IMPACT OF COINHERITANCE OF A-THALASSEMIA ON PHENOTYPE IN IRAQI KURDS WITH HOMOZYGOUS AND COMPOUND HETEROZYGOUS SEVERE B -THALASSEMIA

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ABSTRACT

Background: Patients with homozygous or compound heterozygous β0 thalassemia may present either with thalassemia major or intermedia. This phenotypic variability is the consequence of several genetic modifiers in different populations. We aimed to assess the frequency and the impact of coinheritance of α-thalassemia on phenotype in Iraqi Kurds.

Methods: A total of 125 patients characterized as homozygous or compound heterozygous β0 thalassemia were recruited in thalassemia center Duhok. They were classified based on age of starting and the frequency of transfusion (thalassemia major or intermedia). All patients had their DNA extracted and Gap-PCR performed to identify 3 deletions namely: –α 3.7, –α 4.2, and – –MED.

Results: The patients had a median age of 12 years (Range 2.0-35), with 63 males and 62 females. 96 patient with thalassemia major and 29 with intermedia. The most frequent β-mutations were IVS-2.1 (G>A), Codon 44 (-C), codon 5 (-CT) and codon 8 (-AA). Gap PCR identified α-thalassemia in 9 patients (7.2%), including –α 3.7 /αα in 8 cases and –α 4.2/αα in one patient, while none had a double α-gene deletions. The frequency of α-thalassemia was higher in thalassemia intermedia at 13.8% compared to 5.2% in major. This difference was statistically insignificant (P=0.228).

Conclusions: The patients not appear to be a significant with homozygous or compound heterozygous β0 thalassemia. This may be attributed to low background frequency of α-thalassemia, it being mainly due to a single α-gene deletion. Further studies including more patients with extended β-genotypes and other genetic modifiers may be worthwhile.

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Keywords: *β^0 thalassemia, Coinheritance of α-thalassemia, α-gene deletions, Gap PCR.*

Beta thalassemia is one of the most common inherited blood disorders in Eastern Mediterranean countries, including Iraq[1]. It is characterized by reduced (β+) or absent synthesis (β0) of the β-globin chains of hemoglobin[2]. In patients who are homozygous or compound heterozygous for β0 thalassemia mutations, t is associated with a heterogeneous phenotype, ranging from transfusion dependent severe thalassemia major (TM) to the less severe thalassemia intermedia (TI)[3]. Such heterogeneity of phenotype has been attributed to a variety of modifiers that affect the α/β chain imbalance, which, lies at the very center of the disease pathophysiology[4]. One of the first described modifiers is the coinheritance of alpha thalassemia, which by reduces the amount of alpha chains produced, leads to less α/β imbalance and consequently reduces the toxic impact of redundant free alpha chains on red cell maturation and survival[5]. In several populations where β-thalassemia is prevalent, α-thalassemia may also occur at considerable frequency, and thus serves an important modulator in these populations[6]. The impact of α-thalassemia on β-thalassemia in different populations varies not only because its frequency varies,

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but also because its molecular basis is different[7]. While previous studies on Iraqi Kurds focused on genetic modifiers in thalassemia intermedia[8],[9]. We aimed in the current study to assess the frequency and the impact of one such modifiers namely the coinheritance of α-thalassemia on phenotype (Thalassemia major versus Intermedia), in Iraqi Kurds who are homozygous or compound heterozygous for severe β0 thalassemia.

