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KASPER KATISKO

ALTERATIONS OF IMMUNE SYSTEM FUNCTION IN FRONTOTEMPORAL LOBAR DEGENERATION

Emphasis on Comorbidities and Peripheral Inflammatory Markers

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ABSTRACT

Frontotemporal lobar degeneration (FTLD) is the second most common cause for early onset dementia. FTLD comprises three major clinical subtypes; the behavioural variant of frontotemporal dementia, the non-fluent variant of primary progressive aphasia, and the semantic variant of primary proggressive aphasia. Based on the clinical subtype, FTLD manifests either with behavioural symptoms or different types of linguistic phenotypes. Compared to other neurodegenerative diseases, FTLD has a substantial hereditary nature, and the most common genetic causes include the hexanucleotide repeat expansion in the *C9orf72* gene (*C9*-RE) and mutations in *MAPT* and *GRN* genes. Currently, the knowledge on the pathophysiological pathways causing FTLD are still mainly unknown, and there are no disease-modifying treatments.

Recent genetic studies have suggested that both systemic and neuroinflammation as well as autoimmunity may play a role in the pathogenesis of FTLD in general. The *C9*-RE has also been associated to immune system regulation.

The aim of this study was to evaluate the recent hypotheses regarding the susceptibility of FTLD patients to systemic autoimmunity and inflammation by screening immunological comorbidities, such as autoimmune diseases and cancers, in a Finnish FTLD cohort (N=196), and by analyzing several peripheral inflammatory markers (Bullous pemphigoid (BP) autoantibodies, high sensitivity-CRP, blood cell counts, and levels of different cytokines) from patient plasma/serum samples (N=98). Emphasis was laid on the role of the *C9*-RE in these alterations. Moreover, the aim of the thesis was to detect whether the potential systemic inflammatory changes associate with other specific features under the heterogeneous FTLD spectrum, incuding disease progression or clinical manisfestation.

There was a significantly decreased prevalence of cancer in the FTLD patient group compared to matched control groups (Alzheimer disease and cognitively healthy controls), whereas the prevalence of autoimmune diseases in general was rather high in all groups and did not indicate significant differences between the groups.

Especially the FTLD patients carrying the *C9*-RE most often showed increased levels of specific bullous pemphigoid BP180 autoantibodies in blood. Increased systemic pro-inflammatory activity at baseline, as suggested by increased levels of the pro-inflammatory cytokines RANTES and/or MCP-1 and decreased levels of the anti-inflammatory cytokine IL-10, was associated with parkinsonism and a more rapid disease progression in longitudinal follow-up. These findings were observed in the total FTLD cohort in general and were not affected by the *C9*-RE status.

In conclusion, a sub-group of FTLD patients showed signs of altered immune system function, indicated by decreased cancer prevalence and conversely increased prevelance of some autoimmune conditions. Additionally, peripheral pro-inflammatory state in the early symptomatic phase of FTLD was associated with distinct clinical profiles as well as with more rapid disease progression. The investigations in this thesis provide novel insights into the potential contribution of immune system alterations to the pathogenesis and clinical features of FTLD. This new information may be utilized in designing further studies and for identifying novel biomarkers and/or therapeutic strategies in FTLD.

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TIIVISTELMÄ

Otsa-ohimolohkorappeumat ovat Alzheimerin taudin jälkeen toiseksi yleisin syy alle 65-vuotiaana alkavaan etenevään muistisairauteen. Otsa-ohimolohkorappeumat jaetaan kolmeen kliiniseen alamuotoon; käytösoirein ilmenevä otsalohkodementia, etenevä sujumaton afasia sekä etenevä semanttinen afasia. Kliinisestä alatyypistä riippuen otsa-ohimolohkorappeumat oireilevat joko käytösoirein tai erilaisina kielellisinä ongelmina. Muihin aivorappeumasairauksiin verrattuna otsa-ohimolohkorappeumista huomattava osa periytyy suvuittain, ja taudin yleisimmät geneettiset aiheuttajat ovat *C9orf72* geenissä oleva toistojaksomonistuma (*C9*-RE), sekä mutaatiot *GRN*- ja *MAPT*-geeneissä. Toistaiseksi otsa-ohimolohkorappeumien perimmäiset patofysiologiset syyt ovat pitkälti epäselviä eikä taudinkulkuun vaikuttavaa hoitoa ole pystytty kehittämään.

Viimeaikaiset geneettiset kartoitukset ovat osoittaneet, että systeeminen ja keskushermostossa ilmentyvä tulehdustila sekä autoimmuniteetti voivat olla yhteydessä otsa-ohimolohkorappeumiin. Lisäksi taudin yleisin geneettinen aiheuttaja, *C9*-RE, on aiemmissa tutkimuksissa yhdistetty immuunijärjestelmän säätelyyn.

Tässä tutkimuksessa selvitettiin otsa-ohimolohkorappeumien ja mahdollisen systeemisen tulehduksen ja/tai immuunijärjestelmän muutosten yhteyttä määrittämällä erilaisten immunologisten sairauksien, kuten autoimmuuni- ja syöpäsairauksien, esiintyvyyttä suomalaisessa otsa-ohimolohkorappeumakohortissa (N=196). Lisäksi analysoitiin erilaisia veren tulehdusmerkkiaineita (rakkulainen pemfigoidi (BP) -autovasta-aineet, herkkä CRP, pieni verenkuva, erilaiset sytokiinit) otsa-ohimolohkorappeumapotilailta (N=98). Keskeisenä tavoitteena oli arvioida *C9*-RE:n roolia tulehdukseen ja immuunijärjestelmään vaikuttavana tekijänä, sekä tarkastella mahdollisen tulehduksen yhteyttä erilaisiin taudinkuviin yleisesti varsin heterogeenisessa otsa-ohimolohkorappeumien tautiryhmässä.

Otsa-ohimolohkorappeumapotilailla havaittiin merkittävästi vähemmän syöpiä verrattuna kontrolleihin (Alzheimerin tautikohortti sekä kognitiivisesti terveet verrokit), kun taas autoimmuunisairauksien esiintyvyys oli yleisesti ottaen korkea kaikissa ryhmissä ilman merkittäviä eroja ryhmien välillä. Etenkin *C9*-RE kantajilla havaittiin usein yli viitearvojen kohonneita rakkulaisen pemfigoidi-ihosairauden autovasta-aineita. Tutkimuksessa havaittiin yhteys lisääntyneen systeemisen pro-inflammatorisen aktiivisuuden sekä parkinsonismioireiden ja seurannassa nopeammin etenevän taudinkuvan kanssa. Systeemiseen proinflammatoriseen aktiivisuuteen viittasivat veren kohonneet proinflammatoriset MCP-1 ja RANTES sytokiinitasot sekä alentuneet anti-inflammatoriset IL-10 sytokiinitasot. Nämä löydökset havaittiin kohortissa kokonaisuudessaan riippumatta *C9*-RE genotyypistä.

Yhteenvetona voidaan todeta, että osalla otsa-ohimolohkorappeumapotilaista voidaan havaita merkkejä muuntuneesta immuunijärjestelmän toiminnasta, mihin viittaa poikkeuksellisen matala syöpien esiintyvyys ja käänteisesti mahdollinen lisääntynyt taipumus tiettyihin autoimmuunitauteihin. Osalla potilaista veressä havaittava perifeerinen proinflammatorinen tila taudin oireisessa alkuvaiheessa on yhteydessä erilaisiin kliinisiin piirteisiin sekä nopeampaan taudin etenemiseen. Tämän väitöskirjan tutkimukset ovat tuottaneet uutta tietoa immuunijärjestelmän muutosten mahdollisesta yhteydestä otsa-ohimolohkorappeumien patogeneesiin ja taudinkuvaan. Tietoa voidaan hyödyntää tulevaisuuden tutkimuksissa erilaisten tulehdukseen liittyvien biomarkkereiden ja mahdollisten hoidollisten menetelmien kehittämisessä.

Luokitus: WL 358.5, WM 220, QZ 150, QW 545, QZ 200
Yleinen suomalainen asiasanasto: neurodegeneratiiviset sairaudet; dementia; frontotemporaalilohkon rappeuma; frontotemporaalinen dementia; aivojen Pickin tauti; parkinsonismit; geenit; genotyyppi; mutaatio; tulehdus; kasvaimet; autoimmuniteetti; sytokiinit; autovasta-aineet; biomarkkerit; sairauden eteneminen

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Kuopio, October 2019
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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Katisko K, Haapasalo A, Koivisto AM, Krüger J, Hartikainen P, Korhonen VE, Helisalmi S, Herukka S-K, Remes AM, Solje E. Low Prevalence of Cancer in Patients with Frontotemporal Lobar Degeneration. *Journal of Alzheimer's Disease 2018;62(2):789-794.*

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CONTENTS

ABBREVIATIONS

AD	Alzheimer´s disease
ADCS-ADL	Alzheimer`s disease cooperative study – Activities of daily living inventory
ALS	Amyotrophic lateral sclerosis
Aβ	Beta-amyloid
BBB	Blood brain barrier
BP	Bullous pemphigoid
BP180	Collagen XVII (transmembrane protein)
BP230	Dystonin-e (epithelial isoform of dystonin protein)
bvFTD	Behavioural variant frontotemporal dementia
C9orf72	Chromosome nine open reading frame 72 (gene)
C9-RE	Chromosome nine open reading frame 72 hexanucleotide repeat expansion (pathological repeat expansion in *C9orf72* gene)
CBA	Cytometric bead array
CBD	Corticobasal degeneration
CHCHD10	Coiled-coil-helix-coiled-coil-helix domain containing 10
CHMP2B	Charged multivesicular body protein 2b
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computer tomography
DNA	Deoxyribonucleic acid
DPR	Dipeptide repeat protein
ELISA	Enzyme-linked immunosorbent assay
EWS	Ewing`s sarcoma protein
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration

FTLD-ALS	Frontotemporal lobar degeneration with amyotrophic lateral sclerosis
FTLD-MND	Frontotemporal lobar degeneration with motoneuron disease
FLDnA	Frontal lobe degeneration of non-Alzheimer type
FUS	Fused in sarcoma
GR	Glucocorticoid receptor
GRN	Progranulin (gene)
GWAS	Genome-wide association study
HLA	Human leukocyte antigen
hs-CRP	High sensitive C-reactive protein
IBD	Inflammatory bowel disease
IFN	Interferon
IL	Interleukine
lvPPA	Logopenic variant primary progressive aphasia
MAPT	Microtubule-associated protein tau
MCI	Mild cognitive impairment
MCP-1	Monocyte chemoattractant protein-1
MMSE	Mini-mental state examination
MND	Motoneuron disease
MRI	Magnetic resonance imaging
MSTD	Multiple system tauopathy with dementia
nfvPPA	Non-fluent variant primary progressive aphasia
PD	Parkinson´s disease
PGRN	Progranulin (protein)
PET	Positron emission tomography
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy
RANTES	Regulated upon activation normal T-cell expressed and secreted
RNA	Ribonucleic acid
RP-PCR	Repeat primed – polymerase chain reaction

SD	Standard deviation
Simoa	Single molecule array
SLE	Systemic lupus erythematosus
SPECT	Single-photon emission computed tomography
SQSTM1	Sequestome 1
svPPA	Semantic variant primary progressive aphasia
TAF15	TATA-binding protein-associated factor 15
TARDBP	TAR-DNA binding protein (gene)
TBK1	TANK binding kinase 1
TDP-43	TAR-DNA binding protein of 43 kDa (protein)
TNF	Tumor necrosis factor
TREM2	Triggering receptor expressed on myeloid cells 2
TUBA4A	Tubulin alpha 4a
UBQLN2	Ubiquilin 2
UPS	Ubiquitin positive, FUS and TDP-43 negative inclusions
VCP	Valosin containing protein
WMT-GGI	White matter tauopathy with globular glial inclusions

1 INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is a neuropathological umbrella term for a group of distinct heterogeneous clinical subtypes. Today, FTLD is acknowledged as the second most common dementing disease in people aged under 65 years (Ratnavalli et al., 2002; Rosso et al., 2003a). FTLD is clinically divided to several subtypes, based on the manifested clinical symptoms and localization of the brain atrophy (Gorno-Tempini et al., 2011; Neary et al., 1998; Rascovsky et al., 2011). The most common clinical phenotype of FTLD is the behavioural variant of frontotemporal dementia (bvFTD), characterized by wide-ranging behavioural symptoms from apathy and inertia to disinhibition and aggressive behaviour, combined with impaired executive functions (Neary et al., 2005; Piguet et al., 2011; Rascovsky et al., 2011). Other common clinical phenotypes under the FTLD spectrum are language variants of FTLD, called primary progressive apahias (PPA) (Gorno-Tempini et al., 2011; Neary et al., 1998). PPAs are further divided to subgroups based on the nature of the clinical symptoms: 1) The non-fluent variant of primary progressive aphasia (nfvPPA) characterized by apraxia of speech, agrammatism and impaired comprehension of complex sentences; 2) The semantic variant of primary progressive aphasia (svPPA) characterized by impaired object naming/knowledge and single word comprehension; and 3) The logopenic variant of primary proggressive aphasia (lvPPA) characterized by impaired single word retrieval and repetition of sentences/phrases (Gorno-Tempini et al., 2011).

Etiologies causing FTLD are heterogenous, and thus far the precise mechanisms leading to the disease pathogenesis are unknown. However, the increasing genetic knowledge behind FTLD has provided several new insights and theories about the disease process. Up to 40% of FTLD cases have positive family history of dementia, and 10-27 % of FTLD cases show clear autosomal dominant inheritance (Rohrer et al., 2009a; Seelaar et al., 2008; Sieben et al., 2012). The most common mutations found to cause FTLD worldwide are the hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9*-RE) and mutations in *MAPT* and *GRN* genes (Sieben et al., 2012). The *C9*-RE is the most common genetic cause of FTLD, and it is especially common in Northern Europe (DeJesus-Hernandez et al., 2011; Majounie et al., 2012; Renton et al., 2011). In Finland, the *C9*-RE causes up to 50% of the familial FTLD cases (DeJesus-Hernandez et al., 2011; Majounie et al., 2012; Renton et al., 2011), whereas mutations in *MAPT* and *GRN* genes are extremely rare (Kaivorinne et al., 2008; Krüger et al., 2009).

The normal function of the *C9orf72* gene has recently been associated with immunoregulation in animal model studies. These examinations showed that *C9orf72* loss-of-function, also occuring in humans due to haploinsufficiency caused by the *C9*-RE, causes systemic inflammatory alterations and a severe autoimmune phenotype with elevated levels of pro-inflammatory cytokines and increased mortality (Atanasio et al., 2016; Burberry et al., 2016). Additionally, progranulin

protein encoded by the *GRN* gene, has similarly been associated to immunoregulation in several biological studies (Bossù et al., 2011; Cenik et al., 2012; Martens et al., 2012; Yin et al., 2010). Moreover, genetic studies have recently linked FTLD in general to specific HLA loci associated with immunoregulation (Ferrari R et al., 2014; Pottier et al., 2019), and showed that FTLD shares genetic overlap with several autoimmune diseases (Broce et al., 2018). Altogether, these findings suggest that FTLD may be associated with dysregulated immune system and that both systemic and neuroinflammatory alterations take place in the patients.

Since currently there are no efficacious treatments for FTLD, a better understanding of the complex etiology behind the disorder is crucial for the development of disease-modifying interventions in the future.

The aim of this study was to evaluate the recent hypotheses regarding the altered systemic immunoregulatory state in FTLD with a special emphasis on the *C9*-RE by screening several inflammatory comorbid diseases in a Finnish FTLD cohort and by analysing levels of systemic inflammatory biomarkers in FTLD patients` plasma/serum samples.

2 REVIEW OF THE LITERATURE

2.1 FRONTOTEMPORAL LOBAR DEGENERATION

Frontotemporal lobar degeneration (FTLD) is a heterogeneous neuropathological umbrella term, and it is after Alzheimer`s Disease (AD) the second most common cause for early onset dementia (Ratnavalli et al., 2002; Rosso et al., 2003a). A neurologist, neuropathologist and psychiatrist Arnold Pick was the first to describe FTLD in 1892, in a patient with progressive behavioural symptoms and aphasia (Pick, 1892). The key feature was that the clinical and anatomical profile clearly differed from that of the more common and already described AD. Named by its first describer, "Pick`s Disease" was soon adopted as a term for neurodegenerative syndromes affecting especially frontal and/or temporal brain regions. Later on, the term Pick`s Disease was modified to frontal lobe degeneration of non-Alzheimer (FLDnA), as the actual Pick`s disease, characterized with histopathological Pick bodies, was noticed to account only for a proportion of the FLDnA spectrum.

FLDnA was considered rather as a rare curiosity until 1980s, when researchers in Lund and Manchester identified in a post-mortem analyses a substantial group of patients suffering especially from frontal and anterior temporal lobe atrophy, without signs of classical AD neuropathology (Brun, 1987; Gustafson, 1987; Neary et al., 1986). In 1994, Lund and Manchester consensus criteria were published to clinically and neuropathologically characterize disease referred to as frontotemporal dementia (FTD) (Brun et al., 1994). By that time, it was already noticed that although the clinical manifestations were heterogeneous, the patients tended to manifest different clinical subtypes ranging from behavioural symptoms to linguistic problems. Linguistic problems were also described to manifest more profoundly either as non-fluent or fluent (semantic) types of aphasia (Hodges et al., 1992; Mesulam, 1982; Snowden et al., 1989; Warrington, 1975).

Since the 1990s, FTLD has been divided into clinical subtypes with the clinical diagnostic criteria being first described by Neary and colleagues in 1998 (Neary et al., 1998). The criteria were revised by Rascovsky and Gorno-Tempini with their colleagues in 2011 (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Today, FTLD is acknowledged as a much more common cause of dementia than assumed a few decades ago. At the same time, knowledge about the disorder and its neuropathological, genetic and epidemiological features has evolved tremendously. According to current knowledge, the etiology, neuropathological features, genetic background, and clinical manifestations of FTLD are considered a heterogenic disease continuum with its extremes differing substantially from each other.

Currently, there is some discrepancy in the literature about the terminology of FTLD, since the term 'FTD' is also used as an umbrella term for all the clinical subtypes. On the other hand, the term 'FTD' is sometimes used to refer only to the bvFTD, excluding the linguistic subtypes. In most cases, however, a consensus has

been that 'FTLD' is a pathological umbrella term, and 'FTD' a clinical umbrella term, both comprising all the actual clinical subtypes. In this thesis, the neuropathological term 'FTLD' is used as a general term comprising the whole disease spectrum, and the division into clinical subtypes (bvFTD, nfvPPA, svPPA and lvPPA) is based on the current clinical criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

2.1.1 Clinical syndromes under the FTLD spectrum

FTLD has three main clinical subgroups: 1. bvFTD, 2. nfvPPA and 3. svPPA (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Another variant of primary progressive aphasias is the lvPPA (Gorno-Tempini et al., 2011), which is typically associated with AD pathology (Mesulam et al., 2008; Rabinovici et al., 2008) and therefore could be excluded when considering the neuropathological FTLD spectrum.

All of the FTLD clinical subtypes may also manifest with motoneuron disease (MND), in which case the disease is referred to as FTLD-MND or FTLD with amyotrophic lateral sclerosis (FTLD-ALS) (Burrell et al., 2016). Additionally, several parkinsonian phenotypes (presenting with extrapyramidal symptoms such as tremor, bradykinesia, rigidity and postural instability) that affect fronto-temporal brain regions, mainly corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), are increasingly also included under the FTLD spectrum as 'FTLD-plus' syndromes (Figure 1) (Baizabal-Carvallo and Jankovic, 2016; Deutschländer et al., 2018; Espay and Litvan, 2011; Mackenzie et al., 2009).

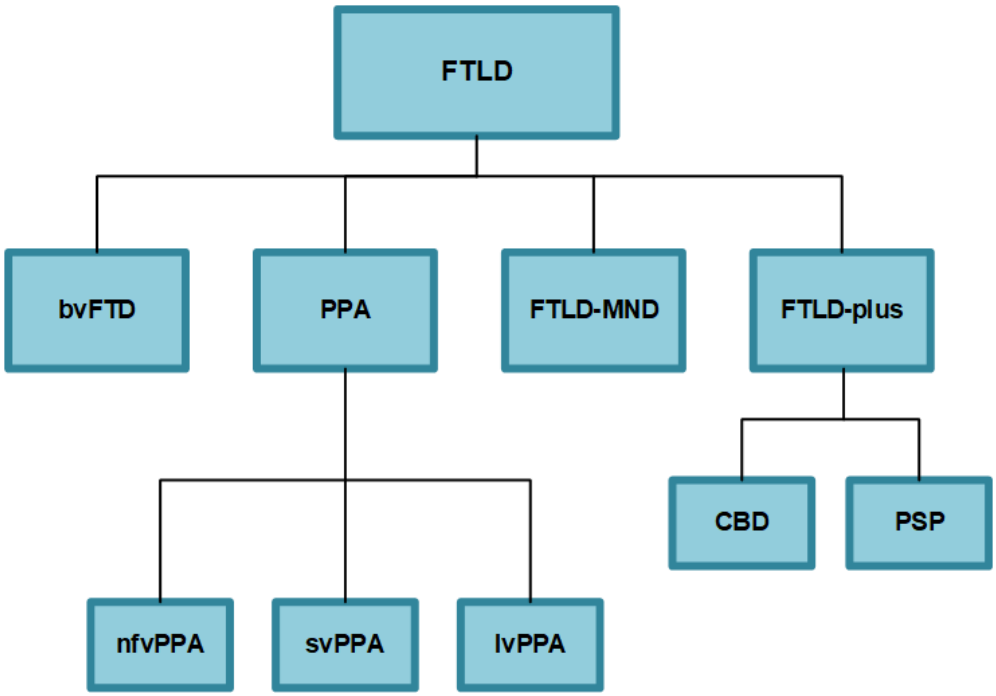


Figure 1. FTLD and its clinical subtypes. Due to overlapping neuropathology and clinical symptoms, also FTLD-plus disorders (mainly PSP and CBD) are currently also included in the FTLD spectrum. Abbreviations: FTLD = Frontotemporal lobar degeneration, bvFTD = Behavioral variant frontotemporal dementia, PPA = Primary progressive aphasia, FTLD-MND = Frontotemporal lobar degeneration with motoneuron disease, nfvPPA = non-fluent variant of primary progressive aphasia, svPPA = semantic variant of primary progressive aphasia, lvPPA = logopenic variant of primary progressive aphasia, CBD = corticobasal degeneration, PSP = progressive supranuclear palsy.

2.1.1.1 Behavioural variant of frontotemporal dementia (bvFTD)

The behavioural variant of frontotemporal dementia (bvFTD) is the most common of the FTLD phenotypes (Johnson et al., 2005; Seelaar et al., 2008), and it is clinically characterized with altered behaviour and deterioration of executive functions (Rascovsky et al., 2011). Behavioural symptoms vary widely between patients, but usually include at least a few of the following: disinhibition, aggression, apathy or inertia, loss of sympathy or empathy, stereotypical/perseverative behavior, hyperorality or other dietary changes, and executive deficits (Rascovsky et al., 2011). Linguistic symptoms may also occur, since clinical phenotypes of FTLD often overlap with each other (Banks and Weintraub, 2008; Blair et al., 2007). Memory and visuospatial functions are more spared, and the neuropsychological profiles usually differ compared to patients with AD (Pasquier et al., 2001; Wicklund et al., 2006).

