementation group	Overall cohort	XP-A subgroup	XP-C subgroup	XP-D subgroup	XP-E subgroup	XP-G subgroup	XP-V subgroup
Patients	69 (100)	3 (4)	38 (55)	4 (6)	8 (12)	1 (1)	15 (22)
Families	52 (100)	3 (6)	29 (56)	3 (6)	7 (13)	1 (2)	9 (17)
Female sex	36 (52)	3 (100)	19 (50)	2 (50)	2 (25)	0 (0)	10 (67)
Age (years), median (IQR)	23 (16–33)	17 (9–23)	18 (12–28)	37 (33–42)	21 (16–39)	34 (NA)	32 (28–36)
Age at clinical diagnosis (years), median (IQR)	9 (2–19)	2 (1–3)	3 (2–10)	22 (8–35)	16 (13–19)	0.6 (NA)	20 (10–27)
Consanguinity	51 (74)	2 (67)	29 (76)	2 (50)	7 (88)	1 (100)	10 (67)
Family member with XP	44 (64)	1 (33)	25 (66)	3 (75)	3 (38)	0 (0)	12 (80)
Skin cancer	59 (86)	1 (33)	34 (89)	3 (75)	8 (100)	1 (100)	12 (80)
BCC	50 (72.4)	1 (33)	30 (79)	2 (50)	8 (100)	0 (0)	9 (60)
SCC	33 (48)	0 (0)	18 (47)	2 (50)	6 (75)	0 (0)	7 (47)
Melanoma, LMM, MIS	26 (38)	0 (0)	19 (50)	2 (50)	0 (0)	1 (100)	4 (27)
Age at first skin cancer (years), median (IQR)	13 (8–24)	9 (NA)	9 (7–15)	35 (10–37)	18 (10–20)	29 (NA)	25 (17–31)
Photosensitivity	44 (64)	3 (100)	24 (63)	4 (100)	4 (50)	1 (100)	8 (53)
Age at freckling (years), median (IQR)	3 (2–6)	1 (0–3)	2 (2–3)	3 (1–14)	12 (4–15)	5 (NA)	6 (3–8)
Solid organ tumour	5 (7)	0 (0)	4 (11)	1 (25)	0 (0)	0 (0)	0 (0)
Neurological involvement	13 (19)	3 (100)	6 (16)	0 (0)	2 (25)	1 (100)	1 (7)
SNHL	6 (9)	1 (33)	4 (11)	0 (0)	0 (0)	1 (100)	0 (0)
Ataxia/difficulty walking	3 (4)	2 (67)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)
NDD	8 (12)	3 (100)	3 (8)	0 (0)	1 (13)	0 (0)	1 (6.7)
Incontinence	1 (1)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Difficulty swallowing	1 (1)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Epilepsy	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Lower extremity contracture	1 (1)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)
Comorbidities	19 (28)	0 (0)	13 (34)	1 (25)	3 (38)	1 (100)	1 (7)
Autoimmune	5 (7)	0 (0)	5 (13)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolic	4 (6)	0 (0)	2 (5)	1 (25)	0 (0)	0 (0)	1 (7)
Developmental	7 (10)	0 (0)	3 (8)	0 (0)	2 (25)	1 (100)	1 (7)
Allergic	2 (3)	0 (0)	1 (3)	1 (25)	0 (0)	0 (0)	0 (0)
Metabolic	4 (6)	0 (0)	3 (8)	0 (0)	1 (13)	0 (0)	0 (0)
Ophthalmopathy	39 (57)	3 (100)	22 (58)	4 (100)	4 (50)	1 (100)	5 (33)
Ocular malignancy	14 (20)	1 (33)	9 (24)	0 (0)	4 (50)	0 (0)	0 (0)
Other[a]	34 (49)	3 (100)	20 (53)	4 (100)	1 (13)	1 (100)	5 (33)

Data are presented as *n* (%) unless otherwise stated. BCC, basal cell carcinoma; IQR, interquartile range; LMM, lentigo maligna melanoma; MIS, melanoma *in situ*; NA, not available; NDD, neurodevelopmental delay; SCC, squamous cell carcinoma; SNHL, sensorineural hearing loss; XP-A, XP complementation group A; XP-C, XP complementation group C; XP-D, XP complementation group D; XP-E, XP complementation group E; XP-G, XP complementation group G; XP-V, xeroderma pigmentosum variant. [a]Other ophthalmopathies include xerophthalmia, cataracts, keratoconus, lagophthalmos, ectropion, entropion, trichiasis and others (see Table S1).

