DEPARTMENT OF PATHOLOGY
UNIVERSITY OF HELSINKI
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NEUROPATHOLOGIC AND GENETIC DETERMINANTS OF NEURODEGENERATIVE PROTEINOPATHIES:

SPECIAL EMPHASIS ON HIPPOCAMPAL SCLEROSIS AND TDP-43 PATHOLOGY

Mia Kero

ACADEMIC DISSERTATION

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To My Family

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I. Kero M, Raunio A, Polvikoski T, Tienari PJ, Paetau A and Myllykangas L. Hippocampal sclerosis in the oldest old: a Finnish population-based study. Journal of Alzheimer´s Disease 2018; 63(1): 263–272.

II. Hokkanen S.R.K*, Kero M*, Kaivola K, Hunter S, Keage H.A.D, Kiviharju A, Raunio A, Tienari PJ, Paetau A, Matthews F.E, Graff C. Polvikoski T.M, Myllykangas L, Brayne C. Old-age hippocampal sclerosis associates with *GRN* and *TMEM106B* but not with *ABCC9* variation in population-representative cohorts. Brain Pathol. 2019 Aug 3. doi: 10.1111/bpa.12773. [Epub ahead of print].

III. Kero M, Paetau A, Polvikoski T, Tanskanen M, Sulkava R, Jansson L, Myllykangas L, Tienari PJ. Amyloid precursor protein (APP) A673T mutation in the elderly Finnish population. Neurobiology of Aging. 2013 May;34(5): 1518.e1-3.

IV. Ferrari R1, Kero M, Mok K, Paetau A, Tienari PJ, Tynninen O, Hardy J, Momeni P, Verkkoniemi-Ahola A, Myllykangas L. Familial frontotemporal dementia associated with C9orf72 repeat expansion and dysplastic gangliocytoma. Neurobiology of Aging. 2014 Feb;35(2): 444.e11-4.

* Equal contribution

ABBREVIATIONS

ABAC7	*ATP-binding cassette transporter A7*
ABCC9	Sulfonylurea receptor 2- encoding gene
Aβ	Amyloid beta
AGD	Argyrophilic grain disease
AICD	Amyloid precursor protein intracellular domain
AKT	Protein kinase B
ALS	Amyotrophic lateral sclerosis
AD	Alzheimer´s disease
APOE	Apolipoprotein E
APP	Amyloid precursor protein
ArG	Agryophilic grain
ATM	Ataxia telangiectasia mutated protein kinase
α-SYN	Alpha synuclein
BACE	Beta-site amyloid precursor protein cleaving enzyme, beta- secretase
B-ASC	Brain arteriolosclerosis
BIBD	Basophilic inclusion body disease
BIN1	Bridging integrator 1
BVFTD	Behavioral variant of frontotemporal dementia
C9orf72	Chromosome 9 open reading frame 72 gene
CA	Cornu ammonis
Ca^{2+}/K^{+}	Calcium/Potassium
CAA	Cerebral amyloid angiopathy
cAMP	Cyclic adenosine monophosphate
CD2AP	CD2 associated protein coding gene
CD33	Sialic acid binding Ig-like lectin 3
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CFAS	Cognitive Function and Ageing Studies
CGI	Granular cell inclusion
CHCHD10	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10 gene
Chi2	Chi-square distribution
CHMP2B	Charged multivesicular body protein 2B gene
CLU	Clusterin gene
CNS	Central nervous system

CTF	Carboxy terminal fragment
CKD5	Cyclin- dependent kinase-5 protein
DCTN1	Dynactin subunit 1 gene
DLB	Dementia with Lewy bodies
DNA	Deoxyribonucleic acid
DTI	Diffusor tensor imaging
EClipSE	Epidemiological Clinicopathological Studies in Europe
ER	Endoplasmic reticulum
FAD	Familial Alzheimer's disease
FDG-PET	Fluorodeoxyglucose positron emission tomography
FET	Fisher's exact test
FFPE	Formalin fixed paraffin embedded
FTLD	Frontotemporal lobar degeneration
FTD	Frontotemporal dementia
FUS	Fused in sarcoma, a nuclear DNA/RNA binding protein
GSK-3β	Glycogen synthase kinase-3β
GRN	Progranulin encoding gene
GWAS	Genome-wide association study
HE	Hematoxylin and Eosin staining
hnRNP	Heterogeneous nuclear ribonucleoprotein gene
HS	Hippocampal sclerosis
HS-AGING	Hippocampal sclerosis of aging
HWE	Hardy Weinberg equilibrium
IDE	Insulin degrading enzyme
IHC	Immunohistochemistry
ILAE	International League Against Epilepsy
KCNMB2	Calcium-activated potassium channel subunit beta-2
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LATE-NC	Limbic-predominant age-related TDP-43 encephalopathy, neuropathological change
LOAD	Late onset Alzheimer´s disease
MAF	Minor allele frequency
MAPT	Microtubule-associated protein tau
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
mRNA	Messenger ribonucleic acid
MS4A	Membrane-spanning four-domains subfamily A
MSA	Multisystem atrophy

mTOR	Mammalian target of rapamycin
NCI	Neuronal cytoplasmic inclusion
NFT	Neurofibrillary tangle
NGS	Next generation sequencing
NIFID	Neuronal intermediate filament inclusion disease
NII	Neuronal intranuclear inclusion
O/N	Over night
OPTN	Optineurin gene
p53	Tumor suppressor protein p53
p62	Ubiquitin-binding protein p62
PD	Parkinson´s disease
PEG	Polyethylene glycol
PICALM	Phosphatidylinositol Binding Clathrin Assembly Protein Gene
PNFA	Progressive nonfluent aphasia
PPA	Primary progressive aphasia
PSEN	Presenilin gene
PTEN	Phosphatase and Tensin homolog
PTK2B	Protein tyrosine kinase 2 beta
RAB38	Ras-related protein Rab-38
RNA	Ribonucleic acid
RT	Room temperature
S6	S6- kinase
SD	Semantic dementia
SNP	Single nucleotide polymorphism
SORL1	Sortilin related receptor 1
SQSTM1	Sequestosome-1, ubiquitin-binding protein p62
TARDP	TAR DNA-binding protein 43 gene
TDP-43	TAR DNA-binding protein 43
TBK1	TANK-binding kinase 1
TLE	Temporal lobe epilepsy
TMEM106B	Transmembrane protein 106b-encoding gene
TREM2	Triggering receptor expressed on myeloid cells 2
UBI	Ubiquitin
UBQLN	Ubiquilin
UPS	Ubiquitin/Proteasome system
VaD	Vascular dementia
VCP	Valosin-containing protein
WGS	Whole genome sequencing

ABSTRACT

One of the leading health challenges worldwide is dementia, the incidence of which is rapidly increasing along with increasing life expectancy. The number of people with dementia is estimated to reach 150 million by 2050. Thus, the estimated financial costs associated will be enormous, and there is tremendous pressure to find better tools for the prevention, early detection and treatments of dementia.

The most common neurodegenerative disease is Alzheimer´s disease (AD), covering at least 50% of patients with dementia. Other common dementing diseases include vascular dementia (VaD) (20%), frontotemporal lobar degeneration (FTLD) (10%) and dementia with Lewy bodies (DLB) (5%). In addition, neuropathological studies have suggested some recently identified neurodegenerative entities to be common in the very elderly population. One such entity is hippocampal sclerosis of aging (HS-Aging), which is characterized by neuronal loss in the hippocampal CA1 and subiculum, and TDP-43 -positive inclusions in the hippocampal dentate fascia.

The general aim of this thesis project was to investigate the frequency and genetic background of age-associated neurodegenerative diseases, particularly HS-Aging and other TDP-43 proteinopathies, in the Finnish population. In Study **I**, we determined the prevalence of HS-Aging and the associated neuropathological changes in a population-based sample of very elderly Finns (Vantaa85+ study). In Study **II**, the associations of previously identified risk variants with HS-Aging were investigated in a combined dataset of Finnish and British population-based cohorts. In Study **III**, the prevalence of an *amyloid precursor protein* (*APP*) mutation, previously shown to be protective against AD, was determined among the oldest old Finns. In the last study, Study **IV**, we investigated the neuropathological and molecular genetic phenotype of Finnish familial patients with FTLD associated with a rare brain tumor, dysplastic gangliocytoma.

HS-Aging was detected in 16% of Finns aged over 85 years. HS-Aging without any other comorbid neuropathologies was seen in only one individual (2% of cases). 51% of subjects with HS-Aging exhibited a bilateral disease, indicating that pathological sections should be taken from both hippocampi for neuropathological diagnostics. Dementia and TDP-43-, p62- and Tau-positive granular cell inclusions were strongly associated ($p < 0.001$) with HS-Aging (**I**). The population -representative cohorts confirmed polymorphisms in *GRN* and *TMEM106* to be genetic risk factors for HS-Aging and accumulation of TDP-43 positive inclusions in hippocampus (**II**). The protective *APP* mutation (A673T) was detected in only one very aged female (0.19%) subject. This individual exhibited HS-Aging, but no AD pathology, indicating that this mutation probably protects

against AD changes (**III**). The familial FTLD was characterized neuropathologically by abundant hippocampal and cortical TDP-43- and cerebellar p62-pathology, and it was shown to be caused by a hexanucleotide repeat expansion mutation in *C9orf72*. In addition, *C9orf72* repeat expansion mutation hypothetically promoted the development of dysplastic gangliocytoma (**IV**).

In conclusion, this study provided new information on the prevalence and genetic background of HS-Aging and other TDP-43-proteinopathies in the Finnish population.

Key words: HS-Aging, population-based, oldest old, risk alleles, *APP* mutation, *C9orf72* expansion

1. INTRODUCTION

The frequency of old-age-associated dementing neurodegenerative diseases is increasing in line with the raising life expectancy of population. Globally, the number of people with dementia is estimated to reach 76 million in 2023. In addition to human suffering, the financial costs of these diseases are enormous, and there is a pressing need to recognize the signs of dementia earlier and to develop effective early interventions.

The most common neurodegenerative disease is Alzheimer´s disease (AD), covering at least 50% of patients with dementia. Other common dementing diseases include vascular dementia (VaD), dementia with Lewy bodies (DLB), Parkinson´s disease (PD) and frontotemporal lobar degeneration (FTLD). The neuropathological hallmarks of the diseases listed above have been described several decades ago; however, more recent neuropathological studies have suggested some new neurodegenerative entities, such as Limbic Age-related TDP-43 Encephalopathy, LATE. The term is considered to include TDP-43 proteinopathy associated with cognitive impairment including, for example hippocampal sclerosis of aging (HS-Aging). However, these are new disorders and need to be studied in representative population-based samples in order to elucidate their impact on society.

The great majority of patients (>95%) suffer from sporadic forms of neurodegenerative diseases, which are multifactorial in origin, so both genetic variants and environmental factors have a role in their pathogenesis. <5% of patients have familial forms of neurodegeneration, caused by gene defects that are inherited in a Mendelian fashion. Genetic technologies, including genome-wide association studies (GWAS, since 2005) and next generation sequencing (NGS, since 2009), have developed very rapidly during the last two decades and have revolutionized the study of genetics of both familial and sporadic neurodegenerative diseases. Gene defects underlying rare inherited forms of diseases can be identified with these technologies with lower costs and workload. Furthermore, the new technologies make it possible to find rare gene variants, either predisposing or protective, which affect the risk of common sporadic forms of diseases. GWAS allows us to use hypothesis-free approaches to find new disease-associated gene variants underlying the sporadic forms of neurodegeneration.

The main aim of this thesis project was to study the frequency and genetic background of old-age-associated HS-Aging in a Finnish elderly population- based sample (the Vantaa 85+ study). In addition, the prevalence of the *amyloid precursor protein (APP)* A673T mutation, previously reported to be protective against AD, was analyzed in this same cohort. The genetic and neuropathological characteristics of a Finnish familial form of FTLD associated with a very rare tumor, dysplastic gangliocytoma, was also described.

2. REVIEW OF LITERATURE

2.1. NEURODEGENERATION AND DEMENTIA

Dementia is a usually incurable, gradually progressive disease causing memory impairment, difficulties with cognition, changes in emotional behavior and motivation caused by neurodegeneration in the specific brain areas (van der Flier and Scheltens 2005, Elahi and Miller 2017). Most prevalence estimates of dementia are based on clinical diagnosis; therefore, the prevalence numbers of various neurodegenerative pathologies causing dementia are not reported precisely (Prince et al. 2013). Identifying early disease stages before the onset of clinical dementia is very challenging, and at older ages, mixed pathologies become more common (Tanskanen et al. 2017). The prevalence of neurodegenerative diseases varies from study to study, even in the few studies with neuropathological assessment (Brunnstrom et al. 2009) (Figure 1), mainly because the criteria and methods used and the brain regions assessed are different. It should be remembered that there are differences between clinical and neuropathological principles to define neurodegenerative diseases. Neuropathological examination to set correct diagnosis of dementia subtype after death is essential (Brunnstrom et al. 2009). However, it is clear that the most prevalent dementing disease is AD (Ferri et al. 2005, Brunnstrom et al. 2009, Prince et al. 2016).

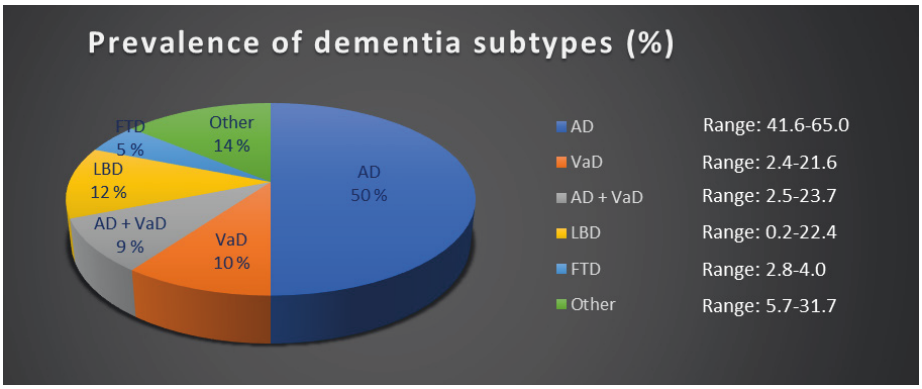


Figure 1. Neuropathologically defined diagnosis of neurodegenerative disorders in seven different studies. There is a great variation in the prevalence estimates between the different studies. Modified from the figure by Brunnström et al 2009.

By 2030, the number of people with dementia is predicted to reach almost 76 million and increase by a further 80% by 2050 (https://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf). There are almost 8 million new dementia patients each year (Ferri et al. 2005). The incidence (Figure 2) and prevalence of dementia are associated with age, but dementia is not considered to be a part of normal aging (Irwin et al 2018). The worldwide costs of dementia were estimated to be $604 billion (USD) in 2010 (Wimo et al. 2013). The World Alzheimer´s Disease Report 2013 (https://www.alz.co.uk/research/GlobalImpactDementia2013.pdf) predicted an 85% increase in costs by 2030.

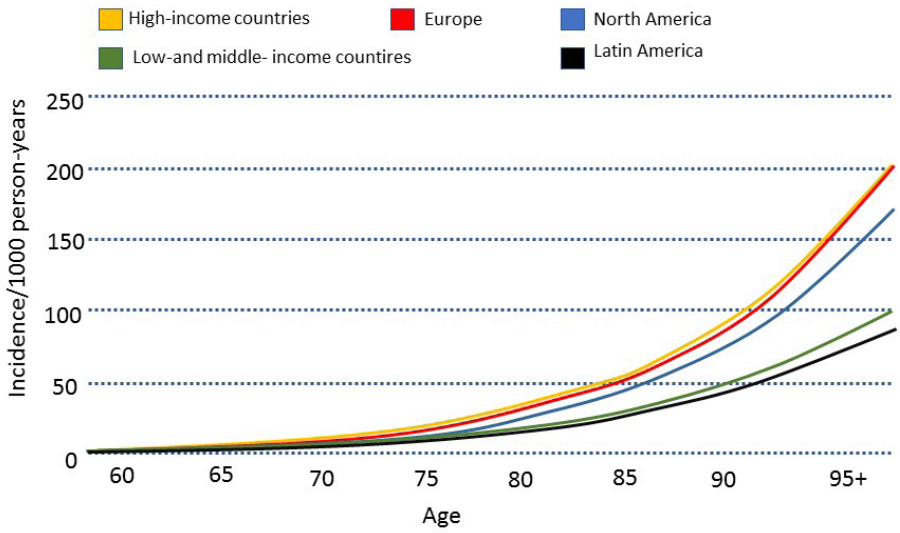


Figure 2. Estimated incidence of dementia divided by region and its development status based on meta-analysis data by WHO. Modified from http://www.who.int./mental_health/neurology/dementia/en/.

2.2. CLASSIFICATION OF NEURODEGENERATIVE DISEASES

The main neuropathological findings in neurodegenerative diseases include neuronal loss and gliosis in certain disease-specific brain areas, and disease-specific intracellular or extracellular protein aggregates found in neuronal and glial cells (Figure 3) (Ross and Poirier 2004, Kovacs 2016). Clinical symptoms can be very different depending on the type of neuropathological changes and their location in the brain, but there are common signs and symptoms for all forms of neurodegenerations, including changes in the person´s cognitive and psychological abilities (Soto and Estrada 2008, Kovacs 2016). The classification of neurodegenerative diseases includes several categories, presented in Figure 3.

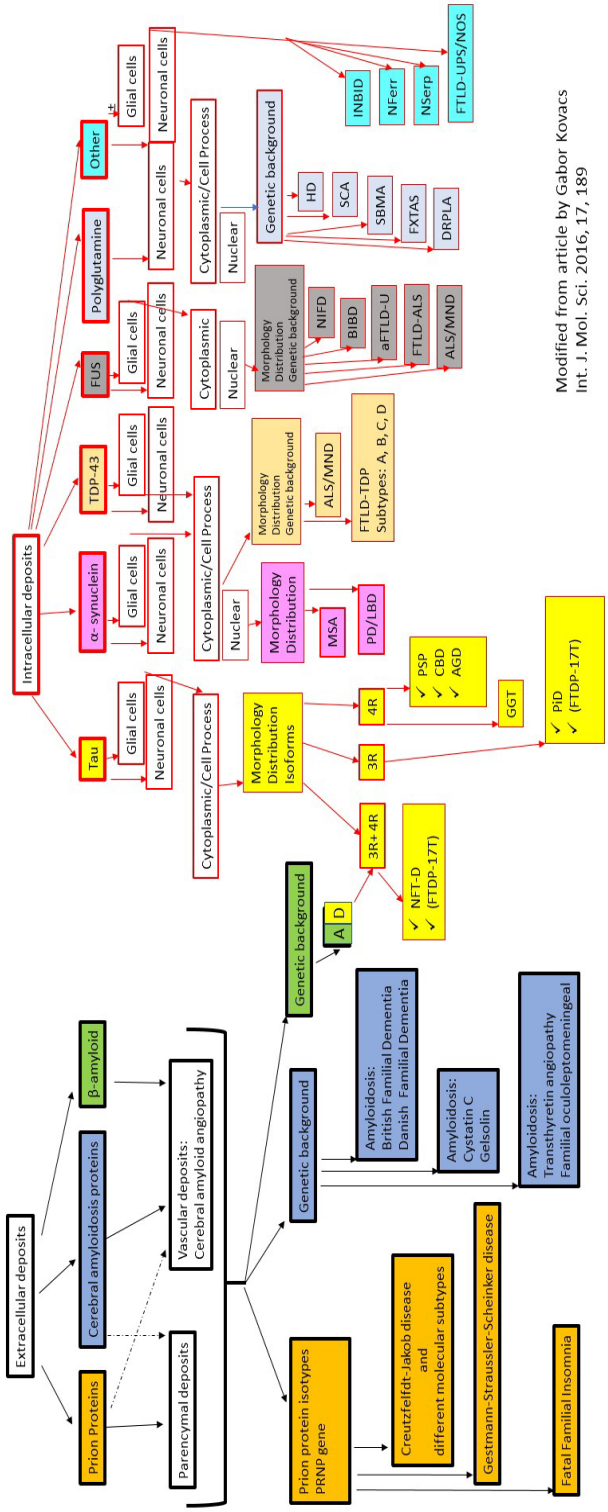


Figure 3. Classification of neurodegenerative diseases based on the cellular location of aggregates.

