Non-Mendelian inheritance

Focus on Human Disorders

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Causes of Non-Mendelian phenotypes

Single gene effects

- Sporadic mutations
- Germline mosaicism
- Reduced penetrance
- Variable expressivity
- Pleiotropy
- Locus Heterogeneity

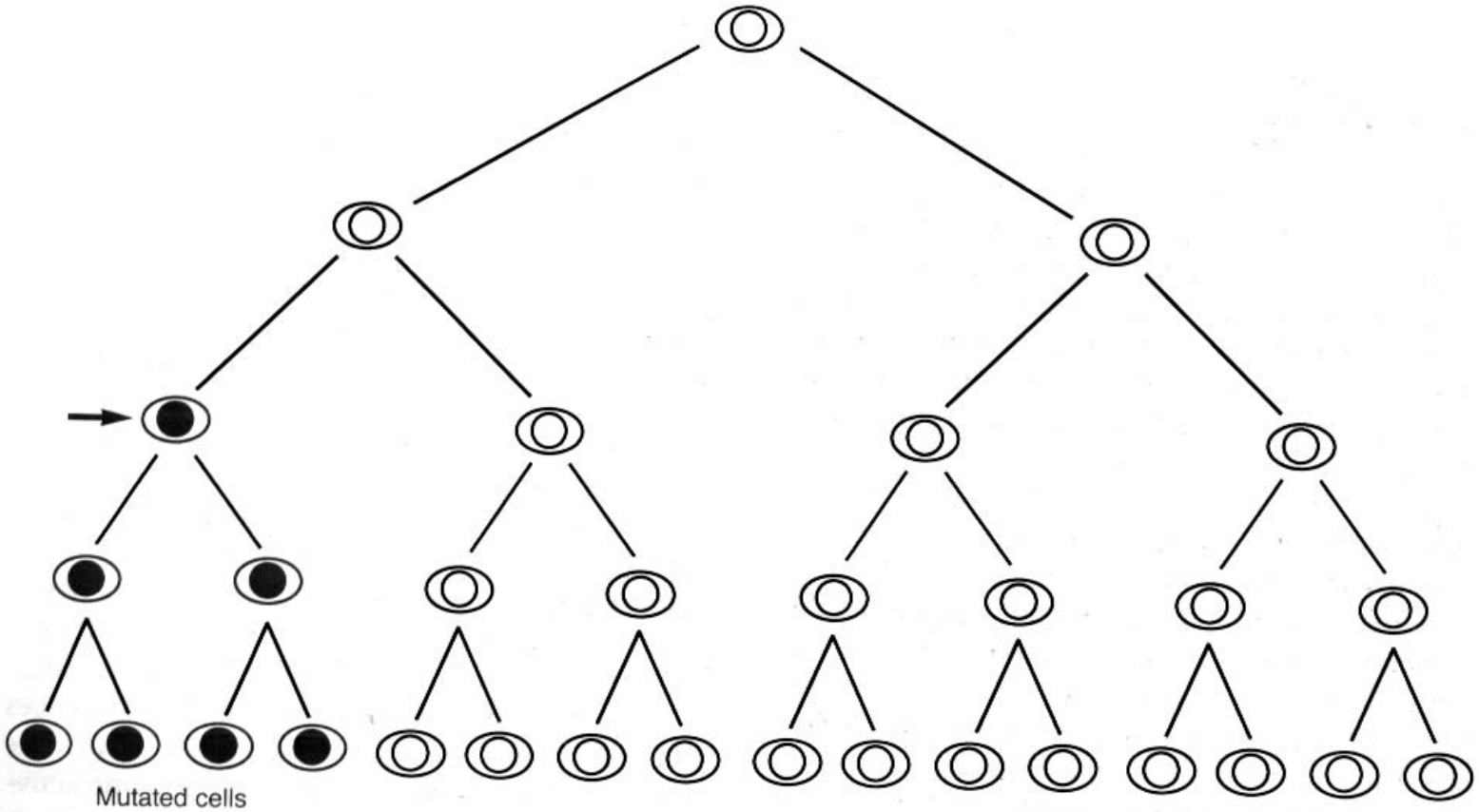
Complex inheritance

- Multi-hit and acquired mutations
- Genomic imprinting
- Mitochondrial transmission
- Anticipation

