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# PHYSICAL MAP OF A YAC CONTIG CONTAINING THE REGION OF THE HUMAN GENE (*HYRC*) COMPLEMENTING HYPER-RADIOSENSITIVITY OF THE SCID MOUSE MUTATION

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*Summary* We previously mapped the putative human *HYRC* (the hyper-radiosensitivity of the scid mutation, complementing gene) to human chromosome 8q11.1 by fluorescence *in situ* hybridization (FISH) using Alu-based PCR products from a mouse-human scid radiation cell hybrid (RD15/5) as probes. From a cosmid library constructed from RD15/5, 57 cosmid clones containing human DNA inserts were isolated, 18 of which were mapped to 8q11. Based on the sequences of plasmid subclones of the 18 cosmids, five novel sequence-tagged-sites (STSs) were made. By a screening of the CEPH-YAC library with these STSs, five yeast artificial chromosome (YAC) clones were isolated. All these YAC clones were confirmed not to be chimeric by FISH, but two of them showed deleted human insert DNAs. Using the other 3 non-deleted YACs, we constructed a physical map covering the *HYRC* region. We confirmed that the recently isolated gene (the DNA-$PK_{cs}$ gene) which is a strong candidate for *HYRC* is located within the present contig and spans less than 200 kb. This map will be useful for the analysis of the genomic structure of the DNA-$PK_{cs}$ gene and for isolation of other complementing genes in the *HYRC* region.

***Key Words*** scid, HYRC gene, DNA-$PK_{cs}$ gene, STS, physical map

## INTRODUCTION

Murine severe combined immunodeficiency (scid) is an autosomal recessive disorder characterized by a lack of functional B and T lymphocytes due to a failure of V(D)J recombination activity that normally mediates somatic assembly of both

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immunoglobulin and T-cell receptor gene elements (Bosma *et al.*, 1983). Investigation of V(D)J recombination in the scid mouse has shown that the immune system gene elements are not correctly rejoined in the coding sequences during V(D)J recombination, because of an aberrant recombinase (Lieber, 1992). Hence, the scid gene (*scid*) is considered to encode a key enzyme involving V(D)J recombination. Moreover, illegitimate rejoining of DNA double-strand breaks in scid cells also gives rise to a marked increase in sensitivity to ionizing radiation (Fulop and Phillips, 1990; Biedermann *et al.*, 1991; Hendrickson *et al.*, 1991). We previously mapped the putative human gene (*HYRC*) for hyper-radiation sensitivity that is complementary to the murine *scid* to human chromosome 8q11.1 by fluorescence *in situ* hybridization (FISH) using Alu-PCR products from human-scid mouse radiation cell hybrids as probes (Komatsu *et al.*, 1993). A strong candidate gene (the DNA-$PK_{cs}$ gene) for *HYRC* has been identified and mapped to the same human chromosomal region (Kirchgessner *et al.*, 1995; Blunt *et al.*, 1995; Lees-Miller *et al.*, 1995), and its partial cDNA has been cloned (Blunt *et al.*, 1995).

We also previously constructed a cell line (RD15/5), a tertiary radiation hybrid cell clone, by repetition of irradiation. Since the cell line contains smaller human DNA fragments that include *HYRC* than its parent hybrid, it was considered as a good source to make a physical map useful for positional cloning of *HYRC*. We report here a cosmid library construction of the human DNA inserted in RD15/5 and isolation of cosmid clones, sequence tagged sites (STSs), their corresponding yeast artificial chromosome (YAC) clones and a physical map of the YAC contig.

