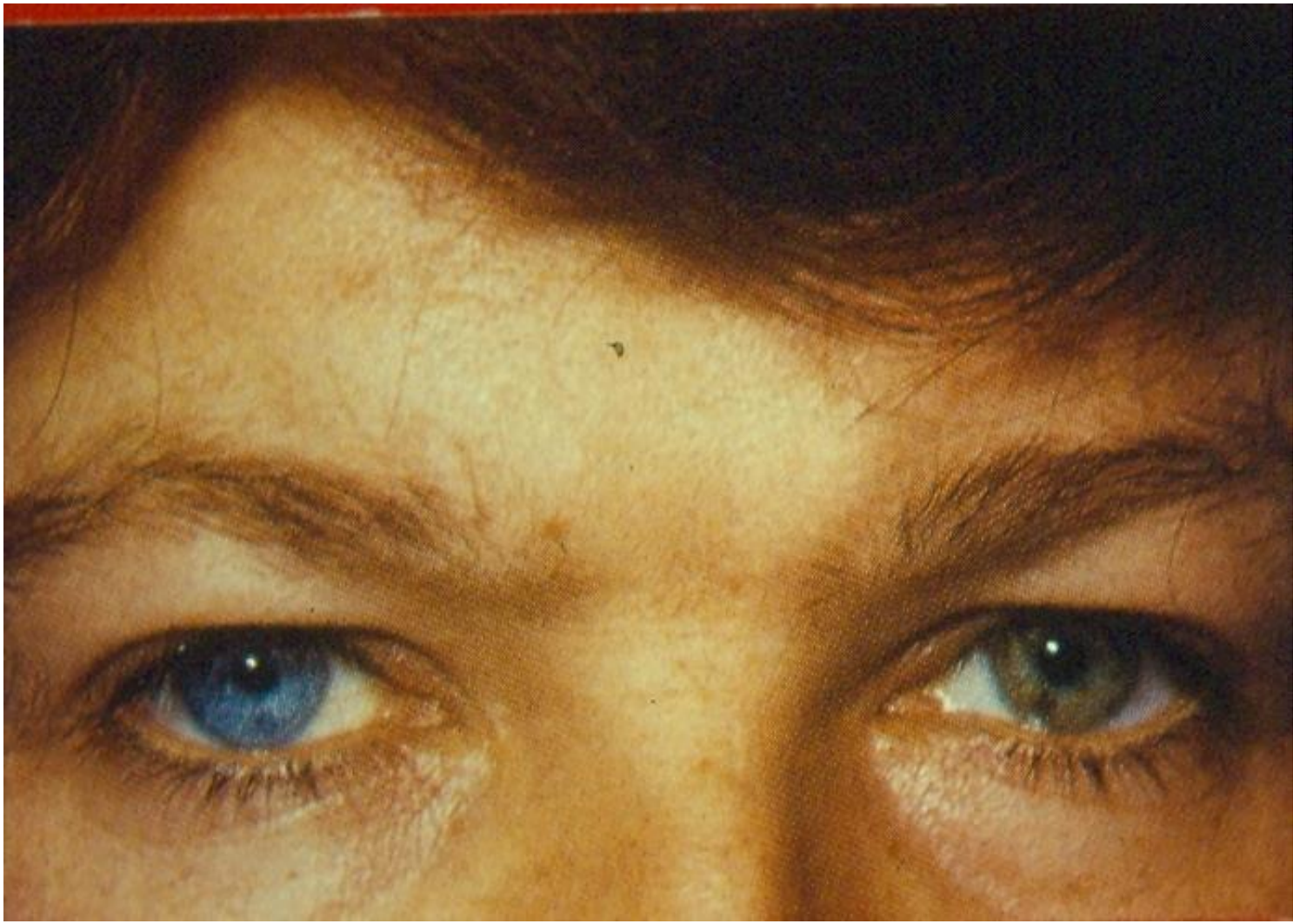
WARRDENBERG SYNDROME



Genetic Disorders

1. Single gene Disorders

2. Chromosomal Disorders

3. Multifactorial Disorders

Single gene Disorder

A disorder that is determined

by

alleles at single locus

Allele

- Alternative variant of genetic information at a particular locus
- Single prevailing version in majority of individuals – "Wild type or normal allele"
- Other version of the gene – "mutant allele"

  shows a permanent change in nucleotide sequence of DNA

- Homozygous: a person with pair of identical alleles

- Heterozygous: a person with pair of different alleles

- Compound Heterozygote: a genotype in which two different mutant alleles of the same gene are present

Single gene Disorders

- Autosomal : Dominant
  : Recessive

- X-linked : Dominant
  : Recessive

1. Males have single X : Hemizygous
2. Females two X : Only one is active

- Dominant : a phenotype expressed in the same way in both homozygotes & heterozygotes

- Recessive : a phenotype expressed only in homozygotes

- Incompletely dominant : a phenotype is different in both homozygous & heterozygous genotype & its severity is intermediate between them

- Codominant : Expression of each allele can be detected even in the presence of the other

SINGLE GENE
INHERITANCE

AUTOSOMAL DOMINANT INHERITANCE

More than half of all mendelian disorders are inherited
as
autosomal dominant traits

AUTOSOMAL DOMINANT INHERITANCE

A trait that manifests in heterozygous state

i.e. one abnormal or mutant gene

&

a normal gene

- Normal gene is often structural protein such as collagen

- Nature of defective protein is still unknown

Features

- Hereditary - Commonest mating is **HETEROZYGOUS** marrying **NORMAL**

- More severe in homozygous state

- More common than Autosomal Recessive disorders

Alleles

- **A- Defective or Mutant Allele**
- **a- Normal Allele**

Genotype :

- **Aa- Heterozygous AFFECTED**
- **AA- Homozygous AFFECTED**
- **aa -Normal**

AUTOSOMAL DOMINANT INHERITANCE

- Incidence of some of the disorders is quite high in specific **geographic areas**

  e.g.

1.1:500 – familial hypercholesterolemia
(Europe & Japan)

2. 1:1000 – mytonic dystrophy
(North America)

3. 1:2500 – Huntingtons disease
(North America)

Heterozygous marrying Normal

	A	a
a	A a	a a
a	A a	a a

Aa X aa

50%CHANCE OF NORMAL

50% CHANCE OF BEING AFFECTED

Marriage between Two heterozygotes

	A	a
A	A A	A a
a	A a	a a

Aa X Aa

50% HETEROZYGOUS AFFECTED

25% HOMOZYGOUS AFFECTED

25% NORMAL

- Statistically each pregnacy is an
  - "independant event"
  - not governed by the outcome of previous pregnancies

- Within a family distribution of affected & unaffected children may be quite different from theoretical 1:1

Criteria for A. D. inheritance

1) Males and Females equally affected

SEX NO BAR

2) Male to male transmission can occur & males can have unaffected daughters

3) Vertical Pattern - Affected person has affected parent all the way up the ancestry till First Mutation occurred

e.g. porphyria variegata

4) Commonest Mating

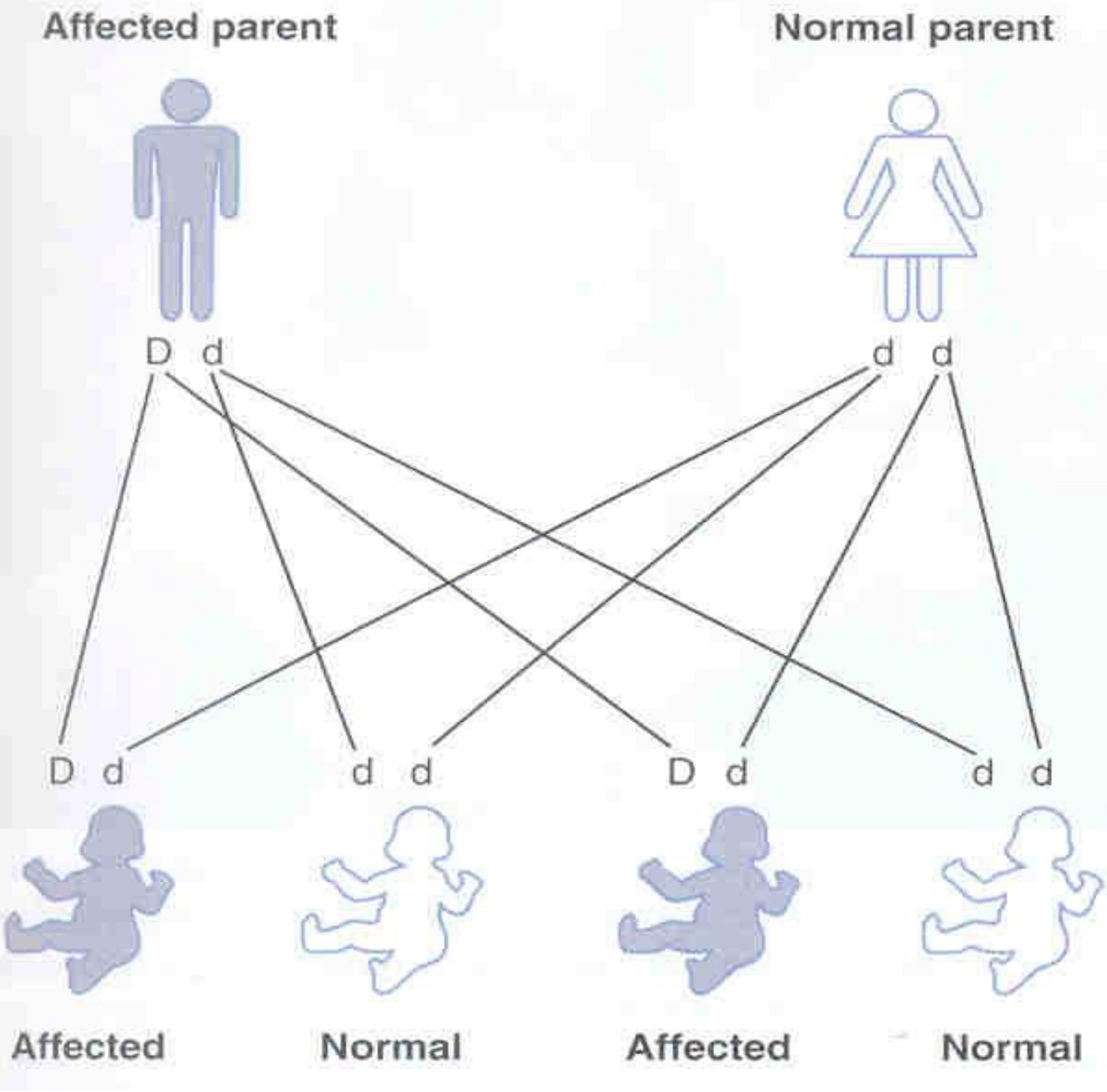
i.e. Heterozygote marrying Normal

Every child has-

50% chance of being normal

50% chance of being AFFECTED

5) Normal members don't transmit the trait


Affected parent
Normal parent
D d
d d
D d
d d
D d
d d
Affected
Normal
Affected
Normal

