- **THE CELL CYCLE:**

—> The cell cycle is the sequence of events that leads to the growth and division of a cell, producing two genetically identical daughter cells. It is essential for development, growth, tissue repair, and regeneration in multicellular organisms.

—>The cell division processes responsible for the creation of new diploid cells from existing ones are termed mitosis (nuclear division) and cytokinesis (cytoplasmic division). Before dividing, a cell must duplicate its contents, including its DNA; this occurs during interphase. The alternation of mitosis and interphase is referred to as the cell cycle.

- Main Phases:

- **Interphase**: The longest phase, where the cell grows, performs normal functions, and duplicates its DNA. **Interphase is subdivided into:**
- **G1** (Gap 1): Cell grows, synthesizes RNA and proteins, and prepares for DNA replication.
- **S** (Synthesis): DNA replication occurs, producing two identical copies (sister chromatids) of each chromosome.
- **G2** (Gap 2): Cell continues to grow, repairs DNA, and prepares for mitosis.
- **M** Phase (Mitosis and Cytokinesis): The nucleus divides (mitosis), followed by division of the cytoplasm (cytokinesis), resulting in two identical daughter cells. —>the cell contains 2 identical copies of each of the 46 chromosomes, these identical chromosomes are referred to as sister chromatids. Sister chromatids often exchange material during or after the S phase, a process known as **sister chromatid exchange.**

—> The length of the cell cycle varies considerably from one cell type to another.

—>Rapidly dividing cells:

- Found in epithelial tissues (skin, intestine, lungs).
- Complete the cell cycle in a short time (e.g., -10 hours). —> Poorly dividing or non-dividing cells:
- Includes liver cells, skeletal muscle cells, and neurons.
- Divide very slowly or lose the ability to divide entirely-> spending extended periods in G0

—>**G0** Phase: Some cells exit the cycle into a resting state (G0), where they no longer divide (e.g., neurons, skeletal muscle cells).

—> The great majority of this variation is due to differences in the length of the G1 phase. When cells stop dividing for a long period, they are often said to be in the GO stage.

—> The cell must respond to extracellular stimuli" growth factors, transcription factors, and hormones" that require increased or decreased rates of division, Ex: if there is a reduction in red blood cells (RBCs) or iron (Fe), mitosis is *induced* in the bone marrow to produce more RBCs.

➔ **Regulation**: Key regulators include cyclins and **cyclin-dependent kinases** (CDKs), which prevent abnormal cell division—> so mutations in their genes or associated proteins can lead to cancer.

- Chromosomal abnormalities occur due to problems in spermatogenesis, oogenesis, and meiosis—> Errors in cell cycle regulation can lead to chromosomal abnormalities or diseases like cancer, characterized by uncontrolled cell division…

- Mitosis produces diploid cells for growth and repair, maintaining chromosome number.
- Meiosis produces gametes (sperm and egg), halving the chromosome number to ensure genetic balance in offspring.

➢ Mitosis

- Mitosis is a slow process of cell division that produces two genetically identical daughter cells with the same chromosome number as the parent cell (46 chromosomes in humans).
- It is essential for growth, tissue repair, and asexual reproduction.
- **Not all** cells divide frequently; for example, mature cardiac and skeletal muscle cells rarely undergo mitosis, whereas skin and bone marrow cells divide continuously.
- The mitotic cell cycle includes **interphase** , in interphase, the DNA replication occurs preparing the cell for mitosis, and any error here will lead to mutations.
- Mitosis is divided into **five phases**:

- **Prophase**: Chromosomes condense and become visible, nuclear envelope breaks down, spindle fibers form.
- **Prometaphase**: Nuclear envelope dissolves completely, chromosomes condense further.
- **Metaphase**: Chromosomes align at the cell's equatorial plane (metaphase plate).
- **Anaphase**: Sister chromatids separate and move to opposite poles.
- **Telophase**: Nuclear envelopes reform, chromosomes decondense, spindle fibers disappear.
- Cytokinesis follows telophase, dividing the cytoplasm to form two identical daughter cells.
- A mnemonic to remember the phases is "Please Meet Ana Today" (Prophase, Metaphase, Anaphase, Telophase).

➢ Meiosis:

- Meiosis is a specialized cell division that produces haploid gametes (sperm and eggs) from diploid precursor cells, halving the chromosome number to ensure correct chromosome number after fertilization.
- It involves two consecutive divisions: meiosis I (reduction division) and meiosis II (equational division).
- Egg + Sperm = **Zygote**, Once the zygote is formed, it then undergoes *mitosis* (growth, baby differentiation).
- In males, meiosis is a continuous process that occurs throughout their life after puberty. In females, meiosis begins during fetal development but then it pauses, until puberty, resuming during the menstrual cycle

- **Meiosis I:** often called the reduction division stage
- **Interphase I** involves DNA replication.
- **Prophase I** is characterized by chromatin condensation, homologous chromosome pairing (**synapsis**), formation of tetradsرباعيات, and crossing over العبور الجيني at *chiasmata*, introducing genetic variation. -> This process does not happen in Mitosis !

  - the chromatids of the two chromosomes intertwine.

- **bivalent** indicating two Chromosomes in the unit = **tetrad** indicating four chromatids in the unit.
    - **Metaphase I** aligns bivalents at the equatorial plane. تترتب الكروموسومات بالمنتصف
    - **Anaphase I** separates homologous chromosomes (centromeres **do not** split).