## MATERIALS AND METHODS

*Cosmid isolation and FISH analysis.* A cosmid library in pWEX15 was constructed from the DNA of a human-mouse scid radiation hybrid cell line, RD15/5, that contained only human chromosome 8q11-q12 DNA in mouse DNA background. Cosmid clones containing human DNA inserts were selected by colony hybridization at 55°C using total human genomic DNA as a pool of probes. To exclude clones with only mouse DNA, another screening was performed by dot-blot hybridization first using total human DNA and subsequently using total mouse DNA as probes. After hybridization at 65°C, dot-blotted filters were washed at 55°C in 0.1×SSC/0.1% SDS. Clones with negative or weak signals by the second dot-blot hybridization were subjected to FISH in order to confirm their localization to human chromosome 8. Cosmid DNAs labeled with biotin-16-dUTP (Boehringer-Mannheim, Germany) by nick translation were hybridized to human metaphase chromosomes, as described previously (Deng *et al.*, 1992).

*Isolation of STSs and YACs from cosmid clones.* The DNA of cosmid clones mapped to 8q11 or hybridized diversely to human chromosomes by FISH was digested with *Sau*3AI and subcloned into pUC19. Colony hybridization was

carried out using total human DNA as probes under the same hybridization/washing conditions as those for cosmid isolation. With an aim to exclude highly repetitive human DNA sequences, 10 to 20 plasmid clones with negative signals were selected from each cosmid and used as probes for Southern blot hybridization to *Eco*RI-digested total human genomic DNA, *Eco*RI-digested DNA from mouse-human hybrid cells (A9Neo8) containing chromosome 8 as only human origin and to *Eco*RI-cut total scid mouse (SC3VA4) genomic DNA. After hybridization at 65°C, membranes were washed at 65°C in 0.1×SSC/0.1% SDS. Plasmid clones showing unique electrophoretic bands for only human and A9Neo8 DNA underwent base-sequencing by means of an autosequencer (Pharmacia, Sweden). Sets of oligonucleotide primers were designed for STSs on the basis of the sequences, and polymerase chain reaction (PCR) was performed for 30 cycles with denaturation at 94°C for 1 min, annealing at 55–60°C for 1 min and extension at 72°C for 1.5 min. Using these STS primers, the CEPH (the Centre d'Etude de Polymorphisme Humaine, France) YAC library was screened with the three-dimensional PCR-based method (Green and Olson, 1990).

*Characterization of YAC clones.* YAC clones identified by STSs underwent pulsed-field gel electrophoresis (PFGE) analysis by means of the PFGE set (Gene Line II, Beckman, USA). Electrophoresis was done on 1% agarose gel at 350 V with pulse-time 120 sec for 12 hr, at 370 V with pulse-time 240 sec for 12 hr and then at 390 V with pulse-time 360 sec for 6 hr, all at 4°C in 0.25×TBE. After Southern hybridization at 65°C using high-molecule human Cot-1 DNA (GIBCO BRL, USA) as a pool of probe, membranes were washed at 65°C in 0.1×SSC/0.1% SDS. Total YAC DNA (1 $\mu$g) was used for subsequent Alu-based PCR using primer 2484, 5′-aggagtgagccaccgcacccagccc-3′ and primer PDJ34, 5′-tgagc(c/t)(g/a)-(a/t)gat(c/t)(g/a)(c/t)(g/a)cca(c/t)tgcactccagcctggg-3′. PCR were cycled 30 times at 94°C for 1 min denaturation, at 55°C for 1 min annealing and at 72°C for 1.5 min extension. The 2484-PCR and PDJ34-PCR products were mixed and used for FISH analysis.

