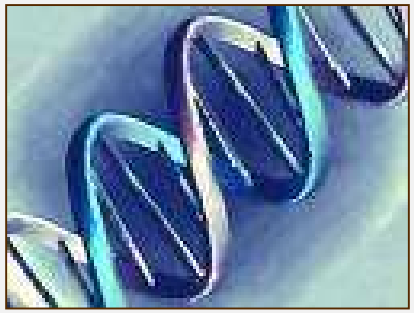
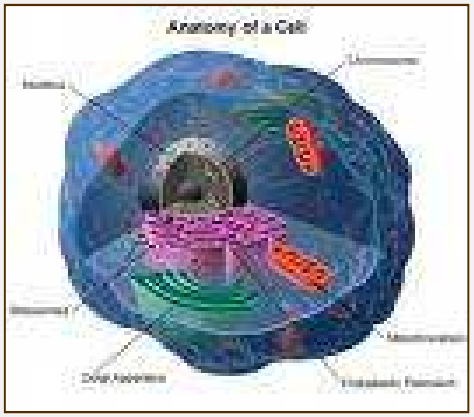
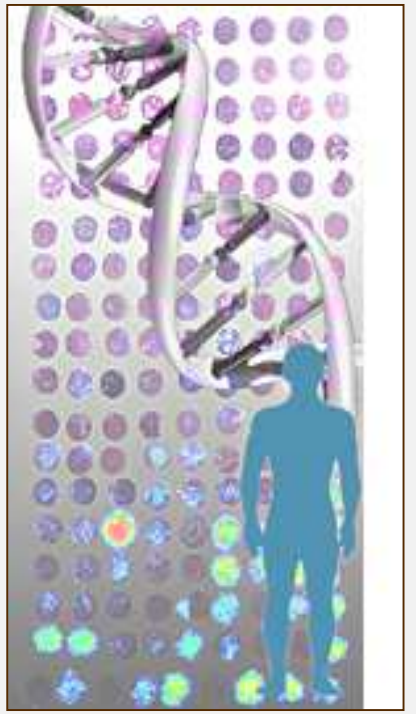


UNUSUAL PATTERN

OF INHERITANCE





Unusual pattern of inheritance of single gene disorders

The reason for studding pattern of inheritance of disorders within families is their adequate genetic counseling (correct clinical diagnosis and recurrence risk on the base of pattern of inheritance)

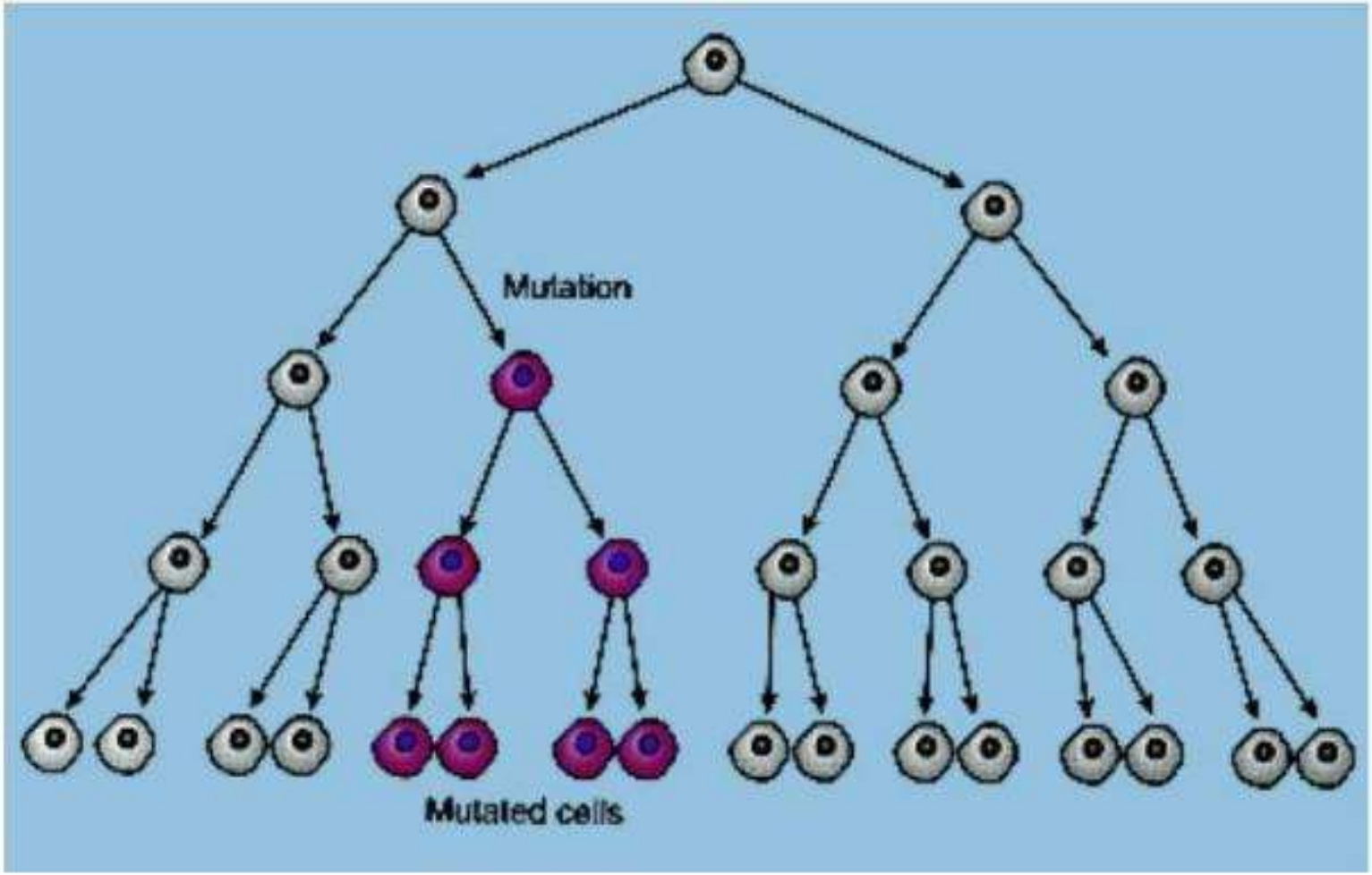
For many single gene disorders, gene characterization has revealed atypical, unusual inheritance mechanisms, that are outside the scope of Mendel` s experiments

Unusual pattern of inheritance can be explained by genetic phenomena such as :

1. Somatic or germ-line mosaicism
2. Uniparental disomy
3. Genomic imprinting
4. Triplet repeat expansion
5. Mitochondrial inheritance

Mosaicism

- Mosaicism: presence of more than one cell line in an individual
- Somatic Mosaicism: usually caused by a post-zygotic mutation which affects a certain percentage of cells in an individual
  - Mosaic Down Syndrome
  - Segmental Neurofibromatosis
  - McCune-Albright Syndrome



Somatic mosaicism for the single gene mutations :

!!! The possibility of somatic mosaicism is suggested by :

1. The features of a single gene disorder **being less severe** in an individual than usual
2. Being confined **to a particular part of the body in a segmental distribution**

Example :

Neurofibromatosis-1,

- the distinctive café-an-lait spots and neurofibroma tumors may occur **in one limb or one body region**

- if a parent is mosaic for disease allele because of postzygotic mutation, he/she may appear clinically unaffected

Neurofibromatosis (AD)

Gonadal Mosaicism

- Gonadal Mosaicism: presence of more than one cell line in the gonads but not in the rest of the body (somatic cells).
- Mutation occurred in a precursor sperm or egg cell and is passed on to all derivatives of that cell. The remainder of germ and somatic cells in the body do not carry the mutation.

