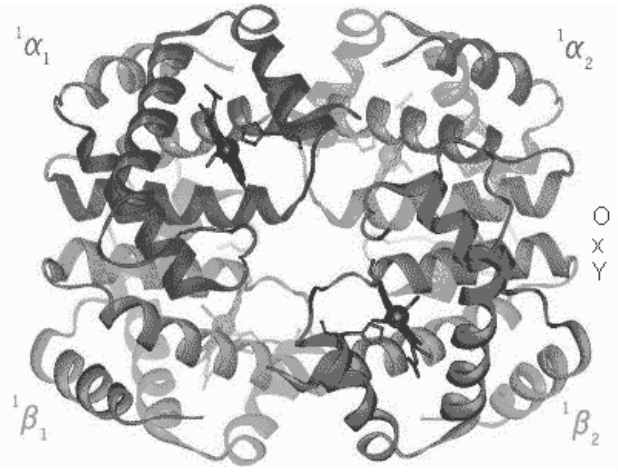
Epidemiologia delle varianti emoglobiniche e della Talassemia

G. Lippi – M. Montagnana (Verona)



O
X
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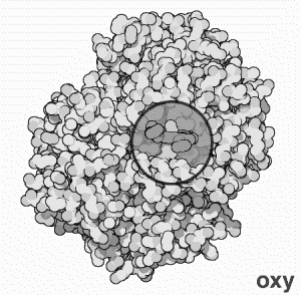

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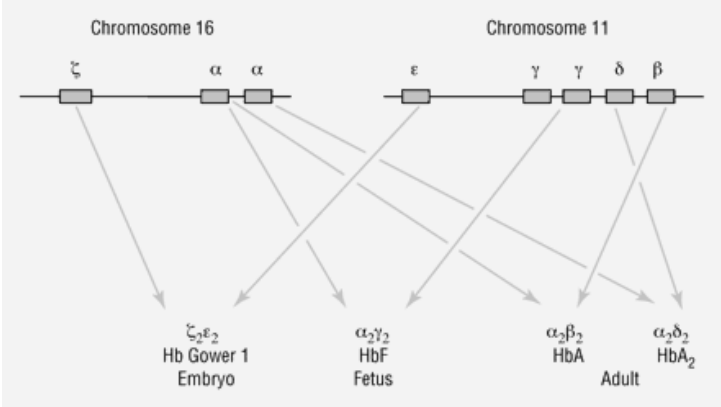
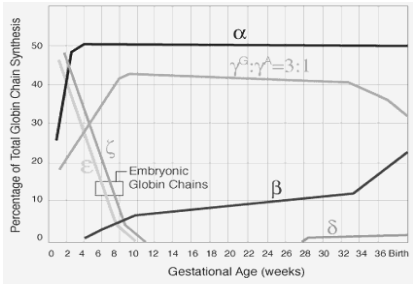
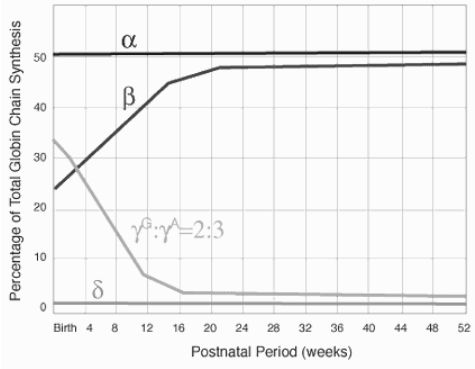

Chromosome 16
Chromosome 11
ζ
α
α
ε
γ
γ
δ
β
$\zeta_2\varepsilon_2$
Hb Gower 1
Embryo
$\alpha_2\gamma_2$
HbF
Fetus
$\alpha_2\beta_2$
HbA
$\alpha_2\delta_2$
HbA_2
Adult


Percentage of Total Globin Chain Synthesis
α
$\gamma^G:\gamma^A$=3:1
ζ
ε
Embryonic
Globin Chains
β
δ
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 Birth
Gestational Age (weeks)


Percentage of Total Globin Chain Synthesis
α
β
$\gamma^G:\gamma^A$=2:3
δ
Birth 4 8 12 16 20 24 28 32 36 40 44 48 52
Postnatal Period (weeks)

- Hemoglobin variants are a part of the normal embryonic and fetal development, but may also be pathologic mutant forms of hemoglobin in a population, caused by variations in genetics.
- **In the embryo:**
  - Gower 1 (ζ2ε2)
  - Gower 2 (α2ε2) (PDB 1A9W)
  - Hemoglobin Portland (ζ2γ2)
- **In the fetus:**
  - Hemoglobin F (α2γ2) (PDB 1FDH)
- **In adults:**
  - Hemoglobin A (α2β2) - The most common (normal amount ~95%)
  - Hemoglobin A2 (α2δ2) - δ chain synthesis begins late in the third trimester and in adults (normal range 1.5-3.5%)
  - Hemoglobin F (α2γ2) - Restricted to a limited population of red cells called F-cells (normal range 0.3-2.0%).

DEFINITION, EARLY KNOWLEDGE AND CAUSES OF BIRTH DEFECTS

Definition

A birth defect is defined as any abnormality affecting body structure or function that is present from birth. It may be clinically obvious at birth or may be diagnosed only later in life. For example, spina bifida is a structural birth defect clinically obvious at birth and hemophilia is a functional birth defect that may present clinically only in infancy or childhood. A few birth defects, like Huntington disease, manifest only in adulthood. Serious birth defects are life-threatening or have the potential to cause lifelong disability (Christianson RE et al., 1981; WHO, 2000b).

MARCH OF DIMES
GLOBAL REPORT ON BIRTH DEFECTS
THE HIDDEN TOLL OF DYING AND DISABLED CHILDREN

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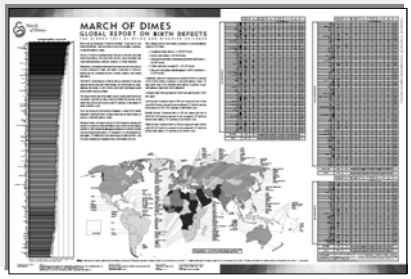
HEMOGLOBIN DISORDERS

Thalassemia and sickle cell anemia are autosomal recessive disorders that became very common in tropical regions because of heterozygote advantage—carriers are protected against the lethal effects of falciparum malaria. These disorders spread through migration of carriers to other regions. Carriers can be detected by simple hematological tests and global data exist on carrier frequencies (Livingstone, 1985).

The characteristic skeletal changes of Thalassemia have allowed archaeologists to identify the presence of the condition as far as back as the Neolithic period. It must have been very common even at that time.

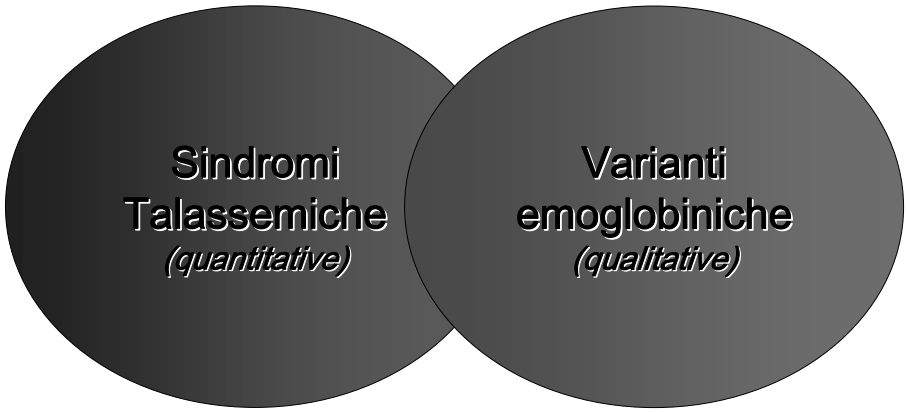
Choirokoitia 7000 BC: Over 150 graves, 47% of children died of thalassaemia. The oldest thalassaemic skeleton in Cyprus was of a child who lived about 8300 BC. Kissonerga, Paphos.



