Turun yliopisto
University of Turku

GENETICS OF INHERITED DEMENTING DISORDERS

Special emphasis on Alzheimer's disease, frontotemporal dementia, Parkinson's disease and primary familial brain calcification

Petra Pasanen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
Sarja - ser. D osa - tom. 1266 | Medica - Odontologica | Turku 2017

University of Turku

Faculty of Medicine
Institute of Biomedicine
Department of Medical Biochemistry and Genetics
Turku Doctoral Programme of Molecular Medicine (TuDMM)
Tyks Microbiology and Genetics, Turku University Hospital

and

University of Helsinki
Faculty of Medicine
Department of Pathology and Department of Medical and Clinical Genetics

Supervised by

Adjunct Professor Minna Pöyhönen, MD, Ph.D
Department of Clinical Genetics
Helsinki University Hospital

and

Department of Medical and Clinical Genetics,
Faculty of Medicine
University of Helsinki

Adjunct Professor Liisa Myllykangas, MD, Ph.D
Department of Pathology, Faculty of Medicine
University of Helsinki and
Helsinki University Hospital

Adjunct Professor Marc Baumann, Ph.D
Meilahti Clinical Proteomics Core Facility
Department of Biochemistry /
Developmental Biology
University of Helsinki

Reviewed by

Adjunct Professor Katarina Pelin, Ph.D.
Department of Biosciences, Division of Genetics
University of Helsinki

Adjunct Professor Maija Castrén, MD, Ph.D.
Faculty of Medicine, Physiology
University of Helsinki

Opponent

Adjunct Professor Peter Hackman, Ph.D.
Folkhälsan Institute of Genetics and
Department of Medical Genetics
University of Helsinki

The originality of this thesis has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-6694-3 (PRINT)
ISBN 978-951-29-6695-0 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy - Turku, Finland 2017

To my family

ABSTRACT

Petra Pasanen

GENETICS OF INHERITED DEMENTING DISORDERS – Special emphasis on Alzheimer's disease, frontotemporal dementia, Parkinson's disease and primary familial brain calcification

University of Turku, Faculty of Medicine, Institute of Biomedicine, Department of Medical Biochemistry and Genetics, Doctoral Programme of Molecular Medicine (TuDMM)

Annales Universitatis Turkuensis, Medica – Odontologica, Painosalama Oy, Turku, Finland, 2016

Advances in genotyping and sequencing technologies have enabled the identification of common and rare genetic variation associated with dementia. This thesis aimed to examine the genetic background of inherited dementing diseases in the Finnish population. Sixty families with several individuals affected by dementia were included in the first study. Twelve of these families were found to carry *C9orf72* expansions. Exome sequencing was performed in 10 families with Alzheimer's disease (AD) and two families with frontotemporal dementia (FTD). A few potentially deleterious rare variants were identified, but further studies are needed to clarify their putative role in neurodegeneration. In the second study, a novel α-synuclein mutation was identified in a family with Parkinson's disease (PD) and multiple system atrophy (MSA) -type disease. The third study showed that this mutation is a rare cause of PD and that, to date, all known families with this mutation originate from a common founder. In the fourth study we described a Finnish family with three patients diagnosed with primary familial brain calcification. Whole–genome sequencing revealed a segregating heterozygous deletion of ~578 kb in size on chromosome 8, supporting *SLC20A2* haploinsufficiency as a pathogenetic mechanism.

This study provided new information on the genetics of α-synucleinopathies and primary familial brain calcification. It also confirmed that *C9orf72* expansions are common causes of dementia in Finland. Exome sequencing proved efficient in identifying rare genetic variants, but further studies are warranted to prove their potential association with dementia.

Key words : Alzheimer's disease, frontotemporal dementia, Parkinson's disease, multiple system atrophy, primary familial brain calcification, dementia, neurodegeneration, haplotype, exome sequencing, genome sequencing

TIIVISTELMÄ

Petra Pasanen

PERINNÖLLISTEN DEMENTOIVIEN SAIRAUKSIEN GENETIIKKAA – Alzheimerin tauti, otsa-ohimolohkorappeuma, Parkinsonin tauti ja primaari familiaalinen basaaliganglioiden kalkkeumatauti

Turun yliopisto, Lääketieteellinen tiedekunta, Biolääketieteen laitos, Lääketieteellinen biokemia ja genetiikka, Turun molekyylilääketieteen tohtoriohjelma (TuDMM)

Annales Universitatis Turkuensis, Medica – Odontologica, Painosalama Oy, Turku, Suomi, 2016

Dementiaan liittyvien yleisten ja harvinaisten geenivarianttien tunnistaminen on tullut mahdolliseksi genotyypitys- ja sekvensointiteknologioiden kehittymisen myötä. Tämän väitöskirjatyön tavoitteena oli tutkia periytyvien dementioiden geneettistä taustaa suomalaisessa väestössä. Ensimmäisen osatyön aineisto koostui kuudestakymmenestä suvusta, joissa oli useita dementiaa sairastavia henkilöitä. Näistä suvuista kahdestatoista löytyi *C9orf72*-geenin toistojaksolaajentumamutaatio. Lopuista suvuista valittiin 10 Alzheimerin tauti –sukua ja kaksi otsa-ohimolohkorappeumasukua eksomisekvensointiin. Tutkimuksessa löytyi muutamia mahdollisesti haitallisia geenivariantteja, mutta lisätutkimuksia tarvitaan varmistamaan, liittyvätkö variantit todella neurodegeneratiivisten dementioiden syntyyn. Toisessa osatyössä kuvattiin uusi α-synukleiinimutaatio ja siihen liittyvät neuropatologiset muutokset epätyypillistä Parkinsonin tautia sairastavassa suvussa. Kolmannessa osatyössä osoitettiin, että tämä mutaatio on harvinainen Parkinsonin taudin aiheuttaja ja että kaikki tähän mennessä löydetyt suvut ovat samaa geneettistä alkuperää. Neljännessä osatyössä tutkittiin sukua, jossa oli kolme primaarista basaaliganglioiden kalkkeumatautia sairastavaa henkilöä. Genomisekvensoinnin avulla löytyi taudin kanssa periytyvä n. 578 kb:n heterotsygoottinen deleetio ennestään tunnetun tautigeenin alueelta. Löydös sopii hypoteesiin *SLC20A2*:n haploinsuffisienssista patogeneesimekanismina.

Väitöskirjatyö tuo uutta tietoa α-synukleinopatioiden ja primaarisen basaali-ganglioiden kalkkeumataudin genetiikasta. Tulokset myös vahvistivat *C9orf72*-ekspansioiden yleisyyden suomalaisilla dementiapotilailla. Eksomisekvensointi on tehokas menetelmä harvinaisten geenivarianttien etsimiseen, mutta niiden mahdollisen dementia-assosiaation varmistaminen edellyttää lisätutkimuksia.

Avainsanat: Alzheimerin tauti, otsa-ohimolohkorappeuma, Parkinsonin tauti, monisysteemiatrofia, primaari familiaalinen basaaliganglioiden kalkkeumatauti, dementia, neurodegeneraatio, haplotyyppi, eksomisekvensointi, genomisekvensointi

TABLE OF CONTENTS

ABBREVIATIONS

6-FAM	6-carboxyfluorescein
ABCA7	ATP binding cassette subfamily A member 7
aCGH	array comparative genomic hybridisation
ACMSD	aminocarboxymuconate semialdehyde decarboxylase
AD	Alzheimer's disease
ADAM10	a disintegrin and metalloprotease family member 10
ADAM17	a disintegrin and metalloprotease family member 17
ADAM9	a disintegrin and metalloprotease family member 9
aFTLD-U	atypical frontotemporal lobar degeneration, ubiquitin type
AICD	APP intracellular domain
AKAP9	A-kinase anchoring protein 9
APH1	anterior pharynx-defective 1
APOE	apolipoprotein E
APP	amyloid beta A4 precursor protein
ATP13A2	ATPase, type 13A2
BACE1	beta-site amyloid beta A4 precursor protein-cleaving enzyme 1
BACE2	beta-site amyloid beta A4 precursor protein-cleaving enzyme 2
BIN1	bridging integrator 1
BST1	bone marrow stromal cell antigen 1
bvFTD	behavioural variant frontotemporal dementia
C9orf72	chromosome 9 open reading frame 72
CA	cornu ammoni
CASS4	Crk associated substrate 4
CBD	corticobasal degeneration
CCDC62	coiled-coil domain containing 62
CCNF	cyclin F
CD2AP	CD2-associated protein
CD33	CD33 antigen
CELF1	CUGBP, Elav-Like Family Member 1
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHMP2B	charged multivesicular body protein 2B
CHRNA6	cholinergic receptor nicotinic alpha 6 subunit
CHRNB3	cholinergic receptor nicotinic beta 3 subunit
CLU	clusterin
CNV	copy number variation
COQ2	coenzyme Q2
CR1	complement component 3b/4b receptor 1
CSF	cerebrospinal fluid
CT	computed tomography
CTF	C-terminal fragment
CTSC	cathepsin C

DaT-SPECT	dopamine transporter activity SPECT
dbSNP	the single nucleotide polymorphism database
DDRGK1	DDRGK domain-containing protein 1
DJ-1/PARK7	parkinsonism associated deglycase
DLB	dementia with Lewy bodies
DN	dystrophic neurite
DNA	deoxyribonucleic acid
DNAJC6	DnaJ heat shock protein family (Hsp40) member C6
DNTC	diffuse neurofibrillary tangle dementia with calcifications
EDTA	ethylenediaminetetraacetic acid
EOPD	early-onset Parkinson's disease
EPHA1	EPH receptor A1
ESP	NHLBI Exome Sequencing Project
ExAC	Exome Aggregation Consortium
FBXO7	F-box protein 7
FDG-PET	fluorodeoxyglucose-PET
FERMT2	fermitin family member 2
FGF20	fibroblast growth factor 20
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
FTLD-FUS	frontotemporal lobar degeneration with FUS-positive inclusions
FTLD-TAU	frontotemporal lobar degeneration with tau-positive inclusions
FTLD-TDP	frontotemporal lobar degeneration with TDP-positive inclusions
FTLD-UPS	frontotemporal lobar degeneration with ubiquitin-positive inclusions
FUS	fused in sarcoma
GAK	cyclin G associated kinase
GBA	glucosylceramidase beta
GCH1	GTP cyclohydrolase 1
GCI	glial cytoplasmic inclusion
GPNMB	glycoprotein NMB
GRN	granulin
GWAS	genome-wide association study
GWLS	genome-wide linkage study
HLA	major histocompatibility complex
HOOK3	hook microtubule-tethering protein 3
IBGC	idiopathic basal ganglia calcification
indel	insertion or deletion
INPP5D	inositol polyphosphate-5-phosphatase D
INPP5F	inositol polyphosphate-5-phosphatase F
kb	kilobase
LB	Lewy body
LN	Lewy neurite

LOAD	late-onset Alzheimer's disease
EOAD	early-onset Alzheimer's disease
NFT	neurofibrillary tangle
LRP	Lewy-related pathology
LRRK2	leucine-rich repeat kinase 2
MAPT	microtubule-associated protein tau
MARCH4	membrane associated ring-CH-type finger 4
Mb	megabase
MCCC1	methylcrotonoyl-CoA carboxylase 1
MEF2C	myocyte enhancer factor 2C
MIR4697HG	MIR4697 host gene
MLPA	multiplex ligation-dependent probe amplification
MRI	magnetic resonance imaging
MS4A4E	membrane spanning 4-domains A4E
MS4A6A	membrane spanning 4-domains A6A
MSA	multiple system atrophy
MSA-C	multiple system atrophy with predominant cerebellar ataxia
MSA-P	multiple system atrophy with predominant parkinsonism
NAC	non-Aβ component
NCI	neuronal cytoplasmic inclusion
NFV-PPA	non-fluent variant primary progressive aphasia
NGS	next-generation sequencing
NINCDS–ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related Disorders Association
NME8	NME/NM23 family member 8
OMIM	Online Mendelian Inheritance in Man
p25α	25α protein
p62	sequestosome 1 protein
PARK2	Parkin RBR E3 ubiquitin protein ligase
PCR	polymerase chain reaction
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PDGFB	platelet derived growth factor beta
PDGFRB	platelet derived growth factor receptor beta
PEN2	presenilin enhancer 2
PET	positron emission tomography
Aβ	amyloid beta
PFBC	primary familial brain calcification
Pi	inorganic phosphate
PICALM	phosphatidylinositol binding clathrin assembly protein
PINK1	PTEN-induced putative kinase 1
PLA2G6	phospholipase A2 group VI

PLD3	phospholipase D family member 3
PPA	primary progressive aphasia
PSEN1	presenilin 1
PSEN2	presenilin 2
PSP	progressive supranuclear palsy
PTK2B	protein tyrosine kinase 2 beta
QMPSF	quantitative multiplex PCR of short fluorescent fragments
qPCR	quantitative PCR
RAB38	RAB38, member RAS oncogene family
RAB7L1	Rab-7-like protein 1
RFLP	restriction fragment length polymorphism
RIN3	Ras and Rab interactor 3
RIT2	RIC-like protein without CAAX motif 2
RNF170	ring finger protein 170
ROS	reactive oxygen species
RP-PCR	repeat-primed PCR
rs	reference SNP accession number
s-APPα	soluble ectodomain of alpha amyloid
s-APPβ	soluble ectodomain of beta amyloid
SCARB2	lysosome membrane protein 2
SD	standard deviation
SHC2	Src homology 2 domain containing
SIPA1L2	signal induced proliferation associated 1 like 2
SISu	Sequencing Initiative Suomi
SLC20A2	solute carrier family 20 member 2
SLC24A4	solute carrier family 24 member 4
SMIM19	small integral membrane protein 19
SNCA	synuclein alpha
SNP	single nucleotide polymorphism
SNV	single nucleotide variant
SORL1	sortilin-related receptor
SPECT	single-photon emission computed tomography
SPTBN1	spectrin beta, non-erythrocytic 1
SQSTM1	sequestosome 1
SREBF2	sterol regulatory element binding transcription factor 2
STK39	serine/threonine kinase 39
STR	short tandem repeat
STX1B	syntaxin 1B
SV-PPA	semantic-variant primary progressive aphasia
SYNJ1	synaptojanin 1
SYT11	synaptotagmin 11
TARDBP	transactive response DNA binding protein
TBK1	TANK binding kinase 1

THAP1	THAP domain-containing protein 1
TMEM106B	transmembrane protein 106B
TREM2	triggering receptor expressed on myeloid cells 2
UBQLN2	ubiquilin 2
UNC13C	Unc-13 homolog C (C. Elegans)
UNC5C	Unc-5 netrin receptor C
VCP	valosin containing protein
VPS13C	vacuolar protein sorting 13 homolog C
VPS35	vacuolar protein sorting-associated protein 35
WES	whole exome sequencing
WGS	whole genome sequencing
XPR1	xenotropic and polytropic retrovirus receptor 1
ZCWPW1	zinc finger CW-type and PWWP domain containing 1

All genes are italicised in the text. Human genes are written in capital. In mouse genes, only the first letter is capitalised.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals (I-IV):

I **Pasanen P.**, Myllykangas L., Pöyhönen M., Siitonen M., Guerreiro R., Hardy J., Bras J., Paetau A., Tienari P. J., Verkkoniemi-Ahola A. Genetics of dementia in a Finnish cohort. *Manuscript.*

II **Pasanen P**., Myllykangas L., Siitonen M., Raunio A., Kaakkola S., Lyytinen J., Tienari P.J., Pöyhönen M., Paetau A. A novel α-synuclein mutation A53E associated with atypical multiple system atrophy and Parkinson's disease-type pathology. *Neurobiol Aging*. 2014, Sep,35(9):2180.e1-5.

III **Pasanen P.**, Palin E., Pohjolan-Pirhonen R., Pöyhönen M., Rinne J. O., Päivärinta M., Martikainen M. H., Kaasinen V., Hietala M., Gardberg M., Saukkonen A. M., Eerola-Rautio J., Kaakkola S., Lyytinen J., Tienari P. J., Paetau A., Suomalainen A., Myllykangas L. *SNCA* mutation p.Ala53Glu is derived from a common founder in the Finnish population. *Neurobiol Aging*. 2016, Oct 19. doi: 10.1016/j.neurobiolaging.2016.10.014.

IV **Pasanen P.**, Mäkinen J., Myllykangas L., Guerreiro R., Bras J., Valori M., Viitanen M., Baumann M., Tienari P. J., Pöyhönen M., Baumann P. Primary familial brain calcification linked to deletion of 5' noncoding region of *SLC20A2. Acta Neurol Scand.* 2016 Oct 10. doi: 10.1111/ane.12697.

1. INTRODUCTION

Dementia is a global concern, affecting an estimated 47 million people worldwide in 2015 (Prince *et al.* 2015). As average life expectancy continues to rise, an increase in dementia prevalence is anticipated, too. The most common causes of dementia are Alzheimer's disease, vascular cognitive impairment, dementia with Lewy bodies, Parkinson's disease dementia, and frontotemporal dementia. Dementia typically afflicts older people, but a significant proportion of patients are under 65 years of age at the time of diagnosis.

The diagnosis of the dementing disorder is based on the patient´s clinical picture, imaging findings and a selective panel of laboratory tests. Because the cause of a dementing disorder is most commonly neurodegeneration in the patient´s central nervous system (brain), in many cases a definite diagnosis cannot be established until post mortem. Then, the neuropathological examination of the deceased patient´s nervous system commonly discloses findings which are specifically diagnostic for each dementing disorder (Kovacs 2016).

Most dementia patients present as sporadic cases; thus, the physicians must rely on the examinations above to determine the diagnosis and nature of the disorder. Familial forms and Mendelian inheritance, often autosomal dominant, are seen especially in the early-onset group of patients. Even though these inherited forms of dementias are rare, they have provided pivotal clues for establishing the definite diagnosis and the underlying pathogenetic mechanisms. Identifying the causative gene, the spectrum of mutations and ultimately the cellular mechanisms by which these mutations exert their damaging effects is crucial in order to identify potential therapeutic targets. The same cellular pathways can be expected to be involved in the non-familial forms of the diseases. Thus, the rare inherited forms have built a foundation for our understanding of several neurodegenerative diseases.

Following the completion of the Human Genome Project in 2003, the field of human genetics has undergone an unforeseen revolution. First, identifying most common variation enabled genome-wide linkage studies (GWLS) and genome-wide association studies (GWAS) to identify genetic variation predisposing to complex diseases. The development of massively parallel sequencing, also known as next-generation sequencing (NGS) technologies made it possible to sequence all coding genes or entire genomes. As a consequence, the causative genes of several monogenic diseases have been identified. NGS-based methods have also been applied to complex diseases to identify rare variants that could not be found using genome-wide association studies. Both GWAS and NGS have proven their strength in neurogenetics, identifying dozens of risk loci and even new causative genes.

This thesis project aimed to explore the genetic background of dementia in the Finnish population. We sought to characterise familial and inherited neurodegenerative dementing disorders by utilising both targeted and genome-wide approaches of variant detection. Specifically, this study concentrated on known and novel genetic variants linked to Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and primary familial brain calcification.

2. REVIEW OF THE LITERATURE

2.1. Dementia

According to the International Statistical Classification of Diseases and Related Health Problems (ICD-10, www.who.int/classifications/icd10/), dementia refers to a clinical syndrome with disturbances in 'memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement'. It results in marked cognitive decline which usually impairs the activities of daily living.

Age is an important risk factor for dementia, and the great rise in human life expectancy during the 20th century has led to global increase in dementia prevalence. The worldwide prevalence of dementia has been estimated to be 46.8 million in 2015 and it is expected to double every 20 years, resulting in 131.5 million affected by 2050 (Prince *et al.* 2015). In Finland, up to 70 000 people are currently affected. Approximately 14 500 persons are expected to become affected by memory impairment every year (Viramo and Sulkava 2015).

