Research Article

Diagnosis of Xeroderma Pigmentosum Groups A and C by Detection of Two Prevalent Mutations in West Algerian Population: A Rapid Genotyping Tool for the Frequent XPC Mutation c.1643_1644delTG

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Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder. Considering that XP patients have a defect of the nucleotide excision repair (NER) pathway which enables them to repair DNA damage caused by UV light, they have an increased risk of developing skin and eyes cancers. In the present study, we investigated the involvement of the prevalent XPA and XPC genes mutations—nonsense mutation (c.682C>T, p.Arg228X) and a two-base-pair (2bp) deletion (c.1643_1644delTG or p.Val548Ala fsX25), respectively—in 19 index cases from 19 unrelated families in the West of Algeria. For the genetic diagnosis of XPA gene, we proceeded to PCR-RFLP. For the XPC gene, we validated a routine analysis which includes a specific amplification of a short region surrounding the 2bp deletion using a fluorescent primer and fragment sizing (GeneScan size) on a sequencing gel. Among the 19 index cases, there were 17 homozygous patients for the 2bp deletion in the XPC gene and 2 homozygous patients carrying the nonsense XPA mutation. Finally, XPC appears to be the major disease-causing gene concerning xeroderma pigmentosum in North Africa. The use of fragment sizing is the simplest method to analyze this 2 bp deletion for the DNA samples coming from countries where the mutation c.1643_1644delTG of XPC gene is prevalent.

1. Introduction

Xeroderma pigmentosum (XP, OMIM 278700–278780) is a rare inherited autosomal recessive disorder characterized by an inability to repair DNA damage caused by ultraviolet (UV) light [1, 2] which induces skin cancers [3, 4] and other skin manifestations including poikiloderma, skin atrophy, telangiectasia, actinic keratoses, angiomas, and keratoacanthomas. XP patients may also have ocular manifestations, like photophobia, conjunctivitis, keratitis, ectropion, and entropion [5]. Neurologic symptoms such as mental deterioration, sensorineural deafness, hyporeflexia, and ataxia are found in severe forms of the disease [1, 6]. XP affects both sexes equally [7] with an incidence of 1/100 000 births in the USA and Europe [8], 1/20 000–100 000 in Japan [9, 10], and 1/10 000–30 000 in North Africa [11–14].

XP is found in all races worldwide and caused by defect in seven complementation groups (XP-A to XP-G) involved
in NER system [15]. Four complementation groups (XP-A, XP-B, XP-D, and XP-G) exhibit neurological manifestations [16]. XP-C, XP-E, and XP-F patients rarely develop neurological disorders [17, 18]. Two different mechanisms of DNA repair can be distinguished: the Global Genome Repair (GGR) recognizes and removes lesions throughout the entire genome [19] while the Transcription-Coupled Repair (TCR) is specific to DNA damage occurring at transcribed strands of active genes [20]. Twenty per cent of XP patients present a normal NER system (XP-V) but a defective DNA polymerase eta (η) gene (POLH) [21]. XP-C and XP-A are the most prevalent groups in North Africa and Southern Europe [22, 23].

Xeroderma pigmentosum complementation group C (MIM ID #278720) is caused by mutations in the XPC gene (MIM ID #613208) and the most frequent mutation is a 2 bp deletion (c.1643delTG, p.Val548AlafsX25) [13]. This gene is located on chromosome 3 (3p25) and contains 16 exons encoding for xeroderma pigmentosum group C (XPC) protein (GenBank accession number AC090645). This protein recognizes the damaged bases at the beginning of GGR pathway and it binds to HR23B to form the stable XPC-HR23B complex [24], which leads to the recruitment of TFIIH involved in the subsequent unwinding of the DNA double helix in concert with the proteins XPG, XPA, and replication protein A (RPA) [25].

Xeroderma pigmentosum complementation group A (MIM ID #278700) is caused by mutations in the XPA gene (MIMID* 611153) and the most frequent mutation is a nonsense mutation (c.682C>T, p.Arg228X) [26]. This gene is located on chromosome nine (9q34.1) [27] and consists of 6 exons that encodes for a 273-amino-acid Zn²⁺-finger protein [28]. The XPA protein plays a crucial role in both GGR and TCR pathways. The complex XPA-RPA provides the verification of the lesion and the binding to the single stranded DNA, so that the NER factors stay positioned around the lesion [29].

