Sickle cell disease: Introduction

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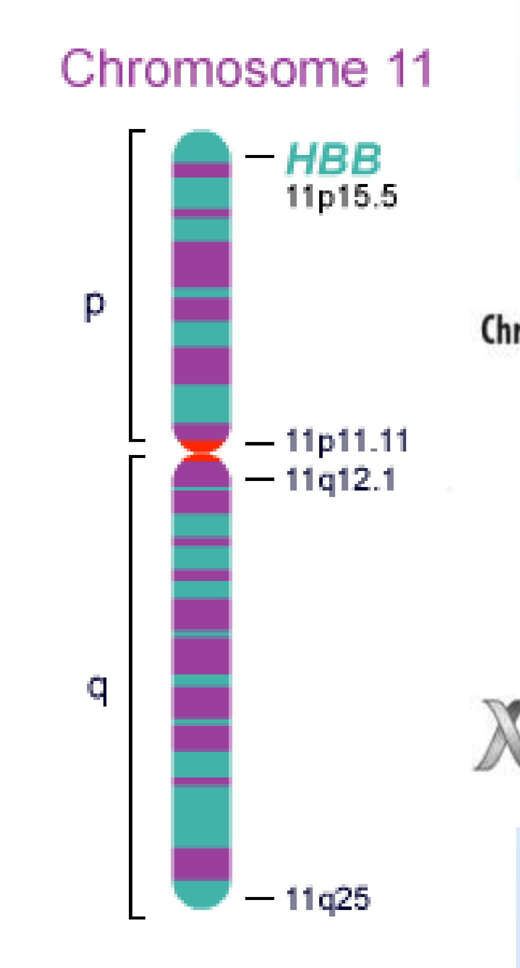
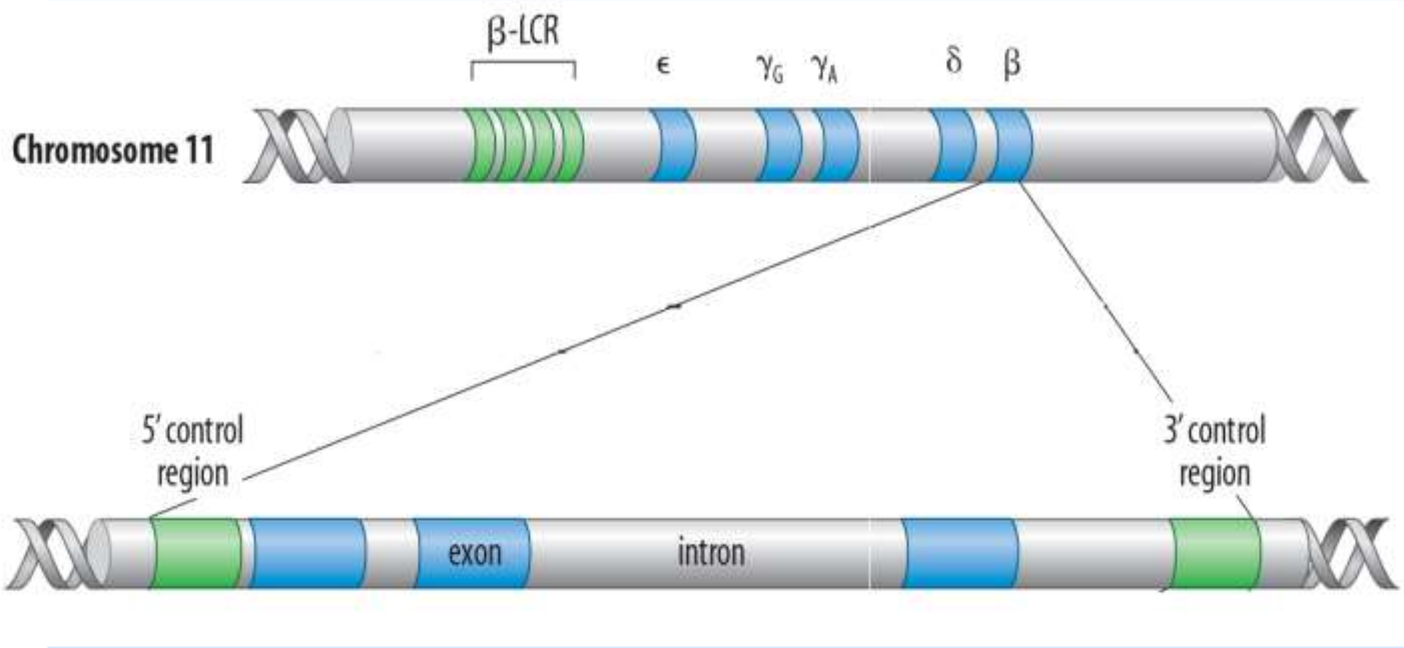
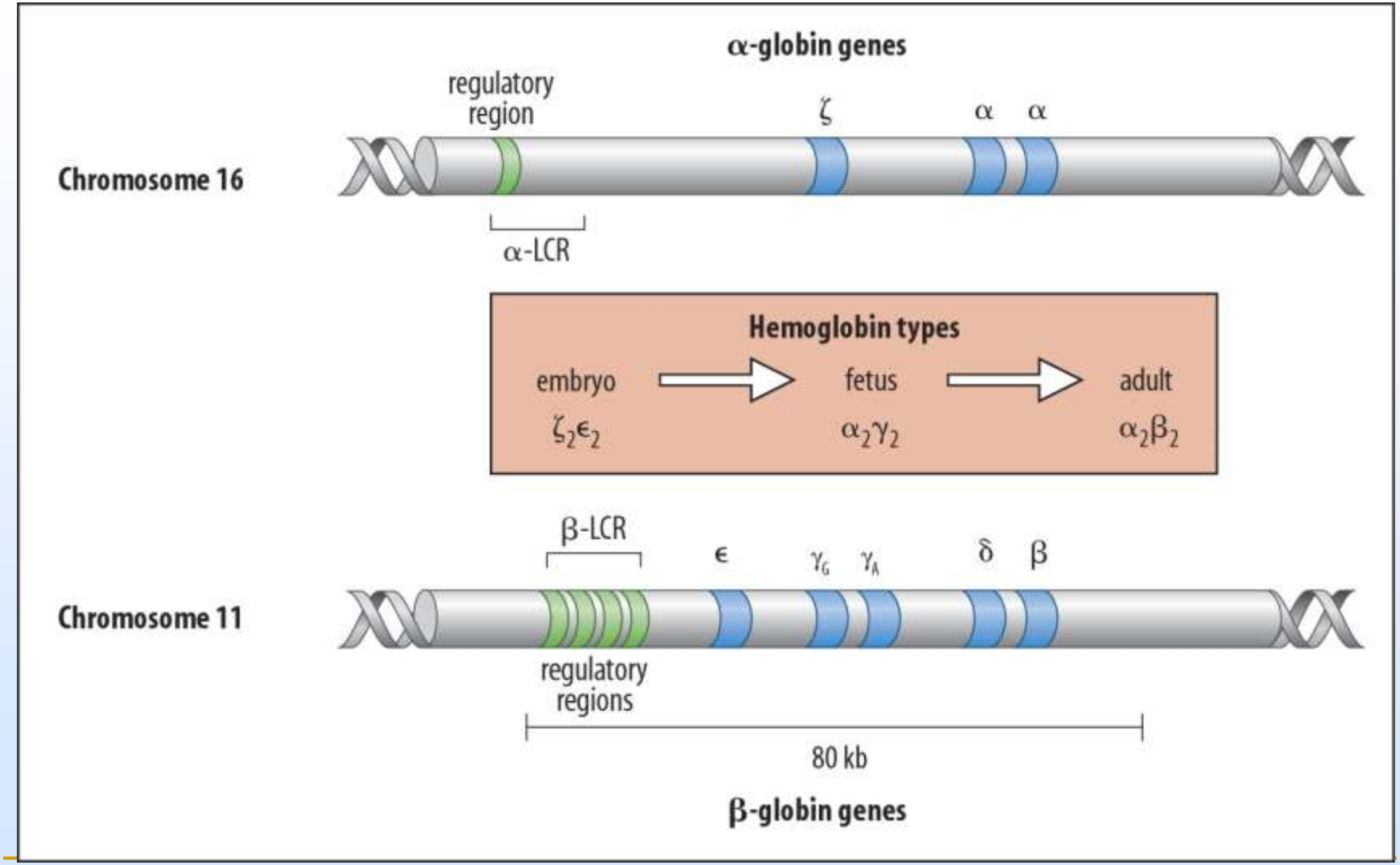
Beta globins gene cluster