The most common causes of progressive or permanent dementia are Alzheimer's disease, vascular cognitive impairment, dementia with Lewy bodies, Parkinson's disease dementia and frontotemporal dementia. In most cases, dementia occurs sporadically but a genetic component is obvious in a significant proportion of cases. Familial or inherited dementia is most common in the early-onset (< 65 years) group with up to 10% of patients having a family history compatible with autosomal dominant inheritance (Cohn-Hokke *et al.* 2012).

2.2. Alzheimer's disease

A case study of a patient with a 'peculiar severe disease process of the cerebral cortex' was presented by Alois Alzheimer in November 1906 in the 37th Meeting of South-West German Psychiatrists (Hippius and Neundörfer 2003). The case report published the following year (Alzheimer 1907) is the first written description of presenile Alzheimer's disease (AD, Online Mendelian Inheritance in Man, OMIM #104300) with its distinctive histological findings that later became known as neuritic plaques and neurofibrillary tangles. The disease was named after Dr. Alzheimer as early as 1910 (Kraepelin 1910), but it was not recognised as the most common form of dementia until 1968, when indistinguishable neuropathological features between presenile AD and senile dementia led to the conclusion that these diseases must represent a single entity (Blessed *et al.* 1968). The implications of increasing human life span and AD prevalence were soon realised (Katzman 1976).

2.2.1. Epidemiology

Alzheimer's disease is the most common neurodegenerative dementia worldwide accounting for from 60 to 70% of all dementia cases (Jellinger *et al.* 1990). A large meta-analysis of published population-based studies of dementia in people over 60 years of age showed that the mean dementia prevalence varies between 5.6% and 7.6%; the highest standardised prevalence was observed in North Africa/Middle East (8.7%) and Latin America (8.4%), while the lowest prevalence of 4.7% was seen in Central Europe (Prince *et al.* 2015).

The incidence of AD increases with increasing age, doubles every 6 years, peaks between the ages of 80 – 89 years and declines in the oldest age group. Women are more often affected than males, most likely due to overpresentation of women in the older age groups (Prince *et al.* 2015).

2.2.2. Clinical features

Alzheimer's disease is characterised by progressive loss of memory. The onset is gradual and typically presents as difficulties in learning new things and remembering recently learned information, that is, deficits in anterograde episodic memory. Impairment of other cognitive functions such as language (deficits in word-finding), executive functions (judgement and reasoning, problem solving) and visuospatial functions (e.g. spatial cognition, face recognition and understanding written language) develop as the disease progresses (McKhann *et al.* 2011).

The key criteria for diagnosing AD have been the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria, first published in 1984 (McKhann *et al.* 1984) and revised in 2011 (McKhann *et al.* 2011). AD is diagnosed based on typical clinical symptoms, combined with laboratory and imaging findings. Impairment of episodic memory can be confirmed in a clinical examination with the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) test (Morris *et al.* 1989). Brain magnetic resonance imaging (MRI) typically shows medial temporal lobe atrophy and hippocampal atrophy. Positron emission tomography (PET) imaging reveals cerebral changes in fluorodeoxyglucose metabolism or evidence of deposition of β-amyloid in the brain. Cerebrospinal fluid (CSF) biomarkers, low Aβ42 and elevated tau or phospho-tau, are also indicative of AD (McKhann *et al.* 2011). However, a neuropathological examination is required for a definite AD diagnosis as only 70 – 80% of patients with clinical AD actually have AD brain pathology (Jicha *et al.* 2006).

Most cases develop the disease after 65 years of age (late-onset AD, LOAD), but up to 10% of patients develop symptoms earlier in life, as early as in their 30s (early-onset AD, EOAD) (Prince *et al.* 2015).

2.2.3. Neuropathology

Gross visual examination of an AD brain shows a symmetric pattern of cortical atrophy. The atrophy is most pronounced in the inferior temporal and the superior and middle

frontal gyri; the inferior frontal and the orbitofrontal gyri are mostly spared (Duyckaerts *et al.* 2009). Microscopically, the two most essential lesions of AD are neurofibrillary tangles (NFTs) and senile plaques (Alzheimer 1907, Hyman *et al.* 2012) (Figure 1).

Neurofibrillary tangles are intraneuronal filamentous aggregates in neuronal perikarya that consist of hyperphosphorylated and misfolded microtubule-associated protein tau (Grundke-Iqbal *et al.* 1986a, Grundke-Iqbal *et al.* 1986b). The progression of NFT pathology follows a stereotypical spatiotemporal pattern: the first lesions appear in the transentorhinal cortex, spread to the limbic structures and finally to all isocortical areas (Arnold *et al.* 1991, Braak and Braak 1991). Hyperphosphorylated tau also accumulates in neuronal processes appearing as neuropil threads (Hyman *et al.* 2012). NFTs are not specific to AD; they are also seen in frontotemporal dementia with tauopathy (Cairns *et al.* 2007) and chronic traumatic encephalopathy (McKee *et al.* 2009), for example.

Senile plaques are extracellular spherical lesions consisting of amyloid beta (Aβ) (Glenner and Wong 1984). Based on their morphology, the plaques can be classified as diffuse or neuritic plaques. Neuritic plaques are associated with deleterious effects on the neuropil, while diffuse plaques are also seen in the normal ageing brain (Davies *et al.* 1988). Neuritic plaques have an amyloid core and are surrounded by dystrophic neurites (Knowles *et al.* 1999), reactive astrocytes, and microglial cells (Itagaki *et al.* 1989).

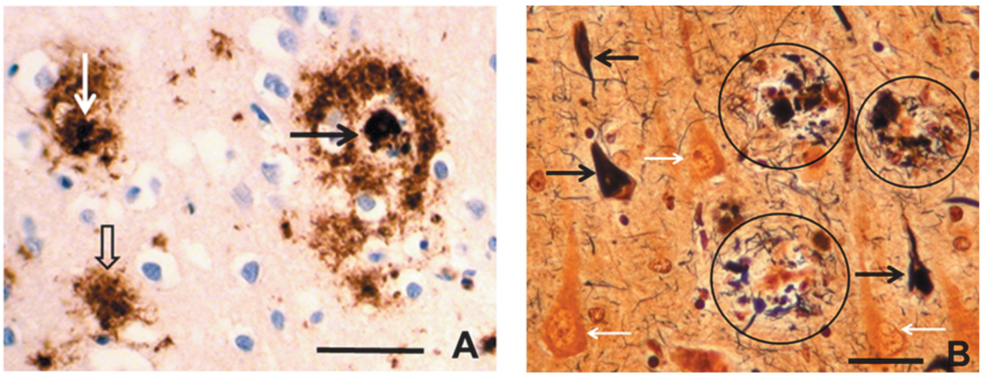

Figure 1. Neuropathological findings in sporadic Alzheimer's disease. **(A)** In two senile plaques of cored type (black and white arrows) β-amyloid forms compact cores surrounded by a corona of more diffuse deposits of β-amyloid. The third plaque (open arrow) is either a diffuse plaque or a tangential section of another cored plaque. **(B)** Three neurons (black arrows) harbour neurofibrillary tangles strongly immunopositive for hyperphosphorylated tau (hp-tau), whereas three other neurons (white arrows) appear relatively intact. The three neuritic plaques (circled) contain irregularly shaped, hp-tau-immunopositive dystrophic neurites, and in the background, there are very thin neuropil threads, also immunopositive for hp-tau. Immunostaining (A) for β-amyloid and (B) for hp-tau with hematoxylin counterstaining. Scale bars (A) 100 µm, (B) 70 µm. Courtesy of Professor Hannu Kalimo.

2.2.4. Genetics

Genetic susceptibility is a significant factor in the occurrence of AD. A heritability of ~90% has been observed in the EOAD group (Wingo *et al.* 2012) while the estimated heritability is 58 to 79% in LOAD (Gatz *et al.* 2006). Autosomal dominant inheritance is seen in 35 to 60% of EOAD patients (Campion *et al.* 1999, Jarmolowicz *et al.* 2015). Causative mutations have been described in amyloid protein precursor (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes, but these account for only from 5 to 10% of EOAD cases (Cruts *et al.* 1998) (Table 1a).

The first genetic risk factor associated with AD, *APOE* ε4 allele, was identified using the candidate-gene approach (Corder *et al.* 1993, Strittmatter *et al.* 1993). The *APOE* ε4 allele is the strongest known genetic risk factor for AD; homozygous individuals have a 10-fold risk for developing AD (Farrer *et al.* 1997). Most other known risk loci have only a low impact on the disease susceptibility, and GWAS studies on large case-control cohorts were required to identify them. Currently, more than 20 risk loci replicated in several cohorts are known (Table 1b).

Identification of AD susceptibility genes and their functions has revealed novel biological pathways implicated in AD pathogenesis, in addition to the well-known beta amyloid cascade. These include lipid metabolism, innate immune responses and inflammation, endocytosis, synaptic function, cytoskeleton function, axonal transport, regulation of gene expression and post-translational protein modification (Table 1b). Interestingly, the *APOE* ε2 allele (Corder *et al.* 1994) and the p.Ala673Thr variant in *APP* (Jonsson *et al.* 2012) have been suggested to be protective against AD, although the *APP* variant is rare in most studied populations (Kero *et al.* 2013, Ting *et al.* 2013, Wang *et al.* 2015). Functional studies have suggested that the *APP* A673T variant results in a diminished aggregation propensity of the corresponding mutant Aβ42 (Benilova *et al.* 2014, Maloney *et al.* 2014, Zheng *et al.* 2015).

Table 1a. Known genetic loci causative of Alzheimer's disease. Numbers of mutations in APP, PSEN1 and PSEN2 reported as pathogenic are from the Alzheimer disease & frontotemporal dementia mutation database (http://www.molgen.ua.ac.be/ADMutations/) (Cruts *et al*. 2012), accessed 08/2016, Alzforum database (http://www.alzforum.org/mutations/), accessed 09/2016 and HGMD Professional (Qiagen), accessed 10/2016.

Disease genes	Pathway	Number of pathogenic mutations	Effect	MAF	Identified with	Reference
APP	Aβ processing	more than 35	causative	< 0.1%	linkage	Goate *et al.* (1991)
PSEN1	Aβ processing	more than 250	causative	< 0.1%	linkage	Sherrington *et al.* (1995)
PSEN2	Aβ processing	~30	causative	< 0.1%	linkage	Levy-Lahad *et al.* (1995), Rogaev *et al.* (1995)

Table 1b. Known genetic loci contributing to Alzheimer's disease risk. GWAS = genome-wide association study, MAF = minor allele frequency, OR = odds ratio, WES = whole exome sequencing, WGS = whole genome sequencing.

Risk loci	Pathway	Risk variant	Impact	MAF	Identified with	Reference
APOE	lipid metabolism	ε4 (rs7412, rs429358)	high (OR ≥ 2)	> 10%	candidate gene approach	Corder *et al*. (1993), Schmechel *et al.* (1993), Strittmatter *et al. (1993)*
CLU	immune system, lipid metabolism	rs9331896	low (OR < 2)	> 10%	GWAS	Harold *et al.* (2009), Lambert *et al.* (2009)
CR1	immune system	rs6656401	low (OR < 2)	> 10%	GWAS	Lambert *et al.* (2009)
PICALM	endocytosis, synaptic function	rs10792832	low (OR < 2)	> 10%	GWAS	Harold *et al.*(2009)
BIN1	endocytosis, synaptic function	rs6733839	low (OR < 2)	> 10%	GWAS	Seshadri *et al.* (2010)
MS4A6A/ MS4A4E	immune system	rs983392	low (OR < 2)	> 10%	GWAS	Hollingworth *et al.* (2011) Naj *et al.* (2011)
ABCA7	immune system, lipid metabolism	rs4147929	low (OR < 2)	> 10%	GWAS	Hollingworth *et al.* (2011)
CD2AP	endocytosis, synaptic function	rs10948363	low (OR < 2)	> 10%	GWAS	Hollingworth *et al.* (2011), Naj *et al.* (2011)
CD33	immune system, synaptic function	rs3865444	low (OR < 2)	> 10%	GWAS	Hollingworth *et al.* (2011), Naj *et al* (2011)
EPHA1	immune system, synaptic function	rs11771145	low (OR < 2)	> 10%	GWAS	Hollingworth *et al.* (2011), Naj *et al.* (2011)
PTK2B	hippocampal synaptic function	rs28834970	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
SORL1	endocytosis, trafficking and metabolism of APP	rs11218343	low (OR < 2)	> 10%	candidate gene approach	Rogaeva *et al.* (2007)
SLC24A4/ RIN3	putative role in neural development	rs10498633	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
INPP5D	immune system	rs35349669	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
MEF2C	immune system, hippocampal synaptic function	rs190982	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
NME8	neuronal cell proliferation and differentiation	rs2718058	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
FERMT2	modulation of angiogenesis, actin assembly and cell shape	rs17125944	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)

Risk loci	Pathway	Risk variant	Impact	MAF	Identified with	Reference
CASS4	regulation of cell spreading and adhesion	rs7274581	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
ZCWPW1	epigenetic regulation	rs1476679	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
HLA-DRB5-DRB1	immune system	rs9271192	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
CELF1	regulation of pre-mRNA alternative splicing	rs10838725	low (OR < 2)	> 10%	GWAS meta-analysis	Lambert *et al.* (2013)
Rare variants	**Pathway**	**Risk variant**	**Impact**	**MAF**	**Identified with**	**Reference**
TREM2	immune system	rs75932628	high (OR ≥ 2)	< 1%	WES, WGS	Guerreiro *et al.* (2013), Jonsson *et al.* (2013)
PLD3	APP processing	rs145999145	high (OR ≥ 2)	< 1%	WES	Cruchaga *et al.* (2014)
UNC5C	neuronal cell death	rs137875858	high (OR ≥ 2)	< 1%	linkage, WGS and WES	Wetzel-Smith *et al.* (2014)
AKAP9	signal transduction	rs144662445	high (OR ≥ 2)	< 1%	WES	Logue *et al.* (2014)
ADAM10	α-secretase activity	rs2305421	unknown, variants suggested to segregate with LOAD in families	N/A	candidate gene approach	Kim *et al.* (2009)

2.2.5. Hypotheses on pathogenesis

As amyloid plaques are the typical finding in AD, an amyloid cascade hypothesis of pathogenesis was proposed more than 20 years ago (Glenner and Wong 1984, Beyreuther and Masters 1991, Hardy and Allsop 1991, Selkoe 1991, Hardy and Higgins 1992). According to the hypothesis, accumulation of Aβ protein is the root cause of neuronal death, and other changes such as NFT formation are consequences of Aβ accumulation. However, it is still unclear whether Aβ accumulation is causal or simply a byproduct of other cellular dysfunctions.

APP is a widely expressed transmembrane precursor protein whose normal physiological function is still elusive despite being extensively studied since its identification. Suggested functions include neurite outgrowth (Hung *et al.* 1992) and synaptogenesis (Moya *et al.* 1994), axonal protein transport (Kamal *et al.* 2000), transmembrane signal transduction (Hass and Yankner 2005) and cell adhesion (Soba *et al.* 2005).

APP is synthesised in the endoplastic reticulum and transported in vesicles to the cell surface where it can be either cleaved to soluble fragments or re-internalised in

clathrin-coated vesicles to the endosome (Nordstedt *et al.* 1993, Caporaso *et al.* 1994). APP can be processed via two pathways to form amyloid polypeptides (Figure 2). The non-amyloidogenic α-secretase pathway (Esch *et al.* 1990) is most active on the cell surface (Sisodia 1992). APP is cleaved by α-secretase within the Aβ domain to release a soluble ectodomain, s-APPα (Sisodia 1992), that regulates neuronal plasticity and protects from excitotoxicity (Furukawa *et al.* 1996). Several proteins with α-secretase activity are known, including members of the ADAM (a disintegrin and metalloproteinase) family: ADAM9 (Koike *et al.* 1999), ADAM10 (Kuhn *et al.* 2010) and ADAM17 (Buxbaum *et al.* 1998).

The amyloidogenic pathway mediated by the two β-secretases, BACE1 (beta-site APP cleaving enzyme) (Sinha *et al.* 1999, Vassar *et al.* 1999, Yan *et al.* 1999) and BACE2 (Hussain *et al.* 2000, Solans *et al.* 2000), is mostly active in the endosome. β-secretase cleaves APP at the junction of the Aβ domain and the ectodomain (β site in Figure 2) or at a more carboxyterminal position (β' site in Figure 2), releasing a soluble s-APPβ fragment. The β' site cleavage eventually results in truncated Aβ peptides, $A\beta_{11\text{-}40}$ and $A\beta_{11\text{-}42}$ (Vassar *et al.* 1999).

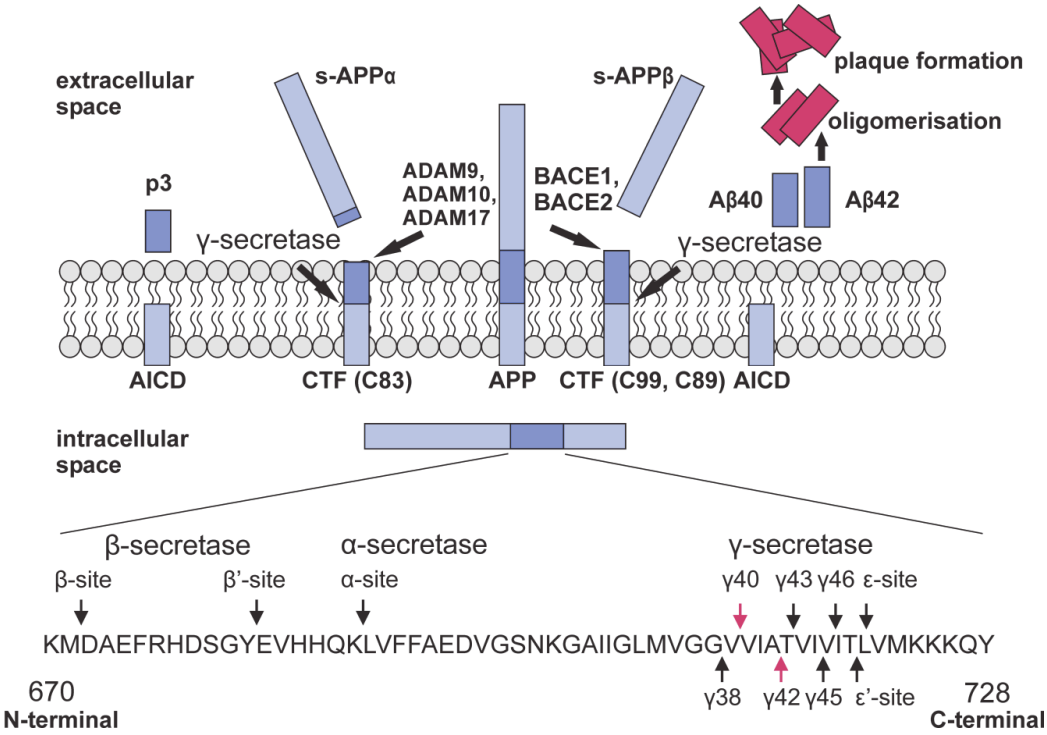

Figure 2. Processing of APP by α- (ADAM9, ADAM10, ADAM17), β- (BACE1, BACE2) and γ-secretases. For clarity, only the most common cleavage sites and the most relevant Aβ peptides are presented in the upper part of the figure. The figure is based on LaFerla *et al*. (2007), Chow *et al*. (2010) and Bulic *et al*. (2011).

After cleavage by α- and β-secretases, the C-terminal fragments of APP, CTF (C83) produced by α-secretase and CTF (C99) or CTF (C89) produced by β-secretase, remain

membrane-bound and are further processed via several γ-secretase cleavages. The γ-secretase holoenzyme is composed of four proteins, PSEN, nicastrin, APH1 and PEN2 (De Strooper *et al.* 1998, Wolfe *et al.* 1999, Kimberly *et al.* 2003). The first endopeptidase cleavage at the ε or the alternative ε' cleavage site produces the APP intracellular domain (AICD). In the non-amyloidogenic pathway, cleavage of C83 releases a small p3 peptide and the AICD fragment. In the amyloidogenic pathway, the ε cleavage of C99 releases AICD in the cytosol. Subsequent carboxylpeptidase cleavages of the membrane-bound peptide produce Aβ peptides of different lengths: Aβ38, Aβ40, Aβ42 or Aβ43 (Qi-Takahara *et al.* 2005, Takami *et al.* 2009, Chávez-Gutiérrez *et al.* 2012). Of these, Aβ40 is the most common. The longer forms, especially Aβ42, have a high propensity to polymerise into oligomers and form plaques.

