Serotonin Transporter Role in Identifying Similarities Between SIDS and Idiopathic ALTE

WHAT’S KNOWN ON THIS SUBJECT: Literature about polymorphic expression of an apparent life-threatening event (ALTE), particularly that concerning discrimination between ALTE with evident cause and idiopathic ALTE, is scarce. Relationships between SIDS and ALTEs have been supposed but data are still controversial and no genetic data are available.

WHAT THIS STUDY ADDS: Genetic analysis (SHTT and MAOA) on ALTEs and idiopathic ALTEs discriminated the 2 syndromes and found a link between the idiopathic form and SIDS. Consequently, we hypothesized that the 2 latter syndromes could be different phenotype expressions of a common genetic base.

abstract

OBJECTIVE: Considering previous genetic studies on sudden infant death syndrome (SIDS) and the role of L/L serotonin transporter (SHTT) genotype and correlated genes monoamine oxidase A (MAOA) and dopamine transporter (DAT) in unexpected death, an investigation was carried out verifying their involvement in apparent life-threatening events (ALTE and idiopathic form [IALTE]), also assessing common molecular basis with SIDS.

METHODS: Differential diagnoses in 76 ALTE infants, distinguishing ALTE from IALTE was elaborated by using clinical-diagnostic data. Genotypes/allelic frequencies of DAT, MAOA, and SHTT were determined in ALTE and IALTE infants and compared with data obtained from 20 SIDS and 150 controls.

RESULTS: No association was found between DAT polymorphisms and ALTE/IALTE groups either at the genotype or allelic level (P range .11–.94). MAOA genotypes and allele data comparison between ALTE and controls was not significant; IALTE data showed a tendency for genotypes (P = .09) and were statistically significant for alleles (P = .036); however, MAOA significance disappeared once the Bonferroni correction was applied. SHTT polymorphisms in IALTE remarked the role of L/L genotype (P < .00001) and L (P < .00001), as previously demonstrated in SIDS.

CONCLUSIONS: Considering correspondence between SHTT and MAOA in IALTE and SIDS, we hypothesize that the 2 syndromes are different expressions of a common etiopathogenesis. In particular, genetic data suggest SIDS events could derive from IALTE episodes occurred during sleep, and therefore out of parental control. Despite its functional role, results highlight the usefulness of SHTT as a valuable tracer of SIDS risk in IALTE infants. Owing to the small sample size, the results are to be considered preliminary and should be reevaluated in an independent sample. Pediatrics 2012;130:e138–e144

AUTHORS: Laura Filonzi, PhD,a Cinzia Magnani, MD,b Luana Nosetti, MD,a Luigi Nespoli, MD,b Camilla Borghi, MD,a Marina Vaghi, Dr.a and Francesco Nonnis Marzano, PhDa

Departments of aEvolutionary and Functional Biology, and bGynecology, Obstetrics and Neonatology, University of Parma, Parma, Italy, and cPediatric Clinic Insubria, University of Varese, Ospedale di Circolo Fondazione Macchi, Varese, Italy

KEY WORDS infant death, SHTT, MAOA, autonomous dysregulation, IALTE, prevention

ABBREVIATIONS
SHTT—serotonin transporter
SHTTLPR—serotonin transporter linked polymorphic region
ALTE—apparent life-threatening event
DAT—dopamine transporter
IALTE—idiopathic apparent life-threatening event
L—long allele
LR—likelihood ratio
MAOA—monoamine oxidase A
S—short allele
SIDS—sudden infant death syndrome
VNTR—variable number of tandem repeats

Dr. Filonzi was responsible for project conception and design, genetic analysis, and data elaboration; Dr. Magnani was responsible for project conception, clinical and diagnostic elaboration, and sample collection; Drs. Nosetti and Borghi were responsible for clinical and diagnostic elaboration and sample collection; Dr. Nespoli was responsible for clinical and diagnostic elaboration; Ms Vaghi was responsible for genetic analysis and data elaboration; and Dr. Marzano was responsible for project conception and design and interpretation of data.

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Address correspondence to Francesco Nonnis Marzano, PhD, Department of Evolutionary and Functional Biology, University of Parma, Viale delle Scienze 11, 43100 Parma, Italy.

E-mail: francesco.nonnismarzano@unipr.it

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An apparent life-threatening event (ALTE) episode was defined in 1986 as “an episode that is frightening to the observer, since it is characterized by some combination of apnea (centrally or occasionally obstructive), color change (usually cyanotic or pallid, but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking or gagging.”1 This definition replaced the term “near-miss sudden infant death syndrome” that implied a close association with sudden infant death syndrome (SIDS) but was subsequently neglected based on scarce evidence of overlap between ALTE and SIDS.

