# Medical Genetics

## LECTURE 1
## Human Chromosomes: Genotypes/Phenotypes

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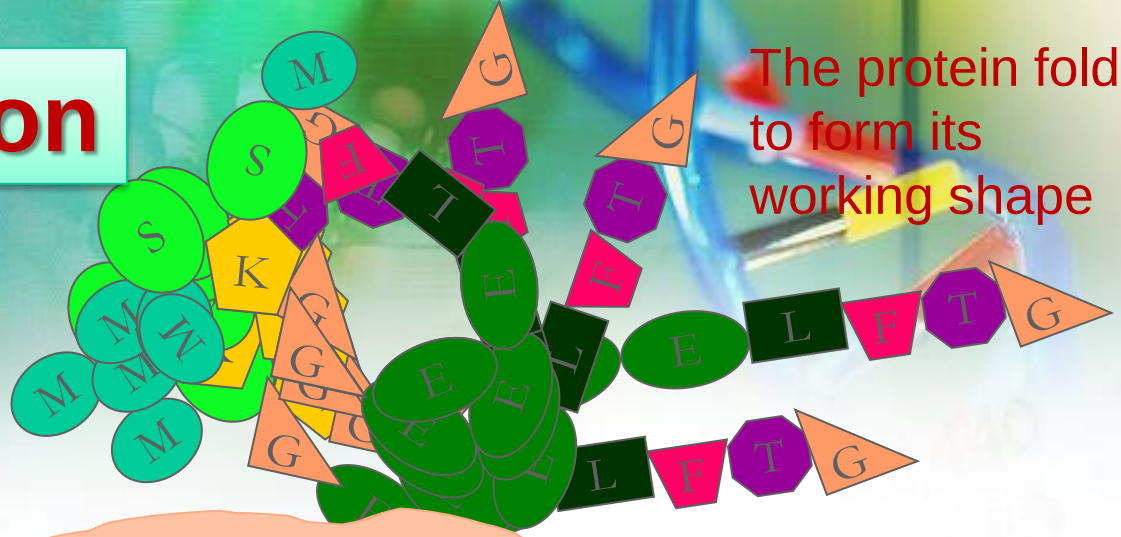
# Lecture Objectives:

**By the end of this lecture, the students should be able to:**

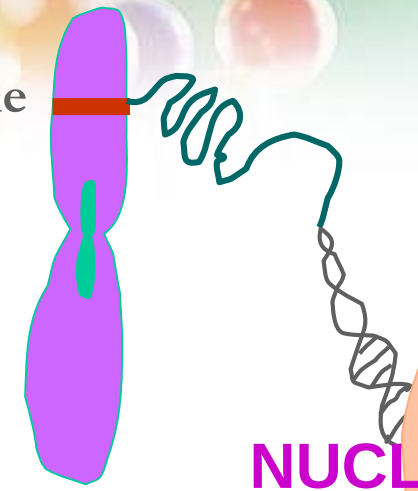
- Describe the number, structure, and classification of human chromosomes.
- Explain what a Karyotype is and how it is obtained.
- Explain Genotype and Phenotype
- Describe chromosomal banding and explain its use.
- Describe the process of in situ hybridization and the information it provides.

# Gene Expression

The protein folds to form its working shape



Gene

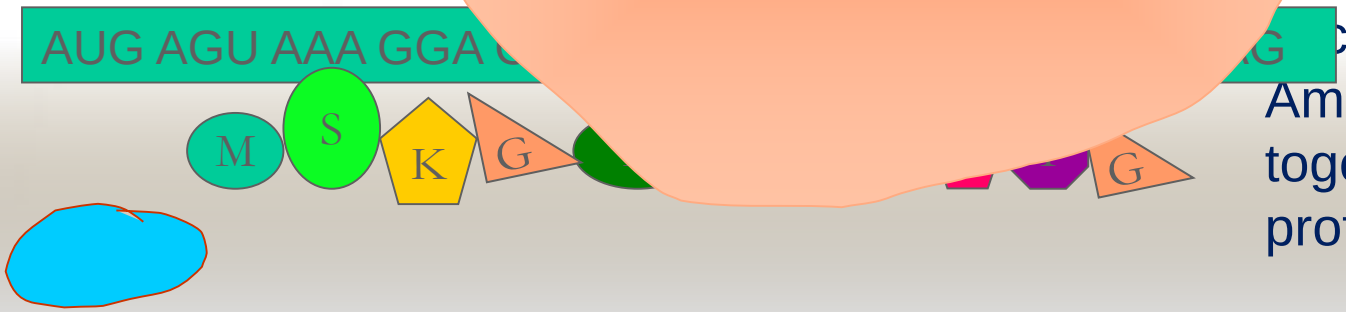


NUCLEUS

CELL

Cell machinery copies the code making an mRNA molecule. This leaves into the cytoplasm.

Ribosomes read the code and accurately join Amino acids together to make a protein



# Eukaryotic cell

Nucleus
Nuclear envelope
Nucleolus
Chromatin
Nuclear pore
Lysosome
Cell coat
Smooth endoplasmic reticulum
Cytoplasm
Free ribosome
Golgi body
Centriole
Mitochondrion

# GENETICS :

- **Cytogenetics:**

The study of the structure and function of chromosomes and chromosome behaviour during somatic and germline division

- **Molecular genetics:**

The study of the structure and function of genes at a molecular level and how the genes are transferred from generation to generation.

# Cytogenetics:

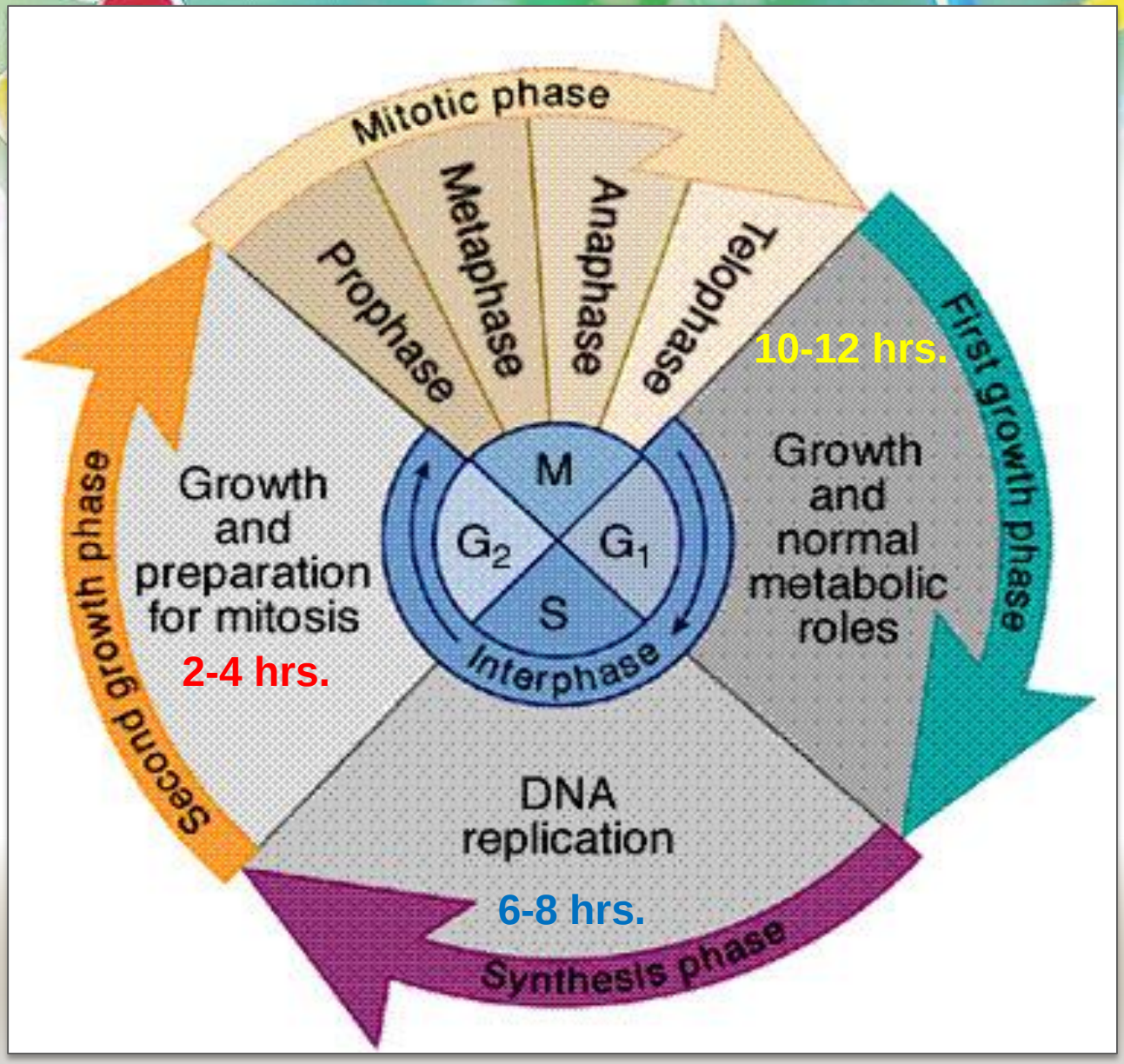
**Human Cytogenetics involves the study of human chromosomes in health and disease.**

