Characterization and Comparative Structural Features of the Gene for Human Interstitial Retinol-binding Protein*

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We have cloned the gene for human interstitial retinol-binding protein (IRBP) and compared its nucleotide sequence with that of the corresponding cloned cDNA. The human IRBP gene is ~9.5 kilobase pairs (kbp) in length and consists of four exons separated by three introns. The introns are 1.6–1.9 kbp long. The gene is transcribed by photoreceptor and retinoblastoma cells into an ~4.3-kilobase mRNA that is translated and processed into a glycosylated protein of 136,000 Da. The amino acid sequence of human IRBP can be divided into four contiguous homology domains with 33–38% identity, suggesting a series of gene duplication events. In the gene, the boundaries of these domains are not defined by exon-intron junctions, as might have been expected. The first three homology domains and part of the fourth are all encoded by the first large exon, which is 3,180 base pairs long. The remainder of the fourth domain is encoded in the last three exons, which are 191, 143, and ~740 base pairs long, respectively. This unusual structure is shared with the bovine IRBP gene. A large (1.7 kbp) fragment appears to have been lost from the 3′-noncoding region of the last human exon. We conclude that the human and bovine genes have similar evolutionary histories.

Interstitial retinol-binding protein (IRBP) is an elongated glycoprotein found in the eyes of all vertebrates (1–8). Its size averages 134,200 Da except in bony fishes, where it is about 2723, EY 07008, and EY 02489. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accord with 18 U.S.C. Section 1734 solely to indicate this fact.

The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EMBL Data Bank with accession number(s) J05243.

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The abbreviations used are: IRBP, interstitial retinol-binding protein; kb, kilobase(s); bp, base pair(s).

(13–15), which has also been demonstrated in mammalian pineal glands (16–18).

We have purified and characterized human IRBP (4) and localized its gene to chromosome 10 (19), where the IRBP locus has been shown to be closely linked to that of multiple endocrine neoplasia type 2a (20, 21). Recently, we cloned the full-length cDNA sequence for human IRBP and demonstrated that the conceptually translated protein sequence is composed of four contiguous homology domains (302–310 residues in length) with 33–38% identity (22). Certain synthetic peptides based on this sequence have been shown to cause uveitis in rats (23). IRBP binds two molecules of all-trans- or 11-cis-retinol (3, 7), and we have suggested that hydrophobic amino acids in the four homologous regions of the molecule participate in the formation of two folding domains that constitute two retinol-binding sites (23). In this work, we report the structure and nucleotide sequence for the entire human gene and part of its flanking region. This provides the basis for future detailed studies on those elements of the IRBP gene structure that regulate its expression in the normal and diseased eye and in retinoblastoma cells.

EXPERIMENTAL PROCEDURES

Isolation of Genomic Clone for Human IRBP—The isolation of a genomic clone (HGL.3) containing the full coding region of IRBP has been described (22). An overlapping clone (HGL.1, ~13 kilobase pairs in length) was isolated from the same library and was found to extend beyond the 3′-end of clone HGL.3.

Restriction Mapping, Subcloning of Overlapping Clones, and DNA Sequencing

A standard restriction map of clone HGL.3 is shown at the top (S, SstI; B, BamHI; E, EcoRI). The distribution of sequences encoding the four protein homology domains (I–IV) is indicated. The four exons (1–4) are shown as bars, and the three introns (A–C) as lines. Blocked exon segments correspond to coding regions. The position of the first polyadenylation consensus encountered in the 3′-noncoding sequence is shown. Arrows at the bottom indicate direction (5′ to 3′) and extent of sequencing.

Fig. 1. Sequencing strategy for the human IRBP gene. The restriction map of clone HGL.3 is shown at the top (S, SstI; B, BamHI; E, EcoRI). The distribution of sequences encoding the four protein homology domains (I–IV) is indicated. The four exons (1–4) are shown as bars, and the three introns (A–C) as lines. Blocked exon segments correspond to coding regions. The position of the first polyadenylation consensus encountered in the 3′-noncoding sequence is shown. Arrows at the bottom indicate direction (5′ to 3′) and extent of sequencing.
FIG. 2. Complete nucleotide sequence of the human IRBP gene. The putative transcription initiation site is located at position 1. The presumptive translation initiation site (ATG), the N-terminal glycine of the mature protein (GGC), the translation terminating codon (TAG), and two polyadenylation consensus sequences (AATAAA) are underlined. Exons are denoted by uppercase letters, and introns by lowercase letters.

