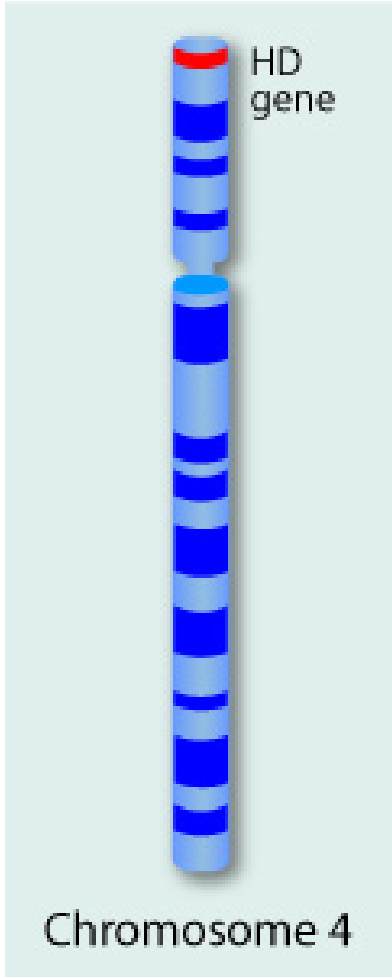
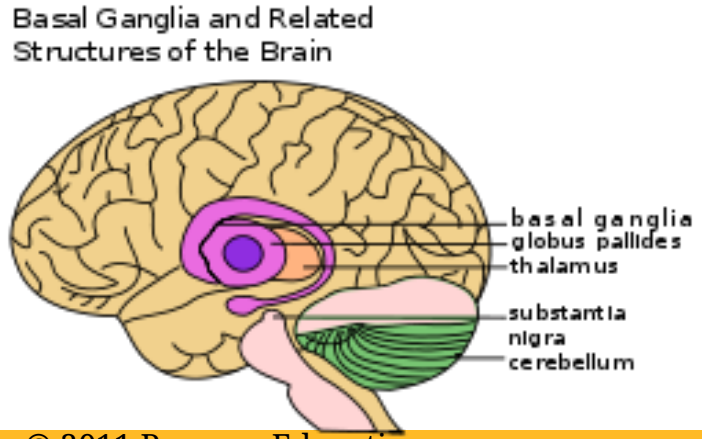
Imprinting

Huntington's Disease: A Late-Onset Lethal Disease

- **Huntington's disease** is a degenerative disease of the nervous system
- The disease destroys cells in the **basal ganglia**, the part of the brain that controls movement, emotion, and cognitive ability
- The disease has no obvious phenotypic effects until the individual is about 35 to 40 years of age
- Once the deterioration of the nervous system begins the condition is irreversible and fatal

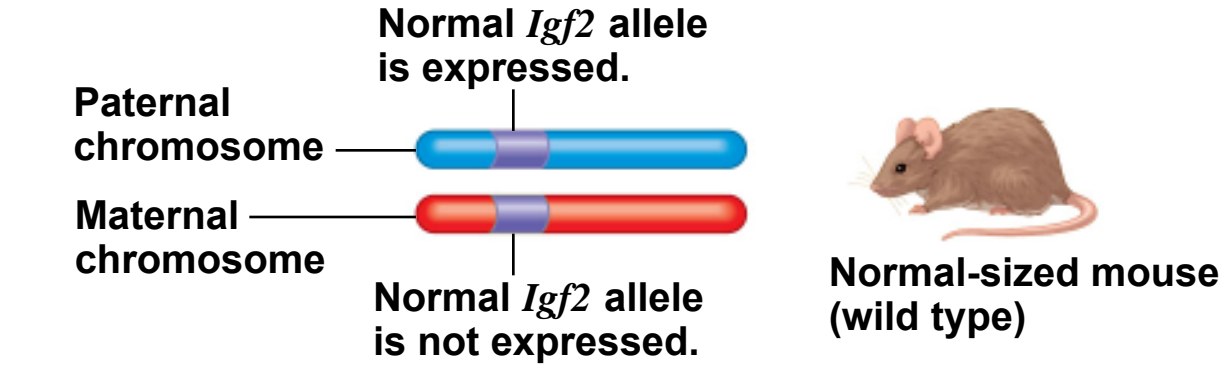




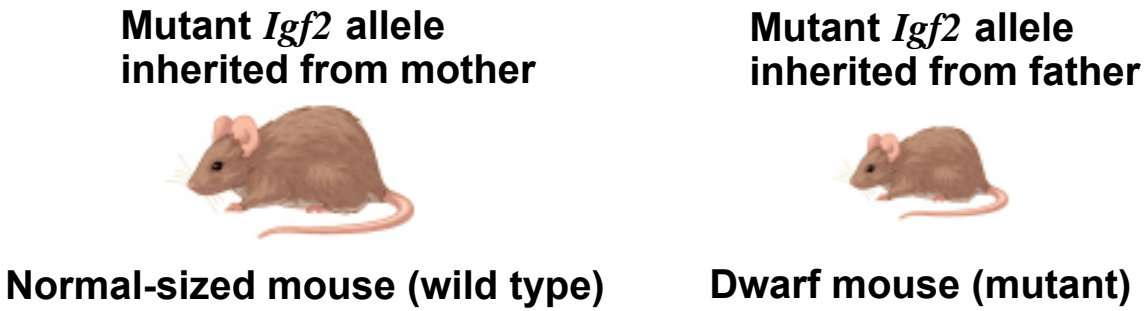
Genomic Imprinting

- For a few mammalian traits, the phenotype depends on which parent passed along the alleles for those traits
- Such variation in phenotype is called **genomic imprinting**
- Genomic imprinting involves the silencing of certain genes that are “stamped” with an imprint during gamete production

