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Association of TCF7L2 Rs12255372 with Obesity and Adiposity Phenotypes Among Indonesian Medical Residents: A Cross-Sectional Genetic Association Study

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ABSTRACT: Obesity is a complex phenotype arising from interactions between genetic susceptibility and environmental influences. This cross-sectional genetic association study examined the relationship between the TCF7L2 rs12255372 polymorphism and obesity and adiposity phenotypes among 152 Indonesian medical residents aged 25–45 years. Anthropometric and body-composition measures included body mass index (BMI), waist circumference, body-fat percentage, and visceral fat. The rs12255372 variant was genotyped by polymerase chain reaction followed by direct sequencing. Overall, 91 participants (59.9%) had obesity and 61 (40.1%) had normal weight. The GG and GT genotypes were identified in 96 (63.2%) and 56 (36.8%) participants, respectively; no TT homozygotes were observed. Obesity was more frequent among participants with the GG genotype than among those with GT (78.1% vs 28.6%; $p<0.001$). GG carriers also had higher BMI, a greater prevalence of increased waist circumference, higher body-fat percentage, and higher visceral-fat values (all $p<0.05$). In multivariable logistic regression, the GG genotype remained associated with obesity after adjustment for sex and family history of obesity (adjusted OR 8.63; 95% CI 3.79–19.65; $p<0.001$). These findings indicate a strong association between rs12255372 and obesity-related phenotypes in this cohort, although the allelic direction differs from some previous populations. Larger population-based studies with ancestry adjustment and broader genetic characterization are needed to replicate these findings.

1. INTRODUCTION

Obesity is a major global metabolic and public-health burden. From 1990 to 2022, adult obesity prevalence increased in 188 countries for women and all but one for men [1]. Common obesity reflects interaction between an obesogenic environment and polygenic susceptibility [2]. Genetic associations vary across populations, while Asian evidence remains less extensive than Western evidence, supporting population-specific evaluation of obesity-related variants [3].

TCF7L2 is a transcriptional effector of canonical Wnt/β-catenin signaling with established roles in glucose homeostasis and adipose biology [4]. Wnt/β-catenin signaling constrains adipocyte differentiation [5]. In mice, adipocyte-specific *Tcf7l2* deletion disrupted lipid metabolism and glucose tolerance, with increased fat mass observed in male heterozygous knockout animals [6]. Human evidence, however, is substantially stronger for type 2 diabetes than for adiposity, and direct obesity associations have been inconsistent [7].

rs12255372 is among the most studied *TCF7L2* diabetes-associated variants. An Asian meta-analysis reported a significant association with type 2 diabetes [3], and a Bangladeshi case-control study similarly found higher diabetes odds among variant carriers [8]. Evidence for obesity is more limited. Mahmood et al. (2025) reported higher obesity odds, body mass index, and waist circumference among Bangladeshi T-allele carriers [9]. In Indonesia, Saraswati et al. (2017) found no significant association between rs12255372 and type 2 diabetes in Bali [10], while a later study examined *TCF7L2* risk alleles in relation to GLP-1 response and β-cell function rather than obesity [11]. We therefore investigated rs12255372 in relation to obesity, body mass index, waist circumference, body-fat percentage, and visceral fat among Indonesian medical residents.

2. MATERIALS AND METHODS

2.1 Study Design and Participants

This single-center cross-sectional genetic association study was conducted among medical residents enrolled in specialist training programs at Universitas Hasanuddin, Makassar, Indonesia, from May to June 2026. The study evaluated the association of the TCF7L2 rs12255372 polymorphism with obesity and adiposity phenotypes, including body mass index (BMI), waist circumference, body-fat percentage, and visceral fat.

Eligible medical residents were identified from the active resident population using total sampling. Of 258 residents screened, 152 fulfilled the eligibility criteria and were included in the final analysis, comprising 91 participants with obesity and 61 with normal weight.