!!! The characteristic of germ-line mosaicism is multiple affected offspring with normal parents (resembles AR), but only for:

- autosomal dominant (AD) diseases

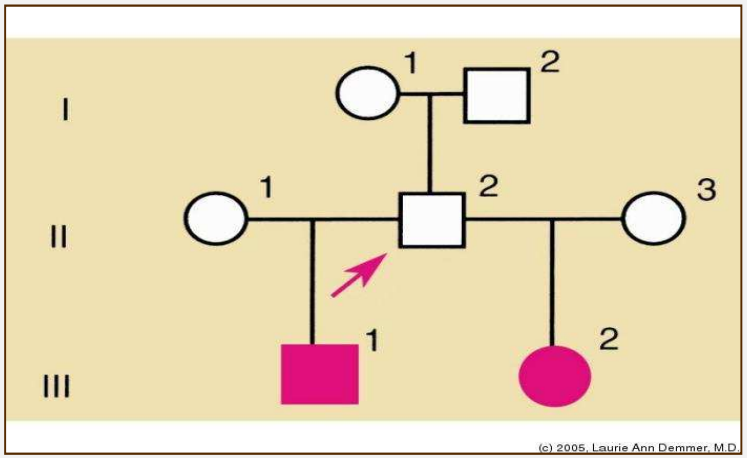
(Achondroplasia, Ostegenesis imperfecta-OI)

- or X-linked (XL) diseases

(Duchene muscular dystrophy, Hemophilia)

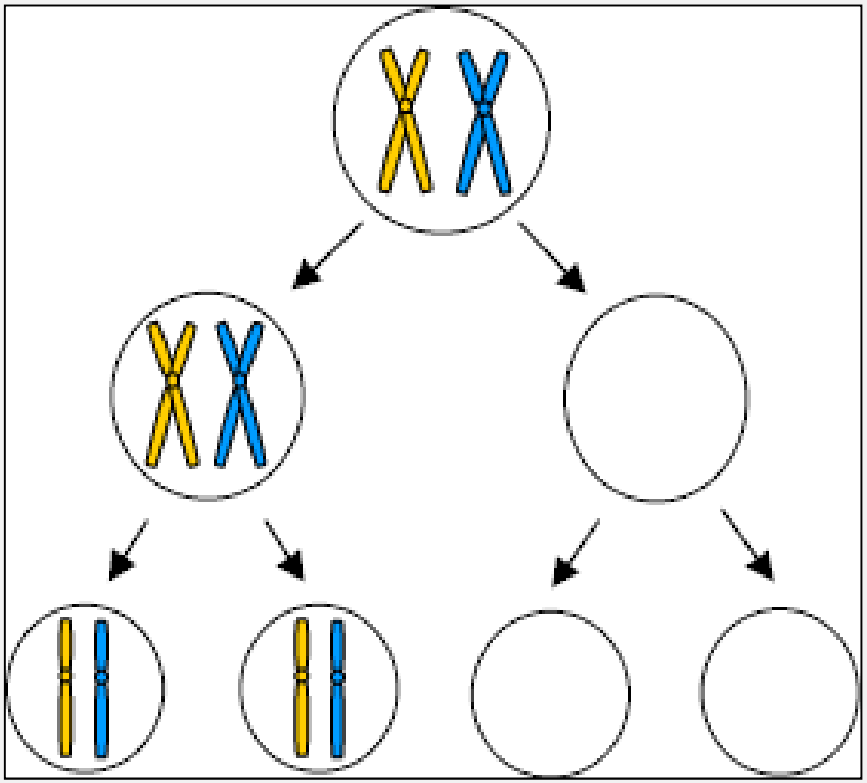
Proven by DNA analysis example - Osteogenesis imperfecta (OI) :

*Demonstration of a mutation in the collagen gene responsible for **OI** in a proportion of individual sperm from* a clinically normal father who had two affected infants with different partners

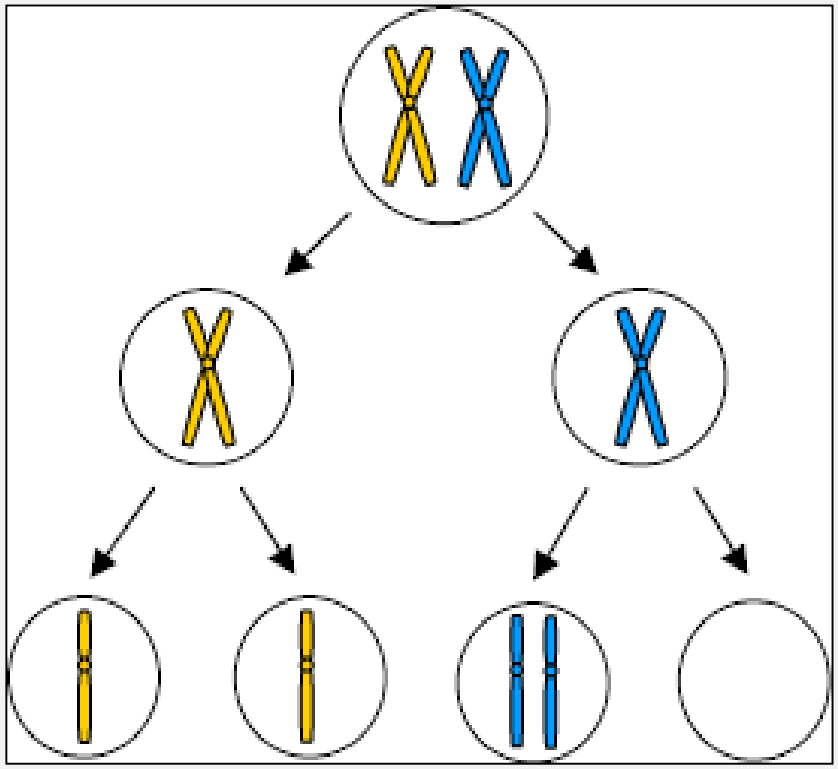


Uniparental Disomy

- Presence of two homologous chromosomes inherited from only one parent
- ISODISOMY: parent passes on two copies of the same chromosome (non-disjunction in meiosis II)
- HETERODISOMY: parent passes on one copy of each homolog (non-disjunction in meiosis I)

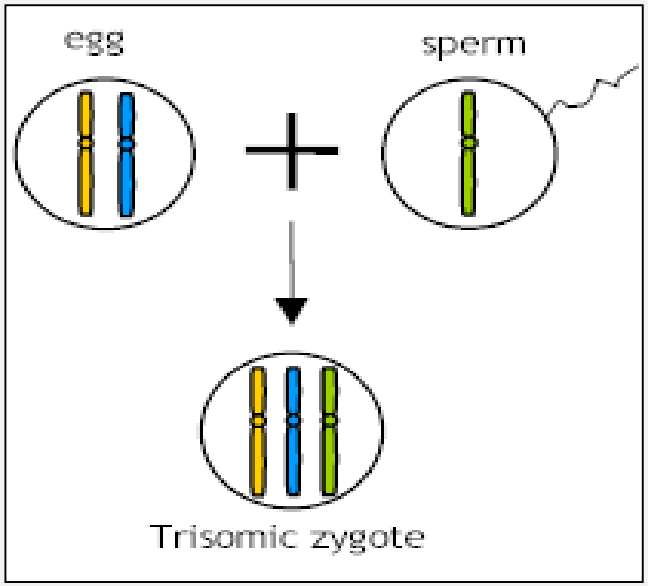


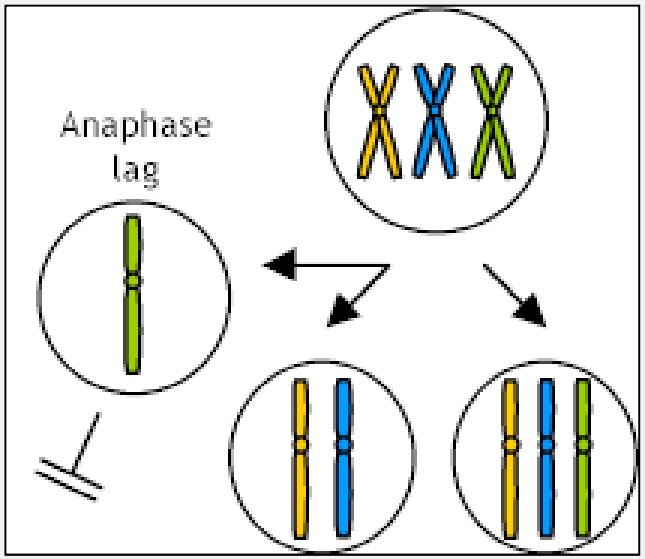
a) Non-disjunction in Meiosis I:



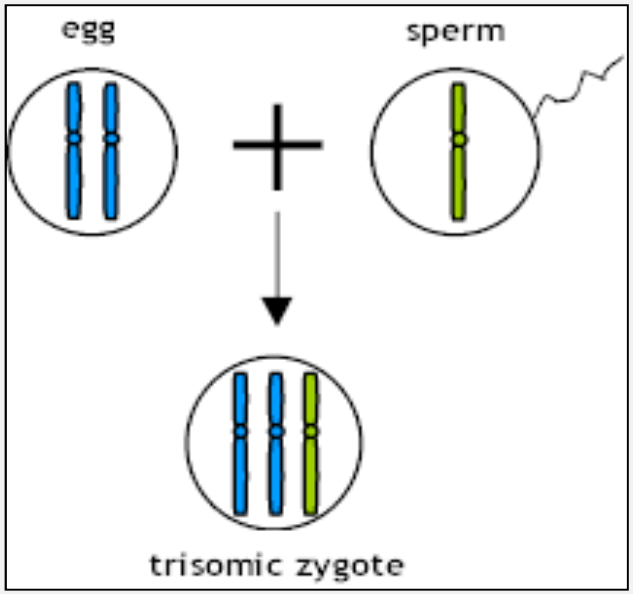
b) Non-disjunction in Meiosis II:

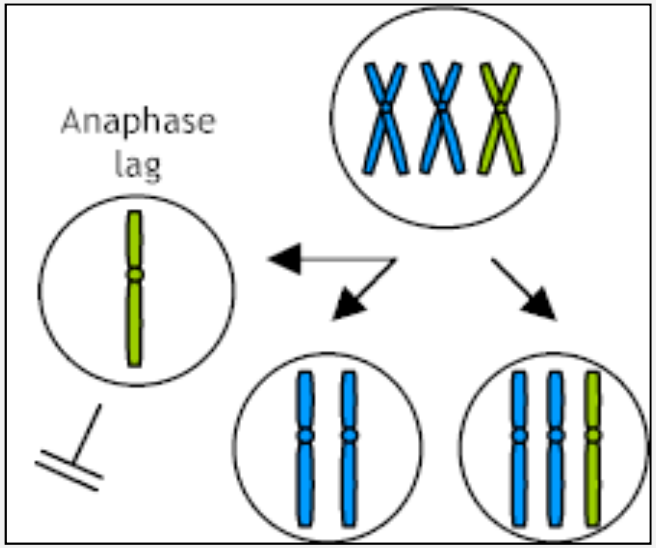
Fertilization following Meiosis I error:





Fertilization following Meiosis II error:





A.Trisomic rescue following an error in meiosis I. **B.Trisomic rescue - an error in meiosis II.**

Uniparental Disomy

- **Clinically significant when it involves chromosomes with imprinted genes.**
- **Likely to play role in the etiology of pregnancy loss and unexplained IUGR**
- **Known clinical phenotypes exist with Paternal UPD 6, 11, 14, 15 and Maternal UPD 7, 14, 15, 16**

Genomic imprinting (GI) or "Parent of origin" effect

"Different expression of a gene, depending on the sex of the parent who transmits it"

Imprinting affects only a minority of genes

- Imprinting is a **functional (epigenetic) change in a gene** (a form of silencing or **temporary gene inactivation**)
- The DNA sequence is not altered (**there is not mutation**), but ***expression*** of the affected gene ***is modified***
- A gene` s **imprint is reversed or removed** when a cell passes **through opposite gametogenesis**
- **Paternally imprinted gene** – is **not** expressed when is inherited from the father
- **Maternally imprinted gene** – is **not** expressed when is inherited from the mother

Mechanism of Imprinting

- ***DNA Methylation***
- **Must occur before fertilization**
- **Must be able to confer transcriptional silencing**
- **Must be stably transmitted through mitosis in somatic cells**
- **Must be reversible on passage through the opposite parental germline (i.e., if an allele is maternally imprinted, this must be removed in the gametes of a male offspring**

Clinical consequences of Genomic imprinting (GI) + Uniparental disomy (UPD)

I. In some single gene disorders there is the "parent of origin" effect :

Examples :

1. Huntington disease (AD)

- there is an increased risk of an earlier and more severe form of the disease when the gene is transmitted by the father

2. Myotonic dystrophy (AD)

- there is an increased risk of a severe neonatal form of the disease, when the gene is transmitted by the mother

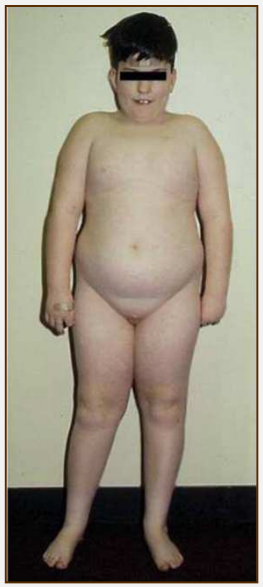
II. Microdelition syndromes can be also **illustration of UPD and GI**

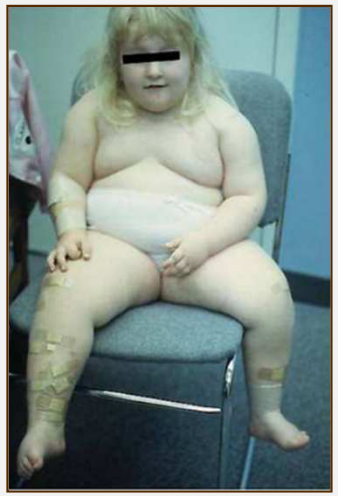
Examples :

Identical microdeletions or UPD with different parental origins cause the Prader-Willi (PWS) and Angelman (AS) syndromes

1. Prader-Willi s-me (PWS) :

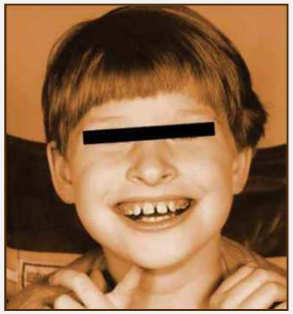
- **Mental retardation (mild)**
- **Obesity ; Short stature**
- **Hypogonadism**
- **Small hands and feet**
- **Skin lesions**

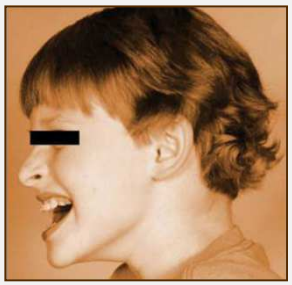




2. Angelman s-me (AS) :

- **Severe Mental retardation**
- **Inappropriate laugther**
- **Epilepsy (convulsions)**
- **Ataxia (poor coordination)**





PWS – genetics :

~ **75 %** : **microdeletion - 15 (q 11-12) –** inherited **from the father**

46, XX/XY, del 15 (q 11-12) pat.

~ **25 %** : **UPD mat.** (both 15 chromosomes are from the mother)

~ **2–3 % :** mutation in gene controlling imprinting

AS – genetics :

~ **70 %** : **microdeletion - 15 (q 11-12) –** inherited **from the mother**

46, XX/XY, del 15 (q 11-12) mat.

