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Research Article

Genetic Variation Detection of XmnI rs7482144 in Patients with Major and Minor β-Thalassemia Infected with B19 and HHV-6

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I N F O

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A B S T R A C T

Background: β-thalassemia is one of the most common inherited hemoglobin disorders worldwide and is characterized by reduced or absent β-globin chain synthesis, resulting in chronic hemolytic anemia.. The XmnI polymorphism (rs7482144, c.−211 C>T) in the promoterregion of the HBG2 gene is a well-established modifier of fetal hemoglobin (HbF) production and disease severity in β-thalassemia patients. Patients with thalassemia may also be at increased risk of viral infections, including Parvovirus B19 (B19) and Human Herpesvirus 6 (HHV-6), due to repeated blood transfusions and immune dysfunction.

*Objectives***:** This (1) determines the allele and genotype frequency distribution of XmnI rs7482144 in β-thalassemia patients compared to healthy controls, (2) assess association between the XmnI rs7482144 SNP and susceptibility to B19 and HHV-6 viral infections, and (3) examine relationship between this polymorphism and demographic characteristics, including age and sex.

*Methods***:** We analyzed 308 specimens, including 208 from patients with beta-thalassemia major or minor, recruited from beta-thalassemia centers in the Middle Euphrates region of Iraq, and 100 from apparently healthy controls. DNA was extracted using the G-Spin™ Total DNA Extraction Mini kit, and viral genomes using the Patho Gene-spin™ kit. Genotyping of XmnI rs7482144 (HBG2, c.−211 C>T) was performed by Sanger sequencing on a representative subset of 50 samples (30 β-thalassemia patients and 20 controls) selected based on DNA quality and disease-group representation. Statistical analyses included the calculation of allele and genotype frequencies, estimation of odds ratios (ORs) with 95% confidence intervals (CIs), Hardy–Weinberg equilibrium testing, and chi-square tests.

Results: The A (T) allele of XmnI rs7482144 was significantly more frequent in thalassemia patients than controls (OR=3.56, 95% CI: 1.02–15.67, p=0.023), while the G (C) allele was predominant in the control group (OR=0.28, p=0.023). No significant association was found between rs7482144 genotype and B19 infection status (X^2=3.915, p=0.141) or HHV-6 infection status (X^2=0.380, p=0.827). No significant

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associations were observed between the SNP and patient age or sex.

Conclusions: The XmnI rs7482144 polymorphism is significantly associated with β-thalassemia susceptibility and serves as a relevant molecular marker for phenotypic modification through HbF upregulation. However, this SNP does not influence susceptibility to B19 or HHV-6 viral infections, which are instead driven by transfusion-related exposure and immune dysfunction. These findings highlight the need for routine screening for viral infections in all thalassemia patients, irrespective of their HBG2 genotype.

Keywords: ββ-thalassemia, XmnI rs7482144, polymorphism, HBG2, B19, HHV-6, genetic modifier

Introduction

Thalassemia is an inherited blood disorder caused by mutations in the alpha, beta, and delta globin genes, leading to impaired production of haemoglobin and ultimately resulting in ineffective red blood cell production (erythropoiesis). It has been classified by the World Health Organisation (WHO) as a major global public health concern and is included in several datasets used to assess the global burden of disease. In developing countries, the vast majority of afflicted children die before they turn five years old; however, carriers of the gene in developed countries often suffer from chronic medical complications. Thalassemia accounts for 3.4% of all deaths among children under five years of age worldwide, with this statistic figure increasing to 6.4% in Africa.[1] The global prevalence of thalassemia is estimated to be 4.4 per 10,000 live births. Thalassemia is an autosomal recessive inherited disorder that is transmitted independently of sex.[2]

