Genomic Organization and Chromosomal Mapping of the Ga\(\beta\)1,3GalNAc/Ga\(\beta\)1,4GlcNAc \(\alpha\)2,3-Sialyltransferase*

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In this report we describe the chromosome mapping and genomic organization of the human Ga\(\beta\)1,3GalNAc/Ga\(\beta\)1,4GlcNAc \(\alpha\)2,3-sialyltransferase gene. The gene is localized to human chromosome 11(q23-q24) by in situ hybridization of metaphase chromosomes. It spans more than 25 kilobases of human genomic DNA and is distributed over 14 exons that range in size from 61 to 679 base pairs. Previous characterization of cDNAs encoding the Ga\(\beta\)1,3GalNAc/Ga\(\beta\)1,4GlcNAc \(\alpha\)2,3-sialyltransferase revealed that the gene produces at least three transcripts in human placenta, which code for identical protein sequences except at the 5′ ends (Kitagawa, H., and Paulson, J. C. (1994a) J. Biol. Chem. 269, 1394–1401). Repeated screening for clones that contain the 5′ end of the cDNA has identified two additional distinct mRNAs that are expressed in human placenta. Comparison of the genomic DNA sequence with that of the five different cDNAs indicates that these transcripts are produced by a combination of alternative splicing and alternative promoter utilization. Northern analysis indicated that one of them is specifically expressed in placenta, testis, and ovary, indicating that its expression is independently regulated from the others.

Sialic acid-containing oligosaccharide structures found on glycoproteins and glycolipids are known to vary with species, tissue type, and stage of development. The structural diversity of these carbohydrates is believed to be used by the cell to mediate specific cellular recognition processes including protein targeting, cell adhesion, and cellular differentiation and development (Kornfeld, 1987; Rademacher et al., 1989; Paulson, 1989; Brandley et al., 1990; Varki, 1992; Powell and Varki, 1995). The high degree of structural diversity observed in the terminal glycosylation sequences of glycoprotein carbohydrates is generally believed to be specified by the sialyltransferases produced by the cell. Accumulating evidence suggests that the regulated expression of these enzymes may account for the synthesis of cell type-specific carbohydrate structures (Paulson et al., 1989; Kleene and Berger, 1993; Kitagawa and Paulson, 1994b; Natsuka and Lowe, 1994). Despite the growing number of glycosyltransferase cDNAs which have been cloned, limited information is available concerning the organization and regulation of the expression of glycosyltransferase genes (J oziasse, 1992; Kleene and Berger, 1993).

The sialyltransferase family consists of 12–15 or more glycosyltransferases grouped by their common function of transferring sialic acid from CMP-NeuAc to terminal positions on the sugar chains of glycoproteins and glycolipids. To date, 11 cDNAs of these enzymes have been cloned (Weinstein et al., 1987; Gillespie et al., 1992; Wen et al., 1992b; Livingston and Paulson, 1993; Sasaki et al., 1993; Kitagawa and Paulson, 1994a; Kurosawa et al., 1994a, 1994b; Lee et al., 1994; Nara et al., 1994; Sasaki et al., 1994; Haraguchi et al., 1994; Kojima et al., 1995; Yoshida et al., 1995; Eckhardt et al., 1995). Of these, only the \(\beta\)-galactosidase \(\alpha2,6\)-sialyltransferase gene has been extensively characterized (Svensson et al., 1990; Wang et al., 1990; O’Hanlon and Lau, 1992; Wen et al., 1992a; Svensson et al., 1992; Ashheim et al., 1993; Wang et al., 1993). This gene was found to be relatively large, spanning over 80 kb in length, producing at least six different messages, via alternative promoter usage and mRNA splicing in a tissue-specific fashion.

In this report we have examined the gene of human Ga\(\beta\)1, 3GalNAc/Ga\(\beta\)1,4GlcNAc \(\alpha\)2,3-sialyltransferase for which the cDNA has recently been cloned from human melanoma cell line WM266-4 and human placenta and partial characterization of the human gene has been recently reported (Sasaki et al., 1993; Kitagawa and Paulson, 1994a; Chang et al., 1995). The gene was found to span more than 25 kb and produce at least five distinct transcripts in human placenta. Northern analysis indicated that one of them is specifically expressed in placenta, testis, and ovary, indicating that its expression is independently regulated from the others.

