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The impact of the rs887829 C>T genetic polymorphism of *UGT1A1* on the response to deferasirox in Iraqi thalassaemia patients

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ABSTRACT

Beta thalassaemia major, also known as transfusion-dependent thalassaemia (TDT), is an autosomal recessive genetic disorder necessitating lifelong blood transfusions. Due to the absence of physiological iron excretion, patients require iron chelation therapy. Despite treatment with the oral iron chelator deferasirox (DFX), many patients exhibit elevated serum ferritin (SF) levels. UDP-glucuronosyltransferase 1A1 (*UGT1A1*) – the principal gene of the UGT1 enzyme family – plays a central role in DFX metabolism. This cross-sectional study was conducted at the Karbala Hereditary Blood Diseases Center between November 2023 and April 2024. A total of 96 Iraqi patients with TDT (aged 8–39 years) were treated with DFX at a daily dose of 30–40 mg/kg for a minimum of three months. Their SF levels, serum erythroferrone levels, and liver and kidney functions were assessed. Genotyping of the rs887829 C>T single nucleotide polymorphism (SNP) in *UGT1A1* was performed using allele-specific polymerase chain reaction. The genotype frequencies for rs887829 were: CC (79.2%), CT (13.5%), and TT (7.3%). The wild-type (C) allele frequency was 0.86, compared to 0.14 for the mutant (T) allele. Patients with the TT genotype had significantly higher total serum bilirubin (TSB) levels compared to those with CC or CT genotypes (p=0.03). The rs887829 SNP was associated with increased TSB levels and may contribute to the development of hyperbilirubinaemia in Iraqi patients with TDT.

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1. Introduction

Thalassaemias are autosomal recessive genetic disorders characterized by a reduced production of either α- or β-globin chains. Approximately 1% of the global population is affected by β-thalassaemia, which is particularly prevalent in the Middle East[1]. Regular blood transfusions can lead to progressive iron overload and associated clinical complications, including hypogonadism (35%–55%), hypothyroidism (9%–11%), hypoparathyroidism (4%), diabetes mellitus (6%–10%), liver fibrosis, and heart failure (33%)[2].

Iron chelation therapy is typically initiated after 10–20 transfusions or when serum ferritin (SF) levels exceed 1,000 ng/mL. Available chelators include deferoxamine, deferiprone, and deferasirox (DFX). DFX was approved as a first-line treatment for transfusion-dependent thalassaemia (TDT) in over 70 countries, including the United States (2005) and throughout the European Union (2006)[3]. It is a potent, orally administered, selective iron chelator that forms a 2:1 stable complex with iron. DFX and its metabolites are primarily excreted *via* the faeces (approximately 84%) following extensive glucuronidation by the uridine glucuronosyltransferase (UGT) enzymes[4]. DFX administered at 10–40 mg/kg/day has been shown to reduce liver iron and SF levels and increase iron excretion. Major adverse effects include hepatic and renal failure, gastrointestinal bleeding, and bone marrow suppression[3].

The UGT1A1 gene, located on chromosome 2q37, encodes the UGT1A1 enzyme; a key component of the UGT1 family. The rs887829 C>T single nucleotide polymorphism (SNP) resides in the main promoter region of *UGT1A1*. Previous research has demonstrated that promoter region polymorphisms in *UGT1A1* are linked to variability in drug response and disease risk[5]. This study aimed at investigating the impact of the rs887829 C>T SNP on the therapeutic response to DFX.

2. Methodology

2.1. Study subject recruitment

This cross-sectional study was approved by the Scientific and Ethical Committee of Karbala University College of Pharmacy (reference number: 2023HU7; approved on August 2, 2023). A total of 96 patients with TDT were recruited from the Karbala Hereditary Blood Diseases Center between November 2023 and April 2024, from a pool of 650 patients. Participant ages ranged from 8 to 39 years. All patients had received DFX monotherapy for at least 3 months at the recommended dose of 30–40 mg/kg/day. Patients with liver disease, those who consumed alcohol, individuals with sickle cell anaemia, and patients with other forms of thalassaemia were excluded.

Each subject provided 5 mL of venous blood *via* a disposable syringe. Of these, 2.5 mL were transferred to a plain tube and left to coagulate for 30 min. Samples were centrifuged at 4,000×g in order to isolate serum for erythroferrone (ERFE) and biomarker analysis, and stored at -20°C. The remaining 2.5 mL were placed in evacuated ethylenediaminetetraacetic acid (EDTA) tubes for haematological testing and DNA extraction.

2.2. Genetic analysis

Genomic DNA was extracted by using the Geneaid DNA Extraction/Genomic DNA Purification Prep Mini Kit (Taiwan), following the manufacturer's protocol. Allele-specific polymerase chain reaction (PCR) was used in order to detect the SNP. Lyophilized primers, designed through the Primer-BLAST program, were obtained from Macrogen-Korea. Each 25-μL PCR reaction included: 12 μL master mix (Promega, USA), 2 μL of extracted DNA (100 ng/μL), 1 μL each of forward and reverse primers, and 9 μL nuclease-free water. PCR conditions involved an initial denaturation at 95°C for 3 min, followed by 30 amplification cycles at an annealing temperature of 62°C and extension at 72°C for 40 sec. PCR products were resolved using 2% (w/v) agarose gel electrophoresis.

