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EINO SOLJE

THE SPECTRUM OF THE PHENOTYPES IN THE C9ORF72 EXPANSION CARRIERS

Insights at the Interface between Neurology and Psychiatry

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ABSTRACT:

Frontotemporal lobar degeneration (FTLD) is the second most common etiology responsible for early onset dementia. The syndrome is clinically divided into behavioural variant frontotemporal dementia (bvFTD) and primary progressive aphasias (PPA). There can be a delay of several years before physicians can make an accurate bvFTD diagnosis, because the early signs of the disease are rather common psychiatric symptoms rather than characteristic memory problems and this problem is accentuated by the lack of diagnostic biomarkers. A considerable number of FTLD cases are familial and the *C9ORF72* repeat expansion has been identified as the most common causative mutation for the FTLD in Finland. The phenotypes associated to the *C9ORF72* expansion are very variable and so far, the exact phenotype has not been accurately described according to the new diagnostic criteria for bvFTD.

The aim of this study was evaluate the phenotypes associated with the *C9ORF72* expansion. The clinical significance of the mutation was analyzed in three distinct cohorts: 1) in patients suffering from the *C9ORF72* expansion associated bvFTD (n=36), 2) in patients with schizophrenia and other psychoses from the Northern Finland Birth Cohort 1966 (NFBC 1966) (n=130) and 3) in the victims of suicide in Northern Finland (n=109). The sensitivity of the latest diagnostic criteria for bvFTD (Rascovsky criteria), the disease course of bvFTD and psychiatric manifestations among the *C9ORF72* expansion carriers were evaluated. The prevalence of the *C9ORF72* expansion and its intermediate length repeats were analyzed in the psychiatric cohorts. In addition, the effect of the *C9ORF72* expansion on the phenotype of Nasu-Hakola disease was assessed.

The sensitivity of the latest clinical diagnostic criteria was 75% for possible and 64% for probable bvFTD among the patients with the *C9ORF72* expansion. However, there was extensive clinical variability of the phenotypes between patients. The carriers of the *C9ORF72* expansion display many psychiatric (mood and psychotic) symptoms and 60% of patients have had a psychiatric consultation before or at the time of the bvFTD diagnosis. According the criteria, brain imaging exhibits rather high sensitivity (86%). However, normal brain imaging was detected in 14% of patients. The full length pathological *C9ORF72* expansion was not detected in any of the schizophrenic patients or suicide victims. In addition, the phenotype of Nasu-Hakola disease was not modified by the pathological *C9ORF72* expansion.

In conclusion, patients with the *C9ORF72* expansion experience psychiatric symptoms years before there is any suspicion of bvFTD. This dementing disease should be suspected in subjects with severe psychiatric symptoms appearing in middle age or slightly later despite normal brain imaging findings.

National Library of Medicine Classification: QZ 50, WM 220, WL 358.5, WL 141
Medical Subject Headings: Neurodegenerative Diseases; Dementia; Frontotemporal Lobar Degeneration; Frontotemporal Dementia; Genetics; Mutation; DNA Repeat Expansion; Phenotype; Early Diagnosis; Cognition; Neuroimaging; Behavioral Symptoms; Impulsive Behavior; Inhibition (Psychology); Diagnosis, Differential; Schizophrenia; Suicide

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TIIVISTELMÄ:

Otsa-ohimolohkorappeumat ovat toiseksi yleisin syy työikäisenä alkavaan etenevään muistisairauteen. Otsa-ohimolohkorappeumat jaotellaan kliinisten oirekuvien perusteella käytösoireiseen otsalohkodementiaan sekä kielellisin oirein ilmenevään etenevään afasiaan. Koska otsalohkodementian oireet ovat alkuun pääasiassa neuropsykiatrisia ja taudille spesifisiä biomarkkereita ei ole käytettävissä, niin epäily muistisairaudesta herää usein myöhäisessä vaiheessa ja diagnostiikka viivästyy. Merkittävä osa otsa-ohimolohkorappeumista on perinnöllisiä ja viime vuosina *C9ORF72*-toistojaksomutaation on osoitettu olevan syynä valtaosaan suomalaisista perinnöllisistä tautitapauksista. Mutaatioon liittyvät oirekuvat on kuvattu hyvin vaihteleviksi ja mutaation ilmiasu on otsalohkodementia diagnostisin kriteerein vielä kuvaamatta.

Tässä tutkimuksessa selvitettiin *C9ORF72*-toistojaksomutaatioon liittyviä kliinisiä ilmentymiä. Mutaation aiheuttamaa oirekuvaa ja sen merkitystä on tutkittu kolmessa eri kohortissa 1) *C9ORF72*-mutaatiota kantavien otsalohkodementia diagnoosin saaneiden potilaiden kohortissa (n=36), 2) vuonna 1966 syntyneiden pohjoissuomalaisten syntymäkohortissa (NFBC1966) skitsofreniaa ja muita psykooseja sairastavien osajoukossa (n=130) sekä 3) pohjoissuomalaisessa itsemurha-aineistossa (n=109). Ensimmäisessä kohortissa tutkittiin uusimpien otsalohkodementian diagnostisten kriteerien (ns. Rascovskyn kriteerit) herkkyyttä, sairaudenkulkua ja sairauden psykiatrisia ilmentymiä *C9ORF72*-mutaatiota kantavien potilaiden joukossa. Kahdessa muussa kohortissa selvitettiin *C9ORF72*-mutaation ja sen välimuotoisten pidentymien esiintyvyyttä psykiatrisessa aineistossa. Lisäksi tutkimuksessa selvitettiin *C9ORF72*-mutaation vaikutusta Nasu-Hakolan taudin kliiniseen oirekuvaan.

Uusimpien kliinisten kriteerien herkkyys mahdolliselle otsalohkodementian diagnoosille oli 75 % ja todennäköiselle diagnoosille 64 % *C9ORF72*-mutaatiota kantavilla potilailla. Diagnostisten kriteerien kuvaamassa oirekirjossa oli merkittävää vaihtelua eri potilaiden välillä. Potilailla todettiin runsaasti psykiatrisia oireita, joista suurin osa oli psykoottisuutta tai mielialahäiriöitä. Lisäksi 60 % potilaista oli ollut psykiatrisessa hoidossa ennen otsalohkodementian diagnoosin asettamista. Kriteeristön mukaisilla aivojen kuvantamistutkimuksilla oli suhteellisen hyvä herkkyys tunnistaa otsalohkodementiaa sairastavia potilaita (86 %), mutta noin seitsemäsosalla potilaista kuvantamistutkimukset olivat normaaleja. Patogeenistä mutaatiota ei todettu ennen keski-ikää puhkeavaa skitsofreniaa sairastavien eikä itsemurhan tehneiden aineistossa, eikä mutaatio vaikuttanut Nasu-Hakolan taudissa sairauden kulkuun.

Yhteenvetona voidaan todeta, että *C9ORF72*–toistojaksomutaation aiheuttamassa otsalohkodementiassa ensioireina ovat monimuotoiset psyykkiset häiriöt, jotka alkavat keski-iässä tai sen jälkeen. Keski-iässä alkavien vakavien psyykkisten oireiden taustalla tulisi epäillä otsalohkodementiaa, vaikka aivojen kuvantamistutkimuksissa ei havaittaisi poikkeavia löydöksiä.

Luokitus: QZ 50, WM 220, WL 358.5, WL 141
Yleinen suomalainen asiasanasto: muistisairaudet; dementia; otsa-ohimolohkorappeumat; perinnöllisyys; geenit; genetiikka; genotyyppi; geenitutkimus; mutaatiot; fenotyyppi; diagnoosi; diagnostiikka; kognitio; kuvantaminen – lääketiede; käyttäytymishäiriöt; skitsofrenia; psykoosit; itsemurha

Music begins where the possibilities of language end.
- Jean Sibelius

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List of the original publications

This dissertation is based on the following original publications:

I Solje E, Aaltokallio H, Koivumaa-Honkanen H, Suhonen NM, Moilanen V, Kiviharju A, Traynor B, Tienari PJ, Hartikainen P, Remes AM. The Phenotype of the *C9ORF72* Expansion Carriers According to Revised Criteria for bvFTD. *PLOS ONE 10(7):e0131817, 2015.*

II Solje E, Miettunen J, Marttila R, Helisalmi S, Laitinen M, Koivumaa-Honkanen H, Isohanni M, Hiltunen M, Jääskeläinen E, Remes AM. The *C9ORF72* expansion sizes in patients with psychosis -a population based study on the Northern Finland Birth Cohort 1966. *Psychiatric Genetics 26:92-4, 2016.*

III Solje E, Riipinen P, Helisalmi S, Särkioja T, Laitinen M, Hiltunen M, Hakko H, Remes AM. The role of the *C9ORF72* expansion in suicide victims. Submitted.

IV Solje E, Hartikainen P, Valori M, Vanninen R, Tiihonen J, Hakola P, Tienari PJ, Remes AM. The *C9ORF72* expansion does not affect the phenotype in Nasu-Hakola disease with the *DAP12* mutation. *Neurobiology of Aging 35(7): 1780.e13-7, 2014.*

Contents

Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
ALS	Amyotrophic lateral sclerosis
APP	Amyloid precursor protein
Bp	Base pair
BvFTD	Behavioural variant frontotemporal dementia
C9ORF72	Chromosome nine open reading frame 72
CBD	Corticobasal degeneration
CBS	Corticobasal syndrome
CHMP2B	Charged multivesicular body protein 2b
CSF	Cerebrospinal fluid
CT	Computed tomography
DAP12	DNAX activation protein of 12 kDa
DENN	Differentially expressed in normal and neoplastic
DNA	Deoxyribonucleic acid
EPM2	Epilepsy, progressive myoclonus type 2A
FBI	Frontal behavioral inventory
FDG	Fludeoxyglucose
FTD	Frontotemporal dementia
FTDC	International Behavioural Variant Frontotemporal Dementia Criteria Consortium
FTLD	Frontotemporal lobar degeneration
FLDnA	Frontal lobe degeneration of non-Alzheimer type
GDP/GTP	Guanosine diphosphate/ guanosine triphosphate
HD	Huntington's disease
FUS	Fused in sarcoma
GRN	Progranulin
GWAS	Genome wide association study
ICD	International classification of diseases
LvPPA	Logopenic variant primary progressive aphasia
MAPT	Microtubule associated protein tau
MCI	Mild cognitive impairment
MND	Motoneuron disease
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSTD	Multiple system taupathy with dementia
NFBC 1966	Northern Finland Birth Cohort 1966
NfvPPA	Non-fluent variant primary progressive aphasia
NHD	Nasu-Hakola disease
OMIM	Online Mendelian Inheritance in Man
OPTN	Optineurin
PD	Parkinson's disease

PGRN	Progranulin
PET	Positron emission tomography
PPA	Primary progressive aphasia
PSEN	Presenilin
PSP	Progressive supranuclear palsy
RAN	Repeat associated non-standard
RNA	Ribonucleic acid
RP	Reverse primer
SD	Standard deviation
SNP	Single nucleotide polymorphism
SPECT	Single photon emission computed tomography
SOD1	superoxide dismutase 1
SvPPA	Semantic variant primary progressive aphasia
TARDBP	See TDP-43
TDP-43	TAR-DNA binding protein of 43 kDa
TMEM106B	Transmembrane protein 106B
TREM2	Triggering receptor expressed on myeloid cells 2
TYROBP	See *DAP12*
UPS	Ubiquitin positive, FUS and TDP-43 negative inclusions
VCP	Valosin containing protein

1 Introduction

Frontotemporal lobar degeneration (FTLD) is the second most common cause for early onset degenerative brain disease (Ratnavalli et al. 2002); it accounts for approximately 10 % of all progressive memory diseases (Cooper-Knock, Shaw & Kirby 2014). Because the age of onset is substantially earlier than in other progressive memory diseases, the significance of FTLD is relatively more important among the working-aged population (Ratnavalli et al. 2002).

FTLD is divided clinically into two major subtypes: 1) behavioural variant frontotemporal dementia (bvFTD) and 2) primary progressive aphasias (PPA) (Neary et al. 1998). BvFTD is a syndrome that leads to changes in both personality and behaviour. These patients may be impulsive or inflexible, even apathetic. Indiscreet behaviour and disinhibition occur and as social skills deteriorate personal relationships may be harmed (Neary, Snowden & Mann 2005, Rascovsky et al. 2011, Piguet et al. 2011). Executive functions required for cognition are impaired quite soon after the initial symptoms, but visuospatial skills are preserved and this is combined with a relative sparing of episodic memory during the early course of the disease (Rascovsky et al. 2011). There is a substantial overlap in the clinical symptoms between bvFTD and many psychiatric disorders, especially with mood and psychotic disturbances (Rascovsky et al. 2011, Snowden et al. 2015).

Autosomal dominant mutations explain 10-20 percentage of all bvFTD cases (Sieben et al. 2012). The hexanucleotide repeat expansion in chromosome 9 (*C9ORF72*) has been detected in the majority of the familial bvFTD cases globally, but the prevalence in Finland is one of the highest, being present in at least half of the familial cases (Renton et al. 2011, Majounie et al. 2012b, DeJesus-Hernandez et al. 2011). On the other hand, other genetic causes are extremely rare in Finland (Kruger et al. 2009, Kaivorinne et al. 2008).

The diagnosis of bvFTD is based on patient and caregiver interviews, neurological assessment, neuropsychological test batteries and structural and functional brain imaging (Rascovsky et al. 2011). The definite diagnosis is made either genetically i.e. by the detection of a pathological mutation or histologically via some recognized neuropathological characteristic in brain samples (Rascovsky et al. 2011). However, the diagnostics of bvFTD are particularly challenging and no biomarkers are available for clinical use. Neuroimaging findings may be normal even when the clinical picture indicates that there is at least moderate dementia (Riedl et al. 2014). In addition, variability in the clinical representation is seen in some families (Cooper-Knock, Shaw & Kirby 2014, Beck et al. 2013). It has been emphasized that patients suffering from early phases of bvFTD have a high risk of being misdiagnosed, being especially likely to be thought of as suffering from a psychiatric syndrome, because of the lack of deficits in episodic memory during the early stage of the disease (Woolley et al. 2011, Khan et al. 2012, Neary, Snowden & Mann 2005).

Although there is no curative treatment for bvFTD, it is crucial that the patient should be correctly diagnosed. The diagnosis of bvFTD reduces human misery and helps the nursing personnel to empathize with this patient who has undergone such major changes in personality and behaviour. Furthermore, the response of the patients to antipsychotic treatment may be much worse than in truly psychotic patients, instead the bvFTD patients are likely to suffer the extrapyramidal side effects of these antipsychotic treatments (Karageorgiou, Miller 2014).

The aim of this study was to evaluate the phenotype of bvFTD patients associated with the *C9ORF72* expansion and the role of the mutation in psychiatric cohorts. It was decided to evaluate the latest diagnostic criteria for bvFTD patients with the *C9ORF72* expansion, diagnosed in neurological outpatient clinics. The prevalence of the *C9ORF72* expansion in cohorts of suicide victims and in subjects developing schizophrenia before the middle age

was also examined. In addition, the effect of the pathological *C9ORF72* expansion was assessed in a family with genetically diagnosed Nasu-Hakola disease (NHD).

2 Review of literature

2.1 FRONTOTEMPORAL LOBAR DEGENERATION

FTLD is an umbrella term for progressive neurodegenerative diseases especially affecting frontal and temporal brain regions. FTLD is the second most common cause of early onset dementia i.e. in individuals under 65 years of age (Ratnavalli et al. 2002). From 5 to 15 % of the total number of patients suffering from dementia have FTLD (Cooper-Knock, Shaw & Kirby 2014). The prevalence of the FTLD is estimated to be generally 15 per 100 000 (Ratnavalli et al. 2002), but in Finland, it can be as high as 20.5 per 100 000 (Luukkainen et al. 2015). The onset of the disease is typically located in the middle-years of life and the mean survival time tends to be eight years (Neary, Snowden & Mann 2005).

FTLD is divided into two major clinical syndromes - bvFTD and PPA, and this latter type is again sub-divided into two clinical subtypes, based on the clinical presentation. These are non-fluent variant primary progressive aphasia (nfvPPA), and semantic variant primary progressive aphasia (svPPA) (fig. 1) (Gorno-Tempini et al. 2011). In addition, the recently recognized logopenic variant of primary progressive aphasia (l-vPPA) (Gorno-Tempini et al. 2008, Gorno-Tempini et al. 2011, Leyton et al. 2015) in clinical terms is reminiscent of other primary progressive aphasias, but actually cannot be exactly included under the umbrella of FTLD because the neuropathology and anatomical location of the atrophy resemble more Alzheimer's disease (AD) than FTLD (Mesulam et al. 2008, Rabinovici et al. 2008, Leyton et al. 2015). BvFTD is the most common clinical syndrome of FTLD, accounting for over half of the cases (Johnson et al. 2005, Seelaar et al. 2008). At least 15% of the patients with FTLD develop motoneuron disease (MND) with amyotrophic lateral sclerosis (ALS) being the most common form of MND (Burrell et al. 2011). Approximately 15% of patients with MND develop FTLD (Ringholz et al. 2005).

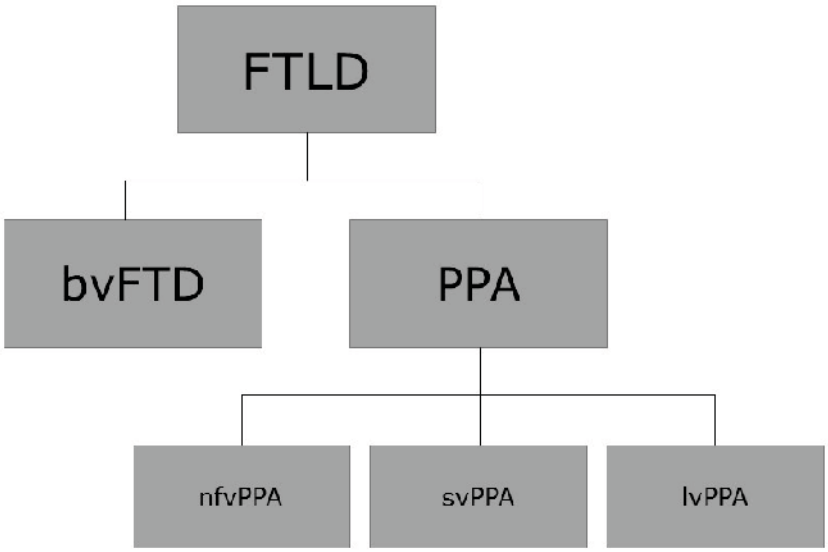

Figure 1. FTLD and its subtypes. FTLD=frontotemporal lobar degeneration, bvFTD= behavioural variant frontotemporal dementia, PPA= primary progressive aphasia, nfvPPA= non-fluent variant primary progressive aphasia, svPPA= semantic variant primary progressive aphasia, lvPPA= logopenic variant primary progressive aphasia.

The mean onset of the initial symptoms of the FTLD spectrum disorders is between 53 and 61 years of age (Rosso et al. 2003, Nunnemann et al. 2011, Ratnavalli et al. 2002, Hodges et al. 2003, Johnson et al. 2005). However, a later onset of the symptoms, even at the age of 80 years, has been reported (Rosso et al. 2003, Johnson et al. 2005). In contrast, patients developing FTLD in their thirties, have also been described (Mackenzie et al. 2008). The mean age at the time of diagnosis is somewhat later i.e. between 56 and 65 years (Nunnemann et al. 2011, Ratnavalli et al. 2002, Hodges et al. 2003). Typically, the disease course of FTLD means that the patient will require institutionalization soon after the initial diagnosis (Hodges et al. 2003). The mean age at death is around 65-67 years (Nunnemann et al. 2011, Hodges et al. 2003, Johnson et al. 2005) as the duration from onset of the symptoms to death is between six to twelve years (Rosso et al. 2003, Nunnemann et al. 2011, Hodges et al. 2003) but also slower disease progression, i.e. as long as 20 years have been recorded (Rosso et al. 2003, Suhonen et al. 2015). The time period from the initial diagnosis to death tends to be between three to seven years (Hodges et al. 2003, Nunnemann et al. 2011). No difference of survival has detected between the clinical FTLD syndromes with the exception of the FTLD-ALS subgroup, which has a clearly shorter survival, compared to patients without features of ALS

(Hodges et al. 2003). The cause of the death in FTLD patients is typically a respiratory system disorder, a circulatory system disorder or cachexia (Nunnemann et al. 2011).

