Medical Genetics

Sheet: 9 Patterns of Inheritance

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In this sheet we'll talk about **phenotypic expression:**

1. Penetrance 2. Expressivity 3. Variable age of onset 4. Pleiotropy

5. Genetic heterogeneity 6. Sex-limited 7. Sex-influenced

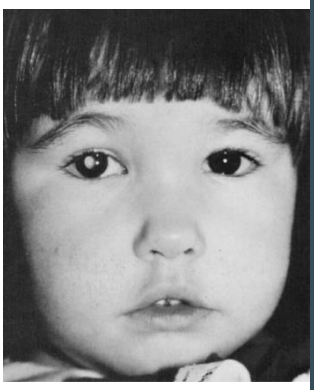
1. The first topic is **Penetrance,** which refers to <u>all or none expression of a mutant genotype</u> (there is a disease **<u>or</u>** there is no disease).

Previously, we said that in the **dominant** mutations, if the patients are **heterozygous** (they have only one mutated gene) they gonna **have the disease** (we took examples, as Huntington, familial hypercholesterolemia, etc...)

Here is what's new: There are **some dominant diseases** where a percentage of people who are **carrying the mutation** in a **dominant** gene are not showing the clinical features / **not affected** (they're supposed to be but they're not).

So, according to the probability of expression of the phenotype given the genotype, we have 2 types:

- **Fully penetrance disease**: An individual carrying the mutation will **always** have the disease.
- **Reduce penetrance diseases**: Even though the mutation exists, some people will not have the disease. Examples of **reduced** penetrance:



A. Retinoblastoma: a dominant disease caused by a mutation in the **Rb gene**, which causes a **tumor in the retina of the eye.** The penetrance is **90%.** For more explanation, let's say that we have **100 individuals carrying the mutation** (what we learned so far <u>these 100 should have the disease</u>) but it's showed that only **90** out of the 100 will **have the disease**, and the last **10** will have **normal clinical phenotype** even though they have the mutation.

B. Waardenburg syndrome: a congenital sensorineural deafness (at birth), individuals affected have heterochromia (each eye have a different color), they also have white forelock, displacement of the inner canthi, and other clinical features. In this syndrome, only 20% will be deaf. Meaning that the **penetrance** for deafness in waardenburg patient is only **20%.**

Hearing loss has 2 types:

- Conductive: If the problem is in the outer or middle ear (such as middle ear ossicles).
- **Sensorineural:** If the problem is in the inner ear like in the hair cells (it affects some signal transduction and neurons).

So, in **penetrance** the disease may appear or not (no in between), but in our next topic which is the **variable expressivity** we may have the disease but in different extents (the severity differs).

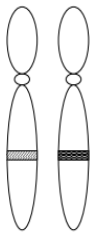
2. **Variable expressivity or variable severity**: The disease is **existing** but **the severity of it differs.** Some individuals will have minimal presentation and mild symptoms of the disease, and other individuals will have severe symptoms, Such as **myotonic dystrophy** and **neurofibromatosis type 1** (café-au-lait spots – skin pigmentation),

3. **Variable age of onset:** At **what age the symptoms of the disease start** (the variation in the time to phenotypic expression of mutant gene).
   As **Huntington**, we said that symptoms start at age of 30s (you start seeing features as stumbling of motor skills, dropping things, etc..) and the symptoms will deteriorate.
   But there are reported people with Huntington disease as early as 20s and others with symptoms delayed till the age of 60s, this is what's called variable age of onset.

4. Another term we talked about is **pleiotropy**, **one mutant gene causing multiple phenotypic effects**, as **marfan syndrome**, this syndrome involves skeletal system (they're taller than average with longer limbs), and cardiovascular as they have aortic aneurism (their aorta might rupture), and ocular system (they have displaced lens of the eye).

5. Another concept is **genetic heterogeneity**, it's either allelic heterogeneity or locus heterogeneity.
   A. **Allelic heterogeneity**: Refers to two or more **different mutant alleles** at the **same genetic locus.**

allelic heterogeneity

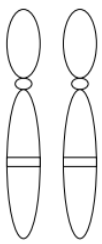


At the CF locus on 7q
a1 = ΔF508 allele
a2 = S549R allele

Examples: Duchenne and (the less severe) Becker muscular dystrophy; cystic fibrosis. Assume we're talking about **cystic fibrosis** (in the picture), maybe one mutant allele is driven by a mutation that causes a deletion in phenylalanine number 508 (a1), or maybe another allele is carrying a different type of a mutation for the same gene (a2). Also, the same person can carry 2 mutant alleles each carrying a different mutation: **compound heterozygous**.

B. **Locus heterogeneity**: When mutations at two **different genetic loci** of different chromosomes result in **similar phenotypes**.

