Relation of Adult Neurogenesis in Alzheimer's Disease: A Review on Past, Present and Future Implications

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease attributed to the loss of neurons causing memory loss and cognitive decline. Many low-grade neurological insults are associated with AD but the ones that have been mostly studied are pathological build-up of amyloid protein ß and hyperphosphorylation of microtubule associated protein tau. Adult neurogenesis is the phenomenon of formation of new neurons in healthy brain via neural stem cells (NSCs). Loss of extrinsic signaling (physical activity, dietary intake) results in impaired neurogenesis during AD, making it a probable biomarker for AD. The alteration of proliferation, differentiation, migration, and integration processes are involved in neurogenesis is clearly evident during AD. Thus, the possible targets for the therapeutic purpose of AD, are interleukin-4 (IL-4), brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), fibronectin type III domain – containing protein–5 (FNDC5) which helps to improve the proliferation and integration of the neural stem cells. Studies carried out in mice models suggest an intrinsic and extrinsic correlation of NSCs for the treatment of AD with an aim to reverse the neurodegeneration. The present review focuses on the novel markers like DCX, NeuN, Sox2, calbindin and Nestin involved in adult neuronal development and its role in pathophysiology of AD. Moreover, this review opens up new avenues for treating AD and developing molecular markers for it.

Keywords

Alzheimer's, amyloid ß, adult neurogenesis, therapeutic, biomarker

Introduction

Alzheimer's disease (AD) lays its origin from 1906 where Dr. Alois Alzheimer first identified Alzheimer's disease in a female patient named Auguste Deter [1]. Epidemiologically, AD affects approximately 5 million people in the US and this number is expected to rise by 35 million by 2050 [2]. In 2015, India reported 4.1 million cases of people living with dementia. Dementia affects 2.7 percent of the population in India, according to epidemiological studies conducted between 1996 and 2006, with Alzheimer's disease being the most common cause (1.3%) [3]. It was estimated in 2010 that 36.5 million people were living with dementia, with 7.7 million new cases each year and a new case of dementia every 4 seconds [4]. The World Health Organization (WHO) estimated that 0.379% of the world's population suffered from dementia in 2005 and its prevalence will increase to 0.441% in 2015 and 0.556% in 2030 [5]. Histological characterization of AD revealed extracellular deposits called cerebral plaques in neocortex and hippocampal region and are made up of a thick proteinaceous core containing the amyloid β (Aβ) peptide surrounded by dead and weakened neurons. The other histopathological hallmarks are the filamentous, hyperphosphorylated form of the microtubule-associated protein tau which forms neurofibrillary tangles in neurons of the same regions of the brain [6]. Although most cases of AD occur occasionally, about 5% of patients develop an early disease as a result of a completely penetrant autosomal dominant gene mutations (APP, APOE, PSEN1, PSEN2) [6]. Till now, evidence pertaining to the specific remedies in preventing Alzheimer's disease remains elusive [7].

As discussed, AD mostly affects the hippocampal area in the brain[8]. Hippocampus is one of the areas in the adult brain where evidence of neural stem cells (NSCs) are documented [9]. Adult NSCs are capable of producing new neurons throughout life in two major parts of the adult mammalian brain: the subventricular zone (SVZ) of the lateral ventricle and the sub granular zone (SGZ) in the dentate gyrus (DG) of the hippocampus [10] this process is called adult neurogenesis. This process consists of different stages such as neural stem cell proliferation, lineage differentiation, migration and the integration of the developing neuron in the pre-existing circuit of the brain. Adult neurogenesis is related to the physiological

functioning of the brain and degeneration. Zhao et al (2008) observed changes in the pattern of neurogenesis which were associated with many neuropsychiatric disorders.

In most cases adult neurogenesis is reduced during AD which is found in SVZ and SGZ. Concurrent studies show a dilemma in the decrease/increase neurogenesis in the brain of mice and human subjects affected with AD [11,12]. Furthermore, reduction of new born neurons causes cognitive defects in AD mice [13]. In line of this, the present review discusses the use of impaired adult neurogenesis in AD as a possible potential therapeutic biomarker for predicting the progression and effective treatment for the disease.

