Apolipoprotein E polymorphism in the Finnish population: gene frequencies and relation to lipoprotein concentrations

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Abstract ApoE phenotypes were determined in 615 unrelated Finnish individuals. The apoE gene frequencies observed (ε2, 0.041; ε3, 0.733; ε4, 0.227) differ significantly from those in other populations. The frequency of the allele ε2 was lower and that of ε4 higher than in all other studied populations. Plasma lipids and apolipoproteins A-I, A-II and B were recorded in 207 of the typed subjects. By comparison with the most frequent homozygous apoE 3/3 phenotype, it was found that total cholesterol, LDL-cholesterol, and apoB concentrations were all markedly higher in apoE 4/4 and to a lesser degree in apoE 4/3 phenotypic groups. On the other hand, these lipid and apolipoprotein levels tended to be lower in E-2 heterozygotes. These data confirm and extend, in a different ethnic group, previous results of an effect of apoE genes on plasma lipoprotein concentrations. The data suggest that the apoE gene locus may be one factor responsible for the high LDL cholesterol concentrations in the Finnish population. — **Ehnholm, C., M. Lukka, T. Kuusi, E. Nikkilä, and G. Utermann.** Apolipoprotein E polymorphism in the Finnish population: gene frequencies and relation to lipoprotein concentrations. *J. Lipid Res.* 1986. **27:** 227–235.

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Apolipoprotein E (apoE) is a constituent of plasma very low density lipoproteins (VLDL), chylomicron remnants, and high density lipoproteins (HDL) (1–3). Recent studies have indicated that apoE plays an important role in lipoprotein metabolism and may also be involved in atherogenesis (4–6). ApoE may regulate lipid metabolism in several ways; it mediates hepatic uptake of certain classes of lipoproteins and interacts with low density lipoprotein receptors in various tissues and may also act in cholesterol transport from peripheral tissues to the liver (7, 8). The human apoE occurs as three major genetic forms which can be separated by isoelectric focusing (IEF). Studies by Utermann et al. (9, 10) and Zannis and Breslow (11, 12) have increased our understanding of the genetics underlying this heterogeneity. The isoforms are coded for by three codominant alleles designated ε2, ε3, and ε4 at one autosomal locus. The allelic products apoE-2, E-3, and E-4 differ from each other by one charge unit. This is due to the presence of two, one, or no cysteine residues in apoE-2, E-3, and E-4, respectively (13, 14). Linkage data indicate that, in man, the apoE locus is close to that for complement component C3 on chromosome 19 (15).

In population studies the gene frequencies observed have ranged from 0.077 to 0.170 for ε2, from 0.720 to 0.783 for ε3, and from 0.110 to 0.175 for ε4 (11, 16–20). Recently several very rare mutants E-1 (21), E-Bethesda (22), E-5 (23), E-2* (13), E-Suita (23), E-2** (24), and also functionally inactive forms of apoE-3 (25, 26) have been reported.

Previous work (10, 20, 27) has suggested that the apoE polymorphism influences plasma lipid levels. It has been reported that E2 homozygotes, and to a lesser degree E2 heterozygotes, have subnormal cholesterol concentrations (20, 27, 28). Some E2 homozygotes do, however, develop type III hyperlipoproteinemia and, in turn, most type III individuals are E 2/2 homozygotes (29).

Moreover the gene ε4 seems to be associated with hypercholesterolemia (30, 31). High frequencies of apoE4 have also been reported in subjects with type V hyperlipidemia by one group (32), whereas other studies have failed to establish this association (33). This investigation was undertaken in order to determine the gene frequencies for the apoE alleles in the Finnish population, and to get further insight into the question of whether apoE phenotypes influence plasma lipid levels.

Abbreviations: VLDL, very low density lipoprotein; HDL, high density lipoprotein; IEF, isoelectric focusing; TBS, Tris-buffered saline.