In the present study, we aimed to screen and detect for the first time the most common mutations in XPA and XPC genes presented in unrelated XP patients from the West of Algeria with clinical features of XP. Knowledge of these mutations is important for genetic counseling. Here, we used a new useful tool for rapid genotyping of the prevalent mutation of XPC gene.

2. Materials and Methods

2.1. Subjects. In this study, we collected 58 DNA samples from 19 unrelated XP families originated from Western Algeria. Among them, there were 19 index cases, 31 parents, and 8 siblings suffering from XP. Recruitment of patients with clinical diagnoses of XP disorder was provided at the Ophthalmology Department, Children's Hospital of Canastel, Oran (Algeria).

2.2. Methods. Informed signed consent for genetic investigation was obtained from all patients or from their parents in case of minors. Families were interviewed using a structured questionnaire to collect information about family history, consanguinity, affected members, and associated diseases. The clinical data of XP patients are summarized in Table 1.

2.2.1. DNA Extraction. DNA was isolated from peripheral blood leukocyte using STRATAGENe kit reagents (Agilent Technologies Division) according to the manufacturer's instructions at the Laboratory of Molecular and Cellular Genetics.

2.2.2. XPA Genotyping. To detect the previously reported nonsense mutation in exon 6 of the XPA gene (p.Arg228X), we used the following primers for the PCR reaction: forward primer 5'-TAC ATG GCT GAA AGC TTG AT-3' and reverse primer 5'-GGG TTT CAT TCA TCT ATG-3'. The fragments were amplified by PCR in a volume of 50 μL containing 50 ng of DNA, 1x PCR buffer, 0.2 mM of each dNTP, 2.5 mM MgCl₂, 10 pmol of each of the primers, and 1 U of Taq polymerase. PCR was performed using a Primus thermal cycler and the program included 95° C for 10 min, 35 cycles of 95° C for 30 s, 52° C for 30 s, and 72° C for 30 s. The cycles were followed by a final step of 72° C for 5 min. The PCR products were then subjected to RFLP analysis. Digestion of the PCR products was carried out according to the manufacturer's instructions. 5 μL of the PCR products was digested overnight with 5 U of HphI at 37° C. The digestion products were separated on 2% agarose gel. The restriction enzyme HphI (New England Biolabs, USA) was used to distinguish the R228X mutation in which the gain of an HphI restriction site occurs in the mutant allele. The wild-type (C) has two bands (320 bp and 31 bp fragments); however, the mutant allele (T) has three bands (245 bp, 75 bp, and 31 bp fragments).

2.2.3. XPC Genotyping. Specific amplification of the short region surrounding the deletion of two bases in exon 9 of the XPC gene was provided by two primers: a fluorescent forward primer 5’-(6FAM)GCATACTGGTATAGACCCAG-3’ and a reverse primer 5’-gtttcttTCGTACCTCTGTGTGACATC-3’, which generates a fragment of 194 bp (normal allele) or 192 bp (deleted allele). PCR was performed in Primus thermal cycler using a final volume of 50 μL containing 100 ng of DNA, 1x PCR buffer, 0.2 mM dNTPs, 2.5 mM MgCl₂, 0.2 μM of each one of the primers, and 1.25 U of Taq polymerase. PCR was performed as follows: 95° C for 10 min, 25 cycles of 94° C for 30 s, 30 s at 60° C, 30 s at 72° C, and a final step at 72° C for 5 min. The PCR products were checked on a 2% agarose gel. A step of purification and dilution was ensured for the PCR product with the addition of 90% formamide and 350 Rox marker in the loading dye. The fluorescent PCR products were separated on an automatic sequencer (ABI 3500, Applied Biosciences). Allele calling by fragment size analysis was performed with the aid of GeneScan software (Applied Biosciences). We also amplified the same exon 9 of XPC with different primers and sequencing products were analyzed by SeqScape software (Applied Biosciences).
Table 1: Clinical features of the nineteen patients with xeroderma pigmentosum.

