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Localization of the Xeroderma Pigmentosum Group B-Correcting Gene *ERCC3* to Human Chromosome 2q21

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The human excision-repair gene *ERCC3* was cloned after DNA-mediated gene transfer to the uv-sensitive Chinese hamster ovary mutant cell line 27-1, a member of complementation group 3 of the excision-defective rodent cell lines. The *ERCC3* gene specifically corrects the DNA repair defect of xeroderma pigmentosum (XP) complementation group B, which displays the clinical symptoms of XP as well as of another rare excision-repair disorder, Cockayne syndrome. The gene encodes a presumed DNA and chromatin binding helicase, involved in early steps of the excision-repair pathway. *ERCC3* was previously assigned to human chromosome 2 (L. H. Thompson, A. V. Carrano, K. Sato, E. P. Salazar, B. F. White, S. A. Stewart, J. L. Minkler, and M. J. Siciliano (1987) *Somat. Cell Genet.* 13: 539–551). Here we report its subchromosomal localization in the q21 region of chromosome 2 via somatic cell hybrids containing a translocated chromosome 2 and *in situ* hybridization with fluorescently labeled *ERCC3* probes.

INTRODUCTION

A number of human genetic diseases are known to involve impairment of one of the DNA repair processes. Among these diseases are xeroderma pigmentosum (XP), the prototype repair disorder, and Cockayne syndrome (CS). Both display defects in the nucleotide-excision-repair pathway. The autosomal, recessive disease XP is clinically characterized by extreme sensitivity of the skin to sunlight (uv), pigmentation abnormalities, predisposition to skin cancer, and frequently neurological abnormalities (see Cleaver and Kraemer, 1989, for a recent review). Most XP patients have a deficiency in one of the early (preincision) steps of the excision-repair pathway. CS patients exhibit sun sensitivity, dwarfism, microcephaly, wizened appearance, deafness, and severe mental retardation. However, unlike XP, CS is not associated with pigmentation abnormalities and a high frequency of skin cancer. Recently, CS cells were found to be disturbed in the subpathway of preferential repair of transcribing genes (Venema *et al.*, 1990). Both syndromes are genetically heterogeneous. Cell-fusion experiments have identified at least seven excision-deficient XP complementation groups (designated XP-A to XP-G)[3] and a minimum of three groups in CS (CS A–C) (Lehmann, 1982, 1987).

A third class of mammalian excision-repair mutants is derived from laboratory-induced uv-sensitive rodent (mainly Chinese hamster ovary; CHO) cell lines, among which so far eight complementation groups have been described (reviewed by Collins and Johnson, 1987; Busch *et al.*, 1989). Complementation tests between rodent and XP mutants—although far from complete—have until recently not revealed any overlap between these classes of repair-deficient cell lines (Thompson *et al.*, 1985; Stefanini *et al.*, 1985; Van Duin *et al.*, 1989). These findings suggest the considerable complexity of the nucleotide-excision-repair process at the molecular level.

Recently, we have cloned the human *ERCC3* gene (*e*xcision *r*epair *c*ross-complementing rodent repair deficiency) by virtue of its ability to correct CHO mutants belonging to complementation group 3 (Weeda *et al.*, 1990a). Microinjection experiments revealed that *ERCC3* also corrects the excision-repair defect of

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[3] XP complementation group H has been reassigned to XP group D. (Johnson *et al.*, 1989; Johnson, 1989; Robbins, 1989; Vermeulen *et al.*, 1991)

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XP group B (Weeda *et al.*, 1990b) and subsequent molecular analysis demonstrated that a defect in this gene is responsible for this combined XP–CS disorder.

The *ERCC3* gene has previously been assigned to chromosome 2 by means of functional complementation (uv resistance) of somatic cell hybrids between uv-sensitive hamster cells and human lymphocytes, exhibiting human-specific chromosomal losses (Thompson *et al.*, 1987). So far, a regional assignment has not been achieved. Here we report the subchromosomal localization of the *ERCC3* gene by Southern hybridization of *ERCC3* probes to DNA of somatic cell hybrids and by *in situ* hybridization with fluorescently labeled cDNA probes.

