

β -Thalassemia in the Korean Population

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Abstract

β -Thalassemia is uncommon in the Korean population, however it must be considered in the differential diagnosis of hypochromic anemia. The molecular characterization of β -Thalassemia is absolutely necessary for molecular diagnosis as well as any genetic epidemiological study in this region. We analyzed the molecular basis of β -thalassemia in 47 Korean families. Using direct sequencing of genomic DNA amplified through PCR and haplotype analysis, 44 β -thalassemia genes were characterized, all of which were heterozygous. Fourteen different mutations were identified. The common mutations noted included the initiation codon (CD) ATG->AGG (23.4%), CD 17 A->T (21.2%), and IVS-II-1 G->A (12.7%). Interestingly, mutations causing dominantly inherited β -thalassemia were common (17.0%). All cases of IVS-II-1 G->A mutations were linked to the silent mutation of CD 91 C->T of the β -globin gene. The initiation CD ATG->AGG and IVS-II-1 G->A with CD 91 C->T were found in the Far East only, and may be inherited from a common origin for each mutation, at least in Koreans. CD17 A->T and CDs 41/42 -TTCT were suggested to be introduced by gene-flow from southern China. Otherwise, Hb Korea, CDs 89/90 -GT and a novel β -thalassemia mutation, CD 131 CAG->TAG, were only identified in Koreans. This mutation spectrum is characteristic of the low prevalent area of β -thalassemia, however it is quite different even from the adjacent countries, Japan or China.

1. Introduction

β -Thalassemia is prevalent in regions previously endemic for malaria including the Mediterranean, Middle East, parts of Africa, India, the Southeast Asia, and southern China [1]. Molecular analysis of the β -thalassemia genes has demonstrated a striking heterogeneity, and population studies indicate that probably only 20 β -thalassemia alleles account for >80% of the β -thalassemia mutations worldwide. This is due to the phenomenon of geographical clustering, where each population has a few common mutations together with a varying number of rarer ones [2,3].

On the contrary, β -thalassemia is uncommon in countries of a temperate climate, such as Britain, northern Europe, Japan and Korea, possibly due to the absence of selection in favor of the β -thalassemia genes. In this respect, it is interesting to compare the spectrum of β -thalassemia alleles in high-frequency areas with that seen in regions where β -thalassemia is uncommon [1].

It is known that β -thalassemia does occur in Koreans [4-7] and the β -thalassemia gene frequency is roughly

assumed to be about 0.1% like Japan. We have carried out a detailed genetic analysis of β -thalassemia in the Korean population, which may be another example of the β -thalassemia mutation spectrum of a low-prevalence area.

2. The spectrum of β -thalassemia alleles

To date, we characterized 44 β -thalassaemic alleles in 47 families with β -thalassemia minor or intermedia, and identified fourteen types of mutations including a case analyzed in the other institute previously [4]. The patients were identified throughout South Korea, and this data may represent the overall trend of β -thalassemia in the Korean population.

Table 1 shows the molecular spectrum of β -thalassemia in Koreans, demonstrating heterogeneity compared to the endemic areas. Recently we found a novel β -thalassemia mutation, CD 131 CAG->TAG. Interestingly, all cases with IVS-II-1 G->A were linked to the silent mutation, CD 91 C->T of the β -globin gene.

Three mutations were relatively common: the initiation CD ATG->AGG (23.4%), CD 17 A->T (21.2%), and

Table 1.
Molecular Spectrum of β -thalassemia in the Korean Population.

Mutation	No. of alleles	%
Initiation codon ATG->AGG	11	23.4
Codons 8/9 +G	1	2.1
Codon 17 A->T	10	21.2
IVS-I-130 G->A	1	2.1
IVS-I-130 G->C	2	4.2
Codons 33/34 -GGT (Hb Korea)	1	2.1
Codons 41/42 TTCT	2	4.2
Codons 89/90 GT	2	4.2
IVS-II-1 G->A with codon 91 C->T	6	12.7
IVS-II-849 A->G	1	2.1
Codon 114 T->C (Hb Brescia)	1	2.1
Codon 121 G->T	4	8.5
Codon 127 CAG->CGG (Hb Dieppe)	1	2.1
Codon 131 CAG->TAG	1	2.1
Unknown	3	6.3
Total	47	100

IVS-II-1 G->A (12.7%). Mutations causing dominantly inherited β -thalassemia were common (17.0%): CD 121 G->T, CDs 33/34 -GGT (Hb Korea), CD 114 T->C (Hb Brescia), CD 127 CAG->CGG (Hb Dieppe), and CD131 CAG->TAG.

