

Research Article

Direct-to-Consumer Genetic Test and Lifestyle Questionnaire Analysis of Body Mass Index and Body Fat Percentage in a Large Korean Population

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Abstract

Background: Direct-to-Consumer (DTC) genetic testing provides genetic risk to consumers and motivates consumers to take care of their own customized health care. In 2018, we developed and provided a DTC genetic testing service (GENESTART™) in collaboration with Herbalife Korea Co. Ltd.

Methods: The analyzed dataset consisted of the body fat percentage (BFP), body mass index (BMI), 31 genetic polymorphism genotypes, and responses to 19 questionnaire items of 24,447 individuals. The genetic main effects for BFP and BMI were examined by linear regression analysis, and the interaction effects were examined using a generalized linear model that controlled age and sex as covariates.

Results: In the case of BFP, the sample average was 31.47% overall, 24.76% for men, and 32.79% for women, showing that men had an average BFP that was 8 percentage points lower than that of women. The average BMI was 25.38 overall, 26.45 for men, and 25.17 for women, showing that men had an average BMI of 1.2 kg/m² higher than that of women. The FTO and MC4R genes, well-known obesity markers, showed a significant correlation with both phenotypes, and the BDNF gene, which is related to stress obesity, showed a highly significant association with BMI but only a weak association with BFP. Among the remaining genes, TRIB1, ABCA1, MYL2, G6PC, GCKR, GLIS3, CYP17A1, HECTD4, and NT5C2 genes showed significant associations with the obesity-related phenotypes. In this study, we found four interaction results for BFP (ABO and fruits, CYP1A2 and sugary foods, FTO and muscle exercise, MC4R and vitamins) and five interactions for BMI (MC4R and proteins, CSK and fruits, MC4R and calcium, DGKB and calcium, CSK and water).

Conclusions: This study is expected to enable the provision of personalized and accurate solutions for BFP and BMI management to customers who have undergone genetic testing.

Keywords: Direct-to-consumer genetic testing; DTC; Interaction; Body fat percentage; Body mass index

Abbreviations: DTC: Direct-to-Consumer; BFC: Body Fat Percentage; BMI: Body Mass Index; SNP: Single Nucleotide Polymorphism

Introduction

After the Human Genome Project, genetic variations were discovered in the human genome [1]. Advancing genotyping technology enhanced the large-scale genome-wide association studies for each disease or phenotype [2]. The genetic markers for each disease or phenotype were discovered [3], and several companies (such as 23 and Me and Pathway Genomics) began to offer Direct-to-Consumer (DTC) genetic testing to check genetic vulnerability by testing genetic markers. In these genetic testing services, customers directly collect DNA test samples with a buccal swab or saliva kit and send them to the company [4]. The companies provide genetic test results to customers as well as customized solutions for those with vulnerable genotypes.

In line with the global DTC genetic testing trend, the Bioethics and Safety Act was amended in Korea to improve the DTC genetic testing regulations. In 2016, the Korean Ministry of Health and Welfare allowed domestic DTC services to test a total of 46 genetic markers of 12 phenotypes [4]. In accordance with these regulatory changes, we (Theragen Bio Co. Ltd.) also provided a DTC genetic testing service under the brand name GENESTART™ through collaboration with a functional health food company called Herbalife Korea [<https://www.genestart.co.kr/>].

The purpose of DTC genetic testing is to inform consumers of their genetic risk and motivate them to take care of their own customized health care. In particular, the GENESTART genetic test mainly aims to identify genetic factors related to obesity and metabolic syndrome. In this study, we examined the association between GENESTART results and obesity-related factors (BFP and BMI) and their interactions with lifestyle habits.

Methods

Samples & Questionnaires

The data of the study population were obtained via the DTC service through Herbalife Korea after confirming the content of genetic testing and the research application. This study was approved by the institutional review board of Theragen Etx Bio Institute (IRB No. 700062-20180905-JR-006-01). The participants collected buccal swab samples and answered the self-reported questionnaires. All the data used for statistical analysis were obtained from the 19 question items about nutrition intake from the self-administered health assessment (Supplementary Table 1). In addition, we provided a food intake guide to increase the accuracy of the survey responses (Supplementary Figure 1).

