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Genetic Identification of a Novel Truncating Mutation p.Thr738Argfs*28 in *XPC* Gene in a Family from Iraq

Fatemeh Yadegari[1], Aseel Rashid Abed[2], Widad Yadallah Abd Ali[2], Haider Hamza Al-Abedi[2], Shiva Zarinfam[1], Rabbie Hanna[2], Fawaz Al-Alloosh[2], Solaleh Aminian[1], Keivan Majidzadeh-A[1*]

[1] *Genetics Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran*

[2] *Warith International Cancer Institute, Karbala, Iraq*

***Corresponding Author:** Keivan Majidzadeh-A, Genetics Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran, E-mail: kmajidzadeh@acecr.ac.ir*

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Introduction: Xeroderma pigmentosum (XP) is a rare, autosomal recessive disorder characterized by extreme sensitivity to UV-induced DNA damage, resulting in symptoms such as severe sunburn, freckles, dry skin, premature skin aging, and, occasionally, neurological symptoms.

Case Report: The study focuses on a 6-year-old girl with XP symptoms since age three. Genotyping was performed to identify the responsible mutation, followed by molecular modeling to predict the structural consequences of the amino acid substitution.

Results: The identified variant is a novel homozygous frameshift mutation *XPC*: c.2213_2216del (p.Thr738Argfs*28) in exon 12, corresponding to genomic coordinates (hg19/GRCh37) chr3:14190347 CTCTG>C based on the canonical transcript NM_004628.5. This variant is predicted to cause XP. Homology modeling reveals that this mutation deletes a critical region at the extreme COOH terminus of the XPC protein, which is crucial for its interaction with TFIIH and CETN2. While the mutant protein can still interact with DNA, it loses its ability to interact with TFIIH and CETN2, leading to loss of protein function.

Conclusions: This study expands the spectrum of mutations observed in the *XPC* gene by identifying a new pathogenic mutation. The results of this study highlight the importance of medical and genetic counseling in protecting future generations against genetic disease.

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INTRODUCTION

Xeroderma pigmentosum (XP) is a rare genetic disorder inherited in an autosomal recessive manner. It is characterized by extreme sensitivity to sunlight and other light sources, leading to redness and sunburn on sun-exposed areas from birth (50%), freckles before age 2, skin hyper- and hypopigmentations, loss of vision, and damage to the eyelids, lips, and tip of the tongue. Neurological deficits such as dysphagia, sensory neural hearing loss, ataxia, intellectual disability, muscle weakness, and premature death have been seen in 25% of patients with XP. They are 10000 times more likely to develop skin cancers, including basal cell carcinoma, squamous cell carcinoma, and melanoma, and 2000 times more likely to develop ocular cancers. These cancers are typically present before age 10 [1-6]. This disease results from a faulty nucleotide excision repair (NER) system, which corrects a wide range of DNA lesions, including helix-distorting DNA damage and bulky adducts. The NER pathway employs two mechanisms to remove DNA lesions: transcription-

Table 1. Comparison of clinical features of syndromes associated with NER deficiencies.

	XP	XP with neurologic changes	De Sanctis – Cacchione syndrome	TRICHOTHIO-DYSTROPHY (TTD)	COCKAYNE SYNDROME (CS)	XP/CS COMPLEX	Cerebro-oculo-facio-skeletal (COFS) syndrome	UV-sensitive syndrome
Skin								
Skin sun sensitivity	+	+	+	±	+	+	+	+
Abnormal skin pigmentation	+	+	+	-	-	+	-	+
Sunlight-induced skin cancer	+	+	+	-	-	+	-	-
Eyes								
Photophobia	+	+	+	±	+	+	-	-
Conjunctival growths	+	+	+	-	-	+	-	-
Congenital cataracts	-	-	-	+	+	-	+	-
Pigmentary retinal degeneration	-	-	-	-	+	+	+	-
Somatic								
Short stature	-	±	+	+	+	+	+	-
Immature sexual development	-	-	+	±	+	+		-
Nervous system								
Deafness	-	+	+	-	+	+	+	-
Mental retardation	-	+	+	+	+	+	+	-
Primary neuronal degeneration	-	+	+	-	-	-	?	-
Progressive neurological degeneration	-	+	+	Unknown (not reported)	+	+	+	-
Demyelination	-	-	-	+	+	+	+	-
Microcephaly	-	+	+	+	+	+	+	-
Calcification	-	-	-	±	+	+	+	-
Cerebral atrophy	-	+	+	±	+	+	+	-
Spasticity	-	±	+	±	+	+	+	-
Inheritance	AR	AR	AR	AR	AR	AR	AR	AR

