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Report

Mutations in the *DLG3* Gene Cause Nonsyndromic X-Linked Mental Retardation

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We have identified truncating mutations in the human *DLG3* (neuroendocrine dlg) gene in 4 of 329 families with moderate to severe X-linked mental retardation. *DLG3* encodes synapse-associated protein 102 (SAP102), a member of the membrane-associated guanylate kinase protein family. Neuronal SAP102 is expressed during early brain development and is localized to the postsynaptic density of excitatory synapses. It is composed of three amino-terminal PDZ domains, an src homology domain, and a carboxyl-terminal guanylate kinase domain. The PDZ domains interact directly with the NR2 subunits of the NMDA glutamate receptor and with other proteins responsible for NMDA receptor localization, immobilization, and signaling. The mutations identified in this study all introduce premature stop codons within or before the third PDZ domain, and it is likely that this impairs the ability of SAP102 to interact with the NMDA receptor and/or other proteins involved in downstream NMDA receptor signaling pathways. NMDA receptors have been implicated in the induction of certain forms of synaptic plasticity, such as long-term potentiation and long-term depression, and these changes in synaptic efficacy have been proposed as neural mechanisms underlying memory and learning. The disruption of NMDA receptor targeting or signaling, as a result of the loss of SAP102, may lead to altered synaptic plasticity and may explain the intellectual impairment observed in individuals with *DLG3* mutations.

X-linked mental retardation (XLMR) is a heterogeneous disorder that is defined as either nonsyndromic (when cognitive impairment is the sole definable clinical feature) or syndromic (when additional dysmorphic, neurological, and/or metabolic features accompany the mental deficit). To date, mutations in the following X-linked genes have been associated with a nonsyndromic mental retardation phenotype, although some of these genes are also associated with a specific syndromic diagnosis: *FMR2, PAK3, OPHN1, GDI, IL1RAPL1, RSK2, ATRX, ARHGEF6, MECP2, TM4SF2, SLC6A8, FACL4, ARX, AGTR2,* and *PQBP1* (Gecz et al. 1996; Gu et al. 1996; Allen et al. 1998; Billuart et al. 1998; D'Adamo et al. 1998; Carrie et al. 1999; Merienne et al. 1999; Guerrini et al. 2000; Kutsche et al. 2000; Orrico et al. 2000; Zemni et al. 2000; Couvert et al. 2001; Hahn et al. 2002; Meloni et al. 2002; Stromme et al. 2002; Vervoort et al. 2002; Kalscheuer et al. 2003). All the genes identified to date are rare causes of XLMR—since only a small number of families have been found to carry mutations