Thalassemia should be considered in patients with microcytic anemia when ferritin levels are either normal or elevated. Clinical manifestations of thalassemias may vary greatly from no symptoms at all to requiring transfusions and/or other forms of ongoing medical treatment. The characteristics of thalassemia subtypes can generally be identified using hemoglobin electrophoresis; however, genetic testing is necessary to confirm the diagnosis. Regular blood transfusions and iron chelation therapy are effective treatments for improving the prognosis of patients with homozygous β-Tthalassemia. Meanwhile, life expectancy for individuals with homozygous β-thalassemia is considerably greater now than ever before, reaching around 30 years of age, -- up from the previous 10 years of lifespan.[3] Early diagnosis and treatment of this disease remain problematic primarily due to a lack of education and awareness regarding both the genetic basis of thalassemia and its possible associated risks to the general public and healthcare providers.[3,4]

Various viruses can integrate into the host genome either through their own replication mechanisms or through host cell–mediated recombination processes.HHV-6 is a common DNA virus. HHV-6 has been recognized as having two types: HHV-6A and HHV-6B. Infection with either of these two viruses usually occurs in children younger than 3 years of age. The most common presentation is fever and rash, although complications such as febrile seizures and encephalitis may occur. Both viruses cause lifelong persistent infection. In addition, both HHV-6A and HHV-6B are able to reactivate, and will do so by rapidly replicating the viruses. The roles of the reactivated human herpes virus type 6 (HHV-6) have been demonstrated in cases involving encephalitis and/or graft rejection among transplanted patients. Within latently infected cells, HHV-6A and HHV-6B establish permanent integration of the viral genome specifically into the telomeres of the infected cell's chromosomes. This is an apparent means of preserving these viral genomes throughout latency for both HHV-6A and HHV-6B.[5,6]

Parvovirus B19 is typically transmitted by droplet transmission (e.g., sneezing, coughing, etc.) means.[7,8] Children are likely to become infected with parvovirus B19 in group settings such as daycares or schools.[9,10]

Parvovirus B19 can be transmitted across the placenta from mother to the unborn fetus, which may potentially cause hydrops fetalis or fetal demise.[11] Blood products can also be a source of parvovirus B19 transmission, although this occurs relatively infrequently. Parvovirus B19 is known to have seasonal peaks in terms of infection (early summer), with pandemics occurring approximately every 4-5 years. The greatest risk of transmission exists just prior to the appearance of the rash when the highest amount of virus is present in the host's bloodstream. In general, B19 infections in immunocompetent persons are self-limited and do not result in any significant morbidity. Acute cytopenia and aplastic crisis may develop in individuals with impaired hematopoiesis, or with decreased red blood cell life span, from the cessation of red blood cell production as well as the increased destruction of red blood cells. Aplastic crisis is characterized by anemia and a low reticulocyte count.[12]

β-thalassemia is characterised by the absence or reduced amounts being produced of β-globin chain which creates an imbalance between α and β chains of HbA (adult hemoglobin, $\alpha 2\beta 2$).[13] The XmnI polymorphism (HBG2 rs7482144, c.–211 C > T) is a sequence variant that has been documented in multiple population groups with reported allele frequencies ranging from 0.32 to 0.35.[14] This variant of DNA accounts for approximately 33 % of the variance in HbF levels among healthy normal individuals. Although it has only a modest effect on the overall increase in HbF levels by those who are homozygous for the mutant allele, they have a greater chance of developing elevated HbF levels due to producing more HbF in response to hematopoietic stress. The XmnI polymorphism and associated increase

in levels of HbF due to reactivation or overexpression of the HBG gene results in decreased severity of anemia, especially among individuals with hemoglobinopathies such as SCD and β-thalassaemia.[15,16]

Materials and Methods

Study Population

The study was conducted on three hundred and eight (308) specimens, of which 208 specimens were collected from patients with Beta-Thalassemia (B-Th) Major or Minor from beta-thalassemia centers in the Middle Euphrates region of Iraq, and 100 specimens from apparently healthy controls (AHC) from the Babylon population. The age of patients and AHC groups ranged from 2 to 55 years. Of the total 308 specimens, a representative subset of 50 samples (30 β-thalassemia patients and 20 controls) was selected for XmnI rs7482144 genotyping by Sanger sequencing, based on DNA quality and proportional representation of all disease subgroups (major, intermediate, and minor) and controls.