	XP	XP with neurologic changes	De Sanctis – Cacchione syndrome	TRICHOTHIO-DYSTROPHY (TTD)	COCKAYNE SYNDROME (CS)	XP/CS COMPLEX	Cerebro-oculo-facio-skeletal (COFS) syndrome	UV-sensitive syndrome
Molecular defect	*XPA, XP-B, XP-C, XP-D, XP-E, XP-F, XP-G*	*XP-A, XP-B, XP-D, XP-F, XPG*	*XP-A, XP-D, CS-B*	*XPB, XPD, TTDA, TTDN1*	*CSA, CSB*	*XPB, XPD, XPG*	*CSB ,ERCC1, XPD, XPG*	*CSA, CSB or UVSSA/KIAA1530*

coupled repair (TC-NER) and global genome repair (GG-NER). TC-NER specifically detects and eliminates damage from the transcribed strand of active genes, while GG-NER repairs DNA lesions throughout the entire genome [7-9]. Except for the mode of DNA damage recognition, these mechanisms are almost identical. In TC-NER, transcription-blocking DNA lesions are identified by Cockayne Syndrome B (CSB) and Cockayne Syndrome A (CSA) proteins, while in GG-NER, DNA damage is recognized by the XPC protein complexed with the human homolog of Rad23-B (hHR23B) and CETN2.

XP is caused by mutations in one of several genes involved in the nucleotide excision repair (NER) pathway, including *DDB2* (*XP-E*), *ERCC1, ERCC2 (XP-D), ERCC3 (XP-G), ERCC4 (XP-F), ERCC5 (XP-B), XPC, XPA,* and *POLH* (*XP-V*). While most groups exhibit nucleotide excision repair (NER) deficiency and can present with or without neurological abnormalities, the variant form (XP-V, caused by POLH mutations) typically shows milder features, limited to cutaneous photosensitivity and a predisposition to skin cancer. In addition to the heterogeneity within XP itself, defects in several of the same NER-related genes can give rise to other overlapping syndromes with XP-like features. A detailed comparison of clinical features across XP complementation groups and related syndromes is described below and summarized in Table 1.

Cockayne syndrome (CS), cerebro-oculo-facio-skeletal (COFS) syndrome, trichothiodystrophy (TTD), and UV-sensitive syndrome are diseases with mutations in some of the same genes as those involved in XP [10, 11]. De Sanctis–Cacchione syndrome (DSC) represents the most severe form of XP characterized by manifestations such as dwarfism, mental disabilities, and immature sexual development [12-14]. The severity of this syndrome depends on the extent of DNA repair damage [15, 16]. Mutations in the *CSA* and *CSB* genes cause CS. This disease is characterized by skin photosensitivity, but unlike XP, it does not increase the susceptibility to skin cancer. Individuals with CS may experience cachectic dwarfism and progressive neurological abnormalities, including microcephaly, retinal atrophy, sensorineural deafness, and difficulty walking and feeding [17-19]. Another disorder, trichothiodystrophy (TTD), a TC-NER-specific disorder, is caused by mutations in the *XPB, XPD, TTDA*, and *TTDN1* genes. TTD shares many symptoms with Cockayne syndrome but presents additional features such as sulfur-deficient brittle hair, nails, and scaly skin [20-23]. Mutations in the *XPB* and *XPD* genes, subunits of the TFIIH complex, can result in XP, TTD, or a combination of both (XP-CS) [22].

