

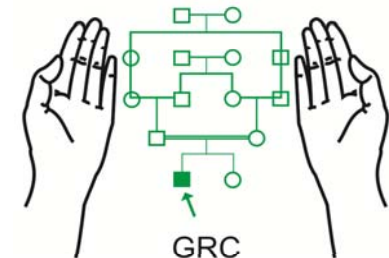
# Genetic Effects of Consanguineous Marriage: Facts and Artifacts

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

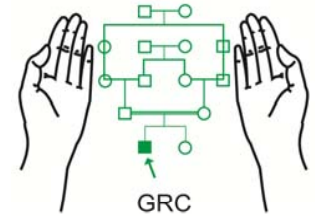
MBBS; MCPS; FCPS; PhD (London)

Genetics Resource Centre (GRC)

Rawalpindi

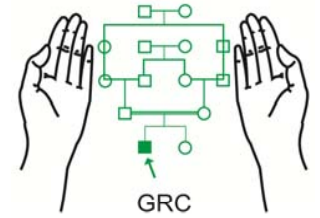


[www.grcpk.com](http://www.grcpk.com)



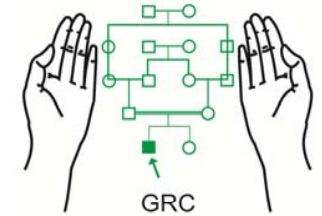
# Consanguinity

The predominant Western stereotype of inbreeding (consanguinity) is of a poor and remote community, a large number of whose inhabitants suffer from obscure physical disorders and exhibit obvious symptoms of mental subnormality.



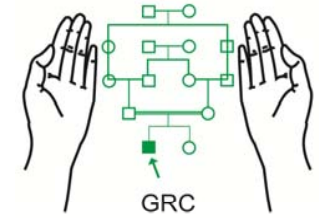
# Consanguinity

- Eight states in USA treat consanguineous marriage as a criminal offence
- In 22 states they are illegal



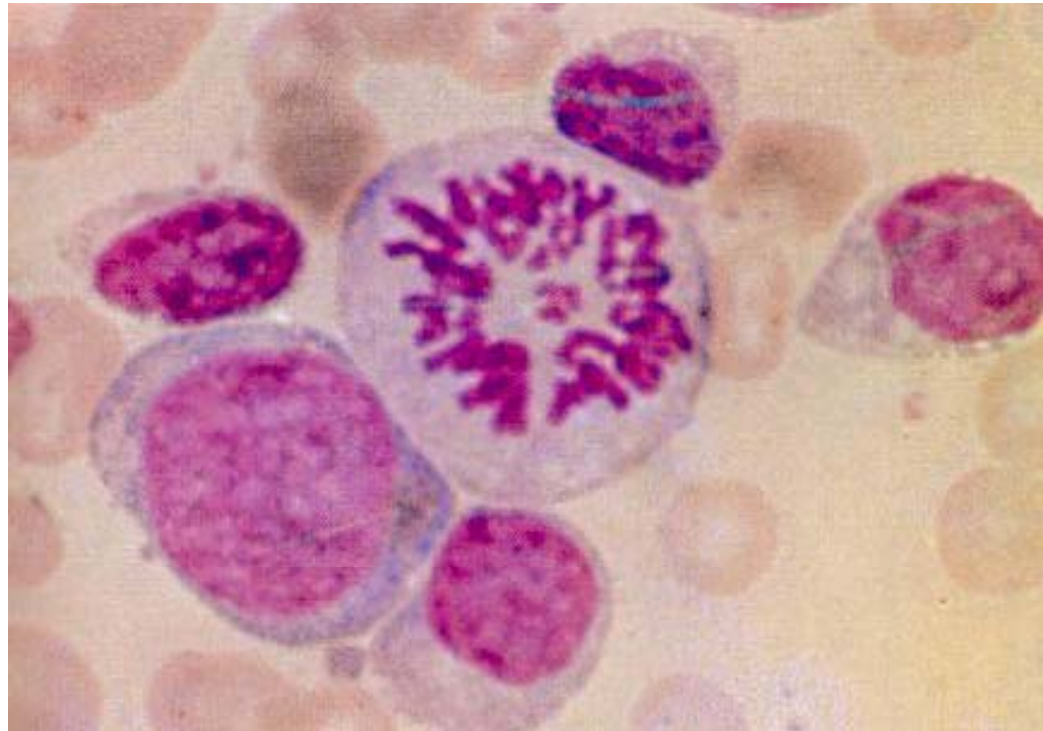
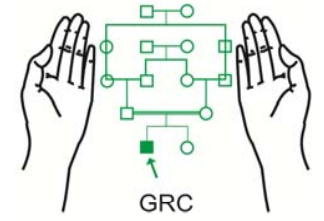
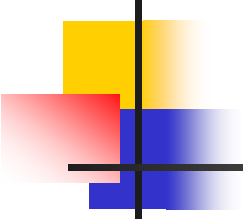
# Burden of Diseases in Pakistan: Distribution by Cause:

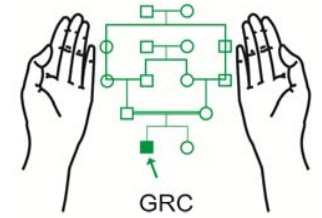
•	<b>Communicable Diseases:</b>		<b>38.4%</b>
–	Infectious and Parasitic diseases	20.4%	
–	Respiratory Infections	8.1%	
–	Childhood Cluster	6.7%	
–	Sexually Transmitted	2.2%	
–	Tropical Cluster	1.0%	
•	<b>Non-Communicable Diseases:</b>		<b>37.7%</b>
–	Cardiovascular	10.0%	
–	Nutritional/Endocrine	5.8%	
–	Malignant Neoplasms	4.3%	
–	Digestive System	3.4%	
–	Chronic Respiratory	2.6%	
–	Neuro-Psychiatric	3.2%	
–	<u>Congenital Abnormalities</u>	<u>3.5%</u>	
–	<u>Other Non-Communicable</u>	<u>4.9%</u>	
•	<b>Maternal and Perinatal Conditions:</b>		<b>12.5%</b>
–	Maternal	2.8%	
–	Perinatal	9.7%	
•	<b>Injuries:</b>		<b>11.4%</b>



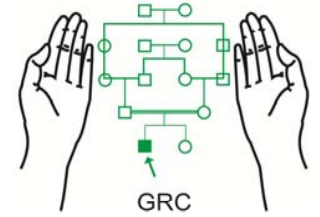
# Genetic Effects of Consanguineous Marriage

- Genetic
- Consanguineous Marriage
- Effects
  - Facts
  - Artifacts





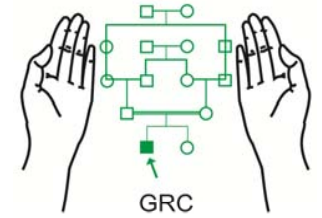
Every character in our body is controlled by at least one pair of genes