MATERIALS AND METHODS

Samples

Samples were obtained from the personnel of the National Public Health Institute and from healthy volunteers. Blood was collected in the morning, after a 12-hr fast, from the antecubital vein into Vacutainer tubes containing either disodium ethylenediamine tetraacetate (EDTA) (final concentration 1 mg/ml) or no additives. The plasma or serum was separated after centrifugation at 2500 rpm for 15 min. The plasma samples from 207 donors were analyzed at the National Public Health Institute, while serum samples from 408 subjects were sent frozen to the Institute for Human Genetics, Marburg, Germany.

ApoE phenotyping

The apoE phenotyping performed in Finland was as follows. Four ml of plasma from fasting subjects (containing EDTA, 1 mg/ml) was ultracentrifuged for 18 hr at 37,000 *g* (TFT 45.6 rotor, Kontron). The VLDL fraction ($d < 1.006$ g/ml) was isolated and the protein content was determined (34). Two samples of VLDL, containing 100 μg of protein each, were taken for apoE phenotyping. One was incubated with 10 μl of cysteamine solution (100 mg of cysteamine, Sigma, per 1 ml of 0.1 M ammonium bicarbonate) and the other with 10 μl of 2-mercaptoethanol (Fluka) for 3 hr at 37°C. The samples were then delipidated in four steps: first with 6 ml of cold ethanol-ethyl ether 3:1 (vol/vol), then with 3 ml of ethanol-ethyl ether 3:2 (vol/vol), and finally twice with 3 ml of ethyl ether. The proteins were dissolved in 100 μl of incubation solution (10 mM Tris, 8 M urea, ultra pure, 20% sucrose, pH 8.6, for the cysteamine-treated sample, and the same solution with added 10 mM dithiothreitol for the samples treated with 2-mercaptoethanol), and incubated overnight at room temperature.

Isoelectric focusing

Analytical isoelectric focusing was performed on polyacrylamide gel (T 5.1%, C 2.2%) containing 8 M urea and 2% Ampholine, pH 4–6 (LKB). Glasses, 1.5-mm spacers, and 20-well combs of an LKB 2001 vertical electrophoresis unit were used. Sixty-μl aliquots of sample were pipetted in every gel slot, the cysteamine-treated sample beside the 2-mercaptoethanol-treated sample. A sample of purified apoE-3 was used as control (5 μg of protein per slot). The slots were filled with 5% sucrose containing 25 μl of LKB Ampholine, pH 4–6, per ml. The gel was focused for 40 min at 300 volts and then 4 hr at 500 volts in an LKB 2001 vertical electrophoresis apparatus at +4°C. Sulfuric acid (0.2%) was used as the anodal solution and 0.4% ethylenediamine was used as cathodal buffer. After isoelectric focusing, the gels were fixed overnight in 30% methanol containing 34.5 g of 5-sulfosalicylic acid and 115 g of trichloroacetic acid per liter. After fixation the gel was washed for 15 min in 25% ethanol and 8% acetic acid, and thereafter was stained for 15 min with 0.1% Coomassie BB R-250 in washing solution at 60°C. The gel was destained in washing solution until the background was clear.

The apoE phenotypes of the 408 serum samples sent to Germany were determined by isoelectric focusing of heparin/Mg^{2+}-precipitated lipoproteins essentially as described (10, 16).

ApoA phenotyping

ApoA phenotyping was done according to Menzel, Kladetzky, and Assmann (35) with some modifications. Five μl of serum was incubated for 1 hr at room temperature in 50 μl of 10 mM Tris, 1% decylsulfate, 2% Ampholine (LKB 4-6), 20% sucrose, 10% 2-mercaptoethanol, pH 8.2. The composition of the polyacrylamide gel, the running buffers, and the equipment were the same as those used for apoE phenotyping. Isoelectric focusing was performed for 16 hr at 200 V. The gels were fixed, stained, and destained as described for apoE phenotyping.

