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Association of transmembrane protease serine 6 (TMPRSS6) gene Polymorphism with iron deficiency anemia in Iraqi women

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Abstract

Iron deficiency anemia (IDA) is a widespread health problem, particularly among women of reproductive age. While physiological demands and nutritional deficiency are common causes, genetic factors such as TMPRSS6 gene polymorphisms may play a significant role in development of IDA. This study aimed to evaluate the relationship between the TMPRSS6 rs855791 (C/T) polymorphism and the risk of IDA in Iraqi women. The current investigation was including IDA patient's women as well as healthy control. Hematological parameters have been measured, along with genotyping distributions of the TMPRSS6 rs855791 variant was performed using PCR-RFLP. Quality control and IDA groups included blinded sample coding and random re-genotyping of 10% of samples. Statistical analysis was used to evaluate allele and genotype frequency and Genetic models and their correlation with Iron deficiency anemia. Hardy–Weinberg equilibrium was assessed using the chi-square test, and no significant deviation was observed ($P > 0.05$).

Demonstrate A case-control study was conducted involving (82) women diagnosed with IDA and (75) age-matched healthy women aged 18–45 years. Participants were recruited from Al Yarmouk Teaching Hospital in Baghdad. In this study, Women carrying the C/C genotype had a lower risk of IDA compared to T allele carriers (OR =0.346, 95% CI = (0.163-0.733), p = (0.0067). therefore, it is considered a protective effect against IDA. While T/T genotype indicate More frequent in IDA group . Hemoglobin, serum iron, and ferritin levels were markedly lower among individuals carrying the T allele. Multiple inheritance models confirmed the significant association between the polymorphism and IDA susceptibility. The TMPRSS6 rs855791 polymorphism appears to influence iron metabolism and may serve as a genetic risk contributors for IDA in Iraqi women. Screening for this variant could enhance early detection and allow for more tailored nutritional and therapeutic interventions.

Keywords: Iron Deficiency Anemia; TMPRSS6; Rs855791; Hepcidin

1. Introduction

Iron deficiency anemia (IDA) stands as one of the most common global health challenges, particularly affecting women during their reproductive years [1]. It results from a prolonged imbalance between iron requirements and availability, ultimately impairing hemoglobin synthesis and red blood cell production. Despite the status of nutritional deficiency along with some physiological instances like menstruation and pregnancy are broadly known contributors, the intricacy of iron metabolism proposes that genetic control had considerable yet underexplored roles [2, 3].

Transmembrane Protease Serine 6 gene (TMPRSS6) (which as well it is called matriptase-2) encodes typeII transmembrane serine protease, which has a pivotal role in the homeostasis of systemic iron [4, 5]. TMPRSS6 primarily exert it's action by negative regulation of hepcidin expression, the principle hepatic hormone responsible for both absorption and distribution of dietary iron. This gene achieves its impacts via cleavage and inactivation of hemojuvelin (HJV), a co-receptor implicated in BMP-SMAD signaling pathway that stimulates the transcription of hepcidin [6, 7]. TMPRSS6 gene is positioned at chromosome 22q12.3 and spans about 51 kilobases; it comprises of 18 exons and is

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expressed mostly in hepatocytes. Consideration the genetic modification that related with TMPRSS6 gene had opened new insights to diagnosis and manage iron-associated disorders, and still a hot topic in fields of hematology and molecular genetics [8,9]. Mutations in TMPRSS6 are associated with Iron-Refractory Iron Deficiency Anemia (IRIDA), a scarce autosomal recessive disease identified by microcytic anemia unresponsive to oral iron therapy and only partially responsive to parenteral iron supplementation [10].

Pathogenic variants in TMPRSS6 have been identified in patients with IRIDA. These mutations impair the proteolytic function of matriptase-2, resulting in abnormally high levels of hepcidin despite systemic iron deficiency [11]. Genetic alterations in TMPRSS6, particularly the single nucleotide polymorphism rs855791 (C>T), have been linked to variations in hepcidin expression, leading to differing susceptibilities to iron deficiency [12, 13].