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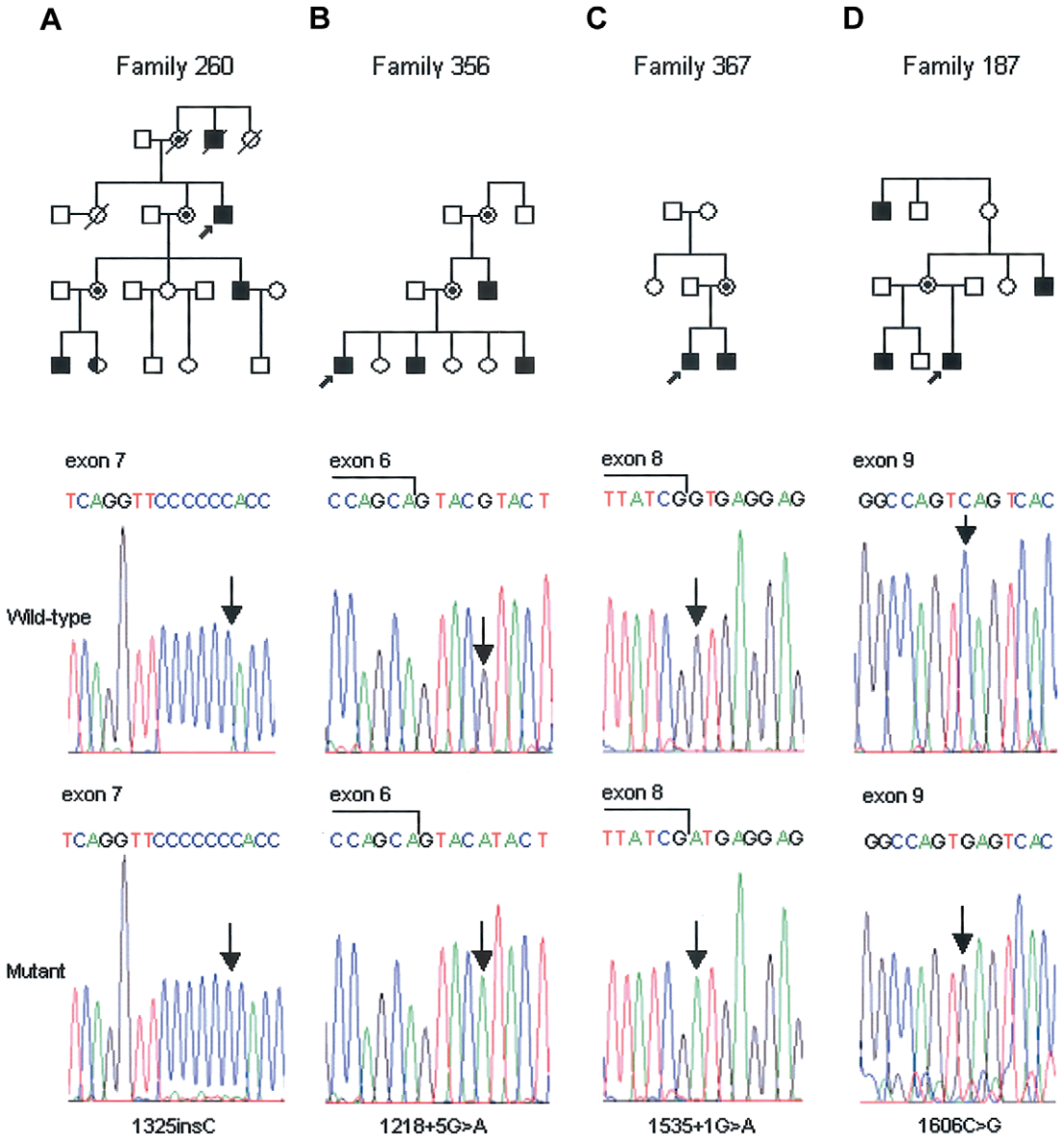

Figure 1 Mutations identified in the *DLG3* gene. The sequence chromatogram of the affected proband (*arrow*) is shown below the wild-type sequence. The respective pedigrees are presented above the chromatograms. *A,* The 1325insC mutation, identified in four affected males, three obligate carrier females, and one mildly affected female. *B,* The 1218+5G→A mutation, detected in two of the affected brothers. Other family members were unavailable for sampling. *C,* The 1535+1G→A mutation, identified in two affected brothers and their mother. The mutation was absent in the sister and mother of the carrier female. *D,* The 1606C→G mutation, identified in two affected half brothers and their mother. Other samples were unavailable.

in the same X-linked gene—and there remains a large number of families with XLMR in which the causative mutation has not been identified yet. To account for the remaining unresolved families with XLMR, it has been estimated that as many as 75 additional genes on the X chromosome remain to be assigned to a mental retardation phenotype (Ropers et al. 2003). This degree of genetic heterogeneity has hampered the identification of novel genes, since linkage information from different families cannot be pooled easily to refine the disease locus on the X chromosome. Consequently, in many families, the refined loci contain a large number of candidate genes to screen for the presence of a causative mutation. To address this problem, we have performed automated high-throughput mutation detection to search systematically for novel genes in families with XLMR. The families with the smallest linkage intervals have been prioritized for analysis, and each gene within

