



HHS Public Access

Author manuscript

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2015 August 26.

Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2006 June 5; 0(4): 426–427. doi:10.1002/ajmg.b.30295.

The Fourth *Apolipoprotein E* Haplotype Found in the Yoruba of Ibadan

Jill R. Murrell¹, Brandon M. Price¹, Olusegun Baiyewu², Oye Gureje², Mark Deeg³, Hugh Hendrie⁴, Adesola Ogunniyi², and Kathleen Hall⁴

¹Department of Pathology, Indiana University School of Medicine, Indianapolis, Indiana

²Department of Medicine, University of Ibadan, Ibadan, Nigeria

³Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

⁴Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana

Keywords

genetics; haplotype; Nigeria; elderly; Africa

Apolipoprotein E (*APOE*) has a common polymorphism determined by variation at codon 112 and 158 resulting in three different haplotypes *APOE* $\epsilon 2$ (TT), *APOE* $\epsilon 3$ (TC), and *APOE* $\epsilon 4$ (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 $\epsilon 2/\epsilon 4$ genotype (Fig. 2 available in supplementary data). Since the rare CT haplotype in combination with the frequent *APOE* $\epsilon 3$ TC haplotype would give an *APOE* $\epsilon 2/\epsilon 4$ HhaI digestion pattern and would not be distinguished by direct

sequencing, all samples resulting in a $\epsilon 2/\epsilon 4$ 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* $\epsilon 3r$ 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* $\epsilon 1\gamma$ because it would be the next haplotype counting backwards since $\epsilon 4$ is the ancestral haplotype. We added the γ for Yoruba to differentiate between the other $\epsilon 1$ proteins already described, which are $\epsilon 2$ or $\epsilon 3$ 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

This work was supported by National Institute of Aging grants R01 AG09956 and P30 AG10133.

References

- Ando M, Sasaki J, Hua H, Matsunaga A, Uchida K, Jou K, Oikawa S, Saito T, Nihei H. A novel 18-amino acid deletion in apolipoprotein E associated with lipoprotein glomerulopathy. *Kidney Int.* 1999; 56(4):1317–23. [PubMed: 10504484]
- Chapman J, Estupinan J, Asherov A, Goldfarb LG. A simple and efficient method for apolipoprotein E genotype determination. *Neurology.* 1996; 46(5):1484–5. [PubMed: 8628509]
- Deeg MA, Bowen RF, Williams MD, Olson LK, Kirk EA, LeBoeuf RC. Increased expression of GPI-specific phospholipase D in mouse models of type 1 diabetes. *Am J Physiol Endocrinol Metab.* 2001; 281(1):E147–54. [PubMed: 11404232]
- Gregg RE, Ghiselli G, Brewer HB Jr. Apolipoprotein EBethesda: a new variant of apolipoprotein E associated with type III hyperlipoproteinemia. *J Clin Endocrinol Metab.* 1983; 57(5):969–74. [PubMed: 6578216]
- Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res.* 1990; 31(3):545–8. [PubMed: 2341813]
- Hoffer MJ, Niththyanathan S, Naoumova RP, Kibirige MS, Frants RR, Havekes LM, Thompson GR. Apolipoprotein E1-Hammersmith (Lys146-->Asn;Arg147-->Trp), due to a dinucleotide substitution, is associated with early manifestation of dominant type III hyperlipoproteinaemia. *Atherosclerosis.* 1996; 124(2):183–9. [PubMed: 8830931]
- Moriyama K, Sasaki J, Matsunaga A, Arakawa F, Takada Y, Araki K, Kaneko S, Arakawa K. Apolipoprotein E1 Lys-146----Glu with type III hyperlipoproteinemia. *Biochim Biophys Acta.* 1992; 1128(1):58–64. [PubMed: 1356443]
- Persico AM, D'Agruma L, Zelante L, Militerni R, Bravaccio C, Schneider C, Melmed R, Trillo S, Montecchi F, Elia M, Palermo M, Rabinowitz D, Pascucci T, Puglisi-Allegra S, Reichelt KL,

- Muscarella L, Guarnieri V, Melgari JM, Conciatori M, Keller F. Enhanced APOE2 transmission rates in families with autistic probands. *Psychiatr Genet.* 2004; 14(2):73–82. [PubMed: 15167692]
- Steinmetz A, Assefbarkhi N, Eltze C, Ehlenz K, Funke H, Pies A, Assmann G, Kaffarnik H. Normolipemic dysbetalipoproteinemia and hyperlipoproteinemia type III in subjects homozygous for a rare genetic apolipoprotein E variant (apoE1). *J Lipid Res.* 1990; 31(6):1005–13. [PubMed: 1973700]
- Weisgraber KH, Rall SC Jr, Innerarity TL, Mahley RW, Kuusi T, Ehnholm C. A novel electrophoretic variant of human apolipoprotein E. Identification and characterization of apolipoprotein E1. *J Clin Invest.* 1984; 73(4):1024–33. [PubMed: 6323533]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript