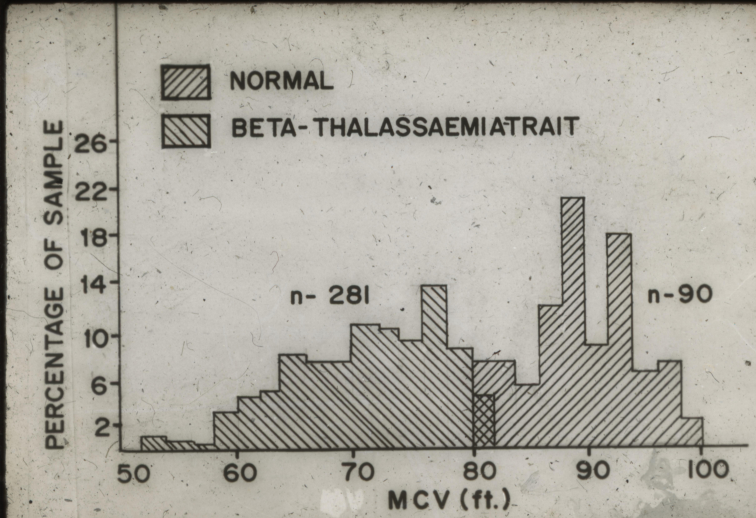
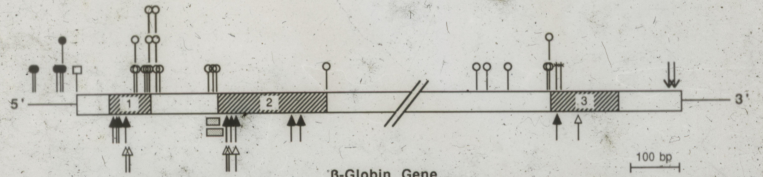

NORMAL
BETA-THALASSAEMIA TRAIT
PERCENTAGE OF SAMPLE
26
22
18
14
10
6
2
n- 281
n-90
50
60
70
80
90
100
MCV (ft.)

Frequency of β-thalassaemia mutations in U.K. Asian Indians

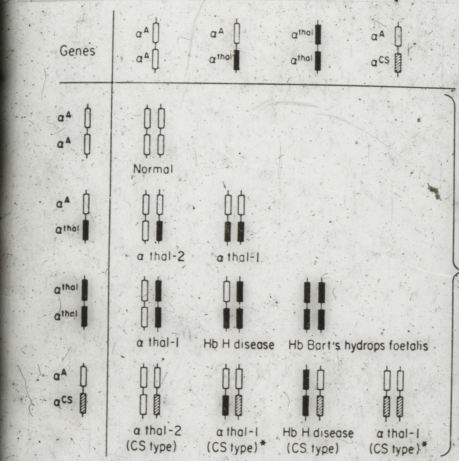
	Mutation			No. of chromosomes TM	TI	Total	Frequency
1	Deletion	600 bp	β^0	20	1	21	0·216
2	IVSI-5	G→C	Severe β^+	19	4	23	0·225
3	F/S Codon 8/9	+G	β^0	14	6	20	0·196
4	IVSI-1	G→T	β^0	7	7	14	0·137
5	F/S Codon 41/42	−TCTT	β^0	8	4	12	0·118
6	Nonsense Codon 15	C→A	β^0	3	2	5	0·049
7	F/S Codon 16	−C	β^0	1	0	1	0·009
8	−88	C→T	Mild β^+	0	2	2	0·019
9	CAP+1	A→C	Mild β^+	0	2	2	0·019
10	Uncharacterized			2	0	2	0·019
Total				74	28	102	1·00

Note: Other mutations looked for and not detected include the 25 bp deletion at the 3′ end of IVS-1, IVS-2 position 1 G→A and codon 37 G→A.



β-Globin Gene

Point mutations in β-thalassemia. The β-globin gene is shown with numbered hatched areas representing the coding regions of exons. Boxed open areas between the exons are introns, and boxed open areas at the 5' and 3' ends of the gene are untranslated regions that appear in the messenger RNA. The various types of mutations are depicted by different symbols. For example, 22 of the 51 mutations affect RNA splicing and are shown as ♀. (♀), transcription; (♀), cap site; (↓), RNA cleavage; (♦), frameshift; (♀), nonsense codon; (↑), unstable globin; (▭), small deletion.

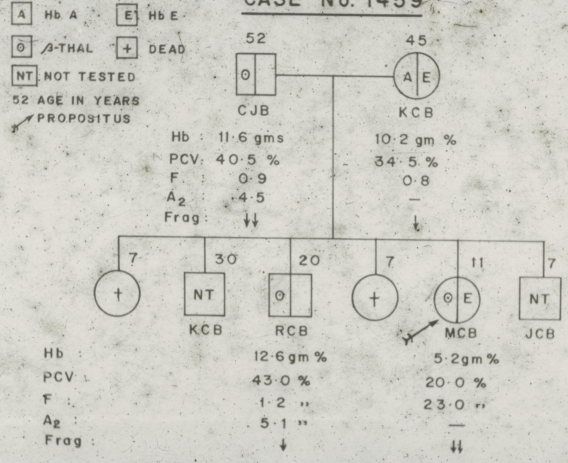


Simplified schematic representation of the correlations between genotypes and phenotypes in α thalassaemia, assuming the existence of duplicate α-chain loci. The Hb Constant Spring mutant is designated by CS. Phenotypes marked with asterisks have not been documented.

Table 1 Haplotypes for the Hinc II and Pvu II polymorphic sites on normal and β-thalassaemia chromosomes in individuals from the Mediterranean area and India–Pakistan

Haplotype		Mediterranean		India–Pakistan		
Hinc II	Pvu II	β^{Thal}	β^{A}	β^{Thal}	β^{A}	Total
+	−	75	12	22	8	117
−	+	15	5	1	15	36
+	+	0	0	0	0	0
−	−	6	1	0	1	8
Total		96	18	23	24	161

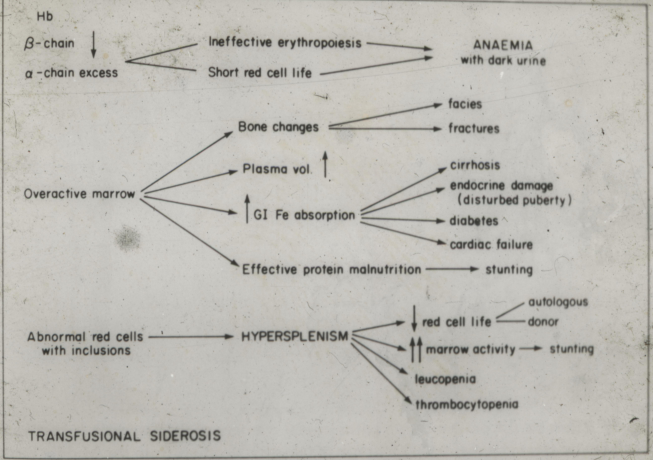
CASE No. 1459


A Hb A
E Hb E
0 β-THAL
+ DEAD
NT NOT TESTED
52 AGE IN YEARS
PROPOSITUS
52
0
CJB
45
A E
KCB
Hb : 11·6 gms
PCV: 40·5 %
F : 0·9
A2 : 4·5
Frag: ↓↓
10·2 gm %
34·5 %
0·8
—
↓
7
+
30
NT
KCB
20
0
RCB
7
+
11
0 E
MCB
7
NT
JCB
Hb
PCV
F
A2
Frag
12·6 gm %
43·0 %
1·2 ,,
5·1 ,,
↓
5·2 gm %
20·0 %
23·0 ,,
—
↓↓

PREGNANCIES AT RISK FOR β-THALASSAEMIA, MONITORED BY FETAL BLOOD SAMPLES WITH PLACENTOCENTESIS AND GLOBIN CHAIN SYNTHESIS OF FETAL BLOOD SHOWED THAT ANTE-NATAL DIAGNOSIS OF HOMOZYGOUS β-THALASSAEMIA IS FEASIBLE AND ACCURATE, WITH ACCEPTABLY LOW FAILURE AND FETAL LOSS RATES.

BESIDES PLACENTAL ASPIRATION, FETAL BLOOD CAN BE OBTAINED BY FETOSCOPY. BOTH TECHNIQUES HAVE A HIGH DEGREE OF SUCCESS, BUT PLACENTAL ASPIRATION REQUIRES LESS SKILL, FACILITIES AND ORGANISATION. THEREFORE, IT CAN BE PERFORMED IN UNDER-DEVELOPED COUNTRIES WHERE THALASSAEMIA IS MORE PREVALENT.

--- A. Cao et al. (1982)



Summary of pathology in β-thalassaemia major.

THERE SEEMS LITTLE DOUBT THAT ANTENATAL DIAGNOSIS OF β-THALASSAEMIA IS POSSIBLE AND THAT CENTRES SHOULD BE SET UP FOR THIS PURPOSE IN HIGH-INCIDENCE COUNTRIES, AS INDEED IS ALREADY HAPPENING IN MANY PARTS OF THE MEDITERRANEAN REGION AND SOUTHEAST ASIA. THE CENTRES REQUIRE EXPERT OBSTETRICIANS WHO ARE WELL TRAINED IN FETAL BLOOD SAMPLING AND A COMPETENT LABORATORY BACK-UP WITH INDIVIDUALS ADEQUATELY TRAINED IN BOTH THE TECHNIQUES OF EXAMINATION AND ENRICHMENT OF FETAL BLOOD CELLS AND THE VARIOUS BIOSYNTHETIC TECHNIQUES DESIGNED TO ESTIMATE THE RELATIVE AMOUNTS OF β AND γ CHAINS BEING PRODUCED IN THE FETAL BLOOD.

β/γ Synthetic ratios in fetal blood at 16 - 23 weeks' gestation (Alter 1979).

Diagnosis*	Number	Mean ± 1 s.d.	Range
Normal abortuses	23	0.109 ± 0.022	0.075 - 0.160
Normal fetuses	15	0.098 ± 0.025	0.070 - 0.141
Fetuses with β thalassaemia trait	17	0.058 ± 0.020	0.039 - 0.108
Fetuses with β thalassaemia major	5	0.013 ± 0.012	0 - 0.025

*Diagnoses were confirmed at birth or at abortion in all cases, except two with presumed β thalassaemia major.

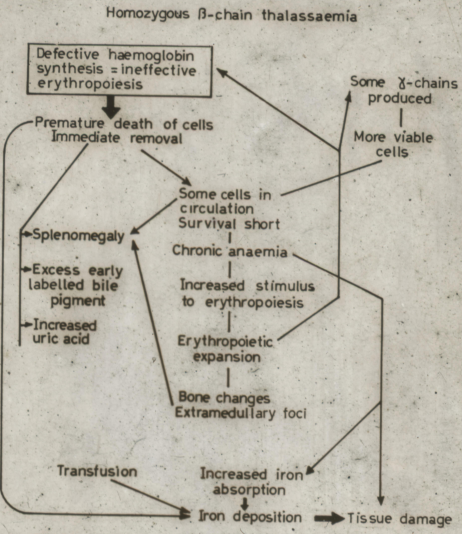


FIG. 7. Schematic representation of some main features of the pathophysiology of homozygous β-chain thalassaemia.

Quantitative distribution of Hb S in seven cases of sickle cell trait with known α genotypes

	Genotypes	Hb S (%)
Tribals		
KD 5	$-\alpha^{4.2}/-\alpha^{4.2}$	18.6
KD 10	$-\alpha^{4.2}/-\alpha^{4.2}$	19.9
KD 19	$-\alpha^{3.7}/-\alpha^{4.2}$	20.7
KD 18	$-\alpha^{3.7}/-\alpha^{3.7}$	22.1
KR 28	$-\alpha^{3.7}/-\alpha^{3.7}$	22.5
KD 15	$\alpha\alpha/-\alpha^{4.2}$	25.2
KD 33	αα/αα	33.2
Nontribals (controls)		
AP 62	αα/αα	34.8
AP 75	αα/αα	31.7
AP 114	αα/αα	33.1

LANDMARKS IN THE STUDY OF THALLASEMIA

COOLEY'S ANAEMIA (THALASSEMIA)	COOLEY & LEE	(1925)
HAEMOGLOBIN A2	KUNKEL & WELLENIUS	(1955)
HAEMOGLOBIN BART'S	AGER & LEHMANN	(1958)
GENETIC BASIS OF THALASSEMIA	INGRAM & STRETTON	(1959)
GLOBIN CHAIN SYNTHESIS IN ALPHA AND BETA THALASSEMIA	WEATHERALL ET AL	(1965)
REVERSE TRANSCRIPTASE FOR SYNTHESIS OF cDNA FROM mRNA	TEMIN & BALTIMORE	(1970)
PRENATAL DIAGNOSIS OF THALASSEMIA USING FETAL BLOOD	ALTER,MODELL ET AL	(1976)
MOLECULAR METHODS IN FETAL DIAGNOSIS OF THALASSEMIA	DOZY ET AL	(1979)
USE OF RFLP TO DEFINE HAPLOTYPE OF INDIVIDUAL CHROMOSOME	ORKIN & KAZAZIAN	(1982)
POLYMERASE CHAIN REACTION (PCR) TO AMPLIFY GENOMIC DNA SEQUENCE	SAIKI ET AL	(1985)
AMPLIFICATION REFRACTORY MUTATIONS SYSTEM (ARMS) FOR POINT MUTATION IN DNA	NEWTON ET AL	(1989)

SUMMARY OF THE INDIAN BETA THALASSEMIA MUTATION SO FAR DISCOVERED AND THEIR ASSOCIATED HAPLOTYPES

THALASSEMIC HAPLOTYPES			MUTATION
+ - - - - - +	...	...	619 bpDELETION IVS-1 p5
+ - - - - + +	...	...	8-9 G INSERT
- + - + + + +	...	...	25 bp DELETION IVS-1 p5
- + + - + + +	...	...	15 NONSENSE MUTATION
+ - - - - + -	...	...	41-42 TCTT

HAPLOTYPING: DNA was prepared from peripheral blood lymphocytes, and 5µg aliquots were used in Southern blot hybridization studies after single digestion with restriction endonucleases AvaII, HindII, Hind III and Bam HI. Later fragments were identified the appropriate ^{32}P-labeled DNA probes and autoradiography.

