Localization of the Photoreceptor Gene *ROM1* to Human Chromosome 11 and Mouse Chromosome 19: Sublocalization to Human 11q13 between *PGA* and *PYGM*

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Summary

Rom-1 is a retinal integral membrane protein that, together with the product of the human retinal degeneration slow gene (*RDS*), defines a photoreceptor-specific protein family. The gene for rom-1 (HGM symbol: *ROM1*) has been assigned to human chromosome 11 and mouse chromosome 19 by Southern blot analysis of somatic cell hybrid DNAs. *ROM1* was regionally sublocalized to human 11p13-11q13 by using three mouse-human somatic cell hybrids; in situ hybridization refined the sublocalization to human 11q13. Analysis of somatic cell hybrids suggested that the most likely localization of *ROM1* is in the ~2-cM interval between human *PGA* (human pepsinogen A) and *PYGM* (muscle glycogen phosphorylase). *ROM1* appears to be a new member of a conserved syntenic group whose members include such genes as *CD5*, *CD20*, and *OSBP* (oxysterol-binding protein), on human chromosome 11 and mouse chromosome 19. Localization of the *ROM1* gene will permit the examination of its linkage to hereditary retinopathies in man and mouse.

Introduction

Rom-1 is a 37-kDa integral membrane protein expressed in rod photoreceptors of the mammalian retina (Bascom et al. 1992). The rom-1 polypeptide is localized to the outer segments of rod photoreceptors and, more specifically, to the rims of the rhodopsin-containing membranous disks of which the outer segment is largely composed. At the disk rim, rom-1 appears to associate with a related protein, peripherin (Connell and Molday 1990; Bascom et al. 1992), which is the product of the retinal degeneration slow (*RDS*) gene (Travis et al. 1989, 1991; Connell et al. 1991). The human rom-1 and peripherin proteins

show 35% identity, and, on the basis of their structural and biological similarity, they define a new photoreceptor-specific protein family (Bascom et al. 1992). In addition, since the phenotype of a homozygous *rds* (retinal degeneration slow) (null allele) mouse is aborted rod photoreceptor-disk morphogenesis (Travis et al. 1989), we have suggested that rom-1, like peripherin, may also play a role in the formation of the photoreceptor disks (Bascom et al. 1992).

The *rds* gene was mapped to mouse chromosome 17 by linkage to the *H-2* locus (van Nie et al. 1978), and its cDNA was cloned, in part, by knowledge of its chromosomal location (Travis et al. 1989). *RDS* was mapped subsequently to human chromosome 6 by using somatic cell hybrids and was further sublocalized on the proximal short arm of chromosome 6 by in situ hybridization (Travis et al. 1991). The map position of human *RDS* on proximal 6p has been recently refined by linkage analysis, which has suggested that the order is tel–D6S89–D6S109–D6S105–HLA–DRA–RDS–TCTE1–cen (Jordan et al. 1992).

Mice homozygous or heterozygous for mutant *rds* develop a degenerative retinopathy (Sanyal et al. 1980; Hawkins et al. 1985), and, consequently, *RDS* is an important candidate gene for both dominant and recessive inherited retinopathies in man. The pathology of the murine *rds* retinopathy is similar to that of some forms of human retinitis pigmentosa (RP) (Travis et al. 1991). Farrar et al. (1991a) have recently mapped a human autosomal dominant RP locus in one family to the short arm of chromosome 6; this locus showed tight linkage to the *RDS* gene. Subsequently, an *RDS* mutation was identified in another family with autosomal dominant RP (Farrar et al. 1991b). In a related study based on the candidate-gene approach, Kajiwara et al. (1991) identified distinct mutations in the *RDS* gene in individuals in three unrelated pedigrees with autosomal dominant RP.

The structural and functional similarities between rom-1 and peripherin (Bascom et al. 1992), together with the genetic heterogeneity of human RP (Humphries et al., in press), make *ROM1* a significant candidate gene for both dominant and recessive degenerative retinopathies. As an initial step in establishing whether mutations in the *ROM1* gene cause inherited human or murine retinal degeneration, we have determined its chromosome location in both species.

