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Genetic and epigenetic factors in alzheimer's disease pathophysiology.

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Introduction

Alzheimer's disease is the most common cause of dementia, characterized by progressive cognitive decline, memory impairment, and functional deterioration. The neuropathological hallmarks of the disease include extracellular amyloid-beta plaque deposition, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic dysfunction, and neuronal loss. Although age remains the most significant risk factor, it is increasingly clear that both genetic and epigenetic mechanisms play crucial roles in determining susceptibility, influencing the onset and progression of the disease. Genetic factors can predispose individuals to Alzheimer's disease through alterations in proteins that regulate amyloid metabolism, tau phosphorylation, lipid transport, and immune responses. Epigenetic modifications, on the other hand, affect gene expression without altering the DNA sequence, thereby linking genetic predisposition to environmental and lifestyle factors that influence disease development [1].

Alzheimer's disease can be broadly classified into early-onset familial Alzheimer's disease and late-onset sporadic Alzheimer's disease. Early-onset familial Alzheimer's disease, accounting for less than five percent of all cases, is typically caused by highly penetrant mutations in specific genes. Mutations in the amyloid precursor protein gene are among the most well-known genetic causes. APP is cleaved by secretases to produce amyloid-beta peptides, and certain mutations increase the production of the aggregation-prone amyloid-beta 42 isoform. This form is more fibrillogenic and neurotoxic, leading to accelerated plaque formation. Similarly, mutations in presenilin 1 and presenilin 2, which encode components of the gamma-secretase complex, alter cleavage of APP and favor amyloid-beta 42 generation. These mutations cause aggressive, early-onset forms of Alzheimer's disease, often manifesting in individuals in their thirties, forties, or fifties [2].

In contrast, late-onset Alzheimer's disease is far more common and arises from a complex interplay between genetic susceptibility and environmental influences. The strongest known genetic risk factor for late-onset Alzheimer's disease is the apolipoprotein E gene. APOE encodes a protein involved in lipid transport, neuronal repair, and amyloid clearance. The APOE gene exists in three major allelic variants: ε2, ε3, and ε4. Carriers of one copy of the ε4 allele have an increased risk of developing Alzheimer's disease and tend to have an earlier onset, while those with two copies have an even greater risk and earlier onset. APOE ε4 is thought to promote disease by reducing amyloid-

beta clearance from the brain, enhancing aggregation, and possibly influencing tau pathology and neuroinflammation. Conversely, the ε2 allele appears to confer some protection, though the mechanisms are not fully understood [3].

Beyond APOE, genome-wide association studies have identified multiple additional susceptibility loci for late-onset Alzheimer's disease. Variants in genes such as TREM2, CLU, PICALM, CR1, BIN1, and ABCA7 have been associated with altered risk. TREM2, which encodes a receptor expressed on microglia, influences the brain's immune response to amyloid deposition. Rare variants in TREM2 significantly increase Alzheimer's disease risk, possibly by impairing microglial ability to phagocytose amyloid and maintain neuronal health. Other genes identified through genome-wide studies implicate diverse biological pathways, including lipid metabolism, synaptic function, endosomal trafficking, and innate immunity, suggesting that Alzheimer's disease pathophysiology is multifactorial and extends beyond amyloid and tau biology [4].

While genetic mutations and polymorphisms establish a baseline level of risk, epigenetic mechanisms mediate dynamic regulation of gene expression in response to developmental, environmental, and lifestyle factors. Epigenetic modifications include DNA methylation, histone modifications, and non-coding RNA regulation. These processes influence chromatin structure and transcriptional activity without altering the DNA sequence. In Alzheimer's disease, epigenetic dysregulation can lead to aberrant expression of genes involved in amyloid metabolism, tau phosphorylation, oxidative stress, synaptic plasticity, and inflammatory responses [5].

Conclusion

In conclusion, Alzheimer's disease arises from a complex interplay between genetic predisposition and epigenetic regulation, with both factors contributing to the initiation and progression of pathological processes. Highly penetrant mutations in APP, PSEN1, and PSEN2 drive rare familial cases, while common risk alleles such as APOE ε4 and numerous susceptibility loci identified through genome-wide studies influence risk in the general population. Epigenetic modifications, including DNA methylation changes, histone alterations, and non-coding RNA dysregulation, modulate gene expression in ways that can exacerbate or mitigate disease mechanisms. These epigenetic processes provide a mechanistic link between genetic susceptibility and environmental influences, explaining individual variability in disease onset and progression.

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