Extraction of the Viral Genome

The viral genome was extracted using the Patho Gene-spin™ DNA/RNA Extraction Kit (INTRON Biotechnology Co., Korea) to isolate high-quality nucleic acid from blood samples. The extracted viral genome was subjected to agarose gel electrophoresis as an initial step before amplification of the target B19 and HHV-6 DNA. Extracted viral genomes were stored at −20°C until use.

- The primer sequence for B19
- 5´-AATGCAGATGCCCTCCACG-3
- ‘5´-ATGATTCTCCTGAACTGGTCCA-3;PCR
- PRODUCT = 493bp Whereas; HHV6A primer
- sequence F- F-GGTTCCTGGCCCAAAACAGA; R
- CGCGTGGATACGAAGAGACA ; PCR PRODUCT = 517 bp.

Extraction of Total DNA from Clinical Specimens

Total DNA was extracted using the G-Spin™ Total DNA Extraction Mini Kit (Cat. No. 17001, Intron, Korea), suitable for use with fresh or frozen whole blood treated with citrate, heparin, or EDTA. Purification does not require phenol/chloroform extraction or ethanol precipitation. DNA is eluted in Buffer CE, TE (10:1), 10 mM Tris (pH 7.5–8.0), or water, and is suitable for direct addition to PCR or other enzymatic reactions, or for storage at −20°C. The purified DNA is protein-free and nuclease-free. The kit is optimized for the extraction of 20–30 kb DNA fragments and is capable of extracting up to 50 kb fragments.

The primer rs7482144 G/A sequence for XmnI rs7482144:

- XmnI F AGACGTTCCAGAAGCGAGTG
- XmnI R ACGGCTGACAAAAGAAGTCCT
- Annealing 59 product 372

Sanger Sequencing

DNA sequencing was performed using the Sanger sequencing method. The target DNA region was first amplified by polymerase chain reaction (PCR), followed by purification of the PCR products to remove excess primers and nucleotides. Cycle sequencing was then carried out using fluorescently labeled dideoxynucleotides (ddNTPs). The resulting extension products were purified and separated by capillary electrophoresis using an automated genetic analyzer. Sequence data were obtained as chromatograms and analyzed to determine nucleotide sequences.

Ethical Certification

The permission criteria established by the Institutional review board and local ethics committee were followed. The study protocol, consent form, and participant information sheet were reviewed and approved by a local ethics commission on January 11, 2025, under project number B250201.

Statistical Analysis

In order to assess the variables examined in this study, the Chi-square test was utilized. Statistical analyses were conducted using the SPSS program, Version 25, and $p < 0.05$ value deemed to indicate statistical significance.

Results

Genotype Frequency of XmnI rs7482144 SNP

The DNA polymorphism distribution for XmnI rs7482144 SNP showed that the GG, GA, and AA genotypes among patients were 36, 7 and 7, respectively. In the control group, these genotypes were 17 .2, AND 1, respectively, as detailed in Table 1 and figure 1.

Allele Frequency of XmnI rs7482144 SNP

The allele frequencies were investigated. The A (T) allele was significantly more frequent in β-thalassemia patients (17 alleles, 28%) compared to controls (4 alleles, 10%), with an odds ratio of OR=3.56 (95% CI: 1.02–15.67, p=0.023), indicating a statistically significant association with increased risk of β-thalassemia. Conversely, the G (C) allele was more frequent in the control group (36 alleles, 90%) compared to patients (43 alleles, 72%), with an odds ratio of OR=0.28 (95% CI: 0.06–0.98, p=0.023), suggesting a possible protective association. The results are summarized in Table 2.

Hardy–Weinberg Equilibrium for rs7482144

The results represented that the distribution of GG observed/expected (Obs/Exp), GA Obs/Exp, and AA Obs/Exp genotypeswhich were 19 / 15, 5 / 12 7and 6 / 3, respectively, in patients with β-thalassemia and 17 / 16; 2 / 4 and 1 / 0, respectively, in the groups of controls.

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Statistically significant variations in genotype frequencies of polymorphism distribution depending on Hardy–Weinberg Equilibrium between β-thalassemia patients and control (P <0.0012), as shown in Table (3).

