Iraqi JMS

Published by College of Medicine, Al-Nahrain University
P-ISSN 1681-6579
E-ISSN 2224-4719
Email: iraqijms@colmed.nahrainuniv.edu.iq
http://www.colmed-alnahrain.edu.iq
http://www.iraqijms.net/
Iraqi JMS 2025; Vol. 23(2)

Investigating the Molecular Map of Transfusion Dependent and Non-Transfusion Dependent β-Thalassemic Patients in Baghdad City

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Abstract

Background β-thalassemia syndrome (BT) is an inherited blood disorder characterized by reduced levels of functional hemoglobin owing to relative reduction or complete lack of β-globin chain synthesis. The severity of the BT phenotype relies highly on the underlying genetic defect affecting the β-globin gene. The high prevalence rate, as well as, the relatively high annual cost for thalassemia patients in Iraq, has imposed a huge burden exhausting both patients and the health institutions.

Objective To study the molecular profile of BT patients in Baghdad city with characterizing the most common β-globin gene mutation among transfusion dependent (TD) and non-transfusion dependent (NTD) patients.

Methods A cross-sectional study was conducted on 80 TD and NTD BT Patients. Molecular profiling of BT mutations was performed using β-Globin StripAssay®IME, a reverse-hybridization assay tailored to detect population-specific mutations within the Middle East, Iran, Arabian Peninsula, and India.

Results In the current study, 13 different BT mutations have been identified, of which 3 alleles accounted for approximately 60% of the total alleles. These were: intervening sequence (IVS) 1.110 {G>A} in 44 (27.5%), IVS 2.1 {G>A}: 35 (21.9%), and Codon 44 {-C}: 14 (8.8%). Other alleles were less frequent including IVS 1.6 {T>C}: 11 (6.9%), Codon 36/37 {-T}:10 (6.3%), while the remaining alleles accounted for 5% or less each.

Conclusion The study has revealed a clustering of discrete BT alleles, indicated by the dominance of (IVS) 1.110 {G>A}, IVS 2.1 {G>A}, and Codon 44 {-C}: alleles in nearly 2/3 of the studied subjects.

Keywords Molecular map, β-thalassemia, mutation, HBB gene, alleles

Citation Alaqidi AA, Al-Mamoori HS. Investigating the molecular map of transfusion dependent and non-transfusion dependent β-thalassemic patients in Baghdad City. Iraqi JMS. 2025; 23(2): 393-403. doi: 10.22578/IJMS.23.2.22

List of abbreviations: A = Adenine, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, BT = β-thalassemia syndrome, C = Cytosine, G = Guanine, HBB = Human beta globin, HbF = Fetal hemoglobin, IVS = Intervening sequence, NTD = Non-transfusion dependent, PCR = Polymerase chain reaction, S. Ca = Serum calcium, S.F. = Serum Ferritin, TSB = Total serum bilirubin, SD = Standard deviation, T = Thymine, Hb = Hemoglobin, TD = Transfusion dependent

Introduction

Thalassemia is one of the most globally distributed hereditary hemoglobinopathies. It is regarded as the single most common monogenic inherited disease in the world [1,2]. It is considered an ample contributor to public health burden in numerous countries especially those with

limited resources. The thalassemia syndrome is defined as a group of primarily autosomal recessive hemoglobin (Hb) disorder owing to mutations in or around the globin genes leading to impaired synthesis of one or other of the globin chains, affecting imbalance of the ratio of α to non-α chains, and consecutively instigating impaired erythropoiesis, hemolysis, and varying levels of anemia [3,4]. Approximately, 4.4 thalassemia patients are born in every 10,000 live births with 280 million carriers worldwide [5]. This syndrome shows highest prevalence in tropical and subtropical areas (i.e., the Middle East, Mediterranean coasts, South-East Asia, Indian subcontinent, and Sub-Saharan Africa) [6,7].

