Gigantism and Acromegaly Due to Xq26 Microduplications and GPR101 Mutation


ABSTRACT

BACKGROUND
Increased secretion of growth hormone leads to gigantism in children and acromegaly in adults; the genetic causes of gigantism and acromegaly are poorly understood.

METHODS
We performed clinical and genetic studies of samples obtained from 43 patients with gigantism and then sequenced an implicated gene in samples from 248 patients with acromegaly.

RESULTS
We observed microduplication on chromosome Xq26.3 in samples from 13 patients with gigantism; of these samples, 4 were obtained from members of two unrelated kindreds, and 9 were from patients with sporadic cases. All the patients had disease onset during early childhood. Of the patients with gigantism who did not carry an Xq26.3 microduplication, none presented before the age of 5 years. Genomic characterization of the Xq26.3 region suggests that the microduplications are generated during chromosome replication and that they contain four protein-coding genes. Only one of these genes, GPR101, which encodes a G-protein–coupled receptor, was overexpressed in patients’ pituitary lesions. We identified a recurrent GPR101 mutation (p.E308D) in 11 of 248 patients with acromegaly, with the mutation found mostly in tumors. When the mutation was transfected into rat GH3 cells, it led to increased release of growth hormone and proliferation of growth hormone–producing cells.

CONCLUSIONS
We describe a pediatric disorder (which we have termed X-linked acrogigantism [X-LAG]) that is caused by an Xq26.3 genomic duplication and is characterized by early-onset gigantism resulting from an excess of growth hormone. Duplication of GPR101 probably causes X-LAG. We also found a recurrent mutation in GPR101 in some adults with acromegaly. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and others.)
SOMATIC GROWTH IS ORCHESTRATED BY A complex hormonal crosstalk involving the hypothalamus, pituitary, and peripheral tissues. Genetic disorders that affect this network can lead to increased secretion of growth hormone, which results in acromegaly. If the excess in growth hormone occurs before epiphyseal fusion, the result can be gigantism. Nonsyndromic gigantism is most frequently caused by pituitary adenomas occurring as familial isolated pituitary adenomas or sporadically, usually as a result of mutations in the gene encoding aryl hydrocarbon receptor–interacting protein (AIP). Other monogenic diseases can cause gigantism, but most of these conditions develop in adulthood in association with other tumors. In young children, somatic overgrowth that is due to an excess of growth hormone is rare, and the cause is unknown. Other syndromic genetic overgrowth conditions in children, such as the Sotos syndrome and the Simpson–Golabi–Behmel syndrome, are not associated with pituitary abnormalities.

We report a striking phenotype of gigantism that has an onset in early childhood and that is caused by an excess of growth hormone. The disorder is associated with heritable microduplications on chromosome Xq26.3. There are four genes in the duplicated stretch of DNA; one of these, GPR101, encodes an orphan G-protein–coupled receptor and is probably the gene that drives the phenotype in young children and the growth of sporadic growth hormone–producing adenomas in some patients with acromegaly.

METHODS

PATIENTS

We analyzed samples obtained from 43 patients with gigantism who had hypersecretion of growth hormone, evidence of an anterior pituitary lesion on magnetic resonance imaging, a height on country-specific growth charts of either more than the 97th percentile or more than 2 SD above the mean height for age, and negative test results for mutations or deletions in genes associated with pituitary adenomas. Details with respect to one family with this syndrome and two patients with sporadic disease have been described previously.

GENETIC ANALYSES

We sequenced the four genes in the duplicated region on chromosome Xq26.3 in 259 germline and tumor DNA samples that were obtained from 248 patients with sporadic acromegaly (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We sequenced GPR101 and performed array comparative genomic hybridization (aCGH) on germline DNA in samples obtained from 13 families with familial isolated pituitary adenomas without AIP mutations. We used quantitative reverse-transcriptase–polymerase-chain-reaction (qRT-PCR) assays to measure the expression levels of duplicated genes in both leukocytes and pituitary tumors. We performed comparative protein-structure modeling on GPR101 using Modeller software, version 9.13. We determined the level of growth hormone and cyclic AMP (cAMP) and the rate of cellular proliferation after transient overexpression of each of the four implicated genes in GH3 cells obtained from rat pituitary tumors.