Sporadic mutations

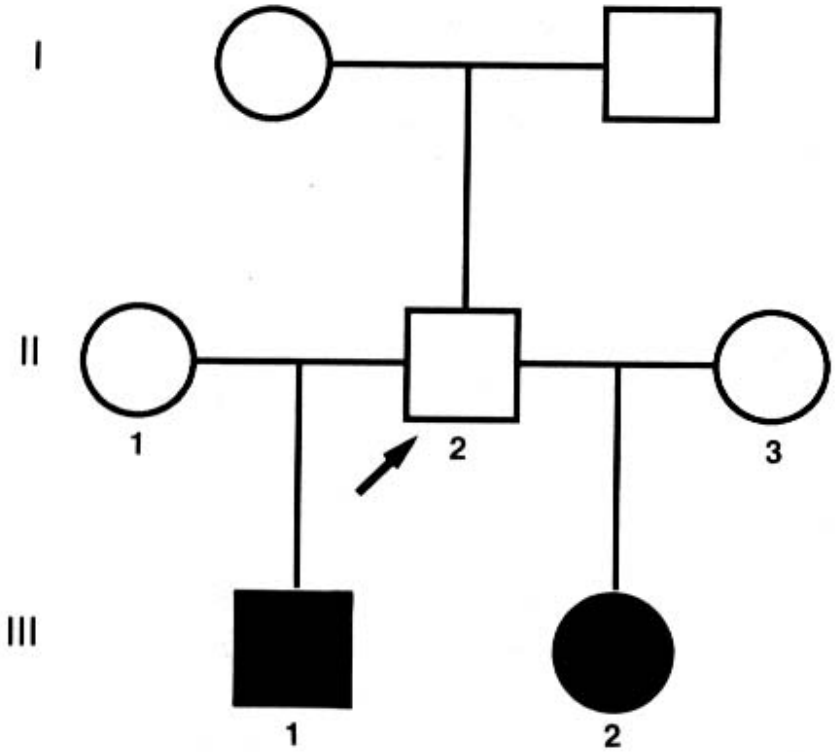
- **Chromosomal: non-disjunction, aneuploidy often maternally derived, most common (~50% of all conceptions)**
- **Other mutations:**
  - **the most frequent de novo intragenic deletions occur in large or duplicated genes (eg. Dystrophin, neurofibromin, 21-hydroxylase).**
  - **point mutations - often paternally derived, most are private, but hot spots have been noted (FGFR1)**

Germline mosaicism:mechanism



Schematic presentation of mitotic cell divisions. Mutations occurring during cell proliferation, in either somatic cells or during gametogenesis, lead to a proportion of cells carrying the mutation—that is, to either somatic or germline mosaicism.

Germline Mosaicism:example

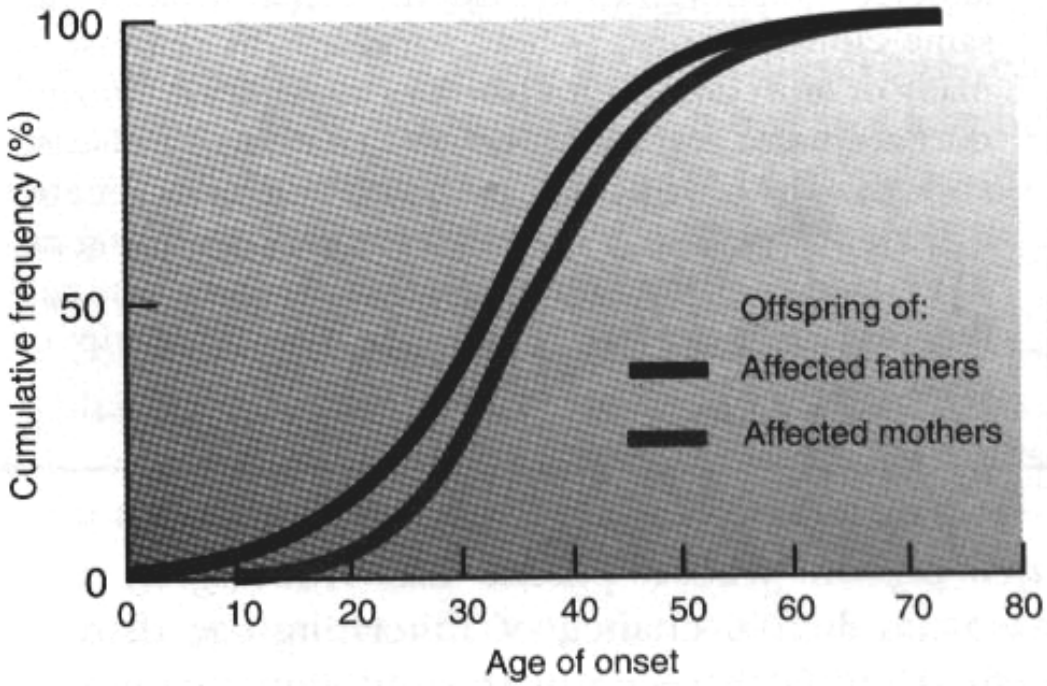


Pedigree demonstrating recurrence of the autosomal dominant disorder osteogenesis imperfecta. Both affected children have the same point mutation in a collagen gene. Their father (arrow) is unaffected and has no such mutation in DNA from examined somatic tissues. He must have been a mosaic for the mutation in his germline.

