MENDELIAN INHERITANCE

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MGL- 6

Genetic Diseases (GD)

- Chromosomal Abnormalities
- **Single Gene Defects**
- Non-Traditional Inheritance
- Multifactorial Disorders
- Cancer Genetics

Topics of Discussion

- Basic concepts of formal genetics
- Autosomal dominant inheritance
- Autosomal recessive inheritance
- Factors that may complicate inheritance patterns
- Probability

Mendelian Inheritance
Single Gene Defects

- Autosomal recessive
- Autosomal dominant

- Factors complicating Mendelian inheritance
- X-linked recessive
- X-linked dominant
- Y-linked

Pedigree

- The family tree
- Representation of the ancestry of an individual's family.
- Symbolic representations of family relationships and inheritance of a trait

Goals of Pedigree Analysis

- Determine the mode of inheritance: dominant, recessive, partial dominance, sex-linked, autosomal, mitochondrial, maternal effect.

- Determine the probability of an affected offspring for a given cross.

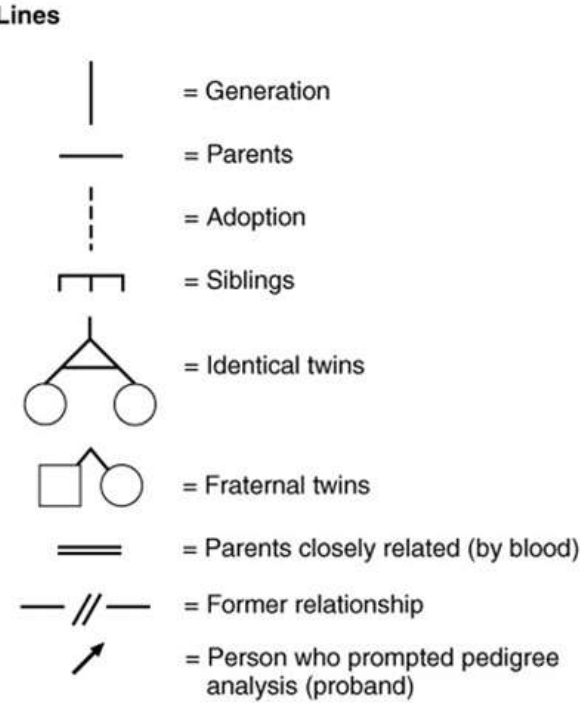
Obtaining a pedigree

A three generation family history should be a standard component of medical practice. Family history of the patient is usually summarized in the form of a pedigree

Points to remember:

- Ask whether relatives have a similar problem
- Ask if there were siblings who have died
- Inquire about miscarriages, neonatal deaths
- Be aware of siblings with different parents
- Ask about consanguinity
- Ask about ethnic origin of family branches

