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APOE signaling in neurodegenerative diseases: an integrative approach targeting *APOE* coding and noncoding variants for disease intervention

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APOE (*apolipoprotein E*) is a key regulator of lipid metabolism and a leading genetic risk factor for Alzheimer's disease. While *APOE* participates in multiple biological pathways, its roles in diseases are largely due to the mutant protein encoded by *APOE*-ε4. However, emerging evidence suggests that some noncoding Alzheimer's disease risk variants residing in *APOE* and its nearby regions exert *APOE*-ε4-independent risks and modify *APOE* gene expression. Moreover, intervention strategies targeting *APOE* are being explored. In this review, we summarize the literature on the genetic risks and roles of *APOE* in biological systems. Moreover, we propose an integrative approach to evaluate disease risk and tailor interventions to aid research on *APOE*-associated diseases.

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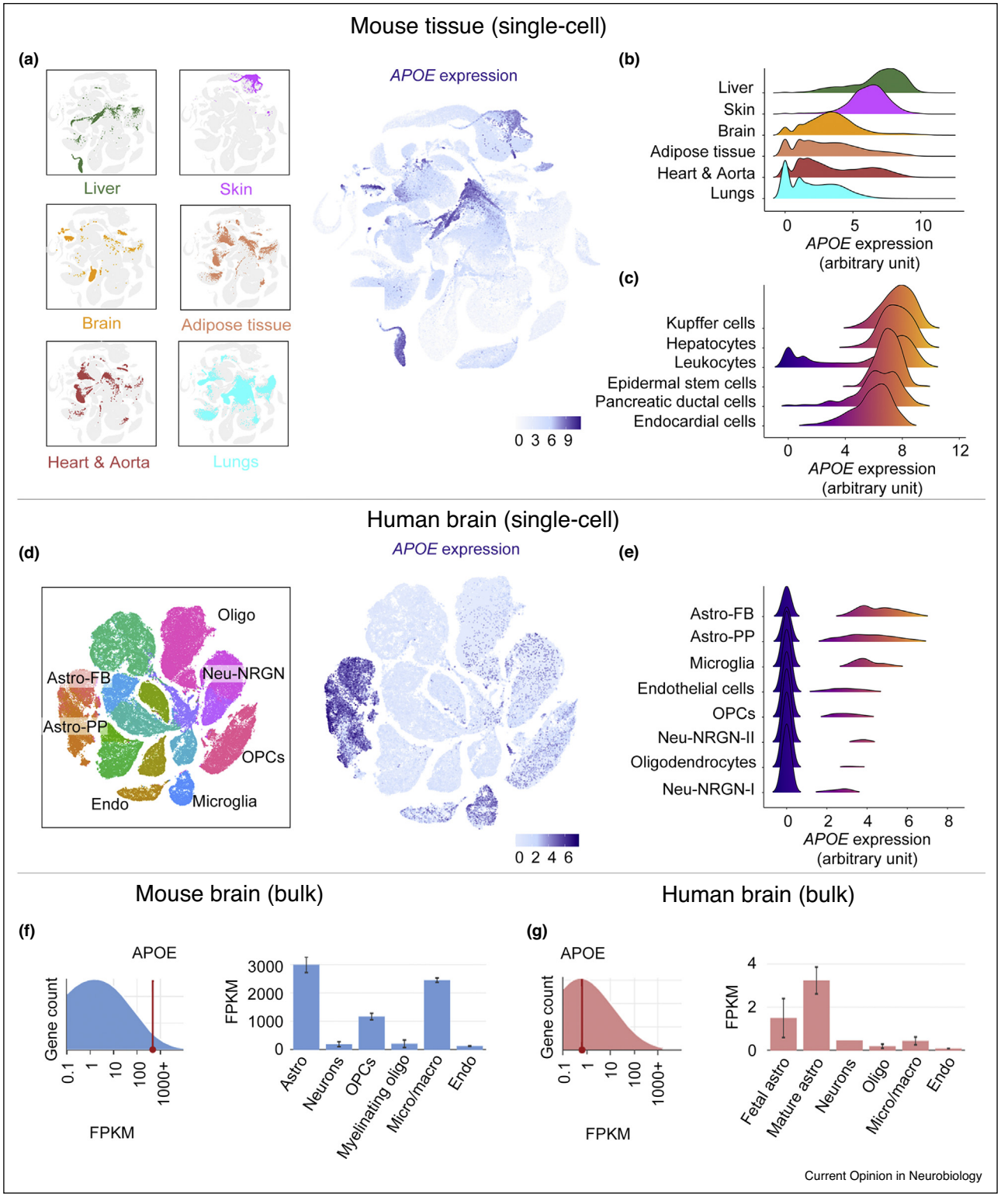
Introduction

