IN THE NAME OF ALLAH,
THE MOST MERCIFUL,
THE MOST BENEFICIENT
Consanguinity and Genetic Disorders - Is there an influence?
Presentation Outline

• Consanguinity:
  - Pros
  - Cons
• Effect of consanguinity on frequency of genetic disorders:
  - Single genes
  - Multifactorial
• Consanguinity in Saudi Arabia:
  - National studies
  - Counselling
• Conclusions.
- Consanguinity: related by blood.
- Consanguineous marriages: marriages between blood relatives.
- Genetics classification: second cousins marriages or closer.
Consanguinity

Preferentially observed in many countries
# Prevalence of Consanguinity in Some Countries

<table>
<thead>
<tr>
<th>Region</th>
<th>Country</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arabs</strong></td>
<td>Kuwait</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Syria</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Egypt</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Lebanon</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Algeria</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Jordan</td>
<td>50</td>
</tr>
<tr>
<td><strong>Asians</strong></td>
<td>Pakistan</td>
<td>38 - 49</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>5 - 61</td>
</tr>
<tr>
<td></td>
<td>Japan</td>
<td>1.6 - 3.9</td>
</tr>
<tr>
<td><strong>Americas</strong></td>
<td>Brazil</td>
<td>0.62 - 9.0</td>
</tr>
</tbody>
</table>

*El-Hazmi et al., 1996*
Consanguinity

Practiced for century’s worldwide

• advantages, and
• disadvantages

Contributing factors

• Economic
• Psychological
• Social

Indications:
Advantages > Disadvantage
Advantages of consanguineous marriages*

- Maintenance of family structure and property
- Stronger family ties
- Financial advantages relating to dowry or bride wealth
- Greater marriage stability and durability
- Closer relationship with in-laws

* Bittles, 1994
Detrimental effects of consanguinity

- Loss of biological fitness
- Increased morbidity levels* (1-4% non-consanguineous couples)
- Rare disorders seen in highly endogamous communities
  - Increased mortality* (>4.4% non-consanguineous couples)
  - Mutations unique to the community
  - Neonatal, post-neonatal, and infant mortality

* Bittles, 1994
Effect of consanguinity on Reproductivity

Conflicting Reports

- Increased sterility
- Increased rate of abortions
- Still births
- Perinatal losses
- Neonatal deaths
- Decreased birth weight

Vs

- Increased fertility in women
- No or very little effect on:
  - abortion rate,
  - still births,
  - perinatal loss,
  - neonatal death.
Effect of consanguinity on reproductive behavior

Reduced fertility*

- Couples share specific HLA haplotype
- Expression of deleterious genes acting during embryonic or fetal development
- Failure to initiate pregnancy
- Spontaneous abortion
- Reduced rate of involuntary sterility and prenatal loss

Increased fertility**

- Greater genetic compatibility between mother and developing fetus
- Reduced rate of involuntary sterility and prenatal loss

Compensatory mechanism for fetal or childhood losses

* Ober et al, 1992
** Tuncbilek & Koc, 1994
More Recently*

Higher total fertility ratio

Lower parental age at marriage and first birth

Shorter birth intervals

Continuation of child-bearing to comparatively later age**

Optimization of the maternal reproduction span

* Bittles, 1995
  ** Tuncbilek & Koc, 1994
Detrimental Health effects of consanguineous marriages due to:

Expression of rare, recessive genes inherited from a common ancestor
Degree of Relationship and Gene Sharing

First degree relation
- Sibs
- Dizygotic twins
- Parents
- Children

Proportion of shared genes
- 1/2

Chance of homo. by descent
- 1/4

Second degree relation
- Half sibs
- Uncles, aunts
- Nephews, nieces
- Double first cousins