Five common serious birth defects of genetic or partially genetic origin in 2001 were:

- Congenital heart defects—1,040,835 births
- Neural tube defects—323,904 births
- Hemoglobin disorders (thalassemia and sickle cell disease)—307,897 births
- Down syndrome (trisomy 21)—217,293 births
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency—177,032 births

	Children Born with Birth Defects Annually[1]	2001 Annual Births (000s)	Birth Defects of the Cardiovascular System[2]	Neural Tube Defects	Pathological Hemoglobin Disorders	Down Syndrome	G6PD Deficiency[3]	Total[4]
			Prevalence (per 1000 live births)					
Italy	21,838	505	7.9	0.5	0.6	1.9	0.0	43.2



SINDROMI TALASSEMICHE

- Delezioni di segmenti genomici (anche HPFH o High Persistence of Fetal Hemoglobin e Hb Lepore).
- Mutazioni che modificano la trascrizione dei geni globinici
- Mutazioni che modificano la corretta maturazione dell'mRNA
- Mutazioni che alterano i siti di splicing e attivano siti criptici.
- Mutazioni che creano siti di splicing alternativi.
- Mutazioni che alterano la traduzione dell'mRNA

VARIANTI EMOGLOBINICHE

- Mutazioni che alterano la sequenza aminoacidica della beta-globina (es. anemia falciforme)

CLASSIFICAZIONE IN BASE AL MECCANISMO MOLECOLARE RESPONSABILE
(MUTAZIONI A LIVELLO DI ESONI)

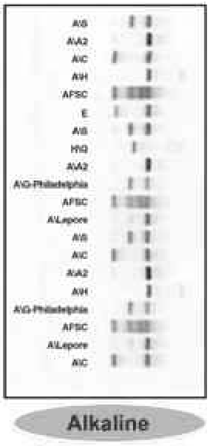
1) MUTAZIONE **PUNTIFORME:** SINONIMA UAA->CAA LEU
MISSENSE GUG->GAG GLU -> VAL Hb S
NON-SENSE UAU->UAA TYR-> STOP
Hb McKees Rock

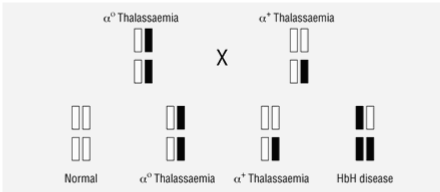
2) MUTAZIONE **PUNTIFORME DOPPIA:**
2 EVENTI GENETICI
BETA 6 GLU->LYS
BETA 95 LYS->GLU
Hb Arlington Park

3) **DELEZIONE** DI UNA O PIU' TRIPLETTE:
BETA 6 GLU->O Hb Leyden

4) MUTAZIONI **FRAMESHIFT:**
Hb Takoma +11 AA

5) **CROSSING OVER** INEGUALE. NON OMOLOGO:
Hb Lepore
Hb Anti-Lepore






DATABASE IN BRIEF

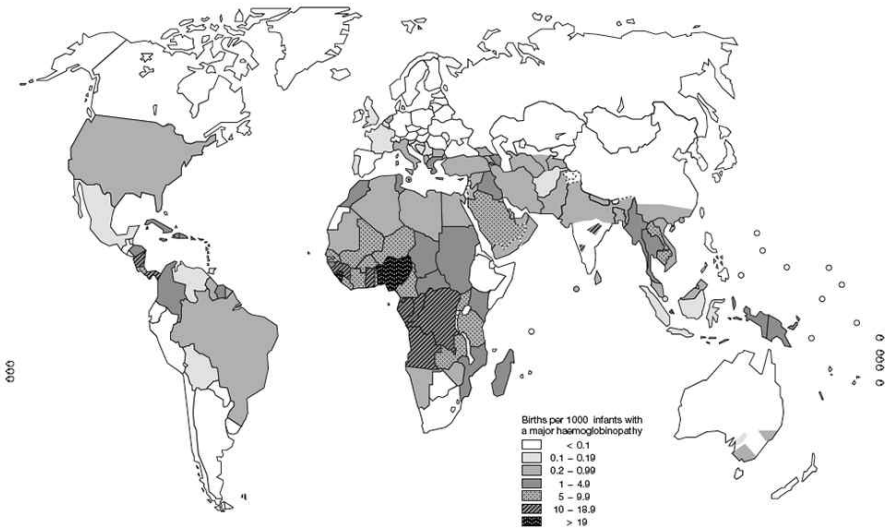
HbVar Database of Human Hemoglobin Variants and Thalassemia Mutations: 2007 Update

Table 1. Summaries of Mutation Categories in the HbVar Database for Hemoglobin Variants and Thalassemia Mutations (Note That Some Entries Appear in More Than One Category)

Entries	Count of results	
	October 2001 [a]	October 2006 [b]
Entries involving the *HBA1* gene (OMIM# 141800)	212	254
Entries involving the *HBA2* gene (OMIM# 141850)	250	295
Entries involving the *HBB* gene (OMIM# 141900)	635	711
Entries involving the *HBD* gene (OMIM# 142000)	57	72
Entries involving the *HBG2* gene (OMIM# 142200)	44	49
Entries involving the *HBG1* gene (OMIM# 142250)	52	55
Entries with a fusion gene mutation	8	8
Entries with a substitution mutation	899	1,031
Entries with an insertion mutation	46	51
Entries with a deletion mutation	116	150
Hemoglobins with high oxygen affinity	79	90
Unstable hemoglobins	121	134
Methemoglobins	9	9
Total hemoglobin variant entries	832	938
Total thalassemia entries	336	383
Total entries in both variant and thalassemia categories	43	48
Total entries in database	**1,125**	**1,273**

Tabella 24 *Classificazione funzionale delle emoglobinopatie*

	Anormalità Funzionale	Luogo Sostituzione	Sintomatologia	Esempio
1	Nessuna	Superficie esterna	Nessuna	Hb G Philadelphia α68 Asn→Lys
2	Aggregazione ridotta sol.	Superficie esterna	Anemia emolitica (omozigote)	Hb S β6 Glu→Val
3	Instabilità ridotta sol.	Eme + contatti subunità	Anemia emolitica	Hb Bristol β67 Val→Asp
4	MetHb	His prossimale e distale	Cianosi	Hb M Hyde Park β92 His→Tyr
5	Aumento affinità per l'O_2	Contatto $\alpha_1\beta_2$, C-terminale β	Eritrocitosi	Hb Chesapeake α92 Arg→Leu Hb Hiroshima β146 His→Asp
6	Diminuita affinità per l'O_2	Eme oppure $\alpha_1\beta_2$	Cianosi	Hb Kansas β102 Asn→Thr
7	Ridotta produzione di catene α	Mutazione a livello del codone C-terminale	Fenotipo α talassemico	Hb Constant Spring (α+31)
8	Ridotta produzione di catene β	Ibrido di fusione	Fenotipo β talassemico	Hb Lepore



Carrier Frequencies for Common Hemoglobin Disorders, by World Health Organization Region, 2001
(percent)

Region	Hb S	Hb C	Hb E	β thalassemia	α^0 thalassemia	α^+ thalassemia
Americas	1–20	0–10	0–20	0–3	0–5	0–40
Eastern Mediterranean	0–60	0–3	0–2	2–18	0–2	1–60
Europe	0–30	0–5	0–20	0–19	1–2	0–12
Southeast Asia	0–40	0	0–70	0–11	1–30	3–40
Sub-Saharan Africa	1–38	0–21	0	0–12	0	10–50
Western Pacific	0	0	0	0–13	0	2–60

Sources: Livingstone 1985; Weatherall and Clegg 2001a, 2001b.
Note: Many of these data are derived from small population samples.

Chapter 34
Inherited Disorders of Hemoglobin

Source: Weatherall and Clegg 2001b.

Chapter 34

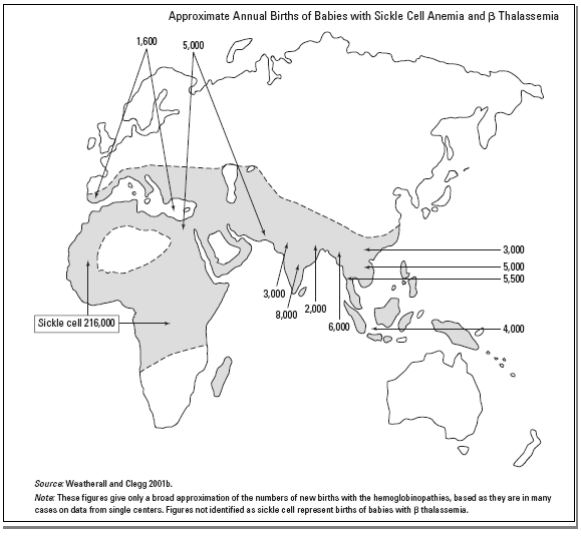
Inherited Disorders of Hemoglobin

Source: Weatherall and Clegg 2001b.

Note: Structural hemoglobin variants are Hb E (innocuous unless interacting with α or β thalassemia) and Hb S (causing sickle-cell disease in the homozygous state).

Chapter 34

Inherited Disorders of Hemoglobin



Source: Weatherall and Clegg 2001b.

Note: These figures give only a broad approximation of the numbers of new births with the hemoglobinopathies, based as they are in many cases on data from single centers. Figures not identified as sickle cell represent births of babies with β thalassemia.

Burden of Sickle Cell Disease by Age Group, Assuming 1,000 Births per Year and Survival to Various Ages,

Category	Age group (years)										Total or average
	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	
Number of survivors	876	834	807	777	727	680	627	564	491	440	682.3
Number of deaths	124	42	27	30	50	47	53	63	73	51	560
Death rate (percent/year)	2.61	0.98	0.66	0.75	1.32	1.33	1.61	2.10	2.73	2.17	1.63
Number of DALYs lost/death	28.90	28.59	27.77	26.84	25.82	24.69	23.43	22.00	20.39	18.58	24.70
Total DALY losses from deaths	3,584	1,201	750	805	1,291	1,161	1,242	1,386	1,488	948	13,856
Number of DALYs lost from background (chronic) anemia	188	171	164	158	150	141	130	119	106	93	1,420
Total DALYs lost from deaths and chronic anemia	3,772	1,372	914	963	1,441	1,302	1,372	1,505	1,594	1,041	15,276
Number of pain crises/year	242.7	381.0	383.8	584.4	886.7	600.5	523.6	473.4	309.6	182.2	4,548
Number of other acute clinical events	77.5	22.2		182.2							281.9
Number of other chronic clinical events	49.8	14.8	12.8	10.9							88.3

Source: Authors' calculations based on Hambleton 2004a, 2004b.