Immunoblotting

After isoelectric focusing, the gel to be blotted was washed briefly in distilled water and put on a glass plate. A Bio-Rad nitrocellulose membrane sheet was wet with water and laid air-tight on the gel. Two pieces of filter paper and a layer of cellulose 1-cm thick were put on top of the membrane. The pocket was then evenly pressed for 1 hr under another glass plate and a weight of 1 kg. After transfer, the nitrocellulose paper was immersed overnight in 10 mM Tris-HCl buffer, pH 7.4, containing 0.9% sodium chloride (TBS) and 3% gelatin (Bio-Rad EIA grade). The membrane was then incubated for 2 hr with rabbit anti-apoE, diluted 1:50 in 1% gelatin-TBS. After incubation, the membrane was washed for 40 min in 100 ml of TBS containing 25 μl of Tween-20 (Bio-Rad EIA grade). The washed membrane was then incubated with affinity purified goat anti-rabbit IgG-horseradish peroxidase (HRP)-conjugated second antibody (Bio-Rad) in a dilution of 1:2000 in 1% gelatin-TBS for 2 hr and thereafter washed as previously. At last the membrane was immersed in color developing solution: 60 mg of HRP color development reagent (Bio-Rad) in 20 ml of cold (−20°C) methanol, 100 ml of TBS, and 60 μl of 30% hydrogen peroxide.

Lipoprotein quantitation

Cholesterol and triglyceride concentrations were determined using Boehringer Kits No. 263 691 and 297 771 (Boehringer GmbH, Mannheim, FRG), respectively, in a Kone Olli-C Discrete Analyzer. The concentration of apolipoprotein B was determined using a radial immunodiffusion kit M-partigen Apolipoprotein (Behringwerke

AG, Marburg, FRG); apolipoproteins A-I and A-II were assayed by a radial immunodiffusion procedure described earlier (36).

Statistical analysis

Statistical treatment of the data was performed in a DPS 8 computer operated with BMDP statistical software (Biomedical Data Processing System, 1981, Department of Biomathematics, UCLA).

The mean lipid values of different apoE phenotypes were compared using the non-paired Student's *t*-test. However, when comparing the lipid and apoprotein values of apoE4/4, E4/3, and E3/2 subjects with those of apoE3/3 subjects (Table 4), we selected a control subject matched to each of the apoE4/4, E4/3, and E3/2 subjects from the group of apoE3/3 subjects, using a computer program. The matched items were sex, body mass index (weight divided by height (in meters) squared), and age. This was done in order to control the effect of sex, body weight, and age on plasma lipids in the statistical comparisons. The subjects were then compared with their matched controls using paired Student's *t*-test. The mean ± SEM values of the apoE4/4, E4/3, and E3/2 subjects and of the three control (apoE3/3) groups are shown in Table 4.

The variances (V) of the gene frequencies (p, q, and r) were calculated according to formulas derived from maximum likehood estimates as follows (37).

$$V_p = \frac{p}{8n}\left(4 - 3p + \frac{pr}{pq + r}\right)$$

$$V_q = \frac{q}{8n}\left(4 - 3q + \frac{qr}{pq + r}\right)$$

$$V_r = V_p + V_q - \frac{pq}{4n}\left(4 - \frac{pq}{pq + r}\right)$$

n = sample size.

The standard deviations are the square roots of these variances.

RESULTS

The banding pattern observed after isoelectric focusing of delipidated VLDL in a pH gradient from 4 to 6 is illustrated in **Fig. 1.** The assignment of protein bands in the gels was based on comparison with focusing patterns of purified apoproteins E-2, E-3, and E-4, immunoblotting (**Fig. 2**), and by comparison to published patterns (10, 11, 16, 20). The nature of the polymorphic forms of apoE was also confirmed by the use of cysteamine treatment as described by Weisgraber, Rall, and Mahley (38). Using these criteria all six common phenotypes of apoE could be distinguished. The determination of apoE gene frequencies was done in two laboratories. Four hundred and eight sera were typed in