ApoE (apolipoprotein E), encoded by *APOE*, was first described as an arginine-rich polypeptide [1–4]. ApoE is a key regulator of triglyceride and cholesterol metabolism in the peripheral system and brain [5]. In the peripheral system, plasma ApoE mainly resides in lipoprotein particles including very-low-density lipoproteins, chylomicrons, and subsets of high-density lipoproteins, facilitating the hepatic endocytosis of intestinal chylomicrons and the lipid redistribution across tissues [6–8]. ApoE is also highly expressed in the brain, which contains the largest proportion of cholesterol in the body (~20% of the total) [9]. In the brain, ApoE mainly exists in high-density, lipoprotein-like particles and maintains lipid homeostasis and proper neuronal functioning [10]. Human and mice lacking *APOE* exhibit functional deficits in both the peripheral system and brain. In particular, *APOE*-deficient mice exhibit elevated plasma cholesterol levels, early onset of atherosclerotic lesions, and elevated inflammation [11]. Moreover, compared to wild-type mice, *APOE*-deficient mice exhibit fewer dendrites and lower synapse density in neurons of the neocortex and hippocampus as well as greater age-dependent neurodegeneration in the neocortex [12]. Meanwhile, humans lacking *APOE* exhibit exceptionally high cholesterol levels; mild atherosclerosis; normal cognitive function with subtle deficits in memory, language, visuospatial abilities and executive functions [13•]. Hence, ApoE has important roles in maintaining normal physiological functions in both the brain and peripheral system.

APOE-associated pathways in the brain and peripheral system

ApoE affects diverse biological pathways in both the nervous and immune systems that are associated with neurodegenerative diseases. Biochemical analysis suggests that *APOE* is predominantly expressed by the liver, adipose tissue, arteries, and brain [6]. Single-cell RNA sequencing technique enable high-throughput assays of comprehensive gene expression profiles at single-cell resolution. Accordingly, reanalysis of publicly available data with mouse tissues revealed that *APOE* is predominately expressed in the liver, skin, brain, adipose tissue, heart, aorta, and lungs, particularly in Kupffer cells, hepatocytes, and leukocytes [14]. Kupffer cells (a type of resident hepatic macrophage) along with hepatocytes are the major sources of peripheral *APOE* expression, although the role of *APOE* expressed by Kupffer cells is not well understood [15]. Meanwhile, in the human brain, *APOE* is mainly expressed by astrocytes, microglia, oligodendrocyte progenitors and oligodendrocytes, endothelial cells, and NRGN-expressing neurons (Figure 1) [16]. *NRGN* encodes neurogranin, a synaptic protein associated with synaptic strength whose level in cerebrospinal fluid is altered in patients with neurodegeneration or Alzheimer's disease (AD) [17–19]. Moreover, according

Figure 1



APOE expression profiles at the single-cell and tissue levels.
(**a–c**) *APOE* expression in mouse tissues and cells. *APOE* expression profiles in selected mouse tissues at the (**a**) single-cell level and (**b**) tissue level. (**c**) *APOE* expression profiles in selected cell types. (**d, e**) *APOE* expression in human brain cells. (**d**) *APOE* expression profiles at the single-cell level in the human brain prefrontal cortex and anterior cingulate cortex. (**e**) *APOE* expression profiles in selected cell types. (**f, g**) *APOE* expression in (**f**) the mouse and (**g**) human brain. Histogram showing the ranking of the *APOE* transcript levels across all detected genes in the

to the Brain RNA-Seq database (https://www.brainrnaseq.org/) that integrates bulk RNA-Seq data from mouse and human brains [20,21], *APOE* expression is higher in the mouse brain than the human brain (Figure 1). These lines of evidence corroborate the findings of biochemical studies on *APOE* expression profiles, providing a basis for further characterization of the roles of *APOE* and associated pathways in neurodegenerative diseases.