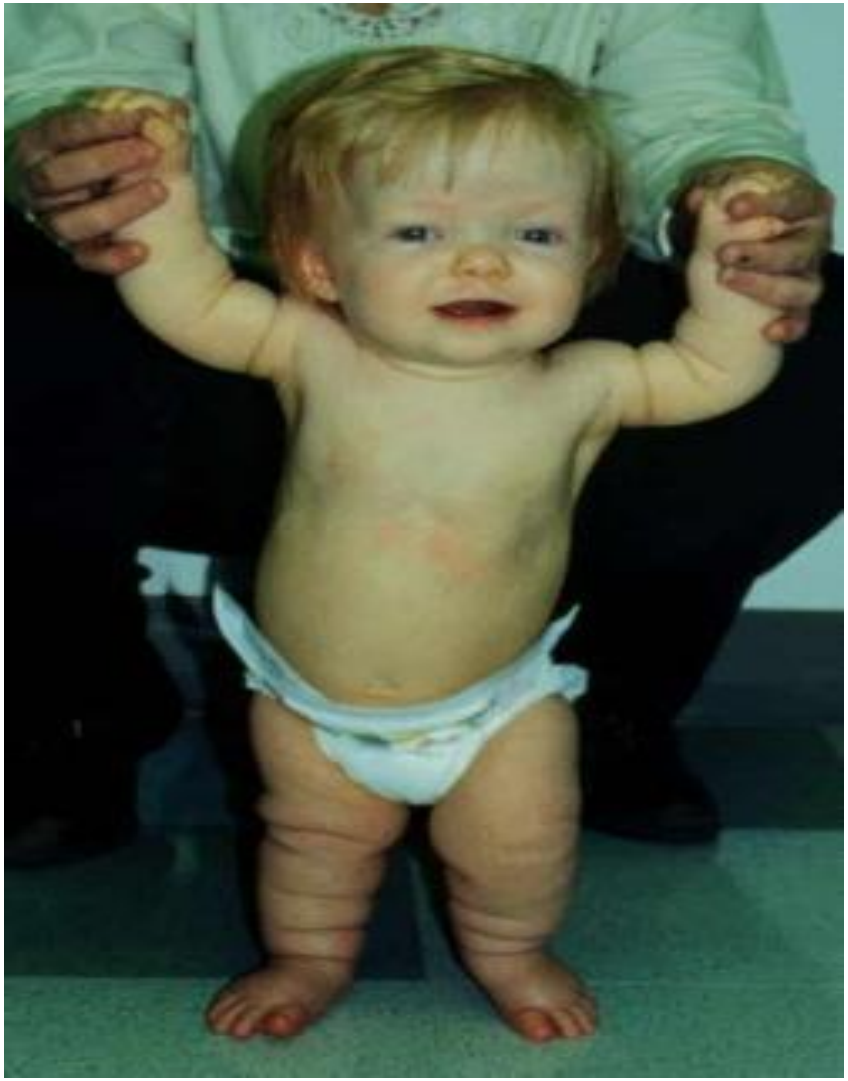
New mutation

- New alleles arise by
  - mutation
  - maintained or removed by selection

- Survival in the population depends on
  - fitness of person carrying it
    (reproductive fitness)
  - many ADD are associated with reduced fitness
  - disorder with new mutations have zero fitness (mutations can not be inherited – patients with such disorders never reproduce)

New mutation

- Trait appears without family history
- Achondroplasia – short limbed dwarfism
- Parents usually with normal stature



Clinical Characteristics

- Genetic risk – 50%
- New mutation
- Variability in phenotypic manifestations of mutant gene occurs by three ways
  - Pleiotrophy
  - Variable expressivity
  - Reduced penetrance

Pleiotrophy

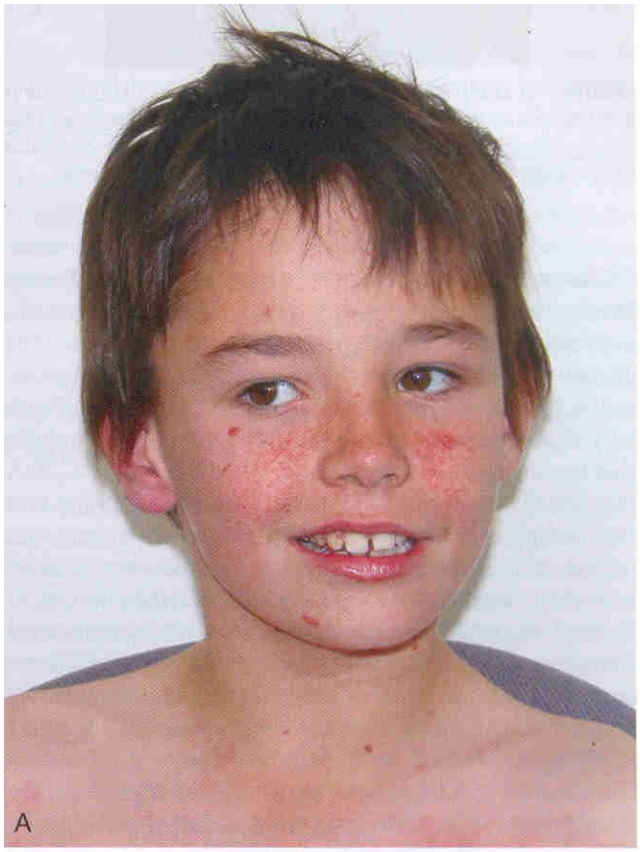
- A single abnormal gene or gene pair may give rise to diverse phenotypic effect
- Manifests in different systems of body in variety of ways
- Same family , same mutant genes, some signs & symptoms in common other manifestations quite different

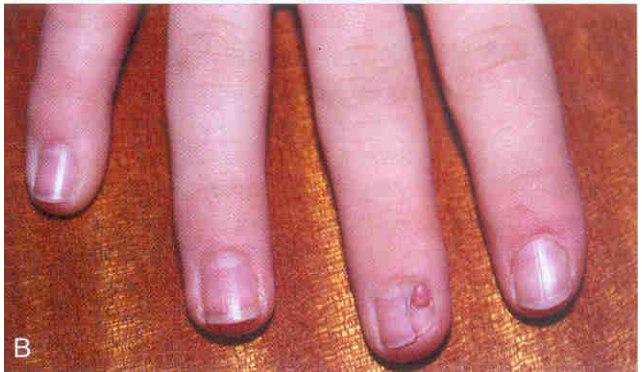
Pleiotrophy

- Tuberculous Sclerosis

1. Epilepsy
2. Facial rash – angiokeratoma
3. Subungual fibroma
4. Learning difficulty

- Some will have all the features
- Others may not have any
- Diverse syndrome - of different mutations in same gene





Neurofibromatosis

Von Recklinghausen disease

Common disorder of nervous system with variable presentation

Expressivity

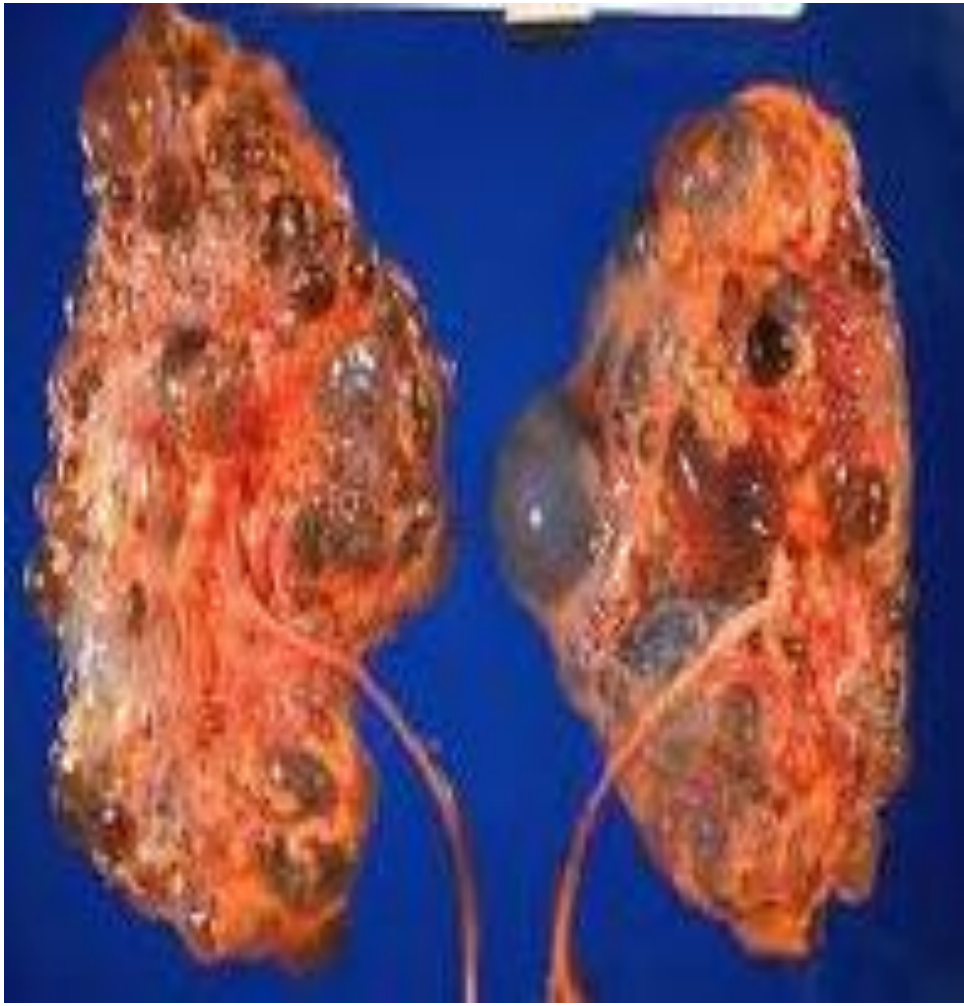
- Expressivity is the severity of expression of the phenotype

- When the severity of the disease differ in the people who have the same genotype

"Variable Expressivity"

Variable Phenotype

- Striking variations from
  - person to person,
  - even in same family
- Effect of
  - aging
  - other genetic loci
  - environment
- Polycystic kidney disease
  - renal failure in early adulthood
  - few renal cysts, not affecting renal function



Penetrance

- The probability that a gene will have any phenotypic expression at all
- Its an all or none concept
- It is age dependent
- Statistically, a percentage of people with a particular genotype who are actually affected, at least to some degree

Penetrance

- Reduced penetrance

  - no abnormal clinical features

  - result of modifying effect of other genes

- Nonpenetrance

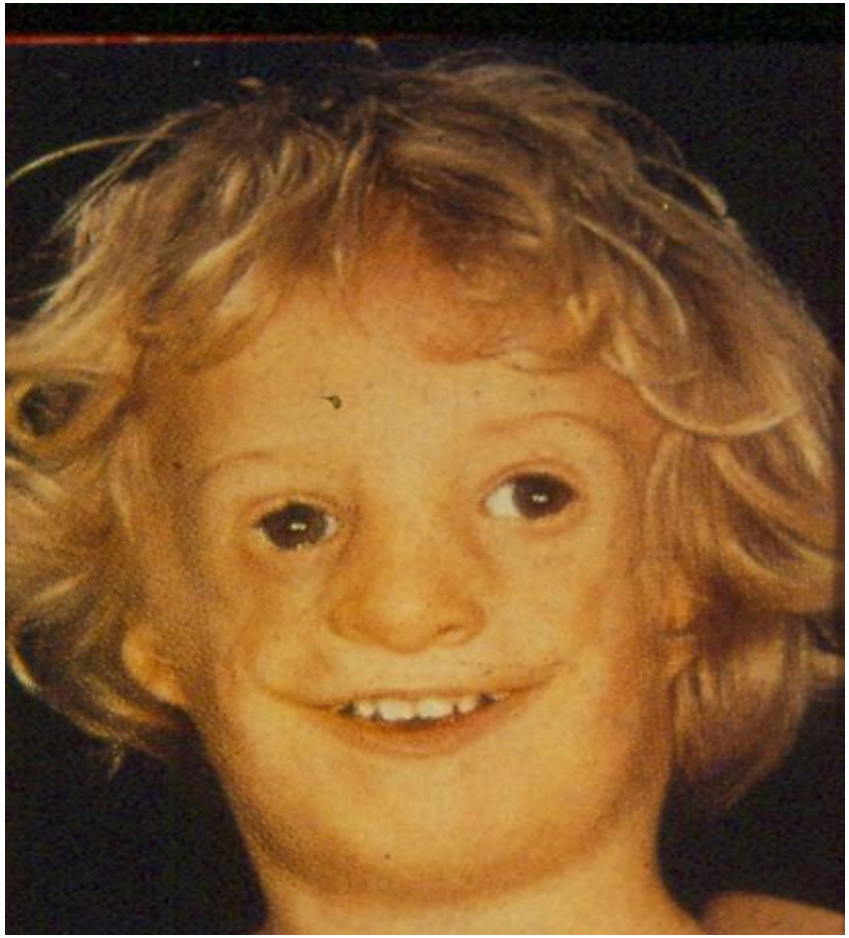
  - no features of a disorder despite being heterozygous

  "Skipping a generation"

