Species-specific Alternative Splice Mimicry at the Growth Hormone Receptor Locus Revealed by the Lineage of Retroelements during Primate Evolution

A NOVEL MECHANISM ACCOUNTING FOR PROTEIN DIVERSITY BETWEEN AND WITHIN SPECIES*

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In humans, growth hormone receptor (GHR) transcripts exist in two isoforms differing by the retention (GHRfl) or exclusion (GHRd3) of exon 3, whereas in mice GHRfl is solely expressed. This species-specific expression pattern is believed to result from an alternative splice event that, on the basis of conflicting data obtained in humans, has been considered to be tissue-, developmentally, and/or individual-specific. To decipher the molecular basis of this unusual trait, we isolated a 6.8-kilobase fragment spanning exon 3 from individuals expressing GHRfl. Sequence analysis revealed the existence of two 99% identical retroelements flanking this exon. Unexpectedly, individuals expressing GHRd3 displayed a 2.7-kilobase deletion involving exon 3, which most likely results from an ancestral homologous recombination between the two retroelements. The lineage of these retroelements during primate evolution revealed the species specificity of the GHRd3 allele. These findings led us to propose a model underlying the existence of the sole GHRfl allele in most species. Such a retrovirus-mediated alternative splice mimicry, which clears up several as yet unexplained phenomena (i.e. the above-mentioned expression data, the Mendelian inheritance of GHR expression patterns, and the deletion of nonconsecutive exons in growth hormone resistant patients), represents a novel physiological mechanism accounting for protein diversity between and within species.

There is a variety of well documented mechanisms underlying the complexity and the diversity of the structure and regulation of eukaryotic nuclear genes during evolution. Several of these mechanisms result from the presence of repetitive DNA sequences that form a substantial fraction of these genomes (1), as well as from the existence, in the great majority of genes coding for proteins, of exonic and intronic sequences (2). Such a genomic organization accounts for several kinds of DNA rearrangements (1, 3) and for mRNA splicing (4). The latter corresponds to the precise excision of introns from nascent transcripts followed by the ligation of exons. Alternative splicing of primary transcripts represents a critical step in the regulation of gene expression, generating different mature mRNAs and thus different proteins from one gene (5). This mechanism can be controlled in a cell type-specific manner, so that, depending on the nature and/or the developmental stages of the tissues examined, different mature mRNA species can be expressed; other alternative splice events appear to be constitutive, with different mRNA isoforms coexisting at constant ratios within the same cells (4).

The description of two different mature growth hormone receptor (GHR)1 transcripts is a particularly attractive example of an unusual phenomenon described as the result of an alternative splice event that, in humans, has been documented as being either constitutive or controlled in a cell type-specific manner (6–12). The GHR protein is an integral cell membrane molecule that, in humans, contains 638 residues (including a membrane signal peptide of 18 residues); it consists of an extracellular hormone-binding domain of 246 amino acids, a single transmembrane domain, and a cytoplasmic domain of 350 residues (13). Upon binding to the growth hormone, the GHR molecule can form homodimers (14) that are essential to receptor activation (15, 16), thereby mediating the well known biological effects of growth hormone. The critical importance of the receptor in the control of body growth was clearly demonstrated by the description of numerous GHR mutations in patients with Laron syndrome, a severe growth hormone-resistant short stature condition transmitted as an autosomal recessive trait (17).

The human GHR gene is a single copy gene that spans 90 kb of the 5p13-p12 chromosomal region (6, 18). It contains nine coding exons (numbered 2–10) and several untranslated exons: exon 2 codes for the signal peptide, exons 3–7 encode the extracellular domain, exon 8 codes the transmembrane domain, and exons 9 and 10 code the cytoplasmic domain (6). The existence of several GHR cDNA clones that diverge within the coding region was first reported by Godowski et al. (6). In one of these clones, the exon 3 sequence (consisting of 66 nucleotides) was missing, in keeping with an alternative splice event lead-

1 The abbreviations used are: GHR, growth hormone receptor; GHRfl, full-length GHR; GHRd3, GHR with exon 3 deleted; HERV, human endogenous retrovirus; LTR, long terminal repeat; MER, medium reiteration frequency sequence; kb, kilobase(s); PCR, polymerase chain reaction; iPCR, inverse PCR; bp, base pair(s).