يتم سحب الكروموسومات المتماثلة وليس الكروماتيدات إلى أقطاب متقابلة من الخلية، ولا ينفصل السنترومير، أي أن الكروماتيدين يبقيان معًا

    - **Telophase I** and **cytokinesis**, The cytoplasm is divided approximately equally between the two daughter cells in male gametes, while in females, the division is **un**equal, resulting in one large egg and smaller polar bodies.
    - Meiosis II:
    - **Interphase II** is brief with **no** DNA replication **!**
    - **Prophase II** resembles mitotic prophase but with haploid نصف العددchromosomes. تتكثف الكروموسومات وتظهر الخيوط المغزلية
    - **Metaphase II** aligns chromosomes at the center.
    - **Anaphase II** separates sister chromatids.

تنفصل الكروماتيدات الشقيقة عن بعضها البعض، ويتم سحبها نحو أقطاب الخلية، الآن كل كروماتيد يصبح كروموسوماً مستقلاً .

    - **Telophase II** and **cytokinesis** produce four 4 haploid gametes in males, all four are functional sperm, while in females, one large egg and polar bodies are formed.
    - The process differs in males and females: spermatogenesis yields four equal sperm cells, while oogenesis produces one large egg and smaller polar bodies that degenerate.
- In oogenesis: the **polar body** divides into two smaller polar bodies, while the **oocyte** divides into a secondary oocyte which matures into an egg and a polar body. The polar bodies will eventually degenerate, and the one mature egg is released during ovulation.

3. Gametogenesis

- **Spermatogenesis** and **oogenesis** are detailed as the processes by which male and female gametes are formed, respectively.
- Spermatogenesis involves symmetrical cell divisions producing four sperm cells.
- Oogenesis involves **a**symmetrical divisions producing one egg and polar bodies.

  - After going through Several mitotic divisions, the spermatogonia produce **primary spermatocytes**.
    - Each primary spermatocyte, which is also diploid, undergoes *meiosis I* to produce a **pair** of **secondary spermatocytes**, each of which contains 23 double stranded chromosomes.
    - These undergo *meiosis II*, and each produces a **pair** of **spermatids** "immature sperms"that contain 23 single-stranded chromosomes‹**4** spermatids in total from one primary spermatocyte…

  - **Diploid oogonia** divide mitotically to produce primary oocytes by the third month of fetal development.
    - More than 2 million primary oocytes are formed during gestation, and these are suspended in prophase I by the time the female is born.
    - Meiosis continues only when a mature primary oocyte is **ovulated**.
    - In *meiosis 1*, the primary oocyte produces one secondary oocyte (containing the cytoplasm) and one polar body.
    - The secondary oocyte then emerges from the follicle and proceeds down the fallopian tube, with the polar body attached to it.
    - *Meiosis II* begins only if the secondary oocyte is **fertilized** by a sperm cell. If this occurs, one haploid mature ovum, containing the cytoplasm, and another haploid polar body are produced.
    -

  - When studying genetic abnormalities, you will observe that many **genetic disorders** result from "**nondisjunction**" This occurs due to one of two main reasons:
    - **Early maternal age**: If a female marries at a very young age (e.g., 14 or 15 years old), her oocytes may not be fully mature or ready for fertilization.
    - **Advanced maternal age**: If a female decides to have a child after the age of 40, her oocytes are considered significantly aged.

  - **Basic Concepts of Formal Genetics**

- Mendel's Contributions: Monogenic traits are determined by a *single gene*, as studied by Gregor Mendel. He studied traits in peas, like height and seed shape, which are determined by different alleles at individual loci. The genetic composition at these loci determines the trait.

- Principle of Segregation: قانون الفصل Sexually reproducing organisms have genes in pairs, and only one member of the pair is transmitted to offspring. Genes remain intact and distinct, without blending يعني ما بندمج جين الأم مع جين الأب . -> describes the behavior of chromosomes in meiosis.

- Principle of Independent Assortment قانون التوزيع الحر ل مندل : Genes at different loci are transmitted independently of one another. The allele transmitted at one locus doesn't affect the allele transmitted at another locus.

- Dominant and Recessive Alleles: The effect of one allele can mask another. Dominant alleles exert their effect in both homozygotes and heterozygotes, while recessive alleles are only expressed in homozygous form.

- **Concepts of Probability**

  - **Probability Definition**: The proportion of times a specific outcome occurs in a

series of events, ranging from 0 to 1. مجموع الاحتمالات يساوي واحد

-> During meiosis, one member of a chromosome pair transmitted to each sperm or egg cell. The probability that a given member of the pair will be transmitted is **½,** and the probability that the other member of the pair will be transmitted is also **½.**

هذا يشبه تمامًا رمي عملة معدنية:

- **احتمال الحصول على وجه = ½**
- **احتمال الحصول على كتابة = ½**

  - **Multiplication Rule**: The probability of obtaining a given outcome in two **independent** trials is the product of the probabilities of each outcome.

