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Apolipoprotein E Polymorphism And It's Lifestyle Impact

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Abstract

The Apolipoprotein E Polymorphism, with its three main allelic variants (APOE2, APOE3, and APOE4), has gained prominence in genetic research due to its critical implications for human health. This review article offers a concise introduction to the APOE protein polymorphism and its influence on individual's way of life. The APOE gene encodes apolipoprotein E, a critical component of lipid metabolism that is essential for both cholesterol transport and neuron repair in the central nervous system. APOE Ɛ4 raises Alzheimer's risk, Ɛ2 protects, and Ɛ3 is neutral. Lifestyle choices, such as diet, exercise, and cognitive engagement, predict susceptibility to chronic illnesses like Alzheimer's and cardiovascular disease (CVD). For APOE Ɛ4 carriers, a heart-healthy lifestyle can reduce elevated risk, while Ɛ2 carriers, being less vulnerable, may need less intervention.

Keyword:- Apolipoprotein E, APOE polymorphism, Alleles, lipid metabolism, Obesity, Alzheimer's disease, Cardiovascular disease, Vascular Dementia, Types II Diabetes Mellitus.

INTRODUCTION

Apolipoprotein E (APOE), a 299-amino acid glycoprotein encoded by the APOE gene on chromosome 19, is present in diverse tissues, such as the liver, brain, skin, and macrophages [1, 2]. APOE interacts with blood lipids, forming lipoproteins, notably very-low-density lipoproteins (VLDL). The APOE gene's three isoforms (E2, E3, and E4) result from single nucleotide polymorphisms, creating six phenotypes potentially affecting protein stability. Crucial for regulating blood lipid levels, APOE acts as a ligand for LDL receptor family members, facilitating lipid removal for liver clearance. Mahley et al.,'s research highlighted the APOE's involvement in chylomicron and VLDL development, influencing proteins in lipid metabolism. Recent studies suggest APOE and its variants may play roles in maintaining normal brain function [3].

Structure of Apolipoprotein E

Wetterau et al., illustrated how genetic variations mold the protein structure, giving rise to a stable amino-terminal domain (residues 20–166) and a less stable carboxy-terminal portion (residues 22–299), interconnected by a hinge region (residues 166–224). Chen et al., pinpointed essential amino acids within residues 136-150 critical for the LDL receptor-binding region [4, 5]. Segrest et al. precisely outlined the primary lipid-binding area in the carboxy-terminal domain [6]. Westerlund et al., showcased HDL binding even in the absence of the carboxyl-terminal domain, while VLDL particle binding relies on specific amino acid residues within 245-266 [7].

Papaioannou et al., highlighted the impact of the Arg158 Cys polymorphism in APOE Ɛ2, disrupting the natural salt bridge between Asp154 and Arg158 associated with HLP type III [9, 6]. Converting Asp154 to alanine restores normal receptor binding. The APOE Ɛ3 allele, characterized by cysteine at position 112 and arginine at position 158, influences Ɛ4 allele characteristics. Changes in Arg61's position in Ɛ4 enhance domain interaction, and altering Arg61 to Thr (or Glu255 to Ala) may reduce interaction, resulting in a Ɛ3-like molecule [1, 3].

Functions of Apolipoprotein E

The APOE gene has a significant impact on various aspects of well-being. The APOE genotype of an individual, whether it is APOE2, APOE3, or APOE4, has unique effects on lipid metabolism and susceptibility to diseases, resulting in a variety of outcomes and risks.