Participants were eligible if they were aged 25–45 years, actively enrolled as medical residents at Universitas Hasanuddin, provided written informed consent, agreed to anthropometric and body-composition measurements, and provided a peripheral venous blood sample for genetic analysis. Nutritional status was classified according to Asia-Pacific BMI criteria. Normal weight was defined as BMI 18.5–22.9 kg/m² and obesity as BMI ≥25.0 kg/m². Participants with BMI 23.0–24.9 kg/m² were not included in the analytic comparison.

Participants were excluded if they had an acute illness or a major metabolic or endocrine disorder likely to substantially influence body weight or metabolism, including type 1 diabetes mellitus, Cushing syndrome, uncontrolled hypothyroidism, or chronic liver disease. Other exclusion criteria included pregnancy or lactation, participation in an active weight-reduction program during the preceding three months, and use of glucocorticoids, antipsychotic agents, antidiabetic medications, or other medications or supplements known to substantially affect body weight or metabolism. Participants who withdrew consent, declined further study procedures, or developed a severe illness preventing completion of study assessments were excluded from the final analysis.

2.2 Clinical, Anthropometric, and Lifestyle Assessment

Data were collected using structured interviews, anthropometric measurements, body-composition assessment, dietary evaluation, physical-activity assessment, and laboratory genetic analysis. Recorded characteristics included age, sex, smoking status, family history of obesity, nutritional status, dietary characteristics, and physical activity. Data were reviewed for completeness and internal consistency before statistical analysis.

Body weight was measured with participants barefoot and wearing light clothing using a calibrated weighing device positioned on a firm, level surface. Standing height was measured using a microtoise with participants barefoot and positioned upright. Weight and height were measured twice, and the average values were used for analysis. BMI was calculated as body weight in kilograms divided by height in meters squared. The primary outcome was obesity, defined as BMI ≥25.0 kg/m², whereas participants with BMI 18.5–22.9 kg/m² constituted the normal-weight comparison group.

Waist circumference was measured using standardized anthropometric procedures. Increased waist circumference was defined as >90 cm in men and >80 cm in women. Body composition was assessed using a Tanita MC-980 bioelectrical impedance analyzer (Tanita Corporation, Japan). Before measurement, age, sex, and height were entered into the analyzer. Participants were instructed to avoid food intake, substantial fluid intake, and exercise for approximately 2–3 hours before assessment and to remove footwear, socks, and metallic accessories. The principal body-composition measures were body-fat percentage and visceral fat. High body-fat percentage was defined as >25% in men and >35% in women. Waist circumference, body-fat percentage, and visceral fat were evaluated as secondary adiposity phenotypes.

Habitual dietary intake during the preceding month was assessed using a Food Frequency Questionnaire comprising 105 food items. Dietary intake was summarized into five domains: processed foods, saturated-fat-source foods, carbohydrate-rich foods, fiber-rich foods, and extra-virgin olive oil (EVOO)/omega-3-source foods. Each domain was categorized as frequent versus never/rare consumption according to the predefined study criteria. Frequent processed-food intake was defined as ≥3 times/week, whereas frequent saturated-fat-source intake was defined as >2 times/week. Dietary variables were considered lifestyle characteristics and candidate covariates rather than principal exposures.

Physical activity was assessed using the International Physical Activity Questionnaire–Short Form (IPAQ-SF) and expressed as metabolic equivalent task minutes per week (MET-min/week). Activity was initially classified as low (<600 MET-min/week), moderate (600–3000 MET-min/week), or high (>3000 MET-min/week). For categorical analyses, low and moderate activity were combined into a low-to-moderate category and compared with high physical activity.

2.3 DNA Extraction and TCF7L2 rs12255372 Genotyping

A 3-mL peripheral venous blood sample was collected into an EDTA-containing tube. The buffy-coat fraction was separated and used for genomic DNA extraction. DNA was extracted using a commercial Geneaid DNA extraction kit and stored at −20°C until molecular analysis.

The genomic region containing TCF7L2 rs12255372 was amplified by polymerase chain reaction using MyTaq HS Red Mix and TCF7L2-specific forward and reverse primers. Amplified products were evaluated by agarose-gel electrophoresis and subsequently subjected to direct sequencing. Sequence chromatograms were aligned against the corresponding GenBank reference sequence and analyzed using BioEdit Sequence Alignment Editor version 7.0.5.1, with sequence comparison supported by the National Center for Biotechnology Information Basic Local Alignment Search Tool (NCBI BLAST).