MATERIALS AND METHODS

Cell Lines

The somatic cell hybrids, including the one containing a translocated human chromosome 2 (t2;8) (p12,q24) (R17A3-3B, R17A3-12B, R17, and A3JA-5B), used in this study, have been described elsewhere (Brownell *et al.*, 1988). This panel of hybrids was generated by fusion of A3 Chinese hamster TK^- fibroblasts with t2;8-containing human Burkitt lymphoma cell line ROS-17. t2;8 involves a reciprocal translocation of the distal portion of 2p (2p12–2qter) and 8q (8q24–8qter).

Southern Blot Analysis

Chromosomal DNA (15 μg) digested with the indicated restriction endonucleases was size-fractionated by electrophoresis in 0.8% agarose gels and blotted onto nylon membranes (Biotrace). The filters were hybridized with ^{32}P-labeled, nick-translated *ERCC3* probes. The filters were washed to 0.3× SSC containing 0.1% sodium dodecyl sulfate at 65°C. DNA probes P1, P2, and P3 (ca. 500-bp *Hha*I, ca. 350-bp *Msp*I/*Hin*dIII, ca. 600-bp *Taq*I fragments, respectively) are genomic fragments from the *ERCC3* locus isolated from cos1 and cos8 (Weeda *et al.*, 1990a).

In Situ Hybridization

In situ hybridization was performed essentially as described by Landegent *et al.*, 1985. Prior to the hybridization, human lymphocyte metaphase spreads were treated with 100 μg RNase A/ml in 2× SSC for 1 h at 37°C and rinsed in 2× SSC, followed by 5 min in 20 m*M* Tris–HCl, 2 m*M* $CaCl_2$, pH 7.4, at 37°C. This was followed by a treatment with proteinase K (20 μg/100 ml) at 37°C for 1 h. The slides were washed with 2× SSC and PBS containing 50 m*M* $MgCl_2$, fixed with 1% formaldehyde, washed, dehydrated in ethanol, and air-dried. The hybridization mixture (10 μl per slide) consisted of 50% formamide, 2× SSC, 40 m*M* Na-phosphate (pH 7.0), 10% dextran sulfate, 20 ng labeled probe, 1000 ng sonicated salmon sperm DNA, and 1000 ng yeast tRNA. The *ERCC3* cDNA clone pCD1 encompassing the entire coding region of the 2.8-kb insert (Weeda *et al.*, 1990a) was used as biotin-labeled probe for the *in situ* hybridization experiments performed as described elsewhere (Pinkel *et al.*, 1986). The probe was denatured at 80°C for 5 min. Hybridization was at 37°C overnight. The slides were washed with 50% formamide in 2× SSC at 45°C followed by 2× SSC plus 0.05% Tween 20 at room temperature. Slides were incubated with 5 μg/ml avidin D–FITC (Vector, U.S.A.) and the fluorescent signal was amplified with biotinylated goat anti-avidin D, washed, dehydrated with ethanol, and air-dried. The slides were either counterstained with propidium iodide in antifade medium or banded with 4′,6′-diamidino-2-phenylindole (DAPI) and actinomycin D.

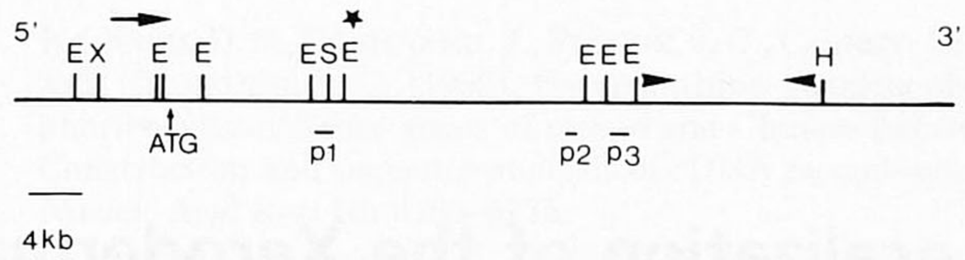

FIG. 1. Restriction map of the *ERCC3* locus. Relevant restriction sites are indicated. Transcriptional orientation is denoted by a large arrow. Arrowheads define a region for which not all *Eco*RI restriction site have been mapped. Abbreviations: E, *Eco*RI; H, *Hin*dIII. The locations of the probes P1, -2, and -3 are indicated. The polymorphic *Eco*RI site is marked by an asterisk.