The diagnostics of bvFTD is based on neurological and neuropsychological examination, imaging findings (preferably magnetic resonance imaging (MRI) and/or positron emission tomography (PET)) and often genetic testing (Rascovsky et al., 2011). Important knowledge about the patients symptoms is provided by co-workers, friends or family members of the patient, since patients with bvFTD often do not recognize their altered behavior or cognitive decline themselves (Neary et al., 1998). No specific blood or cerebrospinal fluid (CSF)-based biomarkers for bvFTD, or FTLD in general, have been identified, although for example AD biomarkers are used to differentiate AD from FTLD (Rascovsky et al., 2011).

As the phenotype of bvFTD is usually mainly behavioural, differential diagnostics between several psychiatric diseases is often challenging (Solje et al., 2015; Woolley et al., 2011), especially in the *C9*-RE-associated disease (Devenney et al., 2014; Snowden et al., 2012; Solje et al., 2015). Although imaging findings suggestive for FTLD (frontal or/and temporal atrophy in MRI/CT or hypometabolism and/or hypoperfusion in PET/SPECT) are used in the diagnostic process (Rascovsky et al., 2011), some patients with clinically evident bvFTD have normal neuroimaging findings at the time of disease onset (Riedl et al., 2014). In addition, sometimes substantial clinical overlap between bvFTD, AD (Gregory et al., 1997; Hodges et al., 1999; Walker et al., 2005) and other neurodegenerative diseases (Karageorgiou and Miller, 2014; Le Ber et al., 2006) occur, further complicating the diagnostics of the disease. Current diagnostic criteria for bvFTD were published by Rascovsky and colleagues in 2011 (Rascovsky et al., 2011). The Rascovsky criteria divide the disease probability into three stages: possible bvFTD, probable bvFTD, and definite bvFTD. The diagnostic process according to the Rascovsky criteria is described in Figure 2.

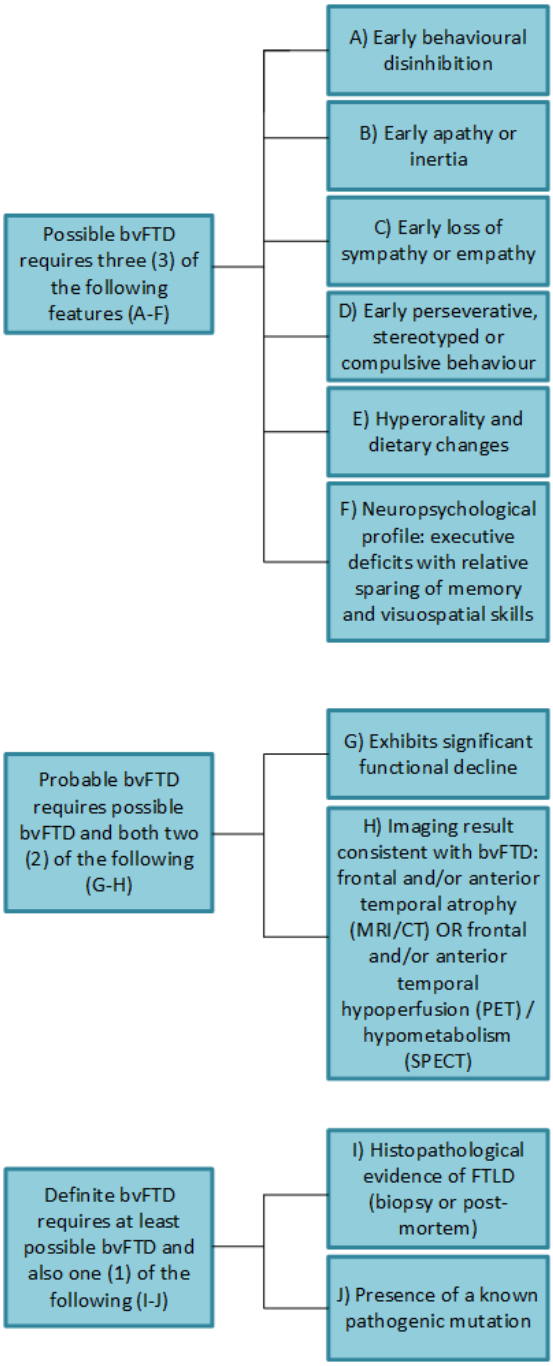


Figure 2. Diagnostic criteria for bvFTD according to Rascovsky et al. 2011. BvFTD = Behavioral variant frontotemporal dementia, MRI = magnetic resonance imaging, CT = computed tomography, PET = positron emission tomography, SPECT = single photon emission computed tomography, FTLD = Frontotemporal lobar degeneration.

The Rascovsky criteria also include exclusionary criteria which state that for disease to be considered as bvFTD, the pattern of deficits should not be better accounted for by other non-degenerative nervous system or medical disorder, behavioural symptoms should not be better accounted for by a psychiatric disorder, and biomarkers strongly indicative of AD or other neurodegenerative diseases should not be present (Rascovsky et al., 2011). However, it should be noted that features of AD may also occur in patients with FTLD, as mixed pathologies are common (Wharton et al., 2011).

2.1.1.2 Primary progressive aphasias (PPA)

The PPAs include linguistic variants of FTLD and can be further divided into two main phenotypes; 1) the nfvPPA and 2) the svPPA. The lvPPA is clinically considered as the third language variant under PPAs (Gorno-Tempini et al., 2011), but it is often considered to be a variant of AD based on neuropathology (Mesulam et al., 2008; Rabinovici et al., 2008).

The current precise diagnostic criteria of nfvPPA and svPPA were published by Gorno-Tempini and colleagues in 2011 (Gorno-Tempini et al., 2011). Before the classification to either nfvPPA, svPPA or lvPPA, the patient must first meet the criteria for PPA in general (Mesulam, 2001). The inclusion criteria for PPA require that 1) linguistic problems are the most prominent clinical feature; 2) the linguistic problems are the principal cause for impaired daily living; and 3) aphasia should be the most prominent symptom at disease onset and for the initial phases of the disease. In addition to the inclusionary criteria, all features meeting the exclusionary criteria (1-4) should be negative. These include: 1) The pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorder; 2) cognitive disturbance is better accounted for by a psychiatric diagnosis; 3) the patient manifests prominent initial episodic memory, visual memory or visuoperceptual impairments; and 4) the patient manifests prominent behavioural disturbances (Mesulam, 2001) (Figure 3).

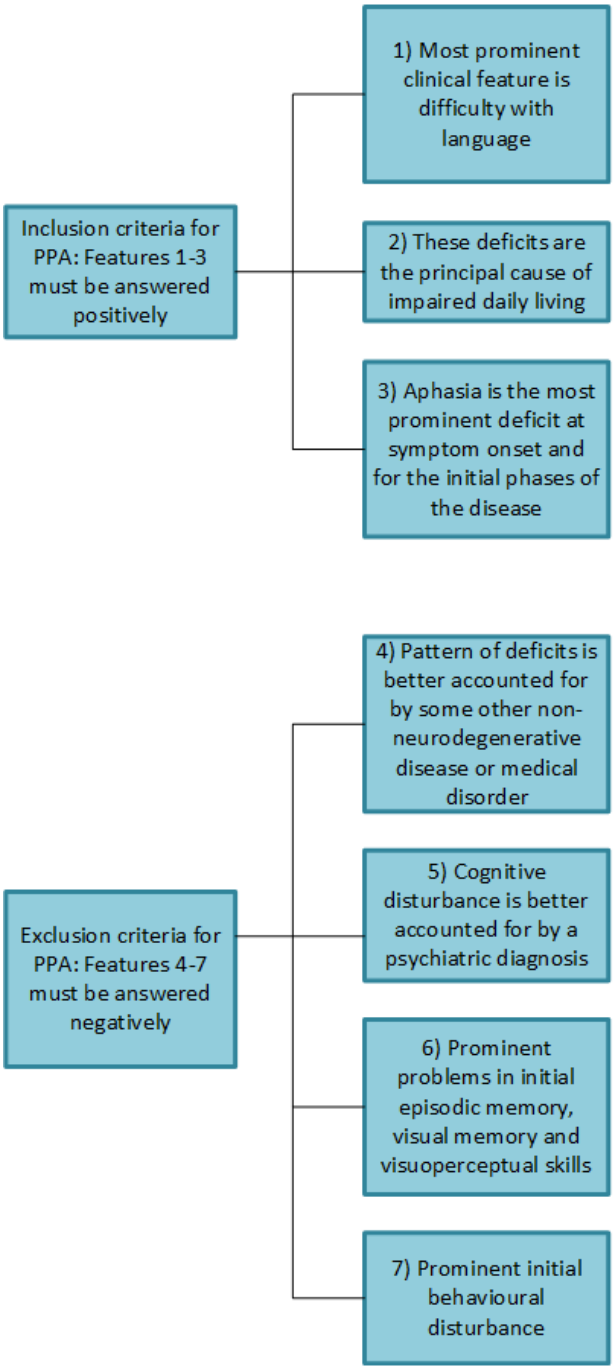


Figure 3. Inclusion and exclusion criteria for PPA according to Mesulam et al. 2001. PPA = primary progressive aphasia.

If the criteria for PPA are met, further classification to nfvPPA, svPPA and lvPPA by Gorno-Tempini and colleagues (Gorno-Tempini et al., 2011) can be used.

The nfvPPA phenotype manifests as agrammatism in language production (omission of function words and affixes when for example asked to describe events in a picture) and/or apraxia of speech (effortful, halting speech and inconsistent speech with sound errors and distortions). Typically, object knowledge is spared, and single-word comprehension is not impaired. However, impaired comprehension may occur in syntactically complex sentences. Because of the symptom profile, nfvPPA resembles a Broca-like syndrome (Kirshner, 2014). Notably, overlap with behavioural symptoms of bvFTD and cognitive decline may occur, especially in the later stages of the disease (Banks and Weintraub, 2008). Based on the clinical profile, the first step/stage of the criteria (clinical diagnosis) is determined. Further steps include imaging result(s) supportive for nfvPPA (stage 2) and histopathological or genetic support (stage 3) (see Figure 4).

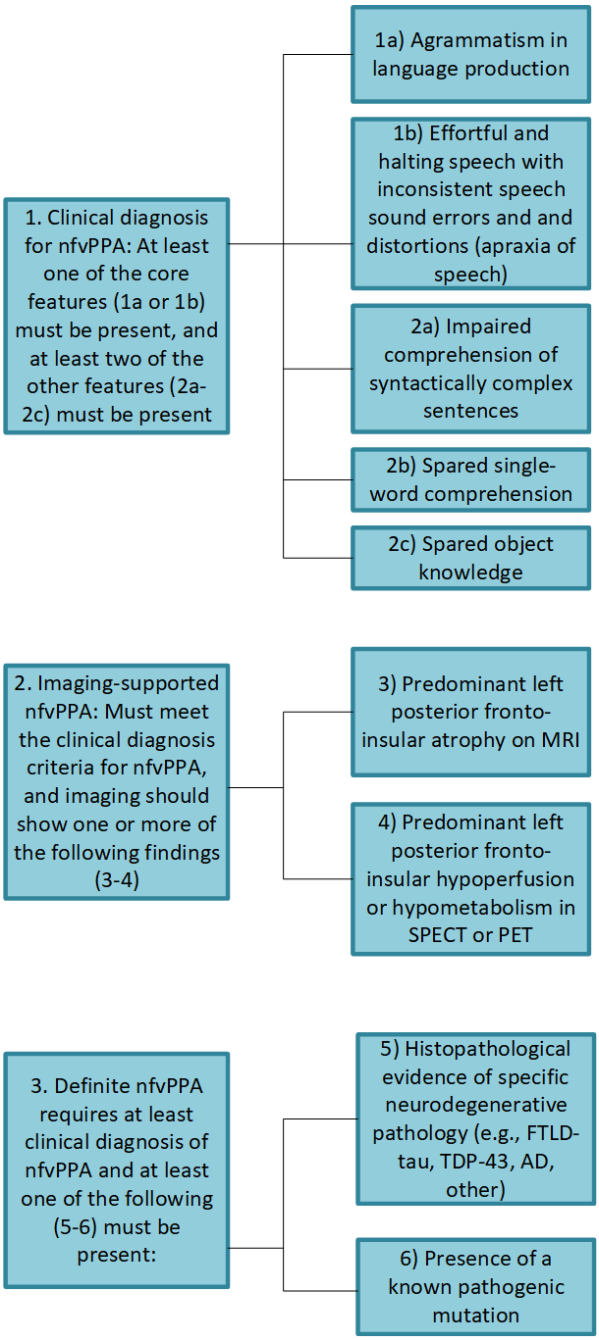


Figure 4. Diagnostic criteria for nfvPPA according to Gorno-Tempini et al. 2011. NfvPPA = non-fluent variant of primary progressive aphasia, MRI = magnetic resonance imaging, SPECT = single photon emission computed tomography, PET = positron emission tomography, FTLD = frontotemporal lobar degeneration, TDP-43 = TAR-DNA binding protein of 43 kDa, AD = Alzheimer`s disease.

The svPPA phenotype manifests as impaired confrontation naming (for example naming objects or actions in a picture) and/or impaired single word comprehension. Patients may also suffer from surface dyslexia (not able to read words such as "island" with non-predictable print-to-sound correspondences) or dysgraphia (inability to write irregularly spelled words). Repetition of words and speech production is spared. The svPPA can be described as the "fluent aphasia", as the speech production in itself is fluent, although words and objects are confused so that the content of the speech is impaired. Similar to the nfvPPA criteria, the clinical diagnosis is further confirmed by imaging (stage 2) and genetic or histopathological testing (stage 3) (Figure 5).

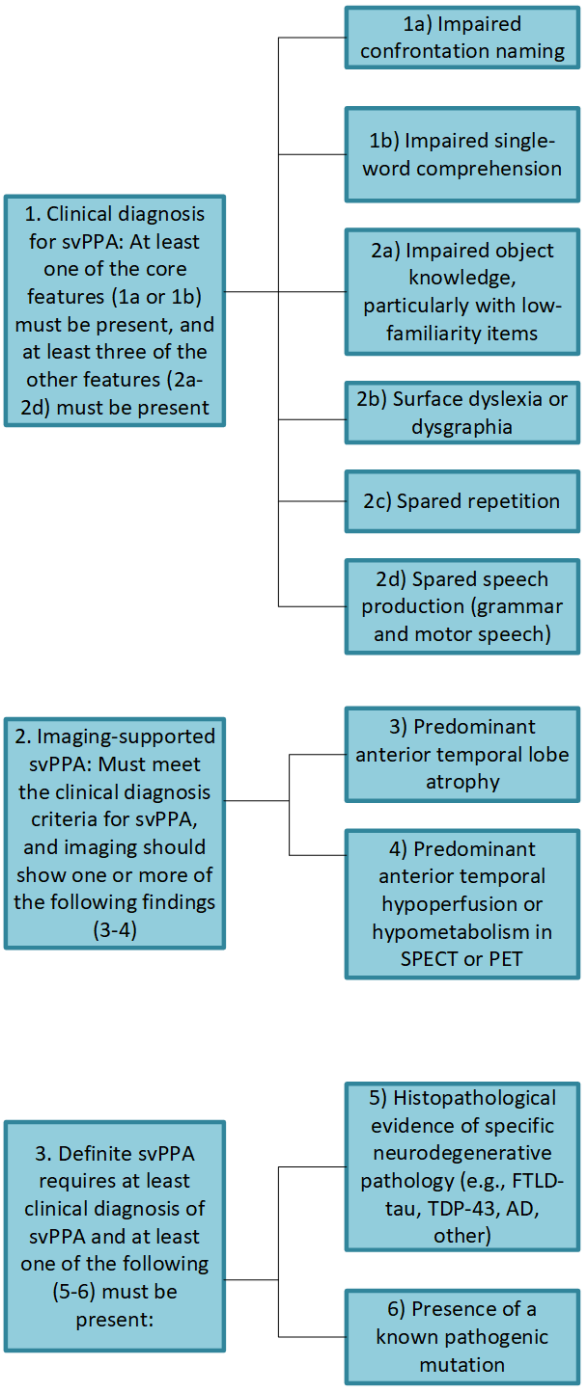


Figure 5. Diagnostic criteria for svPPA according to Gorno-Tempini et al. 2011. SvPPA = semantic variant of primary progressive aphasia, SPECT = single photon emission computed tomography, PET = positron emission tomography, FTLD = frontotemporal lobar degeneration, TDP-43 = TAR-DNA binding protein of 43 kDa, AD = Alzheimer`s disease.

The lvPPA phenotype manifests as impaired single-word retrieval in spontaneous speech and additionally impaired repetition of sentences/phrases must be present. Phonologic speech errors in spontaneous speech and naming are also common. However, object knowledge and single-word comprehension are spared. Similar to the nfvPPA and svPPA criteria, the clinical diagnosis is further confirmed by imaging (stage 2) and genetic or histopathological testing (stage 3) (Figure 6).

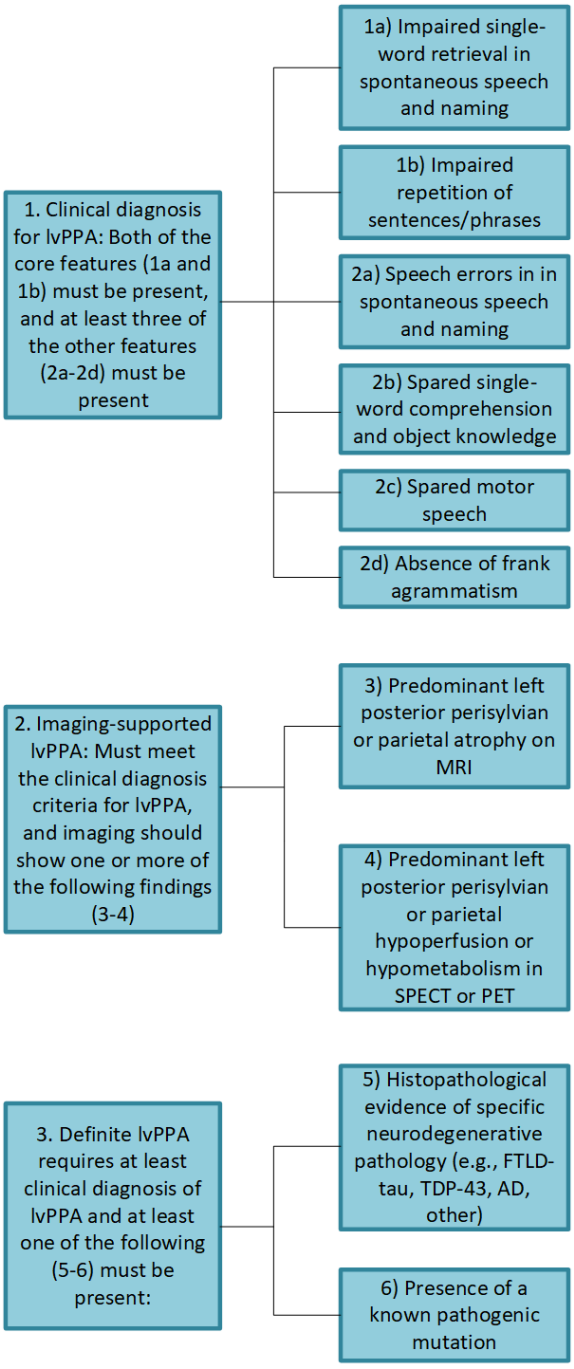


Figure 6. Diagnostic criteria for lvPPA according to Gorno-Tempini et al. 2011. LvPPA = logopenic variant of primary progressive aphasia, MRI = magnetic resoncance imaging, SPECT = single photon emission computed tomography, PET = positron emission tomography, FTLD = frontotemporal lobar degeneration, TDP-43 = TAR-DNA binding protein of 43 kDa, AD = Alzheimer`s disease.

2.1.1.3 FTLD-MND

FTLD-MND, sometimes referred only to as FTLD-ALS, is a clinical phenotype with combination of bvFTD (or PPA) and motoneuron disease. At least 15% of FTLD patients also develop MND, usually manifested as ALS (Burrell et al., 2011; Lomen-Hoerth et al., 2002). ALS is a neurodegenerative disease characterized by progressive loss of motor neurons both in the spinal cord and in the brain (van Es et al., 2017). MND may also occur before bvFTD or PPA, and approximately 15% of MND patients meet the criteria for FTLD (Burrell et al., 2016). The patients with FTLD-MND often share overlapping genetic (*C9*-RE) and neuropathological (TDP-43) background with FTLD and MND/ALS, although notably also FTLD-MND phenotype associates with significant genetic and neuropathological heterogeneity (Figure 7a) (Burrell et al., 2016).

2.1.1.4 FTLD-plus disorders

Recently, a category of 'FTLD-plus' disorders, or the parkinsonian phenotypes of FTLD have been increasingly included in the FTLD spectrum. This category includes mainly CBD and PSP. CBD is characterized with asymmetric rigidity, apraxia, focal dystonia, and cortical sensory loss. PSP manifests as supranuclear vertical gaze palsy, postural instability, axial rigidity, dysarthria, and swallowing difficulties. Both of these syndromes may have substantial genetic, histopathological and clinical overlap with bvFTD or PPAs (Figure 7b) (Baizabal-Carvallo and Jankovic, 2016).

2.1.2 Epidemiology

FTLD is the second most common cause of early onset dementia (Ratnavalli et al., 2002; Rosso et al., 2003a), and bvFTD is the most common clinical phenotype (Johnson et al., 2005; Seelaar et al., 2008). Typically, the patient is 50-70 years old at the disease onset (Johnson et al., 2005; D Neary et al., 2005; Rosso et al., 2003a). However, disease onset varies broadly from youth (Mackenzie et al., 2008; Velakoulis et al., 2009) to older people (Baborie et al., 2012). The incidence of FTLD is 2.2 per 100 000 person-years in people aged 40-49 years, and rises to 8.9 per 100 000 person-years in the 60-69--year-old age group (Johnson et al., 2005). The reported prevalence of FTLD varies tremendously in the literature. In a meta-analysis for people aged under 65 years, prevalences from 3 to 26 per 100 000 persons were reported (Vieira, 2013). Reported prevalence of FTLD in Finland represents the highest part of the range, with the prevalence being 20.5 per 100 000 persons in people aged 45-65 years (Luukkainen et al., 2015). Notably, as also discussed above, the diagnosis of the FTLD clinical subtypes is often difficult, and some of the reported prevalences are likely underestimations. It has been suggested that especially bvFTD patients with psychiatric symptoms are misdiagnosed as psychiatric disease and treated in mental institutions without neurological diagnosis (Galimberti et al., 2015a; Solje et al., 2015)

No clear risk factors for FTLD have been reported, although prior head trauma has been suggested to increase the risk (Rosso et al., 2003b).
FTLD typically affects males and females equally, even though some studies have suggested a trend for slight male-dominance (Hodges et al., 2003; Ratnavalli et al., 2002; Rosso et al., 2003a). Due to the early onset of the disease, FTLD reduces life expectancy (Brodaty et al., 2012). Survival time after diagnosis varies significantly between patients and also between clinical subgroups. Among clinical subgroups, patients with FTLD-MND phenotype typically have the shortest survival time (mean 2 years from disease onset) and patients with PPA the longest survival time (mean 7-11 years from disease onset) (Hodges et al., 2003). Also extremely slow progression has been reported in some patients (Suhonen et al., 2015).