In contrast to XP, individuals with CS and TTD do not have an increased risk of skin cancer or pigmentary abnormalities. Syndromes associated with NER deficiency exhibit similar clinical signs, including photosensitivity and mental problems, making it challenging to differentiate between them. In addition to NER-related disorders, other conditions may present with abnormal pigmentation that can mimic XP or related syndromes. Peutz-Jeghers syndrome, Leopard syndrome, and Carney complex are autosomal dominant lentiginoses that are not directly associated with sun exposure. However, they exhibit a common abnormal pigmentation feature, similar to conditions such as XP, CS, DCS, and the XP/CS

complex [24]. This study presents the clinical and genetic features of a 6-year-old Iraqi girl who exhibited XP-like features.

CASE REPORT

Clinical History

A 6-year-old girl with clinical features indicative of XP was referred to the Alwarith Cancer Institute for genetic counseling. These features included extreme sensitivity to sunlight, freckles in sun-exposed areas, dry skin, and photophobia. After obtaining written informed consent from the proband's parents, pedigree information, including consanguinity, affected family members, associated diseases, and family history, was collected through interviews with both parents and physical examination of the proband and other children in the family (Figure 1). All data were handled confidentially in accordance with institutional guidelines.

Whole exome sequencing (WES)

DNA was extracted from peripheral blood leukocytes using the Blood Mini Kit (Zista Gene, Iran) according to the manufacturer's instructions. The DNA obtained from the proband underwent whole-exome sequencing (WES) on the BGISEQ-500 system, using 100-bp paired-end reads. After quality control (QC), sequence reads were aligned to the GRCh37/hg19 build of the human reference genome using BWA-MEM. Variant filtering was then performed to identify sequence variants associated with the proband's phenotype, focusing on allele frequency and predicted pathogenicity, particularly in genes associated with dermatological or DNA repair disorders.

Homology modeling

Currently, no experimentally determined 3D crystal structure of the human XPC protein is available. To address this, we employed homology modeling, a computational approach that predicts a protein's 3D structure using the known structure of a homologous protein as a template. For this purpose, we used the yeast Rad4–Rad23 complex bound to DNA (PDB ID: 2QSH) (Min & Pavletich, 2007), as yeast Rad4 shares approximately 40% sequence similarity with human XPC. This structure served as a template to construct a model of the human XPC–RAD23B protein bound to DNA using MODELLER version 9.15.

RESULTS

Clinical Findings and Genetic Study

We present the case of a six-year-old girl, born to a consanguineous marriage, experiencing severe skin sensitivity to sunlight. This condition has led to burns, dry skin, and multiple freckles on her face, hands, arms, legs, abdomen, and upper chest. The cutaneous manifestations observed in our patient, including freckling, poikiloderma, and actinic damage, are similar to some of the representative clinical images of XP available on the DermIS – Dermatology Online

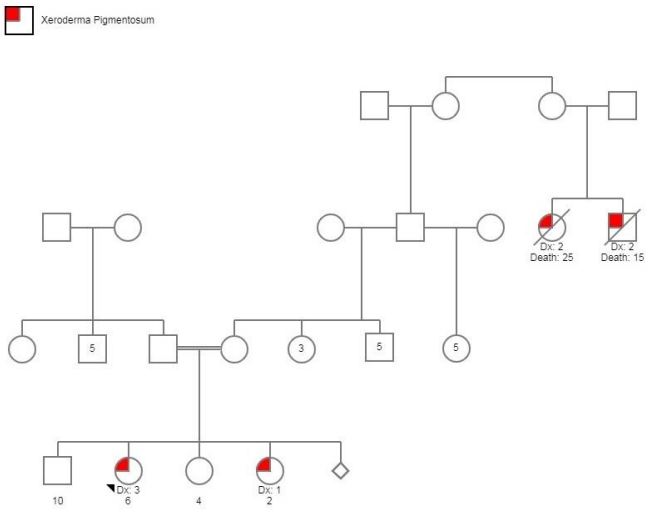


Figure 1. The pedigree information of this family.

