



Introduction to Developmental Diseases

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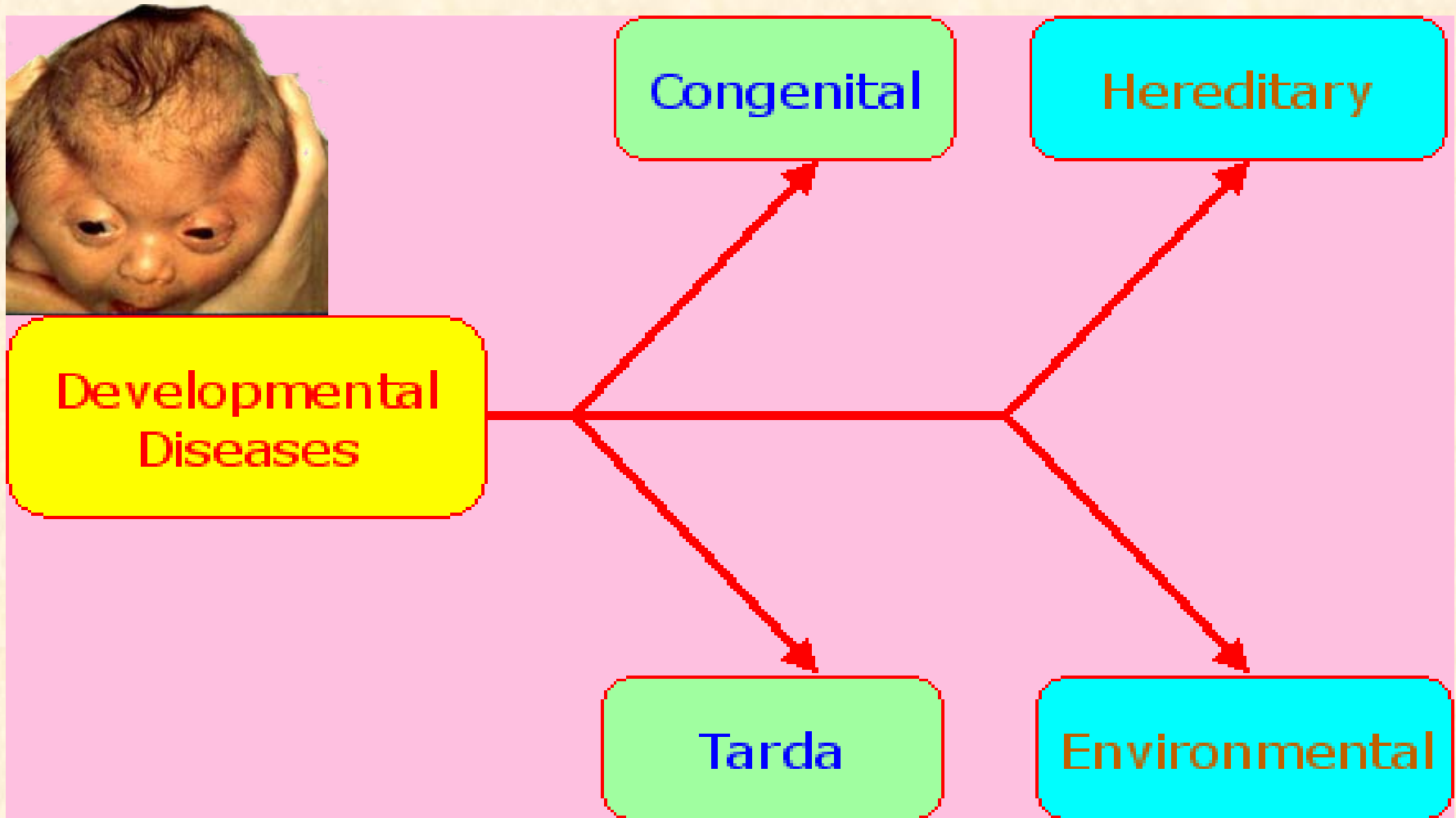
Human Development

- Prenatal period (38 weeks from conception to birth)
 - Embryonic: weeks 1-8
 - Fetal: weeks 9-38
 - Postnatal period
 - From birth to cessation of skeletal growth (18-20 years)
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Developmental Diseases - Definitions

- **Developmental:** Are diseases resulting from disturbance in development
 - **Hereditary:** Are diseases transmitted from one generation to the other through genes
 - **Environmental:** (acquired) Are diseases resulting from the action of teratogenes
 - **Congenital:** Are diseases present at birth
 - **Tarda:** Are diseases present later on life
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Developmental Diseases - Classification



Developmental Diseases - Notes

Note that:

- Not all congenital diseases are hereditary
 - All congenital diseases are developmental
 - Not all developmental diseases are congenital
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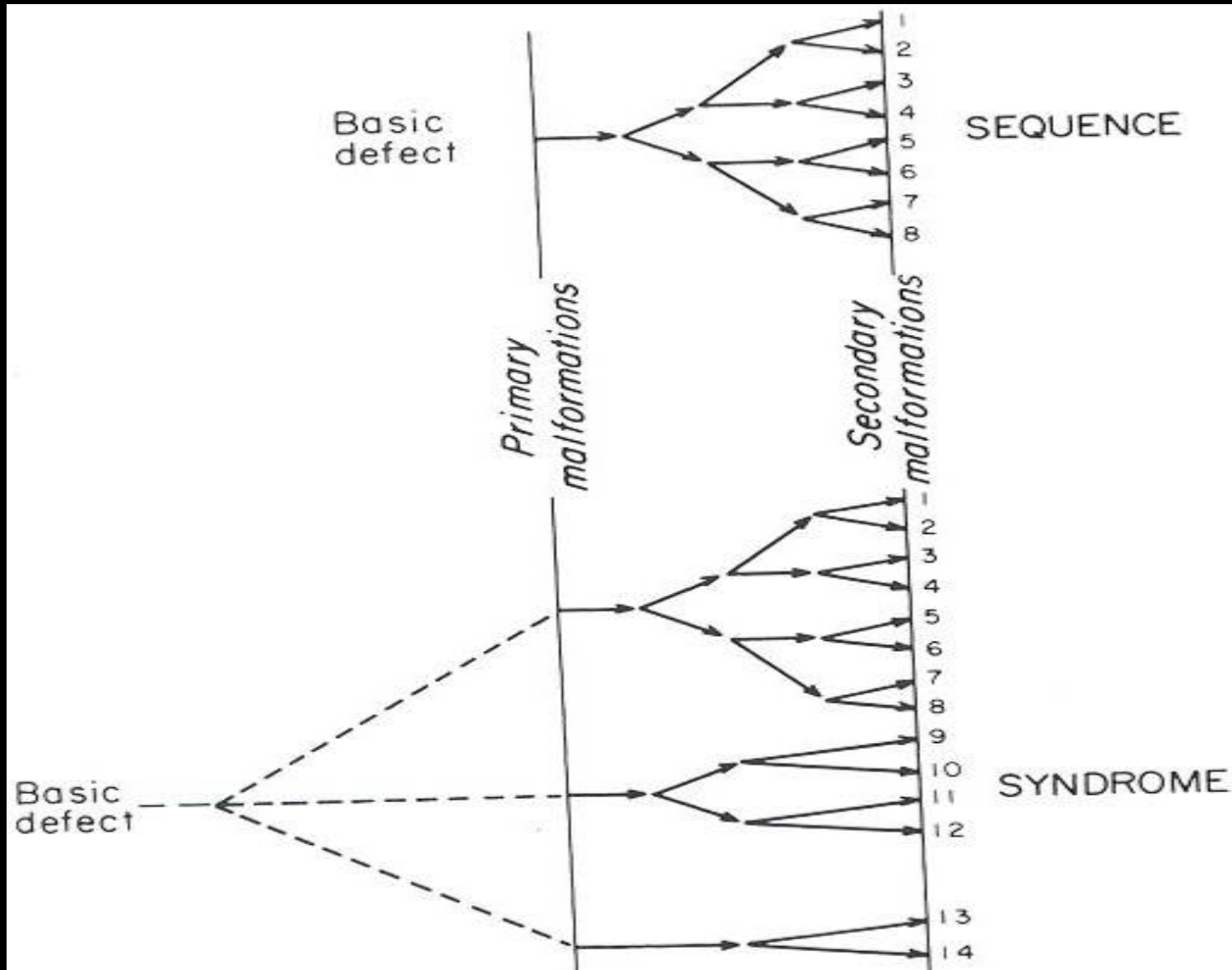
Syndrome

