

The Alpha2-Adrenergic Receptor Gene and Body Fat Content and Distribution: The HERITAGE Family Study

Christophe Garenc,¹ Louis Pérusse,¹ Yvon C. Chagnon,² Tuomo Rankinen,³ Jacques Gagnon,⁴ Ingrid B. Borecki,⁵ Arthur S. Leon,⁶ James S. Skinner,⁷ Jack H. Wilmore,⁸ D. C. Rao,^{5,9} and Claude Bouchard³

¹Division of Kinesiology, Department of Preventive Medicine, Laval University, Ste-Foy, Québec

²Laval University Research Center Robert-Giffard, Laval University, Ste-Foy, Québec

³Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana, USA

⁴Laboratory of Molecular Endocrinology, CHUQ Research Center, CHUL Pavillon, Ste-Foy, Québec

⁵Division of Biostatistics, Washington University Medical School, St. Louis, Missouri, USA

⁶School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, Minnesota, USA

⁷Department of Kinesiology, Indiana University, Bloomington, Indiana, USA

⁸Department of Health and Kinesiology, Texas A&M University, College Station, Texas, USA

⁹Department of Genetics and Psychiatry, Washington University Medical School, St. Louis, Missouri, USA

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Abstract

Background: Among adrenergic receptor subtypes that regulate lipid mobilization, the $\alpha 2$ -adrenergic receptor is involved in the inhibition of fatty acid mobilization from adipose tissue. A C-1291G polymorphism is located in the $\alpha 2$ -adrenergic receptor gene (ADRA2A) but no association with body fat accumulation has been reported yet.

Materials and Methods: Body mass index (BMI), fat mass (FAT), percentage body fat (%FAT), trunk-to-extremity skinfold ratio (TER), sum of eight skinfolds (SF8), and abdominal subcutaneous (ASF), visceral (AVF), and total (ATF) fat areas assessed by CT scan have been measured in adult sedentary white ($n = 503$) and black ($n = 276$) subjects participating in the HERITAGE Family Study. Association between the C-1291G polymorphism and each phenotype was tested separately in men and women of

each race using ANCOVA with the effects of age as covariate in addition to the effects of BMI for TER and of FAT for AVF, ASF, and ATF.

Results: The allele frequencies of the ADRA2A C-1291G polymorphism differed between races. No association was observed in white subjects, except for a moderate effect of the polymorphism accounting for less than 1% of the variance in AVF and ATF in women. In black subjects, however, the G-1291 allele was found to be associated with an increase of TER in men (3.8% of variance accounted for by the polymorphism), while in black women it was associated with a decrease in TER (2.9%) and in AVF (2.5%).

Conclusion: These results suggest a role for the ADRA2A gene in determining the propensity to store fat in the abdominal area, independently of total body fatness.

Introduction

Adrenergic receptor subtypes are involved in the regulation of lipid mobilization. In human adipose tissue, the $\beta 1$ -, $\beta 2$ -, and $\beta 3$ -adrenergic receptors stimulate lipolysis while the $\alpha 2$ -adrenergic receptor inhibits lipolysis through G-proteins (1). It has been suggested that the net lipid mobilization depends on the balance between the stimulatory and the inhibitory effects of catecholamines on β - and $\alpha 2$ -adrenergic receptors, respectively (2,3).

Functional studies have shown that the net catecholamine effect on a specific adrenergic receptor

subtype is not homogeneous across depots of adipose tissue, is different in men and women, and is affected by the level of obesity. The number of $\alpha 2$ sites is higher than the number of β sites in the femoral and abdominal subcutaneous fat depots, but equal in the abdominal visceral fat depots (3,4). Compared to lean subjects, obese men are characterized by a stronger $\alpha 2$ -adrenergic component in the abdominal subcutaneous fat depot; no difference is observed in the femoral depot. However, in obese women, the $\alpha 2$ -adrenergic component is more important in the subcutaneous abdominal and femoral depots (5,6). An $\alpha 2$ -adrenergic antilypolytic effect can partly explain the difference between the gynoid and the android pattern of fat distribution observed on average in women and men, respectively (7). The balance between the β - and the $\alpha 2$ -adrenergic receptor components could potentially

