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RESEARCH

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Genetic association study for three single nucleotide polymorphisms related to type 2 diabetes in Egyptian population

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Abstract

Background Diabetes mellitus is a disease that may result from interaction between environmental factors and a strong genetic component. The current study is aimed at exploring three single nucleotide polymorphisms to identify the associated ones with type 2 diabetes in the Egyptian society. The studied single nucleotide polymorphisms (rs10096097 in GOAT, rs6740584 in CREB1, and rs62521874 in MAFA) were examined via genotyping cases ($n=98$) and irrelevant healthy subjects ($n=82$).

Results Associations were checked using dominant, recessive, genotypic, allelic, and Cochran–Armitage trend models. By comparing diabetic patients with controls, rs6740584 was associated with type 2 diabetes by employing all used models except the recessive model. Rs10096097 was connected with type 2 diabetes using the genotypic association, Cochran–Armitage trend test, and recessive model and not any other model. Rs62521874 was not linked with type 2 diabetes in all models. Moreover, haplotype association for rs10096097 and rs62521874 was conducted as these two single nucleotide polymorphisms were located on the same chromosome. The haplotype pattern rs10096097:G—rs62521874:A was identified as a biomarker for type 2 diabetes susceptibility in the Egyptian community.

Conclusions The GOAT and CREB1 polymorphisms showed susceptibility to type 2 diabetes. Moreover, MAFA had no role in the disease except through the haplotype with GOAT polymorphism.

Keywords Egyptian population, Single nucleotide polymorphisms, Type 2 diabetes, CREB1, GOAT, MAFA

Introduction

Diabetes mellitus (DM) is a set of illnesses that affect the individual's capacity to use blood glucose. Glucose is necessary for human well-being since it provides a significant amount of energy to the cells that comprise tissues and muscles. Furthermore, it serves as the principal energy provider for the brain [1]. Egypt was ranked ninth globally by the International Diabetes Federation (IDF) in terms of the number of type 2 diabetes (T2D) patients. Diabetes is a rapidly expanding public well-being issue in Egypt that has detrimental effects on mortality, morbidity, and the availability of medical resources. T2D affects approximately 15.6% of Egyptians aged from 20 to 79 [2].

T2D is a metabolic disease that arises from insufficient insulin production or inadequate insulin cellular response. Additionally, it is a type of diabetes that affects up to 95% of diabetics [3]. Individuals in their

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sixth decade of life and above experience the highest susceptibility to T2D [4]. Symptoms and indicators of T2D include heightened appetite, excessive thirst, frequent urination, blurred vision, fatigue, and delayed wound healing. Some individuals with T2D, however, have symptoms that are so minor that no one notices them [5]. A healthy diet and frequent exercise can assist T2D patients, but they will mostly need medication if lifestyle changes are not enough to lower their blood sugar [6].

Rs6740584 is located on chromosome 2 at 207564627 base pair (bp) (cytogenetic region: 2q33.3) in the cyclic adenosine monophosphate-responsive element-binding protein 1 (CREB1) gene [7]. CREB1 is a protein that has a role in gluconeogenesis regulation. The genetic variants in the CREB1 promoter area have an impact on transcriptional activity and the risk of T2D [8].

Rs62521874 is found on chromosome 8 at 143429368 bp in the musculoaponeurotic fibrosarcoma oncogene family A (MAFA) gene. The transcription factor MAFA, which activates insulin gene expression, is encoded by this gene. MAFA is a transcription factor that binds to the C1 DNA element-binding complex (RIPE3b1), a conserved enhancer region that controls insulin gene expression in pancreatic beta cells [9]. The MAFA transcription factor is found in high levels in β-cells, the cells in the pancreas that produce insulin. MAFA exerts a pivotal function in the regulation of insulin secretion stimulated by glucose, a process by which the body produces insulin in response to high blood sugar levels. Reduced MAFA expression in T2D contributes to β-cell malfunction and the advancement of the illness [10].

