Susceptibility genes in conformational diseases

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligt försvaras i hörsal Kammaren, SU/Sahlgrenska, Göteborg

Fredagen den 27 november 2009, kl. 09.00

av

MALIN VON OTTER

Fakultetsopponent: Docent Mikko Hiltunen
Department of Neurology, University of Kuopio, Finland

Avhandlingen baseras på följande arbeten:


*Artiklar publicerade före juli 2009 publicerades i namnet Malin E. Andersson

¶Dessa författare bidrog likvärdigt till denna artikel
Susceptibility genes in conformational diseases

MALIN VON OTTER

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology,
University of Gothenburg, Gothenburg, Sweden, 2009

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: Aβ42 (the 42 amino acid form of amyloid β), T-tau (total tau, i.e. all isoforms of tau) and P-tau181 (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