Address correspondence and reprint requests to: Louis Pérusse, PhD, Division of Kinesiology, Department of Preventive Medicine, PEPS—Laval University, Ste-Foy, Québec G1K 7P4, Canada. Phone: (418) 656-7831; fax: (418) 656-3044; e-mail: louis.perusse@kin.msp.ulaval.ca.

explain the high catecholamine-induced lipolysis observed in visceral fat depot as compared to the abdominal subcutaneous fat depot (8,9). In addition, several studies showed that the α 2-adrenoceptor component behaves differently in response to exercise according to the level of obesity. Using microdialysis probes in subcutaneous abdominal fat cells of men, the α 2-adrenergic component has been shown to impair lipid mobilization during exercise through activation of α 2-adrenergic receptors by epinephrine (10) in a greater extent in obese than in normal-weight subjects (11). This effect was observed despite the high catecholamine concentration observed during exercise that was proposed to preferentially stimulate the β -adrenergic component (3). These observations and the evidence suggesting that total adiposity, fat distribution, and visceral fat are influenced by genetic factors (12–14), support the role of the α 2-adrenoceptor gene (ADRA2A) as a candidate gene for adiposity and fat distribution.

The ADRA2A, which maps to chromosome 10q25, is expressed in subcutaneous and visceral fat depots (15). Several DNA polymorphisms have been detected in the ADRA2A gene, including the Dra I restriction fragment length polymorphism (RFLP) (16) that was tested for association with essential hypertension (17) and fat distribution (18,19) in the Québec Family Study. In the Québec Family Study, the Dra I RFLP was associated with the trunk-to-extremity skinfolds ratio measurement in females, suggesting that this polymorphism favors the accumulation of fat in the truncal-abdominal region. Recently, this polymorphism was shown to be associated with abdominal subcutaneous fat areas (19). Another polymorphism of the ADRA2A gene, a C to G transversion in the promoter region (position –1291) was detected by Lario et al. (20) but, to the best of our knowledge, no association or linkage studies between the latter polymorphism and obesity-related phenotypes have been reported yet.

In the present study, we investigated the associations between the C-1291G polymorphism located in the promoter region of the ADRA2A gene and total adiposity and fat distribution measured in subjects from the HERITAGE Family Study.

Methods

Subjects

The sample of the present study includes a total of 503 (245 men and 258 women) white and 276 (91 men and 185 women) black adult subjects, who are participants in the HERITAGE Family Study. In the present study, we used only the baseline HERITAGE data. All subjects had to be sedentary, in good health, and meet a set of inclusion criteria described in detail elsewhere (21). The Institutional Review Board of each university of the HERITAGE Family Study research consortium approved the study protocol. Written informed consent was obtained from each participant.

Phenotype Measurements

Anthropometric and Body Density Measurements These measurements have been described in detail previously (22). Body mass index (BMI) was calculated as weight (kg)/height² (m²). The trunk-to-extremity skinfolds ratio (TER = [subscapular + suprailiac + abdominal + midaxillary]/[biceps + triceps + medial calf + thigh]) was used as an indicator of the propensity to store fat in the truncal-abdominal area relative to the extremities. The sum of eight skinfolds (SF8) was used to assess the level of subcutaneous fat. Hydrostatic weighing was used to assess body density. Percentage body fat (%FAT) was estimated from body density and fat mass (FAT) was derived (22).

Abdominal Visceral, Subcutaneous, and Total Fat Areas Abdominal fat was assessed by computed tomography (CT) as previously described (14). Scans were obtained between the fourth and fifth lumbar (L4-L5) vertebrae, with subjects in the supine position with arms stretched above the head. Total fat area was calculated using an attenuation range of –190 to –30 Hounsfield units. Abdominal visceral fat (AVF) area was defined by drawing a line within the inner portion of the muscle walls surrounding the abdominal cavity. Abdominal subcutaneous fat area (ASF) was obtained by calculating the difference between abdominal total fat (ATF) and AVF areas.

