

ORIGINAL ARTICLE

Investigation of MicroRNA 196a2 Polymorphism with Thalassemia Disease among Middle and South Iraqi Population

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Abstract

Background: Beta-thalassemia is widely recognized as a prevalent genetic hematologic disease. The condition is characterized by a decrease or absence in the synthesis of a specific globin chain, leading to the development of varying degrees of hemolytic anemia and its associated consequences. MicroRNAs (miRNAs) play a significant role in the reactivation of globin expression in individuals with thalassemia. However, the transcriptional patterns of miRNAs in thalassemia have not yet been determined.

The aim of the study: this study examines the polymorphism of miRNA 196a2 in people diagnosed with thalassemia.

Method: The present investigation comprised a sample size of 100 individuals diagnosed with thalassemia in conjunction with an equivalent number of control samples. Samples were collected from patients at the thalassemia center at Babylon Hospital from May 2021 to August 2021. These samples were obtained to assess materiality and pediatrics in Babylon provinces and Iraq in the year 2021.

Results: The findings of the current study demonstrate a significant association between persons possessing the dominant model genotype (TT, TT+TC) and an increased susceptibility to thalassemia disease, compared to patients with the recessive model genotype (CC, TC+TT) (P value = 0.032, OR = 1.85, CI 95% (1.05-3.27).

Conclusions: To our knowledge, this investigation represents the initial examination that establishes a correlation between miRNAs, the rs11614913 single nucleotide polymorphism (SNP), and thalassemia. This study posits that there may be an association between the miRNA196a2 rs11614913 T>C variant T>C and susceptibility to beta-thalassemia illness in the middle and southern Iraqi population. Additional research involving many centers is required to validate our findings. The results suggest that variations in the target sites of the miRNA rs11614913 SNP of miRNA rs11614913 inside genes associated with thalassemia may play a role in modifying the severity of thalassemia phenotypes.

Keywords: β -thalassemia, polymorphism, miRNA, rs11614913.

INTRODUCTION

Thalassemia is one of the most common autosomal recessive hereditary blood diseases in the world. Beta-thalassemia is caused by a decrease or complete absence of globin chain expression, resulting in rate imbalances. Excess alpha chains precipitate in erythroid cells, producing oxidative damage to the cell membrane, poor erythropoiesis, and anemia. Cao and Galanello [1] and Harbi et al. [2] exhibited that at birth, patients with thalassemia have severe fetal health problems, necessitating lifelong blood transfusions and iron elimination medication [3,4]. However, current medications for thalassemia have been associated with substantial side effects [5], and new therapeutic techniques are actively being studied [6]. As a result, procedures for prenatal diagnosis of thalassemia are urgently needed, especially in areas where thalassemia is prevalent [7].

Predicting clinical severity in patients with thalassemia is difficult due to genetic factors recognized as modifiable factors [8]. These factors, including the severity of anemia, myeloid hyperplasia, blood transfusion needs, and splenectomy needs, all contribute to phenotypic diversity [9].

Globin gene diseases, also known as hemoglobinopathies, exhibit two primary manifestations: the presence of aberrant globin chain variations, such as sickle cell anemia, and the decreased synthesis of globin chains in erythroid cells, known as thalassemia, which occurs during the process of hematopoiesis [10]. The inheritance pattern of hemoglobinopathies is predominantly autosomal recessive. The severe forms of α -thalassemia are characterized by a deficiency or absence of α -globin chains, which causes an accumulation of unpaired beta (β)-like globin chains. These

excess β -like globin chains form insoluble homotetramers, precipitating these molecules within the cells. This process results in ineffective erythropoiesis and the development of acute hemolytic anemia [11,12].

