radioimmunoassay based on the Western blot technique, immunoreactivity against the λCI-HTLV-III-β-galactosidase fusion polypeptide was detected in the serum of 19 of the AIDS patients but none of the normal controls. This indicates that the protein encoded by the portion of the *env-lor* region contained in ORF clone 121 is produced in HTLV-III–infected cells and induces antibody production in most if not all AIDS patients.

These and further studies of the expression of the *env-lor* region in other vector systems and of antibodies to different regions of the fusion polypeptides may lead to the development of useful reagents for studying HTLV-III proteins and for preparing means to diagnose and treat AIDS.

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Sequence of the Alpha Subunit of Photoreceptor G Protein: Homologies Between Transducin, *ras*, and Elongation Factors

Abstract. *A bovine retinal complementary DNA clone encoding the α subunit of transducin (T_α) was isolated with the use of synthetic oligodeoxynucleotides as probes, and the complete nucleotide sequence of the insert was determined. The predicted protein sequence of 354 amino acids includes the known sequences of four tryptic peptides and sequences adjacent to the residues that undergo adenosine diphosphate ribosylation by cholera toxin and pertussis toxin. On the basis of homologies to other proteins, such as the elongation factors of protein synthesis and the* ras *oncogene proteins, regions are identified that are predicted to be acylated and involved in guanine nucleotide binding and hydrolysis. Amino acid sequence similarity between T_α and* ras *is confined to these regions of the molecules.*

An early step in the processing of visual information involves transducin, a protein found in the rod outer segments of photoreceptors. It functions to couple the photolysis of rhodopsin to changes in intracellular levels of cyclic guanosine monophosphate (GMP) (*1*). When photoreceptors are illuminated, transducin interacts with rhodopsin, and, as a result of this interaction, guanosine diphosphate (GDP) bound to the α subunit of transducin (T_α) is exchanged for guanosine triphosphate (GTP). In this form, T_α is able to activate a cyclic GMP phosphodiesterase. The activation is terminated when the intrinsic guanosine triphosphatase activity of T_α hydrolyzes the bound GTP, restoring the transducin-GDP complex and completing the cycle. Transducin is a member of a family of proteins collectively called G proteins (*2*). Other G proteins interact with various hormone and neurotransmitter receptors and couple receptor-ligand binding events to changes in amounts of intracellular "second messenger," such as cyclic adenosine monophosphate and perhaps calcium ion (*3*). The G proteins are also substrates for adenosine diphosphate (ADP)–ribosylation by cholera toxin, pertussis toxin, or both. The ADP-ribosylation of transducin by cholera toxin inhibits GTP hydrolysis and fixes the α subunit in the GTP-bound state, whereas pertussis toxin acts to stabilize the GDP-bound form (*4*).

We have shown that the α subunits of transducin and G_o, an abundant GTP-binding protein in brain tissue, have extensive amino acid sequence homology (*5*). Furthermore, the amino acid sequence of an NH_2-terminal tryptic peptide derived from T_α was shown to have 59 percent homology with a corresponding region of the *ras* gene products. The *ras* gene family encodes guanine nucleotide–binding proteins that may be important in regulating cell growth and oncogenesis. On the basis of the sequence homology and other similarities with G proteins, we suggested that *ras* might also function as a coupling protein to transduce signals from receptors that interact with factors that regulate cell growth. In order to study G protein structure and function and more clearly define similarities and differences between the *ras* and G proteins, we isolated a complementary DNA (cDNA) corresponding to the α subunit of transducin and determined its nucleic acid sequence.

The sequences of the mixtures of oligonucleotides that were used to screen the λgt10 library prepared from bovine retinal RNA (*6*) are shown in Fig. 1A. Approximately 125,000 plaques were screened with the T_αA mixed probe and 54 were found to hybridize. These were again screened with the T_αB probe and one clone ($\lambda T_\alpha 1$) hybridized specifically with both probes. By subcloning three fragments of the insert and using synthetic oligonucleotides as primers, we obtained the complete nucleic acid sequence of the insert. The sequencing strategy is shown in Fig. 1B and the nucleotide sequence and predicted amino acid sequence are shown in Fig. 2. The nucleic acid sequence extends 429 base pairs past the TAG codon signaling the end of the coding region, and no extensive stretch of poly(A) (polyadenylate) sequence was found. There is also a 174-base-pair 5′ untranslated segment.