FTLD is not only neuropathologically heterogeneous but the genetic causes also vary (Neary, Snowden & Mann 2005). It has been estimated that 30-50% of the cases are of familial autosomal dominant source (Rosso et al. 2003, Rohrer et al. 2009, Ratnavalli et al. 2002, Ikeda, Ishikawa & Tanabe 2004) but bvFTD seems to be more familial than the other subtypes of FTLD (Rohrer et al. 2009).

Certain procedures can help in the diagnosis of in FTLD i.e. neuroimaging (structural and functional), neuropsychological test batteries, clinical examination (especially careful neurological examination), biochemical analyses of cerebrospinal fluid and genetic screening of previously identified pathogenic mutations. Neuropathological biopsies may also be utilized in the diagnostic procedures. However, the diagnosis has remained challenging. (Neary et al. 1998, Rascovsky et al. 2011)

Although there are only limited benefits gained from pharmacologic-biological treatments (in practice, there are only palliative therapies) the disease exerts a great strain on social relationships. For this reason, the education for patients and caregivers combined with psychosocial support remain as the cornerstone of the clinical management of FTLD.

2.1.1 Historical aspects

The first patient with the clinical syndrome of FTLD was described in 1892 by Arnold Pick, a neurologist practicing in Prague. The first case suffered from the symptoms of presenile dementia, aphasia and lobar atrophy (Pick 1892). Soon after the initial case, the syndrome was referred to as Pick disease. The neuropathological inclusions associated with previously described clinical phenotype, initially characterized by Alois Alzheimer in 1911, were named as Pick bodies. In following years, the term "Pick disease" was extended to comprise syndromes associated with atrophy in frontal lobar regions and dysfunction of frontal and temporal brain areas (Onari, Spatz 1926). In 1957 and 1974, pioneering studies reported the clinical and anatomical distinctions between Alzheimer's disease (AD) and Pick disease; the atrophy was observed in more frontal areas in Pick disease whereas in AD it tended to occur more in posterior regions of brain (Delay, Brion & Escourolle 1957, Constantinidis, Richard & Tissot 1974). These studies also observed that only a small proportion of cases with Pick disease had classical Pick bodies in their brains and extrapyramidal symptoms were present quite often. The term of Pick disease was modernised so that it would refer to the frontal lobe degeneration of non-Alzheimer (FLDnA) type and the first conference on FLDnA was held in 1987 in Sweden (1987) followed by second conference in 1993 (1993). The classification of memory diseases is presented in the figure 2.

From the 1890s until the 1980s, only a few case reports described an unusual progressive aphasia associated with frontal neurobehavioural syndromes. In 1982, Mersel Mesulam published a case series describing gradually progressing aphasia without generalized dementia and thus established the language subtype of FTLD in patients with predominant atrophy in the left hemisphere (Mesulam 1982).

In 1990, Neary and colleagues indicated that "FLDnA" and ALS shared distinct pathological and clinical features (Neary et al. 1990). Soon thereafter, they also found that even in the same families, there was a significant variability in the clinical symptoms encompassing both behavioural and language disturbances (Neary, Snowden & Mann 1993). The behavioural variant syndrome was mainly studied in Lund, Sweden and Manchester, United Kingdom and thus the first clinical and pathological criteria for bvFTD were called the Lund-Manchester criteria (The Lund and Manchester Groups 1994) (see table 1), and they focussed on the non-aphatic form of frontotemporal dementia (FTD). These first criteria originally coined the name "Frontotemporal dementia". As the clinical data on FTD increased, the criteria were revised by Neary and colleagues (Neary et al. 1998) (see table 2). In addition, language variants of the FTLD were included into these criteria and furthermore, the ALS was taken into account as a supportive feature of FTD, hence these two syndromes were formally placed under the same umbrella. Subsequently, research on FTD has progressed dramatically and during recent years, after new gene identifications and new neuroimaging and biochemical methods, knowledge of FTLD has advanced almost exponentially. Rather recently, the diagnostic criteria were revised for bvFTD and language forms of FTLD to take into consideration the expanded understanding of FTLD (Rascovsky et al. 2011, Gorno-Tempini et al. 2011).

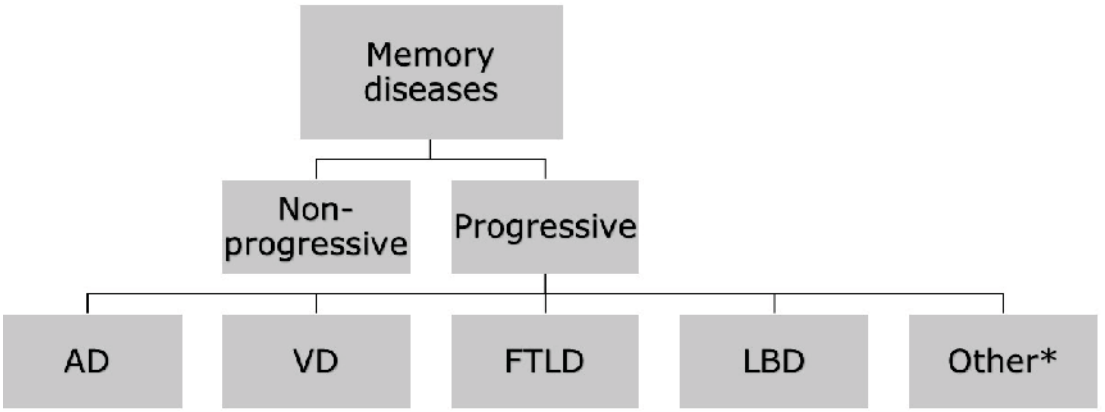

Figure 2. The classification of dementing diseases. AD= Alzheimer's disease, VD= vascular dementia, FTLD= frontotemporal lobar degeneration, LBD= Dementia with Lewy bodies, *E.g. Parkinson's dementia, Alcohol related dementia, Huntington's disease, Creutzfeldt-Jakob disease.

2.1.2 Behavioural variant frontotemporal dementia

BvFTD is characterized with personality changes, delusions/hallucinations, disinhibition, apathy or inertia and deficits in executive tasks with relative sparing of memory functions (Cooper-Knock, Shaw & Kirby 2014, Rascovsky et al. 2011). Patients are often distractible and may lose their jobs (Karageorgiou, Miller 2014). It is common that the patients have a diminished ability to feel/express empathy or sympathy (Rascovsky et al. 2011) e.g. they may ignore acute health problems of their spouses, due to a lack of empathy (Karageorgiou, Miller 2014). It has been reported that stealing is one of the symptoms of bvFTD (Miller et al. 1997, Mendez 2011). Recently, two studies reported that criminality is very common in the early course of bvFTD, perhaps as many as 50% of the patients had committed crimes during the early course of their disease with the most common crimes being traffic violations, sexual advances, theft, wilful damage to property, housebreaking, trespassing and violence toward people/assault (Diehl-Schmid et al. 2013a, Liljegren et al. 2015).

2.1.2.1 Diagnostic criteria for bvFTD

The diagnostic instruments have only started to appear in the most recent decades. Four sets of bvFTD criteria have been presented (The Lund and Manchester Groups 1994, Neary et al. 1998, McKhann et al. 2001, Rascovsky et al. 2011) (see tables 1 for Lund and Manchester criteria, 2 for Neary's criteria and 3 for Rascovsky's criteria). It should be stated that McKhann's criteria never became widely used whereas Neary's criteria were most extensively applied until the introduction of latest set of criteria by Rascovsky and colleagues (Rascovsky et al. 2011). Unfortunately, there are no practical or actual biomarkers which correlate with the Rascovsky criteria for bvFTD (Rascovsky et al. 2011).

In 2007, Rascovsky and colleagues stated that the current prevailing Neary criteria (Neary et al. 1998) were somewhat rigid and limited to clinical and scientific use (Rascovsky et al. 2007). These Neary criteria included 5 core features, 20 supportive features, 11 exclusion features and 3 relative exclusion features thus making the clinical usage quite challenging. It has been stated frequently that the prompt and accurate diagnosis is pivotal for several reasons i.e. correct patient management (Perry, Miller 2001, Robinson 2001, Talerico, Evans 2001, Merrilees, Miller 2003, Merrilees 2007, Boutoleau-Bretonniere et al. 2008), to ensure the patient receives appropriate treatment and to assist in the development of disease modifying drugs. The insensitivity of Neary's criteria in the early stages of bvFTD has been reported by several groups (Mendez, Perryman 2002, Mendez et al. 2007b, Rascovsky et al. 2007, Piguet et al. 2009) as at least one third of the actual bvFTD patients do not meet these criteria (Mendez, Perryman 2002) and a substantial amount of the patients with actual bvFTD have been classified as "normal", or alternatively as psychiatric or AD-patients (Mendez et al. 1993, Mendez et al. 2007b, Varma et al. 1999). Furthermore, the nomenclature and definitions of the features in the criteria were considered as vague. In addition, the progress in neuroimaging and genetic research provided new and more effective tools for the diagnosis of bvFTD (Rascovsky et al. 2011).

The International Behavioural Variant FTD Criteria Consortium (FTDC) devised a new diagnostic battery for clinical and research use (Rascovsky et al. 2011). These FTDC criteria with its three levels of diagnostic certainty (i.e. *possible, probable* and *definite*) are presented in table 3. These criteria are based on behavioural symptoms, neuropsychological assessment, brain imaging (structural and functional) genetic tests and neuropathological analysis. Figure 3 displays a typical positron emission tomography (PET) finding in FTLD.

According to the FTDC criteria for neurodegenerative disease, other causes such as delirium, cerebrovascular disease, cerebellar disorder, trauma, infection, systemic disorder, substance-induced conditions, need to be excluded. In addition psychiatric conditions, which explain better the patient's symptoms, are exclusion criteria for bvFTD (Rascovsky et al. 2011). According to the FTDC criteria, bvFTD should be excluded, if cerebrospinal fluid (CSF) biomarkers or genetic data, e.g. amyloid precursor protein gene (*APP*) or presenilin (*PSEN*)

1 or 2 mutations causing familial AD (Gatz et al. 2006), are indicative of some other brain degenerative diseases (Rascovsky et al. 2011).

Initially, the FTDC revised criteria were found to display 76% sensitivity for probable and 86% for possible bvFTD among neuropathologically confirmed cases, while Neary criteria were found to have only 53% sensitivity. Subsequently, a large autopsy-based study indicated even better sensitivities, i.e. 95% for possible bvFTD and 85 % for probable bvFTD (Harris et al. 2013). One study, based on a clinically gathered cohort (Costa et al. 2013), revealed extremely high sensitivities, as high as 100%, for possible bvFTD, but however, only 60% for probable bvFTD. This study may have been biased by the selection of the patients as the study cohort only consisted of those patients with clearly evident bvFTD. The FTDC criteria were initially suggested to be less sensitive in patients with a later onset of the disease; this was explained by the lower rates of disinhibition, less extensive loss of sympathy or empathy, fewer perseverative behaviours and milder imaging findings consistent with bvFTD (Rascovsky et al. 2011).

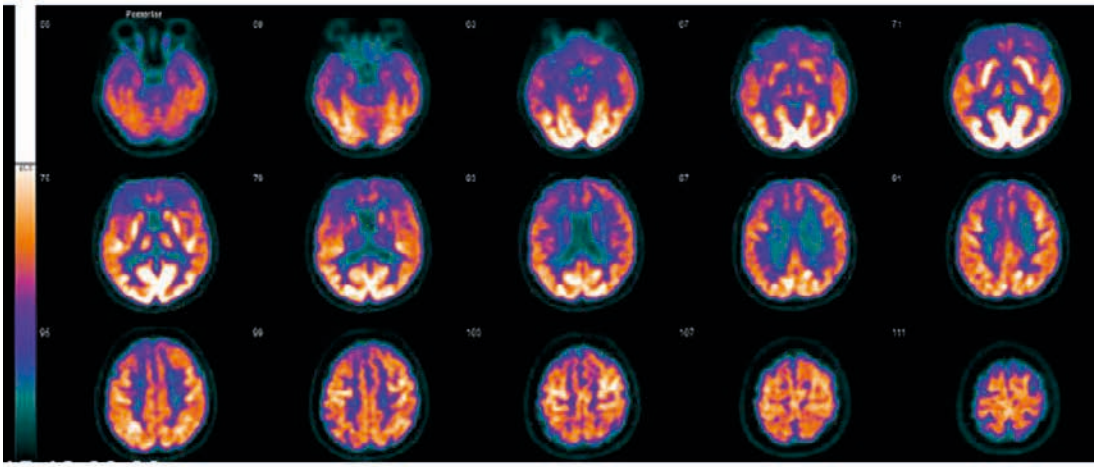

Figure 3. Typical frontal hypoperfusion in FDG-PET.

Table 1. The Lund and Manchester clinical criteria for frontotemporal dementia [1].

Core diagnostic features of frontotemporal dementia

Behavioural disorder

- Insidious onset and slow progression
- Early loss of personal awareness (neglect of personal hygiene and grooming)
- Early loss of social awareness (lack of social tact, misdemeanours such as shoplifting)
- Early signs of disinhibition (such as unrestrained sexuality, violent behaviour, inappropriate jocularity, restless packing)
- Mental rigidity and inflexibility
- Hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and alcohol consumption, oral exploration of objects)
- Stereotyped and perseverative behaviour (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing)
- Utilisation of behaviour (unrestrained exploration of objects in the environment)
- Distractibility, impulsivity, and impersistence
- Early loss of insight into the fact that the altered condition is due to a pathological change of own mental state.

Affective symptoms

- Depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion (early and evanescent)
- Hypochondriasis, bizarre somatic preoccupation (early and evanescent)
- Emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy)
- Amimia (inertia, aspontaneity).

Speech disorder

- Progressive reduction of speech (aspontaneity and economy of utterance)
- Stereotypy of speech (repetition of limited repertoire of words, pharases, or themes)
- Echolalia and perseveration
- Late mutism.

Spatial orientation and praxis preserved (intact abilities to negotiate the environment).

Physical signs

- Early primitive reflexes
- Early incontinence
- Late akinesia, rigidity, tremor
- Low and labile blood pressure

Investigations

- Normal EEG despite clinically evident dementia
- Brain imaging (structural or functional, or both): predominant frontal or anterior temporal abnormality, or both
- Neuropsychology (profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder).

Supportive diagnostic features

- Onset before 65
- Positive family history of similar disorder in a first degree relative
- Bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease).

Diagnostic exclusion features

- Abrupt onset with ictal events
- Head trauma related to onset
- Early severe amnesia
- Early spatial disorientation, lost in surroundings, defective localisation of objects
- Early severe apraxia
- Logoclonic speech with rapid loss of train of thought
- Myoclonus
- Cortical bulbar and spinal deficits
- Cerebellar ataxia
- Choreo-athetosis
- Early, severe, pathological EEG
- Brain imaging (predominant post-central structural or functional deficit. Multifocal cerebral lesions on CT or MRI)
- Laboratory tests indicating brain involvement or inflammatory disorder (such as multiple sclerosis, syphilis, AIDS and herpes simplex encephalitis).

Relative diagnostic exclusion features

- Typical history of chronic alcoholism
- Sustained hypertension
- History of vascular disease (such as angina, claudication).

[1]According to the Lund and Manchester Groups (1994).

Table 2. Neary consensus criteria for frontotemporal dementia[1].

I. Core diagnostic features

A) Insidious onset and gradual progression
B) Early decline in social interpersonal conduct
C) Early impairment in regulation of personal conduct
D) Early emotional blunting
E) Early loss of insight

II. Supportive diagnostic features

A) Behavioral disorder
   1. Decline in personal hygiene and grooming
   2. Mental rigidity and inflexibility
   3. Distractibility and impersistence
   4. Hyperorality and dietary changes
   5. Perseverative and stereotyped behaviour
   6. Utilization behaviour

B) Speech and language
   1. Altered speech output
      a. Aspontaneity and economy of speech
      b. Press of speech
   2. Stereotypy of speech
   3. Echolalia
   4. Perseveration
   5. Mutism

C) Physical signs
   1. Primitive reflexes
   2. Incontinence
   3. Akinesia, rigidity, and tremor
   4. Low and labile blood pressure

D) Investigations
   1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
   2. Electroencephalography: normal on conventional EEG despite clinically evident dementia
   3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

[1]According to Neary and colleagues (Neary et al. 1998). Criteria for language variants and features for common clinical syndromes in FTLD, discussed in original article, not included in this table.

Table 3. Current prevailing FTDC diagnostic criteria for bvFTD[1].

I. Neurodegenerative disease

Patient must show a progressive deterioration of behaviour and/or cognition by observation or history.

II. Possible bvFTD

In order to meet the criteria for possible bvFTD, three of the following behavioural or cognitive symptoms (A-F) must be present. As a general guideline, "early" refers to symptom presentation within the first three years.

E) Early behavioural disinhibition
- A1) Socially inappropriate behaviour
- A2) Loss of manners or decorum

F) Early apathy or inertia
- B1) Apathy
- B2) Inertia

G) Early loss of sympathy or empathy
- C1) Diminished responsiveness to other people's needs and feelings
- C2) Diminished social interest, interrelatedness or personal warmth

H) Early perseverative, stereotyped or compulsive/ritualistic behaviour
- D1) Simple repetitive movements
- D2) Complex, compulsive or ritualistic behaviours
- D3) Stereotypy of speech

I) Hyperorality and dietary changes
- E1) Altered food preferences
- E2) Binge eating, increased consumption of alcohol or cigarettes
- E3) Oral exploration or consumption of inedible objects

J) Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions
- F1) Deficits in executive tasks
- F2) Relative sparing of episodic memory
- F3) Relative sparing of visuospatial skills

III. Probable bvFTD

In order to meet the criteria for probable bvFTD, a patient must meet the criteria for possible bvFTD (A), plus both of the following (B and C)

A) Meet criteria for possible bvFTD

B) Exhibits significant functional decline (demonstrated by caregiver report or instruments e.g. CDR[2], FAQ[3], DAD[4], AMPS[5])

C) Imaging results consistent with bvFTD
- C1) Frontal and/or anterior temporal atrophy on MRI or CT
- C2) Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Definite bvFTD

In order to meet criteria for bvFTD with definite pathology, a patient must present with A, plus one of the following (B-C)

A) Possible or probable bvFTD

B) Histopathological evidence of FTLD on biopsy or at post-mortem

C) Presence of a known pathogenic mutation

V. Exclusionary criteria

A diagnosis of bvFTD may not be given if the patient presents with any of the following (A-B).

A) Pattern of deficits is better accounted for other non-degenerative nervous system or medical disorder

B) Behavioural disturbance is better accounted for by a psychiatric diagnosis

C) Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

[1]According to Rascovsky and colleagues 2011 (Rascovsky et al. 2011); [2]Clinical Dementia Rating Scale; [3]Functional Activities Questionnaire; [4]Disability Assessment for Dementia; [5]Assessment of Motor of Motor or Process Skills.

2.1.2.2 Differential diagnosis and diagnostic challenges of bvFTD

The challenge of the diagnosis of FTD is reflected in the rather long latency between the onset of symptoms and the eventual diagnosis, approximately from three to four years (Diehl-Schmid et al. 2007) even though the revised diagnostic criteria (FTDC criteria) have been proven to have high sensitivity (Rascovsky et al. 2011).During the early stages of the disease, patients may perform normally in neuropsychological tests of language and memory, and even executive functions may remain spared (Riedl et al. 2014). However, it could be argued that the nomenclature misleads clinicians as the FTLD is included and discussed under the umbrella term of memory diseases. Moreover, radiologists occasionally misinterpret the magnetic resonance imaging (MRI) of the patient, failing to recognize the pattern of atrophy (Karageorgiou, Miller 2014) and structural brain imaging may also display quite subtle or apparently age-dependent changes (Riedl et al. 2014).

The first symptoms are rather unspecific and may suggest the appearance of a psychiatric disorder (Riedl et al. 2014). The symptoms of bvFTD include apathy (Rascovsky et al. 2011) and patients tend to withdraw socially and lose interest in everyday activities (Riedl et al. 2014). Family members often (mis-)interpret patient as being depressed (Karageorgiou, Miller 2014). Thus, perhaps most often, the typical misdiagnosis is that the bvFTD patient is suffering from some psychiatric disease, especially a mood disorder or schizophrenia (Galimberti et al. 2015). In addition, patients with extremely slow progression (survival lasting as long as decades from initial symptoms) tend to be misdiagnosed primarily for psychiatric disorders (Khan et al. 2012). As a consequence, a detailed psychiatric examination is required or at least highly recommended to exclude psychiatric etiology for the patient's symptoms (Rascovsky et al. 2011).

