

Spectrum of Alpha Thalassemia Alleles in Kuwait

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Abstract

Background: The frequency of alpha thalassemia trait is about 40% in the Kuwaiti population, but there has been no comprehensive study of the prevalent alleles. This is a report of the patients who were referred for molecular diagnosis over a 20-year period.

Methods: Blood samples from suspected cases were sent to the Hemoglobin Research Laboratory of the Department of Pediatrics, Kuwait University. A retrospective study of the molecular characterization of samples from 1994 to 2015 was carried out. The alpha globin genotypes were determined by a combination of PCR, allele-specific oligonucleotide hybridization and reverse dot-blot hybridization (Vienna Lab Strip Assay).

Results: 400 samples were characterized and analyzed from individuals aged <1 month to 80 years, with a median of 6 years (~60% children and adolescents). Most (90.8%) were Kuwaiti nationals. The common genotype was homozygosity for the polyadenylation-1 mutation (α PA-1 α / α PA-1 α) in 33.3%, followed by heterozygosity ($\alpha\alpha$ / α PA-1 α) for the same mutation in 32.3%. The PA-1 was therefore the most frequent allele (0.733). The frequency of the α^0 , -MED was 0.19. Rare alleles that were found in very low frequencies included the α^0 (-FIL) in a Filipino child, Hb Constant Spring, Hb Adana, and Hb Icaria.

Conclusion: There is a wide variety of alpha thalassemia alleles among Kuwaitis, but the nondeletional PA-1 is by far the most common cause of moderate to severe HbH disease phenotype. The α^0 (-MED) allele is also encountered, which has implications for pre-marital counselling especially the possibility of having babies with alpha thalassemia major (Barts hydrops fetalis).

Background

Alpha thalassemia is one of the most widespread genetic diseases worldwide, with frequencies of the carrier state reaching up to 80 – 90% in some areas [1]. In tropical Africa it is about 25 – 30% [2], while in the Arabian Peninsula, it varies from a low of close to zero in the desert areas to as high as 60% in the agricultural zones of Eastern Saudi Arabia [3, 4].

The normal individual has a complement of four α -globin genes ($\alpha\alpha$ / $\alpha\alpha$), any one of which can be absent, producing varying degrees of alpha thalassemia [1]. In α^0 alleles, both genes on a chromosome are deleted (-), while in α^+ , a variable portion of the α^2 and/or α^1 gene is deleted, resulting in reduction in chain synthesis. The size of the deletion in α^0 alleles is variable and each is named for the part of the world where it is prevalent. Thus -MED, -FIL, -SEA are found in the Mediterranean, Philippines and South East Asia, respectively [5]. The α^+ deletions are designated by their sizes and the commonest is the - $\alpha^{-3.7\text{kb}}$ allele. One- or 2-gene deletions (- α / $\alpha\alpha$, - α / α , -/ $\alpha\alpha$), produce alpha thal trait, which is usually associated with mild microcytic, hypochromic anemia. The loss of 3 genes (-/ α) produces the classical HbH (β_4 tetramers) disease, which is characterized by moderate to severe anemia. The loss of all 4 genes

(-/-) causes Hb Bart's (γ_4) hydrops fetalis, which is incompatible with life in the absence of early onset of chronic transfusion or stem cell transplantation [6].

Apart from deletions, there are a few point mutations that affect the transcriptional efficiency of the α globin genes and are designated $\alpha^T\alpha$ or $\alpha\alpha^T$ depending on whether the α_2 or α_1 gene is affected [7]. Collectively, these nondeletional α -thalassemia alleles commonly affect the promoter, the initiation codon (ATG), splicing signals (GT/AG), the termination codon (TAA), and the polyadenylation signal (AATAAA) of the affected gene. Of these, the most common are the $\alpha^{IVSI(-5\text{ nt})}\alpha$ (in Mediterraneans), polyadenylation site mutations α_2^{AATAAG} , α_2^{AATGAA} and α_2^{AATA-} (in the Mediterranean and Middle East) [7-11], termination codon mutations leading to elongated Hb variants, such as Hb Constant Spring (HbCS), Hb Icaria, Hb Koya Dora, Hb Seal Rock and Hb Pakse [12-14]. Heterozygotes for these alleles have a thalassemia minor phenotype, but homozygotes and compound heterozygotes often have HbH disease of varying severity and blood transfusion requirements.