- 1/4
- 1/8

Third degree relation
- First cousin
- Half uncle, aunt
- Half nephews, nieces

- 1/8
- 1/16
Degree of Relationship and Gene Sharing

Fourth Degree relation
- First cousin once removed

Fifth Degree relation
- Second cousins

Others

Proportion of shared genes
- 2nd cousin once removed*
- 3rd cousins

Chance of homo. by decent
- 1/16
- 1/32
- 1/64
- 1/128
- 1/256

*One step higher
• Consanguinity:
  - Pros
  - Cons
• Effect of consanguinity on frequency of genetic disorders.
• Consanguinity in Saudi Arabia.
• Conclusion.
Effect of consanguinity on congenital malformation

Increased by 2-5 times (of unrelated parents)

Examples:
- Cardiovascular
- CNS
- Urogenital
- Ophthalmic
- Gastro-intestinal
- Skeletal
- Cutaneous
- Multiple malformations

Mechanism?
- AR disorders (↑ Homozygosity at several loci)

AR disorders

Chromosomal structural disorder
Effect of consanguinity on common diseases

**No Effect:**
- DM
- Asthma
- Duodenal ulcers

**Increased Susceptibility**
- Multiple sclerosis
- CHD
- Some cancers

**Significant decrease in cognitive performance**
Consanguinity and Dominant Disorders

- **No significant effect.**
  (as these disorders are transmitted independently of the genetic make-up of the partner)
Consanguineous marriages:
Favor the manifestation of rare recessively inherited disorder (carrier, frequency <1%). including:
- Most inborn errors of metabolism
- Some congenital malformations
- Genetic forms of deafness
- Mild to moderate mental retardation

The rate of homozygous births approx. double the common recessive genes in first cousin marriages, including:
- Hb S
- α-Thalassaemia
- β-Thalassaemia
A large number of disorders are very rare in human populations (carrier frequency <1%).

Even if consanguineous marriages are very common in a population, these disorders remain rare (birth rate < 0.3 per 1000), but is several times more than in random mating.

In customary consanguineous marriages, increase in incidence of rare disorders (e.g. deafness, mental retardation, congenital malformation) is anticipated.
Yemen
Oman
U.A.E
Arabian Gulf
Jordan
Arabian Sea
Red Sea
South
West
Central
East
Rab Al Khali
North
Saudi Arabia
• Consanguinity:
  - Pros
  - Cons
• Effect of consanguinity on frequency of genetic disorders.
• Consanguinity in Saudi Arabia.
• Conclusion.
Studies Conducted in Saudi Arabia

Population screened

Two National Studies

Study of Diabetes Mellitus, HT, Obesity in Saudi Arabia
No. screened: 25,337

Study of Disability in Saudi Arabia
No. Screened: 60,630
### Prevalence (%) of consanguinity

<table>
<thead>
<tr>
<th>Province</th>
<th>1st Cousin</th>
<th>2nd Cousin</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>29.8</td>
<td>13.4</td>
<td>17.6</td>
<td>60.8</td>
</tr>
<tr>
<td>NP</td>
<td>17.9</td>
<td>17.4</td>
<td>17.4</td>
<td>52.1</td>
</tr>
<tr>
<td>NWP</td>
<td>27.3</td>
<td>20.8</td>
<td>19.6</td>
<td>67.7</td>
</tr>
<tr>
<td>SWP</td>
<td>26.0</td>
<td>12.4</td>
<td>12.4</td>
<td>54.2</td>
</tr>
<tr>
<td>EP</td>
<td>40.9</td>
<td>9.1</td>
<td>9.1</td>
<td>59.1</td>
</tr>
</tbody>
</table>
Prevalence of consanguinity in Saudi SCD and β-thalassaemia major patients

