

Mendelian inheritance and the most common genetic diseases

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Mendelian Inheritance

Gregor Mendel demonstrated in ~1850-1870 that the inheritance of certain traits follows particular laws.

He described by his experiments the autosomal recessive and autosomal dominant inheritance.



<http://mendel.imp.ac.at/mendeljsp/biography/biography.jsp>

autosomal dominant inheritance

definition:

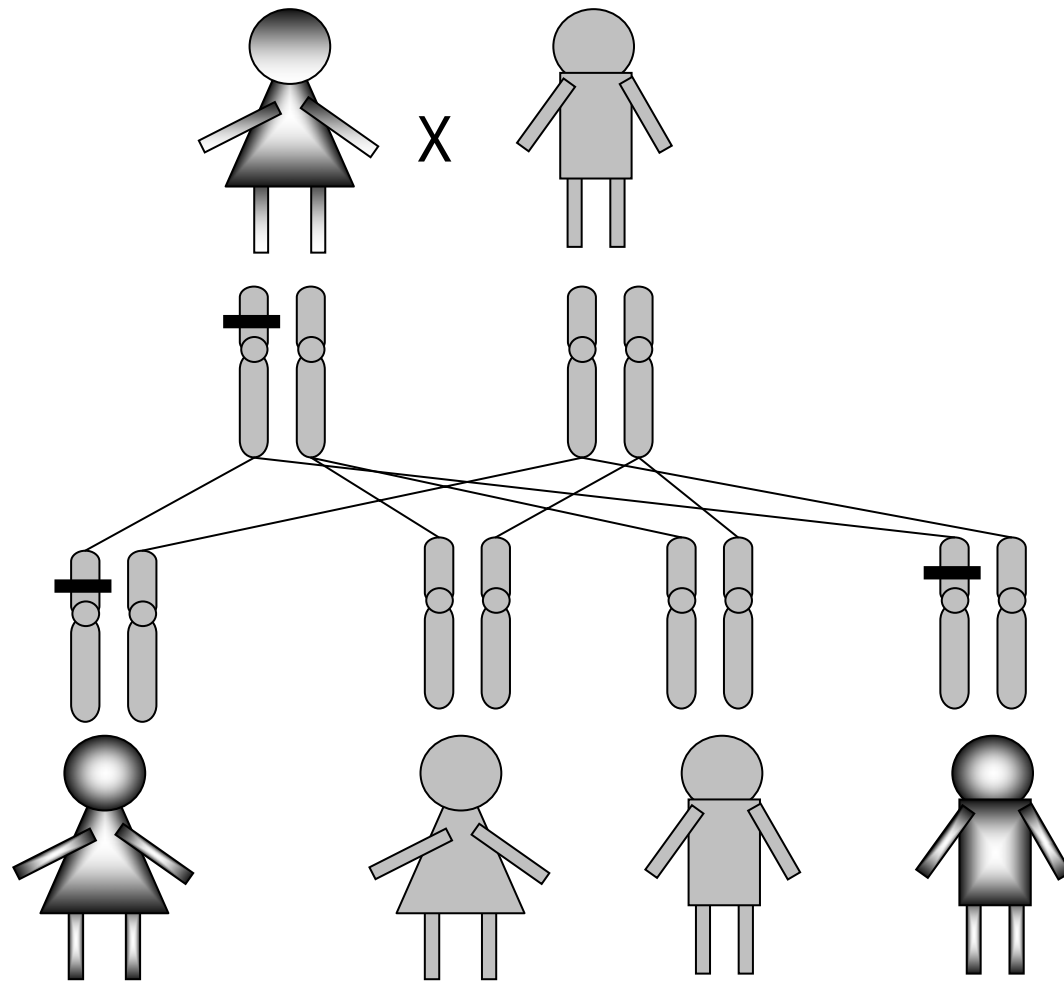
- affected gene locus is located on an autosomal chromosome
- dominant inheritance is given, if the present of a heterozygous mutation causes a phenotype
 - haploinsufficiency: the reduced dosage of the wildtype allele is not enough for the normal gene function
 - gain-of-function: the gene product of the mutated allele gain a new, abnormal function
 - dominant-negative effect: the mutated allele (misshapen protein) acts with the gene product of the wildtype allele and disturb its function

autosomal dominant inheritance

- Disease-spectrum in carriers of homozygous dominant mutation is broad: from identical phenotype as in heterozygous carrier to severe course/lethal

autosomal dominant inheritance

recurrence risk: 50%, vertical transmission, both sex are similarly affected



A = dominant allele (mut)
a = recessive allele (wt)