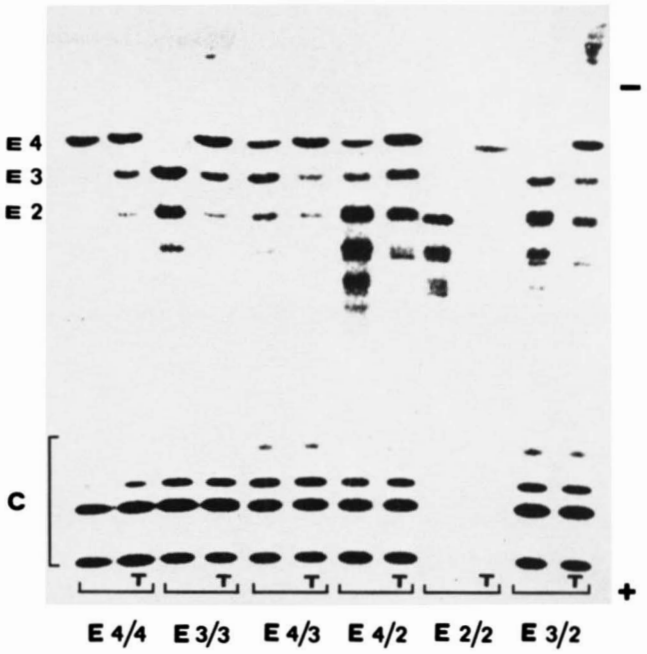

Fig. 1. Isoelectric focusing gel of VLDL from subjects of different apoprotein E phenotypes and purified apoprotein E-2. The untreated samples are to the left and the cysteamine-treated (T) to the right. The location of the main apoE components E-4, E-3, E-2, and the C apoprotein bands are indicated. The cathode (−) is at the top and the anode (+) at the bottom.

Marburg and 207 in Helsinki. The prevalences obtained for the E phenotypes are presented in **Table 1.** It is evident that the gene frequencies obtained in both laboratories are in good agreement. The distribution of different phenotypes observed among the 408 Finns typed in Marburg (Table 1) was statistically different in a 6 × 2 comparison ($X^2 = 67.6$, $P < 0.001$) from the expected Hardy-Weinberg distribution calculated using the German gene frequencies (**Table 2,** ref. 30). Thus the Finns differ from the Germans with respect to their apoE gene frequencies.

To further confirm the lower frequency of ε2 found in Finns as compared to that observed in the German population typed in same laboratory (30), the isoelectric focusing was complemented by phenotyping by SDS-polyacrylamide gel electrophoresis. This method (39) allows the detection of the E2 substitution ($Arg_{158} \rightarrow Cys$). Using this method complete agreement between the results obtained by the two methods was observed, e.g., samples typed by isoelectric focusing as E3/2, E4/2, or E2/2 had an apoE band with abnormal slow mobility in SDS-polyacrylamide gel electrophoresis, whereas E4/4, E4/3, and E3/3 did not. In the identification of 20 duplicate samples examined in both laboratories there was also full concordance. The gene frequencies observed in the Finnish population, ε2 0.041, ε3 0.733, ε4 0.227, differ from those observed in some

