

SHORT COMMUNICATION

Absence of the E2 allele of apolipoprotein in Amerindians

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ABSTRACT

Determination of the ApoE allele distribution in five South American Amerindian tribes revealed absence of the ApoE2 allele, accompanied by high ApoE3 and low ApoE4 allele frequencies for most tribes, a distribution only previously reported for the Inuit Eskimo from Greenland.

INTRODUCTION

Apolipoprotein E (apoE) plays a central role in lipoprotein metabolism thus affecting lipid homeostasis in many tissues (Mahley, 1988). Three common isoforms have been described (apoE2, E3 and E4) encoded by the alleles $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, respectively (Utermann *et al.*, 1977; Davignon *et al.*, 1988; Hallman *et al.*, 1991). Recent studies have linked the $\epsilon 2$ allele to type III hyperlipidemia (Utermann, 1987), and the $\epsilon 4$ variant to coronary heart disease (CHD) (Cumming and Robertson, 1984; Davignon *et al.*, 1988) and Alzheimer's disease (AD) (Strittmatter *et al.*, 1993; Saunders *et al.*, 1993). Consequently, the frequency of apoE genotypes has been determined in several populations such as Caucasians, Blacks, Asians and North American Indians (Kamboh *et al.*, 1990, 1991; Hallman *et al.*, 1991; Kao *et al.*, 1995; Sandholzer *et al.*, 1995; Scheer *et al.*, 1995; Benkmann *et al.*, 1996; Kataoka *et al.*, 1996). We determined the apoE allele distribution in five Amerindian tribes from the Brazilian Amazon region, and found

that it differed from all other populations thus far studied, except for the Inuit Eskimo (Gerdes *et al.*, 1996).

SUBJECTS AND METHODS

Populations sampled

The Amerindian sample comprised 121 individuals from five Brazilian Amazonian tribes: 23 Yanomami, 25 Wayana-Apalai, 26 Wayampi, 21 Arara and 26 Kayapo. The individuals studied were apparently unrelated, except for the Wayampi and the Arara among whom there are high inbreeding levels, making it difficult to select only unrelated individuals.

DNA analysis

DNA samples were obtained from leukocytes by phenol-chloroform extraction and ethanol precipitation and then PCR amplified, using primers and conditions described by Hixson and Vernier (1990). Genotypes were determined by restriction fragment length polymorphism (RFLP) analysis after digestion with *HhaI* restriction enzyme and polyacrylamide gel electrophoresis. ApoE allele frequencies were determined by gene counting.

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RESULTS AND DISCUSSION

The frequencies of apoE alleles obtained for the Amerindians are compared with other populations in Table I. ApoE3 allele had the highest frequency (0.8306), which is in accordance with frequencies described for Tyroleans, French Canadian Caucasians, Chinese and Alaskan natives (Hallman *et al.*, 1991; Kao *et al.*, 1995; Scheer *et al.*, 1995; Robitaille *et al.*, 1996). ApoE4 allele had a lower frequency among the Amerindians when compared to South African Khoi San, Papua-New Guineans, Australian aborigines and African blacks (Nigerians, Sudanese) (Kamboh *et al.*, 1990, 1991; Hallman *et al.*, 1991; Sandholzer *et al.*, 1995; Benkmann *et al.*, 1996) who are known to have high ApoE4 frequencies. The ApoE2 allele was absent in the Amazonian Amerindian populations, a fact that has also been described for an Inuit population residing in Greenland's southeast coast (Gerdes *et al.*, 1996), while a low ApoE2 frequency (0.02) has been found in Alaskan natives (Scheer *et al.*, 1995). ApoE allele frequencies were homogeneous between the different tribes (Table II) except for the Wayampi, where the ApoE4 variant exhibited a frequency (0.423) compared to the highest reported for any human ethnic group to date (Kamboh *et al.*, 1990, 1991; Hallman *et al.*, 1991; Sandholzer *et al.*, 1995; Benkmann *et al.*, 1996). This difference could be explained by isolation and genetic

Table I - Distribution of ApoE alleles in different human populations.

Populations	ε2	ε3	ε4
Caucasians (Tyroleans) (Hallman <i>et al.</i> , 1991)	0.090	0.789	0.117
Blacks (Khoi San) (Sandholzer <i>et al.</i> , 1995)	0.077	0.553	0.370
Asians (Chinese) (Kao <i>et al.</i> , 1995)	0.076	0.875	0.049
Alaskans (Scheer <i>et al.</i> , 1995)	0.020	0.787	0.193
Amazonian Amerindians (present study)	0.000	0.831	0.169

Table II - Distribution of ApoE alleles in five Amerindian populations (No. = number of chromosomes).

Populations	No.	ε3	ε4
Yanomami	46	0.956	0.043
Wayana-Apalai	50	0.820	0.180
Wayampi	52	0.577	0.423
Arara	42	0.928	0.072
Kayapo	52	0.904	0.096

drift. A heterogeneous distribution of genetic polymorphic markers has been observed in these populations when studying other genetic systems, such as the α -globin gene haplotypes and several variable number of tandem repeats (VNTRs) (Zago *et al.*, 1995, 1996).

The frequencies of ApoE alleles in a population may have implications regarding CHD and AD prevalence. The ApoE2 allele is usually associated with lower total cholesterol (TC) and low density lipoprotein (LDL) levels and higher high density lipoprotein (HDL) levels, whereas the ApoE4 allele is usually linked to effects opposite to those described for the ApoE2 allele besides being associated with AD in several populations (Cumming and Robertson, 1984; Davignon *et al.*, 1988; Hallman *et al.*, 1991; Saunders *et al.*, 1993; Strittmatter *et al.*, 1993). Therefore, the absence of the ApoE2 allele as well as the high ApoE4 frequency among the Wayampi could play a role in the prevalence of these diseases in this population, a point which should be further investigated.