Annual Costs of Hemoglobinopathy per Outpatient, Excluding Transfusion, Toronto
(2001 US$)

Category	Thalassemia		Sickle cell disease	
	Chelated	Nonchelated	Chelated	Nonchelated
Clinic staff salaries	1,011.95	183.68	1,011.95	252.99
Clinic supplies	930.19	25.15	930.19	34.65
Medical and surgical outpatient unit	2,069.57	n.a.	2,069.57	n.a.
Consultations	92.58	88.39	92.58	11.94
Diagnostic tests	742.58	281.44	905.89	210.99
Laboratory costs	413.96	31.04	414.01	42.74
Laboratory costs (medical dayunit visits)	665.81	n.a.	665.81	n.a.
Total	5,926.64	609.70	6,090.00	553.31

Source: Estimated costs provided by Nancy Olivieri of the University of Toronto.
Note: n.a. — not applicable.

Costs of Treatment of Thalassemia for One Patient Age 7 to 11, Eastern Mediterranean
(2001 US$)

Category	Minimum treatment		Full treatment	
Costs other than iron chelation				
Day transfusion: hotel and nursing	375		375	
12 transfusions/year	1,088	(600–1,575)	2,250	(1,390–3,150)
Investigations	135	(135–435)	278	(278–870)
Occasional costs (such as operations)	150		645	
Staff salaries	300		620	
Total if no desferrioxamine therapy	2,048	(1,560–2,835)	n.a.	n.a.
Desferrioxamine therapy (iron chelation)	3,080	(1,440–4,725)	6,165	(2,880–9,450)
Total with desferrioxamine therapy	5,128	(3,000–7,560)	10,333	(6,190–15,110)

Source: Alwan and Modell 1997.

Cost-Effectiveness of Treatment for Homozygous β and Transfusion-Dependent Hb E β Thalassemia

Category	Cost/patient (US$)	DALYs gained/patient		Cost/DALY (US$)	
		Disability weight = 0.1	Disability weight = 0.25	Disability weight = 0.1	Disability weight = 0.25
Minimal treatment, transfusion only					
Until death at age 10	17,368	6.96–7.60	6.00–6.39	2,285–2,495	2,718–2,896
Until death at age 15	23,840	10.25–10.81	7.52–7.87	2,206–2,325	3,029–3,170
Full treatment with chelation: incremental compared with minimal treatment					
Until age 15	60,467	1.03–3.80	0.55–2.03	15,912–58,706	29,787–109,940
Beyond age 15 to maximum age 80	132,901	17.25	16.35	7,704	8,129
Total lifetime	193,368	18.28–21.05	16.90–18.38	9,186–10,578	10,520–11,442
Full treatment with chelation: total compared with no treatment					
Until age 15	121,284	11.81	10.84	10,273	11,186
Beyond age 15 to maximum age 80	274,662	17.25	16.35	15,922	16,799
Total lifetime	395,946	29.06	27.19	13,625	14,578

Source: Authors' calculations. All costs and DALYs gained are discounted at 3 percent annually, starting at birth.

Public health reviews

Global epidemiology of haemoglobin disorders and derived service indicators

Bernadette Modell & Matthew Darlison

Table 1. **Estimated prevalences of carriers of haemoglobin gene variants and affected conceptions**

WHO region	Demography 2003				% of the population carrying			Affected conceptions (per 1000)			Affected births (% of under-5 mortality)
	Population (millions)	Crude birth rate	Annual births (1000s)	Under-5 mortality rate	Significant variant[a]	α^+ thalassaemia[b]	Any variant[c]	Sickle-cell disorders[d]	Thalassaemias[e]	Total	
African	586	39.0	22 895	168	18.2	41.2	44.4	10.68	0.07	10.74	6.4
American	853	19.5	16 609	27	3.0	4.8	7.5	0.49	0.06	0.54	2.0
Eastern Mediterranean	573	29.3	16 798	108	4.4	19.0	21.7	0.84	0.70	1.54	1.4
European	879	11.9	10 459	25	1.1	2.3	3.3	0.07	0.13	0.20	0.8
South-east Asian	1 564	24.4	38 139	83	6.6	44.6	45.5	0.68	0.66	1.34	1.6
Western Pacific	1 761	13.6	23 914	38	3.2	10.3	13.2	0.00	0.76	0.76	2.0
World	**6 217**	**20.7**	**128 814**	**81**	**5.2**	**20.7**	**24.0**	**2.28**	**0.46**	**2.73**	**3.4**

[a] Significant variants include Hb S, Hb C, Hb E, Hb D etc. β thalassaemia, α^0 thalassaemia.
[b] α^+ thalassaemia includes heterozygous and homozygous α^+ thalassaemia.
[c] Allows for (1) coincidence of α and β variants, and (2) harmless combinations of β variants.
[d] Sickle-cell disorders include SS, SC, S/β thalassaemia.
[e] Thalassaemias include homozygous β thalassaemia, haemoglobin E/β thalassaemia, homozygous α^0 thalassaemia, α^0/α^+ thalassaemia (haemoglobin H disease).

Public health reviews

Global epidemiology of haemoglobin disorders and derived service indicators

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Table 2. **Indicators of annual service needs for haemoglobin disorders**

WHO and component regions	Indicator 1				Indicator 2	Indicator 3	Indicators 4 and 5	
	Annual affected conceptions				Total annual births (1000s)	Annual pregnant carriers (1000s)	Annual pregnancies	
	Sickle cell disorders	β thalas-saemias	α thalas-saemias	Total disorders			Both parents carriers	At risk
African region	**233 289**	**1 520**	**11**	**234 819**	**22 895**	**4 363**	**1 005 752**	**939 277**
Northern Africa	181	337	0	518	627	35	2 882	2 073
Western Africa	167 224	971	0	168 195	9 622	2 551	738 373	672 781
Middle Africa	40 688	27	0	40 715	4 184	804	162 934	162 861
Eastern Africa	25 184	183	11	25 377	6 974	966	101 510	101 509
Southern Africa	11	2	0	13	1 487	7	53	53
American region	**9 047**	**533**	**442**	**10 022**	**16 483**	**523**	**44 769**	**40 088**
Northern America	2 637	268	429	3 334	4 435	122	15 780	13 337
Central America	175	2	0	176	3 627	20	724	705
Caribbean	3 333	16	0	3 349	778	4 505	14 369	13 394
South America	2 902	248	13	3 163	7 643	278	13 895	12 651
Eastern Mediter-ranean region	**6 491**	**9 715**	**1**	**16 207**	**16 776**	**670**	**66 079**	**64 828**
Northern Africa	1 456	1 829	0	3 285	3 776	152	13 986	13 140
Eastern Africa	8	19	0	27	3 067	19	109	109
Western Asia	4 479	1 815	1	6 294	3 540	218	25 178	25 178
South central Asia	547	6 053	0	6 600	6 393	281	26 806	26 401
European region	**1 292**	**1 347**	**162**	**2 800**	**10 459**	**153**	**12 064**	**11 201**
Northern Europe	429	82	73	533	1 162	15.0	2 660	2 333
Western Europe	387	78	56	521	1 949	23.2	2 556	2 085
Southern Europe	204	313	33	550	1 458	39	2 263	2 202
Eastern Europe	0	25	0	25	2 881	8	98	98
South central Asia	0	365	0	365	1 190	27	1 461	1 461
Western Asia	272	484	0	756	1 819	41	3 027	3 023
South-east Asian region	**26 037**	**21 693**	**1 383**	**49 114**	**38 139**	**2 363**	**421 398**	**196 454**
South central Asia	26 037	9 348	0	35 386	31 210	1 476	230 905	141 542
South-eastern Asia	0	12 345	1 383	13 728	6 929	887	190 493	54 912