The open reading frame predicts an amino acid sequence including 354 amino acids. The predicted molecular weight of the protein (40.1 kD), the amino acid composition, and the size of the tryptic fragments agree with recorded values (*5*, *7*). The predicted amino acid sequences of the amino terminus of the 9-kD tryptic fragment (Lys^{209}-Tyr^{230}) and of the tetrapeptide that includes the

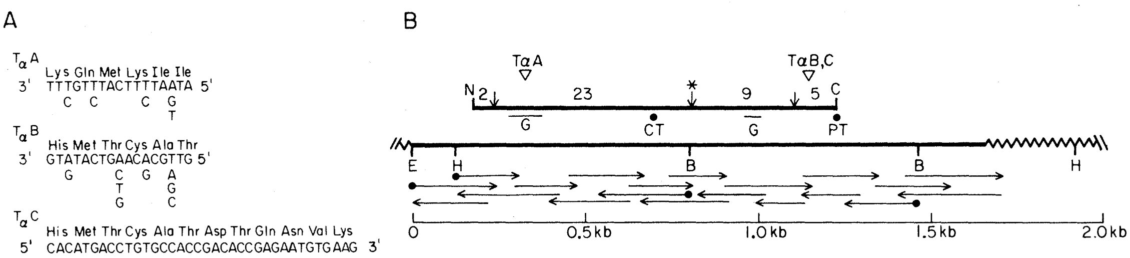

Fig. 1. (A) Synthetic oligonucleotides used to isolate and confirm the identity of a cDNA clone for the α subunit of transducin. Amino acid sequences of tryptic fragments of T_α (5) were selected to synthesize the corresponding oligonucleotides ($T_\alpha A$ and $T_\alpha B$) representing all possible codon combinations. Specifically for $T_\alpha A$, this included 24 molecules, each 17 nucleotides long; for $T_\alpha B$, 64 molecules each 17 nucleotides long; and for $T_\alpha C$, 1 molecule, 36 nucleotides long. Oligonucleotides were synthesized with an Applied Biosystems model 380A automated DNA synthesizer and purified by gel electrophoresis before use. The bovine retinal cDNA library was screened as described (*15*). $T_\alpha A$ and $T_\alpha B$ were hybridized at 35° and 43°C, respectively. The construction of oligonucleotide $T_\alpha C$ was based on codons most commonly found in bovine rhodopsin and other eukaryotic proteins. $T_\alpha C$ was used as a nucleotide sequencing primer (Fig. 1B) to confirm the identity of a clone ($\lambda T_\alpha 1$) which hybridizes to $T_\alpha A$ and $T_\alpha B$. (B) Organization and nucleotide sequencing strategy of $\lambda T_\alpha 1$ cDNA insert. The 0.65-kilobase-pair (kbp) Bam HI, 0.8-kbp Eco RI–Bam HI, and 1.8-kbp Hind III restriction endonuclease fragments of $\lambda T_\alpha 1$ were subcloned into M13mp10 or 11 and sequencing templates were prepared by standard methods (*19*). Nucleotide sequences were determined by the dideoxynucleotide chain–termination method (*20*). Sequences determined with $T_\alpha C$ (Fig. 1A) and a universal sequencing primer (Bethesda Research Laboratories) initially served as the basis for the construction of other synthetic oligonucleotide sequencing primers. Symbols used are as follows: thick top line, extent of protein coding region; vertical arrows, sites of tryptic proteolysis of native T_α (*5*); asterisk, tryptic site accessible in T_α bound to GDP but not in T_α bound to guanosine 5′-(β,γ-imido) triphosphate; numbers, molecular size in kilodaltons of tryptic fragments as determined by gel electrophoresis; triangles, location of amino acid sequences that served as a basis for construction of oligonucleotides shown in Fig. 1A; N and C, amino and carboxyl terminus of T_α, respectively; CT and PT, location of amino acids ADP-ribosylated by cholera toxin and pertussis toxin; G, regions predicted to be involved in guanine nucleotide binding and hydrolysis; thick bottom line, extent of cDNA insert; jagged line, λgt10 DNA; horizontal arrows, direction and extent of nucleotide sequences determined using synthetic oligonucleotides as sequencing primers; and dotted horizontal arrows, direction and extent of nucleotide sequences determined with the use of a universal sequencing primer. A scale of nucleotide lengths in kilobase pairs is shown at the bottom. Relevant restriction endonuclease sites are abbreviated as follows: B, Bam HI; E, Eco RI; and H, Hind III.

