THE EVOLVING SPECTRUM OF THE EPIDEMIOLOGY OF THALASSEMIA

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An estimation of the frequency for the foreseeable future.

The reasons for the high frequency of thalassemia.

The development of partnerships between the poor and richer countries for the better control and management of thalassemia.

INTRODUCTION

The inherited disorders of hemoglobin which include sickle cell anemia and its variants and the thalassemias are the commonest monogenic diseases.[1,2] There are two main forms of thalassemia, α and β thalassemia. The α globin genes, which are duplicated, are on chromosome 16. A deletion of one of them is termed α^+ thalassemia, while if both of the pair are deleted it is termed α^0 thalassemia. Point mutations of the α genes are much less common and only one, hemoglobin Constant Spring, occurs at a very high frequency in some populations. The single β globin genes are on chromosome 11. The β thalassemias result from over 200 different mutations and deletions are much less common. There is a very common structural hemoglobin variant, hemoglobin E, which is synthesized at a reduced rate and behaves like a very mild form of β thalassemia. When inherited together with β thalassemia the result is hemoglobin E β thalassemia which is one of the commonest forms of severe thalassemia in many parts of Asia.

The α^+ thalassemias alone are not associated with any severe hematological changes and their major importance is that when they are inherited together with different forms of β thalassemia they tend to reduce the severity of the disease. Co-inheritance of α^+ and α^0 thalassemia results in a condition of variable severity called hemoglobin H disease while homozygosity for α^0 thalassemia results in hydrops foetalis and death *in utero* or early after birth. The β thalassemias are divided into β thalassemia major or intermedia depending on the severity of the particular mutations or the inheritance of phenotypic modifiers. Hb E β thalassemia is associated with remarkable variability of the phenotype ranging from severe β thalassemia major through various levels of β thalassemia intermedia.

While much progress has been made towards the prevention and management of the thalassemias in the richer countries this is not the case for many of the poorer countries of the tropical belt. In this paper current knowledge about the world

distribution and frequency is discussed together with the reasons for the very high frequency of the different forms of thalassemia. Particular emphasis is placed on likely changes in the frequency of thalassemia in the future and the effects of changes in the environment and of population movement on the global health load caused by this disease. The danger of its continued neglect by international health agencies is also discussed.

WORLD DISTRIBUTION

An approximate distribution of the α and β thalassemias is shown in figures 1 and 2 respectively and summarized in references.[1,2] The α^+ thalassemias, which spread at high frequency right across the tropical belt from sub-Saharan Africa through the Middle East, South Asia and Southeast Asia are undoubtedly the commonest of all single gene disorders. Indeed, their heterozygote frequency in an area of north India and in parts of Southeast Asia appears to be going to fixation with frequency values of over 75% of the population. The more severe form of α thalassemia, α^0 thalassemia, is less common and occurs at a high frequency in parts of the Mediterranean region and particularly in Southeast Asia. The β thalassemias are less common in sub-Saharan Africa and spread across the rest of the tropical belt at a varying frequency. Each of the high frequency regions have their own particular β thalassemia mutations, a finding which suggests that in evolutionary terms they are fairly recent and have not had time to disperse equally across the tropical belt. Hemoglobin E is an extremely common structural hemoglobin variant, occurring in South and Southeast Asia and reaching very high frequencies in parts of Southeast Asia with 70% heterozygote rates in the hemoglobin E triangle of north Thailand and Cambodia. Hence hemoglobin E β thalassemia is extremely common in this region.

The presence of thalassemia is not shown in the richer countries of Europe and the USA in figures 1 and 2. The disease occurs at various frequency in all these regions due to the increasing presence of immigrants from the tropical belt and will almost

certainly increase in Europe as a reflection of the major increase of emigration from the Middle East at the current time.

