

Chromosome disorders

<http://www.biology.iupui.edu/biocourses/N100/2k2humancsomaldisorders.html>



IUPUI DEPARTMENT OF BIOLOGY

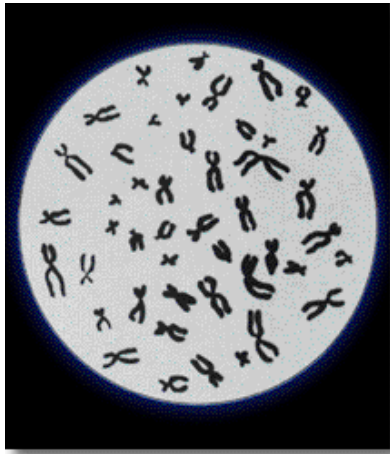
TOPIC: CLASS NOTES

Human Chromosomal Disorders

April 30, 2003

Readings: Web Notes Only!

I. Karyotype Analysis of Human Chromosomes



1. Karyotype preparation and analysis

Cells (from blood, amniotic fluid, etc) are grown *in vitro* (in a cell culture dish) to increase their number

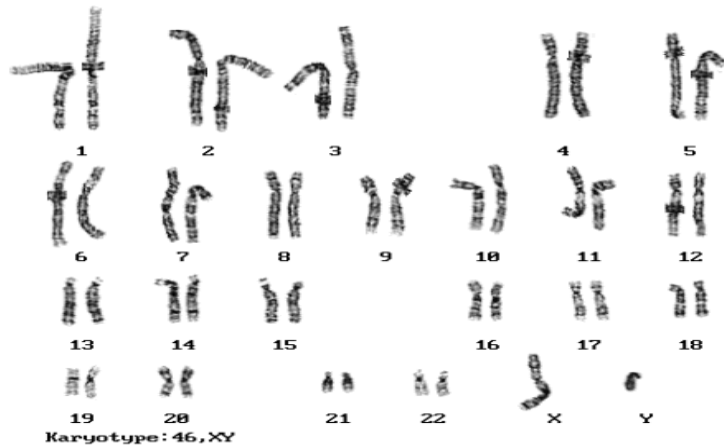
Cell division is then arrested in metaphase with **colchicine** (prevents mitotic spindle from forming)

Cells are centrifuged and lysed to release chromosomes

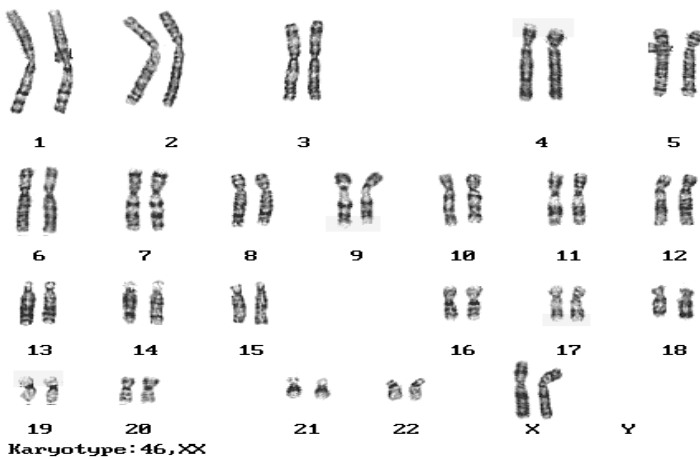
Chromosomes are stained, photographed, and grouped by size and banding patterns

This is a photograph of the **46 human chromosomes in a somatic cell, arrested in metaphase.** Can you see that they are *duplicated sister chromatids*?

2. Normal male karyotype (a Cytogeneticist has lined these chromosomes up, matching homologues up and arranging them by size)



