

GENETICS OF PARKINSON'S DISEASE - WITH FOCUS ON GENES OF RELEVANCE FOR INFLAMMATION AND DOPAMINE NEURON DEVELOPMENT

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

- I. Westberg L, **Håkansson A**, Melke J, Shahabi HN, Nilsson S, Buervenich S, Carmine A, Ahlberg J, Grundell MB, Schulhof B, Klingborg K, Holmberg B, Sydow O, Olson L, Johnles EB, Eriksson E, Nissbrandt H. Association between the estrogen receptor beta gene and age of onset of Parkinson's disease. *Psychoneuroendocrinology* 2004; 29: 993-998.
- II. **Håkansson A**, Westberg L, Nilsson S, Buervenich S, Carmine A, Holmberg B, Sydow O, Olson L, Johnles B, Eriksson E, Nissbrandt H. Interaction of polymorphisms in the genes encoding interleukin-6 and estrogen receptor beta on the susceptibility to Parkinson's disease. *American Journal of Medical Genetics (Part B)* 2005; 13: 88-92.
- III. **Håkansson A**, Westberg L, Nilsson S, Buervenich S, Carmine A, Holmberg B, Sydow O, Olson L, Johnles B, Eriksson E, Nissbrandt H. Investigation of genes coding for inflammatory components in Parkinson's disease. *Movement Disorders* 2005; 20: 569-573.
- IV. **Håkansson A**, Bergman O, Chrapkowska C, Westberg L, Carmine Belin A, Sydow O, Johnles B, Olson L, Holmberg B, Nissbrandt H. Cyclooxygenase-2 polymorphisms in Parkinson's disease. *American Journal of Medical Genetics (Part B)* 2007; 144: 367-369.
- V. **Håkansson A**, Carmine Belin A, Stiller C, Sydow O, Johnles B, Olson L, Holmberg B, Nissbrandt H. Investigation of genes related to familial forms of Parkinson's disease - With focus on the Parkin gene. *Parkinsonism and Related Disorders* 2008; 14: 520-522.
- VI. Bergman O, **Håkansson A**, Westberg L, Nordenström K, Carmine Belin A, Sydow O, Olson L, Holmberg B, Eriksson E, Nissbrandt H. PITX3 polymorphism is associated with early onset Parkinson's disease. *Neurobiology of Aging* 2010; 31: 114-117.
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The papers were published in the name Anna Håkansson.



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Abstract

GENETICS OF PARKINSON'S DISEASE - WITH FOCUS ON GENES OF RELEVANCE FOR INFLAMMATION AND DOPAMINE NEURON DEVELOPMENT

Introduction: The risk to be affected by Parkinson's disease (PD) is considered to be influenced by genetic factors. In some rare cases of familial PD, mutations in some specific genes are known to cause the disease, but in the more common sporadic form of PD the causes are probably environmental factors interacting with genetic vulnerability. The main objective of this thesis was to identify genes of importance for this genetic vulnerability in sporadic PD, by analysing the frequency of polymorphisms in PD patients and control subjects. The investigated genes encode proteins involved in one, or both, of two processes suggested to be of importance for the pathophysiology of PD; inflammation and development of dopaminergic neurons. **Main observations:** A single nucleotide polymorphism (SNP) in the gene encoding estrogen receptor beta was found to be associated with PD with an early age of onset. Furthermore, this SNP seems to interact with a SNP in the gene for the pro-inflammatory cytokine interleukin 6, potentiating the susceptibility to PD, especially among early age of onset patients. In the genes encoding the anti-inflammatory cytokine interleukin 10 and the dopaminergic transcription factor Pitx3, polymorphisms associated with age of onset were identified. **Conclusions:** The results indicate that several of the investigated genes might be of importance for the pathophysiology of sporadic PD. Often the polymorphisms were associated only with PD with an early age of onset, possibly explained by a more important role of genetic factors among patients with an early onset. An alternative explanation is that some of the polymorphisms affect the age of onset of PD, for example by modulating the vulnerability to disease-causing environmental factors. The relevance of the present results can only be confirmed by additional studies in other PD populations. For some of the genes the results of the present thesis have been replicated, while for others no additional studies have been published or the findings have not been confirmed.

Keywords: Parkinson's disease (PD), single nucleotide polymorphism (SNP), gene, age of onset, Pitx3, estrogen receptor beta, interleukin 6