2.1.3 Genetics

Significant amount (approximately 40-50%) of FTLD patients report possible family history, i.e. at least one relative with a similar profile of symptoms (Chow et al., 1999; Goldman et al., 2008, 2005; Lashley et al., 2011; Rosso et al., 2003a). Clear autosomal dominant pattern has been reported in 10-27% of the cases (Rohrer et al., 2009a; Seelaar et al., 2008; Sieben et al., 2012). As the diagnostics of FTLD has evolved substantially during the past few decades, inheritance data are based on described symptoms and estimations rather than actual knowledge of the diagnoses in the family members. Out of the clinical subtypes, the patients with bvFTD most often have a positive family history (45%), especially if bvFTD is accompanied with motoneuron disease manifestation (60%) (Goldman et al., 2005; Sieben et al., 2012). So far, causal mutations have been identified in three major genes: 1) The hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 (*C9orf72*); 2) mutations in *MAPT* gene; and 3) mutations in *GRN* gene. These three together cover the majority of familial cases, even though the reported mutation frequency in different populations significantly varies (Sieben et al., 2012). Other substantially rarer causal mutations in FTLD are in the genes encoding charged multivesicular body protein 2b (*CHMP2B*), valosin-containing protein 1 (*VCP-1*), sequestome 1 (*SQSTM1*), coiled-coil-helix-coiled-coil-helix domain containing 10 (*CHCHD10*), TANK-binding kinase 1 (*TBK1*), TAR DNA-binding protein (*TARDBP*), fused in sarcoma (*FUS*), ubiquilin 2 (*UBQLN2*) and tubulin alpha 4a (*TUBA4A*) (Fenoglio et al., 2018). It is likely, that more FTLD-associated mutations will be identified in the future, since positive family history may occur in patients who do not harbor any known genetic alterations (Blauwendraat et al., 2018).

2.1.3.1 The *C9*-RE

In 2011, two consortia published their results on the discovery of a hexanucleotide (GGGGCC) repeat expansion in *C9orf72* (*C9*-RE) as the most common genetic cause underlying FTLD and also ALS (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The discovery provided a specific genetic cause for the association that had been

identified already five years earlier in chromosome 9 (Morita et al., 2006; Vance et al., 2006). The GGGGCC repeat expansion is located in the non-coding region of the *C9orf72*, and the length of the expansion can largely vary between patients. There is no clear consensus on the pathological threshold length for the expansion. Repeats shorter than 30 (Renton et al., 2011), 24 (van der Zee et al., 2013) or 65 (Loy et al., 2014) have been reported in healthy individuals. As there is no current consensus for the lower limit of the pathological repeat length, the term 'intermediate expansions' has coined to describe repeat expansions that are possibly pathological at least to some extent (van der Zee et al., 2013). These intermediate repeat expansions have been associated at least with psychiatric and parkinsonian syndromes (Cannas et al., 2015; Meloni et al., 2017). Notably, the definitely pathogenic repeat expansions underlying FTLD are usually clearly larger, ranging from hundreds of repeats up to thousands of repeats (DeJesus-Hernandez et al., 2011; Renton et al., 2011). FTLD patients carrying the *C9*-RE are clinically most often associated with the bvFTD or FTLD-MND phenotype. Clinically, especially psychotic symptoms, executive dysfunction and parkinsonism, alongside with classical bvFTD-related behavioural symptoms, have been reported prevalent in the *C9*-RE carriers, but it should be noted that the clinical phenotype caused by the *C9*-RE seems extremely heterogenous (Dobson-Stone et al., 2012; Solje et al., 2015; Van Mossevelde et al., 2017).

The underlying pathogenetic mechanisms of the *C9*-RE are likely multifactorial, and both so called loss-of-function (haploinsufficiency) and gain-of-function mechanisms have been proposed.

First, it is hypothesized that large repeat expansions affect the normal function of the *C9orf72* gene by downregulating its expression. Haploinsufficiency of the *C9orf72* gene is supported by several studies showing that the *C9*-RE carriers have reduced levels of the gene transcripts in brain tissue, lymphoblasts, and fibroblasts (DeJesus-Hernandez et al., 2011; Gijselinck et al., 2012). Also, the C9orf72 protein levels are decreased in the frontal cortex and cerebellum in patients with FTLD spectrum disorder (Waite et al., 2014). As the normal function of *C9orf72* has been associated to regulation of e.g. endosomal transport (Farg et al., 2014) and autophagy (Sellier et al., 2016; Ugolino et al., 2016; Webster et al., 2016; Yang et al., 2016), it is possible that the haploinsufficiency leads to impaired protein trafficking and degradation or other cellular functions. However, knock-out of the *C9orf72* gene in murine models does not lead to neurodegeneration (Koppers et al., 2015), suggesting that the haploinsufficiency alone is not enough to cause the disease. On the other hand, loss-of-function of the *C9orf72* in murine models causes a systemic immunodysregulatory state (Atanasio et al., 2016; Burberry et al., 2016) and impairs microglial function (O'Rourke et al., 2016), all of which could possibly contribute to the disease pathophysiology. Additionally, it has been suggested that the *C9*-RE leads to up-regulated methylation and subsequent down-regulation of the *C9orf72* gene that is not observed in the gene without the expansion (Belzil et al., 2013). Therefore, epigenetic changes caused by the *C9*-RE could also possibly result in reduced normal function of *C9orf72*.

Second, gain-of-toxic-function mechanisms resulting from the *C9*-RE are hypothesized to cause FTLD. The expanded GGGGCC repeats have been suggested to cause RNA-mediated toxicity by formation and aggregation of abnormal RNA foci in the nuclei that sequester and consequently inhibit the normal function of several RNA-binding proteins (Donnelly et al., 2013; Mori et al., 2013a; Xu et al., 2013). Similar pathophysiology ultimately leading to altered RNA metabolism also occurs in other repeat expansion disorders, such as myotonic dystrophy (Mohan et al., 2014).

The third suggested mechanism by which the *C9*-RE causes FTLD is also based on the gain-of-function hypothesis. Neuronal accumulation of five different dipeptide repeat (DPR) proteins from the GGGGCC repeat transcripts has been observed in several studies. The three DPR proteins synthesized from the sense strand are named poly(GR), poly(GA), and poly(GP). In addition, poly(GP) and two other DPR proteins, poly(PR) and poly(PA), are generated from the antisense strand (Ash et al., 2013; Mori et al., 2013b; Zu et al., 2013). So far it is unclear, what kind of role these DPR proteins have in the FTLD pathogenesis, and whether some of them are more toxic than others. However, at least the poly(GR) and poly(PR) have been suggested to be highly toxic, as they have been associated at least with nucleolar dysfunction, altered splicing, impaired nucleocytoplasmic transport, and impaired proteasome function (Freibaum and Taylor, 2017).

In conclusion, all the suggested mechanisms may result in excess protein accumulation, ultimately leading to cell death in the *C9*-RE carriers. This could be further exacerbated by the decreased normal function of the *C9orf72* gene via impaired protein trafficking and/or degradation as a consequence of haploinsufficiency.

2.1.3.2 Other genetic etiologies for FTLD

Besides the *C9*-RE, mutations at least in 11 other genes have been acknowledged to be causal for FTLD. Out of these, mutations in *MAPT* and *GRN* genes explain a great majority.

Mutations in microtubule-associated protein tau (*MAPT*) gene were the first genetic discoveries underlying familial FTLD. The frequency of the *MAPT* mutations varies tremendously (from 0% to 50%) in studies reported from different populations (Sieben et al., 2012). In Finland, mutations in *MAPT* are extremely rare (Kaivorinne et al., 2008). Currently, more than fifty mutations in the *MAPT* gene have been identified in patients with familial FTLD (Ghetti et al., 2015). The *MAPT* gene encodes the tau protein, and *MAPT* mutations lead to hyperphosphorylation of the protein, impairing the binding of tau to tubulin. This results in destabilization of the microtubules and subsequently disturbed neuronal plasticity and axonal transport. *MAPT* mutations also lead to formation of neurotoxic tau-aggregates to neurons and glial cells, resulting histopathologically in FTLD-tau pathology (Figure 7b) (Ghetti et al., 2015).

Mutations in *GRN* gene were found after the discovery of *MAPT* mutations. Chromosomal location of *GRN* is 17q21 similarly to *MAPT*. *GRN* mutations were

found in families suffering from FTLD with autosomal heritance pattern linked to the 17q21 region, but without any detectable mutations in the *MAPT* gene (Baker et al., 2006; Cruts et al., 2006; Gass et al., 2006). The reported frequency of the *GRN* mutations in FTLD cohorts ranges from 3% to 26% (Sieben et al., 2012). Like *MAPT* mutations, also *GRN* mutations are extremely rare in Finland (Krüger et al., 2009).
The *GRN* gene encodes a protein named progranulin. Progranulin has wide-ranging functions in the cell and it has been shown to promote neurite extension, neuronal cell survival and differentiation, and to reduce inflammation (Chitramuthu et al., 2017; Petkau and Leavitt, 2014). So far, more than 70 mutations in the *GRN* gene have been found to cause FTLD (Fenoglio et al., 2018). Mutations that cause FTLD lead to *GRN* loss-of-function in the variant allele, further leading to progranulin deficiency (haploinsufficiency) (Petkau and Leavitt, 2014; Yu et al., 2010). Progranulin deficiency has been associated at least with increased neuroinflammation, increased peripheral inflammation and impaired tissue damage control (Chitramuthu et al., 2017). Besides FTLD, genetic variation in *GRN* is associated with elevated risk for AD, Parkinson´s Disease (PD) and ALS (Chitramuthu et al., 2017). Like the *C9*-RE, also *GRN* mutations histopathologically lead to FTLD-TDP neuropathology (Figure 7a) (Cairns et al., 2007; Snowden et al., 2015).

Other rare mutations found to cause FTLD or FTLD-ALS are located in *CHMP2B*, *VCP-1*, *SQSTM1*, *CHCHD10*, *TBK1*, *TARDBP*, *FUS*, *UBQLN2* and *TUBA4A* genes. The function of the proteins encoded by these genes include regulation of autophagy, protein trafficking and degradation (*CHMP2B, VCP-1, TBK1, SQSTM1, UBQLN2*), cytoskeletal dynamics (*TUBA4A*), mitochondrial functions (*CHCHD10*), and gene expression and transcription (*TARDPB* and *FUS*) (Fenoglio et al., 2018).

2.1.4 Neuropathology

Brain atrophy caused by FTLD is heterogeneous, but it is detected predominantly in frontal, insular, and anterior temporal areas (Pan et al., 2012; Schroeter et al., 2007). In PPAs, the atrophy is mainly asymmetric and left-sided in the temporal areas (Rohrer et al., 2009b).

FTLD comprises several neuropathological entities, and the current neuropathological classification is based on the main proteins found in the inclusions. The major classification categories are based on the presence of tau pathology: 1.) Tau-inclusion-negative (tau-negative) FTLD and 2.) Tau-inclusion-positive (tau-positive) FTLD. The tau-negative neuropathologies are immunoreactive for a regulatory protein called ubiquitin (ubiquitin-positive FTLD). These tau-negative, ubiquitin-positive neuropathologies are further divided based on whether they express abnormal 1a.) TDP-43 (FTLD-TDP) or 1b.) FUS (FTLD-FUS) inclusions. Another tau-negative ubiquitin-positive neuropathology is named as 1c.) FTLD-UPS characterized by ubiquitin-positive but TDP-43- and FUS-negative immunoreactivity (MacKenzie et al., 2010). The FTLD-FUS subtype (1b) has also been

named as FTLD-FET, since besides the FUS protein, also Ewing´s sarcoma protein (EWS) and TATA-binding protein-associated factor 15 (TAF15) inclusions from the same FET-protein family were found in the immunostaining (Mackenzie and Neumann, 2016; Neumann et al., 2011).

1a.) In 2006, FTLD-TDP neuropathology was found to account for most of the tau-negative ubiquitin-positive FTLD and also ALS cases (Arai et al., 2006; Neumann et al., 2006). The TDP-43 protein itself is a DNA/RNA-binding protein with wide ranging functions all related to RNA processing (Buratti and Baralle, 2010). In the FTLD-TDP neuropathology, TDP-43 is abnormally hyperphosphorylated and ubiquitinated leading to ubiquitin-positive inclusions (Neumann et al., 2006). FTLD-TDP neuropathology can be further divided into four pathological subtypes (Types A,B,C and D), based on the morphology and distribution of the TDP-43-containing inclusions (Mackenzie et al., 2011). Even though these neuropathological subtypes overlap, they have correlations with the clinical and genetic FTLD subtypes. The Type A is characterized by numerous neuronal cytoplasmic inclusions and short dystrophic neurites, both predominantly seen in cortical layer 2. It is genetically associated with *GRN* mutations, and clinically with nfvPPA and bvFTD phenotypes. The Type B is characterized by moderate amount of neuronal cytoplasmic inclusions, only few dystrophic neurites, and it is detected in all of the cortical layers (neuronal cytoplasmic inclusions also in lower motor neurons). It is genetically associated with the *C9*-RE, and clinically associated with bvFTD and especially FTLD-MND. The Type C is characterized by many long dystrophic neurites and only a few neuronal cytoplasmic inclusions, predominantly in cortical layer 2. This type is the most common neuropathology in patients with svPPA. The type D is detected in all cortical layers and it is characterized by many short dystrophic neurites, many lentiform neuronal intranuclear inclusions and only a few neuronal cytoplasmic inclusions. This neuropathological subtype is caused by the *VCP-1* mutations (Mackenzie et al., 2011; Mackenzie and Neumann, 2016).

1b.) FTLD-FUS (FTLD-FET) subtype accounts for most of the tau-negative, ubiquitinated, TDP-43 negative neuropathological subtypes of FTLD (Mackenzie et al., 2008). It is characterized by global dysregulation of three proteins from the FET-protein family: FUS, EWS and TAF15 (Neumann et al., 2011). Notably, this particular subtype including all of the FET proteins is not typically associated with *FUS* mutations, that lead more specifically only to FUS inclusions and clinically usually to ALS (Kwiatkowski et al., 2009; Snowden et al., 2011). The FTLD-FUS neuropathology is usually found in young-onset sporadic bvFTD patients (Hartikainen et al., 2012; Seelaar et al., 2010; Snowden et al., 2011; Urwin et al., 2010). The pathophysiology behind the FET protein inclusions has been suggested to occur as a result from defective arginine methylation of the FET-proteins (Dormann et al., 2012).

1c.) FTLD-UPS pathology is characterized by ubiquitin-positive, but tau-, FUS- and TDP-43-negative inclusions, and it is most often detected in FTLD patients carrying the *CHMP2B* mutation (Holm et al., 2009, 2007). It is possible, that also this

pathological subtype includes some specific characteristic protein inclusions, but thus far such proteins have not yet been identified.

The tau-negative, ubiquitin-positive FTLD (1a-1c), and its associations to the genetic and clinical subtypes of FTLD is described in Figure 7a.

2.) The tau protein, encoded by the *MAPT* gene, is an essential protein for microtubule assembly and it assists in cell stabilization and structure (Weingarten et al., 1975). Tau accumulation occurring during neurodegenerative disease pathogenesis is characterized by hyperphosphorylated tau inclusions, out of which the inclusions can further be divided into 3R tau and 4R tau subtypes based on the tau isoforms (Lee et al., 2001; Mandelkow and Mandelkow, 2011). In further pathological subclassification, FTLD-tau group consists of FTLD with *MAPT* mutations (3R or 4R depending on the mutation), Pick`s Disease (3R, "Pick bodies" tauopathy), CBD (4R), PSP (4R), multiple system tauopathy with dementia (MSTD) (4R), white matter tauopathy with globular glial inclusions (WMT-GGI) (4R), and argyrophilic grain disease (4R). These classifications indicate characteristics of the pattern of the pathology, rather than clinical presentations (Ghetti et al., 2015; MacKenzie et al., 2010; Mackenzie and Neumann, 2016). Further, these classifications highlight that the Pick`s Disease is currently considered only as a one neuropathological (tau positive) subtype of FTLD, accounting for approximately 30% of the tau-positive FTLD (Josephs et al., 2011). Notably, hyperphosphorylated tau pathology is not FTLD-specific, since it occurs also in AD (Grundke-Iqbal et al., 1987). FTLD-tau pathology is detected approximately in 40-50% of the FTLD cases as the main neuropathology (Forman et al., 2006; Josephs et al., 2011, 2006; Kertesz et al., 2005; Snowden et al., 2007). Tau-positive FTLD, and its associations to the genetic and clinical subtypes of FTLD is described in Figure 7b.

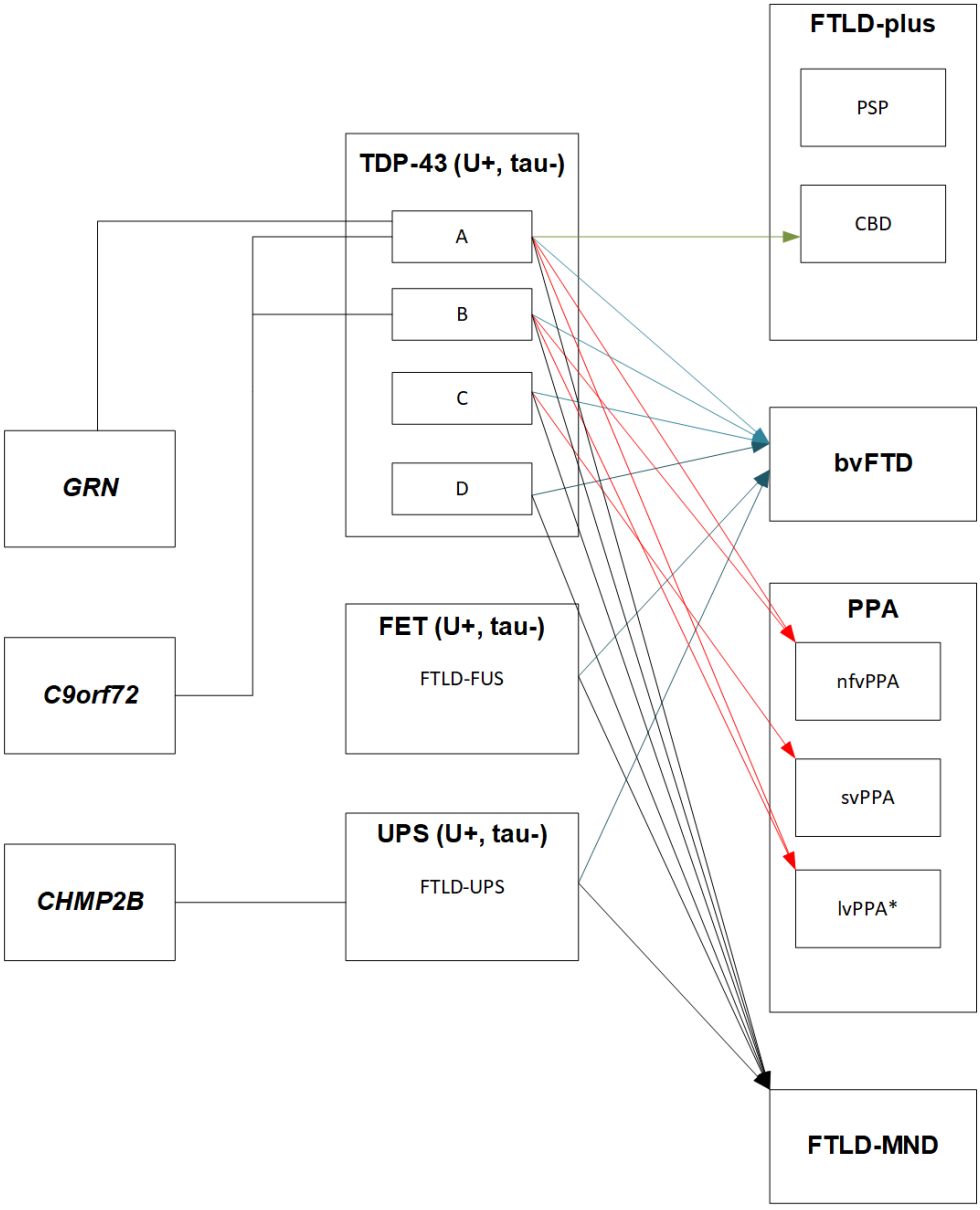


Figure 7a. Tau-negative (tau-), ubiquitin-positive (U+) neuropathological types of FTLD (in the middle), with the most commonly associated genes (on the left) and clinical subtypes (on the right). * = lvPPA is usually associated with AD pathology, but also TDP-43 is found in some cases. Arrow colors represent different clinical subtypes: green for FTLD-plus, blue for bvFTD, red for PPAs and black for FTLD-MND. FTLD = frontotemporal lobar degeneration, PSP = progressive supranuclear palsy, CBD = corticobasal degeneration, TDP-43 = TAR-DNA binding protein of 43 kDa, bvFTD = behavioral variant frontotemporal dementia, PPA = primary progressive aphasia, nfvPPA = non-fluent variant of primary progressive aphasia, svPPA = semantic variant of primary progressive aphasia, lvPPA = logopenic variant of primary progressive aphasia, FTLD-MND = frontotemporal lobar degeneration with motoneuron disease.

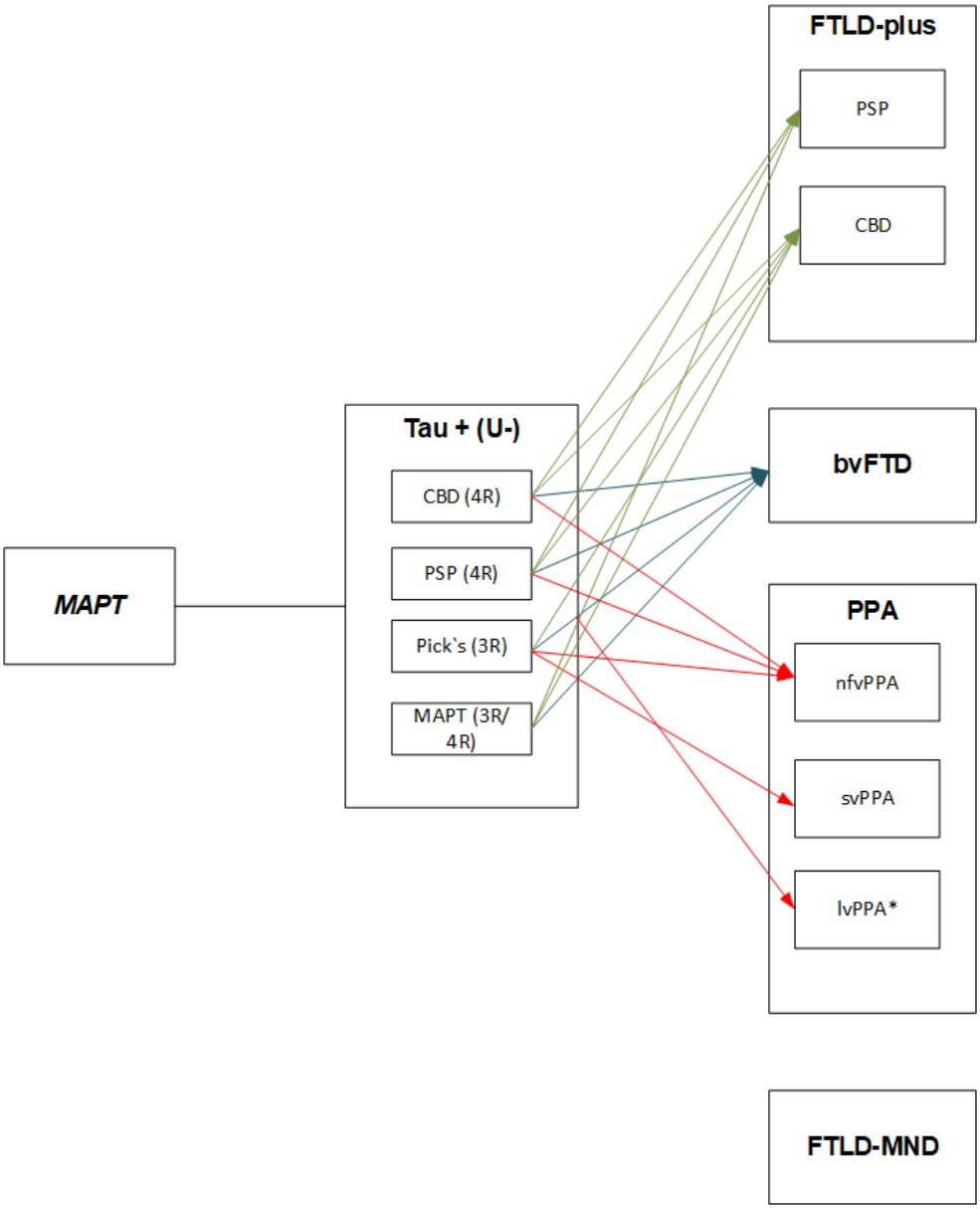


Figure 7b. Tau-positive (tau+), ubiquitin-negative (U-) neuropathological subtypes of FTLD (in the middle), with the most commonly associated gene(s) (on the left) and clinical subtypes (on the right). * = lvPPA is usually associated with AD pathology, but also unclassified tau pathology has been reported. Arrow colors represent different clinical subtypes: green for FTLD-plus, blue for bvFTD and red for PPAs. FTLD = frontotemporal lobar degeneration, PSP = progressive supranuclear palsy, CBD = corticobasal degeneration, bvFTD = behavioral variant frontotemporal dementia, PPA = primary progressive aphasia, nfvPPA = non-fluent variant of primary progressive aphasia, svPPA = semantic variant of primary progressive aphasia, lvPPA = logopenic variant of primary progressive aphasia, FTLD-MND = frontotemporal lobar degeneration with motoneuron disease.

