



Scientific Comment

Comments on: “Clinical, hematological and genetic data of a cohort of children with hemoglobin SD”☆



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Sickle cell disease (SCD) is a group of genetic conditions related to the presence of a sickle hemoglobin (Hb S) mutation (HBB:c.20A>T). People with SCD can be homozygous for Hb S or can have compound heterozygosity for Hb S with other gene mutations.^{1,2} Some hematologic features of SCD are listed in Table 1, but rare genotypes can also be found. Since the concentration of Hb S is a pathophysiological factor of disease severity, the presence of lower concentrations of Hb S due to double heterozygosity can determine phenotypic heterogeneity.^{1,3} However, other genetic and environmental factors can also have an effect on the disease phenotype.⁴

Studies looking for abnormal hemoglobins (Hbs) in the Brazilian population have been performed since the 1950s.⁵⁻⁸ However, the Brazilian Government Directive MS # 822/01 that regulates newborn screening for hemoglobinopathies, has promoted an increase of data about hemoglobinopathies in different Brazilian regions.⁹⁻¹¹ This associated with the use of isoelectric focusing electrophoresis (IEF) and high-pressure liquid chromatography (HPLC) as diagnostic methods, has enabled the identification of an increasing number of abnormal Hbs as well as compound heterozygous states of Hb S.¹²⁻¹⁴ An example is a paper published in this issue of the Revista Brasileira de Hematologia e Hemoterapia that shows data on a cohort of children with hemoglobin SD pattern.¹⁵

Hb D is an abnormal Hb, which migrates to the same position as Hb S in electrophoresis at alkaline pH, and can be separated from Hb S in acid pH.¹⁶⁻¹⁸ Several Hb D have been described in different racial groups, but the majority presented a point mutation in codon 121 of the β -globin gene, which results in the substitution of glutamic acid for

glutamine (HBB:c.364G>C). This abnormal Hb is usually called Hb D-Punjab or Hb D-Los Angeles, however it can also be named Hb D-North Carolina, Hb D-Chicago, Hb D-Portugal, Hb D-Cyprus, and Hb D-Oak Ridge.¹⁹⁻²¹ The estimated prevalence of Hb D-Punjab is 0.1 to 0.4% in African-Americans.²² In Brazil, a study of African descendants showed a similar prevalence.⁵

Sometime after the discovery of Hb D-Punjab, the coinheritance of Hb D-Punjab and Hb S was identified in Caucasian patients with clinical and hematological manifestations similar to those of sickle cell anemia (SCA), because this mutation facilitates Hb S polymerization.²³⁻²⁵ Further clinical studies confirmed the severity of the manifestations of this association and the need to treat these individuals as SCA patients by prescribing hydroxyurea when indicated.^{21,26-29}

There are other types of Hb D due to different point mutations in the β -globin gene, such as Hb D-Iran (HBB:c.67G>C) and Hb D-Ibadan (HBB:c.263C>A). However, individuals with these mutations have normal hematologic values and do not suffer from vaso-occlusive complications, since their red cells do not sickle under physiologic conditions.^{18,30,31}

Hb Korle-Bu (Hb KB) or Hb G-Accra (HBB:c.220G>A) is a frequent mutation in Sub-Saharan Africa.^{32,33} This Hb has the same IEF mobility as Hb D-Punjab but can be differentiated by HPLC. Heterozygotes for Hb KB have no hematologic alterations, and individuals with double heterozygosity Hb S-Hb KB have normal red cells on blood smear and a benign clinical course, similar to sickle cell trait as Hb KB does not participate in the gelation of Hb S.^{33,34}

Interestingly, the Hb KB mutation [β 73(E17)Asp→Asn] can occur in addition to the Hb S mutation [β 6(A3)Glu6Val]

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☆ See paper by Rezende et al. on pages 240-6.

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Table 1 – Hematological features of some sickle hemoglobinopathies.

Genotype	PCV (%)	Retic (%)	MCV (fL)	Hb F (%)	Hb A ₂ (%)	% Variant	Severity ^a
SCA	25	8	90	5	3	>90% Hb S	++++
Hb SC disease	35	3	80	2	3	50% Hb S, 50% Hb C	++
S-β ⁰ thalassemia	27	7	82	7	5	90% Hb S	++++
S-β ⁺ thalassemia	38	2	70	2	6	5–30% Hb A	++
SCA-α thalassemia	30	6	78	5	5	>90% Hb S	+++
Hb SE disease	35	3	75	2	3	~30% Hb E	++
Hb SD disease*	20		86	1–10	2–4	45% Hb S, 45% Hb D	+++
Sickle cell trait	45	1	85	1	2	60% Hb A, 40% Hb S	Θ

SCA: sickle cell anemia; PCV: packed cell volume; Retic: reticulocyte count; MCV: mean cell volume; Hb: Hemoglobin.

^a Severity of disease rated from most severe (++++) to absence of clinical events (Θ) includes complications related to sickle vaso-occlusion and hemolysis.

