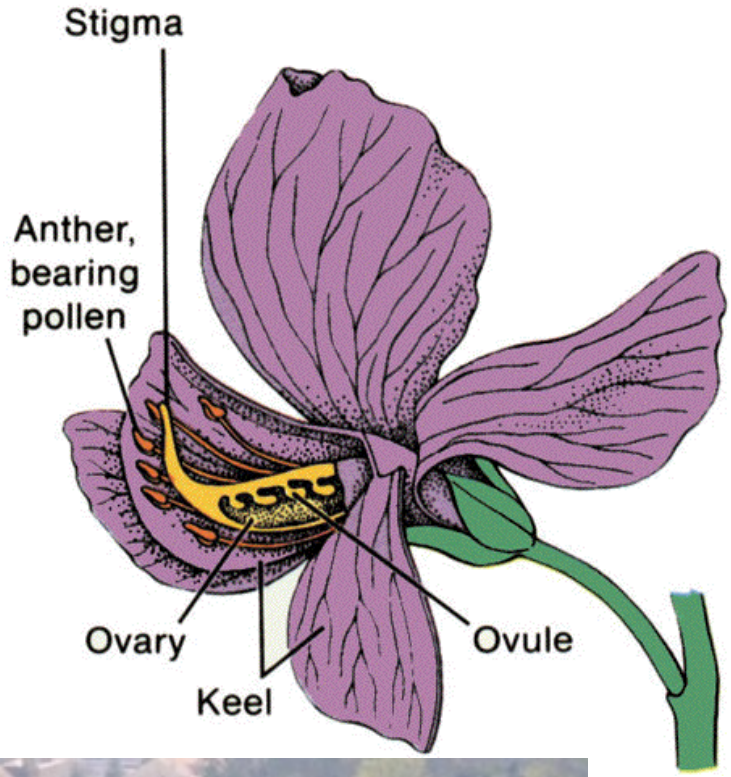
Part 1

PATTERNS OF SINGLE-GENE INHERITANCE

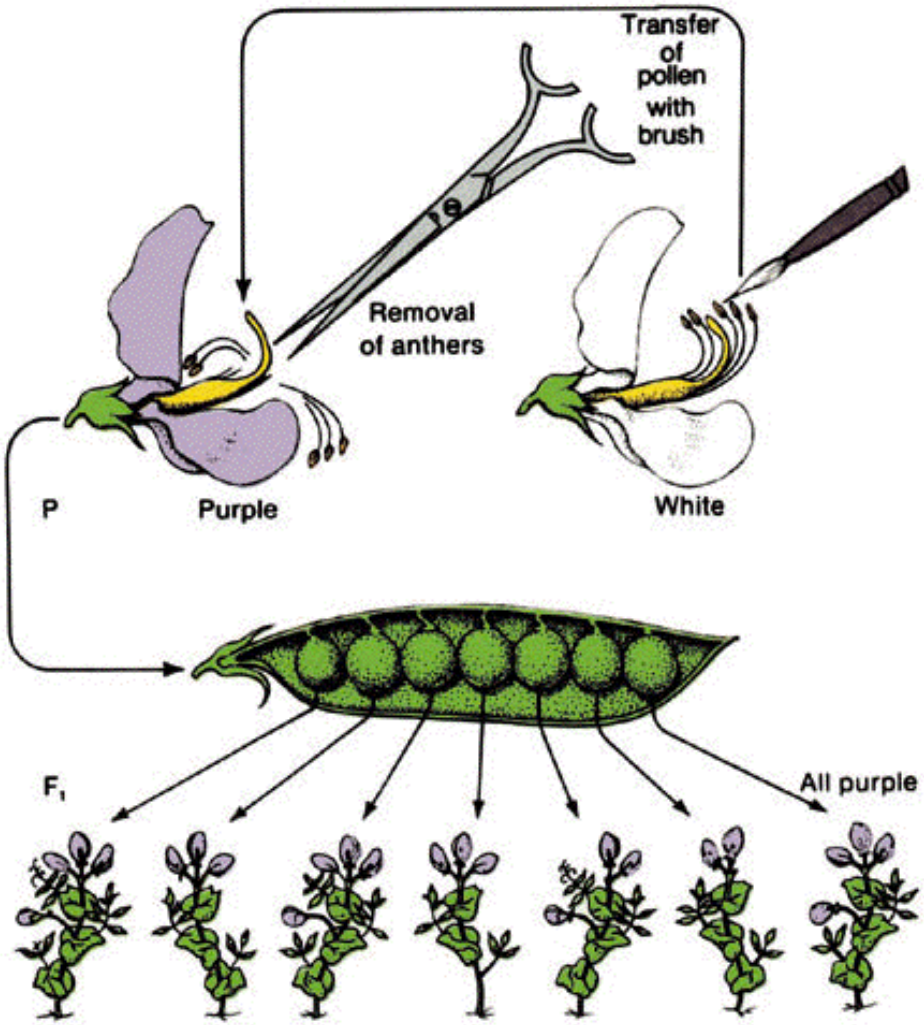
Genetics implies variation

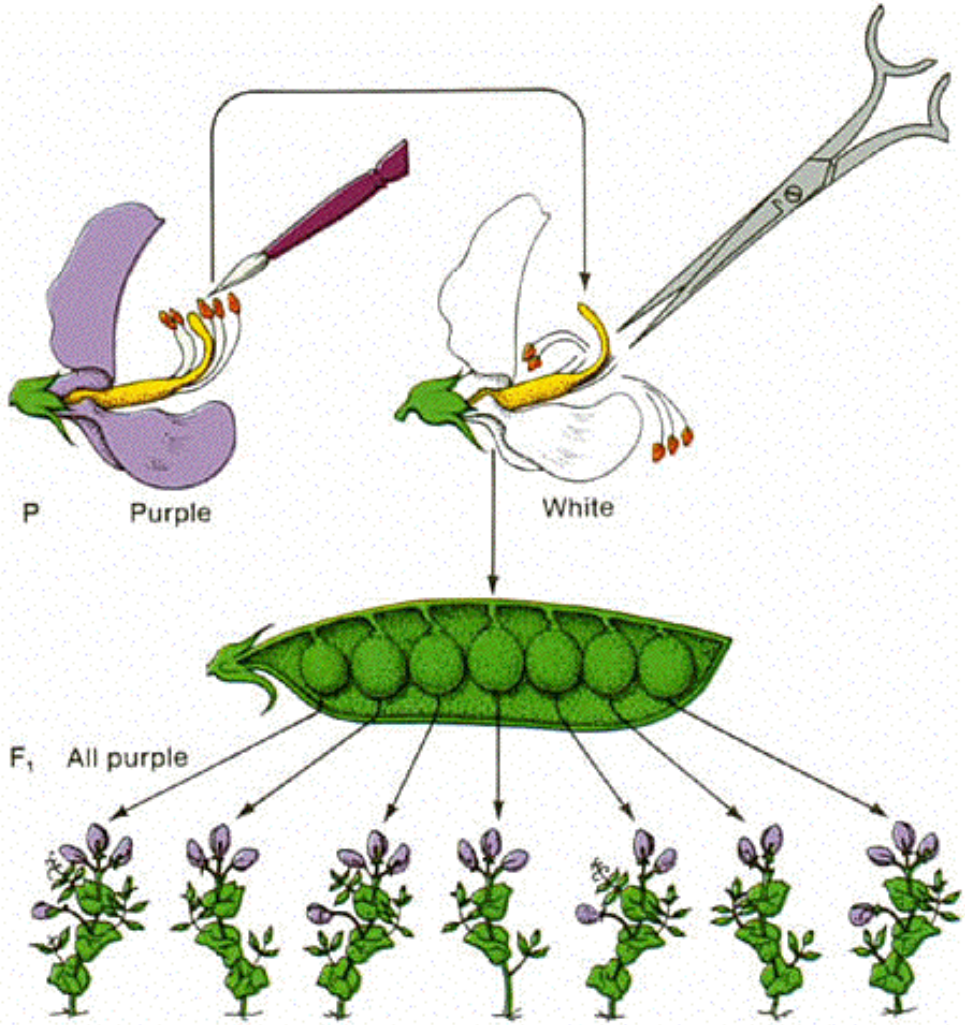
- Genetics = study of inheritance of characters (= traits = features)
- No genetics if no variation

Gregor Mendel (1822-1884)

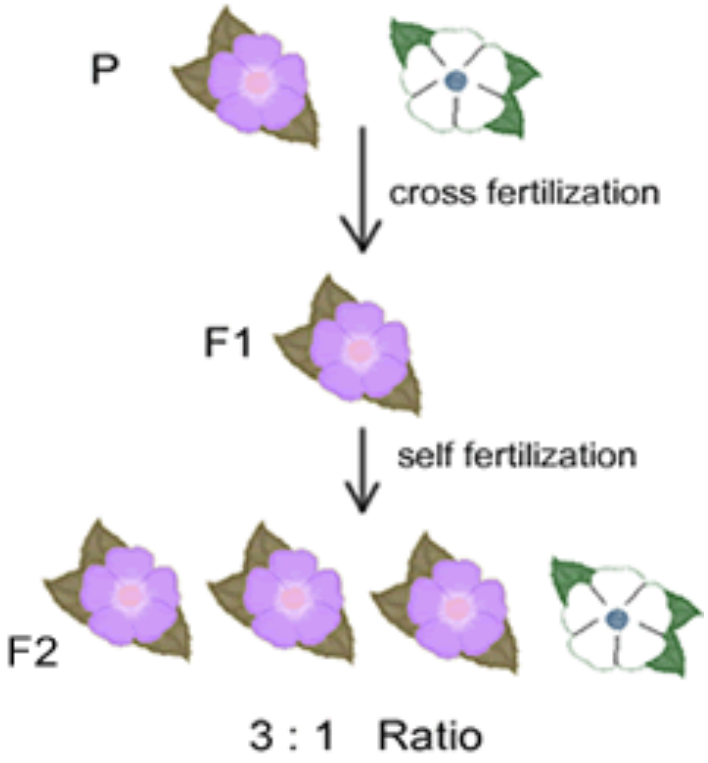


Artificial cross-pollinization



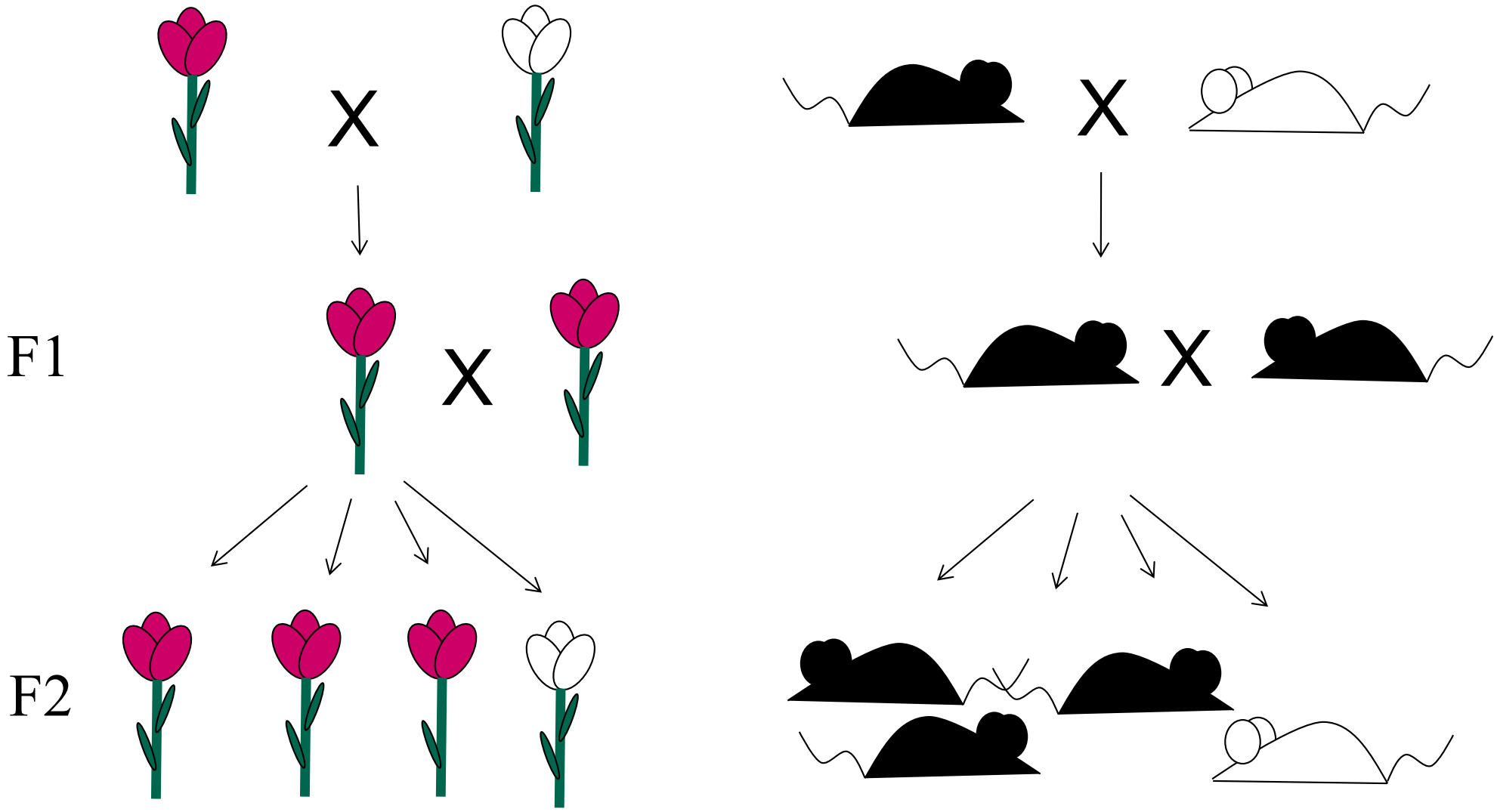


Cross 2 pure strains that differ for 1 character (monohybrid cross)

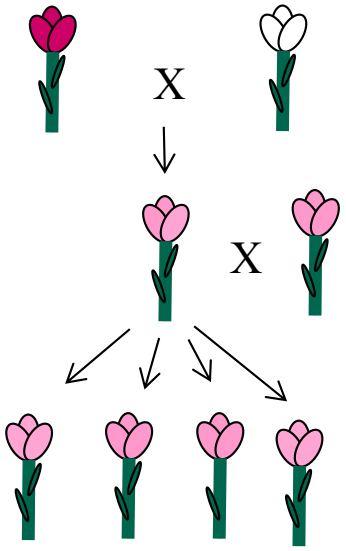


- All purple: not simple dilution
- White character re-appears

Fixed proportions of phenotypes in offspring



Prior Hypothesis: trait dilution



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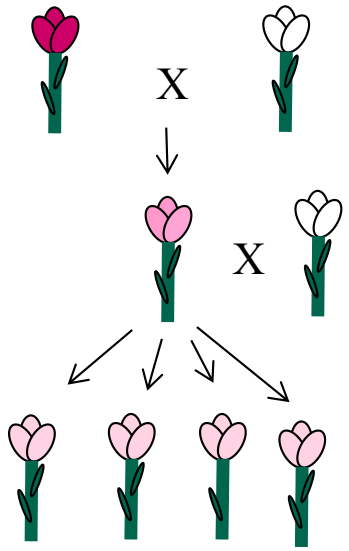

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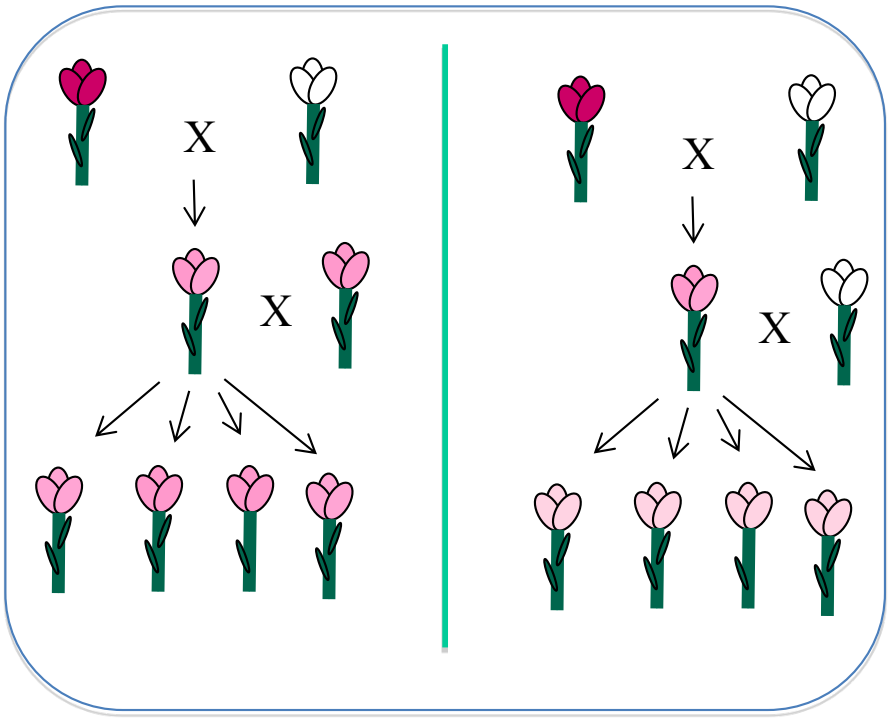

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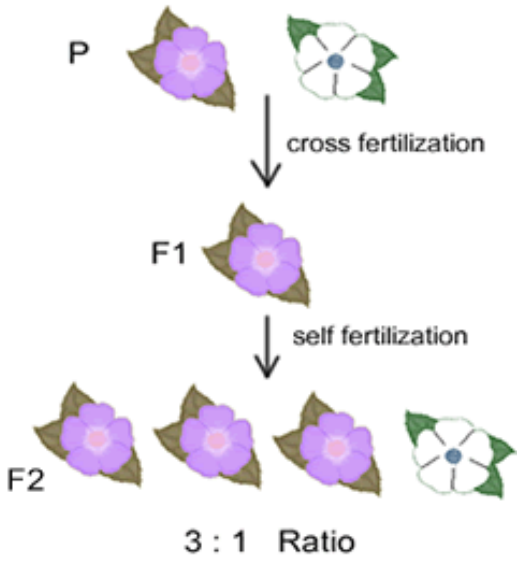

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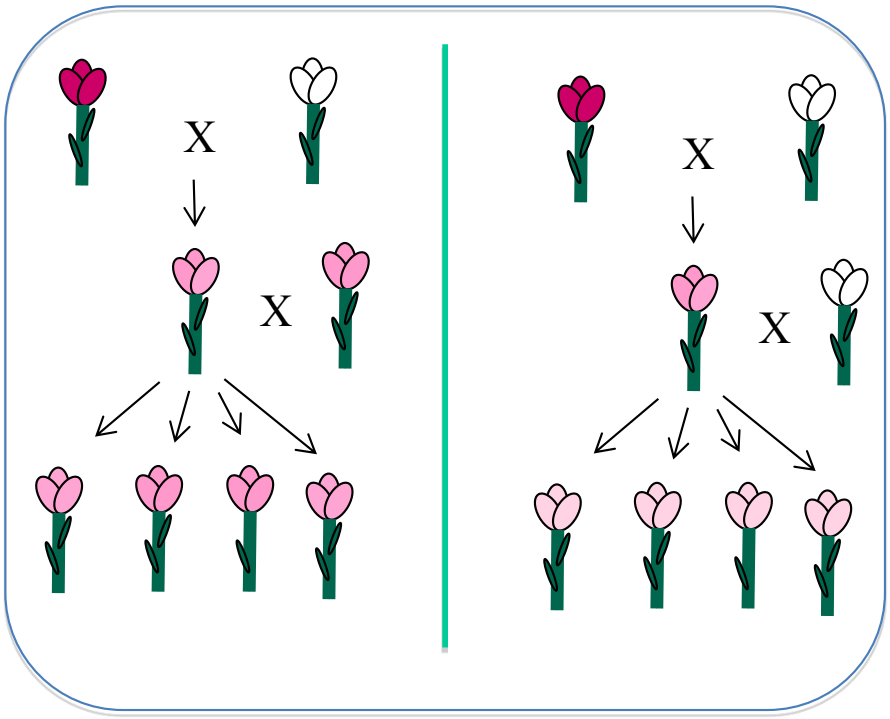
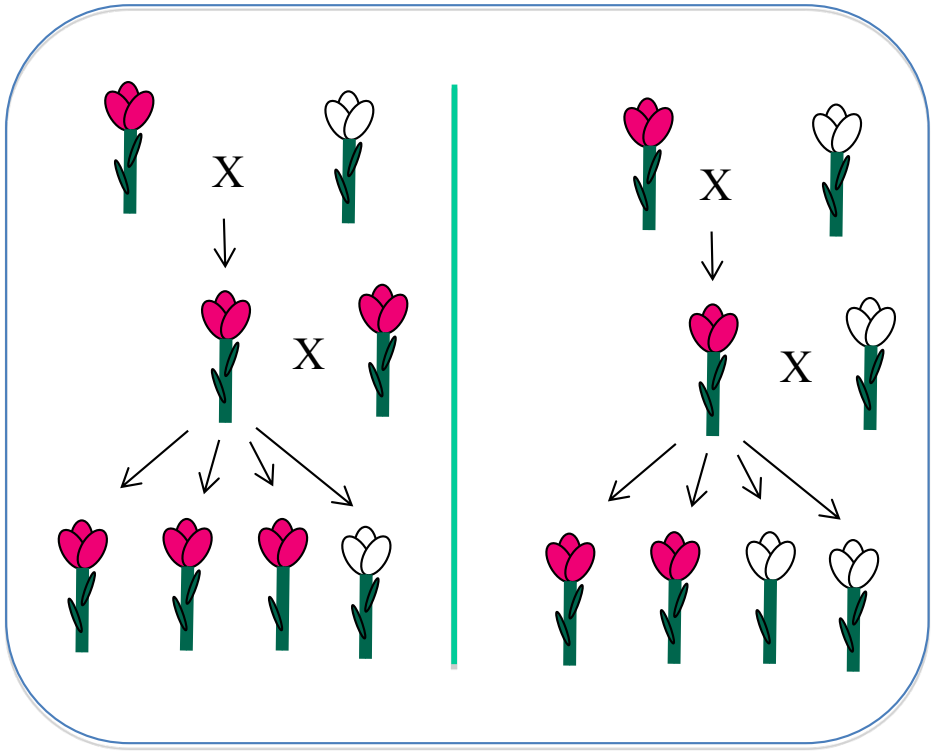


Experimental
evidence



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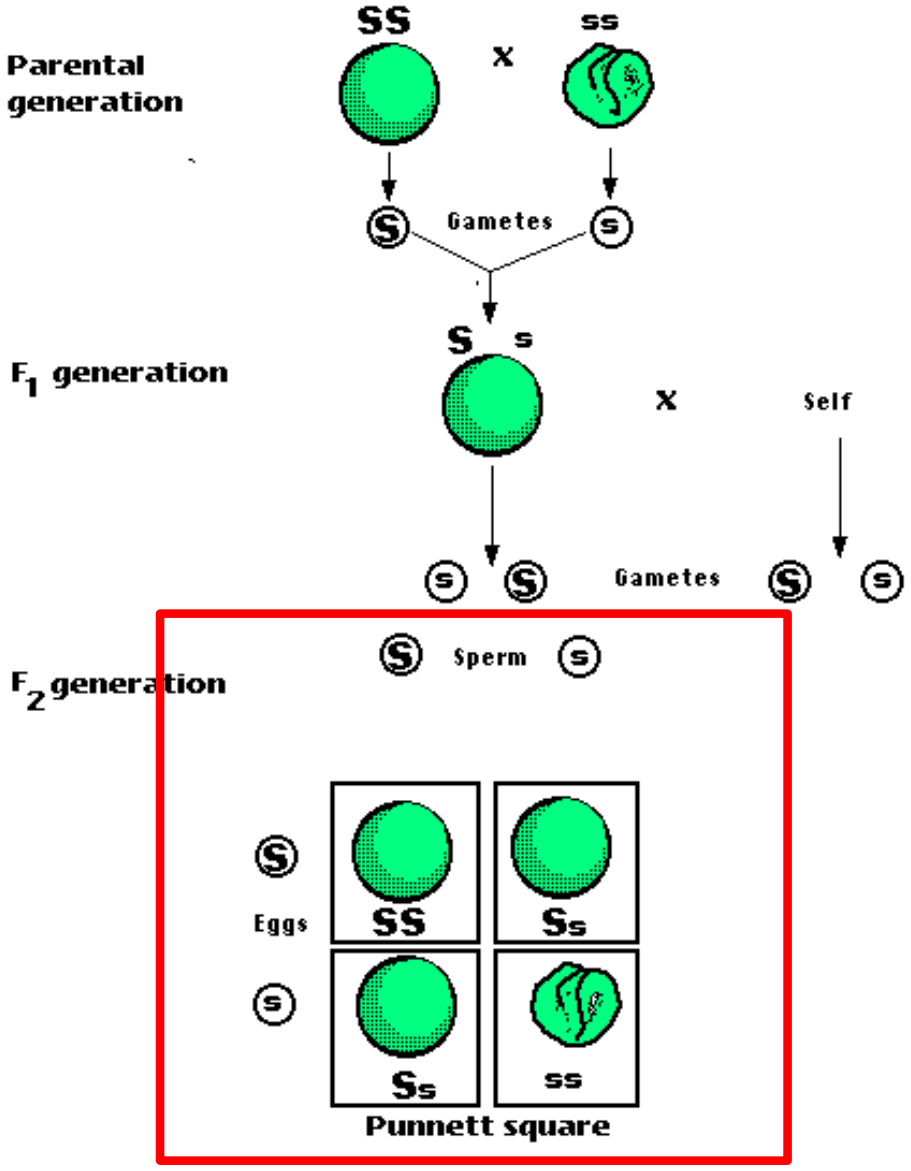
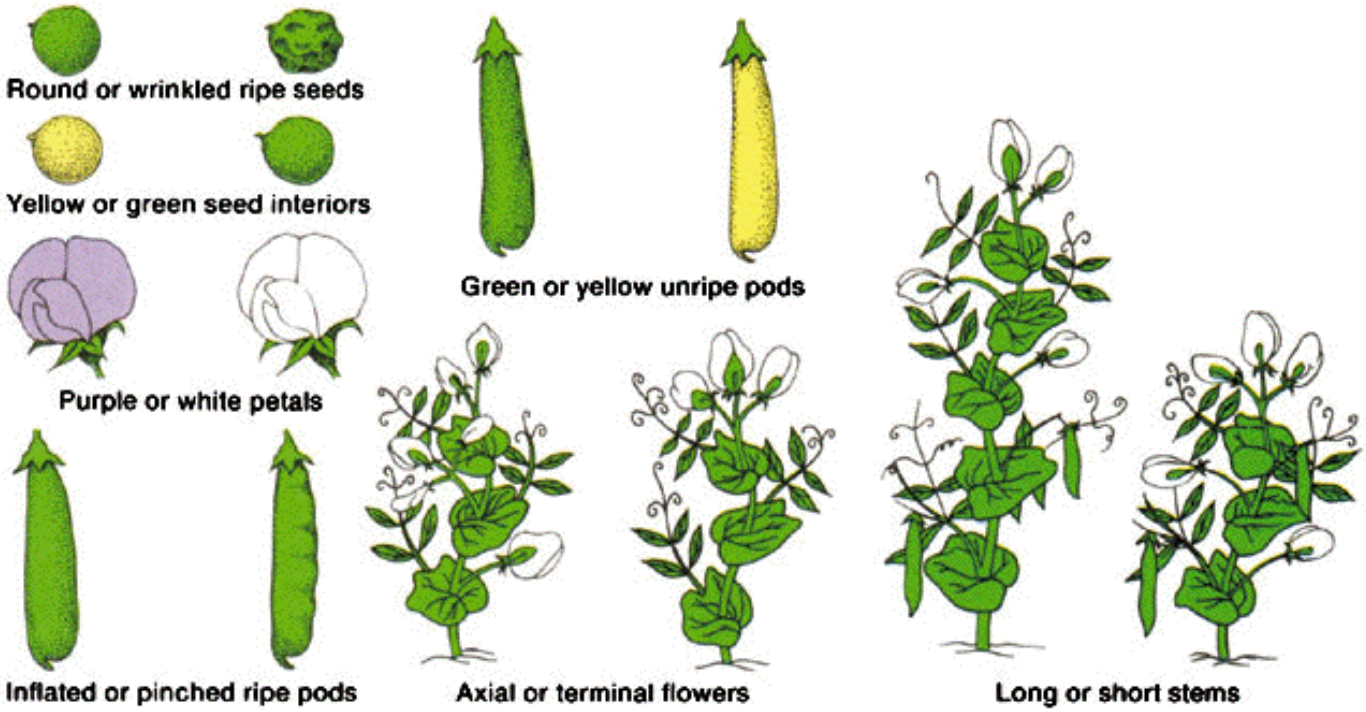
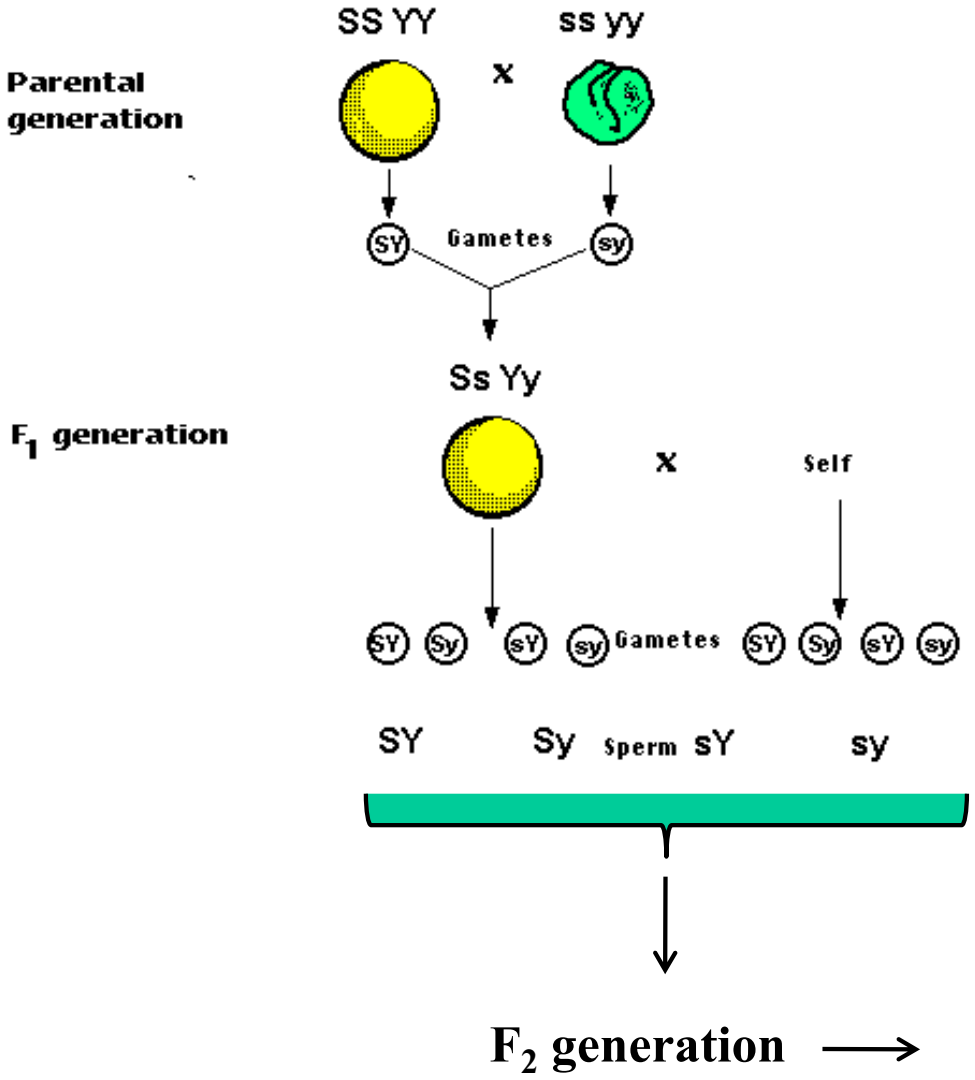


