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A Review: The Role of SNPs in HBB, BCL11A, HBS1L-MYB, and miRNA Networks in Beta-Thalassemia: Insights from Iraqi and Asian Populations

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ABSTRACT

Objective: *Beta-thalassemia is a genetically heterogeneous blood disorder marked by impaired hemoglobin synthesis, resulting in chronic anemia, multi-organ complications, and changing clinical severity. This review analyzes the essential functions of single-nucleotide polymorphisms (SNPs) in the HBB, BCL I IA, and HBS I L-MYB genes, as well as miRNA regulatory networks, in influencing beta-thalassemia phenotypes, particularly in Iraqi and Asian populations.* ***Method:*** *Many research investigations conducted across Iraq and Asia have highlighted the elevated prevalence and pathogenic significance of the HBB rs334 mutation, which acts as a primary genetic determinant of the disease in these regions. Additionally, regional studies have shown strong statistical links between BCL I IA variants (rs1427407, rs11886868) and HBS I L-MYB variants (rs4895441, rs9399137) and higher levels of fetal hemoglobin (HbF).* ***Results:*** *This leads to milder phenotypes, less need for transfusions, and better clinical outcomes. These results demonstrate the vital role of genetic modifiers in influencing disease severity. Moreover, the dysregulation of microRNAs—specifically miR-144/451, miR-15a/16-1, and miR-210—has been demonstrated to impact erythropoiesis, hemoglobin switching, and inflammation, thereby further influencing disease progression. According to epidemiological statistics from the World Health Organization and recent studies, the prevalence of beta-thalassemia in Iraq is around 37.1 per 100,000 individuals, with a carrier rate varying from 1.5% to 3% in different Asian areas and peaking at 20% in some ethnic groups. Up to 20% of patients with beta-thalassemia major in Iraq are co-infected with hepatitis C virus owing to their blood transfusion requirements, underscoring the critical need for comprehensive prevention measures.* ***Novelty:*** *The combination of genetic markers and miRNA profiles makes it possible to use personalized diagnostic and treatment methods, especially gene- and miRNA-based therapies that target specific molecular pathways. This review underscores the necessity of tailoring genetic counseling, screening, and management strategies to accommodate unique regional genetic backgrounds and modifier effects, thereby promoting precision medicine and enhancing the quality of care for beta-thalassemia patients in Iraq, Asia, and analogous populations internationally.*

INTRODUCTION

Thalassemia is a genetic blood disorder marked by defective hemoglobin synthesis or diminished hemoglobin production. Thalassemia is a genetic disorder transmitted from one's progenitors. The term "thalassemia" derives from the Greek word "thalasse", or "sea," since this hereditary illness was first recognized in the Mediterranean area. There are two main types: alpha thalassemia and beta thalassemia; both variants are often seen.

Inherited in an autosomal recessive manner, many causative genes are present, with the *HBB* gene, located on the 11th chromosome, and the *HBA IF* gene on chromosome 16 being the most prominent. Which genetic alterations are most critical for identifying thalassemia? The severity of alpha and beta thalassemia depends on the number of missing genes, namely four for alpha globin and two for beta globin. genetic hemoglobin (Hb) problems are categorized into two types: hemoglobinopathy, which results from structural abnormalities in Hb, and thalassemia, which arises from defective globin production, often of normal organization; both are passed on in a way that is autosomal recessive [1]. The disorder is classified as "alpha, beta, delta-beta, gamma-delta-beta, delta, and gamma thalassemia, based on the specific globin chains implicated in impaired biosynthesis. For example, α- and β-thalassemia demonstrate a shortfall in the production of α- and β-globin chains, respectively [2]. Thalassemia is widespread in several locations worldwide, notably Southeast Asia, the Indian subcontinent, and Africa. The growth in migrant populations in areas like the United States, Europe, Australia, and New Zealand, in particular, has resulted in a heightened incidence of thalassemia in recent years. It is projected that 70,000 infants would be born each year with various kinds of thalassemia [3].

It is estimated that over 7% of the global population has thalassemia. This poses a considerable issue in tackling the worldwide spread of this disease, particularly in Iraq, requiring alerts and preventative strategies against intimate relationships among individuals who are carriers of thalassemia-related genes [4]. Beta-thalassemia is a heterogeneous disorder characterized by varied severity resulting from distinct genetic abnormalities, ranging from asymptomatic thalassemia minor to severe thalassemia major, which requires regular blood transfusions and iron chelation treatment to manage anemia and iron overload. Stem cell and bone marrow transplantation may provide benefits for some thalassemia patients; nevertheless, its implementation is limited by substantial expenses, a scarcity of donors, and the potential for immunological problems [5]. Individuals with beta thalassemia may have organ difficulties, especially in the heart and liver, leading to iron overload. Chelation treatment may provide support [6]. After molecular biology highlighted the importance of miRNAs, their importance in the pathophysiology of beta thalassemia became clear. MicroRNAs are diminutive, non-coding RNA entities that modulate transcription by adhering to complementary sequences in the 3' untranslated regions (UTR) of targeted messenger RNAs (mRNAs), leading to degradation or translational inhibition. There are several miRNAs with altered patterns in beta thalassemia, affecting many processes, most notably the body's response to stress, red blood cell formation, and hemoglobin production [7].