Table modified from 1 with * data obtained from 21,27,32.

in the same beta globin chain. In this case, this Hb with a double mutation is termed Hb C-Harlem (or Hb C-Georgetown) (HBB:c.20A>T, HBB:c.220G>A), because it migrates to the position of Hb C in cellulose acetate electrophoresis at alkaline pH. Individuals heterozygous for Hb C-Harlem are asymptomatic, but the coinheritance of Hb S and Hb C-Harlem has clinical manifestations similar to SCA.^{20,32,35}

Researchers from India and the Middle East are the main authors of the few papers about Hb SD-Punjab; there are less data published about the association Hb S-Hb KB.^{21,27–29,34,36–41} By studying two different groups of patients with Hb SD patterns, specifically Hb SD-Punjab and Hb S-Hb KB, Rezende et al. not only published important clinical data about the coinheritance of two rare Hb but also pointed out the importance of this differential diagnosis.¹⁵

Conflicts of interest

The author declares no conflicts of interest.

REFERENCES

- Steinberg MH. Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches. *Sci World J*. 2008;8:1295–324.
- Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. *Am J Hematol*. 2012;87(8):795–803.
- Steinberg MH. Genetic etiologies for phenotypic diversity in sickle cell anemia. *Sci World J*. 2009;9:46–67.
- Serjeant GR. The natural history of sickle cell disease. *Cold Spring Harb Perspect Med*. 2013;3(10):a011783.
- Tondo CV, Salzano FM. Abnormal hemoglobins in a Brazilian Negro population. *Am J Hum Genet*. 1962;14:401–9.
- Salzano FM, Tondo CV. Hemoglobin types in Brazilian populations. *Hemoglobin*. 1982;6(1):85–97.
- Zago MA, Costa FF. Hereditary haemoglobin disorders in Brazil. *Trans R Soc Trop Med Hyg*. 1985;79(3):385–8.
- Zago MA. Hemoglobinopathies: prevalence and variability. *Rev Paul Med*. 1986;104(6):300–4.
- Paixao MC, Cunha Ferraz MH, Januario JN, Viana MB, Lima JM. Reliability of isoelectrofocusing for the detection of Hb S, Hb C, and Hb D in a pioneering population-based program of newborn screening in Brazil. *Hemoglobin*. 2001;25(3):297–303.
- Ramvalho AS, Magna LA, de Paiva-e-Silva RB. Government Directive MS # 822/01: unique aspects of hemoglobinopathies for public health in Brazil. *Cad Saude Publica*. 2003;19(4):1195–9.
- Lobo CL, Ballas SK, Domingos AC, Moura PG, do Nascimento EM, Cardoso GP, et al. Newborn screening program for hemoglobinopathies in Rio de Janeiro, Brazil. *Pediatr Blood Cancer*. 2014;61(1):34–9.
- Silva MR, Sendin SM, Pimentel FS, Velloso-Rodrigues C, Romanha AJ, Viana MB. Hb Stanleyville-II [alpha78(EF7)Asn→Lys (alpha2); HbA2: c.237C>A]: incidence of 1:11,500 in a newborn screening program in Brazil. *Hemoglobin*. 2012;36(4):388–94.
- Silva MR, Sendin SM, Araujo IC, Pimentel FS, Viana MB. Clinical and molecular characterization of hemoglobin Maputo [beta 47 (CD6) Asp> Tyr HBB: c.142G>T] and G-Ferrara [beta 57 (E1) Asn> Lys HBB: c.174C>A] in a newborn screening in Brazil. *Int J Lab Hematol*. 2013;35(6):e1–4.
- Belisario AR, Sales RR, Silva CM, Velloso-Rodrigues C, Viana MB. The natural history of Hb S/hereditary persistence of fetal hemoglobin in 13 children from the state of Minas Gerais, Brazil. *Hemoglobin*. 2016;40(3):215–9.
- Rezende PV, Costa KS, Domingues Junior JC, Silveira PB, Belisario AR, Silva CM, et al. Clinical, hematological and genetic data in a cohort of children with the hemoglobin SD pattern. *Rev Bras Hematol Hemoter*. 2016;38(3):240–6.
- Itano HA. A third abnormal hemoglobin associated with hereditary hemolytic anemia. *Proc Natl Acad Sci U S A*. 1951;37(12):775–84.
- Lehmann H. Three varieties of human haemoglobin D. *Nature*. 1958;182(4639):852–4.
- Torres Lde S, Okumura JV, Silva DG, Bonini-Domingos CR. Hemoglobin D-Punjab: origin, distribution and laboratory diagnosis. *Rev Bras Hematol Hemoter*. 2015;37(2):120–6.
- Baglioni C. Abnormal human haemoglobins. VII. Chemical studies on haemoglobin D. *Biochim Biophys Acta*. 1962;59:437–49.
- Kinney TR, Ware RE. Compound heterozygous states. In: Embury SH, Hebbel RP, Mohandas N, Steinberg MH, editors. *Sickle cell disease Basic principles and clinical practice*. 1st ed. New York: Raven Press; 1994. p. 437–51.
- Italia K, Upadhye D, Dabke P, Kangane H, Colaco S, Sawant P, et al. Clinical and hematological presentation among Indian patients with common hemoglobin variants. *Clin Chim Acta*. 2014;431:46–51.
- Chernoff AI. On the prevalence of hemoglobin D in the American Negro. *Blood*. 1956;11(10):907–9.
- Sturgeon P, Itano HA, Bergren WR. Clinical manifestations of inherited abnormal hemoglobins. I. The interaction of hemoglobin-S with hemoglobin-D. *Blood*. 1955;10(5):389–404.