2.2 INFLAMMATION IN FRONTOTEMPORAL LOBAR DEGENERATION

2.2.1 Neurodegeneration and inflammation

Over the past couple of decades, awareness and knowledge about the role of immunological factors in several neurodegenerative diseases has increased substantially. In general, it has been suggested that formation of misfolded protein aggregates (common characteristic feature in various neurodegenerative diseases) leads to immune system activation and neuroinflammation. Even though this process is beneficial for the brain homeostasis, chronic activation of the pro-inflammatory responses eventually become harmful (Becher et al., 2017; Molteni and Rossetti, 2017).

Immune system functions can be subclassified into innate and adaptive immune responses. The innate immunity in the CNS comprises mainly microglial, astrocyte and mast cell function. The adaptive immunity, instead, consists of immune responses caused by T - and B-lymphocytes and their subtypes (Amor and Woodroofe, 2014). Innate immune response by microglia/astrocytes is the first to respond to practically any pathological stimulus. This immunological response includes phagocytosis of any unnecessary or harmful molecules and a release of several cytokines or other signaling molecules that recruit other cells and/or promote tissue repair (Cordiglieri and Farina, 2010; González-Scarano and Baltuch, 1999). Under normal conditions, this innate immune response eventually shuts down, when anti-inflammatory pathways overcome the pro-inflammatory stimuli (Ayala et al., 2003; Barton, 2008). Adaptive immunity is more complex and target-specific part of the immune system. B- and T-cells use antigen receptors to detect specific pathogens/tumors, or in some unfavorable autoimmune conditions, organism`s own tissue antigens (Bonilla and Oettgen, 2010). Notably, adaptive and innate immunity often co-operate with each other via activating/inhibiting signaling pathways (Amor and Woodroofe, 2014; Lynch, 2014). In addition to the division between innate and adaptive immunity, also systemic and neuroinflammation should be considered separately, since both may occur in neurodegenerative diseases and contribute to the disease pathogenesis. The division between systemic and neuroinflammation is based on the blood brain barrier (BBB) that regulates the immune system communication between the CNS and systemic circulation (Erickson et al., 2012). However, even in healthy normal stages, the BBB does not completely separate the CNS from the systemic immune responses (Pavlov and Tracey, 2017; Talbot et al., 2016). For example, peripheral cytokines are able to transport to CNS through the BBB and thus modulate CNS functions (Banks, 2005). Furthermore, several studies have shown that lymphatic pathways from the CNS to peripheral immune system enable representation of CNS antigens to peripheral lymph nodes and thus systemic immune responses (Forrester et al., 2018; Harris et al., 2014).

2.2.2 Systemic inflammatory diseases in FTLD

So far, only three small studies evaluating the comorbid association of FTLD and immunological diseases have been published (Miller et al., 2016, 2013; Woollacott et al., 2017). The first two studies by Miller et al, of which the latter is a continuum of the previous, had a special emphasis on FTLD with TDP-43 pathology. The aim was to gather a cohort of patients with high-likelihood of TDP-43 neuropathology, i.e. FTLD patients with *GRN* mutations, asymptomatic *GRN* mutation carriers, FTLD patients with the *C9*-RE, FTLD patients with svPPA, and FTLD patients with motoneuron disease. The reason for this selection was that both *GRN* mutation and *C9*-RE carriers are mostly associated with TDP-43 neuropathology. Additionally, clinical phenotypes FTLD-MND and svPPA have been associated with TDP-43 neuropathology. It should however be noted that these assumptions are not implicit, as for example some svPPA patients present with tau-pathology (Sieben et al., 2012). The results of these two studies led to a conclusion that patients with high-likelihood TDP-43 neuropathology have an increased prevalence of non-thyroid autoimmune diseases when compared to AD control group, patients with PSP and cognitively healthy control group. Out of autoimmune diseases, specifically increased prevalences of inflammatory arthritis, cutaneous conditions and gastrointestinal disorders were highlighted. Regarding the FTLD clinical subtypes, patients with FTLD-MND had more comorbid autoimmune diseases regardless of whether they carried the *C9*-RE or not, whereas bvFTD patients carrying the *C9*-RE had a rather low prevalence of autoimmune diseases (Miller et al., 2016, 2013). A small study conducted in UK by Woollacott and colleagues found that out of genetic FTLD groups, especially the *GRN* mutation carriers had a tendency for high prevalence of non-thyroid autoimmune diseases, whereas patients with the *C9*-RE had no significant differences compared to controls (Woollacott et al. 2017). Interestingly, a rather high prevalence of intermediate *C9*-REs was recently found in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (Fredi et al., 2019). These patients did not express symptoms related to the FTLD/MND spectrum, although it is impossible to predict if neurological symptoms will eventually develop. The intermediate *C9*-REs have also been associated with multiple sclerosis (CNS autoimmune disorder) (Tiloca et al., 2018).

2.2.3 FTLD genetics and inflammation

Genetic evidence suggests an association of FTLD with the immune system. A genome-wide association study (GWAS) by Ferrari and colleagues showed that FTLD is linked to immune system processes via significant association at the 6p21.3 HLA locus. This HLA-DRA/DRB5 region is responsible especially for adaptive immunity (Ferrari, et al., 2014). A more recent GWAS linked FTLD-TDP to another HLA region (HLA-DQA2) (Pottier et al., 2019). Moreover, the association between

FTLD and HLA region was shown in another study indicating significant genetic overlap (especially in the HLA region) between FTLD and several autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease (IBD), celiac disease, type 1 diabetes, and psoriasis (Broce et al., 2018).

The *C9orf72* gene was first associated to immunoregulation in studies with knock-out of the *C9orf72* gene ortholog in murine models (Atanasio et al., 2016; Burberry et al., 2016; O'Rourke et al., 2016). These studies systematically showed that *C9orf72* knock-out causes autoimmune disease in mice characterized by splenomegaly, increased levels of inflammatory cytokines and autoantibodies, and increased mortality. Notably, the inflammatory profile was substantially more evident in homozygous (-/-) knock-out mice compared to heterozygous (+/-) mice. For example, the heterozygous mice did not show increased mortality or clear autoimmune phenotype despite the fact that they showed evidence of intermediate autoantibody activity and altered levels of some cytokines (Atanasio et al., 2016; Burberry et al., 2016; O'Rourke et al., 2016). Another recent study provided further evidence for the role of the *C9*-RE in the immunoregulation by showing that knocking out the C9orf72 stabilizer protein SMCR8 in mice leads to similar autoimmune phenotypes compared to the *C9orf72* gene knock-out (Zhang et al., 2018). Additionally, the C9orf72 knock-down in cells leads to changes in genes involved in the immune system activity and increased activity of the inflammatory mediator NF-kB (Fomin et al., 2018).

Also, progranulin-deficiency in mice (modelling FTLD caused by *GRN* mutations) has been shown to induce a pro-inflammatory state (Martens et al., 2012; Yin et al., 2010). Both C9orf72 and progranulin are highly expressed in cells of the myeloid lineage (Rizzu et al., 2016; Suh et al., 2012), and progranulin is known to attract and stimulate microglial cells (Pickford et al., 2011). Altogether, these similarities regarding inflammation and the *C9orf72* and *GRN*, two of the most common genes behind FTLD, highlight the possibility of inflammation-associated disease mechanisms.

2.2.4 Inflammatory biomarkers in FTLD

In neurodegenerative diseases, the most studied inflammatory markers in both CSF and plasma/serum are several cytokines that function as signaling inflammatory modulators and that are produced by different immune system cells. Cytokines can be divided based on their different roles in immune system responses; pro-inflammatory cytokines (such as IL-1, IL-6 and TNF-alpha) and chemo-attractive chemokines (such as IL-8, RANTES and MCP-1), and conversely anti-inflammatory cytokines (such as IL-10) (Turner et al., 2014). Current reviews have highlighted that a great heterogeneity/inconsistency exists between the findings of different studies analyzing cytokine levels in various neurodegenerative diseases (Hu et al., 2017; Lai et al., 2017; Qin et al., 2016). This may reflect the instability of the inflammatory markers, i.e. levels of different cytokines in the periphery or CSF likely have variance across different time points. One study with ALS patients supported this fact by showing that although inflammatory markers are not systematically elevated in blood, the gene expression phenotype in peripheral monocytes is skewed towards proinflammatory state (Zhao et al., 2017).

Up to date, only a couple of small studies have investigated peripheral inflammatory markers in FTLD patients. These studies have included only *GRN* mutation carriers or sporadic FTLD patients. IL-6 was first found to be elevated in FTLD patients with the *GRN* mutations (Bossù et al., 2011), and later also in sporadic FTLD (Gibbons et al., 2015). In addition, TNF-α levels were elevated in *GRN* mutation carriers and particularly in patients with svPPA (Miller et al., 2013). Another study evaluated 27 inflammatory molecules in sporadic and genetic (*GRN* mutations) FTLD patients and found no differences in the peripheral cytokine levels, including those of IL-6 and TNF-α, compared to controls (Galimberti et al., 2015b). Neither of these studies reported associations between cytokine levels and disease manifestations or progression (Bossù et al., 2011; Galimberti et al., 2015b; Gibbons et al., 2015; Miller et al., 2013). *CHMP2B* mutation carriers were found to have elevated levels of CCL4 compared to non-carriers, with the CCL4 levels apparently peaking at the time of disease onset (Roos et al., 2018). Also, elevated levels of Anti-AMPA GluA3 and antinuclear antibodies in sporadic FTLD patients have been reported, but there were no specific characteristic features (such as disease phenotype or progression) in those patients related to the increased concentrations of these antibodies (Borroni et al., 2017; Cavazzana et al., 2018).

Studies analyzing CSF markers in FTLD have showed increased intrathecal levels of some cytokines (MCP-1, IP-10, IL-15, TNF-α, TGF-β)(D. Galimberti et al., 2015b; Rentzos et al., 2006; Sjögren et al., 2004). Conversely, CSF levels of RANTES were decreased in both sporadic and *GRN* mutation-associated FTLD (Galimberti et al., 2015b). Additionally, higher CSF levels of pro-inflammatory IL-7 were recently shown to correlate with a more rapid disease progression in FTLD (Taipa et al., 2019). Altogether, these studies suggest that inflammation is likely to contribute to FTLD pathogenesis. Systemic/peripheral immune system alterations observed in FTLD are summarized in Table 1.

2.2.5 Inflammation in other neurodegenerative diseases

Although there are substantial differences in the pathogenetic mechanisms of different neurodegenerative diseases, such as FTLD, ALS, AD and PD, it is possible that overlapping immunological disturbances are involved in these disorders. Thus, knowledge from other neurodegenerative diseases might provide insights also for FTLD.

2.2.5.1 Amyotrophic lateral sclerosis

The innate immunity has been shown to be highly active in the motor cortex and corticospinal tract of ALS patients (Turner et al., 2004). In ALS-mouse models, chronic stimulation of the innate immunity exacerbates disease progression via increased activity of innate immunity related-receptors and pro-inflammatory cytokines in the degenerating regions of the spinal cord (Nguyen et al., 2004). Additionally, lymphocyte infiltrates and especially helper T-cells and cytotoxic T-cells are found in the spinal cord of ALS patients (Engelhardt et al., 1993). Both microglia, and T-cells likely interact closely, and at least to some extent are protective against neuronal degeneration in ALS (Chiu et al., 2008). In addition to the co-occurrence of innate and adaptive neuroinflammatory responses, also systemic inflammation seems to be increased in ALS patients. In a meta-analysis, levels of TNF-α, IL-6, IL-1β, IL-8 and vascular endothelial growth factor were increased in the peripheral blood of patients with ALS (Hu et al., 2017). Another recent study showed that although increased levels of inflammatory cytokines are not necessarily always detected, the gene expression profiles of the peripheral monocytes are highly pro-inflammatory-oriented (Zhao et al., 2017). Additionally, higher serum CRP levels have been associated with a more severe functional impairment in ALS patients (Lunetta et al., 2017). Systemic inflammation and especially autoimmunity in ALS has also been suggested in studies that have associated ALS with several immunological diseases, such as asthma, celiac disease, type 1 diabetes, myasthenia gravis, myxedema, multiple sclerosis, Sjögren´s syndrome, SLE, polymyositis, and ulcerative colitis (Turner et al., 2013).

Interestingly, ALS patients have been conversely associated with decreased prevalence of cancer (Gibson et al., 2016). Possible explanation for the inverse associations of cancer and neurodegeneration is proposed in a recent study, which found that transcriptomic alterations in cancer were opposite to those observed in neurodegenerative diseases and that, for example, some cancer risk alleles decreased the risk for neurodegenerative disease (Aramillo Irizar et al., 2018). Also, immune/inflammatory-associated processes were suppressed in cancer, whereas similar processes were induced in neurodegenerative diseases (Aramillo Irizar et al., 2018). Although persistent inflammation mainly increases the risk for several cancers (Schetter et al., 2009), the balance between immune system-mediated pro- and

antitumorigenic (immunosurveillance) responses is extremely complex, i.e. inflammatory responses have also significant antitumorigenic impacts (Zitvogel et al., 2006). In addition, the complex interaction between cancer, neurodegeneration, and inflammation is highlighted by the fact that whereas progranulin protein deficiency in FTLD with *GRN* mutations causes neurodegeneration and inflammation (Martens et al., 2012), increased levels of progranulin promote the development of brain cancers and at least ovarian, prostate, liver, kidney and breast carcinomas (Chitramuthu et al., 2017). These findings suggest that inflammatory pathways may exert opposite effects in FTLD and cancer. Systemic/peripheral immune system alterations observed in ALS are summarized in Table 1.

2.2.5.2 Alzheimer`s Disease

AD is the most common cause of dementia and episodic memory disturbances are the leading symptom in the early course of the disease (McKhann et al., 1984). AD pathophysiology is characterized by extracellular accumulation of amyloid-β (Aβ) plaques and intracellular deposition of neurofibrillary tangles, composed of tau protein (Hardy and Selkoe, 2002). Inflammation, alongside the Aβ- and tau-mediated mechanisms, has been strongly suggested (Akiyama et al., 2000) (Heppner et al., 2015).

Several studies have shown that pro-inflammatory cytokines in plasma/serum and CSF are elevated in AD, especially in the early stages, even though also controversial results have been reported (Brosseron et al., 2014). In AD, meta-analysis suggested for example elevated levels of peripheral IL-1β, IL-2, IL-6, IL-18, sTNF-R1, sTNF-R2, homocysteine, hs-CRP, IFN-γ and CXCL-10. Out of these, IL-6 was found to inversely correlate with mean MMSE scores (Lai et al., 2017). Although the meta-analysis by Lai et. al found no significant differences in peripheral MCP-1 levels (due to inconsistent findings), a recent study showed significant correlation between baseline plasma MCP-1 levels and MMSE decline in a two-year follow-up (Lee et al., 2018). Also increased peripheral pro-inflammatory TNF-α levels have been associated with a more rapid cognitive decline in AD (Holmes et al., 2009). The profile of the inflammatory status has been suggested to change as the disease progresses. Patients with prodromal AD or mild cognitive impairment preceding AD tend to display a prominent pro-inflammatory state, whereas patients in the later stages of the disease have decreased immunological activity in general, with a more anti-inflammatory immunological profile (Cribbs et al., 2012; King et al., 2018; Motta et al., 2007). A recent study indicated that after Aβ accumulation, activated microglia directly promote tau accumulation that further triggers the cognitive decline (Felsky et al., 2019), indicating an early role of inflammation in the disease pathogenesis.

The recent large GWASs have associated AD with genes responsible for immune system function and inflammation (Bis et al., 2018; Kunkle et al., 2019). For example, genetic studies have linked significant AD risk with rare mutations in the gene encoding TREM2, a protein highly associated with immunoregulation and expressed

in microglia and myeloid cells (Jonsson et al., 2013; Sims et al., 2017). Additionally, several genetic studies and further molecular studies have associated increased AD risk to altered monocyte function due to abnormal expression of CD33, a glycoprotein expressed on the surface of myeloid progenitor cells, mature monocytes and macrophages (Bradshaw et al., 2013; Naj et al., 2011). Later, it was specified that dysregulated CD33 protein directly impairs Aβ clearance in cultured microglial cells (Griciuc et al., 2013). Besides *TREM2* and *CD33*, mutations in several other innate immunity-related genes, such as complement receptor 1, myeloid cell-expressed membrane-spanning 4-domains subfamily A member 6A and putative membrane-spanning 4-domains subfamily A member 4E have all been associated with AD (Hollingworth et al., 2011; Lambert et al., 2009).

Altogether, the evidence for the inflammation associated with AD pathogenesis highly suggests innate immunity (including microglia and astrocytes) as a central contributor to the disease progression (Heneka et al., 2014; Heppner et al., 2015; Prokop et al., 2013). However, recent studies have focused more attention also to the adaptive immunity, and found for example interactions between B-cells and microglia in the AD-pathogenesis (Marsh et al., 2016), and increased T-cell reactivity to Aβ (Monsonego et al., 2003). Additional support was provided by a study that showed increased risk for AD in patients with autoimmune diseases, such as Addison´s Disease, psoriasis and pemphigoid (Wotton and Goldacre, 2017). In addition to the epidemiological association between AD and autoimmune blistering skin disease bullous pemphigoid (BP) (Försti et al., 2016), direct immunological association indicated by high prevalence of BP-specific autoantibodies in AD patients has been reported (Kokkonen et al., 2016). BP pathophysiology is characterized especially by BP180 IgG autoantibodies targeting the BP180 (transmembrane protein also known as collagen XVII) in the cutaneous basement membrane (Nishie, 2014). Also BP230 (also known as dystonin-e protein) is targeted by separate BP230 autoantibodies (Schmidt and Zillikens, 2013). Both BP180 and BP230 proteins are important for the cutaneous basement membrane integrity. In BP, specific BP180- and BP230-autoantibodies target these proteins resulting in the BP skin manifestation. The fact that both BP180 and BP230 are expressed not only in the cutaneous tissue, but also in the CNS, has led to a hypothesis that the epidemiological and immunological association between BP and neurodegeneration occurs due to cross-reactive immune response between the CNS and cutaneous tissue (Seppänen, 2013).

Like ALS, also AD has been inversely associated with cancer. For example, patients with AD have a decreased risk for cancer and, on the other hand, patients with the history of cancer have decreased risk for developing AD (Driver et al., 2012; Musicco et al., 2013; Roe et al., 2010, 2005). Although it has been proposed that the epidemiological inverse associations occur due to several biases caused by for example selective mortality/survival bias (Aiello Bowles et al., 2017), the inverse associations have been systematically detected in several subgroup analyses and they have persisted after at least some of those biases have been taken into account in

stratified statistical analyses (Driver et al., 2012; Musicco et al., 2013). Furthermore, in autopsy reports, neoplasms have been reported to be a rather rare cause of death in patients with dementia compared to general population, indicating that the hypothesized lack of cancer diagnoses in patients with dementia does not explain the inverse associations (Brunnström and Englund, 2009). Systemic/peripheral immune system alterations observed in AD are summarized in Table 1.

2.2.5.3 Parkinson`s Disease

PD is a neurodegenerative disease that is neuropathologically characterized by α-synuclein protein aggregates and loss of dopaminergic neurons in the substantia nigra pars compacta (Kalia and Lang, 2015). Inflammation in PD has been suggested to have both beneficial and harmful effects. Innate immunity, similarly to AD, is associated with PD. To mediate neuroprotective effects of the innate immunity system, activated microglial cells have been shown to release trophic factors, such as brain-derived neurotrophic factor and glial cell-derived neurotrophic factor, after mechanical injury (Batchelor et al., 2002). Release of these trophic factors has been shown to be protective and essential for the survival of neurons in the nigrostriatal dopaminergic system (Kirschner et al., 1996; Smith and Cass, 2007; Tomac et al., 1995). In contrast, several studies have also shown that overactive microglial cells mediate neuroinflammation in PD. Activated microglia produce excess amounts of neurotoxic compounds, like reactive nitrogen species and pro-inflammatory prostaglandins and cytokines (Przedborski, 2007). Several pro-inflammatory cytokines are elevated in the serum (Dobbs et al., 1999; Rentzos et al., 2007; Stypuła et al., 1996), CSF (Mogi et al., 1994), and substantia nigra (Mogi et al., 2000) of PD patients. In PD, the most highlighted peripheral cytokines in a meta-analysis were IL-6, tumor necrosis factors, IL-1β, IL-2, IL-10, CRP, and RANTES (Qin et al., 2016). Increased peripheral RANTES levels also correlate with disease severity in PD (Rentzos et al., 2007; Tang et al., 2014).

Increased levels of inflammatory mediators, such as COX-2 and iNOS enzymes, have also been detected in the substantia nigra in patients with PD (Knott et al., 2000). Moreover, inactivation of COX-2 ameliorates dopaminergic neuron degeneration in PD animal models (Teismann and Ferger, 2001). Several mechanisms could explain the excessive microglial activity in PD. For example, decreased glucocorticoid receptor (GR) activity in microglial cells was detected in substantia nigra of PD patients, and the decreased GR levels were associated with dysregulated inflammatory response of the microglia, potentially promoting dopaminergic neuron loss (Ros-Bernal et al., 2011). Additional factors inducing microglial activity in PD brain, and perhaps also in other neurodegenerative diseases, are for example several inflammatory cytokines, α-synuclein aggregates, ATP released from damaged neurons, and neuromelanin released from dying dopaminergic neurons (Long-Smith et al., 2009). Notably, also Aβ aggregates in AD can similarly trigger microglial activation, and therefore microglial overactivity may occur in both AD and PD (Akiyama et al., 2000; Kitazawa et al., 2004).