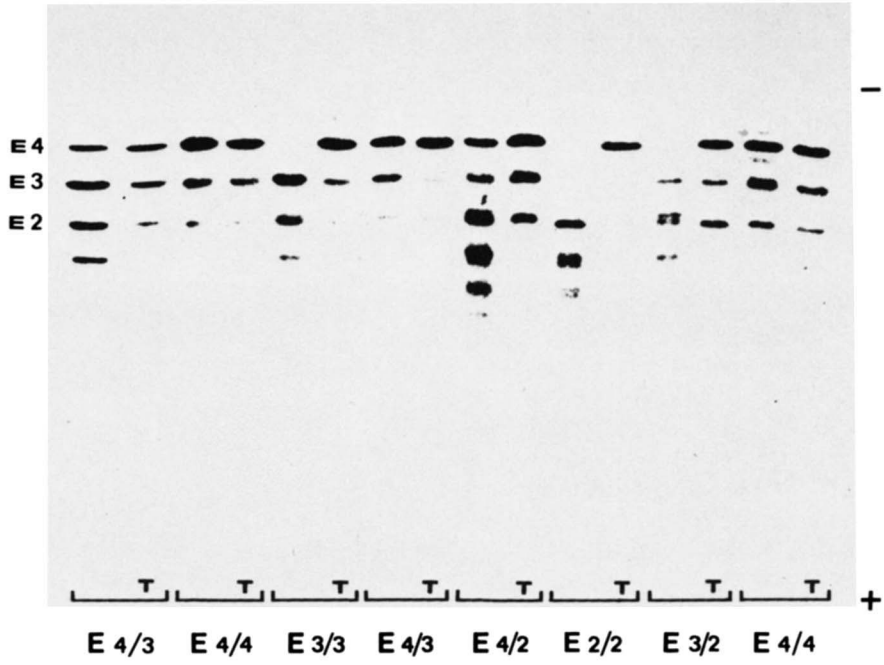

Fig. 2. Immunoblotting of apoE after isoelectric focusing of VLDL from subjects of different apoE phenotypes. The symbols are as in Fig. 1.

other populations (Tables 1 and 2). Thus the ϵ4 frequency is higher and the ϵ2 frequency is lower than observed in previous studies.

In order to study whether the apoE genotype influences plasma lipoprotein levels, plasma lipids and apoproteins A-I, A-II, and B were recorded in 207 subjects. The mean plasma lipid and apoprotein values according to phenotype for those subjects are given in **Table 3.**

The highest concentrations of LDL were seen in the group of E 4/4 homozygotes. On the other hand E2 heterozygotes (E 4/2 and 3/2) had lower plasma cholesterol, LDL-cholesterol, and apoB than E3/3 subjects. These differences were, however, not statistically significant. **Fig. 3** illustrates the differences in mean LDL cholesterol and plasma apoB in the different apoE phenotypes of the 207 Finnish subjects. A comparison of the lipid and apoprotein concentrations observed in different phenotypes with those in the most common homozygous apoE3/3 phenotype on an age-, sex-, and weight-matched basis revealed that total cholesterol, LDL-cholesterol, and apoB concentrations were all significantly higher in the 4/4 and in the 4/3 phenotype, whereas no difference was

TABLE 1. ApoE phenotype and gene frequencies (± SD) in the Finnish population

	Helsinki			Marburg			Combined		
Phenotype	Obs.	(Exp.)	%	Obs.	(Exp.)	%	Obs.	(Exp.)	%
E4/4	12	(11.8)	5.8	27	(20)	6.6	39	(31.7)	6.3
E3/3	98	(100.9)	47.3	234	(230)	57.4	332	(330.4)	54.0
E2/2	1	(0.8)	0.5	1	(0.3)	0.2	2	(1.0)	0.3
E4/3	72	(69.1)	34.8	124	(135)	30.4	196	(204.7)	31.9
E4/2	3	(6.2)	1.4	2	(5)	0.5	5	(11.4)	0.5
E3/2	21	(18.1)	10.1	20	(18)	4.9	41	(37.0)	6.7
Total	207			408			615		
Gene frequencies									
ϵ4	0.239 ± 0.0220			0.221 ± 0.0151			0.227 ± 0.0125		
ϵ3	0.698 ± 0.0297			0.750 ± 0.0207			0.733 ± 0.0170		
ϵ2	0.063 ± 0.0266			0.029 ± 0.0183			0.041 ± 0.0151		

The standard deviations of the gene frequencies were estimated as described in Methods.