GGG CAC CCT GCC TGC TCT TTC ACC CAG CTC CTA CAG ACT GGC TTT TTA GAA GGA CTA AGA AAC TGA TAC TCG ATC CCA ATT TAT TTT TCC TTA TCT TCC CAT CTC TCA GAT AGG AAA CCC (120)

TGG AGG AGA AGC TTA AGG GCT GGA GAA AGC TGC CGA GGA GGA GAC GGA TGA AAG ATG GGG AGT GGA GCC AGT GCC GAG GAC AAA GAA CTG GCC AAG AGG TCC AAA GAG CTA GAA AAG AAG (240)
H
Met Gly Ser Gly Ala Ser Ala Glu Asp Lys Glu Leu Ala Lys Arg Ser Lys Glu Leu Glu Lys Lys
1 10 20

CTG CAG GAG GAT GCT GAC AAG GAA GCC AAG ACT GTC AAG CTG CTA TTG CTG GGT GCT GGG GAG TCA GGA AAG AGC ACT ATC GTC AAA CAG ATG AAG ATT ATT CAT CAG GAT GGC TAT TCG (360)
Leu Gln Glu Asp Ala Asp Lys Glu Ala Lys Thr Val Lys Leu Leu Leu Leu Gly Ala Gly Glu Ser Gly Lys Ser Thr Ile Val Lys Gln Met Lys Ile Ile His Gln Asp Gly Tyr Ser
30 40 50 60

CCA GAA GAA TGC CTG GAG TAC AAG GCC ATC ATC TAC GGC AAC GTG CTG CAA TCC ATC TTG GCT ATC ATC CGG GCC ATG CCC ACA CTG GGC ATT GAC TAT GCT GAA GTG AGC TGT GTG GAT (480)
Pro Glu Glu Cys Leu Glu Tyr Lys Ala Ile Ile Tyr Gly Asn Val Leu Gln Ser Ile Leu Ala Ile Ile Arg Ala Met Pro Thr Leu Gly Ile Asp Tyr Ala Glu Val Ser Cys Val Asp
70 80 90 100

AAT GGG AGA CAG CTC AAC AAC CTG GCT GAC TCC ATT GAA GAG GGC ACC ATG CCT CCT GAG CTA GTG GAG GTT ATC AGG AAG TTG TGG AAG GAT GGT GGG GTG CAA GCC TGC TTT GAC AGA (600)
Asn Gly Arg Gln Leu Asn Asn Leu Ala Asp Ser Ile Glu Glu Gly Thr Met Pro Pro Glu Leu Val Glu Val Ile Arg Lys Leu Trp Lys Asp Gly Gly Val Gln Ala Cys Phe Asp Arg
110 120 130 140

GCT GCA GAG TAC CAG CTC AAT GAC TCA GCA TCT TAC TAC CTG AAT CAA TTA GAC CGA ATT ACG GCC CCT GAC TAC CTC CCT AAT GAG CAA GAT GTG CTA CGA TCC AGA GTC AAA ACC ACA (720)
Ala Ala Glu Tyr Gln Leu Asn Asp Ser Ala Ser Tyr Tyr Leu Asn Gln Leu Asp Arg Ile Thr Ala Pro Asp Tyr Leu Pro Asn Glu Gln Asp Val Leu Arg Ser Arg Val Lys Thr Thr
150 160 170 B CT 180

GGC ATC ATT GAG ACT AAG TTT TCT GTC AAG GAC TTA AAC TTC CGG ATG TTT GAT GTG GGA GGG CAG AGA TCA GAG AGA AAG AAG TGG ATC CAC TGC TTT GAG GGA GTC ACC TGC ATC ATT (840)
Gly Ile Ile Glu Thr Lys Phe Ser Val Lys Asp Leu Asn Phe Arg Met Phe Asp Val Gly Gly Gln Arg Ser Glu Arg Lys Lys Trp Ile His Cys Phe Glu Gly Val Thr Cys Ile Ile
190 200 * 210 220

