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Chapter- 1

The Genetics of Alzheimer's Disease and the role of non-long coding RNAs in disease pathogenesis

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Abstract:

The advancements in medical research and public health have led to a recent relative increase in the global population of elderly persons that is leading to an increase in age-related, non-communicable neurological diseases. Neurodegenerative diseases cause progressive loss of neuron function that tends to the rapid death of neurons. One such neurodegenerative condition is Alzheimer's disease (AD), which is a result of accumulation of misfolded proteins. AD is distinguished into two forms Sporadic Alzheimer's Disease (sAD) and Familial Alzheimer's Disease (fAD). sAD is marked by late onset of the disease, whereas, fAD is characterized as the early onset with Mendellian inheritance. A number of hypotheses were proposed to explain the disease. The widely accepted ones are: Amyloid plaque Hypothesis and Tau pathology Hypothesis. Amyloid plaque hypothesis states that amyloid β (Aβ) peptide accumulates and deposits in the brain, either as oligomers or fibrils, and thus regarded as the main cause of Alzheimer's disease (AD); whereas Tau pathology hypothesis states that the main factor causing neurodegeneration in AD is tau phosphorylation and aggregation. The most significant genes include APP, APOE, PSEN1, PSEN2, etc. The clinical hallmarks are amyloid plaques and neurofibrilary tangles (NFTs). In the recent decade scientists have also seen significant relation between non-coding RNAs and Alzheimer's disease (AD).

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Introduction:

In the recent decade, neurodegenerative diseases have affected the human population widely. With the advancement of medical science and public health, the older global population has increased comparatively in recent times. Coincident with this aging population, age-related, non-communicable neurodegenerative diseases are very common to encounter (Johnson, 2015; Haloi et al., 2023; Biswas et al., 2024; Madhu et al., 2024)). Dr. Alois Alzheimer first reported Alzheimer's Disease (AD) on November 3, 1906. He observed a patient having psychosis, progressive sleep and memory problems, violence, and disorientation symptoms until her passing. Five years later, Dr. Alzheimer found distinctive plaques and neurofibrillary tangles in the brain histology. Later on, he communicated three further cases in 1909 and a "plaque-only" variation in 1911. A 1993 reexamination of the original specimens revealed that the "plaque-only" variety was a distinct stage of the same process (Hippius & Neundörfer, 2003)

In the second decade of studying this disease, scientists were engaged in knowing about the molecular mechanism(s) of the onset of this disease and further characterizing the disease. Differentiating AD became relevant due to the reported mutant variants in several human sub-populations, where individuals were suffering from dementia at a very early stage of life; similarly, some of the variants had no senile plaque deposition in their brains. Thus, AD is distinguished into two forms Sporadic Alzheimer's Disease (sAD) and Familial Alzheimer's Disease (fAD) (Bertram & Tanzi, 2012; Barber, 2012)

sAD is marked by the late onset of the disease, whereas fAD is characterized as the early onset with Mendelian inheritance. fAD is also marked by the presence of mutations in amyloid Precursor Protein (APP), which is considered as the origin of amyloid beta (Aβ) (Barber, 2012). Further fAD has also been classified according to human sub-population and also the particular mutations responsible have also been identified. fAD is of utmost importance as to know about a disease it is always necessary to study about the mutants of the disease. Similarly, fAD has also given various insights about AD pathology (Vélez et al., 2020). Several hypotheses were put forward to explain the disease. The widely accepted ones are: Amyloid plaque Hypothesis and Tau pathology Hypothesis.

Amyloid plaque hypothesis:

This hypothesis is one the most effective explanations of AD pathogenesis. The amyloid beta plaque contains the miss-folded Aβ and the AD is marked by the accumulation of amyloid plaques made of majorly 42-40 amino acid residue peptides called amyloid Beta 42(Aβ42) and amyloid Beta 40(Aβ40). This phenomenon takes place when the rate of accumulation of Aβ is more than the rate of utilization. Aβ is regarded as the clinical hallmark of AD pathogenesis (Shin et al., 2008; Paroni et al., 2019) thus understanding the source of Aβ is of utmost importance. Aβ helps in detection of AD in an individual. It is formed when proteolytic cleavage occurs to Amyloid Precursor Protein (APP) (O'brien & Wong, 2011). APP is an atypical transmembrane protein that undergoes proteolytic cleavage similar to the Delta-Notch