Sequencing—The genomic clone HGL.3 was excised from the EMBL3 vector with Sfl. Restriction fragments generated by Sfl, EcoRI, and BamHI digestion were then subcloned into pUC19 and M13mp19 (24). Sequencing was by the dideoxy chain termination method (25) using Sequenase (United States Biochemical Corp., Cleveland, OH) and the procedure of Dale et al. (26). A 1.5-kilobase pair SstI fragment from clone HGL.1 was used to provide information on the gene sequence beyond the 3'-end of clone HGL.3.

Primer Extension—A synthetic 23-base oligonucleotide complementary to residues -58 to -80 of human IRBP cDNA (22) was used as a primer. After end labeling this oligonucleotide with [γ-32P]ATP (27), it was annealed to 1-2 µg of poly(A) from human retina or cultured retinoblastoma cells, and the extension reaction was carried out in the presence of actinomycin D (40 ng/µl) (28).

S1 Nuclease Protection Analysis The method was based on that of Ausubel et al. (29). The 32P-labeled synthetic oligonucleotide used for primer extension was hybridized to a 2.4-kb SstI IRBP genomic fragment, the 3'-end of which is located at nucleotide 367 on the genomic sequence obtained in this work. The hybrid was extended with Klenow fragment and then digested with HgiAI. The single-stranded radiolabeled probe, defined at its 3'-end by the HgiAI digestion, was isolated on an alkaline agarose gel and hybridized (5 x 10^6 cpm) with 50 µg of human retina total RNA. Five hundred units of S1 nuclease were then added, and the size of the protected probe was determined on an 8% denaturing polyacrylamide gel.

Preparation of RNA from Adult Human Retinas and Cultured Retinoblastoma Cells—The established retinoblastoma cell line RB622A was generously provided by Dr. Brenda Gallie (Departments
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TABLE I

Corrections to published human IRBP cDNA

Thirty-one nucleotide positions are changed. For the amino acid changes, 32 residues have been deleted from the amino acid sequence, 29 of which are at the C terminus. A further 29 residues have been changed. Excluding the putative 16-residue signal peptide, the new sequence consists of 1230 amino acids and is presented in Fig. 6.

| Coding region | Ref. 22 | This work |
|---------------|---------|-----------|
| CAA (631–633) | ACC     |           |
| C (1390)      | T       |           |
| CA (2651–2652)| GC      |           |
| CG (2964–2965)| GC      |           |
| C (3440)      | G       |           |
| G, G, A, C, A, C, G (2994, 3007, 3018, 3020, 3076, 3726, 3747) | Delete |           |
| GAG (3028–3031) | Delete |           |

| Noncoding region |
|------------------|
| Ref. 22 | TT GT GCA CCCACCTTCTTCTTCTTTATCTTTGGCTCTTTT |
| This work | TTGGGGTGGATTTTTACCTTCTTCTTTATCTTTGGCTCTTTT |

of Ophthalmology and Pediatrics, Hospital for Sick Children, Research Institute, Toronto, Canada). RNA was prepared from the tissue or cultured cells by the guanidinium method (29), and polyadenylated RNA was prepared by oligo(dT)-cellulose chromatography (30).

DNA and RNA Blot Analysis—Total RNA was separated by electrophoresis in agarose containing formaldehyde and transferred to nitrocellulose. The blot transfer was hybridized at 42 °C in the presence of 50% formamide (29) with H.12 IRBP cDNA (22) labeled by random priming (Boehringer Mannheim).

Computer Analysis and Sequence Comparisons—Sequences were analyzed with Beckman MicroGenie software on an IBM PC XT computer.

RESULTS AND DISCUSSION

The strategy used to sequence the human IRBP gene is shown in Fig. 1. A comparison of the genomic sequence with our published cDNA sequence (22) reveals that the coding region of the gene is composed of four exons interrupted by three introns. The positions of the four protein homology domains identified previously (22) are indicated above the exon-intron structure. The boundaries of these domains are not defined by exon-intron junctions, as might have been expected. The first three homology domains and part of the fourth are all encoded by the first large (3180 bp) exon, with the remainder of the fourth domain being encoded in the last three exons, which are 191, 143, and ~740 bp in length, respectively.

