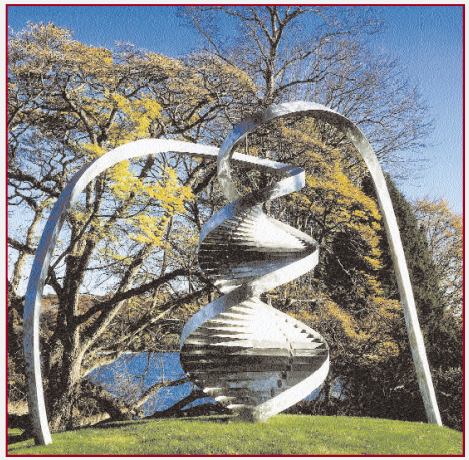


GENETIC AND CLINICAL HETEROGENEITY OF THE SINGLE - GENE DISORDERS

Factors that cause clinical heretogeneity

(or cause variable expression and reduced penetrance) of single gene disorders:

1. Genetic heterogeneity (allelic and locus)
2. Pleiotropy
3. The genomic imprinting
4. The expansion of unstable triplet repeats
5. The mosaicism (somatic and germ-line)
6. Environmental factors
7. The interaction of other genes (modifier genes)
8. The X-chromosome inactivation

!!!! They often cause problems in clinical or / and genetic diagnosis and genetic counseling !!!!

Genetic heterogeneity

Definition:

"The phenomenon that a disorder can be caused by different allelic or non-allelic mutations"

Types :

I. Allelic heterogeneity

II. Locus heterogeneity

I. Allelic heterogeneity :

(synonym: molecular heterogeneity)

" **Different mutations (multiple alleles) in the same gene in the same chromosomal locus that cause a particular phenotype** " (***in the population***)

- **Multiple alleles** are the result of a normal gene having mutated to produce **different alleles in the population,**

but

- **An individual** can possess **any two of these alleles (mutations)** and transmits **only one allele for a certain** particular offspring

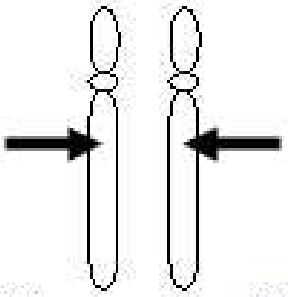
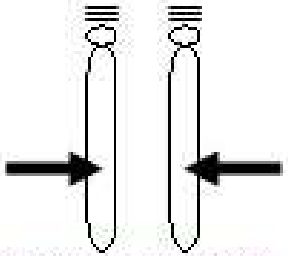
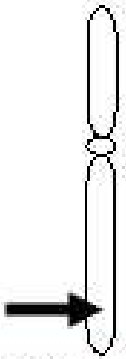
1. Single-gene normal traits and multiple alleles :

- the ABO-blood system (at least 4 alleles – A1, A2, B and 0)
- the HLA system
- the MN and Rh-blood groups
- alfa-antitripsin system etc.

2. Single-gene disorders and multiple alleles :

(almost all single-gene disorders)

- Cystic fibrosis - AR (more than 1000 mutations)
- Phenylketonuria - AR (> 400 mutations)
- Marfan syndrome – AD (> 200 mutations)
- Duchene-Becker muscular dystrophy - XR
- Hemophilia A and B etc. - XR

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

3. Allelic heterogeneity may cause Compound heterozygotes :

" An individual who is affected with an autosomal recessive disorder having two different mutations in homologous genes (instead of two Identical) "

Examples :

Cystic fibrosis, Phenylketonuria, Beta-thalassemia, DMD etc.

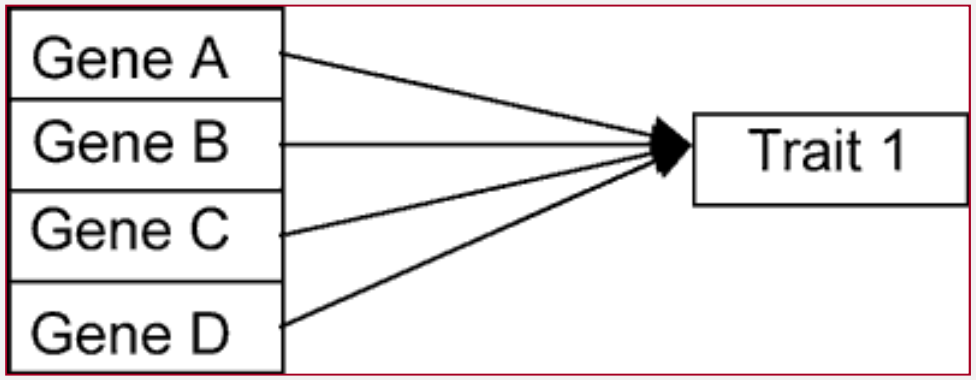
4. Allelic heterogeneity also may cause two distinct phenotypes (disease) :