Alpha thalassemia frequency is about 30 – 40% in Kuwait and HbH disease is mostly linked to the polyadenylation (polyA, α^{PA-1}) mutation [15, 16]. However, there has been no comprehensive study of the spectrum of alpha thalassemia alleles in the country. The present study was carried out to document the frequencies of moderate to severe alpha thalassemia phenotypes among patients referred for molecular diagnosis. In particular, it aimed to investigate the presence of the α^0 allele in the population, to determine the possibility of having a newborn with alpha thalassemia major (Hb Bart's hydrops fetalis) [1, 17]. This will enable more purposeful counselling of patients and empower physicians in the identification of patients who require further investigations. To this end, we have analyzed all cases of suspected α -thalassemia referred to the hemoglobin research laboratory in Kuwait University over a 20-year period.

Methods

The hemoglobin research laboratory in the Department of Pediatrics, Kuwait University receives samples from the hematology clinics in Mubarak Al-Kabeer Hospital and some of the other government hospitals in Kuwait. The study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Kuwait University and the Ministry of Health, Kuwait. Patients were suspected to have some form of α -thalassemia if they have persistent microcytic, hypochromic anemia in the absence of iron deficiency and with normal hemoglobin electrophoresis. Some patients had H inclusions on cresyl blue staining of the peripheral erythrocytes or H band on high performance liquid chromatography (HPLC). Quite often, but not always, there was a record of the clinical presentation and the complete blood count (CBC). This study is a retrospective study of all such samples analyzed from 1994 to 2005.

Blood was obtained by venipuncture into EDTA, complete blood count was done using ABX Pentra 120 cell counter (ABX France, Montpellier). The hemoglobin quantitation was determined using cation-exchange high performance liquid chromatography (HPLC) - Shimadzu LC-20AT, Shimadzu Corporation, Kyoto, Japan. DNA was isolated from peripheral leucocytes using phenol extraction. All the samples were screened for the α -thal-2 (-3.7 kb) deletion [18] and the α_2 -globin gene polyadenylation site

(AATAAA@AATAAG) mutation using a PCR method and allele-specific oligonucleotide hybridization respectively as previously reported [18, 19]. All other samples that were not solved with these methods, were subjected to reverse-dot blot hybridization using the Vienna Lab StripAssay technique (Vienna Lab Diagnostics, Vienna, Austria).

The ethnic origins of the patients were documented by their nationalities. The different α -globin genotypes were identified and the allele frequencies calculated. The mean Hb level and RBC indices compared among patients with different genotypes. Clinical data were collected from the HbH disease patients, especially whether they were being followed in a hematology clinic and if they were on any medications or how often they were transfused with blood.

The disease severity was classified as silent carrier, α -thalassemia trait and HbH disease depending on the number, type and location of mutations detected, in addition to the clinical phenotype and presence of HbH inclusions or H band on HPLC [1, 17, 20]

Data are presented as means \pm SD or as percentages as appropriate. Statistical differences between mean values among the major groups were tested using Student t test.

Results

Over the period of the study from 1994 to 2015, there were 400 samples received as suspected moderate to severe alpha thalassemia or HbH disease. Of these, 183 were females and 217 males, with ages ranging from 1 to 80 years and median of 6 years. Most (90.8%) patients were Kuwaitis with a few other nationalities as shown in Table 1. They were from 283 families with the nationality being documented in 240, of whom 215 (89.6%) were Kuwaiti.

Table 2 shows the distribution of α -globin genotypes in the study. The most common (33.3%) was homozygosity for the α^{PA-1} (c.*94A>G), nondeletional α -thal allele, which gives a HbH disease phenotype, followed by heterozygosity for the same allele (32.3%). The compound heterozygosity of $-\alpha^{3.7}/\alpha^{PA-1}$ was the next common at 20.5%. None of the other frequencies reached double digits.