All causative genes linked to EOAD are part of the APP processing cascade. Most mutations cause an increase in the relative levels of Aβ42 (Scheuner *et al.* 1996). Pathogenic *APP* mutations cluster in the Aβ domain, its vicinity or near the cleavage sites of the secretases. *APP* mutations in the Aβ domain alter the resulting mutant peptide's tendency to self-aggregate (Nilsberth *et al.* 2001). *PSEN1* and *PSEN2* mutations seem to hamper the carboxylpeptidase activity of the γ-secretase complex, resulting in increased production of longer Aβ isoforms (Okochi *et al.* 2013, Fernandez *et al.* 2014).

The molecular mechanisms underlying LOAD are less well-known, though the recent GWAS and NGS studies have shed light on the pathways that are involved in the pathogenesis. In addition to the amyloid pathway, cholesterol/lipid metabolism, endosomal vesicle recycling and the brain's innate immune system and inflammatory response are implicated by the functions of several AD risk genes (Table 1b, Figure 3). Rare mutations in *APP*, *PSEN1*, *PSEN2* and *ADAM10* have been identified in large LOAD families (Kim *et al.* 2009, Cruchaga *et al.* 2012), suggesting that variants in *APP* itself or APP-processing genes can alter the risk for LOAD (Benitez *et al.* 2013) or even segregate with the disease (Kim *et al.* 2009).

APOE and CLU are highly expressed apolipoproteins in the central nervous system (CNS) (Roheim *et al.* 1979, May and Finch 1992), and ABCA7 is involved in the efflux of lipids from cells to lipoproteins (Kim *et al.* 2008). SORL1 is a lipoprotein-binding receptor mediating lipoprotein (including APOE) uptake (Rogaeva *et al.* 2007). All these proteins, along with proteins coded by *CR1* and *PICALM*, are also linked to Aβ clearance from the brain (Lambert *et al.* 2009, Castellano *et al.* 2011, Kim *et al.* 2013, Zhao *et al.* 2015). SORL1, BIN1 and PICALM are involved in regulating endosomal vesicle recycling, controlling the balance between non-amyloidogenic and amyloidogenic pathways. SORL1 is directly involved in APP recycling via endocytic pathways and thus regulating Aβ production (Rogaeva *et al.* 2007). PICALM regulates the production of Aβ42 by modulating γ-secretase activity (Kanatsu *et al.* 2014).

The brain's innate immune system, particularly microglial clearance of Aβ has emerged as an important pathway related to AD pathogenesis. Proteins coded by *CR1*, *CD33* and *TREM2* are involved in the microglial response to Aβ accumulation (Lambert *et al.* 2009, Griciuc *et al.* 2013, Ulrich *et al.* 2014).

Non-genetic factors also contribute to the pathogenesis and many of them act through the amyloid pathway. Brain ischemia activates β-secretase cleavage resulting in increased Aβ production (Sun *et al.* 2006). It also causes increased production of reactive oxygen species (ROS) in the mitochondria which activates BACE1 and further increases Aβ production (Guglielmotto *et al.* 2009). Aβ hinders the oxidative phosphorylation capacity of mitochondria, leading to further increased ROS production (Moreira *et al.* 2009). Glucose metabolism is also linked to AD. Both Aβ and insulin are degraded by the same insulin degrading enzyme (Kurochkin and Goto 1994). Furthermore, Aβ can bind to the insulin receptor, causing insulin resistance (Bedse *et al.* 2015). Thus, the pathogenesis of LOAD seems to result from a complex interplay of genetic and environmental risk factors (Figure 3).

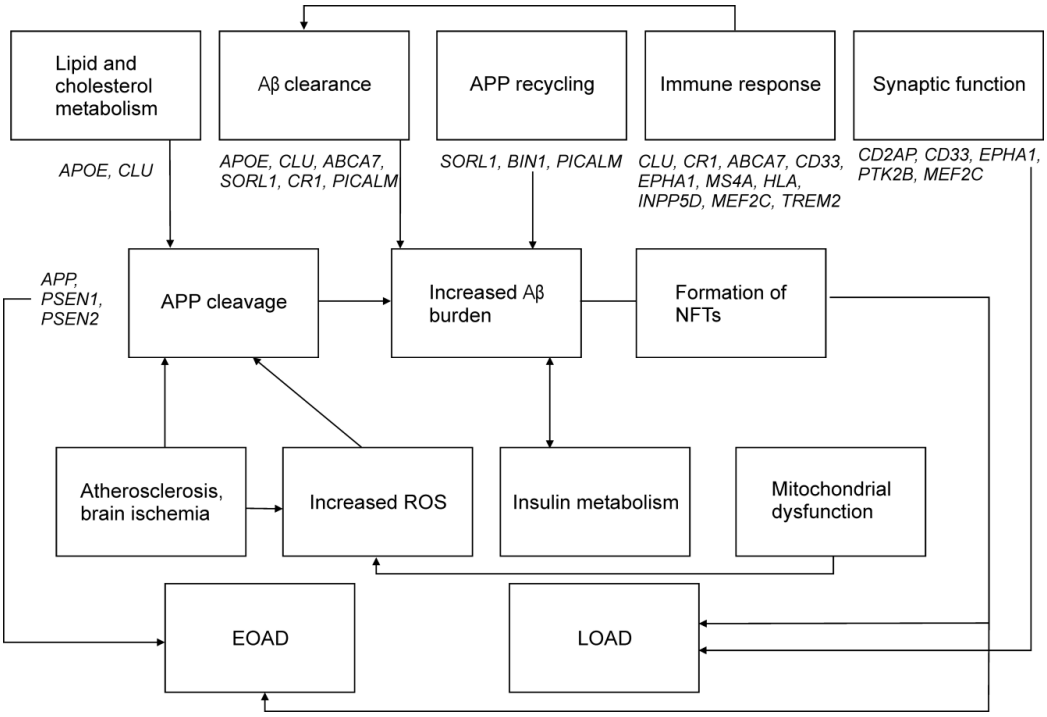

Figure 3. A hypothetical model of the different pathways and genes linked to early-onset (EOAD) and late-onset Alzheimer's disease (LOAD). APP = amyloid beta precursor protein, NFT = neurofibrillary tangle, ROS = reactive oxygen species.

2.3. Frontotemporal dementia

Frontotemporal dementia (FTD, OMIM #600274) is a clinical term referring to a group of progressive neurodegenerative diseases that are clinically characterised by changes in behaviour, deficits in understanding and producing language, and cognitive decline (Bang *et al.* 2015). In 1892, Arnold Pick described a patient with presenile dementia,

aphasia and lobar atrophy (Pick 1892). The distinctive argyrophilic globular neuronal cytoplasmic inclusions and swollen cells were detected by A. Alzheimer (Alzheimer 1911). These histological lesions became known as Pick bodies and Pick cells and the disease was accordingly named Pick's disease (Gans 1925, Onari and Spatz 1926).

Despite the early description of the phenotype, frontotemporal dementia remained mainly unrecognised until the 1980s and most patients were diagnosed as AD (Gustafson 1987, Neary *et al.* 1988). The clinical and neuropathological criteria for diagnosing FTD were suggested in 1994 (The Lund and Manchester groups 1994). The historical term Pick's disease is currently only used to describe a single FTD subgroup with the tau-positive Pick body inclusions.

2.3.1. Epidemiology

Considering all age groups, FTD is the third most common form of degenerative dementia worldwide, preceded by AD and dementia with Lewy bodies (DLB) (Bang *et al.* 2015). In the early-onset group (< 65 years) it is the second most common dementia (Ratnavalli *et al.* 2002, Rascovsky *et al.* 2011) but the estimates on overall prevalence in all age groups vary from 2.7 / 100 000 in the Netherlands (Rosso *et al.* 2003) to 35 / 100 000 in Italy (Bernardi *et al.* 2012, Gilberti *et al.* 2012). In Finland the prevalence of FTD is 26.8 / 100 000 in the age group of 45 – 70 year-olds (Luukkainen *et al.* 2015).

Studies on the incidence of FTD are scarce. The reported incidences range from 1.3 / 100 000 (Garre-Olmo *et al.* 2010) to 3.5 – 4 / 100 000 (Mercy *et al.* 2008, Knopman and Roberts 2011). The mean incidence during a 5-year period was 5.54 / 100 000 in the age group 45 – 65 years in Northern Finland (Luukkainen *et al.* 2015).

2.3.2. Clinical features

FTD can be divided into two main categories depending on the initial clinical manifestations. The behavioural-variant FTD (bvFTD) presents with changes in personality and behaviour, and deficits in executive functions (Rascovsky *et al.* 2011). This type is the most common FTD, comprising 50% of FTD patients, with the typical age of onset before 65 years (Johnson *et al.* 2005, Josephs *et al.* 2011). The other category is characterised by language difficulties as the presenting symptom. Patients with non-fluent variant primary progressive aphasia (NFV-PPA) have progressive impairment of speech production and grammar, while patients with semantic-variant primary progressive aphasia (SV-PPA) have progressive difficulties in naming objects and impairment of single-word comprehension but preserved speech production (Gorno-Tempini *et al.* 2011). NFV-PPA is the second most common type of FTD that accounts for 25% of patients, the remaining 20 to 25% of FTD being SV-PPA (Johnson *et al.* 2005). As the disease progresses, the distinctive clinical features of behavioural and language variants begin to converge. The degenerative pathological process leads to global cognitive impairment and motor deficits (Bang *et al.* 2015). Mild motor neuron disease develops in up to 40% of FTD patients, more often associated with the bvFTD variant

(Burrell *et al.* 2011). Parkinsonism is seen in 20% of patients, again more prominent in the bvFTD group (Bang *et al.* 2015).

A brain MRI or CT reveals bilateral frontal and anterior temporal lobe atrophy (Rosen *et al.* 2002). Hypoperfusion or hypometabolism of the affected brain areas are demonstrable with functional brain imaging, such as fluorodeoxyglucose-PET (FDG-PET), functional MRI or SPECT (single-photon emission computed tomography) (Le Ber *et al.* 2006).

2.3.3. Neuropathology

The clinical manifestations of FTD result from different entities of frontotemporal lobar degenerations (FTLD). The different clinical presentations reflect the underlying patterns of brain atrophy. In bvFTD, symmetrical atrophy of the frontal lobes, insula, anterior cingulate and anterior temporal lobes is the typical pattern. SV-FTD results from asymmetric atrophy of the left anterior inferior temporal lobe. NFV-PPA is characterised by asymmetric atrophy of the perisylvian cortex. (Rosen *et al.* 2002)

Microscopical examination of the brain of a FTD patient reveals neuronal loss, gliosis and microvacuolar changes (spongiosis) in frontal lobes, anterior temporal lobes, anterior cingulate cortex and the insular cortex (Rosen *et al.* 2002). Abnormal protein inclusions are seen in neurons and glia cells (Figure 4). Based on the composition of these inclusions, FTLD can be divided into three main types: FTLD-TAU (with microtubule-associated protein tau -positive inclusions), FTLD-TDP (with transactive response (TAR) DNA-binding protein 43, TDP-43-positive inclusions) and FTLD-FUS (with fused-in-sarcoma, FUS-positive inclusions). These three types comprise nearly all FTLD. Rare FTLD cases, different from the main types, such as FTLD-UPS (with ubiquitin proteasome system/p62, UPS-positive inclusions) are also known (Mackenzie *et al.* 2010).

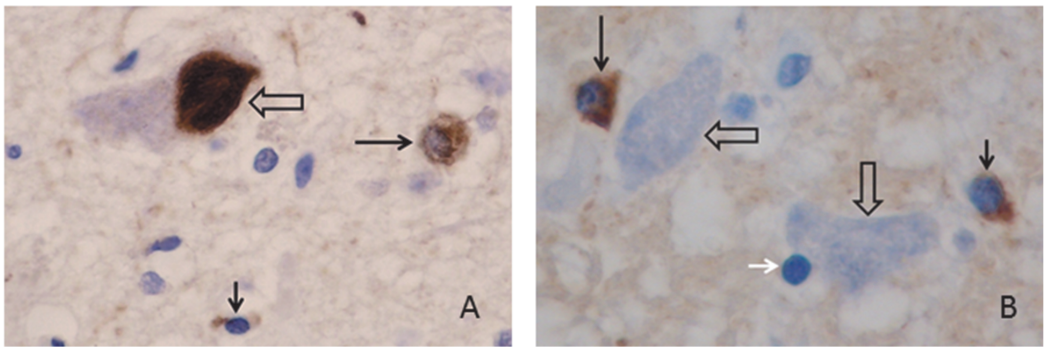

Figure 4. Frontotemporal dementia with parkinsonism due to the tau S305S mutation. **(A)** A frontal cortical neuron harbours a prominent cytoplasmic inclusion positive for hp-tau (open arrow). The cytoplasms of an astrocyte (long arrow) and an oligodendrocyte (short arrow) are more weakly immunopositive for hp-tau. **(B)** The cytoplasm of one oligodendrocyte (short black arrow) and that of one astrocyte (long black arrow) are hp-tau positive. Another oligodendrocyte (short white arrow) is hp-tau negative as is also the cytoplasm of two neurons (open arrows). Courtesy of Professor Hannu Kalimo.

FTLD-TAU accounts for 36 – 50% of all FTLD. It is characterised by paired helical or straight filaments of hyperphosphorylated tau protein in neurons and glia cells. The most common subtypes are Pick's disease, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (Baborie *et al.* 2011, Josephs *et al.* 2011, Sieben *et al.* 2012). Other, less common, subtypes of FTLD-TAU are argyrophilic grain disease (Braak and Braak 1987), multiple system tauopathy with dementia (Bigio *et al.* 2001) and diffuse neurofibrillary tangle dementia with calcifications (Kosaka 1994). The different types are identifiable by the distinctive morphology of the tau-inclusions: Rounded cytoplasmic Pick bodies are seen in neurons in Pick's disease (Dickson 2001), astrocytic plaques, pre-tangles, neuritic threads, ballooned neurons and oligodendroglial coiled bodies are typical of CBD (Dickson *et al.* 2002) and PSP is characterised by astrocytic lesions (tufted astrocytes), granular neuronal inclusions and globose tangles (Dickson 1999).

FTLD-TDP accounts for approximately 50% of all FTLD cases (Josephs *et al.* 2011, Sieben *et al.* 2012). This group can be divided into four subtypes (A, B, C and D) based on the morphology and distribution of the TDP43-positive inclusions (Mackenzie *et al.* 2006, Sampathu *et al.* 2006, Mackenzie *et al.* 2011b). FTLD-TDP type A is the most common form. It is characterised by short dystrophic neurites (DN) and crescent-shaped or oval neuronal cytoplasmic inclusions (NCI) in neocortical layer 2. Moderate numbers of NCIs, but no dystrophic neurites are seen in all cortical layers in type B. Long dystrophic neurites but only a few NCIs can be detected in the upper cortical layers in type C, and short DNs and neuronal intranuclear inclusions are typical of type D (Mackenzie *et al.* 2011b).

Approximately 10% of FTLD cases are classified as FTLD-FUS (Mackenzie *et al.* 2011a). This group includes atypical FTLD with ubiquitin inclusions (aFTLD-U) that clinically manifests as sporadic, early-onset FTD with behavioural disturbances but no language impairment or motor symptoms (Mackenzie *et al.* 2008, Roeber *et al.* 2008, Neumann *et al.* 2009a). Other FUS pathologies are neuronal intermediate filament inclusion disease (Neumann *et al.* 2009b) and basophilic inclusion body disease (Munoz *et al.* 2009). The FUS inclusions in aFTLD-U, NCIs and vermiform neuronal intranuclear inclusions, are prominent in the dentate gyrus (Mackenzie *et al.* 2011a).

2.3.4. Genetics

Up to 40% of FTD patients have a family history of dementia and autosomal dominant inheritance is evident in 10 – 15% of all cases (Goldman *et al.* 2005, Rohrer *et al.* 2009). Mutations in four genes cover more than half of all inherited cases (Table 2a): the most common mutation is the hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9orf72*), followed by mutations in granulin (*GRN*) and microtubule-associated protein tau (*MAPT*).

Table 2a. Genes causative of frontotemporal dementia (FTD). ALS = amyotrophic lateral sclerosis, MND = motor neuron disease. Frequency indicates proportion of inherited FTD. Rare variants are seen in less than 5% of patients. Data adapted from Bang *et al*. (2015) and Woollacott and Rohrer (2016).

Genes	Frequency	Pathways	Clinical presentation	Neuropathological presentation	Reference
C9orf72	13 – 50%	endosomal trafficking, RNA-foci formation, transcription processing	bvFTD (with or without MND), ALS	FTLD-TDP type B or C	DeJesus-Hernandez *et al.* (2011), Renton *et al.* (2011)
GRN	5 – 20%	lysosome-mediated protein degradation, neurotrophic function, inflammatory reaction	bvFTD,NFV-PPA, CBD	FTLD-TDP type A	Baker *et al* (2006), Cruts *et al.* (2006)
MAPT	5 – 20%	microtubule stabilisation	bvFTD, parkinsonism	FTLD-TAU, CBD, PSP	Wilhelmsen *et al.* (1994), Hutton *et al.* (1998)
TARDBP	rare	transcription, translation, splicing, RNA transport	FTD-MND, MND	FTLD-TDP A or B	Borroni *et al*. (2009), Synofzik *et al*. (2014)
FUS	rare	transcription, translation, splicing, RNA transport, DNA damage repair	FTD-MND, MND, bvFTD	FTLD-FUS	Kwiatkowski *et al.* (2009), Ticozzi *et al.* (2009), Van Langenhove *et al.* (2010)
VCP	rare	ubiquitin-proteasome-mediated protein degradation	FTD	FTLD-TDP type D, FTLD-FUS	Watts *et al.* (2004)
CHMP2B	rare	lysosome-mediated protein degradation, autophagy	bvFTD, FTD-MND	FTLD-UPS	Skibinski *et al.* (2005)
TBK1	rare	autophagy, protein homeostasis, vesicle transport	bvFTD with or without MND, PPA	TDP-43	Freischmidt *et al.* (2015), Gijselinck *et al.* (2015), Le Ber *et al.* (2015), Pottier *et al.* (2015)
SQSTM1	rare	autophagy, protein homeostasis, vesicle transport	FTD-MND	TDP-43?	Le Ber *et al.* (2013)
UBQLN2	rare	autophagy, protein homeostasis, vesicle transport	ALS-FTD	TDP-43?	Gellera *et al.* (2013)
CCNF	rare	ubiquitin-mediated protein degradation	ALS-FTD	not known	Williams *et al.* (2016)
CHCHD10	rare	mitochondrial function	ALS-FTD	not known	Bannwarth et al. (2014)

Table 2b. Genes associated with frontotemporal dementia (FTD). OR = odds ratio, MAF = minor allele frequency. Data adapted from Bang *et al*. (2015) and Woollacott and Rohrer (2016).

