

# GENETICS OF THALASSAEMIA IN PAKISTAN

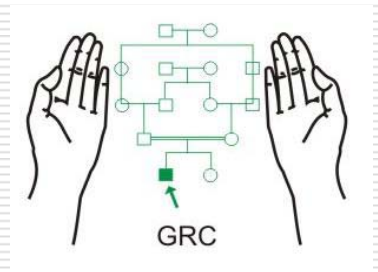
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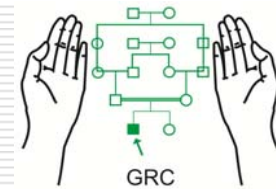
**Maj Gen (R) Suhaib Ahmed, HI (M)**

MBBS; MCPS; FCPS (Pak); PhD (London)

**Genetics Resource Centre (GRC)**

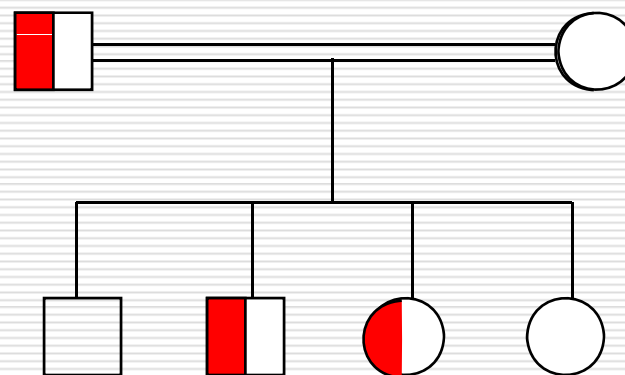
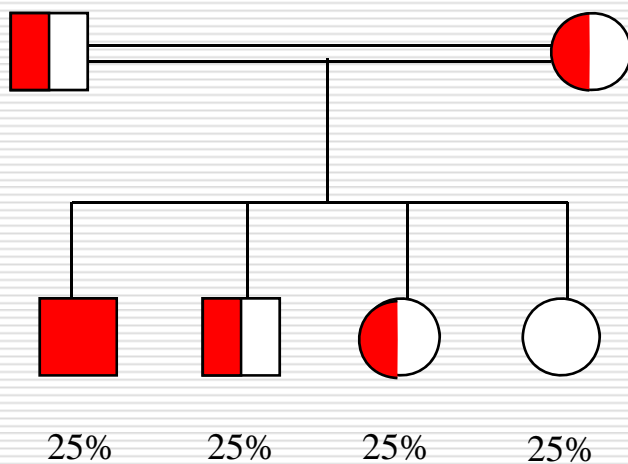
[www.grcpk.com](http://www.grcpk.com)

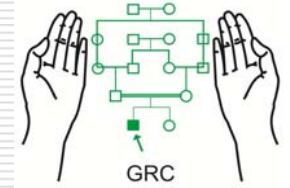




# THALASSAEMIA

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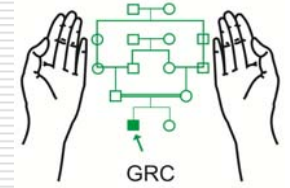




# Haemoglobin Disorders in Pakistan

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- $\beta$ -Thalassaemia
  - $\alpha$ -Thalassaemia
  - $\delta\beta$ -Thalassaemia
  - Abnormal Haemoglobins
    - Hb-S
    - Hb-E
    - Hb-D
  - Miscellaneous Hb disorders
-



# $\beta$ -Thalassaemia in Pakistan

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## Thalassaemia Minor (Trait):

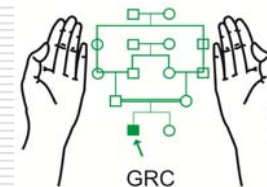
Punjabi:	4.6 %
Pathan:	5.2 %
Baluch:	8.0 %
Sindhi:	4.3 %
Mohajirs:	5.3 %
<b>OVER ALL:</b>	<b>5.1 % (8 million)</b>