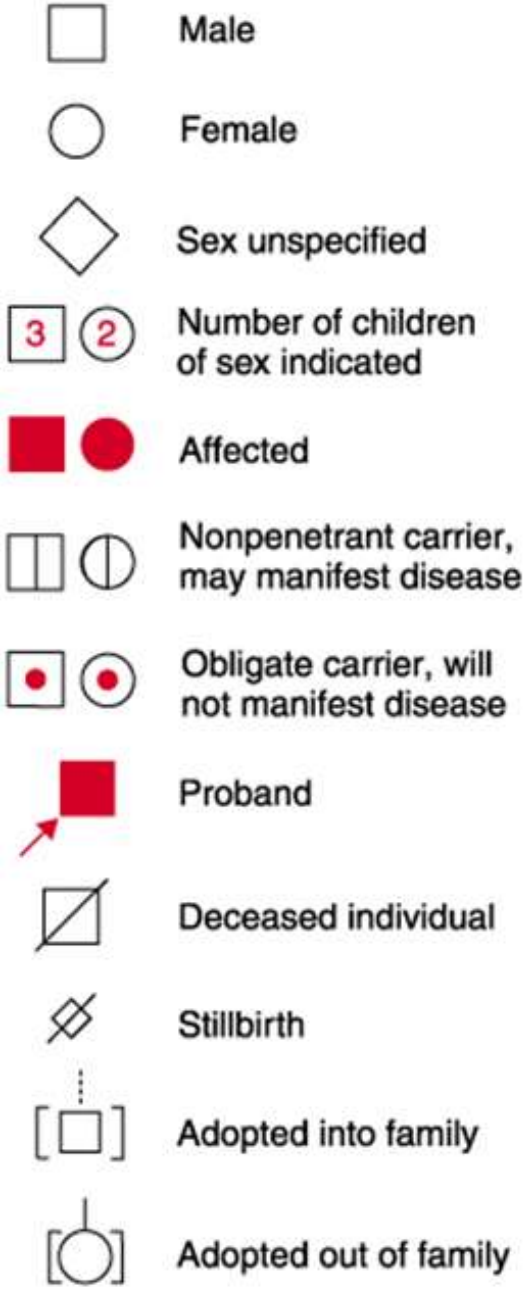
Pedigree Symbols

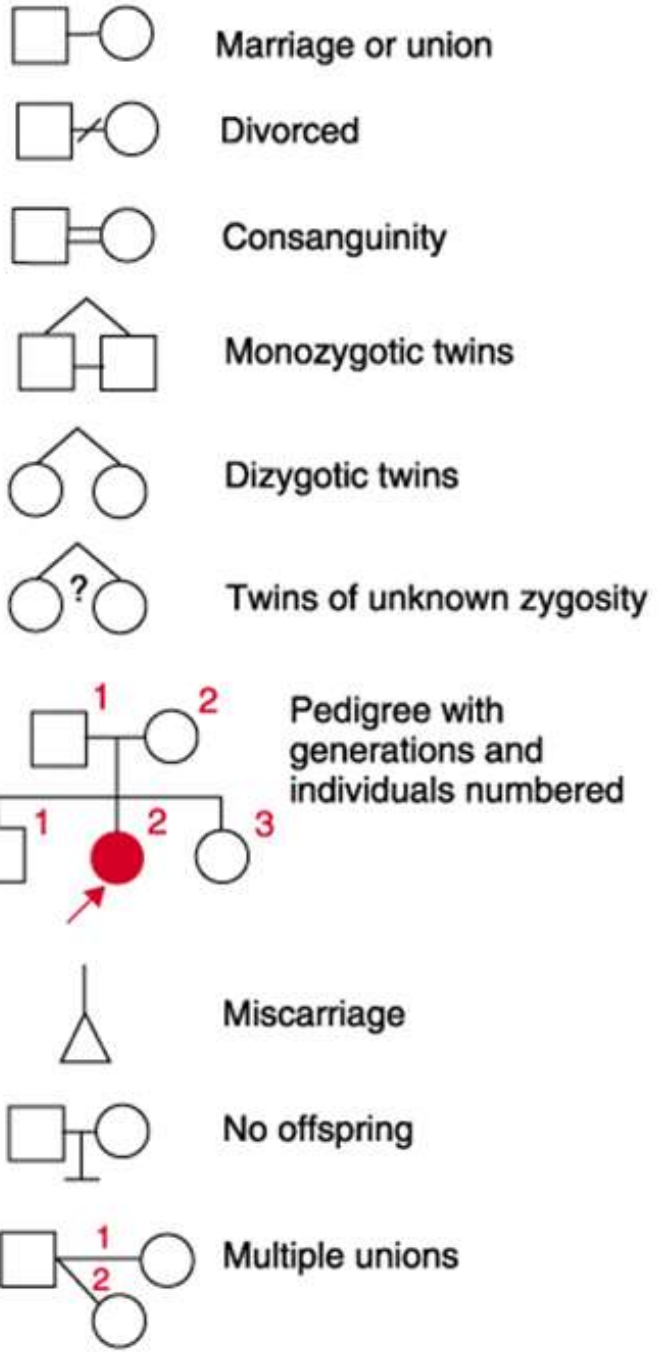


Numbers

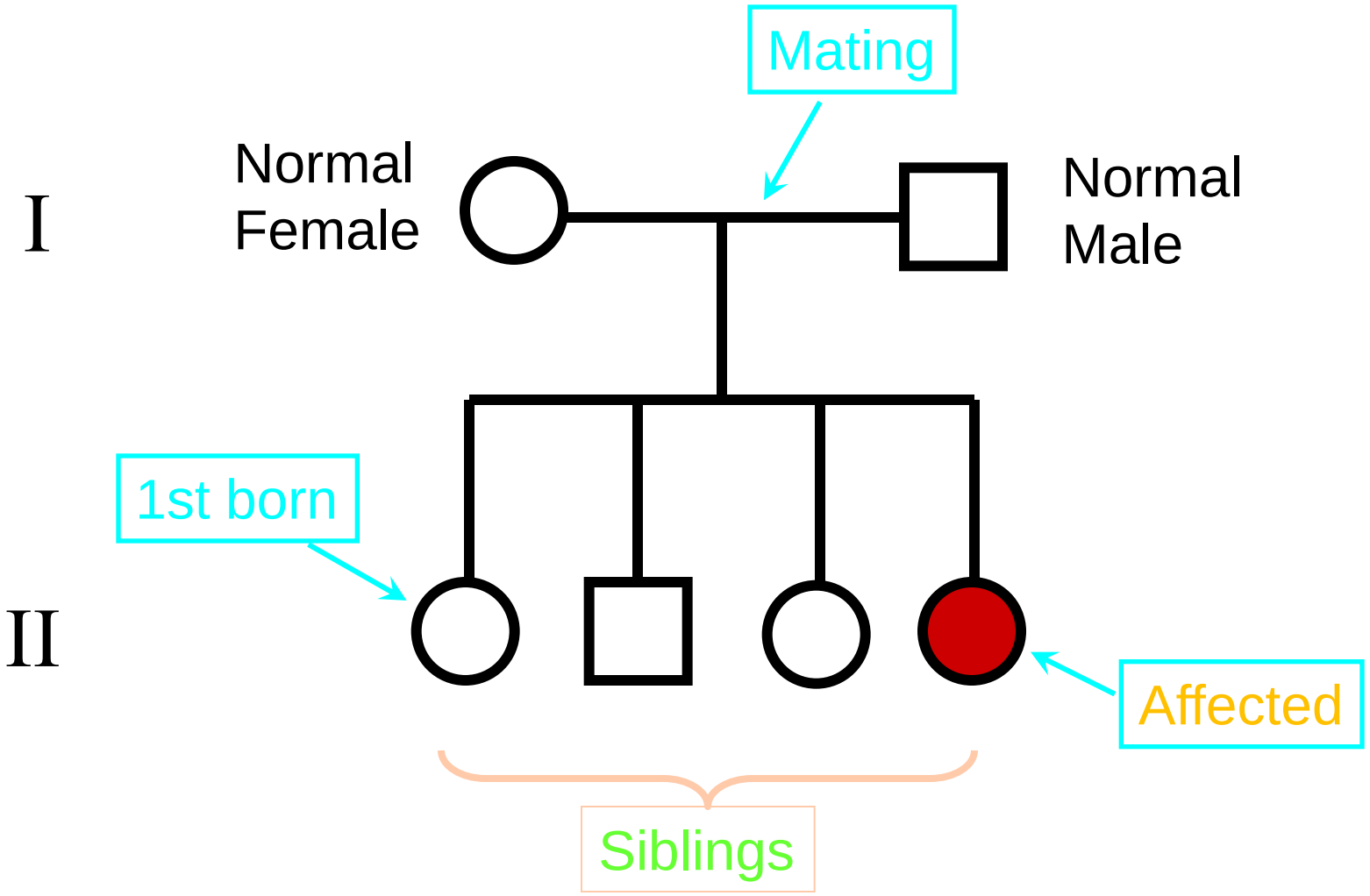
Roman numerals = generations

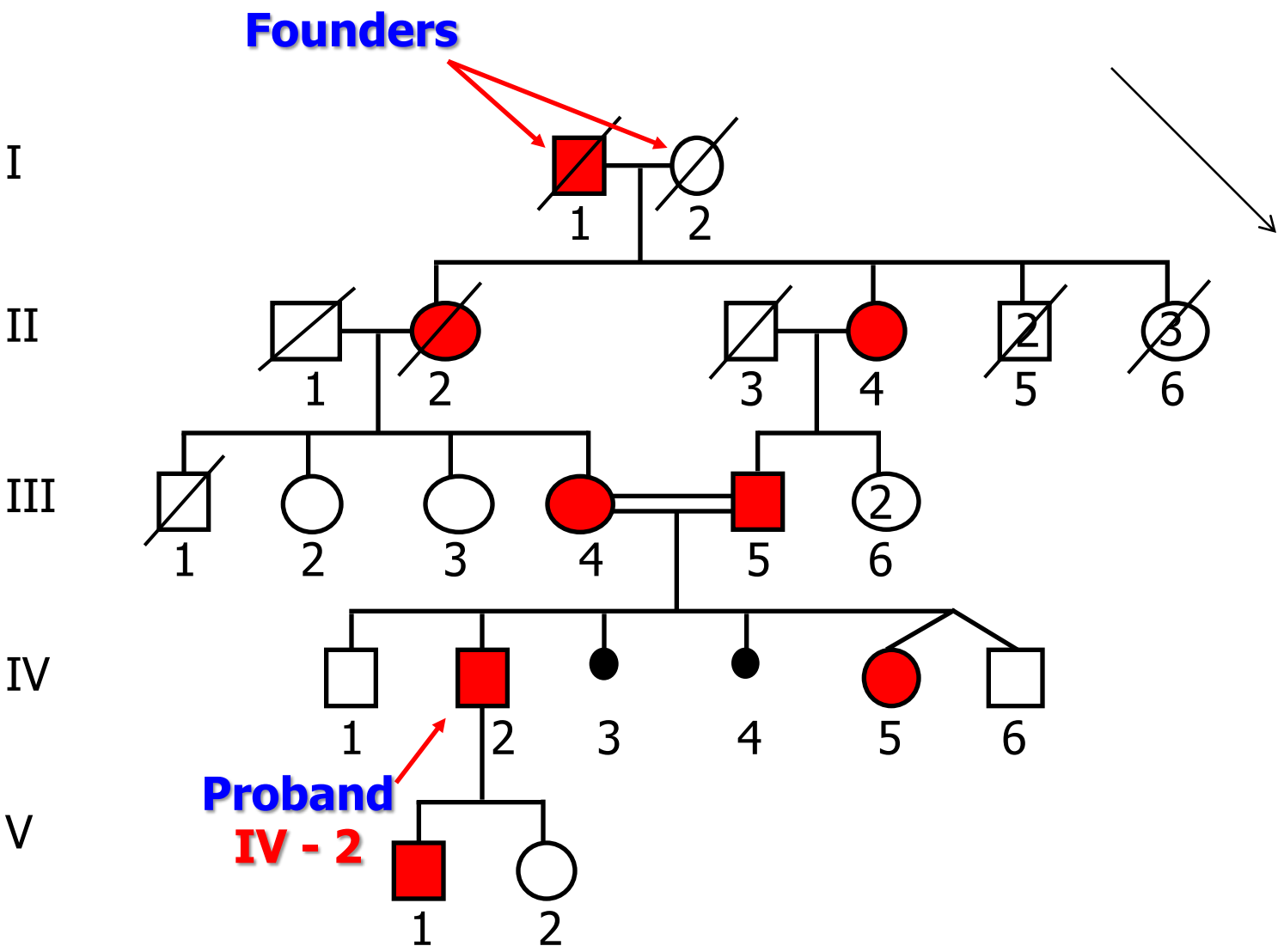
Arabic numerals = individuals in a generation