- Smooth or wrinkled
- All F1 individuals are smooth (= filia 1)
  S character is dominant, wrinkled is récessif
- But wrinkled character reappeasr in F2 !
  25% of F2 individuals are wrinkled
- Best explianed by INDEPENDANT SEGREGATION of 2 allelomorphic variants of one hereditary factor:
  S or s

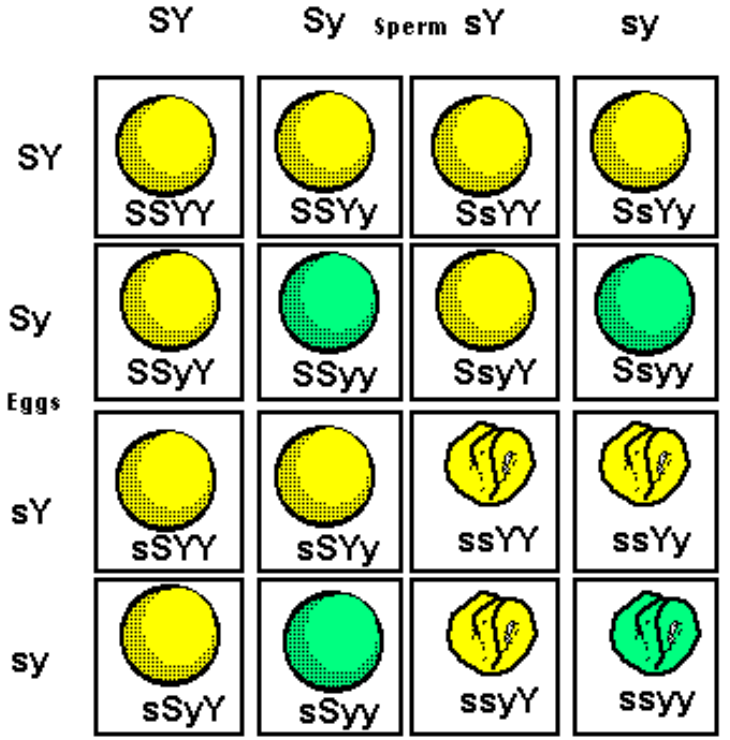
The 7 character differences studied by Mendel



Dihybrid cross (2 characters)

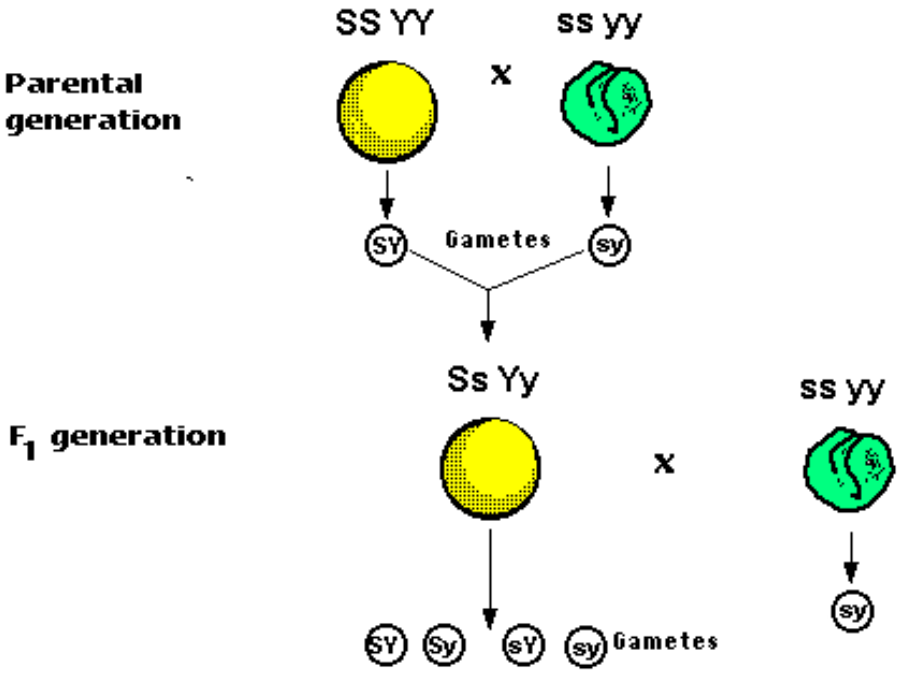


- Independent assortment of hereditary character
- Ratio 9:3:3:1 of phenotypes



Punnett square

Backcross



- Cross F1 hybrid (SsYy) with a double recessive homozygote (ssyy)
- Unmasks the genotype of the F1 hybrid
- With independent assortment of hereditary factors, expect phenotypes in the following proportions: .25/.25/.25/.25

	SY	Sy	sY	sy
sy	sSyY	sSyy	ssyY	ssyy
	1/4 Smooth Yellow	1/4 Smooth green	1/4 rough Yellow	1/4 rough green

Mendel’s observations

- Uniformity of hybrids in first generation (F1)
- Independent segregation of several couples of characters in second generation (F2)
  - « purity of gametes: each contain only one hereditary factor for one character » = one allele of each gene
- Independent disjunction of characters in F2

Mendel's laws

1. Law of **segregation**
   – Each gamete contains or or the other of the two allelomorphic factors (alleles)
   later found to fit meiotic separation of pat and mat chromosomes

2. Law of **independent assortment**
   – Pairs of alleles from different genes enter gametes independetly of one another

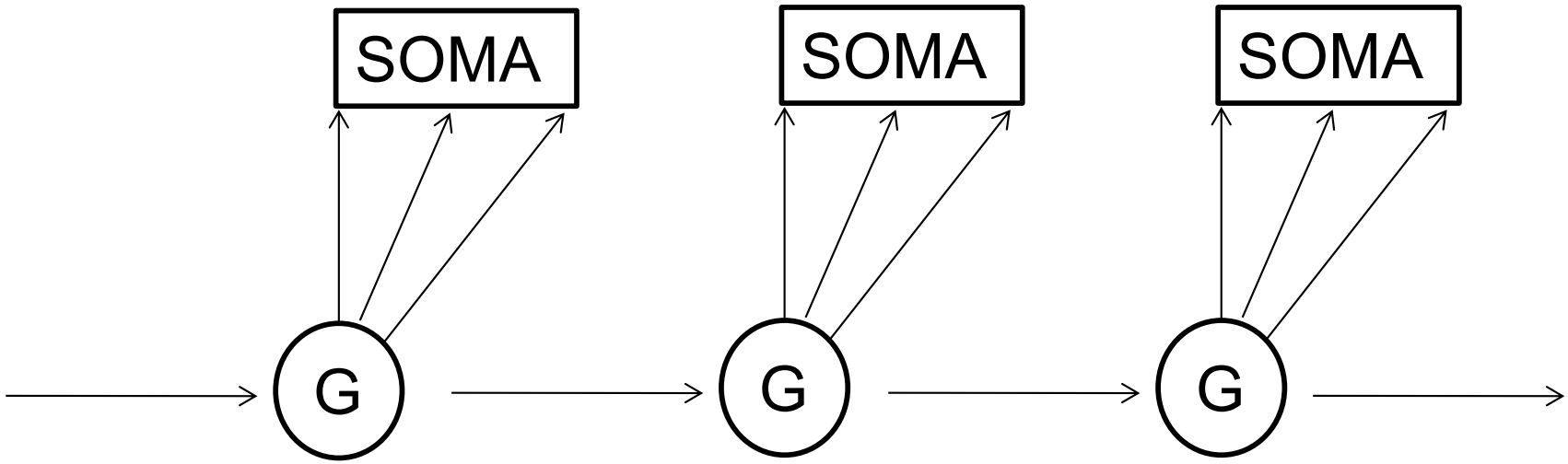
   except if genes closely located on same chromosome (linkage)

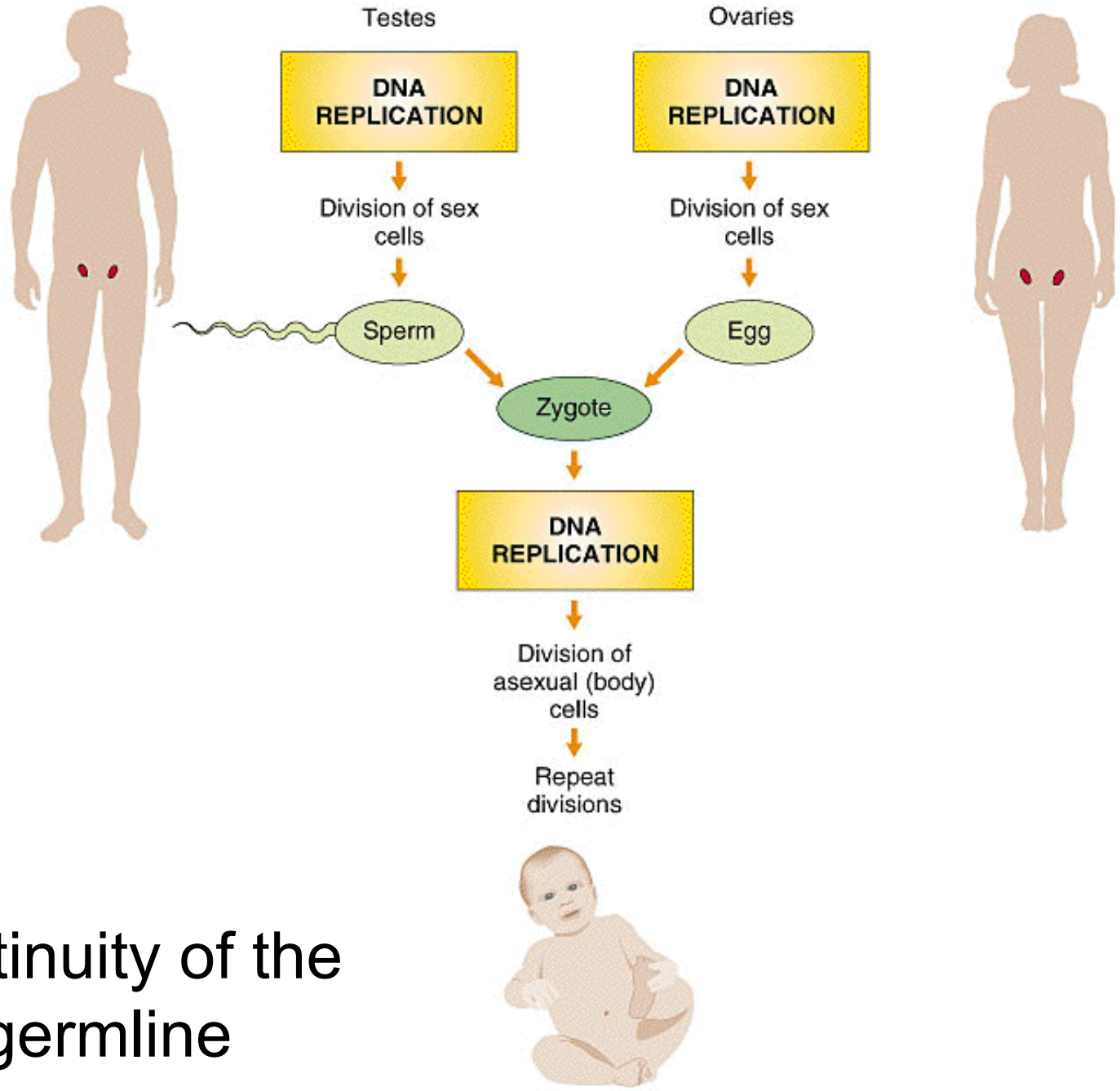
Independant segregation of the two alleles of each gene

Loci, genes, alleles, mutation

- Locus = position in genome
  - gene, or contiguous genes (HLA locus), or SNP, any piece of DNA
- Alleles = alternative variants at one locus
  - Prevailing allele = wild type
- Mutation = change in an allele causing a change in phenotype
- Genotype = individual set of alleles at one locus, or several loci, or whole genome *(music score)*
- Phenotype = observable expression of a genotype *(concert)*
  - Morphological
  - Clinical
  - Cellular
  - Biochemical
  - …
- Pleiotropy = diversity of phenotypic effects
- Gene = ?

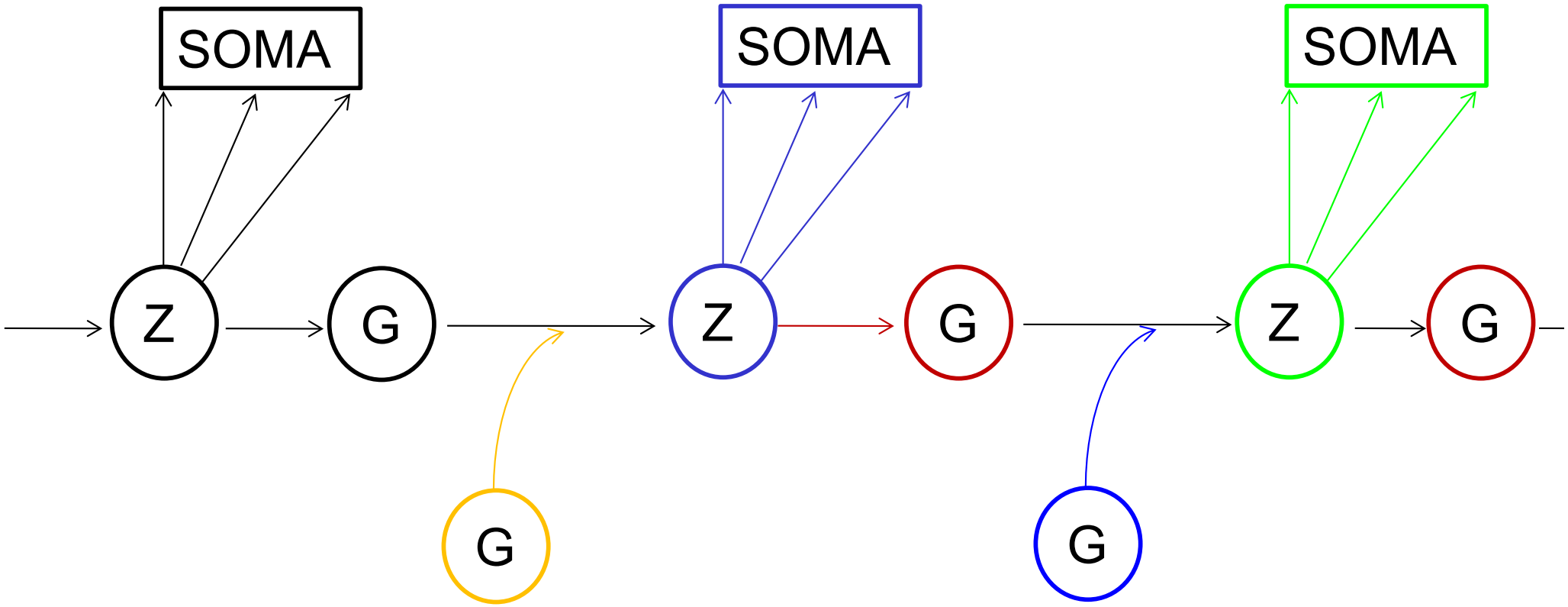
The germ-line



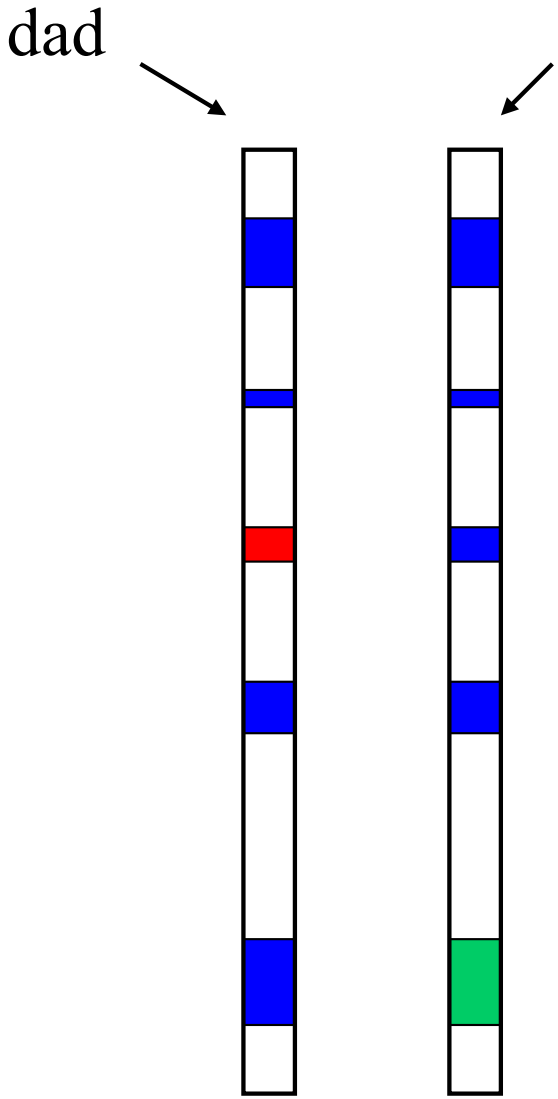


Continuity of the germline

Sexual reproduction

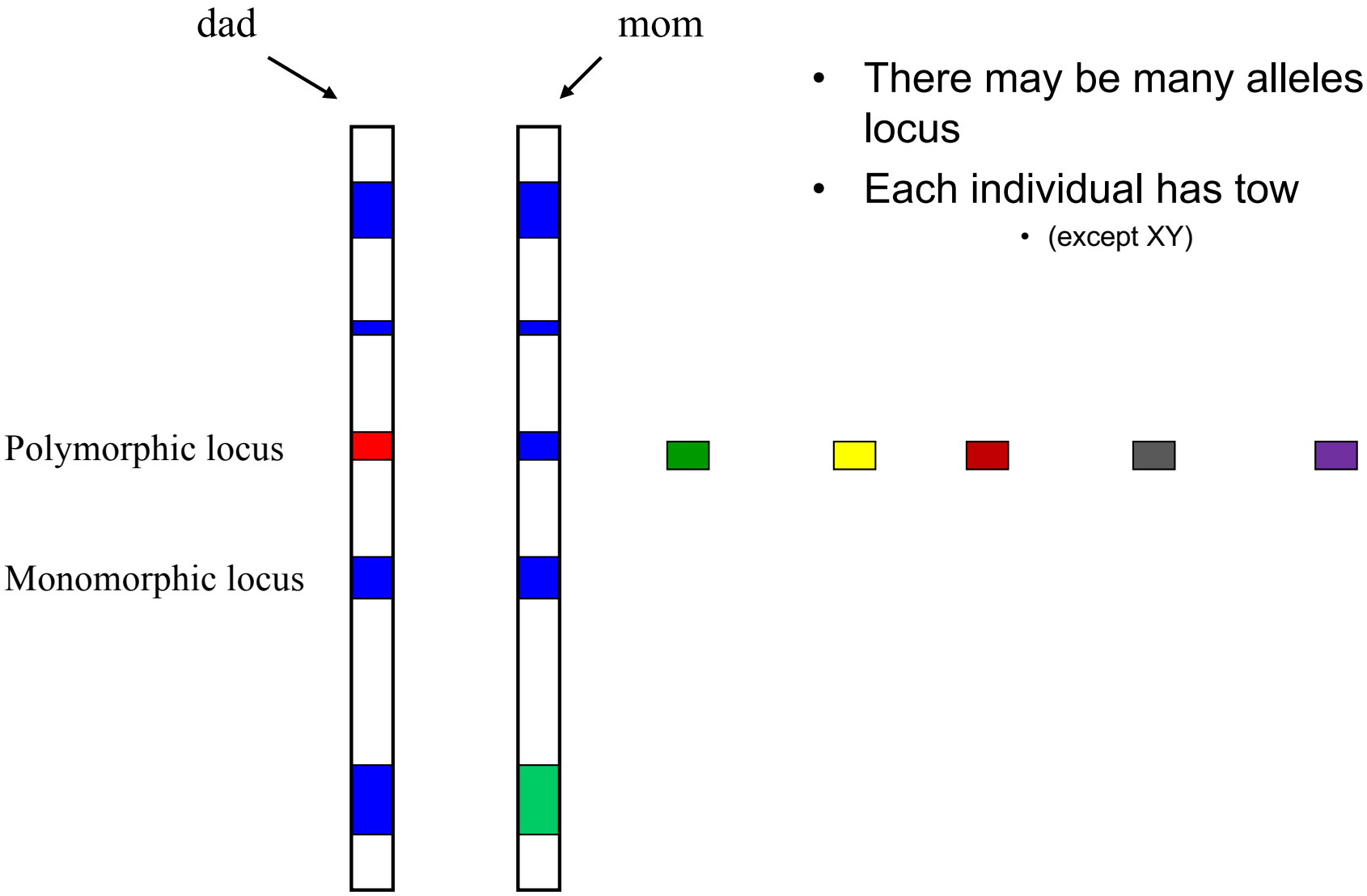


The genome: 20.000 genes, 2 copies each



- 2 alleles of each gene
- Allele polymorphism
  - SNPs: Single Nucleotide Polymorphisms
  - CNPs: Copy Number Polymorphisms
  - other
- Unique combination in each person
- Largely encodes our physical characters (height, weight, coulor, blood groups…) and partly our psychologycal/ behavourial charachters
- No clear limit between polymorphism (normal) and mutation (pathogenic)
- Good our bad in different contexts

Locus: 2 alleles per individual ; Pool of alleles in population



- There may be many alleles per locus
- Each individual has tow
  - (except XY)

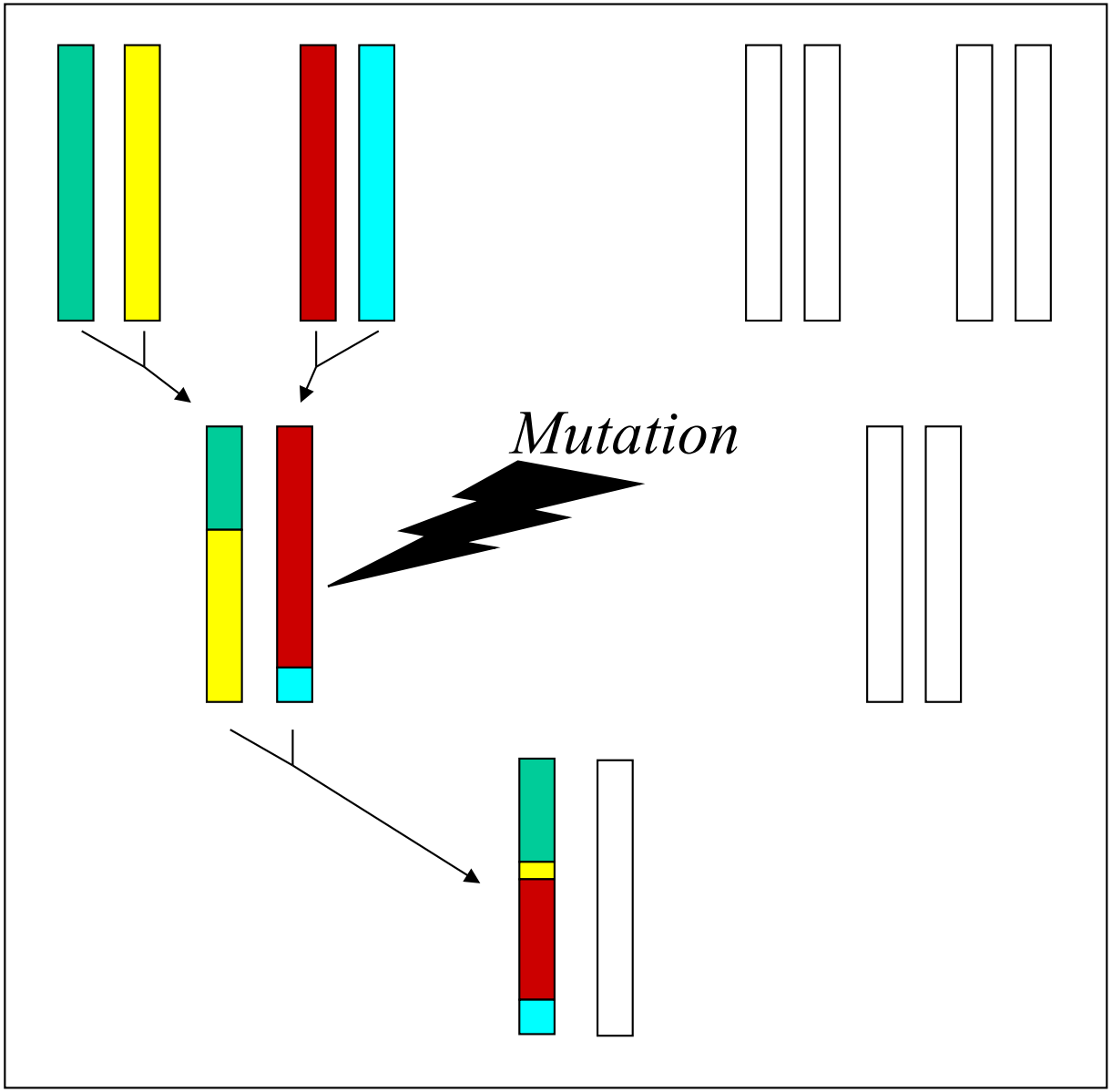
Synteny, linkage, LD

- Synteny = location on the same chromosome
  = pieces of one colinear DNA molecule

- Linkage = synteny close enough for transmission together in >50% gametes

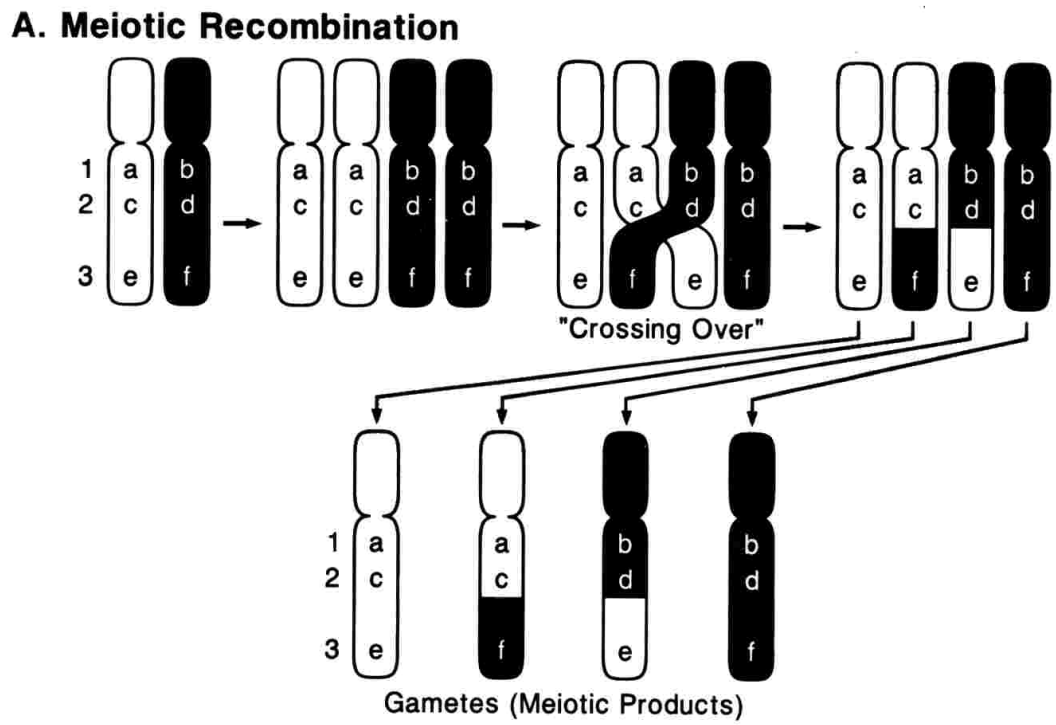
- LDisequilibrium = association of particular alleles at linked loci
  < close linkage / recent ancestor

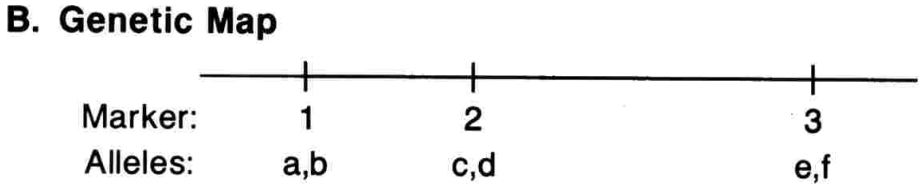
Meiosis produces diversity by assembly



Ultimate origin of diversity = mutation

Meiotic Recombinations (crossing-overs)





- 1 cM = distance between loci that are separated in 1% gametes

  =>genetic distance, genetic map
  - (genetic linkage map)

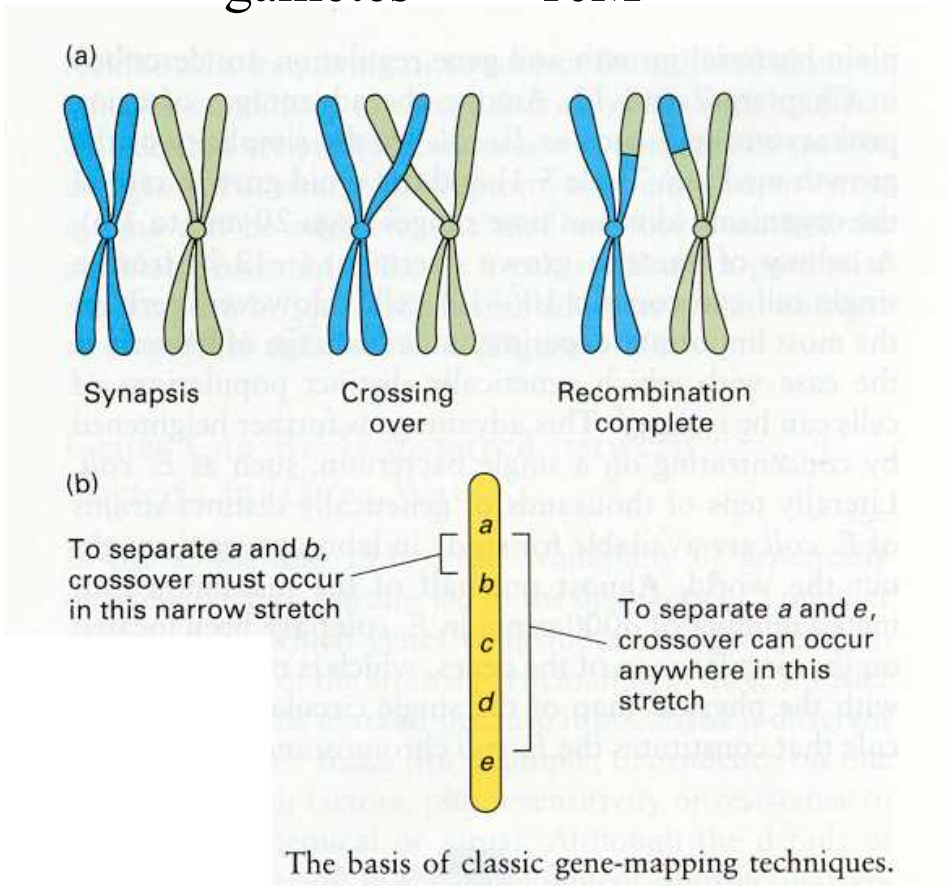
- 1 cM ≈ 1Mb. 3000 cM, 3 Gb.

