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Genetics

# Myelin/oligodendrocyte glycoprotein is a member of a subset of the immunoglobulin superfamily encoded within the major histocompatibility complex

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**ABSTRACT** **Myelin/oligodendrocyte glycoprotein (MOG) is found on the surface of myelinating oligodendrocytes and external lamellae of myelin sheaths in the central nervous system, and it is a target antigen in experimental autoimmune encephalomyelitis and multiple sclerosis. We have isolated bovine, mouse, and rat MOG cDNA clones and shown that the developmental pattern of MOG expression in the rat central nervous system coincides with the late stages of myelination. The amino-terminal, extracellular domain of MOG has characteristics of an immunoglobulin variable domain and is 46% and 41% identical with the amino terminus of bovine butyrophilin (expressed in the lactating mammary gland) and B-G antigens of the chicken major histocompatibility complex (MHC), respectively; these proteins thus form a subset of the immunoglobulin superfamily. The homology between MOG and B-G extends beyond their structure and genetic mapping to their ability to induce strong antibody responses and has implications for the role of MOG in pathological, autoimmune conditions. We colocalized the MOG and BT genes to the human MHC on chromosome 6p21.3–p22. The mouse MOG gene was mapped to the homologous band C of chromosome 17, within the *M* region of the mouse MHC.**

Myelin of the central nervous system (CNS) is composed of a spiraled, wrapped set of closely apposed membranes produced by the oligodendrocytes. The proteolipid proteins (PLP and DM20) and myelin basic proteins make up the bulk of the structural proteins of mature myelin (reviewed in refs. 1 and 2). In contrast, myelin minor proteins, such as glycoproteins (3), are believed to mediate glial–glial and glial–neuronal interactions. The most extensively studied member of this group, the myelin-associated glycoprotein (MAG) is thought to mediate the axon–glial adhesion that precedes myelination (4).

Although much interest has been attached to the first steps of the myelination process, little is known about the late stages and the factors involved. An additional minor myelin/oligodendrocyte glycoprotein, MOG, of 26–28 kDa and forming dimers of 52–54 kDa, was first defined by use of a mouse monoclonal antibody (5). MOG is located on the external surface of oligodendrocytes in culture and mostly on the peripheral lamellae of compact myelin sheaths in the CNS (6–9). MOG is expressed late during brain development relative to other, well-characterized myelin proteins (6, 10). The external location of MOG on myelin sheaths and oligodendrocytes and the late expression argue for a more specific

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GACAGTGGAG ATG GCC AGT TTA TTG AGC TCC TCT CTG CCC AGC TGT CTC     49
            M   A   S   L   L   S   S   S   L   P   S   C   L    -16
CCC TCC CTC CTC TTC CTC CTC CTC CAG TTG ACT TCC AGC TCT GCA GGA    97
 P   S   L   L   F   L   L   L   Q   L   T   S   S   S   A   G      1
CAG TTC AGA GTA ATA GGA CCA GGG CAC CCC ATC CGG GCG CTG GTA GGG   145
 Q   F   R   V   I   G   P   G   H   P   I   R   A   L   V   G     17
GAT GAA GTG GAA TTG CCC TGT CGC ATA TCT CCA GGA AAG AAC GCT ACA   193
 D   E   V   E   L   P   C   R   I   S   P   G   K   N*  A   T     33
GGC ATG GAG GTG GGA TGG TAT CGG CCC CCC TTC TCC AGG GTG GTT CAT   241
 G   M   E   V   G   W   Y   R   P   P   F   S   R   V   V   H     49
CTC TAC CGA AAT GGC AAG GAC CAA GAC GAA GAG CAG GCA CCT GAA TAC   289
 L   Y   R   N   G   K   D   Q   D   E   E   Q   A   P   E   Y     65
CGG GGC CGC ACA CAG CTG CTA AAA GAG ACC ATT GGG GAA GGG AAG GTG   337
 R   G   R   T   Q   L   L   K   E   T   I   G   E   G   K   V     81
ACC CTC AGG ATC CGG AAT GTG AGG TTC TCA GAT GAA GGA GGT TTT ACC   385
 T   L   R   I   R   N   V   R   F   S   D   E   G   G   F   T     97
TGC TTC TTC CGA GAT CAC TCT TAC CAA GAG GAG GCA GCG ATG GAA TTG   433
 C   F   F   R   D   H   S   Y   Q   E   E   A   A   M   E   L    113
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 K   V   E   D   P   F   Y   W  [I   N   P   G   V   L   V   L    129
ATC GCG GTC CTG CCA GTG CTC CTC CTA CAG ATC ACC GTG GGC CTC GTC   529
 I   A   V   L   P   V   L   L   L   Q   I   T   V   G   L   V    145
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 F   L   C   L   Q]  R   R   L   R   G   K   L   W   A   E   I    161
GAG AAT CTC CAC CGG ACT TTT GAT CCC CAC TTC CTG ATG GTG CCC TGC   625
 E   N   L   H   R   T   F   D   P   H   F   L   M  [V   P   C    177
TGG AAG ATA ACC CTA TTT GTC ATC GTG CCG GTT CTC GGA CCC CTG GTG   673
 W   K   I   T   L   F   V   I   V   P   V   L   G   P   L   V    193
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 F   L   E   E   L   R   N   P   F   :                            218
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TCTACTTCCACACCCCATCCAGATGGCCCCTCAGACTTTCCCTTCTCTCATCCTTTCCCTCTC 1478
ATCTTCATACCTAATGGAGATCCACTGTCTTTTTGAACAATTACTACTTGATGGTCTAAAGAAA 1542
CAAGCTAGGTGCTAATTAATAACAATACAAGTTTCCAAGTGCCAAAAAAAAAAAAAAA       1600
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FIG. 1. Nucleotide and deduced amino acid sequences of bovine MOG cDNA. Amino acids are numbered from the N-terminal residue of the mature protein. A putative peptide signal sequence of 28 aa precedes the first residue of the mature protein. An asterisk indicates the single potential site for N-linked glycosylation. Two putative membrane-spanning regions are boxed. Four nonclassical polyadenylylation signal sequences are underlined.