Whether SIDS and ALTE are strictly correlated is still a major dispute among neonatologists.2,3 In any case, ALTE episodes predominantly occur in children younger than 1 year of age, within a period of important completion of the central and autonomic nervous systems.4 Occasionally resuscitation is necessary, ranging from mild stimulation to full cardiorespiratory support measures.

The true incidence of the syndrome is still unknown because the diagnosis of an ALTE episode is mostly subjective.4 Many studies report an incidence ranging from 0.05% to 6.00%.5–7 Kiechl-Kohlendorfer et al8 found an incidence of 2.4 per 1000 live births in a large retrospective study based on 44 184 infants from Tyrol in the period 1993–2001.

The underlying etiology of these events is variable but real causes are still unknown. The most common diagnoses are episodic gastroesophageal reflux, lower respiratory tract infection, and seizure.8 Although in one-half of patients an etiology is found, implying that there is a potential for intervention that could eliminate further events, in the remaining patients a specific diagnosis cannot be reached, placing them in the “idiopathic” category, so-called idiopathic ALTE (IALTE).2,7

In spite of still controversial literature,2,5,9 some ALTE infants die and become classified as SIDS, which raises the possibility that ALTE and SIDS are different expressions of the same pathologic condition.2 Some previous studies reported that from 7% to 12% of SIDS victims had a history of 1 or more prior episodes of ALTE;2,9 however, a clear discrimination between ALTE and IALTE recurrence before SIDS has never been performed, posing serious questions on the correct definition of the generally so-called ALTE as a true SIDS risk factor.10

It is noteworthy observing that SIDS etiopathogenesis is still obscure, although, in most cases, an autonomic nervous system dysfunction in the control of cardiocirculatory and/or respiratory activity has been evidenced. Neurogenic factors are interplaying in all the driving pathogenetic hypotheses (the cardiac-arrhythmogenic, the respiratory-apnea and/or suffocation, and the visceral dyskinetic)11,12 and the role of the central and autonomic nervous system has gained increasing attention.13 Recent studies have identified polymorphisms in the serotonin transporter (SLC6A4, 5HTT) as a predisposing factor in infant death,14,15 supporting evidence of dysregulation of arousal mechanisms linked to neurotransmitters that are strictly correlated to brain physiology during infant development.16

Starting from past experiences on this topic,15,17 the aim of our study was to investigate the etiopathogenic mechanisms of ALTE and define possible molecular markers able to direct treatments to reduce morbidity and mortality rates. The research was carried out at 2 different levels based on (1) clinical experimental and (2) molecular approaches.

The clinical study investigated infants who experienced 1 or more “generally defined” ALTE episodes diagnosed through detection of a combination of apnea, color change, and marked variation of muscle tone. Epidemiologic, diagnostic, and therapeutic data were gathered and analyzed to highlight evident pathologic causes able to differentiate ALTE from IALTE. In fact, exclusion of clear etiopathogenic mechanisms led to the diagnosis of idiopathic ALTE.

Considering recent advances in molecular genetics that have opened new perspectives in the definition of pathogenic mechanisms of SIDS led by brainstem dysfunction and arousal responsiveness,17 the molecular approach investigated genes involved in the neurotransmission pathway regulating breathing, the cardiovascular system, temperature, and sleep-wake cycle. In particular, we analyzed polymorphisms of the SLC6A4 gene (5HTTLPR, 5HTT Linked Polymorphic Regions) coding for 5HTT, of the SLC6A3 gene (commonly referred to as dopamine transporter [DAT]) coding for DAT, and of the monoamine oxidase A (MAOA) gene. Particularly MAOA, which regulates serotonergic and dopaminergic signals through catabolism of vesicular serotonin and dopamine in the presynaptic region, has driven much of later attention because of its possible role in serotonin metabolism.

Genotypes and allelic frequencies of 5HTTLPR, MAOA-u variable number of tandem repeats (VNTR), and DAT exon 15 VNTR were therefore analyzed in separate ALTE and IALTE patients, and results compared with previously obtained data in SIDS victims. Starting from previous evidence of a functional role of genotypes and alleles of serotonin metabolic genes in different populations and ethnicities,15,20,21 an experimental hypothesis has been developed to verify the involvement of the same genes in several cases of ALTE and IALTE.