  -Treacher – Collins Syndrome

Treacher collin or First arch Syndrome

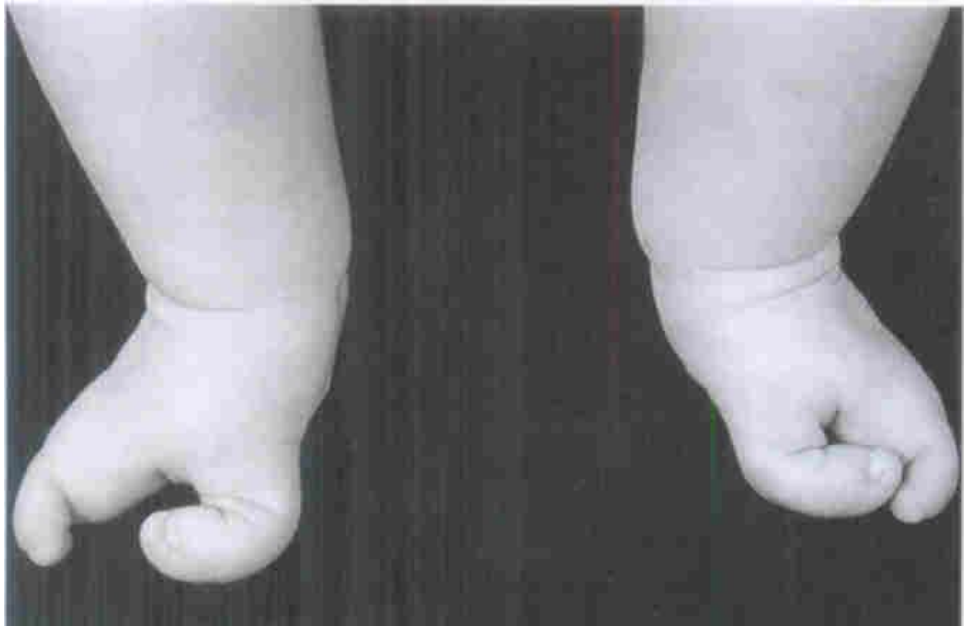
Facial features are unmistakable



Treacher collin Syndrome

- Small mandible
- Downward slanting palpebral fissure
- Defective lower eyelid
- Microtia with hearing impairment
- Baby’s mother has mutation but without obvious signs of the condition

Ectrodactyly



An example of reduced penetrans

- Can lead to apparent skipping of generations
- Complicates genetic counselling
- Capable of children who are affected

Co-dominance

- Two allelic traits are **both expressed** in the heterozygous state
- Blood group '**AB**'
- **Both 'A' & 'B'** blood group substances on the red blood cells

Homozygosity for Autosomal Dominant traits

- When both parents are heterozygous

- Affected individual either seem to be
  - more severely affected
    e.g. achondroplasia

    OR

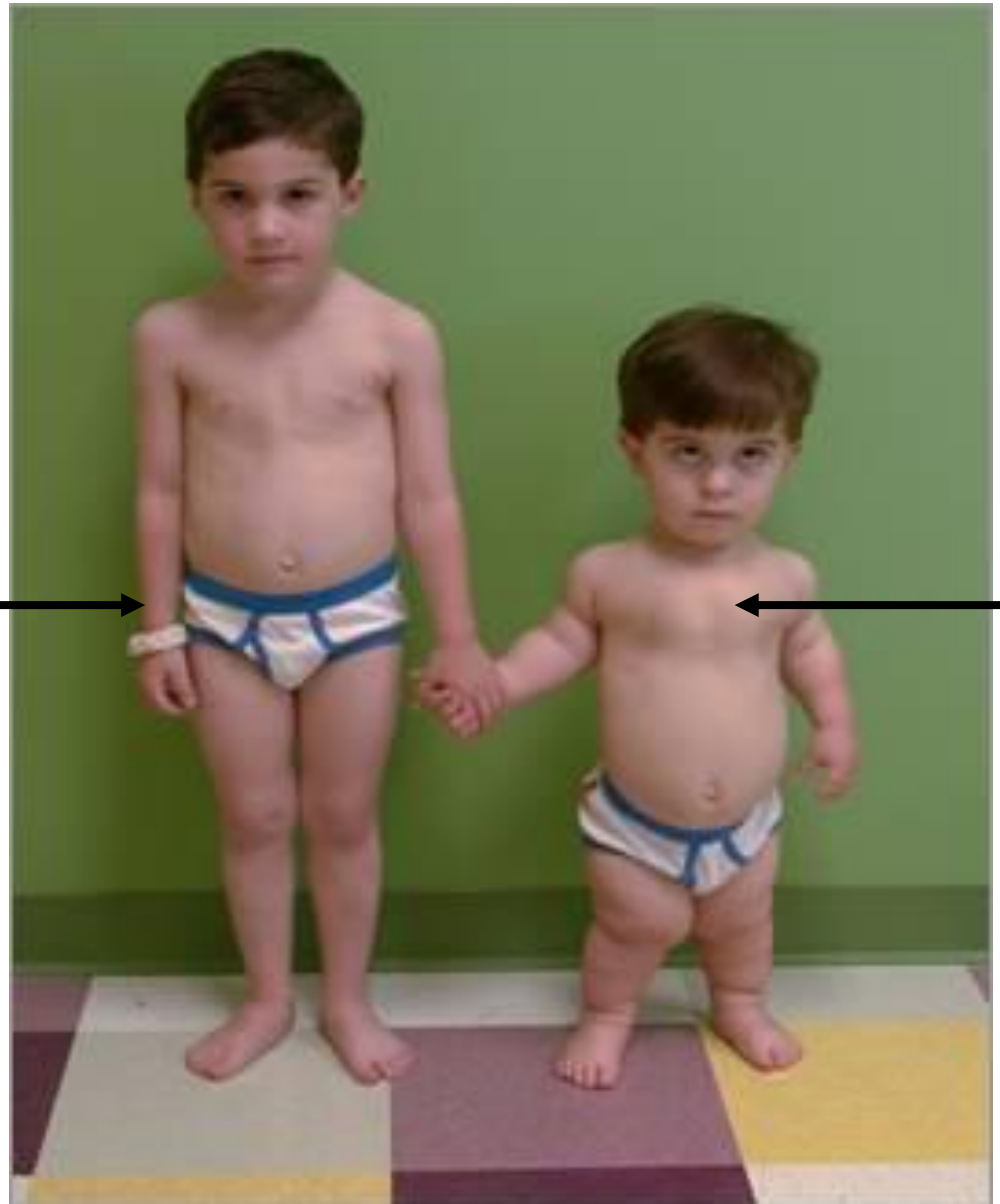
  - earlier age of onset
    e.g. familial hypercholesterolemia

- Exceptions
  e.g. Huntington disease &
  Multiple endocrine neoplasia II

Examples

- **Achondroplasia**
- **Osteogenesis Imperfecta**
- **Marfan syndrome**
- **Huntington chorea**