Dhanadan column (17.7.81)
10.3 mg 0.05 mmol.

5' counts.

γ = 35 → 36 = 27482 − 18252 = 9230

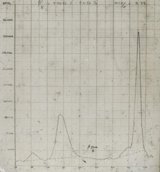
δ = 41 → 60 = 133456 − 43650 = 96366

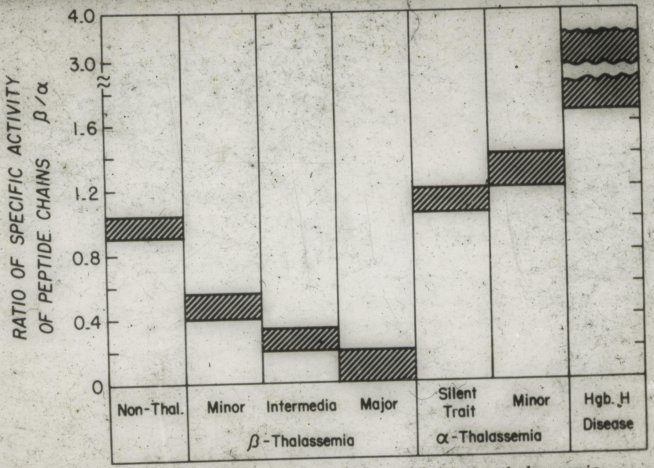
β = 64 → 71 = 14767 − 14735 = 32

α = 84 → 100 = 169962 − 56183 = 113794

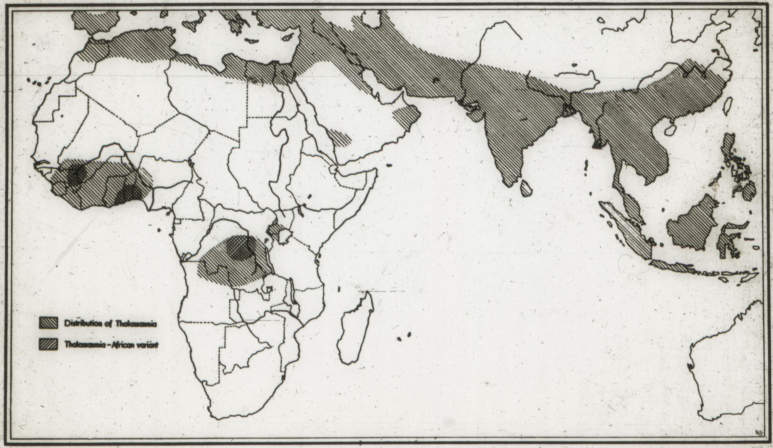
$\beta / (\gamma + \delta + \alpha)$ = 0.00050 = 0.032 % δ / α = 0.87

β / γ = 0.00035 = 0.035 % δ / α = 0.99





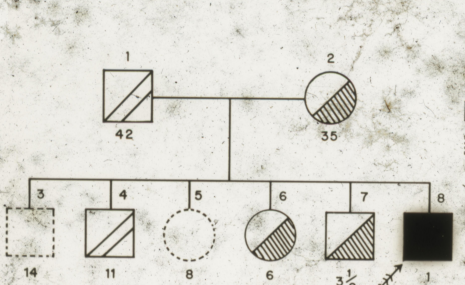
Ratio of β/α chain production in the thalassemia syndromes.


Distribution of Thalassemia
Thalassemia - African variant

Spectrum of β-Thalassemia Mutations in Chinese and Southeast Asians

Frameshift 41-42	28
IVS-2 nt 654	20
Nonsense codon 17	10
−28 A-G	13
−29	3
IVS-1 nt 5 (G-C)	1
Frameshift 71-72	1
Nonsense codon 43	2
Total	78

Similar data are presented in Zhang et al[52] and Chan et al.[76]
Data from Kazazian et al.[75]

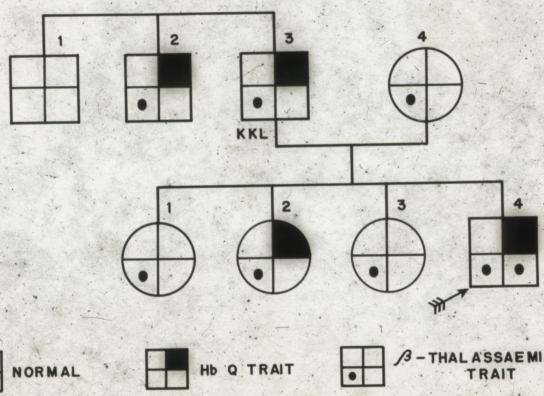


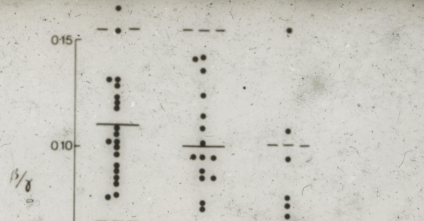
PEDIGREE OF FAMILY No. 642 SHOWING INTERACTION BETWEEN β-THALASSAEMIA TRAIT AND RAISED HAEMOGLOBIN A_2 TRAIT

MEAN VALUES OF HAEMOGLOBIN A_2 IN NORMAL, THASSAEMIA TRAIT AND IRON DEFICIENCY USING DIFFERENT METHODS

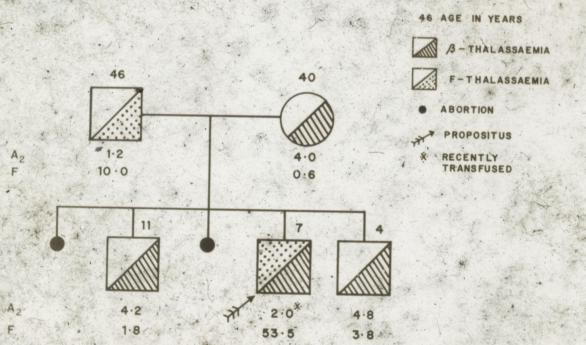
Subjects	Paper		Cellulose Acetate		Starch Block	
	Mean	No. of Subjects	Mean	No. of Subjects	Mean	No. of Subjects
Normal	2.31 ± 0.03	100	2.04 ± 0.03	25	2.04 ± 0.06	20
Thalassaemia trait	4.82 ± 0.06	120	4.39 ± 0.10	23	4.46 ± 0.04	11
Iron Deficiency	1.32 ± 0.04	25	1.00 ± 0.03	5	0.95 ± 0.02	5

"L" – FAMILY





Prenatal β/γ ratio in normal and thalassemic fetuses. ● Diagnosis established in infancy or at abortion. ○ Confirmation not available. ——— Mean and - - - - - 95% confidence limit. The single very high value in β-thalassemia trait was not included. (From reference 12.)



PEDIGREE OF FAMILY No. 713 SHOWING INTERACTION BETWEEN β-THALASSAEMIA TRAIT AND F-THALASSAEMIA TRAIT

Indian Deletion β° Thalassaemia

Haplotypes of normal and thalassaemic chromosomes in Sind and Gujarat

Haplotypes*		β^A	β thalassaemia		Total
			Deletion β^{thal}	Others	
+ − − − −	+ +	15	0	4	4
+ − − − −	+ −	2	0	1	1
+ − − − −	− +	4	23	5	28
− + − + +	+ +	8	0	14	14
− + − + +	− +	6	0	2	2
− + + − +	+ +	5	0	0	0
− + + − +	− +	2	0	0	0
− + + − −	+ −	2	0	0	0
− + − − −	− +	1	0	0	0
+ + − − −	+ −	1	0	0	0
+ − − + +	+ +	1	0	0	0
Total		47	23	26	49

* The haplotypes are represented as two blocks of polymorphic sites: a 5′ block containing the Hinc II-ε, Hind III-$^G\gamma$, Hind III-$^A\gamma$, Hinc II-$\psi\beta$ and Hinc II-3′ $\psi\beta$, 5′ to the δ gene; and 3′ block containing the Ava II-β and the Bam HI-β sites, 3′ to δ gene. This arrangement relates to the haplotype framework as proposed by Antonarakis *et al* (1982a).

Summary of Hematologic Findings in Individuals With α-Thalassemia

Phenotype	Equivalent Number of Functional α-Genes	Level of Hb Bart's at Birth (%)	Hb H% (Inclusions)	MCV*	MCH*	α/β Globin Chain Synthesis Ratio†
Normal	4	0	0 (none)	85-100	~30	~1.0
α-Thalassemia‡ trait (mild)	3	0-2	0 (rare)	75-85	~26	~0.9
α-Thalassemia‡ trait (severe)	2	2-8	0 (occasional)	65-75	~22	~0.7
Hb H disease	1	10-40	1-40 (many)	60-70	~20	~0.4
Hb Bart's Hydrops Fetalis	0	~80	present (present)	110-120	reduced	0.0

*These values vary considerably depending on the age of the patient and the figures given are a guide to the indices seen in adults. More detail is given Table 8.

†These values overlap to a considerable degree (see reference 30 and Table 8).

‡The mild and severe forms of α-thalassemia trait have often been referred to as α-thalassemia 2 and α-thalassemia 1, respectively.

CORD BLOOD SAMPLES FROM NEW-BORN (FTND)
OF PARENTS WITH BETA-THALASSAEMIA TRAIT
(TOTAL - 18)

ELECTROPHORETIC PATTERN

HAEMOGLOBIN-F+A
(14)

BLOOD PICTURE

NORMAL
(5)

ABNORMAL
(9)

HAEMOGLOBIN-F
(4)

BLOOD PICTURE

ABNORMAL
(4)

FOLLOW UP

54 WEEKS

52 WEEKS

26 WEEKS

LABORATORY DIAGNOSIS

NORMAL

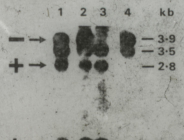
BETA-THAL. TRAIT

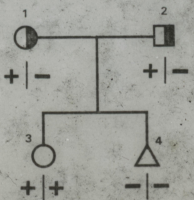
BETA-THAL. MAJOR

(3 died & one on
Blood Transfusion)

2

INDIRECT DETECTION OF β-THALASSEMIA USING LINKAGE OF THE Ava II / ψβ-gene POLYMORPHISM.