AD = Alzheimer´s disease, NFT-D = Neurofibrillary tangle-predominant dementia, FTDP-17 T = Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by MAPT gene mutations, PiD = Pick´s disease, PD = Parkinson's disease, LBD = Lewy body disease, PSP = Progressive supranuclear palsy, CBD = Corticobasal degeneration, AGD = Argyophilic grain disease, GGT = Globular glial tauopathies, FTLD-TDP = Frontotemporal lobar degeneration with TDP-43 inclusions, ALS/MND = Amyotrophic lateral sclerosis/ Motoneuronal disease, aFTLD-U = atypical Frontotemporal lobar degeneration with ubiquitin inclusion, BIBD = Basophilic inclusion disease, NIFID = Neurofilament intermediate filament inclusion disease, HD = Huntington disease, SCA = Spinocerebellar ataxia, SBMA = Spinal and bulbar muscular atrophy, FXTAS = Fragile X-associated tremor and ataxia syndrome, DRPLA = Dentatorubral-pallidoluysian atrophy, INIBD = Intranuclear inclusion body disease, Nferr = Neuroferritinopathy, Nserp= Neuroserpinopathy, FTLD-UPS/NOS = Frontotemporal lobar degeneration with ubiquitin inclusions/not otherwise specified.

2.3. NEURODEGENERATIVE DISEASES, MISFOLDED PROTEINS, AND MIXED NEUROPATHOLOGICAL FINDINGS

The common misfolded proteins (found in neuronal and glial cells) associated with neurodegenerative diseases (Table 1) in the central nervous system are Amyloid-beta (Aβ), Tau, TDP-43, α- Synuclein (α-Syn) and FUS (den Haan et al. 2018, Kovacs 2016, Lee et al. 2013, Neumann et al. 2006, Mackenzie et al. 2010b, Goedert et al. 2017, Kuusisto et al. 2008, Armstrong 2012b, Oshima and Dickson 2009, Ren and Sahara 2013). According to these morphologically variable aggregated proteins (Figure 4), a nomenclature has been created for different proteinopathies: for example tauopathies, α-synucleopathies, TDP-43 proteinopathies, and FUS/FET proteinopathies (Kovacs 2016). A sporadic or inherited mutations are causing the accumulation and aggregation of these proteins (Martin 1999, Jellinger et al. 2001, Kovacs 2016). Inherited forms of neurodegenerative diseases are caused by the mutations in the genes encoding relevant proteins and have usually earlier onset a more severe phenotype compared to sporadic forms of neurodegenerative disease (Martin 1999, Jellinger et al. 2001, Kovacs 2016).

Table 1. The misfolded proteins, the chromosomal locations and genes encoding them, and the associated neurodegenerative diseases.

Protein	Chromosomal location	Gene	Disease associated with the protein
β-amyloid	21q21.3	*APP*	Alzheimer´s disease
Tau	17q21.31	*MAPT*	Pick's disease Corticobasal degeneration Progressive supranuclear palsy Argyrophilic grain disease Multiple system tauopathy with presenile dementia STD Frontotemporal lobar degeneration with Tau inclusions
α-synuclein	4q22.1	*SNCA*	Parkinson's disease Dementia Lewy body Multisystem atrophy
TDP-43	1p36.22	*TARDBP*	Frontotemporal lobar degeneration with TDP-43 inclusions (type A–D) Motor neuron disease with TDP-43 inclusions Frontotemporal lobar degeneration – Motor neuron disease with TDP-43 inclusions
FUS	16p11.2	*FUS*	Atypical FTLD with ubiquitin positive inclusions Neurofilament intermediate filament inclusion disease Basophilic inclusion disease Motor neuron disease with FUS positive inclusions

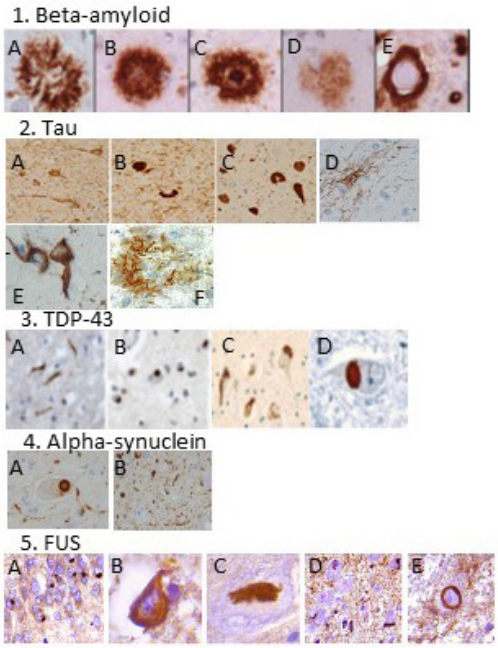


Figure 4. Different morphological aggregates of beta-amyloid, Tau, TDP-43, alpha-sunuclein and FUS.

1.A = Fibrillar plaque, 1.B = Compact plaque, 1.C = Cored plaque, 1.D = Diffuse plaque, 1E = Cerebral amyloid angiopathy (CAA). Images from Haan et al 2018.

2.A = Tau deposits in neuronal perikarya, dendrites and neurophil threads, 2.B = Tau deposits in oligiodendroglial cells, 2.C = Tangles and neurophil threads, 2.D = Tufted astrocytes, 2.E = Coiled bodies in olidendroglial cells, 2.F = Astrocytic plaque. Images from Oshima and Dickson 2009 and Ren et al 2013.

3.A = Short neurites, 3.B = Perinuclear inclusion in neurons, 3.C = Skein-like inclusions in motoneurons, 3.D = Intracytoplasmic round inclusion in motor neuron. Images from Neumann et al 2006, Mackenzie et al 2010.

4.A = Lewy body (large) in neuron, 5.B = Small Lewy bodies and aggegates in neurites. Images modified from https://www.alzforum.org/print-series/554861 by Dennis Dickson.

5.A = Neuronal cytoplasmic inclusions, 5.B = Tangle-like inclusions, 5.C = Conglomerate inclusion in a neuron, 5.D = Vermiform intranuclear inclusions in neurons, 5.E = A ring shaped intranuclear inclusion in a neuron. Images modied from Lee et al 2013.

It is common in neurodegenerative diseases that the pathological findings and clinical features differ between patients categorized into the same disease group. Similarly, the same misfolded protein can be seen in several different neurodegenerative diseases (Table 2) (Kovacs et al. 2008). This phenomenon causes overlap in the neurodegenerative diseases and difficulties in the categorization of subjects not clearly belonging to any basic group (Armstrong 2012a). In addition, the co-existence of classification categories and similar kinds of pathogenic disease pathways complicates the classification (Kovacs et al. 2008). Three different models, based on clinicopathological features, are suggested for neurodegenerative diseases: discrete, overlap and continuum (Figure 5) (Armstrong 2012a).

Table 2. Pathological aggregates overlap in some neurodegenerative diseases. AD = Alzheimer´s disease, FTLD = Frontotemporal lobar degeneration, DLB = Dementia with Lewy Bodies, PD = Parkinson´s disease.

Disease Protein	AD	FTLD	DLB	PD
Aβ				
Tau				
α-Syn				
TDP-43				
FUS				

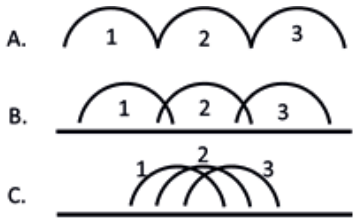


Figure 5. Overlapping models based on clinicopathological features of neurodegenerative diseases. A = Discrete model, B = Overlapping model and C = Continuum model for neurodegenerative diseases. Each number (1, 2 and 3) represents a different disease and its distribution. A: Three different diseases with minor overlap. B: Three different diseases with clear overlap. C: Three different sets of clinicopathological features continuously redefined as one disease to another (Modified from Amstrong et al. 2012a).

2.4. NEURODEGENERATION, CELL DEATH, AND PROTEIN DEGRADATION

Neurodegenerative diseases are progressive and a typical feature is the death of neurons in selected areas of the nervous system (Ross and Poirier 2004). The number, distribution and type of misfolded and aggregated proteins usually correlates with the severity of the disease (Gorman 2008). Misfolded protein aggregates are associated with different neurodegenerative disorders and can be caused by the problems of clearance mechanisms, resulting in cell death (Gorman 2008, Knight and Verkhratsky 2010). Several different cell death mechanisms for

the neuronal cells in neurodegenerative diseases are known: apoptotic, necrotic, autophagic and exitotoxic (Bedford et al. 2009, Ciechanover 2015). In apoptosis, the cells are shrunk , DNA is degraded and apoptotic bodies are formed. The execution of apoptosis can be incited by signals, either extrinsically or intrinsically (Chi et al. 2018). The cellular content of the cell does not leak out during this process, which is the case in necrotic cell death as a consequence of cell swelling (Chi et al. 2018). Autophagocytosis is an intracellular process to degrade aggregated proteins and damaged cell organelles, which are too large to be degraded in the proteasomes (Bedford et al. 2009, Chi et al. 2018). Excitotoxic cell death is caused by excessive neurotransmitter stimulation often mediated by glutamate or other related amino acids (Chi et al. 2018).

Misfolded proteins are formed in different cellular compartments, including the cytoplasm, nucleus, and endoplasmic reticulum (ER) and the proteins are primarily degraded in the ubiquitin proteasome system (UPS) (Bedford et al. 2009, Tanaka and Matsuda 2014). Ubiquitin is activated by an ATP-dependent reaction and conjugated with the targeted protein, and these proteins are subsequently de-ubiquitinated and degraded into short peptides (Figure 6) (Bedford et al. 2009, Ciechanover 2015). Another common form of degradation is autophagocytosis mediated, for example, by p62 (Figure 7), where the autophagosome is finally fused with the lysosome for degradation (Bedford et al. 2009, Tanaka and Matsuda 2014).

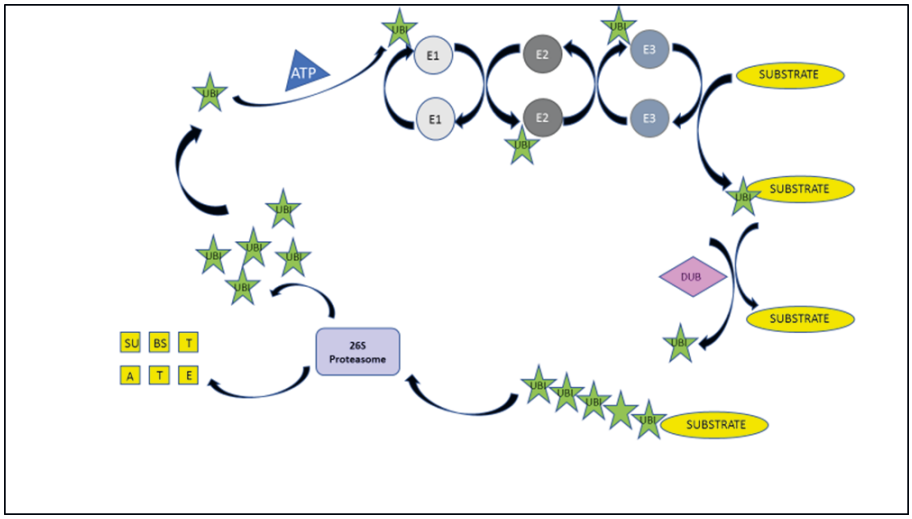


Figure 6. Ubiquitin-activating enzyme E1 activates ubiquitin in an ATP-driven reaction. Next, ubiquitin is relocated to conjugating enzyme E2. E3, the ubiquitin ligase protein, combines the substrate and ubiquitin. A de-ubiquitylating enzyme, DUB, separates ubiquitin and the substrate protein. In the fourth phase, ubiquitin molecules are attached to the substrate to form a chain. This complex is able to bind with the 26S proteasome, where degradation is performed. Modified from Neurodegeneration, the molecular pathology of dementia and movement disorders. Second Edition, 2011. Edited by D. Dickson and R. Weller.

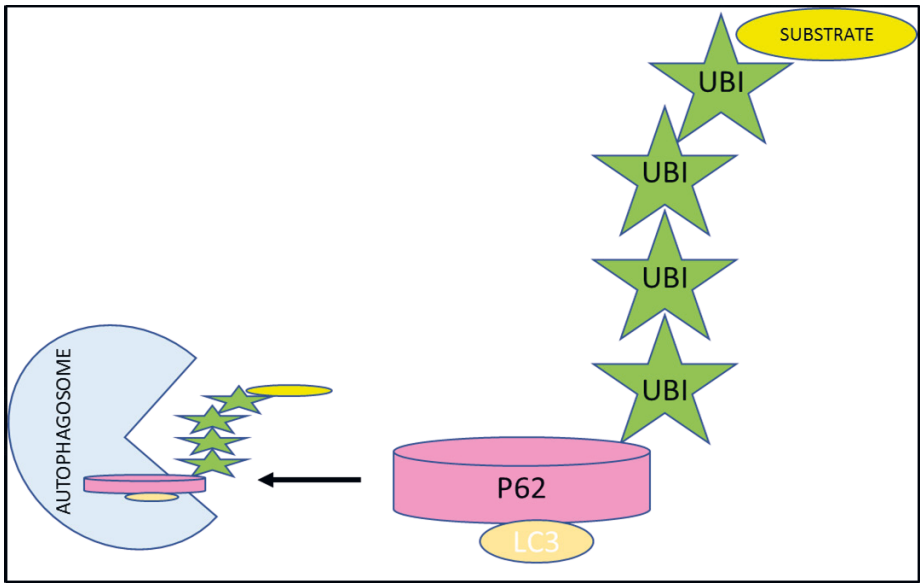


Figure 7. Degradation and autophagy. A polyubiquitinated protein, combined with p62 (conjugated with signaling molecule LC3), is sequestered into the autophagosome. Modified from Tanaka et al. 2014.

2.5. NEURODEGENERATION AND NEOPLASIA

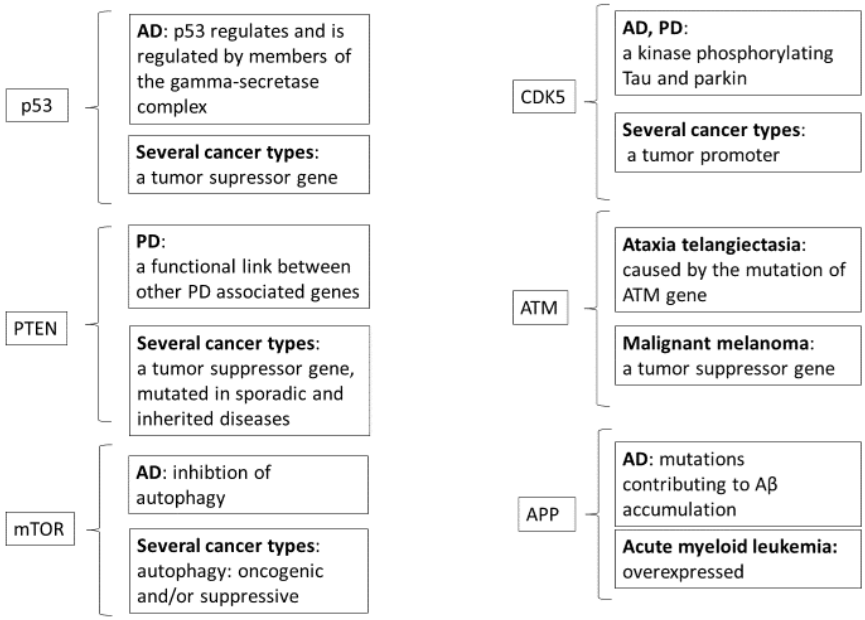
Although neurodegeneration and neoplasia have not traditionally been associated with each other, recent studies have provided evidence suggesting that common mechanisms may be involved in these disease groups.

Some epidemiological studies have shown an inverse correlation between the risk of developing cancer and neurodegenerative diseases (Sorensen et al. 1999, Fois et al. 2010). According to a quite recent, age-adjusted study, AD diagnosis was associated with a 60% reduced risk of cancer, and cancer history with a 30% reduced risk of AD (Bennett 2010). However, there is also evidence that some malignant neoplastic diseases are associated with an increased risk of neurodegenerative disease (Monaco and Vallano 2003, Mavrou et al. 2008).

Neoplasia and neurodegeneration are suggested to be the result of the interaction of genetic and environmental factors. Age is likely to play an important role in the link between the two disorders. Both neoplastic and neurodegenerative diseases are also characterized by the contribution of inherited mutated genes (Plun-Favreau et al. 2010). Many genes and their protein products (Table 3), which are associated with these two disease groups, are kinases and play a role in the cell cycle, DNA repair, and apoptosis (Monaco and Vallano 2003, Mavrou et al. 2008). The pathways of

protein degradation are often dysfunctional in both cancer and neurodegeneration (Plun-Favreau et al. 2010). Mitochondrial dysfunction and oxidative stress have also been shown to cause both diseases (Burchell et al. 2010, Hsu et al. 2016, Ali et al. 2019). Further, the autophagosomal-lysosomal pathway has been recognized as playing a major role in the mechanisms associated with both conditions (Arroyo et al. 2014, Ali et al. 2019). There is a shared feature for these processes – it is age. The frequency of onsets of both diseases have been shown to be increase with age (Plun-Favreau et al. 2010).

Table 3. The proteins associated with both neurodegeneration and neoplasia. Modified from Plun-Favreau et al. 2010). AD (Alzheimer's disease), APP (amyloid precursor protein), ATM (Ataxia telangiectasia mutated protein kinase), CDK5 (Cyclin-dependent kinase-5 protein), mTOR (mammalian target of rapamycin, p53 (tumor suppressor protein p53), PD (Pick's disease) and PTEN (phosphatase and tensin homolog).



2.6. HIPPOCAMPAL SCLEROSIS (HS)

Originally the term 'HS' was related to epilepsy, referring to the hardening and structural abnormality of the Ammon´s horn with epileptic patients described by Meynert, Sommer and Bouchet in 1860 (Eadie 2017). Today, the term 'HS' is used for the most frequent histopathology in patients with drug-resistant temporal lobe epilepsy (TLE), defined by severe neuronal loss and gliosis in the CA1 and CA4 sectors by the International League Against Epilepsy (ILAE) (Blumcke et al. 2013).