MATERIALS AND METHODS:

A total of 125 patients molecularly diagnosed as homozygous or compound heterozygous for severe β0 thalassemia and registered at the Duhok thalassemia center were recruited. Demographic data were obtained, and patients who received at least 8 units per year before the age of 4 years were categorized as thalassemia major, otherwise they were classed as Intermedia10.DNA was extracted by blood DNA extraction Kit (Qiagen, Germany). Gap PCR as detailed elsewhere was used to screen for the three deletions ($-\alpha^{3.7}$, $-\alpha^{4.2}$ and - - Med)[11]. The latter includes three multiplex PCR reactions (A, B and C). The primers that used in these reactions were synthesized by MWG (Germany) and their sequences were: P51 5' CTG CAC AGC TCC TAA GCC AC 3' , P52 5'CCT CCA TTG TTG GCA CAT TCC 3' ,P54 5' CTC AAA GCA CTC TAG GGT CCA3', P55 5' GTC CAC CCC TTC CTT CCT CA3' P59 5' CTC TAG GTC ACC CTG TCA TCA 3', P60 5' CTC TGT CGT GTA GAC GCC GA 3', P715'TAC CCA TGT GGT GCC TCC ATG 3' and P72 5' TGT CTG CCA CCC TCT TCT GAC 3' , Reaction A is a multiplex reaction utilized primers: P51, P52, P54, P59, and P60. Reaction B contained primers P55 and P54. While reaction C contained primers: P71, P72, and P52. All PCR reaction conditions were as detailed elsewhere[11]. The anticipated results for the various α-genotypes are detailed in table 1.

Table 1: Expected PCR product sizes (Base Pairs) in different α-thalassemia genotypes using various primer combinations11.

	Reaction A			Reaction B	Reaction C	
Alleles	P59-P60	P51-P52	P51-P54	P55-P54	P 71-72	P 71-52
− α3.7 / αα	-	298	446	2013-2271	-	233
− α4.2 / αα	-	298	446	2271	1596	233
--MED/αα	561	298	446	2271	-	233
− α3.7/− α3.7	-	-	446	2013	-	233
αα / αα	-	298	446	2271	-	233

The study was ethically approved by the scientific committee at the Department of Scientific Research Center, College of Science, University of Duhok, KRG, Iraq; and informed consent was obtained from all enrollees.

Statistics: An SPSS software was used for statistical analysis (BMI Corp, SPSS, v22; USA). Median and range and Chi squared test were used as appropriate. $P< 0.05$ was considered significant.

RESULTS:

The median age of enrolled patients was 12 years (range 2.0-35), and included 63 females and 62 males. The sample included 96 patients diagnosed with thalassemia major (76.8%) and 29 with thalassemia intermedia (23.2%). The median age of patients with thalassemia major was 10.5 years (range 2-27) with 53 females, while the median age of those with thalassemia intermedia was 15 years (range 4-35 years) with 10 females. The β-genotypes of the 125 enrollees are presented in Table 2. They

included 87 cases who were homozygous for β0-thalassemia mutations and 38 who were compound heterozygous for these mutations. The most common mutations among the enrolled patients were IVS2.1 (G>A), Codon 44 (-C), Codon 5 (-CT) and Codon 8 (-AA).

Table 2: The spectrum of β- genotypes in 125 patients with thalassemia major or intermedia recruited by the current study.

Genotype	NO.	%
IVS2.1(G>A)/IVS2.1(G>A)	25	20%
Codon44(-C)/codon44 (-C)	11	8.8%
Codon5(-CT)/codon5 (-CT)	11	8.8%
Codon8(-AA)/codon8 (-AA)	8	6.4%
Codon39(C>T)/ Codon39(C>T)	7	5.6%
IVS1.5(G>C)/ IVS1.5(G>C)	6	4.8%
IVS 1.1 (G>A)/ IVS1.1(G>A)	6	4.8%
IVS2.1(G>A)/ IVS 1.1 (G>A)	6	4.8%
IVS 1.130(G>C)/ IVS 1.130(G>C)	5	4%
codon44(-C)/ Codon5 (-CT)	4	3.2%
codon 8/9(+G)/ codon 8/9(+G)	4	3.2%
Codon82/83(-G)/ Codon82/83(-G)	4	3.2%
IVS2.1(G>A)/codon8(-AA)	3	2.4%
IVS2.1(G>A)/codon44(-C)	3	2.4%
IVS1.130(G>C)codon8/9(+G)	3	2.4%
Others	19	15.2%
	125	100%

Alpha thalassemia deletions were detected in 9 (7.2%) of the enrolled patients. They were –α3.7/αα in eight and –α4.2/αα in one patient. The Gap PCR results for each of these genotypes are presented in figures the figure1, 2, 3 show reaction A, B, and C respectively.