Peripheral System

In the bloodstream, APOE, a glycoprotein with 299 amino acids, interacts with LDL, VLDL, and HDL [10]. APOE's involvement in various physiological processes was emphasized by Rall et al., [10]. Within the plasma, APOE engages diverse lipoproteins, such as chylomicrons, VLDL, and HDL. Smith et al., revealed APOE's role in facilitating the binding and uptake of lipoprotein particles, contributing to lipid transfer into cells [11]. As the primary ligand for the LDL receptor (LDLR) family, APOE governs lipoprotein removal, influencing lipid homeostasis in the liver and various tissues [11, 12]. The three primary APOE variants in humans are associated with plasma lipoproteins, and their uptake via LDL receptors plays a pivotal role in lipid metabolism and health implications [11, 12]. Clinical studies conducted by Ehnholm et al., and Eichner et al., linked APOE4 to elevated plasma total cholesterol and LDL, with APOE3 and APOE2 displaying similar trends [13, 14]. Nguyen et al., attributed this to APOE4's preference for VLDL and APOE3's preference for HDL [15].

Central Nervous System

Zannis et al., and Zhang et al., investigated APOE production in the CNS, identifying astrocytes, pericytes, microglia, and neurons as key sources, especially under stress or toxin-induced conditions [3, 16, 17, 18]. This intricate process, crucial for maintaining optimal brain function, involves cholesterol, constituting 25% of the body's total and vital for myelin, axonal growth, synapse formation, and processes crucial for learning and memory [19, 20]. Mauch et al., highlighted the separate management of cholesterol levels in the CNS and periphery, potentially linked to neurodegenerative diseases [21, 22].

FUNCTIONS OF APOLIPOPROEIN	PERIPHERAL SYSTEM	CENTRAL NERVOUS SYSTEM	REFERENCES
Interaction in Bloodstream	APOE interacts with LDL, VLDL, and HDL	APOE produced by astrocytes, pericytes, microglia, and neurons under stress or toxin-induced conditions.	[10, 11]
Role in Lipoprotein Binding	APOE engages diverse lipoproteins, facilitating binding and uptake of lipoprotein particles	Cholesterol is crucial for optimal brain function, constituting 25% of the body's total.	[3, 21]
LDL Receptor (LDLR) Family	Acts as the primary ligand for the LDL receptor (LDLR) family, governing lipoprotein removal	APOE governs cholesterol transport within the CNS.	[13]
Impact on Lipid Homeostasis	Influences lipid homeostasis in the liver and various tissues	Blood-brain barrier restricts the exchange of lipoproteins and APOE between CNS and periphery.	[23]
APOE Variants in Plasma	Three primary APOE variants (APOE2, APOE3, APOE4) associated with plasma lipoproteins	Increased APOE protein levels observed in response to brain injury.	[24, 25]
Clinical Studies	Studies link APOE4 to elevated plasma total cholesterol and LDL	Brain APOE regulates the removal of amyloid-β (Aβ), characteristic of many neurological. diseases	[15]

Table: 1: Functions of Apolipoprotein E

APOE governs cholesterol transport within the CNS, but the blood-brain barrier restricts the exchange of lipoproteins and APOE between the CNS and the periphery. Poirier et al. observed increased APOE protein levels in response to brain injury [23]. Recent studies by Bien-Ly et al. and Kim et al. emphasized the role of brain APOE in regulating the removal of amyloid-β (Aβ), a characteristic of many neurological diseases [24, 25]. However, the precise roles and mechanisms of APOE in these processes remain unclear.

METHODS

This review article produces a wide range of research and clinical observations and provide a thorough overview of APOE protein polymorphism and its implications for lifestyle. To discover relevant studies, a comprehensive search of databases such as PubMed and Google Scholar were done. 80 original articles closely connected to the issue were chosen for inclusion from the 20500 review articles. The obtained data were evaluated to reveal crucial insights into the role of APOE protein polymorphism on lifestyle influences.

APOE Polymorphism and Mutation

The APOE gene on chromosome 19q13.2 is associated with apolipoproteins C1 and C2 [26]. Key SNPs, such as rs7412 (C/T) and rs429358 (C/T), determine major alleles Ɛ2, Ɛ3, and Ɛ4, resulting in genotypes 2/2, 2/3, 2/4, 3/3, 3/4, and 4/4 [26]. Amino acid variations at positions 112 and 158 in APOE2, APOE3, and APOE4 typically involve one or two changes, impacting both structure and function [11, 12]. APOE4 (Cys112 Arg) is believed to originate from E3, involving a cysteine-to-arginine substitution at position 112 [11, 12]. APOE2 gene variants include E2 (Arg158 Cys), E2 (Arg145 Cys), and E2 (Lys146 Gln) [10].

