Familial predisposition to TP53/complex karyotype MDS and leukemia in DNA repair-deficient xeroderma pigmentosum

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1 Figure, 1 Table

The online version of this article contains data supplements with Supp. patient data, Supplemental Tables 1-4, Supplemental Figures 1-3, and Supplemental Methods.
TO THE EDITOR:

Xeroderma pigmentosum (XP) patients are abnormally sensitive to sunlight as a consequence of an autosomal recessive defect in nucleotide excision repair enzymes.\(^1\) Seven complementation groups have been reported, of which the most common is XP-C. The XPC protein is the first player in the repair process, and is necessary to recognize bulky DNA adducts and to recruit other DNA repair enzymes.\(^2\) In the absence of photoprotection, this deficiency causes skin tumors with an extremely high frequency.\(^3\)

In the last 30 years, we established a cohort of 161 XP-C patients from 142 consanguineous North African families living in France, all exhibiting a founder homozygous \(XPC\) c.1643_1644 delTG; p.Val548AlafsX572 (delTG) mutation leading to the complete absence of the XPC protein.\(^4\) Here, we report that 13 of these patients (8.07%), 7 men and 6 women, originating from 10 families, developed myelodysplastic syndrome with an excess of blast cells (EB-MDS), acute myeloid leukemia (AML), or T-cell acute lymphoblastic leukemia (T-ALL) at ages ranging 7-29 (Table 1; Supplemental patient data). In these families, 12 additional siblings also suffering of XP-C did not develop an overt MDS or AML during the follow-up period (up to 20 years; Table 1 and Supplemental Figure 1). Overall, the frequency of MDS and AML in this cohort is several thousand times higher than what was reported in the corresponding French general population (0.04 per 100,000 15- to 19-year-olds and 0.19 per 100,000 20- to 24-year-olds)\(^5\). Using PubMed search, we compiled all reported cancer cases in XP patients worldwide between 1958 and 2018. Among 1,510 XP patients, 11 had a hematological malignancy (including three patients also in our cohort, Supplemental Table 1). Of these, five had the North African \(XPC\) founder mutation delTG, while five others originating from the Mediterranean basin may carry the same founder mutation. The remaining patient had neurological signs suggesting \(XPA\) rather than \(XPC\) mutation.\(^6\)

Details on our 13 XP-C patients with MDS and/or AML/T-cell ALL are shown in Table 1 and Supplemental Patient Data. All patients were diagnosed as classical XP due to early sensitivity to sunlight and skin cancers. Specific DNA repair defect was confirmed in skin fibroblasts available from 9 patients.\(^4\) The homozygous founder \(XPC\) delTG mutation was identified in the 13 patients or relatives (Table 1). We had previously calculated the \(XPC\) delTG as being as old as 1,250 years in North Africa, suggesting a common ancestor.\(^4\) XP frequency in Tunisia and carrier frequency in Morocco were estimated to be 1/10,000 and 1/250, respectively.\(^7,8\)

Whole-exome sequencing (WES) of germinal DNA was performed in six patients from distinct families, and in both parents in three. We detected as expected high level of
inbreeding (Supplemental Table 2) and a Middle East population distribution of variants, except in patient #6 which variant distribution was at the boundary between Middle East and European populations (Supplemental Figure 2).

The hematological malignancies were diagnosed at a median age of 22 and median age at death was 25 (Table 1). Only the patient #11, who was diagnosed AML recently and received an allogeneic hematopoietic stem cell transplant (HSCT), remained alive three months after HSCT (Supplemental Table 3). Of the seven patients diagnosed as MDS with excess of blast cells (MDS-EB, previously known as RAEB), two died before transformation, whereas the five others progressed to AML (>20% bone marrow blast cells). One of these patients had been treated for an early-progenitor T-ALL and later an unrelated MDS-EB that progressed to terminal AML (Patient #5, Figure 1A). Five other patients presented directly an overt AML at diagnosis. The thirteenth patient (#9) was diagnosed with a T-ALL. When available, bone marrow cytogenetics showed typical MDS/AML-associated abnormalities, with deletions affecting chromosomes 5q, 7q or 20q and trisomy 8 (Table 1; Figure 1A,B; Supplemental Patient Data). Paired leukemic and germline (skin fibroblast cells) WES analysis in 5 patients with MDS/AML identified somatic TP53 deleterious mutations in every case (Table 1 and Supplemental Table 4). Rare additional somatic myeloid or T-ALL-associated cancer gene mutations were found (Table 1).