DETERMINING THE ACCURATE FREQUENCY OF THE THALASSEMIAS IN DIFFERENT POPULATIONS

Standard methods of assessment

Particularly in the case of the poorer developing countries it is extremely important for their governments to have a reasonable knowledge regarding the cost of the prevention and management of thalassemia in their country. The usual method of determining its frequency in many countries has been to carry out the assessment in one or two centers and then extrapolate the data to the entire country. However, some years ago it was found that in Vanuatu and Vietnam there is remarkable variation in the frequency of the various forms of thalassemia over short geographical distances.[3,4] This was also observed later in northwest India.[5] Until recently there have been no other reports of micromapping of this type.

The clinical value of micromapping

Recently a study to determine the frequency of heterozygous carriers for common inherited hemoglobin disorders has been carried out in over 7500 adolescent children in 25 districts in Sri Lanka.[6] The results have disclosed a highly significant variation in frequency over very short geographical distances. As well as its evolutionary significance this study had practical clinical implications. If this frequency calculation had been carried by the usual approach of assessing it at one or two centers and then extrapolating the results to the entire population it would have underestimated the births of β thalassemia major by 50% and those of HbE β thalassemia by 30%.

REASONS FOR THE HIGH FREQUENCY OF THE DIFFERENT FORMS OF THALASSEMIA

Malaria resistance

Although many years of uncertainty have passed since JBS Haldane proposed that thalassemia was common in the Mediterranean region due to heterozygote resistance against malaria[7] there is now extremely strong evidence that this is the case. This is particularly well described in the case of α thalassemia. For example it has been shown in the northern coast of Papua New Guinea where the frequency of α^+ thalassemia is in excess of 70% of the population there is strong resistance to malaria both by heterozygotes and homozygotes for this condition.[8] Similar findings have been described in the populations of Kenya.[9]

Early studies of the history of the distribution of malaria in the Mediterranean region showed that the highest frequencies were similar to those of β thalassemia[2] and more recent studies have confirmed the relationship between this form of thalassemia and *P. falciparum* malaria.[1] Similarly, HbE has only reached high frequencies in populations with a high level of malaria.

These observations explain why the α^+ thalassemias are the commonest single gene disorders in the world and why the β thalassemias have not reached such high frequencies. In the case of the α^+ thalassemias there is malaria resistance to both heterozygotes and homozygotes and neither of these conditions have any clinical implications. In the case of the β thalassemias there is heterozygote resistance but homozygosity is associated with a severe clinical disorder. In this case an equilibrium has been reached in which heterozygote resistance is counterbalanced by the clinical severity of homozygotes and hence frequencies as high as the α thalassemias have not been attained.

The mechanisms of malaria resistance

The increasing information about the mechanisms of resistance on the part of the thalassemias to malaria suggests that at least more than one mechanism is active in

every form of the condition. In the case of the α thalassemias it has been found that their red cells are deficient in complement receptor 1 (CR1). This is a ligand for rosetting in which unaffected red cells adhere to parasite-infected cells, a phenomenon which is associated with severe forms of malaria due to vascular complications.[10] α thalassemia may also be involved in immunological priming. Young children in parts of Asia have been found to be infected with the milder parasite *P vivax* in early life and because of cross immunity between *P. vivax* and *P. falciparum* they may become more resistant to the latter and increase in number in later life.[11]

In the case of heterozygous β thalassemia there is evidence of reduced invasion and growth of *P. falciparum* and reduced adherence and rosetting, similar to that found in α thalassemia has also been demonstrated. There are limited data on the relationship between hemoglobin E and malaria. It only occurs at a high frequency in districts with a high frequency of malaria and there have been reports of a reduced frequency in patients who are being admitted to hospital with severe malaria.

It has been found that patients with hemoglobin E β thalassemia are more prone to infection with *P. vivax* malaria.[12] This is not surprising because this parasite is more prone to infect young red cell populations. This observation requires further study because *P. vivax* can still be a quite serious form of malaria and those with Hb E β thalassemia require a suitable form of prophylaxis.