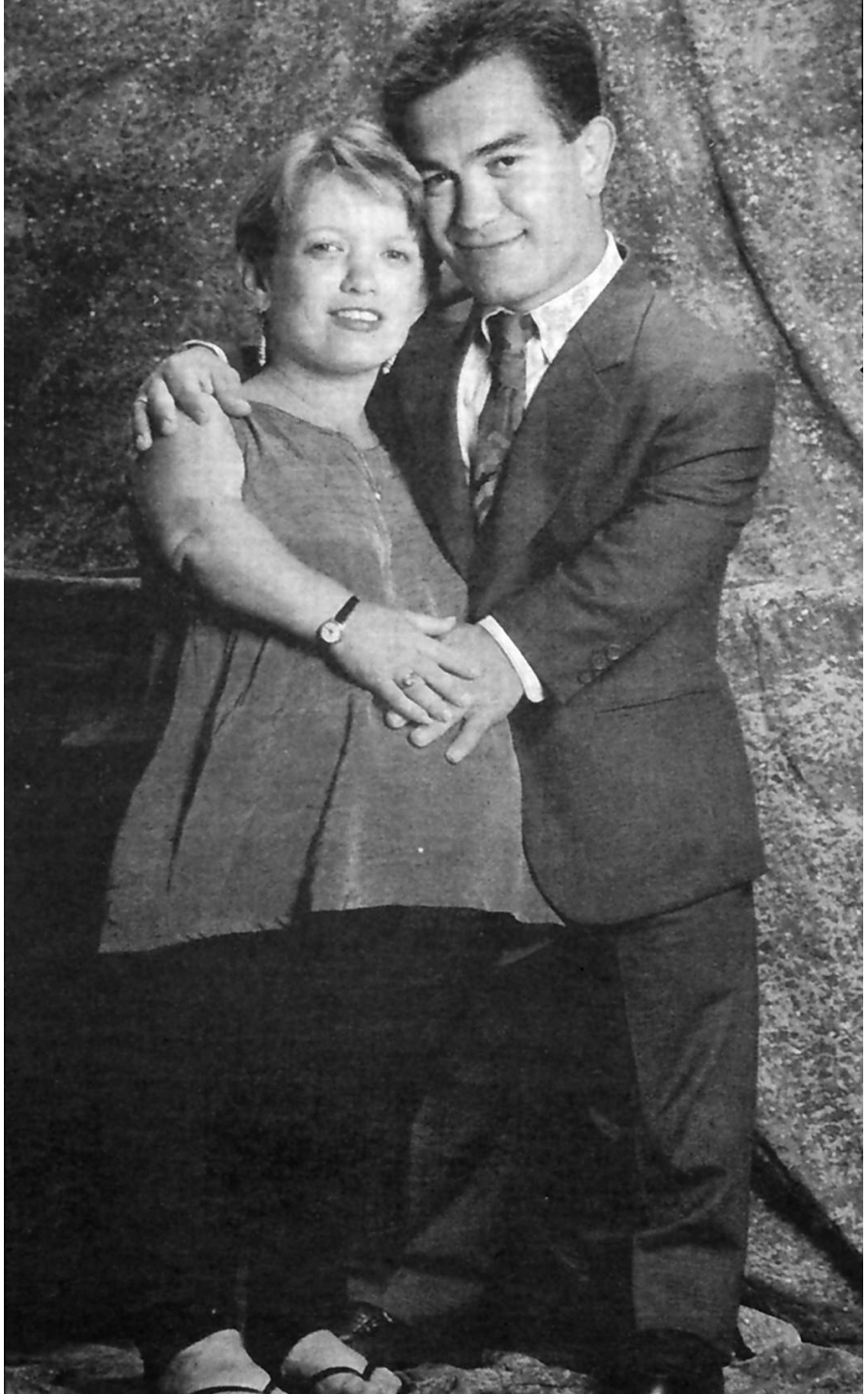
TWINS



Normal

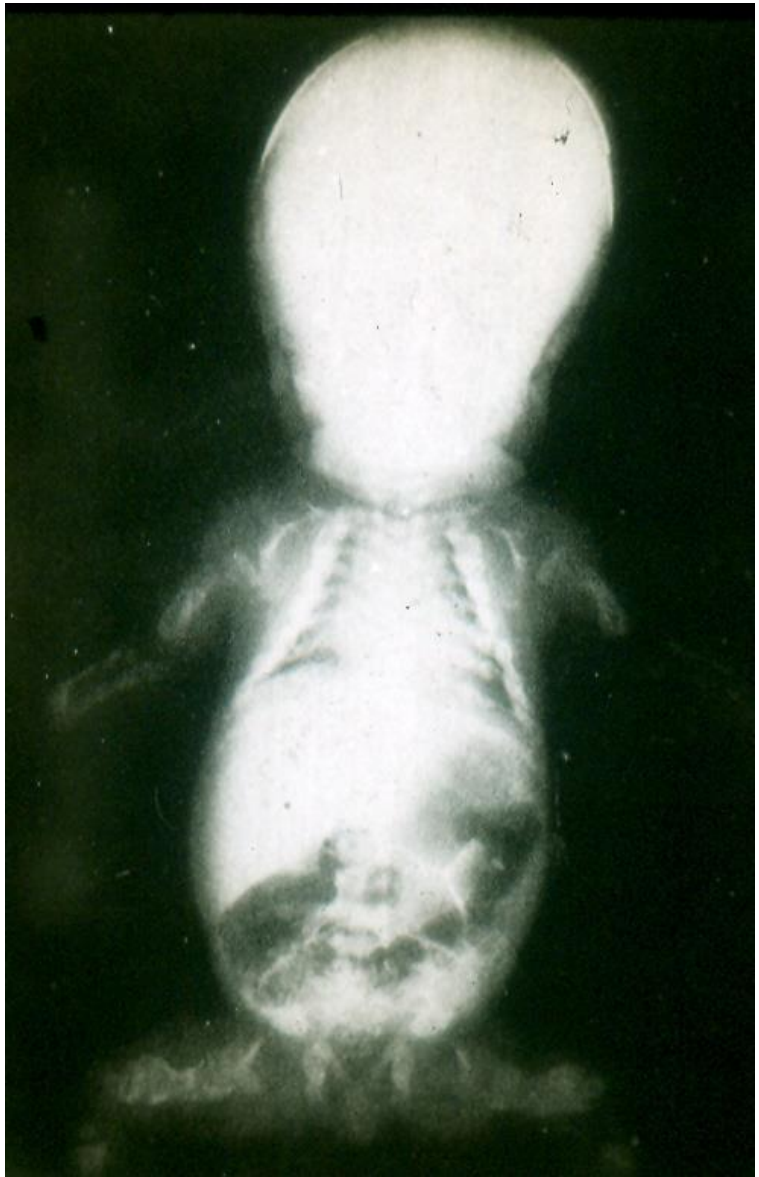
Achondroplastic

Achondroplastic baby of heterozygous married couple

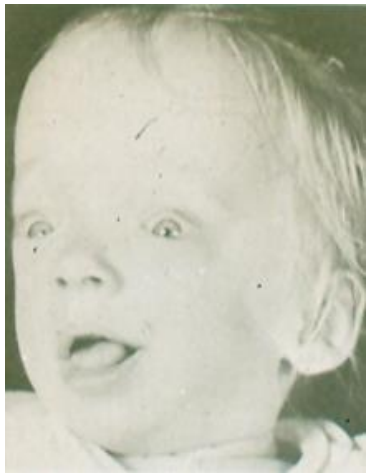


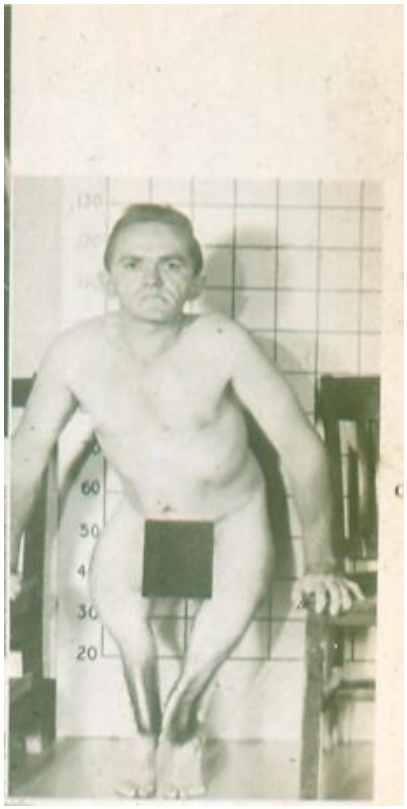

BOY

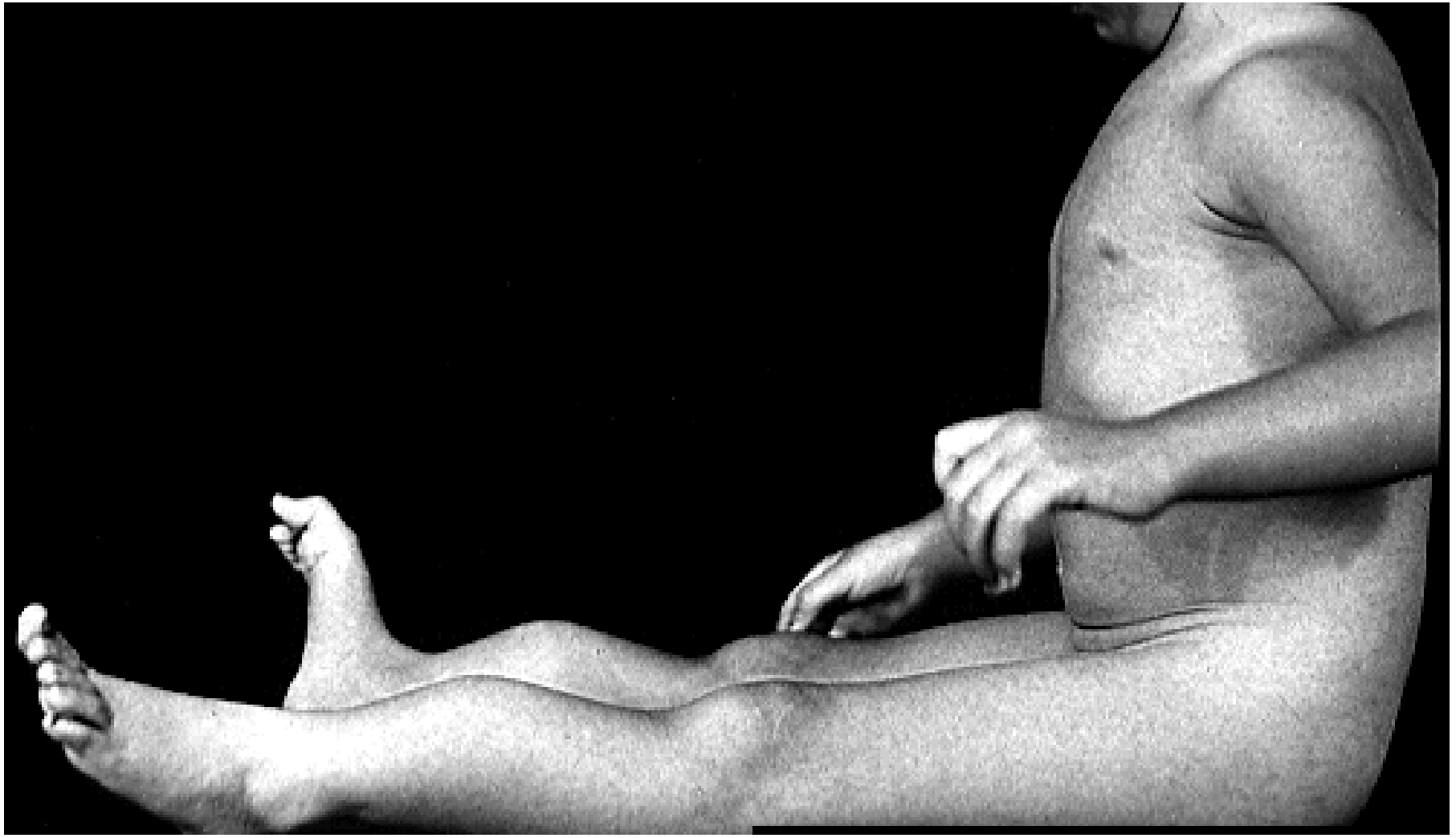
