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Association of GSTM1, GSTT1, and TP53 Genetic Variants with Obesity in Children

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What is already known on this topic?

- *Detoxification pathways may play a role in the development of childhood obesity through multiple mechanisms. Metabolomic analyses suggest that metabolic alterations observed in children with obesity are linked to disruptions in detoxification processes.*

What this study adds on this topic?

- *The study demonstrates a clear association between deletions in GSTM1 and GSTT1 genes and childhood obesity, highlighting their role in detoxification and oxidative stress regulation.*
- *GSTM1-null genotypes were linked to increased cholesterol, low-density lipoprotein, and gamma-glutamyl transferase levels, reflecting impaired detoxification capacity and metabolic imbalance.*
- *While TP53 rs1042522 polymorphism influenced cholesterol metabolism and liver function, it did not directly associate with obesity, suggesting that detoxification-related gene–environment interactions may modulate its effects.*

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ABSTRACT

Objective: This study explores whether *GSTM1*, *GSTT1*, and TP53 rs1042522 polymorphisms, key regulators of detoxification and oxidative stress responses, influence obesity risk and related metabolic profiles in children.

Materials and Methods: Blood samples from 60 obese children and 60 healthy controls were analyzed. *GSTM1* and *GSTT1* deletions were assessed via polymerase chain reaction melting curve analysis, and TP53 rs1042522 was genotyped by direct DNA sequencing. Deviations from Hardy–Weinberg expectations and genotype frequencies in controls were evaluated, and the association of genetic variants with obesity, clinical complications, and metabolic parameters was examined.

Results: In obese children, *GSTM1* and *GSTT1* genotype frequencies deviated from Hardy–Weinberg expectations and differed from controls, whereas TP53 rs1042522 conformed to expected distributions yet was statistically underpowered. The *GSTM1* null genotype increased obesity risk 3.28-fold (95% CI: 1.36–7.93, $P < .05$). The *GSTT1* null genotype conferred a 4.76-fold higher risk (95% CI: 2.08–10.88, $P < .001$). TP53 rs1042522 showed no association (OR = 1.12, 95% CI: 0.44–2.87). The *GSTM1* null carriers had elevated cholesterol, low-density lipoprotein (LDL), and gamma-glutamyl transferase, while TP53 Arg/Arg and Pro/Pro carriers exhibited higher LDL and alanine aminotransferase, respectively. No significant links were observed with insulin resistance or hepatic steatosis.

Conclusion: The *GSTM1* and *GSTT1* null genotypes are significant genetic risk factors for childhood obesity, likely through reduced detoxification capacity and subsequent oxidative stress–related metabolic disruption. These findings highlight the importance of considering detoxification pathways when assessing genetic predisposition to obesity in children.

Keywords: Childhood obesity, genetic predisposition, glutathione S-transferase, metabolic syndrome, TP53

INTRODUCTION

Childhood obesity and its related metabolic disorders represent a significant public health concern, contributing substantially to the global burden of chronic illnesses.[1] Excess weight in childhood is strongly associated with a broad spectrum of health consequences, spanning cardiometabolic and musculoskeletal disorders, reproductive and sleep-related disturbances, as well as psychological burdens such as stigma, depression, and diminished quality of life.[2,3] Global estimates from 2016 reported that nearly 40 million children under 5years of age and over 330 million individuals aged 5–19 were affected by excess weight or obesity.[4] In

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Türkiye, this widespread problem similarly persists, with studies indicating that 20%–25% of children aged 6–19 are overweight or obese.[5] Taken together, these underscore not only the magnitude of the problem but also its complex and multifaceted etiology and its consequences.

Obesity is widely recognized as the outcome of a multifactorial interplay between genetic, biological, behavioral, and environmental factors.[6-8] Hereditary susceptibility remains a central contributor, with more than 1100 genetic loci already linked to obesity-related traits, many of which influence appetite regulation, energy balance, and glucose–lipid homeostasis.[9,10] Dysregulation of key signaling pathways further exacerbates metabolic disturbances. For instance, mitogen-activated protein kinase activation alters insulin sensitivity and adipocyte function, while impairment of the phosphoinositide 3-kinase–protein kinase B (PI3K/Akt) pathway contributes to insulin resistance and obesity-related inflammation.[11,12] Additional mechanisms include hypothalamic IKKβ/NF-κB signaling and endoplasmic reticulum stress, both of which are activated by overnutrition and disrupt energy homeostasis, as well as resistin/toll-like receptor 4-mediated inflammation that promotes insulin resistance and adipose tissue dysfunction.[12,13] Collectively, these biological alterations illustrate how genetic predispositions interact with environmental and dietary exposures to drive the onset and progression of obesity in children.

Recent findings further suggest that these processes are closely connected to detoxification systems. Children with obesity frequently experience heightened oxidative stress, which disrupts redox balance and interferes with normal metabolic regulation.[14,15] In addition, population-specific variants of the tumor suppressor protein 53 (TP53), closely tied to detoxification pathways, have been linked to obesity and related metabolic disorders.[16-18] These insights point toward detoxification dysfunction as a potentially critical, though underexplored, element in the etiology of childhood obesity.

Glutathione S-transferase (GST) enzymes, as major phase II detoxification enzymes, may influence obesity development by modulating oxidative stress.[19] Yet, genomic variations in GSTs remain largely uncharacterized in pediatric obesity. Therefore, the present study aims to investigate polymorphisms in the GST Mu 1 (*GSTM1*) and GST Theta 1 (*GSTT1*) genes, along with the TP53 exon 4 codon 72 single-nucleotide polymorphism (SNP) (rs1042522), in children with obesity. By examining these genetic alterations in relation to clinical and demographic parameters, this study seeks to clarify their potential contribution to congenital susceptibility and overall risk of childhood obesity.