role of MOG in the late stages of myelination—i.e., in completion and maintenance of myelin integrity. The significant demyelination induced in cultures of aggregating brain cells by anti-MOG antibodies (11), the presence of anti-MOG antibodies in sera of guinea pigs with chronic relapsing experimental autoimmune encephalomyelitis (12), and the obvious CNS demyelination in animals injected with anti-MOG monoclonal antibodies (13) support the definition of MOG as an important autoantigen in autoimmune demyelinating diseases of the CNS, such as multiple sclerosis (14).

Abbreviations: MOG, myelin/oligodendrocyte glycoprotein; CNS, central nervous system; BT, butyrophilin; MHC, major histocompatibility complex; MAG, myelin-associated glycoprotein; PLP, proteolipid protein.

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       1                                                           60
Bovine GQFRVIGPGH PIRALVGDEV ELPCRISPGK NATGMEVGWY RPPFSRVVHL YRNGKDQDEE
Rat    ---------- ---------A ---------- ---------- -S-------- --------A-
Mouse  ---------Y ---------A ---------- ---------- -S-------- --------A-

       61                                                         120
Bovine QAPEYRGRTQ LLKETIGEGK VTLRIRNVRF SDEGGFTCFF RDHSYQEEAA MELKVEDPFY
Rat    ---------E ----S----- -A---Q---- -----Y---- ---------- V---------
Mouse  ------E--E ----T-S--- -T---Q---- -----Y---- ---------- M---------

       121                                                        180
Bovine WINPGVLVLI AVLPVLLLQI TVGLVFLCLQ RRLRGKLWAE IENLHRTFDP HFLMVPCWKI
Rat    -------A-- -LV-M----V S------F-- H------R-- V--------- ---R------
Mouse  -V-----T-- -LV-TI---V P------F-- H------R-- V--------- ---R------

       181                               218
Bovine TLFVIVPVLG PLVALIICYN WLHRRLAGQF LEELRNPF
Rat    ---------- ---------- ---------- --------
Mouse  ---------- ---------- ---------- --------
```

FIG. 2. Alignment of bovine, rat, and mouse MOG mature protein sequences. The rat MOG sequence is identical to that published by Gardinier *et al.* (24). The bovine and mouse sequences are 88%, bovine and rat 91%, and mouse and rat 95% identical.

To better understand the process of normal myelinogenesis and to evaluate the role of MOG in autoimmune CNS diseases, we have characterized the cDNA for the bovine, mouse, and rat MOG genes.[‡‡] Developmental expression of MOG mRNA was studied in rat, and the chromosomal location of the MOG gene was determined in mouse and human.

## MATERIALS AND METHODS

**Cloning of MOG cDNA.** MOG was purified from a Wolfgram protein fraction of bovine brain myelin by molecular sieving and preparative gel electrophoresis (9). Two short amino acid sequences of bovine MOG were obtained by microsequencing: the amino-terminal sequence, (A/G)QFRVIGP (9), and the sequence of an internal cyanogen bromide peptide, (M)EVGWYRP (unpublished results). Two deoxyinosine-containing, degenerate primers derived from these two sequences, 5′-CA(A/G)-TT(C/T)-(A/C)GI-GTI-AT(A/C)-GGI-CC-3′ and 5′-ATG-GA(A/G)-GTI-GGI-TGG-TA(T/C)-(A/C)GI-CC-3′, were used for low-stringency screening (15) of a library of bovine brain cDNA in λgt10 phage (Clontech). Positive inserts were subcloned in the pBluescript KS vector (Stratagene) and sequenced by the dideoxynucleotide chain-termination method (16) using Sequenase (United States Biochemical). The bovine MOG cDNA probe was used to screen rat and mouse brain cDNA libraries in λgt10 (Clontech).