Furthermore, 7 sets of primers for published STSs located at a pericentromeric region of human chromosome 8 were used for another PCR study. The sequences (3′–5′) of the primers were as follows: PLAT, 5′-tcagaagaggagccagatctta-3′/5′-actct-agatgtggacttagaga-3′ (Sapru *et al.*, 1994); D8S519, 5′-ctgcaccccagcgtc-3′/5′-agtggcc-tttctgctcc-3′ (Gyapay *et al.*, 1994); D8S531, 5′-ttaggctggatgcctgacctttta-3′/5′-gggaa-cattgtcactttcacgg-3′ (Gyapay *et al.*, 1994); D8S359, 5′-tggctgagaacagtggtagg-3′/5′-agaatggggtagttccttcac-3′ (GDB ID: G00-215-519); D8S589, 5′-aacctccagaatgggga-tag-3′/5′-acttttccagatagttactgtcaca-3′ (GDB ID: G00-228-576); D8S538, 5′-agctgcttg-tcattnactt-3′/5′-tactatttgtggcaattgtaatacc-3′ (Gyapay *et al.*, 1994); DNA-$PK_{cs}$ (3′), 5′-ctgcagatagaaagcattacattg-3′/5′-tcttgatttaaactcatgctacga-3′ (Blunt *et al.*, 1995). PCRs were performed for 30–35 cycles at 93°C for 1 min, 50–58°C for 1 min and 72°C for 2 min, using DNA of SC3VA4, RD15/5 and three YACs as templates.

*PFGE analysis of YAC clones.* *Not*I, *Mlu*I and *Nru*I were used for com-

plete and partial digestions of agarose block DNAs from the three YACs, respectively. Digestion was done in 100 $\mu$l reaction mixture according to the manufacturers' instruction. Gene Navigator system (Pharmacia, Sweden) were used for PFGE. Digested YAC DNA was electrophoresed in 1.2% agarose gel with 180 V, using the following 3 steps of pulse-time: 80 sec for 12 hr, 100 sec for 6 hr and 120 sec for 6 hr. After PFGE, agarose gel was soaked in 0.25 N HCl for 5 min twice, then transferred to a nylon membrane (Hybond N+, Amersham, UK). As probes, 2.7-kb and 1.7-kb products from pBR322 DNA digested with *Bam*HI and *Pvu*II were used for right and left arms of YAC. In addition, high molecular human Cot-1 DNA, the insert of DNA-$PK_{cs}$ clone 1, and PCR products with the primer DNA-$PK_{cs}$ (3′) were used for human contents of YACs, the 5′ region of the DNA-$PK_{cs}$ gene, and for the 3′-UTR of the gene (Blunt *et al.*, 1995), respectively. These probes were radio-labeled by a random primer labeling kit (Amersham, UK) and hybridized at 65°C and washed at 65°C in 0.5×SSC.

## RESULTS

### *Cosmid isolation and FISH analysis*

The cosmid library constructed from RD15/5 contained $3\times10^5$ colonies. By colony hybridization, 379 clones with positive signals for human DNA were obtained, and all of them hybridized to human DNA by dot-blot hybridization. The other hybridization using total mouse DNA as a pool of probes revealed 34 negative and 345 positive clones. The 34 negative clones and 177 weakly-positive clones from the remainder underwent FISH analysis. Of a total of 211 clones analyzed by FISH, 18 gave fluorescence signals at 8q11 (Fig. 1a), 39 showed signals diversely at human chromosomes including chromosome 8, and 154 gave no signal. Thus, at least 57 clones were supposed to contain mainly human DNA inserts and the remaining 154 were in part composed of human DNA.

### *STSs from cosmid clones*

The 57 cosmid clones showing FISH signals at human chromosomes, some of them likely being identical, were subcloned into pUC19. Southern hybridization of the subcloned plasmids to total human DNA, DNA from a mouse-human hybrid cells containing a human chromosome 8 and that to total mouse DNA revealed that five plasmids had only human unique DNA sequences (data not shown), and each of these plasmids was derived from five different cosmid clones. After sequencing of DNA from the five plasmid clones, five oligonucleotide STS-primers were designed as shown in Table 1.