pathway (Kwak et al., 2011). The only difference lies in the fact that, for APP, this cleavage can occur in two separate pathways, giving rise to different cleavage products. The pathways are namely: Non-amylogenic pathway and Amylogenic pathway (O'brien & Wong, 2011). So, it is evident that only a single pathway gives rise to AD pathogenesis in an individual. But to understand AD, both pathways should be taken into consideration. APP, being a transmembrane protein, is susceptible to S2 cleavage at the extracellular domain, giving rise to a small extracellular stump. This stump is very critical; rather the length of stump determines the formation of the type of cleavage product, which will either tend to be harmless or very harmful for an individual. Now, this S2 cleavage can be done by two secretases: Alpha secretase (AS) and Beta secretase (BS). When AS cleaves APP it forms an extracellular stump of 12-amino acid residue, while on the other hand, if BS cleaves APP it forms an extracellular stump of 28-26 amino acid residues. The initial secretase is a part of the non-amylogenic pathway, and the latter one is a part of the amylogenic pathway. From here, both the pathways are similar. Gamma secretase (GS) causes S3 cleavage in the transmembrane domain by identifying the extracellular stump. The S3 cleavage generates a 14 amino acid extra residue linked with the extracellular stump; thus, freeing the cytosolic domain of APP. For the non-amylogenic pathway a 26 amino acid (12+14) residue long partially membrane embed peptide is produced which is not harmful; on the other hand for amylogenic pathway a 42-40 amino acid residue long peptide called Aβ42-40 is produced (Liu et al., 2021; Chow et al., 2010). These Aβ peptides rapidly oligomerize and that lead to accumulation of large amyloid plaques as found in AD. These plaques get deposited in the neurons that eventually cause the cell to disrupt, causing a phenomenon of neurodegeneration. Hence, AAP, the source protein for Aβ in AD undergoes through two cleavage phenomenon in both the pathways; the only difference is caused by the length of the extracellular stump produced by the S2 cleavage of BS, which in turn is a very vulnerable point for the progression of AD pathology.

Although this hypothesis has evolved and changed much through the years, the Aβ oligomers (AβOs) hypothesis represents the modern version of this theory. Basically, it can be said that the hypothesis has stream-lined, as AβOs were long detected in the human brain parenchyma and vasculature and reported while the original amyloid plaque hypothesis was being developed, but was only considered as a mere intermediate in the process of generation of amyloid plaques, which were believed to be the pathogenic form of Aβ (Cline et al., 2018; Walsh & Selkoe, 2007). The clear evidence of considering AβOs as the most toxic and pathogenic form of Aβ came by studying cases of fAD. Particularly one such example is the Osaka fAD mutation of Aβ (APP E693del) (Julia & Goate, 2017), which was marked by very low prevalence of senile plaques that were initially conserved most important. Instead this variant showed very elevated levels of AβOs in the cerebrospinal fluid (CSF) causing severe cognitive impairment. While traditionally AD has been defined as dementia with amyloid plaques, replacing plaques with AβOs is a much closer approach towards defining the disease pathology. Thus it can also be said that AβOs are the building blocks of the amyloid plaques

that are considered as the biological hallmark of AD. Moreover, scientists are trying to define AβOs as a biomarker of AD for early detection of the disease that in turn will help in preventing the disease pathology to spread from the source itself (Delaby et al., 2023).