Relation Between rs7482144 SNP and Sex

Non- significant association was identified between rs7482144 SNP and sex for patients with Beta-thalassemia as showed in Table 4.

Viral Infection Distribution and its Relation to Disease

A highly significant association was found between viral infections and thalassemia disease for both B19 (χ^2 = 74.44, P < 0.0001)and HHV-6 (X^2=17.29, p<0.0001). B19 infection was detected exclusively in β major (55%) and β intermediate (48%) thalassemia patients, while HHV-6 was highest in β intermediate thalassemia (24%), followed by beta major (12.5%). No viral infection was detected in the control group as shown in Table 5 and Figures 2 and 3.

Relation Between rs7482144 SNP and Viral Infections (B19 and HHV-6)

Conversely, non- significant correlation and a robust negative association was identified between the rs7482144 SNP and Viral Infections (B19 and HHV-6) as shownin Table6.

Table 1.Genotype Frequency of rs7482144 SNP

SNPs	Alleles	All Subjects (n=50)	Controls (n=20)	Thalassemia Patients (n=30)	OR	CI (95%)	p-value / Sig.
rs7482144	GG	36	17	19	0.30	0.05–1.46	0.087 NS
rs7482144	GA	7	2	5	1.80	0.25–20.68	0.410 NS
rs7482144	AA	7	1	6	4.75	0.49–229.7	0.139 NS

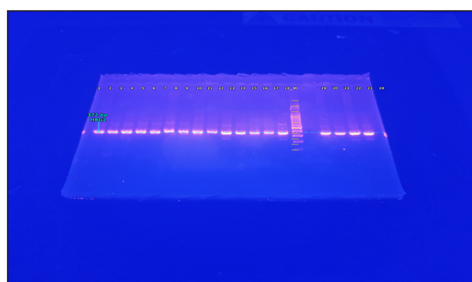

Figure 1.Agarose gel electrophoresis (2%) showing PCR amplification products of the HBG2 rs7482144 (XmnI) polymorphism. M: 100–1000 bp DNA ladder. Lanes 1–24 represent individual patient and control samples. A single band at 372 bp confirms successful amplification of the HBG2 target region in all samples

Table 2.Allele Frequency of rs7482144 SNP

SNPs	Alleles	All Subjects (n=50)	Controls (n=20)	Thalassemia Patients (n=30)	OR	CI (95%)	p-value / Sig.
rs7482144	G	79	36	43	0.28	0.06–0.98	0.023 ★
rs7482144	A	21	4	17	3.56	1.02–15.67	

Table 3.Hardy–Weinberg Equilibrium for rs7482144

Groups	GG Obs/Exp	GA Obs/Exp	AA Obs/Exp	G allele	A allele	p-value / Sig.
All subjects	36 / 31	7 / 17	7 / 2	79	21	<0.0001 ★★★
Controls	17 / 16	2 / 4	1 / 0	36	4	0.0469 ★
Patients	19 / 15	5 / 12	6 / 3	43	17	0.0012 ★★★

Table 4.Relation Between rs7482144 SNP and Sex

Sex	GG	GA	AA	X^2	p-value / Sig.
Male	17	4	3	0.317	0.853 / NS
Female	19	3	4	0.317	0.853 / NS

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Table 5.Distribution of B19 and HHV-6 viral infections among study groups

Virus	Status	Controls (n=101)	Beta Major (n=80)	Beta Intermediate (n=25)	Beta Minor (n=102)	X²	p-value
B19 n(%)	Negative	101 (100%)	36 (45%)	13 (52%)	102 (100%)	74.44	<0.0001
	Positive	0 (0%)	44 (55%)	12 (48%)	0 (0%)		
HHV-6 n(%)	Negative	101 (100%)	70 (87.5%)	19 (76%)	101 (99%)	17.29	<0.0001
	Positive	0 (0%)	10 (12.5%)	6 (24%)	1 (1%)		