Material and Methods

Southern Blot Analyses

A nearly full-length rom-1 cDNA (1,224 bp, subcloned into the *Eco*RI site of Bluescript) was used as a probe for filter and in situ hybridization experiments. The cDNA was isolated from a human retina lambda gt10 cDNA library (Bascom et al. 1992). For Southern blot analysis the probe was labeled with ^{32}P-dCTP by the method of Feinberg and Vogelstein (1983). Blots were incubated in prehybridization buffer (5 × SSC, 0.5% nonfat milk, 50 mM NaPO$_4$ pH 6.7, 40% formamide, 1% SDS, and 273 µg of sheared salmon sperm DNA/ml) at 42°C for at least 4 h. The hybridization buffer was identical except that it contained 10% (w/v) dextran sulfate and ~1.5 × 10^6 cpm of ^{32}P-labeled rom-1 probe/ml. Hybridization was carried out at 42°C for ~16 h. Blots were washed twice at room temperature with 2 × SSC and 0.1% SDS for 15 min each and then at 65°C for the same time. The blots were finally washed with 0.2 × SSC and 0.1% SDS at 65°C for 15–30 min before being exposed to Kodak X-Omat AR film.

Hybrid Cell Lines Used for Chromosomal and Regional Localization

Human chromosomal assignment. — Mouse and human cells were fused, and somatic cell hybrids were isolated as described by Lafrenière et al. (1991). Hybrid clones were harvested for DNA preparation and chromosome analysis at the same cell passage. Human chromosome composition of cell hybrids was determined by detailed karyotyping of a minimum of 25 cells, after trypsin-Giemsa banding (Francke and Oliver 1978). In most cases, chromosomes were scored both before and after DNA preparation. DNA was digested with *Eco*RI or *Hind*III and electrophoresed through 0.8% agarose gels and transferred to Hybond-N nylon membrane (Amersham).

Murine chromosomal assignment. — The origin and characterization of 12 Chinese hamster ovary (CHO)–mouse hybrid cell clones derived from three series of hybrids and of one rat-mouse hybrid clone have been described elsewhere (Yang-Feng et al. 1986).

Somatic Cell and Radiation-reduced Hybrid Lines Used for Subregional Localization

The generation of the human chromosome 11q deletion CHO hybrid, J1-44, has been presented by Jones et al. (1984), while the description of the other 11q deletion CHO hybrids, J1-46 and J1-55, and the molecular characterization of all three hybrids are given by Gerhard et al. (1992). By cytogenetic analysis, J1-44 was found to be deleted for the proximal region of chromosome 11q (Jones et al. 1984). A detailed description of the generation and characterization of the chromosome 11q radiation-reduced somatic cell hybrids has been presented in Gerhard et al. (1992). In brief, in the donor cell line J1-9 (Glaser et al. 1989), the only human chromosome retained is 11, deleted for 11p13-11p15.5; this line was exposed to 8,070 rads of γ irradiation. After fusion with rhodamine-6G–treated CHO cells, eight clones expressing the MDU-1 surface antigen were selected by panning. These cell lines were analyzed by Southern hybridization with chromosome 11 markers whose position and relative distance were known (Julier et al. 1990). *Eco*RI-digested DNA was transferred to a nylon membrane, as described by Gerhard et al. (1992), hybridized to ^{32}P-labeled cDNA probe, and exposed overnight.

In Situ Hybridization

A human female lymphoblastoid cell line of normal karyotype was used for mapping purposes. The cells

were cultured in RPMI medium (Gibco) supplemented with FCS (10%) and L-glutamine. Cells were synchronized by blocking with BrdU (100 µg/ml) for 18 h and then were released by two washes of Hanks' balanced salt solution, followed by incubation for 6 h in fresh medium plus 10^{-3} M thymidine. Harvesting was done by standard methods after treatment with colcemid for 10 min.

In situ hybridization experiments were carried out by following the technique of Harper and Saunders (1981). The rom-1 cDNA was tritium-labeled to a specific activity of ~1 × 10^8 cpm/µg by the method of Feinberg and Vogelstein (1983). The slides were dipped in Kodak NTB2 emulsion and subsequently exposed at 4°C for 6–13 d. After standard development, G-banding was performed using the sodium borate method of Cannizzaro and Emanuel (1984).