**Chromosome studies are an important laboratory diagnostic procedure in**

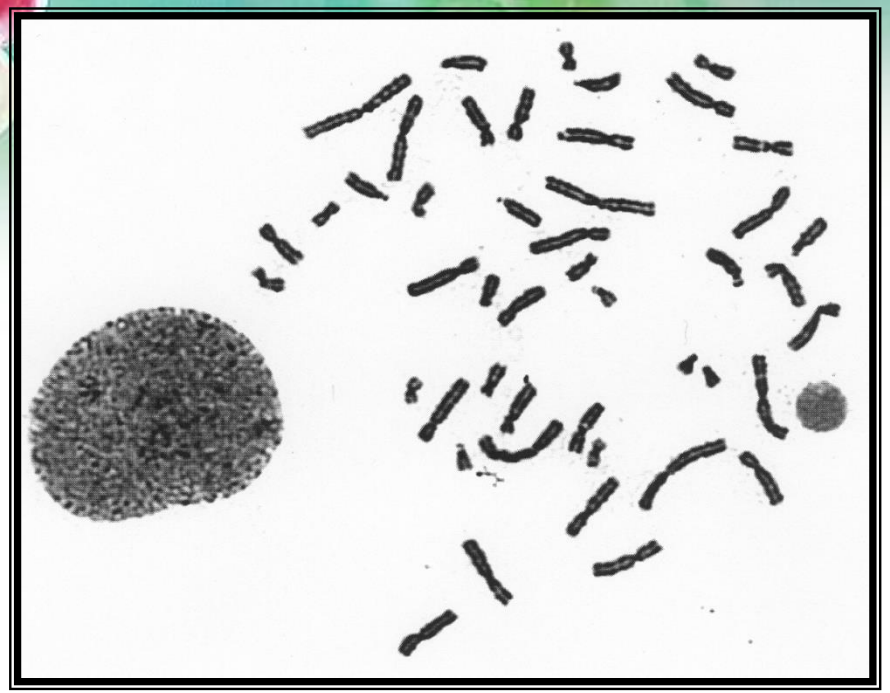
1) prenatal diagnosis
2) certain patients with mental retardation and multiple birth defects
3) patients with abnormal sexual development
4) some cases of infertility or multiple miscarriages
5) in the study and treatment of patients with malignancies & hematologic disorders.

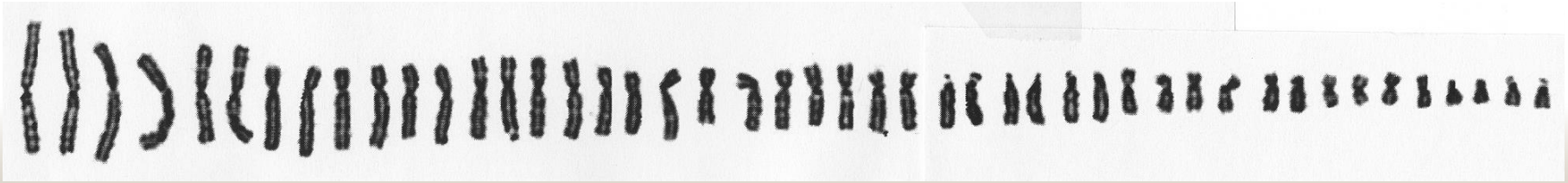
**New techniques allow for increased resolution.**

