Harvard-MIT Division of Health Sciences and Technology
HST.035: Principle and Practice of Human Pathology
Dr. Badizadegan

Genetic Disorders

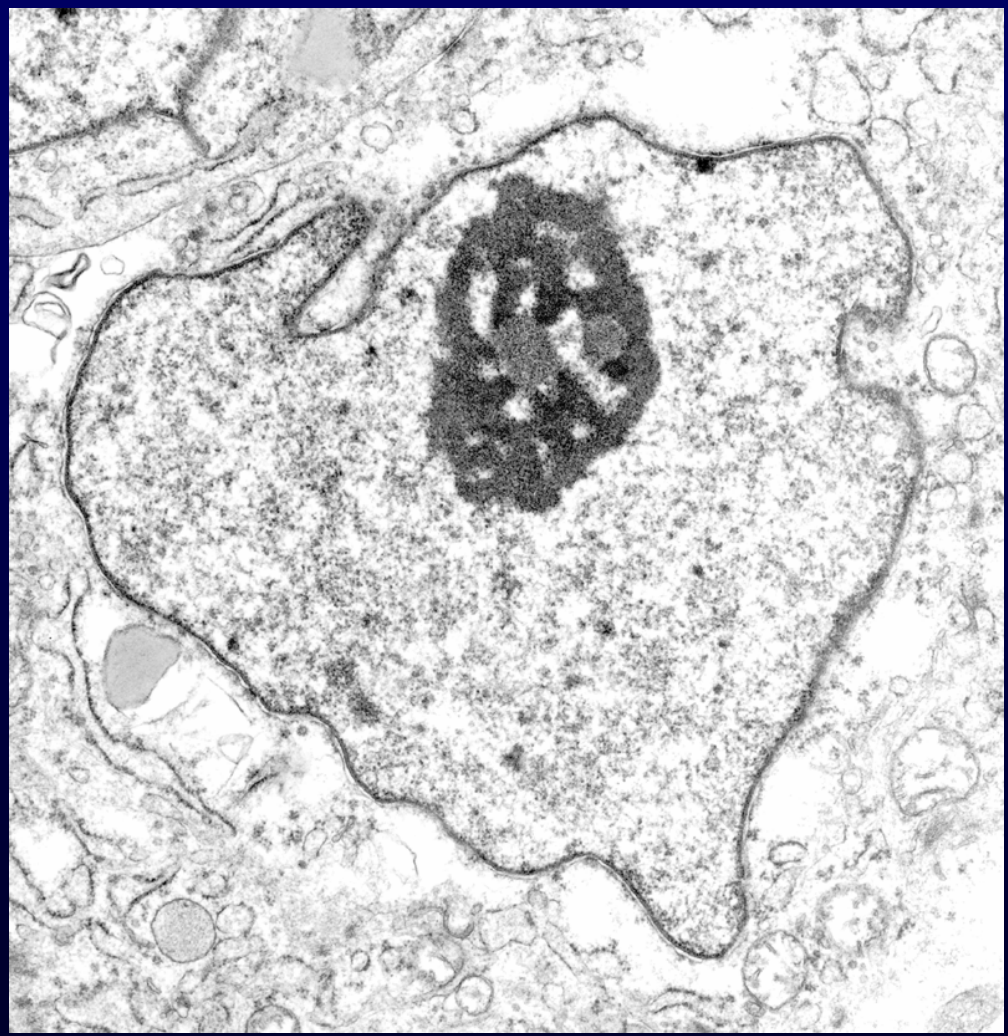
HST.023

Spring 2003

Genetic Disorders

- Cytogenetic Disorders
  - Gross chromosomal abnormalities
- Single-Gene Disorders
  - With classical (Mendelian) inheritance
  - With non-classical inheritance
    - Mitochondrial genes
    - Trinucleotide repeats
    - Genetic imprinting

Cytogenetic Disorders:
Where is the defect?