Genotypes were classified as GG, GT, or TT. In the final analytic sample, 96 participants had the GG genotype and 56 had the GT genotype; no TT homozygotes were identified. Because the TT genotype was absent, genotype-based analyses compared participants with GG and GT genotypes.

The principal genetic exposure was TCF7L2 rs12255372 genotype. The primary outcome was obesity, defined as BMI ≥25.0 kg/m². Secondary adiposity phenotypes included BMI, waist circumference, body-fat percentage, and visceral fat. Potential demographic, hereditary, and lifestyle covariates included age, sex, smoking status, family history of obesity, physical activity, and dietary characteristics.

2.4 Statistical Analysis

Continuous variables were summarized as mean ± standard deviation when approximately normally distributed and as median with minimum–maximum values when non-normally distributed. Categorical variables were presented as frequencies and percentages. Differences in continuous variables between independent groups were assessed using the independent-samples *t* test or Mann–Whitney U test, as appropriate. Categorical variables were compared using Pearson's chi-square test. Comparisons were performed according to obesity status and rs12255372 genotype where relevant.

Genotype and allele frequencies were calculated from the observed rs12255372 genotype distribution. Hardy–Weinberg equilibrium was assessed in the normal-weight comparison group using an exact test based on the observed GG, GT, and TT genotype frequencies.

Associations between candidate factors and obesity were initially evaluated using univariable binary logistic regression and reported as crude odds ratios (ORs) with 95% confidence intervals (CIs). Eleven prespecified demographic, hereditary, lifestyle, dietary, and genetic variables were entered into the initial multivariable model. Backward likelihood-ratio elimination was subsequently applied to derive the final model.

Multivariable binary logistic regression was used to estimate adjusted associations with obesity, with results reported as adjusted ORs and 95% CIs. The final model retained rs12255372 genotype, sex, and family history of obesity. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, while Cox and Snell R^2 and Nagelkerke R^2 were used to describe model explanatory performance. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 30 (IBM Corp., Armonk, NY, USA).

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3. RESULTS AND DISCUSSION

3.1 Results

Of 258 medical residents screened, 152 met the eligibility criteria and were included in the analysis. Of these, 91 participants (59.9%) were classified as having obesity and 61 (40.1%) as having normal weight. The median age was 30 years (range, 25–45), and 95 participants (62.5%) were women. The rs12255372 genotype distribution comprised 96 participants (63.2%) with the GG genotype and 56 (36.8%) with the GT genotype; no TT homozygotes were observed. The corresponding G- and T-allele frequencies were 0.816 and 0.184, respectively. The rs12255372 genotype distribution in the normal-weight comparison group deviated significantly from Hardy–Weinberg equilibrium (GG=21, GT=40, TT=0; exact P<0.001).

As shown in Table 1, age did not differ significantly between participants with obesity and those with normal weight. Male sex, current smoking, family history of obesity, high physical activity, the GG genotype, frequent processed-food intake, and frequent saturated-fat intake were more frequent in the obesity group. Frequent carbohydrate, fiber, and EVOO/omega-3 intake did not differ significantly between groups.