MATERIALS AND METHODS

Study Design and Participants

This study is a retrospective observational case-control genetic study, in which existing clinical records and biological samples from children who underwent obesity treatment were analyzed to assess associations between *GSTM1*, *GSTT1*, and TP53 polymorphisms and relevant clinical and biochemical parameters, compared with healthy controls.

Clinical records of children who underwent obesity treatment in a pediatric clinic were reviewed retrospectively. Eligible participants were those aged between 5 and 18 years with a body mass index (BMI) above the 95th percentile for their age and sex, as determined by standardized growth references.[20] Children included in the study were required to have no history of chronic illnesses or major health conditions such as diabetes, cardiovascular diseases, or other metabolic abnormalities. Individuals diagnosed with genetic syndromes were excluded. Controls were retrospectively selected from the same hospital biobank/record system during the same calendar period as cases and were frequency-matched to cases by age (±1 year), sex, and self-reported ethnicity to reduce selection bias. Inclusion criteria were age 5–18 years, BMI between the 5th and 85th percentiles for age and sex, absence of chronic systemic disease or genetic syndromes, no acute infection records, and no use of medications known to affect metabolic or endocrine parameters. Further exclusion criteria involved a lack of informed consent from the participants or their guardians, as well as cases with missing or incomplete clinical or demographic information. Blood samples were collected at the time of the participants' visit to the department, after which genomic DNA was isolated and stored at −80°C for later analyses. Subsequently, *GSTM1* and *GSTT1* gene deletions were assessed using trimodal genotyping based on melting curve analysis, and TP53 rs1042522 was analyzed by fragment sequencing using the archived DNA. The divergence of observed genotype frequencies from expected Hardy-Weinberg equilibrium proportions was evaluated, and associations with clinical and demographic variables were assessed.

Sample Size and Power Considerations

The study included a convenience sample of 60 patients and 60 healthy controls, with mean ages of 13.5 ± 2.23 and 12.9 ± 2.02 years, respectively, and approximately equal male-to-female ratios. Participants were selected based on the availability of archived clinical and biological specimens. To assess whether these sample sizes were sufficient to detect genetic associations, effect sizes were calculated based on the deviation of observed genotype frequencies from Hardy–Weinberg expectations using Cramér's V. Power analyses were then conducted using these effect sizes for target powers of 60%–80%, depending on the marker.

Diagnosis of Childhood Obesity

The diagnosis of obesity in children was established according to the Turkish Society of Endocrinology and Metabolism recommendations, which are consistent with the World Health Organization (WHO) growth reference for school-aged children.[21] For each participant, body weight was measured to the nearest 0.1 kg using a calibrated digital scale, and height was measured to the nearest 0.1 cm using a stadiometer, with children standing barefoot and in light clothing. The BMI was calculated as weight (kg)/height (m^2). The BMI values were then plotted on age- and sex-specific percentile charts. Classification was performed according to the WHO cut-off points, defined by BMI-for-age and sex z-scores relative to the reference population. Children with overweight are defined as >+1 SD (≈85th percentile) and obesity as >+2 SD (≈97th percentile).

Retrospective Data Collection

A comprehensive checklist was used to systematically collect detailed demographic, anthropometric, clinical, and

metabolic data. Demographic variables included age and sex, while anthropometric measurements comprised waist and hip circumferences, BMI, and body fat percentage. Clinical and biochemical assessments included glycemic (fasting glucose, fasting insulin), insulin resistance, lipid profile (cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL)), liver function markers (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT)), liver steatosis grade, thyroid hormones (thyroxine, thyroid-stimulating hormone (TSH)), and vitamin D level.

Ultrasound Examination

Hepatobiliary ultrasonography was performed in all patients to assess the presence and degree of hepatic steatosis. All examinations were conducted by an experienced radiologist who was blinded to the clinical and laboratory data, using a high-resolution ultrasound system equipped with a 3.5–5 MHz convex transducer. Hepatic steatosis was graded according to established sonographic criteria, which evaluated liver echogenicity in comparison with the right renal cortex, the clarity of intrahepatic vascular structures, and the degree of posterior beam attenuation. Based on these criteria, grade 0 indicated normal echotexture with no steatosis, grade 1 (mild) represented a slight and diffuse increase in hepatic echogenicity with preserved visualization of the diaphragm and intrahepatic vessel borders, grade 2 (moderate) reflected a moderate increase in hepatic echogenicity with mildly impaired visualization of intrahepatic vessels and the diaphragm, and grade 3 (severe) corresponded to a marked increase in echogenicity with poor or absent visualization of intrahepatic vessels and the diaphragm.

Molecular Analysis

Ethics approval and consent to participate: The study protocol was reviewed and approved by the Institutional Review Board of Health Sciences University and Ankara Atatürk Sanatorium Training and Research Hospital (Approval No: 2012-KAEK-15/2491) on April 12, 2022. Prior to enrollment, written informed consent was secured from all participants' legal guardians.

Genomic DNA Extraction

Genomic DNA was obtained from whole blood using a modified salt-out procedure.[22] To start, 20 mL of blood from each participant was diluted with an equal volume of distilled water (final volume 40 mL) and gently agitated for 20 minutes. The samples were then centrifuged at 5000 rpm for 10 minutes, and the supernatant, containing lysed red blood cells, was carefully discarded. The resulting pellet, enriched in white blood cells, was resuspended in 40 mL of cold distilled water, mixed for an additional 20 minutes, and centrifuged again at 5000 rpm for 10 minutes. The supernatant was discarded, and the pellet was resuspended in 5 mL of freshly prepared 1 × STE buffer (100 mM NaCl, 10 mM Tris-HCl, 1 mM EDTA, pH 8.0) using a vortex mixer.