- Multiple anomalies believed to be pathogenetically related and not representing a sequence
 - Pathogenesis less understood
 - e.g., Treacher-Collins syndrome
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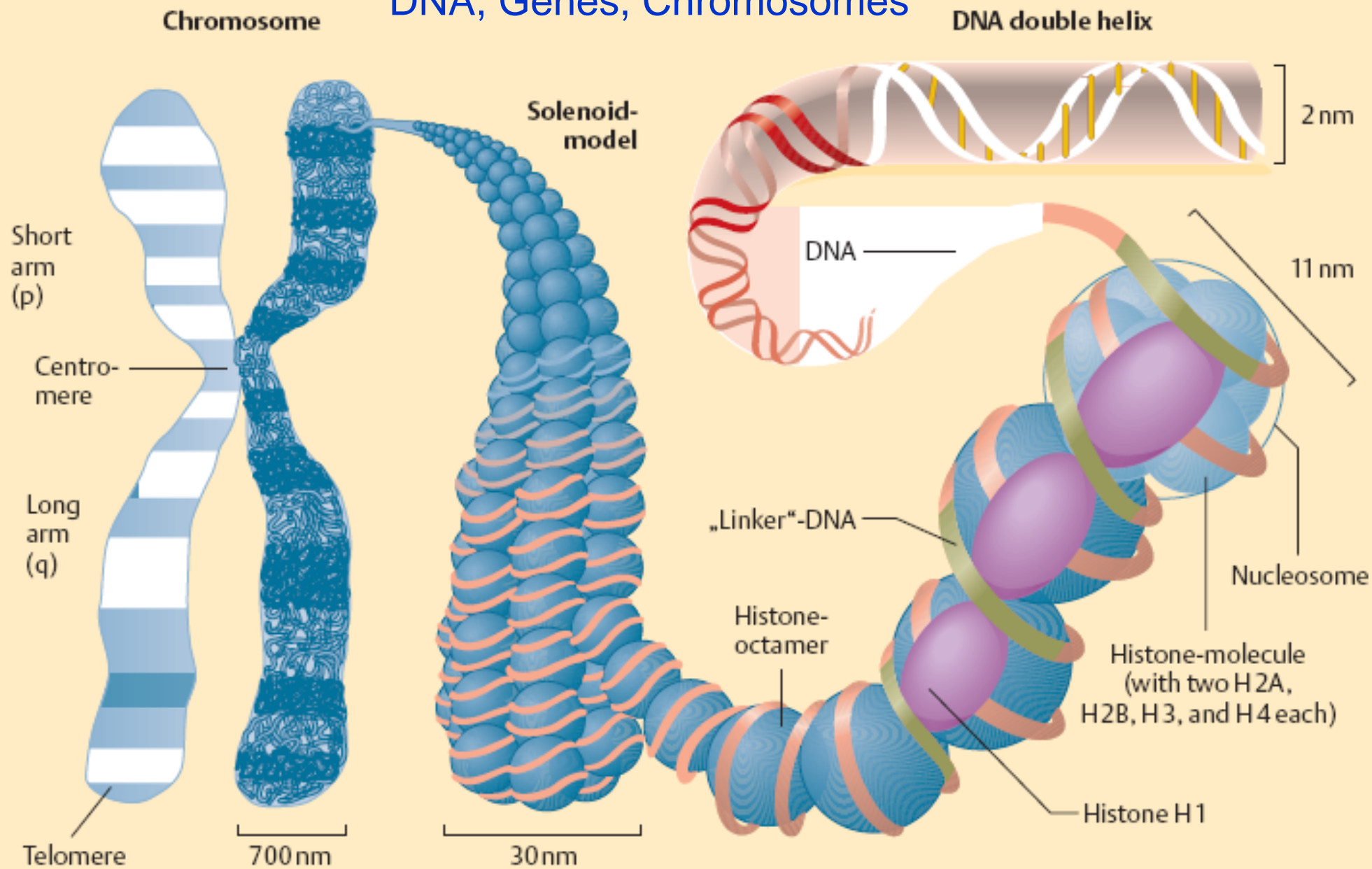
Sequence

- “multiple defects that result from a **single** presumed anomaly”
 - e.g., Pierre Robin sequence
-

Sequence versus Syndrome



DNA, Genes, Chromosomes



Hereditary Diseases

Single gene defect
(Medelian inheritance)

Autosomal

Sex-linked

X-linked

Y-linked
(Holandric)

Dominant

Recessive

Incomplete dominant

Co-dominant

Dominant

Recessive

Multifactorial inheritance
(polygenic inheritance)

Chromosomal
abnormalities

Numerical

Structural

Trisomy

Monosomy

Autosomes

Sex chromosomes

Autosomes - lethal

Sex chromosomes

Mitochondrial inheritance

Deletion

Inversion

Duplication

Translocation

Tutankhamun - King's Mask



What is Genetics?

**Genetics is the study of heredity
and its variation.**

Basic Branches of Genetics

Classical genetics

Passage of traits within families

Meiosis, Mendel's laws, sex linkage, cytogenetics

Molecular Genetics

Study of DNA, RNA and proteins

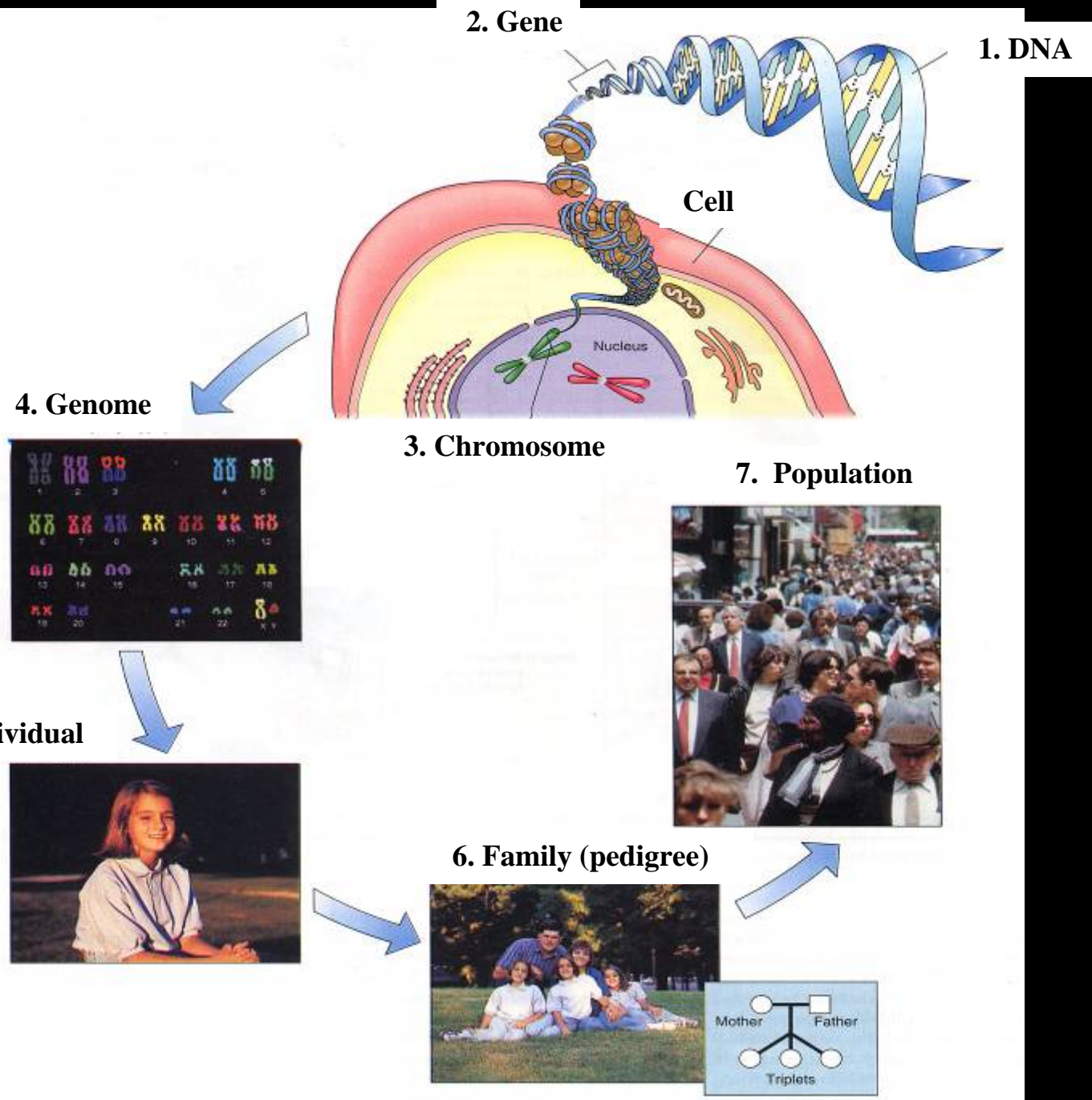
Gene expression, mutation, cloning and genomics

