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ASSOCIATION OF TMPRSS6 (RS4820268) GENETIC POLYMORPHISMS WITH IRON DEFICIENCY ANEMIA RISK AMONG SUDANESE PATIENTS

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ABSTRACT

Background: Iron deficiency anemia (IDA) is a global health problem and common medical condition seen in everyday clinical practice. Matriptase-2 (MT-2) which is encoded by transmembrane protease serine 6 (TMPRSS6) gene regulates hepcidin expression. **Objective** of this study was to detect the association of TMPRSS6 (rs4820268) genetic polymorphisms with 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), (rs4820268) 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. Serum iron, total iron-binding capacity (TIBC), and ferritin levels among IDA patients were 10.00 ± 2.51, 323.75 ± 32.14, and 8.95 ± 45.09, respectively. For IRIDA patients, the values were 8.00 ± 4.21, 353.75 ± 14.36, and 5.854 ± 40.25. The control group exhibited significantly higher levels: 21.80 ± 3.38, 304.65 ± 50.19, and 13.73 ± 80.58. All three parameters showed a significant reduction in patient groups compared to controls (p-values: 0.015, 0.044, and 0.020). Moreover the frequency of SNP rs4820268 (heterozygous and homozygous) did not show a significant difference in IDA patients compared to controls ($p = 0.087$). However, IRIDA patients exhibited a highly significant increase in SNP rs4820268 frequency compared to both the control ($p = 0.001$) and IDA groups ($p = 0.005$). The study found no significant difference in polymorphism frequency between IDA patients and controls ($p > 0.05$). However, IRIDA patients demonstrated a highly significant increase in SNP rs4820268 group compared to controls ($p = 0.001$) and IDA patients ($p = 0.001$). **Conclusion:** The study highlights a significant reduction in serum iron, TIBC, and ferritin levels 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 SNP rs4820268 frequency, distinguishing them genetically from both IDA patients and healthy controls.

KEYWORDS: Iron deficiency anemia, iron refractory iron deficiency anemia, SNP rs4820268, control group, iron profile, blood indices.

1. INTRODUCTION

Iron-deficiency anemia (IDA) is a serious health problem worldwide. Low intake of dietary iron is the main cause of hypochromic, microcytic anemia; however, other conditions, such as bleeding, gastrointestinal mal-absorption, or Helicobacter pylori infection, can also lead to iron deficiency and anemia.[1,2] Recently, a rare iron metabolism disorder was identified, named iron-refractory iron-deficiency anemia (IRIDA). This disorder was first described in 1981 by Buchanan and Sheehan[3] in three siblings with IDA that was refractory to oral iron and only partially responsive to parental iron dextran, suggesting a possible genetic cause. MT-2 cleaves hemojuvelin (HJV), a co-receptor for bone morphogenic protein, which is required for HAMP expression.[4] The reported causative mutations in TMPRSS6 are spread throughout the gene sequence, where they disrupt catalytic activity or protein–protein interactions, deregulating hepcidin production and causing its overexpression.[5] Transmembrane protease, serine 6 (also known as matriptase-2) is an enzyme that in humans is encoded by the TMPRSS6 gene located in

Chromosome 22q12.3. Considering the complexity of iron metabolism, combined with our limited knowledge, IRIDA due to a TMPRSS6 defect can be diagnosed only with certainty when the patient is homozygous or compound heterozygous for a pathogenic mutation.[6]

The most frequently reported TMPRSS6 SNP were rs855791 and rs4820268, linked to biomarkers of poor iron status and low blood indices. Other TMPRSS6 SNPs were also linked to iron deficiency biomarkers such as rs2235321, rs2235324, rs5756504, rs5756506, and rs1421312. These SNPs were commonly found among the African, European, Caucasian, and Asian populations.[7]

The hematological parameters associated with IRIDA are hypochromic, microcytic anemia, with very low levels of serum iron and transferrin saturation (TSAT). Furthermore, serum ferritin levels are within the normal range, with a slight increase following intravenous treatment.[8] This genetic condition is probably underdiagnosed, and should be considered when other common causes of IDA have been ruled out. IRIDA patients have a wide geographic and ethnic distribution[9], with most being diagnosed as children, who despite having anemia, display normal growth, development, and intellectual performance.[10] The IRIDA phenotype is more evident and adolescence, when high amounts of iron are needed for hemoglobin (Hb) synthesis, and becomes milder with aging [8], probably as a consequence of reduced iron requirement.[11] This study investigated the association of TMPRSS6 (rs4820268) and iron deficiency anemia risk in Sudan.