The T allele of rs855791 has been proposed to increase the risk of iron deficiency [14] by enhancing hepcidin activity, thereby restricting iron absorption even when dietary intake is adequate. However, the prevalence and impact of this variant can vary significantly across ethnicities and populations. Despite the high burden of IDA in Middle Eastern countries, especially among women, little is known about the distribution and clinical implications of this polymorphism in regional populations [15,16].

This study aims to fill this gap by examining the association between the TMPRSS6 rs855791 polymorphism and the risk of Iron deficiency anemia in Iraqi women. By identifying genetic factors influencing anemia risk, we aim to provide insights that may inform early diagnosis and personalized nutritional or therapeutic strategies.

2. Materials and Methods

2.1. Study Design and Participants

A case-control study was conducted involving (82) women diagnosed with IDA and (75) age-matched healthy women. Participants were recruited from (Al Yarmouk Teaching Hospital) in Baghdad, Iraq, from January 2025 to February 2026.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria for cases included women aged 18–45 years with confirmed IDA based on hemoglobin, serum iron and ferritin. Individuals have gastrointestinal bleeding, thalassemia, sickle cell anemia ,hereditary spherocytosis , aplastic anemia, megaloblastic anemia, renal insufficiency, menopause, history of gastrointestinal resection, Parasitic infections, Acute or chronic inflammatory bowel diseases, neoplasia, chronic diseases, recent blood transfusion, participants receiving iron supplements or pregnant women were excluded from the current study.

2.3. Blood Sampling and Hematological Analysis

blood samples were collected from all women. Complete blood count (CBC), hemoglobin concentration (HGB), hematocrit (relative volume of erythrocytes) (HCT), mean corpuscular (erythrocyte) volume (MCV), mean corpuscular (erythrocyte) hemoglobin (MCH), mean corpuscular (erythrocyte) hemoglobin concentration (MCHC), Red blood cell count (RBC), Red Cell (erythrocyte volume) Distribution Width (RDW) and platelets counts were Measured by the Sysmex XN-2000 is a quantitative automated hematology analyzer (Sysmex Co, Kobe, Japan). Serum ferritin levels were estimated employing the EIA kit (Advia Centaur, Siemens, NY).

2.4. Genetic analysis of TMPRSS6 rs855791

Genomic DNA samples were extracted from whole blood leukocytes employing DNA Purification Kit (Promega Company/USA). Measured the purity and concentration of DNA with used Nano drop spectrophotometer device.

The analysis of TMPRSS6 rs855791 variant was achieved applying Polymerase Chain Reaction–Restriction Fragment Length Polymorphism) with specific primers (Bioneer, Korea). Forward:5'-TAGAGAACAGGGGCTCCAGG-3' and Reverse:5'-ATGTGGGCA GCATCCTTTC-3'

The PCR technique has been applied to amplify the DNA products for TMPRSS6 rs855791 C/T polymorphism (249 bp); the total volume of PCR tubes was 25µl, which including 12.5µl green master mix (from Promega company, USA), (9.5µl) distilled water , (0.5µl) from each primer, and (2µl) of 100 ng DNA was utilized as a template. Conditions of PCR included: denaturation step at 95°C for five mins; 36 cycles of (95°C) for 45 sec, (63°C) for 45 sec, (72°C) for 45 sec; and

final extension at (72°C) for 10 mins. The amplicon had been digested using restriction endonuclease Stu I (Biolabs Inc. company/England) after incubation period at 37°C for thirty mins.

2.5. Determined Genotype of PCR-RFLP outcomes

The products resulting from digestion process along with ladder marker (100-1000 bp) have been run using 2.5% agarose gel for (l.5 hrs.), after that, they visualized by ultraviolet trans-illuminator after stained with ethidium bromide to identify theTMPRSS6 rs855791 C/T polymorphism. Three genotypes of TMPRSS6 were identified: C/C genotype has a single band for (249 bp) fragment, the C/T genotype has three bands for (249bp, 125 bp, and 124 bp) fragments and the genotype T/T have two bands for (125 bp and 124 bp) fragments.

