Consanguinity and counseling consanguineous couples

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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, having one or more ancestors in common no more remote than a great-grandparent

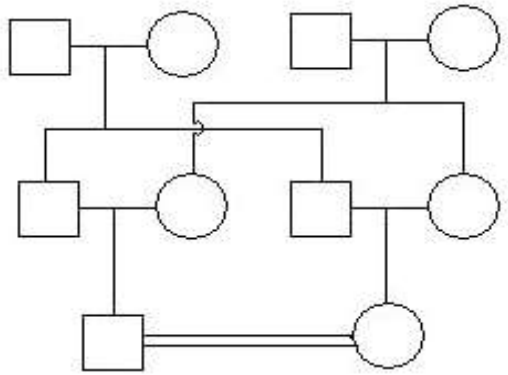
(consag.net; WHO document 1997, EUROCAT)

Consanguineous marriages today…

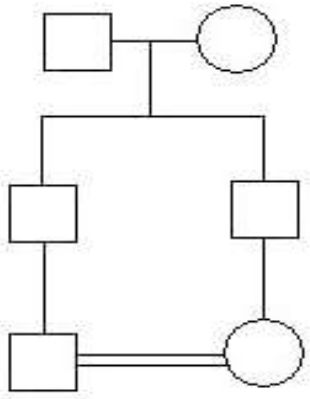
- Approximately 1.1 billion people currently live in countries where consanguineous marriages are customary, and among them one in every three marriages is between cousins.

- Consanguineous marriages remain culturally and socially favored and respected in many counties in North Africa and West Asia as well as among migrants in Europe, North America and Australia.