The regulatory function of microRNAs (miRNAs) in several cellular processes has been comprehensively elucidated. The regulatory mechanisms using miRNA are classified as epigenetic regulatory mechanisms [13]. According to Wang et al. [14], miRNAs are involved in various processes related to erythrocyte generation and maturation, including the expression of hematological factors and the regulation of globin gene expression through post-transcriptional gene silencing. miRNAs are noncoding RNA molecules characterized by their relatively short length, typically consisting of 22 nucleotides. Based on empirical research, miRNAs have been found to influence around 60% of genes responsible for encoding proteins in the human genome. The process involves the integration of fully developed single-strand miRNA into the RNA-induced silencing complex (RISC), which then recognizes specific mRNA 3'-untranslated regions (3'-UTRs) through complementary base pairing between the miRNA seed region and the known position. This recognition subsequently leads to the inhibition of mRNA translation or cleavage, as Ambros [15] and Akhtar et al. [16] documented.

The regulation of globin gene switching is mediated by miRNAs through post-transcriptional mechanisms, as demonstrated by Bartel et al. [17] and Filipowicz et al. [18]. As Zhao et al. [19] and Sankaran et al. [20] show, the MYB transcription factor facilitates globin transcription by targeting hsa-miR-15a and hsa-miR-16. Lai et al. [21]

and Bartel [22] have identified a range of long noncoding RNAs and miRNAs that exhibit differential expression in individuals with advancing thalassemia, employing the Sanger sequencing approach.

As a result, finding human genetic disorder miRNAs would be highly beneficial in understanding the pathophysiology of many diseases. SNPs in miRNA sequences have been shown to affect cellular processes regulated by these miRNAs, changing the expression and synthesis of these regulatory components in the cell [23]. Despite several studies that examined the association between SNPs and various disorders [24], there have been few clinical investigations on the effects of miRNA variations in patients with thalassemia [25]. As a result, to better understand the importance of miRNA variants in thalassemia diseases, we hypothesized links between miRNA miR-196a2 rs11614913 and β -thalassemia.

MATERIALS AND METHODS

PATIENTS

The current study comprised 100 patients with thalassemia illnesses: 60 (60%) men and 40 (40%) women. Male patients ranged in age from 15 to 48 years old. In comparison, women patients ranged in age from 17 to 49 years of age, and samples were taken from the thalassemia center of Babylon Hospital for material and pedigree in Babylon provinces and Iraq from May 2021 to August 2021.

Control group

One hundred healthy individuals made up the control group: 50 men and 50 women. Controls ranging in age from 16 to 46 years for men and 20 to 50 years for women were chosen from the Blood Bank Unit at Morjan Hospital in Babylon, Iraq.

Genotypic identification using RFLP-PCR amplification

Genotyping of the research groups was performed using the RFLP-PCR method after DNA extraction from blood samples. DNA was extracted and purified from blood samples using a Taiwan-sourced fumigant extraction and purification kit. Amplification of the targeted DNA regions was performed using particular primers to identify MIR196A2. The primers used for this purpose were obtained from Bioneer and IDT DNA (USA). The forward primer sequence, 5'- CCCCTTCCCTTCTCCTCCA -3', and the reverse primer sequence, 5'- CGAAAACCGACTGATGTAAC -3', were used in the experiment.

Polymerase chain reaction (PCR) was performed with reaction amounts of 20 μ L. Each reaction consisted of 1 μ L of the forward and reverse primers, 12.5 μ L of the Green Master Mix, 3 μ L of genomic DNA and 2.5 μ L of nuclease-free water. The amplification procedure was performed using a Biometra thermocycler manufactured in Germany. The thermocycler was programmed with the following parameters: an initial pre-denaturation step lasting 2 minutes at a temperature of 94°C, followed by a series of 30 cycles. Each cycle consisted of denaturation for 5 minutes at 94°C, annealing for 1 minute at 57°C, and extension for 1 minute at 72°C. Ultimately, a final extension period of five minutes was implemented. polymerase chain reaction (PCR) was analyzed using electrophoresis using a 1% agarose gel (Cleaver Scientific, UK) at a voltage of 75 V for a certain period of time. The bands obtained were visualized through the application of ethidium bromide staining. Photographs were captured using the gel documentation system developed by Cleaver Scientific, UK.

The amplicons obtained from the selected MIR196A2 sites were cleaved using the *MspI* restriction enzyme, and the RFLP-PCR was performed according to the methodology given by Promega.