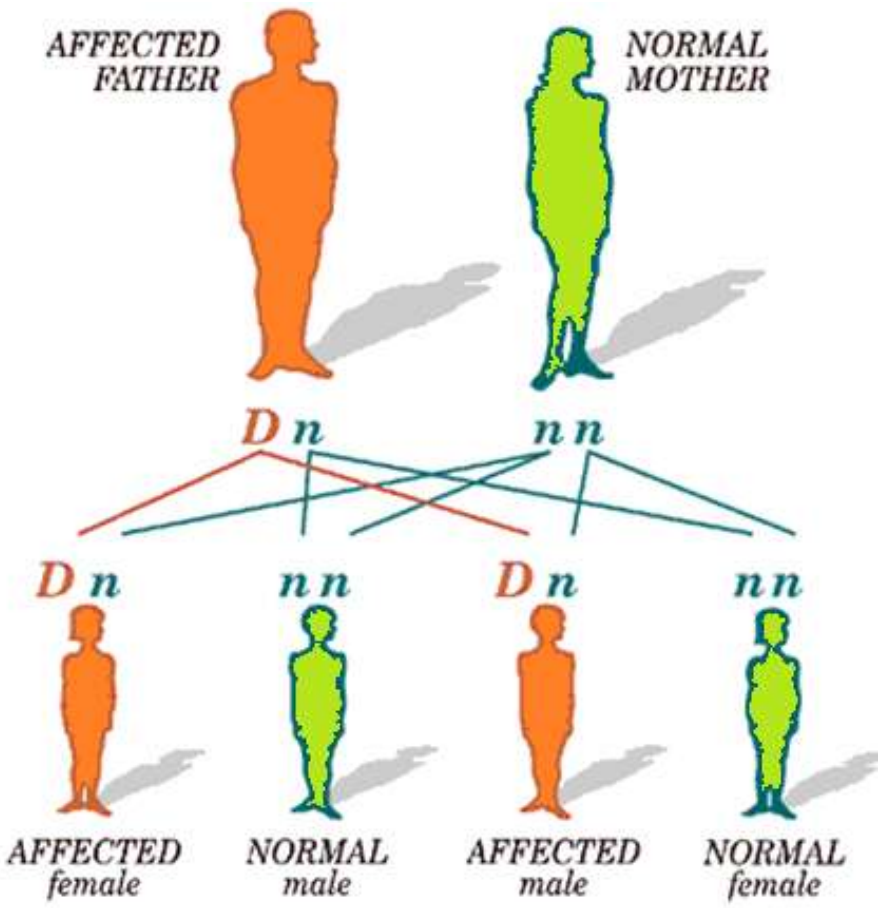


Pedigree Analysis




Founders
I
1
2
II
1
2
3
4
5
6
III
1
2
3
4
5
6
IV
1
2
3
4
5
6
Proband
IV - 2
V
1
2

Autosomal dominant inheritance



- **D** abnormal gene
- **d** normal gene
- Each child of an affected person has a 50% chance of being affected
- Affected persons are usually heterozygous

Characteristics of autosomal dominant inheritance:

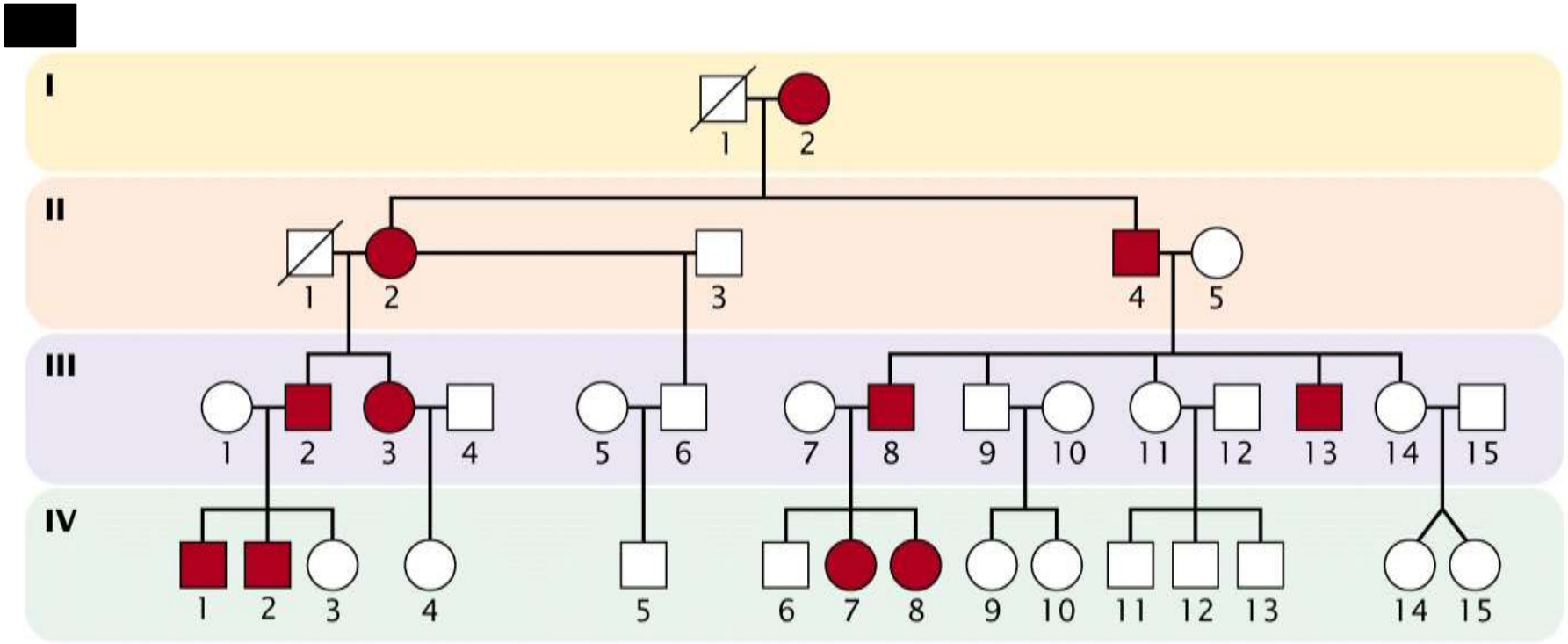
1. A gene is dominant if it is expressed when heterozygous
2. An affected individual has a 50% chance of having an affected child.
3. An affected child will have one affected parent
4. The affected parent can be either the mother or the father
5. Autosomal dominant traits have low frequencies in the population
6. Autosomal dominant traits are usually lethal when homozygous
7. No skipping of generations

Autosomal Dominance

Example:

Waardenburg Syndrome

Hearing loss and changes in coloring (pigmentation) of the hair, skin, and eyes.



- **Hemizygous:** Having half the number of alleles
- **Expressivity:** The severity or intensity of the phenotype of an allele.
- **Penetrance:** The degree to which a gene expresses any observable phenotype

Pitfalls in Recognizing AD Inheritance

- **Incomplete Penetrance**. Some people who have the gene mutation do not show the clinical effects.
- **Penetrance Limited to one gender**. For example, when prostate cancer risk is inherited in an autosomal dominant manner, women who inherit the mutation are not affected; they can, however, pass the mutation on to their sons
- **Variable Expressivity**. The gene mutation has variable clinical manifestations: the disorder may range from mild to severe; or a range of different complications may occur among people with the mutation.

