Structure and Chromosomal Localization of the Gene for the Oligodendrocyte-Myelin Glycoprotein

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Abstract. Utilizing a cDNA clone encoding the oligodendrocyte-myelin glycoprotein (OMgp) to screen a human genomic DNA library, we have obtained a clone that contains the OMgp gene. The genomic clone was restriction mapped and the OMgp gene and its 5' and 3' flanking regions were sequenced. A single intron is found in the 5' untranslated region of the gene, while the coding region is uninterrupted by an intron. This placement of a single intron in the OMgp gene is identical to that of the gene for the α-chain of platelet glycoprotein Ib, which, along with OMgp, belongs to a family of proteins sharing two distinct structural domains: an NH₂-terminal cysteine-rich domain and an adjacent domain of tandem leucine-rich repeats. Hence, it is possible that this family of proteins is not only related in terms of primary structure, but also through similar gene structure. Sequence comparison of the 5' and 3' flanking regions did not reveal striking similarities to other DNA sequences, and no obvious promoter elements were noted. By hybridization of the genomic clone to metaphase cells, we have localized the human OMgp gene to chromosome 17 bands q11-12, a region to which the neurofibromatosis type 1 gene has been previously mapped.

The oligodendrocyte-myelin glycoprotein (OMgp) is a highly glycosylated protein of oligodendrocytes and central nervous system myelin which appears to be localized at the paranodal region of the myelin sheath (Mikol and Stefansson, 1988). OMgp is anchored in the plasma membrane as a 120-kD glycosylphosphatidylinositol-linked form that can be released from the membrane upon incubation with phospholipase C to generate a soluble 105-kD polypeptide. Based on cDNA sequence, the predicted primary structure of OMgp consists of four domains (Mikol et al., 1990). At the NH₂-terminus there is a 32-amino acid cysteine-rich (CR) motif. This is followed by a domain consisting of 7 1/2 tandem leucine-rich repeats (LRs) of 24 amino acids each, and a domain of 4 1/2 repeats of 40 residues each that are rich in serines and threonines. A hydrophobic COOH-terminal segment is most likely cleaved concomitantly with the attachment of a phosphatidylinositol-containing glycan (Cross, 1990).

Several proteins have been found to contain LRs (see Table I) since the first report of the leucine-rich α-2 glycoprotein of serum (Takahashi et al., 1985b). Some of these proteins, including OMgp, share both an NH₂-terminal CR motif and a contiguous series of LRs. On the basis of the sharing of the two structurally unrelated domains, we believe that these proteins are best classified as belonging to a distinct family, the CR-LR family (Mikol et al., 1990). Among these proteins, the platelet glycoprotein Ib is most similar to OMgp, sharing not only the CR and LR domains, but also the serine/threonine-rich region which in both cases probably contains an abundance of O-linked oligosaccharides. Glycoprotein Ib is a transmembrane disulfide-linked αβ heterodimer that plays an important role in the initial adhesion of platelets to the exposed subendothelium of blood vessels during hemostasis, by virtue of the fact that it is a receptor for von Willebrand factor (Clemetson and Lüscher, 1988). Interestingly, both the α- and β-chains of glycoprotein Ib, as well as glycoprotein IX of platelets with which it associates in a noncovalent complex, contain LRs (Table I). The α-chain of platelet glycoprotein Ib (gplbα) is the only other member of the CR-LR family whose gene has been characterized (Wenger et al., 1988).

We have provided evidence that OMgp is encoded by a single gene (Mikol et al., 1990). Here we describe the structure of the gene encoding OMgp, and localize the gene to human chromosome 17q bands 11-12. As is the case for the gplbα gene, the OMgp gene has an uninterrupted open reading frame and an intron that is six nucleotides upstream of the transla-

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tional start codon. This similarity between the gpIbc and OMgp genes raises the possibility that members of the CR-LR family may be related not only by the sharing of two structurally unrelated domains, but also through gene structure.