RESULTS

Subchromosomal Localization by Hybridization to DNA from Somatic Cell Hybrids

Southern blot hybridization of the human *ERCC3* cDNA probe to DNAs from a panel of 17 human × rodent somatic cell hybrids revealed the highest correlation for chromosome 2 (94% concordance). One case of discordance was found for this chromosome), whereas five or more discordances were scored for the other chromosomes (Weeda *et al.*, 1990a). To define the *ERCC3* locus more precisely, we performed Southern blot hybridization to DNA from hamster × human cell hybrids with specific parts of chromosome 2. The unique genomic *ERCC3* probes P2 and P3 (see Fig. 1 for location within the *ERCC3* gene) were simultaneously hybridized to a Southern blot containing DNA of a hybrid panel in which the reciprocal products of a t(2;8)(p12;q24) Burkitt translocation are segregated. Both probes do not recognize rodent sequences under the stringent hybridization

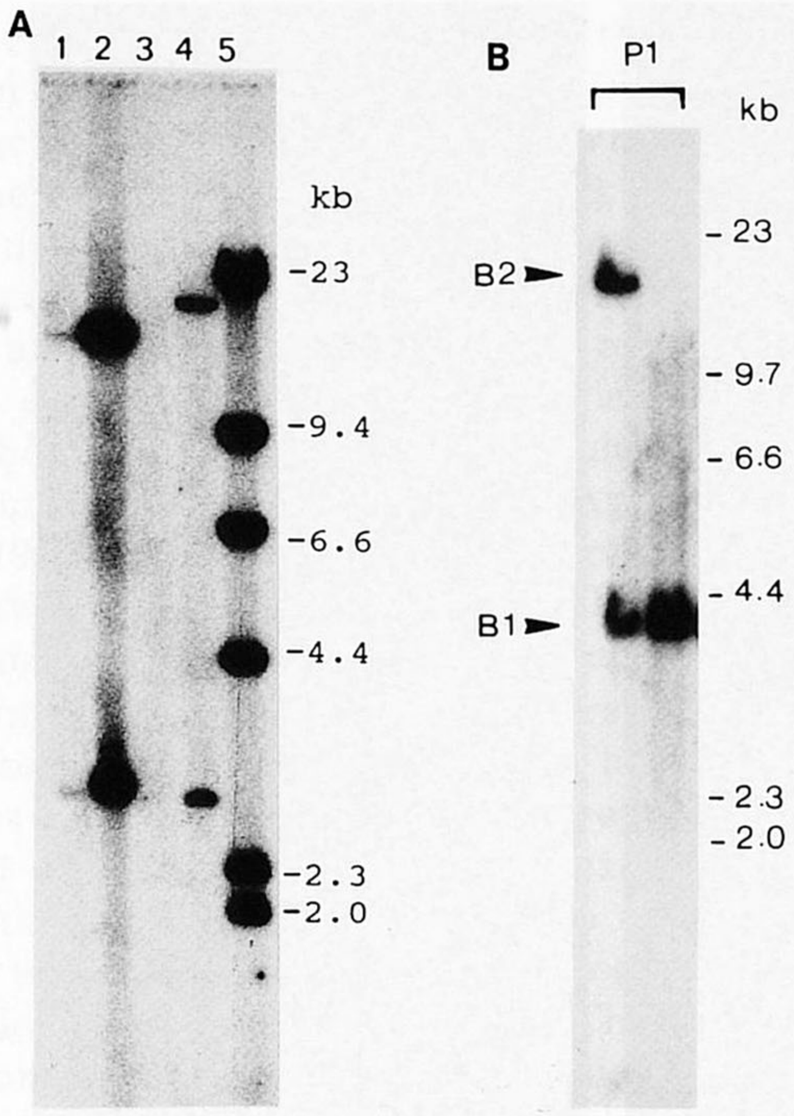

FIG. 2. (**A**) Southern blot analysis of genomic DNA (15 μg) from somatic cell hybrids containing (a part of) chromosome 2 digested with the restriction enzyme *Eco*RI and simutaneously hybridized to two genomic probes: probe P3 (detecting a 3-kb *Eco*RI fragment) and probe P2 (detecting a ca. 15-kb fragment and in lane **4** a larger band of approximately 18 kb; see also Fig. 1). Lane **1**, R17A3-3B; **2**, R17; **3**, R17A3-12B; **4**, A3JA-5B; **5**, molecular weight marker: λ *Hin*dIII. (See Table 1 for presence of specific chromosomes in the hybrids used.) (**B**) Southern blot analysis of genomic DNA (15 μg) from two unrelated individuals digested with the restriction enzyme *Eco*RI and hybridized with the genomic P1 probe (see Fig. 1 for location) detecting the (major) B1 and the (minor) B2 allele indicated.

conditions utilized in this study. Figure 2A and Table 1 show that the *ERCC3* gene segregates with the 2p− chromosome (sample R17A3-3B). Therefore, we conclude that the gene resides in the region between 2p12 and −qter. Cytogenetic analysis indicated the presence of the 2p− translocated chromosome in only a small fraction of the R17A3-3B hybrid cells. This