XP-A

Three patients with XP-A (OMIM #278700) from different families were identified, all of whom had novel, likely pathogenic homozygous variants (Table 2). All were female patients and diagnosed early, at 1, 2.5 and 1.5 years of age, respectively, due to high photosensitivity scores and lentigines, but only patient XP-A1.1 developed skin cancer (BCC on the neck, nose, shoulder and arm). Neurological involvement included walking difficulty and incontinence in XP-A1.1; SNHL, ataxia and swallowing difficulty in XP-A2.1; and neurodevelopmental delay in all three. Ocular pathologies included xerophthalmia (XP-A1.1), exposure keratopathy and xerophthalmia (XP-A2.1), and conjunctival intraepithelial SCC and premalignant melanocytic proliferation (XP-A3.1).

XP-C

We identified 38 patients with XP-C (OMIM #278720) from 29 families; half of these patients were female individuals. Median age was 18 years (IQR 12–28), and median age at diagnosis was 3 years (IQR 2–10). All had early freckling in sun-exposed areas (median age of onset 2 years; IQR 2–3). Most (n=34/38; 89%) developed skin cancers, with a median age at first cancer of 9 years (IQR 7–15). Neurodegeneration occurred in 13% (n=5/38) of patients and 32% (n=22/38) experienced ocular involvement. Almost all patients (n=36/38; 95%) were homozygous and 27 (71%) carried novel variants (Table 2).

Patient XP-C1.1 had a novel nonsense variant. Diagnosed at the age of 2 years, he did not use sun protection until the age of 23 years, resulting in multiple NMSCs and severe myopia. Siblings XP-C2.1 and XP-C2.2 had lagophthalmos and lower eyelid symblepharon; XP-C2.1 also had uveitis, blepharitis and trichiasis, whereas patient XP-C2.2 had ectropion. Patient XP-C3.1, aged 17 years, carried heterozygous variants (1 novel) and developed 2 melanomas and 12 NMSCs; comorbidities included systemic lupus erythematosus and pulmonary sclerosing pneumocytoma.

Ten patients had frameshift variants, mostly novel; all were diagnosed before they were 5 years old. All developed NMSCs before the age of 10 years, with the exception of patients XP-C14.1 and XP-C17.2, probably due to their early diagnosis and strict photoprotection. Patients XP-C9.1, XP-C15.1, XP-C20.1, XP-C21.1 and XP-C27.1 had novel splice-region variants; only patient XP-C20.1 developed melanoma. Patient XP-C28.1 was heterozygous for a pathogenic splice-region variant and a novel VUS affecting splicing. Patients XP-C10.1, XP-C11.1, XP-C11.2, XP-C13.1, XP-C19.1 and XP-C19.2 had novel missense variants.

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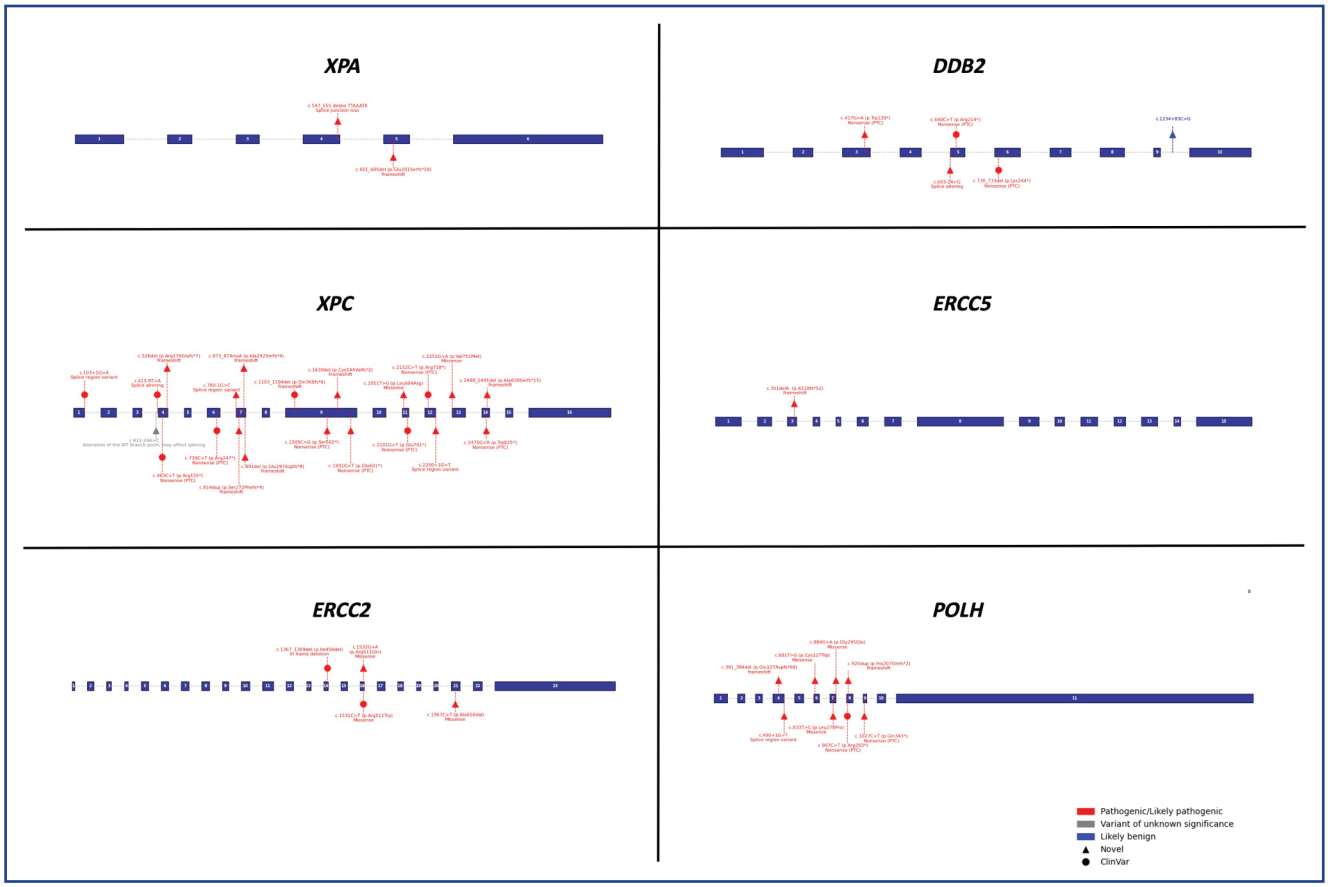