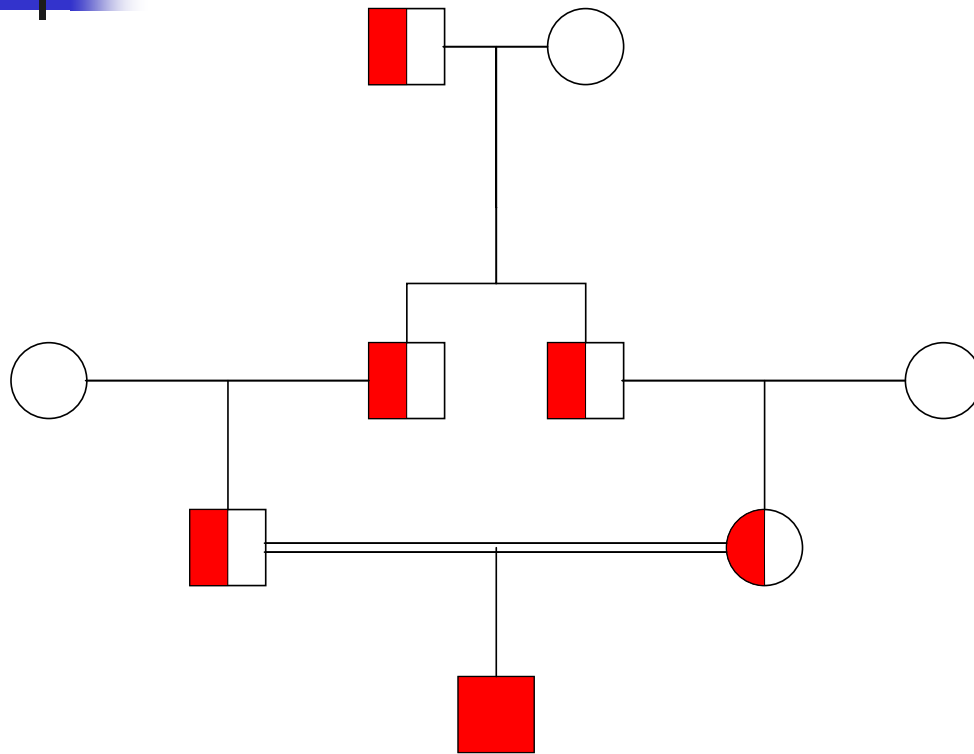
# Genetics

- Genes
  - Dominant
  - Recessive
- Heterozygotes
- Homozygotes

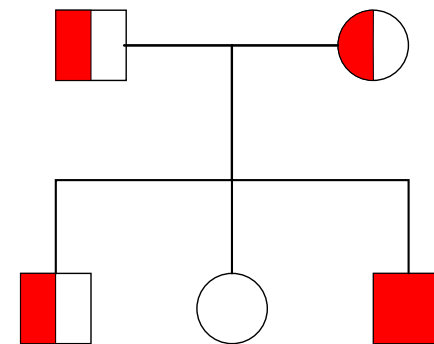




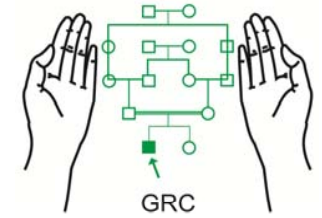
# Identical Genes



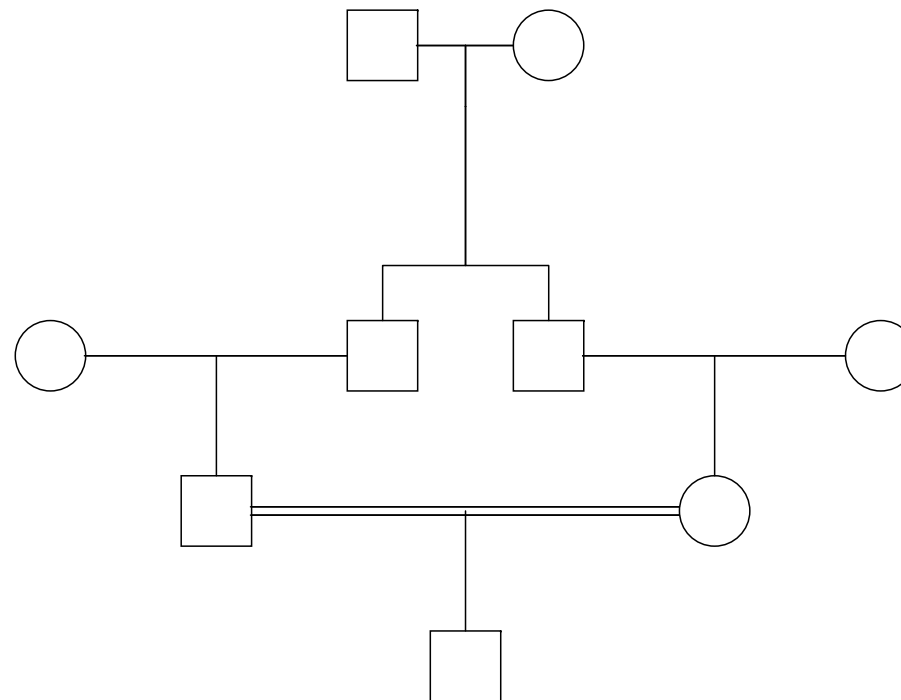
By descent



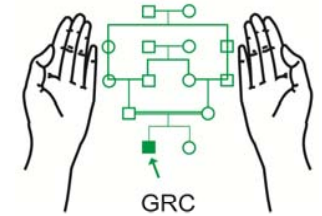
By chance



# Coefficient of Inbreeding (F)

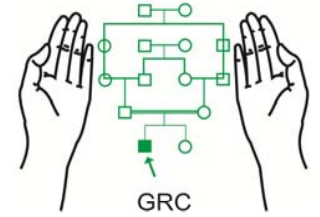


$$F = 0.0625$$



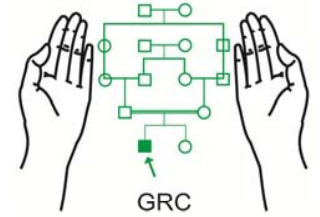
# Coefficient of Inbreeding (F)

Relationship:	Coefficient of Inbreeding (F)
Siblings	0.25
Double 1 <sup>st</sup> Cousins	0.125
1 <sup>st</sup> cousins	0.0625
1 ½ cousins	0.0313
2 <sup>nd</sup> cousins	0.0156
2 ½ cousins	0.0078
3 <sup>rd</sup> cousins	0.0039
3 ½ cousins	0.0020
4 <sup>th</sup> cousins	0.0010



