Role of apolipoprotein E in neurodegenerative diseases

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Abstract: Apolipoprotein E (APOE) is a lipid-transport protein abundantly expressed in most neurons in the central nervous system. APOE-dependent alterations of the endocytic pathway can affect different functions. APOE binds to cell-surface receptors to deliver lipids and to the hydrophobic amyloid-β peptide, regulating amyloid-β aggregations and clearances in the brain. Several APOE isoforms with major structural differences were discovered and shown to influence the brain lipid transport, glucose metabolism, neuronal signaling, neuroinflammation, and mitochondrial function. This review will summarize the updated research progress on APOE functions and its role in Alzheimer’s disease, Parkinson’s disease, cardiovascular diseases, multiple sclerosis, type 2 diabetes mellitus, Type III hyperlipoproteinemia, vascular dementia, and ischemic stroke. Understanding the mutations in APOE, their structural properties, and their isoforms is important to determine its role in various diseases and to advance the development of therapeutic strategies. Targeting APOE may be a potential approach for diagnosis, risk assessment, prevention, and treatment of various neurodegenerative and cardiovascular diseases in humans.

Keywords: apolipoprotein E, pathogenesis, diseases

Introduction

The apolipoprotein E (APOE) gene is located on chromosome 19 and encodes a glycoprotein that is 299 amino acids long.1 It is synthesized in various tissues in the body including the liver, brain, and skin and in macrophages.2 In the blood, APOE protein could interact with lipids, resulting in lipoproteins, including very-low-density lipoproteins (VLDL). Several major APOE isoforms can be distinguished: E2, E3, and E4. Six phenotypes were observed as a result of two single nucleotide polymorphisms (SNPs) at amino acid positions 112 and 158. The amino acid changes could alter the protein charge and stability, inducing distinct physiological functions.

APOE plays multiple roles in the regulation of lipid and lipoprotein levels in the blood. APOE serves as a ligand for members of low-density lipoprotein (LDL) receptor family and is involved in the removal of lipoproteins from the circulation for excretion in the liver. APOE is also involved in the formation of chylomicrons and VLDL and affects the activity of other lipid metabolism-associated proteins and enzymes, such as hepatic lipase and lipoprotein lipase. Emerging study has shown that APOE and APOE isoform functions may extend beyond lipid metabolism to include maintenance of normal brain function.3 In this review, we discuss the biological functions of human APOE and its role in Alzheimer’s disease (AD), Parkinson’s disease (PD), cardiovascular diseases (CVD), multiple sclerosis (MS), type 2 diabetes mellitus (T2DM), vascular dementia (VD), and ischemic (occlusive) stroke (IS). Targeting APOE may be a potential approach for diagnosis, risk assessment, prevention, and treatment of diseases in humans.
Importance of APOE

APOE functions

Peripheral system

APOE is a 299 amino acid plasma glycoprotein associated with LDL, VLDL, and high-density lipoproteins (HDL). Several functions of APOE were identified in the human body. In the plasma, APOE will associate with most lipoproteins. APOE is an integral component of chylomicrons, VLDL, and HDL in the peripheral system (Table 1). It operates as part of an anchoring mechanism that aids the transport of triglyceride, phospholipid, cholesteryl esters, and cholesterol into cells by mediating the binding and internalization of these lipoprotein particles. APOE has a strong affinity for and is the main ligand for members of low-density lipoprotein receptor (LDLR) family, located on liver and other tissues. This super family includes the LDLR, LDLR-related protein 1 (LRP1), VLDL receptor, and APOE receptor 2. APOE interaction with LDLR mediates the removal of APOE-containing lipoproteins and modulates the homeostasis of lipids in the peripheral system.

In humans, there are three major isoforms of APOE, which are associated with lipoproteins in the plasma, and absorption of APOE-containing lipoprotein complexes by LDL receptors through lipid metabolism has important implications in diseases (Figure 1). Clinical studies have shown that APOE4 is associated with higher plasma total cholesterol and LDL, followed by APOE3 and APOE2. This is largely attributed to APOE4 preferentially binding to VLDL and APOE3 to HDL.

The central nervous system

In the central nervous system (CNS), APOE mainly produced by astrocytes (either pericytes or microglia) or under certain pathological conditions (eg, stressors, injurious agents) by neurons. This involves the redistribution of lipids among cells of different organs, including the CNS (Figure 1). The human brain contains up to 25% of the body’s cholesterol, which is essential for myelin production, function, and integrity. Cholesterol homeostasis is important for normal brain functions, since it is an essential component for axonal growth, synaptic formation, and remodeling events that are crucial for learning and memory. Cholesterol in the CNS is regulated independently from that in the peripheral system. Cholesterol dysfunction in the CNS could be associated with aging and the development of certain neurodegenerative diseases. In the CNS, APOE mediates cholesterol neuronal delivery. The blood–brain barrier restricts the exchange of lipoproteins and APOE between the CNS and peripheral system. A study showed that injury to the brain resulted in an increase in APOE protein in the brain. More recently, two reports have suggested that brain APOE regulates the clearance of amyloid-B (Aβ), which is a common hallmark of some neurological diseases. So far, the mechanisms involving APOE in all of these biological processes have not been completely clarified.

APOE polymorphism and mutations

The APOE gene is located on chromosome 19q13.2. It contains four exons and three introns (Figure 2A), totaling 3,597 base pairs in a cluster with apolipoprotein C1 and apolipoprotein C2. Several individual SNPs have been identified in the human APOE gene. In particular, two SNPs, rs7412 (C/T) and rs429358 (C/T), are responsible for the three major alleles: epsilon-2 (ε2), epsilon-3 (ε3), and epsilon-4 (ε4). Because human cells have two copies of each gene, there are six APOE genotypes: ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4, and ε4ε4. They are responsible for three homozygous (ε2ε2, ε3ε3, and ε4ε4) and three heterozygous (ε2ε3, ε2ε4, and ε3ε4) genotypes. The three major protein isoforms, APOE2, APOE3, and APOE4, differ from each other by only one or two amino acids at positions 112 and 158. These differences alter APOE structure and function, respectively (Figure 2C).

APOE4 is thought to be derived from E3 by a cysteine-to-arginine (Cys → Arg) substitution at position 112 and is designated as E4 (Cys112 → Arg). So far, three forms of APOE2 have been described: E2 (Arg158 → Cys), E2 (Arg145 → Cys), and E2 (Lys146 → Gln). In isoelectric focusing, four different mutations give a band at the E2 position, E2 (Arg158 → Cys), E2 (Lys146 → Gln), E2 (Arg145 Cys), and E2-Christchurch (Arg136 → Ser). APOE2 (Arg158 → Cys) is the most common of the ε4. APOE1 has been reported to contain a Cys instead
of an Arg at position 158, similar to APOE2, as well as an additional amino acid substitution, which probably does not have any functional significance. In addition to these common polymorphisms, several mutations have been described (Table 2). APOE3 is the most-common isoform, while APOE4 and APOE2 are less-frequently observed. The APOE ε3 allele is present in 79% of the entire population, whereas APOE ε4 is only present in 13.3% and APOE ε2 in 7.3% of the population. Additionally, there are two rare alleles of the gene, ε1 and ε5, but these are present in <0.1% of the population. The frequencies of the most common alleles of APOE in various populations around the world show that geography, climate, isolation by local adaptations, genetic drift, and possibly evolutionary history selection are responsible for shaping the spectrum of APOE genetic variation (Table 2).

**APOE**

APOE is a 299 amino acid glycoprotein of 34.1 kDa. The structure of this protein varies, depending on the genetic polymorphism. The protein contains two major structural domains, including a compact and stable globular amino-terminal domain (amino acid residues 20–166) and a less-stable carboxy-terminal domain (amino acid residues 225–299). These domains are connected to each other by a hinge region (amino acid residues 166–224). The LDL receptor-binding region is between residues 136–150 of the protein, where multiple basic amino acids are present. The carboxy-terminal domain contains the major lipid-binding region. The amino acid residues 245–266 appear to be critical for binding to VLDL particles, whereas binding to HDL occurs even without the carboxyl-terminal domain. The three major APOE isoforms differ from each other by two cysteine/arginine interchanges at position 112 and 158. APOE2, APOE3, and APOE4 contain cysteine/cysteine, cysteine/arginine, and arginine/arginine at these two positions, respectively (Figure 2C). The APOE ε2 allele carries the Arg158Cys polymorphism. It could disrupt the natural salt bridge between Asp154 and the carboxyl group of Cys158.
and Arg158. In turn, a salt bridge was formed as the result of the interaction between Arg150 and Asp154. This bridge could disrupt receptor binding because Arg150 is part of the LDL binding site. This mutation was related to type III hyperlipoproteinemia (HLP). Exchange of Asp154 to an alanine could induce the disruption of the Arg150 and Asp154 bridge, and the receptor-binding activity could return to the normal level. Arg150 could relocate within the receptor-binding region. APOE ε3 allele presents a cysteine in position 112 and arginine in position 158. Arg12 mediates two key features of the ε4 allele, as it is associated with reduced stability. The ε4 allele could promote the domain interaction by the orientation of Arg61 on the N-terminal domain. Interaction with Glu255 in the C-terminal domain could be an important structural property of the ε4 allele, and ε2 alleles might have less risk for domain interaction. Mutation of Arg61 to Thr (or Glu255 to Ala), was suggested to reduce the domain interaction, causing an ε3-like molecule (Figure 2B). In addition, mutation update and genotype–phenotype correlations of novel and previously described mutations in APOE are available in Table 3.