Results

To determine the chromosomal location of *ROM1* in humans, a panel of 10 mouse-human hybrid DNAs containing defined overlapping subsets of human chromosomes was tested for the presence of *ROM1* sequences. A Southern blot containing *Eco*RI-digested hybrid DNA was probed with the rom-1 cDNA (fig. 1, top left panel). The rom-1 cDNA hybridized to a single human band of ~20 kb and to a single mouse band of ~6.5 kb. The only human chromosome that continually segregated with the rom-1 probe (i.e., there were no discordant hybrids) was chromosome 11. The number of discordant hybrids for each of the other human chromosomes was between two and seven, with the mode being four. These results indicate that *ROM1* maps to human chromosome 11.

The *ROM1* locus was regionally assigned on human chromosome 11 by using DNA from three mouse-human hybrids that contained translocations between human chromosomes X and 11. A Southern blot of *Hind*III-digested DNA was probed with the rom-1 cDNA. Hybrids (Lafrenière et al. 1991) A48-1Fa and A49-5A, which contain the translocation chromosomes Xqter→Xcen::11p11-13→11qter and 11pter→11q13::Xq22→Xqter, respectively, gave positive hybridization signals. The hybrid L48-2A, which contains the translocation chromosome Xpter→Xcen::11p11-13→11pter, was negative with the rom-1 probe. These data show that the *ROM1* locus is within the region 11p11-13 to 11q13 (fig. 1, right panel).

The position of the human *ROM1* gene was further refined by in situ hybridization with a tritium-labeled

rom-1 cDNA probe. Sixty metaphase spreads of a normal human female lymphoblastoid cell line were analyzed, after autoradiography, for grain localization (total 106 grains; 1.76/cell). Twenty-three percent of all the grains were located on chromosome 11. Sixty-four percent of the chromosome 11 grains (15% of the total) were at 11q13 (fig. 1, bottom left panel). The silver grains on the other human chromosomes were randomly distributed. Cytological hybridization thus localizes the *ROM1* gene to 11q13.

Several human-CHO somatic cell hybrids (Jones et al. 1984) were used to confirm the location of *ROM1* and to provide further sublocalization. *ROM1* was absent (data not shown) from three human-CHO hybrids (J1-44, J1-46, and J1-55) that were selected because they did not express the surface antigen MDU-1; these cell lines have deletions with different proximal and distal breakpoints within proximal 11q (Jones et al. 1984; Gerhard et al. 1992). The absence of *ROM1* from J1-46 is the most informative result because this hybrid has the smallest deletion, retaining the markers *PGA* (human pepsinogen A) and *INT2* (mammary tumor integration site 2) but lacking *PYGM* (muscle glycogen phosphorylase) and *MDU1* (fig. 2, left panel).

The examination of radiation-reduced hybrids (Gerhard et al. 1992) corroborated the proximity of *ROM1* to *MDU1* and placed *ROM1* between *PGA* and *PYGM* (fig. 2). The experiments were done both by Southern blotting (fig. 2, left panel) and by PCR analysis (data not shown) of the hybrid DNAs; identical results were obtained by both methods. *ROM1* had the same segregation pattern as *PGA* (Gerhard et al. 1992) in these hybrids. It was present in the six hybrids (fig. 2, left panel, lanes 1–5 and 8) that contain the region of 11q between *PGA* and *MDU1* but was not detected in the two hybrids with deletions extending distally from near the centromere to include *PGA* but not *PYGM* (fig. 2, left panel, lanes 6 and 7). Thus, the smallest region deleted in common in the cells lacking *ROM1* is defined by hybrids J1-46 and R185-1B1, suggesting that the most likely localization of *ROM1* is in the ~2-cM domain between *PGA* and *PYGM* (fig. 2, bottom panel).