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ing to either the retention or the exclusion of exon 3, corresponding to the full-length GHR isoform (GHRfl) or the exon 3-deleted isoform (GHRd3), respectively. Subsequent investigations have yielded contradictory results. Both isoforms have been detected in several human tissues, expressed either independently or simultaneously. In the very first studies, a tissue-specific expression pattern of GHRfl and GHRd3 was documented (7, 8), with GHRd3 mainly expressed in the placental villi (7). However, other studies rather indicated that the expression of these two GHR isoforms was specific for each individual; different tissues obtained from the same individual showed the same expression pattern (10, 11). This individual-specific expression pattern of GHRfl and GHRd3 was found to be maintained in long term cultures of fetal dermal fibroblasts (11). Nevertheless, a cross-sectional study of a large number of human fetal and postnatal tissues also suggested that the expression pattern of GHRfl and GHRd3 may be developmentally regulated (11). Another study showed that this alternative splice event resulted from an unusual genetic polymorphism that is transmitted as a Mendelian trait and that significantly alters splicing (12). Finally, the splicing of exon 3, whose functional consequences are poorly understood (8, 19), was also suggested to be species-specific, because in mice the GHRfl transcript is the only isoform detected (20).

To decipher the molecular basis of this unusual trait in humans, the GHR genomic sequences surrounding exon 3 were studied in individuals expressing GHRfl, GHRd3, or both isoforms. In addition, in an attempt to provide an explanation for such species differences in the expression of GHRd3 and GHRfl, similar studies were performed in various species.

**EXPERIMENTAL PROCEDURES**

**DNA and RNA Samples**—Human genomic DNA was isolated from blood leukocytes by standard procedures. DNA samples were obtained from 150 unrelated control individuals. To assess GHRfl and GHRd3 expression, total RNA was extracted from Epstein-Barr virus-transformed lymphocytes obtained in 11 of the 150 control individuals, using the RNeasyTM protocol (Qiagen GmbH). The genomic DNA samples of various primates including *Lemur catta* (n = 2), *Callitrichus* (n = 8), *Cebus* (n = 1), and *Macocebus* *mullotus* (n = 7) were kindly provided by Drs. Jacqueline Levilliers (Institut Pasteur, Paris) and Florence Richard (Institut Curie, Paris). African green monkey DNA was extracted from the COS-7 cell line. The other monkey DNAs (gibbon, orangutan, gorilla, and chimpanzee) were purchased from the European Collection of Cell Cultures.

**Reverse Transcript PCR**—The GHR transcripts were reverse-transcribed and subsequently amplified, as described (8). Amplified products were analyzed by electrophoresis on a 6% polyacrylamide gel stained with ethidium bromide. The expected distribution of the genotypes at the GHR-exon 3 locus was determined by means of the Hardy and Weinberg law (21), which takes into account the allele frequency of GHRfl and GHRd3 (see below) in our population sample.

**RESULTS**

**Cloning of a 6.8-kb Fragment Surrounding Exon 3 of the Human GHR Gene**—To test whether sequence differences in the exon 3-flanking introns (i.e., introns 2 and 3) of the human GHR gene might correlate with the exclusion or retention of exon 3 in GHR transcripts, we first amplified the exon 3-surrounding region of the genomic DNA from an individual expressing the full-length GHR transcripts only by means of iPCR. Indeed, the sequence of only 253 bp of the 3' end of intron 2 and 71 bp of the 5' extremity of intron 3 has so far been determined (12). These iPCR assays, performed on genomic DNA digested by various restriction enzymes, led to the isolation of a 6.8-kb fragment (Fig. 1A), which was subsequently sequenced (GenBankTM accession number AF155912). The identity of this DNA fragment as *bona fide* 5' and 3' adjacent introns of exon 3 was confirmed in two ways. First, we performed conventional PCR assays on the same DNA template with different sets of primers whose sequences were derived from the newly isolated sequence; as expected, the sequence of exon 3 was present in all these amplified products. Second, restriction enzyme maps of the PCR-amplified products surrounding exon 3 (Fig. 1A) were in agreement with those obtained from the analysis of the products generated through different iPCR assays.

