

# EHA Research Roadmap on Hemoglobinopathies and Thalassemia: An Update

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## Abstract

The inherited disorders of hemoglobin, which include sickle cell disease and thalassemias, are the most common and widespread distributed monogenic disorders. Due to a selective advantage in malaria regions, these hemoglobin defects are particularly frequent in Africa, Asia, or in the Mediterranean areas, where malaria was endemic until the last century. In recent decades, the globalization of migration has contributed to generate multiethnic European societies. Due to migration from countries or regions with high hemoglobinopathy frequencies such as Africa, Middle East, or Asia, large numbers of patients with these disorders are living in almost every European country today. Furthermore, the numbers are increasing because of increasing refugee flows toward Europe. Additional requirements are the development of European recommendations and guidelines for diagnosis and effective therapeutic approaches. These, together with the advancement of clinical trials using new drugs and therapeutic procedures could ameliorate the quality of life of patients affected with these diseases and increase their life expectancy. Lastly, coordinated efforts should be made to develop diagnostic pathways for thalassemias and hemoglobinopathies, in order to plan interventions, including prenatal diagnosis and cure. For these reasons, the development of new tools to reliably diagnose anemias is urgently needed and fits well with the needs of personalized medicine. In the last 15 years, hematology research has made many big leaps forward. Our general aim will be to solve several hematologic problems using these new approaches. We expect that the development of such a diagnostic tool will improve timely diagnosis throughout Europe, especially in those countries where it is difficult to gain access to “classical” diagnostic tests.

## Introduction

Hemoglobin (Hb) is one of the most abundant proteins in the human body and it serves to transport oxygen. Hb production is

almost as abundant as albumin. The inherited disorders of hemoglobin (Hb), which include sickle cell disease and thalassemias, are the most common and widespread distributed monogenic disorders<sup>1–5</sup> (Table 1). Due to a selective advantage in malaria regions, these Hb defects are particularly frequent in Africa, Asia or in the Mediterranean areas, where malaria was endemic until the last century.<sup>1–4</sup>

In recent decades, the globalization of migration has contributed to generate multiethnic European societies. According to the Organization for Economic Co-operation and Development (OECD), the percentage of the foreign-born population within the European Community in 2008 ranged from 4% in Finland to 37% in Luxembourg, with an overall average of 8%.<sup>6</sup> Due to migration from countries or regions with high hemoglobinopathy frequencies such as Africa, Middle East, or Asia, large numbers of patients with these disorders are living in almost every European country today. Furthermore, the numbers are increasing because of increasing migrant flows toward Europe.

Thus, it is important for health care systems to investigate and ensure that they can adequately address the many and complex lifelong needs of these patients. Moreover, the absence of national registries and prevention programs in the great majority of these countries makes it essential to identify ways and tools to better describe the extent of the problem in terms of numbers and distribution across each country in order to deal with the medical needs of patients with severe, chronic and disabling disorders such as hemoglobinopathies, considering the insufficient level of knowledge of medical teams who are now having to take care of these patients. This will map the distribution of the different forms of hemoglobinopathies in each European country and help

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**Table 1****Synopsis of Most Common Diseases Associated With Mutations in the Globin Beta Gene (*HBB*)**

Adult hemoglobin (HbA) consists of globin alpha (encoded by the *HBA1* and *HBA2* genes) and globin beta (encoded by the *HBB* gene). Worldwide distribute monogenic disorders are related to mutations on either beta or alpha globin genes

**Sickle cell disease (OMIM: 603903)**

Sickle-cell disease (SCD) is a monogenic disorder but a multiorgan disease. The pathologic HbS characterizes SCD. The main clinical presentations are chronic hemolysis and acute vaso-occlusive crisis, which recurrence results in progressive organ damage

In Europe, the prevalence of HbS carriers is 1/150 and 1–5/10,000 affected newborns

*Treatment:* Hydroxyurea is the standard treatment for children and adults with SCD. Regular or occasional transfusions as either classic transfusion or exchange is an additional therapeutic strategy in clinical management of both acute and chronic SCD related organ damage. Bone marrow transplantation should be considered as curative option in presence of an HLA matching donor

