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Association of *MAOA* and *COMT* gene polymorphisms with palatable food intake in children☆,☆☆

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Abstract

Several studies have implicated dopamine (DA) in appetite regulation. The enzymes catechol-o-methyltransferase (COMT) and monoamine oxidase A (MAOA) control DA availability and their genes have well-characterized functional variants. In this study, we examined three polymorphisms in these genes, *T941G* and *MAOAu-VNTR* in the *MAOA* gene and *Val158Met* in the *COMT* gene, to investigate how heritable variations in enzymes that determine DA levels might influence food intake and nutritional status. This investigation was a cross-sectional examination of 354 Brazilian children of three to four years old. Polymorphisms were analyzed by PCR-based methods. Means of dietary and anthropometric data were compared among genotypes by one-way analyses of variance or Kruskal Wallis tests. The *MAOAu-VNTR* and *COMT Val158Met* polymorphisms were associated with the amount of palatable food intake in boys. Presence of the *MAOAu-VNTR*long* allele was associated with higher intake of lipid-dense foods (LDF) when compared with the **short* allele (P=.009); the amount of sugar-dense foods (SDF) intake was also higher in males carriers of the *MAOAu-VNTR*long* allele than in carriers of the **short* allele (P=.034). In the girls' sample, *MAOAu-VNTR* polymorphism was not associated with food intake and nutritional status. Carriers of the *COMT Val158Met*Val* allele presented higher intake of LDF when compared with *Met/Met* homozygotes (P=.008). This study provides the first indication that genetic variants of enzymes that control DA availability might be involved in determination of the amount of palatable food intake in children.

Keywords: *MAOA* polymorphisms; *COMT* polymorphisms; Food intake; Childhood obesity; Appetite; Genetic variants

1. Introduction

The obesogenic environments have caused marked increases in the mean weights of many populations over the past few decades [1]. Studies have shown that obese adults exhibit increased food intake in response to palatability [2]. Similar findings have been reported in obese children: they do not compensate after eating an energy-dense food as a preload [3,4], they increase their food intake more than normal-weight controls after exposure to food cues [4], they have higher levels of snack consumption in the absence of hunger [5], and they have higher scores on psychometrically assessed "external eating" [6]. Hoebel [7] suggested that the mesocorticolimbic dopaminergic reward pathways of the brain play a central role in the neuromodulation of appetite. Further evidence for involving of the dopamine in appetite modulation theory comes from the observation that dopaminergic agonists suppress appetite, whereas antagonists tend to enhance it [8]. Since this hypothesis has been proposed, several efforts have been made to identify the key molecular components of dopamine (DA) transmission in obesity. A growing area of research has begun to explore the potential association between specific candidate genes regulating the brain DA system and obesity or associated phenotypes [9]. Candidate genes related to vulnerability to dietary patterns of high energy density or obesity could encode any of the five known DA receptors, important DA metabolism enzymes, or the DA transporter, among potentially many others [10].

Monoamine oxidase (MAO) is a mitochondrial enzyme involved in the degradation of biological amines including serotonin, DA, and norepinephrine. In humans, there are two isozymes: monoamine oxidase A (MAOA) and monoamine oxidase B (MAOB). The *MAOA* gene is located on the short arm of chromosome X [11]. The promoter region of this gene has a variable number tandem repeat (VNTR) polymorphism, *MAOAu-VNTR*, which has been shown to influence

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gene transcription; alleles with 3.5 and 4 repeats were found to transcribe the protein more efficiently than the 3-repeat allele. Studies have been discordant with regard to a rare 5-repeat allele [12,13]. Another polymorphism in the *MAOA* gene is *T941G* (rs6323), a *silent* mutation in exon 8; it was reported to be associated with high (*G* allele) and low (*T* allele) MAOA activity in 40 cell lines [11].

Another important enzyme that acts in the degradation of DA is catechol-o-methyltransferase (COMT). There is evidence that changes in COMT activity cause central and peripheral effects by altering the amounts of DA and norepinephrine in the synaptic cleft between neurons [14]. This enzyme has been involved in mechanisms of reward-motivated behavior, such as those related to obesity [15]. The chromosome 22q11.21 region bears the human *COMT* gene [16]. Several polymorphisms in this gene have been described, but *Val158Met* (24938A>G, rs4680), in the fourth exon, is the most widely studied [17], because of its relationship with enzyme activity.