***In Situ* Hybridization.** Cryostat sections (16 μm) of rat brains (10- to 31-day-old animals) were collected at −20°C on gelatin (0.5%)/chrome alum (0.05%)-coated slides and fixed for 10 min in 4% paraformaldehyde dissolved in phosphate-buffered saline. The sections were pretreated and hybridized under the experimental conditions previously reported (17). The probe (738-bp cDNA of MOG) was labeled to high specific activity ($\approx 0.8 \times 10^9$ dpm/μg) with 50 μCi (1.85 MBq) of [α-[$^{35}$S]thio]dCTP by the multiprime DNA labeling system (Amersham). After development of the x-ray film, the slides were dipped in Ilford K5 emulsion, exposed at 4°C for 10–15 days, and treated as usual (17) for observation under bright- or darkfield illumination with Polyvar (Reichert) or Axiophot (Zeiss) microscopes.

**Chromosomal Localization.** MOG and butyrophilin (BT) genes were located by chromosomal *in situ* hybridization (18). Two $^3$H-labeled probes were used: a 738-bp fragment spanning the coding region of rat MOG cDNA and a 2.7-kb probe corresponding to the full-length bovine BT cDNA. For each *in situ* hybridization, 100 metaphase cells were examined.

**Mice.** Mice were bred in the K.F.L. and K.A. colonies and their DNA was analyzed by standard methods (19, 20). The B10.CAS3(R1) and C3H.CAS3(R4-1) recombinants have

[‡‡]The sequences presented in this paper have been deposited in the GenBank data base (accession nos. L21757, L20942, and L21995).

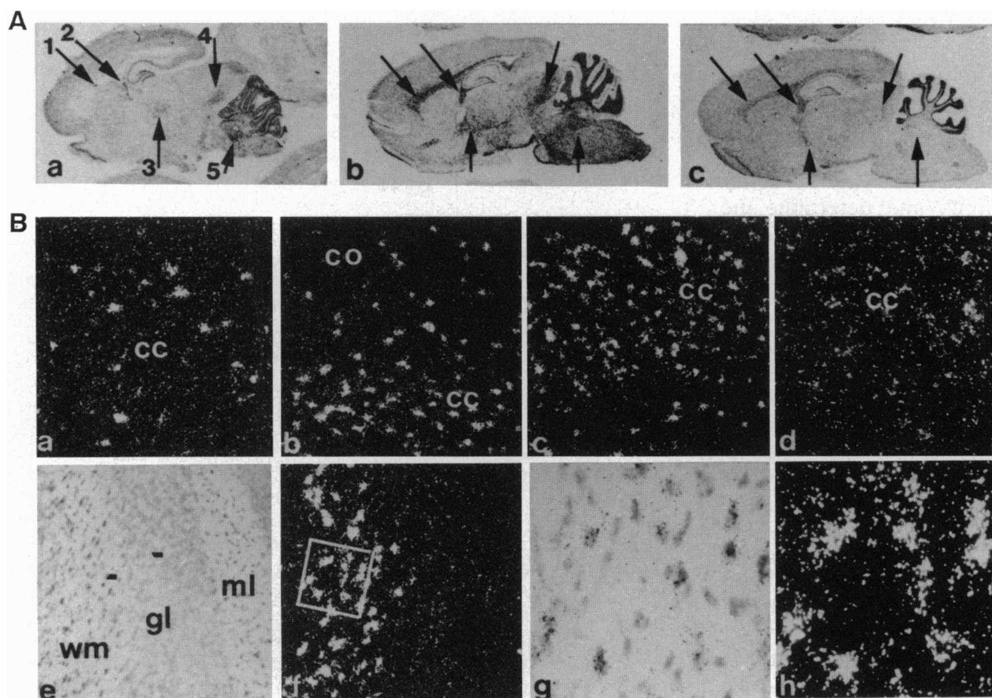


FIG. 3. (*A*) Macroscopic images of MOG mRNA distribution in rat brain after *in situ* hybridization (17) with $^{35}$S-labeled rat coding cDNA on sagittal brain sections of 10-, 18-, and 31-day-old animals (*a–c*, respectively). 1, Corpus callosum; 2, fimbria of hippocampus; 3, internal capsule; 4, brachium inferior colliculus; 5, inferior cerebellar peduncle. At all stages, the granular layer of the cerebellum showed nonspecific labeling. (*B*) *In situ* localization of MOG mRNAs in rat brain at the cellular level. (*a–d*) Corpus callosum of 13-, 18-, 25-, and 31-day-old rats, respectively. (*e–h*) Cerebellum of a 13-day-old rat. (*g* and *h*) Higher magnification of box in *f*. Autoradiograms were photographed under darkfield (*a–d*, *f*, and *h*) and brightfield (*e* and *g*) illumination after thionine blue staining. (*a–f*, ×80; *g* and *h*, ×320.)