TTC TGT GCA GCC CTC AGC GCC TAT GAT ATG GTG CTG GTG GAA GAT GAC GAA GTG AAT CGT ATG CAT GAG TCA CTG CAC CTG TTC AAC AGC ATA TGT AAC CAC AAG TTC TTT GCG GCC ACT (960)
Phe Cys Ala Ala Leu Ser Ala Tyr Asp Met Val Leu Val Glu Asp Asp Glu Val Asn Arg Met His Glu Ser Leu His Leu Phe Asn Ser Ile Cys Asn His Lys Phe Phe Ala Ala Thr
230 240 250 260

TCC ATT GTC CTC TTT CTC AAC AAG AAG GAT CTC TTT GAG GAA AAA ATC AAG AAA GTC CAT CTC AGC ATT TGT TTT CCA GAG TAT GAT GGG AAC AAC TCT TAT GAG GAT GCA GGG AAT TAT (1080)
Ser Ile Val Leu Phe Leu Asn Lys Lys Asp Leu Phe Glu Glu Lys Ile Lys Lys Val His Leu Ser Ile Cys Phe Pro Glu Tyr Asp Gly Asn Asn Ser Tyr Glu Asp Ala Gly Asn Tyr
270 280 290 300

ATC AAG AGT CAG TTC CTT GAC CTC AAC ATG AGA AAA GAT GTC AAA GAA ATC TAC AGT CAC ATG ACC TGT GCT ACA GAT ACA CAG AAT GTC AAA TTT GTA TTT GAT GCA GTT ACA GAT ATT (1200)
Ile Lys Ser Gln Phe Leu Asp Leu Asn Met Arg Lys Asp Val Lys Glu Ile Tyr Ser His Met Thr Cys Ala Thr Asp Thr Gln Asn Val Lys Phe Val Phe Asp Ala Val Thr Asp Ile
310 320 330 340

ATC ATC AAA GAA AAC CTC AAG GAC TGC GGA CTC TTC TAG TTC TCA CCA TTT CTC AAG TAT GTT CTA TAA ACA GGC TCC GAA TCT CGT TAA TTT TAA GCA GAA AAT TTA AGG TCA ATA TAT (1320)
Ile Ile Lys Glu Asn Leu Lys Asp Cys Gly Leu Phe ---
PT 354

TAT TGA ATC CAT AAG AAT GAA TCC ATC CTC CCT TGG AAA TGA GTA TGT ATG ATT GCA ACT GTG TCT CAT TTG GTC TTT TAA AAG CGG GAT AGT TAG CAC AGT TTA AAG AAT GCA GGA CCA (1440)

B
GGA AAT CAG AAG ACC CAG GAT CCA TTA TTG GCT CTG CAA CTT ACT ATT GAT GCA AAA ATG TAA ATA TTT CAT TTG TCT GAG CCT TGA GTC CCT TAT CTA TAA AAT GAA GGT AAT TTC TCT (1560)

ACT ACT TCA CAA GGT TAC TTT AAT GAT CAC AAA CAT AAC TGA AGG CAG GCA CAT AAA AAC TGT GTG GTG ACA CAA AGA AAT CCT ATG TTA AAG GCT CCC ACT AAT (1665)

Fig. 2. Nucleotide sequence of $\lambda T_\alpha 1$ cDNA and deduced amino acid sequence of T_α protein. Numbering of the nucleic acid sequence is shown in parentheses. The predicted amino acid sequence is numbered every ten residues. Amino acid sequences from tryptic peptides of T_α (*5, 8*) are underlined. Other symbols and abbreviations are as in Fig. 1B. The insert of $\lambda T_\alpha 1$ cannot be excised with Eco RI even though the cDNA library was constructed with Eco RI linkers. The nucleotide sequence from bases 1666 to 1672, which was GAAATTC instead of GAATTC, explains this anomaly, but the origin of the extra adenine is unknown.