Based on the hypothesis that brain dopaminergic reward pathways have a central role in the neuromodulation of appetite, we propose that genetic variants that cause altered activities of dopamine-regulating enzymes might be related to palatable food intake and possibly with the physiopathology of obesity. Therefore, we investigated whether the *MAOAu-VNTR*, *MAOA T941G*, and *COMT Val158Met* polymorphisms contribute to the increase of palatable food intake and, consequently, to nutritional status alteration in preschool children of three to four years old.

2. Materials and methods

2.1. Subjects

This was a cross-sectional study undertaken with the cohort from the Ten Steps in Action (BRATSA I) study [18]. The sample consisted of 354 children of three to four years old who were recruited at the Hospital Centenário, located in São Leopoldo, a city in southern Brazil. All eligible mothers were informed by field workers about both the overall aims of the study (advice on the feeding of preschoolers and its effects on the child's health) as well as all research procedures. The study protocol was approved by the Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre, and all parent/guardian of the participants provided written informed consent before commencing the study.

Undergraduate nutrition students were trained to undertake data collection regarding children's anthropometric, dietary, sociodemographic, and health status variables during home visits. The data from 5% of the participants were confirmed by telephone. A clinical assessment was scheduled at a municipal health center, and a dietary assessment was performed once more. Blood samples were collected and brought to the Clinical Analysis Laboratory of the Cardiology Institute of Porto Alegre, where biochemical analyses were performed.

Race or ethnicity was self-defined by skin color (i.e., whites and non-whites) as officially used in demographic censuses in Brazil. More details of the traits studied are described in [19].

2.2. Nutritional status assessed at three to four years old

The child's nutritional status was assessed by means of anthropometric measurements in all visits. Anthropometric measurements were taken as follows: wearing light clothing and unshod, each child was weighed on a digital balance (Filizola - Campo Grande, MS) with 100 g gradations, while stature was measured using a stadiometer (Seca - México, D.F) fixed to a smooth wall, with the child in an erect posture, heels touching the wall. Nutritional status was classified using the body mass index (BMI) for age charts from the International Child Growth Standards released by the World Health Organization (WHO) [20]. Waist circumference was measured at the minimum circumference between the iliac crest and the rib cage using an inflexible measuring tape. Triceps and subscapular skinfolds were measured using a skinfold caliper (Lange - Santa Cruz, CA) to the nearest 1.0 mm. Each skinfold was measured two times on the right side of the body and was analyzed as a z-score according to the WHO *Multicentre Growth Study* standard charts [20].

2.3. Dietary data assessed at three to four years old

Dietary data were obtained using two 24-hour dietary recalls administered at an interval of 15 to 30 days. The first recall was administered during a home visit and the second during the clinical assessment. Mothers were asked about all food and drink consumed by the child on the previous day. The interviewers asked detailed questions about the types of foods, quantities, brands and preparation methods. Portion sizes were confirmed with the aid of an album, specially designed for this study, containing photographs of utensils and foods and based on domestic measures, such as cups, tablespoons, and teaspoons. Calculations to estimate nutritional intake were performed using NutWin, version 1.5, supplemented with information from tables of the chemical composition of foods [21,22] and/or provided by Brazilian manufacturers.

For assessment of the intake of sugar-dense foods (SDF) and lipid-dense foods (LDF), the items listed in response to the dietary recall were classified as SDF if there was 50% or more sugar per 100 g in their composition (soda, Jell-O, candies and artificial juice) and as LDF if they contained more than 30% fat per 100 g (fried pastries, cookies with fillings, cold cuts and sausages, fried foods and chocolate). The means of the results of both recalls was taken and used for analyses.