TABLE 2. ApoE gene frequencies (± SD) in different populations

Allele	Reference	ε4	ε3	ε2
Finland		0.227 ± 0.0125	0.733 ± 0.0170	0.041 ± 0.0151
Germany	(30)	0.150 ± 0.0081	0.773 ± 0.0137	0.077 ± 0.0125
Germany	(20)	0.139 ± 0.0080	0.783 ± 0.0139	0.078 ± 0.0128
USA	(11)	0.110 ± 0.0291	0.720 ± 0.0586	0.170 ± 0.0556
USA	(17)	0.175 ± 0.0307	0.740 ± 0.0484	0.085 ± 0.0441
USA	(18)	0.149 ± 0.0302	0.757 ± 0.0515	0.095 ± 0.0474
New Zealand	(19)	0.141 ± 0.0123	0.739 ± 0.0217	0.120 ± 0.0202
Scotland	(41)	0.15 ± 0.0130	0.77 ± 0.0220	0.08 ± 0.0201
France	(40)	0.152 ± 0.0262	0.770 ± 0.0472	0.078 ± 0.0424

present in HDL-cholesterol or triglyceride (**Table 4**). For the 207 sera studied in Helsinki, the apoA phenotype was also determined by isoelectric focusing. No apoA variants could be recognized by this method. The levels of apolipoproteins A-I and A-II were similar in the different apoE phenotypes.

DISCUSSION

Studies on the polymorphism of apolipoprotein E in several populations have demonstrated the presence of three common apoE alleles, ε2, ε3, and ε4, that code for the genetic isoforms and determine six different phenotypes (10, 11, 16, 19, 20). All six apoE phenotypes were observed in the Finnish population sample studied here. The frequencies of the apoE alleles in the Finnish population are, however, significantly different from those observed in the other previously studied populations, e.g., Germans (20, 30), Americans (11, 17, 18), French (40), New Zealanders (19), Scots (41), Indians, Chinese, and Malays (Saha, N. and G. Utermann, unpublished). Thus in the Finnish population the ε2 gene is less frequent, whereas the frequency of the ε4 is considerably higher than elsewhere resulting in 6.3% E4 homozygotes in the Finnish population. Previous work (42) has demonstrated that the distribution of both polymorphic and rare marker genes in the Finnish population shows evidence of the effect of genetic drift maintained by national and local isolation. This observation may explain the differences in apoE gene frequencies between the Finns and other studied populations. Clinical experience indicates that type III hyperlipidemia is infrequent among Finns, and therefore it was not unexpected to find a lower frequency of apoE-2 in them than in populations where type III hyperlipidemia is more common.

ApoE isoforms differ by single arginine–cysteine interchanges in different positions of the apoE sequence (14). The common form of apoE-2 contains two cysteine residues, apoE-3 has one, and apoE-4 has no cysteine. Our results on the modification of apoE by cysteamine provide indirect evidence that the genetic apoE forms in Finns are identical with those in other populations.

The association of apoE-2 with type III dyslipoproteinemia is well documented; however all E2/2 homozygotes do not develop hyperlipidemia (17, 29, 43). Accordingly subjects with the apoE 2/2 phenotype tend to develop this disorder if some other genetic defect in lipoprotein metab-

TABLE 3. Plasma lipids and apoproteins A-I, A-II, and B in nonmatched subjects with different apoE phenotypes

	E4/4 (n = 12)[a]	E4/3 (n = 72)	E3/3 (n = 98)	E4/2 (n = 3)	E3/2 (n = 21)	E2/2 (n = 1)
			mmol/l ± SEM			
Triglycerides	1.26 ± 0.11	1.24 ± 0.11	1.20 ± 0.07	1.60 ± 0.72	1.00 ± 0.15	1.14
Cholesterol	6.24 ± 0.53	5.74 ± 0.12	5.52 ± 0.13	5.05 ± 0.67	5.21 ± 0.32	4.45
LDL-Chol[b]	4.07 ± 0.47	3.70 ± 0.12	3.44 ± 0.12	2.60 ± 0.63	3.14 ± 0.29	2.49
HDL-Chol	1.60 ± 0.10	1.48 ± 0.04	1.54 ± 0.03	1.72 ± 0.26	1.62 ± 0.06	1.45
			mg/dl ± SEM			
ApoA-I	153 ± 6.7	148 ± 3.1	153 ± 2.3	160 ± 7.1	154 ± 4.1	156
ApoA-II	46 ± 3.2	40 ± 0.8**	44 ± 0.7	48 ± 5.0	41 ± 1.6	44
ApoB	127 ± 13.6	105 ± 3.6	100 ± 2.8	94 ± 32.3	86 ± 6.1*	71

[a] Number of subjects is given in parentheses.
[b] LDL-cholesterol was calculated according to Friedewald, Levy, and Fredrickson (52).
*, $P < 0.05$, significantly different from mean value of the E3/3 phenotype subjects; **, $P < 0.01$, significantly different from mean value of the E3/3 phenotype subjects.

