γ A gene repeats polymorphism for the analysis of haplotypes of abnormal hemoglobins

Nejat Akar, Kadir Sipahi, Ece Akar, Erkan Yilmaz

Department of Pediatric Molecular Genetics, Ankara University, Ankara, Turkey

Abstract

Aim of this study was to analyze γ A gene repeat polymorphism for the analysis of haplotypes of hemoglobin (Hb) variants such as Hb S, Hb D-Punjab, Hb O-Arab. Sickle cell cases had mainly Benin and Arab/Indian haplotype. We found three different haplotypes among Hb S, Hb O Arab and Hb D-Punjab cases. We named these three variants as Anatolian-1 and Anatolian-2 and Asian. Our data revealed that Hb O Arab may arise twice one from Asia and the other from Europe.

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Turkey is situated at the meeting point of three continents of the world and stands as a crossroad between Asia and Europe. Due to its geographical location, Anatolia has historically been in contact with various races and ethnic groups. Although Turks originated mainly in central Asia, they probably mixed with the people formerly living in Asia Minor, Africa and those living in the Balkan countries. Therefore it is not surprising to find numerous examples of hemoglobin (Hb) variants in Turkey today as previously reported. Most common variants are hemoglobin S (B6 Glu-Val), Hb D Punjab (B121 Glu-Gln), Hb O Arab (B121 Glu-Lys) and Hb E Saskatoon (B22 Glu-Lys).¹⁻³

Previously it was reported that a unique repetitive sequence at the γ A gene IVS-II of the β -S globin chain can discriminate African haplotypes of Hb S. These reports analyzed the haplotypes and gave the sequences as follows: Benin (TG)10CGCGCGCG(TG)7TC; Bantu (TG)10(CG)3(TG)9TC; Senegal (TG)13TC; Arab-India (TG)13TC and Cameroon (TG)12(CG)3(TG)7TC.^{4,5}

We aimed to sequence the γ A gene IVS-II region of the β globin gene for hemoglobin S and other common hemoglobin variants in Turkish population.

Materials and Methods

We analyzed individuals with hemoglobin variants Hb S (n:11), Hb D Los Angeles (n:10), Hb O Arab (N:12), Hb C, Hb E Saskatoon, and Hb Beograd (β 121(GH4)Glu>Val) for the γ A gene IVS-II single-nucleotide polymorphism (SNP). These hemoglobin variants were diagnosed by β globin gene sequencing of the exons 1, 2 and 3 (Beckman Coulter 2000; Beckman Coulter, Inc., Brea, CA, USA). Sequencing of the γ A gene IVS-II was performed by the primers F 5' TGCTGCTAAT-GCTTCATTACAA 3' and R 5' TAAATGAGGAG-CATGCACACAC 3' as previously reported.^{4,5}

Results

Our data revealed that six of the HbS case had Benin TG(10)CG(2)CACGTG(7), and one of them had Senegal/Arab-India TG(13) haplotype. Four of them carried TG(10)CG(5)TG(5) which was not found in African haplotypes. All of the Hb D Punjab cases carried TG(9)CG(5)TG(8). Hb O Arab carriers had either TG(9)CG(5)TG(8) or TG(10)CG(5) TG(7). Hb E Saskatoon, and Hb Beograd cases had TG(9) CG(5) TG(8) as similar to Hb D Punjab cases.

Discussion and Conclusions

It is well known that hemoglobin variants may show the historical immigration routes of humans. SNP's may as well have the same property. Our data revealed that most of the Hb S cases are of African origin. Most of them are Benin type and rarely Senegal/Arab Indian type. We did not observe Cameroon type in our sickle cell patients. However in four cases, we detected a haplotype, which did not show any similarity for other previously reported four haplotypes. This haplotype needs further study in more cases. This may be indicative of another mutation arise for hemoglobin S. It is interesting that

Correspondence: Nejat Akar, TOBB-Economy and Technology University Hospital, Pediatrics, Kuru Mah, 2621.sokak, Uyum Sitesi 18, Çayyolu/Ankara,Turkey.

E-mail: akar@medicine.ankara.edu.tr

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our Hb D Punjab cases carried only one distinct haplotype. This may be a clue for the immigration of people with a route from northern India to Anatolia. Previously our group reported three different haplotypes mainly Mediterranean haplotype but in one case Thai haplotype. Based on this data we claimed that this finding might reflect different genetic origins and/or other molecular events like gene conversions or gene rearrangements.⁶⁻⁹ However our present data revealed a distinct one origin, may be reflecting an Asian founder effect. Hb E Saskatoon and Hb Beograd carriers had similar haplotype to Hb D Punjab. The haplotypes of the two hemoglobins may also show immigration from Asia to Europe. We observed two different haplotypes for Hb O Arab cases. This finding indicates that Hb O Arab cases may have two different origins, one possibly Asia and other from Africa. There is a great similarity between the new haplotype we observed in our sickle cell cases. The other haplotype is the same as Hb D Punjab cases indicating Asian origin. We named these three different variants as Asian, Anatolian-1 and Anatolian-2 (Table 1).

A previous report from Greek Pomaks

Table 1. γ A gene repetitive sequence analysis of hemoglobin variants.

Haplotype	Sequence	Hb	No.
Benin	TG(10)CG(2)CACG TG(7)	Hb S	6
Senegal/Arab-India	TG(13)	Hb S	1
Anatolian-1	TG(10)CG(5)TG(5)	Hb S	4
Asian-1	TG(9)CG(5)TG(8)	Hb D Punjab	9
		Hb O Arab	4
		Hb Beograd	1
		Hb E Saskatoon	1
Anatolian-2	TG(10)CG(5)TG(7)	Hb O Arab	8

Hb, hemoglobin.

claimed a marked high incidence of Hb O Arab and difference of the Greek mainland haplotypes. However, their theory may not be true as Pomaks not only exist in Greece but also mainly in Bulgaria dispersed in Balkans. Pomaks are Slav originated Muslims, which may be a clue for the admixture to Ottomans.¹⁰ This point needs further clarification for the Greek Pomaks by using this repetitive sequence. Our data probably opens a new era for the ancestry of abnormal hemoglobins, indicating more concise analysis with more cases.

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