- The beta-globin gene mutations can cause sickle-cell disease or various beta-thalassemias
- The dystrophin gene mutations can cause Duchene or Becker muscular dystrophy

II. Locus heterogeneity :

"The situation in which mutations in genes at different chromosomal loci cause the same phenotype in different affected families "

- "Genocopies" are genetic disorders with the same phenotype due to mutations at distinct genetic loci, sometimes with different models of inheritance (AD, AR, XL)
- "Phenocopy" means that a phenotype (a disorder) resembles the phenotype of genetic disorder but is due to a different, non-genetic factor



Examples – locus heterogeneity (genocopies):

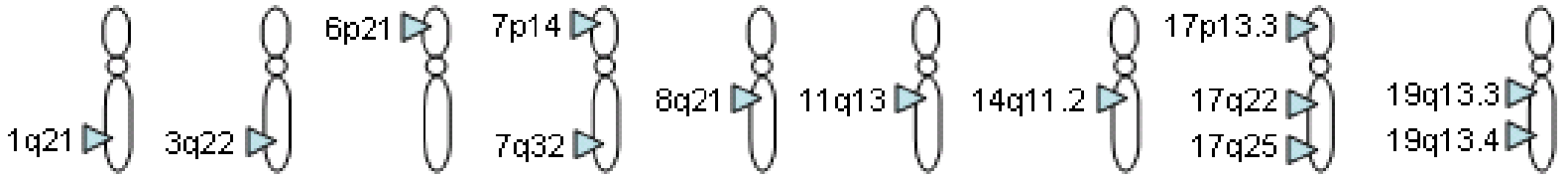
1. **Hemophilia A –** a defect in clotting factor VIII
   Hemophilia B, with a similar phenotype **-** a defect in clotting factor IX

   From the point of view of an affected person, a precise causation is important for the treatment (by factor VIII or factor IX)

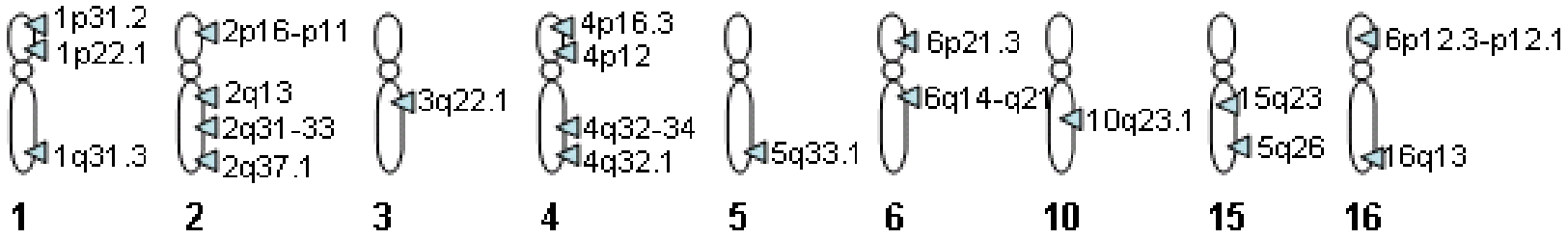
2. **Retinitis pigmentosa (RP) –** progressive rethinopathy and loss of vision
   - **RP** is a type of hereditary blindness caused by degeneration of photoreceptors (rods and cones) in retina
   - Pattern of inheritance can be AD, AR or XL, but only one locus is involved in any particular family

!!! The genetic counselling can be extremely difficult if the locus heterogeneity extends to different models of inheritance

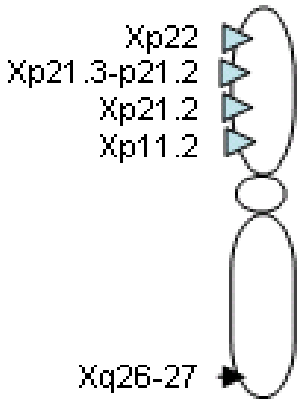
Loci for genes causing autosomal dominant RP