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RESUMO

A determinação da distribuição do alelo ApoE em cinco tribos de índios sulamericanos revelou ausência do alelo ApoE2, acompanhada por frequência alta do alelo ApoE3 e baixa do alelo ApoE4 na maioria das tribos, uma distribuição previamente relatada apenas para os esquimós Inuit da Groenlândia.

REFERENCES

- Benkmann, H.G., Agarwal, D.P., Vasisht, S., Srivastava, L.M. and Goedde, H.W. (1996). Distribution of apolipoprotein E genotypes in Asian Indians, Hungarians, and Papua New Guineans. *Anthropol. Anz.* 54: 31-34.
- Cumming, A.M. and Robertson, F.R. (1984). Polymorphism at the apolipoprotein-E locus in relation to risk of coronary disease. *Clin. Genet.* 25: 310-313.
- Davignon, J., Gregg, R.E. and Sing, C.F. (1988). Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis* 8: 1-21.
- Gerdes, L.U., Gerdes, C., Hansen, P.S., Klausen, I.C., Faergeman, O. and Dyerberg, J. (1996). The apolipoprotein E polymorphism in Greenland Inuit in its global perspective. *Hum. Genet.* 98: 546-550.

- Hallman, D.M., Boerwinkle, E., Saha, N., Sandholzer, C., Menzel, H., Császár, A. and Utermann, G. (1991). The apolipoprotein E polymorphism: a comparison of allele frequencies and effects in nine populations. *Am. J. Hum. Genet.* 49: 338-349.
- Hixson, J.E. and Vernier, D.T. (1990). Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J. Lipid Res.* 31: 545-548.
- Kamboh, M.I., Bhatia, K.K. and Ferrel, R.E. (1990). Genetic studies of human apolipoproteins: XII. Population genetics of apolipoproteins in Papua New Guinea. *Am. J. Hum. Biol.* 2: 17-23.
- Kamboh, M.I., Serjeanston, S.W. and Ferrel, R.E. (1991). Genetic studies of human apolipoproteins. XVIII. Apolipoprotein polymorphism in Australian Aborigines. *Hum. Biol.* 63: 179-186.
- Kao, J.T., Tsai, K.S., Chang, C.J. and Huang, P.C. (1995). The effects of apolipoprotein E polymorphism on the distribution of lipids and lipoproteins in the Chinese population. *Atherosclerosis* 114: 55-59.
- Kataoka, S., Robbins, D.C., Cowan, L.D., Go, O., Yeh, H.L., Devereux, R.B., Fabsitz, R.R., Lee Welty, T.K. and Howard, B.V. (1996). Apolipoprotein E polymorphism in American Indians and its relation to plasma lipoproteins and diabetes. The Strong Heart Study. *Arterioscler. Thromb. Vasc. Biol.* 16: 918-925.
- Mahley, R.W. (1988). Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* 240: 622-633.
- Robitaille, N., Cormier, G., Couture, R., Bouthillier, D., Davignon, J. and Perusse, L. (1996). Apolipoprotein E polymorphism in a French Canadian population of northeastern Quebec: allele frequencies and effects on blood lipid and lipoprotein levels. *Hum. Biol.* 68: 357-370.
- Sandholzer, C., Delport, R., Vermaak, H. and Utermann, G. (1995). High frequency of the apo E4 allele in Khoi San from South Africa. *Hum. Genet.* 95: 46-48.
- Saunders, A.M., Strittmatter, W.J., Schmechel, D., St. George-Hyslop, P.H., Pericak-Vance, M.A., Joo, S.H., Rosi, B.L., Gusella, J.F., Crapper-MacLachlan, D.R., Alberts, M.H., Hulette, C., Crain, B., Goldgaber, D. and Roses, A.D. (1993). Association of apolipoprotein E (allele E4) with late-onset familial and sporadic Alzheimer's disease. *Neurology* 43: 1467-1472.
- Scheer, W.D., Boudreau, D.A., Malcon, G.T. and Middaugh, J.P. (1995). Apolipoprotein E and atherosclerosis in Alaska Natives. *Atherosclerosis* 114: 197-202.
- Strittmatter, W.J., Weisgraber, K.H., Huang, D.Y., Dong, L.-M., Salvesen, G.S., Pericak-Vance, M., Schmechel, D., Saunders, A.M., Goldgaber, D. and Roses, A.D. (1993). Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. *Proc. Natl. Acad. Sci. USA* 90: 8098-8102.
- Utermann, G. (1987). Apolipoprotein E polymorphism in health and disease. *Am. Heart J.* 113: 433-440.
- Utermann, G., Hess, M. and Steinmetz, A. (1977). Polymorphism of apolipoprotein E and occurrence of dysbetalipoproteinemia in man. *Nature* 269: 604-607.
- Zago, M.A., Santos, E.J.M., Clegg, J.B., Guerreiro, J.F., Martinson, J.J., Norwich, J. and Figueiredo, M.S. (1995). α -Globin gene haplotypes in South American Indians. *Hum. Biol.* 67: 535-546.
- Zago, M.A., Silva, W.A., Tavella, M.H., Santos, S.E.B., Guerreiro, J.F. and Figueiredo, M.S. (1996). Inter-population and intrapopulation genetic diversity of Amerindians as revealed by six variable number of tandem repeats. *Hum. Hered.* 46: 274-289.

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