The *Rom-1* gene was mapped in mouse by Southern blot analysis of *Bam*HI-digested DNA from one rat-mouse and 12 CHO-mouse somatic cell hybrids. The rom-1 probe hybridized to 16.0-kb and 2.1-kb mouse restriction fragments (fig. 3) in 10 informative hybrids. The only mouse chromosome that consistently segregated with the murine *Rom-1* fragments (i.e.,
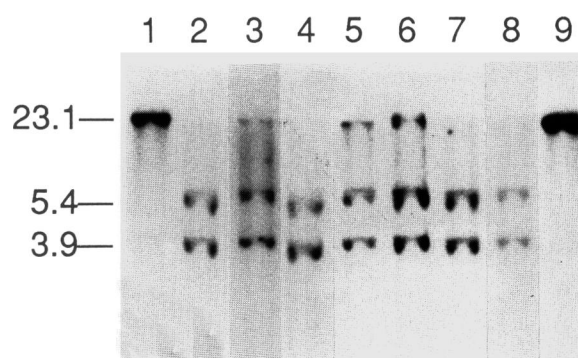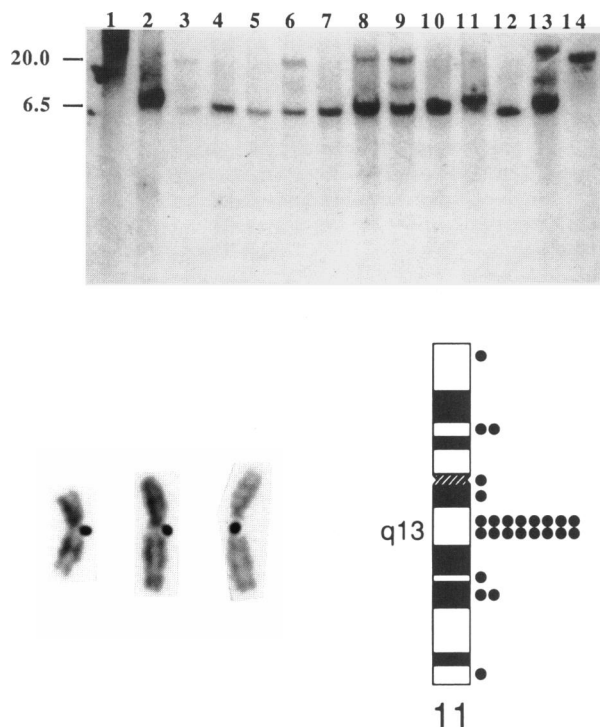
Figure I   Localization of *ROM1* to chromosome 11q13. *Top left,* Chromosomal localization of human *ROM1:* hybridization of ^{32}P-labeled rom-1 cDNA to *Eco*RI-digested human, mouse, and mouse-human hybrid DNA. Lanes 1 and 14, Human genomic DNA; Lane 2, Mouse genomic DNA; Lanes 3–13, Mouse-human hybrid DNAs. The rom-1 probe hybridized to restriction fragments of ~20.0 kb (human) and ~6.5 kb (mouse). Hybrid DNAs in lanes 3, 6, 8, 9, and 13 are positive for the human *ROM1* band. *Top right,* Regional localization of *ROM1* to human 11p13-11q13: composite autoradiogram showing hybridization of the rom-1 cDNA to *Hind*I-II-digested hybrid (mouse-human) and human control DNA. Lane 3 (hybrid A48-1Fa, with the human translocation chromosomes Xqter→Xcen::11p11-13→11qter) and lane 6 (hybrid A49-5A, with the human translocation chromosomes 11pter→11q13:: Xq22→Xqter) are positive, whereas lane 4 (hybrid L48-2A, with the human translocation chromosome Xpter→Xcen::11p11-13→11pter) is negative for the human bands. Lanes 1 and 9, human control DNA. *Bottom left,* Subchromosomal localization of *ROM1* to human 11q13 by in situ hybridization. Examples of three G-banded human chromosomes 11 probed with ^{3}H-labeled rom-1 cDNA are shown on the left. The observed distribution of 25 autoradiographic silver grains plotted on an ideogram of a human G-banded chromosome 11 are shown on the right.

no discordant hybrids) was chromosome 19 (table 1). Thus, *Rom-1* is assigned to mouse chromosome 19.