Genotyping

Buccal swab samples for genotyping were collected using a Buccal DNA Collector (Theragen Bio Co. Ltd, Korea). DNA was extracted by the Buccal DNA Collector using the Exgene™ Tissue SV kit (Gene All Biotechnology Co., Ltd., Seoul, Korea) and genotyped at Theragen Bio using a Quant Studio™ 12K Flex Open Array genotyping plate, custom format 64 (Thermo Fisher, Waltham, MA, USA) according to the manufacturer's recommendation. Analysis of the genotyping results was performed using Quant Studio™ 12K Flex Real-Time PCR Software (Thermo Fisher, Waltham, MA, USA).

Statistical Analysis

To determine the strength of the relationship between the variables, a statistical correlation study was performed using correlation analysis with PASW Statistics (SPSS Inc., Hong Kong).

The data are presented as mean \pm SD (continuous variables) or as a percentage (categorical variables). We performed statistical analysis, including multiple linear regression, ANOVA (one-way and two-way), and the chisquared test. The multiple linear regression models were performed between SNP genotypes and BMI or BFP adjusted for age and sex.

We conducted 20 lifestyle-related surveys, as shown in Supplementary Table 1, to provide suggestions for lifestyle improvements to customers undergoing GENESTART genetic testing. The interaction analyses were conducted using the generalized linear model below.

$$\text{BFP} \sim \text{Age} \times \beta_{\text{AGE}} + \text{Sex} \times \beta_{\text{SEX}} + \text{G} \times \beta_{\text{G}} + \text{Q} \times \beta_{\text{Q}} + \text{GQ} \times \beta_{\text{GQ}}$$

$$\text{BMI} \sim \text{Age} \times \beta_{\text{AGE}} + \text{Sex} \times \beta_{\text{SEX}} + \text{G} \times \beta_{\text{G}} + \text{Q} \times \beta_{\text{Q}} + \text{GQ} \times \beta_{\text{GQ}}$$

Where the β s are the effect sizes of age, sex, genotype (G), questionnaire (Q), and the interaction effect size (GQ). P-values less than 0.05 were considered statistically significant.

Results

Population Characteristics

The study population characteristics are described in (Table 1). A total of 24,447 people who received the GENESTART service were analyzed as the subjects of the study. The average age of the subjects was 45.38 ± 11.73 years old, and the age ranged from 20 to 70 years. Among the subjects, approximately 83.5% (20,425) were women and the remaining 16.7% (4,022) were men.

The average BFP was 31.47% overall, 24.76% for men, and 32.79% for women, showing that men had 8 percentage points lower BFP than women on average. Further broken down by age, both men and women in their 20s and 30s had the highest BFP, though it decreased for both groups beginning in their 40s. The average BMI was 25.38 for the entire sample, 26.45 for men, and 25.17 for women, showing that men had an average BMI of 1.2 kg/m² higher than that of women.

Genetic Association between DTC Genes and BMI or BFP

We listed the genetic markers and described the association between the target genetic markers and the obesity-related phenotypes (BFP and BMI) in Table 2 (5–35). The FTO and MC4R genes—well-known obesity markers—showed a significant correlation with both phenotypes, and the BDNF gene, a gene related to stress obesity, showed a highly significant association with BMI but only a weak correlation with BFP.

Among the triglyceride genes, the TRIB1 gene was observed to have a significant association with increasing BFP. Also, the ABCA1 and MYL2 genes among cholesterol-related genes; G6PC, GCKR, and GLIS3 genes among the blood sugar-related genes; and CYP17A1, HECTD4, and NT5C2 genes among the blood sugar-related genes showed significant associations with obesity-related phenotypes.

Gene and Questionnaire Interaction for BMI and BFP

We analyzed the effect of the interaction between the genotypes of individuals identified through GENESTART and the survey results of BFP and BMI. Of the 30 genetic markers, 21 showed a significant interaction (Supplementary Table 2). Each interaction was further analyzed using a graph (Supplementary Figure 2 & 3). The statistically significant interactions that showed obvious changes when graphed were summarized in

Table 1: Study Population Characteristics.

