Studies on the Etiology of Parkinson's disease

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UNIVERSITY OF GOTHENBURG

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Heredity deals the cards; environment plays the hand.

– Charles L. Brewer

Till Siri och Stella

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world and affects around 1% of the population over 60 years of age. The main symptoms of PD include bradykinesia, resting tremor and rigidity, caused to a large extent by degeneration of the dopaminergic neurons in substantia nigra. Aggregates of the protein α-synuclein can be seen in dopaminergic cells and other neurons. The pathogenesis starts up to 20 years before the patients notice any motor symptoms. Idiopathic PD is a complex multi-factorial disease and the etiology is largerly unknown but several genetic and environmental risk factors have been identified. Treatments of PD aim to alleviate motor symptoms but there is no cure or any treatment to slow down disease progression.

The aim of this thesis was to investigate different factors in relation to PD risk. In Paper I, we investigated the relation between genetic polymorphisms in the S100B gene and the age at onset of PD in two independent Swedish populations. The main finding in Paper I is that the SNP rs9722 is associated with an earlier age at onset of PD. rs9722 has previously been shown to be associated with higher S100B levels. S100B can activate inflammatory pathways through RAGE and may be able to speed up progression of PD.

The work in Paper II and III consisted of population-based prospective studies of late-adolescent men who underwent compulsory military conscription. The main finding of Paper II was that high scores on IQ tests were associated with an increased risk of being diagnosed with PD later in life. In paper III, we found that higher erythrocyte sedimentation rate (ESR) was associated with lower PD risk.

The study in Paper IV investigated the antibody response to measles- and VZV-specific antigens in serum and CSF samples of patients with PD. PD patients had a lower antibody response to VZV-specific antigen in serum and CSF samples.

In conclusion, we present new risk factors for PD in the present thesis. Our findings suggest that inflammation may not be a risk factor for PD., but merely a secondary phenomenon that speeds up disease progression. On the contrary, our data rather suggest that a greater premorbid inflammatory reaction can play a protective role against PD. A decreased immune and inflammatory reaction against pathogens or protein aggregates could contribute to the progression of PD.

Keywords: Parkinson's disease, S100B, age at onset, conscription, IQ, Varicella zoster, measles

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SAMMANFATTNING PÅ SVENSKA

Parkinsons sjukdom är den näst vanligaste neurodegenerativa sjukdomen i världen och drabbar cirka 1 % av befolkningen över 60 års ålder. Sjukdomens utmärkande symtom är långsamma rörelser, stelhet och skakningar i vila, vilka till stor del beror på att dopaminnervceller i hjärnan degenererar. Vid Parkinsons sjukdom ansamlas även proteinet alpha-synuclein i dopaminnervceller och andra nervceller i centrala nervsystemet. Sjukdomsprocessen startar upp till 20 år innan patienten märker några motoriska symtom. Dagens mediciner behandlar symtomen men det finns ingen botande eller bromsande behandling. Idiopatisk Parkinsons sjukdom är en komplex sjukdom vars orsak inte är helt klarlagd, men flera genetiska och miljömässiga faktorer har identifierats som troligtvis tillsammans bidrar till att en individ utvecklar sjukdomen.

Den här avhandlingen utforskar potentiella riskfaktorer för Parkinsons sjukdom. I den första studien (delarbete I) undersöker vi om polymorfismer i genen S100B är associerat med risken att få Parkinsons sjukdom eller om de påverkar insjuknandeåldern. Det huvudsakliga fyndet i delarbete I är att en polymorfism, rs9722, i S100B är associerad till Parkinsons sjukdom bland patienter med tidig debutålder (<50 år).

I delarbete II och III använde vi det svenska värnpliktsregistret för att kartlägga några riskfaktorer bland unga män. Resultatet i delarbete II visar att hög IQ vid mönstringen är associerat med högre risk att bli diagnosticerad med Parkinsons sjukdom senare i livet. I delarbete III visar vi att risken att få sjukdomen minskar ju högre sänka man har vid mönstringen.

I den fjärde studien (delarbete IV) undersökte vi antikroppssvar mot mässling och vattenkoppor i serum och cerebrospinalvätska hos patienter med Parkinsons sjukdom och kontroller. Patienterna hade signifikant lägre antikroppssvar mot vattenkoppsvirus än kontrollerna.

Sammanfattningsvis visar dessa studier på flera nya riskfaktorer för Parkinsons sjukdom. Bland annat tyder fynden på att ett allmänt ökat inflammatoriskt reaktionsmönster skulle kunna ha en skyddande effekt mot Parkinsons sjukdom.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Camilla Fardell**, Anna Zettergren, Caroline Ran, Andrea Carmine Belin, Agneta Ekman, Olof Sydow, Lars Bäckman, Björn Holmberg, Nil Dizdar, Peter Söderkvist and Hans Nissbrandt. S100B polymorphisms are associated with age of onset of Parkinson's disease. *BMC Med Genet.* 2018;19(1):42.

II. **Camilla Fardell**, Maria Åberg, Linus Schiöler, Hans Nissbrandt, Kjell Torén. High IQ in early adulthood is associated with Parkinson's disease. *J Parkinsons Dis*. 2020;10.3233/JPD-202050.

III. **Camilla Fardell**, Linus Schiöler, Hans Nissbrandt, Kjell Torén, Maria Åberg. The erythrocyte sedimentation rate in male adolescents and subsequent risk of Parkinson's disease – an observational study. *Submitted to Journal of Neurology.*

IV. **Camilla Fardell**, Linn Persson, Henrik Zetterberg, Björn Holmberg, Radu Constantinescu, Tomas Bergström, Hans Nissbrandt. Decreased levels of antibodies against Varicella-zoster virus in patients with Parkinson's disease – a pilot study. *Manuscript.*

LIST OF PAPERS (not included in the thesis)

C Ran, RN Mehdi, **C Fardell**, F Xiang, H Nissbrandt, O Sydow, K Wirdefeldt, AC Belin. No Association Between rs7077361 in ITGA8 and Parkinson's Disease in Sweden. *Open Neurol J*. 2016;10:25-29. Published 2016 Jun 30.

C Ran, L Brodin, L Forsgren, M Westerlund, M Ramezani, S Gellhaar, F Xiang, **C Fardell**, H Nissbrandt, P Söderkvist, A Puschmann, E Ygland, L Olson, T Willows, A Johansson, O Sydow, K Wirdefeldt, D Galter, P Svenningsson, AC Belin. Strong association between glucocerebrosidase mutations and Parkinson's disease in Sweden. *Neurobiol Aging*. 2016;45:212.e5-212.e11.

L Pihlstrøm, A Rengmark, KA Bjørnarå, N Dizdar, **C Fardell**, L Forsgren, B Holmberg, JP Larsen, J Linder, H Nissbrandt, OB Tysnes, E Dietrichs, M Toft. Fine mapping and resequencing of the PARK16 locus in Parkinson's disease. *J Hum Genet*. 2015;60(7):357-362.

L Pihlstrøm, G Axelsson, KA Bjørnarå, N Dizdar, **C Fardell**, L Forsgren, B Holmberg, JP Larsen, J Linder, H Nissbrandt, OB Tysnes, E Ohman, E Dietrichs, M Toft. Supportive evidence for 11 loci from genome-wide association studies in Parkinson's disease. *Neurobiol Aging*. 2013;34(6):1708.e7-1708.e1.708E13.

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ABBREVIATIONS

3'-UTR	3' Untranslated region
ALP	Autophagy-lysosomal pathway
ATP	Adenosine triphosphate
ATP13A2	ATPase Cation Transporting 13A2
CI	Confidence Interval
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
CSC	Cargo-selective complex
CSF	Cerebrospinal fluid
DA	Dopamine
DMV	Dorsal motor nucleus of the vagus
DNA	Deoxyribonucelic acid
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte Sedimentation Rate
EVF	Erythrocyte Volume Fraction, hematocrit
GBA	Glucocerebrosidase
HLA	Human leukocyte antigen
HR	Hazard ratio
HWE	Hardy Weinberg equilibrium
ICD	International Classifications of Diseases
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL-1β	Interleukin 1-beta
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
IQ	Intelligence quotient
LISA	Longitudinal Integration Database for Health Insurance and Labor Market Studies
LRRK2	Leucine-rich repeat kinase 2

MAPT	Microtubuli associated protein tau
NF-κB	Nuclear factor kappa B
OD	Optical density
OPC	Oligodendrocyte progenitor cell
OR	Odds ratio
PARK	Genetic loci initially linked to autosomal forms of PD
PBS	Phosphate Buffered Saline
PD	Parkinson's disease
PINK1	PTEN-induced putative kinase 1
PRKN	Parkin
RAGE	Receptor for advanced glycation endproducts
ROS	Reactive oxygen species
S100B	S100 calcium-binding protein B
SD	Standard deviation
SEB	Swedish enlistment battery
SNAC-K	the Swedish National Study on Aging and Care in Kungsholmen
SNCA	α-synuclein
SNP	Single Nucleotide Polymorphism
STAT3	Signal transducer and activator of transcription 3
TNF	Tumor necrosis factor
UCHL1	Ubiquitin carboxyl-terminal esterase L1
UPS	Ubiquitin-proteasome system
UTR	Untranslated region
VPS35	Vacuolar protein sorting-associated protein 35
VZV	Varizella Zoster-virus

1 INTRODUCTION

"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured."