Table 1. Characteristics of the Study Participants According to Obesity Status

Characteristic	Total (N=152)	Normal weight (n=61)	Obesity (n=91)	*p* value
Age, years, median (range)	30 (25–45)	31 (25–45)	30 (25–38)	0.576[a]
Sex				<0.001[b]
Male	57 (37.5)	11 (18.0)	46 (50.5)	
Female	95 (62.5)	50 (82.0)	45 (49.5)	
Smoking status				0.005[b]
Current smoker	15 (9.9)	1 (1.6)	14 (15.4)	
Non-smoker	137 (90.1)	60 (98.4)	77 (84.6)	
Family history of obesity				0.020[b]
Present	46 (30.3)	12 (19.7)	34 (37.4)	
Absent	106 (69.7)	49 (80.3)	57 (62.6)	
Physical activity				0.006[b]
High	35 (23.0)	7 (11.5)	28 (30.8)	
Low–moderate	117 (77.0)	54 (88.5)	63 (69.2)	
TCF7L2 rs12255372 genotype				<0.001[b]
GG	96 (63.2)	21 (34.4)	75 (82.4)	
GT	56 (36.8)	40 (65.6)	16 (17.6)	
Dietary characteristics				
Frequent processed-food intake	113 (74.3)	38 (62.3)	75 (82.4)	0.005[b]
Frequent saturated-fat intake	91 (59.9)	30 (49.2)	61 (67.0)	0.028[b]
Frequent carbohydrate intake	129 (84.9)	51 (83.6)	78 (85.7)	0.722[b]
Frequent fiber intake	81 (53.3)	32 (52.5)	49 (53.8)	0.867[b]
Frequent EVOO/omega-3 intake	79 (52.0)	36 (59.0)	43 (47.3)	0.155[b]

Note: Data are presented as median (range) or *n* (%). Percentages for categorical variables are column percentages. [a]Mann–Whitney *U* test. [b]Pearson's chi-square test. EVOO, extra-virgin olive oil.

Obesity was substantially more frequent among participants with the GG genotype than among those with the GT genotype (78.1% vs 28.6%; p<0.001). As presented in Table 2, the GG group also had a higher median BMI, a greater proportion with increased waist circumference, a slightly higher median body-fat percentage, and higher visceral-fat values. All four adiposity measures differed significantly between genotype groups.

Table 2. Obesity and Adiposity Phenotypes According to TCF7L2 rs12255372 Genotype

Adiposity phenotype	GG (n=96)	GT (n=56)	*p* value
Obesity, n (%)	75 (78.1)	16 (28.6)	<0.001[b]
BMI, kg/m², median (range)	26.8 (18.2–51.7)	21.9 (18.1–57.8)	<0.001[a]
Increased waist circumference, n (%)	56 (58.3)	16 (28.6)	<0.001[b]
Body-fat percentage, %, median (range)	32.7 (19.2–66.1)	31.7 (10.4–68.9)	0.028[a]
Visceral fat, median (range)	9 (1–25)	5 (1–18)	<0.001[a]

Note: Data are presented as median (range) or *n* (%). Increased waist circumference was defined as >90 cm in men and >80 cm in women. [a]Mann–Whitney *U* test. [b]Pearson's chi-square test. BMI, body mass index.

In the univariable analyses shown in Table 3, Panel A, male sex, smoking, family history of obesity, high physical activity, GG genotype, frequent processed-food intake, and frequent saturated-fat intake were associated with obesity. The largest crude point estimate was observed for smoking; however, the estimate was imprecise, as reflected by its wide 95% confidence interval. Age, frequent carbohydrate intake, frequent fiber intake, and frequent EVOO/omega-3 intake were not significantly associated with obesity.

In the final multivariable model (Table 3, Panel B), GG genotype, male sex, and family history of obesity remained associated with obesity after mutual adjustment. The GG genotype showed the largest adjusted association (adjusted OR [aOR], 8.63; 95% CI, 3.79–19.65; p<0.001), followed by male sex (aOR, 5.07; 95% CI, 2.09–12.26; p<0.001) and family history of obesity (aOR, 2.97; 95% CI, 1.21–7.26; p=0.017).

Table 3. Univariable and Final Multivariable Logistic Regression Analyses for Obesity

Panel A. Univariable logistic regression

Variable	Crude OR	95% CI	*p* value
Male sex	5.21	2.36–11.52	<0.001
Age 25–45 years	0.85	0.43–1.66	0.636
Current smoking	10.91	1.40–85.31	0.005
Family history of obesity	2.44	1.14–5.21	0.020
High physical activity	3.43	1.39–8.47	0.006
GG genotype	8.93	4.20–19.00	<0.001
Frequent processed-food intake	2.84	1.34–6.00	0.005
Frequent saturated-fat intake	2.10	1.08–4.09	0.028
Frequent carbohydrate intake	1.18	0.48–2.88	0.722
Frequent fiber intake	1.06	0.55–2.03	0.867

