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Blockage of Alzheimer's gene: Breakthrough effect of Apolipoprotein E4

Babatunde Oluwafemi Adetuyi[1]*, Peace Abiodun Olajide[2], Oluwakemi Semiloore Omowumi[3], Grace Onuwabhagbe Odine[4], Darasimi Deborah Okunlola[5], Anjolaoluwa Maryann Taiwo[6] and Oluwaseun Dorcas Opayinka[7]

[1,2,3,4,5,6,7] Department of Natural Sciences, Faculty of Pure and Applied Sciences, Precious Cornerstone University, Ibadan, Oyo State, Nigeria

Corresponding author: badetuyi@pcu.edu.ng

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Abstract:
One of the essential hereditary hazard factors for AD (Alzheimer's Disease) is the existence of APOE (Apolipoprotein E4 allele). Multivariate lipoprotein called APOE happens to be crucial for the movement of cholesterol in the brain. Along with other things, it has a crucial function in the breakdown of glucose, neuro-inflammation, and neuronal signaling. The 3 Apolipoprotein allele variants include E2, E3, and E4. The most occurring allele in humans is the E3 allele. The risk of Alzheimer's disease is connected to the E4 allele being higher, but the E2 allele is connected with a slighter risk. Building cellular and animal models has taken a lot of effort in order to comprehend the molecular processes behind APOE-related genetic risk. Results from these concepts suggest that APOE4 may increase tau development of disease in a manner similar to that of isoform-dependent and that it aggravates amyloid plaque load in a manner similar to dose-dependent.

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Introduction

Senile dementia is the most prevalent kind of Alzheimer's disease (AD). It's a degenerative nervous condition which starts off with memory loss and cognitive decline but can later have an impact on speech, behavior, visuospatial orientation, and the motor system [1]. Pathological subtypes of Alzheimer's disease have been established, and variant syndromes with early localized atrophy may not always present in the same way [2]. The source of most dementia cases (60 to 80 %) have been traced down to AD with < 40 % being pure AD and the remaining cases being combined dementias [3]. The general occurring dementia-related factors, each accounting for 5 to 10 percent of cases, are; vascular dementia, normal pressure hydrocephalus, frontotemporal lobar degeneration, Parkinson's disease with dementia and Lewy body dementia are some examples of dementias. The most common mixed pathology, including concomitant AD, is related with Lewy body dementia and vascular dementia [3].

Ancient History of the Amyloid-β (Aβ) Pathway in Alzheimer's Disease

The Amyloid-B protein is a 4 kilo Dalton component of the larger APP (amyloid precursor protein), which is produced by astrocytes, blood components, such as platelets, and brain neurons to a lower degree. APP undergoes 2 proteolytic enzymes at the ectodomain and by β-secretase (memapsin 2) at intra-membranous sites, resulting in the production of Aβ [4]. The full amino acid arrangement of the parenchymal Aβ plaque core was discovered to

be similar to the perivascular art explained before, with the exception that the latter only reaches the 42nd residue. In 1984, the first reported primary component of meningovascular polymorphic deposited in down syndrome's patients are Amyloid –β and its amino acid arrangement 1984 [5]. The amyloid precursor protein gene was sequenced, proving that Amyloid-B is an end result of APP's enzymatic activity [6]. Eventually, dense Aβ aggregates and tau neurofibrillary tangles (NFTs) were shown to be the major components of neocortical neuritic plaques, which are a clinical indicator of AD and brain aging are connected [7].

Hereditary Fact of the functions the Amyloid-β Pathway

Early-Onset Alzheimer's Disease (EAOD)

