Research Article

Further Evidence of Mutational Heterogeneity of the XPC Gene in Tunisian Families: A Spectrum of Private and Ethnic Specific Mutations

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Xeroderma Pigmentosum (XP) is a rare recessive autosomal cancer prone disease, characterized by UV hypersensitivity and early appearance of cutaneous and ocular malignancies. We investigated four unrelated patients suspected to be XP-C. To confirm linkage to XPC gene, genotyping and direct sequencing of XPC gene were performed. Pathogenic effect of novel mutations was confirmed by reverse Transciptase PCR. Mutation screening revealed the presence of two novel mutations g.18246G>A and g.18810G>T in the XPC gene (NG_011763.1). The first is present in one patient XP50NEF, but the second is present in three unrelated patients (XP16KEB, XP28SFA, and XP45GB). These 3 patients are from three different cities of Southern Tunisia and bear the same haplotype, suggesting a founder effect. Reverse Transciptase PCR revealed the absence of the XPC mRNA. In Tunisia, as observed in an other severe genodermatosis, the mutational spectrum of XP-C group seems to be homogeneous with some clusters of heterogeneity that should be taken into account to improve molecular diagnosis of this disease.

1. Introduction

Xeroderma Pigmentosum (XP) is a rare monogenic autosomal recessive DNA repair disorder. It is characterized by an extreme sun sensitivity especially to Ultra Violet Radiation (UVR) that induces cutaneous and mucous membranes cancers of the eyes and mouth [1].

XP is the archetype of an expanding family of Nucleotide Excision Repair (NER) diseases where XP cells were found to have defects in seven of the NER pathway proteins (XPA to XPG) [2]. In addition, an XP variant group (XP-V) involving a DNA translesional synthesis (TLS) and polymerase Pol eta (POLH) has also been described [3]. XP-V patients have a normal NER level, but their cells are hypermutable following UVR.

This disease is rare in the United States and Europe (1/100000) [4] but relatively more frequent in Japan (1/22000) [5] and in North Africa [6] especially in Tunisia.
with 1/10000. This high frequency might be due to the high rate of consanguinity in Tunisia (29.8%) especially among families with autosomal recessive diseases (78.4%) [7] and to founder effects reported in XPC [8], XPA [9], and XPV genes (unpublished data) in the Tunisian population.

The XPC gene plays an important role in the early step of Global Genome Repair pathway (GGR). XPC protein is involved in the recognition of the damaged DNA via a complex composed by HR23B-XPC-CEN during GGR pathway [10]. Currently, 46 mutations have been described in this gene. The most common are deletions (36.9%), substitutions (34.7%), splicing (19.5%), and insertions (8.6%). Splice site mutations have been described, in introns 2, 5, 1, 8, 9, and 11 [11].

Molecular investigations of the XP-C group showed that it is the major group among the five North African countries called the Maghreb [6, 8, 12, 13]. Indeed, among the studied patients, about 87% of them shared the recurrent founder mutation c.1643_1644delTG (p.V548AlafsX25) [6]. This was confirmed by its high carrier frequency estimated to be 1/250 in Morocco [12]. Having a homogeneous mutational spectrum for the XPC gene has greatly simplified the molecular diagnosis of XP-C in the region [6, 8, 13]. Furthermore, two other private mutations have been recently reported in North African patients [6]. In this study, we have further enlarged the mutational spectrum of the XPC gene with the identification of two novel gene alterations.

2. Patients and Methods

2.1. Patients. This study was performed on 4 consanguineous Tunisian families originating from Southern Tunisia and encompassing 15 individuals. Among them, 4 patients (2 males and 2 females) were suspected to be XP-C. The age of the investigated XP patients is heterogeneous (ranging from 7 to 22 years). Consanguinity was confirmed in all families.

2.2. Methods. Informed consent was obtained from all available family members or the parents of minor children. Families were interviewed using structured questionnaire to collect information about family history, consanguinity, affected members, and associated diseases. This protocol was approved by the Ethics Committee of the Pasteur Institute of Tunis.