Statistical Analysis

The chi-square test was used to assess the presence of statistically significant disparities between the case and control groups. This analysis included the examination of risk factors and the distribution of a single nucleotide polymorphism (SNP) between both the control and case groups, considering both dominant and recessive models. The

researchers employed logistic regression analysis to compute the initial odds ratio (OR) value and its corresponding 95% confidence interval (CI). All statistical analyzes were performed using the SPSS statistical program (version 25; SPSS Inc., Chicago, IL). A significance level of $p < 0.05$ was used to determine statistical significance.

RESULTS

The results revealed the presence of a single band (149 bp) of the target sequence of pre-MIR196A2 on agarose gel (Fig. 1).

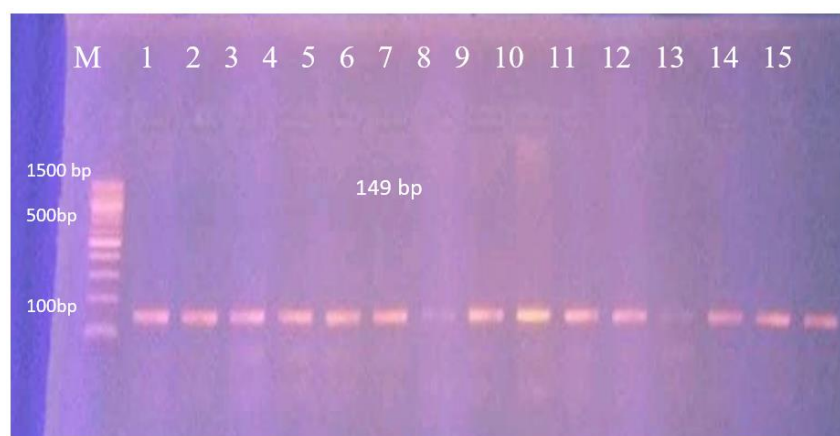


Fig. (1): Agarose gel electrophoresis of pre-MIR196A2 amplified product patterns

M stands for DNA size marker, and lanes 1-14 represent the amplified products (149bp) of the pre-miR-196a2 target sequence. Conditions for electrophoresis were 1% agarose concentration, 75V, 20 mA for 120 minutes. Precast ethidium bromide staining technique.

To examine miRNA genotyping (pre-MIR196A2; rs11614913 SNP) using PCR-

RFLP, the PCR products were cut with a restriction enzyme *MspI* (5' CCG 3') by the Promega company protocol table (1). Figure (2) illustrates the presence of three different allelotypes of pre-MIR196A2 (rs11614913 SNP): homozygous TC and CC and heterozygous TC resulting from a single nucleotide mutation (T C) at the *MspI* recognition site (Fig. 2).

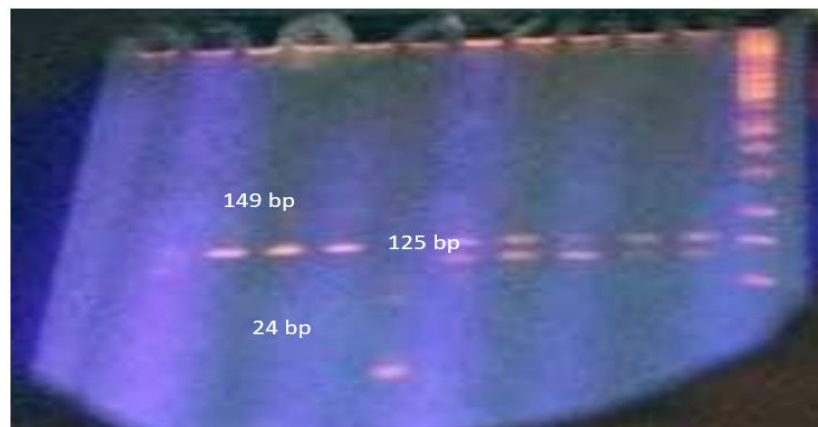


Fig. (2): gel electrophoresis of (rs11614913 SNP) using the *MspI* enzyme by the PCR-RFLP method

M: refers to DNA size marker; lanes 1, 2, and 4 refer to homozygous CC genotyping containing two bands (125 bp and 24 bp); lanes 7, 8, and 9 refer to homozygous T.T. genotyping having a single band (149 bp); lanes 6 refer to heterozygous T.C. genotyping containing three bands (149 bp, 125 bp, and 24 bp).

