The Genetic Basis of AD Incidence and Treatment

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Abstract: Alzheimer's disease (AD) is caused by neuron death and is one of the diseases that cannot be cured under current medical technology. This review provides a summary of the relationship between the expression of three common AD-related gene variants (APP, PSEN1 and PSEN2) and the formation of abnormal Aβ and tau proteins aggregations (plaques and tangles). The possibility of using gene therapy to cure AD is also stated in this review. During research, several recent papers about gene-related AD are viewed. In those papers, researchers did experiment on transgenic mice and matched the results with markers of human AD to confirm that investigated gene variants are AD-related. However, mouse models cannot represent whole human AD characteristics, symptoms like language deficits cannot be investigated on mouse models. Furthermore, researches show that gene therapy such as overexpression of PGC-1α can eliminate AD-like symptoms in transgenic mouse models. It illustrates the potential of treating AD by using this type of gene therapy. Importantly, genetic technology is still under exploration before the safe application of gene therapy on humans due to possible unknown consequences of editing human genes.

1 INTRODUCTION

Among aged people, AD is a common neurodegenerative disease. It is mainly represented by cognitive impairment and memory loss led by death of nerve cells and diminished synapses. In order to reduce the suffering of both AD patients and their families, lots of researchers are trying to know more about the pathogenesis of AD and find out effective therapies. According to known information, carriers of some mutant genes are more possible to develop AD (Jeong 2017). Reviewing previous papers aims to list the most common gene variants, which were confirmed to be able to enhance AD incidence, and show the pathways they use. For example, gene mutations might cause abnormal proteins production to disturb both transmission and survival of neurons (Thal, Fändrich 2015). During investigation on curing AD, it is nonnegligible that the commonly used AD therapies are only for AD symptoms attenuation but do not have real therapeutic effects. However, as gene mutations can cause AD, editing specific gene is possible to treat AD and it has been proofed feasible on mouse models (Katsouri, Lim, Blondrath, Eleftheriadou, Lombardero, Birch, Mirzaei, Irvine, Mazarakis, Sastre 2016). The therapeutic effects on mouse models show that it is worth to keep an eye on how gene therapy can cure human AD without causing unwanted side effects. As there are too many differences between mice and humans, future investigations can focus more on other primates which are closer to humans than rodents.

2 BASIC INFORMATION ABOUT ALZHEIMER'S DISEASE

The degeneration of neurons and their connections in the AD brain is mostly due to accumulation of two misfolded proteins in the brain: amyloid β-peptide (Aβ) and tau-protein (an accessory protein of microtubule). In AD brains, Aβ aggregate to form intercellular plaques; tau-proteins which do not correctly attach to microtubule make intracellular twisted fibres (tangles) (Thal, Fändrich 2015). Aβ oligomers (intermediate before forming fibril from Aβ peptides) disturb synaptic plasticity so they can cause long-term depression and further synapse loss (Jeong 2017). In addition, the extracellular Aβ plaques reduce diffusion among cells, therefore result in decayed neurons communication (Gendron, Petrucelli 2009). Tau filaments inside cells cause neurons death because they can displace the location

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and reduce the number of organelles, disturb cellular homeostasis and impair microtubule dynamics (Thal, Fändrich 2015). Except for the two proteins, neuron degeneration can also arise from several other factors, for instance, chronic inflammation by dysfunctional glial cells and reduced cerebral vascular blood flow (https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease).

Brain shrinking caused by neurodegeneration with a specific pathway is an important characteristic of AD. The entorhinal cortex and the hippocampus, which are significant brain regions about memory, are usually the starting points of it. Then, it slowly spreads into medial parietal, lateral temporal and frontal regions. Finally, the whole cerebral cortex can be affected by atrophy, the patients cannot handle daily tasks (Fjell, McEvoy, Holland, Dale, Walhovd 2014).

Researchers believe that there are various risk factors that are responsible for the pathogenesis of AD, such as, age, genetic inheritance, exposure to aluminium, traumatic brain injury, vascular diseases (A Armstrong 2019). Although family history is not the most prominent risk factor of AD, understanding the mechanisms of the gene mutations that are related to the neurons degeneration and finding out the suitable genetic treatments can be effective in delaying and curing AD.