- Recombinations mix the alleles => equilibrium

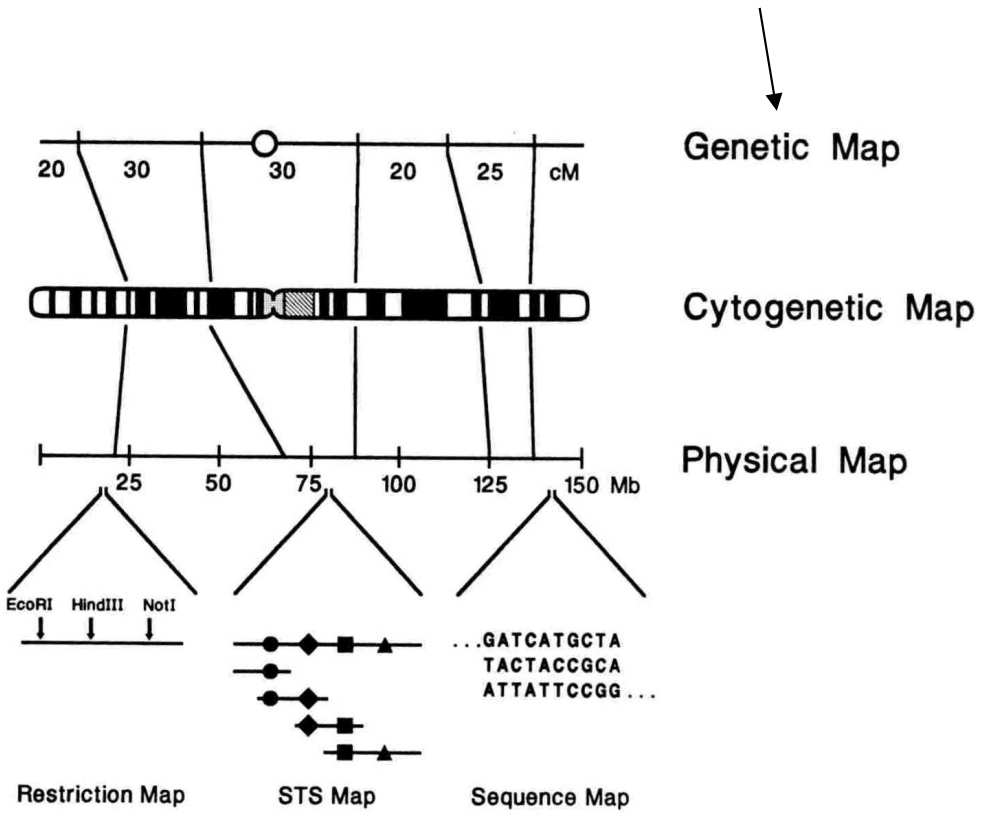
- At least 1 Cr-ov per chromosomal arm

Genetic linkage map (cM), physical map (Mb)

1% recombinant gametes <=> 1cM → 1 centimorgan (1 cM)



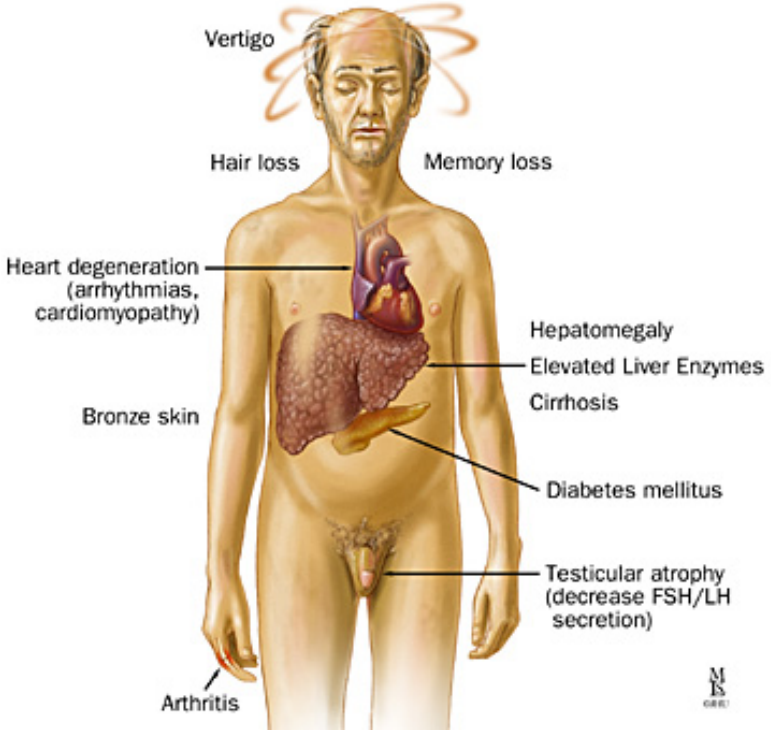
The basis of classic gene-mapping techniques.



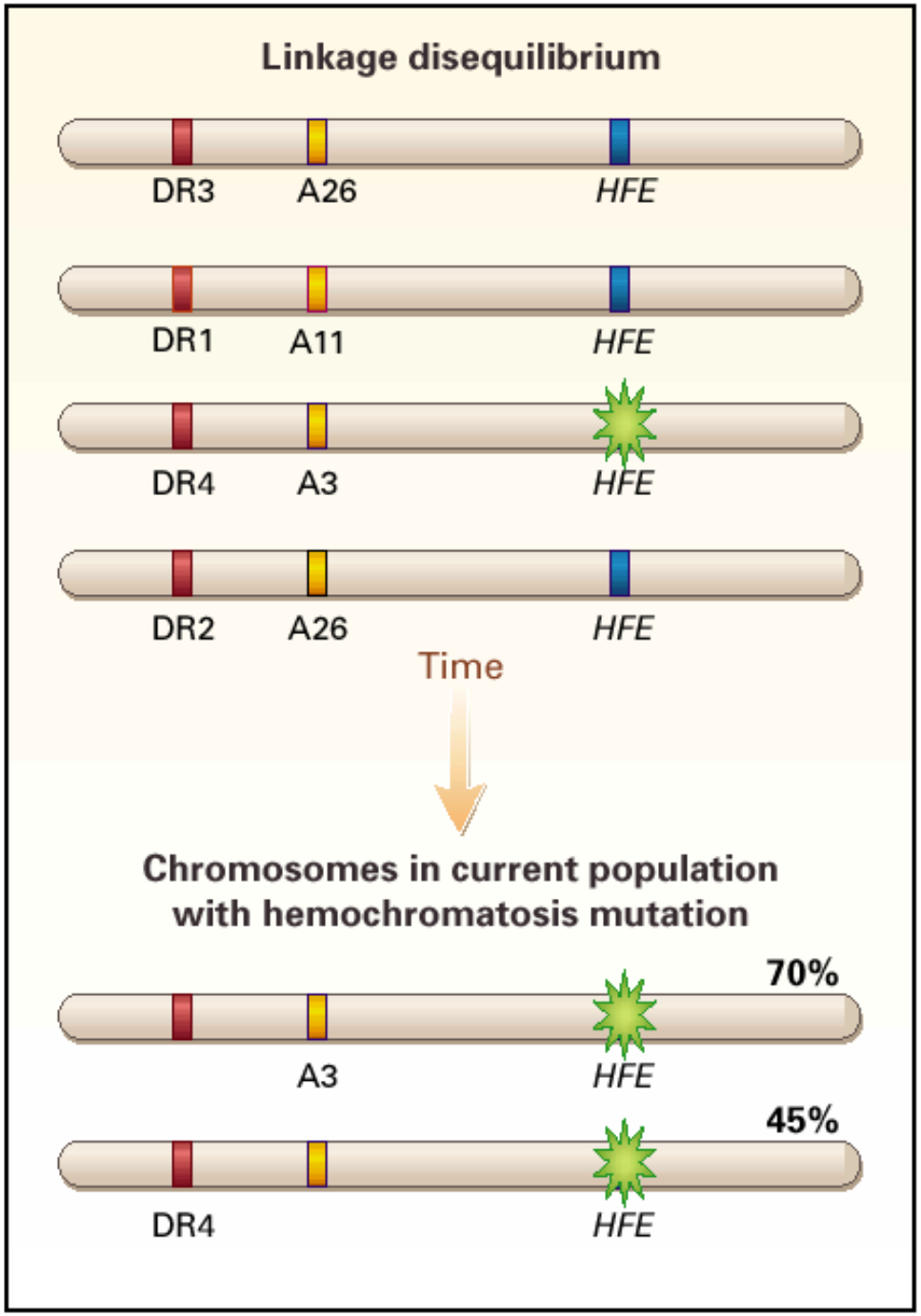
1 cM ≡~1 Mb (1.000.000 bp)

Hemochromatosis: excessive avidity for iron

- Genetic basis, essentially AR, HFE gene
- HFE gene linked to HLA-A gene



- Mutated allele HFE* C282Y which causes hemochromatosis is associated with allele HLA-A3



Linkage disequilibrium LD

- HLA-A3 :
  - General population : 15%
  - Hemochromatosis : 70%

- Mutation appeared 1! x not too long ago

Most common HFE mutation appeared 70 generations ago in a celtic, HLA-A3 subject

Linkage disequilibrium(LD)

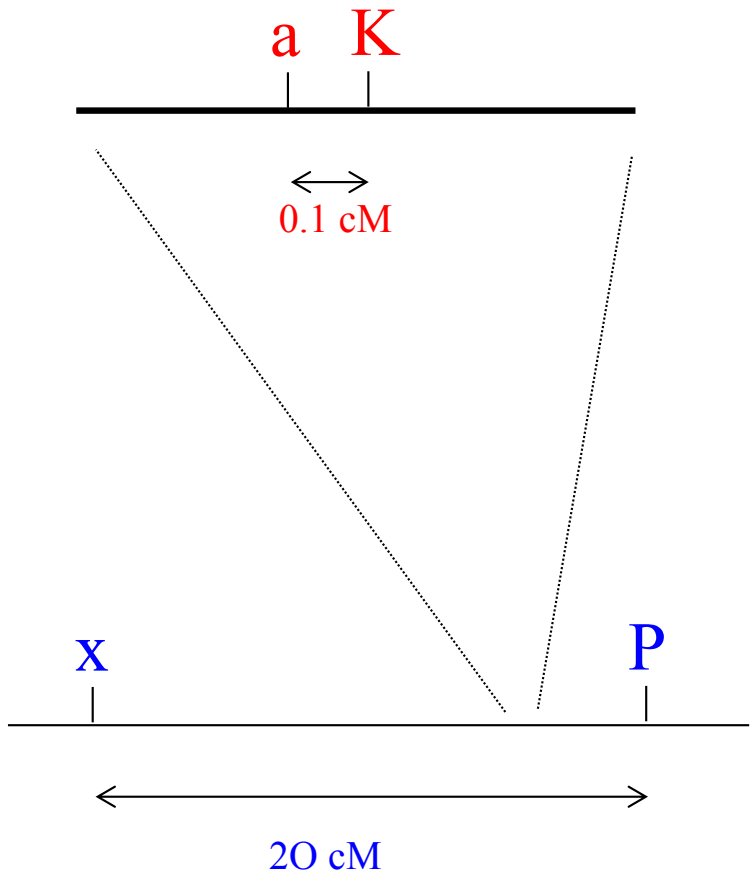
- Locus K,L,M,N
  Locus a,b,c,d

  a remains with K

  f(a,K) >> f(a) . f(K)

- Locus P,Q,R
  Locus x, y

  f(x,P) = f(x) . f(P)



Genetic characters / disorders (traits)

- Single-gene (monofactorial) — Mendelian: fixed proportions in offspring

  + mtDNA: maternal-inherited

- Chromosomal

- Complex

Phenotype inheritance from single-gene cause

- AD — Htz mutation
- AR — Bi-allelic mutation
- X-linked — Hemizygous mutation
- maternal — mtDNA mutation

NECESSARY and SUFFICIENT to cause disease

>5000 diseases. See http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim

MUTATION AFFECTING HEALTH
as % of live birth

- GENE MUTATION

AD	0.90
AR	0.25
X-linked	0.05
Total gene mutation :	1.20

- GENOME / CHROMOSOME MUTATION

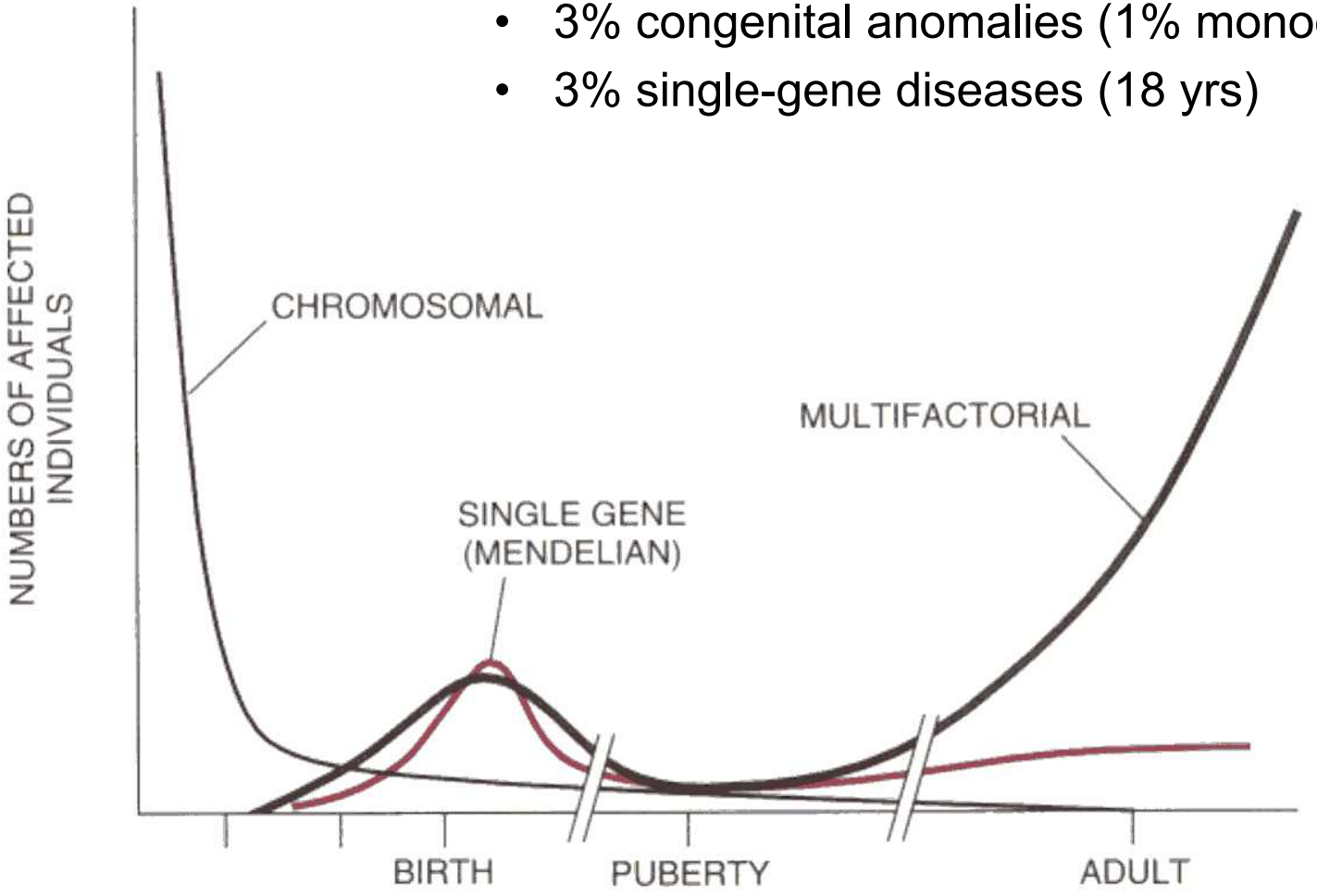
Autosomal trisomies (mainly T21)	0.14
Other unbalanced autosomal aberrations	0.06
Balanced autosomal aberrations	0.19
XO, XXX, XXY	0.21
Total chromosome mutation :	0.60

Impact of genetic diseases

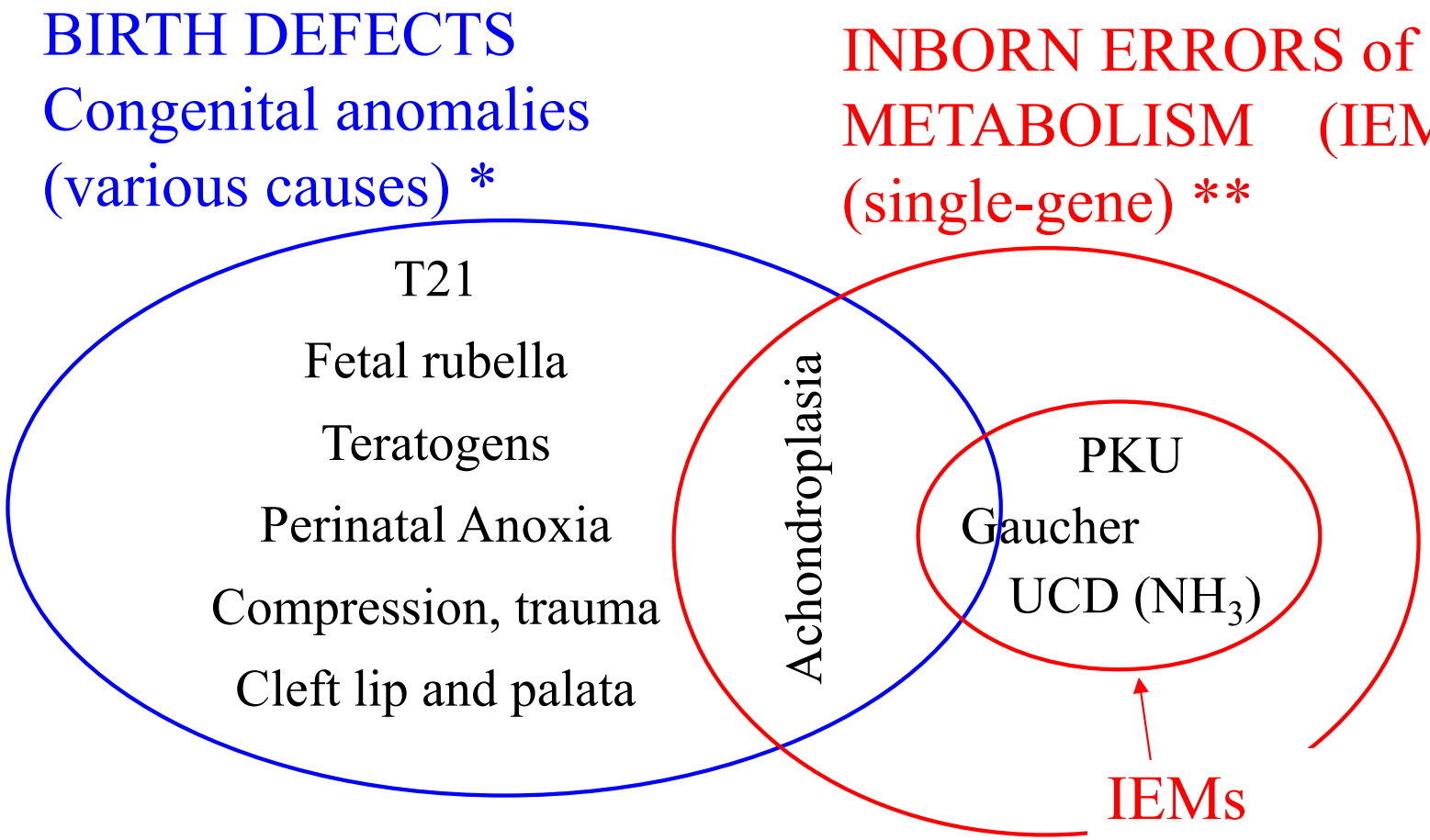
Incidence

Prevalence:

- 3% congenital anomalies (1% monogenic)
- 3% single-gene diseases (18 yrs)



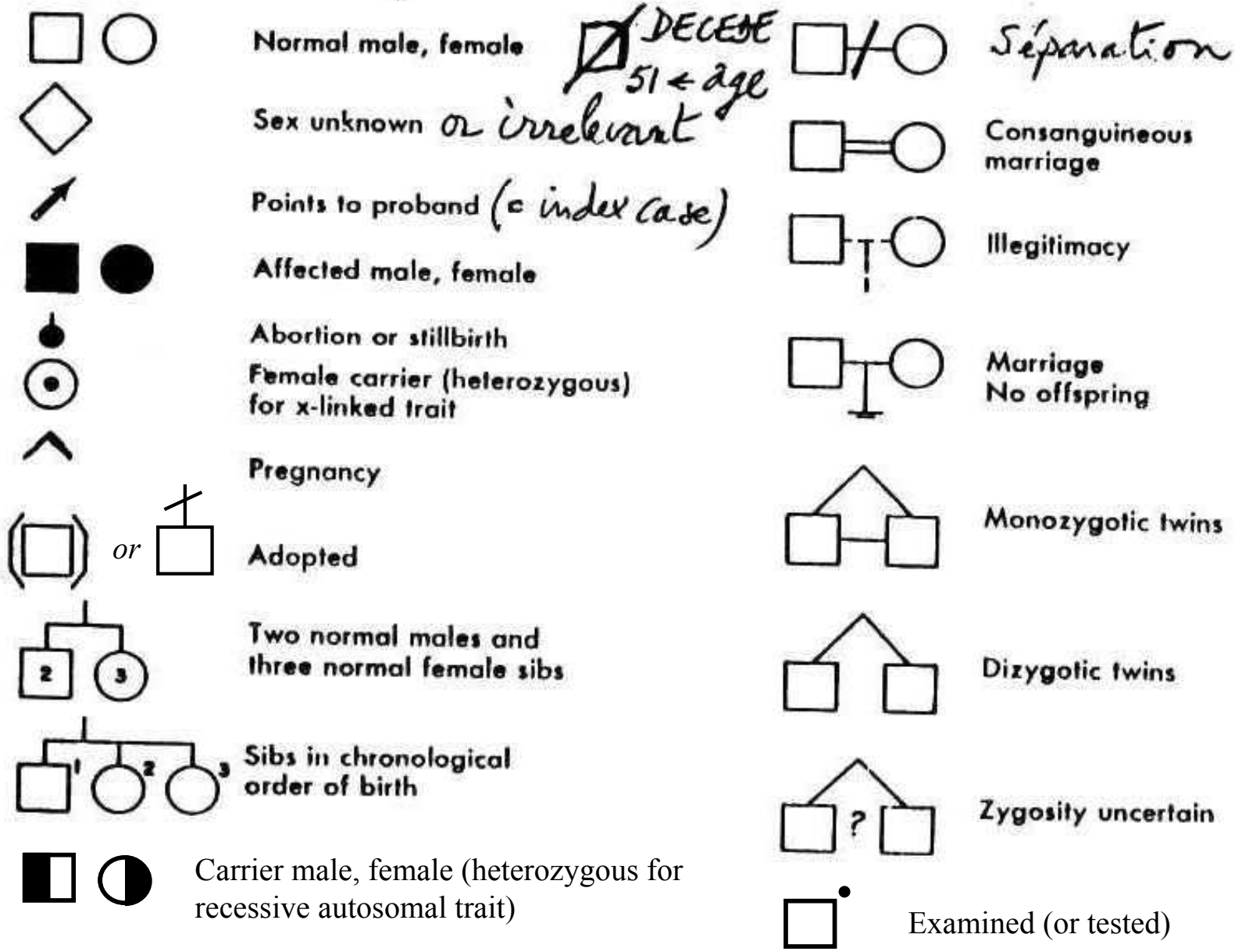
Births defects and Inborn Errors of Metabolism



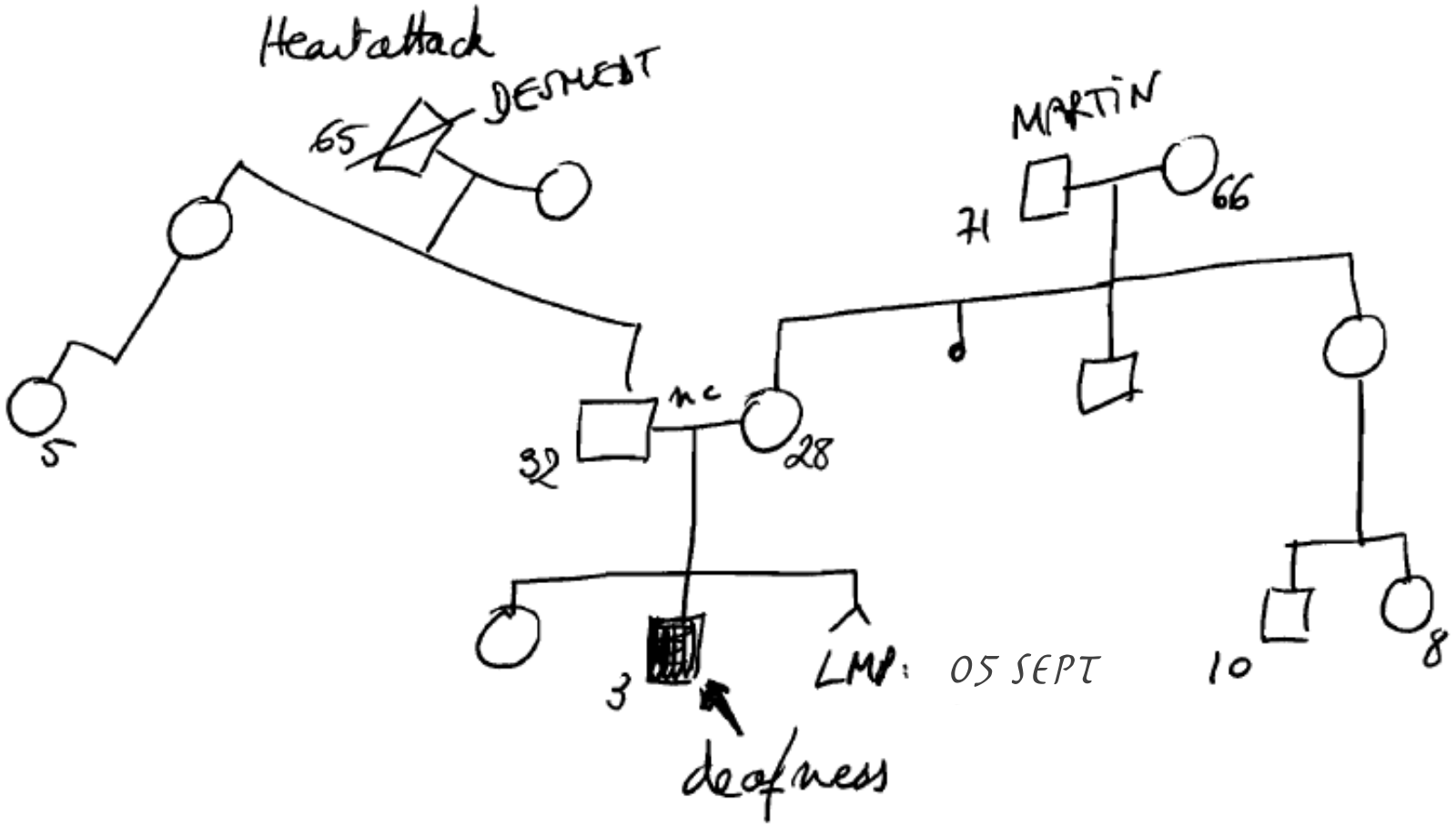
* 3% [live] newborns

** 3 % general population

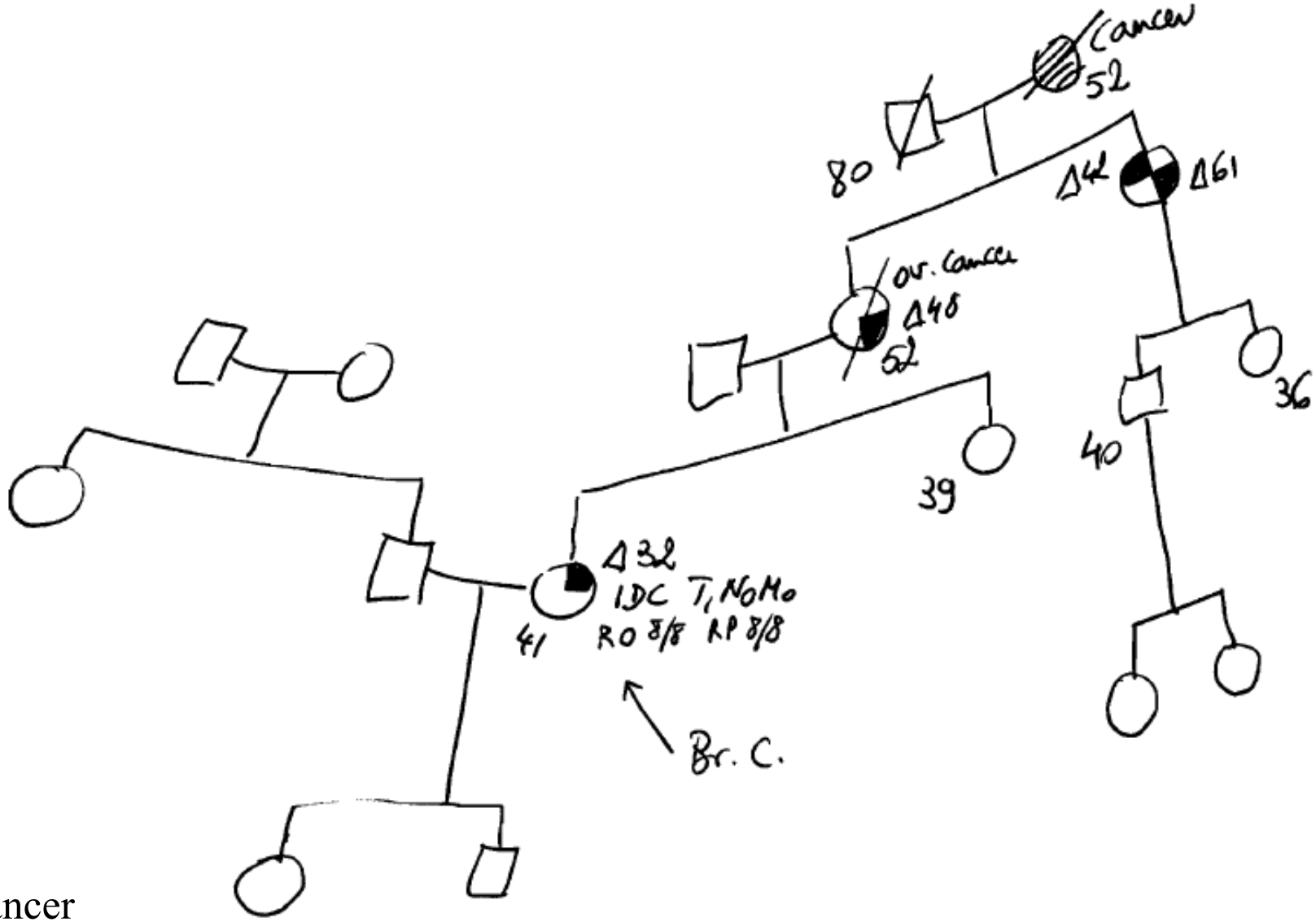
Symbols in pedigree charts



Working pedigree



Working pedigree (breast cancer)



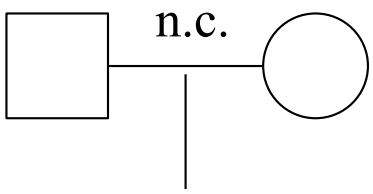
Breast cancer

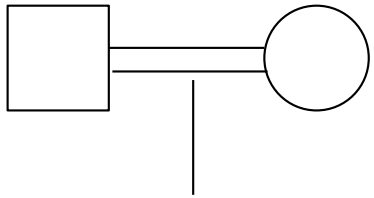
Ovarian cancer

consanguinity

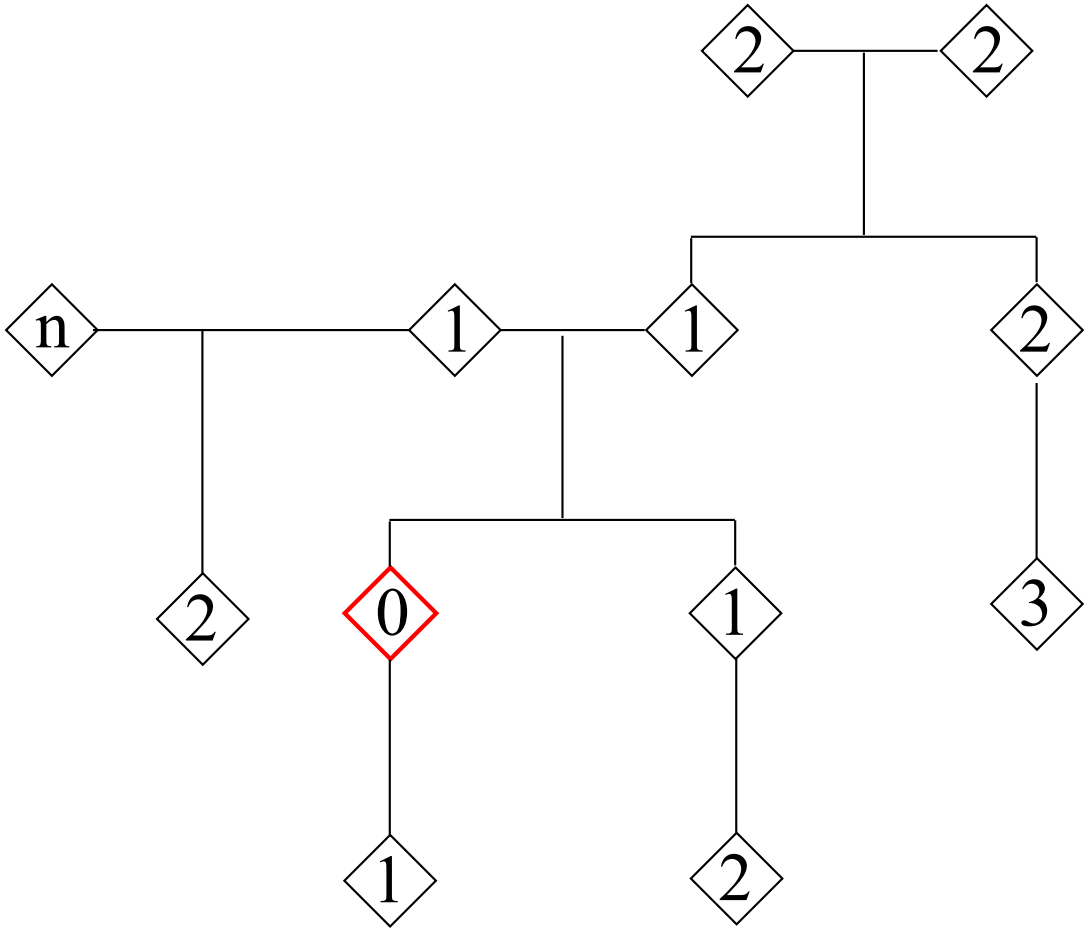
- Always enquire specifically about consanguinity
  - Are your parents cousins? (first cousins, …)
  - Are your grandparents (!) « cross-related » ?

