GMR
The Original

# GENETIC FEATURES OF SICKLE CELL ANEMIA AND TREATMENT PROSPECTS

**Kristina Vasilievna Shandurova[1], Anastasia Alexandrovna Kharitonova[2], Illia Shumskyi[3], Vasiliy Aleksandrovich Konanykhin[4], Ezira Arabovna Bersanukaeva[5], Abubakar Islamudinovich Makasharipov[6], Makka Zhamalaylovna Gishlurkaeva[7], Khadizhat Khalilovna Khalilova[8], Usman Umarovich Mantsigov[9]**

[1]Saratov State Medical University named after V. I. Razumovsky, Saratov, Bolshaya Kazachya St., 112, 410012, 0009-0004-1056-3322, kristi_des@mail.ru
[2]Saratov State Medical University named after V. I. Razumovsky, Bolshaya Kazachya st.,112, Saratov, 410012, Russia. 0009-0006-8058-5118,
[3]Pirogov Russian National Research Medical University, 1 Ostrovityanova str., Moscow, Russian Federation, 117997. ilasumskiy149@gmail.com, 0009-0006-1263-1928
[4]Pirogov Russian National Research Medical University, 1 Ostrovityanova str., Moscow, Russian Federation, 117997. Godynov7777@gmail.com, 0009-0006-1064-1348
[5]Astrakhan State Medical University, Bakinskaya 121, 414000, esirabers@mail.ru, 0009-0005-5365-4053
[6]Astrakhan state medical university, Bakinskaya 121, 414000, makasharipov6056@icloud.com, 0009-0002-7695-9798
[7]Federal State Budgetary Educational Institution of Higher Education "Astrakhan State Medical University" of the Ministry of Health of the Russian Federation, Astrakhan, Bakinskaya, 121, 414000, post@astgmu.ru
[8]Dagestan State Medical University, 367005, 1 Lenin Square, Makhachkala, Republic of Dagestan, Russian Federation, khadizhat_khalilova@bk.ru, 0009-0001-6059-167X
[9]Astrakhan State Medical University, Bakinskaya, 121, 414000, umatsigov02@bk.ru, 0009-0002-6060-575X

**Abstract**

Sickle cell anemia is a monogenic hemoglobinopathy based on a mutation of the HBB gene with the formation of hemoglobin S and the development of chronic hemolysis, vasoocclusion and progressive organ damage. The aim of the work is to summarize information about the genetic features of sickle cell anemia and evaluate the prospects for therapy.

It has been shown that not only the basic HBB mutation is important for the clinical phenotype, but also fetal hemoglobin level modifiers, inheritance of alpha-thalassemia, as well as a variant of HbS combinatorics with other defects of the β-globin cluster. For the Russian Federation, timely detection of HbS-associated conditions, expansion of molecular genetic verification of diagnosis and routing of patients to specialized centers are of the greatest practical importance.

Standard therapy is still based on hydroxyurea, transfusion support, and prevention of complications, while the most promising areas remain hematopoietic stem cell transplantation, exogenous administration of antiserpine constructs, and genome editing with HbF reactivation.

It is concluded that there is a need to strengthen laboratory vigilance towards hemoglobinopathies in the Russian Federation and the high scientific value of genetically oriented personalized approaches to therapy.

**Keywords:** sickle cell anemia, hemoglobin S, HBB, hemoglobinopathies, molecular genetic diagnostics, hydroxyurea, gene therapy.

## INTRODUCTION

Sickle cell anemia (SCA) is one of the classic monogenic blood diseases and develops due to the formation of hemoglobin S (HbS) in the pathogenic variant of the β-globin gene. At the same time, the clinical severity of the disease is determined not only by the HBB mutation itself, but also by a whole complex of modifying factors: the level of fetal hemoglobin (HbF), the combination of HbS with β-thalassemic alleles, the inheritance of α-thalassemia, as well as the intensity of inflammatory and endothelial dysfunction [7].

Modern interest in SCA has further increased due to the development of cell and gene therapy, since hemoglobinopathies became one of the first models for the clinical testing of targeted genome editing and the genetic addition of therapeutic constructs [12].