**Measurement of APOE**

APOE plays a role in the transport and metabolism of triglyceride-cholesterol. Genotyping could be used to improve the diagnosis of triglyceride cholesterol variants, and APOE polymorphisms were also associated with altered odds of having AD and other diseases. Determination of APOE level is of potential interest when studying different forms of brain damage and as a marker of ongoing regenerative processes in the brain. APOE is a polymorphic apolipoprotein exhibiting three major isoforms, ε2, ε3, and ε4, at a single gene locus.

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**Figure 2** Schematic illustration of structural and functional regions of APOE.

**Notes:**

(A) Location and structure of the APOE gene on chromosome 19. (B) APOE protein is a polypeptide chain with 299 amino acids consisting of a receptor-binding region (residues 136–150) in the N-terminal domain (residues 1–167) and a lipid-binding region (residues 244–272) in the C-terminal domain (residues 206–299). (C) Three major APOE isoforms are located at residues 112 and 158 (red circles), where APOE2 has Cys residues at both positions, APOE3 has a Cys residue at 112 and an Arg residue at 138, and APOE4 has Arg residues at both positions.

**Abbreviation:** APOE, apolipoprotein E.
APOE isoform-specific effects on APOE/Aβ complex levels may mediate the increase in soluble Aβ levels that correlate with APOE4. Allelic variations in APOE were consistently associated with plasma concentrations of total cholesterol, LDL cholesterol, and APOB (the major protein of LDL, VLDL, and chylomicrons). APOE ε2 was studied in disorders associated with elevated cholesterol levels or lipid derangements such as type III HLP, coronary heart disease, stroke, peripheral artery disease, and diabetes mellitus. APOE ε2 was established as an important marker for diagnosis. APOE ε4 is a major genetic risk factor for neurodegenerative diseases such as AD and PD.

Methods have been developed to detect individual APOE phenotype or genotype. Studies indicated that the method for detection and the source of the components for APOE/Aβ complex were critical parameters for the experimental outcome. So far, many methods have been developed to measure APOE/Aβ complex, including gel-shift assay on sodium dodecyl sulfate–polyacrylamide gel electrophoresis, Western blot analysis, co-immunoprecipitation, size-exclusion chromatography/gel-filtration, and enzyme-linked immunosorbent assay. Some APOE variants that were defective in their ability to mediate the binding of lipoproteins to the LDL receptor and that are associated with diseases were poorly recognized by antibodies. Moreover, numerous studies have been developed to measure the effect of APOE polymorphism on APOE/Aβ complex formation using these methods (Table 4).

APOE-associated diseases
Understanding structural differences in APOE isoforms helped establish the molecular mechanism responsible for the associated pathology. Defects in APOE could result in alterations in its structure and function. The critical effect of APOE in regulating plasma lipid and lipoprotein levels has been extensively and carefully studied. Evidence indicates its association with neurodegenerative diseases and also other chronic diseases. This review will summarize the critical available data related to APOE defects and their role in AD, PD, CVD, type III HLP, MS, T2DM, VD, and IS (Figure 3).

