

Consanguineous marriages Trends, impact on health and counseling

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Outline

Global consanguinity rates
Factors affecting rates

Impact of consanguinity
on different health
parameters

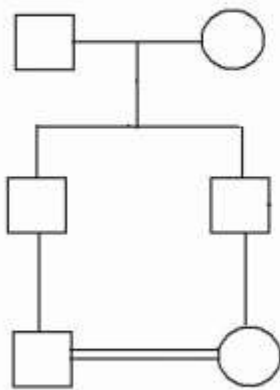
Education and Counseling
for consanguinity in health
care settings

Consanguinity and
rare autosomal
recessive disorders

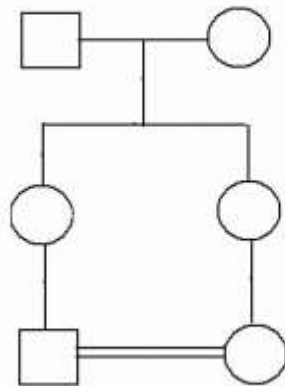
Consanguineous marriages

- Consanguineous means related by blood
- As a working definition, unions contracted between persons biologically related as second cousins or closer are categorized as consanguineous

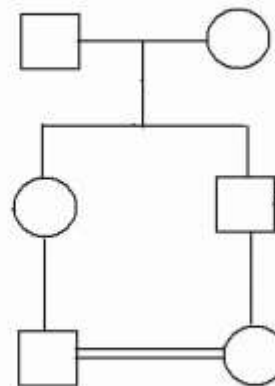
(consag.net; WHO document 1997, EUROCAT)



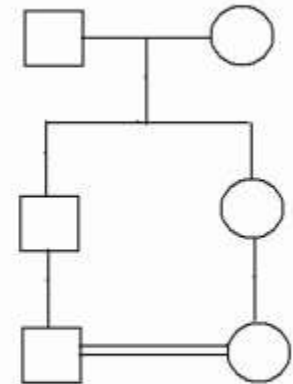
paternal parallel first cousins
father brother daughter
 $F=0.0625$



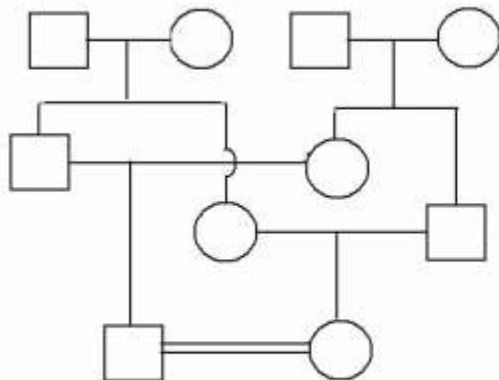
maternal parallel first cousins
mother sister daughter
 $F=0.0625$



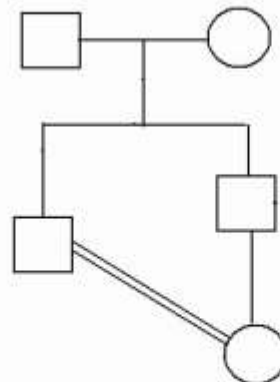
cross first cousins
mother brother daughter
 $F=0.0625$



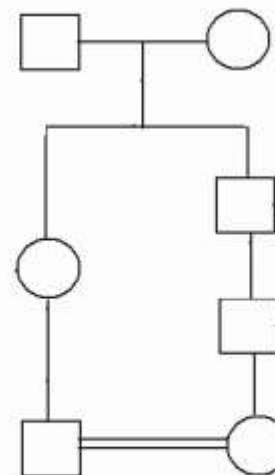
cross first cousins
brother sister daughter
 $F=0.0625$



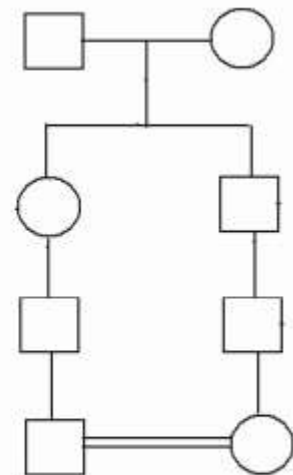
double first cousins
 $F=0.125$



uncle-niece
 $F=0.125$



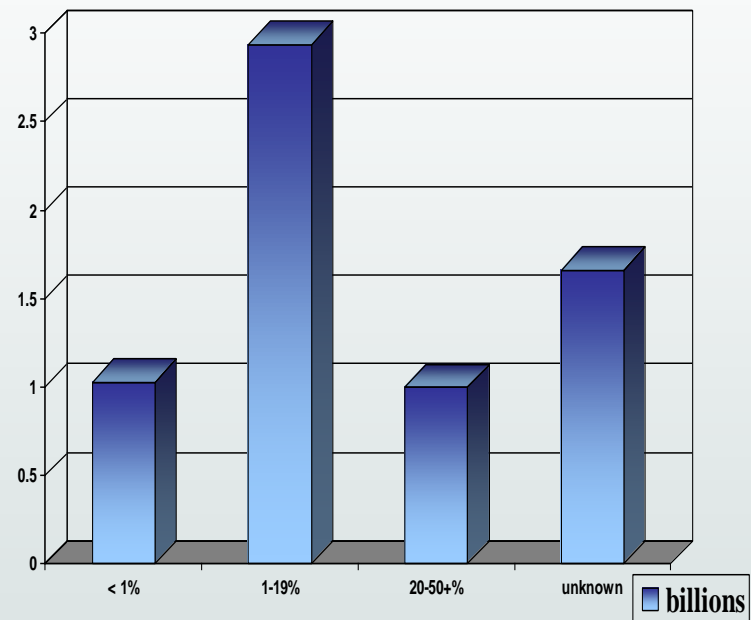
first cousins once removed
 $F=0.03131$



second cousins
 $F=0.0156$

Why are we interested in studying consanguinity?

- Still common and high rates of 20-50% in about one billion of the world population