APOE3 is most common at 79%, with APOE4 and APOE2 less prevalent at 13.3% and 7.3%, respectively [27]. Ordovas et al., identified rare alleles 1 and 5, carried by a mere 0.1% [28]. Common APOE allele distribution is influenced by factors like geography, climate, adaptation, genetic drift, and evolutionary choices.

APOE Polymorphism	Alleles	Effect	References
APOE2	ε2/ε2	Lower cardiovascular disease risk, but elevated type III hyperlipoproteinemia risk.	[29]
APOE3	ε3/ε3	The most common genotype, considered neutral in cardiovascular disease risk.	[30]
APOE4	ε4/ε4	Elevated Alzheimer's risk, greater cardiovascular susceptibility, and impaired lipid metabolism.	[31]

Table: 2: APOE Protein Polymorphism

Life Style impacts of APOE Protein Polymorphism

- ***Obesity***

Chiurazzi M et al., tackle the intricate interplay of genetics, epigenetics, and environmental factors in obesity, posing a persistent challenge [32]. Lumsden A L et al., assert the complexity of regulating the obesity gene, whether monogenic or polygenic. Genetic variations in apolipoprotein E (APOE) are implicated in 18 disorders, spanning various illnesses [33]. APOE 44 links to a lower obesity rate (OR = 0.78) compared to APOE 33, while APOE 22 associates with a higher obesity frequency (OR = 1.22), underlining genetic complexity [33]. The dynamics of APOE genetic variation and obesity may involve apolipoprotein E, altering the lipid-to-white adipose tissue ratio, as suggested by Kypreos et al., Recent findings by Chiurazzi M et al., highlighted the brain's connection of fat accumulation and obesity with apolipoprotein E3, while liver-generated apolipoprotein E3 has the opposite effect [34]. Farup et al.,'s study unveils correlations between the Ɛ2 allele and psychosomatic disease progress, and between C-reactive protein (CRP) and alleles Ɛ2 and Ɛ4, respectively [35]. Exploring APOE alleles' associations with obesity and endocrine abnormalities in bariatric surgery patients, the study underscores crucial factors in obesity, as identified by Chiurazzi M et al.

- ***Nutrirtional Food Intake***

Embracing a health-conscious lifestyle, including optimal micronutrients, a vegetable-rich diet, sufficient sleep, and regular exercise, has been linked to reduced Alzheimer's disease (AD) risk for APOE ε4 carriers [36, 37, 38]. Conversely, APOE Ɛ4 carriers face an increased AD risk with factors like excessive alcohol, low polyunsaturated fat, high saturated fat, and smoking [39]. Fish consumption is beneficial for both APOE Ɛ4 carriers and noncarriers, slowing AD progression and improving neuropathology [40]. A sophisticated lifestyle plan, incorporating wild fish, can enhance cognitive function for APOE Ɛ4 carriers and noncarriers with Alzheimer's disease [36, 41].

Huang T L et al., highlighted the uncertainty surrounding the impact of dietary fish on APOE Ɛ4 carriers, possibly due to low omega-3 fatty acid intake [42, 43]. DHA supplementation at 2g daily is shown to slow cognitive decline in noncarriers but has no effect on APOE Ɛ4 carriers, exacerbating AD pathology only in the former [44, 45, 46, 47]. Berti V., Scarmeas N., Chai B., Cardoso B., globally associates the Mediterranean diet with a lower AD incidence. Vitamin D and selenium deficiency are identified as AD risk factors directly linked to ApoE polymorphism [48, 49, 50, 51, 52, and 53].

