Why are some AR mutations frequent ?

1. **FOUNDER EFFECT**
   - Founder event
   - Population bottleneck

2. **OVERDOMINANCE**
   htz has selective advantage

   ex: HbS and malaria

Both (1) and (2) tend to be population-specific

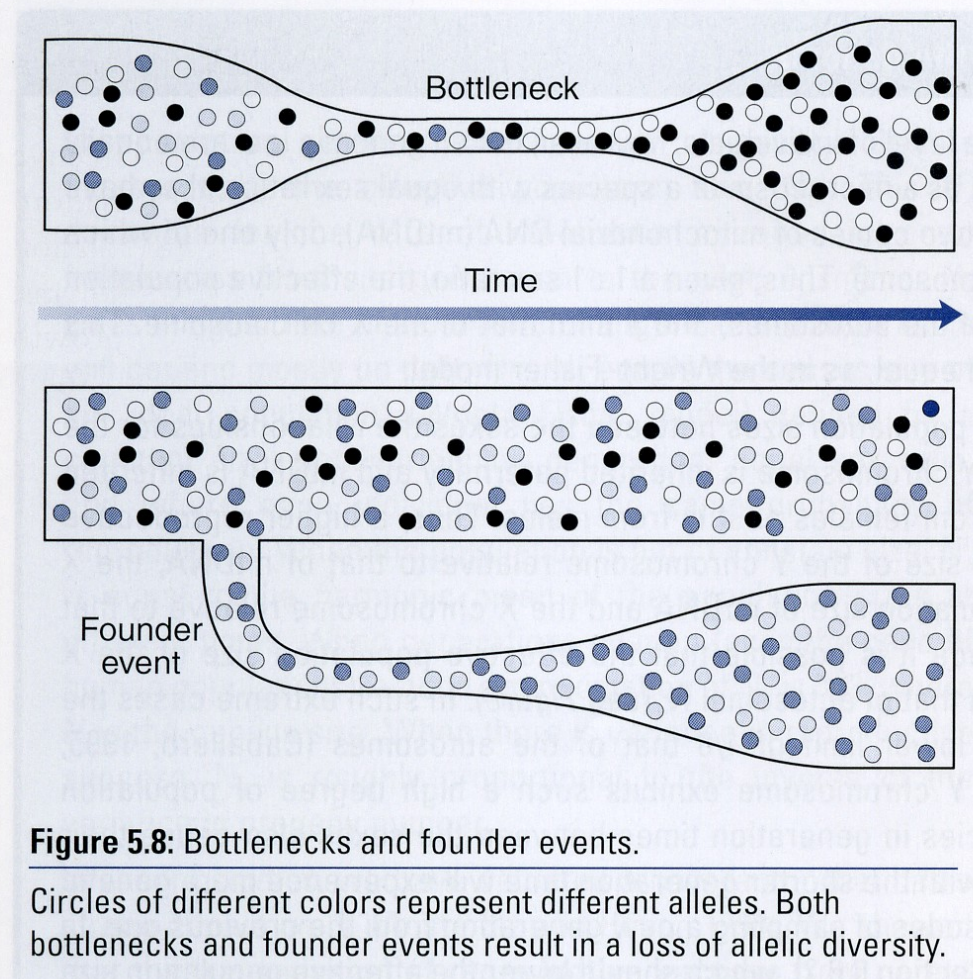


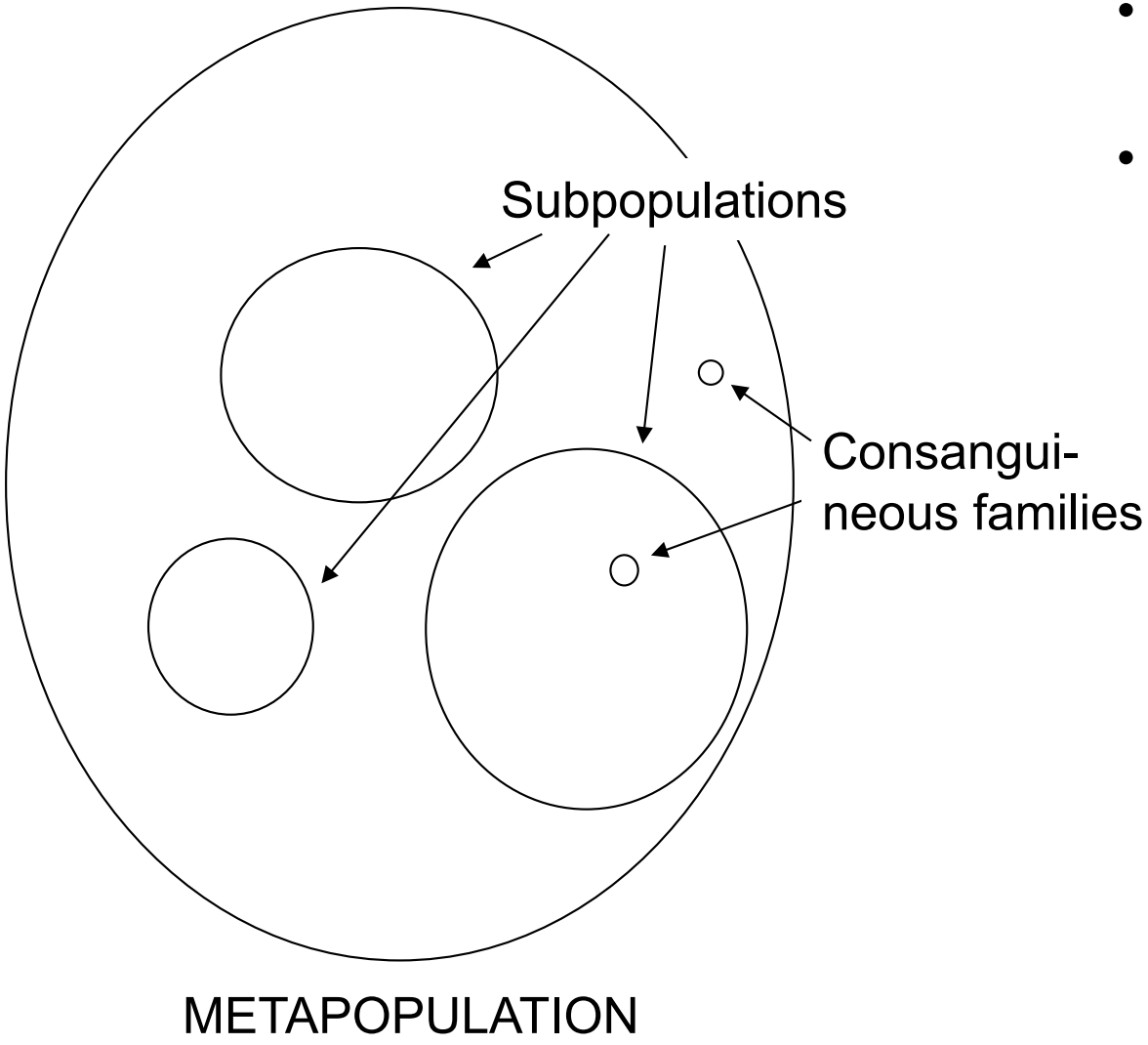
Figure 5.8: Bottlenecks and founder events.

Circles of different colors represent different alleles. Both bottlenecks and founder events result in a loss of allelic diversity.

AR phenotypes tend to be ethnic = population specific

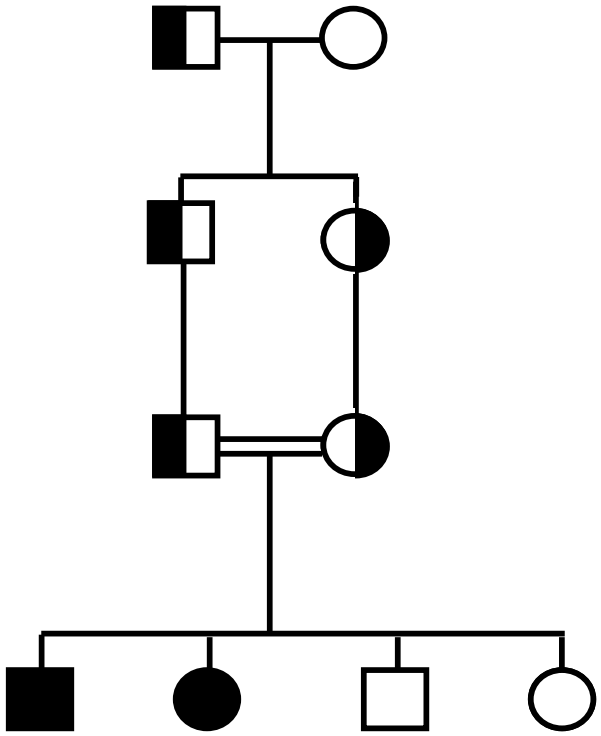
- Founder effects
- Population bottlenecks
- Overdominance < population-specific selection (HbS < malaria)

Subpopulations in Metapopulation



- Cross-fertile individuals (species)
- Subpopulations isolated by
  - Geography
  - Language
  - Religion
  - …
  - Inbreeding
  - Consanguinity

Consanguinity and AR disease



- One ancestral mutation
- Identical-by-descent (**IBD**) in first cousins
- Affected offspring
  = true homozygote
  = homozygote by descent
  = « **autozygote** »
- Rarer mutation <=> more cases due to consanguinity

Burden of consanguinity:
3% excess disease in offspring of 1st cousins

- We all carry one recessive disease [non embryonic-lethal].

- hence :

normal risk of handicap :	3%
additional risk from consanguinity :	3%
total risk:	6%

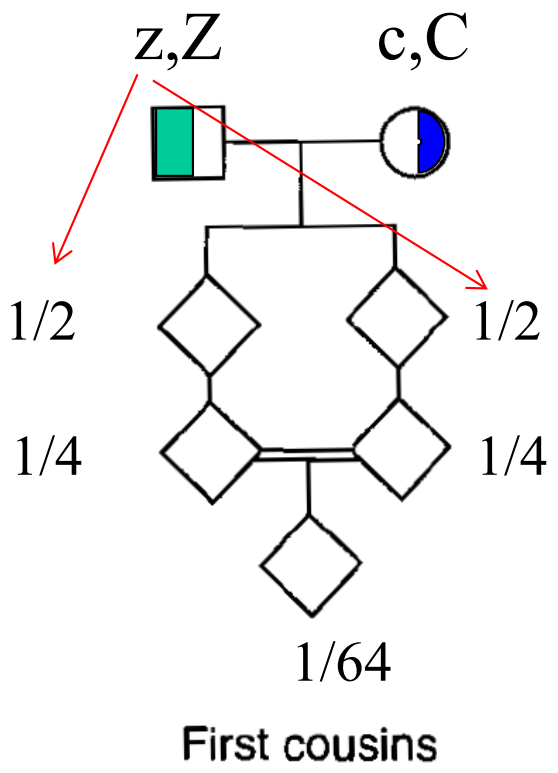
Homozygosity by descent in first cousins

- Assume everyone carries 1! severe recessive disease
  - Grandfather carries Zellweger disease
  - Grandmother carries CF

- Proba hmz (z,z) = 1/64

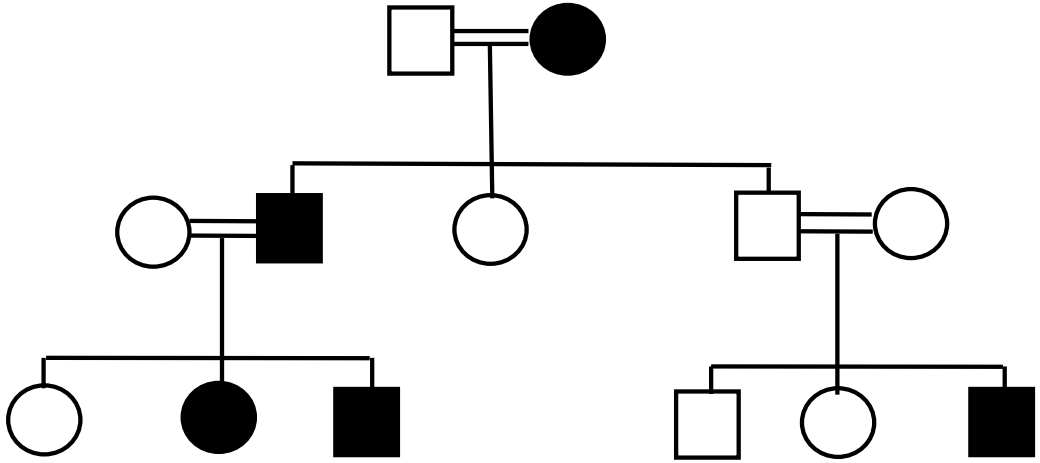
- Proba hmz (c,c) = 1/64

=> excess risk = 1/32
  - fits with observed 3%



First cousins

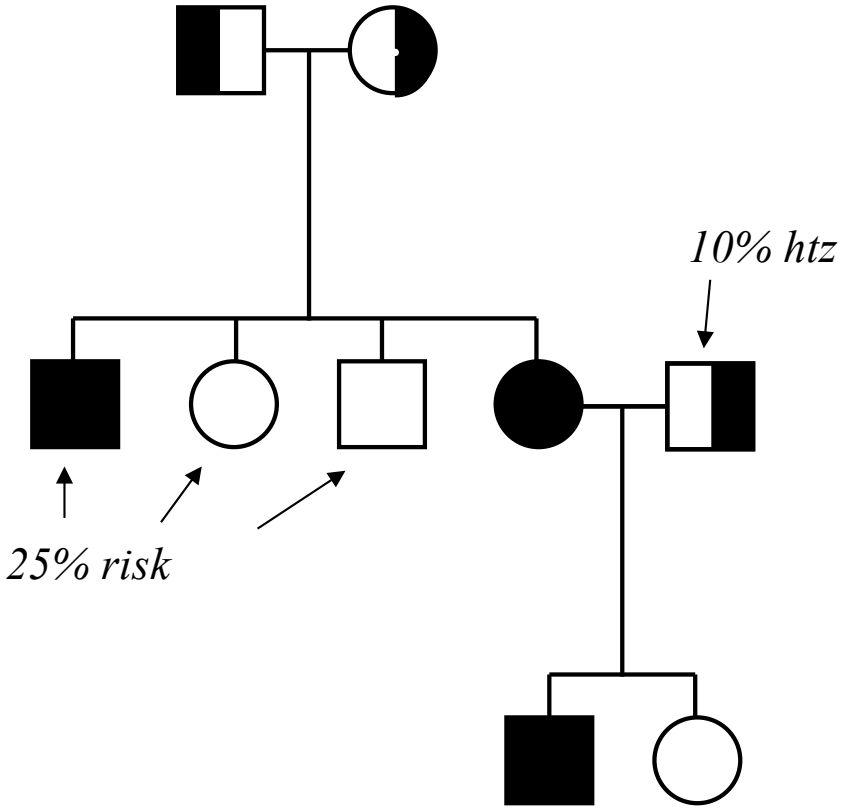
Pseudodominance in rare AR trait



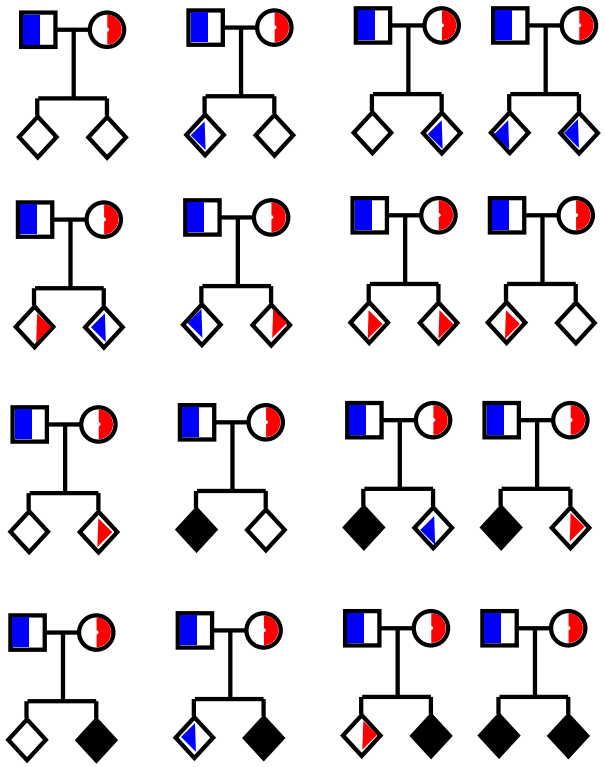
Multi-generation consanguinity => AR disease may seem AD.

Pseudodominance in frequent AR trait: hemochromatosis

- 10% (!) carriers in Western Europe
- Low penetrance of full-blown disease



Ascertainment bias



- AR disease, 2-children families
- 16 possible families, 32 children, 8 affected (8/32 = ¼)

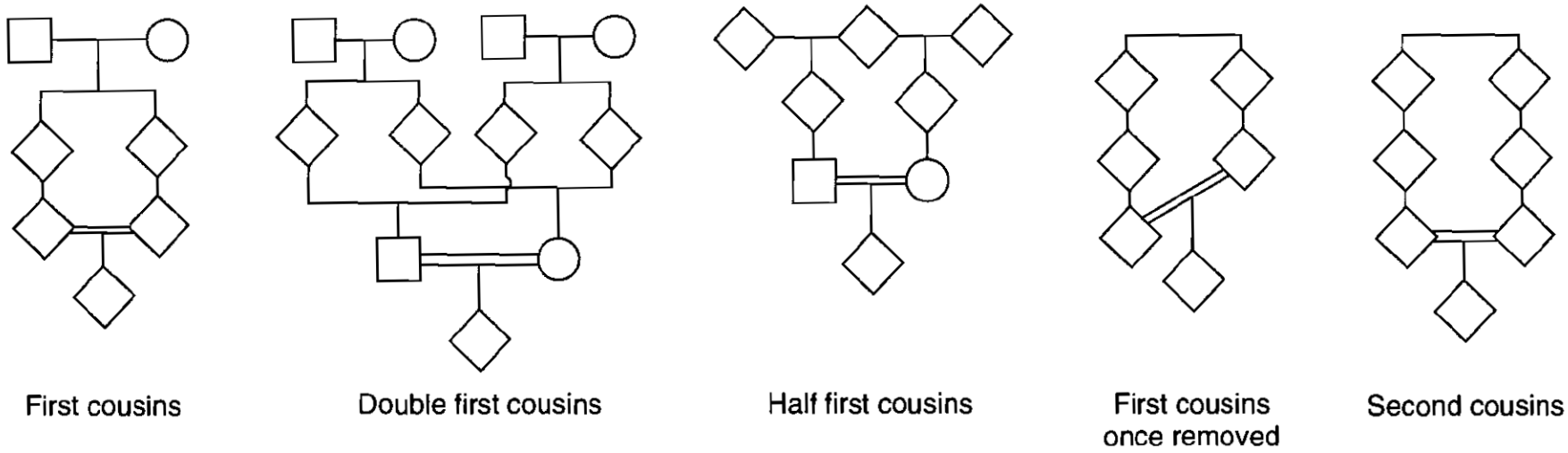
=> Now look only at families with one affected child:

- 7 families, 14 children, 8 affected (8/14)

=> Unaffected families

- Are the majority: 9/16
- Chance for no affected child = .75 x .75 = .56 = 9/16

Consanguinity
= having (relatively) close common ancestors

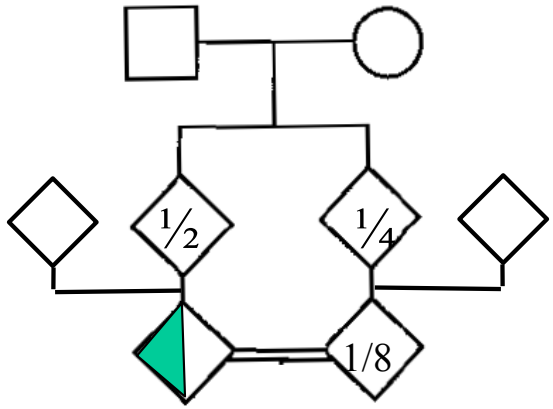


- ✓ « germans » = siblings = brothers and sisters
- ✓ First cousins = offspring of siblings (cousins issus de germains)

First cousins share 1/8 genome

FIRST COUSINS:

- Probability of finding green allele in consanguinity loop

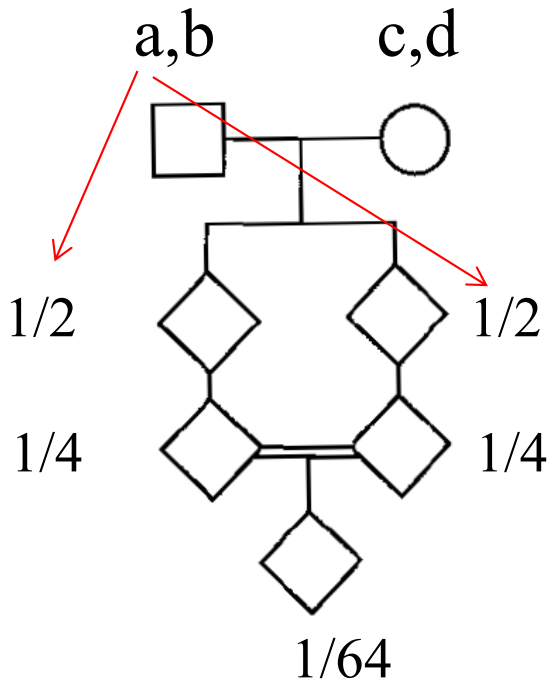


First cousins

F = coefficient of inbreeding
= p(hmz by descent)

FIRST COUSINS:

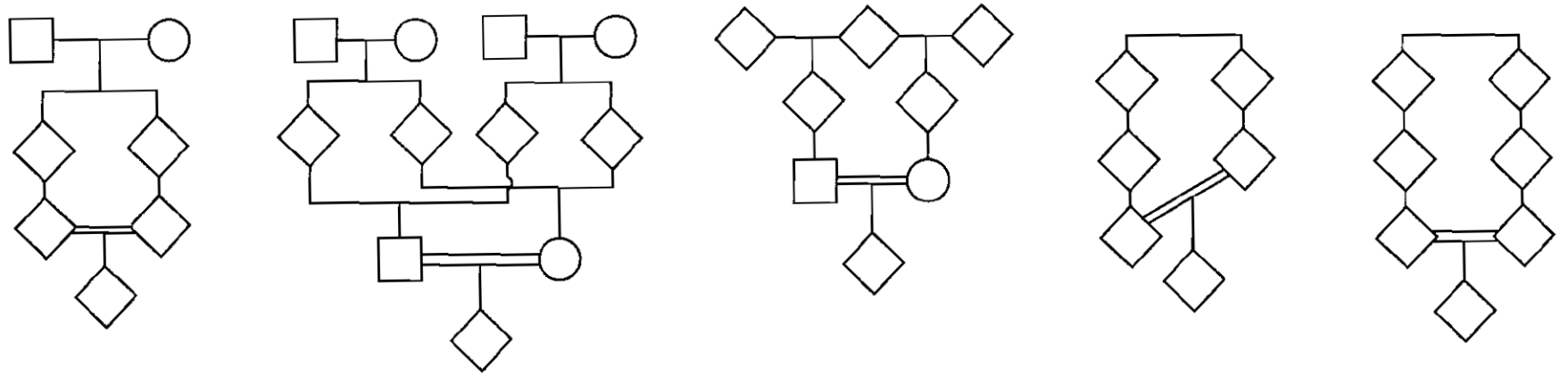
- 4 alleles in common ancestors
- Proba of *one* ancestral allele (a) hmz = 1/64
- Proba *any* of the 4 ancestral alleles hmz = 1/16 = F



First cousins

4 x 1/64 = **1/16**

Coefficient of inbreeding (F)

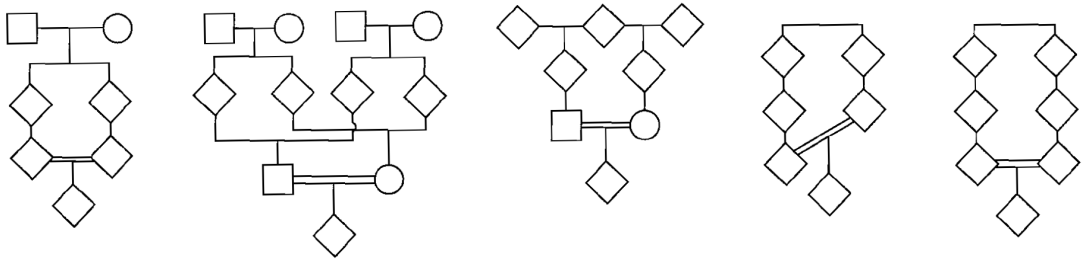


Type	Degree of Relationship	Proportion of Genes in Common	Coefficient of Inbreeding of Child (F)
Monozygotic twins	NA	1	NA
Parent-child	1st	1/2	1/4
Brother-sister (including dizygotic twins)	1st	1/2	1/4
Brother–half sister	2nd	1/4	1/8
Uncle-niece or aunt-nephew	2nd	1/4	1/8
Half uncle–niece	3rd	1/8	1/16
First cousins	3rd	1/8	1/16
Double first cousins	2nd	1/4	1/8
Half first cousins	4th	1/16	1/32
First cousins once removed	4th	1/16	1/32
Second cousins	5th	1/32	1/64

Coefficients of inbreeding for the offspring of a number of consanguineous matings. If a person is inbred through more than one line of descent, the separate coefficients are summed to find his or her total coefficient of inbreeding. NA, not applicable

PS Harper, Practical Genetic Counselling, 6th ed

Coefficient of inbreeding (F)



First cousins | Double first cousins | Half first cousins | First cousins once removed | Second cousins

Type	Degree of Relationship	Proportion of Genes in Common	Coefficient of Inbreeding of Child (F)
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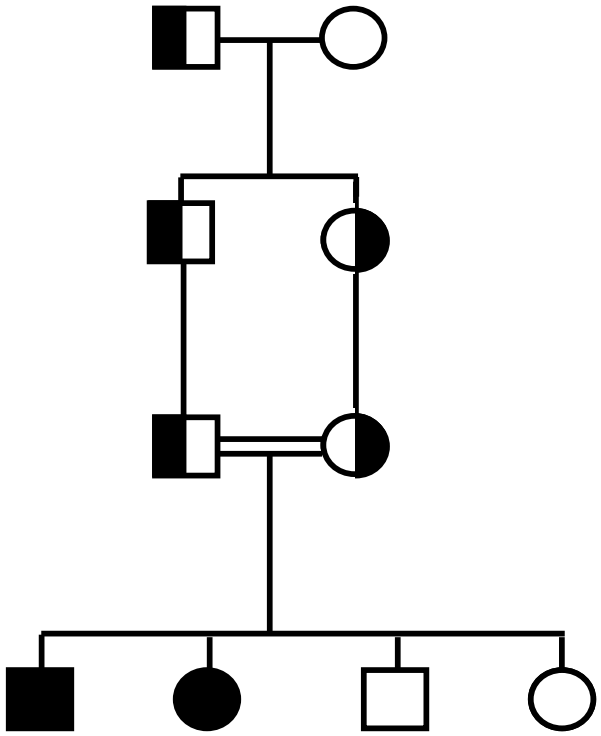
Second cousins	5th	1/32	1/64

Coefficients of inbreeding for the offspring of a number of consanguineous matings. If a person is inbred through more than one line of descent, the separate coefficients are summed to find his or her total coefficient of inbreeding. NA, not applicable

- F = 1/16 in offspring of first-cousin parents
- F = probability of homozygosity at any given locus
  true homozygosity, identity-by-descent, autozygosity

Consanguinity and AR disease



- One ancestral mutation
- Identical-by-descent (IBD) in first cousins
- Affected offspring = true homozygote = « autozygote »
- Rarer mutation <=> more cases due to consanguinity

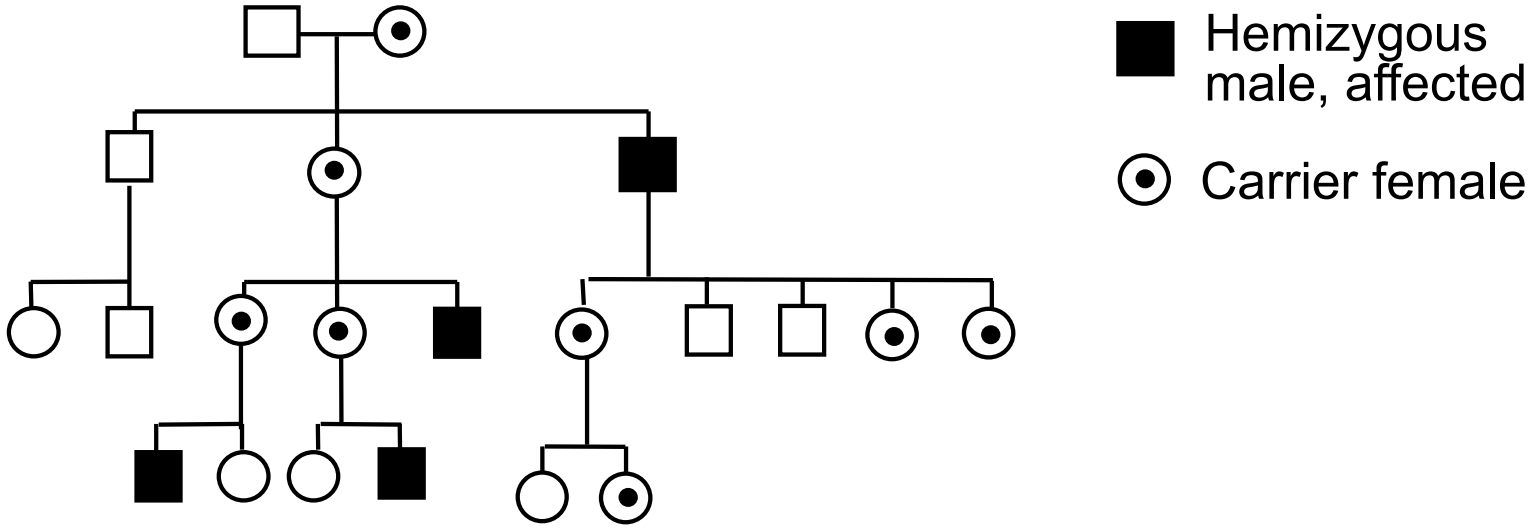
q << F => autozygosity likely to cause the disease

Patterns of single-gene inheritance

X-LINKED DISORDERS

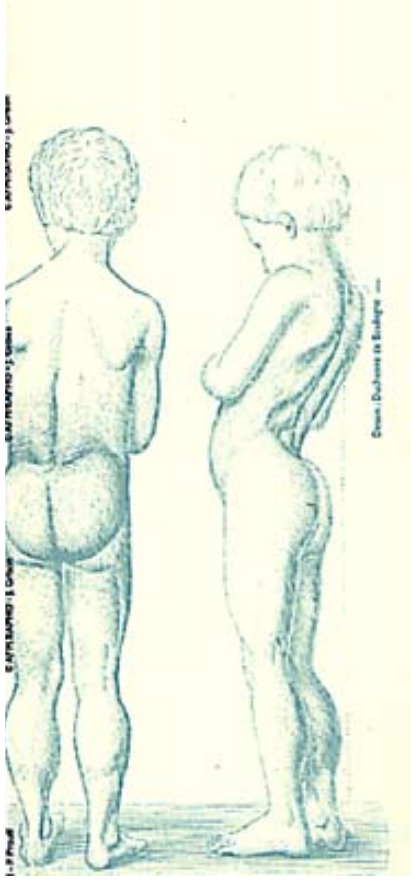
X-linked recessive phenotype: oblique transmission

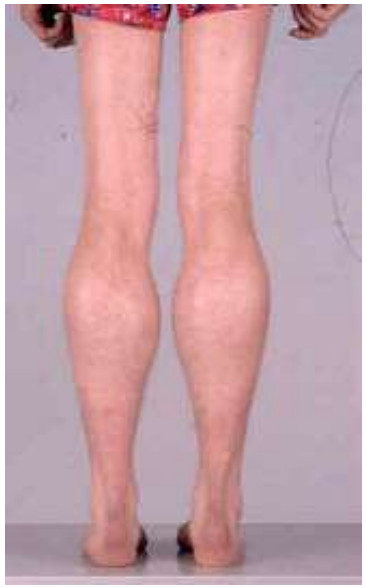
genotype: hemizygous mutation in male



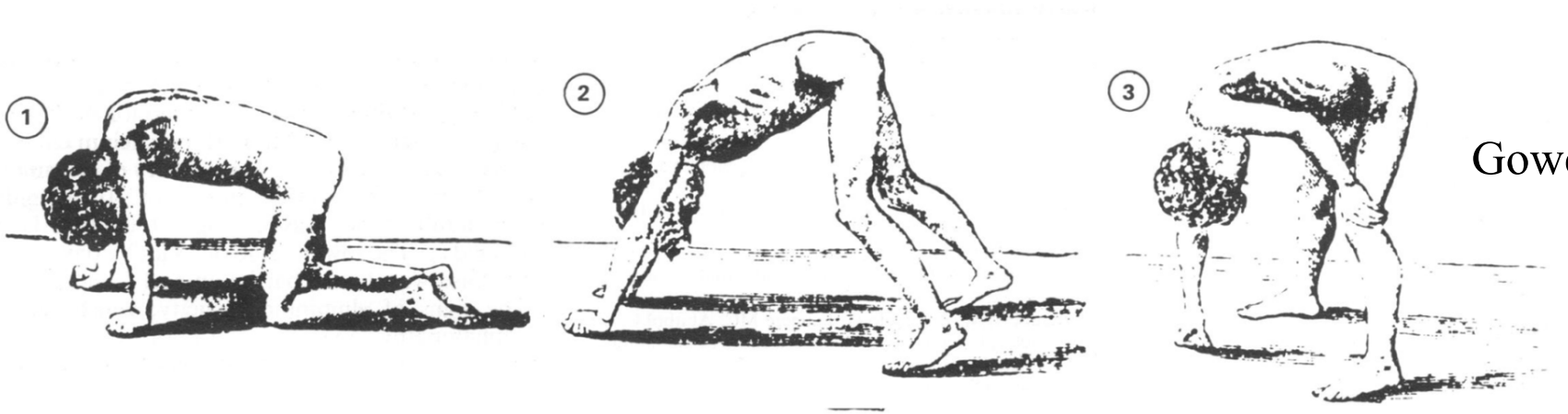
- Ex: hemophilia A, B; Duchenne Muscular Dystrophy (DMD)...
- All daughters of affected males are carriers .
- All sons of affected male are unaffected (Y chromosome).
- No male-to-male transmission.

Duchenne Muscular Dystrophy (DMD)



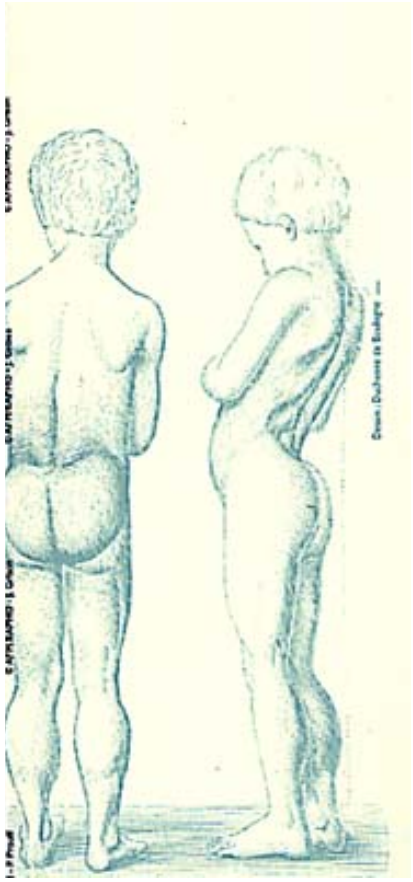


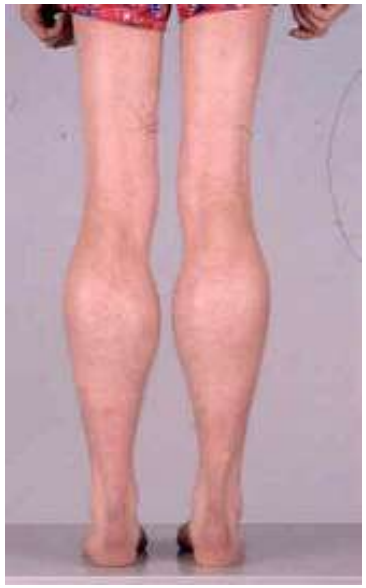
- 1/10,000 birth
- Boys, almost all patients
- Progressive decay of muscular fibres

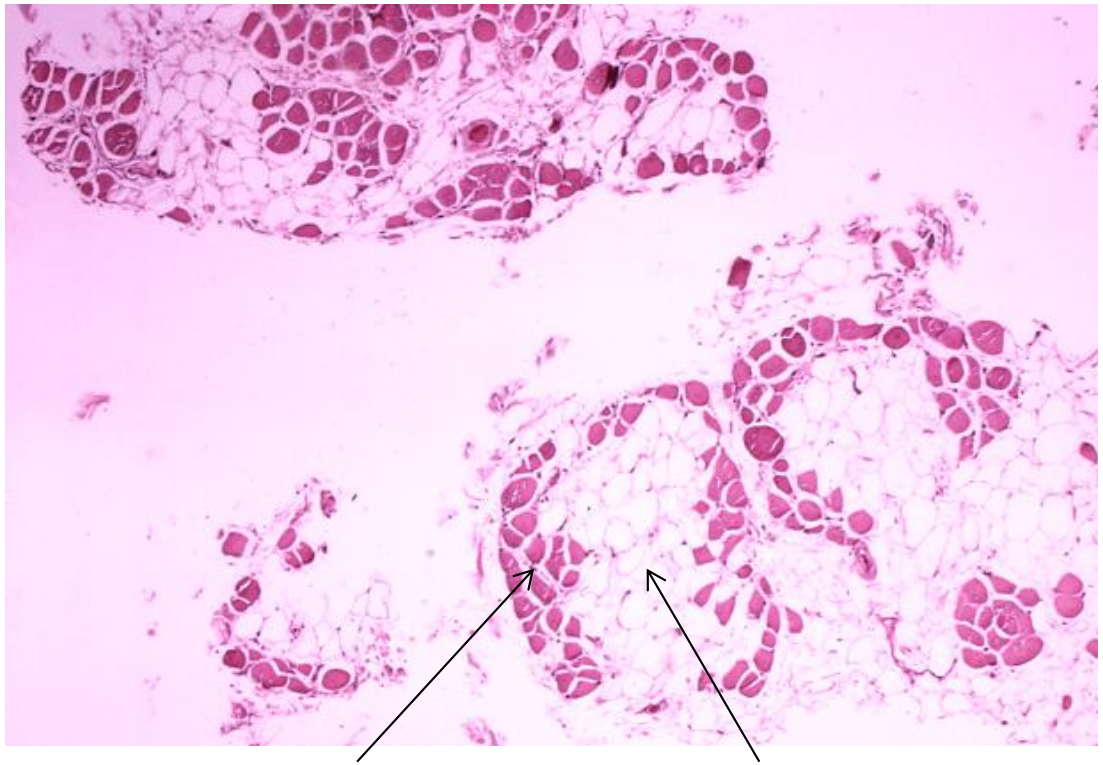


Gowers sign

Duchenne Muscular Dystrophy (DMD)

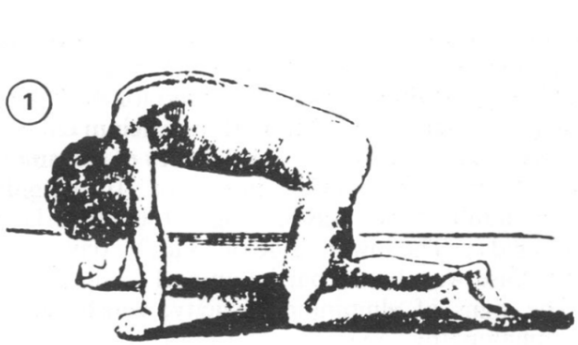


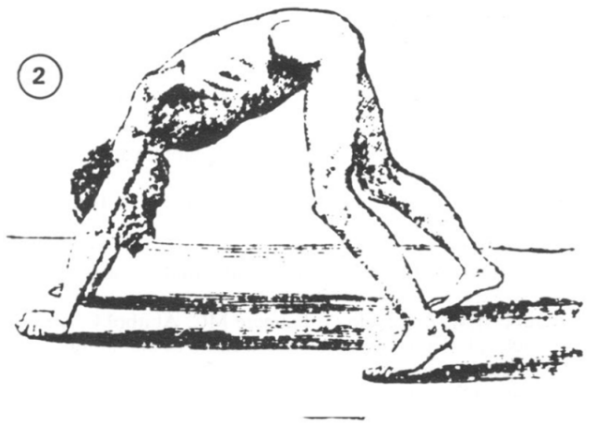




Muscular fiber

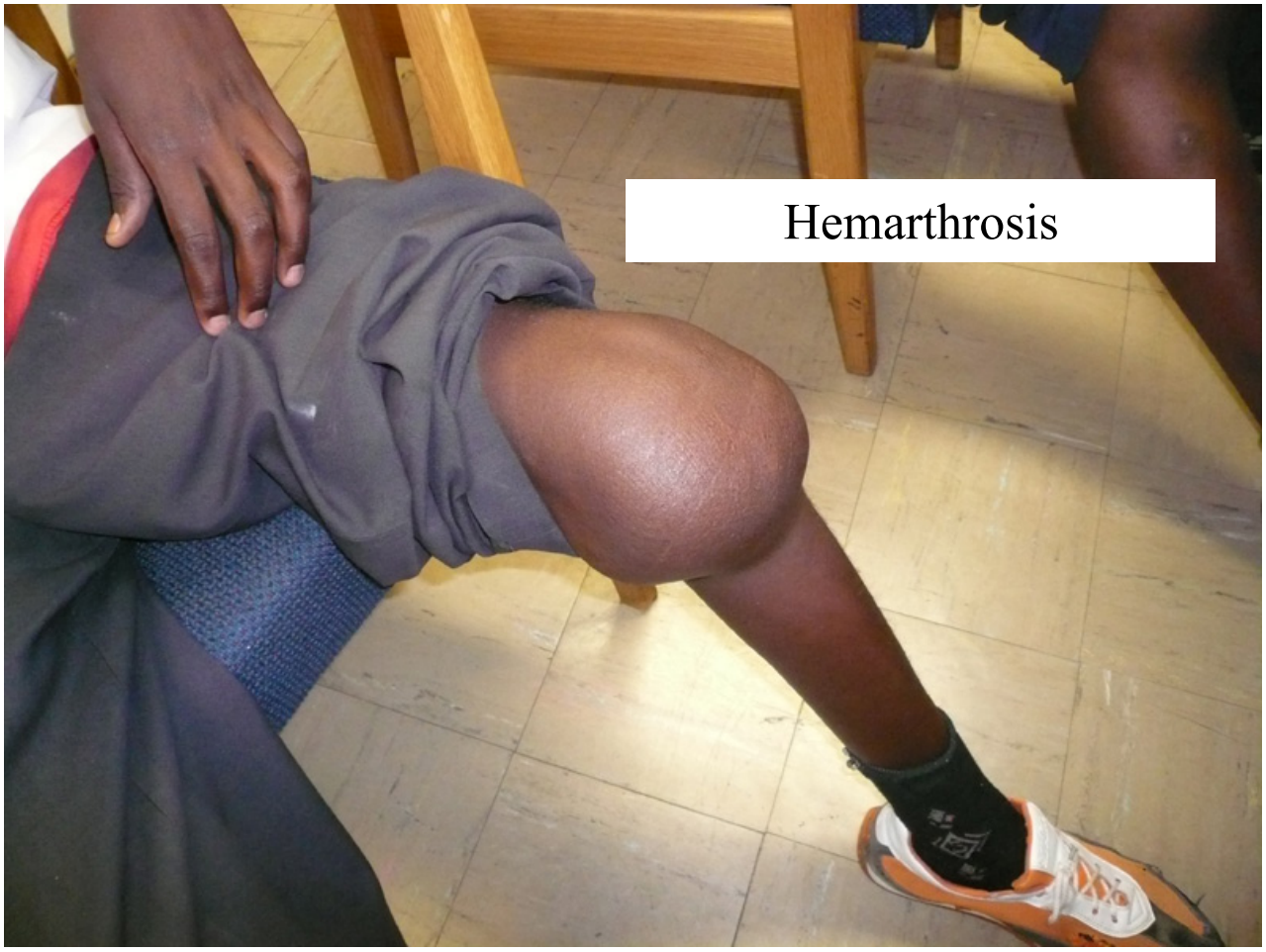
adipose tissue

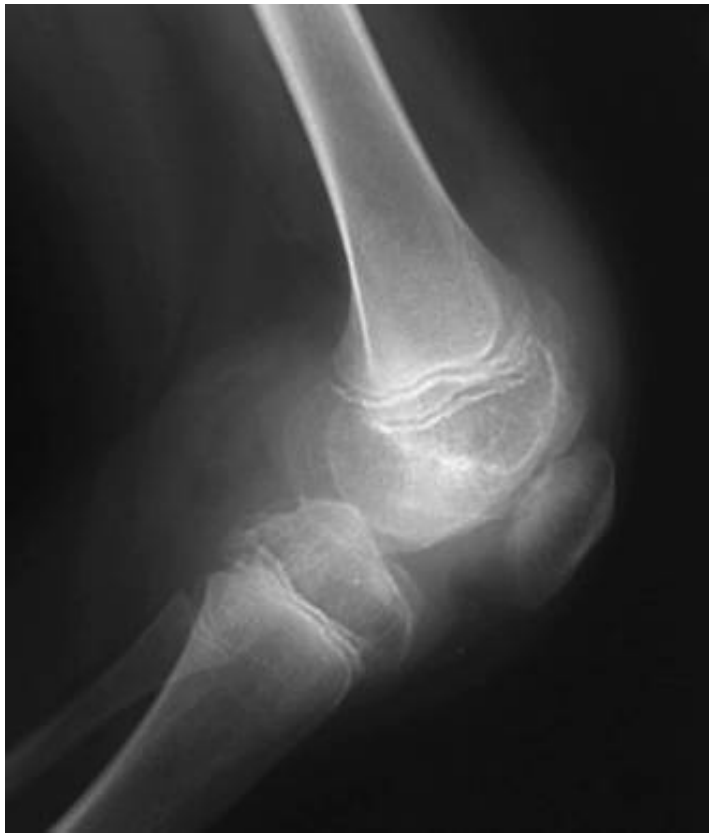




Gowers sign

Hemophilia





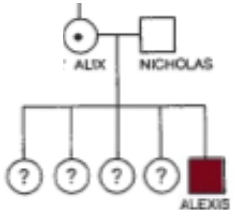
Rx knee

Inherited defect of coagulation. Rare: 1/10.000

Hemophilia

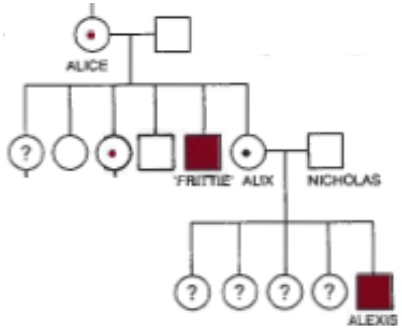
Inherited defect of coagulation. Rare: 1/10.000