Pitfalls in Recognizing AD Inheritance

- **New Mutation.** An affected person may be the first person in the family with the condition, due to a mutation arising for the first time in sperm, egg, or embryo

- **Germline Mosaicism.** A new mutation may arise in testis or ovary, resulting in an unaffected parent transmitting the condition to two or more children

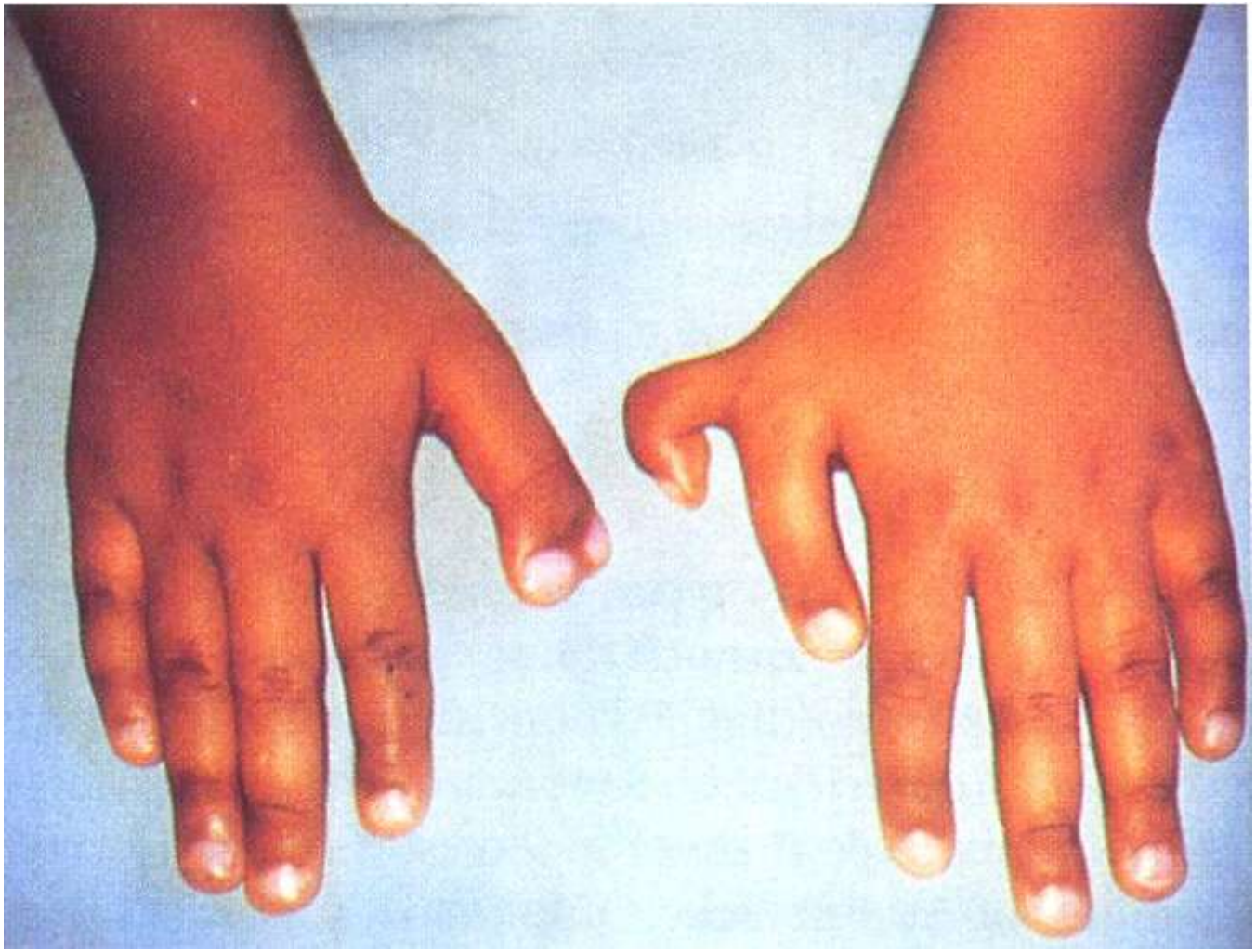
AD Disorders

- Marfan's Syndrome
- Huntington's Chorea
- Osteogenesis imperfecta
- Neurofibromatosis
- Retinoblastoma
- Tuberous sclerosis
- Apert's Syndrome
- Multiple polyposis of colon
- Achonroplacia
- Brachydactylyl
- Ehlers-Dalton Syndrome
- Familial Hypercholeserolemia
- Porphyria

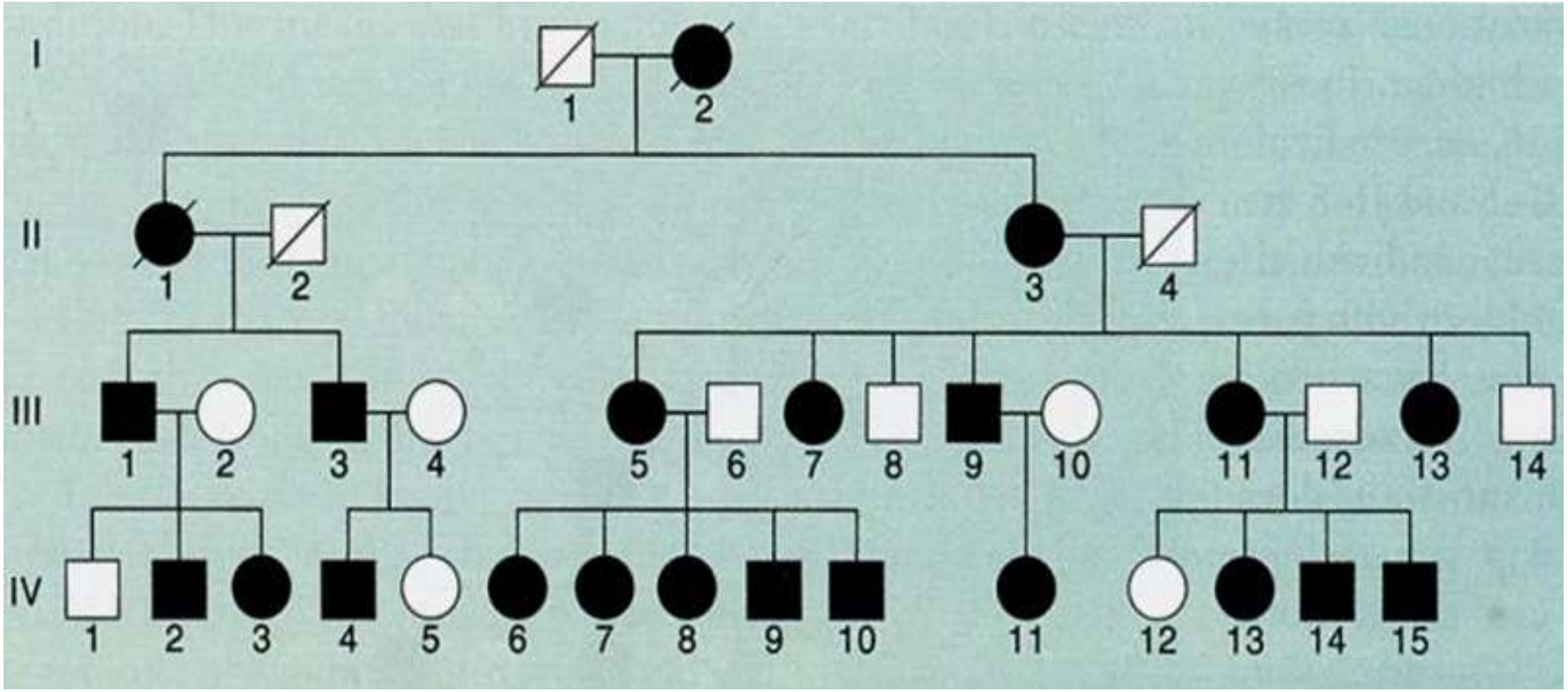
GENETIC TRAITS IN HUMANS CAN BE TRACKED THROUGH FAMILY PEDIGREES

- Recessive traits are often more common in the population than dominant ones.
- E.g. absence of freckles more common than presence.