2.2.1. DNA Extraction. DNA was isolated from peripheral blood leukocyte using salting out method [14] or Qiagen kit DNA extraction. Genotyping for 14 available individuals was determined using 3 microsatellite markers spanning a 1.43 Mb interval that overlaps the XPC gene region (D3S3602, D3S1585, and D3S3613). Microsatellite markers were selected from the genetic maps available on NCBI browsers and the CEPH genotype database (http://www.ceph.fr/en/cephdb/) on the basis of their heterozygosity percentage and closeness to the XPC gene. Genomic DNA amplification was carried using specific primers (Table 2), and the fragments were amplified in a volume of 25 μL containing 10 ng of DNA, 10X PCR buffer, 0.2 mM of each dNTP, 1.5 mL of MgCl₂, 0.5 μM of one of each primer, and 0.5 U AmpliTag DNA polymerase (Invitrogen). Fluorescent PCR products were run on the Genetic Analyzer and analyzed using the Gene Mapper software.

2.2.2. Mutation Analysis. Exons 4 to 16 and their flanking regions were amplified from genomic DNA. Primer pairs were generated using Primer 3 http://frodo.wi.mit.edu/ and UCSC In Silico-PCR (http://genome.ucsc.edu/cgi-bin/hgPcr) (Table 3). PCR conditions used in our laboratory were previously described [8]. PCR products were directly sequenced using the ABI 3130 Genetic Analyzer. Nomenclature mutations were performed using the HGVS version 2.0 (Mutalyzer 2.0.beta-26).

2.2.3. RNA Extraction and RT-PCR. In order to assess the impact of the identified mutations at the RNA level, total RNA was isolated from leukocytes using trizol-chloroform purification and isopropanol precipitation [15]. The only biological material that was available for RNA extraction for the XP45GA and XP50NEF patients was 1 mL of whole blood frozen in 10% Dimethyl Sulfoxide (DMSO) at −80°C, 4 years ago. RT-PCR of the control was performed on a fresh blood sample for a healthy volunteer. The RNA (0.4 μg) was reverse transcribed in a final volume of 20 μL using the reverse transcriptase (Ref 1785826, Roche), OligoDT (Ref 27-7858-01, Pharmacia), Buffer IX (Ref 1785826, Roche), dNTP 1 mM (Invitrogen), and the RNase inhibitor 40 U/μL (1785826, Roche). The cDNA corresponding to the XPC gene was amplified using a new couple of primers (Table 2). In order to evaluate the quality of the cDNA amplification, a PCR for a housekeeping gene GAPDH was conducted using primers showed in Table 2 (Figure 3).

3. Results

3.1. Clinical Findings. All investigated patients had the classical skin abnormalities of XP including xerosis, skin atrophy, and abnormal pigmentation with no neurological abnormalities. In our study, XP symptoms began at a mean age of 39 months. Skin hyperphotosensitivity from UVR was present in all patients. The specific poikilodermic pigmentation pattern (association between achromic spots and poorly limited pigmented maculae) covered the majority of the sun-exposed areas. The mean age at onset of the first skin cancer was 12 years (range 8 to 17). Basal Cell Carcinoma (BCC) occurred in 3 patients (XP28SFA, XP45GB, and XP50NEF). Among them two patients (XP50NEF and XP45GB) developed melanoma (MM) and Spindle Cell Carcinoma (SCC) (Table 1).

In addition, patients XP45GB and XP28SFA developed, respectively, a thyroid cancer and a benign articular tumor of the knee (Table 1). For the patient XP45GB, clinical and ultrasound exams showed bilateral multinodular thyroid without hormonal dysfunction (normal rates of T4, T3, and TSH). After thyroidectomy, histological analysis confirmed thyroid carcinoma. No metastasis was found.
Table 1: Microsatellite markers surrounding the XPC locus.