# Consanguineous Marriage

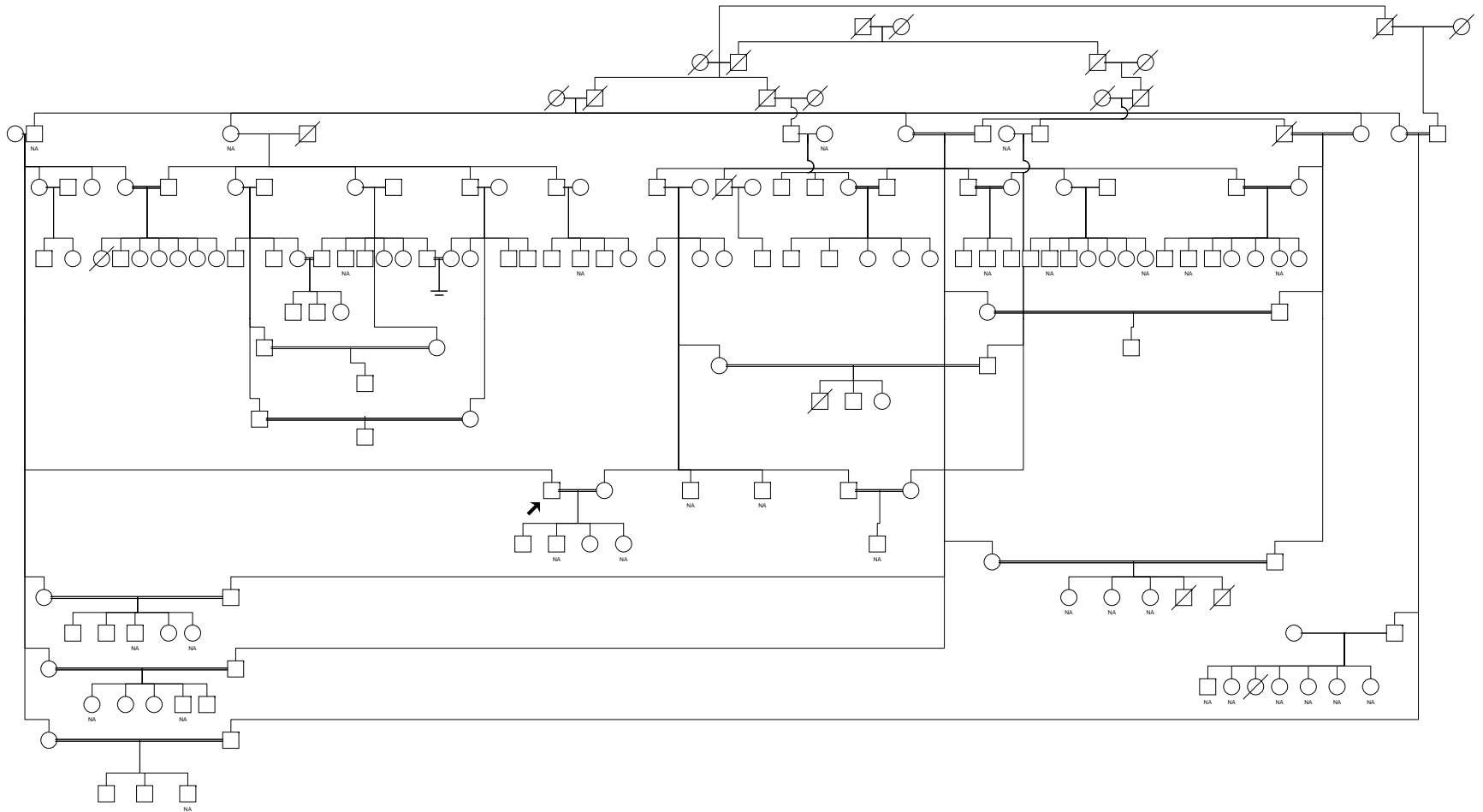
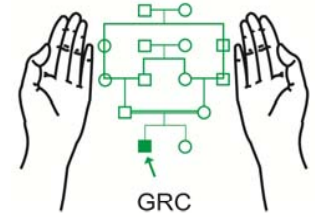
- Marriage between individuals who have at least one, not too remote, common ancestor
- Marriage beyond 2<sup>nd</sup> cousins is considered unrelated



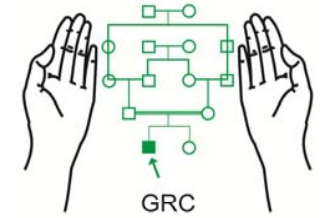
# Genetic Effects of Consanguinity

- Proportion of Homozygotes is increased
  - Normal
  - Abnormal (Pathological)
  - Beneficial
  - Neutral
- The increase in Homozygotes is directly proportional to the Coefficient of Inbreeding ( $F$ )

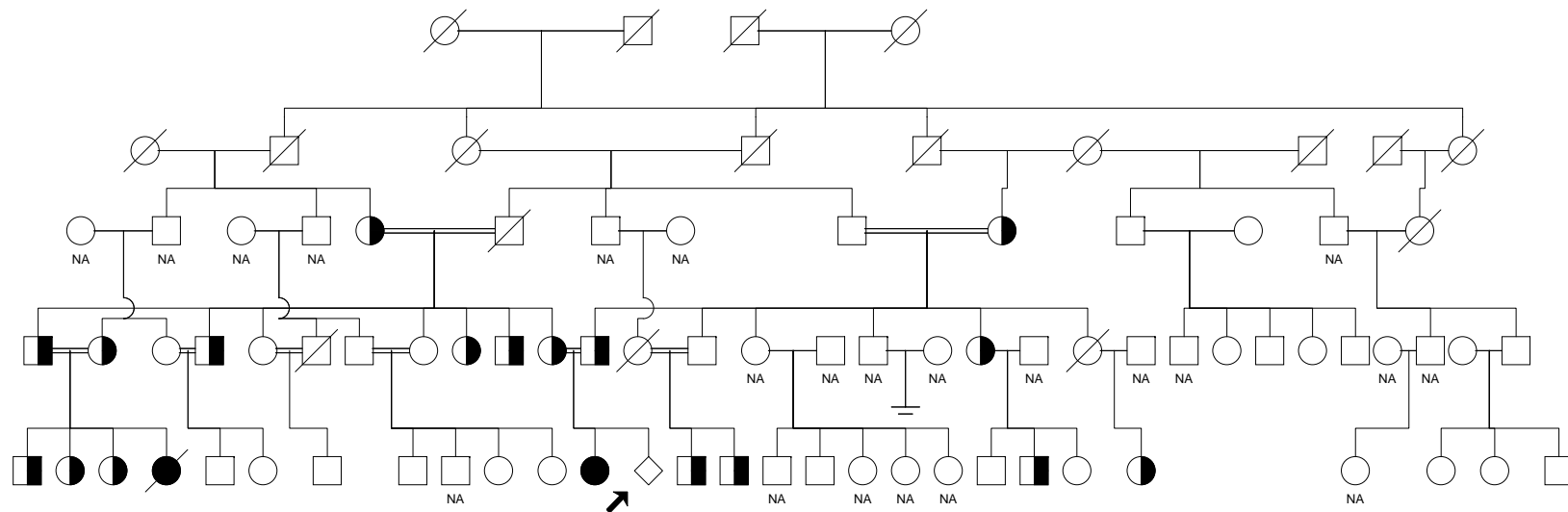
# Consanguinity and Normal Genes



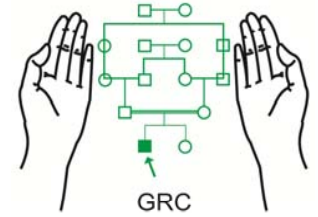
(S. Ahmed, 1998)



# Consanguinity and Abnormal Genes



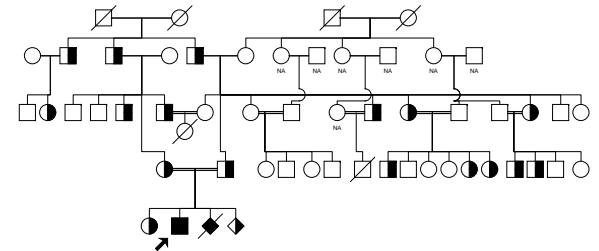
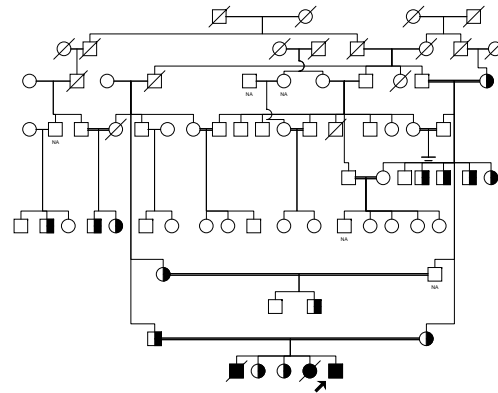
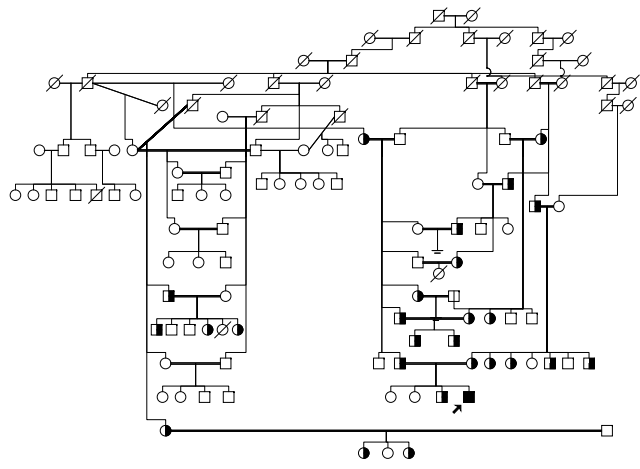
(S. Ahmed, 1998)