Another differential diagnostic challenge is to distinguish between bvFTD and frontal type AD, especially in elderly patients. Neuropsychological examination, fludeoxyglucose positron emission tomography (FDG-PET), molecular PET and CSF biomarkers are useful ways to discriminate bvFTD from AD (Riedl et al. 2014, Karageorgiou, Miller 2014). The neuropsychological examination in bvFTD often reveals a relative sparing of memory and visuospatial functions (Rascovsky et al. 2011) whereas deficits in memory are the most characteristic symptom of early AD. Structural imaging (MRI) may not be specific to ensure a differential diagnosis, because hippocampal atrophy, which has been traditionally considered as a feature of AD (Dickerson et al. 2001, Killiany et al. 2002), is seen in both AD and FTLD (Barnes et al. 2006, Josephs, Dickson 2007, Lindberg et al. 2012). FDG-PET may be useful in borderline cases by revealing glucose hypometabolism in corresponding regions of brain (Riedl et al. 2014). Molecular PET, using amyloid antibody, is indicative for AD (Drzezga et al. 2008, Rabinovici et al. 2007, Karageorgiou, Miller 2014). With regard to CSF biomarkers, high tau levels in CSF are claimed to be specific for AD (Bibl et al. 2011) as well as tau/amyloid beta(42) ratio (Bian et al. 2008). However, in the *C9ORF72* expansion associated FTLD, a reduced Aβ1-42 level has been detected in 25% of cases (Kamalainen et al. 2015).

A remarkable amount of the patients suffer from features of Parkinson's Disease (PD) at the initial stage clinical assessment of bvFTD (Le Ber et al. 2006). When the patient's motor symptoms consist of axial rigidity, relative sparing of the arms and a lack of tremor as well as other features of bvFTD being present, then he/she may be thought to be suffering from corticobasal syndrome (CBS) (Karageorgiou, Miller 2014). In fact, the cortical symptoms of CBS overlap with those of bvFTD (Armstrong et al. 2013, Litvan et al. 1996).

2.1.3 Primary progressive aphasias

PPA is subdivided according to the clinical findings, into three subcategories: nfvPPA, svPPA and logopenic variant primary progressive aphasia (l-vPPA) (Gorno-Tempini et al. 2011).

Before being classified into one of these subcategories of PPA, the patient must first meet the criteria for "general" PPA, devised initially by Mesulam and colleagues (Mesulam 2001),

see table 4. PPA has an insidious onset and speech and language tasks are gradually impaired (Gorno-Tempini et al. 2011). The most prominent initial symptoms are disturbances in language (aphasia) i.e. problems in word-finding, impairment of word comprehension, abnormalities of word-order or other grammatic disturbances (Mesulam et al. 2009). During the initial phases of PPA, activities of daily living (excluding activities that require language) are maintained (Gorno-Tempini et al. 2011).

The PPA diagnosis can be established by describing the specific impairments in language and speech to classify the disorder into one of three subcategories. All these diagnoses can be made with the three different levels of certainty: 1) clinical, 2) imaging supported or 3) definite pathological diagnosis (Gorno-Tempini et al. 2011).

Table 4. Inclusion and exclusion criteria for the diagnosis of PPA[1].

I.	**Inclusion: criteria 1-3 must be answered positively**
	1. Most prominent clinical feature is difficulty with language
	2. These deficits are the principal cause of impaired daily living activities
	3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease
II.	**Exclusion: criteria 1-4 must be answered negatively for a PPA diagnosis**
	1. Pattern of deficits is better accounted for by some other nondegenerative nervous system or medical disorder
	2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
	3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments
	4. Prominent, initial behavioural disturbance

[1]According to Mesulam and colleagues 2011 (Mesulam 2001).

2.1.3.1 Non-fluent variant primary progressive aphasia

NfvPPA is characterized with difficulties in word retrieval, nonfluent speech patterns and a progressive loss of speech (Cooper-Knock, Shaw & Kirby 2014, Neary et al. 1998). The language production is agrammatic and speech is "apractic" but single word comprehension and object knowledge are spared (see table 5) (Gorno-Tempini et al. 2011). Thus, it may be considered as a Broca-like syndrome (Kirshner 2014). Cognitive tests may show mild impairment in working memory and executive functions (Gorno-Tempini et al. 2004). Behavioural disturbances are not as common as in bvFTD or svPPA, but these symptoms may have been observed, especially during the later stages of the disease (Rosen et al. 2006). Left side posterior fronto-insular atrophy is often detected (Grossman et al. 1996, Gorno-Tempini et al. 2004, Nestor et al. 2003, Josephs et al. 2006).

Table 5. Diagnostic features for the nfvPPA[1].

I. Clinical diagnosis of nonfluent/agrammatic variant PPA

At least one of the following core features must be present:

1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)

At least 2 of 3 of the following other features must be present:

1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

II. Imaging-supported nonfluent/agrammatic variant PPA diagnosis

Both of the following criteria must be present

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
   a) Predominant left posterior fronto-insular atrophy on MRI or
   b) Predominant left posterior fronto-insular hypoperfusion or hypometabolism in SPECT or PET

III. Nonfluent/agrammatic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present

1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Histopathological evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

[1]According to Gorno-Tempini et al. 2011.

2.1.3.2 Semantic variant primary progressive aphasia

Loss of memory regarding the understanding of words and objects is the main characteristic feature encountered in svPPA (Cooper-Knock, Shaw & Kirby 2014, Neary et al. 1998)(Cooper-Knock, Shaw & Kirby 2014)(Cooper-Knock, Shaw & Kirby 2014). Motor and grammar speech are often spared as well as is word repetition (Gorno-Tempini et al. 2011) (see table 6). The word loss often appears gradually as first non-familiar words are lost and as the disease progresses, these disturbances develop into multimodal agnosia (Hodges et al. 1992, Neary et al. 1998, Gorno-Tempini et al. 2011). Patients with svPPA display a significant amount of behavioural disturbances (Rosen et al. 2006). Anatomical damage is located in ventral and lateral portions of the anterior temporal lobes bilaterally, but often the atrophy is more severe on the left side (Gorno-Tempini et al. 2004, Mummery et al. 2000, Mesulam et al. 2009, Galton et al. 2001, Rosen et al. 2002b).

Table 6. Diagnostic criteria for the semantic variant PPA[1].

I. Clinical diagnosis of semantic variant PPA

At least one of the following core features must be present:

1. Impaired confrontation naming
2. Impaired single-word comprehension

At least 3 of the following other diagnostic features must be present:

1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)

II. Imaging-supported semantic variant PPA diagnosis

Both of the following criteria must be present

1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one or more of the following results:
   a) Predominant anterior temporal lobe atrophy
   b) Predominant anterior temporal hypoperfusion or hypometabolism in SPECT or PET

III. Semantic variant PPA with definite pathology

Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:

1. Clinical diagnosis of semantic variant PPA
2. Histopathological evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation

[1]According to Gorno-Tempini et al. 2011**.**

2.1.3.3 Logopenic variant primary progressive aphasia

LvPPA is characterized by impaired repetition of sentences and phrases and reduced single-word retrieval in spontaneous speech combined with spared motor speech, absence of frank agrammatism, and spared object knowledge (see table 7) (Gorno-Tempini et al. 2011). It has been estimated that approximately 2.6% of all FTLD patients suffer from lvPPA (Ioannidis et al. 2012). Imaging reveals the presence of atrophy in the left temporal parietal junction area (Gorno-Tempini et al. 2004, Gorno-Tempini et al. 2008, Gorno-Tempini et al. 2011). Moreover, the AD pathology seems to be most common among the lvPPA-patients (Mesulam et al. 2008, Rabinovici et al. 2008).

Table 7. Diagnostic criteria for logopenic variant PPA[1].

I.	**Clinical diagnosis of logopenic variant PPA**
	Both of the following core features must be present:
	1. Impaired single-word retrieval in spontaneous speech and naming
	2. Impaired repetition of sentences and phrases
	At least 3 of the following other features must be present:
	1. Speech (phonologic) errors in spontaneous speech and naming
	2. Spared single-word comprehension and object knowledge
	3. Spared motor speech
	4. Absence of frank agrammatism
II.	**Imaging-supported logopenic variant PPA diagnosis**
	Both criteria must be present
	1. Clinical diagnosis of logopenic variant PPA
	2. Imaging must show one or more of the following results:
	a) Predominant left posterior perisylvian or parietal atrophy on MRI
	b) Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism in SPECT or PET
III.	**Logopenic variant PPA with definite pathology**
	Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
	1. Clinical diagnosis of logopenic variant PPA
	2. Histopathological evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
	3. Presence of a known pathogenic mutation

[1]According to Gorno-Tempini et al. 2011**.**

2.1.4 Epidemiology

The diagnostic criteria have been revised during the last years due to the rapid development of neuroimaging and genetic techniques revealing the presence of the pathogenic mutations behind FTLD. However, the epidemiologic data of the FTLD is sparse. The genetic factors contributing to FTLD vary in different geographical areas which may indicate that the prevalence also is subject to wide diversity. FTLD had been awarded an "orphan disease" status (Orpha number ORPHA282 of http://orphan.net) as the disease was suspected to be quite rare. However, a few reports, describing the epidemiology of the disease, have been published and it is becoming apparent that perhaps FTLD is not at as "orphan" as previously hypothesized.

The incidence of FTLD is 2.2 per 100 000 person-years at age 40-49, 3.3 per 100 000 person-years at age 50-59 and rises to 8.9 per 100 000 person-years in the 60-69 age bracket (Johnson et al. 2005). The estimated point prevalence is 15-22 per 100 000 inhabitants (Onyike, Diehl-Schmid 2013). In Finland, the prevalence of FTLD has been determined to be higher as a recent study estimated it to be 20.5 per 100 000 in 45-65 year olds, rising to 26.8 per 100 000 at 45-70 years (Luukkainen et al. 2015)**.** However, it has been proposed that the calculated prevalences have been underestimated due the inadequate recognition of FTLD syndromes by psychiatrists, psychologists and primary care physicians (Galimberti et al. 2015). There is no significant gender difference in FTLD patients, but overall there is a trend towards male predominance (Rosso et al. 2003, Nunnemann et al. 2011, Ratnavalli et al. 2002, Hodges et al. 2003).

2.1.5 Genetics

A positive family history of FTLD in the patients has been observed in 40-50% of the cases (Lashley et al. 2011, Rosso et al. 2003, Hodges et al. 2003). Approximately 20% of the patients exhibit an autosomal dominant pattern of inheritance (Rosso et al. 2003). The bvFTD has been estimated to have up to 30-50% inheritability and thus bvFTD displays more profound inheritability than the language variants (Seelaar et al. 2008, Chow et al. 1999, Goldman et al. 2005, Rosso et al. 2003, Stevens et al. 1998, Rohrer et al. 2009). FTD-ALS has been estimated to have 10-60% heritability (Seelaar et al. 2008, Goldman et al. 2005, Rohrer et al. 2009). The autosomal dominant pattern of inheritance has identified in genes encoding for microtubule associated protein tau (MAPT), progranulin (GRN), c9orf72, valosin containing protein (VCP), charged in multivesicular body protein 2B (CHMP2B), TARDBP and fused in sarcoma (FUS) proteins (Sieben et al. 2012). Nonetheless, a high proportion of families with FTLD have remained genetically unidentified (Seelaar et al. 2011). For proportions of known genetic factors, see table 8.

Table 8. Gene mutations and their proportions in the FTLD.

Gene	**Proportion (%)**
C9ORF72	14-48
GRN	3-26
MAPT	0-50
CHMP2B	<1
VCP	<1
FUS	Extremely rare
TARDBP	Extremely rare
TMEM106	Extremely rare

Data adopted from Sieben and colleagues (Sieben et al. 2012).

2.1.5.1. The *C9ORF72* expansion

The *C9ORF72* expansion is the most common genetic cause of familial and sporadic FTLD and ALS (Renton et al. 2011, DeJesus-Hernandez et al. 2011). In Finland, the frequency of the *C9ORF72* expansion is one of the highest in the world and it has been stated to explain nearly 50 % of familial FTLD in the Finnish population cases (Renton et al. 2011, DeJesus-Hernandez et al. 2011, Majounie et al. 2012b). The pathogenic *C9ORF72* expansion leads to TDP-43 neuropathology (DeJesus-Hernandez et al. 2011), but in the clinic, extensive diversity is observed in the *C9ORF72* expansion associated FTLD phenotype (Cooper-Knock, Shaw & Kirby 2014, Beck et al. 2013). The characteristics of the *C9ORF72* expansion are reviewed in chapter 2.2.

2.1.5.2 *GRN*

The autosomal dominant loss-of-function mutations in *GRN* account from 3 to 26 % of familial FTLD cases (Baker et al. 2006, Cruts et al. 2006, Sieben et al. 2012) but these mutations are very rare in Finland (Kruger et al. 2009). The normal function of the progranulin protein is to act as a growth factor in wound healing and tumour growth inflammation, and it is seen frequently in neuronal tissues (Ahmed et al. 2007). Mutations have been detected throughout the gene, but the pathological syndrome is attributable to mutations leading to loss-of-function alleles (Yu et al. 2010). This suggests that haploinsufficiency of *GRN* is a pathological process. The neuropathological findings in *GRN* associated FTLD have been associated with the TAR-DNA binding protein of 43 kDa (TDP-43) pathology (Snowden et al. 2015). This type of pathology will be described in greater detail in section 2.1.7.2.

There is substantial diversity seen in onset age, disease duration and symptoms among the *GRN* mutation carriers (Seelaar et al. 2011). The mean age at the onset is around 60 years (range 35 to 89) and the mutation achieves about 90% penetrance by the age of 70 years (van

Swieten, Heutink 2008, Gass et al. 2006). The most characteristic feature of these patients is apathy and social withdrawal (Seelaar et al. 2011). Hallucinations and delusions are often reported (Le Ber et al. 2008, Benussi et al. 2008, Boeve et al. 2006). The clinical picture often includes extrapyramidal symptoms (Ghetti et al. 2015, Karageorgiou, Miller 2014). ALS is a rarely observed in the carriers of pathologic *GRN* mutation (Gass et al. 2006, Kelley et al. 2009, Beck et al. 2008, Pickering-Brown et al. 2008). The phenotype may be bvFTD, PPA, or CBS (Galimberti, Scarpini 2012).

2.1.5.3 *MAPT*

A mutation in *MAPT* has been observed in patients with FTLD and its incidence has been determined to be very diverse i.e. from being extremely rare to being present in as many as 50% of familial FTLD cases (Sieben et al. 2012). This gene is located in chromosome 17q locus 21 (Wilhelmsen et al. 1994, Foster et al. 1997). The *MAPT* mutation leads to impaired composition of microtubules because of hyperphosphorylation of tau, impaired axonal transport and this mutation also causes pathological tau aggregation in neurons/glial cells (Riedl et al. 2014, Seelaar et al. 2011, Brandt, Hundelt & Shahani 2005, Hutton et al. 1998). More than 40 mutations have been detected in familial FTD and Parkinsonism cases (Hutton et al. 1998), but also microdeletion of *MAPT* is known commonly to cause mental retardation in patients of European heritage (Koolen et al. 2006). In addition, one *de novo* mutation has been presented in the literature (Boeve et al. 2005). Some recessive and sporadic cases have also been reported (van Swieten, Spillantini 2007). The frequency of the mutation varies between populations with the highest frequencies being encountered in the Netherlands and the UK (Pickering-Brown et al. 2008, Seelaar et al. 2008, Rohrer et al. 2009). In contrast, the mutation is very rare in Finland, detected only in one family (Skoglund et al. 2008).

The *MAPT* mutation associated FTLD has been claimed to have a rather early onset (Le Ber 2013). The mean age at the onset of the initial symptoms has been estimated to be 55 years (van Swieten, Spillantini 2007), although the range of onset age ranges from under 40 to older than 70 years (van Swieten, Spillantini 2007). The *MAPT* mutations are clinically linked to features of Parkinsonism and oculomotor dysfunction (Le Ber 2013). Two core phenotypes are encountered among the carriers of this mutations (Seelaar et al. 2011) 1) dementia-dominant phenotype with prominent behavioural changes (disinhibition and obsessive-compulsive behaviour) (van Swieten, Spillantini 2007) and 2) parkinsonism-dominant phenotype with CBS or progressive supranuclear palsy (PSP) -like syndromes (van Swieten, Heutink 2008). The psychotic features are not observed among pathologic *MAPT* mutation carriers (Snowden et al. 2015).

2.1.5.4 Other genetic factors

Other hereditary etiological factors associated with FTLD are mutations in genes encoding for four proteins - CHMP2B, VCP, FUS and TARDBP.

The mutation in the CHMP2B gene (Skibinski et al. 2005) is responsible for only a small number of familial FTLD cases (Cannon et al. 2006, Rizzu et al. 2006). The exact function of the *CHMP2B* gene has not yet been identified. Neuropathological and immunohistochemistry analyses have revealed the presence of ubiquitin-reactive inclusions negative for TDP-43 and FUS antibodies (Holm et al. 2007, Holm, Isaacs & Mackenzie 2009) and the pathological classification leads to FTLD-UPS (Majounie et al. 2012b).The mean onset of the *CHMP2B* gene associated FTLD is between 46 to 65 years (Gydesen et al. 2002, Isaacs et al. 2011). According to one carefully described Danish family, the penetrance is suspected to be almost complete (Gydesen et al. 2002). Most often, the *CHMP2B* gene mutation leads to the bvFTD syndrome, characterized by a global cognitive impairment, Parkinsonism, dystonia, pyramidal signs and myoclonus (Gydesen et al. 2002). Clinical ALS has been reported in only two patients (Gydesen et al. 2002). Language deficits are often perceived,

but these are quite mild and thus the diagnosis of svPPA or nfvPPA cannot be made (Gydesen et al. 2002).

Mutations in *VCP* are rare and 17 mutations in *VCP* have been found in about 40 different families (Sieben et al. 2012, Seelaar et al. 2007). The neuropathology of the patients carrying the *VCP* mutation tends to be TDP-43 proteinopathy (Weihl 2011). Mutations in *VCP* have been associated with three clinical presentations: 1) inclusion body myopathy, which almost always can be found in the clinical presentation, 2) Paget´s disease of the bone, which is seen in nearly every second patient, and, 3) FTLD, which is present in approximately one third of the patients. The age at the onset of clinical FTLD syndrome is estimated to be between 40 and 60 years (Watts et al. 2004, Kimonis et al. 2008).

A mutation in *TARDBP* gene in chromosome 1 has been identified as being responsible for five percent of the inheritance of ALS (Yokoseki et al. 2008, Benajiba et al. 2009, Sreedharan et al. 2008, Daoud et al. 2009, Kabashi et al. 2008, Rutherford et al. 2008). Several patients carrying this mutation have been observed to have bvFTD or FTD-ALS syndrome (Benajiba et al. 2009, Borroni et al. 2009).

In addition, mutations in the *FUS* gene have been claimed to be the cause of approximately 5% of the familial ALS cases (Vance et al. 2009, Kwiatkowski et al. 2009, Chio et al. 2009, Groen et al. 2010) and one patient carrying this mutation with clinical bvFTD has been reported (Van Langenhove et al. 2010). The onset of the symptoms takes place when the patients are in their thirties or forties (Lashley et al. 2011). A recent genome wide association study revealed also risk gene "transmembrane protein 106b" (*TMEM106B)* in chromosome 7p21 which was claimed to elevate the risk for FTLD-TDP (Van Deerlin et al. 2010). However, the vast majority of genetic factors remain to be identified.

2.1.6 Neuropathology

As the clinical picture of FTLD syndromes is attributable to several rather different types of mutations, also neuropathological findings display diversity. However, different neuropathological patterns share some distinct commonalities.

First, the brain atrophy is seen predominantly in the frontal, insular or anterior temporal lobar areas (Boccardi et al. 2005, Bocti et al. 2006, Davies et al. 2009, Du et al. 2007, Frisoni et al. 1996, Grossman et al. 2004, Kipps et al. 2009, Lindberg et al. 2009, Perry et al. 2006, Richards et al. 2009, Rosen et al. 2002a, Schroeter et al. 2008, Seeley et al. 2008, Short et al. 2005, Whitwell et al. 2009, Whitwell, Jack 2005). In some patients, there is asymmetric atrophy which is mainly reflected in perisylvian loss on one side of the brain (Cairns et al. 2007).