 **$\beta$ -Thalassemia (OMIM: 613985)**

$\beta$ -Thalassemia is characterized by a reduced production of reduced or absent production of globin beta with accumulation of alpha-free chains

In Europe, the incidence of symptomatic individuals is estimated at 1 in 10,000

Clinical presentation allows the identification of thalassemia transfusion-dependent thalassemia (TDT) and nontransfusion-dependent thalassemia (NTDT), mainly represented by patients with  $\beta$ -thalassemia intermedia. Carriers of thalassemia are defined also as thalassemia minor, who are generally asymptomatic

*Treatment:* Chronic transfusion of packed red cells and iron chelation therapy. Bone marrow transplantation should be considered as curative option in presence of an HLA matching donor

to plan effective health and other care including social interventions. The development and use of national registries is thus of pivotal significance to allow for more accurate mapping of patient numbers, in both space and time. With data from registries we will develop a detailed map of patients affected by these conditions, which is essential for planning social and health interventions (Table 2).

Additional requirements are the development of European recommendations and guidelines for diagnosis and effective therapeutic approaches. These, together with the advancement of clinical trials using new drugs and therapeutic procedures could ameliorate the quality of life of patients affected with these diseases and increase their life expectancy. Lastly, coordinated efforts should be made to develop diagnostic pathways for thalassemias and hemoglobinopathies, in order to plan interventions, including prenatal diagnosis and cure. For these reasons, the development of new tools to reliably diagnose anemias is urgently needed and fits well with the needs of personalized medicine. In the last 15 years, hematology research has made many big leaps forward. For instance, the emergence of sophisticated genetic and molecular tools (e.g., next generation sequencing (NGS) technique) allowed spectacular progresses in our understanding of the structure and function of the blood cells in health and disease. We anticipate that use of these new approaches will solve several hematologic problems.<sup>7,8</sup> We expect that the development of such a diagnostic tool will

improve timely diagnosis throughout Europe, especially in those countries where it is difficult to gain access to “classical” diagnostic tests (Table 2).

**Hemoglobinopathies: Sickle cell disease**

*Background:* Sickle cell disease (SCD) is a worldwide hereditary red cell disorder caused by a point mutation in the  $\beta$ -globin gene. This results in the synthesis of pathological hemoglobin S (HbS), which displays peculiar biochemical characteristics, polymerizing under deoxygenation.<sup>9,10</sup> SCD is a chronic and disabling disorder, associated with high morbidity and mortality. Although significant numbers of patients with sickle cell disease have lived in Europe for many decades (Greece, Turkey, UK, France, Germany, Italy), in the last two decades, due to immigration fluxes from endemic areas, SCD has increased in prevalence throughout Europe. Presently, the estimated prevalence of affected newborns and SCD carriers in Europe are approximately 1 to 5/10,000 and 1/150, respectively. However, epidemiological predictions suggest an increasing global burden of SCD between 2010 and 2050, making SCD an emerging problem of public health with limited therapeutic options. Hydroxycarbamide (HC) therapy and the comprehensive care provided throughout life, from childhood to adulthood have significantly increased the survival of these patients in childhood, but has probably had less impact on adult morbidity and mortality.<sup>11–14</sup>

*Past achievements in Europe:* In the last decades, pathophysiological studies have shown that dense, dehydrated red cells play a central role in acute and chronic clinical manifestations of SCD, in which intravascular sickling leads to vaso-occlusion and impaired blood flow with ischemic/reperfusion injury. In the microcirculation, vaso-occlusive events (VOC) result from complex and still partially understood mechanisms, involving the interactions between different cell types, including dense red cells, reticulocytes, abnormally activated endothelial cells, leukocytes, platelets, and plasma factors. Recently the role of proadhesion molecules such as vascular adhesion molecule-1 (VCAM-1) or selectins such as P-selectin have been shown to be important in recruitment and adhesion of both neutrophils and sickle red cells to the abnormally activated vascular endothelial surface. Thus, new therapeutic agents interfering with either red cell sickling/dehydration or adhesion to inflammatory activated endothelial cells or oxidative stress have been developed.<sup>10,15,16</sup> These results were achieved while large clinical studies,

