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The Fourth A*polipoprotein E* Haplotype Found in the Yoruba of Ibadan

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Apolipoprotein E (*APOE*) has a common polymorphism determined by variation at codon 112 and 158 resulting in three different haplotypes *APOE* ε2 (TT), *APOE* ε3 (TC), and *APOE* ε4 (CC). Due to the strong linkage disequilibrium between the two sites, normally three rather than four haplotypes are observed. While genotyping samples from the Indianapolis-Ibadan Dementia Project, a longitudinal, community-based study that seeks to identify risk factors for dementia in elderly African-Americans living in Indianapolis, Indiana, and in elderly Yoruba residing in Ibadan, Nigeria, the fourth *APOE* haplotype (CT) was discovered in a healthy 70 year-old Yoruba subject.

The local Institutional Review Boards have approved the study and informed consent was obtained from each participating individual. Genomic DNA was isolated from blood and *APOE* was genotyped as described [Hixson and Vernier 1990]. Amplified products resulting in an unusual HhaI pattern were sequenced. Serum was used to measure levels of various biomarkers. Lipoproteins were fractionated by gel filtration or agarose electrophoresis [Deeg et al., 2001].

A sample from a healthy 70 year-old Yoruba female gave a unique HhaI banding pattern (Fig. 1 available in supplementary data). The sequence showed a C at the first nucleotide of codon 112 in both alleles and a C and T at the first nucleotide of codon 158 (data not shown). One gene would code for apoE4 (Arg112-Arg158) and the other would code for a unique apoE protein (Arg112-Cys158). The subject's 34 year-old son had the same genotype and her 67 year-old brother had an ε2/ε4 genotype (Fig. 2 available in supplementary data). Since the rare CT haplotype in combination with the frequent *APOE* ε3 TC haplotype would give an *APOE* ε2/ε4 HhaI digestion pattern and would not be distinguished by direct

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sequencing, all samples resulting in a ε2/ε4 genotype were digested with restriction enzymes AflIII and HaeII (New England Biolabs, Beverly, MA) [Chapman et al., 1996]. The CT haplotype was not found in the subject's brother or the remaining samples from Ibadan and Indianapolis. In addition, the subject's total cholesterol, triglycerides, LDL, HDL, folate insulin, glucose and TSH levels were all within normal limits. Fractionation of lipoproteins by gel filtration and agarose gel electrophoresis revealed a normal distribution of lipoproteins.

The CT haplotype has been reported once before (Genbank accession number AY077451) in an Italian autistic child and his normal mother and was named *APOE* ε3r because the cysteine and arginine are in reverse order (Arg112-Cys158) compared to apoE3 (Cys112-Arg158) [Persico et al., 2004]. We have decided to rename this haplotype *APOE* $\varepsilon 1_Y$ because it would be the next haplotype counting backwards since ε4 is the ancestral haplotype. We added the Y for Yoruba to differentiate between the other ε1 proteins already described, which are ε2 or ε3 variants that contain mutations at different amino acids and run faster using protein electrophoresis [Ando et al., 1999; Gregg et al., 1983; Hoffer et al., 1996; Moriyama et al., 1992; Steinmetz et al., 1990; Weisgraber et al., 1984].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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