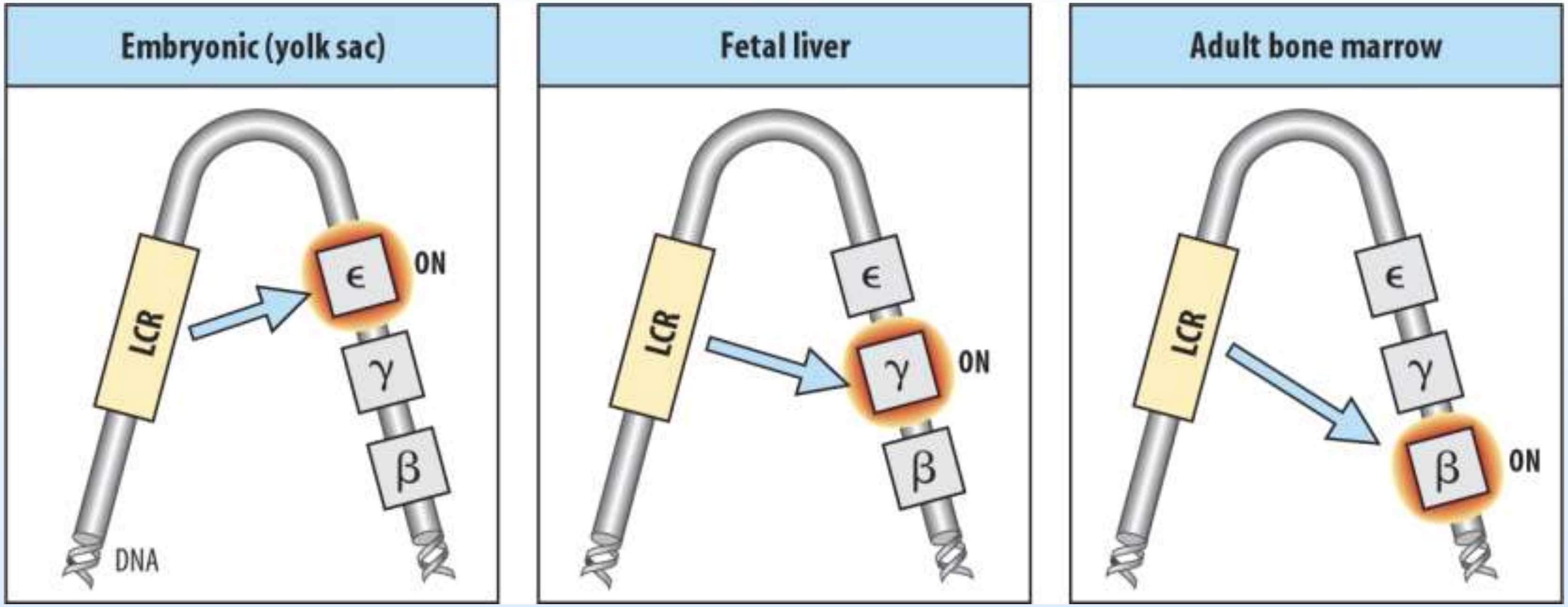




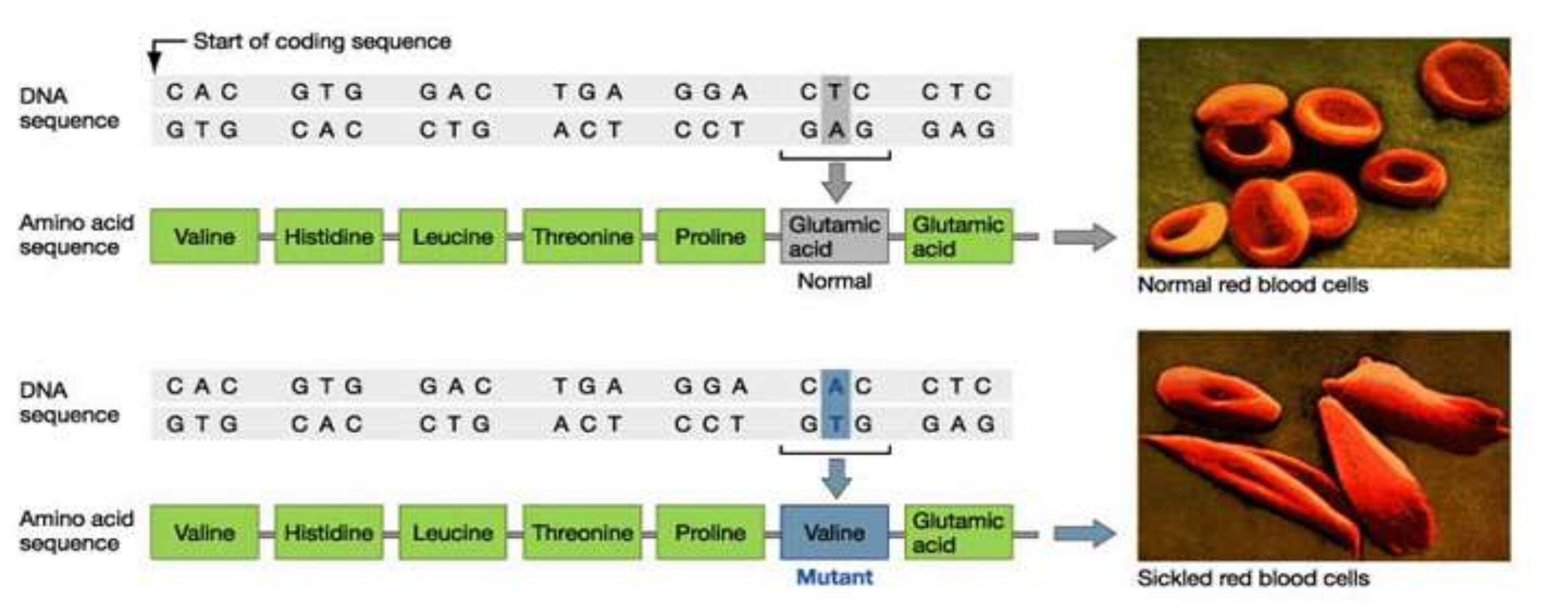
Alpha and Beta genes clusters



Embryonic to adult globin chains expression



Mutation leading to sickle hemoglobin



- An A to T mutation at the sixth codon of the β globin gene produces HbS, with a substitution of glutamic acid by valine at the 6th amino acid position in the β globin polypeptide.
- Individuals homozygous to HbS gene have only HbS in place of Hb A, with concomitant production of Hb F and Hb A2.