Remarkably, miRNA-210 was upregulated in hypoxic conditions in thalassemia patients, whereas miRNA-451 was associated with hemoglobin production and erythroid differentiation [8]. MiRNA-155 expression is also altered in beta-thalassemia, and it plays a key role in regulating immune responses and erythropoiesis. "MiRNA-96 certainly suppresses the synthesis of γ-globin, a major component of fetal hemoglobin. This repression certainly plays a major role in inhibiting fetal hemoglobin expression during adult red blood cell formation [9].

In addition, microRNA-150 is considered to regulate alpha-globin gene expression, which has the potential to control the balance of the globin chain associated with the beta thalassemia chain [10]. These findings shed light on miRNA-based therapies, opening new avenues for innovative therapeutic strategies.

This review will look at the role of miRNAs in the pathogenesis of beta-thalassemia, with a focus on their use as treatment targets and biomarkers. We want to get an understanding of how miRNAs affect disease development and their future implications for beta-thalassemia treatment as studied in current research.

RESEARCH METHOD

1.1 Beta Thalassemia Overview

Beta-thalassemia is defined as a monogenetic hematological disorder characterized primarily by a low level of functional hemoglobin, which is caused by a mutation or deletion in at least one globin gene [11]. This hereditary disorder specifically leads to defective production of the beta globin chain of the adult hemoglobin, which affects multiple organ systems. The main consequences include inefficient erythropoiesis, persistent hemolytic anemia, and hemosiderosis-driven organ damage. To treat beta-thalassemia patients, regular blood transfusions are used; however, this therapy might result in hepatic and cardiac hemosiderosis, which is known as one of the most prevalent causes of mortality in these patients [12]. There are three types of this condition: carrier, intermediate, and major status. Beta-thalassemia severity is mainly correlated to the degree of α-globin chain excess, which accumulates in the red blood cell precursors and leads to mechanical and oxidative damage (insufficient erythropoiesis) [13]. Figure 1 depicts the arrangement of the human β-globin gene cluster situated on Chromosome 11, together with the regulatory components of a standard β-globin gene.

The gene has many regulatory regions at both termini: CCAAT box and TATA box. Promoter elements located at the 5′ end are essential for the commencement of gene transcription.

Enhancer: Located at the 3′ end, it augments transcription efficiency.

The gene comprises exons (E-I, E-II, E-III) shown in purple and turquoise, which encode the protein, and introns, which are non-coding regions interspersed between the exons.

Numerals (1–30, 31–104, 105–146) denote the nucleotide locations corresponding to each exon.

Illustrates the configuration of the β-globin gene cluster inside a 60 kb segment on Chromosome 11. Genes are arranged in the following sequence (from 5′ to 3′):

- Epsilon (epsilon, embryonic hemoglobin)
- Gγ, Aγ (gamma, fetal hemoglobin)
- ψβ1 (pseudogene β-globin, non-functional)
- Delta (delta, minor adult hemoglobin)
- Beta (beta, principal adult hemoglobin)

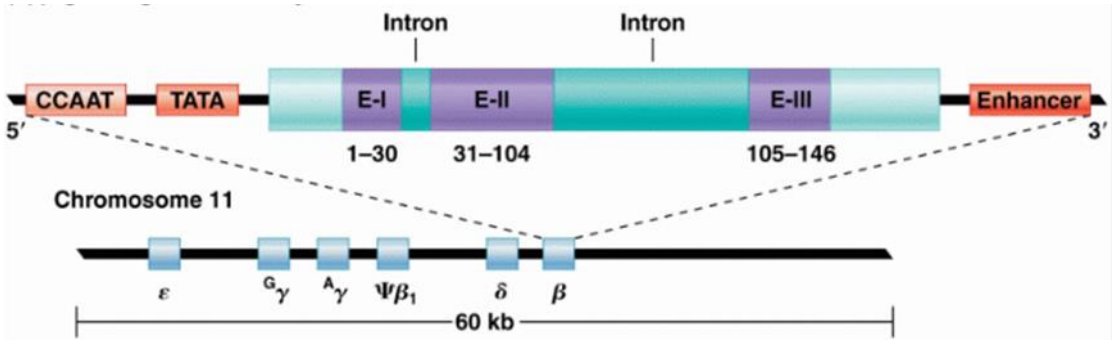

Figure 1. Structure of the genes encoding the beta globin [19].