- Annotate the pedigree, also if not consanguineous : ‘ n.c. ’





Degrees of relationship

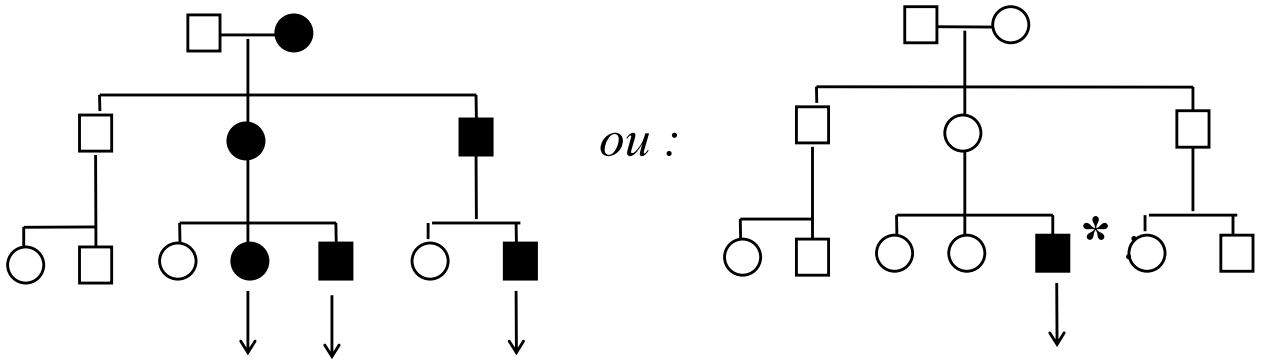


d°	relat	common alleles
1		.50
2		.25
3		.125

Patterns of single gene inheritance

AUTOSOMAL DOMINANT

AD phenotype: vertical transmission.
Genotype: hts mutation in autosome.



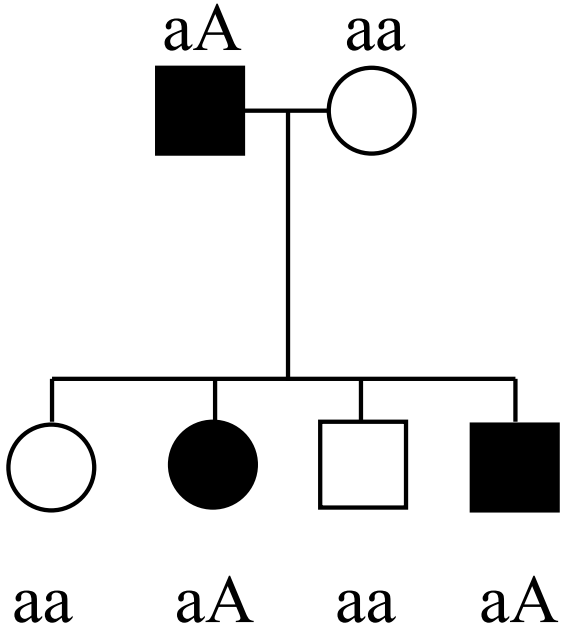
- Risk in each offspring = 50%
- M et F equally affected, equally transmitting
- Male to male transmission possible
- * : Neomutation (fresh mutation): AD disease starts here.
  - No ethnical prevalence (rare exceptions).
  - Increased mean paternal age.

Punnett square
Probability of genotype in offspring

IN FAMILY

Male gametes

Female gametes	a	A
a	aa	aA
a	aa	aA

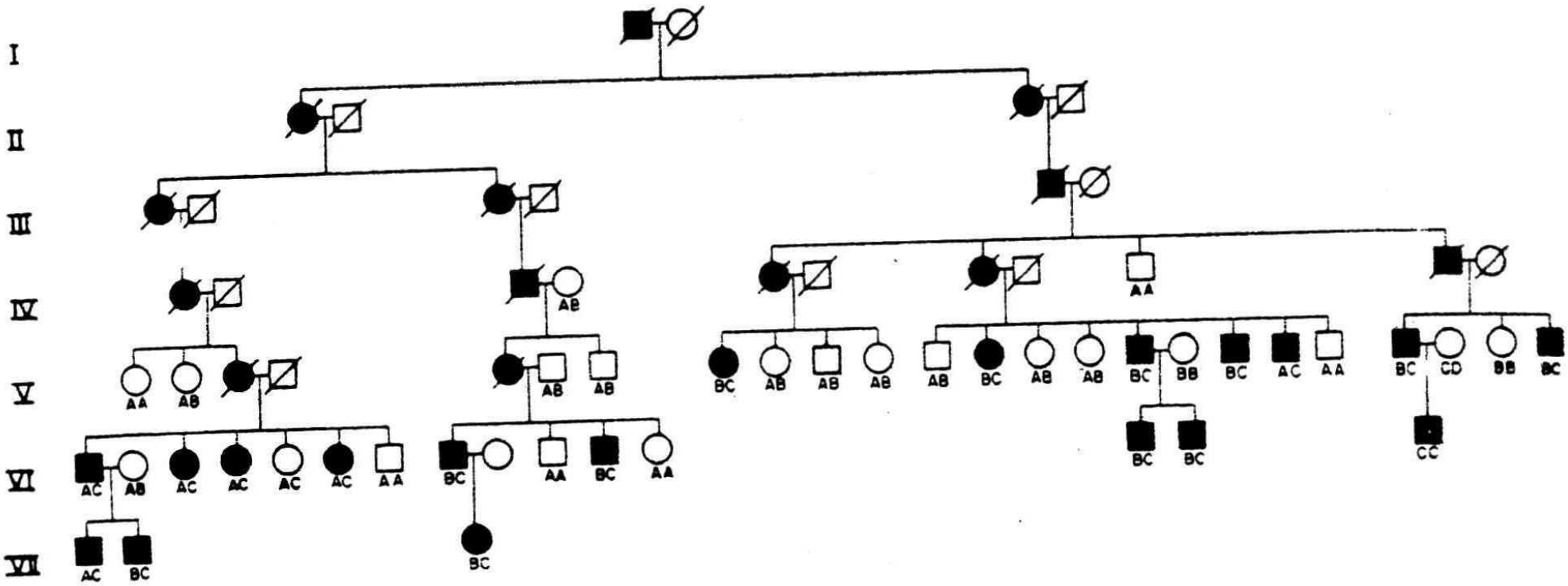


½
heterozygote
(affected)

Huntington : autosomal dominant inheritance

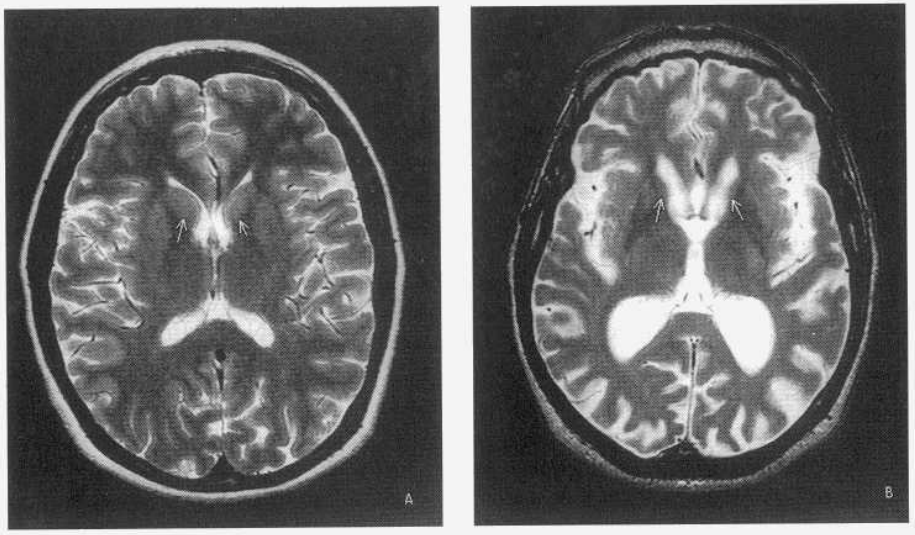
NATURE VOL. 306 17 NOVEMBER 1983

Gusella et al.



=> One single genetic factor causes disease (monofactorial, genetic).

Huntington disease



(a) Normal volunteer
(Courtesy of Dr M. Lowry, Hull, UK.)

(b) Huntington's disease

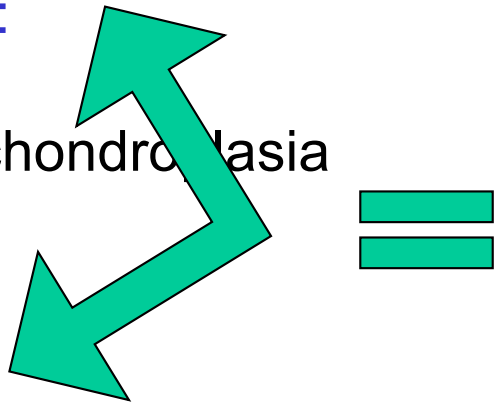
- Neurons in striatum (caudate nucleus) degenerate
- ↓ GABA

AD = approximation

- Dominance: phenotype independent of 2nd allele

- Semi-dominance (incomplete dominance):

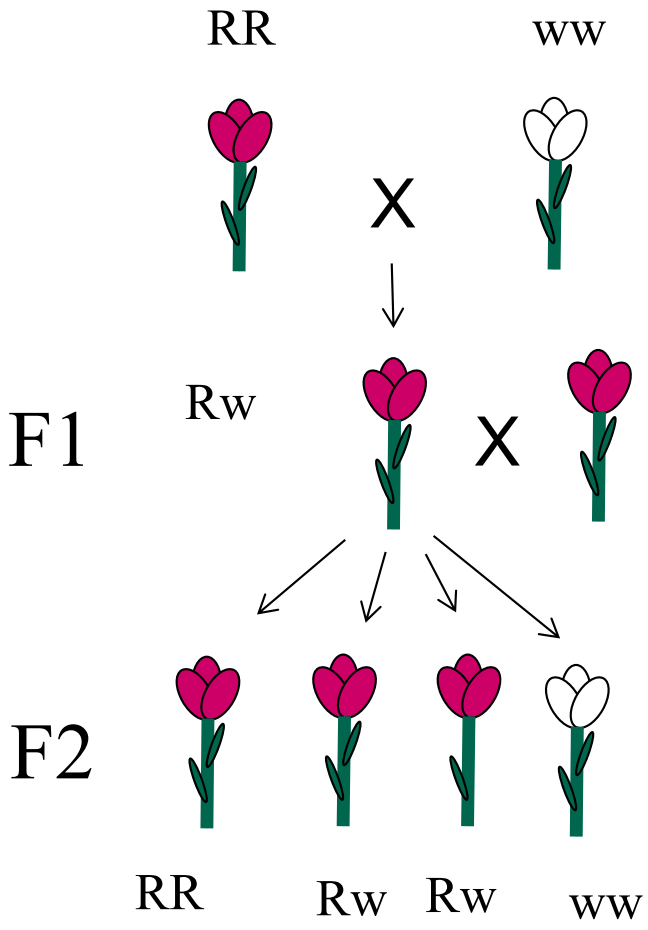
  hmz expresses trait more than htz : eg, achondroplasia



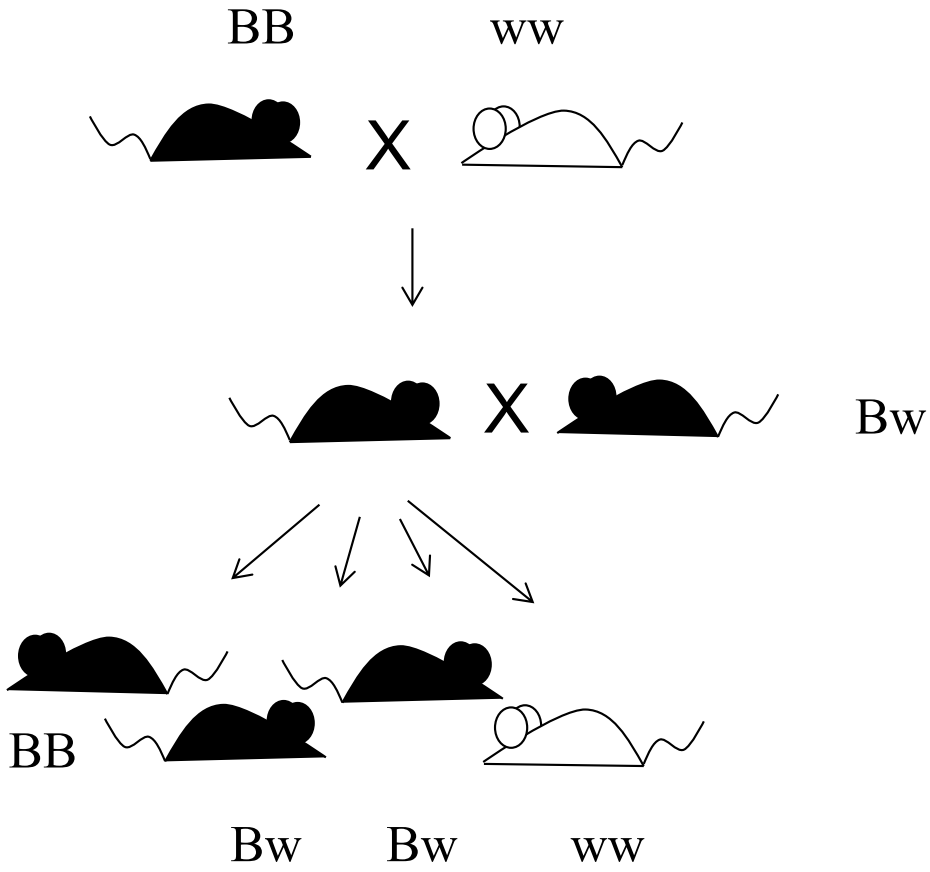
- Co-dominance:

  both alleles expressed : eg, ABO blood group

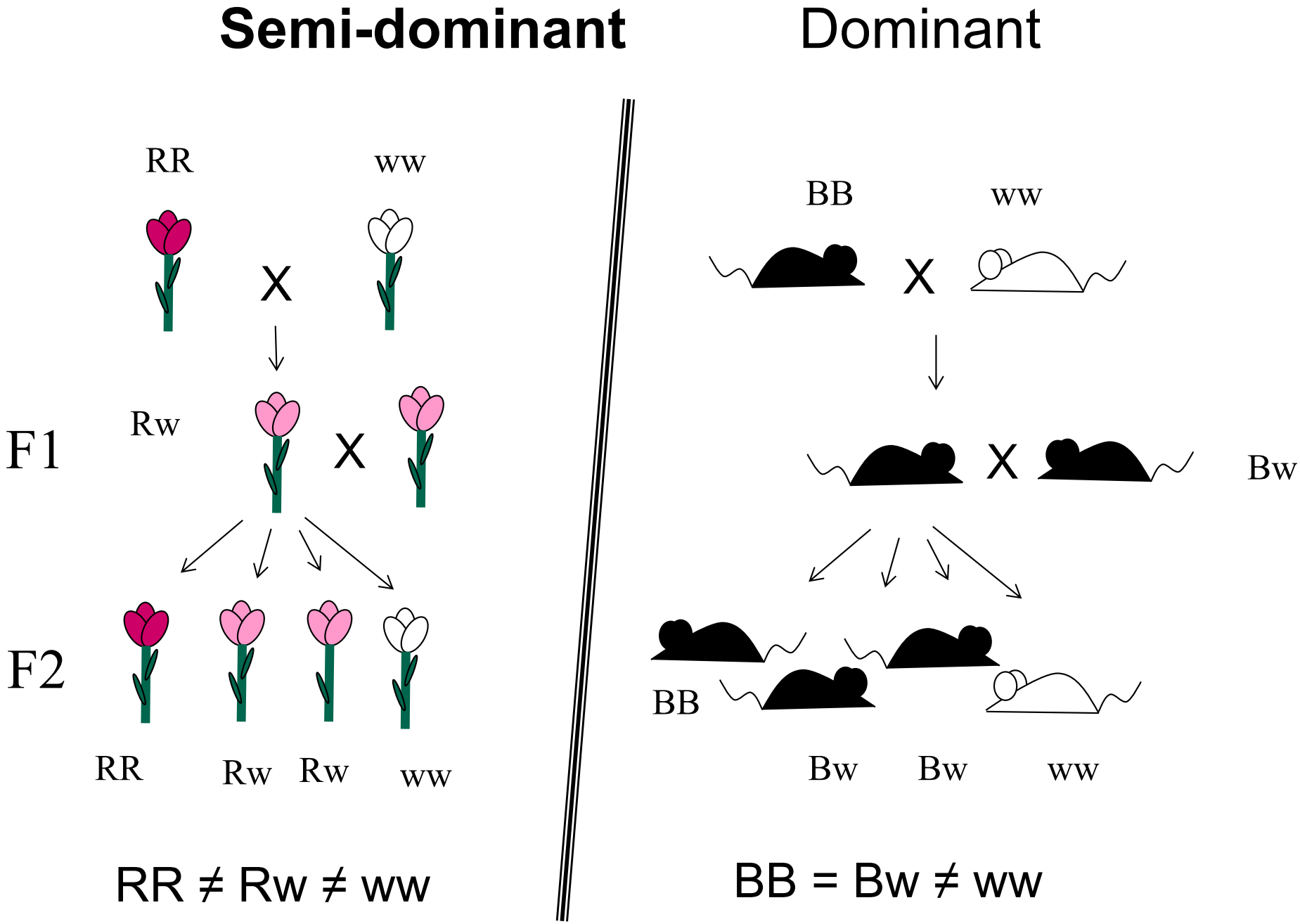
Dominant



RR = Rw ≠ ww

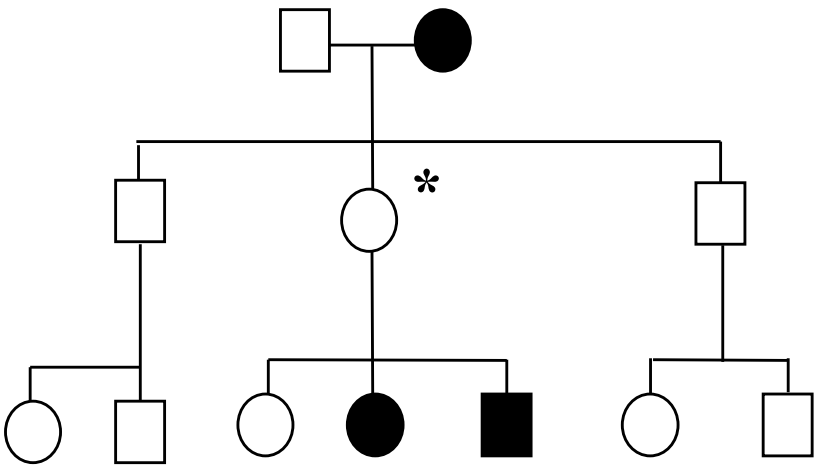


BB = Bw ≠ ww


Semi-dominant
Dominant
RR
ww
X
F1
Rw
X
F2
RR
Rw
Rw
ww
RR ≠ Rw ≠ ww
BB
ww
X
X
Bw
BB
Bw
Bw
ww
BB = Bw ≠ ww

Clinical variability of genetic phenotypes

- **PENETRANCE**: % of mutation carriers who express phenotype
- **EXPRESSIVITY**: clinical severity of the phenotype.



Incomplete penetrance:

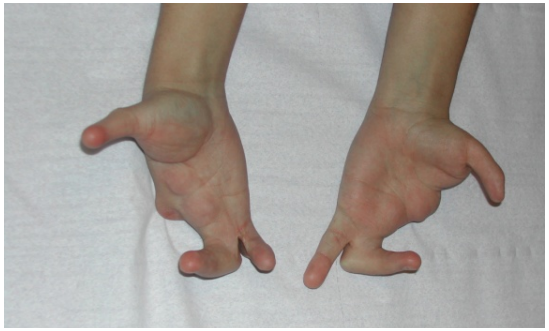
* « non-penetrant » subject :

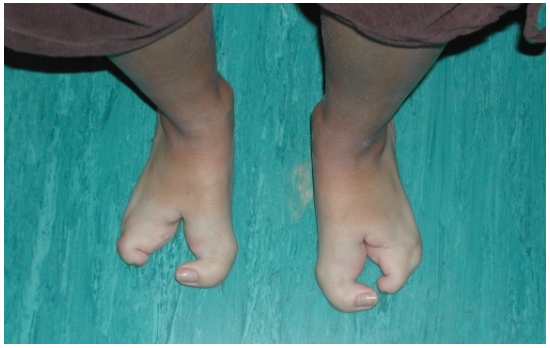
=> Age-related penetrance

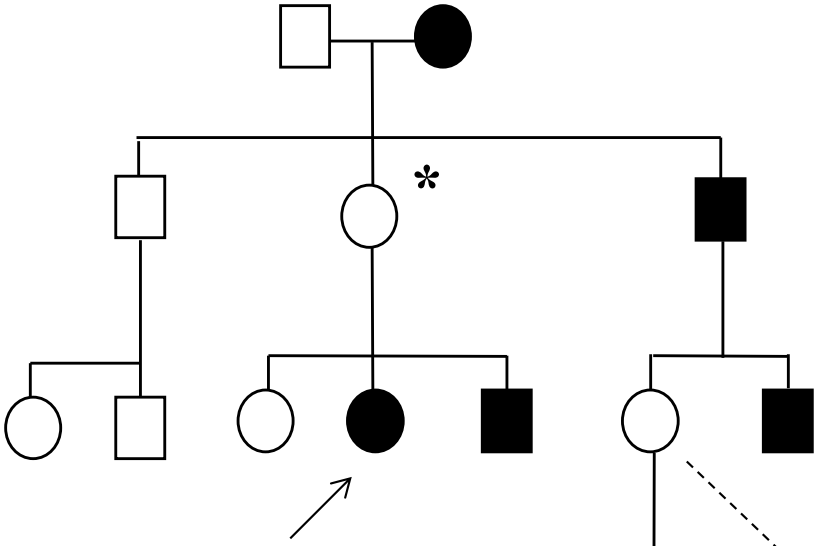
=> Sex-related penetrance

Incomplete penetrance

PENETRANCE: % of mutation carriers who express phenotype

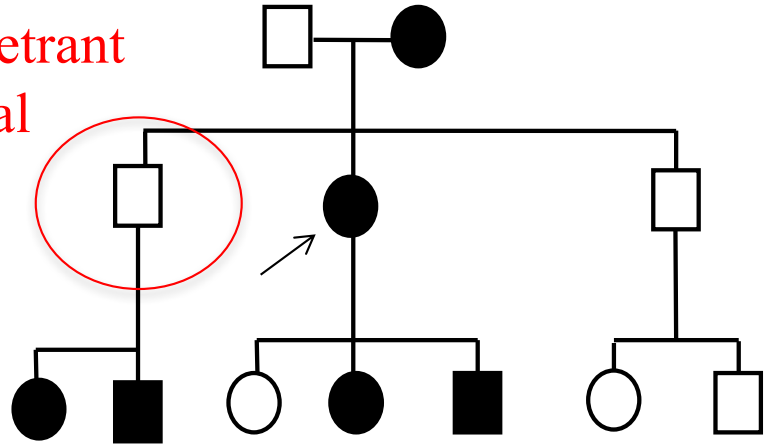






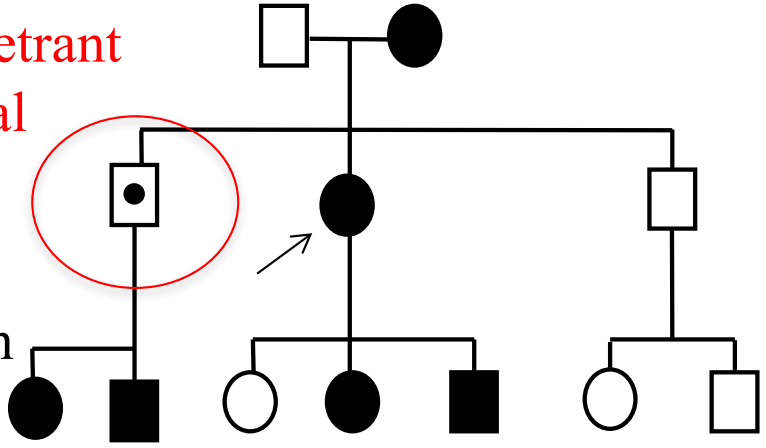
Incomplete penetrance

Non penetrant individual



Non penetrant individual

Dot in symbol = carrier of dominant mutation



Age-related penetrance

MEN2

- Medullary Thyroid Carcin
  Pheochromocytoma
  hyperPTH
- Some have MTC < 15 yrs
- 30% have no sign at 70 yrs

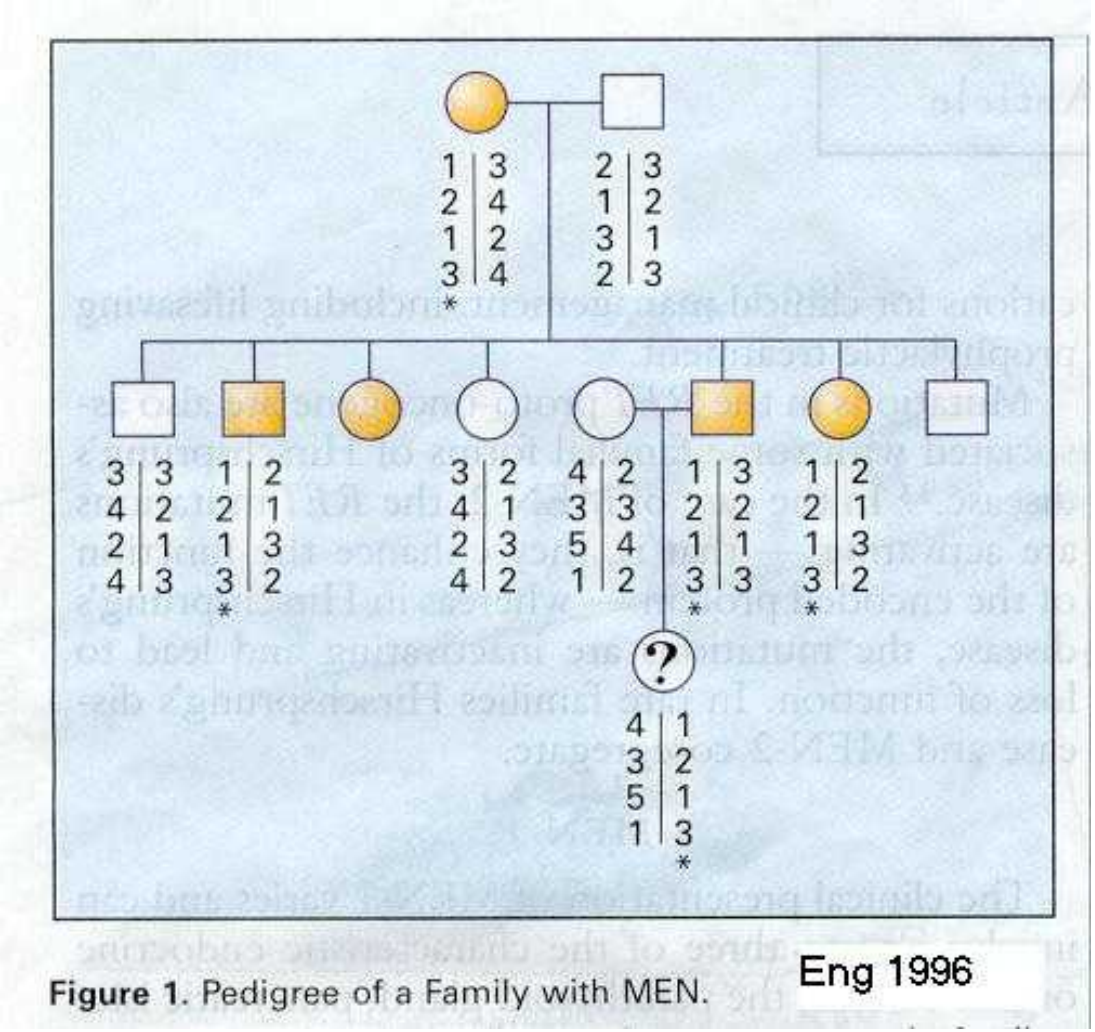
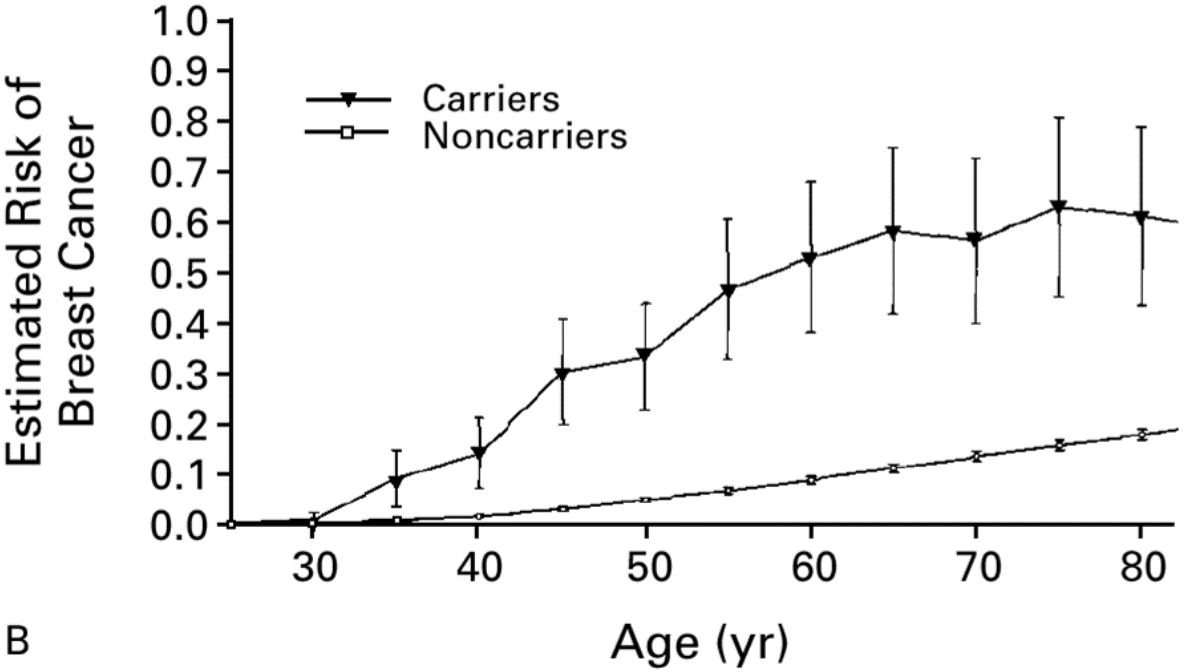


