A prevalence study of single nucleotide polymorphisms in the promoter of the apolipoprotein E gene in different ethnic groups in Malaysia

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Abstract

Background and Objective: The promoter of the apolipoprotein E (APOE) gene is polymorphic at positions -491 A/T, -427 C/T and -219 G/T. These single nucleotide polymorphisms may alter transcriptional activity and impact APOE expression due to differential binding of transcription factors. It has been suggested that the -491 A, -427 C and -219 T alleles are associated with a high risk of developing Alzheimer's disease. This study aims to investigate the frequencies of APOE promoter polymorphisms in three major ethnic groups (Malay, Chinese and Indian) in Malaysia. Method: DNA was extracted from blood obtained from 290 healthy people (Malay: n = 92, Chinese: n = 105; and Indian: n = 93), and the promoter region was amplified using PCR and genotyped by direct sequencing. Results: The Indian group has the lowest frequencies of -491 A, -427 C and -219 T alleles (83.9%, 3.2% and 56.5%, respectively) compared to the Chinese group with the highest frequencies (97.1%, 11.9% and 67.1%, respectively). The frequencies in the Malay group were somewhere in between (94.6%, 8.2% and 61.4%, respectively). Moreover, for the -491 and -427 positions, the frequencies of possible genotypes viz., AA or AT or TT and CC or CT or TT, respectively, were statistically significant (P < 0.05, Chi-Square Test) between the 3 ethnic groups. Conclusion: Based on the frequency of APOE promoter polymorphisms alone, the ethnic Indian may be predisposed to lower risks for AD than the Chinese or Malay.

INTRODUCTION

Apolipoprotein E (ApoE) is a polymorphic protein with three common isoforms encoded by three alleles (ε2, ε3 and ε4) of the APOE gene on chromosome 19q13.2. ApoE represents a major lipoprotein within the central nervous system where it is synthesized by astrocytes. It has been suggested that one role of ApoE in the brain may be neuronal homeostasis, particularly, mobilization of cholesterol in the central nervous system, where it is required for neuronal plasticity. ApoE is also postulated to play a role in neuronal repair by mediating the recycle of damaged cell membranes.

In-vivo and in-vitro studies have suggested an association of certain alleles of the APOE with a higher risk for Alzheimer's disease (AD). The APOE ε4 allele is associated with both early- and late-onset AD. Factors that regulate APOE transcription, such as selected single nucleotide polymorphisms in the promoter or transcriptional regulatory region of APOE, may also contribute to an individual's risk for AD. Several polymorphic site in the gene promoter at positions -491 A/T, -427 C/T, and -219 G/T (also known as TH1E477c) have been variously reported to confer an increased risk for AD. The various genotypes (allelic combinations) for each position are: -491 AA or -491 AT or -491 TT; -427 CC or -427 CT or -427 TT; -219 GG or -219 GT or -219 TT.

The allelic polymorphism at position -491 is the most thoroughly investigated. Several studies have shown that the -491 A allele is associated with an increased risk of AD that is independent of the APOE ε4 status. Others have reported significant linkage disequilibrium between the -491 alleles and APOE ε4 polymorphisms but no independent association. To date, the -427 allelic polymorphism has been the subject of five investigations, only two of which have shown an independent association between the -427 C allele