Population/Evolutionary Genetics

Study of allele frequency within the population

Quantitative genetics, Hardy-Weinberg equilibrium, evolution and speciation

DNA, Genes, Chromosomes



Human Chromosomes



DNA

G: Guanine

A: Adenine

T: Thymine

C: Cytosine

U: Uracil not present in DNA, but takes the place of Thymine in RNA

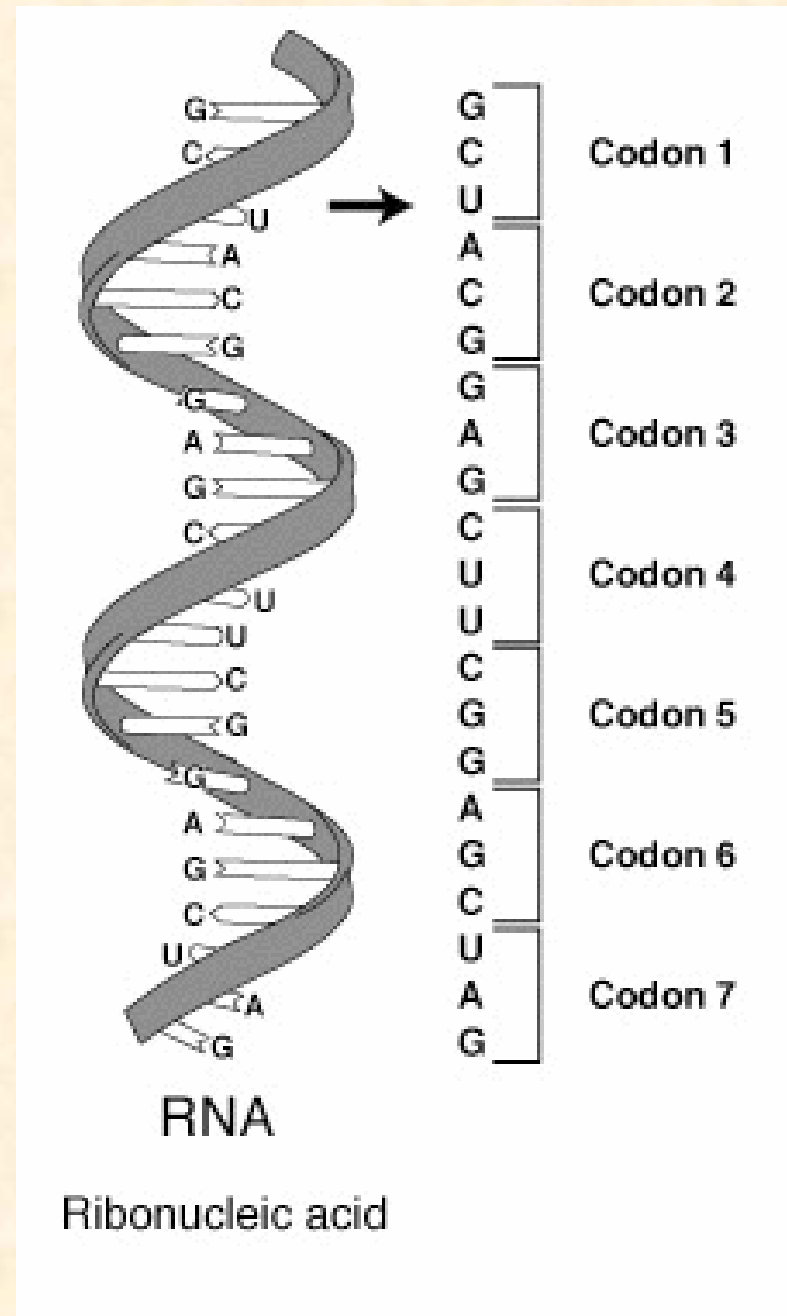
Nucleotide

A nucleotide is a chemical compound that consists of a base, a sugar, and one or more phosphate groups.

Codons

A series of codons in an short RNA molecule. Each codon consists of **three** nucleotides, representing a single amino acid.

George Gamov postulated that a three-letter code must be employed to encode the 20 different amino acids used by living cells to encode proteins.



Codons

Messenger RNA (mRNA) is the template for protein synthesis. It consists of a series of nucleotides, each containing one of four nitrogenous bases, Uracil, Cytosine, Adenine, and Guanine. The order of nucleotides in a strand of mRNA specifies the order in which amino acids are added as a protein is built. Each series of three nucleotides specifies one amino acid. This chart identifies each amino acid by its three-letter codon(s). For example, G under the “first letter” column, C under the “second letter” column, and A under the “third letter” column intersect at alanine, the amino acid specified by the sequence GCA. Most amino acids are identified by more than one codon (for instance, GCU, GCC, GCA, and GCG all encode alanine).

FIRST LETTER	SECOND LETTER				THIRD LETTER
	U	C	A	G	
U	Phenylalanine	Serine	Tyrosine	Cysteine	U
	Phenylalanine	Serine	Tyrosine	Cysteine	C
	Leucine	Serine	Stop	Stop	A
	Leucine	Serine	Stop	Tryptophan	G
C	Leucine	Proline	Histidine	Arginine	U
	Leucine	Proline	Histidine	Arginine	C
	Leucine	Proline	Glutamine	Arginine	A
	Leucine	Proline	Glutamine	Arginine	G
A	Isoleucine	Threonine	Asparagine	Serine	U
	Isoleucine	Threonine	Asparagine	Serine	C
	Isoleucine	Threonine	Lysine	Arginine	A
	(Start)	Threonine	Lysine	Arginine	G
	Methionine				
G	Valine	Alanine	Aspartate	Glycine	U
	Valine	Alanine	Aspartate	Glycine	C
	Valine	Alanine	Glutamate	Glycine	A
	Valine	Alanine	Glutamate	Glycine	G

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Genetic information is transmitted at several levels

DNA

Genes

Chromosomes

Genome

Individual

Family

Population

Genes

- are the basic unit of inheritance.
- are composed of DNA (deoxyribonucleic acid).
- direct the formation of proteins.

Different versions of the same gene are called alleles.

Alleles result from the process called mutation.

The Genome

is the complete set of genetic information characteristic of the organism.

The genome includes:

- all of the genes present in an organism and
- other DNA sequences that do not encode proteins

Human Genome

The human genome

- consists of 3 billion base pairs of DNA
- includes 30,000 to 35,000 genes
- is organized as 23 pairs of chromosomes

Gene content and genome size of various organisms

organism	genes	base pairs
Plant	<50,000	<10 ¹¹
Human, mouse or rat	35,000	3×10 ⁹
Fugu fish	40,000	4×10 ⁸
Fruit Fly	13,767	1.3×10 ⁸
Worm	19,000	9.7×10 ⁷
Fungus	6,000	1.3×10 ⁷
Bacterium	500–6,000	5×10 ⁵ –10 ⁷
Mycoplasma genitalium	500	580,000
DNA virus	10–900	5,000–800,000
RNA virus	1–25	1,000–23,000
Viroid	0–1	~500

Individuals

carry two alleles of each gene.

Genotype is the genetic makeup of an individual.

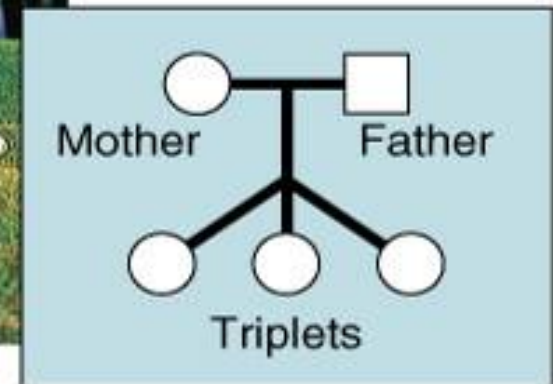
Phenotype is the visible trait that results from a particular genotype.

The Family

Inheritance of traits can be observed in families.

A pedigree indicates the structure of a family schematically.

6. Family (pedigree)



A Population

A population

is a group of individuals who possess a particular collection of alleles or gene pool.

Variations Between Species

Between species

Comparison of DNA sequences indicates the amount of similarity between two species.

98% of human DNA sequences are shared with chimpanzee.

Many genes present in humans are also present in mice, fish, fruit flies, yeast, and bacteria.

Chimpanzee Versus Greece

Chimpanzees, are known as intelligent communicators and problem solvers. They prepare and use a wide variety of tools such as long, peeled digging sticks, grass stems, sponges (made of bark or leaves, chewed until soft), and rags (of leaves). They may use these tools for enlarging the holes of insect dens, pulling termites or ants out of their nest mounds, or smashing the harder-shelled of the 20 kinds of fruit they often eat in a day. Males also use sticks and rocks in their charging displays. Chimpanzees differ from human beings by only 1 percent of their genetic material, making them our closest relative.





Chimpanzee Versus Greece

Chimpanzee	TTCTTTCATGGGGGAAGCAAATTTAA	25
Greece	TTCTTTCATGGGGGAAGCAGATTTGG	
Chimpanzee	GTACCACCTAAGTACTGGCTCATTTC	50
Greece	GTACCACCCAAGTATTGACTCACCC	

Sequence differences are highlighted in blue.
Comparison of modern Greek and a chimpanzee.
Comparison shows 48 differences over 275 nucleotides.

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Human Variations

Human to human, we are very similar

On average two random people share the same DNA sequence in 99.9% of their genome.