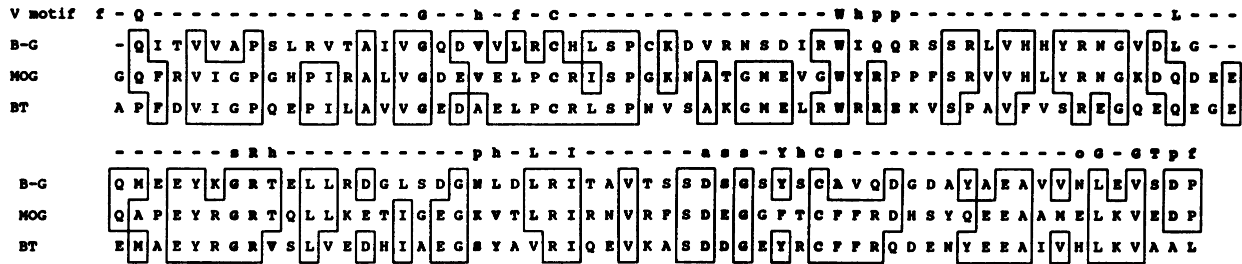


FIG. 4. Alignment, starting from the first residue of the mature protein, of the predicted extracellular domain of chicken B-G antigen (clone bg14/8; ref. 26), bovine MOG, and bovine BT with the Ig variable-region (V) motif (27). Uppercase letters in the Ig V motif represent the single amino-acid code. Lowercase letters identify the amino acids with functional or physical properties as follows: a, acidic (D, E); f, aliphatic (L, I, V); h, hydrophobic (L, I, V, M, Y, F); o, aromatic (Y, F, W); p, polar (K, R, H, D, E, Q, N, T, S); s, small (A, G, S, T, V, N, D). The positions of matches in the three sequences with the V motif are highlighted. Amino acid identities among the three proteins are boxed.

been described (21), as have the SHH1 and SHH2 haplotypes (22), from which the R27 and 12205 recombinants were derived (K.F.L., unpublished work). Strains BTBRTF/Art and C3H/DiSn represent wild-type chromosomes and were homozygous, as was the partial *t* haplotype $t^{w124}$. The other *t* haplotypes were heterozygous with wild type and congenic on C3H/DiSn.

## RESULTS

**Cloning and Sequencing of MOG cDNAs.** A bovine brain cDNA library was screened with the two degenerate primers corresponding to amino-terminal (9) and internal bovine MOG sequences. Three positive clones were plaque-purified and sequenced. The longest (1600 bp) (Fig. 1), comprised a short 5′ untranslated sequence of 10 bp, followed by an ATG start site, an open reading frame of 738 bp, and a 3′ untranslated sequence of 852 bp including a poly(A) tail of 14 nt. Sequences of probes 1 and 2 were found within this clone.

In the amino acid sequence deduced from MOG cDNA, a signal peptide of 28 aa was identified. It precedes the amino terminus of the mature protein, which contains one site, Asn-Ala-Thr (aa 31–33), that fits the consensus sequence [Asn-Xaa-(Ser/Thr)] for N-linked glycosylation, consistent with the N-glycosylated nature of the protein (8, 9). Both these results suggest that the amino-terminal segment of MOG is located on the extracytosolic side of the membrane. Hydropathy analysis (23) of MOG confirmed the presence of an amino-terminal signal peptide and two potential membrane-spanning regions typical of integral membrane proteins (Fig. 1). By using bovine cDNA as a probe, the homologous rat and mouse MOG cDNAs were also cloned and sequenced. The deduced amino acid sequences of MOG from these three species are highly conserved (Fig. 2).

**Developmental Expression of Rat MOG mRNA.** To verify the myelin/oligodendrocyte specificity and determine the developmental pattern of MOG gene expression, cloned cDNA was hybridized *in situ* to rat brain sections at different stages of the myelination process. The most conspicuous labeling was located in areas known to be enriched in white matter (Fig. 3). In contrast, the areas of gray matter showed no evident labeling. A MOG-specific signal was first detected in the caudal part of the brain 10 days after birth. It became progressively more intense in white matter areas of the midbrain and forebrain and appeared maximal at 18 days in these areas. At 31 days, labeling was less intense, especially in the caudal region. A full-length cDNA probe for myelin proteolipid, hybridized in parallel to similar sections, showed identical anatomical distribution of the labeling throughout the brain, except that the signal was far more intense (data not shown). RNase pretreatment of the sections eliminated all hybridization signals (not shown).