		Total		Male		Female	
		n (%)	Mean±SD	n (%)	Mean±SD	n (%)	Mean±SD
Age		24,447	45.38±11.73	4,022	43.26±10.45	20,425	45.86±11.44
Body fat percentage		24,447	31.47±7.18	4,022	24.76±6.54	20,425	32.79±6.53
Age category	20–29	2,691 (11.0)	32.52±8.2	573 (14.2)	25.35±8.4	2,118 (10.4)	34.45±6.99
	30–39	5,012 (20.5)	32.06±7.57	976 (24.3)	25.94±7.22	4,036 (19.8)	33.54±6.87
	40–49	7,129 (29.2)	30.95±7.06	1,066 (26.0)	24.86±5.94	6,063 (29.7)	32.02±6.69
	50–59	6,551 (26.8)	31.23±6.61	878 (21.8)	23.72±5.37	5,673 (27.8)	32.4±5.99
	60–70	3,064 (12.5)	31.28±6.84	529 (13.1)	23.49±5.61	2,535 (12.4)	32.91±5.95
Body mass index		24,447	25.38±4.29	4,022	26.45±4.29	20,425	25.17±4.26
Age category	20–29	2,691 (11.0)	26.13±5.19	573 (14.2)	26.9±5.51	2,118 (10.4)	25.92±5.08
	30–39	5,012 (20.5)	25.85±4.82	976 (24.3)	27.5±4.93	4,036 (19.8)	25.46±4.7
	40–49	7,129 (29.2)	25.16±4.29	1,066 (26.0)	26.57±3.95	6,063 (29.7)	24.92±4.3
	50–59	6,551 (26.8)	25.1±3.73	878 (21.8)	25.66±3.27	5,673 (27.8)	25.01±3.79
	60–70	3,064 (12.5)	22.02±3.4	529 (13.1)	25.08±2.84	2,535 (12.4)	25.01±3.51

Table 2: Analyzed genetic index of GENESTART™ DTC genetic testing service and the association to body fat percentage and body mass index.

Associated Phenotypes	Tested Gene	Tested SNP rsID	Chr	Position	Minor Allele	References	Body Fat Percentage			Body Mass Index		
							Beta	SD	p-value	Beta	SD	p-value
Body mass index	FTO	rs9939609	16	53,786,615	A	(5)	0.36	0.09	<0.0001	0.42	0.06	<0.0001
	MC4R	rs17782313	18	60,183,864	C	(6)	0.28	0.07	<0.0001	0.27	0.04	<0.0001
	BDNF	rs6265	11	27,658,369	T	(7)	0.10	0.06	0.09	0.16	0.04	<0.0001
Triglycerides	ANGPTL3	rs10889353	1	62,652,525	C	(8)	-0.02	0.02	0.37	-0.01	0.01	0.36
	MLXIPL	rs17145738	7	73,568,544	A	(9)	0.15	0.10	0.12	0.01	0.06	0.90
	TRIB1	rs2954029	8	125,478,730	A	(10)	0.17	0.06	0.005	0.04	0.04	0.26
LDL cholesterol	ABO	rs635634	9	133,279,427	T	(11)	0.10	0.07	0.14	0.04	0.04	0.41
	HMGCR	rs12654264	5	75,352,778	A	(12)	-0.01	0.06	0.83	-0.04	0.04	0.27
	SORT1	rs646776	1	109,275,908	C	(13)	-0.03	0.13	0.80	-0.08	0.08	0.30
	ABCA1	rs1883025	9	104,902,020	T	(14)	0.07	0.07	0.30	0.09	0.04	0.04
HDL cholesterol	CETP	rs1532624	16	56,971,567	A	(15)	-0.04	0.07	0.53	-0.06	0.04	0.20
	LIPG	rs4939883	18	49,640,844	T	(16)	0.02	0.07	0.80	0.03	0.05	0.59
	MYL2	rs12229654	12	110,976,657	G	(17)	-0.17	0.08	0.04	-0.04	0.06	0.42
Blood sugar	CDKN2A_B	rs10811661	9	22,134,095	C	(18)	-0.04	0.06	0.45	-0.04	0.04	0.25
	DGKB	rs2191349	7	15,024,684	G	(19)	-0.08	0.06	0.19	-0.06	0.04	0.15
	G6PC2	rs560887	2	168,906,638	T	(20)	0.23	0.18	0.22	0.26	0.12	0.03
	GCK	rs1799884	7	44,189,469	T	(21)	-0.01	0.08	0.94	0.04	0.05	0.39
	GCKR	rs780094	2	27,518,370	T	(22)	0.10	0.06	0.09	0.14	0.04	0.0002
	GLIS3	rs7034200	9	4,289,050	A	(23)	0.18	0.06	0.002	0.11	0.04	0.004
	MTNR1B	rs10830963	11	92,975,544	G	(24)	0.11	0.06	0.07	0.07	0.04	0.07
	SLC30A8	rs13266634	8	117,172,544	T	(25)	-0.07	0.06	0.23	-0.05	0.04	0.15
Blood pressure	ATP2B1	rs17249754	12	89,666,809	A	(26)	0.06	0.06	0.34	0.04	0.04	0.33
	CSK	rs1378942	15	74,785,026	A	(27)	-0.13	0.08	0.11	-0.06	0.05	0.23
	CYP17A1	rs1004467	10	102,834,750	C	(28)	-0.13	0.07	0.06	-0.08	0.04	0.047
	FGF5	rs1458038	4	80,243,569	T	(29)	-0.04	0.06	0.53	0.02	0.04	0.65
	GUCY1A3	rs13139571	4	155,724,361	A	(30)	0.07	0.07	0.30	-0.03	0.05	0.46
	HECTD4	rs11066280	12	112,379,979	A	(31)	0.19	0.08	0.01	0.11	0.05	0.04
	NPR3	rs1173771	5	32,814,922	A	(32)	-0.02	0.06	0.73	-0.01	0.04	0.73
	NT5C2	rs11191548	10	103,086,421	C	(33)	-0.14	0.07	0.04	-0.16	0.04	0.0003
Caffeine metabolism	AHR	rs4410790	7	17,244,953	C	(34)	-0.04	0.06	0.52	-0.04	0.04	0.27
	CYP1A2	rs762551	15	74,749,576	C	(35)	-0.04	0.06	0.48	-0.02	0.04	0.67