STUDY OVERSIGHT

The institutional review board at each of the participating institutions approved our studies. We studied the anonymized samples from international acromegaly cohorts with approval from the National Institutes of Health Intramural Office for Human Research Protections. Written informed consent was obtained from all adult patients and parents or guardians of children with early-onset gigantism.

RESULTS

CLINICAL PRESENTATION

The clinical and biochemical characteristics of the 43 patients who had nonsyndromic gigantism without abnormalities in genes associated with pituitary tumors are presented in Table 1. Genetic analyses delineated two phenotypes: an early-childhood form of gigantism with a typical onset in late infancy (Fig. 1) and a second form with a typical onset in adolescence.

IDENTIFICATION OF Xq26.3 MICROduplication

We detected microduplications on chromosome Xq26.3 in samples obtained from patients with the early-childhood form of gigantism (Fig. 2, and Fig. S1, S2, and S3 in the Supplementary Appendix). Nine of the 13 patients with an Xq26.3 microduplication and the 1 probable carrier (an affected mother with gigantism) were female and were of normal size at birth. All the patients grew rapidly during infancy, attaining a median
height score of +3.8 SD at diagnosis (median age, 36 months). At the time of diagnosis, they showed marked overall somatic growth, with elevated weight and an enlarged head circumference (median, 51.2 cm). The onset of accelerated growth and the onset of accelerated weight gain usually coincided but were not always synchronous (Fig. 1, and Fig. S4 in the Supplementary Appendix). As compared with patients who did not have an Xq26.3 microduplication, those with the microduplication had an earlier median age at the onset of abnormal growth (12 months vs. 16 years), an increased acceleration in height, and elevated levels of insulin-like growth factor 1 and prolactin (Table 1). We did not observe precocious puberty in the microduplication carriers. Levels of peripheral growth hormone–releasing hormone did not suggest ectopic secretion of this hormone, and nuclear imaging scans were negative for other tumors.

Of the 13 patients who underwent surgery, 10 had pituitary macroadenomas alone (median maximum diameter, 16 mm), and 3 patients had pituitary hyperplasia, with or without an identified adenoma (Fig. 3H). In all the patients, hormonal control was not achieved with medical therapy alone. Such control required either radical or repeated neurosurgery alone (in 4 patients) or in combination with the administration of the growth hormone receptor antagonist pegvisomant (in 3 patients) or radiotherapy (in 2 patients). Seven patients had permanent hypopituitarism at the time of this study.

The common duplicated genomic segment was approximately 500 kb in length, from position 135,627,637 to 136,118,269 (GRCh37/hg19).

Table 1. Clinical Characteristics of 43 Patients with Gigantism with and without Xq26.3 Microduplications.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Xq26.3 Microduplication (N = 14)</th>
<th>No Xq26.3 Microduplication (N = 29)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex — no. (%)</td>
<td>10 (71)</td>
<td>7 (24)</td>
<td>0.007</td>
</tr>
<tr>
<td>Median age at onset of rapid growth (range) — yr</td>
<td>1.0 (0.5 to 2.0)</td>
<td>16.0 (5.0 to 18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median age at diagnosis (range) — yr</td>
<td>3 (1 to 22)</td>
<td>21 (5 to 34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median height at diagnosis (range) — cm</td>
<td>116 (99 to 175)</td>
<td>187 (171 to 209)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median standard-deviation score for height at diagnosis (range)</td>
<td>+3.8 (+1.9 to +7.1)</td>
<td>+3.3 (+2.1 to +5.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Elevated levels of growth hormone and insulin-like growth factor 1 at diagnosis — no. (%)</td>
<td>14 (100)</td>
<td>29 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>No suppression of growth hormone during oral glucose-tolerance test — no. (%)</td>
<td>14 (100)</td>
<td>29 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Median factor increase in insulin-like growth factor 1 at diagnosis (range) — multiple of ULN</td>
<td>4.4 (2.4 to 5.2)</td>
<td>2.1 (1.4 to 5.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Elevated prolactin level at diagnosis — no. (%)</td>
<td>13 (93)</td>
<td>6 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median maximum tumor diameter (range) — cm</td>
<td>16 (10 to 39)</td>
<td>20 (9 to 41)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