24. Adachi K, Kim J, Ballas S, Surrey S, Asakura T. Facilitation of Hb S polymerization by the substitution of Glu for Gln at beta 121. *J Biol Chem.* 1988;263(12):5607-10.
25. Steinberg MH. Compound heterozygous and other sickle hemoglobinopathies. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, editors. *Disorders of hemoglobin genetics, pathophysiology, and clinical management.* 1st ed. Cambridge: Cambridge University Press; 2001. p. 786-810.
26. Villanueva H, Kuril S, Krajewski J, Sedrak A. Pulmonary thromboembolism in a child with sickle cell hemoglobin D disease in the setting of acute chest syndrome. *Case Rep Pediatr.* 2013;2013:875683.
27. Oberoi S, Das R, Trehan A, Ahluwalia J, Bansal D, Malhotra P, et al. Hb SD-Punjab: clinical and hematological profile of a rare hemoglobinopathy. *J Pediatr Hematol Oncol.* 2014;36(3):e140-4.
28. Patel S, Purohit P, Mashon RS, Dehury S, Meher S, Sahoo S, et al. The effect of hydroxyurea on compound heterozygotes for sickle cell-hemoglobin D-Punjab – a single centre experience in eastern India. *Pediatr Blood Cancer.* 2014;61(8):1341-6.
29. Iyer S, Sakhare S, Sengupta C, Velumani A. Hemoglobinopathy in India. *Clin Chim Acta.* 2015;444:229-33.
30. Serjeant B, Myerscough E, Serjeant GR, Higgs DR, Moo-Penn WF. Sickle cell-hemoglobin D Iran: benign sickle cell syndrome. *Hemoglobin.* 1982;6(1):57-9.
31. Watson-Williams EJ, Beale D, Irvine D, Lehmann H. A new haemoglobin, D Ibadan (Beta-87 Threonine-Lysine), producing no sickle-cell haemoglobin D disease with haemoglobin S. *Nature.* 1965;205:1273-6.
32. Randolph TR. Hemoglobinopathies (structural defects in hemoglobin). In: Keohane E, Smith S, Walenga J, editors. *Rodak's hematology: clinical principles and applications.* 5th ed. St Louis: Elsevier; 2016. p. 426-53.
33. Ropero P, Villegas A, Gonzalez FA. Hemoglobin Korle-Bu [beta73(E17)Asp→Asn]. First cases described in Spain. *Med Clin.* 2004;123(7):260-1.
34. Akl PS, Kutlar F, Patel N, Salisbury CL, Lane P, Young AN. Compound heterozygosity for hemoglobin S [beta6(A3)Glu6Val] and hemoglobin Korle-Bu [beta73(E17)Asp73Asn]. *Lab Hematol.* 2009;15(3):20-4.
35. Steinberg MH, Chui DH. HbC disorders. *Blood.* 2013;122(22):3698.
36. Mondal SK, Mandal S. Prevalence of thalassemia and hemoglobinopathy in eastern India: a 10-year high-performance liquid chromatography study of 119, 336 cases. *Asian J Transfus Sci.* 2016;10(1):105-10.
37. Jiskoot PM, Halsey C, Rivers R, Bain BJ, Wilkins BS. Unusual splenic sinusoidal iron overload in sickle cell/haemoglobin D-Punjab disease. *J Clin Pathol.* 2004;57(5):539-40.
38. Rahimi Z. Genetic epidemiology, hematological and clinical features of hemoglobinopathies in Iran. *Biomed Res Int.* 2013;2013:803487.
39. Wajcman H, Moradkhani K. Abnormal haemoglobins: detection and characterization. *Indian J Med Res.* 2011;134:538-46.
40. Adekile A, Mullah-Ali A, Akar NA. Does elevated hemoglobin F modulate the phenotype in Hb SD-Los Angeles? *Acta Haematol.* 2010;123(3):135-9.
41. Patel DK, Purohit P, Dehury S, Das P, Dutta A, Meher S, et al. Fetal hemoglobin and alpha thalassemia modulate the phenotypic expression of Hb SD-Punjab. *Int J Lab Hematol.* 2014;36(4):444-50.