- ***Physical Activity***

Regular moderate physical activity can impede or halt the progression of neurological diseases (ND), as indicated by numerous studies [54]. Exercise provides benefits such as improving oxidative stress, enhancing antioxidant capacity, and aiding in the breakdown of amyloidogenic oligomers [54]. In healthy mice, aerobic exercise, as demonstrated by Cunha et al., increases UPS expression [55]. Barrón-Cabrera et al., suggest that environmental and lifestyle factors, including physical activity, significantly influence all epigenetic agents [56, 57]. Recent research by Piccarducci et al., highlighted the crucial role of physical exercise in maintaining the physiological health of erythrocytes, plasma antioxidant capacity, and regulating the accumulation of misfolded proteins related to ND in both healthy individuals and ND patients [58, 59].

- ***Disease Risk***

Cardiovascular disease

Schiele et al., find that "middle-aged males carrying the Ɛ4 genotype face a 40% higher risk of CVD mortality compared to those with 3/3 or Ɛ2 genotypes, indicating elevated risks of cardiovascular disease (CVD) mortality, myocardial infarction, and coronary artery disease" [60]. They also note a higher Ɛ4 frequency in Scotland, Finland, and Northern Ireland, correlating with elevated cholesterol levels and increased CVD death rates [61]. Eichner et al.,'s study on the "APOE genotype-CVD relationship reveals that Asians, American Indians, and Mexican Americans have the highest prevalence of E3 (>84%), while African Americans and Africans exhibit the highest rates of E4 prevalence (20.1% and 31%, respectively). Except for Finns, Caucasians, and African Americans show the highest E2 incidence (7.3%-13.1%) [62]."

Vascular Dementia

In a study led by Jellinger,, Vascular Dementia serves as a broad term encompassing cognitive disorders linked to brain damage resulting from diminished blood flow, impacting processes like planning, judgment, and memory [63]. The challenge within this condition arises from the disagreement regarding the necessary diagnostic criteria for an accurate diagnosis. The prevalence of Vascular Dementia (VD) is estimated to range between 1.2% and 4.2% in individuals over 65, with 6–12 cases reported per 1,000 persons over 70 annually. Differentiating the incidence of VD from other diseases proves challenging, given that 20%–30% of individuals with dementia experience a combination of problems [63].

Kalaria's research emphasizes APOE as a significant risk factor for vascular dementia (VD), alongside conditions like stroke, metabolic disorders, atherosclerosis, and hypertension. However, conflicting findings persist regarding the role of APOE4 in VD development. Laitinen et al., link APOE4 to an increased VD risk, particularly with high cholesterol and saturated fat intake, while Yin et al. find no clear association. Recent meta-analyses by Yin et al., suggest an elevated VD risk in APOE4 carriers compared to APOE3 carriers. APOE4's contribution to VD risk differs from other vascular factors. Angelopoulou et al.,'s pathological evidence indicates APOE's presence in VD patients, implying an increased risk. Their findings propose that younger APOE4 carriers benefit most from lifestyle interventions in preclinical stages, while older APOE4 noncarriers with dementia may experience significant benefits. Overall, these results highlight the intricate interaction between APOE genotype and diet in VD risk.

Alzheimer's disease

Liu et al., underscore APOE's pivotal role in cholesterol transport within the central nervous system, marking it as a significant risk factor for late-onset Alzheimer's disease. In Alzheimer's patients, "APOE alleles—Ɛ2, Ɛ3, and Ɛ4—occur at rates of 3.9%, 59.4%, and 36.7%", respectively. The robust correlation between APOE and Aβ in the brain emphasizes its role as an Aβ-binding protein, influencing structural changes in Aβ. Specifically, APOE Ɛ4 is implicated in initiating and intensifying Aβ accumulation, heightening Alzheimer's disease risk, possibly through functional loss or increased toxicity.