Most studies on *APOE* in the brain are restricted to neurons, astrocytes, and microglia, which have revealed specific function of *APOE* signaling in those cells (Table 1). Astrocytes are the major source of the *APOE* in the brain, which can modulate neurite outgrowth [22]. The activation of *APOE* signaling in neurons triggers phosphorylation cascades that activate several downstream kinases [23]. Specifically, *APOE* signaling modulates neurite outgrowth/extension, synaptogenesis, axon remodeling [24–26], and calcium homeostasis [27] and also prevents neuronal apoptosis [28]. Furthermore, as a protective mechanism induced upon injury or stress, neurons increase their *APOE* expression to recruit lipids from the surrounding environment for repair [8]. Moreover, upon activation, microglia exhibit elevated *APOE* expression [29], which modulates their molecular phenotypes and regulates their cell state transition from a homeostatic state to a disease/neurodegeneration-associated state by influencing gene expression in a *TREM2*-dependent manner [30•]. Furthermore, ApoE4, a mutated form of ApoE protein that is known to associate with AD pathogenesis, can bind to DNA and act as a transcription factor to modulate cytokine production in neuronal cell lines, further indicating that *APOE* plays important roles in transcriptomic regulation of immune-related pathways [31,32]. Notably, a recent human postmortem brain study revealed the presence of *APOE* circular RNA, which accounts for approximately one-third of the total brain *APOE* RNA, although its function and cellular expression profile are unknown [33•]. Therefore, further investigation is required to understand the roles of *APOE* expression and its associated pathways in the brain.

Emerging studies also suggest that *APOE* plays roles in the vascular system. The breakdown of blood–brain barrier (BBB) might account for the neurodegeneration and neuroinflammation in AD [34]; the *APOE*-deficient mice exhibit age-dependent BBB disruption [35]. In addition, disease-associated ApoE4 protein can also lead to BBB dysfunction [36,37]. Moreover, a recent study using an induced pluripotent stem cell-derived BBB model suggests that ApoE4 expressed by pericytes might modulate amyloid deposition near the BBB, making it a possible trigger of microvasculature injury [38•]. Interestingly, although peripheral ApoE cannot effectively diffuse into the brain owing to its limited BBB permeability [39–41], manipulating peripheral ApoE level can potentially affect cognitive functions [42•]. Given the modulatory effects of both vascular and peripheral *APOE* on brain functions, an intervention strategy targeting these sources of *APOE* could be effective for certain neurodegenerative diseases including AD.

APOE coding variants in human diseases

Genetics and biochemical studies revealed the existence of 3 *APOE* isoforms in the general population—*APOE*-ε2 (encoding ApoE2; Cys112–Cys158), *APOE*-ε3 (the most common form; Cys112–Arg158), and *APOE*-ε4 (encoding ApoE4; Arg112–Arg158)—which are defined by combinations of 2 coding mutations in exon 4 of *APOE* [43–47] (Table 2). These mutations of *APOE* modify its protein function by altering internal domain–domain interactions [48]. In ApoE4, the cysteine-to-arginine substitution at residue 112 renders the formation of a new salt bridge between Glu109 and Arg112, and modifies the orientation of Arg61 (a key residue), resulting in ApoE4 having higher affinity for very-low-density lipoproteins [49,50]. Meanwhile, in ApoE2, the arginine-to-cysteine substitution at residue 158 changes the salt bridge within and between the helical structures, which also modifies the charges of the receptor-binding region [50]. Accordingly, ApoE4 does not efficiently interact with high-density lipoproteins and preferentially binds low-density lipoproteins, whereas ApoE2 exhibits greatly reduced affinity for low-density lipoprotein receptor [49,51].