accounts for the low hybridization signal observed in Fig. 2A, lane 1. Probe P2 identifies in the A3JA-5B hybrid cells a genomic *Eco*RI restriction fragment with a length of approximately 18 kb (Fig. 2A, lane 4), instead of the expected 15-kb band (Fig. 2A, lanes 1 and 2; see also Fig. 1), suggesting the presence of a restriction fragment length polymorphism (see below).

In Situ Hybridization

To map the *ERCC3* locus more precisely, *in situ* hybridization was carried out using a biotin-labeled cDNA probe. The cDNA probe pCD1 covers the entire 2.8-kb *ERCC3* transcript. Two representative *in situ* hybridizations of the more than 20 metaphases analyzed are shown in Fig. 3. Although banding in combination with *in situ* hybridization is not optimal (compare Figs. 3A and 3B), the results clearly show that the *ERCC3* gene is located in the q21 region of chromosome 2 and are consistent with the results of the translocation hybrids (Fig. 2). The assignment of this gene to the 2q21 region is also confirmed by *in situ* hybridization experiments using ^{3}H-labeled *ERCC3* cDNA probes (unpublished results).

Restriction Fragment Length Polymorphism in the ERCC3 Gene

The finding of a variable *Eco*RI fragment in one of the translocation hybrids (Fig. 2A) prompted us to analyze more individuals to verify whether it is a restriction fragment length polymorphism (RFLP) and to estimate the frequency and location. *Eco*RI-restricted genomic DNA samples of 10 unrelated Dutch persons were hybridized with a probe (P1) that is localized 5′ adjacent to the 15-kb genomic *Eco*RI restriction fragment described above (see Fig. 1). As shown by Fig. 2B it recognizes a variable, approximately 18-kb *Eco*RI fragment and a constant 3.9-kb *Eco*RI fragment, called B1 and B2. These results identify the 5′ *Eco*RI site of the 15-kb fragment as being polymorphic. Based on this limited set of data, an allelic frequency of ca. 0.9 for the B1 and ca. 0.1 for the B2 allele can be calculated. Obviously, a more extensive analysis is required for a more accurate figure. The presence of this polymorphism may be of use for linkage studies of other genes in the 2q21 area.

