

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

Alain Sarasin<sup>1</sup>, Samuel Quentin<sup>2,3,4</sup>, Nathalie Droin<sup>5,6</sup>, Mourad Sahbatou<sup>7</sup>, Véronique Saada<sup>8</sup>, Nathalie Auger<sup>8</sup>, Yannick Boursin<sup>9</sup>, Philippe Dessen<sup>9</sup>, Anna Raimbault<sup>2,3,4</sup>, Vahid Asnafi<sup>10</sup>, Jean-Luc Schmutz<sup>11</sup>, Alain Taïeb<sup>12</sup>, Carlos F. M. Menck<sup>13</sup>, Filippo Rosselli<sup>1</sup>, Laurianne Drieu La Rochelle<sup>14</sup>, Caroline Robert<sup>15</sup>, Flore Sicre de Fontbrune<sup>4,16</sup>, Marie Sébert<sup>4,17</sup>, Thierry Leblanc,<sup>18</sup> Patricia Kannouche<sup>1</sup>, Stéphane De Botton<sup>6</sup>, Eric Solary<sup>5,6</sup> and Jean Soulier<sup>2,3,4</sup>

<sup>1</sup>Laboratory of Genetic Instability and Oncogenesis, UMR 8200 CNRS, University Paris-Sud and Gustave Roussy, 94805 Villejuif, France.

<sup>2</sup>INSERM/CNRS U944/7212 and University Paris Diderot, University of Paris, France.

<sup>3</sup>Hematology Laboratory, Saint-Louis Hospital, Assistance Publique Hôpitaux de Paris (APHP), Paris.

<sup>4</sup>Centre de référence Maladies Rares des Aplasies médullaires, Hôpital Saint-Louis et Robert Debré, Paris.

<sup>5</sup>INSERM U1170, Gustave Roussy, Université Paris-Sud, Villejuif.

<sup>6</sup>Gustave Roussy, Université Paris-Saclay, Département d'hématologie, Villejuif.

<sup>7</sup>Fondation Jean DAUSSET-CEPH, Paris.

<sup>8</sup>Gustave Roussy, Université Paris-Saclay, Département de biologie et pathologie médicales, Villejuif.

<sup>9</sup>Bioinformatics Core Facility, Gustave Roussy, Villejuif.

<sup>10</sup>Institut Necker-Enfants Malades, INSERM U1151, Paris.

<sup>11</sup>Department of Dermatology, Nancy University Hospital, Vandoeuvre-Lès-Nancy, France.

<sup>12</sup>Department of Dermatology, Bordeaux University Hospitals, and INSERM U1035, University of Bordeaux, Bordeaux, France.

<sup>13</sup>Institute of Biomedical Sciences, University of Sao Paulo, Sao Paulo, Brazil.

<sup>14</sup>Service d'Hématologie, CHU de Tours, Tours, France.

<sup>15</sup>Department of Dermatology, Gustave Roussy, Villejuif.

<sup>16</sup>Hematology/Transplantation, Hôpital Saint-Louis, Paris.

<sup>17</sup>Hématologie Senior, Hôpital Saint-Louis, Paris.

<sup>18</sup>Pédiatrie hématologique, Hôpital Robert Debré, Paris.

Corresponding author: Pr. Alain Sarasin, Laboratory of Genetic Instability and Oncogenesis,  
UMR 8200 CNRS, University Paris-Sud and Gustave Roussy Institute

94805 Villejuif, France.

+33 6 80 34 49 84

alain.sarasin@gustaveroussy.fr

1 Figure, 1 Table

The online version of this article contains data supplements with Supplemental 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.<sup>1</sup> 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.<sup>2</sup> In the absence of photoprotection, this deficiency causes skin tumors with an extremely high frequency.<sup>3</sup>

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.<sup>4</sup> 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)<sup>5</sup>. 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.<sup>6</sup>

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.<sup>4</sup> 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.<sup>4</sup> XP frequency in Tunisia and carrier frequency in Morocco were estimated to be 1/10,000 and 1/250, respectively.<sup>7,8</sup>

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),<sup>9</sup> 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.<sup>10-12</sup> 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,<sup>13</sup> 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.<sup>14-17</sup> 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.<sup>14,15</sup> Interestingly, we and others have also reported the extremely frequent rate of *TP53* mutations in skin tumors that occur in XP patients,<sup>18</sup> 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.