Between 70-80% of SCD and β-thalassaemia major patients are the outcome of consanguineous matings
<table>
<thead>
<tr>
<th>Province</th>
<th>Hb S Carrier Frequency</th>
<th>Homozygous births/1000</th>
<th>Multiplication factor 30% IC/ random</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Random</td>
<td>30% First cousin</td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td>21.3</td>
<td>12.0</td>
<td>14.3</td>
<td>1.2</td>
</tr>
<tr>
<td>CP</td>
<td>0.83</td>
<td>0.009</td>
<td>0.08</td>
<td>8.9</td>
</tr>
<tr>
<td>SWP</td>
<td>12.0</td>
<td>3.25</td>
<td>5.5</td>
<td>1.7</td>
</tr>
<tr>
<td>NWP</td>
<td>7.54</td>
<td>0.8</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>NP</td>
<td>1.3</td>
<td>0.030</td>
<td>0.21</td>
<td>7.0</td>
</tr>
</tbody>
</table>

*In AR high frequency province, the cousin marriages does not significantly increase the homozygous affected birth.
CARRIER FREQUENCY OF β-THAL. IN DIFFERENT AREAS OF SAUDI ARABIA AND EXPECTED HOMOZYGOUS BIRTH RATE IN RANDOM MATING AND IN 30% FIRST COUSIN MARRIAGES

<table>
<thead>
<tr>
<th>Area</th>
<th>β-Thal. Carrier Frequency</th>
<th>Homo. Births/1000 Random Mating</th>
<th>Multiplication factor 30% IC/random</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Hafouf</td>
<td>13.0</td>
<td>3.7</td>
<td>1.6</td>
<td>NS*</td>
</tr>
<tr>
<td>Riyadh</td>
<td>3.6</td>
<td>0.5</td>
<td>2.0</td>
<td>NS*</td>
</tr>
<tr>
<td>Najran</td>
<td>15.3</td>
<td>5.0</td>
<td>1.3</td>
<td>NS*</td>
</tr>
<tr>
<td>Jaizan</td>
<td>5.9</td>
<td>0.72</td>
<td>1.7</td>
<td>NS*</td>
</tr>
<tr>
<td>Khaiber</td>
<td>4.0</td>
<td>0.6</td>
<td>1.83</td>
<td>NS*</td>
</tr>
<tr>
<td>Al-Ula</td>
<td>12.0</td>
<td>3.4</td>
<td>1.4</td>
<td>NS*</td>
</tr>
</tbody>
</table>

*In AR high frequency province, the cousin marriages does not significantly increase the homozygous affected birth.
## Prevalence of Consanguinity in Different Types of Disabilities

<table>
<thead>
<tr>
<th>Type of Disability</th>
<th>Prevalence (%) of Consanguinity</th>
<th>1st Cousin</th>
<th>2nd Cousin</th>
<th>Total Cousin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental</td>
<td></td>
<td>39.0</td>
<td>28.8</td>
<td>67.8</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td>8.8</td>
<td>28.8</td>
<td>37.6</td>
</tr>
<tr>
<td>Speech</td>
<td></td>
<td>37.0</td>
<td>27.3</td>
<td>64.3</td>
</tr>
<tr>
<td>Hearing</td>
<td></td>
<td>35.0</td>
<td>30.2</td>
<td>65.2</td>
</tr>
<tr>
<td>Visual</td>
<td></td>
<td>35.0</td>
<td>25.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Behavioral disorders</td>
<td></td>
<td>37.0</td>
<td>28.4</td>
<td>65.4</td>
</tr>
<tr>
<td>Learning difficulties</td>
<td></td>
<td>38.0</td>
<td>28.2</td>
<td>66.2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
<td>35.0</td>
<td>28.7</td>
<td>63/7</td>
</tr>
<tr>
<td>Chronic diseases</td>
<td></td>
<td>33.0</td>
<td>27.2</td>
<td>60.2</td>
</tr>
<tr>
<td>Other disabilities</td>
<td></td>
<td>27.0</td>
<td>42.0</td>
<td>69.0</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>25.8</td>
<td>14.8</td>
<td>56.8</td>
</tr>
</tbody>
</table>
Prevalence of Consanguinity in Diabetic and Normal Saudis*