Hemophilia



Inherited defect of coagulation. Rare: 1/10.000

Hemophilia



Inherited defect of coagulation. Rare: 1/10.000

Hemophilia

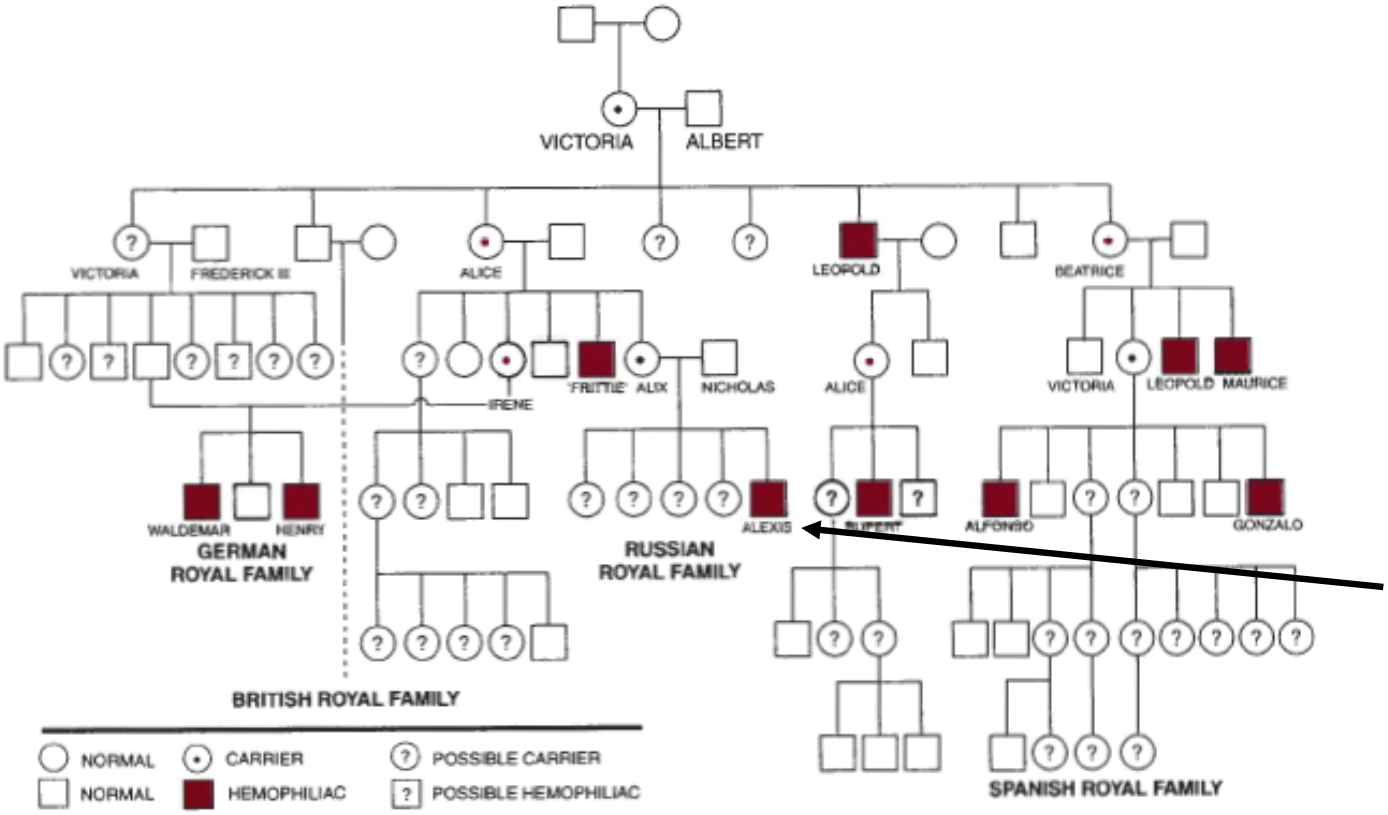


Figure 7.16. **Queen Victoria's pedigree.** Though the X-linked recessive inheritance pat-

- Inherited defect of coagulation. Rare: 1/10.000
- This family shows that the disease must be genetic and monofactorial from mutation on X chromosome

Hemophilia

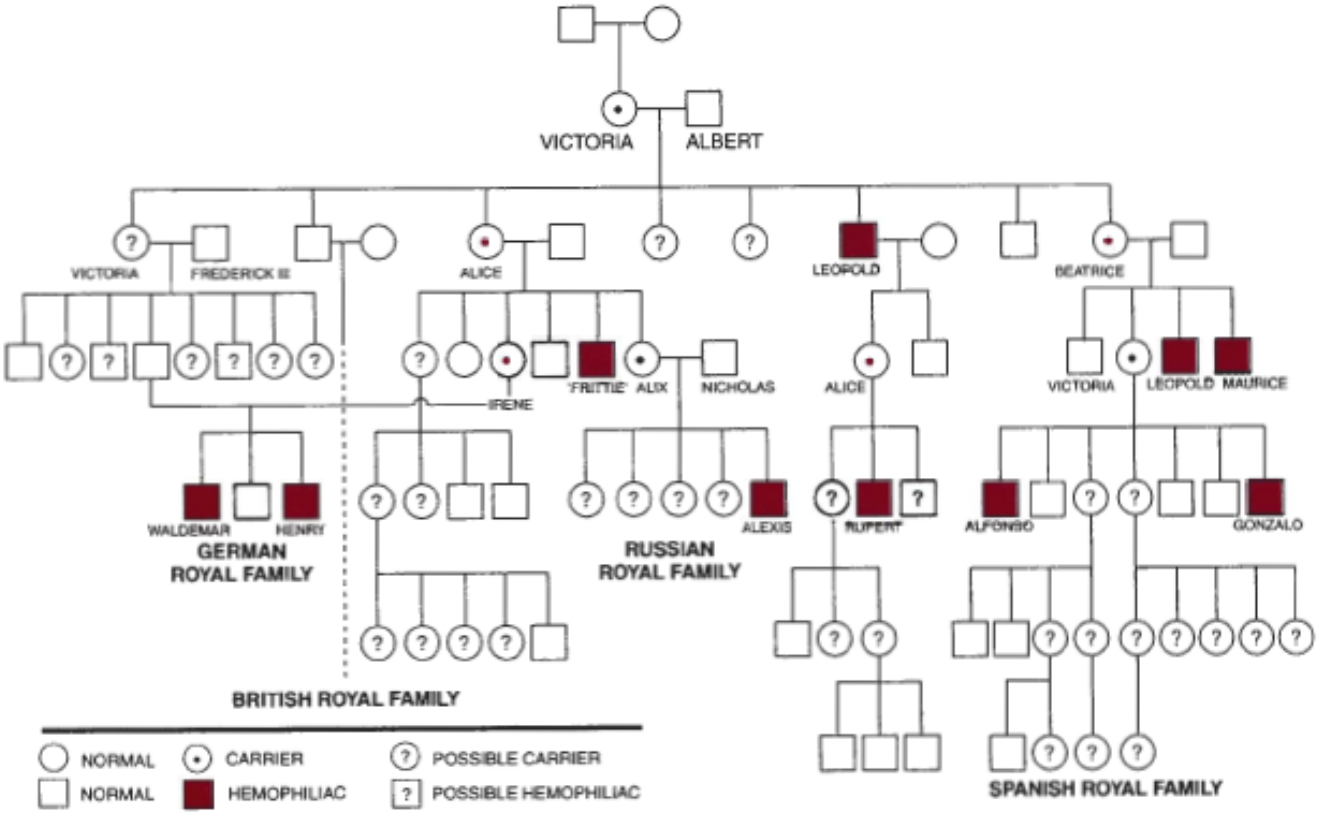
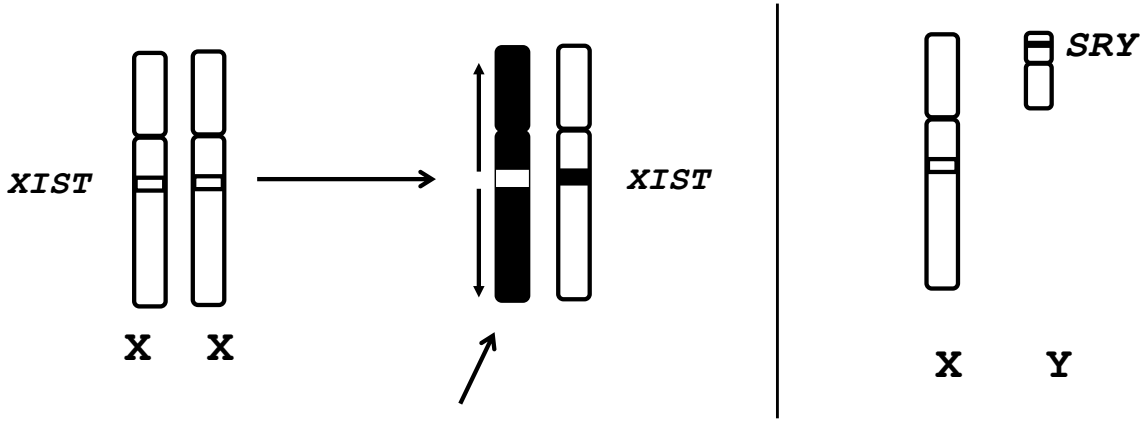


Figure 7.16. Queen Victoria's pedigree. Though the X-linked recessive inheritance pat-

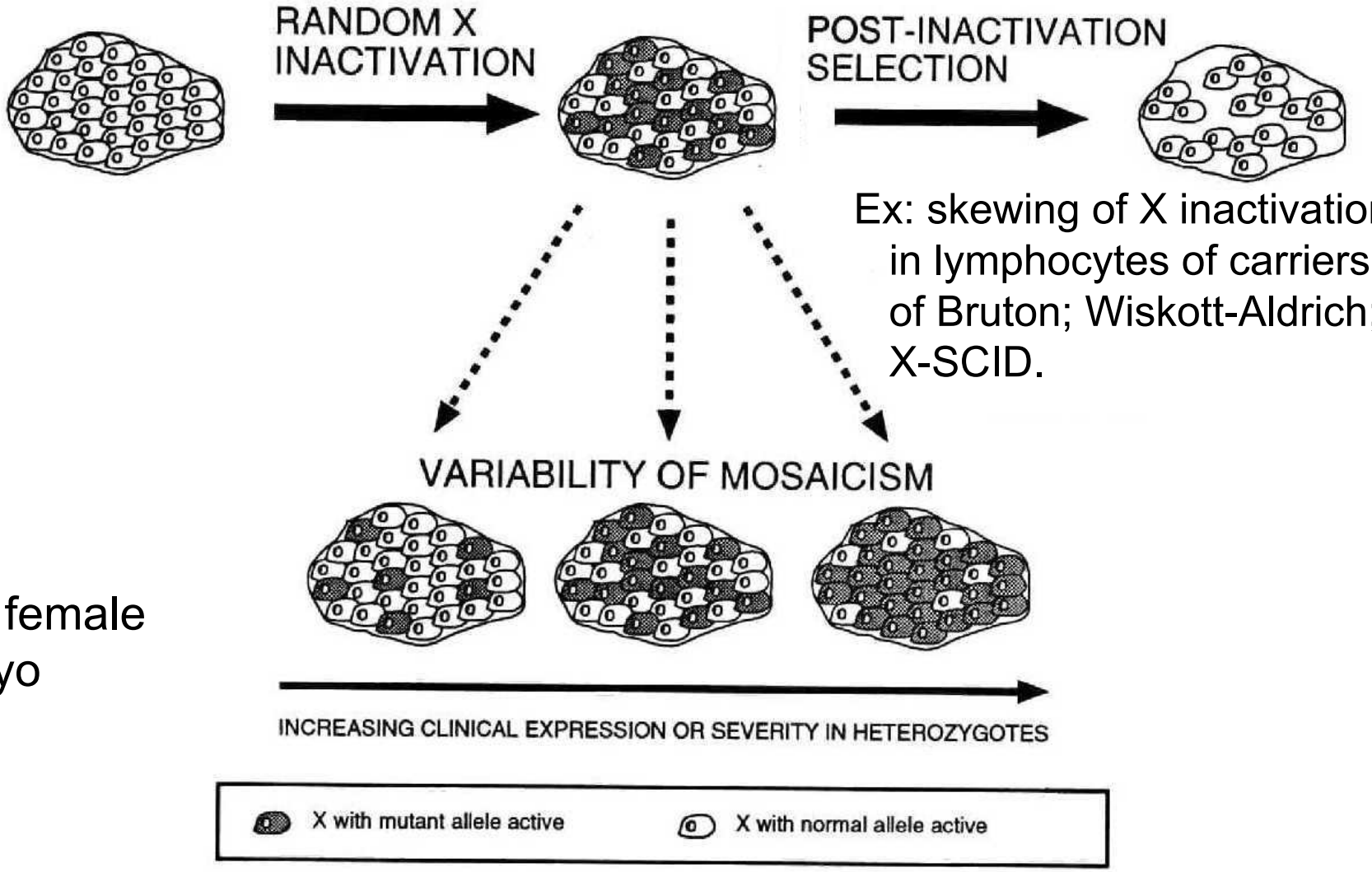
- High penetrance, severe monogenic disease
- Women asymptomatic

Woman are mosaic for 2 cell populations



XX Embryo < 100 cells => random inactivation of one X chromos
(Lyonisation)

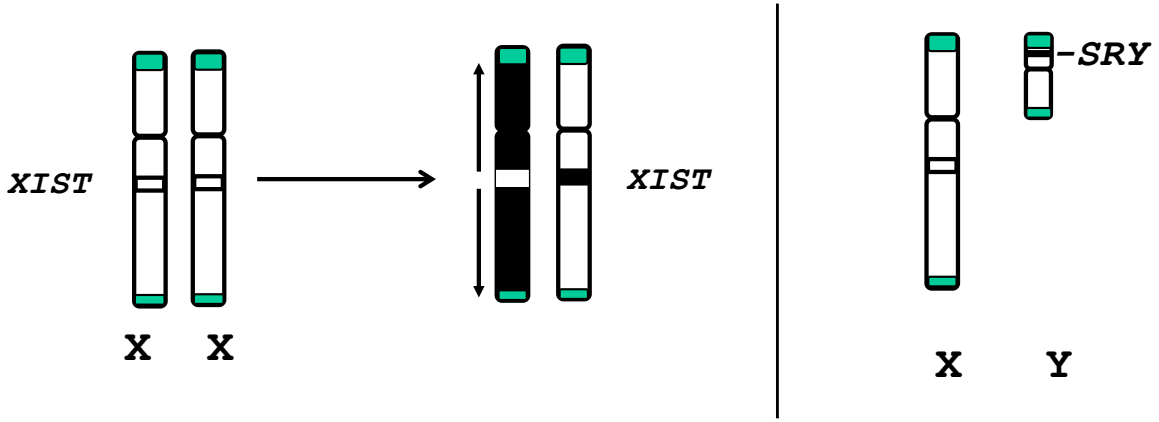
X chromosome inactivation in female somatic cells. Early. Random.



Ex: skewing of X inactivation in lymphocytes of carriers of Bruton; Wiskott-Aldrich; X-SCID.

Early female embryo

Pseudo-autosomal regions

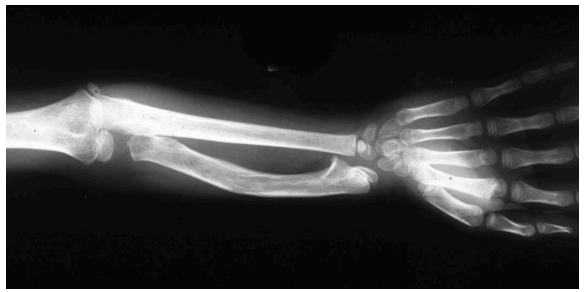


- On X and Y
- Escape X-inactivation
- Recombine by crossing-over

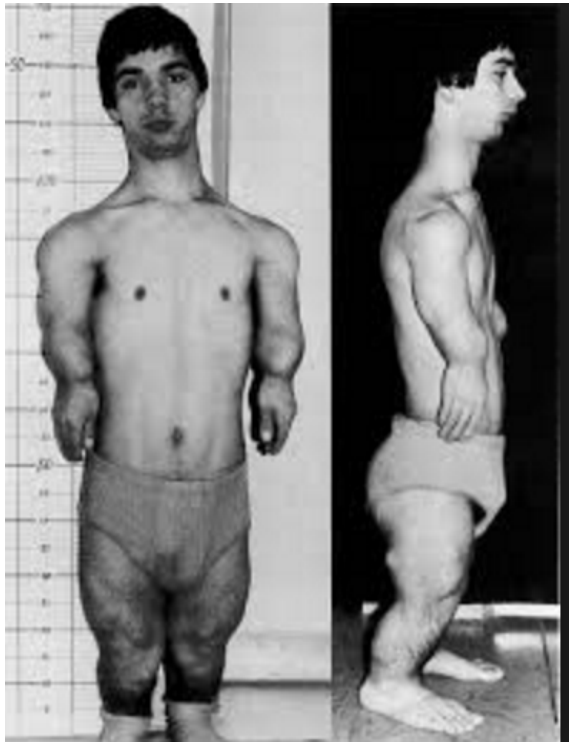
- AD (or AR) heredity, not X-linked
  - eg, SHOX mutations
- SRY very close to Y-PAR
  - Too centromeric cr-ov produces XX males

Pseudo-autosomal inheritance

- A few phenotypes
- Eg: SHOX gene – linked dyschondrosteosis
- Male to male transmission, male and female affected… if dominant: AUTOSOMAL DOMINANT pattern



- Or AUTOSOMAL RECESSIVE: Langer mesomelic dysplasia



Baxova et al. 2008 AJMG

- « 23rd chromosome »

AD inheritance of SHOX-associated phenotype

On the X and Y chromosome, so inheritance is not X-linked

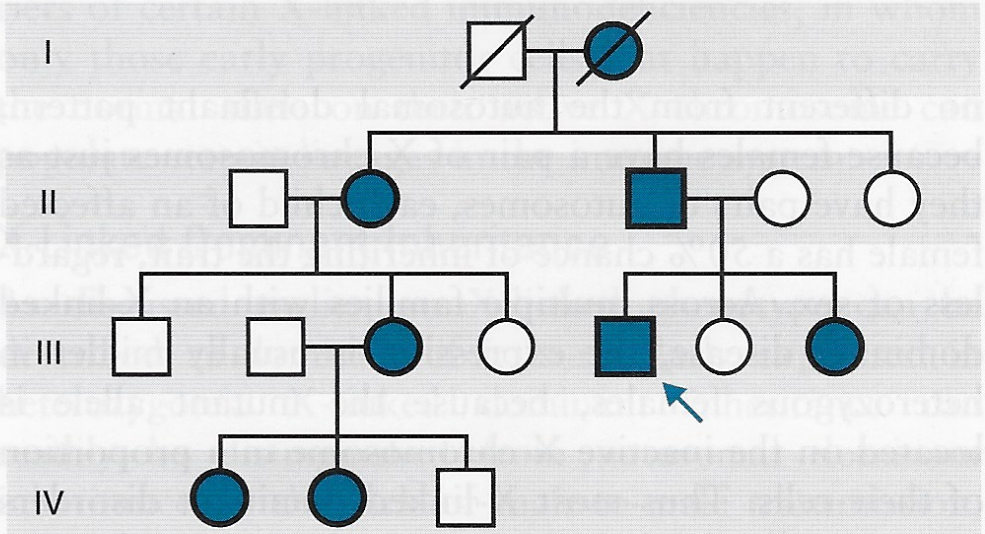
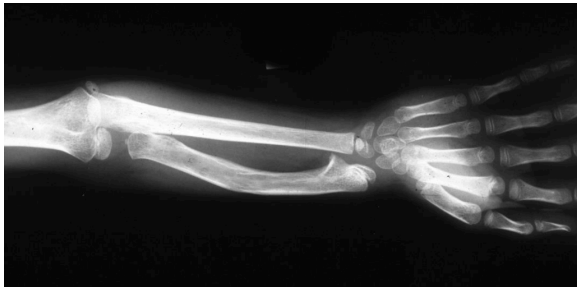
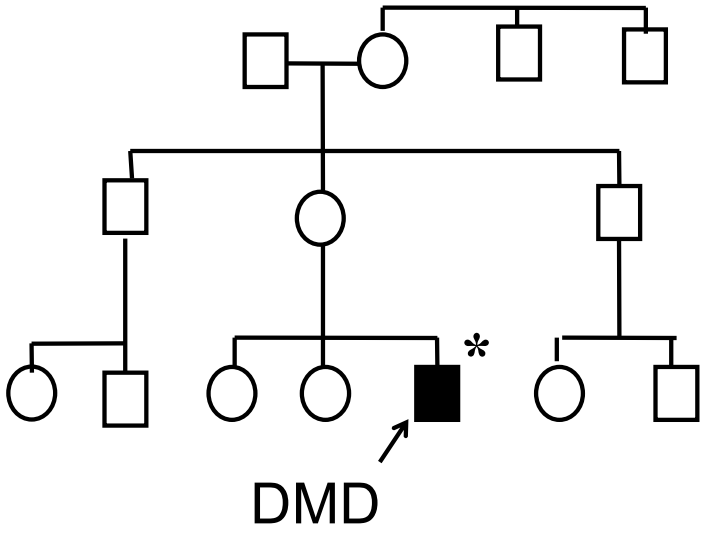


