Thalassaemia Intermedia

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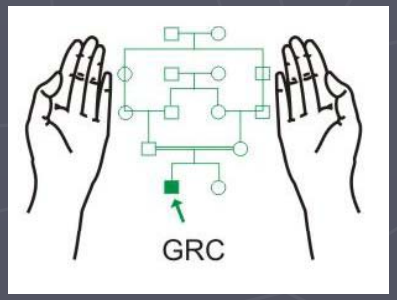
Genetics Resource Centre (GRC)



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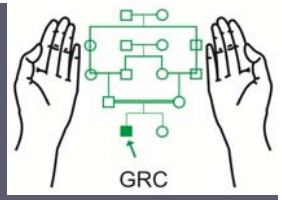
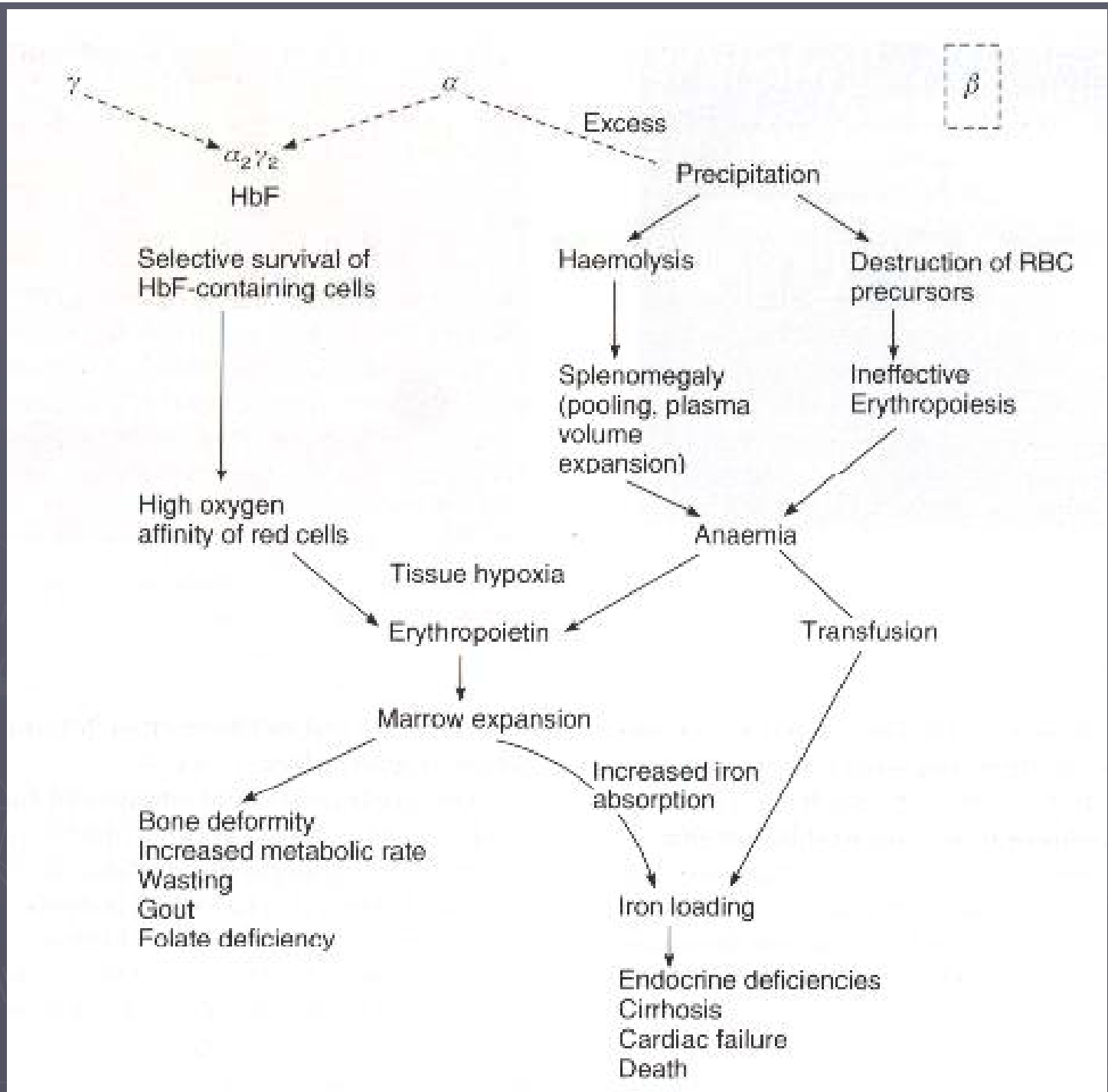
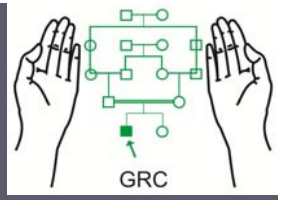