# Consanguinity and Rare Recessive Genes

- Every individual carries on an average 1.4 lethal recessive genes
- Prenatal period
  - Higher miscarriage rates
- Pre-reproductive period
  - Deaths are 4.4% higher amongst 1<sup>st</sup> cousin couples than in the unrelated couples
- Adult age

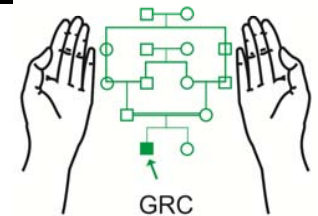


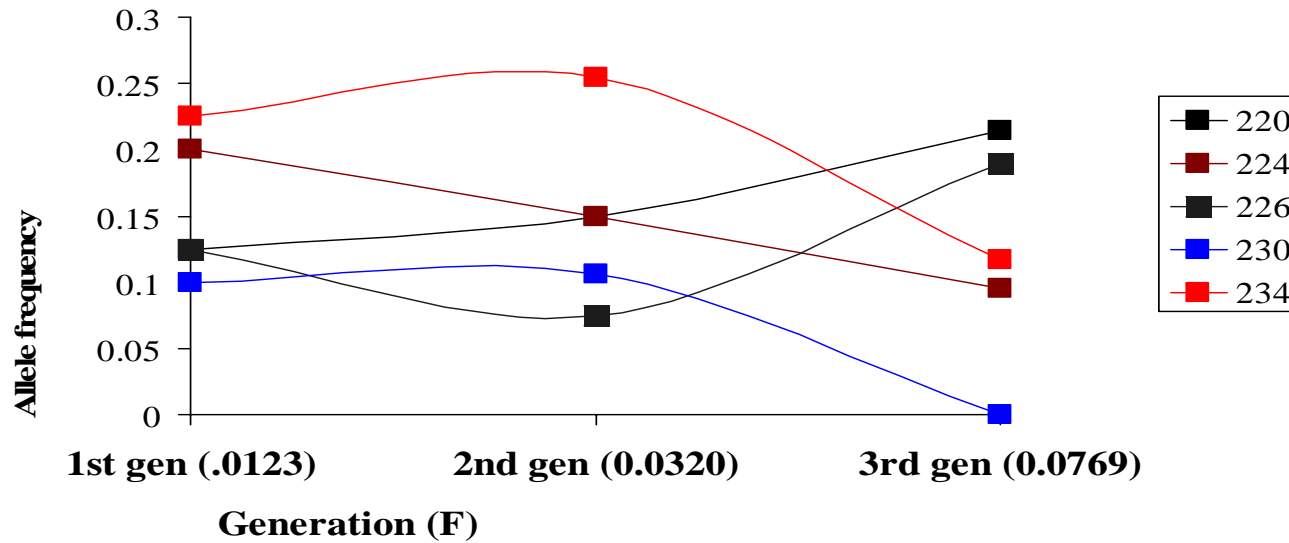
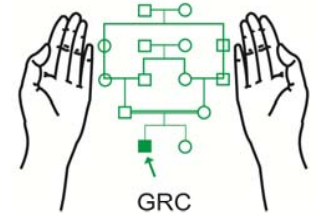
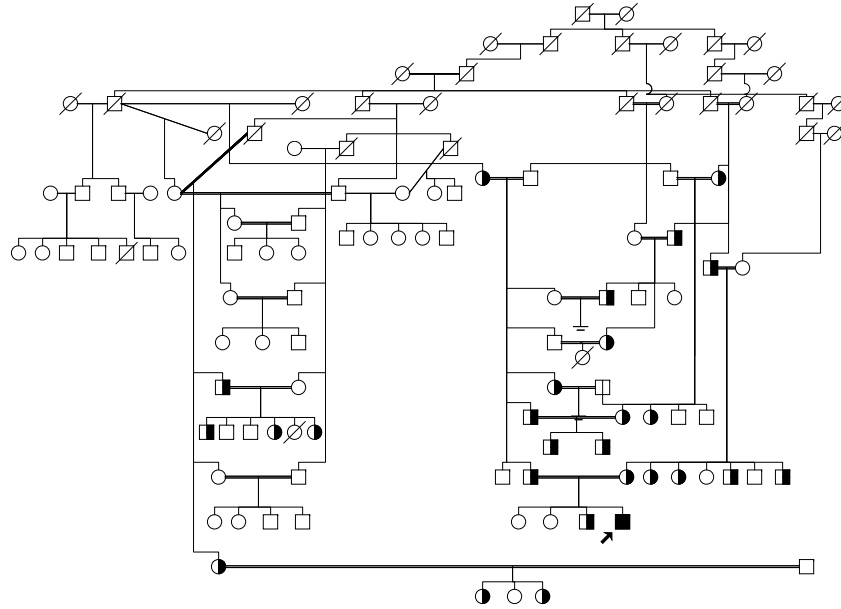
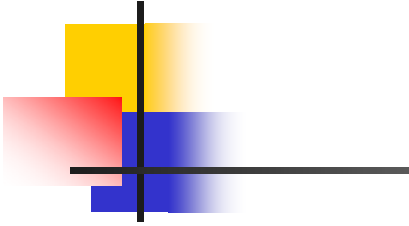


	<b>Awan</b> (F=0.0437)		<b>Khattar</b> (F=0.0320)		<b>Rajput</b> (F=0.0304)	
<b>Chromosome</b>	<b>Obs:</b>	<b>Exp:</b>	<b>Obs:</b>	<b>Exp:</b>	<b>Obs:</b>	<b>Exp:</b>
<b>13</b>	0.345	0.309	0.216	0.280	0.206	0.267
<b>15</b>	0.447	0.369	0.324	0.338	0.275	0.325
<b>13+15</b>	<b>0.409</b>	<b>0.335</b>	<b>0.281</b>	<b>0.315</b>	<b>0.248</b>	<b>0.302</b>