Thalassemia is classified, according to which globin chain of the Hb molecule is absent or insufficiently produced, into two major categories: the α- and β-thalassemia (BT) [8,9]. The molecular pathology of BT syndrome is remarkably heterogeneous with diverse range of genetic defects affecting different stretches of the human beta globin (HBB) gene locus that either abrogate or reduce synthesis of functional β-chain. The site and type of mutation governs the amount of generated β globin peptide that is categorized as "β0" denoting complete absence of Hb subunit beta, while "β+", and "β++" designate variable degrees of reduction from severe to mild thalassaemic output [10-13].

The Middle East has been long known to be a high prevalence area for BT owing to strong cultural tradition encouraging consanguineous marriages amid an already high carrier rate. In in last years, an improved awareness programs, better screening strategies for thalassemia, and genetic counselling have led to significant reduction in number of affected progenies in several Middle Eastern countries including but not limited to Saudi Arabia, Bahrain, the United Arab Emirates and Iran [7,14,15].

In Iraq, however, data have shown an increase in thalassemia prevalence during recent years, from 33.5 to 37.1 per 100,000 live births, in the period between 2010 and 2015. The most recent cross-sectional study has indicated an uprising trend in thalassemia cases (from 12,106 to 13,390) over the last five years, accounting for more than two-third of all hereditary anemias in Iraq. The majority of the aforementioned cases (67%) were BT major, with reported complications rate of more than 50%. Reports have also shown that most of those patients come from large, poorly educated, low-income families with more than 90% having another affected family member. Furthermore, according to last estimates, the cost of health care services for a single thalassemia patient approximated 10,810$ per year. Since most patients require life-long care, along with the extra costs added if patients develop complications, the total cost would pose an enormous pressure on the already frail health system [5,16-18].

Thus, constructing a well-planned preventive program adapting the latest available molecular practices can play a crucial role in reducing BT incidence and ebbing its lifetime suffering and financial burden.

Methods

A cross-sectional study was conducted on a sample of eighty adult BT patients, from the subjects attending thalassemia care centers in Baghdad (i.e., Ibn Albalady Thalassemia Care Centre, and Thalassemia Care Centre at Al Karama General Hospital) using non random sampling method.

Inclusion criteria

Adult patient (18 yrs and above) from Baghdad city and surrounding districts with established diagnosis of BT (patients' diagnosis was based on hematological (red cell indices and blood film), high performance liquid chromatography (HPLC), in addition to clinical presentation.

The sample was then divided into two groups of patients; transfusion dependent (TD) comprising of 56 patients and non-transfusion dependent (NTD) 24 patients according to the specific criteria:

Criteria for TD

Age at initial presentation <2 years, pre-transfusion Hb levels <70 g/l at time of diagnosis, and on a regular transfusion program.

Criteria for NTD

Age at initial presentation ≥2 years, pre-transfusion Hb level between 70 and 100 g/l at time of diagnosis, and not requiring frequent blood transfusion.

Exclusion criteria

Co-inheriting of other hemoglobinopathy, diagnosis with other hematological disorders, and those were unwilling to participate in the study or reluctant to provide a written consent.

All patients have been interviewed and questioned using a pre-prepared comprehensive questionnaire form to obtain detailed clinical information. All medical files of the selected patients have been reviewed including demographic, clinical and laboratory data (Hematological parameters: HbF, HbA2 (at diagnosis), and biochemical parameters: serum ferritin (S.F.) level, liver function tests; total serum bilirubin (TSB), serum calcium (S. Ca.), and renal function tests (at time of testing, or most recent). All relevant data have been collected, evaluated, and catalogued for further analysis.

Five ml of pre-transfusion venous blood was aseptically aspirated from all patients. Two ml of the anticoagulated blood was used to perform hematological testing using Convergy®X5 auto-analyzer (Convergent Technologies/Germany), and the remaining EDTA blood sample (three ml) was frozen at −20° C for later genetic testing.

Molecular analysis

The first step of molecular profiling of BT patients was extraction of genomic DNA from each blood sample after thawing using GENxTRACTTM Resin kit, following the manufacturer's instructions.

The second step was the implementation of the β-Globin Strip Assay IME® Test strips (ViennaLab Diagnostics GmbH, Vienna/Austria). These test strips are based on multiplex polymerase chain reaction (PCR) amplification and reverse hybridization technique.