Penetrance

Definition: Refers to all-or-non expression of a mutant genotype. Usually a dominant trait in heterozygote. If condition expresed in <100% of those with mutation, said to have *reduced penetrance.*

Age-related penetrance

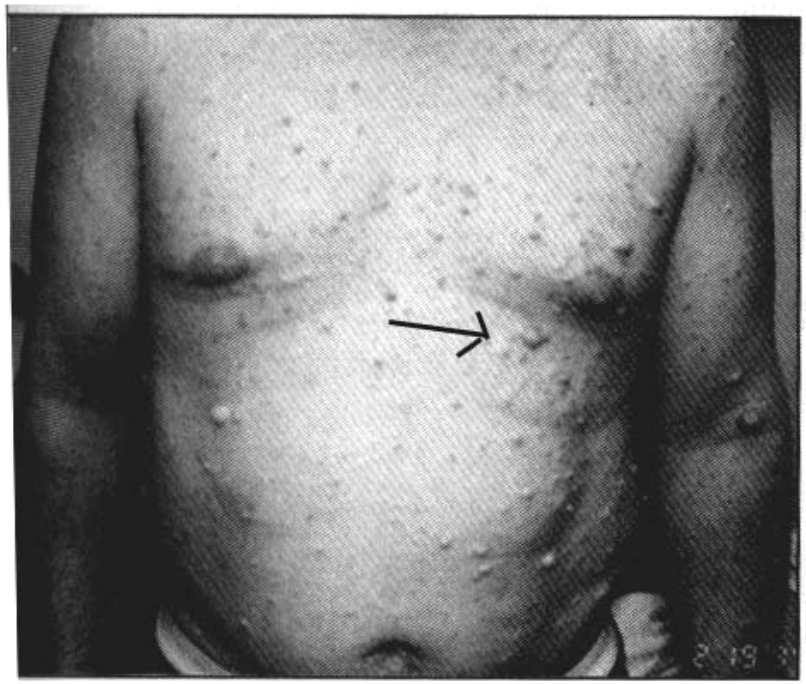


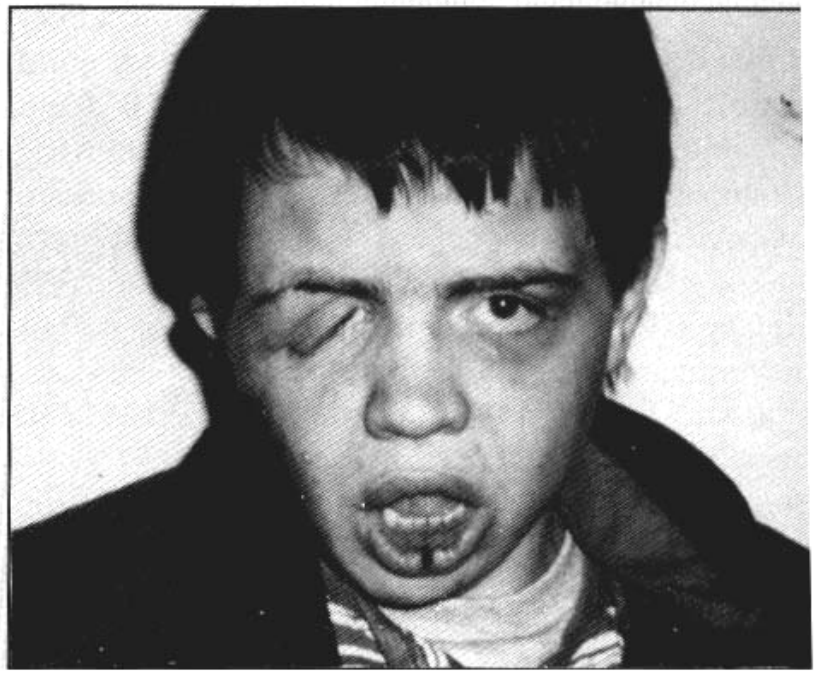
Distribution of the age of onset for Huntington disease. Note that age of onset tends to be somewhat earlier when the affected parent is male.

Variable expressivity

Definition: The extent to which a genetic defect is expressed. If there is variable expressivity, the trait may vary in expression from mild to severe, but it is never completely unexpressed in individuals with the corresponding mutant genotype.

