Genetics
& Cell biology

◉ Sheet ○ Slides

Number

8

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some of the terms that we'll be talking about are familiar some are new first term is penetrance. We talked about the autosomal dominant diseases we said if someone is heterozygous they will have the disease and will present the clinical features. In recessive you need both alleles to be mutant to have the manifestation. I will take the dominant disease one more step and talk about penetrance.

Penetrance:

simply means ALL OR NON EXPRESSION. usually refers to dominant traits in heterozygotes. In an **autosomal dominant disease** if you have the mutant allele you will manifest the clinical features. But I'm going to stretch the term more. You might have the mutation for some dominant diseases and you are supposed to manifest the clinical feature, but there are some diseases you don't. Meaning you have the mutant allele though you have **no clinical features.**

For example: lets talk about a dominant disease called retinoblastoma. Cancer in the retina by a mutation of the RB gene. It turns that in individuals carrying the mutant gene 90% will have the clinical features and 10% will look normal and wont suffer from a disease. The Penetrance in retinoblastoma by the age of 5 is 90% of individuals carrying the mutant allele are showing clinical features, They have a tumor in the eye.

If all individuals carrying a mutant gene are affected(have the clinical features) the penetrance will be 100%. Meaning every time there is a mutation there is a disease. When there is a percentage of individuals who have the mutation but don't show the disease its called **reduced penetration** and the percentage is known like RP in retinoblastoma is 90%.

Another example: in waardenburg syndrome the clinical features are known, congenital sensorineural deafness, heterochromia (each eye has a different color), displacement of the inner canthi, white forelock (the hair growing just above the forehead)and other features. Since only about 20% of people with Waardenburg syndrome are deaf, this shows reduced penetrance of this feature (deafness) of this syndrome.

if you're still lost, In some disorders there is a reduced penetrance where one mutant allele shows disease and another mutant allele doesn't show a disease.

0:00-10:00

From the slides:

- **Penetrance** refers to the all or none expression of a mutant genotype. It usually refers to dominant traits in heterozygotes, and means that even though an individual has inherited the mutant allele, there may be no expression of the phenotype. If a condition is expressed in less than 100 % of persons who have one copy of the mutant allele, it is said to have reduced penetrance.
  If a condition/feature is expressed in less than 100% of individuals who carry the responsible allele, then it is said to have reduced penetrance
- The probability of expression of the phenotype given the genotype
- Term used for dominant conditions

Variable Expressivity(حدة المرض):

• The extent to which a trait is expressed

We took an example on it and it was Neurofibromatosis and we looked at the café-au-lait spots, people you can barley see the pigmentation others the whole back is pigmented associated with the severity of the peripheral tumors. In variable expressivity there is a disease but to how extent mild, modern or severe (variable severity).

• However, it is never completely unexpressed

example: Neurofibromatosis & myotonic dystrophy

variable age of onset:

means of the same disease the features begin at different ages. Huntington disease the damage of the basal ganglia and the consequent neuro-degeneration and loss of Neuro-motor and cognition starts in the 40's average but some people present with clinical features as early as 20's, others at late as 60's.

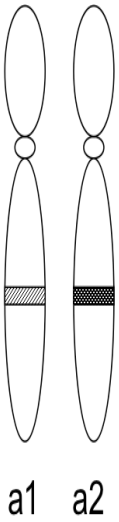
pleiotropy:

we talked about it and said it's simple gene causing multiple phenotypic effect (clinical outcome) example: *Marfan syndrome involves the skeletal, cardiovascular, and ocular systems . And *cystic fibrosis.

Genetic Heterogeneity:

means two thing, either **Allelic heterogeneous or locus heterogeneous.**

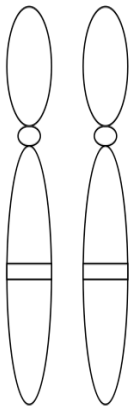
1-Allelic heterogeneity: a gene has two allele for each individuals (except the sex chromosomes). Now maybe one allele has a mutation of phenylalanine at amino acid no. 508, it causes cystic fibrosis. At the same location, same gene there might be another mutation ex: amino acid substitution between ser & arg. When your talking about this gene its mutations are Allelic heterogeneous; in a population there are different mutant alleles and types of mutations are different not a single mutation. (same gene different types of mutations in each allele = allelic).