Figure 1. Pedigree of a Family with MEN. Eng 1996

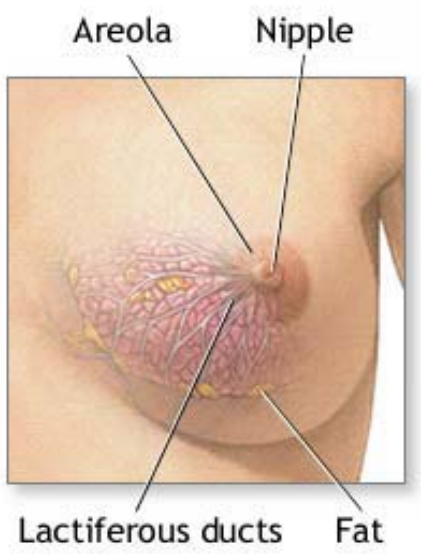
Sex- and age- related penetrance

Penetrance, BRCA1 – linked breast cancer



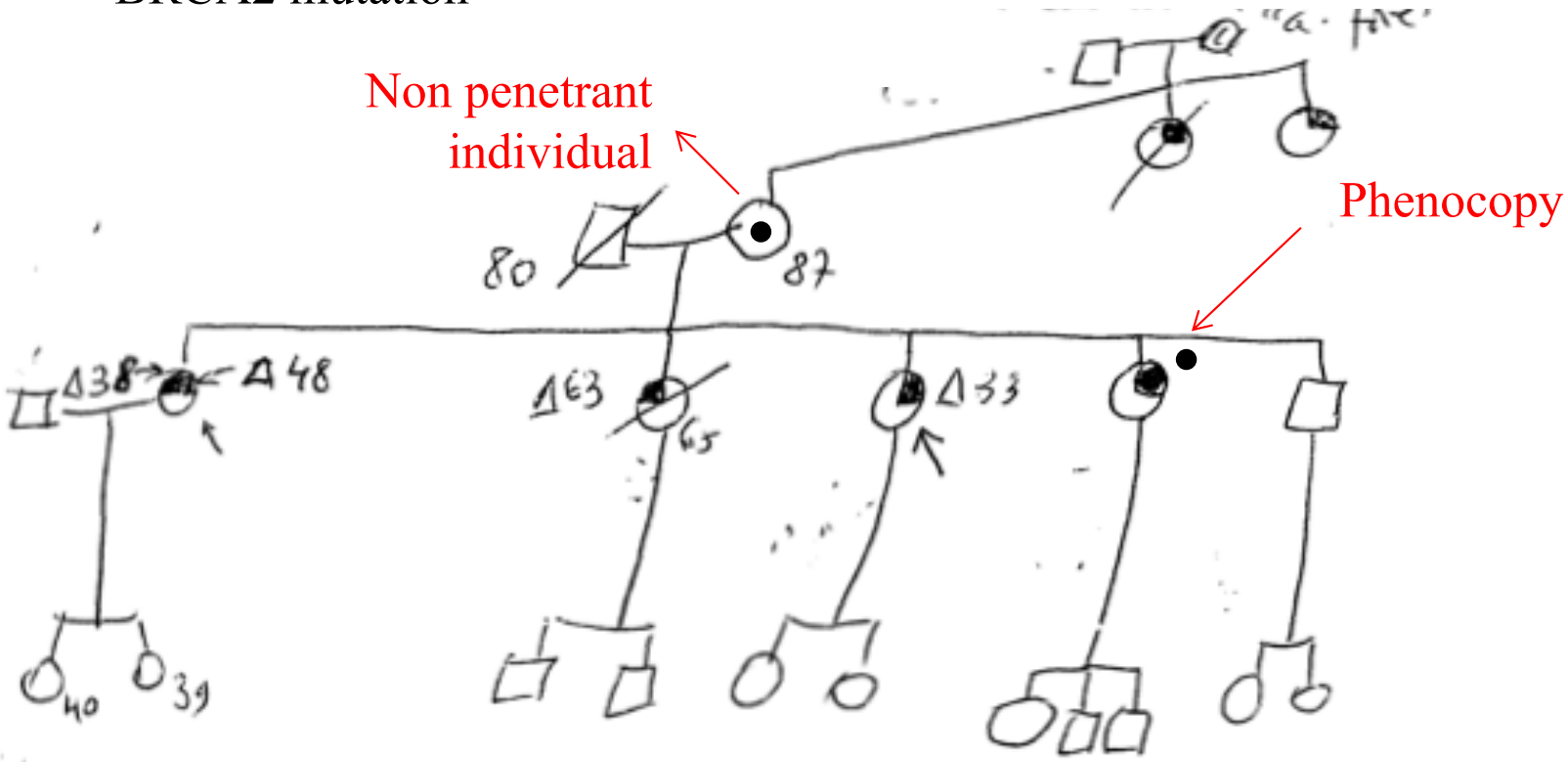
B

Struewing et al. 1997, NEJM 336: 1401-8.



Incomplete penetrance

BRCA2 mutation



Male-limited precocious puberty
is a sex-limited AD dis. expressed only in males

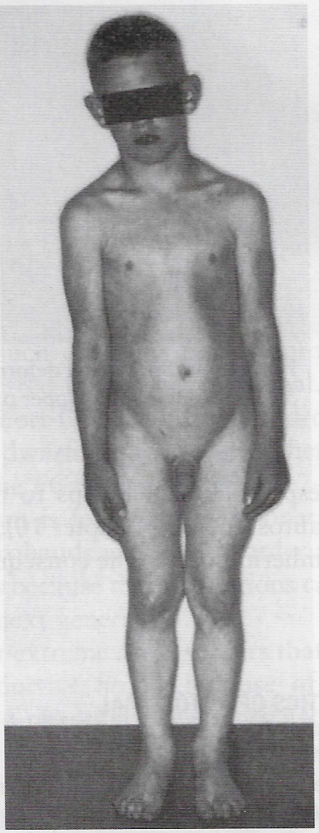


Figure 7-7 **Male-limited precocious puberty, a sex-limited autosomal dominant disorder expressed exclusively in males.** This child, at 4.75 years, is 120 cm in height (above the 97th percentile for his age). Note the muscle bulk and precocious development of the external genitalia. Epiphyseal fusion occurs at an early age, and affected persons are relatively short as adults.

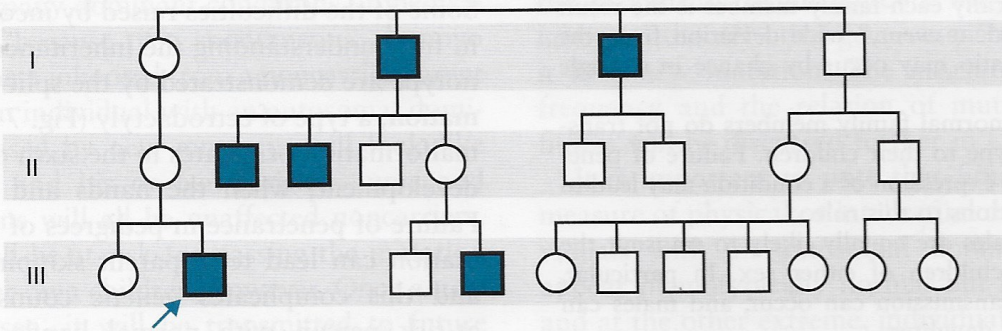
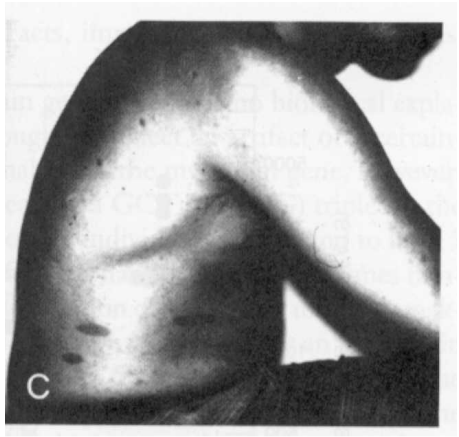


Figure 7-8 **Part of a large pedigree of male-limited precocious puberty in the family of the child shown in Figure 7-7.** This autosomal dominant disorder can be transmitted by affected males or by unaffected carrier females. Male-to-male transmission shows that inheritance is autosomal, not X-linked. Transmission of the trait through carrier females shows that inheritance cannot be Y-linked. *Arrow* indicates proband.

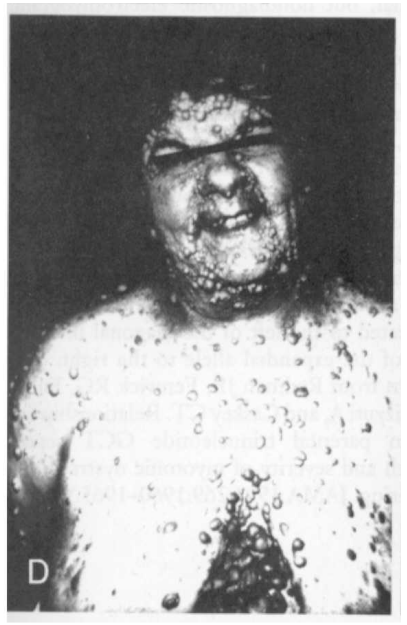
Variable expressivity

Mecanisms :

- Genetic
  - Mutated locus, 2nd allele
  - Modifyer gene(s)
  - Dynamic Mutations (rare)
- Epigenetic
- Environnemental
- Stochastic

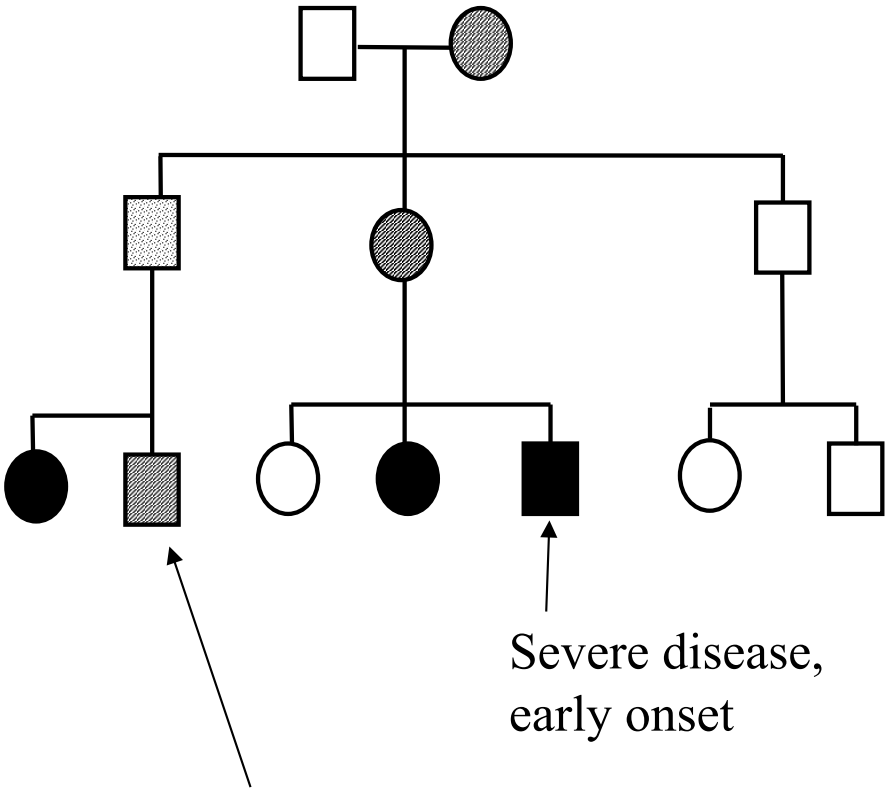


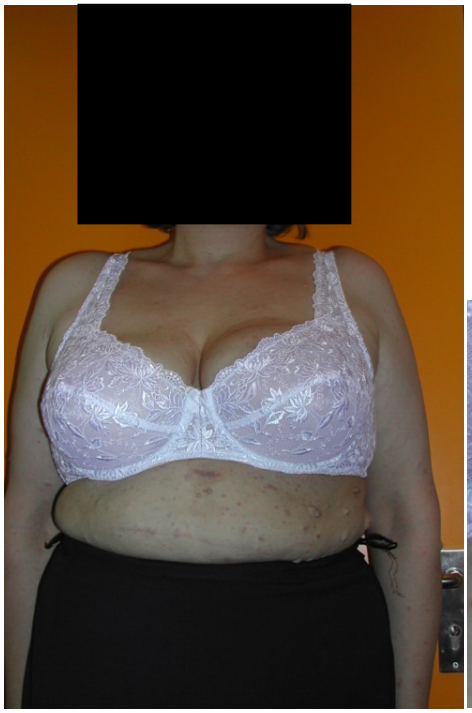
NF1

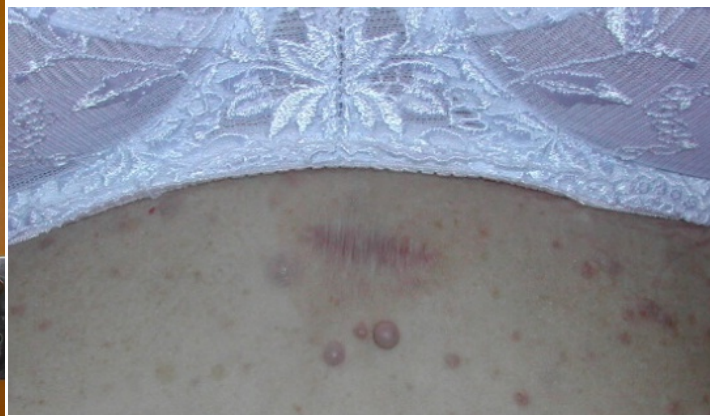


Variable expressivity, intrafamilial

- Same family, same mutation
- Hence, mere detection of mutation (eg prenatally) does not predict severity
- Especially if loss-of-fn mutation
- ex: NF1







Location of spots: truly random

Huntington : anticipation

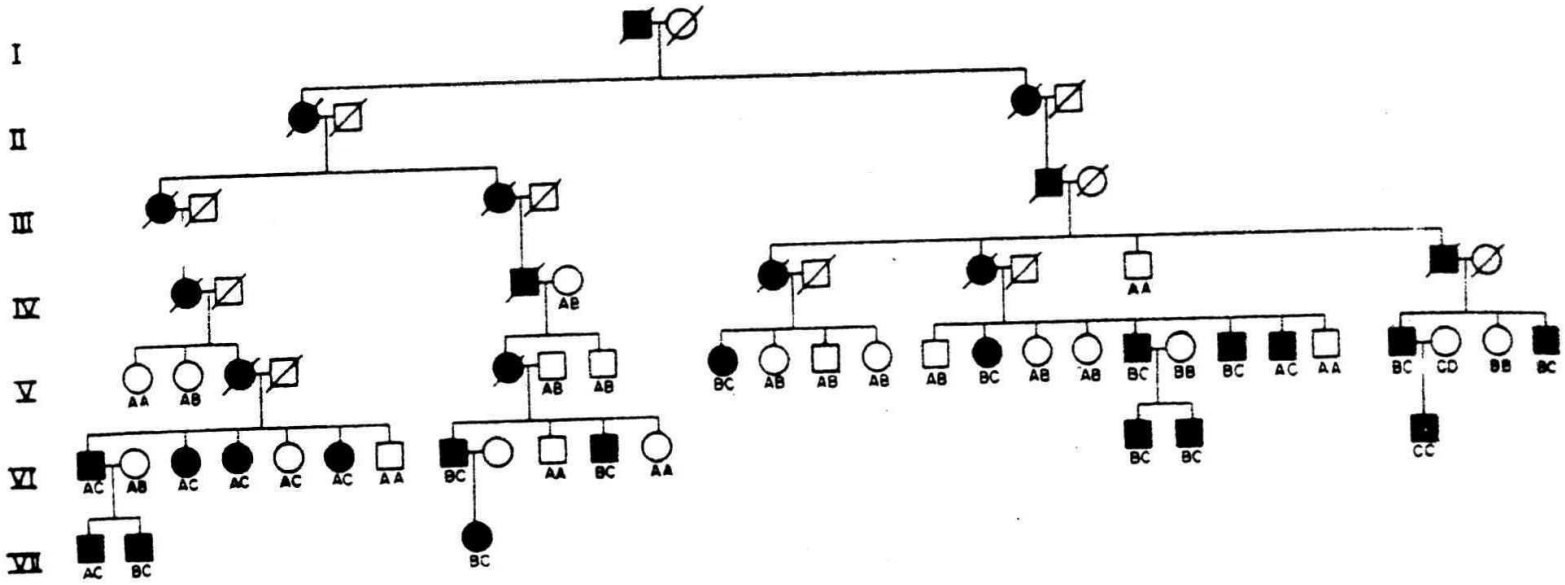
Mean age at onset of symptoms

70

60

50

40



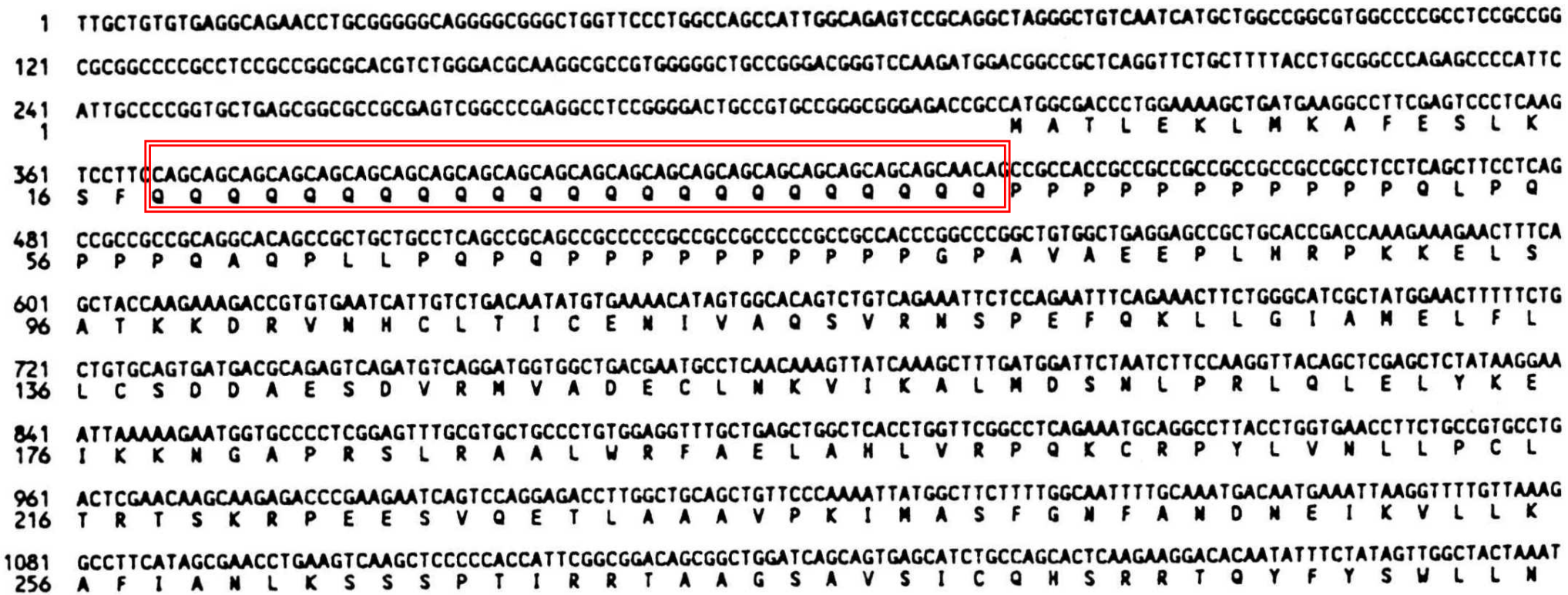
Anticipation = clinical observation (phenotype)

Molecular correlate : progressive expansion of triplets with generations

Near-mendelian inheritance

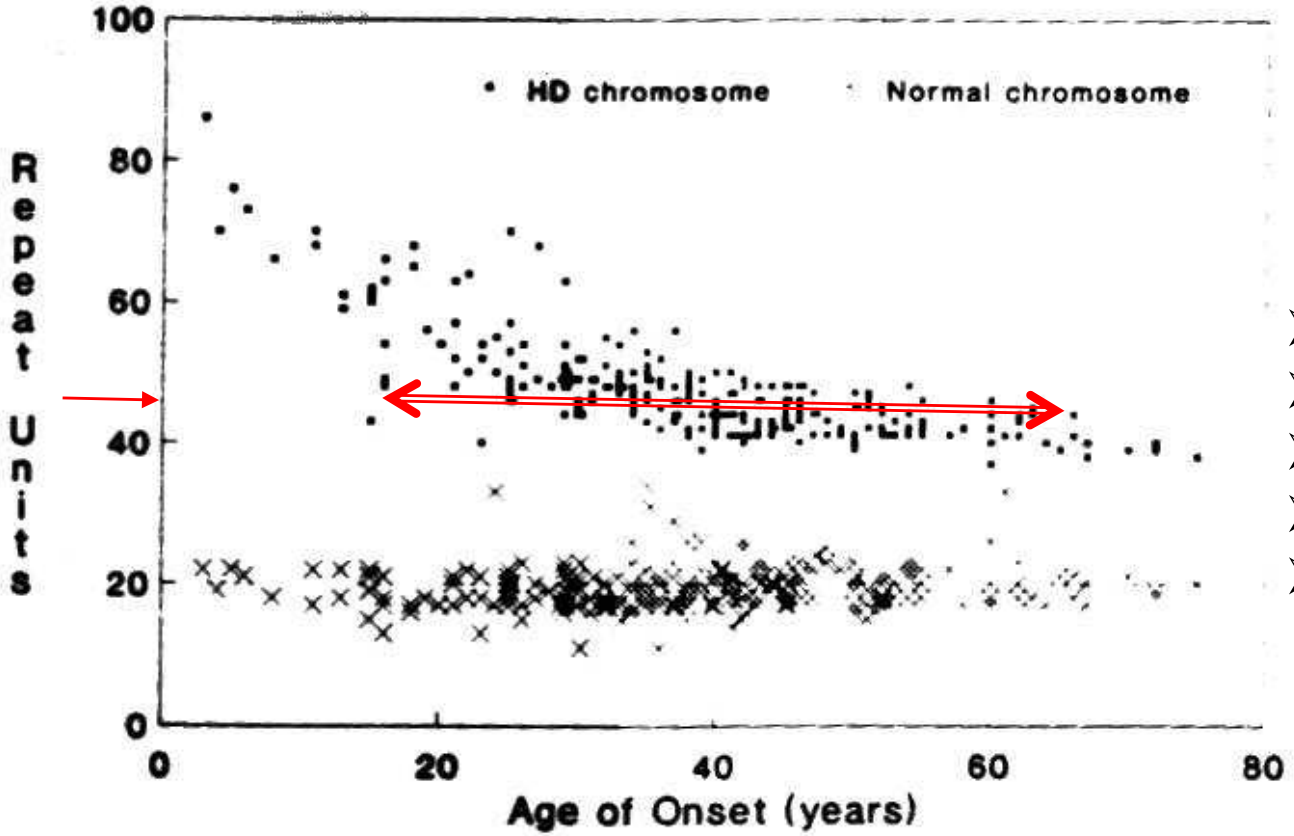
- Penetrance — all-or-nothing presence of phenotype (on/off button)
  - Complete penetrance
  - Incomplete penetrance
- Expressivity — quantitative (volume button)
  - Mild, moderate, severe expressivity
- Phenocopy — acquired, non-inherited mimic
- Anticipation — increased expressivity over generations

Huntington Disease(HD)



- (CAG)n, coding for (Gln)n, N-term part
- n is polymorphic, < 35 , stable, in general population
- n est > 40 in HD chromosomes . And unstable when transmitted, especially through male.
- Larger n causes more severe disease. Explains 2/3 of variability.

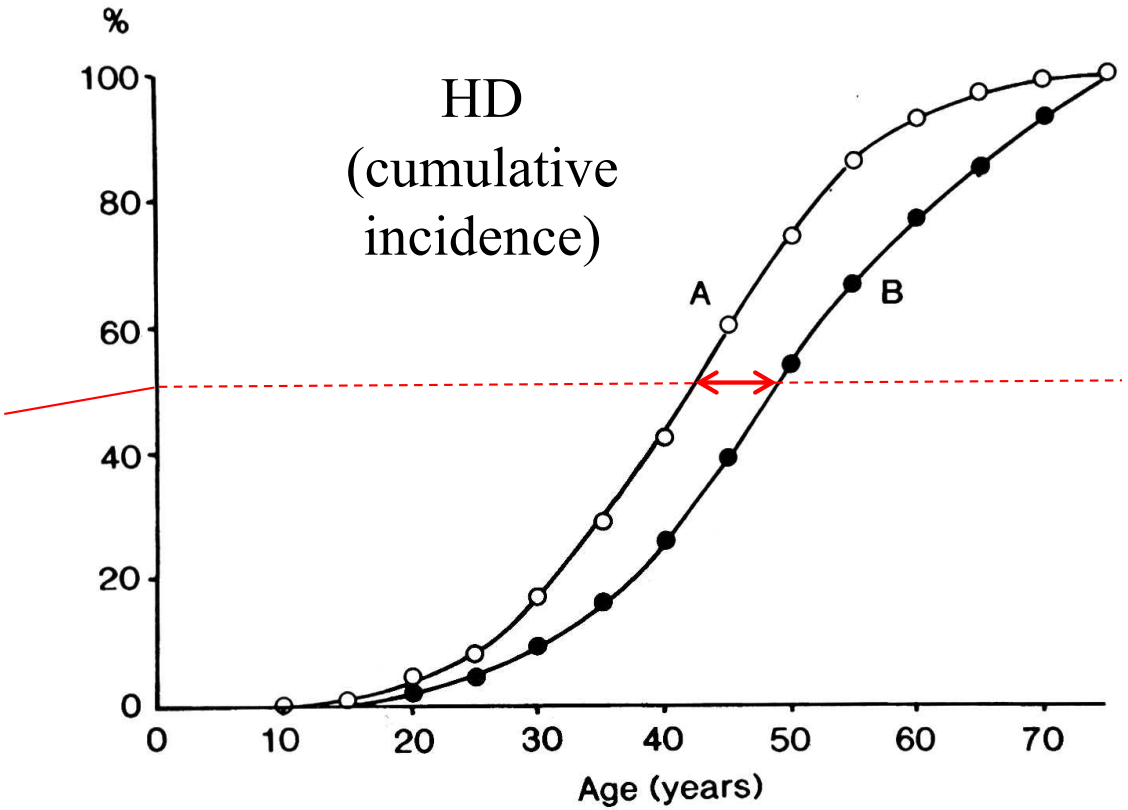
HD: dynamic mutation



- Juvenile HD alleles (>50)
- Classical HD alleles (>36)
- Low penetrance alleles
- Unstable alleles
- Normal alleles

- n ↑ ⇒ age at onset ↓.
- Statistical only.
  No reliable individual predictions.
- Anticipation parallels ↑ n over generations.

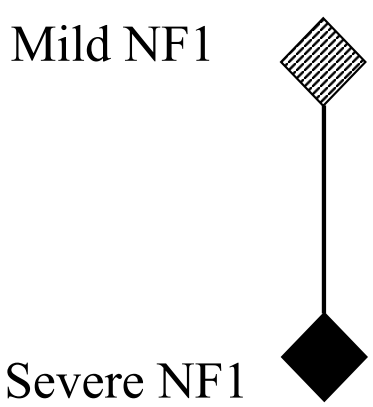
Ascertainment bias (not linked to anticipation)



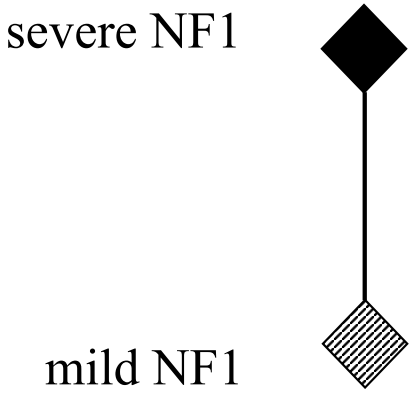
Median age at onset of symptoms

- A: retrospective: patients who consulted because of symptoms
  → biased for increased severity, earlier onset
- B: prospective: mutation carriers.
  → Includes those who would not have consulted.

