ORIGINAL ARTICLE

Significant association between insulin-like growth factor 2 mRNA-binding protein 2, interleukin-6 polymorphisms, and type 2 diabetes mellitus

Elmutuz H Elssaig[1,2,3], Eltayib H Ahmed-Abakur[1,2,4], Tarig M S Alnour[1,2,4], Mohamed A. Alsubai[1,2,3], Aadil Yousif[1,2]

[1]Department of Medical Laboratory Technology, University of Tabuk, Tabuk, Saudi Arabia, [2]Molecular Microbiology Lab, Prince Fahad Bin Sultan Chair for Biomedical Research, University of Tabuk, Tabuk, Saudi Arabia, [3]Department of Clinical Chemistry, Faculty of Medical Laboratory Science, Alzaiem Alazhari University, Khartoum, Sudan, [4]Department of Microbiology and Immunology, Faculty of Medical Laboratory Science, Alzaiem Alazhari University, Khartoum, Sudan

Background: The study aimed to detect the association between insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) and interleukin-6 (IL-6) polymorphisms among type 2 diabetes mellitus (T2DM). **Materials and Methods:** This study involved 500 individuals; 250 obese DM cases and 250 healthy controls. The polymerase chain reaction restriction fragment length polymorphism was used to identify the genotype of the IGF2BP2 gene for the small nucleoproteins rs4402960 (G>T) and small nucleoproteins rs800795 (G>C). **Results:** The results indicated that the mutant C-allele of the single nucleotide polymorphism (SNP) rs1800795 variant was highly significantly associated with the study group (P = 0.002). The occurrence of genotypes (C/G and C/C) versus normal G/G genotype of the IL-6 variant was highly significant (P = 0.004) in the study group (49.2% vs. 50.8%) compared to the control group (62% vs. 38%). Similar findings were observed in SNPs for the rs440960 variant, in which the T-allele indicated a highly significant relationship (P = 0.0001) with the study group; the frequency of G/G genotype versus both (T/T and G/T) genotypes was highly significant (P = 0.0001) in the case group (34% vs. 66%) than in the healthy control group (52% vs. 48%). **Conclusion:** The current study indicated that IGF2BP2 rs4402960 and IL-6 rs1800795 polymorphism were highly significantly associated with the increased risk of obese T2DM among the Saudi Arabian population and presented a genetic model to screen the high-risk individuals with further validations.

Key words: Body mass index, diabetes mellitus, genomic markers, insulin growth factor, interleukin-6, single nucleotide polymorphisms

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that is characterized by elevated plasma glucose level, which over time, leads to cell damage in the eyes, nerves, heart, blood vessels, and renal.[1-5] Statistical data show that the amount of frequency of DM cases has been gradually growing over the time.[6] More than 400 million people globally have diabetes, whereas the most of them live in middle- and low-income countries, which is estimated to be more than 550 million patients in 2030. Diabetes was the main ninth reason of death in 2019.[1-5] The type 2 DM (T2DM) is the most common type of DM, which represents 90%–95% of new-onset diabetes,[2] and results when the body develops resistance to insulin with an insulin secretory deficiency.[4,7] T2DM is a polygenic disease that happens due to connections between numerous environmental factors and genes.[8] One of the genes proposed to be related to the higher occurrence of T2DM is insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2), which encodes binding protein to