James Parkinson, An Essay on the Shaking Palsy, 1817.

1.1 PARKINSON'S DISEASE

When James Parkinson published "An Essay on the shaking Palsy" in 1817, it was the first medical description of the disease later known as Parkinson's disease (PD) (Parkinson, 1817). Much later, dopamine was identified as the key neurotransmitter in PD (Carlsson et al., 1958; Carlsson, 1959). PD is recognized as the most common movement disorder in the world and the second most common neurodegenerative disorder after Alzheimer's disease. PD affects mainly older people and worsens over time, reflecting the progressive loss of neurons throughout the nervous system. The death of dopaminergic neurons in the substantia nigra give rise to the typical clinical features of PD: resting tremor, bradykinesia, and muscular rigidity (Sian et al., 1999), see Figure 1.

The patients suffers from slowness of movement and gait as well as postural instability. However, the pathology is complex and results in a variety of non-motor symptoms, such as constipation, cognitive impairment, olfactory dysfunction, sleep disturbances, psychiatric symptoms, and fatigue. In many cases, the non-motor symptoms precede the motor dysfunction by more than a decade, giving a long prodromal phase of the disease before the patient is diagnosed.

PD is generally divided into two types: familial and idiopathic. Idiopathic PD is a multi-factorial complex disease with both genetic and environmental factors involved. The vast majority of PD cases are idiopathic and only a few percent of cases are considered familial, where the disease etiology is explained solely by a rare highly penetrant genetic mutation. The first mutation found to cause an autosomal dominant form of PD was in the gene coding for α-synuclein, SNCA (Polymeropoulos et al., 1997). Soon thereafter, α-synuclein was discovered to be the major constituent of Lewy bodies (Spillantini et al., 1997).

Several point mutations in and multiplications of the SNCA gene have been found to cause PD (Deng and Yuan, 2014; Pasanen et al., 2014; Ferese et al., 2015). Since then, numerous PD genes have been found displaying autosomal dominant or autosomal recessive inheritance patterns (see Deng et al., 2018 for review).

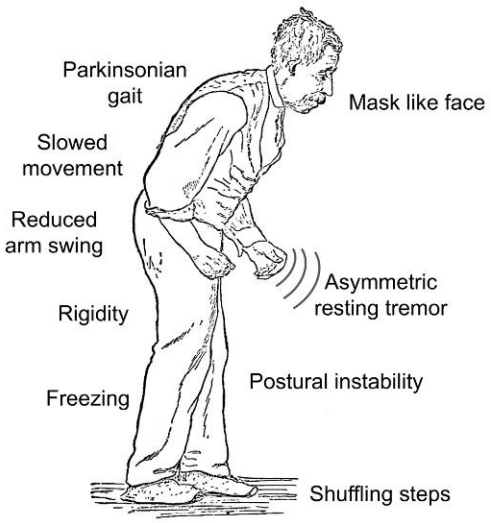

Figure 1. The characteristic symptoms of Parkinson's disease.

The mean age of onset of PD is 55-60 years of age, but in 3-5% of cases the symptoms start before the age of 40 (Quinn et al., 1987; Golbe, 1991). The prevalence of PD is about 1 % in individuals over the age of 60 and 2.6% in individuals over the age of 85 (de Lau and Breteler, 2006: Wood-Kaczmar et al., 2006; Pringsheim et al., 2014; Kalia and Lang, 2015). It is estimated that 6 million people in the world are affected by PD and that it is the fastest growing neurological disease regarding both prevalence and death (GBD 2016; Darweesh et al., 2018) and the incidence of PD has increased over the past few decades (Savica et al., 2017).

Treatments for PD aim to increase the dopamine neurotransmission in the brain and thereby reducing some of the motor symptoms. However, they cannot affect the progression of the disease and do not relieve all of the symptoms.

1.2 PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

The main pathophysiological hallmarks of PD are the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies, consisting of intracellular α-synuclein aggregates, in several brain regions. Similar inclusions within neuronal cell processes, Lewy neurites, can also be present. Glial cells, such as astrocytes and microglia, are also affected.

Motor manifestations of PD display after about 60% of dopaminergic neurons have died, leading to a major decrease in dopamine release in the striatal projection areas of these neurons (Dauer and Przedborski, 2003). Other neurotransmitter systems are also affected, such as noradrenergic, serotonergic and cholinergic, giving rise to the non-motor symptoms of the disease (Forno, 1996; Corti et al., 2011).

Apha-synuclein is a small 140 amino acid protein that can undergo a pathological accumulation and aggregation, resulting in several neurotoxic quaternary states, such as monomers, low molecular weight oligomers and amyloid fibrils of high molecular weight that can be found in Lewy bodies (Poewe et al., 2017). The normal function of α-synuclein is poorly understood, however it is mainly present presynaptically and is involved in the regulation of transmitters and vesicular trafficking (Gitler et al., 2008; Burré et al., 2010; Thayanidhi et al., 2010). Lewy body pathology affects several parts of the central nervous system (CNS) as well as the autonomic and peripheral nervous system (Jellinger, 2012; Del Tredici and Braak 2016).

Several hypotheses on PD pathogenesis have been put forward, and they all have evidence to support them, to some extent. This, together with the different proteins and cellular system failures that can lead to PD point toward it being heterogeneous disease with many possible causes. The anatomical location of the initiation of α-synuclein misfolding and aggregation seems to vary and the initial triggering events differ between patients, but can be a

combination of aging, genetic susceptibility, inflammation or environmental factors.

1.2.1 The Braak and dual-hit hypothesis

Braak and colleagues formulated the hypothesis that the initiation of sporadic PD takes place in the gut triggered by an unknown pathogen (Braak et al., 2003) and that PD Lewy pathology develops in six sequential stages based on the spreading and distribution of α-synuclein (Braak et al., 2003), as can be seen in Figure 2. As an extension of this proposal, the dual-hit hypothesis postulates that the triggering insults of PD take place in the gut and/or the olfactory bulb in the nasal cavity (Hawkes et al., 2007; Hawkes at al., 2009). The pathogen is thought to trigger α-synuclein aggregation, which spreads from these places via the olfactory tract and the vagal nerve and dorsal motor nucleus of the vagus (DMV) in the medulla oblongata, respectively, toward the CNS and eventually the substantia nigra. These hypotheses gain support in that olfactory impairment, sleep disturbances and constipation are common during the prodromal stages of PD, decades before PD diagnosis (Pfeiffer, 2011; Cersosimo and Benarroch, 2012; Doty, 2012).

In addition, studies have shown that Lewy pathology is present in the olfactory tract and enteric nervous system (Wakabayashi et al., 1988; Hubbard et al., 2007; Beach et al., 2009a; Shannon et al., 2012) and occurs in the vagal nerves and the DMV of PD patients before spreading to other parts of the CNS, such as the locus coeruleus, the substantia nigra, the mesocortex, the neocortex, and the prefrontal cortex (Del Tredici et al., 2002; Braak et al., 2003, Bloch et al., 2006; Halliday et al., 2008). Since the nasal cavity and the gut are exposed to the surrounding environment of the individual, air pollutants, pesticides, dietary contaminants or viruses have been proposed as potential triggers.

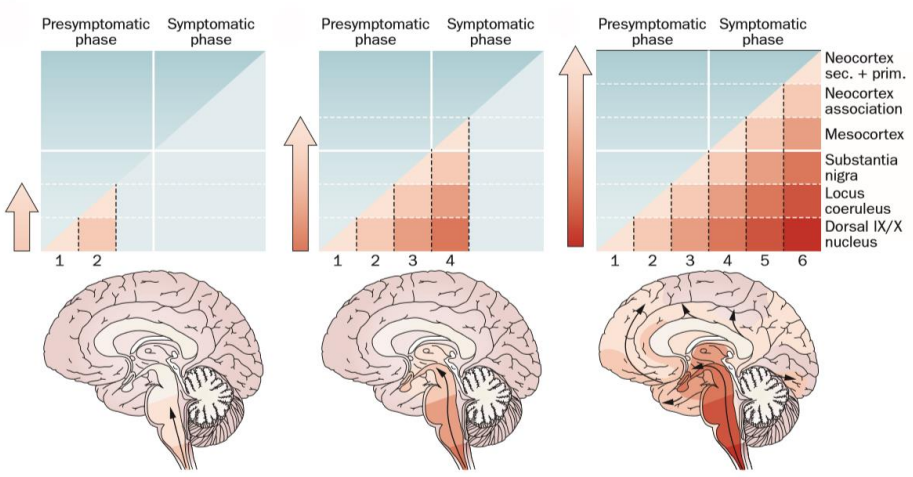

Figure 2. Six stages of the pathology of Parkinson's disease (PD). Stage 1: lesions in the olfactory bulb, the anterior olfactory nucleus and/or the dorsal motor nuclei of the vagal and glossopharyngeal nerves in the brainstem. Stage 2: lesions in the pontine tegmentum. Stages 3 and 4: lesions in the pedunculopontine nucleus, the cholinergic magnocellular nuclei, the substantia nigra pars compacta, the hypothalamus, portions of the thalamus and, the anteromedial temporal mesocortex. Stages 5 and 6: lesions in neocortical high-order association areas. Reprinted with kind permission from Dr. Michel Goedert.