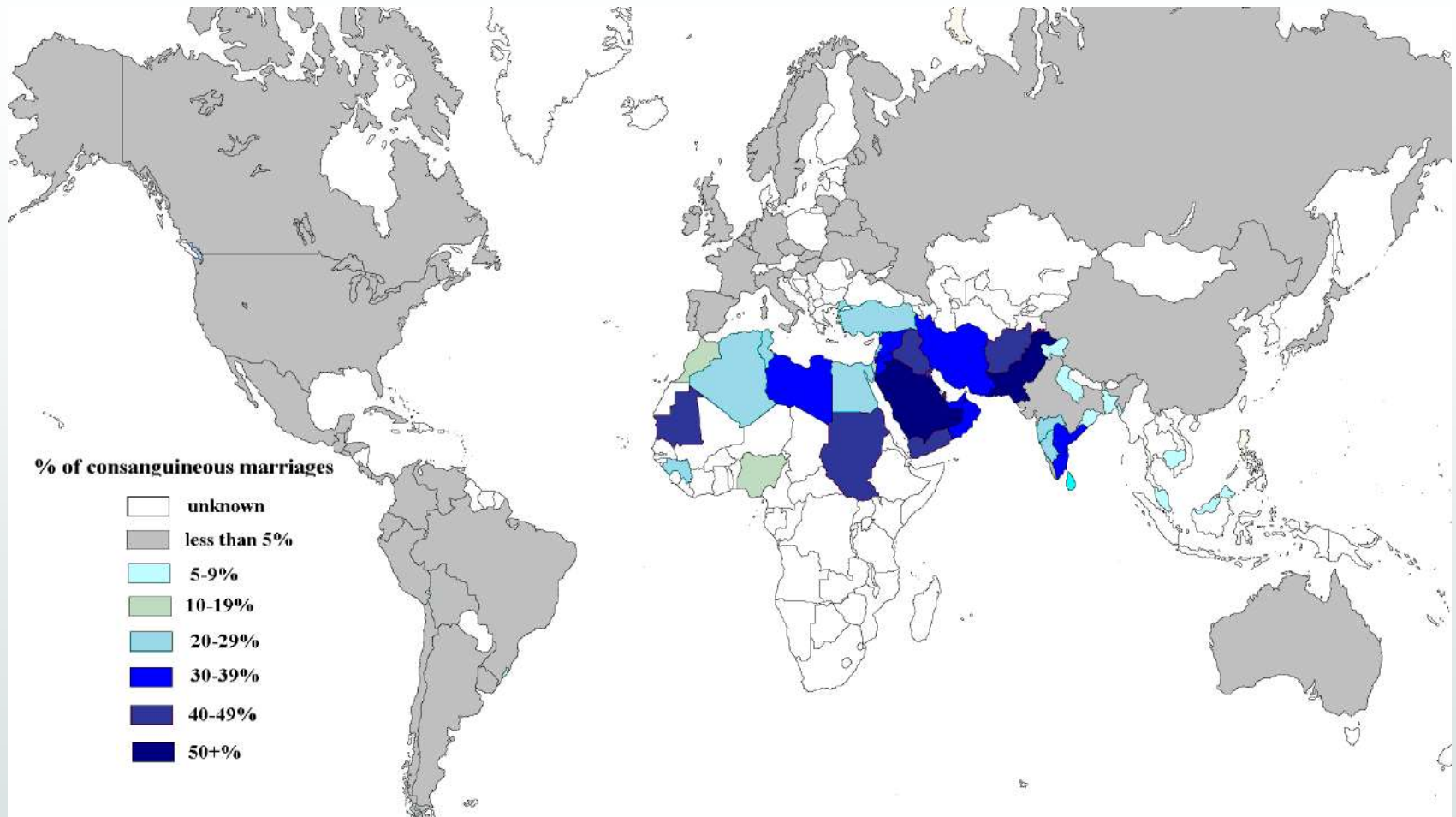
Global Consanguinity Rates
(Bittles, 2008)

Why are we interested in studying consanguinity?

- Do we really know the adverse effects of consanguinity on health and how to minimize them?
- Do we really know if there are advantages versus disadvantages?
- What are the evidence-based guidelines regarding genetic counseling for consanguinity?

Global Consanguinity rates

Global consanguinity rates

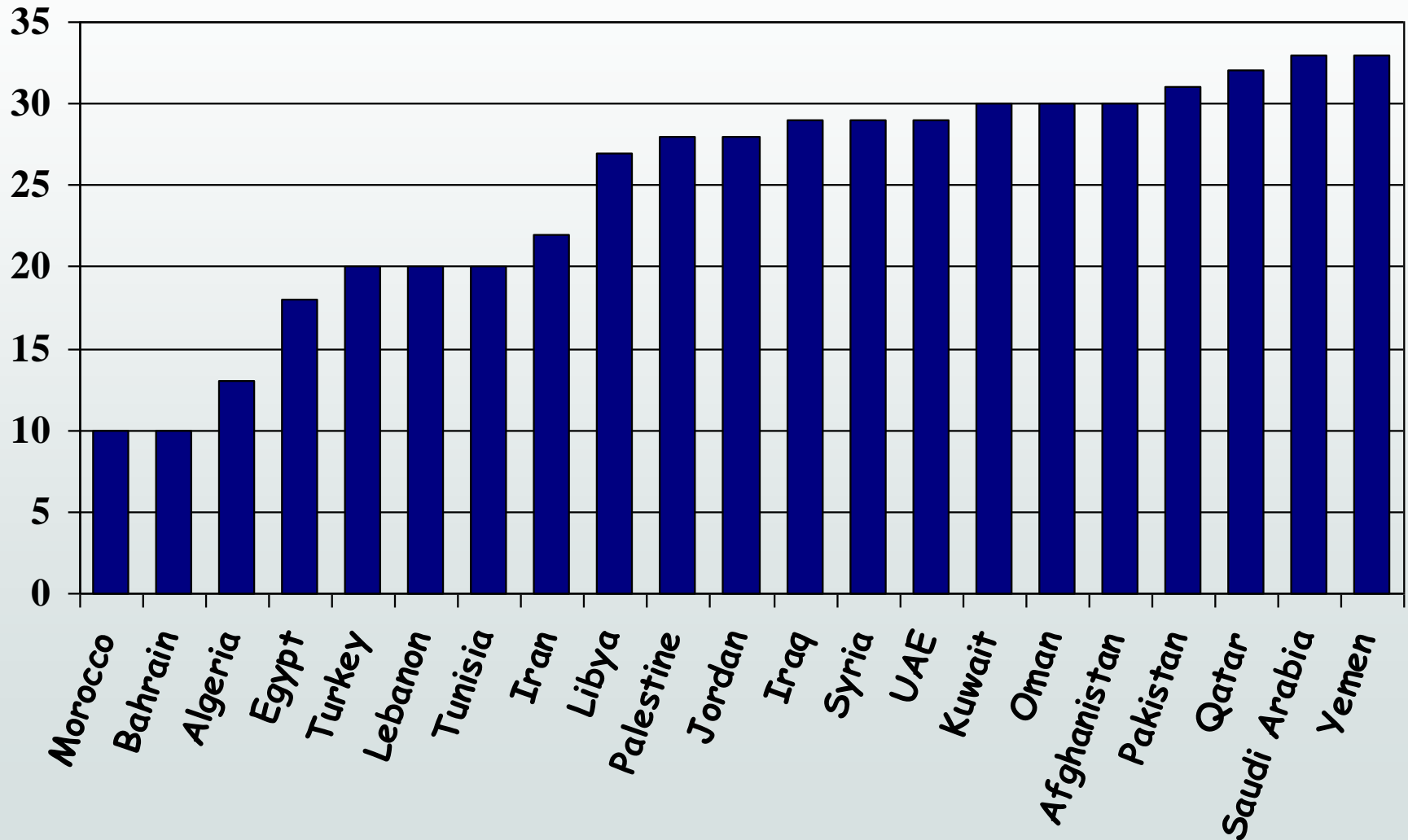


- Less than 1%: United States, Russia, Australia, parts of Latin America and Europe
- 1-10%: China, Latin America, North India, Japan, South Europe and Canada
- 10-50%: Arab countries, Turkey, Iran, Pakistan, Afghanistan, South India.
- Unknown: Parts of South-East Asia, most Africa