1.1.1 Epidemiology

The World Health Organization stated that almost 40,000 infants have beta thalassemia each year, with around 25,500 having a transfusion-dependent beta-thalassemia in 2008. Annually, an expected number of newborns with beta-thalassemia account for about 341 in North, South, and Central America, 9914 in the Eastern Mediterranean, and 20,420 in Southeast Asia [14], which means beta-thalassemia primarily occurs in populations of Southeast Asia, Southern Europe, India, and Africa. The actual prevalence of significant hemoglobin mutation carriers approximated 5-7% of the worldwide population [15].

In Tunisia, beta-thalassemia major constitutes one of the most prevalent hereditary diseases. The true prevalence of this condition is unknown, but it is believed that 4.48% of the Tunisian population has this condition [16]. According to statistical data, in China, major and intermediate thalassemia are observed in around 300,000 Chinese children. In the 1980s, the first surveys were conducted in mainland China. The incidence of thalassemia in china show a wide variation; more than 200 million individuals are believed to be affected with both type alpha and beta-thalassemia, with the incidence rate approximately 4-15% and 1-6%, respectively. In various regions of southern China, the epidemiological rate of globin gene deficiency involved in thalassemia ranges from 2.5% to 20%. Nevertheless, Guangdong and Guangxi demonstrate a high prevalence rate, which account around 10% and 20%, respectively, with the incidence rate of thalassemia cases in both provinces estimated at over 40% of all Chinese thalassemia cases [17].

The incidence rate among Arab people differs by country; the carrier rate in Arab countries ranges from 1%-11%, and the total number of mutations in various Arab countries also differ, ranging from 44 mutations in the USA and 10 in Saudi Arabia. With regard to Iraq, according to statistical data, the incidence rate of thalassemia had elevated from 33.5 per 100,000 in 2010 to 37.1 per 100,000 in 2015, whereas the prevalence rate demonstrates a significant decrease from 72.4 per 100,000 to 34.6 per 100,000 live births in the period between 2010 and 2015 [18].

1.1.2 Clinical Classification (major, intermediate, trait)

There are three identified hematological and clinical manifestations that differ in their severity: major beta-thalassemia, intermedia beta-thalassemia, and minor or trait beta-thalassemia [20]. Beta-thalassemia major is the most serious kind of thalassemia, which is also called Cooley's anemia. It occurs in people who either have a homozygous (B+/B0, B0/B0) or compound heterozygous (B+/B+) for more severe beta-globin mutations. Typically, it takes six months to two years to be induced [21]. Due to deficient HbA synthesis in the three to four months of life, patients who have a homozygous β0-thalassemia frequently demonstrate severe anemia. However, based on the HbF

production and the kind of mutations, the necessity for transfusion might be deferred up to two years. Patients who undergo insufficient transfusion therapy may develop a thalassemic facial characteristic (e.g., frontal bossing, low nasal bridge, and maxillary hyperplasia), hepatosplenomegaly, growth retardation, hypersplenism, and bone changes due to bone marrow expansion [22].

The second type of beta-thalassemia, known as beta-thalassemia intermedia (TI) OR non-transfusion dependent thalassemia (NTDT), refers to patients who don't require a regular transfusion to survive throughout life; nevertheless, they may need them occasionally or even frequently within particular clinical settings and typically for defined periods of time (infection, surgery, pregnancy, etc.). Beta-thalassemia intermedia is a medical disorder of moderate severity between a symptomatic beta-thalassemia minor and the severe major beta-thalassemia, which requires transfusion. It can be identified by a significant clinical polymorphism, which can be linked to its genetic heterogeneity [23]. The majority of patients with β-TI are either homozygous or heterozygous for beta-thalassemia, which indicates that both beta-globin loci are significantly affected, and this disease exhibits a recessive genetic pattern. Mutations that impact the beta-globin gene (HBB) are varied and range from slight promoter mutations (mild β+ thalassemia), which lead to a mild reduction in beta-globin chain production, through β+thalassemia, which leads to a significant decrease in this chain, to β0-thalassemia, which demonstrates a total absence of the beta-globin chain [24].

Finally, when only one copy of this beta-globin gene is affected (B0/B, B+/B), it is known as a beta-thalassemia trait or carrier; this condition primarily occurs during pregnancy or physiological stress as well as in childhood. This disorder is an asymptomatic condition that occasionally causes a mild anemia because of the defect in the erythrocyte morphology, and the Hb levels might be greater than 10 g/dl [22]. Beta-thalassemia trait is also defined as a heterozygous condition. Although the majority of these patients have no symptoms, they are identified inadvertently when their complete blood cell (CBC) count exhibits a sign of microcytosis [25].

