APOE4, DEMENTIA and VASCULAR DISEASE

How genes impact on whether you get a disease or how a disease progresses are varied. Some effects are direct, and some indirect. Huntington's Disease is an example of how a gene mutation has a direct effect. In very simple terms, an abnormality on one of our genetic strands leads to production of an abnormal mRNA protein which leads to a slow, but eventually toxic production of an amino acid which directly causes destruction of brain tissue resulting in movement and other neurologic problems. These neurologic issues progress, eventually resulting in death usually by their 40's to 50's. Indirect effects include things like impacting on how inflammation is reduced or even produced in the first place, or how debris is cleared away or how we process molecules like metals which can build up in tissues. Most cases of dementia fall into this category. 97% of them!

One of the indirect mechanisms genes impact health has to do with how we process lipids. This is particularly important in the development of all forms of dementia, especially Alzheimer's Dementia (AD). Only 3% of AD are purely gene driven. The genes presenilin 1, presenilin 2 and APP impact on how normal transmembrane proteins are caught in the wrong place, leading to increased production of amyloid. Amyloid is normally produced every day, a result of various stresses, but clears when we sleep. Excess levels however cause an inflammatory reaction and overproduction of Tau bodies. These are normal structural proteins but again, if too much is produced, clumps called neurofibrillary tangles develop which impair nerve function leading to among other things, dementia. These 3 genes impact directly on the early development and rapid progression of AD. All the other 97% of cases of AD are a result of lifestyle factors which impact on epigenetics. The most important epigenetic factor is how and what we eat.

A commonly talked about, and very important genetically determined molecule which impacts dementia is the APOE lipoprotein. But as you will see, even the most concerning of these molecules, APOE-4, whose abnormally high level is associated with 50% of AD cases, is influenced by lifestyle.

The APOE gene provides instructions for making a protein called apolipoprotein E. Lipoproteins are responsible for packaging cholesterol and other fats and carrying them through the bloodstream. Maintaining normal levels of cholesterol is essential for the prevention of disorders that affect the heart and blood vessels (cardiovascular diseases), including heart attacks and stroke. Just as a reminder, the brain, and all our tissues for that matter, make all the cholesterol we need. Our dietary requirement for cholesterol is 0, zero. Any cholesterol we consume has to be cleared and that is why the more we consume, the worse our overall health is.

There are at least 4 slightly different versions (alleles) of the APOE gene. The major alleles are called E2, E3, and E4. There is one allele on both chromosomes, so you get 2 copies since there are 2 strands of DNA. There could be 1 copy of E2 and one of E3. Or 2 copies of E4, the worst scenario. All kinds of combinations. The most common allele is e3, which is found in more than half of the general population. E4 is the one which increases AD risk. Having at least one E4 gene (15% of the population) increases the risk of getting Alzheimer's disease 2-3x. Some people have 2 E4 genes, one from each parent. Having two genes (2% of the population) increases the risk of getting Alzheimer's disease even more, about 8-12x.

These lipoproteins are found in most animals but not in birds. This absence in birds may also account for the lack of effect of cholesterol on birds as well.

EPO-2 overall seems to be protective with people expressing this gene having much lower levels of not only dementia but cardiovascular disease in general as well. In fact, even with one copy of APOE-4, the one which increases AD risk, if the other copy is APOE-2, there is a neutralizing effect on AD risk. This is the least common of the three forms of the lipoprotein.

APOE-3 is the most dominant version. We think this is the case because our ancestors who had this version lived longer and healthier lives. They survived longer and this benefited their offspring.

Not all diseases are bad. Some actually provide a survival advantage. A great example of this is sickle cell anemia. This is a condition which affects mostly dark-skinned people and results in their red blood cells losing their round shape, taking on the shape of a sickle. As a result, the oxygen carrying capacity of the red blood cells

is impaired leading to poor oxygenation tissues resulting in pain and even organ damage. In some cases, people die if they don;t get the proper treatment soon enough. But this disease does serve a purpose. This condition protected people from malaria, which is still the #1 killer worldwide. The malaria larva would not survive in the body so those with sickle cells anemia would not become ill from the disease. I mention this because even APOE-4 may have provided some evolutionary survival advantage.

Even the most concerning of the APOE subtypes, APOE-4, provided some survival advantage since it also has a role in immune function, protecting us from infections. There is a population of native people who have a very high prevalence of APOE-4, but despite that, have a very low prevalence of AD. In their population, it is surmised that part of the advantage has to do with the APOE-4 protein's protection against a common parasite. That allowed them to survive longer, along with their overall healthier native lifestyle. This speaks to the issue of epigenetics, meaning whether the gene is turned on or off is influenced by lifestyle.