The term `HS-Aging´ is used for the pathology of severe neuronal loss of the CA1 sector and subiculum in very old people (Dickson et al. 1994). The other CA sectors are not affected. Clinical presentation shows cognitive and functional impairment (Leverenz et al. 2002, Nelson et al. 2011b, Wilson et al. 2013, Snyder et al. 2015, Dutra et al. 2015a), and HS-Aging can be clinically difficult to distinguish especially from late-onset AD (Ala et al. 2000, Attems and Jellinger 2006, Pao et al. 2011, Murray et al. 2014) HS-Aging often occurs with other age-related neurodegenerative pathologies, such as DLB, tauopathy, cerebrovascular disease and FTLD. HS-Aging is also associated with hypoxic ischemic damage, prolonged hypoglycemia, and traumatic encephalopathy. Pure HS-Aging, without any comorbid pathology, is rare (Beach et al. 2003, Blass et al. 2004, Kovacs et al. 2008, Nelson et al. 2011b, Hatanpaa et al. 2014, Neltner et al. 2014, Snyder et al. 2015, Neltner et al. 2016)

2.6.1. EPIDEMIOLOGY

The prevalence range for HS-Aging is wide, varying from 5 to 30% of autopsied brains in old age individuals (Dickson et al. 1994, Jellinger 2000, Leverenz et al. 2002, Barker et al. 2002, Probst et al. 2007, Nelson et al. 2011b, Zarow et al. 2012, Rauramaa et al. 2013, Dutra et al. 2015a, Nelson et al. 2016). There are many factors which may explain this range. In several studies, the individuals of the study cohorts are too young (Corey-Bloom et al. 1997, Blass et al. 2004, Rauramaa et al. 2013), since the prevalence of HS-aging increases heavily in individuals older than 90 years (Nelson et al. 2011b, Nelson et al. 2016). In routine neuropathological sampling, usually only one of the hippocampi is sectioned, which might cause false negative results (Nelson et al. 2011b, Zarow et al. 2012). It is also reported that HS-Aging can be segmental, which is not elucidated in any large study cohorts (Ighodaro et al. 2015). Most of the published study cohorts are biased by selective accumulation of demented individuals from dementia care units, involving individuals with mixed neuropathologies (Bennett et al. 2006, Schneider et al. 2007, Schneider et al. 2009, Nelson et al. 2013). It is not possible clinically to separate HS-Aging from AD. Clinically, most individuals affected by HS-Aging are categorized as having probable (70%) or possible (15%) AD (Nelson et al. 2013, Nelson et al. 2016). The predominance of sex in HS-Aging is controversial, some reports support male predominance (Leverenz et al. 2002, Pao et al. 2011, Zarow et al. 2012), the others female predominance (Hokkanen et al. 2018).

2.6.2. CLINICAL FEATURES

HS-Aging often affects individuals older than 85 years and has a clinical picture involving episodic memory impairment, which is often confused with the clinical phenotype of AD (Leverenz et al. 2002, Zarow et al. 2008, Nelson et al. 2011b, Zarow et al. 2012, Nelson et al. 2013, Murray et al. 2014, Nag et al. 2015, Nelson et al. 2016). In neuropsychological studies, HS-Aging has been compared to AD: deficits in HS-Aging extend beyond episodic memory and mimic the impairments seen in AD. These overlapping pathologies make it very challenging to build up a cognitive profile unique to HS-Aging (Zarow et al. 2008). Problems with memory is the first detected problem in HS-Aging (Jellinger 2000, Ala et al. 2000, Beach et al. 2003, Zarow et al. 2008). It is reported that individuals affected by HS-Aging managed poorly on episodic memory tasks demanding the recollection of recently-learned information (Corey-Bloom et al. 1997). In AD, the findings are very similar. Verbal fluency has been reported to be better preserved in comparison to AD patients (Nelson et al. 2013, Ighodaro et al. 2015). In some publications, individuals with HS-Aging have been older at the onset time of the symptoms and, as result, have a shorter duration of illness compared to those with AD (Ala et al. 2000, Leverenz et al. 2002). There is also some evidence from post-mortem imaging studies that hippocampal atrophy is more severe in HS-Aging than in AD (Dawe et al. 2011, Zarow et al. 2012, Nelson et al. 2013). However, there are no neuroimaging methods to specify the clinical diagnosis of HS-Aging (Nelson et al. 2013).

One overlapping entity with HS-Aging is FTLD. However, in FTLD patients the cortical and brainstem atrophy is much more severe compared to those with HS-Aging (Amador-Ortiz et al. 2007a, Brenowitz et al. 2014) Individuals with associated FTLD pathology are of much younger age at clinical onset and death (Amador-Ortiz et al. 2007a, Brenowitz et al. 2014). Generally, the neurocognitive status of HS-Aging patients is better compared to FTLD (Ighodaro et al. 2015). From the clinical point of view, FTLD-TDP is a very rare entity among very old people (Knopman and Roberts 2011). In contrast, HS-Aging is very frequent among very old individuals (Zarow et al. 2008, Zarow et al. 2012, Nelson et al. 2013). Based on the facts described above, it is more likely that these two diseases are separate entities, although they harbor overlapping features.

2.6.3. NEUROPATHOLOGY

In HS-Aging (Figure 8), the typical histopathological finding is a severe neuronal loss of the CA1 sector. The subiculum may also be affected (Dickson et al. 1994, Zarow et al. 2008, Nelson et al. 2011b, Zarow et al. 2012), but the CA sectors 2 to 4 are intact (Probst et al 2007). One critical feature of HS-Aging is the presence of

TDP-43-positive inclusions, primarily detected in the cytoplasm of the granular cells of the dentate fascia (Bachstetter et al. 2015). Individuals with HS-Aging are very aged and often present with comorbid neuropathologies: Aβ plaques, NFTs, Lewy bodies and argyrophilic grains (Jellinger 1994, Leverenz et al. 2002, Barker et al. 2002, Beach et al. 2003). The term "pure HS" is associated with aged individuals without other neurodegenerative pathological findings (Jellinger 2000, Ala et al. 2000, Amador-Ortiz et al. 2007a). An important diagnostic criterion for HS-Aging is that the observed Tau- pathology is not categorized as severe (Beach et al. 2003, Pao et al. 2011). There is some evidence for vascular pathologies associated with HS-Aging (Corey-Bloom et al. 1997, Ala et al. 2000, Leverenz et al. 2002, Nelson et al. 2011b, Nelson et al. 2013). There are no neuropathological consensus criteria for HS-Aging. Consensus criteria are difficult to define based on the existing data, because variations in study materials and methods make it impossible to compare the different studies thoroughly.

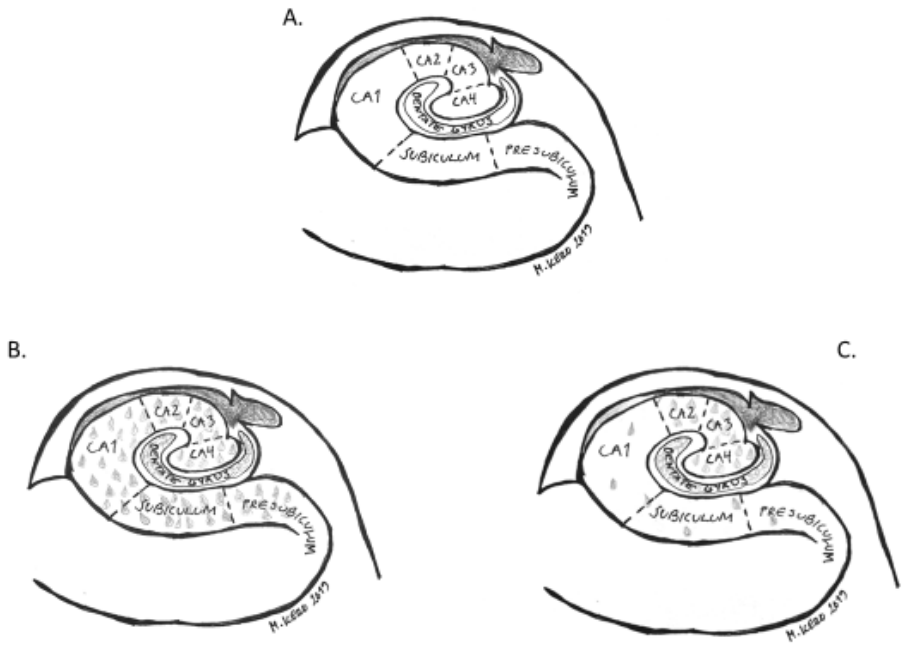


Figure 8. A: The neuroanatomical structure of the hippocampus. CA4-CA1: Pyramidal cells of the cornu ammonis. Dentate gyrus: granular cell layer of neurons. B: Intact CA1-sector and subiculum. C: The neuronal loss of CA1 and subiculum in HS-Aging.

Abundant TDP-43 immunopositivity can be observed in a large proportion (65-70%) of individuals with HS-Aging (Amador-Ortiz et al. 2007b, Nelson et al. 2011b). In HS-Aging, the TDP-43 pathology is described as localizing especially in

CA1, subiculum and granular cells of the dentate fascia. All these locations contain neurites, mainly short dystrophic ones. In the CA1 and subiculum regions, if any neurons are left, some NCIs (neuronal cytoplasmic inclusion) and NIIs (neuronal intranuclear inclusions) can be observed. In dentate, a relatively high number of TDP-43- positive NCIs can be detected (Figure 9) (Murray et al. 2014, Nag et al. 2015, Hokkanen et al. 2018). HS-Aging associated TDP-43 pathology may also be detected on the outside the of hippocampus(Cykowski et al. 2017, Nelson et al. 2019).

FTLD-TDP-43 is suggested to be closely related to HS-Aging based on the high frequency of TDP-43 pathology (Hatanpaa et al. 2008). Hatanpää et al. reported that HS was detected in 42% of FTLD-TDP individuals (Hatanpaa et al. 2004). In the majority of HS-Aging subjects, TDP-43-positive neurites and inclusion bodies can be seen, as with FTLD-TDP (Hatanpaa et al. 2008). However, the TDP-43 pathology seen in HS-Aging and FTLD-TDP is not specific only to these entities (McKee et al. 2010, Davidson et al. 2011, Walker et al. 2013).

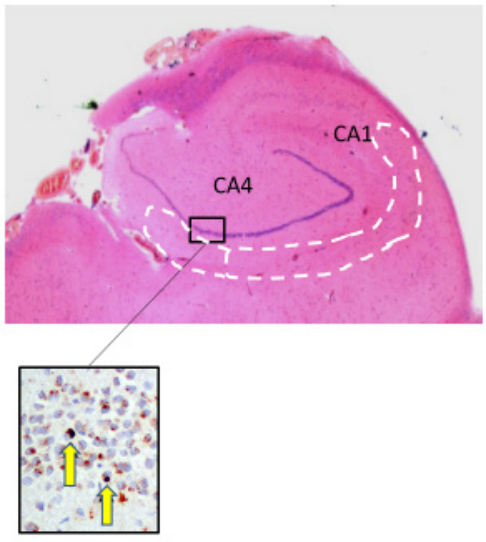


Figure 9. HE-staining of a hippocampal sample from an HS-Aging case. There is severe neuronal loss in the CA1 sector and subiculum (marked with a white dashed line). The area marked with a black box shows the granular cell layer of dentate gyrus with pTDP-43- positive inclusions (yellow arrows). The image enlargement shows the cytoplasmic inclusions of pTDP-43 (IHC staining), which are typical of HS-Aging.

2.6.4. GENETICS

Genetic risk factors can give us insights into disease-specific pathways and hypotheses. Previous research, based on US brain bank data on volunteer and clinical dementia cohorts, has indicated that single nucleotide polymorphism genotypes,

such as *GRN* rs5848 (progranulin-encoding gene), *TMEM106B* rs1990622 (transmembrane protein 106B-encoding gene), rs704180 in *ABCC9* (sulfonylurea receptor 2-encoding gene) and rs9637454 in *KCNMB2* (calcium-activated potassium channel subunit beta-2) are associated with HS-Aging (Beecham et al. 2014, Nelson et al. 2014, Nelson et al. 2015a, Katsumata et al. 2017) (Table 4). Furthermore, it is confirmed in several publications that *apolipoprotein E (APOE*) gene variants are not associated with increased risk of HS-Aging, which may indicate that AD is a different entity (Troncoso et al. 1996, Leverenz et al. 2002, Pao et al. 2011, Brenowitz et al. 2014, Nelson et al. 2015b). The rs5484 SNP of *GRN* is strongly associated with HS-Aging as a disease-modifying factor (Nelson et al. 2016). *TMEM106B,* containing the rs10990622 SNP, is known to encode a lysosomal protein influencing the expression of *GRN* (Brady et al. 2013) and involved in cognitive impairment of ALS patients as well (Vass et al. 2011). This SNP is also linked to HS-Aging and the associated neuropathological findings (Simon-Sanchez et al. 2009, Vass et al. 2011, Aoki et al. 2015, Ighodaro et al. 2015, Yu et al. 2015, Nelson et al. 2015b). The GWAS study by Nelson showed a link between *ABCC9* and HS-Aging, as well as a link between HS-Aging and brain arteriolosceleoris (B-ASC) (Nelson et al. 2014). This gene participates in regulation of potassium channels and plays a role as a metabolic guard for vascular reactions to hypoxia, ischemia and inflammation (Nelson et al. 2015a). The fourth known genetic risk factor for HS-Aging pathology is *KCNMB2*, more precisely the SNP rs9637454 (Beecham et al. 2014). The gene product of *KCNMB2* is involved in the physiology of the hippocampus (Zarei et al. 2007).

Table 4. The risk SNPs associated with HS-Aging.

GENE	SNP	METHOD	REFERENCES
GRN	rs5848	CANDITATE GENE STUDY	Rademakers et al. 2008
TMEM106B	rs1990622	CANDIDATE GENE STUDY	Rutherford et al. 2012
ABCC9	rs704180	GWAS	Nelson et al 2014, Nelson et al. 2015
KCNMB2	rs9637454	GWAS	Beecham et al. 2014

Progranulin, encoded by *GRN* (on chromosome 17), is expressed in the central nervous system (CNS) during early neuronal development, and also at modest levels in neurons and microglia in adults (Dickson et al. 2010, Sun and Eriksen 2011). This protein is proteolytically cleaved into granulin peptides by extracellular proteases, mainly elastase, likely produced by astrocytes and microglia (Dickson et al. 2010). In neurodegenerative diseases, levels of progranulin have an increased association with neuroinflammation. If there is tissue damage in CNS, progranulin can suppress excessive immunity-based microglial activation and protect neurons from reactive oxygen radicals and proinflammatory cytokines such as TNF (Sun and

Eriksen 2011). *GRN* mutations causing FTLD-TDP have been shown to generate null alleles via the haploinsufficiency mechanism, resulting in reduced progranulin protein levels (Rademakers et al. 2008). In FTLD-TDP or other related diseases, progranulin may act as a potential neurotrophic factor, and its malfunction may cause neurodegeneration, leading to the development of TDP-43-positive pathology in HS-Aging (Dickson et al. 2010). Progranulin expression may have effects on the cleavage and distribution of TDP-43 (Keage et al. 2014). The polymorphic rs5848 site in the 3'-untranslated region of *GRN* is associated with variations in progranulin levels and increased risk of HS-Aging, and it is also part of a binding site for microRNA miR-659 (Rademakers et al. 2008). miR-659 may also increase a risk for FTLD-TDP and HS-Aging by an inhibition of progranulin translation and causing an effect explaining those biochemical and pathological findings related to *GRN*-null mutations (Sun and Eriksen 2011).

TMEM106B (on chromosome 7) encodes a transmembrane protein, which is expressed especially in the frontal lobe (Finch et al. 2011). Genetic variation in *TMEM106B* may specifically modify the development of FTLD in subjects with *GRN* mutation (Murray et al. 2014). The *TMEM106B* rs1990622 variant, reported to regulate *GRN* expression, was found to be protective against HS-Aging in a cohort of AD cases (Rutherford et al. 2012).

ABCC9 (on chromosome 12) codes for an evolutionarily conserved large polypeptide sulfonylurea receptor 2 (SUR2) (Nelson et al. 2014). This protein contains multiple membrane-spanning domains and has multiple biologically complex functions (Nelson et al. 2015a) (Nelson et al. 2015a). Intronic SNPs that are clustered in the 3′ portion of *ABCC9* have been associated with a risk for human brain illnesses, including sleep disturbances and HS-Aging (Nelson et al. 2015a). The SUR2 transcript variants discovered may indicate novel alternative splicing in the mRNA's coding region. 3′ untranslated region (3′UTR) variants showing accumulation of a shorter 3´UTR and higher levels of gene expression (Nelson et al. 2014). The risk variant of the gene, associated with HS-Aging, is an expression quantitative trait locus that influences the levels and splice variants of the brain mRNA transcripts derived from *ABCC9* (Nelson et al. 2015a).

KCNMB2 encodes the transmembrane protein β-subunit of a Ca^{2+}/K^{+} channel (Katsumata et al. 2017). This subunit is involved the Ca^{2+}/K^{+} channel inactivation with the other associated subunits of the channel, contributing to neuronal voltage-dependent currents and synaptic transmission (Beecham et al. 2014, Nho et al. 2016, Katsumata et al. 2017). Such Ca^{2+}/K^{+} channels can be found in the CA1 hippocampal neurons (Hicks and Marrion 1998), and this suggest that HS-Aging may be associated with *KCNMB2* thorough Ca^{2+}/K^{+} channel activation (Katsumata et al. 2017).

There is evidence for a shared genetic background in HS-Aging and FTLD-TDP: the SNPs *TMEM106B* rs190622 and *GRN* rs5848 have been associated with both

disorders (Dickson et al. 2010, Nicholson et al. 2013, Murray et al. 2014, Nelson et al. 2015b, Nelson et al. 2015c). Based on this and the shared TDP-43 immunopositivity, it has been suggested that there is a pathogenic link between HS-Aging and FTLD-TDP (Ighodaro et al. 2015, Nelson et al. 2015b, Nelson et al. 2015c).

2.6.5. HYPOTHESES ON PATHOGENESIS

Similar to other sporadic neurodegenerative diseases, HS-Aging is a complex and multifactorial disease, contributed to by environmental factors, risk gene polymorphisms and more specific neuropathological factors (Nelson et al. 2016) (Figure 10). The possible mechanisms/pathways behind HS-Aging are known only superficially. The genetic risk variants of HS-Aging have been suggested to work as upstream or downstream factors.

ABBC9 is a genetic upstream factor that may be linked to brain arteriolosclerosis (B-ASC). In HS-Aging and associated B-ASC (Ighodaro et al. 2015, Ighodaro et al. 2017), the brain arterioles are not thickened by amyloid deposits but instead caused by hyaline, and it is often associated with lymphocytic inflammation around the hyalinized area (Nelson et al. 2016). Fibroid necrosis, microcalcification, degeneration of smooth muscle cells of the vessel wall and multiluminal arteriolar structures can be seen in these small vessels (Nelson et al. 2016). There may also be other structural changes in the small arterioles, such as a complex arrangement of pericytes, endothelial cells, astrocyte endings and extracellular matrix. These arterioles have variable functions that are still somewhat unclear concerning waste removal, blood pressure regulation, neuroglial activity and the neuroimmune system (Nelson et al. 2016). The SNPs of *TMEM106B* and *GRN* have been suggested to act as downstream factors, modifying the phenotype of the disease. These factors may affect the outcome of the disease, possibly causing misfolding and aggregation of the TDP-43 protein (Nelson et al. 2016).

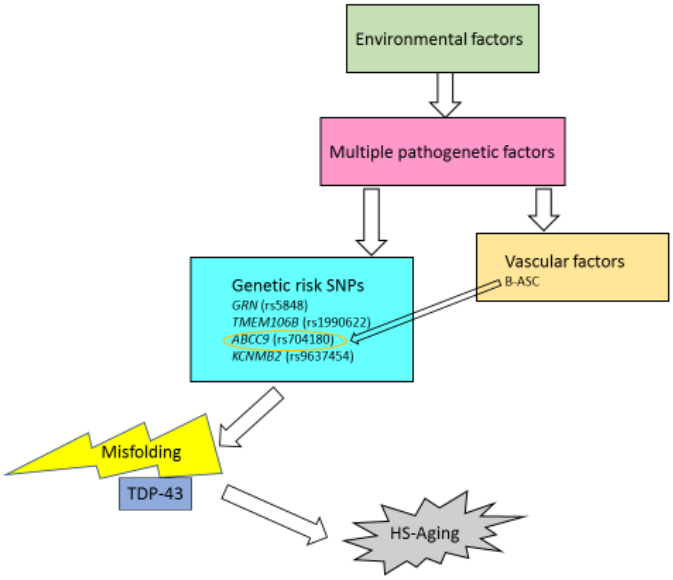


Figure 10. A hypothetical model of the pathogenic pathway involved in HS-Aging. *ABCC9* (marked with yellow circle) is associated with hippocampal sclerosis as well with brain arteriolosclerosis (B-ASC).

