Physiological genetics is about the mapping from

"to"

genotype → Phenotype

The nucleotide sequence of DNA

Any measurable property other than nucleotide sequence, such as

- density of functional CFTR on respiratory epithelium
- thickness of mucus on respiratory epithelium
- having cystic fibrosis

— a DNA molecule, which is packaged in a Chromosome

Gene: A segment of DNA that encodes a functional product

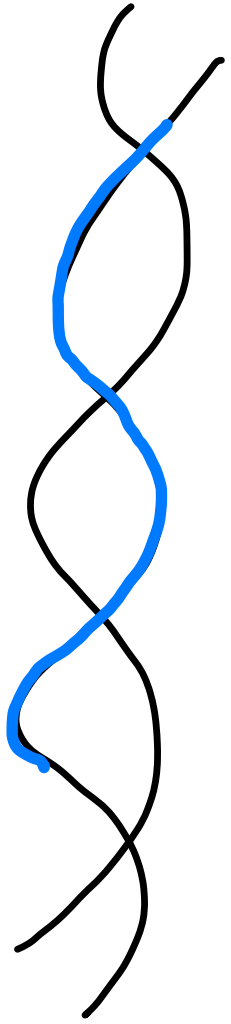
(1) the product may be an RNA or a Polypeptide

(2) "encode" means the information for the sequence of monomers (nucleotides or amino acids) in the product

(3) a gene has a discrete location, or locus, on a chromosome

(4) each gene has a regulatory region of that regulates transcription, or how much product is made. Some This regulatory region is located near the gene.

(5) This is a pretty good but not perfect definition. For example RNA viruses have RNA genes



(6) Human DNA is double stranded

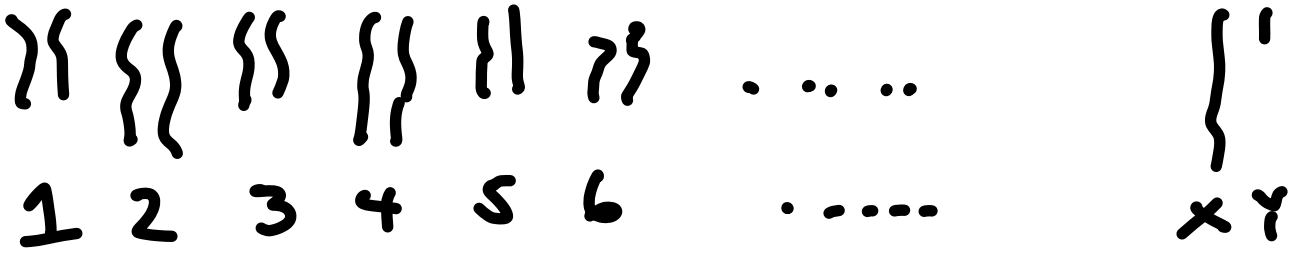
(7) Both strands can contain genes but a gene is only on one

(8) A DNA molecule is about 10^8 bases long.

(9) genes range from 1×10^3 – 40×10^3 bases long

(10) humans have about 20,000 protein coding genes

(11) most genes are nuclear (in the nucleus) but a few are mitochondrial



(12) human nuclear DNA is divided up into 22 pairs of autosomes and 1 pair of sex chromosomes

(13) A chromosome does **NOT** contain all 20,000 genes. instead the genes are divided up amon the 23 pairs

(14) w/ 20,000 genes divided up among 23 chromosomes, this means each pair has about 1000 genes