~ **2 %** : **UPD pat** (both 15 chromosomes are from the father)

~ **2–3 % :** mutation in gene controlling imprinting

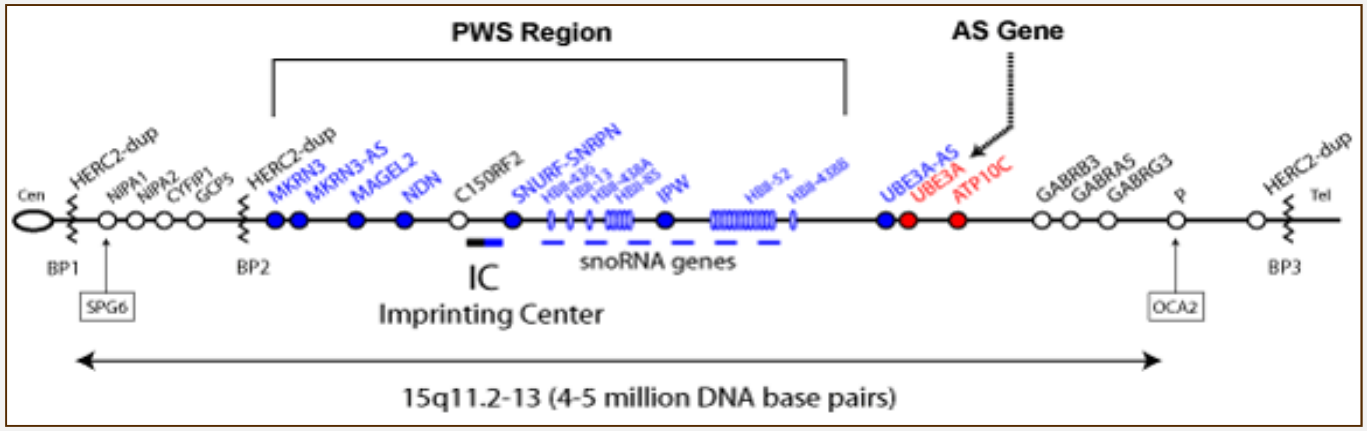
~ **25 %** : maternal gonadal mosaicism or mutation in AS gene

"Critical region" 15 (q 11-12) :

- It **is deleted** in PWS and in AS
- It includes the gene controlling imprinting

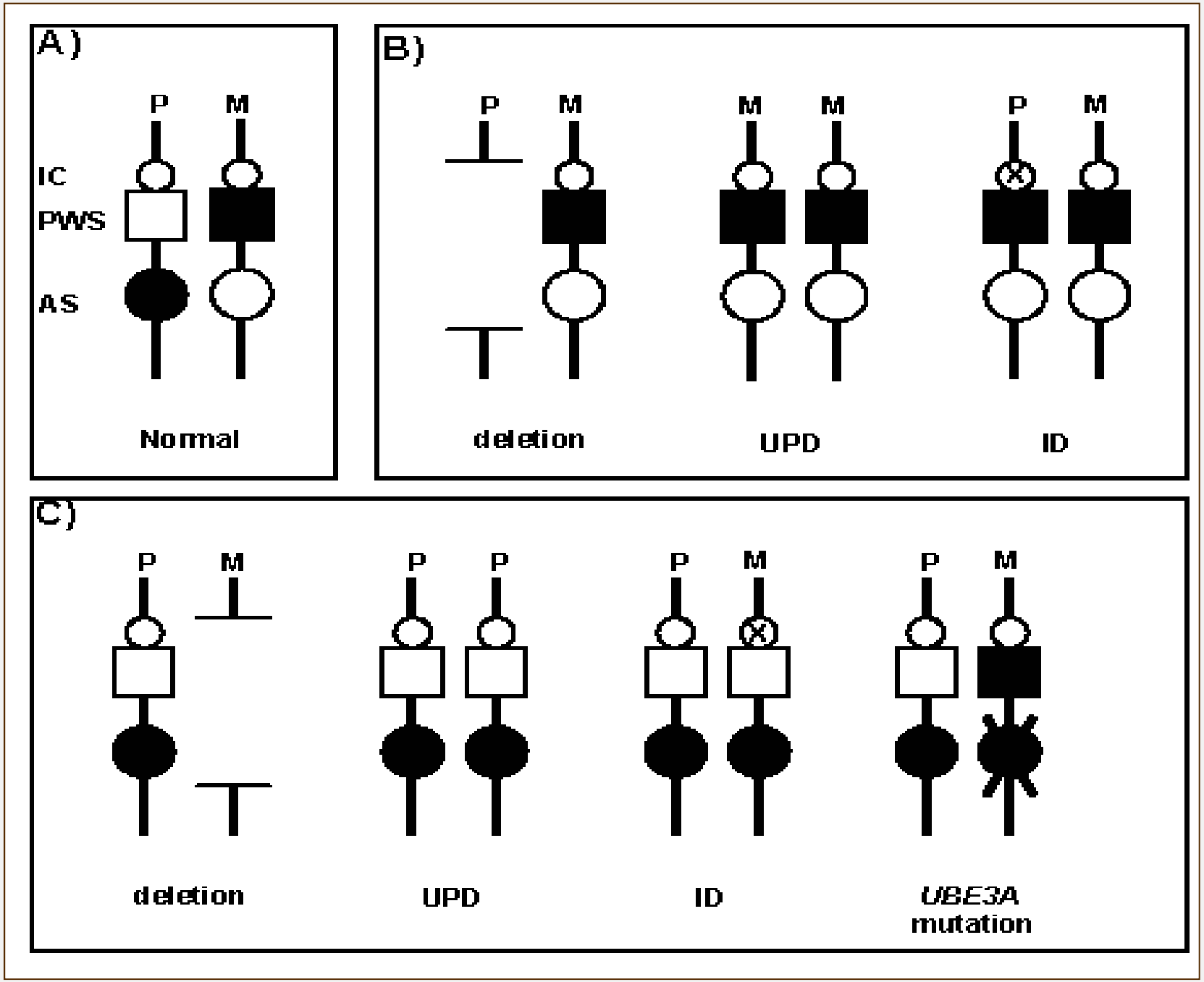
!!! It includes different specific genes (for PWS and for AS) that

are opposite imprinted !!!



1. **The gene for PWS is dominant and is expressed (active) only on chromosome inherited from the father** (maternal imprinting)
   - If single active copy of this paternal gene **is lost by** :
     paternal chromosome deletion **or** maternal UPD 15,
     !!! PWS results because no active paternal genes are present

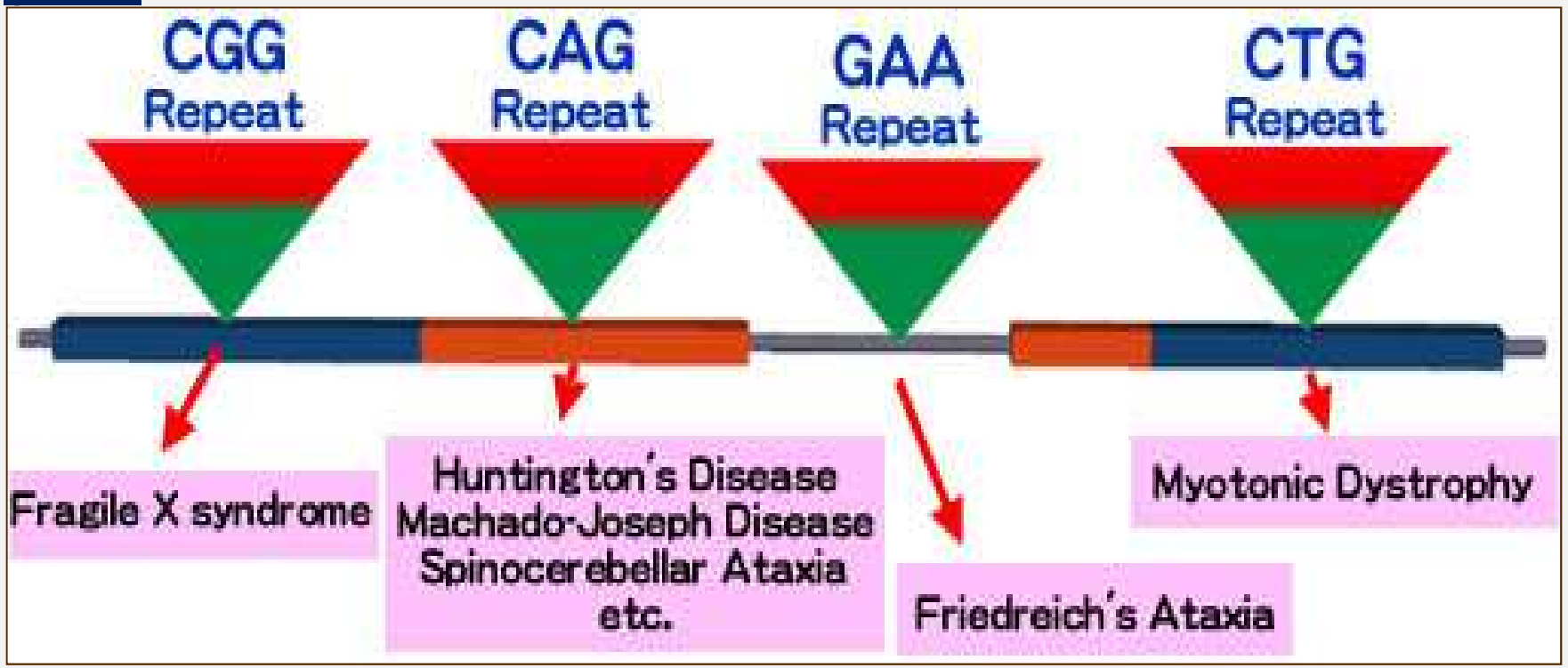
2. **The gene for AS is dominant and is expressed (active) only on chromosome inherited from the mother** (paternal imprinting)
   - If single active copy of this maternal gene **is lost by :**
     maternal chromosome deletion **or** paternal UPD 15,
     !!! AS results because no active maternal genes are present