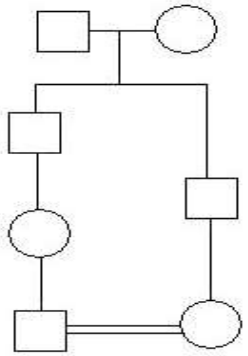
Consanguineous marriages



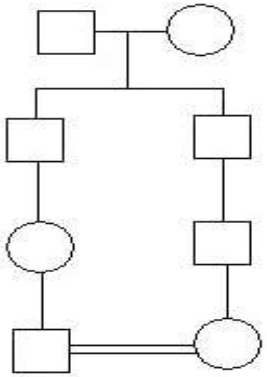
Double First Cousins
F= 0.125



First Cousins
F=0.0625



First Cousins once removed
F=0.0313

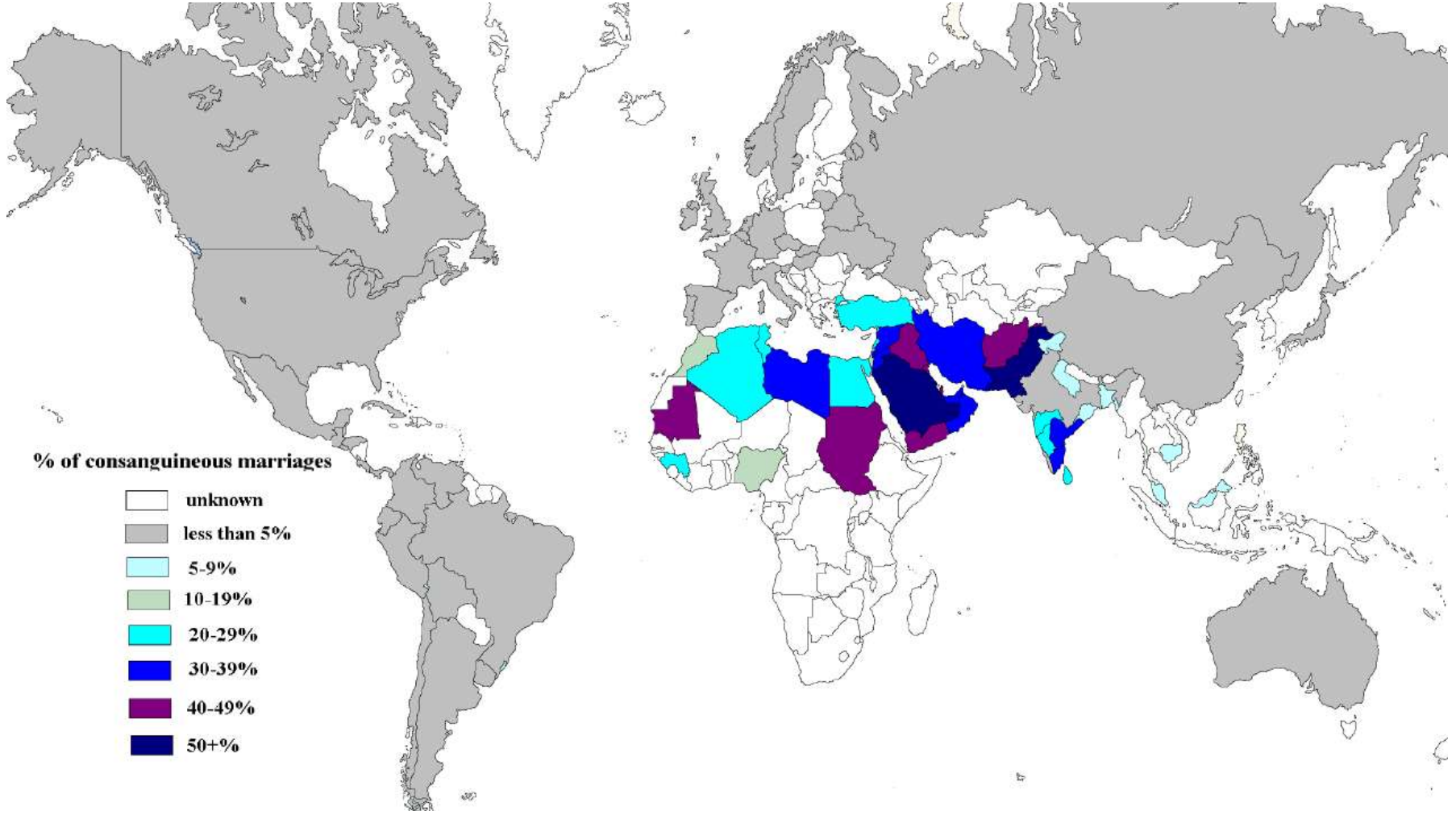


Second Cousins
F=0.0156

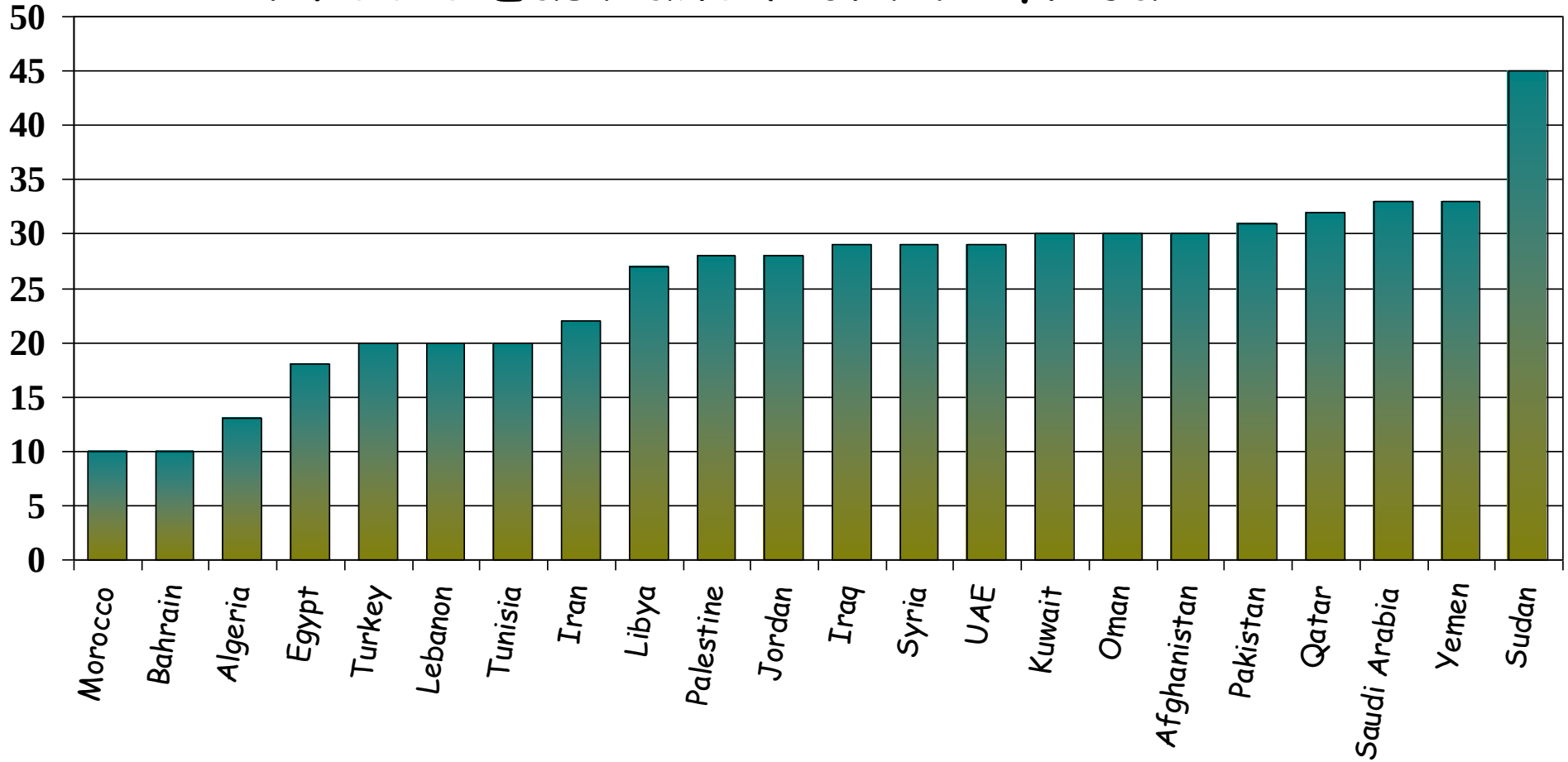
On average, first cousins share 1/8 of their genes inherited from their common ancestors coefficient of relationship, R= 0.125

Their progeny is autozygous at 1/16 of all loci, which is expressed as an inbreeding coefficient (F) of 0.0625

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



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



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.

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.

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 needs further research.