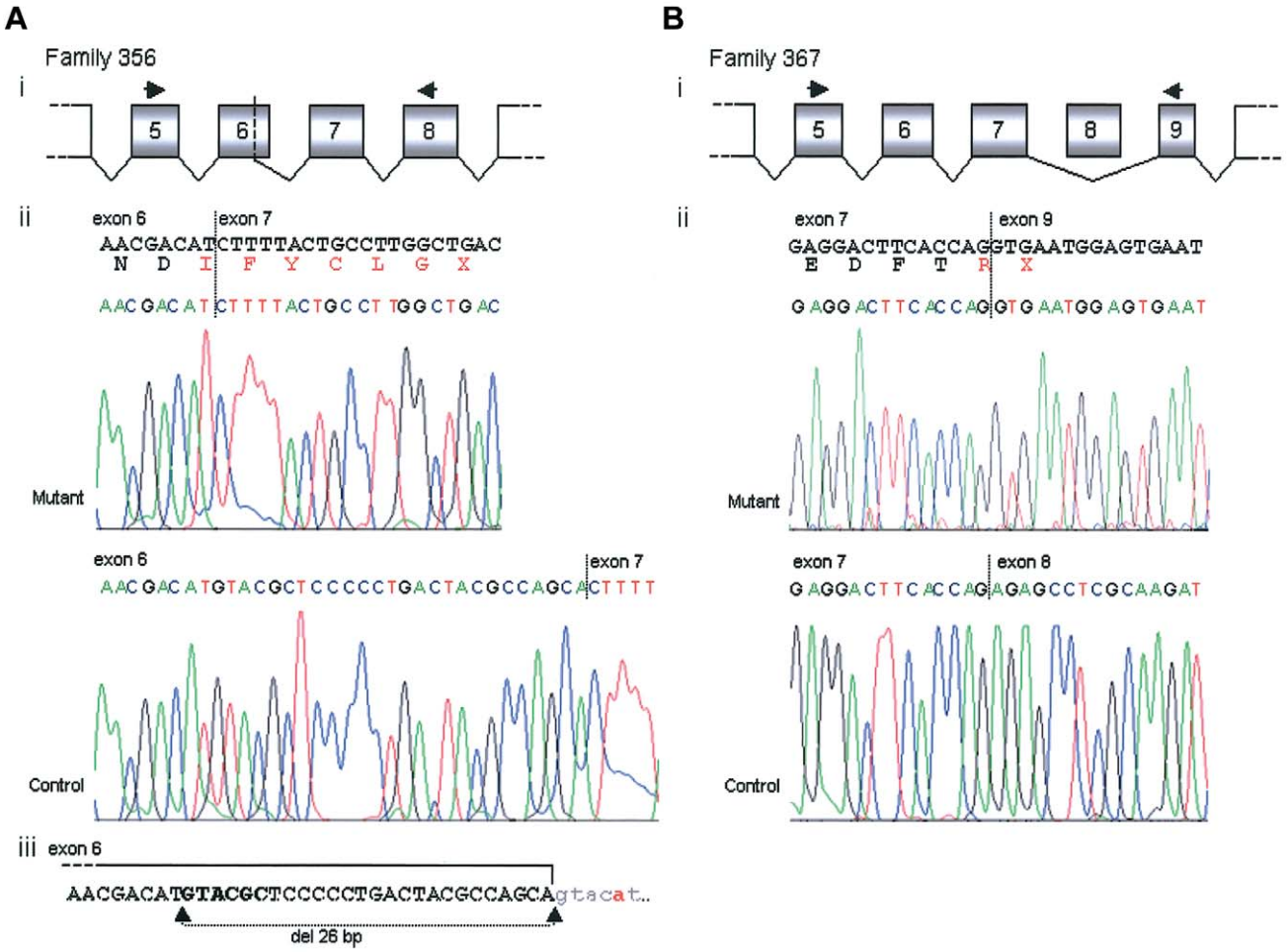

Figure 2 Sequence analysis of *DLG3*. *A,* cDNA analysis of the 1218+5G→A mutation in a lymphoblastoid cell line from the proband of family 356. *A.i,* Schematic representation of *DLG3* exons 5–8. The dashed line indicates the position of the abnormal cryptic splice site. *A.ii,* Sequence chromatogram of amplified cDNA with the use of primers from *DLG3* exons 5 and 8 from mutant and control cell lines. The wild-type and mutant amino acid residues are shown in black and red, respectively. *A.iii,* Position of cryptic splice-donor site (*bold*) identified in exon 6. The 26-nt deletion due to abnormal splicing is indicated. The position of the 1218+5G→A mutation is indicated in red. *B,* cDNA analysis of the 1535+1G→A mutation in a lymphoblastoid cell line from the proband of family 367. *Bi,* Schematic representation of *DLG3* exons 5–9, demonstrating the abnormal splicing removal of exon 8. *Bii,* Sequence chromatogram of amplified cDNA performed by use of primers from *DLG3* exons 5 and 9 from mutant and control cell lines. The wild-type and mutant amino acid residues are shown in black and red, respectively.

the refined interval was screened for mutations by DNA sequencing. In the present study, we report the analysis of a 2-Mb region in Xq13 and the identification of truncating mutations in the human *DLG3* gene (MIM 300189; GenBank accession number NM_021120) in four unrelated families with XLMR.

Families with a history of at least two males with significant intellectual impairment were recruited for the study ($n = 329$). All families were examined by a clinical geneticist and were excluded from further study if there was a known diagnosis, male-to-male transmission, an abnormal G-banded karyotype within the past 5 years, or an expansion in the fragile-X disease range detected in an affected male. In appropriate families, haplotype analysis was performed in-house, with the use of 48 microsatellite markers distributed along the X chromosome at 5-cM resolution. This excluded areas of the X chromosome from further analysis in these families. In some families, haplotype analysis was performed externally, and the positions of the refined loci were provided by the collaborating institutions. From this cohort, 11 families were analyzed in detail for mutations in novel genes in the 2-Mb region of Xq13 described in this study. Where families contained only affected sib pairs or where insufficient samples were available for analysis, no haplotype analysis was performed. In these families