Figure 7-16 Pedigree showing inheritance of dyschondrosteosis due to mutations in *SHOX*, a pseudoautosomal gene on the X and Y chromosomes. The *arrow* shows a male who inherited the trait on his Y chromosome from his father. His father, however, inherited the trait on his X chromosome from his mother. *See Sources & Acknowledgments.*



X-linked gene new mutation: in patient OR mother

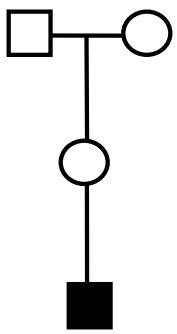


New mutation:

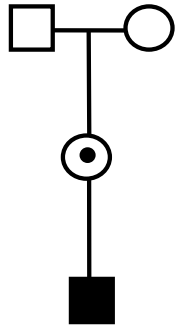
1. Either in patient
   - Mother's egg cell
2. Or in patient's mother
   - Grandmaternal egg cell
   - Grandpaternal sperm

---

1. Risk in further boy very small

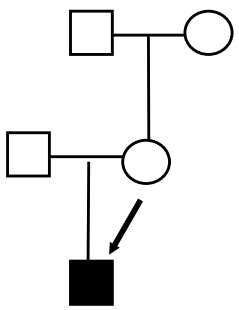


2. Risk in further boy = 50%

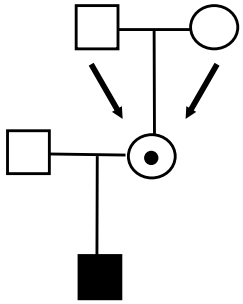


In-between (1) and (2):
maternal germ-line mosaic

Many new X-linked gene mutations arise in maternal Grandfather



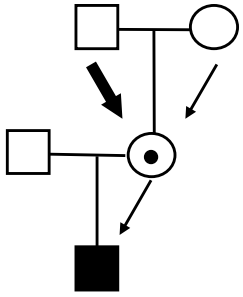
1/3 of cases



2/3 cases

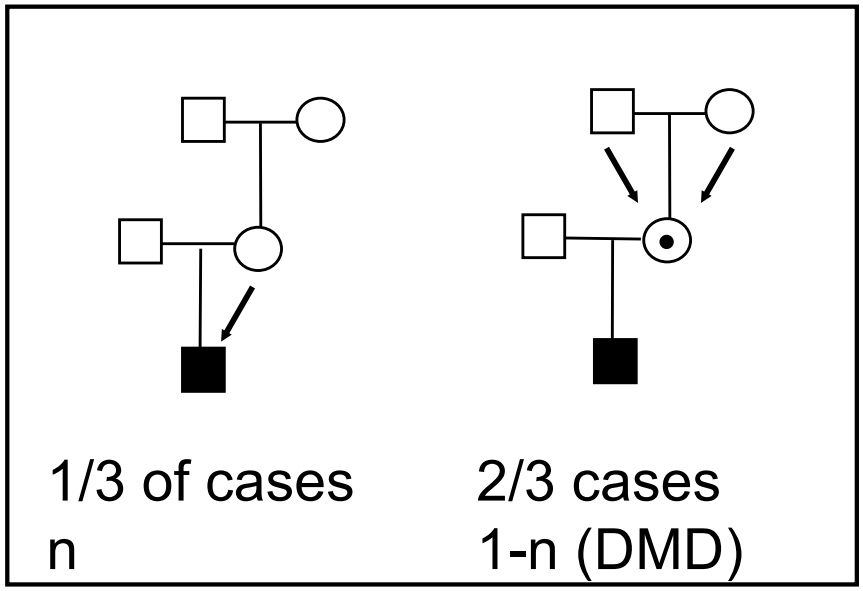
- 66% carrier mothers rate applies to DMD
  - High contribution of large genomic deletions
- Higher (>85%) for most other Xgenes
  - High contribution of testicle-derived point mutations

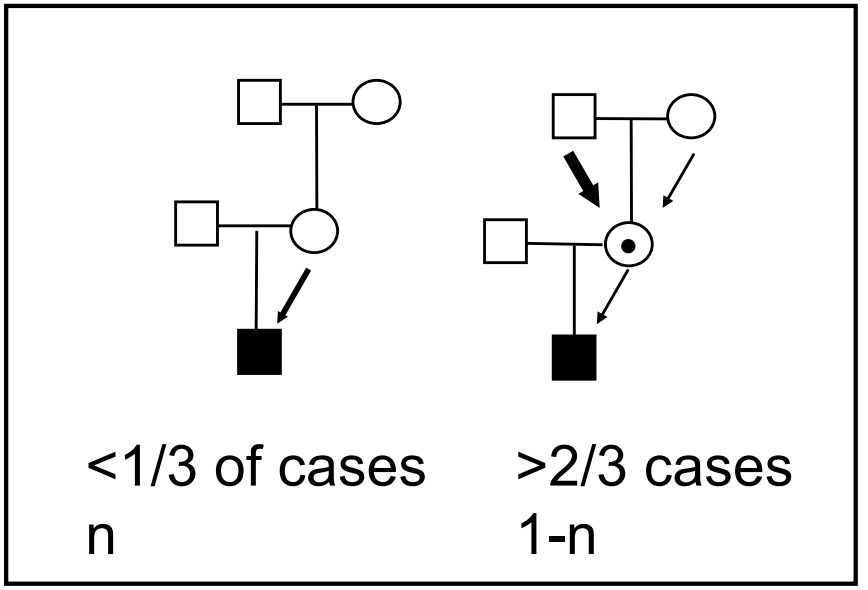
- Grand-paternal age effect



NB: father not involved (Y chromosome)

Many new X-linked gene mutations arise in maternal Grandfather





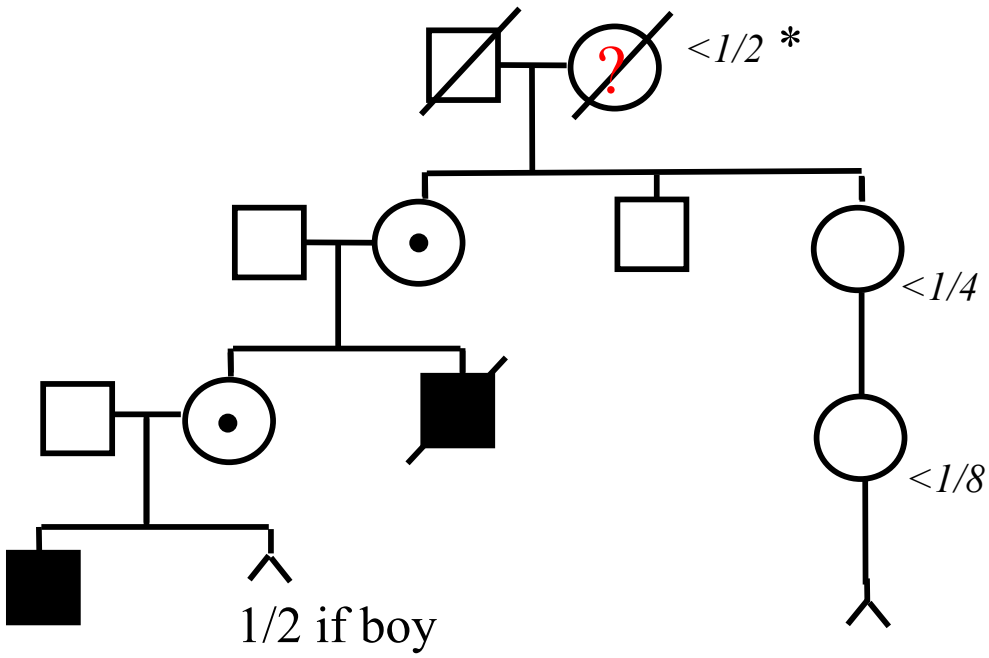
n = frequency of new mutation in affected boy, not in mother

n = (1-f) / (k + 2) where k = male mutation rate / female mutation rate ; f = fitness

- DMD: equal rate in both sexes: k = 1, and f = 0
  => n = 1/3
- Most X genes: k > 1 (k range: 2 – 10) => n < 1/3
- If f = 1 (and patient number constant): no new mutation

Risk in mother of carrier woman?

Ex: DMD



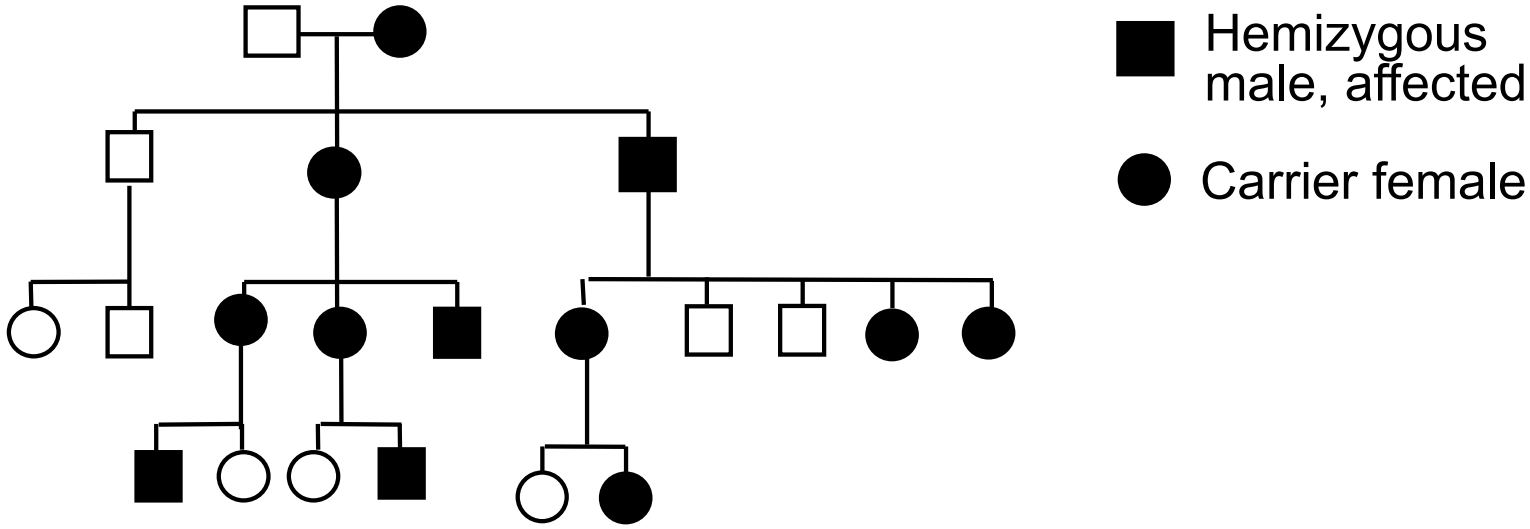
* proportion of carrier women's mothers who are carrier themselves is maximum ½

If male = female mutation rate (k=1) and f=0, maximum risk = 1/2

Risk <1/2 if k>1

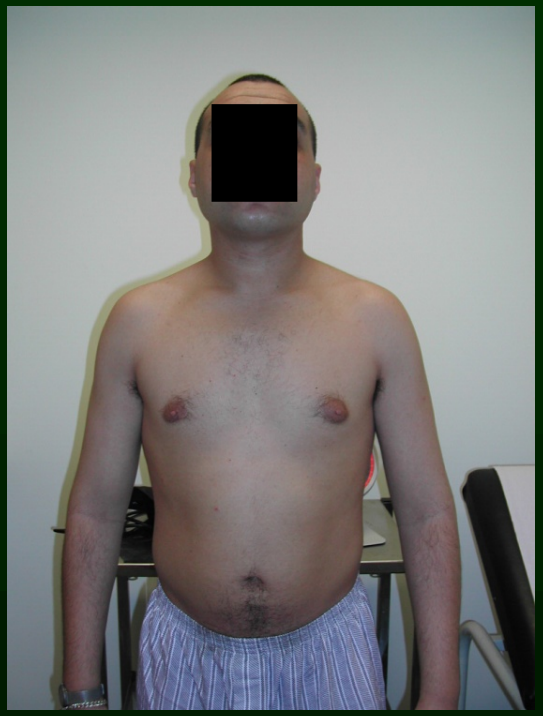
In previous generations of women, risk is halved going up the pedigree (as it is halved going down the pedigree)

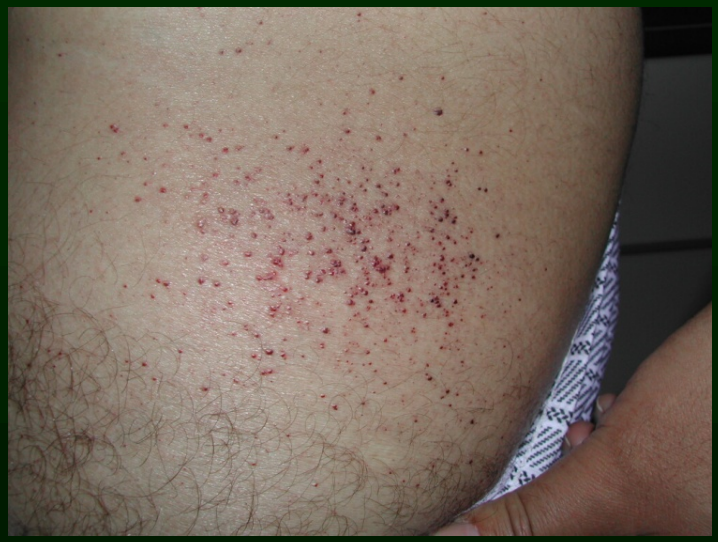
X-linked dominant phenotype



- Females have 2 chromosome X
- F/M ratio = 2/1

Fabry

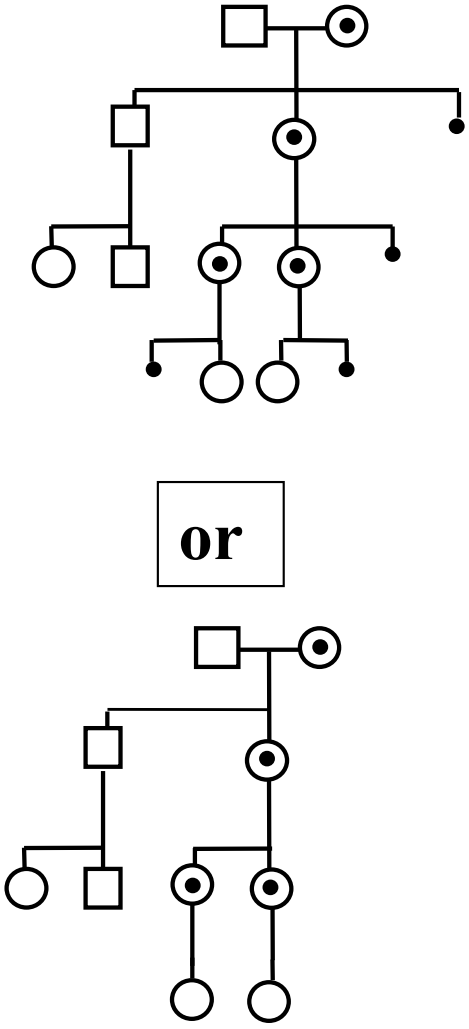




- Renal failure, cardiophaty, stroke.
- X gene, but most carrier females become sick

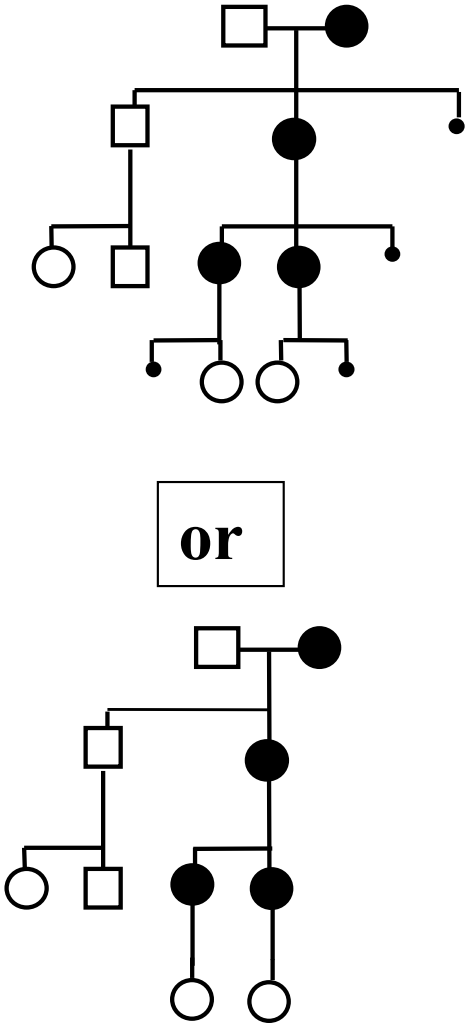
X-linked recessive, lethal in hemizygous male

- 50% of expected male births



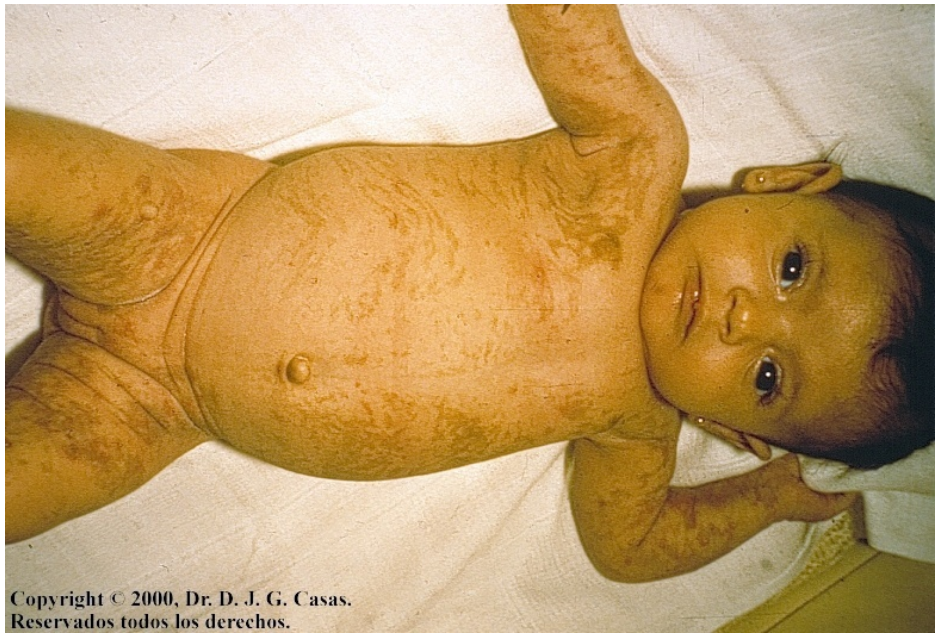
X-linked dominant, lethal in hemizygous male

- 50% of expected male births
- Affected females only

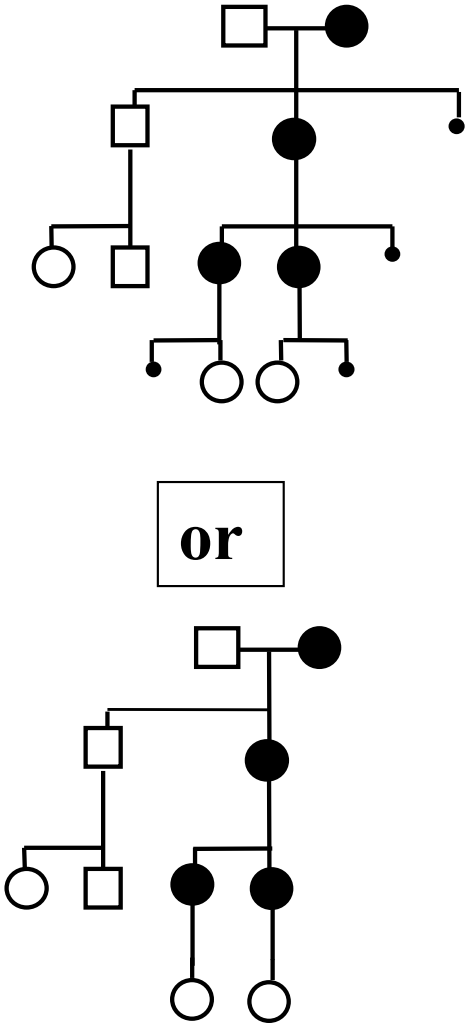


X-linked dominant, lethal in hemizygous male

- 50% of expected male births
- Affected females only
- Ex: Incontinentia pigmentii

