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Geographical Survey of β^S-Globin Gene Haplotypes: Evidence for an Independent Asian Origin of the Sickle-Cell Mutation

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SUMMARY

The haplotypes of 152 β^S-chromosomes were characterized in six different population groups. The chromosomes of individuals from Nigeria and from the southwest of the Arabian peninsula have the haplotype − − − − + + − + previously found in west African, Jamaican, and U.S. American blacks, whereas those from the eastern oases of Saudi Arabia and from the west and the east coast of India showed a different haplotype not found in Africa (+ + − + + + + −). These data are most consistent with an independent Asian origin of the sickle-cell mutation and provide further information about the geographic distribution of β^S-haplotypes in the Old World. The distribution of the Asian β^S-haplotype corresponds to the reported geographic distribution of a mild clinical phenotype of homozygous SS disease.

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INTRODUCTION

Homozygous sickle-cell (SS) disease has a very widespread geographical distribution [1] and is characterized by a severe anemia, recurrent vaso-occlusive episodes, and increased susceptibility to infection in most patients. However, a milder clinical course can be observed in many Asian patients from Saudi Arabia, Kuwait, Iran, and India and sporadically in other racial groups [2–9].

The question whether the extensive geographical occurrence of sickle-cell disease can be explained by a single origin of the mutation with subsequent large-scale migration or whether it relates to multicentric origins has been examined by an analysis of restriction site polymorphisms (RFLPs) linked to the β^S-globin gene. Kan and Dozy [10, 11] found two different alleles of a single *Hpa*I RFLP to be linked to the β^S-globin gene in U.S. American and African blacks and suggested that the mutation had arisen at least twice. Subsequently, studies of an array of RFLPs linked to the β^S-mutation (referred to as a haplotype) in Jamaican [12, 13], U.S. American [13], and African [14] blacks strongly supported the hypothesis that the β^S-mutation has arisen independently on several occasions in Africa.

Here, we have determined the β^S-haplotypes of six different population groups in Africa and Asia. The distribution of the different β^S-haplotypes provides strong evidence for an independent Asian origin of the β^S-mutation. Furthermore, this analysis also suggests a migration of a west African population carrying the β^S-mutation to north Africa, the Mediterranean, and west Saudi Arabia. The geographical distribution of the Asian β^S-haplotype as shown in this study corresponds to the previously reported distribution of a milder clinical phenotype associated with high levels of Hb F [2–7].

PATIENTS AND METHODS

Blood samples were obtained from individuals of six different ethnic groups in five geographical areas. Group one originated from Orissa (northeast India) and consisted of families of the Pan and Kond tribes with patients with sickle-cell anemia. The second group also originated from Orissa but consisted of nontribal unrelated individuals with homozygous SS disease or the trait (AS). Although these patients came from the same area, it has been suggested that tribal Indian populations are genetically different from nontribal populations [15], and we therefore present the results from these two groups separately. The third group originated from Poona (west India) and consisted of unrelated individuals with homozygous SS disease. Group four were from the eastern oases of Saudi Arabia and consisted of unrelated patients with homozygous SS disease. Group five consisted of patients with homozygous SS disease and their families attending the Military Hospital in Riyadh; however, the patients or their parents were born in the southwest of the country or in Yemen. The last group came from Ibadan (Nigeria) and consisted of patients with homozygous SS disease.

DNA was extracted from peripheral blood and digested with restriction endonucleases *Hin*dII, *Hin*dIII, *Bam*HI, *Hpa*I, and *Ava*II according to the manufacturers' recommendations. The β-globin gene haplotype was determined by Southern blot analysis [16] using genomic DNA fragment probes (1.3-kilobase [kb] *Bam*HI/*Eco*RI ε; 3.3-kb *Hin*dIII γ; 1.8-kb *Bgl*II/*Xba*I ψβ; *Bam*HI/*Eco*RI IVS-2 β).

In cases with two different haplotypes, the correct haplotype pair was either derived by family studies or, where this was not possible, it was assumed that a common haplotype was present with a rare haplotype rather than two rare haplotypes [12].

RESULTS

The β^S-haplotypes of a total of 152 chromosomes in six population groups are shown in table 1. The haplotype − − − − + + − + was predominant in the patients from Riyadh originating from the southwest of the Arabian peninsula (77%) and also in those patients from Nigeria (97%). Another β^S-haplotype (+ + − + + + + −) was predominant in east Saudi Arabia (90%), west India (50%), and east India, both in tribal (88%) and in nontribal (100%) populations. Figure 1 shows the geographical distribution of the four major β^S-haplotypes in the Old World as found in this study and in [13, 14]. Nine other haplotypes were found, and of these, seven may be derived from a single mutation of one of the four common haplotypes or by a crossover between two of the common haplotypes.

DISCUSSION

The β^S-mutation is one of the commonest single gene mutations in man and has a very widespread geographical distribution including most of Africa, the Middle East, India, parts of the Mediterranean, and the Americas [1]. There has been considerable anthropological, genetic, and clinical interest in whether the mutation had (a) single or multiple origin(s) and in the geographical site(s) of origin [17]. Evidence from the *Hpa*I RFLP 3′ to the β-globin gene [10, 11, 18, 19] and subsequently from β-globin haplotypes has suggested a multicentric origin of the β^S-mutation in Africa.

The β^S-haplotype (+ + − + + + + −) prevalent in east Saudi Arabia and India differs from any of the African haplotypes both 5′ and 3′ of the proposed "hot spot" of recombination in the β-globin gene cluster [20]. It is likely therefore that the β^S-mutation has had an independent Asian origin.