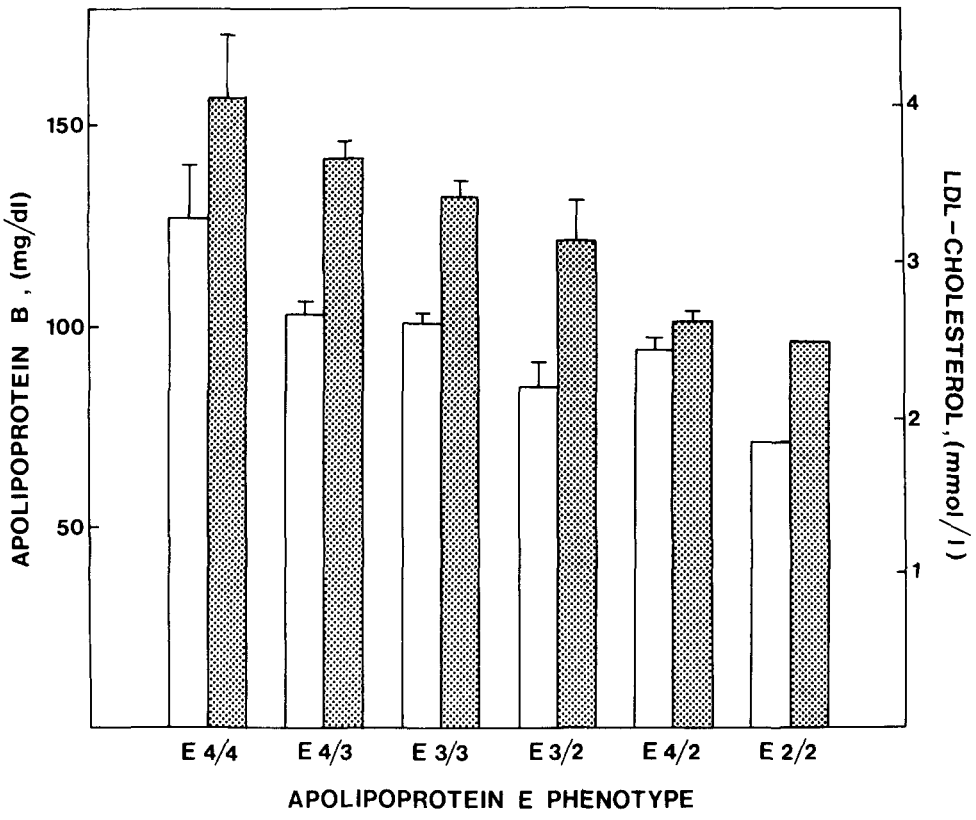

Fig. 3. Plasma LDL cholesterol and apoB concentrations in different apoE phenotypes. LDL-cholesterol, shaded bars; apoB concentration, open bars.

olism is present (28, 30, 44). Our material included only one homozygote E2/2 (age 38) having no signs of type III hyperlipoproteinemia but low cholesterol, triglyceride, and apoB concentrations (Table 3). This is consistent with results of recent studies (45). Both of the parents of the homozygote E2/2 had normal lipid concentrations and an apoE phenotype, E 3/2.

Another interesting association of apoE-2 with serum lipids is the low level of serum cholesterol in E 3/2 subjects (20, 27). In the present study subjects with the E 3/2 phenotype also tended to have a lower concentration of serum total and LDL cholesterol and of apoB than subjects with the most common apoE phenotype, apoE 3/3 (Table 3).