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## **Authorship**

Contribution: A.S. and J.S. are the principal investigators; A.S., N.D., V.S., N.A., A.R., V.A., J-L.S., A.T., C.F.M., L.D.L.R., C.R., F.S.dF., M.S., T.L., F.R., P.K., S.dB., E.S. and J.S. brought clinical and biological data; S.Q., Y.B., M.S., P.D. performed bioinformatic analyses; and A.S., S.Q., E.S. and J.S. wrote the paper. All authors reviewed the manuscript.

## **Conflict of interest**

The authors have no conflict of interest to declare.

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

Patient Number (gender)	ID	Geographic familial origin	XP diagnosis (age)	Mutation on the XPC gene <sup>e</sup>	Hematological malignancies type (age at diagnosis)	Somatic chromosomal abnormalities <sup>d</sup> (recurrent bolded)	Somatic mutations <sup>e,f</sup> (recurrent bolded)	Other clinical information (age)	Familial information (age) <sup>g</sup>
1 (M)	XP10VI	Moroccan	XPC (4y)	HMZ delTG	AML-4 (27y)	N/A	N/A	Death due to major toxicity after chemotherapy (28y)	Cous in of patient #2 1 XP-C brother (death at 6y)
2 (M)	XP82VI	Tunisian	XPC (1.5y)	HMZ delTG	AML-6 (16y)	<b>del(5q), monosomy 7, del(9q), del(20q)</b>	<b>TP53: p.T284P</b>	RIC HSCT (17y) Death of toxicity with persistent leukemia (18y)	Cous in of patient #1 1 XP-C brother (death at 23y)
3 (F)	XP235VI	Tunisian	XPC (9y)	HMZ delTG	RAEB-1 (24y), then RAEB-2 and AML-6 (25y)	<b>Complex karyotype with del(5q)</b>	<b>TP53: p.E346X and c.672+1G&gt;T (splice); CSF3R: p.P467S c.1959+1G&gt;A c.1576+1G&gt;C c.1071+1G&gt;C</b>	5-Aza-C treatment for three years Death (29y)	1 XP brother (death at 18y)
4 (F)	XP309VI	Moroccan	XPC (2y)	HMZ delTG	B-ALL and MDS (7y)	<b>Monosomy 7</b>	N/A	B-ALL treated by reduced-dose chemotherapy Death 10y	N/A
5 (M) <sup>a</sup>	XP924VI	Moroccan	XPC (4.5y)	HMZ delTG	T-ALL (12y) RAEB-1 (13y) AML-6 (15y)	T-ALL: trisomy 20 MDS: <b>del(5q), del(7q)</b> (see Fig. 1B) AML: <b>complex karyotype with additional abnormalities</b>	MDS: <b>TP53: p.R280X</b> T-ALL: <b>PHF6 E150* BCOR G1056s</b>	T-ALL treated by chemotherapy; RAEB diagnosed during maintenance therapy, treated by 5 Aza-C Death AML-6 (15y)	1 XP-C brother (13y)
6 (F)	XP185VI	Spanish but North African mutation	XPC (2y)	HMZ delTG	RAEB-2 (24y) AML with MDS-related changes (25y)	<b>Complex karyotype with del(5q), del(7q), del(20q) and subclonal del(4q)</b>	<b>TP53: p.S215R and p.G154V</b> <b>TET2: p.C1193Y</b>	Treatment 5-Aza-C Death from AML (25y)	No sibling
7 (M)	XP167VI	Algerian	XPC (3y) and trisomy 21	HMZ delTG	RAEB-t (25y) and AML (26y)	N/A	N/A	Numerous skin cancers, Eye radiotherapy (11y) Death (26y)	Brother of patient #12 XP brother (death at 18y for unknown reasons) Cousin of patient #13
8 (M)	XPAHVI	Tunisian	XP (4y)	HMZ delTG	AML (24y)	<b>Del(7q), trisomy 8, abnormal 21</b>	N/A	Multiple skin carcinomas, Curiotherapy at 24y Death (25y)	3 XP-C siblings (24y, 25y, 34y)
9 (F)	XP673VI	Moroccan	XPC (12y)	HMZ delTG	T-ALL (21y)	N/A	<b>NOTCH1: p.R1598P (HD domain)</b> <b>DNMT3A: p.W313*</b> <b>TET2: p.K1438*</b> <b>NRAS: p.Q61R</b>	Multi-organ failure upon infection, anti-tumoral therapy (22y)	1 XP-C brother with astrocytoma at 14y (30y)
10 (M)	XP538VI	Algerian	XPC (4y)	HMZ delTG	AML (29y)	<b>Complex karyotype with UPD(17p/TP53), del(4q), del(5q), del(7q), del(13) and dup(21q)</b>	<b>TP53: p.V272M</b> <b>RAD21: c.937+1G&gt;T (splice)</b>	Numerous carcinomas on exposed sites Death (29y)	1 XP-C sister who died at 12y for unknown reasons but with strong anemia
11 (F)	XP2006VI	Moroccan	XPC (2y)	HMZ delTG	AML-6 (29y) 31% blast cells and myelofibrosis in BM	<b>Complex karyotype with del(5q)</b>	N/A	5-Aza-C; RIC HSCT (29y, Alive 3 months+)	2 XP-C brothers (14y, 25y)
12 (F) <sup>b</sup>	XPGAVI	Algerian	XP (5y)	N/A but Obligatory HMZ delTG	RAEB-2 (24y)	N/A	N/A	Death (25y)	Sister of patient #7 First cousin of patient #13
13 (M) <sup>b</sup>	XPGMVI	Algerian	XP (4y)	N/A but Obligatory HMZ delTG	RAEB-t (27y)	N/A	N/A	Death (27y)	First Cousin of patients #7 and #12