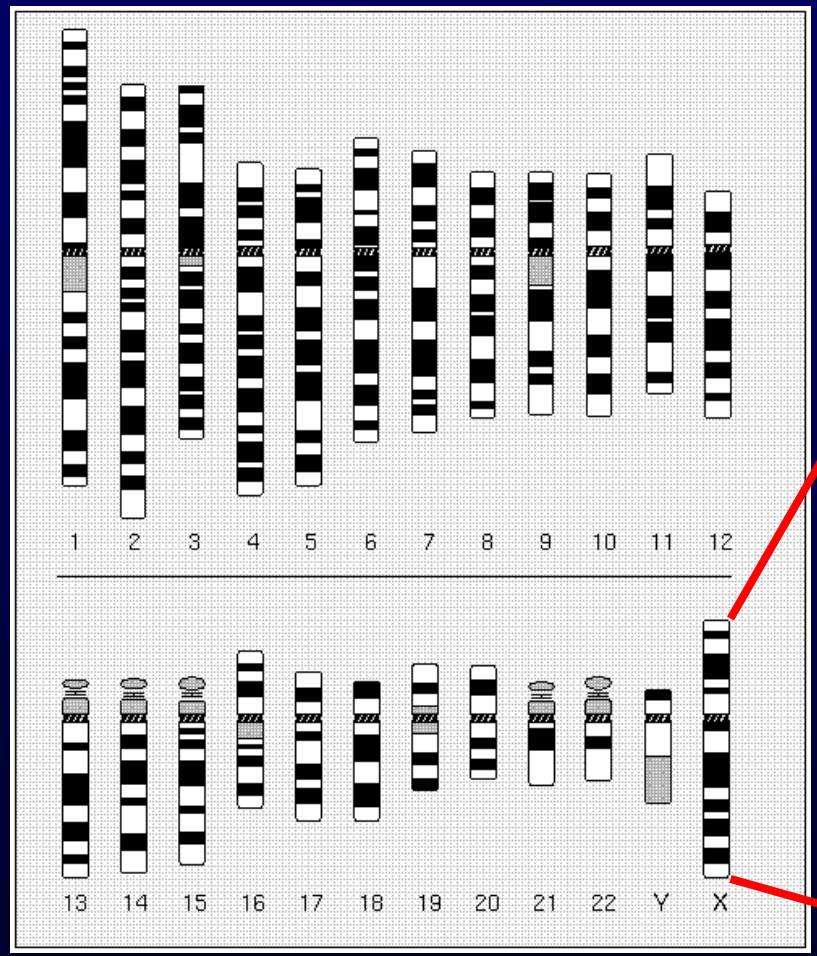


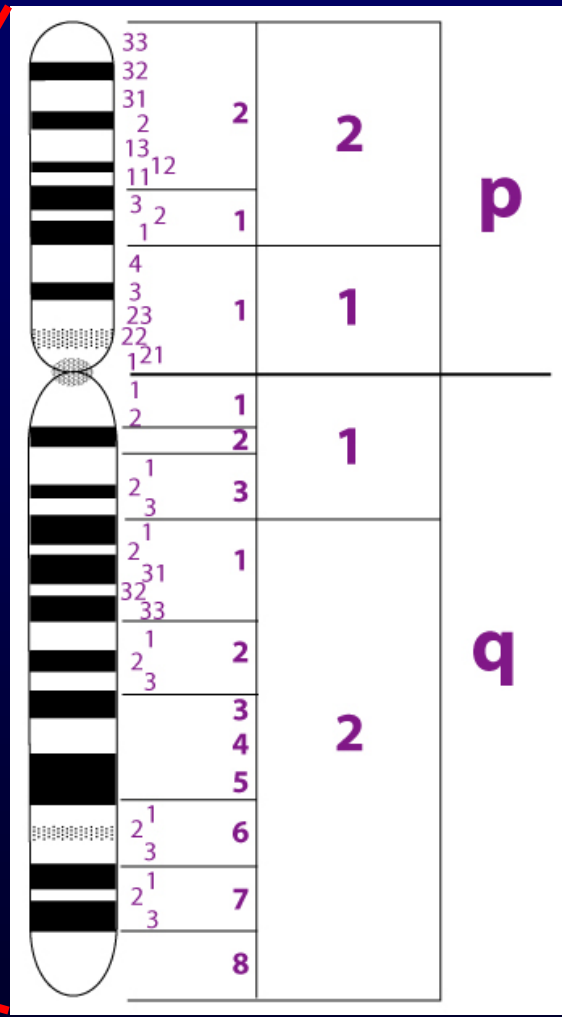
1. Catch the chromosomes in action

2. Stain and arrange them in order

Please see Junqueira & Carneiro. Basic Histology: Text and Atlas. 10th edition. McGraw Hill. 2003. ISBN: 0071378294.