## Thalassaemia Major:

Annual births:	5000
Total number:	50,000

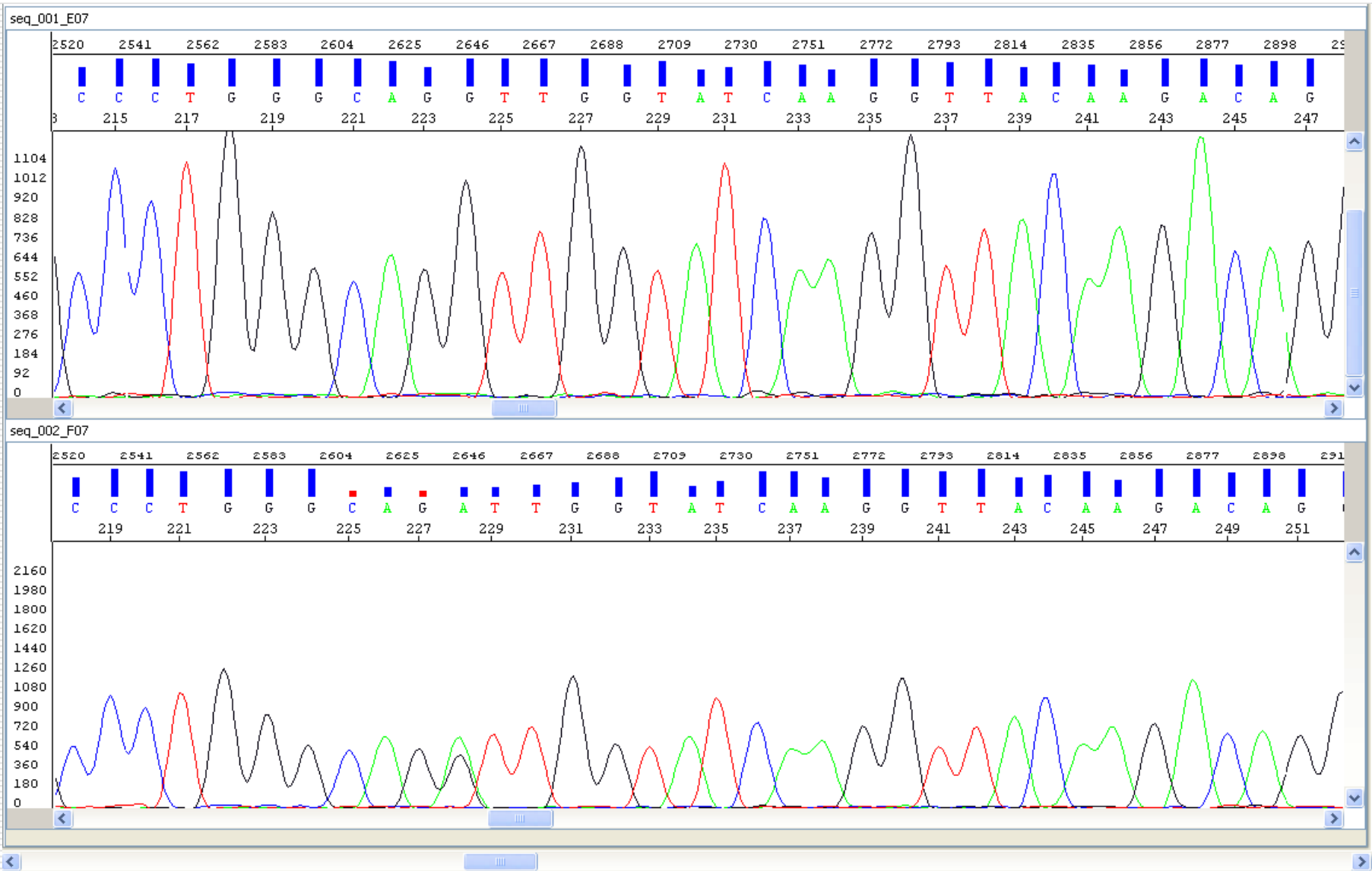
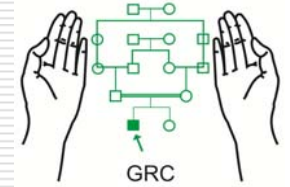
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(Ahmed 1998)

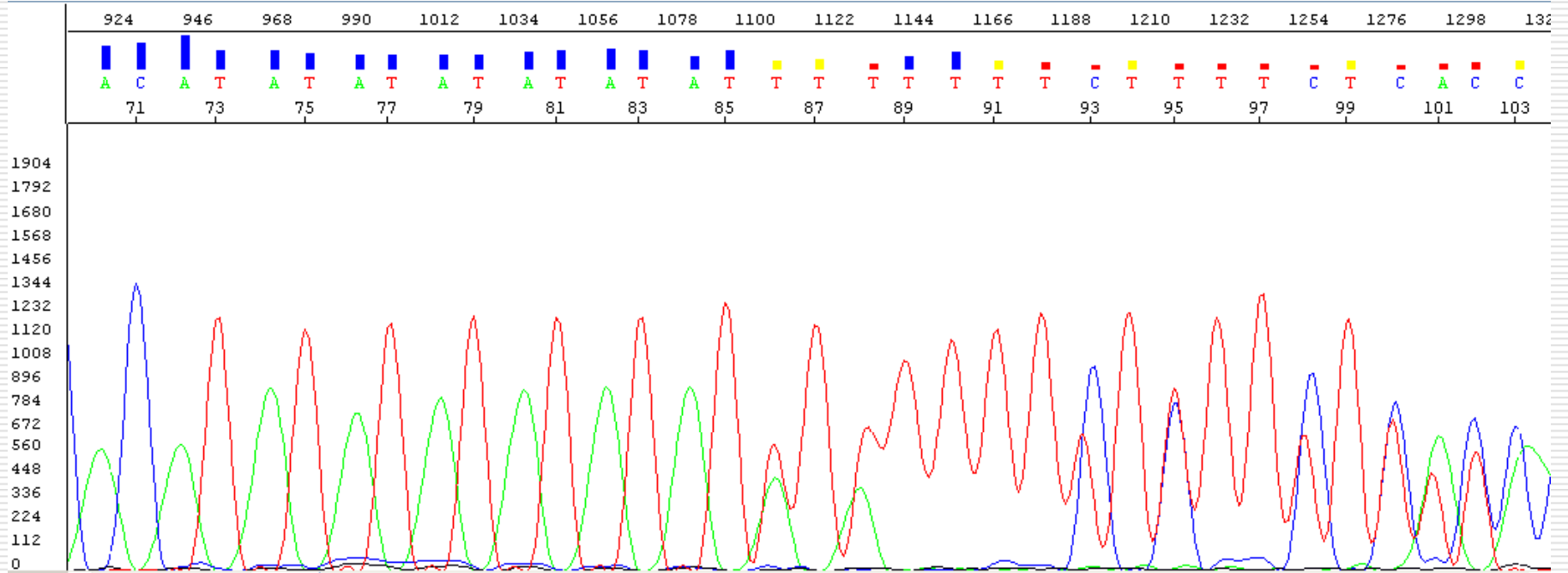
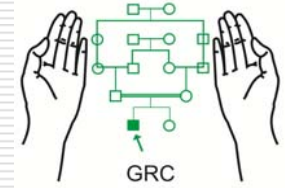


