

THE INFLUENCE OF GENES ON LIPID METABOLISM AND CORONARY VESSEL ATHEROMATOSIS

[EDITORIAL]

KOLOVOU G.

Atheromatosis of coronary vessels is the most frequent cause of ischemic cardiovascular disease. More than 200 risk factors have been described which lead to premature formation of atheromatic lesion.

In our days, gene contribution in the appearance of atheromatosis is undoubted and specifically, some genetic mutations have been recognized as responsible for its premature appearance. The most known mutations are those of LDL receptor gene leading to familiar hypercholesterolemia. Nowadays, approximately 900 mutations of different frequency, according to geographic distribution, have been established. Moreover, apolipoprotein B-100 (ApoB-100) and apolipoprotein E (apoE) take a serious part in lipid metabolism. ApoB-100 familiar deficiency is transmitted with an autosomal dominant manner and is associated with hyperlipemia and premature atheromatosis [1]. As far as the apoE alleles concerns, E4 has been related with high risk of coronary disease [2-4]. Other studies including ours (in greek population) have not found such a relation [5-7]. Framingham Heart Study noticed that not only E4 but also, E2 allele is related with greater risk of cardiovascular incident in men [4].

ABCA1 (ATP-binding cassette transporter A1) gene mutations represent the genetic etiology of Tangier disease [8-10]. In their review, Attie and colleagues [11] indicate that ABCA1 gene mutations seem to lead to premature atherosclerosis. Furthermore, Van Dam and colleagues [12] observed that heterozygous subjects of ABCA1 gene polymorphism show endothelium and vascular wall thickness of peripheral arteries.

Cholesterol ester transfer protein (CETP) plays a major role in the remodeling of lipoprotein particles by mediating the transfer of HDL cholesteryl ester. When the level of triglyceride (TG) rich lipoproteins is normal, CETP transfers HDL cholesteryl esters which are directed with special preference towards LDL particles. Oppositively, when the level of fasting or postprandial TG-rich lipoproteins is increased, CETP transfers HDL cholesteryl esters which are directed now, towards larger very low density lipoprotein particles that result in the formation of small dense LDL particles (atherogenic). TaqIB polymorphism is the best studied CETP gene polymorphism and B2 allele is correlated with the lowest risk of coronary artery disease [13].

Lipoprotein lipase (LpL) is composed in parenchymatous cells, transferred and located in artery endothelium, capillary endothelium and artery internal wall. Deficiency or high reduction of LpL gene expression leads to hyperlipoproteinemia type I, including accumulation of triglyceride-rich lipoproteins and chylomicrons. Concerning LpL gene studied polymorphisms, carriers of Gly188Glu, Asp9Asn and Asn291Ser polymorphisms seem to have atherogenic lipid levels compared with non-

carriers and on the contrary, Ser447Ter carriers seem to have protective lipid profile against atheromatosis. Moreover, in most Gly188Glu carriers, heterozygous subjects present greater risk of ischemic disease while such increase is borderline for Asp9Asn and Asn219Ser polymorphisms. On the contrary, the risk seems to be decreased for Ser447Ter carriers. Finally, only one study concerning women noticed a significant increase of ischemic risk disease among Asn129Ser carriers.

In conclusion, in the future, it is possible that genotypic analysis in patients with cardiovascular disease and later dyslipidemic subjects will be necessary for the diagnosis and treatment planning, in order to reach the point where genetic analysis will be performed as a routine examination. Therefore until today, our knowledge concerning gene action and their interaction with other genes and environmental factors as well is deficient, demonstrating the need for farther research in deep.

REFERENCES

1. Nassar BA. Familial defective apolipoprotein B-100: a cause of hypercholesterolemia and early coronary heart disease. *CMAJ* 1993;148:579-580.
2. van Bockxmeer FM, Mamotte CD, Gibbons FR, Taylor RR. Apolipoprotein epsilon 4 homozygosity--a determinant of restenosis after coronary angioplasty. *Atherosclerosis* 1994;110:195-202.
3. Wilson PW, Myers RH, Larson MG, Ordovas JM, Wolf PA, Schaefer EJ. Apolipoprotein E alleles, dyslipidemias and coronary heart disease: the Framingham Offspring Study. *JAMA* 1994;272:1666-1671.
4. Lahoz C, Schaefer EJ, Cupples LA, Wilson PW, Levy D, Osgood D, Parpos S, Pedro-Botet J, Daly JA, Ordovas JM. Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. *Atherosclerosis* 2001;154:529-537.
5. Kuusisto J, Mykkanen L, Kervinen K, Kesaniemi YA, Laakso M. Apolipoprotein E4 phenotype is not an important risk factor for coronary heart disease or stroke in elderly subjects. *Arterioscler Thromb Vasc Biol* 1995; 15:1280-1286.
6. Kolovou G, Yiannakouris N, Hatzivassiliou M, Malakos J, Daskalova D, Hatzigeorgiou G, Cariolou MA, Cokkinos DV. Association of apolipoprotein E polymorphism with myocardial infarction in Greek patients. *Curr Med Res Opin* 2002;18:118-124.
7. Kolovou GD, Daskalova DC, Hatzivassiliou M, Yiannakouris N, Pilatis ND, Elisaf M, Mikhailidis DP, Cariolou MA, Cokkinos DV. The Epsilon 2 and 4 Alleles of Apolipoprotein E and Ischemic Vascular Events in the Greek Population-Implications for the Interpretation of Similar Studies. *Angiology* 2003;54:51-58.
8. Rust S, Rosier M, Funke H, Real J, Amoura Z, Piette JC, Deleuze JF, Brewer HB, Duverger N, Deneffe P, Assmann G. Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. *Nat Genet* 1999;22:352-355.
9. Kolovou G, Anagnostopoulou K, Cokkinos DV. A new ABCA1 mutation associated with low HDL cholesterol but without coronary artery disease. *Atherosclerosis* 2003;169:345-346.

10. Kolovou GD, Wade DP, Sengupta R, Cokkinos DV. Tangier Disease with unusual clinical manifestations. *Clinic Genet* 2003;63:323-324.
11. Attie AD, Kastelein JP, Hayden MR. Pivotal role of ABCA1 in reverse cholesterol transport influencing HDL levels and susceptibility to atherosclerosis. *J Lip Res* 2001;42:1717-1726.
12. van Dam MJ, de Groot E, Clee SM, Hovingh GK, Roelants R, Brooks-Wilson A, Zwinderman AH, Smit AJ, Smelt AH, Groen AK, Hayden MR, Kastelein JJ. Association between increased arterial-wall thickness and impairment in ABCA1-driven cholesterol efflux: an observational study. *Lancet* 2002;359:37-42.
13. Kolovou GD, Anagnostopoulou KK, Karyofyllis P, Salpea KD, Yiannakouris N, Zarkalis D, Cokkinos DV. Cholesteryl ester transfer protein gene polymorphisms and severity of coronary stenosis. *Clin Invest Med.* 2006 Feb;29(1):14-9.