Genotype Determination

PCR Amplification of the C-1291G Polymorphism DNA was extracted from lymphoblastoid cell lines after digestion by proteinase K and purification with phenol-chloroform (23). PCR amplification was carried out in a volume of 20 μ l containing 150 ng DNA; 200 μ M of each dATP, dCTP, dGTP, and dTTP; 1 \times buffer (50 mM NaCl, 10 mM Tris-HCl, 10 mM MgCl₂, 1 mM DTT, pH = 7.5 at 25°C); 2 \times of Q solution; 50 nM of each primer; and 1 U of Taq polymerase (Perkin Elmer Cetus, Shelton, CT). The forward primer was 5'-TCACACCGGAGGTTACTT-CCCTCG-3' and the reverse primer was 5'-TCCGACGACAGCGCGAGTT-3'. These primers generated a product of 522 bp that was cut into five fragments (5, 62, 116, 165, and 174 bp) with the Msp I restriction enzyme. The 174-bp fragment was cut into two bands (121 and 53 bp) in the presence of the G-1291 allele (20). The amplification protocol was 1) one cycle of denaturation at 94°C for 3 min, annealing at 63°C for 1 min, and extension at 72°C for 1 min; 2) 35 cycles of denaturation at 94°C for 30 sec, annealing at 63°C for 30 sec, and extension at 72°C for 45 sec; and 3) one final elongation cycle at 72°C for 10 min. A negative control without DNA was performed in every run of amplification.

After each amplification, PCR product was digested overnight at 37°C after adding 7.5 U of the restriction enzyme Msp I to the PCR mixture. Resulting fragments were separated by electrophoresis

in 2% agarose gels. Each gel was run for 2 hrs at 150 V, stained with ethidium bromide, and photographed under UV transmitted light. The Φ X174 DNA digested with Hae III was used as length marker to estimate the size of the digested DNA fragments. The allele without the Msp I restriction site is designated here as C-1291 allele (174 bp), whereas the allele with the Msp I restriction site is the G-1291 allele (121 + 53 bp).

Statistical Analysis

All statistical analyses were performed using the SAS (24) software. A Chi-square test was performed to determine whether the genotype frequencies of the C-1291G ADRA2A polymorphism were in Hardy-Weinberg equilibrium, and to test for potential race differences in allele frequencies. We also calculated the polymorphic information content (PIC) (25).

Association Two genotype groups were considered: carriers (genotypes C-1291G and G-1291G) and noncarriers (genotype C-1291C) of the G-1291 allele. Because race and gender differences were previously reported for the body fat phenotypes investigated in the present study (26), associations between the C-1291G polymorphism and each phenotype were investigated separately in each of the four sex-by-race groups using an ANCOVA (general linear model) procedure that included the effects of age (age, age², and age³) as covariables. AVF, ASF, and ATF were further adjusted for FAT. As previously done in the Québec Family study (18,19), and for comparison purpose, TER was also adjusted for BMI to control for the level of adiposity.

Results

Allele and genotype frequencies of the ADRA2A C-1291G polymorphism are presented in Table 1. The allele frequencies are strikingly different between white and black subjects, with blacks exhibiting a greater frequency of the G-1291 allele (0.66) compared to whites (0.27). However, allele frequencies of whites did not differ from those reported in

other healthy (C-1291 allele: 0.71) or hypertensive (C-1291 allele: 0.77) white subjects (20).

The results of the association analyses between the C-1291G polymorphism in the ADRA2A gene and obesity-related phenotypes are presented in Table 2 for whites and Table 3 for blacks. No significant evidence of association was observed in white men. The G-1291 allele was associated with lower AVF (-11.4%; $p = 0.02$) and ATF (-4%; $p = 0.03$) in white women and a greater TER (26.6%; $p = 0.04$) and ASF (14.4%; $p = 0.03$) in black men. However, the low percentage of variance accounted for by the C-1291G polymorphism for AVF (0.74%) and ATF (0.18%) in white women and for ASF (0.37%) in black men suggests that these associations have little biological significance. The strongest results were observed in black women. The carriers of the G-1291 allele exhibited a lower TER (-14.4%; $p = 0.04$) and AVF (-27%; $p = 0.002$) than the noncarriers. The variance accounted for by the C-1291G polymorphism reaches 2.9% and 2.5% for TER and AVF, respectively. The association with TER was caused by a lower trunk skinfolds (carriers: 92 ± 3 mm; noncarriers: 101 ± 10 mm) and a higher extremity skinfolds (carriers: 94 ± 3 mm; noncarriers: 90 ± 10 mm) in carriers compared to noncarriers (data not shown). Black male carriers of the G-1291 allele exhibited a greater TER (TER = 1.91 ± 0.06) than noncarriers (1.57 ± 0.15 ; $p = 0.04$) (Table 3) and the percentage of variance accounted for by the C-1291G polymorphism was 3.8%. The association with TER was caused by a greater trunk skinfolds (carriers: 80 ± 4 mm; noncarriers: 70 ± 12 mm) and a lower extremity skinfolds (carriers: 46 ± 3 mm; noncarriers: 56 ± 8 mm) in carriers compared to noncarriers (data not shown). AVF exhibited a significant association with the C-1291G polymorphism in black women. Because AVF was adjusted for total body fatness, the results support the hypothesis of a role of the ADRA2A C-1291G polymorphism in determining the amount of fat stored in the abdominal depot, independently of body fat mass.