# Mitotic cell cycle



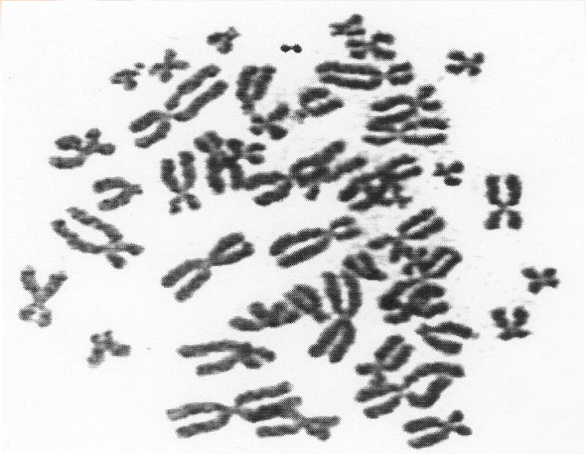
# Human Chromosome

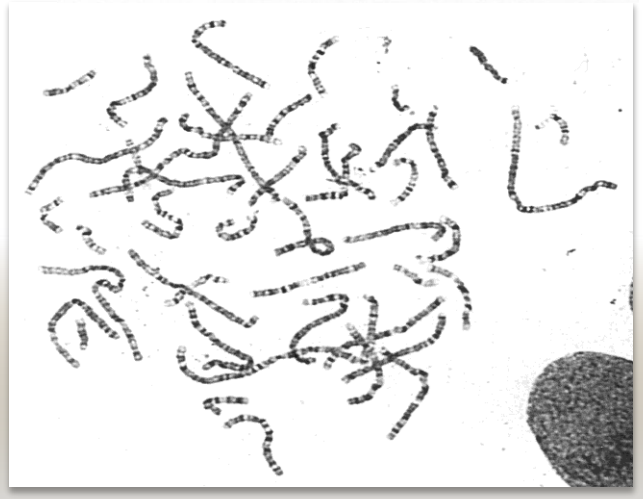


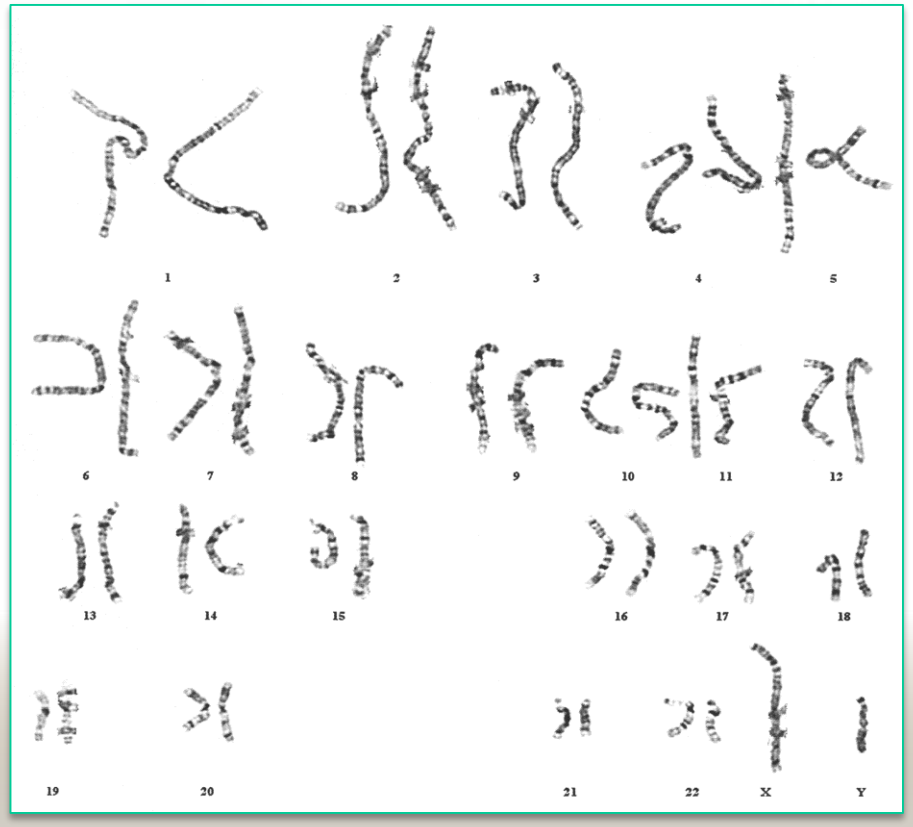


# KARYOTYPE

**The number and appearance of chromosomes in the nucleus of a eukaryotic cell**



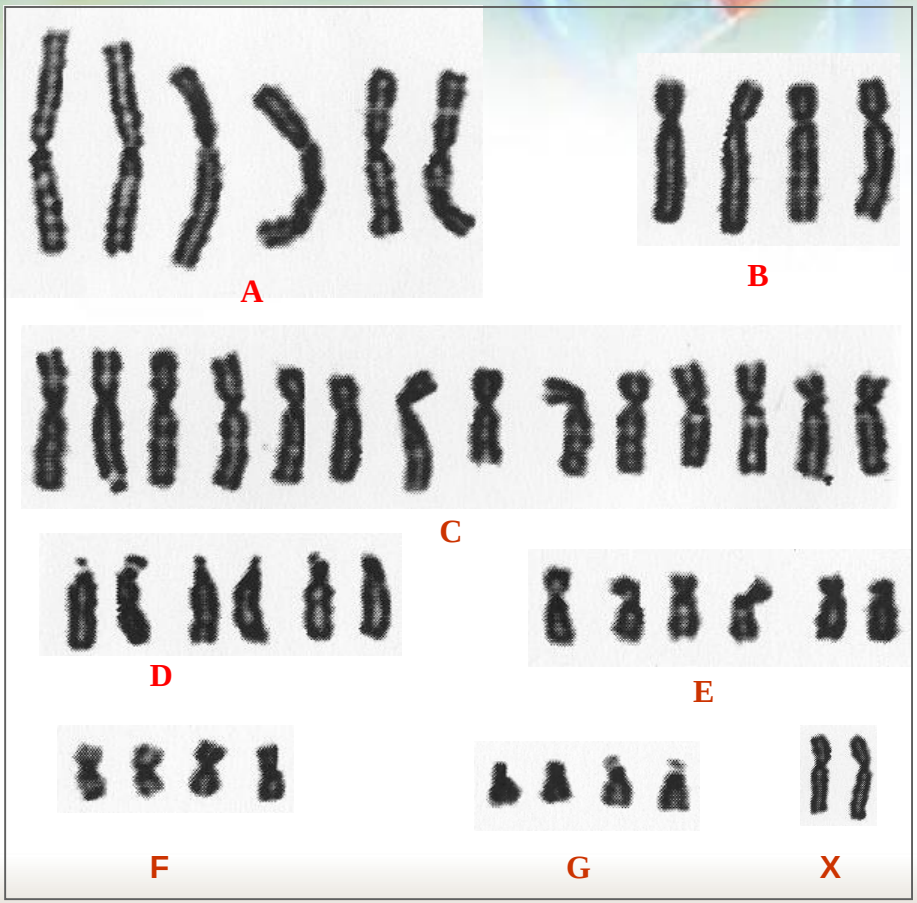




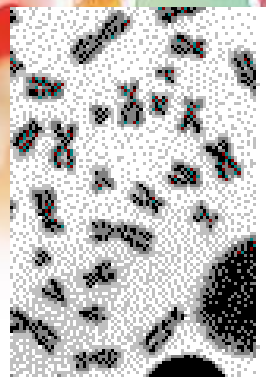
# Karyotyping

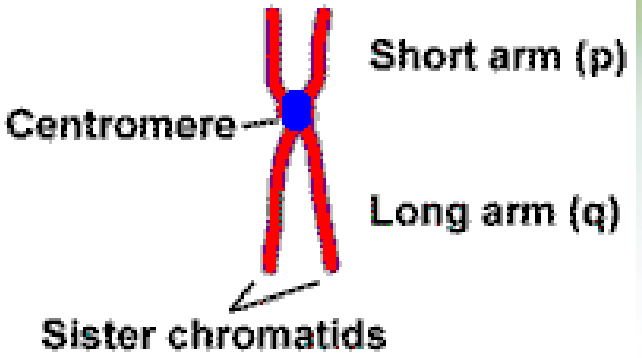
Based on:

1. the length
2. the position of the centromere
3. the presence or absence of satellites

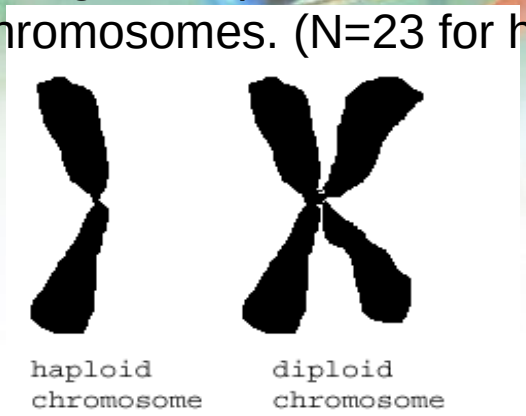


# Metaphase chromosomes:



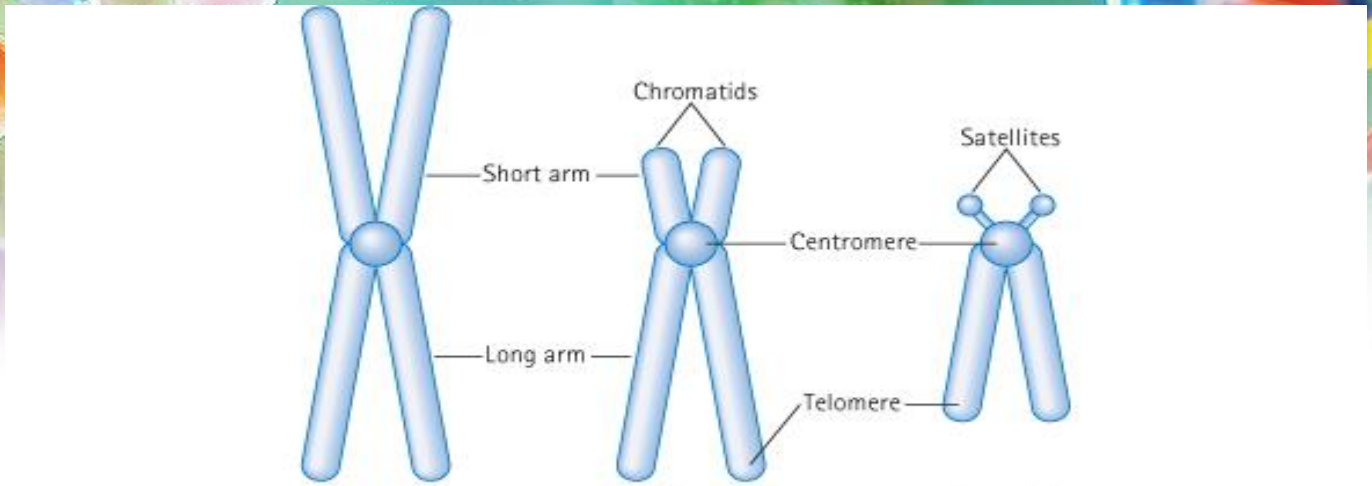



A single complete set of chromosomes. (N=23 for humans)




- The 2 sister-chromatids are principally held together at the centromeric region.
- Each chromosome has a centromere (CEN), region which contains the kinetochore,
- CEN divides the chromosome into two arms: the short arm (p arm) and the long arm (q arm).
- Each arm terminates in a telomere.

# Centromeric position and arm length:




The ratio of the lengths of the two arms is constant for each chromosome.