The genes found to have highly penetrant mutations after extensive genetic study of key monogenic EOAD pedigree datasets are three and they include the Presenilin 1 gene (PSEN1), Presenilin 2 gene (PSEN2) and amyloid precursor protein gene. These mutations are passed down by autosomal dominant inheritance, which causes ADAD (autosomal dominant Alzheimer's disease). Each monogenic mutation that causes ADAD in mice is also responsible for Aβ dyshomeostasis, which causes aggregation, accumulatins and protein misfolding in brain parenchymal Aβ plaques. [8]. This linear patho-mechanistic model, which states that "one mutation leads to one misfolded protein," give rise to the creation of the term "amyloid cascade" [8]. About 1% of all AD cases in humans have genetic causes, and the amyloid precursor protein gene, Presenilin 1 gene and Presenilin 2 gene, which have over three hundred different autosomal dominant mutations, account for the majority of genetic variants [9, 10]. On chromosome 21, there is a gene known as the APP. Down syndrome patients, who possess APP gene in triplicate forms exhibit cognitive impairment that is connected to AD molecular markers, according to a number of genetic linkage studies and observational evidence [8]. Additionally, 25 chromosomal duplications, including amyloid precursor protein, have been seen to co-segregate with Alzheimer's disease in families with ADD (autosomal dominant disease) transmission [11, 12]. The bulk of harmful mutation in the amyloid precursor protein gene cluster near the β- and γ-secretases' proteolytic sites, increasing substrate affinity downstream and altering the ratios of Aβ-peptides or increasing the total amount of Aβ-pools overall. The latter is defined by shorter species levels and a relative increase in Aβ1-42 levels over Aβ1-40 [8, 11, 12]. This imbalance is believed to promote protein self-accumulation [13]. The APP gene's likely pathogenic function in human beings is assisted by the presence of an uncommon protective variant—APP A673T (or A2T)—near the APP β-secretase site which diminishes APP cleavage & the creation of amyloidogenic Aβ peptides [8, 11, 12]. Older Icelanders without dementia had a prevalence of the A673T uncommon variant that is five times greater than that of those carrying Alzheimer's disease. The bulk of identified AD-related mutations are caused by autosomal dominant PSEN1 mutations. In this complex, there have been over 200 mutations discovered [14]. Less than 40 mutations have been found in PSEN2 thus far, making them rare [15].

In vitro and in mouse models with the PSEN1/PSEN2 gene deleted, less APP Intracellular Domain fragment (AICD) with other γ-secretase substrate processing was seen. These results suggest an induced hereditary γ-secretase deficit [16]. A distinct reduction in roles of APP-secretase-dependent cleavage is brought on by a number of pathogenic PSEN1/2 mutations.

This loss of function is accompanied by a change to the Aβ1-42 position cleavage and a reduction in the production of both Aβ1-42 and Aβ1-40 [17]. PSEN2 mutations, in contrast to PSEN1 mutations, allow AD to strike patients of any age, from 40 to 80 years old. Lewy body dementia (LBD), breast cancer, Lewy body dementia (LBD), Behavioral variant Frontotemperol Dementia (bvFTD), and idiopathic cardiomyopathy are additional conditions connected to PSEN2 mutations [18].

Late-Onset Alzheimer's Disease (LOAD)

There are no known genetic mutations (autosomal dominant or recessive) that cause late-onset AD at this time [19]. It is believed that LOAD is a multidimensional illness with a challenging genetic background. More than 50 susceptibility genes/loci have been linked to LOAD risk in large-scale whole-genome association study (WGA study), which have found numerous important hereditarily risk factors in Alzheimer's disease susceptibility (Table 1) [19].

Pathway analysis further demonstrate that heterogeneousness in these genes might have a pleiotropic impact or may not be straightforwardly connected with the Aβ pathway however code for proteins whose changes are connected to a network-wide influence on Aβ homeostasis. Numerous LOAD-related genes are involved in the regulation of immune and inflammatory reaction pathways, cholesterol transport and lipid metabolism,

endocytosis and cellular trafficking, and post-translational regulation, including gelsolination, an important mechanism for cellular protein clearance.

Table 1 Genome-wide significant loci for sporadic late-onset Alzheimer's Disease connection.

Locus	GWS locus or gene	Dataset	Functional Information
1	APOE	Case–control	A multifaceted protein primarily recognized for its function in lipid transport, the ability to bind soluble Amyloid-β.
21	SORL1	ADES-FR	Endocytic receptors involved in the processing of APP, lysosomal targeting of Amyloid-β, and lipoprotein uptake.
25	ADAM10	IGAP+	Metalloprotease in charge of APP proteolytic processing.
36	APP	Icelandic, Finnish and Swedish	APP
37	IGHG3	ADSP	A gene for immunoglobulins whose antibodies react with Amyloid-β.