3. Normal female karyotype

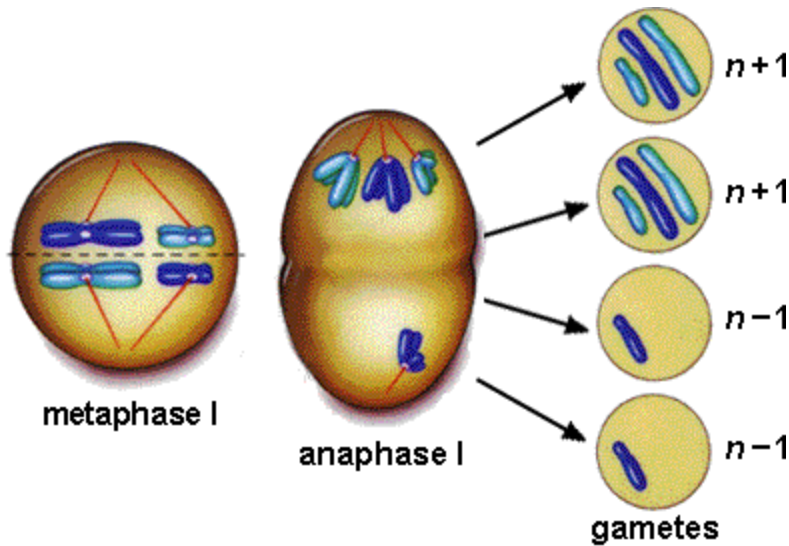


II. Alterations in chromosome number:

Nondisjunction occurs when either *homologues fail to separate* during anaphase I of meiosis, or *sister chromatids fail to separate* during anaphase II. The result is that one gamete has 2 copies of one chromosome and the other has no copy of that chromosome. (The other chromosomes are distributed normally.)

If either of these gametes unites with another during fertilization, the result is **aneuploidy** (abnormal chromosome number)

- A **trisomic** cell has one extra chromosome ($2n + 1$) = example: trisomy 21. (**Polyploidy** refers to the condition of having **three** homologous chromosomes rather than two)
- A **monosomic** cell has one missing chromosome ($2n - 1$) = usually lethal except for one known in humans: Turner's syndrome (monosomy XO).



The frequency of nondisjunction is quite high in humans, but the results are usually so devastating to the growing zygote that miscarriage occurs very early in the pregnancy.

If the individual survives, he or she usually has a set of symptoms - a **syndrome** - caused by the abnormal dose of each gene product from that chromosome.

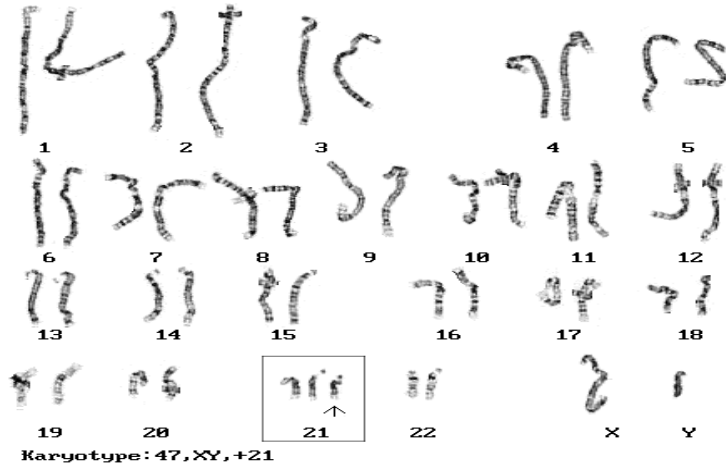
1. Human disorders due to chromosome alterations in autosomes (Chromosomes 1-22). There only 3 trisomies that result in a baby that can survive for a time after birth; the others are too devastating and the baby usually dies in utero.

A. Down syndrome (trisomy 21): The result of an extra copy of chromosome 21. People with Down syndrome are 47, 21+. Down syndrome affects 1:700 children and alters the child's phenotype either moderately or severely:

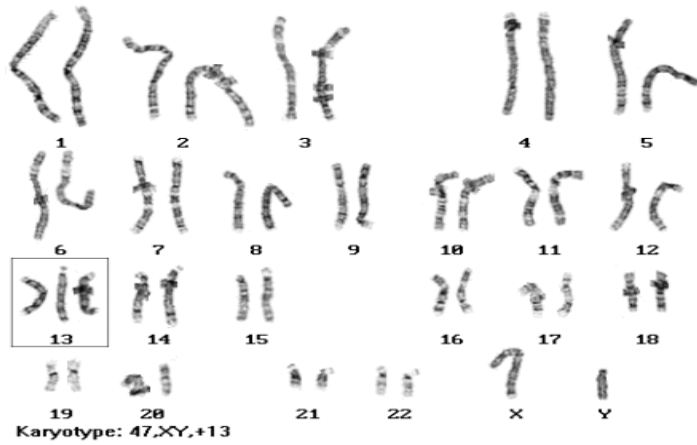


- characteristic facial features, short stature; heart defects
- susceptibility to respiratory disease, shorter lifespan
- prone to developing early Alzheimer's and leukemia
- often sexually underdeveloped and sterile, usually some degree of mental retardation.
- Down Syndrome is correlated with age of mother but can also be the result of nondisjunction of the father's chromosome 21.