Idiogram of G banded Human Karyotype

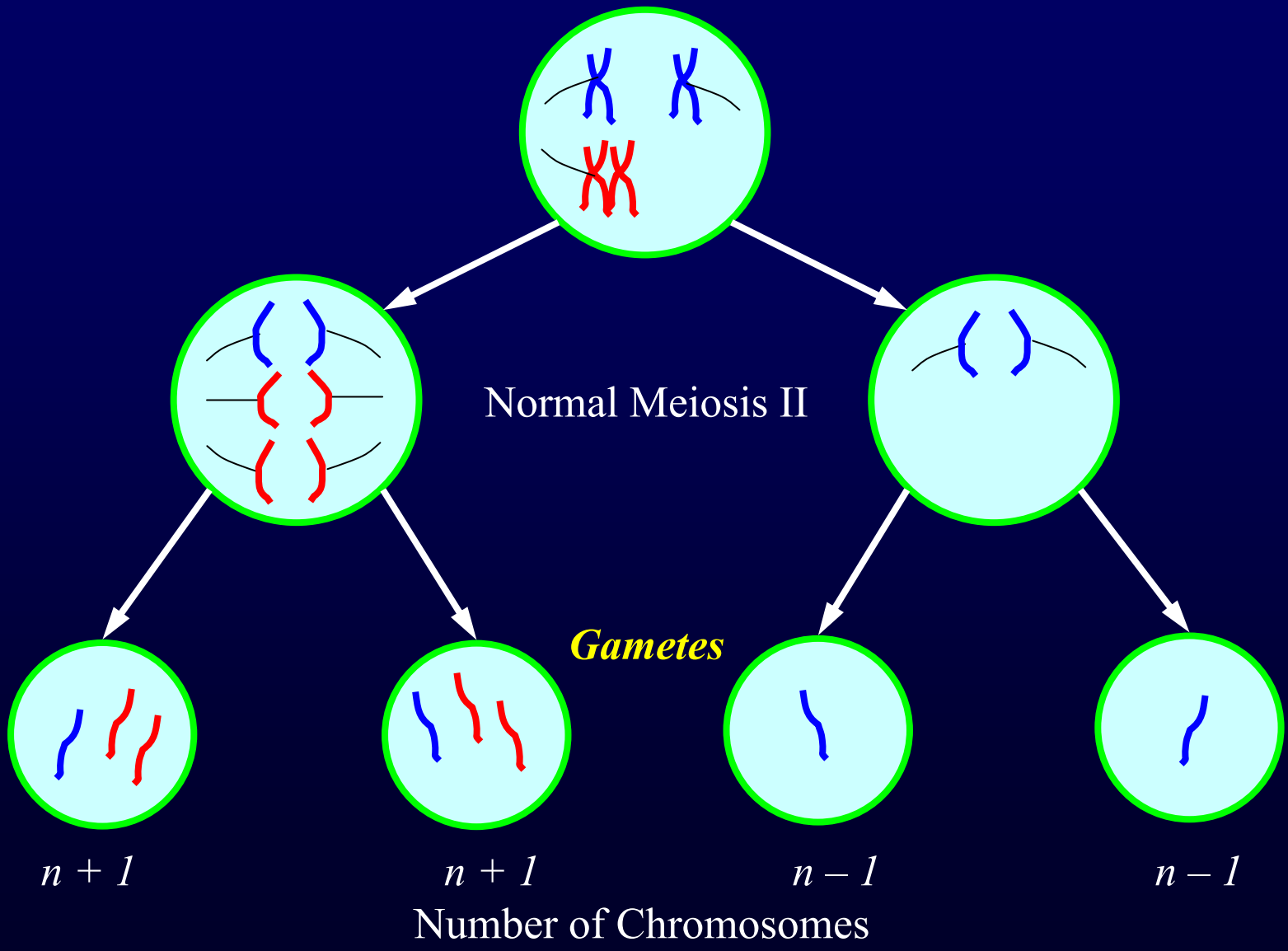




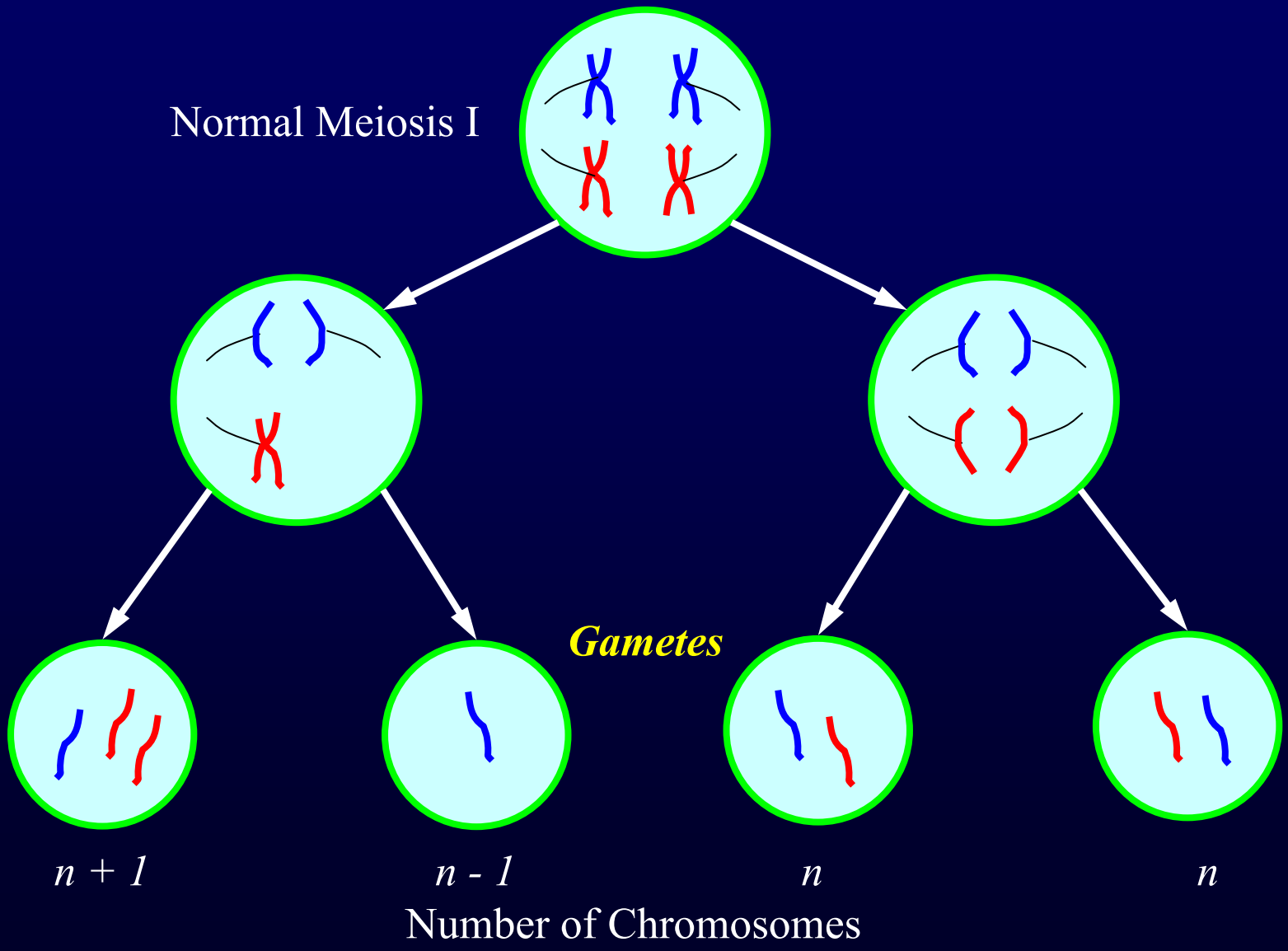
Cytogenetic disorders are characterized by an abnormal constitutional karyotype