At the CF locus on 7q
a1 = ΔF508 allele
a2 = S549R allele

Example: Duchenne and (the less severe) Becker muscular dystrophy; cystic fibrosis.

2-Locus heterogeneity: if you look at chromosome 2q, there is a gene called PAX3. And when you look at chromosome 13q, there is a gene called GJB2. If you mutate either one the consequence is the same, hearing loss. PAX3 causes autosomal dominant hearing loss and GJB2 causes autosomal recessive hearing loss. Those chromosomes are showing the genes at different loci if any is mutated causes the same consequence. (different genes, different location if mutated causes same clinical consequence).



PAX3 on 2q
Auto dom HL

GJB2 on 13q
Auto rec HL

Moving on to another topic,

Sex-limited & sex-influenced:

Sex-limited: there is a mutation but its only limited to one sex and the clinical features wont appear in the other sex. Example: Autosomal dominant male precocious puberty. (Won't appear in females even if they have the mutation).

Sex-influenced: the severity of the disease is influenced by the sex. A mutation autosomal recessive disorder known as hemochromatosis causes iron overload, the same mutation in females the outcome is less severe than in males. Why? Because, its sex influenced how? Female body physiology is in their favor: the have monthly blood loss which lowers the iron level in blood (menstrual cycle), also females in average eats less than males (less iron intake).

So far we've talked about

- Sex-linked: gene is physically on the sex chromosome and the gene could either be related to the sex or not.
- Sex-limited: refers to a phenotype that is autosomally transmitted but expressed only in one sex
  (the clinical features only appear in one sex)
- Sex-influenced: refers to autosomally inherited traits that are expressed differently, in either degree or frequency, in males and females
  (the phenotype for the same mutation is varying between males and females.)

Is the Y chromosome an example of sex-limited? (NO)

By difenition: the same mutation appears in one sex but not the other (both have the mutation but only appear in one sex). And a female doesn't have the Y chromosome.

From the slides:
- *Some disorders do not follow Mendelian patterns of inheritance.*
- *These disorders are clearly genetic (inherited) and their inheritance is classified as non-Mendelian.*
- *We now understand why some of these disorders do not follow Mendelian patterns and examples include:* ***mitochondrial inheritance, unstable trinucleotide repeats,*** *and* ***imprinting****.*

Anticipation:

A mutant allele causes a disease either homozygous recessive or dominant and we have a normal allele. Turns out there is something called dynamic mutations, means the mutation it self is changing in different generations in the family. Example: mytonic dystrophy. Dynamic mutations are unstable repeats (nucleatides di or tri that keep repeating). **Trinucleotide repeats:** These repeats might be within the same gene encoding for an amino acid so when those repeats expand and increase in number there will be more encoded amino acids. Or the repeats may not be in a coding region but in a regulatory sequence.

There is a disease on X chromosome (most common form of mental retardation in males) **"Fragile X MR Syndrome"**

10:00-21:20

What is happening in the genetic level?

In This gene we have repeats “CCG” repeated less than 50 times in normal people more than 50 times, if those repeats are more than 100 times this means that the mutation is happening and the clinical feature will appear. In Fragile X MR syndrome “CCG is repeated 200 times rathr than 50 times. It goes from 50 to 200; It’s a dynamic mutation number of repeats is expanding.