Following the PCR amplification of biotinylated primers, the amplified PCR products were then hybridized to immobilized allele-specific oligonucleotides on test strips. Each test strip contained 22 probes arranged in a parallel array of oligoes tailored to detect 22 different mutations covering more than 90% of β-globin genetic defects found within the Middle East, Iran, Arabian Peninsula, and India population, as listed in table (1). In addition to that, each test strip encompassed 10 wild type (normal) probes which correspond to the aforementioned HBB mutation's sequences.

Following the hybridization step, test results were detected visually via evoking enzymatic (streptavidin-alkaline phosphatase) based color reactions, and subsequently interpreted into the characterized alleles. Patients who are homozygotes for a mutation only showed a positive reaction (purple color) with that mutant probe, while heterozygotes exhibited two positives corresponding to mutant and normal probes' reactions (Figure 1).

Characterization of β-Globin mutation via direct sequencing

For confirmation of results, 11% of DNA templates (9 samples) were randomly selected, amplified, then sent for direct sequencing by Genetic Analyzer system ABI-310 / Macrogen (Seoul, Korea), using the "chain termination method". Once the sequencing results were done, National Center for Biotechnology Information (NCBI) tools and bioinformatics software were used for their analysis.

Table 1. β-globin mutations covered by β-Globin Strip Assay ® IME

No.	HGVS nomenclature	Common name
1	HBB:c.-50A>C	cap+1 [A>C]
2	HBB:c.17_18delCT	codon 5 [-CT]
3	HBB:HbS c.20A>T	codon 6 [A>T]
4	HBB:c.25_26delAA	codon 8 [-AA]
5	HBB:c.27_28insG	codon 8/9 [+G]
6	HBB:c.47G>A	codon 15 [TGG>TAG]
7	HBB:c.51delC	codon 16 [-C]
8	HBB:c.68_74delAAGTTGG	codon 22 [7bp del]
9	HBB:c.92G>C	codon 30 [G>C]
10	HBB:c.92+1G>A	IVS 1.1 [G>A]
11	HBB:c.92+1G>T	IVS 1.1 [G>T]
12	HBB:c.92+5G>C	IVS 1.5 [G>C]
13	HBB:c.92+6T>C	IVS 1.6 [T>C]
14	HBB:c.93-21G>A	IVS 1.110 [G>A]
15	HBB:c.93-21_96de	IVS 1-25 [25bp del]
16	HBB:c.112delT	codon 36/37 [-T]
17	HBB:c.118C>T	codon 39 [C>T]
18	HBB:c.126_129delCTTT	codon 41/42 [-TTCT]
19	HBB:c.135delC	codon 44 [-C]
20	HBB:c.315+1G>A	IVS 2.1 [G>A]
21	HBB:c.316-106C>G	IVS 2.745 [C>G]
22	619bp del	619bp del

Ethical consideration

The study has been reviewed and approved by the Institutional Review Board (IRB) of the College of Medicine at Nahrain University. A written consent was granted from all study participants after a full disclosure about the study objectives and details was offered by the researcher. Data confidentiality has been preserved in accordance to the revised Helsinki Declaration of Bioethics.

Statistical analysis

Data analysis was performed using statistical package for social sciences, version (26). Independent t-test and analysis of variance (ANOVA) (two tailed) was also used to compare the continuous variables accordingly. Chi square test was used to investigate the association between categorical variables, while Fisher exact test was used instead whenever the expected frequency was less than 5. A level of P value less than (0.05) was considered significant.