The term Thalassaemia Intermedia (TI) is used to describe patients with clinical picture of thalassaemia, which, although not transfusion dependent, is associated with a more severe degree of anaemia than that found in heterozygous carriers for α- or β-thalassaemia.

(Weatherall 1996)

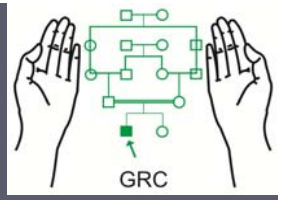

γ
α
β
Excess
$\alpha_2\gamma_2$
HbF
Precipitation
Selective survival of HbF-containing cells
Haemolysis
Destruction of RBC precursors
Splenomegaly (pooling, plasma volume expansion)
Ineffective Erythropoiesis
High oxygen affinity of red cells
Anaemia
Tissue hypoxia
Erythropoietin
Transfusion
Marrow expansion
Increased iron absorption
Bone deformity
Increased metabolic rate
Wasting
Gout
Folate deficiency
Iron loading
Endocrine deficiencies
Cirrhosis
Cardiac failure
Death

Molecular Basis of TI



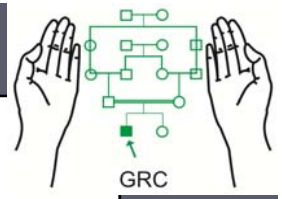
- Mild defects of β-globin chain production
  - Homozygosity for mild β-thalassaemia
  - Compound heterozygosity for mild and severe β-thalassaemia
- Homozygosity or compound heterozygosity for severe β-thalassaemia associated with
  - α-thalassaemia
  - Genetic factors enhansing γ-chain production
    - Gγ promotor mutation (homozygous Xmn-I polymorphism)
    - Heterocellular HPFH
- β-thalassaemia due to large promoter region deletions
- Homozygosity for δβ-thalassaemia or its combination with β-thalassaemia
- Double heterozygosity for β-thalassaemia and triplicated α-globin gene
- Heterozygosity for hyperunstable Hb variants (Dominant thalassaemia)

(Cao et al, 1994)



	Thalassaemia Major	Thalassaemia Intermedia	Thalassaemia Minor
Severity	++++	++	+,±
Genetics	Homozygous/double heterozygous	Homozygous/double heterozygous	Heterozygous
Splenomegaly	++++	++,+++	+, 0
Jaundice	+	++	0
Bony changes	++++,++	+, 0	+, 0
Haemoglobin	<7 g/dl	7-10 g/dl	>10 g/dl
Hypochromia	++++	+++	++
Microcytosis	+++	++	+
Target cells	10-35%	++	+
Stippling	++	+	+
Reticulocytes	5-15%	3-10%	2-5%
Nucleated RBC	+++	+, 0	0
Hb-F	20->94%	30-100%	1-2%
Hb-A_2	1-8.7%	<1-10.0%	3.5-8.0%