Discussion

The data presented here indicate that *ROM1* is a new member of a conserved syntenic group on human chromosome 11 and mouse chromosome 19. This conserved syntenic group has previously been located to the proximal region of mouse chromosome 19 and the proximal long arm of human chromosome 11, which show a similar Q-banding pattern (Tedder et al. 1988). Human band 11q13, to which *ROM1* maps, has been genetically sized at 15 cM and has been tentatively subdivided into two regions on the basis of its interspecies conserved groups (Szepetowski et al. 1992). All known human 11q13 genes with mouse chromosome 19 homologues map centromeric to the *BCL1* breakpoint, whereas all 11q13 genes with mouse chromosome 7 homologues are telomeric to the translocation breakpoint, a finding that led Szepe-towski et al. (1992) to propose that *BCL1* could be the site of a primordial translocation event. This model is consistent with the suggestion of White (1969) that the definition of breakpoints between conserved syntenic groups may lead to the identification of translocation

or inversion hot spots that may be involved in speciation. Seldin et al. (1991) have presented a model depicting possible translocation events of a putative primordial chromosome, which resulted in the present organization of genes on human chromosome 11. Additional studies are needed, however, to confirm that the *BCL1* breakpoint separates the two different conserved groups (Szepetowski et al. 1992).

One member of the *ROM1* conserved syntenic group is the human gene *CD20* (originally termed "B1"), which maps to human chromosome 11 band q12-q13.1 and mouse chromosome 19 band B (close to the centromere) (Tedder et al. 1988, 1989). Our data suggest that *ROM1* is closely linked to the *CD20* gene, as determined by radiation hybrids. Although no significant sequence identity exists between the human rom-1 and CD20 proteins (13% identity and 23% homology, when gaps are ignored), it is interesting
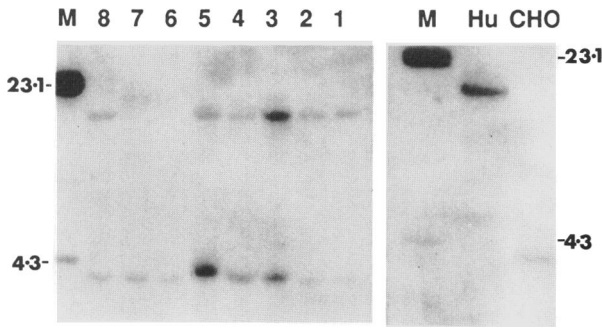
Figure 2   Mapping *ROM1* to human 11q13, between *PGA* and *PYGM*. *Left,* Composite autoradiogram of two filters, showing hybridization of the rom-1 cDNA to human-CHO somatic cell hybrid DNA. In both, lane M is lambda DNA digested with *Hind*III, with the larger fragment being 23.1 kb and the smaller fragment being 4.3 kb. The autoradiogram on the left is of the DNA of eight radiation-reduced hybrids described by Gerhard et al. (1992). Lane 1, R184-2A1. Lane 2, R184-3A1. Lane 3, R184-7C1. Lane 4, R184-5D1. Lane 5, R184-4C2. Lane 6, R185-2C2. Lane 7, R185-1B1. Lane 8, R131-33B1. The autoradiogram on the right is of human (lane Hu) and CHO DNA, showing that the CHO *Rom-1* gene is not detected by the human rom-1 cDNA under the conditions used. *Bottom,* Locus order in the centromeric region of human chromosome 11q, and DNA content of hybrids critical to mapping *ROM1*. Shown are the order of the loci in the centromeric region of human 11q as established by Nakamura et al. (1989), Julier et al. (1990), Byström et al. (1990), and Gerhard et al. (1992), and the relative position of *ROM1*. *CD20* could not be resolved from *PGA;* Richards et al. (1991) have more finely mapped *CD20* and report it to be more centromeric than *PGA*. Also depicted is the DNA content of three radiation-reduced hybrid cell lines (R185-2C2, R185-1B1, and R131-33B; Gerhard et al. 1992) and the human-CHO somatic cell hybrid J1-46 (Jones et al. 1984).
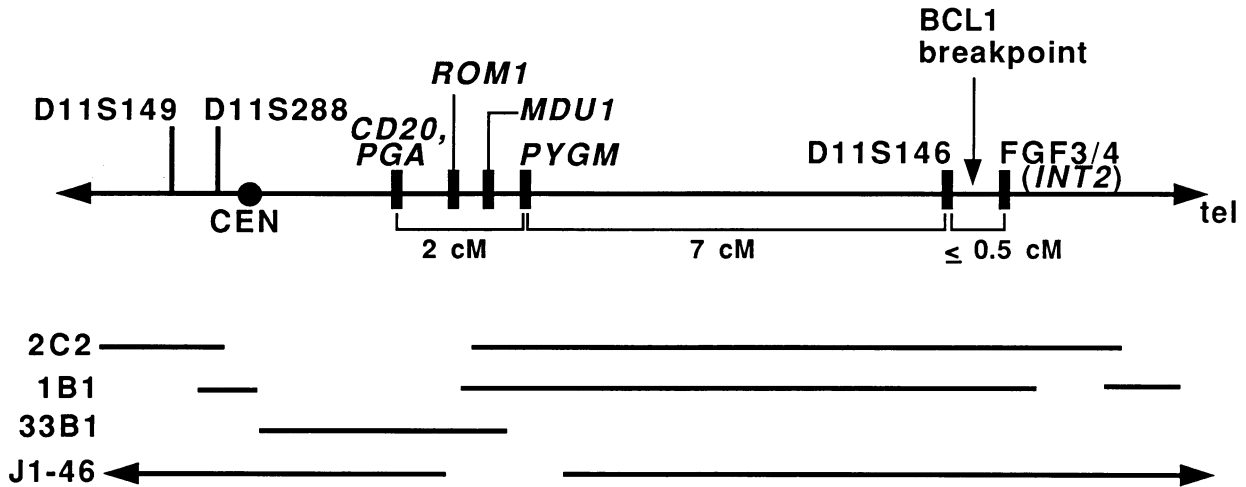
to note that the predicted CD20 protein (291 amino acids, 32 kDa) and the predicted rom-1 protein (351 amino acids, 37 kDa) are both integral membrane proteins with similar topologies: both polytopic proteins are predicted to possess four transmembrane domains with cytoplasmic carboxyl- and amino-terminal ends. A definitive statement concerning a possible relationship between these proteins cannot be made at present.