Genotyping was performed using polymerase chain reaction with restriction fragment length multiplex analysis (PCR-RFLP) under standard laboratory conditions. To minimize potential bias, samples were coded during analysis. For quality control purposes, a randomly selected subset of samples was re-genotyped, and the results showed concordance, demonstrating the reliability of the genotyping process.

2.6. Statistical Analysis

Association between different Allelic and genotypic frequencies of the TMPRSS6 gene were calculated and compared using χ^2-tests and odds ratio (OR) calculation at 95% confidence intervals. Logistic regression has been applied for estimating association between genotypes and IDA risk, adjusting for potential confounders. A p-value<0.01 has been deem as significant, while p-value>0.01 has been deem non-significant.

3. Results

3.1. Clinical Demographic Features:

Table 1 presents the demographic information of participants. The mean age and menarche age did not significantly differ between the iron deficiency anemia (IDA) group and controls ($p > 0.01$). Likewise, BMI was mostly comparable, except for irregular menstrual history, which was significantly more common among IDA patients ($p < 0.01$).

Table 1 Baseline Demographic Features of IDA Patients and Control group.

Parameters	Controls Mean±SD	IDA patient Mean±SD	P-value
Mean age -years	30.35±4.44	31.21±3.23	> 0.01
Menarche -years	12.15±1.31	11.86±1.62	> 0.01
body mass index (Kg/m^2)	23.29±3.76	22.74±4.53	> 0.01
Irregular menstrual history%	10	45	< 0.01

3.2. Hematological and Biochemical Findings

The diagnosis of (IDA) was based on the updated World Health Organization (WHO, 2024/2025) criteria. Specifically, anemia was defined as a (Hb) concentration (<12.0 g/dL) for non-pregnant women, while iron deficiency was defined by serum ferritin levels (<15 μg/L) in the absence of inflammation. (17)

According to Table 2, individuals in the IDA group had significantly lower levels of hemoglobin (HGB), hematocrit (HCT), ferritin, iron, RBC counts, MCV and MCH compared to the control group ($p < 0.01$). while RDW were higher in the IDA group ,the difference was statistically significant ($p < 0.01$).

Table 2 The complete blood count data of IDA patients and controls.

parameters	Normal reference value	IDA group Mean±SD	Control group Mean±SD	P value
Iron	50-150 mg /dl	28.62±1.44	95.56±1.91	$p < 0.01$
Ferritin	15-150 ng/mL	10.23±1.32	87.33±2.11	$p < 0.01$
HGB	12-15 g/dL	9.25±1.16	13.93±2.14	$p < 0.01$
HCT	35-47 %	25.81±2.84	40.34±1.98	$p < 0.01$
RBC	4.5-5.0 $x10^6$ cells/µL	2.92±1.38	4.86±1.21	$p < 0.01$
MCV	82-98 F L	62.72±1.26	90.72±2.31	$p < 0.01$
MCH	26-34pg/cell	19.53±3.12	28.31±2.54	$p < 0.01$
MCHC	32-36 g/dL	30.28±1.21	34.86±2.23	$p > 0.01$
RDW	11.8-15.2%	21.4±1.39	12.9±1.74	$p < 0.01$
PLT	150-400$x10^9$ cells/ L	397±3.55	362±4.92	$p > 0.01$

3.3. Genotypic and Allelic Distribution of TMPRSS6

Table 3, 4 and Figure (1,2) demonstrate genotype frequencies of the TMPRSS6 rs855791 polymorphism. Among IDA patients, the C/C genotype was found in 12.19%, C/T in 53.65%, and T/T in 34.14%. In the control group, C/C was more common (33.33%) and T/T was less prevalent (20%). The differences in genotype and allele distribution between groups were significant ($p < 0.01$).

The genotypes distribution in IDA patients and control groups was in agreement with Hardy-Weinberg probability

Table 3 Genotypes frequency (%) and Allele's frequency (%) of TMPRSS6 gene polymorphism for IDA and control groups.