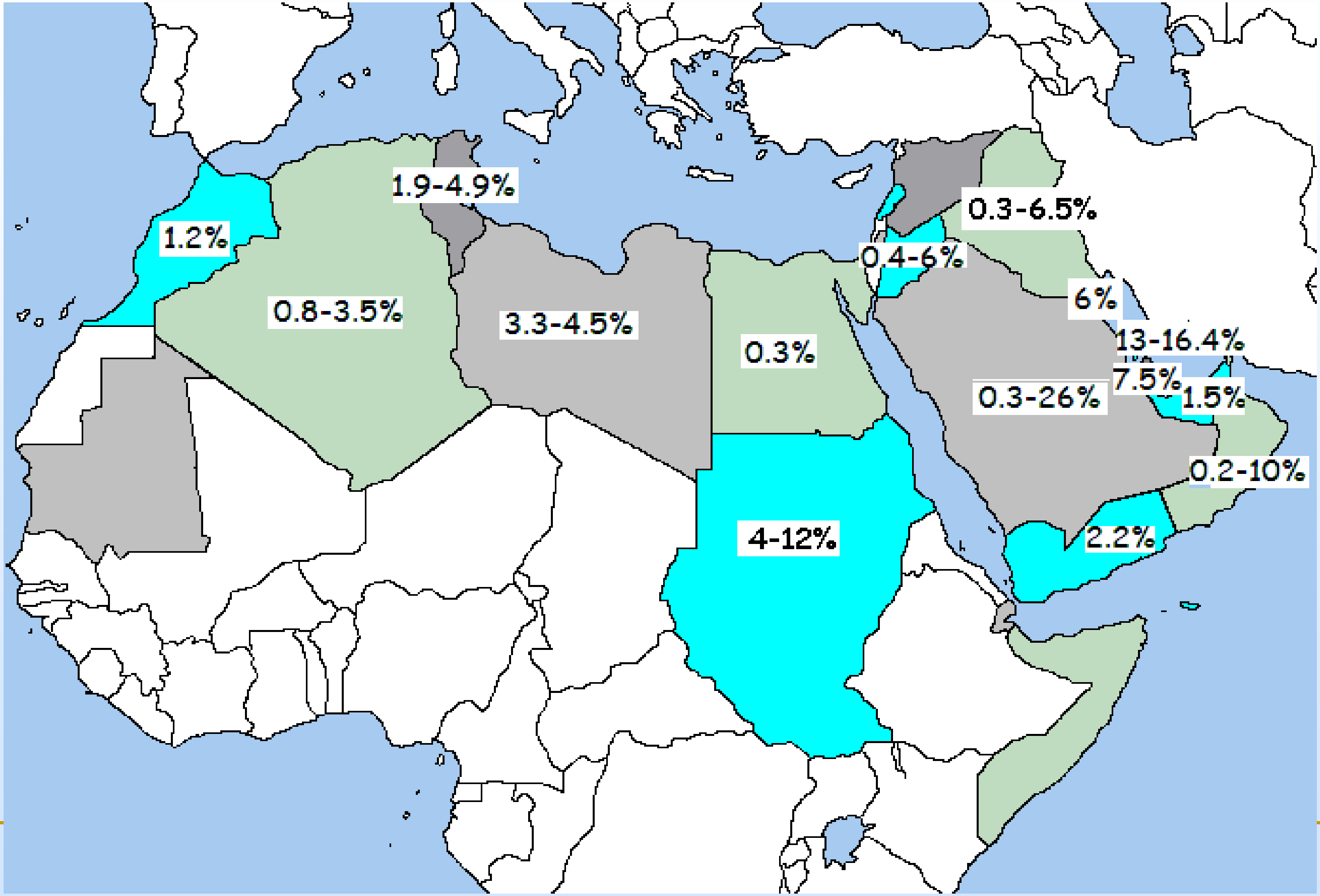
Table 2

Summary of regional annual predicted estimates of HbAS and HbSS neonates

	Population*	Crude birth rate	HbAS neonates/year			HbSS neonates/year	
			Mean	Median (IQR)	%	Mean	Median (IQR)
WHO regions							
AFRO	888 817	0·0357	3 607 022	3 610 851 (3 498 595–3 704 303)	64·2	239 547	238 083 (224 003–253 047)
AMRO	939 833	0·0162	398 279	391 257 (358 199–435 894)	7·6	13 708	13 104 (11 126–15 606)
EMRO	560 803	0·0249	275 365	256 643 (199 839–327 983)	5·7	10 007	8239 (6012–11 951)
EURO	893 002	0·0123	127 494	121 601 (99 414–147 505)	2·6	3653	3271 (2408–4366)
SEARO	1 789 082	0·0200	1 040 033	1 020 489 (900 452–1 154 480)	20·0	44 132	42 597 (35 022–50 750)
