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Association of TMPRSS6 (rs855791) Genetic Polymorphisms with Iron Deficiency Anemia Risk among Sudanese Patients

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Abstract

Background: A prevalent medical illness recognised in routine clinical practice, iron deficiency anaemia (IDA) is a global health concern. Hepcidin expression is regulated by matriptase-2 (MT-2), which is encoded by the transmembrane protease serine 6 (TMPRSS6) gene.

Objective: of this study was to detect the association of TMPRSS6 (rs855791) gen and iron deficiency anemia risk in Sudan.

Materials and Methods: This study was carried out on 129 patients with iron deficiency anemia and 129 age and sex matched individuals as control group. Patients were subdivided into (group 1) 65 patients with acquired iron deficiency anemia (IDA) and (group 2)64 patients with iron refractory iron deficiency anemia (IRIDA). TMPRSS6 gene single nucleotide polymorphisms(SNPS), (rs855791&) was evaluated using real time – polymerase chain reaction (RT-PCR) while serum iron profile was measured by enzyme linked immunosorbent assay (ELISA).

Results: Among 129 patients, 68 were male (mean age: 12.2 ± 4.3 years) and 61 were female (mean age: 12.1 ± 5.6 years). In addition, 129 healthy age-matched and sex-matched individuals served as controls. The (mean ±SD) of HB, Hematocrit, MCV, MCH and MCHC were significantly deceased in both case group compared to control group (p vale =0.01, 0.03, 0.01, 0.01, 0.0483) and were insignificant relation between two groups in mean ±SD of WBCs, RBCs, RDW and PLT. Serum iron, total iron-binding capacity (TIBC), and ferritin levels showed a significant reduction in patient groups compared to controls (p-values: 0.015, 0.044, and 0.020). As regard SNP rs 855791, there was a significant increase in frequency of mutations (heterozygous and homozygous) in IDA group compared to control group (p=0.025) and highly significant increase in frequency of mutations (heterozygous and homozygous) in IRIDA group compared to control group (p=0.001) and compared to IDA group (p=0.003).

Conclusion: The study demonstrates a significant reduction in hematological and iron profile parameters in both IDA and IRIDA patients compared to controls, with IRIDA patients showing the most pronounced deficiency. Additionally, IRIDA patients exhibited a highly significant increase in mutation frequency compared to both IDA patients and controls, suggesting a distinct genetic influence on iron metabolism.

Key words: Iron deficiency anemia, iron refractory iron deficiency anemia, SNP rs855791, control group, iron profile, blood indices

Introduction

Globally, iron-deficiency anaemia (IDA) is a major health issue. Hypochromic, microcytic anaemia is mostly caused by low dietary iron intake, however iron deficiency and anaemia can also result from other disorders such haemorrhage, gastrointestinal mal-absorption, or Helicobacter pylori infection [1, 2]. Iron-refractory iron-deficiency anaemia (IRIDA) is a rare iron metabolism condition that was recently discovered. Three siblings with IDA who were resistive to oral iron and only partially responsive to maternal iron dextran were the first to be documented with this illness in 1981 by Buchanan and Sheehan [3], indicating a potential genetic aetiology. Hemojuvelin (HJV), a co-receptor for bone morphogenic protein that is necessary for HAMP production, is cleaved by MT-2 [4].

Hepcidin synthesis is deregulated and overexpressed as a result of the documented causal mutations in TMPRSS6, which are distributed across the gene sequence and interfere with catalytic activity or protein–protein interactions [5]. The TMPRSS6 gene, which is found on chromosome 22q12.3, encodes the enzyme transmembrane protease, serine 6 (sometimes referred to as matriptase-2). Given the intricacy of iron metabolism and our current understanding of the condition, IRIDA caused by a TMPRSS6 deficiency can only be definitively diagnosed in patients who are homozygous or compound heterozygous for a pathogenic mutation [6].

The two most often reported TMPRSS6 SNPs, rs855791 and rs4820268, were associated with low blood indices and biomarkers of poor iron status.

Additional TMPRSS6 SNPs, including rs2235321, rs2235324, rs5756504, rs5756506, and rs1421312, were similarly connected to iron deficiency biomarkers. The African, European, Caucasian, and Asian populations all shared these SNPs [7].