The ghrelin-o-acyl transferase (GOAT) gene (also known as MBOAT4), which is found on chromosome 8, is the host for rs10096097 at 30169582 bp [11]. The GOAT gene, encoding GOAT protein, plays a crucial role in diabetes development. Inhibiting GOAT activity can reduce weight gain, improve glucose homeostasis, and enhance insulin secretion. Studies on mice show that GOAT inhibition leads to reduced fat mass, lower acyl ghrelin levels, and improved insulin response to glucose challenge. Furthermore, modulators of GOAT signaling, like GOAT inhibitors, can increase insulin secretion and enhance peripheral insulin sensitivity, potentially countering obesity and T2D progression [12, 13].

In Egyptian population, rs6214 and rs10860860 of the *IGF-I* gene were connected with diabetic nephropathy (DN) patients having T2D. It meant that *IGF-1* polymorphisms had a greater impact on DN than its serum concentration [14]. In South Egypt, Apolipoprotein M (*ApoM*) rs805297 (C-1065A) was conjoined with T2D and related microvascular complications. The rs805297 (C-1065A) genotype (CC) might have a role in controlling hyperglycemia. The (A) allele was associated with hyperglycemia and diabetic retinopathy [15].

The *IL-16* rs11556218 (TG) genotype was conjoined with the likelihood of developing T2D in the Egyptian people [16]. In Egyptians, *ELMO1* gene rs741301 was connected with T2D. *ELMO1* rs741301 was a potential gene mutation linked to the vulnerability of DN [17]. In an Egyptian pilot study, T2D and DN were correlated with reduced irisin concentrations. *FNDC5* rs16835198 (TT) genotype was related to lowered likelihood of T2D among Egyptians, without influencing renal complications. Moreover, the presence of the rs16835198 (G) allele resulted in insulin desensitization, without being linked to circulating irisin levels [18].

The purpose of this research is to explore the relationship between three single nucleotide polymorphisms (SNPs) and diabetes in the Egyptian population. In order to uncover SNPs that may be linked to the likelihood of acquiring diabetes, this study analyzed a sample of Egyptians who have and do not have the disease. The findings of this research could result in the creation of novel diagnostic and therapeutic approaches as well as a better knowledge of the genetic variables that lead to diabetes in the Egyptian community.

Materials and methods

Subjects

The study group consisted of 82 controls and 98 cases. 15.8% (13) of the unaffected group were women, while 84.1% (69) were men. Females represented 64.3% (63) of the affected group, while males represented 35.7% (35). The average age for the healthy subjects and standard deviation (SD) were 34.41 ± 8.22 years. The average age for the diabetic patients and SD were 50.09 ± 14.01 years.

The study enrolled individuals aged 30–80 years who had been undergoing antidiabetic therapy for at least one year without experiencing ketoacidosis previously. Those with clinically significant hepatic, renal, neurological, or endocrinological conditions, as well as acute major cardiovascular diseases, chronic inflammation, or cancer, were excluded. Additionally, individuals receiving treatment with glucocorticoids, antipsychotics, antiepileptics, or anticancer medications were not eligible for participation.

Ethical statement

Each participant provided written informed permission, which was authorized by the Cairo University Faculty of Medicine's Ethical Committee.

Molecular genetic methods

Pursuing the producer's specifications, DNA was derived from whole blood using a QIAamp kit supplied by Qiagen

(USA, catalogue number 51306). DNA was amplified by TaqMan genotyping PCR Master Mix Kit supported by Qiagen (catalogue number 201443). The TaqMan genotyping master mix and the rsID primer probes were kept on ice and thoroughly mixed before utilization. A reaction mix was performed as follows: 12.5 ul of TaqMan genotyping Master Mix, 1.25 ul of each rsID assay, and 20 ng DNA were combined in a total volume of 25 ul. The cycling program proceeded as follows: an initial cycle for 10 min at 95 °C, followed by 40 cycles of 30 s at 95 °C and 1 min at 60 °C using the TaqMan assay real-time PCR (Rotor-Gene, Qiagen, USA).

Statistical methods

There are 98 cases and 82 controls in this study. Allelic distribution and frequency of minor alleles (MAF) for the studied population were the marker checks used in this investigation. Five genetic models were implemented to scrutinize the link between the three genetic mutations and T2D susceptibility, including dominant, recessive, genotypic, allelic, and Cochran–Armitage trend models. A *p*-value of less than 0.05 on both sides was considered statistically significant.