This ratio is an important parameter for chromosome identification and allows classification of chromosomes into several basic morphologic types:

i-*metacentric* ii-*sub-metacentric* iii-*acrocentric*

In the human karyotype chromosome pairs 13, 14, 15, 21, 22 are *acrocentric*

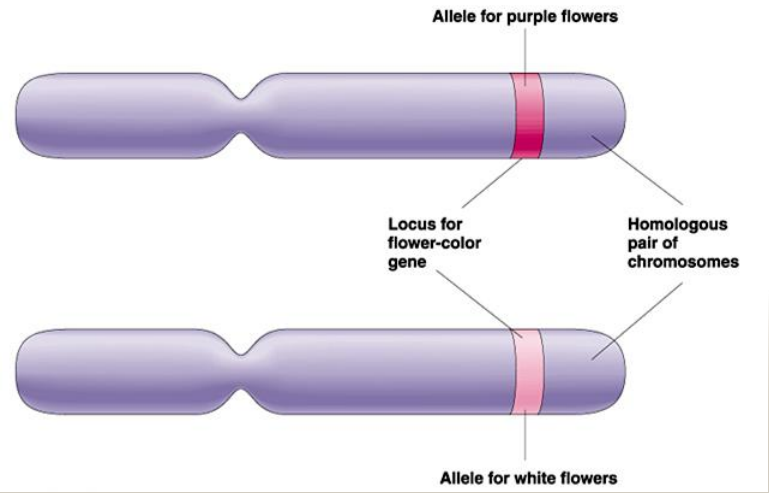
# Chromosomes

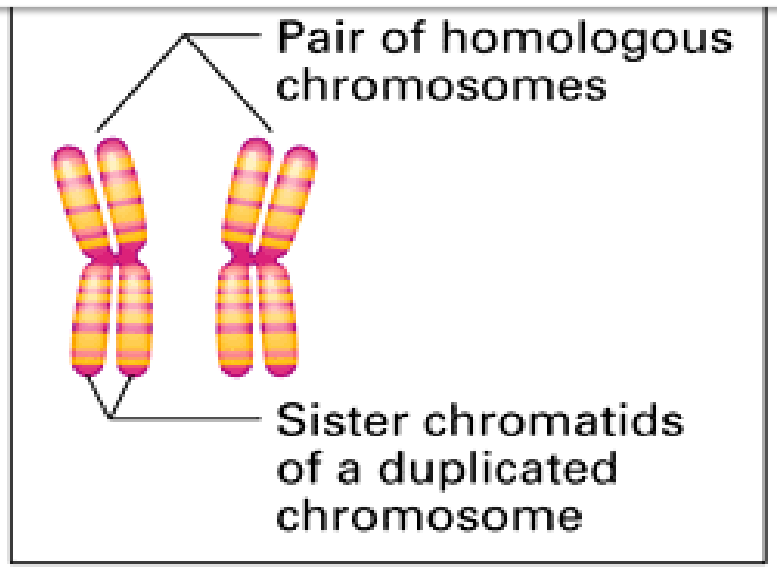
**Genotype:**

Genetic constitution of a cell, an organism, or an individual, that is the specific allele makeup of the individual

**Phenotype:**

A phenotype is any observable characteristic of an organism, such as its morphology, development, biochemical or physiological properties, or behavior

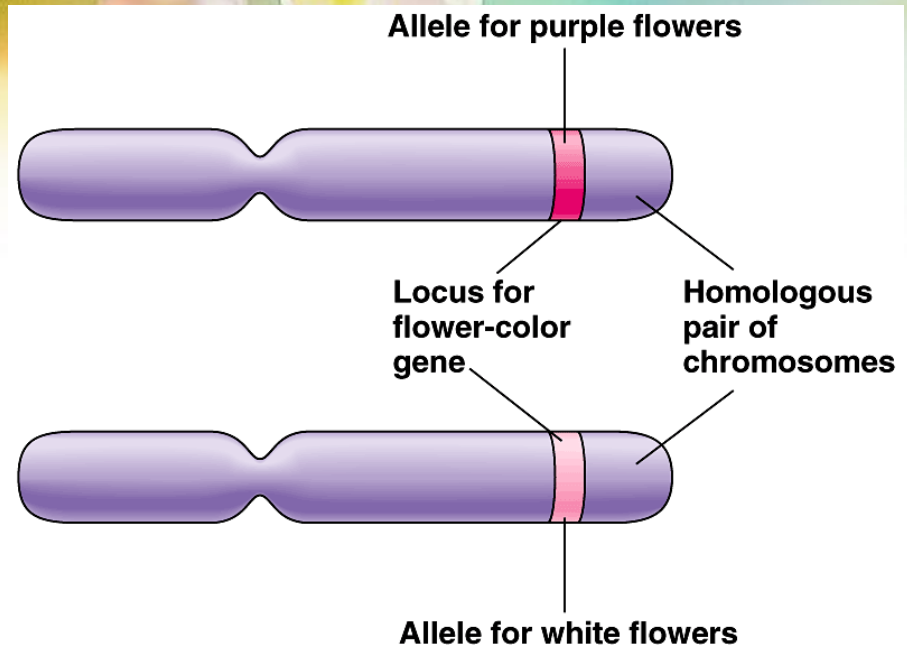


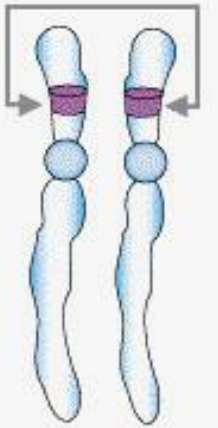

Sister chromatids are identical

**Alleles: alternative versions of a gene.**

The gene for a particular inherited character resides at a specific locus (position) on homologous chromosome.

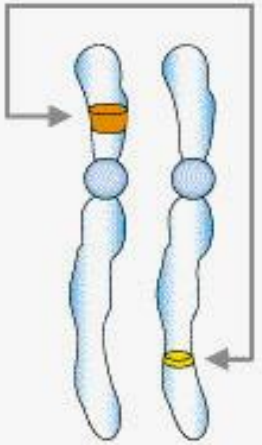



For each character, an organism inherits two alleles, one from each parent



Alleles

(code for same trait, same location on chromosome)