Figure 15.17

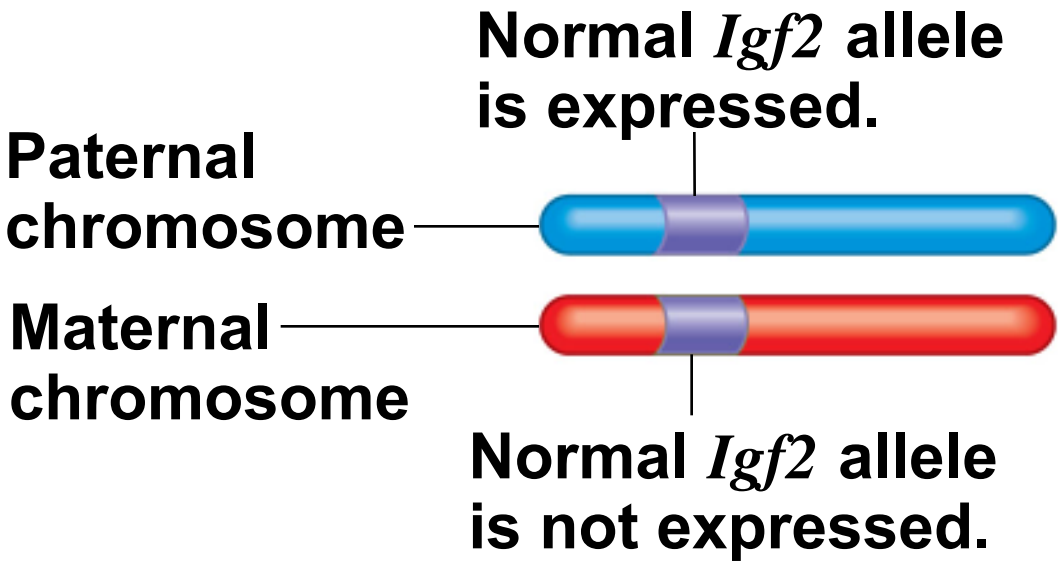


(a) Homozygote



(b) Heterozygotes

Figure 15.17a



Normal-sized mouse (wild type)

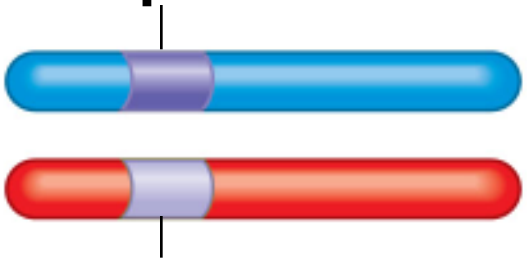
(a) Homozygote

Figure 15.17b

Mutant *Igf2* allele inherited from mother

Normal-sized mouse (wild type)

Normal *Igf2* allele is expressed.

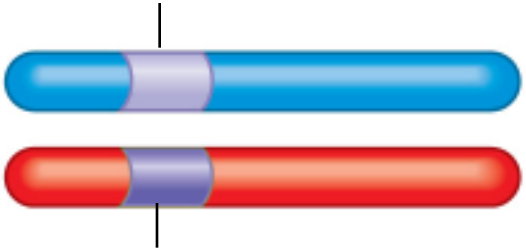


Mutant *Igf2* allele is not expressed.

Mutant *Igf2* allele inherited from father

Dwarf mouse (mutant)