Plausible role of adaptive immunity in PD pathogenesis has also been implicated. CD4+ T-lymphocytes have been suggested to play a major role in the progression of dopaminergic neuron death and PD. Both CD4+ and CD8+ T-lymphocytes were shown to infiltrate to substantia nigra of patients with PD, and mouse models specifically lacking CD4+ cells were resistant to induced dopaminergic cell death (Brochard et al., 2009). Interestingly, another study showed that adoptive transfer of CD3-activated T-regulatory cells into PD mouse models provided over 90% protection of the nigrostriatal system (Reynolds et al., 2007). Thus, additionally to innate immunity, adaptive immunity and especially T-lymphocytes might play a crucial role in PD. However, autoimmune diseases associated with inflammation did not increase the risk for developing PD in one study (Rugbjerg et al., 2009). On the other hand, higher incidence of PD was observed in a recent large retrospective cohort study with IBD (Inflammatory bowel disease) (Crohn`s disease and ulcerative colitis) patients. Moreover, early exposure to anti-TNF treatment in patients with IBD was shown to substantially decrease the risk for developing PD (Peter et al., 2018). As for cancer, a meta-analysis concluded that patients with PD have decreased risk for cancer (Bajaj et al., 2010), even though these findings have been challenged by some studies suggesting that such an inverse association occurs due to diagnostic biases (Freedman et al., 2016). Systemic/peripheral immune system alterations observed in PD are summarized in Table 1.

Table 1. Summary of the immunological findings regarding systemic inflammation in FTLD and other neurodegenerative diseases

Disease group	Genetic associations with immune system	Comorbid immunological / autoimmune diseases	Peripheral biomarkers for inflammation	Peripheral biomarkers indicating autoimmunity
FTLD	Associations with HLA regions (Ferrari 2014, Pottier 2019). Also *C9orf72* and *GRN* genes associated with immunoregulation (Burberry 2016, Martens 2012)	Especially cutaneous, rheumatoid and gastrointestinal autoimmune conditions (Miller 2013)	Suggestions for elevated IL-6 and TNF-α in *GRN* mutation-associated disease (Miller 2013, Gibbons 2015)	Increased prevalence of elevated Anti-AMPA GluA3 and antinuclear antibodies in blood (Borroni 2017, Cavazzana 2018)
ALS	*C9orf72* and *TBK1* genes associated with immunoregulation (Burberry 2016, Oakes 2017)	Especially cutaneous, connective tissue and gastrointestinal conditions (Turner 2013)	Elevated TNF-α, IL-6, IL-1β, IL-8 and hs-CRP (Hu 2017, Lunetta 2017)	Altered T-cell profile in blood (Mantovani 2009)
AD	Associations with HLA regions (Kunkle 2019, Bis 2018) and TREM2 (Jonsson 2013)	Addison`s disease, psoriasis, pemphigoid diseases (Wotton and Goldacre 2017, Försti 2016)	Elevated IL-1β, IL-2, IL-6, IL-18, TNFs, hs-CRP and IFN-γ (Lai 2017)	BP autoantibodies (Kokkonen 2017) and several T-cell population alterations in blood (Sommer 2017)
PD	Associations with several HLA regions (Kannarkat 2013)	IBD patients have increased risk for PD and the risk is reduced with anti-TNF treatment (Peter 2018)	Elevated IL-6, TNFs, IL-1β, IL-2, IL-10, hs-CRP and RANTES (Qin 2016)	T-cell and B-cell population alterations in blood (Sommer 2017) (Stevens 2012)

FTLD = frontotemporal lobar degeneration, ALS = amyotrophic lateral sclerosis, AD = Alzheimer´s disease, PD = Parkinson`s disease, HLA = human leukocyte antigen, TREM2 = triggering receptor expressed on myeloid cells 2, IBD = inflammatory bowel disease, TNF = tumour necrosis factor, IL = interleukine, hs-CRP = high sensitive C-reactive protein, BP = bullous pemphigoid.

3 AIMS OF THE STUDY

The aim of this thesis was to evaluate the altered immune system function and possible systemic inflammation in patients with FTLD in general, and specifically in the *C9*-RE-associated FTLD. These alterations were evaluated by screening several immune system-associated comorbidities (immunological diseases and cancers), and by analyzing several peripheral inflammatory markers in patients with FTLD carrying or not the *C9*-RE.

The specific aims were:

1. To evaluate the prevalence of cancer in FTLD patients with and without the *C9*-RE (I).

2. To evaluate the prevalence of autoimmune and other immunological diseases in FTLD patients with and without the *C9*-RE (II).

3. To analyze the epidemiological association between FTLD and autoimmune skin disease bullous pemphigoid (BP), and the frequency of elevated BP-autoantibody (BP180 and BP230) levels in FTLD (III).

4. To examine the levels of several peripheral inflammatory markers in FTLD patients by comparing the *C9*-RE carriers and non-carriers (IV).

5. To evaluate the associations between the levels of peripheral inflammatory markers and distinct FTLD-related clinical manifestations and disease progression (IV).

4 SUBJECTS AND METHODS

4.1 ETHICAL CONSIDERATIONS

All studies (I-IV) were conducted according to the principles of the Declaration of Helsinki. The study protocol of studies I-IV were approved by the research ethical committees of Northern Ostrobothnia Hospital District and/or Northern Savo Hospital District. All participants and/or their legal representative signed written informed consent before the participant was included into the study. Before any consideration of possible genetic testing (*C9*-RE), patients received genetic counselling and testing was conducted only after genetic counselling and patient approval.

4.2 STUDY POPULATIONS

4.2.1 FTLD cohort (I-IV)

The patients with FTLD were collected during the years 1997-2016 from the memory outpatient clinics of Kuopio University Hospital and Oulu University Hospital. Patients were diagnosed by neurologists specialized in memory diseases. Diagnosis was based on neurological and neuropsychological examination, brain imaging (MRI, further combined with PET, if necessary) and genetic testing (the *C9*-RE), if patient was agreeable after genetic counselling. To be included in the study, all FTLD patients must have had fulfilled the criteria for at least probable bvFTD, nfvPPA or svPPA according to the latest diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Patients who were diagnosed before the publication of the most recent criteria (2011), were first diagnosed according to the criteria of Neary et al., (1998), and retrospectively confirmed to fulfil similarly at least probable diagnosis for the Rascovsky 2011 criteria. To be considered as FTLD-MND, patient must have had at least probable bvFTD, nfvPPA or svPPA and also a manifestation of clinically possible motoneuron disease (ALS) according to the revised El Escorial criteria (Brooks et al., 2000). Alongside with the classification to different clinical subtypes, FTLD patients were also divided based on whether they carried the *C9*-RE or not (FTLD *C9*-RE carriers and non-carriers). FTLD cohorts in studies I-IV are described in Tables 2-3.

4.2.2 AD cohort (I-II)

Patients with Alzheimer´s Disease (AD) were collected as a gender- and age-matched control group from Kuopio University Hospital and Oulu University Hospital

during the years 1999-2017. Patients with AD had at least probable AD diagnosis according to the McKhann criteria (McKhann et al., 1984). Diagnoses were based on neurological and neuropsychological examination, brain imaging, and CSF AD biomarkers (tau, phospho-tau and amyloid-β). AD patients in studies I-II are further described in Table 2.

4.2.3 Control subjects (I-III)

For studies I-III, a cohort of participants without any neurodegenerative disease was collected from three sources. For studies I-II, participants were recruited from the memory outpatient clinic of Kuopio University Hospital and they were confirmed to have only a subjective memory complaint, and no signs for any progressive neurodegenerative disease in follow-up. For study I, participants were also recruited among patients participating in knee replacement surgery at Kuopio University Hospital. Participants collected from the memory outpatient clinic underwent the same diagnostic procedures as the AD patients described in chapter 4.2.2, and the profile did not eventually indicate neurodegenerative disease. Participants recruited through the knee replacement surgery underwent CERAD or TELE tests to exclude cognitive impairment. In study III, the control group included patients from the knee replacement surgery group and additionally 20 healthy control subjects from the personnel of Clinical Research Center in Oulu. Control subjects without neurodegenerative diseases are further described in Table 2.

Table 2. General characteristics of the study participants in studies I-IV

Group	**Study** I	**Study** II	**Study** III	**Study** IV
FTLD (N)	**195**	**196**	**196**	**98**
Age, y, mean	68.0	67.9	67.9	64.7
Gender, % F	49.2 %	49.0 %	49.0 %	53.0 %
BvFTD, N, (%)	131 (67%)	132 (67%)	132 (67%)	71 (72%)
NfvPPA, N, (%)	37 (19%)	37 (19%)	37 (19%)	17 (17%)
SvPPA, N, (%)	8 (4%)	8 (4%)	8 (4%)	4 (4%)
FTLD-MND, N (%)	19 (10%)	19 (10%)	19 (10%)	6 (6%)
C9-RE+, N, (%)	55 (28%)	56 (29%)	56 (29%)	27 (28%)
Neuropathological subtype (confirmed) (N)	6	6	6	-
- TDP-43 (N)	5	5	5	-
- Tau (N)	1	1	1	-
AD (N)	**193**	**193**	**-**	**-**
Age, y, mean	68.0	68.0		
Gender, % F	49.7 %	49.7 %		
Controls (N)	**184**	**92**	**61**	**-**
Age, y, mean	68.4	67.7	60.2	
Gender, % F	52.2 %	54.3 %	62.3 %	

Characteristics of the FTLD cohort (including the proportions of clinical-, genetic- and neuropathological subtypes) and controls in studies I-IV. Compared to study I, the control group in study II did not include participants recruited from the orthopaedics department, due to the high prevalence of rheumatoid arthritis in patients receiving knee replacement surgery. In study III, serum BP autoantibody analyses were performed for 70 FTLD patients. FTLD = frontotemporal lobar degeneration, bvFTD = behavioural variant frontotemporal dementia, nfvPPA = non-fluent variant of primary progressive aphasia, svPPA = semantic variant of primary progressive aphasia, FTLD-MND = frontotemporal lobar degeneration with motoneuron disease, *C9*-RE = chromosome 9 open reading frame 72 repeat expansion, TDP-43 = TAR-DNA binding protein of 43 kDa, AD = Alzheimer`s disease.

4.3 CLINICAL REVIEW (I-IV)

For studies I-III, medical records of the entire FTLD cohort (N=196) were retrospectively screened for the presence of any types of malignant cancers (study I) or autoimmune disease (studies II-III). Category of autoimmune diseases was extended to encompass several other diseases that are not traditionally considered as an autoimmune disease, but have substantial disadvantageous immunological component in the disease pathogenesis (e.g. asthma). From thyroid diseases, hypothyroidism with unknown etiology was considered separately, and only confirmed autoimmune conditions were included in the immunological disease category. Also, the prevalence of asthma was considered separately. Similar medical record screening was performed on the age- and sex-matched AD group and control group without neurodegenerative diseases. The variable for the presence or absence of comorbid cancer or immunological disease was collected as dichotomous variable, and as a continuous variable as some of the participants had a history of more than one cancer/immunological disease.

For the study IV, clinical data for several clinical features and disease progression was collected to enable comparison between different clinical manifestations and inflammatory marker levels (Table 3). Data for presence or absence of parkinsonism, psychotic symptoms, motoneuron symptoms and primitive reflexes was collected as dichotomous variables. Patients were also compared based on whether the clinical profile was either more apathetic or disinhibited during the follow-up. FTLD with parkinsonism required at least two of the following symptoms: bradykinesia, postural instability, rigidity, tremor, prominent hypomimia, loss of automatic movements. FTLD with psychotic symptoms required that at least one evident visual/hearing hallucination and/or delusion was reported. FTLD with motoneuron disease required at least fulfilment of the criteria for possible motoneuron disease (ALS) according to the revised El Escorial criteria (Brooks et al., 2000). FTLD with primitive reflexes required at least one clear positive primitive sign. All of these clinical features were included if they were observed either at the disease onset or during the follow-up. The mean follow-up time was 33.8 months (range 3-123 months, median 24 months). The disease progression rate was longitudinally calculated with the mini-mental state examination (MMSE) and activities of daily living (ADCS-ADL) questionnaire, with the variable being the decline in points per months (higher score indicating more rapid decline). Data were calculated for participants with at least two MMSE / ADCS-ADL test results available (at different time points). Longitudinal data was available from 22 patients in ADCS-ADL scores and from 31 patients in MMSE scores. The mean follow-up period between the tests was 13.7 months (range 6-33 months) in ADCS-ADL and 22-6 months (range 3-78 months) in MMSE.

Table 3. Clinical characteristics of FTLD patients included in the study IV

	FTLD total N (%)[3]	**FTLD with *C9*-RE N (%)[3]**	**FTLD without *C9*-RE N (%)[3]**
Total number (N)	98[1]	27[1]	58[1]
CBA analysis (plasma)	50 (51%)	22 (81%)	28 (48%)
Simoa (sera)	91 (93%)	26 (96%)	52 (90%)
hs-CRP	44 (45%)	19 (70%)	24 (41%)
Gender (F/M, %)	53/47 %	52/48 %	57/43 %
Mean age[2] ± SD	64.7 ± 8.8	61.2 ± 9.3	66.2 ± 8.0
bvFTD (N)	71 (72%)	20 (74%)	39 (67%)
PPA (N)	21 (21%)	5 (19%)	15 (26%)
nfvPPA (N)	17 (17%)	5 (19%)	11 (19%)
svPPA (N)	4 (4%)	0 (0%)	4 (7%)
FTLD-MND (N)	6 (6%)	2 (7%)	4 (7%)
FTLD with Parkinsonism (N)[4]	23 (23%)	8 (30%)	13 (22%)
FTLD with Psychotic symptoms (N)[4]	34 (35%)	10 (37%)	18 (31%)

[1] = FTLD total group includes overall 13 patients without known *C9orf72* HRE status. [2] = Age is calculated from the date of the blood sample. [3] = Percentages are calculated from the total number of cases in each column. [4] = Out of the FTLD patients with parkinsonism (N=23), 17 patients had parkinsonism symptoms at the time of the blood sample and FTLD diagnosis and 6 patients developed parkinsonism after the blood sample and FTLD diagnosis. All of the patients with psychotic symptoms (N=34) had their first psychotic symptoms before the blood sample and FTLD diagnosis. CBA = cytometric bead array, Simoa = single molecule array, hs-CRP = high sensitive C-reactive protein, FTLD = frontotemporal lobar degeneration, bvFTD = behavioural variant frontotemporal dementia, nfvPPA = non-fluent variant of primary progressive aphasia, svPPA = semantic variant of primary progressive aphasia, FTLD-MND = frontotemporal lobar degeneration with motoneuron disease, *C9*-RE = chromosome 9 open reading frame 72 repeat expansion.

4.4 GENETIC ANALYSES (I-IV)

Presence of the *C9*-RE was analyzed from FTLD patients with repeat-primed polymerase chain reaction (RP-PCR) assay (Renton et al., 2011), and the RP-PCR results were further confirmed using Amplicon length analysis (van der Zee et al., 2013). In studies I-III, patients with repeats less than 20 were considered as *C9*-RE non-carriers, and patients with more than 20 repeats were considered as *C9*-RE carriers (also intermediate repeat expansion carriers (repeats from 20 to 30) included in the carrier group). In study IV, the main objective was to compare patients according to the *C9*-RE genotype and the lowest limit for the *C9*-RE carrier group was set to 30 repeats (there were four patients with 20-30 repeats), to ensure homogeneity in the carrier group. We did not systematically screen other FTLD-related causal mutations, as previous reports have shown that these mutations are extremely rare in Finland (Kaivorinne et al., 2008, 2010; Krüger et al., 2009). The proportion of the *C9*-RE carriers in each study is described in Table 2.

4.5 PERIPHERAL BLOOD CELL COUNTS (IV)

Peripheral blood cell counts (haemoglobin, thrombocytes, leukocytes) were measured in the memory outpatient clinic in Kuopio University Hospital as a part of routine diagnostic procedures. If more than one (range 1-3) blood count measurements were taken during the follow-up, median value calculated from these tests was used. Samples taken during acute infection were excluded from the calculations. After exclusions, haemoglobin data was available for 87 FTLD patients and thrombocyte and leukocyte data for 82 FTLD patients.

4.6 INFLAMMATORY BIOMARKER ANALYSES (III-IV)

4.6.1 Bullous pemphigoid autoantibody ELISA (III)

All FTLD patient samples (N=70) and control samples (N=61) were collected at Kuopio University Hospital and Oulu University Hospital. Sample aliquots were stored at -80 °C and thawed only on the day of the analyses. Levels of two Bullous pemphigoid-associated autoantibodies, BP180 and BP230, were measured according to manufacturer`s instructions with commercially available ELISA kits. Groups were compared based on dichotomous variable indicating either positive or negative (normal) BP180 or BP230 result. For both autoantibodies, widely acknowledged cut-off value of 9 U/ml was used as the lowest limit of positive result. The cut-off value for the normal limit has been calculated by two studies (Kobayashi et al., 2002; Sakuma-Oyama et al., 2004), and further studies have shown that clinically it provides high sensitivity 87% and specificity 98% (Tampoia et al., 2012). BP180-NC16A-ELISA was performed in duplicate for each sample, and the mean value

calculated from the duplicates was used. BP230-ELISA was performed only once for each sample.

4.6.2 Cytokine and hs-CRP analyses (IV)

Levels of selected cytokines were analysed from plasma (N=50) and/or serum (N=91), and hs-CRP levels were analysed from plasma (N=44). Cytokines were selected based on the reported alterations in the *C9orf72* knock-out murine model studies (Atanasio et al., 2016; Burberry et al., 2016; O'Rourke et al., 2016) and also based on previous studies showing alterations in ALS and PD patients (IL-8 and RANTES) (Hu et al., 2017; Qin et al., 2016; Tang et al., 2014; Zhao et al., 2017). All samples were collected at Kuopio University Hospital and stored in aliquots at -80 °C until analyses.

Levels of hs-CRP were measured with particle enhanced immunoturbidimetric assay (Cobas 6000 (c 501) –analyzer, Hitachi High Technology Co, Tokyo, Japan), with a measuring range of 0.15-20 mg/L. Samples with concentrations exceeding the measuring range (one sample) were excluded due to the likelihood of an acute inflammation unrelated to FTLD. Samples with concentrations below the measuring range (N=8) were considered undetectable.

The analysed cytokines from plasma were MCP-1, RANTES, IL-10, IL-17A, IL-12p and IFN-γ. Plasma analyses were performed according to manufacturer`s instructions with Cytometric Bead Array (CBA, BD Biosciences, San Jose, CA, USA), a system that enables quantification of several proteins simultaneously. All samples were incubated for 3 h with kit components (beads and detection reagent) according to manufacturer's instructions, and then washed three times with Wash Buffer. FACS Aria flow cytometer (BD Biosciences) was used to run the samples. Samples were analyzed anonymously and in randomized order, and each sample was analyzed in duplicate (mean value calculated from the duplicates was used).

From serum, the analyzed markers were IL-1β, IL-10, IL-8 and MCP-1. Serum samples were collected at Kuopio University Hospital, stored at -80 °C, thawed and divided to aliquots and further frozen until the measurements. After a second thaw, samples were mixed, centrifuged and analyzed in 96-well plates with Single Molecule Array (Simoa) technology, that enables ultra-sensitive detection of the analytes (femtomolar concentrations). Serum IL-8 and IL-1β were quantified using Simoa HD-1 two-step Advantage digital immunoassays, and MCP-1 and IL-10 with three-step advantage digital immunoassays (Rissin et al., 2010). Samples were analyzed anonymously and in randomized order, and each sample was analyzed in duplicate (mean value calculated from the duplicates was used). Samples having a coefficient of variation higher than 15 % were excluded. Also, samples with values below the quantification range were excluded. If both duplicate values exceeded the quantification range, the highest concentration of the assay`s quantification range was systematically used as the final concentration in further statistical analyses.

4.7 STATISTICAL METHODS

Statistical analyses were performed with IBM SPSS Statistics versions 23 and 25. Categorical data (dichotomous variables) were compared with Chi-Square test or Fisher`s exact test when more appropriate (when requirements of the Chi-Square test were not met due to small sample sizes). The Saphiro-Wilk test was used to test the normality of distribution of the data. Continuous variables were compared pairwise with either independent sample t-test (normally distributed data) or Mann-Whitney-U test (non-normally distributed data with skewness). Spearman`s rank correlation was used for correlation analyses in study IV due to non-normally distributed data and several outliers. A p-value of ≤ 0.05 was considered as statistically significant.

5 RESULTS

5.1 PREVALENCE OF CANCER IN FTLD (I)

The prevalence of cancer (all detected malignant neoplasms) was examined in study I in the Finnish FTLD patient cohort and was 9.7% in the FTLD group, 18.7% in age- and sex-matched AD group, and 17.4% in the matched control group (Table 4, Figure 8). The difference between both FTLD *vs.* AD and FTLD *vs.* controls was statistically significant (p=0.012 and p=0.029 in Chi-Square test, respectively), whereas there was no statistically significant difference between AD patients and controls. Within the FTLD group, there were no significant differences in the cancer prevalence between the *C9*-RE carriers (9.1%) and non-carriers (11.7%) (notably, the *C9*-RE carriers were slightly younger than the non-carriers). When evaluating specific cancer types, especially carcinomas were significantly more prevalent in the AD group (16.1%) compared to the FTLD group (8.7%) (FTLD *vs.* AD p=0.028, in Chi-Square test). Also difference in the prevalence of hematologic malignancies showed a non-significant trend towards lower prevalence in the FTLD patients (0.5%) compared to controls (3.3%) (FTLD *vs.* controls p=0.061, Fisher`s exact test). The groups were further compared based on the number of different types of cancer per participant (continuous variable). Five AD patients and three control subjects had a history of two separate types of cancers, whereas only one FTLD patient had two separate cancers. With the variable being continuous (number of cancers per participant in each group), there was a statistically significant difference in FTLD patients compared to AD patients (0.1 *vs.* 0.21, p=0.008, t-test) and in FTLD patients compared to controls (0.1 *vs.* 0.19, p=0.027, t-test).

There were no significant differences in the mean age of patients at the time of the cancer diagnoses in each group (61.6 years in FTLD, 64.4 years in AD, and 62.9 years in control group). In addition, there were no differences based on gender inside any of the participant groups. Out of all cancer diagnoses in the FTLD group, 55% were made before and 45% after the diagnosis of FTLD. In AD, 80% of the cancer diagnoses were made before the AD diagnosis and 20% after the AD diagnosis. Notably, AD patients were slightly older at the time of the neurological diagnosis compared to the FTLD patients (68.5 years *vs.* 65.7 years).