**Table 2****Directions of Research Roadmap in Hemoglobinopathies (Thalassemias and SCD)**

- Epidemiology of Hb-pathies (SCD and thalassemias) in Europe: establish Europe-wide national registries
- Common pathways for prenatal screenings, diagnosis and follow-up
- Support studies on mechanisms of Hb-pathies (SCD and thalassemias)
- Identify new therapeutic targets (e.g., such as preclinical studies on animal models)
- Enhance clinical trials for emerging drugs and strengthen research for new drugs
- Identify specific patients needs and help to train expert-patients
- Develop PRO tools to support the work of patient organizations in better identifying patient needs
- Strengthening and creation of hemoglobinopathy advocacy groups in each country and once on a pan-European level to discuss and provide the patients' perspective and “lobbying” where necessary for change and improvements

PRO = patients reported outcomes, SCD = sickle cell disease.

performed on SCD in pediatric and adult populations, evaluated the possibility of switching from chronic transfusions to HC in selected subjects with previous evidence of abnormal cerebrovascular blood flow.<sup>17</sup>

Past achievements in Europe have included the dissemination of the knowledge on SCD in European countries; the generation of data on the natural history of SCD after hematopoietic stem cell transplantation; the identification of markers to be used in decision making process in patients with SCD and cerebrovascular disease to switch from chronic transfusion regimen to HU in subjects with previous evidence of abnormal cerebrovascular velocities; the successful treatment of a patient with SCD with gene therapy<sup>18,19</sup>; the generation of clinical data on large cohorts of SCD patients in close collaboration with African scientists and physicians. In addition, European research has contributed to the characterization of new mechanisms involved in the pathogenesis of SCD as well as in the identification of new possible therapeutic targets using both in vitro cell-based and in vivo animal-based approach. European research has greatly contributed to the state of the art in the field of SCD and to the progress in the disease knowledge within the international scientific community.

*Proposal:* Although significant progress has been made in increasing the knowledge with regards to the natural history and pathophysiology of SCD, its treatment is still unsatisfactory for both acute and chronic clinical complications. Thus, future research in SCD should face biocomplexity, requiring the support of the European Community on both preclinical studies as well as on clinical trials. Since SCD is an important disease in Europe, the EU should launch dedicated grant calls and actions to support research on SCD in Europe.

The European SCD scientific community has identified the following 5 critical areas of action:

- (1) Comprehensive phenotype characterization of the large European SCD cohort of patients, which will allow us to get epidemiologic information; to establish a European registry of patients; to generate both a clinical database and bio-bank and to facilitate research into clinical management identifying new biomarkers of disease severity and subgroups of patients who might benefit from more personalized medicine.
- (2) Understand the impact of social, economic, and environmental factors on complications of sickle cell disease, which is particularly important in the face of climate change and poor air quality, given that SCD predominantly affects the urban-poor populations in most European countries.
- (3) Increase the synergy between European research teams working on pathophysiology of SCD at preclinical levels. This will ensure the progress on the knowledge of SCD and the exploitation of new therapeutic leads to clinical trial in the near future.
- (4) Dissemination of the knowledge on SCD at different levels: medical school, nurse training, family doctors, nurses and physicians working in the emergency department, hematologists, pediatricians, internal medicine doctors, and psychologists. This might generate common action at the European level to ensure optimal care of SCD patients, who currently do not have access to specialist clinical services in many parts of Europe.
- (5) Early identification of SCD in migrants, who represent marginalized and vulnerable people, exposed to extreme conditions during their travels through Middle-East and Africa to the coasts of Southern European countries. The

delay in the identification of SCD may lead to severe acute organ complications and preventable death. Thus, an action is needed to help manage acute health problems caused by SCD, which might dominate the first phase of transition of migrants. This might include the development of guidelines and algorithms for the management of acute events in emergency department (ED) and the dissemination of knowledge about SCD, to emergency department physicians,<sup>20</sup> pediatricians, hematologists, and internal medicine physicians.

*Impact of proposed projects:* Future European research programs on SCD will contribute to the progress in the knowledge of SCD and will deliver education of health-care professionals throughout Europe about SCD; new therapeutic options for clinical management of SCD, including drugs developed from preclinical studies; new profiling of disease severity for personalized medicine; optimization of SCD patient care; clinical trials addressing basic aspects of clinical care; improvement of early identification and care for refugees with SCD.