Pathophysiology of Alzheimer's disease

The early onset of familial AD is due to genetic mutations in the amyloid precursor protein (APP), presenilin proteins - PSEN1 and PSEN2 [14]. Apolipoprotein E (ApoE) is the strongest genetic risk factor for sporadic AD [6]. Alzheimer's disease (AD) is thought to occur when increase in the abnormal amounts of Aβ accumulate extracellularly forming amyloid plaques. Tau proteins accumulate within cells causing the formation of neurofibrillary tangles in the brain, affecting neuronal function, connectivity and causing progressive brain function loss [15] [16]. Moreover, microscopically the main attribute of AD is the loss in the cerebral cortex of neurons and synapses and the hippocampal portion of subcortical regions due to accumulation of misfolded Aβ and tau proteins [17,18,19]. These losses result in deterioration of the temporal and parietal lobes and severe atrophy in the affected area, including parts of the frontal cortex and cingulate gyrus. Studies using MRI and PET show that the size of affected brain regions in AD patients decreases as they progress from mild to severe cognitive impairment as compared with healthy older adults [20]. Aβ plaques are formed when amyloid precursor protein (APP) undergoes complex sequential proteolytic processing in the CNS through two main processing pathways called amyloidogenic and non-amyloidogenic processing pathways [21]. This APP which is a transmembrane protein is encoded by APP gene which has also gained attention due to high rate of mutation. Thus, misfolded plaques containing small peptides of 39-43 amino acids long are called beta-amyloid (Aβ). APP is important for nerve cell growth, survival, and damage recovery [22,23].

Several enzymes are known to cleave APP at several amino acid positions near C terminal. For instance, α-secretases acts on APP, 83 amino acids from its carboxyl terminus, which belongs

to ADAM protease family ("A disintegrin and metalloproteinase"). Whereas, the β-secretase enzyme contains two or more different complexes called BACE1 and BACE2 which cleaves APP at 99 amino acids from its carboxyl terminus. The third type of APP cleavage is provided by the enzyme complex γ-Secretase. Presenilin-1 and Presenilin-2 mediate the catalytic function of γ-Secretase and is encoded by PSEN1 and PSEN2 gene. APP is cut twice by γ-Secretase generating a 50 amino acid peptide which consists of the APP C-terminal end, and is named as the amyloid intracellular domain (AICD). The second γ-secretase fragment is slightly variable, but tends to be located at 57, 59, or 61 amino acids at the C-terminus of APP. Sequential processing with α- and γ secretases yields a large N-terminal peptide called soluble APPα (sAPPα) and a smaller 3kDa peptide called P3. β-secretase cleavage produces a large N-terminal peptide called soluble APPβ (sAPPβ) and a smaller C-terminal fragment called CTFβ. The γ-secretase cleaves CTFβ, and the Aβ peptide. Depending on the continuous activity of β-γ-secretase, the exact cleavage site of γ-secretase varies, resulting in Aβ peptides, which are usually 38-43 amino acids in length [24]. The α-secretase enzyme in the "nonamyloidogenic pathway" appears to exhibit neuroprotective activity by cleaving APP at the Aβ sequence and releasing the sAPPa fragment through the membrane [6]. Primarily in the hippocampus, neurofibrillary tangles consisting of paired helical filaments are present in the cytoplasm of neurons [25].

Neurofibrillary tangle formation in AD is directly related to protein dysfunction. Tau is a microtubule-associated protein that plays an important role in supporting axonal transport and promoting cellular stability. The main polypeptide of the paired helical filaments is the microtubule-associated protein tau. Tau levels in the AD neocortex are 7 times higher than in the control aged brain group, and this elevation is a result of abnormally phosphorylated proteins (Iqbal and Grundke-Iqbal, 2007). Hyperphosphorylation of τ reduces the binding of τ to microtubules and disrupts subsequent axonal transport [26]. Abnormally hyperphosphorylated tau has shown to have a neurodegenerative effect by inhibiting microtubule function, impairing axonal transport of neurons, and enhancing functional toxicity by forming paired helical filaments [6]. Apart from phenotypic markers, others like inflammatory processes, cytokines and growth factors (BDNF) are attributed to play a role in the pathophysiology of AD. Tissue damage is marked by an elevated immune response resulting in inflammation at the affected site which are considered to be the signs of secondary damage to the tissue [27]. Similarly,

changes in the distribution of various neurotrophic factors such as the brain neurotrophic factor (BDNF) and the expression of its receptors have been found to be associated with AD [28,29].