Public health reviews

Global epidemiology of haemoglobin disorders and derived service indicators

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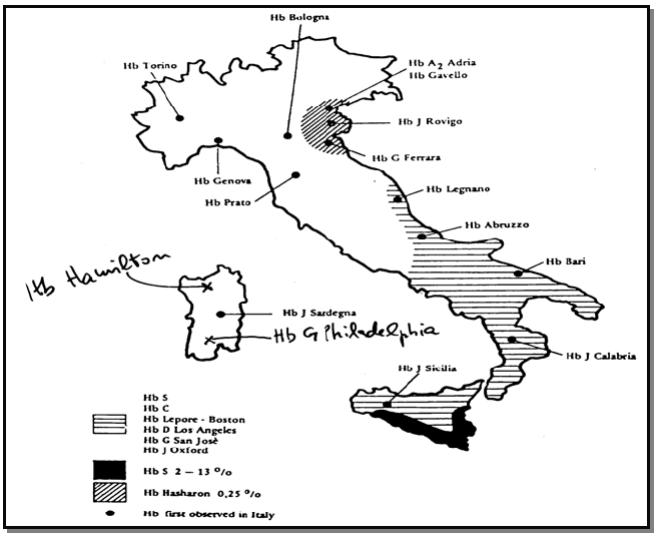
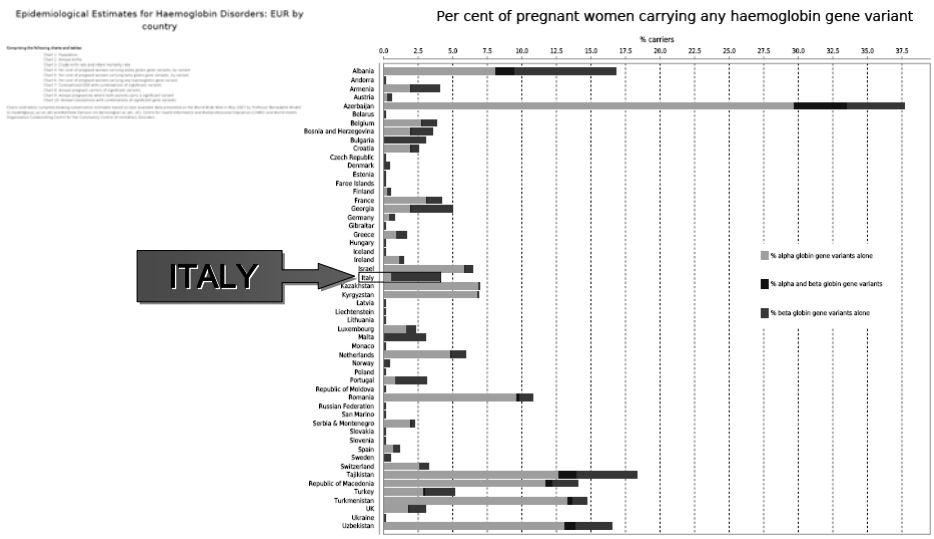
Table 3. **Estimated reach of treatment for β thalassaemia in each WHO region[a]**

WHO region	Estimated annual births β thalassaemias		Transfusion			No. of known patients	Adequate iron chelation		Inadequate or no iron chelation	
	Total	Transfusion-dependent	Annual no. starting transfusion	% of transfusion-dependent patients transfused	Annual deaths because not transfused		% with chelation	No. with chelation	No. of patients	Annual deaths due to iron overload
African	1 386	1 278	35	2.7	1 243	–	–	–	–	–
American	341	255	134	52.4	121	2 750	58	1 604	1 146	57
Eastern Mediter-ranean	9 914	9 053	1 610	17.8	7 443	39 700	27	10 818	28 882	1 444
European	1 019	920	140	15.5	780	16 230	91	14 754	1 476	74
South-east Asian	20 420	9 983	962	9.6	9 021	35 500	19	6 621	28 879	1 444
Western Pacific	7 538	4 022	108	2.7	3 914	3 450	44	1 504	1 946	97
World	**40 618**	**25 511**	**2 989**	**11.7**	**22 522**	**97 630**	**39**	**37 866**	**59 764**	**2 988**

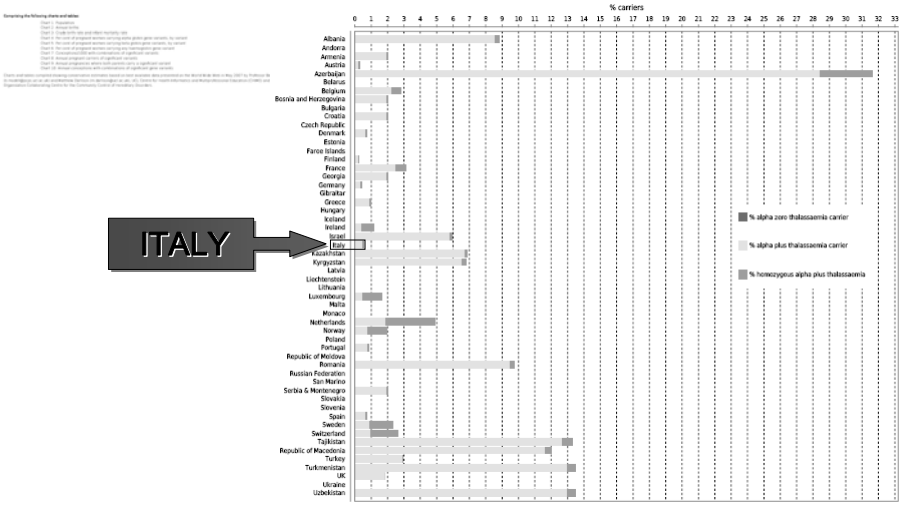
[a] All figures are minimum estimates.


Hb Bologna
Hb Torino
Hb A_2 Adria
Hb Gavello
Hb J Rovigo
Hb G Ferrara
Hb Genova
Hb Prato
Hb Legnano
Hb Abruzzo
Hb Bari
Hb Hamilton
Hb J Sardegna
Hb G Philadelphia
Hb J Calabria
Hb J Sicilia
Hb S
Hb C
Hb Lepore - Boston
Hb D Los Angeles
Hb G San José
Hb J Oxford
Hb S 2 – 13 %
Hb Hasharon 0,25 %
Hb first observed in Italy


Epidemiological Estimates for Haemoglobin Disorders: EUR by country
Per cent of pregnant women carrying any haemoglobin gene variant
% carriers
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0 22.5 25.0 27.5 30.0 32.5 35.0 37.5
Albania
Andorra
Armenia
Austria
Azerbaijan
Belarus
Belgium
Bosnia and Herzegovina
Bulgaria
Croatia
Czech Republic
Denmark
Estonia
Faroe Islands
Finland
France
Georgia
Germany
Gibraltar
Greece
Hungary
Iceland
Ireland
Israel
Italy
Kazakhstan
Kyrgyzstan
Latvia
Liechtenstein
Lithuania
Luxembourg
Malta
Monaco
Netherlands
Norway
Poland
Portugal
Republic of Moldova
Romania
Russian Federation
San Marino
Serbia & Montenegro
Slovakia
Slovenia
Spain
Sweden
Switzerland
Tajikistan
Republic of Macedonia
Turkey
Turkmenistan
UK
Ukraine
Uzbekistan
% alpha globin gene variants alone
% alpha and beta globin gene variants
% beta globin gene variants alone
ITALY

Epidemiological Estimates for Haemoglobin Disorders: I country

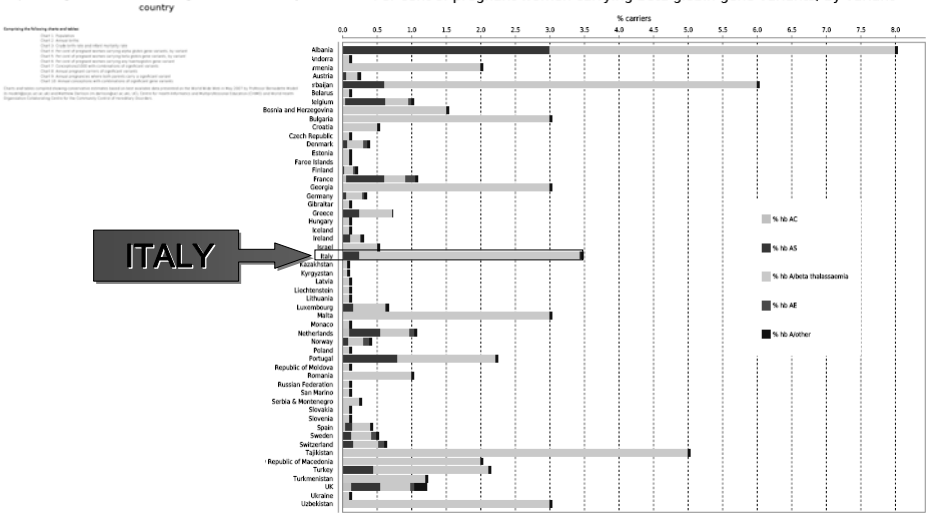
Per cent of pregnant women carrying alpha globin gene variants, by variant