Table 1. Genotype and allele frequencies of the α 2-adrenergic receptor gene C-1291G polymorphism in sedentary white and black subjects of the HERITAGE Family Study

	<i>n</i>	PIC	Allele Frequency*		Genotype Frequencies [†]		
			C-1291	G-1291	C-1291C	C-1291G	G-1291G
Whites	494	0.32	0.73	0.27	0.53	0.40	0.07
Blacks	274	0.35	0.34	0.66	0.09	0.50	0.41

PIC, *n* = number of subjects; polymorphism information content.

* χ^2 for race difference in allele frequencies = 111.8, *df* = 1, $p < 0.0001$.

[†]Hardy-Weinberg equilibrium in whites $\chi^2 = 0.035$, *df* = 2, $p > 0.05$ and in blacks $\chi^2 = 0.75$, *df* = 2, $p > 0.05$.

Table 2. Associations of the $\alpha 2$ -adrenergic receptor gene C-1291G polymorphism with body composition measured in white men and women

	Men					Women				
	<i>N</i>	Noncarriers of the G-1291 allele	<i>N</i>	Carriers of the G-1291 allele	<i>p</i>	<i>N</i>	Noncarriers of the G-1291 allele	<i>N</i>	Carriers of the G-1291 allele	<i>p</i>
BMI (kg/m ²)	137	26.6 ± 0.4	102	26.9 ± 0.4	0.54	123	25.0 ± 0.4	131	25.1 ± 0.4	0.99
FAT (kg)	127	19.5 ± 0.8	99	21.0 ± 1.0	0.24	117	20.8 ± 0.9	127	21.5 ± 0.9	0.60
%FAT (%)	127	22.3 ± 0.6	99	23.6 ± 0.7	0.20	117	29.9 ± 0.8	127	30.4 ± 0.7	0.64
TER	126	1.69 ± 0.04	93	1.75 ± 0.05	0.31	113	0.92 ± 0.02	125	0.89 ± 0.02	0.28
SF8 (mm)	126	130 ± 4	93	133 ± 5	0.63	113	164 ± 5	125	166 ± 5	0.82
AVF (cm ²)	127	108 ± 3	98	110 ± 4	0.70	115	79 ± 3	125	70 ± 3	0.02
ASF (cm ²)	127	225 ± 3	98	226 ± 4	0.84	115	289 ± 5	125	282 ± 5	0.33
ATF (cm ²)	127	333 ± 4	98	336 ± 5	0.66	115	367 ± 5	125	352 ± 5	0.03

Data are Least Square Mean ± SEM (see text for details).

N, number of subjects; BMI, body mass index; FAT, fat mass; %FAT, percentage body fat; TER, trunk-to-extremity skinfold ratio; SF8, sum of eight skinfolds; AVF, abdominal visceral fat area; ASF, subcutaneous fat area; ATF, total fat area.