Hypochromic, microcytic anaemia, and extremely low serum iron and transferrin saturation (TSAT) levels are the haematological characteristics linked to IRIDA. Additionally, after intravenous treatment, serum ferritin levels slightly increased, but they are still within the normal range [8].

When other frequent causes of IDA have been ruled out, this genetic condition—which is likely underdiagnosed—should be taken into consideration. The majority of IRIDA patients are diagnosed as youngsters, who exhibit normal growth, development, and intellectual function despite having anaemia [9]. IRIDA individuals are widely distributed geographically and ethnically [10]. The IRIDA phenotype is more noticeable during adolescence, when haemoglobin (Hb) production requires high levels of iron, and it gets milder as people age [8], most likely due to a decreased need for iron [11]. This study investigated the association of TMPRSS6 (rs855791) and iron deficiency anemia risk in Sudan.

MATERIALS & METHODOLOGY

A case control study was conducted among patients with iron deficiency anemia in Khartoum and Port Sudan state, during the period from November 2022 to September 2024. By probability, simple random sampling technique 129 patients with iron deficiency anemia and 129 healthy individuals with age matched were selected as control group were included. Patients were divided into 2 groups: Group1: patients with Acquired iron deficiency anemia (IDA), and Group2: patients with Iron refractory iron deficiency anemia (IRIDA), diagnosed from history of long-term iron therapy with no response to oral iron and partial improvement of anemia in response to parenteral iron therapy (many CBCs with persistent microcytic hypochromic anemia). At time of study, they were not on iron therapy. Any patient with concurrent infection (C reactive protein (CRP) > 5), chronic inflammatory dis- eases (rheumatic disease, inflammatory bowel disease), chronic disease, parasitic infestation, thalassemia traits α & β (ruled out by reticulocyte count < 2% and hemoglobin (HB) electrophoresis (A2 < 4%), and blood transfusion during the last 6 months were excluded from the study.

Data collection tool

The data was obtained through a face-to-face interviewer-administered questionnaire prepare in English and translated into Arabic, and back-translate to English to ensure its consistency by blinded language experts. Moreover, the questionnaire was pre-tested on 5% of the population in another district to check the impending problems of the data collection tool

All patients and controls was subjected to the following

- Thorough clinical examination.
- Laboratory investigations including CBC and iron profile and CRP
- Determination of TMPRSS6 gene SNPs (rs855791) will be done using Real Time polymerase chain reaction (PCR).

Blood Sampling and examination

A total of nine milliliters of venous blood were aseptically collected from study participants and divided into three portions. Five milliliters were left to clot, and then centrifuged at 1000 ×g for 15 minutes, with the sera subsequently separated for iron, ferritin, total iron-binding capacity (TIBC), and C-reactive protein (CRP) assay testing. Two milliliters were anticoagulated with ethylenediaminetetraacetic acid (EDTA) for complete blood count (CBC) analysis, while the remaining two milliliters were also anticoagulated with EDTA for TMPRSS6 single nucleotide (SNPs) analysis (rs855791) using real-time polymerase chain reaction (RT-PCR).

CBC was estimated by electrical impedance (coulter) method in fully Automated Hematology Analyzer (Derui, china).

Serum total iron, CRP and TIBC concentrations was estimated by Colorimetric method in fully Automated Biochemistry Analyzer (Midray, china). Serum total ferritin concentrations was estimated by specific enzyme-linked immunosorbent assay (ELISA) kit method in fully Automated Biochemistry Analyzer (TOSOH, japan) Transferrin saturation % was calculated using the following formula [12].

TS% = serum iron/TIBC × 100

Body iron store was assessed using the methodology developed by Cook and coworkers as expressed by the following formula (Cook et al.,) [13].

