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Genetics in Alzheimer's Disease

In healthy individuals, normal ageing results in several changes to the structure and functioning of the brain. Reductions in the rate of production and integration of new brain cells, the degradation of vasculature, onset of hypertension, and reduction in white matter volume all combine to reduce performance of the brain's circuitry (Brown et al., 2011; Harada et al., 2013; Manard et al., 2016; Peters, 2006). Functional deficits also manifest in the form of progressive problems with specific types of memory brought on by biochemical changes to the levels of neurotransmitters and hormones, an increased susceptibility to oxidative stress and the failure of protein clearance mechanisms (Finkel et al., 2000; Petralia et al., 2014). These factors progressively contribute to impediments in the integration and processing of signals in the brain, affecting cognition and memory performance (Raz et al., 1997; Terry, 2006).

In some individuals, however, decline in cognitive functioning exceeds age-related expectations, and can progress to such a degree that the decline in an individual's cognitive abilities occurs earlier than expected. This syndrome is referred to as dementia, and can be instigated by a variety of pathologies, the most common of which is Alzheimer's disease (AD) (Alzheimer's Disease International, 2016). AD first presents with symptoms of forgetting, disordered cognition and emotional disruptions, progressing through a worsening of cognitive and behavioural deficits to an inability to self-care, loss of motor control and eventually death (Lenox-Smith et al., 2016). Alzheimer's disease is the most common cause of dementia, accounting for 60-70% of all dementia cases (World Health Organisation, 2015).

The hallmark molecular pathologies seen in post-mortem AD brain are senile plaques formed by the accumulation of sticky amyloid-β fibrils, and neurofibrillary tangles caused by detrimental modification (hyperphosphorylation) of molecules that stabilise the cytoskeleton of neurons, called tau proteins (Selkoe, 1991). The presence of these artefacts is associated with neuronal excitotoxicity, which occurs when the electrochemical balance of neurons becomes disrupted, causing the neurons to fire more readily, and leading to a build up of molecules that becomes toxic and results in synaptic degradation and cell death (Hynd et al., 2004). As more cells become affected, neural circuits and entire regions of the brain become atrophied, causing a loss of brain tissue volume (Bobinski et al., 1996). In Alzheimer's disease, this neuronal loss spreads progressively through a predictable sequence of brain regions, resulting in deficits specific to the forms of memory associated with the

affected brain regions (Almkvist et al., 1993). Structural changes start in the entorhinal cortex and the hippocampus before progressing from the front of the temporal lobe throughout the temporal cortex. Memory deficits in these areas initially affect episodic types of memory (i.e. autobiographical memories), progressing through other forms of hippocampal associated memory such as semantic memory, then procedural memory (memory of general knowledge and abstract facts, then knowledge of how to perform basic, well rehearsed tasks)(Gold et al., 2008). Structural atrophy then progresses to the association cortex, spreading throughout the secondary then primary cerebral cortex (Reid et al., 2013), and eventually resulting in such significant and widespread decay that basic motor functions are lost, and the patient cannot respond to or interact with their environment.

While a great deal of information has been gathered on AD since it was described by Dr Alois Alzheimer in 1905, there is still much that is unknown about the triggers of the disease. This is partly because AD is a multifactorial disease, with a range of potential causes which may develop independently or cumulatively to significant enough pathological levels to produce the AD syndrome. For some people, this might mean AD develops from a single trigger, such as a causative gene, while for others onset might require the combination of a gene that increases AD susceptibility (but is not causative) with other factors such as lifestyle, educational experiences, or the presence of a secondary condition such as diabetes.

It is useful for both clinical and research purposes, therefore, to classify cases of AD by their age of onset and attributable cause, as these categories are likely to develop from different aetiologies and progress and respond to treatments differently. Age of onset is defined as either early (≤60 years of age) or late (>60 years of age), and the attributable cause as either familial (directly inherited) or sporadic (resulting from an accumulation of various risk factors). Genetic factors account for all cases of familial AD, and there are also several genetic risk factors, which when combined with certain lifestyle factors can increase susceptibility to sporadic AD (Reitz, 2015).

Familial Alzheimer's disease is attributable to mutations in the sequences for the genes encoding the amyloid precursor protein (APP) or its processing enzymes (Selkoe, 1996). Inherited forms of AD are typically of early onset, as the presence of the gene in itself causes sufficiently significant pathology to develop the disease. Familial AD accounts for around 5% of the total cases of AD (Alzheimer's Association, 2014).

Sporadic Alzheimer's disease tends to be late onset, and the risk of developing it increases with age and it appears to be caused by the accumulation of a range of risk factors that can vary from individual to individual (hence the term sporadic). Sporadic forms of AD account for the vast majority (~95%) of AD cases (Alzheimer's Association, 2014). The genetic factors that contribute to sporadic AD increase one's risk of developing AD, probably in the presence of other, non-genetic factors, but are not causal by themselves.

As is the case in many genetic disorders, while we can observe the differences in the genetic sequence of people who develop familial AD, this does not reveal which properties of the protein expressed by that gene are affected, or how this contributes to the pathology. It does, however, provide researchers with some critical clues about where to look.