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 <u>autosomal recessive</u> 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 intellectual disability (ID) is associated with consanguinity because many autosomal recessive conditions include moderate-severe ID.
- 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

Ask if:

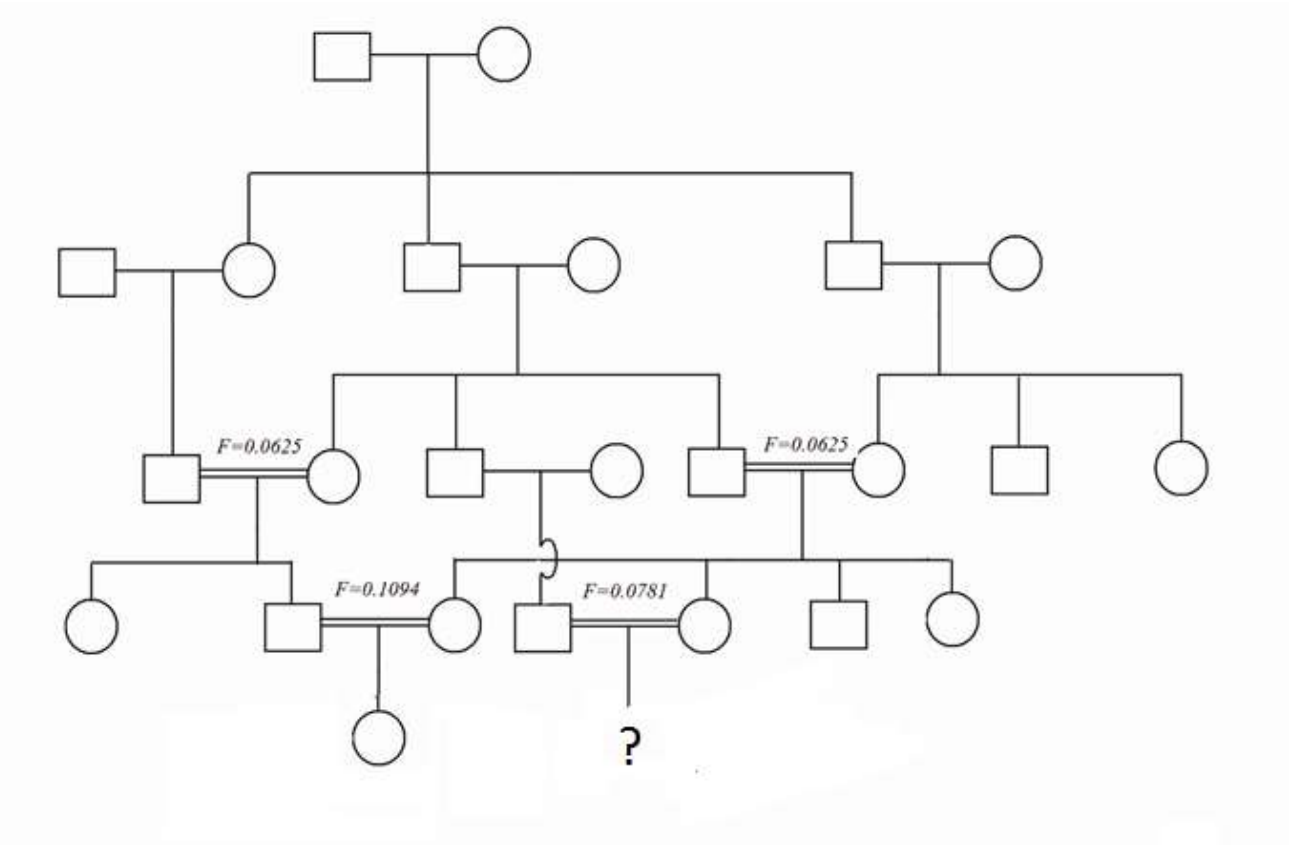
- There is a genetic disease in the family and the couple are consanguineous
- There is no known genetic disease in the family and the couple are consanguineous

A crucial first step is to take a detailed family history and draw a pedigree

In offering counseling for consanguinity, it is crucial to distinguish between:

- Families with a **known genetic** or inherited disorder
- Families 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)



Multiple consanguinity loops are very common in Arab families

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.