**The Human GHR Exon 3 Is Flanked by Two Retroviral Long Terminal Repeat Fragments**—Complete sequence determination of this 6.8-kb fragment revealed the existence of two 251-bp repeated elements (Fig. 1A). These repeats flank exon 3, with the 5' and the 3' repeated elements located 577 bp upstream and 1821 bp downstream of the exon, respectively. The nature of these elements was subsequently determined by computer-assisted homology searches (RepeatMasker and RepBase Web sites); they were found to be composed of a 171-bp-long long terminal repeat (LTR) fragment from a human endogenous retrovirus which belongs to the HERV-P family (22), followed by a 80-bp fragment from a medium reiteration frequency MER4-type sequence (Fig. 1A) (23). The sequence of the two 251-bp-long copies (referred to as 5' repeat and 3' repeat) are 99% identical, differing in only three nucleotides at positions 14, 245, and 246 of the repeat. More precisely, in all the alleles studied (n = 24), the element located upstream from exon 3 carries a guanine at position 14 and a thymine at positions 245 and 246, whereas the element located downstream of the exon carries a guanine, a cytosine, and an adenine at these positions. Extensive analysis of the entire 6.8-kb fragment by means of BLAST-N and RepeatMasker programs revealed the existence of several other sequences of retroviral origin in the vicinity of the exon; as shown in Fig. 1A, these sequences are members of the MER family and of mammalian LTR transposons (23). In all the alleles studied (n = 24), we found an identical genomic organization of the exon 3-surrounding region.

The LTR sequence located upstream from exon 3 derives from the class I of the human endogenous retrovirus HERV-P.
Fig. 1. Genomic organization of the human GHR locus in the vicinity of exon 3. A, GHR exon 3 locus in an individual expressing full-length GHR transcripts. Exon 3 is shown as a black box. The LTR sequences originating from the human endogenous retrovirus HERV-P are indicated by an arrow (complete LTR sequence) or a rectangle (partial LTR sequence). MER elements and the mammalian LTR transposon element are indicated by ellipses and a square, respectively. The 5′- and 3′-251-bp repeated elements (indicated by 5′-R and 3′-R, respectively) are illustrated by the gray areas outlined by a rectangle (bottom). A partial restriction enzyme map of the region is given. Bgl II (B); Ban II (H); HindIII (B). The repeated element is flanked by two short direct repeats differing at a single base (CCAT (5′) CCAG), thereby indicating that this retroelement is actually a solitary LTR. The 3′-repeat found on GHRfl alleles and between sequences located upstream of both the GHRd3-associated retroelement and the 5′-repeat found on GHRfl alleles and between sequences located downstream of both the GHRd3-associated retroelement and the 3′-repeat found on GHRfl alleles. Restriction maps of these sequences are depicted on Fig. 1C. The single 251-bp element that persists on the deleted allele was found to be identical to the 3′-copy identified on GHRfl alleles (i.e. G, C, and A residues at positions 14, 245, and 246, respectively) (n = 24). This arrangement of sequences is precisely what would be expected if recombination between the 5′ and 3′ repeats of the GHRfl allele occurred to delete a 2716-bp fragment, thereby leaving behind a single LTR at the GHRd3 locus.

Distribution of GHRd3 and GHRfl in a Control Population Sample—To evaluate the allele frequencies of GHRd3 and GHRfl, we developed a simple multiplex PCR assay based on the use of three primers: one antisense primer (G3) located in exon 3, and primer set (G1 and G2), which brackets both the single LTR element of GHRd3 alleles and the two repeated elements of GHRfl (Fig. 2A). Under specific experimental conditions, primers G1 and G2 allowed the amplification of GHRd3 alleles only, whereas primers G1 and G3 amplified GHRfl alleles, thereby allowing the accurate discrimination of the three possible genotypes at this locus (i.e. heterozygous GHRfl/GHRfl, heterozygous GHRd3/GHRfl, and homozygous GHRfl/GHRfl). The control population sample consisting of 150 unrelated individuals was investigated using this genotyping assay. The distribution of genotypes, which is presented in Table 1, follows the Hardy-Weinberg equilibrium (χ2 test = 2.5 < 3.84), with allele frequencies for GHRd3 and GHRfl of 25 and 75%, respectively. In a smaller population (n = 11) in which both genomic DNA and total RNA samples were available for study, this PCR assay showed a perfect correlation between the geno-
G2, and G3 used in the multiplex PCR assay are indicated by arrowheads and d3 flannealing 60 °C, 30 s; and elongation 72 °C, 1 min 30 s), primers G1 and G2 allowed the amplification of GHRd3 alleles only, whereas primers G1 and G3 amplify GHRf1 alleles. The homozygous GHRf1, heterozygous GHRf1/GHRd3 and homozygous GHRd3 genotypes are denoted by fl, fl/d3, and d3, respectively.