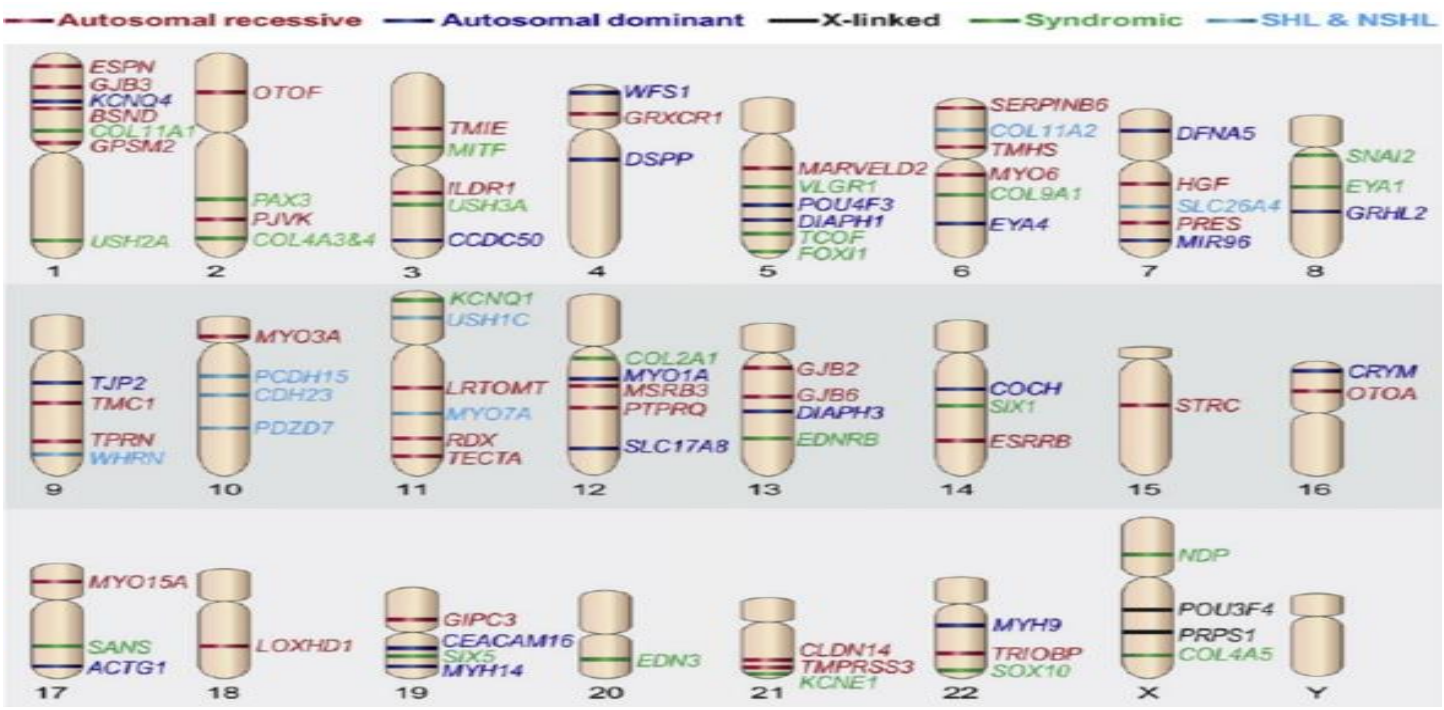
locus heterogeneity



PAX3 on 2q
Auto dom HL

GJB2 on 13q
Auto rec HL

For example in chromosome 2q there's a region carrying the gene PAX3, which if mutated causes an autosomal dominant hearing loss. Also, on gene 13q there's another region carrying GJB2, which causes autosomal recessive hearing loss. Both genes on different loci are causing the same disease (hearing loss). The mode of inheritance of disorders can vary, as in this example one is dominant & the other is recessive, but both cause the same disease.



This figure is showing many genes on different chromosomes any of them if mutated causes the same disease. This is locus heterogeneity. 10:00

We talked previously about sex-linked diseases which exist when the gene is on the sex chromosome either X or Y. We have two new other related terms:

6. **Sex-limited:** the gene and the mutation exist, the disease is **showing** in one gender but not in the other gender, typically these disease are related to sexual organs, as ovaries and testes, it's going to affect only the gender with these organs.
   For example autosomal dominant male precocious puberty.

What is the difference between Y-linked disease and sex-limited disease? Y linked disease is related to a gene that is on **Y chromosome,** in contrast to **sex-limited disease** which is present the gene that is on **an autosomal chromosome and both sexes have it but if mutated only one gender will suffer.**

7. **Sex-influenced:** the **severity** of the disease is influenced by the gender (the same gene and the same mutation **differ in the severity between males and females**)
   For example: hemochromatosis (an autosomal recessive disease that increases the absorption of the iron from the diet, which causes iron overload, leading to tissue damage) the severity of hemochromatosis is less in females than males, why? Firstly because females have menstruation (losing blood and iron), secondly the diet intake in females is lower than in males.

