Chapter 37
Pleiotropic Effects of Apolipoprotein E in Dementia: Influence on Functional Genomics and Pharmacogenetics

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Introduction

The genetic defects identified in Alzheimer’s disease (AD) during the past quarter century can be classified into three main categories: (1) Mendelian or mutational defects in genes directly linked to AD, including 18 mutations in the β-amyloid (Aβ) precursor protein (APP) gene (21q21); 142 mutations in the presenilin 1 (PS1) gene (14q24.3); and 10 mutations in the presenilin 2 (PS2) gene (1q31-q42) [1]. (2) Multiple polymorphic variants of risk characterized in more than 100 genes distributed across the human genome can increase neuronal vulnerability to premature death [1]. Among these genes of susceptibility, the apolipoprotein E (ApoE) gene (19q13.2) is the most prevalent as a risk factor for AD, especially in subjects harboring the ApoE-4 allele, whereas carriers of the APOE-2 allele might be protected against dementia [1–3]. ApoE-related pathogenic mechanisms are also associated with brain aging and with the neuropathological hallmarks of AD [4]. (3) Diverse mutations located in mitochondrial DNA (mtDNA) through heteroplasmic transmission can influence aging and oxidative stress conditions, conferring phenotypic heterogeneity [5]. It is also likely that defective functions of genes associated with longevity may influence neuronal survival, as neurons are potential pacemakers defining life-span in mammals [1]. All these genetic factors may interact in still unknown genetic networks, leading to a cascade of pathogenic events characterized by abnormal protein processing and misfolding with subsequent accumulation of abnormal proteins (conformational changes), ubiquitin-proteasome system dysfunction, excitotoxic reactions, oxidative and nitrosative stress, mitochondrial injury, synaptic failure, altered metal homeostasis, dysfunction of axonal and dendritic transport, and chaperone misoperation [1]. These pathogenic events may exert an additive effect, converging in final pathways leading to premature neuronal death. Some of these mechanisms are
common to several neurodegenerative disorders that differ depending on the gene(s) affected and the involvement of specific genetic networks, together with cerebrovascular factors, epigenetic factors (DNA methylation), and environmental conditions (e.g., nutrition, toxicity, social factors) [1,6,7]. The higher the number of genes involved in AD pathogenesis, the earlier is the onset of the disease, the faster its clinical course, and the poorer its therapeutic outcome [1].

Functional Genomics Studies

Although the amyloid hypothesis is recognized as the primum movens of AD pathogenesis [1,8], mutational genetics associated with APP and PSs genes alone (< 10% of AD cases) does not fully explain the neuropathological findings present in AD. Such findings include amyloid deposition in senile plaques and vessels (amyloid angiopathy), neurofibrillary tangle (NFT) formation due to hyperphosphorylation of tau protein, synaptic and dendritic desarborization, and neuronal loss. These changes are accompanied by neuroinflammatory reactions, oxidative stress, and free radical formation probably associated with mitochondrial dysfunction, excitotoxic reactions, alterations in cholesterol metabolism and lipid rafts, deficiencies in neurotransmitter and neurotrophic factor function, defective activity of the ubiquitin-proteasome and chaperone systems, and cerebrovascular dysregulation [1]. All of these neurochemical events are potential targets for treatment [9–11].

The molecular mechanisms underlying Aβ deposition in brain tissue and blood vessels have been elegantly elucidated during the past two decades by many groups all over the world [8,9,12], defining the fundamentals for promising therapeutic strategies oriented to inhibit the formation of amyloid deposits and oligomeric Aβ forms or to reduce senile plaque burden [8,9,11,12]. Notwithstanding, the complexity of the pathogenic cascade in AD invites one to predict that many other genetic factors may be involved in the etiology of AD, together with epigenetic phenomena, nutritional factors, and environmental circumstances [1].

Functional genomics studies have demonstrated the influence of many genes on AD pathogenesis and phenotype expression [13,14]. Mutations in the APP, PS1, PS2, and MAPT genes give rise to well characterized differential neuropathological and clinical phenotypes of dementia [1].

Pleiotropic Effects of ApoE

The ApoE gene is highly pleiotropic, participating in multiple metabolic pathways that influence the phenotype profile of dementia (Fig. 1). The analysis of genotype-phenotype correlations has revealed that the presence of the ApoE-4 allele in AD, in conjunction with other factors (genetic or nongenetic), influences disease onset, brain atrophy, cerebrovascular perfusion, blood pressure,