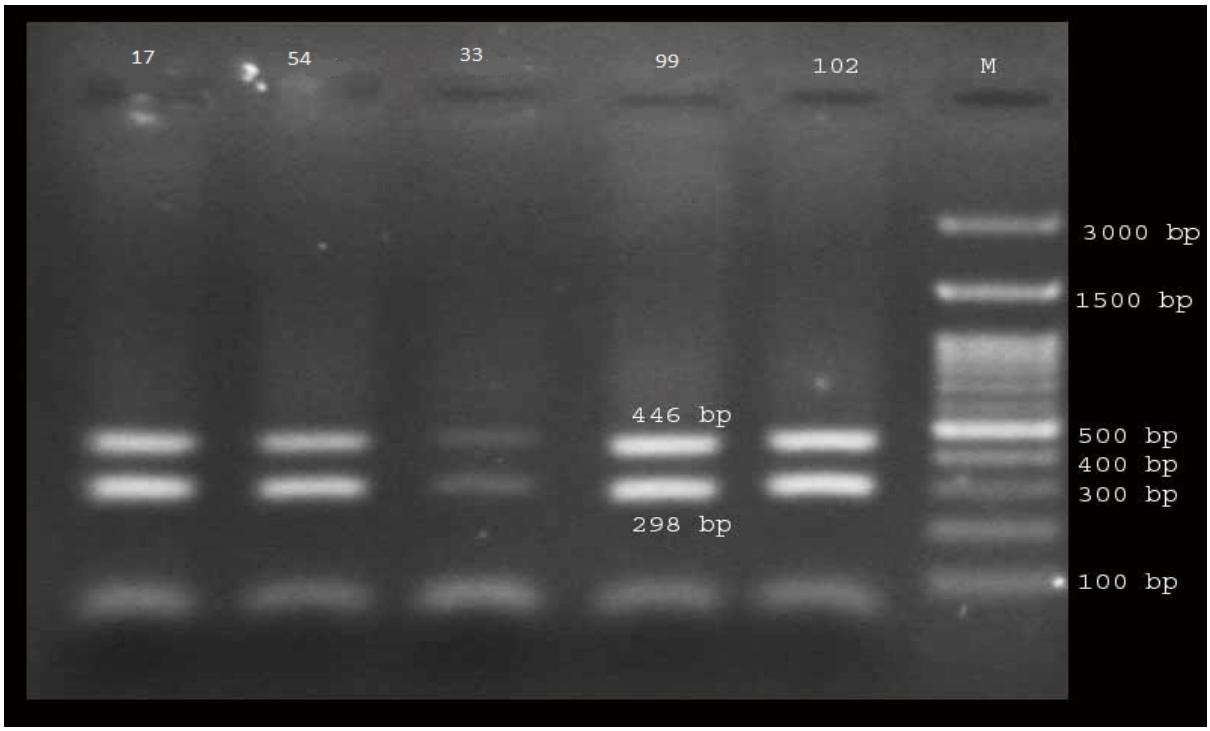

Figure 1: Analysis of the PCR products multiplex reaction A.; two bands are seen 298 bp and 446 bp in all samples (2% agarose gel electrophoresis).