EXPERIMENTAL PROCEDURES

Materials—Bluescript plasmid vector, JFII vector, Escherichia coli strains XL1-Blue, XL1-Blue MRA, and XL1-Blue MRA(P2), Gigapack II XL packaging extracts, and Pfu polymerase were purchased from Stratagene. Restriction enzymes were purchased from New England Biolabs, Pharmacia LKB Biotech Inc., and Life Technologies, Inc. [\(\alpha\)-\(32\)P]dCTP was obtained from Amersham.

Isolation of Human Genomic Clones—Human genomic DNA (Clontech) was partially digested with Sau3A1 and then ligated into Xho-digested JFII (Stratagene). The resulting library was packaged using a Stratagenegigapack II XL packaging extract and plated on E. coli XL1-Blue MRA(P2) (Stratagene). Approximately 1 million plaques were screened with radiolabeled sialyltransferase cDNA as described (Kitagawa and Paulson, 1994a). Multiple clones (C1-C21) were isolated, and

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1 The abbreviations used are: kb, kilobase(s); bp, base pair(s); PCR, polymerase chain reaction; RACE, rapid amplification of cDNA ends; MAF, mammary cell activating factor.
three of them, C1, C11, and C21, were characterized in detail. Insert DNA fragments were initially characterized by restriction digestion and Southern blot analysis (Sambrook et al., 1989). Human genomic DNA fragments that hybridized to the sialyltransferase cDNA probes were subcloned into Bluescript plasmid vectors. Nucleotide sequencing was performed on chromosome preparations obtained from phytohemagglutinin-stimulated human lymphocytes cultured for 72 h. Bromodeoxyuridine was added for the final 7 h of culture (60 μg/ml medium), to ensure a posthybridization chromosomal banding of good quality. The nuclei were dehydrated and subjected to a Southern blot analysis. Three were identified with the type A1 or type A2 form-specific primers, respectively, and three bands were detected with the type B form-specific primer. After subcloning the PCR product and sequencing individual clones, we found that there were two other novel isoforms related to the previously described type B form (Kitagawa and Paulson, 1994a) which differ in their 5’ noncoding sequences and are referred to as type B2 and type B3. The nucleotide sequences of the nonhomologous region at the 5’ end of the three type B forms are presented in Fig. 1. These two additional type B transcripts indicate that the human α,2,3-sialyltransferase gene produces at least five transcripts in human placenta.

Identification of the Novel Isoforms of the Human Galβ1,3GalNAc/β1,4GlcNAc α,2,3-Sialyltransferase—In order to gain information about the organization and the regulation of Galβ1,3GalNAc/β1,4GlcNAc α,2,3-sialyltransferase gene in human tissues, it was necessary to isolate the genomic sequences containing this gene. A cDNA (type A1) was used as a probe to screen a human placenta genomic DNA library. Several independent clones were isolated and subjected to a Southern blot analysis. These were found to overlap with each other and contained all of the exons corresponding to the type A1 form of α,2,3-sialyltransferase cDNA. As summarized in Fig. 2, coding sequences for the type A1 and type A2 forms protein of human α,2,3-sialyltransferase gene are divided into 9 exons, and that for the type B form protein is divided into 10 exons, ranging in size from 61 bp to 679 bp. Exons E3 and E6–E14 contain the coding sequence indicated in Fig. 2. Exon E14 also contains the 3’-untranslated region which included the poly(A) attachment site, ATTAAA.

 RESULTS

Identification of the Novel Isoforms of the Human Galβ1,3GalNAc/β1,4GlcNAc α,2,3-Sialyltransferase—The cDNAs of Galβ1,3GalNAc/β1,4GlcNAc α,2,3-sialyltransferase were reported previously to consist of at least three isoforms in human placenta (Kitagawa and Paulson, 1994a). To identify the 5’ ends of the Galβ1,3GalNAc/β1,4GlcNAc α,2,3-sialyltransferase transcripts and possibly identify other mRNA isoforms that differ in the 5’ end, we employed a rapid amplification of cDNA ends-polymerase chain reaction (RACE-PCR) strategy combined with reverse transcription polymerase chain reaction. Human placenta poly(A) RNA was reverse-transcribed using a common primer among the three isoforms cloned previously (type A1, type A2, and type B; see “Experimental Procedures”). PCR amplification was then performed using the anchor primer, and each isoform-specific internal primer revealing five distinct PCR products. Two bands were identified with the type A1 or type A2 form-specific primers, respectively, and three bands were detected with the type B form-specific primer. After subcloning the PCR product and sequencing individual clones, we found that there were two other novel isoforms related to the previously described type B form (Kitagawa and Paulson, 1994a) which differ in their 5’ noncoding sequences and are referred to as type B2 and type B3. The nucleotide sequences of the nonhomologous region at the 5’ end of the three type B forms are presented in Fig. 1.