Neuropathologically FTLD may be divided into tau positive and tau negative cases (figure 4). Tau negative cases are divided again into TDP-43-positive, ubiquitin positive histopathology and TDP-43-negative, ubiquitin-positive FUS-positive histopathology. The fourth subtype is called FTLD-UPS and it is associated with the presence of ubiquitin-positive, FUS and TDP-43 –negative inclusions and perhaps even some cases without detectable inclusions (Riedl et al. 2014, Mackenzie et al. 2010, Pikkarainen, Hartikainen & Alafuzoff 2010, Pikkarainen, Hartikainen & Alafuzoff 2008).

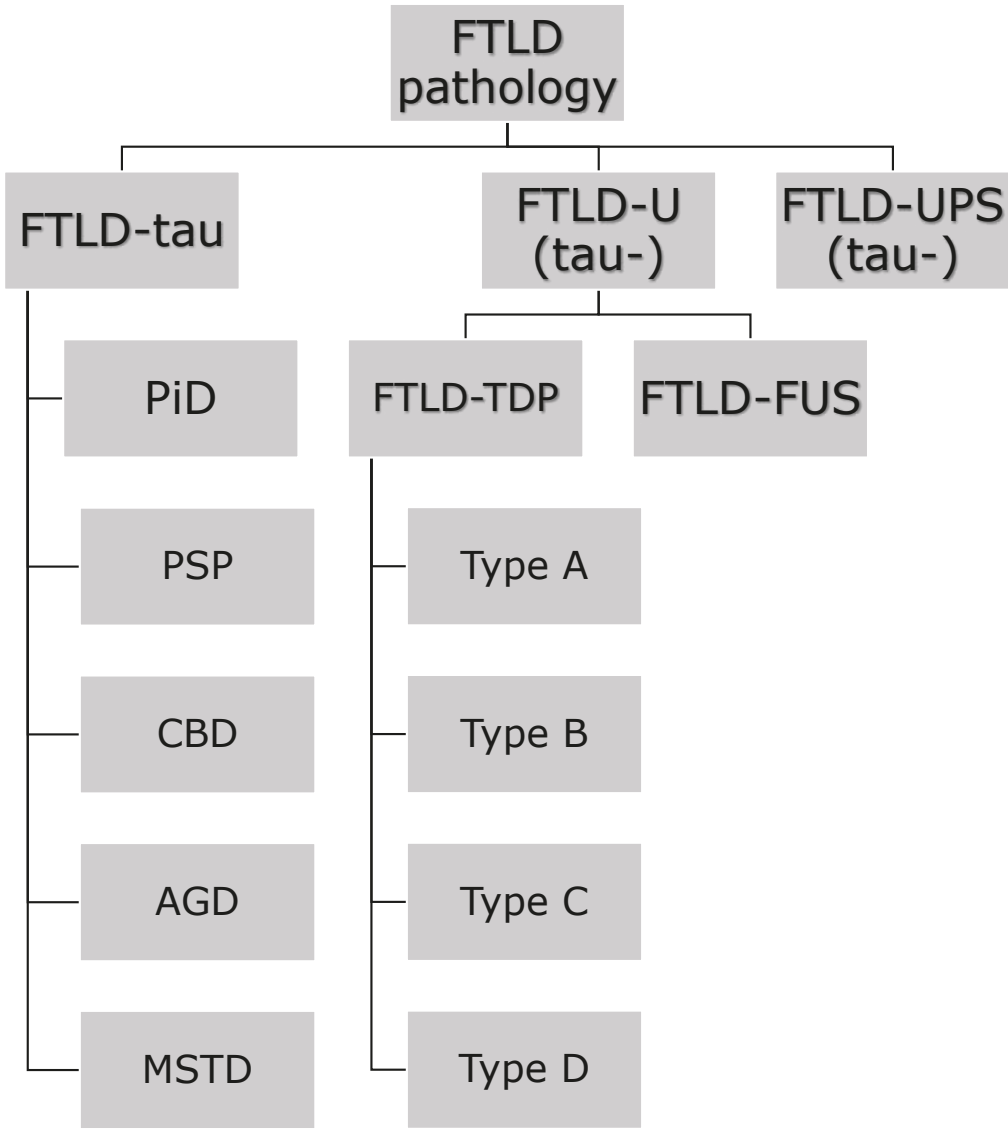

Figure 4. The pathologies and their subtypes in FTLD. PiD = Pick disease, PSP = progressive supranuclear palsy, CBD = corticobasal degeneration, AGD = argyrophilic grain disease and MSTD = multiple system taupathy with dementia.

2.1.6.1 FTLD-tau

In global terms, FTLD-tau represents approximately 40% of the FTLD pathologies (Riedl et al. 2014). The normal function of tau is to be a component of microtubules in the cytoskeleton of cells. Microtubules are also important factors in intracellular trafficking between somal and axonal regions of the nerves (Goedert 2004). In pathological conditions, the tau proteins in microtubules are hyperphosphorylated and this leads to the destruction of microtubules and further to the formation of insoluble tau aggregates, called neurofibrillary tangles in neurons and glial cells (Goedert 2004). These neurofibrillary tangles are the same as those seen in AD (Cairns et al. 2007). FTLD-tau pathology includes FTD-patients with *MAPT* mutations, Pick disease, PSP, corticobasal degeneration (CBD), argyrophilic grain disease and multiple system taupathy with dementia (MSTD) (Mackenzie et al. 2010, Riedl et al. 2014). If there is widespread distribution of neurofibrillary tangles, this is indicative of MSTD (Bigio et al. 2001). When neurofibrillary tangles are located chiefly in subcortical regions, then PSP is more likely. CBD is characterized by the presence of astrocytic plaques and abundant thread pathology (Riedl et al. 2014). Interestingly, the FTLD-tau pathology due the *MAPT* mutation is neuropathologically variable as different types of tau isoforms have been detected in neuronal and glial pathology (van Swieten, Spillantini 2007, Cairns et al. 2007).

FTLD-tau represents mostly clinically bvFTD, but also nfvPPA and features of Parkinsonism are also observed, whereas svPPA and combined ALS are very rare (Josephs et al. 2011). The FTLD-tau pathology is believed to have a shorter survival compared to tau-negative FTLD (Xie et al. 2008).

2.1.6.2 FTLD-TDP

TDP is the most common neuropathology in FTLD (Lipton, White & Bigio 2004, Taniguchi et al. 2004) and it has been observed in familial and sporadic cases with and without ALS (Cairns et al. 2007). The FTLD-TDP pathology is characterized by the abnormal accumulation of TDP-43. The physiological functions of TDP-43 consist of exon skipping and transcription regulation (Cairns et al. 2007). In pathological conditions, the TDP-43 protein is abnormally phosphorylated, ubiquitinated and cleaved, and hence generating C-terminal fragments (Neumann et al. 2006), which form ubiquitin positive inclusions, called S204. TDP-43 neuropathology is associated with p62 and ubiquitin positive inclusions (Arai et al. 2003, Jackson, Lennox & Lowe 1996, Pikkarainen, Hartikainen & Alafuzoff 2008).

FTLD-TDP may be practically divided into four subtypes (Sampathu et al. 2006, Mackenzie et al. 2006, Cairns et al. 2007). However, an overlap between subtypes has been reported (Boeve, Lang & Litvan 2003). The first subtype, called TDP pathology type A, is reflected by the presence of abundant dystrophic neurites and is associated mostly to PPA. The second subtype (TDP pathology type B) is characterized with numerous neuronal cytoplasmic inclusions in superficial and cortical laminae. This subtype is fundamentally associated with the FTD-ALS phenotype. The third subtype (TDP-pathology type C) consists from numerous cytoplasmic inclusions, dystrophic neurites and neuronal intranuclear inclusions. This subtype is associated with the *GRN* mutation. Type C is usually detected in cases with svPPA. The fourth subtype (TDP-pathology type D) is characterized by numerous intranuclear and an infrequent number of neuronal cytoplasmic inclusions and dystrophic neurites. This subtype is associated with *VCP* mutation (Sampathu et al. 2006, Cairns et al. 2007, Arai 2014). The *C9ORF72* expansion associated neurodegenerative disease leads usually to TDP-43 neuropathology. The most common subtypes of TDP-43 neuropathology linked to this mutation are type A (Murray et al. 2011, Mann et al. 2013, Josephs et al. 2013) and type B (Al-Sarraj et al. 2011, Boxer et al. 2011, Murray et al. 2011, Snowden et al. 2012) and although type C has been reported, it is very rare (Josephs et al. 2013).

Patients with FTLD-TDP-pathology typically have bvFTD, nfvPPA or svPPA. The most cases of svPPA represent FTLD-TDP pathology. Furthermore, concomitant ALS symptoms

are indicative for underlying FTLD-TDP pathology although Parkinsonism is rare (Josephs et al. 2011, Arai 2014).

2.1.6.3 FTLD-FUS

FTLD-FUS accounts for around 5-10% of the FTLD neuropathologies (Mackenzie et al. 2008). The neuropathological finding is characterized by neuronal cytoplasmic inclusions and dystrophic neurites in the superficial layers of the frontotemporal neocortex, and dentate granule cells of the hippocampus (Mackenzie, Rademakers & Neumann 2010). The inclusions are immunoreactive for FUS antibody (Neumann et al. 2009, Seelaar et al. 2010, Neumann et al. 2011). The normal function of FUS protein is consisted from DNA repair and the regulation of DNA splicing (Vance et al. 2009, Kwiatkowski et al. 2009). Cases with FTLD-FUS pathology tend to be sporadic (Seelaar et al. 2010, Josephs et al. 2010) and interestingly these patients do not carry the *FUS* gene mutation (Urwin et al. 2010).

Patients with FTLD-FUS pathology are often young at the onset of the symptoms and the clinical disease subtype is bvFTD. However, also older patients with FUS pathology have been reported (Hartikainen et al. 2012).

2.1.6.4 FTLD-UPS

FTLD-UPS neuropathology is rare and the pathological inclusions are only demonstrated with nonspecific markers of the ubiquitin proteasome system and possibly in some cases no inclusions are even detected (Riedl et al. 2014). The inclusions are negative for FUS and TDP-43 (Seelaar et al. 2011). Most of the cases with FTLD-UPS pathology have been reported to carry the *CHMP2B* mutation (Holm et al. 2007, Holm, Isaacs & Mackenzie 2009, Urwin et al. 2010), but also cases with FTLD-UPS pathology without that mutation are possible (Urwin et al. 2010).

2.1.7 Nasu-Hakola disease

NHD (polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, Online Mendelian inheritance in Man, OMIM 221770) is a rare autosomal recessive disease, first described by Nasu (Nasu, Tsukahara & Terayama 1973) in Japan and Hakola (Hakola, Iivanainen 1973) in Finland. The core signs of NHD are painful lipomembranotic cystic lesions in distal bones in the early adulthood (the mean age of 27 years) and progressive brain atrophy combined with personality changes followed a few years later by a cognitive decline (at the mean age of 33 years) (Hakola, Iivanainen 1973, Hakola 1990, Paloneva et al. 2001). This results in frontal type dementia and leads to death at the mean age of 43 years (Paloneva et al. 2001) and thus may be placed clinically under the umbrella of FTDs. At the present time, fewer than 300 cases have been described in the literature.

NHD is divided into four stages: 1) latent phase, 2) osseous phase, 3) early neurological and 4) late neurological phase. The latent phase is asymptomatic and neurological development does not differ from healthy controls. The first symptoms observed by the patient, are pain and tenderness, mostly in ankles and feet leading to first pathological fracture at a mean age of 27 years. This period, when only fractures are present, is called the osseous phase (Paloneva et al. 2001). The fractures tend to heal well, but X-ray reveals trabecular bone loss in the distal ends of the long tubular bones accompanied by a symmetric cystic lesion in the phalanges (Makela et al. 1982, Paloneva et al. 2001). At the mean age of 33 years, the personality starts to change and the disease stage is called the early neurological phase. The neuropsychological symptoms are predominantly frontal, including loss of judgement, disinhibition, euphoria, difficulties in concentration, lack of insight, lack of libido and motor persistence. These symptoms lead to social problems (e.g. divorce, unemployment or financial troubles). Alterations in memory are less severe than personality changes (Paloneva et al. 2001) and hence NHD neurologically resembles bvFTD especially in the early neurological phase. At the same time, a progressive upper motor neuron involvement starts to appear. The last stage is called the late neurological phase with symptoms of motor aphasia, agraphia, acalculia and apraxia. The ability to walk is lost at the mean age of 42 years, leading to a vegetative stage, including the appearance of primitive reflexes (Paloneva et al. 2001). Epilepsy may be seen, although not frequently, during the disease course (Kaneko et al. 2010).

Neuroimaging reveals sclerosing leukoencephalopathy, calcification in basal ganglia (mostly in the putamina), a small head of caudate nuclei, diffuse brain atrophy and white matter changes (Kilic et al. 2012, Paloneva et al. 2001). Reduced blood flow is seen bilaterally in frontal and temporal lobes as well as in thalamus and basal ganglia (Takeshita et al. 2005). Glucose hypometabolism is also seen at the corresponding areas in PET scan (Ueki et al. 2000) and precuneus hypoperfusion may be observed in single photon emission computed tomography (SPECT) imaging of brain (Nakamagoe et al. 2011). Subsequent blood-brain barrier breakdown is found in autopsies, which may be related to alterations in the microcirculation (Paloneva et al. 2001).

There are two known pathological mutations believed to be linked with this disease: *DAP12* (DNAX activation protein of 12 kDa, known also as *TYROBP*) and *TREM2 (*Triggering receptor expressed on myeloid cells 2). Homozygous mutations are required for disease development. Both of these mutations are pivotal for the widespread variety of myeloid and lymphoid lineage cells, for example for microglial and osteoclast functions (Paloneva et al. 2002, Colonna 2003, Paloneva et al. 2000). *DAP12* causes the NHD cases in Finland and mostly in Japan, but *TREM2* has been detected in cases located in other parts of the world (Klunemann et al. 2005, Paloneva et al. 1993).

DAP12 is a protein transmembrane adaptor protein mediating the activation of variety of cells of myeloid and lymphoid origin (Paloneva et al. 1993, Lanier et al. 1998). A heterozygous NHD case with *DAP12* mutation has also been presented in the literature (Kuroda et al. 2007).

TREM2 encodes the protein that is an activating cell surface protein that forms a complex with *DAP12* (Paloneva et al. 1993, Klunemann et al. 2005). It has been postulated that a defect

in *TREM2* could inhibit the phagocytosis by microglia leading to the accumulation of toxic metabolites in the extracellular space in the brain which can directly harm the brain tissue (Bock et al. 2013).

Extensive variety is perceived in the phenotype of pathogenic *TREM2* carriers (compared to *DAP12)*. In particular, *TREM2* is reported in frontotemporal-like family (Guerreiro et al. 2013a) and in dementia without bone cystic lesions (Chouery et al. 2008, Guerreiro et al. 2013c). It has been shown recently that heterozygous variants of *TREM2* are associated with a significant risk increase of AD (Guerreiro et al. 2013b, Jonsson et al. 2013). While *TREM2* may lead to recessive autosomal clinical bvFTD, it is overexpressed in AD brains and is known to be part of the genetic etiology for NHD and therefore it has been assumed that *TREM2* can evoke neurodegeneration in general (Giraldo et al. 2013).

2.1.8 Treatment of FTLD

There is no current pharmacological curative treatment available. However, several studies have evaluated the efficacy of memantine and anticholinesterase treatments (Moretti et al. 2004, Mendez et al. 2007a, Lampl, Sadeh & Lorberboym 2004, Kertesz et al. 2008, Diehl-Schmid et al. 2008, Vercelletto et al. 2011, Chow et al. 2011, Boxer et al. 2013), but no improvement in cognition or behaviour was attributable to the medication (Riedl et al. 2014) and in fact cholinesterase inhibitors may even worsen behavioural symptoms (Karageorgiou, Miller 2014). However, about 30-40% of the FTLD patients receive these treatments (Diehl-Schmid et al. 2012, Bei et al. 2010).

A few studies have evaluated whether dopaminergic drugs exert any benefits in FTLD (Huey et al. 2008, Reed et al. 2004, Rahman et al. 2006), but no improvements or reproducible results have been observed (Karageorgiou, Miller 2014, Riedl et al. 2014). Some atypical antipsychotic drugs may be beneficial in FTLD and positive effects of risperidone, olanzapine and aripiprazole have been reported (Curtis, Resch 2000, Fellgiebel et al. 2007, Moretti et al. 2003), but these should be used with some caution in view of their extrapyramidal side effects (Karageorgiou, Miller 2014), in fact, FTLD patients may be more sensitive to these extrapyramidal symptoms. In addition, the evidence on efficacy is limited and there are no controlled studies on the benefits of antipsychotic treatment in FTLD in the literature (Riedl et al. 2014).

Some positive results on drug efficacy have been described with serotonin uptake inhibitors in FTLD (Moretti et al. 2003, Deakin et al. 2004, Mendez, Shapira & Miller 2005, Lebert et al. 2004, Ikeda et al. 2004, Herrmann et al. 2012, Adler, Teufel & Drach 2003). These drugs may be useful for treating certain aspects of the disease e.g. compulsions, eating disorders, disinhibition, apathy, repetitive behaviours and sexually inappropriate behaviours (Riedl et al. 2014, Karageorgiou, Miller 2014).

Family education programs, changes in the sleep schedule, social worker involvement in financial and legislative issues, evaluating the patient's abilities to drive a car, physical exercise and speech therapy to maximize communication skills, have been seen as useful interventions (Karageorgiou, Miller 2014, Riedl et al. 2014). In addition, improving the awareness of FTLD through better training of health and social care professionals has been claimed to be an important issue (Diehl-Schmid et al. 2013b). Today, there are no international guidelines for the management of FTLD clinical syndromes. In Finland, current care guidelines for the treatment of memory disorders (www.kaupahoito.fi, 2010, referred January 28, 2016) recommend that anticholinergic drugs and memantine should be avoided. The management should consist of well performed care of other diseases, the avoidance of exacerbating factors (e.g. inappropriate pharmaceuticals, depression, poor nutrition), provision of symptomatic medication, regular follow-up, encouragement to participate in healthy activities, access to supportive services (food services, cleaning services etc.) as well

as legislative issues (e.g. wills and testaments, trusteeship), and finally ensuring access of the patient to financial and social benefits.

In the future, targeted pharmacological treatments may become available based on the genetic etiology of the clinical syndrome.

2.2 CHARACTERISTICS OF THE C9ORF72 EXPANSION

It has been known for a long time that FTD and ALS are intensely familial. About ten years ago, several pathogenic mutations (superoxide dismutase, *SOD1*; TAR DNA-binding protein 43, *TARDBP*; *FUS*; Optineurin, *OPTN* and *VCP*) were identified as causing familial ALS, but these mutations accounted for only approximately 25% of all the familial cases. In 2006, a genetic linkage was identified between the familial ALS-FTLD families and short arm of chromosome 9 (Momeni et al. 2006, Morita et al. 2006, Vance et al. 2006, Boxer et al. 2011, Pearson et al. 2011). These findings were followed by a large genome wide association study (GWAS) in a Finnish population. This study revealed the chromosome 9p21 locus as a major cause of familial ALS in Finland (Laaksovirta et al. 2010) and the same locus was also identified as causative for familial FTLD (Van Deerlin et al. 2010). Interestingly, the identical "risk" haplotype was found in all populations (Mok et al. 2012), highlighting the special significance of that specific genetic region. Subsequently, two consortiums identified an expansion mutation in the chromosome 9 open reading frame 72 (*C9ORF72*) resulting the familial FTLD and ALS (fig. 5) (Renton et al. 2011, DeJesus-Hernandez et al. 2011). Today, the *C9ORF72* expansion is known to be the most common genetic etiology for ALS and FTLD (Renton et al. 2011, DeJesus-Hernandez et al. 2011).

