Loss of asymmetry in D\textsubscript{2} receptors of putamen in unaffected family members at increased genetic risk for schizophrenia

Lee KJ, Lee JS, Kim SJ, Correll CU, Wee H, Yoo SY, Jeong JM, Lee DS, Lee SI, Kwon JS. Loss of asymmetry in D\textsubscript{2} receptors of putamen in unaffected family members at increased genetic risk for schizophrenia.

Objective: Dopamine dysregulation has been implicated in the pathophysiology of schizophrenia. The present study was performed to examine whether unaffected relatives at high genetic risk of schizophrenia have dopamine dysregulation in comparison with healthy controls.

Method: Eleven unaffected relatives from families with two or more first- or second-degree relatives with schizophrenia (\(n = 9\)) or with a monozygotic schizophrenic twin (\(n = 2\)) and 11 age- and sex-matched controls were examined using positron emission tomography (PET) with [\(^{11}\text{C}\)]raclopride. Subjects also underwent extensive neuropsychological testing.

Results: Subjects with high genetic risk showed a loss of asymmetry of D\textsubscript{2} receptors in the putamen in comparison with healthy controls. In addition, they showed significantly poorer performance on neuropsychological tests than controls.

Conclusion: Our results suggest that dopamine dysregulation and neuropsychological dysfunction may be present in subjects at high genetic risk of schizophrenia. However, further studies are required to confirm these findings.

Significant outcomes

- Subjects at high genetic risk of schizophrenia showed a loss of asymmetry of D\textsubscript{2} receptors in the putamen compared with healthy controls.
- Subjects at high genetic risk of schizophrenia showed significantly poorer performance on the Wisconsin Card Sorting Test and the Rey-Osterrieth Complex Figure Test, measures of executive and visuospatial memory function compared with healthy controls.
- These subjects may be predisposed to dopamine dysregulation, and thus have increased vulnerability to schizophrenia.

Limitations

- The results did not provide any information about endogenous dopamine levels at baseline.
- This study cannot exclude the effects of endogenous dopamine on raclopride in PET.

Introduction

Since the 1960s, the most notable theories of schizophrenia have focused on dysfunction of the neurotransmitter dopamine. The dopamine hypothesis underlying schizophrenia was supported, in part, by the correlation between clinically effective antipsychotic doses and the affinity of these medications for dopamine D\textsubscript{2} receptors (1), and by the psychotomimetic effects of dopaminergic drugs (2). In addition, an increased number of brain D\textsubscript{2} receptors has been detected in postmortem studies...
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of schizophrenia (3, 4). However, these postmortem studies are limited by the fact that patients had been treated with antipsychotics, which may have contributed to the elevation of D₂ receptors (5). To eliminate these potentially misleading factors, the D₂ receptor density, especially in the striatum, has been studied extensively in drug-naïve patients with schizophrenia using positron emission tomography (PET) (6–9) and single photon emission computed tomography (SPECT) imaging (10). However, the results of these studies have been inconsistent. Despite these discrepant findings, two meta-analyses support the suggestion that patients with schizophrenia have a mild but significant elevation of D₂ receptor density, in comparison with healthy controls (11, 12). Abi-Dargham et al. (10) measured the baseline occupancy of D₂ receptors after partial depletion of endogenous dopamine in patients with schizophrenia, and found that patients with schizophrenia showed an increase in D₂ receptor availability when compared with controls. This observation suggests that dopamine occupies a greater proportion of striatal D₂ receptors in patients with schizophrenia when compared with control subjects. In addition, several molecular imaging studies focusing on the laterality of D₂ receptors also suggested a change in asymmetry in patients with schizophrenia when compared with controls (6, 13–15). It has been shown that the nigrostriatal dopamine system on the right-hand side of the brain differs from that on the left-hand side. The evidence for the functional asymmetry of dopamine is provided by a spontaneous turning bias; healthy right-handed men have a marked preference for turning toward their right side (16). Mohr et al. (17) suggested that these differences in turning behavior may be related to an underlying lateralization of dopamine transmission. Several animal studies have also shown that the dopamine D₂ receptor binding is greater in the right than in the left striatum. Drew et al. (18) showed that in female rats the D₂ receptor density [Bₘₐₓ] measured using [³H]N-methyl spiperone binding was significantly greater on the right-hand side than on the left-hand side, with an average difference of 40%. Cumming et al. (19) reported that the D₂ receptor by [¹¹C]raclopride binding was 10% higher in the right than in the left putamen of female pigs. Furthermore, a review reported a population bias of higher D₂ receptor binding in the right than in the left striatum in healthy human subjects (20). In addition, Vernaleken et al. (21) demonstrated that the D₂ receptor binding potential using [¹⁸F]desmethoxyfallypride (DMFP)-PET showed a rightward asymmetry in healthy young subjects, which decreased with age. However, analyses of D₂/C₃ receptor availability using PET or SPECT have shown differences in asymmetrical patterns between patients with schizophrenia and healthy controls (6, 13–15). Taken together, the elevation of D₂ receptors and differences in asymmetrical patterns of D₂ receptors in striatum support the hypothesis that alterations in striatal D₂ receptor distribution and density occur in schizophrenia.