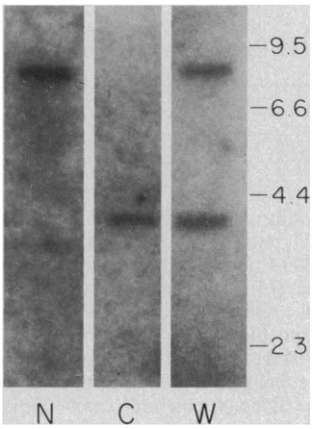

Fig. 3. Hybridization of bovine genomic DNA to T_α cDNA. Twenty micrograms of high molecular weight bovine liver DNA was cleaved with Bam HI, fractionated by agarose gel electrophoresis, transferred to nitrocellulose, and hybridized to primer extended probes (*19*) derived from M13 subclones containing the EcoRI–Bam HI fragment corresponding to the amino-terminal two-thirds of T_α (N), the Bam HI fragment corresponding to the carboxyl-terminal third of T_α (C), or the Hind III fragment that contains the entire coding region (W) (Fig. 1B). The amount of [α^{32}P]dATP (deoxyadenylate) used in the reactions was limited so that a probe of an average length of 1000 bases was made. Therefore, probe W, which begins at base 129, does not extend beyond the last base of probe C at base 1458. Hybridization was at 65°C in 6× SSC (saline sodium citrate), 0.1 percent sodium dodecyl sulfate (SDS), 2× Denhardt's solution, 50 μg per milliliter sheared salmon testes DNA, and 10 percent dextran sulfate. The filter was washed at 42°C in 0.2× SSC and 0.1 percent SDS.

cholera toxin ADP-ribosylation site (Ser^{177}-Lys^{180}) are identical with the amino acid sequences determined by Edman degradation. The amino acid reported to be ADP-ribosylated by cholera toxin is an arginine in the sequence Ser-Arg-Val-Lys (*8*). This sequence is found only once, is preceded by an arginine as expected for a tryptic peptide, and is located on the 23-kD tryptic fragment (*9*). The predicted sequence of the 5-kD tryptic fragment (Asp^{315}-Phe^{354}) is also identical with the amino acid sequence as reported (*5*), except for Cys^{351} and Leu^{353}, which were not identified. It has been suggested that the target for ADP-ribosylation by pertussis toxin is an asparagine residue corresponding to position 350 (*10*). However, the cDNA sequence (Fig. 2) predicts an aspartic acid residue at position 350 in the primary translation product. Thus, a modified form of aspartic acid could be the substrate for pertussis toxin. Alternatively, Cys^{351}, which was not previously detected (*10*), could also be the site of ADP-ribosylation.

There are four amino acid differences between the predicted sequence and the reported sequence of the 23-kD tryptic fragment. They are conservative differences and cluster at the amino terminus. Amino acid sequence analysis resulted in identification of Lys^{24}, Glu^{28}, Asp^{30}, and Arg^{32}. The nucleic acid sequence predicts Gin^{24}, Asp^{28}, Glu^{30}, and Lys^{32}. It is possible that these differences do not arise from multiple transducin genes within an organism but instead represent polymorphisms in the different animals whose tissues were used to prepare transducin protein for sequence determination and poly(A)$^+$ RNA (polyadenylated RNA) for cloning. This argument is supported by the hybridization experiment shown in Fig. 3. Digestion of genomic DNA with Bam HI and hybridization with probes made from the NH_2-terminal, COOH-terminal, and complete coding regions of the cDNA give a pattern that is only consistent with the presence of a single gene corresponding to T_α.

The complete sequence of transducin allows us to compare it with other GTP-binding proteins. Similarities were found in the sequences of mammalian and yeast *ras*, the T_α subunit, and the elongation factors (EF-Tu and EF-1α). In each of these proteins GTP binding and hydrolysis are central to their function. Homologies between EF-Tu and *ras* have been previously noted (*11*). Sequence similarities between T_α and the other proteins are primarily clustered in two regions (Fig. 4). One region is at the NH_2-terminal end starting at Lys^{29} in T_α and extending through Lys^{70}. There is evidence to suggest that this region is involved in GTP hydrolysis in *ras*. Mutagenesis resulting in changes in amino acids in this region affect guanosine triphosphatase and oncogenic activity (*12*). A second region of homology is found toward the COOH-terminal end of the T_α subunit and includes the residues from Ala^{260} to Lys^{276}. This region may participate in GTP binding. The homologous region in all elongation factors includes an asparagine residue (Asn^{135} in EF-Tu) which has been shown by x-ray crystallographic analysis to form a hydrogen bond with the guanosine moiety of GDP (*13*). Furthermore, modification of Cys^{137} in EF-Tu eliminates nucleotide binding. In EF-Tu, this region forms part of a six-stranded β sheet structure common to many nucleotide-binding proteins (*14*).