R libraries were used to calculate marker checks of each SNP in the data using R-4.1.3. Using plink1.9, the chi-square (chisq), *p*-value, and haplotype analysis were determined. To read, write, and format Excel files, the XLSX package in R was employed. The correlation coefficient between two alleles and MAF was estimated using the Genetics package in R.

The flowchart displayed in Fig. 1 illustrates the suggested interrelation scheme. It is necessary to test the haplotypes for T2D associations between bi-allelic SNPs located on the same chromosome. Consequently, since the MAFA and GOAT SNPs are located on chromosome 8, haplotype analysis might be performed to identify any related haplotypes.

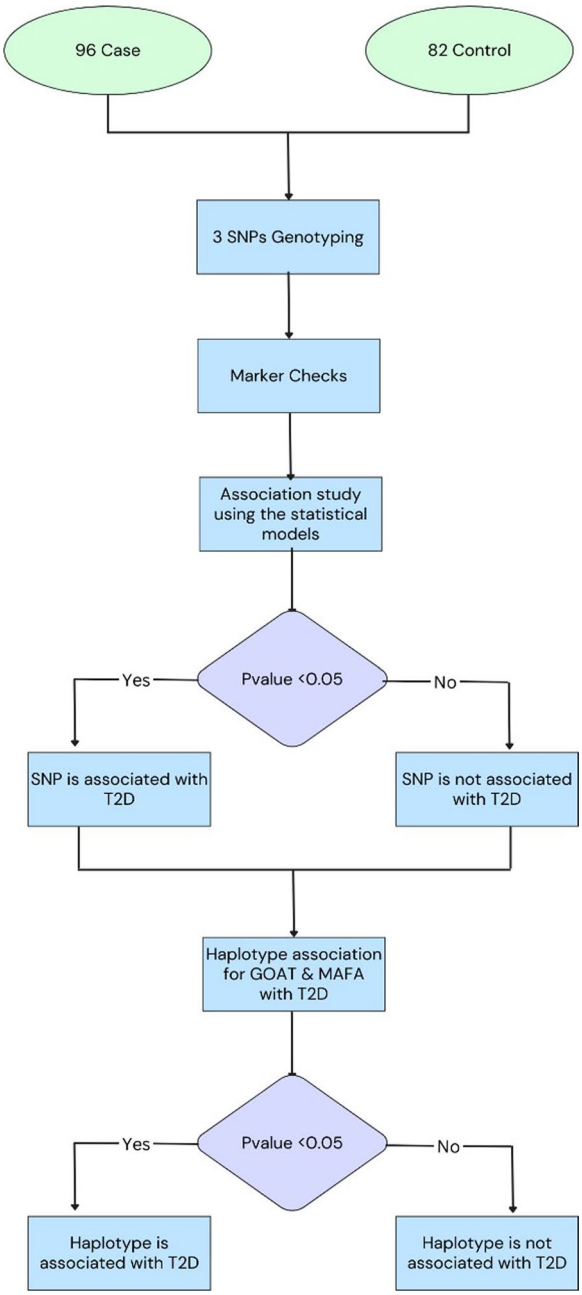

Fig. 1 Flowchart of the proposed analysis scheme

Results

75% of genotypes were considered acceptable at a minimum. The minimum accepted MAF was 0.05. As described in Table 1, every single SNP was properly genotyped for every single individual, and every single SNP made it through the marker checks phase. Additionally, data about each SNP (rsID, physical location, chromosome no., gene name, major allele, and minor allele) is explained in Table 1.

The connection outcomes for the explored SNPs are elucidated in Table 2 that demonstrated the statistically significant SNPs' *p*-values shown in bold. The rs6740584 was significantly associated with T2D vulnerability, which was observed across all models, except for the recessive model. The rs10096097 was significantly connected with T2D in three models (genotypic association, Cochran–Armitage trend test, and recessive model), but not in the other two models (allelic association and dominant model). The rs62521874 was not significantly related to T2D at all.