The entire DNA sequence for the human IRBP gene is shown in Fig. 2. This sequence was used to correct 31 nucleotide positions in the published cDNA sequence (Table I). The sequence starts at the putative cap site; and the positions of the presumptive translation initiation codon (22), the codon for the N-terminal glycine of the mature protein (6, 31, 32), and the TAG translation terminating codon are underlined. The TAG codon is located 87 bases upstream from that reported previously (22). The first of the two closely spaced AATAAA polyadenylation consensus sequences (33) is separated from the cap site by 9499 nucleotides. An SstI restriction fragment from the genomic clone HGL.1 was found to overlap with clone HGL.3 and was used to extend our knowledge of the sequence by a further 700 bases in the 3' -direction (data not shown). However, no other AATAAA sequences were found. Excluding any contribution from the poly(A) tract, we predict an mRNA of ~4.25 kb. Fig. 3, which represents Northern blots of RNA from human retinas and an established retinoblastoma cell line (RB522A; Ref. 15) probed with H.12 IRBP cDNA, indicates a 4.3-kb transcript. Liou et al. (19) previously estimated that IRBP mRNA from adult human retina is 5.2 kb.

The structures of the exon-intron boundaries for the human IRBP gene are shown in Table II. The donor and acceptor splice junction sequences agree closely with published consensus sequences (34), with the 5'- and 3'-ends of each intron conforming to the GT/AG rule. Table III indicates the positions of possible 3'-splice signal sequences corresponding to lariat branch sites that appear to be conserved in animal introns (35).

Total and polyadenylated RNAs prepared from batches of human retinas were used to map the 5'-end of the human
TABLE II
Donor and acceptor splice sites in the human IRBP gene

| Exon | Exon size (bp) | 5' Splice donor | 3' Splice acceptor | Intron size (bp) |
|------|---------------|----------------|-------------------|-----------------|
| 1    | 3180          | ATGCAG          | gtgaga...         | 1785            |
| 2    | 191           | CATGAG          | gccagt...         | 1880            |
| 3    | 143           | TTTGTA               | gccact...         | 1606            |
| 4    | 740           | CAG gtaag...     | (t)11...ncag G   |                 |

*To first AATAAA polyadenylation consensus sequence.

TABLE III
Possible 3'-splice signals (lariat branch sites) in the human IRBP gene

| Intron | Exon |
|-------|------|
| CTCTAAAACGTGGCTCCTTC | 2 |
| AAGGCTACTGTGAGCTCAG | 3 |
| AAGGCTCTGAGCTGACTGTG | 3 |
| GTGCTCCAGGGTCACTGAC | 4 |

IRBP transcript using the techniques of primer extension and S1 nuclease protection. As shown in Fig. 4, at least three transcriptional start points appear to be present. Both methods place them at identical positions on the sequence of Fig. 2, where they occur at nucleotides +1 (adenine), +7 (adenine), and +15 (thymidine). The A residue at nucleotide +7 is one nucleotide downstream from the putative cap site for the bovine gene (36), which corresponds to the C residue at nucleotide +6 in the human sequence. The reason for the relative differences in band intensities obtained from the two techniques was not determined. It should be noted, however, that the two experiments utilized RNA preparations from two different batches of human retinas. Multiple initiation sites are often observed in genes that lack a TATA box (37), a promoter element that we have been unable to find in the human IRBP gene and that also appears to be absent in the bovine gene (36).

We also mapped the 5'-end of the IRBP transcript expressed in one of the retinoblastoma cell lines used in a previous study (15) and for the Northern blot in Fig. 3. The primer extension technique again shows that there are at least three transcriptional start sites at positions identical to those found for normal human retina IRBP RNA (Fig. 4, upper). The major band is observed at nucleotide +7.