Population types favouring consanguineous marriages

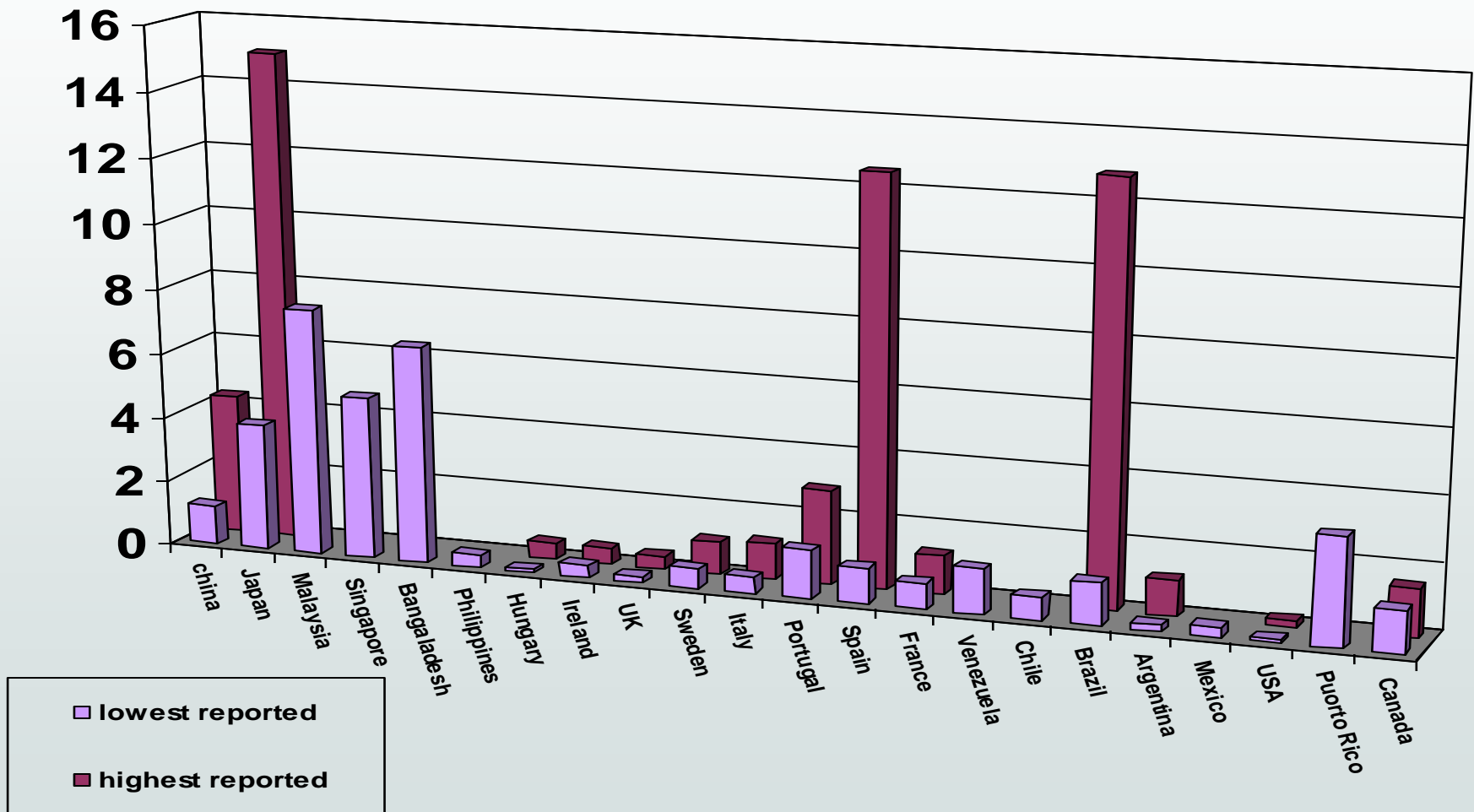
- Major populations in Middle East, North Africa, South Asia (20-50+% of all marriages are consanguineous).
- Major populations in Latin America, Japan, China (1-10% of all marriages are consanguineous).
- Recent migrants from Pakistan, India, the Middle East, North Africa and South Asia, becoming permanent residents in Europe, USA and Canada. (e.g. 2 millions Maghrebians in France, 1.5 million Turks in Germany, 0.5 million Pakistanis in the U.K.).
- Small population isolates where inbreeding is common account for a very small percentage of the world population (e.g. Amish).

Rates of first cousin marriages in the Middle East and North Africa

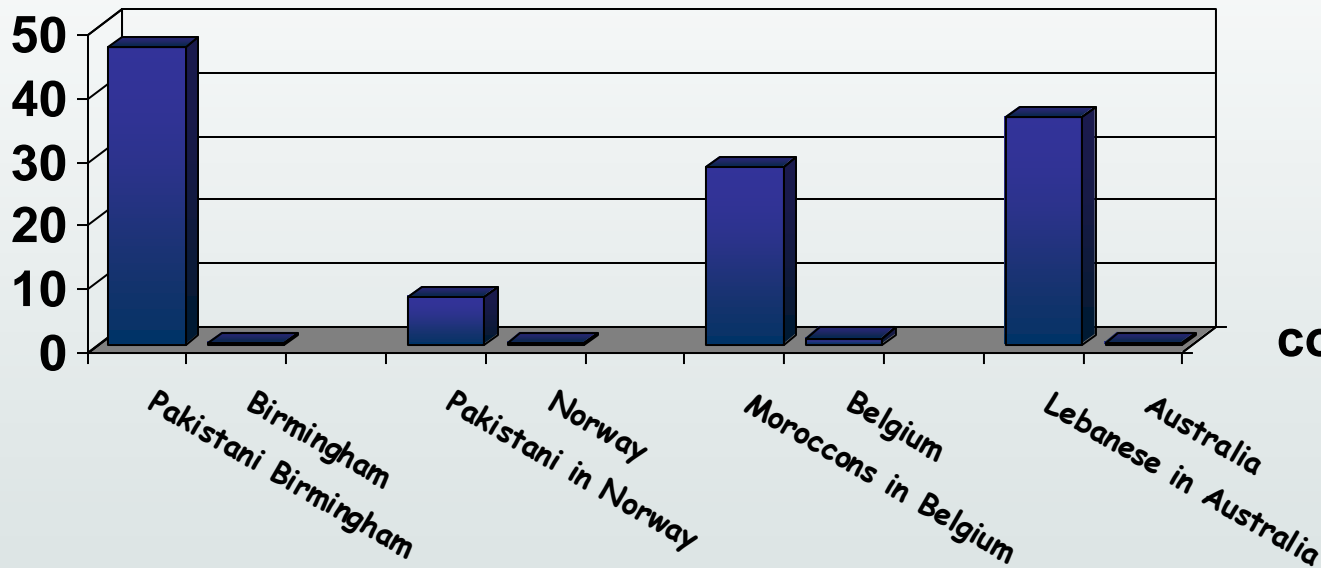


Range of consanguinity rates in East Asia, Europe and Americas

(Number of families 5000+)