Microscopic analysis clearly demonstrated MOG mRNA accumulation in individual cells, as well as clusters or rows of cells whose number and distribution were identical to those of oligodendrocytes, in the corpus callosum (Fig. 3*B a–d*) and the cerebellar white matter (Fig. 3*B e–h*). At high magnification, the silver grains appeared clustered around and above oligodendrocyte cell bodies (Fig. 3*B g–h*). The localization of MOG mRNA in the oligodendrocyte perikaryon was strikingly similar to that observed for PLP (proteolipid protein) mRNA (data not shown).

**Amino Acid Sequence Comparison.** The amino-terminal extracellular domain of MOG (aa 1–118) is most homologous to that of two non-myelin proteins, with 46% identity to bovine BT (25), which is expressed in the mammary gland during lactation, and 41% identity to B-G antigens (26) of the chicken major histocompatibility complex (MHC) region (Fig. 4) (24). The extracellular domains of MOG, BT, and B-G share key features with immunoglobulin (Ig) variable region-like domains (27): (*i*) an invariant tryptophan; (*ii*) two cysteines, appropriately spaced (73 aa for MOG and BT, 71 aa for B-G) and assumed to form the characteristic disulfide bridge; and (*iii*) a small series of conserved amino acids with similar physical properties (Fig. 4).

**Chromosomal Localization of MOG and BT Genes.** The MOG and BT genes were located by *in situ* hybridization on

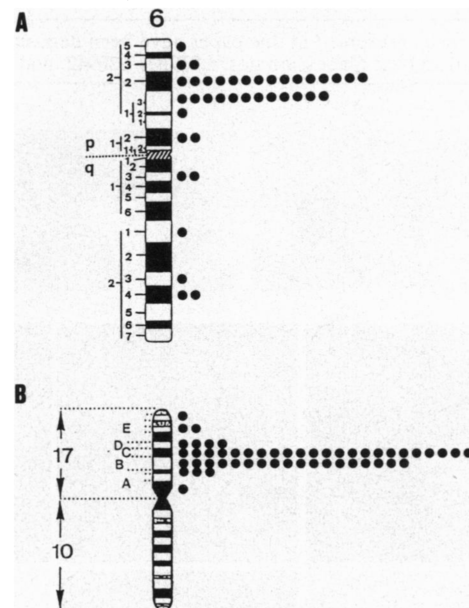


FIG. 5. Chromosomal mapping of the human (*A*) and mouse (*B*) MOG genes. An idiogram illustrates the distribution of the labeled site for $^{3}$H-labeled rat. MOG probe: 12.7% of the silver grains were located on human chromosome 6, and 69.2% of these mapped to p21.3–p22, with the maximum at 6p22 band (*A*); 26.9% of the silver grains were located on mouse chromosome 17, and 86.5% of these mapped to bands 17B–17C, with the maximum at 17C (*B*).

normal human metaphase chromosomes. The MOG gene was localized in bands p21.3–p22 on human chromosome 6 (Fig. 5A), like the BT gene (C. Vernet, M.-G.M., and P.P., unpublished work). Homologous mapping of the MOG gene to band C of murine chromosome 17 (Fig. 5B) was also observed.

**Mapping of the MOG Gene in Mouse MHC.** The mouse MOG gene was further mapped by restriction fragment length polymorphisms (RFLP) to the distal end of the MHC on chromosome 17 in the *H-2M* region. The MOG gene was placed distal to *H-2D* by recombinants R27 and 12205, distal to *Qa-2* by R1, and distal to *Tla* by R4-1 (Fig. 6 *A* and *C*), within the *Hmt* region defined by the R4-e and R4-1 recombinational breakpoints (Fig. 6*E*) (21). The presence of a *t*-haplotype specific band at 4 kb in strain $t^{w18}$ (Fig. 6 *B* and *D*) further located the MOG gene within the short duplication created by the crossover near the end of the distal *t* inversion that led to this partial *t* haplotype (21); similar results were obtained with *Msp* I-digested DNA. The intensity of the bands was not sufficiently consistent between lanes that we could confirm the expected change in stoichiometry for $t^{w18}$ by densitometry.

With all enzymes tested, we detected two to four fragments, of which one or more were monomorphic and hence gave no mapping information; the polymorphic bands were all consistent with a map position in the *M* region. If the mouse has more than one MOG gene, they must map close together, because pulsed-field gel electrophoresis of mouse genomic DNA digested with *Sfi* I, *Bss*HI, *Sac* I, or *Not* I showed only a single band of about 100 or 150 kb (E. P. Jones and K.F.L., unpublished work).