Table 4. Prevalence of cancer in FTLD patients with and without the *C9*-RE compared to AD patients and control participants

Characteristics	FTLD total N=195 (%)	FTLD with *C9*-RE N=55 (%)	FTLD without *C9*-RE N=103 (%)	AD N=193 (%)	Controls N=184 (%)
Age, y, mean (SD)	68.0 (8.0)	64.6 (8.2)	68.8 (7.3)	68.0 (7.8)	68.4 (8.8)
Gender, % Male	50.8%	49.1%	50.5%	50.3%	47.8%
All cancers combined, N (%)	19 (9.7)	5 (9.1)	12 (11.7)	36 (18.7)	32 (17.4)
All carcinomas combined N (%)	17 (8.7)*#	4 (7.3)	11 (10.7)	31 (16.1)*	25 (13.6)#
Non-melanoma skin cancer, N	3	1	2	8	10
Prostate cancer, N	2	1	1	9	3
Breast cancer, N	6	2	3	8	3
Lung cancer, N	0	0	0	0	1
Gastrointestinal cancer, N	2	0	2	5	4
Other carcinoma, N	5	0	4	6	4
Hematologic cancers, N (%)	1 (0.5)	1 (1.8)	0 (0.0)	4 (2.1)	6 (3.3)
Melanomas, N (%)	1 (0.5)	0 (0.0)	1 (1.0)	1 (0.5)	2 (1.1)
Mesotheliomas, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Gliomas, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Sarcomas, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Age is calculated from the date at last visit in special health care. One FTLD patient, five AD patients and three control subjects had two separate cancers. * = FTLD *vs.* AD p=0.012; # = FTLD *vs.* controls p=0.029. FTLD = frontotemporal lobar degeneration, *C9*-RE = chromosome 9 open reading frame 72 repeat expansion, AD = Alzheimer`s disase.

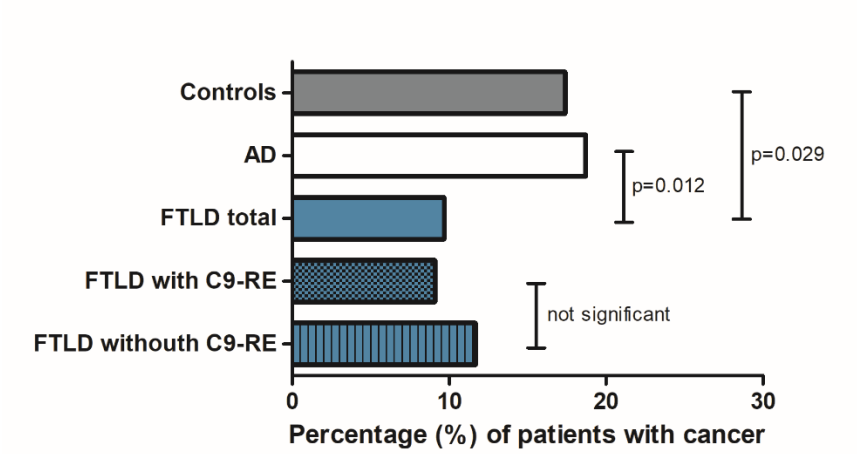


Figure 8. Percentage of cancer (all malignant neoplasms) in each group. There was no significant difference between the AD group and controls. AD = Alzheimer´s disease, FTLD = frontotemporal lobar degeneration, C9-RE = chromosome 9 open reading frame 72 repeat expansion.

5.2 SYSTEMIC INFLAMMATORY DISEASES IN FTLD (II-III)

In study II, the prevalence of all immunological (autoimmune) diseases combined (excluding asthma and hypothyroidism with unknown etiology) was 16.3% in FTLD, 13.5% in AD, and 15.2% in the control group. The differences between the groups were not statistically significant (see Table 5, Figure 9). Furthermore, there were no statistically significant differences between the *C9*-RE carriers and non-carriers in the prevalence of immunological diseases, even though the FTLD patients with the *C9*-RE showed overall the lowest (10.7%), and FTLD patients without the *C9*-RE overall the highest prevalence (18.8%) when compared with other groups. In the disease sub-categories, the most prominent, but non-significant trends, were observed between the *C9*-RE carriers and non-carriers in the prevalence of gastrointestinal diseases and between FTLD and AD patients or controls in endocrine diseases. The statistical analysis of *C9*-RE carriers *vs.* non-carriers showed a trend towards lower prevalence of gastrointestinal diseases and FTLD patients *vs.* AD patients showed an increasing trend of endocrine diseases. Additionally, prevalence of asthma was high especially in FTLD patients without the *C9*-RE, and FTLD patients with the *C9*-RE showed most prominent association to BP (Table 5, Table 6a-6c).

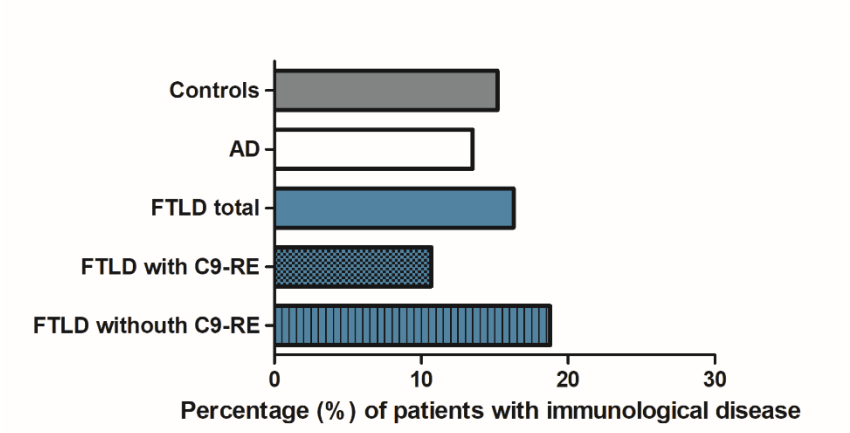


Figure 9. Percentage of immunological diseases (excluding asthma and hypothyroidism with unknown etiology) in each group. There were no statistically significant differences between the groups. AD = Alzheimer´s disease, FTLD = frontotemporal lobar degeneration, C9-RE = chromosome 9 open reading frame 72 repeat expansion.

Table 5. Prevalence of immunological diseases in FTLD patients with and without the *C9*-RE compared to AD patients and control participants

Characteristics	FTLD[a] N=196 (%)	FTLD with *C9*-RE[a] N=56 (%)	FTLD without *C9*-RE[a] N=117 (%)	AD N=193 (%)	NCI N=92 (%)
Immunological disease total N, (%)	32 (16.3)	6 (10.7)	22 (18.8)	26 (13.5)	14 (15.2)
Cutaneous disorders N, (%)	10 (5.1)	3 (5.4)	4 (3.4)	4 (2.1)	5 (5.4)
Gastrointestinal disorders N, (%)	7 (3.6)	0 (0.0)[¤]	7 (6.0)[¤]	5 (2.6)	3 (3.3)
Connective tissue disorders N, (%)	1 (0.5)	0 (0.0)	0 (0.0)	5 (2.6)	0 (0.0)
Inflammatory arthritides N, (%)	4 (2.0)	1 (1.8)	3 (2.6)	5 (2.6)	2 (2.2)
Vasculitides N, (%)	2 (1.0)	0 (0.0)	2 (1.7)	1 (0.5)	0 (0.0)
Endocrine disorders N, (%)	10 (5.1)	2 (3.6)	8 (6.8)[*,#]	5 (2.6)[*]	2 (2.2)[#]
Hematologic disorders N, (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Ocular diseases N, (%)	2 (1.0)	0 (0.0)	2 (1.7)	1 (0.5)	0 (0.0)
Sarcoidosis N, (%)	1 (0.5)	1 (1.8)	0 (0.0)	0 (0.0)	2 (2.2)
Hypothyreosis N, (%)	20 (10.2)	9 (16.1)	11 (9.4)	24 (12.4)	14 (15.2)
Asthma N, (%)	23 (11.7)	5 (8.9)	16 (13.7)[*]	16 (8.3)[*]	10 (10.9)

Four patients in the FTLD group had a diagnosis of two separate immunological diseases and one of three separate diseases. Two AD patients had a diagnosis of two separate immunological disorders. Asthma and hypothyreosis were not included in the "immunological disease total" category. [a] = the whole FTLD group includes 23 FTLD patients without *C9*-RE genotyping data; [¤] = *C9*-RE carriers *vs.* non-carriers, gastrointestinal: Fisher`s exact test p=0.098, [*] = *C9*-RE non-carriers *vs.* AD, endocrine: Fisher`s exact test p=0.084, asthma: Chi-square p=0.131; [#] = *C9*-RE non-carriers *vs.* NCI, endocrine: Fisher`s exact test p=0.191. AD = Alzheimer´s disease, FTLD = frontotemporal lobar degeneration, C9-RE = chromosome 9 open reading frame 72 repeat expansion, NCI = not cognitively impaired.

Table 6a. Prevalence of gastrointestinal immunological diseases in FTLD with and without the *C9*-RE compared to AD- and control participants

Characteristics	FTLD[a] N=196 (%)	*C9*-RE carriers[a] N=56 (%)	*C9*-RE non-carriers[a] N=117 (%)	AD N=193 (%)	NCI N=92 (%)
Immunological disease total N, (%)	32 (16.3)	6 (10.7)	22 (18.8)	26 (13.5)	14 (15.2)
Gastrointestinal disorders total N, (%)	7 (3.6)	0 (0.0)	7 (6.0)	5 (2.6)	3 (3.3)
Crohn`s disease, N	1	0	1	0	2
Ulcerative Colitis, N	2	0	2	1	0
Lymphocytic colitis, N	2	0	2	0	0
Celiac disease, N	2	0	2	2	1
Pernicious anemia, N	1	0	1	2	0

[a] = the whole FTLD group includes 23 FTLD patients without *C9*-RE genotyping data. There were no statistically significant differences between the groups. AD = Alzheimer´s disease, FTLD = frontotemporal lobar degeneration, C9-RE = chromosome 9 open reading frame 72 repeat expansion, NCI = not cognitively impaired.

Table 6b. Prevalence of endocrine immunological diseases in FTLD with and without the *C9*-RE compared to AD- and control participants

Characteristics	FTLD[a] N=196 (%)	*C9*-RE carriers[a] N=56 (%)	*C9*-RE non-carriers[a] N=117 (%)	AD N=193 (%)	NCI N=92 (%)
Immunological disease total N, (%)	32 (16.3)	6 (10.7)	22 (18.8)	26 (13.5)	14 (15.2)
Endocrine disorders total N, (%)	10 (5.1)	2 (3.6)	8 (6.8)	5 (2.6)	2 (2.2)
Basedow`s disease, N	3	0	3	1	1
Autoimmune thyreoiditis, N	4	1	3	1	0
Type 1 diabetes, N	1	0	1	2	1
Latent autoimmune diabetes, N	2	1	1	0	0
Addison`s disease, N	0	0	0	1	0

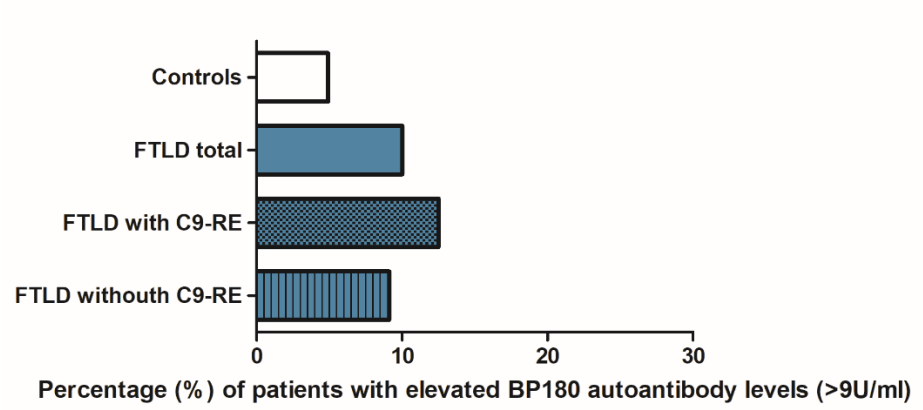
[a] = the whole FTLD group includes 23 FTLD patients without *C9*-RE genotyping data. There were no statistically significant differences between the groups. AD = Alzheimer´s disease, FTLD = frontotemporal lobar degeneration, C9-RE = chromosome 9 open reading frame 72 repeat expansion, NCI = not cognitively impaired.

The association between FTLD and BP was evaluated also by measuring different BP autoantibodies from blood samples (study III). In the total FTLD cohort (N=196), one patient had a clinical diagnosis of BP. The patient was a carrier of the *C9*-RE, and neurologically presented rather rapidly progressive nfvPPA as the clinical manifestation. The nfvPPA diagnosis was made at the age of 64 years, one year after symptom onset. NfvPPA finally led to mutism three years after symptom onset. Alongside with the word-finding problems, the patient also had behavioural symptoms, and eventually severe extrapyramidal symptoms leading to total immobility. The diagnosis of BP was made at the age of 67 years at the Department of Dermatology in Oulu University Hospital, after detection of persistent localized cutaneous blistering. The diagnosis was confirmed with direct IF staining and positive indirect IF result. The frequency of elevated/positive (above the 9 U/ml cut-off) BP180 autoantibody levels was 10% in the total FTLD cohort, and 4.9% in the neurologically healthy control group. The difference was not statistically significant. Altogether, 12.5% of the *C9*-RE carriers, and 9.1% of the non-carriers had elevated BP180 levels. Notably, serum sample of the patient with confirmed BP diagnosis was not available in our study, and thus this patient was not included in the analyses. Frequencies of elevated BP230, another BP autoantibody, levels were 4.3% in total FTLD, 8.3% in FTLD with the *C9*-RE, 2.3% in FTLD without the *C9*-RE and 7.5% in the control group, and there were no statistically significant differences (Table 6c, Figure 10). Elevated BP180 levels were most often detected in patients with bvFTD as the clinical manifestation, as 10.4% (5/48) of bvFTD patients, 7.7% (1/13) of nfvPPA patients, 0.0% (0/3) of svPPA patients, and 16.7% (1/6) of FTLD-MND patients showed elevated BP180 levels. Also, one FTLD-MND patient with elevated BP180 levels presented behavioral symptoms. However, none of these differences were statistically significant.

Table 6c. Prevalence of cutaneous immunological diseases in FTLD patients with and without the *C9*-RE compared to AD patients and control participants

Characteristics	FTLD[a] N=196 (%)	*C9*-RE carriers[a] N=56 (%)	*C9*-RE non-carriers[a] N=117 (%)	AD N=193 (%)	NCI N=92 (%)
Immunological disease total N, (%)	32 (16.3)	6 (10.7)	22 (18.8)	26 (13.5)	14 (15.2)
Cutaneous disorders total N, (%)	10 (5.1)	3 (5.4)	4 (3.4)	4 (2.1)	5 (5.4)
Bullous pemphigoid, N	1	1	0	1	0
BP180 (U/ml)[b]	3.52 (0.0-20.8)	3.85 (0.3-20.8)	3.29 (0.0-12.2)	-	3.06 (0.3-27.1)
BP180 positive % (N)	10% (7/70)	12.5% (3/24)	9.1% (4/44)	-	4.9% (3/61)
BP230 (U/ml)[b]	3.16 (0.1-38.9)	3.80 (0.2-38.9)	2.79 (0.1-19.5)	-	2.71 (0-24.1)
BP230 positive % (N)	4.3% (3/70)	8.3% (2/24)	2.3% (1/44)	-	7.5% (3/40)
Psoriasis, N	6	2	4	3	1
Alopecia areata, N	1	0	0	0	2
Localised scleroderma, N	1	0	0	0	0
Lichen Planus, N	0	0	0	0	1
Chronic autoimmune urticaria, N	1	0	0	0	0
Lichen sclerosus, N	0	0	0	0	1

BP180 autoantibodies were measured from 61 control subjects and BP230 from 40 control subjects. [a] = the whole FTLD group includes 23 FTLD patients without *C9*-RE genotyping data. [b] = Data are given as mean (range). There were no statistically significant differences between the groups in comorbid cutaneous disease prevalence or BP-autoantibody prevalence. AD = Alzheimer´s disease, FTLD = frontotemporal lobar degeneration, C9-RE = chromosome 9 open reading frame 72 repeat expansion, NCI = not cognitively impaired. BP = bullous pemphigoid.



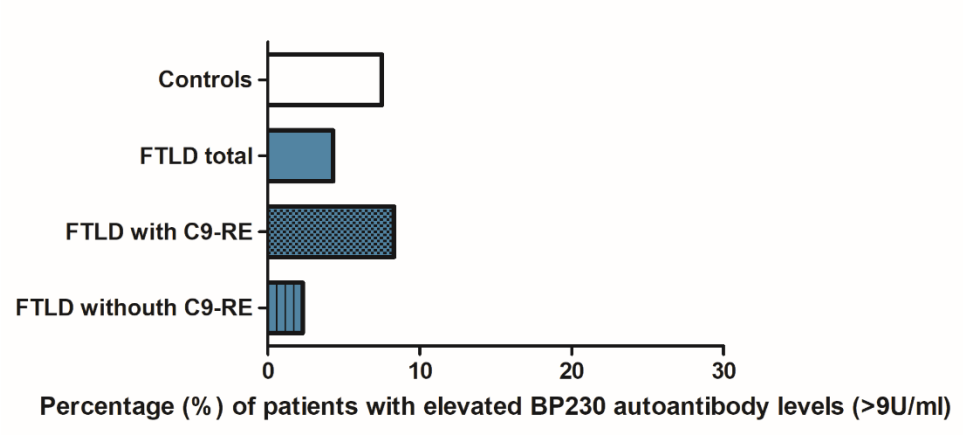


Figure 10. Percentage of patients with elevated BP180 or BP230 autoantibody levels in blood (>9U/ml). There were no statistically significant differences between the groups. FTLD = frontotemporal lobar degeneration, C9-RE = chromosome 9 open reading frame 72 repeat expansion, BP = bullous pemphigoid.

5.3 PERIPHERAL BLOOD CELL COUNTS IN FTLD (IV)

In study IV, blood cell counts and presence of selected inflammatory marker proteins were assessed in blood samples of the FTLD patients. Blood cell count data indicated that FTLD patients with the *C9*-RE had higher haemoglobin levels compared to those without the expansion (U=895, p=0.004). This difference was observed especially in male subjects, as the difference was significant in males (U=209, p=0.001), but non-significant in females, after separate comparisons. Thrombocyte levels were lower in FTLD patients with the *C9*-RE compared to patients without the expansion (U=361, p=0.039), but this difference was not significant when comparing genders separately. There were no significant differences in leukocyte counts when comparing between the *C9*-RE expansion carriers and non-carriers. Females had higher thrombocyte (U=336, p=0.001) levels and conversely lower haemoglobin levels (U=957, p=0.010) compared to males (regardless of the *C9orf72* genotype) (Table 7, Figure 11).

5.4 PERIPHERAL INFLAMMATORY MARKERS IN FTLD (IV)

Out of the cytokines measured from plasma with the CBA method (MCP-1, RANTES, IL-10, IL-17A, IL-12p, IFN-γ), only MCP-1 and RANTES were detectable (concentrations above detection limit). There were no differences in plasma levels of MCP-1 or RANTES between the *C9*-RE carriers and non-carriers. Females had higher RANTES levels compared to males (U=105, p=0.048), regardless of the *C9orf72* genotype. Levels of plasma hs-CRP did not differ between the *C9*-RE carriers and non-carriers. Females had higher hs-CRP levels compared to males (gender comparison regardless of the *C9orf72* genotype) (U=73, p=0.012) (Table 7, Figure 12).

Of the cytokines measured from serum with the more sensitive Simoa method (IL-10, IL-8, MCP-1, IL-1β), all four cytokines were detectable, even though IL-1β levels were below the quantification range in 56/91 (61.5%) of the FTLD patients. MCP-1, IL-1β and IL-8 levels indicated no differences between the *C9*-RE carriers and non-carriers. Male FTLD patients with the *C9*-RE showed slightly higher levels of IL-10 compared to males without the expansion, although the difference did not reach statistical significance (U=201, p=0.093). After exclusion of clear outliers, the difference between the *C9*-RE carriers and non-carriers was significant in males (U=201, p=0.049), but not significant when the genders were combined in the analysis (U=753, p=0.202). Females had higher IL-8 levels compared to males (U=427, p=0.002), regardless of the *C9orf72* genotype (Table 7, Figure 13).

Table 7. Inflammatory molecule concentrations and peripheral blood cell counts in FTLD patients with and without the *C9*-RE (IV)

Molecule	FTLD with *C9*-RE			FTLD without *C9*-RE			P-value
	Males	Females	Males & Females	Males	Females	Males & Females	
Plasma MCP-1 (pg/ml)	52.51 (56.58)	46.12 (38.68)	47.98 (46.09)	25.26 (38.71)	36.74 (62.38)	34.05 (50.96)	NS
Plasma RANTES (pg/ml)	5758.24 (6141.67)	8508.65 (7768.83)	6878.30 (4453.53)	7400.79 (6469.65)	9343.94 (4195.54)	8349.42 (4433.47)	NS
Serum MCP-1 (pg/ml)	364.57 (92.42)	481.91 (233.92)	390.43 (190.43)	359.51 (183.52)	378.80 (186.89)	377.60 (169.89)	NS
Serum IL-10 (pg/ml)	1.31 (1.00)	0.85 (0.99)	1.21 (0.84)	0.86 (0.80)	0.97 (1.22)	0.90 (0.83)	NS*
Serum IL-8 (pg/ml)	32.89 (31.84)	51.28 (30.52)	44.69 (39.76)	34.76 (22.35)	47.23 (36.90)	39.28 (28.24)	NS
Serum IL-1β (pg/ml)	1.52 (2.93)	0.30 (NA)	0.37 (1.38)	0.71 (3.25)	0.50 (6.35)	0.51 (4.23)	NS
hs-CRP (mg/L)	0.60 (0.43)	2.10 (3.10)	1.00 (1.90)	0.80 (1.55)	1.40 (4.38)	1.20 (2.70)	NS
Leukocytes ($x10^9$/L)	5.60 (1.80)	5.95 (3.58)	5.60 (2.80)	6.50 (2.70)	6.00 (1.95)	6.40 (2.10)	NS
Thrombocytes ($x10^9$/L)	198 (34.00)	258 (85.50)	214[1] (88.50)	228 (115.00)	279 (66.25)	272[1] (101.25)	0.039[1]
Hemoglobin (g/L)	153[1] (13.0)	139 (9.5)	144[2] (16.0)	139[1] (18.5)	136 (16.3)	137[2] (16.0)	0.001[1] 0.004[2]

Concentrations are presented as median (interquartile range, IQR). Mann-Whitney-U test was used to compare groups separately (three comparisons per row: between all *C9*-RE carriers and non-carriers, between male carriers and male non-carriers, and between female carriers and female non-carriers). P-value column presents statistically significant differences in each row, and the superscript numbers indicate which two groups were compared. "NS" indicates no significant differences in any of the three separate pairwise comparisons per row. * = In IL-10 levels, *C9*-RE carrier males showed a trend for higher IL-10 concentration compared to non-carrier males (p=0.093), being significant when outliers were excluded (p=0.049). Comparisons between genders are presented in Figures 1 and 2. FTLD = frontotemporal lobar degeneration, C9-RE = chromosome 9 open reading frame 72 repeat expansion, hs-CRP = high sensitive C-reactive protein, IL = interleukine.