(Lukens 1993)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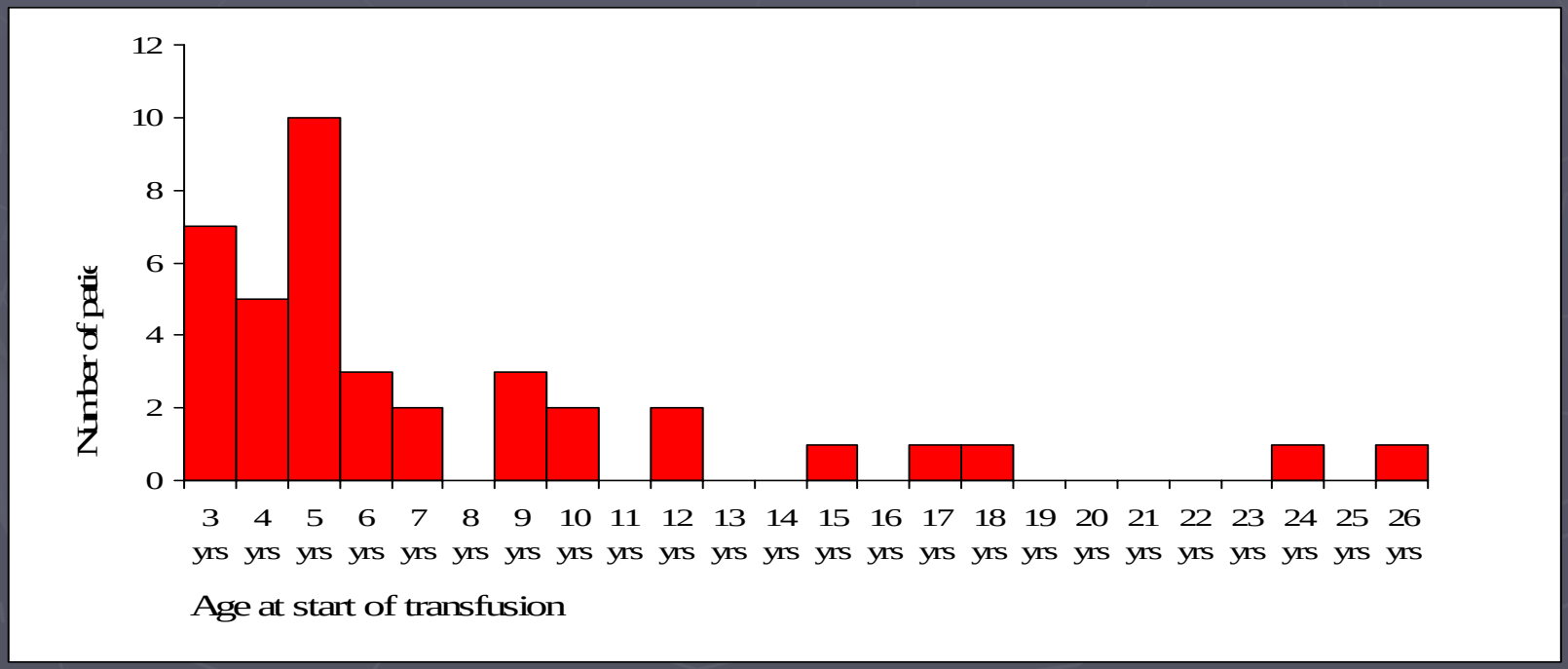
Number of patients
15
10
5
0
<5 yrs
10-15 yrs
20-25 yrs
30-35 yrs
Age group