| Patient (code) | Region of origin in Algeria | Sex | Age | Age of onset (months) | Consanguinity | Clinical symptoms | Neurological abnormalities |
|---------------|-----------------------------|-----|-----|-----------------------|---------------|-------------------|--------------------------|
| XP01          | Northwest                   | M   | 17  | 12                    | 1stD          | +                 | −                        |
| XP02          | Northwest                   | F   | 12  | 7                     | 1stD          | +                 | ++                      |
| XP03          | Northwest                   | F   | 7   | 2                     | 1stD          | +                 | −                        |
| XP04          | Northwest                   | F   | 15  | 12                    | 1stD          | +                 | +                       |
| XP05          | Northwest                   | M   | 8   | 3                     | 1stD          | +                 | +                       |
| XP06          | Northwest                   | M   | 11  | 24                    | 2ndD          | +                 | ++                      |
| XP07          | Northwest                   | M   | 15  | 12                    | 1stD          | +                 | +++                     |
| XP08          | Northwest                   | F   | 10  | 36                    | 1stD          | +                 | −                        |
| XP09          | Northwest                   | M   | 14  | 8                     | 1stD          | +                 | +++                     |
| XP10          | Northwest                   | F   | 13  | 36                    | 1stD          | +                 | +                       |
| XP11          | Northwest                   | M   | 23  | 12                    | 1stD          | +                 | +++                     |
| XP12          | Middle West                 | M   | 4   | 24                    | 1stD          | +                 | −                        |
| XP13          | Northwest                   | M   | 10  | 12                    | 1stD          | +                 | −                        |
| XP14          | Northwest                   | F   | 4   | 12                    | 1stD          | +                 | +                       |
| XP15          | Northwest                   | F   | 6   | 18                    | 1stD          | +                 | ++                      |
| XP16          | Northwest                   | M   | 15  | 36                    | 1stD          | +                 | +++                     |
| XP17          | Middle West                 | M   | 25  | 12                    | AC            | +                 | +++                     |
| XP18          | Southwest                   | F   | 6   | 24                    | 1stD          | +                 | −                        |
| XP19          | Middle West                 | F   | 6   | 11                    | 2ndD          | +                 | −                        |

1stD: consanguinity first degree; 2ndD: consanguinity second degree; AC: absence of consanguinity.
−: absence of clinical symptoms; +: presence of clinical symptoms.

3. Results

3.1. Clinical Findings. All investigated patients presented photophobia, skin photosensitivity, poikiloderma, and xeroderma with a mean age of 11 years. We registered consanguinity in 94.73% (18/19) of families. Among them, 88.89% were of the first degree and 11.11% of the second degree. XP symptoms had begun at a mean age of 16.5 months (range 2–36 months). Skin cancer was described in 73.68% of patients and ocular cancer was reported in 63.15%. Sex ratio (M/F) was 1.1, with different clinical presentations. Neurological symptoms were observed in 2 out of 19 patients. Besides data indicated in Table 1, we had also registered familial medical history, height, weight, and different common parameters.

3.2. Genotyping of XP-A Patients by PCR-RFLP and DNA Visualization by Gel Electrophoresis. Two XP patients (XP03 and XP05; see Table 1) who presented a clinical diagnosis of XP-A (association of different symptoms including neurological ones) were genotyped for the prevalent mutation XPA (p.Arg228X) in Pellegrin Hospital (Bordeaux). To detect the nonsense mutation in exon 6 of the XPA gene, we examined the HphI RFLP in the amplified exon 6 DNA fragments (351 bp). The C-to-T transition in exon 6 leads to a conversion of an arginine residue (CGA codon) to a stop codon (TGA) at amino acid 228. DNA from normal subjects who have a normal XPA allele gives a profile of two bands (320 bp and 31 bp fragments). In contrast, DNA from a XP patient with the homozygous mutation in exon 6 gives a profile of three bands (245 bp, 75 bp, and 31 bp fragments) caused by the creation of a new cleavage site for HphI in the 320 bp fragment by the nonsense mutation. After loading on 2% agarose gel, we found that both patients checked for the R228X mutation presented a profile homozygous for the mutant allele (T/T). Their parents were heterozygous carriers (C/T) with a profile of four bands (320 bp, 245 bp, 75 bp, and 31 bp fragments), confirming that these two patients are homozygous for the nonsense mutation at codon 228 and belong to the XP-A subclass.