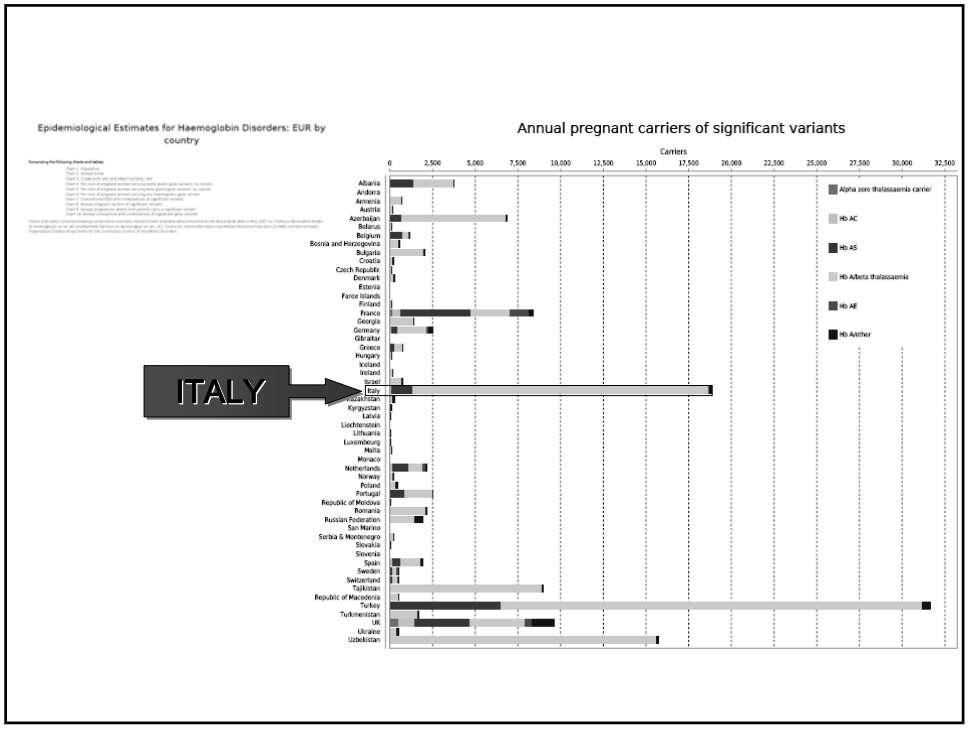
ITALY

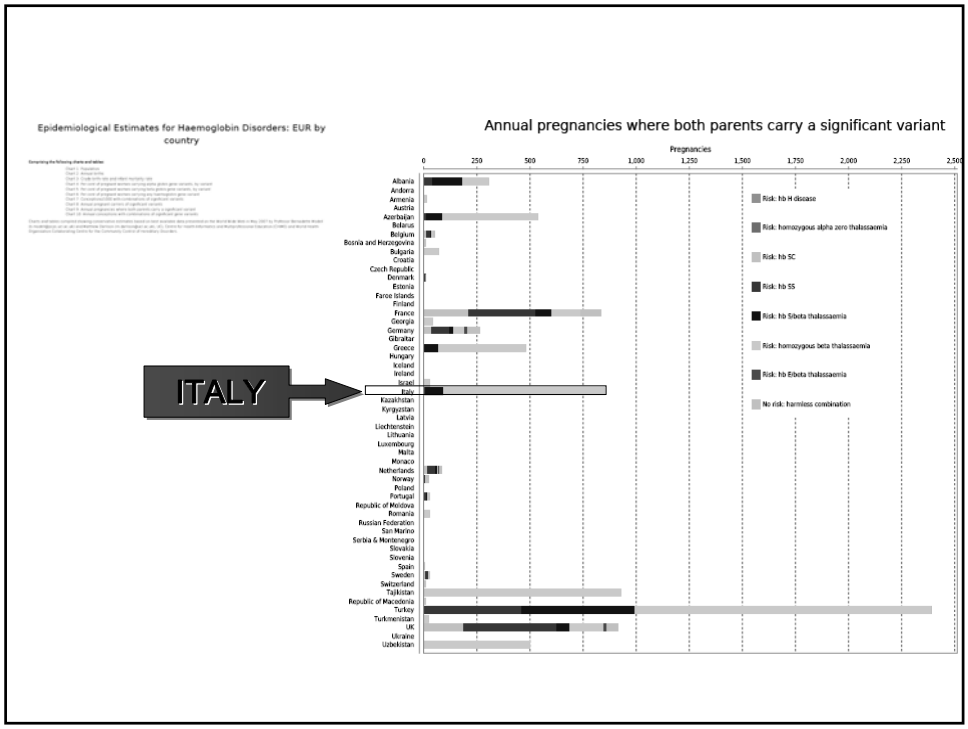
Epidemiological Estimates for Haemoglobin Disorders: EUR by country

Per cent of pregnant women carrying beta globin gene variants, by variant



ITALY

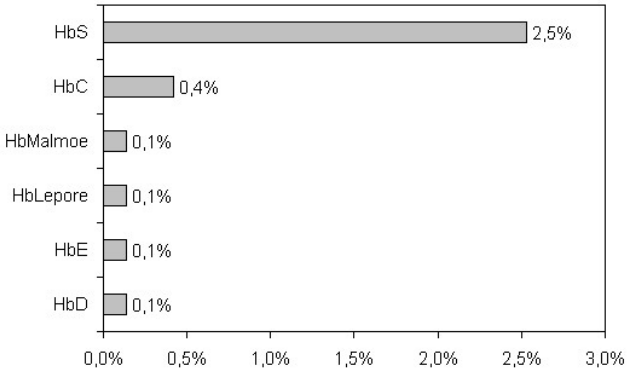

Epidemiological Estimates for Haemoglobin Disorders: EUR by country
Annual pregnant carriers of significant variants
Carriers
0
2,500
5,000
7,500
10,000
12,500
15,000
17,500
20,000
22,500
25,000
27,500
30,000
32,500
Albania
Andorra
Armenia
Austria
Azerbaijan
Belarus
Belgium
Bosnia and Herzegovina
Bulgaria
Croatia
Czech Republic
Denmark
Estonia
Faroe Islands
Finland
France
Georgia
Germany
Gibraltar
Greece
Hungary
Iceland
Ireland
Israel
Italy
Kazakhstan
Kyrgyzstan
Latvia
Liechtenstein
Lithuania
Luxembourg
Malta
Monaco
Netherlands
Norway
Poland
Portugal
Republic of Moldova
Romania
Russian Federation
San Marino
Serbia & Montenegro
Slovakia
Slovenia
Spain
Sweden
Switzerland
Tajikistan
Republic of Macedonia
Turkey
Turkmenistan
UK
Ukraine
Uzbekistan
Alpha zero thalassaemia carrier
Hb AC
Hb AS
Hb Abeta thalassaemia
Hb AE
Hb Aother
ITALY


Epidemiological Estimates for Haemoglobin Disorders: EUR by country
Annual pregnancies where both parents carry a significant variant
Pregnancies
0
250
500
750
1,000
1,250
1,500
1,750
2,000
2,250
2,500
Albania
Andorra
Armenia
Austria
Azerbaijan
Belarus
Belgium
Bosnia and Herzegovina
Bulgaria
Croatia
Czech Republic
Denmark
Estonia
Faroe Islands
Finland
France
Georgia
Germany
Gibraltar
Greece
Hungary
Iceland
Ireland
Israel
Italy
Kazakhstan
Kyrgyzstan
Latvia
Liechtenstein
Lithuania
Luxembourg
Malta
Monaco
Netherlands
Norway
Poland
Portugal
Republic of Moldova
Romania
Russian Federation
San Marino
Serbia & Montenegro
Slovakia
Slovenia
Spain
Sweden
Switzerland
Tajikistan
Republic of Macedonia
Turkey
Turkmenistan
UK
Ukraine
Uzbekistan
Risk: hb H disease
Risk: homozygous alpha zero thalassaemia
Risk: hb SC
Risk: hb SS
Risk: hb Sbeta thalassaemia
Risk: homozygous beta thalassaemia
Risk: hb Ebeta thalassaemia
No risk: harmless combination
ITALY

Frequency and type of newly diagnosed hemoglobin variants in Northern Italy.

Giuseppe Lippi, Martina Montagnana, Elisa Danese, Gian Luca Salvagno, Francesca Bellorio, Gian Cesare Guidi.

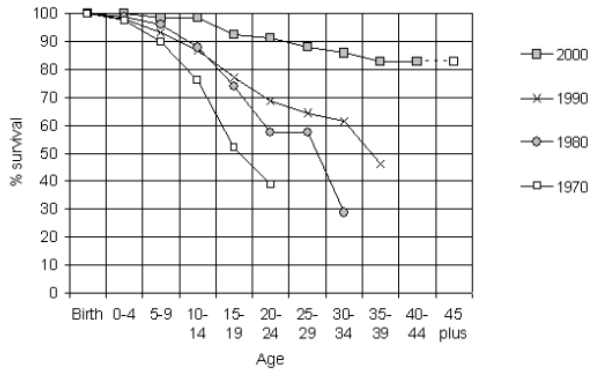
Sezione di Chimica e Clinica, Dipartimento di Scienze Morfologico-Biomediche, Università degli Studi di Verona, Italy.



Model patient register shows use for:

- Supporting equitable delivery of the best possible clinical care of patients with rare disorders
- Monitoring services - both treatment and prevention

Improving life-expectancy in thalassaemia in the UK.