	A	a
a	Aa	aa
a	Aa	aa

autosomal dominant inheritance

- currently, in human so far ~3700 autosomal dominant diseases are known
- incidence of autosomal dominant diseases: 7 in 1,000
- wide range of phenotypic spectrum
- in case of more mild phenotype the mutation is mostly inherited by one of the parents
- in affected person with a more severe phenotype, the mutation occurred mostly spontaneously
- examples of frequent autosomal dominant diseases:
 - neurological diseases (ataxias, paraplegia, dystonia, inherited dementia)
 - familial cancer syndromes (breast, colon, endocrinologically)
 - cardiomyopathy (hypertrophic)
 - skeletal dysplasia

autosomal dominant inheritance

simple dominant (complete dominant):

the phenotype of the dominant allele will be expressed,

the phenotype of the recessive allele will be suppressed

 = affected

A = dominant allele (mut)

a = recessive allele (wt)

	A	a
a	Aa	aa
a	Aa	aa

autosomal dominant inheritance

intermediate dominant (incomplete dominant):
heterozygous genotype creates an
intermediate phenotype (mixed traits)

example: flowering color

A = dominant allele (mut)
a = recessive allele (wt)

	A	A
a	Aa	Aa
a	Aa	Aa

autosomal dominant inheritance

Codominant inheritance:

both alleles are dominant and lead to a phenotype,
in the present of both alleles
(heterozygosity), traits of each phenotype
is present separately

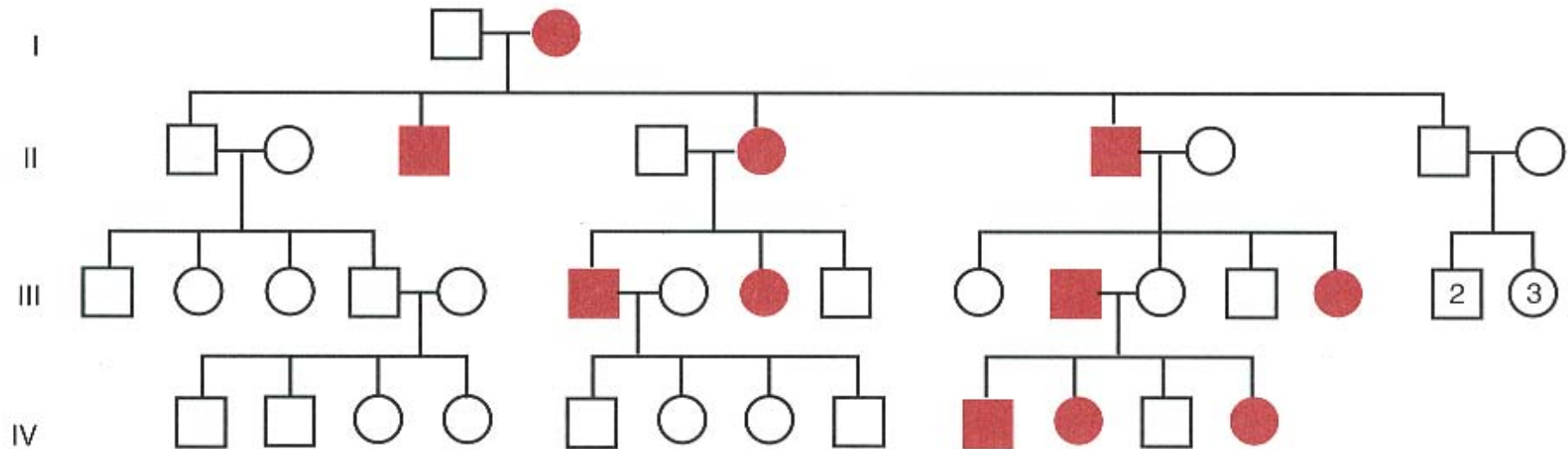
example: blood groups

	A	B
A	AA	AB
B	AB	BB

A = dominant allele (mut)
a = dominant allele (wt)