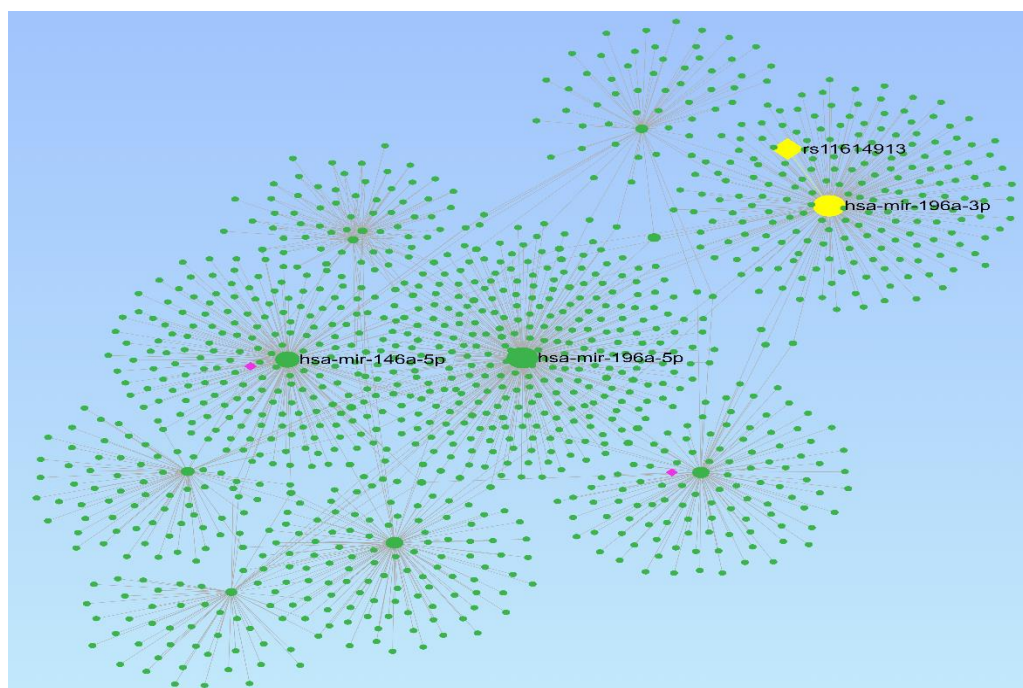


Figure (3) Transcriptional network mediated by *miR196a2* rs11614913 predicated by miRDB and TargetScan

Table (1): The present study investigates the distribution of genotypes for the miRNA196a2 rs11614913 T>C polymorphism and its association with susceptibility to thalassemia.

model	control	Case	or	CI 95	P value
Co-dominant model					
T.T.	65	50			
CC	30	40	1.73	(0.95-3.15)	0.07
TC	5	10	2.60	(0.83-8.09)	0.09
Dominant model					
TT	65	50			
TC+CC	35	50	1.85	(1.05-3.27)	0.032*
Recessive model					
TT+TC	70	60			
CC	30	40	1.55	(0.86-2.79)	0.13
Alleles					
T	135	110			
C	65	90	1.69	(1.13-2.55)	0.01*

Abbreviations: CI, confidence interval; OR, odds ratio, * P< 0.05 significant

Table (2) This study aims to conduct a stratification analysis to investigate the relationship between the miRNA196a2 rs11614913 T>C polymorphism and susceptibility to thalassemia.