Schizophrenia has a strong genetic component (22). Identical twins have a 40–50% concordance rate for the illness (23) and first-degree relatives of patients with schizophrenia are at greater risk for schizophrenia than the general population (24, 25). Recently, the Edinburgh High Risk Study (EHRS) group reported several important findings related to the ‘subjects at high risk’ of developing schizophrenia (26, 27). To obtain a sample population with a high genetic risk of schizophrenia, they selected young persons, between 16 and 25 years old, who had been identified as having at least two first- or second-degree relatives suffering from schizophrenia. They showed that the relatives at high risk of developing schizophrenia have a higher transition rate to schizophrenia compared with controls (26). Furthermore, they reported that the more first-degree relatives affected, the poorer the performance on neuropsychological tests (27). Focusing on brain structures, they showed that the volume of the third ventricle was significantly increased in the high-risk subjects with greater genetic loading, especially in patients with at least one first-degree relative (26). The genetic component of schizophrenia suggested by these observations has prompted further studies of putative predictors of schizophrenia based specifically on phenomenological and genetic markers in first-degree relatives of patients with schizophrenia (28–32).

Aims of the study

The present study was performed to examine whether dopamine dysregulation, especially with regard to asymmetry in D₂ receptor pattern, is related to the genetically mediated trait of schizophrenia using ‘subjects at high genetic risk’ of developing schizophrenia.

Material and methods

To meet our criteria for high genetic risk of schizophrenia, we selected subjects with at least one first-degree relative as well as a first-degree
relative or second-degree relatives with the disease (except one monozygotic twin). The degree of genetic risk in our subjects was greater than in the EHRS. As neuropsychological deficits have been shown to be associated with genetic vulnerability for schizophrenia, all subjects also underwent a neuropsychological test battery to confirm that the unaffected family members had abnormalities compared with controls, thus indicating true genetic risk of schizophrenia.

Subjects

Eleven unaffected family members and 11 age- and sex-matched controls were examined using PET with $[^{11}C]$ raclopride. With the exception of one case (mother of subject 1: disorganized type), all affected relatives had paranoid type schizophrenia. Healthy control subjects were recruited via an advertisement. Exclusion criteria for all study subjects included a history of significant head injury, substance abuse, seizures, severe medical problems, and any history of DSM-IV Axis I disorders, evaluated with the Structured Clinical Interview for DSM-IV (SCID) (34) in genetic high-risk subjects and with SCID-NP (non-patient version) (35) in controls. The Family Interview for Genetic Study (FIGS) (36) was administered to evaluate the family history of psychotic and other mental disorders. The study was approved by the Institutional Review Board of the Seoul National University Hospital and all study subjects provided written informed consent to participation.

