Susceptibility genes in conformational diseases

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Avhandlingen baseras på följande arbeten:

I. **Malin E. Andersson*** Annica Sjölander, Niels Andreasen, Lennart Minthon, Oskar Hansson, Nenad Bogdanovic, Christina Jern, Katarina Jood, Anders Wallin, Kaj Blennow, Henrik Zetterberg. *Kinesin gene variability affects tau phosphorylation in early Alzheimer's disease*. The International Journal of Molecular Medicine. 2007, 20: 233-239.

II. **Malin E. Andersson***, Madeleine Zetterberg, Gunnar Tasa, Mona Seibt Palmér, Erkki Juronen, Pait Teesalu, Kaj Blennow, Henrik Zetterberg. *Variability in the kinesin light chain 1 gene may influence risk of age-related cataract*. Molecular Vision. 2007, 13: 993-996.

III. **Malin von Otter**, Sara Landgren, Staffan Nilsson, Caroline Lundvall, Lennart Minthon, Nenad Bogdanovic, Niels Andreasen, Deborah R. Gustafson, Ingemar Skoog, Anders Wallin, Anna Håkansson, Hans Nissbrandt, Madeleine Zetterberg, Gunnar Tasa, Kaj Blennow, Henrik Zetterberg. *Kinesin light chain 1 gene haplotypes in three conformational disorders*. Accepted for publication in NeuroMolecular Medicine, Oct 2009.

IV. **Malin von Otter**[§], Sara Landgren[§], Staffan Nilsson, Dragana Celojevic, Petra Bergström, Anna Håkansson, Hans Nissbrandt, Marek Drozdzik, Monika Bialecka, Mateusz Kurzawski, Kaj Blennow, Michael Nilsson, Ola Hammarsten, Henrik Zetterberg. *Association of Nrf2-encoding* NFE2L2 *haplotypes with Parkinson's disease*. Submitted manuscript, June 2009.

V. **Malin von Otter**, Sara Landgren, Staffan Nilsson, Madeleine Zetterberg, Dragana Celojevic, Petra Bergström, Lennart Minthon, Nenad Bogdanovic, Niels Andreasen, Deborah R. Gustafson, Ingmar Skoog, Anders Wallin, Gunnar Tasa, Kaj Blennow, Michael Nilsson, Ola Hammarsten, Henrik Zetterberg. *Nrf2-encoding* NFE2L2 *haplotypes influence disease progression but not risk in Alzheimer's disease and age-related cataract*. Submitted manuscript, Sept 2009.

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Abstract

Conformational diseases are characterized by protein misfolding and aggregation in the affected tissue. The aim of this thesis was to find genetic support for mechanisms in common for three prevalent conformational diseases: Alzheimer's disease (AD), Parkinson's disease (PD) and cataract.

The influence of genetic variability in candidate genes hypothesized to be involved in protein aggregation was investigated for association with risk of the sporadic forms of AD, PD and cataract. Furthermore, analysis of association with age at onset (AAO) of disease, and, for AD, association with mini-mental state examination (MMSE) scores and levels of the cerebrospinal fluid (CSF) biomarkers: $A\beta_{42}$ (the 42 amino acid form of amyloid β), T-tau (total tau, i.e. all isoforms of tau) and P-tau_{181} (hyperphosphorylated tau protein as measured by phosphorylation on amino acid 181) was carried out.

The kinesin protein is important for maintaining cell shape and function, especially in elongated cells such as neurons and lens cells. Previous molecular and genetic studies support impaired kinesin-mediated transport as a potential contributor in AD, PD and cataract. We analysed the contribution of variation in the kinesin light chain 1 gene (*KLC1*) encoding the kinesin light chain protein 1 protein (KLC1), initially by using a single nucleotide polymorphism (SNP) approach (paper I and II) and later in a haplotype study (paper III). Altogether, with the possible exception for cataract, the results of these papers do not support genetic influence of *KLC1* on risk of disease.

Oxidative stress is a contributing factor to aging and degenerative diseases. The proteins Nrf2 (nuclear factor (erythroid-derived 2)-like 2) and Keap1 (Kelch-like ECH-associated protein 1), constitute the two main regulators of the induced cellular oxidative stress defense called the phase II response. In paper IV and V we investigated their respective genes *NFE2L2* (Nuclear factor (erythroid-derived 2)-like 2) and *KEAP1* (Kelch-like ECH-associated protein 1) as possible susceptibility genes in AD, PD and cataract. We found that variation in one *NFE2L2* haplotype window, which is in LD with functional promoter polymorphisms in the same gene, was associated with risk of PD in two independent European case-control materials (paper IV). In AD and cataract, variation in the same haplotype window was associated with AAO of the diseases (paper V). No association of *KEAP1* with any of the studied diseases was found.

The major finding of this thesis was the identification of *NFE2L2* as a potential susceptibility gene in PD adding genetic support to current indications that Nrf2 may have an important function in the cellular defense against PD.

Keywords: Conformational disease, Alzheimer's disease, Parkinson's disease, cataract, protein aggregation, cellular transport, oxidative stress, susceptibility genes, SNP, haplotype

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