Alzheimer’s disease
AD was originally described by Alois Alzheimer in 1907. It is the most-common age-related dementing illness, which is currently estimated to affect 35.6 million individuals worldwide. It was estimated that the number of patients with AD will triple by 2050. APOE plays a critical role in transporting cholesterol in and out of the CNS and is also recognized as the most important risk factor for the late-onset form of AD. The distribution of APOE’s three major alleles, ε2, ε3, and ε4, in patients with AD is 3.9%, 59.4%, and 36.7%, respectively. Based on the strong association between APOE and Aβ in the brain, APOE was suggested...
**Table 3 Variants of human APOE**

<table>
<thead>
<tr>
<th>Type of genetic variation</th>
<th>Designation</th>
<th>Disease association</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point mutation</td>
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<tr>
<td>E1 (Gly127 → Asp, Arg158 → Cys)</td>
<td>HLP</td>
<td>85</td>
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<tr>
<td>E1 (Lys146 → Glu)</td>
<td>Type III HLP</td>
<td>81</td>
<td></td>
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<tr>
<td>E1 (Lys146 → Asn; Arg147 → Trp)</td>
<td>Type III HLP</td>
<td>79</td>
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<tr>
<td>E1 (Arg158 → Cys; Arg180 → Cys)</td>
<td>Hypertriglyceridemia</td>
<td>80</td>
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<tr>
<td>E1 (Arg158 → Cys; Leu252 → Glu)</td>
<td>Type IIa HLP</td>
<td>152</td>
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<tr>
<td>E2 (Arg25 → Cys)</td>
<td>Type III HLP</td>
<td>153</td>
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<tr>
<td>E2 (Arg134 → Glu)</td>
<td>Type III or V HLP</td>
<td>82, 84</td>
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<tr>
<td>E2 (Arg136 → Ser)</td>
<td>Type III HLP</td>
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<td>E2 (Arg145 → Cys)</td>
<td>Type III HLP</td>
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<tr>
<td>E2 (Lys146 → Glu)</td>
<td>Type III HLP</td>
<td>78, 83</td>
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<tr>
<td>E2 (Gln187 → Glu)</td>
<td>Type III HLP</td>
<td>157</td>
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<tr>
<td>E2 (Arg224 → Glu)</td>
<td>Xanthomatosis</td>
<td>158</td>
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<tr>
<td>E2 (Arg228 → Cys)</td>
<td>Type IV or V HLP</td>
<td>159</td>
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<tr>
<td>E2 (Val236 → Glu)</td>
<td>Type IIb or IV HLP</td>
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<tr>
<td>E3 (Ala99 → Thr; Ala152 → Prol)</td>
<td>Hypertriglyceridemia</td>
<td>160, 161</td>
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<td>E3 (Ala106 → Val)</td>
<td>Hypertriglyceridemia</td>
<td>162</td>
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<tr>
<td>E4 (Cys112 → Arg; Arg142 → Cys)</td>
<td>Type III HLP</td>
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<tr>
<td>E4 (Cys112 → Arg; Arg251 → Gly)</td>
<td>Type IV HLP</td>
<td>152</td>
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<tr>
<td>E3 (Arg136 → His)</td>
<td>Type III HLP</td>
<td>163</td>
<td></td>
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<tr>
<td>E3 (Thr42 → Ala)</td>
<td>Type III HLP</td>
<td>164</td>
<td></td>
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<tr>
<td>E3 (Arg145 → His)</td>
<td>Hypertriglyceridemia</td>
<td>165</td>
<td></td>
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<tr>
<td>E4 (Glu13 → Lys; Arg145 → Cys)</td>
<td>Type III HLP</td>
<td>135, 166</td>
<td></td>
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<tr>
<td>E4 (Leu28 → Prol; Cys112 → Arg)</td>
<td>Alzheimer’s disease</td>
<td>167, 168</td>
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<td></td>
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<td>Coronary artery disease</td>
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<tr>
<td></td>
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<td>Types IIa, IIb, IV, and V HLP</td>
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<td>Hypercholesterolemia</td>
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<td>Hypercholesterolemia</td>
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<td>Hypercholesterolemia</td>
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<td>Hypercholesterolemia</td>
<td>173, 174</td>
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<td>Hypercholesterolemia</td>
<td>175</td>
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<td>Hypercholesterolemia</td>
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<td></td>
<td></td>
<td>Lipoprotein glomerulopathy</td>
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<td></td>
<td></td>
<td>Systemic atherosclerosis</td>
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<td></td>
<td></td>
<td>Lipoprotein glomerulopathy</td>
<td>178</td>
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<td>Hyperlipidemia</td>
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<td>Hyperlipidemia</td>
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**Abbreviations:** APOE, apolipoprotein E; HLP, Hyperlipoproteinaemia.