OSTEOGENESIS IMPERFECTA



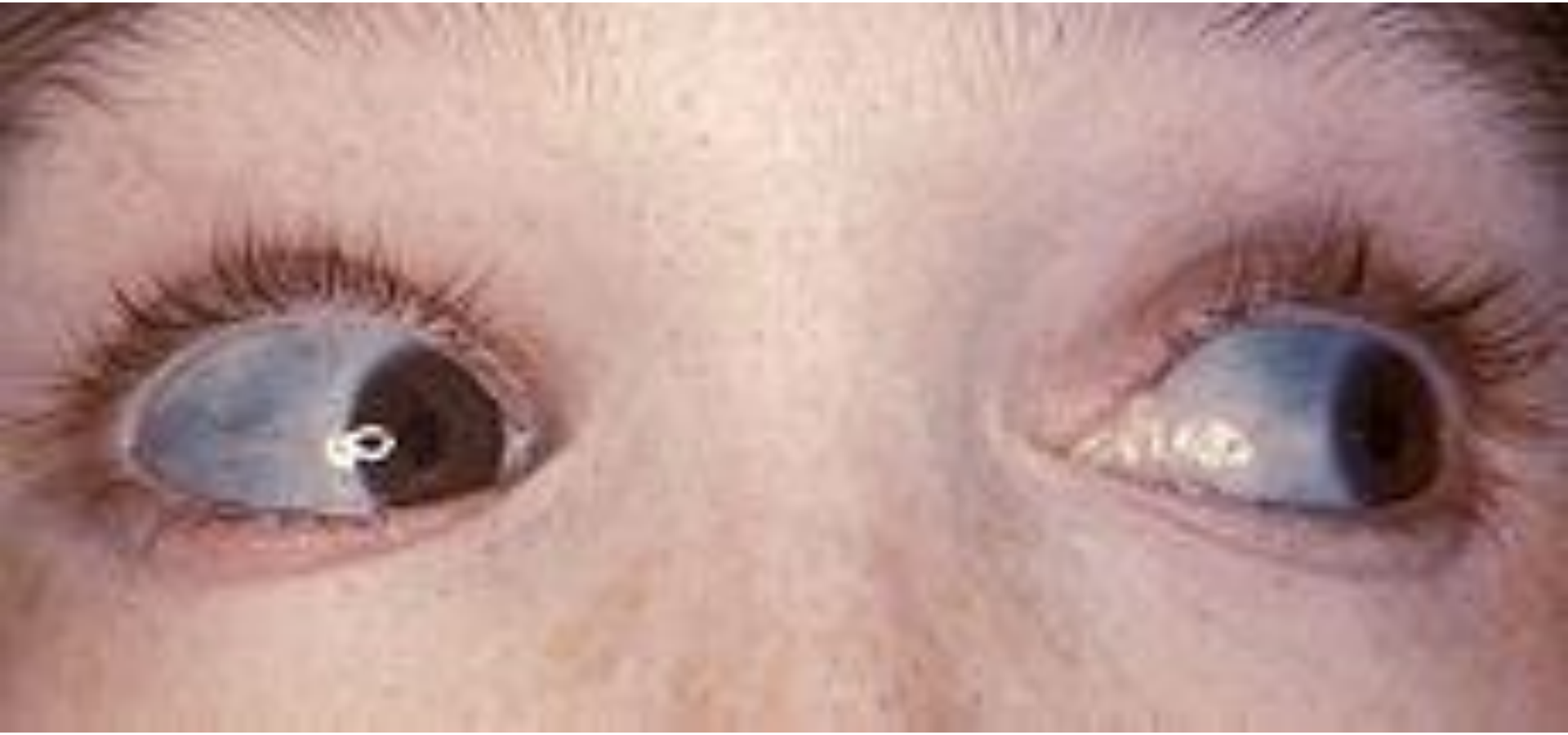
Family of Osteogenesis Imperfecta





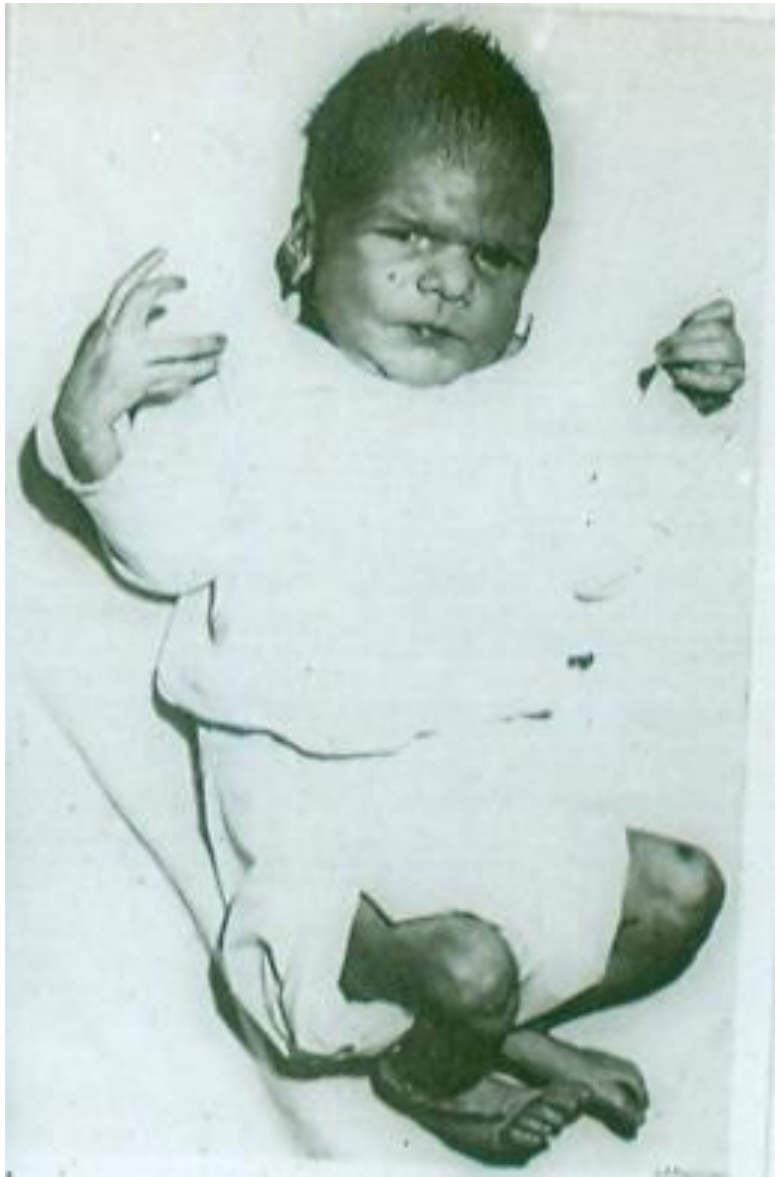


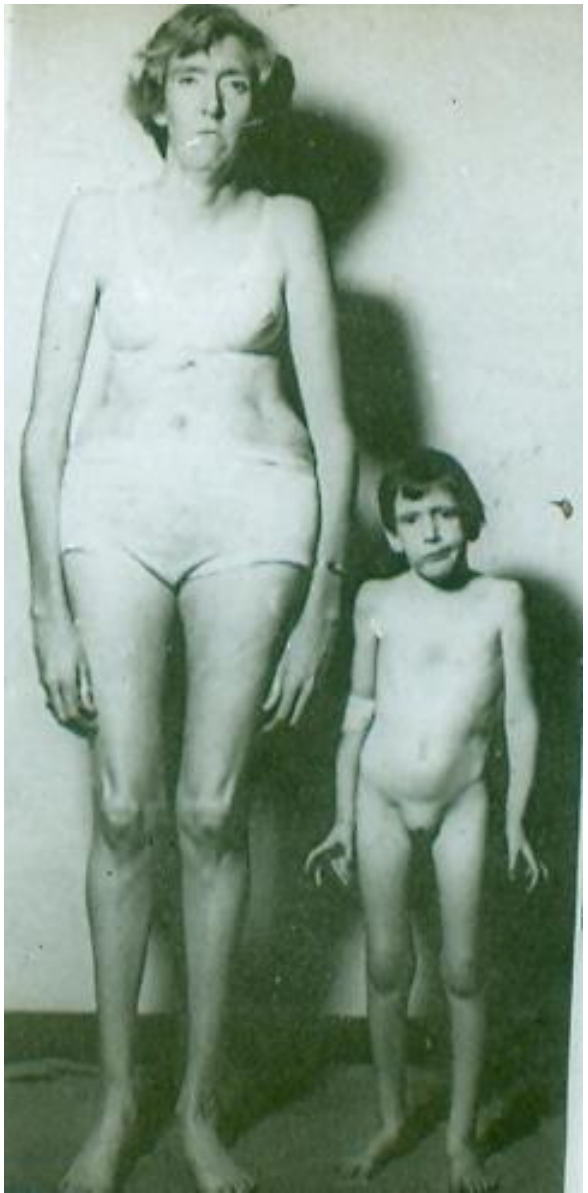
Osteogenesis Imperfecta
Blue Sclera



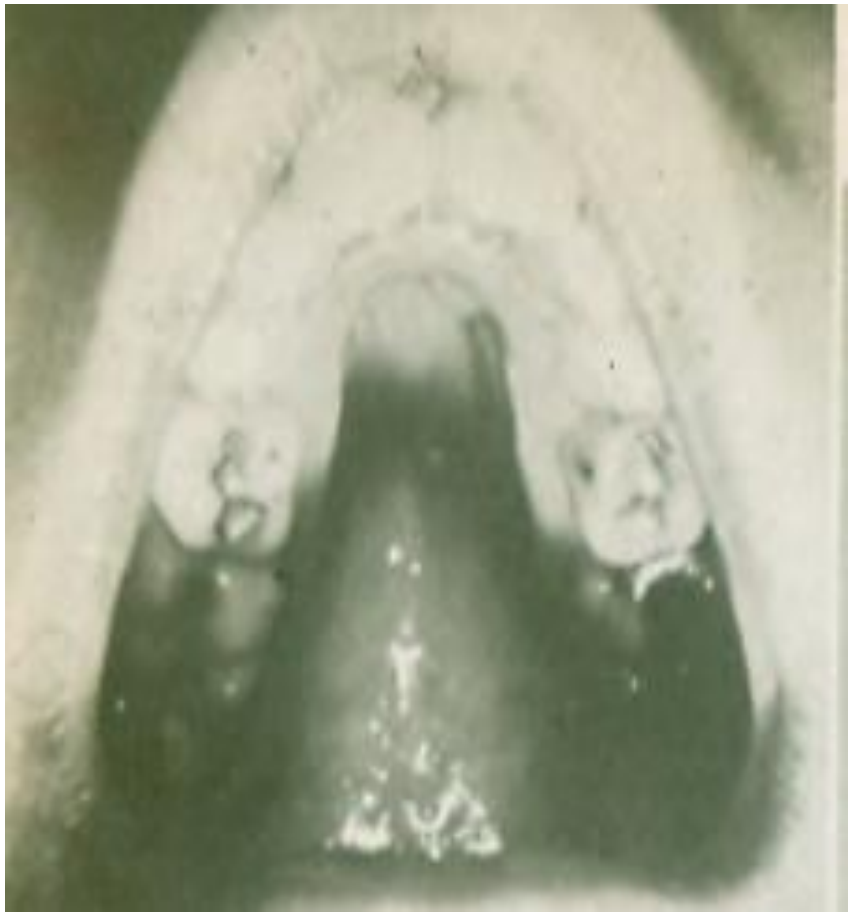
Fracture deformities in **OSTEOGENESIS IMPERFECTA**