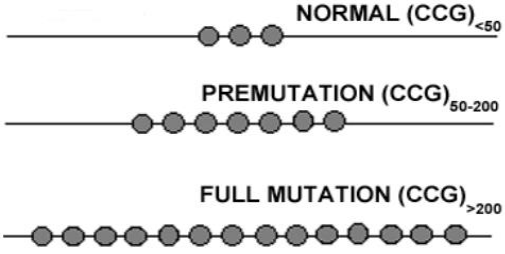
Some disorders do not follow Mendelian patterns of inheritance, these disorders are clearly genetic (inherited) and their inheritance is classified as non-Mendelian, examples include: mitochondrial inheritance, imprinting, and unstable trinucleotide repeats (our next topic).

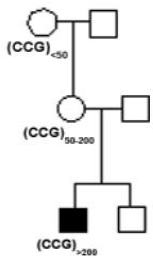
Trinucleotide repeat expansion which was termed **Anticipation** (earlier age of onset & increasing severity). Starting with an example of it: **Fragile X MR syndrome** which is the most common form of inherited mental retardation in males (Incidence: males 1 in 5000, in females is about one-half of that). This syndrome is the first guess from mental retardation in males, and those clinical features will support your guess:

- Moderate mental retardation.
- Large head (macrocephaly).
- Long face with a prominent forehead and chain.
- Protruding and large ears.
- Large testes after puberty.
- Speech delay.
- Loose joints.
- Behavioral abnormalities include: hyperactivity, hand flapping, hand biting, temper tantrums (they get mad), and sometimes autism spectrum disorder.

Anticipation has to do with repeat expansion (dynamic mutation), there is a tandemly repeated trinucleotide: CCG, which is within or adjacent to a gene. An increase or a decrease in the number of repeats during egg or sperm formation disrupts the function of the gene leading to disease

- **Normally**, the repeats are **less than 50.**
- If an individual has **more than 200** repeats this person will have a **full mutation** (affected/ mentally retarded with fragile X).
- If the number of repeats is **more than 50 and less than 200** we call this **premutation**, the premutated person is clinically normal, but (if she was a female) when she forms the eggs during the oogenesis the number of repeats in her eggs will **expand** and jump to more than 200 which will produce an offspring affected with the disease. (This expansion doesn't happen in normal repeats, only in premutation).





- If the affected offspring is a female, the repeats for the next generation will be even higher and the **repeats will expand further**, the disease will become more severe and the age of onset will be earlier, the case is deteriorating with generations, this is what anticipation is, with successive generations the severity of the disease is increasing and the age of onset is becoming earlier. 20:00
- Why we're talking about females only? In turns out that the permutation for fragile X MR only expands for full mutation in **oogenesis** not in spermatogenesis.

We mean that if there's a male carrying 150 repeats his sperms will be carrying the same number of repeats (because there's no expansion in spermatogenesis for this disease) <u>other diseases could be the opposite</u>.

Extra notes on fragile X:

- 50% of female carriers of a full mutation have mental retardation, but less severe than affected males. Why? Because of X inactivation.
- 30% of males who are carrying the premutation are not supposed to be affected, but they will develop milder features for the disease (will develop Fragile X associated tremor/ataxia syndrome (FXTAS) which is late-onset for the clinical features with progressive cerebellar ataxia and intention tremor.
- 20% of carrier females have premature ovarian failure and they're rendered infertile.

Why the number of repeats is expanding in premutation? We humans and our molecules are bad with repeats, if the number of repeats is less than 50, when I do DNA replication with all its steps (crossing-over, aligning homologous chromosomes, the combination, and the recombination, etc..) all of them occur perfectly, but **when the number of repeats increases, the mistakes start appearing in these steps.**

In conclusion, when the normal number of repeats increases to more than 50, It goes to permutation phase, in the next meiosis the number of repeats will even increase.

(1st generation: normal, 2nd: permutated, and 3rd: fully mutated & it further increases).

Unstable trinucleotide repeat expansion is involved with **dynamic mutations** or repeat expansions, individuals having fragile X MR show atypical X-linked inheritance; parent of origin effect (the premutation expands to full mutation only in oogenesis), the CGGs that are repeated when number of repeats increases this causes **abnormal methylation or hypermethylation for the gene FMR-1** → this gene is no longer expressed (silent) → now the product of gene (FMRP) is RNA-binding protein that **shuttles the protein between the nucleus and the cytoplasm**, on the cellular level it affects the cytoskeleton, synaptic transmission, and neuronal maturation.

Examples of anticipation in addition to **fragile X MR** are: **Huntington disease, myotonic dystrophy, spinocerebellar ataxia, kennedy disease, joseph disease, friedreich ataxia.** All are neurological problems that happen because of dynamic mutations which sizes increase in the successive generations due to a repeat expansion.

Myotonic dystrophy

Huntington's disease is a repeat expansion in the HD gene on chromosome 4, but those repeats are encoding for an amino acid, so the protein itself is altered structurally, this causes a neuronal damage in the basal ganglia which affects the motor movement and the cognition ability. We talked about it, it has a late age of onset and variable age of onsets.