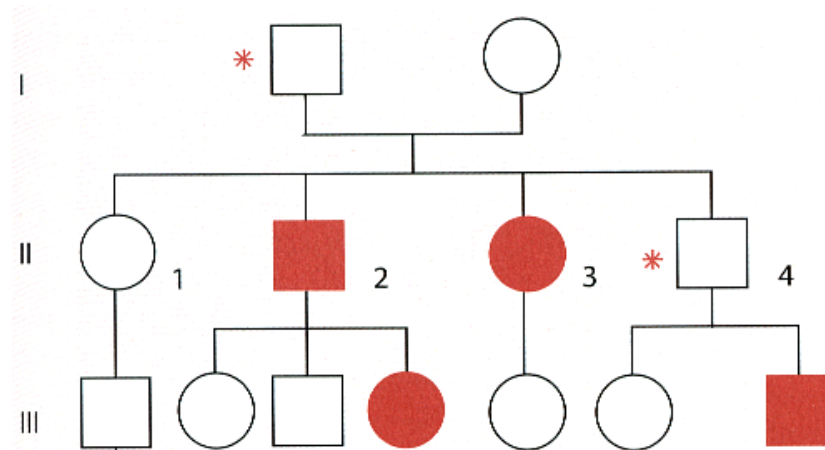
autosomal dominant inheritance

Simple autosomal dominant inheritance with complete dominance



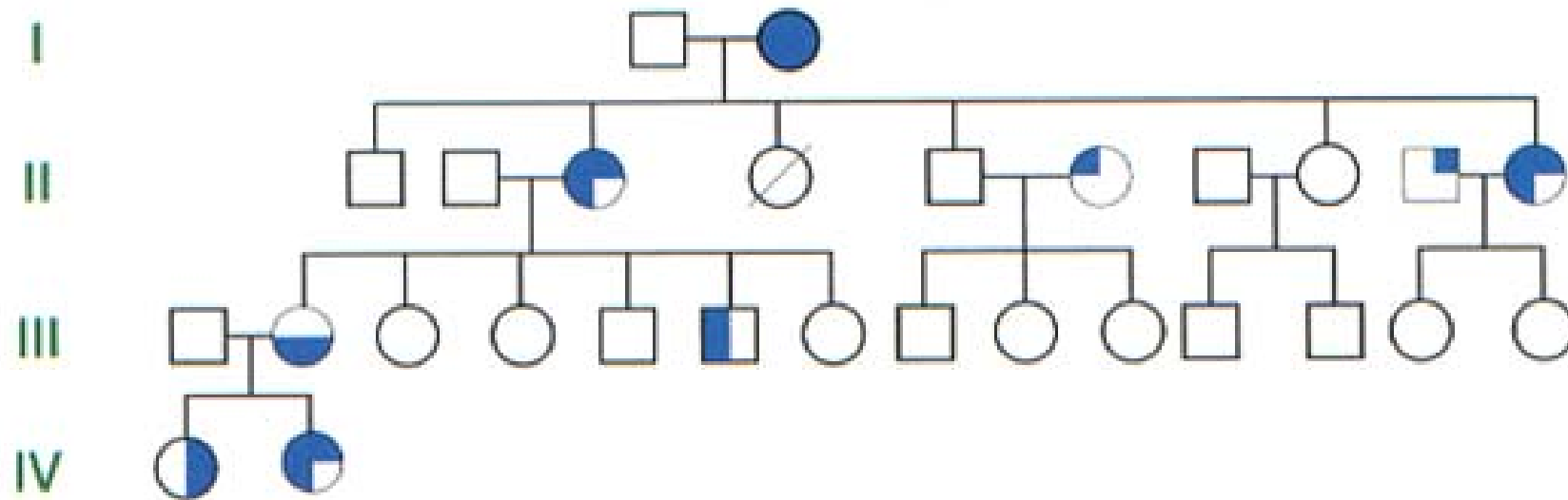
autosomal dominant inheritance

autosomal dominant inheritance
with reduced penetrance



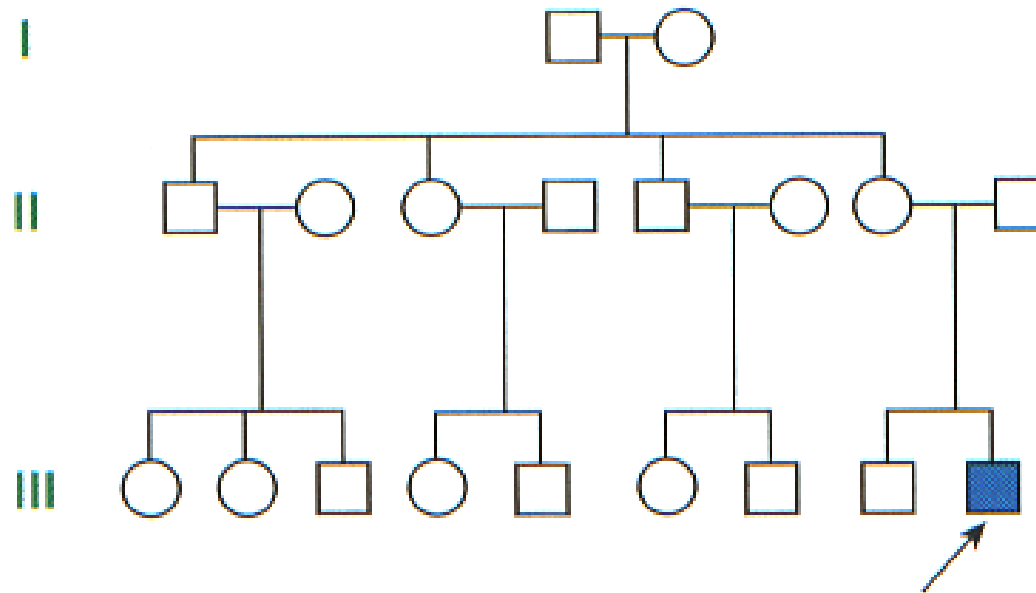
autosomal dominant inheritance

autosomal dominant inheritance
with variable expression



autosomal dominant inheritance

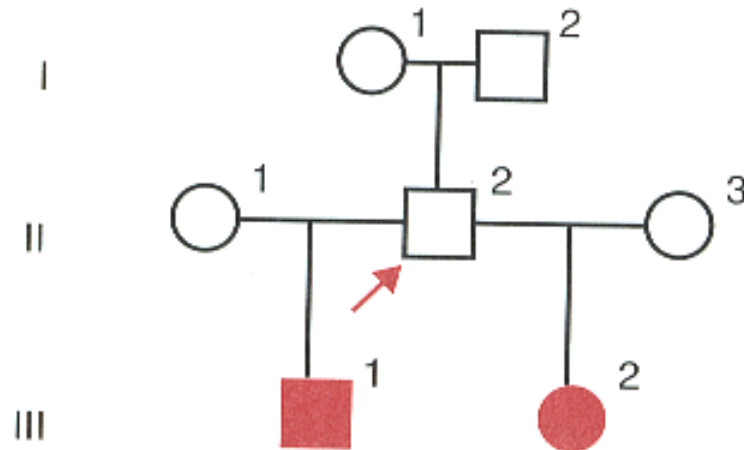
autosomal dominant spontaneous mutation



The further transmission of spontaneous mutations depends on the severity of the phenotype and the reproductive fitness.