**Observed and expected homozygosity for STR alleles  
(Neutral Genes)**

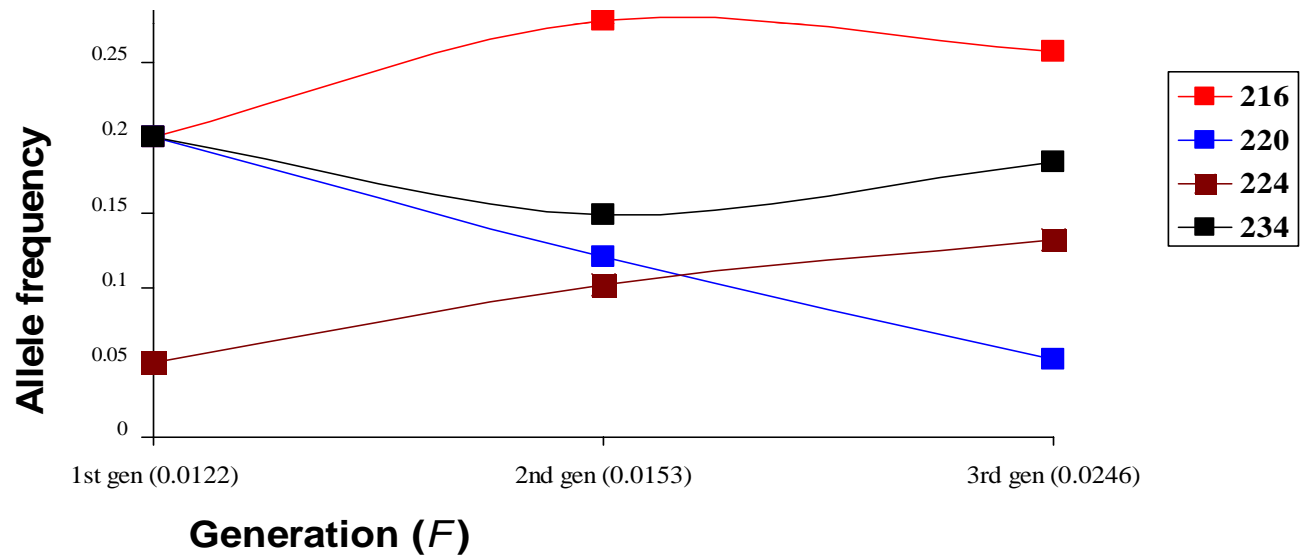
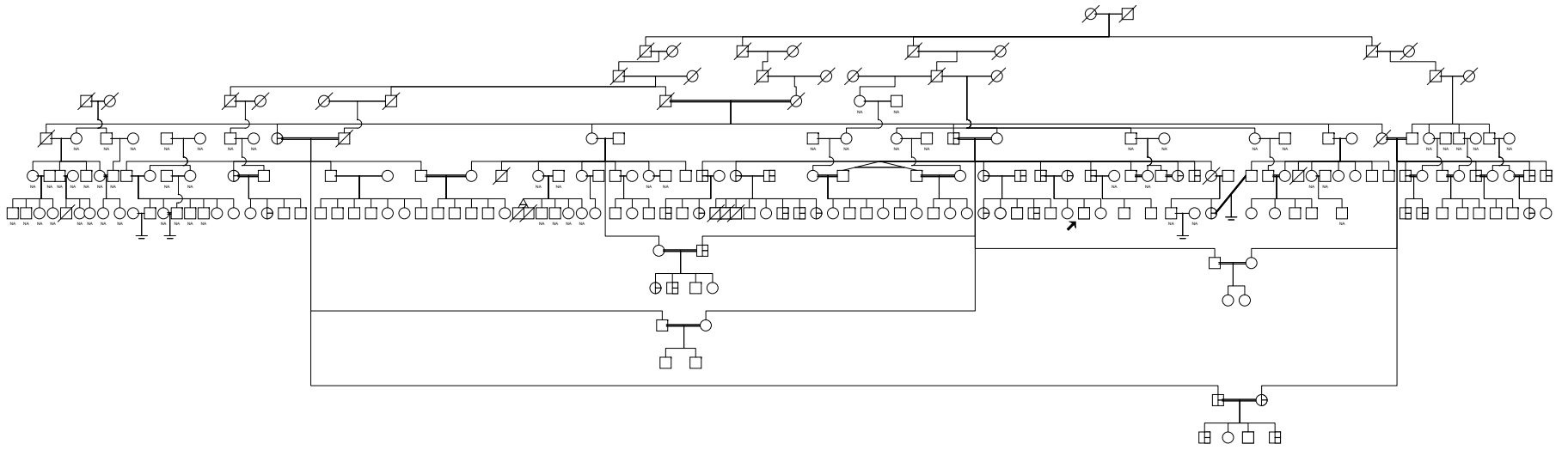
(S. Ahmed et al, DNA Polymorphism 2000)





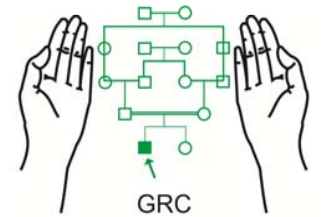
# Genetic Drift

(S. Ahmed, 1998)

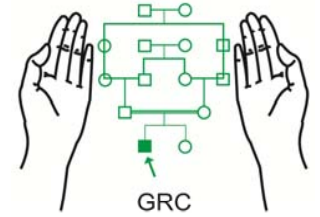


# Genetic Drift

(S. Ahmed 1998)



# Consanguineous marriage and Genetic Diseases

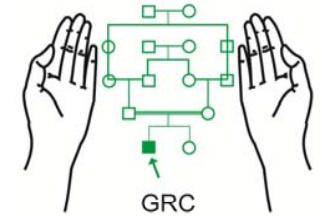


- Affected

- Autosomal recessive
  - Rare
  - Common

- Not affected

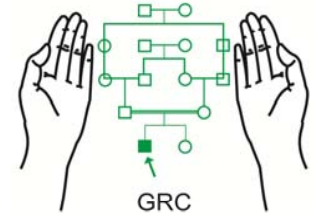
- Autosomal Dominant
- X-linked
- Chromosomal
- Polygenic



## Consanguinity and Beneficial Genes

<b>Xmn-I Genotype:</b>	<b>Thal Intermedia:</b>	<b>Thal Major :</b>	<b>Normal:</b>
-/-	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%)
<b>Total:</b>	39 (100%)	39 (100%)	58 (100%)

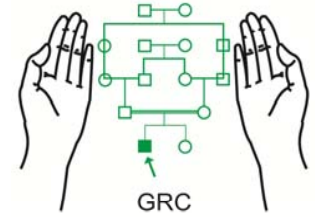
(S. Ahmed, 1998)



# Consanguinity: The Facts

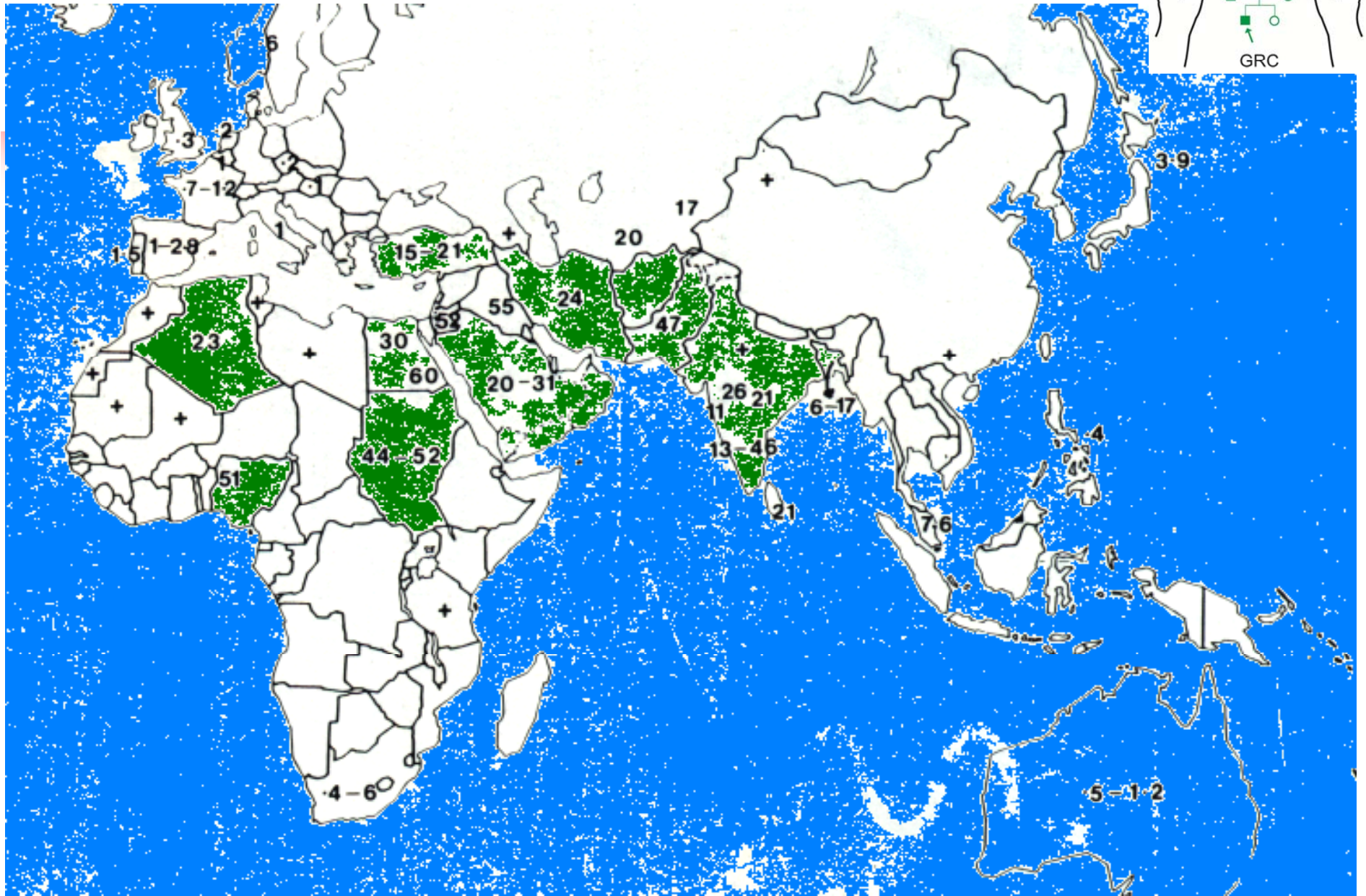
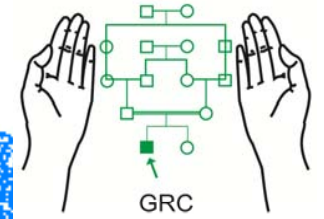
- The total population effect of consanguineous marriage is quite modest and is far less than has often been stated.
- There is an average 4.4% increase in infant mortality among the off-springs of 1<sup>st</sup> cousins compared with unrelated controls.