model	TTTC Case-control	CC	OR	CI 95	P value
Age					
17-27	75	25			
28-38	50	15	0.90	(0.43-1.87)	0.77
39-49	55	30	1.63	(0.86-3.08)	0.12
Gender					
male	70	30			
Female	110	40	0.84	(0.48-1.48)	0.56
Resident					
Urban	130	60			
Countryside	50	10	0.43	(0.20-0.91)	0.025*
Comorbid condition					
Disease	20	5			
No diseases	150	65	1.73	(0.62-4.81)	0.28

Abbreviations: CI, confidence interval; OR, odds ratio, * P< 0.05 significant

Table 2 shows the results of the stratified analysis. No statistically significant differences were observed in the stratified analyzes conducted for age, gender, and other diseases. However, our resident case-control

analysis revealed significant differences.

DISCUSSION

The prevalence of hereditary diseases, such as hemoglobinopathies, including β -

thalassemia and sickle cell anemia, has been increasing in the Iraqi population. SNPs are prominent genetic variations that play a significant role in the development and progression of β -thalassemia. β -thalassemia is a diverse disease with varied clinical presentations in young and old patients [26,27]. Furthermore, determining the phenotype-genotype association is complicated due to modifying influences in thalassemia [28]. Several studies have recently examined the effects of 3'-UTR SNPs on gene expression. These findings suggest that miRNA-target SNPs are crucial in disease susceptibility [29].

Furthermore, computational techniques are essential in biomedical research to prioritize functional miRNA target SNPs. Bioinformatics analysis predicts probable and viable candidate SNPs for future experimental designs [30]. In this study, we examined the connection between micro-rs11614913 SNPs and β -thalassemia.

MiRNAs play a significant role in the maturation, proliferation, regulation, and expression of HbF genes within erythroid cells [31]. The principle of gene expression in β -thalassemia by miRNA poses significant challenges, and understanding its potential as a diagnostic indicator or therapeutic target is further compounded. Previous studies have shown that miRNA modulates the expression of the γ -globin gene in individuals affected by β -thalassemia through the regulation of transcription factors [32].

The diagnostic potential of miRNAs has been extensively explored in various diseases, including cancer, nervous system disease, immunological disease, and cardiovascular disease, due to their remarkable conservation and tissue specificity [33]. The discovery of miRNA-196a occurred almost ten years ago.

According to Ryan et al. [34], miRNA functionality can be modified by 29 SNPs, which activate miRNA transcription and process its precursors, ultimately leading to alterations in miRNA expression: The existing body of literature on miRNA 196a2 polymorphisms focuses primarily on the investigation of cancer-related aspects. According to the findings of Fawzy et al. [35], it has been observed that miRNA196a2 plays a significant role in the progression of gastric cancer. In a study conducted by Zhu et al. [36], it was observed that this particular microRNA (miRNA) has an association with colorectal cancer among the Chinese population.

In this study, changes in the MIR196A2 issue caused by variations in the rs11614913 SNP could lead to the development of thalassemia by changing the binding of MIR196A2 to its target informational RNA [37]. Another study found that the mutant genotype CC of rs11614913 was associated with increased production of mature miRNA196A2 and increased target informational RNA binding. Hu et al., [38] investigations revealed that the MIR196A2 rs11614913C allele was related to the T allele, indicating that the SNP in mature miRNA could result from the various informative RNAs required.

Based on the analysis of the gene expression profile, it was shown that all candidate genes exhibited expression in tissues affected by thalassemia, including the blood, spleen, heart, and liver by Stranger et al. [39]. This finding suggests that alterations in these candidate genes could impact the severity of reported phenotypic manifestations. Furthermore, these genes are involved in genomic characteristics such as antioxidant activity, oxidoreductase activity, peroxidase activity, and glutathione

transferase activity, which play a crucial role in protecting against oxygen free radicals and iron overload and reducing susceptibility to oxidative stress. Examining the relationship between genes and phenotypes also uncovers that disrupted candidate genes lead to abnormalities in heme biosynthesis and erythrocytes, as well as the appearance of splenomegaly and anemia [40].