These approaches will have a positive impact by increasing the visibility of SCD in Europe; improving patient health outcomes and quality of life; generating public-private partnerships for orphan drug development largely based on innovation, generating new opportunities in the context of international competition; attracting a new generation of physicians and researchers working on SCD; improving health systems by reductions of care costs; reducing national and European welfare spending on disabilities of SCD patients and in the level of sickness absence from jobs.

Finally, the European experience of SCD would also have an impact on the management of SCD in other high-income countries such as the USA, as well as low- and middle-income countries, such as Africa and India where SCD is a very significant health problem.

## Hemoglobinopathies: $\beta$ -Thalasseмииs

*Background:*  $\beta$ -thalassemias are a group of inherited hemoglobin disorders that constitute major challenges to health care systems in Europe and across the world owing to their complexity, heterogeneity, clinical outcomes and high cost of disease and its management (Table 1). An estimated 1% to 5% of the global population are carriers of a  $\beta$ -thalassemic mutation.<sup>20</sup> Although the epidemiology of the various clinical forms remains unclear, the disease is known to be highly prevalent in areas extending from sub-Saharan Africa through the Mediterranean region and Middle East, to the Indian subcontinent and East and Southeast Asia. It is conservatively estimated that >40,000 babies with  $\beta$ -thalassemia are born each year worldwide.<sup>21</sup> As a consequence of public health improvements globally and the resulting lower childhood mortality together with population growth and the enduring absence of effective national prevention programs, a substantial increase in the number of affected births all over the world is expected, and has already started. Therefore, despite limited available epidemiological data on hemoglobinopathies in Europe,  $\beta$ -thalassemia is expected to pose an increasingly severe global burden in future years. The annual incidence of symptomatic individuals is estimated at between 1 in 100,000 worldwide and 1 in 10,000 in Europe.<sup>21</sup> Migrations from endemic areas to Europe also led to rising incidence of beta-thalassaemia in large urban centers.  $\beta$ -thalassemic patients experience a high burden of illness and their quality of life is jeopardized.

Progressive increase in life expectancy has been observed in patients with  $\beta$ -thalassemia in recent years which now extends beyond 40 years of age<sup>22</sup> owing to the availability and use of regular red blood cell (RBC) transfusion and effective iron chelation therapy (ICT). Despite important improvements in the management of  $\beta$ -thalassemia, there are still many challenges to overcome before global disease control is achievable. For example, screening and prevention programs in the context of nationally coordinated programs are inadequate or nonexistent in European countries where  $\beta$ -thalassemia was rare in the past or in many resource-constrained countries, and access to effective treatment is far from universal.<sup>23</sup>

*Past achievements in Europe:* Our understanding of the underlying pathophysiological mechanisms of  $\beta$ -thalassemia and its associated clinical morbidity has increased substantially in recent years. Key milestones in optimizing management with transfusion or iron chelation therapy (ICT) have been achieved. Such advances in supportive management have led to significant improvements in survival in this once fatal disease. For example, mortality rates in Western cohorts have declined from 12.7 to 1.65 deaths/1000 patient-years between the periods 1980 to 1999 and 1999 to 2013,<sup>21</sup> with the leading cause of death moving from iron overload and bone marrow transplant complications to infections and hepatitis C virus complications. European clinical and basic research groups have largely contributed to the development of the new oral iron chelators associated with the improvement of the quality of thalassemia care, resulting in improving further to health and survival patient quality of life<sup>24,25</sup> and almost full social integration. In addition, European groups have also contributed to the research and development of gene therapy strategies for  $\beta$ -thalassemia to address the  $\alpha$ -globin or  $\beta$ -globin chain imbalance. Gene therapy is based on the idea that if there is a defect in the production of  $\beta$ -globin in  $\beta$ -thalassemia, exogenous production of  $\beta$ -like globins could correct the disorder. The hemopoietic system is convenient for such approaches, since hemopoietic stem cells from an individual with  $\beta$ -thalassemia can be isolated and transduced with viruses to introduce exogenous genetic material, such as  $\beta$ -like globin transgenes that can allow for such exogenous gene expression.<sup>26</sup> Besides gene therapy, more recent approaches have been developed to directly correct genetic mutations in the endogenous DNA of the cell or to disrupt specific DNA sequences in the genome. This approach is known as genome editing and has been facilitated through the identification of several enzymes, including CRISPR/Cas9, that can introduce DNA breaks in specific regions of the genome.<sup>27</sup> The translation from benchside-to-bedside of new agents stimulating and supporting normal, effective erythropoiesis has also been developed (e.g., Luspatercept or Sotatercept). Additional studies on erythropoiesis and iron metabolism have led to the development of promising new drugs that have the potential to improve erythropoiesis, prevent or minimize splenomegaly and address iron metabolism, some of which are already in clinical trials.<sup>28,29</sup>

