GENETIC ASSOCIATION STUDIES IN STROKE

Akademisk avhandling

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This thesis is based on the following papers:

I Jood K, Ladenvall C, Rosengren A, Blomstrand C, Jern C. Family history in ischemic stroke before 70 years of age: The Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS).
Stroke 2005;36:1383-1387.

II Jood K, Ladenvall P, Tjarnlund-Wolf A, Ladenvall C, Andersson M, Nilsson S, Blomstrand C, Jern C. Fibrinolytic gene polymorphism and ischemic stroke.
Stroke 2005;36:2077-2081.

III Ladenvall C, Gils A, Jood K, Blomstrand C, Declerck PJ, Jern C. Thrombin activatable fibrinolysis inhibitor activation peptide shows association with all major subtypes of ischemic stroke and with TAFI gene variation.
Arterioscler Thromb Vasc Biol 2007;27:955-962.

IV Ladenvall C, Jood K, Blomstrand C, Nilsson S, Jern C, Ladenvall P. Serum C-reactive protein concentration and genotype in relation to ischemic stroke subtype.
Stroke 2006;37:2018-2023.

V Ladenvall C, Csajbok L, Nylén K, Jood K, Nellgård B, Jern C. Association between factor XIII single nucleotide polymorphisms and aneurysmal subarachnoid hemorrhage.
In manuscript

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ABSTRACT

Stroke is the third most common cause of death and the most common cause of disability in adults in developed countries. It is a complex disease in which genetic and environmental factors make about equal contributions. A significant proportion of the environmental component remains to be elucidated and little is known about which genes that are involved. There are two main stroke types; ischemic and hemorrhagic. Both these types have several different etiological subtypes.

The specific aim of the present work was to perform clinical association studies to test the hypothesis that hemostatic and inflammatory gene polymorphisms, and/or plasma levels of the respective proteins, are associated with stroke, and to investigate whether associations differ between stroke subtypes.

The studies on ischemic stroke were based on the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS), in which great emphasize has been put on phenotyping by physical examination and neuroimaging. The study comprises 600 consecutive ischemic stroke patients presenting with ischemic stroke before the age of 70 years and 600 matched population-based controls. Stroke patients were classified according to the main etiological subtypes of ischemic stroke, i.e. large-vessel disease (LVD), small-vessel disease (SVD), cardioembolic stroke (CE stroke) and cryptogenic stroke. The study on aneurysmal subarachnoid hemorrhage (aSAH) was based on patients admitted to the Neurointensive Care Unit, Sahlgrenska. A total of 183 patients with a confirmed aneurysmal origin of the SAH were included. Two matched population-based controls were recruited for each case. Genotyping was performed using 5´nuclease assays (TaqMan) and plasma levels of proteins were determined by immunological methods.

Family history of stroke showed independent association to all ischemic stroke subtypes, except CE stroke. In our first genetic association study, the fibrinolytic pathway was studied. A reduced risk of ischemic stroke was observed for a genotype combination indicating a high gene expression level of both tissue-type plasminogen activator and plasminogen activator inhibitor type 1. This association was not detected in aSAH. However, an increased risk of aSAH was found for subjects carrying the coagulation factor XIII 34Leu allele. This variant has been shown to influence fibrinolysis by affecting the fibrin network. Family history of myocardial infarction (MI) only showed association to one ischemic stroke subtype, i.e. LVD. The explanation for this may be that atherosclerosis is a common denominator for MI and LVD. In support for this hypothesis, increased plasma levels of the inflammatory marker C-reactive protein was only found in the LVD group. This is in contrast to the fibrinolytic pathway. Plasma levels of tPA, PAI-1 and the fibrinolytic inhibitor TAFI were increased in all ischemic stroke subtypes.

In conclusion, the results support a genetic contribution in stroke. This genetic contribution seems to differ between subtypes, which highlights the importance of subtype classification in stroke research. Furthermore, the findings suggest that inflammatory factors may be of more importance for developing LVD, while the fibrinolytic pathway seems to be involved in all ischemic stroke subtypes.

Key words: stroke, ischemic stroke subtypes, subarachnoid hemorrhage, genetics, polymorphism, fibrinolysis, tPA, PAI-1, TAFI, CRP, factor XIII

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