Assessments

Neuropsychological tests. All subjects completed neuropsychological testing. The tests were evaluated for extensive ranges of neuropsychological function. The Wisconsin Card Sorting Test (WCST) was performed to evaluate problem solving and mental set-shifting. The Trail Making Test (TMT) was performed to evaluate attention. The Controlled Oral Word Association Test (COWA) was performed to assess word fluency. The Rey-Osterrieth Complex Figure Test (RCFT) was employed to evaluate visuospatial memory and visuospatial construction ability. The Stroop test was performed to assess selective attention and cognitive flexibility. The d2 test was performed to assess sustained attention. The Korean version of the Wechsler Adult Intelligence Scale (K-WAIS) was administered to provide an intelligence quotient (IQ) estimate.

PET procedures and imaging data analyses. All subjects were scanned at rest without ear plugs or eye pads, using an ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN, USA), which had an intrinsic resolution of 5.2 mm full-width at half-maximum (FWHM) and simultaneously imaged 47 contiguous transverse planes with a thickness of 3.4 mm for a longitudinal field of view of 16.2 cm. Before the injection of the tracer, a 15-min transmission scan was performed using a triple Ge-68 rod source to correct for attenuation. Emission scanning started after intravenous injection of 9.7 (±3.6) mCi of raclopride. Stored data were reconstructed in a $128 \times 128 \times 47$ matrix with a voxel size of $2.1 \times 2.1 \times 3.4$ mm using a filtered back projection algorithm employing a Shepp–Logan filter with a cut-off frequency of 0.3 cycles/pixel. Spatial preprocessing and statistical analyses were performed using SPM 99 (Institute of Neurology, University College of London, UK) implemented in MATLAB (Mathworks Inc., Natick, MA, USA) (37).

For volume of interest-based analysis, the PET images were realigned with the results of magnetic resonance images (MRI). Three-dimensional T1-weighted spoiled gradient echo MRI was acquired on a 1.5 T GE SIGNA Scanner (GE Medical System, Milwaukee, WI, USA). MRI was used to define regions of interest (ROIs) in the caudate nucleus, putamen, and cerebellum (reference region) for each individual. All ROIs were delineated manually and drawn on the coronal plane. ROI analyses were performed using an image processing software package, ANALYZE-version 6.5 (Mayo Foundation, Rochester, MN, USA). We identified the head of the caudate nucleus and the putamen and drew ROIs in at least 10 consecutive re-sectioned MRI. The images obtained by MRI were co-registered with PET images to obtain PET time activity curves. To calculate binding potential ($BP = B_{\text{max}}/K_d$) values in the striatum, the non-invasive Logan method and simplified reference tissue model were used (38).

Voxel-based mapping analyses. To confirm the results of ROI-based analyses of $D_2$ binding potential, voxel-based statistical analyses were used and compared across the groups at the voxel level. Binding potential parametric images for $D_2$ receptors were calculated using the non-invasive Logan plot and simplified reference tissue model with spatial constraints (39). Before statistical analyses, Montreal Neurological Institute (MNI) MR-based spatial normalization (40) and study-specific ligand template-based spatial normalization (41) were performed.
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For the first spatial normalization method, each subject’s co-registered MR image to PET static image was spatially normalized to the MNI template. The transformation matrix from the spatial normalization was applied to each PET binding potential parametric image. To generate the study-specific ligand template in the second spatial normalization method, the co-registered MR image to PET static image was first spatially normalized to the MNI templates by linear transformation, and the transformation matrix was applied to the PET static image. The pixel count of transformed PET images was then normalized to each cerebellum count. Finally, the study-specific ligand template was created by averaging the count normalized PET images and smoothing to the 8 mm Gaussian kernel. Each PET static image was spatially normalized to the templates and the transformation matrix was applied to the binding potential parametric image. Spatially normalized images were smoothed by convolution with an isotropic Gaussian kernel (FWHM = 16 mm) to increase the signal-to-noise ratio and to account for subtle variations in anatomical structures.