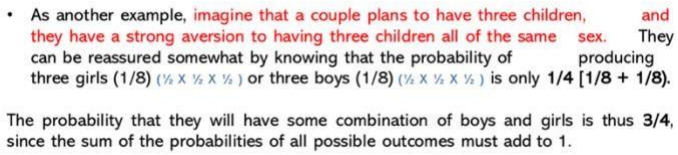
قاعدة الضرب)للتجارب المستقلة(: تستخدم عندما نريد حساب احتمال حدوث نتيجتين أو أكثر **مع** اً، بشرط أن تكون التجارب **مستقلة**)أي أن نتيجة إحداها لا تؤثر على الأخرى.(مثال: إذا كان احتمال نجاح تجربة =0.8، واحتمال نجاح تجربة أخرى مستقلة = 0.5.، فإن احتمال نجاح كلتا التجربتين معا هو:0.4=0.5* 0.8

  - **Addition Rule**: The probability of either one outcome or another occurring is the sum of their

respective probabilities.

-> in this rule we are talking about *two different* outcomes.

قاعدة الجمع: تستخدم لحساب احتمال حدوث واحدة من نتيجتين)وليس كلتاهما معاً(، بشرط أن لا تحدثا في نفس الوقت



Gene and Genotype Frequencies الطرز الجينية

- **Genotype Frequency**: Determined by **dividing** the genotype count by the total number of subjects.

مثال: إذا كان في مجموعة من 100 شخص:

- 25 شخصًا يحملون AA
- 50 شخصًا يحملون Aa
- 25 شخصًا يحملون aa

فإن تكرا رالطرازات يكون:

- AA = 25/100 = 0.25
- Aa = 50/100 = 0.50
- aa = 25/100 = 0.25

- **Gene Frequency**: Calculated by counting the number of **each** allele(a,A) in a population

and *dividing* by the total number of alleles at that locus.

هو نسبة انتشاره بين كل نسخ الجينات في المجتمع، يعني كم مرة يظهر نوع معين من الجينات)أو الأليلات(في مجموعة من الناس،، كل إنسان عنده نسختين من كل جين (واحدة من الأب وواحدة من الأم)، لذلك لما نحسب تكرار الجين، نحسب عدد الأليلات كلها، مش عدد الأشخاص .

طريقة الحساب:

1. نحسب عدد كل نوع من الأليلات مثلاً: A و a.
2. نقسم عدد كل نوع على إجمالي عدد الأليلات في المجتمع.

مثال: تخيل عندك 100 شخص، وكل شخص عنده طراز جيني لأحد الجينات كالتالي:

- 20 شخص معهم AA
- 50 شخص معهم Aa
- 30 شخص معهم aa

نحسب عدد الأليلات:

AA كل شخص معه نسختين =A نسخة 40 = 2 × 20 →A
- 50وa نسخة ،Aنسخة 50 = 1 × 50 → aونسخة A= كل شخص معه نسخة Aa
- a → 60 = 2 × 30 نسخة a= كل شخص معه نسختين aa

المجموع:

- عدد نسخ A = 40 + 50 = 90
- عدد نسخ a = 50 + 60 = 110
- مجموع الأليلات = 90 + 110 = 200

النتيجة:

- تواتر الجين A = 90 ÷ 200 = 0.45
- تواتر الجين a = 110 ÷ 200 = 0.55

Gene and Genotype Frequencies

- The prevalence of many genetic diseases can vary considerably from one population to another.
- For example, cystic fibrosis, a severe respiratory disorder, is quite common among Caucasians, affecting approximately 1/2,500 births. It is rare in Asian populations, affecting only 1/90000 births.
- Sickle cell disease is common among African-Americans, affecting approximately 1/600 births. Yet it is almost never seen among individuals of northern European descent.
- The concepts of genotype frequency and gene frequency help us to measure and; understand population variation in disease genes.

- If we have typed 200 individuals in a population for the MN blood group.
- In the MN system the effects of both alleles can be observed in the heterozygote. M and N are thus said to be codominant: the heterozygote can be distinguished from both homozygotes. Any individual in the population can have one of three possible genotypes : he or she could be

1. homozygous for M (genotype MM),
2. heterozygous (MN),
3. or homozygous for N (NN).

codominant السيادة المشتركة

يعني أن كلا الأليلين (M وN) يظهر تأثيره معاً إذا اجتمعا في الشخص بالتالي إذا كان الشخص يحمل الأليلين المختلفين (M وN)، فإن كلا البروتينين يظهران على سطح خلايا الدم.

• Gene frequencies.

- The gene frequency for each allele (one allele ≠ genotype), M and N, can be obtained here by the process of gene counting. Each : MM homozygote has two M alleles, while each heterozygote has one M allele. Similarly, NN homozygotes have two N alleles, and heterozygotes have one N allele.

- In the sample measured here, there are:

From homozygous MM • (64 X 2) + 120 = 248 M genes

From homozygous NN • (16 X 2) + 120 : 152 N genes

From heterozygous MN

- In total, there are 400 genes at the MN locus (i.e., twice the number of subjects, since each has two alleles).
- To obtain the frequency of M, we then calculate 248/400 = 0.62. The frequency of N, 152/400, is 0.38. The sum of the two frequencies must equal 1.

➢ The Hardy-Weinberg Principle

Describes the expected population frequencies of genotypes (AA, Aa, aa) based on allele frequencies (**p and q)**, assuming **random** mating = **panmixia**

- If the frequency of allele **A is p** and allele **a is q**, then the expected genotype frequencies are:
- **AA: p^2**
- **aa: q^2**
- **Aa: 2pq**

P + q = 1.

