Molecular nature of alpha-globin genes in the Saudi population

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ABSTRACT

الألفا-ثلاسيميا هو اضطراب ناجم عن حذف في جينات الألفا-جلوبين مفردة كانت أو مزدوجة، وقد يكون بسبب أنواع الطفرات الأخرى التي تحدث في سلسلة الألفا-جلوبين. هناك نوعان شائعان من الألفا-جلوبين وهما *HBA2* و*HBA1*. مؤخراً، تم اكتشاف أن الجين *HBA2* قد تم استبداله بواسطة جين أخر فريدٌ من نوعه يسمى *HBA12* وذلك في ما يقارب 5.7% من السكان السعوديين. جين الألفا-جلوبين قد ظهر كهدف جزيئي يستخدم كوسيلة في علاج البيتا-ثلاسيميا. وبالتالي، فمن الضروري أن نفهم الطبيعة الجزيئية لجينات الألفا-جلوبين لتساعد في علاج اضطرابات الهيموجلوبين الأكثر انتشاراً في المملكة العربية السعودية مثل أمراض فقر الدم المنجلي (sickle cell disease) وكذلك أمراض الألفا والبيتا-ثلاسيميا (α and β-thalassemia). وجد أن هناك 32 مورثة جينية مختلفة من الألفا-جلوبين قد لوحظت لدى السكان السعوديين. هذا الاستعراض البحثي سيحدد لنا التصنيف الجيني لسلسلة الألفا-جلوبين بناء على أساس الطبيعة الجزيئية لها ولمجموعات معقدة من جينات الألفا-جلوبين ومتغيراتها السائدة في السكان السعوديين.

Alpha-thalassemia (α-thal) is a disorder caused by the deletion of single or double α-globin genes, and/or point mutations in the α-globin genes. There are 2 common types of α-globin genes; *HBA2* and *HBA1*. Recently, it has been discovered that the *HBA2* gene is replaced by a unique *HBA12* gene convert in 5.7% of the Saudi population. The α-globin genes have been emerging as a molecular target for the treatment of β-thalassemia (β-thal). Hence, it is essential to understand the molecular nature of α-globin genes to treat the most prevalent hemoglobin disorders, such as sickle cell disease, α-thal, and β-thal prevalent in the Kingdom of Saudi Arabia. Thirty-two different α-globin genotypes have been observed in the Saudi population. This review outlines the classification of the α-globin genes on the basis of their molecular nature and complex combinations of α-globin genes, and their variants predominant in Saudis.

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Thalassemia (alpha [α] and beta [β]) and sickle cell disease (SCD) are the most prevalent hemoglobin disorders in the Kingdom of Saudi Arabia.[1-11] Alpha-thalassemia (α-thal) is a disorder caused by the deletion of single or double α-globin genes, and/or point mutations in the α-globin genes.[10] Alpha-thalassemia phenotype varies from very mild or microcytic hypochromic anemia to a lethal form of hemolytic anemia, depending on the type of molecular defects in α-globin genes.[10] Alpha-globin genes are of 2 types; hemoglobin alpha 1 (*HBA1*) and hemoglobin alpha 2 (*HBA2*). The *HBA1* and *HBA2* genes are located in the p arm (short arm) of chromosome 16 at region one, band 3, and sub-band 3. Altogether there are 4 genes ($\alpha_1\alpha_2/\alpha_1\alpha_2$) in a person corresponding to 4 α-globin proteins. Out of the 4 α-globin genes, 2 are inherited from the father, and others from the mother. Loss of single or all of these genes results in different types of α-thal. The α-globin protein is a subunit of hemoglobin, which is a larger protein in red blood cells (RBC) that carries oxygen throughout the body. Alpha-globin proteins of *HBA2* and *HBA1* genes are nearly identical. Alpha-globin protein is subunit of fetal hemoglobin (HbF), which is active only in the human fetus and in the newborn period until roughly 6 months old. Exceptionally, in non-transfusion dependent β-thal cases, HbF is elevated and active throughout life. Reduced synthesis of α-globin protein ameliorates the clinical severity of

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β-thallassemia. Alpha-globin is an emerging molecular target for treatment of β-thal.[12] Hence, it is essential to understand the different types of globin genes and its variants prevalent in Saudi population.