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

<sup>a</sup> Reported in<sup>19</sup>

<sup>b</sup> Reported in<sup>20</sup>

<sup>c</sup> HMZ delTG refers to the homozygous XPC gene mutation c.1643\_1644 delTG; p.Val548AlafsX572 initially described in.<sup>4</sup> Note that all patients are from consanguineous families.

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

<sup>e</sup> 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.

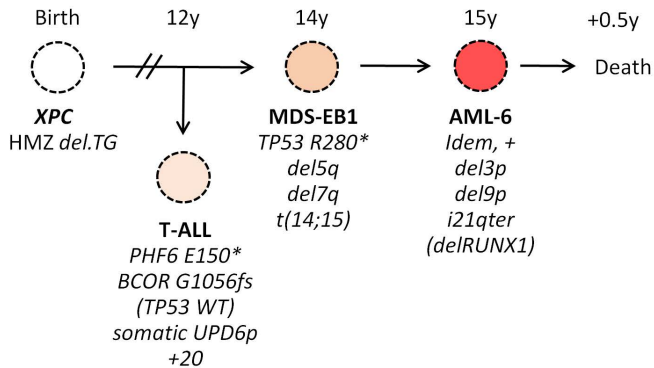
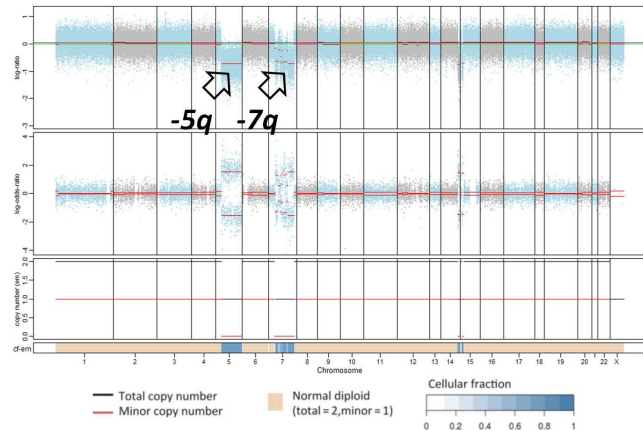
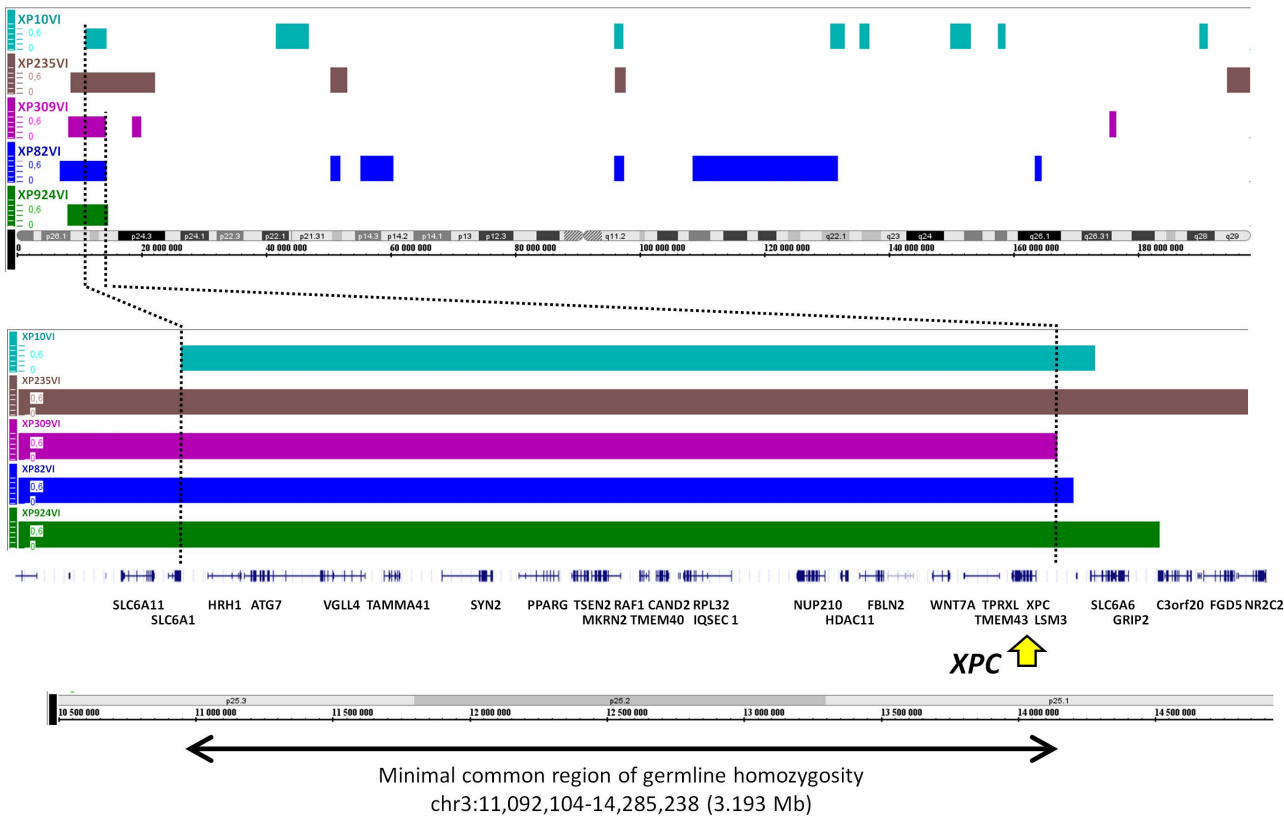
<sup>f</sup> Reference number of transcripts :XPC, NM\_00628.4; TP53, NM\_001126112; TET2, NM\_001127208; CSF3R, NM\_156039; NRAS, NM\_002524; DNMT3A, NM\_022552; RAD21, NM\_006265; BCOR, NM\_001123382; PHF6, NM\_032458; NOTCH1, NM\_017617.

<sup>g</sup> 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****B****C**



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