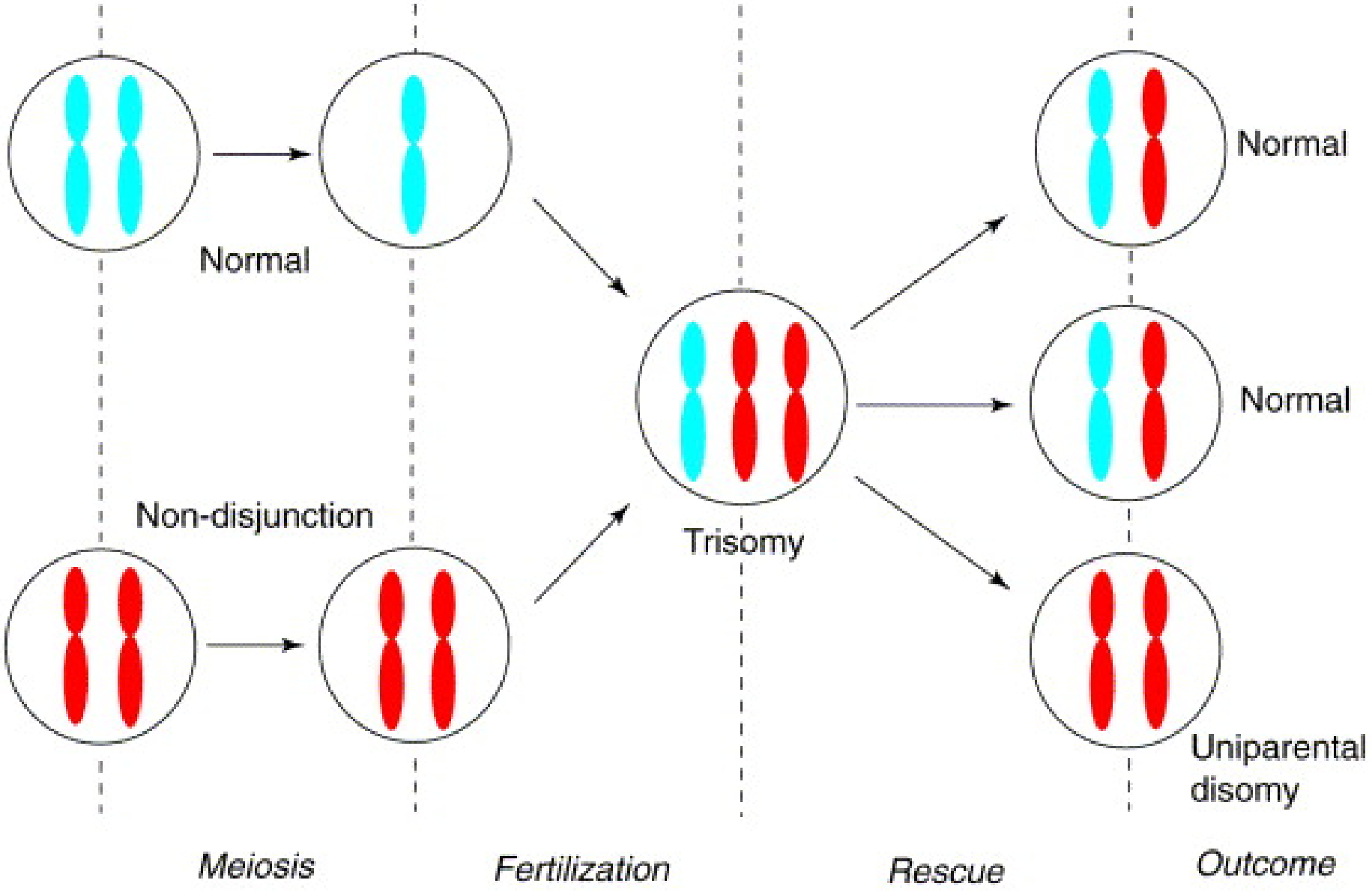
Mutant *Igf2* allele is expressed.



Normal *Igf2* allele is not expressed.

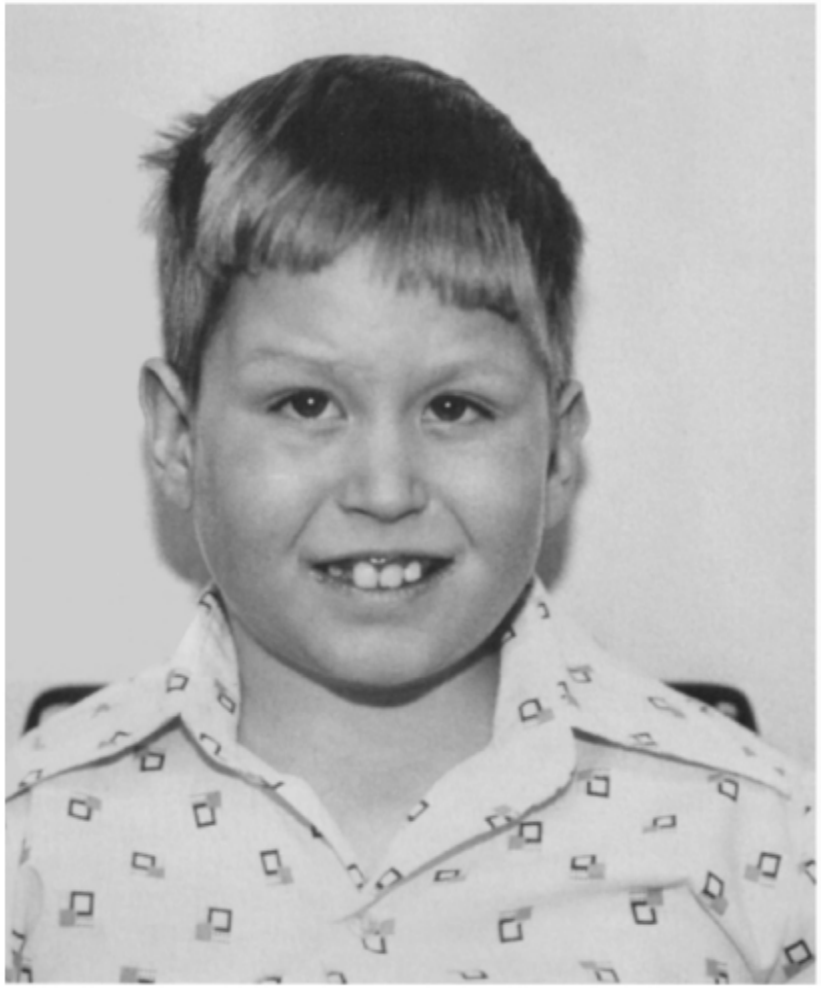
(b) Heterozygotes

- It appears that imprinting is the result of the methylation (addition of $–CH_3$) of cysteine nucleotides
- Genomic imprinting is thought to affect only a small fraction of mammalian genes
- Most imprinted genes are critical for embryonic development



trends in Endocrinology and Metabolism

Imprinti



Prader-Willi syndrome

Angelman syndrome

Imprinting

I. **Definition**: the differential expression of a gene depending on the sex of the parent from which it is inherited (i.e., the parental origin of the gene).