The pathophysiology of SCA is fundamentally different from many other anemias in that a structural defect in hemoglobin leads simultaneously to two interrelated syndromes - chronic hemolysis and recurrent microcirculatory occlusion. Against this background, pain crises, acute thoracic syndrome, ischemic organ damage, functional asplenia, infectious complications and a gradual decrease in the quality of life are formed. Therefore, the genetic characteristics of the disease are necessary not only for diagnosis, but also for prognosis of the course, selection of the volume of prevention and discussion of indications for high-tech interventions [10].

For domestic healthcare, the problem of SCA and related hemoglobinopathies has long been considered as a casuistic one, but in recent years its practical significance has increased. This is due to migration processes, interethnic marriages, increased availability of electrophoretic and molecular genetic methods, as well as the accumulation of Russian clinical observations on abnormal hemoglobins and combined forms of pathology [4]. Thus, SCA in the Russian Federation should be perceived not as a rare "exotic" nosology, but as a real differential diagnostic task for pediatricians, hematologists, laboratory diagnostics doctors, specialists in medical and genetic counseling and primary care physicians.

Of particular importance for the Russian Federation is the correct laboratory routing of a patient with chronic hemolytic anemia, micro- or normocytic phenotype, reticulocytosis, family history of hemoglobinopathy, or ethnogeographic risk factors. Russian publications in recent years show that without a combination of clinical assessment, capillary electrophoresis or high-performance liquid chromatography, as well as confirmatory molecular testing, diagnostic errors persist in both children and adults [5]. Consequently, the genetic verification of the diagnosis becomes not an optional, but a structure-forming stage in the management of such patients.

## MATERIALS AND METHODS OF RESEARCH

The study was conducted at the Moscow City Clinic with access to hematology monitoring and molecular diagnostics. The sample consisted of 70 respondents. It included patients with confirmed or suspected HbS-associated hemoglobinopathies, as well as legal representatives of underage patients.

## RESULTS AND DISCUSSION

From a molecular point of view, SCA is a disease in which a single substitution in HBB triggers a cascade of systemic disorders - polymerization of deoxygenated HbS, red blood cell deformation, hemolysis, vasoocclusion, and chronic inflammation. However, the clinical picture is never limited to the presence of HbS. As shown in the table. 1, the type of genotype (HbSS, HbS/$\beta^0$-thalassemia, HbS/$\beta^+$-thalassemia), the body's ability to maintain elevated HbF levels, the presence of concomitant α-thalassemia, and a set of modifiers affecting endothelial activation and organ damage are of practical importance [11]. That is why the molecular diagnosis of SCA should answer not only the question "is there HbS?" but also the question "what kind of genetic context determines the severity of the disease."

From a practical point of view, three groups of genetic factors are the most significant. The first is the primary pathogenic variant of HBB, which determines the very fact of HbS formation.

The second is HbF modifiers, since a higher level of fetal hemoglobin reduces HbS polymerization and the frequency of vasoocclusive crises; it is on this principle that hydroxyurea and modern editorial technologies aimed at HbF reactivation are based [1].
The third is combined hemoglobinopathies and the inheritance of alpha-thalassemia, which can both mitigate individual manifestations of hemolysis and change blood viscosity, complication profile, and laboratory phenotype [9]. This is especially important for the multiethnic population of large Russian cities, since the genotypic heterogeneity of the patient directly affects the choice of the scope of the examination and therapeutic tactics.

From a genetic point of view, SCA is convenient for personalized medicine because the causal defect is clear, and some of the phenotypic variability can be explained by measurable biomarkers. The HbF level is the most obvious example of such a relationship: its increase mitigates the course of the disease, reduces hemolysis and the frequency of vasoocclusive events. For this reason, both traditional pharmacotherapy and modern editorial strategies are largely aimed at restoring the "fetal" protective phenotype of erythropoiesis [1, 6]. For a clinician, this means that genetic analysis should not be isolated from functional blood parameters, but should be interpreted in the context of HbF and clinical complications.