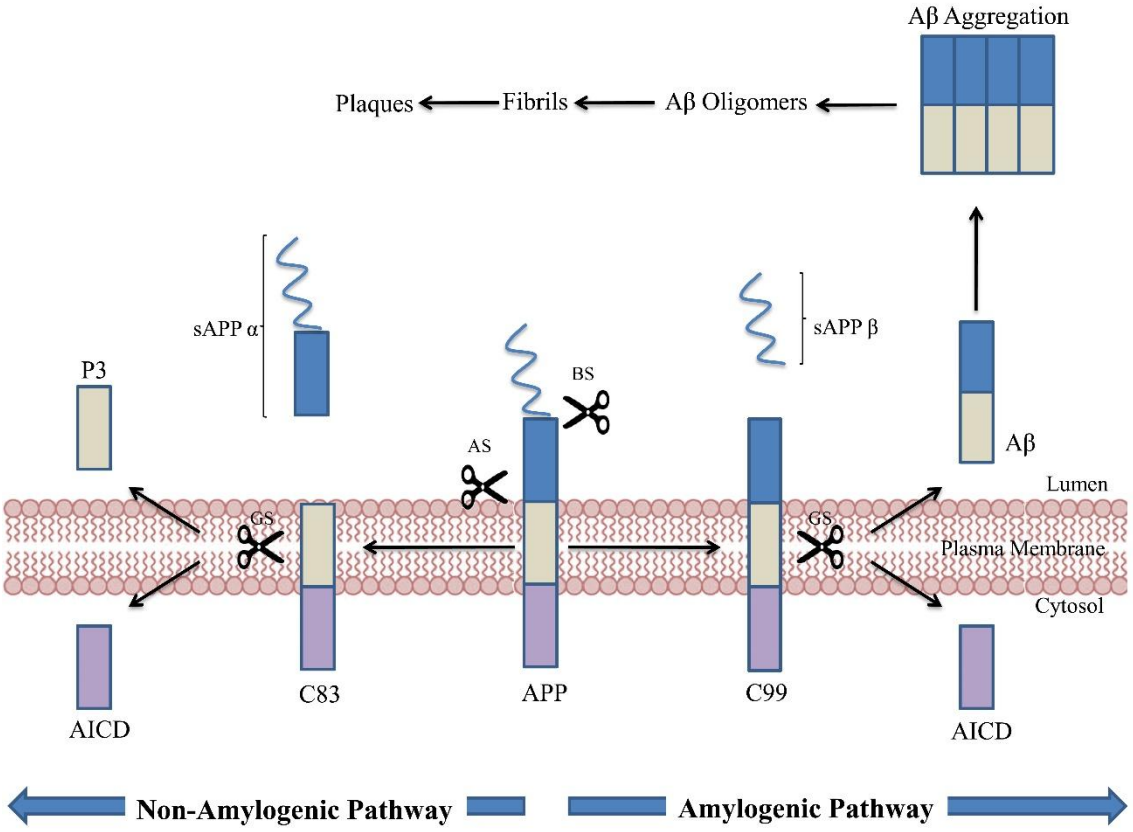

Figure 1. Schematic diagram of APP processing through amylogenic and non-amylogenic pathway. APP is initially subjected to S2 cleavage by either AS or BS and then to S3 cleavage by GS. Aβ is flanked out as a cleavage product in the amylogenic pathway, which in turn forms Aβ oligomers to fibrils and ultimately plaques

Tau pathology hypothesis:

According to the tau hypothesis, excessive or aberrant tau phosphorylation causes normal adult tau to change into paired helical filament Tau (pTau) and Neuro Fibrillary Tangles (NFTs) (Shin et al., 2008; Arnsten et al., 2021). Tau protein is a microtubule-associated protein (MAP) that is very soluble. It interacts with tubulin through its isoforms and phosphorylation to stabilize microtubule assembly. Six isoforms of the tau protein family, with amino acid ranges of 352-441, make up this family (Goedert et al., 2024). In contrast to the smallest isoform, which has three repeats (R1, R3, and R4) and no insert (352 amino acids total), the longest isoform in the CNS contains four repeats (R1 to R4) and two inserts. In paired helical filaments

from AD, all six tau isoforms are present and frequently in a hyperphosphorylated condition. Tau isoform expression and function mutations result in hyperphosphorylation. Without mutations, the exact mechanism by which tau aggregates is unknown, however it may be caused by an increase in phosphorylation, protease activity, or exposure to polyanions such glycosaminoglycans. Microtubules are disassembled by hyperphosphorylated tau, which binds to normal tau, MAP1 (microtubule associated protein 1), MAP2, and ubiquitin to form Paired Helical Filament tangles. This irreversible structure impairs cytoplasmic processes and hinders axonal transport; both can result in cell death and eventually lead towards dementia (Maccioni et al., 2010).