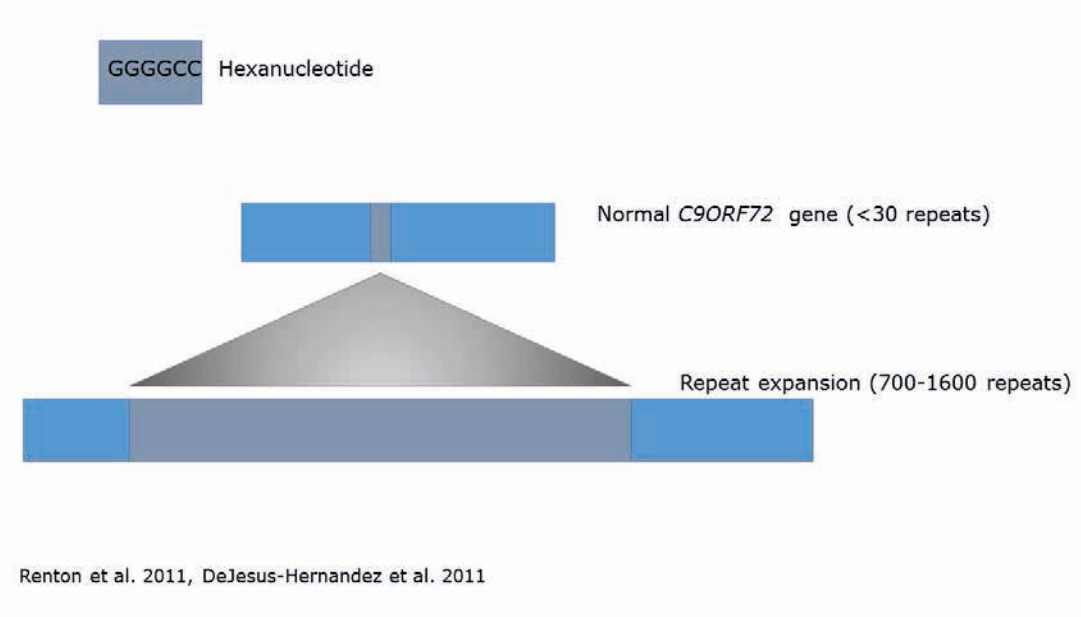

Figure 5. The chromosome 9 open reading frame 72 gene and the repeat expansion.

2.2.1 Molecular biology of the *C9ORF72* expansion

The *C9ORF72* gene, located on the short arm of chromosome 9 (9p21), encodes twelve exons and three different transcript variants. Those are generated by alternative splicing of messenger ribonucleic acid (mRNA). Of these splicing products, variants 1 and 3 encode for the longer protein isoform of the C9orf72 (481 amino acids, isoform a) and variant 2 encodes for the shorter (222 amino acids) isoform b (DeJesus-Hernandez et al. 2011). The normal region GGGGCC (G4C2) repeats is thought to be under 30 times (Renton et al. 2011). However, limits of 24 (van der Zee et al. 2013), 60 (Gijselinck et al. 2012) and 65 (Loy et al. 2014) repeats have also been considered as a lower limit for pathological expansion numbers. In healthy subjects, the genome contains three copies of the repeat sequence (Smith et al. 2013). The pathogenic form of the expansion is conventionally suspected to consist from 400 up to thousands of repeats. The repeat region is located between two non-coding exons 1a and 1b situated in core promotor region of transcript variant 1 leading to loss of transcription and to a significant reduction of the amount of isoform a (Renton et al. 2011, DeJesus-Hernandez et al. 2011).

The C9orf72 protein has been postulated to localize in the cytoplasm of neurons and other cells and it is typically concentrated in synaptic terminals (Renton et al. 2011, DeJesus-Hernandez et al. 2011). It has been proposed that the C9orf72 may be related to "differentially expressed in normal and neoplastic" (DENN)-like proteins, guanosine diphosphate/ guanosine triphosphate (GDP/GTP) exchange factor, which could lead to activation of rab-GTPases which are involved in the maintenance of intracellular vesicular trafficking (Levine et al. 2013, Zhang et al. 2012). This finding has been reproduced 1) in in vitro studies in neuronal cell lines, 2) in mouse cultured neurons, and 3) in human spinal cord motor neurons from an ALS patient with the pathogenic *C9ORF72* expansion (Farg et al. 2014). These studies revealed that C9orf72 is associated with Rab proteins in endosomal, lysosomal and autophagosomal vesicles. Furthermore, the co-localization of the C9orf72 and Rab proteins has been observed in ALS motor neurons. These data suggest that the abnormal function of the *C9ORF72* gene leads to a disturbance in protein trafficking and degradation and thus may be involved in the pathogenesis of ALS and FTLD. The recent study in a zebrafish *C9ORF72* knockdown model revealed that the C9orf72 is expressed in nervous system during developmental stages. In addition, deficits in behaviour and locomotion were seen in fish with a lack of the *C9ORF72* expression, but interestingly, those deficits could be rescued by overexpression of the human C9orf72 mRNA transcripts (Ciura et al. 2013). More specifically, the arborisation of neurons was disturbed and motor neuron axons were shortened. Therefore, it could be speculated that the loss of function of C9orf72 may cause ALS also in humans. The mouse *311004O21Rik* gene (orthologous for the human *C9ORF72* gene) is expressed widely in the neurons of central nervous system, including hippocampus, cortex and spinal cord, but not in the microglia or astrocytes (Suzuki et al. 2013).

Three major competing molecular mechanisms have been postulated to be responsible for the *C9ORF72* expansion associated pathogenesis of FTLD and ALS.

The first mechanism emerges from the theory that the GGGGCC repeat produces nuclear aggregates that inhibit the normal function of several ribonucleic acid (RNA) -binding proteins and this consequently impairs the processing and stability of RNA (Mori et al. 2013b, Xu et al. 2013, Donnelly et al. 2013). Moreover, the RNA aggregates have been observed to be present in the neurons and fibroblasts of the *C9ORF72* expansion carriers (DeJesus-Hernandez et al. 2011, Lagier-Tourenne et al. 2013, Gendron et al. 2013). In addition, GGGGCC-containing toxic foci have been observed to associate with aberrant gene expression and this was proposed to lead to glutamate-induced excitotoxicity in a study conducted in neurons, differentiated from induced pluripotent stem cells from ALS patients (Donnelly et al. 2013). The same study revealed that those outcomes could be reversed with antisense oligonucleotide against the GGGGCC repeat of the *C9ORF72* expansion. Treatment with the antisense oligonucleotide against the *C9ORF72* expansion containing RNA was also

able to decrease the number of RNA foci in mouse central nervous system and human fibroblasts (Lagier-Tourenne et al. 2013).

The second mechanism indicates that the *C9ORF72* expansion results in the formation of repeat associated non-standard (RAN) translation products that lead to translation and accumulation of pathological polypeptides in neurons, and the formation of inclusion bodies. These inclusions have been seen to form from polypeptides containing dipeptide repeats of poly-glycine-alanine, poly-glycine-proline and poly-glycine-arginine (Ash et al. 2013, Mori et al. 2013a, Mori et al. 2013c). Recently it has been shown that the RNA may be translated also in an antisense direction resulting in the synthesis of poly-proline-arginine and poly-proline-alanine containing dipeptide repeats (Gendron et al. 2013, Mori et al. 2013a). This hypothesis is supported by the findings that the histopathology of the FTLD includes intracytoplasmic accumulation of specific type proteins (Riedl et al. 2014).

The third mechanism is based on the concept of haploinsufficiency of the *C9ORF72* expansion. Several studies have shown that patients carrying the *C9ORF72* expansion have reduced levels of the normal gene transcripts in brain tissue as well as in fibroblasts and lymphoblasts. The mRNA levels of the transcription variants of both variants are reduced by up to 50% (DeJesus-Hernandez et al. 2011, Ciura et al. 2013, Gijselinck et al. 2012). The protein levels of the C9orf72 have also been shown to be reduced in the frontal cortex of ALS/FTLD patients (Waite et al. 2014). Intriguingly, also a recent study suggested that cell lines from ALS/FTLD patients have upregulated methylation in the expanded *C9ORF72* area, leading to decreased levels of the transcription variants whereas methylation was not seen in the normal length *C9ORF72* gene (Belzil et al. 2013). These findings indicate that the pathogenic expansion of the *C9ORF72* may lead to disturbances of epigenetic regulation and hence decrease the normal C9orf72 protein levels.

The *C9ORF72* expansion is associated with FTLD-TDP pathology, which has been described in 2.1.7.2.

2.2.2 Genetic epidemiology

Approximately as many as 50% of the familial and 20% of sporadic FTLD cases are caused by the *C9ORF72* repeat expansion. In addition, the expansion is responsible for up to 50% of familial ALS cases and 20 % of sporadic ALS cases (Majounie et al. 2012b, Cruts et al. 2013, van der Zee et al. 2013). Somewhat higher prevalences have been reported from Europe than in America. Moreover, in the Nordic countries, the prevalences of the diseases associated with the *C9ORF72* expansion, have been estimated to be higher than in other parts of Europe. An extremely high prevalence of the *C9ORF72* expansion has been observed in Finnish FTLD cases (Renton et al. 2011, DeJesus-Hernandez et al. 2011, Majounie et al. 2012b). Significantly lower prevalences are encountered among non-European descendants (Ishiura et al. 2012, Jang et al. 2013, Jiao et al. 2014b, Konno et al. 2013, Majounie et al. 2012b, Ogaki et al. 2012, Tsai et al. 2012, Zou et al. 2013).

The same risk *C9ORF72* haplotype has been found to be present in all populations, suggesting a single founder effect (Majounie et al. 2012b, Mok et al. 2012). Single nucleotide polymorphism (SNP) haplotype data estimated that the founder mutation occurred between 1500 (Majounie et al. 2012b) and 6300 years ago (Smith et al. 2013). If one applies a realistic population growth estimate of between 2.5 and 8.5% and intergenerational intervals supported by historical evidence of between 20 to 30 years, the founder event is likely to be thousands of years old (Smith et al. 2013). Moreover, the high prevalences of the *C9ORF72* expansion in Finland and Sardinia are thought to be result from the genetic isolation of these populations (Heutink, Oostra 2002, Service et al. 2006).

There is controversial data about the prevalence of the *C9ORF72* expansion in the healthy population. The pathological length *C9ORF72* expansion has not been detected in control cases in some studies (Cacace et al. 2013, Rollinson et al. 2012, Xi et al. 2012). The prevalence of the *C9ORF72* expansion was systematically analysed among the 54-year old healthy subjects in the UK. The prevalence was found to be 11/7,598 (resulting in 0.15% of healthy population) (Beck et al. 2013). Nonetheless, this result may not indicate the real prevalence among the lifetime-neurodegeneratively-healthy controls as the 50% penetrance of the mutation is seen not until the age of 58 (Majounie et al. 2012b) and full penetrance only seems to be present at the age of 80 (Benussi et al. 2014). Nonetheless, a few individuals have been reported to carry the pathogenic *C9ORF72* expansion without any neurological, cognitive or psychiatric symptoms at the age of 80 years or more (Galimberti et al. 2014a). At the present, the question of whether the penetrance of the *C9ORF72* expansion will be complete, remains slightly unresolved.

2.2.3 The diseases involving the *C9ORF72* expansion

The *C9ORF72* expansion is the most common genetic cause of familial FTLD and ALS cases (DeJesus-Hernandez et al. 2011, Renton et al. 2011). However, the *C9ORF72* expansion has been speculated to associate with other neurodegenerative and psychiatric diseases and the phenotype of the mutation carriers has been established to be extremely variable (Cooper-Knock, Shaw & Kirby 2014, Beck et al. 2013).

2.2.3.1 Clinical aspects of the *C9ORF72* expansion associated FTLD

The *C9ORF72* expansion is associated most commonly with the bvFTD phenotype (DeJesus-Hernandez et al. 2011, Renton et al. 2011). This phenomenon has been noted in different populations around the world and bvFTD is believed to be more prevalent in the *C9ORF72* expansion associated FTLD than in the other mutations (Murray et al. 2011, Snowden et al. 2012, Benussi et al. 2014, Ferrari et al. 2012, Dobson-Stone et al. 2012, Gijselinck et al. 2012, Boeve et al. 2012, Galimberti et al. 2013a, Sha et al. 2012, Kaivorinne et al. 2013, Hsiung et al. 2012, Khan et al. 2012, Simon-Sanchez et al. 2012, Van Langenhove et al. 2013). NfvPPA is the

next common phenotype, but there is no clinical difference between the *C9ORF72* expansion-associated and non-*C9ORF72* expansion associated nfvPPA syndromes. SvPPA is rarely seen among the *C9ORF72* expansion carriers (Snowden et al. 2012, Simon-Sanchez et al. 2012, Cerami et al. 2013).

The age at the onset of the disease seems to be somewhat lower in the *C9ORF72* expansion carriers, compared to those with other genetic factors causing the FTLD, being around 58 years (Snowden et al. 2012). A family history of early onset dementia or ALS is often seen with the *C9ORF72* expansion (Snowden et al. 2012, Kaivorinne et al. 2013). A positive family history of these diseases more than doubles the likelihood of having the *C9ORF72* expansion (Snowden et al. 2012, Kaivorinne et al. 2013, Devenney et al. 2014). One third of the patients with the *C9ORF72* expansion are classified as suffering from FTD-ALS. In fact, the *C9ORF72* expansion has remained almost the only recognized factor causing both FTLD and ALS (Snowden et al. 2012). The features of parkinsonism have been proposed to be more common among the *C9ORF72* expansion carriers than in non-carriers (Devenney et al. 2014).

Significant deficits in executive functions in combination with the relative sparing of episodic memory and visuospatial skills, are seen in the majority of patients with the expansion (Snowden et al. 2012, Devenney et al. 2014). Irrational behavioural disinhibition and apathy combined with a loss of insight are common features displayed by the *C9ORF72* expansion carriers. In addition, ritualistic/stereotypic behaviour is a distinctive trait of the carriers of this mutation. The dietary changes seem to be significantly more infrequent (Mahoney et al. 2012, Snowden et al. 2012, Sha et al. 2012). Anxiety/agitation, obsessionality, effortful speech, low mood, loss of empathy and echolalia are also seen among the *C9ORF72* expansion carriers (Mahoney et al. 2012).

No statistically significant differences in survival between carriers and non-carriers have been observed, but all of the studies have noted a clear trend that there is an earlier onset of the symptoms (by a few years) in the *C9ORF72* expansion carriers (Snowden et al. 2012, Sha et al. 2012, Devenney et al. 2014).

The *C9ORF72* expansion is believed to cause an increasingly earlier disease onset in successive generations within a pedigree (Benussi et al. 2014), which may explain the large variation in the phenotype of the *C9ORF72* expansion associated phenotype. There are controversial findings about whether it is possible to relate the expansion size to the clinical phenotype. No convincing correlation between expansion size and clinical phenotype was detected in one study (Beck et al. 2013). In contrast, another study indicated that the number of expansions could be associated with the onset age of the disease (Benussi et al. 2014).

In the *C9ORF72* expansion associated bvFTD, psychoses are undoubtedly more prevalent especially during the early course of the disease and this may even be considered to be a part of the "core phenotype" of the mutation (Snowden et al. 2012, Sha et al. 2012, Devenney et al. 2014). In addition, two studies comparing mutation carriers and non-carriers among the bvFTD patients, detected a higher frequency of psychosis in the *C9ORF72* expansion carriers compared to sporadic cases. Thus psychosis has been claimed to be the best discriminating feature between the *C9ORF72* expansion carriers and non-carriers (Galimberti et al. 2013a, Kertesz et al. 2013). In a study consisting of 32 patients with the *C9ORF72* expansion, psychiatric disturbances were seen in 69% of the bvFTD cases whereas those symptoms were seen only in less than 4% of the bvFTD cases without the mutation, resulting in high statistical significance between these two groups (Snowden et al. 2012). In more detail, 38% of the patients with the *C9ORF72* expansion exhibited florid psychotic symptoms. These patients had received an initial psychiatric diagnosis such as delusional psychosis, somatoform psychosis or paranoid schizophrenia. Several patients also suffered from somatic symptoms without medical cause and some others presented with confused/ frankly bizarre behaviour. It was considered noteworthy, that no previous history (before the initial symptoms of bvFTD) of psychiatric disease had been identified. The delusional symptoms failed to respond to anti-psychotic medication (Snowden et al. 2012). Typically psychotic symptoms seem to be paranoid type delusions and hallucinations. These results are somewhat

controversial as there seems to be extensive variation in the incidence of hallucinations i.e. from being very rare to being present in up to 50% of the cases among the *C9ORF72* expansion carriers (Boeve et al. 2012, Simon-Sanchez et al. 2012).

The presence of psychiatric illness in the family has been claimed to be significantly more prevalent among the *C9ORF72* expansion carriers than in patients with other mutations associated with FTLD (Devenney et al. 2014).

2.2.3.2 Motoneuron disease

MND due the *C9ORF72* expansion or in more specific terms in the most common form of MND, ALS, is a rapidly progressive neurodegenerative disorder characterized by degeneration in motor neurons in cerebral cortex, brainstem and spinal cord (Brooks et al. 2000). The disease begins first with muscle weakness, then proceeds to atrophy and paralysis of muscles resulting in death within 3-5 years from onset of the disease, typically due to respiratory failure (Rowland, Shneider 2001, McDermott, Shaw 2008). ALS is estimated to affect 6/100 000 persons (Ticozzi et al. 2011) and 5-10 % of the cases are familial (Byrne et al. 2011). The incidence of ALS in Finland is one of the highest in the world, i.e. 2.4 per 100 000 person years (Cronin, Hardiman & Traynor 2007).

Both limb and bulbar onset ALS are seen among the *C9ORF72* expansion carriers (Cooper-Knock et al. 2012, Gijselinck et al. 2012, Murray et al. 2011). Patients carrying other mutations causing ALS, have a higher than expected concurrence with the *C9ORF72* expansions (van Blitterswijk et al. 2012), which may indicate oligogenic inheritance of ALS.

A significant proportion of the *C9ORF72* expansion carriers suffer from the combined disease of FTD and ALS and consequently the *C9ORF72* expansion is present in most of the FTD-ALS cases (Murray et al. 2011, Van Langenhove et al. 2013, Gijselinck et al. 2012, Hsiung et al. 2012, Cooper-Knock et al. 2012, Debray et al. 2013, Ratti et al. 2012, Stewart et al. 2012, Kaivorinne et al. 2013). The presence of the ALS with FTD more than doubles the likelihood that the patient will be carrying the *C9ORF72* expansion (Snowden et al. 2012).

If one examines FTD-ALS patients, then it seems that there is a lower proportion of the *C9ORF72* expansion carriers that meet the FTDC criteria, compared to non-carriers (Sha et al. 2012). The *C9ORF72* expansion carriers may express less depressive symptoms than non-carriers and furthermore these patients have a longer survival in comparison with FTD-ALS without this expansion (Sha et al. 2012).

In the neuroimaging assessment, the *C9ORF72* expansion carriers with FTD-ALS exhibited greater dorsal frontal and posterior cortical atrophy, as well as atrophy of the cerebellum. On the other hand, non-carriers displayed more ventral and temporal lobe involvement than the *C9ORF72* expansion carriers. In addition, the *C9ORF72* expansion carriers seem to have more atrophy in the right thalamus than non-carriers (Sha et al. 2012).

2.2.4 Other diseases with a putative connection with the *C9ORF72* expansion

Soon after the finding of *C9ORF72* expansion, an increasing number of scientific reports have described the possible connections with different neurodegenerative diseases which share some common features. For instance, the *C9ORF72* expansion has been found in some cases with AD, sporadic Creutzfeldt-Jakob disease, Huntington's disease (HD) phenocopy, and Parkinson plus diseases (Loy et al. 2014, Beck et al. 2013).

2.2.4.1 Alzheimer's disease

The *C9ORF72* expansion has been found also in some patients with clinical AD, but the findings have been somewhat controversial. The presence of mutation has been estimated to be only around 1% in families with late onset clinical AD, even in neuropathologically confirmed AD cases (Majounie et al. 2012a, Cacace et al. 2013, Wojtas et al. 2012, Beck et al. 2013, Harms et al. 2013, Bieniek et al. 2014, Jiao et al. 2014a, Kohli et al. 2013). However, these findings could not be confirmed in other studies (Xi et al. 2012, Rollinson et al. 2012, Jiao et al. 2013). One group failed to detect this mutation in an extensive cohort of patients with mild cognitive impairment (MCI) (Cacace et al. 2013).

It has been proposed that the variety of phenotypes in bvFTD patients with the *C9ORF72* expansion associated bvFTD could include AD –like symptoms (Adeli et al. 2014). Moreover, the differential diagnosis between AD and bvFTD may be challenging as the CSF findings in patients carrying the *C9ORF72* expansion have pointed towards AD since there are reduced levels of beta amyloid and an elevated amount of tau and phosphorylated tau (Wallon et al. 2012, Kamalainen et al. 2015). It has been postulated that the presence of the *C9ORF72* expansion in AD may simply be coincidental (Davidson et al. 2013) or that the *C9ORF72* expansion may contribute to the pathogenesis of AD (Kohli et al. 2013).