Even though there is a large number of studies supporting the Braak and the dual-hit hypothesis, they do not accurately describe PD development in all patients. 17-49% of all PD patients do not follow Braak's staging and about 10% of patients do not have Lewy pathology in the DMV while higher brain regions are affected (Jellinger, 2003; Attems and Jellinger, 2008; Kalaitzakis et al., 2008; Parkkinen et al., 2008; Zaccai et al., 2008; Beach et al., 2009b). Additional evidence against the dual-hit hypothesis is that 27-33% of PD patients do not have any Lewy pathology in the enteric nervous system (Lebouvier et al., 2011; Devos et al., 2013).

1.2.2 The prion-like hypothesis

Studies have suggested that misfolded α-synuclein acts in a prion-like fashion, in which it can spread the pathology by turning nearby α-synuclein into aggregates (for review se Jucker and Walker, 2013; Visanji et al., 2013). The prion hypothesis is somewhat controversial and has been debated (Reichmann, 2011; Surmeier et al., 2017). This proposal fits into Braak's hypothesis and the dual-hit hypothesis, but instead of the unknown pathogen triggering the misfolding of α-synuclein, it is suggested that the transmitting agent is the misfolded α-synuclein itself (Brundin et al., 2008).

α-synuclein has spontaneous misfolding properties and is thought to be secreted and taken up by nearby neurons and act as a template for misfolding by oligomerizing with endogenous α-synuclein and seed formation of aggregates (Luk et al., 2009; Nonaka et al., 2010; Hansen et al., 2011; Volpicelli-Daley et al., 2011; Luk et al., 2012; Masuda-Suzukake et al., 2013; Goedert at al., 2017). This theory has gained further support by the notion that peripherally administered α-synuclein aggregates in transgenic rodent models of PD spread and results in neurological symptoms (Holmqvist et al., 2014; Breid et al., 2016).

1.2.3 The microbiome and PD

Several studies suggest that the gut microbiota composition is altered in PD patients compared to controls (Pfeiffer, 2013; Hasegawa et al., 2015; Keshavarzian et al., 2015; Unger et al., 2016; Hopfner et al., 2017; Petrov et al., 2017; Heintz-Buschart et al., 2018) and is also dissimilar between groups of PD patients with different phenotypes (Scheperjans et al., 2015). The abundance of the Prevotellaceae bacteria family was greatly reduced in PD patients compared to sex- and age-matched controls. Being important in the mucin synthesis, this could result in increased intestinal permeability, leading to increased exposure to environmental factors. Five other bacterial families (Lactobacillaceae, Bradyrhizobiaceae, Clostridiales Incertae Sedis IV,

Verrucomicrobiaceae and Ruminococcaceae) were more common in PD patients than in controls. Moreover, Enterobacteriaceae were more common in patients with non-tremor-dominant PD than in patients with tremor-dominant PD and the amount of bacteria was associated with the severity of certain PD symptoms. However, it is not known whether alterations in the gut microbiome is a risk factor for or a consequence of PD.

1.3 ETIOLOGY AND PATHOGENESIS OF PARKINSON'S DISEASE

To a large extent, genetic studies have revealed several cellular pathways that have been implicated in PD pathogenesis, and many of the proteins involved have several roles in the cellular processes. They include, but are not limited to, α-synuclein accumulation, dysfunction of protein degradation systems, mitochondrial dysfunction, neuroinflammation, and oxidative stress (see Corti et al., 2011 for review). Many of the pathways are closely related and overlapping, as can be seen in Figure 3.

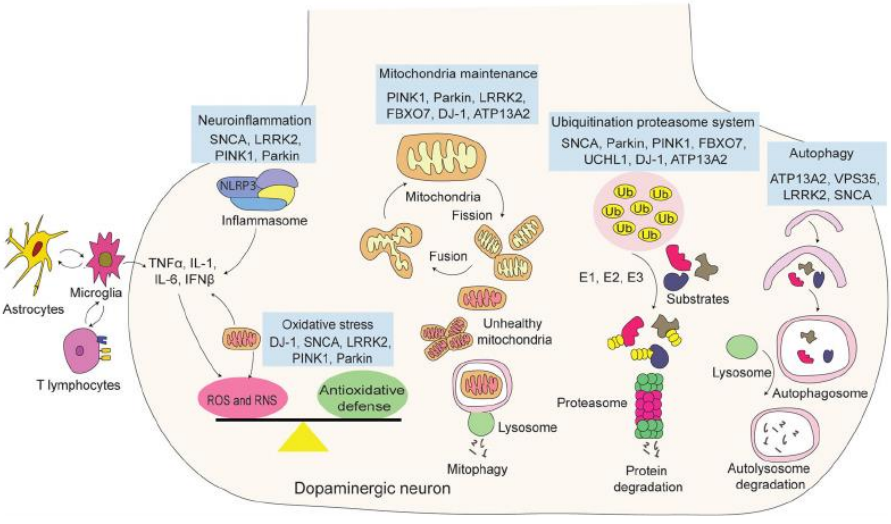

Figure 3. Pathways involved in the pathogenesis of Parkinson's disease (PD). Abbreviations: E1, E1 ligase; E2, E2 ligase; E3, E3 ligase; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; ROS, reactive oxygen species, RNS, reactive oxygen species. Reprinted with permission from John Wiley & Sons, Elsevier B.V. Medicinal Research Reviews, Figure 1, page 6, Copyright 2020 (Li et al., 2020).

1.3.1 The ubiquitin-proteasome system

The ubiquitin-proteasome system (UPS) controls and assists the degradation process of misfolded proteins, and thus is an important part in maintaining protein homeostasis within cells. The UPS plays a critical role in targeting and degrading misfolded α-synuclein, thereby being important in the processes that protect an individual from PD. Misfolded proteins go through an ubiquitination process that makes them targets for degradation by a protease complex, the proteasome. This multi-step process starts with an ubiquitin-activating E1 enzyme, proceeds with a conjugation of ubiquitin by E2 enzyme, and lastly, an ubiquitin ligase (E3) ligates ubiquitin to the target protein (Kwon and Ciechanover, 2017; Pohl and Dikic, 2019). Parkin is an E3 ligase that requires a conformational change initiated by PINK1 (Kondapalli et al., 2012). Mutations in the genes coding for parkin and PINK1 can result in accumulation of misfolded proteins, giving an early-onset autosomal recessive form of PD (Kitada et al., 1998; Valente et al., 2004).

Ubiquitinated proteins are transported to the proteasome where they are deubiquitinated by enzymes, unfolded, and degraded (Liu and Jacobson, 2013). One of the ubiquitinating enzymes is the ubiquitin C-terminal hydrolase L1, UCHL1, and a specific mutation in its gene was shown to cause PD in a German sibling pair (Leroy et al., 1998.)

1.3.2 The autophagy-lysosomal pathway

The autophagy-lysosomal pathway (ALP) is an intracellular process leading to the degradation of protein aggregates and dysfunctional proteins and organelles. These processes involve recognition of ubiquitinated substrates by autophagy receptors and transportation to the lysosome to be degraded (Mizushima, 2007). Dysfunctional autophagy is believed to be involved in PD pathogenesis. For example, ubiquitinated α-synuclein is degraded by the ALP, proposing that this process have a defending effect against the development of PD (Tofaris et al., 2011).

Proteins involved in this process have been shown to cause or increase the risk of PD when mutated. Parkin and PINK1 are involved in the ALP. Furthermore, a rare subtype of juvenile-onset autosomal PD is caused by mutations in ATP13A2, which encodes a lysosomal transport ATPase. Mutations in the gene coding for a sorting protein in the retromer cargo-selective complex (CSC), VPS35, can result in an autosomal dominant form of PD (Zimprich et al., 2011). VPS35 prevents missorting of proteins in the lysosomal degradation pathway and interacts with several other PD-related proteins, such as LRRK2, α-synuclein and parkin (for review see Williams et al., 2017).

1.3.3 Mitochondrial dysfunction

Several important functions of mitochondrial maintenance have been implicated in PD pathogenesis. LRRK2 is widely expressed in the brain and mutations can lead to degeneration and loss of dopamine neurons by affecting several cellular pathways including protein synthesis, mitochondrial fusion/fission, vesicular trafficking, and lysosomal processes. However, the mechanisms of how these mutations lead to PD are not fully understood (for review: Martin et al., 2014). LRRK2 mutations are the most common known genetic cause of PD (Martin et al., 2014) and seven pathogenic variants of LRRK2 have been established (Rubio et al., 2012).

Mitophagy is the autophagic process of removing damaged or excessive mitochondria and PINK1 and Parkin contribute to mitochondrial fusion and fission by ubiquitinating mitochondrial fusion regulators (Narendra et al., 2008, Narendra et al., 2010). PINK1, LRRK2 and Parkin mutations can lead to an impaired mitophagy, resulting in accumulation of dysfunctional mitochondria and ultimately leading to dopaminergic neuron death (Ryan et al., 2015; Lenka and Pal, 2017; Bonello at al., 2019).