Other genes of the conserved group include the lymphocyte cell-surface antigen *CD5* (Ly-1), *Fth* (ferritin heavy chain), *PYGM,* and *OSBP* (oxysterol-binding protein) (Junien and McBride 1989; Levanon et al. 1990). The map order of the genes in the conserved

region remains to be fully defined, but our data from radiation hybrids suggest that *ROM1* appears to be located between *PGA* and *PYGM,* which are separated by ~2 cM (fig. 2, bottom panel). Human *PYGM* and *PGA* are situated ~7.5 cM and ~9.5 cM, repectively, on the centromeric side of the *BCL1* breakpoint. Telomeric to the *BCL1* breakpoint is the *INT2* locus that maps to mouse chromosome 7 (Searle et al. 1987).

Human band 11q13 has been reported to be a site of numerous aberrant chromosomal rearrangements (Tedder et al. 1989) and is thus an area of active research. The *BCL1* locus in this band marks the site of a translocation t(11;14)(q13;q32) that has been re-
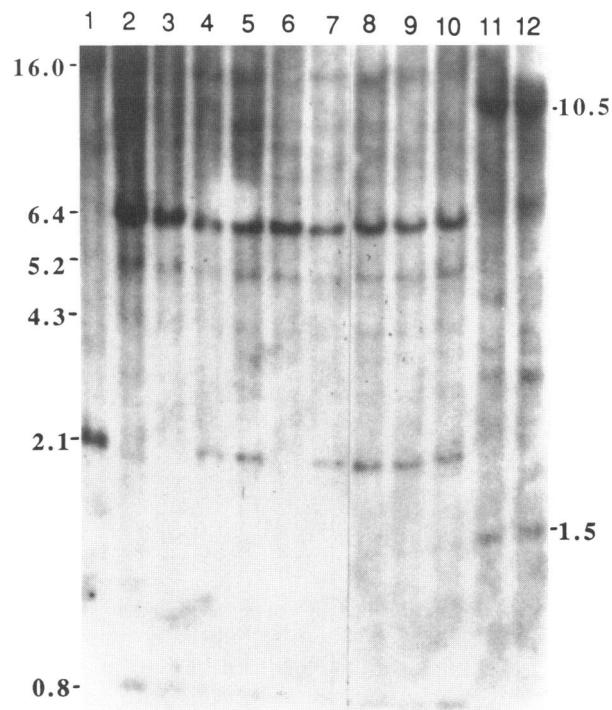
Figure 3 Chromosomal localization of murine *Rom-1*. Hybridization of ³²P-labeled rom-1 cDNA to *Bam*HI-digested DNA from hybrid cell lines and controls. Lane 1, mouse cell line. Lane 2, Chinese hamster lung cell line. Lanes 3–10, Chinese hamster–mouse hybrids. Lane 11, Rat-mouse hybrid. Lane 12, Rat (hepatoma) cell line. The rom-1 probe hybridized to mouse restriction fragments of 16.0 kb and 2.1 kb. Hybrid DNA in lanes 4, 5, and 7–10 are positive for the mouse bands.

