Population genetics and selection of HbS beta-globin haplotypes

Background

The sickle allele (HbS) of the beta-globin gene (*HBB*), which in the homozygous state gives rise to sickle cell disease (SCD), occurs commonly in populations of African ancestry as a result of its protective effect against severe malaria [1-4]. HbS is classically thought to have arisen multiple times around the same time in recent human history (~5,000 years ago), largely driven by observations of distinct haplotype backgrounds across sub-Saharan Africa, Arabia and India [5-7]. These classical βs haplotypes are named according to their putative geographical origins – Benin, Bantu (Central African), Cameroon, Senegal and Arab. In general, in regions where the βs allele is found at substantial frequency, a specific βs haplotype usually predominates, although other haplotype backgrounds – both classical and 'atypical' - are also observed. For example, although the Senegal βs haplotype is the most commonly observed in Senegal, the Benin haplotype is not uncommonly seen [8,9]; similarly, we have observed a commonality of Benin haplotypes among βs haplotypes sampled in Yaoundé, Cameroon, as oppose to the expected 'Cameroon-type' (unpublished data). Combined with observations of broad diversity among even geographically isolated βs haplotypes [8,10,11], there remains some uncertainty surrounding the origins and interpretation of classical βs haplotypes, particularly the contribution of complex genomic rearrangements and ancestral population events [12-15].

Much of the conventional wisdom concerning the origin of βs haplotypes was concluded from the patterns of restriction fragment length polymorphisms observed in the early 1980's [5,6,16]. The authors observed a single major ancestral haplotype in each population as well as several less-common, but more diverse, ancestral haplotype backgrounds. It was postulated that the observed data reflected either a single (most-common) mutation followed by complex genomic rearrangements *or* three to four independent mutations occurring independently. The relative simplicity of the latter explanation subsequently gained traction, bolstered by subsequent population surveys [17] and more detailed haplotype inference [18]. Since those original descriptions, however, there have been significant technological advances that have informed our understanding of the genomic architecture of the beta-globin region and potentially have implications for the accepted dogma of βs haplotypes. In addition to the aforementioned increase in DNA sequence diversity on classical RFLP haplotypes, a propensity for gene conversion/structural chromosomal events in the beta-globin locus has since been described [19-21], and new signatures of selection, punctuated by long-range ancestral haplotypes, have been described in association with the HbS allele [9,22-24]. The dynamics of how these more recent observations interplay with one-another remains uncertain [25], but taken together, they suggest that our understanding of the genetic context and recurrent nature of the HbS allele may be substantially more complex than hitherto thought, and not fully captured by the original βs haplotype descriptions. Given reported associations between βs haplotypes and variability in SCD severity [26-28], and the central contribution of HbS to our understanding of population genetics [29], a updated characterization of βs haplotypes could have profound implications for our understanding of human history and population migration; as well as for the first molecularly understood genetic disease - SCD.

Purpose and Objectives

The primary purpose of this study is the technological re-evaluation and characterization of βs haplotypes. The specific aims are:

1. Describe the distribution of βs haplotypes across multiple populations of African Ancestry

We will provide a robust overview of African βs haplotypes by evaluating the frequency and diversity of Beta-S haplotypes in a cohort of SCD patients from across Africa.

2. Evaluate the genomic evidence for multiple, simultaneous origins for HbS using βs haplotypes

2a. Define traditional beta-globin haplotypes utilizing next-generation sequencing technologies

We will combine next-generation sequencing technology with traditional RFLP genotyping to characterize and define classical βs haplotypes in the context of common sequence variation.

2b. Compare long-range- and classical- βs haplotypes

We will compare extended ancestral βs chromosomes derived from long-range sequencing with ancestral chromosomes inferred from classical βs haplotypes (characterized as in 2a). This data will be evaluated against haplotype expectations consistent with the multi-origin hypothesis for HbS.

Protocol Risks/Subjects/ Design/Procedure

We propose to obtain 500 DNA samples from SCD patients in Africa. For two-hundred of these patients, DNA will also be obtained from the patients' mother and father. Relevant demographic information – age, gender, grandparents' ethnic affiliation – will also be recorded. Samples will be genotyped using RFLP to determine classical beta-S haplotypes. The samples will be sequenced over a 400 kilobase region encompassing beta-globin.

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