

ARIC Study Manuscript Proposal #732

PC Reviewed: 06/20/00

Status: A

Priority: 1

SC Reviewed: 06/20/00

Status: A

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1.a. Full title: apolipoprotein E (apoE) and lipoprotein lipase (LPL) Asn291Ser and Ser447Ter polymorphisms and risk of subclinical and clinical stroke

1.b. Abbreviated title: LPL, apoE genes and stroke

2. Writing group:

Lead: Eric Boerwinkle

First: Alanna Morrison

Address: Human Genetics Center

University of Texas - Houston Health Science Center

PO Box 20334

Houston, TX 77225

Phone: 713-500-9816; **Fax:** 713-500-0900

E-mail: eboerwin@gsbs.gs.uth.tmc.edu

Christie Ballantyne, Richey Sharrett, Woody Chambless and Molly Bray

3. Time Line:

Measurement of the lipoprotein lipase (LPL) Asn291Ser and Ser447Ter polymorphisms and the apoE polymorphism are complete for the MRI cerebral infarct case-cohort and incident stroke case-cohort samples. Analyses will be completed subsequently.

4. Rationale:

Lipoprotein lipase (LPL) plays a central role in lipid metabolism, acting as the rate-limiting enzyme in the hydrolysis of triglycerides in chylomicrons and VLDL.

Both the Asn291Ser and Ser447Ter polymorphisms have been reported as playing a role in the determination of lipid and lipoprotein levels. For example, associations have been reported between the Asn291Ser polymorphism and elevated triglycerides and lower HDL cholesterol (Groenemeijer et al., *Circulation* 95:2628-35, 1997). The Ser447Ter polymorphism, resulting in premature truncation of the LPL protein by two amino acids, is reported to be associated with decreased triglycerides (Jemaa et al., *J Lipid Res* 36:2141-6, 1995) and increased HDL cholesterol levels (Kuivenhoven et al., *Arterioscler Thromb Vasc Biol* 17:595-9, 1997), thus conveying a beneficial effect to its carriers. For these reasons, both the Asn291Ser and Ser447Ter polymorphisms have been investigated with regard to a number of recognized lipid disorders, such as familial combined hyperlipidemia, and other diseases such as coronary heart disease (CHD), coronary artery disease (CAD) and atherosclerosis. The majority of these studies conclude that variation in LPL is associated with altered disease risk. Additionally, one recent study concluded that LPL polymorphisms (Asn291Ser and Ser447Ter) are associated with altered risk of Alzheimer's disease (Baum et al., *Am J Med Genet* 88:136-9, 1999). LPL binds apolipoprotein E (apoE) and low-density lipoprotein receptor-related protein (LRP), an apoE receptor. LPL was a logical candidate gene for Alzheimer's disease since polymorphisms in both apoE and LRP influence

Alzheimer's disease risk, and LPL is present in Alzheimer's disease amyloid plaques in the brain.

While numerous studies have evaluated associations between various polymorphisms of LPL and many pathophysiological conditions, reports of a relationship between LPL polymorphisms and cerebrovascular disease (CVD) are scarce. Huang et al. (Eur J Clin Invest 27:740-2, 1997) reported a negative association between the LPL Asn291Ser polymorphism and ischemic stroke.

Other important components of lipid metabolism are the apolipoproteins. Like the LPL polymorphisms, there is ample and convincing evidence for a role of the apoE polymorphism in affecting plasma lipid levels in atherosclerosis and coronary heart disease (CHD), but its association with cerebrovascular disease (CVD) is controversial.

Recently, Margaglione et al. reported that there is a positive association between the apoE polymorphism, particularly the $\epsilon 4$ allele, and personal history of ischemic stroke. Their study supported the role of the apoE gene as a susceptibility locus for the risk of CVD (Stroke 29:399-403, 1998). Additional studies have concluded that the $\epsilon 4$ allele is an important risk factor for CVD in Chinese uraemic patients (Lim et al., Nephrol Dial Transplant 12:1916-20, 1997) and in macroangiopathy-associated CVD (Kessler et al., Arterioscler Thromb Vasc Biol 17:2880-4, 1997). Studies reporting a negative association between alleles of the apoE polymorphism and CVD include analyses in a Japanese population (Nakata et al., Am J Hypertens 10:1391-5, 1997), in a sample of individuals over the age of 75 from Stockholm (Basun et al., Stroke 27:1310-5, 1996) and in a Finish cohort with subjects aged 65-74 (Kuusisto et al., Arterioscler Thromb Vasc Biol 15:1280-6, 1995).

The controversy over the association between alleles of the apoE gene and CVD is clearly apparent in recent literature and appears to remain unresolved. Ferrucci et al. suggested that this controversy may be due to the "conditioning influence of age on the protection conferred by the apoE $\epsilon 2$ allele on stroke risk," and suggested that this hypothesis should be verified in a population with a wider age range (Stroke 28:2410-6, 1997).

5. Main hypothesis/Study Questions:

- a. Ability of the LPL Asn291Ser and Ser447Ter polymorphisms to predict MRI cerebral infarct and incident stroke case status, both individually and after considering the predictive ability of traditional risk factors. Subgroup analyses will be carried out separately for clinical and subclinical strokes. Race-specific effects will also be explored.
- b. Ability of the apoE polymorphism to predict MRI cerebral infarct and incident stroke case status, both individually and after considering the predictive ability of traditional risk factors. Subgroup analyses will be carried out separately for clinical and subclinical strokes. Race-specific effects will also be explored.

6. Data:

ARIC's MRI cerebral infarct case-cohort and incident stroke case-cohort groups will be used for these analyses. The primary dependent variable is clinical or subclinical stroke case status. Independent variables include, but are not limited to, LPL Asn291Ser and Ser447Ter polymorphisms, apoE polymorphism, race, age, gender, BMI, smoking status, plasma lipid levels, blood pressure, blood pressure treatment and hypertension status.

7a. Will the data be used for non-CVD analysis in this manuscript? No

8a. Will DNA data be used in this manuscript? Yes

8b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA="No use/storage DNA"? Yes