

# Genetic screening in sickle cell anemia



Dr. L.V. K. S. Bhaskar  
Senior Scientist  
Sickle Cell Institute Chhattisgarh (SCIC)  
Raipur (Chhattisgarh), India  
E-mail: lvksbhaskar@gmail.com

Dr. LVKS Bhaskar works as a senior scientist at the Sickle Cell Institute Chhattisgarh (SCIC), Raipur (Chhattisgarh). His research interests include genetics of complex human traits. He Applies genetics and genomics approaches to study vaso-occlusion related pain associated with sickle cell disease and hemoglobinopathies.

**Citation:** Bhaskar LVKS. Genetic screening in sickle cell anemia, Polymorphism. 2019;3:35-37.

## INTRODUCTION

Sickle cell anemia (SCA) is a monogenic genetic disorder characterized by sickle-shaped red blood cells and chronic anemia (Bhaskar and Patra, 2015). SCA is caused by mutations in the HBB gene, inherited in an autosomal recessive fashion. Notably, the diagnosis is made by hemoglobin electrophoresis or high-performance liquid chromatography, rather than by genetic testing. Several lines of evidence report that the SCA complications and other clinical aspects are associated with multiple genetic polymorphisms.

In contrast to polygenic influence on specific phenotypes, the genetics of SCA is more apparent and has led to effective therapy. Further, it has been described that the mutations responsible for the clinical aspects may interact to contribute to the phenotypic heterogeneity and genetic complexity of SCA. Furthermore, disease manifestation in the SCA patients in the same family may have varying severity due to variations in the modifying genes. The clinical variability reported in the SCA patients is due to the variation in fetal hemoglobin (HbF) levels. Among SCA patients, Senegal and Arab-Indian haplotypes have higher HbF levels, which is associated with XmnI polymorphism (rs7482144) located at 158 bp 5' to the  $\gamma$ -globin gene HBG2 (Ballas et al., 1991, Nongbri et al., 2017). Further, variations in the HbF levels have been linked to four trans-acting QTLs, such as FCP locus (Xp22), HBS1L-MYB intergenic polymorphism (HMIP) locus (6q22.3–24), TOX (8q), and BCL11A gene (2p16.1) (Cardoso et al., 2014). Recent genome-wide association studies (GWAS) have identified an association between HbF production and the ORF gene cluster (chromosome 11). Understanding the molecular mechanisms driving the targeted activation of HbF production is essential for the development of advanced therapeutic strategies and better patient outcomes.

Pain is a prominent feature of SCA that starts early in life and increases in severity with age. Inter-individual variability in pain perception may relate to both genetic and environmental factors. Gene-to-gene and gene-to-environment interactions complicate pain perception and response to treatment in humans (Lakkakula et al., 2018). The variability in chronic pain perception depends on the genes associated with pro-inflammatory cytokines. The rs8007267 polymorphism, in the GCH1 gene, encodes an enzyme called GTP cyclohydrolase 1, which is related to sickle cell anemia pain crises in African SCA patients (Belfer et al., 2014). Polymorphic variants influencing serum MBL levels have been associated with vaso-occlusive crisis and SCD severity (Mendonca et al., 2010). In addition, acute chest syndrome (ACS) is associated with polymorphic variants in genes encoding members of the cell-cell adhesion pathways TGFBR3 and PI3K/PI4K (Torres et al., 2013).

Moreover, an association of NOS3 variants with VOC in SCA patients was reported (Tantawy et al., 2015). As the coagulation mechanisms play an important role in osteonecrosis of femoral head, many studies have analyzed the gene polymorphisms involved into hypercoagulability and thrombosis, such as 5,10-methylene tetrahydrofolate reductase (MTHFR), Factor V Leiden (FVL) and prothrombin mutations (Bhaskar, 2019; Lakkakula, 2019). The genetic modulation of the stroke phenotype has been attributed to class I and II HLA genes (Hoppe et al., 2003) and the TGF- $\beta$  pathway genes (Sebastiani et al., 2005). A polymorphism in the promoter region of the uridine diphosphate glucuronosyltransferase 1A (UGT1A) gene was associated with gallstones in children and cholecystectomy in adult SCA patients (Passon et al., 2001).

There is a strong correlation between severity and the number of polymorphic variants, which demonstrates the significance of quantifying

genetic heterogeneity in SCA. It is now appreciated that so-called disease modifiers explain pharmacogenomics of pain management and HbF induction. For this reason, experts involved in the comprehensive care for SCA patients emphasize the prerequisite screening of these genetic predictors to assess the clinical diversity, genetic heterogeneity and management strategy for the patients. At this juncture, next-generation sequencing strategies and genotype-phenotype studies will offer improved diagnosis and management.