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Address for correspondence: Dr. Elmutuz H Elssaig, Department of Medical Laboratory Technology, University of Tabuk, P. O. Box: 741, Tabuk 71411, Saudi Arabia. Molecular Microbiology Lab, Prince Fahad Bin Sultan Chair for Biomedical Research, University of Tabuk, P. O. Box: 741, Tabuk 71411, Saudi Arabia. Department of Clinical Chemistry, Faculty of Medical Laboratory Science, Alzaiem Alazhari University, Khartoum 11111, Sudan.
E-mail: eelssaig@ut.edu.sa ; elmutuz75@yahoo.com
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the untranslated regions of IGF2 mRNA and controls its translation. The genetic variations of the IGF2BP2 gene resulted in a vital metabolic defects by reducing insulin secretion which leads to diabetes susceptibility.[7-10] The genetic variations of the IGF2BP2 gene resulted in a vital metabolic defects by reducing insulin secretion which leads to diabetes susceptibility.[9-11] Adipose tissue plays an important role as one of the endocrine organs, producing some hormones, such as leptin, visfatin, resistin, and adiponectin, together with traditional cytokines, like interleukin-6 (IL-6). These cytokines play a vital role in the management and regulation of metabolism, such as metabolism of lipid, glucose, and immunity; hence, the high level of IL-6 affected the degrees of obesity.[11,12] The pathogenesis of insulin resistance and T2DM with obesity has been associated with subclinical inflammation and activation of the immune system; however, what triggers the release of IL-6 (inflammatory cytokines) is still unclear.[12-14] Many studies have found that IL-6 variants have a vital role in metabolism by reducing the insulin function and increasing the susceptibility to diabetes.[12-15] DM was found to be the major health problem in Saudi Arabia; it has been amplified tenfold during the last three decades.[4] The Kingdom of Saudi Arabia ranks seventh in the world for the occurrence of diabetes and second in the Middle East region.[6] It has been reported that half of the Saudi populations aged 30 years or more were identified as either diabetic (25%) or prediabetic (26%), and 40% of patients were unaware of their condition.[6]

Most diabetes-related research in the Kingdom of Saudi Arabia focused on the occurrence of DM in the different regions, with very few studies investigating the genetic risk.[6] Our study aimed to determine the assessment of the polymorphism of the IGF2BP2 (rs4402960) and IL-6 (174 C◎G) among T2DM in Saudi patients.

Early prediction of DM helps in disease control and facilitates human life. Those who are at a risk and those who have a family history are more susceptible to T2DM. The disease appears suddenly in the 20th or 30th of people lives, although it might appear earlier. The research facilitates early detection of the disease by detection of genetic polymorphism in IGF2 and IL-6 genes.

MATERIALS AND METHODS

Study population and sampling

The present study is a population-based, case–control study, conducted over 4 years (2019–2022) at Tabuk University, Prince Fahad Bin Sultan Chair for Biomedical Research, and King Fahad Specialist Hospital, Kingdom of Saudi Arabia. The participants learned about the study objectives, and on enrollment, the samples were collected from the agreed candidates along with the signed consent. The current study was agreed by the Local Research Ethics Committee, University of Tabuk, with the approval number (UT-78-06-2019).

The study population included the control group, which involved 250 healthy participants who do not have DM, endocrinal disease, hepatic disease, or renal disease, and the case study group, which involved 250 obese T2DM patients, who do not have renal disease, hepatic disease, or endocrinal disease.

Sample size was calculated according to the following formula:

$$n = Z^2 \times P\,(100 - P)/d^2$$

Where n = Sample size

P = Prevalence rate

Z = 1.96 at 95 confidence

d = Desired width of confidence (precision), errors estimate $\alpha = 5$ (α = desired confidence level)

P = Expected incidence from literature

Therefore, the sample size (n) was determined as:

$$1.96 \times 1.96 \times 16 \times 84/5^2 = 206$$

For accuracy and precision, the sample was collected as 250 from type 2 diabetic patients.

Six milliliter of venous blood was collected after overnight fasting from each participant under standard condition. The blood samples were drawn into plain containers and EDTA containers. The serum was collected from the clotted blood at room temperature; then, sera were separated and stored at −20°C until used.

The estimation of body mass index (BMI) using the following formula:

$$BMI = \frac{\text{weight in kilogram}}{(\text{height in square meter})}$$

The T2DM patients were selected according to the criteria of the American Diabetes Association.[16]

Assay of biochemical markers

The following are the biochemical markers: lipid profile (cholesterol, low- and high-density lipoprotein

cholesterol [LDL-C and HDL-C], and triglycerides [TG]), fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c), which are measured using the clinical chemistry autoanalyzer (Cobas c311, Roche Diagnostics).