| Microsatellites markers | Physical distance (pb) | Genetic location (cM) | Heterozygosity | Number of alleles | Primers sequence | Allele size range | Fluorescence |
|-------------------------|------------------------|-----------------------|----------------|------------------|-----------------|-----------------|-------------|
| D3S3602                 | 13.926.066–13.926.191  | 31.40                 | 57.69%         | 7                | F: AAAATCTAACCCTTCTCCTCC R: AATCAGACAATACACAAGGGG | 114–132 | FAM |
| D3S1585                 | 13.941.728–13.941.855 | 33.00                 | 57.14%         | 8                | F: TGGACAGCCAGAAGT G: TTTGACTGTCAGGGG | 126–144 | NED |
| D3S3613                 | 15.361.998–15.362.181 | 35.70                 | 78.57%         | 8                | F: CATCTATGGCTGCACTGAGG | 172–208 | FAM |

Table 2: Sequence primers used for PCR amplification of XPC and GAPDH genes.

| PCR   | Primer Sense | Primer Anti-sense | $T_m$ °C |
|-------|--------------|-------------------|---------|
| Exon 4 | ATGCCTCAGTTCCCTCCTCCTCC | CACTTTGATACGTGTCCTGTCCTCC | 55 |
| Exon 5 | GATCTACTGTGCACTGGAGGAGGAG | CAAAGGCTCAGAGAGAGAAGAAGATTTG | 55 |
| Exon 6 | TGGAAAGCAAGCCAGCCAAAAAAGAGG | GACCTGAACCCAGCCTTCGAG | 55 |
| Exon 7 | CTCCCTCTTTTATTTTTCTTGGCTGTG | GGTGCTGTGACATGGTGAATCAGC | 55 |
| Exon 8 | TTTGAAAGACAGCATACCCCATACACAC | TGCCCAAGCTTTCTTCTACACAG | 55 |
| Exon 9 | CCGGGGCTGTCACATCTGACAGGAG | CAAGGCTTACCTTCCAAACAG | 55 |
| Exon 10 | CCTTGGCTCCACCCTTCTCTGTG | CCTGTTAAGCTTGTATTTTCCCTCCGTG | 60 |
| Exon 11 | AGATTAGGGTGGTTGTAATGTGACATC | GGACCTGGAGGCTCATCATCAG | 55 |
| Exon 12 | CTGTTAGGTGTTGTTCTTGGAGGTC | CGGTGTAGATGGGCAAGGTTC | 60 |
| Exon 13 | GCCAGCATCAAGAGGGGCTTCAC | AAATCCATGTCATATCTCTGAAATTTG | 60 |
| Exon 14 | AGGGTGGAGCAAGGGCTTC | CCTGTTACATGCTTCTGCTGTGC | 60 |
| Exon 15 | CCACATGAAGTTTGGAGTGCTAGTACAAGGAG | ACAGGGCTTGGGGGAGAGGAG | 55 |
| Exon 16 | CCCTTGGCTCCACCAGCTTTCAC | ATGGTGGCTCCTGCTTCCTTC | 60 |
| cDNA | TTGAAGAACTTAGTGAGCCTGTG | GCTGGGTTGCTTCTCCTC | 60 |
| GAPDH | cDNA | GAGTCAAGGGATTTGTTGTGCTG | TTGATTTTGGGAGGATCCTG | 60 |

3.2. Genetic and Molecular Results. For molecular diagnosis, we first screened the recurrent founder mutation for all XP-C suspected patients. Since this gene alteration has not been identified, linkage to the XPC gene was performed. Fourteen individuals were genotyped with 3 informative microsatellite markers. All XP-C patients showed homozygous genotypes for the D3S1585 marker. Three patients (XP16KEB, XP45GB, and XP28SFA) shared the same founder haplotype (126–130), respectively, for D3S3602 and D3S1585 markers (Figure 1), whereas patient XP50NEF presented a private haplotype (Figure 2). Therefore, sequencing of exons 4 to 16 was performed for all XP patients. Two novel variations were identified. The first one is a splicing mutation (g.18246G>A; c.779+1G>A) present at a homozygous state in patient XP50NEF. It likely abolishes the exon 6 splicing donor site as shown by the following bioinformatic tools: “BDGP” (http://www.fruitfly.org/seq_tools/splice.html) and “Human splicing finder mutation” (http://www.umd.be/HSF/). This mutation probably leads to a premature stop codon at position 284 of XPC protein (p284X).