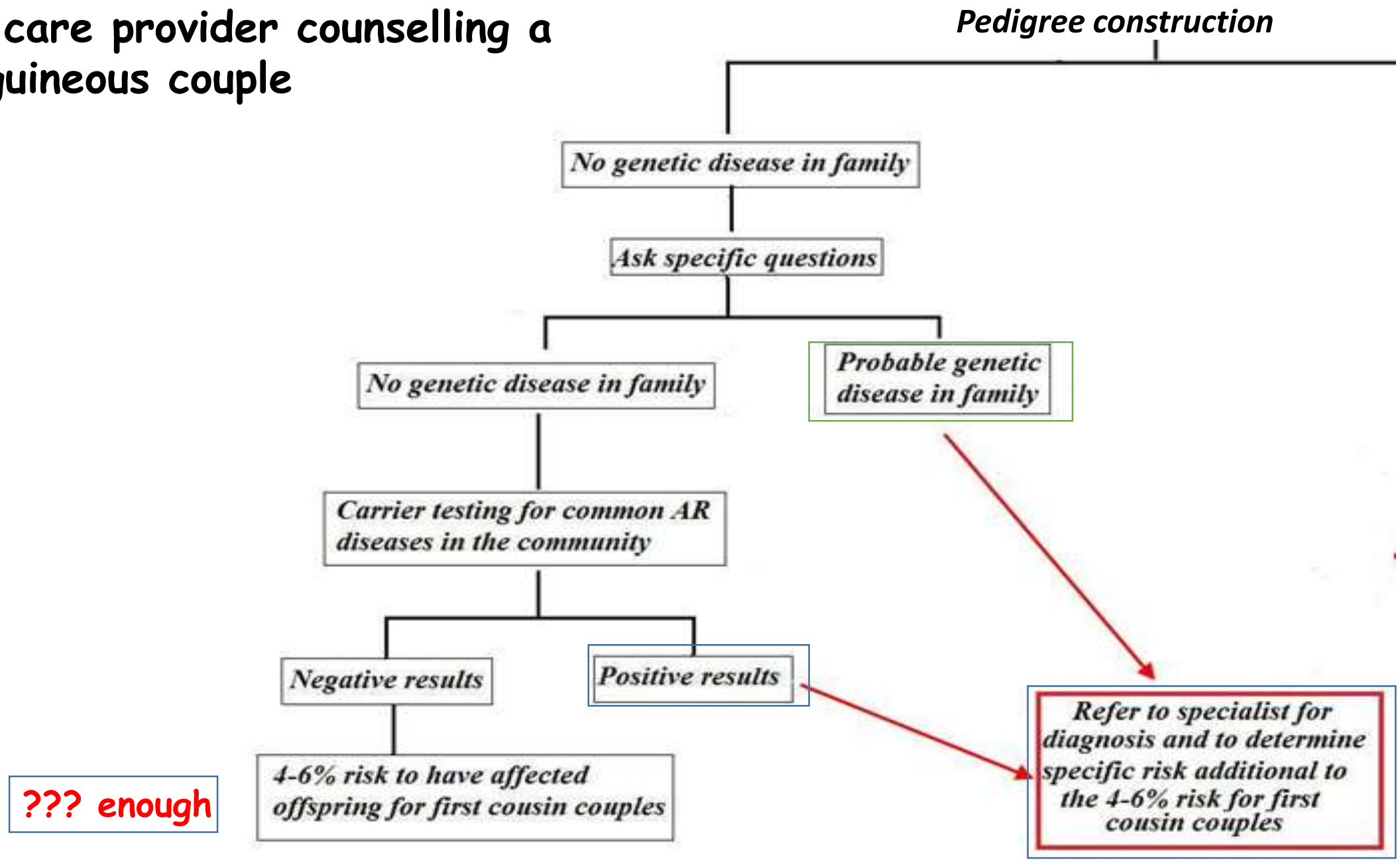
If there is no known genetic disorder in the family

- 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.

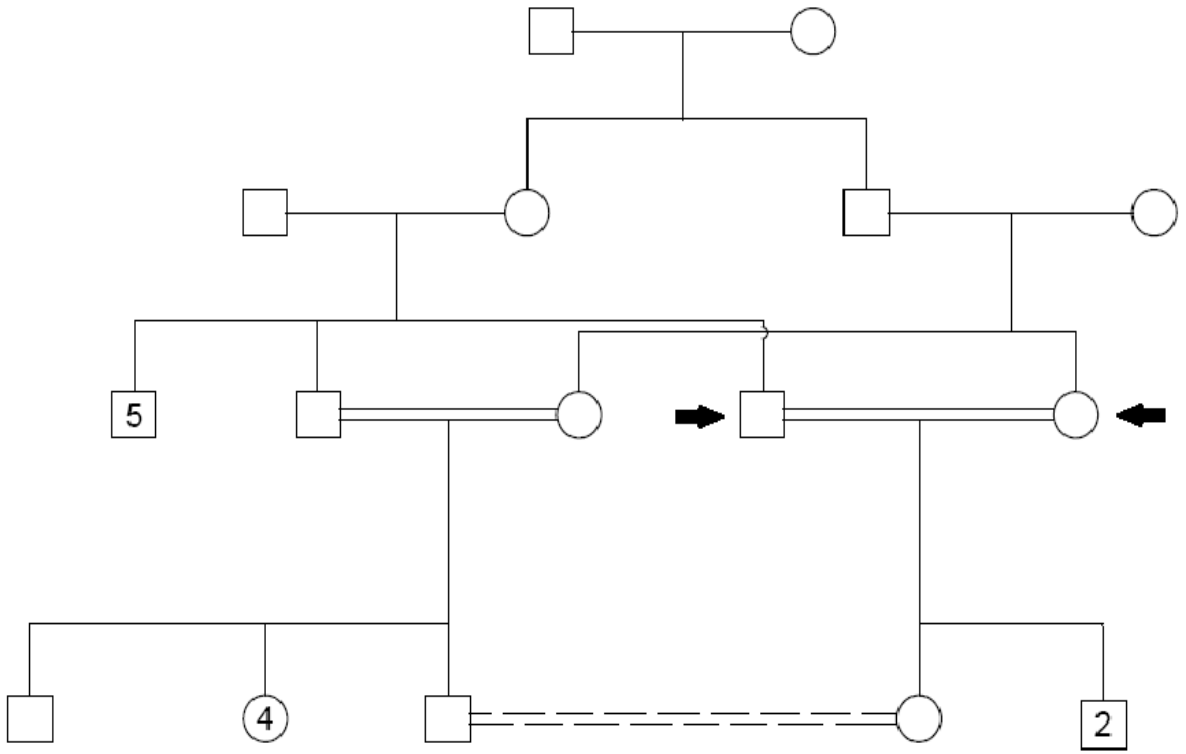
- Risks for other conditions are not established.