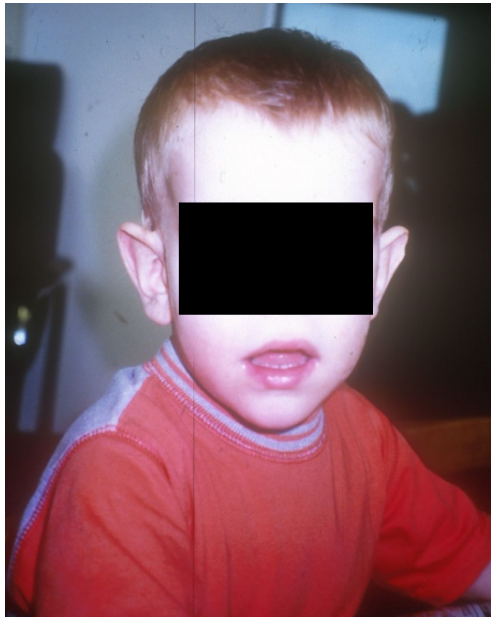


- Ex: Rett syndrome
  - Fitness ~0 => neomut only (except germ-line mosaics)

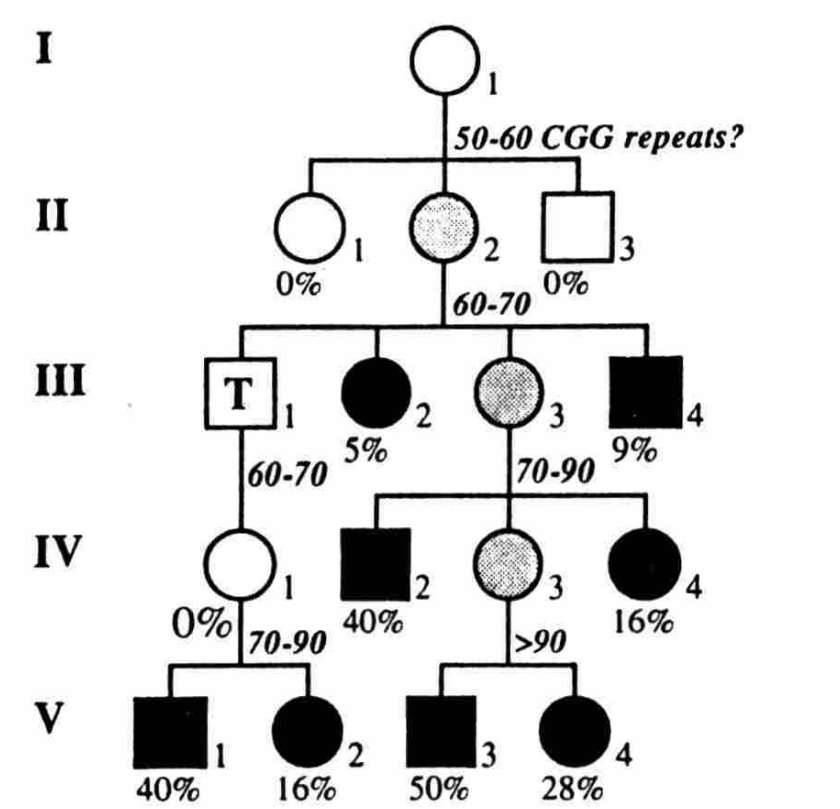


Fragile X syndrome

- 1st cause of hereditary MR ?
- X-linked, complex: « semi-dominant with incomplete penetrance »
  - Women often affected
  - Normal transmitting males
  - MR risk depends on position in pedigree



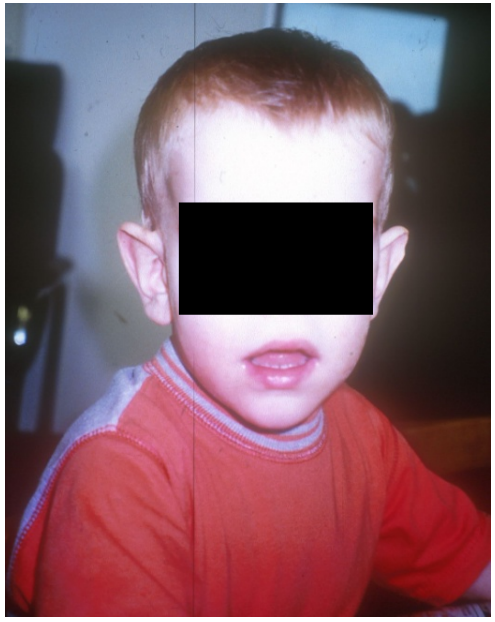
Fra-X: complex X-linked inheritance



Empiric Risk of Mental Retardation Varies with Pedigree Position Fu et al, 1991, Cell.

An example pedigree is given with data from Sherman et al. (1985) showing percent risk (below each individual) of mental retardation based on pedigree position from studies of fragile X families.

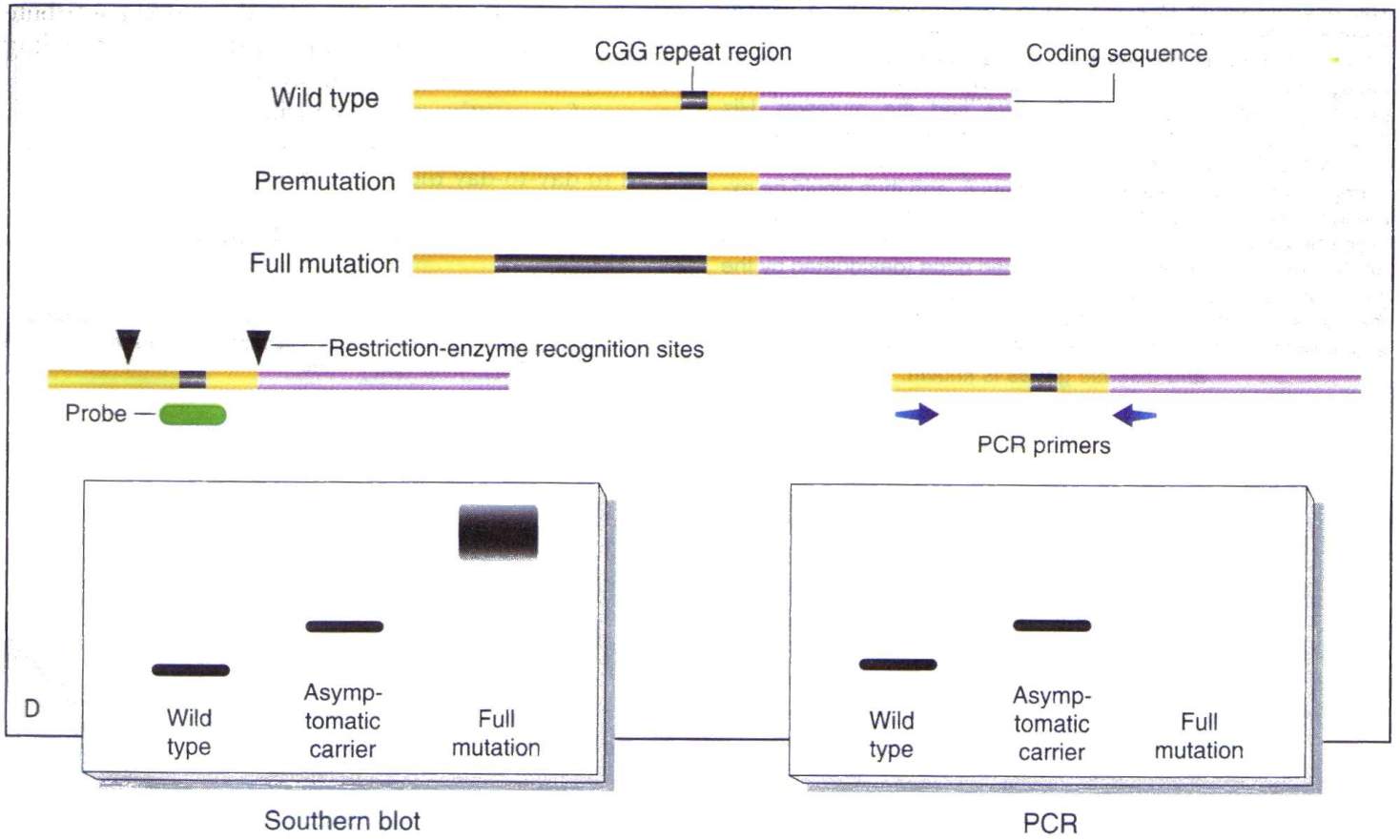
- Women often affected
- Normal transmitting males
- MR risk depends on position in pedigree



Dynamic mutation in Fra-X

- 3 types of alleles
  - Normal n<50
  - Premutated : unstable in femal transmission : n = 50-200
  - Full mutated : loss of function, semi-dominant (?): n usually >300

DNA analysis in Fra-X males

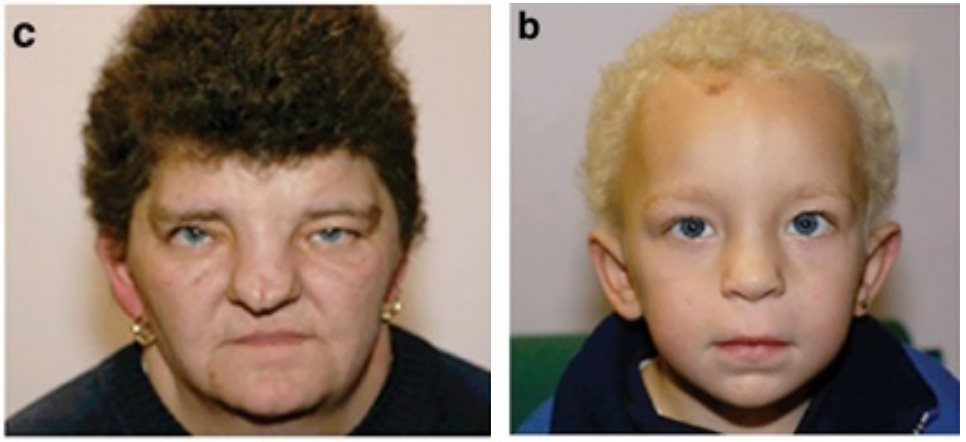


(CGG)n

- Premutation: non-methylated DNA, functional gene.
  May expand further via female meiosis.
  Expansion risk increases with size ÷ taille (n)
- Full Mutation: methylated DNA, loss of gene fn, MR

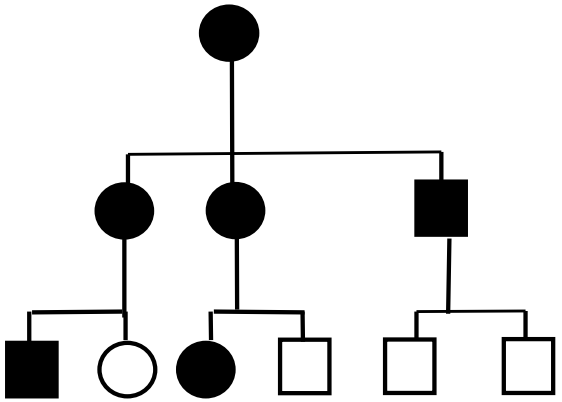
X-linked more severe in females

- Paradoxical
- Cranio-fronto-nasal dysplasia
  – *EFNB1* gene (Xq12)



Mother son

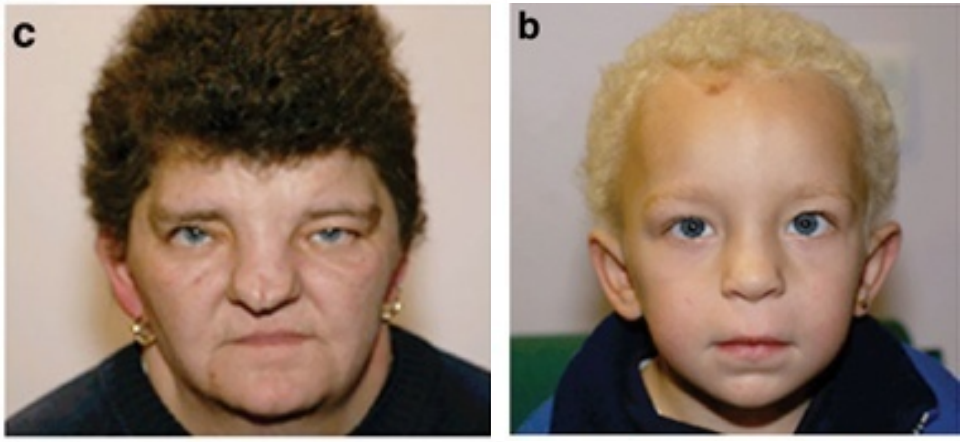
Wilkie&Coll 2006 EJHG



X-dom inheritance

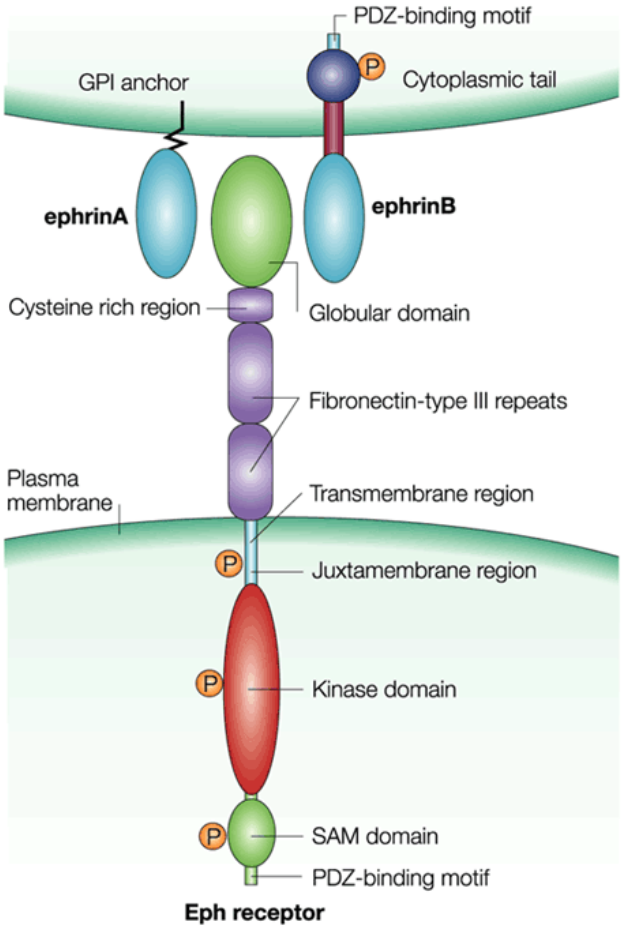
X-linked more severe in females

- Paradoxical
- Cranio-fronto-nasal dysplasia
  - *EFNB1* gene (Xq12)
    cell autonomous
  - CELLULAR INTERFERENCE
    model



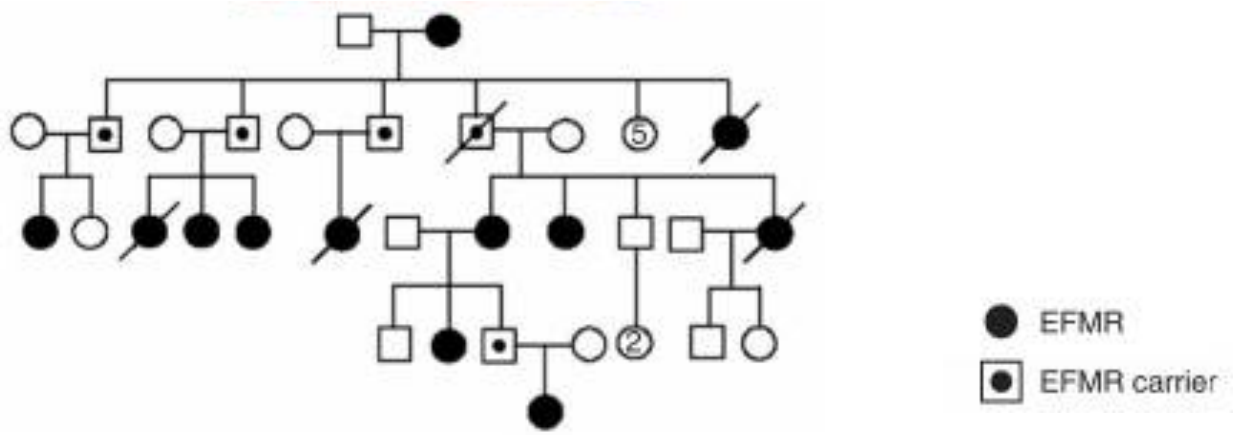
Mother son

Wilkie&Coll 2006 EJHG



Nature Reviews | Molecular Cell Biology

EPILEPSY, FEMALE-RESTRICTED, WITH MENTAL RETARDATION; EFMR

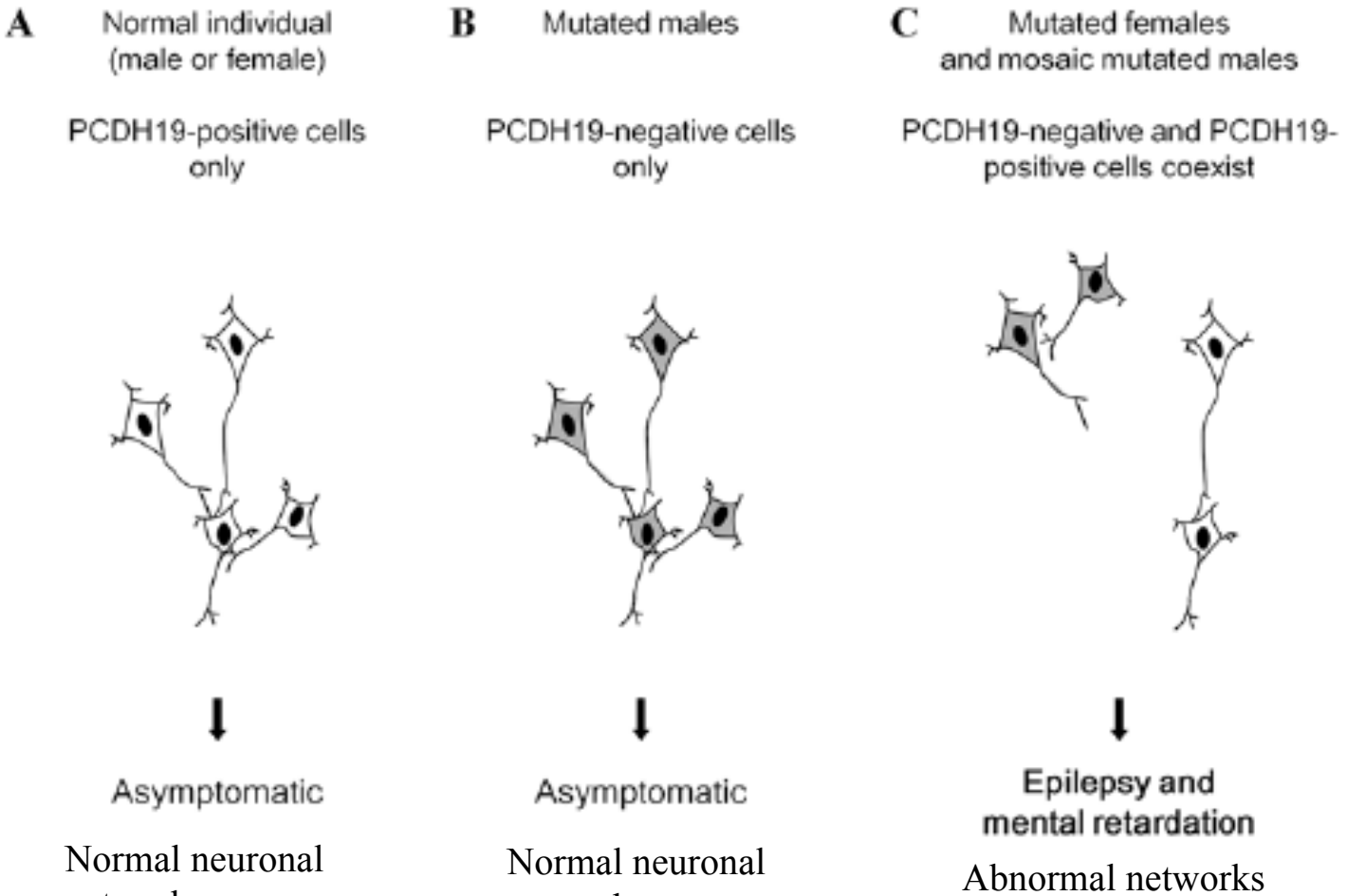


Dibbens LM et al. Nat Genet 2008
PCDH19 gene mutation

Cellular interference in another X-linked disorder

All patients are female, except 1 male who is a mosaic !