RESULTS AND DISCUSSION

Molecular Mechanisms and Genetic Foundation of Beta Thalassemia

A. Regulation of Hemoglobin Synthesis

β-thalassemia results from polymorphisms that impair the synthesis of β-globin chains [26]. Over 400 causes of mutations have been identified. Unlike α-thalassemia, mostly attributed to extensive deletions, the majority of β-thalassemia variations arise from brief changes, typically consisting of single nucleotide substitutions and some deletions or insertions resulting in frame-shifting alterations, and this results in the production of an altered protein. Mutations producing β-thalassemia may impact every phase of expression, including gene transcription, mRNA preparation, translation of mRNA, and stabilization of proteins. Seventy-nine mutations are classified mostly based on the remaining synthesis of beta-globin. SNPs are categorized as mild or silent β-thalassemia variants when they cause mild to moderate reductions in the synthesis of beta-globin chains and β0 when they cause its total absence. The + or β++ polymorphisms relate to the transcription start site of the beta-globin gene (TATA box or CACCC) and the 5′ and the 3′ untranslated regions, or they affect the processing of RNA and the polyadenylation signal.β0 variants include start codon mutations, nonsense mutations, frameshift mutations, and alterations affecting the critical splicing of RNA or processing

sites [27]. Mutations in the beta-globin gene regulatory region are related to elevated Hb-F levels in comparison to other β-thalassemia polymorphisms. This is likely the result of a change in the competition between the gamma-globin promoters and beta-globin for interactions with the β-LCR control region. [28], [29].

The CD39 (CAG>TAG and) IVS I _110 (G>A) are prevalent variants in the regions of the Middle East and Mediterranean area, whereas the (TTCT) CD41/42 mutant is widespread in the Southeast Asian region, and the (G>C) IVS I -5 mutation is prominent in South Asia [30]. The GAG >AAG mutation in the CD26 gene, prevalent across Asia, particularly in Southeast Asia, activates a cryptic splicing site, leading to diminished generation of beta E- globin mRNA capable of translation and formation of the structurally defective beta E-globin chain, which combines with α chains to create hemoglobin E (Hb-E, α2βE2) [31]. In Figure 2, mutations affecting the beta globin gene, besides adding to the δ-, γ-, and E-globin, may infrequently cause beta thalassemia [26].

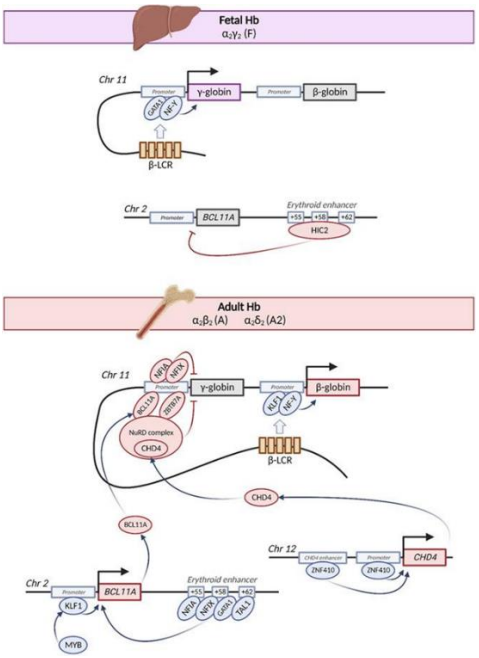

Figure 2. The regulation of the production of hemoglobin from fetal Hb to adult Hb [26].

Removals that eliminate the formation of fetal (γ) β-like chains of globin are composed exclusively of existing documented in the case of heterozygosity, perhaps due to the lethality of identical deletions during early gestation [32]. Heterozygosity presents clinically as self-resolving newborn bleeding and anemia of varying degrees, occasionally necessitating blood transfusions. It advances in adulthood to the hematology phenotype of thalassemia trait, which is characterized by typical levels of HbA2 and HbF [33].

Besides deletions, uneven transit and recombination caused by the misalignment of chromosomes that are identical throughout meiosis may generate unusual hybrid globin genes, leading to atypical types of thalassemia. An internal fusion occurs between the 5' terminus of the delta-globin gene and the 3' terminus of the gene for beta-globin, resulting in Hb Lepore. The hemoglobin (α2[δβ]2) is the merged δ-globin integrated to stabilize and function, and it is known as Hb Lepore.

However, expression of the defective β-globin chain is regulated by the δ-globin activator, showing about 2 to 3% of the activity compared to the β-globin promoter,

leading to a temporary production of this hemoglobin, causing sickle cell anemia in the recovered cases. On the other hand, the integrated β-globin sequence, which pairs with α-globin to generate Hb anti leukemia, is regulated by the beta globin promoter and produces large quantities [34]. While β-thalassemia is typically transmitted as a recessive disorder, it may, on rare occasions, be inherited dominantly. Certain β-globin chain variations, although being produced in normal quantities, show significant instability and fail to assemble stable and functioning hemoglobin tetramers.