**Table 1 – Genetic determinants of the sickle cell anemia phenotype**

| The genetic factor | Pathogenetic role | Clinical significance |
|---|---|---|
| HBB:c.20A>T (p.Glu6Val), HbS | Amino acid substitution in the β-chain of hemoglobin leads to polymerization of deoxygenated HbS and sickle-shaped deformation of red blood cells. | Basic molecular defect of SCA; required for genetic verification of diagnosis. |
| HbSS, HbS/$\beta^0$-thalassemia, HbS/$\beta^+$-thalassemia | The proportion of synthesis of normal β-globin and the severity of hemoglobin imbalance differ. | Determines the severity of the course, the frequency of crises, and the amount of therapy. |
| Modifiers HbF (BCL11A, HBS1L-MYB, HBG) | Maintaining a higher level of HbF reduces the polymerization of HbS and stabilizes the erythrocyte. | Explains phenotypic variability; is a target of hydroxyurea and gene editing. |
| Co-inheritance of alpha-thalassemia | It changes the intracellular concentration of HbS and blood rheology. | It can reduce the severity of hemolysis, but it affects blood viscosity and the interpretation of red blood cell indices. |
| Combination with other hemoglobinopathies | Compound heterozygosity with β-globin cluster defects and rare hemoglobin variants changes the laboratory and clinical phenotype. | It requires advanced molecular diagnostics and family examination. |

An analysis of Russian publications shows that the main vulnerability of domestic practice remains late or incomplete verification of hemoglobinopathies. Clinical observations described in the Russian Federation and a series of laboratory studies demonstrate that abnormal hemoglobins, including HbS, are indeed detected in the Russian population, and differential diagnosis with beta-thalassemia, rare hemoglobin variants, and iron deficiency conditions requires a standardized algorithm [4]. The presence of clinical cases in children and the accumulation of data on the spectrum of pathological hemoglobins confirm that the problem has already gone beyond the limits of individual casuistic publications.
At the first stage of laboratory diagnostics, a general blood test, reticulocytes, bilirubin, lactate dehydrogenase and an assessment of signs of chronic hemolysis are essential. However, the crucial step is the identification of hemoglobin fractions by capillary electrophoresis or HPLC, followed by molecular

confirmation of the HBB variant. In Russian conditions, it is precisely this combination that makes it possible to separate the true HbS-associated pathology from phenotypically similar conditions and choose the correct surveillance tactics [7]. For families with established hemoglobinopathy, medical and genetic counseling, examination of relatives, and predictive discussion of reproductive risks are mandatory.

In the conditions of the Russian Federation, it is advisable to form a two-level routing: the primary level should ensure alertness and referral to electrophoretic research, while the specialized level should provide molecular verification, phenotyping of complications and decision-making on the use of hydroxyurea, chronic transfusions, transplantation or gene therapy strategies. This approach is especially important for Moscow and other metropolitan areas, where the likelihood of meeting patients from regions and countries with a higher prevalence of HbS is higher [3].

Underestimation of the genetic examination in patients with an atypical clinical picture remains a separate problem. When HbS is combined with beta-thalassemia, with moderate anemia outside of crises, in carriers of rare hemoglobin variants or in young children, the disease may disguise itself as more common causes of anemia. Russian publications on the diagnosis of beta-thalassemia and on the laboratory characteristics of hemoglobinopathies actually show that without a molecular stage it is impossible to fully describe the structure of the defect and predict the severity of the course [2]. Therefore, it is important for a doctor to think not only in terms of "there is anemia / no anemia", but also in terms of hereditary red blood cell defect.

This issue is also crucial for reproductive medicine and perinatal counseling. The detection of HbS carriage in one of the partners should be accompanied by an examination of the second partner and a discussion of the likelihood of having a child with severe hemoglobinopathy. For megacities where ethnically mixed marriages and high population mobility are observed, this approach can significantly reduce the proportion of late-diagnosed cases and shorten the time from the first symptoms to the molecular verification of the diagnosis.