A)
P
M
IC
PWS
AS
Normal
B)
P
M
deletion
M
M
UPD
P
M
ID
C)
P
M
deletion
P
P
UPD
P
M
ID
P
M
UBE3A
mutation

Dynamic mutations or Genetic amplification

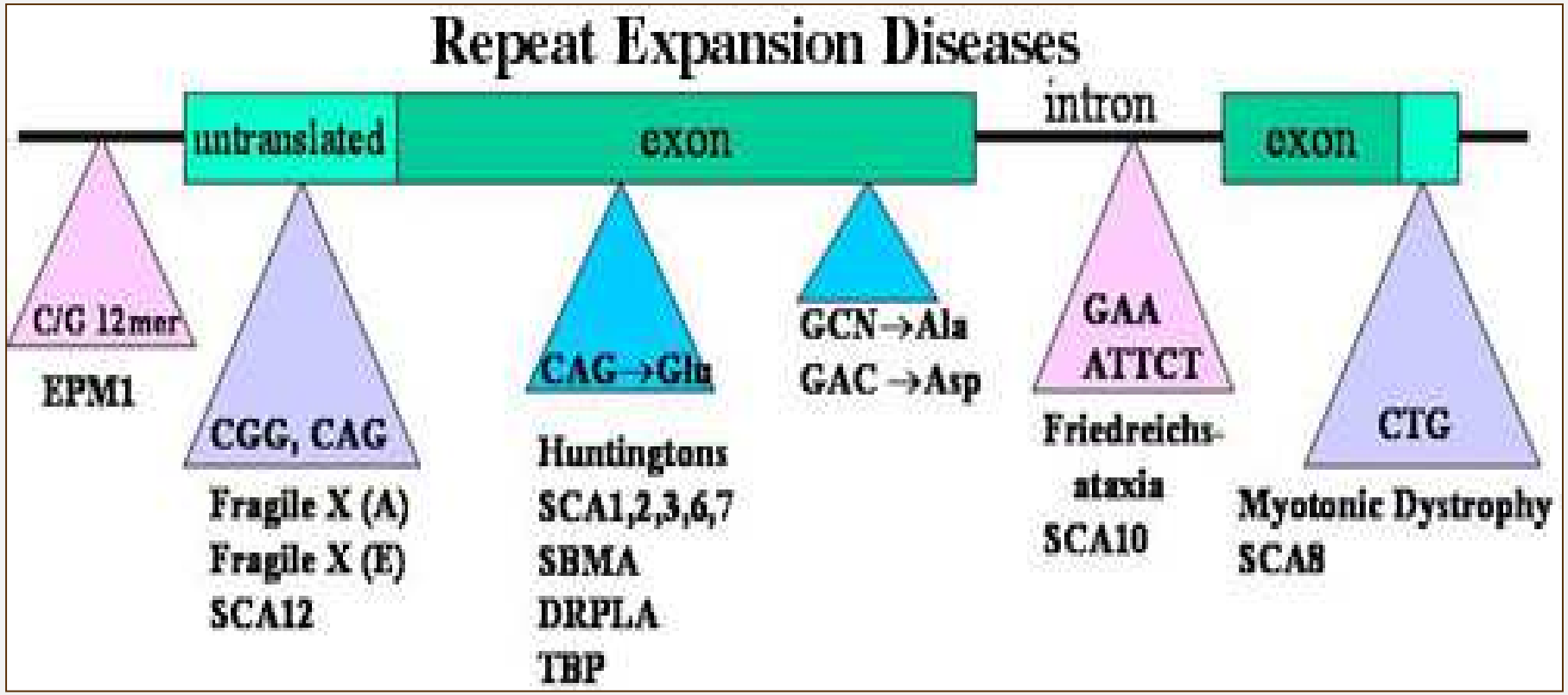
Triplet expansion (Genetic amplification) **causes anticipation**, that is one of the unusual patterns of inheritance

A number of **single gene disorders (Repeat expansion diseases)** are due to **different triplet repeated expansions** (amplifications) **in their own genes.**



Triplet repeats (amplifications) can be present in 5`or 3` un-translated region of the particular gene or in it` s coding region

5`region** **3`region



- Triplet repeats below a certain length for each disorder are faithfully transmitted in meiosis and mitosis and do not lead to disease

- Above a certain repeat number for each disorder, they are unstable and will be transmitted with an increase in triplet repeat number and usually lead to disease, expressing anticipation in following generations

- There is a direct relationship between severity of phenotype and repeat copy number

- Amplifications (Triplet repeats) are named dynamic mutations because the repeat sequence becomes more unstable as it expand in size

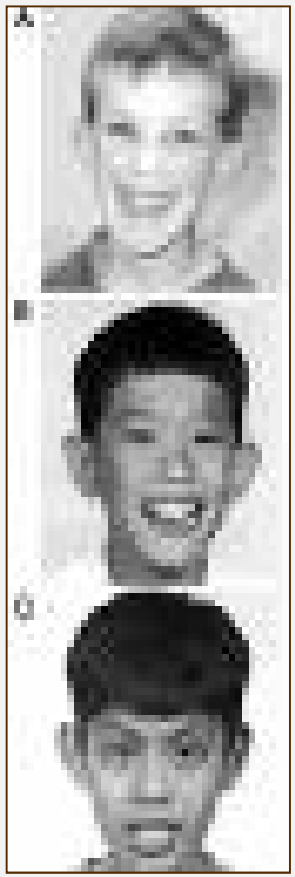
Fragile X syndrome (XL) : repeat triplet : **(CGG)**