Carrasquillo et al., globally established the link between the APOE Ɛ4 allele and Alzheimer's disease through genome-wide association studies [69]. The Ɛ4 allele is associated with both late-onset familial and sporadic Alzheimer's disease, serving as a primary hereditary factor in up to 50% of cases. Individuals with a heterozygous Ɛ4 allele face a two to three-fold increased risk, while those with a homozygous Ɛ4 allele carry about a 12-fold higher risk [70].

Parkinson's Disease

Parkinson's disease (PD), impacting 2% of individuals aged 65 and older, progresses slowly [72]. A connection between APOE and PD in the central nervous system is established by Pulkes et al., [73]. While APOE Ɛ4 is not consistently linked to PD susceptibility or PD-associated dementia [72], Ryu and Kwon's research explores Ɛ4 as a potential factor for the age of dementia onset in PD and reduced cognitive impairment related to dementia, albeit considered a weak or unreliable risk factor for Parkinson's disease [74]. A meta-analysis by Huang et al., suggests an increased risk of Parkinson's disease associated with the Ɛ2 allele [75], whereas Li et al.,'s study proposes the Ɛ4 allele as a potential cause of Parkinson's disease [76].

Types II Diabetes Mellites

Type II Diabetes Mellitus (T2DM), often a chronic condition, becomes more prevalent with age, accounting for about 90% of diabetes cases [77]. Ripsin et al., noted that T2DM's impact on approximately 4% of the global population, with projections suggesting an increase to 5.4% by 2025, influenced by hereditary and environmental factors [78, 79]. Li et al.,'s research highlighted the increased risk of cognitive decline and dementia in elderly individuals with T2DM, also associated with both the clinical diagnosis of Alzheimer's disease and vascular dementia [80].

Ribalta et al., emphasized APOE isoforms' vital role in regulating cellular and plasma lipid levels, highlighting chemical stability variations [81, 82]. Guan et al., investigated APOE polymorphism's potential impact on Type 2 Diabetes Mellitus (T2DM) onset, revealing a clear connection with the APOE Ɛ2 allele and an increased T2DM risk [83, 84]. Global statistics highlighted T2DM prevalence in affluent nations, posing challenges for developing countries like China and India [84]. In the Chinese Han population, Ramachandran et al., analyzed "4,615 T2DM cases and 2,867 controls, identifying associations of APOE Ɛ2 and Ɛ4 alleles with increased T2DM and Diabetic Nephropathy risk [85]."

Xie et al., explored the potential link between APOE Ɛ4 and an increased risk of type 2 diabetes [86]. Dore et al., identified cognitive deficits in individuals with both type 2 diabetes and at least one APOE Ɛ4 allele [87]. The APOE Ɛ4 genotype demonstrated a stronger association between Alzheimer's disease and type 2 diabetes, suggesting a link between reduced cognitive function and a higher risk of dementia, including Alzheimer's disease, in individuals with type 2 diabetes. Investigating the underlying mechanism of this relationship was deemed crucial.

Multiple Sclerosis

Berer and Krishnamoorthy reported that Multiple Sclerosis (MS) is the most common autoimmune disease affecting the central nervous system [88]. Milo and Kahana noted that the condition typically manifests in individuals aged 20 to 50, affecting potentially twice as many women as men [89]. Studies by Pericak-Vance et al. and Sawcer et al., have demonstrated a genetic link between MS and the 19q13 region of the chromosome, although research findings regarding its connection to the APOE genotype remain contradictory [90, 91]. Parmenter et al., suggest that APOE Ɛ4 could impact MS progression, potentially worsening brain damage, cognitive dysfunction, and disease severity [92, 93]. However, Pinholt et al.,'s findings present some disagreement [94]. It is crucial to note that the results published by Pinholt et al. differ slightly.