The differences between two binding potential parametric images of genetic high-risk subjects and controls were evaluated using a two-sample t-test and analysis of covariance (ANCOVA) with age as covariate. The significance level was set at $\alpha = 0.05$. Statistical analyses were performed using the spm2 (Statistical Parametric Mapping) software (Wellcome Department of Imaging Neuroscience, University College London, London, UK).

Statistical analyses. The Mann–Whitney U-test was used to assess differences in the asymmetry index, binding potential, neuropsychological test results, and demographic data between genetic high-risk subjects and controls. Asymmetrical hemispheric differences in binding potential between the two groups were evaluated using an asymmetry index. The asymmetry index was calculated separately for the caudate nucleus and putamen, using the formula $(R - L)/(R + L) \times 100$ (42). A positive value reflects higher levels in the right hemisphere, whereas negative values reflect higher availability in the left dorsal striatum. The chi-squared test was used for the analysis of gender. To assess the degree of genetic risk, we used the familial loading score designed by Pak Sham using MATLAB as a continuous measure (43). The Pearson correlation was used to evaluate the correlations between genetic loading and binding potential and between neuropsychological function and the asymmetry index. The significance level was set at $\alpha = 0.05$. Statistical analyses were performed using spss 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics

Table 1 shows the family history of schizophrenia in genetic high-risk subjects. Nine subjects were unaffected relatives from families with two or more first- or second-degree relatives with schizophrenia and two were monozygotic schizophrenia twins.

The demographic characteristics of the genetic high-risk subjects and healthy controls are shown in Table 2. There were no statistically significant differences between the two groups with regard to age, gender, education, subject socioeconomic status (SES), parental SES, handedness, or IQ.

Neuropsychological function

Genetic high-risk subjects showed a significantly increased error rate ($P = 0.028$) and non-perseverative error response ($P = 0.019$) in the WCST.

Table 1. Family history of schizophrenia in genetic high-risk subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sex</th>
<th>Age (years)</th>
<th>First-degree relatives</th>
<th>Second-degree relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>25</td>
<td>Father, mother</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>30</td>
<td>Monozygotic twin, brother</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>33</td>
<td>Sister, brother</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>17</td>
<td>Mother, brother</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>27</td>
<td>Father, sister</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>22</td>
<td>Father, sister</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>19</td>
<td>Monozygotic twin</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>21</td>
<td>Sister</td>
<td>Uncle</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>28</td>
<td>Sister</td>
<td>Uncle</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>25</td>
<td>Sister</td>
<td>Uncle 1, uncle 2</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>21</td>
<td>Brother</td>
<td>Uncle</td>
</tr>
</tbody>
</table>

Table 2. Demographic and clinical variables of genetic high-risk subjects and healthy controls

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Genetic high-risk subjects (n = 11)</th>
<th>Healthy controls (n = 11)</th>
<th>Significance (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25.1 (5.2)</td>
<td>25.5 (5.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>3/8</td>
<td>3/8</td>
<td>ns</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.9 (2.5)</td>
<td>14.5 (1.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Subject SES*</td>
<td>3.1 (0.5)</td>
<td>2.7 (0.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Parental SES</td>
<td>2.7 (0.9)</td>
<td>2.8 (0.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Handedness (Rt.†)</td>
<td>11</td>
<td>11</td>
<td>ns</td>
</tr>
<tr>
<td>IQ</td>
<td>105.8 (8.4)</td>
<td>113.0 (8.9)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are mean ± SD. IQ, intelligence quotient; ns, not significant.

*SES: socioeconomic status according to the index of Hollingshead and Redlich.
†Handedness: hand preference according to the Annett’s classification measures.
when compared with controls. They also showed decreased response scores in immediate recall \((P = 0.004)\) and delayed recall \((P = 0.004)\) in the RCFT. No statistically significant differences between the two groups were observed with regard to the results of the other neuropsychological tests, including the TMT, COWA, Stroop test, d2 test, and K-WAIS (Table 3).

