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Molecular Patterns of Beta-Thalassemia in Taif Province-Saudi Arabia: Determination of Prevalent genotypes and Regions with High Incidence

Tariq Elfatih. Elmissbah[1], Hayaa Moaid. Huthali[1], Mamdouh Allahyani[1], Amal Shuwman Alosaimi[1] and Heba Mohammed. Elmasry[2]

[1]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Taif University, Taif, Saudi Arabia.
[2]Department of Clinical Pathology, South Egypt Cancer Institute, Assiut, Egypt.
*Corresponding Author E-mail:mesbah@tu.edu.sa

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Thalassemia includes a collection of genetic blood disorders marked by reduced or absent production of the -globin chain caused by mutations in essential regions of the -globin gene found on the chromosome. The severity of the disease can range from asymptomatic cases to anemia requiring transfusions, depending on the type of mutation. It follows an inheritance pattern that is autosomal recessive. This is a descriptive analytical study aimed to examine the varieties and prevalence of B-Thalassemia mutations among various ethnic groups in the Taif province. Ninety samples were gathered and sent for analysis of ß-globin gene mutations via the reverse dot blot hybridization method. Saudi patients not diagnosed with ß-thal were excluded in this study. The findings indicated that codon 6 [A>T] HbS (c.20A>T, heterozygous) was present at a frequency of 44.4%, codon 8/9 [+G] (c.27_28insG) heterozygous at 4%, codon 6 [A>T] HbS (c.20A>T) homozygous, IVS 1.5 [G>C] (c.92+5G>C), 101 [C>T] (c.-151C>T, homozygous, 5%), codon 39 [C>T] (c.118C>T, heterozygous), IVS 1.1 [G>A] (c.92+1G>A) at 1% heterozygous, IVS 1.110 [G>A] (c.93-21G>A, 1% heterozygous), IVS 1.5 [G>C] (c.92+5G>C) 1% heterozygous, IVS 1.6 [T>C] (c.92+6T>C) 1% heterozygous, IVS 2.1 [G>A] (c.315+1G>A) 1% heterozygous, IVS 2.745 [C>G] (c.316-106C>G), IVS 2.848 [C>A] (c.316-3C>A). IVS 2.848 [C>A] (c.316-3C>A). Conclusion.This research shows that the heterozygous mutation codon 6 [A>T] HbS (c.20A>T) is the leading cause of B thalassemia in Taif city.

Keywords: B-Thalassemia; Consanguineous marriages; Genotypes; Saudi population; Taif city.

â-Thalassemia syndromes are a range of genetic conditions resulting from a mutation that causes either a total absence or a substantial or slight decrease in the synthesis of â-globin chains. Thalassemia major or thalassemia intermedia arise from an absolute deficiency or notable insufficiency. [1,19] Total lack or considerable deficiency results in thalassemia major or thalassemia intermedia. The heterozygous state (-thalassemia trait) results in mild to moderate microcytic anemia, while homozygous and compound heterozygous states (thalassemia major/intermedia) result in severe anemia necessitating transfusions. [2] The molecular causes of thalassemia are extremely diverse. Major gene rearrangements seldom cause â-thalassemia cases, which generally arise from point mutations impacting the coding areas of essential parts of the â-globin gene. [3] Three mutations that completely

disable genes (including deletion, start codon, nonsense, frameshift, or splicing mutations) will prevent the gene from producing any -globin chains. This condition is referred to as â thalassemia. Thalassemia is defined by the degree of decreased chain production, as specific genetic mutations lead to partial gene inactivation, resulting in reduced -globin chain synthesis and causing + or ++ (silent). [4] The buildup of free chains in erythroblasts and red blood cells will increase if the -globin chain is missing or decreased. The primary consequences of this condition include irregularities in the skull and facial bone configuration, ineffective erythropoiesis, splenomegaly due to increased hemoglobin F, and tissue hypoxia. The proportion of non-globin chains to free chains varies, along with the severity of the disease.[5] The genes that encode for -globin (HBB) are located on the short arm of chromosome 11 and are controlled by a single locus control region. The HBB gene is made up of 146 amino acids and has a molecular weight of about 1.6 Kb. It includes three exons, two introns, untranslated regions at both the 52 and 32 termini, along with additional elements. Worldwide, 150 million people, accounting for 3% of the population, possess the -thalassemia gene. Studies on populations show that a particular set of 40 mutations in the -globin gene explains the majority of cases among over 300 variants recognized globally. [7] Certain mutations are unique to specific populations, and the prevalence of -globin mutations differs by nation. The prevalence of thalassemia is rising in the Mediterranean region, the Middle East, Central Asia, India, Southern China, the Far East, along with countries on Africa's northern coast and in South America. Additionally, it is common across different frequencies in the Arab region, exhibiting a carrier frequency ranging from 1% to 11%.[8]