DISCUSSION

The localization of the *ERCC3* gene on chromosome 2 has been determined so far on the basis of functional complementation (uv resistance) of the fusion products of a uv-sensitive mutant of rodent com-

TABLE 1

Presence of the Human *ERCC3* Gene in Various Human × Rodent Hybrid Cell Lines

	Presence of the chromosome				Presence of *ERCC3*
	2	8	2p−	8q+	
R17A3-3B[a]	−	−	+	−	+
R17	+	+	−	−	+
R17A3-12B	−	−	−	+	−
A3JA-5B	+	+	−	−	+

[a] Only a small fraction (approximately 10%) contained with 2p− translocation chromosome.

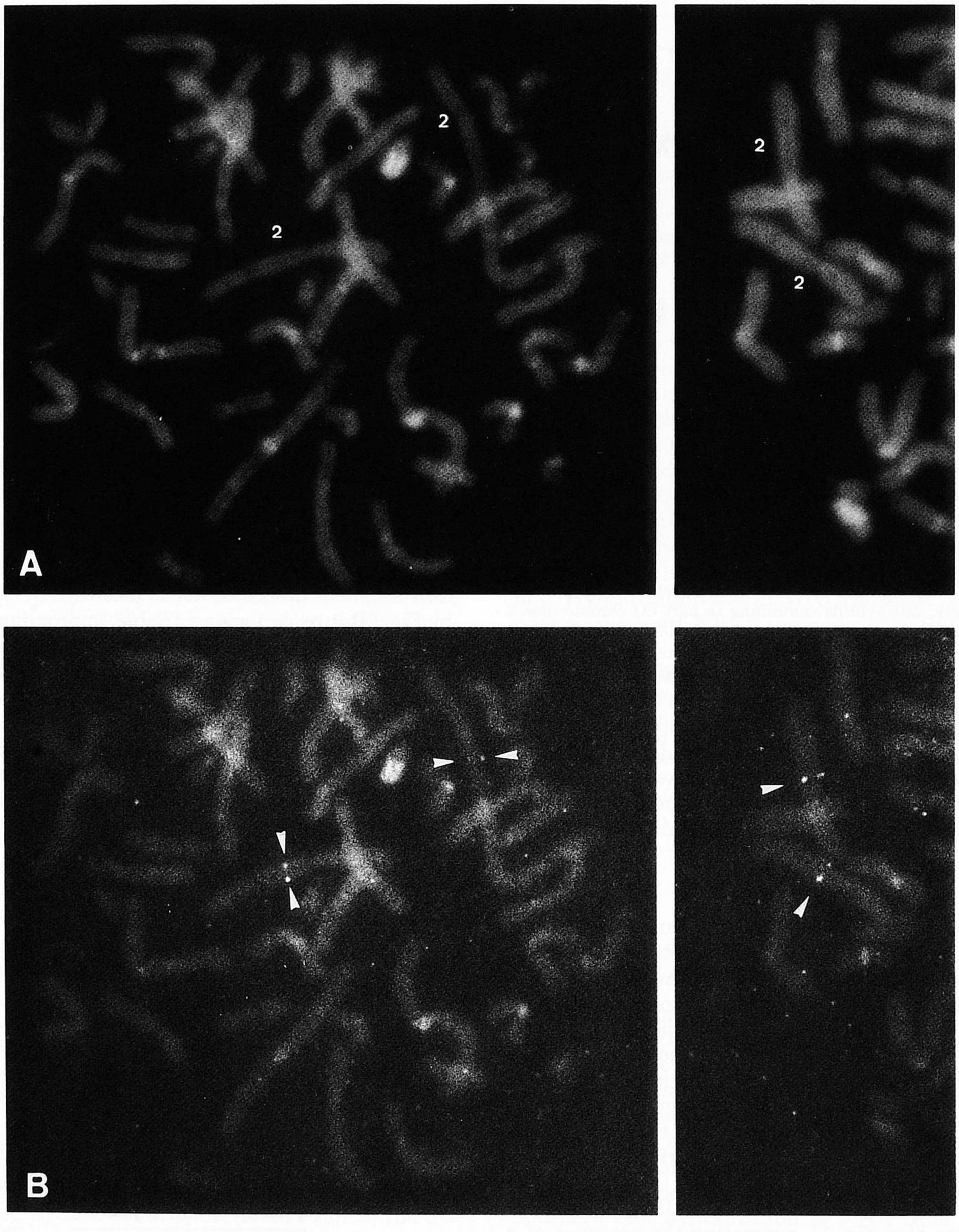

FIG. 3. (**A**) Photograph illustrating karyotypes of one complete metaphase spread with some banding, and part of another metaphase spreading. (**B**) Photograph showing the corresponding fluorescent *in situ* hybridization with the human *XPBC/ERCC3* cDNA probe (pCD1). Arrows indicate the fluorescent label on chromosome 2.

plementation group 3 and human lymphocytes (Thompson *et al.*, 1987). By *in situ* hybridization using *ERCC3* cDNA probes, we report here the subchromosomal assignment of the *ERCC3* gene to 2q21.

So far one other gene involved in XP(XP-A) and several *ERCC* genes correcting specific rodent complementation groups have been chromosomally mapped. After the failure of initial attempts to iden-

tify the chromosome that carries the XP-A gene (Keijzer *et al.*, 1987; Shultz *et al.*, 1987), several groups have recently reported that this gene resides on chromosome 9 (Kauer and Athwal, 1989; Ishizaki *et al.*, 1990), using microcell-mediated transfer of chromosome containing dominantly selectable markers, which allows specific selection for retention of the tagged chromosome. This finding is in agreement with the *in situ* hybridization results obtained recently using ^{3}H-labeled XPAC cDNA probes (Tanaka *et al.*, 1990) and with the early observation of a linkage between the locus involved in XP and the blood-group markers 9q34 (Westerveld *et al.*, 1976).