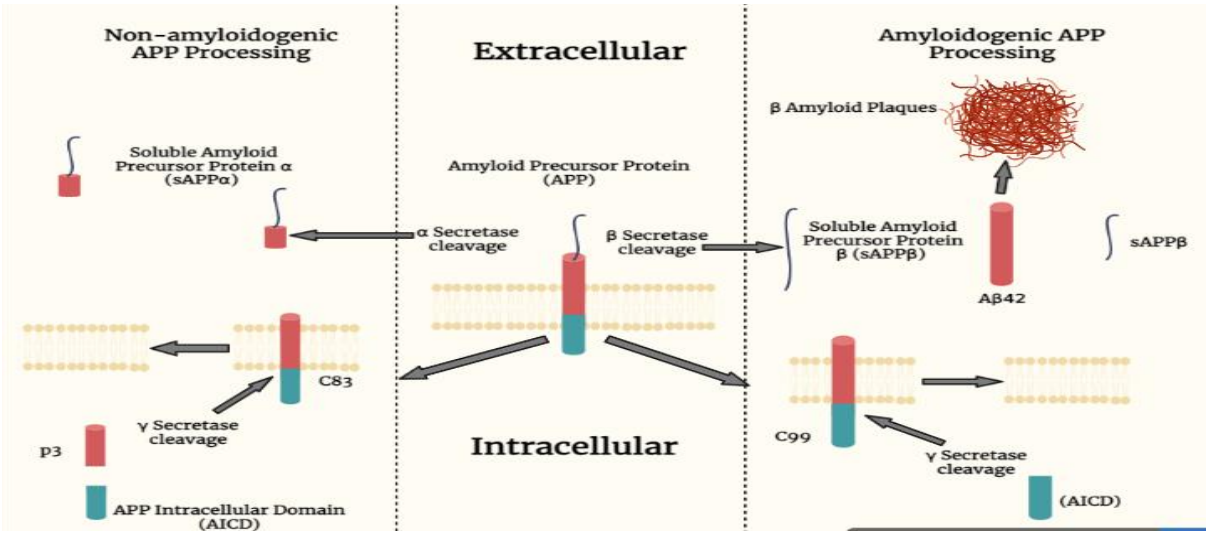

Figure 1: Generation of soluble APP peptides (sAPPα, sAPPß) is processed due to the cleavage by α-secretase, ß – secretase or γ – secretase. The C-terminal membrane anchored fragment (C83) yields P3 peptides by γ – secretase depicting the major secretory pathway which is non-amyloidogenic. The presenilin/nicastrin-mediated γ-secretase processing yields amyloid beta proteins, amyloid-beta 42 (Aβ42) from C99 fragment. Aβ42 is the major component of amyloid plaques.

Adult neurogenesis in the healthy brain

Traditionally, it was believed that no new neurons are produced after birth [30]. But in the late 50s new method on labeling techniques was developed for dividing cells with [H3]-thymidine, that incorporates into the replicating DNA during the S-phase of the cell cycle, and can be detected with the help of autoradiography [31]. Generation of new neurons has already been reported in the embryonic stages of mammalian CNS by Cajal et al, while using the above mentioned technique pioneering work done by Altman and colleagues demonstrated the adult neurogenesis in rats various brain regions, which includes the dentate gyrus [9], neocortex [32] and olfactory bulb [33]. Advancement in staining has been done by [34] where they have used BrdU a synthetic thymidine analogue, for the detection of neuronal proliferation in mammals.

Adult neural stem cells (NSCs) are responsible for the generation and differentiation of new neurons, which were first isolated from the adult CNS of rodents [35] and later from humans [36]. Combined retroviral-based lineage tracing and electrophysiological studies provided the most convincing evidence so far that newborn neurons in the adult mammalian CNS are continually

produced throughout adulthood [37,38,39.] However, human adult neurogenesis is currently under investigation and evidence marks the formation of new neurons throughout the human life, nevertheless the rate of production is too low compared to other mammals [40,12].

NSCs reside in two major parts of the adult brain: the subventricular zone (SVZ) of the lateral ventricle and the sub granular zone (SGZ) in the dentate gyrus (DG) of the hippocampus [41]. These NSCs can self-replicate and differentiate into multiple neural lineages such as neurons, astrocytes, and oligodendrocytes [10].