Materials and Methods

General

Restriction enzymes and other enzymes used in cloning were obtained from commercial sources. [32P]-labeled nucleotides were obtained from DuPont Co. (Wilmington, DE) or ICN Radiochemicals (Irvine, CA). Total RNA was prepared from human brain biopsy specimens, or from a cell line that does not express OMgp, by the guanidinium acid-phenol method as described by Chomczynski and Sacchi (1987). Isolation of genomic DNA and plasmid DNA, restriction digestions, preparation of restriction-deleted clones, end labeling of DNA with [$\gamma$-32P]-ATP, agarose gel electrophoresis, and hybridizations were done according to standard protocols (Sambrook et al., 1989).

Construction and Screening of Human Genomic DNA Library

Human genomic DNA was incompletely digested with Mbo I to create fragments of various sizes. Fragments sized at 15-20 kb were partially filled in and ligated into Xho I-digested XFI I vector (Stratagene Cloning Systems, La Jolla, CA) that was also partially filled in according to the manufacturer’s instructions. Plaques obtained upon infection of bacterial strain P2PLK17 with the genomic DNA recombinants were adsorbed onto Colony/Plaque Screen nylon membrane disks (DuPont Co.) for screening with a partial OMgp cDNA clone (SI) described previously (Mikol et al., 1990). The SI cDNA insert was prepared from agarose gels and labeled with [$\alpha$-32P]-dCTP by random priming using an oligolabeling kit (Pharmacia Fine Chemicals, Piscataway, NJ) (Feinberg and Vogelstein, 1983). The hybridized nylon disks were washed twice for 30 min with 0.1 x SSC, 1% (w/v) SDS at 65°C and exposed with intensifying screens at -80°C. Positive clones were plaque purified and subcloned into Bluescript KS+ plasmid for restriction mapping and sequencing.

Chromosomal Localization

The OMgp gene was localized by hybridizing a radiolabeled 12-kb genomic probe (M5E10) to normal human metaphase chromosomes prepared from phytohemagglutinin-stimulated peripheral blood lymphocytes (Le Beau et al., 1984), as well as by fluorescent in situ chromosomal hybridization using a biotin-labeled M5E10 probe (Lichter et al., 1988). In addition, a panel of rodent-human somatic cell hybrids was used to confirm the chromosomal localization.

DNA Sequencing

The M5E10 genomic clone or restriction deletion clones of the M5E10 clone were used as templates for DNA sequencing. Sequences were determined on both strands, using either double- or single-stranded DNA, by dideoxynucleotide chain termination (Sanger et al., 1977) with Sequenase or Taq polymerase (United States Biochemical Corp., Cleveland, OH) (Tabor and Richardson, 1987). Oligonucleotide primers were synthesized by the phosphoramidite method with a DNA synthesizer (model 381A; Applied Biosystems, Inc., Foster City, CA). Sequences were analyzed by the sequence analysis software package of the University of Wisconsin Genetics Computer Group (Devereux et al., 1984), using the Dasyflow table and the GAP program in the above software package.

Primer Extension

Primer extension analysis of adult human brain RNA, which contains considerable OMgp mRNA (Mikol et al., 1990), or of RNA isolated from a cell line that does not express OMgp mRNA, was carried out by modifications of the methods of Boorstein and Craig (1989) and Sambrook et al. (1989). A 24-mer oligonucleotide primer complementary to the 5' end of OMgp cDNA: OM13, CGTCCTGTCTCGAGACGTGGAAAC, corresponding to nucleotides No. 647-670 (see Fig. 3), and a 24-mer oligonucleotide further upstream on the same strand: OM25, CCACATAGGACCTGACGAGCTTG (nucleotides No. 541-564), were used. Primers were end labeled with [$\gamma$-32P]-ATP and T4 poly nucleotide kinase. 40 g of total RNA coprecipitated with 100 fmol of end-labeled primer was resuspended in 30 ul aqueous hybridization buffer (0.4 M NaCl, 1 mM EDTA, 40 mM PIPES [pH 6.4]), denatured at 80°C for 4 min, and annealed at 55°C for 3 h. The hybridized primer/ transcripts were then digested 10-fold in 10 x reverse transcriptase buffer (10 mM dATP, 10 mM dCTP, 10 mM dGTP, 10 mM dTTP, 10 mM DTT, 600 mM KCl, 500 mM Tris-HCl [pH 7.8]), 100 mM MgCl2, and extended for 2 h at 37°C after addition of 25 U AMV reverse transcriptase plus 100 U RNase inhibitor. Extension was stopped with the addition of 5 µl 0.5 M EDTA, and the RNA was then digested with DNase-free RNase (5 µg/ml) for 30 min at room temperature. After phenol/chloroform extraction and ethanol precipitation the samples were resuspended in 4 µl of TE buffer (10 mM Tris-HCl [pH 7.5], 1 mM EDTA) and 6 µl of formamide loading buffer (95% formamide, 20 mM EDTA, 0.05% bromphenol blue, 0.05% xylene cyanol FF). The primer extension samples, end-labeled molecular size standards (Hae III digest of PhiX174) (Bethesda Research Laboratories, Bethesda, MD), and sequenced products of the genomic clone using end-labeled oligonucleotide primers were analyzed on the same 6% polyacrylamide denaturing gel for comparison.

