Genetics

Subject : Genetic diseases

Lec no : 26

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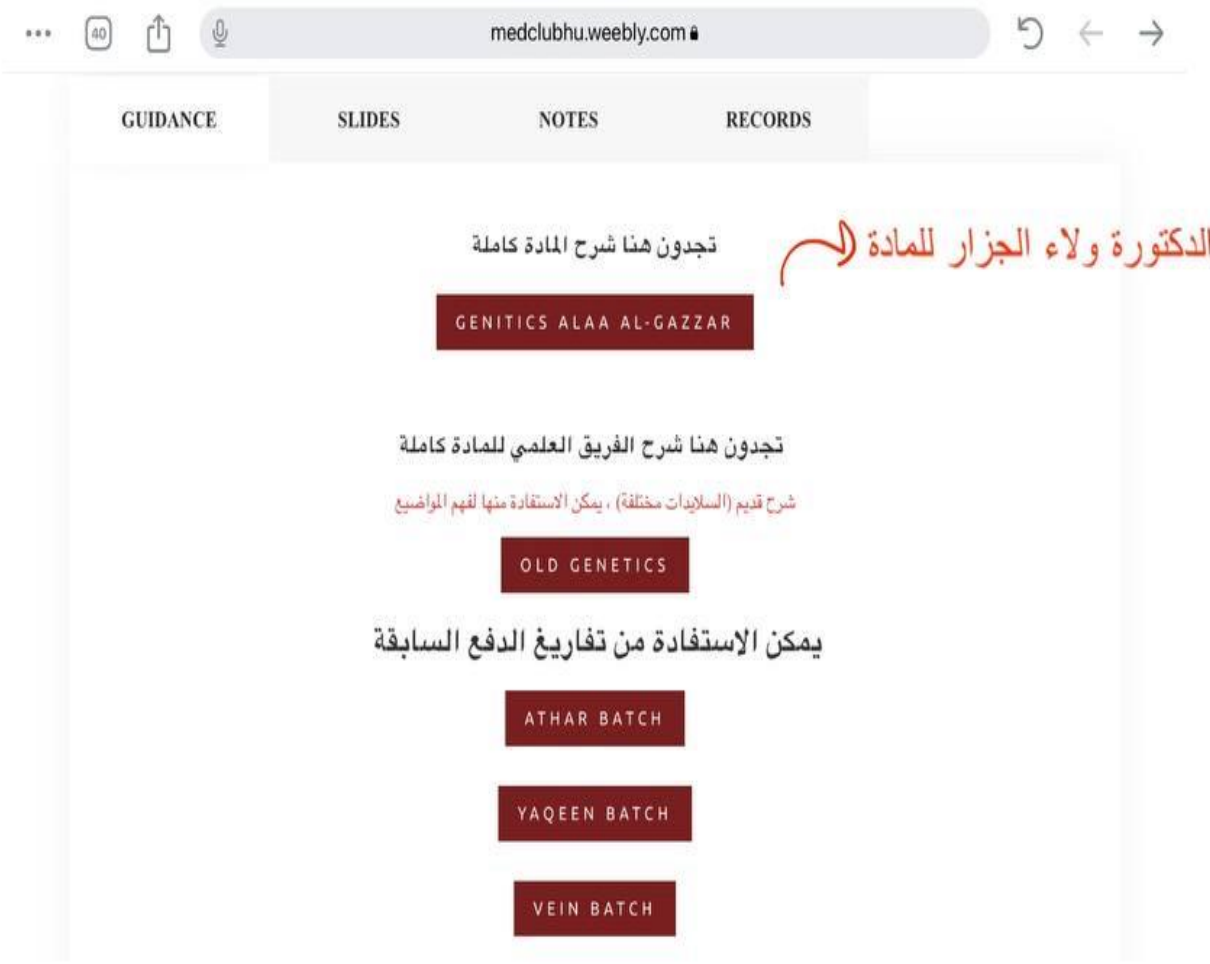
وَقُل رَّبِّ زِدْنِي عِلْمًا

تجدون في guidance مادة الجينتكس على موقع النادي :

للوصول الى guidance الجينتكس و تفاريغ المادة كاملة :



شرح الدكتورة ولاء الجزار للمادة

كل اعمال الفريق العلمي تنشر على قناة التيليغرام

* بالمحاضرة الماضية حكينا عن ال diseases الناتجة من تغيرات في عدد الكروموسومات ، اما بمحاضرة اليوم رح نحكي عن التغيرات الي بتصير في تركيب الكروموسومات