- If we suppose that the frequency, p, of allele A in our population is 0.7. Then 70% of the sperm cells in the population must have allele A, and 70% of the egg cells must have allele A.
- As p and q must sum to 1, then 30% of the egg and sperm cells must carry allele a (ie,= 0.30).
- Under panmixia, the probability that a sperm cell carrying A unites with an egg cell carrying A is given by the product of the gene frequencies: (p=0.7) so ($0.7*0.7=0.7^2 = 0.49$) $p*p= p^2 = 0.49$ (multiplication rule). This is the probability of producing
- an offspring with the AA genotype.
- Using the same reasoning, the probability of producing an offspring with the aa genotype is given by (q=0.3) so ($0.3*0.3=0.3^2 = 0.09$) $q*q=q^2=0.09$.

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- What about the frequency of heterozygotes in the population? There are two ways a heterozygote can be formed.
- Either a sperm cell carrying A can unite with an egg carrying a, or a sperm cell carrying a can unite with an egg carrying A.
- The probability of each of these two outcomes is given by the product of the gene frequencies, pq (0.7*0.3=0.21).
- To know the overall probability of obtaining a heterozygote (i.e., the first event or the second), we can apply the addition rule, adding the probabilities to obtain a heterozygote frequency of 2pq (0.42).
- These operations are summarized in Fig. 3-29.

The Phenotype

➢ **Genotypes do not uniquely correspond to phenotypes.**

" النمط الجيني لا يحدد دائمًا النمط الظاهري بشكل فريد."

- النمط الجيني (Genotype): هو التركيب الوراثي للفرد (مثلاً : AA، Aa، aa).
- النمط الظاهري (Phenotype): هو الصفات الظاهرة الناتجة عن هذا التركيب (مثل لون العين، فصيلة الدم، أو شكل الشعر...).

❖ في بعض الحالات، أكثر من نمط جيني يمكن أن يؤدي إلى نفس النمط الظاهري.

مثال: في حالة الصفة السائدة والمتنحية:

•النمط الجيني AA وAa يمكن أن يُنتجا نفس النمط الظاهري إذا كانت الصفة "A" سائدة أي أن الشخص سيبدو وكأنه يحمل "A" فقط، حتى وإن كان يحمل "a" أيضًا.

Two different genotypes, a dominant homozygote and a heterozygote, may have the same phenotype. An example would be cystic fibrosis Since the disease is recessive, an individual will be healthy when he is carrying either two normal alleles (homozygous dominant) or one normal allele and one affected allele (heterozygous). Another example, HH and Hh both genotypes have the same phenotype (tall plant)

Conversely, the same genotype may produce different phenotypes in different environments. An example of this is the recessive disease phenylketonuria (PKU), seen in approximately 1/10,000 Caucasian births.

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- Genotype refers to an individual's genetic makeup at a locus.
- Phenotype refers to the observable physical or biochemical characteristics of an individual, resulting from the **interaction of genotype and environment.**
  - Phenylketonuria (PKU): Phenylketonuria (PKU) is a genetic metabolic disorder caused by mutations in both alleles of the gene encoding the enzyme phenylalanine hydroxylase, which is necessary to break down the amino acid phenylalanine. Affected individuals (homozygotes or compound heterozygotes) cannot metabolize phenylalanine properly, leading to toxic buildup after birth.

Although babies with PKU appear normal at birth, the accumulation of phenylalanine damages the central nervous system, potentially causing severe mental retardation, with an estimated loss of 1–2 IQ points per week in untreated infants during the first year.

However, early detection through newborn screening and initiating a low-phenylalanine diet within the first month can prevent the disease phenotype. This highlights that phenotype is influenced by both genotype and environment, where "environment" includes external factors and genetic interactions at other loci.

شجرة العائلة:

Basic Pedigree Structure

- **The pedigree is one of the most commonly used tools in medical genetics.**
- Any couple may have a baby with a genetic disorder , the first step they should do is to draw the family pedigree
- It illustrates the relationships among family members, and it shows which family members are affected or unaffected by a genetic disease.
- Typically, an arrow denotes the proband,; the first individual diagnosed in the pedigree. The proband is sometimes also referred to as the index case (the study case) or propositus (proposita for females).
- **When discussing relatives in families, one often refers to degrees of relationship.**

→ First-degree relatives are those who are related at the parent-offspring or sibling (brother and sister) level.

→ Second-degree relatives are those who are removed by one additional generational "step" (e.g., grandparents and grandchildren, uncles/aunts and nieces/nephews).

→ Third-degree relatives would include, for example, first cousins, great-grandchildren, and so on.

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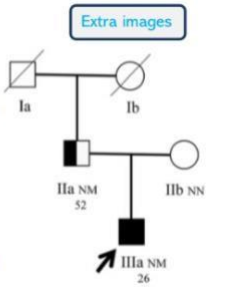

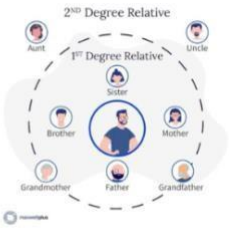

Autosomal Dominant Inheritance الوراثه الجسديه السائدة

- **Definition & Prevalence:**

Over 4,400 autosomal dominant traits are known, mostly rare diseases. A single mutated allele is sufficient to cause disease.

- **Inheritance Pattern:**
- Most commonly, an affected heterozygote (**Aa**) mates with a normal individual (**aa),** resulting in a **50%** chance for each child to inherit the disease.
- Both sexes are equally affected and can transmit the trait.
- The disease appears in every generation (**vertical transmission**) and does not skip generations.
- **Father-to-son** transmission is possible, ruling out X-linked inheritance.
- Homozygous dominant individuals are **rare** and often have **severe** disease.