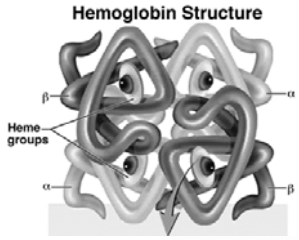
Public health reviews

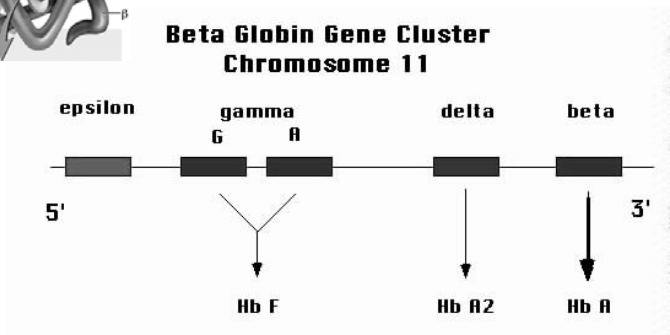
Global epidemiology of haemoglobin disorders and derived service indicators

Bernadette Modell & Matthew Darlison

Conclusion

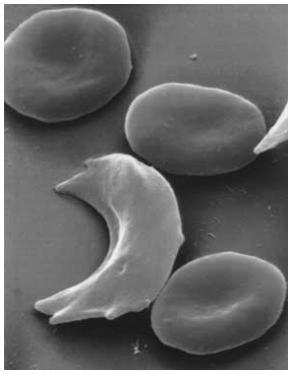
The data summarized here confirm that screening and genetic counselling for haemoglobin disorders should be an intrinsic part of health care



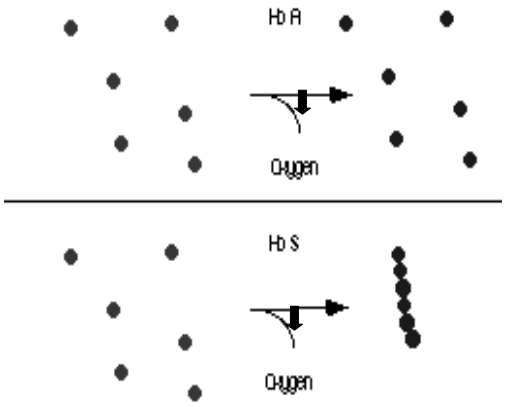


Hemoglobin S: What's the big deal?

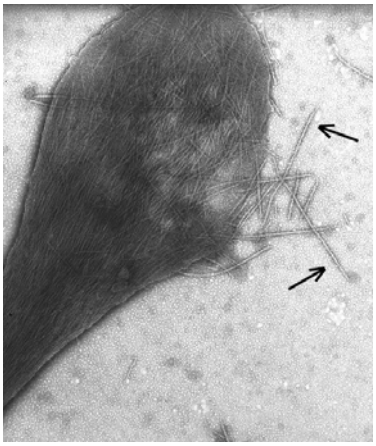
1927 Hahn and Gillespie showed sickling with deoxygenation of red cells in a patient



Hemoglobin S polymer formation



The hydrophobic valine is exposed in the deoxy conformation and burrows within a hydrophobic pocket of neighboring Beta chains



Hemoglobin polymers

Simple pathology-complex disease

- Presence of HbS leads to a variety of clinical manifestations- Cool pathophysiology at work!

Infection	Painful crises
Chest crises	Priapism
Strokes	Pulmonary htn
Splenic sequestration	Avascular necrosis
Renal failure	

Simple pathology-complex disease

- Disease severity variable and difficult to predict
  - Genotype (SS vs SC vs Sthal)
  - Beta globin gene cluster haplotype
    - Senegal most benign, central african republic most severe
  - Fetal hemoglobin levels-Higher is better
  - "Bad" in infant: dactylitis, severe anemia, leukocytosis
- Steinberg MH. Predicting clinical severity in sickle cell anaemia.Br J Haematol. 2005 May;129(4):465-81.

A.J. Epidemiology May 2000

Incidence of SCD complications based on genotype

Complication	HbSS (per 100 pt-years)	HbSC (per 100 pt-years)	HbS/beta^0-thalassemia (per 100 pt-years)	HbS/beta$^+$-thalassemia (per 100 pt-years)
Acute Chest Syndrome	12.8	5.2	9.4	3.9
Bacteremia	6.5	5.8		
Stroke	0.61	0.17	0.10	0.11
Pain crisis	24.0	8.5		

Survival by genotype

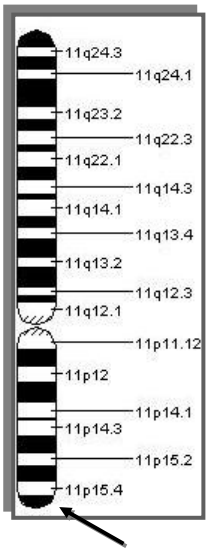
Sex and Genotype	Median Survival
Males with Hb SS	42 years
Females with Hb SS	48 years
Males with Hb SC	60 years
Females with Hb SC	68 years

- In 1973 mean survival with SS disease was 14 years!

Care for sickle cell patients has begun to focus on screening and prevention in addition to symptom management

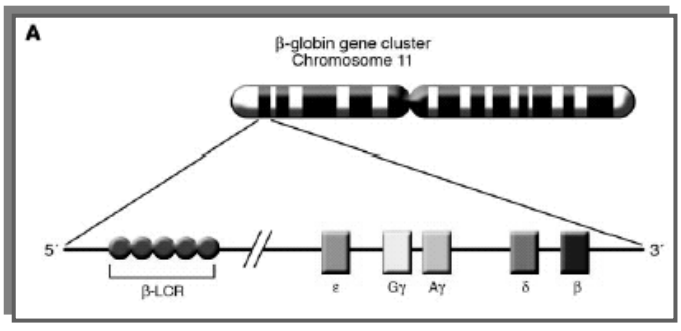
Determinazione degli Aplotipi del cluster genico della β-globina in pazienti affetti da Anemia Falciforme

Martina Montagnana, Giuseppe Lippi



Premessa (1)

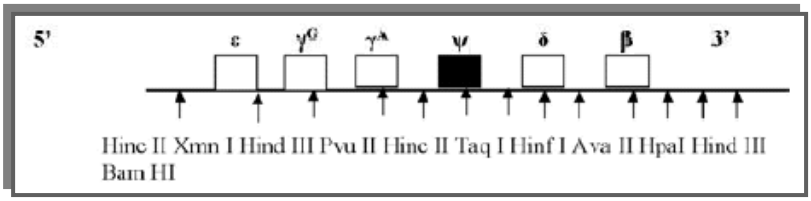
- Il cluster genico della β-globina è localizzato in posizione 11p15.5
- DNA 70Kb



Premessa (2)

Lungo il cluster sono stati individuati dei siti specifici (più di 20) che possono essere riconosciuti e quindi tagliati da determinati enzimi (endonucleasi) di restrizione

(Antonarakis et al. Hum Genet 1985;69:1)



Aplotipo

Si definisce aplotipo una combinazione di varianti alleliche lungo un cromosoma o segmento cromosomico contenente loci in linkage disequilibrium

Sickle Hemoglobin (*Hb S*) Allele and Sickle Cell Disease: A HuGE Review

American Journal of EPIDEMIOLOGY

A. Ashley-Koch,[1] Q. Yang,[2] and R. S. Olney[2]

Determinazione degli aplotipi

1.1. β-Globin-like Gene Cluster Haplotypes in Biology, Medicine, and Anthropology

Haplotypes of the β-globin-like clusters have been used for the following purposes:

1. To provide anthropological correlations: They have been used to give evidence of and/or define the common origin and the likelihood of an ancestral home for the tribals of India *(13)* and their potential origin in the Harappa culture, in the margins of the Indus River; to give a biological basis to the linguistical basis of the Bantu expansion hypothesis in Africa *(8)*; and determine the Indian tribal origin and east African origin of the sickle gene, respectively, in Indian and African inhabitants of Mauritius Island *(14)*.
2. To provide a source of clinical diversity among SC patients: Evidence exists that the linkage of the β^S gene to the Senegal and Arab Indian India haplotypes is associated with higher expression of HbS in SS and more benign hematological profile *(15–17)*. Conversely, the Bantu haplotype has the most severe course *(18)*.

Correlazione genotipo-fenotipo nell'anemia falciforme

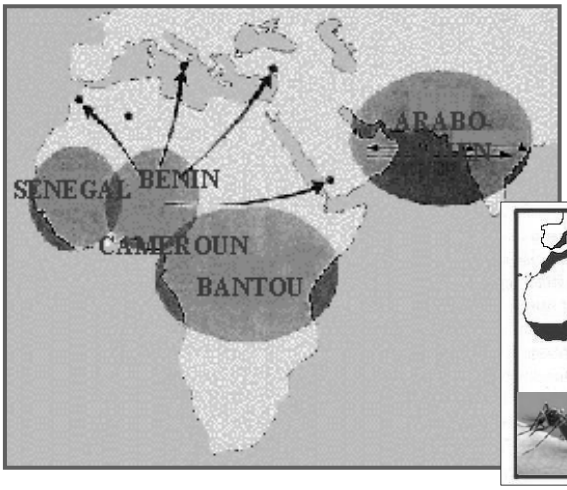
Stessa mutazione ma diversa clinica

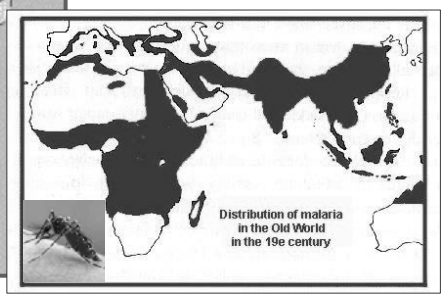
Aplotipo?

- Nei pazienti affetti da anemia falciforme sono stati identificati cinque diversi aplotipi maggiori che risultano in L.D. con la mutazione caratteristica β^S.

While many haplotypes exist for the β-globin cluster region, only specific haplotypes are found on chromosomes that carry the *Hb S* variant (18). These haplotypes are named for the geographic regions of Africa and the Middle East where they predominate (18).