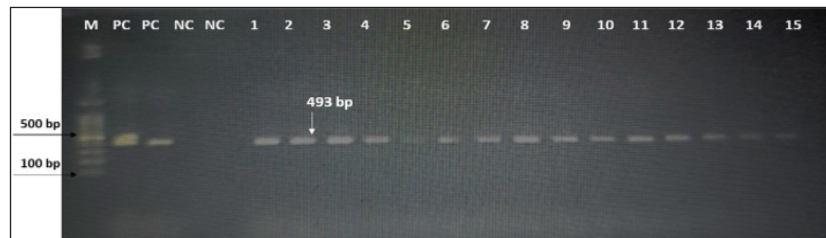

Figure 2.Agarose gel electrophoresis showing PCR amplification products for Parvovirus B19 (B19) detection in study samples. Lanes represent individual patient and control samples. Positive bands at the expected amplicon size confirm the presence of B19 viral DNA. Positive results were detected exclusively in beta major (55%) and beta intermediate (48%) thalassemia patients, with no positivity observed in beta minor patients or healthy controls

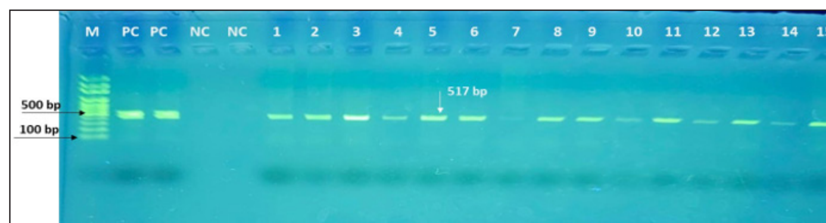

Figure 3.Agarose gel electrophoresis showing PCR amplification products for Human Herpesvirus 6 (HHV-6) detection in study samples. Lanes represent individual patient and control samples. Positive bands at the expected amplicon size confirm the presence of HHV-6 viral DNA. HHV-6 positivity was highest in beta intermediate thalassemia patients (24%), followed by beta major (12.5%), with minimal detection in beta minor patients (1%) and no positivity in healthy controls

Table 6.Relation Between rs7482144 SNP and Viral Infections (B19 and HHV-6)

Viral Infection	Status	GG	GA	AA	X²	p-value	Sig.
B19	Positive	13	1	3	3.915	0.141	NS
B19	Negative	6	4	3	3.915	0.141	NS
HHV-6	Positive	2	1	1	0.380	0.827	NS
HHV-6	Negative	17	4	5	0.380	0.827	NS

Discussion

Allele Frequency Distribution

The results of the present study demonstrated a statistically significant difference in the allele frequency distribution of rs7482144 between thalassemia patients and controls (p=0.023). The A allele (T allele in C>T nomenclature) was significantly more frequent in thalassemia patients (n=17) compared to controls (n=4), with an odds ratio of 3.56 (95% CI: 1.02–15.67), indicating a significant statistical association with disease susceptibility; however, this observational finding does not establish a direct causal relationship. Conversely, the G allele (C allele) was markedly more prevalent in the control group (n=36 vs. n=43 in patients), with an odds ratio of 0.28 (95% CI: 0.06–0.98), suggesting a possible protective association against thalassemia-related

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pathology, though causality cannot be inferred from this cross-sectional data alone.

To understand the biological basis of these findings, it is important to highlight the molecular nature of this variant. The XmnI polymorphism (rs7482144) arises from a C>T substitution at position −158 of the γ-globin gene (HBG2) promoter-region, yielding three possible genotypes: homozygous for the major allele (CC), heterozygous (CT), and homozygous for the minor allele (TT). This substitution lies within a regulatory region that plays a crucial role in the transcriptional control of fetal hemoglobin (HbF) production.[17] The T allele at this position has been repeatedly shown to facilitate increased binding of transcriptional activators to the HBG2 promoter, thereby sustaining γ-globin gene expression beyond the neonatal period and into adulthood, particularly under conditions of hematopoietic stress such as those induced by β-globin chain deficiency.[18]