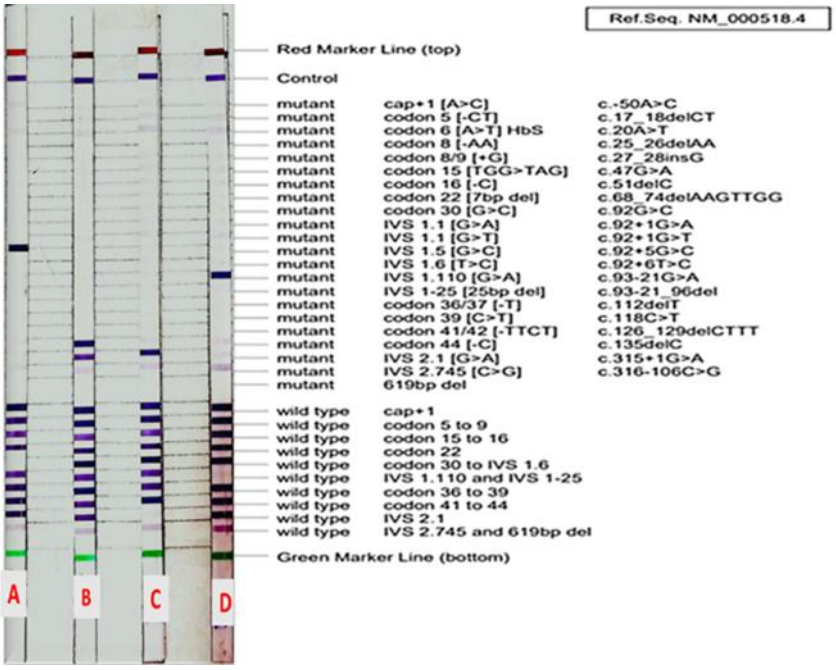

Figure 1. β-Globin test strips results showing from left to right; β-Globin test strips results showing from left to right; A: homozygous IVS 1.5 {G>C}, B: compound heterozygous Codon 44 {-C}/IVS 2.1{G>A}, C: homozygous IVS 2.1 {G>A}, D: homozygous IVS 1.110 {G>A}

Results

Demographic and clinical data

The study included 80 patients (56 TD and 24 NTD patients), with mean±SD age of 27.29±10.8 yr (ranging from 18-67 yr, and male to female ratio of 1.1:1. The mean age at diagnosis for TD group was 1.59±0.7 yr, while that for patients within the NTD group was significantly higher (11.29±13.4 yr). Similarly, the age at initial transfusion was higher among NTD (8.63±7.8 yr) than that of the TD group (1.5±0.5 yr). The majority of patients (59 accounting for 73.8% of the study participants) have had positive family history of BT with one or more affected family members, of those more than two-third were among the TD group (42), and 17 (28.8%) were amongst the NTD group. Additionally, 85% of our recruited patients (68), reported a consanguineous marriage between their parents with 72.1% (49) of those were TD and 27.9% (19) were NTD patients. Furthermore, current data have also demonstrated that 32.5% of the enrolled patients had undergone splenectomy, divided as; 29% of NTD, and 34% of TD. In regards to disease complication; cholelithiasis, osteoporosis, and facial bones deformity were the most frequent disease comorbidities encountered in our study in 43 (53.8%), 41 (51.3%), 35 (43.8%) respectively, followed by leg ulceration, growth retardation, thyroid dysfunction and diabetes mellitus.

Biochemical & Hematological parameter:

As listed in table (2), means of several biochemical and hematological parameters were investigated, and compared between the two study groups. The inferred data have shown significantly lower levels of S.F., ALT, and AST, higher levels of Hb, HbA2, and lower HbF percentage in NTD patients than that in TD patients, whilst the remaining parameters showed imperceptible difference.

Table 2. Hematological & Biochemical parameters in study groups

Hematological & biochemical parameters	TDT n=65 Mean±SD	NTDT n=24 Mean±SD	P value
Hb (g/dl)	6.5±1.9	7.75±1.8	0.031
HbA_2 (%)	2.44±1.6	3.57±1.5	0.004
HbF (%)	89.19±12.0	70.54±13.6	0.001
S.F. (µg/l)	4043.7±2161.9	3019.5±2018.6	0.048
ALT (U/l)	59.41±63.4	31.95±18.5	0.004
AST (U/l)	64.1±73.7	41.83±16.2	0.036
TSB (µmol/l)	40.59±23.7	36.71±20.4	0.461
S. Ca (mmol/l)	2.29±0.3	2.2±0.2	0.152
B. Urea (mmol/l)	3.45±0.9	3.85±1.1	0.117
S. Creatinine (µmol/l)	56.1±15.6	56.23±15.5	0.973