The α-globin genes in Saudis. A number of research reports were available on the analysis of mutations and deletion in the α-globin genes from Saudi population.[1-11,13-20] Commonly, α-globin genes are of 2 types (*HBA2* and *HBA1*), while in Saudis it is of 3 types namely *HBA2* (α_2), *HBA1* (α_1), and *HBA12* (α_{12}).[8] The *HBA12* is a new convert of the *HBA2* gene, discovered in Saudis. The *HBA2* has been replaced with *HBA12* in 5.7% of Saudi population.[8] The poly A mutation [AATAAA>AATAAG] (41%), and the $\alpha^{3.7}$ α^{+} heterozygous deletion are the most reported mutations and deletion in Saudi population. Co-inheritance of α-globin gene and β-globin gene mutations are prevalent in Saudis.[7-9]

The α-globin gene conversion. A recent study by Borgio et al[8] using direct sequencing of *HBA1* and *HBA2* in Saudis revealed a new gene, which was very closely related to the common α-globin genes (*HBA1* and *HBA2*). They named the new gene as *2* They clearly described that the formation the *HBA12* was formed by the combination of *HBA1* and *HBA2* gene sequences through a process called gene conversion (**Figure 1**). Gene conversion is the process of the transfer of genetic material unidirectionally from a donor to an acceptor.[21] Gene conversion between the 2 homologous α-globin genes is common.[8] The *HBA12* gene has the region starting -6bp until 581bp (3' promoter, exon1, IVSI, exon2, and 5'IVSII) from *HBA1* gene, and 774bp (3'enhancer) onwards from *HBA2* gene.[8] The region in-between 581bp and 774bp (3' IVSII, exon 3', and 5' enhancer) were matching with *HBA1* and *HBA2*, hence this region was considered as an indistinguishable region.[8] The α-globin protein from *HBA12* gene is not available in the literature, detailed studies are needed to confirm the similarity of *HBA12* protein with the α-globin protein of *HBA2* and *HBA1* genes.

A total of 5.7% of the study population including sickle cell trait, hemophilia-A patient, SCD patients, and β-thal major patients were reported to have the new gene convert, α_{12} gene. The inheritance of the *HBA12* gene was proven on an elaborated family study, any one of the parent of individual with *HBA12* was a carrier for the *HBA12* gene. The *HBA12* gene was reported to be co-inherited with any one of the common α-globin gene defects like $\alpha^{3.7}$ deletion, $\alpha\alpha\alpha^{3.7}$ triplications, and $\alpha^{4.2}$ deletion, but not always. The reported *HBA12* gene from Saudis was distinguishably different from the α-globin patch works, such as α_{212} and α_{121}.[8] Except the nullizygous, all the other 3 types (hemizygous α_1-/$\alpha_1\alpha_{12}$, heterozygous $\alpha_1\alpha_2/\alpha_1\alpha_{12}$, and homozygous $\alpha_1\alpha_{12}/\alpha_1\alpha_{12}$) of zygosities were observed for the α_{12} gene from Saudi population. α-globin gene convert was highly prevalent in the Saudis due to the high percentage of consanguinity. Slight increase in mean corpuscular volume, elevated HbF ($\alpha_2\gamma_2$), and reduced HbA_2 ($\alpha_2\delta_2$) were noted on the subjects with α_{12} gene convert.[8]