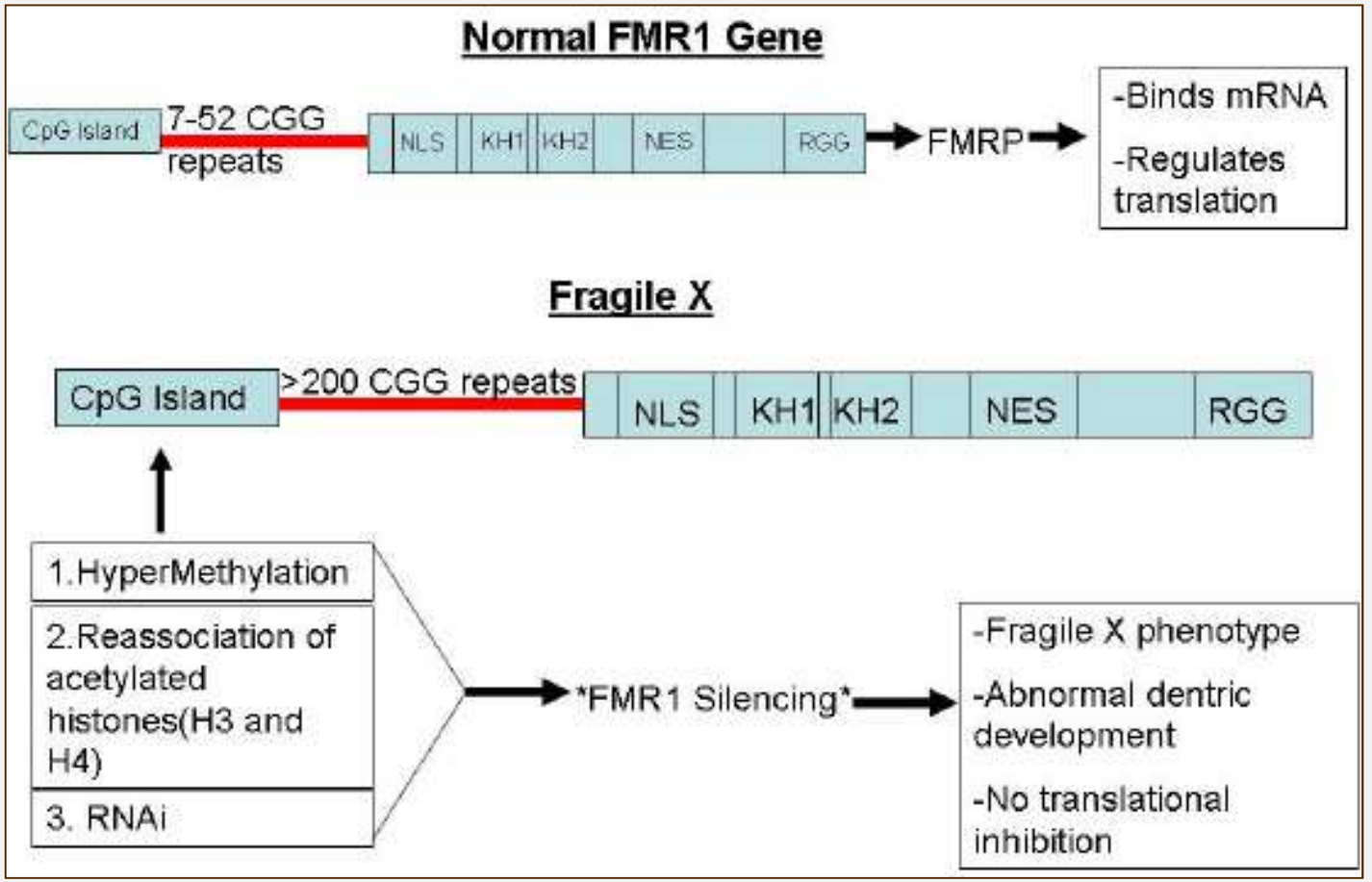
repeat location : **5` UTR**

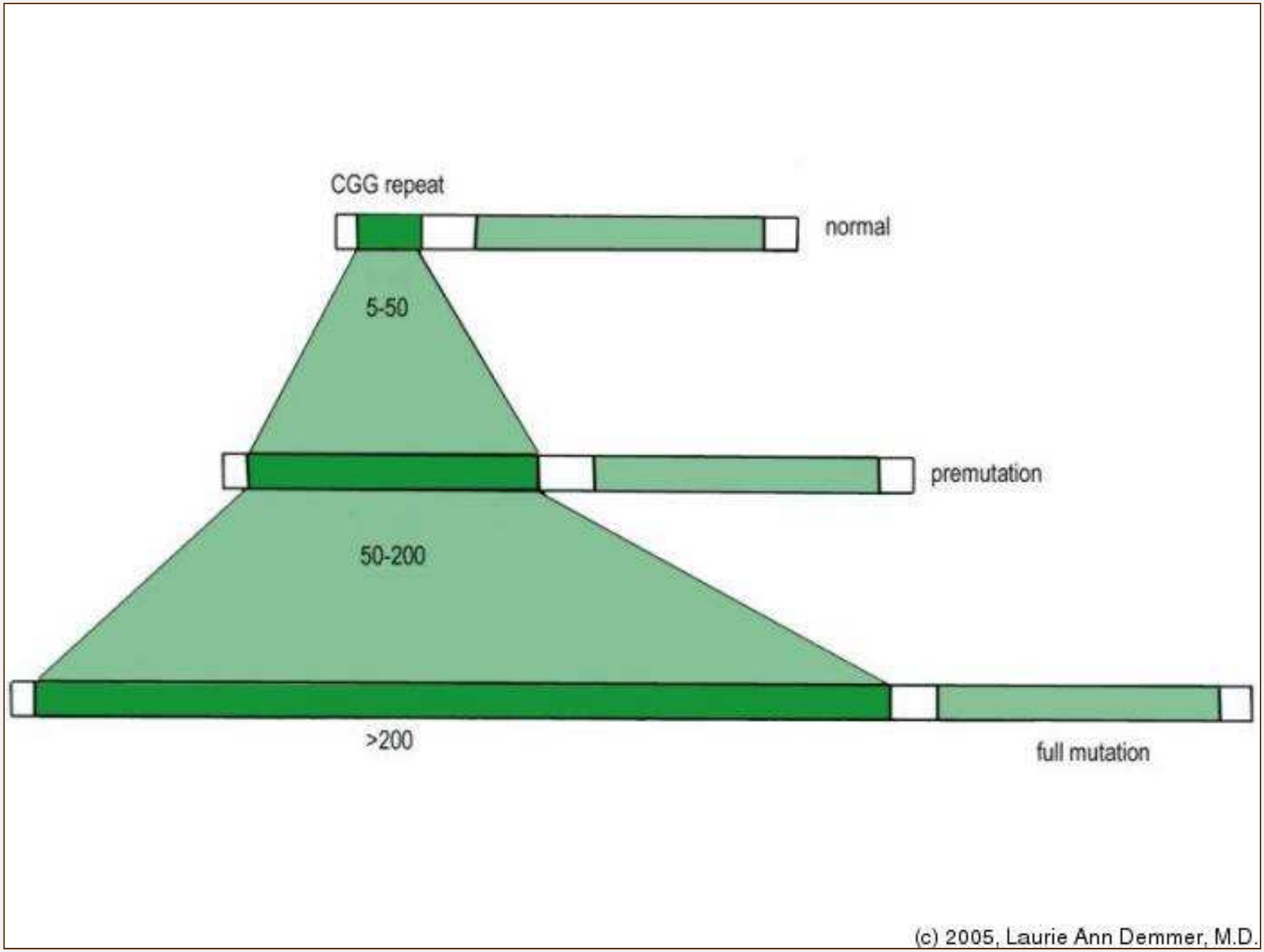
normal range (repeats) **: < 50**

premutation (repeats) : **50 - 200**

mutant range (repeats) **: > 200**



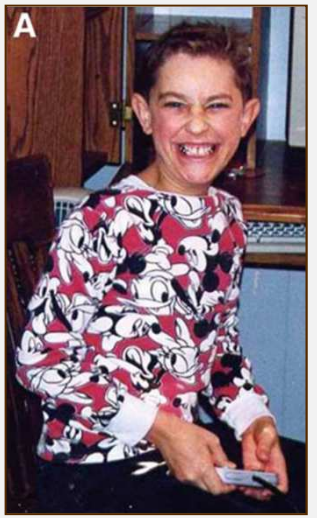



CGG repeat
normal
5-50
premutation
50-200
>200
full mutation
(c) 2005, Laurie Ann Demmer, M.D.