Together with the rates of each genotype for patients and healthy subjects, Fig. 2 presents a detailed representation of every SNP under investigation. From Table 2 and Fig. 2, the identification of genotypes/alleles

Table 1 Quality control-related information for the studied SNPs

	rs6740584	rs10096097	rs62521874
Chromosome	2	8	8
Position (base pair)	207564627	30169582	143429368
Gene	*CREB1*	*GOAT*	*MAFA*
Reference Genome Assembly	GRCh38	GRCh38	GRCh38
Major Allele: Minor Allele	C:T	A:G	A:C
Genotype percentage	100%	100%	100%
MAF*	0.461	0.339	0.4

* MAF: Minor allele frequency

associated with increased or decreased vulnerability to T2D could be probed. Subjects possessing rs6740584 (CT) genotype and (T) allele had an increased risk of T2D. T2D risk was reduced in carriers of the rs6740584 (CC) genotype. T2D risk was higher in people who carried the rs10096097 (GG) genotype. Individuals carrying the rs10096097 (AG) genotype and (A) allele exhibited a reduced risk of T2D. In contrast, rs62521874 was the sole genetic variant that did not demonstrate an association with T2D vulnerability.

Table 3 illustrates the haplotype association for rs10096097 and rs62521874 with T2D. The GA was significantly correlated with T2D susceptibility. Consequently, rs62521874 plays a role in T2D susceptibly but in combination with rs10096097.

Discussion

For our investigation, we used a data collection with three SNPs that corresponded to 180 uncorrelated people. T2D is a disorder characterized by excessive urine production from the kidneys and uncontrollably high blood glucose (a kind of sugar) levels. This condition worsens when the body either produces insufficient insulin or fails to use it appropriately. Given the severity of T2D and its effects on individuals, the etiology of the disease is a topic of current research. Ninety-eight T2D patients and 82 controls from Egypt were included in the current study, and the genotype and allele distributions of three SNPs were utilized to investigate the relationship with T2D susceptibility. The scrutinized SNPs are classified among three genes *CREB1* (rs6740584), *MAFA* (rs62521874), and *GOAT* (rs10096097).

Two SNPs were thought to be potentials for T2D vulnerability which are rs6740584 and rs10096097. The link between rs62521874 and T2D alone was not exposed. A haplotype interrelation analysis showed that the haplotypes rs10096097:G and rs62521874:A were significantly correlated with T2D vulnerability in the Egyptian society.

Disordered eating behaviors are widespread among diabetic patients and can have disastrous consequences for diabetes care, whereas diagnostic threshold eating disorders like anorexia nervosa can be life-threatening. Rs10096097 (GG) genotype in *GOAT* gene increases the susceptibility to anorexia nervosa in the German population [11]. Analysis of visceral adipose tissue from obese individuals with T2D revealed elevated GOAT levels in Spanish population [19]. Obesity increases the risk of T2D. The elevated tissue expression of GOAT in the stomach suggests its potential as a reliable anti-obesity marker [20]. Common variant in *GOAT* was associated with extreme obesity [21].

Significant differences in the genetic distribution of the MU_2 (TT genotype) and MU_3 (AA genotype) variants within the *CREB1* promoter were observed between individuals with T2D and healthy controls. Linkage disequilibrium (LD) analysis revealed a strong dependence between the MU_2 and MU_3 variants in T2D, with the T-A haplotype significantly impacting *CREB1* promoter activity. Additionally, further association analysis demonstrated a significant correlation between *CREB1* variants and key metabolic parameters such as fasting plasma glucose, glycated hemoglobin, and insulin levels

Table 2 A case–control study on the studied SNPs

Test		rs6740584	rs10096097	rs62521874
Genotypic association	*P*-value	**2.493e-09**	**0.02007**	0.2779
	Chisq	39.62	7.817	2.561
Cochran–Armitage trend test	*P*-value	**5.935e-05**	**0.04139**	0.3284
	Chisq	16.12	4.16	0.9551
Allelic association	*P*-value	**4.424e-06**	0.05513	0.4627
	Chisq	21.07	3.678	0.5394
Dominant model	*P*-value	**4.098e-09**	0.3171	0.743
	Chisq	34.58	1.001	0.1075
Recessive model	*P*-value	0.3746	**0.005412**	0.1102
	Chisq	0.7883	7.736	2.551