Associated loci	Pathway	Risk variant	Impact	MAF	Reference
TMEM106B	protein metabolism, RNA metabolism	rs1990622	low (OR < 2)	> 10%	Van Deerlin *et al.* (2010)
RAB38/ CTSC	lysosomal function	rs302668	low (OR < 2)	> 10%	Ferrari *et al.* (2014)
HLA-DRA, HLA-DRB5	immune response	rs9268877	low (OR < 2)	> 10%	Ferrari *et al.* (2014)

The *C9orf72* hexanucleotide expansion was identified in FTD and ALS patients using NGS-based methods (DeJesus-Hernandez *et al.* 2011, Renton *et al.* 2011). The expansion is a common cause for both ALS and FTD in the Finnish population; it was detected in 113 of 402 ALS patients (28.1%) and in 22 of 75 FTD patients (29.3%) (Renton *et al.* 2011). Worldwide, *GRN* and *MAPT* mutations are common in FTD, but among Finnish FTD patients they are rare. Two studies on FTD patients from Northern Finland identified no causative mutations in either *GRN* (Krüger *et al.* 2009) or *MAPT* (Kaivorinne *et al.* 2008). Thus far, only one causative *MAPT* mutation (p.S305S resulting in increased exon 10 splicing and 4R tau in cell models) has been described in Finland (Skoglund *et al.* 2008). Based on data from the Alzheimer Disease & Frontotemporal Dementia Mutation Database (Cruts *et al.* 2012) and the most recent publications, 82 different pathogenic mutations have been reported in *GRN* in different populations (Cioffi *et al.* 2016, Shi *et al.* 2016, Taghdiri *et al.* 2016), and at least 50 causal *MAPT* mutations are currently known (Tacik *et al.* 2015a, Tacik *et al.* 2015b, Shi *et al.* 2016, Tacik *et al.* 2016, Tang *et al.* 2016). Causal mutations in the other associated genes besides *GRN* and *MAPT* are rare in pure FTD (Bang *et al.* 2015). Three risk modifying loci have been identified using GWAS (Table 2b).

2.3.5. Hypotheses on pathogenesis

As FTD is associated with genetic variation in several genes with different biological functions, it is expected that multiple disease mechanisms are involved in the pathogenetic process. It is noteworthy that there is no clear correlation between genetics and neuropathology. A small number of FTD-TAU cases have mutations in the *MAPT* gene, and FTD-TDP is more often linked to mutations in *GRN* and *C9orf72* than *TARDBP* (Table 2a). This suggests that the neuropathology results from more complex interactions.

Known functions of the FTD-associated genes cluster in different pathways. Dysregulation of RNA metabolism (transcription, processing, transport and degradation) is implicated by *C9orf72*, *TARDBP* and *FUS*. Different possible pathogenetic mechanisms of *C9orf72* expansions have been proposed. Several studies point to a gain-of-function mechanism, either by protein-sequestering RNA molecules or dipeptide repeat protein-mediated toxicity. Both have been suggested to induce nuclear stress and impair nucleocytoplasmic trafficking (reviewed by Hausler *et al.* (2016).

Recent co-expression network analysis by Ferrari *et al.* (2016) implicated three pathways (Figure 5): (1) the DNA and chromatin pathway (*MAPT* and *GRN*), (2) immune- and lysosomal-related processes in microglia (the *HLA* locus, *CTSC, GRN* (Lui *et al.* 2016)), and (3) autophagy and ubiquitin-mediated protein degradation (*TMEM106B, C9orf72, VCP, UBQLN2*).

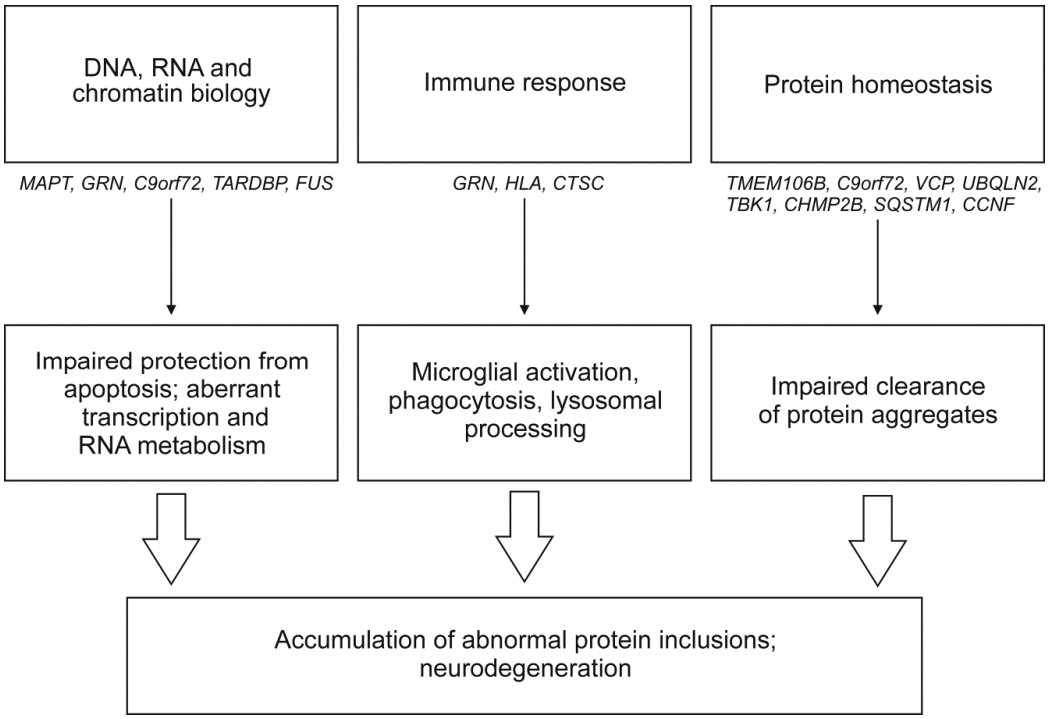

Figure 5. A hypothetical model of the pathways involved in the pathogenesis of frontotemporal lobar degeneration (FTLD). Data adapted from Ferrari *et al*. (2016) and the publications listed in Tables 2a and 2b.

2.4. α-synucleinopathies

The term α-synucleinopathy is used to describe a spectrum of neurodegenerative diseases characterised by the neuropathological hallmark of abnormal accumulation of insoluble α-synuclein aggregates in neuronal or glial cells (Spillantini *et al.* 1997). The characteristic neuronal intracytoplasmic eosinophilic inclusions (Lewy bodies) were first described by Friedrich Lewy in 1912 (Lewy 1912). The group of α-synucleinopathies includes Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), now thought to represent a continuum of the same underlying pathology.

2.4.1. Parkinson's disease

In 1817, James Parkinson described a series of patients with shaking palsy. The patients had resting tremor, disturbances of posture and gait, and diminished muscle strength (Parkinson 1817). This clinical presentation was later named Parkinson's disease (OMIM #168600).

2.4.1.1. Epidemiology

The estimated mean worldwide prevalence of PD is 300 / 100 000 (range 31 – 970 / 100 000) (Wirdefeldt *et al.* 2011). In Finland, the prevalence has been estimated at 166 / 100 000 (Kuopio *et al.* 1999). The frequency increases with increasing age with an estimated 1% of people over 60 years and 4% of people over 80 years of age affected (de Lau and Breteler 2006).

PD incidence across all age groups varies from 1.5 to 22 / 100 000 person-years. A marked increase in incidence, 410 – 529 / 100 000 person-years, is seen in the older age groups (> 65 years of age) (Wirdefeldt *et al.* 2011).

2.4.1.2. Clinical features

PD is characterised by resting tremor, bradykinesia, rigidity and impairment of postural reflexes. The diagnosis is based on these typical clinical symptoms, exclusion of other possible causes and supportive features, such as unilateral onset of the symptoms (Hughes *et al.* 1992).

The first symptoms typically start unilaterally and contralateral symptoms develop within a few years. The patients may develop a shuffling gait and absent arm swing. Bradykinesia may cause hypomimia and decreased letter size in hand writing, micrographia. Limb tremor, especially pill-rolling type of hand tremor, is commonly seen (Jankovic 2008). Impairment of postural reflexes may lead to falls and injuries.

The patients may also have pre-motor symptoms which can appear even a decade before the typical PD symptoms. These include disturbances in autonomic function (orthostatic hypotension, constipation, excessive sweating), sleep disturbances (shallow sleep, frequent awakenings, excessive daytime sleepiness), neuropsychiatric symptoms (visual hallucinations, impulse control disorders, depression, anxiety), dementia and sensory symptoms (olfactory loss, limb pain) (reviewed by Sveinbjornsdottir (2016)).

Conventional MRI or CT imaging are not diagnostic in PD (Hu *et al.* 2001), but MRI can be used to rule out other causes for parkinsonism, such as basal ganglia tumours. Functional imaging can be used to monitor cerebral flow and hypometabolism (PET) or dopamine transporter activity (DaT-SPECT) (Benamer *et al.* 2003).

2.4.1.3. Neuropathology

The pathology of PD primarily affects the dopaminergic neurons of the substantia nigra that project to the putamen and caudate nucleus in the midbrain. This neuronal loss can be seen as depigmentation in the substantia nigra and locus coeruleus, correlating

with loss of dopaminergic and noradrenergic neurons in these brain areas (Dickson 2012). Microscopically, the typical finding in PD is the presence of Lewy bodies (LB) and Lewy neurites (LN), collectively referred to as Lewy-related pathology (LRP) (Figure 7).

LBs are cytoplasmic inclusions composed of fibrillary α-synuclein, whereas LNs are depositions of α-synuclein in neuronal processes (Spillantini *et al.* 1997). LBs are not restricted to the SN; instead, they are seen in multiple brain areas (Jellinger 1991). A staging scheme of α-synuclein pathology based on Lewy neurites has been proposed (Braak *et al.* 2004). The model suggests that α-synuclein inclusions first appear in the dorsal vagal nucleus and in the anterior olfactory nucleus, then the locus coeruleus and substantia nigra, and in the later stages spread to the basal forebrain, amygdala and the medial temporal lobe. The hypothesis is that non-motor symptoms correlate with the earliest α-synuclein pathology and the typical motor symptoms follow when the pathology reaches the substantia nigra. The last stages with cortical α-synuclein pathology would then be associated with cognitive problems. The general principles of this hypothesis have been confirmed in several PD cohorts (Jellinger 2003, Parkkinen *et al.* 2003), but the model does not fit all LB disorders equally well (Dickson *et al.* 2010).

2.4.1.4. Genetics

Most PD cases are sporadic with late onset. Approximately 10% of patients have a positive family history, sometimes compatible with autosomal dominant inheritance (Barrett *et al.* 2015). In the Finnish EOPD cohort a positive family history was reported by 30.6% of the patients with 11.8% of the patients having an affected first-degree relative (Ylikotila *et al.* 2015).

The first causative mutation linked to PD, p.Ala53Thr in the gene coding for α-synuclein (*SNCA*), was found in a large Italian kindred and in Greek PD families (Polymeropoulos *et al.* 1997). Haplotype analysis suggested that the Italian and Greek families originated from a common ancestor (Athanassiadou *et al.* 1999). Only a few other *SNCA* point mutations have been described, p.Ala30Pro (Krüger *et al.* 1998), p.Glu46Lys (Zarranz *et al.* 2004), p.His50Gln (Appel-Cresswell *et al.* 2013), and p.Gly51Asp (Kiely *et al.* 2013), suggesting that they are rare causes of inherited PD. Triplications (Singleton *et al.* 2003) and duplications (Chartier-Harlin *et al.* 2004) of *SNCA* are also causative of autosomal dominant PD and have a dosage-dependent effect on the clinical presentation (Fuchs *et al.* 2007). Genetic variation in *SNCA* has also proven to be associated with a risk for sporadic PD (Nalls *et al.* 2011).

Linkage analyses in large families allowed the identification or several other loci causative of familial PD. In addition to *SNCA*, *LRRK2* and *VPS35* have been linked to autosomal dominant PD. Eight genes have been detected in autosomal recessive PD: *PARK2*, *PINK1*, *DJ-1/PARK7*, *ATP13A2*, *PLA2G6*, *FBXO7*, *DNAJC6*, and *SYNJ1*. However, these causative genes explain only a small fraction of all PD cases. The clinical presentation varies from typical early-onset PD to atypical parkinsonism with juvenile onset (Table 3a).

Family-based studies and candidate gene studies identified high-risk variants in *LRRK2* and *GBA*. GWAS on sporadic PD have identified 25 additional predisposing loci with common variants that confer a low risk (Table 3b).

Table 3a. Known causative genes in Parkinson's disease (PD). Data from Bras *et al*. (2015) and the original publications. AD = autosomal dominant, AR = autosomal recessive, DLB = dementia with Lewy bodies.

Disease genes	Pathway	Inheri-tance	Frequency	Type of mutations	Clinical presentation	Reference
SNCA	synaptic function, mitochondrial function, autophagy/lysosomal degradation	AD	rare	point mutations, duplication and triplication	early-onset PD, sometimes with DLB features (multiplications, p.Glu46Lys, p.Ala53Thr)	Polymeropoulos *et al.* (1997)
LRRK2	synaptic function, immune system, autophagy/lysosomal degradation, mitochondrial function	AD	1 – 2% (10% of AD PD)	point mutations	late-onset PD (familial and sporadic), levodopa-responsive, slow progression	Paisán-Ruíz *et al.* (2004), Zimprich *et al. (*2004*)*
VPS35	autophagy/lysosomal degradation, endocytosis	AD	rare	point mutations	late-onset PD, levodopa-responsive	Zimprich *et al.* (2011), Vilariño-Güell *et al.* (2011)
PARK2 / Parkin	mitochondrial function, ubiquitination, synaptic function	AR	1%	exonic deletions and duplications, point mutations	early-onset PD (familial and sporadic), foot dystonia, psychiatric symptoms	Kitada *et al.* (1998)
PINK1	mitochondrial function	AR	rare	point mutations	young-onset (< 40 years) PD, lower limb dystonia, slow progression, levodopa-responsive	Valente *et al.* (2004)
DJ1/ PARK7	immune system, mitochondrial function	AR	rare	point mutations	young-onset (< 40 years) PD, levodopa-responsive	Bonifati *et al.* (2003)
ATP13A2	mitochondrial function, autophagy/lysosomal degradation	AR	rare	point mutations	juvenile-onset parkinsonism (Kufor–Raked syndrome), supranuclear gaze palsy, spasticity, dementia, poor response to levodopa	Ramirez *et al.* (2006)
PLA2G6	mitochondrial function	AR	rare	point mutations	young-onset (< 40 years) parkinsonism, dystonia, cognitive decline, brain iron accumulation in most patients	Paisan-Ruiz *et al.* (2009)
FBXO7	ubiquitination, mitochondrial function	AR	rare	point mutations	young- or early-onset parkinsonism, pyramidal signs	Di Fonzo *et al.* (2009)
DNAJC6	synaptic function, endocytosis	AR	rare	point mutations	young-onset parkinsonism with rapid progression, early-onset parkinsonism with slow progression	Edvardson *et al.* (2012)
SYNJ1	synaptic function, endocytosis	AR	rare	point mutations	early-onset parkinsonism, levodopa-induced dyskinesia	Quadri *et al.* (2013), Krebs *et al.* (2013)

Table 3b. Known risk genes and loci in Parkinson's disease (PD). Data from Bras et al. (2015) and the original publications. GWAS = genome wide association study, MAF = minor allele frequency, OR = odds ratio.

Risk genes	Pathway	Risk variant	Impact	MAF	Identified with	Reference
GBA	immune system, autophagy/lysosomal degradation, metabolic pathways	rs76763715, rs421016	high (OR ≥ 2)	< 10%	candidate gene approach	Tayebi *et al.* (2003)
LRRK2	synaptic function, immune system, autophagy/lysosomal degradation	rs34778348, rs33949390	high (OR ≥ 2)	< 10%	candidate gene approach	Di Fonzo *et al.* (2006) Ross *et al.* (2008b)
SNCA	synaptic function, mitochondrial function, autophagy/lysosomal degradation	Rep1 allele-length, rs356182	low (OR < 2)	> 10%	candidate gene approach, GWAS	Maraganore *et al.* (2006), Nalls *et al.* (2014)
Risk loci	Pathway	Risk variant	Impact	MAF	Identified with	Reference
MAPT	microtubule stabilisation, axonal transport	rs17649553	low (OR < 2)	> 10%	GWAS	Simón-Sánchez *et al.* (2009)
RAB7L1	autophagy/lysosomal degradation	rs823118	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
BST1	immune system	rs11724635	low (OR < 2)	> 10%	GWAS	Satake *et al.* (2009)
HLA-DRB5	immune system		low (OR < 2)	> 10%	GWAS	Pankratz *et al.* (2009)
GAK	autophagy/lysosomal degradation, synaptic function, endocytosis	rs34311866, rs34884217	low (OR < 2)	> 10%	GWAS	Pankratz *et al.* (2009)
ACMSD	tryptophan metabolism, metal ion binding	rs6430538	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
STK39	immune system, protein kinase binding, cellular stress response	rs1474055	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
SYT11	synaptic function, transporter activity, metal ion binding, substrate for PARK2	rs35749011, rs114138760	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
FGF20	growth factor activity, FGF receptor binding	rs591323	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
STX1B	synaptic function, SNAP receptor activity, protein domain-specific binding	rs14235	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
GPNMB	integrin binding, heparin binding	rs199347	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
SIPA1L2	GTPase activator	rs10797576	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
INPP5F	phosphoric ester hydrolase activity	rs117896735	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
MIR4697HG	non-protein coding RNA	rs329648	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
GCH1	GTP binding, calcium ion binding	rs11158026	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
VPS13C	endocytosis	rs2414739	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
DDRGK1	protein binding	rs8118008	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
MCCC1	biotin carboxylase activity, methylcrotonoyl-CoA carboxylase activity	rs12637471	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
SCARB2	autophagy/lysosomal degradation, receptor activity, enzyme binding	rs6812193	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
CCDC62	nuclear receptor coactivator	rs11060180	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
RIT2	synaptic function, GTP binding, calmodulin binding	rs12456492	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)
SREBF2	chromatin binding, cholesterol and steroid metabolism	rs11868035	low (OR < 2)	> 10%	GWAS meta-analysis	Nalls *et al.* (2014)

2.4.1.5. Hypotheses on pathogenesis

Several molecular pathways interacting with environmental factors are involved in the pathogenesis of PD (Figure 6), but the exact mechanisms are still elusive. The central pathway involves the formation of α-synuclein aggregates and defective clearance of these aggregates leads to the accumulation of LBs and LNs. Several PD-associated genes are known to regulate mitochondrial function, especially mitochondrial dynamics. Mitochondrial dysfunction is linked to oxidative damage, α-synuclein aggregation, toxins, Ca^{2+} metabolism and glutamate-mediated excitotoxicity (Ryan *et al.* 2015). Excitotoxicity is also controlled by dopamine (Vaarmann *et al.* 2013). Local immune response (microglial activation) is suggested by DJ-1/PARK7. Impairment of synaptic function is implicated by several risk genes.

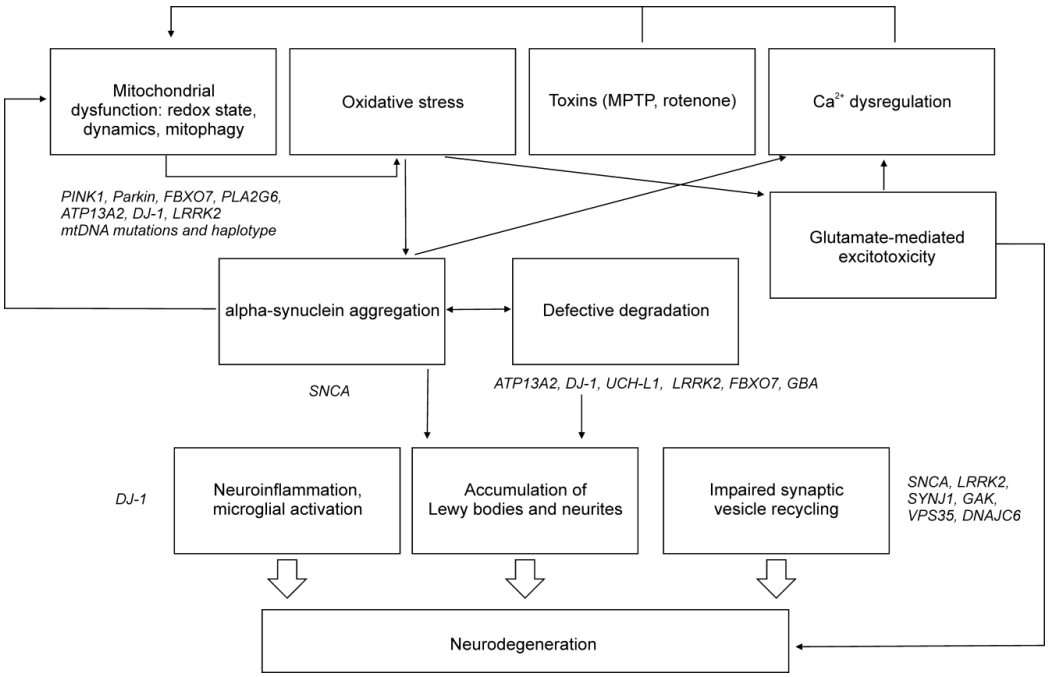

Figure 6. A hypothetical presentation of the pathways implicated in the pathogenesis of Parkinson's disease (PD). MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

2.4.2. Dementia with Lewy bodies

Dementia with Lewy bodies (DLB, OMIM #127750) is a common form of dementia, estimated to represent up to 20% of all dementias (McKeith *et al.* 2004). The association between dementia and cortical Lewy bodies was noted by Okazaki *et al.* (1961). Some twenty years later, the disease entity was named 'diffuse Lewy body disease' (Kosaka *et al.* 1984) but variable terminology was in use until the consensus term 'dementia with Lewy bodies' was adopted in 1996 (McKeith *et al.* 1996).