- الأشخاص الذين يرثون نسختين من الجين الطافر (AA نادراً ما يُشاهدون، وغالباً تكون حالتهم شديدة أو قاتل ة

- **Example**:

Postaxial polydactyly (extra digit)ظهور إصبع زياده بعد الإصبع الصغير سواء بالقدم أو الكف is an **autosomal dominant** condition.

- **Recurrence Risk:**

Each child of an *affected heterozygote* and a *normal parent* has a 50% risk, regardless of previous children's status.

فإن الطفل الرابع لا تزال لديه نفس نسبة الخطر (50%(أن يكون مصاباً – ولا تقل النسبة أو تزيد بناءً على عدد الأطفال المصابين سابق اً

➢ **Autosomal Recessive Inheritance** الوراثه الجسديه المتنحية

- **Definition & Prevalence:**

Autosomal recessive diseases are **rare** and require both parents to be carriers for a child to be affected.

- **Inheritance Pattern:**
- Most affected individuals have carrier (heterozygote) parents. **Aa &Aa**
- Offspring distribution: 25% affected **(aa),** 50% carriers (Aa), 25% unaffected (AA).
- The disease often appears among **siblings** الأخوة من نفس الجيلbut not in previous generations (**horizontal pattern**).
- Both sexes are equally affected.
- **Consanguinity** زواج الاقارب(mating between relatives) increases risk.
- **Example**:

Albinism البرص (*tyrosinase deficiency*) is a classic autosomal recessive disorder.

- **Recurrence Risk:**

Two carrier parents have a 25% risk per child for the diseaseAa & A. If a carrier mates with an affected individual, the risk is 50% for each child Aa & aa.

Attribute	Autosomal Dominant	Autosomal Recessive
Recurrence Risk	50%	25% (carrier parents)
Transmission Pattern	Vertical (every generation)	Horizontal (siblings, not every generation)
Sex Ratio	Equal	Equal
Consanguinity	Rare	More common, especially for rare diseases
Father-to-son Transmission	Possible	Not a distinguishing feature

➢ Factors Complicating Inheritance Patterns

- **New Mutation:**

Affected child with no family history may be due to a new mutation (e.g., **achondroplasia قصر القامة الوراثي**, where 7/8 cases are new mutations). Recurrence risk for siblings is not elevated but affected child's offspring أطفال هذا المصاب may have higher risk.

- **Germline Mosaicism:**

Mutation occurs in a parent's germ cells, not somatic cells, increasing recurrence risk for future children. Seen in disorders like osteogenesis imperfecta type II, neurofibromatosis type I, DMD, and hemophilia A.

- **Delayed Age of Onset:**

Some diseases (e.g., **Huntington's disease**) manifest symptoms in adulthood, after reproductive age, allowing the gene to persist in the population.

بعض الأمراض لا تظهر إلا في سن متقدم(بعد الثلاثين)، مما يسمح بانتقال الجين المصاب دون معرفة الشخص بأنه مصاب

- **Reduced Penetrance:** النفاذية المنخفضه أو القابليه غير الكامله على الظهور

Not all individuals with a disease genotype show symptoms (e.g., **retinoblastoma** has 90% penetrance).

نسبة النفاذية = 90%، هذا يعني أن 10% من الأشخاص الذين لديهم الطفرة لا تظهر عليهم الأعراض أبداً.

خلاصه: عندك الجين، بس ما عندك أعراض وهي أحد الأسباب اللي تخلي بعض الأمراض الوراثية "تتخطى" جيل وتظهر في الجيل التالي فجأة

- **Variable Expression:**

Severity of disease can vary among individuals with the same genotype (e.g., neurofibromatosis type 1), due to environmental factors, modifier genes, or different mutations (allelic heterogeneity).

المرض قد يظهر بشدة مختلفة من شخص لآخ ر حتى وإن كان لديهم نفس الطفرة الجينية. مثال: التليف العصبي النوع الأول)NF1(، البعض قد يكون لديه بقع جلدية فقط، وآخرون أورام عديدة، السبب: تفاعل مع الجينات الأخرى أو البيئة أو أنواع
مختلفة من الطفرات في نفس الجين) تغاير أليلي - allelic heterogeneity(

- **Pleiotropy and Heterogeneity:**
- *Pleiotropy* تعدد التأثيرات الجينيه : One gene affects multiple body systems (e.g., **Marfan syndrome** affects eyes, skeleton, and cardiovascular system).
- *Allelic heterogeneity*: Different mutations in the same gene cause variable disease severity.

هي حالة تحدث عندما توجد طفرات مختلفة في نفس الجين، لكنها تؤدي إلى نفس المرض أو إلى درجات مختلفة من شدة المرض

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1. Chromosomal Basics

- Humans have 46 chromosomes: 22 pairs of autosomes and 1 pair of sex chromosomes (XX in females, XY in males).
- The X chromosome is large (~155 Mb, ~1,100 genes), while the Y chromosome is much smaller (~60 Mb, few dozen genes) and contains genes crucial for male development (e.g., SRY gene).