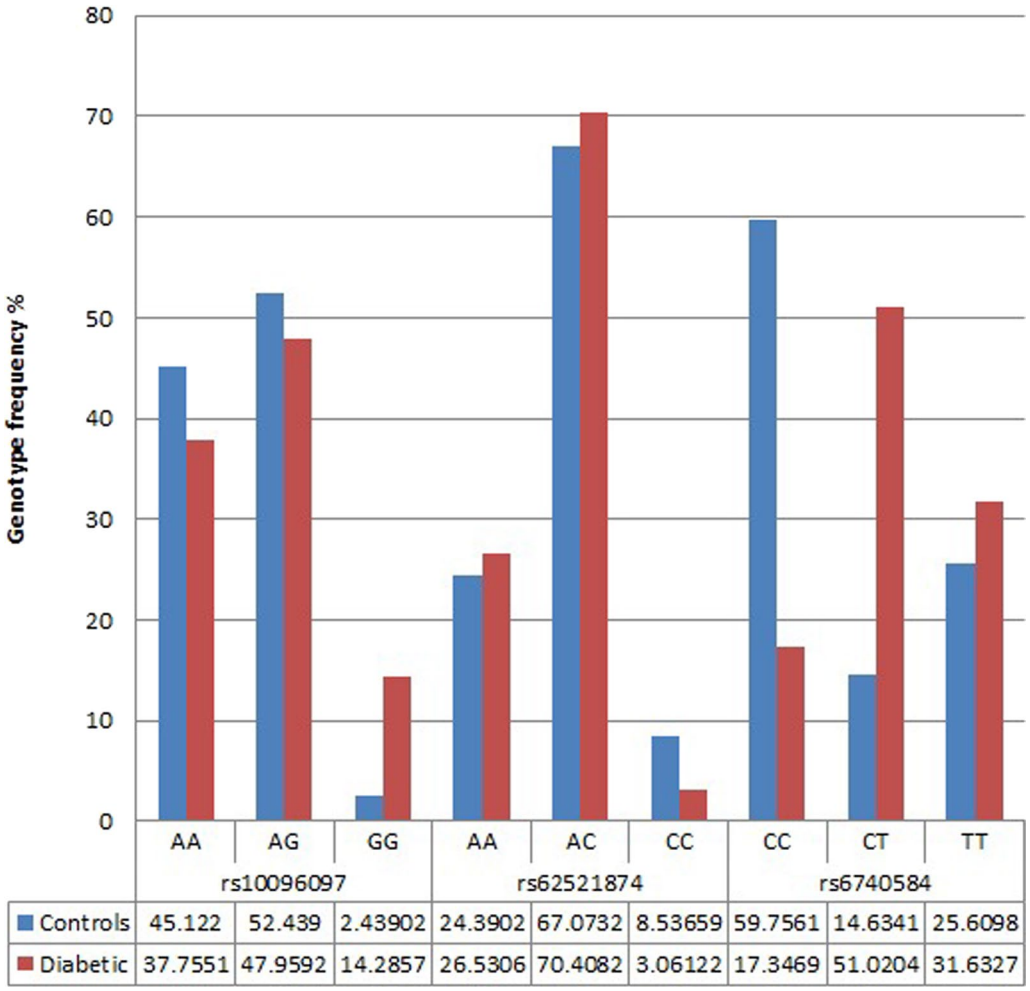

Fig. 2 Genotype dispersions in diabetic cases and healthy subjects for the three studied SNPs

Table 3 Haplotype association for rs10096097 and rs62521874

Haplotype rs10096097	Haplotype rs62521874	F_A	F_U	CHISQ	DF	*P*
A	A	0.3808	0.4331	1.014	1	0.3141
A	C	0.2365	0.2803	0.8973	1	0.3435
G	A	0.2365	0.1461	4.639	1	0.03125
G	C	0.1461	0.1404	0.02357	1	0.878

Haplotype: haplotype identifier, F_A: frequency in cases, F_U: frequency in controls, CHISQ: test for association, DF: degrees of freedom, and *P*: asymptotic *p* value

in T2D cases, highlighting *CREB1*'s integral role in glucose metabolism [8]. An integrated analysis of gene expression and function data identified shared pathways between T2D and bone and joint disorders, pinpointing CREB1 transcription factor with potential regulatory roles [22]. A genetic association study on 253 bipolar patients (104 with suicide attempt and 149 without suicide attempt) showed that *CREB1* (rs6740584) was significantly associated with suicide risk. In terms of physical health conditions, there were no discernible distinctions between individuals who had attempted suicide and those who had not in terms of the occurrence rates of diabetes [23].

