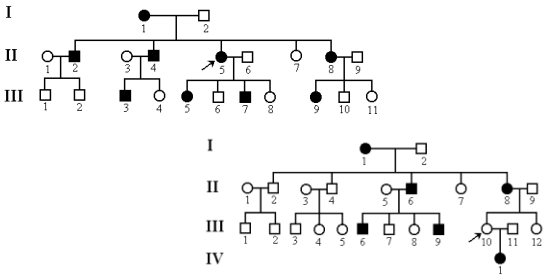
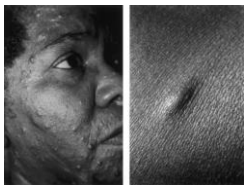
Mendelian pedigree patterns

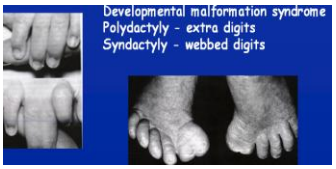
- Autosomal dominant
- Autosomal recessive
- X-linked dominant
- X-linked recessive
- Y-linked

Autosomal-dominant inheritance

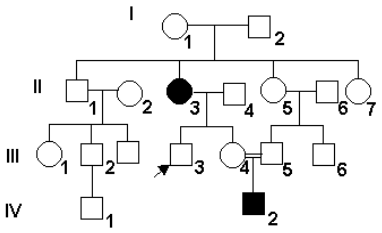


Examples of AD inheritance



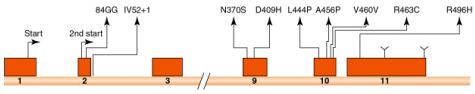


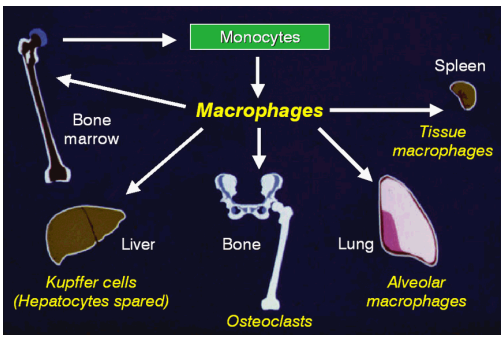
Autosomal-recessive inheritance



Gaucher disease

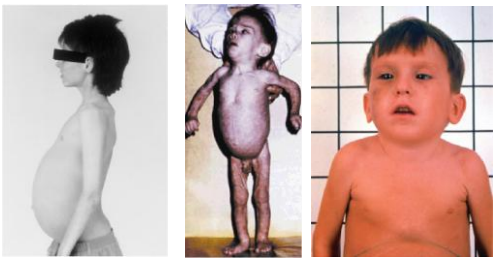
Multiple mutations in gene (chrs 1) which encodes the enzyme GLYCOCEREBROZIDASE





	Type 1	Type 2	Type 3
Age of appearance	In any age	In childhood	In childhood
Duration of life	6 - 80	2 years	6 - 80
Primary deffects of CNS	-	++	+ →+++
Hepatospleno-megaly	+ →+++	+++	+ →+++
Hematological abnormalities	+ →+++	++	+ →+++
Skeletal abnormalities	- →+++	-	- →+++

Gaucher disease



Nonmendelian inheritance

- Nonmendelian monogenic characters
- Genetic heterogeneity
- Mitochondrial inheritance
- Polygenic characters

Monogenic characters

Mendelian

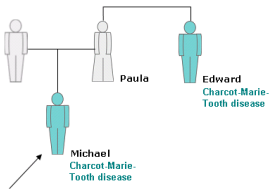
Have biallele determinism
Follow mendelian patterns
Correspond to one of the basic pedigree patterns
Have bimodal distribution in population (normal phenotype/pathologic)