Figure 1 Schematic representation of identified variants of *XPA*, *DDB2*, *XPC*, *ERCC5*, *ERCC2* and *POLH*. Exons are shown as blue boxes and introns as lines. Variants are colour-coded: pathogenic/likely pathogenic (red), variant of unknown significance (blue) and likely benign (dark blue). Novel variants are indicated by triangles and ClinVar-annotated variants by circles. Mutation positions are based on coding DNA sequences (cDNA), with corresponding amino acid changes indicated where applicable.

XP-D

Four individuals with XP-D (OMIM #278730) from three families were identified; half were female patients. Median age was 37 years (IQR 33–42) and median age at diagnosis was 22 years (IQR 8–35). All reported photosensitivity and pigmentary changes at sun-exposed sites, with lentigines beginning at a median of 3 years (IQR 1–14). Patients XP-D1.1, XP-D2.1 and XP-D2.2 had homozygous missense variants, while patient XP-D3.1 carried a compound heterozygous in-frame deletion and a novel missense variant (Table 2).

Siblings XP-D2.1 and XP-D2.2, from consanguineous parents, shared a novel missense variant. Patient XP-D2.1 was diagnosed at the age of 10 years after BCC and later developed SCC at 33 years of age; patient XP-D2.2 was diagnosed at the age of 6 years with generalized lentigines but has not developed malignancies. Patients XP-D1.1 and XP-D3.1 had freckling in infancy but were diagnosed in their fourth decade with pigmentary changes and no initial cancers; patient XP-D1.1 developed MIS and BCC at 37 years of age. Patient XP-D3.1 developed SCC *in situ* and MIS in his late thirties, with a milder course possibly related to lifelong photoprotection. None had neuropathy.

XP-E

We identified eight patients with XP-E (OMIM #278740) from seven families; six of these individuals were of male sex. Median age was 21 years (IQR 16–39); median age at diagnosis was 16 (IQR 13–19). All developed freckling (median age of onset 13 years, IQR 4–15). Patients showed mild changes at sun-exposed sites and no melanomas. Four had no photosensitivity, one had mild photosensitivity and three had severe photosensitivity. All carried homozygous variants (Table 2).

The oldest patients were 54-year-old twin brothers (XP-E1.1 and XP-E1.2) with changes at sun-exposed sites seen at 15 years of age, diagnosis of XP at 19 years of age and the development of SCC at 20 years of age; both later had multiple BCCs and severe photosensitivity. Patient XP-E2.1 developed lentigines at 1 year of age, had a photosensitivity score of 3, was diagnosed with XP at the age of 9 years and by 13 years of age had SCC and BCC at the right medial canthus, with SCC invading the orbit. This patient had multiple comorbidities and died from metastatic disease at the age of 14 years.

Novel variants occurred in patients XP-E4.1 and XP-E7.1. Patient XP-E4.1, diagnosed at the age of 17 years with

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Table 2 Genetic profiles of 69 patients with xeroderma pigmentosum (XP) included in this study