Variable expressivity: Neurofibromatosis Type I



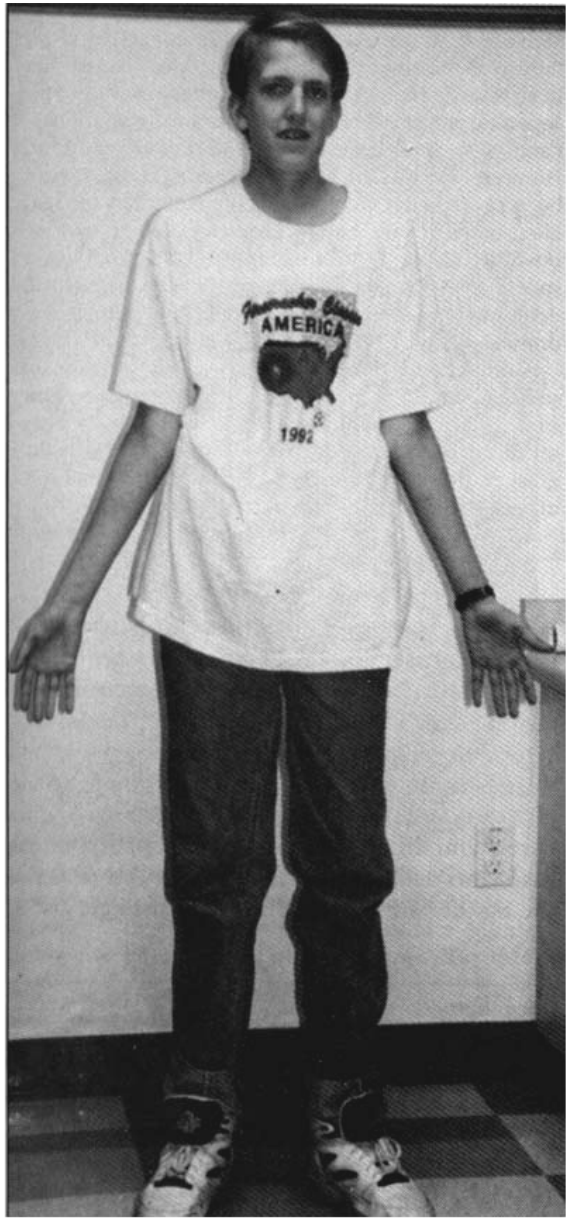


■Neurofibromatosis 1
trunk. Note also a *café-au-lait* sp
plexiform neurofibroma of the l
facial asymmetry

Pleiotropy

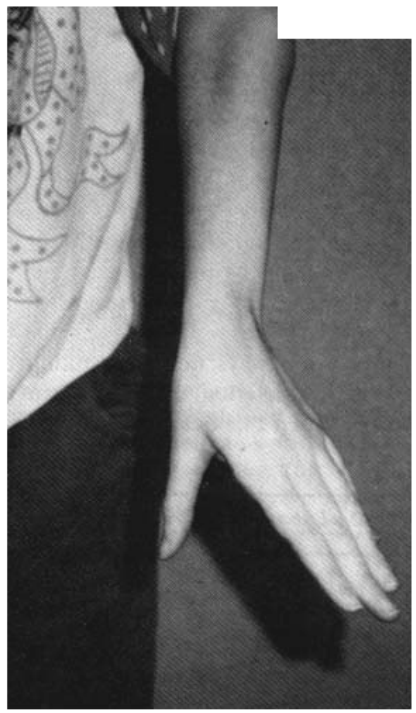
Definition: Multiple phenotypic effects of a single gene or pair of alleles. The term is used particularly when the effects are thought to be unrelated.

Example:



Pleiotropy: Marfan syndrome

Left: long limbs, narrow face, pectus carinatum
Right: arachnodactyly
Not shown: ectopia lentis, mitral valve prolapse



Locus heterogeneity

Definition: The situation in which mutations at 2 or more distinct gene loci can produce the same or closely similar phenotypes.

Examples of diseases in which there is locus heterogeneity

Disease	Description	Chromosomes on which known loci are located
Retinitis pigmentosa	Progressive retinopathy and loss of vision	1, 3, 6, 7, 8, 11, 14, 16, 19, X
Osteogenesis imperfecta	Brittle bone disease	7, 17
Charcot-Marie-Tooth disease	Peripheral neuropathy	1, 17, X
Familial Alzheimer disease	Progressive dementia	14, 19, 21
Familial melanoma	Autosomal dominant melanoma (skin cancer)	1, 9
Hereditary nonpolyposis colorectal cancer	Autosomal dominant colorectal cancer	2, 3
Adult polycystic kidney disease	Accumulation of renal cysts leading to kidney failure	4, 16