2.4. DNA analyses

Genomic DNA was extracted from peripheral blood leukocytes by a standard salting-out procedure [23]. The *MAOAu-VNTR* polymorphism was genotyped using the polymerase chain reaction (PCR). The primer sequences were as follows: forward 5′- ACAGCCTGACCGTGGAGAAG - 3′ and reverse 5′- GAACGGACGCTCCATTCGGA -3′ [9]. The PCR products containing the tandem repeat polymorphism were resolved by electrophoresis on 6% polyacrylamide gels with ethidium bromide. The primers used yielded 291, 321, 336, 351 and 381 base pair (bp) fragments corresponding to the 2-, 3-, 3.5-, 4-and 5-repeat alleles, respectively. These were then visualized under UV light to determine the fragment sizes by comparison with a 100 bp DNA ladder. The *MAOA T941G* (rs6323) polymorphism was detected by PCR-RFLP analysis with the following primers: forward 5′- GACCTTGACTGCCAAGAT -3′ and reverse 5′- CTTCTTCTTCCAGAAGGCC -3′[24]. PCR products were digested with the *Fnu*IV restriction enzyme according to the manufacturer's instructions. Genotypes were determined after electrophoresis on 1.5% agarose gels stained with ethidium bromide. The *COMT Val158Met* (rs4680) polymorphism was detected by PCR-RFLP analysis with the following primers: forward 5′ - TCGTGGACGCCGTGATTCAGG - 3′ and reverse 5′ – AGGTCTGACAACGGGTCAGGC - 3′[25]. PCR products were digested with the *Nla*III restriction enzyme according to the manufacturer's instructions. Genotypes were determined after electrophoresis on 7% polyacrylamide gels stained with ethidium bromide.

2.5. Statistical analyses

Allele frequencies were estimated by gene counting. A chi-square goodness-of-fit test was used to determine whether the distribution of observed genotype frequencies agreed with those expected under Hardy-Weinberg equilibrium. For *MAOA* polymorphisms, association analyses were performed separately in boys and girls because this gene is located in the X chromosome; consequently, boys bear only one allele for each *MAOA* variant, while girls have two X chromosomes and are carriers of two *MAOA* alleles. Median kilocalories of each food cluster intake (SDF and LDF), mean kilocalories of total food intake per day, and means of anthropometric parameters (waist circumference, triceps and subscapular skinfolds Z-score and BMI Z-score) were compared among carriers of the different genotypes by one-way analysis of variance (ANOVA), T-test, Kruskal Wallis or Mann-Whitney U tests, depending on the distribution of variables. All tests and transformations were performed using the Statistical Package for Social Sciences, Version 16.0 (SPSS, Chicago, IL, USA).

3. Results

The mean age of children in this study was 4.08±0.95 years (mean±SD), 41.7% of children were white, and the percentage of boys in the sample was 57.2%.

Genotype frequency distributions observed for the gene variants studied did not reveal statistically significant departures from those expected under Hardy–Weinberg equilibrium for *MAOAu-VNTR* (χ^2=0.546, 2DF, *P*=.761) and for *MAOA T941G* (χ^2=0.405, 2DF, *P*=.817) in girls; and for *COMT Val158Met* in the whole sample (χ^2=0.027, 2DF, *P*=.987). Allele and genotype frequencies for the three polymorphisms studied are presented in Table 1. No statistically significant differences in genotype frequency distributions were detected between white and non-white samples (data not shown).

In the boys' sample, the *MAOAu-VNTR*long* allele presence was associated with higher intake of LDF (median: 134.98 kcal [interquartile range: 26.44–270.16 kcal]) when compared with the *MAOAu-VNTR*short* allele presence (median: 60.10 kcal [interquartile range: 0.00–192.31 kcal]; *P*=.009; Table 2); the SDF intake was also higher in male carriers of the *MAOAu-VNTR*long* allele (median 100.45 kcal [interquartile range: 54.41–163.32 kcal]) when compared with *MAOAu-VNTR*short* allele carriers (median: 80.01 kcal [interquartile range: 37.45–127.11]; *P*=.034; Table 2). No differences

Table 1
Distributions of the *MAOA-u VNTR, MAOA T941G and COMT Val158Met* polymorphisms, alleles, and genotype frequencies in children from three to four years of age