Mutation	Punjabi	Pathan	Sindhi	Baluchi	Mohajir	All
<b>Common mutations</b>						
IVSI-5 (G-C)	107 (27.2%)	27 (12.9%)	114 (43.9%)	131 (76.2%)	75 (41.4%)	454 (37.3%)
Fr 8-9 (+G)	146 (37.2%)	103 (49.1%)	29 (11.2%)	14 (8.1%)	23 (12.7%)	315 (25.9%)
Del 619 bp	14 (3.6%)	4 (1.9%)	36 (13.9%)	2 (1.2%)	29 (16.0%)	85 (7.0%)
Fr 41-42 (-TTCT)	36 (9.2%)	18 (8.6%)	16 (6.2%)	1 (0.6%)	11 (6.1%)	82 (6.7%)
IVSI-1 (G-T)	19 (4.8%)	4 (1.9%)	33 (12.7%)	2 (1.2%)	7 (3.9%)	65 (5.4%)
<b>Uncommon mutations</b>						
Cd 15 (G-A)	14 (3.6%)	13 (6.2%)	5 (1.9%)	9 (5.2%)	8 (4.4%)	49 (4.0%)
Cd 30 (G-C)	15 (3.8%)	1 (0.5%)	19 (7.3%)	3 (1.7%)	4 (2.2%)	42 (3.5%)
Cd 5 (-CT)	11 (2.8%)	16 (7.6%)	0 (0.0%)	1 (0.6%)	2 (1.1%)	30 (2.5%)
Fr 16 (-C)	6 (1.5%)	8 (3.8%)	6 (2.3%)	6 (3.5%)	3 (1.7%)	29 (2.4%)
Cap+1 (A-C)	9 (2.3%)	8 (3.8%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	20 (1.6%)
Hb-E	3 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (5.5%)	13 (1.1%)
Cd 30 (G-A)	3 (0.8%)	2 (1.0%)	0 (0.0%)	2 (1.2%)	4 (2.2%)	11 (0.9%)
IVSII-1 (G-A)	6 (1.5%)	1 (0.5%)	0 (0.0%)	1 (0.6%)	2 (1.1%)	10 (0.8%)
<b>Rare mutations</b>						
-88 (C-T)	1 (0.3%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.3%)
IVSI-1 (G-A)	1 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Fr 47-48 (+ATCT)	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Fr 126-131 (-17 bp)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Cd 39 (C-T)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
IVSI minus 25	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
<b>Total</b>	<b>393 (100%)</b>	<b>210 (100%)</b>	<b>260 (100%)</b>	<b>172 (100%)</b>	<b>181 (100%)</b>	<b>1216 (100%)</b>

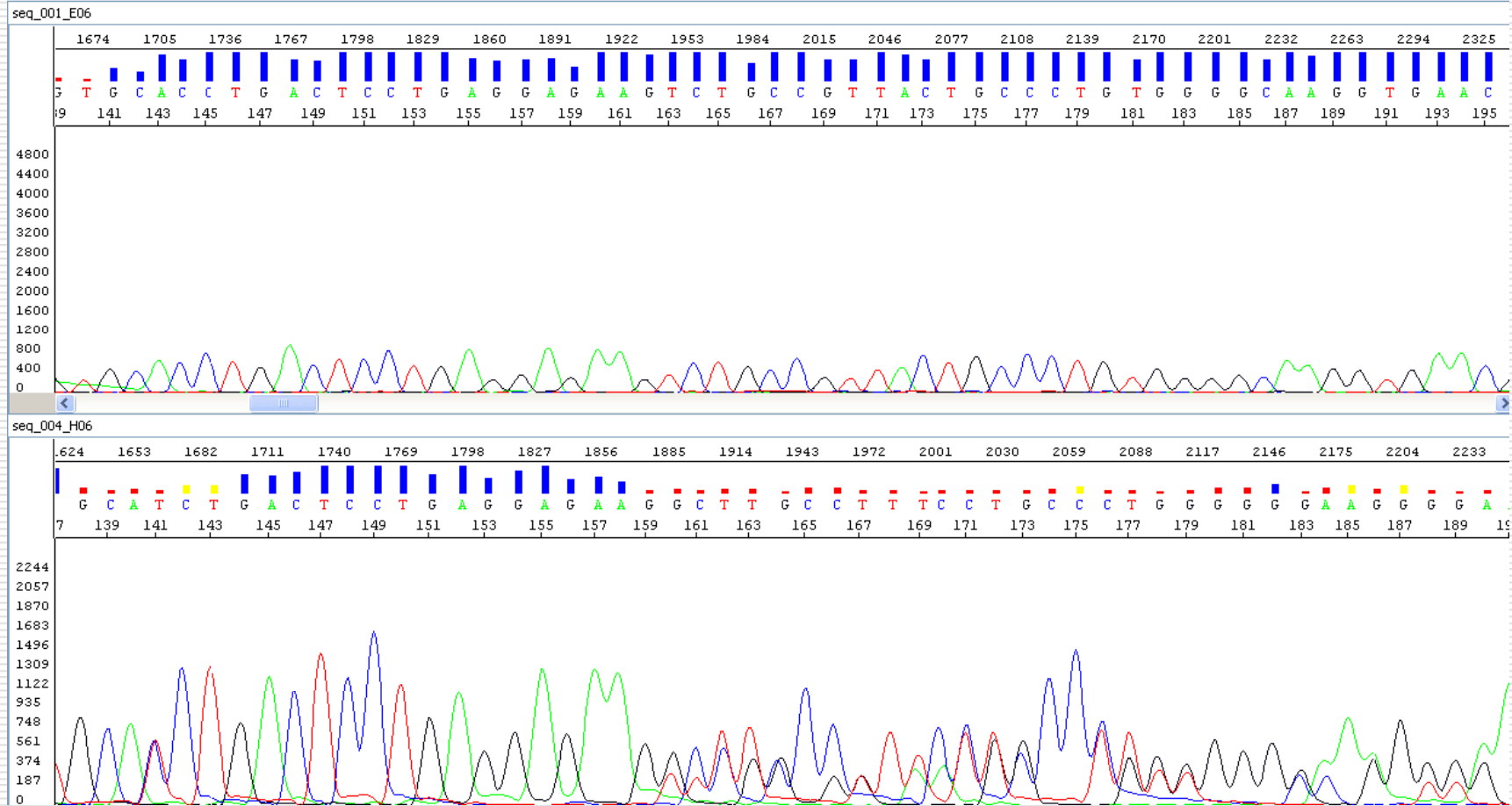
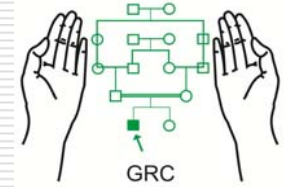
# IVSI-1 (G-A)