12
10
8
6
4
2
0
3 yrs
4 yrs
5 yrs
6 yrs
7 yrs
8 yrs
9 yrs
10 yrs
11 yrs
12 yrs
13 yrs
14 yrs
15 yrs
16 yrs
17 yrs
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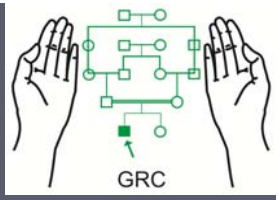
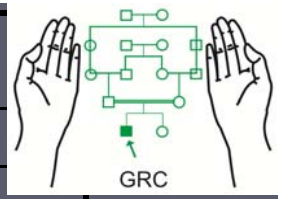
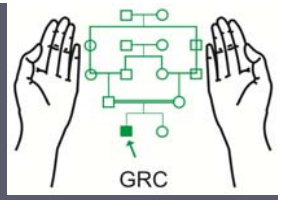
19 yrs
20 yrs
21 yrs
22 yrs
23 yrs
24 yrs
25 yrs
26 yrs
Age at start of transfusion



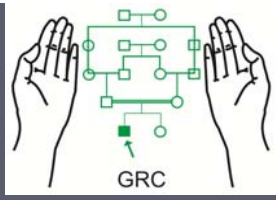
Sr. No	Age: (yrs)	First Trans#	β-thalassaemia Mutations	Xmn-I genotype	α-Thal genotype*	Probable cause of Thalassaemia Intermedia
Punjabi:						
1	3 yrs	None	IVSI-5 (G-C)/ IVSI-5 (G-C)	+/+	αα/αα	Xmn-I +/+
2.	5 yrs	3 yrs	IVSI-5 (G-C)/ IVSI-5 (G-C)	+/+	αα/αα	Xmn-I +/+
3.	12 yrs	4½ yrs	IVSI-5 (G-C)/ IVSI-5 (G-C)	+/+	αα/αα	Xmn-I +/+
4.	12 yrs	3½ yrs	IVSI-1 (G-T)/ IVSI-1 (G-T)	+/+	αα/αα	Xmn-I +/+
5.	5½ yrs	3 yrs	IVSI-1 (G-T)/ IVSI-1 (G-T)	+/+	αα/αα	Xmn-I +/+
6.	7 yrs	5½ yrs	IVSI-1 (G-T)/ IVSI-1 (G-T)	+/+	αα/αα	Xmn-I +/+
7.	6 yrs	5 yrs	IVSII-1 (G-A)/IVSII-1 (G-A)	+/+	αα/αα	Xmn-I +/+
8.	8 yrs	5 yrs	IVSII-1 (G-A)/IVSII-1 (G-A)	+/+	αα/αα	Xmn-I +/+
9.	8 yrs	4½ yrs	Cd 30 (G-C)/Cd 30 (G-C)	+/+	αα/αα	Xmn-I +/+
10.	13 yrs	3½ yrs	IVSI-5 (G-C)/Cap+1 (A-C)	-/-	αα/αα	β^+ thal mutation
11.	5½ yrs	2 yrs	IVSI-5 (G-C)/Cap+1 (A-C)	-/-	αα/αα	β^+ thal mutation
12	6 yrs	3 yrs	IVSI-5 (G-C)/Cap+1 (A-C)	-/-	αα/αα	β^+ thal mutation
13.	13 yrs	5 yrs	Fr 8-9 (+G)/Cap+1 (A-C)	-/-	$-\alpha^{3.7}\alpha/\alpha\alpha$	β^+ thal mutation & $-\alpha^{3.7}$
14.	10 yrs	None	Fr 8-9 (+G)/ IVSII-1 (G-A)	-/+	?	Xmn-I -/+, Coincident α-thal ??
15.	7 yrs	3 yrs	IVSI-5 (G-C)/Fr 8-9 (+G)	-/-	$-\alpha^{3.7}\alpha/-\alpha^{3.7}\alpha$	Coincident α-thalassaemia
16.	20 yrs	15 yrs	Fr 47-48 (-ATCT)/Fr 47-48	-/-	$-\alpha^{3.7}\alpha/-\alpha^{3.7}\alpha$	Coincident α-thalassaemia