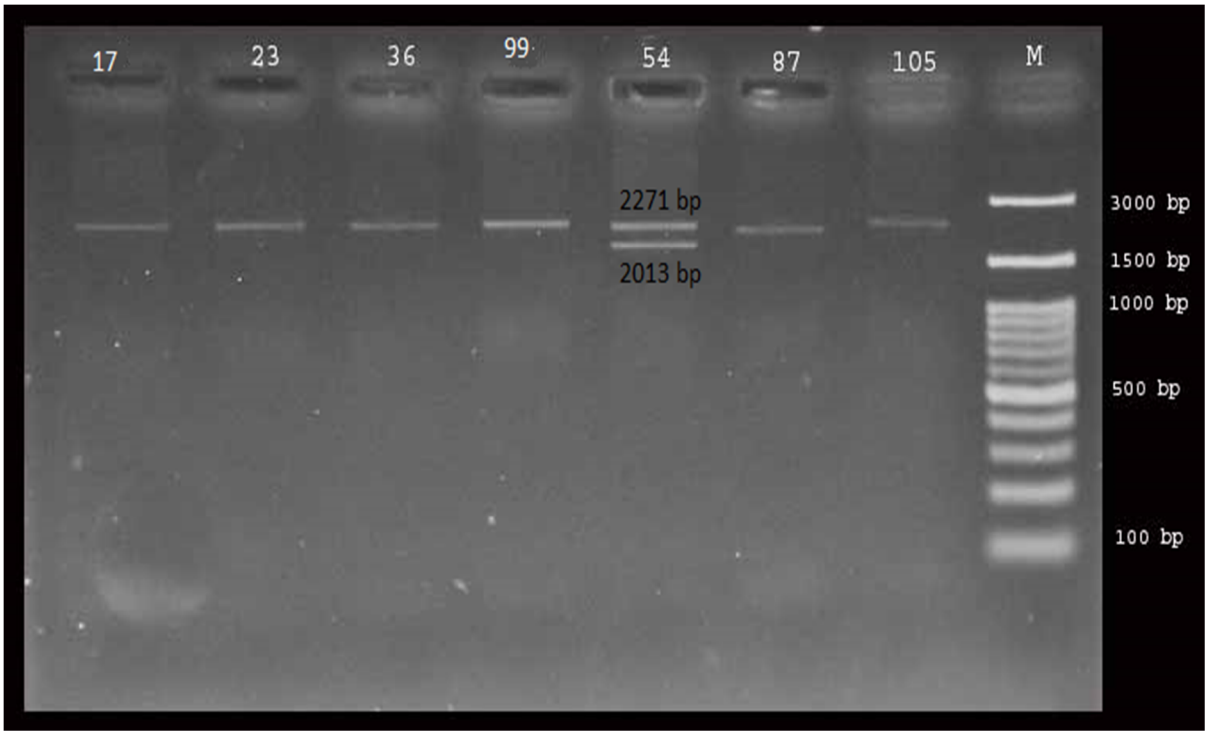

Figure 2: Analysis of the PCR products multiplex reaction B; Two bands are seen 2271 bp and 2013 bp in sample 54 while sample 17, 99 one band is seen 2271 bp (1% agarose gel electrophoresis)