Nonmendelian

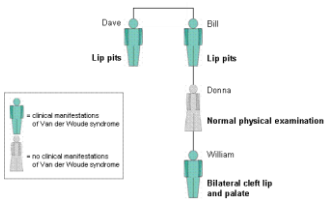
Have biallele or monoallele determinism
Do not follow mendelian patterns
Do not correspond to basic pedigree patterns
Show variable manifestation in phenotype: nonpenetrance, variable expression

Phenomena which influence the expression of AD genes

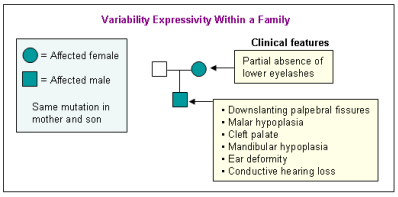
- Nonpenetrance
- Variable expression
- Tissue specificity
- Sporadic cases by *de novo* mutations



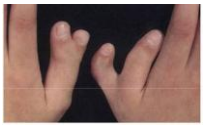
Nonpenetrance

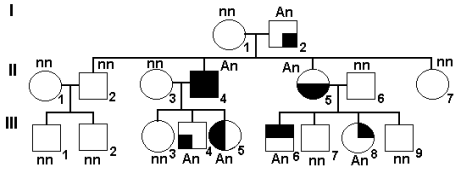


Variable expression



Polydactily



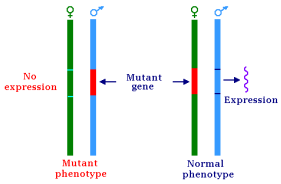


Phenomena which influence the expression of AR genes

- Single allele expression (genome imprinting, lyonization, allele exclusion)
- Uniparental disomy
- Compound heterozygotes

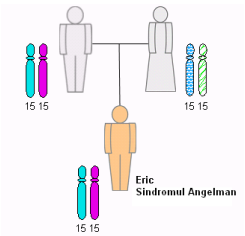
Genome Imprinting

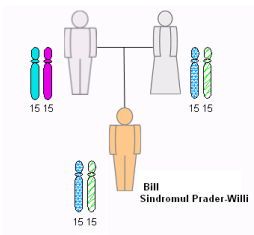
- Expression of genes is controlled by patterns of methylation that differ according to the parental origin of gene



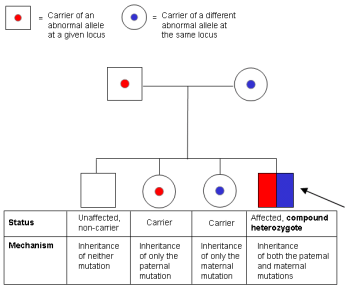
Uniparental disomy

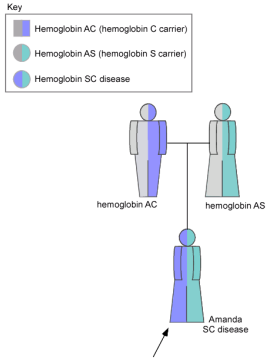
Angelman and Prader-Willi syndromes





Compound heterozygotes



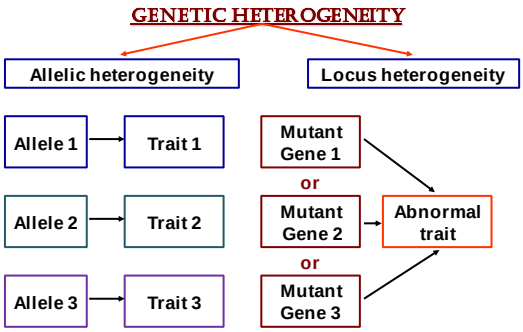


Mechanisms involved in variable expression of pathological genes

- Allele and non-allele interactions
- Allele and locus heterogeneity
- Pleiotropy
- Unstable expanding repeats
- Environmental factors