2.4.2.1. Epidemiology

The estimated prevalence of DLB varies greatly between studies. A recent systematic review of 22 studies by Hogan *et al.* (2016) showed point prevalence estimates from 0.02 to 33.3 per 1000 person years, increasing with age. The highest of these point prevalences (33.3/1000) was from a Finnish population-based study (Rahkonen *et al.* 2003). The incidence of DLB ranged from 0.5 to 1.6 per 1000 person years (Hogan *et al.* 2016).

2.4.2.2. Clinical features

Clinically, DLB typically manifests as a combination of dementia and parkinsonism. The revised diagnostic criteria of DLB list the defining clinical features. The central feature of DLB is progressive fluctuating cognitive decline that interferes with daily living. The clinical findings overlap those seen in Parkinson's disease dementia (PDD) (Lippa *et al.* 2007). Cognitive impairment is often the first symptom in DLB, and its onset is used for distinguishing DLB from PDD: when dementia develops within 12 months of the onset of parkinsonian symptoms (if they are present), the primary diagnosis is DLB. Two of the core features, fluctuating cognition, visual hallucinations and parkinsonian symptoms, are required for DLB diagnosis (McKeith *et al.* 2005, Fujishiro *et al.* 2008).

2.4.2.3. Neuropathology

In addition to the typical Lewy bodies and Lewy neurites (Figure 7), neuritic plaques and neurofibrillary tangles are frequently seen in DLB (Mattila *et al.* 1998). Consequently, the neuropathological diagnosis of DLB is based on the abundance and distribution of Lewy-related pathology and absence of concurrent severe (≥ Braak stage IV) neurofibrillary AD pathology (McKeith *et al.* 2005). Three patterns of LRP, i.e. brainstem predominant, limbic and neocortical, have been described and thus the severity of LRP in all these brain areas should be scored (McKeith *et al.* 2005).

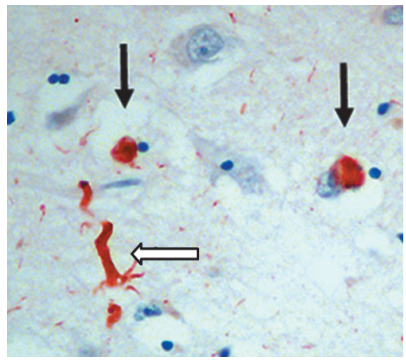

Figure 7. Dementia with Lewy bodies (DLB). α-synuclein immunostaining discloses two rounded Lewy bodies (red inclusions; black arrows), a discontinuous thickened Lewy neurite (open arrow) and tiny scattered background threads in the hippocampal CA2-sector of a patient with DLB. α-synuclein and hematoxylin counterstaining. Courtesy of Professor Hannu Kalimo.

2.4.2.4. Genetics

DLB has been considered a sporadic disorder, but familial aggregation of the clinical core features has been observed (Nervi *et al.* 2011). Large case-control studies have identified AD- and PD-related genes, such as *APOE, LRRK2* and *GBA*, as risk factors for developing DLB (Table 4). Causal segregating variants have not been identified. Linkage to 2q35-36 has been reported in one large family, but the causal gene has not been identified despite extensive candidate gene screening (Bogaerts *et al.* 2007). However, individuals with pathogenic variants in AD- and PD-related genes may have clinical or neuropathological findings compatible with DLB (Table 4). Well-known examples of this clinical variability are the *SNCA* mutations (triplication, p.Glu46Lys and p.Ala53Thr) with diverse phenotypes ranging from typical PD to DLB even within families. The same phenomenon has been noticed for the *APP* (Guyant-Marechal *et al.* 2008), *PSEN1* and *PSEN2* mutations (Meeus *et al.* 2012), supporting the hypothesis that AD, PDD and DLB might in fact represent different clinical presentations of the same underlying pathological continuum.

Table 4. Genes linked to dementia with Lewy bodies (DLB). N/A = not analysed, OR = odds ratio.

Gene / locus	**Mutation**	**Reference**	
SNCA	triplication	Singleton *et al.* (2003)	
	p.Glu46Lys	Zarranz *et al.* (2004)	
	p.Ala53Thr	Morfis and Cordato (2006)	
unknown locus on 2q35-36	not known	Bogaerts *et al.* (2007)	
Risk genes	**Variant**	**Impact**	**Reference**
APOE	ε4	high (OR ≥ 2)	Hardy *et al.* (1994), Bras *et al.* (2014)
GBA	pathogenic mutations (p.Asn370Ser the most frequent)	high (OR ≥ 2)	Clark *et al*. (2009), Tsuang *et al.* (2012)
LRRK2	p.Gly2019Ser	N/A	Ross *et al.* (2006)
SCARB2	rs6812193	low (OR < 2)	Bras *et al.* (2014)
SPTBN1	rs7595929	N/A	Peuralinna *et al.* (2015)
HLA-DPA1/DPB1	rs9277685	N/A	Peuralinna *et al.* (2015)

2.4.2.5. Hypotheses on pathogenesis

The pathogenetic mechanisms leading to DLB are poorly known. As mutations in PD- and AD-linked genes may also manifest as DLB, it can be presumed that the same molecular mechnisms apply to them all. Lysosomal function is suggested to be involved in the aetiology of DLB based on associations with *GBA* and *SCARB2* (Bras *et al.* 2014). The role of environmental or epigenetic factors has not been studied. The role of α-synuclein inclusions in the pathogenesis of PD, DLB and MSA is discussed in Chapter 2.4.4.2.

2.4.3. Multiple system atrophy

Multiple system atrophy (MSA, OMIM #146500) is a rare neurodegenerative disease with progressive autonomic failure, parkinsonism and cerebellar and pyramidal features. The clinical features can occur in various combinations. Early reports of patients with possible MSA date back to the early 1900s (Dejerine and Thomas 1900, Bradbury and Eggleston 1925). For decades, varying nomenclature was used to describe the disease then thought to represent three different entities: olivopontocerebellar atrophy (Dejerine and Thomas 1900), striatonigral degeneration (Adams *et al.* 1964) and Shy–Drager syndrome (Shy and Drager 1960). The term 'multiple system atrophy' was suggested by Graham and Oppenheimer (1969) to combine the three manifestations under a single entity for practical reasons. This practical approach proved to be correct on the neuropathological level when glial cytoplasmic inclusions (GCIs) in oligodendrocytes were identified in the brains of patients from all three entities (Papp *et al.* 1989).

2.4.3.1. Epidemiology

The epidemiology of MSA is poorly known. Based on two retrospective studies, the estimated point prevalence of MSA is 3.4 – 4.9 per 100 000 person years and 7.8 per 100 000 when considering the age group of over 40 year-olds (Schrag *et al.* 1999). Incidence is estimated to be 0.6 – 0.7 per 100 000 person years (Bower *et al.* 1997).

2.4.3.2. Clinical features

The characterisctic clinical features of MSA are autonomic failure, parkinsonism, cerebellar ataxia and/or corticospinal tract dysfunction (Gilman *et al.* 2008). The mean age of onset is 55 – 58 years and the mean survival 7 – 9 years (O'Sullivan *et al.* 2008). Autonomic symptoms involve the gastrointestinal, cardiovascular and urogenital systems. Typical symptoms include bladder or erectile dysfunction and orthostatic hypotension. Parkinsonism including bradykinesia with rigidity, tremor or postural instability is seen in most MSA patients. However, the typical pill-rolling rest tremor of PD is uncommon and postural instability is worse in MSA than in PD. Cerebellar ataxia typically manifests as gait ataxia and concurrent cerebellar dysarthria (Gilman *et al.* 2008). Recent reports suggest cognitive decline of variable degree in 14 – 18% of cases (O'Sullivan *et al.* 2008, Brown *et al.* 2010).

Based on the most prominent motor symptom at the time of evaluation, MSA is divided into two categories: MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C). Diagnostic classification is divided into three classes of probable, possible and definite MSA. Probable MSA can be diagnosed in a sporadic patient with adult-onset severe autonomic failure and poorly levodopa-responsive parkinsonism or cerebellar syndrome. Parkinsonism or cerebellar syndrome combined with at least one symptom suggestive of autonomic dysfunction and one additional feature (e.g. structural or functional brain imaging findings suggesting possible MSA-P or MSA-C) are required in possible MSA (Gilman *et al.* 1999).

Neuropathological confirmation of α-synuclein positive glial cytoplasmic inclusions (GCIs) in oligodendrocytes together with neurodegenerative changes in olivopontocerebellar and striatonigral structures is required for a definite MSA diagnosis (Gilman *et al.* 2008).

Structural and functional brain imaging can be useful in diagnostics. Atrophy of the putamen, pontine, and middle cerebellar peduncle revealed by MRI is suggestive of MSA (Seppi *et al.* 2005). Functional FDG-PET imaging can be used to demonstrate striatal or brainstem hypometabolism and differentiate between parkinsonian and cerebellar MSA (Gilman 2005).

2.4.3.3. Neuropathology

Macroscopic examination of an MSA brain shows olivopontocerebellar or striatonigral atrophy of varying degree, broadly corresponding to clinical MSA-C and MSA-P, respectively. Depigmentation of the substantia nigra is a typical finding, especially in MSA-P (Ahmed *et al.* 2012).

Microscopically, MSA is characterised by neuronal loss, gliosis, myelin loss and axonal degeneration (Ahmed *et al.* 2012). Severe neuronal loss is seen especially in the substantia nigra (Ozawa *et al.* 2004). The defining neuropathological finding in MSA is the presence of glial cytoplasmic inclusions in a widespread distribution in multiple brain areas (Figure 8). These inclusions are found in oligodendrocytes near the nucleus or surrounding it. Additionally, neuronal cytoplasmic, neuronal nuclear and glial nuclear α-synuclein-positive inclusions may be detected (Ahmed *et al.* 2012). The morphology of GCIs is variable, with triangular, sickle, half-moon, oval and conical inclusions being the most common (Papp *et al.* 1989). The main constituent of GCIs is α-synuclein (Spillantini *et al.* 1998, Wakabayashi *et al.* 1998), but immunohistochemistry has revealed several other proteins (e.g. ubiquitin, LRRK2, Parkin, p25α) to be part of the protein aggregates (Jellinger and Lantos 2010). GCIs are especially abundant in pyramidal, extrapyramidal, corticocerebellar and preganglionic autonomic regions (Papp and Lantos 1994).

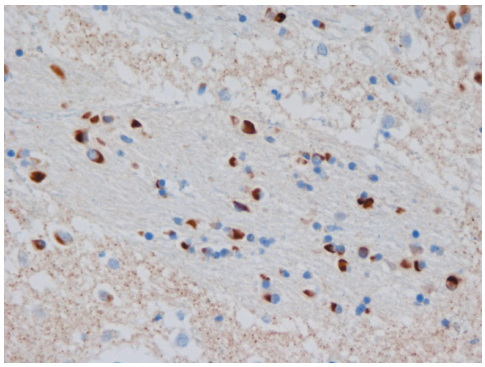

Figure 8. Multiple system atrophy (MSA): In a striatal bundle of myelinated nerve fibres (running from upper left to lower right) the majority of oligodendroglial cells harbour α-synuclein positive cytoplasmic inclusions (brown dots). α-synuclein and hematoxylin counterstaining. Courtesy of Professor Hannu Kalimo.

2.4.3.4. Genetics

Most MSA cases are sporadic. However, a few families with autosomal dominant or recessive inheritance have been described (Soma *et al.* 2006, Hara *et al.* 2007, Wüllner *et al.* 2009, Multiple-System Atrophy Research Collaboration 2013, Itoh *et al.* 2014). For most cases, the underlying mutation is unknown. *SNCA* seems to be involved in two ways. Pathogenic mutations such as p.Gly51Asp and multiplications may result in MSA-like clinical and neuropathological features (Fuchs *et al.* 2007, Kiely *et al.* 2013). Furthermore, certain variants in *SNCA* have been demonstrated to increase MSA risk in European patient cohorts (Al-Chalabi *et al.* 2009, Scholz *et al.* 2009). However, a recent larger GWAS on MSA patients of European ancestry failed to confirm this association (Sailer *et al.* 2016).

An association between MSA and variants in *COQ2* coding for coenzyme Q_2 has been proposed in Japanese patients (Multiple-System Atrophy Research Collaboration 2013), but the finding has not been replicated in other populations (Schottlaender *et al.* 2014, Sharma *et al.* 2014). Similarly, copy number variations of *SHC2* have been linked to MSA in Japanese patients (Sasaki *et al.* 2011), but this association was not replicated in a US patient cohort (Ferguson *et al.* 2014). These discordant findings in different populations suggest a specific genetic aetiology for MSA in Japan.

2.4.3.5. Hypotheses on pathogenesis

The pathogenetic mechanisms of MSA are poorly known. However, a hypothetical model of primary oligodendroglial degeneration has been proposed (Ahmed *et al.* 2012, Fanciulli and Wenning 2015) (Figure 9): *in situ* immunofluorescence protein localisation assays on a human MSA brain have suggested relocalisation of the myelin-stabilising protein p25α from the myelin into the soma of oligodendroglia (Song *et al.* 2007), causing myelin dysfunction, oligodendrocyte swelling and abnormal uptake or overexpression of α-synuclein in the oligodendrocytes (Asi *et al.* 2014, Reyes *et al.* 2014). Myelin dysfunction leads to microglial activation. Oligodendroglial α-synuclein forms fibrils that aggregate into GCIs along with p25α, resulting in the death of oligodendroglia and further microglial activation (Ahmed *et al.* 2012). Misfolded α-synuclein is released into the extracellular space from the dysfunctional oligodendrocytes and may spread in a prion-like manner to other brain areas (Watts *et al.* 2013, Goedert 2015).

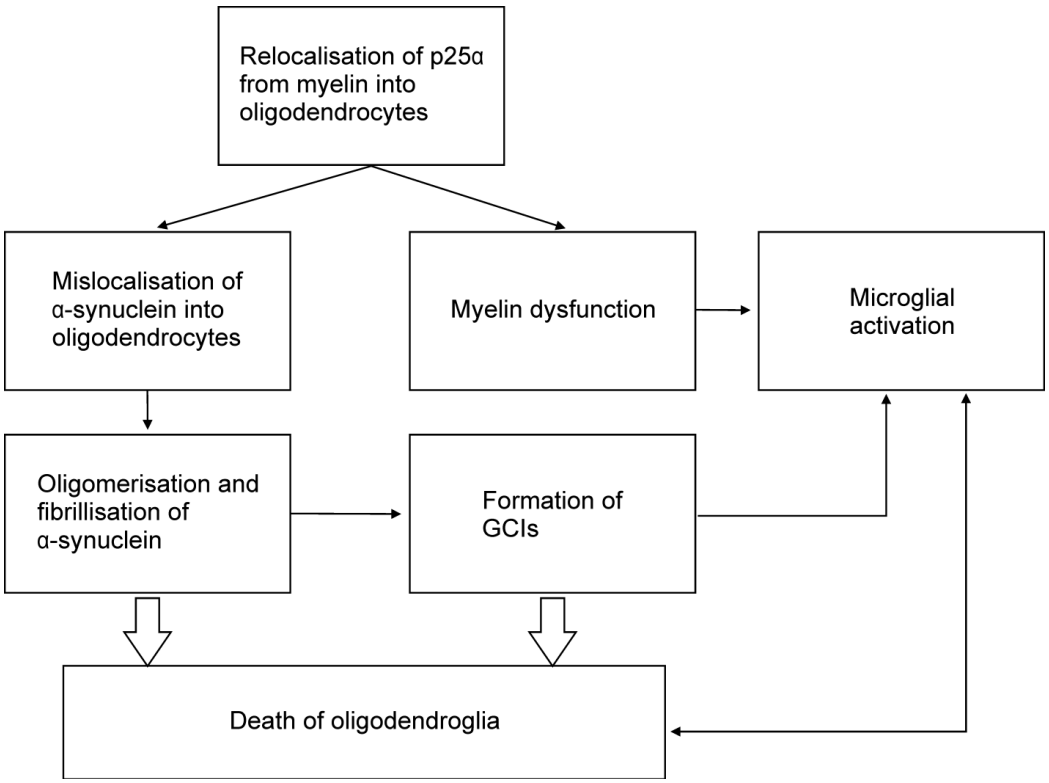

Figure 9. A hypothetical model for the pathogenesis of multiple system atrophy (MSA). Figure based on Ahmed *et al*. (2012), and Fanciulli and Wenning (2015). GCI = glial cytoplasmic inclusion.

2.4.4. Mechanisms of α-synuclein aggregation

2.4.4.1. The structure and function of α-synuclein

SNCA codes for a member of the synuclein protein family. The gene consists of six exons and produces a polypeptide of 140 amino acids. Three different domains have been identified. The N-terminal end (amino acid residues 1 – 60) contains six apolipoprotein binding motifs that can form amphipatic helices, followed by a central hydrophobic NAC region (non Aβ component) essential for aggregation (amino acid residues 61 – 95), and an acidic carboxyterminus (amino acid residues 96 – 140) (Figure 10) (Stefanis 2012).

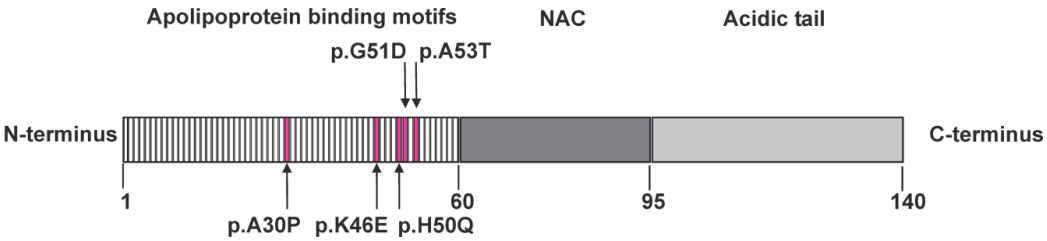

Figure 10. Schematic presentation of the SNCA gene with the locations of pathogenic point mutations marked in pink, based on Stefanis (2012). The N-terminal apolipoprotein binding motifs contain the pathogenic mutations. The NAC domain is essential for β-sheet formation. The N-terminal acidic tail does not form secondary stuctures. Pathogenic point mutations (marked in pink) cluster in the N-terminal portion.

SNCA is highly expressed in the nervous systems, especially in the presynaptic terminals (Maroteaux *et al.* 1988, Jakes *et al.* 1994). The exact functions of SNCA are still somewhat unclear, but it is likely involved in modulation of synaptic activity by participating in vesicle release (Bendor *et al.* 2013). The structure of SNCA is still under debate, but under physiological conditions it seems to reside in the cytoplasm, predominantly as unfolded monomers that interact with membranes forming α-helical assemblies (Fauvet *et al.* 2012, Theillet *et al.* 2016). The balance between unfolded and α-helical structures may be shaken by disease or normal ageing (Gibb and Lees 1988, Parkkinen *et al.* 2003), resulting in excessive amounts of unfolded monomers (Peelaerts and Baekelandt 2016b). The unfolded state is thermodynamically unfavourable, resulting in aggregation of small oligomeric assemblies stabilised by β-sheet formations. These oligomers can assemble into insoluble protofibrils that stack together to form amyloidogenic fibrils (Peelaerts and Baekelandt 2016a).