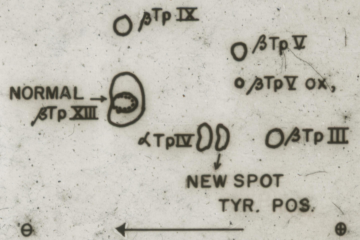
Ethnic distribution of β-thalassemia mutations from the Indian subcontinent

Mutation	Ethnic Group						Total
	Sindhi	Punjab Sikh	Gujarati	Indian Muslim	Pakistani Muslim	Others	(%)
IVS1n5	1	5	13	4	10	6	39(35.4)
619 bp deletion	7	4	1	5	6	2	25(22.7)
Fr c8/9	2	3	2	4	5	2	18(16.4)
Fr c41/42	3	5	1	0	0	1	10(9.0)
IVS1n1	3	1	1	0	1	0	6(5.4)
Fr c16	0	0	1	0	4	0	5(4.5)
Nons c15	0	0	2	1	0	0	3(2.7)
Cap site (+1)	0	2	0	0	0	0	2(1.8)
-88	0	1	0	0	0	0	1(0.9)
25 bp deletion	0	0	0	0	1	0	1(0.9)
Total	16	21	21	14	27	11	110

DELETION MUTATIONS OF BETA GENE CLUSTER

ETHNIC GROUP	DELETION SIZE (kb)	DELETION COORDINATES	Hb F LEVEL IN HETEROZYGOTES (PERCENT)	OTHER INFORMATION
A. β THALASSEMIAS				
1. INDIAN	0.619	63.4 - 64.0	UNAVAILABLE	
2. BLACK (USA)	1.4	61.6 - 63.0	7.0	
3. DUTCH	10.0	60.6 - 70.6	4 to 11	
B. $\delta\beta$ THALASSEMIAS				
1. MEDITERRANEAN	6.1	49.1 - 55.2	1.1 to 1.6	
2. SICILIAN	12.8	55.4 - 68.2	5 to 15	
3. SPANISH	100.0	52.2 - UNKNOWN	5 to 15	
4. BLACK (USA)	12	52.3 - 64.1	UNKNOWN	PANCELLULAR
5. JAPANESE	24	43.7 - UNKNOWN	5 to 7	
6. GREEK; ITALIAN	7.4	55.3 - 62.7	1 to 5	Hb LEPORE FUSION

THE RELEVANT AREA OF THE FINGERPRINT



MALAYA & SINGAPORE

NORTH	Hb.E. (2-8%)
NORTH EAST	Hb.E. (8-45%)
NORTH WEST	Hb.E. (0.7-7.7%)
WEST	Hb.E. (2-6%)
SOUTH	Hb.E. (0.5-7%)
NORTH EAST	BETA THAL (PRESENT)
WEST	BETA THAL (6%)
WEST	ALPHA (5%)
WEST	BARTS (4%)
WEST	C.S. (3%)
SINGAPORE	Hb.E (4.3%)
"	BETA THAL (PRESENT)
"	ALPHA THAL (6.3%)
"	BARTS (3.6%)

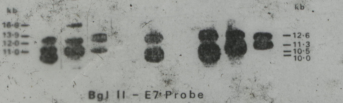
Hb-S
Hb-KOLN
Hb-Q
Hb-D
Hb-K
Hb-J SINGAPORE
Hb-F KUALALUMPUR

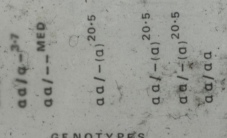
RARE
(SOME SEEN IN INDIANS)

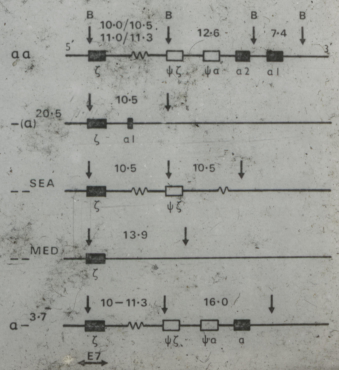
INDONESIA

SUMATRA	Hb.E. (2-7%)
JAVA - EAST	Hb.E. (3-5%)
JAVA - SOUTH	Hb.E. (3-6%)
BALI	Hb.E. (4%)
TIMOR & SIMBAVA	Hb.E. (4-11%)
SULAWESI	Hb.E. (1-2%)
SARAWAK	Hb-E. (0.2-6%)
MADURA	Hb.E. (13%)
SULAWESI	Hb.O (1-2.5%)
BETA THALASSEMIA	PRESENT
ALPHA THALASSEMIA	0.7%
Hb-A_2 INDONESIA	RARE

DIRECT DETECTION OF α-THALASSEMIA — Bgl II / ζ-probe

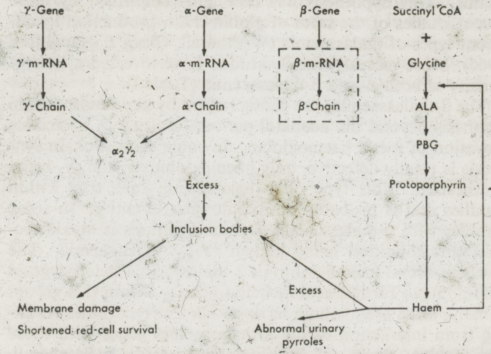






HAEMOGLOBIN-E		THALASSEMIA	
THAILAND	8 -32·7	ITALY	7 - 19
INDONESIA	2·4-14·0	SICILY	3 - 3
MALAYA	7·5	ALGIERS	2·9- 9·2
BURMA	7 - 14		
CEYLON	2·0		
BENGAL	3·7		

The break-down of haemoglobin control mechanisms in β-thalassaemia



In this situation no β-chains are produced. Excess of haem and α-chain are probably responsible for the haemolytic component in this disorder. A secondary defect in haem synthesis follows a pile-up of haem with inhibition of ALA synthesis

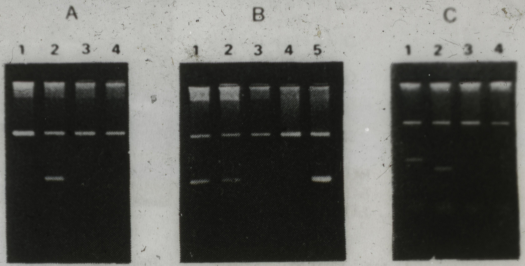


Fig 1—ARMS analysis of Indian mutations.

Gel A shows analysis of an unknown DNA sample with the primer for the IVSI nt5 mutation (lane 1), IVSI nt1 (2) Fr 41–42 (3), and Fr 8–9 (4). Gel B shows a prenantal diagnosis for the IVSI nt5 mutation: lanes 1 and 2 = maternal and paternal DNA, respectively, with IVSI nt5 mutant primer; lane 3 = normal DNA with IVSI nt5 normal primer; lane 4 = chorionic villus DNA with IVSI nt5 normal primer; lane 5 = chorionic villus DNA with the IVSI nt5 mutant primer. Gel C shows chorionic villus DNA with IVSI nt5 mutant primer (lane 1) and Fr 8–9 mutant primer (2), and normal DNA with IVSI nt5 mutant primer (3) and Fr 8–9 mutant primer (4). The upper bands in each gel are the 861 bp control bands.

HAEMOGLOBIN PROFILE IN LEUKAEMIA AND LYMPHOMA - OUR SERIES

Case	Number examined	Hb F (%)	Hb A_2 (%)
C M L	28	0.7 - 4.3	1.6 - 5.2*
A M L	25	1.9 - 16.2	1.8 - 2.5
A L L	11	0.6 - 1.8	1.9 - 2.3
Erythroleukaemia	1	6.3	2.8
Lymphoma	9	0.7 - 1.6	1.0 - 2.7

* Includes 2 cases of beta-thalassaemia trait

STUDIES ON SS COMB BLOODS (TYPE) BORN OF PARENTS :

(a) BETA THALASSAEMIA TRAIT \ BETA THALASSAEMIA TRAIT .. (8F)

(β) BETA THALASSAEMIA TRAIT \ HBH TRAIT .. (5)

(c) Hb D-BETA THALASSAEMIA \ NORMAL .. (1)

(d) Hb G-BETA THALASSAEMIA \ NORMAL .. (1)

REFERAL INVESTIGATIONS TO INTERNATIONAL
FOR CONFIRMATION.

D. $(\gamma\delta\beta)^{o}$ THALASSEMIA

1. ENGLISH	LARGE	UNKNOWN* - 34.0
2. DUTCH	100.0	UNKNOWN - 60.0
3. ANGLO-SAXON	LARGE	UNKNOWN - 62.4 **
4. MEXICAN	105.0	UNKNOWN - UNKNOWN **
5. SCOTCH-IRISH	150.0	UNKNOWN - UNKNOWN **

E. HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

1. BLACK (USA)	70.0	51.2 - UNKNOWN	20 to 30	HPFH-1
2. BLACK (GHANA)	70.0	47 - UNKNOWN	20 to 30	HPFH-2
3. ITALIAN	38.0	50.0 - 88.0	17 to 30	
4. INDIAN	44.0	45.0 - 89.0	21 to 23	
5. KENYAN	22.8	40.0 - 62.8	5 to 8	Hb KENYA

---

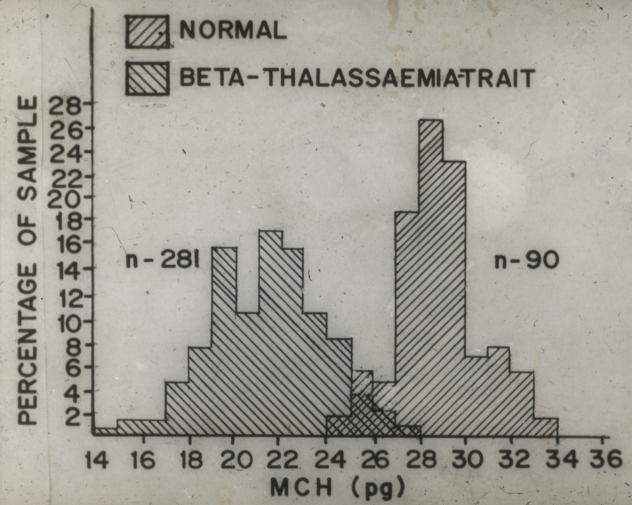
* 5 SITE UPSTREAM FROM EPSILON

** THE WHOLE β CLUSTER IS DELETED.

The pathophysiology of α and β thalassaemia

1. Large scale Population Studies for abnormal haemoglobin and thalassaemia traits in different ethnic groups.
2. Genetic Counselling (Prospective).
3. Intra-uterine diagnosis and therapeutic abortion.
4. Bone marrow transplantion.
5. Reverting Genetic Constitution - Genetic Engineering.

A model of the genetic basis for α thalassaemia In α° thalassaemia both α globin genes are inactivated, while in α+ thalassaemia one of the linked pair of genes is inactivated. In the case of α° thalassaemia both α genes are deleted. In α+ thalassaemia one α gene may be deleted, or it may be intact but have a mutation which prevents its normal function. Normal α genes are shaded red and deleted or inactivated α genes are unshaded


NORMAL
BETA-THALASSAEMIA-TRAIT
PERCENTAGE OF SAMPLE
28
26
24
22
20
18
16
14
12
10
8
6
4
2
n-281
n-90
14 16 18 20 22 24 26 28 30 32 34 36
MCH (pg)

The deletion forms of α thalassemia The α° thalassemias result from deletions of 3.7 or 4.2 kb. The different origins of the α° thalassemias are represented as follows: MED is Mediterranean, SEA is South-east Asian, BRIT is British. The αα deletion removes the genes and is of no clinical importance. The shaded regions represent deleted DNA. The hatched regions indicate uncertainty about the full length of the deletions

THALASSEMIA SYNDROMES – COMPARATIVE DATA ON LABORATORY FINDINGS

Syndrome	Case	Age	Sex	RBC $10^6/mm^3$	Hb gm %	MCV μ^3	MCHC %	Retic. %	Fragility	Target cells %	Serum iron μg %	Foetal Hb %	Electrophoretic pattern
Thal + Hb S	DJT	4¾	M	4·70	11·5	68	36	2·8	8·9	+ +		15·6	S + F
	NrPZ	4	M	2·41	7·0	83	35	9·2	31·7	+ +		24·5	S + F
	SoPZ	8	F	4·87	11·0	62	36	4·6	32·0	+ +		15·7	S + F
Thal + Hb E	JAR	7¼	F	2·90	5·7	76	27	11·0	21·6	+		35·0	E + F
	AAR	6	M	3·88	7·2	64	29	3·4	14·0	+++		38·0	E + F
	NAR	10	M	4·41	7·4	61	27	2·6	11·0	+++		32·0	E + F
Thal + Hb D	SDJ	34	M	6·48	13·0	65	31	3·4	5·0	+++	173	1·7	D
	JJT	25	F	5·68	7·2	50	26	2·2	13·0	+++	41	0·8	D
	NMT	16	M	6·33	13·3	70	31	2·0	9·0	+++	138	6·5	D
	MMT	11	F	5·21	10·2	65	30	2·8	9·0	+ +	129	3·4	D
Thal + High F	BIR	31	F	5·20	10·0	65	30	3·0	41·0	+ +	116	60·5	F
	CR	23	M	4·69	9·0	61	30	3·2	31·4	+ +	88	47·2	F
Thal + Hb J	MK	28	F	5·61	12·0	68	31	2·8	38·0	+	125	2·8	A + J

ALPHA-THALASSAEMIA (Hb. BART'S) IN INDIAN POPULATION

GROUP	NO. OF CORD BLOODS TESTED	Hb. BART'S (NUMBER)	REFERENCE
BENGALEE	100	4	SWARUP ET AL (1965)
BOMBAY (MIXED GROUP)	438	9	CHOUHAN ET AL (1970)
BOMBAY (MIXED GROUP)	219	2	SUKUMARAN & MASTER (1974)
BOMBAY (MIXED GROUP)	240	1	VORA ET AL (1975)

