Leukotriene C_4 synthase and risk of cardiovascular disease

Jacob Freiberg, MD

This PhD dissertation was accepted by the Faculty of Health Sciences of the University of Copenhagen, and defended on June 5, 2009.

Official opponents: Lars Køber, Klaus Juul, and Genovefa D. Kolovou, Greece.

Tutors: Børge G. Nordestgaard and Anne Tybjærg-Hansen.

Correspondence: Jacob Freiberg, Department of Clinical Biochemistry, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark.

E-mail: jajofr01@heh.regionh.dk

Dan Med Bull 2009;56:172

ABSTRACT

This PhD dissertation is based on studies conducted in the period 2005-2009 at the Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital. The results are presented in the form of three articles.

Ischemic cardiovascular disease is today considered to be a chronic inflammatory disease. In this respect leukotrienes have been identified to play an important role. The genetic variation examined in the gene coding for leukotriene C_4 synthase is limited. In this thesis both known and hitherto unknown genetic variation in leukotriene C_4 synthase is associated with risk of developing ischemic cardiovascular disease and obstructive pulmonary disease.

In two studies we examined how two known promoter polymorphisms were associated with risk of cardiovascular disease and obstructive pulmonary disease. We found that the -1072 AA genotype predicted increased risk of ischemic cerebrovascular disease, transient ischemic attack, and ischemic stroke while the -444 CC genotype predicted decreased risk. These genotypes did not confer risk of ischemic heart disease, asthma, or COPD. Resequencing the gene coding for leukotriene C_4 synthase revealed 17 hitherto unknown mutations. Four of these new mutations could potentially change protein function and were associated to increased risk of venous thromboembolism and ischemic stroke.

We conclude that genetic variation in leukotriene C_4 synthase is associated with risk of ischemic cardiovascular disease. We speculate that cysteinyl leukotrienes may mediate their primary effect in ischemic cardiovascular disease through changes in hemostatic control, rather than playing an important role in atherosclerotic inflammation.