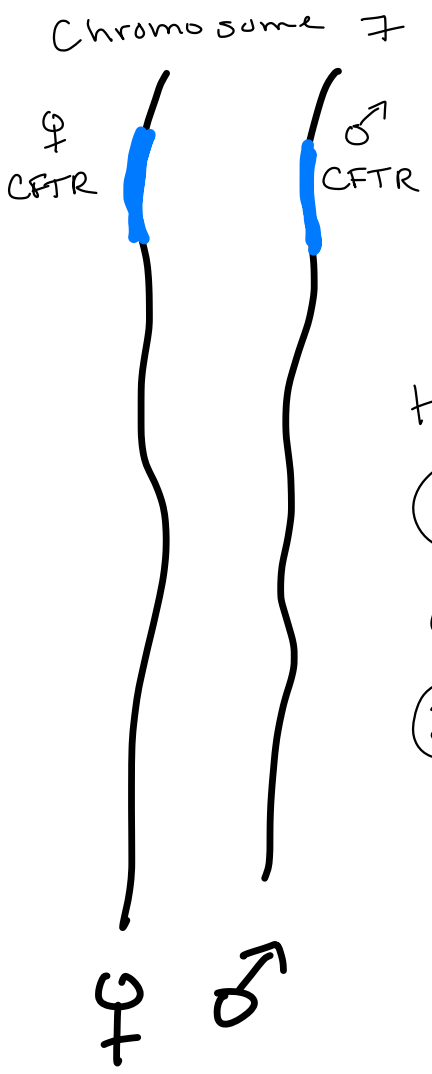
(15) The two chromosomes in a pair are homologous, which means "identical" but there are many subtle variations of usage.

(16) homologous here means that the set of genes on both chromosomes of a pair are the same.

(17) example - we each inherit a chromosome 7 from both mom (♀) and dad (♂). Each chromosome contains a copy of CFTR gene (see next page)

(18) genes are given names.

- SLC2A4 (solute carrier family 2 member 4) is on Chromosome 11 and encodes the GLUT4 protein (insulin-sensitive glucose transporter 4)
- HBA1 (hemoglobin Subunit alpha 1) is on Chromosome 16 and encodes the alpha subunit of the hemoglobin protein
- CFTR (cystic fibrosis transmembrane conductance regulator) is on Chromosome 7 and encodes the CFTR protein, which is a Cl^- channel



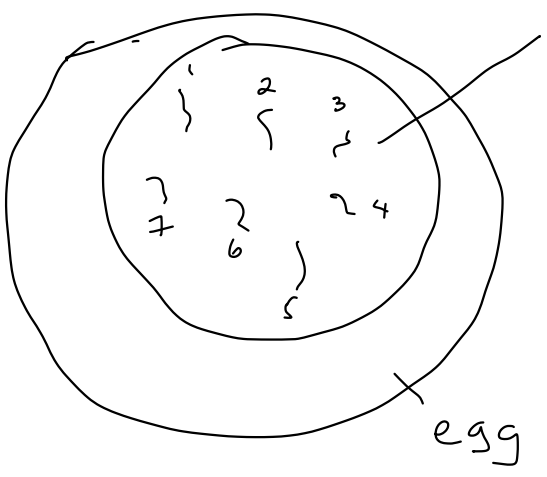
(19) The two copies of a gene are called alleleles. Here is a slightly different usage of the word "allele"

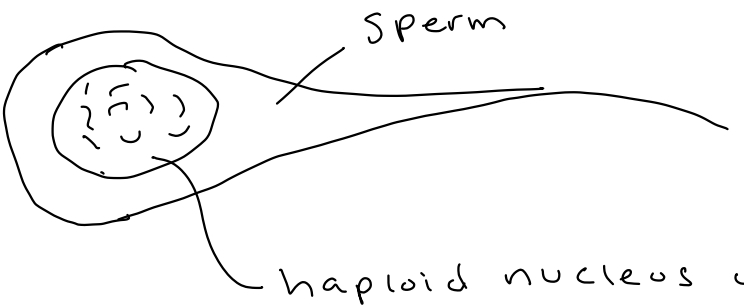
(20) An allele is a gene variant dve to a nucleotide sequence difference

(21) There are many versions (alleleles) of each of our genes within humans.