Results

Isolation of the Human OMgp Gene

Using the SI cDNA probe, a 12-kb Eco RI genomic fragment (AM5E10) in XFI I vector was isolated. The genomic clone was then subcloned into Bluescript KS+ plasmid for further analysis by restriction mapping (Fig. 1). Interestingly, cDNA restriction sites were found to map with the same distribution and spacing on M5E10, suggesting an intronless structure for the OMgp gene.

Figure 1. Restriction map of the 12-kb M5E10 genomic clone. Orientation of OMgp within this clone is shown by the arrow (5' to 3', left to right). The positions of exons 1 and 2 are indicated by boxes (open boxes, noncoding; solid boxes, coding) below M5E10, with the intron represented by a line between them. The cDNA restriction map is shown at the bottom, with the intron spliced out as indicated. An adjacent open reading frame (Ad-ORF) 3' of OMgp on the antisense strand has also been found within M5E10, and may correspond to an exon of the NF1 gene. Restriction enzymes sites are A, Acc I; C, Sac I; D, Dra II; E, Eco RI; H, Hind III; P, Pst I; S, Spe I; X, Xho I.
ATG codon for the first methionine is placed just six nucleotides from the start sites based on deduced sequence (see Fig. 3). The OMgp gene might not contain introns. Upon sequencing the M5E10 genomic probe to human chromosome 17 (data not shown), an intron of 815 nucleotides was found at the 5' end of the gene, interrupting the gene between the sixth and seventh nucleotides upstream of the ATG start codon (relative to cDNA). No introns were found within the coding region of OMgp. Hence, the first exon encodes 5' untranslated mRNA sequences, while the second exon encodes the remainder of the 5'-untranslated sequence (six nucleotides), the entire coding sequence, and the entire 3'-untranslated sequence. Several proteins are known to be encoded by genes with uninterrupted coding regions (see Discussion).

**Chromosomal Localization**

We localized the OMgp gene by hybridizing radiolabeled M5E10 genomic probe to normal human metaphase cells. Hybridization resulted in specific labeling of only chromosome 17, bands q11-12 (Fig. 2). To confirm and refine this localization, we performed fluorescence in situ hybridization using a biotin-labeled M5E10 probe. Specific labeling of 17q11 was observed on one (3 cells) or both (17 cells) chromosome 17 homologues in each of 20 cells examined. Signal was not detected on other chromosomes. A panel of rodent–human hybrids was used to confirm the mapping of the OMgp gene to human chromosome 17 (data not shown).

**Sequence of the OMgp Gene**

Where the cDNA and genomic sequences overlap they are identical. Furthermore, the OMgp gene does not appear to be very polymorphic, based on sequence identity of the genes from six individuals (data not shown). Overall the OMgp gene is extremely A-T rich. The coding region consists of 60% A + T, while the intron of OMgp consists of 64% A + T. There are three possible polyadenylation signals, the first two of which were noted in the cDNA; the third signal was discovered 3' to the end of the cDNA sequence. Curiously, ~600 bp downstream of the 3' end of the OMgp gene there is a long open reading frame of ~170 amino acids on the antisense strand (Fig. 1). This potential coding region may correspond to a hitherto undescribed exon of the recently described NFI gene, which is a large gene spanning at least 100 kb (Cawthon et al., 1990; Wallace et al., 1990), previously mapped to the centromeric region of chromosome 17 (Barker et al., 1987; Seizinger et al., 1987; Goldgar et al., 1989).