(Bittles AH, Clinical Genetics 2001)



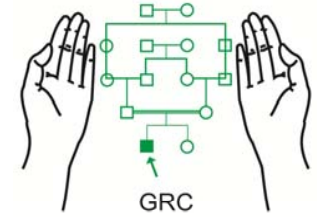
# Consanguinity: The Artifacts

- Personal biases
- Lack of population based data
- Failure to control for the confounding variables:
  - Lack of education
  - Poverty
  - Others



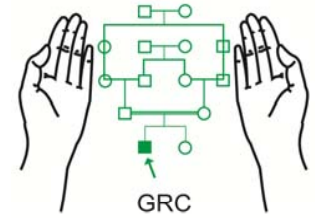


# Consanguineous Marriage in Pakistan



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

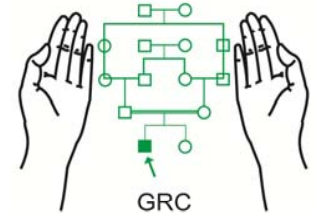
(Bittles AH, 1994)



# Consanguineous marriage

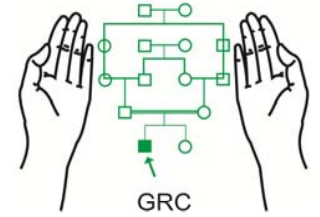
- The Solution ?

# EXTENDED FAMILY TESTING FOR A RECESSIVE DISORDER: EXPERIENCE IN PAKISTAN



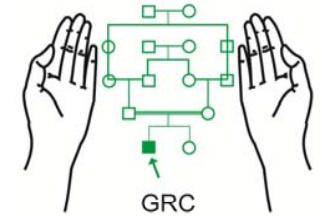
## Thalassaemia

- Classical example of a recessive disorder
- Common (5% carrier rate)
- Carriers can be detected by a simple blood test



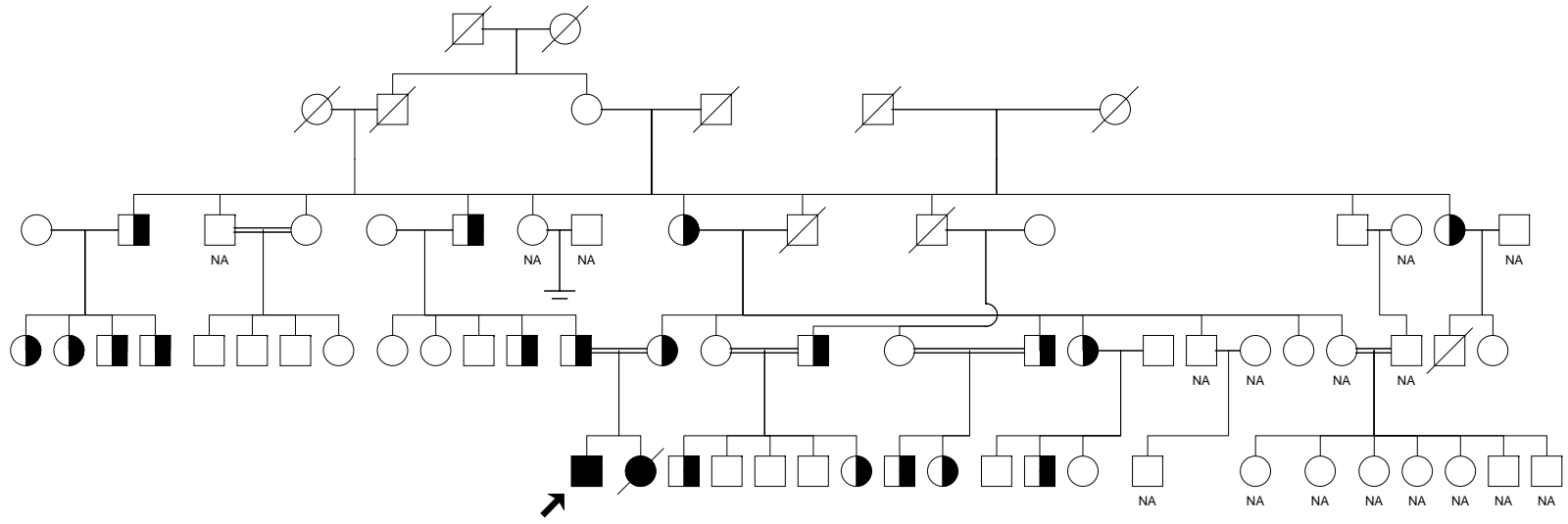
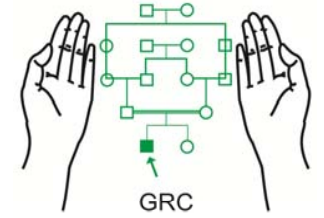
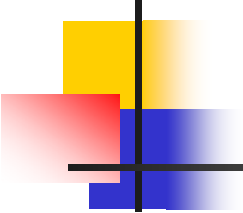
# The Hypothesis