**D2 receptor binding potential**

Table 4 shows the means and standard deviations of \([11C]\) raclopride binding potential values in genetic high-risk subjects and healthy controls.

**Healthy subjects** (mean = 4.88, SD = 3.58) had significant hemispheric asymmetry in the putamen as determined from the asymmetry index \((P = 0.045)\), with greater binding potential values in the right than in the left putamen, while this was not the case in genetic high-risk subjects (mean = 1.76, SD = 3.04) (Fig. 1). The Pearson correlation revealed a relationship between the asymmetry index and the results of several neuropsychological tests, such as copy \((P = 0.02)\) and delayed recall \((P = 0.028)\) in RCFT and error rate \((P = 0.026)\), perseverative response \((P = 0.013)\), and perseverative error response \((P = 0.018)\) in WCST. There was no statistically significant difference in the binding potential between the genetic high-risk subjects and healthy controls on either side (Fig. 2). There was no significant correlation between genetic loading and binding potential.
The results of the present study indicated that genetic high-risk subjects did not have the rightward asymmetry of D₂ binding potential in the putamen, which was typically found in healthy subjects. In addition, they showed significantly poorer performance than controls on the WCST and the RCFT, which are measures of executive and visuospatial memory function.

The asymmetrical patterns of the human brain are normal and can be documented as early as 16 weeks of gestation and are also seen clearly in newborn infants (44, 45). This finding has been explained by genetic factors, and both hormonal and environmental influences (46, 47). The asymmetry of the brain in healthy subjects has been demonstrated in both its gross cerebral anatomy and its functional metabolism (45, 46, 48, 49). Molecular imaging studies, such as PET and SPET, provided further insight into the asymmetry of the dopaminergic system in healthy subjects. The investigation of postsynaptic dopamine D₂ receptors indicated asymmetric lateralization of the right-hand side in healthy subjects (17, 18). In contrast, patients with schizophrenia show a difference in asymmetrical patterns from healthy controls (6, 13–15). Similarly, PET studies with the presynaptic tracer 6-FDOPA revealed a right-sided higher dopamine synthesis capacity in healthy subjects (50). Striatal dopamine transporter with PET also showed a similar pattern (51). However, the rightward asymmetry of the dopamine synthesis capacity seen in the caudate of healthy subjects was not found in neuroleptic-naïve patients with schizophrenia (50). Dopamine transport density using PET or SPECT also revealed the loss of asymmetric patterns in patients with schizophrenia (51, 52). The results of the present study indicated that healthy controls had rightward asymmetry of D₂ binding potential in the putamen, while subjects at high genetic risk of developing schizophrenia did not show this pattern. This result suggests that the lack of hemispheric asymmetry of D₂ binding potential in the putamen may be a genetically mediated trait of schizophrenia. This is the first evidence of a lack of laterality of dopamine binding potential in subjects at high genetic risk of schizophrenia.