Loci for genes causing autosomal recessive RP

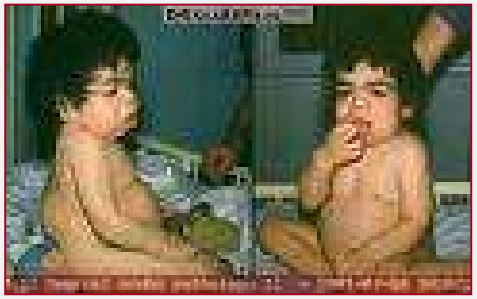


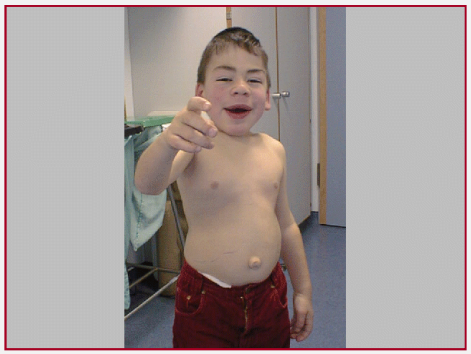
Loci for genes causing X-linked RP



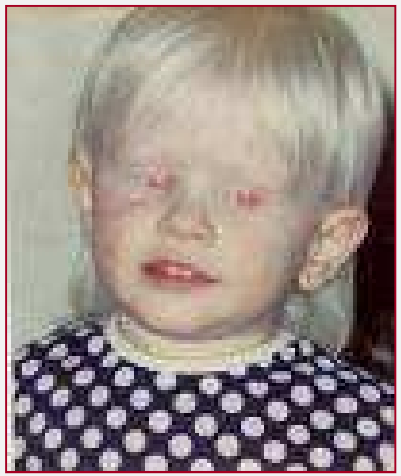
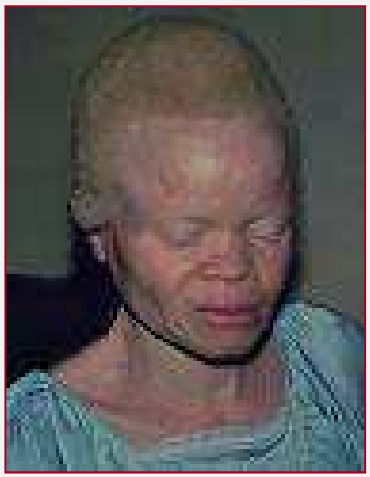
Genocopies :

3. Mucopolysaccharidoses - Hurler s-me (AR) and Hunter s-me (XR)



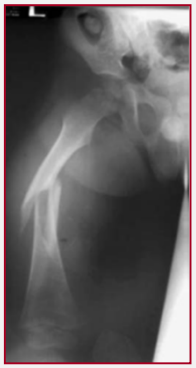
4. Albinism : AR and XR - forms

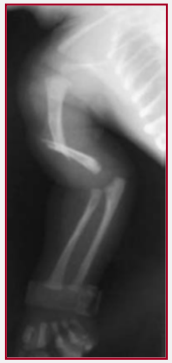



5. Osteogenesis imperfecta OI (AD ; AR) :

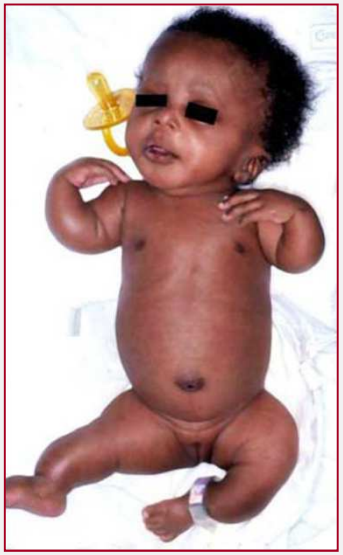
Clinical features : fractures ; hyperextensible joints ; hypoplasia of dentin ; thin skin ; blue appearance sclerae

- mutations are in genes on either **chromosome 17 or chromosome 7**
- **OI** is a good example for phenomena such as pleiotropy, locus and allelic heterogeneity





OI : I тип (AD)



OI : II тип (AR)