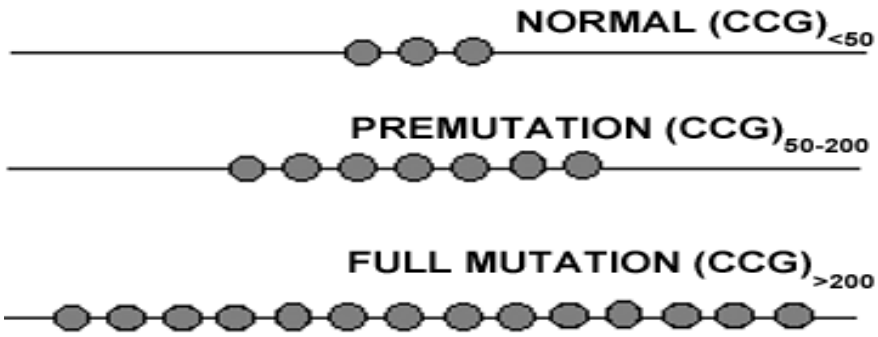
Typically people with less than 50 repeats are normal, And people with more than 50 but less than 200 are in permutation there won’t be clinical features but the problem is that, those repeats would expand (beyond 200) during the formation of gametes specifically the oocyte to a full mutation. A female with those repeats (>50 & <200) would have a higher risk of having an affected child. On the molecular level those repeats are X-linked on the X chromosome (has to do with the parent of origin). In males with this permutation the repeats won’t expand during the formation of sperms it will continue to be a permutation. Some genes like Huntington disease, it is a repeats disorder and its in a coding region (Fragile X MR syndrome is in a promoter region). In Other diseases the premutation might be maintained as a permutation in females. And expand to a full mutation during sperm formation in males.

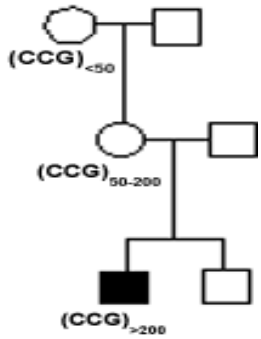
Trinucleotide Repeats

Some disorders were observed to increase in severity from one generation to another, and/or the age of onset of symptoms became earlier in successive generations.
This was termed **anticipation** and the mechanism was a mystery since mutations were presumed to be inherited in a stable manner from one generation to another.
Furthermore, in some disorders the sex of the parent who passed on the disorder seemed to influence the severity or age of onset of symptoms.
This too was a puzzle because in Mendelian traits maternal and paternal DNA was assumed to be equivalent.
Anticipation and **parent of origin** effects are now known to be due to a novel type of **dynamic mutation** known as unstable trinucleotide repeats.
Tandemly repeated trinucleotides (i.e. CGG, CTG) within or adjacent to a gene that may increase or decrease in number during formation of egg or sperm cells and thus disrupt the functioning of the gene and lead to disease
Examples:

• Fragile X Mental Retardation syndrome • Huntington disease• myotonic dystrophy• spinocerebellar ataxia• Kennedy disease• Joseph disease• Friedreich Ataxia

Example: in this case the mother has normal repeats <50 and so her egg should carry the normal sequence this is the normal scenario, what might happen abnormally is the expansion of the premutation to a full mutation. Even the affected individual carrying the full mutation their offspring (if they are able to be fertile) would have larger repeats. Causing the disease to be more deteriorated. And this is exactly what anticipation is, you can predict that the next generation will be affected and the following generation would be affected with worse clinical outcome.





Notes:

- It is NOT sex-Influenced because you will have clinical features in both male and female.
- Why Normal repeats turns into a permutation? It has to do with the alignment of chromosomes and recombination (People are bad with repeats).
  *the same reason that alignment of repeats sometime lose control during DNA replication. Remember the homologues chromosomes they align together and then recombination happens .

  a student asked: if a male carrying a permutation it will not turn into a full mutation, can it skip a generation?
  -permutation can stay in more than one generation

*when a male is carrying the permutation. He forms the sperms that will have the permutation. The egg is fertilized by the sperm and it's a female, she's carrying the permutation. Now she made an egg and that egg will be a carrying the full mutation.

- Approximately 50% of females carrying the full mutation have a milder clinical features due to X inactivation, less severe than affected males (hemizygous).
- 30% of males carrying the permutation they might have milder symptoms of FXTAS (fragile X-associated tremor/ataxia), late age of onset and mild tremor.
- females carrying the permutation have a 20% chance of developing pre-mature ovarian failure.
- The change from phenotypically normal to affected state (i.e. expansion of the trinucleotide repeats into the full mutation range) has only been observed following oogenesis NOT spermatogenesis for fragile X MR syndrome.
  Now on the protein level, when trinucleotide repeats CCG numbers expand they will be hyper-methylated (cytosine becomes methyl cytosine). This will cause gene silencing (FMR-1 gene that causes mental retardation) and it will not be expressed. Normally the product of that gene is an RNA binding protein that shuttles between the nucleus and cytoplasm. They looked at cytoskeleton of the cell, the synaptic transmission and the neurons are affected because. And gene translation is suppressed.