Frequent EVOO/omega-3 intake	0.62	0.32–1.20	0.155

Panel B. Final multivariable logistic regression model

Variable	Adjusted OR	95% CI	*p* value
Male sex	5.07	2.09–12.26	<0.001
Family history of obesity	2.97	1.21–7.26	0.017
GG genotype	8.63	3.79–19.65	<0.001

Note: ORs were estimated using binary logistic regression with obesity as the dependent variable. Panel A presents separate univariable models. Panel B presents variables retained in the final backward likelihood-ratio multivariable model. Reference categories were female sex, the younger age category, non-smoking, no family history of obesity, low-to-moderate physical activity, GT genotype, and the corresponding non-frequent dietary category. CI, confidence interval; EVOO, extra-virgin olive oil; OR, odds ratio.

The final multivariable model had a −2 log likelihood of 148.842, Cox and Snell R^2 of 0.308, and Nagelkerke R^2 of 0.416. The Hosmer–Lemeshow goodness-of-fit test was non-significant (χ^2=2.029, p=0.845), indicating no evidence of poor calibration by this test.

3.2 Discussion

The main finding of this study was a strong association between *TCF7L2* rs12255372 and obesity among Indonesian medical residents. Participants with the GG genotype had higher odds of obesity than those with the GT genotype, and this association remained after adjustment for sex and family history of obesity. The same direction was observed for BMI, increased waist circumference, body-fat percentage, and visceral fat. These parallel findings across related adiposity measures strengthen the internal consistency of the observed association, but they do not establish a causal role for rs12255372. Common obesity is a complex polygenic phenotype shaped by both genetic susceptibility and environmental exposures [2,12].

The allelic direction deserves particular caution. Mahmood et al. (2025) reported higher obesity odds among Bangladeshi carriers of the rs12255372 T allele and GT genotype, which is opposite to the pattern observed here [9]. In Mexican children, GT carriers were more common among lean than obese participants and had lower odds of obesity, whereas no significant rs12255372–obesity association was identified in Cameroonian adults [13,14]. More recently, Abbaspour et al. (2025) evaluated three *TCF7L2* variants in northern Iranian adults with type 2 diabetes and found an obesity association for rs7903146, but not rs12255372 [15]. The present GG association should therefore not be interpreted as identifying G as a universal obesity-risk allele. It should also be distinguished from the type 2 diabetes literature, in which the rs12255372 T allele has shown more consistent susceptibility associations, including in Asian populations [3,8].

There is nevertheless biological support for considering *TCF7L2* relevant to adipose biology. *TCF7L2* functions within canonical Wnt signaling and participates in metabolic regulation and adipocyte development [4]. Human adipose-progenitor experiments have shown that its effects on adipogenesis vary according to expression level and fat depot, while adipocyte-specific manipulation in mice alters lipid metabolism and glucose homeostasis [6,16]. In Asian Indians, rs7903146 genotype and visceral-adipose *TCF7L2* expression have also been associated with postprandial triglyceride and glycemic phenotypes [17]. These data establish biological plausibility at the gene level, but they do not demonstrate that rs12255372 itself is the functional variant responsible for the present association.

The findings across several adiposity measures are relevant because BMI alone provides limited information about fat distribution. Asian populations may experience greater central adiposity and cardiometabolic risk at lower BMI values than many Western populations, making waist and body-composition measures particularly informative [18,19]. A review of Asian GWASs also showed that the genetic architecture of BMI, waist-related traits, and body-fat measures is only partly shared, supporting evaluation of multiple adiposity phenotypes rather than BMI alone [20].

Male sex and family history of obesity also remained associated with obesity in the final model. This is compatible with the broader multifactorial architecture of common obesity, in which inherited susceptibility coexists with behavioral and environmental influences [2,12]. Several lifestyle variables were associated with obesity in univariable analyses but were not

retained in the final model. These findings should not be described as gene–environment interactions because genotype-by-exposure interaction terms were not tested. Evidence from another *TCF7L2* variant, rs7901695, suggests that associations with metabolic and obesity-related traits may vary according to macronutrient intake, but that observation cannot be extrapolated directly to rs12255372 [21]. The unexpected univariable association between high physical activity and obesity may reflect reverse causation, behavioral change following weight gain, or limitations of self-reported activity rather than a causal adverse effect of physical activity.