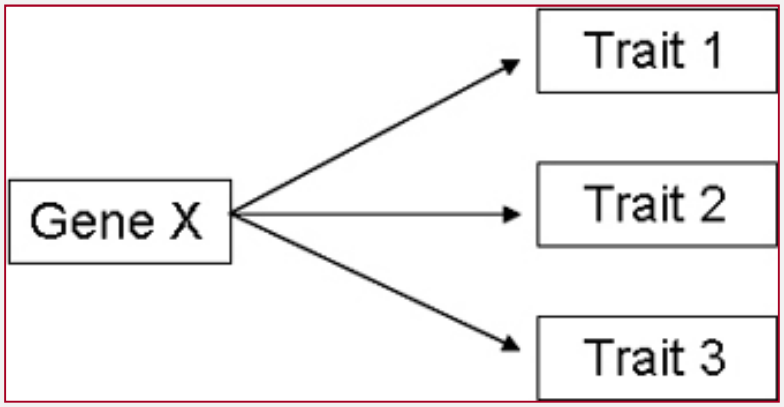
OI : III тип (AR)

OI : 4 тип (AR)

Pleiotropy

Definition : " Multiple penotypic effects of a gene " or
"Multiple traits determined by single mutation "

- **Pleiotropy is a common feature of human genes and is the rule rather than exception in the single gene disorders**
- **Pleiotropy is a patogenetic phenomena – one gene product can be involved in many biochemical processes affecting different pathways of growth and maturation of different organs / systems**



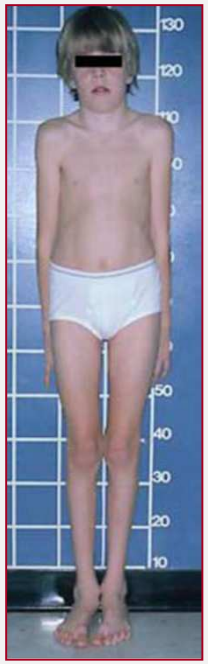
- **Many Mendelian disorders** can be manifested in a number of different systems of the body in a variety of ways

- But sometimes the disorder can involve only one organ or system

!!! Usually only one or two symptoms of a syndrome (AD) are present in the proband, **but a family study can show other relatives** of the patient **having one or more of the remaindered symptoms** of the syndrome (**dispersed in family symptoms**)

Examples :

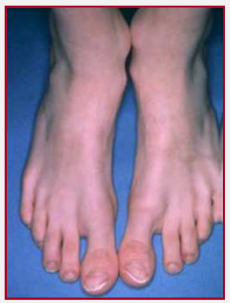
- **Marfan `s syndrome (AD)**
- **Waardenburg syndrome (AD)**
- **Osteogenesis imperfecta (AD)**
- **Cystic fibrosis (AR)**

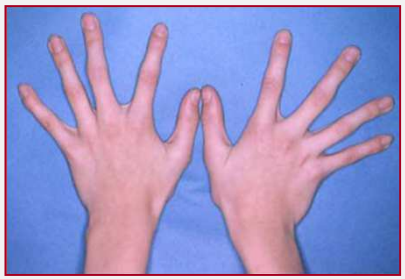


Marfan syndrome (AD) :

Clinical phenotype - defects involve connective tissue of three major systems :

1. **The ocular** - Myopia (present in most patients)
   - Detached lens / ectopia lentis (***in ~ 50%***)
2. **The skeletal -** Long, slender limbs with arachnodactyly "spider fingers"
   - Scoliosis and joint hypermobility
3. **The cardiovascular -** Dilatation of the aorta (***in ~90%)*** !!!





- **The gene** encoding **fibrillin** (connective tissue protein) is mapped to **15q**

- More than 200 different fibrillin mutation are identified in Marfan patients (**allelic heterogeneity**)

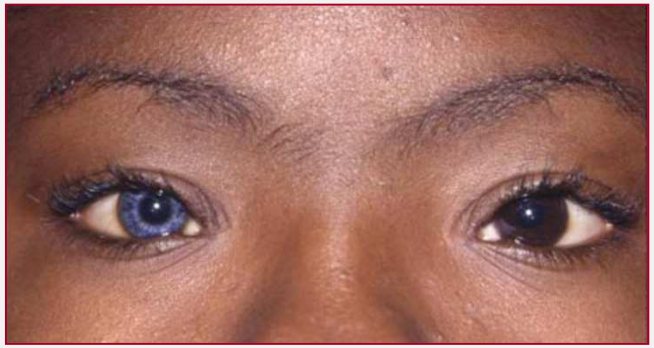
- Fibrillin is found in the aorta, the ligaments of the lens and the skeleton

!!!! The location of the gene product (fibrillin) and its role as component of connective tissue explain the pleiotropic effects – in the eye, the skeleton and the cardiovascular system