Genotypes	Gender % (n)		Alleles	Gender group %	
	Boys	Girls		Boys	Girls
MAOA-u VNTR			*MAOA-u VNTR*		
Long/Long	-	42.4 (59)	*Long* allele	65.5	64.0
Long/Short	-	43.2 (60)	*Short* allele	34.5	36.0
Short/Short	-	14.4 (20)			
MAOA T941G			*MAOA T941G*		
G/G	-	3.6 (5)	G allele	20.7	20.15
T/G	-	35.9 (50)	T allele	79.3	79.85
T/T	-	60.5 (84)			
Genotypes	All % (n)	Alleles	All %		
COMT Val158Met		*COMT Val158Met*			
Met/Met	37.7 (123)	Met allele	61.5		
Val/Met	47.5 (155)	Val allele	38.5		
Val/Val	14.8 (48)				

n=number of carriers of each genotype.

regarding children`s nutritional status were observed among genotypes, assessed by means of anthropometric measurements (BMI Z-score, waist circumference and Z-score of triceps and subscapular skinfolds). In the girls' sample, the *MAOAu-VNTR* polymorphism was not associated with food intake and anthropometric data (Table 3). For the *MAOA T941G* polymorphism, no significant associations were verified with eating behavior or nutritional status in both genders (Table 2 and 3).

In the whole sample, the *COMT Val158Met*Val* allele presence was associated with higher intake of LDF foods when compared with *Met/Met* homozygotes (P=.008); the medians were 133.79 kcal [interquartile range: 44.23–265.80 kcal] and 83.37 kcal [interquartile range: 0.00–252.95 kcal], respectively (Table 4). This single nucleotide polymorphism (SNP) was not associated with nutritional status in these children.

4. Discussion

There is increasing evidence for a role of the dopaminergic pathway in the development of obesity. Food rewards and their associated stimuli elevate DA levels in crucial components of brain reward circuits [26]. In fact, food might be the most important natural stimulus for the reward system in the brain [27]. Small et al. [28] suggest that the amount of feeding-induced released dopamine correlates with the degree of experienced pleasure. Individual differences in reward sensitivity have been implicated in food intake. In this work, we evaluated the association of polymorphisms in genes of enzymes that affect dopamine availability, MAOA and COMT, with palatable food intake and nutritional status in preschool children. In a literature review no similar studies were found and few works evaluated the association of *MAOA* and *COMT* genetic variants with obesity risk in adults.

In this study, our results demonstrated that the *MAOAu-VNTR* polymorphism was associated with the amount of palatable food intake in boys: those with the high-activity (*long*) allele intake higher amounts of sugar- and lipid-dense foods than those with the low-activity (*short*) allele. Our findings are corroborated by functional polymorphism studies. The presence of the *MAOAu-VNTR*long* allele is associated with higher MAOA activity and this might result in lower DA levels in presynaptic neurons [29,30]; women with one copy of this allele also have higher levels of homovanillic acid (HVA), the main metabolite of DA [31]. This finding implies that those who have a high activity MAOA allele have increased DA metabolism, and consequently might have lower DA levels, which might enhance the individual's motivation for pleasurable activities, such as overcompensatory palatable food intake.

To our knowledge, only two studies have evaluated the association of the *MAOAu-VNTR* polymorphism with obesity. Camarena et al. [29], using the transmission disequilibrium test approach, found that the low-activity allele was preferentially transmitted from parents to their obese offspring. In a large population-based study, Need et al. [32] found that European white female carriers of the low-activity variant were significantly more likely to be obese (BMI>30). These studies are not totally comparable with our study, but these results are in apparent opposite direction from our data. This discrepancy might be explained by the possibility of no association between SDF

Table 2
Food intake according to *MAOA-u VNTR* and *MAOA T941G* polymorphisms genotypes of boys from three to four years old

Food intake					
MAOA-u VNTR	Long allele	n	Short allele	n	*P*
SDF (kcal)	100.45 [54.40–163.32][a]	120	80.01 [37.45–127.11][a]	63	.034[b]
LDF (kcal)	134.97 [26.43–270.16][a]	120	60.10 [0.00–192.31][a]	63	.009[b]
Average energy intake daily (kcal)	1544.49±389.73 [c]	120	1512.37±423.94[c]	63	.608[d]
T941G	G allele	n	T allele	n	*P*
SDF (kcal)	82.30 [40.75– 128.10] [a]	38	97.15 [49.43–159.47][a]	145	.105[b]
LDF (kcal)	53.23 [0.00– 228.19] [a]	38	127.71 [20.58–256.50][a]	145	.154[b]
Average energy intake daily (kcal)	1545.58±430.21 [c]	38	1530.25±394.45 [c]	145	.834[d]

SDF indicates high sugar density foods; LDF indicates high lipid density foods.
n=number of carriers of each allele/genotype.
[a] Median [Interquartile Range].
[b] Mann-Whitney U.
[c] Mean±standard deviation.
[d] Test T for independent sample.