Predisposition to cancer: germline mutations in tumor suppressor genes

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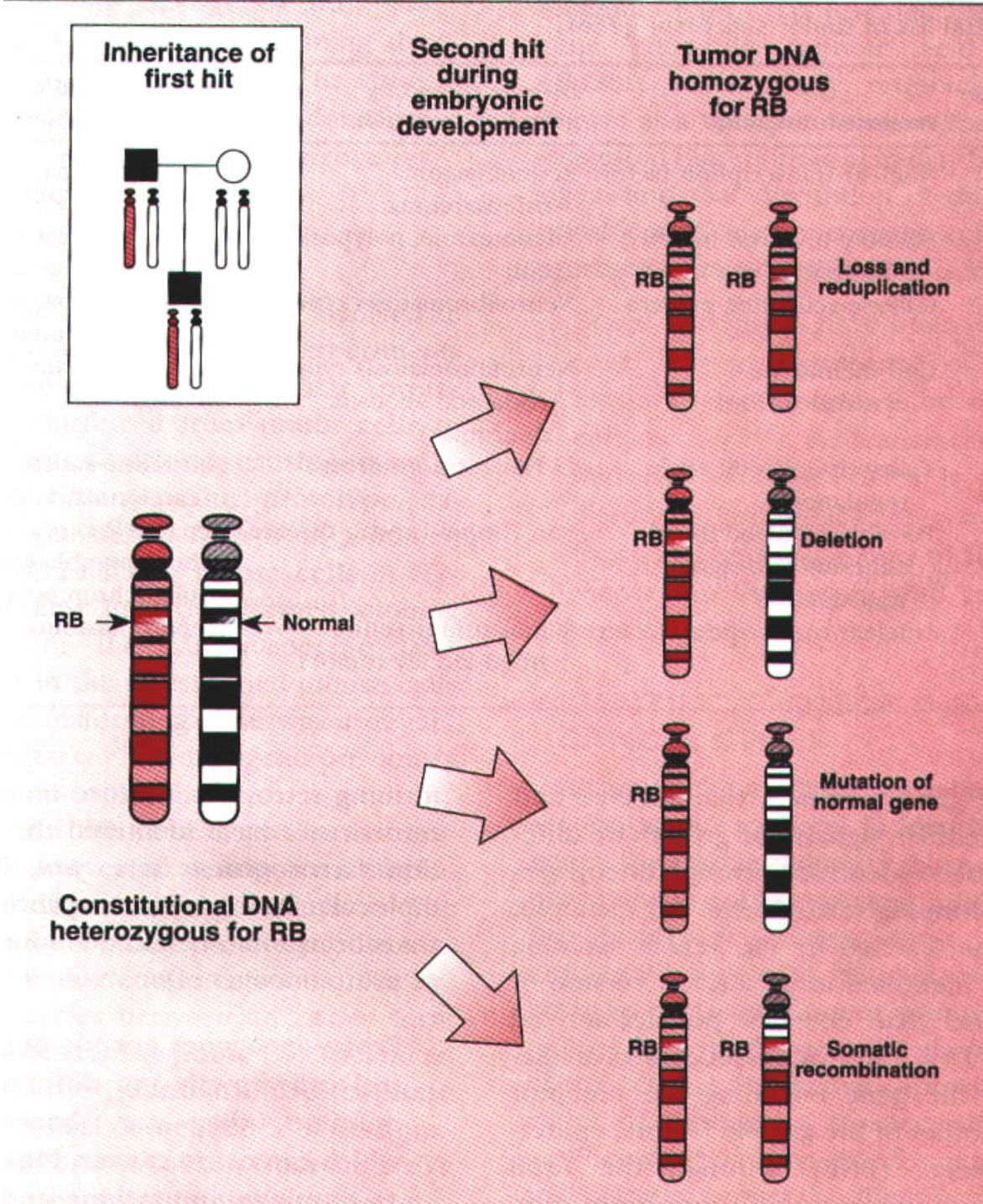
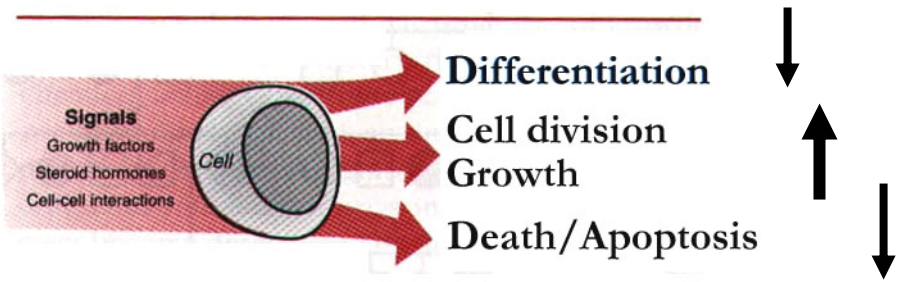


The neoplastic phenotype

All cells in the body are "programmed" to develop, grow, differentiate, and die in response to a complex system of biochemical signals. Cancer results when any cell is freed from these constraints and its abnormal progeny are allowed to proliferate.



