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Scientific comment

Comment on "Molecular analysis and association with clinical and laboratory manifestations in children with sickle cell anemia"☆

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Sickle cell anemia (SCA) is a severe disease characterized by a recessive autosomal inheritance. However, despite being a monogenic disease, SCA has clinical heterogeneity as different individuals with the same genotype have different clinical aspects.[1] Thus, the clinical diversity of SCA has been attributed to socioeconomic and environmental factors, and also to genetic modulators, which have been widely investigated in order to explain the heterogeneous pattern of the disease.[1] Regarding the classic genetic modulators associated with SCA, we can mention the beta (β)-globin gene cluster haplotypes, alpha-thalassemia (α-Thal), as well as epistatic genetic variations related to quantitative trait loci (QTLS) of several genes which act singly or interacting with each other, for instance the presence of a gene polymorphism in *BCL11A* and the *olfactory receptor* gene and its association with fetal hemoglobin (Hb F) concentration.[2–4] Genome-wide studies emphasize multigene interactions and the clinical profile of SCA patients.[5,6] β-globin gene cluster haplotypes have been described and named according to the geographic region where they were first identified, and have also been correlated to differential Hb F levels,[7,8] with some haplotypes (Bantu and Benin) associated with lower Hb F levels and less disease severity.[9,10] Several studies related to β-globin gene cluster haplotypes have been performed and show differential distribution related to the studied group as these markers have been used as an anthropological tool, as well as their role in modulating laboratorial and clinical characteristics of SCA patients.[9–16]

α-Thal is characterized by a deficiency or absence of α-globin chain synthesis and its combination with β chain variants decreases the concentration of abnormal hemoglobin.[17–19] The reduced synthesis of the alpha globin chain results in changes in hematological parameters, decreasing the degree of hemolysis and cellular dehydration, and increasing the ratio between the volume and the cell membrane area of red blood cells in sickle cell patients.[17,20] The coexistence of α-Thal with SCA has been associated to greater survival, and also with a reduction in the occurrence of chronic ulcers in the malleolar region. However, with the reduction of hemolysis and increase of hematocrit, there is an increase of blood viscosity; this is a risk for vaso-occlusion, and consequently, an increase in the frequency of painful crises and other clinical complications, such as retinopathies and bone necrosis.[21] Kato et al., in a review of reports related to sickle cell disease phenotypes, proposed that patients with the α-Thal trait have less hemolysis and endothelial alterations, but present a sub-phenotype associated to increases in blood viscosity and vaso-occlusion.[22] Therefore, the coexistence of β-globin gene cluster haplotypes and α-Thal has shown changes in the severity of the clinical profile of sickle cell disease patients (Table 1).

Despite several studies describing the presence of these markers and their possible influences on the phenotype of SCA patients, changes described in a specific population are not necessarily found in others; this consolidates the concept that although the genetic event is unique and related to one

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Table 1 – Description of studies related to the coexistence of β-globin gene haplotypes and α-Thal and possible changes in the severity of clinical profile of sickle cell disease (SCD).