<table>
<thead>
<tr>
<th>Region</th>
<th>Consanguinity (%)</th>
<th>Consanguinity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM</td>
<td>Normal</td>
</tr>
<tr>
<td>Arabian Gulf</td>
<td>41.2</td>
<td>52.1</td>
</tr>
<tr>
<td>Jordan</td>
<td>40.2</td>
<td>67.6</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>42.4</td>
<td>54.2</td>
</tr>
</tbody>
</table>

*p-value: NS
Prevalence of Consanguinity in Obesity and Normal Saudis*

<table>
<thead>
<tr>
<th>Region</th>
<th>Consanguinity (%)</th>
<th>Consanguinity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(NP)</td>
<td>(WP)</td>
</tr>
<tr>
<td>Obese</td>
<td>Normal</td>
<td>Obese</td>
</tr>
<tr>
<td>43.1</td>
<td>52.1</td>
<td>46.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consanguinity (%)</td>
<td>(EP)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>37.5</td>
<td>59.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consanguinity (%)</td>
<td>(CP)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>50.6</td>
<td>60.8</td>
<td></td>
</tr>
</tbody>
</table>

*p-value: NS
Prevalence of Consanguinity in Hypertensive and Normal Saudis*

Consanguinity (%) (NP)

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>51.5</td>
<td>52.1</td>
<td></td>
</tr>
</tbody>
</table>

Consanguinity (%) (WP)

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.8</td>
<td>67.7</td>
<td></td>
</tr>
</tbody>
</table>

Consanguinity (%) (EP)

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.4</td>
<td>59.1</td>
<td></td>
</tr>
</tbody>
</table>

Consanguinity (%) (CP)

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.1</td>
<td>60.8</td>
<td></td>
</tr>
</tbody>
</table>

*p-value: NS
CONSANGUINITY AND GENETIC COUNSELLING

The following aspects deserve special considerations:

- Relationship of two individuals?
- Risk of genetic disorders influenced by consanguinity?
- Likelihood of a harmful gene being transmitted by both parents to the child?
How to provide genetic counselling in Arab/Islamic societies that favor consanguineous marriages

Dilemma for families and health workers

- Research information on role of consanguinity and adverse effects of consanguinity on fertility, infant and childhood mortality and morbidity:
  - Stability of the family
  - Stability of the society
If a genetic disorder exists in the family?

- Consanguineous marriages have serious implications as genetic risk is increased.
- Social benefits/genetic risks

It is important for the counselor to provide clear information on the precise genetic risk.

Risk declines with distance of relationship.
A proposed genetic counselling plan in societies favoring consanguineous marriages

- Families with consanguinity
  - Family with a high risk of a recessively inherited genetic defect: Provide genetic counselling, Discourage consanguinity
  - Families with no adverse effects: Provide genetic counselling, Do not discourage consanguinity
  - Access to appropriate services
National Primary health centers
Regional Office
National Referral and Consulting Unit and WHO Collaborating Centre

Exchange of:
- Expertise
- Facilities

Sickle Cell and Allied Syndrome Study Group
National Working Group

Regional WHO Regional Office for the Eastern Mediterranean Working Group

Exchange of:
- Expertise
- Facilities

Inter national WHO Working Group

Exchange of:
- Expertise
• Consanguinity:
  - Pros
  - Cons
• Effect of consanguinity on frequency of genetic disorders.
• Consanguinity in Saudi Arabia.
• Conclusion.
Conclusion

• Consanguinity is of frequent occurrence in Saudi Arabia.
  - First cousin marriages are most frequent.
• Prevalence of consanguinity is higher in patients with AR (SCD, β-thal.) disorders.
• Rare AR disorders occur at a significantly higher frequency in consanguineous marriages.
• Multifactorial disorders are not significantly higher in consanguineous marriages.
Thank you for Listening