2.4.4.2. Formation of α-synuclein inclusions

Increased expression resulting from duplications and triplications of wild-type *SNCA* is sufficient to cause aggregation of the protein resulting in neurodegeneration (Singleton *et al.* 2003, Ross *et al.* 2008a, Devine *et al.* 2011). All pathogenic point mutations identified thus far cluster in the N-terminal domain that can form alpha-helical structures upon binding to lipids (Figure 6). They may alter the fibrillisation rate (Conway *et al.* 1998), aggregation propensity (Rutherford *et al.* 2014) and membrane-binding capacity of the protein (Jensen *et al.* 1998).

Oligomeric and fibrillar forms of α-synuclein are toxic to neurons (Winner *et al.* 2011, Pieri *et al.* 2012). They have been shown to impair synaptic (Cheng *et al.* 2011) and mitochondrial function (Elkon *et al.* 2002), increase production of intracellular reactive oxygen species (Junn and Mouradian 2002), disrupt plasma membrane integrity (Volles *et al.* 2001, Volles and Lansbury 2002), and inhibit ubiquitin-mediated protein degradation (Emmanouilidou *et al.* 2010). The oligomers seem capable of spreading from cell to cell and by 'seeding' even initiate pathology, in a similar manner to prions (Yonetani *et al.* 2009, Luk *et al.* 2012, Goedert *et al.* 2016).

Recent reports by Guo *et al.* (2013) and Peelaerts *et al.* (2015) suggest that different α-synuclein fibrillary polymorphs with different conformations (also called strains) lead to different disease phenotypes in mouse models. This concept could well explain the neuropathological and clinical variability observed in α-synucleinopathies.

2.5. Primary familial brain calcification

Primary familial brain calcification (PFBC, OMIM #213600) has previously been known as idiopathic basal ganglia calcification (IBGC) and Fahr's disease. The case described by Theodor Fahr (1930) was generally considered the first report of PFBC and thus the term 'Fahr's disease' was widely adopted to describe the radiological and pathological findings of this disease. However, the calcifications were predominantly found in the white matter and were virtually absent in the basal ganglia (Fahr 1930). According to current knowledge, the calcifications and clinical presentation of this patient could be attributable to hypoparathyroidism (Klein and Vieregge 1998). Additionally, bilateral striatal calcifications in an elderly demented patient were described in the 1850s (Delacour 1850), more likely representing a true case of bilateral basal ganglia calcification. IBGC was the other term used for this disease, but it can no longer be regarded as idiopathic since the genetic aetiology is known in many cases. In addition, the calcifications are not limited to basal ganglia (discussed in detail in Chapter 2.5.3). Consequently, the term 'primary familial brain calcification' is currently the preferred term for this clinical entity (Sobrido *et al.* 2014).

2.5.1. Epidemiology

Bilateral calcifications in the basal ganglia, cerebellum, thalamus and brainstem may be encountered upon brain imaging in 1 – 20% of elderly individuals (Simoni *et al.* 2008, Yamada *et al.* 2013). Most commonly, the calcifications are isolated findings that may be related to ageing (Westenberger and Klein 2014). The calcifications can also be secondary findings caused, for example, by hypoparathyroidism, infection and inflammation, autoimmune disease (lupus erythematosus) and mitochondrial (Kearns-Sayre syndrome), sporadic (Down syndrome) or inherited genetic disease (pseudohypoparathyroidism, Krabbe disease) (Baba *et al.* 2005, Sobrido *et al.* 2014).

PFBC is a rare cause of brain calcifications with an estimated prevalence of less than 1 / 100 000 (Ellie *et al.* 1989, Manyam *et al.* 2001b) and unknown incidence. Some studies have suggested male predominance (Manyam *et al.* 2001b, Nicolas *et al.* 2013a).

2.5.2. Clinical features

PFBC is a progressive disease with clinical manifestations limited to the nervous system. The clinical symptoms of PFBC typically start at the fourth decade of life, but the age at onset can vary from 30 to 60 years even within families (Manyam *et al.* 2001b, Nicolas

et al. 2013a). In a large series of PFBC patients, the most common manifestations were cognitive impairment, psychiatric symptoms and movement disorders (Nicolas *et al.* 2013a). The manifestation of the neuropsychiatric symptoms may range from mild disturbances in memory and focus to psychosis and dementia (Geschwind *et al.* 1999, Benke *et al.* 2004, Shakibai *et al.* 2005, Nicolas *et al.* 2013a). The movement disorder may manifest with parkinsonian features (bradykinesia, rigidity, unsteady gait, mask-like face, diminished blinking, hypophonia) or as hyperkinesia (dystonia, tremor, chorea, dyskinesia) (Manyam *et al.* 2001b). The clinical presentation is variable within and between families and even asymptomatic individuals with calcifications are known (Manyam *et al.* 2001a, Dai *et al.* 2010, Wang *et al.* 2012, Nicolas *et al.* 2013a). Anticipation has been observed in several families, but the contributory factors are not known (Kobari *et al.* 1997, Geschwind *et al.* 1999, Shirahama *et al.* 2010).

PFBC patients have normal serum levels of calcium, phosphorus, alkaline phosphatase, calcitonin and parathyroid hormone, in contrast to patients with calcium metabolism disorders (Bonazza *et al.* 2011).

Brain imaging with CT or MRI reveals bilateral calcifications in the basal ganglia, especially in the internal globus pallidus. The putamen, thalami, caudate and dentate nuclei are often also affected (Manyam *et al.* 1992). Calcifications may also be detected in other brain areas, such as cerebellar gyri, the centrum semiovale, subcortical white matter and the brain stem (Manyam 2005). These calcifications often appear several years before the onset of the clinical symptoms (Manyam *et al.* 2001b) and a 4-year old invididual with a pathogenic mutation and calcifications visible on CT has been reported (Zhang *et al.* 2013). The radiological penetrance of the disease has been estimated to be 95% by 50 years of age (Sobrido *et al.* 2014).

2.5.3. Neuropathology

Reports on autopsied PFBC cases have revealed underlying microvascular pathology: the calcifications are seen in capillary walls, arteries and arterioles (Larsen *et al.* 1985, Kobayashi *et al.* 1987, Miklossy *et al.* 2005, Wszolek *et al.* 2006, Wider *et al.* 2009, Kimura *et al.* 2015). The lesions consist of hydroxyapatite, iron, zinc, magnesium, traces of other heavy metals and mucopolysaccharides (Smeyers-Verbeke *et al.* 1975, Duckett *et al.* 1977, Kimura *et al.* 2015). Neuronal degeneration and gliosis has been reported (Kozik and Kulczycki 1978), but usually the neuron morphology is preserved (Miklossy *et al.* 2005, Kimura *et al.* 2015).

2.5.4. Genetics

PBFC is typically inherited in an autosomal dominant manner. Linkage analyses in large kindreds suggested genetic heterogeneity with significant LOD scores at 8p21.1-q11.23 (Dai *et al.* 2010), 14q13 (Geschwind *et al.* 1999) and 2q37 (Volpato *et al.* 2009). The genetics of PFBC began to be unravelled in 2012, when the first causative mutations were identified in *SLC20A2* (solute carrier family 20 member 2) (Wang *et al.* 2012). Pathogenic mutations in *SLC20A2* have later been found in the pedigrees that defined

linkages to 14q13 and 2q37, demonstrating that phenocopies with brain calcifications can lead linkage studies astray (Hsu *et al.* 2013, Grütz *et al.* 2016). Mutations in *SLC20A2* are detectable in up to 50% of familial cases and 5% of the seemingly sporadic cases (Hsu *et al.* 2013, Nicolas *et al.* 2013a, Yamada *et al.* 2014). Most mutations are missense or nonsense mutations, small deletions or splice site mutations. A large deletion covering the entire coding region has been detected in one family (Baker *et al.* 2014) and smaller exonic deletions in four patients (David *et al.* 2016).

Three other causative genes are currently known. Mutations in *PDGFRB* (platelet derived growth factor receptor beta) were identified by the whole exome sequencing of two affected individuals from a large PFBC pedigree (Nicolas *et al.* 2013b). Soon thereafter, mutations in *PDGFB* (platelet derived growth factor beta, coding for the ligand of PDGFRB) were detected in six other families (Keller *et al.* 2013). Mutations in these genes are typically missense or nonsense mutations. One partial deletion covering exons 3 – 5 of PDGFB has also been reported (Nicolas *et al.* 2014b). The most recently identified causative gene is *XPR1* (xenotropic and polytropic retrovirus receptor 1). However, *SLC20A2* is the most commonly mutated gene in PFBC. Mutations in other genes are rare, accounting for approximately 20 – 30% of patients (Table 5). Therefore, new causative genes may still exist.

Patients with brain calcifications in the absence of postitive family history are frequently encountered, but it is difficult to determine whether they are actual sporadic cases or examples of incomplete clinical penetrance in the family (de Oliveira *et al.* 2013). However, truly sporadic cases can occur as *de novo* mutations have been described in *PDGFB* (Nicolas *et al.* 2014a) and *SLC20A2* (Ferreira *et al.* 2014).

Table 5. Known causative genes in primary familial brain calcification (PFBC). The number of pathogenic mutations was retrieved from the LOVD database (Leiden Open Variation Database at Coppola Lab, https://coppolalab.ucla.edu/lovd/genes), accessed 09/2016. WES = whole exome sequencing, WGS = whole genome sequencing.

Gene	Pathway	Proportion of PFBC	Mutation types	Number of pathogenic mutations	Identified with	Reference
SLC20A2	phosphate homeostasis	40 – 50%	point mutations (coding and splicing), small indels, exonic and whole gene deletions	61	linkage, fine mapping, candidate gene analysis	Wang *et al.* (2012)
PDGFRB	pericyte function	< 10%	point mutations	4	WES	Nicolas *et al.* (2013b)
PDGFB	pericyte function	< 10%	point mutations, exonic deletion	12	WGS	Keller *et al.* (2013)
XPR1	phosphate homeostasis	< 10%	point mutations	4	WES	Legati *et al.* (2015)

2.5.5. Hypotheses on pathogenesis

Both *SLC20A2* and *XPR1* are involved in the regulation of phosphate metabolism. *SLC20A2* codes for PiT-2, a member of the type III sodium-dependent phosphate transporter family (Wang *et al.* 2012), which is a transmembrane protein that imports inorganic phosphate into the cell together with Na+ (Kavanaugh *et al.* 1994, Olah *et al.* 1994). XPR1 is also a transmembrane protein that mediates Pi export across the cell membrane (Giovannini *et al.* 2013).

Studies on *Slc20a2* knock-out mice have confirmed that the calcification begins around the inside walls of brain vessels (Wang *et al.* 2012, Jensen *et al.* 2013). Functional studies of Pi transport in a cell model suggested that the deleterious consequences of *SLC20A2* mutations are due to haploinsufficiency rather than dominant-negative effects (Wang *et al.* 2012). This hypothesis is supported by the observation of exonic and whole-gene deletions in PFBC patients (Baker *et al.* 2014, David *et al.* 2016). Work on the *Slc20a2* knock-out mouse model has suggested that the impaired Pi uptake into cells might lead to an increased extracellular Pi concentration, which in turn could result in passive accumulation of calcium-phosphate products in the vulnerable brain areas. Either the local increase in [Pi] alone or in the calcium-phosphate compounds could activate a cell-mediated mineralisation process (Jensen *et al.* 2013). *XPR1* mutations have been shown to impair Pi export from the intracellular compartment and lead to an increased concentration of intracellular Pi in human embryonic kidney cells and peripheral blood mononuclear cells (Legati *et al.* 2015).

Recent work has shown that *SLC20A2* has an important role in maintaining the normal low level of Pi in the cerebrospinal fluid (Jensen *et al.* 2016, Wallingford *et al.* 2016). A hypothesis of increased CSF Pi concentration due to defective PiT-2, leading to pericyte transformation to a mineralising cell type, and thus calcification of blood vessels was proposed by Jensen *et al.* (2016). However, no evidence of this kind of cell phenotype change was observed by Wallingford *et al.* (2016). SCL20A2 also seems to have an anti-calcific property that could protect vascular smooth muscle cells from the effects of increased Pi concentration (Keasey *et al.* 2016, Wallingford *et al.* 2016). *XPR1* is also expressed in the choroid plexus. Jensen *et al.* (2016) hypothesised a possible link between *SLC20A2* and *XPR1*: Impaired Pi export from cells due to defective XPR1 could lead to increased cellular [Pi], which has been shown to downregulate PiT-2 expression in cell models. This decrease in PiT-2 expression could reduce Pi uptake from the CSF, resulting in elevated CSF Pi concentration.

A different pathogenetic route is suggested by the known functions of PDGFRβ and PDGFβ. PDGFRβ codes for a tyrosine-kinase receptor expressed in neurons, vascular smooth muscle cells and pericytes in the brain (Andrae *et al.* 2008, Nicolas *et al.* 2013b). PDGFβ is the ligand of PDGFRβ. Binding of PDGFβ to PDGFRβ triggers the downstream signalling cascade that controls cell proliferation, differentiation, survival and migration (Andrae *et al.* 2008). Deficient PDGFβ signalling is damaging to vascular smooth muscle cells and pericytes, leading to hypoplasia or complete lack of pericytes, endothelial hyperplasia, increase in vessel diameter and vascular permeability (Lindahl *et al.* 1997, Hellström *et al.* 2001, Tallquist *et al.* 2003). Additionally, it is linked to

impairment of the blood-brain-barrier integrity in mouse models (Armulik *et al.* 2010, Keller *et al.* 2013). The pathogenic mutations linked to PFBC identified thus far have been shown to result in reduced PDGFRβ expression and autophosphorylation (Sanchez-Contreras *et al.* 2014) or haploinsufficiency of PDGFβ (Keller *et al.* 2013, Nicolas *et al.* 2014a, Nicolas *et al.* 2014b).

Although the molecular mechanisms of the known PFBC genes are beginning to unravel (Figure 11), it is still unclear how defects in such different pathways as Pi metabolism and growth factor signalling eventually lead to identical brain pathology and clinical presentation.

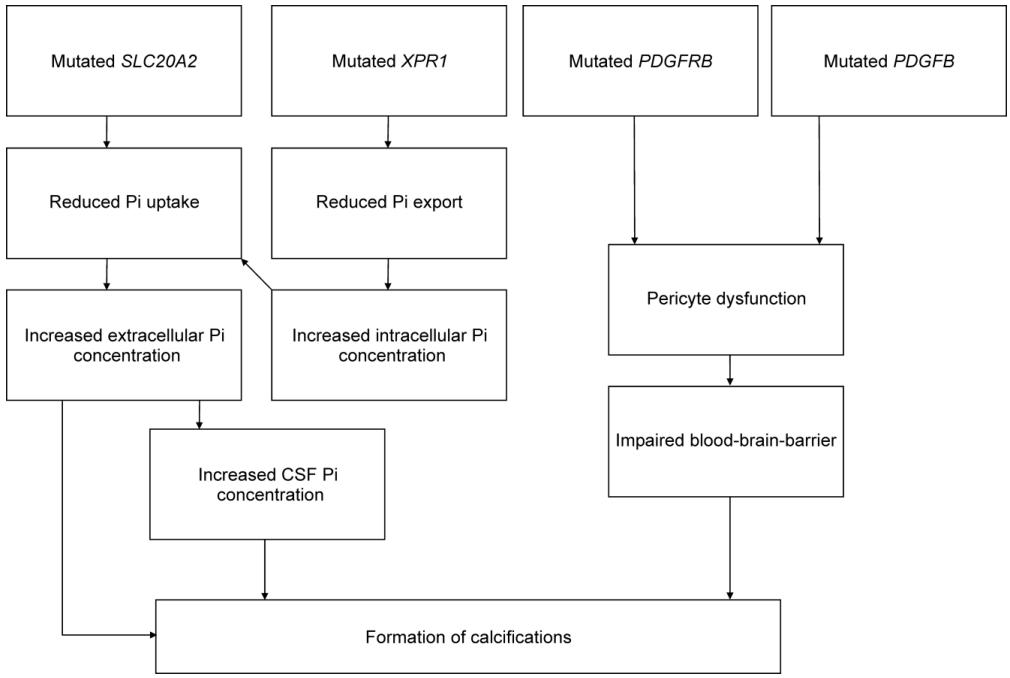

Figure 11. A hypothetical model of the pathogenesis of primary familial brain calcification (PFBC). CSF = cerebrospinal fluid, Pi = inorganic phosphate.

2.6. Approaches to mutation detection in neurogenetics

The methods for identifying disease-causing mutations and risk variants have changed dramatically since the completion of the Human Genome Project (International Human Genome Sequencing Consortium 2004). Prior to the post-genomic era, linkage analysis followed by positional cloning and candidate gene sequencing was needed to identify a causative mutation. Identifying disease suspectibility loci relied on the candidate gene approach in a case – control setting, based on *a priori* assumptioms on the possible functions of the selected genes. Currently, disease-associated genes, causative mutations

and risk variants can be searched for using both targeted and untargeted genome-wide methods.

2.6.1. Targeted screening of known causative genes

Direct screening of known disease genes is sensible in situations where there are a limited number of causative genes and the patient's clinical phenotype or neuropathological findings are strongly suggestive of a particular trait. Major mutations in monogenic diseases can be readily identified using PCR-based methods such as RFLP (restriction fragment length polymorphism), TaqMan assays (Holland *et al.* 1991) and Sanger sequencing (Sanger and Coulson 1975). Sanger sequencing can also be used to determine the sequence of selected region, for example the coding regions of a known disease gene. However, Sanger sequencing is unable to detect copy number variants larger than the expected size of the PCR amplicon. The only exceptions are homozygous deletions that prevent PCR amplification of a particular genomic region and the fact that a lack of the specific PCR product can be regarded as an indirect evidence of the deletion. Alternative methods are thus needed to identify exonic or whole gene copy number variants. The most commonly used methods are quantitative real-time PCR – based assays, multiplex ligation-dependent probe amplification (MLPA), array comparative genomic hybridisation (aCGH) and SNP arrays.

2.6.2. Genome-wide genotyping

Genome-wide approaches enable the assesment of genetic variation across the entire genome, thus removing the bias introduced by selecting candidate genes based on biological plausibility (Manolio *et al.* 2009). The data from the International HapMap project (International HapMap Consortium 2005) demonstrated that genotyping ~500 000 selected haplotype-tagging SNPs reveals most of the common variation present in the human genome. This enabled genome-wide linkage (GWLS) and genome-wide association studies (GWAS) of complex diseases. Of these, GWAS proved effective in uncovering several risk variants for different complex neurological diseases. However, GWAS assesses common variants with small effect size. Hence, extremely large case and control cohorts are needed to reach statistically significant associations in complex diseases such as AD and PD. Meta-analysis combining several GWASs have proven a succesful approach, identifying several AD- and PD-associated risk genes that could not have been detected in smaller studies (Lambert *et al.* 2013, Nalls *et al.* 2014). GWAS studies also miss rare variants (frequency < 5% in the population) that may well have a significant effect on a disease risk (Hardy and Singleton 2009).