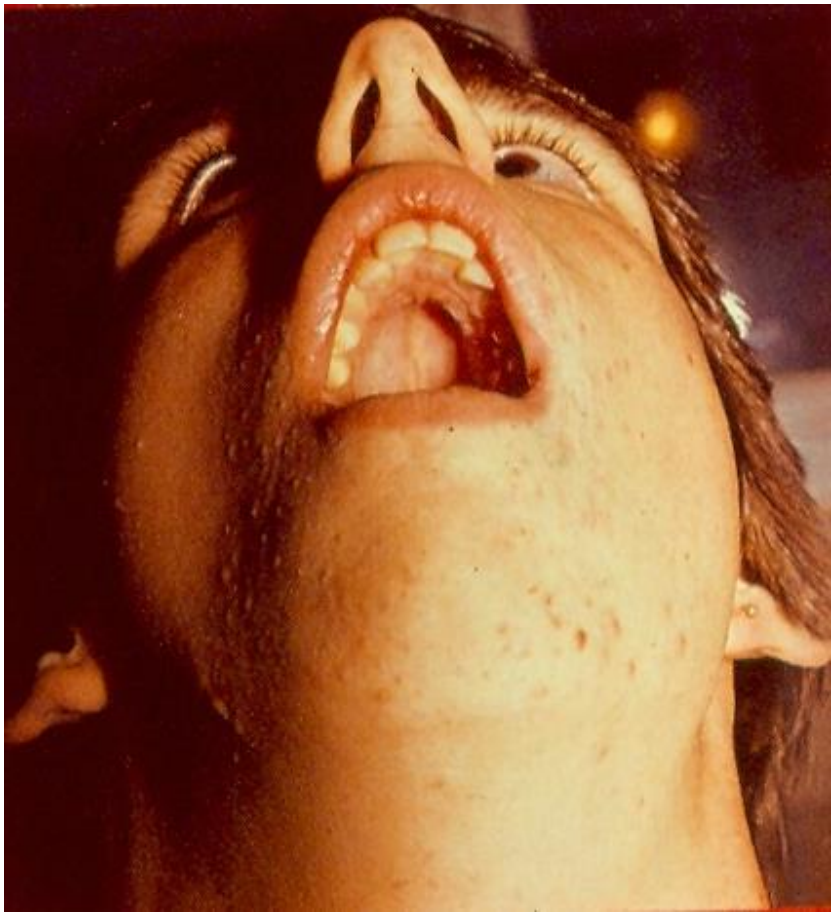
Marfan Syndrome



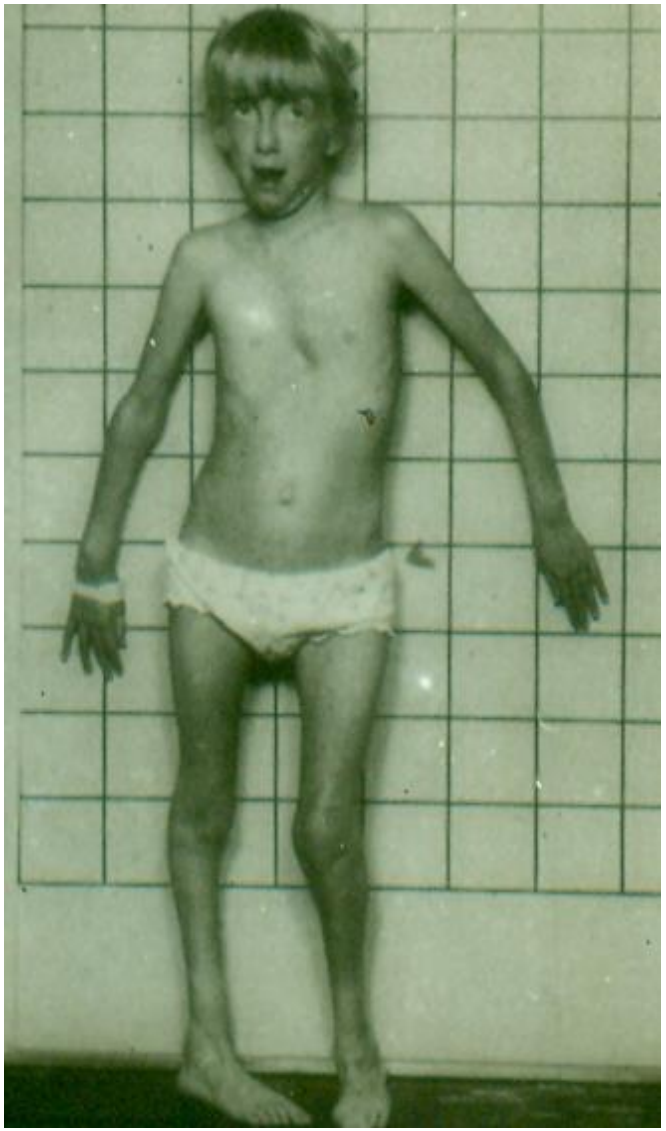


MARFAN SYNDROME
HIGH ARCHED PALATE

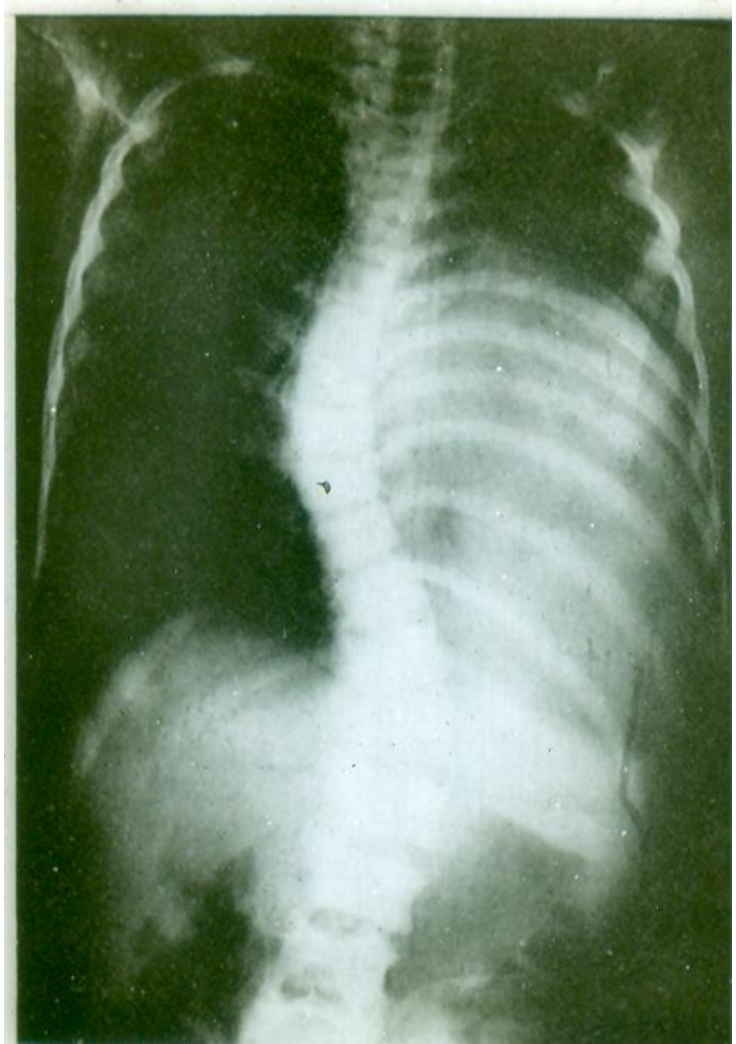




MARFAN SYNDROME
NOTE SCOLIOSIS

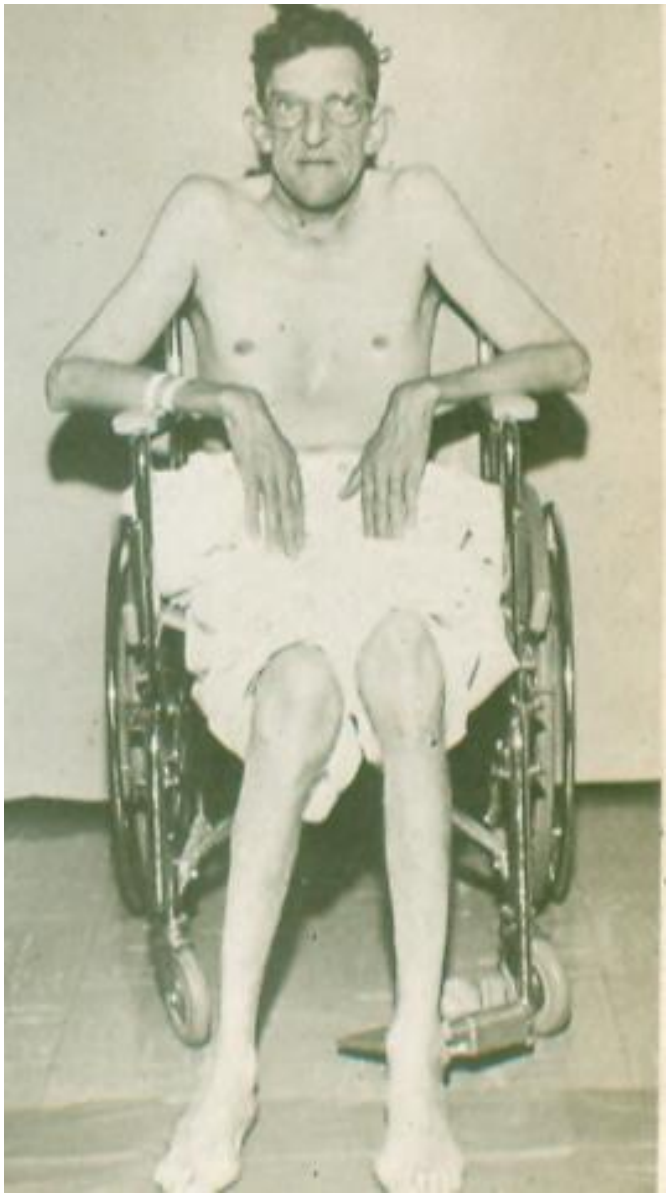


MARFAN SYNDROME-SCOLIOSIS

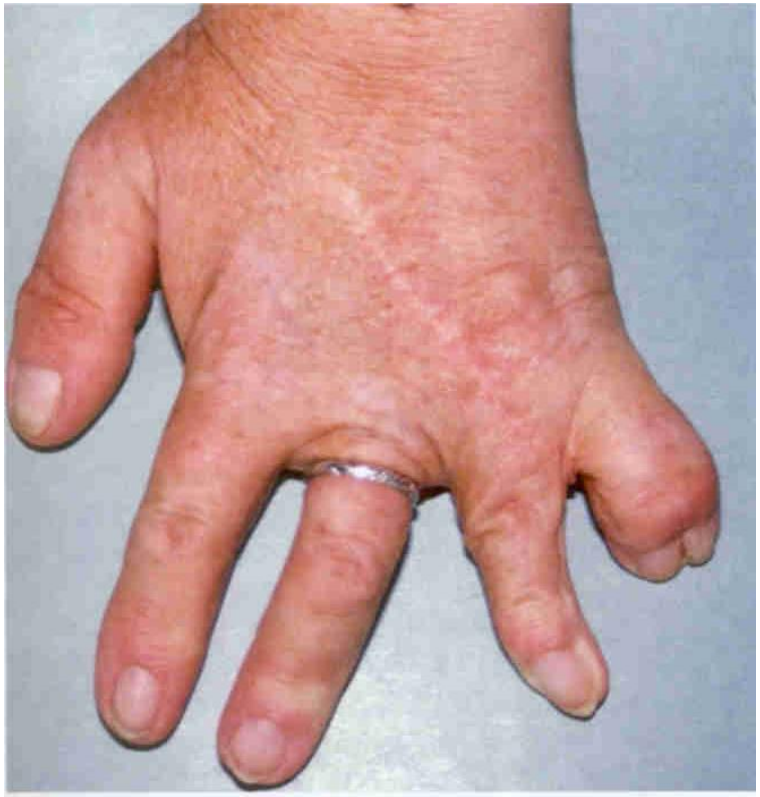


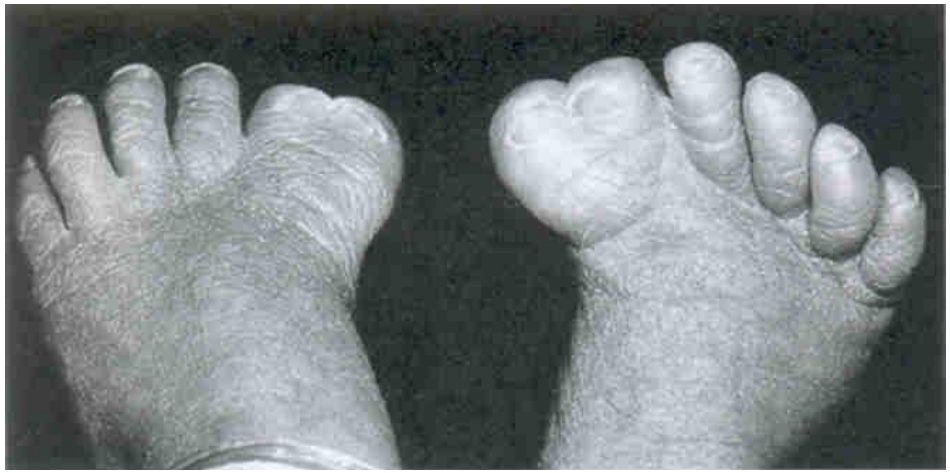
Marfan Syndrome

Marfan Syndrome

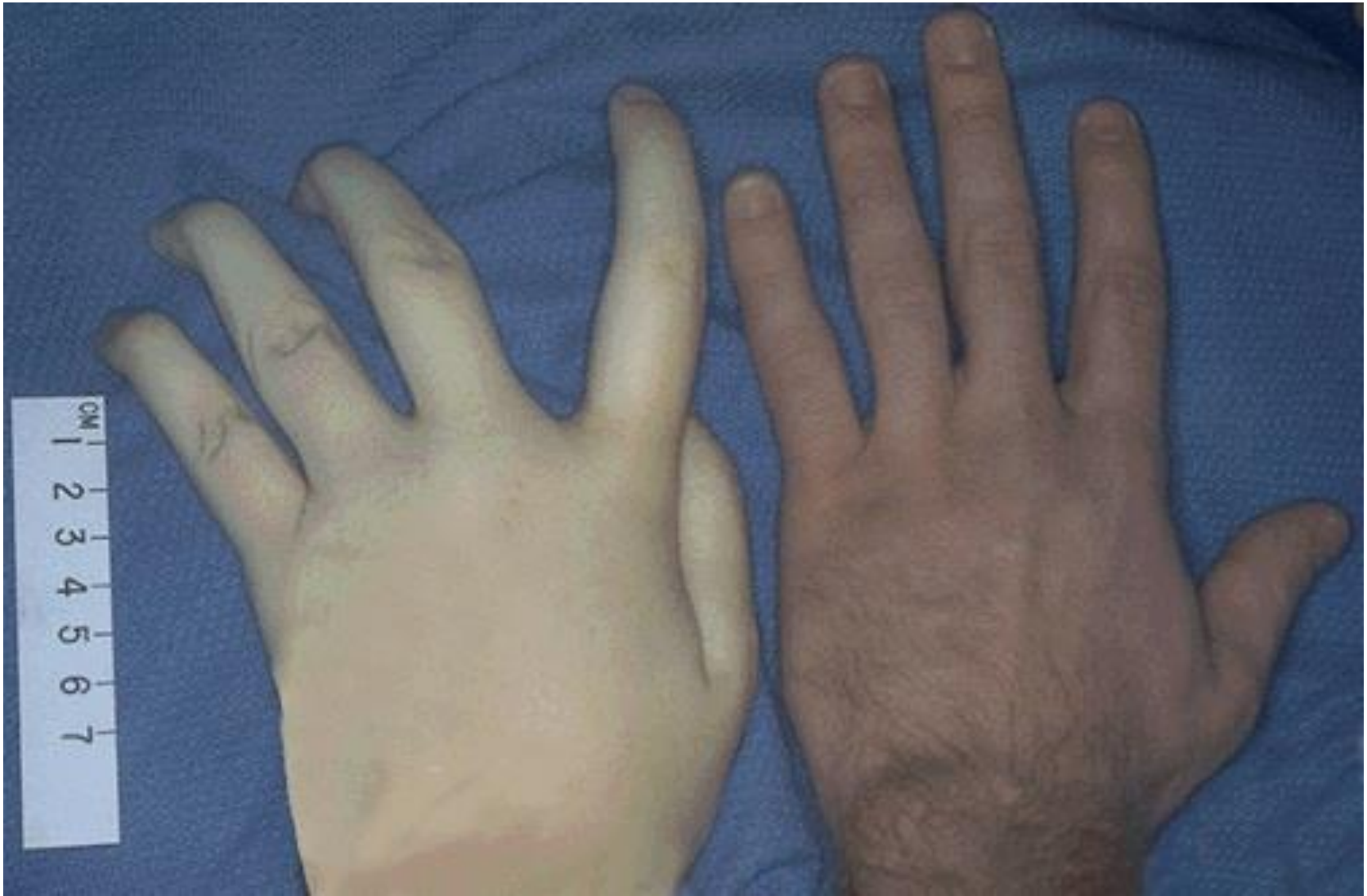


Syndactyly Polydactyly

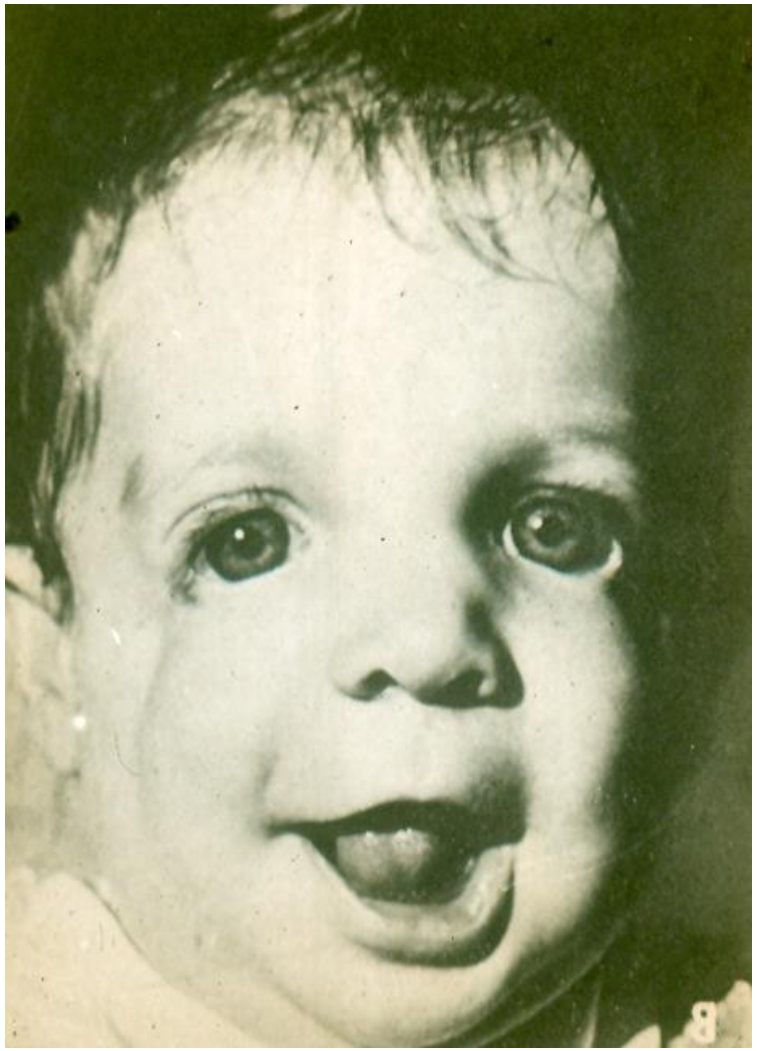




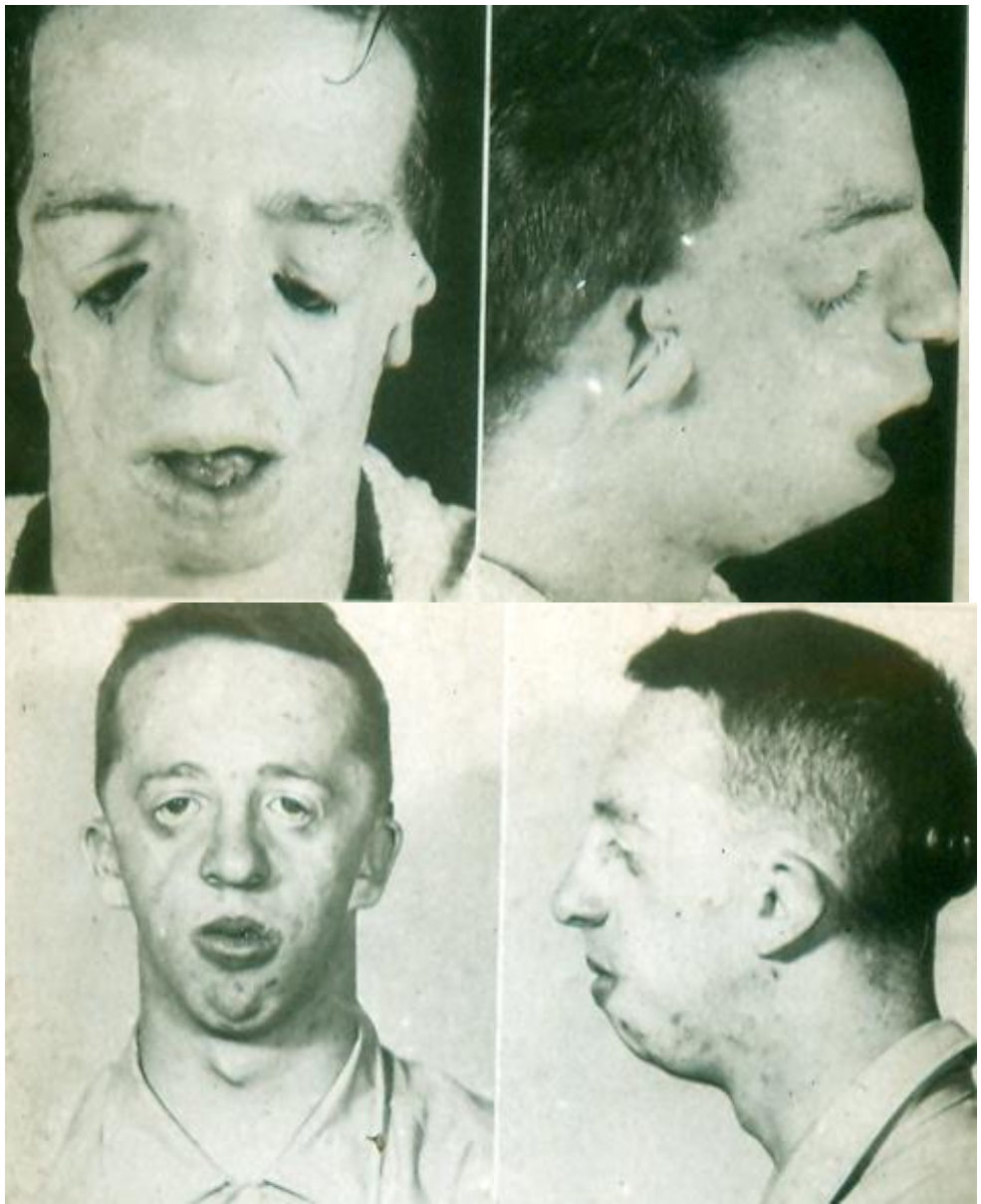
MARFAN SYNDROME