FIG. 2. Genotyping assay at the GHR-exon 3 locus. A, schematic representation of the human GHRf1 region including exon 3 (black box) and the repeated elements (gray boxes). The GHRd3 allele contains a single copy of the repeat (gray box). The position and orientation of primers G1, G2, and G3 used in the multiplex PCR assay are indicated by arrowheads. B, under specific experimental conditions (i.e. denaturation 94 °C, 30 s; annealing 60 °C, 30 s; and elongation 72 °C, 1 min 30 s), primers G1 and G2 allowed the amplification of GHRd3 alleles only, whereas primers G1 and G3 amplify GHRf1 alleles. The homozygous GHRf1, heterozygous GHRf1/GHRd3 and homozygous GHRd3 genotypes are denoted by fl, fl/d3, and d3, respectively.

Distribution of the genotypes at the human GHR-exon 3 locus in a large population sample

| Genotype      | n  | %  |
|---------------|----|----|
| GHRf1/GHRf1   | 88 | 58 |
| GHRf1/GHRd3   | 49 | 33 |
| GHRd3/GHRd3   | 13 | 9  |
| Total         | 150| 100|

Phylogenetic Analyses at the GHR-Exon 3 Locus—To investigate the phylogeny of these retroelements on a time scale spanning primate evolution, we performed PCR amplifications on various primate genomic DNAs, using different sets of primers derived from the human genomic sequence spanning exon 3. The absence of a retroelement (HERV-P, MER-4, and/or mammalian LTR transposon sequences) from a species was confirmed, in all cases, by PCR amplification of the uninterrupted cellular target sequence. The retroviral sequences identified in the vicinity of exon 3, which are compiled in Table II, provide the following information. First, the two retroelements that closely flank exon 3 (i.e. MER49 and MaLR) are present in the hominoid lineage and in the genomes of Old World monkeys, whereas they are absent from the genomes of New World monkeys and great apes, respectively. Third, the absence of a retroelement (HERV-P, MER-4, and/or MaLR) are present in Old World monkeys and great apes, respectively. Second, the GHRd3 allele contains a single copy of the repeat identified in humans is present in all the documented species differences in the expression pattern of GHR isoforms.

It is well established that in humans GHR transcripts are present in two isoforms that differ by the retention or exclusion of exon 3, whereas in mice the GHRf1 isoform is solely expressed. We have demonstrated that in humans the GHRd3 isoform is actually transcribed from a GHR allele that carries a 2.7-kb genomic deletion spanning exon 3, as compared with GHR alleles expressing GHRf1 isoforms. More precisely, we observed the association of exon 3 with two flanking retroelements in the genomic DNA samples from individuals who solely express GHRf1, whereas DNA samples from individuals who express GHRd3 contain only a single retroelement without exon 3. These observations led us to assume that the 2.7-kb size difference documented between the GHRd3 and GHRf1 alleles is due to a deletion that occurred on an ancestral GHRf1 allele. As shown in the model depicted in Fig. 3, an intrachromosomal recombination event most likely accounts for the generation of a GHRd3 allele from a GHRf1 template. Interchromosomal recombination between misaligned GHRf1 alleles was put aside as the basis for the exon 3 deletion; indeed, such an event would also generate a reciprocal chromosome with an exon 3 duplication, this gene rearrangement having never been detected in the population tested. Sequence analysis of 24 deleted alleles supports the existence of a unique recombination breakpoint located within the first 13 bases of the 251-bp repeated element (Fig. 3). In this model, the excision of exon 3 and its flanking sequences results from a homologous recombination event between the two retroelements located on the same GHRf1 allele.

The identification of such an alternative splice mimicry clears up several as yet unexplained phenomena. First, depending on the different studies performed in humans since 1992 (7–12), the expression pattern of GHRf1 and GHRd3 has been considered to be tissue-, developmentally, and/or individual-specific; in the light of the above-described mechanism underlying GHRf1 and GHRd3 expression, such conflicting results are now easily reconcilable. Second, our results provide a rational explanation for the Mendelian mode of inheritance of GHRf1 and GHRd3 expression patterns (12). Third, these findings also provide a clear-cut explanation for the deletion of nonconsecutive exons involving exons 3, 5, and 6 in patients with Laron syndrome (6); in fact, the latter would rather be the product of a deletion of the consecutive exons 5 and 6 on a GHRd3 allele. However, the amplification of exon 3 in DNA samples from human tissues expressing the GHRd3 transcripts only (11, 12) appears not to be consistent with the discovery of such a frequent genomic deletion of this exon found in 75 of the 300 GHR alleles of our population sample.