Origine degli aplotipi





(Pagnier et al. Proc Natl Acad Sci USA 1984;81:1771-73)

Altri aplotipi riconosciuti nel cluster β-globinico

Linkage of β-thalassaemia mutations and β-globin gene polymorphisms with DNA polymorphisms in human β-globin gene cluster

Stuart H. Orkin*, Haig H. Kazazian Jr†, Stylianos E. Antonarakis†, Sabra C. Goff*, Corinne D. Boehm*, Julianne P. Sexton*, Pamela G. Waber* & Patricia J. V. Giardina‡

Nature Vol. 296 15 April 1982

Haplotype	Thalassaemia defect identified
I	IVS-1 β^+
II	Nonsense codon 39
III	5′ IVS-2 splice
IV	Frameshift codon 8
V	5′ IVS-1 splice 5′ IVS-2 splice
VI	IVS-1 consensus substitution
VII	IVS-2 position 745
VIII	-87 substitution
IX	Nonsense codon 39

Sickle Hemoglobin (*Hb S*) Allele and Sickle Cell Disease: A HuGE Review

A. Ashley-Koch,[1] Q. Yang,[2] and R. S. Olney[2]

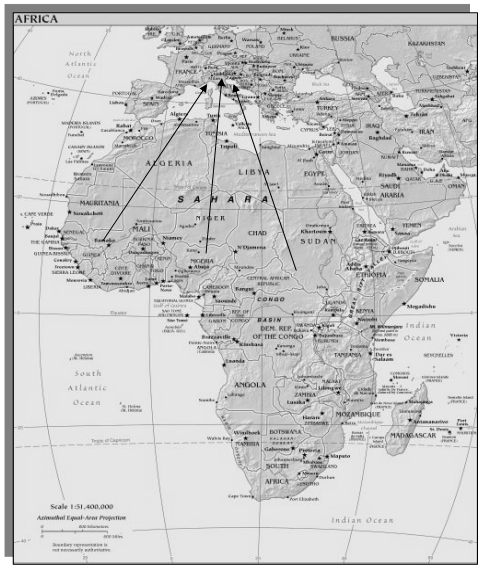
American Journal of EPIDEMIOLOGY

The β-globin cluster haplotypes are associated with differing clinical severities in sickle cell disease. This is probably due to variation in hemoglobin and fetal hemoglobin concentrations. Both hemoglobin and fetal hemoglobin levels vary with respect to haplotype (19) and are correlated with clinical expression of sickle cell disease (14, 20).

The Senegal haplotype remains associated with a higher level of HbF compared to other African haplotypes

[Nagel et al. N Engl J Med 1985;312:880-884]

Among the three most common haplotypes in sickle cell disease, the Senegal haplotype is associated with the most benign form of sickle cell disease, followed by the Benin haplotype. The Central African Republic haplotype is associated with the most severe form of the disease (19). In Africa, as well as in the United States, sickle cell patients with the Central African Republic haplotype have a twofold increased risk of complications and early mortality when compared with sickle cell patients with other haplotypes (19).



Flussi migratori dall'Africa

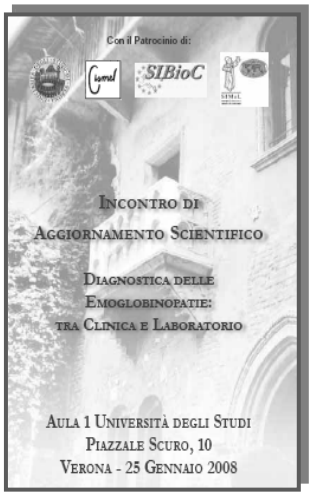
Studi di popolazione hanno mostrato che il 13% dei neonati affetti da emoglobinopatie si trovano nei paesi Occidentali (Europa ed Italia), a causa dei flussi migratori

It is therefore vital that international health agencies and governments of countries where the haemoglobin disorders occur at a high frequency become aware of the future extent of this problem and develop programmes for their control and management.

Inherited haemoglobin disorders: an increasing global health problem

D.J. Weatherall[1] & J.B. Clegg[2]

Bulletin of the World Health Organization, 2001, **79**: 704–712.

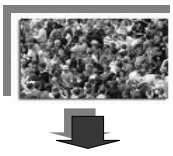


Scopo dello studio

- Sviluppare una metodica di laboratorio per lo studio degli aplotipi, allo scopo di determinare la prevalenza e la distribuzione degli aplotipi nei soggetti con anemia falciforme residenti in Italia

Popolazione studiata

- 68 pz.
- Sesso: 30 maschi e 38 femmine
- Età: 1-59 anni
- 18 SS, 38 AS, 4 SC, 8 S/beta talassemia



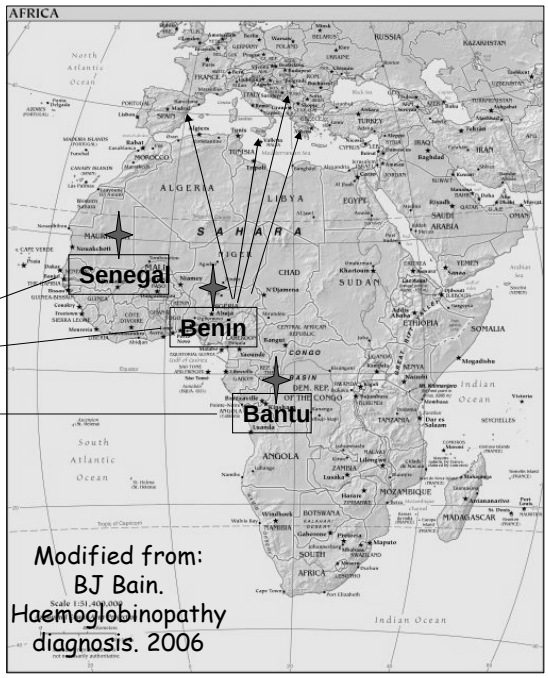
62 Africa
1 Italia
1 Cuba
1 Rep. Dom.
1 Albania
2 Brasile

Rogers ZR, et al.
Nonblack patients with sickle cell disease have African beta S gene cluster haplotypes.
JAMA. 1989;261:2991-4.

18 pazienti non africani affetti da AF.

"These data strongly support the concept that the beta s gene on chromosome 11 of these individuals is of African origin.
The clinical severity of the disease in these nonblack patients is appropriate to their haplotype and is comparable with that of black patients."

Migration
from Africa to…



1. Estrazione del DNA

2. Amplificazione di 7 frammenti del cluster beta-globinico

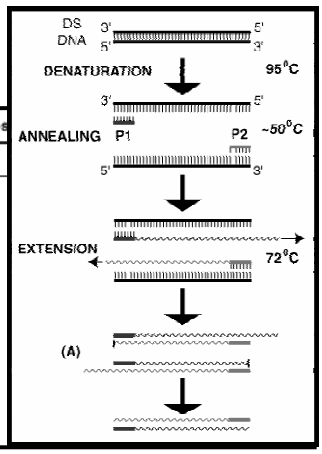
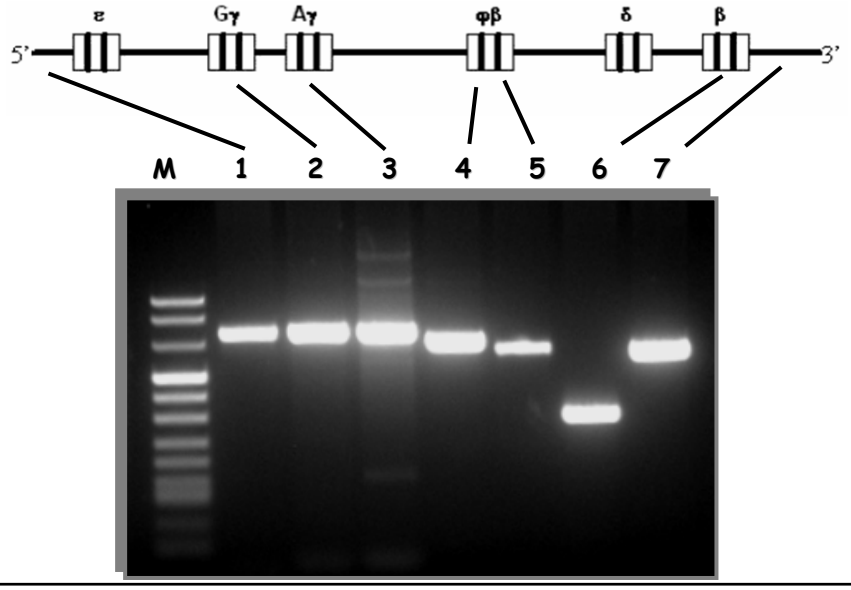


TABLE I. Oligonucleotide Primers Used for PCR-RFLP Analysis of Seven RFLP Sites

Genes	Primer sequence 5–3	Product size (bp)
ε 5′	TCTCTGTTTGATGACAAATTC	760
	AGTCATTGGTCAAGGCTGACC	
$^{G_\gamma/A_\gamma}$	1. AAGTGTGGAGTGTGTACATGA	1/2 = 781
	2. TGCTGCTAATGCTTCATTACAA	2/3 = 766
	3. TAAATGAGGAGCATGCACACAC	
5′ψ β	GAACAGAAGTTGAGATAGAGA	701
	ACTCAGTGGTCTTGTGGGCT	
3′ψ β	TCTGCATTTGACTCTGTTAGC	592
	GGACCCTAACTGATATAACTA	
5′ β	GTGGTCTACCCTTGGACCCAGAGG	328
	TTCGTCTGTTTCCCATTCTAAACT	
3′ β	AGTTAGAGGCTTGATTTGGAGG	638
	GTTAAGGTGGTTGATGGTAAC	

Primer sequences were those given by Old [Old JM. Hemoglobinopathies. In: Elles R, editor. Methods in molecular medicine: molecular diagnosis of genetic disease. Totowa, NJ: Humana Press; 1996:169–183] with minor modifications.