3. Association of β -thalassemia with β -globin haplotypes and other polymorphisms

All of the cases with the three common mutations, the initiation CD ATG->AGG, CD 17 A->T, and IVS-II-1 G->A, were shown to be linked to the same haplotype and/or framework (Table 2). These results suggested that at least three common mutations may be inherited from the same origin for each mutation. CDs 41/42 -TTCT and CDs 89/90 -GT were shown to be from different haplotypes in two families. The silent mutation, CD 91 C->T that was linked to all cases with IVS-II-1 G->A was not found in any of the 550 normal individuals (1100 chromosomes), and it was thought as a very rare polymorphism.

4. Characteristics of the β -thalassemia Mutations Found in Koreans

The molecular epidemiology of the initiation CD ATG->AGG mutation is very interesting. Geographically, this mutation is quite unique to the population of the Far East Asia. So far, all 27 probands reported, including those in this report, have been restricted to the Chinese, the Japanese and the Korean populations [5,6,8,9,11-13]. In this study, RFLP haplotypes and framework linked to the mutation were type IV [-+---+] in all of three available families, and the FW3 Asian type in nine probands. These results suggest a common origin of this mutation, at least in Koreans.

Table 2.
 β -Thalassaemic Mutations and Their Associated Haplotypes and Frameworks in Koreans.

Mutation	Number of alleles	β -Haplotype	Framework
Initiation codon ATG->AGG	3	-+---+	FW3A
	6	n.d.	FW3A
Codons 8/9 +G	1	+----+	FW1
Codon 17 A->T	2	+----+	FW3A
	2	n.d.	FW3A
IVS-I-130 G->C	1	n.d.	FW3A
IVS-I-130 G->A	1	n.d.	FW1
Codons 41/42 TTCT	1	+----+	FW1
	1	+----+	FW3A
Codons 89/90 GT	1	-+---+	FW1
	1		FW2
IVS-II-1 G->A with codon 91 C->T	4	n.d.	FW2
Codon 114 T->C (Hb Brescia)	1	+----+	FW2
Codon 121 G->T	1	n.d.	FW2

*n.d.: not determined

Unfortunately, there were no comparable reports on the haplotype and framework analysis in the Chinese or the Japanese populations.

CD 17 A->T nonsense mutation is one of the most common mutations in southern China and Southeast Asia. This mutation has been linked to FW2 and/or to the haplotype of [+----+] in the all of four families available in this study, and also in the Chinese and the Thai [14]. It suggests that this mutation was introduced by gene-flow from southern China.

The IVS-II-1 G->A mutation has been identified from different ethnic groups [3]. Surprisingly, this mutation was linked to CD 91 C->T in all of six unrelated Korean families and four Japanese families previously reported [10,15]. However, this type of linkage has not been reported in other ethnic groups. All Korean families had FW2, and all four Japanese cases showed the same haplotype [-+---+] and FW2. These results strongly suggest that this type of mutation in Koreans and Japanese may be inherited from an identical origin.

We found five types of β -thalassemia mutations that are dominantly inherited in eight probands (17.0%). CD 121 C->T was found in four of the Korean families studied (8.5%) and is probably the most common dominant β -thalassemia allele in other ethnic groups as well [16]. Otherwise, Hb Brescia and Hb Dieppe has been observed very rarely in several racial populations, and Hb Korea and CD 131 CAG->TAG were found in Koreans only. A Korean proband with CD 121 C->T had FW2 and Japanese patients with the mutation showed haplotype [+----+] and/or FW2 [10,17], which was different from the British -haplotype [-+---+] linked with CD 121 G->T [18]. These findings support the hypothesis that most of dominant β -thalassemia

mutations have an independent origin and are sometimes caused by spontaneous mutations [1].

CDs 41/42 -TTCT is one of the most common β -thalassemia mutations in southern China and Southeast Asia, but there seems to be relatively weak correlation between this mutation and haplotypes in most Asian populations [14]. Two families in this study with CDs 41/42 -TTCT were associated with two predominant haplotypes in southern China and Southeast Asia, suggesting that this mutation was also introduced by gene-flow from southern China, similar to CD 17 A->T.

In conclusion, the molecular basis of β -thalassemia in Koreans is heterogeneous. The three most common mutations made up 57.4% of 44 β -thalassemic genes identified, and dominant type mutations 17.0%. According to the geographical distribution and the haplotype analysis, we were able to classify the β -thalassemic mutations found in Koreans into three groups: the Far East Asian type (the initiation CD ATG-AGG, IVS-II-1 with CD 91 C->T), the South China type (CD 17 A->T, CDs 41/42 TTCT), and the Korean type (Hb Korea, CDs 89/90 GT, CD 131 CAG->TAG). This mutation spectrum is characteristic of a low prevalence area of β -thalassemia, however it is quite different even from the adjacent countries of Japan and China. This data will be quite useful in molecular diagnosis as well as further genetic epidemiological studies of β -thalassemia in the Korean population.

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