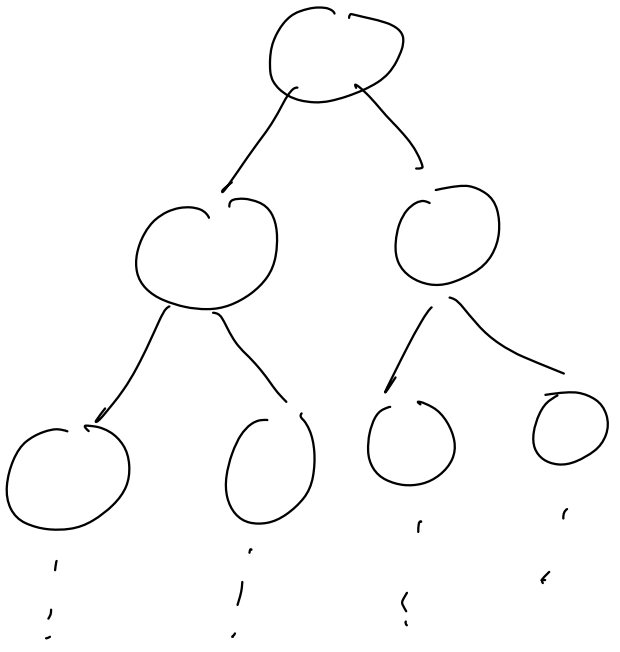
(22) The two alleleles in a single person may have the exact same nucleotide sequence, but we still say - "the two alleles"

(23) All nucleated cells in the body have the same set of 20,000 protein coding genes, and the same two versions (♀ and ♂) of each. This is why:





A Zygote is a fertilized egg. When the nuclei of the sperm and egg join, the united nucleus has 22 pairs of homologous autosomes and 1 pair of sex chromosomes



(24). The zygote divides and divides. Prior to each division the nucleus goes through mitosis; the daughter cells of each division each inherit the complete DNA of the parent, so each cell contains the same 23 pairs of chromosomes, one set that is ♀ and one set that is ♂

(25) The cell lineage differentiate into the different tissues, but every cell still contain the 23 pairs, one set from ♀ and one from ♂

Genetics of Cystic Fibrosis (CF)

(1) CF is an inherited disease with a Mendelian pattern of inheritance. It is *very simple* genetically. But very complex physiology results.

(2) Some consequences of CF include

- Thick, mucosy secretions in respiratory tubes.

Background - respiratory Epithelia secretes mucus and cilia move this mucus up to pharynx where we swallow the mucus. The mucus traps microbes, dust, pollen etc, so moves these out of resp. system to gut. In CF, the thick secretions are too viscous to move up and out. It partially obstructs airflow (making ventillation difficult) but also fails to clear Pathogens from lungs

- thick, secretions in pancreas limit delivery of digestive enzymes to intestine. This causes reduced digestion and absorption of nutrients. The secretions can also obstruct pancreatic ducts which cause fibroblasts to come in and remodel as scar tissue. This creates **fibrous cysts** in the pancreas, which is the origin of the name.

- ditto for ductus deferens. This causes sterility in males.

CFTR - Cystic fibrosis Conductance regulator gene.

The protein product is a Cl^- channel expressed in many epithelia and is also called CFTR

this is the mapping

genotype		Phenotype
+/+	→	no cystic fibrosis
+/-	→	no cystic fibrosis
-/-	→	Cystic fibrosis

A person has two alleles at the CFTR locus and each allele can be either the + allele or the - allele so these are the 3 possible genotypes

what we call the genotype	genotype	Phenotype
"homozygous +"	+/+	no cystic fibrosis
"heterozygous"	+/−	no cystic fibrosis
"homozygous −"	−/−	Cystic fibrosis

- A genotype that has two of the "same" versions is homozygous. A genotype that has two different versions is heterozygous

what we call the genotype	genotype	Phenotype
"homozygous +"	+/+	no cystic fibrosis
"heterozygous"	+/-	no cystic fibrosis
"homozygous -"	-/-	Cystic fibrosis

- The + allele is dominant for the CF trait.
  because
- A person needs to inherit **only** one copy of the + allele to have not have CF. or
- The - allele is recessive for CF, because a person needs to inherit 2 - alleles to have CF

- A Mendelian trait is a phenotype, like CF, in which there are two alleles, w/ one dominant to the other. Again "dominant" means only 1 copy is necessary to present the trait.

misconceptions

- dominant does NOT mean the most common allele
- dominant does not mean the non-disease allele

Dominance is not a property of a gene but of a specific genotype → phenotype map.