MATERIALS AND METHODS

This is a descriptive analytical study aimed to determine the various mutations found in patients with â-thalassemia in the Taif region of Saudi Arabia. Samples for molecular screening of â-thalassemia were gathered at Al Borg Diagnostic Lab and evaluated in Saudi Arabia during the last two years. The study comprised individuals with hypochromic microcytic anemia, those showing increased HbA2 or HbF levels in hemoglobin electrophoresis, having a family history of B-thalassemia, and exhibiting one of the specified traits.

The hospital's ethics committee and the Research Advisory Council approved this retrospective review study. The samples were cases forwarded to KFSH & RC for potential treatment from different areas of the kingdom. Selection criteria were applied. The criteria for including the samples involved microcytosis, with MCV<80. fL or hypothermia, MCH<26 pg, or either condition without iron deficiency anemia (IDA) [20]. Criteria for exclusion included individuals suffering from iron deficiency anemia presenting decreased RBC indices and atypical iron profiles, including serum iron<65/50 µg/dl for males and females, respectively, and ferritin<30 ng/l that showed improvement following a brief treatment of iron therapy .[20] the existence of any chronic illnesses and, blood transfusions within the previous three months, and pregnancy.

This research involved ninety participants from Saudi Arabia who were diagnosed with â-thalassemia. A 2.7 ml blood specimen was acquired in a polypropylene container with sodium citrate anticoagulant for molecular analysis. DNA extraction from blood samples was performed using a QIAamp blood micro kit (Qiagen, Hilden, Germany) following the guidelines provided by the manufacturer. Following DNA extraction, the genetic material of the patients was analyzed for mutations in the á-globin genes. The samples underwent analysis for multiple B-globin gene mutations through multiplex-PCR and reverse dot blot hybridization (RDBH). The analysis of the data was conducted using the suitable statistical tests in SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were presented as mean±standard deviation (SD). Qualitative data were reported as frequencies and percentages, and a chi-square (÷2) test was utilized. The confidence interval was established at 95%, and significance was noted when the P-value was <0.05.

RESULTS

The majority of patients originated from various regions of the Kingdom (Figure 1). The male cohort consisted of 46 out of 90 patients

(51.1%), while female patients accounted for 44 of 90 (48.9) (Table 1). The proportion of Saudi patients was 44.4%, whereas the proportion of non-Saudi patients was 56.6% (Table 2). Table 3 displays the average age differences among the study participants.

In the B-globin gene associated with B-thalassemia, fourteen distinct alleles were identified (n=100). The variant alleles along with the distribution of various B-thalassemia mutations in Taif province are presented in (Table 4). Among mutations of the B-globin gene, the heterozygous á variant at codon 6 [A>T] HbS (c.20A>T) was the most prevalent. Eight alleles displayed the lowest percentage, as indicated in (Table 5).

Table 1. Distribution of male and female in the study

	Frequency	Percent
Male	46	51.1
Female	44	48.9
Total	90	100

Table 2 Frequenicies of B-Thalassemia according to nationality

	Frequency	Percent
Saudi	40	44.4
Non Saudi	50	55.6
Total	90	100

DISCUSSION

Thalassemia primarily affects individuals of Mediterranean and Middle Eastern heritage, particularly those from the Gulf region. Thalassemia is known for its significant occurrence in the western parts of Saudi Arabia. [9, 12, 13] Currently, there is no national study available that provides data on the prevalence of â-thalassemia trait in Saudi Arabia. Estimates suggest that the occurrence of the â-thalassemia gene varies between 0.01 and 0.15 across different regions of the country.[20]

Variations in globin genes vary between ethnic groups and geographical areas globally, with numerous variations documented in Saudi Arabia. Prior research has investigated particular documented mutations in the globin gene to evaluate their occurrence and prevalence in Saudi patients. [14]

In this research, we present the range of mutations in the â-globin gene. in a group of â-TM patients located in the western region of Saudi Arabia and our initial encounter in prenatal