Epistatic interactions of thalassemia and hemoglobin variants

Recent studies in Africa have shown that while individuals with α^+ thalassemia or sickle cell trait have significant protection against *P. falciparum* malaria in those that inherit the genes for both variants this protection is completely lost and they are as liable to have severe malaria as those who carry neither of these mutations.[13] These observations have recently explained the different frequencies of the sickle cell trait and different forms of thalassemia in the Mediterranean population and will

undoubtedly be of great value for studying the population genetics of the thalassemias in the future.[14]

Malaria and the different frequencies of the thalassemias over short geographical distances

As described earlier a recent study[6] in Sri Lanka has demonstrated that there is a remarkable difference in frequency of the different forms of thalassemia over very short geographical distances. Because there are such excellent records of malaria frequency over the island over many years, first using spleen rates and later blood analysis, it has been possible to relate it to the frequency of thalassemia in different areas. The spleen is not palpable in thalassemia heterozygotes.[2]

It was found that there were significant differences in frequency of malaria in different parts of the island. The frequency was related closely to the level of rainfall. It was significantly less in the southern parts of the island where rainfall is very heavy and where the lakes are being constantly refilled. The frequency of malaria in this environment compares with the much higher frequencies in the centre and north of the island where the rainfall is limited and hence where sluggish pools of water provide a much more effective breeding ground for the mosquitoes. It was found that different frequencies of malaria in the island were significantly related to the varying frequency of different levels of thalassemia over short distances (Figure 3). Although there are limited data for the dispersal and flight range of vectors such data as there are suggest that the commonest vector for *P. falciparum*, *Anopheles culicifacies,* probably can travel only 1-2 km. This limited dispersal distance could also be a factor in the different frequency of the hemoglobin variants over short distances. The latter may also relate to altitude; malarial transmission is gradually reduced to zero with increasing altitude. In the north coast of Papua New Guinea the heterozygote frequency of α thalassemia exceeds 70% of the population yet

careful studies of the closely related mountains reveals no cases of α thalassemia at all.[15]

It appears therefore that the remarkable difference in frequency of the different forms of thalassemia over short geographical distances is very much related to the present or past frequency of malaria. Since the latter is dependent on different breeding requirements for the mosquito vectors it seems likely that the same situation exists in many parts of the tropical belt.

Other factors involved in the frequency of the thalassemias

Given the extreme frequency of the thalassemias it seems very likely that other factors must be involved as well as malaria. As mentioned earlier there is some evidence that immune response plays a role although more work is required in this area. Another important question relates to the frequency of consanguinity, particularly in the tropical belt. Unfortunately there is very limited work being carried out to assess its frequency. Although consanguineous marriages are known to be an important factor for the frequency of all recessive genetic disorders and are thought to be common in many Asian countries very few studies of their frequency have been reported. In a recent family study in Sri Lanka[6] marriage registrars asked a group of newly married couples to fill in a questionnaire regarding information about their relationship to their families and patterns of partner selection. Overall the consanguinity rate was approximately 7% for the total island. Further studies of this type of families across the tropical belt is required.

Clinical implications of the studies of the relative distribution of the thalassemias

It appears therefore that the remarkable difference in frequency of the different forms of thalassaemia over short geographical distances is largely although not completely related to the present or past frequency of malaria. Since the latter is strongly

related to different environments and breeding requirements for the mosquito vectors it seems likely that the same situation will exist in many part of the tropical belt. These findings offer further evidence towards the importance of at least a limited form of micromapping as part of the management of thalassemia in the countries of the tropical belt. As discussed earlier it provides a very much more accurate way of defining the genuine birth rate of the thalassemias, information which is essential for the governments of affected countries for assessing the financial aspects required for the prevention and management of the different forms of thalassemia. A more accurate assessment of the birthrate of babies with different forms of thalassemia, particularly in the poorer countries of the world, might also be helpful in persuading the international health agencies about their global importance.