**METHODS**

The study population consisted of 76 generally defined ALTE infants (age ranging between 0 and 10 months old) hospitalized at the Parma University...
Neonatological Division and at the Pediatric Clinic Insudria, University of Varese, between 2007 and 2009. Age of appearance of ALTE episodes was overlapping that of previously analyzed SIDS infants (see refs 15 and 17 for detailed data). The ALTE study group included 42 girls and 34 boys. The separation between ALTE with a proper cause and the idiopathic form IALTE was obtained through a deep clinical and familiar investigation performed according to recently defined Italian National Guidelines for ALTE diagnosis and management.22 In particular, the diagnostic process started with a careful history of the event and physical examination of the patient. Laboratory tests (complete blood count, electrolytes, magnesium, calcium, serum bicarbonate, inflammatory tests, serum lactate, ammonia, urea, arterial blood gases, urine analysis, liver function tests), electrocardiogram, and a 16-channel polysomnography (EEG, electrocardiogram, electro-oculogram, electromyogram, nasal airflow detection, thoracic and abdominal bands, pulse oximetry, end-tidal CO2, PtCO2, microphone and video by E-Series-Compumedics, Charlotte, NC) were previously described in Nonnis Marzano et al.15 The SLC6A3 (DAT) VNTR polymorphism was amplified by PCR by using specific primers suggested by Cohen et al26; forward 5’-TGGGTGAGGGAGCGCCT-3’; and reverse 5’-CTCTTGGAGGTACGGCTCAAAGG-3’. The MAOA VNTR polymorphism was analyzed by using primers suggested by Cohen et al26; forward 5’-ACAGCCTGACGTGGAGAAG-3’; reverse 5’-GAACGGACGGCTCACCGCTGAGGGA-3’. Methodological procedures to detect DAT VNTR and MAOA VNTR polymorphisms were described in detail in a previously published article.17

To investigate possible associations between genotypes/alleles and experimental groups, a likelihood ratio (LR) χ² test was performed. It is a more robust test than the classic Pearson χ² to deal with low-number categories, such as genotype and allele groups. In addition, the Yates correction was applied to the χ² test considering the limited number of analyzed samples. Statistical analyses were performed by using Statistica software (version 8.0) by StatSoft Inc (Tulsa, OK). Values of P were considered highly significant when lower than .01 and significant in the range .01 < P < .05. In addition, values in the range of .05 ≤ P ≤ .10 were considered as a trend of significance. Degrees of freedom were equal to 1 less than the number of alleles/genotypes. Bonferroni correction was also applied and the statistical significance level was calculated as 0.05/4, 4 being the number of possible comparisons of ALTE and IALTE and controls, either genotype or allele frequencies. Therefore, the significance level after Bonferroni correction was 0.013.

The investigation was carried out in agreement with current national laws on scientific research in medical topics. An official authorization, Protocol Number 36198, was assigned by Parma University Hospital Ethical Committee on November 12, 2009, to perform our investigation.

RESULTS

5HTT

Data referred to genotype and allelic frequencies of 5HTT linked polymorphic region (5HTTLPR) of the promoter detected in ALTE, IALTE, and control samples are reported in Table 1. Both short (S) and long (L) alleles of 5HTTLPR were found. In particular, 3 homozygote genotypes L/L (10.7%), 14 heterozygote genotypes S/L (50.0%), and 11 homozygote genotypes S/S (39.3%) were detected in 28 ALTE patients. Similarly, data in controls (n = 150) were 21 L/L (14.0%), 86 S/L (57.3%), and 43 S/S (28.7%). On the opposite, 28 homozygote genotypes S/L (58.3%), 18 heterozygote genotypes S/S (37.5%), and 2 homozygote genotypes S/S (4.2%) were found in the IALTE group (n = 48). The frequency of the L/L genotype was much higher in IALTE cases (58.3%) than in the ALTE group (10.7%) and controls (14.0%) and overall statistical significance of genotype differences between IALTE and controls was defined by LR χ² = 29.98, P < .0001, whereas no statistical significance emerged between ALTE and controls considering genotype frequencies (LR χ² = 0.70, P = .40). Considering allelic frequencies, the L
allele was 77.1% in IALTE infants and 42.6% in the control group (LR $\chi^2 = 33.82$, $P < .00001$). L allele frequency determined in the ALTE group was 35.7% and no statistical significance emerged between these cases and control samples ($LR \chi^2 = 1.03$, $P = .31$).

