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Genetic Modulators of Hemolytic Anemia in Angolan Children with Sickle Cell Anemia

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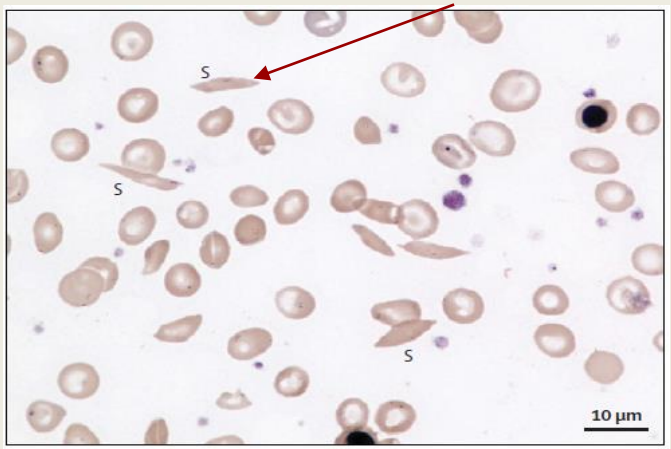
Introduction

Sickle cell anemia (SCA)

- autosomal recessive genetic disease
- homozygous change c.20A>T in the beta-globin gene → HbS
- main clinical manifestations: chronic hemolytic anemia and vaso-occlusive crisis
  - ↳ Very heterogeneous due to environmental and genetic modifying factors



Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376(9757):2018–31.

Aim

The aim of this study was to investigate genetic modifiers of hemolytic anemia in pediatric SCA patients living in Africa, where the disease is a severe public health problem

Methods and Materials

- 200 SCA Angolan children, between 3-12 years old
- 13 polymorphic regions in 4 genes (*HBA, CD36, NOS3* and *VCAM1*)

- PCR, RFLP, GAP-PCR and Sanger automatic sequencing methodologies
- Hematological, biochemical and clinical phenotypes were obtained at steady state and from medical records

Results & Discussion

Erythrocyte hemoglobinisation - *HBA*

- high level (67.5%) of α-thalassemia co-inheritance (del. 3.7kb in *HBA*)

improved patients' health
by delaying the onset of the disease, decreasing anemia and the number of blood transfusions

	αα/αα		αα/-α3.7		-α3.7/-α3.7		*p*
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
No. Transfusons (year)	65	0.48 ± 0.68	110	0.35 ± 0.41	25	0.18 ± 0.17	0.031
Erythrocyts (10^{12}/L)	65	2.65 ± 0.42	110	2.91 ± 0.45	25	3.92 ± 0.68	0.000
Reticulocyts (%)	65	11.56 ± 4.25	110	10.43 ± 4.56	25	6.15± 3.42	0.000
Hemoglobin (g/dL)	65	7.24 ± 0.93	110	7.28 ± 0.86	25	7.94 ± 1.31	0.005
LDH (U/L)	58	475.94± 167.72	100	415.63 ± 153.16	23	381.75± 105.10	0.017

Vascular Tonus - *NOS3*

- rs2070744_allele C was associated with higher LDH levels and a higher number of hospitalizations

possible risk factor for increased hemolytic rate

	Polymorphism		N	Mean ± SD	*p*
LDH (U/L)	rs2070744	TT	145	418.94 ± 150.69	0.047
		TC+CC	36	477.79 ± 168.66	
No. hospitalizations (year)	rs2070744	TT	145	0.43 ± 0.48	0.008
		TC+CC	36	0,65 ± 0,53	

Results & Discussion

Vascular Cell Adhesion

CD36

- rs1984112 and rs1413661 showed impact on anemia severity
- Genotypes containing the rs1413661_alleleC were associated with lower hemoglobin levels, increased number of hospitalizations and transfusions

↓

risk factors for severe anemia

	Polymorphism		N	Mean ± SD	p
Hemoglobin (g/dL)	rs1984112	AA	109	7.47 ± 0.95	0.031
		AG+GG	89	7.18 ± 0.97	
	rs1413661	GG	22	7.79 ± 1.28	0.022
		GC+CC	176	7.28 ± 0.91	
No. Transfusions (year)	rs1413661	GG	22	0.25 ± 0.33	0.008
		GC	85	0.50 ± 0.62	
		CC	91	0.28 ± 0.39	
No. Hospitalizations (year)	rs1413661	GG	22	0.32 ± 0.37	0.021
		GC	85	0.58 ± 0.57	
		CC	91	0.41 ± 0.42	

VCAM1

- rs1041163_allele C in VCAM1 was associated with lower LDH levels

	Polymorphism		N	Mean ± SD	p
LDH (U/L)	rs1041163	TT	96	456.58 ± 168.30	0.014
		TC+CC	84	401.03 ± 136.05	

Conclusion

- This study contributed to the understanding of SCA complex pathophysiology.
- Confirmed the positive role of α-thalassemia both in SCA related anemia and in its clinical manifestations.
- Reinforced the importance of vascular cell adhesion in hemolytic anemia variability.
- In this context, we propose the SNP rs1413661 in CD36 as an important novel genetic modulator of SCA in Africa.

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