2.7. ALZHEIMER´S DISEASE

2.7.1. EPIDEMIOLOGY

Worldwide, AD is the most common neurodegenerative disease-causing dementia, covering 50-70% of all subjects with the condition (Jellinger 1991, Breteler et al. 1992). Both the prevalence and incidence significantly increase with age (Hy and Keller 2000). The average prevalence is settled between 5-7%, varying from continent to continent (Prince et al. 2013). The incidence of AD in Europe has been reported to be 1.3 times greater than in the USA (mean in USA 15/1000 person-years, mean in Europe 19.4/1000 person-years) (Kawas et al. 2000, Kukull and Ganguli 2000, Fratiglioni et al. 2000). One possible, though not the only explanation for the higher incidence rate among women might due to longevity of women compared to men, (Vina and Lloret 2010). The incidence has been shown to peak at the age range of 80-89 years, decreasing in the older age groups (Prince et al. 2016).

2.7.2. CLINICAL FEATURES

In 2011, the National Institute on Aging and Alzheimer´s Association (NIA-AAA) published new combined (based on genetic and biomarker) diagnostic guidelines for AD, allowing the diagnosis of probable AD to be set with increasing certainty among living patients. However, examination of brain after death is necessary for definite AD diagnosis (Grandy 2012). The clinical diagnosis of AD is not always obvious and simple because frequently there are mixed pathological processes behind cognitive dysfunction. The clinical progression of AD is seen as increasingly severe memory problems, behavioral changes as well as difficulties in managing with daily life (Allan et al. 2017). Clinically there are three different stages seen in AD: 1. Early/mild, 2. Middle/Moderate, 3. Late/severe. (Li et al. 2014). From stage one to three, memory loss worsens, problems with language are more obvious, daily tasks become more difficult to handle and social activity decreases. At the final stage, the selfhood and autonomy of the patient is lost.

Individuals suspected to have dementia should be tested with neuropsychological tests in order to determine the correct diagnosis early enough and organize the follow-up for disease progression. For clinical assessment of progressed dementia there are many cognitive screening tests available, though the most widely used is Mini-Mental Status Examination (MMSE) (Yang et al. 2016).

Different imaging methods are used for detecting changes in AD brains. Magnetic resonance imaging (MRI) can detect atrophy in the medial temporal lobes. Damage in the brain might be severe (quite large areas of atrophy can be seen in the entorhinal cortex and hippocampus), even though the patient is asymptomatic or presents only mild symptoms. MRI alone cannot be used for diagnosis because the typical findings in AD often overlap with the other dementing diseases, and sometimes subjects with AD have atypical findings in MRI (Bonifacio and Zamboni 2016). Positron emission tomography (PET) imaging methods are sometimes used as diagnostic help as well. FGD-PET (fluoro-2-Deoxy-D-glucose) measures decreased glucose metabolism as an indirect measure of the synaptic activity. Amyloid PET is based on several β- amyloid radioligands, which bind to β-amyloid in the brain, and in turn Tau PET radioligands bind to Tau protein. Neither of these methods can be used to make a definitive AD diagnosis because it is possible for healthy elderly people to have positive β-amyloid or Tau PET results (Gordon et al. 2016, Villemagne et al. 2017). It is also possible to detect AD-related pathology using biomarkers found in the cerebrospinal fluid (CSF). In the AD brain, the levels of Tau and phospho-Tau increase because these proteins no longer bind with microtubules to stabilize these structures. This is caused by Aβ accumulation, which in turn causes activation of several kinases causing hyperphosporylation of Tau. Soluble Aβ, especially Aβ42, levels decrease as a consequence of increased aggregation of Aβ to plaques (Spies et al. 2013, Herukka et al. 2017).

2.7.3. NEUROPATHOLOGY

AD pathology may begin decades before the onset of the clinical symptoms are seen. In postmortem brains, macroscopic atrophy is seen in different brain areas: the temporal, parietal and frontal lobes and sometimes occipital lobe as well as the motor cortex. The amount of white matter is decreased when ventricular systems are dilated and sulci are widened (Rani et al. 2016).

The typical histological changes in AD include the following findings (Braak and Braak 1991, Thal et al. 2002, Perl 2010, Hyman et al. 2012a): 1) parenchymal Aβ deposits called neuritic plaques, 2) intraneuronal neurofibrillary tangles (NFTs) mainly consisting of Tau protein, 3) dystrophic neurites and neuropil threads (NTs) consisting of Tau formed as misrepresentation of neuronal processes, 4) loss of synapses, 5) loss of neurons, 6) cerebral amyloid angiopathy (CAA) and 7) leptomeningeal Aβ deposits. Other commonly seen histological features are granulovascular degeneration, Hirano bodies, lipofuscin and corpora amylacea (Singhrao et al. 1995, Mitake et al. 1997, Funk et al. 2011, Moreno-Garcia et al. 2018), but none of these changes are specific to AD and can also be seen to some degree in normal aged brains.

Aβ deposits (Figure 11) can be divided into two categories: diffuse and focal. Diffuse deposits harbor an irregular shape and inaccurate borders, and they are often seen in normal aging. Focal deposits are categorized into three subcategories: primitive plaque, neuritic plaque and compact plaque (Masters et al. 1985, Selkoe 2001, Murphy and LeVine 2010).

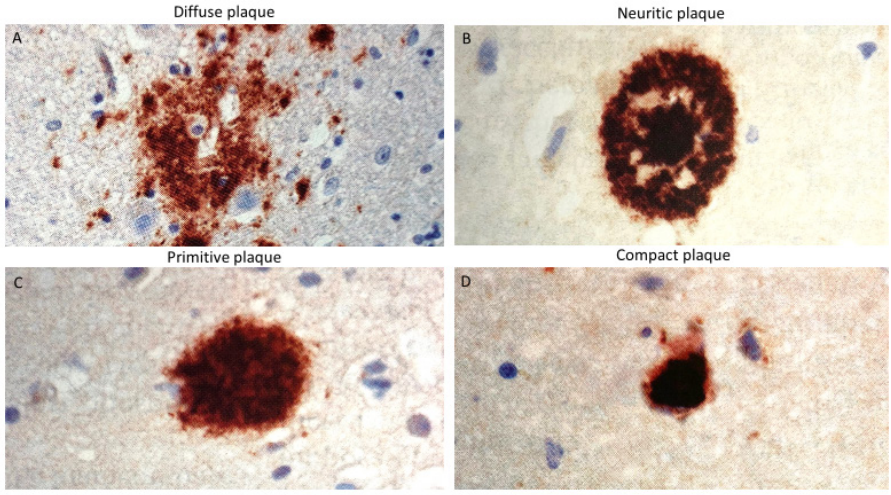


Figure 11. Morphological types of Aβ plaques. Images constructed from Neuropathology, 3rd Edition, 2012, by David Ellison and Seth Lowe.

NFTs are composed of paired helical filamentous aggregates of hyperphosphorylated Tau protein. Those NFTs can be classified as intra- and extracellular tangles (ghost tangles) (Kosik et al. 1986, Trojanowski and Lee 1995, Binder and Smrzka 2006). NFTs (Figure 12) form plaques composed of dystrophic neurites, often merged with Aβ plaques and unorganized NTs (Kosik et al. 1986, Trojanowski and Lee 1995, Binder and Smrzka 2006). NFTs might present in multiple forms, depending on the brain area where the neuron is located. In pyramidal cells, band-shaped NFTs can be observed, flame-shaped NFTs are mainly seen in large pyramidal cells (Fahn et al. 2011), small globose tangles are detected in small neurons in some cortical layers, whereas large globose tangles are seen, for example in the substantia nigra (Fahn et al. 2011). Ghost tangles are extracellular remnants of the Tau protein in a dead neuron (Miyasaka et al. 2005).

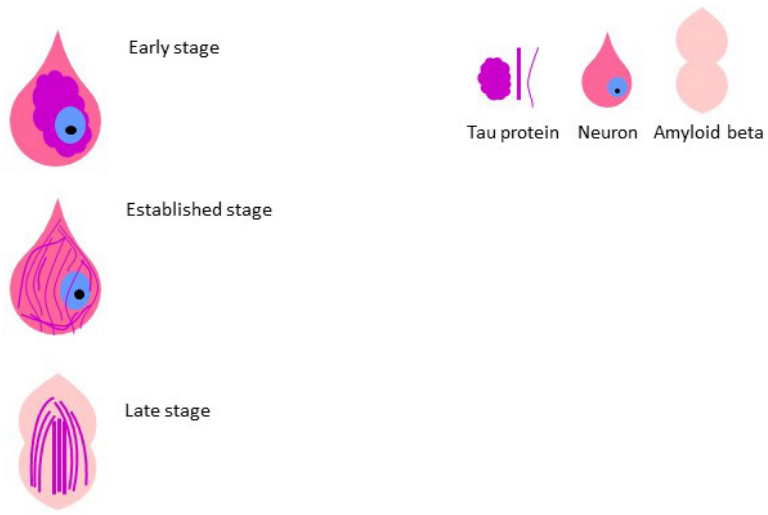


Figure 12. Maturation of NFTs. At the early stage, Tau protein is accumulated into the neuron in a diffuse manner, often around the nucleus. At the established stage, there are paired helical straight Tau filaments. The late stage is represented by ghost tangles, in which Tau filaments are left, but the neuronal material is dead and phagocytosed. Modified from Neuropathology, 3rd Edition, 2012, by David Ellison and Seth Lowe.

Three different staging systems (Braak, Thal and CERAD) are used to set the neuropathological diagnosis of AD (Braak and Braak 1991, Thal et al. 2002, Hyman et al. 2012a). Each of these schemes seek to offer an estimate of the probability that cognitive impairment of the subject is caused by AD.

The Braak stages (I-VI) are determined by the number of NFTs and other tau pathology found in different cortical areas (Figure 13): In stages I-II, NFTs are found in the transenthorinal region of the brain; in stages III-IV, NFTs progress into limbic regions, including the hippocampus; and in stages V-VI, NFTs spread into the neocortical regions as well (Braak and Braak 1991, Braak et al. 2006).

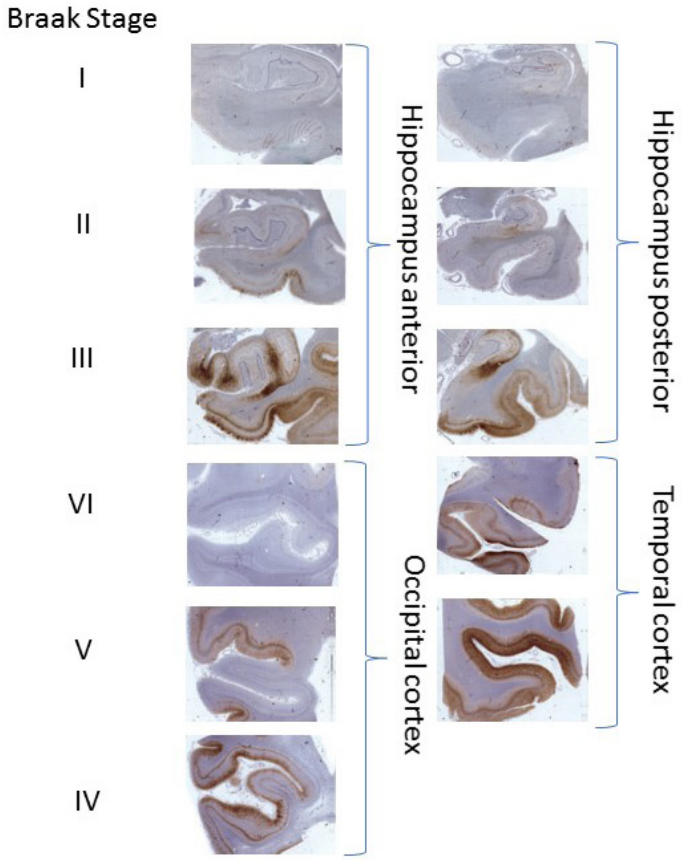


Figure 13. Brain areas studied for Braak staging with Tau immunohistochemistry in suggested order of assesment. Block 1= Occipital cortex, Block 2= Temporal Cortex, Block 3 = Anterior hippocampus and Block 4 = posterior hippocampus. Modified from Alafuzoff et al. 2008.

CERAD (The Consortium to Establish a Registery for Alzheimer´s disease) scores (0, sparse, moderate or frequent) are defined by semiquantitative neuritic plaque density in different cortical areas (Hyman and Trojanowski 1997) (Figure 14). The plaque score is age-related (age at death), which determines the probabilty of AD behind dementia.

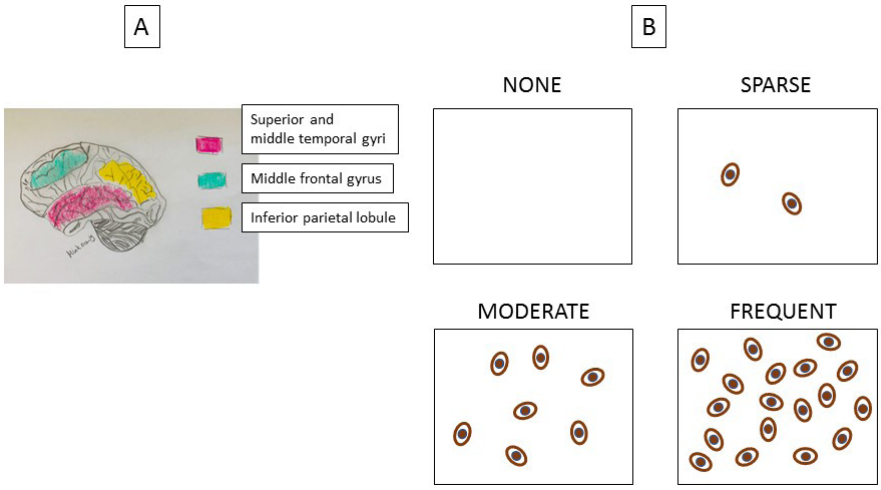
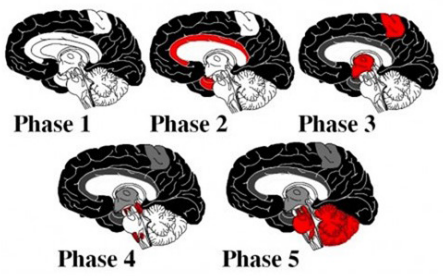


Figure 14. A. Brain neocortical sections used to obtain CERAD score, B. CERAD neuritic plaque densities.

Thal phases are Aβ deposits, accumulating in a progressive hierarchical fashion, from phase 1 to phase 5, in certain brain areas (Figure 15). Phase 1 Aβ deposits are found in the neocortex, Phase in 2 the allocortex, Phase 3 in the interbrain and the striatum, Phase 4 in the brainstem, and Phase 5 in the cerebellum and the other locations in the brain (Thal et al. 2002).



Phase	Aβ plaques
1 and 2	Neocortex and hippocampus
3	Striatum
4	Brainstem
5/6	Cerebellum

Figure 15. Progression of Aβ plaques in the brain categorized by the Thal Phase scheme. Images from the article Thal et al. 2002.

The NIA-AAA ABC scoring system combines all three schemes into one, called the ABC score (A for Aβ plaques = Thal Phases, B for Braak NFTs and C for CERAD). The ABC score gives the probability for AD based on neuropathological findings: NOT, LOW, INTERMEDIATE AND HIGH (Kovacs and Gelpi 2012, Hyman et al. 2012b).

2.7.4. GENETICS

The majority (>95%) of AD patients suffer from the sporadic form of AD, but a small quantity of patients (1-5%) have familial AD (FAD). FAD is defined as early-onset (age at onset before 65 years) and is known to be caused by mutations in three known genes: *presenilin 1* (*PSEN1* on chromosome 14) (Lanoiselee et al. 2017, Kelleher and Shen 2017), *presenilin 2* (*PSEN2* on chromosome 1) (Cai et al. 2015, Lanoiselee et al. 2017) and amyloid precursor protein (*APP* on chromosome 21) (Lanoiselee et al. 2017).

Over 300 detected mutations (https://www.alzforum.org/mutations) in the *PSEN1* gene are found in ~50% of all familial AD patients (Cai et al. 2015, Kelleher and Shen 2017, Mengel et al. 2019). Mutations in *PSEN2* are less common compared to *PSEN1* as only 38 mutations have been discovered to date (Cai et al. 2015). Mutations in both genes increase the carboxylpeptidase proteolytic activity of the γ-secretase and production of more toxic and longer Aβ42 peptide, but the effect of the *PSEN1* gene causes more harm (Giri et al. 2016).

APP mutations are mainly found within or in a close proximity of the sites where Aβ protein is cleaved from APP. Subjects with trisomy of chromosome 21 (Down syndrome) have three copies of the *APP* gene, causing excessive APP production and Aβ accumulation and thus predisposing to early onset of AD (Hithersay et al. 2019). Most of the *APP* mutations are harmful as they increase Aβ42 production and its aggregation and deposition in blood vessels. The Swedish double mutation (KM670/671NL) of *APP* is known to increase abnormal cleavage of cellular APP by β-secretase (Goate et al. 1991, Mullan et al. 1992). The London mutation (V717I) is a point mutation localized close to the γ-secretase cleavage site (Goate et al. 1991, Mullan et al. 1992), causing increased production of the most pathogenic form of Aβ, Aβ42. The Flemish mutation (A692G) is located within the Aβ sequence, near the α-secretase cleaving site. It increases Aβ production as well Aβ deposition in brain blood vessels, which can cause intracerebral hemorrhages (Hendriks et al. 1992). Another mutation located within the coding region of Aβ is the Arctic mutation (E693G), causing increased Aβ protofibril formation and aggregation (Kamino et al. 1992, Jonsson et al. 2012a, Maloney et al. 2014). Protective *APP* mutations have been reported as well. One of these is the Icelandic mutation (A673T), near to the β-secretase cleavage site in amino acid number 2 of the Aβ sequence (Kamino et al. 1992, Jonsson et al. 2012a, Maloney et al. 2014).This mutation has been shown to reduce β-secretase cleavage of APP, resulting in a reduction in the formation of Aβ peptides (Kamino et al. 1992, Jonsson et al. 2012a, Maloney et al. 2014). Aβ levels are also decreased in plasma (Martiskainen et al. 2017). The other FAD-associated *APP* mutations and associated cleavage sites are shown in Figure 16.