autosomal dominant inheritance

autosomal dominant germline mutation



A gonadal mosaicism has to be considered if the same autosomal dominant mutation occurs in more than one offspring and causes a severe phenotype with nearly complete penetrance.

autosomal recessive inheritance

Definition:

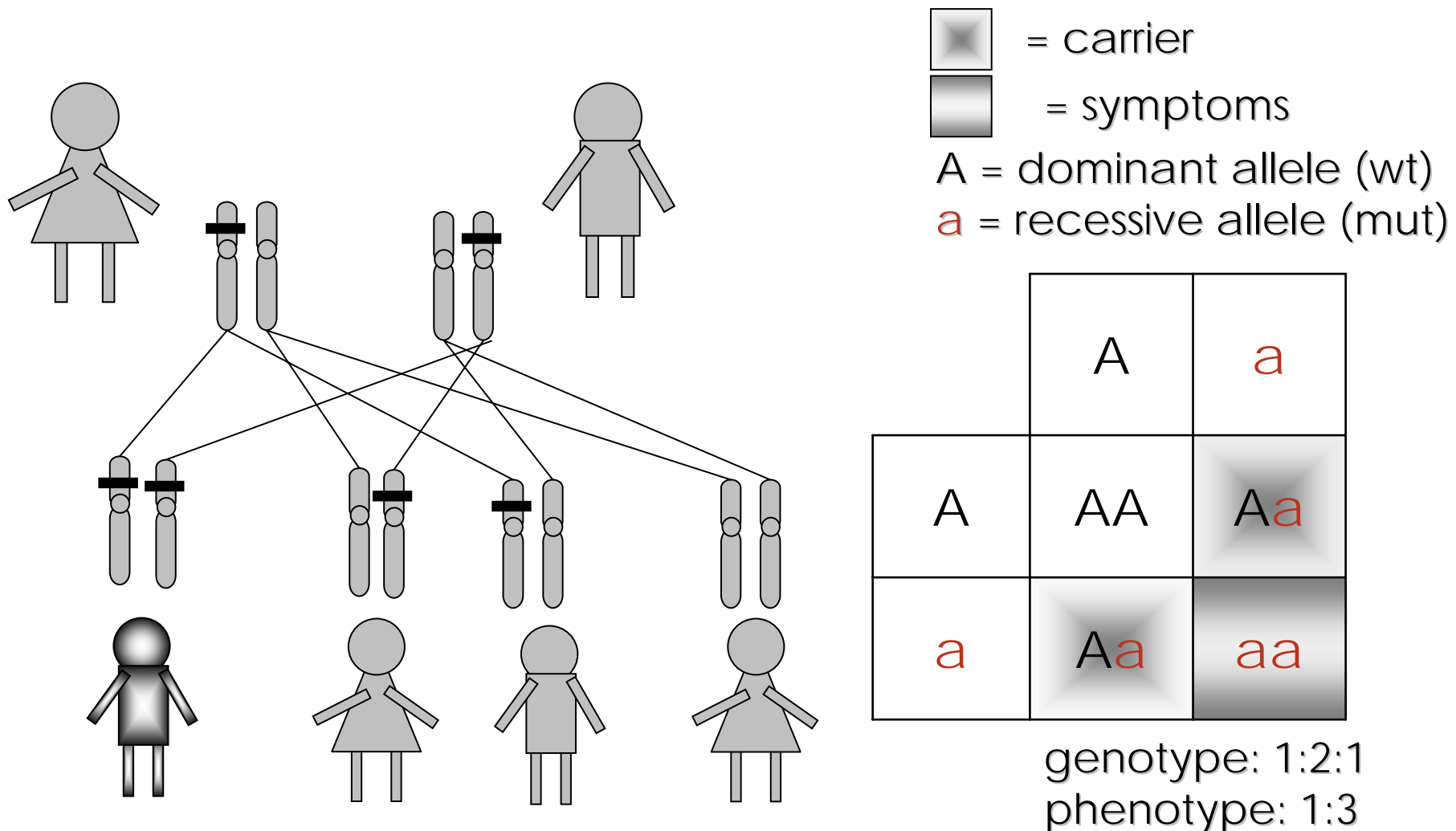
- mutations are located on an autosomal chromosome (gene)
- a phenotype/disease is present if both allele are mutated,
- in recessive genes one wildtype allele is enough for a sufficient gene function