Implications:

A. Implies that there is a critical or sensitive period during development (i.e. during or before gametogenesis) during which the genetic information is marked or imprinted in order to permit differential expression based on parental origin.

B. The imprint must persist stably through DNA replication and cell division in the body cells.

C. The imprint must be capable of affecting gene expression (i.e. turning genes on or off).

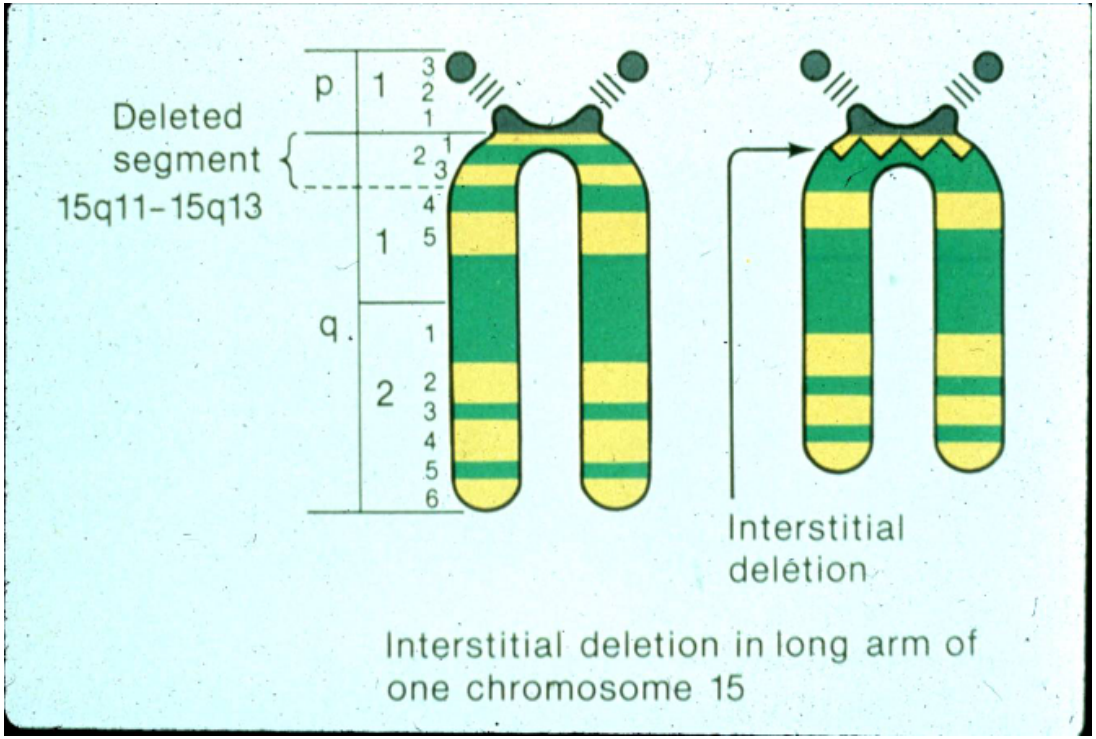
D. Imprinting is not a permanent alteration since it must be erased in the germ cell line of every individual so that new imprinting may be introduced.

Example of Imprinting in Humans

Prader-Willi syndrome (PWS) and Angelman syndrome (AS)

1. Both map to and may involve deletions of 15q11-13 but they have distinct phenotypes.
2. PWS is characterized by obesity, voracious appetite, and mental retardation, whereas, Angelman is characterized by gait ataxia, smiling facies and happy demeanor, and mental retardation.
3. Deletions are found in about 50-60% of cases of PWS and AS.
4. If the deletion is paternally derived (only maternal 15q11-13 present) then PWS.
5. If the deletion is maternally derived (only paternal 15q11-13 present) then AS.
6. Some cases of PWS (about 30%) have been attributed to maternal uniparental disomy and some cases of AS (about 5%) have been attributed to paternal uniparental disomy. About 10-15% of cases of AS are caused by a single gene mutation in the UBE3A gene. Other causes of PWS and AS include defects in the imprinting center, chromosomal translocation within the PWS/AS critical region, and unknown cause.