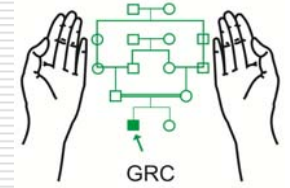
# -527 (+ATA)



# Cd 45 (+T)





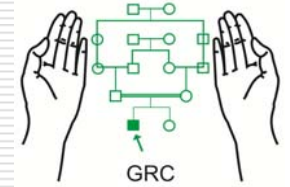


# $\alpha$ -Thalassaemia in Pakistan

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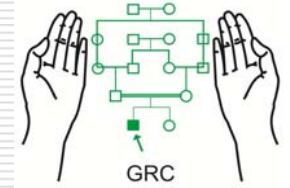
- $-\alpha^{3.7} \alpha / \alpha \alpha$  8.3%
- $-\alpha^{3.7} \alpha / -\alpha^{3.7} \alpha$  2.0%
- $-\alpha^{4.2} \alpha / \alpha \alpha$  0.2%
- Anti  $-\alpha^{3.7} \alpha \alpha \alpha / \alpha \alpha$  0.9%
- $-\alpha^{SEA} -\alpha^{SEA} / -\alpha^{3.7} \alpha$  ?
- Non deletional  $\alpha$ -thal ?

# $\delta\beta$ -Thalassaemia in Pakistan



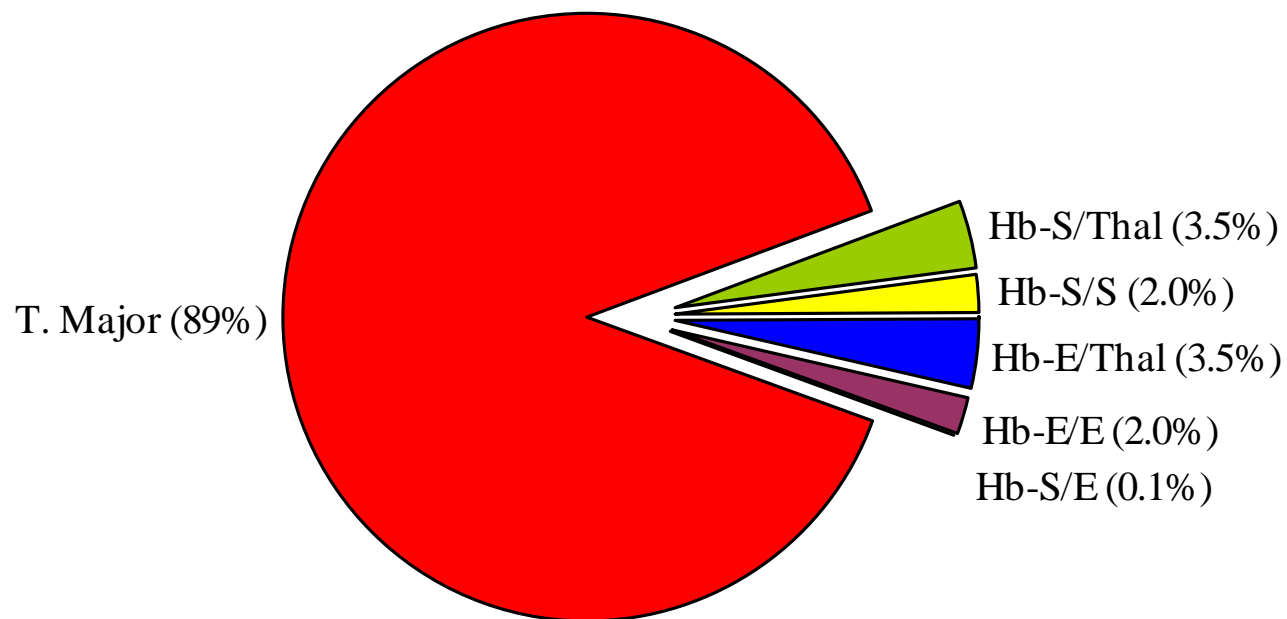
Sr.	Fam	Ethnic	Sex	Age	Trans	Spl	Hb	TRBC	MCV	MCH	HbF	HbA <sub>2</sub>	Mutation	Xmn-I
<b>Heterozygous (<math>\Delta\gamma\delta\beta</math>)<sup>o</sup>/Nor</b>														
1.	1.	Pathan	F	30	No	-	11.5	5.15	73.2	22.3	15%	2.4%	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> /Nor	-/+
2.	2.	Punjabi	M	33	No	-	13.4	5.61	78.3	23.9	17%	2.9%	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> /Nor	-/+
3.	2.	Punjabi	F	28	No	-	10.4	4.48	72.1	23.2	15%	2.6%	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> /Nor	+/+
4.	3.	Punjabi	F	27	No	-	12.5	5.67	71.6	22.0	12%	2.8%	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> /Nor	-/+
5.	3.	Punjabi	M	6	No	-	11.3	5.91	64.0	19.1	12%	2.4%	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> /Nor	-/+
6.	3.	Punjabi	F	4	No	-	10.5	5.41	66.2	19.4	14%	2.3%	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> /Nor	-/+
Mean							11.6	5.37	70.9	21.7	13%	2.6%		
<b>Homozygous (<math>\Delta\gamma\delta\beta</math>)<sup>o</sup>/<math>\Delta\gamma\delta\beta</math>)<sup>o</sup></b>														
7.	2.	Punjabi	M	8	No	+	10.5	5.50	63.3	19.1	100%	Nil	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> / $\Delta\gamma\delta\beta$ ) <sup>o</sup>	+/+
8.	3.	Punjabi	M	33	No	+	10.5	6.30	65.1	20.0	100%	Nil	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> / $\Delta\gamma\delta\beta$ ) <sup>o</sup>	+/+
9.	3.	Punjabi	F	2	Yes	++	5.0	2.27	71.8	22.0	70%*	1.3%	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> / $\Delta\gamma\delta\beta$ ) <sup>o</sup>	+/+
10.	4.	Punjabi	F	34	No	++	11.2	4.40	76.9	25.4	100%	Nil	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> / $\Delta\gamma\delta\beta$ ) <sup>o</sup>	+/+
11.	5.	Bohra	F	10	No	++	10.3	5.32	70.1	19.0	100%	Nil	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> / $\Delta\gamma\delta\beta$ ) <sup>o</sup>	+/+
12.	6.	Bohra	M	29	No	++	10.7	5.17	70.6	20.7	100%	Nil	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> / $\Delta\gamma\delta\beta$ ) <sup>o</sup>	+/+
Mean							9.7	4.82	69.6	21.0	100%	Nil		
<b>Compound heterozygous (<math>\Delta\gamma\delta\beta</math>)<sup>o</sup>/IVSI-5 (G-C)</b>														
13.	6.	Bohra	F	3	Yes	++	8.0	3.8	72.3	21.3	20%*	1.3%	( $\Delta\gamma\delta\beta$ ) <sup>o</sup> / $\beta$ ) <sup>o</sup>	-/+

