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Sickle cell disease: Genetics, challenges, and advances in care.

John Parker*

Department of Medicine, University of Guelph, United Kingdom

Correspondence to: John Parker, Department of Medicine, University of Guelph, United Kingdom, E-mail: johnprkr@csl.edu

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Introduction

Sickle Cell Disease (SCD) is a hereditary blood disorder that affects millions worldwide, particularly individuals of African, Middle Eastern, Indian, and Mediterranean descent. Characterized by the presence of abnormal hemoglobin—hemoglobin S—SCD leads to the distortion of red blood cells into a sickle or crescent shape. These misshapen cells can obstruct blood flow, cause severe pain, and result in long-term organ damage. Despite being one of the most studied genetic disorders, SCD continues to pose significant clinical and social challenges. However, recent advances in treatment and research offer new hope for affected individuals [1].

SCD is caused by a mutation in the HBB gene located on chromosome 11, which encodes the beta-globin subunit of hemoglobin. The mutation results in the substitution of valine for glutamic acid at the sixth position of the beta-globin chain. This single amino acid change causes hemoglobin molecules to polymerize under low oxygen conditions, leading to the sickling of red blood cells. The disease follows an autosomal recessive inheritance pattern. Individuals with one copy of the mutated gene (heterozygotes) have sickle cell trait and are usually asymptomatic, while those with two copies (homozygotes) manifest the full-blown disease. Genetic counseling and newborn screening have become essential tools in identifying carriers and managing early diagnosis [2].

Sickled red blood cells are rigid and sticky, leading to vaso-occlusion—blockage of small blood vessels. This results in ischemic pain episodes known as sickle cell crises, which are the hallmark of the disease. Other complications include: Chronic hemolytic anemia due to the shortened lifespan of sickled cells, Stroke, especially in children, Acute chest syndrome, a life-threatening lung complication, Splenic sequestration, leading to sudden enlargement and dysfunction of the spleen, Organ damage, including kidney failure, retinopathy, and avascular necrosis [3].

The severity of symptoms varies widely among patients, influenced by genetic modifiers, environmental factors, and access to care. SCD affects approximately 20–25 million people globally, with the highest prevalence in sub-Saharan Africa, where up to 2% of newborns may be affected. In India, the disease is particularly common among tribal populations in central and southern regions. Despite its prevalence, SCD remains underdiagnosed and undertreated in many low-resource settings. Health disparities are evident even in high-income countries. In the United States, for example, African American patients with SCD often face barriers to care, including delayed diagnosis, inadequate pain management, and limited access to specialized treatment [4].

Early diagnosis is critical for preventing complications. Newborn screening programs using techniques such as isoelectric focusing and high-performance liquid chromatography (HPLC) have become standard in many countries. Genetic testing can confirm the diagnosis and identify carriers. Routine monitoring includes complete blood counts, reticulocyte counts, and transcranial Doppler ultrasound to assess stroke risk in children. Regular follow-up with hematologists is essential for managing disease progression. Management of SCD involves both preventive and symptomatic strategies: A cornerstone of therapy, hydroxyurea increases fetal hemoglobin (HbF) levels, reducing sickling and frequency of pain crises. Opioids and NSAIDs are used during vaso-occlusive episodes,

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though concerns about opioid dependence persist [5].

Conclusion

Allogeneic hematopoietic stem cell transplantation (HSCT) from a matched sibling donor can cure SCD. However, its use is limited by donor availability and risks such as graft-versus-host disease. Gene editing technologies like CRISPR-Cas9 are revolutionizing SCD treatment. By correcting the HBB mutation or reactivating fetal hemoglobin production, these therapies offer a potential cure without the need for a donor. Clinical trials have shown encouraging results, though long-term safety and accessibility remain concerns. New drugs such as voxelotor (which increases hemoglobin's affinity for oxygen) and crizanlizumab (a monoclonal antibody that reduces vaso-occlusion) have been approved for SCD management. These agents provide alternatives for patients who do not respond to hydroxyurea. Despite therapeutic advances, several challenges persist: Limited access to care in rural and underserved areas. Addressing these issues requires coordinated efforts in public health policy, education, and infrastructure development. International initiatives such as the WHO's Global SCD Strategy and the NIH's Cure Sickle Cell Initiative aim to reduce the global burden and improve outcomes.

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