2.6.3. Next-generation sequencing

The first next-generation sequencing systems were introduced in 2005. The concept is based on massively parallel sequencing of clonally amplified (short-read sequencing) or single strand (long-read sequencing) templates. The basic workflow is similar in all

applications, including template preparation, sequencing and data acquisition (e.g. fluorescence or change in ion concentration), and analysis of the resulting sequences. Short-read sequencing approaches use either sequencing by ligation or sequencing by synthesis. Currently, sequencing by synthesis is the most widely used short-read sequencing method (Goodwin *et al.* 2016). The NGS instruments produce a vast amount of data for a relatively low cost, enabling the sequencing of entire genomes. NGS can be applied in assessing various aspects of the genome. Variant detection can be achieved by targeted sequencing of a set of genes (gene panels), whole exome sequencing (WES) or whole genome sequencing (WGS). RNAseq allows the analysis of gene expression and splice isoforms. DNA–protein interactions can be analysed with Chip-seq and epigenetic changes such as methylation with methyl-seq (Goodwin *et al.* 2016).

WES has been successfully used in neurogenetics to identify new disease genes, such as *VPS35* in PD (Vilariño-Güell *et al.* 2011, Zimprich *et al.* 2011), and risk variants, such as R47H in *TREM2* (Guerreiro *et al.* 2013). The main limitation of WES is the poor or absent coverage of some genes, especially in GC-rich regions. Different algorithms for CNV detection from WES data have been developed, but these can be affected by uneven read coverage within and between samples, resulting in erroneous calls.

WGS produces a sequence from the entire genome at a reasonably uniform coverage. Consequently, it also covers the entire exome. Copy number variations and structural variants can be reliably detected from the sequence data (Lelieveld *et al.* 2015). However, the vast amount of data originates mainly from the noncoding regions of the genome, making the data filtering and analysis step laborious and time-consuming.

2.6.4. Assessing the pathogenicity and origin of rare variants

NGS techniques have enabled the detection of rare variants from the entire exome or genome. The data from the 1000 Genomes and more recently, the Exome Aggregation Consortium (ExAC), demonstrated that variation is far more common than previously thought. Any given human genome contains on average approximately 4 million variants (SNVs and indels) and ~25 000 of these occur in the protein coding parts of the genome (Abecasis *et al.* 2010) and ~100 of them are rare loss-of-function variants predicted to hamper gene function (Sulem *et al.* 2015). ExAC data revealed an unexpectedly high number of rare and singleton variants and also a set of ~3000 genes that could be implicated in human disease due to their intolerance of protein truncating variants (Lek *et al.* 2016). The data also revealed that variants in causative dominant disease genes are found in ExAC, probably reflecting false assignment of pathogenicity and incomplete penetrance (Minikel *et al.* 2016).

These facts warrant careful population-based allele frequency filtering when determining the possible effects of a novel variant. Sequence data from 10 490 Finnish samples has been gathered by The Sequencing Initiative Suomi project (SISu, Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland), providing a population-specific reference database. Segregation analysis in a family setting or enrichment of deleterious variants in the putative disease gene in cases compared

against appropriately population-matched controls are powerful approaches in assigning pathogenicity (Lek *et al.* 2016). Functional analyses can be used to demonstrate that the putative pathogenic variant produces a measurable effect on gene function. However, not all variants with functional effects are pathogenic (MacArthur *et al.* 2014).

Rare disease mutations may be recurrent or derived from a single mutation event in the past. Recurrent mutations represent so-called hot spots of the genome, that is, positions that are prone to mutation, typically a CpG dinucleotide (Kong *et al.* 2012). A possible shared origin for a given variant may be determined by haplotype analysis using microsatellites or SNPs. The phase of the markers can be determined from the segregation patterns in a pedigree or by computational methods using haplotype structures derived from population-based data. More recent mutations show a longer flanking region of linkage disequilibrium between markers, whereas the haplotype has decayed due to recombination events in the case of ancestral mutations.

3. AIMS OF THE STUDY

The general aim of this study was assess the genetic background of inherited dementing diseases in the Finnish population.

The specific aims of this study were:

1. To examine the genetics of Alzheimer's disease and frontotemporal dementia in a cohort of 60 Finnish families. (I)

2. To characterise a new *SNCA* mutation in a Finnish family with atypical Parkinson's disease. (II)

3. To assess the prevalence of the novel *SNCA* mutation in a larger cohort of Parkinson's disease patients and to determine if the mutation is derived from a common founder in the Finnish patients. (III)

4. To identify the causative mutation in a Finnish family with primary familial brain calcification. (IV)

4. SUBJECTS AND METHODS

4.1. Subjects

4.1.1. The AD and FTD families (I)

Sixty (60) families were included in this study. 364 blood-derived DNA samples were available from both affected and unaffected family members. The clinical diagnosis was AD in 38 families, FTD in 10 families, DLB in one family and unspecified dementia in 11 families. The samples included in the SNP array and exome sequencing studies are listed in Table 6.

Table 6. Samples from the twelve Alzheimer's disease (AD) or frontotemporal dementia (FTD) families selected for SNP array and whole exome sequencing (WES).

Family ID	Individual	Affected / diagnosis	SNP array	WES
Fam-13	II:2	yes / FTD	yes	yes
	II:3	no		yes
	II:5	yes / FTD		yes
Fam-15	II:4	yes / AD	yes	yes
	III:4	yes / AD		yes
Fam-29	II:1	yes / AD	yes	yes
	II:2	yes / AD		yes
Fam-32	II:1	yes / AD	yes	yes
	II:4	no		yes
	II:5	yes / AD		yes
Fam-35	III:3	yes / AD	yes	yes
	III:13	yes / AD		yes
	III:17	no		yes
Fam-38	II:1	yes / AD		yes
	II:2	yes / AD	yes	yes
Fam-49	II:2	yes / AD	yes	yes
	II:3	yes / AD		yes
	II:5	no		yes
Fam-52	II:1	possibly / AD		yes
	II:3	yes / AD		yes
	II:5	yes / AD	yes	yes
Fam-55	II:4	no		yes
	II:6	yes / AD		yes
	II:7	yes / AD	yes	yes
Fam-56	II:3	yes / AD	yes	yes
	II:4	yes / AD		yes
	II:5	no		yes
Fam-57	II:1	yes / AD	yes	yes
	II:2	yes / AD		yes
Fam-59	II:2	yes / FTD		yes
	II:4	yes / FTD	yes	yes
	II:5	no		yes

4.1.2. The *SNCA* family (II, III)

Three affected patients of a Finnish family with PD-like phenotype were included in the study. An autopsy-derived liver sample was available for DNA extraction from the index patient. EDTA blood samples were drawn from the other two patients. The causative mutation was identified in a diagnostic laboratory (Medizinische Laboratorien Westmecklenburg, Germany). DNA samples from two unaffected family members were available for segregation analysis and haplotyping.

4.1.3. *SNCA* mutation screening and haplotype analysis (III, unpublished)

This study included samples from three separate Finnish families with PD due to the same novel mutation in *SNCA*. Three affected patients and two unaffected family members were included from the first family (reported in study II), two affected patients from family 2 originally reported by Martikainen *et al.* (2015) and one affected patient from a third family (reported in III). DNA extracted from peripheral EDTA blood was available from these patients.

An additional 160 DNA samples from PD patients were screened for the *SNCA* mutation. Of these, 80 were DNAs from autopsy-derived brain samples (45 males and 35 females) and 80 blood-derived DNA samples (50 males and 30 females). Information on age at onset and disease duration was available from 45 autopsied patients (24 males, 21 females): the mean age at disease onset was 64.2 years (range 47 – 80 years, SD ± 4.4 years), the mean disease duration 11.5 years (range 3 – 20 years, SD ± 4.4 years) and the mean age of death 75.7 years (range 50 – 88 years, SD ± 7.3 years). The age at onset and disease duration was known of 65 PD patients (40 males, 25 females) from whom a blood-derived DNA samples were available: the mean age at onset was 57.8 years (range 37 – 79 years, SD ± 9 years) and the mean disease duration 10.3 years (range 2 – 21, SD ± 5.6 years).

4.1.4. The PFBC family (IV)

Two affected patients and five unaffected subjects belonging to a single family were included in the study. EDTA blood samples were drawn after obtaining informed consent.

4.2. Ethical aspects

All individuals included in this study were adults. Informed consent was obtained from all participants or their appropriate next of kin.

Study I was approved by the Ethics committee of the Neurology department at HUCH (4.6.1997 and 11.1.2012) and the HUCH Ethics Committee of Medicine (Dnro104/13/03/01/14). Approval for using patient tissue specimens (studies I, II, III) was given by Valvira (Dnro 2855/06.01.03.01/2012). Approval for using medical records

and autopsy reports of the patients living outside the HUS district (study I) was obtained from the National Institute for Health and Welfare (Dnro THL/701/5.05.00/2013). The PFBC study (IV) was approved by the Ethics Committee of Oulu University Hospital. Approval for genetic analysis of the PD samples (III) was obtained from the ethics review board of Turku University Hospital (Dnro ETMK:69/1801/2015).

4.3. Methods

The molecular genetic methods used in the study are listed in Table 7 and described briefly in the following chapters.

Table 7. Molecular genetic methods used in this study. PCR = polymerase chain reaction, RP-PCR = repeat-primed PCR, MLPA = multiplex ligation-dependent probe amplification, STR = short tandem repeat, SNP = single nucleotide polymorphism.

Method	Used in study
DNA extraction	
from blood leucocytes	I, III, IV
from deep-frozen brain tissue	III
PCR	I, II, III, IV
RP-PCR	I
MLPA	II
Sanger sequencing	I, II, III, IV
Haplotype analysis with STR markers	III
Genome-wide SNP array	I, III, IV
Whole exome sequencing	I, IV
Whole genome sequencing	IV

4.3.1. DNA extraction (I, III, IV)

Leukocyte DNA was extracted from EDTA blood with the Illustra Nucleon BACC3 Genomic DNA Extraction Kit (GEHealthcare, Little Chalfont, Buckinghamshire, UK). DNA from fresh-frozen brain tissue samples was extracted with the NucleoSpin Tissue Kit (Macherey-Nagel, Düren, Germany).

4.3.2. PCR and Sanger sequencing (I, II, III, IV)

Standard PCR in 25 µl reaction volume was used in all studies for amplifying specific DNA fragments prior to Sanger sequencing. Purified PCR products were sequenced in both directions using the BigDyeTerminator v3.1 Cycle Sequencing Kit (Applied Biosystems) and run using a capillary sequencer, the ABI3730xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Sequence quality was assessed with the Sequence Scanner v1.0 software (Applied Biosystems). All chromatograms were also checked visually and compared to the appropriate reference sequences manually.

4.3.3. Repeat-primed PCR (I)

Repeat-primed PCR (RP-PCR) was used to detect the *C9orf72* hexanucleotide repeat expansion. The primers and PCR conditions were adapted from Renton *et al.* (2011); the resulting 6-FAM-labelled PCR products were run on an ABI 3730xl capillary sequencer (Applied Biosystems, Foster City, CA, USA) and analysed with the GeneMapper software (Applied Biosystems, Foster City, CA, USA).

4.3.4. Multiplex ligation-dependent probe amplification (II)

Multiplex-ligation dependent probe amplification (MLPA) was used to assess the copy number of the *SNCA* gene. Commercial probe mix P051 (MRC-Holland, Amsterdam, the Netherlands) was used in this analysis. The MLPA analysis was performed by Medizinische Laboratorien Westmecklenburg, Germany.

4.3.5. Haplotype analysis with STR markers (III)

Short tandem repeat (STR) markers are di-, tri- or tetranucleotide repeat sequences that are highly polymorphic in length between individuals. Their polymorphic nature makes them highly informative in, for example, haplotype analysis. Eight markers (D4S2361, D4S2460, D4S2371, D4S2461, D4S1089, D4S3006, D4S414, and D4S2380) flanking a 10 Mb area around the *SNCA* locus were selected based on previous publications (Athanassiadou *et al.* 1999, Puschmann *et al.* 2009). 6-FAM-labelled reverse primer was used in PCR. The PCR products were run using an ABI 3730xl capillary sequencer (Applied Biosystems, Foster City, CA, USA) and analysed with the GeneMarker software (Softgenetics LLC, State College, PA, USA). Haplotype phasing was performed manually from the parent-offspring pairs in PD families 1 and 2.

4.3.6. Genome-wide SNP array (I, III, IV)

SNP arrays were used in three studies (I, III and IV). In study three, an SNP array was used to determine the extent of haplotype sharing in the three PD families carrying the same *SNCA* mutation. The genotyping was performed by the Institute for Molecular Medicine Finland FIMM Technology Centre, University of Helsinki using the Human CoreExome BeadChip (Illumina, San Diego, CA, USA). The region of interest on chromosome 4 was extracted from the genome-wide SNP profiles with PLINK (Purcell *et al.* 2007). Haplotype phases were determined manually from the parent-offspring pairs in PD families 1 and 2. The haplotype of the patient from family 3 could not be phased due to lack of other samples from the family, but the possible shared haplotype was determined as a segment with at least one allele at each position consistent with the phased haplotypes from families 1 and 2.

In studies I and IV, a SNP array was used to detect copy number changes and loss of heterozygosity. The HumanOmniExpress Bead Chip (Illumina, San Diego, CA, USA) was used in both studies. The data were checked visually and analysed with CNVPartition in

the Genome Studio (Illumina, San Diego, CA, USA). Resulting CNVs were checked against the Database of Genomic Variants (MacDonald *et al.* 2014).

4.3.7. Whole exome sequencing (I, IV)

Whole exome sequencing of three members, two affected and one unaffected, of the PFBC family (IV) was performed by the Institute for Molecular Medicine Finland (FIMM, University of Helsinki, Finland). The target enrichment was carried out using the SeqCap EZ Human Exome Library v3.0 (Roche Nimblegen, Basel, Switzerland), and the resulting libraries were sequenced on the Illumina HiSEQ platform (Illumina, San Diego, CA, USA).

Exome sequencing of the AD and FTD families (I) was performed by the University College London (UCL, London, UK). Exome enrichment was carried out with the TruSeq Exome Capture kit (Illumina, San Diego, CA, USA). The sequencing run was performed on HiSeq 2000 (Illumina, San Diego, CA, USA).

In both experiments, the reads were aligned to GRCh37/hg19. Variants were annotated with ANNOVAR (Wang *et al.* 2010). *In silico* analysis of the functional effects of coding non-synonymous variants was performed with SIFT (Kumar *et al.* 2009), Polyphen2 (Adzhubei *et al.* 2010), MutationTaster (Schwarz *et al.* 2014), MutationAssessor (Reva *et al.* 2011), and CADD (Kircher *et al.* 2014).

Variants were filtered based on the inheritance model and their frequency in the control populations (dbSNP (Sherry *et al.* 2001), 1000G (Auton *et al.* 2015), ESP (http://evs.gs.washington.edu/EVS/) , ExAC, and SISu). Validation of selected variants was done by Sanger sequencing as described in section 4.3.2.

4.3.8. Whole genome sequencing (IV)

Whole genome sequencing of one affected patient from the PFBC family was performed by NGI Sweden (The National Genomics Infrastructure, Science for Life Laboratory, Solna, Sweden). Libraries were prepared using the TruSeq DNA PCR-free kit and sequenced on a HiSeq X Platform (Illumina, San Diego, CA, USA). Reads were aligned to GRCh37/hg19 and variants called according to the GATK best practice guidelines. Small indels and SNVs were annotated with SnpEff (Cingolani *et al.* 2012) and ANNOVAR (Wang *et al.* 2010). Structural variants and larger copy number variants were identified by cn.mops (Klambauer *et al.* 2012) and Manta (https://github.com/Illumina/manta).

Variants in the coding and splice site regions were analysed in addition to large structural variants and CNVs. Intergenic regions were excluded from analyses at this stage.

4.3.9. Imaging and histological methods

The imaging and histological methods used in this study are listed in Table 8. Details of these methods can be found in the original publications marked with their assigned Roman numerals.

Table 8. Imaging and histological methods used in this study. CT = computed tomography, MRI = magnetic resonance imaging.

Method	Used in study
Brain CT	IV
Brain MRI	IV
Histopathological and immunohistochemical stainings	
Haematoxylin & Eosin	I, II
pTDP-43	I, II
SNCA	II
amyloid beta	II
p62	II
tau	II

5. RESULTS AND DISCUSSION

5.1. The genetic background of Alzheimer's disease and frontotemporal dementia in a Finnish family cohort (I)

Application of GWAS and NGS-based methods has widened our understanding of the genetics of dementia. Several risk loci with small effect sizes have been identified and the NGS methods have revealed rare variants with significant impact on the disease risk.

In this study, we combined traditional gene-based analyses and genome-wide methods to dissect the molecular genetics of dementia in 60 Finnish families. All families were first screened for the *C9orf72* expansion. From the families with no expansion, we selected 12 families for disease-gene screening, exome sequencing and SNP array studies (Table 6).

5.1.1. The *C9orf72* repeat expansions are common among Finnish dementia patients

The *C9orf72* repeat expansion was screened in all available members of the 60 dementia families. Expansions were detected in 12 families, representing 20% of the cohort. The clinical diagnosis was FTD in seven families, AD or variant AD in four families and unspecified degenerative disease in one family. The expansion explained most FTD cases in our cohort (7 / 10 families, 70%). The *C9orf72* expansion was exceptionally common in our small sample as the frequency of the *C9orf72* expansion has previously been estimated to be 48.1% in Finnish familial FTD cases (Majounie *et al.* 2012b).

In addition to ALS and FTD, the *C9orf72* repeat expansion has been linked to several other neurological diseases, such as PD, AD and Huntington's disease phenocopies (Chi *et al.* 2016). The possible association between AD and *C9orf72* remains controversial. Rare examples of clinically diagnosed (Majounie *et al.* 2012a, Cacace *et al.* 2013, Harms *et al.* 2013, Saint-Aubert *et al.* 2014) and neuropathologically verified AD patients (Murray *et al.* 2011, Kohli *et al.* 2013) with the *C9orf72* expansion have been reported. Some patients with clinical AD had a CSF biomarker profile indicative of AD (Wallon *et al.* 2012, Cacace *et al.* 2013). However, recent work by Kämäläinen and coworkers (2015) demonstrated that a reduced CSF $A\beta_{1\text{-}42}$ level may be seen in 25% of patients with the *C9orf72* expansion and clinical bvFTD. Several clinically diagnosed AD patients actually had TDP-43 pathology consistent with FTLD on autopsy (Murray *et al.* 2011, Majounie *et al.* 2012a). Thus, many clinically diagnosed AD cases with the *C9orf72* expansion may well represent misclassification of actual FTD as AD, possibly due to early memory impairment, and some of them may show concomitant AD pathology on autopsy (Majounie *et al.* 2012a). However, the rare patients with definite AD neuropathology and no evidence of FTLD (Kohli *et al.* 2013) cannot be regarded as misdiagnosed FTD. Hence, it is possible that the *C9orf72* expansion could contribute to

the pathogenesis of AD but the molecular mechanisms behind this putative association are still elusive.

We noted that in four families, the *C9orf72* expansions were segregating with the clinical diagnosis of AD or variant AD. Since the samples had been collected in the late 1990s, the clinical diagnosis was based on the guidelines and methods available at that time. Retrospective examination of patient records and available neuropathological data suggested that in at least some families the clinical presentation could also reflect FTD.

5.1.2. Mutations in *APP*, *PSEN1*, *PSEN2* and *GRN* are rare in Finland

Sanger sequencing of the known causative genes revealed no mutations in *APP*, *PSEN1* or *PSEN2* in the 10 AD families or in *GRN* in the two FTD families. This result is in agreement with previous studies on larger Finnish cohorts. The screening of *APP*, *PSEN1* and *PSEN2* in a cohort of 140 Finnish EOAD patients revealed no pathogenic mutations in these genes (Krüger *et al.* 2012). Only a few *PSEN1* mutations have thus far been reported in the Finnish AD patients. A 4.6-kb deletion, Δ9Finn (c.869_955del) (Crook *et al.* 1998, Prihar *et al.* 1999, Hiltunen *et al.* 2000) has been linked to presenile dementia frequently combined with spastic paraparesis and cotton wool plaques on neuropathological examination (Verkkoniemi *et al.* 2000). The p.Met146Val mutation has been found in a Swedish family of Finnish descent (Alzheimer's Disease Collaborative Group 1995), and p.Pro264Leu in a family with three affected patients (one with AD and spastic paraparesis and two with either probabale or possible DLB) (Martikainen *et al.* 2010).

