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Letters

Comment

– to: F. M. Nackhoul et al. (2001) Haptoglobin phenotype and diabetic nephropathy. Diabetologia 44: 602–604

To the Editor: In a recent issue, Nackhoul et al. reported an interesting association of the haptoglobin 2 allele with an increased incidence of nephropathy in diabetic patients [1]. Based on studies on the inheritance of lecithin-cholesterol acyl transferase (LCAT) deficiency, Teisberg et al were the first to suggest a close linkage of the haptoglobin locus and the LCAT gene [2]. The close linkage of these two genes on chromosome 16 (16q22.1) was repeatedly reported and is now definitely confirmed after the public release of the draft version of the human genome. LCAT is synthesized in the liver and circulates in the blood plasma in complex with components of high density lipoproteins (HDL). By mediating esterification of free cholesterol in peripheral tissues and thereby facilitating uptake of cholesterol in HDL, LCAT plays a pivotal role in the process termed reverse cholesterol transport [3]. Multiple rare mutations in the LCAT gene leading to complete or partial loss of enzyme function have been reported, with considerable variation in the clinical presentation of affected individuals [4]. However, consistent manifestations have been nephropathy with marked proteinuria, corneal opacities, decreased erythrocyte life span and a variable degree of atherosclerosis. LCAT knockout mice develop glomerulosclerosis and proteinuria when fed a fat and cholesterol rich diet [5]. It is reasonable to speculate, that a yet unknown polymorphism in the LCAT gene accelerates the development of diabetes induced renal damage. Due to the very close physical linkage, the probability of recombination events between the LCAT and haptoglobin gene locus is very low and thus a significant association between a certain haptoglobin genotype and the hypothetical disease susceptibility LCAT allele could eventually be observed. In this case, the two alleles are thought to be in linkage disequilibrium. Two earlier studies could depict the significance of the mentioned phenomenon. In one investigation patients with major depression had lower serum concentrations of esterified cholesterol than healthy subjects, consistent with a decreased activity of LCAT [6]. In a larger study conducted by the same authors, the haptoglobin 1 allele was reported to be over-represented among patients with major depression [7].

The apparent association of diabetic nephropathy and the haptoglobin α2 allele provides suggestive evidence for the presence of a genetic variation on chromosome 16 mediating susceptibility for nephropathy in diabetic patients. However, future epidemiological studies and laboratory investigations in animal models of diabetic nephropathy and haptoglobin deficiency are indispensable to confirm the haptoglobin locus as a real disease susceptibility gene or merely a genetic marker of a hitherto unrecognized LCAT variation.

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References

1. Nakhoul FM, Zoabi R, Kanter Y, Zoabi M, Skorecki K, Hochberg I et al. (2001) Haptoglobin phenotype and diabetic nephropathy. Diabetologia 44: 602–4
2. Teisberg P, Gjone E. (1974) Probable linkage of LCAT locus in man to the alpha haptoglobin locus on chromosome 16. Nature 249: 550–551
3. Santamarina-Fojo S, Lambert G, Hoeg JM, Brewer HB, Jr. (2000) Lecithin-cholesterol acyltransferase: role in lipoprotein metabolism, reverse cholesterol transport and atherosclerosis. Curr Opin Lipidol 11: 267–275
4. OMIM – Online Mendelian Inheritance in Man database, at : www:ncbi.nlm.nih.gov
5. Lambert G, Sakai N, Vaisman BL, Neufeld EB, Marteyn B, Chan CC et al. (2001) Analysis of glomerulosclerosis and atherosclerosis in lecithin cholesterol acyltransferase-deficient mice. J Biol Chem 276: 15090–15098
6. Maes M, Delanghe J, Meltzer HY, Scharpe S, D'Hondt P, Cosyns P (1994) Lower degree of esterification of serum cholesterol in depression: relevance for depression and suicide research. Acta Psychiatr Scand 90: 252–258
7. Maes M, Delanghe J, Scharpe S, Meltzer HY, Cosyns P, Suy E et al. (1994) Haptoglobin phenotypes and gene frequencies in unipolar major depression. Am J Psychiatry 151: 112–116

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