1.3.4 Oxidative stress and reactive oxygen species (ROS)

Oxidative stress is a reaction resulting in accumulation in free radicals which causes protein and DNA oxidation, or lipid peroxidation. Dopaminergic neurons might be particularly exposed or sensitive to oxidative stress (Surmeier et al. 2011). Impairment in the mitochondrial regulation increases the production of ROS, and some PD-related proteins, like Parkin and PINK1, contribute to oxidative stress through regulating mitochondrial homeostasis or mitophagy as discussed in previous sections. α-synuclein can bind to mitochondria resulting in decreased mitochondrial respiration and increased ROS production (Di Maio et al., 2016).

DJ-1 is a protein that acts as a sensor of oxidative stress (Raninga et al., 2017) and has antioxidant properties as it is involved in several cellular pathways that are protective against oxidative damage (Cookson, 2012). Mutations in DJ-1 have been found in PD patients, causing an autosomal recessive early onset PD (Bonifati et al., 2003).

1.3.5 Glial cell pathology and neuroinflammation

Neuroinflammation is recognized as a feature of neurodegenerative disorders and appears to play a role in PD progression, where both the innate and adaptive immune system are involved. A widespread neuroinflammatory process is often present in PD patients, resulting in activated glial cells (microglia and astrocytes) and an increase of inflammatory cytokines, chemokines and prostaglandins (McGeer et al., 1988; Mogi et al., 1994a; Mogi et al., 1994b; Mogi et al., 1996; Teismann and Schultz, 2004; Gerhard et al., 2006).

Misfolded protein such as α-synuclein can activate microglia (Sanchez-Guajardo et al., 2015; Zhang et al., 2017). LRRK2 is involved in inflammatory processes as it activates caspase-1 through interaction with inflammasome

proteins and LRRK2 mutations can result in activation of microglia. Mutations in parkin and PINK1 can lead to increased inflammatory processes as they are involved in prevention of mitochondrial-induced inflammation (Sliter et al., 2018). Furthermore, loss of function mutations of PINK1 increase inflammatory cytokines, such as TNF-α and IL-1β (Sun et al., 2018). It has also been proposed that aggregated α-synuclein in PD promotes the inflammatory response in microglia (Lim et al., 2016).

1.4 RISK FACTORS FOR PARKINSON'S DISEASE

Although the etiology of idiopathic Parkinson's disease remains elusive, it is believed to affect individuals with a genetic susceptibility in combination with exposure to environmental triggers. Several genetic, environmental and lifestyle factors have been proposed to be involved with the development of PD. However, twin studies show that the concordance among monozygotic twins is rather low and an estimation suggests the heritability of PD to be 27% (Tanner et al., 1999; Wirdefeldt et al., 2011; Goldman et al., 2019).

The single most important risk factor for PD is aging. Both the incidence and the prevalence of PD increase with increasing age of the population. PD seem to be slightly more common among males than females, but conflicting results have been reported. A Swedish study reports that the male-female ratio was 1.2:1 (Linder et al., 2010), whereas others report 3:2 or no differences (Fall et al., 1996; de Lau and Breteler; 2006; Hirtz et al., 2007; Wirdefeldt et al., 2011).

It has been proposed that ethnicity may play a role, as some studies suggest that Caucasians have a higher occurrence of PD (Kessler 1972a; Kessler 1972b). However, this has been a subject of controversy, since the design of those studies is questionable, for example, the reported differences may be due to socioeconomic factors, which further complicates the issue. Different access to a functional health system affects the possibilities of being diagnosed. Door-to-door screening of a geographically defined population can address this issue, and similar prevalence for all ethnicities has been found using that method. (Schoenberg et al., 1985; McInerney-Leo et al., 2004; Ferreira et al., 2017).

1.4.1 Environmental risk factors

Examples of factors that have been proposed to contribute to PD are head trauma, low physical activity, pesticide exposure, rural living, beta-blocker use,

agricultural occupation, high intake of dairy or milk, and well water drinking (Wirdefeldt et al., 2011). These associations have been shown in multiple studies, however they are rather weak in strength and there have been much debates about the causality for most of these associations.

Prodromal PD may change the lifestyle and behavior of an individual rather than the other way around. Regarding physical activity, there is a possibility that individuals experiencing prodromal PD stages have lower physical capacity and thus are less active during many years prior to receiving the PD diagnosis. Some of the symptoms of prodromal PD may affect the lifestyle of the individuals. For example, sleep disturbances may lead to fatigue and pain, causing a lower physical activity.

Other factors have been proposed as protective factors, since they have been shown to have an inverse association with PD. The main factor in this category is cigarette smoking, as there is around 50% lower risk of PD among active smokers as compared to never smokers (ref 8). Furthermore, studies have shown an inverse correlation with passive smoking and smokeless tobacco, snus (O'Reilly et al., 2005; Mellick et al., 2006; Tanaka et al., 2010; Searles Nielsen et al., 2012; Chen et al., 2015; Yang et al., 2016; Liu et al., 2017). Although these data suggest smoking or nicotine to be neuroprotective, the causality has been intensely debated (Ritz and Rhodes, 2010). Two alternative explanations have been proposed: 1) confounding by personality suggesting that individuals predisposed to PD are less likely to start smoking; and 2) the reverse causation hypothesis that smokers in prodromal PD stages are more likely to quit smoking.

1.4.2 Genetic risk factors

Numerous common genetic variants have been identified as risk factors for PD but they are not sufficient to single-handedly cause the disease. These variants are present in the general population with a very low penetrance. The most robust associations have been found in the genes encoding for α-synuclein

(SNCA), glucocerebrosidase (GBA), LRRK2 and microtubuli-associated protein tau, MAPT (Kalinderi et al., 2016).

Several GBA variants have been reported to significantly increase the risk for PD development (Thaler et al., 2017); the most severe *GBA* mutations can increase PD risk up to 19-fold (Gan-Or et al., 2015). The protein product of GBA, glucocerebrosidase, is a lysosomal enzyme and mutations can lead to accumulation of α-synuclein (Sidransky and Lopez, 2012).

The microtubule-associated protein tau is involved in regulating axonal transport and cytoskeleton stability in neurons (Pascale et al., 2016). Dysfunctional tau protein can accumulate and is associated with several neurodegenerative disorders including Alzheimer's disease, frontotemporal dementia, and progressive supranuclear palsy (Pascale et al., 2016; Fagan and Pihlstrom, 2017). Genetic variants in MAPT have been reported to be significantly associated with an increased risk of PD and disease severity (Pascale et al., 2016; Wang et al., 2016; Fagan and Pihlstrom, 2017).

2 AIMS

The specific aims of the individual papers were:

I. To study the possible association between polymorphisms in the S100B gene and Parkinson's disease.

II. To study the relation between IQ in young men and risk for Parkinson's disease.

III. To study the relation between the erythrocyte sedimentation rate (ESR) in young men and risk for Parkinson's disease.

IV. To study the relation between levels of antibodies against Varicella Zoster-virus and measles and Parkinson's disease.

3 SUBJECTS AND METHODS

In the present thesis, association studies were performed to investigate the relations between different factors and PD. We used two kinds of association studies: case-control studies and cohort studies.

A case-control study is an epidemiological study aiming to detect association between an exposure and a trait, in this case PD. Subjects with the trait are compared to controls without the trait in relation their exposure status to calculate the risk of the disease with the exposure. For the present thesis, case-control studies were performed to analyze the association of genetic variations in the S100B gene and the levels of antibodies against VZV and measles (Paper I and IV).

A cohort study is an epidemiological study in which a particular outcome is compared in groups of people who differ by a certain characteristic or exposure. For this thesis, cohort studies were performed in Paper II and III to investigate the influence of IQ and ESR in late adolescence on the risk of being diagnosed with PD later in life.

3.1 GENETIC ASSOCIATION STUDY (PAPER I)

3.1.1 Subjects and samples

Two separate Swedish populations were studied in Paper I. The discovery cohort consisted of 431 PD patients and 465 control subjects. The PD patients were recruited from hospitals and care centres in Göteborg, Stockholm, Skövde and Falköping. Control subjects comprised of unrelated outpatients in primary care in Gothenburg and participants in the SNAC-K project (The Swedish National Study on Aging and Care in Kungsholmen), a community-based cohort in Stockholm of people aged 75 years and older (Fratiglioni et al., 1992). Participants in the SNAC-K project underwent physical, neurological and psychiatric evaluations and have been confirmed not to have PD. The validation cohort included 195 PD patients and 378 control subjects. The PD patients were recruited from the hospitals in Linköping and Jönköping and control subjects were randomly collected from the population registry in the same recruitment area.

The PD patients had underwent examinations by neurologists and/or movement disorders specialists and fulfilled the criteria for idiopathic PD by The Parkinson Disease Society Brain Bank (Daniel and Lees, 1993), except that the presence of more than one relative with PD was not considered as an exclusion criterion. Nearly all subjects (>99%) were of Caucasian origin.

Age at disease onset was expressed as the age for the appearance of the first PD symptoms. An early age at onset was defined as a disease onset ≤50 years of age, as previously used by our group and others (Mizuta et al., 2001; Wang et al., 2002; Håkansson et al., 2005). A total of 87 patients (20%) in the discovery cohort and 25 patients (13%) in the validation cohort were categorized as having early-onset PD. A peripheral blood sample was collected from all the subjects and DNA was extracted using standard procedures.