THALASSEMIA FOR THE FORESEEABLE FUTURE

It is clear from the other papers in this edition of Hematology/Oncology Clinics of North America that major progress continues to be made towards prevention and management of the thalassemias in the richer countries of the world. The application of genomics to the field looks very promising. Particularly because it is likely that progress in the latter work will still be some years before it reaches the clinic, especially in the poorer countries of the world, it is important that we try to assess the likely pattern of frequency of the thalassemias for the foreseeable future. Without this information it will be difficult to persuade the international health agencies about the increasing finance required for the better control and management of these diseases in the poor countries of the world.

The frequency of thalassemia in the foreseeable future

Although some progress has been made towards the control of malaria there is still widespread drug resistance and, with the exception of protective bednets, prophylactic approaches are still having limited success.[16,17] Even if malaria transmission is eradicated it may take many generations, possibly up to 250 years,

to have a significant effect on the frequency of the thalassemias.[18] Meanwhile, many of the poorer countries of the world may be going through an epidemiological transition reflecting slow improvements in hygiene, nutrition, public health care and other factors which are combining to reduce both neonatal and childhood mortality rates. It follows therefore that babies with severe forms of thalassemia who previously would have died undiagnosed early in life may be surviving to present for diagnosis and treatment. Hence the global burden of disease caused by the thalassemias is likely to increase. Of course much depends on how long it takes for the poorer countries to develop programs for prevention and management of the different forms of thalassemia.

The effects of emigration

Most of the richer countries now have varying numbers of patients with thalassemia resulting from emigration from high frequency tropical countries over many years. However, it appears that this phenomenon is on the increase. A particularly good example is the USA.[19,20]

Once rare in North America the thalassemias have become a major public health problem in some parts of the country. It is estimated that there is a 2000% increase in Asian and other at-risk populations emigrating to the USA in the last three decades. A screening programme for the thalassemias in Californian newborn babies over eight years demonstrated over 500 with different forms of α thalassemia and 79 with different β thalassemias.

Given the enormous number of emigrants from the Middle East and related regions over the last few years it seems likely that there will be a major increase in different forms of thalassemia throughout the richer countries of Europe.

Risks of different forms of malaria for some types of thalassemia

As mentioned earlier not all forms of malaria offer resistance to carriers for different forms of thalassemia. It has been shown fairly recently that patients with hemoglobin E β thalassemia are significantly more prone to infection with *P. vivax* malaria.[11] Since this severe form of thalassemia is extremely common in many parts of Asia its management in the future will depend on the prevention and treatment of this variety of malaria. Because the observations on the interaction between *P. vivax* malaria and thalassemia have only been reported once from Sri Lanka,[12] further work is required to confirm the frequency of this interaction in countries like north India where HbE β thalassemia and *P. vivax* malaria are both so common.

REQUIREMENTS FOR THE FUTURE

As is clear from the other articles in this edition considerable progress has been made towards the prevention and management of the different forms of thalassemia by centers in the richer countries and we are moving forward towards the successful applications of gene therapy towards a cure for many forms of thalassemia, although this will probably still take a long time. As regards the very high frequencies of thalassemia over the tropical belt some progress has been made but, overall, the situation is still very unsatisfactory. In 2002 the World Health Organization (WHO) published a report entitled *Genomics and World Health*[21] that recommended the formation of what were called North/South and South/South partnerships as an approach to the control and management of common genetic diseases such as the hemoglobin disorders. These recommendations were later confirmed by the WHO Executive Board and at the 59th World Health Assembly. North/South indicates partnerships between centers in the rich countries with those in the poorer countries of the tropical belt while South/South partnerships relate to those poorer countries in the tropical belt who have improved their management of thalassemia and other common genetic diseases sufficiently to help other countries in their vicinity where very little or no progress has been made. More recently the inherited hemoglobin disorders have been included in the current edition of the *Global Burden of Disease*

Study and have been clearly defined as significant factors in the global burden of anemia.[22]

There seem to still be relatively small numbers of North/South partnerships even though they were encouraged by the WHO. An example of a partnership of this kind is that between the University of Oxford in the UK and the University of Toronto in Canada with Sri Lanka. This 20 year program has combined research into the many different forms of thalassemia in Sri Lanka together with capacity building, that is training medical staff in the prevention and management of the severe forms of thalassemia in their country together with raising funds to build a new national thalassemia treatment centre and various research laboratories for the study of these diseases.[23,24] This program has required sending some of the medical staff from Sri Lanka to Oxford for training purposes and journeys to Sri Lanka for the teaching staff from Oxford and Toronto at least four times per year. The program has developed quite well over the years and has had the approval of the Sri Lankan government.