Patient[a]	Complementation group	Gene affected	Transcript	Variant	Zygosity	Consequence	Reference	Classification (ACMG criteria)
XP-A1.1	A	*XPA*	NM_000380.4	c.601_605del p.Glu201Serfs*18	Homozygous	Frameshift (PTC + 18aa)	Novel	Likely pathogenic
XP-A2.1	A	*XPA*	NM_000380.4	c.601_605del p.Glu201Serfs*18	Homozygous	Frameshift (PTC + 18aa)	Novel	Likely pathogenic
XP-A3.1	A	*XPA*	NM_000380.4	c.547_555 delins TTAAATA	Homozygous	Splice junction loss	Novel	Likely pathogenic
XP-C1.1	C	*XPC*	NM_004628.5	c.2475G>A p.Trp825*	Homozygous	Nonsense (PTC)	Novel	Likely pathogenic
XP-C2.1/2.2	C	*XPC*	NM_004628.5	c.2152C>T p.Arg718*	Homozygous	Nonsense (PTC)	ClinVar	Pathogenic
XP-C3.1	C	*XPC*	NM_004628.5	c.739C>T p.Arg247*	Compound heterozygous	Nonsense (PTC)	ClinVar	Pathogenic
				c.2051T>G p.Leu684Arg		Missense	Novel	Likely pathogenic
XP-C4.1	C	*XPC*	NM_004628.5	c.891del p.Glu297Aspfs*8	Homozygous	Frameshift (PTC + 8aa)	Novel	Likely pathogenic
XP-C5.1	C	*XPC*	NM_004628.5	c.2488_2491del p.Ala830Serfs*15	Homozygous	Frameshift (PTC + 15aa)	Novel	Likely pathogenic
XP-C6.1	C	*XPC*	NM_004628.5	c.463C>T p.Arg155*	Homozygous	Nonsense (PTC)	ClinVar	Pathogenic
XP-C7.1	C	*XPC*	NM_004628.5	c.2101G>T p.Glu701*	Homozygous	Nonsense (PTC)	ClinVar	Pathogenic
XP-C8.1	C	*XPC*	NM_004628.5	c.526del p.Arg176Glufs*7	Homozygous	Frameshift (PTC + 7aa)	Novel	Likely pathogenic
XP-C9.1	C	*XPC*	NM_004628.5	c.2250+1G>T	Homozygous	Splice region variant	Novel	Likely pathogenic
XP-C10.1	C	*XPC*	NM_004628.5	c.2251G>A p.Val751Met	Homozygous	Missense	Novel	Likely pathogenic
XP-C11.1, XP-C11.2	C	*XPC*	NM_004628.5	c.2051T>G p.Leu684Arg	Homozygous	Missense	Novel	Likely pathogenic
XP-C12.1, XP-C12.2, XP-C12.3	C	*XPC*	NM_004628.5	c.1801G>T p.Glu601*	Homozygous	Nonsense (PTC)	Novel	Likely pathogenic
XP-C13.1	C	*XPC*	NM_004628.5	c.2051T>G p.Leu684Arg	Homozygous	Missense	Novel	Likely pathogenic
XP-C14.1	C	*XPC*	NM_004628.5	c.814dup p.Ser272Phefs*4	Homozygous	Frameshift (PTC + 4aa)	Novel	Likely pathogenic
XP-C15.1	C	*XPC*	NM_004628.5	c.780-1G>C	Homozygous	Splice region variant	Novel	Likely pathogenic
XP-C16.1, XP-C16.2, XP-C16.3	C	*XPC*	NM_004628.5	c.1505C>G p.Ser502*	Homozygous	Nonsense (PTC)	Novel	Likely pathogenic
XP-C17.1, XP-C17.2	C	*XPC*	NM_004628.5	c.1630del p.Cys544Valfs*2	Homozygous	Frameshift (PTC + 2aa)	Novel	Likely pathogenic
XP-C18.1	C	*XPC*	NM_004628.5	c.873_874insA p.Ala292Serfs*4	Homozygous	Frameshift (PTC + 4aa)	Novel	Likely pathogenic
XP-C19.1, XP-C19.2	C	*XPC*	NM_004628.5	c.2051T>G p.Leu684Arg	Homozygous	Missense	Novel	Likely pathogenic
XP-C20.1	C	*XPC*	NM_004628.5	c.2250+1G>T	Homozygous	Splice region variant	Novel	Likely pathogenic
XP-C21.1	C	*XPC*	NM_004628.5	c.2250+1G>T	Homozygous	Splice region variant	Novel	Likely pathogenic
XP-C22.1	C	*XPC*	NM_004628.5	c.413-9T>A	Homozygous	Splice altering	ClinVar	Pathogenic
XP-C23.1	C	*XPC*	NM_004628.5	c.2152C>T p.Arg718*	Homozygous	Nonsense (PTC)	ClinVar	Pathogenic
XP-C24.1	C	*XPC*	NM_004628.5	c.1103_1104del p.Gln368fs*6	Homozygous	Frameshift (PTC + 6aa)	ClinVar	Pathogenic
XP-C25.1, XP-C25.2	C	*XPC*	NM_004628.5	c.1103_1104del p.Gln368fs*6	Homozygous	Frameshift (PTC + 6aa)	ClinVar	Pathogenic
XP-C26.1	C	*XPC*	NM_004628.5	c.413-9T>A	Homozygous	Splice altering	ClinVar	Pathogenic
XP-C27.1	C	*XPC*	NM_004628.5	c.2250+1G>T	Homozygous	Splice region variant	Novel	Likely pathogenic
XP-C28.1	C	*XPC*	NM_004628.5	c.103+1G>A	Compound heterozygous	Splice region variant	ClinVar	Pathogenic
				c.413-24A>C		Alteration of the WT branch point, may affect splicing	Novel	VUS
XP-C29.1	C	*XPC*	NM_004628.5	c.413-9T>A	Homozygous	Splice altering	ClinVar	Pathogenic
XP-D1.1	D	*ERCC2*	NM_000400.4	c.1531C>T	Homozygous	Missense	ClinVar	Likely pathogenic
XP-D2.1, XP-D2.2	D	*ERCC2*	NM_000400.4	c.1967C>T p.Ala656Val	Homozygous	Missense	Novel	Likely pathogenic

