

# Is There Any Relationship between Apolipoprotein E Polymorphism and Idiopathic Parkinson's Disease?

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## Abstract

Apolipoprotein E is a plasma protein that has an important role in transport and metabolism of lipids in serum as well as in central nervous system. Among the three common alleles, the  $\epsilon 2$  allele has the most stable structure followed by  $\epsilon 3$  and  $\epsilon 4$  in order. There is evidence for a deleterious role of apolipoprotein  $\epsilon 4$  by atherosclerosis and amyloid beta accumulation in brain and body by the differences of three-dimensional structures among the apoE isoforms. APOE  $\epsilon 4$  also seems to be related to cognitive decline in Parkinson's disease but not too related to the age at onset of Parkinson's disease.

**Keywords:** Apolipoprotein E; Polymorphism; Parkinson's disease; Cognition

## Introduction

The human apolipoprotein E (apoE) protein is an important protein in plasma, cerebrospinal fluid, and interstitial fluid of central nervous system [1]. It consists of single chain lipoprotein with 299 amino acids, produced in the liver, brain, spleen, lung, etc. The amino-terminal, having four helices, binds to low-density lipoprotein and the carboxy-terminal, an amphipathic alpha helix, binds to lipid. The three common wild types of APOE alleles are  $\epsilon 2$ ,  $\epsilon 3$ ,  $\epsilon 4$  which located on chromosome 19q. These three alleles encode similar proteins different only in 112th residue and 158th residue, respectively [2] (Figure 1). The roles of apoE are catabolism of lipoprotein constituents, lipid transportation, and membrane repair process [3]. In the human brain, glial cells, vascular smooth muscle cells, and choroid plexus produce apoE. Intriguingly, neurons also produce apoE under neuronal injury or other stressful conditions, and the newly synthesized apoE recruit cholesterol and phospholipids from the body and central nervous system to protect neurons and to repair damaged neurons. In these process apoE4 causes a direct toxic effect on the neurons [4]. Apolipoprotein E was known as a protein constituting lipid-rich plasma lipoproteins in the early 1970s. In 1993, Clinical characteristics of APOE polymorphism was reported through genetic linkage study. APOE  $\epsilon 4$  allele considered as harmful to human cognition because the frequency of the  $\epsilon 4$  allele in patients with Alzheimer's disease was more than three times higher than that of cognitively normal person. Moreover, APOE  $\epsilon 4$  allele carriers with normal cognition develop Alzheimer's disease earlier than people without APOE  $\epsilon 4$  allele [5]. On the other hand, APOE  $\epsilon 2$  allele was considered protecting cognitive function because the frequency of  $\epsilon 2$  allele was lower in patients with Alzheimer's disease than that of cognitively normal person. The most common APOE  $\epsilon 3$  allele was considered to be neutral or protective effect because the biochemical characteristics is between APOE  $\epsilon 2$  and APOE  $\epsilon 4$  [6,7].

There are several explanations of the harmful effect of APOE  $\epsilon 4$ . A mouse model study on the apoE effect on blood-brain barrier revealed that apoE4 cause blood-brain barrier more susceptible to injury by increased cytokine and increase matrix metalloproteinase 9 pathways [1]. Domain interaction theory may explain the harmful effect of APOE  $\epsilon 4$ . In this theory, the Arg-61 of the amino domain and the Glu-255 of the carboxy-domain interacts ionically to cause a structural change which results in apoE4 becomes the more compact, meaning of the distance between the two domains becomes shorter than other alleles.

When a significant amount of apoE4 is in neurons by the response to injury, it again give stress to the neurons to begin a pathological response. Compact apoE4 is recognized as abnormal in central nervous system, and neuron-specific protease cut off the carboxy terminal of apoE4. The fragmented apoE4 is neurotoxic, and it impairs neuronal mitochondrial function and also causes cytoskeletal changes. Damaged neurons by apoE4 toxicity are destroyed by proteolysis [1]. Interaction of the two domain is less efficiently occur in other alleles because Cys-112 is firmly bound into the amino terminal [4,8] (Figure 1). The other theory is that proteolytically cleaved apoE4 can do major role in the development of Alzheimer's disease. A fragment of apoE4 was found in the pathologies of Alzheimer's disease which is indicative of a toxic effect of apoE4 on the disease [9]. Lastly, apoE4 may cause neurotoxicity by mitochondrial dysfunction and formation of neurofibrillary tangles supposed by an animal study [10].