Table 3
Food intake according to *MAOA-u VNTR* and *MAOA T941G* polymorphism genotypes in girls from three to four years old

Food intake							
MAOA-u VNTR	Long/Long	n	Long/Short	n	Short/Short	n	*P*
SDF (kcal)	97.62 [44.70–144.74][a]	57	100.66 [28.06–169.45][a]	58	151.68 [41.69–199.26] [a]	20	.318[b]
LDF (kcal)	106.84 [47.73–282.79][a]	57	146.31 [37.25–271.34][a]	58	98.67 [0.00–254.53] [a]	20	.671[b]
Average energy intake daily (kcal)	1472.04±406.36 [c]	57	1543.14±434.21[c]	58	1406.79±235.16 [c]	20	.370[d]
T941G	G/G	n	G/T	n	T/T	n	*P*
SDF (kcal)	139.37 [56.81–203.52][a]	5	108.80 [39.14–173.46][a]	49	94.75 [36.95–154.27][a]	81	.586[b]
LDF (kcal)	253.60 [15.67–303.82][a]	5	122.11 [46.88– 247.55][a]	49	106.84 [20.77–282.79][a]	81	.265[b]
Average energy intake daily (kcal)	1308.26±214.69 [c]	5	1477.26±402.75 [c]	49	1513.79±405.83[c]	81	.509[d]

SDF indicates high sugar density foods; LDF indicates high lipid density foods.
n=number of carriers of each genotype.
[a] Median [Interquartile Range].
[b] Kruskal Wallis Test.
[c] Mean±standard deviation.
[d] One-Way ANOVA.

and LDF intake, in young children, and obesity in adults. However, in an animal model, Frazier et al. [33] described that early life diet was associated with adult feeding behavior and body weight and, additionally, Johnson et al. [34] have demonstrated that in humans, an energy-dense, low-fiber, high-fat diet at ages 5 and 7 y were associated with higher fat mass and greater odds of excess adiposity in childhood 2 or 4 y later. Anyway, there is lack of robust evidence, from prospective studies, of association between dietary patterns in young children with obesity in adult life.

In this study, the *MAOAu-VNTR* polymorphism association with SDF and LDF was only detected in boys. In association studies of multifactorial characteristics with genetic variants, gender-specific associations have been much more common, possibly due to genotype interaction with other variables that are diverse between genders. Additionally, two studies on children have reported some gender differences in food preferences [35,36]; considering the gender differences already reported, is possible that genotype associations with food intake were influenced differently in boys and girls.

The other polymorphism investigated in this gene, *MAOA T941G*, was not associated with food intake or anthropometric data of children in our study. In a previous work, Hotamisligil and Breakefield [11] reported an association of the *MAOA T941G*T* allele with lower MAOA enzyme activity in 40 cell lines of known MAOA activity. However, this SNP is located in the third base of a codon and does not affect the amino acid sequence of the enzyme [11], and no other works were found that evaluate the association of this variant with food intake or obesity risk.

COMT is the exclusive enzyme that o-methylates DA. This o-methylation may occur before or after deamination by MAO enzymes, leading to DA inactivation. The *Met* allele of the *COMT Val158Met* polymorphism produces a labile protein with significantly lower activity [37], thus conferring slow degradation and inactivation of DA [37], resulting in higher DA levels. Individuals with the *Met/Met* genotype have a three to four-fold reduction in enzymatic degradation activity compared to *Val/Val* homozygotes; heterozygotes have intermediate activity [38]. We found an association between the *Val* allele presence and higher intake of lipid-dense foods, which is consistent with the suggested role of the *COMT Val158Met* polymorphism in obesity physiopathology [14]. However, there is still no agreement regarding this gene variant in previously published association studies with obesity risk. Need et al. [32] and Happonen et al. [39], assessing the possible association between this polymorphism with BMI and waist-hip ratio (WHR), did not find any such relationship, while Annerbrink et al. [40] found that subjects homozygous for the low-activity allele (*Met/Met*) displayed higher WHR and abdominal sagittal diameter compared to *COMT Val158-Met*Val* allele carriers.