The results of the present study indicated that subjects at high genetic risk of schizophrenia do not differ from controls with regard to D₂ receptor binding potential on either side of the hemisphere. These results are different from the recently published findings of Hirvonen et al. (53) suggesting that dopamine receptor up-regulation is a trait factor for schizophrenia. The authors demonstrated that D₂ receptor binding potentials were higher in five monozygotic unaffected co-twins compared with healthy controls. However, in the study by Hirvonen et al., the unaffected dizygotic co-twins did not differ in their caudate D₂ density from control twins. They suggested that these findings may be related to increased genetic vulnerability. In this study, the Pearson correlation did not show the relationship between genetic loading and binding potential. While our results are not entirely clear, the cohort in the study of Hirvonen et al. had a higher mean age (mean age: > 50 years), which was more than twice that of our sample. Differences in age have been considered a reason for the discrepant findings in PET (18, 21, 54). Further studies are required to confirm these findings.
Deficits in the WCST have been reported in first-degree relatives of schizophrenic patients (29, 32), suggesting that the WCST performance could be considered a vulnerability marker of schizophrenia. The present study showed that genetic high-risk subjects had significant impairment in the WCST. This result is consistent with these previous studies and also raises the possibility that WCST deficits may be a specific familial indicator of vulnerability. In addition, the genetic high-risk subjects in the present study also showed deficits in RCFT, which assesses visuospatial memory and visuospatial construction ability. Chiulli et al. (55) proposed that the conditions of copy, immediate, and delayed recall on the RCFT provide different information. They hypothesized that while the copy condition reflects perceptual, visuospatial, and organizational skills, the immediate recall condition reflects the amount of information that is encoded, stored, and retrieved from memory. In comparison with healthy controls, the genetic high-risk subjects in the present study showed impairment in immediate recall and delayed recall, but not the copy condition. These results indicate that the genetic high-risk subjects did not have perceptual, visuospatial, or organizational dysfunction, but rather global visuospatial memory dysfunction. Taken together, genetic high-risk subjects showed impairments not only in executive function but also in visuospatial memory. These neuropsychological deficits could represent a vulnerability marker of schizophrenia. In addition, the Pearson correlation showed that the asymmetry index score was associated with poor performance in cognitive tasks, which have been shown previously to be related to psychotic vulnerability (29, 32). We tentatively suggest that the loss of lateral asymmetry may be a trait marker related to the vulnerability of psychosis.

There were several limitations in this study. First, this study did not provide any information about endogenous dopamine levels at baseline. Abi-Dargham et al. (10) measured occupancy of striatal D2 receptors by dopamine in untreated patients with schizophrenia and matched controls, by comparing D2 receptor availability before and during acute endogenous dopamine depletions using the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine in SPECT. They reported that there were no differences were observed in D2 receptor availability at baseline, but that after removal of endogenous dopamine, D2 receptor availability was significantly higher in patients with schizophrenia when compared with controls. This approach to evaluate the endogenous dopamine levels at baseline provided indirect evidence that schizophrenia may be associated with excessive endogenous dopamine. Further studies are required to obtain additional information regarding endogenous dopamine levels at baseline in subjects at high genetic risk of schizophrenia. Second, we cannot exclude the possible effect of endogenous dopamine on raclopride in PET. Benzamide-class radioligands, such as raclopride or iodobenzamide, are more vulnerable to endogenous dopamine competition compared with butyrophenone-class radioligands such as N-methylspiperone (56). Some [11C] raclopride PET studies demonstrated the effect of endogenous dopamine on raclopride in the measurement of D2 receptor binding potential (57, 58). These findings may have important implications for interpretation of the results of [11C] raclopride PET neuroreceptor studies. This suggests that the increase in endogenous dopamine in genetic high-risk subjects may block detection of the increase in D2 receptor binding potential by [11C] raclopride. Third, although several molecular imaging studies related to the laterality of D2 receptors supported the change in asymmetry in schizophrenia when compared with controls, some controversial issues remain. For example, one postmortem study demonstrated increased densities on the right-hand side in both patients and controls, in vivo using SPECT and [11Br] spiperone (59). However, subsequent studies indicated left lateralized asymmetry of striatal D2 receptor binding only in male patients with schizophrenia (14, 15). These discrepancies may be due to the effects of medication, small sample size, and varying analytic methods of PET and SPECT investigations. In fact, the previously mentioned postmortem study did not explain the effects of neuroleptic medication. The small sample size in our study makes it difficult to explain these discrepancies. Further studies, with large sample sizes and with unified analytic methods are required to confirm these findings.

In summary, the results of the present study indicated that subjects at high genetic risk of schizophrenia showed a loss of D2 receptor asymmetry in the putamen when compared with controls, which was related to the reduced performance on the WCST and RCFT. These findings suggest that the high-risk subjects may be interrelated with dopamine dysregulation for high genetic vulnerability of schizophrenia.

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