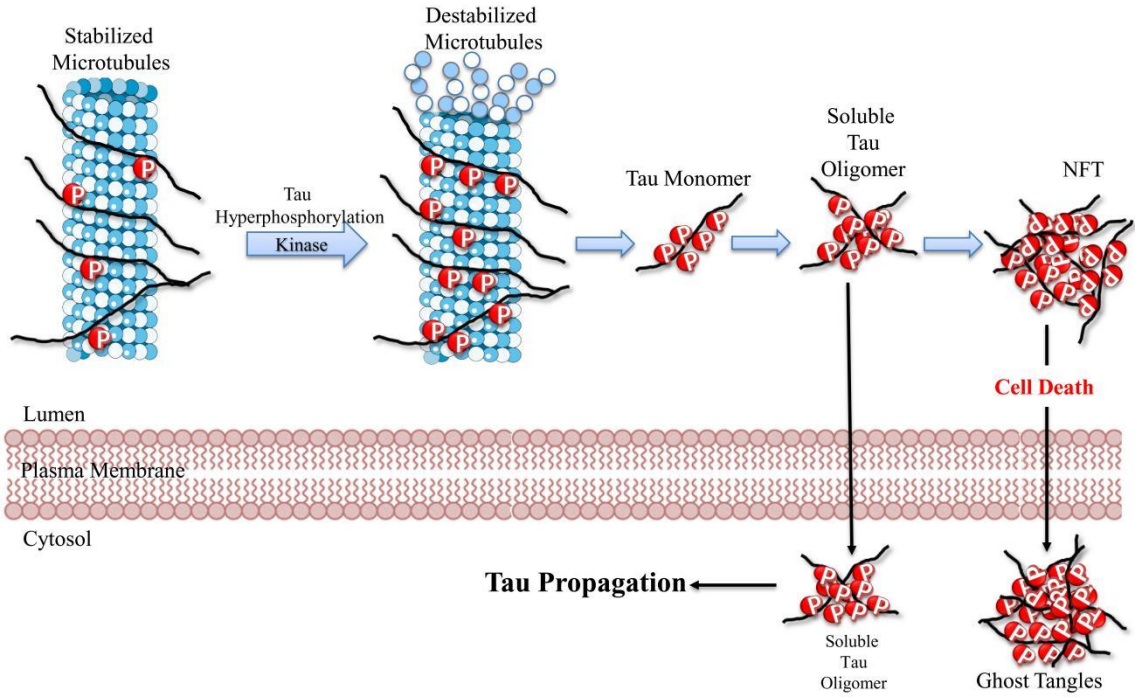

Figure 2. Schematic representation of Tau propagation, where the black thread with red bead (representing phosphate) represents the phosphorylated Tau protein stabilizing the microtubules. When subjected to hyperphosphorylation more red beads get added causing destabilization of the microtubules. The tau monomers then aggregate one upon other forming Tau oligomers and eventually NFTs

Later, it was marked that pTau also induces Aβ formation creating a brutal cycle where both pTau and Aβ induces each other's production. For example, in sAD, cell biology alterations in the ageing association cortex (such as calcium dysregulation) might worsen early-stage tau pathology, which in turn causes endosomes to become trapped in aggregated pTau, leading to a cleavage. Because "endosomal traffic jams" promote the cleavage of APP to Aβ in endosomes,

genetic changes in retromersignaling (such as SORL1) may make sAD risk worse (Garbuz et al., 2021). Contrarily, in fAD, basic genetic changes in amyloid signaling (such as APP duplications) might start the degenerative process, which then causes Tau hyperphosphorylation to rise. In either scenario, a vicious cycle regulated by Fyn Kinase an Src family kinase, that eventually results in amyloid plaques and neurofibrillary tangles would be set in motion (Nygaard et al., 2014).

The neuropathological indicators of Alzheimer's Disease (AD) include extracellular Aβ plaque buildup and formation of neurofibrillary tangles (NFTs), making both hypotheses crucial for understanding AD's origin.

Genes involved in AD:

The first-degree relatives of AD patients exhibit an increased risk of dementia, despite difficulties in investigations of early hereditary cases. Early-onset cases provide insight into familial inherited neuropathology and identify the underlying genes regulating pathology, thus leading to the identification of potential risk factors and regulatory genes of AD.