GENETICS IN FAMILIAL ALZHEIMER'S DISEASE

There are several mutations that have been associated with directly inherited familial AD, particularly in the genes coding for the amyloid precursor protein (APP) and its processing enzymes. APP is a large protein expressed in neurons that is cleaved into smaller proteins and peptides by several processing enzymes called secretases (Selkoe, 1989). One of the peptides produced from processing of APP is amyloid β, the peptide that aggregates into the plaques seen in AD brains (Masters et al., 1985). Early investigations into the genetic causes of AD were guided by the discovery that amyloid β was the same protein seen in plaques developed in the brains of people with Down syndrome, who frequently develop a similar form of dementia (Glenner et al., 1984). As Down syndrome was known to be caused by the presence of an extra copy of chromosome 21, research into potential sites of genetic causes for AD were focused around this locus (St George-Hyslop et al., 1987). This assisted in the discovery of the first mutation found in families with AD, a change in the DNA coding for the APP gene. This specific polymorphism came to be referred to as "the Swedish mutation", as it was isolated in two Swedish families with genetically caused AD (Murrell et al., 1991; Wisniewski et al., 1992). The Swedish mutation results in a change in the amino acid sequence of APP on either side of the site that amyloid β is generated from. The mutation makes the site more attractive to the enzyme that makes this cut, the β-secretase, resulting in increased activity and therefore an increased production of amyloid β. Since this discovery, several other mutations have been identified within the APP gene that also lead to an increase in its amyloidogenic processing, thus upregulating the amount of amyloid β in the system (Cole et al., 2008).

Other genetic mutations associated with familial AD involve mutations on chromosomes 14 and 1, which make changes in the genes encoding components of the γ-secretase, the enzyme that makes the second cut into APP to release amyloid β. This secretase is formed by an assembly of four smaller proteins, including presenilins 1 and 2 (Chouraki et al., 2014). Mutations in the coding sequence for presenilin 1 are the most common cause of inherited AD (Piccoli et al., 2016). In the most common form of the mutation, changes cause the γ-secretase to cut slightly downstream of the usual amyloid β generating site, resulting in a slightly longer form of amyloid β. This form of the peptide, referred to as Aβ42 because it contains 42 amino acids instead of the usual 38-40, is 'stickier' than other forms of amyloid β, as the additional amino acids it contains make it more more attractive to other amyloid β peptides, causing them to clump together more readily to generate plaques (Haass et al., 2012). This sticky form of amyloid β forms into aggregates around synapses, preventing neurons from communicating with one another, ending in neuronal death (Scheuner et al., 1996).

Other mutations in the PS1 gene that also cause familial AD result in changes to the secretase subunits that alter their charges in minor but significant ways (Piccoli et al., 2016). These changes in the charge across the molecule affect the way it can fold itself around other charged areas, disrupting the arrangement of the final construct in such a way that the rate of reactions between ϒ-secretases and APP is increased, again contributing to the upregulated expression of amyloid β (Nadav et al., 2015).

SPORADIC ALZHEIMER'S DISEASE

Uncovering the genetic factors that contribute to sporadic forms of AD has proven more difficult, because the methods rely upon the collection of massive sets of detailed data about the genetic sequence of individuals over very large population samples in order to pick up correlations between

the presence of a specific mutation and the onset of AD. This is obviously complicated by the fact that some people in the AD-affected population will not have any genetic contribution to their pathology, and some people from the unaffected population may possess a risk gene that has not developed into AD (Marei et al., 2015). Further, the use of correlative analysis means that even if a mutation is identified as more frequent within the AD-affected population, it may be contributing to another factor that increases the risk for AD, such as development of diabetes or vascular problems (Karch et al., 2015). Additionally, many of the mutations associated with an increased risk of AD occur at low frequency, meaning that although those who carry the variant consistently have an increased risk of AD, the mutated genes may not occur with high frequency within cohorts of AD patients, making them particularly hard to detect (Del-Aguila et al., 2015).

Despite these methodological constraints, genome-wide association studies of large cohorts of AD patients have identified several mutations that contribute towards an increased risk of developing the disease, or towards reducing the age of onset (Chouraki et al., 2014). These genetic polymorphisms affect pathways that include amyloid-β production and clearance, cholesterol processing, immune responses, and general protein clearance (Karch et al., 2015; Marei et al., 2015). The genetic variant that confers the highest risk for development of AD without being causal occurs in the gene for the apolipoprotein E (ApoE) (Strittmatter et al., 1993). APOE alleles are found in 3 different isoforms, ε2, ε3 and ε4. Having one allele of the APOEε4 isoform increases the risk of developing AD by threefold, and having both alleles as APOEε4 increases risk 12-fold, also reducing the age of onset (Corder et al., 1993). Conversely, it appears that the APOE ε2 isoform may protect against the development of AD, as people with at least one allele in this isoform are less likely to develop AD than the general population, and if they do it is significantly later in life (Corder et al., 1993). While the mechanism of increased risk or protection is not well understood, ApoE is known to be involved with clearance of excess proteins including amyloid β, and can bind with amyloid β to prevent it from aggregating into plaques (Kim et al., 2009).