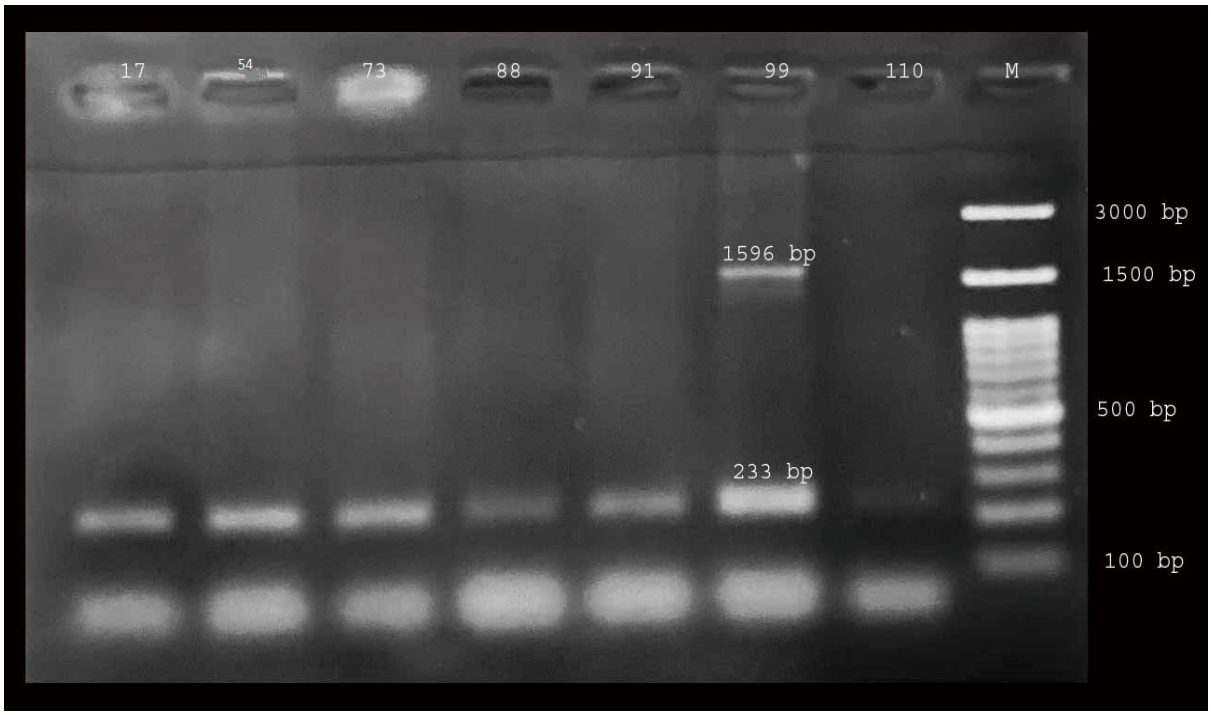

Figure 3: Analysis of the PCR products multiplex reaction C; two bands are seen 1596 bp and 233 bp in sample 99 while sample 17, 54 one band 233bp is seen (1.3 % agarose gel electrophoresis).

Alpha deletions were documented in 4/29 cases of TI (13.8%), compared to 5/96 cases of TM (5.2%). However, the difference was statistically not significant (P=0.228). The age, sex, β- and .As is showed α-genotypes, and phenotypes or each of the nine cases with alpha thalassemia are presented in Table 3.

Table 3: The age, sex, phenotype, β and α-genotypes in 9 patients who were identified as carriers of α-thalassemia in the current study

Case #	Age(year)	Sex	β-Genotype	α-deletions	Phenotype
1	4	Male	Codon5 (-CT) /IVS 1.130 (G>C)	− α3.7 / αα	Thalassemia major
2	9	Male	IVS 1.1 (G>A)/ IVS1.1(G>A)	−α3.7 / αα	Thalassemia major
3	2.5	Male	IVS 1.130(G>C)/ codon 8/9(+G)	− α3.7 / αα	Thalassemia major
4	15	Female	IVS 1.130(G>C) /IVS 2.1 (G>A)	− α4.2 / αα	Thalassemia major
5	6	Female	IVSI.5(G>C) /codon 8/9(+G)	− α3.7 / αα	Thalassemia major
6	7	Male	Codon8(-AA)/IVS2.1(G>A)	− α3.7 / αα	Thalassemia intermedia
7	24	Male	IVS2.1(G>A)/codon44(-C)	− α3.7 / αα	Thalassemia intermedia
8	25	Female	IVS2.1(G>A)/IVS2.1(G>A)	− α3.7 / αα	Thalassemia intermedia
9	13	Male	IVS2.1(G>A)/ IVS2.1(G>A)	− α3.7 / αα	Thalassemia intermedia

DISCUSSION:

Several genetic modifiers have been implicated in the heterogeneity of the phenotype of β- thalassemia in various populations. One of the key modulators that ameliorate phenotypes is the β-genotype, where a mild β+ or β++ mutation appears to have the most impact7.However, in the current study, we restricted our sample to those with severe β0 mutations, so that the β-genotype would not affect our analysis, leaving other factors that affect α/β chain imbalance as the main culprits and one of main modulators left is the coinheritance of α-thalassemia5.In the current study, it was documented that the most frequent α-thalassemia defect identified was the –α3.7 (rightwards deletion), while the leftwards deletion (–α4.2) was only seen in one case. The –α3.7deletion has been identified as the most frequent α-thalassemia determinant in three earlier studies from the Kurdistan region of Iraq12,13,14, and it is also the most prevalent α-thalassemia deletion worldwide 15. The former three studies also identified –α 4.2 as a much less frequent cause of α+ defects among Kurds. Although our study did not include screening for non-deletion α-thalassemia, this subcategory of α-thalassemia determinants is quite infrequent in our province and constitutes a mere 5% of characterized α-determinants12. Furthermore, all the nine α-thalassemia cases detected were single gene deletions (–α3.7/αα and –α 4.2/αα), and no cases with double gene deletions were identified (--/αα or –α/–α). Single α-gene deletions are also the most frequent or sole α-thalassemia determinant co-inherited with β-thalassemia from some other parts of the world, e.g. Iran, France, Italy, Malta, Cyprus, and Tunisia6,16,17,18,19. This is contrast to Southern and Southeast Asian countries, where double gene deletions are also frequently encountered6,20.

The overall frequency of α-thalassemia was a mere 7.2% in our cohort (corresponding to an allele frequency of 0.036). Galanello et al, in their study on Sardinian patients whose genotypes were β0β0 with TM and TI found that the allele frequency of α-thalassemia was 0.3621. Danjou et al in their study on Italians, revealed an overall α-allele frequency of 0.2922, while a study from India revealed an allele frequency of 0.135 among 100 patients with TI/TM23 .While, and similar to our study, a low allele frequency of α-thalassemia of 0.04 was documented by Baden et al in their French TI/TM cohort17.

The frequency of α-thalassemia in patients with TI in the current study was found to be 13.8%, which is consistent with earlier Iraqi studies that were restricted to TI and where frequencies of 14.9-16% were reported among those with β0β0 genotypes8,9.

However, our figures were lower than those reported among β0β0 patients with TI in a multicenter study including patients from India, Iran, Pakistan, Mauritius and Cyprus where the frequency was 29.8% 6 ,or from those reported among Sardinians with TI, where it was 76%21.Studies from Indian and Iranian TI patients documented α-thalassemia rates of 26% and 20.4%16,23 . On the other hand, lower frequencies of α-thalassemia were reported in TI among Palestinians (7.8%), French (9%) and Tunisians patients (5.9%)17,18,24.

Several studies have documented significantly higher frequencies of α-thalassemia among TI as compared to TM, including studies from Italy where the allele frequency of α thalassemia in TI was more than double that in TM21. Another multicenter study from three Mediterranean populations revealed a highly significant association between α-thalassemia and amelioration of phenotype in β-thalassemia19. Likewise, a study on French patients revealed a significantly higher frequency of α-thalassemia among TI vs TM by multivariate analysis 17.The findings of the current study revealed a higher frequency of α-thalassemia in TI vs TM (13.8% vs 5.2%), however, this was not significant, which is consistent with studies from Iran and India23. The absence of significant association in the current study may be explained by the low background frequency of α-thalassemia, and also by the fact that all α-genotypes detected were single gene deletions. It is believed that single α-gene deletions have little effect on the α/β imbalance, and thus their ability to ameliorate phenotypes is limited7.