as an Aβ-binding protein that induces a pathological β sheet conformational change in Aβ. APOE ε4 suggests probably increases the risk of AD by initiating and accelerating Aβ accumulation, aggregation, and deposition in the brain. Cleavage of APOE4 may increase AD risk in two ways, either through a loss of function or gain of toxicity. Genome-wide association studies have shown that the APOE ε4 allele is associated with AD and was detected in homogeneous and heterogeneous populations in North America, Europe, and Asia.
Since the relationship between APOE immunoreactivity and amyloid plaques was first reported,\textsuperscript{42,49} the ε4 allele has shown to be strongly associated with both late-onset familial\textsuperscript{45,50} and sporadic AD.\textsuperscript{43,44} It is estimated to be the principal genetic factor in up to 50% of all cases of AD.\textsuperscript{51,52} Moreover, risk for AD was increased two- to threefold in individuals who carried the heterozygous ε4 allele and about 12-fold in those who carried the homozygous ε4 allele.\textsuperscript{51,53} Conversely, there was evidence suggesting that the APOE ε2 allele may be protective against AD or associated with a marked reduction in AD risk.\textsuperscript{54,55} AD risk in the APOE ε2/ε2 or ε2/ε3 carriers was lower than in those carrying ε3/ε3.\textsuperscript{55} APOE’s role in AD is well established. Therefore, further studies are needed to understand the possible association between APOE and the rate of disease progression. APOE was classified as a risk factor for AD, but the molecular events that precede dementia remain elusive.

### Table 4 The methods utilized to measure APOE/β levels

<table>
<thead>
<tr>
<th>Human APOE source</th>
<th>Detection method</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human plasma (purified)</td>
<td>SDS–PAGE (nonreducing), WB</td>
<td>APOE4/β &gt; APOE3/β</td>
<td>45</td>
</tr>
<tr>
<td>Human plasma (purified)</td>
<td>SDS–PAGE (nonreducing), WB</td>
<td>APOE3/β &gt; APOE4/β</td>
<td>184</td>
</tr>
<tr>
<td>Human brain (AD and NAD)</td>
<td>SDS–PAGE</td>
<td>APOE3/β &gt; APOE4/β</td>
<td>41</td>
</tr>
<tr>
<td>Human plasma (purified)</td>
<td>Surface plasmon resonance</td>
<td>APOE3/β &gt; APOE4/β = APOE2/β</td>
<td>185</td>
</tr>
<tr>
<td>Human plasma</td>
<td>SDS–PAGE (nonreducing), WB</td>
<td>APOE3/β = APOE2/β &gt;&gt; APOE4/β (ND)</td>
<td>186</td>
</tr>
<tr>
<td>Human plasma APOE</td>
<td>IP with SDS–PAGE, WB</td>
<td>NAD APOE3/β = NAD APOE34/β &gt;&gt; AD APOE33/β &gt;&gt; AD APOE44/β</td>
<td>31</td>
</tr>
<tr>
<td>Recombinant (nonlipidated and lipidated)</td>
<td>ELISA</td>
<td>APOE2/β &gt; APOE3/β &gt; APOE4/β</td>
<td>174</td>
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<tr>
<td>RAW264 and HEK293 (CM, delipidated)</td>
<td>ELISA</td>
<td>CM and SP (lipidated): APOE3/β &gt; APOE4/β</td>
<td>32</td>
</tr>
<tr>
<td>S9 insect cells (delipidated and lipidated)</td>
<td>ELISA</td>
<td>All sources (delipidated): APOE3/β = APOE4/β</td>
<td></td>
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<tr>
<td>HEK293 (CM)</td>
<td>SDS–PAGE (nonreducing), WB</td>
<td>APOE3/β &gt; APOE3/β fibrils &gt; APOE4/β fibrils</td>
<td>33</td>
</tr>
<tr>
<td>Escherichia coli (purified and lipidated)</td>
<td>EPR spectroscopy</td>
<td>Purified APOE: APOE3/β &gt; APOE4/β</td>
<td>190</td>
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<tr>
<td>Human plasma (NAD)</td>
<td>SEC, SDS–PAGE (nonreducing), WB</td>
<td>95% Aβ elutes with lipoproteins</td>
<td>34</td>
</tr>
<tr>
<td>Human CSF (NAD)</td>
<td>SEC, SDS–PAGE (nonreducing), WB</td>
<td>100% Aβ associated with APOE-containing lipoproteins</td>
<td></td>
</tr>
<tr>
<td>Human plasma</td>
<td>SDS stable: E2FAD &gt; E3FAD &gt; E4FAD</td>
<td>Total complex: E2FAD = E3FAD &gt; E4FAD</td>
<td>191</td>
</tr>
<tr>
<td>Human CSF (AD and NAD)</td>
<td>SEC, SDS–PAGE (nonreducing), WB</td>
<td>95% Aβ elutes with lipoproteins</td>
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<tr>
<td>Human CSF (AD and NAD)</td>
<td>SEC, SDS–PAGE (nonreducing), WB</td>
<td>100% Aβ associated with APOE-containing lipoproteins</td>
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</tbody>
</table>