APP

Strong evidence between some rare forms of fAD and particular genetic factors were first surfaced in the early 1990s, APP gene alterations were observed. Many amyloid peptides are produced when APP is cleaved; the most prevalent one is Aβ42, while the more soluble Aβ40 is also linked to cerebral micro-vessels and may appear later in the disease. Furthermore, Aβ38 may be deposited in vascular walls as a result of APP mutations in the amyloid coding region, particularly in patients with severe cerebral amyloid angiopathy (CAA). Depending on the kind of mutation, early soluble peptide oligomers may potentially be involved, offering a genetic foundation for variances in fAD pathogenesis. Genome-wide association studies (GWAS), have identified a significant number of genes that have a functional effect on APP, including at least 832 genes that have the ability to modulate APP metabolism, eight of which are located within regions known to be prone to AD. Among these genes is the "fermitin family homolog 2 gene" (FERMT2), a co-activator of β-3-integrin that is strongly correlated with changes in Aβ in cerebrospinal fluid (CSF). Down regulation of this gene may elevate Aβ by raising the level of mature APP and facilitating its recycling at the cell surface. In addition, ATP-binding cassette transporter A1 (ABCA1) gene may also have a role in Aβ deposition and clearance, which is associated with many variants of AD. It can easily concluded that APP gene processes the stretch of Aβ within it which is easily the most important clinicopathological evidence of the disease, thus categorizing APP as one of the chief regulatory gene of AD (Lanoiselée et al., 2017; Chouraki & Seshadri, 2014).

PSEN1/2

PSEN is a nine trans-membrane protein located in the endoplasmic reticulum which is endoproteolytically cleaved, assembled into an Gamma Secretase (GS) complex, and then

transported to the cell surface, where it may have an impact on the processing of APP. Researchers reported that one of the most prevalent types of fAD is linked to PSEN1/2 gene alterations. Mutant PSEN1 interacts with APP by promoting normal APP's 42-specific-GS cleavage, which would boost Aβ deposition. PSEN generally functions as the following:

Firstly, it could be influenced by decreasing the activity of GS. Secondly, the PSEN1 gene could have a role in cell differentiation as it could be connected to Delta-Notch signalling. Thirdly, PSEN1/2 may be engaged in interactions with the transcriptional coactivator cAMP-response element binding (CREB-binding) protein, which is essential for controlling gene expression, or in disruption of the calcium homeostasis within the cell. Hence, a decrease in all these kinds of protection may be connected to AD (Lanoiselée et al., 2017; De Strooper, 2007; Kelleher & Shen; 2017).

APOE

Numerous research works have highlighted the significance of genes related to cholesterol transfer as risk factors for AD. These genes include clusterin apolipoprotein J (APOJ), apolipoprotein E (APOE), and apolipoprotein C1 (APOC1), all of which have a significant role in breakdown of cholesterol homeostasis. Further study shows a significant risk factor for sAD is allelic variation in the APOE gene, as persons with AD have an elevation of 2-3 times the frequency of allele ε4 in comparison to healthy control cases. Moreover, ε4 may have a direct impact on cognitive function as it has been linked to lower test results on memory and learning skills for adults. As allele ε4 may hasten the ageing brain's development of AD pathology, it is frequently linked to an earlier onset of the illness. Additionally, most studies show that people who express ε4 have higher levels of Aβ deposition. Furthermore, peripheral inflammation, APOE, and Aβ may combine to cause cerebrovascular dysfunction and cognitive decline, and in transgenic mice, ε4 significantly promotes age-dependent CAA. Moreover, APOE also act as a regulatory gene for the various types of cancer induction. From the above discussion it is thus evident that APOE is a key gene in establishing the sAD pathology as well as to investigate any relation of AD with other harmful diseases (Lanoiselée et al., 2017; Kim et al., 2009).

Other genes

Less than 5% of AD cases are caused by the combination of the APP and PSEN1/2 genes (Giau et al., 2019). Thus, to identify other genes linked to AD, GWAS was performed which revealed the association of AD-associated genes on chromosomes 6, 9, 10, 11, 12, 14, 18, and 19 (Bertram & Tanzi, 2009). To mention some of the significant ones: the vitamin D receptor (VDR) gene is located at 12q13 on chromosome 12, which is where the gene on chromosome 12 was located. Since this gene is a key modulator of vitamin D activity, AD may be associated with vitamin D deficiency (Ghahremani et al., 2023). Furthermore, a 9p21.3 gene variation may influence Caucasian susceptibility to AD. A more recent GWAS finds 26 unique risk factor genes that are involved in many processes such as immune response, endocytic trafficking, and cholesterol and lipid metabolism. Additional genes that have been linked to risk include

glyceraldehyde-3-phosphate dehydrogenase (GAPDH), genetic variations in the estrogen receptor (ESR) gene, polymorphisms in the clusterin gene, the transferrin (Tf) gene, and a rare variant of the triggering receptor expressed on myeloid cells 2 (TREM2) gene, where upregulation of the TREM2 gene has been observed in the frontal cortex of sAD patients (Armstrong, 2019).