(Ahmed & Anwar 2005)



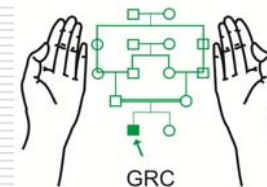
# Abnormal Haemoglobins in Pakistan

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(Ahmed 1998)

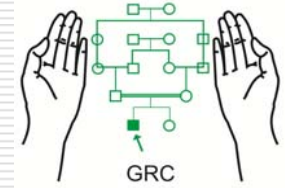
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## Thalassaemia Intermedia in Pakistan

Cause of Thalassaemia Intermedia:	n:	Mean age:	
		At 1 <sup>st</sup> transfusion:	At examination:
Xmn-I +/+ genotype	14	6 years	13 years
$\beta^+$ -mutation	6	3 years	8 years
$\beta^+$ -mutation and coincident $\alpha$ -thal	6	11¼ years	18 years
Unidentified thalassaemia mutation	2	7½ years	12½ years
Coincident $\alpha$ -thalassaemia	11	9½ years	13½ years
Total	39	7 years	14 years

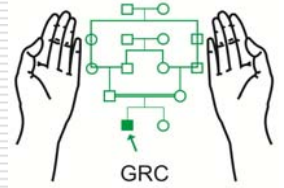
(Ahmed 1998)



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# Distribution of Thalassaemia Genes in the Community

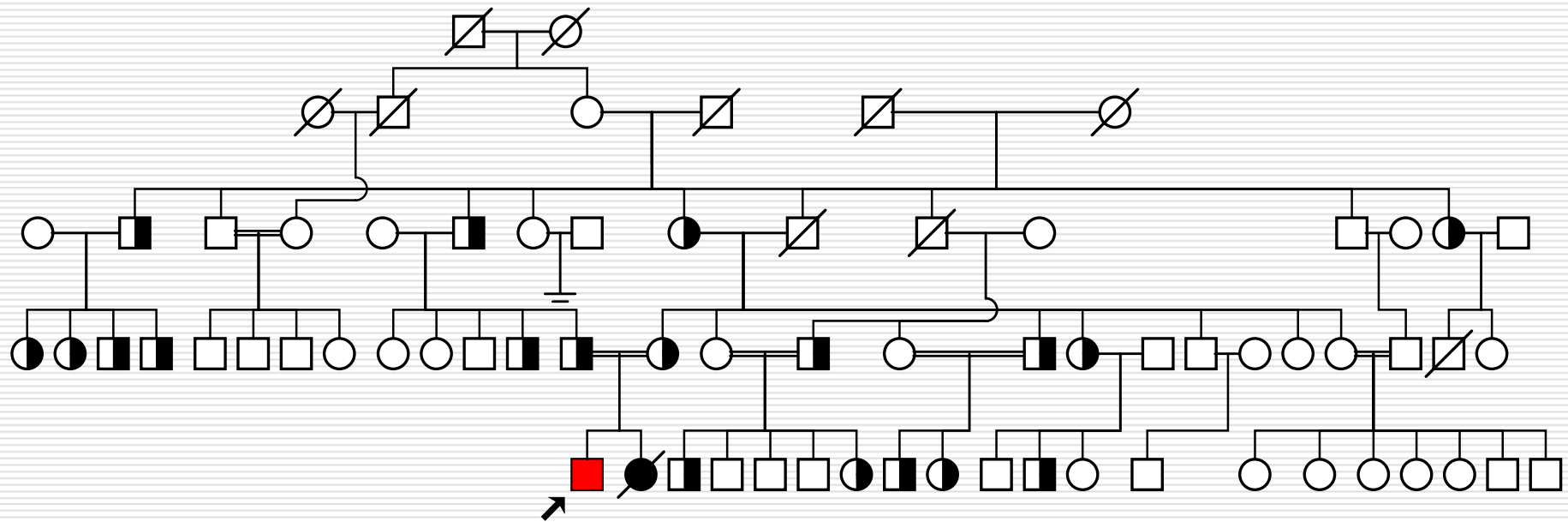
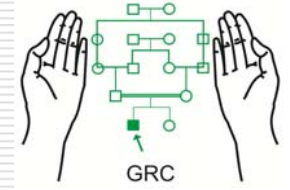
# Consanguineous Marriage in Pakistan