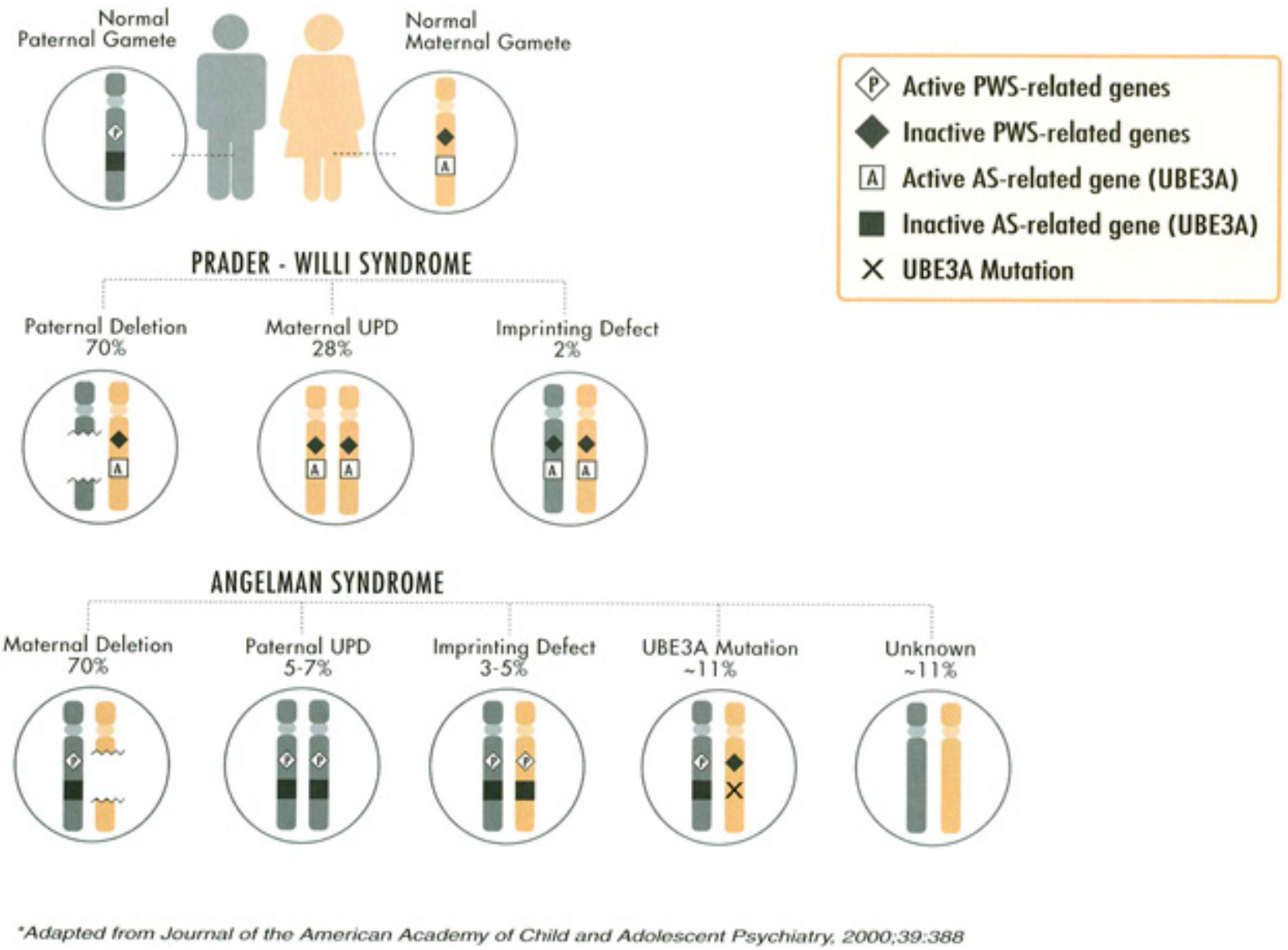
PWS & AS both involve chromo 15q11-13



Deletions account for ~ 70% cases of PWS & AS

- If paternal deletion of 15q11-13 → PWS
- If maternal deletion of 15q11-13 → AS

Causes of PWS and AS

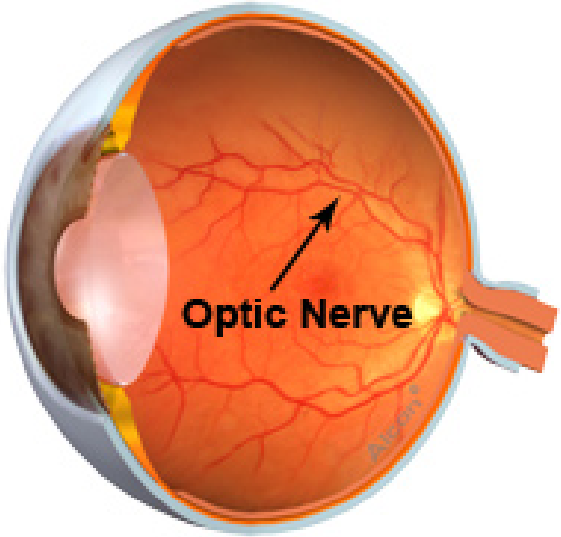


*Adapted from Journal of the American Academy of Child and Adolescent Psychiatry, 2000;39:388