WALFORD ET AL (1976) REPORTED ALPHA$_1$ - THALASSAEMIA IN GUJARATI INDIANS

HAEMATOLOGICAL DATA

	CONTROLS	SICKLE CELL THALASSAEMIA	Hb. D-THALASSAEMIA	Hb. E-THALASSAEMIA	H.P.Hb.F-THALASSAEMIA	H.P.Hb.F-TRAIT
Hb. (g/100 ml.)						
MALES	14·4 ± 0·14 (50)	8·1 ± 0·29 (13)	10·6 (9)	7·0 (6)	7·7 (4)	13·4 (5)
FEMALES	12·5 ± 0·18 (40)					
R.B.C. (10^6/Cu.mm.)						
MALES	4·97 ± 0·04 (50)	3·74 ± 0·56 (13)	5·52 (9)	3·79 (6)	4·25 (4)	4·80 (5)
FEMALES	4·48 ± 0·06 (40)					
P.C.V. (%)						
MALES	45·0 ± 0·40 (50)	26·5 ± 1·23 (13)	35·2 (9)	24·3 (6)	27·8 (4)	41·4 (5)
FEMALES	39·7 ± 0·39 (40)					
RETICULOCYTES (%)						
MALES	0·6 ± 0·06 (50)	9·2 ± 2·08 (13)	1·9 (9)	6·9 (6)	4·1 (4)	0·9 (5)
FEMALES	0·6 ± 0·07 (40)					
OSMOTIC FRAGILITY (% HAEMOLYSIS IN 0·4% TYRODE)	91·0 ± 0·46 (90)	25·3 ± 4·88 (13)	10·3 (9)	19·7 (6)	44·0 (4)	84·8 (5)
ALKALI-RESISTANT HAEMOGLOBIN (%)	0·92 ± 0·03 (90)	17·3 ± 1·80 (13)	2·46 (9)	33·6 (6)	61·1 (4)	25·5 (5)

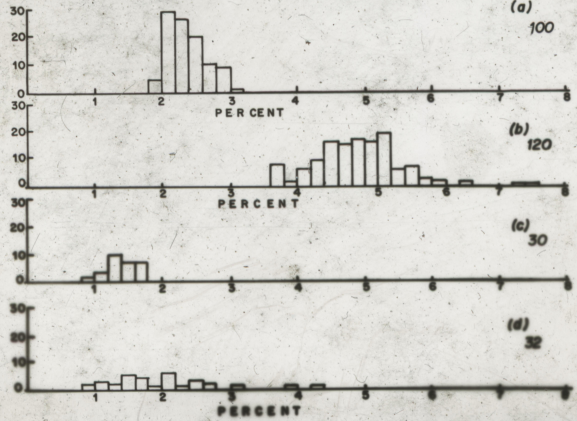
FIGURES ARE MEANS ± S.E., WITH NUMBER EXAMINED IN PARENTHESES

The β thalassaemias

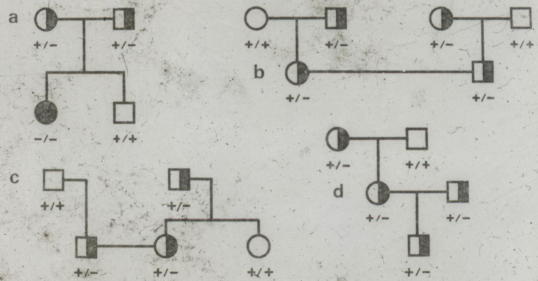
Type of thalassaemia	Homozygote	Heterozygote	Molecular defect
β^+ Thal	Cooley's anaemia; Hb A + Hb F + Hb A_2	Thal. minor	Reduced β-chain mRNA; cause unknown
β^+ Thal (Negro)	Thal. intermedia; Hb A + Hb F + Hb A_2	Thal. minor; raised Hb A_2	No data
β^+ Thal (High F)	Thal. intermedia; Hb A + Hb F + Hb A_2	Thal. minor; 5–12% Hb F; raised Hb A_2	No data
β^0 Thal	Cooley's anaemia; Hb F + Hb A_2	Thal. minor; raised Hb A_2	Absent β-chain mRNA*; β-chain genes present
β^0 Thal (Ferrara)	Cooley's anaemia; Hb F + Hb A_2	Not described in detail	β-Chain mRNA present*; ?β-chain synthesis inducible
$\delta\beta^0$ Thal	Cooley's anaemia; Hb F only	Thal. minor; 5–15% Hb F; Hb A_2 normal	Absent β- and δ-chain mRNA; β genes deleted
$\delta\beta^+$ Thal (silent)	Not described	Minimal blood changes; normal Hb F and Hb A_2	No data
(δβ) Lepore	Cooley's anaemia; Hb F + Hb Lepore	Thal. minor; Hb A + Hb Lepore + Hb A_2	δβ-Fusion gene; differing points of crossing-over produce distinct variants, i.e., Hb Lepore (Washington, Hollandia, Baltimore); ?unstable δβ-chain mRNA
Excess α-chain	Not described	Thal. intermedia + inclusion bodies; raised Hb A_2	No data
Hb K Woolwich	Not described	Thal. minor; Hb A + Hb K; raised Hb A_2	Inefficiently synthesized β-chain variant

* There is further heterogeneity among the β^0 thalassaemias. In some cases there appears to be β-chain mRNA present which is not inducible (Kan *et al.* 1975c)

HAEMOGLOBIN A_2 LEVELS IN (a) NORMAL; (b) β-THALASSAEMIA TRAIT; (c) IRON DEFICIENCY ANAMIA; (d) β-THALASSAEMIA MAJOR- BEFORE BLOOD TRANSFUSION



XAMPLES OF FAMILY STUDIES WHICH ALLOW ASSIGNMENT OF LINKAGE OF DNA POLYMORPHISMS TO β-THALASSEMIA



RESTRICTION ENDONUCLEASE DATA ON INDIAN DELTA-BETA THALASSEMIA FOLLOWING HYBRIDIZATION TO GAMMA IVS II PROBE*

Enzymes	Normal DNA	Indian δ B Thalassemia
Bam HI	4·9; 15·4	4·9; 15·4
Bcl II	17·2	15; 17·2
Bgl II	12·9	10·5; 12·5
Eco RI	2·6; 7·0	2·6; 7·0
Hind HI	3·3; 6·8	3·3; 6·8
Pst	0·8; 4·0; 4·9	0·8; 4·0; 4·9
Xba I	3·2; 4·9; 7·4	7·4; 3·2; 4·9; 7·4
XmnI	7·0	7·0

* FROM AUGUSTA GROUP

(A) Annual itemized* costs ($US) of treating a patient with thalassaemia major at University College Hospital, London, in 1982

Basic Hospital Care :	
Admissions (12 per year at $169/24 h)	2 028
Out-patient visit (12 per year at $65)	780
Blood: mean = 26·4 U prepared blood (500ml) at a final average cost of $43·3 per unit	1 143
Investigations (X-ray, ECG, biochemistry etc): average	128
Total	4 079
Desferrioxamine ($6 per g)	
Subcutaneous infusion, 40mg for kg per day average = 534g per year	3 204
Extension tubes etc. $0·9 each	230
Total	3 434
Total Annual Cost (average)	7 513
Non-recurrent	
Splenectomy, 12 hospital days	2 030
Portable syringe pump	266
Total	2 296

(B) Cumulative cost of treating one patient with thalassaemia major in the UK (1982)

	Hospital care	Desferal s.c. plus hospital care
Average per year	4 079	7 513
Total for 20 years	81 580	150 260

*Some costs increase with the age (and size) of the patient, for example blood transfusion and Desferal, while others such as hospital admissions remain constant. No allowance has been made here for visits to a general practitioner or for visits of a district nurse to the home. This estimate also excludes costs to the family of time off work, time spent travelling to and from hospital, etc.

From WHO Working Group, 1983, with permission

Feasibility of prenatal diagnosis in thalassaemia major patients: total 37 families

	Full diagnosis	50% diagnosis	Diagnosis not possible	Total
Del/del	7 (19%)	—	—	7
Single oligoprobe	24 (65%)	2 (5%)	—	26
Two oligoprobes	4 (11%)	—	—	4
Total	35 (95%)	2 (5%)	—	37


GEOGRAPHIC DISTRIBUTION OF Hb-S, Hb-Dβ PUNJAB, Hb-E,
BETA- AND ALPHA-THALASSEMIA
S
Dβ PUNJAB
E
β-THALASSEMIA
EVIDENCE FOR α-THALASSEMIA

DIAGNOSIS OF HAEMOGLOBINOPATHIES

BY FETAL DNA ANALYSIS

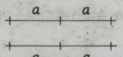
1) GENE DELETIONS
   1) α^{+}-thalassaemia
   2) α^{0}-thalassaemia
   3) β^{0}-thalassaemia in Asian Indians
   4) Hb Lepore thalassaemia

2) ALTERED RESTRICTION SITE
   1) Hb S
   2) β-thalassaemia (6/35)

3) RFLP LINKAGE ANALYSIS
   1) β-thalassaemia
   2) Hb E

4) OLIGONUCLEOTIDE HYBRIDISATION
   1) β-thalassaemia - most types

α THALASSEMIA GENOTYPES



NORMAL

"Classical" α Thalassemia

α $Thal_2$ Trait
("Mild" Trait, Silent Carrier)

α $Thal_1$ Trait
("Severe" α Thal Trait)

Hemoglobin H Disease

Hb Barts-Hydrops Fetalis

α Thalassemia with Hb Constant Springs

Heterozygous Hb CS
(Resembles α $Thal_2$)

~1% Hb CS

Homozygous Hb CS
(Resembles α $Thal_1$)

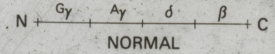
~5% Hb CS

Hb H Disease
with Hb CS

2-3% Hb CS
10-15% Hb H

Hydrops Fetalis Not
Observed with α^{CS}

β THALASSEMIA AND RELATED GENOTYPES



NORMAL

Syndrome	Genotype	Phenotypic Expression
β^+ Thalassemia	N — Gγ — Aγ — δ — βT^+ — C	βmRNA = 5-30% Normal βglobin = 5-30% Normal
β^o Thalassemia	N — Gγ — Aγ — δ — βT^o — C	βmRNA = 0-30% Normal βglobin Absent
δβ Thalassemia	N — Gγ — Aγ — ---- — C	γ/α << 1; Thal Intermedia
Hereditary Persistence Hb F ($G\gamma$ Type)	N — Gγ — ---- — C	γ/α = 0.5-1; Normal Phenotype
HP HF with $G\gamma$ and $A\gamma$ (Postulated)	N — Gγ — Aγ — ---- — C	Normal Phenotype
Hb Lepore	N — Gγ — Aγ — (δβ) — C	Resembles β^o Thalassemia (δβ)mRNA = 2-10% of αmRNA
Anti-Lepore Hbs	N — Gγ — Aγ — δ — (βδ) — β — C	Non Thalassemic Phenotype
Hb Kenya	N — Gγ — (γβ) — C	Resembles HP HF, $G\gamma$ Type

DIFFERENCES BETWEEN "AFRICAN" AND
"MEDITERRANEAN" BETA - THALASSAEMIA

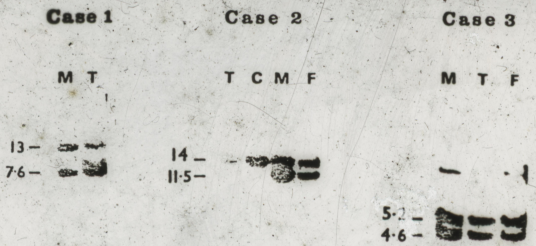
	"African"	"Mediterranean"
Race	Africans, mainly W.Africans	Caucasians, Asians
Clinical course	Homozygotes: mild or intermediate, occasionally thalassaemia major	Homozygotes: thalassaemia major. Occasionally intermediate
Haemoglobin A_2	In homozygotes high Mean 5.0%	In homozygotes not very high. Mean 3.2%
Haemoglobin F	In homozygotes not high. Mean 45%	In homozygotes high. Mean 73%
Imbalance in chain production ($\beta : \alpha$)	More than half of heterozygotes have higher ratios Mean 0.84%	Heterozygotes have lower ratios Mean 0.57%
Linkage	Beta thal and delta structural genes are linked	?

Table IV

Association of β-haplotypes and β-thalassemia mutations: total 102 chromosomes

β-haplotype*	Mutation											Unknown	Total
	600 bp del	FI/S 8	βº15	F/S 16	IVS-1 nt1	IVS-1 nt5	FI/S 41/42	−88 C→T	CAP +1				
+ − − − − ++		14	2			1	2						19
− + − ++ ++		5			14		1						20
− + + − ++		1											1
+ − − − − +D	21												21
+ − − − − − +						12			2				14
+ − + + − +			3										3
− + + − +						8							8
− + − − − +						1						1	2
+ − + − +						1							1
+ − − − − + −				1			8	2					11
− + − ++ + −							1					1	1
+ + − ++ + −													1
Total	21 (21·6%)	20 (19·6%)	5 (4·9%)	1 (0·9%)	14 (13·7%)	23 (22·5%)	12 (11·8%)	2 (1·9%)	2 (1·9%)	2 (1·9%)	102 (1·9%)		

* β-haplotype refers to the different arrangements of the seven common polymorphic restriction enzyme sites in the β globin cluster: Hind II-ε, Hind III-$^{G}\gamma$, Hind III-$^{A}\gamma$, Hind II-ψβ, Hind II-3′ ψβ, Acc II-β, and Bam HI-β. It is frequently divided into the 5′ β haplotype which includes the first five polymorphic sites and the 3′ β haplotype also referred to as the β gene framework, which includes the Acc II-β and Bam HI-β sites.