| Adenoma or hyperplasia — no. (%)†                 | 2 (14)                          | 0                                 |
| Adenoma only                                       | 10 (71)                         | 29 (100)                          | —       |
| Hyperplasia only                                   | 1 (7)                           | 0                                 |
| Type of syndrome — no. (%)                         | 9 (64)                          | 29 (100)                          | —       |
| Sporadic                                           | 5 (36)‡                         | 0                                 |
| Familial                                           | 9/11 (82)                       | 29/29 (100)                       | —       |

* ULN denotes upper limit of the normal range.
† The presence of hyperplasia or adenoma could not be determined in one patient who did not undergo surgery.
‡ In one patient with the familial syndrome, pituitary gigantism was diagnosed in the mother and son at the same visit, when the son was 8 years of age and the mother was 22 years of age. The mother had had tall stature and acromegalic features since childhood for which she had not been referred for medical attention. The clinical data for the mother, for whom DNA was not available, are included.
Gigantism and Acromegaly Due to Xq26.3 Microduplications

(Fig. 2). One patient had a complex genomic rearrangement, with two duplicated segments that were separated by a short region of normal genomic sequence. No other patterns of duplication or deletion or homozygosity were shared among the affected patients. One family with familial isolated pituitary adenomas included an affected mother and two affected sons (who have been described previously\(^8\)) with the same Xq26.3 microduplication; the unaffected father did not have the duplication. In another family with this condition, the mother had childhood-onset gigantism and a histologically confirmed pituitary macroadenoma but had died of complications of hypopituitarism. She had two children: the son carried the Xq26.3 microduplication and had childhood-onset gigantism (Patient F2A), and the healthy daughter did not have the duplication. The most parsimonious explanation is that the son inherited the X-linked disease from his carrier mother. Hence, Xq26.3 microduplications can be considered to be a new pathogenic explanation in certain kindreds with familial isolated pituitary adenomas that have acrogigantism without AIP mutations.

![Figure 1 (facing page). Familial and Sporadic Cases of Gigantism and Male and Female Growth Patterns Due to the Xq26.3 Microduplications.](image)

Panel A shows Patient F1C, who has familial gigantism, at the age of 3 years. His growth chart up to 24 months of age shows the rapid acceleration in weight, although the acceleration in height did not begin until after his second birthday (Fig. S4 in the Supplementary Appendix). Panel B shows an unaffected mother and her daughter (Patient S6), who has sporadic gigantism and whose height was 120 cm at the age of 3 years. A growth chart for Patient S4 (Panel C), another girl with sporadic gigantism, illustrates the typical early increase in height and weight seen in patients with Xq26.3 microduplications, starting at the age of 6 months in this child.

![Figure 2. Summary of the Genomic Gains on Chromosome Xq26.3.](image)

Shown are 10 different Xq26.3 microduplications, as seen on array comparative genomic hybridization, that were found in 12 patients with familial or sporadic gigantism (with the inheritance pattern indicated at right). Duplicated genomic segments (red) and nonduplicated segments (white) are shown. The genomic coordinates are provided at base-pair resolution on the x axis. The two smallest regions of overlap (SRO), SRO1 and SRO2, are identified, showing the genomic contents in the corresponding regions. The symbols next to the gene names represent the structure of the genes, with vertical lines representing exons and horizontal lines (with or without arrows) representing introns. Adapted from the UCSC Genes track in the UCSC Genome Browser.
Figure 3. Imaging and Histopathological Findings in Patients with Xq26.3 Microduplications.