3 GENETIC EFFECT ON INCIDENCE OFAD

3.1 Early-onset Familial AD

Early-onset familial AD(EOFAD) usually happens under 65-year-old and has high heredity, which is about 92-100%. EOFADs that follow Mendelian inheritance occupy about 10-15% of all EOFADs and are confirmed to be associated with mutations on APP (Amyloid protein precursor), PSEN1 (Presenilin-1) and PSEN2 (Presenilin-2) genes (duplications and missense) (Ayodele, Rogaeva, Kurup, Beecham, Reitz, 2021). These mutations have a similar effect, which is increased Aβ42 to Aβ40 ratio. Because Aβ42 is more prone to aggregation, plaques are more possible to be formed (Tanzi 2012).

APP is the gene that is mapped into chromosome 21, which codes for amyloid precursor protein (APP) (Tanzi 2012). Both 40 and 42 amino acids long Aβs (Aβ40 and Aβ42) can be produced by proteolytic processing of APP by β-secretase and γ-secretase (Jeong 2017). In Nilsson and colleagues' APP knock-in mouse models, as figure 1 shows, 2 clinical mutations are introduced to mice APP genes. The Swedish mutation (KM670/671NL) increases β-cleavage so enhance total Aβ production and the Beyreuther/Iberian (I716F) mutation increases γ-cleavage to increase Aβ42/Aβ40 ratio. Observation shows formation of plaques that mainly contained Aβ42 appears at the age of 6 months. In addition, microglia and astrocytes also accumulated near the plaques. These observations in APP mutant mice are consistent with the pathology that can be found in the human AD brains. The abnormal Aβ accumulation later reduced synaptic plasticity and led to memory impairment in the 18 months old transgenic mice, which also match the symptom of AD (Nilsson, Saito, Saido 2014).

PSEN1 gene locates on chromosome 14 and codes PS1 protein, which comprises the γ-secretase catalytic site (Tanzi 2012, Sasaguri, Nagata, Sekiguchi, Fujioka, Matsuba, Hashimoto, Sato, Kurup, Yokota, Saido 2018). In the analysis of PSEN1-P436S and PSEN1-P117L transgenic mice, results show that these mutations induce abnormal cleavage activity of γ-secretase and increase Aβ42/Aβ40 ratio (Sasaguri, Nagata, Sekiguchi, Fujioka, Matsuba, Hashimoto, Sato, Kurup, Yokota, Saido 2018). The reason is that changes in PS1 protein can affect the conformation of catalytic component of γ-secretase and eventually change its activity. Only a single PSEN1 mutation might be

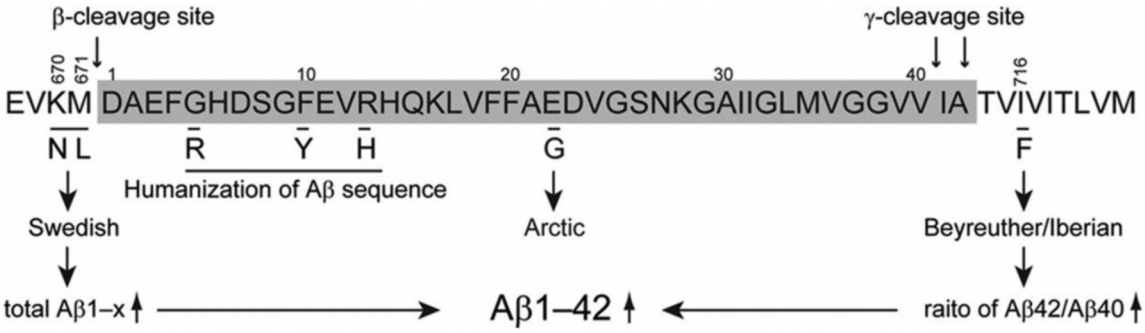

Figure 1: Different mutations and their effects (Nilsson, Saito, Saido 2014).

