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Commentary

A Major Susceptibility of Large Gene Instability in Alzheimer's Disease

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ABOUT THE STUDY

Phase III medication trials for Alzheimer's disease (AD) have all failed to slow the progression of dementia, and the best therapeutic approach is still up for debate because the illness's mechanisms aren't well understood. Since many years ago, the dominant focus for AD treatment development has been on amyloid beta (Aβ) and its cascade, but accumulating data suggests that the underlying molecular processes of AD are more complex than the traditional reductionist models.

Recently, a number of hypothesis-free Genome-Wide Association Studies (GWAS) have illuminated hidden facets of AD. Here, I make the argument that the amyloid cascade theory may not be the best model for developing AD treatments. I examine 23 unique genetic risk loci and demonstrate that they have the common trait of encoding for receptor proteins and signal transducers of cell adhesion pathways. This has obvious consequences for the emergence, maintenance, and function of synapses. The traditional AD hallmark genes, such as the Amyloid Precursor Protein (APP), Presenilins (PSEN), and Apolipoprotein E (APOE), also participate in related pathways of growth cone adhesion and contact-guidance during brain development, contradicting the A-based interpretation but supporting the unbiased genome-wide insight. On the basis of this, I suggest that the key point of convergence in AD mechanisms may not be protein aggregation, but rather a disturbed synaptic adhesion signaling nexus. I demonstrate through an exploratory bioinformatics analysis that the biggest known human genes, which encode synaptic adhesion proteins, may be particularly prone to DNA damage accumulation in ageing due to their mutational fragility. I propose that the key etiological factor for the breakdown of APOE/dab1 signaling in late-onset AD may be mutational instability of the big Lrp1b tumor suppressor gene, as a prototypic example and an immediately testable hypothesis based on this argument. Our model centers the disease pathways around the cell adhesion process by utilizing the unbiased genomic architecture of AD. Cell migration, neurite outgrowth, and the construction of synaptic circuits are all controlled by focal adhesion regulators, like as integrin's. These canonical pathways play critical functions in preserving the adhesion and plasticity of synapses in the post-developmental brain. Post-Synaptic Density (PSD) sites and dendritic spines both develop a thick scaffold made of synaptic adhesion molecules. The extracellular matrix and intracellular actin cytoskeleton are connected to neurotransmitter receptors and ion channels by this scaffold, which promotes the dynamic remodeling and maintenance of synapses.

Human ageing is the most significant risk factor for various dementias, including Alzheimer's disease. Given the high prevalence of Alzheimer's disease in old age, this disease may represent a continuation of the global ageing process, and cellular disruptions that occur in "normal" ageing may give rise to AD when accelerated. A recent study found that healthy human frontal cortex cells accumulate new point mutations every year, and that these mutations may be the end result of a larger DNA damage process. One of the factors already implicated in AD etiopathogenesis is genomic integrity loss, but its relevance to molecular disease pathways has not been determined.

To summarize, the large gene instability hypothesis proposes that evolutionary forces of brain complexity have resulted in the emergence of large and fragile synaptic genes, and that these unstable genes are the bottleneck etiology of ageing disorders such as senile dementias. A paradigm shift in Alzheimer's disease prevention and treatment design is required.

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