Genotyping analysis of tumor necrosis factor-alpha

The genomic DNA was extracted from the blood leukocytes of each participant using the Promega-USA DNA Purification Kit. The polymerase chain reaction (PCR)-restriction fragment length polymorphism technique was used to recognize the genotypes and alleles of the IGF2BP2 variants (rs4402960).[10,11] Specific sets of primes were used; the primer set for the rs4402960 variant was 5′GACCAGCCTTGGCAATGTAGTG-3′, f5′CTAAAGCACTGAGAGAAACAGCCCT3′. The PCR programs were run, which included initial denaturation temperature at 94°C for 10 min and 30 cycles; this consists of 45 s denaturation at 94°C, 30 s annealing at 62°C, 35 s extension at 72°C for each cycle, and the final extension for 10 min at 72°C.[10,11]

Visualization of polymerase chain reaction products

The PCR products of the rs4402960 variant were digested using Mob II enzyme. The reaction mixture for digestion included 10 μL (0.2 μg) of PCR products, 1 μL of restriction enzyme (Thermo Fisher Scientific) with 17 μL nuclease-free water, and 2.0 μL of 10XNE buffer. The cocktail was incubated at 37°C for 5 h. The digested PCR products were loaded into 2.0% ethidium bromide agarose gel. The results were interpreted according to the patterns and the size of the bands; for the rs4402960 variant, one band of the size 439 bp indicated homozygote (TT), two bands of the size 157 bp and 282 bp indicated homozygous (GG), and three bands of the size 439, 282, and 157 bp indicated heterozygous (GT) [Figure 1].[10,11]

Detection of interleukin-6 rs1800795 G>C gene polymorphisms

The detection genetic polymorphisms was done using amplification-refractory mutation system PCR (ARMS PCR) techniques. The enzyme-coding region of IL-6 gene contains well-investigated single nucleotide polymorphisms (SNPs) rs1800795 C>G. The ARMS primers were designed by Primer3 Software. The primers' mixture F0/R0 generates a band of 537 bp as a control band, F0/RI produces a band of 242 bp for C-allele, whereas FI/R0 generates a band of 342 bp for G-allele [Figure 2 and Table 1].

The reaction was done in a 20 μL reaction mixture containing 10 μL master mix, 2.0 μL of DNA, and 2.0 μL of 25 pmol of all 4 primers, and 6 μL Master mix (Microgen Inc., Corea). The thermocycling circumstances were denaturation at 94°C for 10 min and 35 cycles; each cycle consists of 45 s of denaturation at 94°C, 35 s of annealing at 62°C, and the final extension for 10 min at 72°C for 5 min. The PCR products were examined using 2.0% agarose gel electrophoresis and then visualized using ultraviolet transilluminator.

Statistical analysis

Descriptive statistics analysis such as frequency, percentage, and mean were calculated in this study. The IBM SPSS Statistics version 22 (USA), namely, independent *t*-test was used to measure the relation between the study population and biochemical markers, whereas the Chi-square test indicated that there are no abnormalities detected in Hardy–Weinberg equilibrium of SNPs by matching the observed and estimated incidences of the study group, control group, and genotypes.

RESULTS

Table 1: Primers sequences of amplificationrefractory mutation system polymerase chain reaction and allelespecific polymerase chain reaction

Site of the primers	Type of primers	Primers sequence
Fo-outer primer	F1	CGATGGAGTCAGAGGAAACTCA
Ro-outer primer	R1	GGAGATAGAGCTTCTCTTTCGTTCCCG
F I-G-inner primer	G allele	TTTTCCCCCTAGTTGTGTCTTGCC
R I-C-inner primer	C allele	GACCAATGTGACGTCCTTTAGCATC

