Name of disorder: Alzheimer's disease
Essay Title: The on/off switch of a major disease gene in Alzheimer's disease
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Content: Alzheimer's disease is a form of dementia that generally occurs later in life (65 years +), though in rare cases the disease can be present in middle-age persons. The condition is marked by a progressive loss of memory, which occurs as neurons (brain cells) die. Senile (neuritic) plaques in the intercellular space containing amyloid-ß protein and neurofribrillary tangles formed by abnormal microtubule associated protein tau (Tau), which normally stabilises nerve cells support system (cytoskeletal structures), are the two key diagnostic hallmarks of AD. The disease can last for years, with secondary infections generally being the cause of death rather than the condition itself. Given this, the disease is an enormous financial and emotional burden as later stages require round-the-clock care from family members the sufferers often do not recognise. Alzheimer's disease is a complex condition with poorly understood origin. One area under investigation in our lab is DNA methylation.

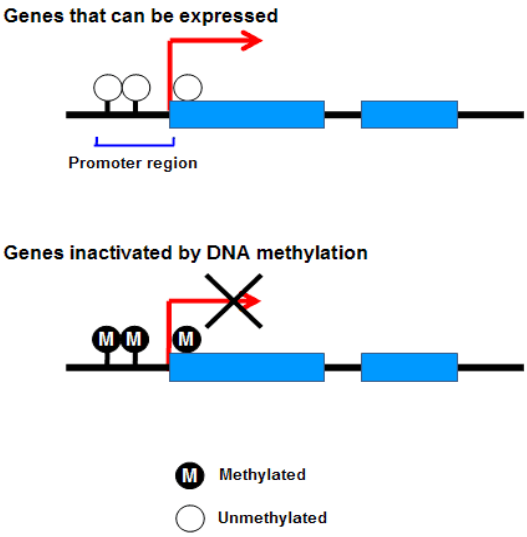

Figure 1: Schematic illustrating the blocking of gene expression by methyl groups bound to the gene promoter region.

DNA methylation is the reversible binding of a methyl group to specific patterns of code in DNA. When an area of the gene called the 'promoter', which is important in turning gene from code into functioning protein, is methylated the gene is switched off (see figure 1). This is an important mechanism for switching genes on or off as required. When the mechanism goes wrong, disease can result as is already well documented in cancer. The interesting thing about DNA methylation is that it can be altered by everyday lifestyle factors such as diet and smoking, meaning it is potentially an easily exploitable avenue for Alzheimer's treatment.

Our work thus far has focused on the role of the microtubule associated protein Tau gene (*MAPT*) in Parkinson's disease. Our investigations have found that a higher level of *MAPT* methylation led to a delay in Parkinson's disease onset in blood samples from disease sufferers and healthy subjects. We also found that in regions of the brain that are strongly affected by Parkinson's the disease sufferers had less *MAPT* methylation than their healthy counterparts. We have also conducted a preliminary study of *MAPT* methylation in Alzheimer's disease brains. We determined that disease brains had a higher level of methylation compared to their healthy counterparts. Furthermore brains carrying a mutation in a gene linked with an early-onset form of Alzheimer's disease (Presenilin 1) had 2-times less methylation than the late-onset Alzheimer's patients. This hints that methylation of *MAPT* may alter the age that Alzheimer's disease occurs in patients, as we saw in the Parkinson's disease cohort. Furthermore there could be an interesting interaction occurring between Presenilin 1 and *MAPT* methylation.

If successful, our project will provide further insight into the role of Tau in AD, providing a novel avenue for therapeutic strategies. DNA methylation is a reversible process and one that is known to be altered by environmental and lifestyle factors, such as diet and pesticide exposure. Should our research find similar links between AD risk and DNA methylation as we have in our investigations into PD there is the potential for disease risk management for a large proportion of our population through simple lifestyle changes.