Sr. No	Age: (yrs)	First Trans#	β-thalassaemia Mutations	Xmn-I genotype	α-Thal genotype*	Probable cause of Thalassaemia Intermedia
Pathan:						
17.	35 yrs	24 yrs	IVSI-1 (G-T)/IVSI-1 (G-T)	+/+	αα/αα	Xmn-I +/+ & α-thal (nd ??)$
18.	5 yrs	2½ yrs	IVSI-5 (G-C)/Cap+1 (A-C)	-/+	αα/αα	Xmn-I -/+, β^+ thal mutation
19.	15 yrs	3 yrs	IVSI-5 (G-C)/Cap+1 (A-C)	-/-	αα/αα	β^+ thal mutation
20.	5 yrs	2½ yrs	Cd 5 (-CT)/Cap+1 (A-C)	-/-	αα/αα	β^+ thal mutation
21.	23 yrs	17 yrs	Fr 8-9 (+G)/-88 (C-T)	-/-	αα/αα	β^+ thal & α-thal (nd ??)$
Sindhi:						
22.	18 yrs	3½ yrs	IVSI-5 (G-C)/Cd 30 (G-C)	+/+	?	Xmn-I +/+
23.	13 yrs	5 yrs	IVSI-1 (G-T)/del 619 bp	-/+	?	Xmn-I -/+,Coincident α-thala ??
24.	15 yrs	5 yrs	IVSI-5 (G-C)/Cd 30 (G-C)	-/+	?	Xmn-I -/+,Coincident α-thala ??
25.	16 yrs	9 yrs	IVSI-5 (G-C)/IVSI-5 (G-C)	-/-	?	Coincident α-thala ??
26.	15 yrs	12 yrs	IVSI-5 (G-C)/IVSI-5 (G-C)	-/+	?	Xmn-I -/+,Coincident α-thala ??
Baluchi:						
27.	16 yrs	7 yrs	IVSI-5 (G-C)/IVSII-1 (G-A)	-/+	?	Xmn-I -/+,Coincident α-thala ??
28.	11 yrs	10 yrs	IVSI-5 (G-C)/?	-/+	?	Unknown mutation ??
Mohajir:						
29.	9 yrs	5 yrs	IVSI-5 (G-C)/IVSI-5 (G-C)	+/+	?	Xmn-I +/+
30.	30 yrs	9 yrs	IVSI-5 (G-C)/IVSI-5 (G-C)	+/+	?	Xmn-I +/+
31.	17 yrs	6 yrs	IVSII-1 (G-A)/IVSII-1 (G-A)	+/+	?	Xmn-I +/+
32.	26 yrs	12 yrs	IVSI-5 (G-C)/Hb-E	-/+	?	Xmn-I -/+, β^+-mut & α-thal ??
33.	21 yrs	18 yrs	IVSI-5 (G-C)/Hb-E	-/+	?	Xmn-I -/+, β^+-mut & α-thal ??
34.	15 yrs	9 yrs	IVSI-5 (G-C)/Hb-E	-/+	?	Xmn-I -/+, β^+-mut & α-thal ??
35.	7 yrs	None	Cd 15 (G-A)/Cap+1 (A-C)	-/-	?	Xmn-I -/+, β^+-mut & α-thal ??
36.	21 yrs	5 yrs	IVSI-5 (G-C)/del 619 bp	-/+	?	Xmn-I -/+, Coincident α-thal ??
37.	31 yrs	26 yrs	IVSI-5 (G-C)/IVSI-5 (G-C)	-/+	?	Xmn-I -/+, Coincident α-thal ??
38.	6 yrs	5½ yrs	IVSI-5 (G-C)/IVSI-5 (G-C)	-/+	?	Xmn-I -/+, Coincident α-thal ??
39.	14 yrs	5 yrs	IVSI-5 (G-C)/?	-/+	?	Unknown mutation ??