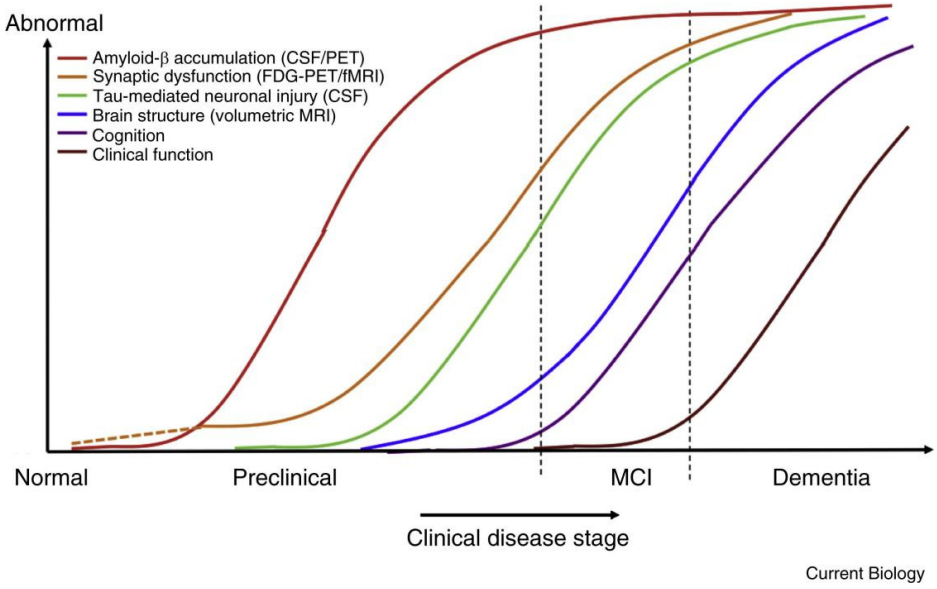

Figure 2. Sequential changes of biomarkers of AD over time (Grøntvedt, Schröder, Sando, White, Bråthen, Doeller 2018)

insufficient to observe all AD characteristics such as change in behaviors on transgenic mice (Sasaguri, Nagata, Sekiguchi, Fujioka, Matsuba, Hashimoto, Sato, Kurup, Yokota, Saido 2018). Nevertheless, figure 2 illustrates that the abnormal rising Aβ level is an important biomarker for AD which shows up first (Grøntvedt, Schröder, Sando, White, Bråthen, Doeller 2018). The observation on PSEN1 gene mutant mice is consistent with the biomarker so PSEN1 mutations can be proofed to be AD-related.

PSEN2 is mapped on chromosome 1 (Tanzi 2012). Similar to PSEN1 mutations, mutant PSEN2 gene also raises Aβ42 level by altering γ-secretase activity (Giau, Bagyinszky, Youn, An SSA, Kim 2019). It might be even harder to investigate the influence of mutant PSEN2 individually because its expression is about 10 folds lower than that of PSEN1 in the brain (Ayodele, Rogaeva, Kurup, Beecham, Reitz 2021). However, researches show that PSEN2 mutation can accelerate Aβ accumulation and memory impairment in transgenic mice with APP mutation. In Fedeli and colleagues' experiment, to introduce PSEN2 mutation into APP mutant mouse, they cross PSEN2 mutant female (N1411) with Swedish APP mutant male which expresses humanized Aβ sequence (Tg2576). The double mutant mouse shows early Aβ aggregation at 2-3 months of age (6 months in Tg2576 mice), and also early impaired learning and memory function at 4-5 months of age (7-8 months in Tg2576 mice) (Toda, Noda, Ito, Maeda, Shimizu 2011). The observations fit human AD biomarker and symptoms respectively.

The rest 85-90% EOFADs do not follow Mendelian inheritance and are caused by other unknown gene mutations. They are believed to be induced by undentified or mixed genetic variants (Ayodele, Rogaeva, Kurup, Beecham, Reitz 2021). It might be helpful in developing gene therapy of AD if more AD-related gene variants can be discovered in the future.

3.2 Late-onset Familial AD

Late-onset sporadic AD (LOSAD) patients are usually more than 65 years old. Unlike EOFAD, LOSAD does not have a particular mode of transmission so weaker familial clustering (Tanzi 2012). APOE gene on chromosome 17 is popular while studying AD since it is considered the most common gene that is related to AD (Safieh, Korczyn, Michaelson 2019). It codes for apolipoprotein E (apoE protein), a lipid binding and transporting carrier protein, which is important for the cholesterol transport in and out the central nervous system (CNS), Aβ binding, clearance and synaptic function in the brain (Theendakara, Peters-Libeu, Bredesen, Rao 2018, Dorey, Chang, Liu, Yang, Zhang 2014). There are 3 types of alleles of APOE gene, APOE ε4, APOE ε3 and APOE ε2 (sequence from high to low risk of developing AD) (Theendakara, Peters-Libeu, Bredesen, Rao 2018). APOE4 allele is considered as a significant risk factor of LOSAD (Jeong 2017).