There has been some progress towards the concept of the South/South partnerships. Several meetings have been arranged, mainly in Thailand, which are attended by representatives from many of the countries in South and Southeast Asia. Major attention has been focused on the current state of progress and available facilities for the management of the thalassemias. Also particularly the teams in Thailand have been able to develop thalassemia programs with nearby countries where no such programs had previously existed.

Although it is still early days, it does appear as though programs of this type can be extremely valuable for the future management of the thalassemias, particularly in countries where little progress has hitherto been made.

One of the main problems with this approach is lack of financial support. The major international funding bodies, with a few exceptions, and the WHO and related

international agencies do not seem to feel that the thalassemias are worth supporting in comparison with infectious disease, cancer or other common non-infectious disorders. It is vital therefore that they appreciate the global importance of the thalassemias. It is also important to modify the activities of some of the hematology societies of the richer countries. Over recent years they have tended to have increasingly neglected the red cell in general and the hemoglobin disorders in particular. This observation is mirrored by the relative lack of published work in their journals in this field with its major focus on other aspects of hematology.

It is also quite likely that some of the current problems of the thalassemia field relate to the quality of teaching of some aspects of hematology and tropical medicine, particularly in the richer countries of the world.[25] The further development of the North/South concept will certainly require improvement in the teaching of these subjects and of encouraging medical students and young trainees in hematology throughout the richer world to spend at least short periods of their training in the tropics to gain some experience of global diseases like the thalassemias.

SUMMARY

The thalassemias and other inherited disorders of hemoglobin are likely to remain a serious global health problem for the foreseeable future. Currently, they are most frequent in the tropical belt and an assessment of their true frequency and the likely cost of management for the governments of these countries will require a form of micromapping. Over recent years there has been major progress towards the better prevention and management of the thalassemias in the richer countries and it is likely that using the tools of molecular genetics they eventually will be completely curable, although this is probably a long time in the future. To facilitate the global management of these diseases it will require North/South partnerships between rich and poor countries and related activities so that they can be better controlled over the tropical belt in the future. Unfortunately, the thalassemias are going through a

phase of neglected diseases by the WHO, related international health bodies and also by the hematology societies in the richer countries and hence the hematological literature. With a few exceptions they are also neglected by the fund raising bodies of the richer countries. It is vital that the current status of the thalassemias as increasingly common and severe global disorders is brought to the attention of the medical world as a whole.

Figure 1

The approximate distribution of the α thalassemias

Figure 2

The approximate distribution of the β thalassemias

Figure 3

The distribution of inherited disorders of hemoglobin among over 7,000 adolescent children studied in 69 schools across Sri Lanka. Pie charts are proportional to the number of individuals with an inherited disorder of hemoglobin. The boundaries of the 25 districts and the spleen rates from the 1921-1922 nationwide malaria survey (digitized from[26]) are shown in the background.