**Abbreviations:** Aβ, amyloid-β; AD, Alzheimer’s disease; agg Aβ, aggregated amyloid-β; APOE, apolipoprotein E; CHO, Chinese hamster ovary cell; CM, conditioned media; co-IP, co-immunoprecipitation; CSF, cerebrospinal fluid; EFAD, essential fatty acid deficiency; EPR, electron paramagnetic resonance; ELISA, enzyme-linked immunosorbent assay; IP, immunoprecipitation; NAD, non-Alzheimer’s disease or nondementia control; ND, not detectable; oAβ, oligomeric amyloid-β; PAD, probable Alzheimer’s disease; PAGE, polyacrylamide gel electrophoresis; sAβ, soluble amyloid-β; SP, Spodoptera frugiperda insect cells; SDS, sodium dodecyl sulfate; SEC, size-exclusion chromatography; WB, Western blot.
Vascular dementia
VD is a general term describing problems with reasoning, planning, judgment, memory and other thought processes caused by brain damage from impaired blood flow to your brain. The problem with this disease is the lack of consensus on the pathological criteria required for the exact diagnosis. The prevalence of VD in individuals older than 65 years of age is estimated to be 1.2%–4.2%. Moreover, there are an estimated 6–12 cases per 1,000 persons older than 70 years of age per year.\(^5\) It is difficult to distinguish the prevalence between VD and other pathologies, as 20%–30% of demented subjects show mixed pathologies.\(^5\) Clinically, VD and AD share pathological features such as the presence of neurofibrillary tangles, amyloid plaques, white-matter lesions, and cerebral amyloid angiopathy.\(^5\)

There are many VD risk factors, including hypertension, stroke, atherosclerosis, and other metabolic disorders. However, APOE was also considered as an important risk factor for VD. The role of APOE4 in the development of VD might be an area of intensive investigation, with conflicting conclusions. The consumption of highly saturated fat and cholesterol may confer added risk for the development of VD, which would be aggravated even more in people carrying the ε4 allele.\(^5\,^6\) Some studies have shown a positive association between harboring the ε4 allele and increased risk for VD;\(^6\,^6\) while others have indicated that ε4 allele might not be associated with VD risks.\(^6\,^6\) Recent meta-analyses have revealed evidence of an increased VD risk in individuals with APOE ε4 compared with APOE ε3.\(^6\) Besides, APOE ε4 contribution to the risk of vascular cognitive impairment is independent of other vascular risk factors, including hypertension, dyslipidemia, and atherogenesis.\(^6\) The presence of APOE in patients with VD could provide pathological evidence supporting the potential link between APOE polymorphism and enhanced risk for VD.

Cardiovascular diseases
CVD, including coronary heart disease, refers to any diseases that affect the cardiovascular system – principally cardiac
disease, vascular diseases of the brain and kidney, and peripheral artery disease. The biological activity of APOE can be influenced by modification of its structure and/or quantity. Epidemiologic studies have indicated the direct association between APOE and CVD as well as its impact on cholesterol levels. In a study in middle-aged men, it was estimated that 40% of the e4 carrier population had an increased risk for CVD mortality compared with individuals with the e3/e3 or e2 genotypes. Studies indicated that e4 carriers had an increased risk of death from CVD. Certain studies have linked the e4 allele with a greater risk for coronary artery disease and myocardial infarction. Indicatively, higher frequency of e4 was associated with higher cholesterol levels and higher CVD mortality rates in Finland, Scotland, and Northern Ireland. Furthermore, an increased CVD risk was also associated with the e2 allele. A report on the frequency of APOE genotype and its related CVD indicated that American Indians, Asians, and Mexican Americans presented the highest frequency of E3 (>84%). Africans and African Americans presented the highest frequency of E4 (20.1% and 31%, respectively). African Americans and Caucasians (except Finns) presented the highest frequency of E2 (7.3%–13.1%).

