OFFICIAL NOTES FOR PRESENTATION

**Slide 1, TITLE)**

Effect of DNA methylation on neurological diseases,

Before I explain methylation, I wanted to select a neurological disease

**Slide 2) FRAGILE X SYNDROME**

Most common cause of inheritable intellectual disability

Affects 1:4000 males, and half as many females

This is due to the X chromosome, and is inherited on the X chromosome since males are XY, they only get one X so if their x chromosomes has it they are more likely to express the disease

Females have 2 X’s, so if one X has it then hey have a 50% chance to not express the disease

Caused by methylation of FMR protein

**Slide 3) FMRP1 fragile x mental retardation protein 1**

For the sake of this presentation I will call it the FMR protein for short

Caused by insertion of CGG trinucleotide repeats, but what the heck is a trinucleotide repeat???

DNA, look at pic on right, made up of 4 nucleotides, abbreviated ATCG,

Insertion of excessive Cytosine and guanine result in the ‘CGG’ trinucleotide repeats

Normal individual has blah blah

FMRP1 is expressed in neurons, blocks a certain neurotransmitter called metabotrophic glutamate receptor 5

If FMRP1 is not working, then it cannot block the receptor mGlu5

This build up of mGlu5 results in weakened synapses and longer dendritic spines, which is results in the intellectual disability

BUT WHAT THE HECK DOES THIS MEAN???

**Slide 4) happy neurons**

Shows a basic neuron function, electrochemically sends ‘synapsis’ to other neurons. These nucleotides represent normal, happy neurons

FUN FACT- neuron firing occurs 200 times per second per neuron, and each neuron is connected to on average 1000 other neurons. Doing the math, your body can have a range of 100 trillion to 20 quadrillion neuron fires per second!! Which is cool

**Slide 5) unhappy neurons**

We see the nucleotide sequence has changed with the addition of the CGG repeats, lead to misfunctioning neurons. These misfunctioning neurons result in the intellectual disability that is accompanied with Fragile x syndrome

So looks easy, can easily pick out the CGG repeats, like a little pattern right? Can easily pick apart this sequence

**Slide 6) ENTIRE SEQUENCE AAA**

But when you look at the ENTIRE sequence for this genome, it obviously can be EXTREMELY hard to find patterns. This is the recipe for an FMRP1 protein. If you have any extra nucleotides around, and place them in this EXACT order, you can make yourself an FMRP1 protein!!

This is a HUGE protein

In total, about 40,000 nucleotides, estimates for the average nucleotide length of a gene is 1000 nucleotides

This specific sequence has 117 CGG repeats, which means that this falls within the criteria for a carrier of this disease, which is 55-230 CGG repeats

Ok so now we know what this protein does, and that these CGG repeats can really mess things up. But why? Whats so special about CGG repeats?

DNA METHYLATION!!

Have to think about a normal scenario first. DNA is the tracks, and the entire mechanism to make proteins is like a train

**Slide 7) CHOO CHOO**

Happy train, running on DNA

Pops out little blue dots, those are proteins that will go do their thing

**Slide 8) unhappy choo choo**

DNA methylation can be thought of as ‘rocks’ on the train tracks. Will completely STOP the train.

So it will stop the creation of these proteins

**Slide 9) DNA methylation**

Addition of a methyl group on a cytosine

The methyl group is the ‘rocks on the traintrack’

But why silence anyways? We don’t want our ENTIRE genome turned on, that would be EXTREMELY energetically taxing for the organism

Way to silence genes

Females are XX, but only one is turned on so that females do not get double the proteins produced

THINK OF CALICO CATS

Almost all calico cats are female, XX

Have the orange and black fur, one X has the instructions for orange fur, the other for black

In areas where there is orange fur, the X chromosome with the instructions for ‘black’ fur is turned off and vice versa

This is a living example of DNA methylation !!!

As we age, methylation can change, and that is how the aging process begins

Individuals over 100 had a total genome methylation of 73% while newborns had 80.5% of total genome methylation

**Slide 10) FMRP methylation**

**SLIDE STILL IN CONSTRUCTION**

Average CpG island length per gene is 1,260 base pairs

CpG island are clusters of the ‘CGG’ repeats

Average length of CpG islands on FMR is 2,200 base pairs

Makes FMR EXTREMELY susceptible to methylation

Don’t forget this ‘highly methylated’ means the pile of rocks on the train tracks, many rocks present

The pie chart shows the methylation percent per gene, in an individual with Fragile X syndrome, 71% of the gene is methylated.

On the flip side, over the ENTIRE genome, only 55% of genes were methylated

**Slide 11) methylation of other neurological diseases**

Parkinsons – park 7

Encodes a protein that protects neuron cells from cell death

If this gene is ‘turned off’ (rocks on the traintrack), the neurons will not be protected from cell death and begin dying, leading to the early stages of parkinsons

Alzheimers – PPP2R3C

This helps w calcium binding

Important in cellular signalling

If this gene is turned off (rocks on the train tracks), cells have a difficult time communicating and this results in memory loss and the beginning of alzheimers

Right, bar chart showing the CpG islands length by Gene, the red bar indicates the average CpG island length, so FMR and Park7 are pretty susceptible to DNA methylation

**Slide 12) Other diseases caused by methylation**

Head and neck cancers, irx1, acts as a tumor suppressor, obviously if this gene is ‘turned off’ it cannot suppress tumors

Paralytic poliomyelitis – tspan4

Encodes for cell membrane organizers

After a viral infection, your body can change in bizarre ways. For example, after polio, your body’s methylation can change and this gene could become methylated and lead to paralysis that can occur after a polio infection

Epilepsy – GRIN 2

Grin2 encodes a neuron cell receptor, and is voltage dependent

Remember we talked about neurons earlier, and I stated it was an electrical interaction? Has to do with that

Grin2 responds to calcium, resulting in the ‘firing’ between enurons

If GRIN2 is turned off (rocks on the traintrack), cells cannot initiate signaling cascades

If you look at the bar chart, you can see the CpG island length. For reference I put FMR protein on there, from the last slide you can see how its kind of near the average CpG island length. and these three genes are EXTREMELY susceptible to DNA methylation. Still a TON of research as to why

**Conclusion**

Dna methylation is extremely important in regulating pysciological equilibrium

Any unwanted methylation can lead to severe disease such as parkinsons and alzheimers

Lots of research needs to be conducted, a lot of studies are aimed at methylation of genes

Fragile X syndrome is the most common cause of inherited intellectual disability

Lots of research into drugs

Takes a long time and a lot of money to put a drug on the market

BE KIND TO YOURSELF!!! Studies have showed that introduction of filate, vitamin B and choline can help support healthy levels of DNA methylation

Questions??