FIG. 1. Comparison of the sequences in the 5’-untranslated region of the type B1, type B2, and type B3 forms of α,2,3-sialyltransferase cDNA isolated from human placenta. Homologous sequence (only the first 16 bp) is represented by boldface letters.
mRNA isoforms are produced by a combination of alternative splicing of exon E3 without splicing. These results suggest that the five more than 15 kb upstream of exon E2 (data not shown).

The exon E2 for the 5'-most exon (exon E1) of the type B1 form, restriction mapping by Southern blot analysis indicates that the exon is found to be more than 15 kb upstream of exon E2 (data not shown).

In summary, the analysis suggests that the entire \( \alpha_2,3 \)-sialyltransferase gene spans over 25 kb of human genomic DNA. It should be noted that, in contrast to the genomic organization of \( \alpha_2,6 \)-sialyltransferase (Svensson et al., 1990), the highly conserved sialylmotif, used to clone this \( \alpha_2,3 \)-sialyltransferase cDNA (Kitagawa and Paulson, 1994a), is divided into two exons, exon E10 and E11 (Fig. 2). In addition, the unique sequence found on the 5'-end of the type B2 and type B3 forms (see Fig. 1) were mapped between exon E1 and exon E3, indicating that these were produced by alternative promoter utilization (Fig. 2). The exon E2 for the 5'-end of type B2 form was located 397 bp upstream of exon E3. The 5'-most transcriptional start site of the type B3 form was located only 44 bp upstream of exon E3, and the mRNA was formed to the 3'-end of exon E3 without splicing. These results suggest that the five mRNA isoforms are produced by a combination of alternative splicing and alternative promoter utilization, and, consequently, that the mRNA is formed from a combination of 14 exons of the \( \alpha_2,3 \)-sialyltransferase gene.

Analysis of the Transcriptional Start Sites and the Sequence of the \( \alpha_2,3 \)-Sialyltransferase Promoter Region—The sequence of the 5'-flanking region of the type A1, type A2, and type B3 forms, and the type B2 form of the \( \alpha_2,3 \)-sialyltransferase gene is shown in Figs. 3 and 4, respectively. The transcriptional start sites were determined by sequencing the RACE-PCR products as described above and were marked by arrows in the figures. Sequencing of the PCR product of the type A1, type A2, the type B2, and the type B3 forms also revealed that transcription of the former two forms, type A1 and type A2, initiates at two positions and that of the latter two forms, type B2 and type B3, initiates at several positions, indicated by arrows in Figs. 3 and 4. As expected from the observation that there are multiple sites of transcription initiation, both of the 5'-flanking regions lack canonical TATA or CCAAT boxes, but do contain several other well characterized promoter elements as shown in Tables III and IV. As shown in Fig. 3 and Table III, this region contains six sequence motifs similar to AP2 recognition elements.
element (Mitchell et al., 1987), of which four are just upstream of the transcriptional start sites of the type B3 form and two are just upstream of those of the type A1 and type A2 forms. In addition, three potential mammary cell activating factor (MAF) consensus sequences (Mink et al., 1992) were identified; one potential Sp1 consensus sequence (Kadonaga et al., 1986) was found; and four ETF consensus sequences which stimulate transcription of promoters lacking TATA boxes (Kageyama et al., 1989) were identified. Moreover, two LF-A1 consensus sequences (Hardon et al., 1988), one HLH consensus sequence (Blackwell and Weintraub, 1990), and one NF-1-like protein binding site (Paonessa et al., 1988) were found.