### *Characterization of isolated YAC clones*

Using the STSs generated, five YAC clones were isolated from the CEPH-YAC library (Table 2). PFGE analysis revealed that YAC clones (924b10, 923a12,

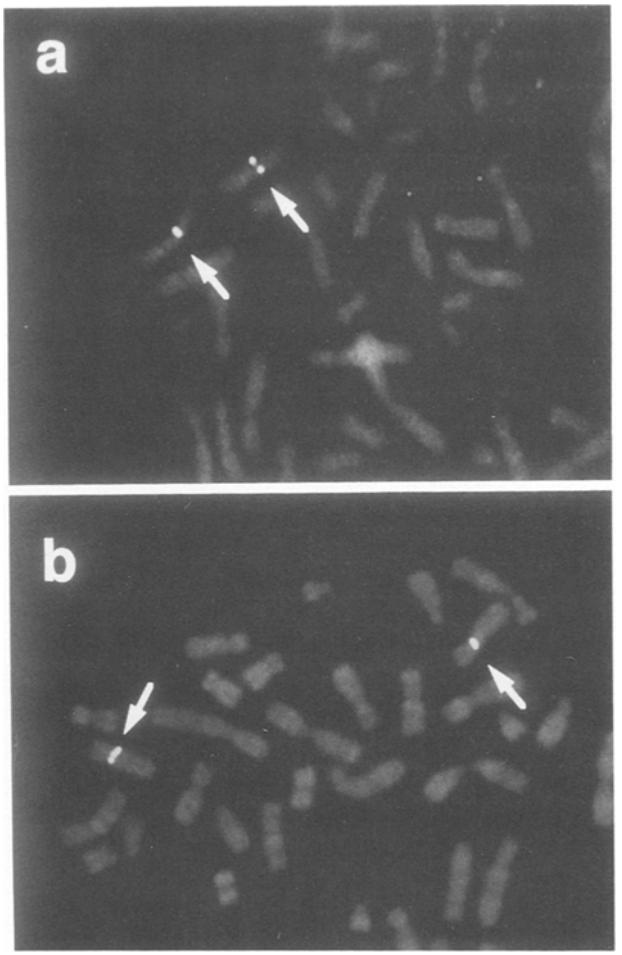


Fig. 1. Fluorescence *in situ* hybridization (FISH) analysis. Human metaphase chromosomes were hybridized with biotinylated DNA of a cosmid clone (RD15/5-J1) constructed from inserted human DNA of RD15/5 (a), and with biotinylated DNA of 943g4-YAC (b). Arrows show FISH signals at 8q11.

943g4, 911f10 and 822h3) contained 1.1-Mb, 1.2-Mb, 1.7-Mb, 1.6-Mb and 1.7-Mb human DNA inserts, respectively. According to the CEPH-YAC data, 924b10 and 923a12 were judged to have deleted-human DNA inserts. Therefore, the other three YAC clones (943g4, 911f10 and 822h3) were used for further analysis. FISH using YAC-derived Alu-PCR products as probes demonstrated that there was no evidence of chimerisim in these three human-DNA inserts, and mapped all these YACs to human chromosome 8q11 (Fig. 1b). Newly generated and previously published STSs information (Table 2) suggested that the three YAC clones overlapped each other.

Table 1. STSs derived from human DNA inserted in RD15/5 cell line.

| Name of STS | Product size (bp) | $T_a$(°C) | Primer sequence |
|---|---|---|---|
| W143-4 | 166 | 60 | TGGTGCTCCCAACTGCATCT |
| | | | GCTCCTCTATTTCCTATTCC |
| J47-2 | 177 | 60 | AGCAGACCCTGCAAGACAAG |
| | | | ACAAGGAGCTTGGGCTAGAA |
| J4-9 | 202 | 55 | ATGGCTCTCTGGCTGATGGA |
| | | | CGACTTCTCTGCCCTATGCA |
| J110-10 | 224 | 60 | CCCATCACCTTCATTTCAGG |
| | | | ACAAGTAGTGGCAGGGACTA |
| J1-6 | 156 | 60 | CCTGCTATTCCAACACTCAT |
| | | | AACTAGACTGCATCTTCAGG |

$T_a$, annealing temperature.