autosomal recessive inheritance

- mutations are homozygous or compound-heterozygous
- carrier of heterozygous mutations are clinically unaffected
- parents of an affected child are usually healthy and are carriers of a heterozygous mutation
- the risk for a healthy person to be a genetic carrier of a recessive disease is 1:10 to 1:200 (carrier frequency of normal population)

autosomal recessive inheritance

recurrence risk: 25%, horizontal transmission,
both sex are similarly affected

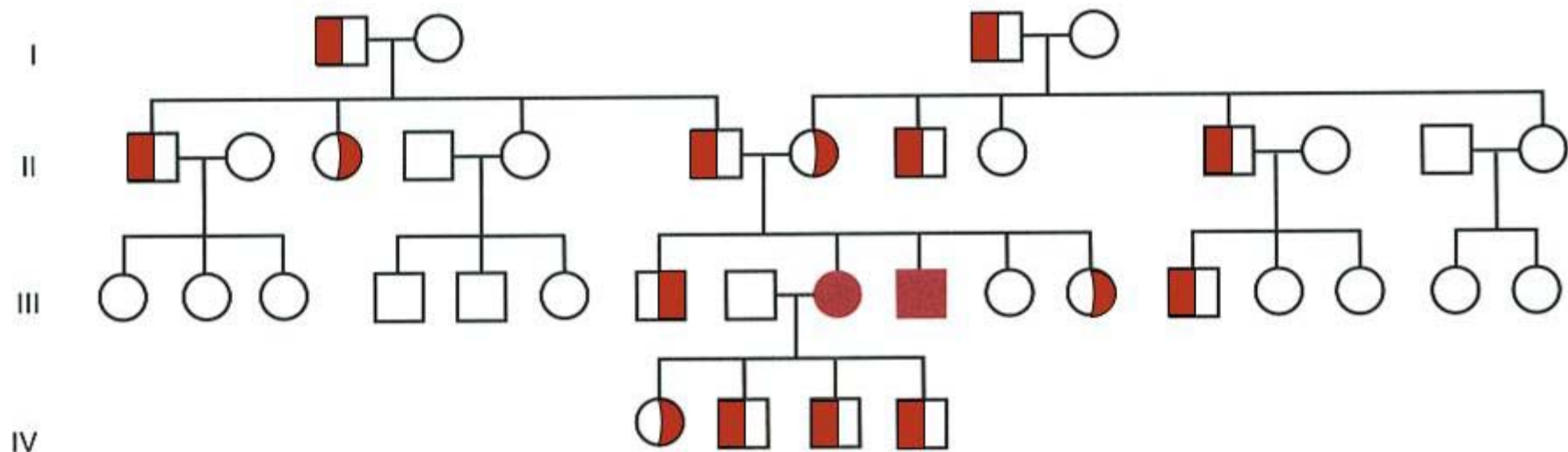


autosomal recessive inheritance

- currently, in human so far ~4000 autosomal recessive diseases are known
- incidence of autosomal recessive diseases: 2.5 in 1,000 newborns
- wide range of phenotypic spectrum
- examples of frequent autosomal recessive diseases: metabolic disorders (enzyme defects) often with no external malformations
 - cystic fibrosis (incidence 1:2,500)
 - hemochromatosis (incidence 1:400)
 - phenylketonuria (1:5,000)
 - spinal muscular atrophy (1:10,000)