Discussion

Previous reports suggest that there is a genetic component in the response of catecholamine-stimulated lipolysis of abdominal subcutaneous fat cells to prolonged overfeeding (27), exercise training (28), or a very-low-calorie diet (29). The adrenergic receptor genes are reasonable candidates to account for these genetic effects. The present study focuses on one

such candidate gene, the ADRA2A gene. In the present study, a polymorphism in the promoter region of the ADRA2A gene (C-1291G polymorphism) was investigated for its effect on body fat and fat distribution in black and white subjects. The impact of the ADRA2A polymorphism was marginal in white subjects; the association observed with AVF ($p = 0.02$) and ATF ($p = 0.03$) in women explained

Table 3. Associations of the $\alpha 2$ -adrenergic receptor gene C-1291G polymorphism with body composition measured in black men and women

	Men					Women				
	<i>N</i>	Noncarriers of the G-1291 allele	<i>N</i>	Carriers of the G-1291 allele	<i>p</i>	<i>N</i>	Noncarriers of the G-1291 allele	<i>N</i>	Carriers of the G-1291 allele	<i>p</i>
BMI (kg/m ²)	12	26.9 ± 1.5	77	27.3 ± 0.6	0.81	13	28.1 ± 1.7	168	28.2 ± 0.5	0.97
FAT (kg)	12	23.5 ± 3.2	74	20.6 ± 1.2	0.40	12	28.0 ± 3.5	129	27.9 ± 1.1	0.99
%FAT (%)	12	26.1 ± 2.1	74	22.9 ± 0.8	0.17	12	35.0 ± 2.4	129	36.1 ± 0.7	0.65
TER	10	1.57 ± 0.15	68	1.91 ± 0.06	0.04	10	1.18 ± 0.08	125	1.01 ± 0.02	0.04
SF8 (mm)	10	126 ± 18	68	121 ± 7	0.80	10	178 ± 18	125	179 ± 5	0.98
AVF (cm ²)	12	94 ± 10	74	75 ± 4	0.08	12	89 ± 7	125	65 ± 2	0.002
ASF (cm ²)	12	208 ± 12	74	238 ± 5	0.03	12	338 ± 16	125	346 ± 5	0.63
ATF (cm ²)	12	302 ± 16	74	313 ± 6	0.53	12	427 ± 17	125	412 ± 5	0.39

Data are Least Square Mean ± SEM (see text for details).

N, number of subjects; BMI, body mass index; FAT, fat mass; %FAT, percentage body fat; TER, trunk-to-extremity skinfold ratio; SF8, sum of eight skinfolds; AVF, abdominal visceral fat area; ASF, subcutaneous fat area; ATF, total fat area.

less than 1% of the variance. In black subjects, the association analyses revealed that the G-1291 allele was associated with a 27% increase of TER in men (3.8% of variance accounted for by the polymorphism), whereas in black women it was associated with a 14% decrease in TER (2.9% of variance accounted for by the polymorphism) and a 27% decrease in AVF (2.5% of variance accounted for by the polymorphism). The association observed with ASF in black men, although significant ($p = 0.03$), explained only 0.4% of the variance. Because TER is an indicator of the propensity to store fat in the truncal-abdominal area relative to the extremities, these results suggest that black men who are carriers of the G-1291 allele are more prone to develop an android pattern of fat distribution while their female counterparts are more susceptible to develop a gynoid pattern of fat distribution. This gender difference in fat distribution is supported by the association observed in black women in whom the C-1291G polymorphism of the ADRA2A gene is associated with a reduced amount of abdominal visceral fat after adjustment for total body fatness.

The race differences observed in the impact of the ADRA2A C-1291G polymorphism on the phenotypes investigated are most likely attributable to the difference in the allele frequencies between the two groups. With more than a 2-fold higher frequency of the G-1291 allele in blacks (0.66) compared to whites (0.27), the impact of the polymorphism is expected to be higher in the black population compared to the white population. It is not rare to encounter such a difference between races for a polymorphism in a given candidate gene. Previous reports have shown such race difference for lipid metabolism candidate gene polymorphisms in other cohorts (30,31). Several evolutionary forces such as mutation, migration, natural selection, or random genetic drift can produce changes in allele frequencies and thus contribute to explaining the difference observed between blacks and whites for the frequency of ADRA2A C-1291G polymorphism.