An early genetics study revealed an association between *APOE* and abnormal lipid metabolism [8]. Specifically, *APOE*-ε2 is one of the genetic risk factors of type III hyperlipoproteinemia, a familial lipoprotein metabolic disorder characterized by elevated blood cholesterol and triglyceride levels along that incurs risks of severe atherosclerotic vascular diseases [52]. In contrast, *APOE*-ε2 is also associated with longevity, reduced age-associated cognitive decline, and reduced AD risk [53]. Meanwhile, ApoE-ε4 is associated with neurodegenerative diseases including AD, vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, and multiple sclerosis; some cerebrovascular disorders such as cerebral amyloid angiopathy and stroke; and poor outcomes after traumatic brain injury [54]. Given that these diseases are predominately associated

(Figure 1 Legend Continued) corresponding tissues. Data obtained from the Brain RNA-Seq database. (**a, d** right panels) *APOE* expression in individual cells was visualized by *t*-distributed stochastic neighbor embedding (*t*-SNE) plots; color denotes normalized *APOE* expression in individual cells. Astro, astrocytes; Astro-FB, fibrous astrocytes; Astro-PP, protoplasmic astrocytes; Endo, Endothelieal cells; FPKM, fragments per kilobase of transcript per million mapped reads; Neu, neurons; Neu-NRGN, NRGN-expressing neurons; Oligo, oligodendrocytes; OPCs, oligodendrocyte progenitor cells; Macro, macrophages; Micro, microglia.

Table 1

Roles of *APOE*-associated pathways in the brain and peripheral system

Tissue or cell type	Function	References
Peripheral system	• Redistribute lipids	[6–8]
	• Modify cognitive function	[42•]
Astrocytes	• Produce majority of the ApoE protein in the brain	[8]
	• Modulate neurite outgrowth	[22]
Neurons	• Modulate neurite outgrowth and extension, synaptogenesis, and axon remodeling	[24–26]
	• Regulate calcium homeostasis	[27]
	• Confer neuroprotection	[28]
	• Repair damaged neurons by recruiting lipids from the surrounding environment	[8]
	• Induce microglial activation	
Microglia	• Regulate transcriptome profile	[30•]

Table 2

Summary of *APOE* isoforms and associated phenotypes

Isoform (or alias)	Mutations	Phenotypes/Notes	References
ε1 (Weisgraber allele)		Obesity	
	Asp127–Cys158	Non insulin-dependent diabetes Hypertension Moderate lipid disturbances	[64]
ε1y (ε3r)	Arg112–Cys158	No obvious phenotypic change	[65]
ε2		Longer lifespan	
	Cys112–Cys158	Type III hyperlipoproteinemia (elevated blood cholesterol and triglyceride levels) Atherosclerotic vascular diseases Reduced risk of Alzheimer's disease	[52,53]
ε3	Cys112–Arg158	Most frequent isoform in the general population	
ε4	Arg112–Arg158	Neurodegenerative diseases including Alzheimer's disease Cerebrovascular disorders	[54]
ε5	Lys3	Mild hypertriglyceridemia	[66]
ε5	Arg84–Arg112	Elevated blood cholesterol level Triple-vessel disease	[67]
ε7	Lys244–Lys245	Diabetes mellitus Hypertriglyceridemia	[68]
Christchurch allele (R136S)	Ser136	Significant enrichment of mutated ApoE in very low-density lipoprotein Type III hyperlipoproteinemia	[69,72••]

with the nervous and vascular systems and involve altered immune status, *APOE* might have broad roles in modulating specific pathways associated with neuronal, vascular, and immune functions.

Of note, *APOE*-ε4 is a well-recognized genetic risk factor for AD, which is one of the most common neurodegenerative diseases [55]. *APOE*-ε4 modulates various AD-associated endophenotypes covering a broad spectrum of disease signatures including synaptic plasticity [56], neuronal activity [57], brain volume [58], cognitive performance [59], onset age [60], and brain immune status [61]. Compared to *APOE*-ε2 and *APOE*-ε3, *APOE*-ε4 can also modify the pathological hallmarks of AD, including amyloid-beta (Aβ), tau neurofibrillary tangles, and neurodegeneration by promoting Aβ aggregation, inhibiting Aβ clearance, and exacerbating tau-mediated neurodegeneration in tau transgenic mice [62,63]. Hence, *APOE*-ε4 plays critical roles in the pathogenesis of AD by modulating a plethora of biological pathways involved in the disease pathogenesis.