Body iron store (mg/kg) = [–log (sTfR / SF) – 2.8229]/0.1207

DNA Extraction Procedure

DNA was extracted from peripheral blood manually. After blood collected, Add 8 ml of RBCs lysis buffer then vortex and centrifuged at 6000rmp for 5 mint, then discard the superannuate. Repeat the previous step until a clear pellet of white blood cells appear at the bottom of the tube. Add 2 ml of WBCs lysis buffer, 1 ml of guanidine chloride, 300 ml of ammonium acetate and 10 ml of protenase k , then vortex and incubated overnight at 37C. Add 2 ml of chloroform then vortex and centrifuged at 6000rmp for 10 mint, transfer the upper layer to new tube. Add 9 ml of clod absolute ethanol and mix by hand then incubate at 20C overnight. Centrifuged at 6000 rmp for 10 mint and discard superannuate. Added 4ml of 70% ethanol mixed well and centrifuged at 6000 rmp for 10 mint and discarded superannuate and allowed the pellet to dry. Rehydrated the DNA by adding 50 ml of H2O and stored at 20C

Genetic study for detection of TMPRSS6 gene SNPS (RS4820268) using (RT-PCR)

For Detection of TMPRSS6 gene SNPs (rs 855791) kits was using uses real-time fluorescence binding dye (SYBR GREEN).

Table 1: Sequence of used primers of SNPs rsrs 855791

	rs 855791
Forward	5' TGA CCT CAG GTG TTC CGT C 3'
Reverse	5' AGG CTT CAG CAG GCT GAT G

The TaqMan SNP Genotyping Assay: Each TaqMan probe contains:
A reporter dye at the 5' end of each probe. VIC® dye is linked to the 5' end of the Allele 1 probe and FAM™ dye is linked to the 5' end of the Allele 2 probe.

A non-fluorescent quencher (NFQ) at the 3' end of each probe.
During PCR, each TaqMan probe anneals specifically to its complementary sequence between the forward and reverse primer sites. The increase in fluorescence signal occurs when probes that have hybridized to the complementary sequence are cleaved. Thus, the fluorescence signal generated by PCR amplification indicates which alleles are present in the sample. A substantial increase in VIC-dye fluorescence only indication to Homozygosity for Allele 1. A substantial increase in FAM-dye fluorescence only indication to Homozygosity for Allele 2. A substantial increase in Both VIC- and FAMdye fluorescence indication to Homozygosity for Allele 1 and 2.

Allelic Discrimination Plate Read and Analysis after PCR amplification, an endpoint was performed using an Applied Bio-systems RealTime PCR System. The Sequence Detection System (SDS) Software uses the fluorescence measurements made during the plate read to plot fluorescence. Values were based on the signals from each well. The plotted fluorescence signals indicate which alleles were in each sample

Data analysis

Data were collected, revised, coded and entered to the statistical package for social science (SPSS) version 17 and Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviation and ranges. The comparison between groups with qualitative data were done by using Chi-square test and Fisher exact test was used only when the expected count in any cell was found less than 5. The comparison between two groups with quantitative data and parametric distribution were done by using Independent t-test. Mann- Whitney test was used when the data were non parametric or data were not normally distributed. The comparison between 3 groups with quantitative normally distributed data were done by ANOVA test, Pearson correlation coefficients were used to assess the significant relation between two quantitative parameters.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p value was considered significant as the following: P > 0.05:Non significant , P < 0.05: Significant and P < 0.01: Highly significant.

Ethical Considerations

An approval from Institutional Ethics Committee Karari University-Sudan. The objective of the study was explained to all participants, and their consent was taken. Participants who fulfilled the above criteria were included in the study after taking consent.

RESULTS

During the study period, caregivers of children seeking medical attention at the hospital were contacted, leading to the recruitment of 258 participants. This included 129 patients diagnosed with acquired iron deficiency anemia (IDA) or iron refractory iron deficiency anemia (IRIDA), comprising 68 males (mean age: 12.2 ± 4.3 years) and 61 females (mean age: 12.1 ± 5.6 years). Patients were enrolled through medical camps, hospital visits, and direct personal interactions. Additionally, 129 healthy age- and sex-matched individuals served as the control group, with 68 males and 61 females, having mean ages of 12.3 ± 4.7 and 12.2 ± 5.1 years, respectively.