## Parkinson's Disease and Apolipoprotein E

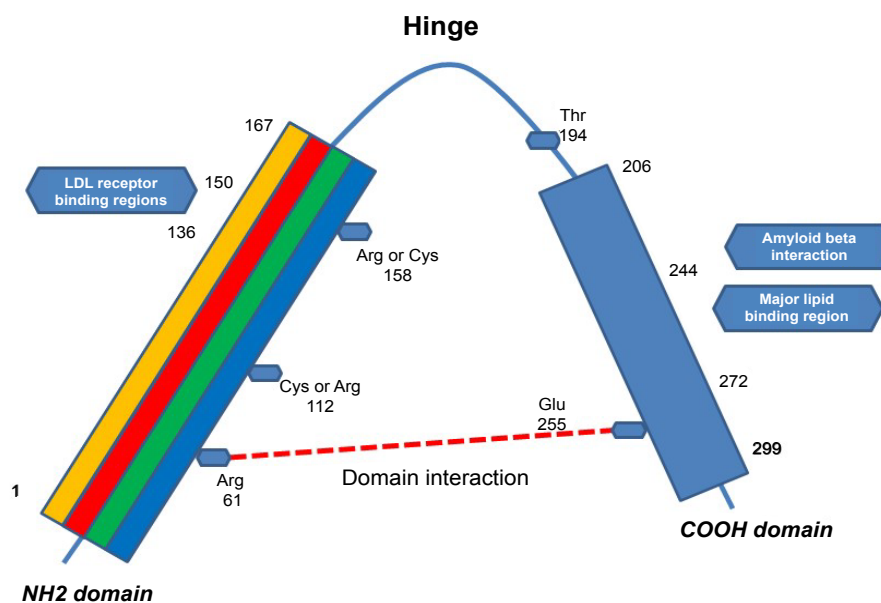
Parkinson's disease is the second most common neurodegenerative disease that shows specific movement symptoms such as bradykinesia, resting tremor, rigidity, and postural instabilities. One fourth of this debilitating illness is seemed familiar suggesting strong genetic effect of onset [11]. The association of APOE polymorphism and Parkinson's disease were proposed by several features of Parkinson's disease. First, cognitive decline develops frequently in the early or late stage of the illness, and Parkinsonism often develops in Alzheimer's disease [12,13]. Second, Deposition of abnormal protein in the nervous system is seen in both conditions [14]. Third, pathologic changes similar to Alzheimer's disease are frequent in Parkinson's disease. Forty-two percent of patients with Parkinson's disease showed senile plaques and neurofibrillary tangles in the cerebral cortex [14]. Fourth, the level of cerebrospinal biomarkers such as Amyloid-beta and Tau protein is

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**Figure 1:** Human apolipoprotein E structure and functional areas. A flexible hinge region connects the amino-terminal domain and carboxy-terminal domain. Arginine at residue 61 and Glutamate at residue 255 in apolipoprotein E  $\epsilon 4$  allele interacts, and the distance between two domains shortened which results in the adverse effect of apoE4 protein. The ionic interaction between the two domains determines compactness of the protein.

changed in both degenerative diseases and the levels have a correlation with the severity of cognitive impairment in Parkinson's disease [15]. Pathological studies suggest two kinds of pathological changes related to cognitive decline. One is Lewy bodies, frequently seen in brainstem and cerebrum of Parkinson's disease as well as Lewy body disease. The other is the neuritic plaque that is main pathological findings of Alzheimer's disease [16,17]. The prevalence of Alzheimer's disease in Parkinson's disease is more than six times than that of the cognitively healthy population. Moreover development of Alzheimer's disease shortens the survival period of the patients with Parkinson's disease [14].