($n = 318$), sequencing was performed to search for additional mutations only after a gene of interest had been identified in the initial screen.

The locus responsible for disease in family 312 mapped to a 2-Mb region in Xq13, bound by markers DXS8111 and DXS559, and contained 26 genes. Each exon from these genes was sequenced in the proband from this family and in one affected male from 10 additional families with evidence of linkage overlapping Xq13. A single-nucleotide insertion, 1325insC, was identified in the human gene *DLG3*, also known as "discs large homolog 3" (neuroendocrine dlg, *Drosophila*), in family 260 (fig. 1*A*). In this family, mental retardation mapped to a 43-Mb interval from Xp11.23 to Xq21.31, which included the Xq13 genes under investigation. The *DLG3* gene contains 19 exons and encodes synapse-associated protein 102 (SAP102), a member of the membrane-associated guanylate kinase (MAGUK) protein family (Muller et al. 1996; Makino et al. 1997). MAGUK proteins are important regulators of epithelial polarity and are known to play a major role in the organization of receptors and in downstream signaling pathways within the synapse. The frameshift mutation in family 260 is predicted to introduce a stop codon at position 377, removing 54% of the normally translated protein. The mutation was shown to segregate with the disease in four affected males and three obligate carrier females (fig. 1*A*).

Sequence analysis of *DLG3* was extended to the remaining 318 families in the study. Three additional families harboring likely disease-causing mutations were identified. In family 356, a putative splice-donor mutation was identified in intron 6 (1218+5G→A) (fig. 1*B*). Sequence analysis of *DLG3* cDNA, prepared from a lymphoblastoid cell line from the proband and amplified with PCR primers sited within exons 5 and 8, identified a predominant transcript that lacked the terminal 26 nt from exon 6, introducing a frameshift and a premature stop codon at position 326. This transcript appears to use preferentially a cryptic splice-donor site located within exon 6, rather than the mutated donor site (fig. 2*A*). This mutation was identified in two affected brothers, but relevant samples were not available to track the segregation of the variant further in this family.