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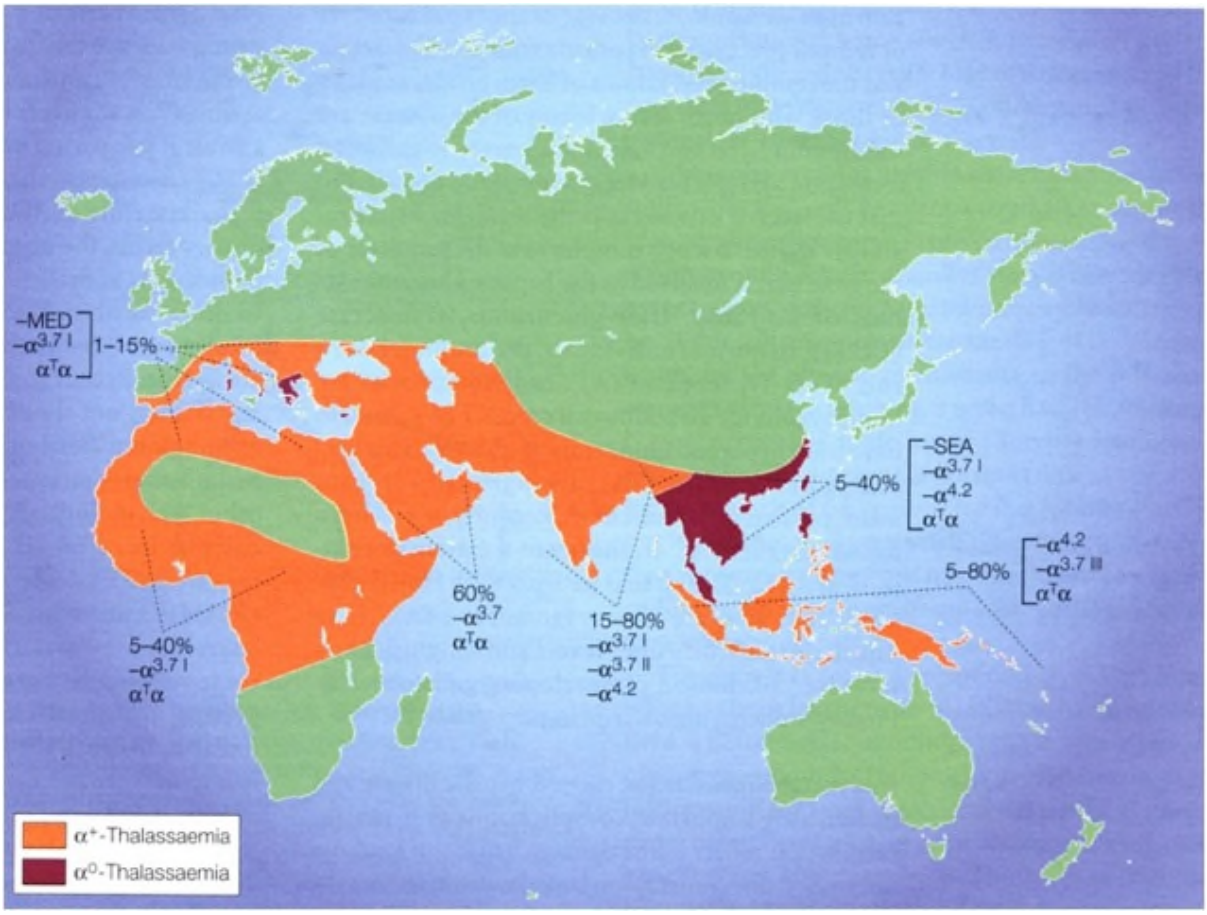
Figure 1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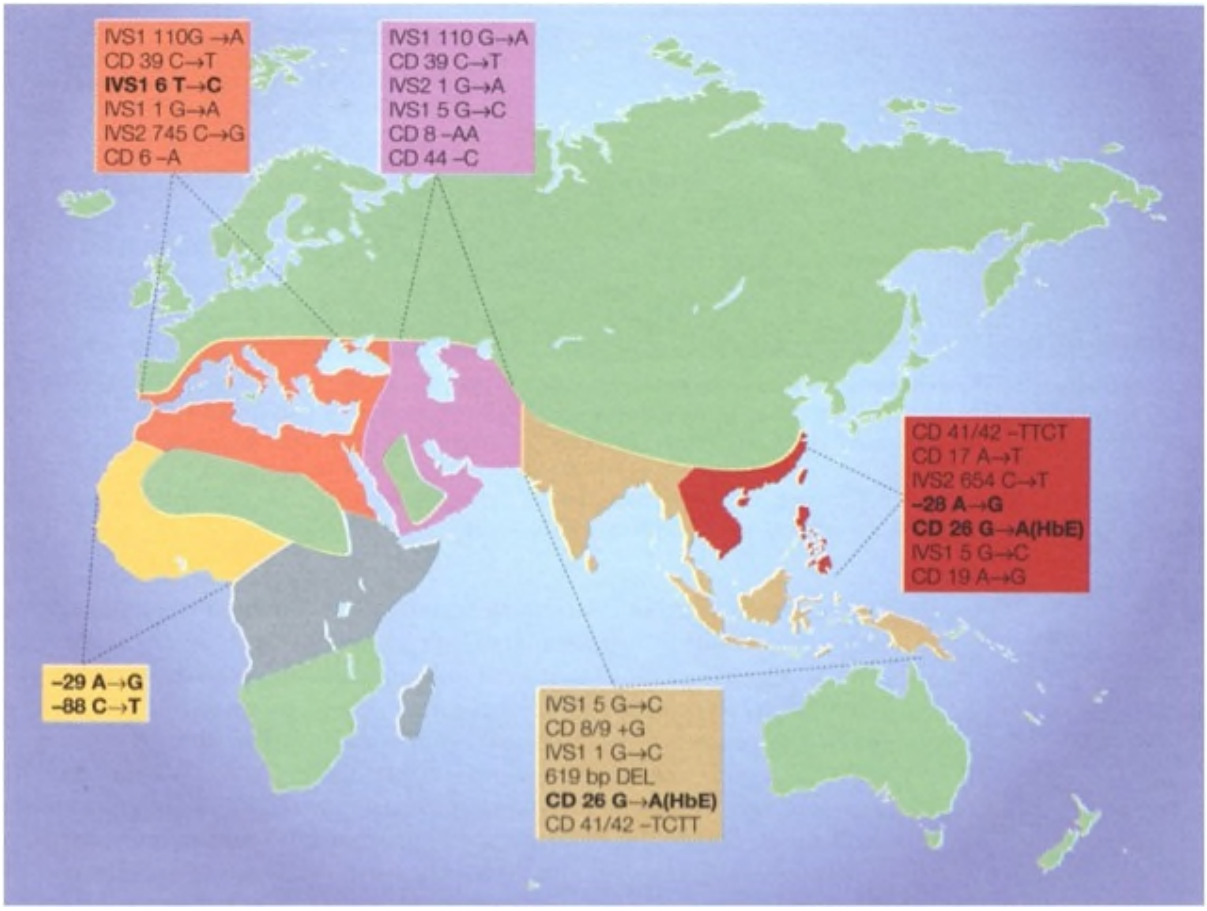
$\alpha^{T}\alpha$
1–15%
5–40%
$-\alpha^{3.7\,I}$
$\alpha^{T}\alpha$
60%
$-\alpha^{3.7}$
$\alpha^{T}\alpha$
15–80%
$-\alpha^{3.7\,I}$
$-\alpha^{3.7\,II}$
$-\alpha^{4.2}$
5–40%
-SEA
$-\alpha^{3.7\,I}$
$-\alpha^{4.2}$
$\alpha^{T}\alpha$
5–80%
$-\alpha^{4.2}$
$-\alpha^{3.7\,III}$
$\alpha^{T}\alpha$
α^{+}-Thalassaemia
α^{0}-Thalassaemia