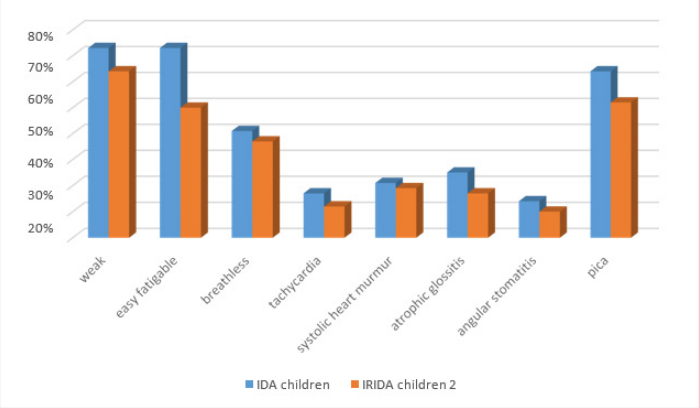

Figure 3.1 Comparative clinical symptoms among in group 1 compared to group 2 (N=258)

Clinical symptoms reported in children with IDA, were 73% experienced weakness, 73% reported easy fatigue, 41% suffered from breathlessness, 17% exhibited tachycardia, 21% presented with systolic heart murmurs, 25% had atrophic glossitis, 14% displayed angular stomatitis, and 64% demonstrated pica. In contrast, IRIDA patients exhibited similar symptoms at slightly lower frequencies: weakness (64%), easy fatigue (50%), breathlessness (37%), tachycardia (12%), systolic heart murmurs (19%), atrophic glossitis (21%), angular stomatitis (12%), and pica (59%), as illustrated in (Figure 3.1).

Complete Blood Count (CBC) Comparison

Regarding CBC parameters, the mean ± SD values for hemoglobin (HB), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) in IDA patients were 10.75 ± 0.82, 35.6 ± 2.4, 73.8 ± 3.7, 24.4 ± 1.7, and 31.7 ± 1.5, respectively. IRIDA patients showed lower values of 9.4 ± 1.5, 30.4 ± 3.5, 66.5 ± 2.7, 22.4 ± 3.9, and 30.5 ± 2.5. The control group recorded higher values of 12.3 ± 0.94, 36.5 ± 2.4, 77.6 ± 2.5, 26.7 ± 2.3, and 34.6 ± 1.4. As detailed in (Table 3.1)

Table (3.1): Comparative of CBC parameters among studied children (N=258)

Parameters	Group 1(Control)	Group 2((IDA l)	Group 3(IRIDA	P-value
WBCs (X109/L)	7.8±0.79	7.4±0.73	8.7±0.82	0.472
RBCs (X1012 /L)	4.4±0.54	4.6±0.63	4.7±0.36	0.185
HB (g/L)	12.3 ± 0.94	10.75±0.82	9.4 ± 1.5	0.01
Hematocrit (%)	36.5 ± 2.4	35.6 ± 2.4	30.4 ± 3.5	0.03
MCV (fl)	77.6 ± 2.5	73.8 ± 3.7	66.5 ± 2.7	0.01
MCH (pg)	26.7 ± 2.3	24.4 ± 1.7	22.4 ± 3.9	0.01
MCHC (g/dl)	34.6 ± 1.4	31.7 ± 1.5	30.5 ± 2.5	0.483
RDW	20±1.98	19.7±1.62	20.6±0.61	0.518
PLT (X109/L)	328±21.3	310±16.5	318±16.0	0.874

However, the mean ± SD values for white blood cells (WBCs), red blood cells (RBCs), red cell distribution width (RDW), and platelets (PLT) were 7.4 ± 0.73, 4.6 ± 0.63, 19.7 ± 1.62, and 310 ± 16.5 for IDA patients, and 8.7 ± 0.82, 4.7 ± 0.36, 20.6 ± 0.61, and 318 ± 16.0 for IRIDA patients. The control group recorded values of 7.8 ± 0.79, 4.4 ± 0.54, 20 ± 1.98, and 328 ± 21.3. Hemoglobin, hematocrit, MCV, MCH, and MCHC levels were significantly lower in both patient groups compared to controls (p-values: 0.01, 0.03, 0.01, 0.01, 0.05), whereas WBCs, RBCs, RDW, and PLT levels showed no significant differences between IDA and IRIDA groups.(Table 3.1).