There are several issues not conclusive on the relation between Parkinson's disease and APOE polymorphism. The first issue is the relationship between APOE  $\epsilon 4$  allele and the age at onset of Parkinson's disease. Some studies of patients with Parkinson's disease suggested a significant association between APOE  $\epsilon 3/\epsilon 4$  and  $\epsilon 4/\epsilon 4$  genotype with earlier age at onset of motor symptoms in Caucasians [18,19]. In contrast, studies done with Mexican Mestizo, Korean, as well as research in the United States did not show any relationship between APOE polymorphism and age at onset of Parkinson's disease [11,20,21]. A meta-analysis showed the relationship between APOE  $\epsilon 4$  and lower prevalence of Parkinson's disease [22]. They suggested relatively higher cholesterol level induced by APOE  $\epsilon 4$  was the reason for the lower occurrence of Parkinson's disease. However, followed studies did not show any relationship between ApoE polymorphism and age at onset of Parkinson's disease [23,24]. Intriguingly, a genome-wide linkage study comparing siblings with and without Parkinson's disease showed that APOE  $\epsilon 4$  might be a weak risk locus for PD with unknown mechanism [25]. Overall, above studies indicate that age at onset of Parkinson's disease is not related to the existence of APOE  $\epsilon 4$ . The reports supporting the relationship have weak evidence and larger prospective study will reveal the answer to the question. The second issue is the relationship between the existence of APOE  $\epsilon 4$  allele and cognitive status of Parkinson's disease. A study of Caucasians with

Parkinson's disease showed ApoE  $\epsilon 4$  as a risk factor for dementia in patients with Parkinson's disease [26]. The other study comparing Parkinson's disease with family and without family history showed the frequency of APOE  $\epsilon 4$  allele in Parkinson's disease with dementia was twofold than without dementia ( $P=0.026$ ). This result also supported APOE relationship with dementia associated with Parkinson's disease [11]. In concordance with these study, a meta-analysis showed an association between APOE  $\epsilon 4$  and dementia in Parkinson's disease [27]. Though this study was challenged by its heterogeneous sources of data, it was supported by another meta-analysis with 786 non-Hispanic Caucasians, which showed a higher prevalence of dementia in patients with APOE  $\epsilon 4$  carriers [22]. In contrast to these two meta-analyses, a longitudinal study and a cross-sectional study did not prove such relationship between APOE polymorphism and the early development of dementia in patients with Parkinson's disease [21,23]. Overall, the relationship between APOE polymorphism and Parkinson's disease is weaker than that of Alzheimer's disease. However, APOE  $\epsilon 4$  may affect the cognitive symptoms of this degenerative disease sharing a similar mechanism of neurotoxicity.

## Summary and Conclusion

The human apoE protein is an essential protein in brain function including cognitive function. Among the three common APOE alleles are  $\epsilon 4$  allele is most harmful, followed by,  $\epsilon 3$  allele and  $\epsilon 2$ . Higher prevalence of APOE  $\epsilon 4$  allele in Alzheimer's disease can be an epidemiologic evidence of the detrimental effect of the allele. The structurally compact shape of APOE  $\epsilon 4$  allele and mitochondrial dysfunction may be laboratory proof of the mechanism of APOE  $\epsilon 4$  toxicity. There are many pieces of evidence of the association between APOE polymorphism and Parkinson's disease suggested by cognitive decline of Parkinson's disease, pathological similarities, and cerebrospinal fluid biomarkers. Studies searching possible correlation between the age at onset of Parkinson's disease and APOE

polymorphism was not successful. However, shreds of evidence are convincing APOE  $\epsilon 4$  allele negatively affect the cognitive symptoms of Parkinson's disease.

In conclusion, the most significant effect of human APOE polymorphism can be cognitive decline by the APOE  $\epsilon 4$  allele. It is prominent in Alzheimer's disease and less prominent in Parkinson's disease. Therefore, genotyping APOE polymorphism may be a diagnostic test for the evaluation of risk of earlier cognitive decline in AD but adjusting this test for PD is not established until now. In future, modification of the harmful effect of APOE  $\epsilon 4$  should be done to change the relentless cognitive decline in Parkinson's disease and other neurodegenerative diseases.

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