In family 367, a splice-donor mutation was identified in intron 8 (1535+1G→A) (fig. 1*C*). Sequence analysis of *DLG3* cDNA, prepared from a lymphoblastoid cell line from the proband and amplified with PCR primers sited within exons 5 and 9, identified an abnormal transcript lacking exon 8 (fig. 2*B*). This abnormal splicing is predicted to introduce a frameshift and a premature stop codon at position 383. The mutation was present in the proband and his affected brother and was found to have arisen de novo in their mother. In family 187, a nonsense mutation was detected within exon 9 (1606C→G, S458X) (fig. 1*D*). This mutation was present in two half brothers and their mother, but additional samples from other family members were not available for analysis. The sequence variants identified in families 260, 356, 367, and 187 were absent in 350 normal chromosomes. The absence of additional SNP variants is in contrast to the relatively high frequency of truncating mutations identified in the families with XLMR under investigation. A causative *DLG3* mutation was not identified in family 312, despite the sequencing of the entire coding sequence from both genomic DNA and cDNA from an affected male. The possibility remains that the disease-causing gene is as yet unassigned or unidentified within Xq13 or that the mutation lies within regulatory regions of the 26 genes analyzed to date.

The phenotype in all four families was that of nonsyndromic mental retardation. In family 260, formal IQ test results of two affected individuals were in the moderate mental retardation range (Wechsler Intelligence Scale for Children [WISC] Verbal IQs of 49 and 54, Performance IQs of 46 and 50, and Full Scale IQs of 43 and 48, respectively). One female in the pedigree had mild mental retardation (WISC Verbal IQ 59–69, Performance IQ 59–69, and Full Scale IQ 56–65) and also carried the mutation. In this family, there was no correlation between the X-inactivation pattern in lymphocytes and carrier status or clinical manifestation in females (data not shown). The possibility of a skewed X-inactivation pattern in brain cells during neurodevelopment in the affected individual could explain the phenotype, as could the presence of a phenocopy, since mild mental retardation is a common occurrence in the general population. In family 356, one male was severely mentally retarded, with limited speech and an WISC Full Scale IQ of 31. The other two affected brothers are described as showing moderate mental retardation, with some limited reading skills and the ability to hold a reasonable conversation. Details on the uncle are unavailable, but he is said to be illiterate and intellectually slow. In family 367, the affected males presented with developmental delay and currently are attending special schools for moderate learning disability. The X-inactivation pattern of the carrier mother was not skewed in favor of the normal allele (data not shown). In family 187, the two affected half brothers were severely mentally retarded, with IQs of 41 and 36 (Stanford-Binet IQ test), respectively. Their obligate carrier mother had a history of seizures, and her WISC Full Scale IQ was 71.

Synapse-associated proteins are thought to have important functional roles within neuronal cells, including targeted distribution of receptors and ion channels within specialized domains of the plasma membrane, scaffolding of functional molecules, and modulation of downstream signal transduction pathways (Fujita and

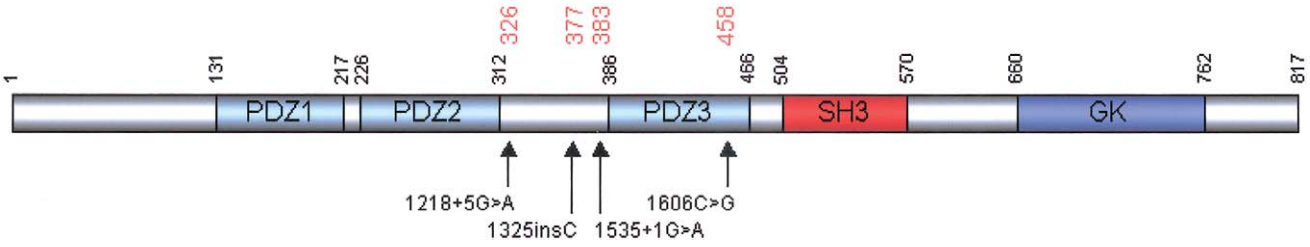

Figure 3 Schematic representation of the SAP102 protein, showing the position of the introduced stop codons (*red*) in families with *DLG3* mutations. The wild-type amino acid sequence numbering is in black. The positions of the PDZ, SH3, and GK protein-interacting domains are indicated.