A notable clustering of several repair genes has been observed on chromosome 19. This chromosome appears to contain at least three repair genes: the *ERCC1* and *-2* (correcting rodent excision-deficient mutants of complementations group 1 and 2, respectively) and *XRCC1* (*X*-ray-*r*epair *c*ross *c*omplementing rodent repair deficiency gene). The latter human gene corrects CHO mutant EM9, which harbors a defect in strand-break repair and displays an elevated level of sister chromatid exchanges (Siciliano *et al.*, 1986a). The *ERCC1* and *-2* genes have been found to be separated by less than 250 kb on band 19q13.2–13.3 (Mohrenweiser *et al.*, 1989; Smeets *et al.*, 1990). Finally, the *ERCC4, -5,* and *-6* genes are located on different chromosomes, respectively chromosome 16, 13, and 10 (Siciliano *et al.*, 1986b; Thompson *et al.*, 1987; Troelstra, personal communication).

The *ERCC3* gene is located in an area of chromosome 2q to which relatively few genes have so far been assigned. The protein C gene, which encodes an inactivator of coagulation factor Va and VIIIa and may be deficient in recurrent thrombosis, resides in this area (Kato *et al.*, 1988; Patracchini *et al.*, 1989). Furthermore, the liver-specific oncogene LCA has been mapped recently to a region close to 2q14 (Tokino *et al.*, 1988). Also, the interleukin Ia gene is thought to be situated in this vicinity (Modi *et al.*, 1988; Lafage *et al.*, 1989).

The *ERCC3* gene is involved in the prevention of carcinogenesis, as it participates in the excision-repair pathway that removes a wide range of potentially mutagenic and carcinogenic lesions in DNA. Consequently, inactivation of this gene results in a dramatic increase in skin cancer, as observed in the sole patient comprising the XP-B complementation group. In this context it is of interest to note that the *ERCC3* gene is located in a region that is reported to be occasionally involved in chromosomal aberrations found in malignant lymphomas (Bloomfield *et al.*, 1983, 1985; Slavutsky *et al.*, 1986). The possible relationship between these chromosomal abnormalities and the tumor-preventing *ERCC3* gene, if any, is as yet unknown but deserves further investigation.

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