To determine the extent to which other species are able to generate GHRd3 transcripts by means of a mechanism identi-
differing at only three nucleotide positions, which were used to identify involved in the recombination event. The two repeats are 99% identical, resulting in the genomic deletion of exon 3. Because the Hominina subtribe carry both the 5′ and 3′ repeats within the same species.

According to the studies performed on GHRf1 alleles.

| Taxa (prosimian)                      | Species                  | Solo LTR | MER49 | exon 3 | MaLR | 3′ repeat |
|---------------------------------------|--------------------------|----------|-------|--------|------|-----------|
| Strepsirhini (NWM)                    | Lepilemur                | –        | –     | +      | –    | –         |
| Haplorhini (NWM)                      | Callimico                | –        | –     | +      | –    | –         |
| Platyrhini (NWM)                      | Capuchin monkey          | –        | –     | +      | +    | –         |
| Catarhini (OWM)                       | African green monkey     | + (6.4%)| +     | +      | +    | –         |
| Cercopithecidae (OWM)                 | Rhesus monkey            | + (5.8%)| +     | +      | –    | –         |

% Percentage of sequence change between the solo-LTR element of the mentioned species and the corresponding LTR sequence found in humans.

According to the studies performed on GHRf1 alleles.

**Fig. 3.** Model for the origin of the genomic deletion of exon 3. Exon 3 is shown as a black box. Gray boxes denote the 5′ and 3′ repeats involved in the recombination event. The two repeats are 99% identical, differing at only three nucleotide positions, which were used to identify the location of the breakpoint (√).

**Fig. 4.** Schematic representation of the proposed phylogenetic model accounting for the structure of the GHR-exon 3 locus in various primate species. Exon 3 is indicated by a black box; the MER-type and MaLR proviral sequences are indicated by empty circles and boxes, respectively. The HERV-P provirus is presented in gray, with each arrow denoting an LTR sequence.
the analysis of DNA samples from a large number of unrelated gorillas and chimpanzees.

A model that accounts for this sequence of events during molecular evolution of the GHR locus is presented in Fig. 4. The proposed events include proviral insertions leading to the MER49 and MaLR sequences prior to the HERV-P proviral insertion upstream from exon 3, which occurred after the emergence of New World monkeys. In this model, the latter event is followed by (i) the generation of a HERV-P solo LTR through a homologous recombination event between the 5′ and 3′ LTRs of the proviral sequence, (ii) the partial duplication of the solo LTR within the 3′ flanking region of exon 3, after the divergence of Pongina and Hominina, and (iii) the homologous recombination between the two repeated elements, which occurred recently, at least in the human species, and led to the GHRd3 allele. The GHR gene exists in species from distinct orders, such as Primates, Carnivora, Cetartiodactyla, Scanden- tia and Rodentia (28). In mice, the GHRfl transcript is the only isoform detected (20), and remarkably, genomic DNA does not hybridize to HERV-P sequences, as judged by Southern blotting experiments (Ref. 24, and data not shown); this latter finding therefore further supports our molecular model inferring a key role of these sequences of retroviral origin in the genesis of GHRd3 transcripts. Such a species-specific GHR structural difference, which underlies the existence of the sole GHRfl allele in several species, relates to the evolutionary differences of the mechanisms by which the GHR gene gives rise to a soluble growth hormone-binding protein (29, 30), thereby making this gene a particularly interesting model to investigate its encoded isoforms through evolution.

The functional consequences of proviral integrations in mammalian genomes were first reported as interfering widely with gene expression when the cellular target sequence involves an exon (31), whereas it was generally believed that insertions into noncoding regions would have little or no effect on gene expression. This view, however, has been challenged by the identification of mammalian sequences of retroviral origin that are associated with a promoter activity (32–34) or that induce a modification of mRNA splicing (35, 36). In contrast with these situations, the present study reveals the existence of a retrovirus-mediated mechanism underlying the physiological expression, in humans, of two transcripts that differ by the skipping of a single coding exon. This as yet unknown phenomenon, which mimics alternative splicing and accounts for protein diversity between and within species, may represent one of the mechanisms underlying the expression of structurally related isoforms at other loci.

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