Datasets: Alzheimer's disease sequencing project (ADSP); International Genomics of Alzheimer's Disease Consortium (IGAP); Alzheimer's Disease Exome Sequencing-France (ADES-FR)

Apolipoprotein E4

The primary heredarily risk factor for AD is apolipoprotein E4. The most prevalent neurodegenerative dementia, AD, affects lots of human beings in world. Neuropathologically, it's identified by the deposition of intracellular tau protein neurofibrillary tangles (NFT) and extracellular amyloid (A) [20]. The existence of the APOE protein's E4 isoform is among the main hereditary risk factors for rare Alzheimer's Disease, which is known as late-onset Alzheimer's Disease. The three primary APOE alleles in human beings are E2 alleles, E3 alleles, and E4 alleles [20]. While the APOE2 variant is connected to a lower risk of Alzheimer's Disease, the APOE4 allele raises the risk of Alzheimer's disease in a dose-dependent pattern and age-dependent pattern. The most well-known allele in the populace is APOE3 [20].

The APOE Peripheral and CNS Pools

Transporting cholesterol is the main job of APOE. It has 299 amino acids and an apparent molecular weight of 36 kDa [21]. The 3 isoforms contrast from each other at 112 position and 158 position of the amino acid, which has a substantial impact on how each of them functions. APOE2 (Cys112, Cys158) & APOE3 (Cys112, Arg158) prefer to associate with little, phospholipid-rich HDL (high-density lipoproteins), whereas APOE4 (Arg112, Arg158) tends to associate with huge, triglyceride-rich lipoproteins (VLDL) [22]. Another difference is that APOE2 has the most reduced binding affinity for LDL receptors among all the isoforms [20].

In the central nervous system, astrocytes are the main origin of APOE production, while microglia and neurons can also produce it sometimes. Therapeutic approach, transcriptional regulation, gene regulatory control, and synapse formation are a few of the CNS functions of APOE [21, 23]. The liver produces more peripheral plasma APOE than the adrenal medulla and monocytes combined. APOE is crucial for regulating peripheral systemic inflammation, cardiovascular function, and other processes in addition to lipid metabolism [24]. This APOE pool typically survives under ordinary conditions virtually independently of the Central nervous system pool. Only peripheral APOE4 has a greater turnover rate than APOE3 and APOE2 compared to the central nervous system and peripheral APOE pools in humans and humanized mice [23, 24].

Function of the human APOE in rodent models

APOE impaired mice, APOE knock-in mice, and APOE hypomorphic mice are useful in the research of peripheral inflammation, dyslipidemia and cardiovascular disease [25]. Studies on mice and those on people typically produce comparable findings [26]. However, several significant variations between animal models and human triglyceride biology may have an impact on how animal research on APOE should be interpreted. The circulating cholesterol in mice and in human beings is mostly connected to high density lipoproteins and low density lipoproteins respectively [20]. The gene encoding CETP (cholesteryl ester transfer protein), which is responsible for transferring triglycerides and cholesteryl esters between lipoproteins, is also absent in mice [27].

The blood brain barrier (BBB) leakiness, abnormal cholesterol transport in the brain, and cognitive deficits are only a few of the symptoms displayed by the APOE4 targeted replacement (TR) mice, who have had the human

APOE4 gene substituted for their native APOE gene [28,29]. The two main neuropathologies (Aβ and NFT) found in people with Alzheimer's disease cannot be caused by merely substituting the endogenous mouse APOE gene with the human APOE4 gene. The use of APOE4 TR mice as a stand-alone AD model has frequently been constrained because to the lack of naturally occurring pathology comparable to AD.