Proto-oncogenes regulate growth. {Mutations in these genes are dominant and are often acquired.}

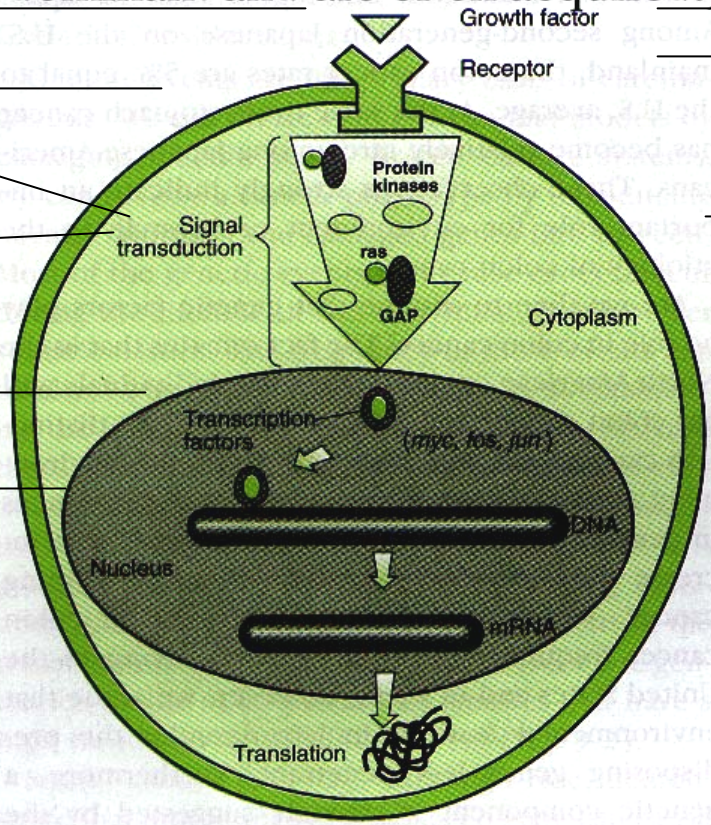
Growth factor

Receptor

Protein kinase,
G-protein

Transcription factor

Nuclear DNA binding proteins



Examples:

sis,

erbA,src,raf1

H-ras,abl,trk

jun

myb,fos,myc

The regulation of cell growth is accomplished by substances that include: (1) polypeptide growth factors that transmit signals from one cell to another, (2) growth factor receptors on the cell surface, (3) signal transduction molecules that activate a cascade of phosphorylating reactions within the cell, and (4) nuclear transcription factors.

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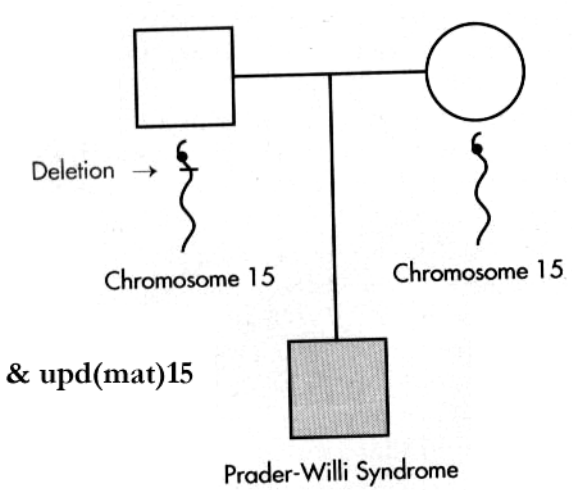
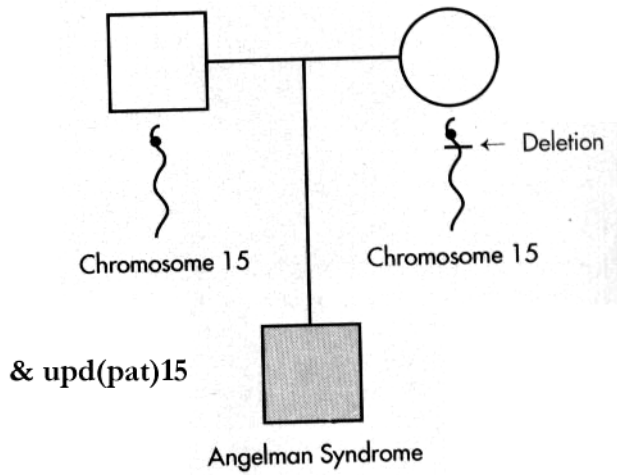
Genomic imprinting

Definition: a process in which genetic material is expressed differently when inherited from the mother than when inherited from the father.