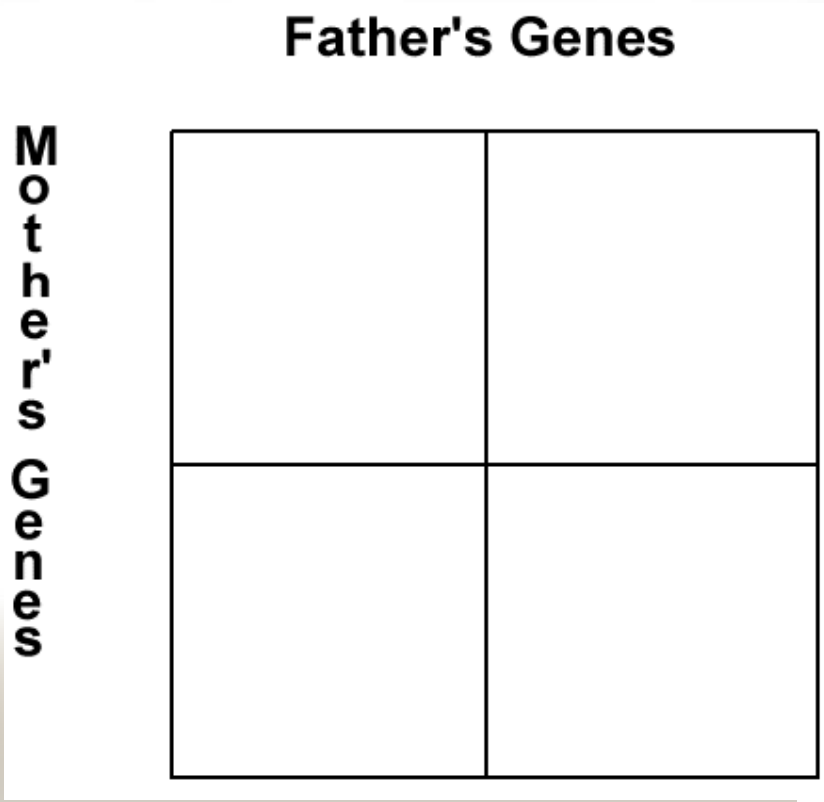


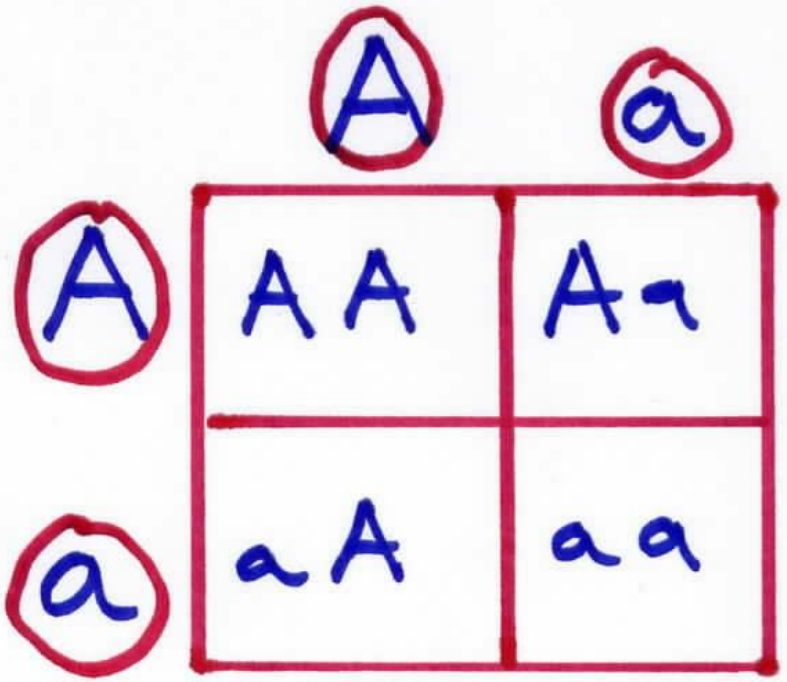
Genes, but *not* alleles

(code for different trait, different locations on chromosome)

For example, the human albino gene has two allelic forms, dominant A and recessive a, and there are three possible genotypes-

AA (homozygous dominant),
Aa (heterozygous), and
aa (homozygous recessive).



# Chromosomal classification

-22 pairs of autosomes, numbered from 1 to 22 by order of decreasing length

-1 pair of sex chromosomes:

XX in the female,

XY in the male.

# Items in the Description Of Karyotype:

- **Normal Karyotypes**

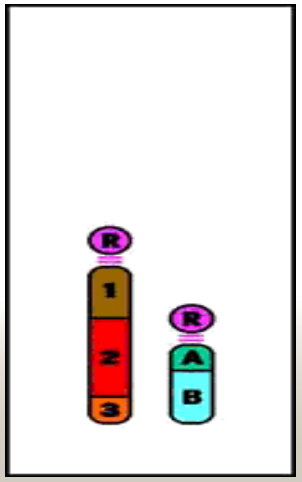
  **46, XY**

  **46, XX**

- **Abnormal Karyotypes**

  **47, XY, + 21**

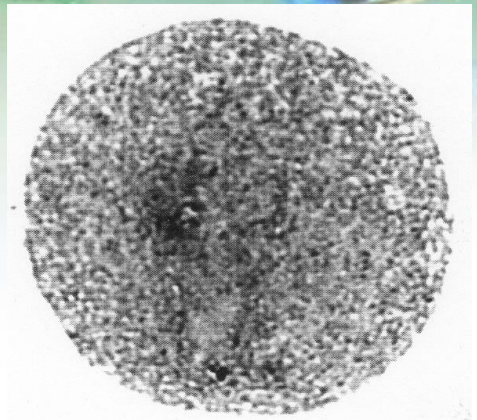
  **45, XY, t (D;G)** →

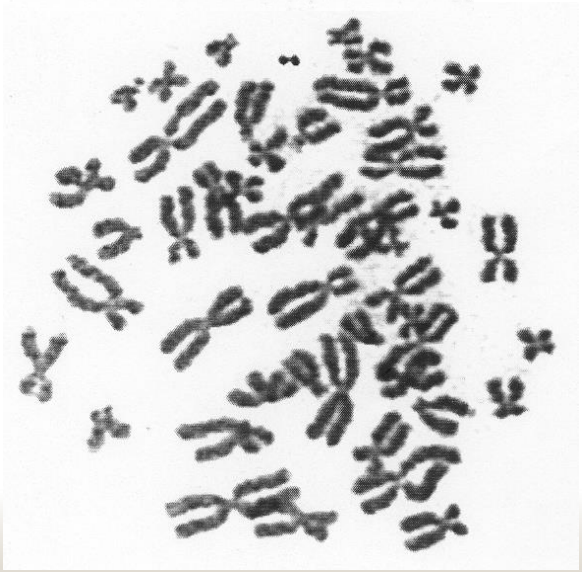


# Karyotype

**A series of steps involved :**

- **CULTURING**
- **HARVESTING**
- **Slide-Making**
- **Banding**
- **Staining**
- **Karyotyping**
- **Chromosome Analysis**





## Cytogenetics:

- Non-Banded Karyotype
- Banded Karyotype
- High resolution Karyotype

## Molecular cytogenetics:

- Fluorescent in situ hybridization (FISH).

# Banding

❖Certain staining techniques cause the chromosomes to take on a banded appearance,

❖Each arm presenting a sequence of dark and light bands .

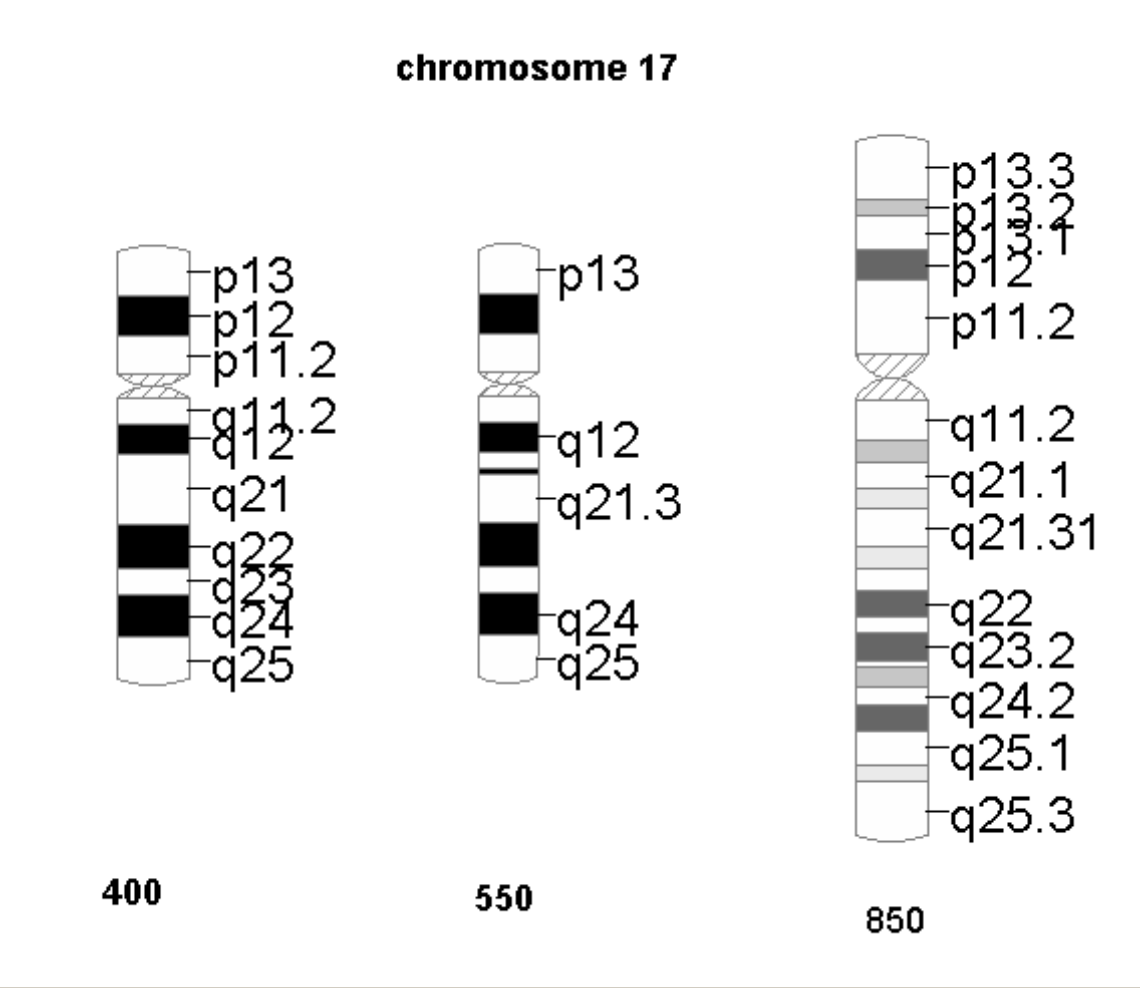
❖Patterns are specific and repeatable for each chromosome,

❖Allowing accurate identification and longitudinal mapping for locating gene positions and characterising structural changes.