$Alpha_{12}$ and HbA_2. Deep analysis by Borgio et al[8] revealed the influence of the α_{12} gene on the level of hemoglobin A_2 (HbA_2). Subgrouping the population with the α_{12} gene into 6 groups ($HbS^{carrier}$; β-$thal^{carrier}$; β-$thal^{major}$/α-$thal^{carrier}$; SCD^{+ve}, and α-$thal^{carrier}$; $HbS^{carrier}$ α-$thal^{carrier}$; and $Normal^{No\ \alpha\text{-}thal\&\beta\text{-}thal}$) by the authors was able to identify the reduced level of HbA_2 in the first 5 groups with α_{12} gene.[8] Thorough investigation on the large-scale micromapping of phenomics for this α_{12} gene is mandatory to uncover the hematologic effects of the new α_{12} gene.

Alpha-globin genotypes. The term "α-globin genotype" refers to the genetic makeup of an individual's complete set of α-genes. Two alleles (α/α) at each α-globin gene position is called diploid. In general, 2 pairs of alleles from 2 α-globin genes, α_1/α_1 (*HBA1*) and α_2/α_2 (*HBA2*) represents the genotype ($\alpha_1\alpha_2/\alpha_1\alpha_2$) of an α-globin gene. In terms of Saudi population, the *HBA2* gene has been replaced with *HBA12* gene convert, a pair of alleles α_{12}/α_{12} of an α-globin gene convert, *HBA12* specific to Saudis represents the genotype, $\alpha_1\alpha_{12}/\alpha_1\alpha_{12}$. Hence there are 3 genotypes, $\alpha_1\alpha_2/\alpha_1\alpha_2$, $\alpha_1\alpha_2/\alpha_1\alpha_{12}$, and $\alpha_1\alpha_{12}/\alpha_1\alpha_{12}$ are the possible normal genotypes in Saudi population (**Table 1**). There were 32 different genotypes reported from Saudi population (**Table 1**). The α-globin genotypes, -$\alpha^{3.7}$/αα, and -$\alpha^{3.7}$/-$\alpha^{3.7}$ are the most prevalent in Saudis.[7,15] Alpha-globin genotype of each individual contributes to its α-thal phenotype. On the basis of genotypes, α-thal can be classified into 4 types, group one: deletion of 4 α-globin genes, termed Hb Bart's; group 2: deletion of 3 α- globin genes, called HbH disease; group 3: deletion of 2 α- globin genes, named α-thal trait; group 4: deletion of one α-globin gene, designated α-thal Silent (**Table 1**, **Figure 2**). Two particular identical alleles are described as homozygous (for example, $\alpha^{3.7}$ homozygous deletion -$\alpha^{3.7}$/-$\alpha^{3.7}$), and if the 2 alleles differ, it is termed as heterozygous (for example, $\alpha^{3.7}$ heterozygous deletion -$\alpha^{3.7}$/αα). Hemizygous (for example, α_1-$^{4.2}$/$\alpha_1\alpha_{12}$) form of α-globin genotypes were also reported from Saudis.[8] Severity of the α-thal disorder is indirectly proportional to the number of functional α-globin genes. The severities of α-thal tend to be more in group one results from the loss of all 4 α-globin genes, while signs and