These gene mutations show a dominant negative impact, resulting in beta-thalassemia trait even when only one copy is present. In some cases, beta-thalassemia is attributed to mutations beyond the beta-globin gene region. Mutations in the typical transcription factor *TFIIH* gene may lead to beta-thalassemia in association with photodermal sclerosis and trichothiodystrophy. Furthermore, mutations in erythrocyte-specific transcription factor genes such as *KLF I* and *GATA1* can disrupt globin-forming expression of genes, leading to the beta-thalassemia trait. Recently, mutations in the *SUPT5H* gene, which regulates transcription and mRNA processing by the RNA polymerase II, have shown to be linked to the development of the beta-thalassemia trait [35]. Aberrations in the 11p15 chromosomal region influencing β-globin expression in certain erythrocyte populations were identified as an uncommon cause of β-thalassemia when seen in individuals with a constitution hybrid genotype for a β-thalassemia mutation [36].

Furthermore, monoallelic partial inheritance involving chromosome 11p among beta-thalassemia carriers has been recognized as an underlying contributor to β-thalassemia major [37]. Infrequently, Congenital mutations of the somatic beta globin region may be associated with myelodysplastic syndromes [38].

B. Modifier Genes and SNPs in β-Thalassemia

Beta thalassemia is one of the most prominent chronic hereditary blood diseases due to the variability of its clinical symptoms, which differ from one patient to another depending on the genetic mutations and the multiple modified genes associated with it. This variation among patients is due to the presence of more than one primary mutation in the *HBB* gene and several other genes. These genes and SNPs play an important role in determining the patient's clinical condition [39]. I will now start a review of the genes to be examined in our study. I shall begin with the *HBB* gene. This gene is considered the direct genetic cause of the disease and is responsible for producing the beta chain in the hemoglobin protein, which is found in red blood cells and is essential for oxygen transport [40]. Mutations in it include many SNPs, the most important of which is the rs334 variant. This variant alters a nitrogenous base, which disrupts the hemoglobin structure and can lead to beta thalassemia and sickle cell anemia by inserting or deleting an amino acid in the chain. This change reduces the efficiency of oxygen transport in the blood [41]. Iraqi and Asian studies have shown a strong statistical significance for the rs334 variant in its association with the genetic symptoms observed in beta, while its effects have varied in some European and African countries as well. However, its direct impact on hemoglobin disorders and the determination of disease severity is most evident [42].

The *BCL I I A* gene is considered a major regulator of fetal hemoglobin (HbF) production, as it works after birth to gradually inhibit HbF, allowing the body to start

producing adult hemoglobin. The mutations that occur in it increase the level of fetal hemoglobin, which alleviates the symptoms of beta thalassemia [43]. Extensive studies in Iraq, India, Pakistan, and other Asian countries have proven that the variants rs1427407 and rs11886868 have a clear and statistically significant moderating effect on the severity of beta-thalassemia by increasing the level of fetal hemoglobin (HbF) in the blood [44], [45], [48]. One of the studies in Kurdistan, Iraq, showed that the modified alleles in this gene explain about 14% of the variation in HbF levels among patients [46]. Meanwhile, an Indian study and another Pakistani study showed a high statistical significance ($p < 0.01$), confirming that carriers of these SNPs exhibit less severe symptoms and require fewer blood transfusions. [44], [47].

There is a region between the *HBS I L* gene and the *MYB* gene where a mutation occurs in a nitrogenous base. The *HBS I L* gene regulates the survival and maturation of blood cells, helping to control their survival and development. Some studies suggest that it has an indirect role in regulating the gene expression of other genes related to hemoglobin [50]. Meanwhile, the *MYB* gene is considered a major transcription factor called MYB-c, which is the primary driver of the growth and proliferation of blood cells and the regulation of fetal hemoglobin production. The *HBS I L-MYB* (HMIP) region performs a crucial function in promoting the synthesis of fetal hemoglobin and modifying the severity of beta thalassemia, as genetic mutations here increase the HbF level, thereby improving the clinical condition of patients for the better, especially among Asian populations [49]. Asian studies, particularly in Indonesia, Thailand, Iraq, Pakistan, and some regions of Asia, have shown a clear statistical significance for the variable rs4895441 in modifying HbF levels and the severity of symptoms in beta-thalassemia patients. [51], [52]. As for the variable rs9399137, despite the strong statistical significance in some Asian groups, Iraqi studies have not yet proven any clear and independent effect. Instead, it showed limited statistical significance among the local populations compared to other modified genes such as *BCL I I A* and *HBB* [54], [55]. However, these SNPs have shown varying effects on disease severity in Egypt and some other countries [52], [56].

The BMP6 gene is responsible for regulating the distribution and absorption of iron in the body. It is considered an indirect factor affecting the iron status in beta-thalassemia patients. Therefore, any disorder in it affects the iron stores in the organs, but it is not considered a primary factor in the severity of the disease itself [50]. Several studies in Iraq, Asia, and the Middle East have not proven a significant statistical association of rs17557 with the severity or symptoms of beta-thalassemia among the populations of these regions [57], [58], [59]. International and regional evidence has converged on the fact that its primary role is related to regulating iron balance without directly affecting the severity of the disease itself [60]. Through this review, it becomes clear that the analysis of modified genes and SNPs associated with beta-thalassemia provides a clear scientific explanation for the variation in the severity of the disease symptoms and highlights the importance of *BCL I I A, HBS I L-MYB (HMIP),* and *HBB*, as well as their statistical significance in Iraq and Asia. The comparison with global studies confirms that the impact of these modified

Genes vary from one place to another depending on the genetic backgrounds of the populations, leading to the need to update specific programs for diagnosis and genetic counselling according to local results for each region.