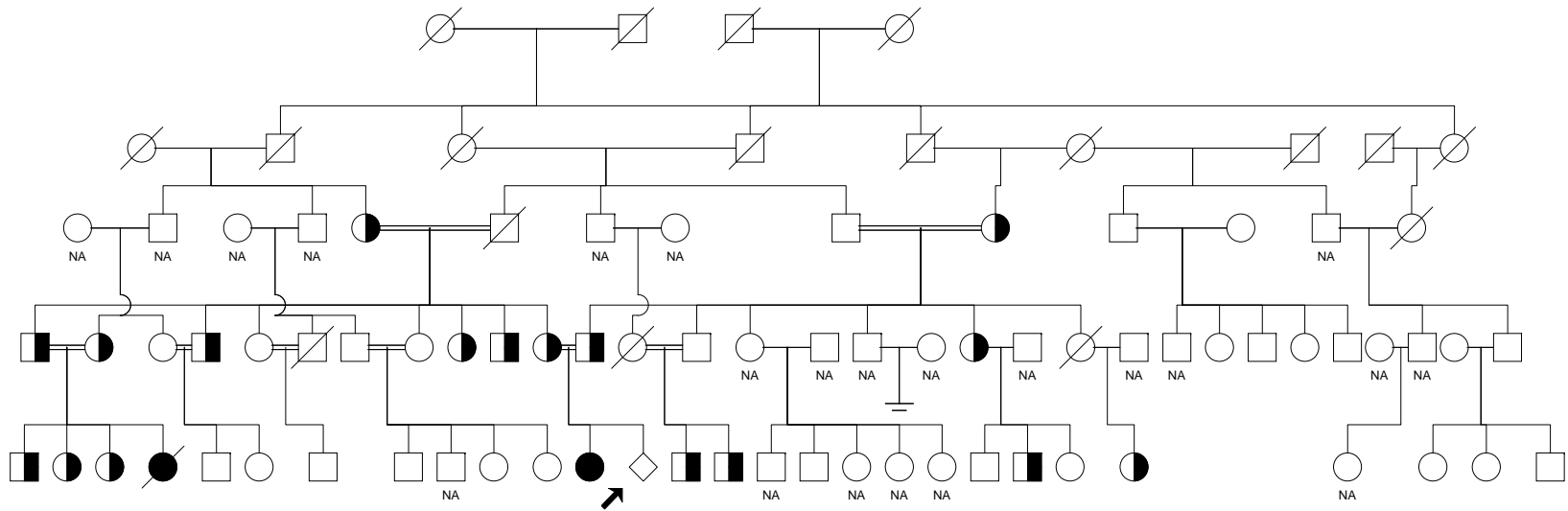
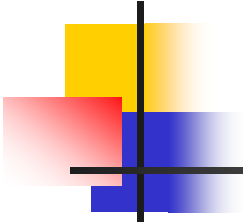
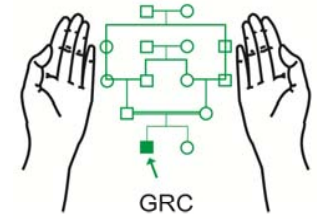
- In families that practice frequent consanguineous marriage, genes are effectively trapped within the extended family network.
- An index child with a recessive disorder in such families could provide an opportunity to detect a large number of present and future at risk couples.

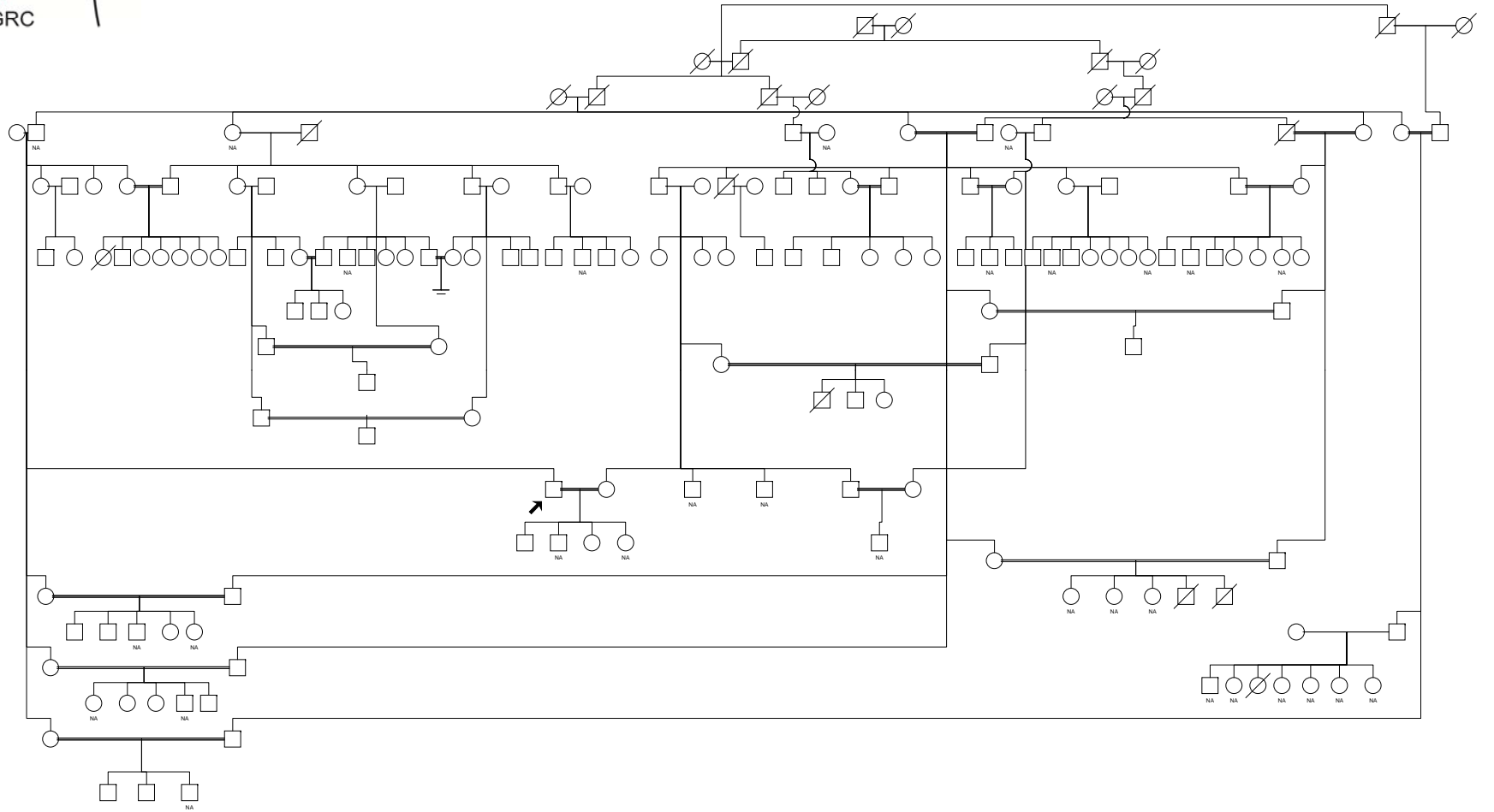
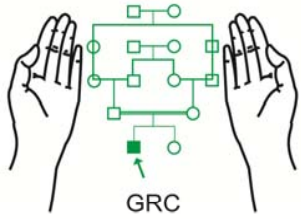


# Extended Family Testing

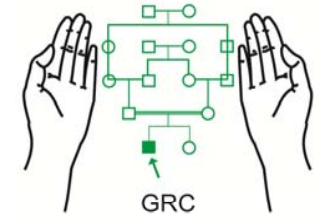
<b>Families:</b>	<b>Offered:</b>	<b>Accepted:</b>	<b>Declined:</b>
Index:	16	10	6
Control:	8	5	3
Total:	24	15	9