Population context is another plausible contributor to the discrepant allelic direction. Allele frequencies and linkage-disequilibrium patterns vary across ancestries, and an observed marker may tag functional variation differently in different populations; uncontrolled population structure may also generate or distort genotype–phenotype associations [22]. Asian adiposity genetics remains heterogeneous and less extensively characterized than European-ancestry genetics, particularly for central and body-composition phenotypes [20]. Thus, the present result could reflect local linkage structure, sampling variation, residual confounding, or a combination of these factors. The relatively large adjusted OR also warrants restraint because individual common variants contributing to polygenic obesity generally have modest effects [12].

Several features strengthen this study, including a well-defined occupational cohort and assessment of obesity together with complementary anthropometric and body-composition phenotypes. The limitations are nevertheless important. The sample size was modest for a genetic association study, no TT homozygotes were observed, and the rs12255372 genotype distribution in the normal-weight comparison group deviated from Hardy–Weinberg equilibrium. Although genotyping was performed using direct sequencing, this deviation may reflect the relatively small and selected occupational sample, population structure, or other sampling-related factors and therefore warrants cautious interpretation and independent replication. Exclusion of the intermediate overweight category also limits inference across the full BMI continuum and may accentuate contrasts between groups. The single-center design restricts generalizability, while the cross-sectional design precludes temporal or causal inference. Body composition was measured using bioelectrical impedance rather than reference imaging, and diet and physical activity were self-reported. Only one *TCF7L2* variant was examined, ancestry-informative markers were unavailable, and residual confounding cannot be excluded. These considerations are particularly relevant for a phenotype as genetically complex as common obesity [12,23].

Replication is therefore needed before clinical or predictive implications are considered. Larger Indonesian studies should include the full BMI spectrum, sufficient numbers of minor-allele homozygotes, ancestry adjustment, and additional *TCF7L2* variants or haplotypes, particularly rs7903146. Functional studies would also be required to determine whether rs12255372 has regulatory activity or instead tags another functional signal through linkage disequilibrium [16,22]. At present, the results support an association between rs12255372 and obesity-related phenotypes in this cohort, rather than a deterministic or universally applicable genetic effect.

4. CONCLUSION

The TCF7L2 rs12255372 polymorphism was associated with obesity and several adiposity phenotypes among Indonesian medical residents. Participants with the GG genotype had higher odds of obesity than those with the GT genotype, and this association remained after adjustment for sex and family history of obesity. Differences in BMI, increased waist circumference, body-fat percentage, and visceral fat were also observed between genotype groups. However, the direction of association differs from some previous populations, and the relatively large effect estimate should be interpreted cautiously given the modest sample size, absence of TT homozygotes, and cross-sectional design. These findings therefore support an association within this cohort rather than a causal or universally applicable genetic effect. Larger studies across diverse Indonesian populations, incorporating ancestry adjustment, additional TCF7L2 variants, and functional analyses, are needed to confirm and clarify this relationship.

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AUTHOR CONTRIBUTIONS

NRM: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, and Writing – Original Draft.

AB: Conceptualization, Methodology, Supervision, Validation, and Writing – Review & Editing.

A: Methodology, Formal Analysis, Validation, and Writing – Review & Editing.

SA: Conceptualization, Methodology, Supervision, Validation, and Writing – Review & Editing.

HR: Methodology, Supervision, Validation, and Writing – Review & Editing.

NS: Methodology, Supervision, Validation, and Writing – Review & Editing.

All authors critically reviewed the manuscript, approved the final version, and agreed to be accountable for the integrity of the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ETHICS STATEMENT

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia (Approval No. 623/UN4.6.4.5.31/PP36/2026; Protocol No. UH26040551; 8 May 2026). All participants provided written informed consent before enrollment. Participation was voluntary, and participant confidentiality was maintained throughout the study. Personally identifying information was excluded from the analytic dataset.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable ethical and institutional restrictions.

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