**Primer Extension**

In four separate experiments a single major primer extension product (Fig. 4) was obtained using the OM13 oligonucleotide primer that marks the transcriptional start site (TSS) (at the guanine at position 527 in Fig. 3). The sequence around the TSS, TCAG, is also found in the gene for the PO protein of peripheral myelin (Lemke et al., 1988), the myelin basic protein gene (Takahashi et al., 1985a), and the proteolipid protein gene (Diehl et al., 1986). No extension product was seen from OM13 primer hybridized to RNA from a cell line that does not express OMgp (data not shown). The OM25 primer did not generate any detectable extension product, perhaps because the TSS as defined by the OM13 primer extension is too close to the end of OM25.

There are several TATA and CAAT elements upstream of the proposed transcriptional start site (Fig. 3), although the positioning of these elements is not conventional. TATA and CAAT boxes are typically found at 20-30 and 40-100 nucleotides, respectively, upstream of the TSS of a gene (Breathnach and Chambon, 1981). Three TATA sites are found at positions −79, −81, and −95 relative to the proposed TSS. However, a segment 17 nucleotides in length containing only A/T is also found 42-58 bases upstream of the TSS, which may be analogous to the A-T rich segment in another myelin gene, the PO gene, where it is thought to serve as a TATA box (Lemke et al., 1988). A CCAATCT sequence is found at position −158, and three CAAAT sequences are found at positions −90, −148, and −179. A potential AP-1 binding site TGAATCA spans the TSS and is of questionable significance. No GC boxes or binding sites for other transcriptional factors were identified.

**Discussion**

OMgp is a protein containing four domains and is encoded by a single exon. A number of genes have been discovered...
to have their coding regions uninterrupted by introns. The proteins encoded by these genes are functionally and structurally diverse and include the histones (Kedes, 1979), the \( \beta \)-adrenergic receptor (Kobilka et al., 1987), gpIba (Wenger et al., 1988), interferons (Lawn et al., 1981; Nagata et al., 1981), the JUN protooncogene (Hattori et al., 1988), thrombomodulin (Jackmann et al., 1987), and a gene within an intron of the Factor VHI gene (Levinson et al., 1990). Therefore, it is unlikely that a coding region uninterrupted by introns indicates a close evolutionary relationship between genes or a functional relationship between their products.

OMgp and gpIb are polypeptides consisting of several distinct structural elements, some of which they share. Each of the structural elements found in these polypeptides, for example the CR and LR domains, are found separately in other proteins, where they are likely to have specific functions. Remarkably, however, both OMgp and gpIb are each encoded by a single exon. Therefore, it is conceivable that these domains might have originally been encoded by separate exons and were assembled independently and the introns between them lost during evolution, though it is unclear what advantage the intron loss might grant.

We localized the OMgp gene to chromosome 17q11-12, a region which by linkage studies had previously been shown to contain the gene for NFI (Barker et al., 1987; Seizinger et al., 1987; Goldgar et al., 1989). The NFI gene has recently been discovered and its structure partially characterized (Cawthon et al., 1990; Wallace et al., 1990). It is a large (>100 kb) gene whose mRNA transcript measures 11-13 kb. Astonishingly, it appears that the NFI gene may contain at least three genes, including OMgp, within its introns but in an antisense orientation (Cawthon et al., 1990). In mammals, the presence of a gene within the intron of another gene had previously been described only for a gene embedded in an antisense orientation within a Factor VHI gene intron (Levinson et al., 1990). Upon sequencing downstream of the OMgp gene, we have identified a long open reading frame ~600 bp away which may correspond to an exon of the NFI gene not yet characterized (our unpublished results). Thus, the A-T rich character of the OMgp gene may reflect the fact that it is contained within an intron,
We have previously described the primary structure of OMgp in the context of the CR-LR family of proteins (Table I) that share two structurally unrelated domains: an NH₂-terminal CR that is fairly similar to an EGF motif (Gray et al., 1983; Scott et al., 1983), and an adjacent series of LRs, which by virtue of their amphipathic character (Takahashi et al., 1985b) have been implicated in adhesive processes (Katoaka et al., 1985; Vicente et al., 1988; Reinke et al., 1988). We have now shown that two members of the CR-LR family, namely gplba and OMgp, are encoded by genes that are highly similar. Thus, proteins within the CR-LR family, which share features of their primary structure and perhaps some aspects of function, may also share gene structure, in particular an uninterrupted coding sequence and an intron in the 5' noncoding region. This intron, just upstream of the translation start site, may serve some regulatory role (Smith et al., 1989).