Table 3. Mean & median of age in Study

Mean	26.000
Median	26.000
Std. Deviation	9.5537
Minium	2.0
Maximum	44.0

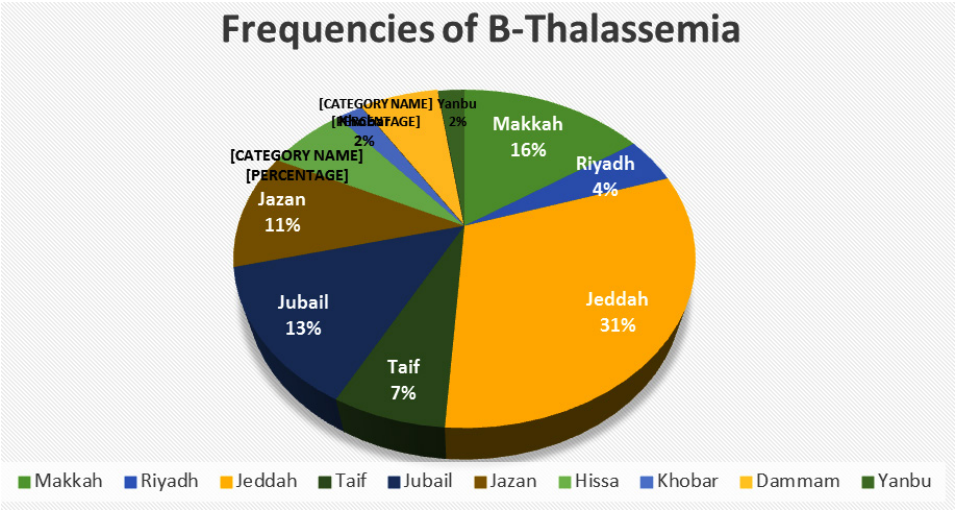

Fig. 1. Frequenicies of B-Thalassemia among Saudi Population

diagnosis. A substantial level of homozygosity for the the identical â-thal alleles (69%) were noted in this research, as anticipated from the elevated frequency of interrelated marriages within the Saudi populace. Frequencies of â-globin gene mutations vary across different geographical areas worldwide and among ethnic groups, in which a few mutations are accountable for the illness in every case demographic. Saudi Arabia holds a distinctive geographic location situated between the Mediterranean and Southeast Asian areas where individuals from multiple zones transitioned to various parts of Saudi Arabia. [12]

Abuzenadah et al. have recently discovered 23 mutations associated with thalassemia. Among these variations, seven were frequent, with IVSI5G>C being the most widespread.[15] The remaining 16 mutations were rarer, including the FSC 20/21 mutation, a completely new mutation that has not previously been documented in Saudi Arabia. [15] Mutations in the globin gene vary across ethnicities and geographic locations globally; many

Table 4. The distribution of various B-thalassemia mutations in Taif province

B-thal allels	Frequency	%	P value
codon 6 [A>T] HbS (c.20A>T) heterozygous	40	44.4	0.31
-101 [C>T] (c.-151C>T) heterozygous	10	11.1	0.25
codon 8/9 [+G] (c.27_28insG) heterozygous	8	8.88	0.8
codon 6 [A>T] HbS (c.20A>T) homozygous	6	6.7	0.41
IVS 2.1 [G>A] (c.315+1G>A) heterozygous	6	6.7	0.62
IVS 1.6 [T>C] (c.92+6T>C) heterozygous	4	4.4	0.52
IVS 1.5 [G>C] (c.92+5G>C) heterozygous & IVS 2.745 [C>G] (c.3	2	2.2	0.76
-101 [C>T] (c.-151C>T) heterozygous, IVS 2.745 [C>G] (c.316-10	2	2.2	0.22
codon 39 [C>T] (c.118C>T) heterozygous	2	2.2	1.0
IVS 1.1 [G>A] (c.92+1G>A) heterozygous	2	2.2	0.02
IVS 1.110 [G>A] (c.93-21G>A) heterozygous	2	2.2	0.12
IVS 1.5 [G>C] (c.92+5G>C) heterozygous	2	2.2	0.71
IVS 2.745 [C>G] (c.316-106C>G) heterozygous	2	2.2	0.33
IVS 2.848 [C>A] (c.316-3C>A) heterozygous	2	2.2	0.01
Total	90	100.0	

The confidence interval was established at 95%, and significance was noted when the P-value was <0.05.

Table 5. The distribution of various B-thalassemia mutations according to gender

B-thal allels	Male	Female
codon 6 [A>T] HbS (c.20A>T) heterozygous	21	13
-101 [C>T] (c.-151C>T) heterozygous	4	6
codon 8/9 [+G] (c.27_28insG) heterozygous	3	5
codon 6 [A>T] HbS (c.20A>T) homozygous	4	2
IVS 2.1 [G>A] (c.315+1G>A) heterozygous	3	1
IVS 1.6 [T>C] (c.92+6T>C) heterozygous	3	2
IVS 1.5 [G>C] (c.92+5G>C) heterozygous & IVS 2.745 [C>G] (c.3	0	2
-101 [C>T] (c.-151C>T) heterozygous, IVS 2.745 [C>G] (c.316-10	2	2
codon 39 [C>T] (c.118C>T) heterozygous	2	4
IVS 1.1 [G>A] (c.92+1G>A) heterozygous	1	2
IVS 1.110 [G>A] (c.93-21G>A) heterozygous	1	1
IVS 1.5 [G>C] (c.92+5G>C) heterozygous	1	1
IVS 2.745 [C>G] (c.316-106C>G) heterozygous	1	1
IVS 2.848 [C>A] (c.316-3C>A) heterozygous	0	2
Total	46	44
	90	