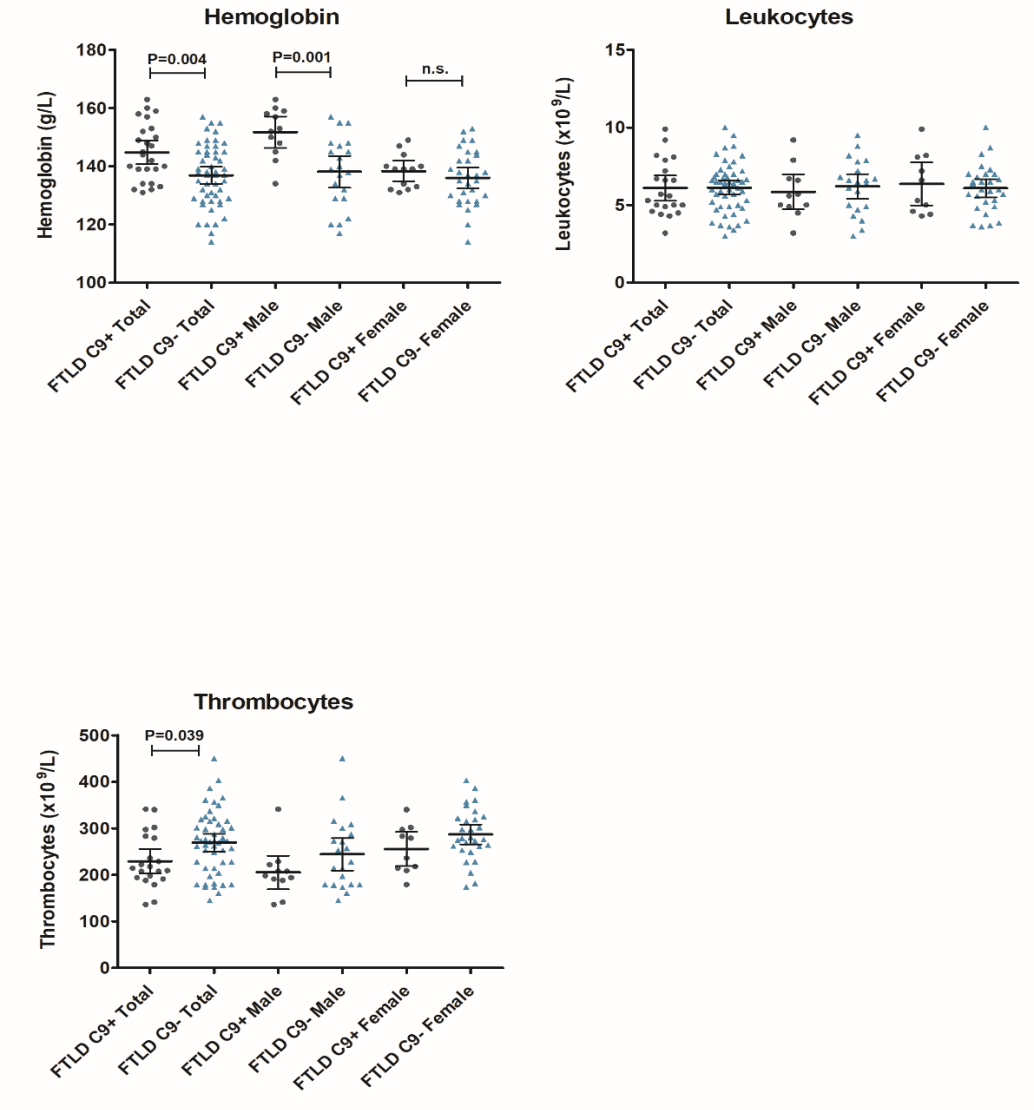


Figure 11. Peripheral blood cell counts in FTLD patients with or without the *C9*-RE. Symbols represent separate cases and horizontal lines represent median with interquartile range. Mann-Whitney-U test was used to compare the groups separately. FTLD = frontotemporal lobar degeneration, C9+ = FTLD patients with the chromosome 9 open reading frame 72 repeat expansion, C9- = FTLD patients without the chromosome 9 open reading frame 72 repeat expansion. n.s. = not significant.

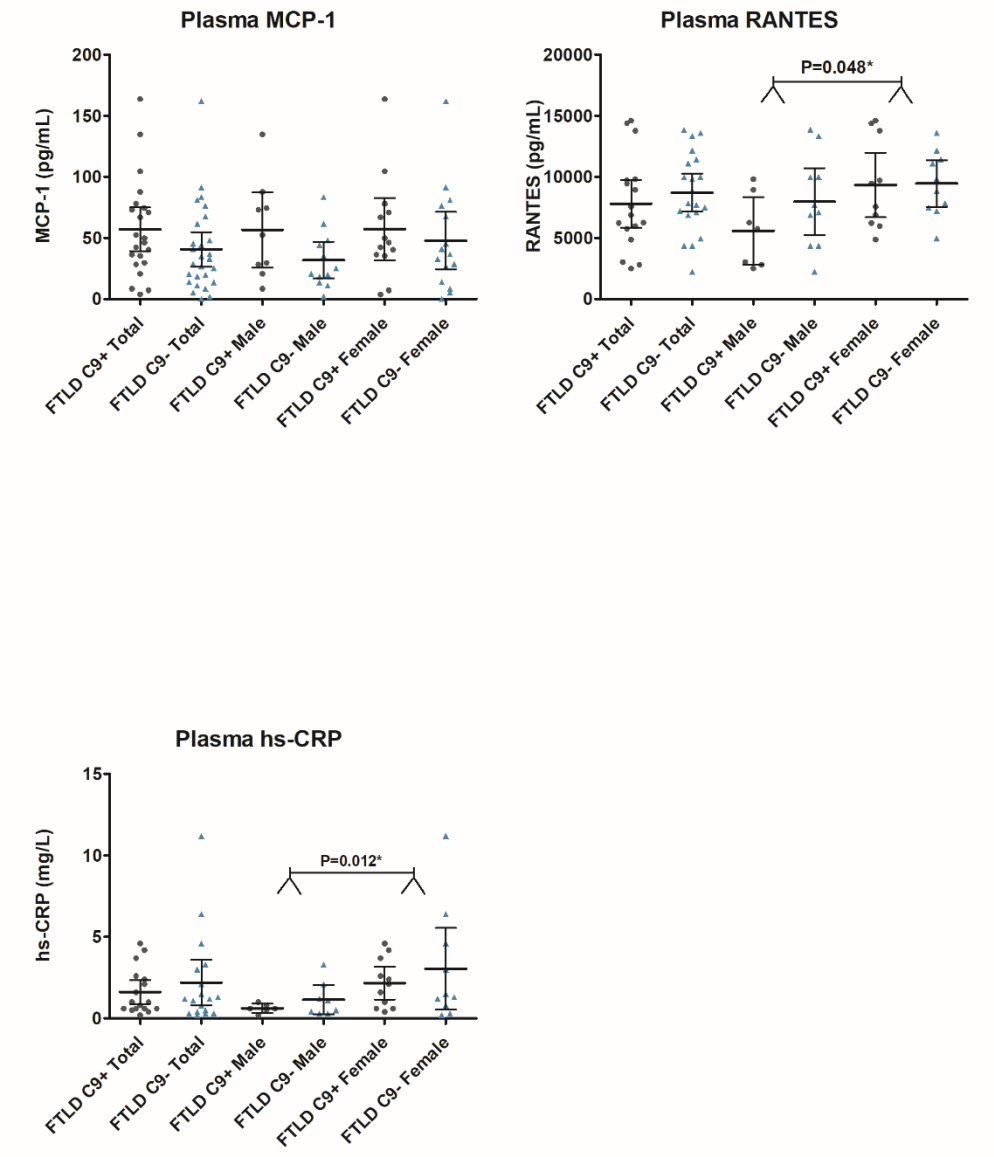


Figure 12. Concentrations of MCP-1, RANTES, and hs-CRP in the plasma in FTLD patients with or without the *C9*-RE. Symbols represent separate cases and horizontal lines represent median with interquartile range. Mann-Whitney-U test was used to compare the groups separately.* = For RANTES and hs-CRP, the p-value is calculated for all males compared to all females, regardless of the *C9*-RE status. FTLD = frontotemporal lobar degeneration, C9+ = FTLD patients with the chromosome 9 open reading frame 72 repeat expansion, C9- = FTLD patients without the chromosome 9 open reading frame 72 repeat expansion. n.s. = not significant.

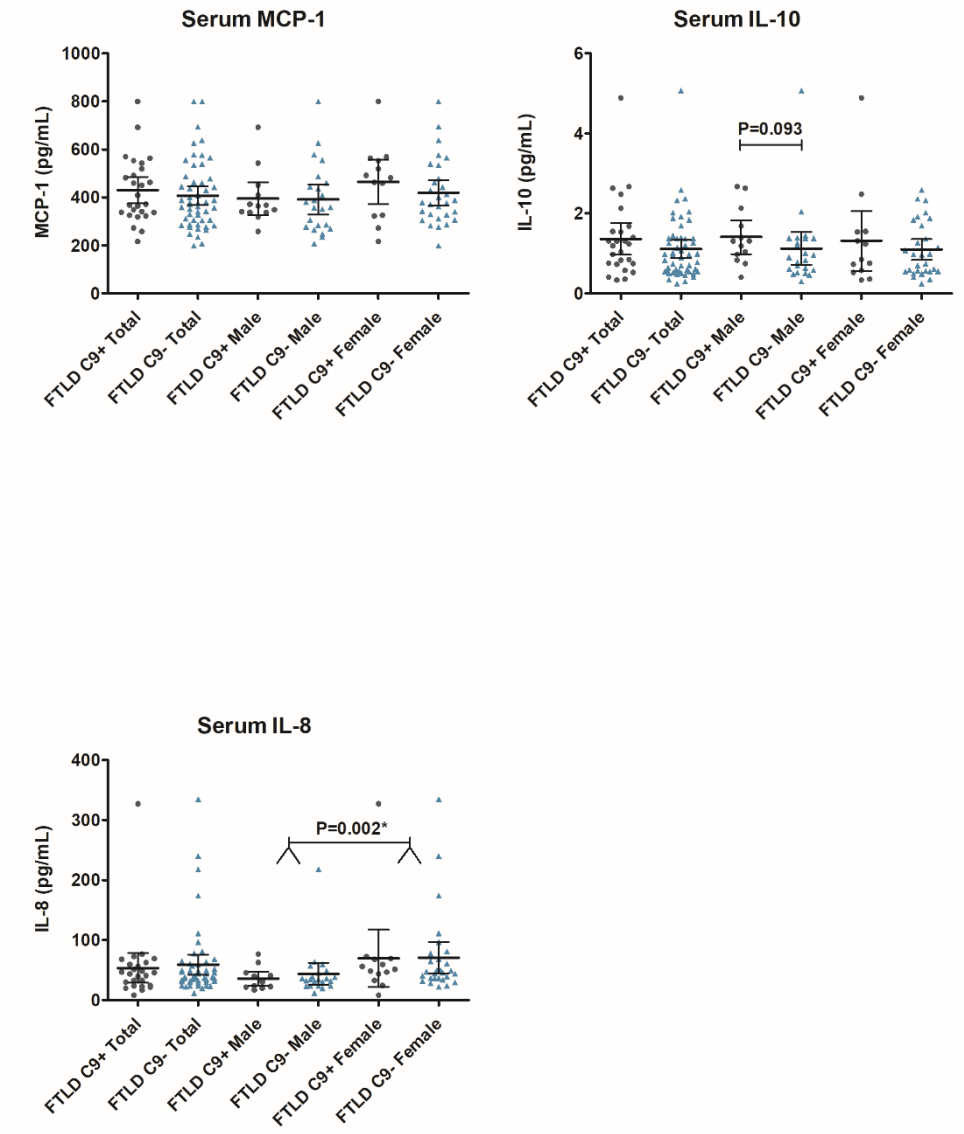


Figure 13. Concentrations of MCP-1, IL-10 and IL-8 in serum (Simoa analyses) of FTLD patients carrying or not the *C9*-RE. The data for IL-1β are not shown due to extremely low or undetectable levels in most of the cases. Symbols represent separate cases and horizontal lines represent median with interquartile range. Mann-Whitney-U test was used to compare the groups separately.* = For IL-8, the p-value is calculated for all males compared to all females, regardless of the *C9*-RE status. For IL-10, the difference between male *C9*-RE carriers and male non-carriers was significant after outlier exclusion (p=0.049). FTLD = frontotemporal lobar degeneration, C9+ = FTLD patients with the chromosome 9 open reading frame 72 repeat expansion, C9- = FTLD patients without the chromosome 9 open reading frame 72 repeat expansion. n.s. = not significant.

The levels of the measured cytokines and blood cell counts were further compared to the clinical features of the patients. IL-8 was the only cytokine that correlated with age (r_s=0.231, p=0.029). A history of an autoimmune disease did not affect the inflammatory marker levels (autoimmune disease history was reported in 11/98 patients). Three patients had systemic (oral administration) immunomodulatory medication, but these patients did not have distinct differences in the inflammatory marker levels compared to other patients. Out of the clinical features, parkinsonism was associated with higher plasma levels of the pro-inflammatory MCP-1 (U=345, p=0.030) and, conversely, lower serum levels of the anti-inflammatory IL-10 (U=404, p=0.016). Additionally, there was a non-significant trend towards higher plasma levels of the pro-inflammatory RANTES in patients with parkinsonism (U=216, p=0.088). Psychotic symptoms were associated with higher levels of IL-10 (U=963, p=0.026) (Figure 14). Presence of pathological primitive reflexes, possibly indicating progressed deterioration of the CNS, was associated with elevated hs-CRP levels (U=302.5, p=0.029). This difference was highly driven by the fact that females in general had more often positive primitive reflexes compared to males (53.3% *vs*. 13.5%, respectively, p<0.001). There were no differences in the cytokine levels when comparing patients with motoneuron symptoms to those without them (notably only seven patients had motoneuron symptoms), or when comparing patients with apathetic clinical manifestation to those with disinhibited profile.

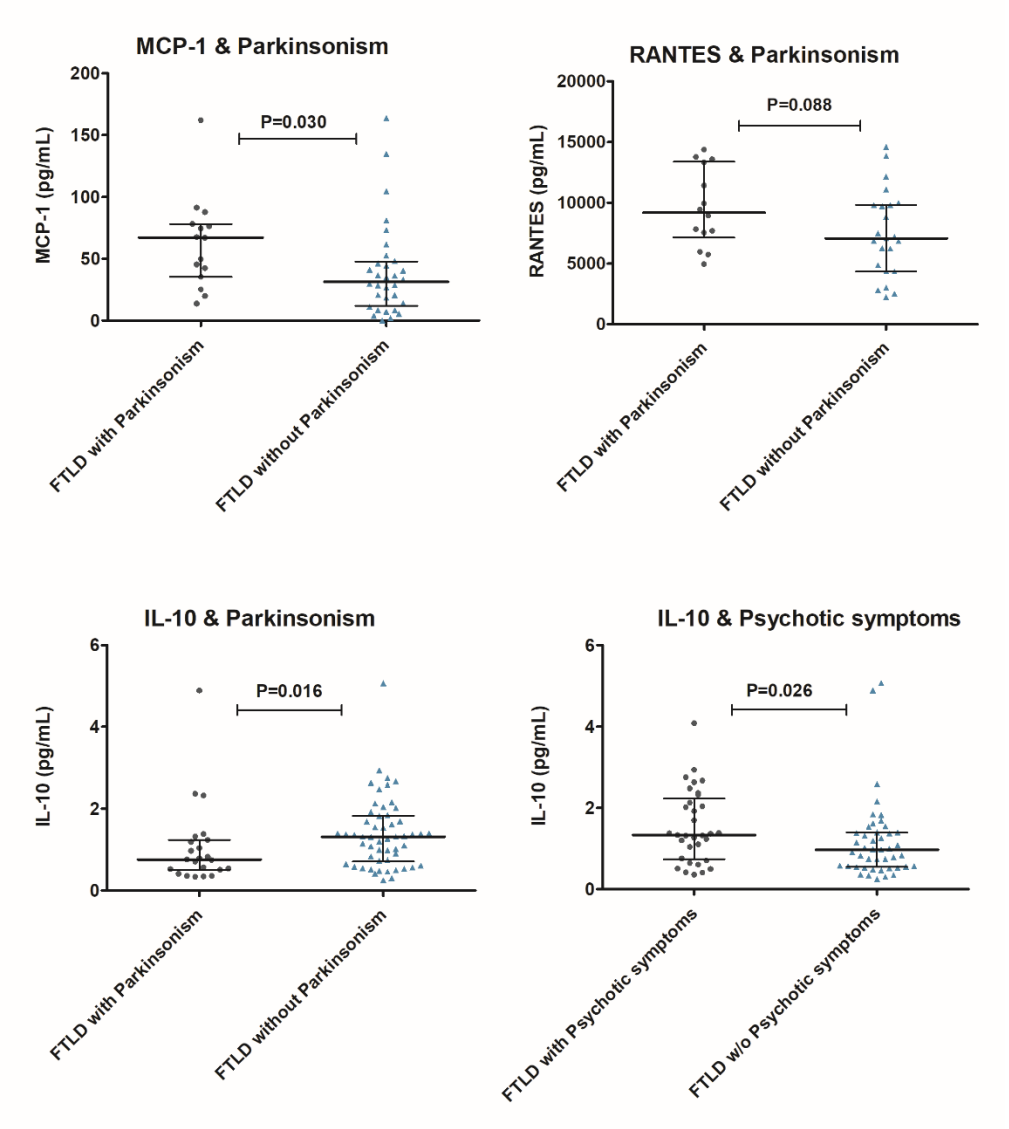


Figure 14. Concentrations of the inflammatory cytokines MCP-1 (plasma), RANTES (plasma) and IL-10 (serum) in FTLD patients with or without parkinsonism or psychotic symptoms. Symbols represent separate cases and horizontal lines represent median with interquartile range. Mann-Whitney-U test was used to compare the groups. FTLD = frontotemporal lobar degeneration.

There was a strong positive correlation between plasma levels of the pro-inflammatory RANTES and functional decline rate measured by ADCS-ADL decline (points per months, higher score = more rapid decline) (r_s=0.694, p=0.001), and conversely, a moderate negative correlation between serum levels of the anti-inflammatory IL-10 and ADCS-ADL decline (r_s= -0.550, p=0.010). Additionally, there was a moderate positive correlation between cognitive decline rate in MMSE and serum levels of the pro-inflammatory MCP-1 (r_s=0.457, p=0.011) (Figure 15).

Cross-correlation of the different cytokines indicated that IL-8 levels correlated with serum MCP-1 (r_s=0.553, p<0.001) and IL-10 levels (r_s=0.239, p=0.024). MCP-1 levels in serum (Simoa analyzes) correlated with MCP-1 levels in plasma (CBA analyzes), cross-validating our results.

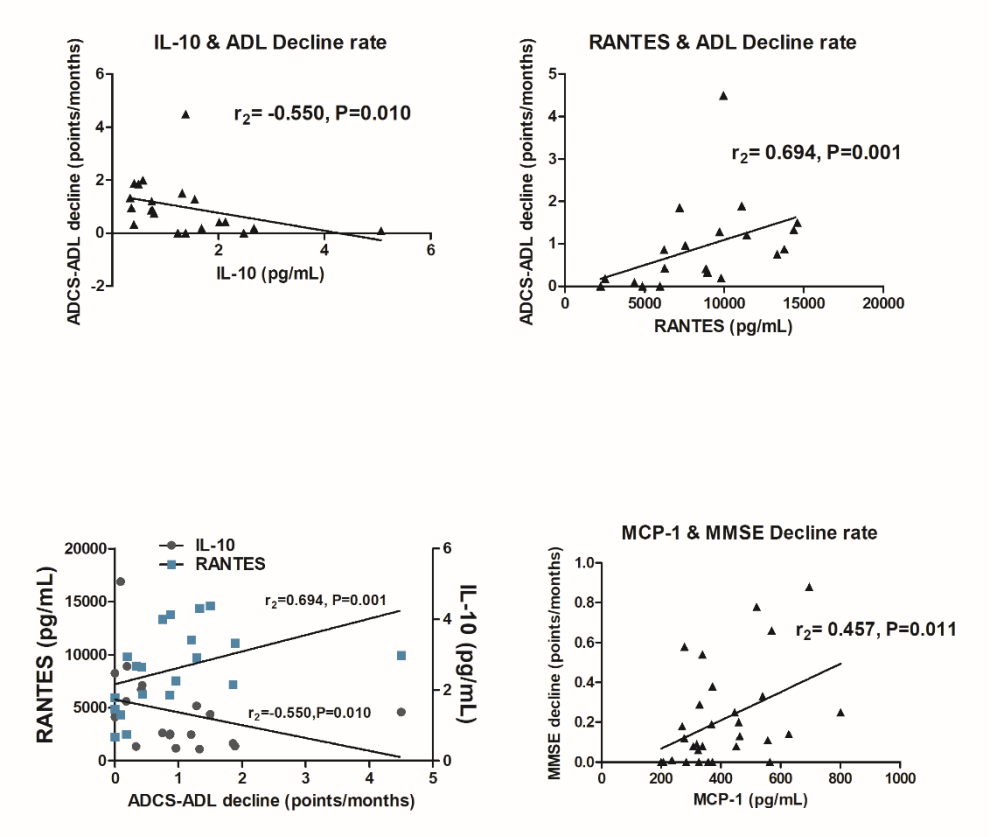


Figure 15. Correlations of the levels of inflammatory cytokines (plasma RANTES, serum MCP-1 and serum IL-10) and functional or cognitive decline rates. Functional decline was assessed using ADCS-ADL and cognitive decline using MMSE examination. Higher decline ratio score indicates more rapid progression. Correlation analyses were performed with Spearman`s rank correlation test. ADCS-ADL = Alzheimer`s disease cooperative study – Activities of daily living (questionnaire), MMSE = mini mental state examination.

6 DISCUSSION

Constantly increasing evidence in the literature indicates that immunological factors play an important role in FTLD. Previous studies have associated both sporadic and genetic (especially the *C9orf72* and *GRN* genes) FTLD to dysregulated immune system and autoimmune conditions. This study is the first to evaluate systemic inflammatory markers in FTLD patients especially due to the *C9*-RE. Before the publication of the results of this thesis, no previous studies had evaluated peripheral inflammatory marker levels in *C9*-RE-associated FTLD or associations between these markers and clinical manifestations or progression of the disease. In addition, only limited data have previously existed for the comorbid autoimmune conditions in FTLD patients, and the association between FTLD and cancer has not been evaluated in previous studies.