When the patients were classified according to the α -thalassemia severity, 3 (0.8%) were carriers, 154 (38.5%) were α -thalassemia trait, while 243 (60.8%) had HbH disease. Table 3 shows the Hb and RBC indices in the 3 groups of patients. When values are compared between the patients with α -thal trait and those with HbH disease, all the indices were significantly lower in the latter ($P < 0.05$), although the mean Hb was not lower than 10 g/dl in all groups, showing that α -thalassemia phenotypes are relatively mild in this population. None of the patients was on a chronic transfusion therapy, but many had received sporadic transfusions. The patients with the most severe phenotypes in the study were 2 siblings with $-\text{MED}/\alpha^{CD19}\alpha$ genotype. They both had poor growth parameters and baseline Hb of < 6 g/dl and are now transfused every 6 to 8 weeks. Interestingly, they have 2 other affected siblings who do not require transfusions.

Table 4 shows the frequencies of the common individual alleles in the whole population and among the Kuwaiti individuals in the study. The PA-1 allele was the most frequent, at ~0.60 in both groups, followed by the $-\alpha^{-3.7\text{ kb}}$ deletion at 0.153. Interestingly, the $\alpha^0\text{-MED}$ (0.019), $-\alpha^{-4.2}$, $\alpha^{2\text{cd}142\text{ (T}\delta\text{C)}}$ (Hb Constant Spring, c.427T>Cp.X143Gln), $\alpha^{2\text{cd}59\text{ (G}\delta\text{A)}}$ (Hb Adana, c.179G>Ap.Gly60Asp), $\alpha^{\text{PA-2}}$ (c.*92A>G), $\alpha^{2\text{cd}142\text{ (T}\delta\text{A)}}$ (Hb Icaria, c.427T>Ap.X143Lys) alleles were all found only among Kuwaitis. When the frequencies were computed based on the total number of families in the study, again, PA-1 allele was most frequent at 0.0552, followed by $-\alpha^{-3.7\text{ kb}}$ deletion in 0.18. This was approximately the same when only Kuwaiti families were considered.

Discussion

The molecular diagnosis of α -thalassemia is not straight forward and requires resources that are not readily available in many centers. Moreover, in many countries with a high prevalence, it is economically unviable to provide this service to all suspected cases. It is therefore necessary to have a good understanding of the prevalent genotypes and phenotypes, which will facilitate genetic counselling and the identification of patients who really deserve molecular diagnosis. This report is limited to patients who were suspected to have moderate to severe alpha thalassemia based on persistent microcytic, hypochromic anemia, no laboratory evidence of iron deficiency and normal hemoglobin electrophoresis or HPLC. It also included patients with H inclusion bodies and/or H band on HPLC.

Given the selection criteria for screening patients in this study, it is not surprising that only 0.3% were carriers, 38.3% had thalassemia trait and 60.8% had HbH disease. A previous study from Kuwait had shown that most alpha thal carriers had Hb levels >10 g/dl. Therefore individuals with mild microcytosis and hypochromia, but with Hb >10 g/dl and no HbH inclusions or band, should not be considered for molecular diagnosis, but counselling should be offered after screening the family with CBC and HPLC, to rule out β -thalassemia. Resources can then be channeled to individuals with a more severe picture to identify those with HbH disease that need to be followed in the clinic.

The study has revealed the extent of the diversity among individuals with alpha thalassemia in Kuwait. As expected, the vast majority of the patients had the $\alpha^{\text{PA-1}}$ nondeletional allele, which has been reported as the commonest cause of HbH disease in Kuwait and in the region. The frequency of the allele in this study was 0.733. It was found as homozygote in 33.3% of the patients, while heterozygotes accounted for 32.3%. It was present as a compound heterozygote with $-\alpha^{-3.7\text{ kb}}$ in 20.5% and in combination with other alleles like $-\text{MED}$, $-\alpha^{-5\text{ nt}}$, $\alpha^{\text{cd}59}$ and $\alpha^{\text{PA-2}}$.