variants have been discovered in Saudi Arabia. In this research when a person is heterozygous for the HbS mutation and possesses a â-thalassemia mutation as well, they have Sickle-â-thalassemia (HbS/â-thal), which is a form of sickle cell disease. The "function" of the HbS gene in this interaction is to create abnormal hemoglobin that can polymerize (sickle), whereas the â-thalassemia gene decreases or stops the production of normal Hemoglobin A (HbA).[21]

Prior research examined particular recorded globin gene variants to determine their occurrence and how often they affected Saudi patients.[16] A recent study was conducted to identify the precise statistics and occurrence rates of thalassemia mutations in a specific area of Saudi Arabia. [12, 13, 18, 19] Forty-four cases of beta thalassemia were associated with the mutation at codon 6 [A>T] HbS (c.20A>T) heterozygous at codon 39 (C > T), common in Bahrain and several Western Mediterranean countries (24%) and previously linked to a high frequency in the Saudi population. Notably, the IVSI-5 (G > C) mutation has been observed at a low occurrence rate of 1.8% in the Eastern Province population, [17] and a higher rate of 12% across the country.

While â-thalassemia is an autosomal recessive condition, we did not notice a significant gender difference between males and females. The notable molecular variety seen in this research arises from the presence of an immigrant community in the Taif province. A significant factor contributing to the elevated prevalence of B-thalassemia in Saudi Arabia is the widespread lack of awareness about the diagnostic choices accessible, particularly prenatal testing, for the prevention of thalassemia. Our data distinctly indicates that 98% of families seeking prenatal diagnosis for B-thalassemia had a child diagnosed with thalassemia major. Furthermore, routine B-thalassemia carrier screening and genetic counseling for couples at risk has greatly reduced the risk of disease transmission.. [17, 18, 19]

Recommendations

The importance of conducting research on B-thalassemia stems from the fact that it is a genetic disease that affects society, and therefore the study recommends that premarital examinations include testing for the presence of B-thalassemia.

Limitations

Although the strict methodology used in this research is commendable, various inherent limitations should be recognized. Initially, the sample size was quite limited and concentrated on a particular geographic region, which might restrict the applicability of the results to a wider population. Secondly, the dependence on self-reported information creates the possibility of response bias, as respondents may give socially acceptable answers instead of accurately representing their actual behaviors. Moreover, the research design's cross-sectional aspect prevents the determination of definitive causal connections between the variables. Ultimately, limitations in resources, such as time and budget, constrained the extent of the longitudinal analysis that might have offered more profound insights into the topic

CONCLUSIONS

The research indicated that the major mutation responsible for thalassemia in the samples gathered in Taif is the codon 6 [A>T] HbS (c.20A>T) heterozygous. Carrier Status being heterozygous indicates that the person "carries" the trait without actually having the disease.

Compound Heterozygosity: When this variant is passed down with another HBB mutation (such as HbC or Beta-Thalassemia), it may result in different types of Sickle Cell Disease. The primary consequence of being a carrier is the possibility of transmitting the gene to offspring.This study noted that the thalassemia gene is widespread due to ethnic intermingling between countries.

In conclusion, the current study discovers four novel mutations in the Taif Province population. The mutation frequencies observed in this study align with those reported in nearby population

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Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

Ethics approval and consent for participation were obtained following the approval of the biomedical ethics unit at Al Borg Diagnostic Lab, and the study was carried out (02/22).

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required

Clinical Trial Registration

This research does not involve any clinical trials

Permission to reproduce material from other sources

Not applicable

Author Contributions

Conceptualization: Tariq Elfatih Elmissbah and Amal Alosaimi; Design: Tariq Elfatih Elmissbah and Hayaa Moaid Alhuthali; Methodology: Tariq, Hayaa, and Amal; Software and validation: Tariq, Amal, and Hayaa; Formal examination: Hayaa and Tariq; Writing—Initial draft creation, Tariq; Writing—revision and editing: Heba; Data management: Hayaa and Heba; General revision: Mamdouh Allahyani.

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