3.1.2 Selection of single nucleotide polymorphisms (SNPs) and genotyping

In Paper I, we used the candidate gene approach where the gene S100B was selected for genetic assessment based on prior knowledge of the function of S100B. The S100B gene is located at 21q22.3 and contains 3 exons and the protein product S100B consists of 92 amino acids. We conducted a search for known SNPs in public databases (dbSNP http://www.ncbi.nlm.nih.gov/SNP.). We selected a SNP (rs9722) located in the 3' untranslated region (UTR) and a synonymous SNP in a coding region (rs1051169).

Three other SNPs in the S100B gene were selected as Tag-SNPs (rs99847665, rs881827, and rs2239574) by pair wise tagging ($r^2 \geq 0.80$) from the International HapMap Project database (release 27, Phase II + III, February 2009, on NCBI B36 assembly, dbSNP b126). Markers in close proximity are often inherited together. Data from the HapMap consortium give information about the correlation between different SNPs. If two SNPs are highly correlated it may be possible to only genotype one of them and let that SNP act as a proxy for the correlated SNPs, this approach is referred to as tagging. The genotyping of SNPs was performed using the KASP^{TM} genotyping system (KBiosciences, LGC, Herts, UK).

3.2 POPULATION-BASED COHORT STUDIES (PAPER II & III)

3.2.1 National population registers

The unique personal identification number given to all Swedish residents allows for studies using linkage between different national registers to be performed. The conscripts underwent standardized physical and cognitive examinations conducted by a psychologist and a physician at one of six conscription centers in Sweden (Southern, Western, Eastern, Central, Northern Lower, and Northern Upper).

The Military Service Conscription Register

The Military Service Conscription Register was established in 1952 and digitalized in 1968. During the study period in Paper II and III, military conscription was compulsory and only 2%–3% of all Swedish men were exempted from conscription, in most cases due to severe disorders or imprisonment.

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

LISA contains data for the labor market and the educational and social sectors. Every 5 years between 1960 and 1990, the Statistics Sweden sent out a questionnaire to collect data on variables such as age, sex, civil status, country of birth, citizenship, education, employment, and occupation. Most data in LISA from 1990 and onwards are collected automatically from schools and institutions. LISA is updated annually for all Swedish residents 16 or older. This database gave us information on the educational level of the conscripts and their parents.

The National Patient Register

Diagnoses in the National Patient Register were recorded according to the ICD (International Classification of Disease, 9th revision from 1987 to 1996 and 10th revision from 1997 to 2001) at outpatient visits or upon hospital discharge. Primary care data are not included. The diagnoses recorded in the register have been validated and have a predictive value of 85-97% (Ludvigsson et al., 2011). The primary discharge diagnosis (and up to seven contributory medical diagnoses if applicable) is assigned by the treating physician.

The Cause of Death Register

All deceased Swedish residents are recorded in The Cause of Death Register and contains information on cause of death according to the ICD classifications. This registry was initiated in 1911 and covers all deaths in Sweden since 1961.

3.2.2 Study population

The study population in Paper II consists of all Swedish males who were born in the period of 1949–1975, and enlisted for military service in the period of 1968–1993. The study population in Paper III consists of all Swedish males who were born between 1951 and 1965, and conscripted for military service between 1969 and 1983. Among the subjects who developed PD during the follow-up, only those who were diagnosed at or after the age of 40 years were included in the present study. Figure 4 shows an overview of the exclusion and inclusion criteria for the cohorts in Paper II and III.

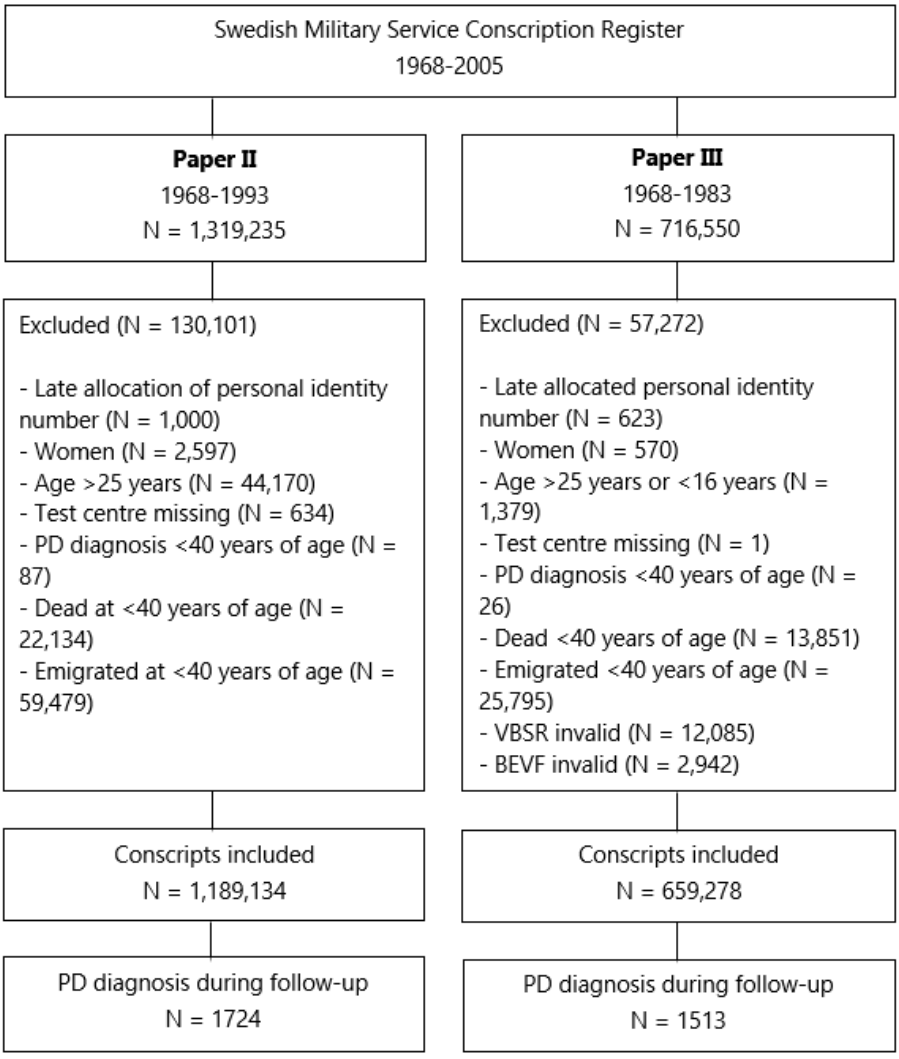

Figure 4. Overview of included and excluded participants in Papers II and III.

3.2.3 Tests and variables

Blood samples (Paper II)

At conscription, blood samples were taken for analysis of the erythrocyte sedimentation rate (ESR) and the erythrocyte volume fraction (EVF, also known as hematocrit). The ESR is defined as the distance that a column of anticoagulated blood falls in 1 hour. The EVF is defined as the ratio of the volume occupied by red blood cells relative to the volume of whole blood. ESR was measured according to standard laboratory procedures by the Westergren method (Jou et al., 2011). The EVF analyses were performed by the microhematocrit method and were consistent with the National Committee for Clinical Laboratory Standards. In the analyses, ESR were adjusted for EVF.

IQ measurements

The Swedish Enlistment Battery (SEB) were used to assess the cognitive abilities at conscription. During the study period, two different versions of the SEB were used: SEB67 and SEB80. Both consisted of four subtests measuring verbal, logical, visuospatial, and technical abilities. The scores of the four subtests were summed to give a global IQ score. The outcome of each subtest and the global IQ score were divided into stanines, which is a method of scaling test score on a nine-point standard scale with a mean of five and a standard deviation of two. It ranks the results from lowest (1) to highest (9).

The SEB67 battery was used during the period of 1968–1979. The four sub-tests were as follows:

- "Instructions" - a logical test comprising 40 items that measured the ability to understand instructions and apply them to solve a problem.

- "Concept Discrimination" – a verbal test consisting of 40 items assessing verbal ability by having the conscript choose which

word out of five alternatives did not agree with the others conceptually.

- "Paper Form Board" - a visuospatial test with 25 items, containing questions about two-dimensional puzzles.

- "Technical Comprehension" - a 52-item test comprising illustrated technical and physical problems.

The SEB80 battery was used during the period 1980–1993. The four subtests were as follows:

- "Instructions" – the logical test with some improvements.

- "Synonyms" – a verbal test which replaced "Concept Discrimination", comprising 40 items to assess vocabulary by letting the conscript identify which out of four alternatives was the synonym of a given word.

- "Metal Folding – a visuospatial test replacing "Paper Form Board". This 40-item test measured geometrical perception by having the conscript identify the correct three-dimensional object from a series of two-dimensional drawings.

- "Technical Comprehension" – was modified to measure knowledge of mathematics, physics and chemistry, consisting of 40 items.

Educational level

The LISA database was used for obtaining information on the level of education of the conscripts and their parents. In the analysis, education was categorized into three groups (educational levels): pre-high school up to 9 years (low); high school up to 12 years (medium); and university ≥2 years and postgraduate

(high). Each category was then divided in groups based on the period in which the subject was conscripted: conscription before 1975, in the period 1975–1984, and in the period 1985–1993. For the parents of the conscripts, the highest level of education attained by either parent was used.