Description of study	Possible changes	Author
Association of β-globin haplotype and chronic inflammatory profile in sickle cell anemia (SCA)	β-Globin haplotype is associated with inflammatory profile	Bandeira et al.[23]
Influence of the β(S) haplotype and α-thalassemia on stroke development in SCA.	Result suggest that only the β(S) haplotypes and the α (3.7 kb)-thalassemia genotype modulate the prevalence of stroke in the studied SCA population	Domingos et al.[24]
Study of pediatric severity score in SCD patients	Alpha-gene deletions were not associated with a lower pediatric severity score, but patients were clearly differentiated by their β-globin genotype	Joly et al.[25]
Genetic polymorphisms and cerebrovascular disease (CVD) in children with SCA	Children with Bantu/Atypical β(S)-globin gene haplotype had 15 times more chance of CVD and there was no difference in CVD among α-Thal carriers	Filho et al.[26]
Association of β-globin gene haplotypes and α-Thal as a risk factor of glomerulopathy in SCA	Results suggest a strong protective effect of α-Thal against glomerulopathy in adult SCA patients	Nebor et al.[27]
Influence of β-globin gene haplotype, co-inherited α-Thal trait and Hb F on steady-state serum bilirubin levels in SCA	The β-globin haplotype and co-existing α-Thal trait did not have any significant influence on serum bilirubin levels	Adekile et al.[28]
The β-globin gene cluster haplotypes in SCA	β-Globin gene haplotypes showed differences related only to Hb F levels and blood transfusion therapy, presence of α-Thal was associated to hematological alteration and spleen sequestration events	Adorno et al.[29]
Molecular characteristics of pediatric patients with SCA and stroke	Neonates with four or more alpha-genes, whose β-haplotype is Ben/CAR, atypical, or CAR/CAR seem to be at a higher risk for stroke	Sarnaik et al.[30]
Effect of microdeletions in the alpha globin gene and sickle cell glomerulopathy	Coinheritance of microdeletions in the alpha-globin gene locus in SCA patients confers “renoprotection”	Guasch et al.[31]
Genotype-phenotype correlation of SCD in the United Arab Emirates	African haplotypes (Bantu and Benin) are related to a severe clinical presentation, and coinheritance of α-Thal trait in the African haplotypes had an ameliorating effect on hemolytic episodes, but vaso-occlusive crises were more frequent	el-Kalla et al.[32]
Effect of α-Thal on SCA linked to the Arab-Indian haplotype in India	α-Thal is a powerful and additional epistatic factor on the Indian subcontinent	Mukherjee et al.[33]
β(S) haplotype and alpha-globin gene patterns among SCA patients in Kuwait	SCA patients with coexistent alpha-Thal trait did not have severe recurrent infections and none had gallstones. The high frequencies of the Saudi Arabia/India β(S) haplotype and α-Thal trait contribute to the mild nature of the disease among Kuwaiti Arabs	Adekile et al.[34]
Influence of α-Thal trait on spleen function in SCA patients with high Hb F	α-Thal trait appears to be associated with normal splenic function in SCA patients	Adekile et al.[35]
Effect of α-Thal and β-globin gene cluster haplotypes on the hematological and clinical features of SCA in Brazil	The CAR haplotype may be associated with more severe disease	Figueiredo et al.[36]
β(S) haplotypes, alpha-globin gene status, and hematological data of SCD patients in Guadeloupe	β-Haplotypes and alpha-gene status have been correlated with hematological parameters in these patients	Keclard et al.[37]
Gender and haplotype effects upon hematological manifestations of adult SCA	Alpha thalassemia reduced the MCV, increased hemoglobin concentration, and lowered reticulocyte counts, regardless of haplotype. Hb F levels were not affected by the presence of α-Thal, and gender and β-globin gene cluster haplotype interact significantly in the modulation of Hb F and anemia in adults with hemoglobin SS	Steinberg et al.[38]

Table 1 (*Continued*)

Description of study	Possible changes	Author
β-Globin gene cluster haplotype and α-Thal do not correlate with the acute clinical manifestations of SCD in children	Absence of association of β-globin gene cluster haplotype and α-Thal in acute clinical pattern of SCD patients	de Montalembert et al.[39]
The Senegal DNA haplotype is associated with the amelioration of anemia in African-American SCA patients	The Senegal β-like globin gene cluster haplotype is associated with an amelioration of the hemolytic anemia that characterizes SCD	Nagel et al.[40]

point mutation in the β globin gene (*HBB*), the clinical pattern of the disease involves multiple organs and systems, which affects the activation of a complex network of mechanisms and pathways not clearly understood. In this context, there is a high diversity of findings which are not yet globally consolidated about a common prognostic marker involving the SCA profile, except the genetic origin of the disease, the presence of hemoglobin S.

In this issue of the *Revista Brasileira de Hematologia e Hemoterapia*, Camilo-Araújo present an analysis of the frequency of βS-globin haplotypes and alpha-thalassemia, and their influence on clinical manifestations and the hematological profile of children with sickle cell anemia.[41]

Conflicts of interest

The author declares no conflicts of interest.

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