MicroRNAs (miRNAs) also possess epigenetic capabilities, governing post-transcriptional developmental processes such as cellular proliferation, differentiation, metabolism, and apoptosis across several cell types [41]. Because microRNAs (miR) play a crucial role in orchestrating the maturation and proliferation of early erythroid cells, as well as regulating the expression of fetal globin genes and the enucleation process, it seems improbable that this regulatory mechanism would have an impact on erythrocytes. Furthermore, previous studies have shown that miRs can increase globin gene expression through overexpression. However, it was observed that miR-96 positively impacted the expression of globin genes. This was achieved by its ability to directly attach to the globin transcript, resulting in suppression of globin expression [42]. Consequently, inhibition of this inhibitory microRNA (miR) may lead to

increased fetal hemoglobin (HbF) production. Consequently, microRNAs (miRs) have the ability to enhance hematopoiesis in cases of anemia and certain hematologic disorders [43-44].

The findings of our research indicated a potential relationship between the miRNA196a2 rs11614913 T>C variant and susceptibility to thalassemia disease in a population of the middle and south regions of Iraq. However, when performing a stratified analysis, no statistically significant association was observed. One notable strength of this work was its novelty since it represented the initial investigation into the association between miRNA196a2 rs11614913 T>C and susceptibility to thalassemia.

However, certain limitations exist. The present study investigated the prevalence of thalassemia disease among hospitalized patients but was limited by the lack of data and the lack of long-term follow-up. Future studies, require a sustained effort to examine and evaluate these individuals. Additionally, it should be noted that this study was conducted in a single center. As discussed in the subsequent section, the presence of heterogeneity within the population may lead to varying outcomes.

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دراسة تعدد الاشكال الوراثي في ار ان اي المايكروي 196a2 في مرضى التلاسيميا في سكان وسط وجنوب العراق

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الملخص

الخلفية والاهداف: يُعرف بيتا ثلاسيميا على نطاق واسع بأنه مرض وراثي منتشر. تتميز الحالة بانخفاض أو غياب تخليق سلسلة جلوبين محددة، مما يؤدي إلى تطور درجات متفاوتة من فقر الدم الانحلالي. تلعب MicroRNAs (miRNAs) دورًا مهمًا في إعادة تنشيط تعبير الجلوبين لدى الأفراد المصابين بالتلاسيميا. وكان هدف الدراسة: تبحث هذه الدراسة في تعدد أشكال miRNA 196a2 لدى الأشخاص المصابين بالتلاسيميا.

منهجية الدراسة: يتكون البحث الحالي من 100 فرد تم تشخيص إصابتهم بالتلاسيميا بالإضافة إلى عدد مماثل من عينات السيطرة. تم جمع عينات من المرضى في مركز التلاسيميا في مستشفى بابل في الفترة من مايو 2021 إلى أغسطس 2021 .

النتائج: تظهر نتائج الدراسة الحالية وجود ارتباط كبير بين الأشخاص الذين يمتلكون النمط الجيني النموذجي السائد (TT, TT+TC) وزيادة القابلية للإصابة بمرض التلاسيميا، مقارنة بالمرضى ذوي النمط الجيني المتنحي (CC, TC+TT) قيمة $P = 0.032$ ، $OR = 1.85$ ، $95\% CI (1.05-3.27)$

الاستنتاجات: يمثل هذا البحث الفحص الأولي الذي يثبت وجود علاقة بين تعدد الأشكال النوكليوتيدات المفردة (SNP) rs11614913، والتلاسيميا. تفترض هذه الدراسة أنه قد يكون هناك ارتباط بين rs11614913 T>C miRNA196a2 البديل T>C والقابلية للإصابة بمرض بيتا ثلاسيميا في وسط وجنوب العراق. تشير النتائج إلى أن الاختلافات في المواقع المستهدفة لأشكال النوكليوتيدات المفردة (SNP) miRNA rs11614913 داخل الجينات المرتبطة بالتلاسيميا قد تلعب دورًا في تعديل شدة أنماط التلاسيميا الظاهرية.

الكلمات الدالة: بتا ثلاسيميا، تعدد الاشكال الوراثي، الرنا المايكروي، rs11614913.

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