6.1 PREVALENCE OF CANCER IN FTLD (I)

The significantly low prevalence of cancer observed in our FTLD cohort is a novel finding (I) and it indicates inverse association between FTLD and malignant neoplasms. The fact that we observed lower prevalence of cancer in patients with FTLD compared to AD further indicates that the inverse associations observed between neurodegeneration and cancer might be even more prominent in FTLD patients. Interestingly, AD diagnosis seemed to decrease the incidence of cancer diagnoses (indicating possible diagnostic bias), as 80% of the cancer diagnoses were made before the AD diagnosis. However, this was not the case in the FTLD group, as cancer diagnoses were made almost in equal proportions both before (55%) and after (45%) the FTLD diagnosis. The fact that we did not observe reduced cancer prevalence in the AD group compared to control group may be due to the limited cohort size, or for example due to differences in the AD population in our study compared to AD cohorts in other countries. There appears to be no difference in the cancer prevalence (despite the slight trend for higher prevalence in the non-carriers compared to carriers) between the *C9*-RE carriers and non-carriers, as the *C9*-RE carriers were four years younger on average compared to the non-carriers. Currently, there is no explicit explanation for the inverse associations observed between neurodegeneration and cancer, although reasonable hypotheses have been proposed. The characteristic feature of cancer is the uncontrollable cell growth and division, a process that is not driven only by the local tumor itself, but rather also includes substantial systemic changes (McAllister and Weinberg, 2014). Conversely, neurodegeneration largely affects neurons, which are postmitotic cells, and it is characterized by increased apoptosis and tissue atrophy. It is thus possible, that at the systemic level, these two opposite processes are less likely to occur together in the same individual. A transcriptomics study has indeed supported this idea by showing that in the elderly, the transcriptomic activation is opposite in cancer

compared to degenerative diseases. Moreover, neurodegenerative diseases were associated with induction of inflammatory genes and down-regulation of cell-cycle genes, whereas the opposite took place in cancer (Aramillo Irizar et al., 2018). These findings highlight that the biological pathways in FTLD might include immune system dysfunction that at the same time oppositely influences cancer growth. In addition to these contrasting gene expressional changes that affect the inverse association between cancer and neurodegeneration in general, it is also possible that the overactive immune system itself protects from cancer development in FTLD. Currently, it is already known that several types of cancers can be treated or even prevented by enhancing our immune system defenses (Corthay, 2014; Palladini et al., 2018). It is clear, that at least immunodeficiency is harmful and increases the risk for cancer (Mortaz et al., 2016). However, it is unclear whether an overactive immune system provides any additional protection compared to normal state, although studies have suggested, for example, that consequent activation of natural killer cells and CD8+ T-cells can prevent cancer growth *in vivo* (Diefenbach et al., 2001) and that having a comorbid autoimmune disease is associated with significantly better survival at least in melanoma and renal cell carcinoma patients receiving immunological treatments (Gogas et al., 2006; Scalzo et al., 1990). Moreover, a possible key molecule between the inverse pathways of cancer and autoimmunity, microRNA-142, was recently identified as a regulator of T-cell activity that further regulates peripheral immune tolerance. It was shown that microRNA-142 regulates regulatory T-cells that in turn control self-reactive effector T-cells. Suppressed antitumor effector T-cell responses due to increased microRNA-142 and regulatory T-cell activity enables cancer growth, whereas decreased microRNA-142 via suppressed regulatory T-cell activity leads to autoimmunity through overactive effector T-cells (Anandagoda et al., 2019). These findings further suggest that immune system activity may induce opposite molecular pathways for the development of cancer and autoimmunity. On the other hand, the role of the immune system in cancer is currently considered two-faceted, as both tumor-protecting and -promoting effects have been described (Schreiber et al., 2011). Additionally, although autoimmune diseases and cancer may be considered as opposite processes from an immunological perspective, it is also well known that chronic inflammation, often associated with autoimmune diseases, promotes cancer growth (Grivennikov et al., 2010). Therefore, it is important to discriminate inflammation from autoimmunity, as they possess different and potentially opposite mechanisms considering association with cancer. In summary, the fact that FTLD patients might be more prone to autoimmune diseases and less prone for developing cancer might arise from opposite gene regulation and/or immunological pathways. On the other hand, the systemic inflammation that was observed in some of our patients with a rapid disease progression (IV) is not likely the underlying factor of the decreased cancer prevalence, whereas tendency for autoimmunity (II-III) might play an explanatory role.

6.2 SYSTEMIC INFLAMMATORY DISEASES IN FTLD (II-III)

In our study (II), we found similar prevalences of autoimmune diseases in the total FTLD cohort compared to earlier studies that have suggested increased prevalence of non-thyroid autoimmune diseases especially in FTLD due to TDP-43 neuropathology (Miller et al., 2016, 2013). However, we found rather similar prevalences also from our AD patient and control cohorts. This could imply differences in the control populations, especially as the groups have been rather small for epidemiological data. Notably, existing TDP-43 pathology is not likely the only factor associated with increased autoimmune disease prevalence, as in our cohort, the prevalence of autoimmune diseases in the *C9*-RE carriers and svPPA patients was actually the lowest from all of the study groups, whereas the *C9*-RE non-carriers had the highest prevalence of immunological diseases. A small study from UK by Woollacott et al. suggested that FTLD with *GRN* mutations have increased prevalence of non-thyroid autoimmune diseases, whereas the prevalence was not significantly higher in *C9*-RE carriers (Woollacott et al., 2017). Interestingly, also the study by Miller and colleagues found a rather low prevalence of autoimmune diseases in *C9*-RE-associated FTLD, but only specifically in patients with the bvFTD phenotype, which is the most common phenotype in our FTLD patients with the *C9*-RE. In that cohort, the high prevalence of autoimmune diseases in *C9*-RE carriers was highly driven by the FTLD-MND phenotype, as also FTLD-MND patients without the *C9*-RE had increased prevalence of autoimmune diseases (Miller et al., 2016). Thus, also the clinical manifestation likely affects the association between FTLD and autoimmune diseases. It should be noted that a proportion of our *C9*-RE non-carrier group also has likely TDP-43 neuropathology despite the lack of any known high-likelihood etiology, and thus our comparison between the *C9*-RE carriers and non-carriers cannot be directly correlated with comparison between FTLD-TDP and FTLD non-TDP. It is still possible that FTLD-TDP is more likely to be associated with immunological diseases compared to e.g. FTLD-tau, as suggested in the previous studies (Miller et al., 2016, 2013). Interestingly, a rather high prevalence of intermediate *C9*-REs (repeats from 9 to 30) in patients with SLE and rheumatoid arthritis was recently reported (Fredi et al., 2019), suggesting that also the lower repeat sizes may affect autoimmunity phenotypes in the *C9*-RE carriers.

Another important factor regarding the possible immunological comorbidity burden in FTLD is the fact that some autoimmune diseases might more specifically associate with FTLD, and not all autoimmune diseases should be considered equal. Indeed, especially cutaneous, rheumatoid, and gastrointestinal autoimmune diseases have been suggested to most likely associate with FTLD (Miller et al., 2016, 2013). Furthermore, out of the cutaneous autoimmune diseases, particularly BP has been associated with several neurological and psychiatric conditions in both epidemiological, and biological studies (Brick et al., 2014; Försti et al., 2016; Foureur et al., 2006; Kokkonen et al., 2016; Langan et al., 2011; Messingham et al., 2016). In our novel study (III), we report one FTLD case (carrier of the *C9*-RE) with biopsy-

confirmed diagnosis of BP. In addition, the percentage of patients having increased levels of BP180 autoantibodies was higher especially in FTLD patients carrying the *C9*-RE (12.5%) compared to controls (4.9%), although statistical significance was not reached. Nevertheless, especially the *C9*-RE-associated FTLD appears to associate with BP, as 12.5% of the carriers had increased blood BP180 autoantibody levels and additionally, one carrier (with no blood sample available for BP180 autoantibody testing) had a clinically and histologically proven diagnosis of BP. Furthermore, the *C9*-RE carrier group was noticeably young (mean age 61 years) considering that both the BP incidence and the levels of the autoantibodies increase dramatically after the age of 70. The incidence and the autoantibody levels are the highest in patients aged over 90 years (Marazza et al., 2009; Schmidt et al., 2000). Our findings thus indicate that especially the *C9*-RE carriers are in a higher risk of developing BP, although the association between BP and neurological diseases still appears rather unspecific. In addition to the *C9*-RE genotype, specifically the bvFTD phenotype was often associated with elevated levels of BP180 autoantibodies. Interestingly, these subgroups are associated with high prevalence of psychiatric/behavioural symptoms (Solje et al., 2015), and on the other hand, also psychiatric disorders have been shown to associate with BP in epidemiological studies (Försti et al., 2016). A recent report provided one possible explanation for these findings by showing that several drugs used to treat psychiatric patients, and often also FTLD patients, increase the risk for BP (Varpuluoma et al., 2019). Moreover, it was recently shown that BP180 autoantibodies in AD and multiple sclerosis target at least partially different epitopes compared to those in clinical BP patients (Tuusa et al., 2019). This finding could explain the high prevalence of BP autoantibodies in neurological diseases without any skin symptoms. On the other hand, some patients might still develop autoantibodies that target the cutaneous BP180 through epitope spreading, which is suggested by the epidemiological (clinical) associations (Brick et al., 2014; Försti et al., 2016; Langan et al., 2011). These findings further indicate that the association between BP and neurological/ psychiatric diseases is likely multifactorial and that both overlapping etiological pathways (shared antigens, epitope spreading, immunological disturbances) and several extrinsic factors may contribute to the association. Our finding regarding the BP230 autoantibody levels in FTLD patients is in line with previous studies showing that rather similar prevalence is found also from control subjects. Notably, BP180 is considered more crucial in the pathogenesis of clinical BP compared to BP230 (Di Zenzo et al., 2011). Moreover, the isoform of dystonin differs in cutaneous tissue compared to central nervous system, and the BP230 ELISA mostly targets those epitopes observed only in the cutaneous dystonin isoform (Hamada et al., 2001; Künzli et al., 2016).

6.3 PERIPHERAL INFLAMMATORY MARKERS AND BLOOD CELL COUNTS IN FTLD (IV)

In our study (IV), we found associations between several peripheral inflammatory markers and distinct clinical manifestations and/or disease progression. Particularly elevated levels of pro-inflammatory chemokines MCP-1 and RANTES were associated with parkinsonism and a more rapid disease progression measured either as cognitive decline (MMSE decline rate and MCP-1 levels) or functional decline (ADCS-ADL decline rate and RANTES levels). At the time of writing of this thesis, no other studies have evaluated/reported the association of peripheral inflammatory markers with the clinical manifestation or progression of FTLD. However, the findings that elevated blood MCP-1 levels correlated with a more rapid MMSE decline in FTLD patients are in line with a recent study in AD patients (Lee et al., 2018). In prodromal AD, also CSF MCP-1 levels similarly correlate with MMSE decline rate (Westin et al., 2012). Additionally, increased peripheral MCP-1 and RANTES levels have both been previously associated with Parkinson`s disease (Qin et al., 2016; Reale et al., 2009). This is in accordance with our findings that elevated MCP-1 and RANTES levels associated with FTLD with parkinsonism. These findings altogether imply that these two pro-inflammatory chemokines might play a role as disadvantageous pro-inflammatory mediators in specific subpopulations of FTLD and indicate a more rapid disease progression in these patients. It still remains unclear whether the levels of these cytokines in blood rise as a consequence of neuroinflammation spreading to circulation, or if peripheral immune system cells themselves are primarily activated due to FTLD-related genetic characteristics.

In addition to the associations between pro-inflammatory chemokines and unfavourable disease phenotypes, we found opposite associations regarding the anti-inflammatory cytokine IL-10. Lower IL-10 levels indicated a more rapid disease progression and additionally also parkinsonism. These observations further support the idea of the harmful consequences of the imbalanced activity of pro- and anti-inflammatory cytokines in FTLD, especially in disease manifestation and prognosis. However, it is possible that the inflammatory activity (anti-inflammatory *vs.* pro-inflammatory) differs during different disease stages (asymptomatic FTLD, MCI, early FTLD, progressed FTLD) and the effects of the inflammatory stimuli might vary from being advantageous to being harmful. For example, one recent study comprising AD and FTLD patients showed that in the CSF, increased levels of some pro-inflammatory cytokines, such as IL-1β, IL-6, and IFN-γ, were associated with better clinical prognosis in AD (Taipa et al., 2019). However, in the same study, increased levels of the anti-inflammatory IL-10 similarly correlated with better clinical prognosis in AD and increased levels of pro-inflammatory CSF IL-7 correlated with a more rapid progression in FTLD (Taipa et al., 2019). These findings are in line with our results. It is likely, that the optimal balance of the immune system function in different disease stages is both subtle and complex, but balance between

anti- and proinflammatory responses should be pursued for the most favourable prognosis.

We also found that IL-10 levels were higher in FTLD patients with psychotic symptoms. Some previous studies in patients with first-onset psychosis have found similarly elevated IL-10 levels (De Witte et al., 2014; Lesh et al., 2018), suggesting that IL-10 activation might be associated with development of psychosis. It could be hypothesized that IL-10 activity is specifically associated with brain regions affected in psychosis, regardless of whether the affecting disorder is a neurodegenerative disease or a primary psychiatric disorder.

Another possible explanation for the association between elevated IL-10 levels and psychotic symptoms may arise from the fact that *C9*-RE carriers showed a trend towards higher IL-10 levels compared to non-carriers, especially when comparing only males. This together with the fact that the *C9*-RE carriers have more often psychotic symptoms compared to the non-carriers (Devenney et al., 2017) (also observed in our FTLD cohort) suggests that all of these three factors, the *C9*-RE, IL-10, and psychotic symptoms may have a mutual connection. Apart from IL-10, no other cytokine showed differences between the *C9*-RE carriers and non-carriers.

The levels of haemoglobin were higher in the *C9*-RE carriers compared to non-carriers, a finding mostly driven by the more prominent difference particularly in male subjects. Recent *C9orf72* knock-out murine model studies have shown that homozygous knock-out leads to excessive systemic inflammation with elevated levels of several cytokines and decreased levels of haemoglobin (anaemia). Similarly prominent alterations were not detected in the hemizygous knock-out mice that resemble more closely the human *C9*-RE carriers with one diseased and one healthy allele (Atanasio et al., 2016; Burberry et al., 2016; O'Rourke et al., 2016). Our findings with human patients are in line with the mouse studies as the *C9*-RE haploinsufficiency in FTLD patients does not appear to cause prominent differences in the levels of inflammatory cytokines, except for IL-10, which showed potential as a differentiating marker. In addition, the *C9*-RE does not appear to cause anemia in human patients similarly to the homozygous knock-out mice. Rather, the *C9*-RE might be associated with increased hemoglobin levels. A previous study has shown that transcriptomic changes at least in motoneurons of *C9*-RE carriers include dysregulation of gene networks especially associated with erythrocyte homeostasis (Cooper-Knock et al., 2015). Additionally, the *C9orf72* gene has been shown to be highly expressed in cells of the myeloid lineage (Rizzu et al., 2016). These observations indicate potential associations between *C9*-RE and possibly altered function of myeloid cells (including e.g. monocytes, macrophages, and microglia) and warrant further studies in the future.

It should be noted that the levels of all of the measured cytokines showed substantial heterogeneity inside the FTLD cohort. However, this is also the case in FTLD in general, considering the clinical, neuropathological and genetic heterogeneity. Thus, in line with the findings from the comorbidity studies (I-III), our findings from the inflammatory marker analyses (IV) suggest that specific subgroups

of FTLD patients might have a more prominent inflammatory component associated with the disease pathogenesis. It could even be hypothesized, that distinct inflammatory profiles might explain at least some of the substantial heterogeneity in the FTLD spectrum (heterogeneity in disease progression and different clinical symptoms). As another example of this, females showed several independent differences in the levels of hs-CRP, RANTES and IL-8 that were higher compared to those in males. Additionally, patients with pathological primitive reflexes were often females and had elevated hs-CRP levels, suggesting that these three factors could also be connected. In fact, the substantial role of gender in autoimmunity is commonly acknowledged (Fairweather et al., 2008) and thus the role of gender should also be considered when evaluating the immune system function in FTLD. In summary, the inflammatory profiles appear to vary from one FTLD patient to another, which should be taken into account when considering further studies and clinical implications.

As our study provides information of the inflammatory status only at one cross-sectional time point, the role and state of inflammation in different disease stages still remain to be investigated. However, all samples in our analyses were collected from symptomatic patients and the samples were usually taken in the early symptomatic phase, although the diagnostic delay from symptom onset generates variability. Nevertheless, our cohort represents early symptomatic FTLD and our present studies suggest that at that stage, increased pro-inflammatory activity is disadvantageous and might even serve as prognostic tool. Interestingly, a recent case-report of a *MAPT* mutation carrier suggests that neuroinflammation and microglial activity (studied with positron emission tomography) occur in the very early pre-symptomatic stages of the disease, even before signs of considerable tau aggregate burden (Richard Bevan-Jones et al., 2019). Similar findings have now arisen also in AD research, as increased microglial activity was detected before tau accumulation that further led to cognitive decline (Felsky et al., 2019). Although the finding regarding FTLD is based on only a single case report, together with the knowledge from AD research it intriguingly suggests that immunological factors may not only affect FTLD in its late stages, but that inflammation might be a key contributor already at early stages of the disease that induces or accelerates the characteristic abnormal protein aggregation or neurodegeneration, resulting in brain atrophy and clinical manifestations of the disease.

6.4 STRENGTHS AND LIMITATIONS

This study provides novel insights into disease characteristics and mechanisms in the rapidly evolving fields of FTLD and immunology research. The high proportion of patients carrying the *C9*-RE in the Finnish FTLD patient cohort enables more specific evaluation in an otherwise rather heterogenous disease group. The FTLD cohort in this study is large and well-characterized compared to many other cohorts worldwide, especially when considering the proportion of definite cases according

to the latest diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). The longitudinally gathered cognitive and functional data (MMSE and ADCS-ADL questionnaires) that were collected in annual follow-ups in the same memory clinic enable reliable and important assessment of disease progression rates. Analyses in study IV were performed with two different analytic platforms. The Simoa platform enables extremely sensitive and reliable detection of molecules even with low concentrations. Our results indicate that Simoa offers a remarkably more sensitive analysis technology compared to the CBA method, as it enables quantitative evaluation of even the lowest grades of inflammation. On the other hand, it has been shown that concentrations analysed with the CBA method highly correlate to those measured with the Simoa method (Costa et al., 2018), validating the feasibility of both of these platforms.

Despite the fact that our cohort is large compared to many other previous cohorts, it is still limited in size for making explicit conclusions and evaluation of causality, especially from a statistical point of view. Additionally, we cannot exclude that other factors (confounders) that were not considered in our study setting/analyses affect the results of this study. Thus, our findings provide associations and correlations between the parameters and do not necessarily indicate causality. Further studies in larger cohorts are required to replicate our results. In studies I and II, the prevalence of cancers and autoimmune diseases were screened retrospectively from the medical records. Prospective study setting with active screening of these diseases could possibly result in different prevalences regarding the comorbidities. Additionally, the inflammatory marker analyses in the study IV were performed only at one cross-sectional time point and thus do not provide longitudinal data.

6.5 CLINICAL IMPLICATIONS

Although the findings of this study may be considered preliminary and require replication, some clinical implications may be hypothesized. First, the observed comorbidity burden in FTLD should be acknowledged by clinicians so that patients with FTLD will receive proper diagnoses and treatment also for co-occurring diseases, especially several immunological diseases showing increased prevalence in FTLD. Second, the disadvantageous systemic pro-inflammatory profile observed in the early stage of the disease could be used as a prognostic factor and thus it might help clinicians to allocate appropriate resources and to provide prognostic information to these particular patients. Last, if further studies are able to confirm that systemic pro-inflammatory state is indeed detrimental for the disease, those patients with abnormal inflammation may benefit from immunomodulatory treatments.

7 CONCLUSIONS

Based on the results of the work in this thesis, following conclusions can be made:

1. The prevalence of cancer is lower in FTLD patients compared to AD or control subjects (I).

2. The prevalence of comorbid immunological diseases in FTLD patients may be affected by both genotype and clinical manifestation. Some specific autoimmune conditions, such as cutaneous diseases, may be more prevalent than others in FTLD patients (II-III).

3. FTLD patients especially carrying the *C9*-RE may have an increased risk for developing BP, but the association is not likely specific to FTLD. BP180 autoantibodies are more likely associated with FTLD compared to BP230 autoantibodies (III).

4. The *C9*-RE might be associated with elevated blood IL-10 and hemoglobin levels, but also the gender may contribute to these factors as differences were observed only in male patients (IV).

5. Specific peripheral inflammatory markers may be associated with distinct clinical manifestations in patients with FTLD. Elevated levels of pro-inflammatory RANTES and MCP-1 and lower levels of anti-inflammatory IL-10 were found to associate with parkinsonism and a more rapid cognitive and/or functional decline (IV).

6. Systemic pro-inflammatory state in the early stage of FTLD may predict worse prognosis (IV).

8 FUTURE PERSPECTIVES

According to the current estimations, the global burden of dementia will dramatically increase over the next few decades and thus the need for better pathophysiological understanding eventually leading to disease-modifying treatments or disease prevention is urgent. The recent findings suggesting an important role of the immune system in the pathogenesis of neurodegenerative diseases have created several new perspectives on the immunological mechanisms as potential targets for future treatment options. However, these perspectives require further investigations, as the immune system in neurodegeneration most likely plays a dual role (either beneficial or harmful) that must be better understood before appropriate treatments at a specific disease stages could be considered.

Furthermore, in the future, it will be essential to be able to classify patients within the heterogenous FTLD spectrum into specific subgroups that would eventually benefit from specific personalized treatments, such as immunological or genetic therapies. These specific subgroups should ideally include patients only with specific neuropathological and genetic backgrounds, or perhaps immunological profiles. These demands require more specific discriminative neuropathological and immunological fluid (blood or CSF) biomarkers (e.g. fluid biomarkers discriminating FTLD-TDP from FTLD-tau), and also longitudinal data that would allow evaluation of the immunological alterations at different disease stages (before and after neuropathological inclusions, at the clinical disease onset etc.). Discriminative biomarkers could be utilized to differentiate between patients that would benefit from certain treatment from those that would not or for whom the treatment might even be disadvantageous. Also, biomarkers could aid in the differential diagnostics between FTLD and other diagnostic groups, such as AD and psychiatric disorders. Notably, the current diagnostic criteria for FTLD includes only clinical symptom profile (stage 1), imaging findings (stage 2) and genetic measurements (stage 3). On the other hand, especially bvFTD patients show significant clinical overlap with psychiatric patients and patients with other neurodegenerative diseases, the visual brain MRI assessment provides only moderate specificity and sensitivity and lastly most of the FTLD cases are sporadic and thus can not be confirmed with genetic testing. These limitations highlight the need for new FTLD specific biomarkers that could be included in the current criteria for more accurate FTLD diagnostics. Lastly, biomarkers could provide important prognostic knowledge to the clinician, the patient, and the caregivers. Regarding the systemic immune system alterations, it would be important to evaluate fluid biomarkers from both blood and CSF and to measure the correlation between these two biofluids to gain information on the possible interaction between the periphery and central nervous system. The immunological markers should be reflectors of inflammation in general, but also

especially markers of adaptive immunity and autoimmunity should be explored. Extensive screening for different types of autoantibodies from blood and CSF, as well as analyses aiming to evaluate the activity of different types of T-cells, B-cells, and glial cells would be especially informative. Another interesting topic would be to evaluate the role of gut microbiota in FTLD, considering that it can regulate both systemic and neuroinflammation.

Regarding future studies related to the *C9*-RE, there are only limited data on the role of the intermediate expansions in the FTLD disease spectrum in general. Additionally, the potential effects of the repeat expansion size on the immunological factors and the function of the immune system in FTLD is unclear, warranting further studies on this matter. As currently ongoing studies are aiming to modulate the *C9*-RE-associated toxicity via gene therapy, these approaches might also provide possibilities to evaluate the association between the *C9*-RE and immunoregulation.

Finally, as the spectrum of FTLD is both rather rare and heterogenous, there is a great need for national and international multicenter collaboration that enables sufficient patient cohort sizes with appropriate profiling of the genotypes and phenotypes of the patients.

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Recent studies have indicated potential immune system dysfunction in both genetic and sporadic frontotemporal lobar degeneration (FTLD). Especially the most common genetic cause of FTLD, the C9orf72 repeat expansion, has been associated with immune system regulation. This thesis sheds light on the potential immune system changes in FTLD patients with and without the C9orf72 repeat expansion with an emphasis on immunological comorbidities and peripheral inflammatory markers.

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