Importantly, the clinical relevance of this polymorphism has also been confirmed specifically in the Iraqi population context. A study on 224 Iraqi β-thalassemia patients found that *HBG2* rs7482144 was one of four key genetic modifiers — alongside β+ alleles, α-thalassemia deletions, and *BCL11A* rs1427407 — capable of significantly predicting the disease phenotype (major versus intermedia) with an overall accuracy of 83.9% and an area under the curve of 0.917 (95% CI: 0.882–0.953).[19] This finding directly supports the results of the current study and underscores the population-specific importance of rs7482144 as a genetic determinant of thalassemia severity among Iraqi patients.[20]

On the other hand, the predominance of the G (C) allele in the control group of the present study supports the concept that this allele is associated with normal, baseline globin gene regulation in the absence of hematopoietic pathology.[21] In healthy individuals, the C allele at position −158 is associated with the standard γ-to-β globin gene switching during the perinatal period, and its higher frequency in controls reflects the expected genotype distribution in a population without hemoglobin disorders. Notable differences have been reported when comparing the minor allele frequency of rs7482144 in a normal population with those in transfusion-dependent β-thalassemia patients, confirming the disease-associated enrichment of the T allele specifically in patient populations.[17]

Relationship Between rs7482144 SNP and Viral Infections

Relationship Between rs7482144 SNP and B19 Viral Infection

The present study found no statistically significant association between rs7482144 genotype distribution and Parvovirus B19 infection status among the study groups ($X^2=3.915$, $p=0.141$). The GG genotype was observed in 13 B19-positive and 6 B19-negative patients, the GA genotype in 1 positive and 4 negative, and the AA genotype in 3 positive and 3 negative individuals. These results indicate that the XmnI polymorphism at the HBG2 locus does not influence susceptibility to B19 infection, and that viral acquisition operates through pathways independent of this genetic variant.

This finding is biologically plausible, as rs7482144 is fundamentally a regulatory polymorphism affecting γ-globin gene transcription and fetal hemoglobin production, residing within the promoter-region of HBG2 on chromosome 11 — a locus with no established role in innate or adaptive antiviral immunity. The susceptibility to B19 infection is primarily determined by the expression of the P antigen (globoside) on erythroid progenitor cells, which serves as the cellular receptor for viral entry, alongside the host's humoral immune status. High-throughput mRNA sequencing confirmed that productive B19 infection is strictly restricted to erythroid progenitor cells expressing mature differentiation markers and the specific receptor for the viral VP1u region, confirming that B19 tropism is governed entirely by erythroid receptor expression rather than by globin gene promoter variants such as rs7482144.[22] The immune response to B19 is mediated through immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies targeting the viral capsid proteins VP1 and VP2, as well as through natural killer cell and T-cell responses — pathways entirely independent of HbF-regulatory SNPs.[23]

Recent molecular evidence further explains the mechanism by which thalassemia major patients are disproportionately susceptible to B19 infection regardless of their HBG2 genotype.[24] B19V has been shown to infect not only erythroid progenitor cells but also hematopoietic stem cells (HSCs), activating the JAK2/STAT5 signaling pathway to promote viral persistence and multilineage hematopoietic suppression —a mechanism driven entirely by the P antigen receptor and the erythroid differentiation state, not by globin gene promoter variants.[25] This finding explains why B19 infection leads to more severe and prolonged aplastic crises in thalassemia patients, irrespective of their rs7482144 genotype, as the underlying susceptibility is rooted in their expanded erythroid progenitor compartment and compromised immunity rather than in their HBG2 allelic profile.[26]

Relationship Between rs7482144 SNP and HHV-6 Viral Infection

Similarly, no significant association was found between rs7482144 genotype and Human Herpesvirus 6 (HHV-6) infection status ($X^2=0.380$, $p=0.827$). Among HHV6-positive individuals, 2 carried the GG genotype, 1 the GA genotype,

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and 1 the AA genotype, while among HHV6-negative individuals, the GG genotype predominated (n=17), followed by GA (n=4) and AA (n=5). The p-value of 0.827 firmly confirms the complete absence of a relationship between this SNP and HHV-6 susceptibility.