Variable expressivity interpreted as anticipation



May be reported as possible anticipation



Not reported as possible anticipation

Less frequent (reduced fitness)

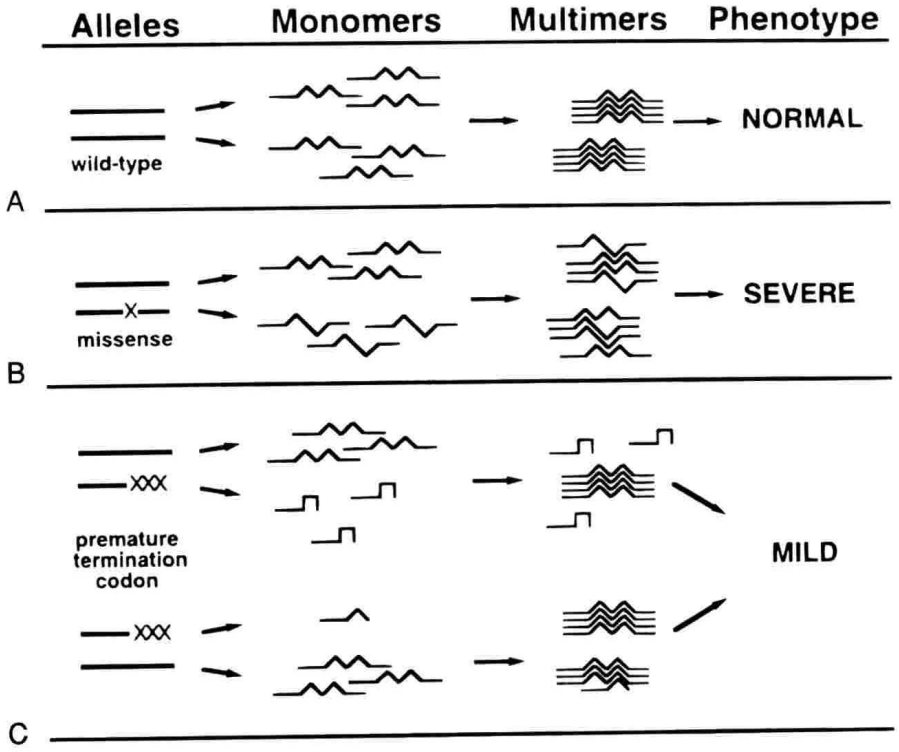
Some mecanism for dominance

Most genes have robust functional reserve:

>10% gene activity (e.g. enzymic) enough for normal fn
==> why phenotype in htz?

- Haploinsufficiency (>50% not enough) → Acute intermittent Porphyria
- Gain of toxic fn → Huntington
- Dominant negative effet (multimer) → Marfan, THR,
- Somatic mutation of 2nd allele frequent → Cancers héréditaires
- Dose effect (triplication) → Charcot Marie Tooth
- Ectopic expression → Corticoids-remediable HTN

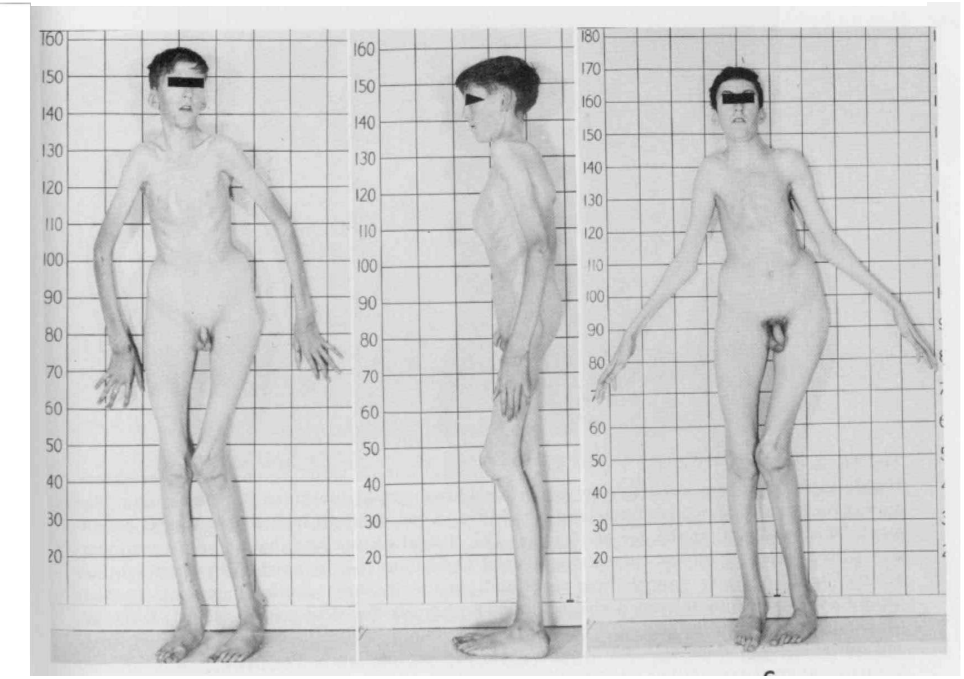
Dominant negative (antimorphic) alleles



- Mutated allele loses fn AND interferes with wt allele
- >1 subunit (dimers, multimers): 1 mutation hampers whole structure

- Usually causse more severe phenotype than null mutation
  - Ostogenesis imperfecta
  - Marfan

Marfan Syndrome (FBN1 gene)



Mutations affect Fitness

- Natural selection favours or hampers chances to transmit gene
  - Survival, up to reproducing age
  - Find a mate (sexual selection)
  - Be fertile
  - Raise children to reach reproducing age
  - …
- Positive selection (adaptive change)
- Negative selection (purifying selection)
  - Fitness = (# offspring) / (mean # offspring in population)

ex: f=.95

after 10 generations: $.95^{10} = .60$

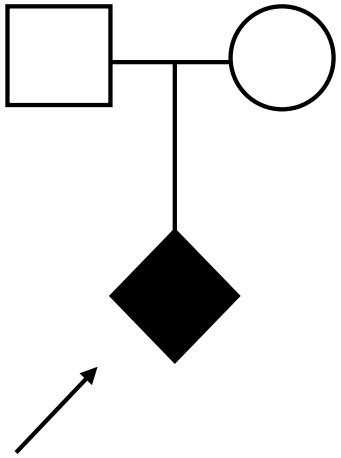
after 20 generations: $.95^{20} = .36$

after 100 generations: $.95^{100} = .0060$

New mutations (fresh mut, neomutations)

- Sporadic. No ethnic preponderance
- Cause a fraction of AD cases, disease-specific
- Fraction reflect effect of disease on *fitness* (f)

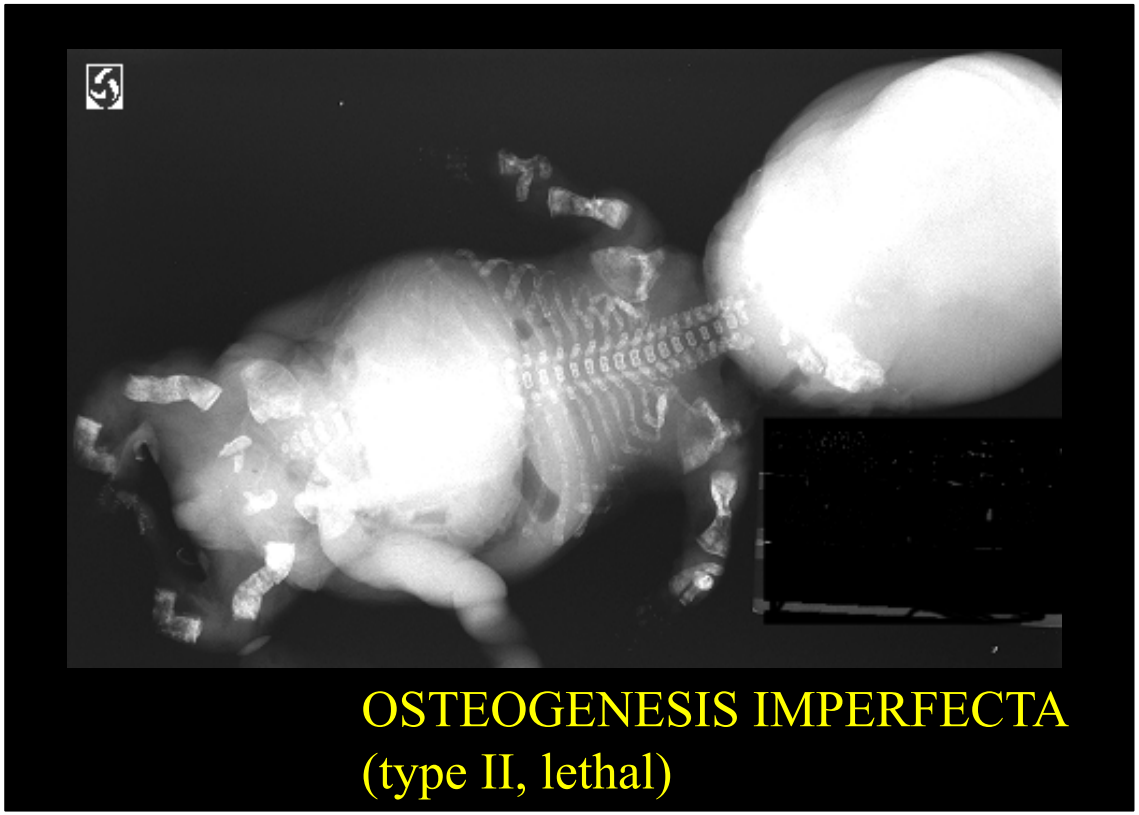
  f = (No offspring of individual) / (mean No offspring in population)

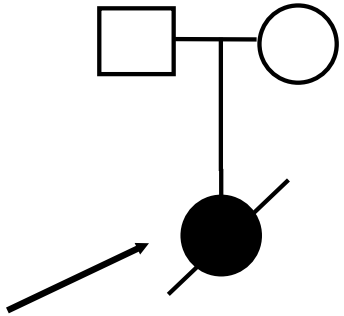


disease	*% neomutations*
Huntington Chorea	*< 1%*
Fam Adenom Polyposis	*10-25%*
Polykystosis	*25%*
NF1	*50%*
Tuberous sclerosis	*80%*
Achondroplasia	*90%*
Lethal OI	~100%

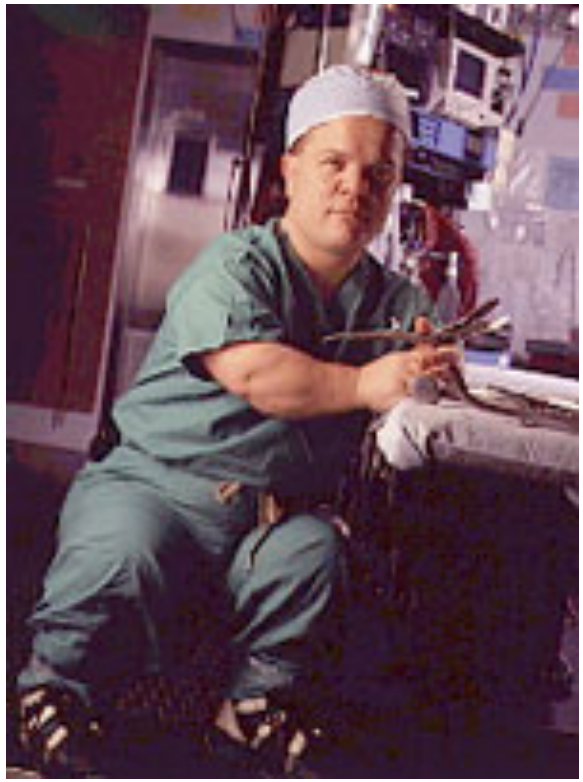
New mutation lethal OI

- Procollagen gene, hts mutation, lethal phenotype (fitness = 0)
- New mutations only



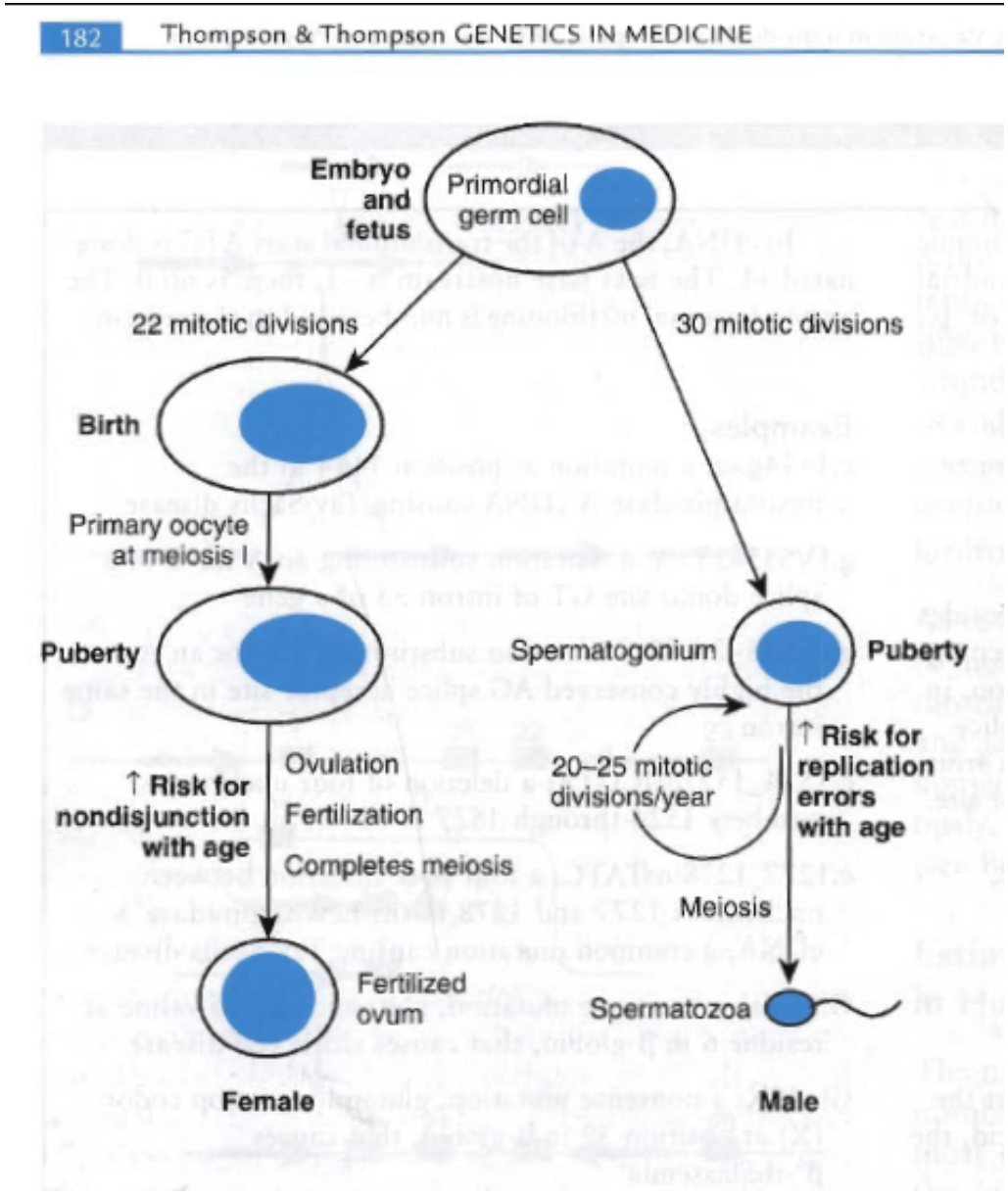


Achondroplasia



- FGFR3 gene
- Neomutations => no LD with close markers in different subjects

New mutations are more frequent in male germ-line + paternal age effect



DNA replication:
mutation rate 10^{-10}
2×3.10^9 bp/cell
10^{11} cells

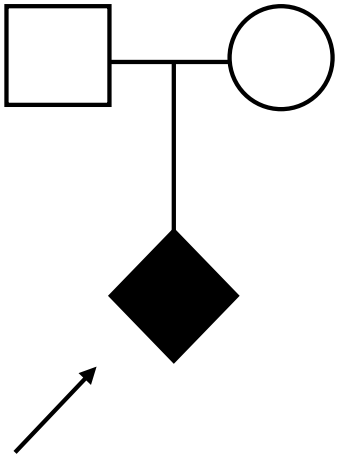
This is true for point mutations

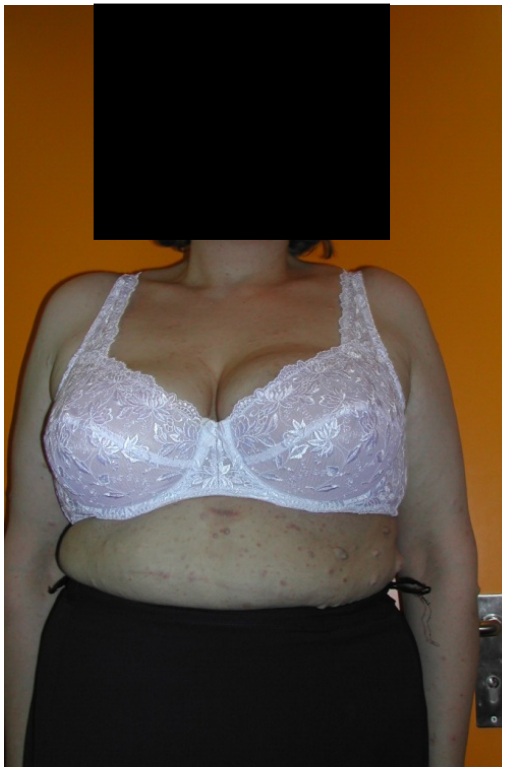
Large deletions are more frequent in female transmission

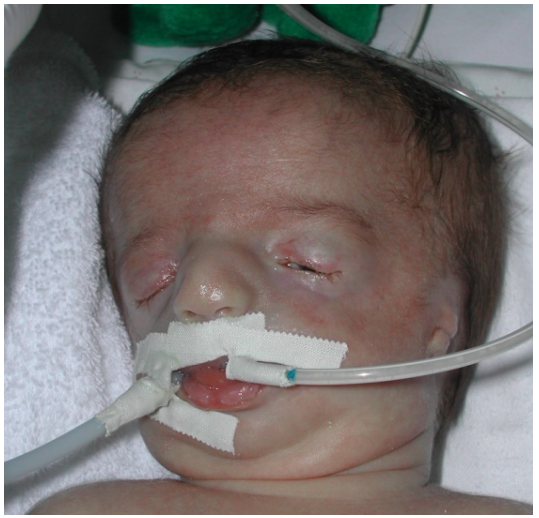
New mutations in AD disease

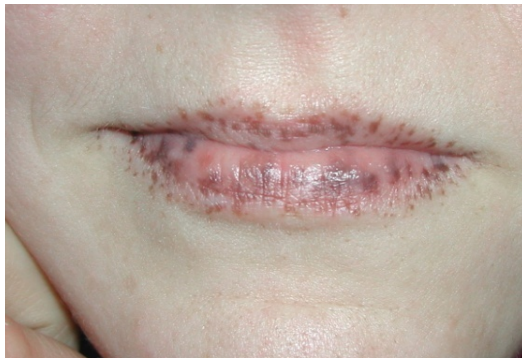
- f = fitness
  μ = mutation rate / generation
  q = allele frequency

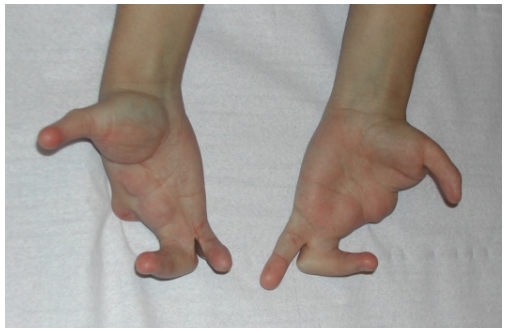
- μ = (1-f)q
  f = 0 → q = μ

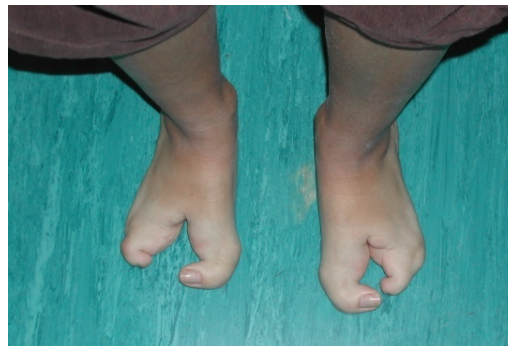




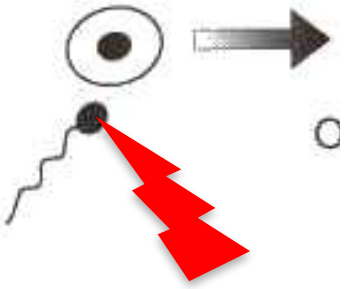








Neomutation in germline

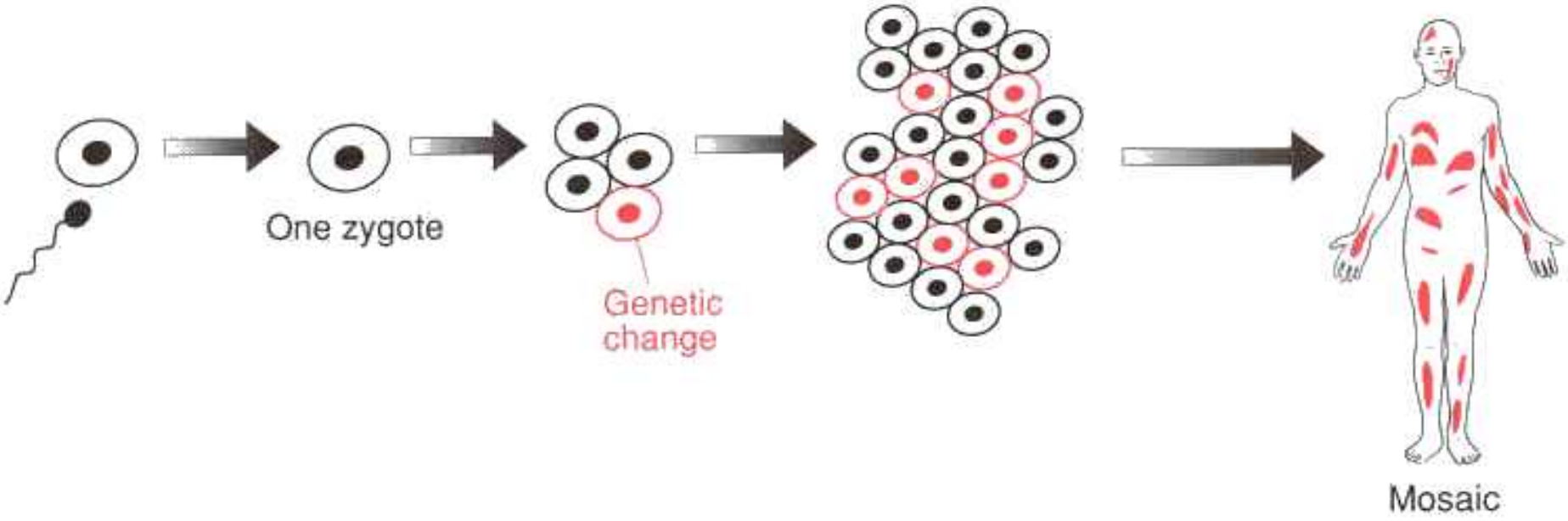


- Affects one allele
- In one gamete
- heterozygous
- May be lethal in utero
- Or asymptomatic
- Or in between: phenotype in heterozygous carrier subject