ported in diffuse large and small lymphomas, lymphocyte leukemia, and multiple myeloma (Tsujimoto et al. 1985). Other notable loci in this band include a heritable fragile site (Yunis and Soreng 1984), a highly

polymorphic locus potentially useful for DNA fingerprinting and linkage analysis (Eubanks et al. 1991), and the *MEN1* (multiple endocrine neoplasia type 1) gene (Larsson et al. 1988).

Substantial locus heterogeneity has been found in autosomal dominant RP; to date, three and possibly four different loci have been linked to the disease in various families (McInnes and Bascom 1992; Wright 1992; Humphries et al., in press). The genes at two of these loci have been identified—rhodopsin on chromosome 3q and peripherin/*RDS* on chromosome 6q. One of the unidentified genes is located in the pericentric region of chromosome 8 (Blanton et al. 1991). Another is suspected of being on chromosome 3q near rhodopsin, because a large Irish pedigree that segregates a 3q locus does not appear to have a mutation in the rhodopsin gene and also demonstrates recombination between rhodopsin and the marker (D3S47) most closely linked to the disease locus; however, defects in distant regulatory elements of the rhodopsin gene have not been unambiguously excluded (Inglehearn et al. 1992). Although it is not certain at present how many patients have mutations at either of these latter loci, mutations in rhodopsin and peripherin/*RDS* account for only ~25% (Humphries et al., in press) and probably ~2%–3% (Kajiwara et al. 1991) of cases, respectively. Thus, unless the unidentified genes on chromosomes 3q and 8 unexpectedly account for all the remaining cases (and this does not appear to the case [S. Daiger, personal communication]), additional loci will be associated with the autosomal dominant RP phenotype in the future. In view of the structural and biological similarity of *ROM1* and peripherin/*RDS* (Bascom et al. 1992), mutation studies and linkage analysis are being performed to determine

Table I

Correlation of Mouse-specific *Rom-1* Sequences with Mouse Chromosomes in Chinese Hamster–Mouse Somatic Cell Hybrids

HYBRIDIZATION CHROMOSOME[a]	NO. OF CORRELATIONS, BY CHROMOSOME																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	X
+ / + ...	6	8	6	5	3	4	6	6	2	3	0	5	3	3	7	4	7	4	8	5
– / –	2	3	5	5	4	4	3	5	4	4	4	3	4	4	3	3	3	5	4	2
+ / –	2	2	2	2	3	2	1	2	5	4	8	3	4	5	1	3	1	3	0	2
– / + ...	2	0	0	0	0	1	2	0	1	1	1	2	1	1	2	2	2	0	0	3
Discordant hybrids	4	2	2	2	3	3	3	2	6	5	9	5	5	6	3	5	3	3	0	5
Informative hybrids ...	12	13	13	12	10	11	12	13	12	12	13	13	12	13	13	12	13	12	12	12

[a] Symbols before the slash indicate the presence (+) or absence (–) of the mouse *Rom-1 Bam*HI restriction fragments (2.1 and 16.0 kb), and symbols after the slash indicate the presence (+) or absence (–) of a particular mouse chromosome in the somatic cell hybrids analyzed. Hybrids in which a particular chromosome was structurally rearranged or present in fewer than 10% of cells were excluded.

whether *ROM1* is one of the other loci associated with human retinopathies.

Acknowledgments

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