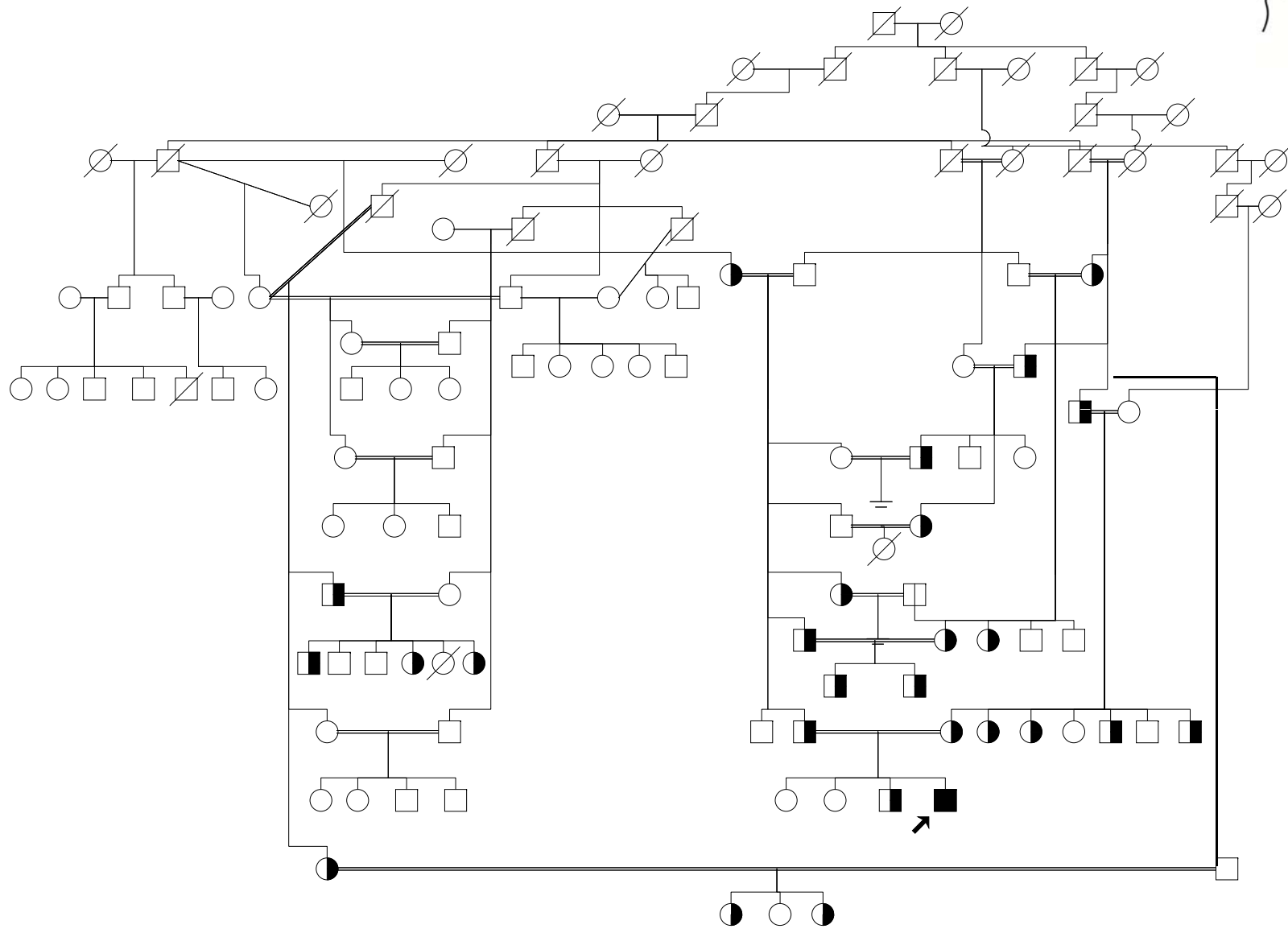
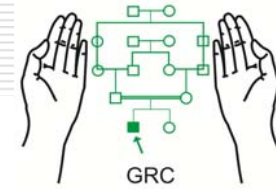


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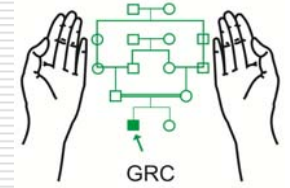
<b>Double 1<sup>st</sup> cousins</b>	<b>1%</b>
<b>1<sup>st</sup> cousins</b>	<b>37%</b>
<b>1½ cousins</b>	<b>12%</b>
<b>2<sup>nd</sup> cousins</b>	<b>1%</b>
<b>Biradri/tribe members</b>	<b>33%</b>
<b>Unrelated</b>	<b>16%</b>