### MAOA

MAOA VNTR (30-bp repeated sequence) polymorphisms were detected in ALTE and IALTE groups and results are reported in Table 2. Alleles previously defined by Sabol et al. were high in cases (3 (320 bp), 3.5 (335 bp), 4 (350 bp), and 5 (380 bp) repeats were identified in 28 ALTE and 48 IALTE samples. The 2.5 repeat was not found in either group. Frequency of homozygote genotype 3R/3R was higher in the controls (26%) compared with ALTE (17.8%) and IALTE infants (18.7%). Genotype 3R/4R was almost twofold higher in the control group (28.7%) than ALTE (17.8%) and IALTE (12.5%). Homozygote 4R/4R was the most represented genotype. In particular, frequencies were respectively 66.7% (IALTE), 57.2% (ALTE), and 42.7% (control group). Considering allele frequencies, the 4 allele was 74.4% in IALTE infants and 62.5% in ALTE infants versus 60.5% in the controls. On the opposite, allele 3 was 24.3% in the IALTE group and 30.0% in ALTE patients versus 37.8% in the control group. Alleles 3.5 and 5 were marginally represented in the IALTE group and controls (range 0%–1.7%), whereas allele 5 was slightly higher in the ALTE group (7.5%).

### TABLE 1 Frequencies of 5HTTLPR Genotypes and Alleles With Corresponding Statistical Elaborations Obtained in the Comparisons Between ALTE and IALTE With the Control Group

<table>
<thead>
<tr>
<th>5HTTLPR</th>
<th>Controls (n = 150)</th>
<th>ALTE (n = 28)</th>
<th>IALTE (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>L/L</td>
<td>21</td>
<td>14.0</td>
<td>3</td>
</tr>
<tr>
<td>L/S</td>
<td>86</td>
<td>57.3</td>
<td>14</td>
</tr>
<tr>
<td>S/S</td>
<td>43</td>
<td>28.7</td>
<td>11</td>
</tr>
</tbody>
</table>

### TABLE 2 Frequencies of MAOA Genotypes and Alleles With Corresponding Statistical Elaborations Obtained in the Comparisons Between ALTE and IALTE With the Control Group

<table>
<thead>
<tr>
<th>MAOA VNTR</th>
<th>Controls (n = 150)</th>
<th>ALTE (n = 28)</th>
<th>IALTE (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>3/3/3</td>
<td>39</td>
<td>26.0</td>
<td>5</td>
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<td>0</td>
</tr>
<tr>
<td>3/4</td>
<td>45</td>
<td>29.7</td>
<td>5</td>
</tr>
<tr>
<td>3/5</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>3.5/3/3</td>
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</tr>
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<td>2.6</td>
<td>0</td>
</tr>
<tr>
<td>3.5/5</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>4/4/4</td>
<td>64</td>
<td>42.7</td>
<td>16</td>
</tr>
<tr>
<td>4/5</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>5/5/5</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
</tbody>
</table>

### DAT

DAT genotypes and allele frequencies determined in ALTE and IALTE patients are shown in Table 3. VNTR alleles with 9, 10, and 11 repeats were detected both in pathologic and nonpathologic samples. Four different genotypes were detected; the most represented allelic combinations were heterozygotes 9/10 (ALTE 42.9%, IALTE 41.7%, and controls 54.7%) and homozygotes 10/10 (ALTE 46.4%, IALTE 47.9%, and controls 36.0%). The 9 and 10 repeats were the most common forms in all 3 experimental groups with the 10-repeat allele being the highest in all classes and showing highly comparable values (ALTE 69.6%, IALTE 68.9%, and controls 68.0%). The 11-repeat was limited only to a few 10/11 heterozygotes in healthy control (9.3%), ALTE (3.6%), and IALTE (2.1%) groups, with allele frequencies ranging from 1.1% to 4.7%. Homozygotes 11/11 were never detected in control or pathologic groups. Considering overall data of DAT polymorphisms, no statistical significance emerged between pathologic and control samples both at the genotype (ALTE LR $\chi^2 = 1.31$, $P = .25$; IALTE LR $\chi^2 = 2.53$, $P = .112$) and allele levels (ALTE LR $\chi^2 = 0.00$, $P = .94$; IALTE LR $\chi^2 = 0.02$, $P = .88$).
DISCUSSION

ALTE predominantly affects children younger than 1 year. The syndrome is characterized by a frightening constellation of symptoms in which the child exhibits some combination of apnea, change in color, modification in muscle tone, coughing, or gagging. In spite of the importance of threatening events, the underlying etiology is variable and real causes are still unknown according to a highly variable expression of the syndrome. Although an etiology is found in one-half of patients, implying that there is a potential for intervention that could eliminate further events, in the remaining patients a specific diagnosis is never made, placing them in the idiopathic category. Some of these infants die and are subsequently classified as SIDS, which raises the possibility that ALTE events are a risk factor to be monitored to prevent SIDS. A number of previous studies reported that up to 12% of SIDS victims had experienced 1 or more prior episodes of generally defined ALTE, but the literature is still controversial and no specification on a clear differentiation between ALTE and IALTE recurrence in SIDS has ever been reported.