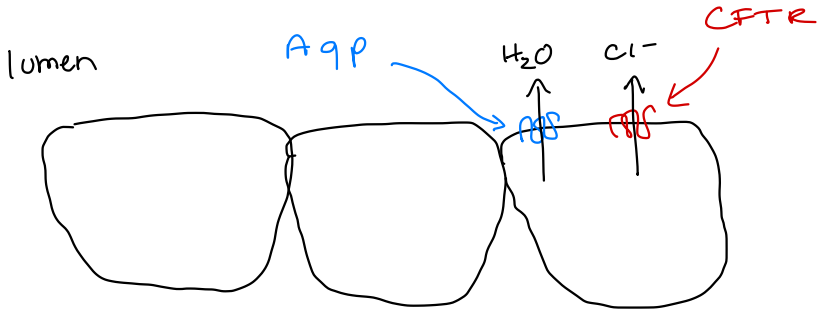
These are the two alleles:

$CFTR^+$ - produces a functional Cl^- channel

$CFTR^-$ - produces a nonfunction Cl^- channel

- I'm calling the + allele "+" because it produces a functional product!

- so a +/+ person produces only functional Cl^- transporters, a +/- person produces some dysfunctional Cl^- transporters and a -/- person produces only dysfunctional Cl^- transporters



A model for CF is Cl^- transport drives H_2O transport. if CFTR is non-functional, there is less H_2O transport and the secretion is more viscous (less flowy)

This leads us to this genotype to phenotype mapping or "pathway of gene action"

genotype	density of functional Cl^- channel	secretion	disease
+/+	high	watery	NO CF
+/−	intermediate	intermediate	NO CF
−/−	none	thick	CF

Each of these is a phenotype

genotype	density of functional Cl^- channel	secretion	disease
+/+	high	watery	NO CF
+/−	intermediate	intermediate	NO CF
−/−	none	thick	CF

a +/+ person has a high density of functional Cl^- channels and no disease. A +/− person has only an intermediate density of functional Cl^- channels, but still has no disease. Only the −/− person with no functional Cl^- channels has CF

Let's focus on disease as the Phenotype

genotype	density of functional Cl^- channel	secretion	disease
+/+	high	watery	NO CF
+/−	intermediate	intermediate	NO CF
−/−	none	thick	CF

This is a classic Mendelian trait with 3 genotypes that map to 2 phenotypes and one of the alleles is dominant (the other recessive)

genotype	density of functional Cl^- channel	secretion	disease
+/+	→ high	→ watery	→ NO CF
+/−	→ intermediate	→ intermediate	→ NO CF
−/−	→ none	→ thick	→ CF

But now looking at the mapping of genotype to secretion — there are 3 phenotypes the heterozygous genotype maps to an intermediate (kinda thick) phenotype. This is called Incomplete dominance and is **NOT** Mendelian, because **there is no dominant or recessive allele**

genotype	density of functional Cl^- channel	secretion	disease
+/+	→ high	→ watery	→ NO CF
+/−	→ intermediate	→ intermediate	→ NO CF
−/−	→ none	→ thick	→ CF