autosomal recessive inheritance

typical pedigree of an
autosomal recessive inheritance

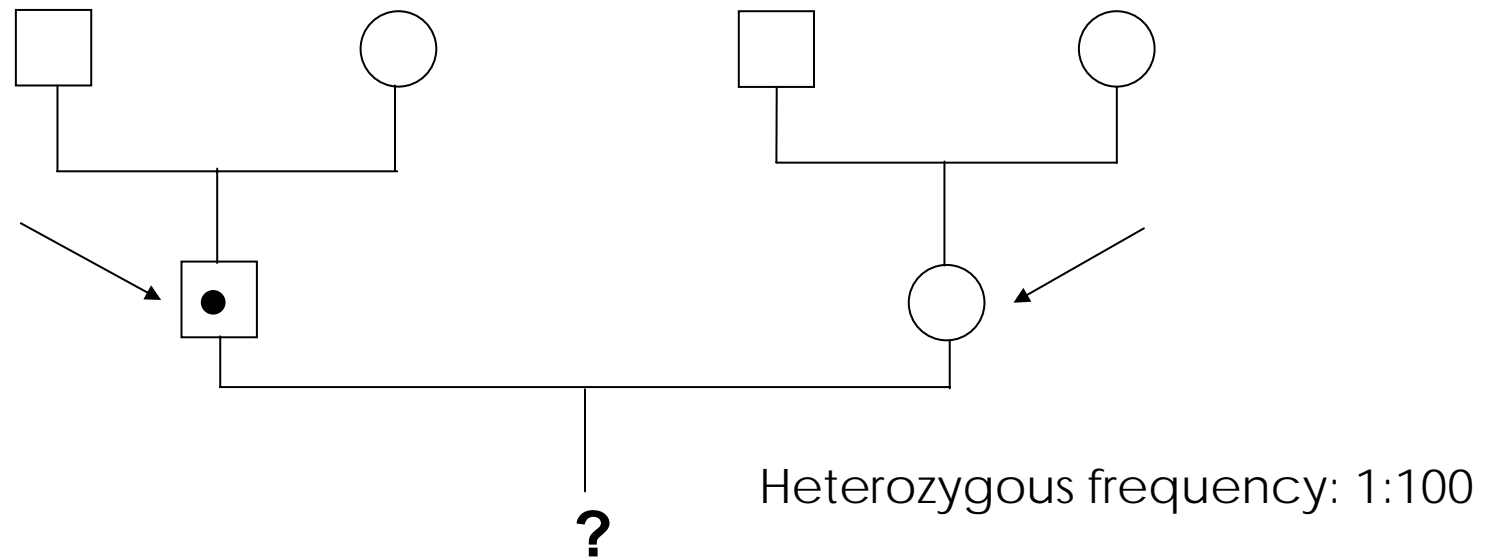


The offspring of an affected person are in 100% genetic carrier of disease!

Healthy siblings of an affected person are in 2/3 genetic carrier of disease!