In addition to OMgp, the genes of several myelin proteins have been reported, including the proteolipid protein (Diehl et al., 1986), which is expressed in the central nervous system, the PO protein of the peripheral nervous system (Lemke et al., 1988), and the myelin basic proteins (Takahashi et al., 1985a) which are found in both the central and peripheral nervous systems. All of the above genes, including OMgp, have been found to have the sequence TCAG around the TSS, but no other sequence similarities between the OMgp gene and the other myelin genes have been identified. In contrast to OMgp, these other proteins are abundant, constituting the major proteins of myelin. It is unresolved how these myelin proteins are coordinately regulated during the process of myelination.

While we do not yet understand the function of OMgp, it is a glycoprotein of central nervous system myelin and oligodendrocytes which may play a role as an adhesion mole-

**Table I. Proteins That Contain LRs and CR-LRs**

| Protein                          | Species       | No. of repeats | Adjacent NH₂-terminal Cys-rich region | Reference                      |
|----------------------------------|---------------|----------------|---------------------------------------|--------------------------------|
| OMgp                             | Human         | 7 1/2          | yes                                   | (Mikol et al., 1990)           |
| Platelet Ibo                     | Human         | 7              | no                                    | (Lopez et al., 1988)           |
| Platelet Ibof                    | Human         | 1              | yes                                   | (Lopez et al., 1988)           |
| Platelet Ibof                    | Human         | 1              | yes                                   | (Lickey et al., 1989)          |
| Biglycan                         | Human, bovine | 12             | yes                                   | (Fisher et al., 1989)          |
| Decorin                          | Human, bovine | 10             | yes                                   | (Fisher et al., 1989)          |
| Fibromodulin                     | Bovine        | 10             | yes                                   | (Oldberg et al., 1989)         |
| α3 (collagen VI)                 | Avian         | 1              | no                                    | (Bonaldo and Colombatti, 1989) |
| Toll                             | Drosophila    | 15             | yes                                   | (Hashimoto et al., 1988)       |
| Chaoptin                         | Drosophila    | 41             | yes                                   | (Reinke et al., 1988)          |
| Leucine-rich                     | Human         | 8              | no                                    | (Takahashi et al., 1985b)      |
| α-2 glycoprotein                 | Human         | 1              | no                                    | (Katoaka et al., 1985)         |
| Adenylate cyclase                 | Yeast         | 26             | no                                    | (Katoaka et al., 1985)         |
| Lutropin-choriogonadotropin      | Rat           | 14             | yes                                   | (Mcfarland et al., 1989)       |
| receptor                         | Human         | 12             | yes                                   | (Tan et al., 1990)             |
| Carboxypeptidase N                | Human         | 15*            | no                                    | (Schneider et al., 1988)       |
| (noncatalytic subunit)           | Human, porcine|                | no                                    | (Leung and Straley, 1989)      |
| RNase inhibitor                  | Yersinia pestis| 6*            | no                                    |                                 |

* Contains repeats of 28 amino acids.
+ Contains repeats of 14 amino acids.
The table lists all of the proteins known to date that contain LRs; proteins that contain an adjacent NH₂-terminal CR domain (and hence belong to the CR-LR family) are indicated.
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