First, APOE4 can increase Aβ deposition in the brain. In Youmans and colleagues' mouse models,

They cross female mice, which have five familial AD-related gene muations, with male homozygous APOE2-, APOE3- and APOE4- mice to produce EFAD mice. The results indicate that E4FAD mice have higher Aβ42 levels and plaque deposition than both E2FAD and E3FAD mice (Youmans, Tai, Nwabuisi-Heath, Jungbauer, Kanekiyo, Gan, Kim, Eimer, Estus, Rebeck, Weeber, Bu, Yu, Ladu 2012). According to figure 3, APOE4 gene have these effects by increasing production and reduce loss of Aβ (Dorey, Chang, Liu, Yang, Zhang 2014). APOE4 protein alters γ-cleavage on APP gene to enhance Aβ42 production, therefore following plaque deposition as well. Additionally, APOE4 carriers have reduced elimination of Aβ because: It impairs degradation of Aβ; it can not cross the blood brain barrier effectively; APOE3 can form complex with Aβ to stop fibrillation but APOE4 cannot (Safieh, Korczyn, Michaelson 2019).

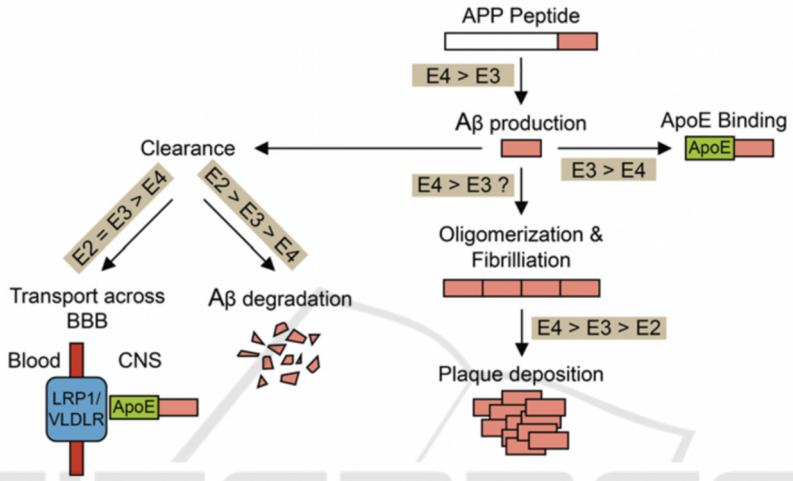

Figure 3. comparison of interaction between APOE gene alleles and Aβ (Dorey, Chang, Liu, Yang, Zhang, 2014)

In addition, APOE4 gene can interact with tau-protein to increase risk of AD as well (Safieh, Korczyn, Michaelson 2019). In Shi and colleagues' investigation, tau transgenic mice (P301S) are treated by human APOE knock-in or APOE knock out. The comparison among observations in P301S/E2, P301S/E3, P301S/E4 and P301S/KO mice shows that P301S/E4 mice have higher tau level in the brain, which might results from weak autophagy-mediated tau clearance caused by APOE4 (Shi 2017). Additionally, APOE protein can affect the hyperphosphorylation of tau. APOE3 protein can bind tau effectively to prevent accumulation while APOE4 protein cannot; APOE4 protein is stronger in escaping secretion so it can stay in cytoplasm to phosphorylate tau to greater extent through both direct and indirect interaction (Safieh, Korczyn, Michaelson 2019). The P301S/E4 mice are shown to have greater hyperphosphorylated tau (ptau) covered area (Shi 2017). Since neurofibrillary tangles are mainly constituted by hyperphosphorylated tau and can directly lead to neurodegeneration, APOE4 significantly raises the risk of developing AD.

There are still problems with AD-related gene mutations investigations. As scientists cannot do transgenic experiments on human, and also AD patients might be affected by various other factors like different lifestyles, the variables cannot be controlled strictly while investigating relationship between mutant genes and the incidence of AD. In addition, although mouse models are a quite useful tool, it is impossible to present AD symptoms on functions beyond rodents' memory system including language and episodic memory on them. It is also important to know that human AD is not only decided by a single gene mutation, it might comes from the combination of several mutations and even some environmental factors. In this case, it is difficult to present all of these on mouse models. Nevertheless, the experimental results are still meaningful after bringing the biomarkers for human AD and other AD-like symptoms on the transgenic mice together. Hence, the screening of AD-related genes can be a reference while evaluating the AD onset possibility of a person, and also help to make a judgment on whether early treatment is needed or not. People should also understand that having AD-related genes does not mean that they will develop AD for sure, those genes only means their possibility of having AD is higher.