As shown in Fig. 4 and Table IV, the 5’-flanking region of the type B2 form also contains three sequence motifs similar to the

FIG. 3. Sequence of the type A1, type A2, and type B3 forms of human α2,3-sialyltransferase promoter region. The start sites of transcription for each isoform are shown by arrows. The consensus binding sites for the transcription factors AP2, Sp1, LF-A1, HLH (helix-loop-helix proteins), νNF-1, and MAF are underlined and those for the transcription factor ETF are boxed.

FIG. 4. Sequence of the type B2 form of human α2,3-sialyltransferase promoter region. The start sites of transcription are shown by arrows. The consensus binding sites for the transcription factors AP1, AP2, MAF, CARG, HLH, PEA3, νNF-1, and OCT are underlined, and those for the transcription factor ETF are boxed.
MAF recognition element, one sequence similar to the AP1 binding site (Lee et al., 1987), four sequences similar to the AP2 binding site, seven ETF consensus sequences, one HLH consensus sequence, and one NF-1-like protein binding site. Moreover, three additional sequence motifs were detected. Three CArG consensus binding sites are present, a sequence motif required for expression of smooth muscle-specific genes (Reddy et al., 1990), one OCT (octamer binding transcription factor) consensus binding site (Cox et al., 1988) is identified, a sequence motif recognized by an octamer-related proteins which have been implicated in the control of the histone 2b gene and the melanocyte-specific tyrosinase-related protein TRP1 (Lowings et al., 1992), and one PEA3 consensus sequence is also present (Faisst and Meyer, 1992).

### Table III

Potential regulatory elements in the type A1, type A2, and type B3 forms of human α2,3-sialyltransferase (α2,3ST) promoter. Upper case indicates agreement with consensus.

| Motif                | Sequence (5'...3') | % identity | Ref.       |
|----------------------|--------------------|------------|------------|
| MAF consensus        | G(A/G) A(G)G(C/G)AA(G/T) |           | Mink et al., 1992 |
| α2,3ST homology      |                     |            |            |
| −1                   | G G A G G Agt T     | 78         |            |
| −2                   | G G t G G AAG G     | 89         |            |
| −3                   | t c A G C AAG T     | 78         |            |
| AP2 consensus        | CCCAGGC             |            | Mitchell et al., 1987 |
| α2,3ST homology      |                     |            |            |
| −1                   | CCCgAGtC            | 75         |            |
| −2                   | tCCClGGC            | 75         |            |
| −3                   | CCCgAGga            | 75         |            |
| −4                   | CCCcaGGg            | 88         |            |
| −5                   | CCCGAGGC            | 88         |            |
| −6                   | CCCcaGa             | 88         |            |
| SP1 consensus        | (G/T)GGGGG(G/A)(G/A)(CT) |        | Kadonaga et al., 1986 |
| α2,3ST homology      | aGGCCGG ctAT       | 80         |            |
| LF-A1 consensus      | TG(A/G) (A/C)CC     |            | Hardon et al., 1988 |
| α2,3ST homology      |                     |            |            |
| −1                   | TG G A CC           | 100        |            |
| −2                   | TG G C CC           | 100        |            |
| HLH consensus        | CANNTG              |            | Blackwell and Weintraub, 1990 |
| α2,3ST homology      |                     |            |            |
| −1                   | CACCTG              | 100        |            |
| αNF-1 consensus      | TGGCA               |            | Paonessa et al., 1988 |
| α2,3ST homology      |                     |            |            |
| −1                   | TGGCA               | 100        |            |

### Table IV

Potential regulatory elements in the type B2 form of human α2,3-sialyltransferase (α2,3ST) promoter. Upper case indicates agreement with consensus.