Figure 2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IVS2 1 G→A
IVS1 5 G→C
CD 8 –AA
CD 44 –C
CD 41/42 –TTCT
CD 17 A→T
IVS2 654 C→T
–28 A→G
CD 26 G→A(HbE)
IVS1 5 G→C
CD 19 A→G
–29 A→G
–88 C→T
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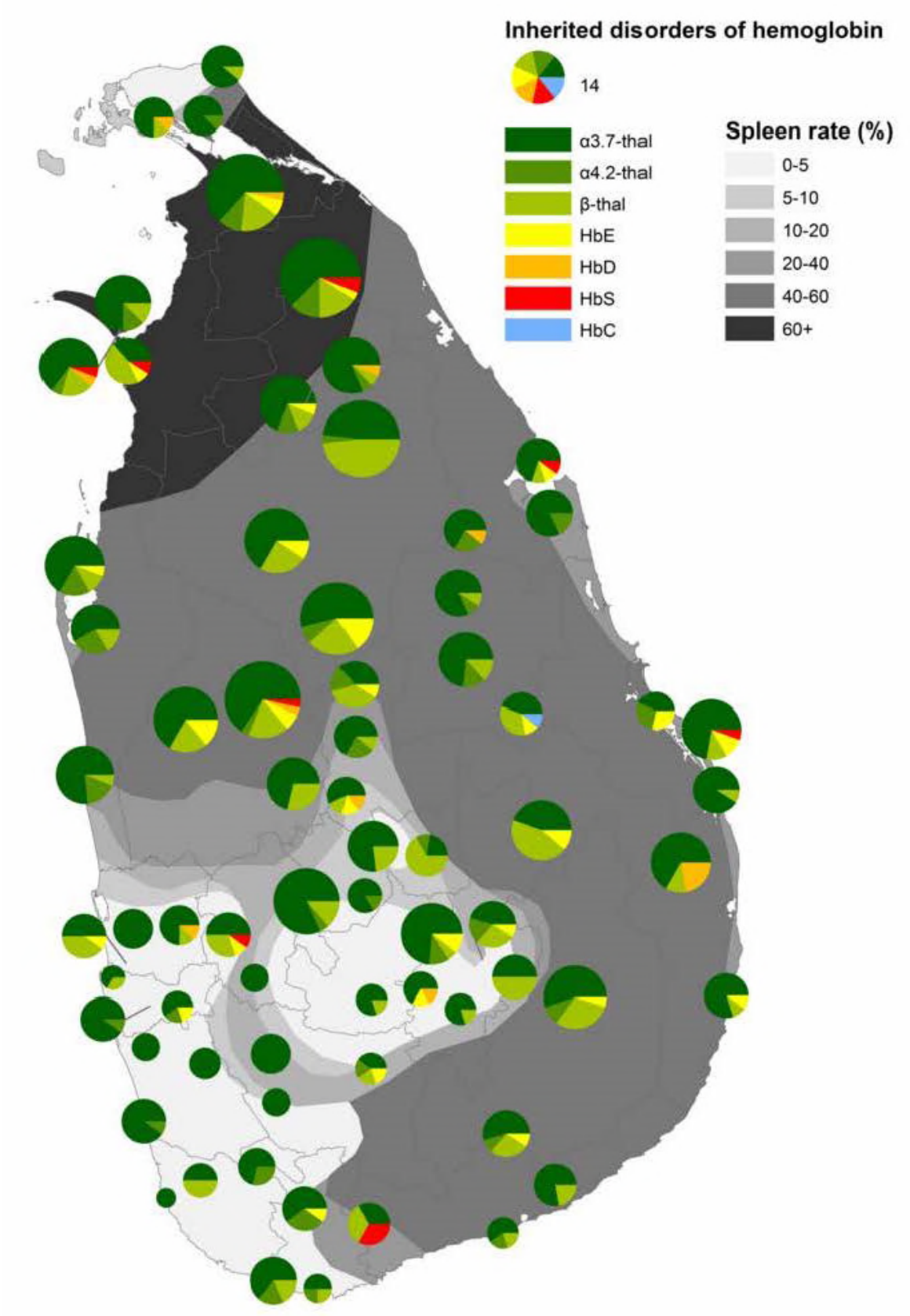
CD 26 G→A(HbE)
CD 41/42 –TCTT

Figure 3


Inherited disorders of hemoglobin
14
α3.7-thal
α4.2-thal
β-thal
HbE
HbD
HbS
HbC
Spleen rate (%)
0-5
5-10
10-20
20-40
40-60
60+