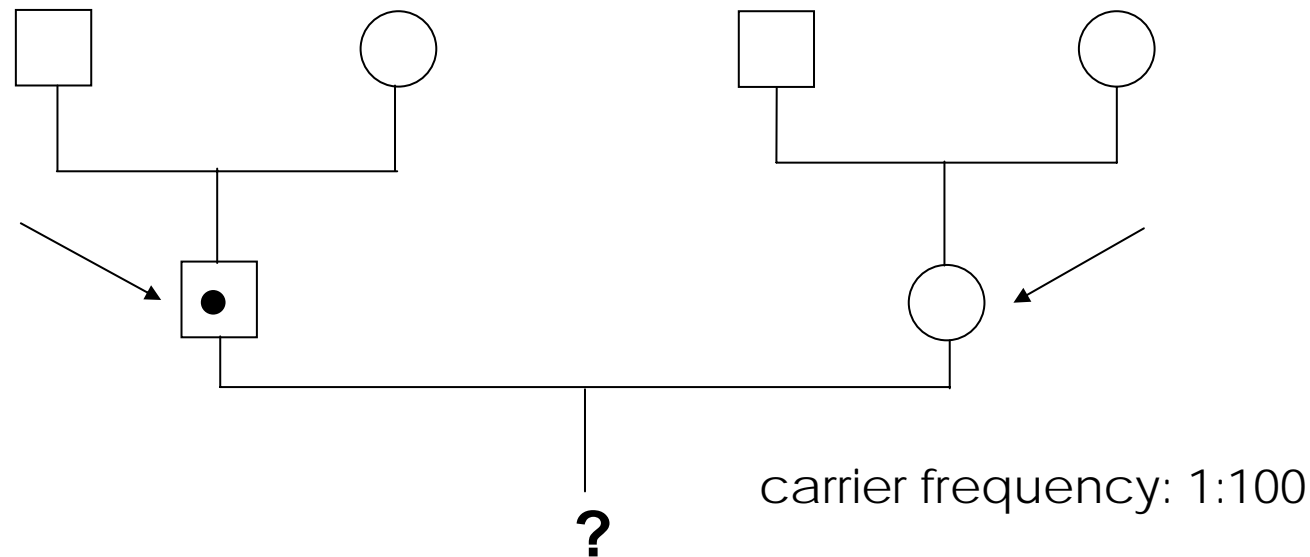
autosomal recessive inheritance

Risk for an autosomal recessive disease
in non-consanguine couple



autosomal recessive inheritance

Risk for an autosomal recessive disease
in non-consanguine couple

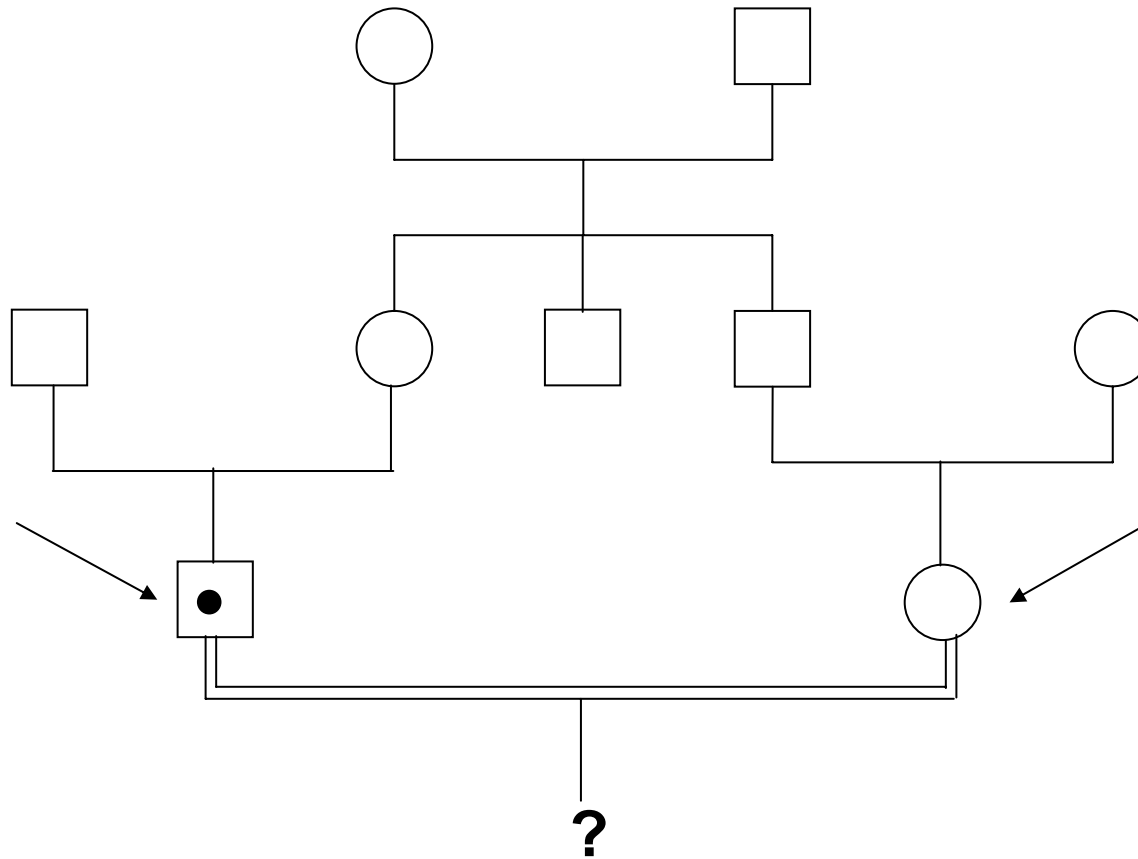


$$\begin{array}{c} (1 \times 1/2) \\ \text{♂} \end{array} \times \begin{array}{c} (1/100 \times 1/2) \\ \text{♀} \end{array} = 1/400 = 0,25\%$$