To lyse the white blood cells and digest proteins, 500 µL of 10 × SDS solution and 100 µL of proteinase K were added, and the mixture was gently inverted to ensure uniform mixing. Samples were incubated overnight at 37°C. After incubation, 2.5 mL of 7.5 M ammonium acetate or saturated sodium chloride solution was added, and the tubes were gently inverted and left at room temperature for 10 minutes. Samples were centrifuged at 5000 rpm for 15 minutes, and the clear supernatant was transferred to a fresh tube.

Genomic DNA was precipitated by adding 30 mL of cold absolute ethanol to the supernatant. The DNA strands formed visible precipitates, which were carefully collected. After the ethanol evaporated, the DNA was dissolved in distilled water and stored at a minimum concentration of 500 ng/µL for downstream analyses.

Melting Curve Analysis

A quantitative polymerase chain reaction (qPCR) paired with melting curve analysis was employed to identify deletions within the *GSTM1* and *GSTT1* gene regions. This analysis was performed using the Roche LightCycler 480 platform, in conjunction with Bio-Rad's SSO Advanced Universal SYBR Green Supermix to ensure high sensitivity and specificity. The primers used for amplification were designed based on the reference sequences NM_000853 for *GSTT1* and NM_000561 for *GSTM1*, as previously described.[23]

Prior to qPCR, the reaction mixture was prepared by combining 5 µL of SYBR Green PCR Master Mix (Power), 0.4 µL each of forward and reverse primers, 1 µL of DNA template at a concentration of 100 ng/µL, and 3.2 µL of DNase-free water, resulting in a total volume of 10 µL. The melting curve analysis protocol commenced with a single initial denaturation step at 98°C for 3 minutes. This was followed by 40 cycles of amplification, each consisting of denaturation at 95°C for 10 seconds and annealing at 60°C for 15 seconds. The procedure was completed with a melting curve phase, where the temperature was gradually increased from 65°C to 95°C at a rate of 0.3°C per second to analyze product specificity.

Relative Quantification of Gene Copy Number and *GSTM1* and *GSTT1* Genotyping

Genotyping was conducted using a qPCR technique combined with melting curve analysis to assess gene dosage. For each sample, the fluorescence intensity over temperature (dF/dT) values corresponding to the target gene and the reference gene from healthy controls were compared to determine the relative DNA copy number. These values were calculated independently in 3 replicates.

The gene dosage was calculated as the mean of the dF/dT values of the replicates, standardized relative to the mean of the control group using the following formula:

$$\text{Normalized Value} = \frac{\text{Sample dF / dT}}{\text{Mean Control dF / dT}}$$

The mean values of dF/dT in healthy controls for *GSTM1* and *GSTT1* were 0.9971 and 1.1899, which align with the European population previously established by Girault et al (2005).[23] Hence, gene dosage measurements for *GSTT1* and *GSTM1* distinctly clustered into 3 groups, according to the classification adapted from Girault et al (2005).[23]

For the *GSTM1* gene, normalized dosage values ranging from 1.00 to 0.80—or values exceeding 1.00—indicate the presence of

both gene copies, consistent with the wild-type genotype (−/−). Values between 0.79 and 0.42 suggest a partial gene deletion representing a heterozygous state (wt/null, +/−), whereas values between 0.41 and 0.0 correspond to a complete gene deletion, or null genotype (+/+). Similarly, *GSTT1* gene dosage values from 1.00 to 0.80 or higher denote the wild-type genotype (−/−) with both alleles intact. Partial deletions (heterozygous, wt/null, +/−) fall within the 0.79 to 0.36 range, while values between 0.35 and 0 indicate a null genotype (+/+), signifying full deletion at this locus.[23]

TP53 rs1042522 Genotyping

To detect the presence of the TP53 rs1042522 SNP in the study population, the amplified gene fragment generated by PCR was analyzed using the Applied Biosystems 3130XL sequencing platform. Specific primers targeting the TP53 gene region (NM_000546.6) were employed for this purpose.

Statistical Analysis

Data analysis was carried out using R version 4.3.2 (R Foundation; Vienna, Austria). Continuous variables are summarized as means with their corresponding standard deviations, whereas categorical variables are reported as counts (n) and percentages (%). Deviation from the Hardy–Weinberg proportion for allele frequencies was tested via chi-square for goodness of fit for both patients and healthy controls.

Genotype distributions were compared between patients and controls via chi-square analysis, and genotype association was tested with metabolic parameters using ANOVA. For significant ANOVA results, Tukey's HSD test was used for post hoc comparisons. T-tests evaluated differences in anthropometric, glycemic, lipid profile, liver and thyroid function markers, and vitamin D level between patients and healthy control groups. Risk of null genotypes, both in recessive and allelic models, was calculated by odds ratio (OR) with a 95% CI.

Statistical significance was set at $P < .05$ (2-tailed). Effect sizes were calculated using Cramér's V (chi-square) and Cohen's d (mean differences). Statistical power was also computed to assess the probability of detecting true effects.

RESULTS

Demographic and Clinical Characteristics of the Study Population

The demographic and clinical characteristics of the 60 children with obesity and the 60 healthy controls are presented in Table 1. The 2 groups were well-matched for age and sex ($P > .05$). As expected, the obesity group had significantly higher anthropometric measures compared to the control group (all $P < .05$) (Table 1). Moreover, several metabolic parameters—including glycemic markers (HOMA-IR and insulin levels), lipid profile (triglycerides, HDL, LDL), liver function markers (ALT, GGT), and vitamin D levels, were significantly altered in the patient group compared to healthy controls (Table 1).