## DISCUSSION

The predicted sequence of the mature MOG protein is remarkably conserved among rats, mice, and cattle. Similar conservation is characteristic of other myelin proteins (29–31). The predicted structure shows an Ig variable region-like extracellular domain and two transmembrane segments linked by a short cytoplasmic loop, with the carboxyl terminus facing the extracellular space. MOG is thus a member of the Ig superfamily (32).

The Ig-like extracellular domain suggests a role for MOG in adhesion or cell surface interaction (27). MAG, present in peripheral and CNS myelin, and protein zero (P0), the major peripheral myelin glycoprotein, also contain Ig-like domains. Both have been classified as morphogenic factors (27), because they are implicated in adhesion and neurite outgrowth (33–35).

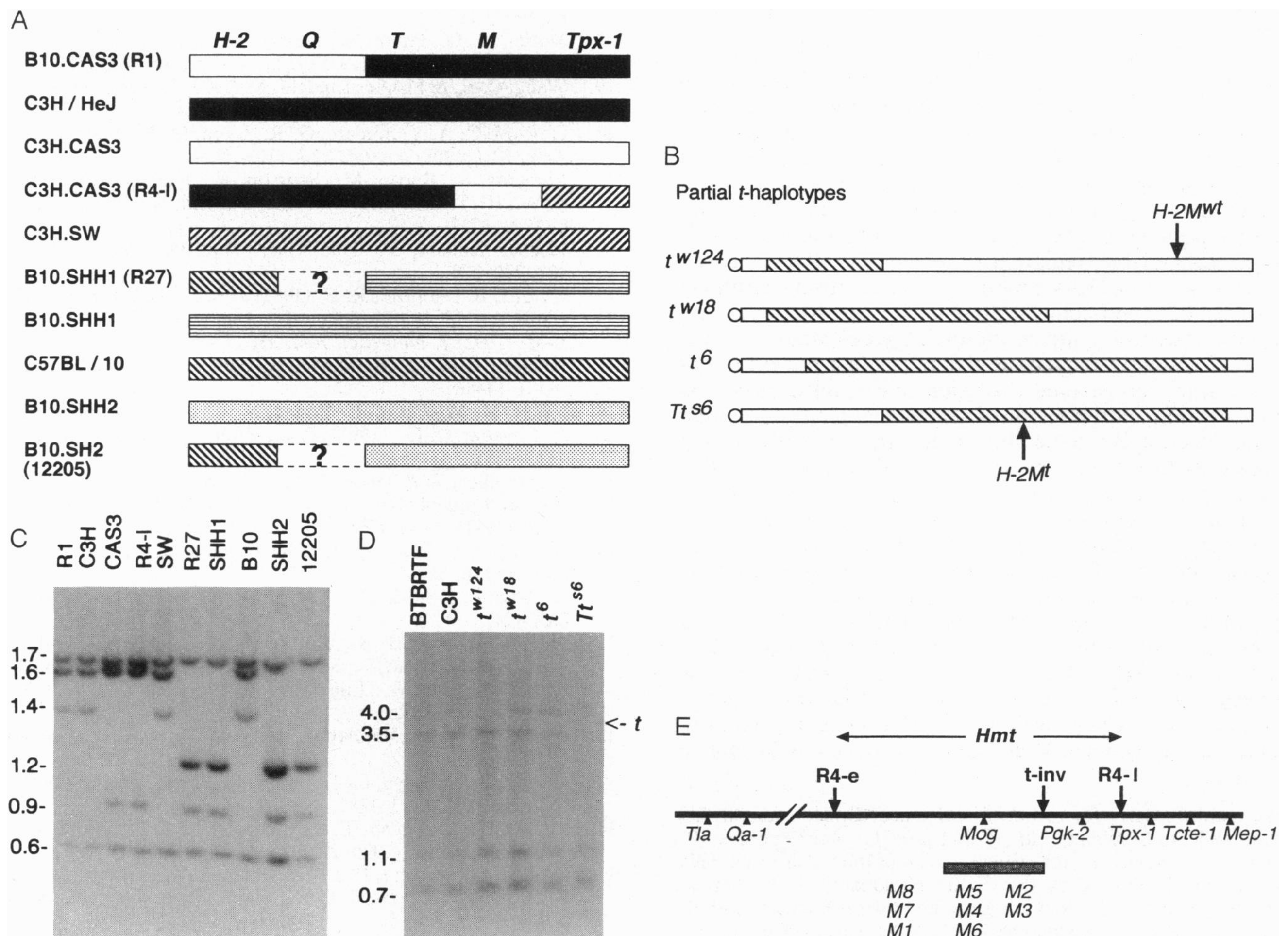


FIG. 6. RFLP mapping of the mouse MOG gene (*Mog*) to the distal end of the MHC. (*A*) Composition of mosaic haplotypes from inbred, MHC-congenic, and intra-MHC recombinant mouse strains with respect to the marker loci *H-2D* (*H-2*), *Qa-2* (*Q*), *Tla* (*T*), *H-2M3* (*M*), and *Tpx-1*. (*B*) Positions of the *H-2M* genes in wild-type (wt) and complete and partial *t* haplotypes (hatched). (*C* and *D*) Genomic DNA was digested with *Rsa* I (*C*) or *Taq* I (*D*) and electrophoresed, and the Southern blots were hybridized with the rat MOG cDNA probe, which was labeled by random priming; sizes of hybridizing bands are given in kilobases at left. From left to right, abbreviated strain designations in *C* correspond to designations from top to bottom in *A*. (*E*) Region surrounding *Mog*; short bar represents the region duplicated in $t^{w18}$; t-inv, breakpoint of the distal inversion in *t* haplotypes; genes are named below the chromosome; *Tla*, *Qa-1*, and *M1–M8* are MHC class I genes (19, 21, 28).