3.3. Genotyping of XP-C Patients by Fragment Size and Sequence Analyses. Seventeen XP patients without neurological troubles (and their parents) were genotyped for the prevalent XPC mutation (c.1643_1644delTG, p.Val548AlafsX25) in Pellegrin Hospital. The GeneScan analysis performed for all samples tested showed three possible genotypes: wild-type (194 bp), heterozygous (192 and 194 bp), and homozygous (192 bp) for the deletion (Figure 1). All 17 index cases were homozygous for the 2bp deletion. This deletion is responsible for a frame shift causing the occurrence of a premature stop codon 25 residues downstream; then we checked for the same mutation on their siblings and found that they were also homozygous for the 2bp deletion. These results were confirmed by amplification of the fragment and sequencing: the presence of the deletion was identified by the SeqScape software (Applied Biosciences) (Figures 2 and 3).
Figure 1: Characterization of the 2 bp deletion in exon 9 of the XPC gene. Fragment sizing analysis from electropherograms (GeneScan software) showed three possible profiles for the c.1643_1644delTG mutation: wild-type (a); homozygous deleted (b); heterozygous (c) profile.

4. Discussion

We report here a DNA analysis for 19 unrelated XP families. Our study focused on two frequent mutations, the frame shift mutation (c.1643_1644delTG, p.Val548AlafsX25), located in exon 9 of the XPC gene, and the nonsense mutation (c.682C>T) in exon 6 of the XPA gene, both already described. XPA mutations were present in 2 of 19 (10.5%) patients with the same nonsense mutation, c.682C>T (p.Arg228X), and XPC mutations were identified in 17 of 19 (89.5%) with the common XPC mutation, c.1643_1644delTG, present at the homozygous state in all XP-C patients. Obviously, there is a correlation between the phenotype and genotype, which highlights the importance of the precocious diagnosis in these patients and an early full protection against sun-exposure to allow them to have almost a normal life.

The analysis of both parents (13 cases/19) or one parent (5 cases/19) showed that they were heterozygous carriers for the same mutation. In addition, the eight siblings suffering from XP were all homozygous for the frame shift mutation.

Molecular investigation of Soufir et al. [22] on 66 unrelated families from the Maghreb region showed that 85% of patients had mutations in the XPC gene; among them 87% shared the founder mutation (c.1643_1644delTG). 12% of XP patients had mutations in the XPA gene with a frequency of the mutation (c.682C>T) about 87.5%.

The XPA protein plays a central role in the first steps of NER and contains specific binding sites for other NER proteins such as DNA damage-binding protein 2 (DDB2) and RPA [30]. Hence, the severity of clinical manifestations decreases while the mutation moves from the N terminal to the C terminal of the protein, with the exception of the cases where splice site mutations permit the synthesis of small amount of normal protein [31]. Since the nonsense mutation is located on the sixth, N-terminal exon, we can speculate that most of the mRNA of the XPA gene would be produced, and it does not affect the major function of the XPA gene [32]. Of interest, the c.682C>T mutation occurs outside of the important domains such as the DNA-binding domain (exons 2–5, residues 98–219) and the zinc-finger motif (residues 105–129), but the XPA-TFIIH interaction region (residues 226–273 aa) essential for the excision reaction is lost, which explains the defective DNA repair system [26, 33, 34]. Therefore, the moderate phenotype of Tunisian XP-A patients may be explained by a residual DNA-binding activity of mutant XPA protein in comparison with the Japanese XP-A patients who had a splicing mutation at intron 3 at the homozygous state [26, 32]. A recent study of Tunisian XP-A patients showed
the presence of a recurrent mutation R228X with a founder effect by haplotype analysis [26]. The R228X mutation was described in North Africa patients [22, 26, 32, 35].

The deficient XP-C human cells lead to a reduction of the cisplatin repair and increased mutagenesis [36]. This protein is a major factor in damage recognition to initiate global genome NER. The presence of the common 2 bp deletion leads to a premature termination codon and absence of normal XPC protein [37]. Indeed, it affects interaction capacities between XPC protein, HR23B, CETN2 (centrin-2 protein), and TFIIH molecules, which are necessary for DNA damage recognition [22]. The DNA repair ability was found to be only 20% of proficient normal cells with the presence of this previous mutation [38]. This same mutation was described by Ben Rekaya et al. [39] in 100% of 14 XP-C families from different regions of Tunisia and also in two other African patients with XP [40]. Interestingly, Mahindra et al. [41] also described the XPC mutation in two brother patients from North Sudan. Furthermore, the molecular analysis of 24 Moroccan patients showed that 17 were homozygous for the c.1643_1644delTG mutation [42]. Most XP-C African patients with delTG mutation in both alleles have similar clinical features consisting of photosensitivity, pigmentedary lesions, and early onset of skin cancer without neurological involvement as our XP-C patients [22, 39, 41]. However, two patients were reported to be homozygous for the delTG but with neurological involvement [22].