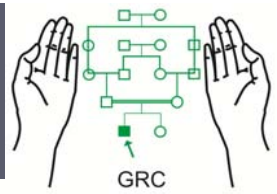


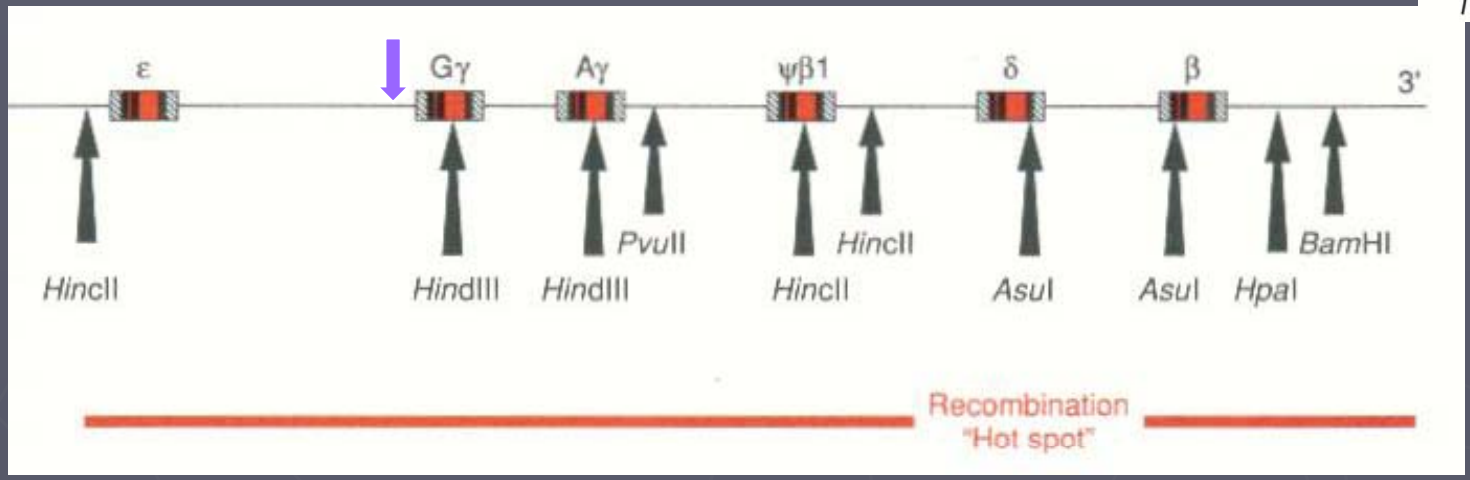


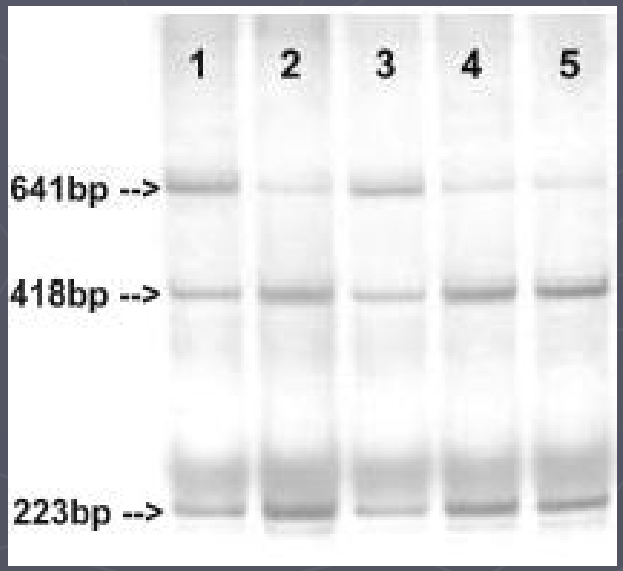
Cause of Thalassaemia Intermedia:	n:	Mean age:	
		At 1st transfusion:	At examination:
Xmn-I +/+ genotype	14	6 years	13 years
β^+-mutation	6	3 years	8 years
β^+-mutation and suspected coincident α-thal	6	11¼ years	18 years
Unidentified thalassaemia mutation	2	7½ years	12½ years
Confirmed coincident α-thalassaemia	2	9½ years	13½ years
Suspected coincident α-thalassaemia	9	9½ years	16 years
Total	39	7 years	14 years