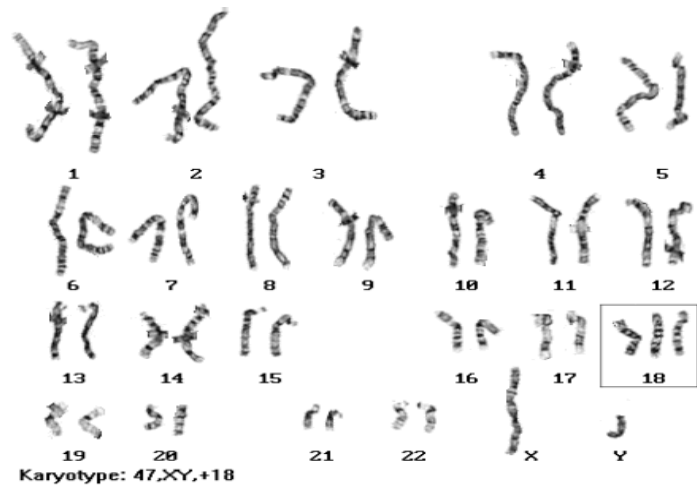
Karyotype of a boy with Down Syndrome:



B. **Patau syndrome (trisomy 13)**: serious eye, brain, circulatory defects as well as cleft palate. 1:5000 live births. Children rarely live more than a few months.

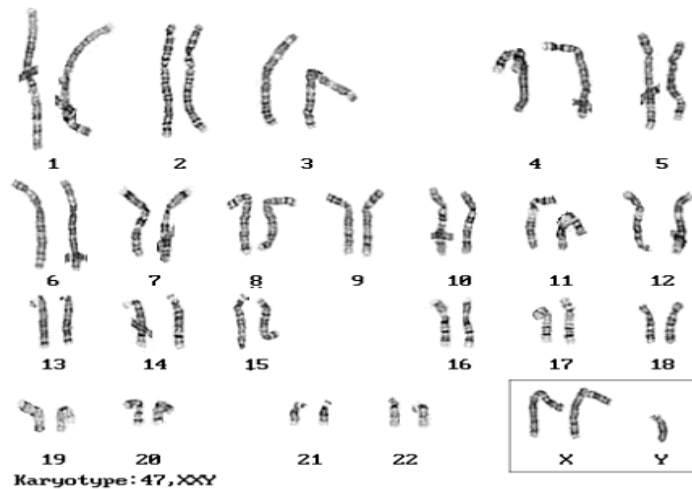


C. **Edward's syndrome (trisomy 18)**: almost every organ system affected 1:10,000 live births. Children with full Trisomy 18 generally do not live more than a few months.

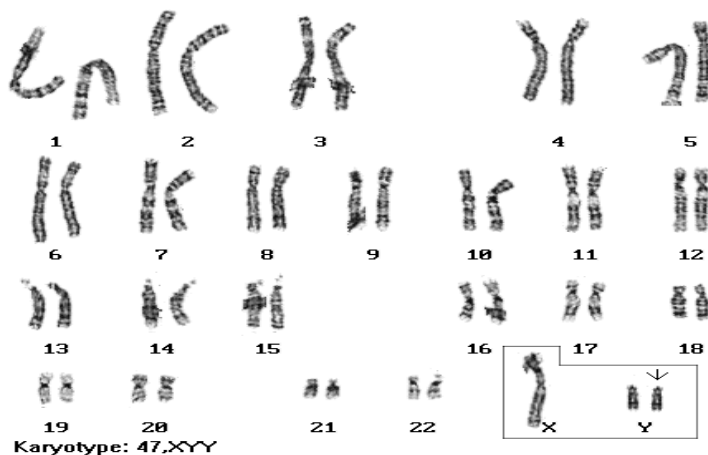


2. Nondisjunction of the sex chromosomes (X or Y chromosome): Can be fatal, but many people have these karyotypes and are just fine!