Table 1. The effect of SNPs on HbF in beta-thalassemia modifying genes in different areas and their statistical significance.

Genre	Genetic Variant	(P-Value)	The effect on HbF/severity of the disease	Region	References
HBB	**rs334**	<0.001	Major (Cause of disease)	Iraq, Asia	[47] [46] [48]
BCL I I A	**rs1427407**	<0.01	Raising HbF, alleviating symptoms	Iraq, Asia	
BCL I I A	**rs11886868**	<0.01	Raising HbF, alleviating symptoms	Asia, Europe	[51] [53] [54]
HBS I L-MYB	**rs4895441**	<0.05	Raising HbF	Asia	
HBS I L-MYB	**rs9399137**	Differentiated	Raising HbF especially in Asia	Iraq, Asia	[59] [60] [61]
BMP6	**rs17557**	>0.05	No apparent effect	Iraq, Asia	[56] [63] [65]

This table shows the ranking of SNPs according to the strength of their statistical significance and their clinical importance based on the results of local (Iraq), regional (Asia), and international studies. This classification shows researchers and interested parties the priorities for genetic analysis in population studies and identifies the factors most affecting the severity of beta-thalassemia symptoms. The table also reveals that mutations in both the BCL I I A and HBS I L-MYB genes show stronger significance in some regions of Asia and Iraq, while the HBB gene remains the main causative factor globally. However, it has not been extensively studied in Iraq.

On the other hand, the table shows that the effect of the BMP6 gene on most of the studied populations does not reach the statistical significance that indicates its impact on the disease. The importance of this arrangement in the table and shown in Figure 3 is highlighted to support diagnostic and research decisions, as well as to guide future therapeutic strategies according to the priorities of the geographical region. With this analytical approach, the evaluation of genetic determinants in beta thalassemia becomes more accurate and reflects the genetic differences among populations in different regions, thereby enhancing the prediction of high efficacy for treatments and genetic counselling in the fields of modern medicine.

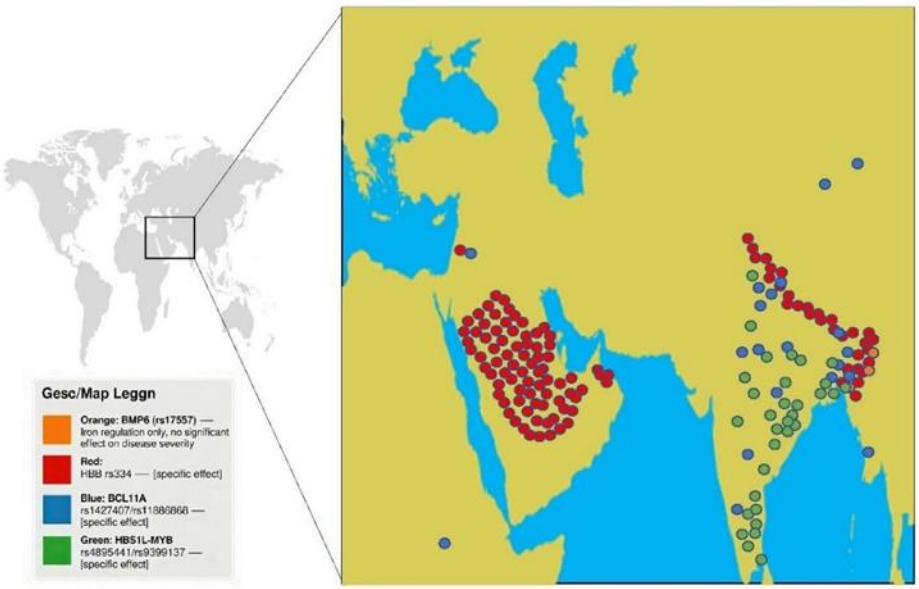

Figure 3. Geographic distribution of gene mutations associated with beta-thalassemia according to the effect of each SNP for specific Asian regions [created by the author].

C. MicroRNAs and Their General Role in Gene Regulation

miRNAs recognize short, often imperfectly complementary target sites—typically within the 3′ untranslated regions (3′UTRs) of mRNAs—and repress protein output via translational inhibition and mRNA degradation [61], [62]. A single miRNA can target hundreds of mRNAs, while most mammalian protein-coding genes are regulated by at least one miRNA. Because of this wide range of connections, miRNA can fine-tune gene expression instead of just turning it on and off. They control how cells grow, change, die, and respond to stress. When they don't work right, they can cause cancer, heart disease, neurological diseases, and immune diseases. [62], [63]. By having such a wide effect, miRNA helps maintain homeostasis and makes gene networks more stable by buffering transcriptional noise and allowing for precise control of protein expression levels. Because of this, their disruption leads to disease phenotypes, making miRNA both biomarkers and targets for treatment [63].