Results of restriction enzyme mapping of trophoblast DNA

DNAs from trophoblast (T), Father (F), Mother (M) and a previously born child with β-thalassaemia major (C) were digested with the restriction enzymes shown and hybridised to a β-globin gene in cases 1 and 3, ψβ-globin gene probe in case 2. Fragments are in kilobase pairs.

TABLE I. The thalassaemia syndromes

Type of thalassaemia	Homozygous state	Heterozygous state
β-Thalassaemia (with haemoglobin A production)	Severe anaemia; high level of haemoglobin F	Increased level of haemoglobin A_2
β-Thalassaemia (with no haemoglobin A production)	evere anaemia; haemoglobin consists of F and A_2 only	As above
β-Thalassaemia (with no haemoglobin A production) *	ɔderate anaemia; haemoglobin consists of F and A_2 only	Increased level of haemoglobin A_2 and high levels of haemoglobin F (5–15% range)
β-δ-Thalassaemia	Severe anaemia; haemoglobin consists of F only	Haemoglobin F in 5–20% range; normal levels of haemoglobin A_2
Haemoglobin Lepore thalassaemia	Severe anaemia; haemoglobin consists of Lepore and F	Normal levels of haemoglobin A_2; haemoglobins F and Lepore present
β-Thalassaemia with β-chain haemoglobin variants	Clinical severity depends on level of haemoglobin A, and proportion of haemoglobin variant. In some cases no haemoglobin A is produced. Most important are S thalassaemia, C thalassaemia and E thalassaemia	
α-Thalassaemia 1 †	Death in utero; haemoglobin consists mainly of Bart's	Difficult to detect in adults; haemoglobin Bart's in 5–10% range in infancy
α-Tha emia 2 †	Not yet recognized	Not detectable in adults; slight elevation of haemoglobin Bart's in infancy
Haem globin H disease	—	Probably heterozygous for α-thalassaemia 1 and 2
α-Thalassaemia 1 and 2 with haemoglobin E	—	Severe anaemia; haemoglobins Bart's, F, E and A present
δ-Thalassaemia	—	Reduced haemoglobin A_2 levels
Thalassaemia-like states	Normal levels of haemoglobin A_2 and F, with clinical picture of thalassaemia	

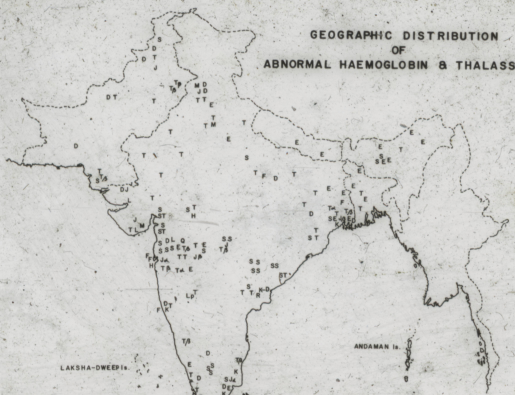
* Probably a distinct form of β-thalassaemia with more haemoglobin F synthesis than in typical β-thalassaemia (see Schokker, Went & Bok (1966))

† May represent different genetic disorders in different populations

Table 6.20. Possible molecular sub-types of β thalassaemia.

1	β^+ thalassaemia β^0 thalassaemia	? Processing defect	Nienhuis *et al.*, 1977a
2	No β mRNA; no β HnRNA	? Transcriptional defect	Comi *et al.*, 1977
3	No β mRNA; β HnRNA present	? Processing defect	Comi *et al.*, 1977
4	Abnormal β mRNA	Defective at 3′ end	Old *et al.*, 1978
5	Full length β mRNA	? Defective initiation site	Old *et al.*, 1978
6	Full length β mRNA	Chain terminator at β17	Chang and Kan, 1979
7	Full length β mRNA (not translated in cell, active in cell-free system)	? Soluble inhibitor of initiation	Conconi *et al.*, 1972
8	Partial β gene deletion	600-bp deletion at 3′ end of gene	Orkin *et al.*, 1979b Flavell *et al.*, 1979

GEOGRAPHIC DISTRIBUTION OF ABNORMAL HAEMOGLOBIN & THALASSEMIA



MATERNAL COMPLICATIONS IN SICKLE CELL ANAEMIA OR SICKLE CELL-THALASSAEMIA

TOXEMIA

JOINT AND BONE PAINS

ANAEMIA

JAUNDICE

CARDIOMEGALY

URINARY TRACT INFECTIONS

PYELONEPHRITIS

HEMATURIA

PULMONARY INFARCTION

POSTPARTUM SEPSIS

PNEUMONIA

PHLEBITIS

ENDOMETRITIS

POSTPARTUM HAEMORRHAGE

ABORTION

FOETAL DEATH

MATERNAL DEATH

GEOGRAPHIC DISTRIBUTION OF ABNORMAL HAEMOGLOBINS & THALASSEMIAS

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PAKISTAN

SOUTH	Hb-S (1.3%)
NORTH WEST	Hb-S RARE
" "	Hb-D RARE
" "	Hb-J RARE

SOUTH	BETA THAL (PRESENT)
EAST	" " "
NORTH	" " "
NORTH WEST	" " "
CENTRAL	" " "

BANGLADESH

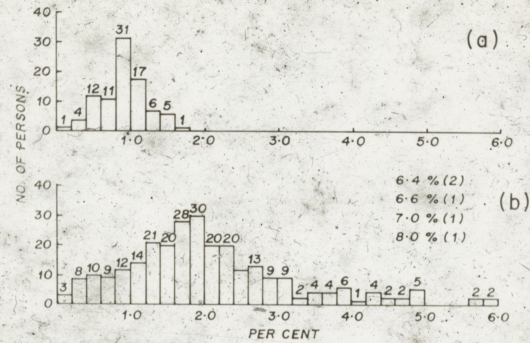
HEMOGLOBIN E (8.7%)
BETA THAL (PRESENT)

SRI LANKA

NORTH	Hb-E (15%)
CENTRAL	" (13-30%)
CENTRAL BETA THAL	PRESENT
W. CENTRAL BETA THAL	PRESENT
ALPHA THAL	OCCASIONAL
Hb-S	OCCASIONAL
Hb-D	RARE

MALADIVE I

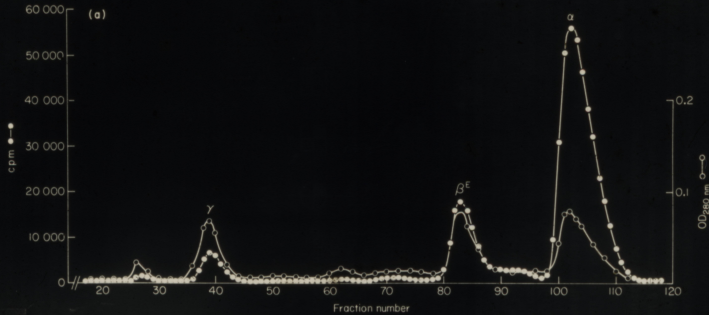
HAEMOGLOBIN-S	PRESENT
HAEMOGLOBIN-E	PRESENT
BETA THAL	PRESENT



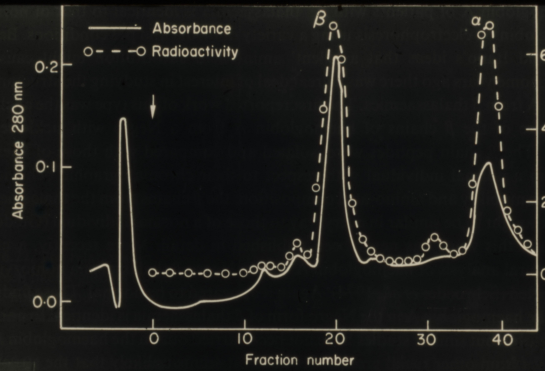
ALKALI-RESISTANT HAEMOGLOBIN PER CENT (MALES AND FEMALES, AGED 3 YRS AND OVER). (a) NORMALS (b) β-THALASSAEMIA TRAIT. INDIVIDUALS WITH >6·0 %. NUMBERS IN PARENTHESIS.

MUTATIONS IN BETA THALASSEMIA IN INDIANS

MUTANT CLASS		TYPE	
NONFUNCTION mRNA			
NONSENSE MUTANTS			
CODON 15 (G - A)	... ...	β^0	
FRAMESHIFT MUTANTS			
-1 CODONS 8,9	... ...	β^0	
-1 CODON 16	... ...	β^0	
-4 CODON 41,42	... ...	β^0	
RNA PROCESSING MUTANTS			
SPLICE-JUNCTION CHANGES			
IVS-1 POSITION 1 (G - T)	...	β^0	
IVS-1 3'-END - 25 BASE PAIRS	...	β^0	
INTERNAL CHANGES IN CODING REGION			
CODON 26 (G - A)	... ...	β^E	SOUTHEAST ASIAN



Haemoglobin synthesis in haemoglobin E thalassaemia. Reticulocytes were incubated with [^{14}C]leucine for 1 h, the cells were washed and globin was prepared from a total cell lysate. The globin chains were separated by CM-cellulose chromatography in 8M urea and the radioactivity incorporated into each chain determined. The profiles show: (a) β^0 thalassaemia with no β chain synthesis; (b) (facing page) β^+ thalassaemia in which there is a small amount of β chain synthesis in the reticulocytes.

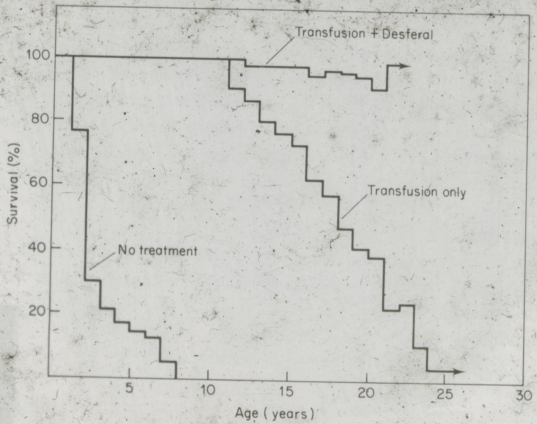


Globin chain synthesis in non-thalassaemic reticulocytes. The reticulocytes are incubated with radioactive leucine for 1 h and then the globin chains separated by column chromatography. The amount of radioactivity incorporated into the α and β chains (broken line) is approximately equal, indicating that during the period of the experiment almost equal numbers of α and β chains were synthesised.

Some characteristic findings in the β or $\delta\beta$ thalassaemias and their interaction with β chain haemoglobin variants.

Thaiassaemia type	Homozygote	Heterozygote
β^0	Thal. major Hb F 98%; Hb A_2 2%	Thal. minor Hb A_2 3·5–7·0% α/β 2·0
β^+ (Mediterranean)	Thal. major Hb F 70–95%	Thal. minor Hb A_2 3·5–7·0% α/β 2·0
β^+ (Negro)	Thal. intermedia Hb F 20–40%; Hb A_2 2·2–5%	Thal. minor Hb A_2 3·5–7·0% α/β 1·2–2·0
β^+ (Normal Hb A_2 'Silent') β^+ or β^0 (Normal Hb A_2)	Mild thal. intermedia 10–30% Hb F; 5% Hb A_2 —	Normal α/β 1·2–1·5 Thal. minor Hb A_2 normal α/β 2·0
$^GA\gamma$ $\delta\beta$	Thal. intermedia 100% Hb F	Thal. minor Hb F 5–20%; Hb A_2 1·5–2% α/non-α 1·3–1·8
$^G\gamma$ $\delta\beta$ $\delta\beta$ Lepore	As above Thal. major 80% Hb F; 20% Hb Lepore	As above Thal. minor Hb Lepore 8–20%
$^GA\gamma$ HPFH	Thal. minor 100% Hb F	Normal blood picture 15–30% Hb F; 1·5–2% Hb A_2

Interaction	Compound heterozygote
Hb S β^+ (Negro)	Thal. minor 65% Hb S; 25% Hb A; 5% Hb A_2; 5% Hb F
Hb S β^+ (Mediterranean)	Sickle-cell anaemia 80% Hb S; 10% Hb A; 5% Hb A_2; 5% Hb F
Hb S β^0	Sickle-cell anaemia 85% Hb S; 10% Hb F; 5% Hb A_2
Hb E β^0	Thal. major or intermedia 60–70% Hb E; 30–40% Hb F



Survival in thalassaemia in relation to treatment. The left-hand curve gives the survival of untreated children with Ferrara β⁰-thalassaemia; the middle curve, of high-transfused unchelated patients in England, and the top curve, high-transfused chelated patients in England.