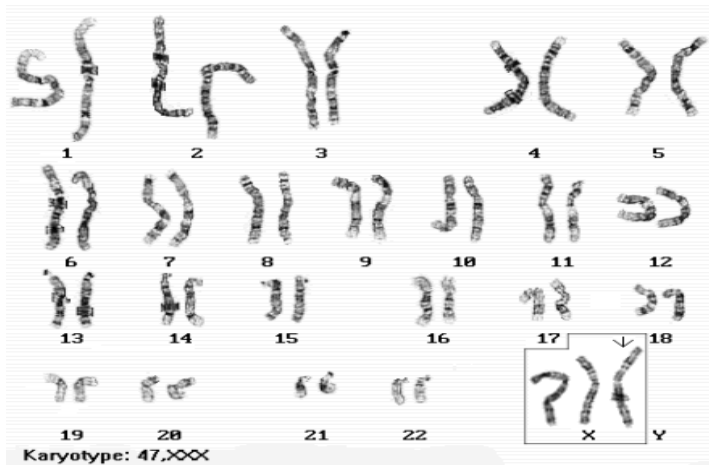
A. Klinefelter syndrome: 47, XXY males. Male sex organs; unusually small testes, sterile. Breast enlargement and other feminine body characteristics. Normal intelligence.



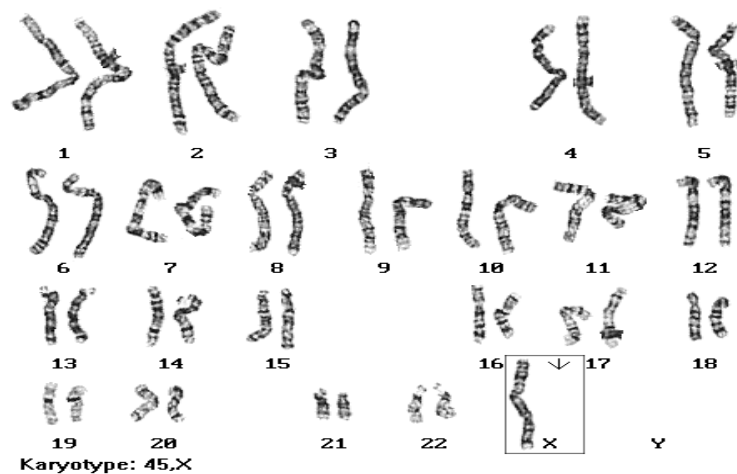
B. 47, XYY males: Individuals are somewhat taller than average and often have below normal intelligence. At one time (~1970s), it was thought that these men were likely to be criminally aggressive, but this hypothesis has been **disproven** over time.



3. Trisomy X: 47, XXX females. 1:1000 live births - healthy and fertile - usually cannot be distinguished from normal female except by karyotype



4. **Monosomy X (Turner's syndrome):** 1:5000 live births; **the only viable monosomy** in humans - women with Turner's have only 45 chromosomes!!! XO individuals are genetically female, however, they do not mature sexually during puberty and are sterile. Short stature and normal intelligence. (98% of these fetuses die before birth)

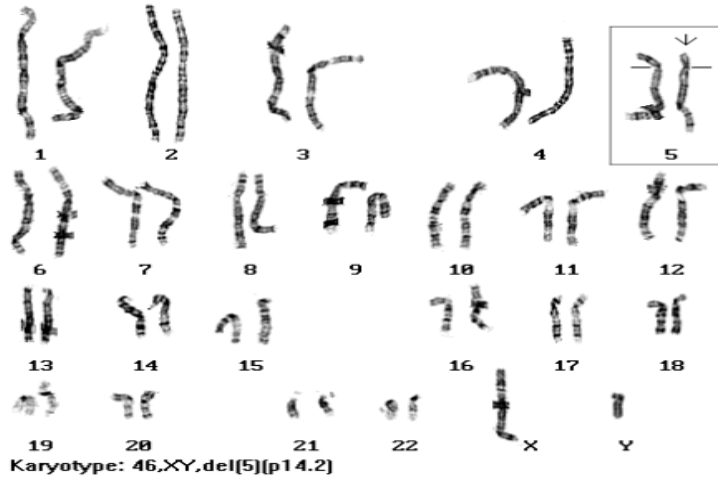


III. Alterations in chromosome structure:

Sometimes, chromosomes **break**, leading to 4 types of changes in chromosome structure:

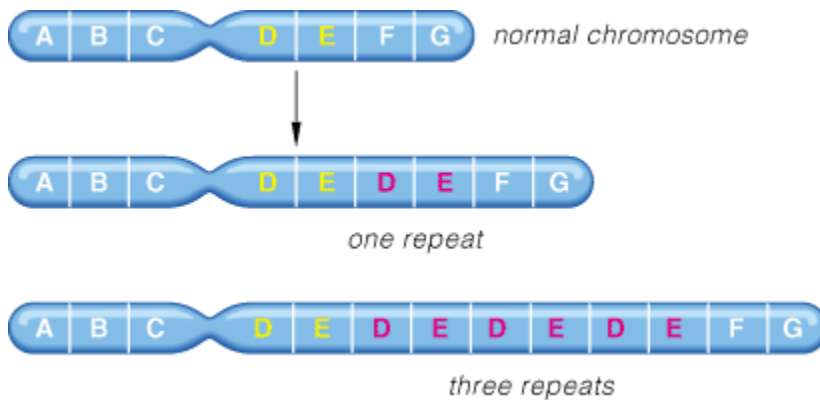
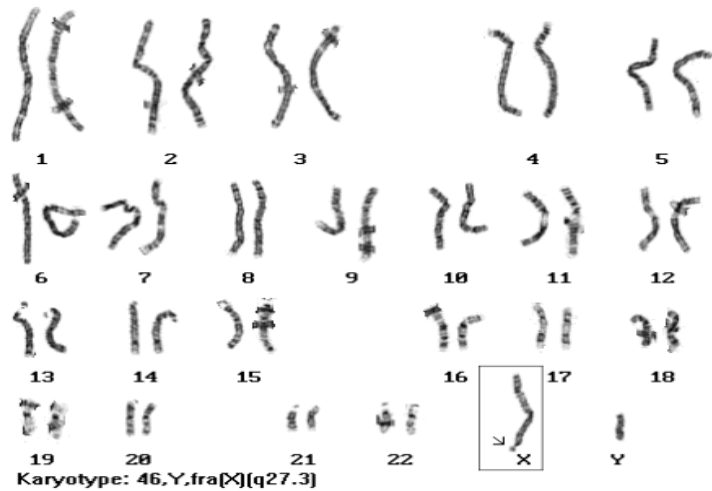
1. **Deletion:** a portion of one chromosome is **lost** during cell division. That chromosome is now missing certain genes. When this chromosome is passed on to offspring the result is usually lethal due to missing genes.

Example - *Cri du chat (cry of the cat)*: A specific deletion of a small portion of chromosome 5; these children have severe mental retardation, a small head with unusual facial features, and a cry that sounds like a distressed cat.

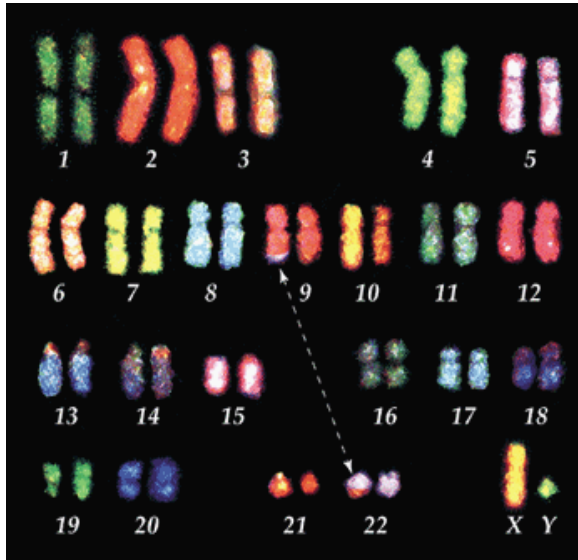


2. Duplication: if the fragment joins the homologous chromosome, then that region is **repeated**

Example - Fragile X: the most common form of mental retardation. The X chromosome of some people is unusually fragile at one tip - seen "hanging by a thread" under a microscope. Most people have 29 "repeats" at this end of their X-chromosome, those with Fragile X have over **700** repeats due to duplications. Affects 1:1500 males, 1:2500 females.



3. Translocation: a fragment of a chromosome is *moved* ("trans-located") from one chromosome to another - joins a non-homologous chromosome. The balance of genes is still normal (nothing has been gained or lost) but can alter phenotype as it places genes in a new environment. Can also cause difficulties in egg or sperm development and normal development of a zygote. [Acute Myelogenous Leukemia](#) is caused by this translocation:



Interested in finding out more about [Chromosomal Conditions](#)? UKMC website
Interested in finding out more about [Genetic Counseling](#) or [Cytogenetics](#) as a profession (at IUPUI)?

Objectives:

1. What is a karyotype, and how is this analysis performed?
2. What is nondisjunction?
3. Distinguish between the **chromosomal alterations** that are involved in the following human disorders:
 - Down syndrome, Patau's syndrome, Edwards syndrome
 - Klinefelters syndrome, XYY syndrome
 - Trisomy X, Monosomy X
5. Distinguish between the 3 different alterations in chromosome structure, and how *Cri du Chat*, *Fragile X*, and *Acute myelogenous leukemia* occur.