Clinical Genotypic Correlation of Beta S-Globin Haplotypes in Sickle Cell Anemia

Ghazi A. Damanhouri and Jummanah S. Jarullah

Hematology Research Unit, King Fahd Medical Research Centre, King Abdulaziz University, Jeddah, Saudi Arabia

Corresponding author: Jummanah S. Jarullah, Hematology Research Lab, King Fahd Medical Research Center, King Abdulaziz University, P.O. Box 80216, Jeddah 21589, Saudi Arabia, Tel: 966-12-640-0000, extn. 25020; Fax: +966-12-695-2076; E-mail: jumanaj@gmail.com

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Abstract

Sickle cell disease played a pioneering role in the establishment of the field of molecular medicine. Even though this disease was identified many years ago its clinical course is still not clear. Clinical severity ranges across individuals, even within the same ethnic group. Molecular studies have identified different haplotypes across the globin gene cluster. Correlating individual haplotypes with clinical severity has become the primary focus in the endeavor to establish a successful treatment. Even though numerous studies have been performed, most have shown a negative correlation between beta S-globin haplotypes and clinical phenotype. After a review of recent medical literature, the authors conclude that further research translating genetic analysis to positive therapeutic response for sickle cell disease patients is needed.

Keywords: Sickle cell disease; Haplotype; Beta S-Globin

Abbreviations:

SCD: Sickle Cell Disease; β-globin: Beta-globin; CAR: Central African Republic; Hb F: Hemoglobin F; TNF-α: Tumor Necrosis Factor Alpha; SNP: Single Nucleotide Polymorphism

Biochemical Basis of Sickle Cell Disease

Sickle cell disease (SCD) is a genetic disorder attributed to the replacement of nucleotide thymine for normal adenine nucleotide resulting in replacement of negatively charged amino acid, glutamic to valine at sixth position of beta (β)-globin chain to amino acid. In vivo stacking of the hemoglobin into long polymers is seen in the deoxygenated state of hemoglobin due to the formation of hydrophobic bonds between valine and neighbouring phenylalanine and leucine residues of sickle hemoglobin [1,2]. This single amino acid replacement causes configuration changes in the structure of β-globin leading to an enormous growth of hemoglobin S polymers associated with different clinical outburst. Sickle shaped red blood count can occlude blood flow leading to tissue and organ damage, anemia and spleen sequestration.

Haplotypes

Currently five major haplotypes are known for sickle cell disease, namely Benin, Bantu or Central African Republic, Cameroon, Arab-Indian, and Senegal; each designated according to the geographical area of origin [3,4]. Uncharacteristic haplotypes were described more recently [5,6]. All of the haplotypes have an African origin except the Arab-Indian type.

A high molecular diversity in the microsatellite configuration was described when β-globin cluster was explored in Tunisia. These results confirm the utility of the β-globin haplotypes for population studies and contribute to awareness of the Tunisian gene pool, as well as establishing the role of genetic markers in the physiopathology of SCD [7].

Studies carried out in Saudi Arabia showed the presence of seven haplotypes, of which the Arab-Indian haplotype was predominant. Benin, Bantu and Senegal were also documented [8].

Influence of Hemoglobin F on Haplotype of Sickle Cell Disease

Hemoglobin F (Hb F) is the main modulator of the phenomenon of sickle cell anemia [9]. Higher levels of Hb F clearly play a role in decreasing clinical severity possibly due to interference with hemoglobin S sickling process [10]. However, SCD clinical presentation is also influenced by unidentified genetic loci, since many patients who have neither SI haplotype nor elevated Hb F nor other ameliorating factors suffer only mild disease.

In genome-wide association studies the common Hb F BCL11A enhancer haplotype in sickle cell patients with African origin and AI has a similar effect on Hb F [9]. Stimulation of Hb F gene expression will unravel the genetic basis of Hb F regulation. This can lead to successful treatment of the most prevalent yet most mystifying SCD.

Correlation of Haplotype with Clinical Manifestation

Banderia et al. [11] have associated with a higher incidence of clinical complications in Bantu haplotype than the other haplotypes and thus considered the worst prognosis. On analysis of pro-inflammatory cytokines interleukin-, tumor necrosis factor alpha (TNF-α) and interleukin-17, it was shown that genetic polymorphism in SCD is associated with inflammatory profile IL-6 and TNF-α were greater in Bantu/Bantu than Benin/Benin [11].

Studies in the Eastern province of Saudi Arabia on the Arab-Indian haplotype documented that adults with SCD showed clinical outburst while children did not. Complications like acute chest syndrome was...
seen in 47%, osteonecrosis in 18%, priapism in 17% and stroke in 6%. This variation in AI haplotype between adults and children can be due to a decline in Hb F in adults and a variable distribution of Hb F in F cells [12].

Another study was carried out in Saudi Arabia to evaluate the correlation of haplotypes with clinical symptoms. The focus was on acute chest syndrome. It was found that the African haplotype had severe and recurrent acute chest syndrome in comparison with the Arab-Indian haplotype [13]. Christopher, in his study on linkage disequilibrium across the locus control region of entire β-globin gene in SCD children, has documented that single nucleotide polymorphism (SNP) defined in β haplotype may be associated with acute chest syndrome but not pain or silent cerebral infarct [14].

Various studies done in Brazil suggest that genetic signature could influence stroke development in SCD [15-19]. Flanagan et al. [20] established an association between reported polymorphism and stroke. However, his studies had a small sample size. Studies carried out by Domingos et al. [21], utilizing a large population size of SCD, were unable to find any association between the five known polymorphisms and stroke. Although those patients who were homozygous of CAR (CAR/CAR) haplotype had a three-fold higher risk of developing stroke [21].

**Conclusion**

Variegated results from different studies prevents drawing any conclusion other than that more research is required to unravel the mystery of sickle cell anemia treatment. The genetic modulators responsible for clinical outburst must be identified in order to develop a successful treatment.

**Future Research Directions**

In order to improve clinical complications, develop specific treatments aimed at targeting modifiers of sickle cell disease.

**References**