(*Continued*)

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Table 2 (*Contunued*)

Patient[a]	Complementation group	Gene affected	Transcript	Variant	Zygosity	Consequence	Reference	Classification (ACMG criteria)
XP-D3.1	D	*ERCC2*	NM_000400.4	c.1367_1369del p.Ile456del c.1532G>A p.Arg511Gln	Compound heterozygous	In frame deletion Missense	ClinVar Novel	Likely pathogenic Likely pathogenic
XP-E1.1, XP-E1.2	E	*DDB2*	NM_000107.3	c.417G>A p.Trp139*	Homozygous	Nonsense (PTC)	Novel	Likely pathogenic
XP-E2.1	E	*DDB2*	NM_000107.3	c.1234+83C>G	Homozygous	Deep intronic	Novel	Likely benign
XP-E3.1	E	*DDB2*	NM_000107.3	c.640C>T p.Arg214*	Homozygous	Nonsense (PTC)	ClinVar	Pathogenic
XP-E4.1	E	*DDB2*	NM_000107.3	Exon 1–3 deletion	Homozygous	Big deletion	Novel	Pathogenic
XP-E5.1	E	*DDB2*	NM_000107.3	c.730_733del p.Lys244*	Homozygous	Nonsense (PTC)	ClinVar	Pathogenic
XP-E6.1	E	*DDB2*	NM_000107.3	c.730_733del p.Lys244*	Homozygous	Nonsense (PTC)	ClinVar	Pathogenic
XP-E7.1	E	*DDB2*	NM_000107.3	c.603-2A>G	Homozygous	Splice altering	Novel	Likely pathogenic
XP-G1.1	G	*ERCC5*	NM_000123.4	c.351delA p.A118fs*52	Homozygous	Frameshift	Novel	Likely pathogenic
XP-V1.1	V	*POLH*	NM_006502.3	c.833T>C p.Leu278Pro	Homozygous	Missense	Novel	Likely pathogenic
XP-V2.1, XP-V2.2	V	*POLH*	NM_006502.3	c.381_384del p.Glu127Aspfs*68	Homozygous	Frameshift (PTC + 68aa)	Novel	Likely pathogenic
XP-V3.1, XP-V3.2, XP-V3.3, XP-V3.4, XP-V3.5	V	*POLH*	NM_006502.3	c.920dup p.His307Glnfs*2	Homozygous	Frameshift (PTC + 2aa)	Novel	Likely pathogenic
XP-V4.1	V	*POLH*	NM_006502.3	c.907C>T p.Arg303*	Homozygous	Nonsense (PTC)	ClinVar	Pathogenic
XP-V5.1	V	*POLH*	NM_006502.3	c.681T>G p.Cys227Trp	Homozygous	Missense	Novel	Likely pathogenic
XP-V6.1	V	*POLH*	NM_006502.3	c.884G>A p.Gly295Glu	Homozygous	Missense	Novel	Likely pathogenic
XP-V7.1, XP-V7.2	V	*POLH*	NM_006502.3	c.1027C>T p.Gln343*	Homozygous	Nonsense (PTC)	Novel	Likely pathogenic
XP-V8.1	V	*POLH*	NM_006502.3	c.490+1G>T	Homozygous	Splice region variant	Novel	Likely pathogenic
XP-V9.1	V	*POLH*	NM_006502.3	c.1027C>T p.Gln343*	Homozygous	Nonsense (PTC)	Novel	Likely pathogenic

aa, amino acid; ACMG, American College of Medical Genetics and Genomics; PTC, premature termination codon; VUS, variant of unknown significance; WT, wild type; XP-A, XP complementation group A; XP-C, XP complementation group C; XP-D, XP complementation group D; XP-E, XP complementation group E; XP-G, XP complementation group G; XP-V, xeroderma pigmentosum variant. [a]Patients from the same family are labelled with the same initial number following the gene type, and siblings are presented in the same row.

invasive BCC of the cheek, later developed multiple BCCs and had a meningocoele repair in infancy. Patient XP-E7.1, diagnosed at the age of 10 years, developed basosquamous cell carcinoma, SCC and SCC *in situ* on the face with mild pigmentary changes. Patients XP-E3.1, XP-E5.1 and XP-E6.1 had nonsense variants; XP-E3.1 and XP-E6.1 developed BCCs at 20 and 16 years of age, respectively. Three patients (XP-E1.1, XP-E2.1, XP-E4.1) showed neurological findings; however, meningocoele and carpal tunnel syndrome may represent coincidental comorbidities rather than manifestations of XP.