Studies of variation among humans indicates humans arose in Africa and migrated across the globe with relatively little change.

We are also very different

On average two random people differ at 3 million base pairs (approximately one nucleotide of every thousand).

Greece Versus Japan

Greece	CCACATCAAACCCCTCCCCATGC	150
Japan	CCACATCAAACCCCGCGC	
Greece	TTACAAGCAAGTACAGCAATCAACC	175
Japan	TTACAAGCAAGTACAGCAATCAACC	

Sequence differences are highlighted in blue.
Comparison of modern Greek and Japanese humans shows 6 differences over 275 nucleotides.

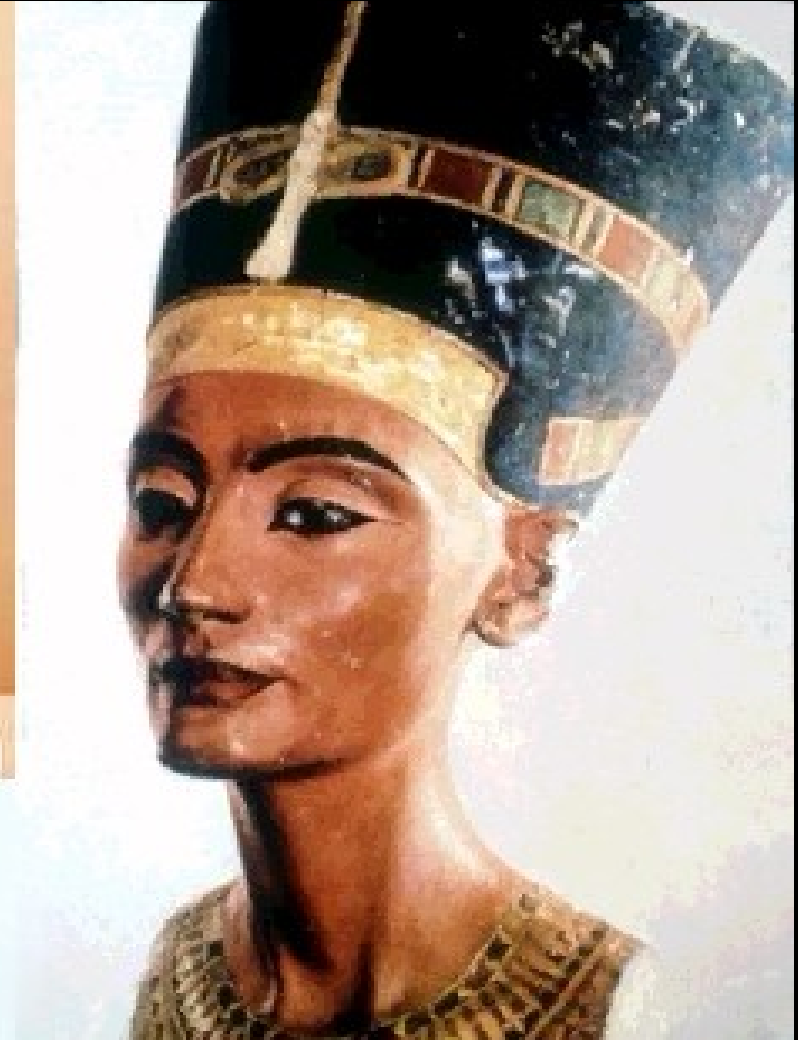
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Genetic Mapping

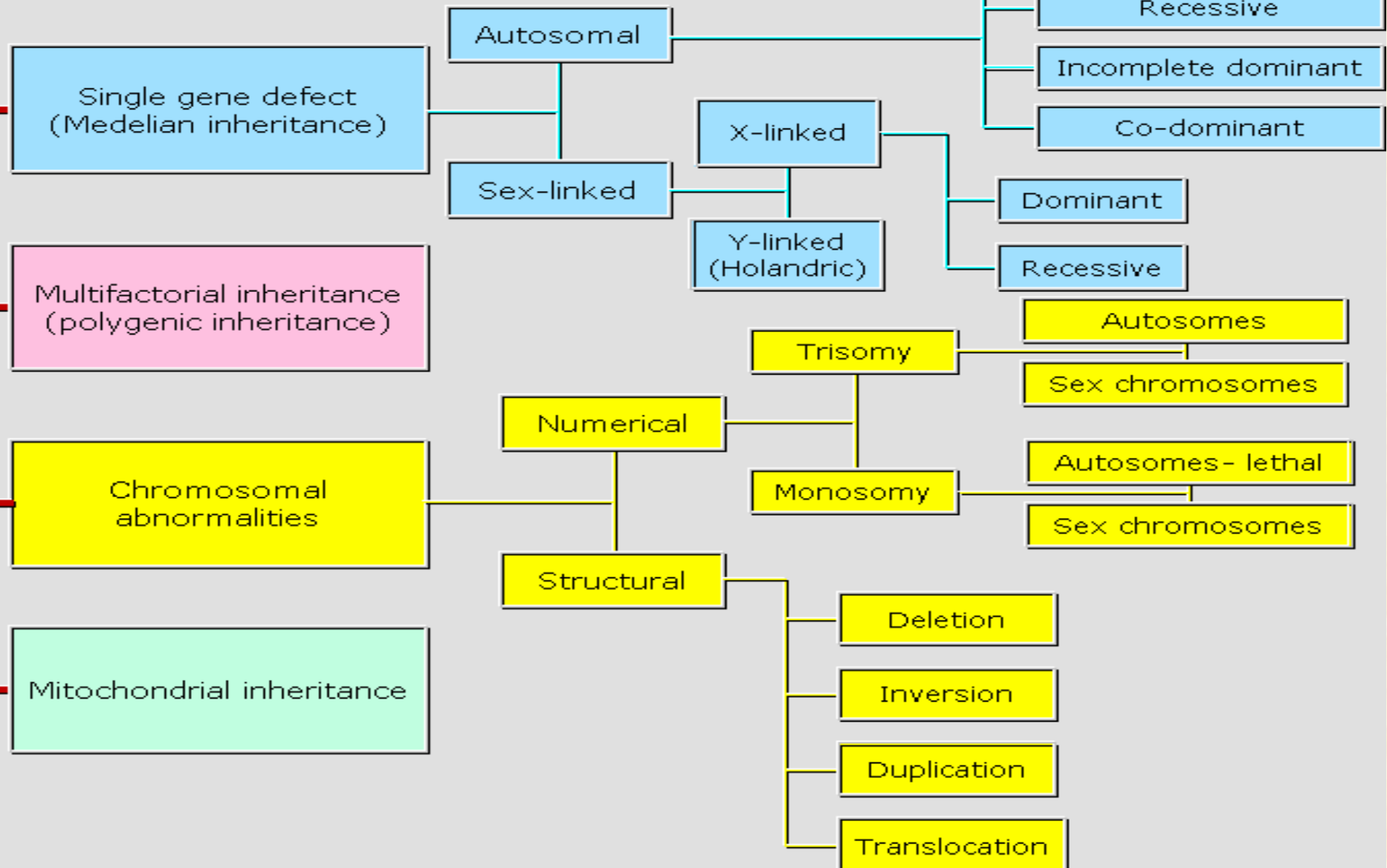
- Is the process by which the arrangement of genes on a chromosome is determined.
 - To produce a genetic map, blood or tissue samples are collected from family members where a certain disease or trait is prevalent.
 - DNA is examined for the unique patterns of bases **seen only** in family members who have the disease or trait.
-

Nefertiti – The Beautiful

The right Statue is from Berlin Museum, Germany and the left one is from Florence Museum, Italy



Hereditary Diseases



Hereditary Diseases - Classification

- **Single gene defect (monogenic)**
 - **Chromosomal abnormalities**
 - **Multifactorial inheritance**
 - **Mitochondrial inheritance**
-

Single gene defect

- Usually follow Mendelian pattern of inheritance
 - May be sex-linked or autosomal
 - May be dominant, recessive or of incomplete dominance
 - May show varying degrees of expressivity
 - May show varying degrees of penetrance
 - May show sex limited features such as male pattern baldness
-

Autosomal dominant disorders

- both homozygotes and heterozygotes are affected
 - usually heterozygotes (inherited from one parent)
 - both males and females are affected
 - transmission from one generation to the other
 - If one of the parents is heterozygous, 50% of children are affected
 - If one of the parents is homozygous, 100% of children are affected
 - If both parents are heterozygous, 75% of children are affected
-

Punnett Square

		Mother's egg cells (Gametes)	
		A	A
Father Sperm Cells (Gametes)	Crossed with	A	A
	A	AA	AA
	a	Aa	Aa

Autosomal dominant disorders

1- $AA + Aa =$ Normal parent + Heterozygous parent

2- $AA + Aa + AA + Aa = 50\%$ affected children

1- $AA + aa =$ Normal parent + Homozygous parent

2- $Aa + Aa + Aa + Aa = 100\%$ affected children

1- $Aa + Aa =$ Heterozygous parent + Heterozygous parent

2- $AA + Aa + Aa + aa = 75\%$ affected children, 33.3% of them are homozygous (pure)