RT-PCR results showed the absence of XPC mRNA for (XP50NEF and XP45GB) patients having, respectively, the c.779+1G>A and c.850G>T mutations, although we succeeded the amplification of the GAPDH cDNA (Figure 3).

4. Discussion

XP is a highly heterogeneous disease at clinical and genetic levels. XP-A and XP-C are the most frequent groups, especially in Southern Europe and North Africa [4, 6]. Previous studies have shown that all XP-C Tunisian patients shared the same mutation c.1643_1644delTG (p.V548AlafsX25) affecting exon 9 [8]. We report here two novel mutations in XP-C Tunisian patients. All investigated patients have classical symptoms of XP with varying severity. BCC occurred in three among four patients confirming that it is the most frequent skin cancer observed in XP patients [16]. Among the studied patients, two (XP28SFA and XP16KEB) have benefited from a complete UVR protection thanks to the help of the patients support group “Helping Xeroderma Pigmentosum children” (http://www.xp-tunisie.org.tn/) (Table 1). Consequently, XP28SFA patient developed one BCC at the age...
of 17 years that is higher than the median age at onset of Non-Melanoma Skin Cancer (NMSC) in XP patients (9 years) [17]. Regarding XP16KEB patient, until the age of 7 years, he did not develop skin cancer. Melanoma occurred in two patients XP50NEF and XP45GB at the age of 17 years which is lower than the median age at onset of melanoma (22 years) in XP patients [17]. Regarding the XP45GB patient, she was treated by retinoid at age 13 during a period of 3 years; after that the number of NMSC was increased. At age 16, she developed nodular thyroid. During the last consultation at age 17, we discovered that the patient showed resistance to cisplatin chemotherapy used to treat multiple spindle-cell carcinomas of the face. The precise role of retinoid in cancer inhibition has not been clearly demonstrated in XP patients. Recent studies have shown a key role of GGR pathway especially XPC protein to repair cisplatin and eventually UV lesions in melanogenesis [18, 19]; further investigation possibly will explain the resistance of XP-C patient to chemotherapy.

In addition to skin cancers, XP45GB developed a thyroid cancer. She was not treated by X-rays or radiotherapy. According to the genetic questionnaire filled by the interview of the parents, there is no other cancer case in the family. Generally, XP patients can rarely develop internal cancer because they die at an early age. A recent study demonstrated that multinodular thyroid was the most frequent kind of internal tumor in XP-C patients [16], while adenocarcinoma of the thyroid was reported in only one 18-year-old XP-C patient [20]. This might be due to the accumulation of oxidative damage in the thyroid [21].

In the absence of the recurrent mutation XPC c.1643_1644delTG, genotyping and haplotype analysis showed that...
all XP-C patients are homozygous for the closest marker to XPC gene, D3S1585. Sequencing and mutation analysis confirmed the presence of the two novel mutations. Thus showing that the D3S1585 marker is the most informative marker.

In order to test the impact of the two identified mutations at the functional level, we performed an RT-PCR experiment for patients when RNA was available. For XP50NEF and XP45 GB patients, XPC mRNA was absent. The same result was obtained in XP-C patients bearing the recurrent mutation (c.1643-1644delTG) in exon 9. The presence of these mutations probably reduces transcription of the XP-C gene or alters the stability of its mRNA which could be degraded by the NMD system (Nonsense Mediated mRNA Decay) [22].

Although the two patients XP45GA (having a nonsense mutation) and XP50NEF (having a splice site mutation) underwent a low UV protection and have the same age, the second patient XP50NEF had a milder phenotype than the first (Figures 1 and 2). A small amount of normally spliced mRNA of the XPA gene is sufficient to explain relatively mild clinical features of XP-A patients [23]. Previous study reported that XP-C patient with a splice site mutation has a very low level of normal XPC mRNA transcript (3%) resulting in 29% of normal level of normal sized XPC protein [24]. For the XP50NEF patient, cell lines are not available to confirm the presence of a small amount of XPC mRNA isoforms.