2.2.4.2 Huntington's disease

HD is an autosomal dominant disorder; it is the most common cause of classical chorea (Walker 2007). The clinical features of the HD include movement disorders, mainly chorea, psychiatric symptoms and a progressive cognitive decline leading to dementia (Walker 2007). BvFTD and HD share some common symptoms e.g. cognitive and psychiatric disturbances. In HD, the gene mutation is located on chromosome 4p16.3 with the type of mutation being a trinucleotide expansion (over 39 expansions) of CAG (The Huntington's Disease Collaborative Research Group 1993). Nonetheless, a substantial number of patients with clinical HD deliver a negative result from genetic testing and those clinical subtypes are termed as HD-like disorders (Moore et al. 2001).

The *C9ORF72* expansion has been detected in 1.7% of HD patients in the UK (Beck et al. 2013) and the *C9ORF72* expansion has been estimated as being the most common cause of HD phenocopy syndrome (Koutsis et al. 2015, Kostic et al. 2014, Hensman Moss et al. 2014). The expansion sizes have been somewhat similar for other diseases associated with the *C9ORF72* expansion, but the onset age has had a lower tendency, even including one paediatric case, indicating that the penetrance of the *C9ORF72* expansion may be even earlier than previously thought in some infrequent cases.

2.2.4.3 Parkinson's disease and other motor disorders

Parkinsonism is present in up to 35% of the *C9ORF72* expansion carriers and an increased risk of Parkinsonism has been identified in their relatives (Boeve et al. 2012, Cruts et al. 2013, Takada et al. 2012, Savica et al. 2012, Luigetti et al. 2013, Hsiung et al. 2012, Van Langenhove et al. 2013). A recent meta-analysis of the role of the *C9ORF72* expansion in PD concluded that the *C9ORF72* expansion appeared to be specific for FTD/ALS and it was not associated with idiopathic PD (Theuns et al. 2014), but the role of intermediate repeats of the *C9ORF72* has remained unresolved. The intermediate length, but not the large repeat numbers, of the *C9ORF72* expansion has been proposed to be a contributing factor for PD and essential tremor plus Parkinsonism i.e. its presence elevates the subject's risk of developing these syndromes (Nuytemans et al. 2013).

2.2.4.4 Psychiatric disorders and suicidal behaviour

The bvFTD patients exhibit a wide diversity of neuropsychiatric symptoms. Hence, it has been proposed in some studies that there is an association between the *C9ORF72* expansion and certain psychiatric conditions.

The *C9ORF72* expansion has been speculated to be a rare cause of schizophrenia (Galimberti et al. 2014b, Watson et al. 2016) and there are several case reports describing the extremely florid psychiatric symptoms of subjects with the *C9ORF72* expansion associated bvFTD (Holm 2014, Gramaglia et al. 2014, Sommerlad et al. 2014). Nonetheless, a few studies have detected no connection with the *C9ORF72* expansion and schizophrenia (Yoshino et al. 2014, Huey et al. 2013, Fahey et al. 2014). In addition, the results seem to depend on the geographical location of the screened population. Patients carrying the *C9ORF72* expansions are thought to be at an elevated risk of receiving an erroneous psychiatric diagnosis prior to the correct one because they might not display any neurological symptoms in fact, the presenting symptoms at the early disease course may be exclusively psychiatric (Gramaglia et al. 2014).

Some studies have reported the possible connection of the *C9ORF72* expansion and bipolar disorder (Floris et al. 2013, Meisler et al. 2013, Galimberti et al. 2013b) suggesting that there is a 0.5-1.0 % prevalence in bipolar disorder patients. However, a later screening in 206 Sardinian patients suffering from bipolar disease did not detect any abnormal expansions. These researchers suggested that the *C9ORF72* expansion could affect the early neurodevelopment and later it could be involved in neurodegeneration, predisposing the individual to bipolar disorder or alternatively bipolar disorder could even be a prodromal phase of the bvFTD (Floris et al. 2014).

There are several reports that there is a possible connection between suicide and bvFTD (Alberici et al. 2012, Mendez, Bagert & Edwards-Lee 1997). Moreover, a suicide attempt is proposed to be a putative symptom of bvFTD and the odds ratio value shows that suicidal behaviour may be more common among subjects with bvFTD compared to their age and gender matched controls (Fonseca et al. 2014). The same study also revealed that depressive episodes elevate the risk for suicide attempt in bvFTD. One interesting hypothesis was proposed by Synofzik and colleagues; they speculated that in particular the *C9ORF72* expansion associated early dementia could cause suicide as a presenting symptom. They also suggested that the relatively high rate of apparently sporadic bvFTD patients associated with the *C9ORF72* expansion could be explained by the fact that suicides in the other bvFTD patients may have gone unreported or alternatively these subjects had not been diagnosed with bvFTD prior to their suicide (Synofzik et al. 2012).

3 Aims of the study

The main goal of this thesis was to extend our understanding of the spectrum of clinical symptoms and the core phenotypes due the *C9ORF72* expansion. As the *C9ORF72* expansion is known to cause many neuropsychiatric symptoms, the aim was to evaluate the presence of these symptoms. Another aim was to assess the applicability of the revised FTDC criteria for bvFTD among the Finnish *C9ORF72* expansion carriers.

As there is an extensive overlap in the symptoms of schizophrenia and bvFTD, especially when bvFTD is due the *C9ORF72* expansion, the prevalence of this mutation was analysed in the cohort of patients with early onset schizophrenia. In addition, suicide has been repeatedly proposed to be a presenting symptom of bvFTD, especially in the *C9ORF72* expansion associated syndrome. Thus, the prevalence of the *C9ORF72* expansion was analysed in a well characterized cohort of victims of suicide. The role of the *C9ORF72* expansion in clinical presentation of NHD was also evaluated.

The specific aims of the thesis were:

1. To describe the sensitivity of FTDC criteria among the *C9ORF72* expansion carriers (I).

2. To assess the clinical features of the *C9ORF72* expansion associated bvFTD (I).

3. To analyse the frequency of the *C9ORF72* expansion in early onset schizophrenia (II).

4. To evaluate the presence of the *C9ORF72* expansion in suicide victims (III).

5. To clarify the role of the *C9ORF72* expansion in the NHD phenotype (IV).

4 Materials and methods

4.1 ETHICAL ASPECTS

The ethics committee of Kuopio University Hospital approved the research protocols in studies I and IV. The ethics committee of the Northern Ostrobothnia Hospital District approved the research protocols in the studies I, II and III. Permission to gather data was obtained from the Ministry of Social and Health Affairs of Finland in study II. The permission for investigation of the suicide victims (study III) was granted by National Authority for Mediolegal Affairs of Finland.

All the studies were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all the participants and/or their legal represent. In studies I-III, patients/victims' records were anonymized and de-identified prior to analysis.

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The thesis was performed in Kuopio with data being collected from Kuopio and Oulu University Hospital Districts.

4.2 STUDY POPULATIONS

4.2.1 BvFTD cohorts (I)

The patients of bvFTD cohorts in Oulu and Kuopio were collected from the outpatient clinics of Kuopio University Hospital and Oulu University Hospital from the years (1995-2014). A total of 43 patients was identified with the *C9ORF72* expansion and FTLD clinical syndrome. Individuals with language variants were excluded (N=7) and thus the total cohort consisted of 36 patients with the phenotype of bvFTD. Sixteen patients were males (44%). Four of the patients had bvFTD-ALS and 32 patients suffered from pure bvFTD. BvFTD had presented before ALS in three out of four cases. The characteristics of the study participants are shown in table 9.

Table 9. Characteristics of the study participants.

	Years		
	Mean (SD)	Range	95%CI
Age at the onset of the symptoms	59.3 (6.6)	44-76	57.1-61.3
Age at the diagnosis	61.2 (6.5)	46-79	59.1-63.4
Duration of the symptoms until diagnosis	2.1 (1.7)	0-7	1.5-2.6
Age at the death (N=18)	67.1 (6.5)	56-81	63.9-70.3
Duration of the disease until death			
Total cohort	6.7 (3.9)	1-13	4.8-8.7
Pure bvFTD without ALS (N=14)	7.8 (3.8)	1-13	5.6-10.0
bvFTD with ALS (N=4)	3.0 (0)		

Ages, standard deviations (SD), ranges and 95% confidence intervals of characteristics of the study participants (N=36).

4.2.2 NFBC 1966 (II)

The Northern Finland Birth Cohort 1966 (NFBC) consists of subjects who were born in the two most northern provinces of Finland (Oulu and Lapland) with expected birth in 1966. The total number of births was 12,231 (including 178 stillbirths) and their regional coverage was 96.3% (http://www.oulu.fi/nfbc). The cohort has been followed since pregnancy and evaluated regularly by means of clinical examinations and health questionnaires.

The present birth cohort study is based on 11,017 subjects. Eighty-three of them did not provide permission to access their data which meant that there were 10,934 participants. Information on diagnosis for psychoses was based on several sources including case note validation, register information and interviews (Keskinen et al. 2013). The validity of the diagnoses has been established and published (Moilanen et al. 2003). The subjects having a psychosis with an organic etiology were excluded. Thus, the present study population consisted of 94 subjects with schizophrenia spectrum disorder (45% women) and 36 subjects with other psychosis (56% women). Supporting data was collected from national registers, medical records and psychiatric examination at the age of 34- and 43-years. A blood sample was obtained to perform genetic analyses and screened for the presence and length of the *C9ORF72* expansion. The characteristics of the study population are presented in table 10.

Table 10. Characteristics of the study subjects (N=130).

Characteristics	
Females (n, %)	62 (48%)
Education (n, %)[1]	
Basic	20 (15%)
Secondary	100 (77%)
Tertiary	10 (8%)
Family history of psychosis (n, %)	32 (25%)
Family history of any psychiatric disorders (parents or twins; n, %)	48 (37%)
Diagnosis (n, %)	
Schizophrenia (DSM-codes; 295, 297.1)	94 (72%)
Other psychoses (DSM-codes; 29604, 29624, 29634, 29644, 29654, 29664, 2973, 2988, 2989)	36 (28%)
Age at onset of psychosis, years (mean, SD)	27.9 (7.0)

[1]Level of education. Basic = under 10 years, secondary = 10-12 years and tertiary = over 12 years of education.

4.2.3 Suicide cohort (III)

The study sample consisted of 109 patients who had committed suicide in the province of Oulu, Northern Finland, between the years 1988-2004. The mean age at death by suicide was 46 years (range 18-86, SD 17.0) and 31.2% (n=34) of suicide victims were 55 years old or older at the time of death. Clinical information of the suicide victims was collected from official death certificates, obtained from forensic medico-legal investigations. The life-time hospital admission diagnoses of the subjects were gathered from the Finnish Hospital Discharge Register collated by the National Institute of Health and Wellbeing. This nationwide register covers all inpatient hospital admissions in primary and specialized level care in Finland since the year 1969. The characteristics of the study population are shown in table 11.

Table 11. Characteristics of the suicide victims (N=109).

Characteristics	
Age at death, years (mean, SD, 95% Confidence interval)	46.1 (17.0, 42.9-49.63)
Female gender (n, %)	15 (13.8%)
History of psychiatric treatment, diagnosis (n, %)[1]	
Mental and behavioural disorders due to psychoactive substance use (F10-19)	23 (21.1%)
Schizophrenia, schizotypal and delusional disorders (F20-29)	8 (7.3%)
Mood (affective) disorders (F30-39)	28 (25.7%)
Neurotic, stress-related and somatoform disorders (F40-48)	7 (6.4%)
Behavioural syndromes associated with physiological disturbances and physical factors (F50-59)	3 (2.8%)
Disorders of adult personality and behaviour (F60-69)	8 (7.3%)
Mental retardation (F70-79)	1 (0.9%)
Disorders of psychological development (F80-89)	None
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence (F90-98)	None
Violent method of suicide[2]	95 (87.2%)
Method of suicide	
Hanging	36 (33.0%)
Shooting	48(44.0 %)
Gassing (carbon monoxide, butane etc.)	6 (5.5 %)
Jumping from high place	4 (3.7 %)
Poisoning	8 (7.3 %)
Drowning	4 (3.7 %)
Other	3 (2.8 %)
Suicide done under the influence of alcohol	54 (49.5%)
History of previous attempts of suicide	
None	90 (82.6%)
Once	12 (11.0%)
Twice or more	7 (6.4%)

[1]According to International classification of diseases, version 10 (ICD-10). At least one inpatient treatment period in the following diagnosis; [2]All methods except poisoning and gassing were classified as a violent method of suicide.

4.2.4 Siblings with Nasu-Hakola disease (IV)

The first study examined three siblings with NHD. The genetic data was available on two out of three cases. The clinical data was available from official hospital charts as well as from forensic psychiatry records. One of the siblings carried the *DAP12* mutation and one carried both the *C9ORF72* expansion and the *DAP12* mutation. All of the cases were male. The first of the siblings had not suffered any fractures but the others had fractured bones at the age of 32 and 29 years. All of the cases revealed bone cysts in X-ray. The mean age at the personality change was 33 years (range 25-40) and the mean age at death was 42.8 years (range 37-48).

4.3 CLINICAL AND IMAGING ASSESSMENT

The clinical characterization of the patients was conducted by experienced physicians i.e. neurologists specializing in neurodegenerative diseases for the neurological assessment and an experienced psychiatrist undertook the psychiatric assessment. The demographical data of the patients was collected systematically from patient records and registers. A neuropsychological analysis was done during the normal diagnostic procedures.

The assessment conducted in the memory outpatient clinics consisted different combination of clinical and laboratory tests including CEDAD test battery, questionnaire of activities of daily living and mood symptoms, laboratory tests (ECG, blood count, glucose, potassium, sodium, calcium, thyroid tests, alanine aminotransferase, creatinine, B12-vitamin, albumin, serum proteins, glutamyl transferase, carbohydrate deficient transferrin), clinical (general and neurological) examination, structural neuroimaging (CT or MRI), CSF analyses (beta-amyloid, tau), neuropsychological assessment during diagnostic procedure, genetic analyses and PET/SPECT.

Psychiatric symptoms were retrospectively assessed both prior to and at the phase of the diagnosis (I).

Structural neuroimaging of the patients was undertaken by visual analysis of an experienced neuroradiologist. PET/SPECT scans were analysed systematically by visual analysis.

4.4 GENETIC ANALYSES

The *C9ORF72* expansion (studies I-IV) was analysed in Kuopio by the repeat priming polymerase chain reaction assay (Renton et al. 2011). The sensitivity for that method has been estimated to be 94.3% and 97.3% for specificity (Akimoto et al. 2014). The length of the expansion was estimated by fluorescent fragment length analysis (ABI 3500x1 genetic analyser; Applied Biosystems Inc., Foster City, CA, USA). Previously confirmed pathological *C9ORF72* expansion samples were used as positive controls and a specimen with a known four repeat expansion as a negative control. Borderline cases were confirmed by southern blot analysis (DeJesus-Hernandez et al. 2011) in Tampere University Hospital. Southern blot analysis has been regarded as a gold standard for detecting large polynucleotide repeat expansions (Akimoto et al. 2014).

The homozygous deletion in *DAP12 (*Study IV) (Paloneva et al. 2000) was analysed by direct polymerase chain reaction assay with 1 forward primer (FP: 5′-GGCCACATCCGTATGACTG-3′) and 2 reverse primers (RP1: 5′-TAGTATGTCCAG TCTCGAGTTCTCA-3′ and RP2: 5′-CTAGTCTGGGCGTGCATTC-3′). In the *DAP12* deletion allele, the assay produces a 695-base pair (bp) amplicon (primers FP and RP2) and no product with primers FP and RP1. In the wild-type allele, the assay produces a 454-bp amplicon (primers FP and RP1) and no product with primers FP and RP2 (theoretical product size 5959

bp). The homozygous *DAP12* deletion was detected in both of the siblings (cases II-2 and II-3) providing a genetic confirmation to the diagnosis of NHD.

Exome sequencing was performed in two out of three NHD cases using an Agilent HaloPlex Exome kit for target enrichment followed by sequencing on an Illumina MiSeq instrument to an average depth of 80× coverage. The resulting reads were mapped with Burrows-Wheeler Aligner (Li, Durbin 2009) after which the Genome Analysis Toolkit was used to identify variants (McKenna et al. 2010). The variants were annotated with ANNOVAR (Wang, Li & Hakonarson 2010).

4.5 STATISTICAL METHODS

All statistical test performed were two-tailed and a p value less than 0.05 was considered as statistically significant. Analyses were done with SPSS 19. Survival assessment was performed with Kaplan-Meyer survival analysis. Sensitivities of the FTDC criteria were analysed statistically.

5 Results

5.1 THE SENSITIVITY OF FTDC CRITERIA IN THE *C9ORF72* EXPANSION CARRIERS (I)

The total cohort of patients suffering from genetically defined bvFTD evaluated against the FTDC criteria. All those patients met the definite bvFTD criteria i.e. they were carrying a known pathogenic mutation (the *C9ORF72* expansion*)* according to FTDC criteria. The sensitivities of these clinical criteria were evaluated in the total cohort, in the pure bvFTD cohort i.e. patients with no features of ALS and in a cohort of patients with bvFTD-ALS. These results are presented in table 12.

Table 12. Sensitivities of FTDC clinical criteria in total cohort and subgroups.

Characteristics	***Number of patients***	***Sensitivity of criteria***	***SD[1]***	***95%CI[2]***
Total cohort (N=36)				
Possible bvFTD[3]	27	0.75	0.44	0.57-0.87
Probable bvFTD[3]	23	0.64	0.49	0.46-0.79
bvFTD(N=32)[4]				
Possible bvFTD[3]	26	0.81	0.40	0.63-0.92
Probable bvFTD[3]	22	0.69	0.47	0.50-0.83
bvFTD-ALS (N=4)[5]				
Possible bvFTD[3]	4	0.25	N/A[6]	N/A[6]
Probable bvFTD[3]	4	0.25	N/A[6]	N/A[6]

[1]Standard deviation; [2]95% confidence interval; [3]According to the FTDC criteria for bvFTD (Rascovsky et al. 2011); [4]Pure bvFTD without the features of early ALS; [5]Combined clinical picture of early ALS and bvFTD; [6]Not available.

The average number of behavioural and cognitive features required in the criteria of possible bvFTD in the total cohort was 3.19 (SD 1.26, 95%CI 2.77-3.62, range 1-6). Every case had at least one behavioural or cognitive feature determined as a bvFTD symptom from these criteria. The vast majority, 88.9%, of the patients had two or more symptoms and 75.0% exhibited three or more symptoms. Four or more features were encountered in 38.1% of the cases, five or more in 11.1% of the cases. The total amount of all six cognitive and behavioural features was observed only in 5.6% of the cases. In pure bvFTD patients without ALS, the mean number of possible bvFTD features was 3.38 (SD 1.2, 95%CI 2.95-3.80, range 1-6), while in FTD-ALS patients, the number of possible bvFTD features was only 1.75 (range 1-3). All bvFTD-ALS cases demonstrated a positive neuropsychological profile for bvFTD, but most of the behavioral changes were not detected in clinical picture of these patients.

5.2 THE CLINICAL PHENOTYPE OF THE *C9ORF72* EXPANSION CARRIERS ACCORDING TO FTDC CRITERIA (I)

When the clinical features required for possible FTDC criteria were assessed, the neuropsychological profile revealed deficits in executive tasks combined with a relative sparing of both episodic memory and visuospatial skills in all the cases. Nonetheless, a neuropsychological analysis had been performed in only 32 of the total 36 cases during the early course of the disease.

There were some relatively common behavioural findings (percentages in brackets) i.e. early behavioural disinhibition (66.7%) early apathy or inertia (61.1%) and early loss of empathy or sympathy (61.1%). Hyperorality and dietary changes were observed in 30.6% of the cases. A rather small number of the cases, a mere 8.3%, suffered from early loss of sympathy or empathy. These behavioural symptoms were retrospectively analyzed on all the cases.

The mean age at death in the total cohort was 67.1 years (N=18, SD 6.5, 95%CI 6.39-70.3, range 56-81). The survival functions are displayed in figure 6.