2. X Inactivation (Lyon Hypothesis)

- Females have two X chromosomes; to balance gene expression with males (who have one X), one X chromosome in each female somatic cell is randomly **inactivated** early in embryonic development.
- This process is called **dosage compensation**, resulting in females being genetic mosaics for X-linked genes. Males, with only one X, are hemizygous and do not undergo inactivation.
- The **inactivated X** appears as a Barr body in the nucleus.

- X inactivation is random but fixed in cell lineages, so tissues are mosaics of cells with either the maternal or paternal X active. سواء وُرّث من الأم أو الأب

- Some genes on the X chromosome escape inactivation, particularly at the tips, which are important for chromosomal alignment during meiosis.

3. Evidence for X Inactivation ادله التعطيل

- Phenotypic mosaics in female animals (e.g., calico cats, dappled mice) and patchy manifestations in human X-linked traits (e.g., ocular albinism).

- Biochemical evidence: Heterozygous females for certain X-linked enzymes (like **G6PD**) have cells expressing only one variant.

- الإناث الحاملات لطفرة في إنزيم معين على X مثل G6PD يكون لديهن نوعان من الخلايا، بعضها يُظهر النسخة الطافرة، وبعضها يُظهر النسخة الطبيعية، وهذا يُثبت أن كل خلية تعُبر فقط عن واحد من كروموسومي X

- Barr bodies are visible in female cells, not in males.

4. Mechanism of X Inactivation الآليه

- Initiated at the X inactivation center (**XIST gene**), which produces an RNA that coats the X chromosome, leading to its **condensation** and **inactivation**.

- Inactivation involves **DNA methylation** and **histone deacetylation.**

- Barr body count is always one less than the number of X chromosomes (e.g., XX = 1, XXX = 2, XY = 0, XXY متلازمة كلاينفلت ر= 1).

1.نقطة البداية - مركز التعطيل->

يوجد جين يُسمى XIST على الكروموسوم X, هذا الجين لا يُترجم إلى بروتين، بل يُنتج RNA غير مشفر (non-coding RNA). هذا الـRNA يلتصق بالكروموسوم X الذي سيتم تعطيله، ويغلفه بالكامل.

2.التعديلات على الكروموسوم

- تثُبتّ DNA (methylation): يحصل تكثيف (Condensation) للكروموسوم، ويُصبح غير نشط وظيفيًا، يترافق ذلك مع: حالة التعطيل، نزع الأسيتيل من الهستونات يجعل الكروموسوم أقل قدرة على التفعيل الجيني

5. X-Linked Recessive المتنحيةInheritance

- Examples: Hemophilia A, Duchenne muscular dystrophy DMD, red-green color blindness.

- Males (hemizygous) are more frequently affected; females must inherit two copies of the mutant allele to be affected.
- Disease frequency in males = gene frequency **(q);** in females = $\mathbf{q^2}$ (much rarer).
- Fathers cannot pass X-linked traits to sons; affected fathers pass the allele to all daughters (who become carriers if mother is normal).
- Carrier mothers have a 50% chance of passing the allele to each child.

6. Special Cases

- Manifesting heterozygotes: Some heterozygous females may express X-linked recessive diseases if X inactivation is skewed.

بعض النساء الحاملات لطفرة متنحية على الكروموسوم X قد يظهر عليهن المرض، بالرغم من أنهن من المفترض أن يكنّ غير مصابات، السبب: X-inactivation)تعطيل أحد كروموسومي X(قد يكون غير عشوائي)skewed(، فيتم تعطيل X السليم في أغلب الخلايا، وتبقى الطفرة هي الفعال ة

- **Turner syndrome** (**X0**) females may manifest X-linked recessive diseases due to absence of a second X.

X-Linked Dominant Inheritance

- X-linked dominant disorders are **less common** than X-linked recessive ones.
- Examples: Hypophosphatemic rickets, incontinentia pigmenti type 1 (primarily affects females; lethal in males), and Rett syndrome (caused by **MECP2** mutations, leading to loss of gene repression and neurological symptoms).
- Females are more frequently affected due to two X chromosomes; heterozygous females usually show milder symptoms, while homozygous cases are rare and severe.
- In pedigrees, X-linked dominant inheritance can resemble autosomal dominant patterns. Affected fathers pass the trait to all daughters but not to sons; affected mothers can pass it to both sons and daughters, with a 50% chance for each child to inherit the disorder.

Fragile X Syndrome

- **Most common** inherited cause of intellectual disability تراجع عقلي , especially in **males** (1/4,000 males; 1/8,000 females).

- Caused by CGG trinucleotide repeat expansion in the **FMR1** gene, leading to hypermethylation and silencing of the gene, which prevents production of FMRP protein necessary for neural development.
- Males are more severely affected; females show milder, variable symptoms.
- "*Premutation*" alleles (50–230 repeats) can expand in subsequent generations, especially when transmitted by females.
- A related disorder, **FRAXE**, involves the **FMR2** gene and also results from CGG repeat expansion.

Y-Linked (Holandric) Inheritance نادره جدا

- The Y chromosome is small and contains few genes, including **SRY** (sex determination), spermatogenesis factors, and some housekeeping genes.
- Y-linked traits are transmitted strictly from father to son.

Sex-Limited and Sex-Influenced Traits

- **Sex-limited traits** appear only in one sex due to anatomical differences (e.g., uterine or testicular defects).