Inheritance of Organelle Genes

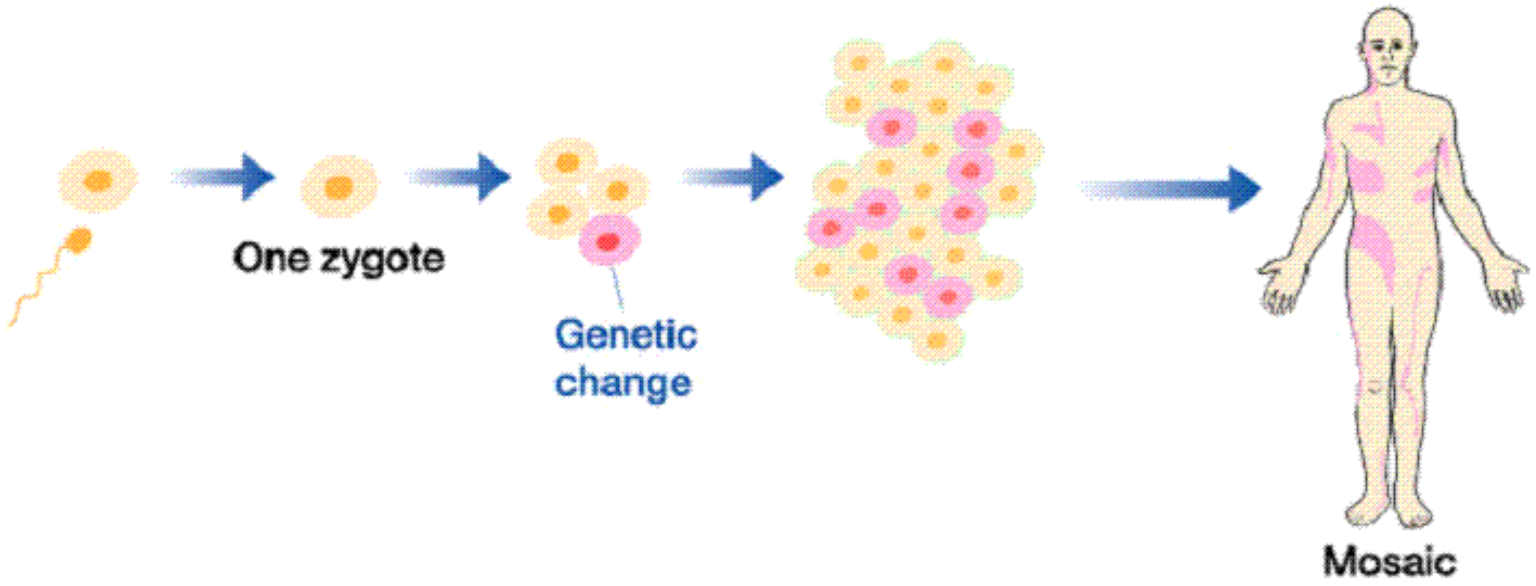
- Extranuclear genes (or cytoplasmic genes) are found in Mitochondria
- Extranuclear genes are inherited maternally because the zygote's cytoplasm comes from the egg

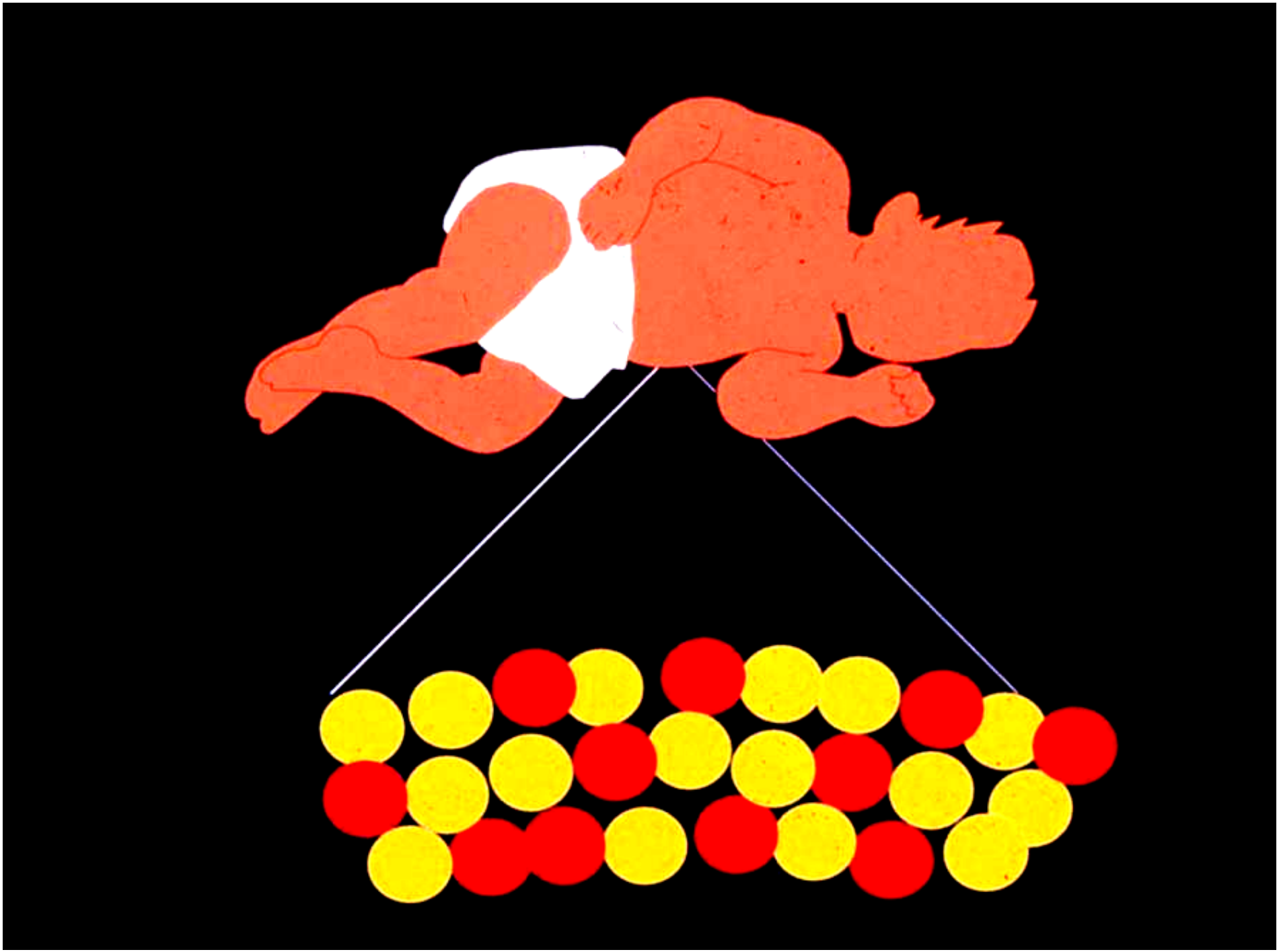
- Some defects in mitochondrial genes prevent cells from making enough ATP and result in diseases that affect the muscular and nervous systems
  - For example, mitochondrial myopathy (**myopathy** is a muscular disease) and Leber's hereditary optic neuropathy (damage to nerves)