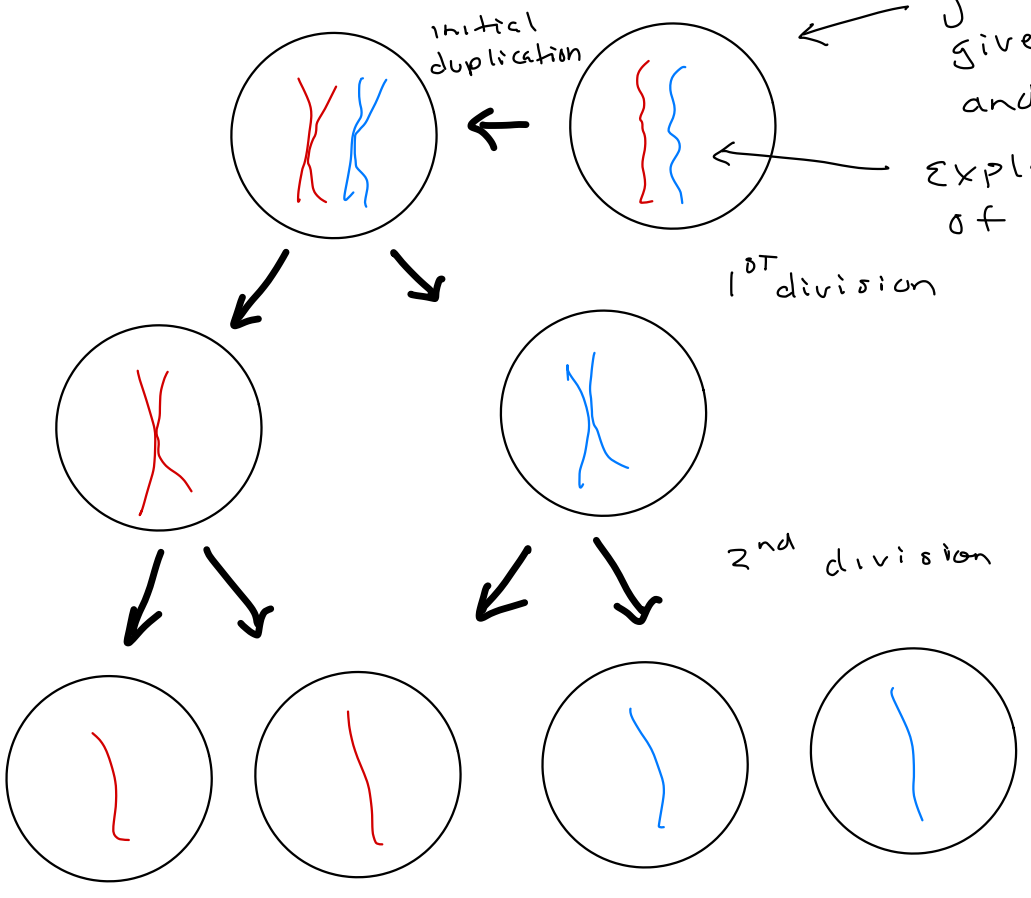
The + allele is not dominant because the heterozygous genotype maps to a different phenotype than that of +/+

The − allele is not dominant because the heterozygous genotype has a different phenotype than that of −/−

- CF is a Mendelian trait but CFTR is not a Mendelian gene. It doesn't make any sense to call a gene "Mendelian" because Mendelian applies to a specific pattern of mapping.

- That said, many people in Medicine and related fields refer to genes, such as CFTR, as "Mendelian".

Inheritance is Easy!



germ cell (a stem cell that gives rise to egg cells in females and sperm in males

Explanation using one pair of chromosomes

- ♀ (from mother)
- ♂ (from father)

- each chromosome contains 1 set of alleles, either from ♀ or ♂
- **BUT** which (♀ or ♂) will differ among chromosomes, and result is random

So a gamete (sperm or egg) inherits only 1 of the 2 alleles of each gene. The probability that the allele is ♀ or ♂ is 50% / 50%.