Kurachi 2000). The SAP102 protein encoded by *DLG3* is concentrated in the postsynaptic density (PSD) of excitatory synapses and is the major MAGUK expressed in neurons during early brain development (Sans et al. 2000). Along with other neuronal MAGUKs, such as PSD93/chapsyn110, SAP97/dlg (MIM 601014), and PSD95/SAP90 (MIM 602887), the SAP102 protein is composed of three tandem PDZ domains at the amino terminus, an src homology (SH3) domain, and a carboxy-terminal guanylate kinase (GK) domain. PDZ domains are thought to mediate protein-protein interactions and to bind to short amino acid motifs at the carboxyl termini of interacting proteins (Muller et al. 1996; O'Brien et al. 1998). The PDZ domains of SAP102 interact with the (E)S/TXV/I/L recognition motif that is present in the cytosolic C-terminus of the NR2 subunits of the NMDA receptor (MIM 138252, MIM 138253). This suggests a role for SAP102 in the clustering and targeting of NMDA receptors in the PSD (Lau 1996; Muller et al. 1996). The first two PDZ domains of SAP102 also bind Sec8 (MIM 608185), a member of the exocyst complex that is important in NMDA receptor transport through the secretory pathway, indicating an additional role for SAP102 at the early stages of NMDA receptor processing (Sans et al. 2003). The SH3 region of SAP102 has been shown to bind calmodulin (MIM 114180) in a calcium-dependent manner and also to interact with PSD95/SAP90 (Masuko et al. 1999). It has been proposed that these interactions may regulate the clustering of neurotransmitter receptors, resulting in structural changes within the synapse.

The *DLG3* mutations identified in this study all truncate SAP102 within or before the third PDZ domain (fig. 3). The truncated SAP102 products are predicted to have impaired affinity for the NR2 subunits of the NMDA receptor and other neuronal protein-binding partners. This putative impaired functionality could lead to the disruption of the domain-dependent distribution and anchoring of NMDA receptors within the plasma membrane and to dysfunctional NMDA receptor signaling. NMDA receptors have been implicated in the induction of certain forms of plasticity, such as long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus. LTP and LTD are long-lasting activity-dependent increases and decreases in synaptic efficacy, respectively (Bliss and Collingridge 1993; Malenka 2003). These synaptic changes are thought to be molecular mechanisms underlying the process of learning and memory, and it is accepted that triggering these changes requires synaptic activation at NMDA receptors.

A mouse model for SAP102 has not been reported; however, a mouse carrying a targeted insertion mutation, introduced into the third PDZ domain of PSD95/SAP90, has been described (Migaud et al. 1998). In PSD95/SAP90 mutant mice, NMDA receptor–mediated synaptic plasticity was dramatically altered, and the mice demonstrated severely impaired spatial learning. In these mice, the location and concentration of NMDA receptors was normal, suggesting that PSD95/SAP90 is important in coupling NMDA receptors to downstream signaling pathways, rather than in facilitating their proper cellular location. The mutations we have identified in SAP102 are sited in an equivalent position to that identified in the PSD95/SAP90 mutant mouse. Further work is required to determine if mutated SAP102 leads to aberrant NMDA receptor localization directly or to disrupted downstream signal transduction as a result of impaired binding to alternate signaling proteins. Irrespective of the mechanism, altered synaptic plasticity due to abnormal NMDA receptor signaling offers a plausible mechanism to explain the mental deficit observed in individuals with *DLG3* mutations.

DLG3 is the first XLMR gene that is linked directly to NMDA receptor–mediated signaling and synaptic plasticity. The identification of four mutations in 4 (1.2%) of 329 families indicates that *DLG3* makes a significant contribution to the etiology of XLMR, relative to other genes described elsewhere. Detailed investigation of other genes involved in glutamate signal-

ing pathways may identify further deleterious mutations linked to intellectual impairment in humans.

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Electronic-Database Information

Accession number and URLs for data presented herein are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *DLG3* [accession number NM_021120])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *DLG3*, SAP97/dlg, PSD95/SAP90, NR2 subunits of NMDA receptor, Sec8, and calmodulin)

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