Polydactyly



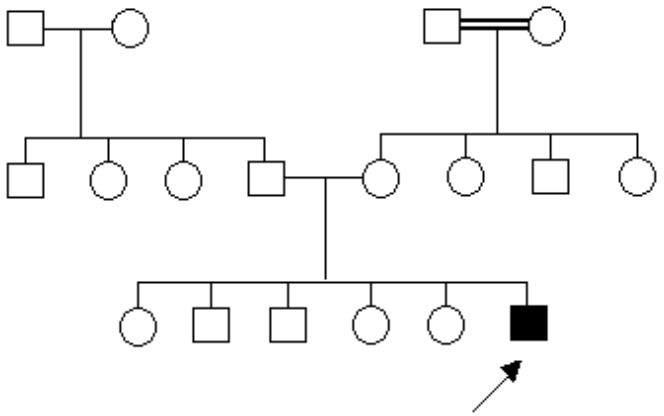
Polydactaly

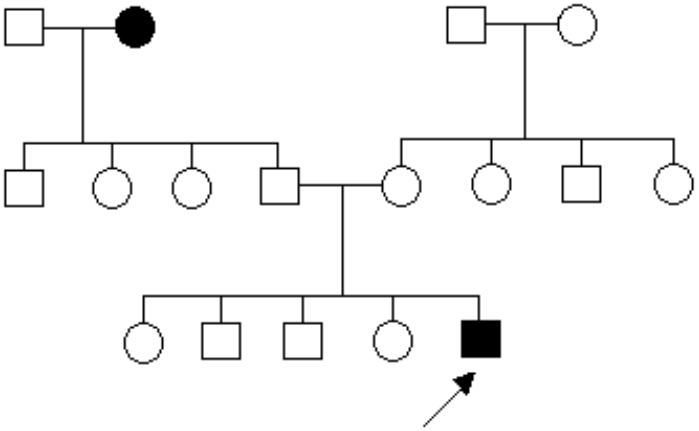


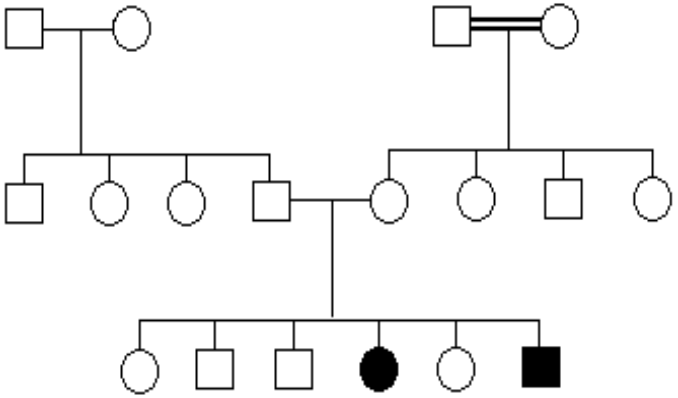
Autosomal Dominant Inheritance

Apparent sporadic cases
Possible explanations

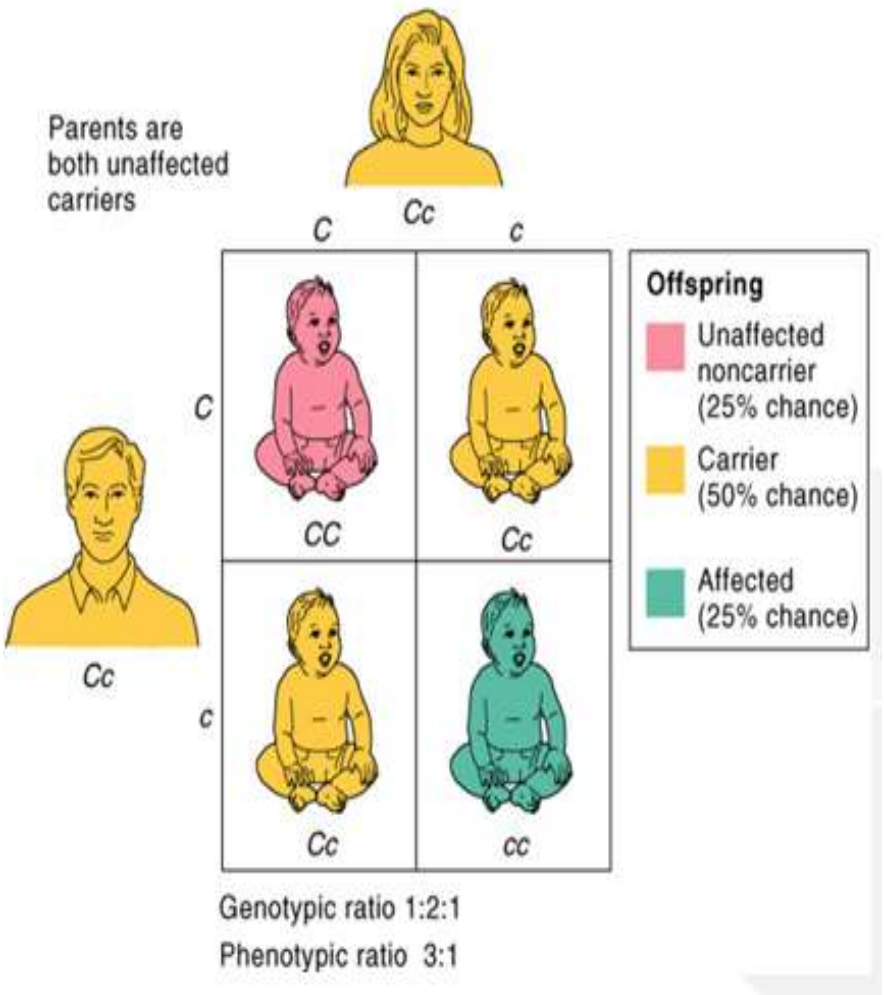
- Variable expressivity
- New mutation
- Non-penetrance
- Gonadal mosaicism