Genotype Deviations from Hardy–Weinberg and Controls

The genotypic distributions of *GSTM1*, *GSTT1*, and TP53 rs1042522 for both patients and healthy controls are detailed in Tables 2 and 3. The patients' genotypic distribution showed a notable deviation from the Hardy–Weinberg expectations in the *GSTM1* ($P = .01$) and *GSTT1* ($P = .0006$). Conversely, TP53 rs1042522 genotype frequencies in the patient cohort conformed to Hardy–Weinberg expectations ($P = .58$). Genotype distributions in the control group for all 3 polymorphisms were in Hardy–Weinberg equilibrium ($P > .05$), indicating no major genotyping errors or population stratification. In the

Table 1. Comparative Demographic and Clinical Characteristics of Patients and Controls

Parameters		Patients Mean ± SD	Healthy Mean ± SD	Reference Range	*P*	Effect Size	Power
Anthropometric	Waist Circumference (cm)	97.6 ± 11.1	69.4 ± 8.4	Male <94 Female <80	<.00001	2.84	1
	Hip Circumference (cm)	112.1 ± 10.2	83.3 ± 9.9	Male <0.9 Female <0.85	<.00001	2.87	1
	Fat percentage (%)	37.8 ± 6.3	19.3 ± 4.2	Male 11%–25% Female 16%–30%	<.00001	3.45	1
	Body Mass Index (kg/m^2)	31 ± 3.9	19.4 ± 2.8	*	<.00001	3.37	1
Glycemic	Glucose (mg/dL)	93.1 ± 7.3	91.9 ± 7.9	60–100	.4	0.16	0.21
	Insulin (μIU/mL)	22.1 ± 17.3	8.22 ± 3.6	<2–17	<.00001	1.10	1
	HOMA-IR	5.2 ± 4.4	1.8 ± 0.8	**	<.00001	1.09	1
Lipid profile	Cholesterol (mg/dL)	165.9 ± 27.6	157 ± 33.8	<150	.14	0.29	0.51
	Triglycerides (mg/dL)	144.3 ± 83.6	87.3 ± 49.5	<100	.0001	0.82	0.99
	HDL (mg/dL)	43.2 ± 6.9	53.1 ± 10.9	≥45	<.00001	-1.07	1
	LDL (mg/dL)	96.4 ± 22.4	86.4 ± 28.3	<100	.048	0.39	0.76
Liver function	ALT (U/L)	25 ± 15	18.7 ± 13.4	0–35	.03078	0.45	0.85
	AST (U/L)	22.6 ± 7.4	23.3 ± 6.1	0–35	.59	-0.10	0.11
	GGT (U/L)	19.7 ± 7.8	16.2 ± 7.1	0–30	.021755	0.47	0.87
Thyroid function	Thyroxine (ng/dL)	0.9 ± 0.1	0.93 ± 0.1	0.8–2.3	.81462	-0.30	0.46
	TSH (mIU/L)	2.9 ± 1.6	2.69 ± 1.45	0.5–4.8	.433243	0.14	0.18
Vitamin D	Vitamin D (ng/mL)	15.7 ± 7.6	19.5 ± 12.8	20–100	.030599	-0.36	0.68

*5–85 percentile is normal, ≥85 percentile is overweight, ≥95 percentile is obese.
**Boys: pubertal HOMA-IR >5.22, non-pubertal HOMA-IR >2.5, Girls: pubertal HOMA-IR >3.82, non-pubertal HOMA-IR >2.5.

Table 2. Concordance of *GSTM1*, *GSTT1*, and TP53 Codon 72 Allele Frequencies with Hardy–Weinberg Expectations in Patients

Genotyping	Observed Frequency n (%)	Expected Frequency n (%)	*P*	*Effect Size	Statistical Power
GSTM1 wild genotypes (−/−)	19 (31.6)	13.5 (22.5)			
GSTM1 wild/null genotypes (+/−)	19 (31.6)	29.9 (49.8)	**P = .018** χ^2 = 8.03	0.258	0.41
GSTM1 null genotypes (+/+)	22 (36.6)	16.5 (27.5)			
Total	60 (100)	60 (100)			
GSTT1 wild genotypes (−/−)	15 (25)	8 (13.3)			
GSTT1 wild/null genotypes (+/−)	14 (23.3)	27.9 (46.5)	**P = .0005** χ^2= 15.066	0.35	0.689
GSTT1 null genotypes (+/+)	31(51.6)	24 (40)			
Total	60 (100)	60 (100)			
TP53;rs1042522 Arg/Arg (wild)	22 (36.6)	21 (35)			
TP53;rs1042522 Arg/Pro (wild/mutant)	27 (45)	29 (48.3)	*P* = .86 χ^2 = 0.285	0.048	0.060
TP53;rs1042522 Pro/Pro (mutant)	11 (18.3)	10 (16.6)			
Total	60 (100)	60 (100)			

*The effect size calculated via Cramér's V values measures the magnitude of deviation from Hardy–Weinberg expected frequency. V = 0, no association; V ≈ 0.1, small effect; V ≈ 0.3, medium effect; V ≈ 0.5 or more, large effect.

obese case group, distributions for *GSTM1* and *GSTT1* significantly deviated from Hardy–Weinberg expected proportions ($P < .05$), which is consistent with their association with the disease state.

Among the patient group, the frequencies of *GSTM1* genotypes were 31.6% for −/− (wild-type/wild-type), 31.6% for +/− (wild-type/null), and 36.6% for +/+ (null/null), compared to 35%, 50%, and 15% in the healthy control group. For *GSTT1,* genotype frequencies in patients were 25% for −/− (wild-type/wild-type), 23.3% for +/− (wild-type/null), and 51.6% for +/+ (null/null), while the control group exhibited frequencies of 36.6%, 45%, and 18.3%, respectively. Regarding the TP53 codon 72 polymorphism, the most prevalent genotype in patients was Arg/Pro (wild-type/mutant) at 45%, followed by Arg/Arg (wild-type/wild-type) at 36.6%; these frequencies were 50% and 36.6%, respectively, in healthy individuals.