Fragile X syndrome (atypical X-linked)

1. The mutation consist of an increase in size of a **long CGG in the 5`UTR of the FMR-1 gene (Xq27.3),** that causes **methylation** and decreased gene expression

2. Afected mails **(full muttation)** have **:**
   - Mental retardation (moderate to severe)
   - Speech delay or autistic features
   - High forehead, large ears, long face
   - Hypermobile joints, Macroorhidism
3. **~ 50%** of affected femails (**full mutation**) have **:**
   - Mental retardation or educational difficulties
4. Males and females **with pre-mutation are unaffected !!**
5. **Anticipation**



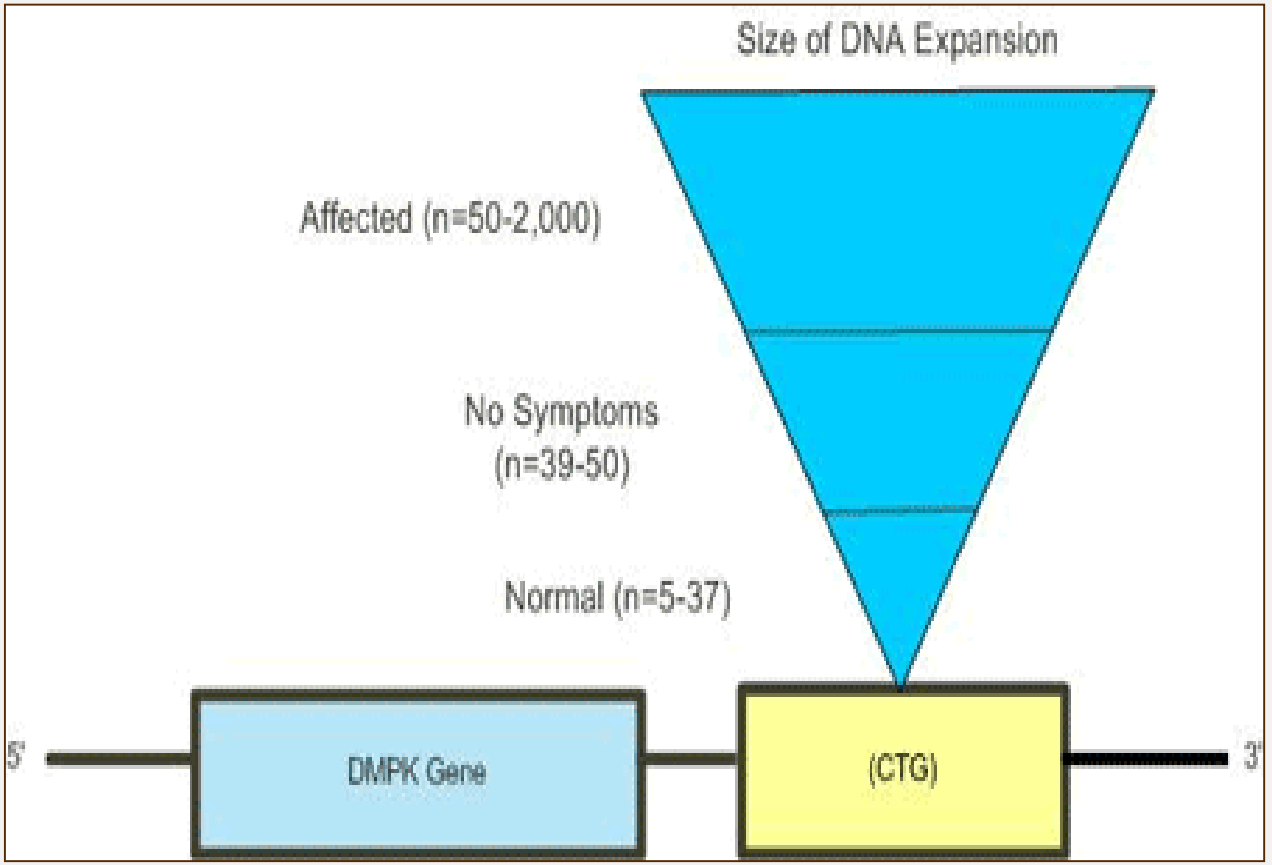
Myotonic dystrophy (AD) : repeat triplet : **(CTG)**

repeat location : **3` UTR**

normal range (repeats) **: < 35**

premutation (repeats) : **35 - 50**

mutant range (repeats) **: 50 - 4000**



Myotonic Dystrophy

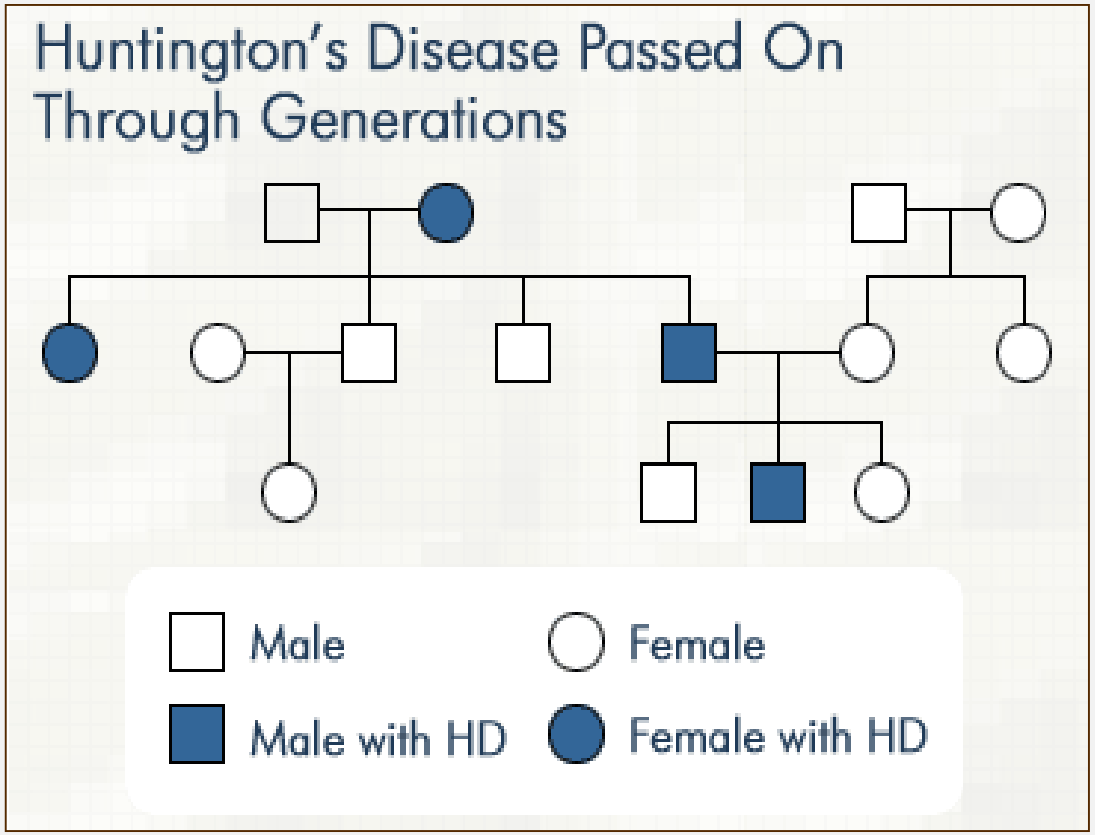
- Autosomal Dominant Disease showing anticipation
- Clinical findings include myotonia, cataracts, cardiac arrhythmias, temporal balding, endocrinopathies
- Unstable GCT repeat in the MT-PK gene
- Congenital form with maternal transmission only