Based on three major factors like morphology, molecular markers and proliferative behavior, two types of neural stem cells were identified. The SGZ of hippocampus contains type 1 neural progenitor cells (NPCs) also abbreviated as radial like neural stem cells (rNSCs), contains radial projections that spans entire granule cell layer and ramifying in the inner molecular layer of DG. They can be detected by the molecular markers such as Glial fibrillary acidic protein (GFAP), Sox2 and Nestin. These stem cells are quiescent but gets activated due to environmental factors that generate the type 2 NPCs. These cells express Sox2, Nestin, Tbr2 and MCM2 except GFAP. These cells generate both astrocytes and DCX expressing neuroblasts that migrate into the granular cell layer and undergoes maturation. These maturing/surviving cells receive inputs from the entorhinal cortex (EC) and send axonal projections through the hilus towards the CA3 area of the hippocampus [42,43]. These newborn immature granular neurons in the DG receives GABAergic synaptic input around one week after birth followed by glutamatergic inputs by two weeks, and full maturation is achieved within 4 weeks in development [44]. Mature granule cells mostly become glutamatergic dentate granule cells (DGCs) and express neuronal nuclear antigen (NeuN) and calbindin [43,42].

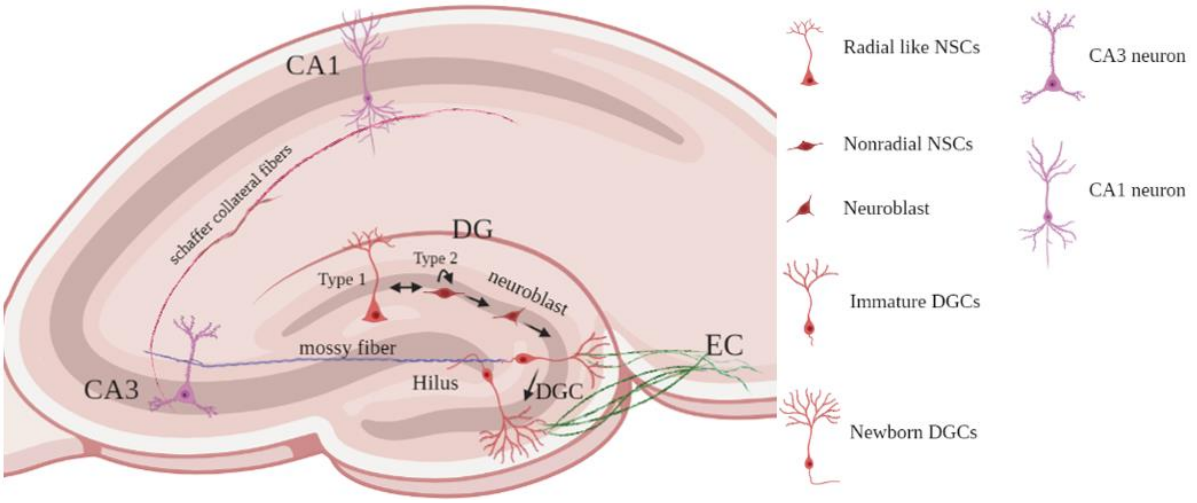

Figure 2: Neurogenesis in adult mammalian hippocampus: Radial-like neural stem cells (Type-1) which are quiescent stem cells that produce non-radial precursor cells (Type-2) which are actively proliferating and produce astrocytes and neuroblasts; Neuroblast cells migration into the granular layer; Differentiate into dentate granule cells; Maturation of Newborn dentate granule cells takes place and they receive EC input and send their axons to hilar interneurons, mossy cells, and CA3 pyramidal neurons.

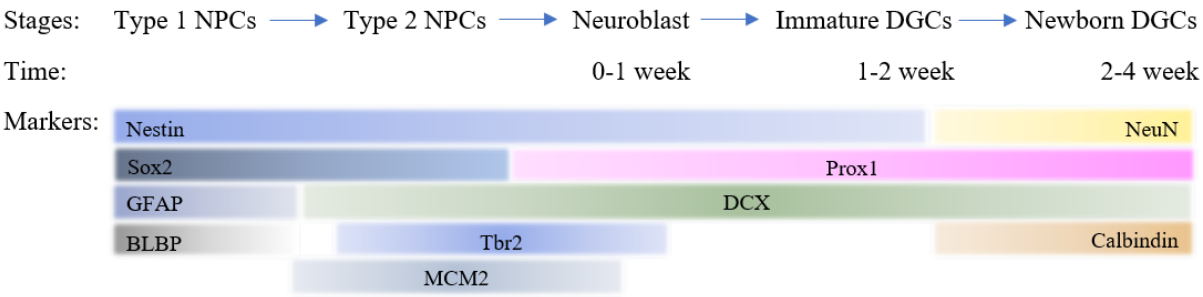

Figure 3: Stage specific markers of neuronal development in adult neurogenesis depicts time specific differentiation.