Comparison of genotype frequency distributions revealed a significant association between *GSTM1* ($P = .018$) and *GSTT1* ($P = .0005$) polymorphisms and childhood obesity (Table 3). In a recessive model, the *GSTM1* null genotype was more frequent in children with obesity, with an OR of 3.28 (95% CI: 1.36-7.93, $P < .05$). In the allelic model, each copy of the *GSTM1* null allele was associated with 1.66-fold higher odds of obesity (95% CI: 0.995-2.77) (Figure 1). The *GSTT1* null genotype showed a stronger effect. Children with the complete null genotype had a 4.76-fold higher risk of obesity (95% CI: 2.08-10.88, $P < .001$) compared to those carrying wild or heterozygous genotypes. The allelic model confirmed this effect, with each copy of the null allele increasing the odds of obesity 2.50-fold (95% CI: 1.49-4.20, $P < .05$) (Figure 1). In contrast, the TP53 rs1042522 polymorphism showed no significant association with obesity under either the recessive (OR = 1.12, 95% CI: 0.44-2.87) or allelic model (OR = 1.00, 95% CI: 0.60-1.67) (Figure 1).

Power analyses indicated that *GSTT1* results were robust (>80% power), while *GSTM1* achieved ~60% power, acceptable for exploratory interpretation. The TP53 analyses were underpowered, and results for this marker should therefore be considered preliminary.

Table 3. Comparison of GSTM1, GSTT1, and TP53 Codon 72 Genotypic Frequency Distribution Between Patients and Healthy Controls

Genotyping	Patients' Frequency n (%)	Healthy Frequency n (%)	*P*	*Effect Size	Statistical Power
GSTM1 wild genotypes (−/−)	19 (31.6)	21 (35)			
GSTM1 wild/null genotypes (+/−)	19 (31.6)	30 (50)	*P* = .018 χ^2 = 8.021	0.18	0.41
GSTM1 null genotypes (+/+)	22 (36.6)	9 (15)			
Total	60 (100)	60 (100)			
GSTT1 wild genotypes (−/−)	15 (25)	22 (36.6)			
GSTT1 wild/null genotypes (+/−)	14 (23.3)	27 (45)	**P = .0005** χ^2 =14.9	0.25	0.68
GSTT1 null genotypes (+/+)	31(51.6)	11 (18.3)			
Total	60 (100)	60 (100)			
TP53;rs1042522 Arg/Arg (wild)	22 (36.6)	22 (36.6)			
TP53;rs1042522 Arg/Pro (wild/mutant)	27 (45)	30 (50)	*P* = .72 χ^2 = 0.63	0.073	0.10
TP53;rs1042522 Pro/Pro (mutant)	11 (18.3)	8 (13.3)			
Total	60 (100)	60 (100)			

*Effect size indicates the strength of the association or the magnitude of difference in the genotypic frequency distribution between patients and healthy controls. V = 0, no association; V ≈ 0.1, small effect; V ≈ 0.3, medium effect; V ≈ 0.5 or more, large effect.

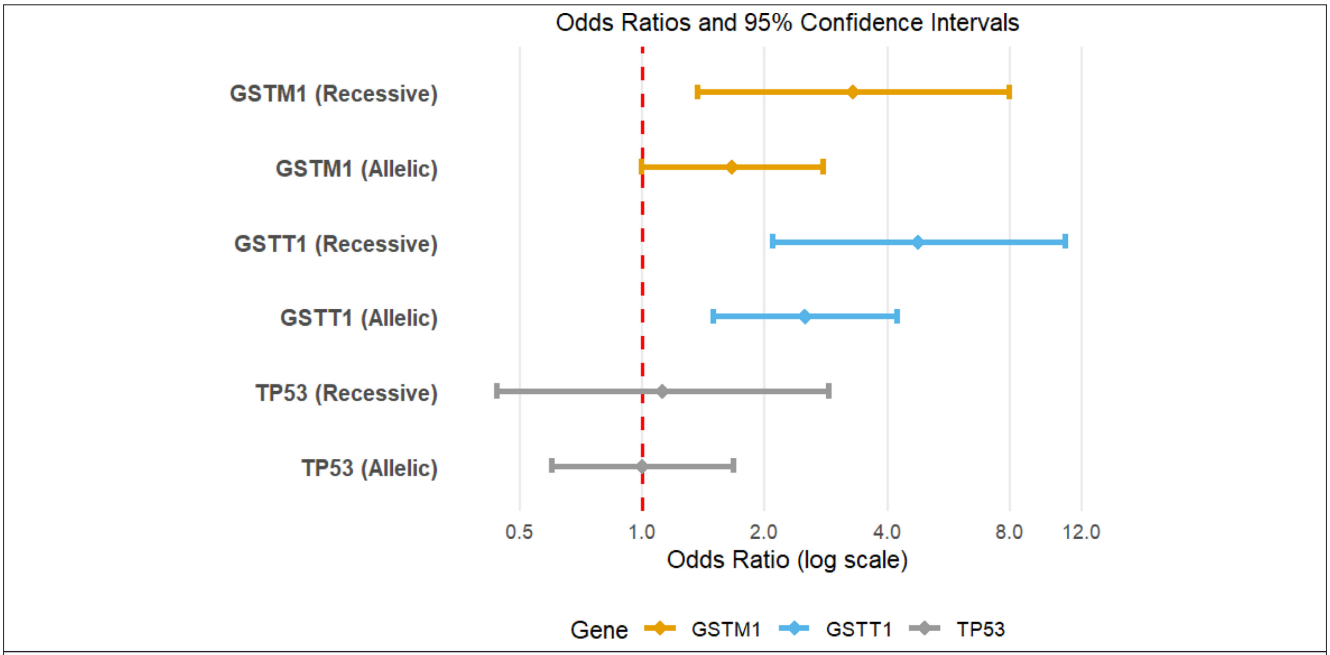

Figure 1. Risk of genetic variants of *GSTM1, GSTT1,* and TP53 with childhood obesity. Odds ratios (OR) and 95% CI are shown for both allelic and recessive genetic models of the *GSTM1, GSTT1,* and TP53 genes. The vertical solid line represents the null value (OR = 1.0). An OR > 1 indicates increased risk, while an OR < 1 indicates decreased risk. Points to the right of the line represent risk-increasing associations, while points to the left suggest protective associations.