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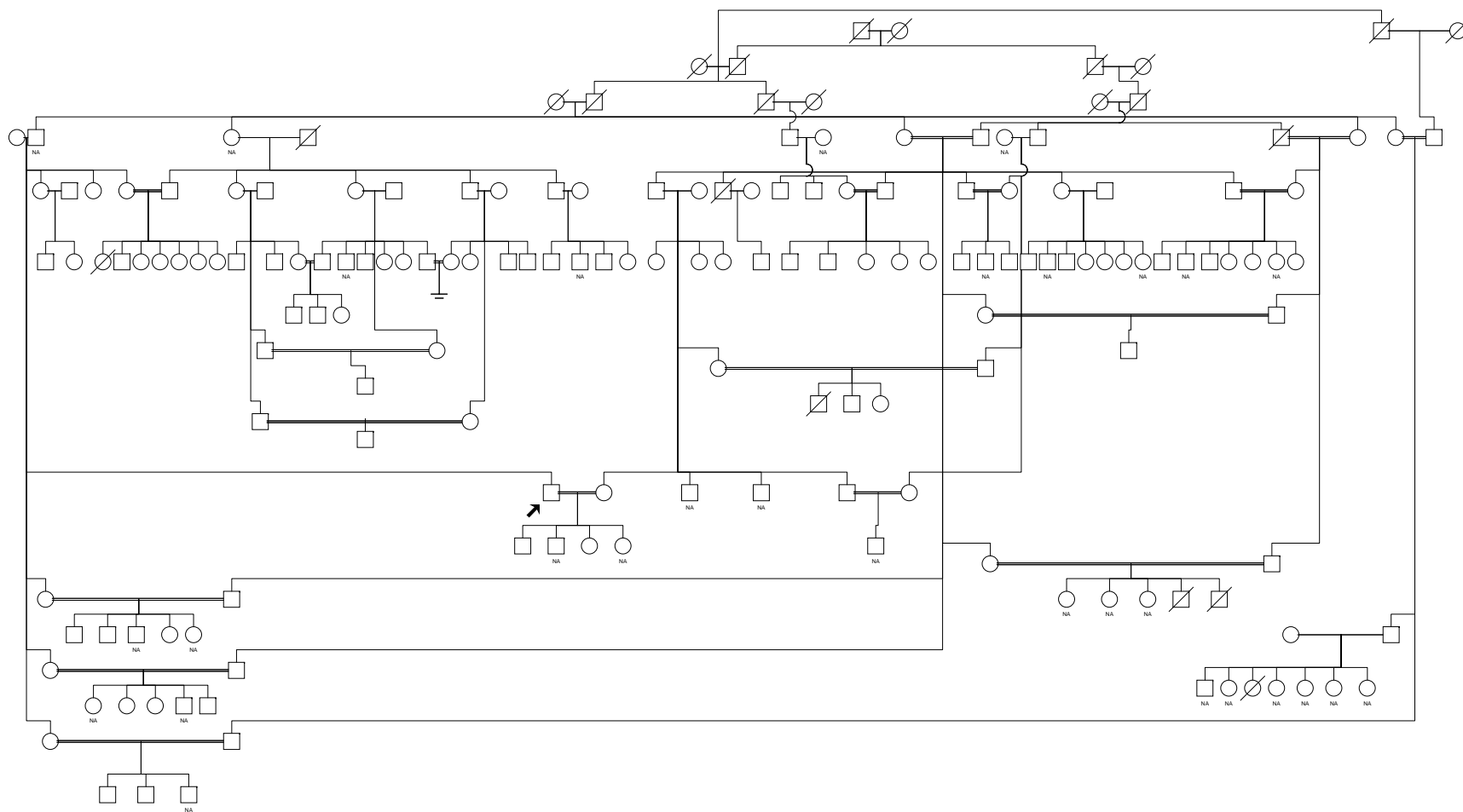
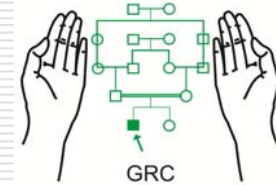


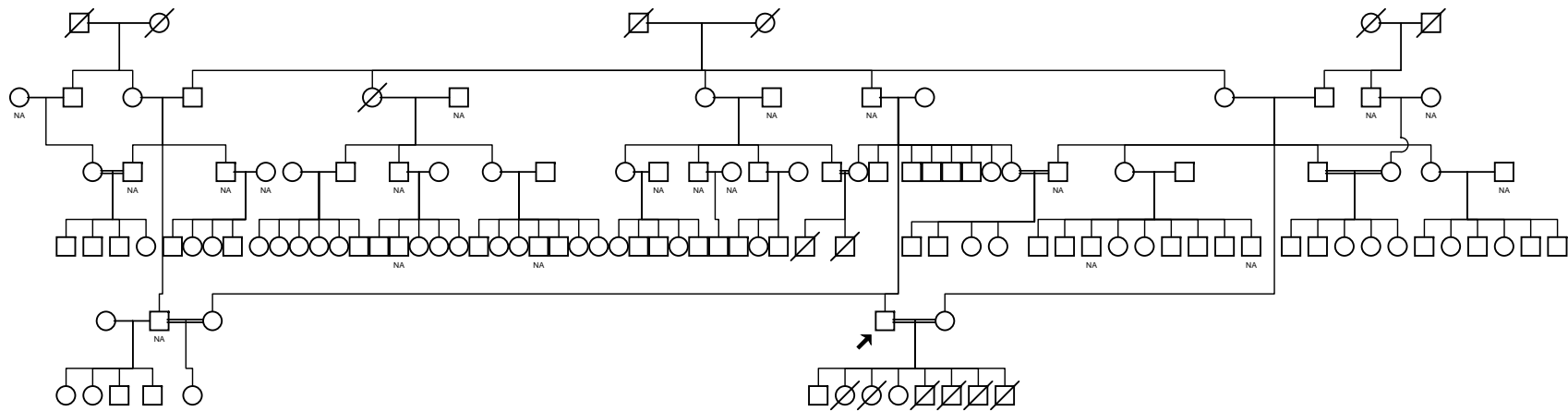
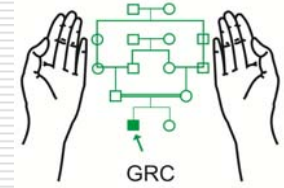
# DNA analysis in Families