Cause of Thalassaemia Intermedia:	n (%):	Mean age:	
		At 1st transfusion:	At examination:
Xmn-I +/+ genotype	14 (36%)	6 years	13 years
β^+-mutation	6 (15%)	3 years	8 years
β^+-mutation and coincidental α-thalassaemia	6 (15%)	11¼ years	18 years
Unidentified thalassaemia mutation	2 (6%)	7½ years	12½ years
Coincidental α-thalassaemia	11 (28%)	9½ years	13½ years
Total	39	7 years	14 years


GRC


ε
Gγ
Aγ
ψβ1
δ
β
3'
HincII
HindIII
HindIII
PvuII
HincII
HincII
AsuI
AsuI
HpaI
BamHI
Recombination
"Hot spot"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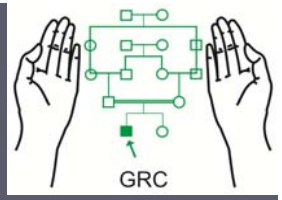
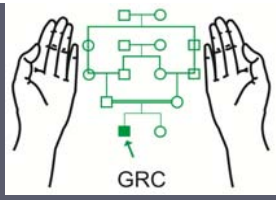
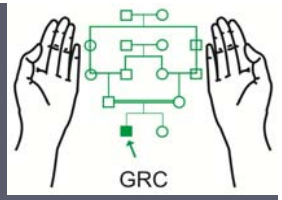


Xmn-I genotype:	Thal Intermedia:	Thal Major :	Normal:
-/-	12 (30.8%)	30 (76.9%)	30 (51.7%)
-/+	13 (33.3%)	9 (23.1%)	20 (34.5%)
+/+	14 (35.9%)	None	8 (13.8%)
Total:	39 (100%)	39 (100%)	58 (100%)

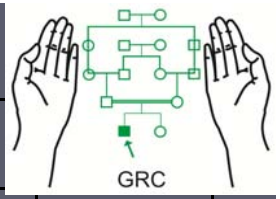


Mutation:	Xmn-1 genotype:	Mutation:	Xmn-1 genotype:	Mutation:	Xmn-1 genotype:
IVSI-5/IVSI-5	-/-	IVSI-5/Fr 8-9	-/-	Fr 8-9/IVSII-1	-/+
Fr 41-42/Fr 41-42	-/-	Fr 8-9/Hb-E	-/-	IVSI-5/Hb-E	-/+
Fr 41-42/Fr 41-42	-/-	Fr 8-9/Fr 8-9	-/-	IVSI-5/IVSII-1	-/+
IVSI-5/IVSI-5	-/-	Fr 8-9/Fr 8-9	-/-	IVSI-5/Cap+1	-/-
Fr 41-42/Cd 5	-/-	Fr 8-9/IVSI-5	-/-	IVSI-1/del 619	-/+
IVSI-5/IVSI-5	-/-	Cd 15/Cd15	-/-	Cd 5/Cap+1	-/-
Del 619/Cd 5	-/-	IVSI-5/IVSI-5	-/-	Fr 8-9/Cap+1	-/-
Fr 41-42/Fr 41-42	-/-	IVSI-5/IVSI-5	-/-	Fr 8-9/Fr 8-9	-/-
IVSI-5/IVSI-5	-/+	IVSI-5/Cd 15	-/+	IVSI-5/Cap+1	-/-
Fr 8-9/Fr 8-9	-/-	IVSI-5/IVSI-5	-/-	Cd 15/Cd 15	-/+
Fr 8-9/Fr 8-9	-/-	Fr 8-9/Fr 41-42	-/+	Fr 41-42/Fr 41-42	-/-
Fr 41-42/Cd 15	-/+	IVSI-5/IVSI-5	-/-	Fr 8-9/Fr 41-42	-/-
Fr 8-9/Fr 8-9	-/-	Fr 8-9/Fr 8-9	-/-	IVSI-5/IVSI-5	-/-