WPRO	1 840 667	0·0128	2292	1150 (477–2374)	0·0	4	9 (2–33)
HbS regions							
Americas	939 724	0·0162	389 892	386 430 (349 253–425 791)	7·4	13 309	12 802 (10 869–15 210)
Arab-India	1 771 305	0·0219	1 168 805	1 147 477 (1 010 443–1 299 147)	22·7	48 951	46 826 (39 147–56 000)
Eurasia	1 098 104	0·0139	271 474	256 163 (216 499–310 758)	5·4	8784	7493 (5919–10 090)
Southeast Asia	2 215 004	0·0133	4854	2535 (1324–5171)	0·1	80	21 (7–63)
Sub-Saharan Africa	888 065	0·0365	3 579 982	3 580 207 (3 473 117–3 684 718)	64·4	237 253	235 681 (220 993–250 568)

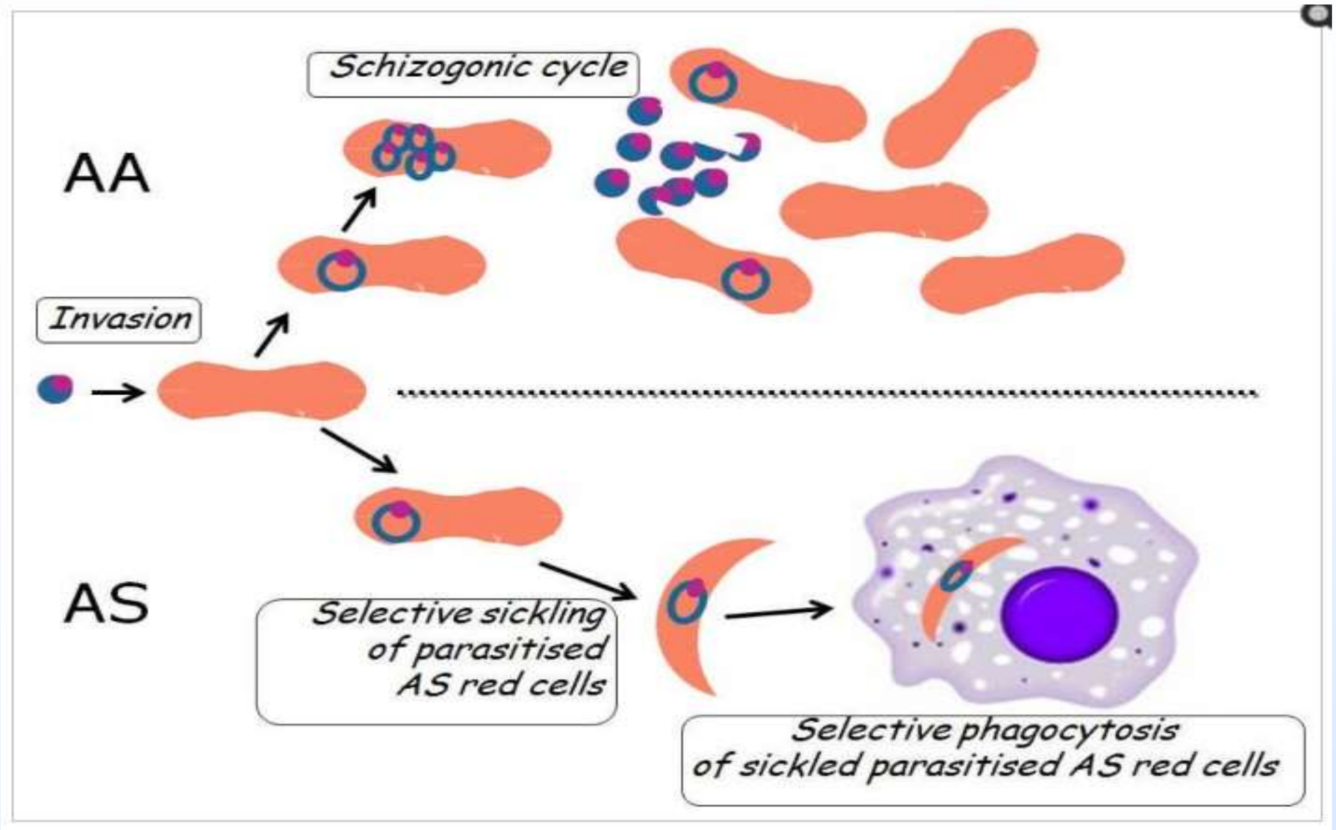
Piel F et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet. 2013 Jan 12;381(9861):142-51.