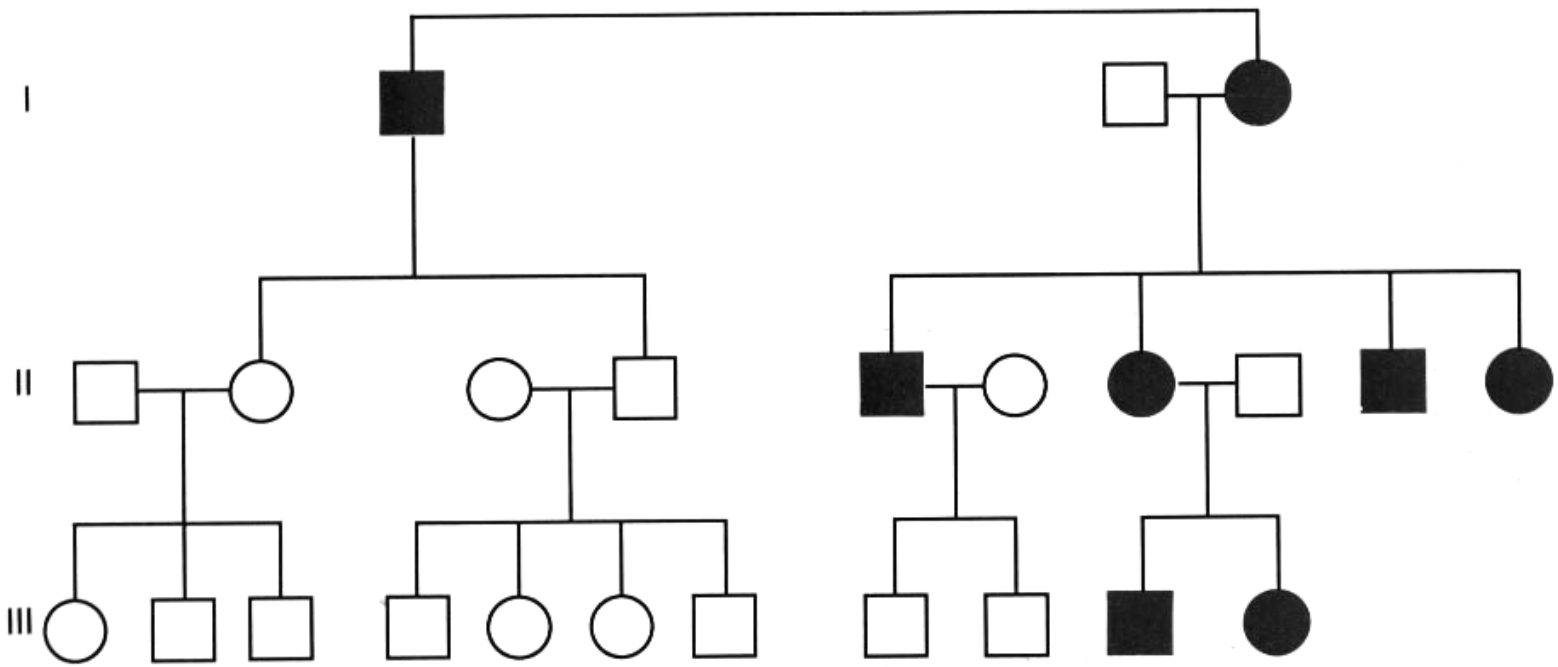


Mitochondrial inheritance

Definition: Inheritance of a disorder encoded by the mitochondrial genome. Always maternal; hundreds to thousands of mtDNA genomes per cell. Because of heteroplasmy*, only those progeny with mutant mtDNA exceeding a threshold will exhibit an abnormal phenotype.

*Heteroplasmy: The existence of differing DNA sequences at a locus within a single cell.

Mitochondrial inheritance: pedigree



Pedigree of Leber's hereditary optic neuropathy, a disorder caused by a defect in mitochondrial DNA. Inheritance is only through the maternal lineage, in agreement with the known maternal inheritance of mitochondrial DNA. No affected male transmits the disease.