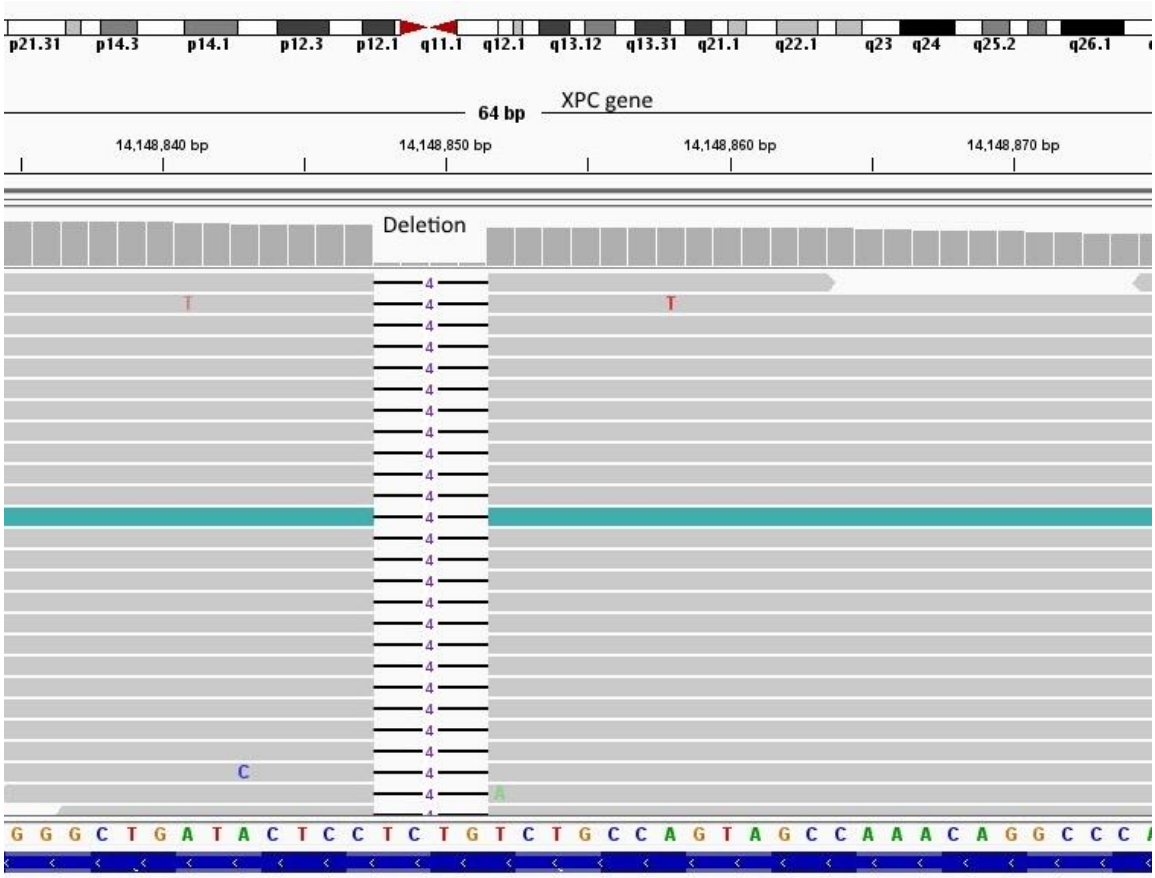


Figure 2. Identification of a novel homozygous frameshift deletion (c.2213_2216del, p.Thr738Argfs*28, NM_004628.5, hg19: chr3:14190347 CTCTG>C) using whole exome sequencing.

Atlas (Diepgen TL, Yihune G et al., published online at: https://www.dermis.net/dermisroot/en/40662/diagnose.htm). These symptoms have been present since she was three years old. The child has also exhibited ocular symptoms such as photophobia and red eyelids. These characteristics were all suggestive of Xeroderma Pigmentosum, an autosomal recessive disorder. However, no signs of skin malignancy and neurological involvement, including microcephaly, retinal atrophy, sensorineural deafness, and walking and feeding difficulties, have been observed. WES was performed on the proband's genomic DNA to elucidate the genetic basis of these symptoms further. A novel homozygous frameshift deletion in exon 12 of the *XPC* gene (c.2213_2216del, p.Thr738Argfs*28, NM_004628.5, hg19: chr3:14190347 CTCTG>C) was detected (Figure 2). This deletion changes threonine to arginine at codon 738, creating a premature stop codon and resulting in truncation of the translated protein at codon 765 (p.Thr738ArgfsX28).