Chromosome structural changes

- Deletions
- Duplications
- Inversions
- Translocations

أخدنا بالمحاضرات السابقة عن أنواع ال mutations

Classification of mutation types

هون التغير ببين على شكل الكروموسوم

Mutations in the structure of genes can be classified as:

1. **Large scale mutations** in chromosomal structure
2. **Small scale mutations** affecting a small gene in one or a few nucleotides

Deletions

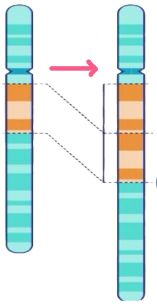
وسموه هيك لأنه الأطفال المصابين فيه اول ما ينولدو بكون صوت عياطهم زي صوت البسس 😃

إسم فرنسي معناه (Scream of the cat)

Short arm of chromosome 5

- In humans, **cri-du-chat syndrome**, also known as chromosome 5p deletion syndrome, is a rare genetic disorder due to a missing part (deletion) of the short arm of chromosome 5. The symptoms of this deletion, include severe mental retardation and an abnormally small head.

مشكلة هاد المرض انه الكروموسوم رقم 5 ال p arm تبعته بكون فيها جزء مفقود



Duplications

بهاد المرض صار في تكرار لعدد ال trinucleotide الي هو CGG في ال 5' untranslated region

عبارة عن nucleotides ما الها علاقة بال protein إنما الها علاقة بتنظيم ال gene expression

- **Fragile X syndrome** is a genetic disorder which occurs as a result of a **mutation of the fragile x mental retardation 1 (FMR1) gene on the X chromosome**, most commonly an increase in the number of CGG trinucleotide repeats in the 5' untranslated region of FMR1
- In unaffected individuals, the FMR1 gene contains 5–44 repeats of the sequence CGG, most commonly 29 or 30 repeats.

* الطبيعي انه ال CGG متكرر من 5 ل 44 مرة و اغلبنا متكرر تقريباً 29 مرة أو 30 مرة

- Individuals with fragile X syndrome have a full mutation of the FMR1 allele, with over 200 CGG repeats.

* الناس المصابين بهاد المرض عندهم عدد ال CGG nucleotides وصل ل 200 و ممكن يوصل ل 400 repeats

* طيب وين المشكلة انه يصير في تكرار ، مهو بصير بال untranslated regions يعني ال protein products مش رح يتأثرو

* الفكرة انه احنا بنهتم بكل شي يعني مثلاً بال gene expression ما بنهتم فقط بال gene sequence انه يكون طبيعي ، لازم نهتم باشياء تانية لأنه هاي عبارة عن منظومة متكاملة فبنهتم بالجين و المنطقة التي تسبق الجين و هكذا عشان هيك هون ال untranslated region ما لازم يكون فيها تكرار بال CGG

- In these individuals with a repeat expansion greater than 200, there is methylation of the CGG repeat expansion and FMR1 promoter, leading to the silencing of the FMR1 gene and a lack of its protein product which is most commonly found in the brain and is essential for normal cognitive development and female reproductive function.

المشكلة هون انه وجود ال cytosine بشكل كبير رح يصيرله methylation و لما نحط ال methyl group رح يعمل turn off للجين

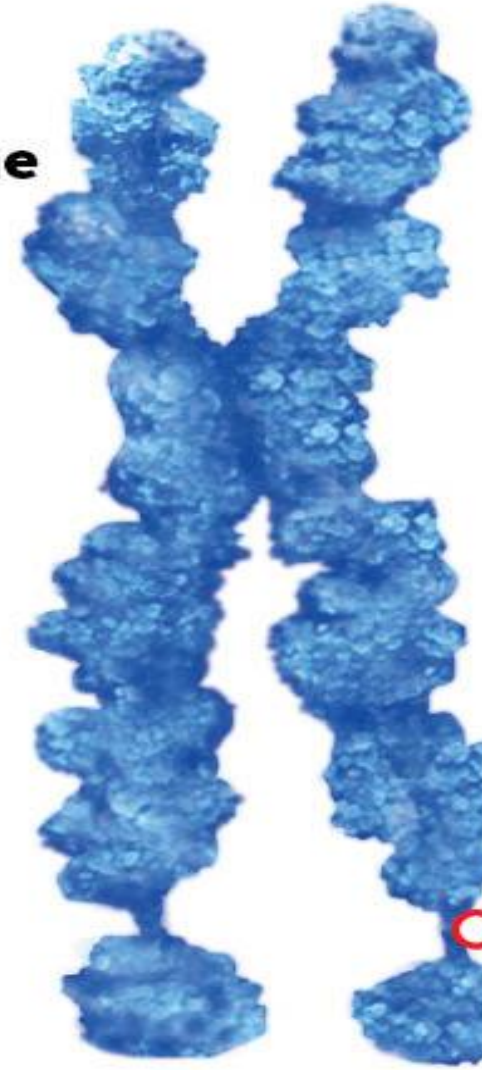
الدكتورة حكت مش مهم كثير نعرف التفاصيل عن الرقم بس اعرفو انه الكروموسوم فيه banding pattern بكون فيه مناطق فاتحة و غامقة و انه هاي الأرقام بتدل عليها و بتساعدنا نعرف إذا الكروموسوم طبيعي أو لا