So a mom that is +/+ at CFTR will produce what gametes? 100% +

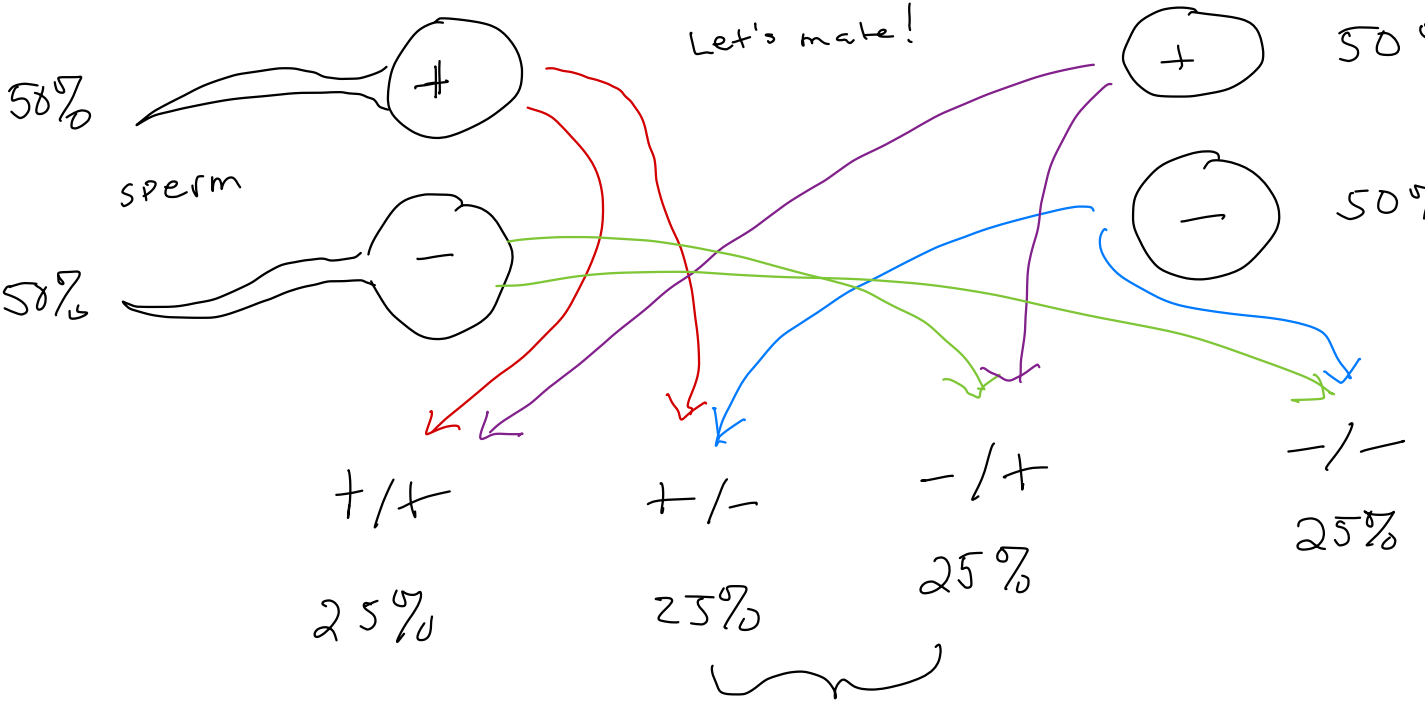
a mom that is +/− at CFTR will produce 50% + and 50% − gametes

a mom that is −/− at CFTR will produce 100% − gametes

So now let's mate gamets (sperm + egg)

+/− dad produces

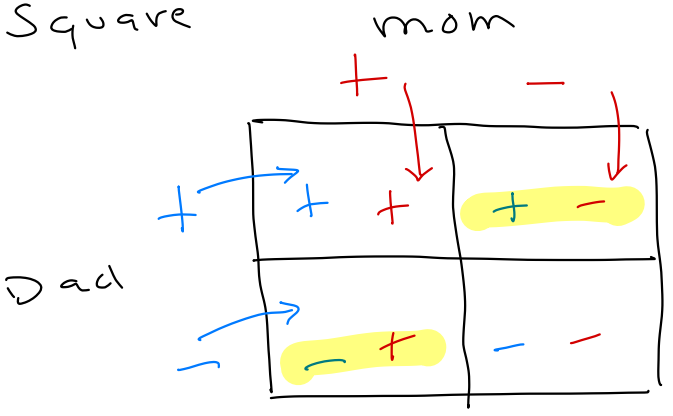
+/− mom produces



+/− and −/+ are the same genotype – it doesn't matter which parent an allele is inherited from

An easier way to do this is with ...