Many studies showed that the mutation c.1643_1644delTG was spread in North Africa such as in Egypt, Italy, and Spain, which attracted the eyes of the researchers to the possibility of having the same ancestor. Soufir et al. proved the presence of a founder effect in the Mediterranean region using mathematical tools based on microsatellites haplotyping. They also showed that this common ancestor mutation was carried about 1250 years ago corresponding to 50 generations and approximately when Muslims from Arabia invaded Europe.

5. Conclusion

The high frequency of the founder mutation in XP patients from North Africa simplified the molecular diagnosis. In Algeria, the molecular investigation of XP confirmed that XPC and XPA genes were the most frequent with the mutations XPC-p.Val548AlafsX25 and XPA-R228X. Early diagnosis and full protection against sun-exposure are essential for preventing skin cancer and preserving vision in XP patients and can save lives.
It is important to do simple screening tests in risk families to detect heterozygous carriers for gene counseling, especially in communities with high marriage consanguinity. Moreover, prenatal diagnosis is greatly simplified when the molecular defect is easily accessible with the knowledge of the prevalent mutation in a given population, as observed in XP-C and XP-A patients.

Considering the efforts and costs required for the unscheduled DNA synthesis on cultured fibroblasts, we therefore recommend the use of DNA fragment sizing as the simplest and faster method for screening in XP diagnosis. In the population tested for this study, the high level of consanguinity, the large families with numerous siblings affected, and a high rate of premature death lead to the conclusion that the disease is clearly a major health concern. This simple screening test in risk families may greatly facilitate genetic counseling in exposed families as well as early management of affected patients. Furthermore, early diagnosis may improve prognosis of the disease, with extensive protection against the sun.

**Competing Interests**

The authors report that they have no competing interests relevant to the subject of this paper.

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**References**

[1] K. H. Kraemer, M. M. Lee, and J. Scotto, “Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases,” *Archives of Dermatology*, vol. 123, no. 2, pp. 241–250, 1987.

[2] L. Daya-Grosjean and A. Sarasin, “The role of UV induced lesions in skin carcinogenesis: an overview of oncogene and tumor suppressor gene modifications in xeroderma pigmentosum skin tumors,” *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 571, no. 1-2, pp. 43–56, 2005.

[3] A. G. Abdou, A. H. Maraaee, E. M. M. El-Sayed, and N. F. Elnайдany, “Immuno histochemical expression of ezrin in cutaneous basal and squamous cell carcinomas,” *Annals of Diagnostic Pathology*, vol. 15, no. 6, pp. 394–401, 2011.

[4] J. Albores-Saavedra, A. M. Schwartz, D. E. Henson et al., “Cutaneous angiosarcoma. Analysis of 434 cases from the surveillance, epidemiology, and end results program, 1973–2007,” *Annals of Diagnostic Pathology*, vol. 15, no. 2, pp. 93–97, 2011.

[5] D. Bootsma, K. H. Kraemer, J. E. Cleaver, and J. H. Hoeijmakers, “Nucleotide excision repair syndromes: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy,” *The Genetic Basis of Human Cancer*, vol. 2, pp. 211–237, 1998.

[6] M. Kaposo and F. Hebra, *On Diseases of the Skin, Including the Exanthemata*, New Sydenham Society, London, UK, 1875.

[7] R. E. Unlü, M. N. Koç, H. Orbay, and Ö. Şensoz, “Two extreme conditions of xeroderma pigmentosum,” *Journal of Craniofacial Surgery*, vol. 17, no. 6, pp. 1240–1242, 2006.

[8] W. J. Kleijer, V. Laugel, M. Berneburg et al., “Incidence of DNA repair deficiency disorders in western Europe: xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy,” *DNA Repair*, vol. 7, no. 5, pp. 744–750, 2008.

