THE DISTRIBUTION OF APOLIPOPROTEIN E GENOTYPE OVER THE ADULT LIFESPAN AND IN RELATION TO COUNTRY OF BIRTH

Apolipoprotein E (ApoE) is encoded by the codominant alleles ε2, ε3, and ε4, resulting in 6 bi-allelic genotypes (1–4). The corresponding protein isoforms differ in their lipoprotein receptor affinity, antioxidant activity, and inflammation modulatory properties (1, 5–8). APOE ε4 carriehership is associated with an increased risk of atherosclerosis and dementia (9). Approximately 65%–75% of patients with Alzheimer’s disease carry the ε4 allele (9–11). Several studiess in which the relative proportion of APOE alleles over the lifespan were examined showed stable ε4 frequencies at middle age and a decrease after a certain turning point. The age for this turning point differed between studies (10, 12–15). Furthermore, the APOE allele distribution seems to depend on ethnicity and varied with latitude (15–22), with higher ε4 frequencies being more common close to the equator and in the northern polar region (16, 17, 19, 21, 22). This might introduce confounding in gene-association studies. Therefore, the aim of the present Swedish population-based study was to consider APOE allele distribution in relation to age and country of birth.

METHODS

The study included persons who were 25–99 years of age from 4 different population-based studies in Gothenburg, Sweden (23–26). Both people living in private households and those living in residential care were included. The Swedish Ethics Committees for Medical Research approved the studies. APOE status was available for 4,579 persons (2,742 women and 1,837 men). Country of birth was self-reported. A total of 4,210 subjects came from countries of northern latitude (≥55°N), hereafter referred to as Nordic countries. Nordic and non-Nordic countries (25–80 years). The α4 carrier frequency was lower in participants who were older than 90 years of age, which is a high age turning point. This result was observed in the Nordic population because there were insufficient numbers of non-Nordic participants in the highest age groups, and it is possibly related to death from dementia or cardiovascular disease. Our finding is in line with the theory that there is an increased genetic influence with age (27, 28), with several factors contributing to longevity. In contrast to our study, McKay et al. (14) reported a continuous decrease in ε4 prevalence after 60 years of age. Participants in that study were controls from a study of Alzheimer disease (29–32). Controls from studies of APOE-related diseases might display an altered age-specific prevalence of ε4, with fewer participants having dementia compared with population controls. In our elderly, dementia was neither an exclusion criterion nor selection criterion, suggesting higher representativeness. Our study emphasizes the importance of being aware of selection bias in descriptive studies when excluding prevalent diseases. In association studies, the same exclusion criteria for cases and controls should be applied. In our study,
we showed stable allele frequencies up to age 80 years when stratified by ethnicity and not explicitly excluding subjects with dementia. In previous studies, ethnicity has not been considered when examining US citizens of European descent (14, 15). Because the number of non-Nordic participants was small, our data have to be interpreted cautiously. However, our findings underscore the fact that population studies in Western countries contain participants with different ethnic backgrounds because of globalization. To further decrease bias, it has become more important for descriptive studies to study allele frequency by age and for association studies to consider ethnicity.

Figure 1. Frequencies of apolipoprotein E (APOE) alleles by region of origin (A) and age (B) in 4 population-based studies, Gothenburg, Sweden (1996–2009). A) Frequencies of the ε4 (dashed-dotted line), ε3 (solid line), and ε2 (dotted line) alleles by region of birth with increasing latitude from left to right: Middle East, including North Africa (30°N); Southern Europe (40°N); Mid Europe (50°N); Finland and the Baltic States (60°N); and Scandinavia (Sweden, Norway, and Denmark; 60°N). B) ε3 allele frequencies for subjects of Nordic (solid line) and non-Nordic (dashed line) origin and the ε4 allele frequencies for subjects of Nordic (dashed-dotted line) and non-Nordic (dotted line) origin. Nordic countries included Scandinavia, Finland, and the Baltic States (n = 4,210). Non-Nordic countries included Mid and Southern Europe, the Middle East, and North Africa (n = 246). Bars, 95% confidence intervals.

Paralleling previous studies, we found higher ε4 frequencies in subjects who lived at higher latitudes (17, 22, 33). Nevertheless, higher dementia prevalence in the Northern European countries was not demonstrated (34). In different populations, ε4 may exert differential influence on dementia, as shown in the Nigerian-Ibadan study that found high ε4 frequencies and low dementia prevalence (35). In the relationship between hypercholesterolemia and dementia risk, ε4 may be an intermediate factor, suggesting that lifestyle factors leading to longevity in Sweden might attenuate the negative influences of ε4.

The strength of the present study is the large age interval (25–99 years) and the inclusion of persons regardless of comorbid conditions. A limitation was the low overall participation rate and the small numbers of non-Nordic participants. Further, the representativeness of the non-Nordic participants of their countries of origin is unclear. However, our allele frequencies were similar to those from previous studies (17, 22, 33). The low overall participation rate was mainly determined by the youngest participants (25, 26, 36), who had relatively stable APOE allele frequencies. In the older age groups, the participation rate was higher. Equal mortality between participants and nonparticipants among elderly subjects suggests similar APOE allele distribution (36).

In conclusion, in genetic epidemiologic studies, it is important to consider ethnicity and selection bias resulting from exclusion of prevalent diseases. Similar evaluations in other independent populations are required to fully understand the impact of ethnicity and age in epidemiologic studies regarding the APOE allele.

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