XP-G

Only one patient with XP-G (OMIM #278780) was included. This individual was a 34-year-old man diagnosed in infancy; he was born to consanguineous parents with no family history of XP. He showed features of XP/Cockayne syndrome (XP-CS), including photosensitivity with blistering and ulceration, freckling from the age of 5 years, cataracts, severe myopia with astigmatism, kyphosis, short stature (1.40 m), characteristic facies (sunken eyes, progeroid appearance), microcephaly, SNHL and gait difficulty. He had multiple benign skin lesions and two MIS. A novel homozygous *ERCC5* frameshift variant (c.351delA, p.A118fs*52) suggested a milder XP-CS phenotype (Table 2).

XP-V (MIM: 278750)

We identified 15 patients with XP-V (OMIM #278750) from 9 families, 10 of whom were female individuals. Median age was 32 years (IQR 28–36); median age at diagnosis was 20 (IQR 10–27). Eight patients (53%) had photosensitivity (score 1). All had lentigines on sun-exposed areas (median onset 6 years, IQR 3–8). None showed neurodegeneration, and all were homozygous (Table 2).

Five siblings (XP-V3.1, XP-V3.2, XP-V3.3, XP-V3.4, XP-V3.5) had novel frameshift variants. Patient XP-V3.5, diagnosed at the age of 28 years, developed melanoma and died at 33 years of age. His siblings, diagnosed between the ages of 9 and 12 years, did not practise sun protection. Siblings XP-V2.1 and XP-V2.2 also had novel frameshift

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variants and lentigines. Patients XP-V1.1, XP-V5.1 and XP-V6.1 had novel missense variants; patient XP-V1.1 was diagnosed at the age of 47 years with dysplastic naevus, lentigines and NMSC. Patients XP-V5.1 and XP-V6.1, diagnosed at the age of 20 years, developed NMSC by the age of 24 and 25 years, respectively.

Patient XP-V4.1 and siblings XP-V7.1 and XP-V7.2 carried nonsense variants. Patient XP-V4.1 developed SCC *in situ* and BCCs. Patient XP-V7.1 developed skin cancer at the age of 18 years with photosensitivity, while patient XP-V7.2 developed skin cancer at 34 years of age and had keratoconus and no photosensitivity. Patients XP-V8.1 and XP-V9.1 had novel variants; patient XP-V8.1 developed only benign lesions, whereas patient XP-V9.1 developed multiple NMSCs.

Discussion

In this study, we found distinct patterns of clinical manifestations and outcomes in patients with XP, as well as unexpected heterogeneity across complementation groups. All patients exhibited lentigines and freckling, with severity varying by subtype and the mildest cases seen in XP-E. Consistent with National Institutes of Health (NIH) data, the median age at first NMSC diagnosis was much younger (12 years) than that of the general population.[15]

Patients with XP-A and XP-C were diagnosed earlier than those with XP-D, XP-E and XP-V, probably due to the marked photosensitivity seen in XP-A and early cancers linked with XP-C. In our cohort, patients with XP-D, XP-E and XP-V exhibited comparatively milder phenotypes, with a lower cumulative burden of skin cancers. The literature highlights patients with XP-A, XP-B, XP-D, XP-F and XP-G as the most prone to photosensitivity.[1] In our cohort, all patients with XP-A and some with XP-D exhibited severe sun reactions and early pigmentary changes, leading to early sun protection and minimal or no skin cancers. By contrast, patients with XP-C experienced more severe disease, despite a similar age at diagnosis, reflecting the critical role of the XPC protein in global genome repair; loss of this function leads to widespread mutagenesis and earlier, more aggressive cancer development.[16,17]

Unexpectedly, siblings with the XPE1.1/1.2 (p.Trp139*) nonsense variant showed marked photosensitivity, suggesting that truncated DDB2 (damage-specific DNA-binding protein 2) fragments may exert a dominant negative effect beyond simple loss of function. In contrast, patient XPE4.1 (exon 1–3 deletion) had no photosensitivity, probably because complete loss of protein avoids toxic fragment effects, while residual XPC-mediated repair remains functional.[17]

Ophthalmopathy was also a major concern: 57% of patients (n=39/69) showed anterior segment involvement (Table S1), lower than the ~90% reported in the literature,[1] highlighting the protective effect of UV avoidance measures such as sunglasses. Oral mucosal disease was less frequent, with three siblings showing erythroleucoplakia and three patients having SCC of the lips or tongue – the most common oral malignancies in XP. In the literature, 93 mucosal SCCs have been reported in 130 patients aged ≤ 18 years with XP, most often involving tongue and lips.[18]

We identified three internal malignancies (papillary thyroid carcinoma, vertebral angiosarcoma and leiomyosarcoma) but no haematological cancers. While thyroid carcinoma and sarcomas are recognized in cohorts of patients with XP, haematological malignancies, especially in patients with XP-C with the North African delTG founder mutation, are emphasized in pooled analyses.[4,5] Their absence in our cohort may reflect allelic background, younger median age (23 years) or cohort size.