Punnett Square



Copy the allele down – copy to each cell in the column

The four combinations of the mom's + Dad's gametes for alleles at CFTR

Copy the allele across – copy to each cell in the row

1 of 4 (25%) combinations are +/+

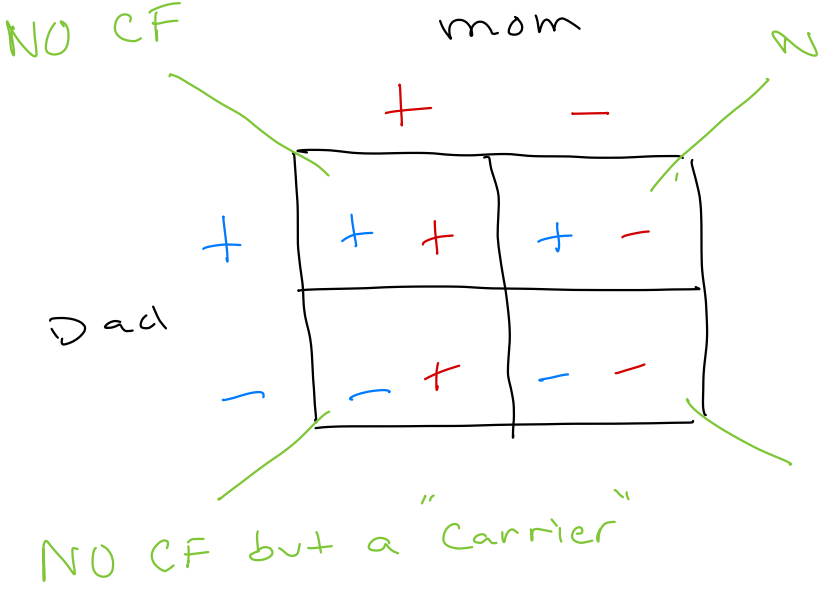
2 of 4 (50%) of combinations are +/−

1 of 4 (25%) of combinations are −/−

~~X~~ again

+/− and −/+ are the same!

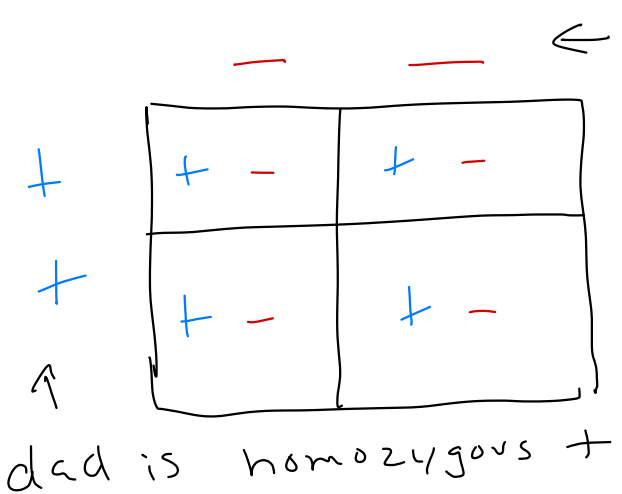
What about Phenotypes of Kids?



+/+ → No CF 25% of kids } 75% have no CF

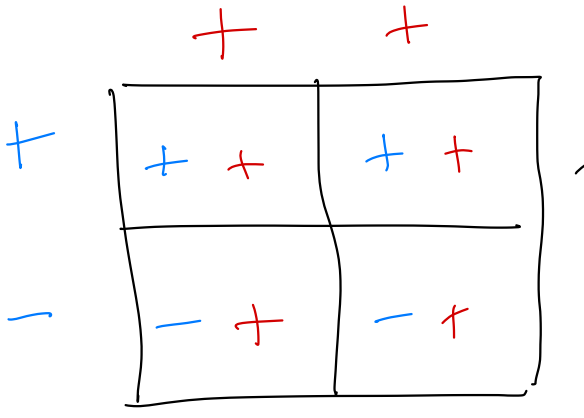
+/− → No CF 50% of kids
↳ but a carrier

−/− → CF 25% of kids



→ 100% +/−

- All are carries of recessive allele for CF
- None have CF



50% +/+

50% −/+

no CF Kids but 50% are carriers.