Rates of sickle cell trait in North Africa and Middle East

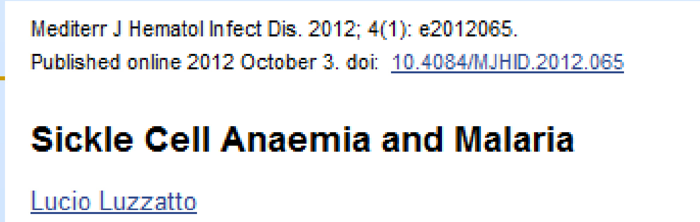


Selective advantage of AS carriers and falciparum malaria

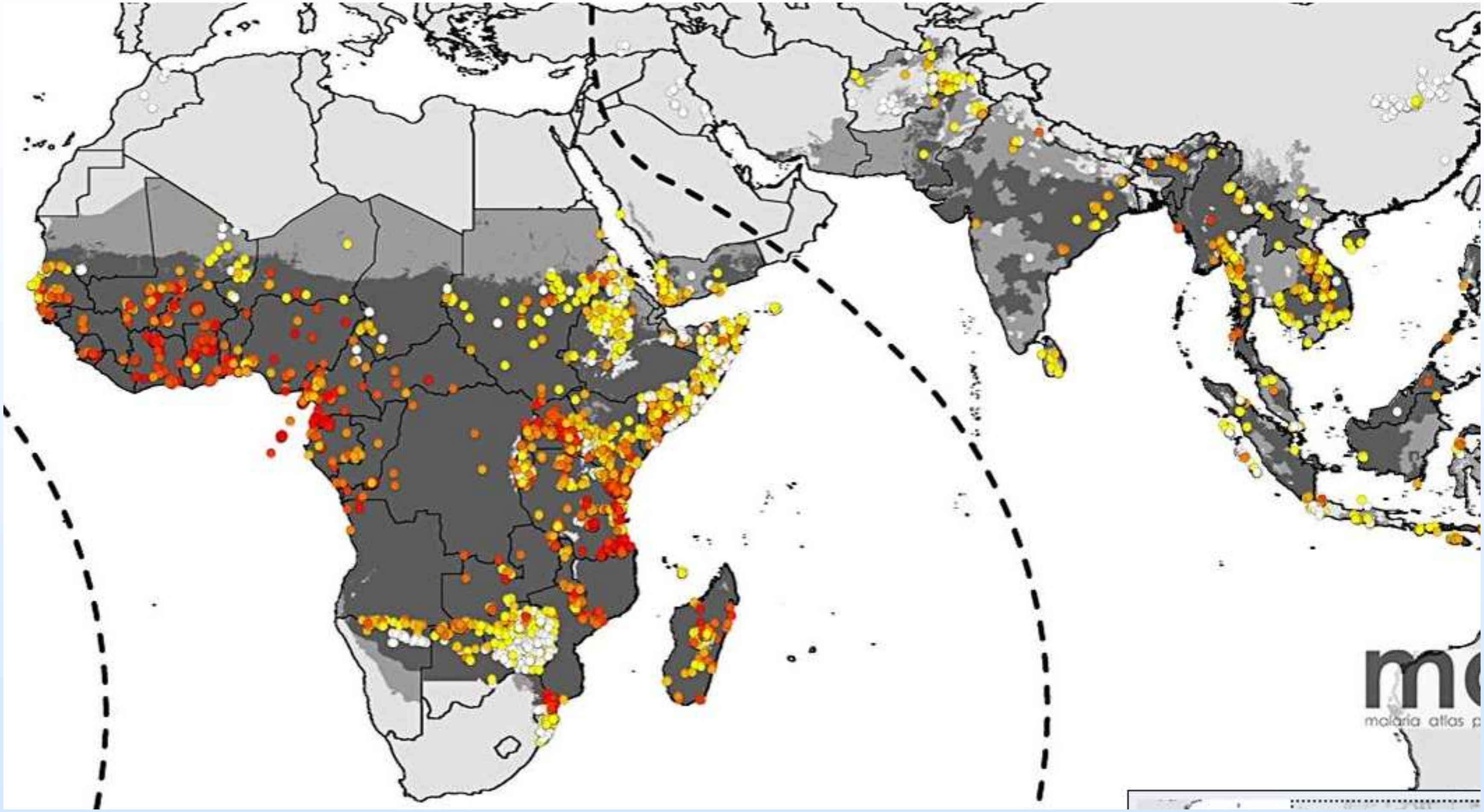
In AS heterozygotes *P falciparum*-infected red cells sickle preferentially and are then removed by macrophages



The clinically relevant consequence of this process is to keep parasitemia relatively low in AS heterozygotes



The Spatial Limits of *P. falciparum* Malaria Risk Defined by *P. falciparum* annual parasite incidence [*Pf*API]



Hay S et al, A world map: Plasmodium falciparum endemicity in 2007. PloS Med 2009 March 6(3)

FEB. 6, 1954 SICKLE-CELL TRAIT AND MALARIA BRITISH MEDICAL JOURNAL 291

PROTECTION AFFORDED BY SICKLE-CELL TRAIT AGAINST SUBTERTIAN MALARIAL INFECTION

BY

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It is concluded that the abnormal erythrocytes of individuals with the sickle-cell trait are less easily parasitized by P. falciparum than are normal erythrocytes. Hence those who are heterozygous for the sickle-cell gene will have a selective advantage in regions where malaria is hyperendemic. This fact may explain why the sickle-cell gene remains common in these areas in spite of the elimination of genes in patients dying of sickle-cell anaemia.