Huntington disease (AD) : repeat triplet : **(CAG)**

repeat location : **coding**

normal range (repeats) **: < 35**

mutant range (repeats) **: 40 - 70**

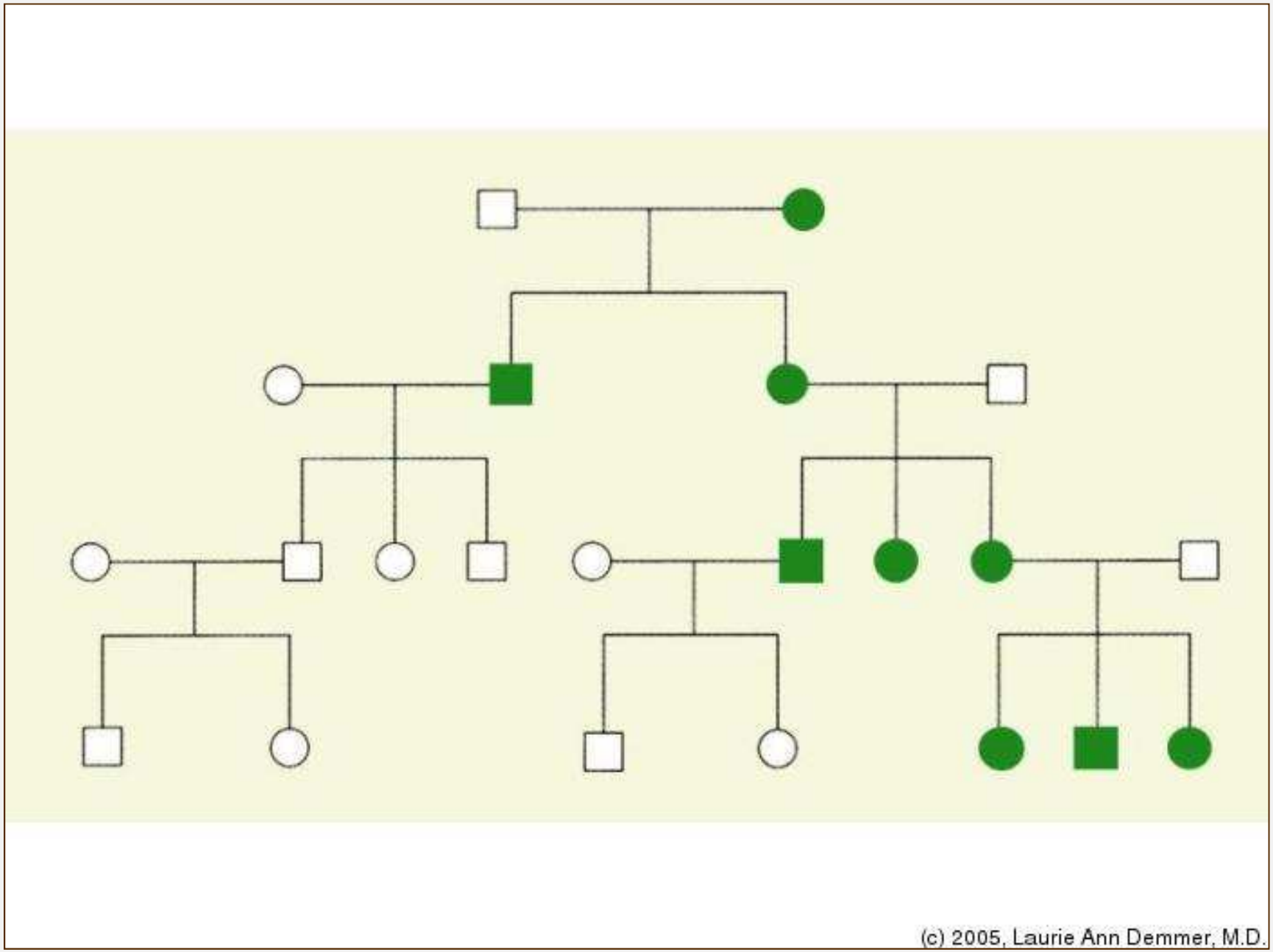


Huntington Disease

- Autosomal Dominant Disorder; typically without anticipation
- occasional juvenile-onset: always paternal transmission
- Clinical findings include progressive involuntary movements and cognitive loss, leading to complete debilitation. Psychiatric problems (depression) also common

Mitochondrial Inheritance

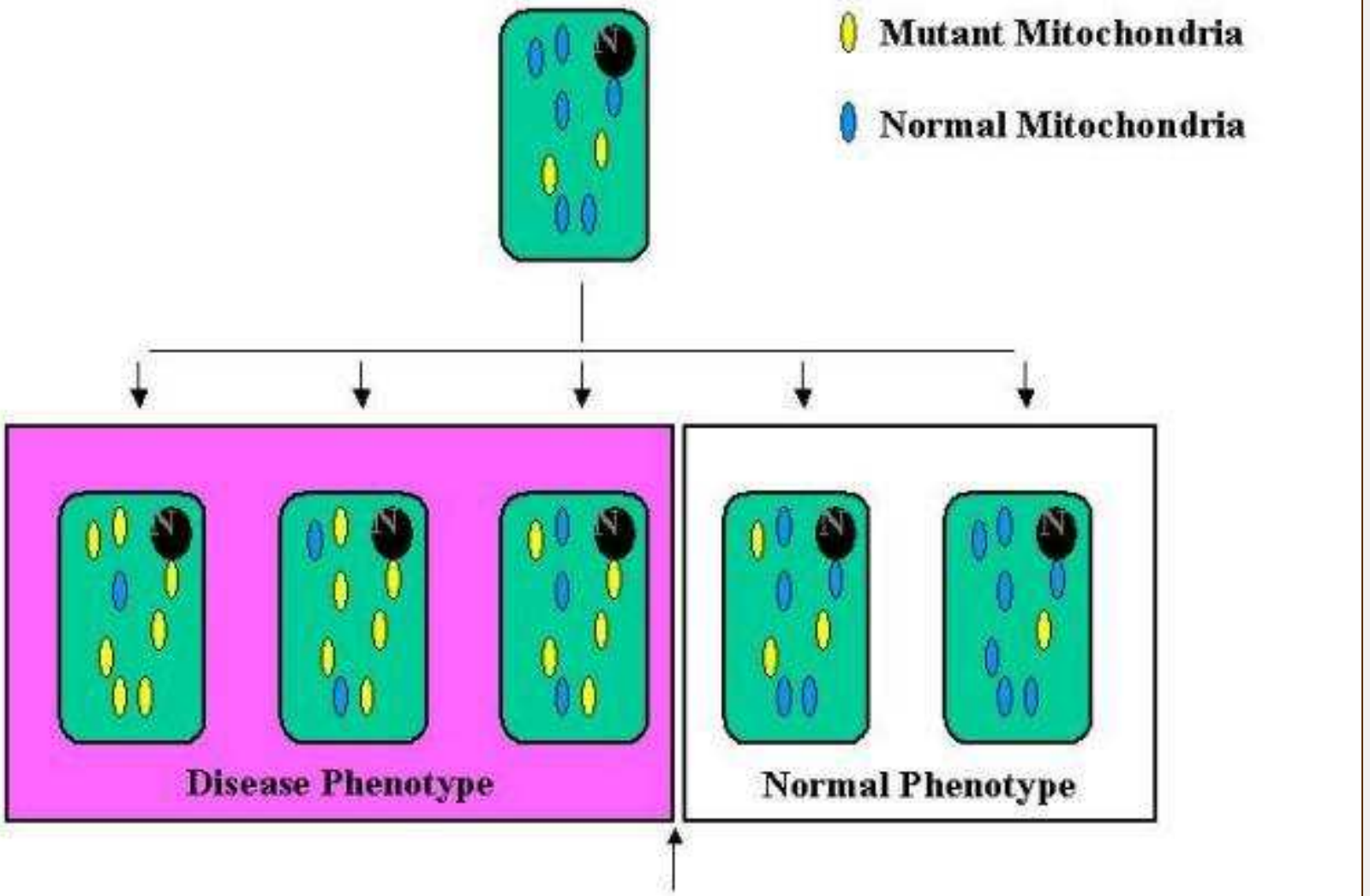
- MITOCHONDRIA HAVE THEIR OWN DNA!!!!
- 16.5kb circular dsDNA containing 37 genes
- 2 rRNAs, 22 tRNAs, 13 ox. phos. subunits
- only mitochondria from **oocyte** contribute to zygote
- MATERNAL INHERITANCE


(c) 2005, Laurie Ann Demmer, M.D.

Mitochondrial Inheritance

- Each cell contains hundreds of copies of mtDNA
- ***HETEROPLASMY***: mixture of normal and abnormal mtDNA
- ***HOMOPLASMY***: all mtDNA is the same (either normal or abnormal)
- with cell division, the many copies of mtDNA segregate randomly into the 2 daughter cells

Heteroplasmy



Mitochondrial Inheritance

- Different eggs can vary from mostly normal mtDNA to mostly abnormal
- Clinical phenotype will vary according to %-age of abnormal DNA
- %-age of abnormal DNA can change over time due to **random drift** as cells divide, or to a possible **replicative advantage** of one type of mtDNA over another

Mitochondrial Inheritance

- Tissues with **high energy requirements** are most likely to be affected (brain, muscle)
- Symptoms typically progress with age
- Often need **muscle biopsy** to confirm diagnosis
- Prenatal diagnosis is possible but prognosis difficult to predict due to heteroplasmy

Examples : - Leber`s hereditary optic atrophy

- Kearns-Sayre syndrome , MELAS s-me etc.