Table 2 Effects of APOE consistent across human research, AD mouse models, and in vitro cell culture models

Pathogenic effect of APOE isoforms on AD related pathways	Mouse models	In vitro cell culture models	Human studies
Aβ Burden	E4 > E3 > E2	E4 > E3 > E2	E4 > E3 > E2
Insulin Signaling	E4 > E3 > E2	E4 > E3 > E2	E4 > E3 > E2
Neuronal Toxicity	E4 > E3 > E2	E4 > E3	E4 > E3 > E2
Glucose Metabolism	E4 > E3 > E2	E4 > E3 > E2	E4 > E3 > E2
Synaptic Function	E4 > E3 > E2	E4 > E3	E4 > E3 > E2
Inflammatory responses	E4 > E3 > E2	E4 > E3 > E2	E4 > E3 > E2
Tau-mediated neurodegeneration	(E4, E2) > E3	E4 > E3	E2 – E3 – E4
BBB Integrity	*E4 > E3 = E2	E4 > E3 – E2	E4 > E3 – E2
Cerebrovascular Function	E4 > E3 > E2	E4 > E3	(E4, E2) > E3
Lipid Transport	E4 > E3 > E2	E4 > E3	#E4 > E3 > E2
Network Connectivity	E4 > APOE4	N/A	E4 > E3 – E2

APOE affects the cascade of several pathways in an isoform-dependent way. E4 is associated with a larger pathogenic risk than E3 or E2 isoforms (E4 > E3 > E2), according to the pathways highlighted in green, which point to a general consensus on the APOE isoform effect in mice, men, and in vitro models. Between human study, animal model tests, and in vitro outcomes, the data from the paths shown in grey are inconclusive. The order of the APOE isoforms with the greatest pathogenic impact is indicated by the symbols (or >). The outcomes stated here are particular to the classical AD pathophysiology [20].
* and # indicate reports that contradict each other.

Lifestyle and Diet Serves as a Regulatory Function for APOE

Dyslipidemia, diabetes, and hypertension are linked to a set of illnesses collectively referred to as the metabolic syndrome (MetS). It has also been traced down to dementia. Few reviews have discovered a link between the APOE4 allele and an elevated risk of dementia brought on by MetS [30]. As a result, various case studies have investigated the relationship between reducing the risks associated with the APOE4 polymorphism and dietary and activity modifications. Even though there isn't much evidence that these lifestyle choices can significantly reduce the risk of metabolic dysfunction and AD by altering APOE function, their safety profiles make them appealing as potential future therapies in the field of personalized medicine that can be quickly implemented.

Exercise

Exercise appears to be a natural therapy option for Alzheimer's patients based on epidemiological statistics and rodent research. Exercise improves memory in humans by increasing blood flow to the brain, neurogenesis, and hippocampal volume [31]. Exercise stopped age-related neurovascular changes in wild-type mice, especially when the APOE gene was present [32]. This was consistent with the idea that aging-related functional decline in neurovascular units is significantly influenced by APOE and that exercise can mitigate these effects through altering neurovascular health. According to human case studies and animal studies, exercise can improve neuroplasticity, hence assisting people dealing with AD [33].

Statins

HMG-CoA reductase inhibitors, generally referred to as statins, are a class of medication used to lower blood cholesterol levels. Researchers believe that altered lipid homeostasis or, at the very least, elevated brain cholesterol

levels affect disease and risk. Different studies done in epidemiology have found a connection between higher blood cholesterol levels and a higher risk of AD, independent of APOE genotype [34]. Statin medication gave rise to a markedly reduced rate of cognitive loss through the course of six months, which led to numerous epidemiological investigations on the impact of statins on dementia in general [35]. However, neither the LEADe trial from 2010 nor the CLASP study from 2011, which both looked at the utiliztions of statins in Alzheimer's patients, showed a net advantage or damage as regards brain impairment as compared to the placebo group [36,37]. More convincing evidence that statins don't typically benefit Alzheimer's disease patients is provided by a thorough review [38]. These results, however, are at odds with a major Medicare senior study that discovered a connection between utilization of statin and a reduced risk of AD in specific populations [39]. The results showed significant differences in statin efficacy on the basis of sex and race, for instance, pravastatin was solely related with a lower risk of Alzheimer's disease in white women, whereas atorvastatin was efficacious in Hispanic men, black women and white women. This investigation proposes that while statin utilization might not be advantageous for everyone at risk for AD in the future of individualized medicine, clinicians should consider whether statins may have a greater potential effects in patients with chronic diseases based on gender, race, prevalent ailments, and APOE genotype.