Knowledge of the geographical distribution of different β^S-haplotypes enables an analysis of possible population migrations. Nagel [17] analyzed the β^S-

TABLE 1

THE β^S-GLOBIN GENE HAPLOTYPES IN SIX DIFFERENT POPULATION GROUPS

	India Orissa (tribal)	India Orissa (nontribal)	India Poona	Saudi Arabia Eastern Oases	Saudi Arabia Riyadh	Nigeria Ibadan
+ + − + + + + −	22	13	4	45	...	...
+ + − + + + + +	...	...	...	2	...	...
+ − − + + + + −	1	...	...	...	...	...
+ − − + + + + +	1	...	...	...	...	...
+ − − − − + + +	1	...	...	2	5	...
+ − − − − − + −	...	...	1	...	...	...
− + − + + + + −	...	...	...	1	...	...
− + − + + − + +	...	...	2	...	...	...
− + − − − + + +	...	...	1	...	...	...
− + + − + + − +	...	...	...	...	...	1
− − − − + + − +	...	...	...	...	17	33
Total	25	13	8	50	22	34

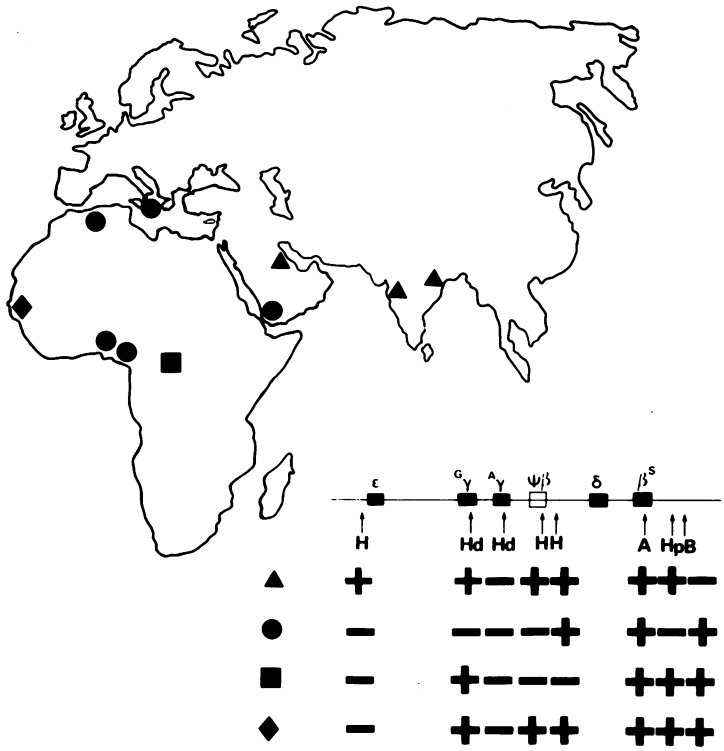

FIG. 1.—Distribution of major β^S-globin gene haplotypes in Africa and Asia. The haplotype is characterized by the presence or absence (+ or −) of an array of polymorphic restriction sites within the β-globin gene cluster. *H* = *Hin*dII, *Hd* = *Hin*dIII, *A* = *Ava*II, *Hp* = *Hpa*I, *B* = *Bam*HI. The Nigerian, Saudi Arabian, and Indian haplotypes are from the present study. The Mediterranean haplotypes are from Antonarakis et al. [13]; the Benin, Senegalese, and Central African haplotypes are from Pagnier et al. [14].

haplotype data of Jamaican [12], U.S. American [13], and African blacks [14] in relationship to movements of the slaves transported to the New World and concluded that estimations of the composition of slaves by origin, based either on historical data or on β^S-haplotypes, both arrived at similar figures, that is, 70% Central West Africa, 17% Bantu Africa, and 13% Atlantic West Africa. Nagel also proposed that the limited data on β^S-haplotypes in Africa agreed with the linguistic concept of the Bantu migration having started in west Africa (present-day eastern Nigeria) followed by an eastward expansion. The β^S-mutation characterized by the − − − − + + − + haplotype is likely to have arisen in west Africa where the β^A-globin gene is commonly present on the same haplotype [21]. Our survey of β^S-haplotypes as shown in figure 1 suggests a migration of a west African population carrying the − − − − + + − + β^S-haplotype to north Africa, to the Mediterranean, and to southwest of the Arabian peninsula. This haplotype was not found at all in our Indian and east Saudi Arabian samples that predominantly showed the major Asian β^S-haplotype. Whether the Asian β^S-mutation characterized by the haplotype + + − + +

+ + − originated in east Saudi Arabia and spread to India possibly with the Arab expansion in the first millennium A.D. [22] as suggested previously [23] or vice versa, possibly carried by Indian Arabic trade routes [22], is not known.

The different β^S-haplotypes seem to be associated with different clinical phenotypes possibly determined by levels of Hb F; for example, the β^S-haplotype found in Senegal (− + − + + + + +) is reported to be associated with slightly higher levels of Hb F (mean 12.3%) than is the haplotype found in Benin (− − − − + + − +) (mean 8.0%) [24, 25]. Furthermore, it has been previously proposed that the + + − + + + + − haplotype might be linked to a high Hb F determinant in at least some families [9, 26–28] and its distribution as shown in the present study (fig. 1) corresponds to the reported distribution of mild homozygous SS disease associated with high levels of Hb F [2–8]. However, it is also possible that this haplotype is an ethnic characteristic and that in Middle Eastern and Asian populations there might exist transacting high Hb F determinants unlinked to the β-globin gene cluster [29]. Our survey shows that the Indian and east Saudi Arabian populations are the most informative for further study of this important question.

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