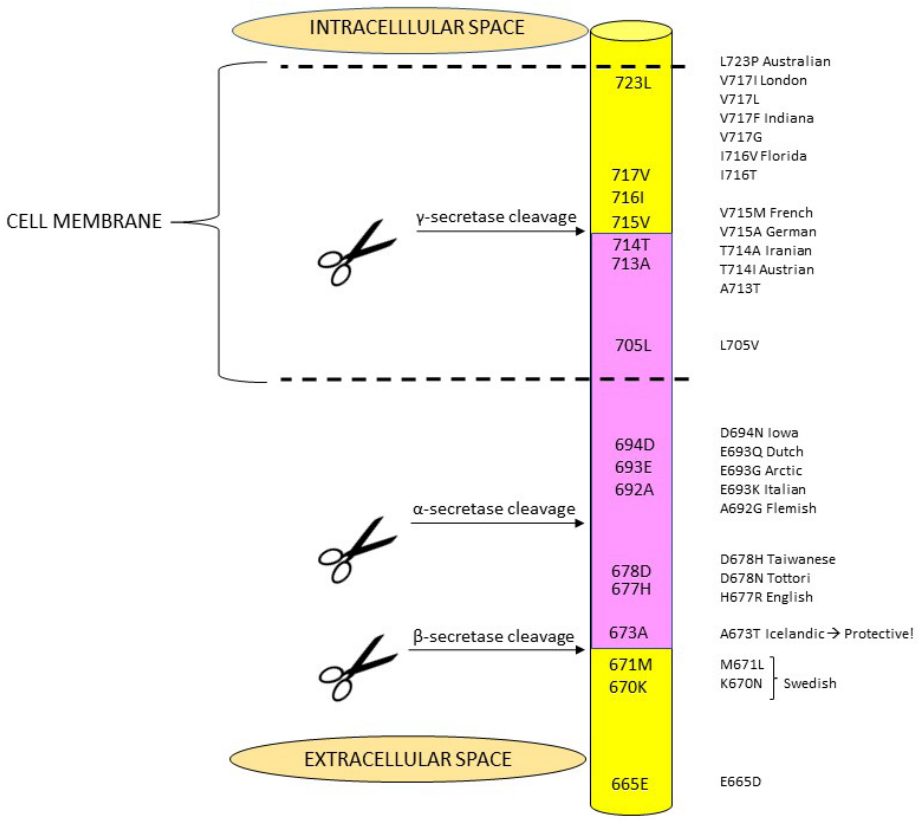


Figure 16. Summary of *APP* mutations and their locations in APP protein.

Sporadic AD (~95%) is caused by a combination of genetic and environmental factors, and is characterized by onset after the age of 65 (Lambert et al. 2009, Awada 2015, Hinz and Geschwind 2017, Kunkle et al. 2019) (Figure 20). GWAS studies have identified ~30 genetic risk gene variants, which are mainly categorized into four separate categories based on the function of the proteins these genes encode (Bertram and Tanzi 2009, Kunkle et al. 2019): immunity, synaptic function, endocytosis and lipid metabolism (Figure 20). Inheritance of several of these genetic risk polymorphisms is believed to result in an increased risk of developing AD (Lambert et al. 2009, Awada 2015, Hinz and Geschwind 2017, Kunkle et al. 2019).

Human apolipoprotein E (ApoE) is a ~34-kDa polypeptide coded by the polymorphic *APOE* gene, located on chromosome 19q13, is the most well-known and the most influential risk gene of late-onset AD (Strittmatter et al. 1993).The ApoE protein is needed for transporting cholesterol for synapse development, dendrite formation, long-term potentiation and axonal guidance (Huang and Mahley 2014). ApoE may have an effect on Aβ metabolism, aggregation and deposition in the brain (Kim et al. 2009, Kim et al. 2013).There are three *APOEε* isoforms separated from

each other by two cysteine-arginine interchanges at the polypeptide chain: *APOEε2, APOEε3 and APOEε4* (Kim et al. 2009). *APOEε3* allele is the most common, *APOEε4* is found in ~15% of the normal population (Figure 17), but among AD patients 44% carry this allele (Liu et al. 2013). Even one copy of this allele increases the risk of developing AD threefold and two copies increase the risk 10-fold. *APOEε2* has some protective effect on AD development, and *APOEε3* carriers have a lower risk of developing AD than carriers of *APOEε4* (Corder et al. 1994a, Huang and Mahley 2014). This risk is reported to vary by demographic factors including sex, ethnicity, geography and even age (Heffernan et al. 2016). The *APOE* haplotype modulates AD risk in ε3/ε3 homozygotes, indicating that there is another risk variation at the *APOE* locus in addition to the protein isoform (Myllykangas et al. 2002, Rantalainen et al. 2016).

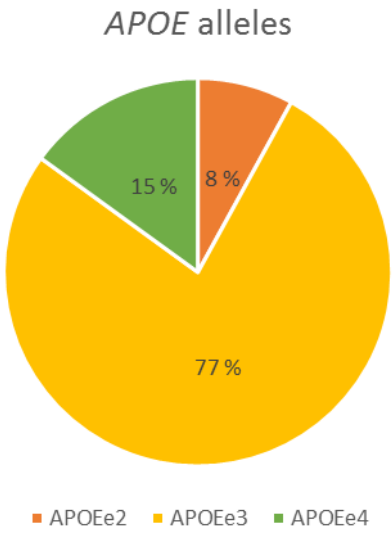


Figure 17. Proportions of *APOE* alleles in the general population.

2.7.5. HYPOTHESES ON PATHOGENESIS

The most predominant hypothesis on the neurobiological progression leading to familial AD, as well sporadic AD, is the Amyloid Cascade Hypothesis (Figure 18) (Selkoe 1991, Hardy and Higgins 1992). This hypothesis assumes that, with age, Aβ protein begins to accumulate in the brain, caused by increased production (mainly in FAD) and/or decreased degradation of Aβ (in sporadic form), co-affected by genetic and environmental factors. When Aβ accumulates in the brain, it causes the activation of many kinases (glycogen synthase kinase-3β, cAMP-dependent protein kinase and cyclin-dependent kinase-5), which in turn cause hyperphosphorylation

of Tau (Selkoe 1991, Hardy and Higgins 1992). Hyperphosphorylated Tau forms NFTs, which cause synaptic dysfunction and neuronal loss leading to memory loss and cognitive problems (Arendt et al. 2016).

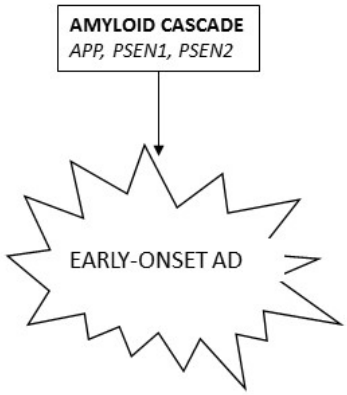


Figure 18. Early-onset AD, risk genes and amyloid cascade.

APP is an integral membrane protein concentrated in the synapses of neurons but also expressed in other tissues, and it is transported in vesicles into the cell surface after being synthesized in the endoplastic reticulum (ER) (Caporaso et al. 1994). Aβ can be produced from APP by the amyloidogenic pathway (Hardy and Higgins 1992) (Figure 19).

α-secretase cleaves within the Aβ-domain, which produces sAPPα. sAPPα participates in neuronal plasticity and protects against excitotoxity (Furukawa et al. 1996). Certain members of the ADAM-family metalloproteases harbor α-secretase activity (Kojro and Fahrenholz 2005). This pathway blocks the production of Aβ (Figure 19), called the non-amyloidogenic pathway (Hardy and Higgins 1992). In this pathway, γ-secretase (composed of PSEN1 or 2, nicastrin APH1 and PEN2) cleaves CTF 83 (C-terminal fragment) and produces soluble p3 peptide and AICD (APP intracellular domain). p3 peptide is proposed to have a role in AD but is not especially harmful because it does not form oligomers or β-sheet structures as easily when compared to Aβ, and it does not activate microglia. AICD fragments (C59 and C57) can be compared to Aβ, and AICD is known to modulate gene expression, apoptosis and cytoskeletal dynamics in AD (Zhang et al. 2012).

In the amyloidogenic pathway (Figure 19) (Hardy and Higgins 1992), APP is first cut by the β-secretase enzyme (BACE1), producing sAPPβ, CTF 89 and 99. Then γ-secretase (composed of PSEN1 or PSEN2, nicastrin APH1 and PEN2) cleaves CTF 89 or CTF 99 to generate the different isoforms of Aβ, such as Aβ40, Aβ42 and Aβ43 (Takami et al. 2009). The aggregation ability of Aβ42 is high and it forms

Aβ-plaques. However, recently it has been indicated that the oligomeric as well the fibril forms of Aβ might be the most toxic molecules for the brain (Arbor et al. 2016). This may explain the ability of Aβ oligomer to form calcium ion (Ca^{2+}) channels within the neuronal cell membrane lipid raft domains, causing an uncontrollable influx of Ca^{2+} ions into cells, leading to neuronal cell death (MacLeod et al. 2015, Arbor et al. 2016).

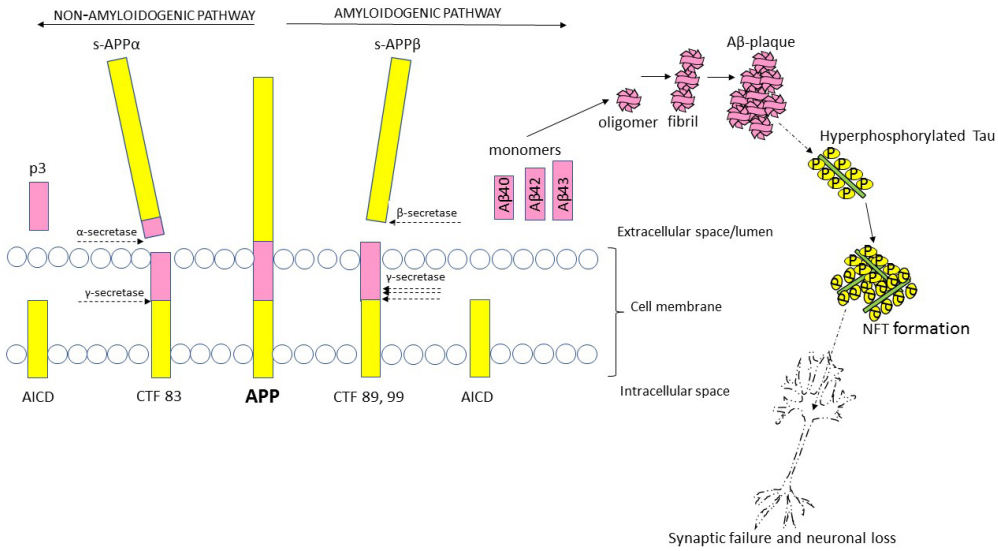


Figure 19. The amyloidogenic and non-amyloidogenic pathway of APP processing. APP (amyloid precursor protein, AICD (amyloid precursor protein intracellular domain, CTF (c-terminal fragment), s-APPα (soluble APP alpha), s-APPβ (soluble APP beta) and NFT (neurofibrillary tangles).

The sporadic late-onset form of AD is a multifactorial disease driven by several different genes and environmental factors (Lambert et al. 2009) (Figure 20). GWAS have identified 30 common loci increasing the risk of developing the disease and highlighted possible pathways concerning innate immunity, synaptic function, endocytosis, lipid metabolism and Aβ metabolism (Chen et al. 2017). How these pathways are related to each other is still under investigation (Lambert et al. 2009, Hinz and Geschwind 2017).

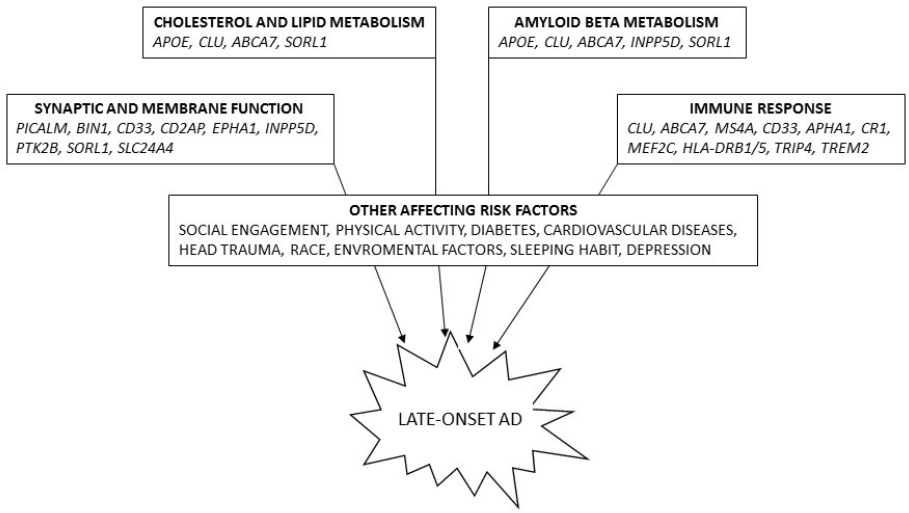


Figure 20. Late onset AD pathways.

Gene polymorphisms associ ated with endocytosis functions are located in *PICALM* (Thomas et al. 2016), *SORL1* (Yin et al. 2015) and *CD2AP* (Naj et al. 2011). These genetic changes are, for example, involved in modulating autophagy, Tau pathology and APP trafficking to amyloidogenic endocytic pathways (Chouraki and Seshadri 2014). Polymorphisms of *PTK2B* (Li et al. 2016), *BIN1* (Seshadri et al. 2010), and *MS4A* cluster (Antunez et al. 2011) are involved in the regulation of calcium signaling and homeostasis. Polymorphism in genes *CD33* (Cao and Crocker 2011) and *TREM2* (Jonsson et al. 2013) produce immunity-associated proteins regulating inflammatory responses and microglia survival as a reaction to Aβ accumulation (Guerreiro et al. 2013, Jiang et al. 2014). The genes associated with lipid metabolism and Aβ clearance are *CLU* (Harold et al. 2009) and *ABAC7* (Hollingworth et al. 2011). *CLU* also functions as part of the complement system involving modulating the immune system (Wang et al. 2019). Several of these risk genes are multifunctional, working in two or even three categories of hypothesized pathways. Rare mutations in genes associated with FAD (*APP*, *PSEN1* and *PSEN2*) have also been found to cause some forms of late-onset AD (Cruchaga et al. 2012).

Non-genetic factors are also associated with the risk of late-onset AD. Cholesterol-rich lipid rafts of the cell membrane offer a location for γ-secretase cleavage of APP and Aβ oligomers are able to form Ca^{2+} ion channels through the cell membrane (Arbor et al. 2016). If cholesterol levels in the brain are increased, the amyloidogenic processing of APP and Aβ production is also increased (Mendiola-Precoma et al. 2016). Patients with Type 2 diabetes have a doubled risk of having AD. It has been hypothesized that AD may be Type 3 diabetes (de la Monte and Wands 2008). AD patients have decreased insulin sensitivity in the periphery caused by prolonged

hyperinsulinemia (Ferreira et al. 2018). They also have increased insulin resistance and decreased insulin receptor expression as well as decreased insulin transport into the brain. The abnormalities caused by insulin are most notable in the medial temporal lobe (the area heavily affected by Aβ accumulation among AD patients). A decreased level of insulin in the brain activates the cascade, decreasing the amount of the insulin degrading enzyme (IDE), which in turn reduces the breakdown of Aβ (Zilliox et al. 2016).

2.8. FRONTOTEMPORAL LOBAR DEGENERATION (FTLD)

FTLD is a term describing a group of different disorders with various clinical presentations, genetics and histopathological features. Shared cognitive and motoric features are seen in different FTLD subtypes, but the biological mechanisms and proteinopathies behind the clinical symptoms are different (Irwin et al. 2015).

2.8.1. EPIDEMIOLOGY

FTLD is thought to be the third most common neurodegenerative dementing disease. For those with dementia onset at < 65 years, FTLD is estimated to cover 10-20% of the cases (Luukkainen et al. 2015). It might be more frequent in males, according to some studies (Mercy et al. 2008, Garre-Olmo et al. 2010). The prevalence figures for FTLD have varied between 4.0-29.9/100,000 in different European studies (Ratnavalli et al. 2002, Harvey et al. 2003, Garibotto et al. 2011). In the Finnish population (ages between 45-70 years), the prevalence was 26.8/100000 (Luukkainen et al. 2015). In the population aged 45-65 years in Northern Finland, the mean 1-year incidence of FTLD was 5.54/100000 and the prevalence was 20.5/100000 (Luukkainen et al. 2015). Incidence figures from other European countries have varied from 1.3-3.5/100000 (Mercy et al. 2008, Garre-Olmo et al. 2010).

2.8.2. CLINICAL FEATURES

In clinical practice, the term FTD (frontotemporal dementia) is used for those diseases grouped neuropathologically under the term FTLD. FTD can be categorized into three main groups: behavioral variant FTD (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA) (Ghosh and Lippa 2015). FTD is a more "aggressive" disorder than other common forms of dementias. The mean survival period in all FTD forms is estimated to vary between 6 and 10 years after first symptoms are seen (Roberson et al. 2005, Knopman and Roberts 2011).

In bvFTD (~ 50% of FTD types), the apparent clinical features are variable and multiple changes in the personality are seen, such as lack of empathy, unexpected and uncontrolled spontaneous reactions (disinhibition), difficulties with motivation and ability to concentrate, change in eating, inability to maintain daily routines, decreased ability of executive functions and lack of social contacts due to increasing apathy (Michotte et al. 2001, Mychack et al. 2001, Mendez et al. 2008). Those patients with bvFTD (Bang et al. 2015) might have also motor neuron disease (up to 40%) or parkinsonism (about 20% of patients) (Burrell et al. 2011).

SD covers 20- 25% of patients with FTD (Johnson et al. 2005). These patients often have different problems with language, problems recollecting words as well as problems in understanding information without words (Roberson 2006, Rosen et al. 2006). Disinhibition and obsessive-compulsive behavior is often seen, and patients with semantic dementia have no idea of their social shortcomings (Roberson 2006, Rosen et al. 2006). In semantic dementia, semantic memory is poor, but episodic memory is preserved relatively well (Ghosh and Lippa 2015).

In PNFA (~ 25% of FTD), the first disability is slow speech, which is also not fluent. (Johnson et al. 2005, Knibb et al. 2009). The style of speech might be telegraphic, with mistakes in grammar (Johnson et al. 2005, Knibb et al. 2009). These patients have difficulties understanding multilayered sentences and some of the patients may become mute (Josephs 2007).

SD and PNFA are sometimes referred together as a primary progressive aphasia, which includes three clinical variants based on the specific speech and language features (Gorno-Tempini et al. 2011).

Neuroimaging studies, traditional volumetric MRI, MRI-based fMRI (resting state functional) and DTI (diffusion tensor imaging), and FDG-PET (hypometabolism on 18-F fluorodeoxyglucose) are used to identify different FTD types (Ghosh and Lippa 2015). For structural imaging, MRI should be used. In FTD, atrophy is seen bilaterally in both frontal and temporal lobes, especially in the front part of the cingulum, uncus and parahippocampal gyrus, but also in the borders of parietal and occipital lobes (Munoz-Ruiz et al. 2012). Functional imaging, such as PET, is improving the reliability of diagnosis. Through PET imaging hypoperfusion or hypometabolism in the frontal and/or temporal lobes can be seen (Rascovsky et al. 2011). DTI is not used routinely for FTD imaging, but it is shown to be even more sensitive in detecting the changes in FTD brain (Santillo et al. 2013).

2.8.3. NEUROPATHOLOGY

Table 5. The pathological subtypes of frontotemporal lobar degeneration. Modified from Neuropathology, 3rd Edition, 2012, by David Ellison and Seth Lowe.