The spatial and temporal expression of the rat MOG gene was studied by *in situ* hybridization. MOG mRNA was clearly restricted to oligodendrocytes, and during brain ontogenesis the MOG mRNA level increased following a caudorostral gradient. MOG mRNA content was the highest in the white-matter areas of the midbrain at the time when myelin deposition was at its maximum. These findings agree with immunocytochemical observations concerning MOG deposition during brain development (8, 9) and further indicate that MOG mRNA does not accumulate significantly before MOG becomes detectable in myelin. A similar posterior-to-anterior developmental pattern has been observed for PLP mRNA (36), but, by contrast, PLP mRNA is found some days before PLP is detected immunocytochemically. MOG is thus specific for CNS myelin and its expression coincides with the late steps of myelination.

Computer sequence analysis disclosed the strongest homology for MOG with the Ig-like domains of two non-myelin proteins, BT and B-G, as recently shown (24). We colocalized the human MOG and BT genes on 6p21.3–p22, bands corresponding to the MHC. The colocalization of the BT and MOG genes and the 46% identity of their Ig-like domains suggest they belong to a subset of the Ig superfamily. The shared Ig variable region-like domain could have arisen through exon shuffling, and the association of Ig-like domains with unrelated functional motifs, such as the carboxyl-terminal domains of BT (25), B-G (26), and MOG, is characteristic of the Ig superfamily (27).

Whether MOG, BT, and B-G have any functional similarity has yet to be evaluated. BT is specifically expressed in mammary tissue during pregnancy and lactation, indicating a function in milk-fat secretion (25). Chicken B-G antigens are expressed in many tissues (37); they have been associated with immunological phenomena, in particular a strong adjuvant effect (38) and a much faster primary response with higher antibody production compared to other antigens. The related Ig variable region-like domain in MOG may be responsible for MOG's ability to induce strong antibody responses in experimental autoimmune encephalomyelitis.

Conservation of syntenic groups of genes among the genomes of distantly related species presents a powerful tool for the study of genome evolution and allows, as a first approximation, extrapolation of genetic mapping information among species. We have shown that the first mammalian proteins MOG and BT are structurally related to the chicken B-G antigens, and it is intriguing that the genes map to homologous chromosomal regions in humans and birds.

The mapping of the MOG gene in the mouse MHC is of particular interest. To our knowledge, it is the first non-class I gene to be located in the *M* region, which contains at least eight MHC class I genes (19), one of which is adapted to presentation of N-formylated prokaryotic peptides (28). Whereas the MHC class I genes do not exhibit obvious orthologies between species as distantly related as humans and mice, conserved genes like the MOG gene may identify the region of the human MHC that corresponds to the mouse *M* region.

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1. Lees, M. B. & Brostoff, S. W. (1984) in *Myelin*, ed. Morell, P. (Plenum, New York), pp. 197–224.
2. Lemke, G. (1988) *Neuron* **1**, 535–543.
3. Poduslo, S. E. (1983) *Biochem. Biophys. Acta* **728**, 59–65.
4. Poltorak, M., Sadoul, R., Keilhauer, G., Landa, C., Fahrig, T. & Schachner, M. (1987) *J. Cell Biol.* **105**, 1893–1899.
5. Linington, C., Webb, M. & Woodhams, P. L. (1984) *J. Neuroimmunol.* **6**, 387–396.
6. Scolding, N. J., Frith, S., Linington, C., Morgan, B. P., Campbell, A. K. & Compston, D. A. S. (1989) *J. Neuroimmunol.* **22**, 169–176.