TMPRSS6rs 855791	Genotypes frequency (%)				Allele's frequency (%)	
Parameter	N	(C/C) homozygote	(C/T) heterozygote	(T/T) homozygote	Allele (C)	Allele (T)
IDA n (%)	82	10 (12.19%)	44 (53.65%)	28 (34.14%)	64 (39.02 %)	100(60.97 %)
Control n (%)	75	25 (33.33%)	35 (46.66%)	15 (20%)	85 (56.66 %)	65 (43.33 %)
P value		0.0067	0.5896	0.1108	0.0051	0.0043

Table 4 Observed and expected genotype frequencies of (TMPRSS6) gene) Polymorphism.

Genotype		C/C	C/T	T/T	Hardy–Weinberg probability
(IDA) Patient (N :82)	Observed	10	44	28	(P>0.05)
	Expected	12.47	38.95	30.41	
Control (N :75)	Observed	25	35	15	(P>0.05)
	Expected	24.02	36.76	14.06	

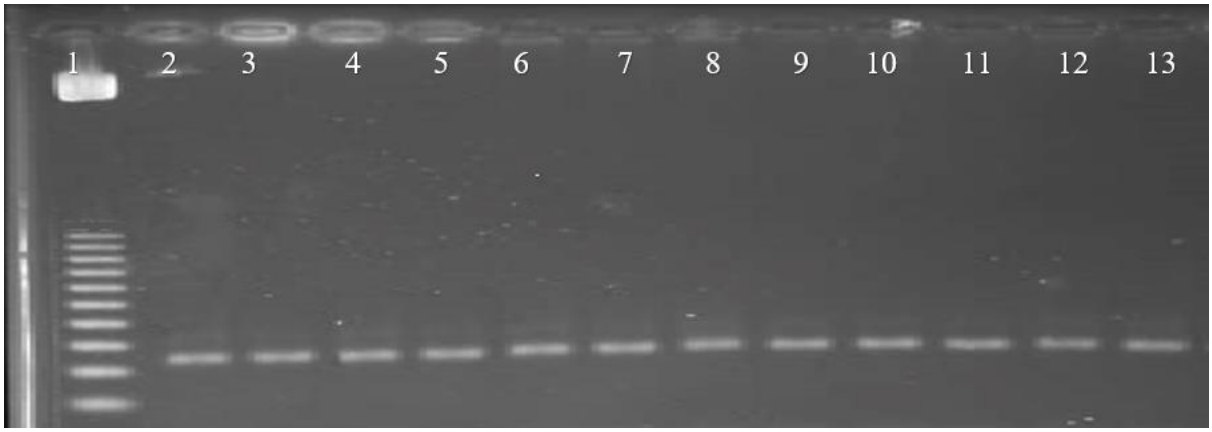

Figure 1 The electrophoresis image of the PCR products for theTMPRSS6 rs855791 C/T with size of (249 bp). Lane 1 DNA ladder (100-1000 bp) ,Lanes (2-13)PCR products of the theTMPRSS6 gene from IDA patient .