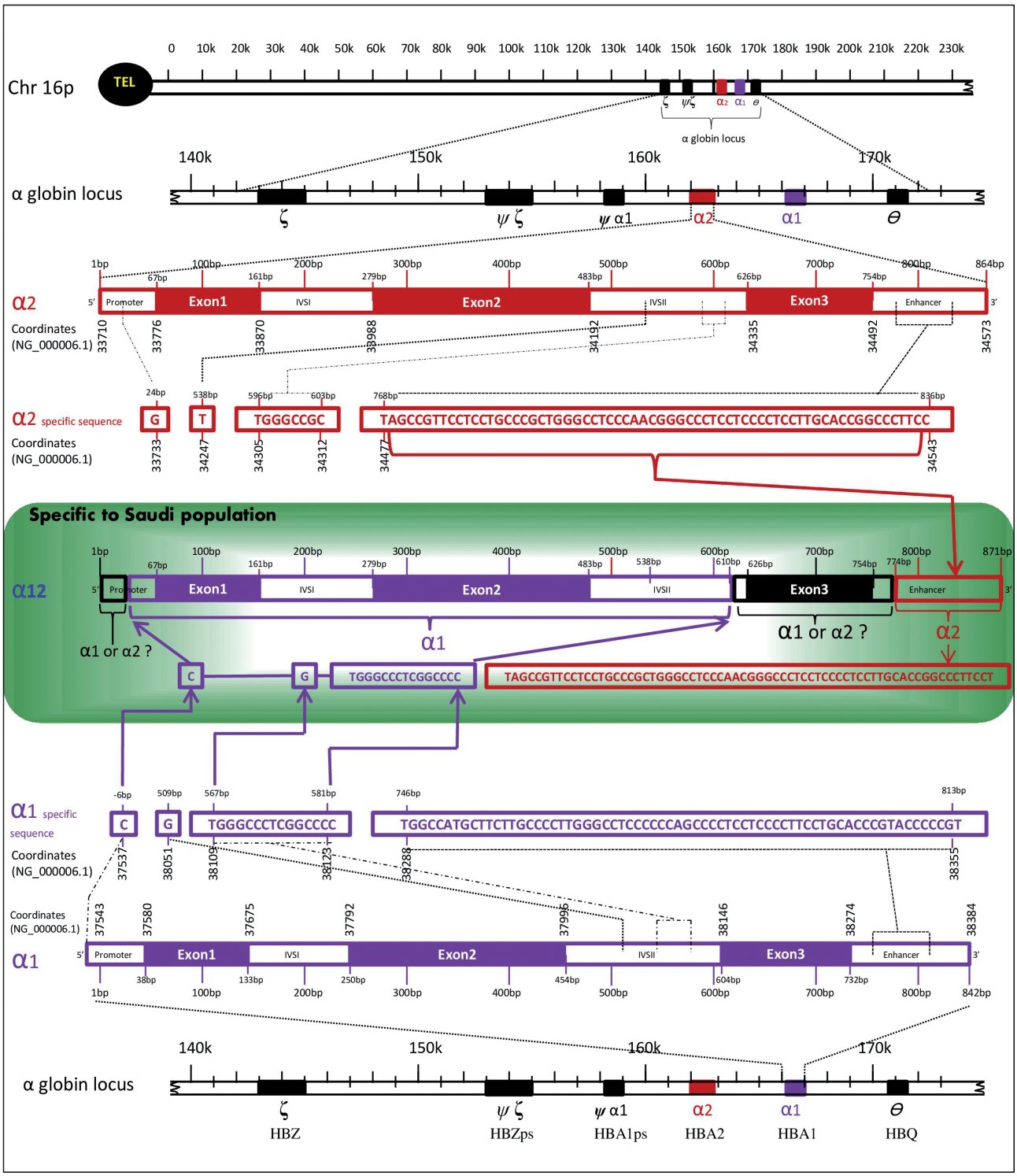

Figure 1 - An image showing 3 types of globin genes prevalent in the Saudi population: *HBA2* (α2), *HBA1* (α1), and *HBA12* (α12). The α2 gene is colored in nut brown and α1 gene is colored in violet. The undistinguished sequences (α1 or α2 ?) are colored in black. Reproduced and modified from: Borgio JF, AbdulAzeez S, Al-Nafie AN, Naserullah ZA, Al-Jarrash S, Al-Madan MS, et al. A novel *HBA2* gene conversion in cis or trans: "α12 allele" in a Saudi population. ***Blood Cells Mol Dis*** 2014; 53: 199-203.[8] With permission from Elsevier.

symptoms are almost nil in group 4 (**Figure 2**). Techniques for the updated genotyping (the process of determining a genotype) of α-globin genes in Saudis for the proper diagnosis should be given to health professional.