Table 2. Summary of STS study.

| STSs | YAC clones | | | Cell lines | |
|---|---|---|---|---|---|
| | 943g4 | 911f10 | 822h3 | RD15/5 | SC3VA4 |
| Present STSs | | | | | |
| W143-4 | + | − | − | + | − |
| J47-2 | + | − | − | + | − |
| 4-9 | + | + | + | + | − |
| J110-10 | + | + | + | + | − |
| J1-6 | − | − | + | + | − |
| Published STSs | | | | | |
| PLAT | − | − | − | − | − |
| D8S519 | + | + | − | + | − |
| D8S531 | + | + | − | + | − |
| D8S359 | + | + | + | + | − |
| D8S589 | − | − | − | − | − |
| D8S538 | − | − | − | − | − |
| DNA-PK | + | + | + | + | − |

+, positive; −, negative.

*Restriction map of YACs, YAC-contig and localization of the DNA-PK$_{cs}$ gene*

The three YACs were aligned according to their restriction sites (Fig. 2). A YAC contig constructed encompassed about 2.7 Mb. The DNA-PK$_{cs}$ clone 1 (5′ region) was hybridized to 200-kb *Not*I-fragments of the three YACs, and its 3′-UTR PCR product was also hybridized to the same fragments (Fig. 3). These results indicated that the genomic region of the DNA-PK$_{cs}$ gene spans less than 200 kb. At each side of the fragment, a cluster of restriction sites was observed, indicating the possible presence of CpG islands flanking the gene.

## DISCUSSION

We isolated a total of 379 cosmid clones containing human DNA, from a

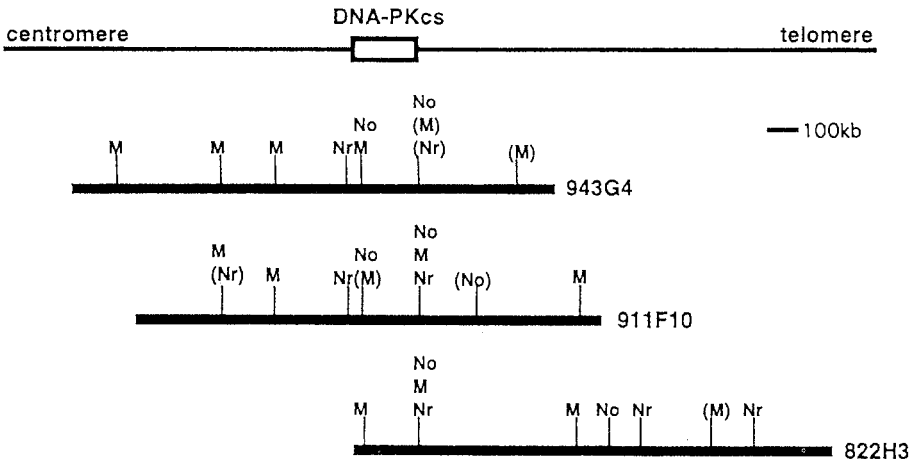


Fig. 2. Physical map of a YAC contig. Thick bars indicate YAC clones, and vertical lines restriction sites. No, M and Nr are *Not*I, *Mlu*I and *Nru*I, respectively.

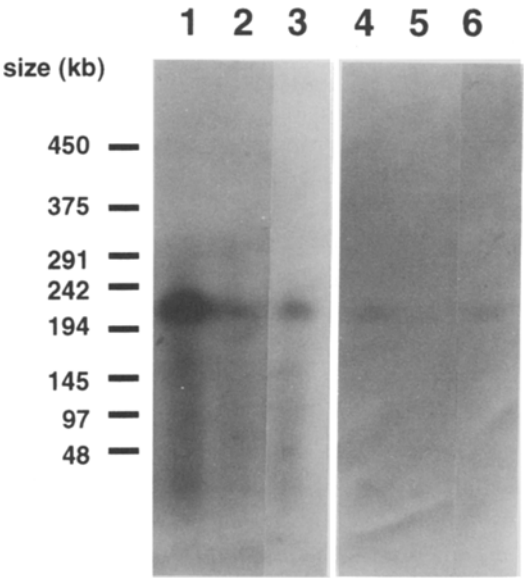


Fig. 3. Localization of the DNA-$PK_{cs}$ gene. Lanes 1–3 show *Not*I-digested YAC clones (822h3, 943f4 and 911f10) hybridized with DNA-$PK_{cs}$ clone 1 (the 5′ region of the DNA-$PK_{cs}$ gene), lanes 4–6 the same YACs hybridized with the 3′-UTR PCR product, respectively. The former probe DNA on membrane was stripped and hybridized with the latter again.