Multiple rare *APOE* coding risk variants have also been identified, including the *APOE*-ε1 Weisgraber allele (Asp127–Cys158) [64], *APOE*-ε1y (Arg112–Cys158) [65], several forms of *APOE*-ε5 (including Lys3 and Arg84–Arg112) [66,67], *APOE*-ε7 (Lys244–Lys245) [68], and the Christchurch mutation (R136S or Ser136) [69], which potentially modify disease risk by altering ApoE function (Table 2). For instance, ApoE with the Christchurch mutation tends to exist in a higher-order oligomerization state with a larger aggregate size when compared with the normal ApoE protein [70], which consequently reduces the binding affinity of *APOE* for low-density lipoprotein receptor by 60% [71]. In particular, in a case report of a homozygous carrier who exhibited high brain Aβ load, the Christchurch mutation elicited a strong neuronal protective effect against the causal *PSEN1*

E280A coding risk variant, as indicated by low tau tangle load, low plasma neurofilament light chain level, and mild cognitive issues [72••]. This implies that appropriately manipulating the *APOE* signaling pathway alone might be sufficient for AD intervention.

Notably, besides altering protein function, mutations of *APOE*-ε2 and *APOE*-ε4 are located in a well-defined genomic region with DNA methylation modification (i.e., a CpG island) [73]. Moreover, an *APOE*-ε4 variant introduces a cytosine base that is highly methylated (65–90%) across human tissues [74]. Concordantly, the *APOE*-ε4 allele is associated with reduced brain *APOE* expression [75,76••]. In addition, compared to noncarriers, *APOE*-ε4 heterozygous carriers exhibit decreased *APOE*-ε4 mRNA expression in the brain and blood [76••,77]. Therefore, *APOE-ε4* potentially exerts disease risk effects by encoding a mutated protein with altered *APOE* expression and functions, which leads to the dysregulation of *APOE*-associated signaling pathways and consequently modifies disease risk.

Contributions of *APOE* noncoding risk variants to Alzheimer's disease

APOE coding risk variants unequivocally impact associated signaling pathways, while the dysregulation of *APOE* expression might also trigger or modulate AD onset and progression. The expression of *APOE* is controlled in a tissue-specific manner by multiple enhancers in nearby regions [74,78], which might also be modified by variants located in noncoding regions [79–83]. Association analyses have revealed numerous AD-associated noncoding variants and haplotypes residing in *APOE* and its nearby regions [84–86]. Interestingly, several studies also show that a specific haplotype structure with an ethnic-specific distribution might account for the variable AD risk of *APOE*-ε4 carriers among populations [87•,88•]. Nevertheless, it remains controversial whether those noncoding variants exert risk effects for AD.

Accordingly, our group conducted a comprehensive fine-mapping analysis of *APOE* genetic risk in *APOE* and its nearby regions based on whole-genome sequencing data [76••]. Our analysis enabled the identification of all genomic variants and their haplotype structures in the study cohort for association analysis, which identified noncoding risk variants and haplotypes residing in the *PVRL2* and *APOC1* regions that exert AD risk effects independent of *APOE*-ε4. Further analysis revealed their potential regulatory functions in the modification of brain *APOE* expression; specifically, carriers of *PVRL2* or *APOC1* haplotypes exhibited higher brain *APOE* expression than noncarriers. Moreover, if the noncoding risk variants and *APOE*-ε4 reside in the same chromosome, those noncoding variants might modify the disease penetrance of *APOE*-ε4 via enhanced expression of ApoE4. Meanwhile, the identified risk haplotypes are more prevalent in populations of European descent than those of African descent, corroborating the lower AD risk of *APOE*-ε4 observed in the latter [89]. Taken together, the discoveries of these noncoding risk factors and their putative regulatory functions provide a genetic basis for the variable *APOE*-ε4 AD risk across ethnic groups and suggests that changes in *APOE* expression alone might also confer AD risk.