autosomal recessive inheritance

pedigree of a consanguine family

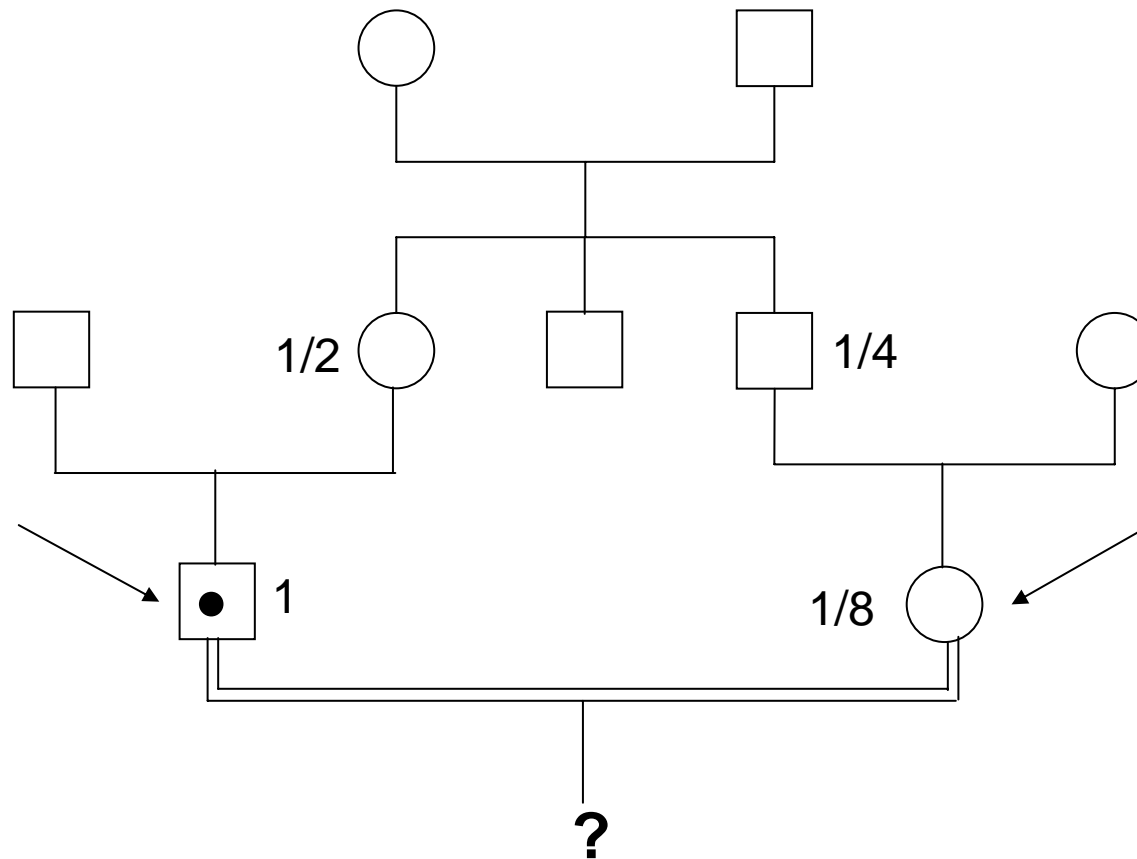
Risk for an autosomal recessive disease ?



autosomal recessive inheritance

pedigree of a consanguine family

Risk for an autosomal recessive disease ?



$$(1 \times 1/2) \times (1/8 \times 1/2) = 1/32 = \sim 3\%$$



autosomal recessive inheritance

consanguine families and isolate ethnic groups (Jewish people or Amish people) are on a higher risk for recessive disease

consanguine families are on a ~ 3 to 20 fold higher risk for autosomal recessive disease in comparing to non-consanguine-couples

X-chromosomal recessive inheritance

- the mutations are recessive and they are located in X-chromosomal genes
- men are hemizygous for X chromosomal genes > they present symptoms
- women are diploid for X chromosomal genes > they are without symptoms
- usually the transmission of X chromosomal disease occurred by healthy women (carrier)

X-chromosomal recessive inheritance

- examples for X chromosomal disease:
(incidence ~ 1:1,000 male newborn)
 - Hemophilia A and –B (1:10,000-25,000)
 - color blindness (1:500-2,000)
 - muscular dystrophy type Duchenne or Becker (1:3,000)
 - Fragile X syndrom (1:4,000-6,000)

X-chromosomal recessive inheritance

female carrier & unaffected man

	X	Y
X	XX	XY
x	Xx	xY

healthy woman & affected man

	x	Y
X	Xx	XY
X	Xx	XY


affected man & female carrier

	X	x
x	Xx	xx
Y	XY	xY

X = dominant allele

x = recessive allele

 = affected

 = carrier