- Closer consanguineous relationship such as a double first cousins couple may be given a higher risk for their offspring.

Health care provider counselling a consanguineous couple



Premarital: No known genetic disease in family

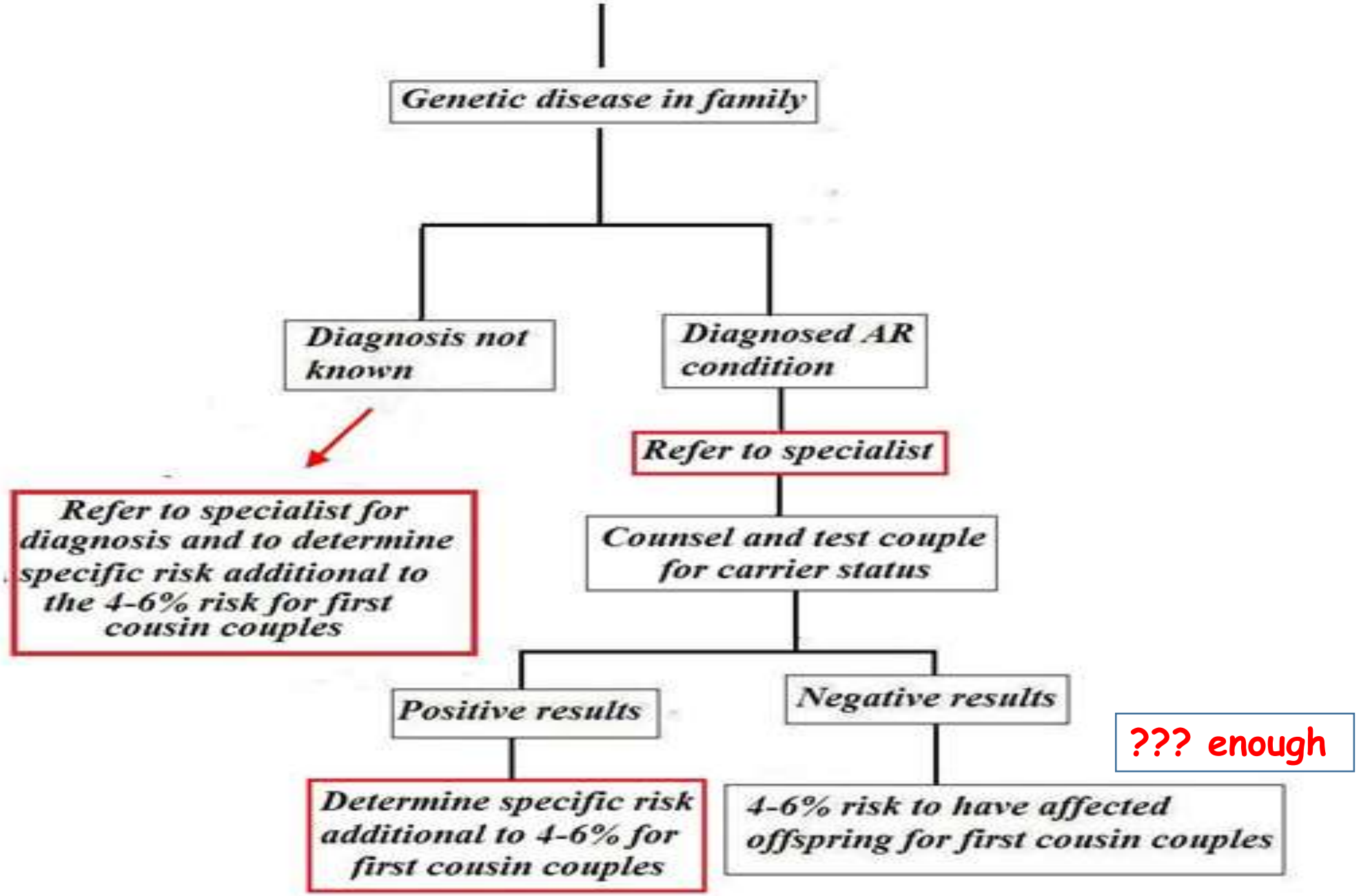


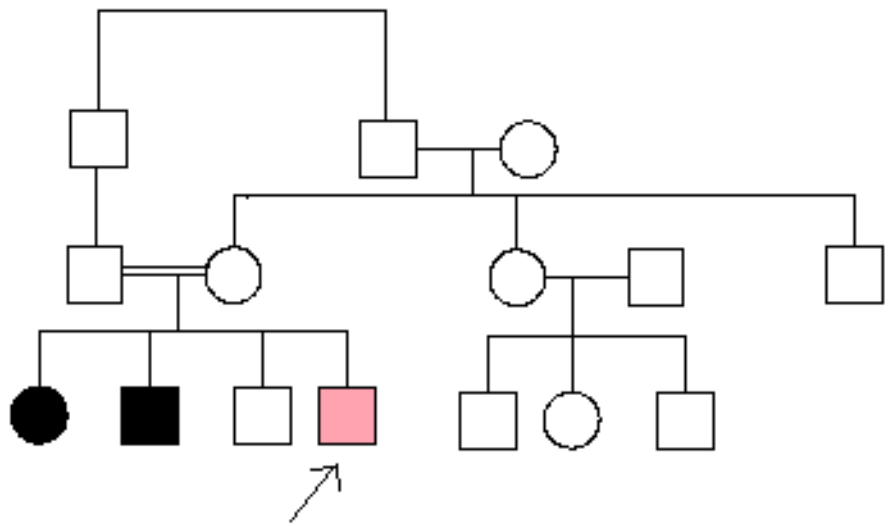
- Parents were first cousins and they wanted to marry their daughter to her double first cousin…
- Father was eager to proceed with the marriage because he did not want to upset his relatives or possibly stigmatize his daughter in a community with minimal genetic literacy
- Mother reluctant because she understood the risk for birth defects cited by the counselor
- How to counsel them ???
- What did they expect???

- 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

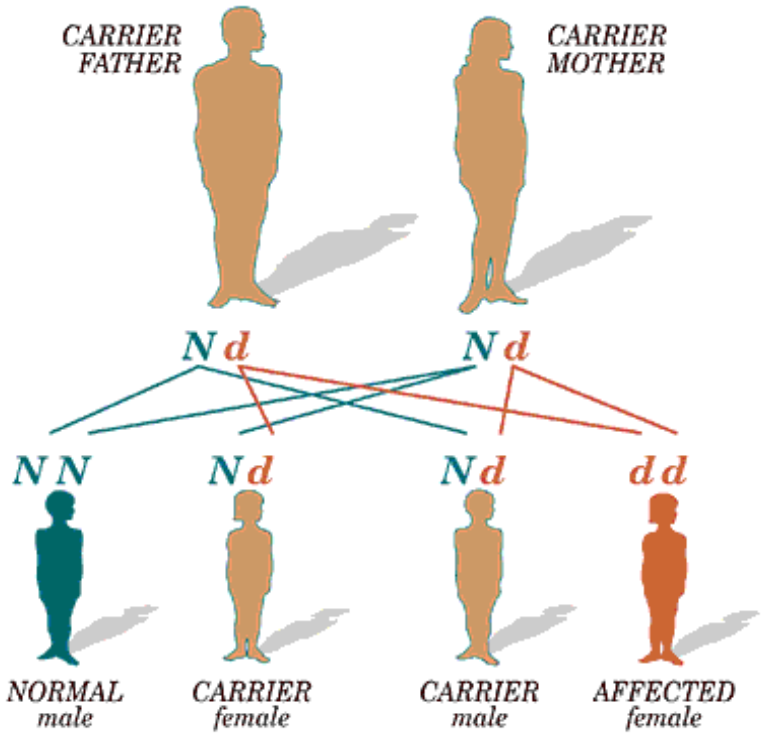
- Establish Clinical and Molecular diagnosis whenever possible
- Premarital and preconception carrier testing for the consanguineous couple
- If carriers cannot be diagnosed, give risk estimate
- Counseling to minimize further consanguinity unless carriers can be diagnosed
- Counseling couples with affected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


Genetic disease in family
Diagnosis not known
Diagnosed AR condition
Refer to specialist for diagnosis and to determine specific risk additional to the 4-6% risk for first cousin couples
Refer to specialist
Counsel and test couple for carrier status
Positive results
Negative results
Determine specific risk additional to 4-6% for first cousin couples
4-6% risk to have affected offspring for first cousin couples
??? enough



What is the probability that this person is a carrier?