Down regulation factors of the α-globin gene expression. In general, down regulation of the expression of the α-globin genes due to mutations in *ATRX* (α-thal x-linked mental retardation) gene, usually lead to α-thal like phenotype.[22,23] Very recently, there were 4 novel mutations (*IVS I-5*(*G→C*), *Cd39*(*C→T*), *c.623delA*, and *c.848T>C*) on ATRX gene reported in Saudi population. The 2 exonic mutations (*c.623delA* and *c.848T>C*) were reported in patients co-inherited with α-globin genes mutations.[9] The study is a clear alarm that the α-thal-like phenotype in Saudi population may be due to mutations in α-globin genes, or in *ATRX* gene. It seems reasonable to suggest that screening for the presence of mutations in the *ATRX* gene along with mutations in the *HBA2*, *HBA1*, and *HBA12* genes are essential for proper identification of the disease burden in this population.

Table 1 - Alpha-globin genotypes prevalent in Saudi population according to various studies in Saudi Arabia.

Types of α-thalassemia	Alpha-globin genotype	Functional α-genes	Reference
Group 1: Hb Bart's	--/--	-	Pembrey et al[13]*
Group 2: HbH disease	$--^{FIL}/-\alpha^{3.7}$	α_2	Akhtar et al[7]
	$--^{FIL}/\ \alpha^{cd\ 14}\alpha$	α_2	Akhtar et al[7]
	$--^{FIL}/\ \alpha^{Adana}\alpha$	α_2	Akhtar et al[7]
	$--^{FIL}/\ \alpha\alpha^{\ polyA\text{-}1}$	α_1	Akhtar et al[7]
	$-\alpha^{3.7}/\ \alpha^{cd\ 14}\alpha^{\ KD}\alpha^{anti\text{-}3.7}$	α_2	Akhtar et al[7]
	$\alpha^{\ Adana}\ \alpha^{cd\ 59}/\alpha\alpha^{KD}$	α_1	Akhtar et al[7]
	$-\alpha^{3.7}/\alpha^{\ cd\ 14\_4.2}$	α_2	Akhtar et al[7]
Group 3: Trait	$-(\alpha)^{20.5}/\alpha\alpha$	α_1 & α_2	Akhtar et al[7]
	$--^{FIL}/\alpha\alpha$	α_1 & α_2	Akhtar et al[7]
	$--^{MED}/\alpha\alpha$	α_1 & α_2	Akhtar et al[7]
	$-\alpha^{4.2}/-\alpha^{4.2}$	α_1 & α_1	El-Hazmi and Warsy[14]