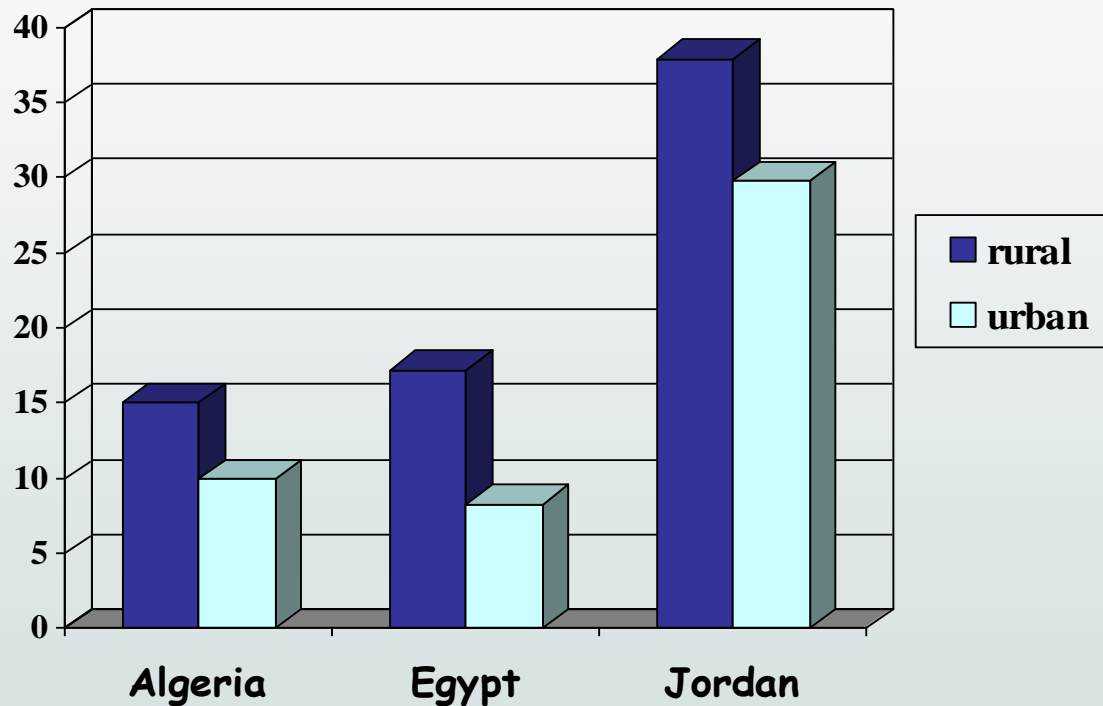
Consanguinity rates in some immigrant communities



consanguinity rates

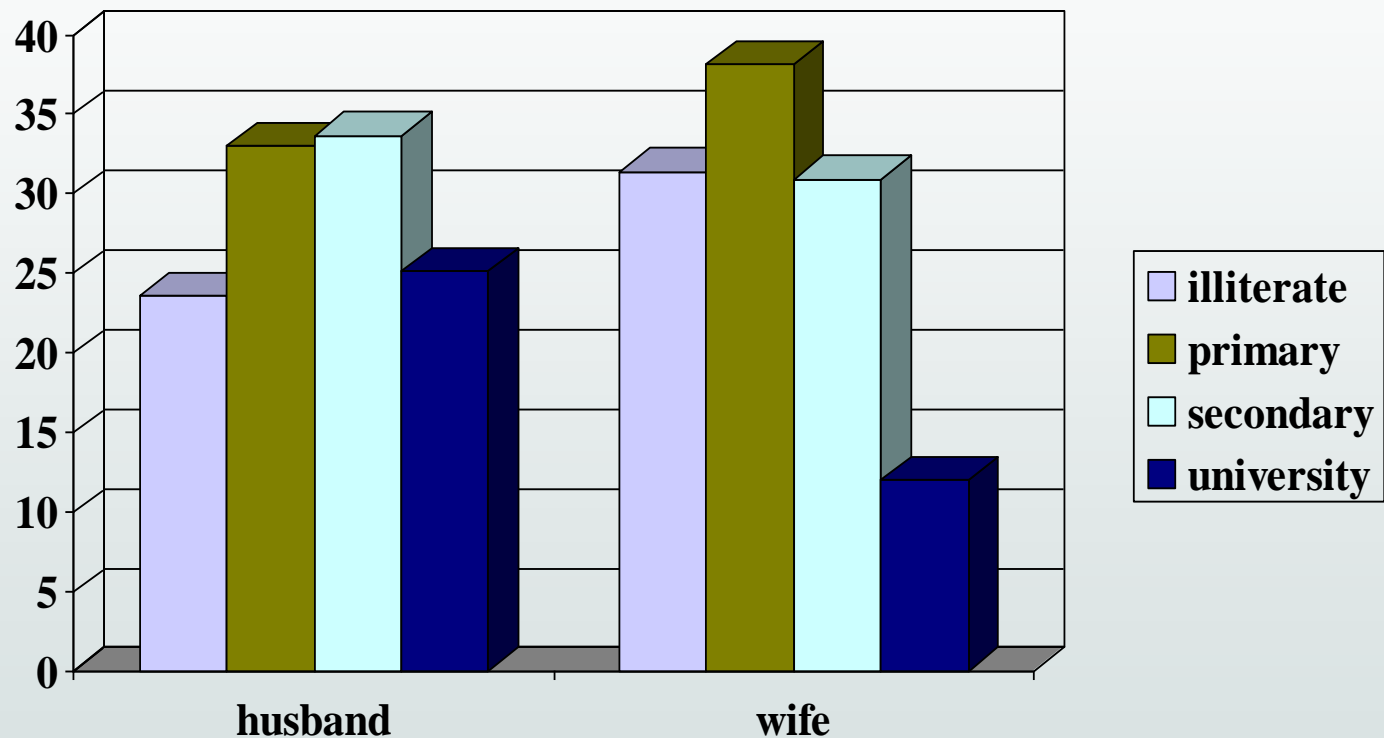
Factors that affect consanguinity rates

Urban/rural percentages of 1st cousin marriages among all marriages



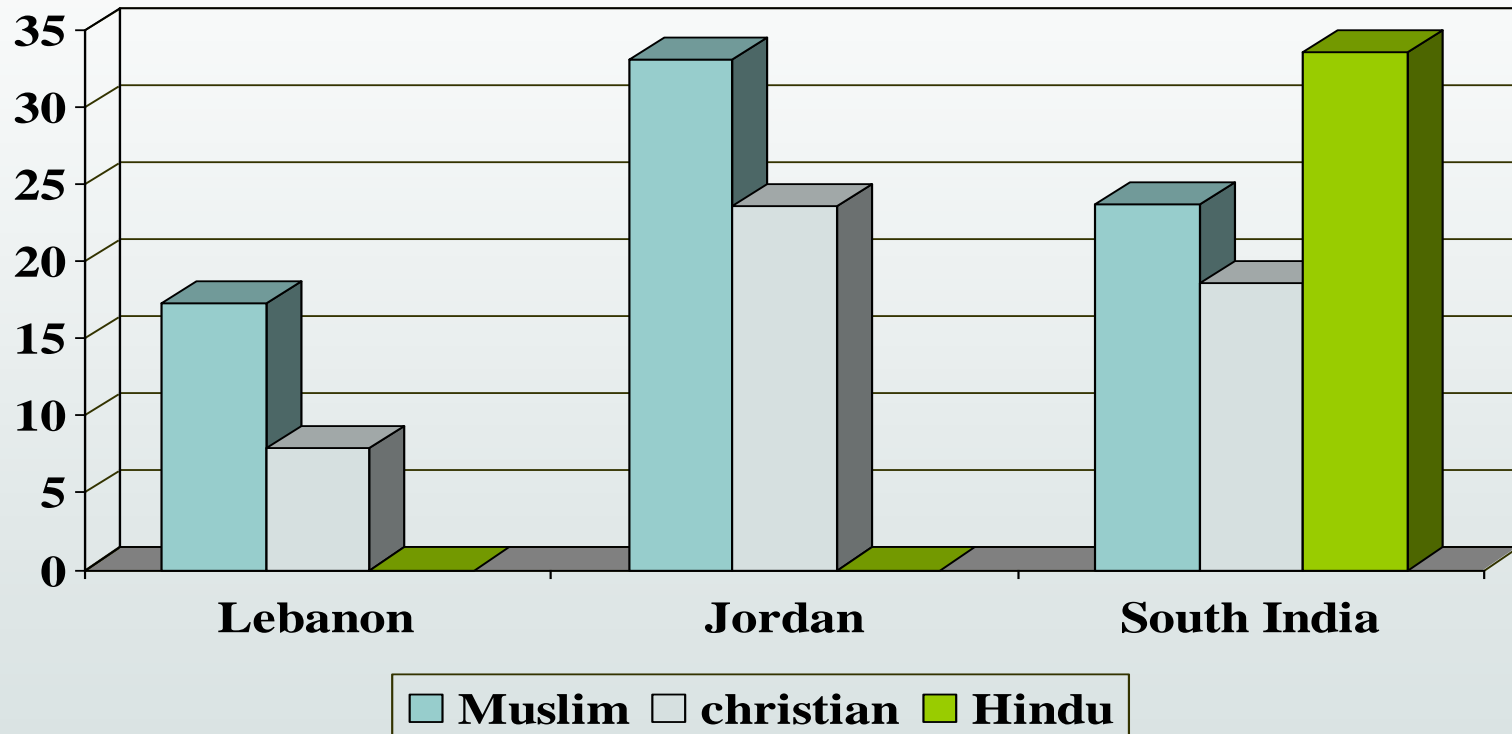
In most countries, consanguinity rates are higher in rural versus urban settings