Typically

- 30-60 new point mut in newborn
- Of which 1 is in coding sequence

Mosaic

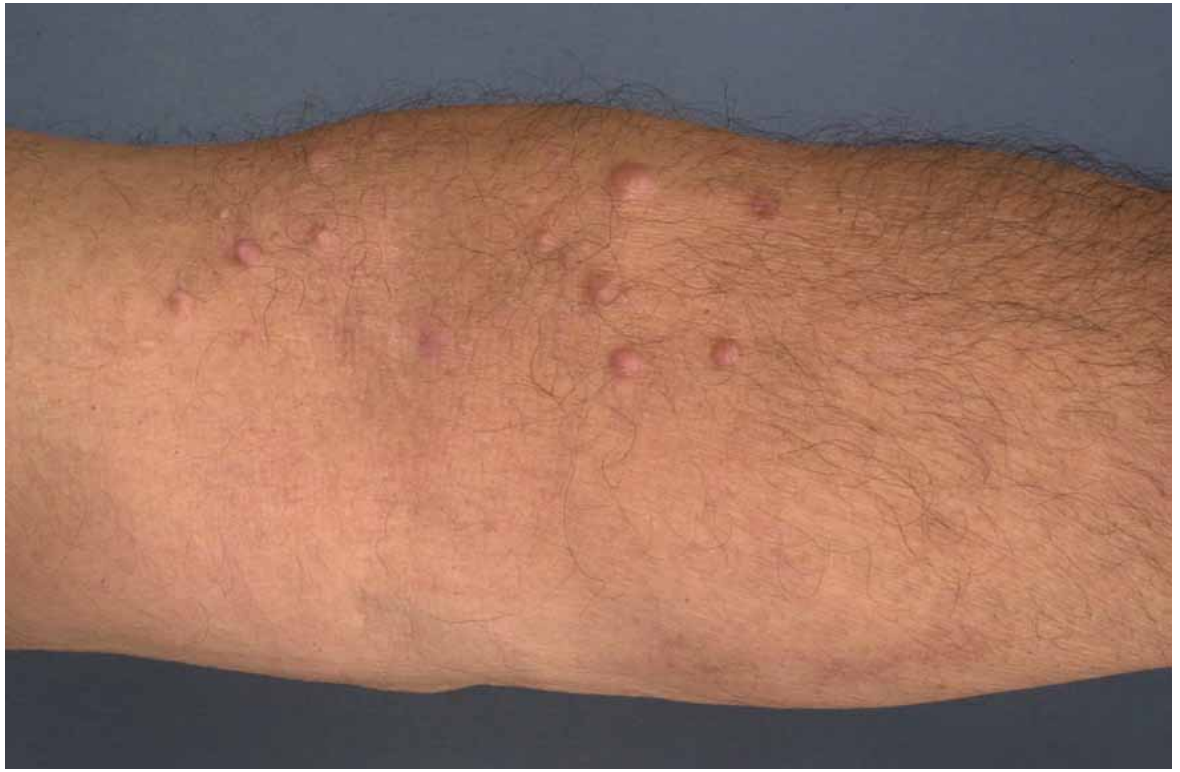


Neomutation in one postmitotic cell during development

Heterozygous

Phenotype if mutation produces dominant effect in mutated cells

Somatic mosaic: segmental NF1

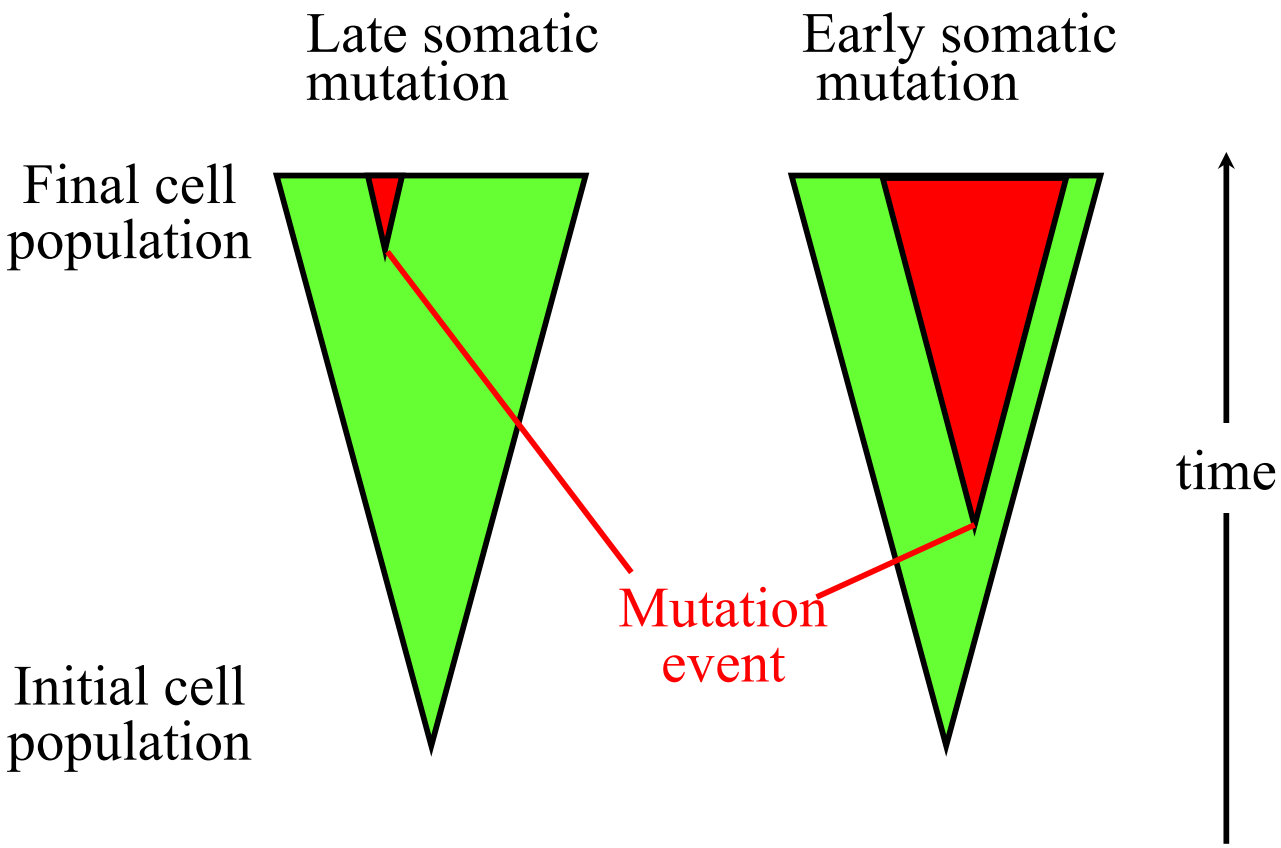


FC Victor Dermatology Online Journal 11 (4): 20

NF1 gene mutation, in population of patient's cells

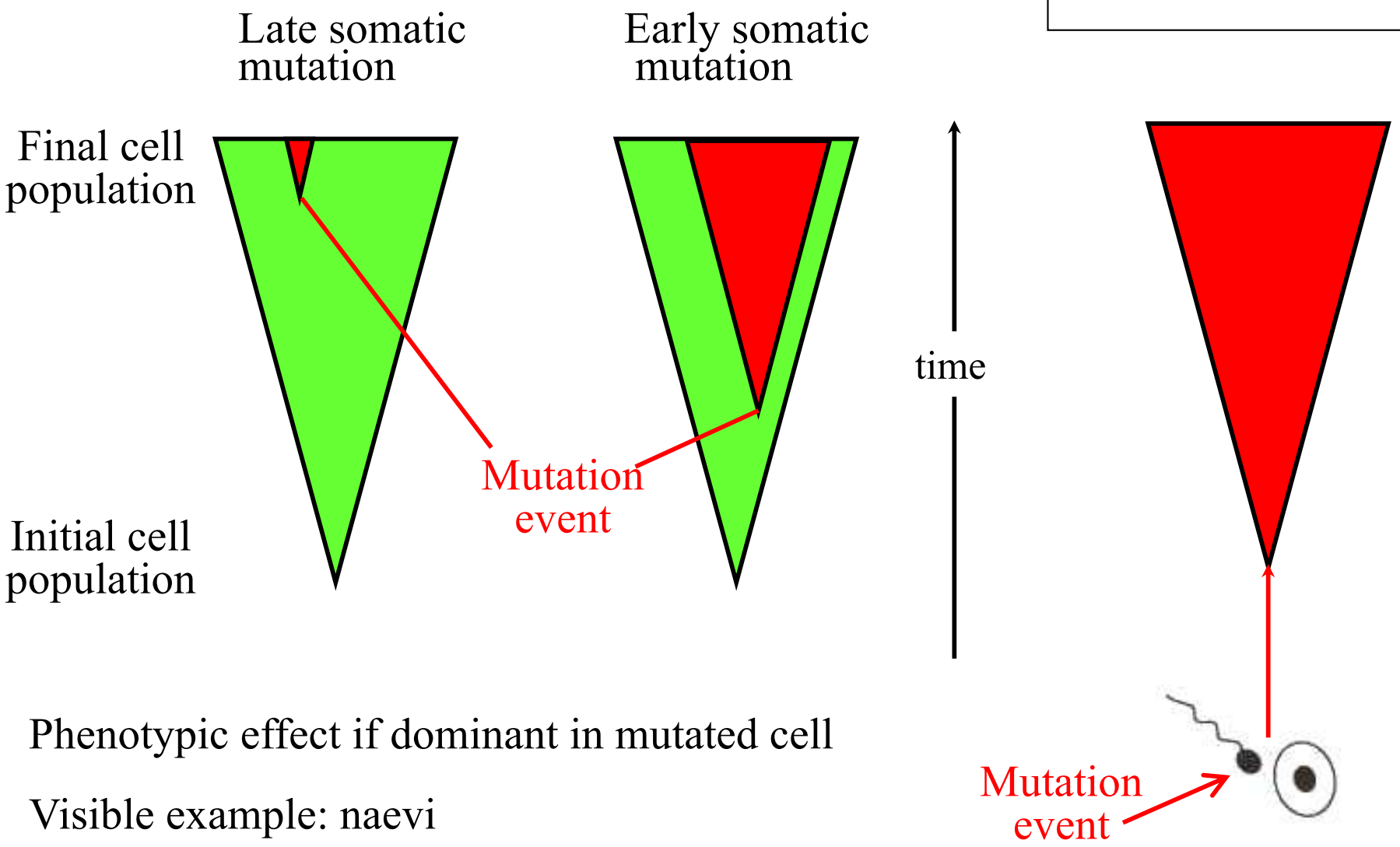
Sporadic

Somatic mutation in embryo => Mosaic



Somatic mutation in embryo => Mosaic

mutation in germline

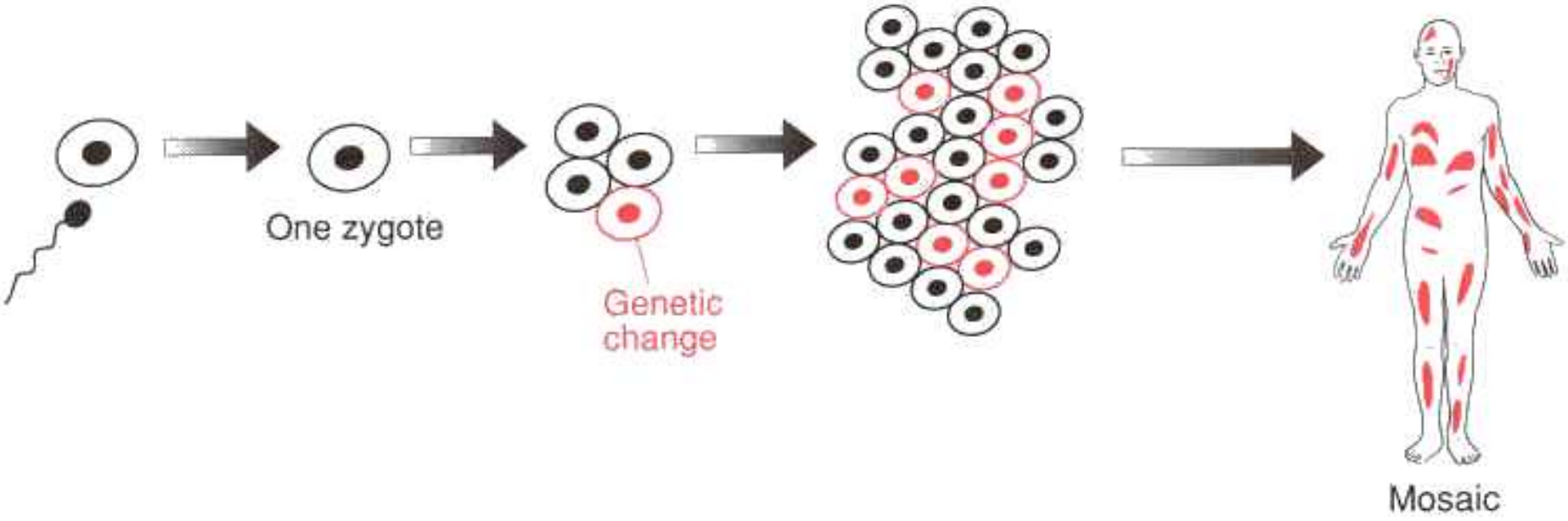


Phenotypic effect if dominant in mutated cell

Visible example: naevi

Proportion of mutated allele in blood: 0 – 50%

Mosaic



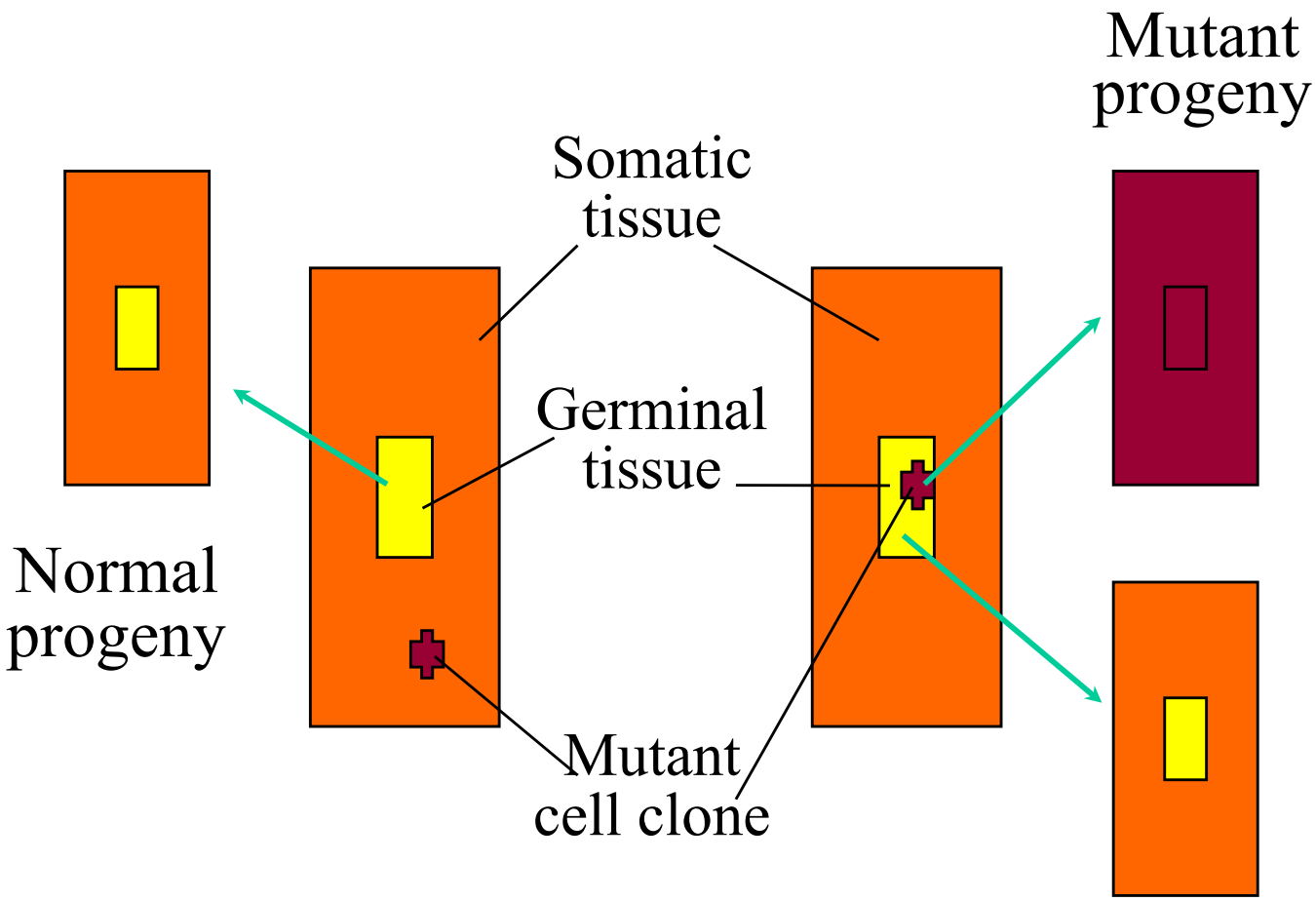
Neomutation in one postmitotic cell during development

Heterozygous

Phenotype if mutation produces dominant effect in mutated cells

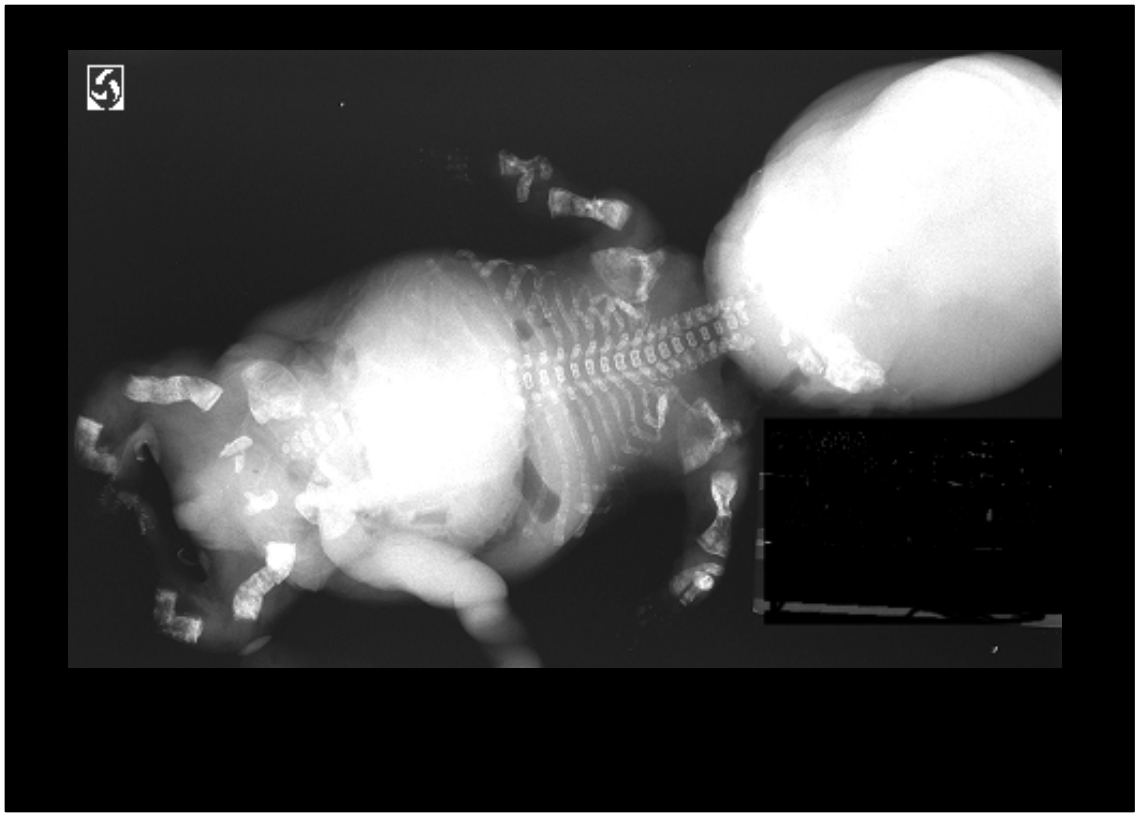
Proportion of mutation in individual = 0 – 50%

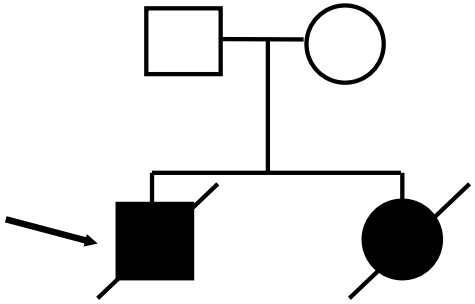
Somatic and/or **germ-line mosaic**



Germ-line mosaic in lethal OI

- Procollagen gene, hts mutation, lethal phenotype (fitness = 0)
- New mutations only
- 2 affected children here because germ-line mosaic in father (no mutation in bone cells)





OI

Germ-line mosaics

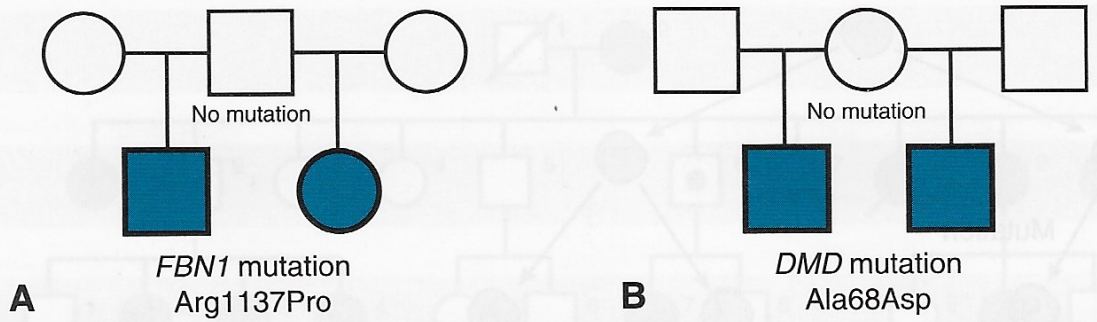


Figure 7-18 **Pedigrees demonstrating two affected siblings with the autosomal dominant disorder Marfan syndrome (Family A) and the X-linked condition Becker muscular dystrophy (Family B).** In Family A, the affected children have the same point mutation inherited from their father, who is unaffected and does not carry the mutation in DNA from examined somatic tissues. He must have been a mosaic for the *FBN1* mutation in his germline. In Family B, the affected children have the same point mutation inherited from their mother who is unaffected and does not carry the mutation in DNA from examined somatic tissues. She must have been a mosaic for the *DMD* mutation in her germline.

Parent-of-origin effect

See part about Genomic Imprinting

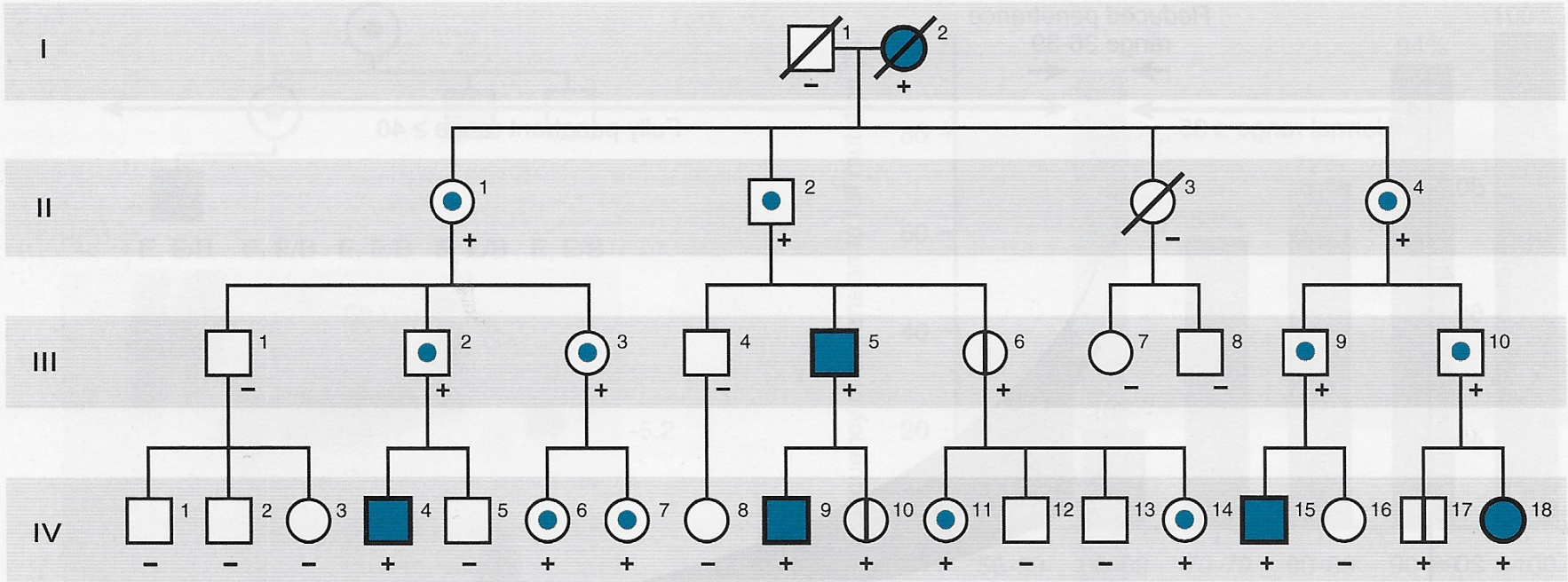
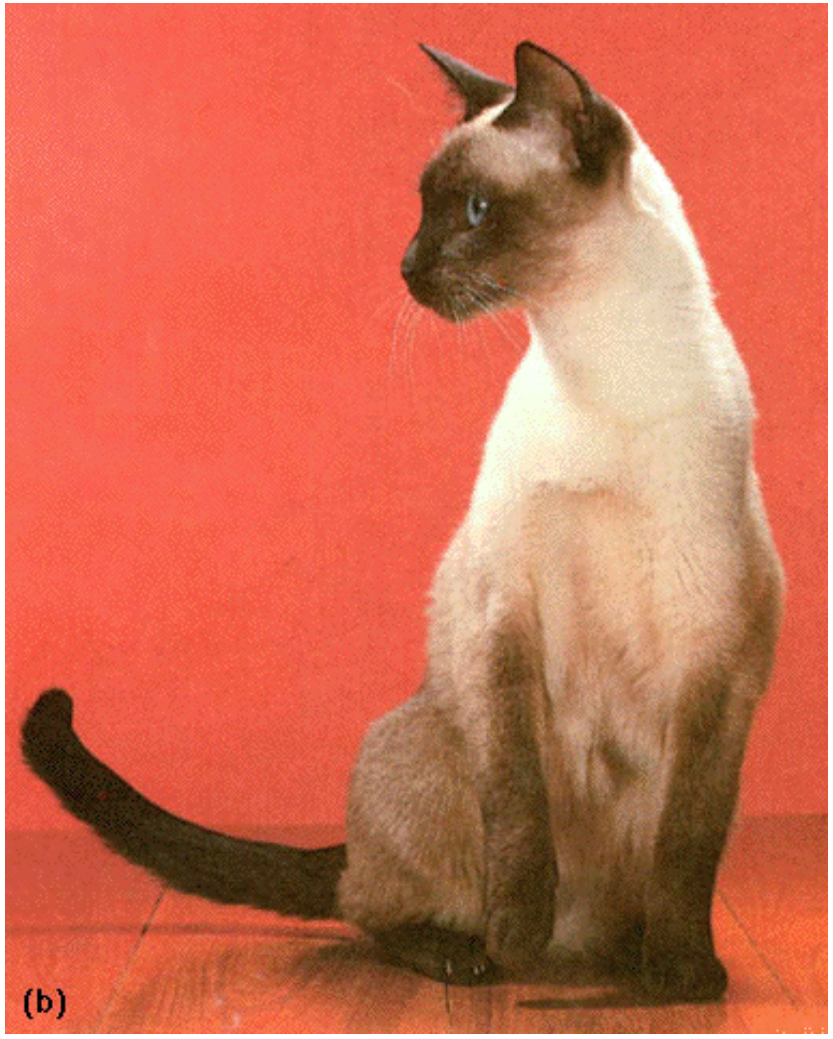


Figure 7-19 **Pedigree of a family with paraganglioma syndrome 1 caused by a mutation in the *SDHD* gene.** Individuals II-1, II-2, II-4, III-2, III-3, III-9, III-10, IV-6, IV-7, IV-11, and IV-14 each inherited the mutation from their mothers but are unaffected. However, when the males in this group pass on the mutation, those children can be affected. In addition to the imprinting, the family also demonstrates the effect of reduced and age-dependent penetrance in the children (III-6, IV-10, IV-17) of heterozygous fathers. The + and – symbols refer to the presence or absence of the *SDHD* mutation in this family.

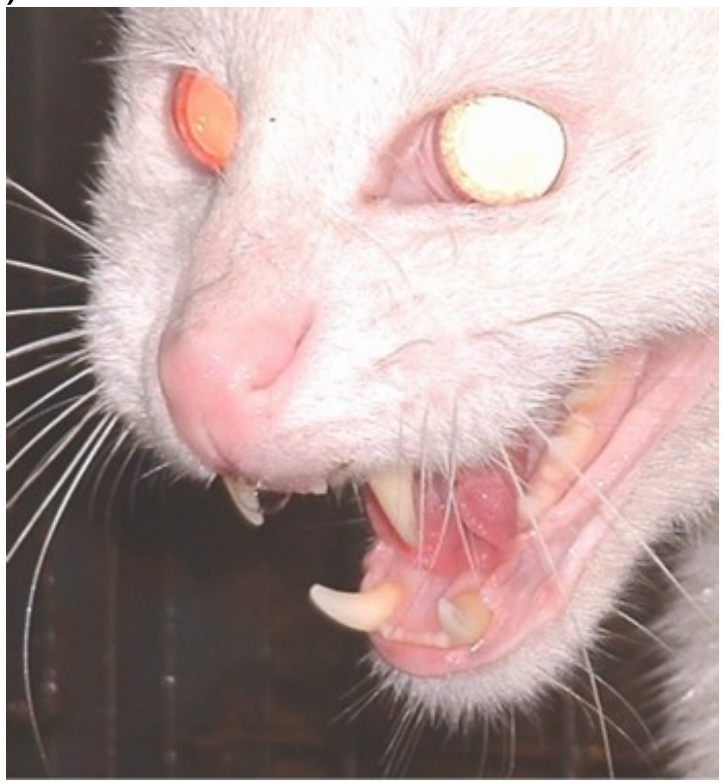
Gene interactions

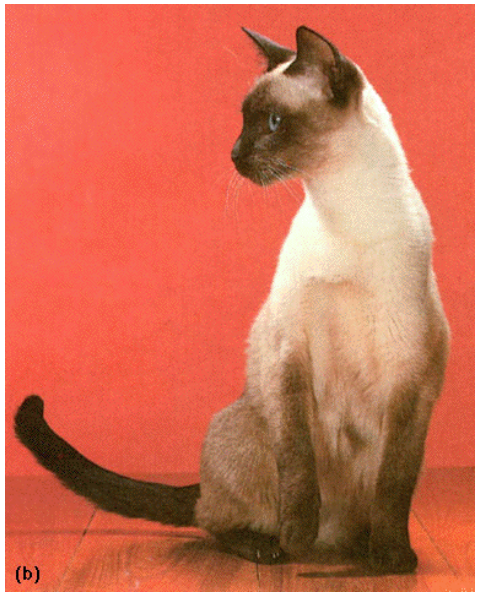


- Siamese cat
  Himalayan mouse
  Himalayan rabbit

  t° -sensitive allele in C gene of colour deposition. Recessive. C^h/C^h prevents colour deposition in warmer parts of the body

- Albino cat: No pigment produced (tyrosinase -/-)





EPISTASIS

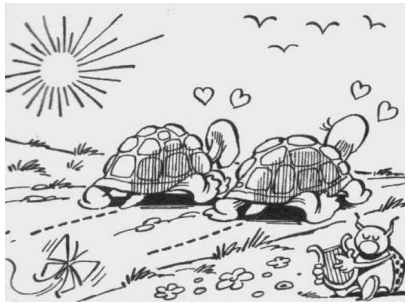
epistatic gene (Albino) masks the effect of another gene (Siamese)

Siamese albino

Non-Siamese albino

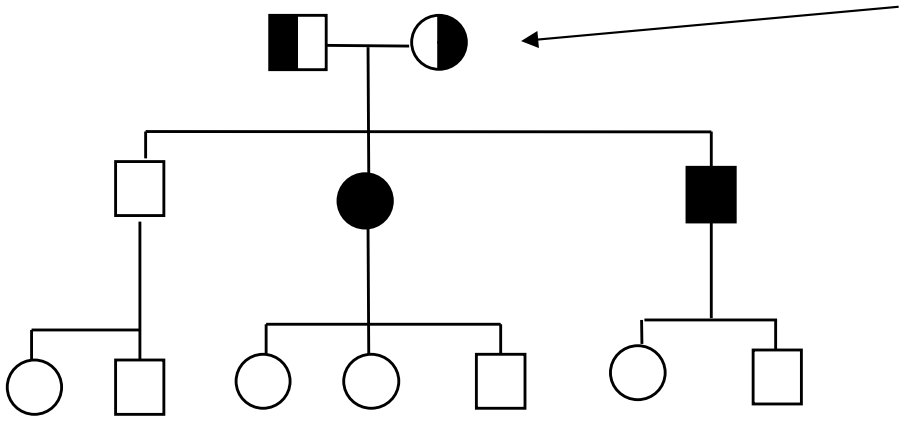
Patterns of single-gene inheritance

AUTOSOMAL RECESSIVE



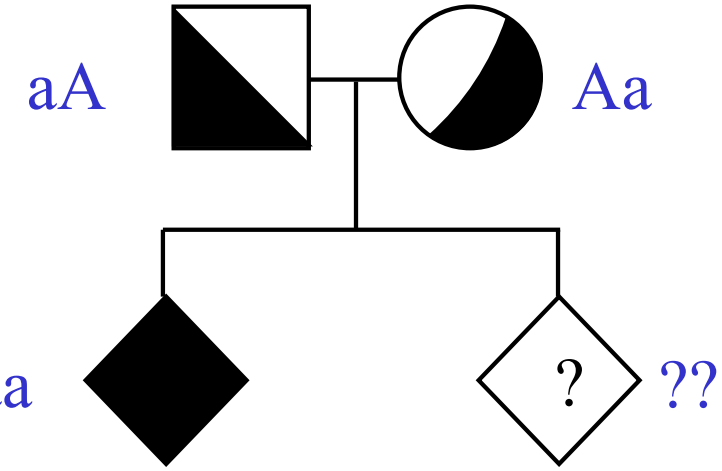
AR phenotype: horizontal transmission

Genotype: bi-allelic mutations, one gene, autosome

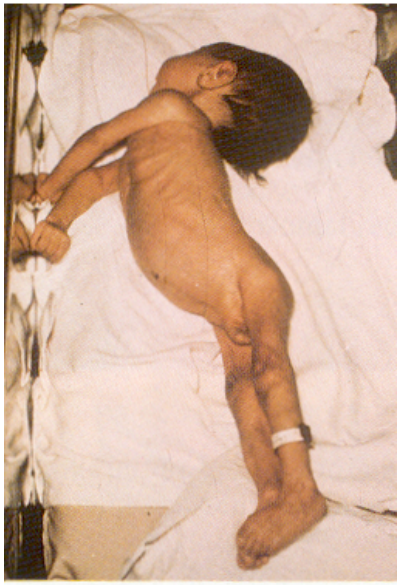


- Heterozygote, healthy carrier
- We all are healthy carriers of hts mutation which, when hms, cause severe disease
  - ~1 mutation compatible with post-natal life
  - 2-3 mutations causing miscarriage / non-implantation (?)

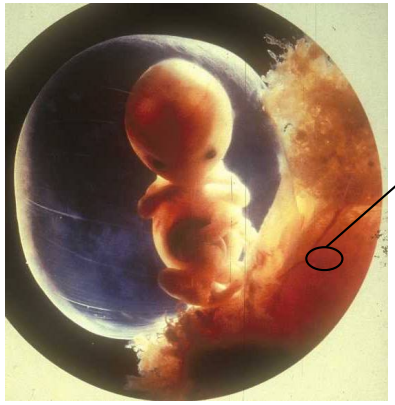
Krabbe disease (AR)



Affected child



New pregnancy
risk = 25 %



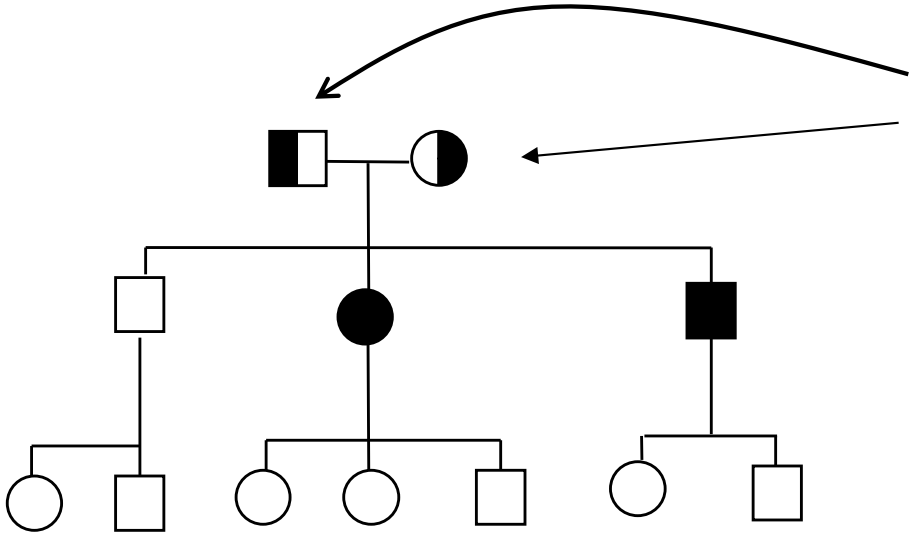
→ Prenatal diagnosis
(CVS, 10 wks.)