Modern SCA therapy combines basic pathogenetic and supportive measures with high-tech approaches. A comparative description of the main directions is given in the table. 2. Hydroxyurea currently remains the clinical standard, the effectiveness of which is associated with an increase in HbF, a decrease in the frequency of crises and a decrease in inflammatory activation. In severe cases, chronic transfusion programs, prevention of infectious complications, treatment of pain syndrome and organ lesions are used [1, 7, 8]. Despite the fact that these measures do not eliminate the primary genetic defect, they still determine the daily clinical practice.

Allogeneic hematopoietic stem cell transplantation remains the only known potentially curative method for a long time, but its use is limited by the search for a compatible donor, the risk of conditioning toxicity, the graft-versus-host reaction, and infrastructure requirements. Therefore, in recent years, the key scientific interest has shifted to autologous cellular technologies: either to the introduction of antiserpine β-globin constructs using viral vectors, or to editing the genome of the patient's own hematopoietic stem cells with HbF reactivation by modifying the regulatory elements of BCL11A/γ-globin switching. International studies have shown the fundamental achievability of both strategies, which makes SCA one of the flagship models for clinical genomic medicine [11, 12].

For the Russian Federation, the most realistic short-term prospect is not the immediate mass introduction of expensive gene therapy platforms, but the consistent creation of infrastructural prerequisites: patient registries, laboratory centers for molecular diagnostics, dispensary surveillance programs, autologous cell processing capabilities, and pharmacoeconomic evaluation of innovative technologies [6, 8]. At the same time, it is already necessary to train specialists, form routes to federal centers, and include hemoglobinopathies in the broader agenda of rare diseases.

It should be emphasized that gene therapy approaches in SCA do not eliminate all organizational and biological limitations yet. They require the mobilization and harvesting of autologous stem cells, high-precision cell processing, conditioning, inpatient support, and long-term post-therapeutic monitoring. In addition, there are still issues of cost, reproducibility of the result, long-term safety and equal access of

patients to such technologies [2]. That is why a step-by-step scenario is important for Russian practice: from improving diagnostics and standard therapy to creating highly specialized sites for selecting patients for transplantation and gene-cell interventions.

The conducted empirical research can perform two tasks. The first is descriptive: to show what the real route structure of a patient with HbS-associated pathology is in a big city, how early the diagnosis is made, and how often hydroxyurea and chronic transfusions are used.

The second is prognostic: to assess which subgroups of patients could potentially be considered candidates for discussing transplantation or future gene therapy programs.

**Table 2 – Current and promising areas of therapy for sickle cell anemia**

| Approach | Mechanism/target | Advantages | Limitations |
|---|---|---|---|
| Hydroxyurea | Induction of HbF, reduction of neutrophil-endothelial adhesion and frequency of crises. | An affordable and clinically proven basic method. | It does not eliminate the genetic defect; it requires commitment and laboratory control. |
| Transfusion programs | Reducing the proportion of HbS and preventing acute vascular complications. | They are applicable in severe cases, stroke prevention and preparation for interventions. | Alloimmunization, iron overload, the need for chelation therapy. |
| Allogeneic HSCT | Replacement of pathological hematopoiesis with donor stem cells. | A potentially curative approach. | Shortage of donors, toxicity of conditioning, risk of GVHD. |
| Lentiviral addition of antiserpoid β-globin | Ex vivo modification of autologous HSCs with the introduction of a therapeutic construct. | There is no dependence on the allogeneic donor; the effect on the causal mechanism. | High cost, complex cellular infrastructure, long-term monitoring. |
| Genome editing with HbF reactivation | Modification of regulatory regions of BCL11A/γ-globin switching in autologous HSCs. | High pathogenetic accuracy and promising clinical response. | The need for specialized centers, conditioning, and remote safety assessment. |

## CONCLUSION

1. Sickle cell anemia should be considered in the Russian Federation as a clinically significant hemoglobinopathy that requires systemic diagnostic attention rather than episodic attention. The increasing detection of abnormal hemoglobins and the multi-ethnicity of large cities make HbS-associated conditions a real challenge in everyday hematology practice.
2. The severity of SCA is determined not only by the presence of the pathogenic HBB variant, but also by HbF level modifiers, inheritance of other hemoglobinopathies, and features of the vascular-inflammatory response. Therefore, molecular genetic verification should be extended and clinically interpretable.
3. Therapeutically, hydroxyurea, transfusion support, and specialized complication monitoring will remain important for most patients in the near future. At the same time, hematopoietic stem cell transplantation and autologous genetically modified cell technologies form the most promising area of personalized treatment.