Mosaicism

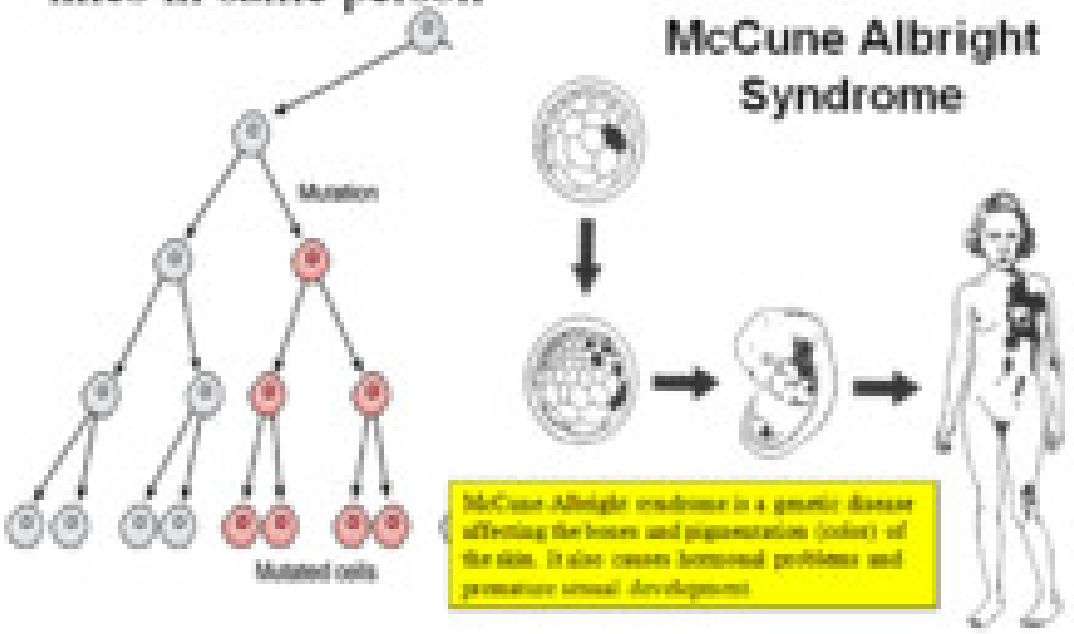
Two or more distinct cell lines from single zygote differing because of mutation or nondisjunction.