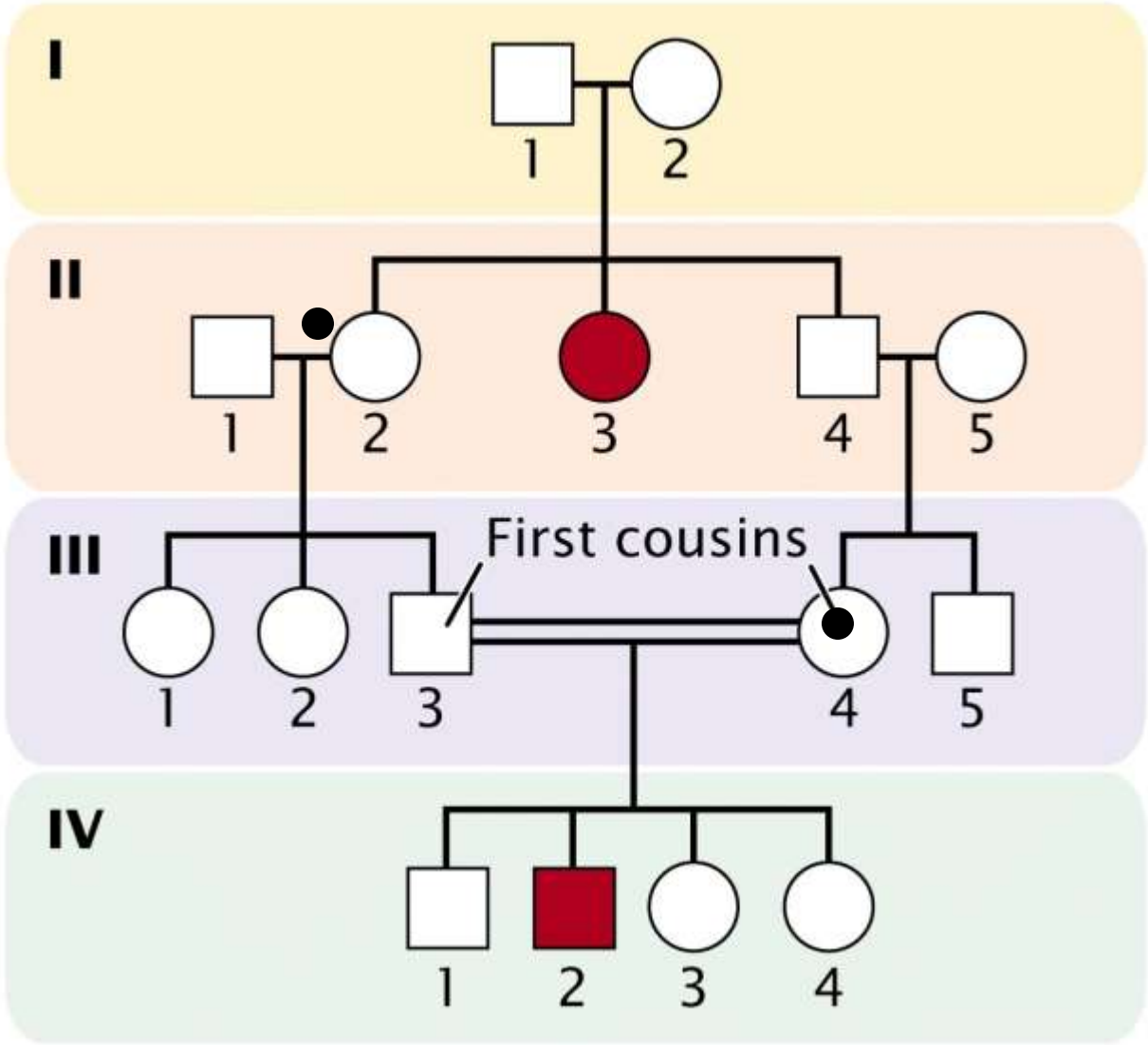


Autosomal Recessive



- **Carrier parents are Heterozygotes carry the recessive allele but exhibit the wild type phenotype.**
- **Normal parental phenotype**
- **75% chance for normal offspring**
- **25% chance for affected offspring**
- **Males & females equally affected**
- **“Inborn errors of metabolism”**
- **Associated with specific ethnic groups**

Autosomal Recessive



Heterozygote Advantage in Recessive Conditions

Condition	Carriers protected against
1. Thalassaemia	falciparum malaria
2. Sickle cell	falciparum malaria
3. (G-6-PD deficiency	falciparum malaria)

Examples of AR conditions

- Beta thalassemia
- Sickle cell anemia
- Congenital adrenal hyperplasia
- Familial Mediterranean fever
- Cystic fibrosis
- Phenylketonuria

Factors that may complicate Inheritance Patterns

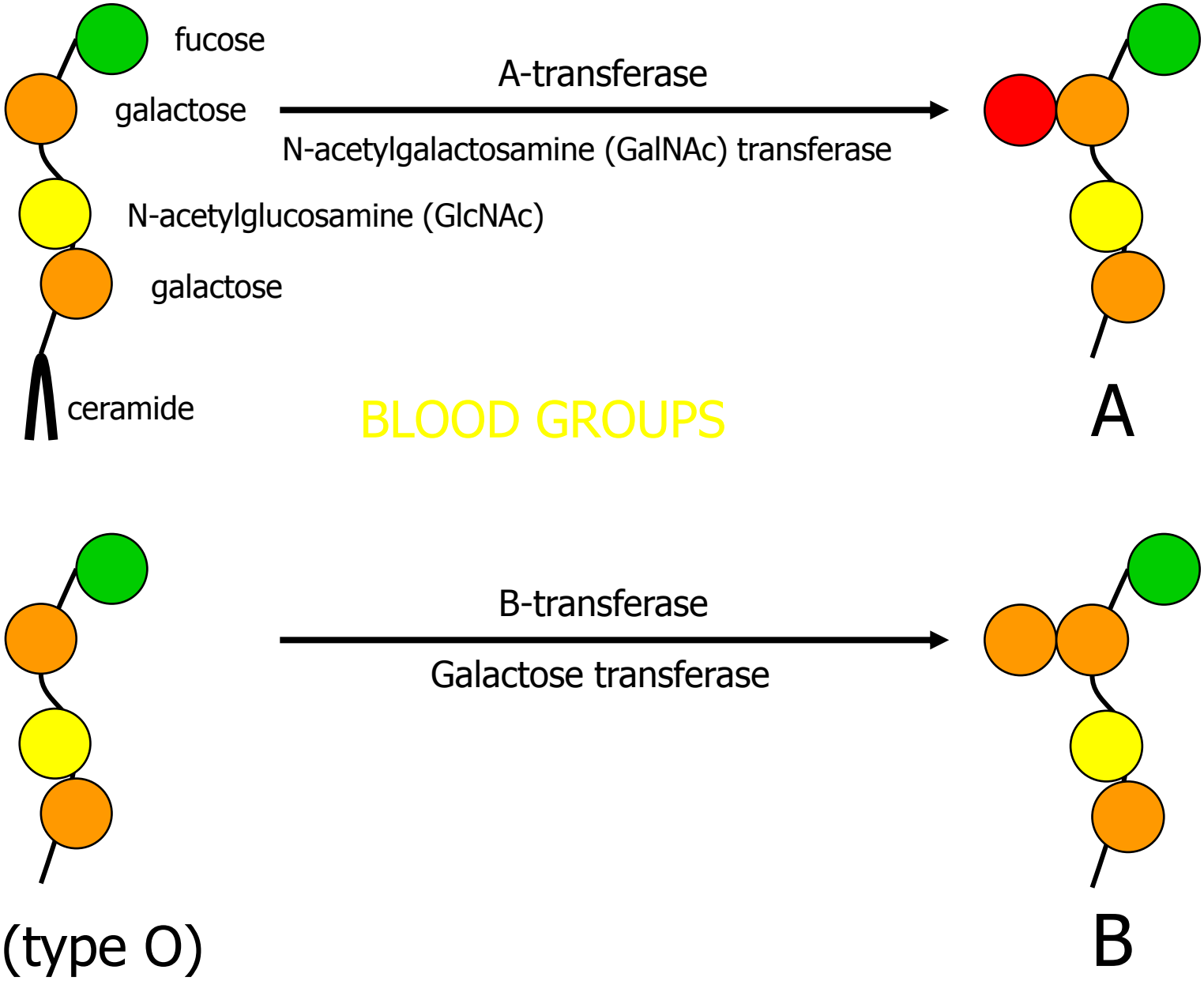
- Codominance
- Epistasis
- New mutation
- Germline Mosaicism
- Delayed age of onset
- Reduced penetrance
- Variable expression
- Pleiotropy and Heterogeneity
- Genomic Imprinting
- Anticipation

Pitfalls in Providing Genetic Counseling for AR Inheritance

- **Misassigned paternity.** If the biologic father of an affected individual is someone other than the person assumed to be the father, misleading carrier test results might occur (the apparent father would usually not be a carrier) and risk of additional affected children could be misstated.