Frontotemporal lobar degeneration = FTLD					
Pathological subtypes	FTLD-TDP	FTLD-Tau	FTLD-UPS	FTLD-FUS	FTLD-ni
IHC- findings	TDP-43 inclusions	Tau-pathology	p62 or/and ubiquitin positive inclusions. No positivity with other subtype IHC- markers	FUS inclusions	No inclusion detected with IHC- markes for other subtypes
Anatomical region	Prefrontal and anterior temporal	Frontotemporal	Temporal	Temporal	Frontotemporal
Shared histological features	Microvacualation superficial cortical layers, transcortical microvacualation and status spongiosus, astrocytic gliosis, neuron loss and in some cases motor neuron loss				
Clinical manifestations	bvFTD*	PNFA**	SD***	SD	PNFA

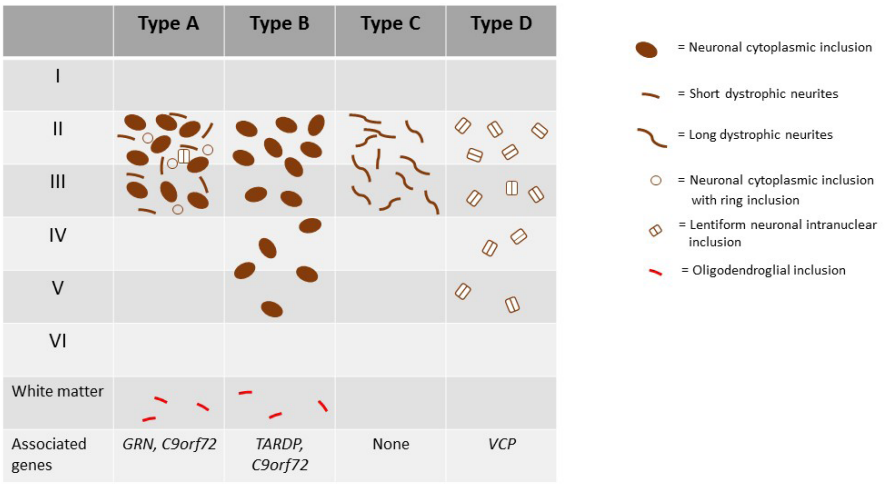
*bvFTD = behavioral variant FTD
**PNFA = progressive nonfluent aphasia
***SD = semantic dementia

The pathological subtypes of FTLD are divided into five main groups (Sieben et al. 2012, Mackenzie and Neumann 2016): FTLD-Tau, FTLD-TDP, FTLD-UPS, FTLD-FUS, FTLD-ni (Table 5) This categorization is based on immunohistochemical stainings, typically involving the following: Tau, TDP-43, FUS, ubiquitin or p62. The most common neuropathological subtype is FTLD-TDP (~50%), the second most common is FTLD-Tau (~45%), and the third most common is FTLD-FUS (~5%). FTLD-UPS and FTLD-ni are rare (<1%) (Bigio 2013).

2.8.3.1. FTLD-TDP

The most common subtype (50%) of FTLD is FTLD-TDP. Common neuropathological features of FTLD-TDP include progressive neuronal loss, astrocytic gliosis and microvacuolation of the superficial laminas of the frontal and temporal cortical areas (Sampathu et al. 2006). As the disease becomes more severe, these changes can be seen transcortically. FTLD-TDP is classified into four different groups (Table 6) A, B, C and D according to a harmonized classification system (Mackenzie et al. 2011b) based on the different TDP-43 positive pathological findings (Figure 21): 1. neuronal cytoplasmic inclusions (NCI), 2. neuronal intranuclear inclusion (NII) and 3. dystrophic neurites (DNs) (Cairns et al. 2004, Mackenzie et al. 2006, Sampathu et al. 2006, Davidson et al. 2007, Dickson 2008a).

Table 6. The neuropathological subtypes of FTLD-TDP



FTLD-TDP classification with typical neuropathological findings is based on the different morphological TDP-43 deposits (Mackenzie et al. 2011b). Type A is the most prevalent (~40%), and this type typically shows numerous NCIs and short DNs in cortical neurons. In the dentate gyrus of the hippocampus some NCIs can be seen, as well as a moderate number of NIIs. In Type B (prevalence ~35%), NCIs are seen in layer 2, but also in deeper cortical layers. In the granular cell layer of the dentate gyrus of the hippocampus, NCIs are quite common. DNs may be found transcortically, and NIIs are seen in some cases. Hippocampal sclerosis is possible. In type C (prevalence ~25%), NCIs may be seen both neocortically and in the granular cell layer of the dentate gyrus. In layer 2, but also in deeper layers, numerous long and thick DNs are seen. NIIs are possible, and severe neuronal loss and gliosis in the hippocampus are seen occasionally. Type D is very rare, typically showing many short DNs in the neocortex. Some NCIs may be demonstrated neocortically and in the granular cell layer of the hippocampus. NIIs are lentiform shaped and frequent (Lee et al. 2017).

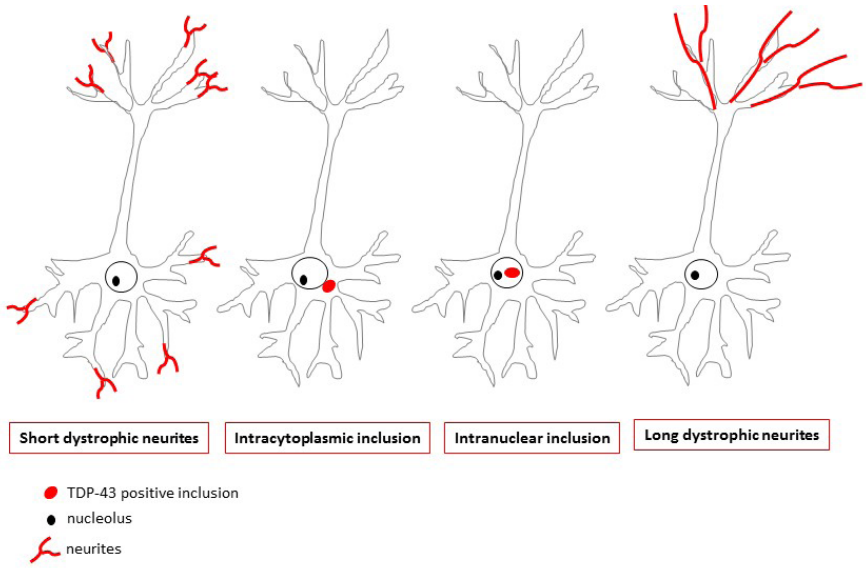


Figure 21. Different types of TDP-43 pathology found in neurons in FTLD-TDP.

2.8.3.2. Other FTLD types

Mutations in the microtubule-associated protein tau (*MAPT*) gene on chromosome 17 were first detected in families with frontotemporal degeneration and parkinsonism (FTDP-17) (Hutton et al. 1998). 50% of these families harbor a nearby mutation in *GRN* in chromosome 17 (Baker et al. 2006). Pathologically, patients with mutations in *GRN* show FTLD with TDP-43 pathology (FTLD-TDP), whereas familial *MAPT* mutations are considered to belong to FTLD-Tau, having the Tau pathology (Rademakers et al. 2013, Forrest et al. 2018). FTLD-Tau cases with familial mutations in *MAPT* are separated from sporadic cases, based upon the independent pathogenic mechanisms of these two entities (Forrest et al. 2018). Further subclassification of sporadic FTLD-Tau is based on different tau protein isoforms, 3-repeat TAU (3R) and 4-repeat Tau (4R). Pick´s disease (PiD) is a 3R tauopathy, whereas progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and argyrophilic grain disease (AgD) are 4R diseases (Braak and Braak 1987, Baborie et al. 2011, Josephs et al. 2011, Sieben et al. 2012). These diseases share neuropathological features such as accumulation of paired helical or straight Tau filaments in neurons and glial cells. In PiD, Tau-positive intracytoplasmic spherical inclusions (Pick bodies) are seen in pyramidal neurons, dentate granule cells in the hippocampus and neocortical areas (Dickson 2001). In PSP, CNS regions harbor Tau aggregates or diffuse Tau deposits in neuronal and glial cells (Dickson 1999).

In CBD, (Dickson et al. 2002) findings are neuronal loss and gliosis of astrocytes, swollen neurons and superficial spongiosis. In Argyrophilic grain disease (AgD), spindle-shaped argyrophilic grains (ArG) in dendrites and axons, as well as coiled bodies in oligodendrocytes, are mainly found in limbic regions (Braak and Braak 1987, Togo et al. 2002, Tolnay et al. 2004).

FTLD-FUS is characterized by FUS-immunoreactive inclusions in neurons (NCIs, NIIC) and glial cells (GCIs), and three subtypes are described: 1. atypical FTLD-U (aFTLD-U), 2. basophilic inclusions body disease (BIBD), and 3. neuronal intermediate filament inclusion disease (NIFID) (Mackenzie et al. 2009, Mackenzie et al. 2010a, Mackenzie et al. 2011a). FTLD-U is the most common, and neuronal inclusions (NCIs and NII) in this group are FUS, ubiquitin and p62 positive, but TDP-43 and Tau negative (Mackenzie et al. 2008, Mackenzie et al. 2011a), and the inclusions are mainly found in the frontal and temporal neocortex, and the hippocampus. NIFID is characterized by FUS-positive NCIs, NIIs and GCIs (Mackenzie et al. 2008, Mackenzie et al. 2011a). NIIs are rare in BIBD, but GCIs are common (Yokota et al. 2008, Munoz et al. 2009, Mackenzie et al. 2011a).

In FTLD-UPS, inclusions are immunopositive only for ubiquitin and p62 antibodies. After the TDP-43 antibody was discovered, many cases in the FTLD-UPS category were regrouped into FTLD-TDP (Mackenzie and Neumann 2016, Hernandez et al. 2018). In rare FTLD-ni, no pathological inclusions are detected with any other FTLD IHC-markers (Mackenzie et al. 2009, Mackenzie et al. 2010a).

2.8.4. GENETICS

In the FTLD-Tau group, the inherited causative gene is *MAPT* on chromosome 17, encoding the Tau protein and covering 6-18% of all mutations in FTLD patients (Sieben et al. 2012, Mackenzie and Neumann 2016). There are several different *MAPT* mutations associated with FTLD- Tau. The H1 haplotype of *MAPT* is associated with sporadic FTLD-Tau (Kaivorinne et al. 2008a, Kaivorinne et al. 2008b). Mutations in the *FUS* gene are not demonstrated in the FTLD-FUS group (Sieben et al. 2012, Mackenzie and Neumann 2016). A link to *FUS* mutations has been shown in juvenile onset of BIBD (Baumer et al. 2010, Lee et al. 2013). Mutations in charged multivesicular body protein 2B (*CHMP2B)* are associated in some cases with FTLD-UPS (Holm et al. 2009, Sieben et al. 2012). Causative mutations for FTLD- ni have not been detected (Sieben et al. 2012). The FTLD-TDP Type A is often associated with the gene mutations *GRN* and *C9orf72*. Family history is seen in about 50% of cases (Sieben et al. 2012, Mackenzie and Neumann 2016). Type B involves genetic mutations in *TARDP* and *C9orf72*, and a positive family history occurs in 30% of affected subjects (Sieben et al. 2012, Mackenzie and Neumann 2016). In Type C, about 30% of subjects have a positive family history. In type

D, mutations in the valosin-containing protein *(VCP)* gene have been described (Sieben et al. 2012, Mackenzie and Neumann 2016). The frequency of familial *VCP* mutations is <1% of all FTLD mutations (Takada 2015). The gene mutations and FTLD subtypes are summarized below (Table 7).

Table 7. General summary of FTLD-subtypes and associated genes.

	FTLD-TDP	FTLD-FUS	FTLD-UPS	FTLD-ni	FTLD-Tau
Genetics	*GRN* *C9orf72* *TARDBP* *VCP*	No mutations *FUS* (juvenile BIBD)	*CHMP2B*	Cases largely assigned to FTLD-TDP group	*MAPT*/Ch17 *MAPT*/H1

2.8.4.1. C9orf72 hexanucleotide repeat expansion mutation

Hexanucleotide expansion mutation in *C9orf72* was recognized in FTLD/ALS (amyotrophic lateral sclerosis) patients in 2011 (Renton et al. 2011, DeJesus-Hernandez et al. 2011). In Finland, the *C9orf72* expansion is the most common genetic cause of ALS and FTLD (Renton et al. 2011, DeJesus-Hernandez et al. 2011, Majounie et al. 2012). Neuropathologically the C9orf72 repeat expansion mutation is known to cause the cytoplasmic TDP-43-positive inclusions seen in motor neurons, and p62-immunopositive inclusions in cerebellar granular cells (Davidson et al. 2011, Al-Sarraj et al. 2011, Mackenzie et al. 2011b). The *C9orf72* expansion mutation is able to cause the formation of toxic RNA-foci, which in turn cause regulation error of the glutamate receptor, RNA-editing, increased Ca^{2+} influx, breakdown of the nuclear transporting system and accumulation of dipeptide proteins in the cytoplasm (Donnelly et al. 2013, Mizielinska and Isaacs 2014, Freibaum et al. 2015, Zhang et al. 2016). It is still under debate which of the repeat lengths is pathological and causes the disease onset (Byrne et al. 2014, Beer et al. 2015, Kaivola et al. 2019).

2.8.5. HYPOTHESES ON PATHOGENESIS

FTLD is known to be related to several different genes with complex biological functions. The correlation between different aspects, genetics and neuropathological findings is not straightforward. There are at least four different pathways associated with FTLD (Figure 22). Protein degradation, clearance and autophagy pathways are linked with the genes *SQSTM1* (Rubino et al. 2012) *UBQLN* (Ugwu et al. 2015), *TBK1* (Gijselinck et al. 2015), *VCP* (Watts et al. 2004), *CHMP2B* (Skibinski et al. 2005) and *OPTN* (Pottier et al. 2015). These genes and their protein products are specifically involved in autophagy and proteasomal degradation. In the second pathway, the genes *GRN* (Gass et al. 2006) and *CHMP2B* (Han et al. 2012) are

involved in lysosomal and endosomal function pathways. Genetic risk factors for FTLD, *TMEM106B* (Lang et al. 2012) and *RAB38* (Ferrari et al. 2014), are involved in the same pathway as described for *GRN* and *CHMP2B*. The third pathway includes the genes *FUS* (Zhou et al. 2013), *TARDBP* (Borroni et al. 2010), *C9orf72* (van Blitterswijk and Rademakers 2015), *hnRNPA1* and *hnRNPA2/B1* (Kim et al. 2013) and the protein products of these genes are involved in the RNA/DNA metabolism pathway. Mutations in *CHCHD10* (Bannwarth et al. 2014) are associated with mitochondrial dysfunction. The *MAPT* (Ghetti et al. 2015) and *DCTN1* (Vilarino-Guell et al. 2009) genes are involved in protein aggregation and intracellular transport.

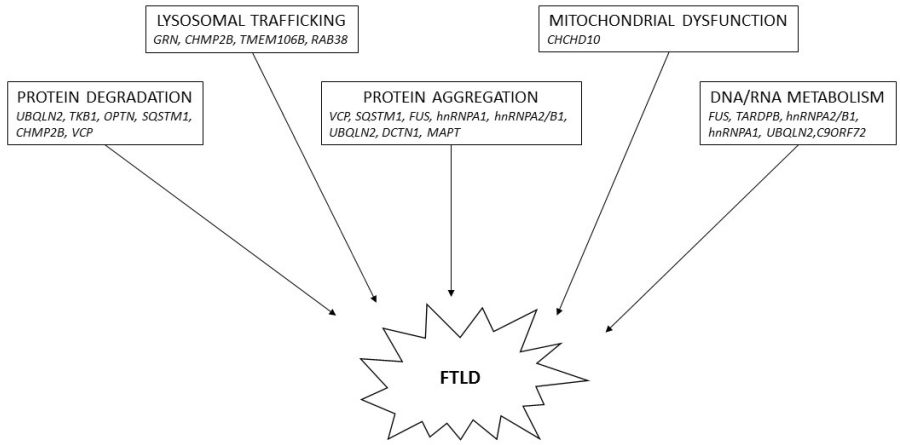


Figure 22. The cellular pathways associated with FTLD (modified from Pottier et al. 2016). **Protein degradation**: Ubiquitinated proteins (UBQLN2) are decomposed and transported into the proteasome (VCP) or into preautophagosomal structures (OPTN/TBK1 complex, SQSTM1), which fuse to become the autophagosome (CHMP2B). **Lysosomal trafficking**: Selective material recycling (CHMP2B, Rab38, TMEM106, GRN) and fusion with vesicles (CHMP2B, Rab38). **Mitochondrial dysfunction**: Recycling of damaged mitochondria (CHCHD10) into autophagosomes. **DNA/RNA metabolism**: Aberrant RNA splicing (TDP-43, FUS, hnRNPA1, hnRNPA2/B1), transcription regulation (TDP-43, hnRNPA1, hnRNPA2/B1), RNA transport (TDP-43, FUS, UBQLN2, hnRNPA1, hnRNPA2/B1) and RNA foci (C9orf72) disturb DNA/RNA metabolism. **Protein aggregation**: Associated with many genes (VCP, p62, hnRNPA1, hnRNPA2/B1, TDP-43, FUS, UBQLN2, C9orf72, MAPT, and DCTN1) which are mutated in FTLD.

3. AIMS OF THE STUDY

The general aim of this study was to investigate the neuropathological and genetic background of age-related neurodegenerative disorders, especially HS-Aging and other TDP-43 proteinopathies.

The specific aims were as follows:

1) To assess the frequency of HS-Aging in a study cohort of Finns aged over 85 years (Vantaa 85+ study).
2) To investigate the possible association of known genetic variants of *GRN*, *TMEM106B,* and *ABCC9* with HS-Aging in the Vantaa 85+ study material.
3) To determine the frequency of the protective *APP* mutation A673T in the Vantaa 85+ study cohort.
4) To identify the causative gene defect and to describe the neuropathological phenotype of a familial FTLD associated with a rare tumor, dysplastic gangliocytoma.

4. MATERIAL AND METHODS

4.1. SUBJECTS

4.1.1. PUBLICATION I–III

The Vantaa 85+ study consists of all people aged over 85 years old living in Vantaa in Finland on 1st of April, 1991. In the baseline in 1991 there were 601 subjects included in this study, and 553 subjects could be clinically examined. As of 2001, 565 subjects were dead, and an autopsy was carried out for 304/565. This is known to be the second highest autopsy rate in a population-based autopsy study (Zaccai et al. 2006). 273 of the autopsied subjects had given a peripheral blood sample for DNA extraction. The neuropathological and clinical data of this study cohort was first described by Tuomo Polvikoski in 1995 (Polvikoski et al. 1995).

4.1.2. PUBLICATION II

The Cambridge City over-75s Cohort (CC75C) and the Medical Research Council (MRC) Cognitive Function and Ageing Study (CFAS) are two population-based clinicopathological studies. CC75C began in 1985 and 2610 individuals (aged 75) participated in this study, resulting in 241 brain donations to date. The CFAS study involved 18 226 people (aged ≥65 years), and at the time of the current study, 562 CFAS brain donations had been collected. Both cohorts have been described earlier (Brayne et al. 2006, Fleming et al. 2007, Hokkanen et al. 2018).

4.1.3. PUBLICATION IV

This study consists of the index patient (death at age 56) and his sister (death at age 62). Two other siblings and four other family members were included in this study. The blood samples were collected from all subjects described above.

4.2. NEUROPATHOLOGICAL PARAMETERS

4.2.1. ORIGINAL SAMPLING PROCEDURE FOR VANTAA 85+

Originally, the brains of the 306 autopsied subjects were fixed in 10% formalin for at least two weeks. The tissue samples of the right side (from middle frontal,

superior temporal, middle temporal gyri and inferior parietal lobule) were processed into FFPE blocks according to the CERAD protocol (Polvikoski et al. 1995). The entorhinal cortex, hippocampus and occipital lobe samples were embedded in polyethylene glycol (PEG) for Braak staging (Polvikoski et al. 1995). The other hemispheres (left) of the brains were left in formalin and were processed into FFPE blocks after several years.