	$-\alpha^{3.7}/-\alpha^{3.7}$	α_2 & α_2	El-Hazmi and Warsy,[14] El-Hazmi,[15] Akhtar et al,[7] Al-Nafie et al[13]
	$\alpha^{cd\ 14}\alpha/\alpha^{Adana}\alpha$	α_2 & α_2	Akhtar et al[7]
	$-\alpha^{3.7}/\alpha\alpha^{\ polyA\text{-}1}$	α_1 & α_1	Hellani et al,[31] Akhtar et al,[7] Al-Nafie et al[13]
	$\alpha^{cd\ 14}\alpha^{init}/\alpha\alpha$	α_1 & α_2	Akhtar et al[7]
	$\alpha\alpha^{\ cd\ 59}/\alpha\alpha^{KD}$	α_1 & α_1	Akhtar et al[7]
	$\alpha^{T\text{-}Saudi}\alpha/\alpha^{T\text{-}Saudi}\alpha$	α_2 & α_2	Qadri and Islam[16]
	$\alpha^{cd14}\alpha\ /\alpha\alpha^{\ polyA\text{-}1}$	α_1 & α_2	Akhtar et al[7]
	$\alpha\alpha^{\ polyA\text{-}1}/\alpha\alpha^{KD}$	α_1 & α_1	Akhtar et al[7]
Group 4: Silent	$\alpha\alpha\alpha^{anti\text{-}3.7}/\alpha\alpha^{KD}$	α_1, α_2, & α_2	Akhtar et al[7]
	$\alpha\alpha^{KD}/\alpha\alpha$	α_1, α_1, & α_2	Akhtar et al[7]
	$\alpha\alpha\alpha^{anti\text{-}3.7}/\alpha\alpha$	α_1, α_2, & α_2	El-Hazmi[15]
	$-\alpha^{4.2}/\alpha\alpha$	α_1, α_1, & α_2	Akhtar et al[7]
	$-\alpha^{3.7}/\alpha\alpha$	α_1, α_2, & α_2	Hellani et al,[31] Akhtar et al,[7] Borgio et al[12]
	$\alpha^{cd\ 14}\alpha/\alpha\alpha$	α_1, α_2, & α_2	Akhtar et al[7]
	$\alpha\alpha^{Handsworth}/\alpha\alpha$	α_1, α_1, & α_2	Al-Awamy et al[17]
	$\alpha\alpha^{\ F\text{-}Dammam}/\alpha\alpha$	α_1, α_1, & α_2	Al-Awamy et al[18]
	$\alpha\alpha^{Riyadh}\ /\alpha\alpha$	α_1, α_1, & α_2	El-Hazmi and Lehmann[19]
	$\alpha\alpha^{\ Setif}/\alpha\alpha$	α_1, α_1, & α_2	Al-Awamy et al[20]
	$-\alpha_{12}^{\ 3.7}/\alpha_1\alpha_{12}$	α_1, α_{12}, & α_{12}	Borgio et al[8]
	$\alpha_1-^{\ 4.2}/\alpha_1\alpha_{12}$	α_1, α_1, & α_{12}	Borgio et al[8]
Group 5: Normal	$\alpha_1\alpha_2/\alpha_1\alpha_2$	α_1, α_1, α_2, & α_2	Akhtar et al,[7] Borgio et al[8]
	$\alpha_1\alpha_2/\alpha_1\alpha_{12}$	α_1, α_1, α_2, & α_{12}	Borgio et al[8]
	$\alpha_1\alpha_{12}/\alpha_1\alpha_{12}$	α_1, α_1, α_{12}, & α_{12}	Borgio et al[8]