Relation of education level to 1st cousin marriage percentages in Jordan *(Khoury and Massad, 1992)*



In some communities consanguinity rates are reported to be lower among females who have attained university education

Rate of first cousin marriages in relation to religion



Consanguineous marriages are practiced by all religions in a certain population, though with different rates

Factors affecting consanguinity rates

- Consanguinity rates are higher in rural than urban settings of a certain community.
- Higher female education reduces the rate of first cousin marriages.
- First cousin marriages are more common when the parents of the couple are consanguineous.
- In the same community, consanguinity rates are higher among Muslims than among Christians, for example in Lebanon, Jordan, South India.

*Secular trends in
consanguinity rates*

Are consanguinity rates changing with time?

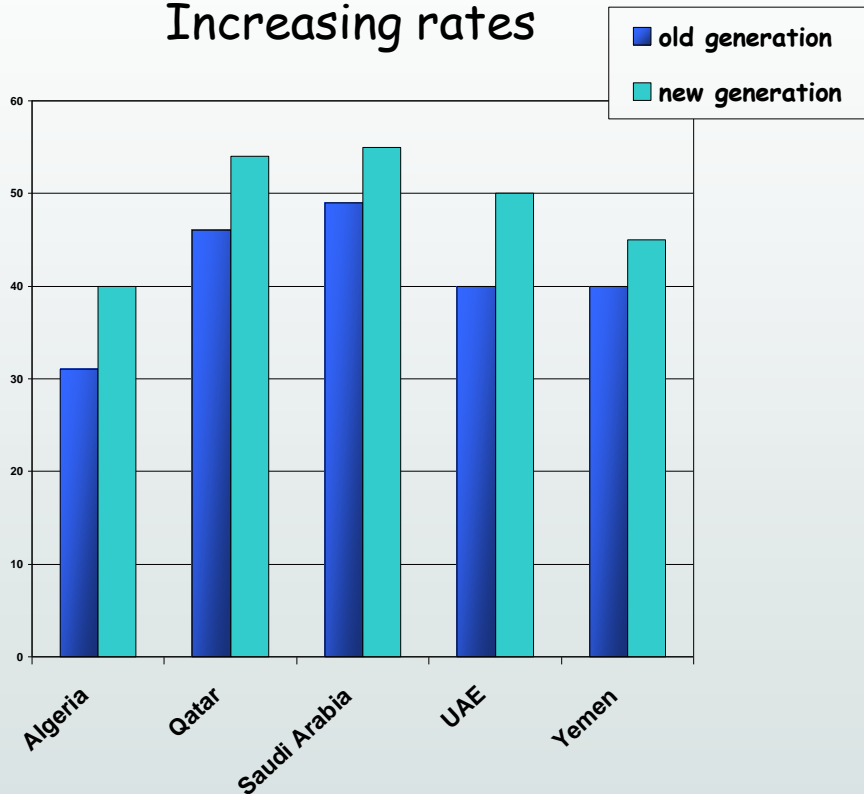
- They have declined in North America and Western Europe. First cousin marriages rate now is around 0.6%.
- They have also declined in Japan: cousin marriages accounted for 5.9-14.7% until 1960's, 5.7% in 1972, and 3.9% in 1983.

Are consanguinity rates changing with time?

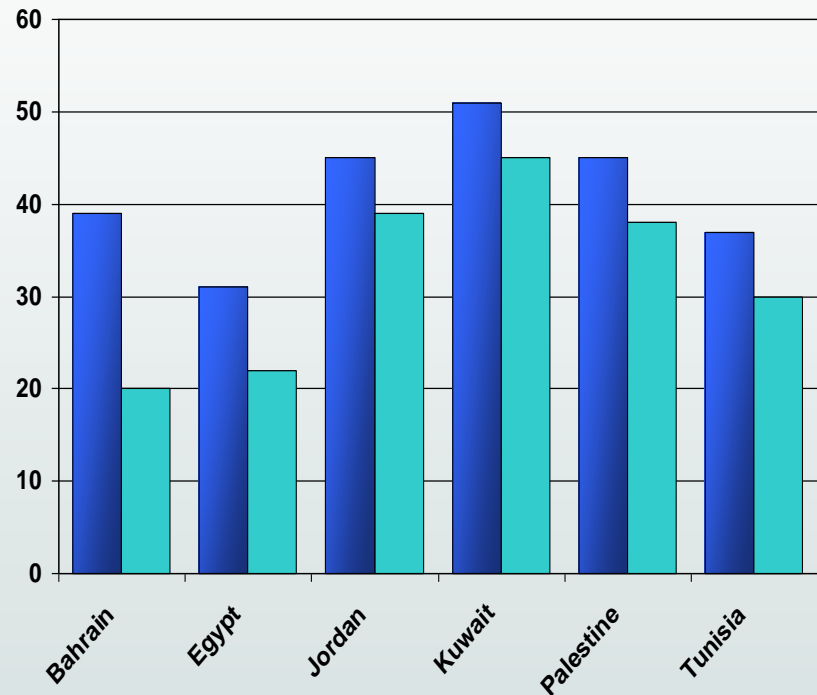
- **Variable secular changes were** reported in most countries of North Africa, the Middle East, and South Asia. However, the rate in the present generation in most countries remains at 20-55+%.

Secular trends in consanguinity rates in highly consanguineous populations

Increasing rates



Decreasing rates



Why are consanguinity rates not declining in North Africa, West and South Asia?

- Consanguinity is a deeply rooted cultural trend.
- It might offer social, psychological and economic advantages.
- With improvement in health, there will be more relatives to intermarry.
- The adverse genetic effects on health do not affect 90% of all related marriages.

What factors may decrease consanguinity rate?

- ❖ Higher female education
- ❖ Higher age at marriage
- ❖ Lower fertility
- ❖ More mobility from rural to urban
- ❖ Better economic status of families

Reasons for choosing to marry a cousin

- Consanguinity is a deeply rooted cultural trend in certain communities.
- More favourable for the women`s status. The wife would have better relationship with her in-laws and could be protected by them in time of need.
- There is a general belief that marrying within the family reduces the possibilities of hidden health and financial uncertainties.
- Premarital negotiations regarding financial matters of marriage are more easily conducted, keeping the money and property within the family.
- Strengthens family ties, and enforces family solidarity.