What mechanisms would result in cytogenetic abnormalities?

Nondisjunction in Meiosis I



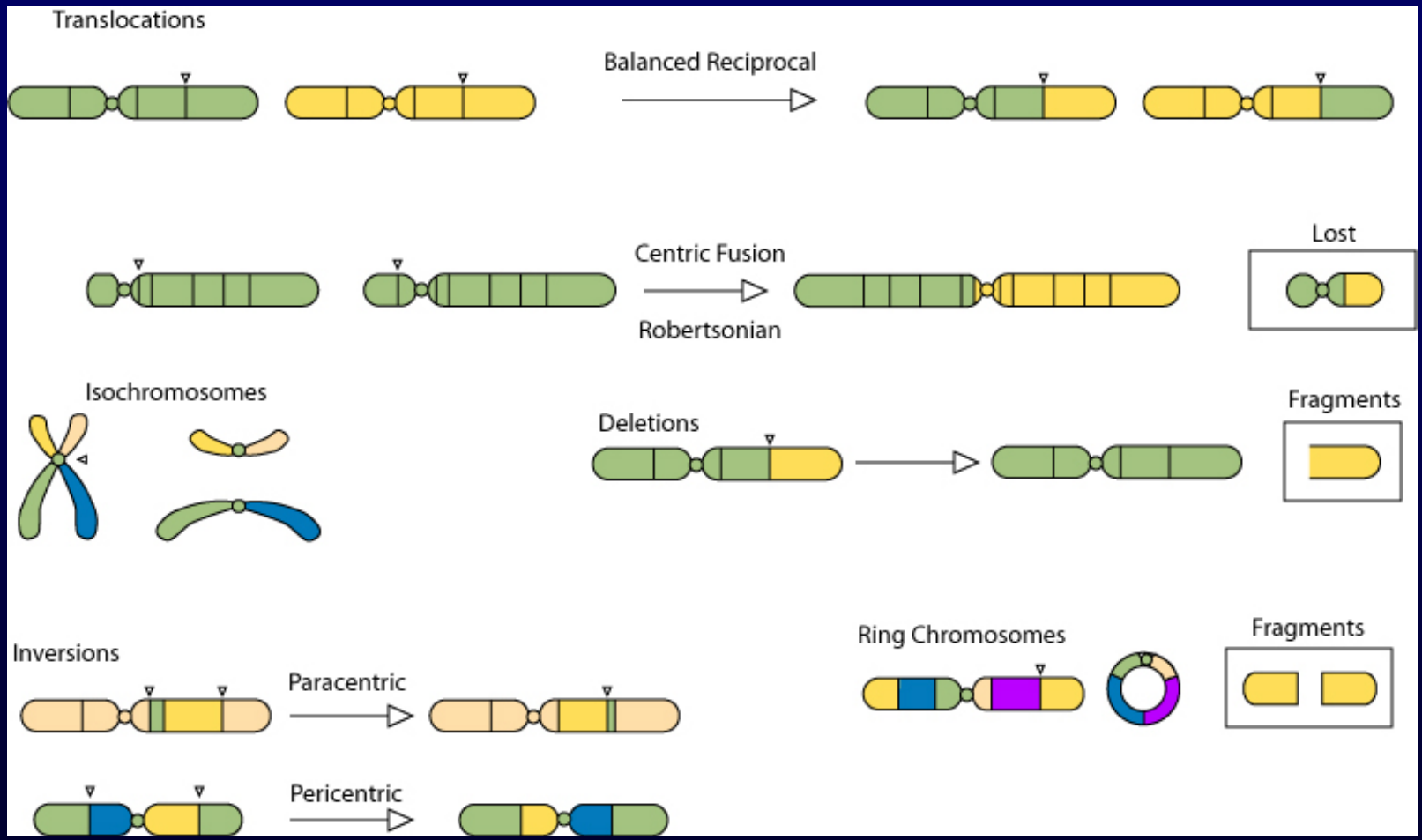
Nondisjunction in Meiosis II



Nondisjunction can also happen during mitosis.