هي صفات لا تظهر إلا في أحد الجنسين فقط، حتى لو كان الجين موجود عند الجنسين. ليش؟ لأن التعبير عن الجين يعتمد على وجود أعضاء جنسية أو هرمونات معينة. مثال: العيوب في الرحم: حتى لو الجين موجود عند الذكر، ما راح يظهر لأنه ما عنده رحم، إنتاج الحليب: الجينات موجودة عند الذكر والأنثى، لكن الحليب يظهر فقط عند الإناث بعد الولادة.

- **Sex-influenced traits** (e.g., male-pattern baldness الصلع) can appear in both sexes but are more common in one; inheritance patterns differ between males and females.

هي صفات تظهر في الجنسين، لكنها تكون أوضح أو مختلفة في أحد الجنسين بسبب تأثير الهرمونات. مثال: الصلع الوراثي عند الذكور Male-pattern baldness: الذكر الذي يحمل الجين يُصاب بالصلع، الأنثى التي تحمل نفس الجين قد لا تصُاب ً أو يظهر الصلع عندها بشكل خفيف جد اً لأن هرمون التيستوستيرون عند الذكوريزيد من تأثير الجين

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1. X-linked and Mitochondrial Abnormalities

➢ **Hemophilia A**:

- X-linked **recessive** disorder caused by deficient or defective **factor VIII. 8**
- Affects approximately 1 in 5,000 to 1 in 10,000 males worldwide.
- Severity correlates with factor VIII levels; severe cases have <1% activity.

- Treatment involves administering factor VIII, but early methods led to viral transmissions.
- **Caused by** chromosome inversion disrupting the factor VIII gene in about 45% of severe cases.

➢ **Hemophilia B:**

- X-linked **recessive** disorder caused by a deficiency of clotting factor **IX.**
- Less common and generally less severe than hemophilia A.
- Can be treated with donor-derived factor IX.
- *Queen Victoria* was the first known carrier in the British royal lineage.

➢ **Von Willebrand Disease:**

- Autosomal **dominant** disorder with variable expression, affecting up to 1% of Caucasians. القوقازيين
- Caused by a deficiency or defect in **von Willebrand factor**, which stabilizes factor

VIII.

- Mutations in the **VWF** gene can cause a Hemophilia A-like clinical picture.

2. Clinical Cytogenetics

- Study of chromosomes at the **cellular level**, focusing on numerical and structural abnormalities.
- **Chromosomal abnormalities** are a **major cause** of intellectual disability "**mental retardation**"and pregnancy loss "**abortion الاجهاض**".
- *Numerical abnormalities* involve extra or missing chromosomes.

  ○ متلازمة داون) Down Syndrome: وجود نسخة إضافية من الكروموسوم 21)ثلاثي 21(. ○ متلازمة تيرنر: أنثى تملك X واحدة فقط)45,X . ○ متلازمة كلاينفلتر: ذكر لديه XXY بدلاً من XY

- *Structural* abnormalities include inversions, deletions, translocations, and duplications.

3. Cytogenetic Technology & Nomenclature

❖ Chromosome Banding: التلوين الشريطي للكروموسومات

- Uses spindle poisons (colchicine/colcemid) to arrest cells توقف انقسامها in metaphase لأنها تكون اكثر تكثفًا ووضوحا .
- Hypotonic solutions cause cells to swell لتسهيل رؤيتها , improving chromosome separation.
- Staining materials create unique banding patterns for each chromosome.
- Fluorescence In Situ Hybridization (FISH)
- Comparative Genomic Hybridization (CGH)
- **Euploidy**: 👇

تعني أن الخلية تحتوي على عدد صحيح من مجموعات الكروموسومات.(Diploid (2n = 46: الطبيعي في الخلايا الجسدية.(Haploid (n = 23: الطبيعي في الأمشاج)الحيوانات المنوية والبويضات(، عكسها هو **Aneuploidy**، وهي وجود عدد غير طبيعي) مثل 47 أو 45 كروموسوم(

❖ Chromosomal Analysis and Karyotyping:

- Involves collecting tissue, culturing cells, arresting them in metaphase, and staining chromosomes.

- **Karyotypes** are visual representations تمثيل صوري of chromosomes arranged by size and pattern.

- Trypsin technique with Giemsa staining produces banded appearance of chromosomes.

- Chromosomes are classified by *size*, *centromere position* (metacentricبالمنتصف, submetacentricقريب من المنتصف , acrocentricقريب من الطرف), and banding patterns.

key points

- Hemophilia A and B: X-linked recessive disorders. Hemophilia A is due to Factor VIII deficiency, while Hemophilia B is due to Factor IX deficiency. Severity varies with factor levels.

- Von Willebrand Disease: Autosomal dominant disorder caused by a deficiency or defect in von Willebrand factor, which stabilizes Factor VIII.

- Chromosome Analysis: Uses spindle poisons to arrest cells in metaphase, hypotonic solutions to swell cells, and staining to create unique banding patterns.

- Karyotyping: Visual representation of chromosomes arranged by size and pattern to detect abnormalities. Trypsin technique with Giemsa staining is used to produce banded appearance. Chromosomes are classified by size, centromere position, and banding patterns.

Chromosome Number Abnormalities

❖ Autosomal Aneuploidy

- **Aneuploidy** refers to an abnormal number of chromosomes, either a deficiency (**monosomy**) or an excess (**trisomy**). The body typically tolerates extra genetic material better than a deficit. Aneuploidy often results from nondisjunction (failure of chromosomes to separate during meiosis).