The *MAFA* (rs62521874) was linked to type 1 diabetes (T1D) and not to T2D among individuals of Japanese descent [24]. The association of *MAFA* (rs62521874)

and T1D was confirmed in the Japanese population [25]. The *MAFA* (rs62521874) was not associated with monogenic diabetes in Caucasians [26]. A missense *MAFA* mutation (p.Ser64Phe, c.191C > T) was associated with familial insulinomatosis and diabetes mellitus by affecting MAFA protein stability and its ability to activate transcription. This underscores MAFA's physiological role both as an oncogene and as a critical transcription factor in islet β-cells [27].

The diminishing presence of MAFA is indicative of early β cell inactivity, leading to overt dysfunction associated with T2D [28]. MAFA expression was found deregulated in T2D patients [29, 30]. DNA and RNA sequencing were conducted on human pancreatic islets obtained from 89 deceased donors to pinpoint genes potentially pivotal in the development of T2D. The examination revealed no significant disparity in the contribution of endocrine tissues between diabetic and nondiabetic islets. This was evidenced by the expression patterns of pancreatic-specific endocrine (including MAFA in beta cells) genes, which remained consistent across both diabetic and nondiabetic samples [31].

A meta-analysis was conducted encompassing a cohort of 34,840 T2D cases and 114,981 controls, primarily of European ancestry for understanding T2D. The comprehensive genome-wide analyses conducted revealed a multitude of common variant loci contributing significantly to T2D susceptibility. An integration of the meta-analysis findings with protein–protein interactions uncovered shared interactors including MAFA [32].

Conclusion

This research found a direct association between rs6740584 and rs10096097 polymorphisms and T2D. Apart from the fact that there is no confirmed undeviating effective impact of the rs62521874 genetic heterogeneity on T2D, our findings showed that rs62521874 played a complex role in T2D susceptibility in combination with rs10096097 through the AG haplotype.

Additional research is warranted to explore factors such as smoking habits, climate conditions, and geographical positioning. It is imperative to carry out more expansive probes with larger amounts of samples drawn from the same demographic to enhance statistical power and validate our findings within the Egyptian population. Furthermore, delving into other polymorphisms and their potential associations with T2D susceptibility could offer valuable perceptions into the underlying processes of the illness.

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Author contributions
Conceptualization was done by Mohamed N. Saad and Olfat G. Shaker. Data curation was done by Mohamed N. Saad, Galena W. Zareef, Ibrahim M. Moatmed, Nourhan W. Shehata, and Olfat G. Shaker. Formal analysis was done by Mohamed N. Saad, Galena W. Zareef, Ibrahim M. Moatmed, and Nourhan W. Shehata. Investigation was done by Mohamed N. Saad, Galena W. Zareef, Ibrahim M. Moatmed, and Nourhan W. Shehata. Methodology was done by Mohamed N. Saad and Olfat G. Shaker. Resources were done by Olfat G. Shaker. Software was done by Galena W. Zareef, Ibrahim M. Moatmed, and Nourhan W. Shehata. Supervision was done by Mohamed N. Saad and Olfat G. Shaker. Validation was done by Mohamed N. Saad. Visualization was done by Mohamed N. Saad, Galena W. Zareef, Ibrahim M. Moatmed, and Nourhan W. Shehata. Writing—original draft was done by Mohamed N. Saad, Galena W. Zareef, Ibrahim M. Moatmed, and Nourhan W. Shehata. Writing—review and editing was done by Mohamed N. Saad and Olfat G. Shaker.

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Availability of data and materials
The data used during the current study are not publicly available due to subject confidential agreement but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethical Committee of Faculty of Medicine, Cairo University, and an oral and written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interests.

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