The Haemoglobinopathies (haemoglobin disorders) are the commonest genetic disorders in humans. The most frequent ones are sickle cell syndromes (sickle cell anaemia and other related disorders) and thalassaemias (alpha and beta). Other types of abnormal haemoglobins (Hb) leading to clinically significant disorders are very rare and include unstable haemoglobins or haemoglobins with an abnormal affinity for oxygen.

Haemoglobinopathies are inherited as Mendelian traits with, in most cases, an autosomal recessive inheritance pattern; homozygotes or compound heterozygotes (for example those with two abnormal beta globin genes on the 2 chromosomes of the same pair) display the clinical manifestation of the disorder, whereas carriers (heterozygotes, bearing only one abnormal beta globin gene), usually have little or no symptoms.

In the most severe forms, the diagnosis of haemoglobinopathies relies on clinical manifestations, mainly anaemia and its consequences. The aetiology of the anaemia may subsequently be related to a haemoglobin disorder through relatively simple blood tests, including complete blood count (CBC) and haemoglobin studies. However, the part played by genetic diagnosis, which is based on molecular biology techniques, has significantly increased during the last decades. In the last century, it was initially limited to very specific clinical indications, particularly prenatal diagnosis, or was used with the aim of improving scientific knowledge or to feed epidemiological studies.

The increasing number of available data has demonstrated that genetic results can also contribute to improve the diagnosis, predict in some cases the evolution and thus the prognosis of the disease and may help to adapt therapeutic measures. Old examples of this use include the determination of the beta globin gene cluster haplotypes for the characterisation of severe (Bantu haplotype) or milder forms (Senegal or Arabian/Indian haplotypes) of sickle cell disease (SCD).

In severe forms of beta thalassaemia, the type of mutation has been known for a long time to be of importance to determine the severity of the disorder. Mutations leading to the total absence of production of beta chains (beta zero alleles) usually have a poorer prognosis than those where a small amount of beta globin chain is produced (beta + alleles).1

In both SCD and beta-thalassaemia, the notion of genetic modifiers has progressively emerged and is now used to explain differences in clinical severity of patients harbouring the
same globin mutation(s). These modifiers comprise mainly the association of alpha thalassaemia deletions (or mutations), which lowers the imbalance between alpha and beta chains in beta thalassaemia, and the association of alleles contributing to the persistence and/or increase of Hb F synthesis after birth, leading to increased circulating total Hb levels. The latest category includes the known XmnI-158 polymorphism of the G gamma gene and other more recently identified genetic modifiers located on other chromosomes (BCL11A on chromosome 2 and HBS1L-MYB on chromosome 6)\(^2\,^3\). Using these parameters, authors have proposed severity scores, which may help establishing the prognosis and adapt the follow-up and therapeutic proposals for patients with thalassaemia and SCD\(^4\,^5\). However these strategies have to be validated on bigger cohorts of patients.

Laboratories working on the molecular diagnosis of haemoglobinopathies should now be able to propose a comprehensive panel of techniques able to cover these new approaches of the disease. Even in less severe haemoglobin disorders, molecular biology is useful to allow characterizing the defect and sometimes deciphering complex, unexpected associations of alpha and beta globin gene cluster abnormalities. It is indeed worthy to note that some patients who bear two (or more) abnormal alleles may have a very mild phenotype (if any), but can nevertheless be at risk of transmitting a severe form of haemoglobinopathy if the spouse is also a carrier of an abnormal globin allele.

New technical approaches of molecular biology, particularly next generation sequencing (NGS), which allows the analysis of very large fragments of the genome, or nearly the entire genome (or exome), may offer in the near future the possibility to study the whole alpha and beta globin clusters in addition to known modifier loci and may allow rapid and comprehensive view of all the partner genes playing a role in the regulation of haemoglobin synthesis. This has the potential to completely change our approach of the molecular diagnosis of haemoglobin disorders (as of many other inherited diseases). These new methods are increasingly available in high-income countries. The way we are going to integrate these new approaches of genetics into medical practice is still not obvious, even for specialists.

In most European countries, genetic counselling is available for people seeking advice in the context of a family risk of haemoglobinopathy. It is aimed at explaining the risk of an individual or a couple to be affected, or have children affected, with severe forms of the disorder and may also be useful for reassuring those who are not at increased risk. In 2010, the World Health Organisation (WHO) has published an expert report stressing the role of genetic counselling in primary care in all countries\(^6\), especially low-income ones, where
people or couples at-risk often do not have an easy access to specialised consultations. A more recent WHO report from an expert meeting in 2012, has highlighted the importance of preconception care and included genetic counselling among the measures which have to be widely implemented in that period of life, in order to prevent several pathologies including haemoglobinopathies.

During the third phase of the project ENERCA, partners have published a policy report summarizing the current situation of haemoglobinopathies in 10 European countries, in collaboration with TIF and the international office for migrations (IOM). This report highlights the gap between the advances of the knowledge and the practical implementation of services at the nation level in many EU member states. The increasing number of available tools and data on genetic diagnosis will become a new challenge for genetic counsellors all over the world. These will undoubtedly have consequences on the approach of genetic counselling and may completely change its practice at the individual level in the next decades.


6 Community genetics services, Report of a WHO consultation on community genetics in low and middle income countries, Geneva, Switzerland, 13-14 Sept 2010

7 Meeting to Develop a Global Consensus on Preconception Care to Reduce Maternal and Childhood Mortality and Morbidity, WHO, Geneva, 6–7 February 2012, Meeting report