D. Scientifically identified miRNA in beta thalassemia

The role of miRNA in the pathogenesis of beta thalassemia

miRNAs play an essential regulatory function in the etiology and exacerbation of beta thalassemia by modulating the expression of miRNA may disrupt the formation of normal red blood cells, leading to ineffective erythropoiesis and exacerbating anemia [64]. Some miRNAs stop important genes that help make fetal hemoglobin (HbF), while others boost pathways that help people with thalassemia who have trouble making beta globin [69].

Moreover, miRNAs may influence inflammation, oxidative stress, and iron metabolism, all of which exacerbate the severity of the illness and its repercussions in individuals with beta-thalassemia. Certain markers are regarded as essential indicators of illness development and are under investigation as potential targets for forthcoming medicines and diagnostic instruments [65]. Generally, miRNAs have considerable influence on red blood cell development, globin switching, and the regulation of the genetic and epigenetic processes associated with beta-thalassemia [66].

Statistical Identification of Selected microRNAs in Beta Thalassemia

MicroRNAs are diminutive regulators that modulate gene activity and expression. In beta-thalassemia, several microRNAs display aberrant patterns, resulting in many changes, including modifications in red blood cell formation, inflammation, and tissue integrity [76]. The table illustrates: 2 Recognizing these patterns and comprehending their implications facilitates improved diagnosis and novel therapy methods for beta thalassemia.

Table 2. Essential microRNAs and their biological functions in beta thalassemia.

miRNA	Main Target(s)	Impact on Beta Thalassemia	Expression Change	Biological Aspects	References
miR-125a/b	Hematopoietic differentiation genes	Marker for severity; affects anemia/hemolysis	Down	Controls hematopoietic stem cell differentiation and apoptosis	[64]
miR-126	Vascular integrity, angiogenesis	Modulates vascular complications; myocardial protection	Down	Regulates angiogenesis, endothelial cell function	[65]
miR-155	Immune/inflammation genes, *c-Myb*	Promotes inflammatory, immune complications	Up	Immune response modulates inflammation	[65], [66]
miR-150	c-Myb, B-cell differentiation	Inhibits erythropoiesis, B cell maturation, and immune modulation	Down / Up	Governs B and T cell differentiation, erythropoiesis	[64], [65]

miR-181a	Differentiation /immune genes	Regulates immune response and erythropoiesis	Down	Lymphocyte development, red blood cell differentiation	[65]
miR-223	Inflammation, sepsis markers	Biomarker for inflammation complications	Down	Myeloid lineage, neutrophil function, anti-inflammatory	[64], [65]
miR-144/451 cluster	*KLF I, Myc, α-* and *β-globin, BCL I I A*	Regulate erythropoiesis, suppress α/β-globin, HbF induction	Up/ Down	Regulates erythroid maturation, oxidative stress response	[64], [66], [67]
miR-29a	Apoptosis, fibrosis-related genes	Potentially regulates fibrotic response, iron metabolism	Down	Anti-fibrotic, controls extracellular matrix genes	[65]
miR-142-3p	Erythropoiesis, immune genes	Affects red cell differentiation and immunity	Down	Cytoskeleton regulation, hematopoietic cell development	[65]
miR-15a/16-1	*MYB*, cell cycle genes	Enhance γ-globin (HbF), inhibit ineffective erythropoiesis	Down	Promotes fetal hemoglobin production, cell cycle control	[68], [69], [70]

miR-34a	Cardiomyocyte genes, apoptosis	Cardiac function, sex-dependent effects	Down	Regulates apoptosis, DNA damage response	[65]
miR-451a	β-globin, α-globin, erythropoiesis genes	Induces α, β, γ-globin; marker of severity/iron overload	Down / Up	Erythropoiesis, response to oxidative stress	[64], [68], [71]
miR-9	*FoxO3, ROS* genes	Regulates ROS and red cell maturation; affects oxidative stress	Down	Controls red cell maturation, oxidative stress response	[65]
miR-146a	*NF-kB*, inflammation-related genes	Controls inflammation, sepsis biomarker	Down	Regulates immune tolerance, inflammation	[65]
miR-221/222	c-Kit, erythroid differentiation	Impairs erythropoiesis by targeting c-Kit	Up	Inhibits erythroid progenitor growth	[65], [72]
miR-17-92 cluster	*MYC, γ-globin*, cell proliferation	Induces γ-globin, proliferation	Up	Controls cell proliferation, fetal hemoglobin	[64], [73]
miR-29b	Fibrosis-related genes	Modulates fibrotic pathways	Down	Regulates collagen, anti-fibrotic action	[65]

miR-10a	Notch signaling	Associated with HPFH, gamma-globin/HbF regulation	Up	Differentiation of erythroid lineage, Notch signaling	[74]
miR-21	*PDCD4,* liver/heart fibrosis genes	Biomarker for iron overload, liver/cardiac complications	Down	Anti-inflammatory, tissue fibrosis regulation	[64]
miR-210	*EPO, hypoxia*, and iron-related genes	Inhibits erythropoiesis, response to hypoxia/oxidative stress	Up	Hypoxia adaptation, erythroid response, and iron metabolism	[64], [65], [67]
miR-96	*γ-globin* genes, HbF regulation	Promotes HbF expression	Down / Up	Induces fetal hemoglobin, erythropoiesis regulation	[64], [74]