PCDH19 Mutations in Dravet-Like Syndrome
Depienne et al 2009



X-linked, cell autonomous lethal

PLP gene mutations

- X-linked disorder severe in affected boys => no sign in carrier mothers
- X-linked disorder milder in affected boys => carrier mothers are symptomatic

  paradoxical

X-linked, cell autonomous lethal

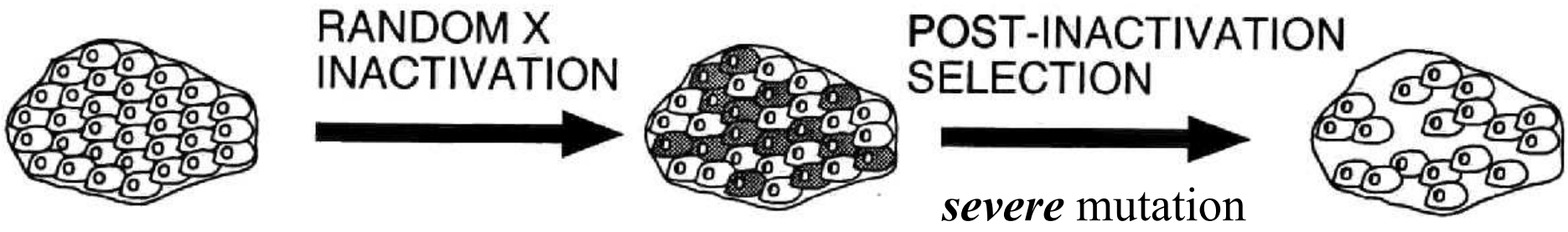
PLP gene mutations

- X-linked disorder severe in affected boys => no sign in carrier mothers
- X-linked disorder milder in affected boys => carrier mothers are symptomatic

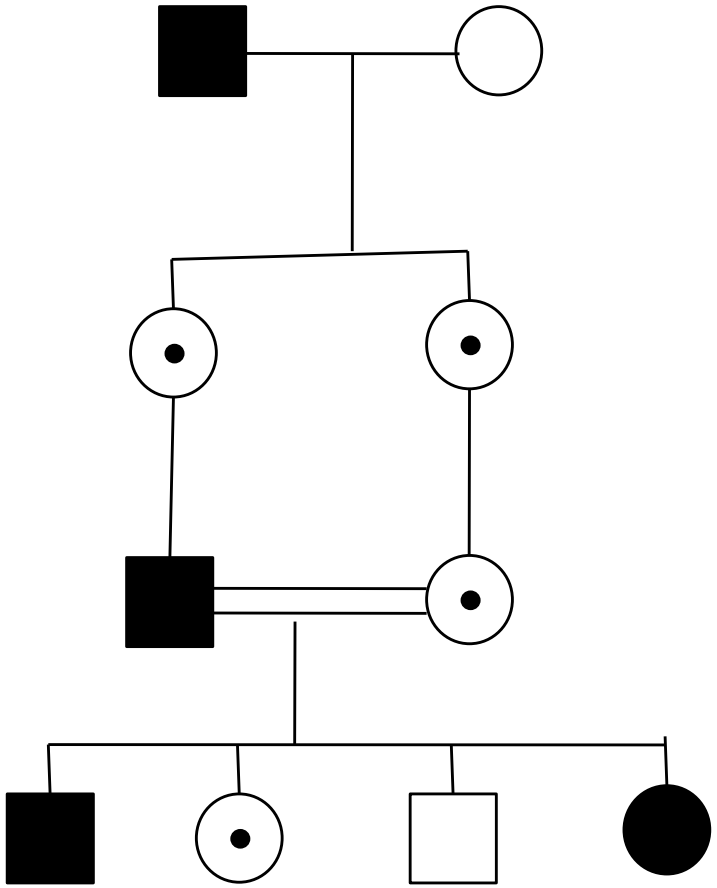
paradoxical

Mechanistic model:

- severe mutation in carrier => cell die after lyonisation healthy cell repopulate
- Mild mutation in carrier => all cells survive lyonisation, mutated cell degenerate in adult



X-linked in consanguineous family



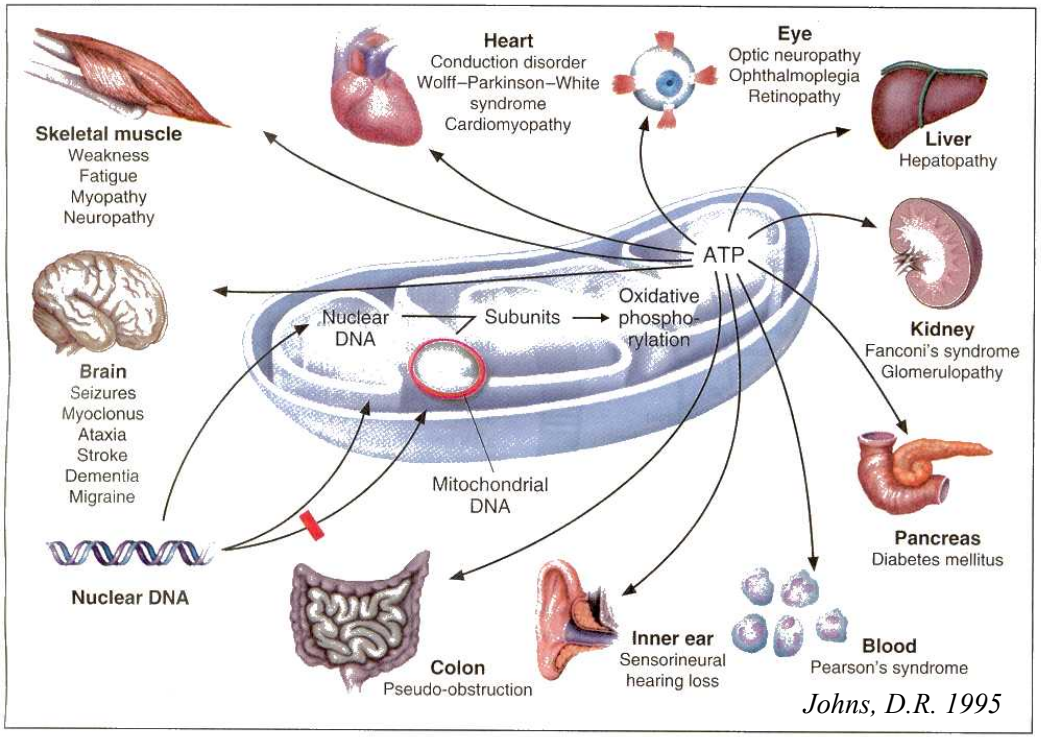
- Affected females
- Male-to-male transmission

- Also if frequent X-linked trait red-green colour-blindness

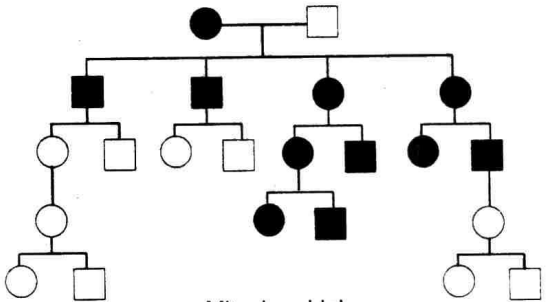
Patterns of single-gene inheritance

MITOCHONDRIAL DISORDERS

Maternal transmission
mtDNA mutation

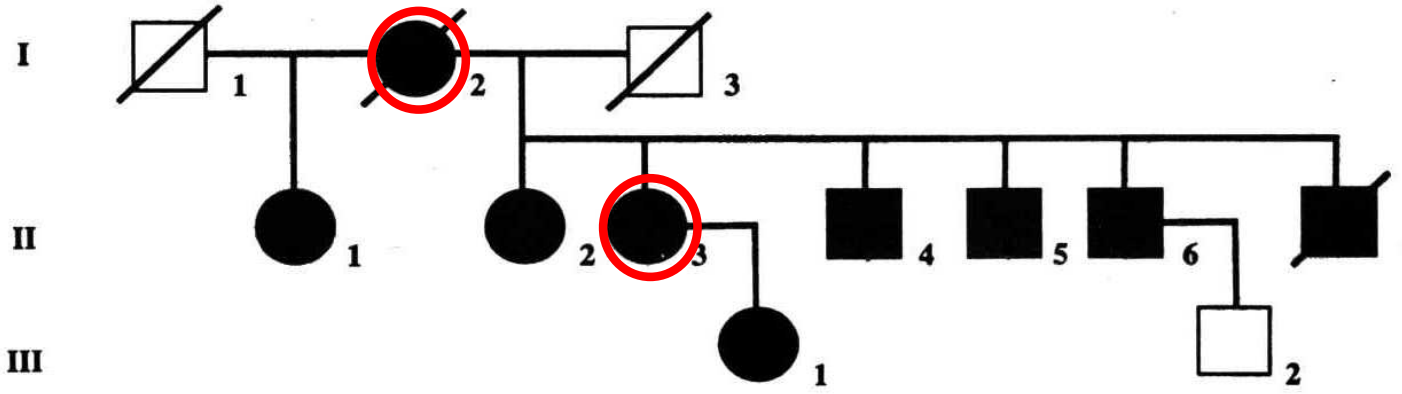


- 100 – 1000 mitoch/cell
- Few genomes/mitoch
- mtDNA: 16 kb
- Encode some components of mitochondrial respiratory chain complexes
- Variable phenotypes
  - Mostly neuro-muscular
- MATERNAL INHERITANCE
- Disease or susceptibility
  - Hearing loss ← aminosides



- Other components <= nucl. genes
- Respiratory chain defects: >1/10,000

Variable expressivity in mt disease

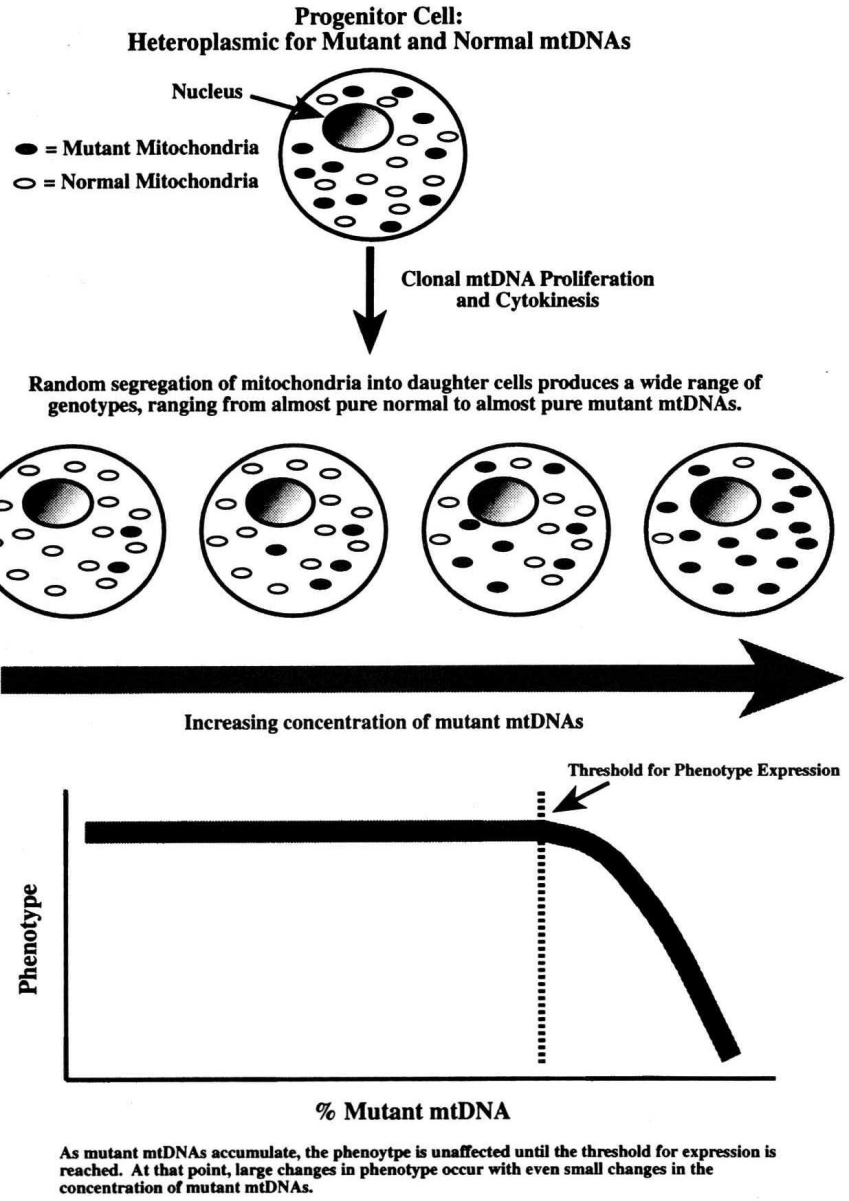


	II-1	I-2	II-2	II-3	III-1	II-4	II-5	II-6	III-2	II-7
Age	53	-	51	49	25	46	45	-	29	-
%Deletion	39	ND	42	44	44	38	43	ND	0	ND
Insulin Dependent Diabetes Mellitus	+	+	+	+	+[1]	+	+	+	-	+
Diabetic Ketoacidosis	-	-	-	+	-	+	+	-	-	-
Deafness	+	+	+	+	+	+	+	+	-	+
Stroke	-	+	-	+	-	-	-	-	-	-
Ophthalmoplegia	-	-	-	-	-	-	-	-	-	-
Ptosis	-	-	-	-	-	-	-	-	-	-
Mitochondrial Myopathy	ND	ND	ND	-	ND	-	-	ND	ND	ND
OXPHOS Biochemistry	ND	ND	ND	+	ND	+	+	ND	ND	ND

[1] Diabetes mellitus has recently developed and the patient is currently managed with oral hypoglycemics. + = abnormal; - = normal.

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes

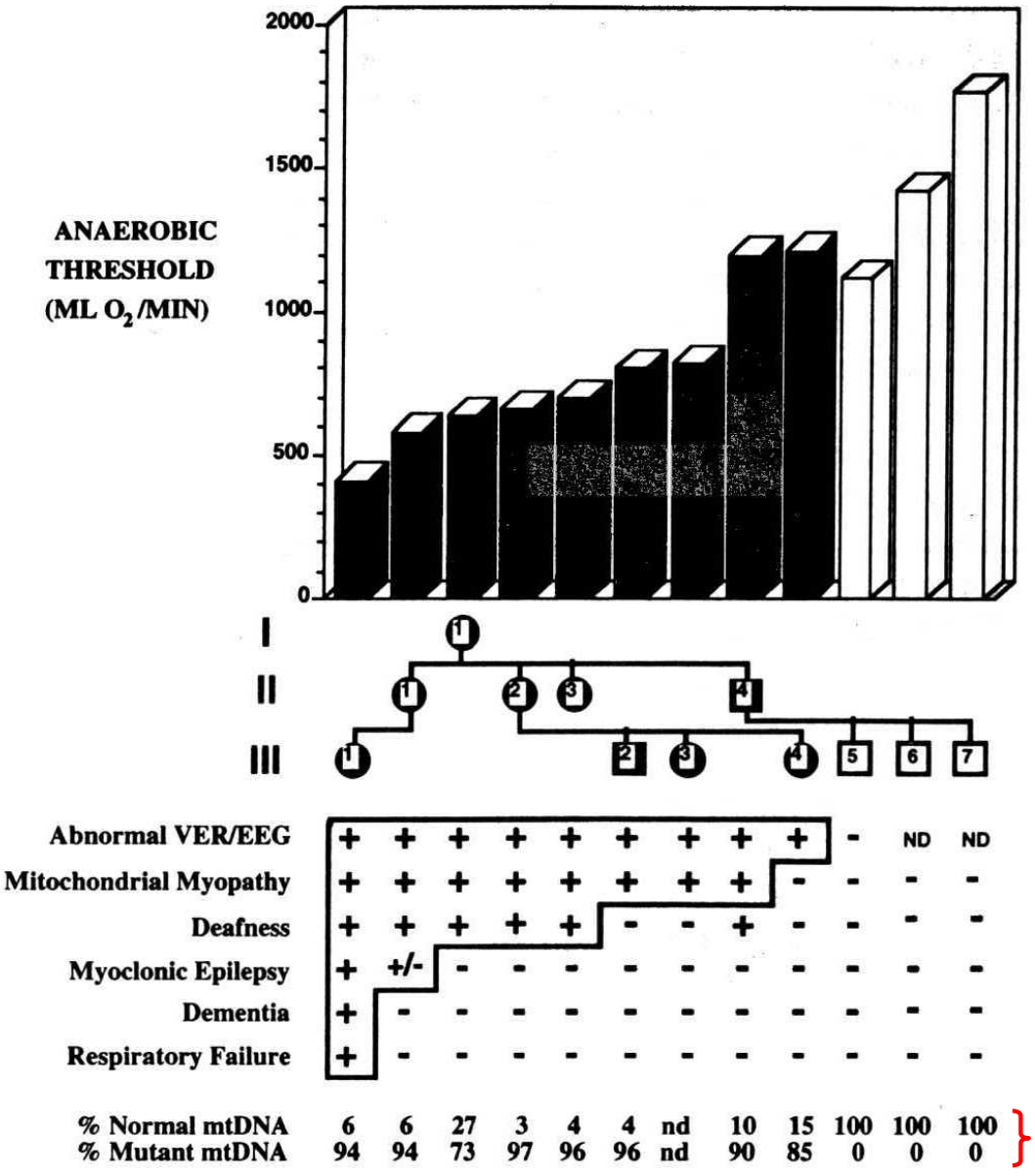
heteroplasmy



- Normal and mutated mtDNA mixed in one cell:
  « intracellular mosaic »

- TRESHOLD EFFECT

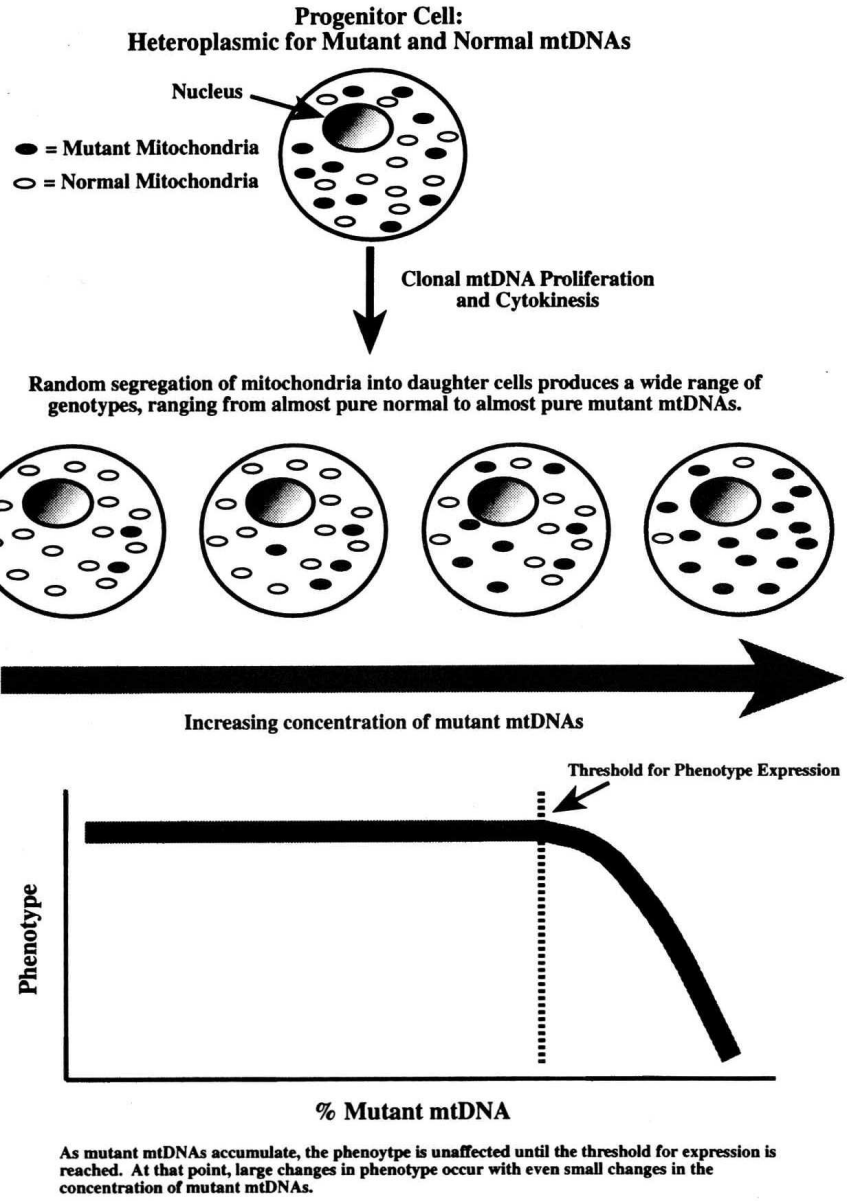
Heteroplasmy



Variable penetrance of clinical manifestations due to replicative segregation in MERRF.

- Normal and mutated mtDNA mixed in one cell: « intracellular mosaic »
- TRESHOLD EFFECT

Mitotic segregation



- Random distribution of mitoch to daughter cells
- Modifies heteroplasmy => modifies clinical course

Respiratory chain disorders

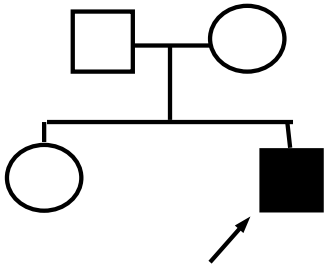
mtDNA

- Maternal inheritance
- Heteroplasmia, treshold effect
- Mitotic segregation

Nuclear DNA

- AD
- AR
- X

In small families, it may be difficult to identify mode of heredity

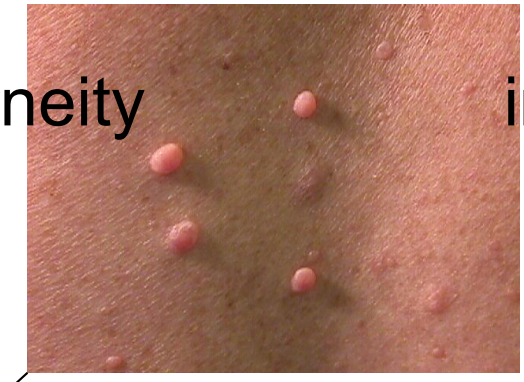


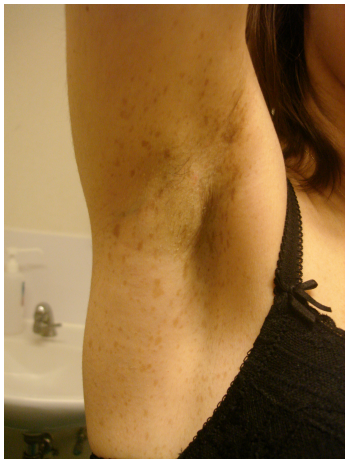
- Recessive?
- Dominant with low expressivity in affected parent ?
  — *(forme fruste)* ?
- Dominant with incomplete penetrance in carrier parent?
- Dominant, neomutation ?
- X chromosome-linked ?
- Multigenic/ Multifactorial ?
- Mitochondrial ?
- Non genetic ?

