Proposed nomenclature of apoE isoproteins, apoE genotypes, and phenotypes


Children’s Hospital Medical Center/Harvard Medical School, Boston, MA 02115; Institut für Humangenetik und Genetische Poliklinik der Philipps-Universität Marburg, Bahnhofstrasse 7A, West Germany; Gladstone Foundation Laboratories, San Francisco, CA 94140; Cardiovascular Research Institute, University of California, San Francisco, CA 94143; Health Science Center, University of Texas, Dallas, TX 75235; Lipid Research Center, Washington University School of Medicine, St. Louis, MO 63110; Harborview Medical Center, Seattle, WA 98104; and Columbia College of Physicians and Surgeons, New York, NY 10032

Electrophoretic studies of human apoE have shown that it is composed of numerous isoprotein components (1–6). The complexity of apoE results from post-translational modification with carbohydrate chains containing sialic acid (7, 8) and from genetic polymorphism in the human population (3, 8–10). The early genetic models could not explain satisfactorily the genetic polymorphism of human apoE (3, 10). According to the currently accepted genetic model (8, 9), there exist three alleles at a single genetic locus that specify six different apoE phenotypes. These phenotypes can be presently recognized by two-dimensional gel electrophoresis and one-dimensional isoelectric focusing (11–13). Consistent with this genetic model, recent studies suggest that the different apoE alleles may result from point mutations in the structural apoE gene (11). Amino acid analysis and sequence data demonstrate that the three major isoforms of apoE (E-2, E-3, and E-4) differ by a single amino acid involving cysteine-arginine interchanges. These interchanges account for the known charge differences between the major apoE isoforms (8, 11). As a result of the cysteine-arginine interchanges, the apoE-2 has two cysteine residues per mole, apoE-3 has one cysteine, and apoE-4 has no cysteine.

There is no current controversy regarding the apoE isoprotein phenotypes and genotypes. However, the original work based on one-dimensional isoelectric focusing resulted in one nomenclature system (1–3, 10), whereas the later work with two-dimensional polyacrylamide gel electrophoresis resulted in a different nomenclature (8, 9, 14). In order to avoid confusion, we are proposing a uniform system of nomenclature, which can meet the needs of clinical or research laboratories utilizing either one or two-dimensional systems. The overriding considerations in proposing this nomenclature are simplicity and clarity. The proposed nomenclature describes the apoE isoproteins, alleles, genotypes, and phenotypes as follows: the apoE alleles are called ε4, ε3, and ε2. The major asialo apoE isoforms seen in plasma by two-dimensional gel electrophoresis (9) are designated apoE-4, apoE-3, and apoE-2, respectively. ApoE-4 is the most basic and apoE-2 is the most acidic isoprotein. The minor plasma apoE isoproteins, which are eliminated by treatment with neuraminidase (8), have been collectively designated apoEα. Thus, the sialo apoE isoforms of apoE-4, apoE-3, and apoE-2 are designated apoE-4α, apoE-3α, and apoE-2α, respectively (Fig. 1). If distinction between the different sialo apoE isoforms is necessary, they can

Abbreviation: apoE, apolipoprotein E.
Fig. 1. Schematic presentation and proposed nomenclature of apoE isoproteins of subsets homozygous (top) or heterozygous (bottom) for the apoE alleles. *, The sialo apoE isoprotein groups S2 and S3 contain more than one isoprotein with slight differences in molecular weight. Minor asialo isoproteins more acidic than isoproteins S3 have been observed in plasma apoE and apoE synthesized by hepatic cells or hepatic tissues in culture (30, 32). **, Differences have been occasionally noted in the relative concentrations of the major asialo apoE isoproteins of the heterozygous apoE phenotypes. In addition, the relative concentrations of the sialo to the asialo apoE isoproteins can vary.

be named as apoE-3z1, apoE-3z2, apoE-3z3, etc. from basic to acidic. Minor protein components of the same molecular weight as the major asialo apoE isoproteins appear on the basic and acidic sides of the major apoE isoproteins. We have decided not to name these protein components until more is known about their biochemical nature. The model of apoE inheritance of three alleles at a single genetic locus provides for six genotypes and phenotypes which have been recognized and designated:

\[ e_4, e_4 = E_4/4 \quad e_3, e_3 = E_3/3 \quad e_2, e_2 = E_2/2 \]
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The relationships of apoE alleles and phenotypes along with previously used designations are shown in Fig. 2. The relationships of phenotypes and isoproteins seen by one- and two-dimensional techniques are shown in Fig. 3. This figure shows that what was previously called apoE-IV corresponds to apoE-4 in the present nomenclature. However, apoE-III corresponds to different combinations of isoproteins depending on the apoE phenotype from which it was derived. For instance, apoE-III corresponds to apoE-3 when it is derived from an individual with the apoE phenotype E3/3 or E3/2. However, apoE-III corresponds mainly9 with apoEz when it is derived from individuals with the apoE phenotype E4/4 or E4/2. Furthermore, the apoE-III cor-

9 The asialo components which appear to the acidic side of the major asialo apoE isoproteins in the two-dimensional system may occasionally contribute significantly to the total apoE isoproteins (E-III, E-II, and E-I) observed by one-dimensional isoelectric focusing.

Fig. 1. Schematic presentation of the three-allele model of apoE inheritance and nomenclature of the apoE alleles and phenotypes. *, E*, E+a, and E+a, were thought to be regulatory or structural genes at different, but closely linked, loci which were assumed to control apoE phenotypes (10). Previous haplotypes E*/E+a*, E*/E+a*, and E+a*/E+a* (10) correspond to alleles e4, e3 and e2. **, The original cII, cIII, cIV, or the corresponding e4, e3, and e2 alleles represent three alleles at the structural apoE gene locus (9). The closed circles represent the major asialo apoE isoproteins.

Fig. 2. Schematic presentation and proposed nomenclature of apoE isoproteins of subsets homozygous (top) or heterozygous (bottom) for the apoE alleles. *, The sialo apoE isoprotein groups S2 and S3 contain more than one isoprotein with slight differences in molecular weight. Minor asialo isoproteins more acidic than isoproteins S3 have been observed in plasma apoE and apoE synthesized by hepatic cells or hepatic tissues in culture (30, 32). **, Differences have been occasionally noted in the relative concentrations of the major asialo apoE isoproteins of the heterozygous apoE phenotypes. In addition, the relative concentrations of the sialo to the asialo apoE isoproteins can vary.

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Fig. 3. Schematic presentation and proposed nomenclature of apoE isoproteins and phenotypes seen by one-dimensional isoelectric focusing and two-dimensional gel electrophoresis. *Phenotypes E4/4 and E4/3 were not differentiated in the original work of Utermann, et al. (10). Both were collectively designated EN/4*. **Phenotype E4/2 (aIV) ought to correspond to Utermann’s hypothetical apoE phenotype ED/4* (10). Due to interference of the sialo apoE isoprotein E4s (13), the phenotype observed was not originally recognized as such, but was designated as END/4* (10). * Phenotypes and isoproteins observed by one-dimensional isoelectric focusing. ** Phenotypes and isoproteins observed by two-dimensional gel electrophoresis.

Genetic variation or post-translational modification may affect lipoprotein catabolism (28–31). We urge that this nomenclature be adopted by all investigators in the field so that future scientific communication will be facilitated.

REFERENCES