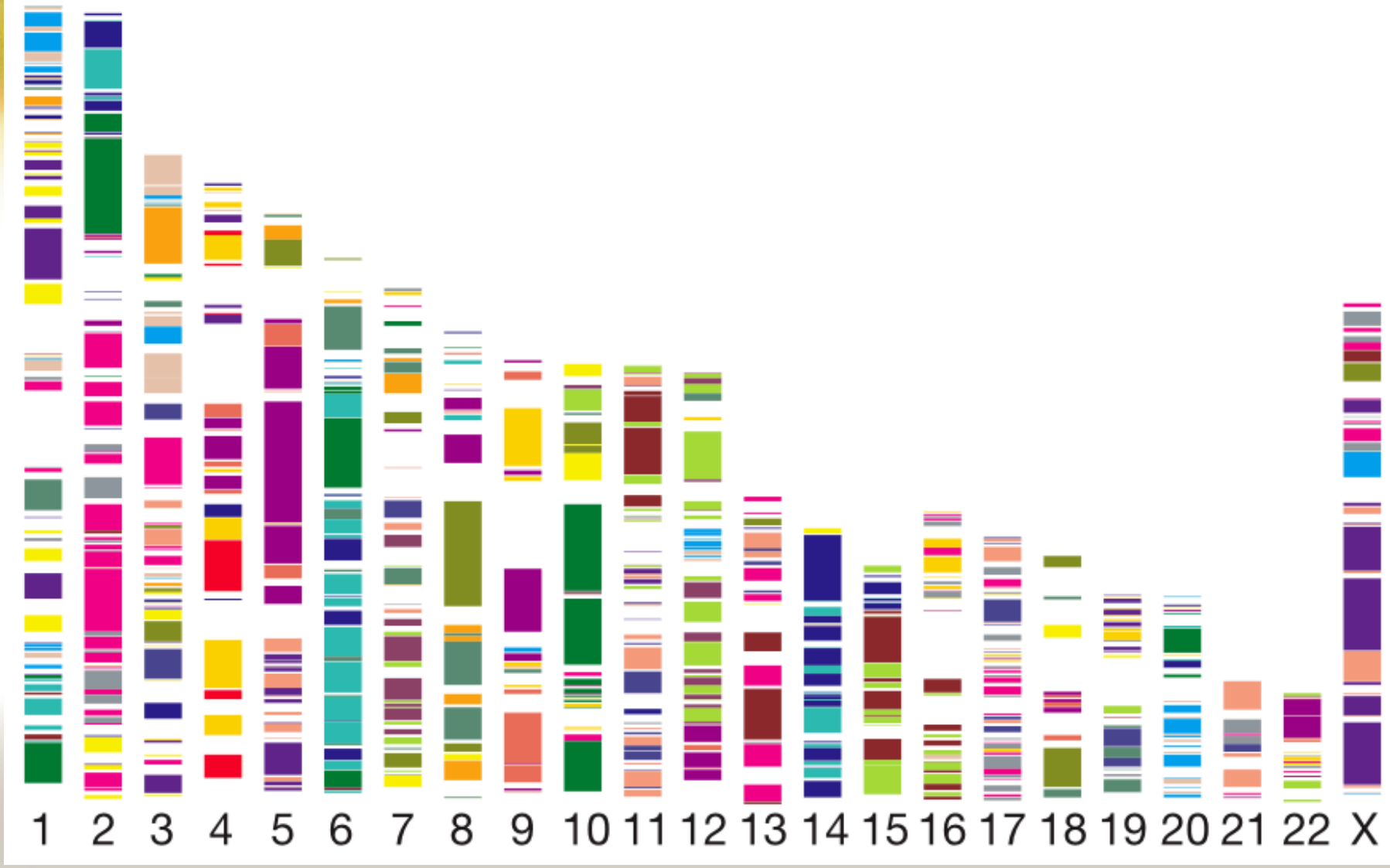
❖Patterns, and the nomenclature for defining positional mapping have been standardised

# Chromosome Banding

- Band resolution = estimate of number of light + dark bands per haploid set of chromosomes
- 400 → 850+



# Human Chromosome



**G Banding:**

Treat with trypsin and then with Geimsa Stain.

**R Banding:**

Heat and then treat with Geimsa Stain.

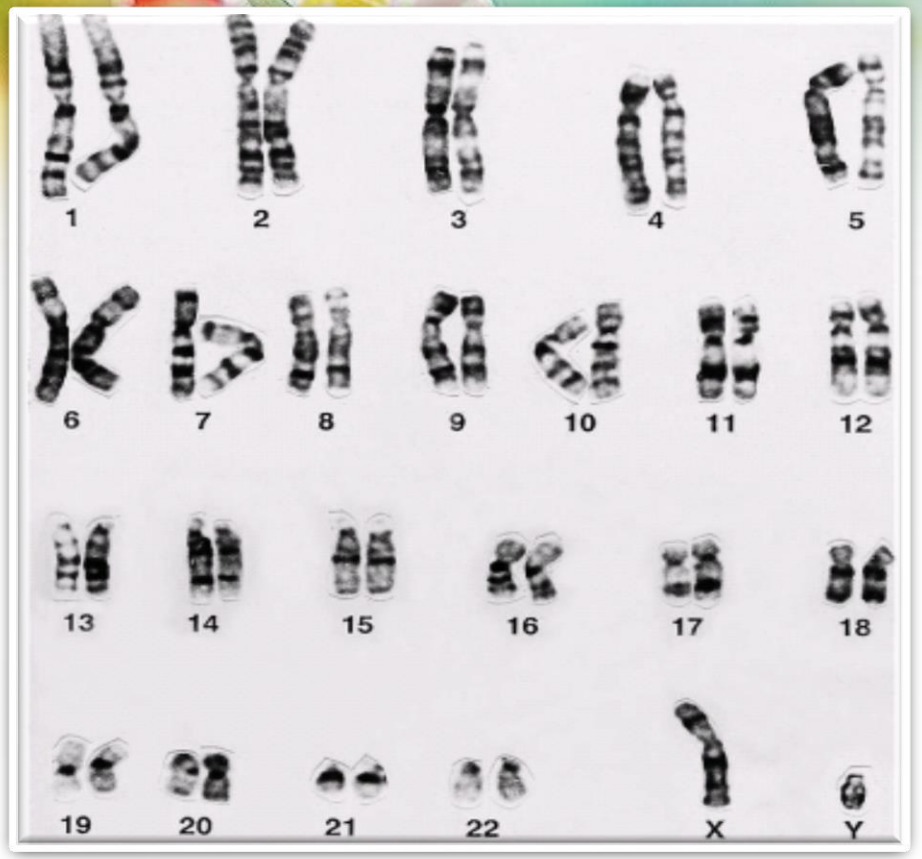
**Q Banding:**

Treat with Quinicrine dye giving rise to fluorescent bands. It requires an ultraviolet fluorescent microscope