- This methylation of FMR1 in chromosome band Xq27.3 is believed to result in constriction of the X chromosome which appears 'fragile' (ضعيف) under the microscope at that point, a phenomenon that gave the syndrome its name.

Long arm

An X chromosone affected by Fragile X Syndrome

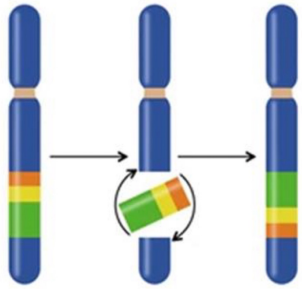
CAUSE
Trinuoleotide repeat in the FMR-1 gene on the X chromosone



APPEARANCE
Portion of chromosone X appears fragile and about to break

نتيجة ال methylation بتصير ضعيفة و سهلة الكسر

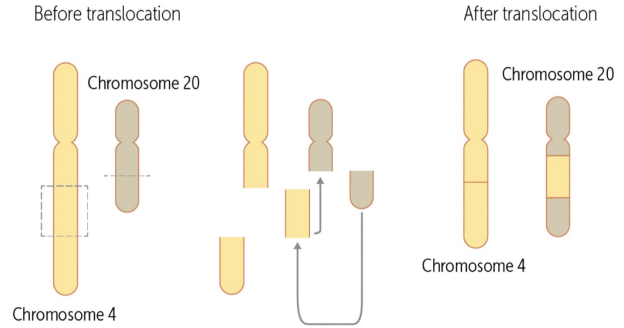
Inversions



- An inversion occurs when a chromosome breaks in two places and the region between the break rotates 180° before rejoining with the two end fragments. Inversions do not result in a gain or loss of genetic material, and they have damaging effects only if one of the chromosomal breaks occurs within an essential gene or if the function of a gene is altered by its relocation to a new place in the chromosome.

ممكن يصير ضرر من هاد التبديل مثلاً إذا صار القطع في جينات الها وظائف مهمة أو
ممكن تتغير وظيفة الجين بسبب نقله لمكان بعيد عالكروموسوم

Translocations



- 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.

تبديل بين كروموسومات 15 و 17

- Acute promyelocytic leukemia **(APL)** is caused by translocation.

BCR-ABL
9 : 22

في ال Chronic promyelocytic leukemia يصير تبديل بين كروموسومات 9 و 22

الميتوكوندريا برضه فيها مادة وراثية ممكن تتعرض لخلل معين

Mitochondrial disorders

- Mitochondria are large organelles present in all aerobic cells to use food and oxygen to make energy.

- The body uses this energy for daily function and growth.

المايتوكندريا جواها بصير oxidative phosphorylation عن طريق ال Electron transport chain

- Cells contain hundreds or thousands of mitochondria molecules; **each mitochondrion contains two to ten copies of a small circular double stranded DNA molecule that makes up approximately 1% of total cellular DNA.**

❖ The mitochondrial genome differs from the nuclear genome in the following Properties:

- The mitochondrial genome is circular, whereas the nuclear genome is linear

- The mitochondrial genome is built of 16,569 DNA base pairs, whereas the nuclear genome is made of 3.3 billion DNA base pairs.

- The mitochondrial genome contains 37 genes that encode 13 proteins, 22 tRNAs, and 2 rRNAs.

الميتوكوندريا عندها genes و ribosomes خاصين فيها

- ***Mitochondrial ribosome*** *or* ***mitoribosome*** *is a protein complex that is active in mitochondria and functions as a riboprotein for translating mitochondrial mRNAs encoded in mtDNA. Mitoribosomes, like cytoplasmic ribosomes, consist of two subunits — large (mtLSU) and small (mt-SSU)*

Mitochondrial large subunit ← Mitochondrial DNA

* ال ribosomes في الميتوكوندريا اسمهم Mitoribosomes و زي ال ribosome اللي عنا بكون عندهم large & small subunits

- A cell can contain several thousand copies of its mitochondrial genome, but only one copy of its nuclear genome.