Note. Chr: chromosome number; Beta: effect size of linear regression analysis with controlling age and sex as the covariates; Bold and underline: significant association (p<0.05) with at least one phenotype.

(Table 3), and the interactions are described in (Figure 1 (BFP and 2) (BMI)).

As shown in (Figure 1a), in the high- or medium-risk groups for ABO, body fat decreased to some extent when fruit was consumed but increased again when too much was consumed. When a large amount of sweet food was consumed, BFP gradually increased regardless of the genotype of the CYP1A2 gene (Figure 1b).

However, in the high-risk group, eating a lot of sweet foods was shown to have little or no effect on changes in BFP. (Figure 1c) shows that muscle exercise has a great effect on the reduction of BFP regardless of genotype, but in the high-risk group of the FTO gene, the higher the frequency of muscle exercise, the more effectively the BFP decreased. (Figure 1d) shows that regular vitamin intake had an effect on BFP reduction in the low- and medium-risk groups of the MC4R gene but had little effect in the high-risk group.

(Figure 2a) shows that when subjects frequently ate protein meals, their BMI tended to decrease little by little; however, if they ate too much, their BMI increased. In particular, in the high-risk group of the MC4R gene, it was found that eating a lot of protein resulted in a sharp increase in BMI. (Figure 2b) shows that increased fruit intake tended to decrease BMI, but in the high-risk group, eating too much fruit increased BMI. (Figure 2c) shows that high calcium intake does not appear to have had a significant effect on BMI changes, but in the high-risk group of the MC4R gene, too much calcium intake may have increased BMI. Furthermore, high calcium intake seemed to slightly increase BMI, except in the high-risk group of DGKB where it seemed to decrease BMI (Figure 2d). In the low-risk group of the CSK gene, drinking a lot of water was shown to decrease BMI (Figure 2e).