*Not reported in genomic level

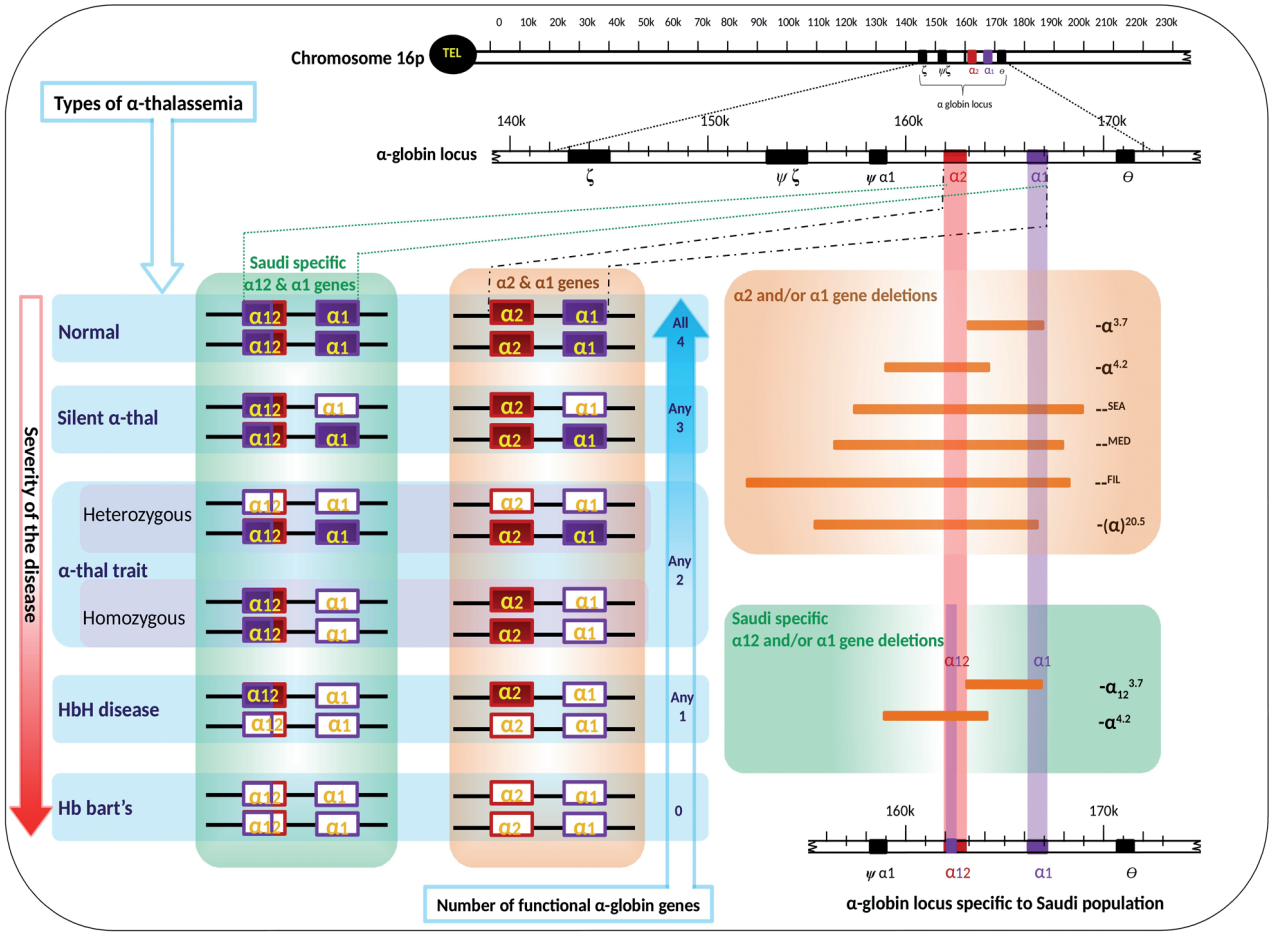

Figure 2 - Molecular types of thalassemia and types of globin gene deletions prevalent in the Saudi population. Filled boxes of genes α1, α2, and α12 indicates normal genes, while empty boxes of genes α1, α2, and α12 indicate the deleted genes.

The main limitation of this review is that, some of the articles dealing with α-thal within the Saudi population were not publicly accessible full text scholarly articles. Health sector professional should keep themselves updated with the genotyping techniques for α-globin and *ATRX* genes in Saudis. The very high frequency of α-thal, SCD, and β-thal in the Kingdom and their co-inheritance obliges the addition of sequence based testing system for *HBA2*, *HBA1*, *HBA12,* and *ATRX* genes along with the existing pre-marital testing program, to detect the risk for the offspring of affected individuals.

In conclusion, large-scale screening is mandatory to identify the influence of point mutations and deletion on the phenotype of Saudi population. In-depth, the studies on the prevalence of the sequence variations in α_{12} and their influence on the phenotypes are needed. Comparative studies on the protein structure and molecular modeling of α_1, α_2, and α_{12} have to be initiated. Specific diagnostic kits for Saudi population should be developed to identify the sequence defects in α_1, α_2, and α_{12} genes. The clinical effects due to the changes in α-globin gene expression from the α_{12} gene should be studied at large-scale. Cellular studies are needed to understand the process of down regulation of α-globin gene expression due to *ATRX* gene mutation in Saudis.

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