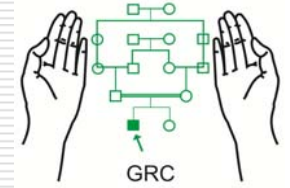
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<b>Families:</b>	<b>Mutation(s):</b>
No: 1	IVSI-1 (G-T)
No: 2	IVSI-5 (G-C)
No: 3	IVSI-5 (G-C)
No: 4	IVSI-5 (G-C)
No: 5	Fr 41-42 (-TTCT)
No: 6	Fr 8-9 (+G)
No: 7	Del 619/IVSI-1 (G-T)
No: 8	IVSI-5 (G-C)
No: 9	Hb-S
No: 10	Hb-S

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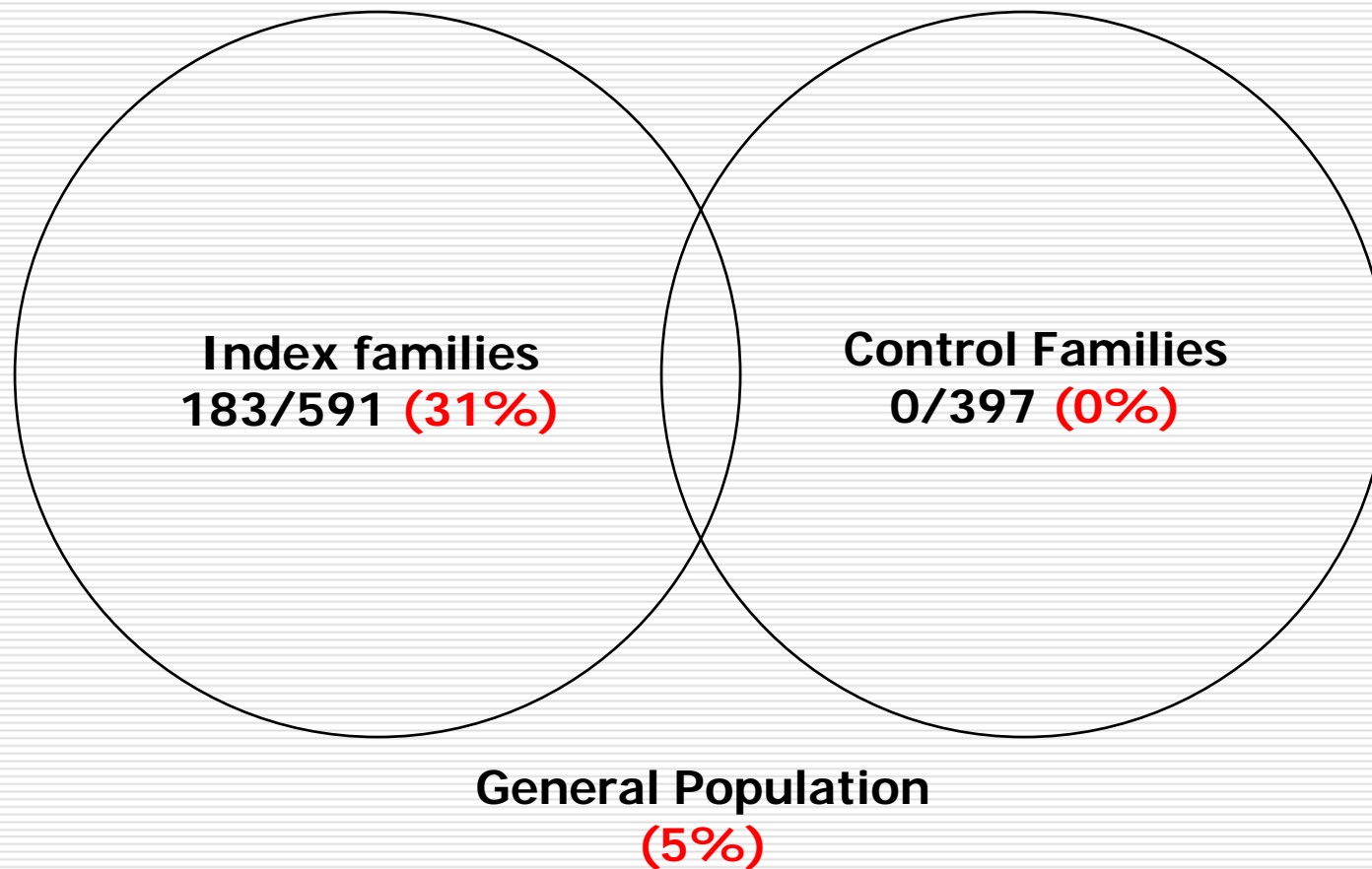


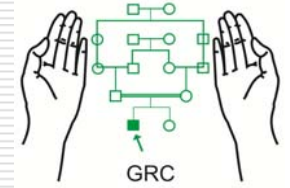




# Distribution of Thalassaemia Genes

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# SUMMARY

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- ❑ Alpha thalassaemia is the most common genetic haemoglobin disorder in Pakistan.
  - ❑ Beta thalassaemia, although less common than alpha thalassaemia, is the most significant genetic haemoglobin disorder in Pakistan.
  - ❑ The distribution of Thalassaemia genes in Pakistan is extremely heterogeneous.
  - ❑ Abnormal recessive genes are effectively trapped within the families.
  - ❑ Targeting the “Index Families” could be an exceptionally powerful tool for developing community based screening of Thalassaemia in Pakistan.
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