Consanguineous marriages today...

- Approximately 1.1 billion people currently live in countries where consanguineous marriages are customary, and among them one in every three marriages is between cousins.
- Consanguineous marriages remain culturally and socially favored and respected in many countries in North Africa and West Asia as well as among immigrants in Europe, North America and Australia.
- This emphasizes the need for increasing our understanding of the health impact of consanguinity and promoting future research on consanguinity.

Impact of consanguinity on different health parameters

Consanguinity and....

- Reproductive health
- Birth defects (congenital disorders)
 - Congenital malformations
 - Genetic diseases
 - Disabilities
- Chronic adult non-communicable diseases

Consanguinity and Reproductive Health

Consanguinity and prenatal losses

- ❖ Generally speaking, abortion rates among consanguineous and non-consanguineous couples are comparable.
- ❖ Available data suggest that stillborn rates are either similar or slightly higher among consanguineous couples than the non-related couples.

Consanguinity and fertility

Most studies have shown similar or higher fertility rates among consanguineous versus non-consanguineous couples.

This may be attributed to:

- younger female age at marriage leading to increased maternal reproductive span
- compensation for the higher infant mortality among consanguineous couples
- lower prenatal losses among consanguineous couples

Reproductive health parameters in first cousin marriages as opposed to non-consanguineous marriages

- Earlier parental age at marriage
- Younger maternal age at first live-birth
- Fertility rate is slightly higher
- Similar rates of abortion
- Slightly higher rates of stillbirths and infant mortality

Consanguinity and Birth defects

- Generally speaking, frequency of congenital malformations among newborns of first cousin unions is about 2 times the frequency among the general population. *In other words instead of a rate of 2-3% of birth defects in the general population, the risk to first cousin couples is around 4-6%.*
- Another estimate puts the offspring of first cousin unions at a 1.7-2.8% increased risk above the population background risk (Bennett et al, 2002).

Consanguinity and specific congenital malformations

- Many studies have shown a positive association between parental consanguinity and congenital heart defects.
- The association of consanguinity with cleft lip and palate, and neural tube defects is not clear.

Summary of Reproductive Health Parameters among consanguineous versus non-consanguineous couples

- Earlier parental age at marriage
- Younger maternal age at first live-birth
- Higher number of infants born to consanguineous parents
- Lower rates of primary sterility
- Same or lower rates of abortion
- Higher rates of postnatal mortality in offspring
- Higher rates of congenital malformations in offspring
- Higher risk of having offspring with autosomal recessive disorder if present in the family

Consanguinity and Genetic diseases

- No association of consanguinity with
 - autosomal dominant
 - X-linked
 - chromosomal disorders (such as Down syndrome)
- Consanguinity increases the risk of expression of autosomal recessive conditions in the offspring.
- This effect is more pronounced for rare disorders.

Relation between consanguinity rate , carrier frequency and birth rate of affected

The less frequent the disease, the higher the association with consanguinity

Carrier frequency in the population	Population with random matings Affected/1000 births	Population with 30% 1st cousin marriages Affected/1000 births	Multiplication factor
0.1%	0.000025	0.0093	37
0.5%	0.00625	0.053	8.5
1%	0.025	0.119	4.8
5%	0.63	1.1	1.7
10%	2.5	3.44	1.4
16%	6.4	7.91	1.23

Consanguinity and disabilities

Offspring of consanguineous parents are over represented among those with mental retardation, blindness and deaf-mutism. These conditions have many etiologies and a proportion are due to autosomal recessive genes thus the association with consanguinity.

Consanguinity and chronic adult non-communicable diseases (NCD's)

- The association of NCD's (such as diabetes, hypertension) with parental consanguinity is still not clear. Controlled studies in populations with high consanguinity rates are needed.

Consanguinity and intelligence

- Severe mental retardation (MR) is associated with consanguinity because many autosomal recessive conditions include moderate-severe MR.
- Association of consanguinity with low intelligence is not confirmed.

Summary

First cousin couples have:

- Slightly higher risk of stillbirths and infant mortality rates among offspring
- 4-6% risk to have an offspring with birth defect
- **Higher risk of having offspring with autosomal recessive disorder if present in the family**

Consanguinity and Genetic Counseling

Premarital and preconception counseling for consanguinity

- There is a genetic disease in the family and the couple are consanguineous.
- There is no known genetic disease in the family and the couple are consanguineous.

Proposed steps in counseling a consanguineous couple

- In offering counseling for consanguinity, it is crucial to distinguish between families with a known genetic or inherited disorder and those with no known such disorder by taking a detailed family history and constructing a four generations pedigree (including offspring, siblings, parents, grandparents, aunts, uncles, nieces, nephews, and first cousins).

Specific questions addressed to the couple to elicit the presence of a genetic disorder in the family.

Inquire about the presence of any of the following in blood relatives:

- Birth defects or congenital anomalies
- Early hearing impairment
- Early vision impairment
- Mental retardation or learning disability
- Developmental delay or failure to thrive
- Inherited blood disorder
- Unexplained neonatal or infant death in offspring
- Epilepsy
- Undiagnosed severe condition

- In families with hearing, vision or mental disabilities, informative family history coupled by clinical data and investigations could differentiate cases that are associated with consanguinity from cases caused by other factors.