Serum Iron Profile

Table (3.2): Comparative of Iron profile among studied children (N=258)

Parameters	Group 1(Control)	Group 2((IDA l)	Group 3(IRIDA	P-value
Total Iron (µg/dl)	21.80±3.38	10.00±2.51	8.00±4.21	0.015
TIBC (µg/dl)	304.65±50.19	323.75±32.14	353.75±14.36	0.034
Ferritin (ng/dl)	13.73±80.58	8.95±45.09	5.854±40.25	0.020
% Transferrin saturation	27.4 ± 2.85	15.3±3.5	13.2±1.7	0.035
Body iron store (mg/kg)	1.7 ± 0.2	-4.4 ± 0.2	-8.6 ± 0.9	0.021

The serum iron, total iron-binding capacity (TIBC), and ferritin concen-

trations among study groups. IDA patients recorded mean ± SD values of 10.00 ± 2.51, 323.75 ± 32.14, and 8.95 ± 45.09, respectively, while IRIDA patients exhibited lower values of 8.00 ± 4.21, 353.75 ± 14.36, and 5.854 ± 40.25. The control group displayed significantly higher values of 21.80 ± 3.38, 304.65 ± 50.19, and 13.73 ± 80.58. These reductions in patient groups compared to controls were statistically significant (p-values: 0.015, 0.044, 0.020). (Table 3.2)

Genetic Analysis

As regard SNP rs 855791, there was a significant increase in frequency of mutations (heterozygous and homozygous) in IDA group compared to control group (p=0.025) and highly significant increase in frequency of mutations (heterozygous and homozygous) in IRIDA group compared to control group (p=0.001) and compared to IDA group (p=0.003). Figure 3.2

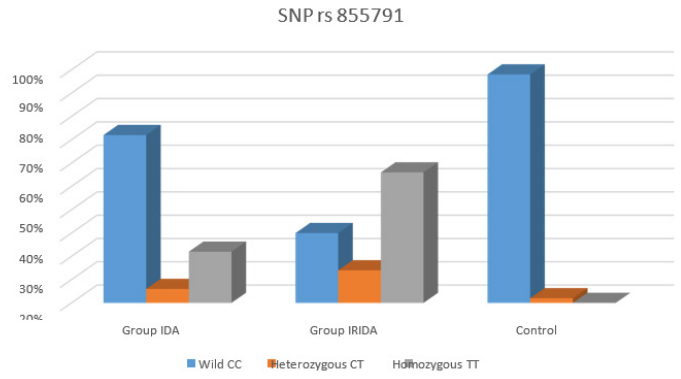

Figure: 3.2: Frequency of SNP rs 855791genotypes among studied children (N=258)

DISCUSSION

Iron deficiency anemia originates primary from dietary, blood loss and other environmental factors. Many discoveries concerning iron metabolism disorders revealed that there is a genetic contribution to the development of iron deficiency. In particular, TMPRSS6 gene polymorphisms have been implicated as influencing iron metabolism in human studies [14].

MT-2 is encoded by TMPRSS6 gene that regulates hepcidin expression. Polymorphisms of TMPRSS6 leads to diminshed ability of MT-2 to down-regulate hepcidin production which persist elevated in spite of iron deficiency, preventing iron stores refilling leads to IRIDA. Iron refractory iron deficiency anemia is an autosomal recessive hereditary disorder of iron metabolism characterized by hypochromic microcytic anemia unresponsive to oral iron treatment, low transferrin saturation and inappropriate normal to high levels of hepcidin [15].

Transmembrane protease serine 6, is likely to be involved in iron metabolism through its pleiotropic effect on hepcidin concentrations. Recently, genome-wide association studies have identified common variants in the TMPRSS6 gene to be linked to anemia and low iron status. The strongest association was found between lower hemoglobin and iron and SNP rs855791 [16].

Among the Asian, African, and European populations there is a significant divergence in the minor allele frequency distribution of SNPs [16-19]. The minor allele frequency (MAF) of SNP rs855791 found to be less in African than Asian and European populations [18]. The difference may be attributed to the selective role of certain environmental conditions that alter the frequency of the genetic variants among populations [16].