4.2.2. PUBLICATION I AND II

The pathology of the hippocampi were studied bilaterally. The hippocampal samples of the left hemisphere were fixed for several years in neutral buffered formalin before tissue processing and paraffin embedding. The PEG blocks, assessed from the right hemisphere and containing the hippocampal area, were re-processed into paraffin. The PEG matrix was removed by immersing the blocks in distilled water and then in neutral buffered formalin overnight at room temperature. After that, the blocks were processed in a tissue processor according to standard protocol for brain samples (Thermo Shandon Excelsior, Thermo Fisher, USA), and embedded in paraffin.

Hematoxylin-eosin staining of the bilateral histological sections (6 µm) was used to determine the general histological alterations in these samples, as well as the severity and distribution of neuronal loss in each field of the hippocampus, CA4-CA1 and subiculum by the observers Mia Kero, Liisa-Myllykangas and Anders Paetau. The severity of neuronal loss was classified: I: Intact/Infrequent; no sign or minor loss of pyramidal neurons in the CA1 and subiculum. II: Frequent; severe marked loss of pyramidal neurons in the CA1 and subiculum. III: Complete; total loss of pyramidal neurons in the CA1 and subiculum. For the statistical analysis, the next scheme was followed: subdivision I was the non-HS-Aging group and subdivisions II and III were combined into an HS-Aging group.

For publication II, the Finnish study material (Vantaa 85+) and the two British study cohorts were combined for the studying of genetic alterations, and different scoring criteria for HS were used. The severity of neuronal loss of the hippocampus was determined in the British study cohorts based on the criteria described by Hokkanen et al. 2018. For the sake of clarity and unity, the Vantaa 85+ study material was also scored according to a semi-quantitative protocol, which captures various hippocampal neuron loss patterns (extent, severity and location), comparing their occurrence in the context of HS-Aging (Hokkanen et al. 2018).

Other variables, used in publication I, have been described earlier: CERAD scoring (Polvikoski et al. 1995) and Braak-staging (Polvikoski et al. 2001), α-synuclein pathology/LB (Oinas et al. 2009), brain infarcts, atherosclerosis and

coronary disease (Myllykangas et al. 2001) and the severity and frequency of CAA (Makela et al. 2016).

4.2.3. PUBLICATION III

HE-staining was used to determine the histopathological changes of a patient with a protective *APP* mutation. The neuritic plaques were originally determined by Bielschowsky staining and later with IHC (details are described in 4.3.2). NFTs and NTs were originally stained with Gallyas-staining, Aβ plaques were determined with methenamine silver, but IHC stainings were performed for this study. CAA was identified with both Congo Red and IHC.

4.2.4. PUBLICATION IV

The neuropathologic examination and sample collection of the index patient and his diseased sister was performed using standardized methods after fixing the brain for at least 10 days. HE and IHC stainings were used to evaluate the changes in the brains of the index patient and his sister.

4.3. IMMUNOHISTOCHEMISTRY

4.3.1. PUBLICATIONS I AND II

The hippocampus samples of the right hemisphere (4µm) were stained with the LabVision immunostainer. The polymer-based detection kits were used to detect the following antigens: p62, TDP-43, and Tau (Table 8). The reactions were visualized with DAB chromogen. TDP-43-, p62-, and Tau-positivity was observed in the granular cell layer of the dentate fascia and the pyramidal cell sectors CA4, CA3, CA2, CA1 and subiculum. The results were ascertained in consensus sessions by Mia Kero, Liisa Myllykangas and Anders Paetau. We used p62 IHC staining as a screening method to confirm the neuropathological findings, such as TDP-43 IHC-positivity, and any other accompanying pathology.

4.3.2. PUBLICATION III

In selected cases, Aβ and Tau immunohistochemistry (Table 8) was performed with immunostainer LabVision. All samples positive in Congo red were further stained using antibodies against Aβ. The cerebrovascular Aβ deposition was analyzed in 4

neocortical areas (frontal, temporal, parietal, occipital), and in the hippocampus and cerebellum (Tanskanen et al. 2012). The analysis of Lewy-related pathology was performed as described earlier (Oinas et al. 2009).

4.3.3. PUBLICATION IV

The following brain areas were selected for IHC staining: the spinal cord (C6-C7), cerebellum, hippocampus, and frontal cortex. In addition, cerebellar tumor samples of dysplastic gangliocytoma were analyzed. IHC for p62, ubiquitin, TDP-43 and Tau was performed using Lab Vision 480 Autostainer (Table 8).

Table 8. The details of the IHC stainings in publications I, II, III and IV.

Antibody	Clone (catalog no., producer)	Pretreatment		1° antibody dilution and incubation time/°C		Detection kit (catalog no., producer) and incubation time/°C		Instrument (producer)
p62	D-3 (sc-28359, Santa-Cruz)	I TE (pH 9,0) Autoclave 121°C/10min	IV TE (pH 9,0) Micro	I 1:500 60 min/RT	IV 1:500 30min/RT	I Advanced (K3468, Agilent) 30 min/RT link ab 30 min/RT anti-link ab	IV Envision (K5007, Agilent) 30 min/RT	LabVision 480 (Thermo Fisher Scientific, USA)
TDP-43	11-9 (CAC-TIP-PTDM01, Cosmobio)	I, II TE (pH 9,0) PT-module 98°C/20min	IV TE (pH 9,0) Micro 100°C/24 min	I, II 1:2000 45min/RT	IV 1:2000 30min/RT	I, II Envision (K5007, Agilent) 45min/RT	IV Envision (K5007, Agilent) 30 min/RT	LabVision 480 (Thermo Fisher Scientific, USA)
Tau	AT8 (BR-03, Innogenetics)	I TE (pH 9,0) PT-module 98°C/20min	III, IV Trypsin dig. 20min/37°C	I 1:800 60min/RT	III IV 1:600 1:800 30min/RT	I Advanced (K3468, Agilent) 45 min/RT link ab 45 min/RT anti-link ab	III, IV Envision (K5007, Agilent) 30 min/RT	LabVision 480 (Thermo Fisher Scientific, USA)
Ubi	polyclonal (Z0458, Agilent)	IV Citrate (pH 6,0) Micro 100°C/24min		IV 1:1000 30min/RT		IV Envision (K5007, Agilent) 30 min/RT		LabVision 480 (Thermo Fisher Scientific, USA)
Aβ	6F/3D (M0872, Agilent)	III TE (pH 9,0) Micro 100°C/24 min		III 1:5 30min/RT		III Envision (K5007, Agilent) 30 min/RT		LabVision 480 (Thermo Fisher Scientific, USA)

4.4. GENETIC ANALYSES

4.4.1. PUBLICATION II

For the Vantaa 85+ cohort, the genotypes of *GRN* rs5848, *TMEM106B* rs1990622 and *ABCC9* rs407180 were partly determined from the WGS data and partly by Sanger sequencing, which was performed on the remainder of the neuropathologically examined subjects (variant containing sequences were first amplified using the primers described in Table 8. ABI3730xl DNA Analyzer was used to run the

fragments at the Institute of Molecular Medicine Finland, and the sequencing data were analyzed using the Sequencher 4.0 analysis software (Applied Biosystems).

Single nucleotide polymorphism (SNP) analysis of *GRN* rs5848, *TMEM106B* rs1990622 and *ABCC9* rs407178 for CC75C/CFAS was done at the Karolinska Institute, Sweden, using a TaqMan SNP 7500 genotyping assay on real time PCR (Applied Biosystems, CA, USA). Pre-designed TaqMan SNP Genotype Assays were available from ThermoFischer Scientific.

The rs407180 polymorphism was in nearly complete linkage disequilibrium with rs704178, and the genotype for *ABCC9* rs704178 was imputed from the Vantaa85+ material with Beagle 4.1 (version 27Jan18.7e1) using the population-specific SISu v3 imputation reference panel (dx.doi.org/10.17504/protocols.io.nmndc5e). The imputed data was shown to be reliable in this dataset (Makela et al. 2018). The quality of imputed rs704178 genotypes was high and post-imputation quality control was passed (INFO score =1, a similar MAF in our imputed dataset and in the Finnish GnomAD population [0.44 vs. 0.41] and 98.6% concordance between imputed and whole genome sequencing-derived genotypes of internal control samples).

Table 8. The primers of the studied SNPs

SNP	Gene	Forward primer (5'–3')	Reverse primer (5'–3')
rs5848	*GRN*	GCCAGGGGTACCAAGTGTTT	GCAGGGCGGCAAATCAGA
rs1990622	*TMEM106B*	ACACACGGCATTGTGTTTGATT	TGAGATGACCAGCCACTCCA
rs704180	*ABCC9*	CTTGAGAACAGGCCCCTGAC	TGGGCCTTACCTAGTCCTGG

4.4.2. PUBLICATION III

DNA was extracted from peripheral blood leukocytes using standard methods. *APP* exon 16 and flanking intronic sequences were amplified by polymerase chain reaction using the forward primer 5´-TTGGAACAAAGCCCCAAAGTAG-3´ (intron 15) and reverse primer 5´-GGCAAGACAAACAGTAGTGGAAAG-3´ (intron 16). The 618 base pair polymerase chain reaction products were sequenced by the Sanger method. Cycle sequencing was carried out by the forward primer in all samples and all suspected variants were also confirmed by sequencing with the reverse primer. Sequence data analysis was carried out with the Sequencer 4.5 Software (Gene Codes Corp., Ann Arbor, MI, USA).

4.4.3. PUBLICATION IV

The candidate genes microtubule-associated protein tau (*MAPT*; exons 1, 9, 10, 11, 12, and 13 and intronic flanking regions), progranulin (*GRN*), and *TDP-43* (all exons

and intronic flanking regions) were sequenced in all 5 siblings. Similarly, the repeat expansion mutation in *C9orf72* was determined by repeat-primed polymerase chain reaction (RP-PCR) in all 5 siblings (Renton et al. 2011). All reactions (sequencing and RP-PCR) were run on an ABI3730 DNA Analyzer (Applied Biosystems, Foster City, CA, USA), and the results were analyzed and visualized using Sequencher 4.9 (Gene Codes Corporation, Ann Arbor, MI, USA) and Gene Mapper software (GeneMapper v4.0). The range of ≥40 repeats were kept as the threshold to discriminate presence versus absence of expansion in *C9orf72*. *PTEN* was sequenced (coding regions) through multiplex ligation–dependent probe amplification for the index patient because this gene has been found to be mutated in the majority of patients with adult-onset dysplastic gangliocytomas (Zhou et al. 2003, Abel et al. 2005).

4.5. STATISTICS

4.5.1. PUBLICATION I

IBM SPSS Statistics version 22.0 was used for statistical analyses. The Chi-Square test was used to compare the differences of sex in individuals with and without HS-Aging, and with and without TDP-43 IHC-positivity in the granular cell layer of the hippocampus. The Mann-Whitney U test was used to compare age at death in these groups. Binary logistic regression, adjusted for age at death and sex, were used to analyze all the other variables.

4.5.2. PUBLICATION II

Using the Hardy-Weinberg Equilibrium (HWE), expected frequencies were determined and tested using the Chi2 goodness of fit. Chi2 (or Fisher's exact test) was used to determine the association of genotype or allele frequency and LATE-NC+HS or TDP-43 pathology. All SNP was analyzed using an additive mode of inheritance (number of risk alleles determined 0, 1, or 2). *ABCC9* rs704178 was also analyzed using a recessive mode of inheritance (MOI) (2 risk alleles = 1; 0 otherwise), which has been proved to be an appropriate method based on the earlier studies (Nelson et al. 2014, Nelson et al. 2015, Katsumata et al. 2017). Effect size, using Cramér's phi, was determined as well. Logistic regression (Odds ratio, 95% confidence interval) was used to clarify genotype associations with LATE-NC+HS or TDP-43 pathology when taking the effect of age at death and sex into account. α was set at 0.05. The STATA14 software (Stata Corporation 2015, Texas, USA) was used to analyze data in this study.

4.6. APPROVAL OF THE STUDY

Publications I, II and III

The Vantaa 85+ study material was approved by the Ethics Committee of the Health Centre of the City of Vantaa and by Helsinki University Central Hospital Coordinating Ethics Committee. The Finnish Health and Social Ministry accepted the use of the health and social records as death certificates. Blood samples were collected only from those subjects from whom informed consent was obtained (either provided by the subjects themselves or their relatives). The National Authority for Medicolegal Affairs (VALVIRA) approved the collection of tissue samples at autopsy as well as their use for research. A written consent for autopsy was obtained from the closest relatives.

Publication IV

The Ethics Committee of the Department of Neurology, Helsinki University Central Hospital, approved the study of familial dementing disorders (the approval was updated in 2011 and 2014).

5. RESULTS AND DISCUSSION

5.1. PUBLICATION I

The frequency of HS-Aging and its associations with other dementia-related neuropathologies among very elderly individuals were studied in a population-based study setting.

1. In our study, the prevalence of HS-Aging was 15.6%, which lies within the range (10-25%) of the earlier studies (Leverenz et al. 2002, Barker et al. 2002, Lippa and Dickson 2004, Rauramaa et al. 2011, Malek-Ahmadi et al. 2013, Keage et al. 2014, Jellinger and Attems 2015, Uchino et al. 2015a, Hokkanen et al. 2018). However, because the definitions, diagnostic criteria, study settings and study cohorts for HS-Aging have varied (Nelson et al. 2011b, Zarow et al. 2012, Rauramaa et al. 2013, Jellinger and Attems 2015, Dutra et al. 2015a, Uchino et al. 2015b, Hokkanen et al. 2018, Nelson et al. 2019), it is difficult to estimate the actual prevalence of HS-Aging and directly compare the different studies.

Female gender was more prevalent in our study (~90%), but not associated with HS-Aging. A similar trend for female predominance with lack of statistical significance has been shown in some other studies (Murray et al. 2014, Oveisgharan et al. 2018). In some younger study cohorts, male gender has been shown to be more prevalent (Leverenz et al. 2002, Pao et al. 2011, Zarow et al. 2012). Females are more likely to live until very advanced age (Neltner et al. 2016), and thus in our study, focused on the very elderly, the female gender is prominent.

2. The pure form of HS-Aging without any comorbid neuropathological changes was very rare (~2%) in this very elderly study population. The prevalence of pure HS-Aging has also been low (0.5%- 5.4%) in other publications (Ala et al. 2000, Jellinger 2000, Leverenz et al. 2002, Probst et al. 2007, Amador-Ortiz et al. 2007a, Dutra et al. 2015b, Ihara et al. 2018). Comorbid pathologies are very common in the aged brain (Kovacs et al. 2008, White 2009, Rahimi and Kovacs 2014, Murray et al. 2014, Robinson et al. 2018).

3. Both hippocampi were investigated, and 51% (47/302) of the samples showed bilateral HS changes. Solely unilateral changes were more frequent (25%) in the left side hippocampus. In general, the neuronal loss in the CA1 sector was more severe (> 80%) compared to neuronal loss in the subiculum.

There are only very few studies where both hippocampi have been studied (Nelson et al. 2011b, Zarow et al. 2012). HS-Aging was shown to be unilateral in 40-50% of cases evaluated from HE-stainings (Nelson et al. 2011b, Zarow et al. 2012) in accordance with our results. However, it is known that HS-Aging may also be segmental and observed only in some histological sections of the hippocampus (Ighodaro et al. 2015). Thus, HS-Aging cases might be more prevalent (Nelson et al. 2016), but the routine practice for neuropathological examination and sampling of the hippocampus is unilateral and non-segmental. There are no earlier publications concerning the severity of the neuronal loss between the CA1-sector and the subiculum, nor are published data available on the preferable side in the unilateral cases.

4. In our study, most of the HS-Aging (96%) patients were demented at the time of death, and there was a strong association between HS-Aging and dementia ($p< 0.001$). We also discovered that TDP-43 positivity in the dentate fascia granular cell layer was independently associated with dementia ($p< 0,001$).

Dementia has also been prevalent and associated with HS-Aging in other publications (Nelson et al. 2010, Nag et al. 2015, Nelson et al. 2019). In HS-Aging, the decline of cognitive functions and dementia develops at a slower rate when compared to AD (Smirnov et al. 2019).

5. Several different neuropathological and vascular variables were studied for possible associations with HS-Aging. A weak association was seen with CERAD score ($0.01< p \leq 0.05$), but the other AD associated variables did not achieve statistical significance. The studied vascular variables, except for heart infarct ($0.01< p \leq 0.05$), were not associated with HS-Aging.

The distribution of the CERAD score among HS-Aging patients has been studied in other publications (Zarow et al. 2012, Brenowitz et al. 2014, Hokkanen et al. 2018). HS-Aging individuals have been found in each CERAD score class, from none to frequent. Hokkanen et al. did not find a significant association between HS-Aging and CERAD score (Hokkanen et al. 2018), and in our study the significance was weak. In our study, individuals with HS-Aging were more aged compared to the study by Hokkanen et al. (Hokkanen et al. 2018). However, the distribution of CERAD scores of HS-Aging cases were similar. Braak NFT stage was not associated with HS-Aging in our study, and the result was also the same in other studies (Brenowitz et al. 2014, Hokkanen et al. 2018)

Myocardial infarction was weakly associated with HS-Aging in our study, but this has not been studied or confirmed by other studies focusing on different vascular variables and HS-aging (Neltner et al. 2014, Nag et al. 2015, Nelson et al. 2016, Hokkanen et al. 2017). Previously, B-ASC (Bridges et al. 2014) has been associated with HS-Aging (Neltner et al. 2014, Ighodaro et al. 2015, Neltner et al. 2016, Nelson

et al. 2016). We were not able to study the association between HS-Aging and B-ASC because this variable has not been assessed in our study. Non-Aβ-based thickening of brain arterioles (B-ADC) has been shown to be associated with the gene variant rs41780 of *ABCC9* (Neltner et al. 2014), which is one of the HS-Aging associated risk SNPs. Interestingly, B-ASC is associated with sleep fragmentation (Lim et al. 2016) and the *ABCC9* variant is associated with sleeping problems (Parsons et al. 2013).

6. Immunohistochemical stainings with TDP-43, p62 and Tau showed a strong association ($p < 0.001$) with HS-Aging. TDP-43 positivity as NCIs was detected in the granular cell layer of dentate fascia. In the CA1 sectors, TDP-43 immunopositivity was shown in some residual neurons as NCIs. Tau-positive neurofibrillary lesions and neuropil threads in dentate fascia cells, and p62 immunopositivity in the granular cell layer was associated with HS-Aging.

HS-Aging is known to be associated with robust TDP-43 IHC pathology in the granular cell layer of the dentate fascia (Amador-Ortiz et al. 2007b, Dickson 2008b, Rauramaa et al. 2013, Nag et al. 2015, Nelson et al. 2016, Hokkanen et al. 2017). In previous studies, it has been hypothesized that neuronal loss of HS-Aging begins in the subicular end of the CA1 when it is associated with the TDP-43 pathology (called pre-HS-Aging), developing later into end-stage HS-Aging (Aoki et al. 2015, Hokkanen et al. 2017). TDP-43 positivity in the dentate fascia granular cells as an early marker for HS-Aging has also been suggested by Nelson et al. (Nelson et al. 2016).

In our study, the Tau immunopositive pathology was strongly associated with HS-Aging. This may indicate a general neurodegenerative process in the dentate fascia granule cells as well as comorbid neuropathologies (Beach et al. 2003, Pao et al. 2011). In recent studies, granular cell layer Tau-positivity was found to be a key feature in late-stage HS-Aging, independent of Braak stage (Nelson et al. 2016, Hokkanen et al. 2017). Immunopositivity of p62 in the dentate fascia granular cells and its association with HS-Aging is rational, because p62 reacts with many accumulated protein aggregates in neurodegenerative diseases and it is widely used as a primary screening tool for those aggregates (Kuusisto et al. 2008).

