Linkage of the APOE locus with ApoE plasma levels in adolescent Dutch twins is completely explained by APOE ε2/ε3/ε4 alleles

M Beekman*[1], D Posthuma[2], BT Heijmans[1], N Lakenberg[1], HED Suchiman[1], C Kluft[3], GP Vogler[4], P de Knijff[5], GJB van Ommen[5], RR Frants[5], PE Slagboom[1], DI Boomsma[2]

*email: M.Beekman@lumc.nl; fax: +31 71 527 1985; phone: + 31 71 527 1914. 1. Molecular Epidemiology, Dept of Medical Statistics and Bioinformatics, LUMC, Leiden, The Netherlands. 2. Dept of Biological Psychology, Free University of Amsterdam, The Netherlands. 3. Gaubius Laboratory, TNO Prevention and Health, Leiden, The Netherlands. 4. Center for Developmental and Health Genetics and Dept of Biobehavioral Health, Pennsylvania State University, USA. 5.Dept. of Human and Clinical Genetics, LUMC, Leiden, The Netherlands.

Background

Apolipoprotein E (ApoE) plasma level and isoform influence the clearance rate of lipoprotein particles by the liver. The APOE ε2/ε3/ε4 alleles underlying the isoforms have been indicated to be one of the determinants of ApoE plasma level. The effect of additional genetic variation at the APOE locus remains unclear. We determined the contribution of the APOE ε2/ε3/ε4 alleles to variation in ApoE plasma level and tested for the existence of additional genetic variation within the APOE region influencing ApoE plasma levels using a recently developed combined linkage-association approach.

Methods

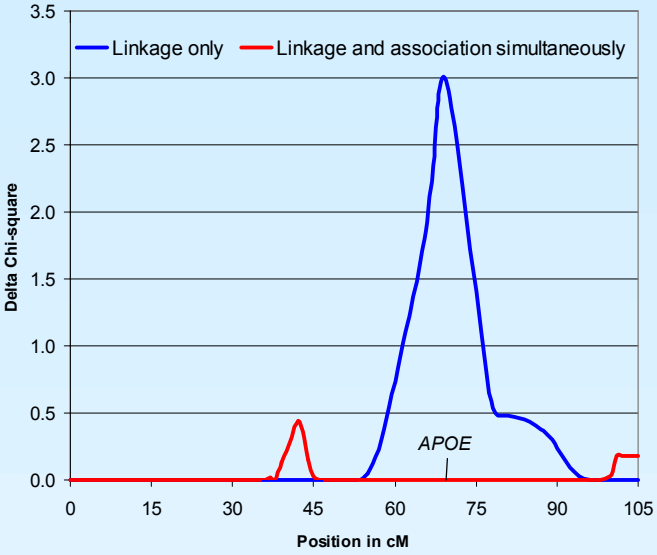
We genotyped the *APOE* ε2/ε3/ε4 polymorphism and 16 short tandem repeats on chromosome 19 in 82 dizygotic and 65 monozygotic Dutch twin pairs. A two-step analysis procedure was applied. First, multi-point variance-components linkage analysis was performed using the Mx software which is making use of IBD probabilities estimated in Genehunter. Next, linkage and association with the APOE e2/e3/e4 alleles were modelled simultaneously. Association was implemented as the between and within twin pair effect of the alleles, which allows to separate genuine associations from associations due to population stratification.

Results

The model that fits the data best included additive and dominant genetic components and a unique environmental component. The between and within pair effect of alleles could be equated (Table 1 bold).

When modelling a QTL without any association of the *APOE* ε2/ε3/ε4 polymorphism, a putative QTL explaining 38% of the variation in ApoE plasma level was found at the *APOE* locus (19q13.2; p=0.08) (Figure 1 blue line). In the analysis including the effect of a QTL as well as association, association with ε2/ε3/ε4 alleles explained 41% of the variation in ApoE plasma level ($p<0.0005$) and neutralized the linkage due to the putative QTL (Figure 1 red line).

Figure 1. Linkage and association analysis of chromosome 19 in adolescent Dutch twins



Conclusions

*There is no population statification, since the between and within pair allelic effects could be equated.

*41% of the population variation in ApoE levels is attributable to the association with the *APOE* ε2/ε3/ε4 polymorphism. Since 86% of the total variance of ApoE level in the adolescent Dutch twins is attributable to genes, this implicates that additional genes are influencing ApoE levels.

*There was no additional effect of a putative QTL on ApoE plasma levels, when association of the ε2/ε3/ε4 alleles with ApoE plasma levels was modelled. These findings exclude the presence of other genetic variation at the *APOE* locus with a major independent effect on ApoE plasma level in adolescent Dutch twins.

Table 1. Model fitting on the ApoE data in adolescent Dutch twins

Additive and **dominant genetic** component and **unique environmental** component included (no linkage)									
	Full association with age regression			Effect between pairs = effect within pairs		No dominance effect		No effect of the APOE ε2/ε3/ε4 polymorphism	
	obs	-2ln likelihood	Degrees of freedom	-2ln likelihood	Degrees of freedom	-2ln likelihood	Degrees of freedom	-2log likelihood	Degrees of freedom
Dutch twins	294	1108.76	280	**1116.07**	**285**	1132.96	288	1235.26	290