Single nucleotide polymorphisms of rs855791 of TMPRSS6 gene has been widely described to affect iron indices and to be correlated with the risk of IDA in Europeans [17] and Asians [20,21]. As regard SNP rs 855791, our result reported significant increase in frequency of mutations (heterozygous and homozygous) in IDA group compared to control group and highly significant increase in frequency of mutations (heterozygous and homozygous) in IRIDA group compared to control group and compared to IDA group. In concordance with the present study, the results obtained by Delbini et al. who found that there was highly significant increase in frequencies of SNP rs855791 in subjects with IRIDA compared with healthy controls [17]. In agreement with the present study, the results obtained by An et al who identified a significant increase of rs 855791 mutation in iron deficiency anemia than in normal individuals [21]. In agreement with the present study results reported by Gonçalveset al., who found an increase in frequency of heterozygous and homozygous rs855791 in women with IDA more than in control group. Sequencing analysis of TMPRSS6 gene in IRIDA patients revealed the presence of rs855791 [22]. Parallel to our results those obtained by Pei et al., who found that theTMPRSS6 rs855791 CC genotype (wild) is less frequent in reproductive age women with IDA than in healthy women and suspected that the wild genotype (CC) for rs855791 plays a protective role against IDA, especially for those with menorrhagia. It is likely that women with the CC genotype increase the iron absorption from the intestine through decreased hepcidin production and then can offset the menstrual losses. For those with CC genotypes, diet modification may be enough to keep iron balance; otherwise, long-term iron replacement till menopause may be considered [23]. The findings of our study contradict those of Kumar et al. [24] and Macdougall et al. [25], who reported that CC genotype is protective in IDA, whereas TT genotype is pathological. Later studies by [22], reported that patients with IDA were less likely to have CC genotypes. Variations in the study may be attributable to a difference in the study population and ethnicity. These data demonstrated that TMPRSS6 (rs855791C>T) genotypes serve as effective predictors of IDA. Therefore, patients with IDA should be tested for TMPRSS6 (rs855791C>T) genotype. This can help guide baseline investigations and treatment decisions. Our study also agreed with Elmahdy et al., [26]. Shinta et al., [27] found that both iron deficiency and iron deficiency anemia were associated with minor homozygote allele of rs855791 genotype. On the other hand, Momodou et al., [28] didn't find any association with iron status biomarkers. In concordance with the present study, the results obtained by Erika et al., who found that the TMPRSS6 SNP rs855791 resulted more frequent in anemic patients than in healthy controls, suggesting their possible contribution in the refractoriness to oral iron. This effect would be imputable to reduced ability of TMPRSS6 polymorphisms to down-regulate hepcidin production, which persists elevated despite iron deficiency, preventing iron stores refilling [29].

Comparison of CBC parameters and serum iron profile among study groups, the serum iron, TIBC and ferritin were significantly deceased in case group compared to control groups in contract to our results. In a study by Gan et al. [30], observed elevated serum ferritin and hemoglobin levels in TMPRSS6 (rs855791C>T) mutants. The mutant genotype has decreased CRP and ESR levels. These parameters were statistically significant. In theTMPRSS6 genotype (rs855791C>T), the total iron-binding capacity level and transferrin saturation level were increased, and the P values were significant. Symptoms of iron-deficiency anaemia are less frequent in individuals carrying the rs855791C>T mutation in TMPRSS6. Previously, Nai et al. [31] reported that rs855791C>T is strongly associated with serum iron, transferrin saturation, and hematological parameters; it was also shown to increase iron parameters in patients by inhibiting hepcidin. Pei et al. [23] further confirmed this role of rs855791C>T, reporting that it protects women against iron-deficiency anemia. The results of our study demonstrate that the heterozygous (TC) genotype confers protection against iron-deficiency anemia, in agreement with previous studies [17, 32].

This study faced some limitations that the children were recruited from a single center due difficulties of war; it could be better to be a multicenter study which could not be fulfilled due to budget limitation.

Conclusion

This study showed clinical manifestations in IDA and IRIDA children, the most frequent of which were weakness, easy fatigability, and pica. Furthermore, increased frequency of mutations at SNP rs855791 in IDA patients compared to controls, and even greater in IRIDA patients. This suggests a more significant role of SNP rs855791 in IRIDA genetics, further backing its likely role in iron metabolism and anemia physiology.

As per the outcome of this research, the Government and Ministry of Health need to enact policies favoring exclusive breastfeeding up to the first six months and healthy eating. This may be achieved by making public awareness about iron-rich foods and their utilization by the human body often, improving the environmental situation, and adopting reliable, inexpensive, and accessible hemoglobin and serum ferritin estimation techniques. Moreover, future research is invited to conduct a longitudinal exploration of the interaction between genetic variants and iron biomarkers in a larger population size across various environmental components in order to better understand the genetic and nutritional factors influencing iron deficiency.

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