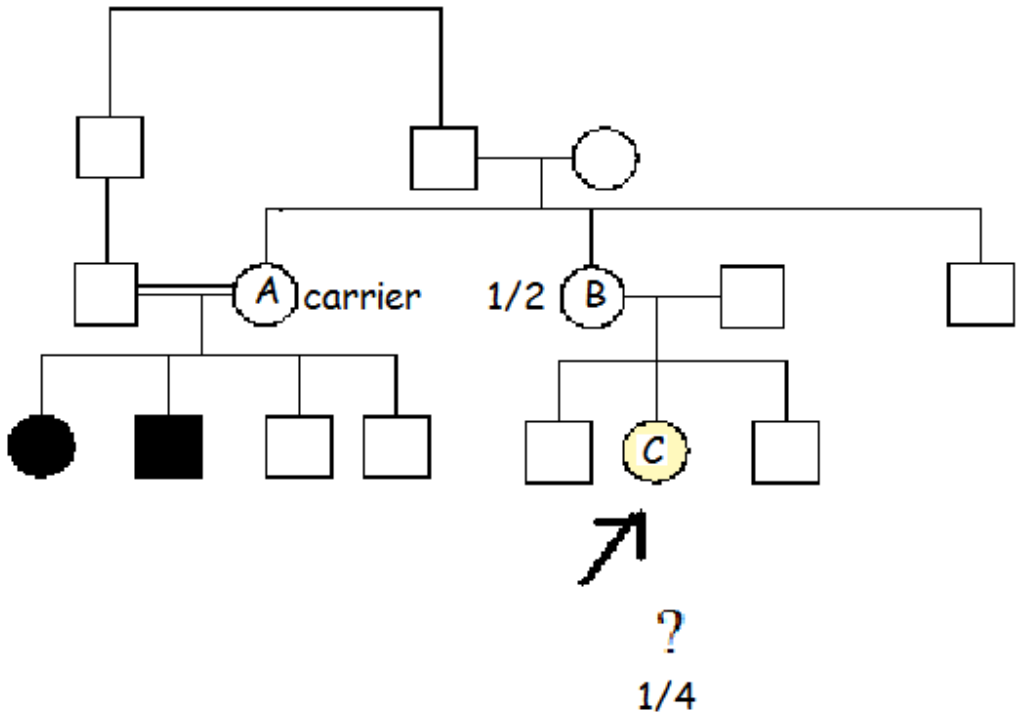
Autosomal recessive inheritance



- 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)

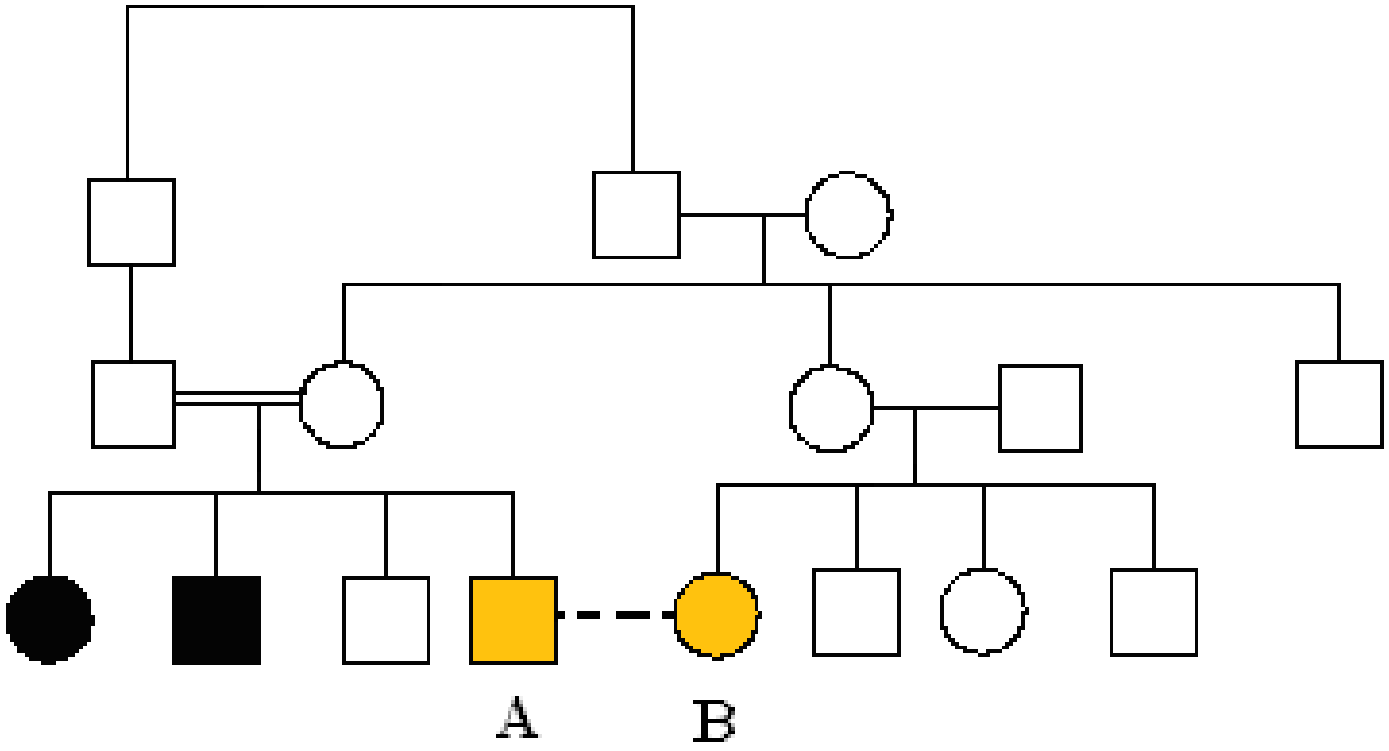
Calculating probabilities of being a carrier?