If there is no known genetic disorder in the family

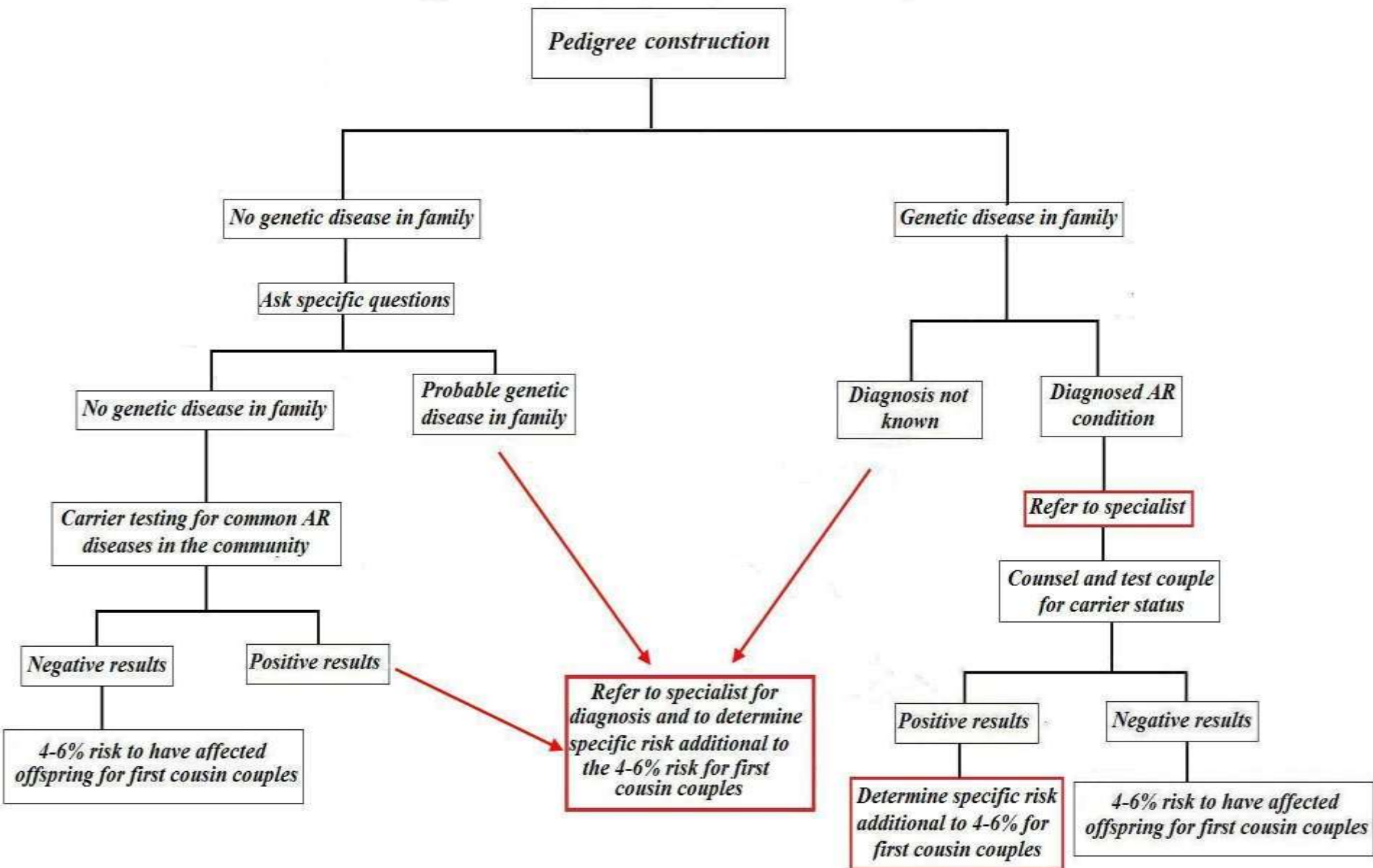
- First cousin couples can be given a risk for birth defects in their children of about 4-6%, however studies are still needed to verify this risk figure.
- Risks for other conditions are not established.
- Closer consanguineous relationship such as a double first cousins couple may be given a higher risk for their offspring.

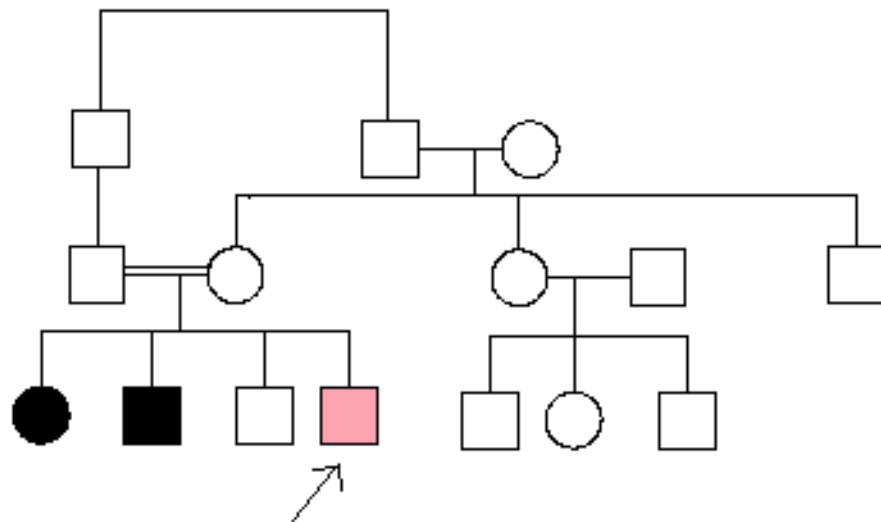
- Couples who are more distantly related could have a similar risk of birth defects in their offspring as first cousin couples in highly inbred populations. This may be due to the fact that in such inbred populations the actual relationship coefficient among two individuals is much higher than the one calculated based on information given by the couple.
- Among non-inbred general population, the risk to offspring of a couple related more distantly than first cousins could be close to that of a non-related couple.

Counseling families with a known autosomal recessive disorder

- Establish Clinical and Molecular diagnosis whenever possible.
- Premarital and preconception carrier testing for the consanguineous couple.
- If carriers cannot be diagnosed, give risk estimate.
- Counseling to minimize further consanguinity unless carriers can be diagnosed.
- Counseling couples with affected children by giving reproductive options such as prenatal diagnosis if feasible.

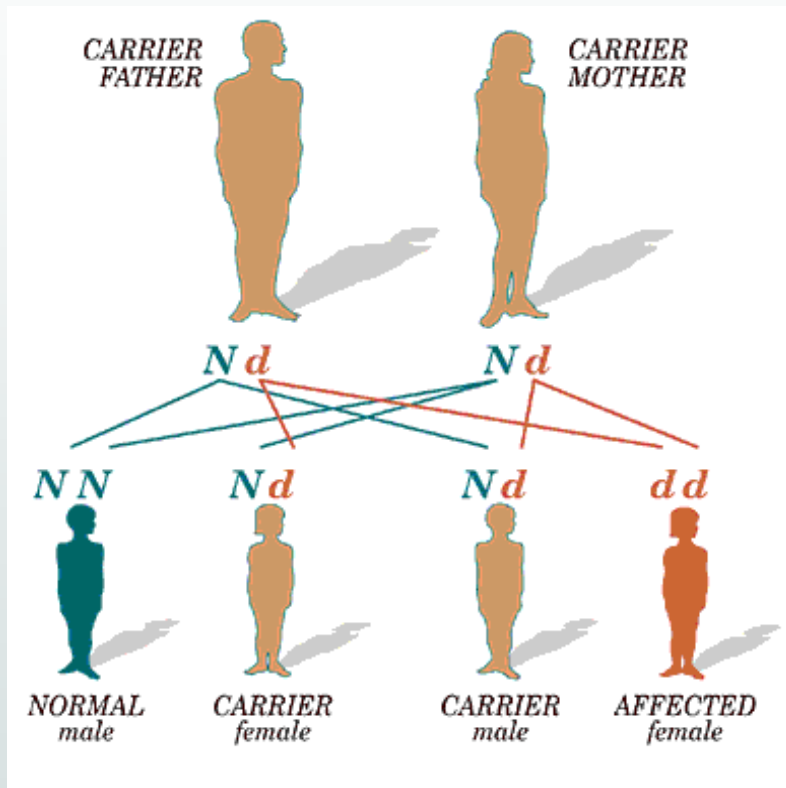
Counseling for consanguinity in primary health care settings





What is the probability that this person is a carrier?