So far, several studies have suggested that the APOE e4 allele is a risk allele for CVD, while others failed to find any association. The dual role of APOE remains enigmatic and needs to be further explored in order to elucidate its precise role in cardiovascular and cerebrovascular diseases.

Type III hyperlipoproteinemia

Type III HLP, also known as dysbetalipoproteinemia or broad beta disease, is a genetic disorder characterized by accumulation of remnant lipoproteins in the plasma and development of premature atherosclerosis. Type III HLP results from the accumulation of chylomicron remnants from intestinal lipoproteins and VLDL remnants derived from hepatic lipoproteins. The expression of different isoforms of APOE that do not bind to the receptor and APOE deficiency was associated with the development of type III HLP. The primary molecular cause of type III HLP was also associated with the presence of APOE2. APOE2 increased triglyceride and cholesterol levels, leading to delayed clearance of hepatic and intestinal remnant lipoproteins, resulting in Type III HLP. The development of overt hyperlipidemia requires the inheritance of two alleles of APOE e2, and most e2/e2 allele carriers are either normolipidemic or even hypocholesterolemic. Some studies showed that type III HLP could occur with a frequency of 1–5 per 5,000 individuals.

Meanwhile, in Caucasian populations, type III HLP occurred with a frequency of 0.5–1.0 per 100 individuals with the appearance of e2/e2 homozygosity. Moreover, more than 90% of patients with type III HLP were homozygous for the e2/e2 (Arg158 → Cys) allele, and the disease is normally considered as a recessively inherited multifactorial trait. On the other hand, a variety of rare naturally occurring APOE mutations were also described that are associated with the dominant mode of inheritance of type III HLP at an early age.

Parkinson’s disease

PD and AD share some clinical and neuropathological features. PD progresses slowly in most people, affecting 2% of the population older than 65 years of age. APOE isoforms might affect degenerative processes by changing the lipid metabolism. In the CNS, the association between APOE and PD has been demonstrated. Studies failed to report any association between APOE e4 and susceptibility to PD and PD-associated dementia. Thus, several studies focused on e4 as a risk factor for age of onset and decrease in cognitive impairment associated with dementia in PD. However, e2 was considered as a weak or inconsistent risk factor for PD. One meta-analysis indicated that the e2 allele was associated with higher risk of PD development, whereas another study indicated that the e4 allele could be responsible for PD development. So far, studies focusing on the role of APOE in PD remain largely inconclusive.

Type 2 diabetes mellitus

T2DM is typically a chronic disease, and its prevalence increases with age. T2DM is also the predominant type, accounting for 90% of diabetes mellitus cases. T2DM has been affecting nearly 4% of the world’s population, and it may be increasing up to 5.4% by year 2025. The development of T2DM could be caused by a combination of lifestyle and genetic factors. Recently, studies have showed that older patients with T2DM have a higher risk of cognitive dysfunction or dementia. Moreover, T2DM was related not only to VD, but also to the clinical diagnosis of AD-type dementia. APOE could play an important role in the regulation of plasma and cellular lipid concentrations, and APOE isoforms could present differences in chemical stability. APOE polymorphism could be one of the factors that affects the development of T2DM. Some studies demonstrated that APOE e2 allele was associated with an increased risk of T2DM. In addition, global statistics show that the large burden of T2DM is restricted to developed countries.
It is also a remarkable problem for developing countries such as People’s Republic of China\(^\text{102}\) and India.\(^\text{106}\) A meta-analysis of 29 studies, which included 4,615 T2DM cases and 2,867 controls in the Chinese Han population, indicated that the APOE \(\varepsilon2\) and \(\varepsilon4\) alleles may be associated with increased risk of T2DM and diabetic nephropathy.\(^\text{107}\) In addition, some studies have indicated that APOE \(\varepsilon4\) associated with the risk of T2DM.\(^\text{108-110}\) In fact, deficits in cognitive performance were observed only for those with T2DM and, at least, one APOE \(\varepsilon4\) allele.\(^\text{111}\) The association between T2DM and AD was particularly strong among carriers of the APOE \(\varepsilon4\) allele. T2DM is associated with reduced cognitive function and the incidence of dementia, including AD. The underlying mechanism of this association should be elucidated.