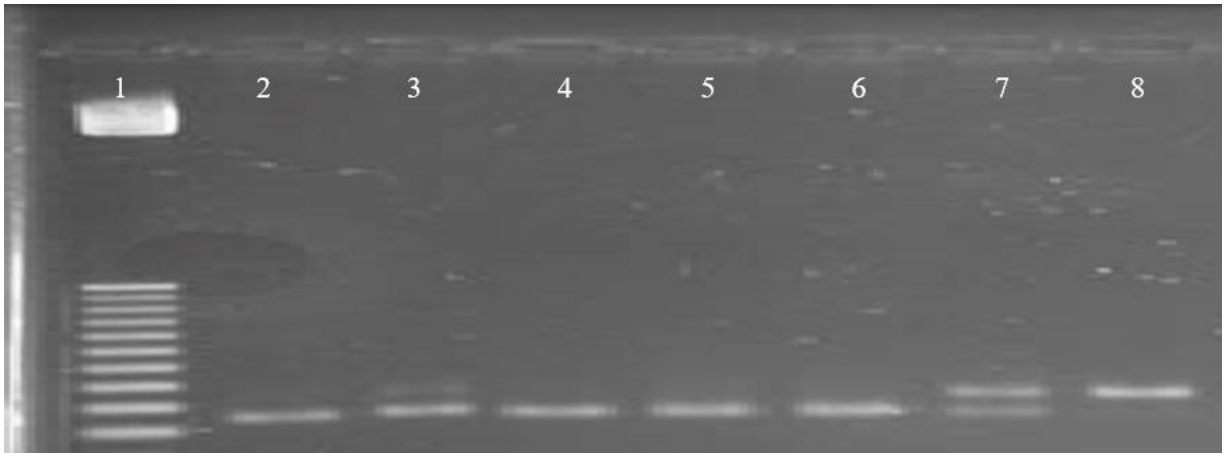

Figure 2 RFLP analysis of the (C/T) polymorphism in theTMPRSS6 rs855791 gene. Lanes 1- DNA ladder (100- 1000 bp); Lanes (2-6) homozygous (T/T) for mutant allele genotype - (125 bp and 124 bp) Lane (7) heterozygous for mutant allele (C/T) genotype - (249, 125, 124 bp) ,The Lane: (8) homozygous (C/C) for normal allele genotype - (249 bp).

3.4. Genetic Models

Table-5 analyzes the Genotype distribution under different inheritance models:

3.4.1. Codominant Model

C/C Genotype

Significantly less frequent among IDA patients (10 cases) compared to controls (25 cases), and P-value (0.0067) indicating a significant difference. OR was 0.346 and CI ranging between 0.163 to 0.733, suggesting a protective effect of the C/C genotype against IDA.

C/T Genotype:

Similar distribution between IDA (44 cases) and controls (35 cases). And P-value (0.5896), indicating No significant association. OR = 1.173, 95% CI (0.730, 1.885), implying a neutral effect.

T/T Genotype:

More frequent in IDA group (28 cases) vs controls (15 cases). P-value (0.1108), not statistically significant. OR (1.773), 95% CI (0.928- 3.389), indicating a possible increased risk that needs further investigation.

3.4.2. Dominant Model (C/C vs C/T + T/T):

the dominant model reveal a trend toward increased risk of IDA among carriers of at least one T allele (C/T or T/T), the association is not statistically significant P-value = 0.1162. A larger sample size would be necessary to determine whether this trend reflects a true genetic influence on IDA susceptibility.

3.4.3. Recessive Model (T/T vs C/C + C/T):

the observed difference in T/T frequency between IDA patients and control group is not statistically significant (P value : 0.1108). The OR of 1.773 suggests that individuals with the T/T genotype carriers may have a higher risk to develop IDA versus those have CC or CT genotypes.

However, the 95% confidence interval includes 1, which means this increase could be due to random variation, and the association cannot be confirmed statistically in this study.

3.4.4. Overdominant model (C/T vs. C/C + T/T):

In the overdominant genetic model, the heterozygous genotype (C/T) is compared against the combined homozygous genotypes (C/C and T/T).

The C/T genotype does not demonstrate a significant association with IDA in this model.

Table 5 The Genotype distribution analyzes in inheritance Models.

Gene	Genetic models	Genotypes	IDA No(%)	Control No(%)	P value	OR (95 % Cl)
TMPRSS6	Codominant	C/C	10 (12.19 %)	25 (33.33%)	0.0067	0.346 (0.163-0.733)
		C/T	44 (53.65 %)	35 (46.66%)	0.5896	1.173 (0.730-1.885)
		T/T	28 (34.14 %)	15 (20%)	0.1108	1.773 (0.928- 3.389)
	Dominant	C/C	10 (12.19 %)	25 (33.33%)	0.0067	0.346 (0.163-0.733)
		C/T+ T/T	72 (87.79 %)	50 (66.66 %)	0.1162	1.406 (0.942-2.099)
	Recessive	C/C+ C/T	54 (65.84 %)	60 (79.99%)	0.2961	0.788 (0.525-1.184)
		T/T	28 (34.14 %)	15 (20%)	0.1108	1.773 (0.928-3.389)
	Overdominant	C/C+ T/T	38 (46.33 %)	40 (53.33 %)	0.5876	0.852 (0.530- 1.369)
		C/T	44 (53.65 %)	35 (46.66%)	0.5896	1.173 (0.730-1.885)

4. Discussion

The current study investigated the association between iron deficiency anemia (IDA) and the TMPRSS6 gene polymorphism (rs855791) among Iraqi women of reproductive age. Our findings revealed significant hematological differences between IDA patients and healthy controls, along with notable variations in the frequency of TMPRSS6 genotypes and alleles.