7. Brunner, C., Lassmann, H., Waehneldt, T. V., Matthieu, J.-M. & Linington, C. (1989) *J. Neurochem.* **52**, 296–304.
8. Amiguet, P., Gardinier, M. V., Zanetta, J. P. & Matthieu, J.-M. (1992) *J. Neurochem.* **58**, 1676–1682.
9. Birling, M. C., Roussel, G., Nussbaum, F. & Nussbaum, J.-L. (1993) *Neurochem. Res.*, in press.
10. Matthieu, J.-M. & Amiguet, P. (1990) *Dev. Neurosci.* **12**, 293–302.
11. Kerlero de Rosbo, N., Honegger, P., Lassmann, H. & Matthieu, J.-M. (1990) *J. Neurochem.* **55**, 583–587.
12. Lebar, R., Boutry, J.-M., Vincent, C., Robineaux, R. & Voisin, G. A. (1976) *J. Immunol.* **116**, 1439–1446.
13. Linington, C., Bradl, M., Lassmann, H., Brunner, C. & Vass, K. (1988) *Am. J. Pathol.* **130**, 443–454.
14. Sun, J., Link, H., Olsson, T., Xiao, B. G., Andersson, G., Erkre, H. P., Linington, C. & Diener, P. (1991) *J. Immunol.* **146**, 1490–1495.
15. Sambrook, J., Fritsch, E. & Maniatis, T. (1989) *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Lab. Press, Plainview, NY), 2nd Ed.
16. Sanger, F., Nicklen, S. & Coulson, A. R. (1977) *Proc. Natl. Acad. Sci. USA* **74**, 5463–5467.
17. Roussel, G., Felix, J. M., Dautigny, A., Pham-Dinh, D., Hindelang, C., Jollès, P. & Nussbaum, J.-L. (1989) *Dev. Neurosci.* **13**, 98–103.
18. Mattei, M.-G., Philip, N., Passage, E., Moisan, J.-P., Mandel, J.-L. & Mattei, J.-F. (1985) *Hum. Genet.* **69**, 268–271.
19. Wang, C.-R. & Fischer Lindahl, K. (1993) *Immunogenetics* **38**, 258–271.
20. Howard, C. A., Gummere, G. R., Lyon, M. F., Bennett, D. & Artz, K. (1990) *Genetics* **126**, 1103–1114.
21. Richards, S., Bucan, M., Brorson, K., Kiefer, M. C., Hunt, S. W., III, Lehrach, H. & Fischer Lindahl, K. (1989) *EMBO J.* **8**, 3749–3757.
22. Fischer Lindahl, K. (1986) *Curr. Top. Microbiol. Immunol.* **127**, 272–278.
23. Kyte, J. & Doolittle, R. F. (1982) *J. Mol. Biol.* **157**, 105–132.
24. Gardinier, M. V., Amiguet, P., Linington, C. & Matthieu, J.-M. (1992) *J. Neurosci. Res.* **33**, 177–187.
25. Jack, L. J. W. & Mather, I. H. (1990) *J. Biol. Chem.* **265**, 14481–14486.
26. Miller, M. M., Goto, R., Young, S., Chirivella, J., Hawke, D. & Miyada, C. G. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 4377–4381.
27. Hunkapiller, T. & Hood, L. (1989) *Adv. Immunol.* **44**, 1–63.
28. Fischer Lindahl, K., Hermel, E., Loveland, B. E. & Wang, C.-R. (1991) *Annu. Rev. Immunol.* **9**, 351–372.
29. Nadon, N. L., Duncan, I. D. & Hudson, L. D. (1990) *Development* **110**, 529–537.
30. Schliess, F. & Stoffel, W. (1991) *Biol. Chem. Hoppe-Seyler* **372**, 865–874.
31. Patel, P. I., Roa, B. B., Welcher, A. A., Schoener-Scott, R., Trask, B. J., Pentao, L., Snipes, G. J., Garcia, C. A., Francke, U., Shooter, E. M., Lupski, J. R. & Suter, U. (1992) *Nat. Genet.* **1**, 159–165.
32. Williams, A. F. & Barclay, A. N. (1988) *Annu. Rev. Immunol.* **6**, 381–405.
33. Owens, G. C., Boyd, C. J., Bunge, R. P. & Salzer, L. (1990) *J. Cell Biol.* **111**, 1171–1182.
34. Filbin, M. T., Walsh, F. S., Trapp, B. D., Pizzey, J. A. & Tennekoon, G. I. (1990) *Nature (London)* **344**, 871–872.
35. D'Urso, D., Brophy, P. J., Staugaitis, S. M., Gillepsie, C. S., Frey, A. B., Stempak, J. G. & Colman, D. R. (1990) *Neuron* **4**, 449–460.
36. LeVine, S. M., Wong, D. & Macklin, W. B. (1990) *Dev. Neurosci.* **12**, 235–250.
37. Salomonsen, J., Dunon, D., Skjodt, K., Thorpe, D., Vainio, O. & Kaufman, J. (1991) *Proc. Natl. Acad. Sci. USA* **88**, 1359–1363.
38. Salomonsen, J., Eriksson, H., Skjodt, K., Lundgreen, T., Simonsen, M. & Kaufman, J. (1991) *Eur. J. Immunol.* **21**, 649–658.