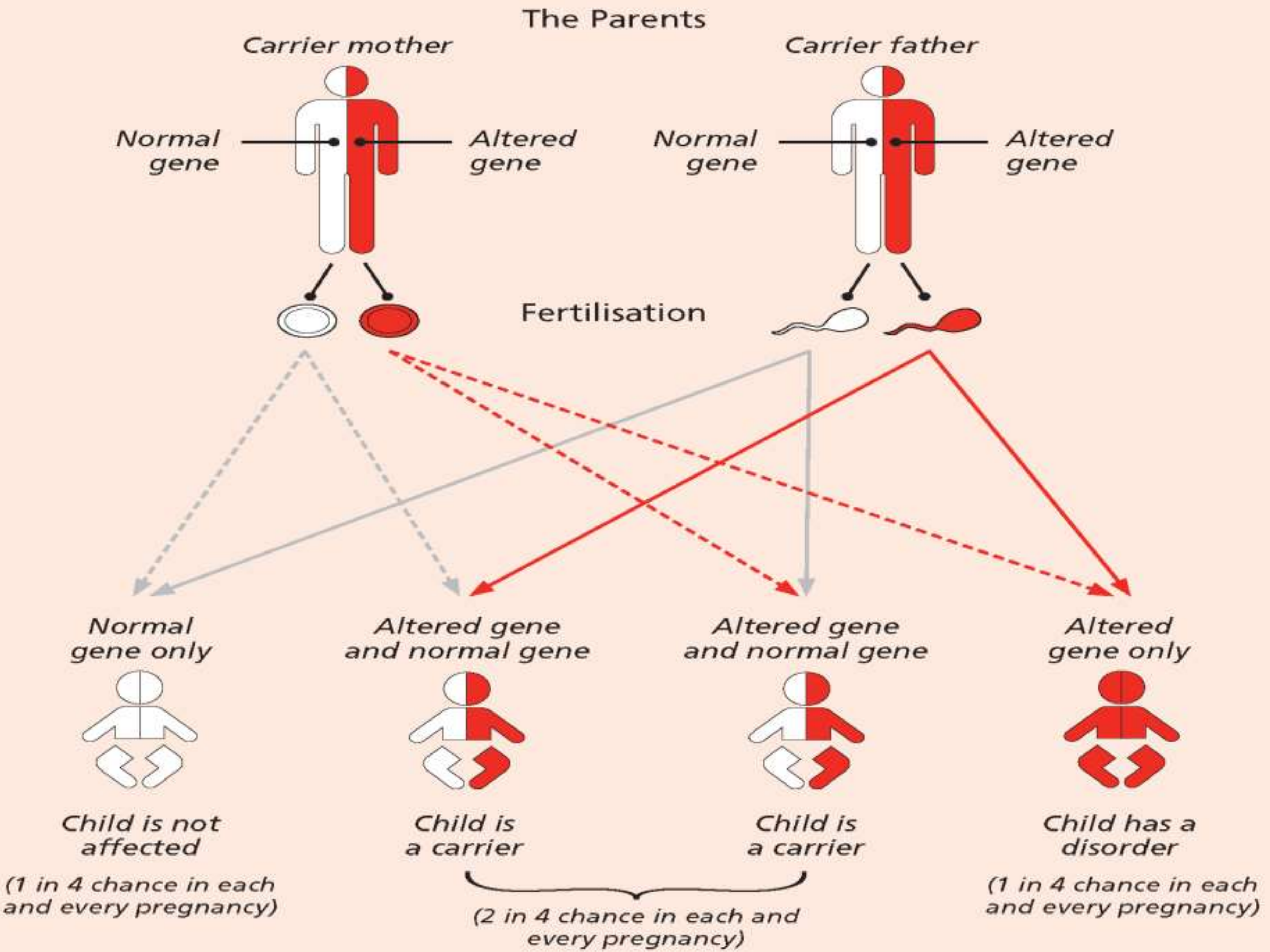
Evidence for both innate and acquired mechanisms of protection from Plasmodium falciparum in children with sickle cell trait

A study in Uganda showed that AS heterozygous children (age 1–10) are protected from:

- (i) the establishment of blood-stage infection,
- (ii) the development of high densities of parasites,
- (iii) the progression of infection to symptomatic malaria

Gong et al. Blood. 2012 119:3808-14

Consanguinity and autosomal recessive diseases



The Parents
Carrier mother
Carrier father
Normal gene
Altered gene
Normal gene
Altered gene
Fertilisation
Normal gene only
Altered gene and normal gene
Altered gene and normal gene
Altered gene only
Child is not affected
(1 in 4 chance in each and every pregnancy)
Child is a carrier
Child is a carrier
(2 in 4 chance in each and every pregnancy)
Child has a disorder
(1 in 4 chance in each and every pregnancy)

Most frequent sickle cell gene associated haplotypes in North Africa and Middle East (MENA)