Homology modeling

The carboxy-terminal domain of the XPC has been shown to have critical interactions with damaged DNA (residues 607-742), RAD23B (residues 496-734), CETN2 (residues 847-866), and TFIIH (residues 816-940) [25-29]. CETN2 and RAD23B have been reported to enhance the stability and DNA damage–recognition sensitivity of XPC [26, 30]. According to the 3D structural model constructed in this study, the truncated protein (p.Thr738Argfs*28) lacks the essential residues required for interaction with CETN2 (residues 847–866) and TFIIH (residues 816–940). However, it retains its ability to interact with DNA and RAD23B, as illustrated in Figure 3.

CONCLUSIONS AND DISCUSSION

XP is a hereditary disease with varying incidence across regions, affecting approximately 1 in 100,000 individuals in the United States and Europe, 1 in 20,000 to 100,000 in Japan, and 1 in 10,000 to 50,000

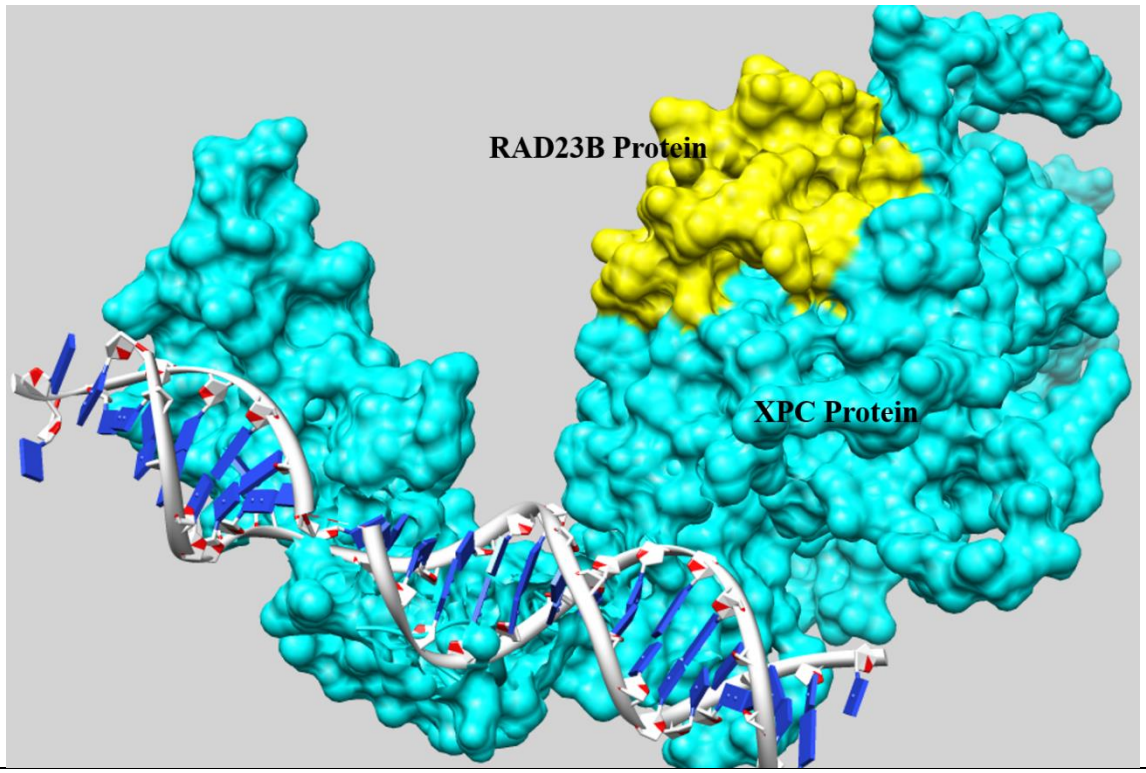


Figure 3. Structural model of the putative XPC in complex with RAD23B and DNA.