Genetic counseling was performed for four related individuals. The sister of XP28SFA and the brother of XP45 GB were healthy with a homozygous genotype, whereas the cousin of XP45 GB and the brother of XP50NEF were healthy heterozygous carriers (Figure 1).

A recent study showed that in Tunisian patients among 174 genetic diseases with identified molecular defect, 73 (41.9%) were founder mutations. For the majority of them,
Table 3: Clinical features of the XP-C patients.

| Patients code | Sex | Age at first consultation (years) | Age at onset of the first skin tumor (years) (number) | City geographic origin | Internal cancer (age at onset) | Protection from UVR |
|---------------|-----|---------------------------------|------------------------------------------------------|-----------------------|--------------------------------|---------------------|
| XP16KEB       | M   | 2                               | —                                                    | Kebelli               | —                              | —                   |
| XP28SFA       | F   | 3                               | 17 (1)                                              | Sfax                  | Benign articular tumor of the knee (18) | +++                |
| XP45GB        | F   | 2                               | 17 (1) 8 (> 20) 9 (> 10)                            | Gafsa                 | Thyroid cancer (16)            | +                   |
| XP50NEF       | M   | 6                               | 17 (1) 11 (>5) 17 (1)                               | Nefta                 | —                              | +                   |

MM: melanoma; BCC: Basal Cell Carcinoma; SCC: Spino Cell Carcinoma; +++: high protection; +: low protection.

Figure 3: Agarose gel electrophoretic analysis of the RT-PCR showed the absence of the XPC cDNA amplification for XP50NEF and XP45GB patients compared to healthy control. The cDNA of the GAPDH gene was successfully amplified for all individuals. The variability of intensity of amplification between XP45GA patient and control is due to the quality of conservation of the blood sample. (M: 1 kb DNA ladder molecular size marker (GeneRuler)).

geographic distribution is limited to a region of the country [25]. A similar situation is observed in our study where the c.850G>T founder mutation seems to be restricted to the South of Tunisia. Knowing the disease features in a given population is important to offer a suitable management of the patients and their families [25]. As XP-C is the most common group in North Africa with a high morbidity and an early mortality, primary diagnosis is important. As XP-C patients do not show neurological impairment, they could live a nearly normal life if they benefit from an early full protection against sunexposure. This is the case of patient XP28SFA who has been protected during early infancy and is now following “normal” university studies. But other clinical exams should be programmed especially thyroid ultrasound for early detection of internal cancer. Since dermatological exam could not confirm exactly the XP group, specifically for young patients, molecular diagnosis is necessary to confirm clinical diagnosis and to propose genetic counseling.

The high frequency of the same founder mutations in patients from North Africa has greatly simplified the molecular diagnosis of XP syndrome in Maghreb region. Considering the efforts and costs required for the unscheduled DNA synthesis on cultured fibroblasts, we therefore suggest, for suspected XP-C patients without XPC-p.Val548AlafsX25 mutation, genotyping analysis to confirm linkage to XPC gene especially for consanguineous or endogamous families. If linkage to XPC gene is confirmed, the second founder mutation, c.850G>T in exon 7, should be investigated. In the absence of this mutation, sequencing of exon 6 must be performed. This exon contains three different mutations (c.652delT, c.658C>T, and c.779+1G>A) described in North African patients. Cascade screening should be proposed to all the families in which an index case has an identified mutation [26, 27].

5. Conclusion

Our results show that private mutations, ethnic specific mutations, and recurrent founder mutations could explain the mutational heterogeneity of XP-C group in Tunisia. In addition, our findings provide a valuable tool for molecular diagnosis and carrier screening of this severe genodermatosis at the regional level where endogamy is still culturally favored.

Conflict of Interests

All authors declare that they have no conflict of interests.

Authors’ Contribution

Mariem Ben Rekaya and Manel Jerbi contributed equally to this work.

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