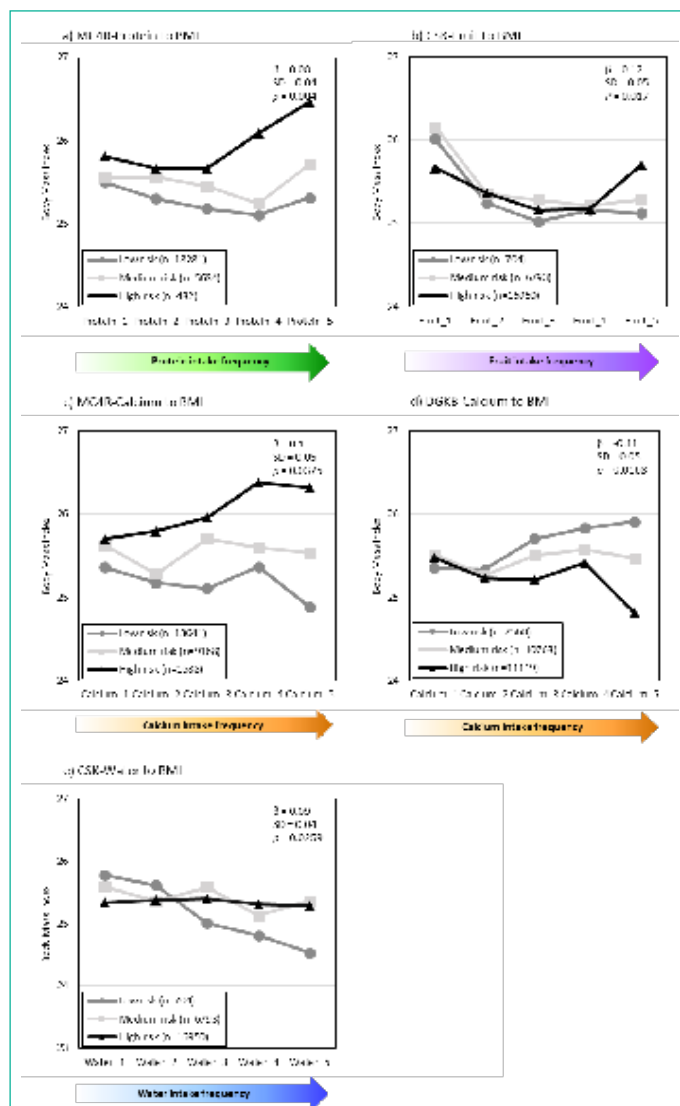
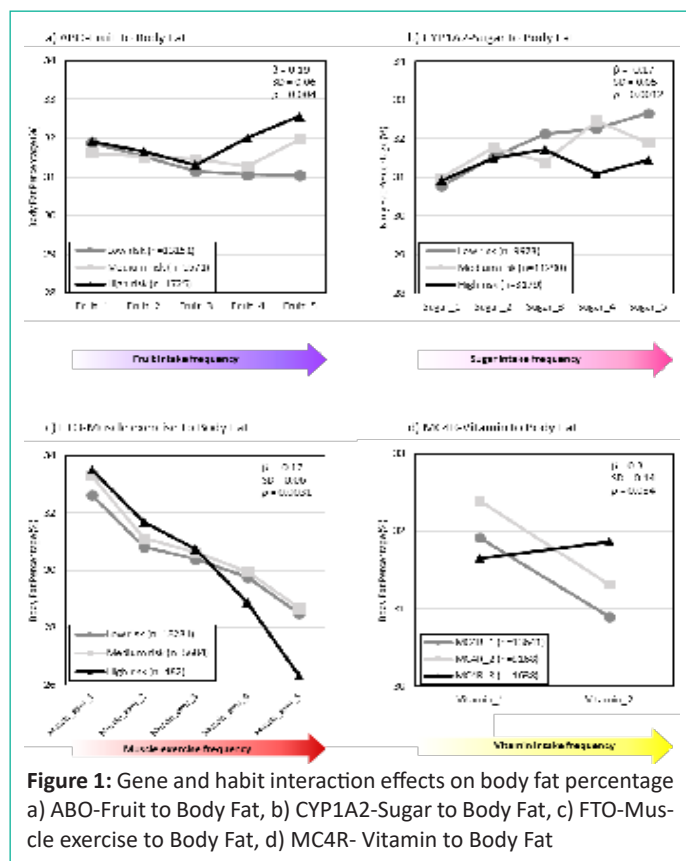


Figure 2: Gene and habit interaction effects on body mass index. (a) MC4R-Protein to BMI, (b) CSK-Fruit to BMI, (c) MC4R-Calcium to BMI, (d) DGKB-Calcium to BMI, (e) CSK- Water to BMI

Discussion

This study analyzed genetic information and food frequency questionnaire information collected through the Korean DTC genetic testing service called GENESTART. This analysis was conducted to provide future customers with solutions to improve their habits more effectively.