In conclusion, it appears that the coinheritance of α-thalassemia does not appear to be a significant contributor on its own to ameliorating of phenotype in Iraqi Kurds with thalassemia, despite the fact that it is more prevalent in thalassemia intermedia. However, such a conclusion should be guarded, and larger studies including screening for other genetic modifiers concomitantly, and expanding to include patients with β0β+ and β+β+ as well as β0β0 may be more informative.

Conflict of interest:

None

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پوختە

کارتێکرنا بوماویی یا ئەلفا تالەسیمیا لسەر شێوە دەرەکی یێ کوردێن ئیراقێ ئەوێن هەلگرێن بێتا تالەسیمیا گران و دوو رەگی

پێشەکی و ئارمانج: دبیت نیشانێن نەخوشیێ دەرکەڤن ل نەخوشێن هەلگرێ تالەسیمیا یێت جورێ زایگوتێن وەکەڤ یان زایگوتێن نەوەك هەڤ ژ جورێ β^0 وەك تالەسیمیا مەزن یان مام ناوەند. رەنگە ئەڤ جورە جێوازییێن لسەر رووییێ نەخوشا دەرکەڤن ژ ئەنجامێ چەندین لیگورینێن جینی بن کو ب جێواز دەرکەڤن ب پێی جیوازییێن خەلکێ دەڤەرا.ئارمانج د ئەڤێ ڤەکولینا نافبری ئەوبوو کو جێوازییێن روخساری یێن نەخوشێن تالەسیمیا ژ جورێ ئەلفا دەربینین ل دەف کوردێن ئیراقێ.

ڕێك: 125 نەخوش هاتنە دەست نیشانکرن ئەوێن هەلگرێ تالەسیمیا یێت زایگوتێن وەکە ك هەڤ یان زایگوتێن نەوەك هەڤ ژ جورێ β^0 کو سەردەانا سەنتەرێ تالەسیمیا ل دهوك, ئیراق کرین. نەخوش هاتنە دابەشکرن لسەر بنەمایێ ژیێ دەستپێکێ ب توشبون ب تالەسیمیا و بەردەوام خوین وەرگرتن هەتا گەهشتیە تالەسیمیا مەزن یان مام ناوەند. ترشێ ناوکی (DNA) هاتەدەرئێخستن بۆ هەمی نەخوشا و Gap-PCR هاتە بکارئینا بو دەست نیشانکرنا سێ جورە کرداریێن ژێبرنێ کو بریتی بوون $\alpha^{3.7}$ – , $a^{4.2}$ –، و MED– –.

ئەنجام: تەمەنێ نافنجی یێ نەخوشێن هاتینە تومارکرن بریتی بوو ژ 12 سالا (2-35) دگەل 32 نێر و62 مێ. نافێ ئەڤاندا 96 نەخوش هەلگرێن تالەسیمیا ژ جورێ مەزن و 29 ژ جورێ مام ناوەند بوون. و زورترین بازدانێن جینی بریتی بوون ژ IVS-2.1 (G>A), Codon 44 (-C) ، Codon 5 (-CT),Codon 8 (-AA) ب ڕێکا Gap PCR دیاربوو کو ئەلفا تالەسیمیا یا نەھ نەخوشا (7.2٪) بوو و $\alpha^{3.7}$/αα – د نافێ هەشت نەخوشا دیاربوو, و $a^{4.2}$/αα – ل ئێك نەخوش دەرکەفت, ل دەمەکی دا هیچ نەخوشەك هەلگرێ ژێبرنا جوت ل جینێ ئەلفا دیارنەبوو. دوبارەبوونا ئەلفا تالەسیمیا ژ جوری مام ناوەند13.8٪ بلندتربوو ژ جورێ تالەسیمیا مەزن 5.2٪ و سەرەرای ئەڤێ جێوازییێ هیچ ئاماژێن بەراوەرکر نێن ئەرێنی نەبوون (P = 0.228).