Collectively, these data strongly suggest a familial predisposition to hematological malignancies that co-segregates with the homozygous founder Mediterranean delTG mutation with an intermediate penetrance. No other clinical phenotypes, personal or family history of cytopenia or cancer predisposition were reported in these families. Given that MDS/AML are extremely rarely seen in XP patients with different XPC or other XP gene mutations, and that the delTG XPC mutation leads to the total absence of XPC protein like >90% of XPC mutations (Supplemental Figure 3), we searched for an additional predisposing genetic variant that would co-segregate with the MDS/AML phenotype. First, WES of germline DNA performed in six patients did not identify any variant in known familial MDS/AML genes, including GATA2, RUNX1, CEBPA, DDX41, TP53, BRCA1, BRCA2, FANC, SBDS, SRP72, ERCC6L2, DNAJC21, MBD4, SAMD9, SAMD9L, telomere genes, and other genes involved in hematopoietic malignancies. Secondly, genome-wide search for shared homozygous or heterozygous single nucleotide polymorphisms (SNPs) from filtered variant files only retrieved the delTG XPC mutation (Supplemental Methods). Thirdly, SNP-array analysis of fibroblast DNA detected no copy number variation but a unique shared homozygosity region that delineated 3.2 mega base pairs (Mbp) at chromosome 3p25, confirmed using WES
analysis, which, as expected, included the XPC gene (Figure 1C). We captured and sequenced this complete region, but none of the rare variants common to all patients were predicted to be deleterious, nor located in genes that would suggest a relevant predisposition. Since the Fanconi anemia (FA) gene FANCD2 is located in the vicinity of this region at 3p25, we sequenced this gene but did not find any suspect variant, while mitomycin-C testing in skin fibroblasts ruled out a FA pathway deficiency.

TP53 mutations and complex karyotypes involving del5 and del7q are often associated with secondary or therapy-related MDS or AML. However, with the exception of three patients (#5, #7 and #8; Supplemental Patient Data), the other patients did not receive chemo- or radio-therapies before their hematological malignancies were discovered. Importantly, if hematological malignancies were caused by genotoxic environmental exposure in the context of XP DNA repair-deficiency, the very high frequency of hematological malignancies should have been reported for XP patients whatever their ethnic and genetic backgrounds, which is not the case.

In conclusion, we report the exceptionally high frequency of hematological, mostly myeloid, malignancies in a subpopulation of XP-C patients with the same XPC mutation, this later having been spread in North African families for more than 1,000 years. MDS/AML in these patients display early age onset, bone marrow dysplastic features, low-intermediate blast cell counts, somatic TP53 mutations, and complex karyotypes including del5q and del7q. This is reminiscent of MDS/AML associated with ageing, genotoxic stress or post-therapeutic in the general, in the DNA repair proficient population. Interestingly, we and others have also reported the extremely frequent rate of TP53 mutations in skin tumors that occur in XP patients, suggesting hypermutability and common oncogenesis pathways. While the complete absence of XPC protein in patients with the Mediterranean delTG XPC mutation rules out a specific role of this particular mutation in MDS/AML development, a distinct genome variation, located or not in the minimal region of homozygosity, and still to be identified, may contribute to MDS/AML development in the XP-related, DNA repair-deficient background. Whatever the molecular mechanism, the reported myeloid cancer predisposition should prompt a careful monitoring of blood diseases in delTG XPC homozygous patients who originate from Mediterranean South basin, i.e. annual blood examination, to enable early detection of cytopenias or blast cells. Clinicians must have a high degree of MDS/AML suspicion in these patients and perform bone marrow examinations if blood counts are consistently abnormal.
Acknowledgements

The authors are very thankful to the physicians who took care of some of these XP patients: Dr. C. Blanchet-Bardon, Pr. M. F. Avril, Dr. S. Hadj-Rabia and Dr. R. Itzykson (Paris, France), Dr. L. Schirmer (Nancy, France), Dr. C. Hardy (Vaison-la-Romaine, France), Pr. J. F. Stalder (Nantes, France), Pr. L. Sutton and Dr. J. Lejeune (Tours, France), Pr. G. Michel (Marseille), and Pr. M. Beylot-Barry (Bordeaux, France).

We are also thankful to I. Plo (Villejuif, France), D. Stoppa-Lyonnet (Paris, France), and A. Remenieras, M. Lafage-Pochitaloff and I. Arnoux (Marseille, France) for their helpful discussion. We are thankful to Pr. J. C. Ehrhart (Villejuif) for critical reading of the manuscript.

Part of this work was supported by the “Association des Enfants de La Lune” (Bellegarde sur Valserine, France) (to A.S.), the ERC St Grant Consolidator #311660, the ANR-10-IBHU-0002 Saint-Louis Institute program, and the PAIR program CONECT-AML (Collaborative Network on research for children and teenagers with AML) INCa-ARC-LIGUE_11905 (to J.S.).