Neurological involvement was present in patients with XP-A but absent in those with XP-V, consistent with the literature.[1,6] In XP-A, neurodegeneration typically progresses from early childhood,[1] consistent with our findings (normal at age 9 years, abnormal by the age of 17 and 23 years, respectively). In contrast, none of our patients with XP-D exhibited neurodegeneration, despite having an older age of onset than typical (median 12.5 years with peaks at < 20 years and > 45 years).[19] This may reflect the milder effects of missense mutations, as reported for the p.Arg511Trp variant.[20] Although diagnosed relatively late (median 22 years), they also showed a low cancer burden. While patients with XP-D without neurodegeneration have been described,[3,21] none of our variants has previously been reported. In patients with XP-E included in our study, neurological features may be related to consanguinity, while the epilepsy found in our cohort could be coincidental; nonetheless, neurological involvement remains clinically important as the second leading cause of death in patients with XP.[1]

In our cohort, all four patients with XP-D carried missense or in-frame *ERCC2* variants (p.Arg511Trp; p.Ala656Val; p.Ile456del/p.Arg511Gln) that are consistent with hypomorphic function. Structural and functional data indicate that these substitutions do not directly disrupt the catalytic helicase motifs or critical transcription factor II H (TFIIH) interfaces, thereby preserving TFIIH stability and transcription-coupled repair, which probably explains the absence of neurological impairment and lower skin cancer burden vs. classic cases of XP-D and XP-CS. In contrast, canonical severe *ERCC2* mutations such as p.Arg683Trp (motif VI region) or p.Arg616Pro, as well as frameshift/splice loss-of-function alleles, more profoundly compromise TFIIH and are strongly associated with neurodegeneration (XP-CS/trichothiodystrophy). These genotype–mechanism relationships align with prior XP syntheses and TFIIH structural work.[20]

Although hearing loss is uncommon in patients with XP-C vs. XP-A or XP-D, we recorded this feature in four patients with XP-C with truncating or splice-altering variants. Totonchy *et al.* described 4 such cases among 38 patients with XP-C at the NIH (1971–2012) but related this to environmental factors or consanguinity.[22] The association is still uncertain and may reflect coincidental findings, consanguinity or environmental influences rather than a direct effect of the variants themselves. Nonetheless, these observations suggest that hearing should be carefully monitored in patients with XP-C, even if hearing problems are not classically expected.

The severe photosensitivity in siblings XP-E1.1/1.2 (p.Trp139*) and XP-E2.1 (c.1234+83C>G) warrants further attention. The latter is a deep intronic variant not predicted to alter splicing by *in silico* tools and presents at low frequency in gnomAD (absent in Turkish VariOM), initially classified as likely benign (American College of Medical

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Genetics and Genomics: BP4, BS1). However, the severe phenotype suggests pathogenicity through cryptic splicing or *in cis* with an undetected change. Functional validation, such as RNA analysis, is needed. Similarly, the nonsense variant may escape decay and produce toxic fragments that impair UV-DDB (DNA damage binding protein) and residual XPC function. Together, these cases show that truncating and intronic variants can cause severe XP-E by disrupting UV-DDB/XPC repair balance. The XP-E2.1 phenotype shows considerable overlap with XP-C, and the presence of only a probably benign intronic *DDB2* variant raises the possibility that an alternative genetic mechanism may be involved.

One patient with XP-G presented with the rare XP-CS complex. Natale and Raquer reported 43 patients with XP-CS, half of whom had XP-G.[23] Our case represents the first homozygous *ERCC5* (c.351delA, p.A118fs*52) frameshift variant described in a male individual with XP-CS.

Early photoprotection remains crucial, yet adherence was poor in our cohort, with only two homeschooled patients, despite Türkiye's sunny climate. This probably contributed to the cumulative cancer burden. Education and support groups could improve adherence and outcomes.

The limitations of our study include potential recall bias for self-reported sun protection, lack of functional assays for novel variants, possible missed phenotype-modifying mutations and incomplete national coverage. Furthermore, the absence of parental samples prevented segregation analysis for several variants, which limits definitive interpretation of uncertain or novel findings.