2. MATERIALS AND 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 (rs4820268) 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 (rs4820268) 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 (WHO, 2001)[12]:

$$TS\% = \text{serum iron}/TIBC \times 100$$

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

$$\text{Body iron store}(mg/kg) = [-\log (sTfR / SF) - 2.8229]/0.1207$$

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.

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

For Detection of TMPRSS6 gene SNPs (rs 4820268) kits was using uses real-time fluorescence binding dye (SYBR GREEN).

Table 1: Sequence of used primers of SNPs rs 4820268.

	rs 4820268
Forward	5' TGT AAA ACG ACG GCC AGT 3'
Reverse	5' CAG GAA ACA GCT ATG ACC 3'

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.

3. 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.

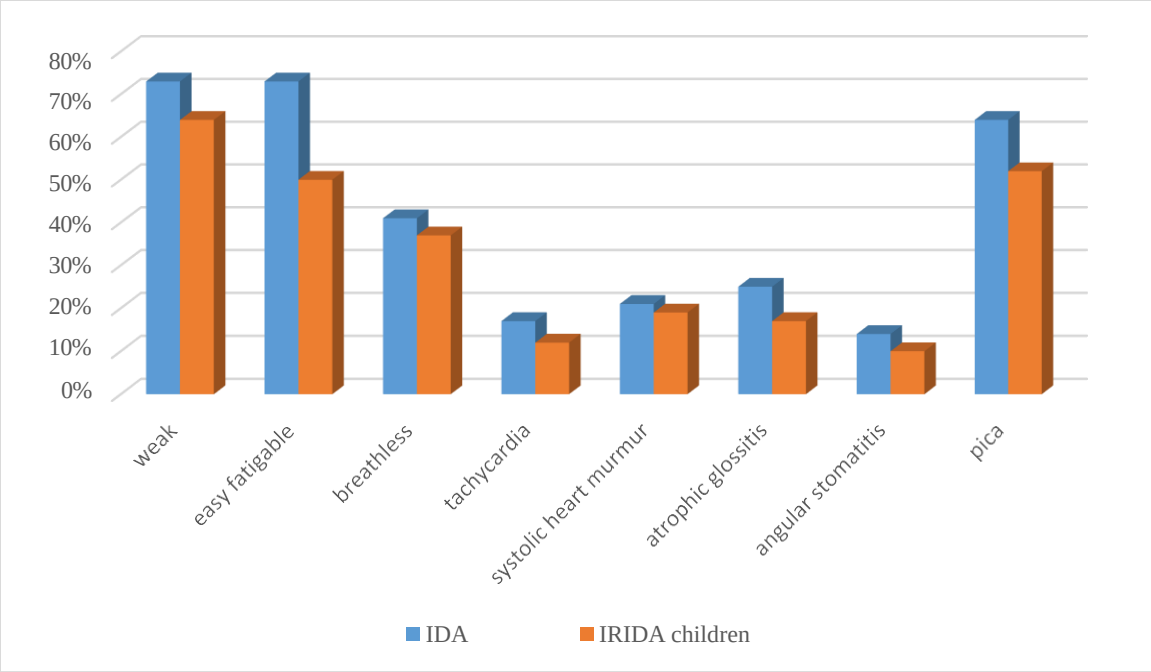

Figure 3.1: Comparative clinical symptoms among in group 1 compared to group 2 (N=258).

Clinical symptoms were documented in children with IDA, revealing that 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 concentrations 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

No significant difference was observed in the frequency of SNP rs4820268 (heterozygous and homozygous) among IDA patients compared to controls (p = 0.087). However, IRIDA patients demonstrated a highly significant increase in SNP rs4820268 frequency compared to both controls (p = 0.001) and IDA patients (p = 0.005), as seen in Figure 3.2.