Hb: Hemoglobin, S.F.: Serum ferritin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TSB, total serum bilirubin, S. Ca: Serum calcium

BT mutations

In the current study, 14 different BT alleles were characterized (including 13 mutated and one wild type) using reverse hybridization technique. The most frequent allele among TD patients was IVS 1.110{G>A}:35 (31.3%), followed by IVS 2.1 {G>A}:22 (19.6%). While in NTD, IVS 2.1 {G>A} was the most frequent allele with frequency of 13 (27.1%). Furthermore, this study showed that 55% of alleles were β0; while 41.3% of them were β+ and only 3.8% were wild type alleles. β0 alleles were primarily exhibited among TD patients, while β+ alleles were more frequently exhibited among NTD group. The various alleles' frequencies are further detailed in table (3).

Table 3. BT alleles identified in this study

β- thalassemia alleles	Thalassemia phenotype	Study groups		Total no of alleles (%) n= 160 (80*2)
		TD alleles (%) n= 112 (56*2)	NTD alleles (%) n= 48 (24*2)	
IVS 1.110 {G>A}	β^+	35 (31.3)	9 (18.8)	44 (27.5)
IVS 1.6 {T>C}	β^+	1 (0.9)	10 (20.8)	11 (6.9)
IVS 1.5 {G>C}	β^+	6 (5.4)	1 (2.1)	7 (4.4)
IVS 2.745 {C>G}	β^+	1 (0.9)	3 (6.5)	4 (2.5)
IVS 2.1 {G>A}	β^0	22 (19.6)	13 (27.1)	35 (21.9)
Codon 44 {-C}	β^0	12 (10.7)	2 (4.2)	14 (8.8)
Codon 36/37 {-T}	β^0	10 (8.9)	0 (0.0)	10 (6.3)
IVS 1-25 {25bp del}	β^0	6 (5.4)	2 (4.2)	8 (5.0)
Codon 41/42 {-TTCT}	β^0	7 (6.3)	0 (0.0)	7 (4.4)
Codon 8 {-AA}	β^0	4 (3.6)	2 (4.2)	6 (3.8)
Codon 5 {-CT}	β^0	5 (4.5)	0 (0.0)	5 (3.1)
Codon 39 {C>T}	β^0	2 (1.8)	0 (0.0)	2 (1.3)
Codon 15 {TGG>TAG}	β^0	1 (0.9)	0 (0.0)	1 (0.6)
Wild type	β	0 (0.0)	6 (12.5)	6 (3.8)

The characterized alleles arrayed into 27 distinct genotypes (converging from 14 different alleles). The most predominant genotypes were homozygous IVS 1.110 {G>A}, and IVS 2.1 {G>A} mounting for 38.8% of the identified genotypes (Figure 2).