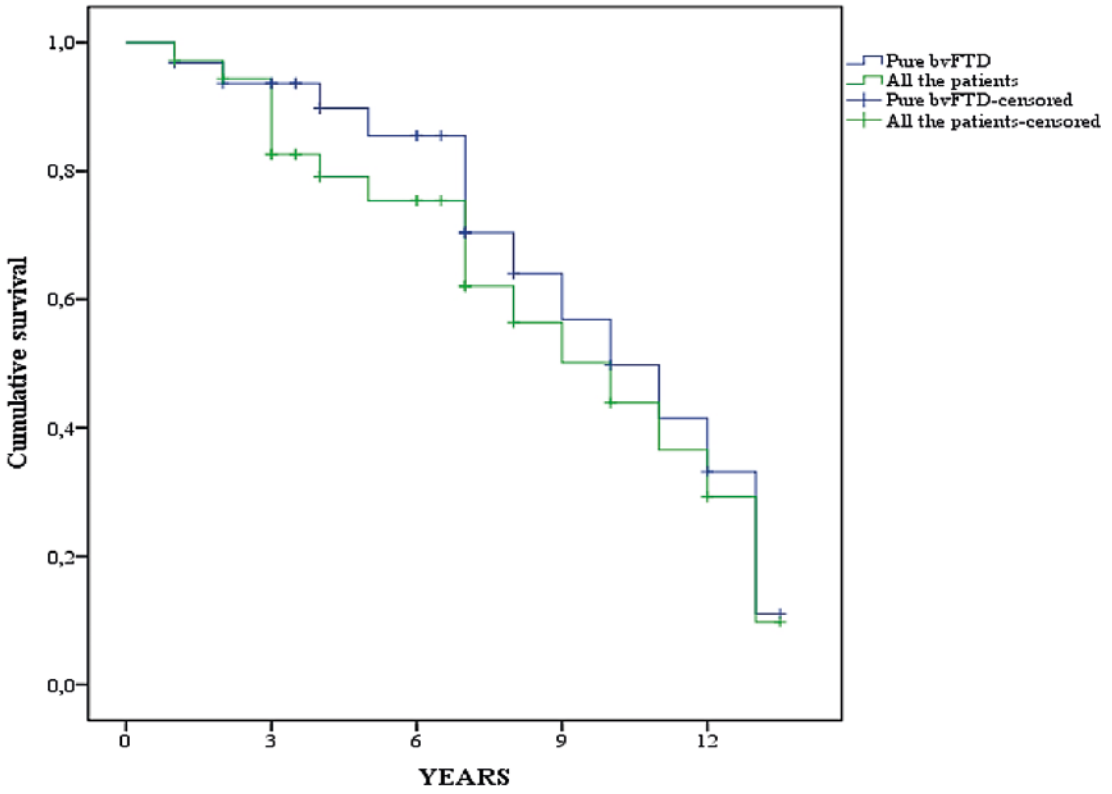

Figure 6. Kaplan-Meyer survival of the C9ORF72 expansion carriers.

5.3 NEUROIMAGING FINDINGS IN THE PATIENTS WITH THE *C9ORF72* EXPANSION ACCORDING TO FTDC CRITERIA (I)

Neuroimaging (PET/SPECT and MRI or computed tomography, CT) alone displayed the highest sensitivity (0.86 sensitivity, SD 0.35, 95%CI 0.70-0.95) for recognition of bvFTD. MRI or CT criteria were fulfilled in 26 out of 36 cases (0.72 sensitivity) and PET/SPECT in 14 out of 17 cases (0.82 sensitivity). A diffuse cortical and central atrophy without a frontal or temporal predominance was detected in eight cases that did not fulfill the MRI criterion and the two remaining cases had normal findings in brain MRI imaging. A bilateral parietal hypoperfusion in PET scanning was identified in one case who did not fulfill PET criterion and the PET scan was assessed as normal in two of cases.

The PET/SPECT was normal in 17.6% of the scanned individuals (three out of 17 patients) and thus they did not meet the PET/SPECT criteria for probable bvFTD. All these cases suffered from pure bvFTD without ALS. Their mean age at onset (53.7 years, SD 1.5, 95%CI 49.9-57.5, range 52-55) and at their time of death (63.5 years, SD 2.1, 95%CI 44.4.-82.6, range 62-65) they were significantly younger than the other patients. They displayed a mean number of 3.3 (SD 1.5 95%CI -0.46-7.13, range 2-5) possible bvFTD features and in addition, psychiatric symptoms were prevalent in all these cases. On the other hand, structural brain imaging provided evidence of bvFTD in all of these PET/SPECT negative cases. The mean duration of the disease from onset of symptoms to PET/SPECT scanning was 2.0 years in the PET/SPECT negative cases compared to a mean duration of 1.6 years in the PET/SPECT positive cases.

When the neuroimaging results were combined with functional decline (possible FTDC criteria apart from behavioural features included in the probable bvFTD criteria), these figures achieved a slight enhancement in the sensitivity for the *C9ORF72* expansion carriers i.e. 81% (N=29) of the patients were found to be positive with these criteria (0.81 sensitivity, SD 0.40, 95%CI 0.63-0.91).

There were no signs of false positive cases in the MRI/CT or PET/SPECT results. A few of the cases that were initially interpreted as negative in PET/SPECT were corrected to positive in the second, more thorough, analysis.

5.4 CLINICAL FEATURES OF THE *C9ORF72* EXPANSION CARRIERS THAT DID NOT MEET THE FTDC CRITERIA (I)

In all, 25% of the patients (N=9) did not meet the FTDC criteria for possible bvFTD. This subsection consisted of three patients with FTD-ALS and six with pure bvFTD. Their mean age at the onset of symptoms was 56.6 years (SD 6.4, 95%CI 51.6-61.5, range 44-66) and 59.3 years (SD 6.7, 95%CI 54.2-64.5, range 46-69) at the diagnosis. The corresponding values for the patients meeting the criteria (N=27), were as follows – onset of symptoms 60.2 years (SD 6.5, 95%CI 57.7-62.8, range 46-76) and diagnosis 61.9 years (SD 6.5, 95%CI 59.3-64.4, range 48-79). Furthermore, the mean number of possible bvFTD features among the patients that did not meet the possible bvFTD criteria was 1.56 (SD 0.5, 95%CI 1.15-1.96, range 1-2). All of them exhibited disturbances in executive functions in the neuropsychological examination. Apathy or inertia was present in four of these subjects and one patient suffered from disinhibition, but none of the other possible bvFTD criteria were observed in any of these patients. However, 77.8% of these cases (N=7) did exhibit a positive neuroimaging result for FTLD and 66.7% of these cases (N=6) were positive in terms of both cognitive decline and neuroimaging.

5.5 PSYCHIATRIC SYMPTOMS IN THE PATIENTS WITH THE *C9ORF72* EXPANSION (I)

The majority of the patients (61.1%; N=22) were found to be suffering from these symptoms. Psychotic symptoms without mood disturbances were detected in 30.6% (N=11) of the patients; 11.1% of the patients (N=4) displayed only mood symptoms, while 19.4% of the cases (N=7) experienced both psychotic and mood symptoms. The mean delay from the appearance of psychiatric symptoms to diagnosis of bvFTD was 4.6 years (95%CI 0.8-8.4, SD 8.5). Although one patient had a 40 year history of a progressive atypical psychiatric disorder before diagnosis, the delay was less than ten years in the others. Psychiatric symptoms were present in 55.6% (N=5) of the subgroup of patients that did not meet the FTDC possible criteria.

5.6 THE *C9ORF72* EXPANSION IN SCHIZOPHRENIA AND SUICIDES (II-III)

No pathological length *C9ORF72* expansions as characterized by the typical descending saw-tooth pattern (over 40 repeats) were detected in either of the two cohorts examined i.e. schizophrenia/psychosis patients or victims of suicide. In the schizophrenia/psychosis cohort, four samples were determined to have an intermediate amount of repeats (over 20 repeats). For intermediate length expansion, see figure 7. In the same cohort, the mean number of the repeats was five, but there was great diversity in the range; from one to 30.

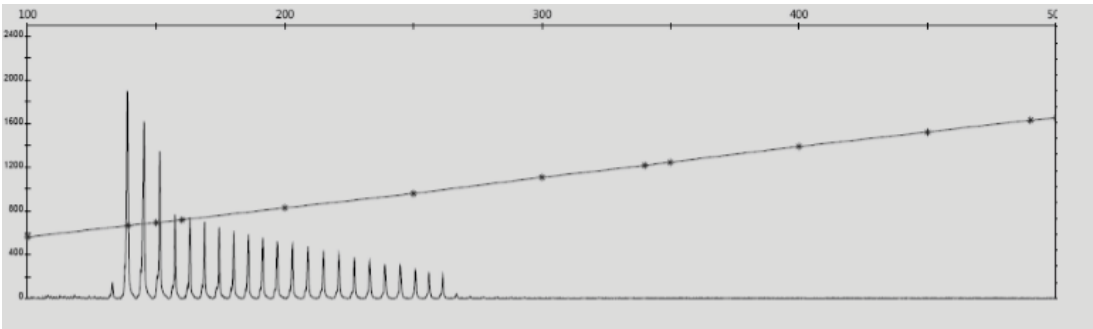

Figure 7. Intermediate amount of the C9ORF72 repeats (22 repeats).

5.7 THE EFFECT OF THE *C9ORF72* EXPANSION IN NASU-HAKOLA DISEASE (IV)

One of the siblings was found to carry the pathological length *C9ORF72* expansion. The homozygous *DAP12* deletion was readily detected in the exome data of the analyzed NHD-cases this being evidenced by the lack of any sequence reads in the *DAP12* exons 1–4. All nonsynonymous variants in the presently known FTLD genes were screened (*C9ORF72, CHMP2B, FUS, GRN, MAPT, TARDBP, VCP*). Only one such variant was found in one out of the three cases, a MAPT*Y441H (NM_001123066:exon8:c.T1321C) heterozygote variant with a population frequency of 32% (1000 genomes), which was not predicted to be deleterious on the basis of PolyPhen2 and SIFT in silica tools (Adzhubei et al. 2010, Ng, Henikoff 2003). However, this same individual had also the heterozygous SOD1*D90A (NM_000454:exon4:c.A272C) mutation that, when homozygous, is known to cause a slowly progressive form of ALS (Andersen et al. 1995). In addition, a novel heterozygous mutation in the gene implicated in Lafora progressive myoclonic epilepsy type 2 (EPM2*A46P NM_001018041:exon1:c.G136C) was detected in this same individual (Serratosa et al. 1999). This variant was not found in either the 1000 genomes or in a Finnish population database of more than 5000 exomes (Sequencing Initiative Suomi, sisu.fimm.fi). The *SOD1* and *EPM2* variants were confirmed by Sanger sequencing.

All the patients displayed the typical features of NHD; bone cysts, personality changes, cognitive decline leading to severe frontal type dementia. In clinical terms, a slightly more severe picture of the disease was seen in the one of the patients without the *C9ORF72* expansion. The structural brain imaging revealed calcification in putamen and nucleus caudatus in all of the siblings but atrophy was also observed in nucleus caudatus, thalamus, frontal neocortic regions, frontal gyri, corpus callosum genu and parietal regions. No difference in the pattern of atrophy was detected between the *C9ORF72* expansion carrier and non-carriers.

6 Discussion

At the present time, no curative treatment is available for patients suffering from the *C9ORF72* expansion associated diseases. Patients are often initially diagnosed as having some psychiatric disease even when the appropriate diagnosis is bvFTD. Even today, it is not known how many bvFTD patients remain undiagnosed in geriatric care institutions, forensic psychiatric institutions and psychiatric wards, especially during an era when postmortem neuropathological analyses are the exception rather than the rule (Ahlblad 2015).

This is the largest study conducted to date (at least at the time when the reports were published) which has assessed the clinical picture of the *C9ORF72* expansion associated bvFTD with and without ALS by applying the revised criteria for bvFTD (Rascovsky et al. 2011) as well as being the first study to analyze the effect of this mutation in NHD. Due the intense research around the *C9ORF72* expansion and FTLD, this thesis is particularly timely. The current set of studies provide essential information of the clinical phenotypes of patients with the *C9ORF72* expansion. In addition, the prevalence of the mutation has not been analyzed previously in these types of cohorts.

6.1 THE DISEASE COURSE IN THE *C9ORF72* EXPANSION CARRIERS

In the present study, the mean onset age was 59.3 years, which is in line with values in the literature. The onset of the bvFTD (all reported cases without genetic identification) has been estimated to occur typically between 50 and 60 years of age (Ratnavalli et al. 2002, Ikeda, Ishikawa & Tanabe 2004). Some reports have suggested that there might be an earlier onset of the disease for the *C9ORF72* expansion associated bvFTD (Snowden et al. 2012, Devenney et al. 2014). Patients with the *C9ORF72* expansion more often have a positive family history of early onset dementia or ALS (Snowden et al. 2012, Kaivorinne et al. 2013), and this may well aid the physician in making the correct diagnosis of these patients. Furthermore, the prominent behavioural features (Snowden et al. 2012), psychosis (Snowden et al. 2012, Sha et al. 2012, Devenney et al. 2014) and executive task deficits (Snowden et al. 2012) may lead to an earlier detection of bvFTD. However, the onset of bvFTD in the patients examined here was not evidently earlier although it has to be stated that there was extensive variability in the onset ages (from 44 to 76 years), which is in line with other reports of *C9ORF72* expansion carriers (Snowden et al. 2012, Devenney et al. 2014).

The mean age at the death of patients was 67.1 years in the present study. The duration from onset to death was observed to be 6.7 years in the total cohort (bvFTD and bvFTD+ALS), with the survival being slightly prolonged in the subgroup of patients with pure bvFTD (7.8 years); in contrast it was much shorter, only 3.0 years, in the group of patients with bvFTD-ALS. In previous studies, the mean survival in FTLD from onset to death has been estimated as eight years (Neary, Snowden & Mann 2005).

6.2 THE PHENOTYPE OF THE *C9ORF72* EXPANSION CARRIERS

The validity of the FTDC criteria were investigated among the bvFTD and bvFTD-ALS patients with the *C9ORF72* expansion diagnosed in the neurology outpatient clinic. The sensitivities in the total cohort were rather high, 75%, for possible bvFTD and 64% for probable bvFTD. After the patients with bvFTD-ALS were excluded then these sensitivity figures increased i.e. 81% for possible and 69% for probable bvFTD, these values being significantly higher than those previously reported (60% and 38% respectively) for the *C9ORF72* expansion carriers (Devenney et al. 2014). In cases with neuropathologically confirmed definite bvFTD (in whom there was no knowledge of the genetic basis of the disease), the sensitivities were the highest i.e., 86%-95% for possible bvFTD and 75%-85% for probable bvFTD (Rascovsky et al. 2011, Harris et al. 2013). In summary, it seems that FTDC criteria identify a significant proportion of bvFTD patients with the *C9ORF72* expansion at the time of examination in the neurological outpatient clinic.

The main features of bvFTD according to recent FTDC criteria (Rascovsky et al. 2011), are disinhibition, apathy or inertia, loss of sympathy or empathy, perseverative, stereotyped or compulsive/ritualistic behaviour, hyperorality and dietary changes and executive deficits. In the *C9ORF72* expansion associated bvFTD, apathy and inertia, disinhibition and repetitive/stereotyped behaviour have been observed very frequently (Snowden et al. 2012, Devenney et al. 2014). These three features; disinhibition, apathy/inertia and repetitive/stereotyped are also the principal symptoms encountered in the present study, representing the "core" behavioural signs of the *C9ORF72* expansion associated bvFTD. In contrast, hyperorality and dietary changes were observed relatively rarely in the *C9ORF72* expansion associated disease (Snowden et al. 2012). Similarly there were a rather low number (one out of every three) of hyperorality and dietary changes detected in the carriers of the *C9ORF72* expansion. In the present study, the lowest sensitivity was found for early loss of sympathy or empathy (8.3%). This trend was reported also in the neuropathologically confirmed but genetically unconfirmed cohorts from UK and Australia (Chare et al. 2014).

In general, the core distinctive symptom in bvFTD seems to be disinhibition of behaviour (Barber, Snowden & Craufurd 1995, Levy et al. 1996, Hirono et al. 1999, Bozeat et al. 2000, Bathgate et al. 2001, Srikanth, Nagaraja & Ratnavalli 2005, Blair et al. 2007, Heidler-Gary et al. 2007, Liscic et al. 2007, Rankin et al. 2008). However, the most common and prominent symptom in bvFTD is apathy and/or inertia (Diehl-Schmid et al. 2006, Le Ber et al. 2006, Mendez et al. 2008a). Initially, hyperorality was considered to be the rarest behavioural symptom, although it has been subsequently detected in approximately 55% of the cases (Rascovsky et al. 2011).

It is possible that cultural factors may influence the detection of behavioural symptoms of bvFTD patients. A recent study suggested that in eastern Mediterranean culture bvFTD symptoms may not be considered as a medical issue, instead, these symptoms can be viewed as normal ageing (Papatriantafyllou et al. 2009). Similarly, in Finnish patient records, the presence/loss of empathy or sympathy was not often mentioned and it may be that the expression of emotions in Finnish culture is not considered appropriate and is probably less common than in English-speaking cultures; one could argue convincingly that the failure to express emotions may be thought of as normal behaviour in Finland.

Initially, the neuropsychological profile was found to be consistent with bvFTD in only approximately 60% of the cases (Rascovsky et al. 2011). However, in the *C9ORF72* expansion associated disease, the cognitive profile was found to be consistent with bvFTD in almost all of the subjects (Snowden et al. 2012). These results consolidate this impression as there was very high sensitivity detected for neuropsychological assessment in the *C9ORF72* expansion carriers (i.e. all the cases fulfilled these criteria). Hence, the neuropsychological assessment seems to be a major distinguishing feature in differentiating between the cohorts of the *C9ORF72* expansion carriers and non-carriers.

Initially, the imaging for the FTDC criteria (without distinguishing functional or structural method of imaging) for bvFTD were found to have approximately 80% sensitivity (Rascovsky et al. 2011). Subsequently, in the *C9ORF72* expansion carriers, the sensitivity was found to be 61% for structural and 94% for functional imaging (Snowden et al. 2012). Snowden and colleagues did not detect any difference in neuroimaging findings between the expansion carriers and non-carriers. In another study, the *C9ORF72* expansion carriers presented more parietal and bilateral thalamic atrophy than non-carriers, whereas non-carriers with bvFTD displayed more medial frontal atrophy (Sha et al. 2012).

In the present study, results are more in line with the results of Snowden and colleagues; values of 72% for sensitivity with MRI/CT and 82% for sensitivity with PET/SPECT. However, this sensitivity for PET/SPECT scan is surprisingly low because the scan was taken after the disease had been clinically present only for a mean of three years. When PET/SPECT scans and structural brain imaging findings were combined for detecting bvFTD, the sensitivity reached 86%. This underlines the fact that the *C9ORF72* expansion associated bvFTD may lead to the emergence of devastating clinical symptoms, consistent with those listed in the bvFTD diagnostic criteria, but with no detectable hypoperfusion or brain atrophy in neuroimaging. However, the clinical benefit of the neuroimaging may even be slightly lower as the specificity of the neuroimaging was not assessed. This issue needs to be noted in clinical work in memory clinics, but also psychiatrists need to consider a somatic reason for psychiatric symptoms; it is not possible to exclude a somatic reason simply by neuroimaging of the patient. The reason for occasional lack of atrophy or hypoperfusion in the *C9ORF72* expansion associated bvFTD has remained unknown. Nonetheless, there are no validated radiological assessment scales for evaluating frontotemporal atrophy, and this is very different from the situation in AD where there are clearly defined terms to be applied in any assessment of the hippocampal atrophy. Furthermore technical limitations in the current neuroradiological methods may be a reason for not detecting signs of atrophy. In addition, it would be very useful to conduct a post-mortem analysis of those cases in which there were no neuroradiological signs of atrophy.

6.3 PSYCHIATRIC SYMPTOMS IN THE *C9ORF72* EXPANSION CARRIERS

Psychiatric symptoms were rather prominently displayed in the early course of the *C9ORF72* expansion associated bvFTD. A total of 61 % of the patients were suffering from psychotic, mood or both psychotic and mood symptoms.