What is the consequence of nondisjunction during mitosis?

Chromosomal Rearrangements



Do chromosomal rearrangements always lead to cytogenetic disorders?

What is the diagnosis?

Trisomy 21 (Down Syndrome)

- The most common chromosomal disorder with incidence of 1:700 live births in the US
- 95% trisomy 21; 4% Robertsonian translocation involving the long arm of 21; 1% mosaic
- High correlation between maternal age and meiotic nondisjunction leading to trisomy 21
- Congenital heart disease; dysmorphic features; mental retardation; predisposition to leukemias; neurodegenerative changes; abnormal immune response and autoimmunity

Sex Chromosome Disorders:
More common than autosomal disorders

Klinefelter syndrome (47, XXY)

- 1:850 male births
- Rarely diagnosed before puberty
- Tall stature, hypogonadism, lack of secondary male characteristics, gynecomastia
- The principal cause of male infertility due to reduced spermatogenesis

Turner syndrome (45, X)

- 1:3000 female births
- Extensive karyotype heterogeneity with question about existence of pure monosomy X (99% of 45, X eggs are non-viable)
- Short stature, webbing of the neck, cardiovascular abnormalities, lack of secondary sex characteristics, streak ovaries (accelerated loss of oocytes)

Image from http://history.nih.gov/exhibits/genetics/introf.htm

Single-Gene "Mendelian" Disorders

- ***Structural proteins***
  - Osteogenesis imperfecta and Ehlers-Danlos (collagens); Marfan syndrome (fibrillin); Duchenne and Becker muscular dystrophies (dystrophin)
- ***Enzymes and inhibitors***
  - Lysosomal storage diseases; SCID (adenosine deaminase); PKU (phenylalanine hydroxylase); Alpha-1 antitrypsin deficiency
- ***Receptors***
  - Familial hypercholesterolemia (LDL receptor)
- ***Cell growth regulation***
  - Neurofibromatosis type I (neurofibromin); Hereditary retinoblastoma (Rb)
- ***Transporters***
  - Cystic fibrosis (CFTR); Sickle cell disease (Hb); Thalassemias (Hb)

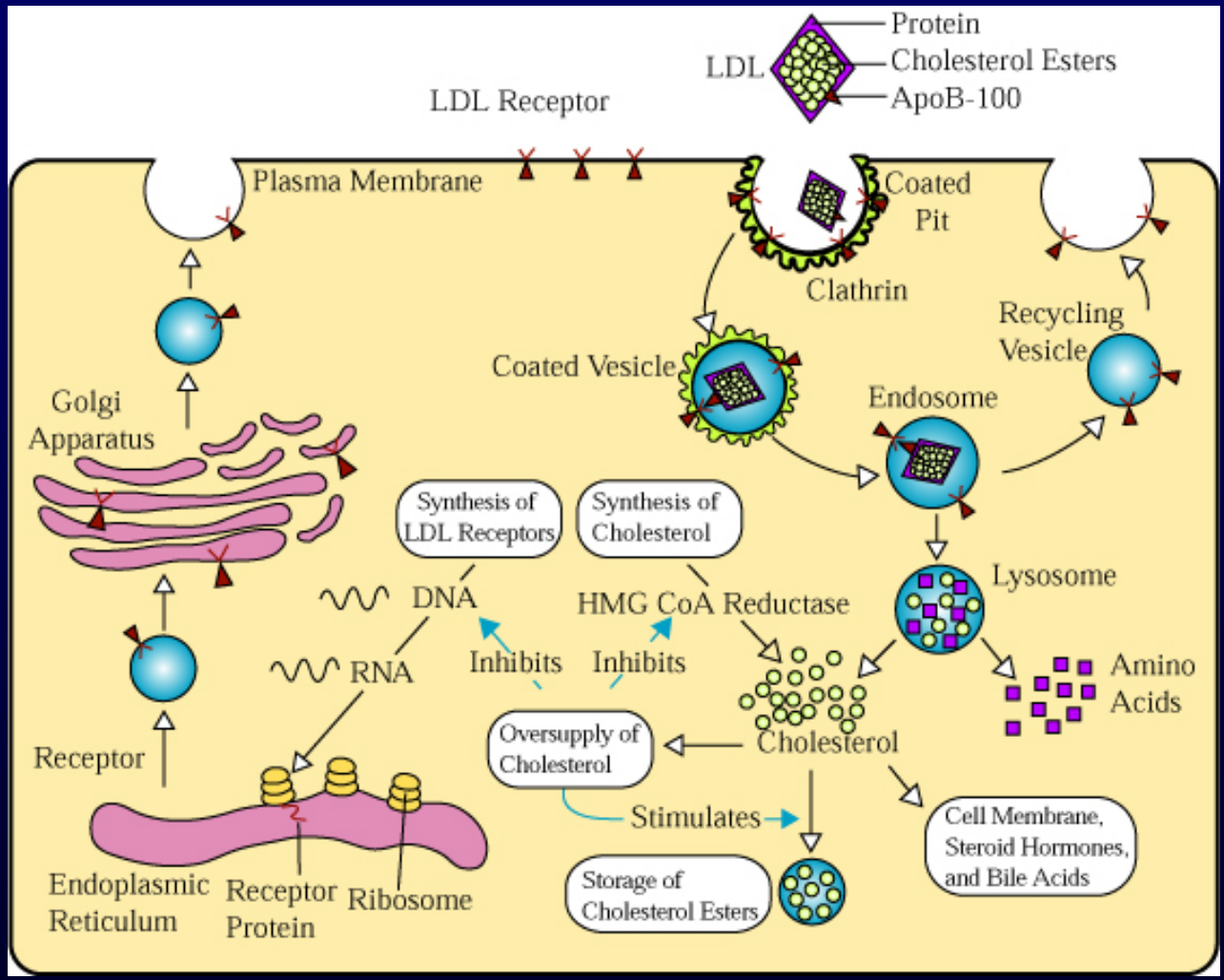
Neurofibromatosis Type 1 (NF1)