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



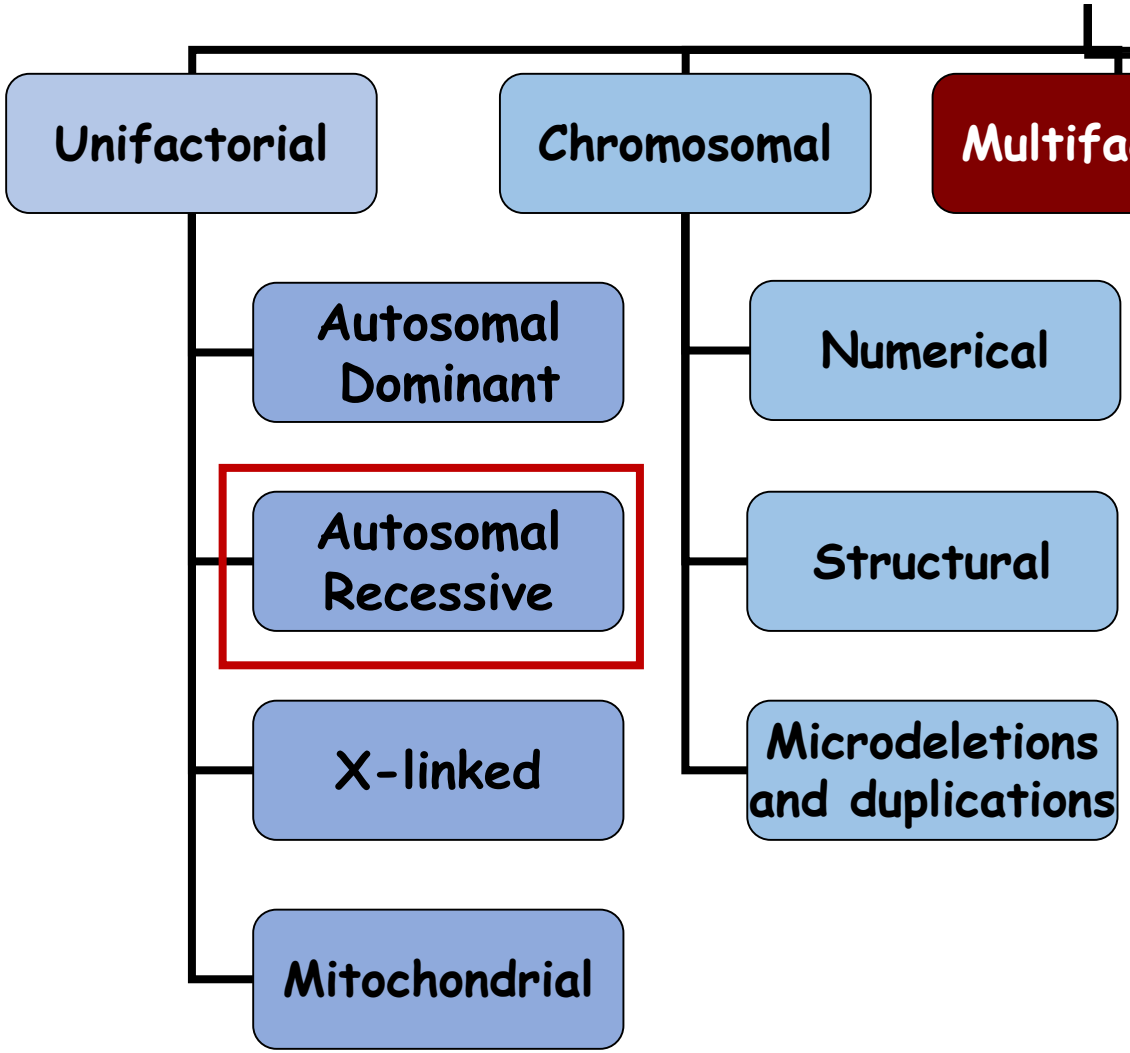
what is their risk of having an affected child?

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 (1X1X1/4)
- In this pedigree, the risk for A and B to have an affected child is 2/3X1/4X1/4= 1/24 (about 4%)

Conclusions

Underlying causes of birth defects



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.

Reproductive Health Parameters among first cousins 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 pathological infertility
- Same or lower rates of abortion
- Higher rates of stillbirths and postnatal mortality in offspring

Compiled data from 38 populations (600000 pregnancies) indicated a 4.4% excess pre-reproductive mortality in first cousin progeny *(Bittles and Neel, 1994)*

This level of excess mortality equates to 1.4 lethal equivalents per zygote

- **4-6% risk to have an offspring with birth defect**
- **Higher risk of having offspring with autosomal recessive disorder if present in the family**

Consanguineous marriages remain culturally and socially favored and respected in many counties, 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, only autosomal recessive disorders are strongly associated with consanguinity.
- No association of consanguinity with autosomal dominant , X-linked and chromosomal disorders.
- 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

In highly consanguineous populations:

Factors that may decrease consanguinity rate?

- ✓ **Higher female education and engagement in work force**
- ✓ **Later age at marriage**
- ✓ **Lower fertility**
- ✓ **More mobility from rural to urban ?**
- ✓ **Better economic status of families ?**
- ✓ **Community education programs?**

Factors that are maintaining /increasing consanguinity rates

- ➢ Cultural beliefs and norms
- ➢ Political and civil unrest
- ➢ Among first generation immigrants
- ➢ Financial difficulties/wealth
- ➢ Female illiteracy

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 Summary

First cousin couples have:

- Slightly higher risk of stillbirths and infant mortality rates among offspring
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Examples of using novel technology to identify carriers

A preconception carrier screen for 448 (later increased to 592) severe recessive childhood disease genes based on target enrichment and NGS was developed and used on 104 unrelated DNA samples *(Bell et al. 2011, Kingsmore et al 2011)*

The screening platform (Universal Genetic Test, Counsyl, South San Francisco, CA) uses high-throughput genotyping to identify disease-causing variants and corresponding wild-type alleles. In total, 417 disease-causing mutations associated with 108 recessive diseases were assayed and interpreted via fluorescent sequences among a study population of 23,453 individuals *(Lazarin,2013)*

References

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