The *MAOAu-VNTR* and *COMT Val158Met* polymorphisms were associated with palatable food intake; however, they were not associated with nutritional status or total energy intake in our study, probably because our sample consisted of young children, which still have the innate ability to match energy intake to energy needs, compensating higher energy intake at subsequent meals and thus preventing excess weight or fat gain [41–42].

The present and potential discrepancies between studies may be explained by different genetic and lifestyle characteristics of the populations studied, which may modify the effects of these gene variants. Additionally, our study is not totally comparable with previous published works because we examined food intake in children and previous research investigated obesity risk in adults. Moreover, our findings of association of high-activity alleles of *MAOAu-VNTR* and *COMT Val158Met* polymorphisms with higher amounts of palatable food intake are supported by several studies that suggest that the Reward Deficiency Syndrome (RDS) is implicated in the genesis of obesity [15,27,28]. The study by Chen et al. [43] in humans also presents findings consistent with a reward deficiency model of obesity, whereby low brain dopamine levels

Table 4
Food intake according to the *COMT Val158Met* polymorphism genotype in children from three to four years old

Food intake					
	Met/Met	n	Val carries	n	*P*
SDF (kcal)	88.25 [43.65–138.14][a]	120	101.64 [42.35–168.61][a]	198	0.154[b]
LDF (kcal)	83.37 [0.00–252.95][a]	120	133.79 [44.23–265.80][a]	198	0.008[b]
Average energy intake daily (kcal)	1501.93±424.77[c]	120	1524.90±385.27[c]	198	0.620[d]

SDF indicates high sugar density foods; LDF indicates high lipid density foods.
n=number of carriers of each genotype.
[a] Median [Interquartile Range].
[b] Mann-Whitney U.
[c] Mean±standard deviation.
[d] Test T for independent sample.

predict overeating and obesity, and shows that administration of agents that increase dopamine results in reduced feeding behavior.

An inherent limitation to our study is the moderate sample size, which may not have enough power to detect an association of polymorphisms with small effects on food intake and anthropometric measurements, such as *MAOA T941G*. However, we believe that the size of our sample was sufficient to detect relatively large genetic effects, reinforcing the importance of our findings relating the *MAOAu-VNTR* polymorphism to a higher intake of LDF and SDF and the *COMT Val158Met* polymorphism to a higher intake of LDF. Another apparent limitation of our study is that the subjects are only three to four years of age and might not have free access to food. However, according to several authors, it is widely held that children "eat what they like", and research has repeatedly shown that children's food preferences are highly predictive of their intake [35,44–48]. Obviously, parents may influence their children's food choices by exerting feeding practices; there also exist data on family correlations that provide further evidence for a familial transmission of food preferences [49]. This familial transmission of food preferences may be evidenced not only by environmental influence but also because this characteristic also has a hereditary component. Our study and findings are innovative because we detected candidate genes for childhood eating patterns and found that polymorphisms already influence palatable food intake in early life. Faith and Keller [49] describe how, despite changes in childhood obesity prevalence in recent decades, the prominent role of genes cannot be dismissed and that the genetics of childhood eating patterns is a relatively understudied field. The same authors point to the importance of genetic factors in the "eating in the absence of hunger" trait.

In summary, our results suggest that the *MAOAu-VNTR* and *COMT Val158Met* polymorphisms might have an impact on children's eating behavior. The presence of high- activity alleles for both polymorphisms was associated with higher palatable food intake. These results therefore strongly suggest a role for heritable variation in DA metabolism in palatable food intake and they underscore the need for additional research to replicate these results and to identify the complex interplay between the examined gene polymorphisms and their functions. Furthermore, the investigation of other variants in genes related with food reward may be interesting. In a recent review, Fortuna [50] described the hedonic effect of sugar rich meals is also mediated through the endorphin system via Mu receptors. For *OPRM1*, the Mu receptor gene, there are 39 SNPs described in the Single Nucleotide Data Base of National Center for Biotechnology Information, and the investigation of the association of these polymorphisms with food intake patterns seems promising.

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