Mutation:	Thalassaemia major:				Thalassaemia Intermedia:			
	-	+	+?*	Total:	-	+	+?*	Total:
IVSI-5 (G-C)	21	1	3	25	12	12	9	33
Fr 8-9 (+G)	20	-	1	21	3	-	1	4
Fr 41-42 (-TTCT)	10	-	2	12	-	-	-	-
IVSI-1 (G-T)	-	-	1	1	-	8	1	9
IVSII-1 (G-A)	-	-	2	2	-	6	2	8
Cd 15 (G-A)	3	1	2	6	1	-	-	1
Cd 30 (G-C)	-	-	-	-	-	3	1	4
Cap +1 (A-C)	4	-	-	4	7	-	1	8
Cd 5 (-CT)	3	-	-	3	1	-	-	1
Hb-E	1	-	1	2	-	-	3	3
Del 619	1	-	1	2	1	-	1	2
Others	-	-	-	-	3	-	2	5
Total:	63	2	13	78	28	29	21	78

* Suspected “+”



Mutation:	**All patients:**	**Thalassaemia major (TM):**			**Thalassaemia Intermedia (TI):**	***p* value:**	
		< 3 years:	**≥ 3 years:**	**All:**		**TM: < 3 years versus ≥ 3 years:**	**TI vs TM:**
IVSI-5	413 (39.8%)	97 (36.7%)	283 (40.7%)	380 (39.6%)	33 (42.3%)	-	-
Fr 8-9	236 (22.7%)	87 (33.0%)	146 (21.0%)	233 (24.3%)	3 (3.8%)	0.003	0.0003
Del 619	80 (7.7%)	12 (4.5%)	66 (9.5%)	78 (8.1%)	2 (2.6%)	0.01	-
Fr 41-42	67 (6.5%)	15 (5.7%)	52 (7.5%)	67 (7.0%)	-	-	-
IVSI-1 (G-T)	57 (5.5%)	5 (1.9%)	43 (6.2%)	48 (5.0%)	9 (11.5%)	0.009	0.025
Cd 15	40 (3.9%)	13 (4.9%)	25 (3.6%)	38 (4.0%)	2 (2.6%)	-	-
Cd 30 (G-C)	39 (3.8%)	6 (2.3%)	29 (4.2%)	35 (3.6%)	4 (5.1%)	-	-
Fr 16	26 (2.5%)	10 (3.8%)	16 (2.3%)	26 (2.7%)	-	-	-
Cd 5	18 (1.7%)	11 (4.2%)	6 (0.9%)	17 (1.8%)	1 (1.3%)	< 0.0001	-
Cap+1	17 (1.6%)	4 (1.5%)	5 (0.7%)	9 (0.9%)	8 (10.3%)	-	<0.0001
Hb-E	11 (1.1%)	1 (0.4%)	7 (1.0%)	8 (0.8%)	3 (3.8%)	-	-
IVSII-1	10 (1.0%)	1 (0.4%)	1 (0.1%)	2 (0.2%)	8 (10.3%)		<0.0001
Cd 30 (G-A)	9 (0.9%)	2 (0.8%)	7 (1.0%)	9 (0.9%)	-	-	-
-88	3 (0.3%)	-	2 (0.3%)	2 (0.2%)	1 (1.3%)	-	-
IVSI-1 (G-A)	2 (0.2%)	-	2 (0.3%)	2 (0.2%)	-	-	-
Fr 47-48	2 (0.2%)	-	-	-	2 (2.6%)	-	-
Cd 126-132	2 (0.2%)	-	2 (0.3%)	2 (0.2%)	-	-	-
Unknown	6 (0.6%)	-	4 (0.9%)	4 (0.4%)	2 (2.6%)	-	-
Total:	1038 (100%)	264 (100%)	696 (100%)	960 (100%)	78 (100%)	-	-

Management

- Observe
- Blood Transfusion
- Iron Chelation
- Splenectomy
- Hb-F Inducers