Authorship


Conflict of interest

The authors have no conflict of interest to declare.
References


Table 1. Clinical and genetical descriptions of XP-C patients with MDS/AML

<table>
<thead>
<tr>
<th>Patient Number (gender)</th>
<th>ID</th>
<th>Geographic origin</th>
<th>XP diagnosis (age)</th>
<th>Mutation on the XPC gene</th>
<th>Hematological malignancies type (age at diagnosis)</th>
<th>Somatic/numerical abnormalities (un Troublestated)</th>
<th>Somatic mutations (un Troublestated)</th>
<th>Miscellaneous (age)</th>
<th>Familial information (age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M)</td>
<td>XP10VI</td>
<td>Moroccan</td>
<td>XP (6y)</td>
<td>HMZ deITG</td>
<td>AML-4 (27y)</td>
<td>N/A</td>
<td>N/A</td>
<td>Death due to major toxicity after chemotherapy (28y)</td>
<td>Cousin of patient #12 (13y) brother (death at 6y)</td>
</tr>
<tr>
<td>2 (M)</td>
<td>XP2VI</td>
<td>Tunisian</td>
<td>XP C (3y)</td>
<td>HMZ deITG</td>
<td>AML-6 (16y)</td>
<td>del(5q); monosomy 7; del(7q); del(13q)</td>
<td>TP53 p.T284F</td>
<td>RR HCTD (10y) Death of toxicity with persistent leukopenia (12y)</td>
<td>Cousin of patient #13 13y brother (death at 27y)</td>
</tr>
<tr>
<td>3 (f)</td>
<td>XP28VI</td>
<td>Tunisian</td>
<td>XP (9y)</td>
<td>HMZ deITG</td>
<td>Complex karyotype with del(9q)</td>
<td>TP53 p.E150*</td>
<td>N/A</td>
<td>Treatment for three years Death (27y)</td>
<td>1.35 brother (13y)</td>
</tr>
<tr>
<td>4 (f)</td>
<td>XP30VI</td>
<td>Moroccan</td>
<td>XP C (2y)</td>
<td>HMZ deITG</td>
<td>Monosomy 7</td>
<td>N/A</td>
<td>N/A</td>
<td>Death treated by reduced dose chemotherapy Death (10y)</td>
<td>N/A</td>
</tr>
<tr>
<td>5 (M)</td>
<td>XP30VI</td>
<td>Moroccan</td>
<td>XP C (3y)</td>
<td>HMZ deITG</td>
<td>T-ALL (21y)</td>
<td>Complex karyotype with del(9q), del(7q), del(13q), and additional del(1q)</td>
<td>TP53 p.E150*</td>
<td>Treatment for chronic myeloid leukemia Death (10y)</td>
<td>1.35 brother (13y)</td>
</tr>
<tr>
<td>6 (f)</td>
<td>XP167VI</td>
<td>Spanish but North African mutation</td>
<td>XP C (2y)</td>
<td>HMZ deITG</td>
<td>Complex karyotype with del(9q), del(7q), del(13q), and additional del(1q)</td>
<td>TP53 p.E150*</td>
<td>N/A</td>
<td>Treatment-5 Ac Death from AM (20y)</td>
<td>No sibling</td>
</tr>
<tr>
<td>7 (M)</td>
<td>XP167VI</td>
<td>Algerian</td>
<td>XTC(3y) and trisomy 21</td>
<td>HMZ deITG</td>
<td>RA Bb (25y) and AMI (25y)</td>
<td>N/A</td>
<td>N/A</td>
<td>Multiple skin cancers, Cytotherapy at 54y Death (27y)</td>
<td>Brother of patient #12 37 brother (death at 13y for unknown reasons) Cousin of patient #13</td>
</tr>
<tr>
<td>8 (M)</td>
<td>XP30VI</td>
<td>Tunisian</td>
<td>XP (2y)</td>
<td>HMZ deITG</td>
<td>AML-2 (24y)</td>
<td>Del(7q); trisomy 7; monosomy 7</td>
<td>N/A</td>
<td>24/25 sibs (24y, 25y, 34y)</td>
<td>N/A</td>
</tr>
<tr>
<td>9 (f)</td>
<td>XP41VI</td>
<td>Moroccan</td>
<td>XP C (2y)</td>
<td>HMZ deITG</td>
<td>T-ALL (21y)</td>
<td>N/A</td>
<td>N/A</td>
<td>Multiple skin carcinomas, Cytotherapy at 54y Death (27y)</td>
<td>1.35 brother (13y)</td>
</tr>
<tr>
<td>10 (M)</td>
<td>XP58VI</td>
<td>Algerian</td>
<td>XP C (4y)</td>
<td>HMZ deITG</td>
<td>AML-2 (24y)</td>
<td>Complex karyotype with UPOD(1)(p1)TP53, del(13q), del(9q), del(13q), and additional del(9q)</td>
<td>TP53 p.E150*</td>
<td>N/A</td>
<td>1.35 brother who died at 12y for unknown reason but with strong anemia</td>
</tr>
<tr>
<td>11 (f)</td>
<td>XP106VI</td>
<td>Moroccan</td>
<td>XP C (2y)</td>
<td>HMZ deITG</td>
<td>AML-2 (24y)</td>
<td>Complex karyotype with del(9q)</td>
<td>N/A</td>
<td>5-Aza-C; Maintenance therapy 3 months</td>
<td>2.35 brothers (14y, 25y)</td>
</tr>
<tr>
<td>12 (f)</td>
<td>XP50VI</td>
<td>Algerian</td>
<td>XP C (6y)</td>
<td>N/A but Chimeric HMZ deITG</td>
<td>RA Bb (24y)</td>
<td>N/A</td>
<td>N/A</td>
<td>Death (25y)</td>
<td>Sister of patient #8 first cases of patient #13</td>
</tr>
<tr>
<td>13 (M)</td>
<td>XP30VI</td>
<td>Algerian</td>
<td>XP C (6y)</td>
<td>N/A but Chimeric HMZ deITG</td>
<td>RA Bb (24y)</td>
<td>N/A</td>
<td>N/A</td>
<td>Death (27y)</td>
<td>First cousin of patients #7 and #12</td>
</tr>
</tbody>
</table>