- Multiple neurofibromas; pigmented skin lesions; pigmented iris hamartomas (Lisch nodules); plus a variety of other abnormalities
- Incidence of at least 1:3000
- Autosomal dominant trait with complete penetrance
- ~50% of cases are “sporadic”
- Mutation rate 1/10,000 gametes; the highest observed in humans
- Neurofibromin mapped to 17q11.2 down-regulates the function of *p21 ras* oncoprotein

Familial Hypercholesterolemia (FH)

- ? The most frequent Mendelian disorder
- Heterozygotes, representing 1:500, have 2-3x elevation of cholesterol levels with xanthomas and premature atherosclerosis
- Homozygotes develop extensive xanthomas, as well as coronary, cerebral and peripheral vascular disease at an early age, and may develop MI before the age of 20

FH: Defect of Receptor-Mediated Endocytosis



Non-classical Inheritance

- Genetic imprinting
  - *Parents do make a difference!*
- Trinucleotide repeats
  - *Genetic instability and anticipation*
- Mitochondrial genes

Genetic Imprinting

- For most (non-imprinted) genes, the maternal copy is functionally equivalent to the paternal copy
- Imprinted genes, however, are expressed differently from maternal and paternal alleles
- In most cases, imprinting selectively inactivates either the maternal or the paternal allele of a particular gene

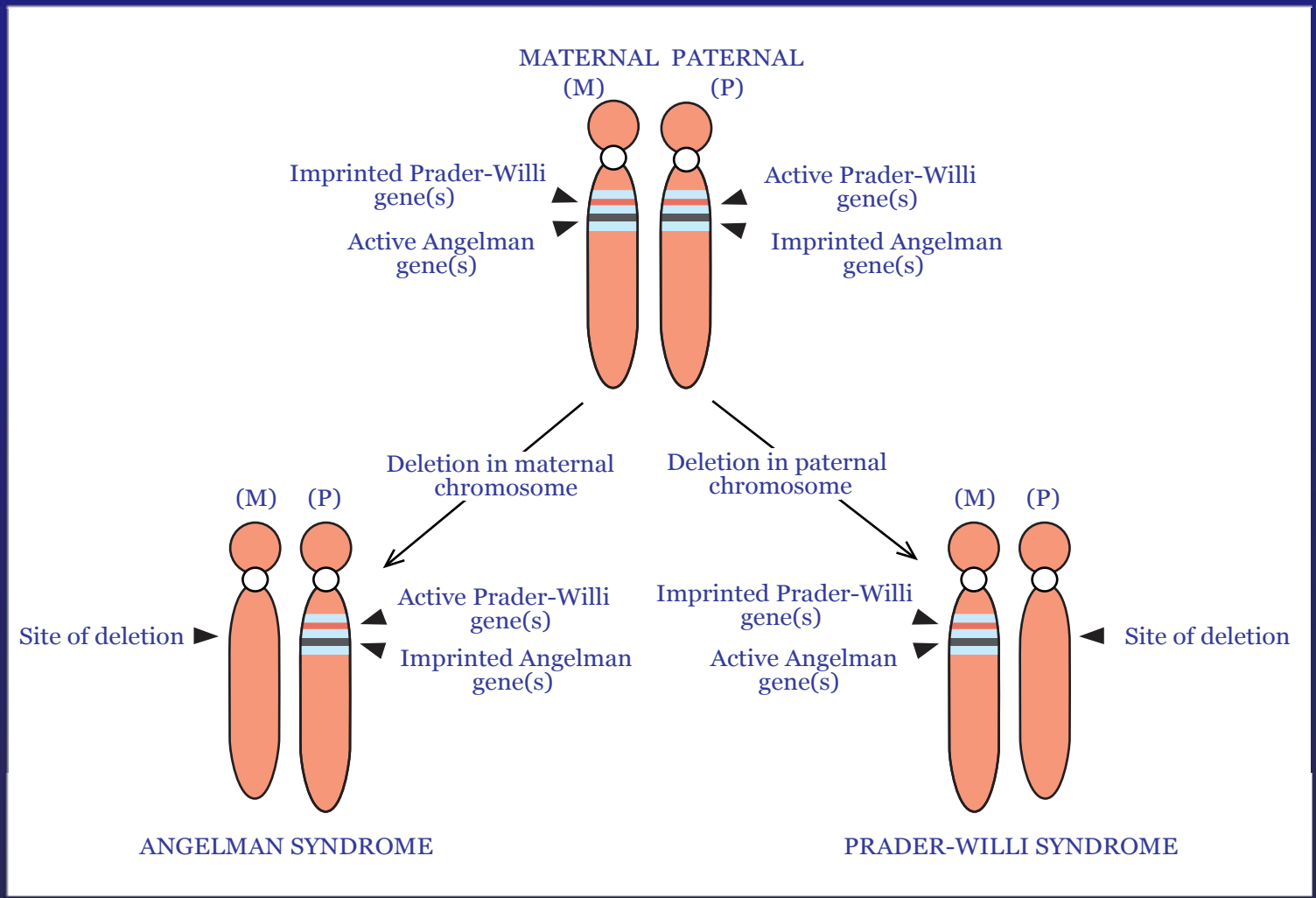
Complete Hydatidiform Mole:
Too much paternal influence