Evidence regarding the potential link between APOE Ɛ4 and cognitive dysfunction in Multiple Sclerosis (MS) emerges from studies by Shi et al. and Van der Walt et al. [93, 95, 96]. Nevertheless, the presence of the APOE Ɛ4 allele is associated with cognitive impairment in MS [95, 96]. Koutsis et al. identified verbal memory issues in MS patients carrying the Ɛ4 allele [95, 97]. Additionally, Lill et al. found significant effects of both Ɛ2 and Ɛ4 on MS susceptibility, analyzing data from 13,913 MS cases and 15,831 controls. While most APOE association studies for MS report negative results, some indicate significant impacts, and others do not support these associations [98].

Ischemic Stroke

Lopez et al., identify Ischemic Stroke (IS) as a major global cause of mortality and disability [99]. APOE's impact on stroke incidence is evident, with the Ɛ4 allele associated with higher LDL, cholesterol levels, and ischemic heart disease. In contrast to Treger et al.,'s findings, a meta-analysis indicates a strong connection between APOE Ɛ4 and significantly higher IS prevalence [100]. Paternoster et al.'s analysis of 30,879 patients reveals that the Ɛ4 variant is linked to increased carotid thickness, a feature associated with Ischemic Stroke (IS) [101]. IS results from complex genetic and environmental interactions.

Type III Hyperlipoproteinemia (HLP)

Visser et al., linked APOE deficiency to the onset of type III Hyperlipoproteinemia (HLP). APOE Ɛ2 presence correlated with the molecular basis of type III HLP, marked by delayed lipoprotein clearance, leading to elevated triglyceride and cholesterol levels. Developing hyperlipidemia necessitated inheriting two APOE Ɛ2 alleles, with carriers of the 2/2 allele often exhibiting normolipidemic or hypocholesterolemic traits. According to Visser M E et al., type III HLP frequency was reported at 1–5 cases per 5,000 persons, and 2/2 homozygosity occurred at a rate of 0.5-1.0 per 100 individuals in Caucasian populations. This type of HLP was generally considered a recessively inherited multifactorial trait, with over 90% of patients being homozygous for the 2/2 (Arg158 Cys) gene [102].

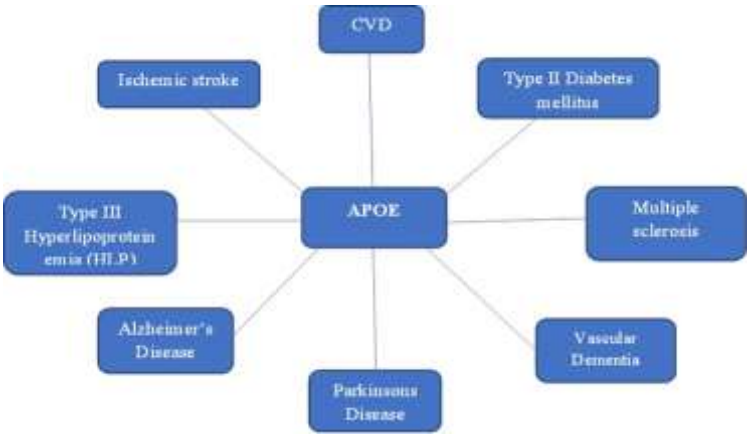

Figure (1): APOE Associated diseases

CONCLUSION

The APOE protein polymorphism, comprising APOE Ɛ2, APOE Ɛ3, and APOE Ɛ4, plays a crucial role in influencing the risk of various chronic conditions. These include Alzheimer's disease, cardiovascular issues, Parkinson's disease, type II diabetes, Type III Hyperlipoproteinemia, ischemic stroke, vascular dementia, and multiple sclerosis. Research suggests that lifestyle factors such as diet, exercise, and cognitive engagement can effectively modify the impact of APOE Ɛ4 on Alzheimer's risk, offering a means for APOE Ɛ4 carriers to mitigate their susceptibility. Conversely, these lifestyle changes may not be as pivotal for APOE Ɛ2 carriers, given their lower risk profile. Recognizing this genetic variability holds significant implications for enhancing public health outcomes.

CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTIONS

All of the authors were involved in data collection, manuscript drafting, and revisions, with shared responsibility for all aspects of this research.

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