in North Africa and the Middle East. This condition arises from mutations in the NER pathway, including XPA-XPG and XPV [31, 32]. In North Africa, Europe, and the Middle East, mutations in the *XPC* gene are the most commonly observed cause of XP [33]. Conversely, in Japan, XPA mutations are the predominant cause of the disease [31]. Various types of mutations have been identified in the *XPC* gene, although most of them are frameshift or nonsense mutations. For example, a Chinese XP-C patient was found to carry two novel compound heterozygous *XPC* variants and also presented with an ovarian teratoma, illustrating that XP-C can sometimes affect internal organs [34]. In another report, a 19-year-old XP patient harbored a 13-bp deletion and a splice-site mutation in *XPC* [35]. Additionally, a consanguineous Pakistani family was found to carry a novel protein-truncating mutation (c.291dupT; p.Asp98*) in *XPC*, resulting in a truncated protein and confirming the autosomal recessive inheritance pattern [36]. A homozygous missense mutation (c.919C>T; p.Arg307Trp) was reported in a family with multiple melanoma cases, and the *MC1R* p.I155T variant appeared to modify the severity of the disease [37]. Additionally, a 4-year-old Korean boy with an *XPC* splice site mutation presented with typical cutaneous XP manifestations as well as autistic features and metabolic abnormalities, including hypoglycinemia [38].

In this case study, we present a 6-year-old girl who developed pigmented lesions on sun-exposed areas of her skin at age 3. Analysis revealed a homozygous frameshift mutation in exon 12 of the *XPC* gene (c.2213_2216del, p.Thr738Argfs*28, NM_004628.5, hg19: chr3:14190347 CTCTG>C)

Based on the clinical and molecular findings, XP was diagnosed in this case. The homozygous deletion variant (Thr738Argfs*28) found in our case created a premature termination codon (PTC) that reduced the length of the XPC protein from 940 to 765 residues. mRNA transcripts containing a PTC resulting from DNA mutations or RNA processing errors are typically recognized and degraded via nonsense-mediated mRNA decay (NMD) [39]. Generally, mRNA transcripts with premature termination codons within 50–55 nucleotides upstream of an exon-exon

junction are subject to degradation by NMD [40, 41]. However, exceptions to this rule have been reported [42], suggesting that a larger proportion of transcripts with premature termination codons may potentially undergo degradation via NMD [43]. Based on the 50–55-nucleotide rule, it is likely that NMD would target and remove the mRNA containing the Thr738Argfs*28 mutation, leading to loss of gene function. If no NMD occurs, it produces a truncated protein at the extreme C-terminus of XPC (Thr738Argfs*28). The functional consequences of such truncation mutations depend on the extent of protein loss. As illustrated in Figure 3, the truncation mutation (Thr738Argfs*28) identified in this study does not appear to affect the interaction between XPC and DNA or between XPC and HR23B. However, this specific mutation disrupts XPC's binding to CETN2 and TFIIH. Previous studies have demonstrated that human cells lacking XPC-TFIIH interaction exhibit a complete deficiency in NER [29]. Therefore, if the XPC protein carrying this mutation (Thr738Argfs*28) had been expressed, it would likely be non-functional.

Genetic testing plays a key role in high-risk populations, especially in regions with frequent consanguineous marriages. Early identification of pathogenic *XPC* variants can help families make informed reproductive decisions and implement preventive measures, thereby reducing the risk of affected children in future generations.

The diagnosis can be made before birth by chorionic villus sampling (CVS) and amniocentesis, to identify related mutations. While there is no cure for XP after birth, adopting sun protection measures can reduce skin and eye problems associated with XP. Photoprotection actions, including sun-protective clothing, sunglasses, face shields, staying in the shade, and minimizing outdoor activities during midday, can effectively reduce skin damage caused by ultraviolet radiation. Topical retinoids and vitamin D supplements may also help reduce problems associated with XP [44].To facilitate education on sun protection methods, we have compiled a catalog of informative materials in both English and Arabic, offering parents quick and easy-to-follow instructions. The English version of these instructions, in the form of a brochure complete with photos and detailed descriptions of recommendations, is attached to this study as supplementary material (Brochure S1).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ETHICS APPROVAL

Not applicable.

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