Non-Coding Genome and AD:

There is growing evidence that the majority of the human genome is actively being translated into non-coding RNAs. Many of these non-coding RNAs have been found to be novel regulators of gene expression at different levels while not having evident protein-coding potential. Among these, circular RNAs (circRNAs) are a novel class of non-coding RNAs that form continuous loops by covalent bonding and lack the typical 5′ caps and 3′ poly-A tails. circRNAs are extensively expressed in mammalian brains in comparison to other organs, and they have functionality in synaptic activity and neurological development, which are important in neuropsychiatric illnesses. With a longer half-life than linear RNAs and no free hydroxyl endings that provide resistance to exonucleases, circRNAs are incredibly stable and tend to accumulate during brain ageing. Hence is an excellent candidate for biomarker (Patrick et al., 2020; Akhter & Rumana,2018).

Similarly, long non-coding RNAs (lncRNAs) that are typically longer than 200 nucleotides have been demonstrated to have a role in brain development and function, and the dysregulation of their expression has been linked to a variety of neurological illnesses. The majority of cases of AD are categorized as sAD, when there is no known genetic basis and when symptoms typically appear beyond the age of 65. Instead, autosomal mutations in three genes (APP, PSEN1, and PSEN2) involved in the APP amylogenic pathway, which result in the generation and aggregation of lethal Aβ peptides, cause uncommon monogenic forms of fAD to be inherited. However, twin-based genetic studies of dementia have suggested that 60–80% of instances of sAD are heritable; indicating that genetics play a significant role in disease progression. As mentioned earlier a significant portion of this heritability is explained by the alleles of the APOE gene, which codes for the APOE, notably the APOE epsilon 4 (ε4) allele. Even yet, the aetiology of sAD is complicated and oligogenic, and numerous genome-wide association studies (GWAS) have shown risk mutations for sAD in more than 40 loci. However, due to linkage disequilibrium, several of these genetic variations or single nucleotide polymorphisms (SNPs) are frequently inherited collectively. Furthermore, a number of these SNPs are found in non-coding areas of the genome, predominantly in the lncRNAs. Classical AD diagnosis depends on clinical manifestation of the disease, considering these identified lncRNAs as biomarkers will lead the way towards establishing a definition of AD based on biomarkers that reflect such biological alterations at early stages of the disease. A number of disease-associated variations have also been found to map to non-coding regions of the genome, including genomic locations that include lncRNA genes, as a result of recent advancements in AD GWAS. Finally, these lncRNAs may also open up new and creative

biomarker approaches or therapy options for AD (Patrick et al., 2020; Li et al., 2021; Lan et al., 2022).

Micro RNAs (miRNAs) are about 19-25 nucleotides long RNA. The majority of miRNAs are produced by converting DNA sequences into primary miRNAs, or pri-miRNAs, which are then processed into mature miRNAs and precursor miRNAs, or pre-miRNAs. In AD, miRNA regulates in various processes of the disease pathology for instance miR-101, miR-17 etc negatively regulate APP. miR-125b has been seen to influence hyperphosphorylation of Tau protein. Other than these various miRNAs have been recorded in influencing the neuronal function, inflammation and oxidative stress to nerve cells. Lastly, many miRNAs have been found in the cerebro spinal fluid (CSF) of AD patients leading its way towards recognizing miRNAs as a potential biomarker of AD (Patrick et al., 2020; Wang et al., 2019).

Conclusion and future prospective:

AD is accounted as the most prevalent of all the neurodegenerative diseases. Although several hypotheses are present; but, significant among them are amyloid plaque Hypothesis and Tau pathology Hypothesis. Similarly, the genes like APP, PSEN1/2, APOE, etc are also important for AD induction. In spite of all the advancements in the last three decades scientists have encountered an abysmal failure in targeting AD with any drug, which is concerning. The recent findings of involvement of non-coding genome in AD pathogenesis and the relation between the two hypotheses has been rewarding in better understanding of the disease. Moreover, AD has also been linked with various other diseases like cancer, diabetes, etc; paving its way towards finding any relation between the said diseases and also repurposing drugs already in use.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors approved the final version of the manuscript for publication.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions:

SR executed all review works. SB, DG helped SR in writing the manuscript. RDG and AB conceptualized, supervised and finalized the manuscript.

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