Panels A through D show progressive changes from normal pituitary tissue (Panel A) to adenoma (Panel D), as indicated by reticulin staining of the pituitary gland in Patient F1C. In Panel A, normal pituitary gives way to the expanded hyperplastic acini (Panel B), and in Panel C, areas of transformation are evident (circled) with enlarged, hyperplastic, confluent acini that are caused by breakdown of reticulin fibers and that lead to adenoma (Panel D) with disruption of the reticulin fiber network. Increased GPR101 expression was observed in five tested patients with Xq26 microduplications, whereas there is little if any expression in normal pituitary tissue or growth hormone–producing tumors without Xq26.3 microduplications or GPR101 defects (see also Fig. S7 in the Supplementary Appendix); an example is shown here (Panels E through G) from Patient S3. When the staining of growth hormone (Panel E) and the staining of GPR101 (Panel F) are merged, GPR101 seems to be expressed in some of the growth hormone–secreting cells (Panel G, arrows) but not in all such cells. Nuclei (blue) were stained with DAPI. Panel H shows a sagittal view of a macroadenoma on magnetic resonance imaging of Patient S5 with the Xq26.3 microduplication.
FURTHER CHARACTERIZATION OF Xq26.3 MICRODUPPLICATION

Using high-definition analysis of the critical duplicated region, we analyzed 10 distinct genomic duplications in 12 patients, including 4 patients with the familial form of the disease and 8 patients with the sporadic form (Fig. S1 and S3 in the Supplementary Appendix). On genomewide aCGH, these mutations appeared to be simple duplications. However, using high-resolution aCGH, long-range PCR, and Sanger sequencing of the breakpoints, we found various underlying genomic complexities (Fig. S3 in the Supplementary Appendix).

All sporadic Xq26.3 duplications were nonrecurring; the boundaries of the duplicated segment were unique to each patient. On both aCGH and breakpoint PCR assays, samples obtained from unaffected parents and siblings of patients with sporadic disease showed negative results, documenting the microduplication as a new mutation (Fig. S3A and S5A in the Supplementary Appendix). The same duplication was transmitted from an affected mother (Patient F1A) to her affected offspring, Patients F1B and F1C (Fig. 2, and Fig. S3 and S5 in the Supplementary Appendix).

The duplicated genomic regions that were shared by all affected persons consisted of the two smallest regions of overlap (SRO), which were designated as SRO1 and SRO2 (Fig. 2). SRO1 (chromosomal position, 135,627,637 to 135,986,830; hg19) encompassed three genes in the Online Mendelian Inheritance in Man (OMIM) database: CD40LG (OMIM number, 300386), ARHGEF6 (OMIM number, 300267), and RBMX (OMIM number, 300199), whereas SRO2 (chromosomal position, 136,045,310 to 136,118,269; hg19) included GPR101 (OMIM number, 300393) (Fig. 2).

INVESTIGATION OF CANDIDATE GENES

Sequencing of each of the four genes in the 43 patients with gigantism did not reveal any single-nucleotide variants of likely pathogenicity. A quantitative RT-PCR assay of pituitary tumor RNA from 2 patients with Xq26.3 microduplications suggested that CD40LG was not expressed in the pituitary tumors. Neither ARHGEF6 nor RBMX showed up-regulated expression in the pituitary tumors of 2 patients with the duplication (Fig. 4). In contrast, the expression of GPR101 in the pituitaries of the children carrying an Xq26.3 duplication was increased by a factor as high as 1000, as compared with unaffected pituitary tissue and pituitary tumors from persons who tested negative for microduplications (Fig. 4A). This result was confirmed at the protein level by increased immunostaining for GPR101 in pituitary tumors from patients with Xq26.3 duplications (Fig. 3G, and Fig. S7 in the Supplementary Appendix). Experimental overexpression of ARHGEF6, RBMX, and GPR101 alone in the rat GH3 cell line did not significantly increase either cell proliferation or the secretion of growth hormone (Fig. 4D and 4E, and Fig. S8 in the Supplementary Appendix). Nonmutated GPR101 in combination with ARHGEF6, RBMX, or both modestly increased cell proliferation but not the secretion of growth hormone (Fig. S8 in the Supplementary Appendix).

The X-chromosome–inactivation pattern was random in the female patients with sporadic disease and skewed in Patient F1A, who had familial disease; CpG islands were identified in silico only in RBMX and GPR101 (Fig. S9 and S10 in the Supplementary Appendix).