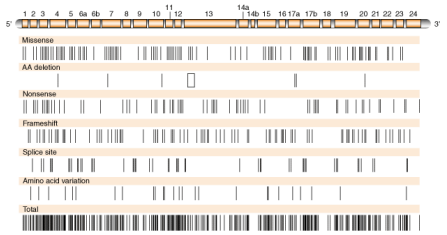
Genetic heterogeneity

- Heterogeneity is a phenomenon when different mutation produce the similar phenotype
- There are two types:
  - Locus heterogeneity – different nonallele gene mutations produce the similar phenotype
  - Allelic heterogeneity – different allelic mutation in the same locus produce the similar (but not identical) phenotype

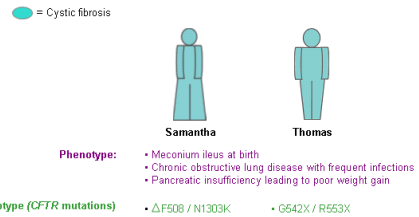


Allelic heterogeneity

Numerous mutations in gene which encode Cl^- channel produce the cystic fibrosis



Allelic heterogeneity (cystic fibrosis=mucoviscidosis)

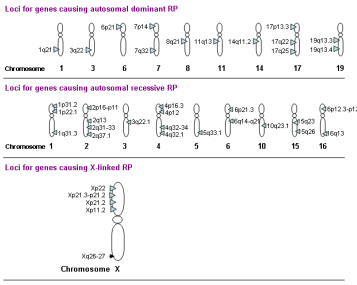


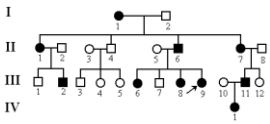
Allelic heterogeneity

Mode of Inheritance	Genotype		Phenotype
Autosomal recessive	Over 400 mutations in *PAH* (encoding phenylalanine hydroxylase) (locus 12q23.2)	**Phenylketonuria** Chromosome 12	Without dietary intervention, accumulation of phenylalanine causes severe to profound mental retardation
Autosomal dominant	Over 200 mutations in *FBN1* (encoding fibrillin1) (locus 15q21.1)	**Marfan syndrome** Chromosome 15	Disproportionate tall stature, lens dislocation, mitral valve prolapse, aortic dilatation and possible rupture
X-linked	Multiple mutations in *F8* (encoding coagulation factor VIII) (locus Xq28)	**Hemophilia A** X Chromosome	Prolonged bleeding, excessive bruising

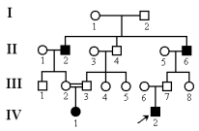
Locus heterogeneity

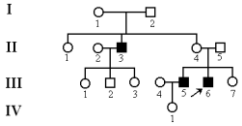
35 different A-D, R-D, X-R mutant genes are manifested as *Retinita pigmentosum*





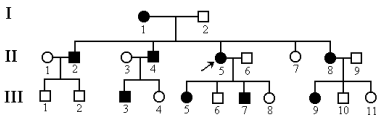
Retinita pigmentosum



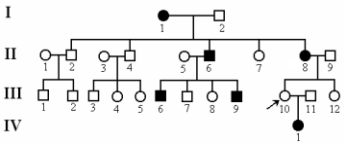


Pleiotropy

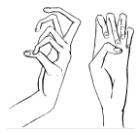
– one gene determine many different traits

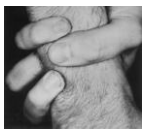


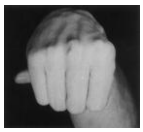
Marfan Syndrome



Marfan Syndrome

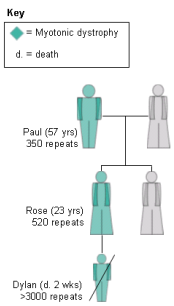






Unstable expending repeats

	CTG repeats	Appearance	Pathological traits
Paul	350	After 30 years	Myotony; muscle weakness
Rose	520	After 20 years	Myotony; muscle weakness
Dylan	>3000	prenatal	Sever muscle weakness; pulmonary insufficiency



