
Sickle Cell Disease: History And Origin

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Abstract

INTRODUCTION

The genetically determined conditions characterized by structurally abnormal hemoglobin variants give rise to hemolytic disease by virtue of their property to polymerize and assume the sickle or crescent shapes. They are known as sickle hemoglobinopathies.

Inclusive in this category are:

1. Heterozygous state (Hb AS): where the red cells contain both normal adult hemoglobin (Hb A) and sickle hemoglobin (Hb S). As they rarely have phenotypic expression of clinical significance, they are said to have the Sickle cell trait.
2. Homozygous state (Hb SS): where the red cells are totally lacking normal adult hemoglobin and occupied mainly by sickle hemoglobin. They phenotypically express severe hemolytic anemia along with other manifestations. They are known as Sickle cell anemia.
3. Doubly heterozygous state: where the red cells contain, in addition to Hb S, the other alpha or beta chain structural variants or thalassemia because of inheritance of both abnormal genes.

The term sickle cell disease (SCD) is used in a generic sense to refer to all the clinically severe sickling syndromes.

The genetic abnormality involves the substitution of thymine with adenine in the sixth codon of beta gene (GTG ? GAG). So glutamic acid is replaced by valine and Hb S is produced, which upon deoxygenation undergoes polymerization leading to expression of sickling syndromes.

HISTORICAL ASPECTS

The symptoms related to sickle cell crises were known by

various names in Africa, long before they were recognized in the western hemisphere¹. Symptoms of sickle cell anemia could be tracked back to year 1670 in one Ghanian family². It was in 1910 when James Herrick³ observed, "peculiar elongated sickle shaped RBCs" in the blood of an anemic black medical student, and then the scientific community came to know about it.

It was the discovery of Emmel⁴ in 1917 of the sickling phenomenon, in vitro, in the members of a family which first suggested the genetic basis for sickling. So it was discovered to be an inheritable condition. Later on it was explained that the sickling phenomenon, in vitro, was due to deprivation of oxygen⁵. Both Huck and Sydenstricker, who did the detailed analysis of the pedigrees of Huck's patients, concluded that the sickle cell phenomenon was inherited as a Mendelian autosomal recessive characteristic⁶.

In the two separate studies^{7, 8}, heterozygous state for sickle gene in sickling positive without significant symptoms and homozygous state for sickle gene in symptomatic individuals were established. In the same year the abnormal slow rate of migration of sickle hemoglobin on electrophoresis was found⁹. The difference in amino acid sequence in one part of polypeptide chain of Hb S was demonstrated in the later years¹⁰.

Since then there has been a rapid expansion of information about sickle cell disease and it is still unfolding.

ORIGIN OF SICKLE GENE

Initially the single mutation theory was postulated in which it was conveyed that a single mutation occurred in Neolithic times in the then fertile Arabian Peninsula¹¹. Then, the changing climatic conditions and conversion of this area to a desert caused the migration of people that could have carried the gene to India, Eastern Saudi Arabia and down to Equatorial Africa. This hypothesis was supported by citing

the distribution of certain agricultural practices and anthropological evidences.

But it is now quite clear that the sickle cell mutation has occurred as several independent events. By using a series of different restriction endonucleases, different chromosome structures (haplotypes) are identified and Hb S gene has been found to be linked to certain commonly occurring haplotypes that are generally different from those bearing the Hb A gene^{12, 13}.

In Africa the Hb S gene is associated with at least three haplotypes representing independent mutations.^{14, 15} They are the Benin haplotype, the Senegal haplotype and the Central African Republic or the Bantu haplotype found in the central west Africa, the African west coast and the Central Africa (Bantu speaking Africa) respectively. A fourth haplotype, the Asian haplotype is found in the eastern province of Saudi Arabia and central India.

It appears that the sickle cell mutation has occurred on at least three occasions in the African continent and at least once in either the Arabian Peninsula or the Central India and from the primary sites the migration to the other regions has occurred. This can explain the observation made by many investigators that there is wide spread chromosomal heterogeneity of B[[[s]]] gene cluster haplotypes in United States as compared to the homozygous condition in Africa, Arab or Asia.¹⁶ The slaves with sickle cell trait who were exported from various parts of Africa to United States had the specific B[[[s]]] gene haplotype found in their region but after arrival in US, Jamaica and Brazil, over the years there have been considerable admixture of African ethnic groups.^{14,17,18} Available calculations suggest that this gene has developed between 3000 and 6000 generations, approximately 70000-150000 years ago.^{19, 20}

The existence of haplotypes specific to certain regions of the world suggests that the mutant beta globin gene arose separately in these locations.²¹ All of the areas in question have been or are now endemic locations of malarial infestation. This observation is consistent with the idea that the high incidence of sickle mutation in these areas is derived from natural selection.²² The mutation that produces sickle hemoglobin occurs spontaneously at a low rate. People with one sickle hemoglobin gene and one normal hemoglobin gene (sickle cell trait) are somewhat more resistant to malaria than people with two normal hemoglobin genes. The widely accepted theory is that Hb S offers selective protection against falciparum malaria probably

because of induction of sickling even at physiological oxygen tension by *P. falciparum* followed by sequestration of parasitized red cells deep with in reticulo-endothelial system where microenvironment is hostile for parasite growth.^{23, 24} Thus people with sickle cell trait would have a better chance of surviving an outbreak of malaria and passing their genes (sickle and normal hemoglobin) to the next generation when they have children. The remarkable stability of sickle gene in Africa which allows it to remain at a relatively constant level in a population without being eliminated is thought to be because of most widely accepted theory of balanced polymorphism.^{25,26,27}

The Senegal haplotype is represented most prominently in Senegal and in the most western regions of Africa above Niger River. The Benin haplotype designates those found in Nigeria, Benin and countries in the right of the Benin. The Bantu or CAR haplotype encompasses those haplotypes discovered in the Central African Republic and countries in south central Africa.

The existence of identical haplotypes in India and in the Persian Gulf region lacks an obvious explanation. Sickle cell disease in India exists mainly in tribal populations, who to this day remain relatively isolated from the mainstream of the society. The likelihood is low that an influx of a sickle cell gene from outside India occurred to a degree to account for rates of heterozygosity that reach up to 35% in some tribes. Although current information precludes a conclusive answer, gene flow from India to the Persian Gulf area through commerce and migration seems the more likely scenario.

Interestingly, there are small pockets of sickle genes of the African haplotypes in the regions along India's western coast. Sickle cell disease here exists in the descendants of African people who came to India during the mogul period, often as "praetorian guards" for the Indian princes.

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