Ketogenic Diet

High-carbohydrate, low-fat diets raise blood sugar levels after consumption and thus can impair APOE activity due to glycosylation and oxidative stress-induced [40]. These diets are linked to poor glucose metabolism in the brain, a biomarker for Alzheimer's disease. The levels of APOE in the serum (E4>E3) as well as hippocampus (E3<E4) changed in an isoform-dependent way when APOE TR rats were fed a high-fat diet [41]. Since APOE4 carriers have unusual reduce rates of carbohydrate metabolism in comparison to other APOE genotypes, these diets may have a significant impact on the metabolic status of APOE4 patients [42]. When young, healthy mice are fed either a ketogenic diet or a high-fat, low-carbohydrate diet, it has been discovered that ketones modify the microbiota and improve neurovascular functioning [43, 44].

APOE and Insulin Resistance

Hyperglycemia and insulin deficiency signaling, as already established, increase the incidence of MetS and are linked to an increased risk of AD [45]. Peripheral insulin resistance, which is also prevalent in APOE4 carriers, has been linked to decreased brain glucose metabolism and poorer memory performance [46-49]. On the other hand, a complex sex/APOE relationship was revealed in a clinical trial with insulin inhalers. In the APOE4 negative group of patients with Alzheimer's disease, women's cognitive performance decreased while men's improved, whereas both sexes' mental acuity remained stable in the APOE4 positive group [50-52].

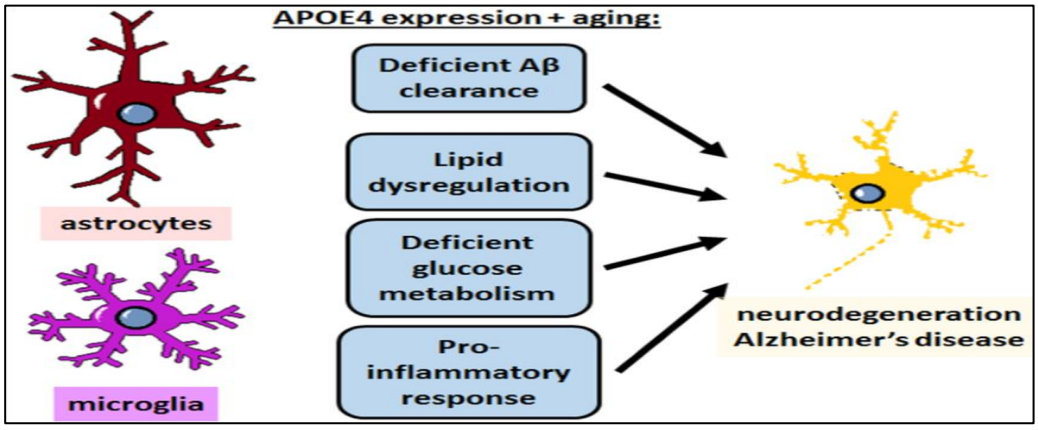

Figure 1 APOE4 disrupts homeostatic processes in astrocytes and microglia, leading to AD and neurodegeneration. It is conceivable that AD treatments could focus on specific processes that are damaged by APOE4 expression and the aging process itself in glial cell and its function. Recent studies have concentrated on lipid dysregulation, insufficient glucose oxidation, and neurological pro-inflammatory responses in neurons and, to a lesser extent, microglia, in addition to deficient Aβ clearance. In the end, each of these pathways combines with similar aging-related deficits to induce neurodegeneration [53-56].

Conclusion

When creating APOE-directed medications, it is important to take into account the complicated and multidimensional role that APOE4 plays in modulating the risk of acquiring AD. The understanding of these roles and how aging may alter the course of APOE4-mediated AD has advanced significantly in recent years. In particular with aging, LD formation and lipid transfer from neurons to glia, carbohydrate metabolism from glia to neurons, and APOE4's pro-inflammatory character and reduced cytolytic capacity all appear to be important routes in preserving cognitive performance. They may also be a factor in neurodegeneration (Figure 1). Although the specific mechanisms and interactions with APOE4 are not yet fully known, these pathways could lead to potential treatment interventions for the treatment of AD. Since it is unclear how APOE4-mediated altered function in glial cells could perhaps synergistically increase the risk of AD, more research is required.

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