O Trisomy 21 (**Down Syndrome**):

- Karyotype: 47, XY, +21 للذكر or 47, XX, +21 للأنثى

- Clinical Presentation: Distinct facial features (low nasal root, upward slanting palpebral fissures ميل العينين لاعلى), Simian creaseخط واحد بالكف , Hypotonia ضعف بالعضلات .

- Epidemiology: Occurs in 1:800-1000 live births. Frequency increases with maternal age (especially over 35 or under 20).

- Medical Complications: Duodenal obstruction, increased risk of leukemia, structural heart defects (atrioventricular canal). Moderate to severe mental retardation is common.
    - Survival: Decreased survival rates due to heart defects. Males are usually sterile عقيم; females have a 50% risk of producing a gamete with two copies of chromosome 21.
    - Etiology: **95%** caused by **nondisjunction** during meiosis (mostly maternal contribution). Mosaicism occurs in 2-4% of live births.

- Trisomy 18 (**Edwards Syndrome**):
    - Karyotype: 47, XY, +18.
    - Epidemiology: 1 per 6,000 live births; most common chromosome abnormality in stillbirths.
    - Clinical Features: Reduced weight relative to gestational age, distinctive facial appearance, small ears, short sternum, short big toes, congenital heart defects, and marked developmental disabilities.
    - Prognosis: About 50% die within the first few weeks of life; most cannot walk.
    - Etiology: >95% have complete trisomy 18, with 90% resulting from a maternally contributed extra chromosome.

- Trisomy 13 (**Patau Syndrome**):
    - **Karyotype**: 47, XY, +13 / 47, XX , +13
    - Clinical Features: Facial clefts شقوق بالوجه (cleft lip and palate), broad nose, small eyes, polydactyly تعدد الأصابع , and significant developmental delays.
    - Prognosis: Approximately 95% die within the first year of life.
    - Etiology: 80% have full trisomy 13; most cases involve translocation. Risk increases with advanced maternal age.
    - **Nondisjunction** and **Maternal Age**: The risk of trisomies, including Down Syndrome, increases with maternal age. This is largely attributed to the age of oocytes in older women, increasing the likelihood of nondisjunction.

Sex Chromosome Aneuploidy

-
    - Occurs in about 1 in 400 males and 1 in 650 females. Generally less severe than autosomal aneuploidies due to X inactivation. All sex chromosome aneuploidies, except for the complete absence of X chromosome material, are compatible with survival.

➢ Monosomy X (**Turner Syndrome**): تيرنر

- Karyotype: 45, X or 45, XO.
- Clinical Features: Proportionate short stature, sexual infantilism, ovarian dysgenesis غيابها , triangle-shaped face, broad "webbed" neck, broad chest, congenital heart defects, and structural kidney defects. Normal intelligence.
- Management: **Estrogen treatment** during teenage years to promote secondary sexual characteristics and prevent osteoporosis.
- Etiology: **50%** have a 45, X karyotype; 30-40% are mosaics (45,X/46,XX or 45,X/46,XY). 60-80% of cases result from the absence of a paternally derived sex chromosome. Most 45,X conceptions are lost prenatally.

➢ XX Males, XY Females, and the **Genetic Basis of Sex Determination:**

- During male meiosis, crossover occurs between the tips of the short arms of the X and Y chromosomes. The **SRY gene** (sex-determining region on the Y) initiates male development. Faulty crossover can result in XX males (with the SRY gene on the X chromosome) or XY females (with the SRY gene missing from the Y chromosome).
- SRY encodes a transcription factor that interacts with other genes to initiate the development of the undifferentiated embryo into a male by the secretion of müllerian-inhibiting substance.
- The protein product of SRY binds to an enhancer element that regulates expression of the **SOX9 gene**, which in turn regulates a series of genes that promote male development while repressing ovarian developmentتوقف تطور المبايض

Abnormalities of Chromosome Structure

❖ **Types:**

Abnormalities can be **unbalanced غير متوازنه** (deletion or duplication of genetic material) or **balanced** (exchange of segments between two chromosomes).

->*Unbalanced abnormalities* typically result in genetic diseases with severe clinical presentations, while *balanced abnormalities* usually do not cause genetic diseases. These abnormalities occur due to improper homologous chromosome alignment during meiosis or chromosome breakage during meiosis or mitosis, influenced by factors like ionizing radiation, viral infections, and certain chemicals (Clastogens).

❖ Translocations :

These involve the interchange of genetic material between **non**homologous chromosomes. **Balanced** translocations are of two types: reciprocal and Robertsonian.

○ Reciprocal Translocations

Breaks occur in two different chromosomes, and material is mutually exchanged, with **no** net loss or gain of genetic material. Carriers are usually **un**affected لا تظهر أعراض, but their offspring جيلهم can have normal karyotypes, carry the translocation, **or** have duplications or deletions of genetic material -> leading to potential developmental issues. ➢ **Robertsonian Translocations**

The short arms of two **non**homologous chromosomes are lost, and the long arms fuse at the centromere. This typically involves chromosomes 13, 14, 15, 21, and 22. Carriers are phenotypically normal دون اعراض with 45 chromosomes but may pass on missing or extra long arms to their offspring. Gamete segregation during meiosis can result in normal, balanced translocation carriers, **or** unbalanced combinations leading to conditions like **translocation Down syndrome** or **monosomies** فقدان كروموسوم أو جزء منه .

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