- **Uniparental disomy.** If a couple in which only one partner is a carrier has an affected child, it may rarely be due to uniparental disomy: in this case both gene mutations are inherited from the parent who is a carrier, due to an error in the formation of sperm or ovum.

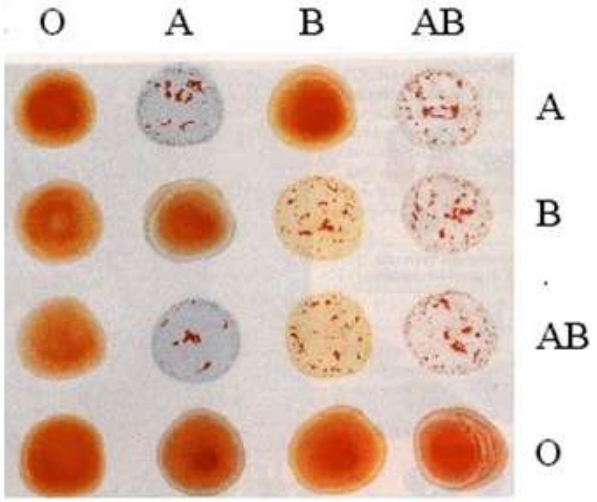
- ***De novo* mutations.** Although also rare, *de novo* mutations can account for ~1% of gene mutations in some disorders and thus provide another explanation for the birth of an affected child when only one parent is a carrier.

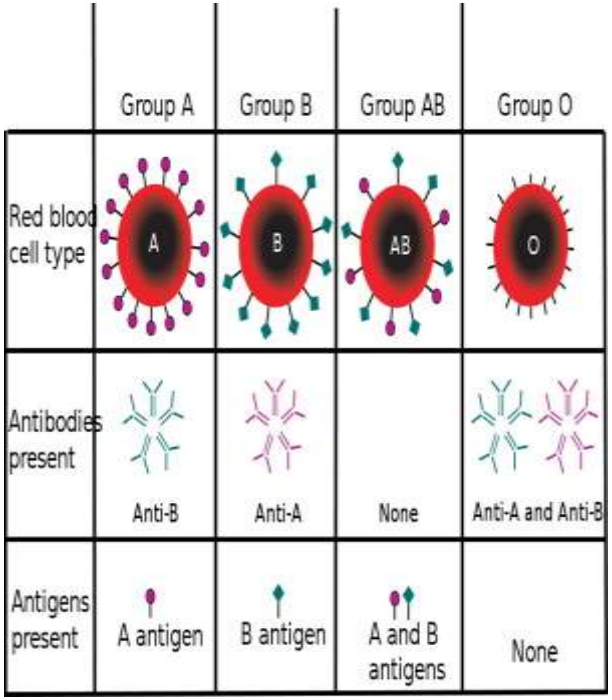

fucose
galactose
N-acetylglucosamine (GlcNAc)
galactose
ceramide
A-transferase
N-acetylgalactosamine (GalNAc) transferase
BLOOD GROUPS
A
B-transferase
Galactose transferase
H (type O)
B

Co-domiance

- Has three alleles: A, B & O
- AB co-dominant, O recessive
- Genotype represented using I^A, I^B & i

Phenotype	Genotype
Type A	I^AI^A or I^Ai
Type B	I^BI^B or I^Bi
Type AB	I^AI^B
Type O	ii





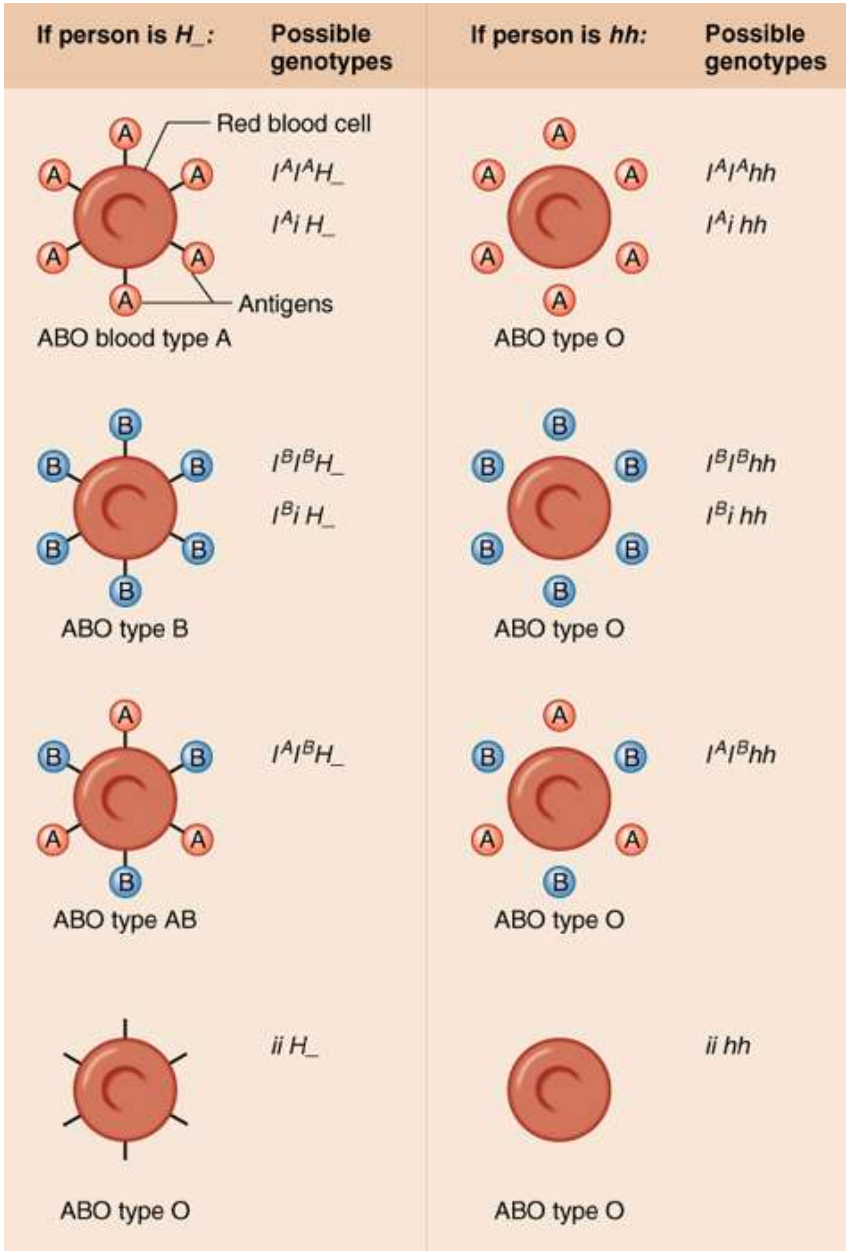
Epistasis

when one gene affects the expression of a second gene.

H gene is epistatic to the ABO gene.

- H protein attaches the A or B protein to the cell surface.

- hh genotype = no H protein.
  All ABO genotypes appear as type O.