Adult neurons generated in these two neurogenic areas are integrated into existing neuronal circuits[39]. New adult neurons have a high input resistance and a subthreshold Ca^{2+} conductance, which enables new neurons for action potential firing with very small excitatory currents. This unique development may allow them to integrate easily into a mature brain without altering existing cognitive processes[44]. This integration plays important functions such as the migration of new neurons born in the SVZ migrate to the olfactory bulb via the rostral migration stream (RMS) and are encapsulated by the complex network of astrocyte tunnels in rodents [10,45] and in humans [46]. Decreased adult neurogenesis in SVZ in mice has been reported to induce abnormal olfactory and sexual behavior[47]. New neurons born in the SGZ are

integrated into the DG neural circuitry, which plays an important role in short-term memory generation. Impaired adult neurogenesis of SGZ in mice has been reported to impair new memory formation[48,49]. In particular, these new neurons are important for spatial memory formation[50]. Furthermore, new integrated neurons in the DG have also been important in memory consolidation during Rapid eye movement (REM) sleep in rodents [51].

Adult rats produce approximately 9,000 new neurons daily in the SGZ, with a survival rate of approximately 50%[52]. In an adult human, the data showed that 700 new neurons are added to the SGZ every day. About as many are also lost, keeping the total number of hippocampal cells roughly constant. The annual yield is almost 2%[53].

This process of neural stem cell proliferation, lineage differentiation, migration and integration of the developing neuron in the adult brain has been regulated by both intrinsic, genetic, epigenetic factors and extrinsic signaling pathways [54]. Membrane-bound extracellular factors and their intracellular signaling cascades have been identified in the regulation of the SVZ and SGZ neurogenesis, which includes Wnt, sonic hedgehog (Shh), Notch, BMPs, neurotrophins, growth factors (BDNF, FGF-2), various neurotransmitters (glutamate, GABA and dopamine), cytokines (IL-6), and hormones (estrogen, corticosterone) [44;54]. Further, intrinsic mechanisms including miRNAs, transcription factors and epigenetic regulators have been shown to be crucially involved in regulating neurogenesis in the adult mammalian brain [54]. Thus, future research trends will be based upon modulation of these factors, manipulating the production of new neurons, and improving the disease condition.

Association of Adult neurogenesis and AD

Adult neurogenesis reduces during normal aging in healthy brains and during Alzheimer's disease (AD). Hippocampal adult neurogenesis helps in cognition and memory formation [55]. Aging is the greatest risk factor for AD. The reduction of new born neurons during aging and AD leads to cognitive loss and impairment of memory [56]. The integration of the new neurons is impaired during aging. This is because of loss of extrinsic signals (physical activity, dietary intake) or reduced response of the precursor cells/stem cells to normal signalling during aging, or AD [57].

Adult neurogenesis of both SVZ and SGZ are affected during AD. The alteration of neuronal proliferation, differentiation, maturation and survival in both SVZ and SGZ is observed in

different transgenic adult mouse models of AD[42], in human iPSC cell lines [58], and clear reduction shown in the post-mortem of AD patients compared to healthy donors [59,13]. As discussed earlier there is a lack of evidence in the increase or decrease of new neurons in AD patients and some show increase in the generation of new neurons [43,60,61]. This alteration in outcome may be related to the observation of different stages of AD in relation to neurodegeneration. According to various hypotheses, enhanced new born neurons may arise in the affected brain as a homeostatic self-healing mechanism[62] ; and decreased neurogenesis might be contributing to the AD pathophysiology[63,64]. So, in the decreased condition of neurogenesis in AD, Amyloid-beta (Aβ) peptide, would deregulate new born neurons for facilitating disease progression [63]. The mechanisms of how the various Aβ species affect adult neurons remain unclear, and defining the pathophysiological environment of the AD brain remains an area of research.