The third most frequent allele in this study turned out to be the α^0 , $-\text{MED}$, which was found in 13 patients, in whom it presented a HbH disease phenotype in 10. Of the latter, it was in compound heterozygosity with the $\alpha^{2\text{cd}19\text{-G}}$ in 6 patients from 2 related families, with the $-\alpha^{-3.7\text{ kb}}$, in 2 patients, the $\alpha^{\text{IVS1-5nt}}$ and the $\alpha^{\text{PA-1}}$ in 1 patient each.

The α^{PA-1} allele was first described from Eastern Saudi Arabia[10] and previous studies from Kuwait[2, 16] had highlighted its role in the etiology of HbH disease among our patients. It has also been reported as the commonest cause of HbH disease in Saudi Arabia[21], Jordan, [22], Bahrain[23] and UAE[24]. The allele is therefore widespread in the Arabian Gulf, especially in the countries adjoining Saudi Arabia. It is uniformly associated with a moderate thalassemia intermedia phenotype with only occasional blood transfusion requirement, usually with intercurrent infection [16]. HbH disease is mainly a disease of childhood in Kuwait. Most patients are referred to the clinic for investigation of persistent microcytic, hypochromic anemia not responding to iron therapy. Indeed, the anemia tends to improve as the child stops rapid growth and enters puberty.

This study is the first to report the presence of the α^0 , $-\text{MED}$ allele among Kuwaiti patients. In 3 cases, it was as simple heterozygotes while in 10 cases, it was as compound heterozygotes with the pentanucleotide (5nt) deletion in the $\alpha^{\text{IVS1-5nt}}$ in 1, the α^{PA-1} mutation in 1, the $-\alpha^{-3.7}$ in 2, and the α^{cd19} (G/A) in 6 (from 2 related families). In all these instances, the phenotype was mild with moderate anemia. However, in 2 patients with the $-\text{MED}/\alpha^{\text{cd19}}$ genotype, the patients were stunted in growth and were on regular transfusion. The other rare alleles found in the study included the α^0 ($-\text{FIL}$) in a Filipino child, HbCS ($\alpha^{\text{Cd 142 TAA} \rightarrow \text{CAA}}$), Hb Adana ($\alpha^{\text{cd59G/A}}$), α^{PA-2} ($\text{AATAAA} \rightarrow \text{AATGAA}$), Hb Icaria ($\alpha^{\text{Cd 142 TAA} \rightarrow \text{AAA}}$).

Conclusions

This study has demonstrated the diversity of the alpha thalassemia alleles among Kuwaitis. While the deletional allele is quite widespread, the nondeletional α^{PA-1} is responsible for most of the moderate to severe HbH disease. Interestingly, the $\alpha^{0-\text{MED}}$ allele is also encountered, with implications for pre-marital genetic counselling to prevent the birth of babies with alpha thalassemia major (Bart's hydrops fetalis).

List Of Abbreviations

PCR	Polymerase chain reaction
PA	Polyadenylation
MED	Mediterranean
FIL	Filipino
SEA	Southeast Asia
Kb	Kilobases
Hb	Hemoglobin
CS	Constant Spring

CBC	Complete blood count
EDTA	Ethylenediaminetetraacetic acid
SD	Standard deviation
ANOVA	Analysis of variance
UAE	United Arab Emirates

Declarations

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Declarations

Authors' Contributions

1. AA was the lead physician who planned the study and carried out the analysis and wrote the first draft
2. MH was the head of the laboratory and carried out the molecular characterization. He contributed to the writing
3. JS, DT and MS all contributed to sample and data input/analysis
4. All authors have read and approved the manuscript

Ethics Approval and Consent to Participate

The study was approved by the Human Research Ethics Committees of the Faculty of Medicine, Kuwait University and the Ministry of Health, Kuwait.