PUNNET'S SQUARE

Female gametes \ Male gametes	A	a
A	AA	Aa
a	aA	aa

AR phenotype: **bi-allelic mutations**,

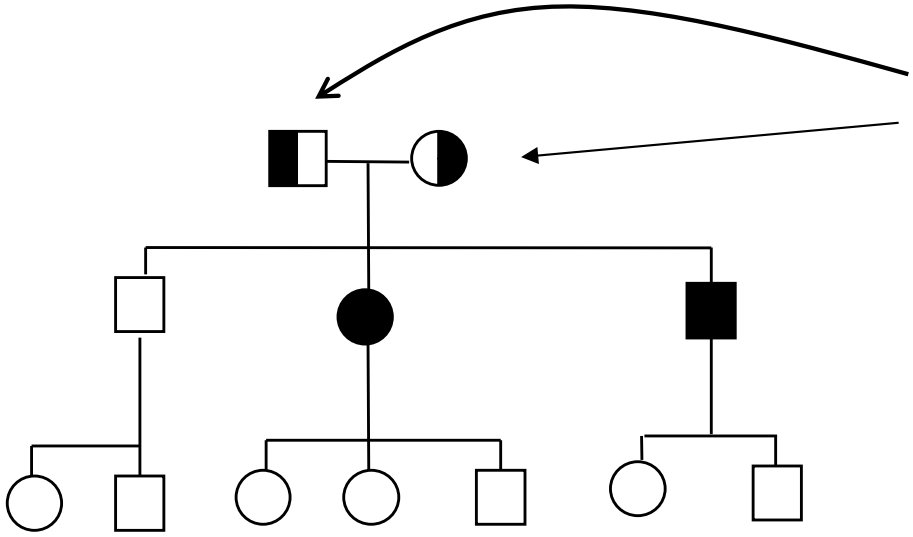
loss of function



- Same parental mutation
  => hmz
- Different parental mutations
  => compound htz

AR phenotype: **bi-allelic mutations**,

loss of function

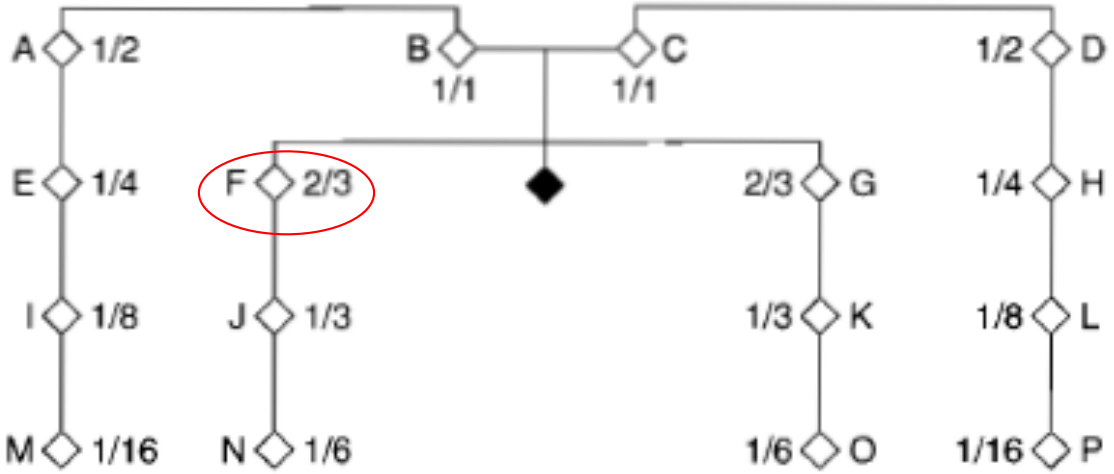


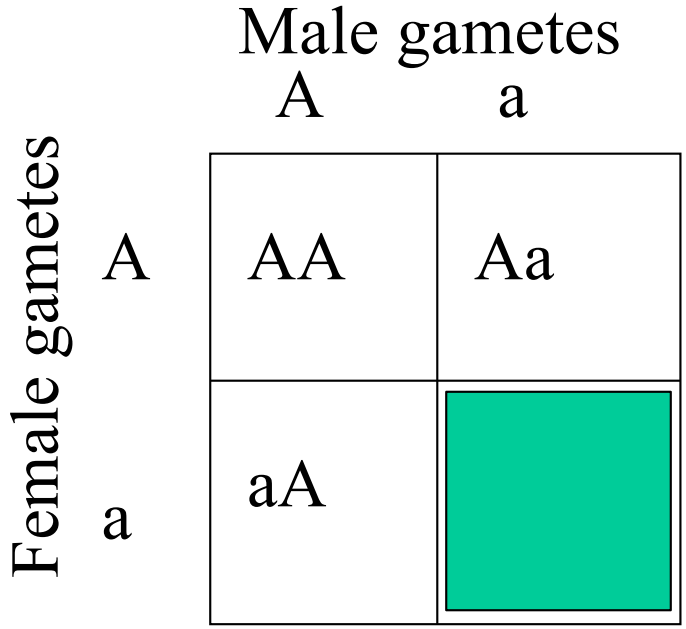
- Same parental mutation
  => hmz
- Different parental mutations
  => compound htz

Loss of function: variable

- Complete (severe mutation)
- Partial (mild mutation)
- Minimal (minor mutation, polymorphism)

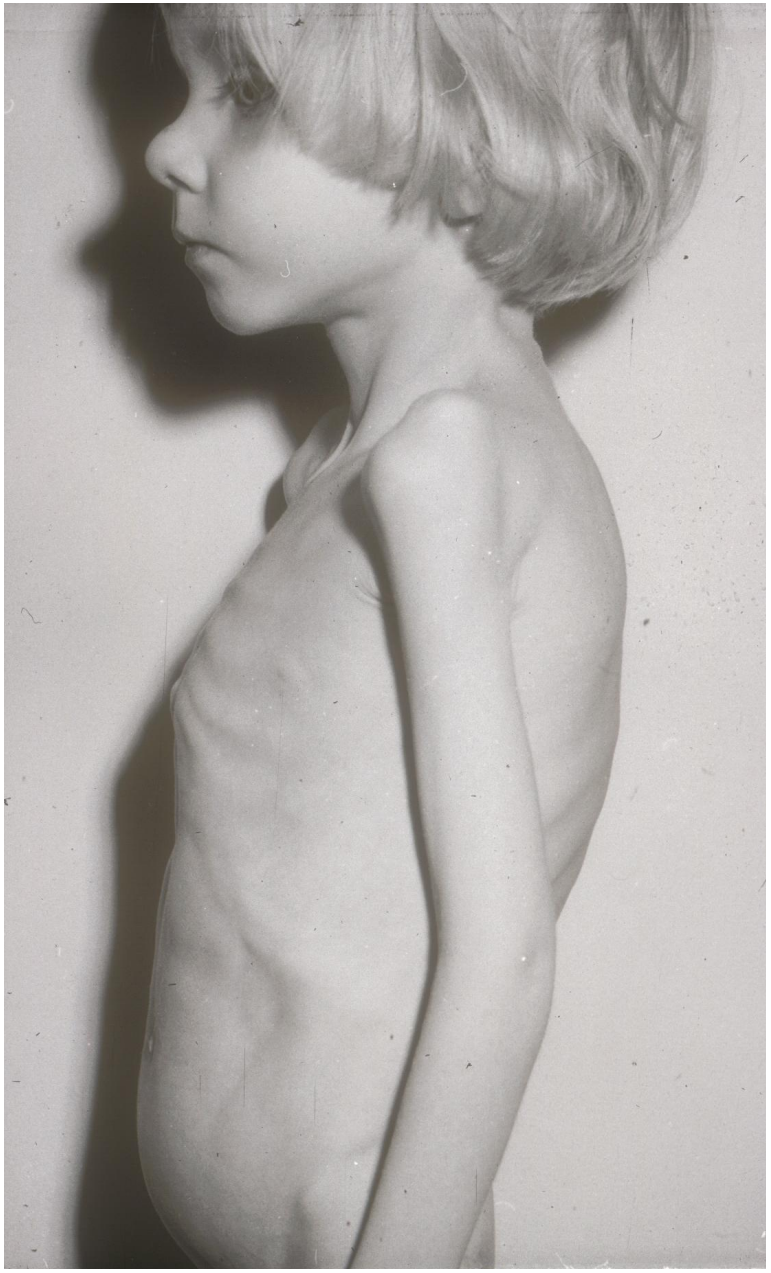
Probability of being a carrier, AR disease





PS Harper, Practical Genetic Counselling, 6th ed

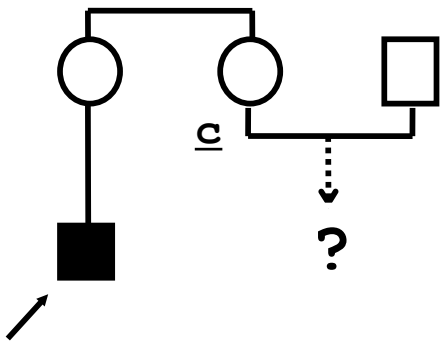
Cystic Fibrosis, CF



- Syndrome :
  - COPD
  - Pancreatic insufficiency
  - Na et Cl elevated in sweat
- Vas deferens agenesis (CBAVD)
- No MR

- 1/2500 children affected at birth
  1/25 healthy carriers

Genetic counselling in CF

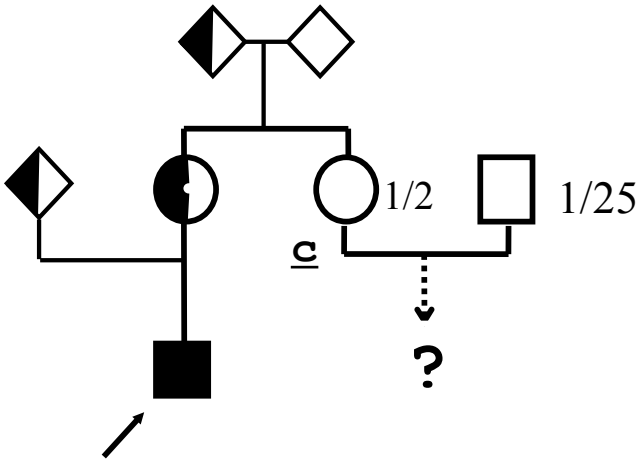


Cystic Fibrosis (Northern EU) 1/2500

- Carriers in general population (1/25)
- Risk = 1/2 x 1/25 x 1/4 = 1/200

.

Genetic counselling in CF

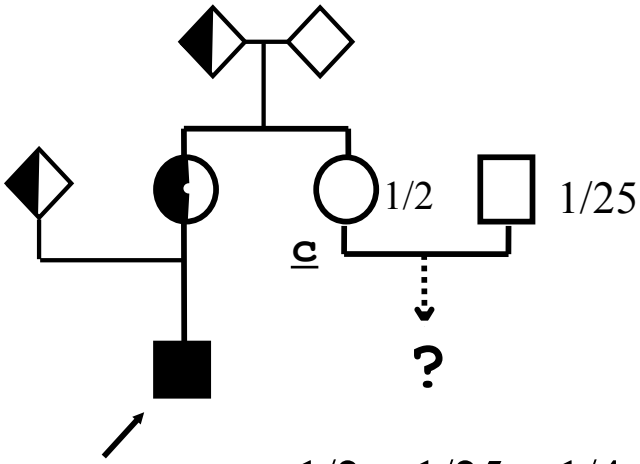


Cystic Fibrosis (Northern EU) 1/2500

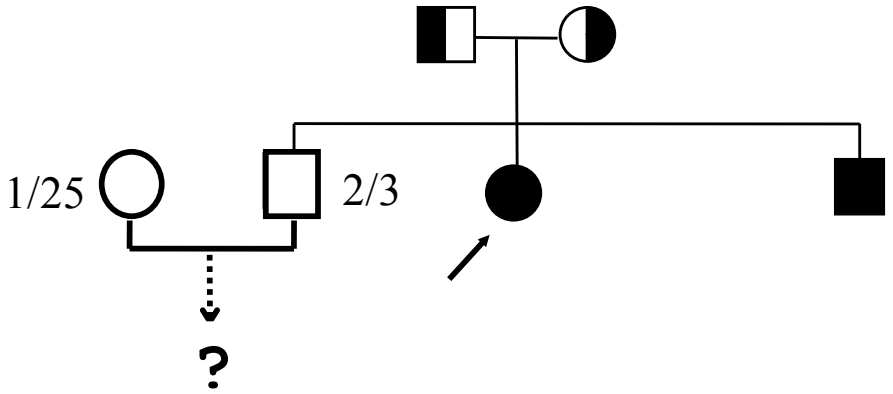
- Carriers in general population (1/25)
- Risk = 1/2 x 1/25 x 1/4 = 1/200

.

Genetic counselling in CF



1/2 x 1/25 x 1/4
= 1/200 = 0.05



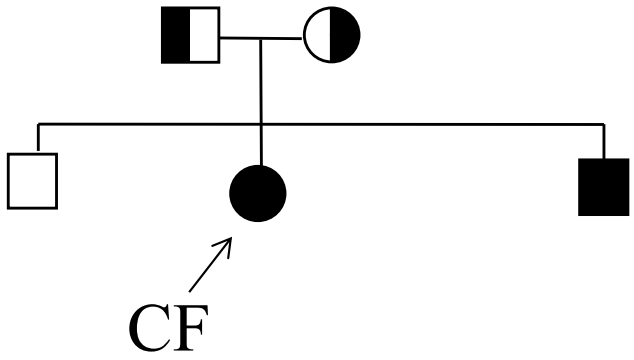
2/3 x 1/25 x 1/4
= 2/300 = 0.067

Cystic Fibrosis (Northern EU) 1/2500 affected at birth

– Carriers in general population 1/25

Genotype – phenotype correlation

- Pancreatic sufficiency is concordant in sibs
  - Depends on mutation

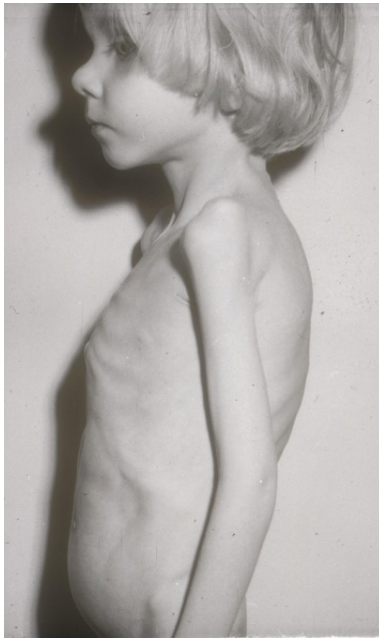


- Lung disease severity is less concordant
  - Depends on mutation and on environment (Pseudomonas infection, …)

Variable expressivity, AR disease (CF)

DF508 W1282X

DF508 / W1282X

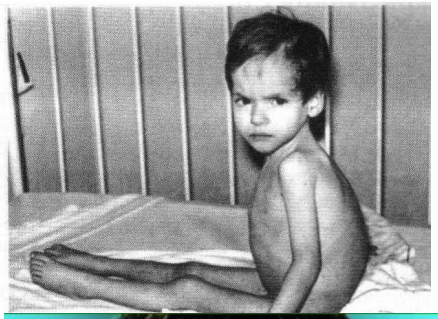


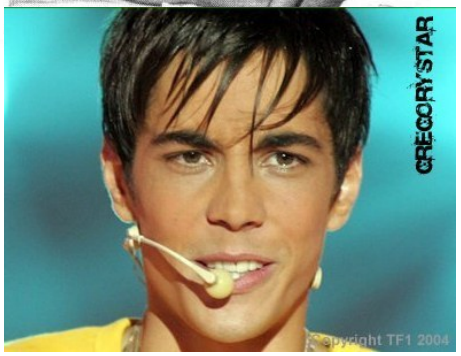
No sign in hts parents

Homoz severe mutation

DF508 DF508

DF508/DF508





Modifyer genes (TGFb1,…)

Severe + mild mutation

DF508 A445E

DF508/A445E

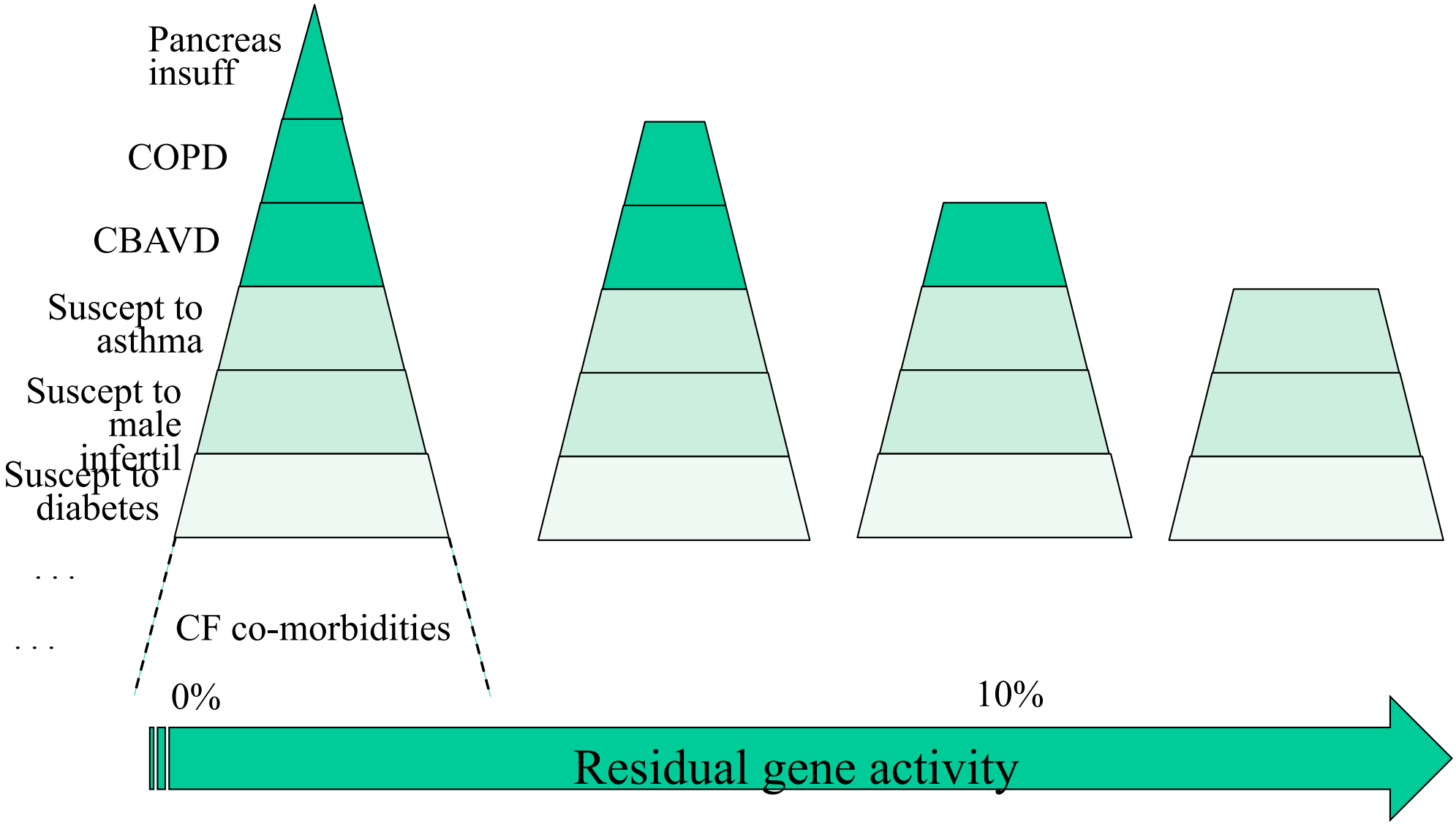
Pancreas sufficient
Lung variable

Severe + minor mutation

DF508 hypomorphic allele

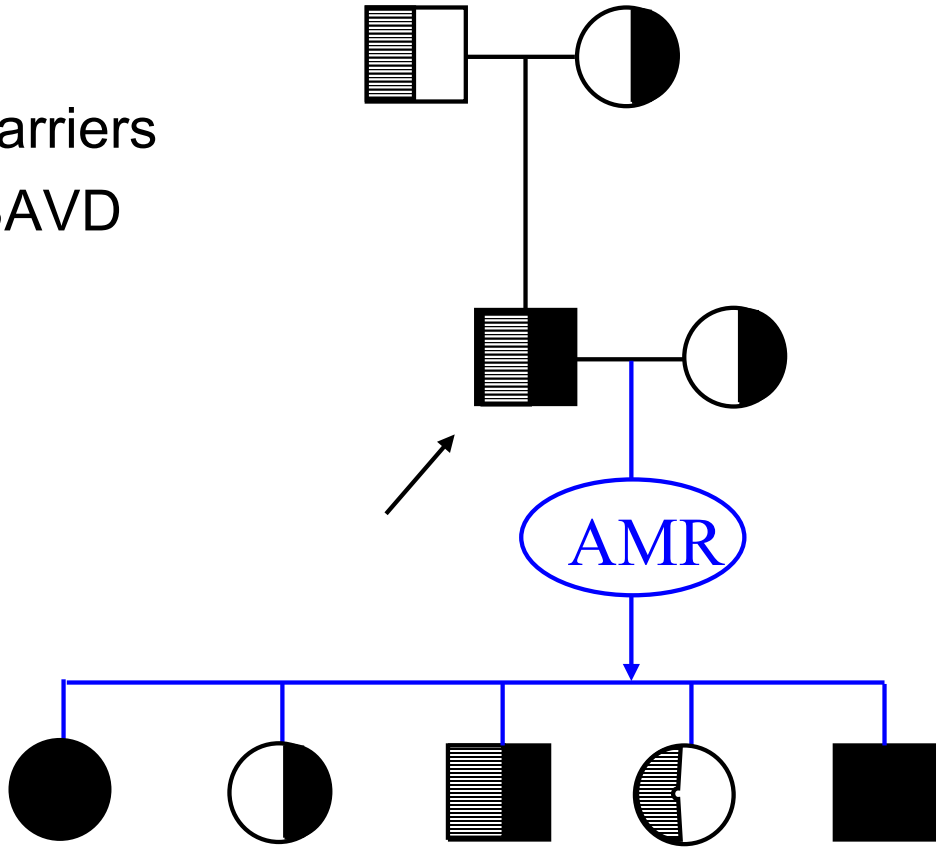
Healthy… or almost (CBAVD)

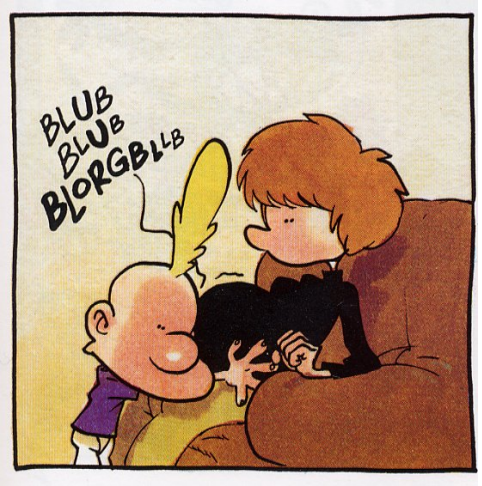
Increased gene activity removes phenotypic features



CBAVD, AMR and CF

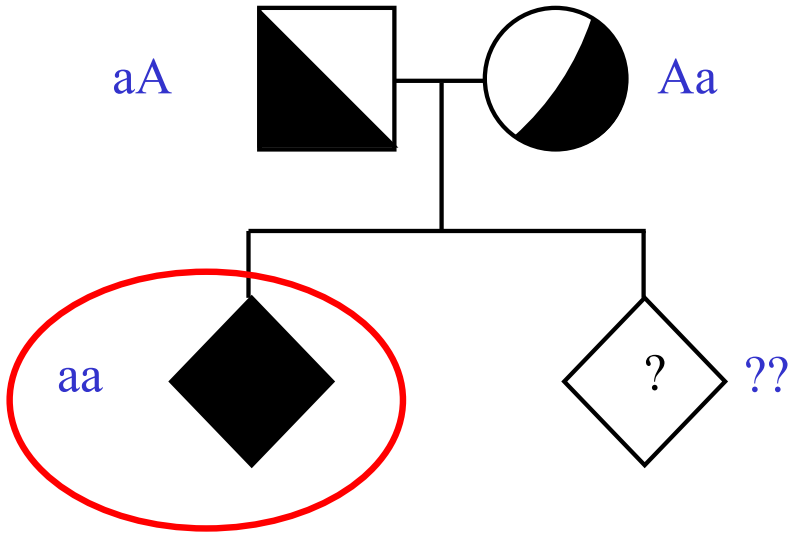
- Assisted Medical Reproduction for men with CBAVD
- 4% of partner women are CF carriers
- If carrier, offspring at risk of CBAVD and of CF



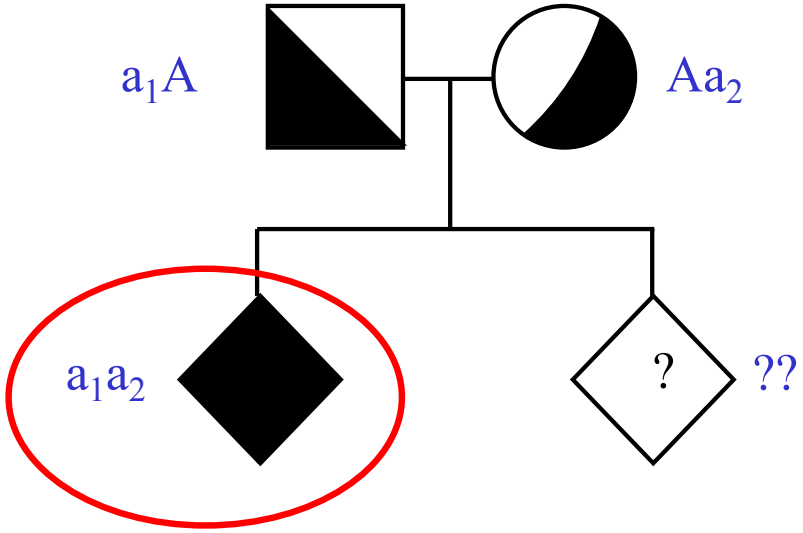


bi-allelic mutations

- homozygote



- compound heterozygote



Heterogeneity of mutations

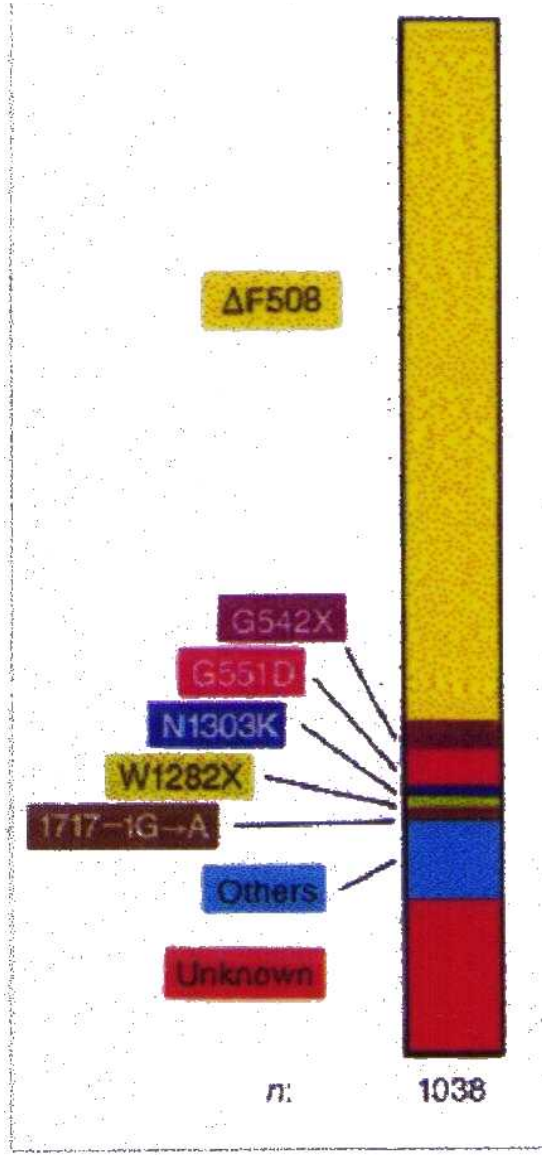
- Practical nomenclature A / a of alleles conceals a great diversity of DNA sequences : $a = a_1 + a_2 + a_3 + \ldots + a_n$

- Ex: CF (CFTR gene): mutations with complete loss of function
  - Many missense mutations G551D, N1303K
  - Many nonsense mutations W1282X, G542X
  - Many indels DF508
  - Many splicing mutations 1717-1 G>A
  - Many chromosomal mutations

All severe mutations = allele « a » in A,a nomenclature

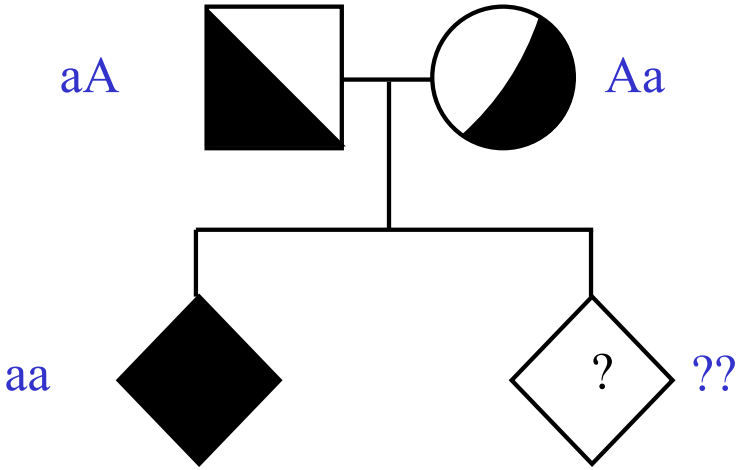
All are silent in htz, and cause CF when hmz or compound htz

Allelic heterogeneity

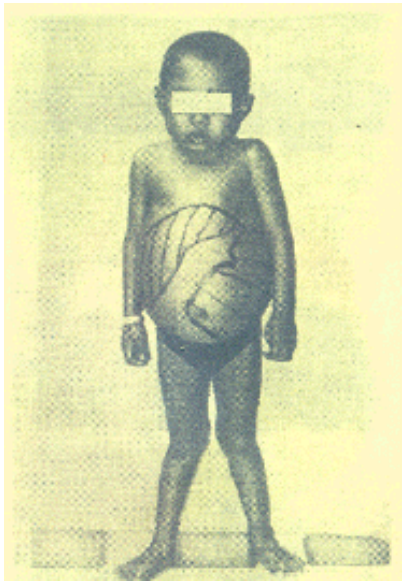


- CF: one gene, one locus
- Many mutations
- Ethnic prevalences

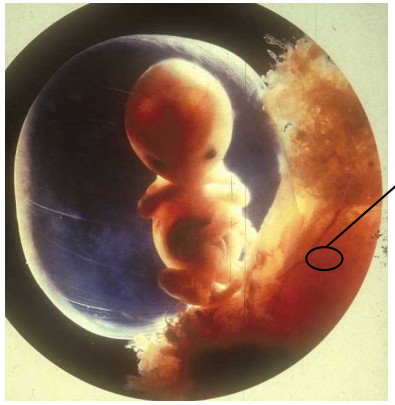
b-thalassemia (AR)



Affected child



New pregnancy
risk = 25 %

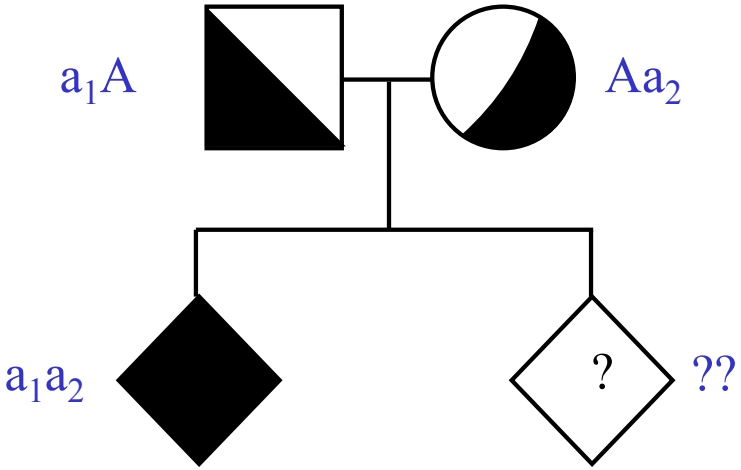


→ Prenatal diagnosis
(CVS, 10 wks.)

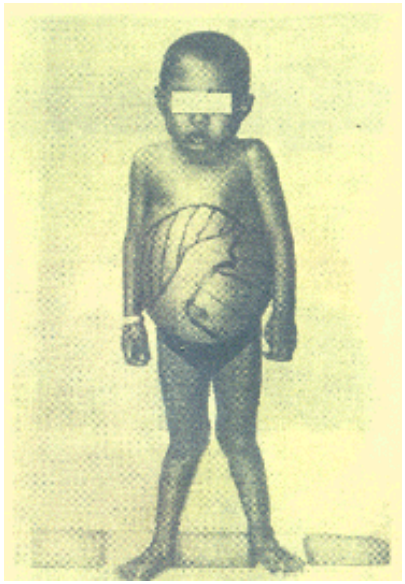
PUNNET'S SQUARE

Female gametes \ Male gametes	A	a
A	AA	Aa
a	aA	aa

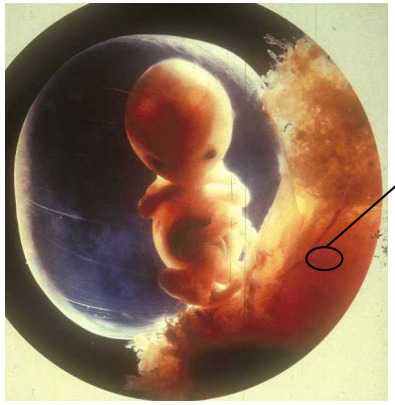
b-thalassemia (AR)



Affected child



New pregnancy
risk = 25 %



→ Prenatal diagnosis
(CVS, 10 wks.)

PUNNET'S SQUARE

Female gametes \ Male gametes	A	a_1
A	AA	Aa_1
a_2	a_2A	a_1a_2

AR transmission = approximation

- CF is truly recessive (?)
- HbS carriers have some signs if hypoxia
- Beta-thalassemia carriers have microcytosis (sometimes low Hb)
- Some carriers of Wilson disease have low Ceruloplasmin
  - Because their 2nd allele is hypomorphic?