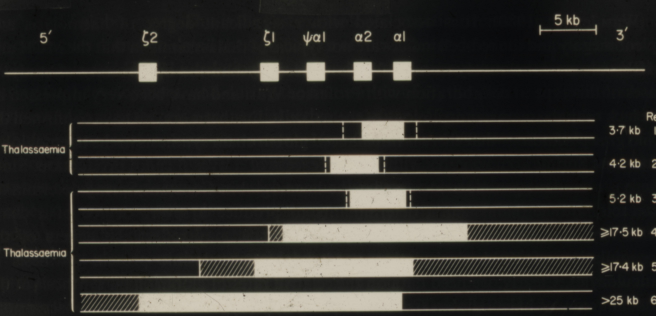
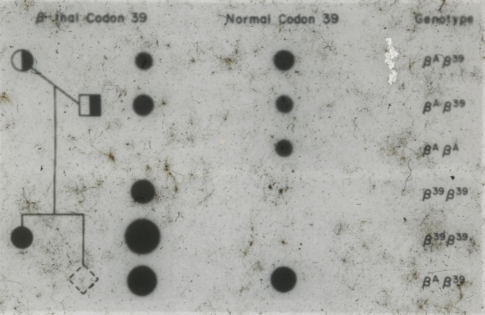


Fig. 15.2. Deletions in the various α thalassaemia haplotypes with the phenotype of α^+ and α^0 thalassaemia: 1 Orkin (1978); 2 Embury *et al.* (1979); 3 Pressley *et al.* (1980b); 4 and 5 Pressley *et al.* (1980a); 6 Orkin and Michelson (1980). In the case of the 3·7, 4·2 and 5·2 kb deletions the black areas represent the amount of DNA that has been deleted from within the area defined by the vertical dotted lines. In the other three cases areas known to be deleted are shown in black; where the limits of the deletion are not defined their maximum extremes are indicated by hatched areas.

The sizes of gene fragments identified in restriction endonuclease digests of DNA from the father of the propositus (FM) and from a normal control.

Type of Probe	Enzyme	FM	Control
Gγ IVS-II	Bgl II	12.8; 7.7	12.8
	Bcl I	20; 15	20
	Eco RI	7.2; 2.7	7.2; 2.7
	Bam HI	15.5; 5.0	15.5; 5.0
	Xba I	7.5; 5.0; 3.7	7.5; 5.0; 3.7
	Bgl I	5.0; 3.1	5.0; 3.1
	Hind III	7.5; 6.9; 3.4	7.5; 3.4
γδ 1.6 BX	Bam HI	15.5	15.5
	Xba I	7.5	7.5
	Bgl II	4.2	4.2
δ IVS-II	Bam HI	4.5	4.5
	Xba I	10.8	10.8
	Bgl II	7.7	7.7
β IVS-II	Eco RI	5.4	5.4
	Bam HI	8.3	8.3
	Xba I	10.8	10.8
	Bgl II	5.2	5.2

Figure 2. DNA fragments obtained with three restriction endonucleases as listed, and the G_γIVS-II probe. FM is the heterozygous father of a homozygous newborn; N is a normal control.



Dot blot showing the use of ASO probes on amplified β-globin DNA for prenatal diagnosis of β-thalassemia. Both parents in the pedigree at the left carry the nonsense codon 39 mutation as demonstrated by hybridization of their amplified DNAs to the mutant ASO. Control samples, essential for monitoring the specificity of the wash, are in the third and fourth dots from the top and represent amplified DNA from individuals homozygous for normal β-globin alleles and homozygous for the nonsense codon 39 β-thalassemia allele, respectively. Amplified DNA from this couple's affected child hybridizes to mutant ASO only and from the fetus to both the mutant and normal ASOs, which demonstrates that the fetus is a carrier of β-thalassemia.

HAEMATOLOGICAL DATA ON SUBJECTS
BETA THALASSAEMIA TRAIT

SUBJECTS	AGE (wks)	Hb (gm%)	FRAGILITY (%)*	Hb-A_2 (%)	Hb-F (%)	ELECTROPHORETIC PATTERN
S.L.	BIRTH	10.4	80.0	-	61.5	F+A
	54	9.3	60.6	3.80	2.1	A
S.T.	BIRTH	-	64.0	-	83.5	F+A
	52	8.4	29.3	4.24	6.3	A
H.K.	BIRTH	-	-	-	58.0	F+A
	30	9.0	70.0	3.4	9.0	A
S.M.	BIRTH	-	65.0	-	77.5	F+A
	13	8.7	56.0	3.2	24.3	A+F
P.T.**	BIRTH	-	-	-	88.5	F+A
	28	10.1	50.0	4.61	7.7	A+F

* PERCENTAGE HAEMOLYSIS IN 0.4 OILUTION OF TYRODE (NORMAL : 80-100%)

** MALE CHILD (G-6-PD : DEFICIENT)

INCIDENCE OF BETA-THALASSAEMIA TRAIT

OF SOME INDIAN POPULATION.

GROUPS	NO TESTED	BETA-THALASSAEMIA TRAIT PERCENT	REFERENCES
1. SIKH (Vancouver)	80	6.3	SIDDU ET AL (1956)
2. BENGALI (Calcutta)	100	3.7	CHATTERJEE ET AL (1957)
3. COCHIN JEWS (Israel)	66	15.2	RAMOT ET AL (1964)
4. BN&I JEWS (Israel)	172	13.9	- " -
5. CUTCHI BHANUSHALI (Bombay)	296	14.9	MEHTA ET AL (1972)
6. MIXED GROUP (Trivandrum)	1000	0.6	PILLAY & K.DAS (1972)
7. G.S. BRAHMAN (Mangalore)	113	0.9	SHANBAUGH & BHATIA (1974)
8. - " - (Bombay)	154	2.6	- " -
9. CHITPUR SARASWAT (Bombay)	202	5.9	- " -
10. GOAN CATHOLIC BRAHMIN (Bombay)	118	4.3	- " -
11. CUTCHI LOHANA (Bombay)	121	10.7	- " -
12. HALAI LOHANA (")	116	17.2	- " -
13. SINDHI LOHANA (")	33	6.2	- " -
14. PANJABI KHATRI (")	194	5.2	- " -
15. MIXED SINDHI (")	70	7.1	- " -
16. SINDHI (Ulhasnagar, Thana)	82	12.4	SUKUMARAN & MASTER (1974)
17. VARLI	134	2.3	JOSHI ET AL (1975)
18. DHODIA	80	3.0	- " -
19. KOKANAS	84	3.6	- " -

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Gamma thalassemia resulting from the deletion of a γ-globin gene

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Population Specificity of β-Thalassemia Mutations

Ethnic Group	Number of Alleles
Mediterranean	15 (6 account for 92% of genes)
Chinese/SE Asian	9 (4 account for 91% of genes)
Asian Indian	10 (5 account for 90% of genes)
Black	9
N African/Middle Eastern	12 plus Mediterranean alleles and 1 Asian Indian allelle

Spectrum of β-Thalassemia Mutations in Mediterranean Peoples

Mutation	Ethnic Group			
	Greeks/Italians[31]	Sicilians[37]	Turks[72]	Spanish[73]
IVS-1 nt 110	53	26	40	5
Nonsense codon 39	44	35	2	37
IVS-1 nt 6	17	28	22	9
IVS-1 nt 1 (G-A)	15	3	4	2
IVS-2 nt 1	12		8	
Frameshift 6	3			
Frameshift 8	1		13	1
IVS-2 nt 745	9	3	1	
IVS-2 nt 705				1
-87	2	1	2	
IVS-1 nt 5 (G-T)	2		2	
Frameshift 76		1		
Total no. surveyed	158*	97	94	58

*Four other genes in the initial survey[71] were not available for reanalysis.

HISTORICAL PERSPECTIVE

1925 - 1940: FIRST DESCRIPTIONS OF THE CLINICAL FEATURES OF HOMOZYGOUS & HETEROZYGOUS STATES FOR DIFFERENT TYPES.

1940 - 1950: TRUE GENETIC BASIS OF THE DISORDER AND CLEAR PICTURE OF INHERITANCE

1960 - : "THALASSAEMIA" A DIVERSE GROUP OF DISORDERS RESULTING FROM ABNORMALITIES OF HAEMOGLOBIN SYNTHESIS; BIOCHEMICAL NATURE OF SOME OF THESE DISORDERS PINPOINTED AT MOLECULAR (GENE) LEVEL.

British Journal of Haematology, 1984, 57, 663–670

Restriction endonuclease gene mapping studies of an Indian $(^{A}\gamma\delta\beta)^{0}$-thalassaemia, previously identified as $^{G}\gamma$-HPFH

T. NAKATSUJI, J. G. GILMAN, P. K. SUKUMARAN* AND T. H. J. HUISMAN
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MANAGEMENT

PROPER MANAGEMENT AIMED FOR PROLONGING AND IMPROVING LIFE, EVEN THOUGH SPECIFIC TREATMENT IS NOT AVAILABLE.

THALASSAEMIA

1. IMPROVED MANAGEMENT OF INFECTION AND HEALTH CARE. SUPPLEMENT INCREASED NUTRITIONAL REQUIREMENTS.
2. THALASSAEMIA PATIENTS UNLIKE SICKLE CELL PATIENTS, CANNOT MAINTAIN NORMAL Hb LEVELS FOR SURVIVAL AND DEVELOPMENT - REQUIRE LIFE LONG BLOOD TRANSFUSIONS.
3. IRON OVERLOADING DUE TO REPEATED BLOOD TRANSFUSIONS TO BE CONTROLLED BY IRON CHELATORS.

   DESFERRIOXAMINE (DF) - PARENTERAL, ORAL Vit.C

   2,3 - DIHYDROXYBENZOIC ACID (DHBA) - ORAL (UNDER TRIAL)

Some possible causes of 'β thalassaemia with normal haemoglobin A_2 levels'.

With normal or minimal haematological changes.
- Additional α chain genes†
- Anti-Lepore genes in *cis* position*
- Other mild defects in β chain production

With haematological changes of β thalassaemia
- β Thalassaemia + δ thalassaemia*
- Hb Lepore variants with same charge as Hb A
- $\gamma\delta\beta$ Thalassaemia*
- ?Other $\delta\beta$ thalassaemias in which γ chain synthesis is not augmented

β Thalassaemia with acquired disorders
- β thalassaemia with iron deficiency anaemia*

---

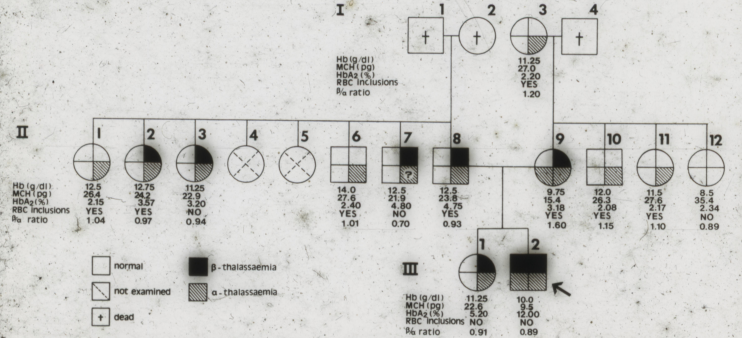
* Have already been observed.

† Observed but not shown to interact with β thalassaemia.

The α thalassaemias

Type of thalassaemia	Homozygote	Heterozygote	Molecular defect
α Thal 1	Hb Bart's hydrops; 80% Hb Bart's	Thal. minor; 5–10% Hb Bart's at birth	Deletion of both α-chain genes
α Thal 2	Thal. minor; 5–10% Hb Bart's at birth	Thal. minor or silent; 1–2% Hb Bart's at birth	Deletion of one α-chain gene
Hb Constant Spring	Thal. minor; 5–6% Hb Constant Spring	Silent; 0.5–1% Hb Constant Spring; 1–2% Hb Bart's at birth	α-Chain-termination mutation: α142 Gln UAA→CAA
Hb Icaria	Not described	?Silent; 0.5–1% Hb Icaria	α-Chain-termination mutation: α142 Lys UAA→AAA
Hb Koya Dora	Not described	?Silent; 0.5–1% Hb Koya Dora	α-Chain-termination mutation: α142 Ser UAA→UCA
Hb Seal Rock	Not described	?Silent; 0.5–1% Hb Seal Rock	α-Chain-termination mutation: α142 Glu UAA→GAA

Of the potential α-chain-termination mutants four out of seven have been discovered. Of the remaining three, two (UAA→UAU or UAC-142 Tyr; UAA→UUA-142 Leu) would produce detectable variants, and one (UAA→UGA) would produce an alternative termination codon and hence Hb A (Weatherall & Clegg, 1975b; T. B. Bradley, personal communication)



Pedigree of the family of the propositus (indicated by an arrow).

