Genetic Effects of Consanguineous Marriage: Facts and Artifacts

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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:

- **Communicable Diseases:** 38.4%
  - Infectious and Parasitic diseases 20.4%
  - Respiratory Infections 8.1%
  - Childhood Cluster 6.7%
  - Sexually Transmitted 2.2%
  - Tropical Cluster 1.0%

- **Non-Communicable Diseases:** 37.7%
  - Cardiovascular 10.0%
  - Nutritional/Endocrine 5.8%
  - Malignant Neoplasms 4.3%
  - Digestive System 3.4%
  - Chronic Respiratory 2.6%
  - Neuro-Psychiatric 3.2%
  - Congenital Abnormalities 3.5%
  - Other Non-Communicable 4.9%

- **Maternal and Perinatal Conditions:** 12.5%
  - Maternal 2.8%
  - Perinatal 9.7%

- **Injuries:** 11.4%
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 chance

By descent

By chance
Coefficient of Inbreeding (F)

\[ F = 0.0625 \]
# Coefficient of Inbreeding (F)

<table>
<thead>
<tr>
<th>Relationship:</th>
<th>Coefficient of Inbreeding (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings</td>
<td>0.25</td>
</tr>
<tr>
<td>Double 1\textsuperscript{st} Cousins</td>
<td>0.125</td>
</tr>
<tr>
<td>1\textsuperscript{st} cousins</td>
<td>0.0625</td>
</tr>
<tr>
<td>1 ½ cousins</td>
<td>0.0313</td>
</tr>
<tr>
<td>2\textsuperscript{nd} cousins</td>
<td>0.0156</td>
</tr>
<tr>
<td>2 ½ cousins</td>
<td>0.0078</td>
</tr>
<tr>
<td>3\textsuperscript{rd} cousins</td>
<td>0.0039</td>
</tr>
<tr>
<td>3 ½ cousins</td>
<td>0.0020</td>
</tr>
<tr>
<td>4\textsuperscript{th} cousins</td>
<td>0.0010</td>
</tr>
</tbody>
</table>
Consanguineous Marriage

- Marriage between individuals who have at least one, not too remote, common ancestor
- Marriage beyond 2nd 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 1st cousin couples than in the unrelated couples
- Adult age
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Awan (F=0.0437)</th>
<th>Khattar (F=0.0320)</th>
<th>Rajput (F=0.0304)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs:</td>
<td>Exp:</td>
<td>Obs:</td>
</tr>
<tr>
<td>13</td>
<td>0.345</td>
<td>0.309</td>
<td>0.216</td>
</tr>
<tr>
<td>15</td>
<td>0.447</td>
<td>0.369</td>
<td>0.324</td>
</tr>
<tr>
<td>13+15</td>
<td>0.409</td>
<td>0.335</td>
<td>0.281</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Xmn-I Genotype:</th>
<th>Thal Intermedia:</th>
<th>Thal Major:</th>
<th>Normal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>-/-</td>
<td>12 (30.8%)</td>
<td>30 (76.9%)</td>
<td>30 (51.7%)</td>
</tr>
<tr>
<td>-/+</td>
<td>13 (33.3%)</td>
<td>9 (23.1%)</td>
<td>20 (34.5%)</td>
</tr>
<tr>
<td>+/+</td>
<td>14 (35.9%)</td>
<td>None</td>
<td>8 (13.8%)</td>
</tr>
<tr>
<td>Total:</td>
<td>39 (100%)</td>
<td>39 (100%)</td>
<td>58 (100%)</td>
</tr>
</tbody>
</table>

(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 1st 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

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double 1\textsuperscript{st} cousins</td>
<td>1%</td>
</tr>
<tr>
<td>1\textsuperscript{st} cousins</td>
<td>37%</td>
</tr>
<tr>
<td>1\frac{1}{2} cousins</td>
<td>12%</td>
</tr>
<tr>
<td>2\textsuperscript{nd} cousins</td>
<td>1%</td>
</tr>
<tr>
<td>Biradri/tribe members</td>
<td>33%</td>
</tr>
<tr>
<td>Unrelated</td>
<td>16%</td>
</tr>
</tbody>
</table>

(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

<table>
<thead>
<tr>
<th>Families:</th>
<th>Offered:</th>
<th>Accepted:</th>
<th>Declined:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index:</td>
<td>16</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Control:</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Total:</td>
<td>24</td>
<td>15</td>
<td>9</td>
</tr>
</tbody>
</table>
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
- 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 into 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

![Consanguineous Marriage in Families](image)

The diagram illustrates the frequency of consanguineous marriages in different generations and the percentage of individuals involved in each category.

- **1st Gen (121)**
  - DIC: 0%
  - 1st cousin: 100%
  - 1 1/2 cousin: 0%
  - 2nd cousin: 0%
  - Biradri: 0%
  - Non Biradri: 0%

- **2nd Gen (186)**
  - DIC: 0%
  - 1st cousin: 80%
  - 1 1/2 cousin: 20%
  - 2nd cousin: 0%
  - Biradri: 0%
  - Non Biradri: 0%

- **3rd Gen (12)**
  - DIC: 0%
  - 1st cousin: 60%
  - 1 1/2 cousin: 40%
  - 2nd cousin: 0%
  - Biradri: 0%
  - Non Biradri: 0%
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