TABLE 4. Differences between the apoE4/4, E4/3, and E3/2 subjects and age-, sex-, and weight-matched control (apoE3/3) subjects

	E4/4 (n = 9)[a]	E3/3	E4/3 (n = 67)	E3/3	E3/2 (n = 20)	E3/3
			mmol/l			
Triglycerides	1.24 ± 0.13	1.03 ± 0.12	1.18 ± 0.10	1.09 ± 0.09	0.91 ± 0.12	1.24 ± 0.25
Cholesterol	6.14 ± 0.63	4.94 ± 0.28*	5.74 ± 0.13	5.26 ± 0.14**	5.14 ± 0.33	4.81 ± 0.19
LDL-Chol	3.96 ± 0.54	2.90 ± 0.34*	3.71 ± 0.12	3.20 ± 0.15**	3.10 ± 0.30	2.76 ± 0.19
			mg/dl			
ApoB	124 ± 15.8	91 ± 7.5	104 ± 3.8	95 ± 2.5*	83 ± 5.9	97 ± 3.8

Each subject with the apoE phenotype indicated was compared with a control apoE3/3 subject matched for age, sex, and body mass index as described in Methods. The paired *t*-test was used. The mean ± SEM values of each group and the corresponding subgroup of apoE3/3 subjects formed from the matched controls is shown.

[a]Number of subjects in each group is given in parentheses.

*, $P < 0.05$; **, $P < 0.01$.

Recently Utermann et al. (30) and Assmann et al. (31) studied apoE phenotypes in hyperlipidemic patients and observed that the apoE-4 isoform was significantly more frequent in subjects with hypercholesterolemia than in patients with hypertriglyceridemia or in the general population. In the present material we have observed an association of apoE-4 with elevated cholesterol, LDL-cholesterol, and apoB levels in a randomly selected population sample. Similar results were recently obtained in a population sample from Germany (G. Utermann, unpublished results). Hence, the observed associations are independent of the ethnic background and differences in environment, and are probably true effects of the apoE gene locus.

There is no in vitro evidence so far that apoE-4 is functionally different from apoE-3. The receptor binding activities of apoE-3 and apoE-4 are identical (46, Utermann, G., W. Weber, S. Motzny, and U. Beisiegel, unpublished results) and both genetic isoforms activate the enzyme lecithin:cholesterol acyltransferase to the same extent (Steinmetz, A., H. Kaffarnik, and G. Utermann, unpublished results). The mechanism underlying the association of apoE-4 with hypercholesterolemia is therefore unclear. Two possibilities may be considered. It has been shown that apoE isoforms contain cysteine and may form mixed disulfides with apoA-II (47). The binding of apoA-II to apoE blocks the binding of apoE-containing lipoproteins to LDL-receptors (48). Apo-E-4, in contrast to apoE-2 and apoE-3, does not contain cysteine and therefore is unable to form complexes with apoA-II. This may result in an enhanced hepatic uptake of apoE-4-containing very low density lipoproteins and a down-regulation of LDL-receptors. This, in turn, could result in an elevated LDL concentration in plasma. Evidence for enhanced catabolism of apoE-4 relative to that of apoE-3 in in vivo turnover tests has recently been reported by Gregg et al. (49).

A second possibility is that the alleles of the apoE gene locus are in linkage disequilibrium with those of the LDL-receptor locus. Both loci are linked with the complement component C3 on chromosome 19 (15, 50) but the actual distance between these two loci is not yet known. Several mutant genes are known to exist at the LDL-receptor locus, and it has been postulated that the LDL-receptor locus is polymorphic (51). ApoE-4, therefore, might be in coupling with an allele at the LDL-receptor gene locus that has a mild hypercholesterolemic effect.

The higher frequency of the ε4 gene in Finns is in accordance with the higher serum cholesterol values in this population. Together, our data indicate that the apoE gene locus may be one of several factors contributing to the higher serum cholesterol in the Finnish population.

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