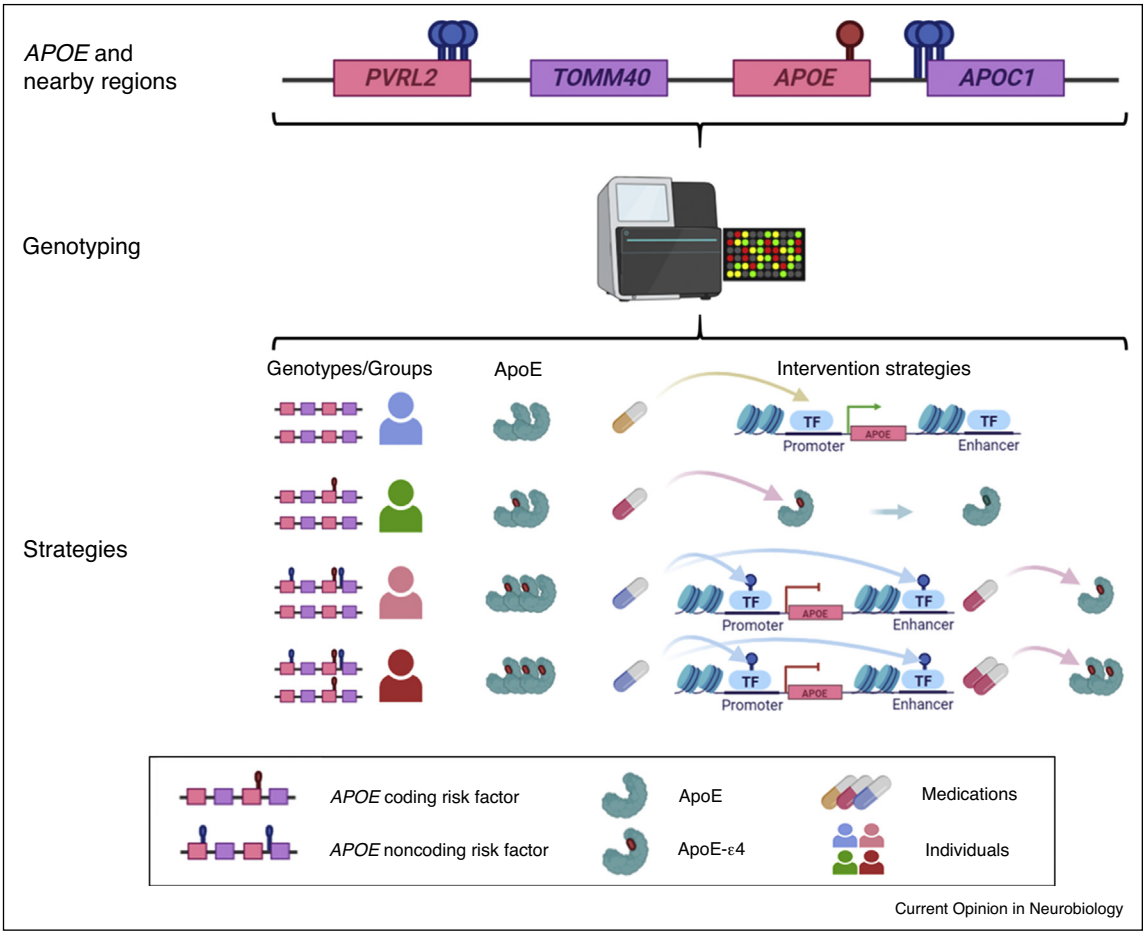
Notably, the AD-associated *APOE* noncoding variants span the *PVRL2–TOMM40–APOE–APOC1* region, potentially affecting the expressions of those genes and influencing several other AD-associated mechanisms in parallel to the Aβ cascade, including viral infection, mitochondrial dysfunction, and neuroinflammation [90–92]. Specifically, *PVRL2* encodes a surface protein that abets herpes and pseudorabies viruses entering cells—a process potentially associated with AD pathogenesis [93,94]. Meanwhile, *TOMM40* encodes a mitochondrial membrane protein that facilitates protein transport into mitochondria, potentially accounting for the observed mitochondrial dysfunction in the AD brain [95]. Furthermore, *APOC1* encodes a protein involved in lipid metabolism that is implicated in atherosclerosis, which is a possible trigger of neuroinflammation [96,97]. Hence, the identified noncoding *APOE* risk factors might elicit additional effects on neurodegenerative diseases in addition to modifying *APOE* expression.