Egg and sperm nuclei contain the same genetic information, but neither two eggs nor two sperms can support embryonic development.

The Puzzle of del(15)(q11q13)

Mental retardation
Ataxic gait
Seizures
Inappropriate laughter

Mental retardation
Short stature
Hypotonia
Obesity
Hypogonadism

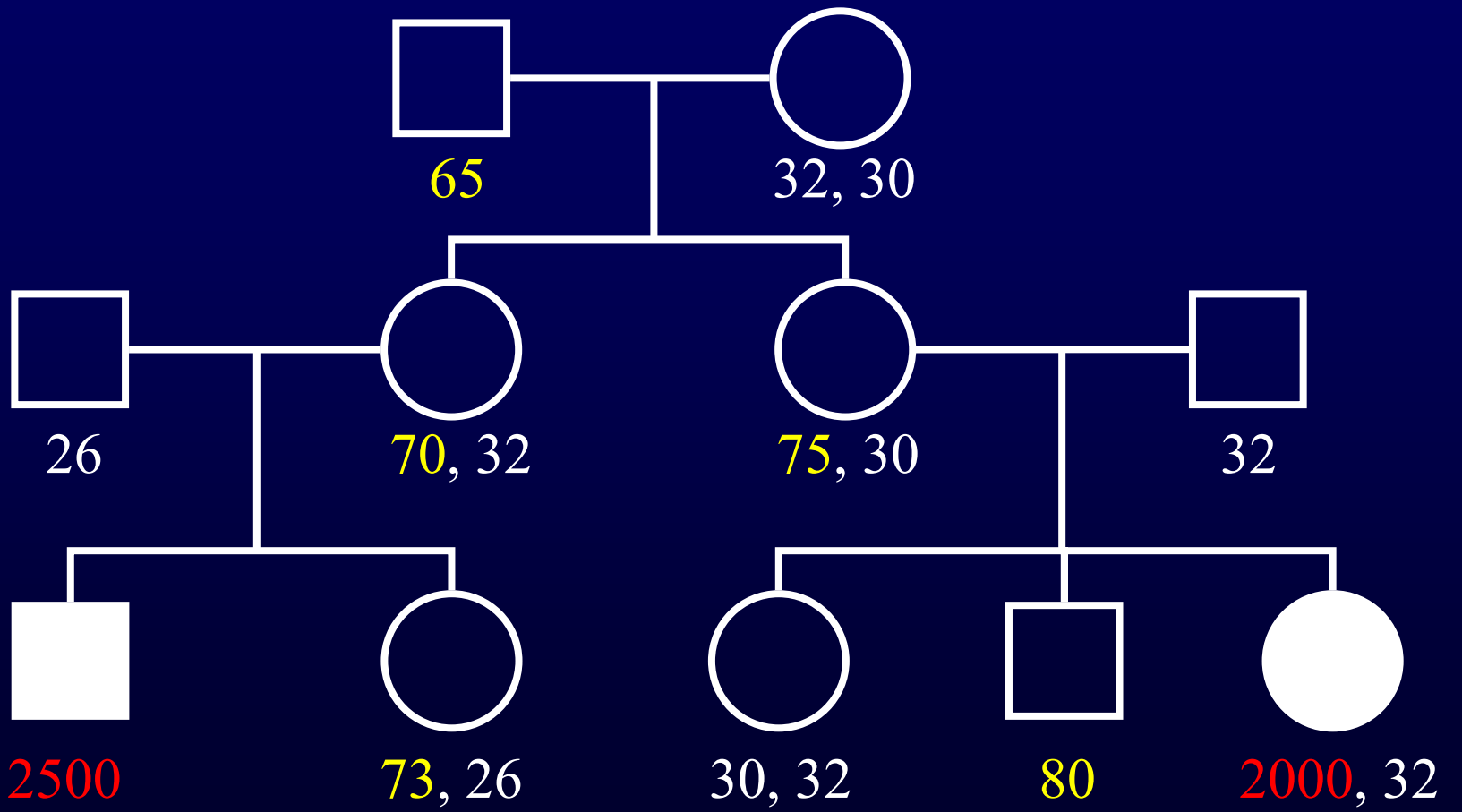

MATERNAL
(M)
PATERNAL
(P)
Imprinted Prader-Willi gene(s)
Active Angelman gene(s)
Active Prader-Willi gene(s)
Imprinted Angelman gene(s)
Deletion in maternal chromosome
Deletion in paternal chromosome
(M)
(P)
Site of deletion
Active Prader-Willi gene(s)
Imprinted Angelman gene(s)
(M)
(P)
Imprinted Prader-Willi gene(s)
Active Angelman gene(s)
Site of deletion
ANGELMAN SYNDROME
PRADER-WILLI SYNDROME

Besides deletions, how else can imprinted genes result in cytogenetic disease?

Fragile X Syndrome

- Prototype of diseases in which amplification of trinucleotide repeats results in disease (also includes Huntington, Mytotonic dystrophy, Myoclonus epilepsy)