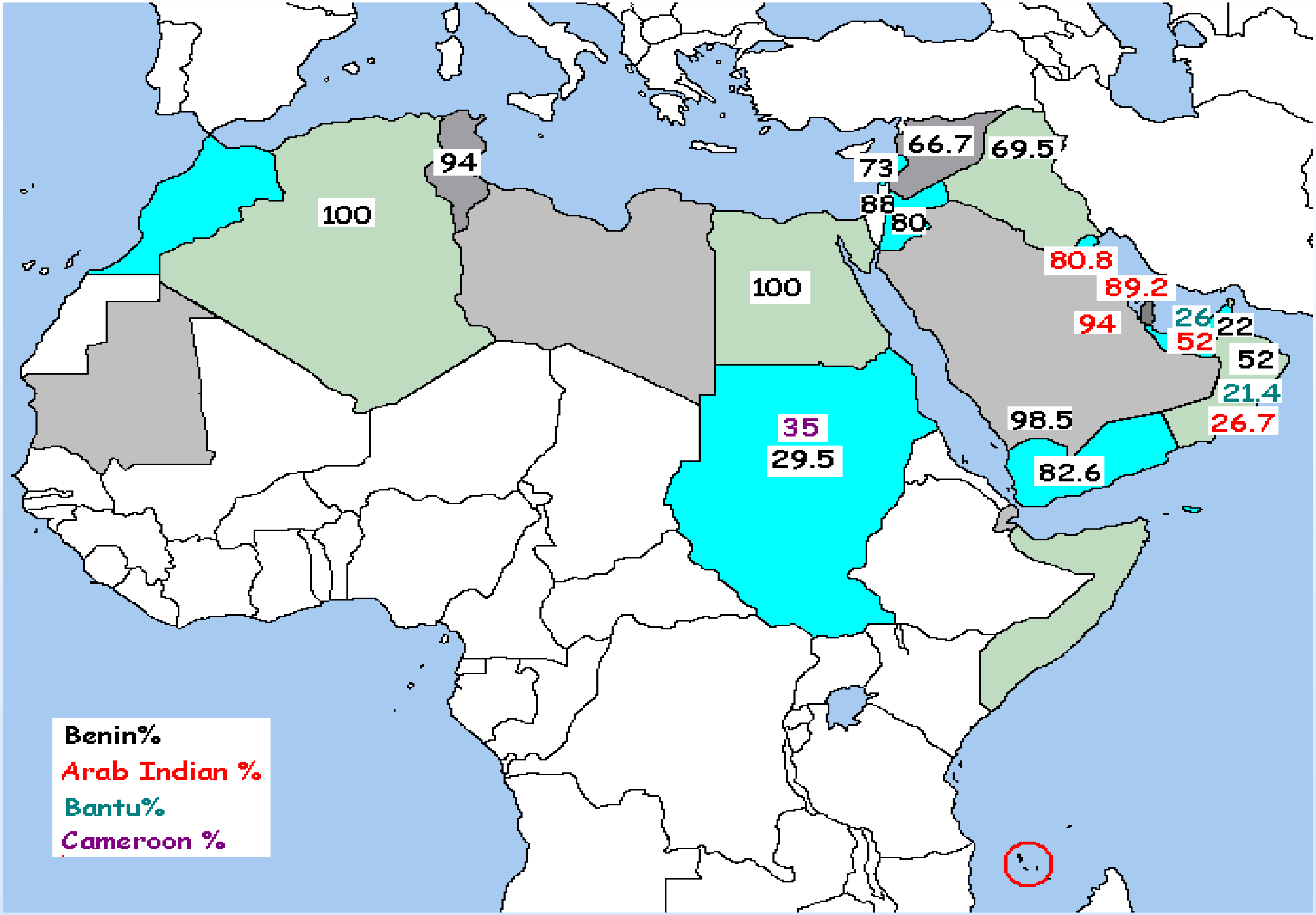
Sickle cell gene associated haplotypes

1. Benin (Central West Africa),
2. Senegal (West Africa),
3. Bantu (Central, East and Southern Africa),
4. Cameroon,
5. Arab-Indian haplotypes (Arabian Peninsula and India)

Arab-Indian and Senegal haplotypes are associated with higher Hb F levels and milder clinical presentation in homozygous patients.

The other three haplotypes are associated with low Hb F and more severe clinical phenotypes with the Bantu haplotype being the most severe.

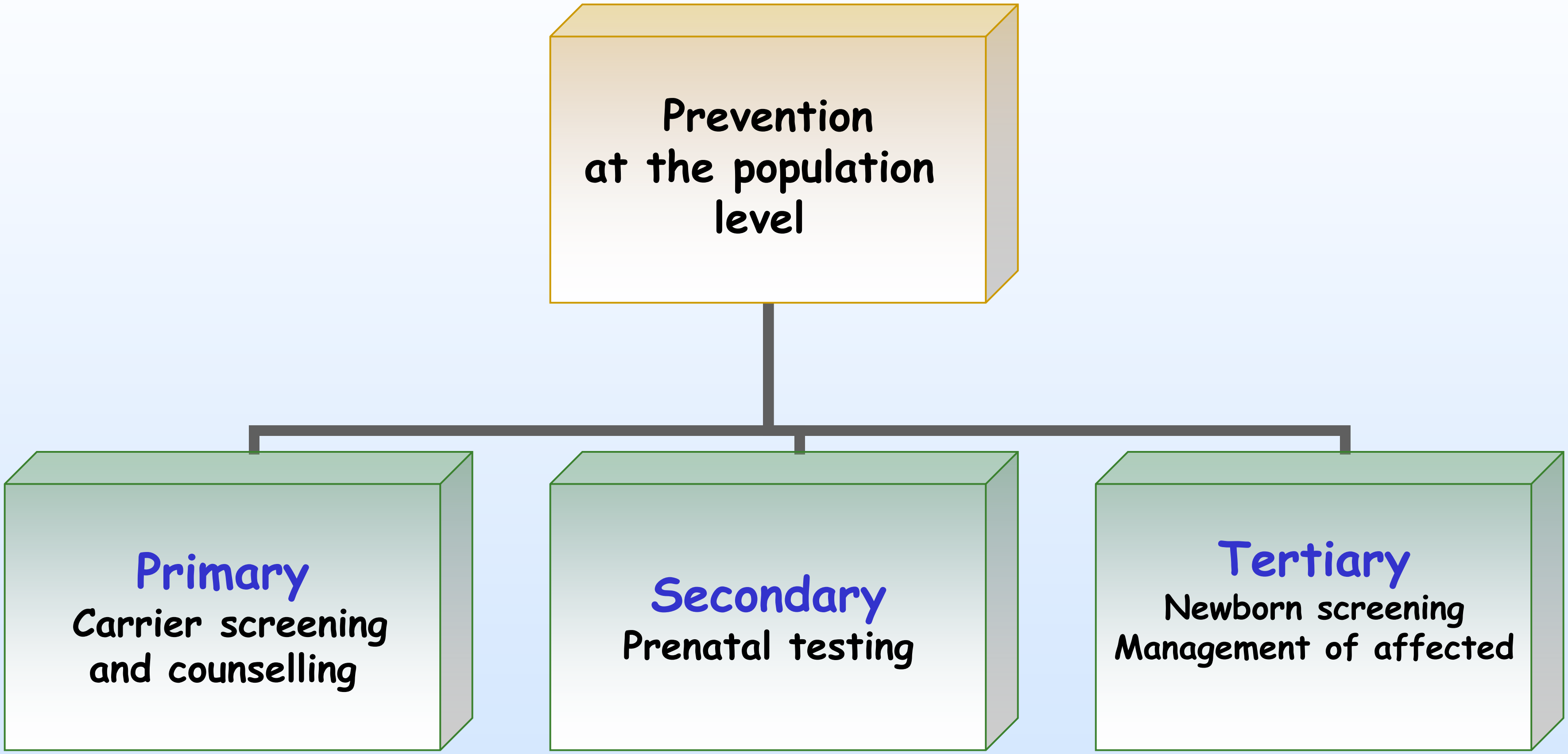
% of the most frequent sickle cell gene associated haplotypes MENA