IDENTIFICATION OF p.E308D MUTATION IN GPR101

In a series of 248 patients with sporadic acromegaly, none carried a microduplication at Xq26.3. However, 11 patients had a c.924G→C substitution (p.E308D) in GPR101, which was not found in 7600 control samples obtained from public databases (Tables S1 and S2 in the Supplementary Appendix). Of the 11 mutation carriers, 3 appeared to carry a constitutive mutation, which was detected in DNA from peripheral blood mononuclear cells (PBMCs). We detected the mutation in the tumor DNA in the remaining 8 patients (Fig. 5A). In one patient, we determined that the mutation was a de novo somatic mutation — that is, the GPR101 mutation occurred only in the tumor DNA sequence and not in the PBMC sequence (Fig. 5B). None of the 13 families with familial isolated pituitary adenomas carried the p.E308D mutation in GPR101.

GPR101 encodes an orphan G-protein–coupled receptor that is highly expressed in rodent hypothalamus (Fig. S11 and S12 in the Supplementary Appendix) and is predicted to couple to the stimulatory G protein (Gs), a potent activator of adenyl cyclase. A model of human GPR101 in complex with a Gs heterotrimer shows the physical relationship between the p.E308D amino acid change and the activating p.A397K change, a mutation that has been described previously. The two amino acids, which are predicted to be
Figure 4. Expression of GPR101 in Pituitary Tissue from Children with Xq26.3 Microduplications.

The expression of GPR101 in pituitary tissue from children carrying Xq26.3 microduplications was increased by a factor as high as 1000, as compared with the expression in unaffected pituitary tissue (in five samples [NP1 through NP5] obtained on autopsy) and in pituitary tumors from two patients with sporadic acromegaly (GH1 and GH2) who tested negative for the microduplication (Panel A). These findings, which were obtained on quantitative reverse-transcriptase–polymerase-chain-reaction (qRT-PCR) assay and normalized by a housekeeping gene, contrast with those for two other genes, ARHGEF6 (Panel B) and RBMX (Panel C), in the duplicated stretch of DNA; neither of these two genes showed up-regulated expression. Also shown are cell proliferation (Panel D), growth hormone secretion (Panel E), and activation of DNA sequences called cyclic AMP response elements (CRE) (Panel F) in rat GH3 cells transfected with mutant (p.E308D and p.A397K) and nonmutant GPR101 constructs. Values for cells transfected with empty (control) vector were set at 1. Also shown are values for untreated cells (vehicle) and forskolin (which increases CRE activation). Data are expressed as the mean results of three to five independent experiments, each of which was performed in triplicate. The T bars indicate standard deviations. One asterisk denotes P<0.05, two asterisks P<0.01, and three asterisks P<0.001.
Figure 5. Effect of the p.E308D Mutation in GPR101 in 11 Patients with Sporadic Acromegaly. Panel A shows the sequence for GPR101 in growth hormone–producing pituitary tumors obtained from patients with sporadic acromegaly, as compared with normal tissue. Panel B shows results for a patient with a somatic mutation, which was determined by the presence of the mutation in the GPR101 sequence of DNA in the tumor sample but not in the sequence in peripheral-blood mononuclear cells. None of the 13 families with familial isolated pituitary adenomas carried the p.E308D mutation in GPR101. Panel C shows a structural model of GPR101 bearing the p.E308D mutation. Residue A397 is located at the cytosolic end of transmembrane (TM) 6 of GPR101. The mutated D308 residue and the nonmutated A397 residue are shown in space-filling representation and colored according to elements, with carbon atoms in gray, oxygen atoms in red, and nitrogen atoms in blue. The backbone of the receptor and the G protein heterotrimer is schematically represented as a ribbon, with the receptor shown with a spectrum of colors that ranges from red at the N-terminal to purple at the C-terminal; the α, β, and γ subunits of the G protein are in gray, blue, and pink, respectively. The cytosolic ends of TM 5 and TM 6 and intracellular loop (IL) 3, which connects them, are indicated by labels. The blue arrows show directions of the β-sheet domains of the β subunit of the G protein.
affected by the mutations, are on the cytosolic side of the receptor (Fig. 5C). The E308 residue is located in the long intracellular loop 3, which connects transmembrane domains 5 and 6.

