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Genes involved in Parkinson's disease - focus on mitochondrial and detoxifying enzymes

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ABSTRACT

Parkinson's disease is a common progressive neurodegenerative disorder which mostly affects the elderly population, with a prevalence of more than 1.5% in the population over the age of 65 years. Clinical motor symptoms are mainly caused by degeneration of dopamine neurons in substantia nigra pars compacta. In order to identify genes with potential roles in the pathology of Parkinson's disease, the candidate gene approach has been applied. Investigated genes assumed to play a role in mitochondrial maintenance were *DJ-1*, PTEN-induced putative kinase 1 (*PINK1*), the serine-protease *OMI/HTRA2*, mitochondrial translation initiation factor 3 (*MTIF3*), DNA polymerase gamma 1 (*POLG1*), mitochondrial Ras homolog gene family, member T1 and T2 (*MIRO1*, *MIRO2*). Genes involved in detoxification including paraoxonases (*PON1*, *PON2*, *PON3*) and alcohol dehydrogenases (*ADH1C*, *ADH4*) were also studied. Association studies were performed in a Swedish case-control material consisting of 619 Parkinson patients and 1564 neurologically healthy controls. The screening resulted in identification of several potential risk or protective factors such as *DJ-1* Ala167Ala (c.501A>G), *MTIF3* rs7669 (C>T), *POLG1* CAG repeat variability and *PON1* rs854571 (G>A). *MIRO1* and *MIRO2* need further investigations before they can be excluded as contributing factors. The investigation of *OMI/HTRA2* A141S (G>T) in Parkinson and Alzheimer patients resulted in an association with Alzheimer's disease. *In situ* hybridization of human postmortem brain tissue was used to detect any alteration of *PINK1* mRNA expression in Parkinson patients and of *OMI/HTRA2* mRNA in patients with either Parkinson's or Alzhemier's disease. No differences compared to control levels were observed for the two genes. Protein quantification of OMI/HTRA2 in frontal cortex indicated reduced levels of the active enzyme form and increased protease activity in patients with Alzheimer's disease. Using quantitative real-time PCR we detected a reduction of mRNA expression from the *MTIF3* rs7669 minor allele. Based on previous report on association of genetic variants in *ADH1C* and *ADH4* with Parkinson's disease, we studied spontaneous and drug induced locomotor behavior in *Adh1* and *Adh4* knockout mice, and in *Adh1/4* double knockout mice with respect to dopamine-system-related activity and olfactory function. Neurotransmitter levels were analyzed with high-performance liquid chromatography in different brain regions. All three knockout strains displayed increased drug induced behavior, as well as alteration of levels of monoamines and their metabolites compared to wild-type littermates. *Adh4*-/- mice had a reduced sense of smell as well as reduction of dopamine in the olfactory bulb, and results from *Adh1/4*-/- pointed in the same direction. In conclusion, the findings presented in this thesis suggest genetic variability has an important role in the pathogenesis of Parkinson's disease. The disease is a multifactorial and genetically complex disorder for which the etiology is unknown in most of the cases. It needs to be resolved how different molecular pathways involving different genes individually or together, contribute to disease by causing degeneration of dopamine neurons and other neuron types.

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