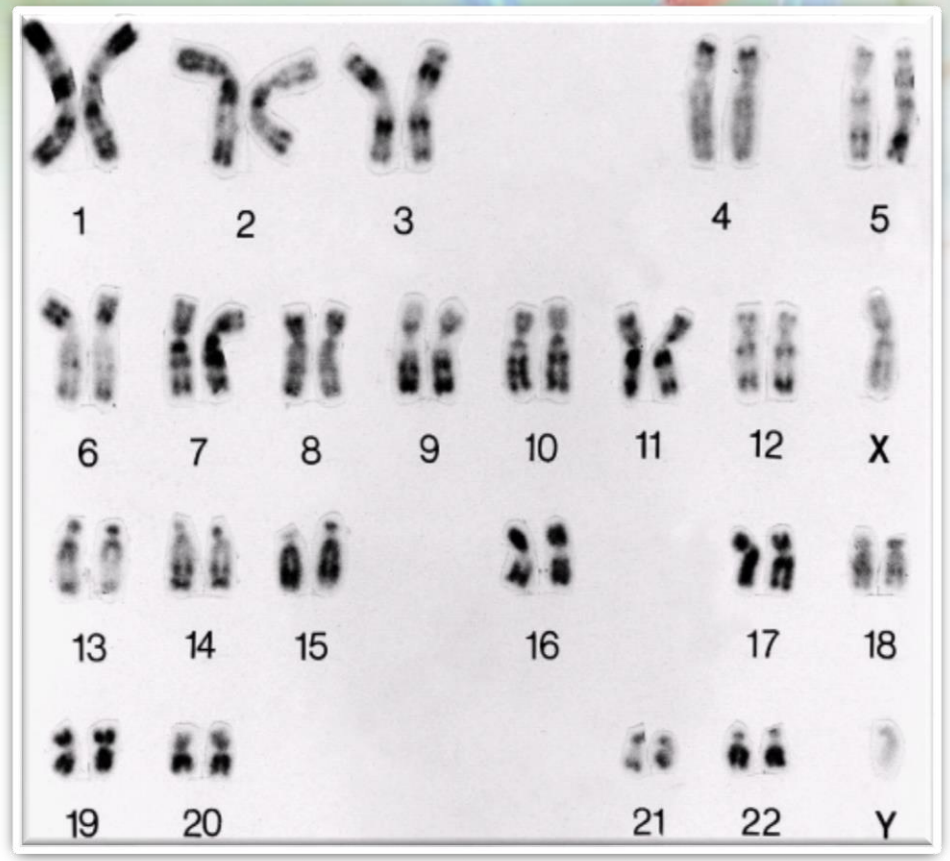
**C Banding:**

Staining of the Centromere. Treat with acid followed by alkali prior to G banding