There is evidence to suggest that the guanyl nucleotide binding site in T_α interacts with a region of the protein that is located between amino acids 177 to 208. Thus, for example, bound analogs of GTP block trypsin cleavage at Arg^{208} (*7*). Furthermore, the ADP ribosylation site at Arg^{178} is only recognized by cholera toxin when T_α binds nonhydrolyzable GTP analogs (*4*). Finally, ADP ribosylation at this site blocks the GTP hydrolysis activity of transducin.

A striking feature that is conserved between T_α and *ras* is the presence of a

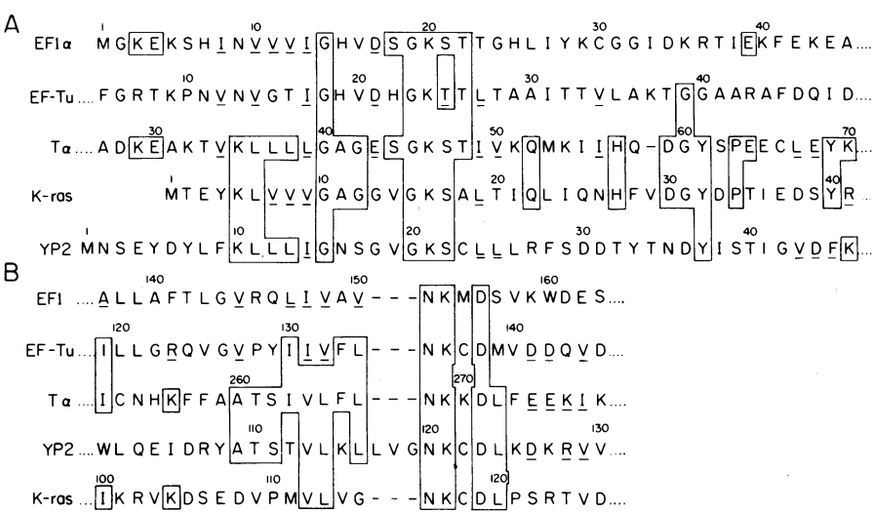

Fig. 4. Homologies of T_α to the protein sequences of translation elongation factors and *ras* oncogenes (*21*). Homologies were identified with the use of a computer homology matrix program (*22*) which determines the degree of identity found over an adjustable number of amino acids. (A) Homologies among regions predicted to play a role in guanine nucleotide hydrolysis. (B) Homologies among regions predicted to be involved in guanine nucleotide binding. Sequence identities to T_α are boxed and close functional homologies are underlined. Single letter abbreviations used for amino acids are: A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; and Y, tyrosine.

cysteine residue as the fourth amino acid from the carboxyl terminus. Both the α and the γ (*15*) subunits of transducin as well as 11 *ras* gene products that have been examined (*16*) have a cysteine in this position. This residue is acylated with lipid in *ras* and is important for *ras* function (*17*). Acylation could occur at Cys^{351} in T_α. Another possible site for acylation in T_α is on Gly^2. The amino terminus of T_α is blocked, and all proteins known to have NH_2-terminal myristic acid blocking groups have glycine as the NH_2-terminal amino acid (*18*).

The homologies found between *ras*, elongation factors, and T_α reflect the guanine nucleotide binding and hydrolytic activities that are necessary for an alternation between GDP- and GTP-bound conformations that determine the nature of the reversible association of these proteins with other macromolecules. The portions of *ras* and T_α that are not directly involved in nucleotide binding or hydrolysis may govern the specificity for interaction with different subcellular components. The availability of the intact cDNA clones makes it possible to overproduce T_α and to modify the gene product by mutagenesis. Reconstruction of the G protein–coupling system in vitro and in vivo will provide an experimental system that may allow us to understand in detail how these proteins function.

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