Recent advances in molecular genetics have opened new perspectives in the definition of pathogenic mechanisms of SIDS connected to brainstem dysfunction and arousal responsiveness. In relation to this, the involvement of genes regulating neurotransmission pathways was supposed and several studies identified polymorphisms in 5HTT as a predisposing factor in infant death. Considering controversial clinical aspects of ALTE, the discovery of molecular markers to improve the diagnostic pathway could bring helpful innovations for improved dedicated assistance.

Results obtained in this investigation open new perspectives in the relationship among ALTE, IALTE, and SIDS. In particular, the aim of our experimental project was to investigate the possible correlation between polymorphisms of genes regulating neurotransmitters in the metabolic pathway in the brainstem and define their possible role in the etiopathogenesis of ALTE and IALTE.

The DAT gene, coding for the DAT, and particularly the 40-bp VNTR associated with differential expression activity, did not display significant differences between pathologic samples (ALTE and IALTE) and controls. The frequencies of the 3 alleles (9, 10, 11 repeats) were similar in both ALTE, IALTE, and control samples, with 9 and 10 repeats being the most common forms in accordance with a previous publication. According to experimental results and their statistical elaboration, dopamine did not seem to be involved in either ALTE or in IALTE patients, as previously determined for SIDS.

Novel important results emerged from analyses of 5HTTLPR, considering previously defined allelic variants S and L that differentially modulate transcription of 5HTT gene. In this article, increased frequency of L/L genotype, which is related to enhanced gene expression, was associated with IALTE (P < .00001) but not to ALTE (P = .40). Interestingly, statistical significance determined in 5HTTLPR both at the genotype and allelic levels was strictly similar between IALTE and SIDS (see refs 15 and 17 for SIDS data), whereas no statistical overlapping emerged in the case of ALTE (Fig 1). In the latter case, molecular data overlapped those of controls. More precisely, L allele frequencies were twofold higher both in IALTE and SIDS than in controls. It must be remarked that enhanced recurrence of the L allele as high as twofold in SIDS infants has previously been highlighted in different ethnicities.

The controversial involvement of MAOA different genotypes and their functional role in unexpected infant deaths remains still not clarified in our IALTE patients. In fact, statistical analysis performed on genotype and allelic data obtained in IALTE were fluctuating between slight significance and a tendency, although statistical significance disappeared after application of Bonferroni correction. Despite this, consistently with 5HTT data reported previously, behavior of MAOA results showed strong parallelisms with SIDS. In particular, genotype frequencies showed a tendency of P = .047 to .090 (SIDS and IALTE, respectively), whereas data concerning allelic frequencies were statistically significant with P in the range of .018 to .036 (SIDS and IALTE, respectively). On the opposite, data on ALTE were not statistically supported.

Considering strict correspondence between 5HTT and MAOA molecular data in IALTE and SIDS, we hypothesize that the 2 syndromes could be different.

### Table 3: Frequencies of DAT Genotypes and Alleles With Corresponding Statistical Elaborations Obtained in the Comparisons Between ALTE and IALTE With the Control Group

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls (n = 150)</th>
<th>ALTE (n = 28)</th>
<th>IALTE (n = 48)</th>
<th>Test</th>
<th>Value</th>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleles</td>
<td>n</td>
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<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>9/9</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>7.1</td>
<td>4</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>9/10</td>
<td>82</td>
<td>54.7</td>
<td>12</td>
<td>42.9</td>
<td>20</td>
<td>41.7</td>
<td></td>
</tr>
<tr>
<td>9/11</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>10/10</td>
<td>54</td>
<td>36.0</td>
<td>13</td>
<td>46.4</td>
<td>23</td>
<td>47.9</td>
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<td>9.3</td>
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<td>3.6</td>
<td>1</td>
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<td></td>
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<td>0.0</td>
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<td>Alleles</td>
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phenotype expressions of a common, still unknown, biological or environmental cause. More precisely, the SIDS event could be an IALTE episode that occurred during sleep, out of parental control. That explains the increased incidence of SIDS during nighttime or generally during sleep. On the opposite, IALTE crises during the day are usually promptly managed with emergency assistance, avoiding further fatal events. Therefore, experimental data support the conclusion that despite the still debated role of 5HTT in unexpected infant death, this molecular marker can be considered a valuable tracer of SIDS risk in IALTE infants. Because of the small sample size, however, the results are considered preliminary and should be reevaluated in an independent sample.

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