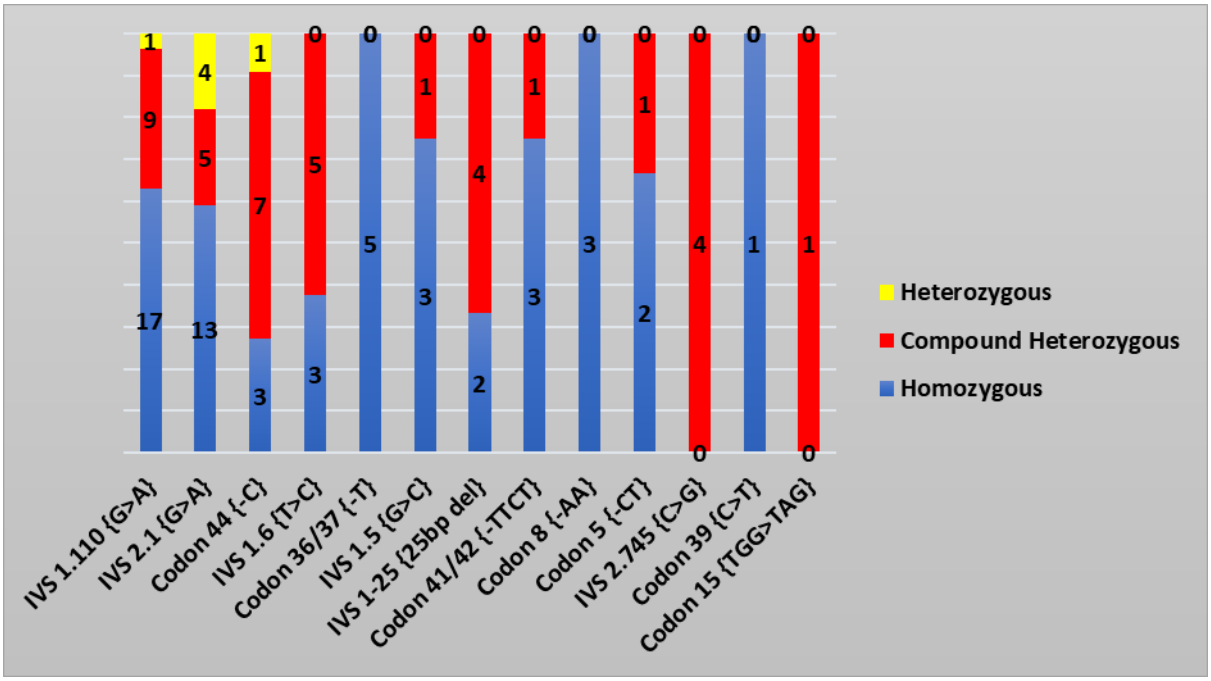

Figure 2. Distribution of β-thalassemia alleles according to genotypes

Discussion

Molecular mapping of hereditary hemolytic disorders is an intricate realm that yet to have been fully ventured specifically in Iraq. The new advances in molecular detection techniques providing population-specific molecular detection kits for a wide variety of genetic diseases, have allowed for their use in research and their potential application in routine screening practices. This work is an attempt to delve deeper into the molecular terrain of BT in Baghdad city.

In current study, 14 distinct alleles (amongst 160 enrolled alleles) were characterized. The most frequent allele was IVS 1.110 {G>A} comprising 27.5% of the total number of alleles, representing the main contributing mutation in 31.3% of TD patients. The origin of this mutation stems from Eastern-Mediterranean regions, including Turkey, Lebanon, and Egypt, it is believed to have been passed on to other regions by a variety of settler's diffusion [19]. It may be hypothesized that this mutation was introduced to Iraqi population through Seljoukids settlers (11th century), and the Ottomans (from 16th century until world war I), who have possibly served as a genetic vehicle for this mutation. The highest frequency rates documented to date being that of 34% in Nineveh Province [20].

The highest reported rate among neighboring non-Arab countries with (40%) was documented among Turkish population, being the most common mutation there [19]. The above data substantiate this research hypothesis, as the frequency of this mutation tend to follow the historic route of the Greeks and the Turks incursion of the country, with highest allele frequency reported in provinces with significant Turkoman population.

It has been reported that it is the most widespread mutation among Arabs with higher rates ranging from 12-38% in Arab countries of