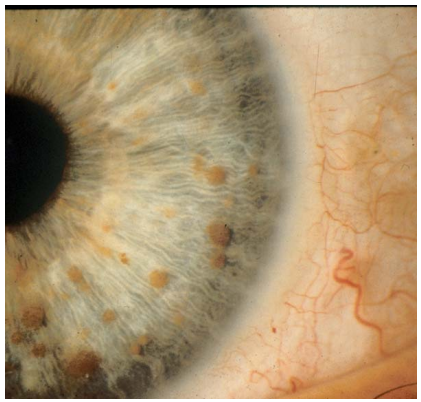
Locus heterogeneity

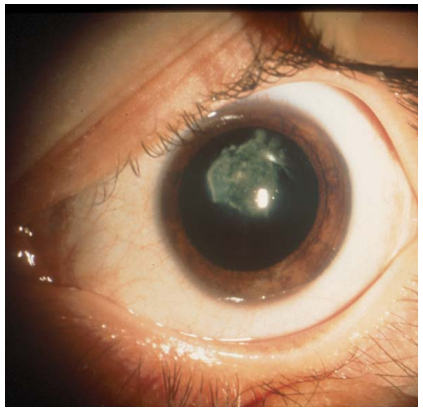
- MEN1 and MEN2
- NF1 and NF2; NF1-Like
- BRCA1 and BRCA2
- SCA1, SCA2, SCA3, SCA6, ….
- … and many disorders : identical phenotype, several loci

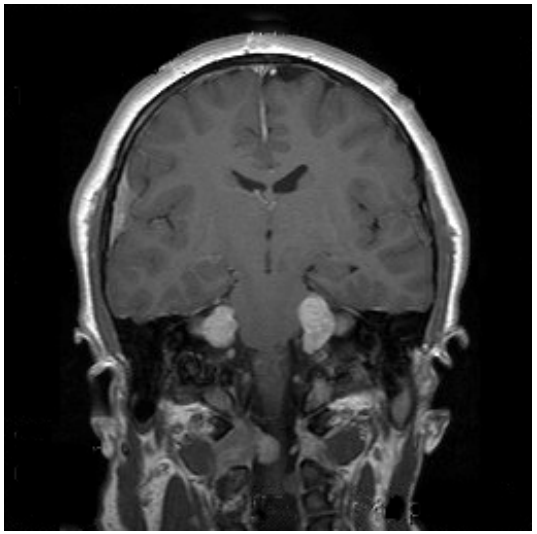
Genetic heterogeneity in Neurofibromatosis









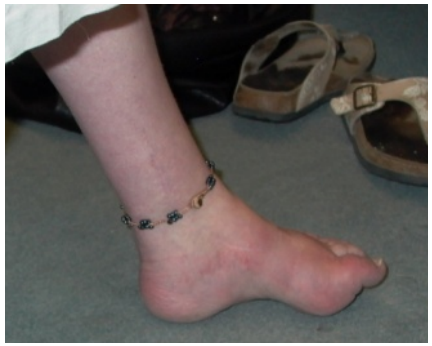


<u>NF1 (Von Recklinghausen) 1/3000</u>
Peripheral NF; >6 café-au-lait spots;
iris hamartomas (Lisch nodules);
freckling;
f/u: optic tract gliomas; PNST
NF1 gene, #17

<u>NF2 : 1/25000</u>
CentralNF; few café-au-lait spots;
VIII schwannomas;
f/u: meningiomas

NF2 gene, #22

Genetic heterogeneity in Charcot-Marie-Tooth disease = HSMN, Hereditary Sensory-Motor Neuropathy



CMT1 demyelinating

CMT1a PMP22 gene

CMT1b

CMT1c

…..

CMT1n

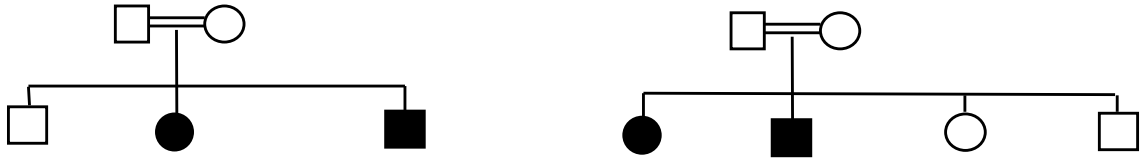
CMT2 axonal

CMT2n

…..

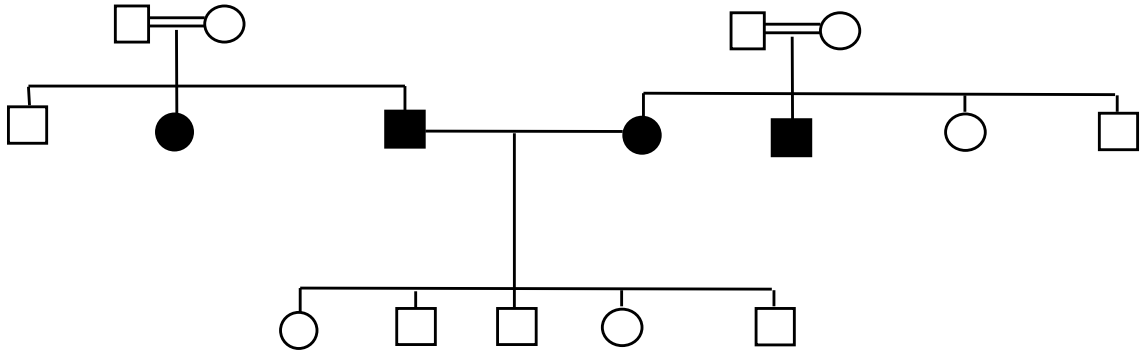
- CMT1 is heterogeneous beyond our ability to distinguish sub-phenotypes (>< NF1 and NF2)
- CMT2 also

Locus heterogeneity, AR disease



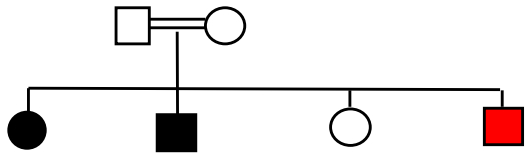
ex: deafness (> 100 db) prelingual onset

Locus heterogeneity, AR disease



ex: deafness (> 100 db) prelingual onset

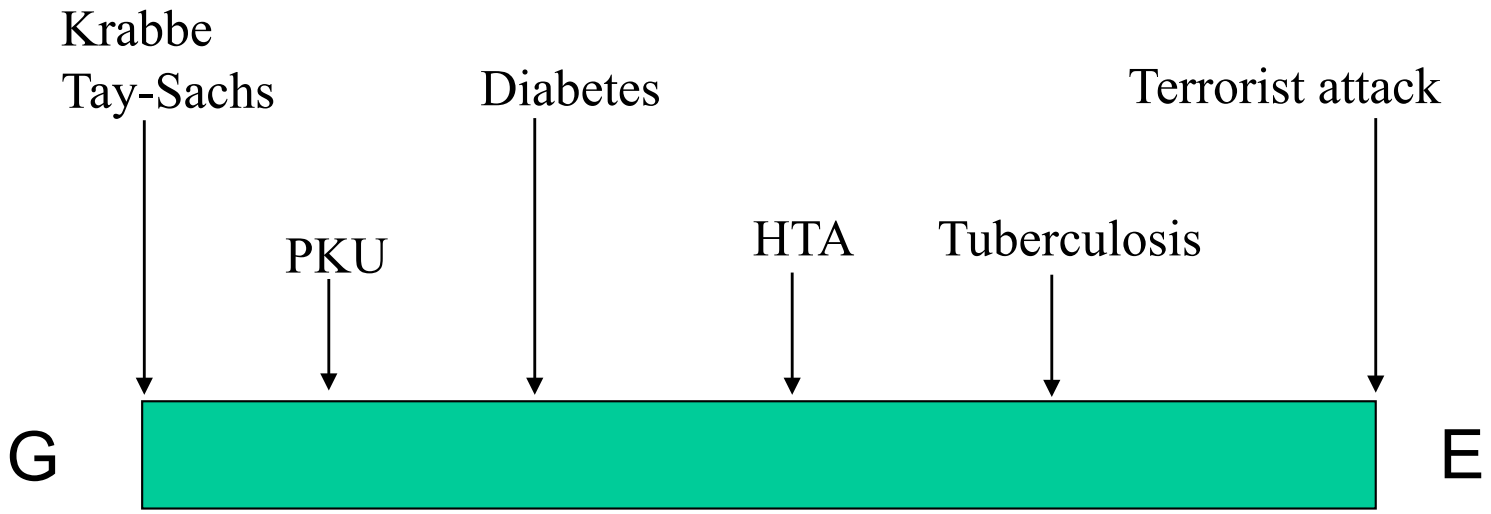
Phenocopy



Deafness, AR

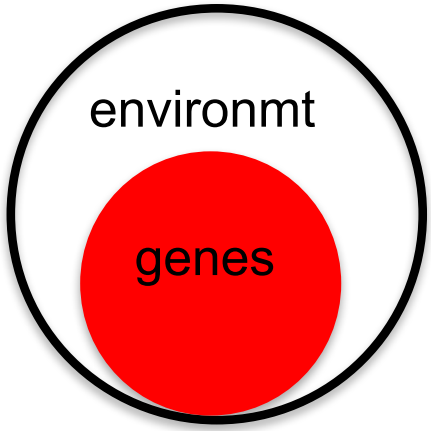
Deafness < fetal rubella

Gene – Environment interactions



Multifactorial characters

- Genetic contribution to phenotype is **COMPLEX** because it is due to many genes
- Genetic contribution to phenotype is globally **LIMITED** : ***globale penetrance of the genome*** is incomplete



Multifactorial, complex

Mendelian, simple

Multifactorial characters

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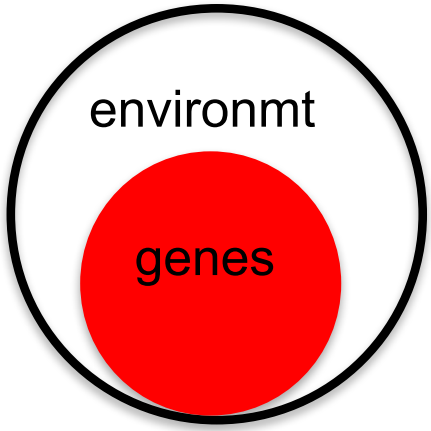
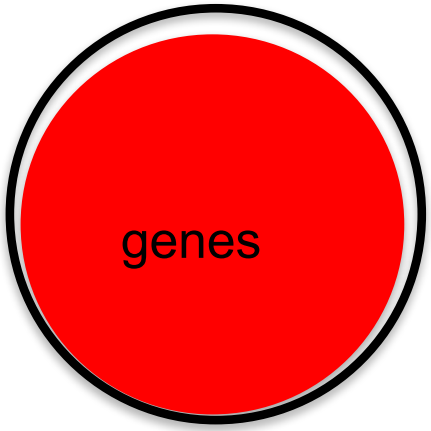


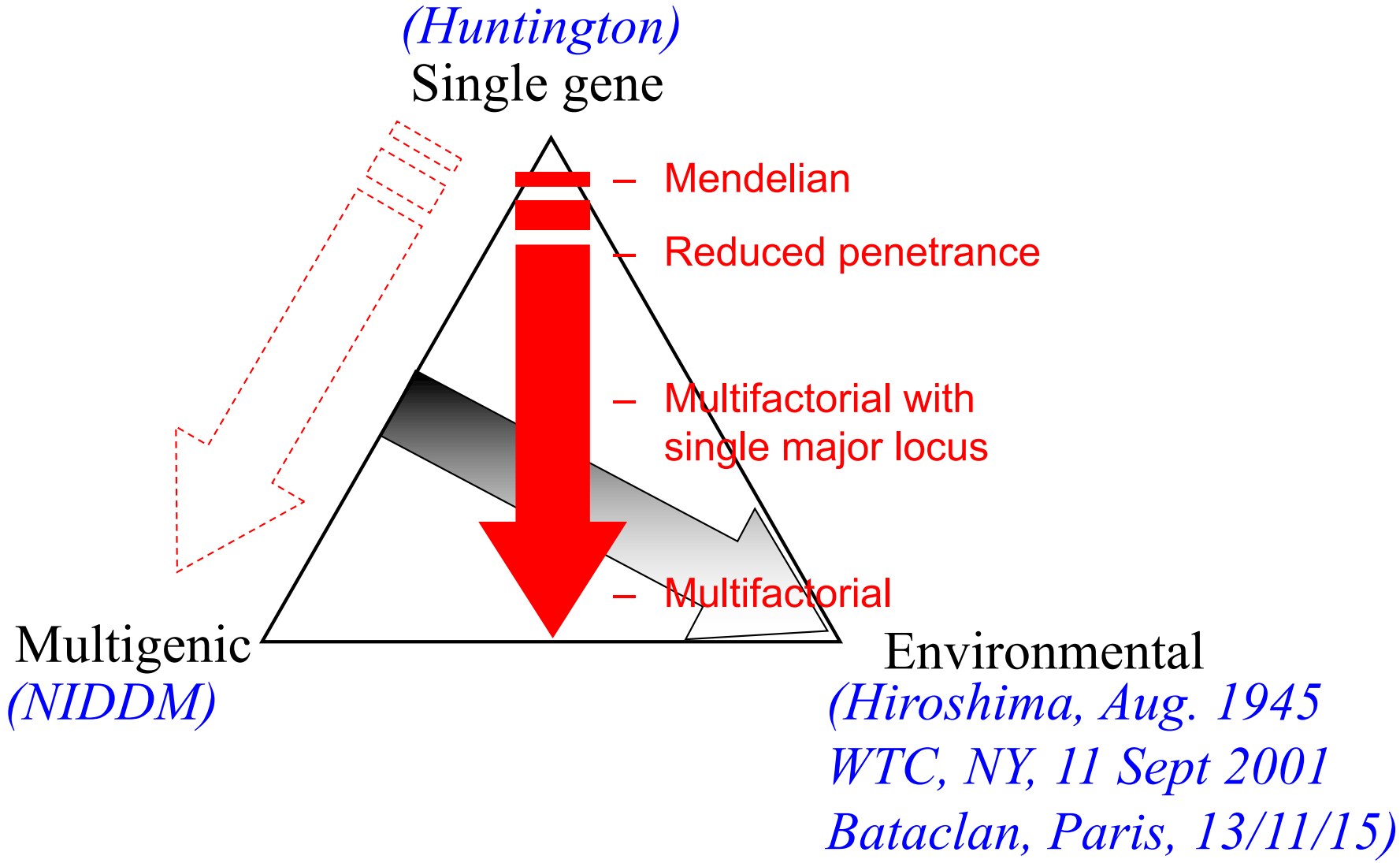
Multifactorial, complex



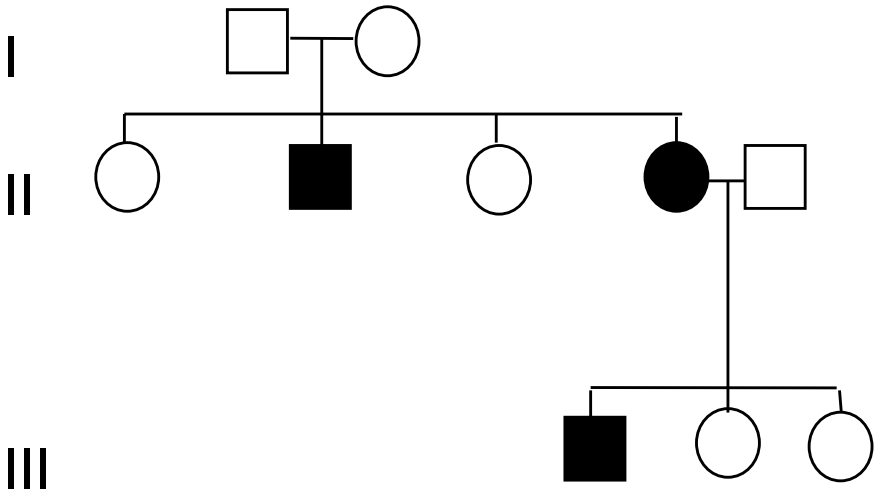
Multigenic, pure (exceptionnel)

Mendelian, simple

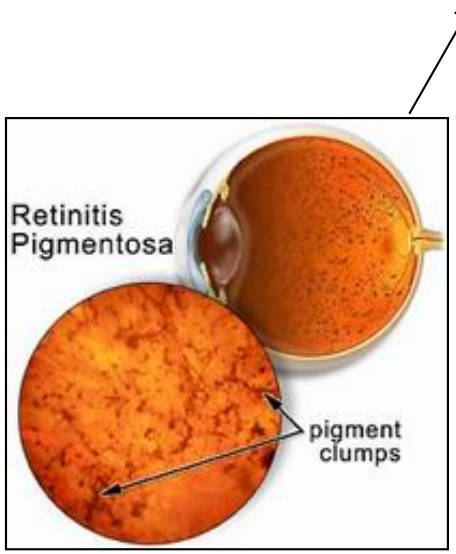
Gene-Gene and Gene-Environment interactions

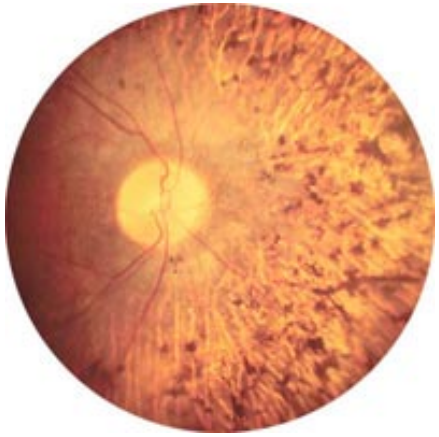


Complex inheritance of a case of pigmentary retinitis



Non mendelian: dominant?
Recessive? X-linked? …

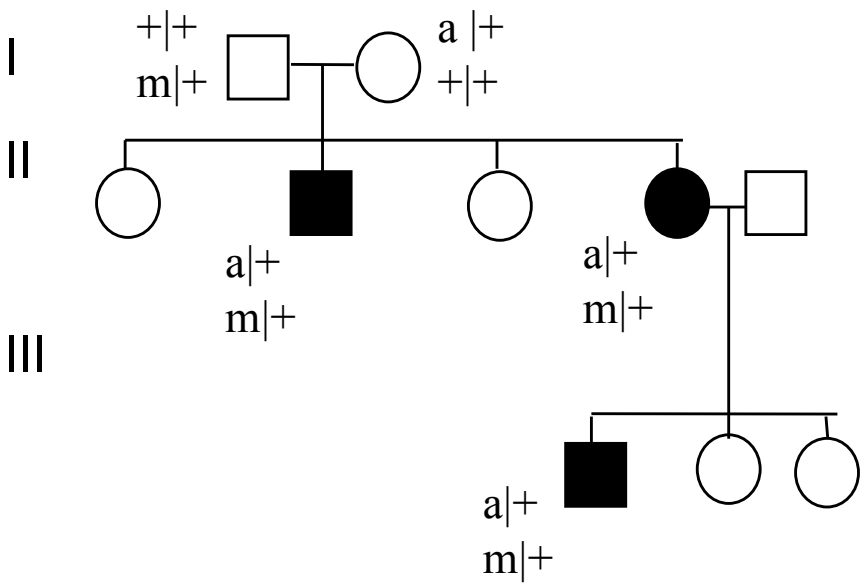




Tunnel vision

Digenic inheritance of a retinitis pigmentosa

ex: mutations a and m
non genetically linked
(+ = wt allele)

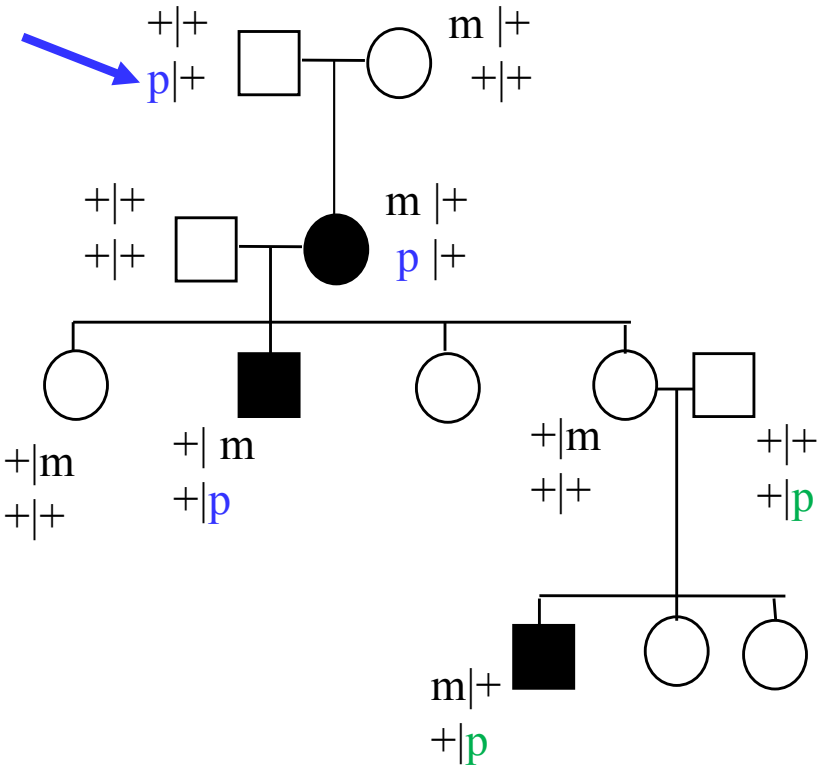


Ex: Rétinite pigmentaire from mutations at 2non-linked loci peripherin/*RDS* and*ROM1*. (Kajiwara et al. Science 1994)

- Disease if **double heterozygote** (htz at 2 ≠ loci). Complete penetrance then.
  - Parents are simple heteroz and unaffected
  - 1/4 of children will be affected in génération II ; resembles AR
- Over next generations (génération III etc...) :
  - ¼ offspring will be affected: very different from AR

- a et m are 2 rare mutations, independently inherited

Digenic inheritance, with 1 rare mutation rare (m), 1 frequent polym (p)



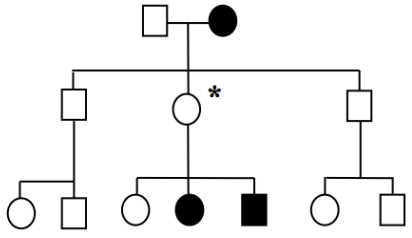
- AD with penetrance <1
- Penetrance = 1 if p present in everyone

Re-entry *of p in the pédigree*

Fqcy of allele m=1/10,000
Fqcy of allele p= 1/10

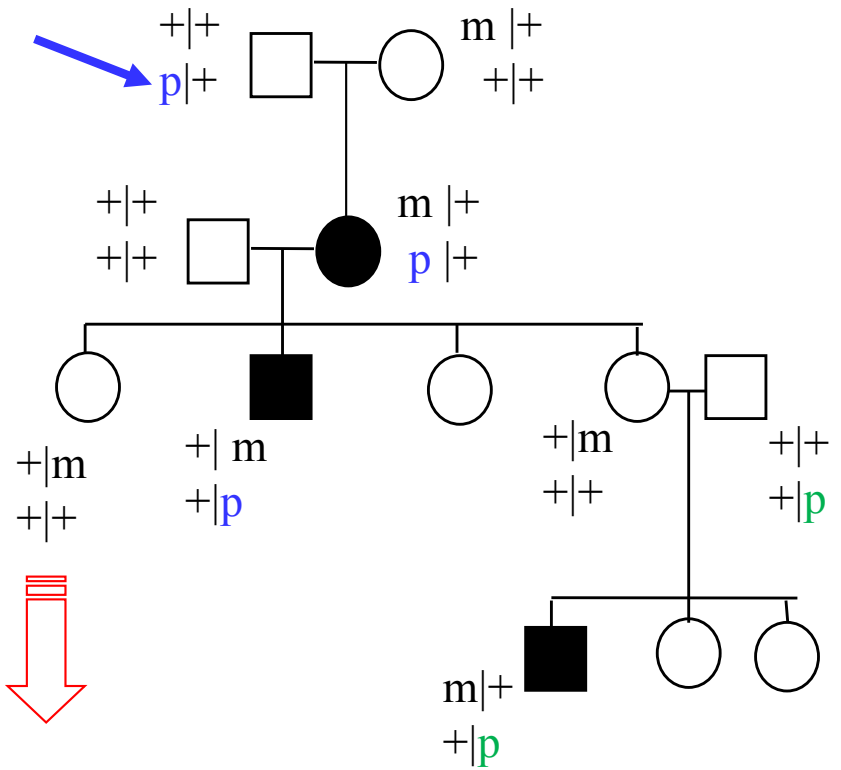
Incomplete penetrance

- **PENETRANCE**: % of mutation carriers who express phenotype



* « non-penetrant » subject :