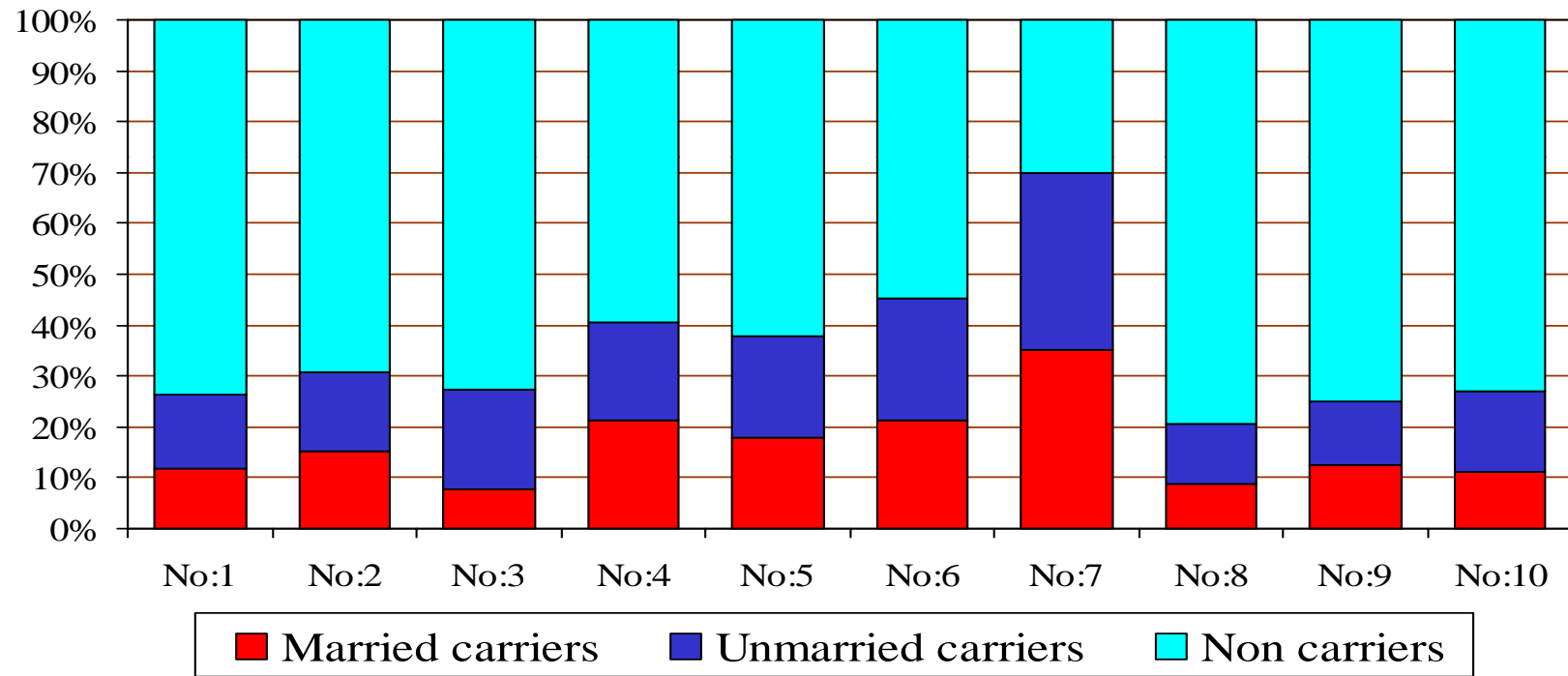


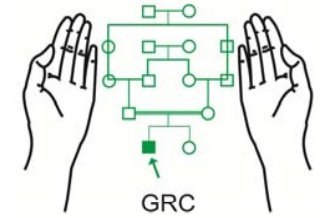






# Carrier Screening in the Index Families



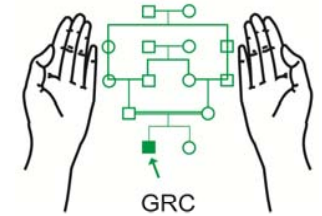


# Carrier Rate for Thalassaemia

Index families  
183/591 (31%)

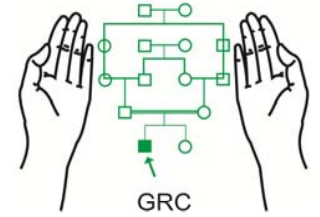
Control Families  
0/397 (0%)

General Population  
(5%)



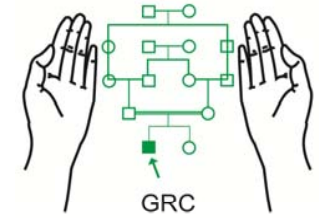
## At risk couples in the Index Families

■ Parents of index children:	9
■ Detected through history:	6
■ Prospectively detected:	2
<hr/>	
■ Total:	17

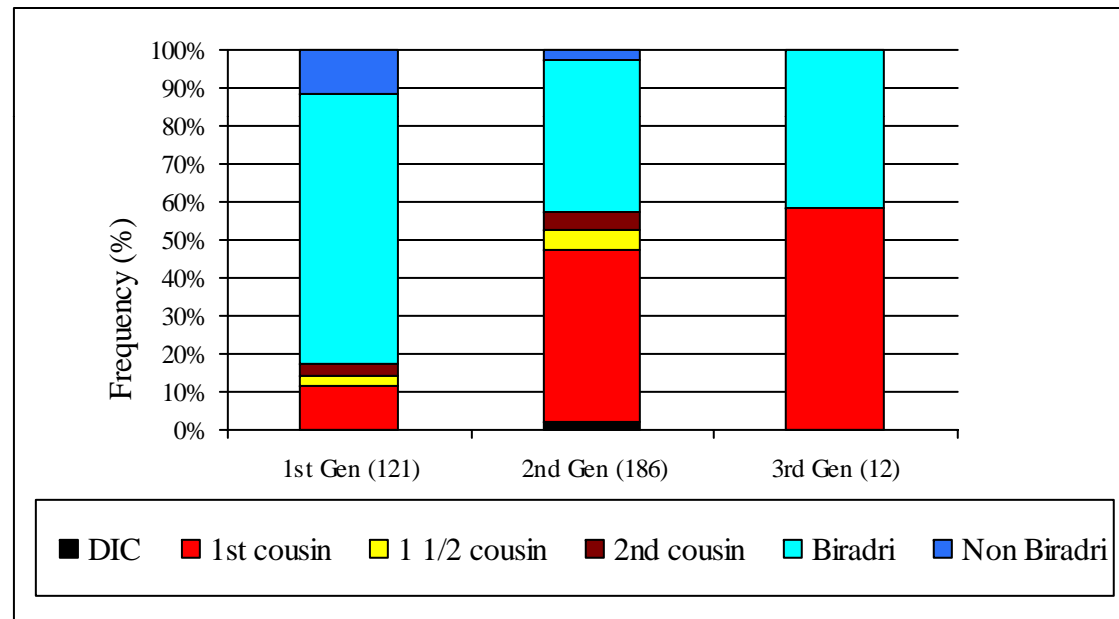


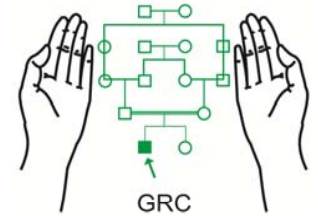
## Effect on Choice of Partner

- Seven families were followed-up for five years
- Seven marriages/engagements took place
- Six couples were consanguineous and one was between Biradri members
- Test results were taken in to account in all seven marriages/engagements
- One carrier male had problems in marriage
- No reports that a marriage was explicitly avoided because both partners were carriers



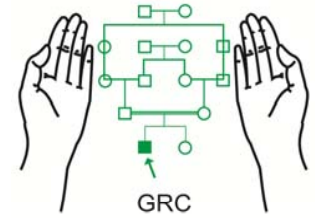
# Consanguineous Marriage in Families





# Summary

- Over 90% of marriages in Pakistan are either consanguineous or within the Biradri.
- Discouraging this practice on genetic grounds alone is not only ethically unacceptable, it is also totally unrealistic.
- The only real option for providing genetic counselling lies in a way that is compatible with the social mores and kinship structure of the Pakistani population and provides accurate carrier testing and precise risk information.
- Targeted family screening focuses on high risk families, and produces a high yield of carriers and at risk couples.
- It avoids the problem of a low level of literacy, because information and personal experiences are communicated directly amongst the family members.
- It is realistic to visualise expanding the recommended approach across the spectrum of inherited diseases wherever consanguineous marriage is common.



- Be careful in providing information
- People develop antibodies to information
- De-sensitization may be a very slow process