The hematological results demonstrated significantly lower levels of hemoglobin, serum iron, ferritin, MCV and MCH in the IDA group compared to controls, confirming the typical biochemical profile of iron deficiency anemia, consistent with classic presentations of IDA [18].

These outcomes are align with previous research that had reported similar hematological abnormalities in patients with hemolytic anemia, feature impaired red blood cell formation and iron metabolism [19].

The rs855791 SNP in this gene was revealed to possess an important genotypic association. Among IDA cases, TT genotype was considerably more common than CC genotype. This finding means that T allele may be a genetic risk factor for IDA, possibly infuencing the pathway that enable TMPRSS6 to control hepcidin. These outcomes are align with previous investigations indicated that subjects have T allele typically express higher hepcidin levels, which may impede absorption of iron and leads to anemia [20,21].

The explained association between the rs855791 polymorphism and IDA susceptibility can be mechanistically explained by the TMPRSS6-hepcidin axis. Specifically, the T allele of rs855791 leads to a functional alteration in matriptase-2 activity. Under normal circumstances, matriptase-2 suppresses hepcidin expression to allow iron absorption [22] However, this genetic variant impairs the inhibitory function of matriptase-2, leading to abnormally high hepcidin levels. These elevated hepcidin concentrations induce the degradation of ferroportin, the sole cellular iron transporter, thereby limiting the absorption of dietary iron in the duodenum and causing its sequestration in macrophages. This cascade of events ultimately leads to decreased systemic iron availability and the development of microcystic hypochromic anemia [23,24].

Investigation of the inheritance pattern emphasized the consequence of the T allele. Also, studying the codominance, dominant, recessive, and hyper dominance patterns demonstrated significant associations, suggesting a potent genetic impact. Particularly, both dominant and recessive patterns revealed that possessing one or two T alleles significantly expands risk of iron deficiency anemia.

The meta-analysis study of Mañalac et al. demonstrated a significant association between rs855791 SNP and anemia in female at reproductive age, which supporting the roles of these genes in iron metabolism [25].

The current findings are align with study of Hoshe et al., which revealed a higher prevalence of TT genotype in cases with IDA, along with significantly lower levels of hemoglobin, red blood cells indices (MCV, MCH, MCHC), iron, and ferritin as compared with healthy individuals [26].

Furthermore, a recent investigation on Egyptian patient demonstrated that C/T genotype of rs855791 SNP was significantly related with iron deficiency, this study suggested that even the individuals have heterozygous genotype this gene, they may be at high risk [27]. These outcomes are highlighting the significance of investigation genetic factors, like TMPRSS6 gene polymorphisms, in rating and administration of IDA.

In conclusion, TMPRSS6 rs855791 SNP has a significant role in iron metabolism and progression of iron deficiency anemia. Studying the effect of this genetic variant may help diagnosis at-risk subjects and design an appropriate intervention.

Limitations

The current investigation is limited by its relatively small samples size and its regional and ethnic context, which may influence the final interpretation of results. Future investigations should include larger, more diverse populations and inspect the functional impacts of TMPRSS6 polymorphism.

5. Conclusion

Our findings reveal an association between rs855791 SNP of TMPRSS6 and susceptibility to IDA among women. It is found that C allele has a significant associated with lower risks of IDA, while T allele may serve as a genetic indicator for IDA risk and could have effects for early diagnosis and personalized therapeutic strategies. The current outcomes emphasized the possible roles of TMPRSS6 variants in susceptibility to IDA.

Compliance with ethical standards

Disclosure of conflict of interest

The authors confirm that there are no conflicts of interest

Statement of ethical approval

The Research Ethical Committees of the College of Sciences/University of Baghdad accepted this study protocol (Ref. CSEC/0126/0006).

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