Association of *GSTM1, GSTT1,* and TP53 Genotypes with Clinical Complications and Metabolic Parameters

The distribution of *GSTM1, GSTT1,* and TP53 (rs1042522) genotypes was analyzed in relation to clinical outcomes, including insulin resistance, hepatic steatosis grade, and a comprehensive panel of metabolic parameters, which may indicate the risk of a metabolic syndrome phenotype.

No statistically significant associations were observed between the distribution of *GSTM1, GSTT1,* or TP53 rs1042522 genotypes and either insulin resistance or hepatic steatosis, each demonstrating small effect sizes (Cramér's V = 0.05-0.18) and insufficient statistical power (0.06-0.17) (Figure 2).

While no significant differences were observed in metabolic parameters between *GSTT1* variants ($P > .05$) across a range of metabolic factors, the study detected meaningful genotype-dependent differences involving *GSTM1,* and the TP53 rs1042522 polymorphism (Figure 3).

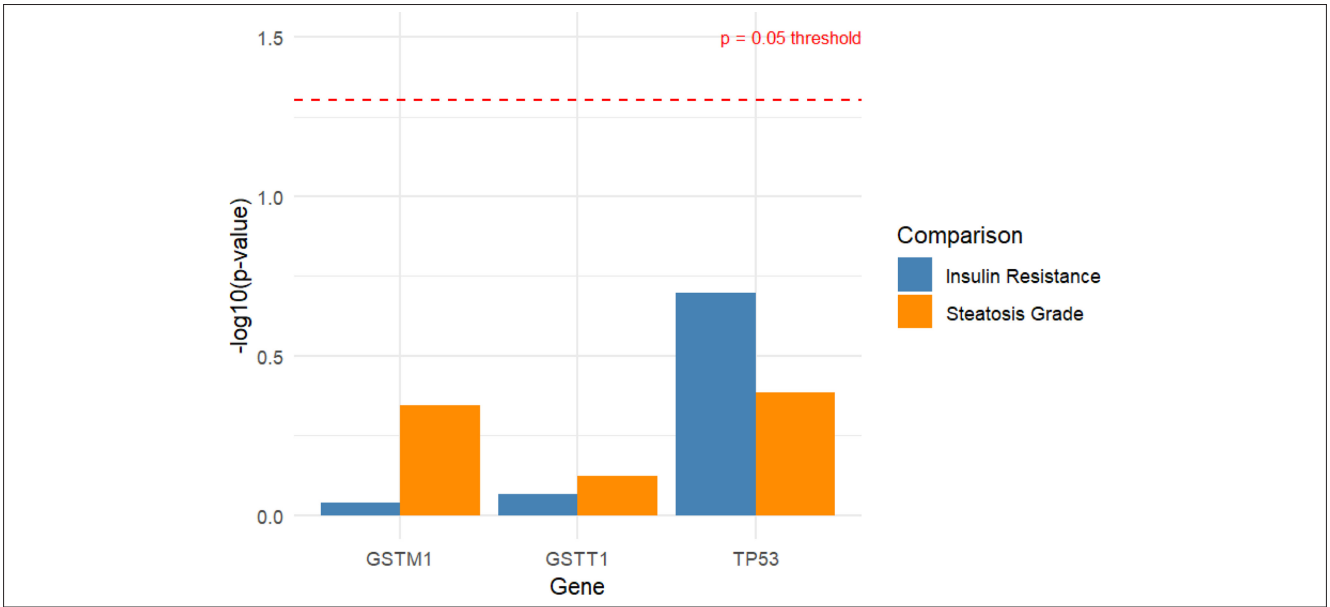

Figure 2. Statistical significance of genetic associations with clinical complications. The plot displays the statistical significance ($-\log_{10}$ (*P* value)) for the associations between the specified genes (*GSTM1, GSTT1,* TP53) variants and the traits of insulin resistance and steatosis grade. The dashed line indicates the threshold for statistical significance ($P = .05$).