The following table presents a selection of the most researched microRNAs in beta thalassemia patients, including their gene targets, biological roles, and influence on disease severity and treatment.

Therapeutic Approaches Using miRNAs in Beta Thalassemia

Contemporary therapy strategies for beta-thalassemia mostly emphasize the use of miRNAs to rectify the aberrant gene expression that leads to the production of defective red blood cells and hemoglobin by altering certain causative miRNAs. This is accomplished by using miRNA mimics to reinstate the advantageous function impaired by gene expression insufficiency(down), while inhibitors may attenuate the detrimental miRNAs associated with gene expression overactivity(up). This technique resembles the reactivation of fetal hemoglobin (HbF) production to offset beta-globin deficit [75], [68].

Preclinical studies have shown that important miRNAs, such as the miR-144/451 cluster, may significantly elevate HbF levels, while alterations to other miRNAs, including miR-15a/16-1 and miR-486-3p, can promote red blood cell functionality. These alterations specifically address the regulatory mechanisms affected in the principal genes of beta thalassemia [76].

Recent advancements in drug delivery methods, such as gene therapy and nanoparticle technologies, improve the viability of miRNA-based therapies by increasing specificity, stability, and targeted distribution to red blood cells. Although still in preclinical or early experimental stages, the combination of miRNA therapeutics with gene editing technologies like CRISPR-9 and modern pharmaceuticals holds considerable promise for improving outcomes and reducing the therapy burden for thalassemia patients in the future.

CONCLUSION

Fundamental Finding : This review has clarified the genetic and molecular foundations of beta-thalassemia, emphasizing its prevalence and diversity among Iraqi and Asian populations. The disorder is primarily attributed to mutations in the HBB gene, with the rs334 variant recognized as the principal causative factor due to its high prevalence and clinical relevance, especially in Iraq and Asia, where studies have demonstrated a significant statistical correlation ($P < 0.001$) between this mutation and disease manifestation. The significance of genetic modifiers was underscored by research on the BCL I I A gene, revealing that the rs1427407 and rs11886868 variants substantially increase fetal hemoglobin (HbF) levels and mitigate disease symptoms. Statistical data from Iraq, India, and Pakistan corroborate these results, demonstrating a clear and statistically significant association ($P < 0.01$) with less severe clinical outcomes and diminished transfusion requirements. The HBS I L-MYB region, especially rs4895441, was also moderately linked ($P < 0.05$) with increased HbF levels and less severe disease in Asian populations. The rs9399137 variant, on the other hand, had different statistical significance in different areas. The BMP6 rs17557 variant, on the other hand, was always shown to have no effect on disease severity (>0.05), and it mainly helps regulate iron. **Implication :** Epidemiological data indicate that the carrier prevalence of beta-thalassemia in Arab nations varies from 1% to 11%, with a significant rise in incidence in Iraq—from 33.5 to 37.1 per 100,000 between 2010 and 2015—while the prevalence among live births decreased from 72.4 to 34.6 per 100,000 during the same period. The results highlight the imperative for customized diagnostic, counseling, and therapeutic approaches that align with the genetic characteristics of local populations. The findings advocate for the incorporation of genetic and miRNA profiles in clinical practice to improve precision genetic diagnostics, individualized therapy, and effective management of beta-thalassemia, emphasizing the necessity for population-specific strategies in Iraq and Asia to maximize patient good outcomes. **Limitation :** While this study provides critical insights into the genetic factors influencing beta-thalassemia, it is limited by the scope of its data sources and the regional focus on Iraq and Asia. The findings may not fully apply to other geographic regions with differing genetic backgrounds. Additionally, the effects of the BMP6 gene variant on disease severity are inconclusive, and further research is needed to clarify its role in beta-thalassemia across different populations. **Future Research:** Future research should focus on expanding the study to other regions outside Iraq and Asia to better understand the global applicability of the findings. Additionally, more extensive studies on the role of microRNAs, including their upregulation and downregulation patterns, are necessary to explore their potential in influencing erythropoiesis, hemoglobin switching, immune modulation, and iron

metabolism. Investigating gene- and miRNA-based therapies could further optimize the management of beta-thalassemia and pave the way for precision medicine approaches globally.

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