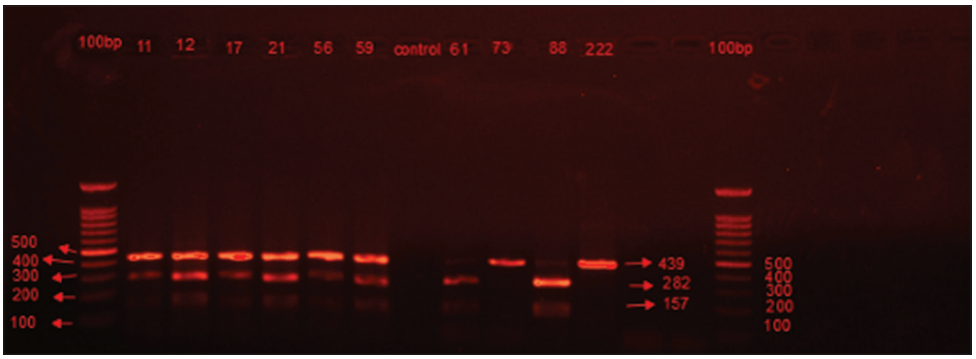

Figure 1: Agarose gel electrophoresis of restriction digests of polymerase chain reaction products of (rs4402960) insulin-like growth factor 2 mRNA-binding protein 2 gene using Mbo II restriction enzyme on 2% agarose gel. M: 100 bp marker, sample no. 61, 88 are GG genotype, sample no. 11, 12, 17, 21, 56, and 59 are GT genotype, sample no. 73, 222 are TT genotype

Table 1 shows the results of general biochemical markers of the study population; the results displayed significant relations between BMI, LDL, FPG, HDL, total cholesterol, HbA1c, and TG and study group (T2DM patients) with $P = 0.0001$, $P = 0.0020$, $P = 0.0010$, $P = 0.0040$, $P = 0.0010$, $P = 0.0010$, and $P = 0.0010$, respectively. The ratio between male and female was almost similar with $P = 0.8800$. There is no significant difference between the mean of the age for both groups. Type 2 diabetic patients showed significant elevation in BMI, fasting blood glucose (FBG) level, HbA1c, and lipid profile [Table 2].

Our study showed highly significant difference ($P = 0.0001$) between the frequency of homozygous TT genotype (rs440960 variant) in the control group compared to the case group, which appeared to be 5.6% versus 14.8%, respectively, as reported in Table 3. Similar results were obtained regarding the frequency of the mutant T-allele, as the T-allele appeared in 26.8% of the control group related to 40.4% of the case group, which was also significant ($P = 0.0001$). It was further noted that as shown in Table 4, the association remained significant under recessive ($P = 0.0010$), dominant ($P = 0.0001$), and additive ($P = 0.0001$) genetic models [Table 4].

The result showed a highly significant difference ($P = 0.0160$) between the frequency of CC genotype (rs1800795 variant) in the control group compared to the subject group, which appeared to be 4.0% versus 8.4%, respectively, as reported in Table 5. Similar results were obtained regarding the frequency of the C-allele, as the C mutant allele appeared in 21% of the control group compared to 29.6% of the subject group, which was also significant ($P = 0.0020$). It was further noted that as shown in Tables 5 and 6, the association remained significant under dominant, recessive, and additive ($P = 0.0040$, 0.0460, and 0.0170).

DISCUSSION

The genetic risk facets of T2DM have not yet been precisely defined and might vary based on genetic variations and ethnicity of the given population.[9,17] Furthermore, the variants – rs4402960 and rs1800795 are the common SNPs in the disease; they participate in the progression and development of metabolic disorders such as diabetes and obesity.[13,18] Furthermore, exploring the current literature shows that the present study might be considered one of the few studies investigating the genetic polymorphism of a critical gene associated with DM in the Saudi Arabian population.

The results showed significant increases in BMI among the study group; this finding suggested that BMI was one of the important risk factors for T2DM among Saudi T2DM patients. Similar findings were reported by several authors,

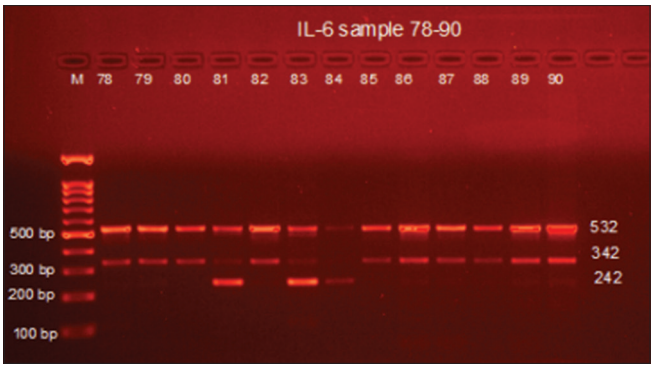

Figure 2: Detection of interleukin-6 G<C gene variation with allele specific polymerase chain reaction in obese diabetes mellitus cases. M – 100 bp DNA ladder. Homozygous GG – 78, 79, 80, 82, 85, 86, 87, 88, and 90. Hetrozygou GC – 83. Homozygous CC – 84. IL = Interleukin