دەرئەنجام: د ئەنامان دا وەسا دیاربوو کو ئەلفا تالەسیمیا ل دەف کوردێن ئیراقێ جێوازیەکا ئەرێنی نینە دناف هەردوو جورێن زایگوتێن وەکەڤ و نەوەك هەڤ ئەگەر ب جودا بهێنە دەرئێخستن. دبیت کو ئەڤە ب زفریت بۆ کێمتر دەرکەفتنا کریارا دوبارەبونێ ل جورێ ئەلفا تالەسیمیا کو هەمی دزفریت بۆ گوهرینا ئێك جورە جین ل ئەلفا تالەسیمیا. هەروەسا دبیت یا مفابیت کو زێدەتر ڤەکولین بهێنەئەنجام دان تایبەت لسەر ئەو نەخوشێن ژ جورێ بێتا تالەسیمیا β هەروەسا کو دبیت ئەنجامین جێوازتر بهێنە دەرئێخستن.

الخلاصة

تأثير توارث الفا ثلاسيميا على النمط الظاهري في كورد العراق المصابين ب بيتا ثلاسيميا الحادة الهجين والمركبة

الخلفية والأهداف: من الممكن للمرضى الذين يعانون من الثلاسيميا متماثل الزيجوت أو متغاير الزيجوت نوع β0 أن يظهرون سريريا" كثلاسيميا كبرى أو متوسطة. هذا التباين المظهري هو نتيجة للعديد من المعدلات الجينية التي يختلف تأثيرها باختلاف المجموعات السكانية. هدفنا في الدراسة الحالية إلى تقييم تواتر وتأثير مرض الثلاسيميا ألفا على النمط الظاهري لدى الأكراد العراقيين.

الطرق: تم تجنيد ما مجموعه 125 مريضاً بالثلاسيميا يتميزون جزيئياً بأنهم متماثلي الزيجوت أو متغايري الزيجوت نوع β0 من مركز الثلاسيميا في دهوك، العراق. تم تصنيف المرضى على أساس عمر البداية وتكرار نقل الدم إلى ثلاسيميا كبرى أو متوسطة. تم استخراج الحمض النووي لجميع المرضى وإجراء Gap-PCR لتحديد ثلاث عمليات حذف وهي: α 3.7-، α4.2–، وMED – –.

النتائج: كان متوسط عمر المرضى المسجلين 12 عامًا (النطاق 2-35)، مع 63 ذكرا و62 أنثى. وكان من بينهم 96 مريضا بالثلاسيميا الكبرى و29 مريضاً بالوسطى. وكانت الطفرات الأكثر شيوعا هي2.1 IVS- (G>A) , و Codon 44 (-C) , Codon 5 (-CT) وCodon 8 (-AA). حدد Gap PCR الالفا ثلاسيميا في تسعة مرضى (7.2٪)، بما في ذلك αα/ α3.7 – في ثمان حالات و αα/α4.2 – في مريض واحد، في حين لم يكن لدى أي منهم حذف مزدوج لجين ألفا. كان تواتر ألفا ثلاسيميا أعلى في الثلاسيميا المتوسطة بنسبة 13.8% مقارنة بـ 5.2% في الكبرى. ومع ذلك، كان هذا الاختلاف غير مهم إحصائيا (P = 0.228).

الاستنتاجات: لا يبدو أن الثلاسيميا نوع ألفا تشكل معدلا هاما في الأكراد العراقيين المصابين بمرض الثلاسيميا متماثل الزيجوت أو متغاير الزيجوت بيتا، أذا أخذت لوحدها. ويمكن أن يعزى ذلك إلى انخفاض تواتر لثلاسيميا ألفا، أضافة أنها بجلها نتيجة حذف جين ألفا واحد. قد يكون من المفيد إجراء مزيد من الدراسات بما في ذلك المزيد من المرضى الذين لديهم أنماط β ثلاسيميا وراثية مختلفة ومعدلات وراثية أخرى.