| Motif                | Sequence (5'...3') | % identity | Ref.       |
|----------------------|--------------------|------------|------------|
| MAF consensus        | G(A/G) A(G)G(C/G)AA(G/T) |       | Mink et al., 1992 |
| α2,3ST homology      |                     |            |            |
| −1                   | G A t G G AAG a     | 78         |            |
| −2                   | t G A G G AAG c     | 78         |            |
| −3                   | G G A t c AAG G     | 89         |            |
| AP1 consensus        | (C/G)TGACT(A/C)A    |           | Paonessa et al., 1988 |
| α2,3ST homology      | G TGACT g c        | 75         |            |
| AP2 consensus        | CCCAGGC             |            | Mitchell et al., 1987 |
| α2,3ST homology      | gCCtlGGC           |            |            |
| −1                   | tCCclGC            | 75         |            |
| −2                   | CCCAACC            | 75         |            |
| −3                   | CCCAACC            | 75         |            |
| CArG consensus       | CC(A/T)GG          |            | Lee et al., 1987 |
| α2,3ST homology      | CCCtAtCCG         |            |            |
| −1                   | CTAgaAAGG          | 80         |            |
| −2                   | CTCAtAgG           | 80         |            |
| OCT consensus        | ATTGCAAT           |            | Reddy et al., 1990 |
| α2,3ST homology      | gTTGCAT            | 88         |            |
| HLH consensus        | CANNTG             |            | Blackwell and Weintraub, 1990 |
| α2,3ST homology      |                     |            |            |
| −1                   | CATCTG             | 100        |            |
| αNF-1 consensus      | TGGca              |            | Paonessa et al., 1988 |
| α2,3ST homology      |                     |            |            |
| −1                   | TGGca              | 100        |            |
| PEA3 consensus       | AGGAA(A/G)         |            | Lowings et al., 1992 |
| α2,3ST homology      | AGGAA G            | 100        |            |

Tissue-specific Expression of the Type A1 Form—As described in the previous paper (Kitagawa and Paulson, 1994a), the α2,3-sialyltransferase exhibits a unique tissue-specific pattern of expression. In order to determine whether the α2,3-sialyltransferase transcripts are tissue-specifically expressed by a combination of alternative splicing and alternative promoter utilization, Northern blots with mRNAs from human adult and fetal tissues were probed with the type A1 formspecific fragment (Fig. 5b). For comparison, the same Northern blot was probed by a full-length cDNA probe of the α2,3-sialyltransferase shown in Fig. 5a, which should detect all five transcripts. This result indicates that the type A1 form mRNA
is specifically expressed in placenta, ovary, and testis. For the three type B forms, however, the length of the cDNA specific for each type is relatively short so that it was not possible to get a visible signal.

Chromosomal Mapping of Two Human α2,3-Sialyltransferase Genes—Using a cDNA probe of the Galβ1,3GalNAc/Galβ1,4GlcNAc α2,3-sialyltransferase, in situ hybridization to normal metaphase chromosomes was performed to determine the chromosomal localization of the human gene. Of 100 metaphase cells examined from this hybridization, 197 silver grains were associated with chromosomes, and 42 of these (21.3%) were located on chromosome 11. The distribution of grain on this chromosome was not random, and 83.3% of them were mapped to the q23-q24 region of chromosome 11 long arm (Fig. 6a). These results clearly indicate that the gene is located at human chromosome 11q23-q24.

Comparison of sequences of nine cloned sialyltransferases revealed that the highest homology of Galβ1,3GalNAc/Galβ1,4GlcNAc a2,3-sialyltransferase to the other 10 sequences was with that of Galβ1,3(4)GlcNAc a2,3-sialyltransferase. Accordingly, an experiment similar to that described above was carried out to determine the chromosomal location of the Galβ1,3(4)GlcNAc a2,3-sialyltransferase gene. Of 100 metaphase cells examined for hybridization, 188 silver grains were associated with chromosomes, and 51 of these (27.1%) were located on chromosome 1. As shown in Fig. 6b, 78.4% of them were mapped to the p34-p33 region of chromosome 1 short arm. These results indicate that the Galβ1,3(4)GlcNAc α2,3-sialyltransferase gene is localized at chromosome 1p34-33.

DISCUSSION

To date, the genomic organization has been reported for several glycosyltransferases (Joziasse, 1992; Kleene and Berger, 1993; Chang et al., 1995). The rat α2,6-sialyltransferase gene is divided into at least 12 exons which span over 80 kb in length (Wen et al., 1992a). Similarly, the α1,3-galactosyltransferase gene is distributed over 9 exons that span over 35 kb (Joziasse et al., 1992), and the β1,4-galactosyltransferase gene is also distributed over 6 exons that span over 40 kb of genomic sequence (Hollis et al., 1989). This α2,3-sialyltransferase gene falls into the same pattern. In contrast, several exceptions to this pattern are β1,2-GlcNAc-transferase I, β1,4-GlcNAc-transferase III, several α1,3-fucosyltransferases, and β1,6-GlcNAc-transferase genes. The entire coding sequence of these genes appears to be contained within a single exon (Hull et al., 1991; Lowe et al., 1991; Weston et al., 1992a, 1992b; Bierhuizen et al., 1993; Ihara et al., 1993). It is unclear whether the occurrence of two patterns of glycosyltransferase genomic organization has an evolutionary significance.