Psychotic symptoms have been claimed to be very rare among the patients with bvFTD (Bathgate et al. 2001, Mendez et al. 2008a, Mendez et al. 2008b) and it has been estimated that the prevalence of delusions would be 2.3% with hallucinations being absolutely totally absent (Mendez et al. 2008b). In 2011, Snowden and colleagues (2012) detected a strong association between psychotic symptoms with the *C9ORF72* expansion. They estimated that the odds of having the expansion would be 15-fold higher if the patient displayed features of psychosis. Interestingly, psychosis has not been reported in patients carrying *MAPT* (Hutton et al. 1998) or progranulin (*PGRN)* (Baker et al. 2006) mutations. Nonetheless, cases with FUS pathology have reported to have an elevated incidence of psychotic symptoms (Seelaar et al. 2010, Urwin et al. 2010, Snowden et al. 2011). Therefore, Snowden and colleagues hypothesized that psychotic symptoms would be encountered only in those cases that are attributable to the factors that can cause also ALS (FUS pathology and the *C9ORF72* expansion), since *MAPT* and *PGRN* are not associated with ALS (Snowden et al. 2012). In other words, one could argue that the familial bvFTD cases with psychotic symptoms would be caused by the *C9ORF72* expansion, since the FUS pathology is much rarer and tends to be present in sporadic cases.

At present, three studies have analysed the types of psychotic symptoms found in the *C9ORF72* expansion carriers. The first publication did not determine the number of psychotic symptoms, instead it focussed on the extensive delusions as a presenting symptom of bvFTD (Sha et al. 2012). In two other studies, psychotic symptoms were present in 35-40% of cases (Devenney et al. 2014, Snowden et al. 2012). No difference was detected in functional or structural neuroimaging between patients with psychotic and non-psychotic symptoms of the disease (Snowden et al. 2012). In the present study, the number of psychotic symptoms was even higher than previously reported i.e. 50% of the patients had been reported by a psychiatrist to have psychotic symptoms and 31% to have mood symptoms and in fact about one in every five (19%) had both psychotic and mood symptoms. The mood symptoms consisted mainly of depressive episodes but a few manic conditions were detected. There are no previous studies published analysing or indicating major depressive symptoms in the *C9ORF72* expansion carriers. Patients with the *C9ORF72* expansion associated bvFTD show a remarkable amount of apathy or inertia in the early course of the disease. Therefore apathy or inertia may be interpreted as symptoms of depression.

In the present study, psychiatric symptoms were observed either during the diagnostic process or before the initial suspicion of bvFTD. The estimated figures for psychiatric (mis-)diagnoses may reflect the confusion of clinicians when they are examining these patients, i.e. very often the patients have been subjected to both neurological and psychiatric diagnostic batteries. Nonetheless, the diagnostic process seems to be adequate, as the present patients received the correct diagnosis quite rapidly after the initial symptoms, at least as soon as reported in some other studies (Rosso et al. 2003, Nunnemann et al. 2011, Hodges et al. 2003).

One other interesting claim has been that the *C9ORF72* expansion seems to predict psychiatric illnesses and symptoms in family members of the carriers (Devenney et al. 2014), which may indicate that a lower expansion copy number may cause milder neuropsychiatric syndromes than in the full-blown bvFTD. This hypothesis is supported by the finding that the *C9ORF72* expansion seems to anticipate the onset of symptoms in successive generations within a pedigree (Benussi et al. 2014).

6.4 THE ROLE OF THE PATHOGENIC *C9ORF72* EXPANSION IN PSYCHIATRIC CONDITIONS

The *C9ORF72* expansion associated bvFTD seems to cause an exceptionally large number of psychotic symptoms (Snowden et al. 2012, Devenney et al. 2014). On the other hand, schizophrenia and other psychoses are associated with structural brain abnormalities, but it is controversial whether these are static or progress over time (Tanskanen et al. 2010). There is convincing evidence that patients with schizophrenia suffer from cognitive impairments (Murray et al. 2006, Rajji, Ismail & Mulsant 2009). The most pronounced deficit areas are found in attention, executive functions and memory, which are the same deficit areas as encountered in patients with FTLD. In spite of these connections, there was no evidence of the pathological length *C9ORF72* expansion in the members of Northern Finland Birth Cohort 1966 in patients diagnosed with early onset schizophrenia or other psychoses. This indicates that the pathological length *C9ORF72* expansion does not play a major role in early onset schizophrenia or in other early onset psychoses. These findings support the concept that the onset of the *C9ORF72* expansion associated psychiatric phenotypes occur mainly in middle age or even later. However, even although no expansions with over 40 repeats were found, there were a few intermediate length repeat expansions. The role of intermediate expansion will be discussed in chapter 6.6.

Suicide is typically a long process with a multimodal etiology. Pathological neurobiological factors, certain genetic abnormalities and in particular, psychosocial factors are known to raise the risk for suicidal behaviour and suicide (Furczyk et al. 2013, Statham et al. 1998, Pandey 2013, Hawton, van Heeringen 2009). In particular, mutations affecting the proteins in the serotonergic pathway are known to elevate the risk of suicide. For example, polymorphism of the tryptophan hydroxylase 1 gene is a quantitative risk factor for suicidal behaviour and the polymorphism of serotonin transporter gene has been found to elevate the risk for violent method and repeated suicide attempts (Bondy, Buettner & Zill 2006). It is clear that the genetic architecture behind a suicide attempt may be rather polygenic but unfortunately GWAS studies have not found any clear genetic risk factor combinations in the polygenic score studies (Mullins et al. 2014). Impulsivity is a known risk factor for suicide (Mann 2003, Hawton, van Heeringen 2009) and malfunction of the prefrontal cortex has been associated with impulsivity which increases the suicide risk (Mann 2003).

Suicide is observed more than would be expected in the patients with dementia and usually these patients also have a higher risk for suicide ideation (Erlangsen, Zarit & Conwell 2008, Purandare et al. 2009). The suicidal behaviour and suicide attempts seem to be higher in non-Alzheimer dementia (Peisah et al. 2007). The frontal type dementia has been most commonly related to suicide (Alberici et al. 2012) and suicide attempts have been seen also in patients with semantic dementia (Hsiao et al. 2013). It has been speculated that the risk for suicide in the dementia patients is highest in patients suffering from bvFTD (Erlangsen, Zarit & Conwell 2008). This hypothesis is supported by the fact that bvFTD is characterized by personality changes, social dysfunction, apathy, impairments in the functions governed by frontal brain areas and a substantial amount of neuropsychiatric symptoms, including impulsivity (Rascovsky et al. 2011). Self-injurious behaviour has been described in bvFTD (Mendez, Bagert & Edwards-Lee 1997). Impulsive behaviour, rash or careless activities when combined with psychiatric symptoms may be present several years before there are any cognitive changes or features of dementia (Rascovsky et al. 2007). Interestingly, the suicide risk in patients with dementia seems to be highest at the time of initial diagnosis (Erlangsen, Zarit & Conwell 2008). There are other factors which if present are known to elevate the risk for suicide in dementia patients i.e. depression, young age and retained insight (Haw, Harwood & Hawton 2009, Lim et al. 2005, Purandare et al. 2009, Seyfried et al. 2011). However, there are very few studies which have examined suicide and suicidal behaviour in patients suffering from dementing diseases and even in these reports, the sample sizes have been limited (Haw, Harwood & Hawton 2009).

A suicide attempt has been reported to be a potential initial symptom of bvFTD (Fonseca et al. 2014). In addition, a suicide attempt has reported as being the first sign of bvFTD in one case with the *C9ORF72* expansion (Synofzik et al. 2012). While the risk of suicide seems to be increased among the patients with bvFTD (Erlangsen, Zarit & Conwell 2008) on the other hand, suicidality has been suggested to have over 40% heritability (Statham et al. 1998, Furczyk et al. 2013, Pandey 2013). Therefore it seemed reasonable to analyse the *C9ORF72* expansion in postmortem blood samples of victims of suicide. Although there is a high prevalence of the *C9ORF72* expansion associated bvFTD in Finland (Majounie et al. 2012b, Renton et al. 2011) in the present cohort of suicides, it was not possible to detect any pathological length expansions. This indicates that a suicide in a patient with the *C9ORF72* expansion associated bvFTD would simply be a coincidence rather than a typical symptom. However, there are no other studies which have examined the prevalence of the *C9ORF72* expansion in suicide victims and thus other trials with larger sample sizes will be needed to confirm this finding.

6.5 THE ROLE OF THE *C9ORF72* EXPANSION LENGTH

The intermediate length *C9ORF72* expansion was observed in 3% of early onset schizophrenia/ early onset psychosis patients. The exact repeat length size for pathogenic mutation is not known. It has become a convention to state that there should be a length of 30 repeats or more for it to be interpreted as being positive for the *C9ORF72* expansion (Renton et al. 2011). On the other hand, repeats as high as 60-65 have been considered as a lower limit of pathological expansion repeat numbers (Loy et al. 2014, Gijselinck et al. 2012). The normal physiological amount of repeats is thought to range from 2 to 24 repeats, whereas repeat numbers from 7 to 24 have been interpreted as being potential risk alleles; this is called an intermediate length expansion (van der Zee et al. 2013). At present, there is no data about the frequency of the intermediate length *C9ORF72* repeat expansions in the Finnish healthy population.

A correlation has been found between the number of repeats and an earlier onset age of FTLD (Benussi et al. 2014). There is an earlier appearance of the disease in successive generations within a pedigree i.e. the mean difference in onset age between parent and child was 9.8 years. Recently, there have appeared a few published studies that intermediate expansions would be seen more in familial and sporadic FTLD than in healthy controls (van der Zee et al. 2013, Xi et al. 2012) and the intermediate length *C9ORF72* expansions may cause a later onset of the disease and milder disease. The same kind of earlier appearance (so-called anticipation) associated with repeat expansion mutation has been observed also in some other neurodegenerative diseases e.g. in HD, where onset age is earlier in those patients with a higher number of repeats (Wexler et al. 2004). In general, these recent findings emphasize the fact that the threshold between normal and pathological expansion should be lowered to even as low as seven repeats.

Some authors have suggested that the intermediate length *C9ORF72* expansion would possess some disease modifying significance. A study of 127 Chinese patients suffering from spinocerebellar ataxia type 3/ Machado-Joseph disease revealed that those patients having 7-30 repeats had an earlier onset of the disease, i.e. by nearly three years, compared to non-carriers (Wang et al. 2015). Another study claimed that repeats from 20 to 30 in length would be a risk factor for PD (Nuytemans et al. 2013). Finally, one Italian group postulated that it was the intermediate repeats (20-30) that would be either modifying PD into a non-classical atypical form of PD without dementia or to change the disease so that it was typical PD complicated with psychosis (Cannas et al. 2015). The role of these intermediate repeats in different diseases is still unknown and especially their role in psychiatric diseases and other slowly progressive and atypical neurodegenerative syndromes should be evaluated. It has also been claimed recently that instead of the length of the mutation, it is epigenetical factors that may be responsible for the pathogenesis of the *C9ORF72* repeat expansion (Gijselinck et al. 2015).

6.6 THE EFFECT OF THE *C9ORF72* EXPANSION IN NASU-HAKOLA DISEASE PHENOTYPE

NHD is a rare neurodegenerative disease leading to frontal dementia at a very young age. (Hakola 1990, Hakola, Iivanainen 1973, Paloneva et al. 2001). NHD is caused by *TREM2* or *DAP12* mutations. Both of those genes have important functions in myeloid lineage cells and therefore it has been postulated that the mechanism behind the NHD would be attributable to disturbances in the function of osteoclasts and microglial cells. However, one research group indicated that *DAP12*/*TREM2* function might not be responsible for development of the neuropathological manifestation of NHD (Satoh et al. 2011). Disturbances in calcium homeostasis have also been suggested to be one component of the pathogenesis of NHD (Satoh et al. 2011) but no elevated calcium levels have reported in the patients with NHD. These findings emphasize the necessity of identifying other mechanisms to explain rapid neurodegeneration in the NHD affected brain.

The present study evaluated three deceased siblings known to possess a mutation in *DAP12*. A DNA sample was available in two cases and also the *C9ORF72* expansion was identified in one of those two samples. The onset of the NHD is about 10-30 years earlier than is the case with the *C9ORF72* expansion associated bvFTD (Majounie et al. 2012b). It is known that in general the neurodegeneration and neuropathological changes may appear even decades before the clinical symptoms of dementing disease (Jack et al. 2010). Therefore, since the *C9ORF72* expansion was detected in one patient with the NHD, it was tempting to speculate that the *C9ORF72* expansion would impact on the NHD phenotype and lead to a more progressive phenotype. However, it was not possible to detect any differences in the clinical signs, onset ages or disease progression in the *C9ORF72* expansion carrier versus the non-carrier. Furthermore, the imaging findings were similar in both subjects.

6.7 STRENGTHS AND LIMITATIONS

The present cohort of *C9ORF72* expansion carriers is extensive and all of the patients have been carefully examined by a neurologist specializing in dementing diseases. Furthermore, a large number of functional brain imaging scans were performed. The study performed in patients with early onset schizophrenia and other psychoses was extremely well designed from a clinical point of view as these patients have been part of a birth cohort study and thus the data is accurate and well validated. Since there was a strong consistent result, it means that these results can be generalized to represent early onset schizophrenia. In contrary, our study cannot be generalized to late onset schizophrenia or psychosis.

In Finland, forensic autopsies are performed routinely in violent deaths which made it possible characterize reliably the prevalence of the *C9ORF72* expansion among suicide victims. In addition, both younger and older subjects could be included into that study. This study's accuracy is also increased because of the genetic isolation of the Finnish people and the high prevalence of the *C9ORF72* expansion in Finland. Hence the validity of research is rather high.

The validity of our genetic analysis of the *C9ORF72* expansion was confirmed by analyzing both positive and negative controls. The numbers of expansions were also counted among the positive and intermediate cases, thus these present results may be considered as reliable and accurate.

Even though the cohorts are quite large in comparison with previously published reports, the main limitation of this study is the limited number of patients in each cohort. The minor limitations include the fact that no neuropathological data were assessed (due the low number of samples) in the present set of studies.

6.8 CLINICAL IMPLICATIONS

Based on the present findings, the FTDC criteria (Rascovsky et al. 2011) may be used for screening for the *C9ORF72* associated bvFTD. The most significant symptoms which should lead to a suspicion of bvFTD, are apathy or inertia, disinhibition and loss of manners and repetitive/stereotyped behaviour. These symptoms should be systematically screened in clinical practice, for example by subjecting the subject to the frontal behavioral inventory (FBI) query (Kertesz et al. 2000, Kertesz, Davidson & Fox 1997). The appearance of deficits in executive tasks, while visuospatial skills and episodic memory remain undisturbed, should reinforce this suspicion. One cannot dismiss the possibility that it is a somatic disease, especially bvFTD, behind the psychiatric symptoms simply by performing structural brain imaging or PET/SPECT as the sensitivities of these approaches are rather low for the *C9ORF72* associated bvFTD. The exclusion of neurological etiology should be done by a neurologist specializing in dementing diseases, especially in neuropsychiatric diseases. When there is a clear suspicion of bvFTD, genetic tests to identify the *C9ORF72* expansion should be conducted as some of the carriers may present with only a limited number of neuropsychiatric symptoms and may have rather minor or even non-detectable in changes in neuroimaging.

In addition, middle-age or later life onset of severe psychiatric disease should be considered as a possibility of bvFTD. In particular, patients with no clear environmental etiological factors, with features of ALS or parkinsonism, with a poor or even untoward response to antipsychotic medication (e.g. the development of extrapyramidal side effects), with a progressive deterioration of ADL-functions and with first or second degree relative with dementia or ALS should be screened for the *C9ORF72* expansion. However, suicidal behavior in general or schizophrenia before middle age should not be considered as a *C9ORF72* expansion associated disease.

7 Conclusions

Based on the findings of the present set of studies, the following conclusions can be drawn:

1. The revised criteria for bvFTD (Rascovsky et al. 2011) recognize a substantial amount of the *C9ORF72* expansion carriers (I).

2. The *C9ORF72* expansion carriers display a remarkable number of psychotic and mood symptoms. The diversity of the clinical phenotypes is extremely broad (I).

3. Functional and structural brain imagings do not detect all of the patients with the *C9ORF72* expansion. Thus neuroimaging on its own is not sufficiently sensitive and cannot solely be used as exclusionary method in ruling out a somatic etiology behind the psychiatric symptoms (I).

4. Despite the high frequency of psychiatric symptoms in bvFTD patients, the development of schizophrenia before the age of 43 is not associated with the full length pathogenic *C9ORF72* expansion (II).

5. The *C9ORF72* expansion is not associated with suicide. A suicide attempt in a carrier of the *C9ORF72* expansion should be considered as a coincidence rather than a cause and effect relationship (III).

6. The presence of the *C9ORF72* expansion does not influence the phenotype or disease course in NHD (IV).

8 Future perspectives

At the present time, neurodegeneration is the subject of the very intense and ground-breaking research. The mechanisms involved in both the genetic and environmental factors are still largely unknown for these diseases. The finding of the *C9ORF72* expansion has helped to clarify the situation in FTLD and ALS but the role of this expansion in milder neurodegenerative diseases has remained far from clear. In addition, it is not understood why the same mutation should cause such very different clinical phenotypes. Assessing the clinical phenotypes of the *C9ORF72* expansion is a very important issue, it is hoped that we will soon see the discovery and clinical approval of disease modifying drugs, based on the mutation (especially highly specific drugs and gene therapy).

In the future, other phenotypes of the *C9ORF72* carriers and also other clinical conditions which may be associated with the mutation may well be revealed. There is very limited data about the *C9ORF72* expansion associated language variant of FTLD and the clinical and neuroradiological profile should be characterized. However, the PPA phenotype is rare and if one wishes to examine large cohorts then one will need international collaboration. Another aspect worth consideration is the phenomenon that bvFTD is associated with psychotic behaviour, disinhibition and lack of emotionality. In addition, recent studies have reported criminal behaviour and rather high numbers of crimes committed by patients with bvFTD. Thus, as a short term continuum for this project, screening patients in forensic psychiatric facilities, prisons and geriatric/psychogeriatric facilities could provide essential information to reveal the true clinical spectrum of bvFTD. If undiagnosed bvFTD patients are held in facilities such as prisons or forensic psychiatric institutions, this knowledge may have legal implications and thus change those individuals' lives as well as being of considerable scientific interest. Hence, that kind of research topic could be deemed as both highly ethical and necessary. In addition, the connections between the *C9ORF72* expansion and conditions like treatment resistant depression, social marginalization, ADHD, and atypical alcoholism should be analysed.

Many studies have reported that the prevalence of the *C9ORF72* expansion in Finland is one of the highest in the world. However, there is no data about the prevalence of the *C9ORF72* expansion or intermediate length expansion repeats in the Finnish population. One way to analyse the prevalence of the mutation and its intermediate forms in Finnish population would be to utilize Finnish biobanks, Finnish Red Cross blood samples or/and, birth-cohort samples. The knowledge emerging from that kind of study would also help to clarify the essential characteristics of undiagnosed individuals with the pathological mutation as well as the role of the intermediate length of the expansion.

Even though the *C9ORF72* expansion is gradually becoming better understood, there is still no explanation for the enormous diversity within the phenotype – in fact it is very difficult to pin down the so-called core phenotype. Factors that contribute to the phenotypic diversity have not been described in the literature. Thus, for example, it could be predicted that GWAS analyses in patients carrying the *C9ORF72* expansion may reveal the genetic factors that lead to a certain clinical subtype of the *C9ORF72* associated disease.

Until recently, dementia used to be considered to be a psychiatric syndrome. In fact, not so long ago neurology and psychiatry were part of the same speciality. Subsequently these specialities have divided and drifted surprisingly far away from each other. In fact, the development of neurology may be viewed as having emerged from the identification of neurobiological factors which evoke the observed behavioural and cognitive syndromes. In particular, bvFTD has only rather recently been understood as being a neurobiological disease. Today our understanding of the reason why certain biological factors are responsible for the behavioural and cognitive disturbances is increasing rapidly, and therefore it would

now seem to be a suitable time to conduct ground-breaking research at the interface between these two specialities; exploring the neurological factors behind the psychiatric conditions by combining neuroimaging, genetics, neuroimmunological techniques as well as performing inflammatory factor analyses and exploiting other neurobiological approaches.

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EINO SOLJE

Behavioural variant frontotemporal dementia (bvFTD) is a less well-known neurodegenerative disease. The C9ORF72 expansion is the most common genetic etiology for bvFTD in Finland. There is a broad phenotype in the C9ORF72 expansion associated bvFTD; psychiatric symptoms are pronounced. This thesis focuses on characterizing the clinical phenotype and diagnostics of the C9ORF72 expansion carriers; this will be an important issue when new targeted pharmaceuticals become available.

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