Smoking

During the conscription years 1969 and 1970, the conscripts participated in a survey collecting information on smoking. The number of conscripts included from these years were 49,321 in Paper II, and 21,846 in Paper III. The conscripts were asked to report their smoking habits according to one of the following five levels: non-smoker, 1–5 cigarettes per day, 6–10 cigarettes per day, 11–20 cigarettes per day, and >20 cigarettes per day.

3.3 VIROLOGICAL ANALYSES (PAPER IV)

3.3.1 Subjects and samples

We recruited 30 PD patients at the Neurology Department, Sahlgrenska University Hospital, Gothenburg, Sweden. They had all been examined by movement disorders specialists and fulfilled the Parkinson Disease Society Brain Bank criteria for idiopathic PD (Daniel and Lees., 1993). Exclusion criteria were dementia, a family history of parkinsonian disorders, prior treatment with deep brain stimulation, and a disease duration of less than 3 years. The PD patients were born between 1922 and 1968 and the mean disease onset age was 49 years (range 29 to 71 years). The controls (N = 30) were anonymized samples from routine clinical investigations of outpatients in hospital clinic without signs of neuroinflammatory or neurodegenerative disease. The mean age at the time of sampling was 60.3 and 67.2 years for patients and controls, respectively. Seventy percent among patients and 53 % in the control group were males. Paired serum and CSF samples were collected from patients and controls and total IgG levels were measured at the time of sampling.

3.3.2 Serological analyses

The serological analyses were performed using the antigens N_{CORE} and VZVgE. N_{CORE} consist of recombinant measles virus nucleoprotein expressed *E coli* (Novagen) (Longhi et al., 2003). VZVgE consists of the recombinant glycoprotein E (gE) from Varicella zoster virus (VZV) expressed in Chinese Hamster Ovary cells (Grahn et al., 2011; Thomsson et al., 2011). gE is a structural component of the viral envelope of VZV (Kutinová et al., 2001).

The antibody production was measured using indirect competitive enzyme-linked immunosorbent assay (ELISA) technique. N_{CORE} and VZVgE were diluted with carbonate buffer to concentrations of 2.5 µg/ml for N_{CORE} and 1:2000 for VZVgE. All CSF and serum samples were tested in triplicates.

Wells were coated with the given antigen and washed with PBS and 0.05% Tween 20. Unspecific binding was blocked with 2% milk. Serum and CSF, respectively, were added to each microplate well and the plates were incubated and then washed. An alkaline phosphatase-conjugated goat anti-human IgG antibody (Jackson ImmunoResearch Laboratories Inc., West Grove, USA) was added to a concentration of 1:1000, again incubated and washed. The substrate solution containing phosphatase substrate (SIGMA-ALDRICH Inc., St. Louis, USA) and diethanolamine buffer pH 9.8 was added. The enzyme reaction was stopped and the absorbance values (optical density, OD) were measured at 405 nm and 620 nm, respectively, using a spectrophotometer.

Further, we assessed the intrathecal antibody production. First, IgG concentrations were determined in all CSF/serum paired samples using a human IgG ELISA kit (Novakemi AB, Handen, Sweden). We diluted the paired CSF and serum samples (from the same individual) with 1% milk in PBS with 0.05% Tween 20 to an identical IgG concentration of 1 µg IgG/ml and 100 µL was added to each well for determination of viral IgG by ELISA. We calculated an antibody index of OD_{CSF}/OD_{serum}, and an index of ≥2.0 indicates that the IgG concentration against the specific antigen in CSF is twice the amount as in serum, which was interpreted as an enhanced intrathecal production (Hansen et al., 1990; Schultze et al., 2004).

3.4 STATISTICAL ANALYSES

A significance level of $P < 0.05$ was used for all tests.

3.4.1 Paper I

Differences in allelic distributions were analyzed using Chi-square tests in Haploview 4.0 (Broad Institute, Cambridge, MA, USA) and logistic regression in SPSS 19.0 (IBM Corporation, Armonk, NY, USA). Cox proportional hazard tests were executed in SPSS 19.0 on the pooled data including controls, as well as on patients only. The relationship between the alleles and age at disease onset was assessed using linear regression in SPSS.

Correction for multiple testing was performed on the pooled data by Bonferroni procedures. A Bonferroni corrected p-value is generated through multiplication of the original p-value by the number of tests performed.

3.4.2 Papers II and III

In Paper II and III all statistical analyses were performed using SAS ver. 9.4 software (SAS Institute, Cary, NC). The follow-up period started at the date of conscription (baseline) and subjects were followed until the time of: 1) first hospitalization for PD or hospital-based outpatient clinic contact for PD; 2) death; 3) emigration; or 4) the end of follow-up, on December 31, 2016 (follow-up: minimum, 15 years; maximum, 48 years). Cox proportional hazards models were used to evaluate the influences of plausible predictors on PD diagnosis. There was no violation of the proportional hazards assumption, according to tests based on scaled Schoenfeld residuals.

Intelligence scores were scaled on a nine-point standard scale (stanine = standard nine) and then divided into three groups: low (stanine score 1–3); medium (4–6); and high (7–9), with the latter used as the reference. Education and parental education was trichotomized (low, medium, and high). To account for temporal differences and procedural differences across the participating

sites, we adjusted for test center and conscription year in all regression models. A cubic restricted spline with knots at the 5th, 35th, 65th and 95th percentiles was used for conscription year.

As the data was skewed to the right, we performed a logarithmic transformation of the distribution of ESR. Since the number of red blood cells can affect the ESR, the EVF was used as a covariate in the Cox regression model. Height, weight, and systolic and diastolic blood pressure were set as continuous variables. The association of ESR with PD risk was assessed with adjustments for age at conscription, year of conscription, test center, and EVF in Model 1. Model 2 has additional adjustments for parental education and systolic and diastolic blood pressure. Model 3 was additionally adjusted for IQ. Spline plots were generated based on the three models described, with ESR as a restricted cubic spline with knots at the 5th, 35th, 65th and 95th percentiles.

3.4.3 Paper IV

The statistical analyzes were performed using SPSS, version 19. The nonparametric Mann-Whitney *U* test was used to analyze the differences between the groups. The *p*-values presented are two-sided.

3.5 ETHICS

Paper I and IV: All subjects provided informed consent and the study were approved by the ethical committees at University of Gothenburg, Karolinska Institute and Linköping University.

Papers II and III: The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved the study. The investigations conforms to the principles outlined in the Declaration of Helsinki in relation to ethical principles for medical research involving human subjects.

4 RESULTS AND DISCUSSION

4.1 ASSOCIATION BETWEEN POLYMORPHISMS IN S100B AND AGE OF ONSET OF PARKINSON'S DISEASE (PAPER I)

The study in Paper I was set to investigate the relation between genetic polymorphisms in the S100B gene and the risk of PD in two independent Swedish populations. We genotyped five SNPs in the S100B gene, including a functional promoter SNP in the 3'-UTR region of the S100B gene, rs9722.

We compared the PD patients with an early age at onset (≤50 years) to controls and to PD patients with a late age at onset (>50 years). The results of Paper I showed that several of the genotyped SNPs were associated with an early age at PD onset. Logistic regression and Cox regression analysis showed that the T allele of rs9722 increased the risk of having an early age at onset (OR = 2.9, 95% CI = 1.8-4.7; HR = 1.49; 95% CI = 1.17-1.90, p = 0.001, respectively, in the pooled population). Linear regression showed that each T allele of rs9722 lowered disease onset by 4.9 years.

Previous reports indicate that rs9722 is an interesting SNP in that individuals with the TT genotype of rs9722 have significantly higher levels of S100B in plasma than individuals with CC (Hohoff et al., 2010; Lu et al., 2018; Chen et al., 2020). Several studies have investigated the S100B levels in PD patients and conflicting results have been reported. Schaf and collegues (2005) reported no differences in serum levels of S100B when comparing patients and controls. In another study by Sathe et al. (2012), the PD patients had significantly higher S100B levels in the substantia nigra. Wilhelm et al. (2007) reported a 50% mean increase of the autoimmune responses to S100B in PD patients compared with controls (Wilhelm et al., 2007). Furthermore, animal studies show that mice over-expressing S100B display features similar to PD, such as impaired motor coordination (Liu et al., 2011). Elevated S100B serum levels have been reported in acute brain injuries, schizophrenia, multiple sclerosis and Alzheimer's disease

(Michetti et al., 1979; Griffin et al., 1989; Rothoerl et al., 1998; Rothermundt et al., 2004; Schmitt et al., 2005).

S100B belongs to the S100 family of calcium binding proteins and is expressed by certain astrocytes and oligodendrocyte precursor cells (OPCs), but is present in numerous brain cells, including neurons, as well as extracellular fluids and serum (Nishiyama et al., 1999; Donato, 2001; Deloulme et al., 2004; Hachem et al., 2005). S100B seems to have different properties depending on the concentration in cells. At low levels it promotes cell survival (Winningham-Major et al., 1989; Haglid et al., 1997; Ahlemeyer et al., 2000; Businaro et al., 2006) whereas higher S100B levels promote inflammatory processes, by activating glial cells and inducing reactive oxygen species (ROS), resulting in cell death (Huttunen et al., 2000; Li et al., 2000; Adami et al., 2001; Bianchi et al., 2011). Teismann et al. (2012) showed that S100B can induce dopaminergic cell death. These processes are partially mediated by the receptor for advanced glycation end products (RAGE), illustrated in Figure 5.