The gene for human Galβ1,3GalNAc/Galβ1,4GlcNAc α2,3-sialyltransferase is distributed over 14 exons that span at least 25 kb of genomic sequence. Transcription of this gene results in the production of five distinct mRNAs (type A1, type A2, type B1, type B2, and type B3 forms) in human placenta, each approximately 2.0 kb in size, that are generated by a combination of alternative splicing and alternative promoter utilization. Translation of these individual mRNAs predicts the biosynthesis of three related protein isoforms of the α2,3-
sialyltransferase which were previously referred to as the Long A, Long B, and Short forms, of 332, 333, and 322 amino acids, respectively, which has been confirmed by in vitro translation.² Structurally, these three protein isoforms differ from each other only at its N-terminal that is the cytoplasmic tail and the part of transmembrane domain (Kitagawa and Paulson, 1994a). The biological significance of the three different protein isoforms is presently unclear.

The observation of multiple transcripts for this α2,3-sialyltransferase gene has also been observed with other glycosyltransferase genes including those of the α2,6-sialyltransferase and the α1,4-galactosyltransferase (Paulson et al., 1989; Russo et al., 1990; Wen et al., 1992a; Aasheim et al., 1993; Wang et al., 1993). In case of the α2,6-sialyltransferase, at least six different transcripts were produced via alternative splicing and alternative promoter usage. The most well-characterized one is a 4.3-kb mRNA found almost exclusively in the liver (Wen et al., 1992a), which is generated from six exons of the gene (Svensson et al., 1990). Two distinct forms of a 4.7-kb mRNA, one is highly expressed in B-cells and another is expressed at low levels in most tissues (Aasheim et al., 1993; Wang et al., 1993), have been identified. The two transcripts are also produced from the same six exons as the 4.3-kb one with the addition of one or two 5′-untranslated exons (Aasheim et al., 1993; Wang et al., 1993). Thus, these three transcripts have identical coding sequences but having different 5′-untranslated sequences. Since the coding sequences are identical, the different mRNA isoforms is presently unclear.

2 H. Kitagawa and J. C. Paulson, unpublished data.

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The sequence analysis of the 5′-flanking region of the α2,3-sialyltransferase isoforms revealed the heterogeneous transcriptional start sites and the absence of typical TATA and CCAAT boxes coupled with the presence of GC boxes (Figs. 3 and 4). These structural features are believed to be typical of the so-called housekeeping genes, which are expressed at low levels in essentially all tissues (Kadonaga et al., 1986), suggesting that their regulation would be governed, at least in part, by the Sp1 binding sites like that of the α1,4-galactosyltransferase (Haraldsen et al., 1993). Further work is required to confirm this mechanism.

Chromosomal assignments have been reported for several glycosyltransferases including two sialyltransferases, Galα1,4GalNAc α2,6-sialyltransferase and NeuAcα2,3Galβ1,4GlcNAc α2,8-sialyltransferase, which reside at human chromosome 3q27–q28 and on human chromosome 12, respectively (Kleene and Berger, 1993; Wang et al., 1993; Sasaki et al., 1994). The present study demonstrates that the two additional sialyltransferases, the Galα1,3GalNAcGalβ1,4GlcNAc α2,3-sialyltransferase and the Galα1,3GlcNAc α2,3-sialyltransferase, are also localized on entirely different human chromosomes, 11q23-2q4 and 1p34–33, respectively, despite the fact that their four genes share the highly conserved region, sialylmotif. These results strongly suggest that the four sialyltransferases diverged from an ancestor gene early in evolution. It remains to be determined whether the rest of the sialyltransferase genes are likewise dispersed in the human genome.
Chromosomal Mapping and Organization of α2,3-Sialyltransferase Gene

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