2.3. Biochemical analysis

Red blood cell (RBC) and haemoglobin (Hb) lev-

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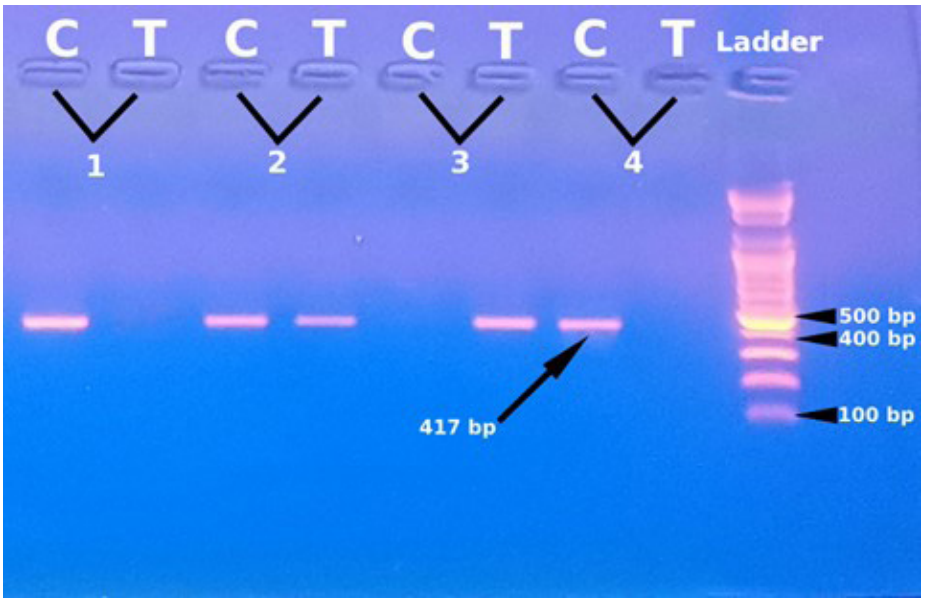

Figure 1. *Agarose gel electrophoresis using allele-specific polymerase chain reaction in order to detect the rs887829 C>T single nucleotide polymorphism in the UGT1A1 gene. The wild-type genotype (CC) is represented in lanes 1 and 4, the heterozygous genotype (CT) in lane 2, and the homozygous mutant genotype (TT) in lane 3.*

els were measured using the Swelab Alfa Analyzer. ERFE levels were quantified by using a sandwich-method enzyme-linked immunosorbent assay (ELISA) with a Sunlong Biotech kit. SF levels were measured by using the Cobas e411 analyser (Germany), while liver and kidney function tests were performed by using the Mindray BS 240 system.

2.4. Statistical analysis

Data were analysed using the SPSS v. 22 (SPSS Inc., Chicago, US). Chi-squared testing was applied to categorical data. Group means for haematological and biochemical parameters were compared using *t*-tests (two groups) and one-way analysis of variance (ANOVA) (≥ three groups). A *p*-value <0.05 was considered as statistically significant.

3. Results and Discussion

Ninety-six patients (43% male) with TDT were included in our study. Indicative PCR results are shown in Figure 1. The age distribution ranged from 8 to 39 years, with 67% of the patients being younger than 19 years; only two participants were older than 30 years. Parental consanguinity or marital relativity was reported in 88% of patients. Genotype distribution for rs887829 C>T SNP was as follows: CC (79%), CT (14%), and TT (7%). Significant differences were noted in total serum bilirubin (TSB) levels among genotypes, with the TT group showing elevated TSB (p=0.03), while other parameters did not differ significantly.

Consanguinity has been suggested to increase the risk of TDT[4]. In the present study, 88.5% of patients were born to first- or second-degree consanguineous unions.

Elevated TSB levels were significantly associated with the homozygous TT genotype (p=0.03). UGT1A1 is the primary UGT1 gene product and plays a critical role in bilirubin conjugation. Unconjugated bilirubin is the principal cause of hyperbilirubinaemia. Functional or structural disruptions in the UGT1A1 enzyme, often due to promoter or exon mutations, may impair glucuronidation[6].

Because both bilirubin and DFX undergo hepatic

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glucuronidation[7] – primarily *via* UGT1A1 – polymorphisms such as rs887829 C>T may reduce *UGT1A1* expression[8], leading to elevated DFX serum concentrations[9]. Higher DFX levels may enhance iron chelation efficiency, thereby lowering SF levels over time. In this study, the SF levels in TT carriers (2,321.14 ± 1,071.80 ng/mL) were lower than those in CC (3,333.48 ± 1,050.18 ng/mL) and CT (3,739.15 ± 1,113.79 ng/mL) carriers, but the differences were not statistically significant.

Finally, ERFE levels, which rise in thalassaemia due to ineffective erythropoiesis and influence hepcidin regulation[10], were lowest in the TT group (38.16 ± 20.13 ng/L), compared to those in the CC (43.74 ± 28.56 ng/L) and the CT (47.87 ± 20.89 ng/L) groups, though the differences did not reach statistical significance. Lower ERFE levels may partly explain the reduced SF levels observed in the TT group.

4. Conclusion

The rs887829 C>T SNP in the UGT1A1 gene is significantly associated with elevated TSB levels, thereby suggesting a potential role in the development of hyperbilirubinaemia in patients with TDT. No significant associations were observed for other haematological or biochemical parameters.

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Conflicts of interest

None exist.

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