Pleiotropy

- The appearance of several apparently unrelated phenotypic effects caused *by a single gene*
- Refers to a Mendelian disorder with several symptoms
- Different subset of symptoms in different individuals.
- Usually means that a genes is involved in multiple processes

PLEIOTROPY

- **MARFAN SYNDROME**: AD. Affects EYE, Skeleton and Cardiovascular
- **CF**. AR, Sweat glands, Lungs and Pancrease
- **OI**: , Bones, Teeth, and Sclera
- **Albinism**, Pigmentation and Optic Fiber development

Genetic heterogeneity

Different genes can produce identical phenotypes.

Individuals with identical phenotypes may reflect different genetic causes.

- Deafness
- Albinism
- Cleft palate
- Poor blood clotting

HETEROGENEITY

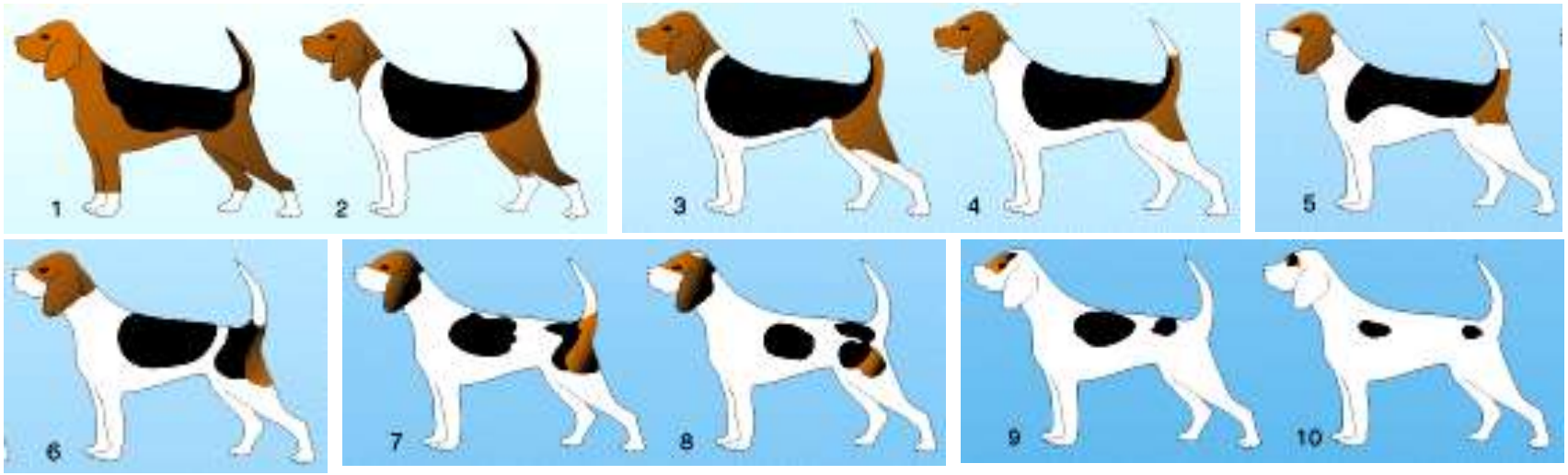
A disease that can be caused by mutations at a different loci in different families.

Disease	Description	Chromosomes on which known loci is located
Retinitis pigmentosa	Progressive retinopathy and loss of vision	> 20 chromosome regions identified
Osteogenesis imperfecta	Brittle bone disease	7, 17
Charcot-Maric-Tooth diseas	Peripheral neuropathy	1, 5, 8, 11, 17, X
Familial Alzheimer disease	Progressive dementia	1, 14, 19, 21
Familial melanoma	Autosomal dominant melanoma (skin cancer)	1, 9
Hereditary nonpolyposis colorectal cancer	Autosomal dominant colorectal Ca	2p, 2q, 3, 7
Autosomal dominant breast cancer	Predisposition to early-onset breast and ovarian cancer (chromosome 17 form)	13,17
Tuberous sclerosis	Seizures, facial angiofibromas, hypopigmented macules, mental retardation	9,16
Adult polycystic kidney disease	Accumulation of renal cysts leading to kidney failure	4,16

VARIABLE EXPRESSION

Penetrance is complete, but severity of the disease is variable,

- Environmental effects,
- Modifier genes, Different expression in different families
- Allelic heterogeneity- Beta-Thal, Sickle Cell
- Osteogenesis imperfecta,
  - Mutations at COOH terminal more sever than NH2 terminal,
  - Accidental fracture Complecations,



DELAYED AGE OF ONSET

Observed in many genetic diseases. It complicate the interpretation of inheritance patterns in the families.

- Huntington Disease – AD
- Hemochromatosis – AR FATAL
- Familial Alzheimer Disease
- Familial Breast Cancer

REDUCED PENETRANCE

Diseases genes in which an individual may have the disease genotype without expressing of the disease.

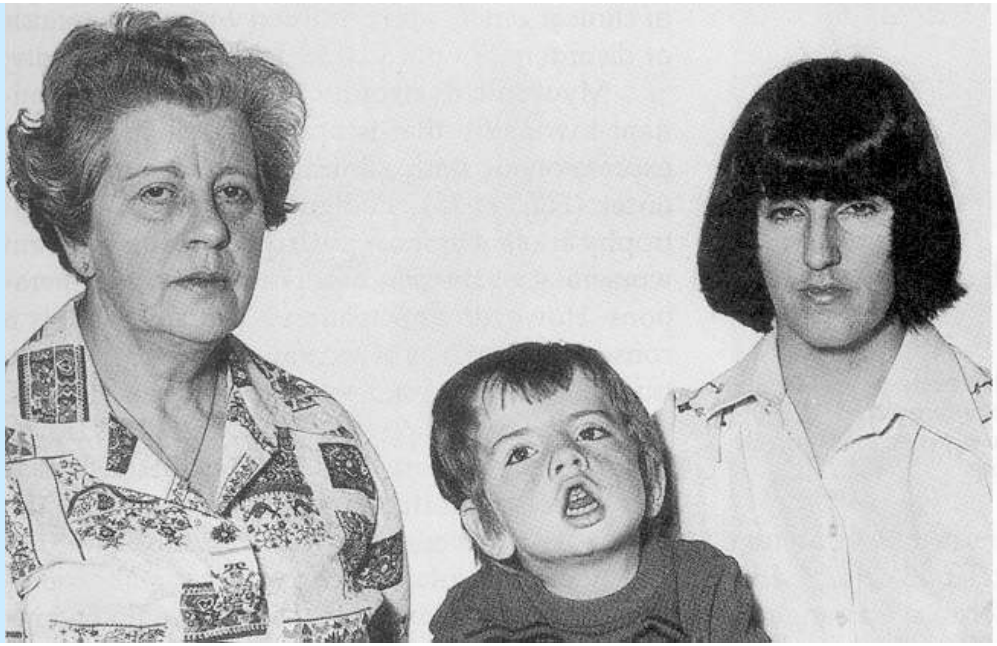
Phenotype

- Retinoplastoma. Autosomal Dominant
- 10% of gene carriers do not show the disease = OBLIGATE CARRIERS: Penetrance = 90%

Anticipation

Myotonic dystrophy

Number of CTG repeats	phenotype
5	normal
19 - 30	premutant
50 - 100	mildly affected
2,000 or more	severely affected



GERMLINE MOSAICISM

Occurs when all or part of a Parent's germ line is affected by a disease mutation but the somatic cells are not. It elevates the recurrence risk for future offspring of the mosaic parent

Osteogenesis Imperfecta

NEW MUTATION

- New mutations are frequent cause of the appearance of a genetic disease in an individual with no previous family history of the disorder. The recurrence risk for the individual's sibling is very low, but it may be substantially elevated for the individual's offspring
- Achnondroplasia = 7/8 are new mutations,
- 1/8 inherited