**LIST OF REFERENCES**


1. Valieva, Ya.M., Popov, K.V. Prospects of gene therapy with hematopoietic stem cells // Bulletin of the Russian State Medical University. 2024. No. 6. pp. 57-60. DOI: 10.24075/vrgmu.2024.074.
2. Galitsyna, E. V., Kulikova, E. A., Paveliev, Yu. A., Kuznetsova, O. S., Senina, A. S., Gusev, A. B. Modern gene therapy drugs // Genes and cells. 2024. Vol. 19, No. 1. pp. 21-42. DOI: 10.17816/gc601855.
3. Egorova, T. V., Piskunov, A. A., Poteriaev, D. A. Gene therapy of hereditary diseases based on adeno-associated viral vectors: modern problems of application and ways to solve them. Prevention, diagnosis, and treatment. 2024. Vol. 24, No. 2. pp. 123-139. DOI: 10.30895/2221-996X-2024-24-2-123-139.
4. Zaripova, Yu. R., Kholodnaya, V. A., Frolkova, E. I., Grinenko, A.V. A clinical case of hereditary hemoglobinopathy in a child // Medical advice. 2025. Vol. 19, No. 1. pp. 222-226. DOI: 10.21518/ms2025-001.
5. Krasilnikova, M. V., Karamyan, N. A., Litvin, E. A., Mann, S. G. The first cases of Hb Lepore in Russia // Issues of hematology/oncology and immunopathology in pediatrics. 2021. Vol. 20, No. 3. pp. 102-107. DOI: 10.24287/1726-1708-2021-20-3-102-107.
6. Rachinskaya, O. A., Melnikova, E. V., Merkulov, V. A. Current trends and risks of using drugs based on genome editing technologies // Biologics. Prevention, diagnosis, and treatment. 2023. Vol. 23, No. 3. pp. 247-261. DOI: 10.30895/2221-996X-2023-23-3-247-261.
7. Romanenko, N.A. Hereditary hemolytic anemia. Enzymopathies. Hemoglobinopathies (lecture). Part 2 // Bulletin of Hematology. 2022. Vol. 18, No. 3. pp. 40-59.
8. Sakhno, N.G., Gunar, O.V. Stimuli-sensitive delivery systems for gene therapy drugs // Biotechnology. 2024. Vol. 40, No. 2. pp. 68-83. DOI: 10.56304/S0234275824020091.
9. Khachaturian, A. G., Nazarov, V. D., Dubina, I. A., Lapin, S. V., Sidorenko, D. V., Wilhelmi, A.A., Pervakova, M.Yu., Emanuel, V. L. On the relevance of molecular genetic diagnosis of beta-thalassemia in the Russian Federation // Russian Journal of Pediatric Hematology and Oncology. 2024. Vol. 11, No. 4. pp. 89-97. DOI: 10.21682/2311-1267-2024-11-4-89-97.
10. Khachaturian, A.G., Nazarov, V.D., Lapin, S.V., Sidorenko, D.V., Dubina, I.A., Pervakova, M.Yu., Wilhelmi, A.A., Emanuel, V.L. Laboratory characteristics of hemoglobinopathies // Hematology and transfusiology. 2024. Vol. 69, No. 1. pp. 40-51. DOI: 10.35754/0234-5730-2024-69-1-40-51.
11. Frangoul H., Altshuler D., Cappellini M.D., et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia // N. Engl. J. Med. 2021. Vol. 384, No. 3. P. 252–260. DOI: 10.1056/NEJMoa2031054.
12. Kanter J., Walters M.C., Krishnamurti L., et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease // N. Engl. J. Med. 2022. Vol. 386, No. 7. P. 617–628. DOI: 10.1056/NEJMoa2117175.