Some diseases caused by unstable expanding repeats

Disease	Location of gene	Repeat sequence	Stable repeat no.	Unstable repeat no.
Fragile-X-syndrome	Xq27.3	CGG/CCG	5-50	>200
Myotonic dystrophy	19q13.3	CTG/CAG	5-35	50-4000
Huntington disease	4p16.3	CAG/CTG	6-35	>42
Freidreich ataxia	9p13	CAG/CTG	7-22	200-1700

Fragile- X-syndrome



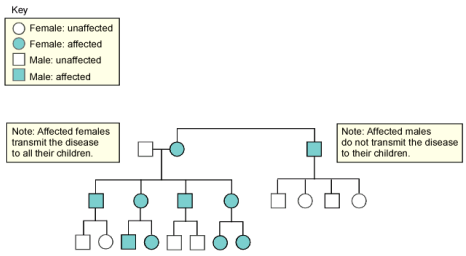
Mitochondrial inheritance

- Matrilineal inheritance, giving a recognizable pedigree pattern
- Disease is caused by mutation in mtDNA⇒ energy metabolism defects
- Mutations usually produce nervous and muscle systems diseases, but can affect any other organ
- Mitochondrial diseases have a early appearance, progressive evolution and variable expression

Mitochondrial diseases

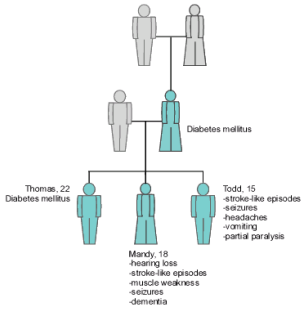
- CPEO – chronic progressive external ophthalmoplegy
- Ocular myopathy
- Hereditary cardiomyopathy
- MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes)
- Leber's hereditary optic atrophy
- MERFF (myoclonic epilepsy with ragged-red-fibers)

Mitochondrial disease



MELAS

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes

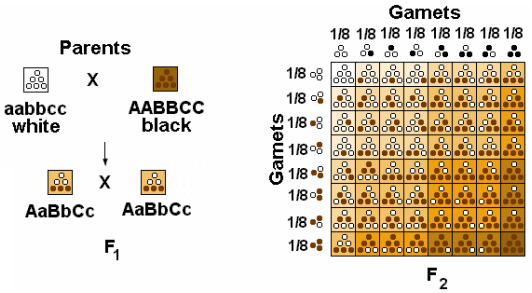


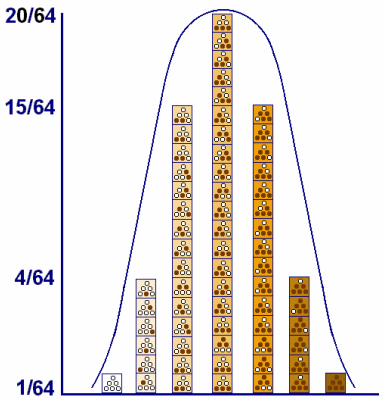
Multifactorial inheritance

Characters depend on many genetic loci, with greater or smaller contributions from environmental factors

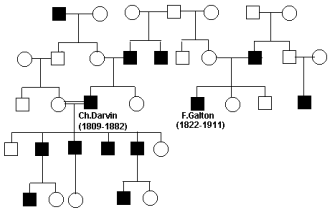
The genetic determination may involve a small number of loci (oligogenic) or many loci each of individually small effect (polygenic)

Most human normal traits, such as height, weight, eye and skin color, intelligence and metabolic rate are governed by the cumulative effects of many genes





Pedigree pattern of multifactorial transmission



Polygenic diseases

- Are determined by many genes;
- Have familial aggregation;
- Have bimodal or multimodal distribution;
- Recurrence risk depends on severity of disease, grade of relationship with sick person, number of affected relatives, coefficient of heredity,
- Ex.:common diseases; isolated congenital diseases; cancer; some forms of mental retardation.