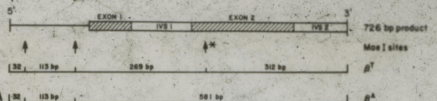
NONDELETION ALPHA THALASSEMIA MUTATIONS

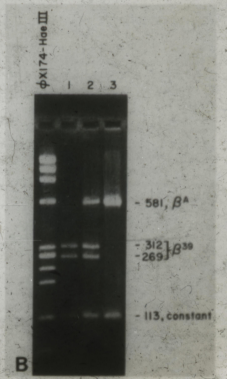
Class	Ethnic Group
1. RNA Processing Mutation −5 bp IVS-1 splice junction	Mediterranean
2. Nonfunctional RNA Initiator mutation (ATG–ACG)	Mediterranean
3. 3′-End processing defect AATAAA-AATAAG	Saudi Arabian
4. Unstable α globin Hb Quong Sze (codon 125)	Chinese
5. Chain-termination mutations Hb Constant Spring, Koya Dora, etc.	Southeast Asian and others

Spectrum of β-Thalassemia Mutations in Indians and Pakistanis

IVS-1 nt 5 (G-C)	23
619 bp deletion	21
Frameshift 8-9	20
IVS-1 nt 1 (G-T)	14
Frameshift 41-42	12
Nonsense codon 15	5
Frameshift 16	1
−88	2
Cap site	2
Uncharacterized	2
Total	102

Data from Thein et al.[74]





(A) *Mae*I map of a β-globin region 726-bp amplified DNA product that contains the sequence altered by the codon 39 β-thalassemia mutation. The 5′ and 3′ end points of amplified product are determined by the two primers used in the amplication reaction. Arrows represent *Mae*I sites, and the arrow with an asterisk represents the *Mae*I site created by the codon 39 mutation.[19] (B) Distinguishing codon 39 β-thalassemia allele by EtBr staining after *Mae*I digestion of amplified DNA. Ethidium bromide stain of *Mae*I-digested, amplified DNA product from (*a*) an individual homozygous for the nonsense codon 39 β-thalassemia allele, (*b*) an individual with β-thalassemia in whom one allele is of the nonsense codon 39 type, and (*c*) an individual with normal β-globin alleles. Staining is carried out after electrophoresis in a 3% Nu-Sieve agarose, 1% agarose minigel.

MOLECULAR LESIONS IN THALASSAEMIA

I. GENE DELETION

A. CLASSIC FORMS OF ALPHA THALASSAEMIA

B. DELTA-BETA THALASSAEMIA

II. GENE REARRANGEMENT - STRUCTURALLY ABNORMAL GLOBINS

A. LEPORE - UNEQUAL CROSSOVER GIVES DELTA-BETA FUSION GENE

B. ELONGATED ALPHA GLOBINS ; MUTATION IN TERMINATOR CODON ; ELONGATED GLOBIN PRODUCED AT VERY LOW RATE

III. ABNORMAL mRNA SYNTHESIS OR METABOLISM

β^+ THALASSAEMIA - QUANTITATIVE DEFICIENCY OF β - GLOBIN mRNA ; A SMALL AMOUNT OF NORMAL BETA GLOBIN IS PRODUCED.

IV. IMPAIRED mRNA TRANSLATION

β° THALASSAEMIA - BETA mRNA PRESENT IN LOW AMOUNTS (0-30%) ; NO BETA GLOBIN IS PRODUCED

HAEMATOLOGICAL DATA

	CONTROLS	β-THALASSAEMIA TRAIT	THALASSAEMIA MAJOR
HAEMOGLOBIN (g/100 ml)			
MALES	14·4 ± 0·14 (50)	12·5 ± 0·06 (135)	4·7 ± 0·30 (72)
FEMALES	12·5 ± 0·18 (40)	10·3 ± 0·07 (148)	4·4 ± 0·10 (50)
RED BLOOD CELLS (10^6/c mm)			
MALES	4·97 ± 0·04 (50)	5·80 ± 0·14	25 ± 0·17 (72)
FEMALES	4·48 ± 0·06 (40)	5·13 ± 0·13 (	2·19 ± 0·24 (50)
PACKED CELLS VOLUME (%)			
MALES	45·0 ± 0·40 (50)	41·8 ± 0·37 (135)	16·8 ± 0·68 (72)
FEMALES	39·7 ± 0·39 (40)	35·8 ± 0·31 (148)	15·6 ± 0·79 (50)
RETICULOCYTES (%)			
MALES	0·6 ± 0·06 (50)	1·40 ± 0·07 (135)	6·3 ± 0·44 (72)
FEMALES	0·6 ± 0·07 (40)	1·40 ± 0·06 (148)	6·6 ± 0·54 (50)
OSMOTIC FRAGILITY (% HAEMOLYSIS IN 0·4% TYRODE)	91·0 ± 0·48 (90)	34·7 ± 1·09 (283)	44·4 ± 1·67 (122)
ALKALI-RESISTANT HAEMOGLOBIN (%)	0·92 ± 0·03 (90)	2·17 ± 0·08 (277)	61·2 ± 1·82 (122)

FIGURES ARE MEANS ± S.E., WITH NUMBER EXAMINED IN PARENTESES.

TROPHOBLAST SAMPLING AND PROGRESSION OF PREGNANCY IN SEVEN CASES

Case no.	Gestational age (wk)	Nucleic acid (μg obtained)	Continuation of pregnancy after sampling (days)	Outcome
1	8	56	2	Missed abortion at +2 days
2	11	50	4	Abortion for medical reasons*
3	7	55	4	
4	9	65	4	
5	11	37	20	Termination of pregnancy for thalassaemia major*
6	9	80	30+ continues	Diagnosis thalassaemia trait*
7	10	100	20	Termination of pregnancy for thalassaemia major*

*Normal progression of pregnancy.

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Restriction endonuclease gene mapping studies of an Indian ($^{A}\gamma\delta\beta$)°-thalassaemia, previously identified as $^{G}\gamma$-HPFH

T. NAKATSUJI, J. G. GILMAN, P. K. SUKUMARAN* AND T. H. J. HUISMAN
Department of Cell and Molecular Biology,† Medical College of Georgia, Augusta, U.S.A.

BONE MARROW TRANSPLANTATION IN THALASSAEMIA

BONE MARROW TRANSPLANTATION IS STILL A HIGH TECHNOLOGY PROCEDURE AND IS EXTREMELY EXPENSIVE. HOWEVER, AT PRESENT OTHER CONSTRAINTS BESIDES THOSE OF MONEY LIMIT THE NUMBER OF PATIENTS FOR WHOM THIS APPROACH IS APPROPRIATE. BECAUSE AN ALTERNATIVE TREATMENT IS AVAILABLE, TRANSPLANTATION SHOULD BE CARRIED OUT ONLY IN CENTRES WITH MAXIMUM EXPERIENCE OF TRANSPLANTATION IN CHILDREN AND SHOULD BE LIMITED TO PATIENTS IN WHOM MAXIMUM CHANCE OF SUCCESS WITHOUT GRAFT REJECTION OR FATAL COMPLICATION DUE TO BONE MARROW SUPPRESSION OR TO GRAFT-VERSUS-HOST DISEASE.

BASIC REQUIREMENTS ARE A CHILD AS YOUNG AS POSSIBLE, WITH A FULLY COMPATIBLE DONOR (USUALLY A SIBLING) WHO MAY OR MAY NOT CARRY THALASSAEMIA TRAIT, AND VERY FEW PREVIOUS BLOOD TRANSFUSIONS.

THALASSEMIA VARIANTS※

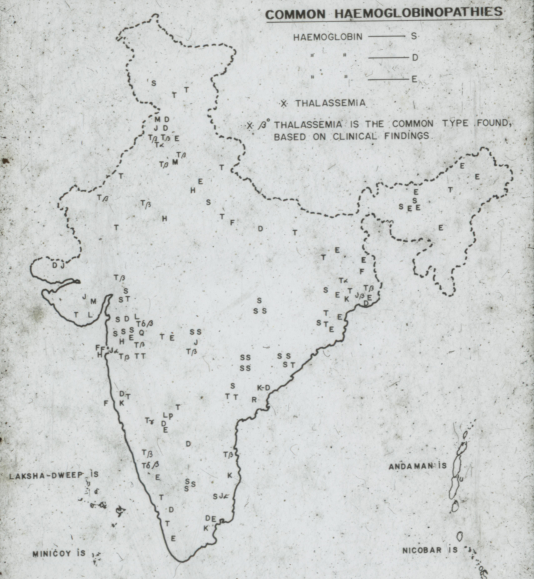
BETA GENE CLUSTER		ALPHA GENE CLUSTER
β°	THALASSEMIA	Hb - H DISEASE
β^{+}	THALASSEMIA	Hb - BART'S
$\delta\beta$ -	THALASSEMIA	Hb - S-H DISEASE
$\delta\beta$-β-	THALASSEMIA	
$\delta\beta$-HPFH	THALASSEMIA	HbS - α THALASSEMIA
HPFH-β-	THALASSEMIA	
γ -	THALASSEMIA	
HbS - β°	THALASSEMIA	
HbS - β^{+}	THALASSEMIA	
HbD - β	THALASSEMIA	
HbQ - β	THALASSEMIA	
HbJ - β	THALASSEMIA	
HbE - β	THALASSEMIA	

※ Seen in Bombay

LANDMARKS IN THE STUDY OF THALASSEMIA (INDIAN SCENE)

COOLEY'S ANAEMIA -MEDITERRANEAN ANAEMIA	MUKHERJI	(1938)
COOLEY'S ANAEMIA	NAPIER,LE ET AL	(1939)
	PAREKH,PJG ET AL	"
	PATEL,ND ET AL	"
	COELHO,G ET AL	"
HAEMOGLOBINOPATHIES,G6PD DEF ETC	CHATTERJEE	(1966)
THALASSEMIA SYNDROME IN BOMBAY	SUKUMARAN	(1967)
ALPHA THALASSEMIA IN INDIA- REVIEW	CHOUHAN ET AL	(1970)
HAEMATOLOGICAL AND GENETICAL CHARACTERISATION OF THALASSEMIA	MEHTA ET AL	(1971)
HB LEPORE IN AN INDIAN FAMILY	CHOUHAN ET AL	(1971)
MILD FORMS OF ALPHA THALASSEMIA IN INDIANS IN THE U.K.	WALFORD & DEACON	(1976)
GENE MAPPING STUDIES IN SOME INDIAN THALASSEMIA VARIANTS	SUKUMARAN ET AL COLLABORATIVE STUDY	(1983)
ANTENATAL DIAGNOSIS OF THALASSEMIA	PAYRI ET AL	(1988)
AMPLIFICATION REFRACTORY MUTATION SYSTEM (ARMS).RAPID DETECTION AND PRENATAL DIAGNOSIS.	OLD, VARAWALA & WEATHERALL	(1990)

GEOGRAPHIC DISTRIBUTION OF ABNORMAL HAEMOGLOBIN & THALASSEMIA



HAEMOGLOBIN-E (β26(B8) Glu-Lys)

Presentation

Homozygotes - Hb EE

Double Heterozygotes

Hb E - Thalassemia (both beta and alpha type)

Hb D-E disease

Hb D-E-HPFH disease

Haemoglobin E is mostly seen in Eastern part of India. Ranges from 3.6 to as high as 70%. Highest in Kachari and Khasi in Upper Assam. Seen also occassionally in other parts of India.

VIETNAM

NORTH	Hb.E	(2-5%)
CENTRAL	Hb.E	(2-3%)
SOUTH	Hb.E	(3-8%)
NORTH	BETATHAL	(3%)
SOUTH	BETATHAL	(8.2%)

LAOS

NORTH	Hb.E	(2-10%)
NORTH WEST	Hb.E	(20-27%)
WEST	Hb.E	(30-45%)
SOUTH WEST	Hb.E	(37-48%)
SOUTH	Hb.E.	(40%)
SOUTH EAST	Hb.E.	(23-40%)
SOUTH WEST	BETATHAL	(8.4%)
SOUTH WEST	ALPHA THAL	(31%)

DELTA / BETA THAL - RARE

CAMBODIA

NORTH EAST	Hb.E	(30-40%)
SOUTH	Hb.E	(0.5-29%)
CENTRAL	Hb.E	(6-45%)
SOUTH EAST	Hb.E	(22-32%)
SOUTH & SOUTH WEST	BETA THAL & ALPHA THAL	

HAEMOGLOBIN-J Birmingham/Meerut(α 120(H3)

(Ala-Glu)

Double Heterozygote

Hb J-Beta Thalassemia

Seen in a Gujarati family in Bombay.

HAEMOGLOBIN J Rajappan (α90(FG2) Lys-Thr)

HAEMOGLOBIN-J (Uncharacterized)

Presentation

Double Heterozygote

Hb J-Thalassemia

Seen in Gujarati Lohanas, Sindhi Lohanas about 2%. Reported from other parts of India (Nagpur). Hb-J, presumably beta-type with beta-thalassemia seen in 2 cases in Bengal. Hb-J, presumably alpha type with beta thalassemia seen in one family in Bombay.

HAEMOGLOBIN-Hofu (β126(H4)Val-Glu)

Presentation

Double Heterozygote

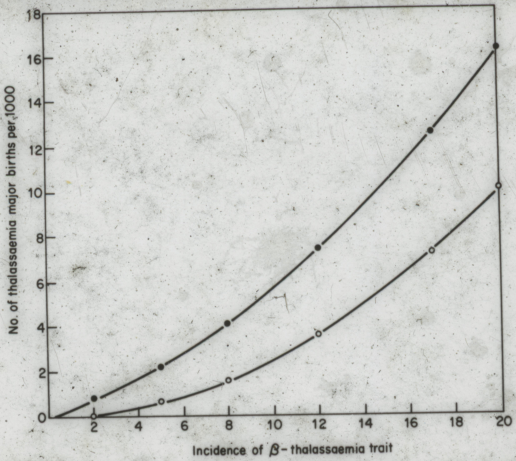
Hb Hofu-beta Thalassemia (seen in Bombay)
Hb Hofu presumably homozygote seen in Andhra Pradesh, also seen in heterozygous form.