Overexpression of the p.E308D and p.A397K mutants, but not of nonmutant GPR101, significantly increased cell proliferation and secretion of growth hormone in rat GH3 cells (Fig. 4D and 4E). As in the construct containing the nonmutant receptor, the two mutant constructs resulted in increased cAMP signaling in GH3 cells in an in vitro reporter assay, both at baseline and in the presence of 10 μM forskolin, a direct stimulator of adenyl cyclase (Fig. 4F).

**Discussion**

Several lines of evidence support the identification of a new pituitary gigantism syndrome in young children carrying microduplications on chromosome Xq26.3, a disorder that is probably caused by GPR101 overexpression. We propose that this syndrome be called X-linked acrogigantism (X-LAG). First, we did not find disruption of Xq26.3 in patients with later-onset gigantism (Table 1). Second, the finding that patients with other conditions had different duplications within the same region narrowed our focus to the smallest region of overlap. A duplication encompassing CD40LG and ARHGEF6 but not RBMX and GPR101 occurred in a family with low birth weight, intellectual disability, and craniofacial abnormalities, which suggests that duplications with the exclusion of RBMX and GPR101 do not lead to gigantism. Third, short stature has been reported in several patients with deletions in this region, which suggests that the absence of these genes may lead to the opposite phenotype (Table S4 in the Supplementary Appendix). Other investigators have described at least 15 additional patients with the same phenotype of early-onset growth who may be good candidates for a diagnosis of X-LAG (Table S3 in the Supplementary Appendix).

The breakpoint features of Xq26.3 duplications suggest that they were generated by means of a replication-based mechanism that underlies the genesis of other copy-number variants (CNVs) and the pathogenesis of other genomic disorders.

The cytogenetic data narrowed the smallest region of overlap to a segment spanning CD40LG, ARHGEF6, RBMX, GPR101, one microRNA (miR-934), and a small nucleolar RNA (SNORD61) of unknown function. We did not detect CD40LG expression in the pituitary tissues from our patients (Fig. 4). Messenger RNA for ARHGEF6 and RBMX was expressed to a similar degree in affected and unaffected tissues from duplication carriers. Of all the genes and the noncoding RNAs in the duplicated segment, only GPR101 had markedly increased expression in the pituitary tumors from the duplication carriers (Fig. 4).

GPR101 is an orphan G-protein–coupled receptor that is strongly expressed in the hypothalamus in rodents (Fig. S11 and S12 in the Supplementary Appendix). It was recently shown that a fragment of the gonadotropin-releasing hormone could be a ligand for this receptor. The GPR101 protein may also play a role in hypothalamic control of energy homeostasis. The effect of a mutation (p.A397K) that is predicted to activate GPR101 when tested in vitro and in mice supports such a role. The pituitary-specific overexpression of GPR101 may be due to a gene-dose effect (as described in many genomic disorders) or to an unknown promoter sequence created by chromosomal rearrangement, although we did not identify any putative new promoter, or to perturbed chromatin regulation due to the genomic structural alteration from duplication CNVs.

On the basis of our data from transfection experiments, we cannot rule out a modest contribution of RBMX and ARHGEF6 coexpression to cell proliferation. However, unlike GPR101, neither ARHGEF6 nor RBMX was overexpressed in the pituitary tumors from children with microduplications.

Our studies of sporadic acromegaly provide further support for a role of GPR101 in X-LAG. We found a recurrent GPR101 mutation, p.E308D, in 4.4% of DNA in tumor samples and in 1.9% of DNA in PBMC samples obtained from patients with isolated acromegaly. In at least one patient, the mutation was present only in the tumor DNA. We did not identify GPR101 mutations in families with familial isolated pituitary adenomas. A model of human GPR101 in complex with a Gs heterotrimer showed that both the p.E308D mutation and the previously described p.A397K mutation are on the cytosolic side of the receptor that interacts with heterotrimeric G proteins. Residue E308 is located in a remarkably long intracellular loop, which connects two transmembrane domains. But in the absence of a model template for the GPR101 intracellular loop in which E308 resides, it is difficult to estimate the structural
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