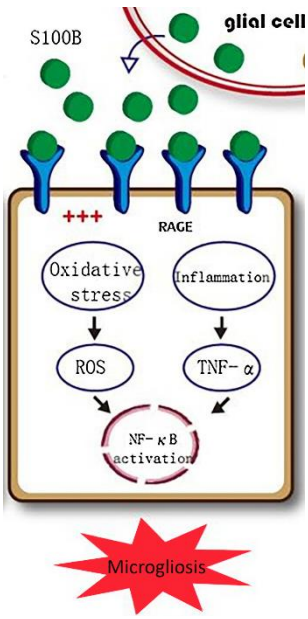

Figure 5. S100B-RAGE interaction and inflammatory mechanism. Reprinted from Elsevier B.V. Neuroscience Letters, adapted from Figure 2, page 68, Copyright 2018 (Jiang et al., 2018).

Excessive S100B stimulates RAGE activation in microglia which initiates a signaling cascade resulting in activation of NF-κB and STAT3. NF-κB production leads to production of inflammatory cytokines and enzymes such as interleukins and TNF-α (Bianchi et al. 2010) as well as upregulation of the expression of inducible nitric oxide synthase (iNOS) (Adami et al., 2001) and cyclooxygenase-2 (COX2), in both astrocytes and microglia (Bianchi et al., 2007).

The results in Paper I support the concept of modulation of age at disease onset by genetic factors. Previous studies in cohorts of PD patients have found significant associations between age at onset of PD and SNPs in other genes including SNCA, GBA, MAPT, PARK3, PRKN and COMT (DeStefano et al., 2002; Clark et al., 2007; Klebe et al., 2013; Davis et al., 2016). Susceptibility to a disease and age at onset of a disease may be two distinct but related phenomena. Modifiers of age at onset possibly propagate the pathological processes leading to earlier development of PD. The SNPs studied in Paper I might be able to do that by activating inflammatory pathways that can be detrimental to dopaminergic neurons and speed up disease progression.

4.2 ASSOCIATION BETWEEN IQ AND PARKINSON'S DISEASE (PAPER II)

In Paper II, we performed a population-based prospective study of late-adolescent men who underwent compulsory military conscription examinations. We investigated the relationship between IQ scores at conscription and risk of being diagnosed with PD later in life. We evaluated the education levels of the conscripts and their parents, smoking histories, and IQ levels in relation to the risk of developing PD. Our study sample consisted of 1,319,235 conscripts, which is the vast majority of all Swedish men born between 1951 and 1965.

The main finding of Paper II is that high scores on IQ tests at conscription were associated with an increased risk of being diagnosed with PD later in life. When dividing the IQ test scores into three categories (1–3, 4–6, 7–9), high global IQ at conscription was associated with a 1.3- fold (95% CI 1.17–1.55) increase in risk for PD later in life when comparing to low global IQ. High test scores on the three subtests that measured verbal, logical, and technical IQ levels were significantly associated with a 1.2-fold (95% CI 1.02–1.37) and 1.3- fold (95% CI 1.15–1.55), and 1.3-fold (95% CI 1.09–1.45) increased risk for PD, respectively.

Parental education and conscript education was correlated (r = 0.4, p<.0001) as well as parental education and conscript IQ (r = 0.5 p<.0001). Conscript education was prospectively associated with PD in analyses adjusted for age, conscription year and conscription test center with HR 1.2 (95% CI 1.01-1.32) for high school and HR 1.4 (95% CI 1.19-1-58) for University and postgraduate studies (both compared to pre-high school). Parental educational level was not associated with an increased risk of PD.

An extensive number of studies have established that smoking is inversely associated with PD (Hernán et al., 2002; Allam et al., 2004a; Allam et al., 2004b; Wirdefeldt et al., 2011; Li et al., 2015) and our study confirmed these results; individuals who later retrieved a PD diagnosis reported smoking significantly fewer cigarettes at conscription. Additionally, we demonstrate an inverse

association of smoking with IQ. However, IQ at conscription was not associated with later diagnosis of PD in this sub-cohort. This is probably due to a lack of power in this analysis, as the number of PD cases in the 1969-1970 sub-cohort was only 256.

To the best of our knowledge, this is the first study investigating IQ levels and the risk of PD. Previous studies have reported that low IQ scores are correlated with cardiovascular disease and schizophrenia (David et al., 1997; Hart et al., 2004; Batty et al., 2005; Silventoinen et al., 2007; Dobson et al., 2017; Lindgren et al., 2018). The IQ level of an individual would probably influence the individual's exposure to environmental factors, such as trauma, toxins and infections, since the IQ influences the occupation and lifestyle of an individual. Individuals with a high IQ level may be more prone to a sedentary lifestyle. There is also a possibility that individuals with a lower IQ are exposed to protective factors to a larger extent. Since we did not have any information about the environmental and behavioral factors possibly affecting the subjects after conscription, such as infections, physical activity, and dietary habits, we cannot investigate possible mediating factors for the IQ-PD association.

Another possibility would be that certain genetic variants influence both IQ level and the risk of developing PD. Twin studies suggest that genetic factors explain between 57% and 73% of the variance in intelligence among individuals (Bouchard and McGue, 2003). However, IQ is a polygenic trait with hundreds of genes influencing intelligence (Davies et al., 2016).

Even though the study in Paper II has a unique strength in the number of subjects investigated, there are some limitations. Firstly, since the study was based on men only, we cannot draw any conclusions regarding our findings for women. Secondly, the subjects included in Paper 1 were relatively young at follow-up (56 years). There is a possibility that the etiology of their disease is different compared to PD later in life.

4.3 ASSOCIATION BETWEEN ERYTHROCYTE SEDIMENTATION RATE AND PARKINSON'S DISEASE (PAPER III)

In Paper III, we investigated the relationship between erythrocyte sedimentation rate (ESR) at conscription and risk of being diagnosed with PD later in life. The study included 659,278 men followed from 1969 to 2016 and 1,513 were diagnosed with PD during the follow-up. ESR was inversely associated with PD risk; conscripts with higher ESR were significantly less likely to be diagnosed with PD later in life.

The hazard ratio (HR) for PD with basic adjustments (age at conscription, year of conscription, test center and EVF) was 0.94 (p = 0.02, 95% CI 0.89-0.99) per 2-log increase in ESR, corresponding to a two-fold increase in ESR. Additional adjustments for possible confounders (parental education, systolic and diastolic blood pressure, and IQ) did not change the significance and resulted in very small differences in HR. The restricted cubic splines generated from the different adjustment models are shown in figure 6.

To the best of our knowledge, this is the first study to report the association between the levels of ESR in adolescence and the risk of PD in adulthood. ESR is a non-specific marker of inflammation that indirectly represents the activity of pro-inflammatory cytokines (Saadeh, 1998; Bochen et al., 2011; Jou et al., 2011). Other studies investigating inflammation in PD have looked at other inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), or tumor necrosis factor (TNF), in patients already diagnosed with PD. Those studies show that neuroinflammation and/or peripheral inflammation is present in PD patients as they display increased levels of inflammatory cytokines in the brain and cerebrospinal fluid, as well as microglial activation (Mogi et al., 1996; Gerhard et al., 2006; Loeffler et al., 2006; Ouchi et al., 2009; Qin et al., 2016). Furthermore, several studies have shown a significant association between the levels of pro-inflammatory markers and PD severity (Lindqvist et al., 2012; Herlofson et al., 2018; Kouchaki et al., 2018; Rocha et al., 2018).

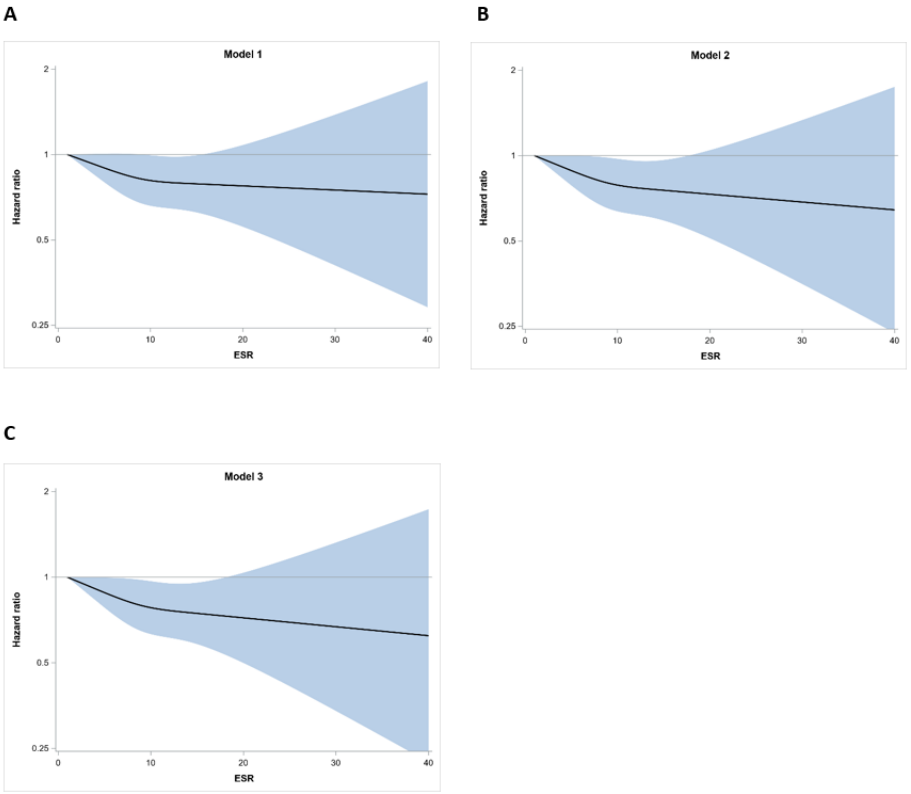

Figure 6. Spline regression of the relation between erythrocyte sedimentation rate (ESR) at conscription and prospective risk for Parkinson's disease (± 95% CI, shaded area). ***A****. Basic adjustments for year of conscription, age at conscription, test center and EVF (erythrocyte volume fraction).* ***B****. Adjusted for year of conscription, age at conscription, test center, EVF, parental education, systolic and diastolic blood pressure.* ***C****. Adjusted for year of conscription, age at conscription, test center, EVF, parental education, systolic and diastolic blood pressure, and IQ.*