Multiple sclerosis
MS is the most-common autoimmune disorder affecting the CNS.\(^\text{112}\) The disease usually begins between the ages of 20 and 50, and it could be twice as common in women as in men.\(^\text{113}\) A genetic linkage between the chromosome 19q13 region and MS has been demonstrated.\(^\text{114,115}\) So far, its association with APOE genotype remains unclear, and study results have been inconsistent. Some studies suggested that APOE \(\varepsilon4\) might be a modifier of MS progression, increasing damage to the brain and worsening cognitive dysfunction and disease severity.\(^\text{116,117}\) However, these conclusions remained controversial.\(^\text{118}\) The possible association between \(\varepsilon4\) and cognitive dysfunction in MS has been investigated in a handful of studies with conflicting results.\(^\text{117,119,120}\) However, APOE \(\varepsilon4\) allele has been indicated as a risk factor for cognitive impairment in MS.\(^\text{116,117,119,121}\) Furthermore, patients with MS who carried the \(\varepsilon4\) allele were also reported to present verbal memory deficits.\(^\text{119,122}\) Recently, a study indicated that both \(\varepsilon2\) and \(\varepsilon4\) exert relevant effects on MS susceptibility, on the basis of combined data from 13,913 MS cases and 15,831 controls.\(^\text{123}\) So far, APOE association studies in MS have mostly yielded negative results, with some studies reporting significant effects and others being unable to confirm these associations.

Ischemic stroke
IS is one of the most frequent causes of mortality and disability worldwide.\(^\text{124}\) Approximately 17 million people had a stroke in 2010, and 33 million people have previously had a stroke and were still alive according to the World Health Organization. Moreover, overall two-thirds of strokes occurred in individuals older than 65 years of age.\(^\text{125}\) IS shares several risk factors with heart disease and it also occurs when an artery to the brain is blocked. APOE may have an impact on stroke occurrence. The \(\varepsilon4\) allele was associated with increased levels of LDL and cholesterol as well as ischemic heart disease.\(^\text{8,126}\) Initial studies assessing outcomes after IS demonstrated that APOE \(\varepsilon4\) was not associated with poor prognosis,\(^\text{127,128}\) and a meta-analysis reported a significant association between IS and the \(\varepsilon4\) allele.\(^\text{129}\) Recently, IS prevalence was demonstrated to be significantly greater in \(\varepsilon4\) carrier patients.\(^\text{130}\) Furthermore, a meta-analysis of 22 published studies with a total of 30,879 subjects showed that the \(\varepsilon4\) allele was related to increased carotid intima-media thickness, a factor associated with IS.\(^\text{131}\) IS is a result of complex interactions between environmental and genetic factors. The influence of each gene is expected to be modest. However, it is possible that the tremendous impact of acquired risk factors on stroke occurrence may obscure or eliminate a possible genetic influence on the disease pathophysiology. APOE \(\varepsilon4\) seems to be the best candidate for studying the interplay between genetic and acquired risk factors.

Conclusion
This review highlighted the association between APOE function and the development of associated diseases. Increasing evidence has suggested a central role for APOE in modulating processes of neurodegeneration, as described. APOE isoforms differentially regulate Aβ aggregation and clearance in the brain and have distinct functions in regulating brain lipid transport, glucose metabolism, neuronal signaling, and neuroinflammation. APOE isoforms probably accelerate the rate of disease conversion and progression. Therefore, studying APOE and its function may enable the identification of disease risks, which may allow an earlier identification of individuals with the disease. APOE genotype status might help predict a clinical diagnosis and assess treatment efficacy using tools such as putative AD biomarkers, magnetic resonance imaging scans, and measurements of Aβ. In addition, APOE isoforms have differential roles in maintaining vascular health, which is crucial because vascular pathology is strongly associated not only with AD, but also with others diseases as described above. Determination of the association between APOE and the risk of pathogenesis is a considerable challenge, but it is essential for diagnosis, risk assessment, prevention, and treatment of disease in humans.

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