Digenic inheritance, with 1 rare mutation rare (m), 1 frequent polym (p)



- AD with penetrance <1
- Pénétrance = 1 if p present in everyone

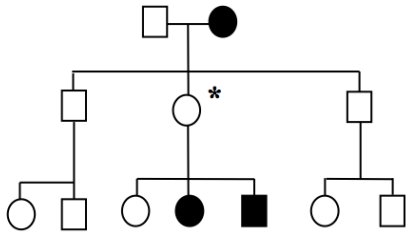
Re-entry *of p in the pédigree*

Migrates into island where all are p|p
=> AD , following transmission of m

Fqcy of allele m =1/10,000
Fqcy of allele p= 1

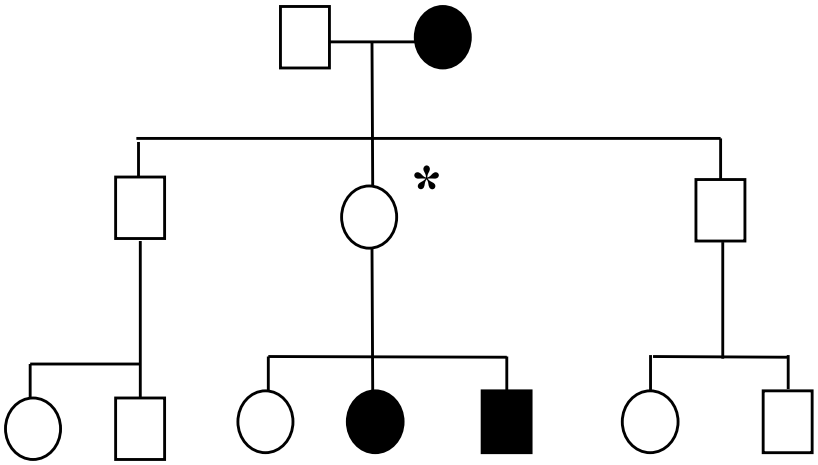
Incomplete penetrance

- **PENETRANCE**: % of mutation carriers who express phenotype



* « non-penetrant » subject :

MAJOR GENE: necessary but not sufficient
Modifyer gene: modifies penetrance/expressivity



Incomplete penetrance:

* "non-penetrant » individual

Human genetic diversity:

MUTATION and POLYMORPHISM

Mutations and polymorphisms

- MINOR MUTATIONS = Polymorphisms

  Little or no functional effect on phenotype

  (Little or no penetrance)

- MILD MUTATIONS

- MAJOR (SEVERE) MUTATIONS High penetrance

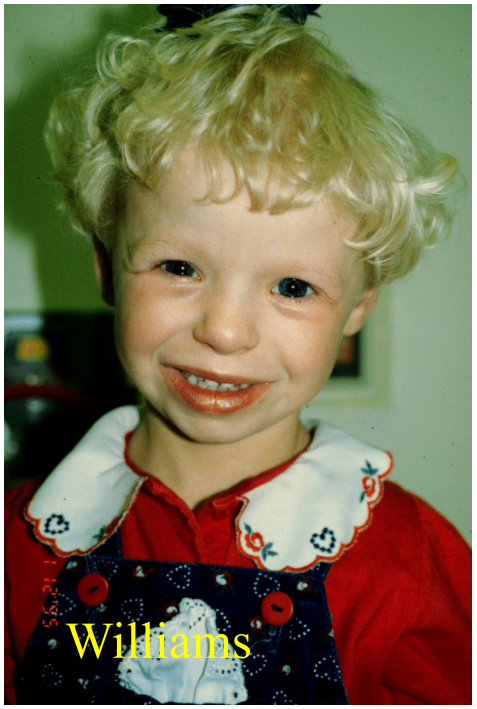
ALL are genetic VARIANTS = not wild type

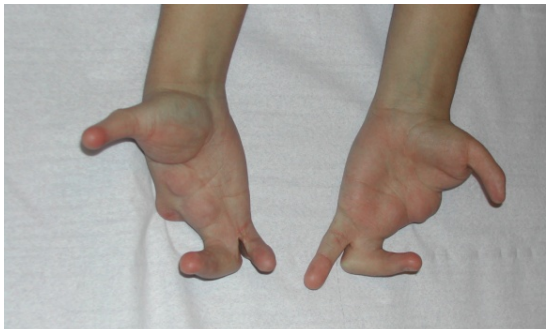
Mutations : tentative classification

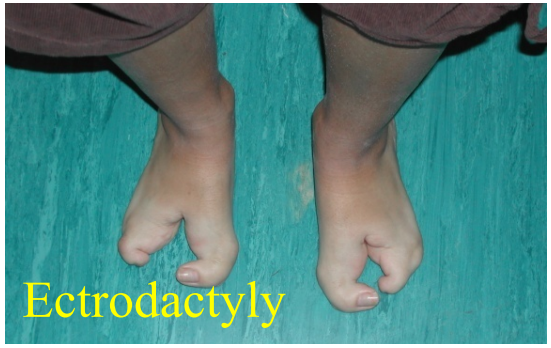
Class	Mechanism	Frequency	Examples
Genome mutation	Chromosome missegregation	>10% meioses	T21, other aneuploidies
Chromosome mutation	Chromosome rearrangement	1/1000 meioses	Microdeletion, translocation
Gene mutation	Base pair mutation	Varies with loci ~10^{-6} /locus /generation	Point mutations, indels

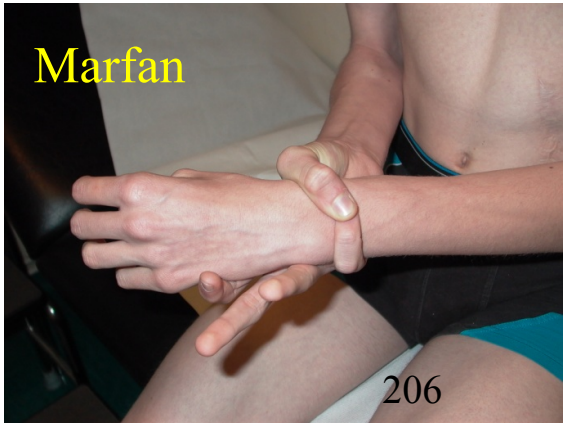
Most Genome mutations and Chromosome mutation affect survival and/or fertility => fitness ~0

Mutant phenotypes





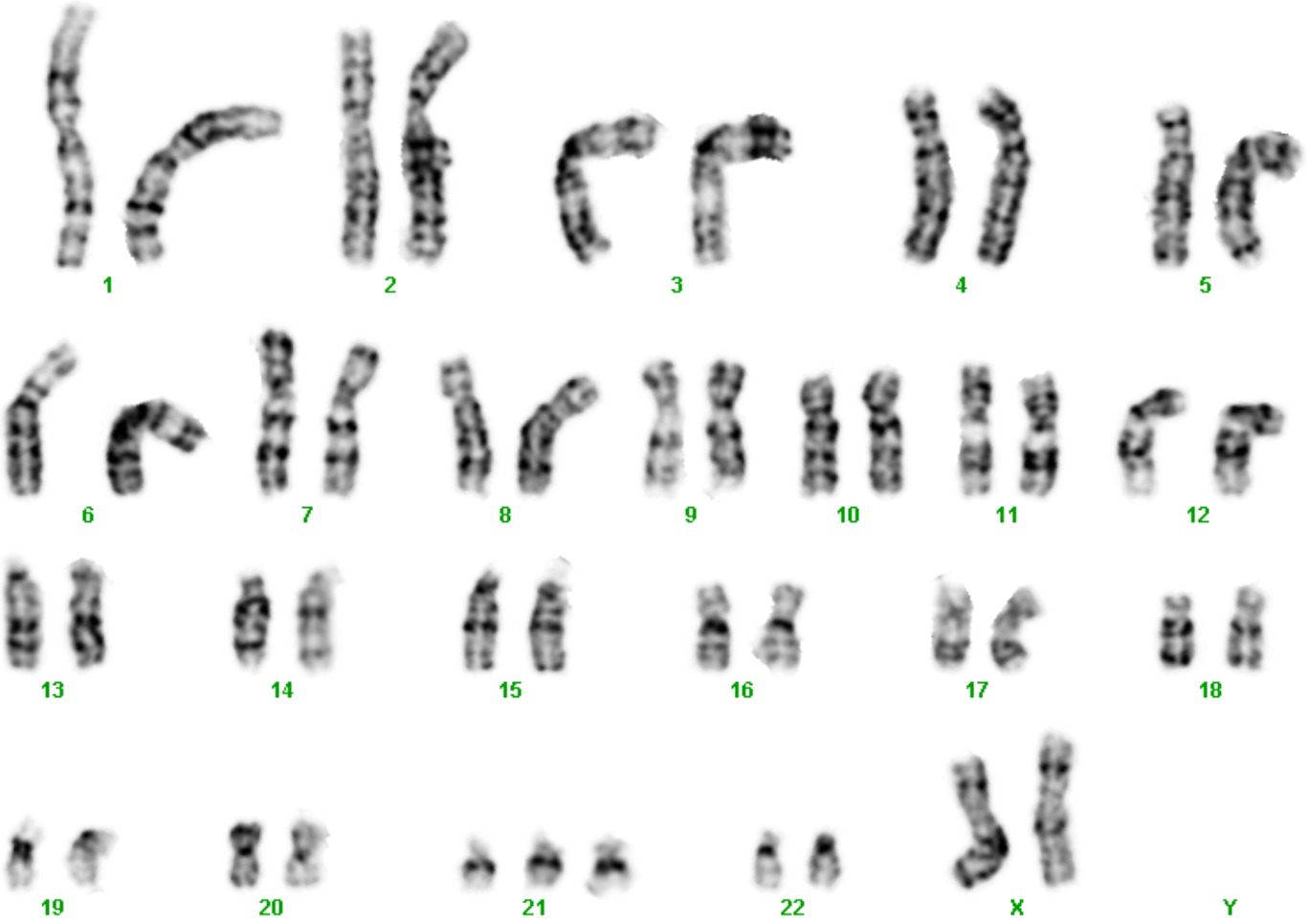




Genome mutation (T21) are new mutations

PHENOTYPE
= Down syndrome

GENOTYPE = T21



Mutations

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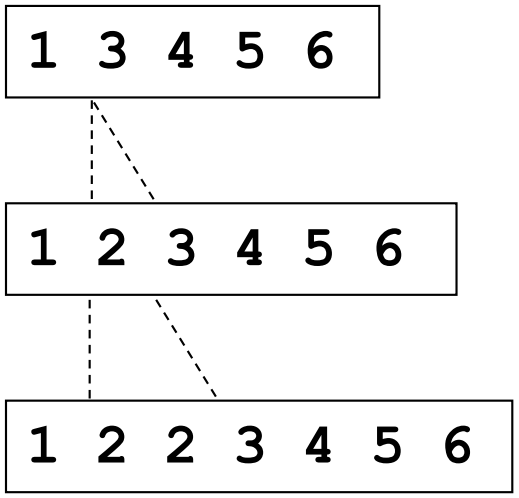
- Most Genome mutations and Chromosome mutation affect survival and/or fertility => fitness ~0

Chromosome mutations (chromosomal rearrangements; structural anomalies)

INTRACHROMOSOMAL:



INTERSTITIAL DELETION

NORMAL

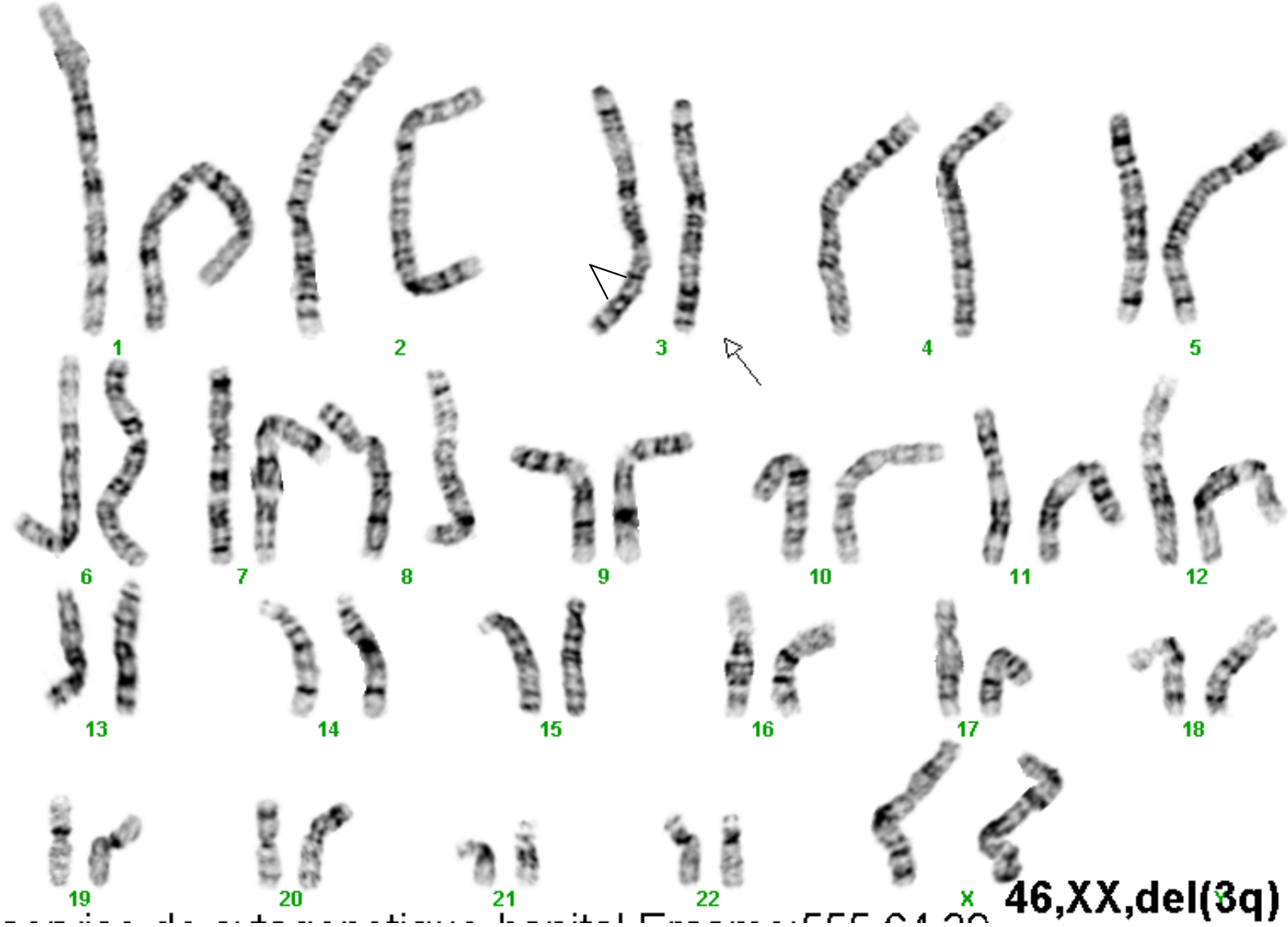
INTERSTITIAL DUPLICATION

=> Partial monosomies and trisomies (or tetrasomies…)
may be compatible with live birth

INTERCHROMOSOMAL

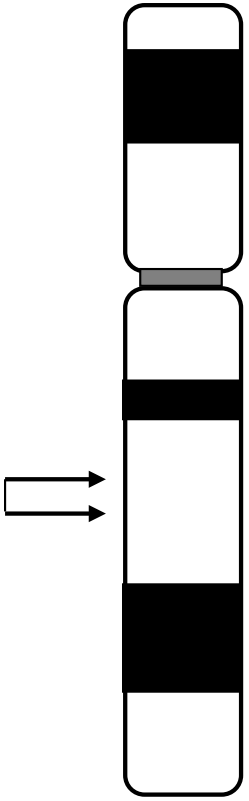
- translocations
- Inversions : pericentric, paracentric

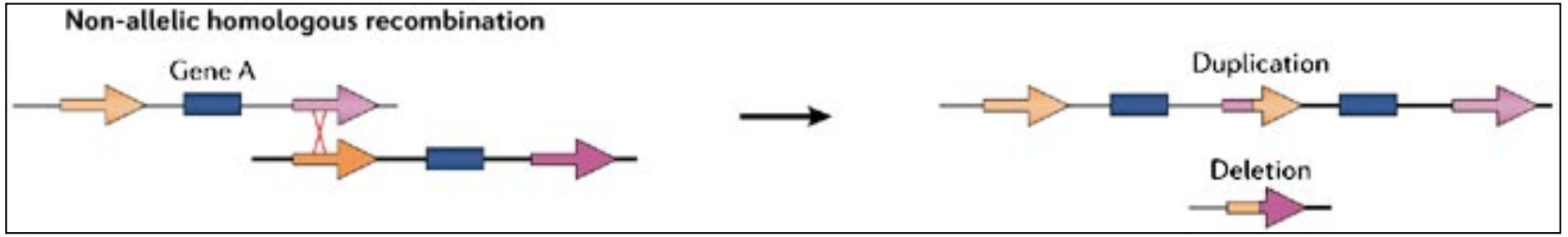
Interstitial deletion, long arm, # 3



Sub–microscopic chromosomal interstitial del (microdeletions)

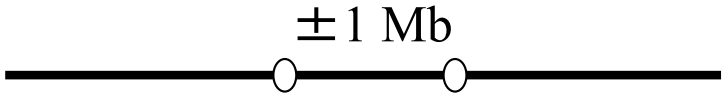
- Unseen on standard K
- May cause MCA+ID
  - Partial monosomy
  - Phenotype if involves haplo-insufficient genes
- Recurrent Microdeletions => known syndromes
- Single gene or contiguous genes
- Same for microduplication.





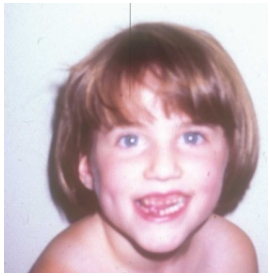
Recurrent microdeletions => Known syndromes

- Breakpoint hot-spots
  (interspersed repeats)
  – 1 meiose / 10,000

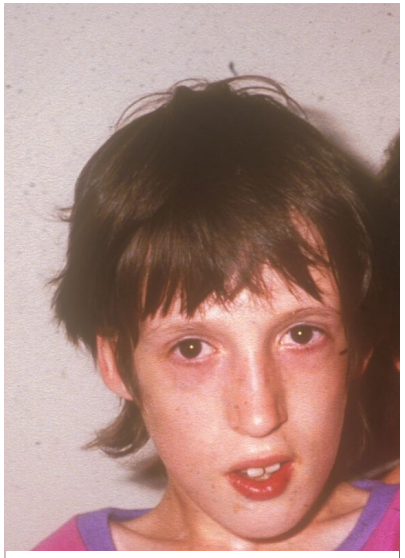


- Known Syndromes
  – **Williams** syndrome (7q)
  – **DiGeorge** syndrome (22q)
  – Prader-Willi / **Angleman**
  (15q, imprinting)
  – …et autres…

St. Ao, ↑Ca^{++}…



Ataxia, laughter,…



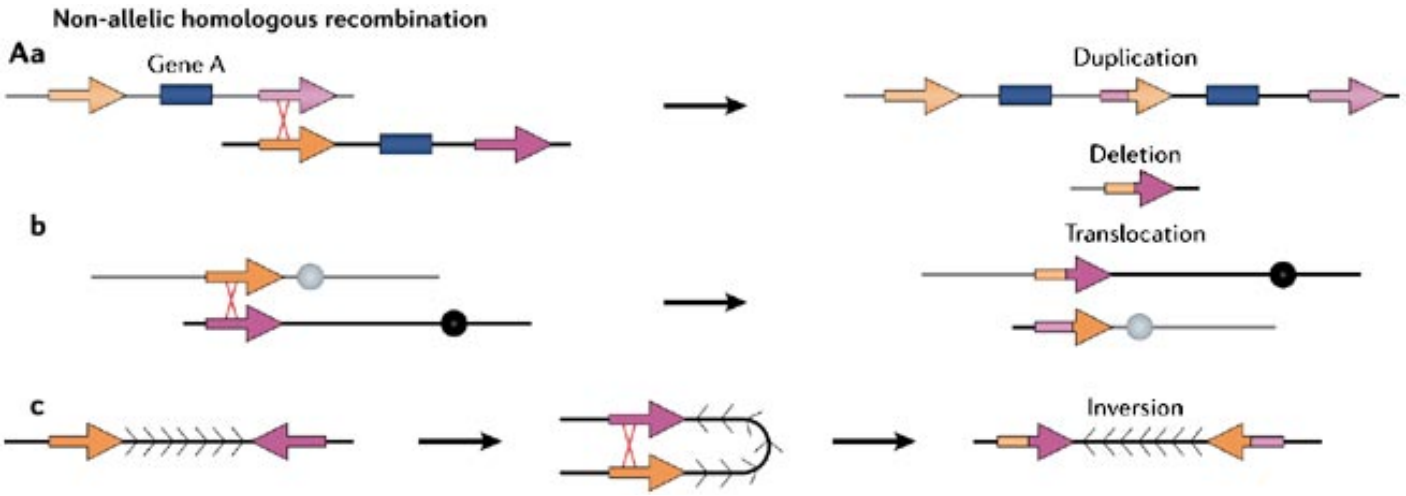
Lymphopenia T,
hypoPTH,…

Non Allelic Homologous Recombination (NAHR)

eg, Deletion PMP22 => HNPP
Duplication PMP22 => CMT1a

Bailey & Eichler

NAHR



Bailey & Eichler

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