HHV-6 is a ubiquitous beta-herpesvirus that establishes lifelong latency following primary infection in early childhood, with the capacity to reactivate under conditions of immunosuppression. Its pathogenesis is primarily governed by the host immune environment — particularly the status of CD4+ T-cell immunity and natural killer cell activity — rather than by erythroid-specific genetic modifiers. Since rs7482144 is a promoter-region variant acting exclusively within the erythroid-lineage to regulate HbF production, it has no mechanistic basis through which it could influence HHV-6 reactivation or primary infection susceptibility. HHV6A utilizes CD46 — a complement regulatory receptor present on all nucleated cells — for cellular entry, while HHV6B reactivation affects approximately half of all allogeneic hematopoietic cell transplant recipients and is the most frequent infectious cause of encephalitis in this immunosuppressed setting, driven entirely by the degree of immunosuppression rather than by any erythroid genetic modifier.[27] Furthermore, HHV-6 can integrate its genome into the telomeres of host chromosomes, establishing lifelong latency with the potential to reactivate in any immunocompromised state — a mechanism entirely unrelated to the β-globin gene cluster on chromosome 11.[27]

The overall prevalence of HHV-6 infection in the present study — 12.5% in Beta major and 24% in Beta intermediate thalassemia, compared to only 1% in Beta minor and 0% in controls — suggests that the degree of immune dysfunction associated with transfusion dependency and disease severity, rather than specific genotypic factors, is the primary driver of HHV-6 susceptibility. A comprehensive review established that β-thalassemia patients exhibit profound innate and adaptive immune dysregulation, including neutrophil dysfunction, T-cell senescence, impaired B-cell function, and NK-cell suppression — together with expansion of myeloid-derived suppressor cells — all of which promote viral persistence, reactivation, and expansion of pathogenic viral communities including HHV-6. Transfusion-related iron overload is a key driver of this immune dysfunction, as iron accumulation in immune cells causes oxidative damage and impairs cell-mediated immunity, creating a favorable environment for opportunistic viral infections.[28]

Beyond neutrophil dysfunction, the impact of iron overload extends to natural killer (NK) cells, which are essential for antiviral surveillance. A significant reduction in both CD56*bright* and CD56*dim* NK-cell subsets was demonstrated in a pediatric cohort of transfusion-dependent β-thalassemia major patients compared to healthy controls ($p<0.001$), alongside a strong negative correlation between serum ferritin levels and CD56*dim* NK cells ($p=0.003$), confirming that iron overload directly suppresses cytotoxic NK activity.[29,30] This NK-cell dysfunction, which is independent of the patient's HBG2 genotype, creates a critical gap in antiviral immune defense that facilitates HHV-6 persistence and reactivation. Furthermore, integrated bioinformatics and experimental validation confirmed that β-thalassemia patients show a significantly decreased proportion of immune cells, including NK cells, T cells, macrophages, neutrophils, and monocytes alongside an increased proportion of erythroid cells, further confirming the broad immune suppression that underlies viral susceptibility in this population — entirely independently of the rs7482144 genotype.[31]

Conclusions

The present study provides evidence that the HBG2 rs7482144 (XmnI) polymorphism is significantly associated with β-thalassemia susceptibility and phenotypic severity. The A (T) allele was significantly enriched in thalassemia patients compared to healthy controls, consistent with the known modulatory role of this variant in promoting residual fetal hemoglobin (HbF) production as a compensatory mechanism. It is important to note that this association does not establish a direct causal relationship, and further functional studies are warranted to clarify the mechanistic contribution of this polymorphism to disease pathology.

With regard to viral infections, the study demonstrates that the rs7482144 SNP has no significant association with susceptibility to either Parvovirus B19 (B19) or Human Herpesvirus 6 (HHV-6) infection. The HBG2 locus functions exclusively as an erythroid- lineage modifier and does not participate in innate or adaptive antiviral immune pathways. The high frequency of B19 and HHV-6 infections observed among thalassemia major and intermediate patients in this study is instead attributable to the combination of repeated transfusion exposure, iron overload-induced immune dysfunction, and the expanded erythroid progenitor compartment that characterizes these patients.

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