Autosomal recessive Disorders

- majority of Mendelian disorders
 - only homozygotes are affected, heterozygotes (parents) are only carriers
 - 25% of descendants are affected if the two parents were carriers
 - onset of symptoms often in childhood
 - frequently enzymatic defect
 - testing of parents and amniotic cells
-

Autosomal recessive disorders

1- AA + Aa = Normal parent + Heterozygous parent

2- AA + Aa + AA + Aa = No affected children (50% carriers)

1- AA + aa = Normal parent + Homozygous parent

2- Aa + Aa + Aa + Aa = No affected children (100% carriers)

1- Aa + Aa = Heterozygous parent + Heterozygous parent

2- AA + Aa + Aa + aa = 25% affected children (pure), 50% carriers, 25% normal (pure)

X-linked diseases

- Usually transmitted by heterozygous mother to sons
 - daughters - 50% carriers, 50% healthy
 - sons - 50% diseased, 50% healthy
 - Children of diseased father - sons are healthy, all daughters are carriers
-

X-linked diseases

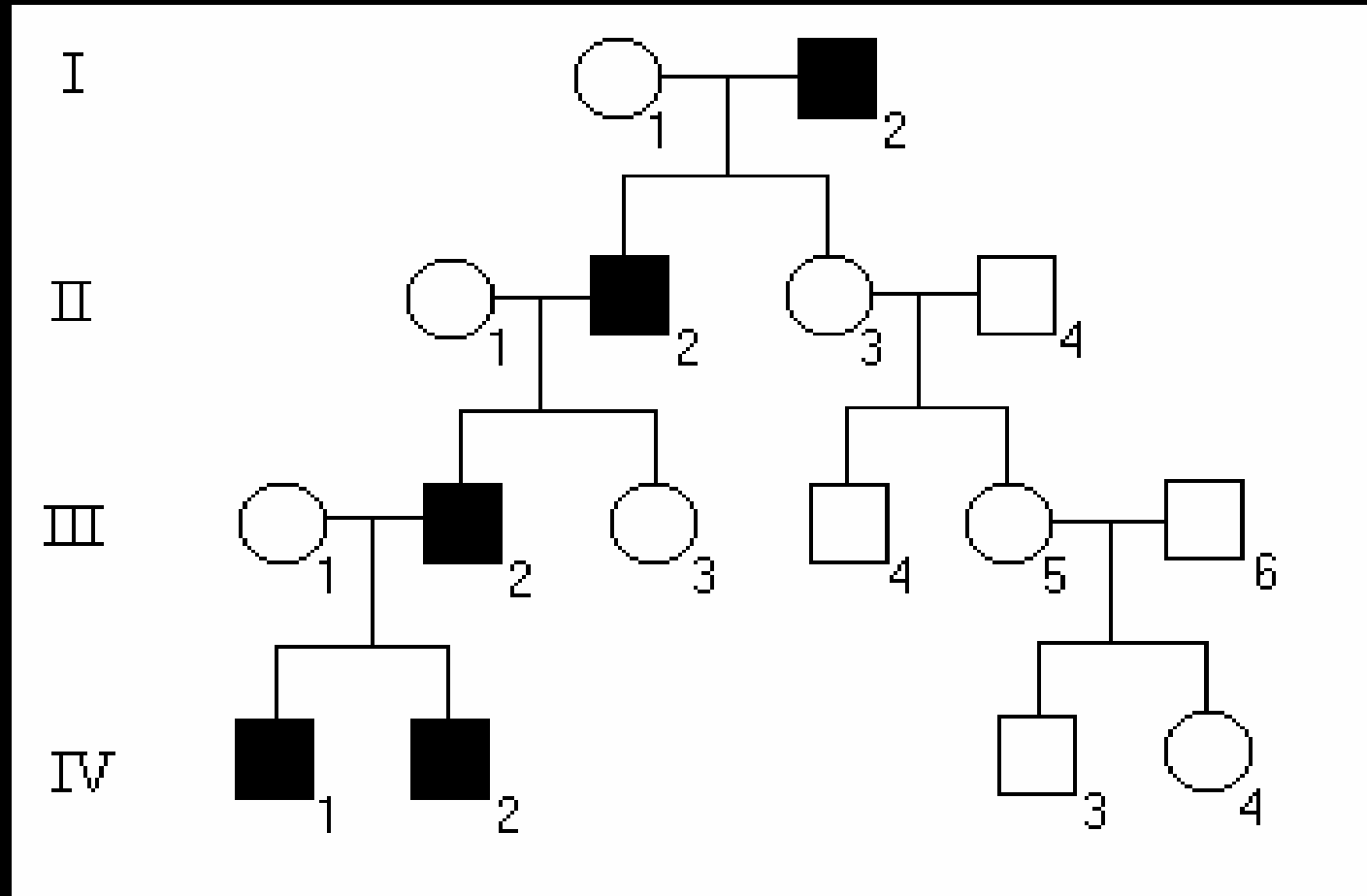
- X-linked dominant disorders (rare):
 - Hereditary Hypophosphatemia (Vit D-Resistance Rickets)
 - Focal dermal hypoplasia (Goltz syndrome)
 - Incontinentia pigmenti (genodermatosis that may also involve other structures; characterized by pigmented lesions in linear, zebra-stripe, and other bizarre configurations, sometimes preceded by vesicles and bullae containing eosinophils, occasionally accompanied by other developmental abnormalities e.g. **peg shaped teeth**; the disorder is lethal in males. Cf. Naegeli syndrome. Syn: Bloch-Sulzberger disease, Bloch-Sulzberger syndrome.
 - Orofaciodigital syndrome
-

X-linked diseases

- X-linked recessive disorders (more common):
 - Hemophilia A (defect of Factor VIII)
 - Hemophilia B (defect of Factor IX)
 - Muscle dystrophy (Duchene disease)
 - Streeter's Syndrome
 - Color blindness
 - Occular albinism
 - Hunter's syndrome (mucopolysaccharidosis II)
 - Lesch-Nyhan syndrome
 - Glucose-6-phosphate dehydrogenase deficiency
-

Holandric (Y-Linked) Inheritance

Transmitted
form male to
male



Single gene defect (3 Important Terms)

- **Expressivity:**
 - Is the ability of the gene to express itself in different individuals
 - **Penetrance:**
 - Is the ability of the gene to produce its effect in every generation (i.e. the ability to penetrate through generations)
 - **Sex-limited traits:**
 - Is the failure of some genes to produce its effect in one sex e.g. male pattern baldness
-

Genetic Imprinting

- Genomic imprinting – Is the modification of the genetic expression depending on whether the inherited gene is paternally or maternally derived
 - e.g. chromosome 15:
 - Paternal deletion = Prader Willi syndrome
 - Maternal deletion = Angleman's syndrome
-

Chromosomal abnormalities

- Can affect autosomes or sex chromosomes
 - May be numerical or structural abnormalities
 - Numerical abnormalities may involve gain or loss of chromosomes
 - Gain of one chromosome is termed **trisomy**, while loss of a single chromosome is termed **monosomy**
 - Autosomal monosomy is lethal to the developing individual and no cases have been reported
 - Structural abnormalities may involve deletion, inversion, duplication or translocation of a part of a chromosome
-

Non-disjunction in Sex Chromosomes

Results:

XXX Survivable with problems

XXY Survivable with problems

XYY Survivable with problems

X0 Survivable with problems

0Y Lethal

Classification of banded chromosomes and banding nomenclature

- The main banding nomenclature is based on the appearance of chromosomes after staining with one of a group of techniques which produced a series of transverse bands
 - **A band:** that part of a chromosome which is clearly distinguishable from its adjacent segments by appearing darker or lighter
 - The banding patterns of each pair are unique and stem from underlying variation in DNA structure and activity in different parts of the chromosome.
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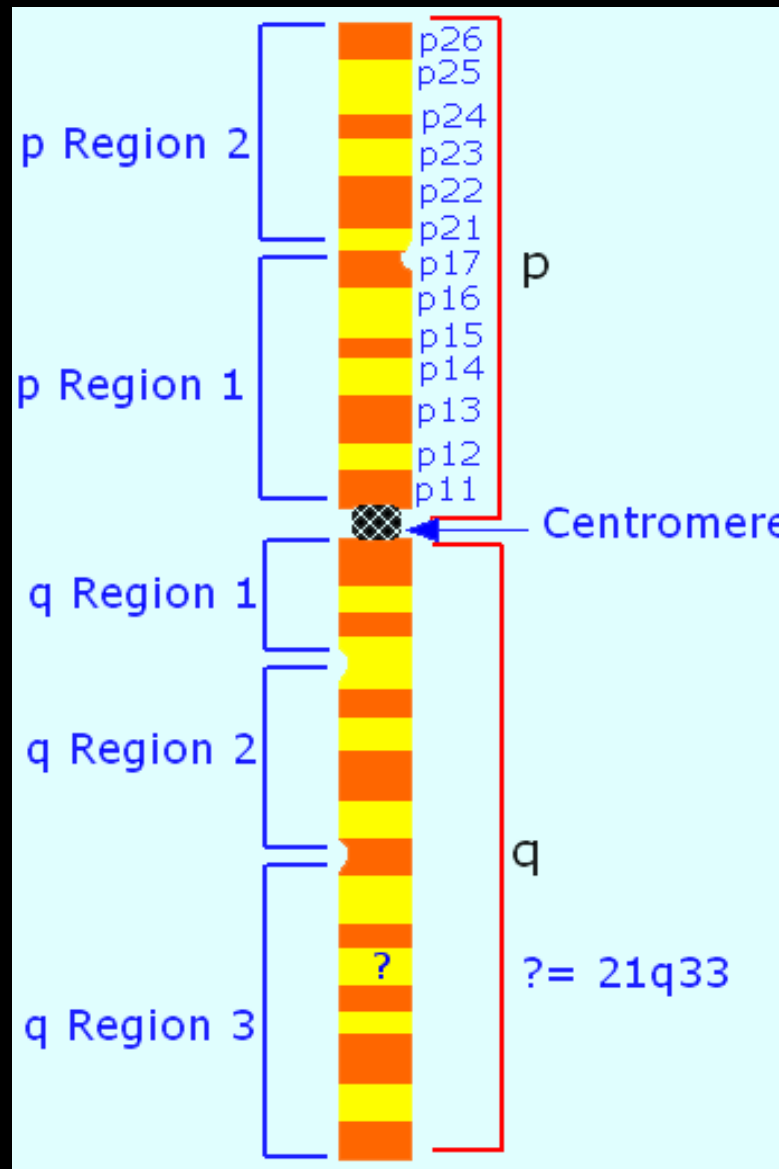
Regions and landmarks

- To divide the chromosome into convenient segments (**regions**) of roughly equal size, various fixed points or landmarks are defined along their length.
 - These landmarks are the end of chromosome (telomere), the centromere, and certain suitably-placed prominent bands.
 - Each region is numbered sequentially moving outward from the centromere, and can be define by giving the chromosome number, the arm (p or q) and region number
 - 2p2 means chromosome 2, short arm, region 2
-

Band nomenclature

- Each major band within a region is numbered in sequence with band 1 being nearest to the centromere
 - The centromere is designated as 10
 - The part facing the short arm is p10
 - The part facing the long arm is q10
 - The telomeres of the chromosome mark the ends of the short arm and the long arm are termed pter or qter respectively.
-

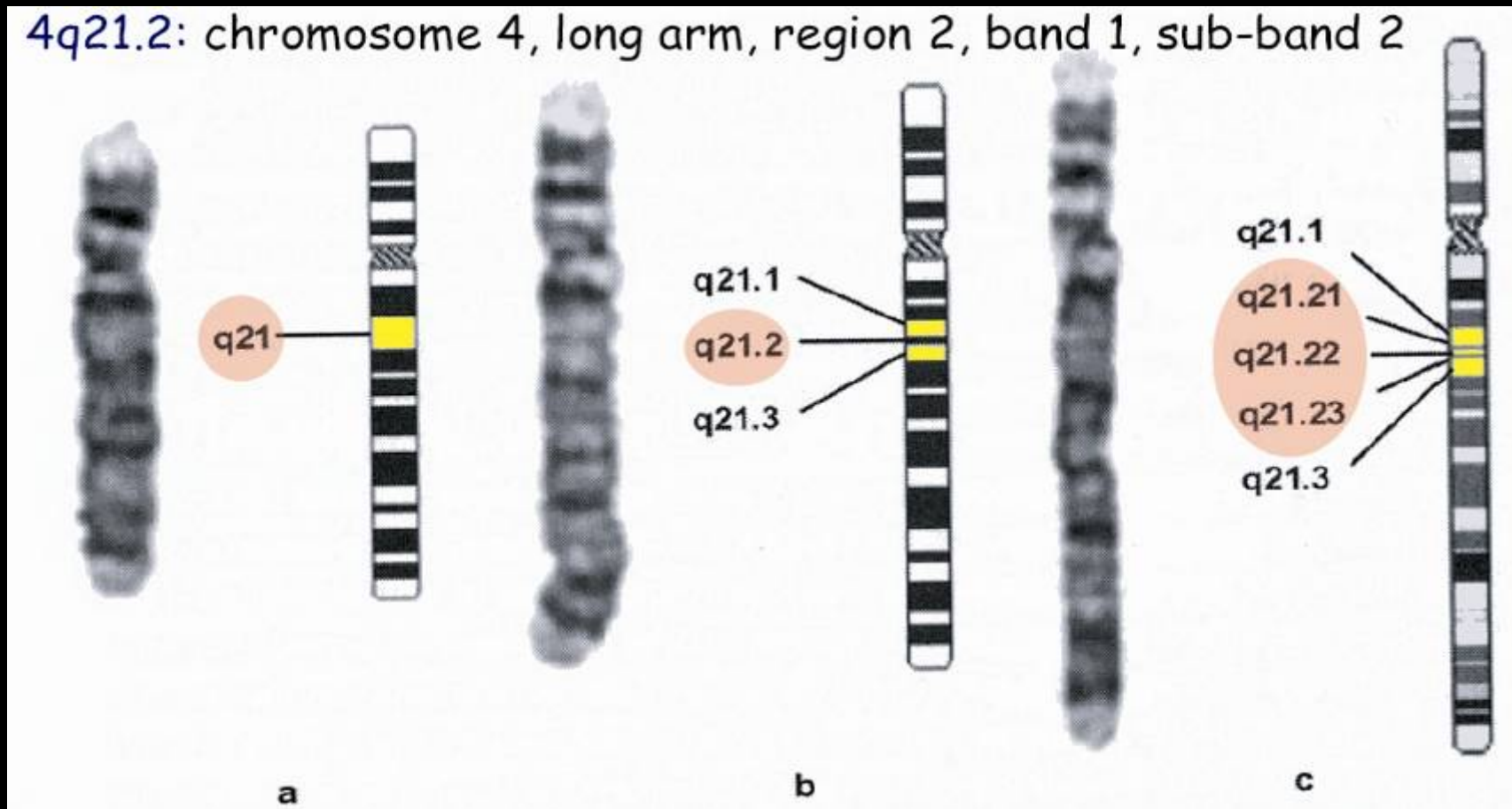
Chromosomal Nomenclature: Chromosome 21 showing landmarks, regions and band numbering