[9] Y. Hirai, Y. Kodama, S.-I. Moriwaki et al., “Heterozygous individuals bearing a founder mutation in the XPA DNA repair gene comprise nearly 1% of the Japanese population,” *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 601, no. 1-2, pp. 171–178, 2006.

[10] S.-I. Moriwaki and K. H. Kraemer, “Xeroderma pigmentosum- Bridging a gap between clinic and laboratory,” *Photodermatology, Photoimmunology and Photomedicine*, vol. 17, no. 2, pp. 47–54, 2001.

[11] B. Fazaa, M. Zghal, C. Bailly et al., “Melanoma in xeroderma pigmentosum: 12 cases,” *Annales de Dermatologie et de Venereology*, vol. 128, no. 4, pp. 503–506, 2001.

[12] M. L. Khatri, M. Bemghazil, M. Shafi, and A. Machina, “Xeroderma pigmentosum in Libya,” *International Journal of Dermatology*, vol. 38, no. 7, pp. 520–524, 1999.

[13] L. Moussaid, H. Benchikhi, E.-H. Boukind et al., “Cutaneous tumors during xeroderma pigmentosum in Morocco: study of 120 patients,” *Annales de Dermatologie et de Venereology*, vol. 131, no. 1, pp. 29–33, 2004.

[14] Z. Mohamed, E. F. Nadia, F. Becima et al., “Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 49 Tunisian cases,” *Tunisie Medicale*, vol. 83, no. 12, pp. 760–763, 2005.

[15] M. Hayashi, T. Ohito, K. Shioda, and R. Fukatsu, “Lesions of cortical GABAergic interneurons and acetylcholine neurons in xeroderma pigmentosum group A,” *Brain & Development*, vol. 34, no. 4, pp. 287–292, 2012.

[16] J. E. Cleaver, E. T. Lam, and I. Revet, "Disorders of nucleotide excision repair: the genetic and molecular basis of heterogeneity," *Nature Reviews Genetics*, vol. 10, no. 11, pp. 756–768, 2009.

[17] K. H. Kraemer, “Sunlight and skin cancer: another link revealed,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 1, pp. 11–14, 1997.

[18] E. C. Friedberg, *DNA Repair And Mutagenesis*, American Society for Microbiology, Washington, DC, USA, 2006.

[19] L. Guarente, L. Partridge, and D. C. Wallace, *Molecular Biology of Aging*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, USA, 2008.

[20] C. P. Selby and A. Sancar, “Molecular mechanism of transcription-repair coupling,” *Science*, vol. 260, no. 5104, pp. 53–58, 1993.

[21] A. Stary and A. Sarasin, “The genetics of the hereditary xeroderma pigmentosum syndrome,” *Biochimie*, vol. 84, no. 1, pp. 49–60, 2002.

[22] N. Soufir, C. Ged, A. Bourillon et al., “A prevalent mutation with founder effect in xeroderma pigmentosum group C from north Africa,” *Journal of Investigative Dermatology*, vol. 130, no. 6, pp. 1537–1542, 2010.

[23] M. Ben Rekaya, M. Jerbi, O. Messaad et al., “Further evidence of mutational heterogeneity of the XPC gene in tunisian
families: a spectrum of private and ethnic specific mutations,” *BioMed Research International*, vol. 2013, Article ID 316286, 7 pages, 2013.

[24] K. Sugasawa, J. M. Y. Ng, C. Masutani et al., “Xeroderma pigmentosum group C protein complex is the initiator of global genome nucleotide excision repair,” *Molecular Cell*, vol. 2, no. 2, pp. 223–232, 1998.

[25] A. Uchida, K. Sugasawa, C. Masutani et al., “The carboxy-terminal domain of the XPC protein plays a crucial role in nucleotide excision repair through interactions with transcription factor IIH,” *DNA Repair*, vol. 1, no. 6, pp. 449–461, 2002.

[26] O. Messaoud, M. Ben Rekaya, W. Cherif et al., “Genetic homogeneity of mutational spectrum of group-A xeroderma pigmentosum in Tunisian patients,” *International Journal of Dermatology*, vol. 49, no. 5, pp. 544–548, 2010.

[27] K. Tanaka, N. Miura, I. Satokata et al., “Analysis of a human DNA excision repair gene involved in group A xeroderma pigmentosum and containing a zinc-finger domain,” *Nature*, vol. 348, no. 6296, pp. 73–76, 1990.