Other mutations that consistently appear to be associated with an increased risk for AD occur in the genes coding for SORL1, ADAM10 and TREM2 (Del-Aguila et al., 2015). SORL1 is the gene that codes for sortilin–related receptor L, which is an ApoE receptor, and this mutation results in reduced expression of these receptors (Rogaeva et al., 2007). ADAM10 is a gene that encodes for the α-secretase, which cuts APP within the domain that becomes amyloid β, effectively precluding its production. In addition, this nonamyloidogenic processing of APP produces alternative proteins that stimulate neuroprotection and neurogenesis, which can help protect against AD symptoms and slow down its progress (Furukawa et al., 1996). AD risk mutations in ADAM10 reduce the activity of α-secretase, resulting in reduced neuroprotection while simultaneously facilitating the production of amyloid β (Vassar, 2013). The TREM2 mutation affects the "triggering receptor expressed on myeloid cells 2" protein, a receptor expressed on microglial cells (Sims et al., 2017). Microglia are a type of cell in the brain responsible for immunological protection of the neurons, also digesting toxins to maintain a balanced, healthy environment for neurons to function properly. While the mechanism of TREM2 mutations in susceptibility to AD is unclear, it is known that microglia are capable of removing amyloid plaques, as well as triggering the destruction of dead cells or waste proteins, all of which could contribute to worsening AD (Ulrich et al., 2016). It therefore seems likely that this mutation in some way alters the activity of TREM2 receptors, reducing microglial functioning and exacerbating AD pathology.

Genetic contribution to the development of sporadic forms of AD is important, but there are also environmental factors that have been consistently associated with an increased risk for sporadic AD. For example, sporadic AD is associated with a range of metabolic complications, such as diabetes and insulin resistance (Sridhar et al., 2015), hypertension (Yaffe et al., 2014), and high cholesterol (Nishimura et al., 2014). Neurons use a disproportionately high amount of the body's energy, almost exclusively in the form of glucose, so disruptions in glucose availability can have a significant detrimental impact on neuron transmission and survival (Schubert, 2005). The hippocampus, one of the first brain regions to be affected by AD, is one of the highest energy-consuming regions of the brain, and is therefore particularly vulnerable to disruptions in glucose metabolism (Sun et al., 2016). Vascular degeneration is also associated with the onset of sporadic AD, and significantly reduces neurogenesis and disturbs glucose exchange and waste removal between brain tissue and the blood (Nelson et al., 2016), resulting in increased oxidative stress and the spread of toxic amyloid species across the central nervous system (Smith et al., 2009). Insulin tolerance has been directly linked to tau hyperphosphorylation and has been shown to increase amyloidogenic processing of APP (Freude et al., 2005).

Longitudinal studies also consistently implicate lifestyle factors such as diet, physical inactivity, social isolation/depression, and smoking for increasing the risk of developing sporadic AD (Williams et al., 2010). Imbalances in brain activity such as sleep disruptions and seizures also contribute to increased sporadic AD susceptibility (Eshkoor et al., 2013). As much of the information available on risk factors is from longitudinal lifestyle studies, it is difficult to prove contribution to risk rather than correlative relationships between these factors and the occurrence of AD because of the high interaction between a variety of upstream and downstream factors. There is, however, evidence that the prevalence of AD is reducing in well-developed countries with educational programs in place promoting preventative adjustment of lifestyle risk factors such as improvements in lifelong physical activity, mental health support and diet (Alzheimer's Association, 2015).

Despite the positive steps in reducing the prevalence of AD (the proportion of the population that develop the disease), the incidence of AD continues to rise (the total number of people with the disease). This occurs because the risk of developing AD increases with age, and for those at age 85, there is a 50% incidence rate (Cornutiu, 2015). Improvements in quality of life and access to sophisticated medical care contribute to increases in the number of people living to an age where they are likely to develop AD. So despite improvements in our understanding of potential risk factors and the effectiveness of associated education campaigns, the incidence of AD is projected to continue to rise (Prince et al., 2016). In fact, the World Health Organisation estimates that nearly 46.8 million people worldwide are currently living with AD, and expects this to increase to 131.5 million by 2050 (World Health Organisation, 2015). The global health costs associated with managing AD in 2010 were US$ 818 billion, and in Australasia, the costs involved in responding to AD account for almost 1% (0.97%) of the total GDP (Alzheimer's Disease International, 2016).

Alzheimer's disease constitutes a serious world health burden, and one that is anticipated to grow. Research into AD has largely been guided by the genes that are involved, pointing scientists in the direction of proteins and pathways that contribute to the disease. While genetics may not be the whole story in conquering all cases of AD, the knowledge imparted from genetic studies has been essential in advancing our knowledge of AD pathology and in developing potential therapies, assisting researchers to address this critical public health issue for the future.

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