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Case Report

Identification of a Rare Synonymous Beta Globin Mutation, HBB:c.180G>A codon 59 (G>A) in an Iranian Patient

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Beta thalassemia is the most common autosomal recessive disorder. The present study reports a rare β globin gene mutation, HBB: c.180G>A: codon 59 (AAG/AAA), in a patient from Gilan province, northern Iran. Nucleotide sequencing of amplified DNA belonging to a 35 years old man presenting mild hypochromia revealed a synonymous mutation due to a G>A conversion at the third position of codon 59 of the beta globin gene. The haplotype combination of 2 restriction enzyme sites in beta globin cluster was determined for this mutation. To our knowledge, this is the first article reporting a synonymous mutation at codon 59 (G>A) among the Iranian population highlighting once again the high heterogeneity of this population.

Keywords: Beta globin, HBB: c.180G>A mutation, Iran

Beta thalassemia is the most common hereditary hemoglobinopathy with a high prevalence among Asian, Indian, Middle Eastern and Mediterranean populations (1, 2). The disease causes reduction in beta globin chain production and consequently an imbalance in alpha and beta globin chain ratio, leading to the formation of abnormal hemoglobin tetramers (3). More than 200 different mutations in the beta globin gene have been reported worldwide among which more than 60 have been reported in Iran, demonstrating the high heterogeneity of this population (4, 5). Beta thalassemia carrier frequency varies between 4-8% in most provinces (6). However, northern and southern provinces which border the seas show 10% carriers rate and present higher heterogeneity of beta globin mutations (7, 8). Correspondingly, rare beta globin mutations are still being reported as new cases from northern provinces (9, 10) . Here we describe a novel beta globin synonymous mutation, HBB: c.180G>A: codon 59 (AAG/AAA), together with its associated haplotype in beta globin gene cluster in a young Iranian male originating from north Iran and presenting microcytic anemia with normal level of HbA2.

Case report

A 35 years old male patient originating from Gilan province, situated at northern Iran, who was diagnosed with mild hypochromic (MCH: 26.7 pg), normocytic (MCV: 85.7 fl), and normal HbA_2 level (1.9%), RBC ($5.16x10^6/\mu l$), normal hemoglobin

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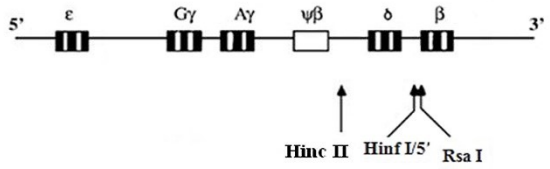

Figure 1. Position of studied polymorphic sites on beta globin gene cluster.

level (13.8g/dl) and MCHC (31.2g/dl) was referred to Amirkola genetic center, Babol, Mazandaran, for mutation analysis in the context of a suspect carrier couple. His wife presented hematological indices typical of beta thalassemia.

Molecular analysis of common beta globin gene mutations in Iran using in-house reverse dot blot assay (7) revealed no mutation in the patient. Haplotype analysis was performed after amplification of 2 different fragments of beta globin cluster harboring known single nucleotide polymorphic sites recognizable by restriction enzymes. These restriction sites correspond to Hinc II/3'ψβ, and Hinf I/5′β, Rsa I/5′β, respectively (Figure1). The haplotype analysis revealed homozygous genotype at 2 out of 3 studied polymorphic sites. Therfore we concluded that [-,+,±] haplotype was associated to the mutant chromosome. The linkage phase to the Rsa I/5′β could not be determined due to absence of other family members. Finally, direct sequencing of amplified β globin gene revealed a transition (G>A) at codon 59 (AAG) of exon 2, which is a silent mutation leading to the translation of the same amino acid (lysine) at codon 59 which should result in production of normal beta globin chain (Figure 2).

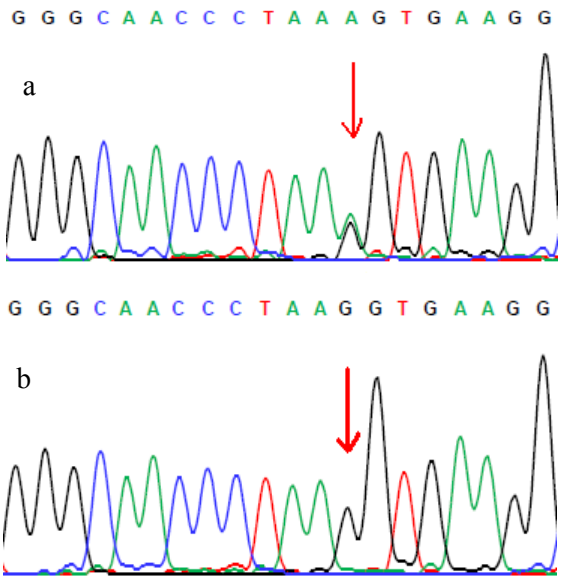

Figure 2. Electropherogram sequences of the β globin gene. a: codon 59(G>A) mutation in a heterozygous subject; b: sequence of normal beta globin gene at the same site. Red arrows indicate the position of the mutation

Discussion

Regarding the high heterogeneity of β globin gene mutations in northern provinces of Iran, encountering rare or new mutations is to be expected. Correspondingly, we described previously two rare mutations belonging to either a non-transfused beta thalassemia intermedia subject carrying Hb Knossos in compound heterozygous form, or a thalassemia minor subject carrying HBB: c.165delT: codon 54 (-T) living in Mazandaran province (9,10).

HBB: c.180G>A is another rare synonymous mutation which is reported for the first time in a mild hypochromic subject. This mutation is not expected to create any change in beta globin chain sequence. We did not find any population study report concerning this mutation in ncbi and ensembl databases.

The analysis of common single nucleotide polymorphisms of the beta globin gene cluster showed that this mutation is associated with haplotype [-, +, ±] corresponding to 3 different polymorphic restriction enzyme sites (Hinc II/3'ψβ, Hinf I/5′β, Rsa I/5′β), respectively. Further molecular studies of subjects presenting this mutation could help to elucidate its origin.

Conflict of interest

The authors declared no conflict of interest.

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