The results of association analyses in blacks also revealed sex differences in the impact of the polymorphism, which is associated with a tendency to store fat in the trunk for males compared to a tendency to store fat in the extremities for females. A few studies have suggested that the antilipolytic effect of the $\alpha 2$ -adrenergic receptor varies between subcutaneous and visceral fat depots according to gender and obesity status. For instance, the $\alpha 2$ -adrenergic receptor exhibited a lower antilipolytic sensitivity in abdominal than in gluteal subcutaneous fat of nonobese females, leading to a higher catecholamine-induced lipolysis through the β -adrenergic receptor component in the former compared to the latter, and this regional difference was more pronounced in women than in men (7). Also, it

has been proposed that the number of $\alpha 2$ -adrenergic receptors varies between fat depots being lowest in AVF and highest in gluteal fat depots with intermediate values in ASF (4). Furthermore, the maximal antilipolytic response was shown to be more pronounced in abdominal and gluteal subcutaneous fat depots of obese women compared to their nonobese counterparts, suggesting that a strong $\alpha 2$ -component could lead to subcutaneous fat accumulation (4). Thus, if we speculate that the G-1291 allele is associated with a higher $\alpha 2$ -adrenergic component than the C-1291 allele (change in promoter sequence that leads to a higher ADRA2A gene expression), the effect should be stronger in the gluteal region of women, which has a high $\alpha 2$ -adrenergic component, than in the abdominal subcutaneous region. This will lead to a greater fat accumulation in extremities of women as compared to men, which is in agreement with the results observed in the present study. The $\alpha 2$ -component of the AVF behaves differently. It has been hypothesized, although direct experimental evidence in support of the hypothesis is lacking, that the increase in fat mobilization from the visceral depot in upper-body obesity results in a higher free fatty acid release draining through the portal vein (32). The blunted metabolism observed in abdominal visceral obesity is characterized by high lipolytic $\beta 3$ -adrenergic receptor and low antilipolytic $\alpha 2$ -adrenergic receptor sensitivities in men (8).

Considering the evidence showing that it is the balance between the $\alpha 2$ - and the β -adrenergic receptors that provides the most important physiological information about fat accumulation and distribution, other polymorphisms in the $\beta 2$ - and $\beta 3$ -adrenergic receptors are also important to consider because they could have an impact on the $\alpha 2$ -/ β -adrenergic balance. Several studies reported evidence of association between polymorphisms in the ADRA2A gene (18,19), the ADRB2 gene (19,33–37), the ADRB3 gene (19,38–40), and obesity-related traits. The effects of the ADRA2A polymorphism on TER reported in the present study are in agreement with those previously observed in the Québec Family Study (18) in which women without the 6.3-kb allele of the Dra I polymorphism in the ADRA2A gene were characterized by a low TER (18). There is good evidence showing that the Gln27Glu polymorphism in the $\beta 2$ -adrenergic receptor is associated with an increased risk of obesity in men (33,36) and a greater accumulation of fat in women (33,35). Also, the rare allele of the $\beta 3$ -adrenergic receptor is more frequent in obese men (38) and is associated with elevated BMI (39) and with visceral obesity in women (40). Results from a recent study on interactions between polymorphisms in adrenergic receptor genes reported an interaction effect between $\alpha 2$ - and $\beta 2$ -adrenergic receptor gene polymorphisms on total, high- and low-density lipoprotein cholesterol content, and between $\alpha 2$ - and

β 3-adrenergic receptor gene polymorphisms on abdominal fat content (19). These results suggest that, in addition to the main effects of candidate gene polymorphisms taken one at a time, interaction effects are also important in studying the impact of candidate genes on variation in obesity-related traits.

The results reported in this study should be interpreted with caution. First, there is no evidence showing any functional effect of the C1291G polymorphism in the promoter region of the ADRA2 gene. To the best of our knowledge, no study has investigated the impact of this polymorphism on the expression of the ADRA2 gene. However, even if this polymorphism has no effect on the expression of the gene, one must keep in mind that it could be in linkage disequilibrium with another functional polymorphism within the gene and thus explain the association observed. Second, considering the number of tests performed and the borderline *p* values observed for some of the positive findings, we cannot exclude the possibility that the observed associations are due to chance. Replication of these findings in other populations would be needed to evaluate the real impact of this polymorphism on body fat and fat distribution.

In summary, the results of this study indicate that a polymorphism in the promoter region of the ADRA2A gene is associated with an android pattern of fat distribution in black men and that their female counterparts are more prone to develop a gynoid pattern of fat distribution. The results can be seen as supportive of those previously obtained in the Québec Family Study and suggest that DNA sequence variation in the ADRA2A gene influences the propensity to store fat in the abdominal area independently of total body fatness.

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