- Macro-orchidism, mental retardation, large head, long face, large ears
- X chromosomes of cells grown in folate deficient media show “breaks” at the end of their long arm
- Accumulation of CCG repeats in the 5’ untranslated region of the FMR1 gene (Xq27.3) result in gene inactivation

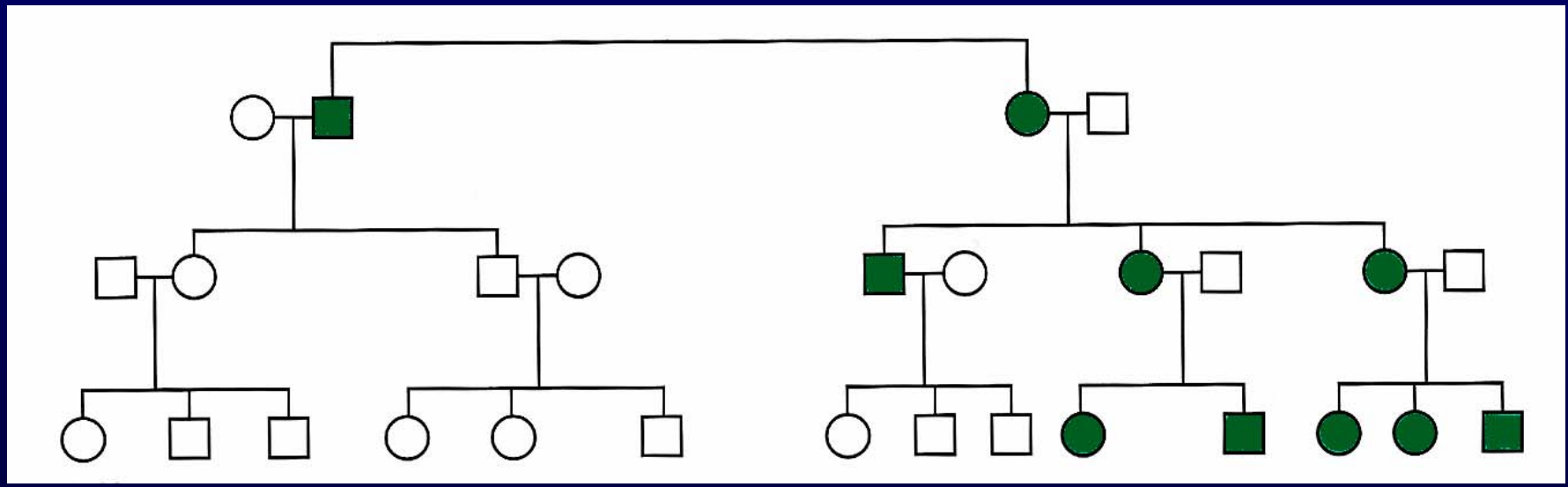
Fragile X Inheritance



Anticipation

- Clinically observed phenomenon of increasing severity of disease in each succeeding generation
- Trinucleotide repeats tend to increase in generation to generation
- Age of onset and disease severity is directly linked to the number of trinucleotide repeats

Pedigree of Leber Optic Neuropathy



What is the pattern of inheritance?

Mitochondrial Genes

- Mitochondrial DNA encodes 22 tRNAs, 2 rRNAs, and 13 proteins involved in the respiratory chain
- Most respiratory chain complexes have subunits from the nuclear as well as the mitochondrial genome, therefore, completely unrelated mutations can lead to similar clinical presentations

Genetic Disorders:
It is just the beginning!