L= Landmark

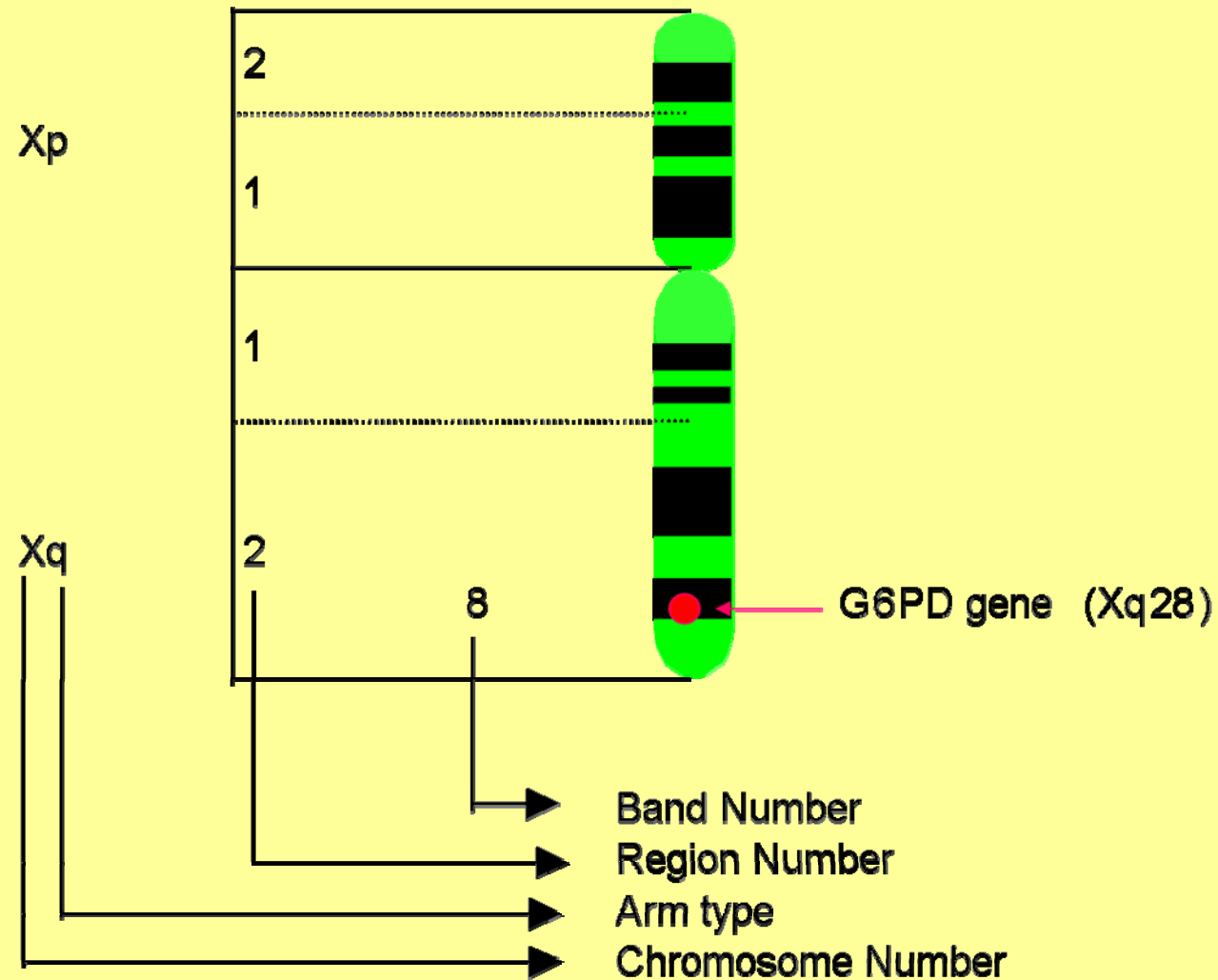
Chromosomal Nomenclature - Subbanding

4q21.2: chromosome 4, long arm, region 2, band 1, sub-band 2



Chromosome 4 shown at increasing levels of resolution approximating to: (a) 400, (b) 550, and (c) 850 bands per haploid set. Note the subdivisions of bands and sub-bands as resolution increases.

Chromosomal Nomenclature



A simplified map of the X chromosome

Multifactorial inheritance

- Do not follow the Mendelian pattern of inheritance
 - Result from the action of more than one gene and can be modified by the environmental factors
 - Many diseases follow this pattern e.g. hypertension, diabetes mellitus, rheumatoid arthritis, peptic ulcer, ischemic heart disease and cleft lip and palate
-

Environmental Diseases

- Result from the action of **teratogens**
 - Teratogens are agents which can induce developmental disturbances
 - Teratogens may be:
 - Chemicals e.g. tetracycline, fluorides, alcohol and hormones
 - Irradiation
 - Infection e.g. German measles (rubella)
 - Maternal diseases e.g. diabetes mellitus
-

Genetic make up alone does not determine the individual

- The epigenetic effect
 - The phenotype is influenced by environmental factors from the moment of conception.
 - Genes vary in their **expressivity** – how strongly a gene is expressed. There can be a wide range of phenotypes for a single genotype.
 - e.g. Neurofibromatosis
-

Genetic make up alone does not determine the individual

- Genes can vary in their **penetrance** – the likelihood that an individual with a dominant trait will show the phenotype for that allele.
 - Suppressor genes may suppress the effects of dominant harmful alleles.
 - The environment and interaction with other genes affect the expression of individual genes.
 - We cannot tell just from the genotype what the phenotype will be.
-

Genetic make up alone does not determine the individual

- A single gene may affect many traits. This is called **pleiotropy**.
 - A single trait may be influenced by many genes; these traits are **polygenic**.
 - A single gene may have multiple alleles.
 - Recessive alleles are not necessarily rare and dominant alleles are not necessarily common.
-

Human Genome Project

- Begun in 1988 completed in April 2003.
 - Genetic linkage maps of 40,000 genes allows geneticists to determine the position of any gene.
 - Physical map of each human chromosome
 - The sequence of all 3 billion base pairs on one set of human chromosomes
 - The genome sequence of several other species.
-

What good is a sequenced gene?

- It may help us understand how the gene does its damage.
 - Then we could devise a treatment for the disease.
 - Individuals can be tested for the presence of an abnormal gene.
-

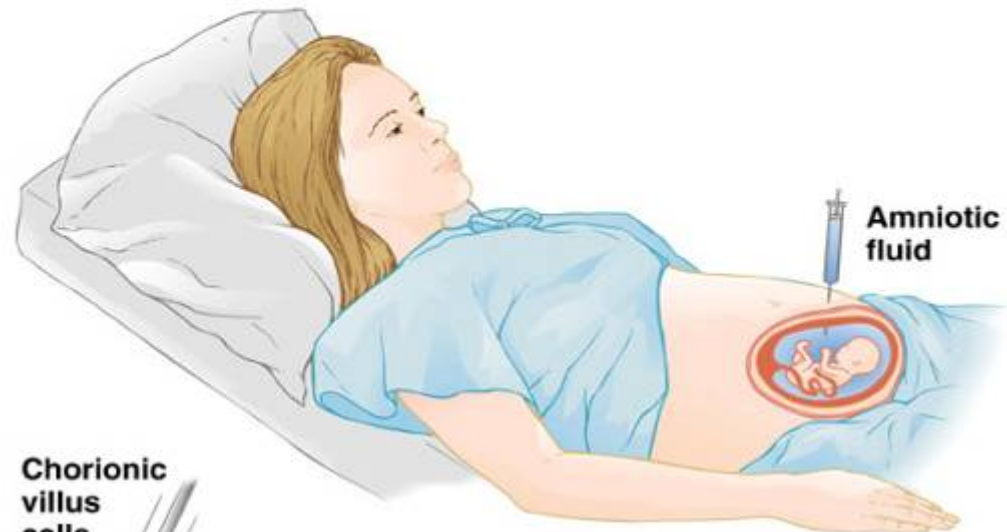
What good is a sequenced gene?

- **We can test for the alleles for more than 100 different defects.**
 - **A genetic counselor can calculate the odds that a child of a particular couple will have the defect.**
 - **We can also examine chromosomal abnormalities before birth.**
 - **Amniocentesis**
 - **Chorionic villus sampling**
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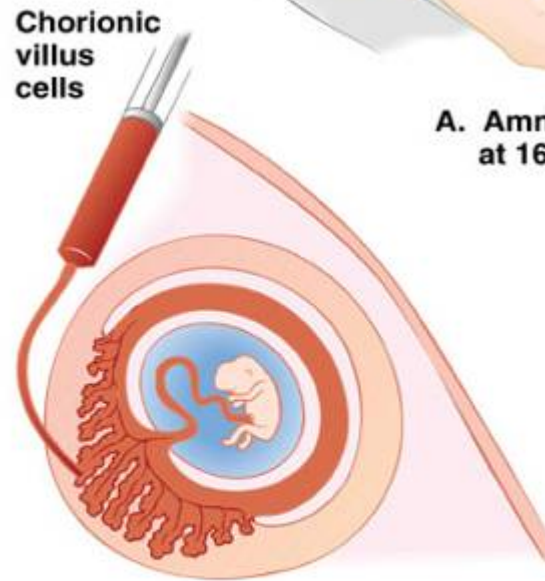
What good is a sequenced gene?

Amniocentesis is the surgical insertion of a hollow needle through the abdominal wall and into the uterus of a pregnant female to obtain amniotic fluid especially to examine the fetal chromosomes for an abnormality and for the determination of sex

Tobin/Dusheck, Asking About Life, 2/e
Figure 14.14



A. Amniocentesis
at 16 weeks



B. Chorionic villus sampling
at 6–12 weeks

DNA fingerprinting

- **Every cell that has a nucleus contains the DNA fingerprint for that individual.**
 - **Only 2% to 4% of our DNA codes for proteins.**
 - **The rest can freely mutate without causing harm.**
 - **If we took note of every base pair difference, we could identify every individual on earth, with the exception of clones (twins).**
-

DNA fingerprinting

- **There are now two ways of determining a DNA fingerprint: RFLP and PCR.**
 - **RFLP – restriction length polymorphisms**
Takes a lot of DNA and several days.
 - **We can use restriction enzymes to cut DNA into fragments, which vary in length depending on where the site is located on a chromosome.**
(Variable Number Tandem Repeats – VNTR)
 - **We can use several enzymes, or “markers”.**
The segments are separated by gel electrophoresis.
-

DNA fingerprinting

- While RFLP is more accurate, PCR can be used on very small DNA samples, even just a few strands of DNA. (But this makes it easier to contaminate).
 - PCR uses specific primers to amplify sections of DNA that contain areas of variation, and these are separated by electrophoresis.
-