الخلية فيها نواة و هاي النواة فيها نسخة وحدة من ال genome تبعها
بالمقابل هاي الخلية فيها مايتوكندريا كثير فبالتالي الخلية فيها اكثر
من نسخة من ال genome تبع المايتوكندريا

- The mitochondrial genome is not enveloped, and is it not packaged into chromatin.

- The mitochondrial genome contains very few noncoding DNA sequences.

- The 13 mitochondrial gene-encoded proteins are mainly involved in electron transport and oxidative phosphorylation. These proteins are inherited from the mother since the sperm has little or no mitochondria and therefore, all zygote mitochondrial DNA are mainly contributed by the ova.

ال genome في ال mitochondria بيجي بس من الام مش زي ال genome في ال nucleus بيجي نصه من الأب و النص التاني من الام

- The small mitochondrial genome is not able independently to produce all of the proteins needed for functionality; thus, mitochondria depend heavily on imported nuclear gene products to facilitate its complete functions.

البروتينات الي جاية من ال nucleus

ال gene 13 الي جايين من الميتوكوندريا و بعطو بروتينات معينة ما بكفو لكل وظائفها فبتضطر تستعين بجينات من النواة عشان تصنع بروتينات تانية مهمة و تقوم بوظائفها الكاملة

ال mitochondria اكثر عرضة للطفرات لأنه فيها مركبات ممكن تنتج ال ROS

- A mutation can cause the mitochondria to fail in their function of making energy, allowing both normal and mutated mtDNA to coexist within the patient's tissues, a condition known as **heteroplasmy**. Therefore, clinical phenotype can vary among tissues.

❑ ***Heteroplasmy*** *: the presence of more than one type of organellar genome within a cell or individual. It is an important factor in considering the severity of mitochondrial diseases.*

يعني بنلاقي جوا ال cell أشياء طبيعية و غير طبيعية

- Every human organ system can be affected, but tissues with high requirements for oxidative energy metabolism, such as muscle, heart, eye, and brain are particularly vulnerable for mitochondrial mutations.

- Most mitochondrial genetic diseases are associated with myopathies (muscular diseases) and neuropathies disorders.

* ال severity of mitochondrial disease بتبين على حسب عدد ال abnormal على ال normal فلو أغلبية ال DNA في الميتوكوندريا صارلها damage رح تكون ال severity of disease عالية

- Mitochondrial diseases are inherited from 2 types of genetic material:

- Mitochondrial DNA, which are passed on from the mother to all children حكينا انه الأم فقط بتنقل ال mitochondrial genome

- Nuclear DNA, which is passed on from both parents. Therefore ,mitochondrial disease can be inherited as:

إذا كانت الإصابة بجينات الميتوكوندريا ، رح تنقلها الأم لاولادها بس الأب ما بينقل
و إذا كانت الإصابة بجينات جاية من ال nucleus هون الأم و الأب بنقلوها لاولادهم

- **1. Maternal inheritance**

A mother with a mitochondrial DNA gene mutation will pass this abnormal gene to all of her children, but these children will be affected with different degrees of severity. The inheritance of the disease does not follow Mendelian pattern .

- **2. Autosomal recessive inheritance**
- The nuclear DNA that make part of the mitochondria is inherited from both parents (half from each parent).

- Autosomal recessive mitochondrial disease can be passed on only if both mother and father are “carriers”.

- The inheritance of the disease trait will follow Mendelian low of distribution between born children.

- **3. Autosomal Dominant inheritance**

- **4.X-linked inheritance**

الميتوكوندريا بتتوزع عال ova بطريقة عشوائية عشان هيك ال severity of disease بتختلف
من ابن لابن يعني ممكن ابن يكون عنده 10 mitochondria سليمين و الباقي defected و
ابن تاني عنده 20 defected mitochondria و الباقي سليمين و هكذا

- Some evidence suggests that mutations of mitochondrial DNA might be major contributors to the **aging process** and age-associated pathologies.
- Particularly in the context of disease, the proportion of mutant mtDNA molecules in a cell is termed heteroplasmy. The within-cell and between-cell distributions of heteroplasmy dictate the onset and severity of disease.