- Usually only one symptom of Marfan s-me is present in the proband, but **taking a family history** (dispersed remaindered symptoms in other relatives) **can itself provide a diagnosis !!!!!**

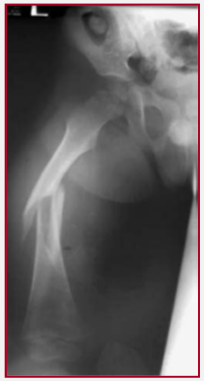
Waardenburg syndrome (AD) :

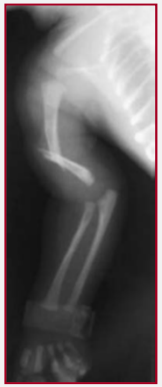
- **Hypopigmentation** (white-forelock, heterochromic iridis)
- **Hearing impairment** (bilateral deafness) etc.



Osteogenesis imperfecta (AD/AR):

Fractures of bones; blue scleral; hypoplasia of dentin etc.



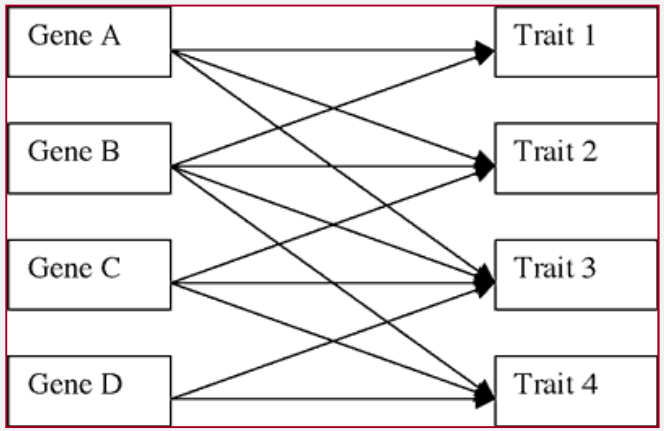


Variable expression and reduced penetrance leading to clinical heretogeneity of single gene disorders

I. Variable expressivity : "The **differences in the degree of severity** of a clinical phenotype" or

"Variation in clinical manifestations between individuals"

- In the real organism many genes influence any trait and any gene influences many traits
- It is not usually possible to pinpoint specific modifying genes and nearly all mutant phenotypes can be shown to vary from one affected person to another



- Variable expressivity ***is a characteristic of AD – disorders***

- Mutant genes with pleiotropic effects frequently show variable expressivity

- The variation in clinical manifestations between affected individuals can give rise to ***considerable problems in genetic counselling*** **:**

  A parent with mild exxpression of the disease - so mild that she / he is not aware of it - may transmit the gene to a child who can have severe expression

- However, minimally the gene may be expressed clinically, any individual carrying the gene has 50% risk to transmit the gene to any offspring

- Unfortunately, ***there is no way of predicting how severely any offspring might be affected*** **!!!**

Examples :

Almost all AD disorders with pleiotropic effect :

***Marfan s-me*; *Waardenburg s-me*; *Osteogenesis imperfekta*;**

***Achondroplasia*; *Tuberous sclerosis etc*.**

- An individual may have **only one, two or more symptoms** of the s-me and the severity of the s-me may vary widely

✓ **Variable age of onset is another aspect of Variable expressivity -** many AD disorders appear at a later age :

Huntington disease (HD)

~ 60% of cases are diagnosed between the age of 35 and 50

- age of onset of HD is highly correlated with the # of CAG repeats

Phenylketonuria (PKU)

- even thought the metabolic error in it can diagnosed at birth, there are no overt clinical abnormalities for a few months

Myotonic dystrophy (MD)

Adult polycystic kidney disease ; Familial hyperholesterolemia etc.

II. Reduced penetrance (RP), leading to clinical heretogeneity is:

" A dominant gene which does not manifest itself in a proportion of heterozygotes"

- RP is another important characteristic of many AD-disorders

- RP is an all-or-non phenomenon – either a particular genotype is expressed or it is not expressed
- RP is an exception to a rule that unaffected persons do not transmit an AD-trait
- Delay in age of onset complicate the interpretation of inheritance pattern in families and can cause age-dependent non-penetrance

- Penetrance rates are estimated by examining a large number of families and determining what proportion of the obligate carriers develop the disease **(it is use in genetic counseling to individual at risk for a AD dis.)**

!!! The possibility of reduced penetrance, variabile expressivity, genetic heterogeneity and pleiotropic effects of a mutant gene need to be taken into account during genetic counseling for single gene disorders !!!