However, the study in Paper III supports the idea that the inflammation observed in PD could be a secondary phenomenon and not causal of the pathogenesis. In line with our results, a Swedish longitudinal prospective cohort study recently showed that increased concentrations of leukocytes were associated with a lower risk of PD (Yazdani et al., 2019). A high ESR could possibly be protective against PD.

Fibrinogen, which is contributing to a higher ESR, can activate microglia and it has been debated whether microglial activation protects against or aggravates neuronal loss (Vila et al., 2001; Teismann et al., 2003).

An alternative explanation is that individuals who later develop PD have a weaker ability to produce a high ESR from start. Studies suggest an altered immune response in PD and it is debated whether the altered immune response plays a causal role or is purely secondary to the neuronal damages in PD (McCombe and Henderson, 2011; Kannarkat et al., 2013). Our study in Paper IV shows that patients with PD have weaker antibody responses to Varicella Zoster Virus, as compared to controls. Studies from other groups show that patients with PD have a reduced number of T-helper cells, regulatory T cells and B lymphocytes (Stevens et al., 2012; Kustrimovic et al., 2018).

Since smoking is a possible confounder in this study, we explored if ESR was associated with smoking in a sub-cohort of 21,846 conscripts (Li et al., 2015). In line with previous reports from this cohort (Toss et al., 2013), we did not find a significant correlation.

4.4 THE RELATION BETWEEN LEVELS OF ANTIBODIES AGAINST VARICELLA ZOSTER-VIRUS AND MEASLES AND PARKINSON'S DISEASE (PAPER IV)

The study in Paper IV is an exploratory pilot study investigating measles- and VZV-specific antibodies in serum and CSF samples of patients with PD. The main finding of the study in Paper IV was that PD patients had lower antibody response to VZVgE antigen in serum and plasma than controls (Figure 7). Mean serum OD for VZV was 0.55 ± 0.13 in PD patients and 0.63 ± 0.08 in controls, while the mean CSF OD for VZV was 0.50 ± 0.12 in patients and 0.58 ± 0.08 in controls. These findings were statistically significant in serum (p = 0.063) but failed to reach significance in CSF (p = 0.089). There were no differences between PD patients and controls regarding antibodies against measles.

VZV belongs to the Herpesviridae family and causes chickenpox and herpes zoster. The measles virus belongs to the Paramyxoviridae family and can cause rare infections of the CNS, such as acute postinfectious measles encephalitis.

Previous studies investigating measles and VZV in relation to PD have shown conflicting results. Some studies show that PD patients had fewer self-reports of measles or lower antibody production against measles (Sasco and Paffenberger, 1985; Harris et al., 2012). Other studies investigating measles and/or VZV showed no significant association (Kessler, 1972a; Kessler, 1972b; Marttila et al., 1977; Marttila et al., 1982; Hertzman et al., 1990; Semchuk et al., 1993; Wang et al., 1993; Morano et al., 1994; Martyn and Osmond, 1995; Powers et al., 2006; Vlajinac et al., 2013). In line with our results, a study by Elizan et al. (1979), reports lower antibody levels against VZV in PD patients. However, the studies investigating VZV in PD patients used whole-virus antigen, which has shown to cross-react with Herpes Simplex virus 1 (Schmidt et al., 1969; Vandvik et al., 1985; Roberg et al., 1995; Studahl et al., 1998; Schultze et al., 2004).

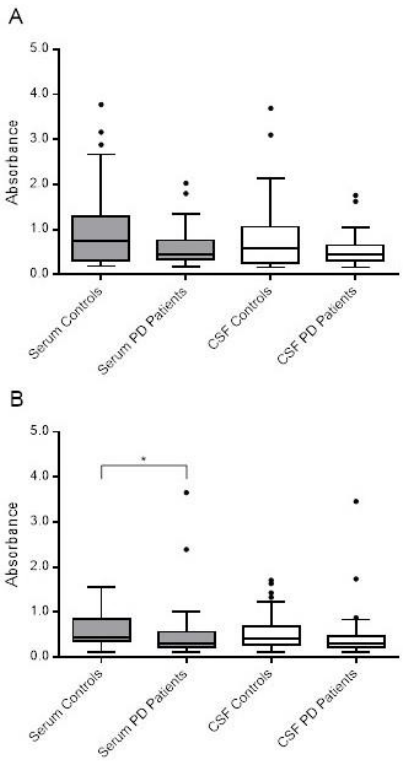

*Figure 7. Tukey boxplots of absorbance values in serum (gray boxes) and CSF (white boxes) comparing PD patients and controls of (A) measles and (B) VZV. The level of significance was analyzed using the Mann-Whitney U test. The boxplots show the median (horizontal line), values from the 25th to the 75th percentiles (boxes), maximum and minimum result within 1.5 times box height (bars); • outlier; * P ≤ 0.05.*

There are several possible explanations for our results. The first is the possibility of PD patients having had a milder VZV infection than the controls and thereby having a lower antibody production. This suggests that having a more severe VZV infection in younger years, decreases the risk for PD later in life.

Another possible explanation is that PD patients may have a decreased ability to produce antibodies in response to VZV. Since the PD patients in the present study also had lower levels of antibodies against measles (although not statistically significant) there could be an immunological deficiency present.

An extensive number of studies show that the immune system in PD is altered (for review see Kannarkat at al., 2013). Being a part of the adaptive immune system, antibodies are produced by B cells with assistance of CD+ T helper cells. Several studies have shown a reduction in these cells in PD patients (Bas et al., 2001; Baba et al., 2005; Niwa et al., 2012; Stevens et al., 2012; Kustrimovic et al., 2018), which could play a role in the decreased antibody production to certain viruses.

Third, individuals with a reduced capacity of antibody production might be more susceptible to infections. In fact, it has been shown that patients with PD have a higher infection burden (Bu et al., 2015).

Furthermore, there is evidence of an immune-mediated susceptibility to PD. Genetic variation in the HLA locus, which is important in antigen recognition, and loci involved in T cell regulation, have been shown to be associated with PD (Saiki et al., 2010; International Parkinson Disease Genomics Consortium, 2011; Holmans et al., 2013; Gagliano et al., 2016).

5 CONCLUSIONS

Idiopathic PD is a complex multi-factorial disease and the etiology is largerly unknown but involves both genetic and environmental factors. In this thesis, several potential risk factors were investigated in relation to PD.

The specific findings were:

- SNPs in the S100B gene were associated with an earlier age at onset of PD in two independent Swedish populations (Paper I).

- High scores on IQ tests at conscription were associated with an increased risk of being diagnosed with PD later in life (Paper II).

- Higher ESR in males at conscription was associated with lower PD risk (Paper III).

- PD patients had a lower antibody response to VZV-specific antigen in serum and CSF samples (Paper IV).

The findings in Paper I, III and IV support the notion of the role of immunity and inflammation in PD. The study in Paper III supports the idea that the inflammation observed in PD could be a secondary phenomenon and not necessary causal of the pathogenesis. This is further supported by Paper I, where SNPs in the gene coding for the inflammatory S100B protein, were not associated with the risk of developing PD but instead with age at disease onset. This supports the notion that inflammatory pathways may not be a main cause of the disease per se, but merely speed up disease progression.

The large amount of studies on the etiology of idiopathic PD do not point on a sole factor giving rise to the disease, but rather could be viewed as a combination of risk factors that together eventually leads to disease. Each risk

factor probably contributes to a small extent to the causal pathophysiologic events of PD. This supports the concept of a total risk factor burden.

Our findings suggest that inflammation may not be a risk factor for PD. On the contrary, our data rather suggest that a greater premorbid inflammatory reaction can play a protective role against PD. It is possible that PD is partially generated by an infectious pathogen. A decreased immune and inflammatory reaction against pathogens could contribute to the progression of PD. Furthermore, it is possible that individuals with decreased immune and inflammatory reactions have an impaired ability to identify and degrade α-synuclein, resulting in a greater spreading of Lewy pathology.

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