Phenotypes of mitochondrial disorders

Examples of Mitochondrial Disorders

Disease	Chief Distinguishing Features
Kearns-Sayre syndrome (KSS)	External ophthalmoplegia, retinal degeneration, heart block, high cerebrospinal fluid protein; usually sporadic; mitochondrial DNA deletions demonstrated
Leber's hereditary optic atrophy (LHON)	Rapid optic nerve death leading to blindness in young adult life; maternal inheritance; mutation in mitochondrial DNA demonstrated
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)	As described in name, plus sensorineural hearing loss, dementia, short stature; sporadic mitochondrial DNA deletions demonstrated
Myoclonus epilepsy with ragged red fibers (MERRF)	As described in name; maternal inheritance

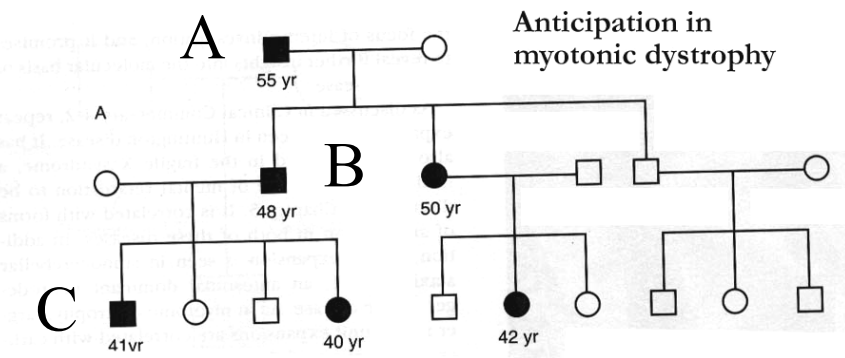
Genetic anticipation

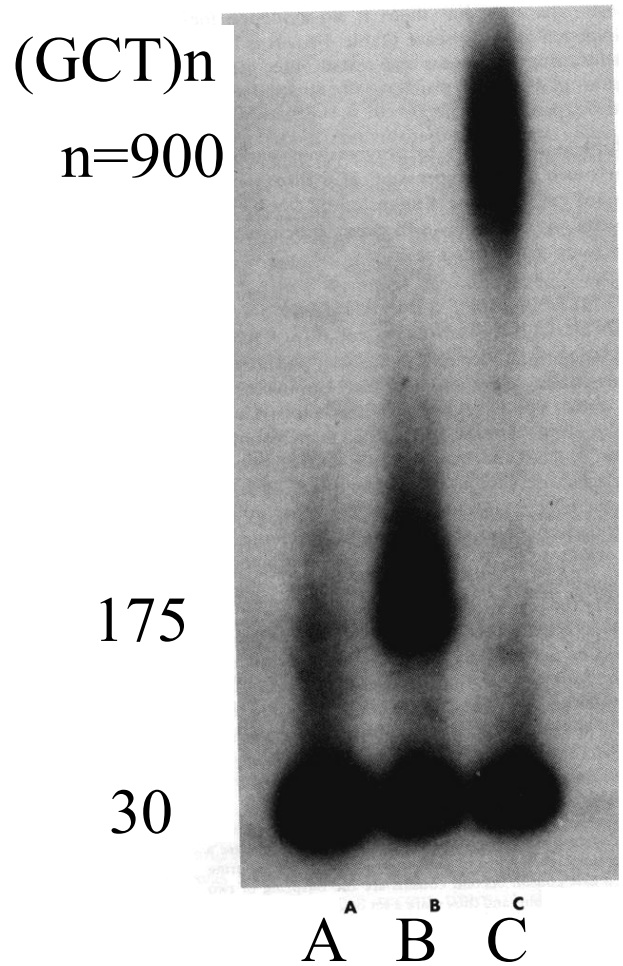
Definition: Term used to denote progressively earlier appearance and increased severity of a disorder in successive generations. Until its molecular basis was understood, it was thought to result from biased ascertainment.

Example disorders include:
Fragile X disease
Myotonic dystrophy
Spinocerebellar ataxia
Huntington disease
X-linked spinal bulbar muscular atrophy
Freidrich's ataxia

Biological basis of anticipation

The disease mutations are expanded trinucleotide repeats that lie within the affected gene. The number of repeats increases in each successive generation. Expansion of the DNA repeats (probably by slipped mispairing) has been shown to cause anticipation in Fragile X syndrome, myotonic dystrophy, spinocerebellar ataxia (but not in spinal bulbar muscular atrophy).





Summary: Non-Mendelian inheritance

- Incomplete penetrance and variable expressivity produce deviations from expected inheritance patterns for Mendelian diseases.
- Certain types of sporadic mutations may be quite common- no family history is evident.
- Parent of origin effects, mitochondrial disease, germline instability or multi-hit mutation mechanisms also alter inheritance patterns. However, the genetic lesion must be known to predict who is at risk.