"Fragile X MR Syndrome"
FX MR Clinical Features

. 1. Incidence of about 1 in 5000 males; presumed incidence in females is about one-half that of males.
. 2. Most common cause of inherited mental retardation in males.
. 3. Phenotype in males includes moderate mental retardation, large head, long face, prominent forehead and chin, protruding and larger ears, large testes after puberty, speech delay, and loose joints. Behavior abnormalities include hyperactivity, hand flapping, hand biting, temper tantrums and sometimes autism spectrum disorder.
. 4. Approximately 50% of female carriers of a full mutation have retardation that is usually less severe than in affected males.
. 5. About 30% of males who carry a premutation will develop Fragile X-associated tremor/ataxia syndrome (FXTAS) which is characterized by late-

onset, progressive cerebellar ataxia and intention tremor. About 20% of females who carry a premutation will develop premature ovarian failure (POF)

Genetic Features

A. Atypical X-linked inheritance showing parent of origin effect. .

B. In affected males associated with a fragile site at Xq27.3 in 10-40% of . metaphase spreads, however, this cytogenetic testing is no longer used for diagnostic testing.

C. Amplified 'CGG' trinucleotide repeat as well as abnormal methylation . (hypermethylation) of the FMR-1 gene. The normal protein product, FMRP, is an RNA-binding protein that seems to function as a nucleocytoplasmic shuttling protein and it binds several mRNAs including its own. It also seems to affect cytoskeletal structure, synaptic transmission and neuronal maturation. The FMR-1 gene mutation results in gene silencing and the loss of function results in suppression of translation of proteins from its RNA targets.

D. Allele sizes (these categories are not absolute): - Normal alleles: 5-54 . repeats - Premutation alleles: **55-200 repeats** (not associated with MR but there is risk for FXTAS and POF; may expand to full mutation in . female carrier) - Full mutation alleles: > 200 repeats (affected individuals) .

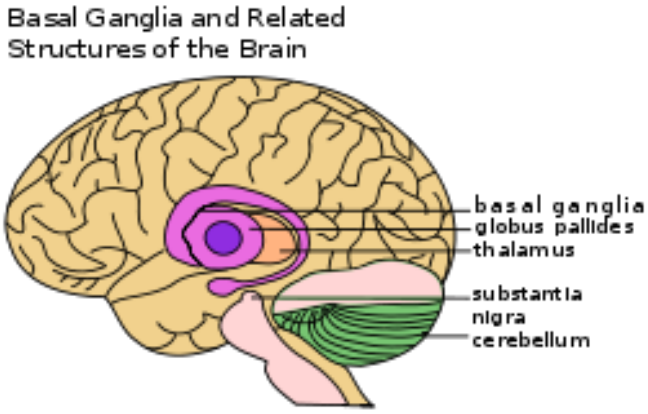
E. Existence of transmitting males who are of normal intelligence but can . transmit the Fragile X chromosome to their daughters. These daughters are of normal intelligence, however, their children are at risk for mental retardation.

F. The change from phenotypically normal to affected state (i.e. . expansion of the trinucleotide repeats into the full mutation range) has only been observed following oogenesis.

Huntington's Disease: A Late-Onset Lethal Disease

• **Huntington's disease** is a degenerative disease of the nervous system

- Autosomal dominant disorder
- The disease destroys cells in the **basal ganglia**, the part of the brain that controls movement, emotion, and cognitive ability
- The disease has no obvious phenotypic effects until the individual is about 35 to 40 years of age
- The HD gene is located on chromosome p4
- Once the deterioration of the nervous system begins the condition is irreversible and fatal.



21:20-38:00