Digestione con enzimi di restrizione

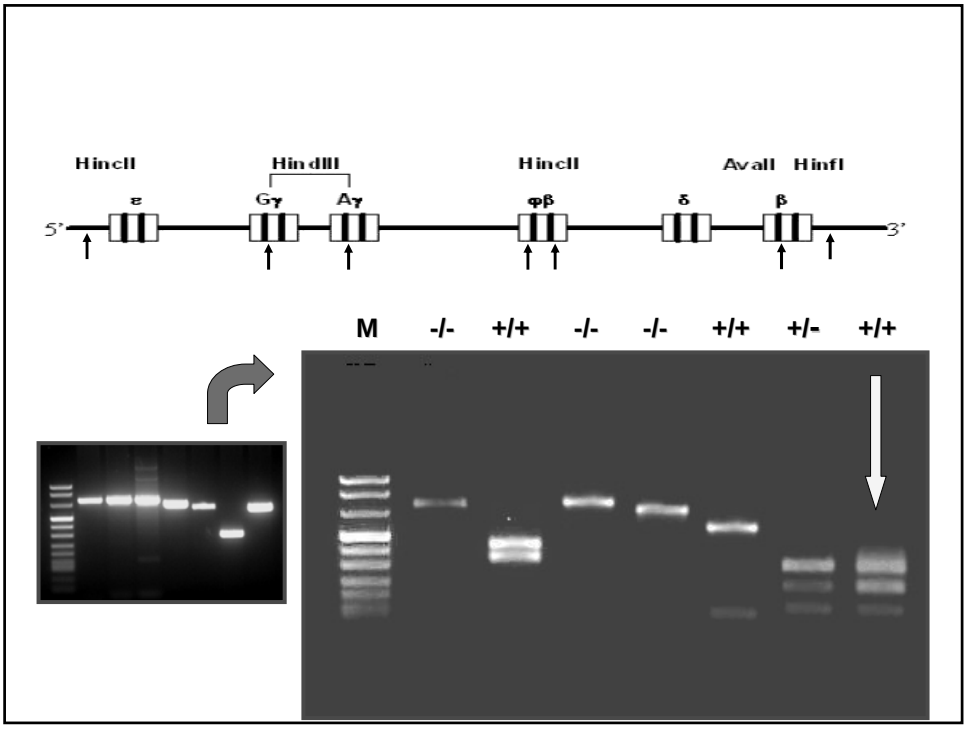
I prodotti della PCR di ciascun pz. (7 per ogni pz.) sono stati incubati con l'appropriato enzima di restrizione (3h 37°C) ed i frammenti risultanti sono stati fatti migrare su gel di agarosio al 3%.

Siti di restrizione studiati:
HincII (5' to ε), HindIII (within IVS2 of the Gγ and Aγ), HincII (in 5' and 3' of ψß), AvaII (5' to ß) and HinfI (3' to ß).

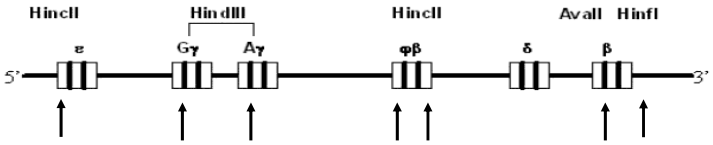
Analisi dei risultati

Per determinare gli aplotipi eterozigoti, abbiamo assunto che i pazienti eterozigoti possedessero un aplotipo comune ed un aplotipo raro, come riportato da Steinberg, piuttosto che due diversi aplotipi rari.

(Steinberg et al. Am J Hematol 1995;48:175–181)

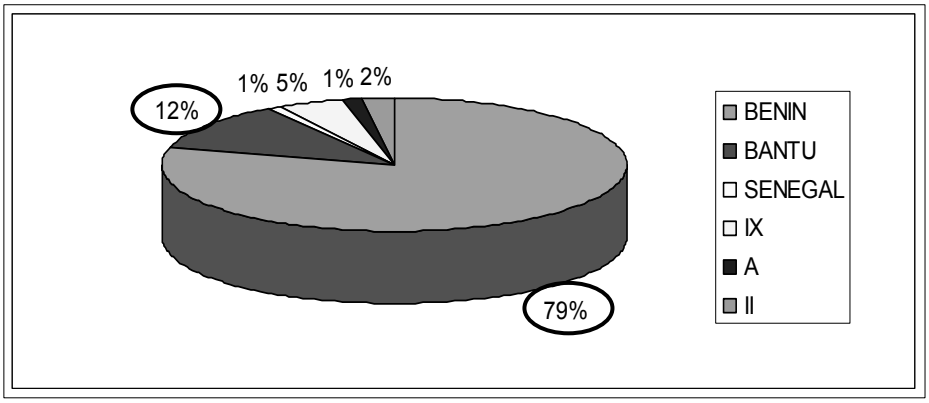


Costruzione dell'aplotipo



	Hinc II	Hind III	Hind III	Hinc II	Hinc II	Ava II	Hinf I
Benin	-	-	-	-	+	+	+
Bantu	-	+	-	-	+	+	+
Arab-Indian	+	+	-	+	+	+	+
Senegal	+	+	-	+	+	+	+
Cameroon	-	+	+	-	+	+	-

Frequenza determinata sugli 86 cromosomi S



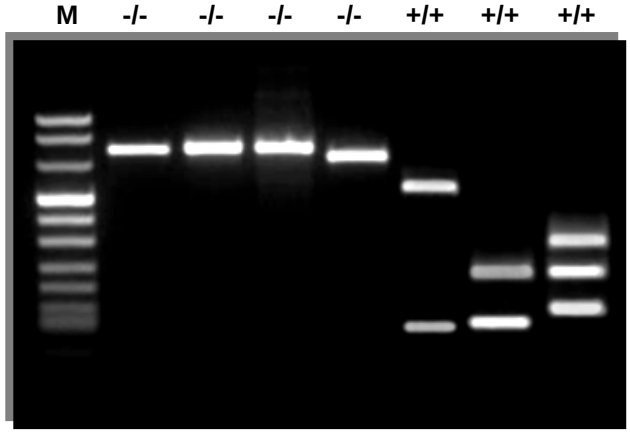
Original Research Article AMERICAN JOURNAL OF HUMAN BIOLOGY 00:000–000 (2008)

β-Globin Gene Cluster Haplotypes and α-Thalassemia in Sickle Cell Disease Patients from Trinidad

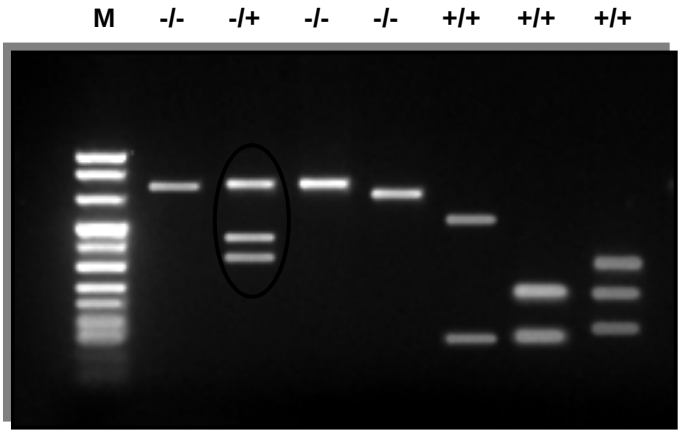
ALTHEIA JONES-LECOINTE,[1] ERSKINE SMITH,[1] MARC ROMANA,[2] MARIE-GEORGES GILBERT,[1] WAVENEY P. CHARLES,[1] CHRISTIAN SAINT-MARTIN,[3] AND LISIANE KÉCLARD[2]*

β^S Haplotype	Cuba[a]	Guadeloupe[b]	Jamaica[c]	Trinidad[d]
N^e 86	198	832	244	283
Benin **79%**	101 (51%)	622 (74.8%)	184 (75%)	175 (61.8%)
Bantu **12%**	81 (41%)	92 (11.1%)	24 (10%)	49 (17.3%)
Senegal **1%**	16 (8%)	51 (6.1%)	7 (3%)	24 (8.5%)
Cameroon	NA	19 (2.3%)	5 (2%)	10 (3.2%)
Arab-Indian	NA	6 (0.7%)	2 (1%)	9 (3.2%)
Other	NA	42 (5%)	22 (9%)	16 (5.7%)

Es. 1: aplotipo Benin-Benin



Es. 2: aplotipo Benin-Bantu



Conclusioni

I nostri dati rivelano delle frequenze sovrapponibili a quelle osservate in altri paesi

Rimaniamo in attesa dei dati clinici per verificare la nostra ipotesi di partenza…