the Eastern-Mediterranean and lower rates ranging from 0-2% in Gulf council countries [19].
IVS 2.1 {G>A} was the second most frequent allele, which was exhibited in approximately 22% of the total number of studied alleles, and represented the foremost contributing allele in 27.1% of our NTD patients. The study data is consistent with findings from another study in Baghdad, in which the predominant alleles were IVS 1.110 in 30.1%, and IVS 2.1 in 18.4% [21]. While in an earlier smaller sized study from Baghdad, IVS 1.110 was the second most common allele following IVS 2.1 that accounted for 29.03% [22]. Similarly, IVS 2.1 mutation was the highest documented mutation in Karbala [23], and in northeastern provinces of Iraq [24,25] It's worth mentioning that the above-mentioned allele was the most common HBB gene defect related to BT in all regions of Iran, with prevalence of more than 60%, which is the highest recorded prevalence in the world. It is believed that IVS 2.1 {G>A} mutation is native to Iran and one of the oldest known BT gene defects [26-28]. The authors propose that this mutation was introduced to the Iraqi genetic pool through recurrent episodes of invasions, migrations, and pilgrimage since antiquity. This proposition is implied by the higher mutation frequency in provinces with shared borders with Iran, or those with strong cultural, and ancestral ties to Iran.
The third ranking allele in the current study was Codon 44 {-C} that accounted for 8.8% of alleles, concentrating primarily among the TDT group. This mutation of Kurdish origin was also documented in other studies from Iraq. This mutation of Kurdish origin was also documented in other studies from Iraq; the closest to current finding is that of Al-Fatlawi et al., who reported a frequency of 8.33% [23] whilst previous molecular data from Baghdad city were quite heterogeneous, with one study characterizing this allele in only 4.9%, [21] and the other exhibited in 14.5% [22]. Generally, the present result lies in between those two values. The frequency of this mutation was higher in Kurdistan region, as it would be expected, with the highest documented frequency (23.2%) in Koya city, and lowest (12.5%) in Duhok city [29]. Data from neighboring countries have shown a considerably lower rates for the aforementioned allele, as it comprised a mean prevalence of 3.9% across Iran, 2% in Saudi Arabia and Syria, 1% in Kuwait, and 0.63 in Jordan [30]. However, the prevalence was expectedly higher in provinces with prominent Kurdish population as in South-Eastern Turkey [31,32] and North-East Iran [33].
Furthermore, other less common alleles characterized in the current study were: IVS 1.6 {T>C}, and Codon 36/37 {-T}, contributing to 13.2% of total alleles. The former allele is mostly frequent in the Middle-East, Italy and Greece [34] and it has been observed in most Arab countries, particularly in those in Eastern Mediterranean region like Palestine [35], Egypt [36]. In Iraq, this allele was detected in Baghdad [22], Karbala [23], and in Kurdistan [25], in which Erbil city has recorded the highest rate [37]. Codon 36/37, on the other hand, is believed to be an ancient Kurdish variant, that has been documented in Turkey [33], and West Central Iran, where large percentage of Lur and the Bakhtiaris resides [28]. In Iraq, interestingly, this allele was only reported twice, once in Baghdad [38], and once in northeastern provinces [39]. This is probably attributed to use of β globin detection kits lacking this specific variant, which has led the previous studies to miss its characterization.
The rest of the identified alleles namely; IVS 1.5 {G>C}, IVS 2.745 {C>G}, IVS 1-25 {25bp del}, Codon 41/42 {-TTCT}, Codon 8 {-AA}, Codon 5 {-CT}, Codon 39 {C>T}, and Codon 15 {TGG>TAG}, were relatively rare variants as each accounted for 5% or less of the total number of alleles, and have displayed sporadic distribution as mentioned in prior studies across different Iraqi provinces [20,23,25,37,40,41] (Figure 3). It is worth mentioning that the latter allele is novel to Baghdad city. Furthermore, we have noticed that the majority of the alleles identified in current study were quite familiar to those found in the neighboring countries in the Middle-East and the Arabian Peninsula, which can be attributed to the phenomenon of genetic continuity among the aforementioned populations that has been evidenced by demonstration of several shared population

genetic markers in recent studies [42]. The recent use of such molecular tools has permitted for the better understanding of the Iraqi population genetic makeup and its potential links to other populations.