4 TREATMENT OF AD

The treatment of AD is usually a hot topic among researchers who are interested in AD. Nowadays, a common drug for AD patients is Tacrine. Because acetylcholine is an important neurotransmitters in the brain and it is broken down by acetylcholinesterase. These drugs can increase acetylcholine level in synapses by inhibiting acetylcholinesterase activity. Therefore the loss of neurons in AD brains can be offset by the increased activity of survived neurons. However, these drugs can only attenuate the symptoms of AD but have no curative effect since they are not reducing the plaques and tangles, neurons keep degenerating and AD keeps getting worse.

In order to cure AD, the death of neurons should be stopped, so the plaques and tangles which cause this must be eliminated. Hence, both reducing the formation and increasing the clearance of plaques and tangles should be considered. In this case, gene therapy might be the most efficient way to achieve the aim because proteins are coded by DNA. By editing patients' DNA, increasing the expression of proteins which can inhibit the formation or promote the clearance of key AD proteins, might be able to decrease or even remove the plaques and tangles in AD brain. Gene therapy of AD is proofed feasible on mouse models. Katsouri and colleagues found that overexpression of PPARγ coactivator-1α (PGC-1α) gene can reduce the secreted level of insoluble Aβ by reducing the transcription of β-secretase through co-activating nuclear peroxisome proliferator activated receptor-γ (PPARγ) and other transcription factors (Katsouri, Parr, Bogdanovic, Willem, Sastre, 2011). To investigate the therapeutic effect of PGC-1α gene on AD patients, they inject human PGC-1α (hPGC-1α) gene to hippocampus and cortex of APP23 transgenic mice. The result shows that selectively inducing hPGC-1α gene to specific brain regions can reduce Aβ aggregation, β-secretase expression and neuroinflammation; improve the spatial and recognition memory of these mice; provide some neuroprotective effects. However, this therapy has no effect on wild-type mice (Katsouri, Lim, Blondrath, Eleftheriadou, Lombardero, Birch, Mirzaei, Irvine, Mazarakis, Sastre 2016).

To provide the treatment on humans, there is still such a long way to go because there might be unpredictable consequences on editing human gene. Nevertheless, the PGC-1α gene therapy can be an inspiration for future research direction since it effectively reduces neurons degeneration in mouse models, which shows the potential of gene therapy to be applied in early AD treatment. Unfortunately, for late AD patients who have great extent of neurons degeneration, nearly fully impaired memory and cognition, gene therapy like PGC-1α overexpression is not useful because it aims to stop neurons degeneration but not generating new neurons. Producing new neurons is another aspect of treating AD, which might be related to stem cell therapy and still need lots of effort on the methods to unfrozen the differentiation of stem cells.

5 CONCLUSIONS

For now, what people know is that AD is an irreversible disease, which means patients' symptoms worsen gradually until they die as recent medical technology is not able to stop AD effectively. Therefore, more researches on both the pathogenesis and treatment of AD are necessary for finding effective precautions and therapies of AD. This review only talks about AD pathogenesis which is related to genes but there are lots of other non-negligible factors can cause AD such as age and lifestyle. The reason of focusing on gene is that gene screening can help early prevention or even early treatment if already diagnosed as AD. Except for the four most common genes discussed, there are still lots of other suspectable gene mutations might affect AD pathogenesis but they appear fewer and are less understood. If more AD-related genetic variants can be confirmed, there can be more target for AD gene therapy researches no matter direct or indirect. Currently, gene therapy is still in the laboratory stage and cannot be applied on humans. Because the gap between researches on animals and humans is large, and also the knowledge about human gene is still insufficient. People are not capable to take the risk of developing possible unknown side effects by editing human gene nowadays. Importantly, ethic problems on genetic therapy should not be neglected as well. Hence, scientists still have loads of tasks like discovery and elimination of unwanted side effects before actual application of gene therapy on human. To achieve the goal, it is more helpful to do experiments on other primates such as monkeys because their brain structures are much more similar to human brains than rodents. This might be the general direction of researching gene therapy in the future. After all, gene therapy has the potential to stop and even cure AD, people will understand more about human gene and finally apply safe and effective gene therapy on AD treatment in the future.

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