DNA Ploidy

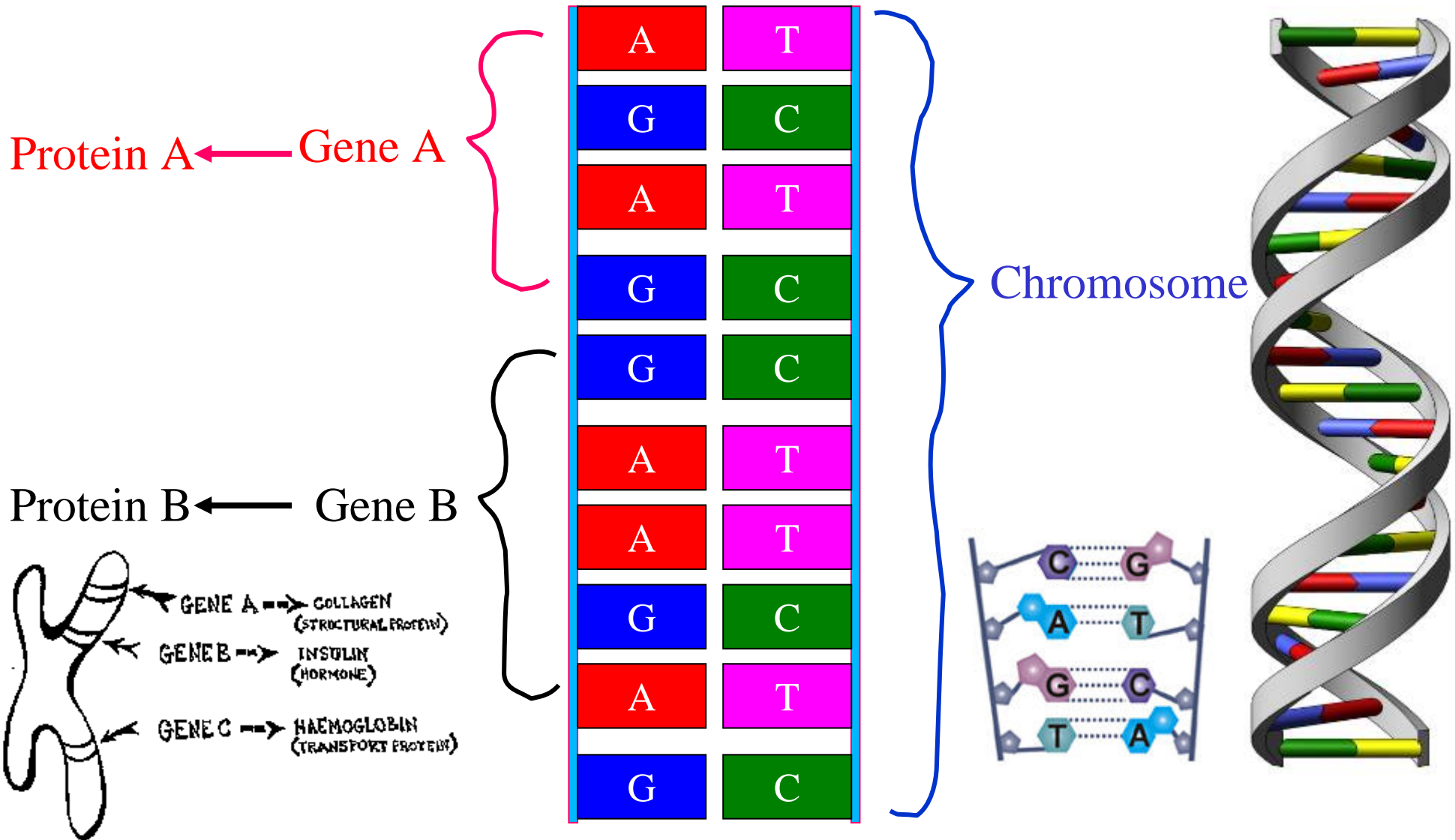
- **Ploidy** (fold): the number changes of chromosome are usually described as variations in the ploidy
 - **Euploid** (good/fold): organisms with complete, or normal, sets of chromosome
 - **Polyploid** (many/fold): organisms that carry extra sets of chromosome. **diploids = $2n$; triploid = $3n$; tetraploid = $4n$**
 - **Aneuploid** (not/good/fold): organisms in which a particular chromosome, or chromosome segment, is under- or overrepresented. Genetics imbalance
 - **Aneuploid implies a genetics imbalance, but polyploidy does not.**
 - **Chromosome rearrangements:** structure changes of chromosome, fused, inverted
-

“Seven Daughters of Eve”

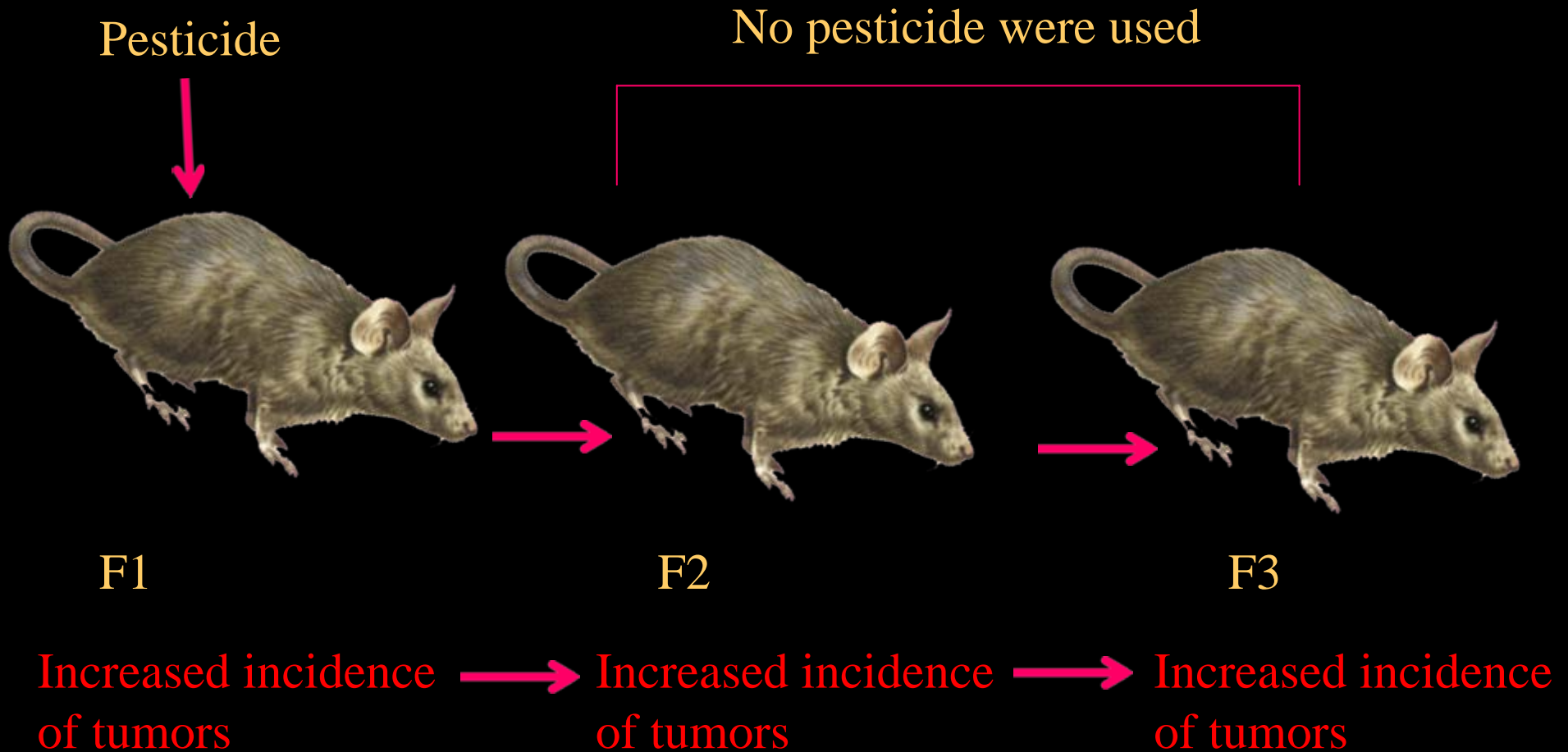
“Daughters”	Age	Origin	% of Modern Europeans
Ursula	45,000	Greece	11
Xenia	25,000	Southern Russia	6
Helena	20,000	Southern France	46
Velda	17,000	Northern Spain	5
Tara	17,000	Central Italy	9
Katrine	15,000	Northeastern Italy	6
Jasmine	10,000	Middle East	17

The fictitious names given by Bryan Sykes to the founders of the seven major European **mitochondrial** haplogroups are based on the alphabetic classification system of Antonio Torroni.

DNA Molecule, Gene, Chromosome



Epigenetic Effect



Homeobox Genes

- Provide the cell with a “memory” of its position. The cell “remembers” its original address and determination throughout an unlimited number of cell divisions.
 - This causes a cell group to change its rostral-caudal, posterior-anterior, and proximal-distal growth gradients, resulting in asymmetry and a specific growth pattern.
-

Genetic Risk

- Absolute risk** the probability that an individual will develop a condition or trait
- Relative risk** the likelihood that an individual from one group will develop a condition in comparison to another group (usually the general population)
- Empiric risk** risk determined by observing incidence of a trait in the population
- Risk factor** a situation that alters incidence of a disease (or trait)