Most variants in our cohort were predicted to be deleterious, as they were mainly nonsense, splice site or frameshift changes. Novel missense variants were evaluated using structural and evolutionary conservation data. In total, we identified 30 novel variants, many of them homozygous, consistent with consanguinity and possible founder effects. Their absence from global databases highlights the need for population-specific variant data. Although *in silico* findings and clinical features support pathogenicity, functional studies, particularly for uncertain intronic or noncoding variants, remain necessary but were not feasible due to limited sample availability and technical constraints.

This study of a large cohort of patients from Türkiye with XP has revealed numerous novel variants and distinct genotype–phenotype correlations, including unexpectedly mild XP-D and photosensitive XP-E presentations. These findings underscore the importance of population-specific data and functional validation to improve patient management and prognostication.

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Author contributions

Defne Baskurt (Conceptualization, Data curation, Investigation, Methodology, Resources, Visualization, Writing—review & editing [equal], Formal analysis, Writing—original draft [lead]), Sule Altiner (Data curation, Methodology, Resources, Validation, Visualization, Writing—original draft, Writing—review & editing [equal], Formal analysis [lead]), Tugba Atci (Data curation, Writing—review & editing [equal]), Bengü Nisa Akay (Data curation, Writing—review & editing [equal]), Nilay Duman (Data curation, Writing—review & editing [equal]), Burhan Engin (Data curation, Writing—review & editing [equal]), Aysenur Botsali (Data curation, Writing—review & editing [equal]), Serkan Yazici (Data curation, Writing—review & editing [equal]), Mehmet Bugrahan Düz (Data curation, Writing—review & editing [equal]), Esra Adisen (Data curation, Writing—review & editing [equal]), Irem Özdemir (Data curation, Writing—review & editing [equal]), Deniz Aksu Arica (Data curation, Writing—review & editing [equal]), Leyla Baykal Selcuk (Data curation, Writing—review & editing [equal]), Pinar Kaderi (Data curation, Writing—review & editing [equal]), Ayça Aykut (Data curation, Writing—review & editing [equal]), Zeynep Topkarci (Data curation, Writing—review & editing [equal]), Asude Durmaz (Data curation, Writing—review & editing [equal]), Yildiz Gürsel Ürün (Data curation, Writing—review & editing [equal]), Vefa Asli Erdemir (Data curation, Writing—review & editing [equal]), Ferhan Bulut Demir (Data curation, Writing—review & editing [equal]), Isil Karaarslan (Data curation, Writing—review & editing [equal]), Ayse Deniz Yücelten (Data curation, Writing—review & editing [equal]), Sibel Ersoy Evans (Data curation, Writing—review & editing [equal]) and Secil Vural (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing—original draft [equal], Writing—review & editing [lead]).

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

This study was approved by the Committee on Human Research of Koç University Hospital, Istanbul, Türkiye (2022.388.IRB1.143).

Patient consent

Informed consent was obtained from all patients and/or their legal guardians. Consent for the publication of recognizable patient photographs or other identifiable material was obtained by the authors; all patients and/or their guardians gave consent with the understanding that this information may be publicly available.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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Appendix S1 Complete list of author affiliations

[1]School of Medicine, Koç University, Istanbul, Türkiye
[2]Department of Medical Genetics, Ankara University School of Medicine, Ankara, Türkiye
[3]Department of Dermatology and Venereology, Istanbul Medical Faculty, Istanbul University, Istanbul, Türkiye
[4]Department of Dermatology, Ankara University School of Medicine, Ankara, Türkiye
[5]Department of Dermatology, Faculty of Medicine, Ege University, Bornova, İzmir, Türkiye
[6]Department of Dermatology, Cerrahpasa Faculty of Medicine, Istanbul University–Cerrahpasa, Istanbul, Türkiye
[7]Department of Dermatology and Venereology, Gulhane Medical Faculty, University of Health Sciences, Ankara, Türkiye
[8]Department of Dermatology and Venereology, Bursa Uludag University School of Medicine, Bursa, Türkiye
[9]Department of Medical Genetics, Memorial Sisli Hospital, Istanbul, Türkiye
[10]Department of Dermatology, Gazi University Faculty of Medicine, Ankara, Türkiye
[11]Department of Dermatology and Venereology, Karadeniz Technical University, Trabzon, Türkiye
[12]Department of Medical Genetics, Ege University School of Medicine, Izmir, Türkiye
[13]Department of Dermatology and Venereology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Türkiye
[14]Department of Dermatology and Venereology, Faculty of Medicine, Trakya University, Edirne, Türkiye
[15]Department of Dermatology, Göztepe Training and Research Hospital, Istanbul Medeniyet University, Istanbul, Türkiye
[16]Department of Dermatology and Venereology, Marmara University Faculty of Medicine, Istanbul, Türkiye
[17]Department of Dermatology, School of Medicine, Hacettepe University, Ankara, Türkiye
[18]Department of Dermatology and Venereology, Koç University Hospital, İstanbul, Türkiye

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