*Proposal:* Our improved understanding of the pathophysiology and disease burden in patients with  $\beta$ -thalassemia and the significant contribution of the educational program of the Thalassemia International Federation (TIF), including its Guidelines (for prevention and management)<sup>30</sup> have helped to optimize disease management and to construct a plan for the development of novel therapeutics. However, sadly these have been adopted and/or implemented in the context of national programs in very few countries across the world, thus calling for concentrated international action. Nonetheless, the clinical and medical

complexity of  $\beta$ -thalassemia as a disease, together with major advances in understanding the genotypic basis of the disease, might imply the need for individualized therapy, to identify the most appropriate treatment for each individual patient.

We propose the following five guidelines/procedures/steps to further improve the global care of thalassemia patients:

- (1) Improve the treatment of immigrant populations and refugees, through increasing awareness among patients and caregivers in European and other countries where thalassemia was not a health priority but is now more common due to migration and refugee flows of people from countries with high hemoglobinopathy prevalence.
- (2) Promote patients reported outcomes (PRO). Understanding the degree of patient-perceived health impairment is essential to determine the burden of illness of  $\beta$ -thalassemia and to recommend suitable therapy. Patient reported outcomes (PROs), including QoL, are considered an important aspect of effective health care in  $\beta$ -thalassemia, as in every chronic disease. Further, PROs have been increasingly recognized as critical to understanding the burden of disease and treatment efficacy by both regulatory agencies and health technology assessment bodies. One step could be to document the burden of illness (defined as impairment of quality of life, QoL) in nontransfusion-dependent and transfusion-dependent thalassemia patients receiving standard care in Europe with a focus on patient-reported physical, mental, and social impairment in QoL.
- (3) Support the development and implementation of new safe and effective therapeutic approaches, including gene therapy, genome editing and targeting the alpha and beta globin chain imbalance to reduce ineffective erythropoiesis. To improve this important field, there is a need to sustain research with adequate funding (grant calls favoring translational research).
- (4) Implement the activities of European networks (i.e., Euro-BloodNet) in order to involve a larger number of patients in clinical trial for new therapeutic approaches. A dedicated educational program for family doctors is needed to properly recognize and manage these new patients.
- (5) Promote actions for strengthening more dedicated EU programs for grants on preclinical and clinical studies on  $\beta$ -thalassemia.

*Networking with patient associations:* Patient associations play a crucial role in present and future actions of our scientific community devoted to improve patient care and to support research on hemoglobinopathies. The TIF has been working with national patient associations in more than 62 countries across the world, including 15 EU countries, for more than three decades now. Based on the experiences, voices and opinions gathered, we can confidently state that in order to see substantial progress in the field of thalassemia in Europe, efforts need to focus on dissemination of knowledge about the prevention and care of thalassemia in the patient community. Thus, patients will become knowledgeable and productive partners to healthcare professionals and decision-making bodies, at the national, regional, and international levels. Up to now, the involvement of thalassemia patients in these processes has been extremely confined, especially when compared to their counterpart peers in oncology. This might mainly be due to the nature of the disease (i.e., that it is a pediatric disorder, which with appropriate management has become a chronic disease). Thus it is understandable that in the past thalassemia patients were more focused on dealing with the complex and varied repercussions of their disease on their life,

which in contrast to oncology patients was not *acute* but chronic. This is evidently witnessed in the development for many years now of oncology-related PROs, and the absence of hemoglobinopathy-specific PROs, which will contribute to the development of services specific for patients with hemoglobinopathies.

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