ARACHNODACTYLY



Mandibulofacial dysostosis

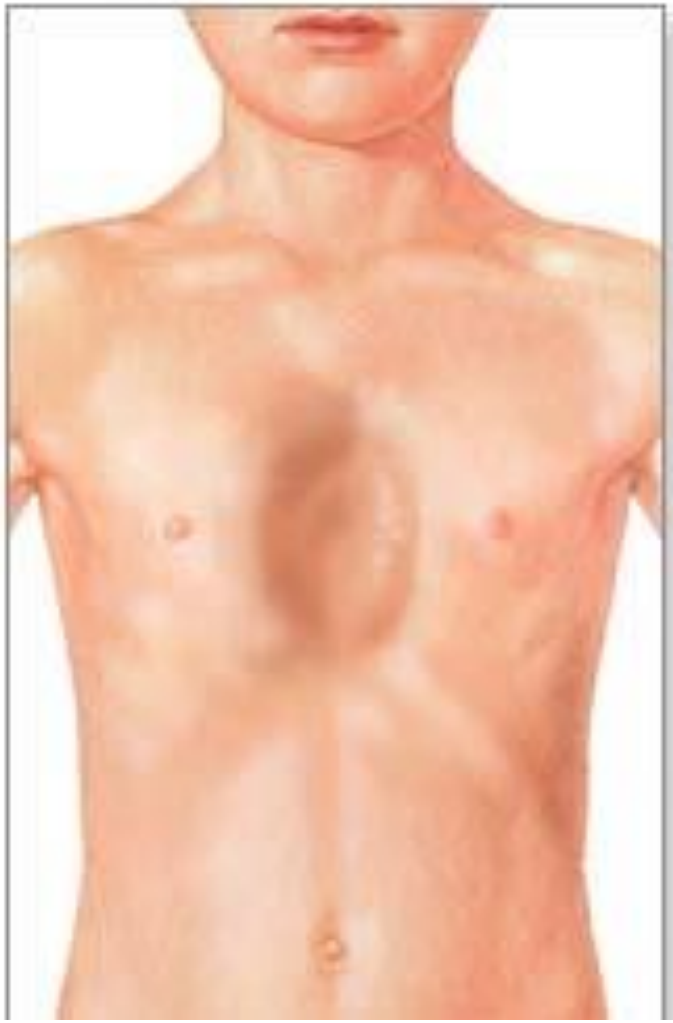


Mandibulo-facial dysostosis

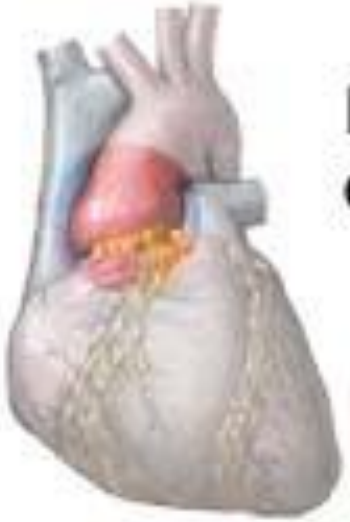


CLEIDODYSTROPHY

Pectus excavatum



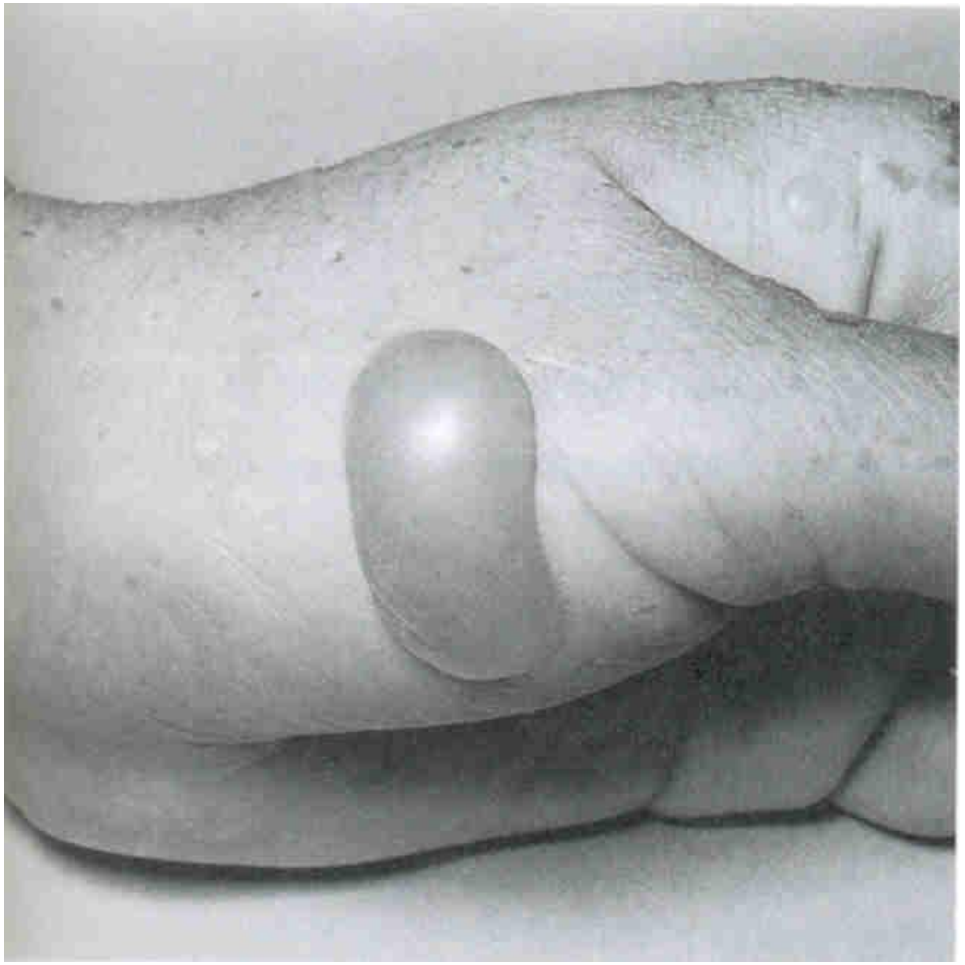
arachnodactyly



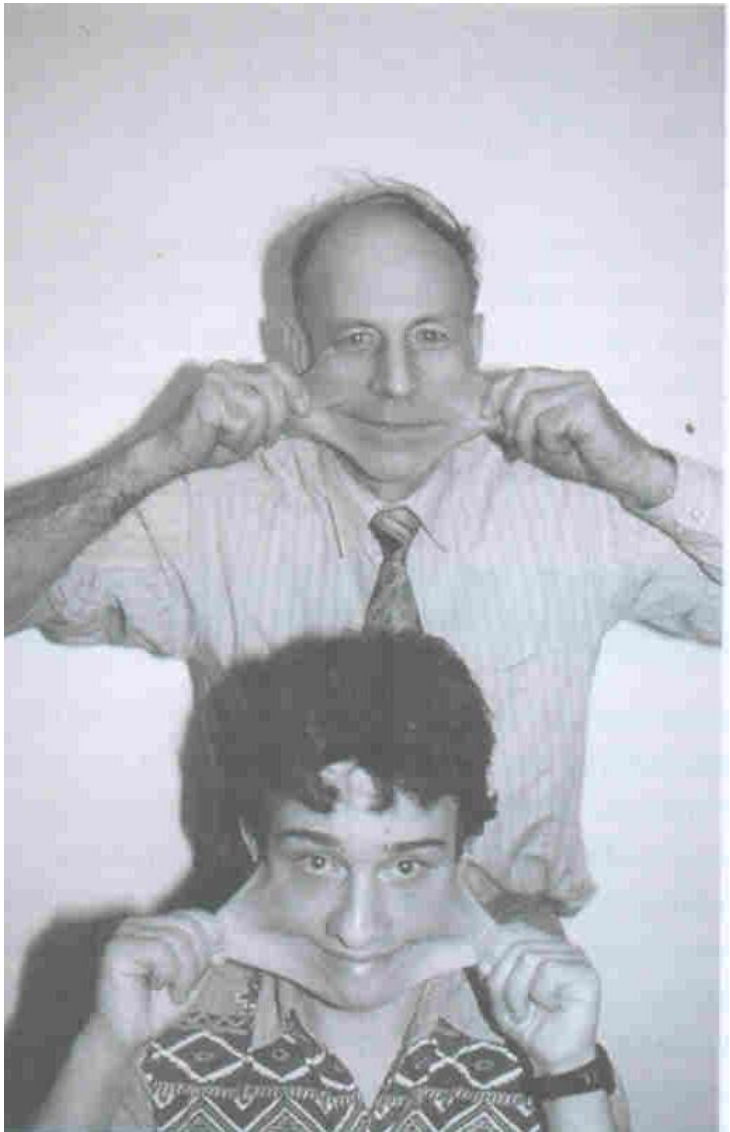
Dilation of aorta

Porphyria Variegata

- Can be traced back to one couple in the late seventeenth century in South Africa
- Metabolic disorder
- Skin blistering as a result of increased sensitivity to sunlight
- Urine becomes 'port-wine' coloured on standing (porphyrins)