Consent for Publication

No identifying images or other personal or clinical details of participants are presented. Hence, consent for publication is not applicable to our manuscript.

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Competing Interests

There are no other competing financial or non-financial interests.

Availability of Data and Materials

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1

Nationalities of the Patients of the Patients in the study

Nationality	n	%
Kuwaiti	317	90.8
Iraqi	10	2.9
Egyptian	6	1.7
Lebanese	4	1.1
Non Kuwaiti Bedouin	3	0.9
Syrian	3	0.9
Others	6	1.7
Total	349	100.0

Table 2

Distribution of Alpha Globin Genotypes of the Patients in the Study

Genotype	Number	%
$\alpha^{PA-1}\alpha/\alpha^{PA-1}\alpha$	133	33.3
$\alpha^{PA-1}\alpha/\alpha\alpha$	129	32.3
$-\alpha^{3.7}/\alpha^{PA-1}\alpha$	81	20.5
$-\alpha^{3.7}/-\alpha^{3.7}$	20	5.0
$--MED/\alpha^{CD19}\alpha$	6	1.5
$\alpha^{CD59}\alpha/\alpha\alpha$	4	1.0
$-\alpha^{3.7}/\alpha\alpha$	3	0.8
$--MED/\alpha\alpha$	3	0.8
$\alpha^{5nt}\alpha/\alpha^{5nt}\alpha$	3	0.8
$-\alpha^{3.7}/\alpha^{5nt}\alpha$	2	0.5
$-\alpha^{3.7}/--MED$	2	0.5
$\alpha\alpha/\alpha^{CD19}\alpha$	2	0.5
$\alpha^{5nt}\alpha/\alpha^{PA-1}\alpha$	1	0.3
$--MED/\alpha^{5nt}\alpha$	1	0.3
$--MED/\alpha^{PA-1}\alpha$	1	0.3
$\alpha^{CS}\alpha/\alpha^{CD142}\alpha$	1	0.3

$\alpha^{PA-2}\alpha/\alpha\alpha$	1	0.3
$\alpha^{5nt}\alpha/\alpha\alpha$	1	0.3
$-\alpha^{4.2}/-\alpha^{4.2}$	1	0.3
$\alpha^{CD19}\alpha/\alpha^{CD19}\alpha$	1	0.3
$\alpha^{PA1}\alpha/\alpha^{PA2}\alpha$	1	0.3
$\alpha^{CD59}\alpha/\alpha\alpha$	1	0.3
$\alpha^{CD59}\alpha/\alpha^{PA-1}\alpha$	1	0.3
$\alpha^{CD59}\alpha/\alpha^{5nt}\alpha$	1	0.3
$--SEA/-\alpha^{3.7}$	1	0.3
Total	400	100

Table 3

Red Blood Cell Indices in Patients

Group	Hb g/dl	MCV fl	MCH pg
Carrier	10.4 ± 0.8	60.7 ± 9.5	19.8 ± 2.5
Trait	11.3 ± 2.0	64.4 ± 11.0	21.1 ± 3.5
HbH	10.0 ± 1.6	59.2 ± 8.7	18.3 ± 3.1
Total	10.5 ± 1.9	61.2 ± 10.0	19.4 ± 3.5

Table 4

Frequency of the Common Alpha Thalassemia Alleles in the Study

Allele	All population		Kuwaiti	
	N = 698	Frequency	N = 634	Frequency
AATAAA□AATAAG (PA-1)	412	0.590	386	0.608
-α-3.7 single gene deletion	107	0.153	91	0.143
--MED double gene deletion	12	0.017	12	0.019
α2 cd19 (-G)	10	0.0143	9	0.0141
α2 IVS-1 (-5nt)	8	0.011	5	0.008
α2 cd59 (GàA)	4	0.006	4	0.006
-α-4.2 single gene deletion	2	0.003	2	0.003
AATAAAàAATGAA (PA-2)	2	0.003	2	0.003
α2 cd 142 (TàC) Hb Constant Spring	2	0.003	2	0.003