HbA synthesis predicted in fetuses with different thalassemia genes

Genetic constitution	HbA synthesis (%)			
	Mean	SD[a]	Range (±2 SD)	
Normal	9·8	1·72	6·36–13·2	
β^+-thalassaemia trait	6·5	1·15	4·2–8·8	Assuming $\frac{1}{3}$th normal synthesis by the β^+ gene
β^0-thalassaemia trait	4·9	0·86	3·2–6·6	
β^+-thalassaemia major	1·96	0·34	1·3–2·6	Calculated at $\frac{1}{3}$th normal synthesis, a maximum value
$\beta^+\beta^0$-thalassaemia major	0·98	0·17	0·64–1·3	
β^0-thalassaemia major	0	0	0	

[a]Calculated on the basis of the normal range, as one 5·7th of the mean.

[illegible] practised but has been superseded by the Orskov method of



Relationship between heterozygote prevalence and homozygote birth-rate: (O—O) random mating; (●—●) first cousin marriage

THAILAND

NORTH	Hb.E. (30-33%)
NORTH WEST	Hb.E. (6-13%)
NORTH EAST	Hb.E. (10-59%)
CENTRAL	Hb.E. (20-44%)
SOUTH	Hb.E. (16-22%)
SOUTH EAST	Hb.E. (18.8%)
NORTH	ALPHA THAL (30%)
SOUTH	ALPHA THAL$_1$ (10%)
SOUTH	ALPHA THAL$_2$ (6%)
SOUTH	Hb. CS (4%)

BETA THAL° MUCH MORE THAN BETA THAL$^+$

HPFH DELTA / BETA THAL SILENT BETA THAL	OCCASIONAL
Hb. MAHIDOL (Q)	OCCASIONAL
Hb. TAK (BETA ELONG.)	OCCASIONAL
Hb. J BANGKOK	RARE
Hb. SIRIRAJ	"
Hb. D PUNJAB	"
Hb. NEW YORK	"
Hb. SIAM	"
Hb. AMRITRAJ	"
Hb. THAILAND	"

Haematological and biochemical data on members of four families with the HPFH or the HPFH–β-thalassaemia condition

Case	Age	Relation	Condition	Hb (g/100 ml)	PCV (%)	RBC (10^6/μl)	MCV (fl)	MCH (pg)	MCHC (%)	Osmotic fragility	Hb-F distribution	$Hb\text{-}A_2$ (%)	% Hb-F* A.D.	% Hb-F* Ile	Peptide γCB-3 Gly	Peptide γCB-3 Ala
FAMILY C																
B.P.C.	29	Mother	HPFH	13.6	43	4.81	89	28	32	Normal	Even	1.6	24	30	0.73	2.38
R.P.C.	7	Daughter	HPFH	14.5	44	4.74	93	31	33	Normal	Even	2.2	25	28	0.68	2.34
FAMILY D																
N.H.D.	38	Father	HPFH	14.8	45	5.47	82	27	33	Normal	Even	1.8	17	23	0.72	2.36
K.H.D.	32	Brother§	HPFH	14.5	47	4.75	99	30	31	Normal	Even	1.5	24	27	0.71	2.33
V.N.D.	31	Mother	β-Thal.	11.6	37	5.66	66	21	31	Decreased	—	4.9	1.0	1.9	—	—
P.N.D.‡	7	Son	HPFH–β-thal.	5.5	21	3.73	56	15	26	Decreased	Even	2.5	52	84	0.75	2.27
FAMILY T.R.†																
Raj.R.‡	8	Brother	HPFH–β-thal.	6.7	25	3.51	72	19	26	Decreased	Even	3.2	63	87	0.70	2.33
Ram.R.	5	Brother	HPFH	12.2	36	4.06	89	30	34	Normal	Even	1.5	21	22	0.66	2.36
FAMILY R																
Ca.G.	6	Niece	HPFH	13.0	44	4.81	92	27	30	Normal	Even	2.0	24	29	0.72	2.33
Cl.R.‡	23	Uncle	HPFH–β-thal.	9.0	30	4.69	61	19	30	Decreased	Even	3.3	63	84	0.70	2.32

* F_{AD} = %Hb-F determined by alkali denaturation (Betke *et al*, 1959). F_{11e} = Hb-F determined by a chemical procedure (Schroeder *et al*, 1970b).
† Father has been identified as a HPFH heterozygote and the mother as a β-thalassaemia heterozygote.
‡ DEAE-Sephadex chromatography showed the presence of small amounts of Hb-A namely 4.4% (P.N.D.), 4.3% (Raj.R.) and 4.6% (Cl.R.)
§ K.H.D. is the brother of N.H.D.

The β Thalassaemias

Inherited disorders of β, $\delta\beta$, $\gamma\delta\beta$ or δ chain synthesis.

β Thalassaemia

With elevated levels of haemoglobin A_2 in heterozygotes

β^0 Thalassaemia

Several types defined at the molecular level

Ferrara type partly defined at the molecular level

Dutch type defined at phenotypic level only

β^+ Thalassaemia

Severe Mediterranean type

Mild Negro type

β^0/β^+ Thalassaemia

With normal levels of haemoglobin A_2 in heterozygotes

'Silent' β thalassaemia (type 1)

Symptomatic form (type 2) (may be β thalassaemia + δ thalassaemia)

Others

δβ Thalassaemia

$^{G_\gamma A_\gamma}\gamma(\delta\beta)^0$ Thalassaemia

$^{G_\gamma}\gamma(\delta\beta)^0$ Thalassaemia

Hb Lepore $(\delta\beta)^+$ thalassaemia

γδβ Thalassaemia

$(\gamma\delta\beta)^0$ Thalassaemia

δ Thalassaemia

δ^0 Thalassaemia

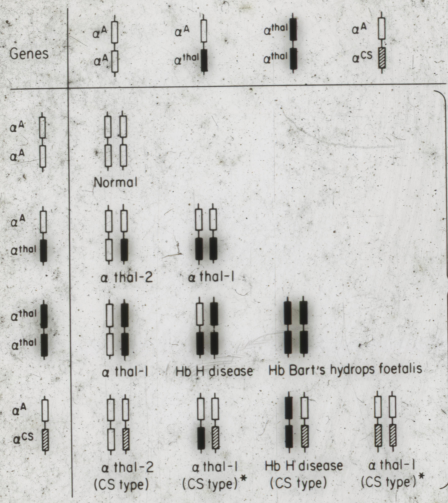
β Thalassaemia-like disorders

Highly unstable β chain variants

Inefficiently synthesised β chain variants

?Excess α chain production

See Table 6.18.



Simplified schematic representation of the correlations between genotypes and phenotypes in α thalassaemia, assuming the existence of duplicate α-chain loci. The Hb Constant Spring mutant is designated by CS. Phenotypes marked with asterisks have not been documented.

POSSIBLE APPROACH TO TREATMENT OF BETA-THALASSAEMIA

(Kan, Y.W., et al, 1979)

BETA GLOBIN STRUCTURAL GENE IS IN TACT IN MAJORITY OF β^0-THALASSAEMIA

GENETIC LESIONS

VARIABLE AMOUNTS OF GLOBIN mRNA IN RETICULOCYTES - COMPLETELY ABSENT OR BARELY DETECTABLE IN SOME - SUBSTANTIAL AMOUNT PRESENT BUT NOT FUNCTIONAL IN OTHERS.

in vitro EXPERIMENT

PATIENT WITH NON-FUNCTIONAL β-GLOBIN mRNA (β^0-THALASSAEMIA HOMOZYGOUS) FOUND TO BE DUE TO MUTATION OF NORMAL (AAG) LYSINE AT 17 POSITION OF β-CHAIN TO TERMINATION CODON (UAG) - A NONSENSE MUTATION.

CORRECTION

SERINE-INSERTING YEAST SUPPRESSOR tRNA ADDED TO mRNA IN A CELL-FREE SYSTEM IN THE PRESENCE OF RADIO ACTIVE ^{35}S-METHIONINE, SYNTHESIZED β-GLOBIN CHAIN IN AN in vitro TRANSLATION EXPERIMENT USING GLOBIN mRNA FROM RETICULOCYTES OF PATIENT.

CONCLUSION

NONSENSE MUTATION IN BETA-GLOBIN mRNA (IN β^0-THALASSAEMIA) HOMOZYGOUS) CAN BE SUPPRESSED in vitro USING APPROPRIATE YEAST SUPPRESSOR tRNA.

IT IS HOPED THAT SIMILAR DELIVERY OF SUPPRESSOR tRNA TO ERYTHROID PRECURSSORS OF PATIENTS WITH β^0-THALASSAEMIA DUE TO NONSENSE MUTATION MAY CORRECT BETA-GLOBIN DEFECT.

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Gamma thalassemia resulting from the deletion of a γ-globin gene

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Alpha-thalassaemia in Indian population

Group	No. of Cord Bloods tested	Hb. Bart's (Number)	Reference
Singapore (Mixed)	222	2	Vella (1959)
Bengali	100	4	Swarup et al (1965)
Mixed group	438	5 (α_1) 4 (α_2)	Chouhan et al (1970)
Bengali Hindu	720	8	Das et al (1973)
Mixed group	459	3 (α_1) 2 (α_2)	Sukumaran & Master (1974, 1981)
Mixed group	240	1	Vohra et al (1975)

Walford et al (1976) reported alpha-thalassaemia in Gujarati Indians in England
Alpha Thalassaemia 1 (< 2% Hb. Bart's); Alpha Thalassaemia 2 (> 4% Hb. Bart's)

C. $(A\gamma\delta\beta)^{\circ}$ THALASSEMIA

1.	INDIAN	8.3 kb DELETED	40.1 - 40.9	10 to 15
			55.5 - 63.0	
		14.6 kb INVERTED	40.9 - 55.5	
2.	BLACK (USA)	34.0	40.8 - 76.0	6 to 16
3.	TURKISH BLACK (USA)	34.0	36.5 - 70.5	10 to 13
4.	TURKISH	36.1	37.0 - 73.1	10 to 15
5.	MALAYSIAN	UNKNOWN	37.9 - UNKNOWN	UNKNOWN
6.	CHINESE	100.0	40.5 - UNKNOWN	10 to 15
7.	GERMAN	53.0	37.0 - 90.0	10 to 15

Physical problems of thalassaemic patients more than 12 years old[a]

Failure of growth: **dwarfism**
Failure of puberty: **eunuchism**
Endocrinopathy:
hypoparathyroidism
diabetes
hypothyroidism
GH deficiency
Cardiac disease
Hepatic disease
Risk of post-splenectomy infection
Danger of death

[a]Major problems of management are in bold
From Modell and Petrou (1982) with permission

Summary of haematology and haemoglobin analyses for the ($^{A}\gamma\delta\beta$)°-thalassaemia of this report, and for the two homozygous ($^{A}\gamma\delta\beta$)°-thalassaemia cases that have been characterized by restriction endonuclease mapping

	Patient of Sukumaran *et al* (1972)	Patient of Dincol *et al* (1981)	Patient of Amin *et al* (1979)
Homozygote:			
Identification	I.A.R.	Case 2	Family B
Age	7 12 20	6	4
Hb (g/dl)	7·5 6·1 10·4	9·0	9·9
MCV (fl)	69 75 72	73	71
MCH (pg)	21 18 20	25	20
Retics (%)	6·8 10	15	2·6
α/γ synthesis	3·0	5·0	5·1
Clinical D_x and condition	Initial diagnosis: *β*-thalassaemia major; anaemia, jaundice, hepatosplenomegaly, bone changes	Thalassaemia intermedia; anaemia, bone changes	Thalassaemia intermedia; anaemia, splenomegaly, bone changes
Heterozygous relatives:			
No. of cases*	5	2	4
Hb (g/dl)	11·5±1·3	11, 14	12·0±0·6
MCV (fl)	78·0±1·2	70, 74	78·0±5·4
MCH (pg)	24·0±1·0	24, 24	24·0±1·2
Hb F (%)	13·5±3·5	10, 13·5	11·3±1·2
Hb F (pg/cell)	3·3±0·9	2·4, 3·2	2·7±0·4
α/non-α synthesis	1·2±0·01	1·9, 2·0	1·6±0·6
Cellular distribution of Hb F	Pancellular	Heterocellular	Pancellular

Data on I.A.R. at age 7, and for his family, are from Sukumaran *et al* (1972), while data for age 12 are from Ringelhann *et al* (1977). Data for I.A.R. at age 20 are from the present study. Restriction endonuclease studies on the case from Dincol *et al* (1981) were done by Orkin *et al* (1979) and Fritsch *et al* (1979), while those on the patient from Amin *et al* (1979) are described by Jones *et al* (1981a), as discussed in the text.

* Mean ± SD are given when there are data on more than two heterozygous relatives; full data are not always available for every relative.