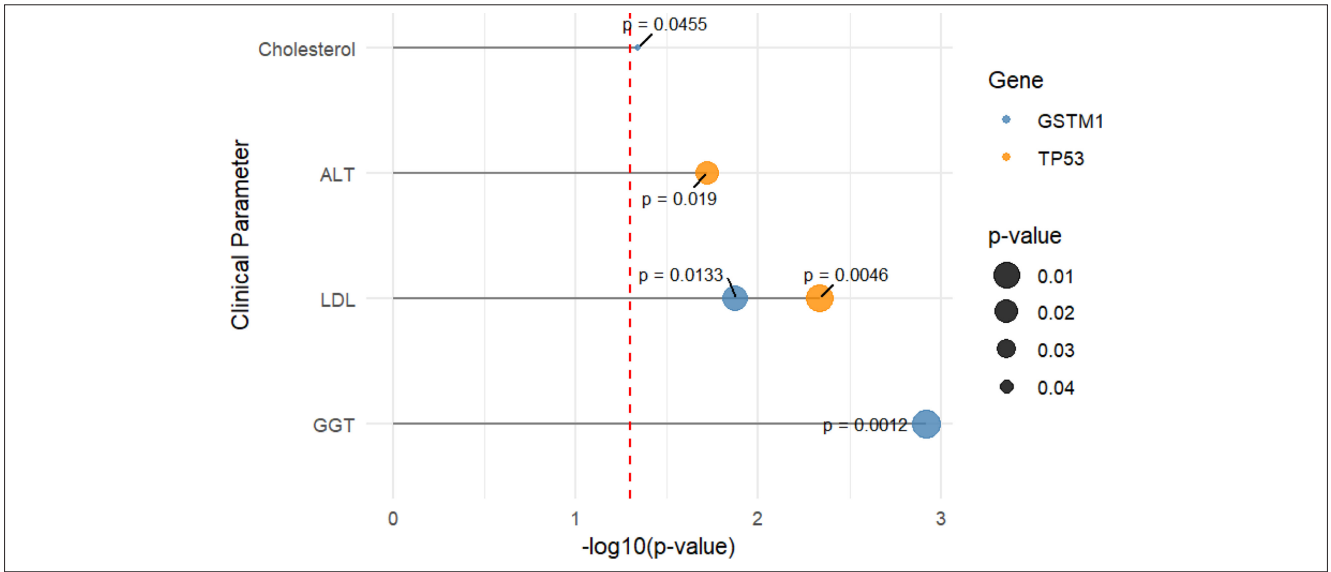

Figure 3. Genotype association with metabolic parameters. The bar plot displays the statistical significance of changes, expressed as $-\log_{10}$ (*P* value), for various serum biomarkers (cholesterol, ALT, LDL, GGT) in accordance with genetic variation (*GSTM1*, TP53). *P* values were derived from a *t*-test comparing the null genotype vs. others having a functional allele, either wild or heterozygote. Higher bars indicate greater statistical significance. The dotted line represents a common significance threshold ($P < .05$).

A significant association was observed between *GSTM1* genotypes and lipid metabolism and liver function. Individuals carrying the null genotype (+/+) exhibited higher total cholesterol (176.59 ± 25.36 mg/dL) and LDL (106.86 ± 20.97 mg/dL) levels compared to carriers of wild-type (−/−) and heterozygous (+/−) genotypes ($P = .045$ and $P = .013$, respectively). Additionally, GGT, a liver enzyme, was markedly elevated in the null genotype group (24.22 ± 8.56 U/L) ($P = .0012$).

The TP53 rs1042522 polymorphism was associated with selected lipid metabolism and liver function parameters. Homozygous Arg/Arg carriers displayed higher LDL levels (107.77 ± 18.48 mg/dL) compared with other genotypes ($P = .0046$). Individuals with the Pro/Pro mutant genotype showed significantly higher ALT levels (36.0 ± 24.4 U/L) compared with Arg/Arg and Arg/Pro carriers ($P = .019$). No other metabolic parameters were significantly influenced by TP53 genotype. The mean values of other assessed parameters did not significantly differ across genotype groups, neither TP53 nor GSTs ($P \geq .05$).

DISCUSSION

This research represents the first examination of *GSTM1*, *GSTT1*, and TP53 rs1042522 genotype distribution in Turkish children with obesity and their association with obesity and related possible clinical and metabolic complications. While previous adult studies reported varying frequencies of *GSTM1* (14%–57%) and *GSTT1* (8%–52%) null genotypes across populations, data in children remain scarce. Adult studies suggest an association between GST null genotypes and increased obesity risk, and significant violations of the Hardy–Weinberg proportion for both *GSTM1* and *GSTT1* genotypes were observed in the cohort of children with obesity. Comparison with healthy controls further confirmed that *GSTM1* and *GSTT1* genotype distribution is associated with childhood obesity, suggesting a possible dose-dependent contribution to childhood obesity.

The obese group recruited in this study displayed a clear metabolic syndrome phenotype. The dramatic significance ($P < .00001$) of anthropometric measures highlights that central adiposity is a well-established risk factor for metabolic complications[24–37] as metabolic markers strongly supported this phenotype among children in the current cohort. Insulin and HOMA-IR values reflect severe insulin resistance and hyperinsulinemia, a classic early metabolic dysfunction of obesity[28,29] and a major risk factor for type 2 diabetes. Moreover, the lipid profile showed an atherogenic dyslipidemia typically associated with obesity and insulin resistance, increasing cardiovascular disease risk.[30–32] Liver function parameters also suggested early organ stress. Elevated levels of ALT and GGT are early indicators of non-alcoholic fatty liver disease,[33,34] and ultrasound findings confirmed that hepatic steatosis is prevalent among children with obesity. In contrast, the comparable levels of thyroid hormones suggest that thyroid dysfunction is not a primary driver of obesity in this cohort. Slightly higher TSH within the normal range may reflect an adaptive response to adiposity, rather than thyroid complications.[35] Finally, vitamin D deficiency was common, consistent with obesity-related findings in the literature, though causality remains unclear, and is thought to be a bidirectional relationship with obesity.[36,37]

The study found that obese children with the *GSTM1* null genotype had significantly higher LDL, total cholesterol, and GGT compared to those with functional *GSTM1*. This identifies a subgroup at higher risk of dyslipidemia and liver stress. However, in the analysis of metabolic parameters within the obese group, no significant associations were found with *GSTT1*. This suggests its main effect might be on the overall risk of becoming obese rather than on determining the metabolic severity once obesity is established.