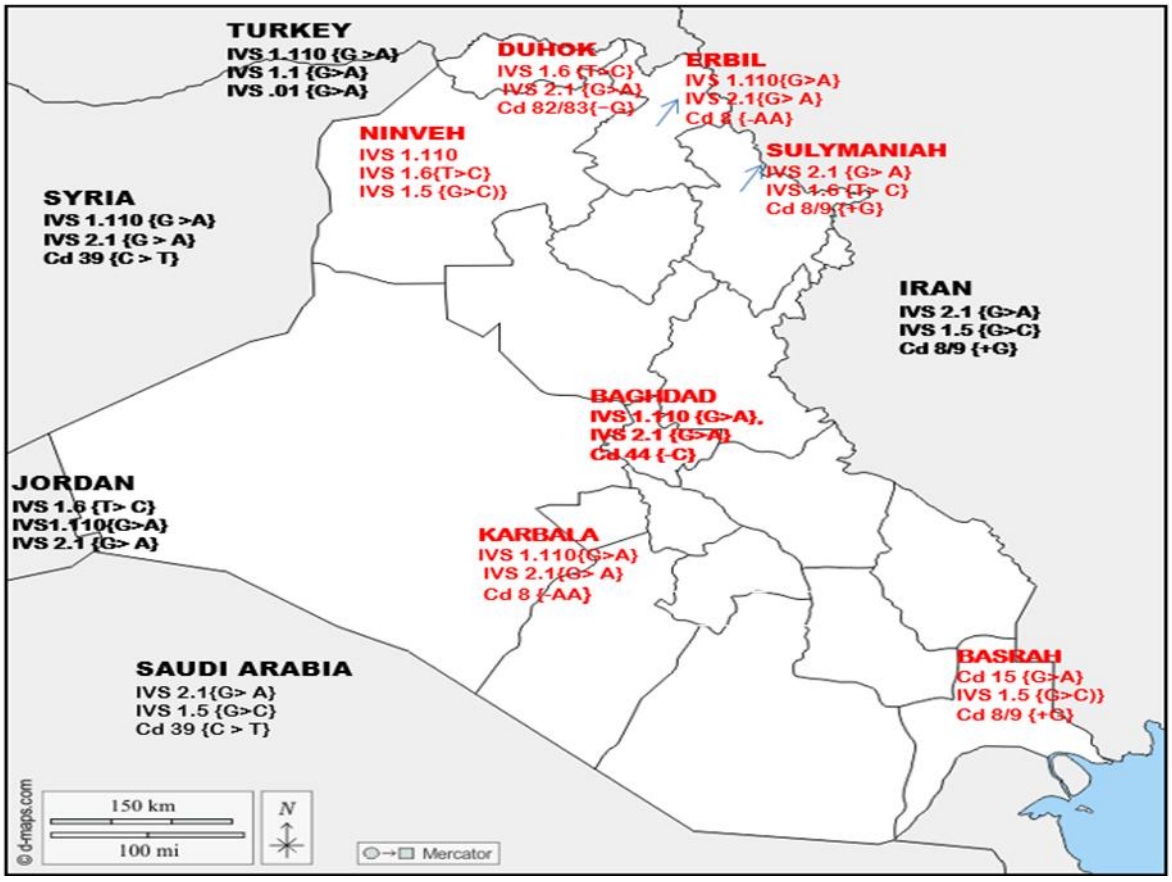

Figure 3. Distribution of dominant β-thalassemia alleles in Iraq and neighboring countries

In conclusion, the current study has provided data discerning the molecular landscape of BT in Baghdad, revealing a predominance of IVS 1.110 {G>A}, IVS 2.1 {G>A}, and Codon 44 {-C} mutations, together accounting for nearly two-thirds of alleles. The clustering of these discrete variants underscores both geo-historical diffusion and population-specific aggregation, reflecting genetic continuity with neighboring Middle Eastern populations. The predominance of the former allele among TD patients highlights potential direct clinical relevance. These findings not only refine the Iraqi mutational spectrum but also emphasize the urgent need for larger, representative molecular studies to capture rarer alleles. This hopefully will allow for the future construction of allele-specific preventive programs. Such initiatives are pivotal to reducing disease incidence, alleviating the economic burden, and strengthening public health strategies in limited- resource settings.

Acknowledgement

The authors are thankful to Professor Najwa Shihab of Biotechnology Research Centre, Al-Nahrain university for her assistance during the course of this work. The authors would also wish to extend their gratitude to all the members of the Ibn Al-Balady and Al-Karamah Hematology Centres for their help and support in carrying out this project work successfully.

Author contribution

Both authors have contributed directly to the construction of this paper, both authors have conceptualized, and designed the study plan. Dr. Al-Aqidi: did the sampling, lab work, results' interpretation, and wrote the manuscript, under direct supervision and support of Dr. Al-Mamoori.

Conflict of interest

There are no conflicts of interest.

Funding

Nil.

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Received Jun. 24th 2024
Accepted Sep. 10th 2024