By studying and targeting the molecular players involved in the different stages of adult neurogenesis it can be used as a potential biomarker for AD and creating an alternative therapeutic option for the treatment. Current therapeutics for AD only provide symptomatic relief but doesn't reverse the damage of neurodegeneration. Adult neurogenesis in the hippocampus could be an option to reverse the process of neurodegeneration. But scientists are still figuring out at what point in the disease, adult hippocampal neurogenesis plays a role in AD's pathophysiology. Also, studies show in rodents, there is no negative impact of increased neurogenesis in AD models[42], but there might be ethical concerns in humans. Adult neurogenesis is restricted in humans but there is a possibility to induce human neural precursor cells to generate new neurons, to cure neurodegenerative diseases, such as AD [11]. We can enhance neurogenesis either by stimulating the production of endogenous NSCs by manipulating the extrinsic and intrinsic signals or by providing exogenous NSCs. For instance, transplanting stem cells into the AD mouse model reversed cognitive deficits [65]. Additionally, more research is conducted to understand this stem cell therapy carried out in clinical trials pertaining to humans. Whereas, endogenous therapeutic targets would be to neutralize intracellular Aβ oligomers in the adult NSCs by using gene therapy, and at the same time restoring functional neurogenesis [11]. Another target to cure AD through adult neurogenesis could be interleukin-4. Studies have shown that interleukin-4 inhibits Aβ42 aggregation and restores the proliferative and neurogenic ability of NSCs by suppressing Aβ42 in zebrafish [66].

Other therapeutic approaches like increasing adult neurogenesis with the help of different modulators had neuroprotective effects on mice with cognitive impairment [67], so modulating neurogenesis could be helpful in reversing the process of AD. Studies show that the help of running/exercise promotes the rapid integration of new neurons in the aging brain through modulating neurotrophins, which promotes the plasticity of aging networks in the hippocampus [56]. In AD condition exercise also helps in enhancing neurogenesis and improved cognition along with reduced Aβ load and also increased levels of brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), fibronectin type III domain – containing protein–5 (FNDC5), and synaptic markers which helps to improve adult neurogenesis survival and maturation [68].

Future directions:

The alteration of adult neurogenesis during AD, could be proposed as biomarkers for AD progression in humans, and new literature indicates impaired neurogenesis in the early stages of AD patients, i.e. prior to amyloid plaque formation, so it would be of potential to use adult neurogenesis as an early stage biomarker for AD [11,59]. Although AD is a multifactorial disease whose phenotypic characteristics revolves around the neuronal death. Multiple protein aggregates in the different stages of AD maybe a connecting link in neurogenesis impairment. Thus, by using advanced techniques like NGS, immunohistochemical localization and electrophysiological recordings will open new avenues for the treatment of AD. Hence, more research should be focused on extrapolating and unravelling the mechanistic base and targeting its therapeutic biomarker.

Conclusion

Current therapies for AD aim at symptomatic relief and are futile once neurodegeneration crosses a certain stage. Adult neurogenesis is a well-examined phenomenon and is still under exploration as a therapeutic mode for neurodegenerative diseases. Artificial induction of neurogenesis can be a much efficient treatment mode for AD as it can overcome the loss of neurons caused due to neurodegeneration and replenish the source of healthy neurons. However, further research is required to study the effect of induction of neurogenesis on an aging brain and its feasibility as a biomarker for Alzheimer's disease.

Glossary:

β-amyloid protein- Peptides of 36-43 amino acids in size that cause plaques in brains of people having Alzheimer's Disease.

Microtubules- polymers of tubulin protein that form cytoskeleton to support the eukaryotic cell.

Tau protein- microtubule associated proteins which are known to maintain stability of axons.

Neural stem cells- self-renewing cells in the nervous system that give rise to neurons and glia.

Dementia- A group of thinking and social symptoms that interferes with daily functioning.

Autosomal- located on one of the non sex chromosomes.

Cognitive- Involved in gaining knowledge and comprehension.

Familial- Family-related or occurring within a family.

Atrophy- Reduction in size of cell, organ, or tissue, after attaining its normal mature growth.

Neurotrophins- Neurotrophins are a family of proteins that promote the survival, development, and function of neurons.

Homeostatic- The process by which an organism tends to maintain stability while adjusting to the best conditions for survival is termed homeostasis.

Wnt- The Wnt signaling pathway consists of a group of signal transduction pathways that begin with proteins that transmit signals to cells via cell surface receptors.

Sonic hedgehog (Shh)- Sonic hedgehog is a protein that is encoded by the SHH gene. Different types of animals use this signaling molecule to regulate embryonic morphogenesis.

Notch signaling pathway- Notch is a highly conserved signaling pathway that is found in most animals.

Calbindin- it function is in mediating calcium absorption.

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