## REFERENCES

- Ballas SK, Talacki CA, Adachi K, Schwartz E, Surrey S and Rappaport E. The Xmn I site (-158, C>T) 5' to the G gamma gene: correlation with the Senegalese haplotype and G gamma globin expression. *Hemoglobin*. 1991;15:393-405.
- Belfer I, Youngblood V, Darbari DS, Wang Z, Diaw L, Freeman L, Desai K, Dizon M, Allen D, Cunningham C, Channon KM, Milton J, Hartley SW, Nolan V, Kato GJ, Steinberg MH, Goldman D and Taylor JGt. A GCH1 haplotype confers sex-specific susceptibility to pain crises and altered endothelial function in adults with sickle cell anemia. *American journal of hematology*. 2014;89:187-193.
- Bhaskar LV. Factor V Leiden and prothrombin G20210A mutations and risk of vaso-occlusive complications in sickle cell disease: A meta-analysis through the lens of nephrology. *Journal of Nephro pharmacology*. 2019;8:e16. 1-5.
- Bhaskar LVKS and Patra PK. Sickle cell disease is autochthonous and unique in Indian populations. *Indian Journal of Physical Anthropology and Human Genetics*. 2015;34: 201-210.
- Cardoso GL, Diniz IG, Silva AN, Cunha DA, Silva Junior JS, Uchoa CT, Santos SE, Trindade SM, Cardoso Mdo S and Guerreiro JF. DNA polymorphisms at BCL11A, HBS1L-MYB and Xmn1-HBG2 site loci associated with fetal hemoglobin levels in sickle cell anemia patients from Northern Brazil. *Blood cells, molecules & diseases*. 2014;53:176-179.
- Hoppe C, Klitz W, Noble J, Vigil L, Vichinsky E and Styles L. Distinct HLA associations by stroke subtype in children with sickle cell anemia. *Blood*. 2003;101:2865-2869.
- Lakkakula B. Association between MTHFR 677C>T polymorphism and vascular complications in sickle cell disease: A meta-analysis. *Transfusion clinique et biologique : journal de la Societe francaise de transfusion sanguine*. 2019; doi.org/10.1016/j.tracli.2019.01.003.
- Lakkakula B, Sahoo R, Verma H and Lakkakula S. Pain Management Issues as Part of the Comprehensive Care of Patients with Sickle Cell Disease. *Pain management nursing: official journal of the American Society of Pain Management Nurses*. 2018;19:558-572.
- Mendonca TF, Oliveira MC, Vasconcelos LR, Pereira LM, Moura P, Bezerra MA, Santos MN, Araujo AS and Cavalcanti MS. Association of variant alleles of MBL2 gene with vasoocclusive crisis in children with sickle cell anemia. *Blood cells, molecules & diseases*. 2010;44:224-228.
- Nongbri SRL, Verma HK, Lakkakula B and Patra PK. Presence of atypical beta globin (HBB) gene cluster haplotypes in sickle cell anemia patients of India. *Revista brasileira de hematologia e hemoterapia*. 2017;39:180-182.
- Passon RG, Howard TA, Zimmerman SA, Schultz WH and Ware RE. Influence of bilirubin uridine diphosphate-glucuronosyltransferase 1A promoter polymorphisms on serum bilirubin levels and cholelithiasis in children with sickle cell anemia. *J Pediatr Hematol Oncol*. 2001;23:448-451.
- Sebastiani P, Ramoni MF, Nolan V, Baldwin CT and Steinberg MH. Genetic dissection and prognostic modeling of overt stroke in sickle cell anemia. *Nat Genet*. 2005;37:435-440.
- Tantawy AA, Adly AA, Ismail EA and Aly SH. Endothelial nitric oxide synthase gene intron 4 VNTR polymorphism in sickle cell disease: relation to vasculopathy and disease severity. *Pediatr Blood Cancer*. 2015;62:389-394.
- Torres LS, Belini Junior E, Silva DG, Lobo CL, Ruiz MA and Bonini-Domingos CR. Frequencies of -308G/A (TNFA) and -509C/T (TGFB1) polymorphisms in sickle cell anemia patients from Brazil. *Genetics and molecular research: GMR*. 2013;12: 6762-6766.