Origin of SC gene associated haplotypes

Community genetic services targeting SCD

Community genetic Services for SCD



Pillars for introduction of services for the prevention and care of SCA in low and middle income countries

Main community services for the prevention and management of SCD

- Newborn screening
- Premarital carrier screening
- Prenatal diagnosis
- Genetic counselling
- Education of the health sector and of the public
- Timely management of affected

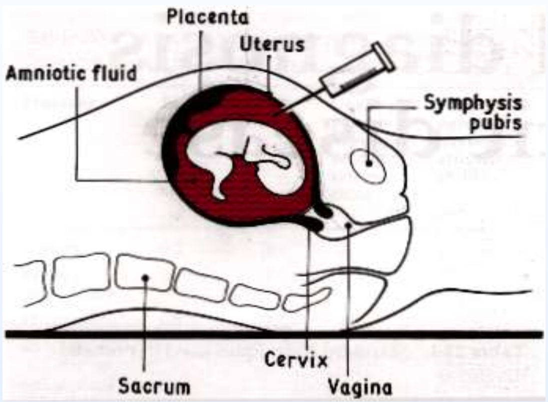
Newborn screening (NBS) for SCD

NBS provides important data on birth rates and allowing both the prophylactic management of diseased infants and counselling for carrier parents

Prenatal and preimplantation genetic diagnosis for SCA

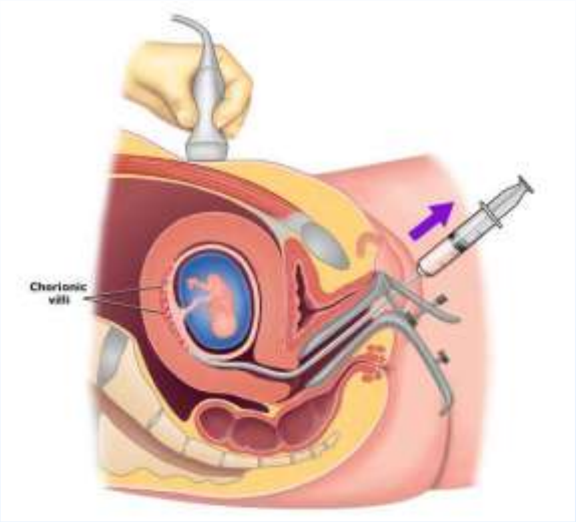
Prenatal diagnosis

Amniocentesis



- Done around the 16th week of gestation
- aspiration of 20 ml of amniotic fluid through the abdominal wall under ultrasound guidance

Chorion villus sampling



- Usually performed at 11-12 weeks gestation
- transcervical aspiration of chorionic villi under ultrasound guidance

Diversity of opinions regarding the selective termination of an affected fetus

- There are several ethical, legal, social and religious implications regarding pregnancy termination of an affected fetus.
- Among Islamic institutions on the issue of pregnancy termination, positions range from an absolute prohibition of abortion at any time to permission for pregnancy termination before the 120th day of gestation under specific circumstances.

Preimplantation genetic diagnosis for SCA

Hemoglobin. 2011;35(5-6):547-55. doi: 10.3109/03630269.2011.608457. Epub 2011 Sep 12.

Preimplantation genetic diagnosis for hemoglobinopathies.

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Abstract

Hemoglobinopathies are the most frequent indications for preimplantation genetic diagnosis (PGD), allowing couples at-risk of bearing offspring with thalassemia and sickle cell disease to reproduce without fear of having an affected child. The present experience includes PGD for sickle cell disease, α- and β-thalassemia (α- and β-thal). We present here the results of the world's largest experience of over 395 PGD cycles for hemoglobin (Hb) disorders, resulting in the birth of 98 healthy, hemoglobinopathy-free children, with seven pregnancies still ongoing. One-third of these cases were performed in combination with HLA typing, allowing the birth of unaffected children who were also HLA identical to the affected siblings with hemoglobinopathies in these families, with successful or pending stem cell transplantation in a dozen of them. The results show that PGD is presently a practical approach for prevention of hemoglobinopathies, gradually also becoming a useful approach to improving access to HLA-compatible stem cell transplantation for this group of diseases.

Conclusions

- Two major phenotypes of SCD can be seen; a mild one associated with the Arab-Indian and a severe one with the Benin and Bantu haplotypes.

Factors that affect the frequency of SCT and SCA

- Selective advantage of carriers against falciparum malaria
- Large family size with multiple affected children
- High consanguinity rates
- General low availability of public health measures directed at the care and prevention of these disorders
- Other as yet unknown factors

- Public health approaches targeting prevention of sickle cell disease include mainly newborn screening with early management.
- Prenatal diagnosis with selective termination of affected fetus is debatable.
- These services are still patchy and inadequate in many low and middle income countries recommending the upgrade of these services with strengthening of the education and training of health care providers and raising public awareness on the feasibility of prevention and care for sickle cell disease.

Impediments facing prevention and care initiatives

- Low genetic literacy among the health sector
- Low genetic literacy among the public
- Lack of awareness about genetic risks and possibilities for prevention and timely management
- Cultural, legal and religious limitations such as the legal and religious restrictions to selective abortion of an affected fetus