Notes and abbreviations: N/A, not available; RIC, reduced intensity conditioning regimen; HSCT, hematopoietic stem cell transplantation.

a Reported in19

b Reported in20

c HMZ deITG refers to the homozygous XPC gene mutation c.1643_1644 delITG; p.Val548AlafsX572 initially described in.7 Note that all patients are from consanguineous families.

d According to karyotype and/or CGH-array analysis and/or WES analysis

e Following Whole-Exome Sequencing of the tumor, except patient #5 and #9 where T-ALL samples that were analyzed with a dedicated T-ALL gene panel.

f Reference number of transcripts :XPC, NM_00628.4; TP53, NM_001126112; TET2, NM_001127208; CSF3R, NM_156039; NRAS, NM_002524; DNMT3A, NM_022552; RAD21, NM_006265; BCOR, NM_001123382; PHF6, NM_032458; NOTCH1, NM_017617.

g Age of XP siblings at last follow up or death.
Figure Legend

Figure 1. Germline genetics and clonal evolution in XP-C patients with MDS and leukemia

(A) Bone marrow progression in patient #5 (XP924VI) showing clonal evolution. Chromosomal abnormalities and somatic point mutations are shown. (B) Copy number and allele heterozygosity analysis of the bone marrow MDS-EB1 sample showing deletion 5q and 7q (arrows) in patient #5. Whole-exome sequencing (WES) data were analyzed using the FACETS tool; top panel, total copy number log-ratio (logR); second panel, allele-specific log-odds-ratio data (logOR); third panel, corresponding integer (total, minor) copy number calls. The estimated cellular fraction (cf) profile is plotted at the bottom. (C) Minimal common region of germinal homozygosity in 3p25 including the XPC gene (yellow arrow), as shown by the analysis of SNP array data in the five patients with available fibroblast cell DNA (Affymetrix array) and confirmed using WES data (Illumina). Data are shown using the Genome Wide SNP6 Array and the Chromosome Analysis Suite. Top panel, LOH segments on chromosome 3; the bottom panel shows the minimal region of homozygosity as mapped by patient XP10VI and XP309VI, on the left and right sides (genomic position on chr3: 11,092,104 and 14,285,238 using hg19 reference, NM_00628.4), respectively.
A

Birth

12y

14y

15y

+0.5y

Death

XPC

HMZ del.TG

T-ALL

PHF6 E150*

BCOR G1056fs

( TP53 WT)

somatic UPD6p

+20

MDS-EB1

TP53 R280*

del5q
del7q

t(14;15)

AML-6

Idem, +
del3p
del9p
i21qter
(delRUNX1)

B

-5q

-7q

Chromosome

Genes

C

Minimal common region of germline homozygosity
chr3:11,092,104-14,285,238 (3.193 Mb)
Familial predisposition to TP53/complex karyotype MDS and leukemia in DNA repair-deficient xeroderma pigmentosum

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