Proposed model for *APOE*-associated intervention strategies

Corroborating the critical involvement of *APOE* in AD pathogenesis, intervention strategies targeting *APOE* expression or ApoE4 mutant proteins can ameliorate AD-associated symptoms. For instance, administration of the RXR agonist bexarotene, which can trigger *APOE* expression, rapidly enhances Aβ clearance and improves neuronal and cognitive functioning in AD mouse models [98]. Meanwhile, PH002, a small molecule structure corrector that can reshape ApoE4 protein into an ApoE3–like structure, can ameliorate the neuronal toxicity of ApoE4 and reduce p-tau, $A\beta_{40}$, and $A\beta_{42}$ levels in induced pluripotent stem cell-derived neurons [99•]. Moreover, other intervention strategies including ApoE-neutralizing antibody [100], *APOE* antisense oligonucleotides [101], and virus-mediated ApoE2 overexpression [102] can also elicit protective effects against AD by modulating ApoE2 expression and its accompanying signaling pathways. Thus, such *APOE*-targeting therapeutic strategies could be developed as treatments for neurodegenerative diseases.

Nevertheless, considering the complexity of *APOE* signaling, which involves multiple cell types, *APOE* signaling must be manipulated in a cell-type-specific and genotype-aware manner. Moreover, applying the aforementioned intervention strategies at a population scale might yield inconsistent effects owing to variations in

Figure 2



Integrative approaches targeting *APOE*-related diseases.
The coding and noncoding genotypes of *APOE* and its nearby regions are detected by array or sequencing methods. Individuals harboring different combinations of coding and noncoding mutations are segregated and subjected to different intervention paradigms using drugs targeting *APOE* expression and ApoE mutant proteins. TF, transcription factor.

genetic background. For instance, among AD patients treated with bexarotene, *APOE*-ε4 carriers exhibit no significant change in Aβ load, whereas *APOE*-ε3 homozygous patients exhibit a regional reduction in Aβ load [103•]. On the other hand, the presence of certain *APOE* noncoding genetic risk variants might modify the chromatin state of nearby regions and consequently interfere with the *APOE* expression-inducing effect of bexarotene [104]. Therefore, a rigorous investigation of the genomic contexts of *APOE* and nearby regions may facilitate the development of more-effective and genotype-specific intervention strategies. For instance, a multistage screening assay can be applied to individuals identified as having *APOE*-ε4, both *APOE*-ε4 and noncoding risk variants, or only noncoding risk variants—each of whom may be submitted to a different treatment paradigm for AD.

Accordingly, by combining coding and noncoding genetic information, a polygenic risk score model can be designed to stratify patients and assess an individual's risk of developing a given disease [105–107]. Furthermore, long-read sequencing technology can directly capture all genomic contexts of the *APOE* and its nearby regions, including single nucleotide polymorphisms, insertions, deletions, structural variations, and haplotype information, which would more accurately stratify individuals for subsequent preclinical or clinical investigation [76••]. The results of such research might yield tailored intervention strategies applicable to a broad range of diseases associated with *APOE* (Figure 2).

Conclusion

APOE is expressed in various cell types and involved in diverse biological functions. The contributions of *APOE* coding and noncoding genetic variants to human diseases

through the modulation of protein functions and gene expression highlight the roles of the dysregulation of *APOE* signaling in modifying disease risk. Meanwhile, *APOE*-targeting intervention strategies have demonstrated beneficial effects in decreasing disease-associated phenotypes, which are influenced by genetic contexts. Thus, properly integrating genetic information and *APOE*-targeting interventions will enable early disease risk prediction for individuals and help stratify individuals for appropriate intervention strategies.

Conflict of interest statement

Nothing declared.

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