library constructed from a human-scid mouse radiation cell hybrid which may contain *HYRC*. Three-steps of screening (colony hybridization, dot-blot hybridization and FISH) adopted in the present study demonstrated that 18 (4.7%) of the

379 clones contained human unique-DNA inserts. It is likely that a part of the remaining 361 clones were still composed of human DNA inserts, because some clones also gave FISH signals to human chromosome 8. Finally, five STSs and their corresponding three YACs overlapping each other were identified at the 8q11 region (Table 2).

A main goal of our study was to construct a contig of genetic clones at the *HYRC* region. In the present study, we adopted two different approaches: a bottom-up way from cosmid clones followed by STS construction and a subsequent top-down strategy from YACs. YACs still remain problematic, because they tend to become rearranged and chimeric, while rearrangements less frequently occur in cosmid clones. Since our STSs were acquired directly from the inserted human DNA in the complemented human-scid mouse hybrid cell line, they were useful for the isolation of a YAC that covers the *HYRC* locus. It was expected that a contig assembly starting from YACs followed by cosmid subcloning can be compared with the cosmid clones coming from a different source, and STSs will join them.

It has been confirmed that double-strand DNA breaks as well as V(D)J recombination in scid cell lines are restored by human *HYRC* region (Komatsu *et al.*, 1995; Kirchgessner *et al.*, 1995; Blunt *et al.*, 1995), indicating that the *HYRC* locus encodes the scid factor that involves double strand DNA repair and all V(D)J recombination coding joint formation. A strong candidate gene for *HYRC* has been identified (Kirchgessner *et al.*, 1995; Blunt *et al.*, 1995; Lees-Miller *et al.*, 1995) and its partial cDNA has been cloned (Blunt *et al.*, 1995). This gene encodes a huge 350-kDa protein acting as a DNA-dependent protein kinase catalytic subunit (DNA-$PK_{cs}$). The expression of the DNA-$PK_{cs}$ gene was observed in several cell types with a variety of doses, especially being highly expressed in Hela cell (Carter *et al.*, 1990; Lees-Miller *et al.*, 1990; Kirchgessner *et al.*, 1995; Blunt *et al.*, 1995). Analysis of gene expression in radiation sensitive or resistant tumor cells may develop new insights for radiation therapies. The DNA-$PK_{cs}$ gene is contained within a 280-kb YAC clone (Blunt *et al.*, 1995). Our study indicated that it spans 200 kb. The physical map of our YAC-contig may be useful for the construction of a cosmid contig covering this huge gene as well as other genes of the region. Involvements of the 8q11-q12 region in chromosome aberrations have been reported many times. They were often associated with various diseases, such as acute lymphoid leukemia (Testoni *et al.*, 1993), malignant lymphoma (Huret *et al.*, 1990), salivary gland pleomorphic adenoma and carcinoma (Bullerdiek *et al.*, 1993; Jin *et al.*, 1994), lymphoblastoma (Sawyer *et al.*, 1994), Silver-Russell syndrome-like features (Schinzel *et al.*, 1994) and another congenital anomaly (Walker and Bocian, 1987). There must be in this region some disease-related genes other than *HYRC* (Kirchgessner *et al.*, 1995; Blunt *et al.*, 1995; Lees-Miller *et al.*, 1995) and C/EBP$\delta$ (Cleutjens *et al.*, 1993; Kirchgessner

*et al.*, 1995). Therefore, our physical map of YAC contig is also useful to isolate such genes.

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