Homology of Human and Bovine IRBP Genes—Fig. 5 is a dot matrix comparison of the structure and homology of the human and bovine genes. They are very similar, each consisting of four exons interspersed with three introns. The human introns have lengths of 1785, 1860, and 1606 nucleotides, respectively, compared with 2230, 1961, and 1491 nucleotides in the bovine gene. Exons 2 and 3 in the human and bovine genes are identical in length (191 and 143 nucleotides, respectively), whereas the first exons differ by only seven nucleotides, i.e. 3180 in human and 3173 in bovine. There is a large difference in exon 4, which is 700 bases shorter in the human gene (740 for human, 2447 for bovine), which accounts for the larger size of the bovine IRBP transcript (Fig. 3) (19, 38). The dot matrix plot in Fig. 5 suggests that this difference is due to loss by the human gene of a large 1700-base segment of DNA between the translation terminating codon and the 3'-AATAAA consensus sequence.

The nucleotide sequences for the coding regions of the human and bovine exons display identities ranging from 81.1% (exon 3) to 90.1% (exon 4), averaging 85.1%. The degree

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![Fig. 4. Mapping the 5'-end of the human IRBP gene by primer extension and S1 nuclease protection. Upper, primer extension. The two right-hand lanes contain the primer-extended cDNAs obtained by using polyadenylated RNAs from adult human retina (Ret) or retinoblastoma cell line RB522A (Rb). The primer was a 23-base oligonucleotide complementary to residues -58 to -80 of the cDNA sequence (22) (residues 47-69 of the gene sequence in Fig. 2). Lower, S1 nuclease protection. The right-hand lane shows the products of S1 nuclease digestion of human retina total RNA hybridized with a probe generated from an Stul genomic fragment and the same 32P-labeled 23-base oligonucleotide used in the primer extension experiment. The sequencing ladders were obtained from the same labeled 23-base primer and the Stul genomic fragment used for the S1 nuclease protection experiment.](http://www.jbc.org/Downloaded from)
FIG. 5. Homology of the human and bovine IRBP genes. The bovine sequence is from Ref. 36. Introns and noncoding and coding regions of exons are depicted as described for Fig. 1. Analysis was with Beckman MicroGenie software, using an 85% match criterion for a length of 15 nucleotides.

Homology of Human and Bovine IRBPs—Fig. 6 presents a sequence comparison of the human and bovine IRBPs. Excluding the unmatched regions at the N and C termini of the human and bovine proteins, respectively, but including a 2-residue gap introduced into the bovine sequence, there is an 84.2% identity over a length of 1225 residues. This value is somewhat lower than the 87% identity found previously (22) on the basis of alignment with 605 bovine IRBP residues determined by amino acid sequencing of the tryptic peptides and reflects some variation in the degree of identity over the length of the sequence. The determination of the complete nucleotide sequence of the human IRBP gene has now permitted a comparison of the IRBP gene in two mammalian species and has revealed that they are remarkably similar. Their unusual structures (in particular, the very large exon that encodes all three homology domains and part of the fourth) suggest they have had a complicated history. Future comparative studies are likely to provide new insights into the mechanism of evolution of the IRBP gene as well as the function of the protein it encodes.

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Addendum—Since the present manuscript was submitted, a paper containing the partial sequence of the human IRBP gene was published (41). The authors report a size of 3176 for exon 1, compared with 3180 bp in the present work, due to differences in the number of nucleotides in the 5'-noncoding region and in the choice of transcription initiation site (see below). The authors did not determine the length of exon 4 and did not sequence the introns. They report the same intron-exon boundaries as we do, but their estimates of intron sizes (2.1, 2.0, and 1.3 kb) differ significantly from ours (1.785, 1.860, and 1.606 kb), calculated from the nucleotide sequence. There are three nucleotide differences in the exon sequences. Liou et al. (41) insert a C between nucleotides 72 and 73, a G between nucleotides 120 and 121, and substitute a G for an A in position 9286. These positions are in the 5'- and 3'-noncoding regions and do not affect the conceptually translated amino acid sequence. However, the CAG
human retina RNA, the authors report 5 transcription initiation sites corresponding to nucleotides +1, +7, +13, +21, and +24 in our sequence. They assign a preferred site to nucleotide +7. We used RNA from an IRBP-expressing retinoblastoma cell line as well as adult human retinas and find at least 3 transcription initiation sites at +1, +7, and +15.

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