[28] H. Asahina, I. Kuraoka, M. Shirakawa et al., “The XPA protein is a zinc metalloprotein with an ability to recognize various kinds of DNA damage,” *Mutation Research-DNA Repair*, vol. 315, no. 3, pp. 229–237, 1994.

[29] I. L. Hermanson-Miller and J. J. Turchi, “Strand-specific binding of RPA and XPA to damaged duplex DNA,” *Biochemistry*, vol. 41, no. 7, pp. 2402–2408, 2002.

[30] M. Asmuss, L. H. F. Mullenders, A. Eker, and A. Hartwig, “Differential effects of toxic metal compounds on the activities of Fpg and XPA, two zinc finger proteins involved in DNA repair,” *Carcinogenesis*, vol. 21, no. 11, pp. 2097–2104, 2000.

[31] O. Messaoud, M. Ben Rekaya, H. Ouragini et al., “Severe phenotypes in two Tunisian families with novel XPA mutations: evidence for a correlation between mutation location and disease severity,” *Archives of Dermatological Research*, vol. 304, no. 2, pp. 171–176, 2012.

[32] C. Nishigori, M. Zghal, T. Yagi, S. Imamura, M. R. Komoun, and H. Takebe, “High prevalence of the point mutation in exon 6 of the xeroderma pigmentosum group A-complementing (XPAC) gene in xeroderma pigmentosum group A patients in Tunisia,” *American Journal of Human Genetics*, vol. 53, no. 5, pp. 1001–1006, 1993.

[33] J. C. States, E. R. McDuffie, S. P. Myrand, M. McDowell, and J. E. Cleaver, “Distribution of mutations in the human xeroderma pigmentosum group A gene and their relationships to the functional regions of the DNA damage recognition protein,” *Human Mutation*, vol. 12, no. 2, pp. 103–113, 1998.

[34] K. Amr, O. Messaoud, M. El Darouti, S. Abdelhak, and G. El-Kamah, “Mutational spectrum of Xeroderma pigmentosum group A in Egyptian patients,” *Gene*, vol. 533, no. 1, pp. 52–56, 2014.

[35] J. E. Cleaver, L. H. Thompson, A. S. Richardson, and J. C. States, “A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy,” *Human Mutation*, vol. 14, no. 1, pp. 9–22, 1999.

[36] Z. Chen, X. Susan, J. Yang, and G. Wang, “Defining the function of XPC protein in psoralen and cisplatin-mediated DNA repair and mutagenesis,” *Carcinogenesis*, vol. 24, no. 6, pp. 1111–1121, 2003.

[37] H. R. Rezvani, C. Ged, B. Bouadjar, H. de Verneuil, and A. Taieb, “Catalase overexpression reduces UVB-induced apoptosis in a human xeroderma pigmentosum reconstructed epidermis,” *Cancer Gene Therapy*, vol. 15, no. 4, pp. 241–251, 2008.

[38] F. Chavanne, B. C. Broughton, D. Pietra et al., “Mutations in the XPC gene in families with xeroderma pigmentosus and consequences at the cell, protein, and transcript levels,” *Cancer Research*, vol. 60, no. 7, pp. 1974–1982, 2000.

[39] M. Ben Rekaya, O. Messaoud, F. Talmoudi et al., “High frequency of the V548A fs X572 XPC mutation in Tunisia: implication for molecular diagnosis,” *Journal of Human Genetics*, vol. 54, no. 7, pp. 426–429, 2009.

[40] S. G. Khan, K.-S. Oh, T. Shahalvi et al., “Reduced XPC DNA repair gene mRNA levels in clinically normal parents of xeroderma pigmentosum patients,” *Carcinogenesis*, vol. 27, no. 1, pp. 84–94, 2006.

[41] P. Mahindra, J. J. DiGiovanna, D. Tamura et al., “Skin cancers, blindness, and anterior tongue mass in African brothers,” *Journal of the American Academy of Dermatology*, vol. 59, no. 5, pp. 881–886, 2008.

[42] M. A. Senhaji, O. Abidi, S. Nadifi et al., “C.1643-1644delTG XPC mutation is more frequent in Moroccan patients with xeroderma pigmentosus,” *Archives of Dermatological Research*, vol. 305, no. 1, pp. 53–57, 2013.