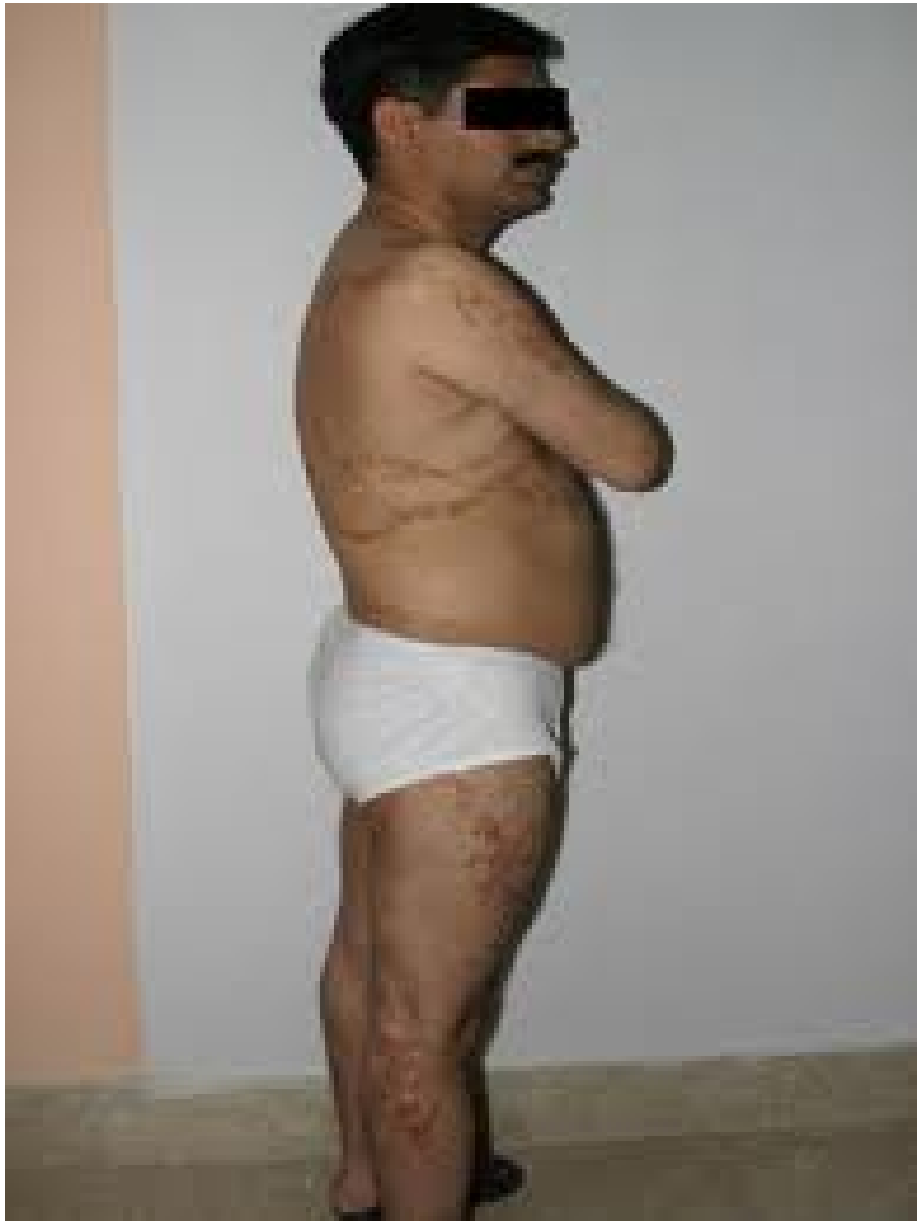

One zygote
Genetic change
Mosaic

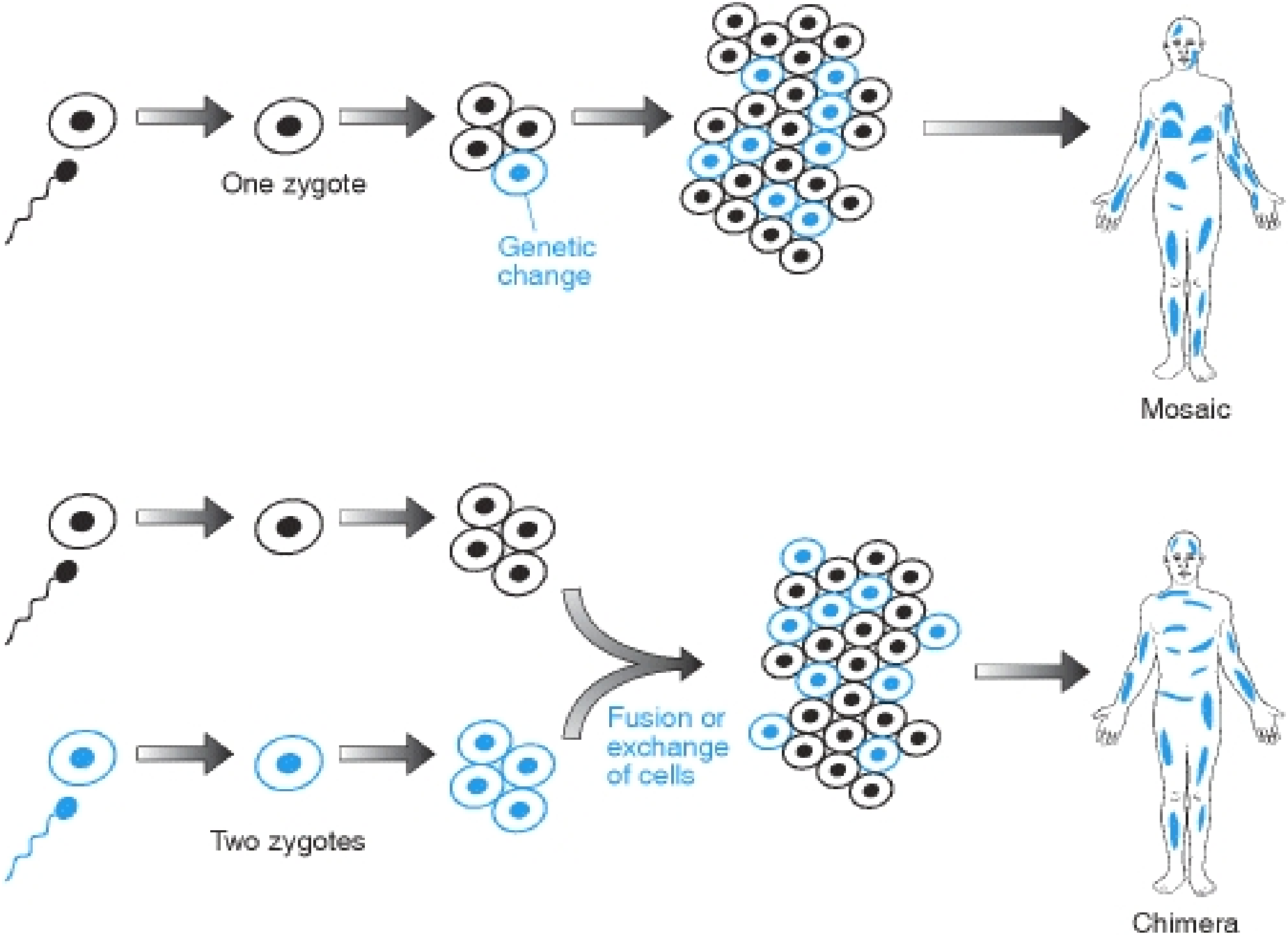


Somatic Mosaicism Gives Different Cell Lines

- *Mosaicism*: occurrence of two or more cell lines in same person






One zygote
Genetic change
Mosaic
Two zygotes
Fusion or exchange of cells
Chimera