# Banded Karyotype: Normal Banded Karyotypes

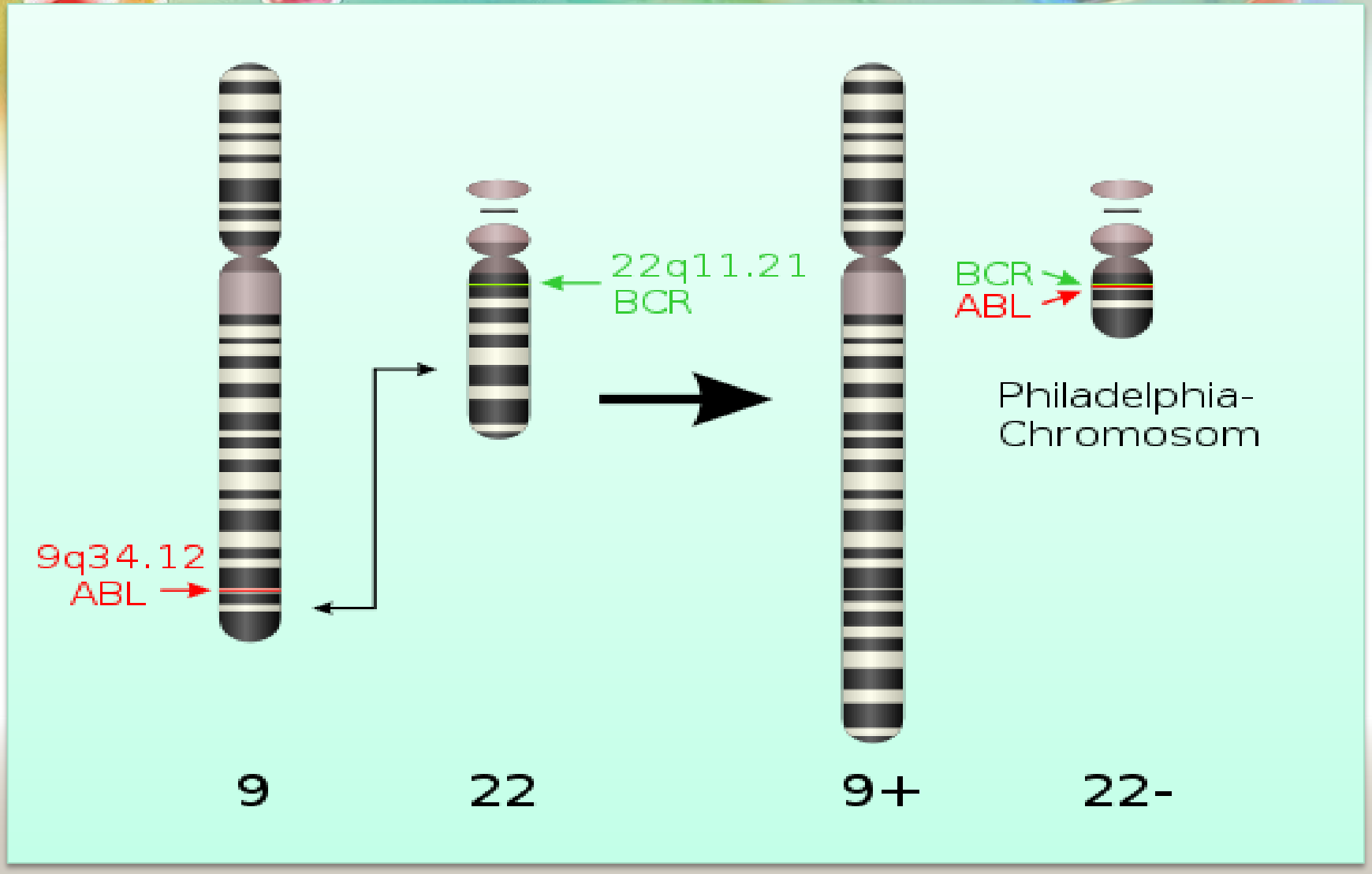



A normal G-banded male Karyotype

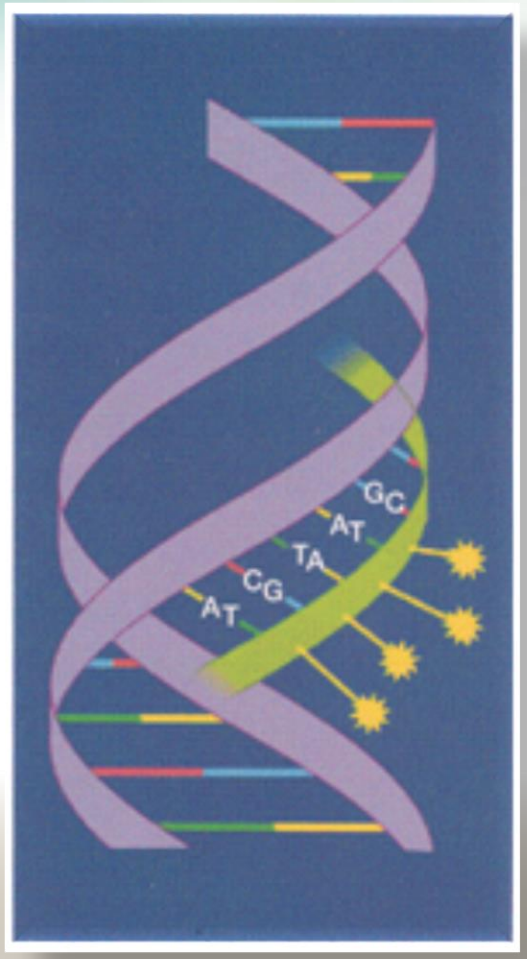



A normal R-banded male Karyotype

# 46, XY, t (9;22)(q34;q11)



# Fluorescence In-Situ Hybridization (FISH)



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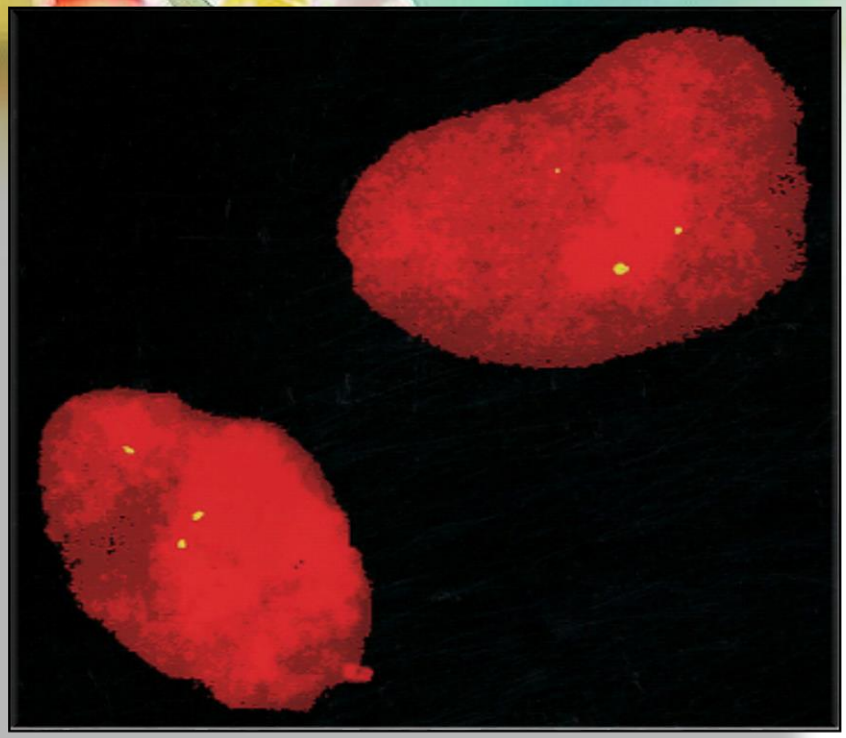
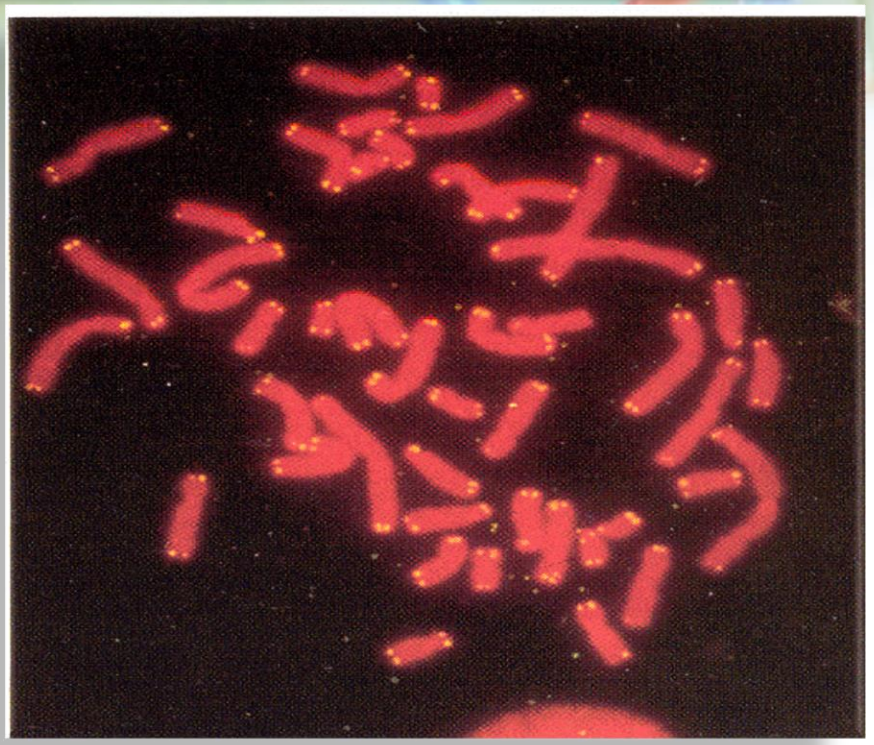
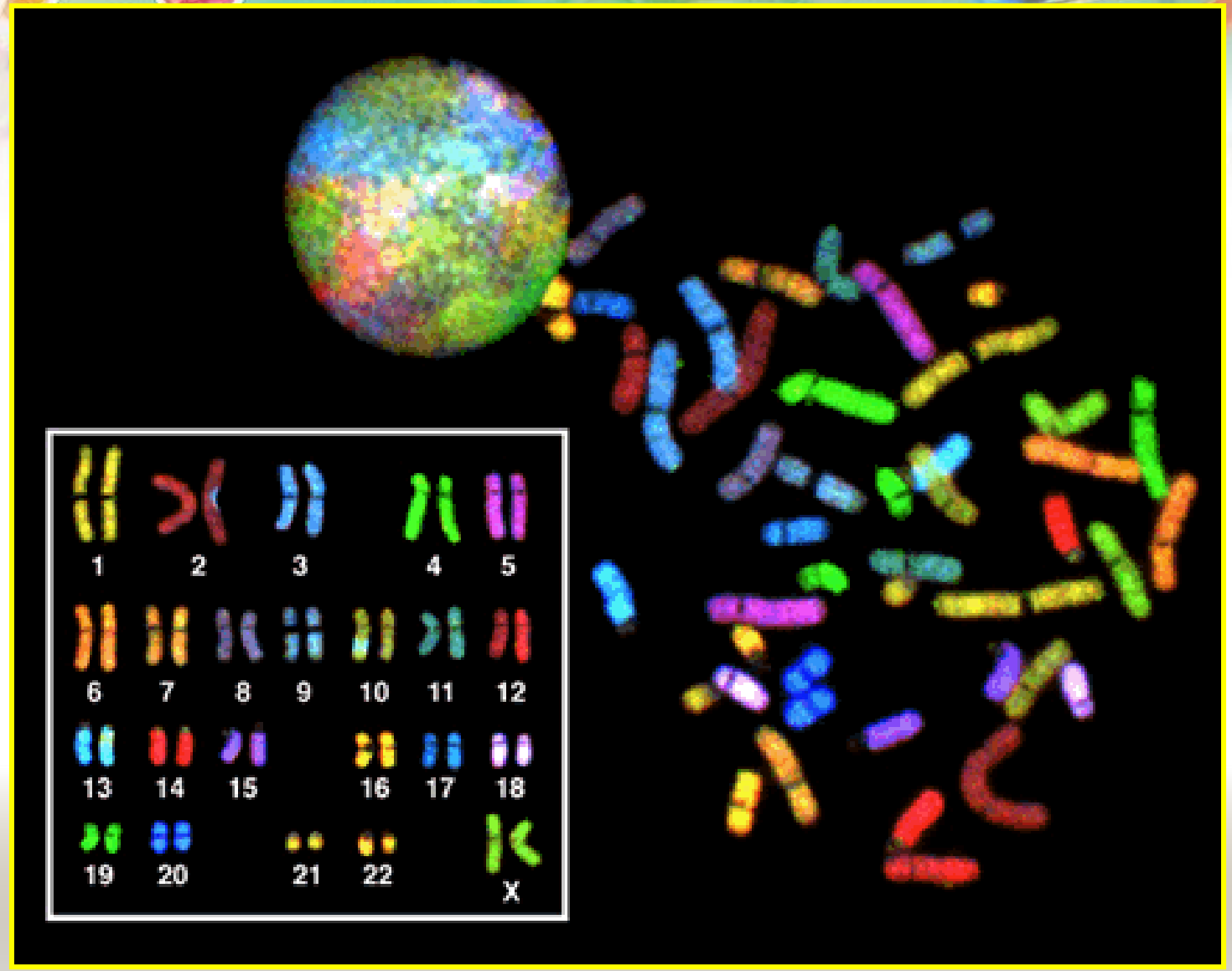


FISH of interphase nuclei with a chromosome 21 centromeric probe showing 3 signals consistent with trisomy 21



FISH of metaphase with a probe for telomere showing signals at the end of each chromatid

# Spectral Karyotype



# Take Home Message

- The normal human karyotype is made up of 46 chromosomes consisting of 22 pairs of autosomes and a pair of sex chromosomes, XX in the female, and XY in the male.
- Each chromosome consists of a short (p) and a long (q) arm joined at the centromere.
- Chromosomes are analyzed using cultured cells and specific banding patterns can be identified using special staining techniques.
- Molecular cytogenetic techniques (e.g. FISH) are based on the ability of a single-stranded DNA probe to anneal with its complementary target sequence. They can be used to study chromosmes in metaphase or interphase.

# THANK YOU ☺