Table 2: Comparative results of biochemical markers in obese type 2 diabetes mellitus patients and healthy subjects

Variables	Patient (*n*=250)	Control (*n*=250)	*P*
Gender (male/female)	130/120	132/118	0.8008
Age (Years)	58±15	56±14	0.7005
BMI (kg/m^2)	28.5±1.2	23.2±1.1	0.0001*
Fasting plasma glucose (mg/dl)	201±70.5	99±10	<0.001*
Total Cholesterol (mg/dl)	205±44	174±25	<0.0010*
Triglyceride (mg/dl)	156±35	125±30.5	<0.0010*
LDL-C (mg/dl)	109±32	79.8±26	0.0020*
HDL-C (mg/dl)	40±8.1	45±16	0.0040*
Heamoglobin A1c(%)	9.8±2.3	5.7±0.44	<0.0010*

*P<0.05 is statistically significant. Comparisons were performed by independent samples ttest; data are mean±SD. *n*=Number of individuals; BMI=Body mass index; TG=Triglyceride; HDLC=Highdensity lipoprotein cholesterol; LDLC=Lowdensity lipoprotein cholesterol; HbA1c=Glycated hemoglobin; SD=Standard deviation; FPG=Fasting plasma glucose

Table 3: Genotypes distribution and allele frequency of the IGF2BP2 gene rs4402960 variant among the study population

Variant (rs 4402960)	Frequency (%)[a]		OR (95% CI)	*P*
	Patients group	Controls group		
Genotypes[b]				
GG	85 (34)	130 (52.0)		
GT	128 (51.2)	106 (42.4)	0.542 (0.372-0.788)	0.0014*
TT	37 (14.8)	14 (5.6)	0.247 (0.126-0.485)	0.0001*
Alleles[b]				
G	298 (59.6)	366 (73.2)	0.540 (0.414-0.705)	0.0001*
T	202 (40.4)	134 (26.8)		

*P<0.05 is statistically significant, [a]Data are represented as *n* (%), [b]GT versus TT, G alleles versus T alleles. Comparisons were performed by the Chisquare test. CI=Confidence interval; OR=Odds ratio

which also noted higher statistics of obese individuals in the population.[11,19,20] Moreover, the study group showed high levels of FBG levels and HbA1c compared to the healthy group, indicating uncontrolled T2DM. Such uncontrolled DM among patients is common and stated in several studies.[11,14-18] Abnormal lipid profiles, including high

Table 4: Genetic models of the IGFBP2 gene rs4402960 variant among study population

Variant (rs 4402960) Genotypes	Frequency (%)[a]		OR (95% CI)	*P*
	Patient (*n*=250)	Control (*n*=250)		
Additive				
GG	85 (34)	130 (52)	0.247 (0.126-0.485)	0.0001*
TT	37 (14.8)	14 (5.6)		
Recessive[b]				
TT	37 (14.8)	14 (5.6)	0.342 (0.180-0.650)	0.0010*
GG + GT	213 (75.2)	236 (94.4)		
Dominant[b]				
GG	85 (34)	130 (52)	0.476 (0.332-0.682)	0.0001*
GT + TT	165 (66)	120 (48)		

**P*>0.05 is statistically significant; [a]Data are represented as *n* (%); [b]GT versus TT. Comparisons were performed by the Chisquare test. Additive model (TT vs. GG), recessive model (TT vs. GG + GT), dominant model (GG vs. + GT + TT). CI=Confidence interval; OR=Odds ratio

Table 5: Genotypes distribution and allele frequency of the IL-6 gene rs1800795 variant among study population

Variant (rs1800795)	Frequency (%)[a]		OR (95% CI)	*P*
	Patients group	Controls group		
Genotypes[b]				
GG	123 (49.2)	155 (62)		
CG	106 (42.4)	85 (34)	0.636 (0.439-0.922)	0.0170*
CC	21 (8.4)	10 (4.0)	0.378 (0.172–0.832)	0.0160*
Alleles[b]				
G	352 (70.4)	395 (79)	0.632 (0.470-0.844)	0.0020*
C	148 (29.6)	105 (21)		