7. As TDP-43 positivity in the granular cell layer has been proposed to be a robust marker for early HS-Aging (Neltner et al. 2014, Nelson et al. 2016), its associations with other neuropathological markers and vascular variables were studied to confirm this. Significant associations were found between TDP-43-positivity and dementia, the CERAD score and immunopositivity of p62 as well as Tau. Weak associations were seen with age at death, Braak stage, α-synuclein pathology and infarcts of posterior circulation.

Associations found between the TDP-43 immunopositivity in the granular cell layer and different studied variables were similar to associations of these variables

with HS-Aging. This indicates support for the hypothesis that TDP-43 might be an early marker for HS-Aging and a secondary phenomenon as a reaction to abnormal proteostasis caused by different factors (Neltner et al. 2014, Nelson et al. 2016). Small end-arterioles from the anterior choroidal and posterior cerebral arteries are feeding of CA1 sector of hippocampus, which is sensitive for hypoxia. In our study, an infarct of the posterior circulation showed a modest association with TDP-43 positivity in the granular cell layer. It has been published earlier that TDP-43 positivity in the hippocampus and entorhinal cortex are seen more often in individuals with clinical dementia and that it correlates well with the severity of dementia and more advanced age (Uchino et al. 2015a). In addition, those elderly individuals who died after the age of 90 and had dementia were more likely to show TDP-43 inclusions (Keage et al. 2014). This is in accord with the fact that the probability for HS-Aging is known to increase strongly after 90 years of age (Nelson et al. 2011a, Neltner et al. 2016, Nelson et al. 2016). In advanced age, NFTs are inevitably detected, and the association with Tau immunopositivity in the dentate fascia granule cells might be related to this. Data from several studies have showed that NFTs can be accumulated in the hippocampus via at least two different processes. One is combined accumulation of Aβ and Tau positive NFTs, and the other is accumulation of only NFTs, resulting in milder symptoms of cognitive impairment (Jellinger and Attems 2007, Nelson et al. 2009, Brenowitz et al. 2014). The association of TDP-43 with CERAD and α-synuclein pathology may be related to the issue that TDP-43 pathology is observed in neurodegenerative processes sharing common disease mechanisms, especially AD type pathology (Brenowitz et al. 2014). The etiological significance of the TDP-43 pathology seen in HS-Aging and AD as well as in other age-related neurodegenerative processes is largely unclear (Dutra et al. 2015a, Nelson et al. 2016) and more studies are needed to clarify this topic.

5.2. PUBLICATION II

The associations between known risk gene alleles and HS-Aging and the association with TDP-43 was studied in three European population-based cohorts (Vantaa 85+, CFAS and CC75C = EClipSE), a total of 744 patients.

1. The *GRN* rs5848 genotype was strongly associated with HS-Aging ($p < 0.001$). The C/T and T/C genotypes were more frequent in HS-Aging subjects compared to non- HS-Aging subjects. The T allele was shown to be the risk allele ($p < 0.001$).

GRN rs5484 has been proven to be a genetic risk factor for HS-Aging in previous studies (Rademakers et al. 2008, Dickson et al. 2010, Murray et al. 2014, Nelson et al. 2015b, Nelson et al. 2015c, Nho et al. 2016). It has been hypothesized that rs5848 is a disease-modifying variant promoting the manifestation of several different diseases

(Cruts et al. 2006, Snowden et al. 2012, Chang et al. 2013, Kamalainen et al. 2013, Nelson et al. 2016) not only of HS-Aging. The T allele has been shown to be a risk allele in HS-Aging subjects (Dickson et al. 2010, Murray et al. 2014, Nelson et al. 2015b), similarly to our study. The TT genotype has been reported to be associated with lower proganulin levels in the brain (Rademakers et al. 2008).

2. *TMEM106B* rs1990622 was found to be associated with HS-Aging ($p < 0.001$). A/A was the most frequent genotype in the HS-Aging group, and the A allele was shown to be the risk allele.

HS-Aging has been associated with *TMEM106B* rs1990622 (Murray et al. 2011, Rutherford et al. 2012, Nelson et al. 2015b, Nelson et al. 2015c), and this variant has been found to be associated with other diseases, such as FTLD, chronic traumatic encephalopathy and ALS (Vass et al. 2011, Cherry et al. 2018). Other studies have pointed out the same risk allele A that was detected in our study (Nelson et al. 2015b, Nelson et al. 2015c).There are also some publications showing that this SNP is associated with AD (Satoh et al. 2014, Lu et al. 2014). Lysosomal protein produced from *TMEM106B* is known to affect the expression levels of progranulin (Finch et al. 2011, Lang et al. 2012, Brady et al. 2013).

3. *ABCC9* rs704178 was not associated with HS-Aging in this study. C/G was the most frequent genotype in both the HS-aging and non-HS-Aging groups.

The association of rs704180/rs704178 (in near perfect LD) and HS-Aging was published some years ago based on GWAS data (Nelson et al. 2014, Nelson et al. 2015a). We were not able to confirm this finding in our study, but it should borne in mind that the power of statistical analysis might be low due to the relatively small cohort size. This SNP is known to affect mRNA levels of the *ABCC9* gene (Nelson et al. 2015a). *ABCC9*-derived proteins participate in the regulation of potassium channels (Zarei et al. 2007, Nelson et al. 2015b, Nelson et al. 2015c), acting as a sensor needed in vascular responses to hypoxia, ischemia and inflammation (Nelson et al. 2015a). A decreased level of thyroid hormone is known to be linked to the *ABCC9* risk genotype (Nelson et al. 2015b, Trieu et al. 2018, Nelson et al. 2019).

4. TDP-43 positivity of the dentate fascia granular cells showed an association with the genotypes T/C and T/T in *GRN* rs5848 ($p < 0.001$) and the risk allele T ($p < 0.001$) as well as with the genotype A/A in *TMEM106B* rs1990622 ($p = 0.006$) and the risk allele A ($p = 0.001$). TDP-43 positivity was not associated with *ABCC9* rs704178. 48/56 (~83%) of the HS-Aging subjects had TDP-43 immunopositive NCIs in the dentate fascia. When the subjects with HS-Aging were deleted from the analysis, the association with TDP-43 positivity of dentate fascia granule cells and the associations of the genotypes T/C and T/T in *GRN* rs5848 remained significant ($p = 0{,}018$), as did the T allele ($p = 0.006$). The *TMEM106* B rs1990622 genotype

or allele were not associated with TDP-43 positive NCIs in dentate when all the LATE-NC + HS individuals were excluded.

The known mutations of *GRN,* for example, in FTLD-TDP cause a reduction of expressed progranulin levels (Katsumata et al. 2017). Progranulin is suggested to act as a neurotrophic factor and loss of function may lead to TDP-43 accumulation in HS-Aging as well (Zhang et al. 2007, Nelson et al. 2015b, Nelson et al. 2015c). The polymorphic rs5484 site in the 3´UTR region of *GRN* is related to variations in progranulin levels and a higher risk for HS-Aging. rs5484 is also a binding site for microRNA miR-659, which may inhibit progranulin translation and predispose to increased risk to HS-Aging (Rademakers et al. 2008). *TMEM106B* is known to be able to modulate progranulin levels (Finch et al. 2011). The risk alleles of *GRN* and *TMEM106B* together can lead to alterations of proganulin levels, which are not tolerated in aged brains, causing neuronal damage and loss of CA1 sector neurons and accumulation of TDP-43 positive NCIs in the dentate fascia granule cells (Zhang et al. 2007, Nelson et al. 2015b, Nelson et al. 2015c).

5.3. PUBLICATION III

The mutations in the *APP* gene are usually pathogenic, causing accumulation of Aβ in the brain. However, a protective *APP* mutation (A673T) against AD has also been described (Jonsson et al. 2012a). This mutation reduces β-cleavage of the APP protein, thus leading to lower levels of Aβ (Jonsson et al. 2012a, Jonsson et al. 2012b, Li et al. 2019). We investigated the frequency of this mutation among very old Finns and the phenotype that the mutation carriers have.

1. The A673T mutation of the *APP* gene was found only in one very old individual (104.8 years) of the 515 subjects (0.19%), indicating that this is not a frequent variant in the Vantaa 85+ study cohort.

In the Nordic countries (Norway, Sweden, Finland and Iceland) the average frequency of the A673T mutation has been described as 0.43% (Mengel-From et al. 2015). In the Danish population, this variant has been shown to be very rare (0.0014%). Whether this is due to genetic drift or natural selection is not known. This variant has not been found in Asian populations (Ting et al. 2013, Liu et al. 2014), and two studies on the US population showed that this variant is extremely rare in the US (Wang et al. 2015). One of these studies found zero A673T variant carriers (Bamne et al. 2014) and the other showed as small a frequency as seen in the Danish population (Mengel-From et al. 2015). Thus, this variant seems to be enriched in the Nordic population, excluding the Danes. A Finnish group has managed to generate a human induced pluripotent stem cell line from a patient with the A673T variant. This may provide an opportunity to study the mechanisms

behind this mutation more carefully and discover possible treatment strategies for AD in the future (Lehtonen et al. 2018). Another Finnish group showed in addition that carriers of this mutation had 30% lower Aβ levels determined from blood samples (Martiskainen et al. 2017).

2. In the neuropathological characterization of the A673T variant carrier, no Aβ pathology was seen when using methenamin silver staining: the CERAD score was 0. However, immunostaining with the Aβ antibody showed some diffuse Aβ deposits in the parietal lobe, but no neuritic plaques were found. Aβ positivity was seen mainly in the meningeal arteries (1-2%), and mild amyloid angiopathy (CAA) was also seen in these arteries. The Braak stage was determined as 3 based on some NFTs and NT found in the temporal cortex using immunohistochemistry. Neuronal loss in the CA1 sector of the hippocampus and subiculum was seen bilaterally, consistent with HS-Aging. Some vascular pathology, mainly small infarctions, was also observed. Some Lewy bodies were detected in the brain stem and limbic areas. The *APOE* genotype was ε2/ε3.

The neuropathological phenotype of our patient cannot be compared to other A673T variant carriers, because the neuropathological details of other carriers have not been reported. The neuropathological findings of our mutation carrier were mild and for the most part similar to that which is commonly seen in the aged brain (Bennett et al. 2006, Fjell et al. 2014). CAA is strongly associated with AD in most elderly subjects (Yamada 2002, Attems and Jellinger 2006), but not all. Our mutation carrier had moderate CAA only in some leptomeningeal areas. Interestingly, our patient had the *APOE* ε2/ε3 genotype, known to be a protective factor for EOAD and LOAD (Corder et al. 1994a, Corder et al. 1994b, Panza et al. 2000). This *APOE* genotype combined with the A673T variant may have protected our patient from AD.

5.4. PUBLICATION IV

Relatively soon after the *C9orf72* repeat expansion mutation was discovered to be linked to both the sporadic and familial forms of ALS and FTD some years ago (Renton et al. 2011, DeJesus-Hernandez et al. 2011), it was found that this gene defect was associated with more heterogenous phenotypes and entities, than had been described earlier, for example PD, AD and Huntington disease phenocopies (Murray et al. 2011, Kohli et al. 2013, Chi et al. 2016). On the other hand, there has been great interest in the connection between neoplasia and neurodegeneration. In this study, we studied a family with *C9orf72*-associated FTLD, possibly connected with a rare form of neoplasia, dysplastic gangliocytoma.

In the autopsy of the index patient, cerebral atrophy, in addition to a cerebellar tumor dysplastic gangliocytoma, was seen. His sister suffered from more severe cerebral atrophy, especially in the frontal lobes. Neuropathological findings in the index patient and his sister showed abundant p62 immunopositive (but TDP-43 negative) inclusions in the cerebellum. Both siblings were diagnosed after autopsy with FTLD-TDP-43, subtype A in the index patient and subtype A/B in his sister. Both siblings had moderate to severe problems in cognitive functions. The duration of the illness was only one year in our index patient, but the sister lived 6 years after disease onset and also developed more serious clinical symptoms during that period. Both died because bronchopneumonia.

The cerebellar inclusions in the cerebellar granular cells were p62 and ubiquitin immunopositive but TDP-43 negative. These kinds of inclusions were originally found in some familial FTLD-TDP cases, and they have been shown to be a specific feature for the *C9orf72* repeat expansion mutation (Pikkarainen et al. 2010, Hsiung et al. 2012, King et al. 2013). Interestingly, these inclusions have been found in subjects with the *C9orf72* repeat expansion mutation, though with another type of neuropathologic phenotype than FTLD-TDP-43 (Pasanen et al. 2018).

The *C9orf72* hexanucleotide expansion is common among Finnish FTLD/ALS patients; almost 30% of FTLD and ALS patients have this mutation (Renton et al. 2011). The other common genetic causes of FTLD/ALS, *GRN* and *MAPT* mutations are rare among Finns (Kaivorinne et al. 2008a, Kaivorinne et al. 2008b, Kruger et al. 2009). Most often, the *C9orf72* repeat expansion mutation is related to FTLD-TDP subtype B, but other subtypes can be found, especially the combined subtype A and B (Mackenzie et al. 2011b), as was found in our study.

2. The index patient had a rare tumor in the cerebellum, dysplastic gangliocytoma, (Lhermitte-Duclos disease, LDD). Mutations in the *PTEN* gene have been found to be a cause for this tumor in previously published patients, but not in our index patient.

Germline mutations in the *PTEN* gene on chromosome 10 are associated with LDD (Staal et al. 2002, Abel et al. 2005). The exact mechanisms concerning how *PTEN* mutations are involved in the development of LDD are unknown. However, some LDD patients do not have germline mutations in the *PTEN* gene (Zhou et al. 2003). Mutations inactivating *PTEN* cause increased expression levels of phosphorylated Akt, which exaggerates cell growth via different downstream routes, for example mTOR (Abel et al. 2005, Stopford et al. 2017). In the mouse *PTEN* knockout model, mimicking LDD, disturbed precursor granular cell migration and control of cell size have been demonstrated (Kwon et al. 2001). In these cells phosphorylated Akt is highly expressed as well as p-S6, which is one component of the mTOR signaling pathway (Kwon et al. 2001, Backman et al. 2001, Abel et al. 2005).

We did not detect germline mutations in the coding sequence of *PTEN*. The other candidate genes (*MAPT*, *GRN* and *TDP-43*) were sequenced and no mutations were found within their coding sequence either. Our patients showed a pathological length of C9orf72 repeat expansion mutation, which is known to have inhibitory effects (most probably through toxic gain of function) in the mTOR/Akt/S6 pathway, resulting in adverse consequences for neuronal cells (Stopford et al. 2017). It has been shown in a cell line model of motoneurons that even partial depletion of the *PTEN* gene can protect cells from the toxicity of the *C9orf72* repeat expansion mutation (Stopford et al. 2017). Because the patients showed pathological length in the genetic analysis as well as p62 inclusions in the cerebellum in the neuropathological examination, we hypothesized that there might be some link between these features. The *C9orf72* repeat expansion mutation had possibly induced depletion of *PTEN*, hypothetically promoting the development of dysplastic gangliocytoma in our index patient (Snowden et al. 2012, King et al. 2013).

3. Three subjects in this family (the index patient and his diseased sister as well as another sibling) were found to have >40 repeats of *C9orf72* repeat expansion mutation.

Recently, it has been reported that *C9orf72* repeat expansion mutations containing over 30 repeats are pathological and harmful (Byrne et al. 2014, Stopford et al. 2017), but the pathogenic repeat length threshold is still unclear and other repeat lengths associated with disease have also been suggested (Kaivola et al. 2019). However, expansions between 200-5000 have been found in ALS patients (Cooper-Knock et al. 2014, Byrne et al. 2014, Stopford et al. 2017, Kaivola et al. 2019).

6. STRENGTHS AND LIMITATIONS OF THE STUDY

In publications I-III, we have investigated the Vantaa 85+ study material, which is population-based and thus lacks selection bias. Most of studies and materials concerning elderly people are focused on demented and cognitively impaired people, collected from specific nursing homes (Nelson et al. 2016, Hokkanen et al. 2018).

The prevalence of hippocampal sclerosis increases as a function of advanced age, and after the age of 90 years, the increase is most aggressive (Nelson et al. 2016). Underlining this fact, our study material represents a group old enough to study HS-Aging.

Frequently, studies of elderly people are clinically but not neuropathologically defined. HS-Aging has been relatively rarely studied bilaterally, but we were able to determine the bilateral status of HS-Aging lesions. In all publications, I-IV, we were able to show the findings on the histological level, clarifying the neuropathological phenotype behind the described entities. Using genetic methods, we were able to study biological processes more carefully and to compare the results between histological and genetic findings.

Concerning genetic studies, our study material (Vantaa 85+) is relatively small, which might decrease the power of statistical analysis. However, the genetic results from Vantaa 85+ were confirmed in the British study cohorts CFAS and CC75C.

For TDP-43 IHC stainings we had to use reprocessed, originally PEG-embedded material. It is known that the TDP-43 epitope may be influenced by long fixation and preservation of blocks (Cykowski et al. 2017). We managed to counteract those problems with stronger pretreatment and a more sensitive detection system.

HS-Aging has been described as segmental/patchy-like in one study (Ighodaro et al. 2015), but unfortunately it was not possible for us to study different levels of hippocampi because our samples were collected only at the level of the lateral geniculate body.

B-ASC is thought to be associated with HS-Aging. We were not able to confirm this finding because of the lack of B-ASC data in the Vantaa85+ sample.

7. CONCLUSIONS

Based on the results presented in this thesis, the following specific conclusions can be drawn.

Publication I
HS-Aging is very common among the oldest old (16%), but it occurs very seldom without any other type of old-age associated neuropathological changes (pure HS-Aging). Almost half of the HS-Aging cases appeared unilateral. This finding should be taken into consideration in routine neuropathological examination, in which only one hippocampus is often sampled. TDP-43 immunopositivity was strongly associated with HS-Aging but was not specific for this entity.

Publication II
We confirmed the previously reported genetic associations between *GRN* rs5848 and *TMEM106B* rs199062 and HS-Aging in three European population-based cohorts. The *ABCC9* variants, however, were not significantly associated with HS-Aging in these population-based studies.

Publication III
We showed that the previously reported, protective *APP* mutation A673T is very rare among the very old Finns. The only mutation carrier of the Vantaa85+ material lived an extraordinarily long life with virtually no AD pathology identified in the neuropathological examination after death. Our results support the hypothesis that the A673T mutation is protective against AD, inhibiting the β-secretase cleavage of APP and reducing the production of the harmful Aβ.

Publication IV
A familial FTLD-TDP phenotype was shown to segregate with a hexanucleotide repeat expansion in *C9orf72*. One diseased family member has a rare cerebellar dysplastic gangliocytoma, in which *PTEN* germline mutations were not detected. It is possible that the *C9orf72* repeat expansion mutation has induced the depletion of *PTEN* in the granular cells in the cerebellum of the index patient. This might also indicate that *C9orf72* repeat expansion mutation is involved in more heterogenous neuropathological conditions than originally described. The results support the view that the PTEN pathway may be involved in the pathogenesis induced by the *C9orf72* repeat expansion mutation, and that there may be significant overlap between neoplastic and neurodegenerative processes.

Taken together, this thesis provided new information on the prevalence and genetic background of HS-Aging and other TDP-43 proteinopathies in the Finnish population and forms a basis for further studies on old-age associated TDP-43 accumulation, particularly in the context of LATE-NC.

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