BFP was lower in men than in women and decreased with age, and this result was confirmed to be the same as the results of other studies [36]. In contrast, BMI was higher in men than in women.

GENESTART examined 30 gene markers to predict the genetic predisposition of seven items. Although the genes to be tested include genes for which no effects on obesity or body fat are reported, most metabolic syndrome-related symptoms and obesity-related indicators are considered to be highly related. Therefore, in this study, all genetic markers were analyzed for correlation with BFP or BMI. FTO, MC4R, and BDNF genes have all been repeatedly reported to be correlated with obesity. Both the FTO and MC4R genes also showed significant results for both BFP and BMI in this study; however, the BDNF gene showed a significant association with BMI but only a weak association with BFP.

Table 3: Gene and Questionnaire interaction to BFP and BMI

Gene	Phe	Main Effect		Questionnaire	Interaction p-value
		Beta	p-value		
ABO	BFP	0.1±0.07	0.14	Fruit	0.004
CYP1A2		-0.04±0.06	0.48	Sugar	0.0012
FTO		0.36±0.09	<0.0001	Muscle exer	0.0031
MC4R		0.28	<0.0001	Vitamin	0.034
CSK	BMI	-0.06±0.05	0.23	Fruit	0.017
				Water	0.0259
0.27		<0.0001	Protein	0.0419	
			Calcium	0.0375	
DGKB		-0.06±0.04	0.15	Calcium	0.0168

Among the genetic indicators assigned to metabolic syndrome, other than obesity; the triglyceride-related TRIB1 gene; low-density lipoprotein cholesterol-related ABCA1 gene; high-density lipoprotein cholesterol-related MYL2 gene; blood sugar-related G6PC2, GCKR, and GLIS3 genes; and blood pressure-related CYP17A1 gene, the HECTD4 and NT5C2 genes showed significant correlation with BFP or BMI ($p < 0.05$). Among these, the correlation between the triglyceride-related TRIB1 gene and BFP, the blood sugar-related GCKR and GLIS3 genes and BMI, and the NT5C2 gene and BMI were more clearly observed.

The TRIB1 gene has been reported as highly correlated with blood lipid levels and brown adipose respiratory chain [37], and our study showed its association with BFP. The G6PC gene encodes the glucose-6-phosphatase catalytic subunit as a key enzyme in glucose homeostasis [38], and our study showed its association with BMI. The GCKR gene encodes the glucokinase regulator and controls glucose metabolism by inhibiting glucokinase in the liver and pancreatic cells [39]. The GLIS3 gene was previously reported to have a genetic susceptibility role in type 2 diabetes and obesity [40].

In this study, we found four interaction results for BFP (ABO and fruits, CYP1A2 and sugary foods, FTO and muscle exercise, and MC4R and vitamins) and five interaction results for BMI (MC4R and protein, CSK and fruits, MC4R and calcium, DGKB and calcium, CSK and water). Unfortunately, the current study does not fully reveal the mechanism of the interaction effects on obesity-related factors. However, the purpose of DTC genetic testing is to provide consumers with information on their genetic risk and motivate them to take care of their own customized health care. In particular, the GENESTART genetic test, which was the subject of this study, is mainly used to identify genetic factors related to obesity and metabolic syndrome. It is known that the most representative indicator for managing metabolic syndrome is the obesity index. In this study, according to such genotypes, we tried to confirm—in a population group of 20,000 or more—that the obesity index could be improved by more closely examining eating habits.

Conclusion

In conclusion, this study yielded interesting gene–diet interactions, four for BFP and five for BMI. If these results are utilized, it is expected that it will be possible to present a personalized and accurate solution for BFP and BMI management for customers who have undergone genetic testing. For example, the low-risk group of the ABO genetic index can eat a lot of fruit, but the medium- and high-risk groups may face increased BFP

upon doing so and should therefore control the amount of fruit consumed each day. The results of this study have academic value in confirming the significant effect of the interactions between genes and eating habits on obesity indicators. The results are also expected to serve as reference materials for accurate, evidence-based solutions in actual DTC services.

Supplementary Files

This is a list of supplementary files associated with this article.

- SupplementaryFigure1
- SupplementaryFigure2hekim
- SupplementaryFigure3hekim

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