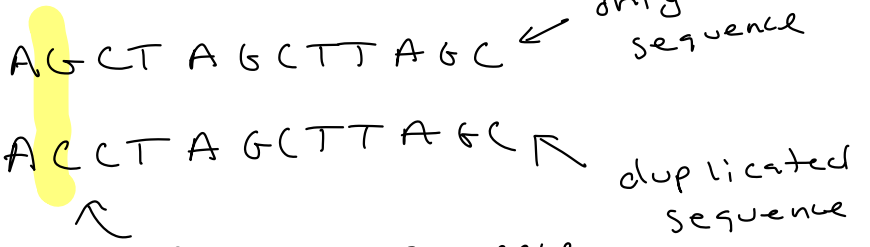
Mutation - A mutation is a change in DNA sequence

- mutations are **random**. random does not mean "uncaused." random (here) means, there is no goal or purpose of the specific mutation.
- mutations typically occur during DNA duplication prior to cell division.
- The probability of a change in nucleotide at a single spot during replication is about 10^{-8}. That is 1 in 100 million. That is pretty rare!
- But you have millions of cells dividing every day so we are constantly accumulating mutations
- most of the mutations will have zero consequence on your health An exception is Cancer. The next few pages are why.

Mutation I - Kinds of mutations

1. Point mutation

- A mutation occurring at a single nucleotide location
- gives rise to variation among humans called Single nucleotide polymorphism, abbreviated to SNP (Know what polymorphism means)



(2.) insertions and (3.) deletions

orig : ATCGGCAATCAGG

duplic: ATGCAATCAGG

- The 2 nucleotide sequen is deleted in the duplicate
- deletions can be of any lenyth

ATCGGCAATCAGG

ATCGGCAACGATCAGG

- The three nucleotide sequence has been inserted.
- insertions can be of any lenyth

There are other kinds of mutation but this is a good start

Mutations II - What are physiological consequences of mutations?

- most mutation have zero consequence because they occur in parts of the DNA that have no function or at least the function doesn't depend on sequence
  - Only ab ~2% of a DNA molecule contains genes
  - another ~2% is transcription regulation

- if a mutation occurs in a regulatory region it *might* change how much protein is made (expression level)
- if a mutation occurs in a coding region it might affect protein function

*"might" is important here

Mutations II - Why might a mutation not affect function?

1. The mutation could be at a "3rd base pair." Because of the redundancy of genetic code (and restriction of this redundancy to 3rd base pairs) a substitution of one nucleotide for another at a 3rd base pair can map to the same amino acid. So a change at nucleotide sequence level does not change AA sequence level of protein.

2. The mutation results in the substitution of an amino acid but this substitution has little affect on protein function

mutation II - What about mutations that do cause functional change?

- some SNPs and most insertions/deletions do cause functional change in the protein. Most changes are bad - the protein functions worse or not at all. Rarely, a changes makes a protein function "better." Sometimes a change makes a protein function differently. So for example a mutation may make a steroid hormone receptor less good at binding aldosterone but better at binding cortisol. is this overall bad or good? probably neither... it's bad under some conditions and good under others.

mutations II - when we can ignore mutations and when we cannot.

- most mutations are somatic - meaning they occur in no germ cells (germ cells are the stem cells that differentiate into egg or sperm).

- So say a cell in the sm intestine epithelium acquires a catastrophic mutation that destroys some function such as dipeptide transport. Well that's a tiny fraction of cells that can't do this. The mutation won't spread all along the intestine (how would it do that?) So, it's just one small set of cells that function perfectly fine except they can't transport dipeptides.

mutations III

- so typically, mutations in somatic cells don't result in major physiological issues except:

1) if the mutation occurs early in development - the earlier the worse. Why? if it's an early stem cell then many, many cells develop from this and will inherit the mutation

2) if it's a mutation that increases the probability of cell becoming tumorogenic or cancerous

- more later!)

mutations IV - germ line mutations

- a mutation in a germ cell is inherited by all future cells in this line. If the germ cell differentiates into the sperm or egg that makes a new Zygote - then every cell in the future person inherits this mutation.

Cancer.

- a mutation in a gene that regulates the cell cycle will increase the probability that the cell will become tumorogenic.