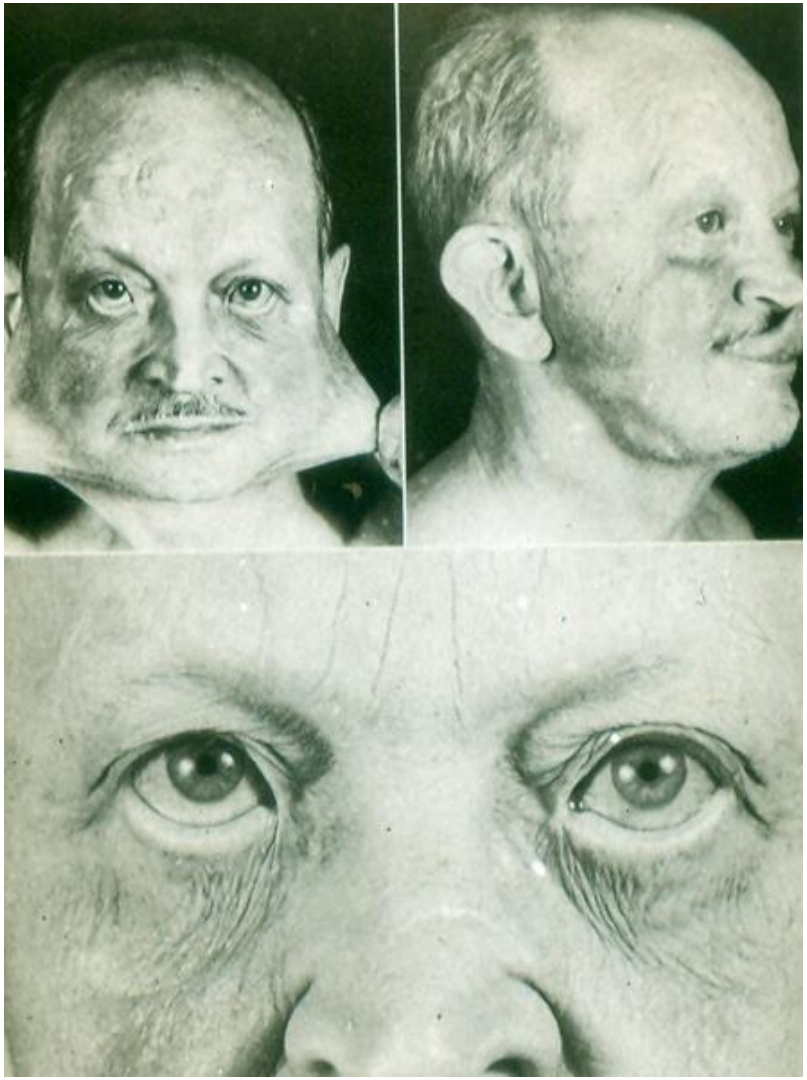


EHLER DANLOS SYNDROME



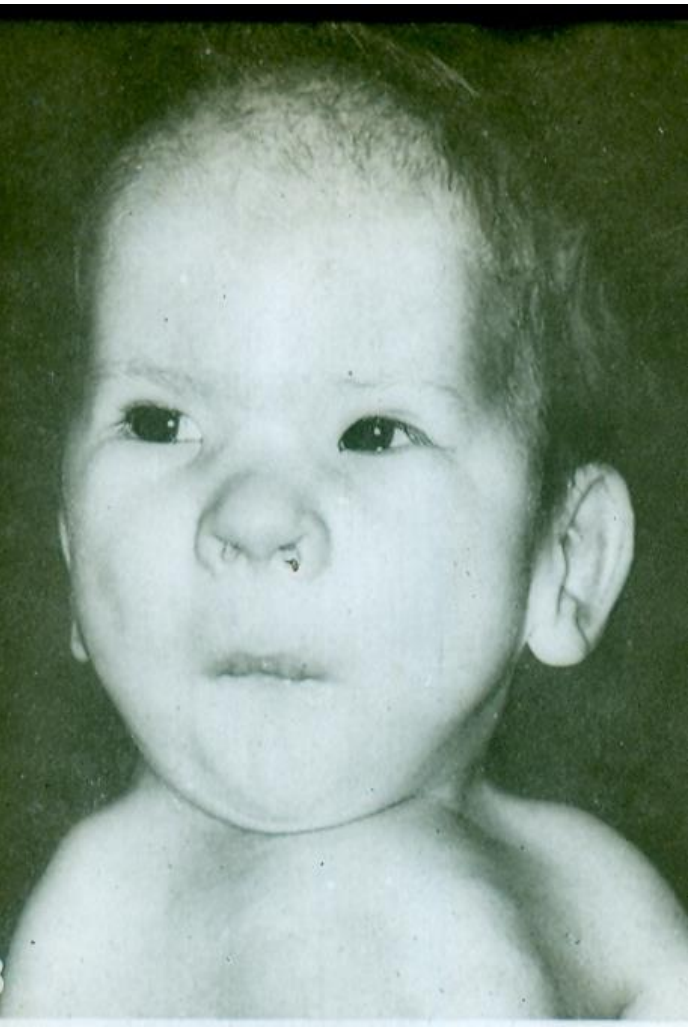
EHLER DANLOS SYNDROME

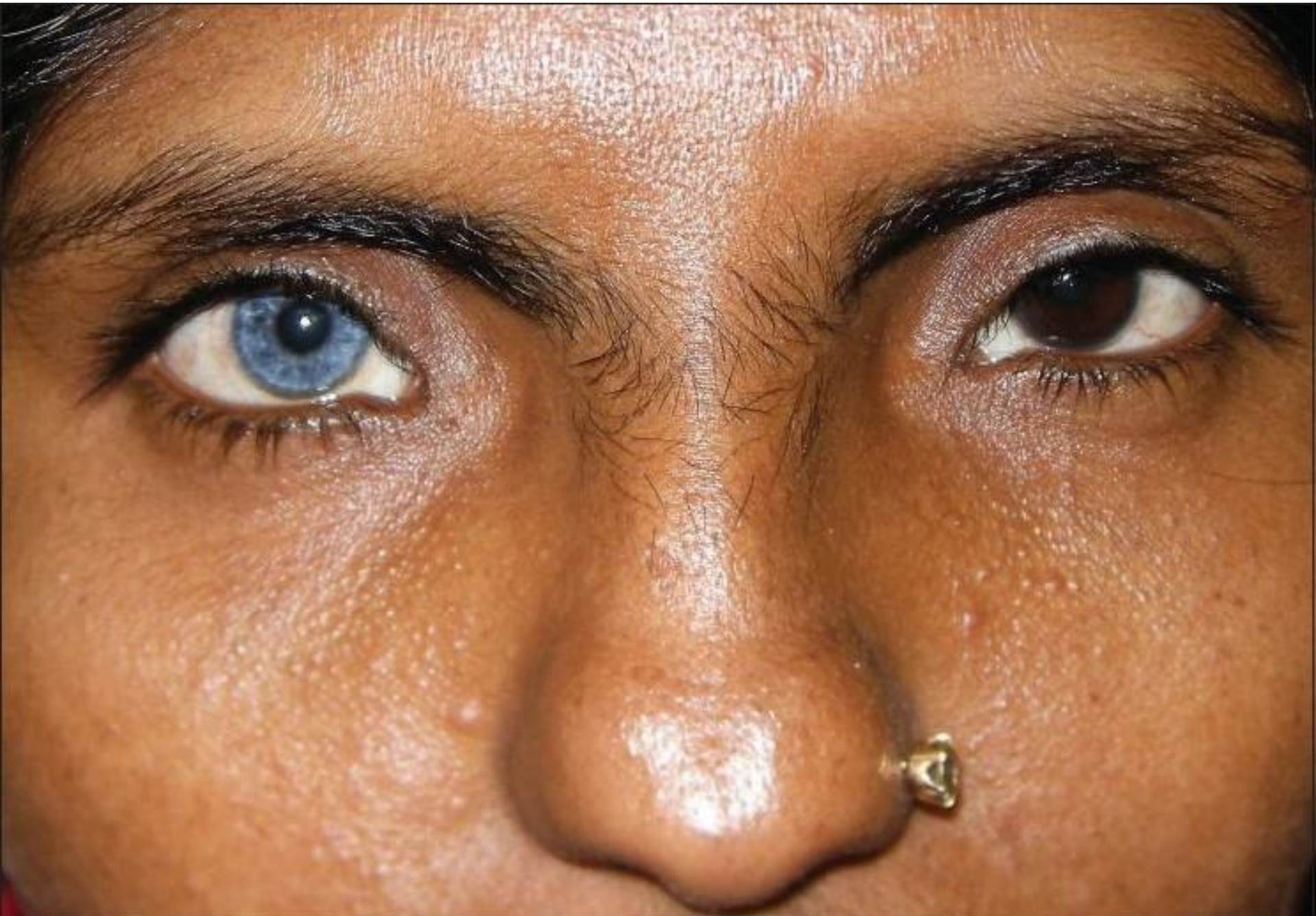
Hyper-elastosis cutis



CRANIAL CARPO-TARSAL DYSPLASIA

Whistling face Syndrome





THANK YOU

Clinical Characteristics of Autosomal Dominant Disorders

- Variable expressivity
- Penetrance (the proportion of people who carry the gene who present with any of the known phenotypic effects of the gene)
- Variation in the age of onset
- New mutations with advanced paternal age ("hot spots" in the genome)