The findings on childhood obesity are consistent with recent evidence. A 2016 study reported that *GSTM1* and *GSTT1* null genotypes increase obesity risk and related complications

such as dyslipidemia, elevated LDL, and hypertension, implicating impaired GST function in oxidative stress and metabolic dysregulation.[38] Similarly, a 2024 study associated these null genotypes with greater risk and severity of hepatic steatosis, aligning with the observation of liver enzyme abnormalities in GSTM null carriers.[39]

The GSTs are central enzymes in detoxification pathways. Mechanistically, lacking *GSTM1* may reduce the ability to buffer oxidative and metabolic stress.[40] This can lead to the accumulation of reactive oxygen species (ROS), lipid peroxidation, mitochondrial dysfunction, and liver inflammation, all of which are strongly implicated in the pathogenesis of obesity.[40]

Oxidative stress is known to impair insulin receptor signaling through activation of stress kinases, such as c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ), leading to phosphorylation of insulin receptor substrate-1 and inhibition of downstream PI3K–Akt signaling, thereby promoting insulin resistance.[41,42] In adipose tissue, increased ROS levels can stimulate preadipocyte differentiation and hypertrophy, further promoting adiposity.[43,44] Additionally, GSTs interact with peroxisome proliferator-activated receptor gamma (PPAR-γ), a master regulator of adipogenesis, suggesting that loss of GST activity may indirectly enhance lipid storage and adipocyte expansion.[45] Beyond metabolism, GST deletions may exacerbate systemic inflammation by allowing accumulation of lipid peroxidation products and cytokine activation. This proinflammatory environment contributes to the observed dyslipidemia and liver enzyme abnormalities.[46,47] Thus, *GSTM1* and *GSTT1* deletions likely influence obesity through a multi-layered mechanism involving impaired detoxification, oxidative stress, defective insulin signaling, and altered adipocyte biology.

Though the study was underpowered to detect an association of TP53 with obesity risk, the observed genotype-specific effects within the obese cohort are noteworthy. However, some studies note effects of TP53 expression variation on lipid metabolism and liver function,[48] which could be consistent with the findings. The Arg/Arg variant was linked to elevated LDL cholesterol, which may indicate impaired cholesterol regulation, while the Pro/Pro variant was associated with higher ALT levels, reflecting greater predisposition to hepatocellular injury (steatohepatitis, or NASH). These findings suggest that TP53 may act less as a determinant of obesity onset and more as a modifier of metabolic outcomes in the context of obesity. The Arg/Arg variant may make it harder for the body to regulate cholesterol properly, and when combined with obesity, this weakness is exposed, leading to exceptionally high LDL. On the other hand, patient children with the Pro/Pro genotype had significantly higher ALT levels, reflecting greater predisposition to hepatocellular injury (steatohepatitis, or NASH). This TP53 variant may impair the liver's ability to cope with the fat overload and inflammatory signals from obesity, making hepatocytes more vulnerable to damage, which leaks more ALT into the bloodstream. Mechanistically, this aligns with p53's known role in lipid metabolism, mitochondrial regulation, and hepatocellular stress responses. Thus, TP53 variants may not increase the likelihood of becoming obese, but once obesity is established, they could modulate the severity and pattern of metabolic complications.

Taken together, GST deletions likely promote obesity by weakening antioxidant defenses and disrupting insulin and adipogenesis pathways, while TP53 variants modulate the severity of metabolic complications via differential effects on apoptosis, lipid metabolism, and hepatic stress responses. These findings support a gene–environment interaction model in which obesity provides the metabolic stressor, and *GSTM1*, *GSTT1*, and TP53 genotypes determine the magnitude and organ-specific outcomes of that stress.

From clinical implications, these results emphasize the potential of personalized medicine in childhood obesity. Genetic testing could help stratify children into risk categories, allowing early interventions tailored to their genetic vulnerability—such as more aggressive lipid management in *GSTM1* null or TP53 Arg/Arg carriers, or closer liver monitoring in Pro/Pro carriers. This approach could ultimately improve outcomes by targeting therapy to those most at risk of cardiovascular or hepatic complications.

Study Limitations

While this study offers important insights into the genetic factors contributing to childhood obesity in the Turkish population, several limitations should be acknowledged. First, the case–control design and reliance on retrospective data limit the ability to establish causality between the identified polymorphisms and obesity risk. Second, although the sample size was adequate for initial evaluation, power analyses indicated that only the *GSTT1* findings were sufficiently robust with 60 samples. The *GSTM1* associations can be considered exploratory, whereas the TP53 analyses were clearly underpowered to detect a real effect. Third, the genetic scope of this study was restricted to *GSTM1*, *GSTT1*, and TP53 rs1042522, without examining other GST enzyme classes that may also play a role in detoxification pathways. In addition, oxidative stress biomarkers such as total antioxidant and total oxidant status were not available in the archived records, preventing a direct assessment of redox balance and oxidative status. Fourth, although standardized protocols were used for anthropometric and biochemical measurements, reliance on single time-point data from archived records may have introduced measurement variability. Fifth, this study examined *GSTM1*, *GSTT1*, and TP53 variants individually; however, possible gene–gene interactions could not be evaluated due to the limited sample size and the complexity of potential genotype combinations. Finally, although the findings support a gene–environment interaction model, the current study did not include environmental or lifestyle variables. This limits the ability to directly evaluate how TP53 or GST variants interact with external factors to influence obesity risk and metabolic outcomes. Future studies incorporating detailed lifestyle, nutritional, and socioeconomic data will be essential to fully delineate the gene–environment interactions underlying childhood obesity.

This study identifies *GSTT1* and *GSTM1* null genotypes as strong genetic risk factors for childhood obesity in a Turkish cohort, with *GSTT1* null conferring nearly 5-fold increased risk. *GSTM1* null further predicted worse metabolic outcomes, including elevated LDL, total cholesterol, and GGT, indicating impaired stress response. While the study was underpowered to detect an association of TP53 rs1042522 with obesity risk, Arg/Arg and Pro/Pro variants modified complications by predisposing to

dyslipidemia and hepatocellular injury, respectively. Together, these findings highlight a gene–environment model where GST variants drive obesity susceptibility and *GSTM1* and TP53 shape metabolic severity, supporting genetic screening as a tool for early risk stratification and personalized interventions.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of Health Sciences University and Ankara Atatürk Sanatorium Training and Research Hospital (Approval no: 2012-KAEK-15/2491; Date: April 12, 2022).

Informed Consent: Verbal informed consent was obtained from the patients' legal guardians who agreed to take part in the study.

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