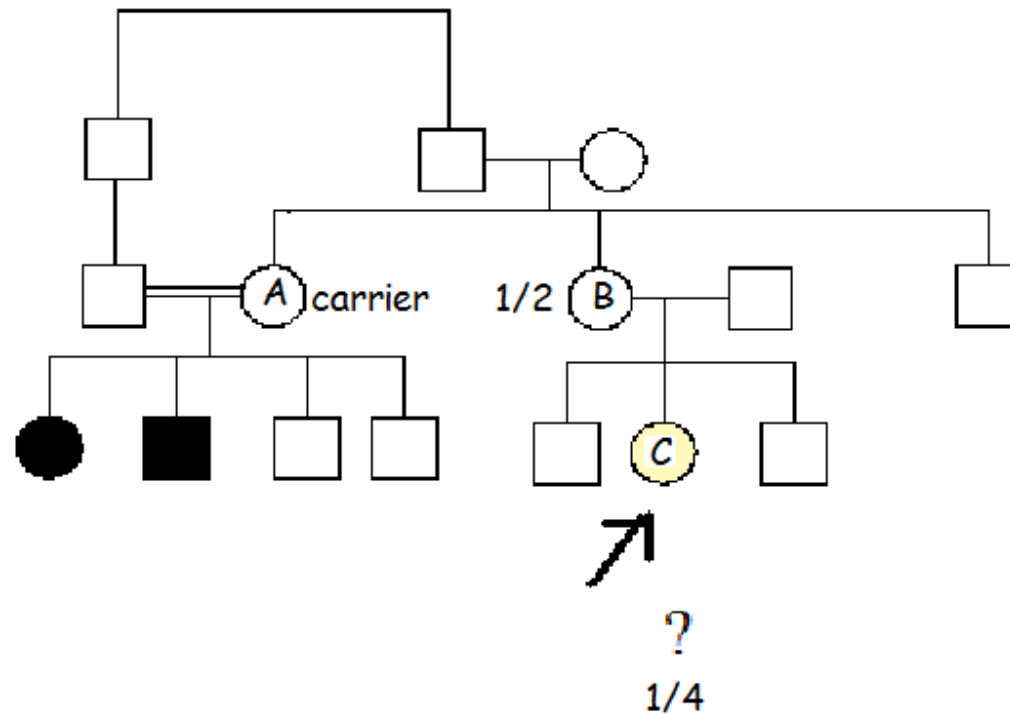
Autosomal recessive inheritance



- Both parents of an affected person are heterozygous for the mutant gene
- Each sibling of an affected person has a 25% chance of being affected
- 2/3 of non affected children are carriers

(answer to previous slide)

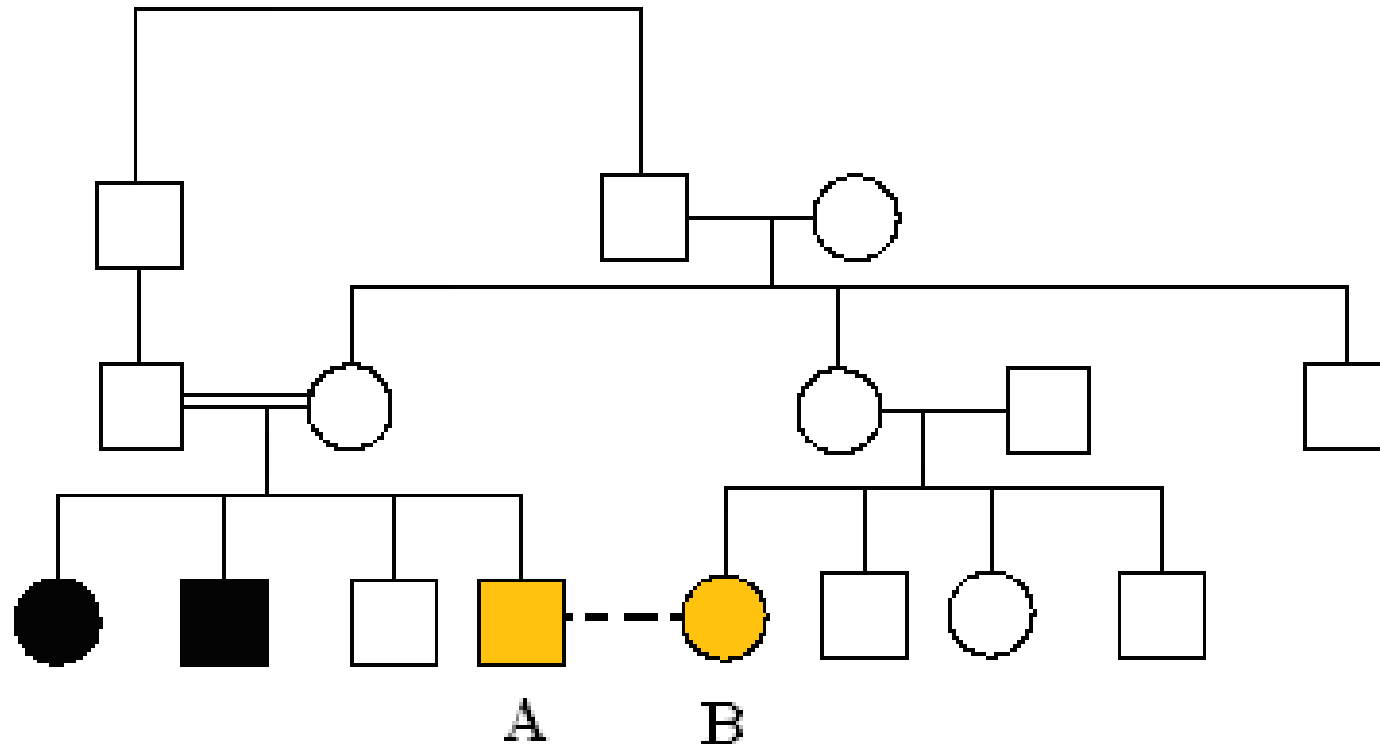
Calculating probabilities of being a carrier?



Solution

- The mother *A* is definitely a carrier, her father is most probably a carrier (*Nd*), so *B* has a chance of $1/2$ to be a carrier (inherits either the *N* or the *d* allele) and *C* has a risk of $1/4$ to be a carrier.

Risk calculation in counseling for consanguinity



what is their risk of having an affected child?

Solution

- A has a risk of $2/3$ to be a carrier
- B has a risk of $1/4$ to be a carrier
- The offspring of 2 carrier parents for an autosomal recessive condition has a risk of 25% to be affected ($1 \times 1 \times 1/4$)
- In this pedigree, the risk for A and B to have an affected child is $2/3 \times 1/4 \times 1/4 = 1/24$ (about 4%)

Conclusions

Consanguineous marriages remain culturally and socially favored and respected in many countries, mostly in Arab countries, Iran, Pakistan, Turkey and parts of India, as well as in Europe and North America among immigrants from highly consanguineous countries.

Consanguinity and genetic disorders

- Among genetic disorders, mostly autosomal recessive disorders are strongly associated with consanguinity
- Approximately 30% of sporadic undiagnosed cases of mental retardation, congenital anomalies and dysmorphism may have an autosomal recessive etiology with risks of recurrence in future pregnancies. (*Hamamy et al 2007 SMJ*)

Consanguinity counseling in primary health care

- Primary health care providers can counsel for consanguinity provided they possess the recommended education and training
- Education of the public in general and of primary health personnel in particular is an important pillar in clarifying the health and social effects of consanguineous marriages.

Barriers and limitations to counseling on consanguinity

- Minimal knowledge and training of primary health care providers for counseling on consanguinity.
- No or limited genetic services and specialists in genetics in some countries.

Novel technology and consanguinity

- New technologies including next generation sequencing could eventually help in diagnosing patients affected by conditions known to be genetically heterogeneous. Such technologies could also diagnose if both couple carry the same autosomal recessive gene that causes a severe disorder and thus facilitating counseling on consanguinity.

Research on consanguinity could focus on:

- ✓ Formulating evidence-based practical guidelines for counseling
- ✓ Formulating scientific and feasible Community-based recommendations
- ✓ Deciding research priorities
- ✓ Establishing joint research projects