**P*<0.05 is statistically significant; [a]Data are represented as *n* (%); [b]GC versus CC, G alleles versus C alleles. Comparisons were performed by the Chisquare test. CI=Confidence interval; OR=Odds ratio

Table 6: Genetic models of the IL-6 gene rs1800795 variant among study population

Variant (rs1800795) Genotypes	Frequency (%)[a]		OR (95% CI)	*P*
	Patient (*n*=250)	Control (*n*=250)		
Additive[b]				
GG	123 (49.2)	155 (62)	0.636 (0.439-0.922)	0.0170*
GC	106 (42.4)	85 (34)		
Recessive[b]				
CC	21 (8.4)	10 (4.0)	2.201 (1.014-4.775)	0.0460*
GG + GC	229 (91.6)	240 (96)		
Dominant[b]				
GG	123 (49.2)	155 (62)	0594 (0.416-0.847)	0.0040*
GC + CC	127 (50.8)	95 (38)		

**P*<0.05 is statistically significant; [a]Data are represented as *n* (%); [b]GC versus CC. Additive model (CC vs. GG), recessive model (CC vs. GG + GC), dominant model (GG vs. + GC + CC). Comparisons were performed by the Chisquare test. CI=Confidence interval; OR=Odds ratio

cholesterol, triglyceride, and LDL with low HDL, have also reflected the effects of DM among the study group. Furthermore, the present study displayed significant associations between BMI, HbA1c, TG, total cholesterol, LDL, HDL, and the patients' group. These results were in alignment with numerous earlier reports as these are the typical clinical manifestations observed with DM.[11,17,19-21] The consequence of uncontrolled DM with elevated BMI and abnormal lipid profile may lead to the risk of having atherosclerosis inflammatory condition and worsen patients' situation.

Our findings showed significant associations between genetic variations in the rs1800795 and rs4402960 among patients' group (T2DM) compared to control group. On the other hand, the T-allele and C-allele were more common among the patients' group. In alignment with our findings, many studies have suggested that IGF2BP2 (rs4402960) and IL-6 (rs1800795) polymorphisms increased the development of T2DM.[13,15,22-24]

Similarly, Jia *et al*. studied the association between IGF2BP2 polymorphism and their risk for developing T2DM and reported that IGF2BP2 polymorphisms modulate the islet beta-cell function.[25] However, contradictorily to our findings, few authors stated that there is no relationship between the IGF2BP2 gene and T2DM;[26,27] Ibrahim *et al*. showed an insignificant correlation between rs4402960 variants and T2DM among the Sudanese population.[28] These variations could be race dependent, as several reports showed that different populations and ethnicities yielded varying results.[19,20,26] However, the Genome-Wide Association Studies specified that the IGF2BP2 gene is one of the genes associated with T2DM.[7,23] Our results were aligned with the results done in several populations of Indian, Asian, Tunisian, Chinese, Japanese, Moroccan, Lebanese, Czechs, Greek Cypriot, and Germania who reported that IGF2BP2 - rs4402960 variant was associated with type 2 diabetic patients.[10,17,19-21,23,29,30]

The study revealed that the association is significant under dominant, recessive, and additive genetic models for rs4402960 SNP. These results agreed with the recent results of Zubaida *et al*., who reported dominant and recessive effects of rs4402960 SNP.[31] In addition, Benrahma *et al*. reported a highly significant relationship between T2DM and rs4402960 variant under recessive and additive models,[30] and similar results were reported by Mohammed *et al*., 2018.[11] However, interestingly, some research on such investigations has shown that those recessive IGF2BP2 polymorphisms were associated with T2DM risk,[32,33] whereas other authors have found the risk associated with the dominant genetic models.[34,35]

CONCLUSION

The current study indicated that IGF2BP2 rs4402960 and IL-6 rs1800795 polymorphism were highly significantly associated with the increased risk of obeseT2DM among the Saudi Arabian population and presented a genetic model to screen the high-risk individuals with further validations.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

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