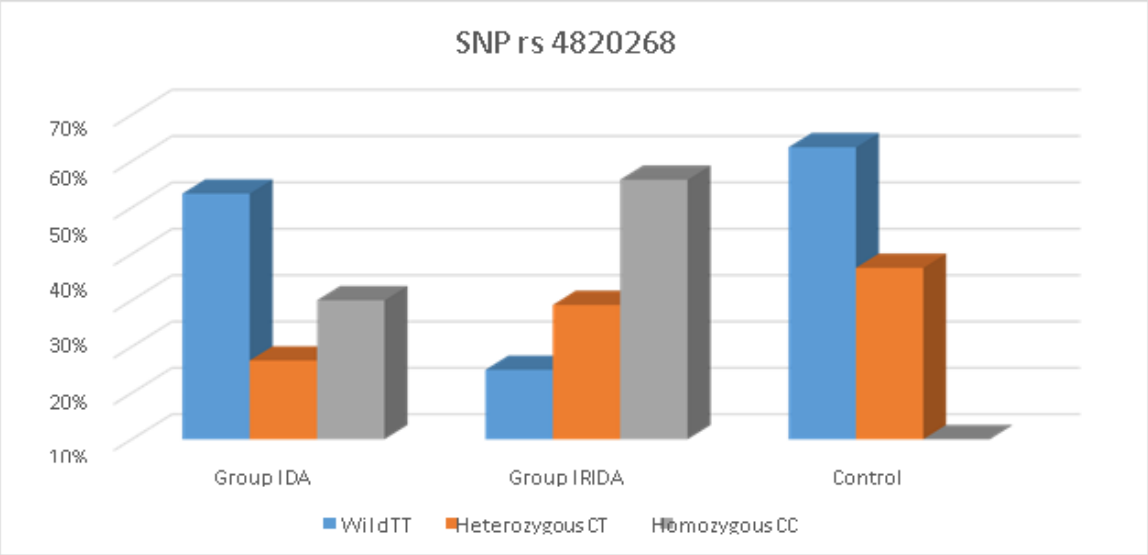

Figure: 3.2: Frequency of SNP rs 4820268 genotypes among studied children (N=258).

4. 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 (SNP rs 4820268 genotypes) 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 diminished 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, iron, and SNPs rs4820268.[16]

Among the Asian, African, and European populations, there is a significant divergence in the minor allele frequency distribution of SNPs.[16,17,18,19] The minor allele frequency (MAF) of SNP rs4820268 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]

In the present study, there was non-significant difference in frequency of SNP rs 4820268 (heterozygous and homozygous) in IDA group compared to control group.

On the other hand, IDA group showed highly significant increase in frequency of SNP rs 4820268 compared to control group. There was highly significant increase in frequency of rs4820268 in IRIDA group compared to IDA group. In agreement with the present study, results obtained by Beutler et al and Batar et al who reported that the TMPRSS6 SNPs rs 4820268 was not likely to be associated with iron deficiency anemia.[20,21] In concordance with the present study, the results obtained by Keskin and Yenicesu who noted that there was highly significant increase in frequency of SNP rs4820268 in subjects with IRIDA compared with healthy controls.[15]

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 indicated clinical symptoms in children diagnosed with IDA and IRIDA, identifying weakness, easy fatigability, and pica as the most prevalent. Regarding TMPRSS6 (rs4820268), there was no significant difference in SNP rs4820268 frequency in IDA patients compared to controls, whereas IRIDA patients demonstrated a highly significant increase in frequency compared to both controls and IDA patients. Furthermore, IRIDA patients exhibited a highly significant increase in the frequency of mutations compared to both controls and IDA patients. These findings underscore the genetic distinction of IRIDA patients, particularly in TMPRSS6-related mutations.

Based on the findings of this study, it is essential for the Government and Ministry of Health to implement policies that encourage exclusive breastfeeding for the first six months and promote proper nutrition. This can be achieved through ongoing public awareness campaigns about iron-rich foods and their absorption by the human body, improving environmental conditions, and adopting reliable, cost-effective, and accessible methods for hemoglobin and serum ferritin estimation. Additionally, a longitudinal study examining the interaction between genetic variants and iron biomarkers across a larger sample size from diverse environmental sectors is recommended for future research to provide deeper insights into the genetic and nutritional factors affecting iron deficiency.

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