Huntington's Chorea, Sickle Cell Anemia, as well as conditions like Cystic Fibrosis and Muscular Dystrophy are examples of diseases resulting from a single gene mutation. Then we have diseases influenced by multiple gene mutations impacting on disease presence, severity and progression. Heart disease, Diabetes and even some cancers like Breast Cancer are examples of this.

And then there are chromosomal diseases, like Down's Syndrome, which manifests as a variety of physical and mental abnormalities resulting from an extra copy of Chromosome 21. One of the issues they struggle with is a much earlier onset of dementia, occurring as early as in their 40's. This is because one of the 3 well known genes which cause dementia, APP, is on chromosome 21. So, you get a third copy of this damaging gene.

There are different types of cells in the brain which make apolipoprotein.

- Astrocytes, a subtype of glial cells which make up most cells in the human central nervous system (CNS) and produce the most APO. Astrocytes perform metabolic, structural, homeostatic, and neuroprotective tasks such as clearing excess neurotransmitters, stabilizing, and regulating the blood-brain barrier, and promoting synapse formation.
- Microglia, which regulate brain development, maintenance of neuronal networks, and injury repair,
- Oligodendrocytes, which produce the myelin sheaths (insulation) that insulate axons in the central nervous system.
- Neurons, which are responsible for sending and receiving neurotransmitters, the chemicals that carry information between brain cells.

It is made in the endoplasmic reticulum in cells and is processed in the Golgi apparatus and then is extruded from the cell. They are supposed to be carriers of cholesterol molecules. At times, APO molecules get glycosylated (a glucose molecule attaches to it). The interplay between the degree of glycosylation and cholesterol carrying capacity affects the onset and progression of vascular health, amyloid clearance and eventually dementia occurs. This is why dementia is also referred to as type 3 diabetes. The worse your blood sugar control, the earlier and faster dementia develops.

APOE-4 is the least efficient at this process. It is the worst of the APO molecules at carrying and removing cholesterol. APOE-2 does a good job. APOE-3 is a wash. However, it still does something. As bad as APOE-4 is at clearing debris and cholesterol, its abilities are further impaired by glycosylation.

With 1-2 copies of APOE-4, people are also at greater risk of vascular disease, all over the body. Including the heart. And this vascular compromise also contributes to dementia.

Exercise improves APOE-4s efficiency and function. For example, exercise leads to production of brain derived neurotrophic factor (BDNF) which stimulates the liver X receptor (LXR). This results in greater APO production so there is more of it with increased cholesterol removing capacity, especially by astrocytes in the brain. Exercise also increases the mfsd2d receptor, which is responsible for transport of omega 3s fatty acid across the blood brain barrier.

ATP binding cassette transporter (ABCA1), which are on our cell membranes which have various functions. One of the important ones is to assist in cholesterol transport in and out of the cell. APOE-4 impairs this receptor's effect.

As mentioned above, if you have 2 genes, about 2% of the population, the risk of AD increases by 12x. 15% of the population have at least 1 copy. It increases vascular disease throughout the body. Chronic impairment of blood flow leads to cardiovascular disease, strokes, kidney disease, peripheral vascular disease, dementia and even premature hearing loss. There is also a tendency to have worsening immune issues and inflammatory issues.

It impairs the efficiency of the blood brain barrier, resulting in greater deposition of things like heavy metals in the brain. Even things like greater pharmaceutical transport occur (not necessarily a good thing) resulting in things like a greater potential to have fatigue when taking the newer “non-drowsy” antihistamines.

It impairs neuroplasticity, the ability of the brain neurons to make new connections.

APOE-4 also impacts on how the body transports DHA into cells. This is why those with copies of this gene need higher doses of the essential O3 fatty acids to see benefit. At least 1 gram of DHA is needed for benefit. 57% of the brain is made of DHA. Higher doses of Omega 3s however can also increase bleeding risks since these fatty acids also impact platelet function.

APOE-4 impacts on cholesterol metabolism, specifically increasing LDL, even early in life.

DIET.

- Cutting out saturated fats is absolutely necessary.
    - Red meats, processed meats, high fat dairy products, tropical oils
- Adding polyunsaturated fatty acids is questionable. There is some evidence that increasing these fats improves the function of the receptors which help reduce LDL.
    - nuts, seeds, avocados, extra virgin olive oil.

EXERCISE

- Through production of BDNF, along with some other vascular mechanisms, exercise impacts on how APOE-4 metabolizes cholesterol. LDL is metabolized faster and to a greater degree.
- It also impacts on the BBB receptors. Omega 3’s are increased in the brain as a result of improved receptor function.
- Also impacts on glucose and insulin receptors improving glucose metabolism improves. Less glucose in the brain leads to less APOE-4 glycosylation resulting in improved cholesterol and amyloid transport.