The *APP* duplication (Rovelet-Lecrux *et al.* 2006) was not present in our series of 10 AD families, nor was it detected in 64 Finnish familial EOAD cases (Blom *et al.* 2008). Only one Finnish family with an *APP* duplication and early-onset dementia, cerebral amyloid angiopathy and frequent intracerebral haemorrhages has been reported before (Rovelet-Lecrux *et al.* 2007).

GRN mutations are also rare among Finnish FTD patients (Krüger *et al.* 2009), even though they are seen in up to 20% of familial FTD cases in other populations. The first pathogenic *GRN* mutation (p.Tyr229X) in a Finnish family was characterised only recently (Kuuluvainen *et al.* 2016).

5.1.3. Applying whole exome sequencing to the search for rare variants

Whole exome sequencing, WES, was performed on at least two affected patients from each of the twelve selected families. When available, the oldest unaffected family member was exome sequenced as a control (Table 6).

The variants were filtered based on the predicted effect (non-synonymous, nonsense, frameshift, or splice site mutation) and frequency in 1000 Genomes, dbSNP, Exome Variant Server, ExAC and SISu databases. We assumed a dominant inheritance model and removed variants that were present in the unaffected family member.

Potential variants were validated with Sanger sequencing and segregation was tested in all available samples from the family.

We observed no mutations in the known causal genes for AD or FTD in the twelve families. In addition, SNP array ruled out large genomic rearrangements or CNVs in known AD and FTD genes.

5.1.3.1. Variants in known Alzheimer's disease-associated genes

In two families, we found variants in genes associated with susceptibility to AD. The two affected patients of family Fam-56 carried a heterozygous *CLU* c.608C>T (p.Thr203Ile) variant (rs41276297) (Table 9). The variant was not present in the four unaffected family members from whom samples were available. A previous study identified this rare variant in a cohort of British AD patients (frequency 0.003) as well as in unaffected controls (frequency 0.006). Based on SISu and ExAC, this variant is present in the Finnish population with a frequency of 0.000698324 to 0.00121. *In silico* predictions of possible pathogenicity suggest that this variant has no deleterious effect. Based on this evidence, we presume that this variant is a rare polymorphism even though it segregates with AD in the small family reported here.

Two affected individuals of family Fam-15 had a heterozygous c.2279A>T (p.Asp760Val) in *PCDH11X* (Table 9). This variant (rs781770086) is present as a singleton in ExAC (a low-quality site) and in SISu. Segregation analysis by Sanger sequencing showed that the variant was also present in two currently unaffected individuals (born in the 1930s and 1940s) and in one individual with possible memory impairment but no definite AD diagnosis. Two other unaffected family members did not have the variant. *In silico* pathogenicity predictions suggested a possible deleterious effect (Table 9). The role of *PCDH11X* in AD is controversial: two studies have reported an association with AD (Carrasquillo *et al.* 2009, Jiao *et al.* 2015), but several studies habe failed to replicate the association (Beecham *et al.* 2010, Lescai *et al.* 2010, Wu *et al.* 2010, Miar *et al.* 2011). *PCDH11X* is located in chromosome X. No male to male transmission of AD was seen in the pedigree, making X-linked inheritance possible, but the segregation pattern does not support a direct link to AD in family Fam-15.

5.1.3.2. Rare variants in other genes

In the remaining 10 families, no variants in known dementia-associated genes were shared by the affected family members included in the exome sequencing. Therefore, we searched for rare variants (MAF frequency less than 1%) in genes that could be relevant in dementia. This approach yielded two genes, *UNC13C* and *MARCH4* (Table 9).

The two affected patients from family Fam-49 shared an inframe deletion of 3 bp in *UNC13C*. The variant (rs746069739) has been reported as a singleton in both ExAC and SiSu. While variants in a related gene, *UNC5C*, have been implicated as risk factors for AD (Wetzel-Smith *et al.* 2014), *UNC13C* has not been directly linked to any neurological phenotype. The gene is highly expressed in the brain, especially in the cerebellum. Functional studies on the mouse homologue, *Munc13-3*, have shown a role in

regulating synapse function (Augustin *et al.* 1999, Chen *et al.* 2013) and controlling critical-period neuronal plasticity in the visual cortex (Yang *et al.* 2002, Yang *et al.* 2007). Gene expression studies in human AD and control brain samples have shown increased *UNC13C* expression in hippocampal CA3 relative to CA1 in Alzheimer patients when compared to controls, suggesting that *UNC13C* might have a neuroprotective role in the brain (Miller *et al.* 2013). The variant detected in WES is an inframe deletion, and its possible effects on gene function and protein structure are unknown. While it is compelling to speculate that the gene might be involved in AD pathogenesis by hampering synaptic function, more evidence is needed to establish this putative connection.

Exome sequencing revealed that the two affected patients of FTD-family Fam-13 had an extremely rare missense variant, p.Lys211Glu (rs756981946) in *MARCH4*, which was not present in the unaffected family member. Interestingly, two affected patients of the other FTD-family, Fam-59, also shared a rare p.Trp13Cys variant (rs145386484) in this same gene. Segregation analyses showed that p.Lys211Glu segregated with the disease in family Fam-13, while several unaffected members of family Fam-59 had the p.Trp13Cys variant, suggesting non-segregation. *MARCH4* codes for an E3 ubiquitin ligase predominantly expressed in the brain (Bartee *et al.* 2004). The p.Lys211Glu variant affects a conserved amino acid residue, replacing a positively charged lysine with a glutamic acid that has a negative charge. The position coding for the p.Trp13 residue is less well conserved. No protein model of MARCH4 is available, precluding any conclusions on the possible effects of the observed variants on the protein structure. *In silico* predictions suggested that p.Lys211Glu might be pathogenic, whereas p.Trp13Cys might be a rare non-pathogenic variant.

The ubiquitin-related protein degregation pathway is implicated in several neurodegenerative diseases (McKinnon and Tabrizi 2014). Recently, mutations in cyclin F (*CCNF*), a member of an E3 ubiquitin-ligase complex, were identified in ALS-FTD (Williams *et al.* 2016). E3 ligases function in the last step of ubiquitination by recruiting the ubiquitin-carrying E2 enzyme and transferring ubiquitin from E2 to the target protein (Chaugule and Walden 2016). MARCH4 is known to regulate the degradation of cell-surface glycoproteins, such as CD81 (Bartee *et al.* 2004, Bartee *et al.* 2010), but it has not been linked to neurodegeneration.

Table 9. Rare variants identified by exome sequencing and validated with Sanger sequencing. CADD = Combined Annotation Dependent Depletion, SIFT = Sorting Intolerant From Tolerant, 1000G = 1000 Genomes, ESP = the NHLBI GO Exome Sequencing Project, ExAC = The Exome Aggregation Consortium , SISu = Sequencing Initiative Suomi. CADD Phred-like scaled C-score: a score of ≥ 10 indicates that the variant is amongst the 10% of the most damaging variants in the genome.

Gene	cDNA change	amino acid change	rs number	SIFT	PolyPhen2	CADD	Freq. 1000G	Freq. ESP	ExAC	SISu
CLU	NM_001831:c.608C>T	p.(Thr203Ile)	rs41276297	tolerated	benign	8.521	0.005	0.0027	0.0016	0.0007
PCDH11X	NM_001168360:c.2279A>T	p.(Asp760Val)	rs781770086	damaging	possibly deleterious	14.33	absent	absent	singleton	singleton
UNC13C	NM_001080534:c.1324_1326del	p.(Lys443del)	rs746069739	N/A	N/A	N/A	absent	absent	absent	singleton
MARCH4	NM_020814:c.39G>C	p.(Trp13Cys)	rs145386484	tolerated	benign	2.416	0.0006	7.7e-05	0.0002	0.001
MARCH4	NM_020814:c.631A>G	p.(Glu211Lys)	rs756981946	damaging	deleterious	19.62	absent	absent	singleton	singleton

5.2. *SNCA* p.Ala53Glu is linked to Parkinson's disease and multiple system atrophy -type pathology (II)

A neuropathological examination of the index patient of family F1 revealed severe α-synuclein pathology throughout the brain. This exceptionally grave pathology combined with an early onset of the parkinsonian symptoms at 36 years of age suggested the possibility of an inherited condition. At the time of the autopsy, the index patient's niece had also developed similar symptoms, further emphasising a probable genetic component linked to the disease aetiology.

5.2.1. Neuropathological changes

After a disease duration of 24 years, the index patient's brain weighed only 886 g. Prominent frontotemporal and hippocampal atrophy as well as degeneration of the substantia nigra were evident on macroscopic examination. Atrophy of the caudatus, putamen, pallidus, thalamus, and subthalamic nuclei and the pallor of the locus coeruleus were also noted. Severe neuronal loss, gliosis and spongiosis were pronounced in the neocortical regions with eosinophilic cytoplasmic inclusions seen in neurons and glial cells. Loss of dopaminergic neurons in the substantia nigra was almost total, accompanied by severe gliosis. Diffuse mild neuronal loss was seen in the cornu ammonis (CA) 1, CA2 and CA3 regions of the hippocampus. The cerebellum was intact.

SNCA immunoreactivity was seen in all brain areas and spinal cord sections investigated. SNCA positive cytoplasmic inclusions of varying morphology were seen in neurons and glial cells, the latter mostly in oligodendrocytes. Most inclusions were crescent shaped or annular; globular LB-like inclusions were also seen. In most affected areas, SNCA positive neurites and threads were present as well. The pathology was most abundant in the cortical and subcortical areas. An especially pronounced SNCA pathology was seen in the temporal and insular cortex, cingulate gyrus, putamen, caudatus, amygdala and hippocampus. The hippocampal SNCA pathology was most severe in the CA2 and CA3 areas.

Beta-amyloid staining was negative in all areas. Modest tau-positivity corresponding to Braak stage II was seen in the entorhinal cortex. Immunostaining with pTDP-43 and p62 showed modest reactivity in the brain areas with SNCA pathology.

5.2.2. Characteristics of the *SNCA* p.Ala53Glu mutation

MLPA ruled out duplication or triplication of *SNCA*. Sanger sequencing of the coding regions of *SNCA* revealed a heterozygous NM_0003435.3:c.158C>A mutation, resulting in the substitution of an alanine (Ala, A) with glutamic acid (Glu, E) at amino acid position 53 (p.Ala53Glu, p.A53E). This mutation has not been described in any public repositories (dbSNP, ESP, SISu, 1000 Genomes, and ExAC) of variants. Segregation analysis showed that this variant is also present in the index patient's sister and her daughter.

The p.Ala53Glu mutation affects the same amino acid residue as does the first reported *SNCA* mutation, p.Ala53Thr (Polymeropoulos *et al.* 1997). Curiously, the position coding for Ala53 is not well-conserved. Many higher order mammals have the disease-associated Thr at the corresponding position, and the highly homologous human γ-synuclein also harbours Thr at this position (Kara *et al.* 2013).

The p.Ala53Glu replaces a hydrophobic, non-polar Ala residue with Glu that has a negatively charged side chain. The mutation site is within the second α-helix of the polypeptide (Ulmer *et al.* 2005), suggested to form the protein loop and hairpin structure necessary for tetramer formation (Kara *et al.* 2013) (Figure 12). It was hypothesised that the mutation might alter the secondary structure of SNCA thereby altering the fibrillation kinetics of the resulting mutant α-synuclein.

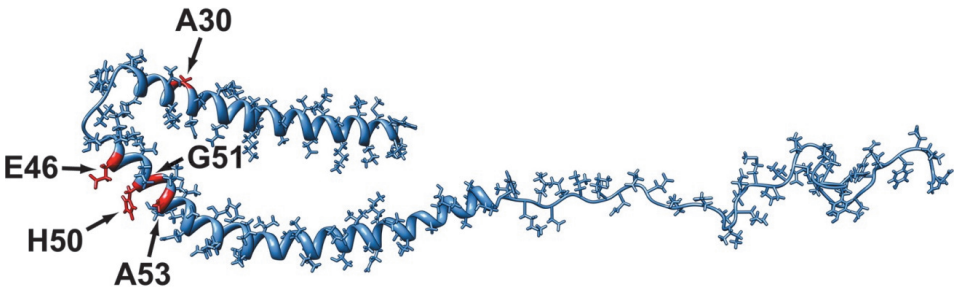

Figure 12. The putative structure of the SNCA polypeptide and the locations of the pathogenic mutations. The figure is adapted from Kara *et al*. (2013), available under the terms of the Creative Commons Attribution Licence.

Subsequent functional studies confirmed some of these assumptions. An *in vitro* analysis showed that in contrast to the p.Ala53Thr mutation, the p.Ala53Glu mutation delays the fibrillation and aggregation of α-synuclein, likely resulting in increased amounts of oligomeric α-synuclein (Ghosh *et al.* 2014, Rutherford and Giasson 2015). Interestingly, the mutation does not seem to alter the secondary structure of the protein, but the charged Glu residue may disrupt fibril formation (Rutherford and Giasson 2015). Directly observable functional effects of the mutation include the lower membrane-binding capacity of the resulting mutant α-synuclein (Ghosh *et al.* 2014) and increased cellular toxicity in a cell model under mitochondrial stress (Rutherford and Giasson 2015).

5.3. The *SNCA* p.Ala53Glu mutation is a rare cause for Parkinson's disease in Finland and originates from a common founder (III)

After the initial report describing the p.Ala53Glu mutation (I), another Finnish family with the same mutation was reported (Martikainen *et al.* 2015). The families had no known connection, but finding several patients with the same extremely rare mutation raised the possibility of a shared ancestor. Thus, we proceeded to a haplotype analysis

using both STR markers and SNP markers. We also screened a larger cohort of both late-onset and early-onset PD patients to assess this mutation's frequency among Finnish PD patients.

5.3.1. Frequency in Parkinson's disease cohorts

Two cohorts totalling 157 PD patients (110 with late-onset PD, 47 with familial early-onset PD) were screened to assess the frequency of the p.Ala53Glu mutation. No individuals with the mutation were detected in the cohort of 110 mostly late-onset PD patients. This result was expected since the majority of patients had late-onset PD, most likely representing sporadic cases. No detailed family history of these patients was available.

Screening of 47 early-onset familial PD patients revealed one individual with the p.Ala53Glu mutation. The patient was diagnosed with PD at the age of 41 years. Progression of the symptoms was slow and no levodopa was required two years after diagnosis. Family history was compatible with autosomal dominant inheritance: the patient's mother and sister both had PD, and the maternal grandmother may also have been affected.

Thus far, only three families with the p.Ala53Glu mutation are known, suggesting that this mutation is a rare cause of PD in Finland. *SNCA* mutations are also globally rare, they are seen in only ~1% of all PD. Accordingly, another study of 22 Finnish familial EOPD patients revealed no mutations in *SNCA* (Autere *et al.* 2002).

5.3.2. Evidence of a shared haplotype

Currently, three families with the same p.Ala53Glu mutation in *SNCA* are known. These families had no known connections based on patient interviews. However, two of the families originated from Southwestern Finland, raising the possibility of more distant ancestry. In order to search for a shared genomic segment, haplotype analysis with STR markers and SNP genotyping was performed. An analysis of eight STR markers flanking *SNCA* showed an identical haplotype of 5.7 Mb (starting at marker D4S2371, genomic location on chr4: 90132775 and extending to D4S2380, genomic location on chr4: 95883055) segregating in families F1 and F2. Allele sharing analysis suggested that the affected patient of family F3 also carried this haplotype (Figure 1 in III). SNP genotyping revealed definite breakages of the shared haplotype at SNP rs2116325 (chr4: 90,115,197) and rs6842919 (chr4: 106,958,170) located 16.8 Mb from each other.

5.3.3. Clinical manifestations of the p.Ala53Glu mutation

Clinical presentations linked to a single mutation can exhibit marked variability within and between families. While *SNCA* mutations typically cause early-onset PD, variation in age-at-onset is common. The index patient of family F1 developed symptoms at 36 years; her sister only noted the first symptoms at 62 years, whereas the index patient's niece was severely affected by 32 years. The same trend was noted in family F2 with

the index patient presenting at 42 years and her daughter at 25 years of age. The index patient from family F3 developed symptoms at 41 years of age. A similar variability in age-at-onset has been reported for the p.Gly51Asp mutation with the youngest patient presenting at 19 years and a patient from another family at 69 years of age (Kiely *et al.* 2015).

The clinical manifestations of the p.Ala53Glu mutation are also variable. The index patient from family F1 developed levodopa-responsive parkinsonism with long disease duration (24 years). A neuropathological examination showed features of both PD and MSA. The two affected members of family F2 had hypokinetic-rigid PD and no clinical signs of MSA. Both developed severe levodopa-induced dyskinesia. The affected patient from family F3 had typical PD, but also severe dysarthria and dysphagia, which may suggest cereberral involvement and thus features of an MSA-C type disease. Similar variation in age-at-onset and clinical manifestations has been observed in other *SNCA* mutations. The age-at-onset in three patients with the p.Gly51Asp mutation varied from 19 to 69 years and their response to levodopa treatment was variable (Kiely *et al.* 2015).

5.4. Deletion of *SLC20A2* 5' noncoding regions linked to primary familial brain calcification (IV)

The genetic background of PFBC has proven heterogenous with four causative genes identified thus far. We sought to identify the pathogenic mutation responsible for PFBC in a Finnish family with three affected patients.

5.4.1. Identifying the mutation

Sanger sequencing of the coding and flanking splice site regions of *SLC20A2*, *PDGFB* and *PDGFRB* revealed no mutations. WES was applied in order to search for variants shared by the two affected patients and absent in one unaffected family member. Variants were filtered based upon their frequencies in public databases and their predicted functions. This approach failed to identify any plausible pathogenic variants related to the disease. We hypothesised that the disease might be caused by a noncoding variant or a copy number variant involving a known disease gene, or by a variant in a previously unidentified gene. Thus, whole genome sequencing of one affected patient and an unaffected family member was performed.

Analysis of the WGS data revealed a heterozygous deletion of ~578 kb on chromosome 8p11.2 (genomic coordinates chr8: 42,338,721 - 42,916,885) in the affected patient. The telomeric breakpoint of the deletion maps to the 5' noncoding region of *SLC20A2*, removing the noncoding exon 1 and the putative promoter region of the gene. The coding region remains intact. The centromeric breakpoint is located between the second and third exons of *FNTA*. The deletion covers the entire coding regions of *SMIM19*, *CHRNB3*, *CHRNA6*, *THAP1*, *RNF170*, and *HOOK3.*

The unaffected family member included in the WGS did not have the deletion. We tested for co-segregation in all available family members using an SNP array. Only the two affected patients and none of the unaffected family members harboured the deletion, suggesting complete co-segregation with the disease.

5.4.2. Characteristics of the novel mutation

Most of the pathogenic mutations in *SLC20A2* are missense and nonsense mutations, small deletions or splice site mutations, readily detectable by Sanger sequencing (Lemos *et al.* 2015). Initial functional studies suggested that mutations in *SLC20A2* act through haploinsufficiency rather than dominant negative effects (Wang *et al.* 2012). Identification of a large deletion abolishing the whole coding region of *SLC20A2* gave further support for haploinsufficiency as the disease mechanism (Baker *et al.* 2014). Recently, smaller exonic deletions were identified in several PFBC families (David *et al.* 2016, Grütz *et al.* 2016). We identified a deletion that only covers the 5' noncoding regions of *SLC20A2*, including the putative promoter region. Generally, no transcript is produced if the promoter is missing. We thus propose that this deletion causes PFBC through the haploinsufficiency of *SLC20A2*.

The deletion is almost identical in size to the whole-gene deletion reported by Baker *et al*. (Baker *et al.* 2014) (Figure 13). Both deletions cover *SMIM19*, *CHRNB3*, *CHRNA6*, *THAP1* and *RNF170*. Of these genes, only *THAP1* and *RNF170* have been linked to neurological disease. *THAP1* mutations cause early-onset torsion dystonia (DYT6, OMIM 602629) (Fuchs *et al.* 2009), and a missense mutation of *RNF170* has been reported as causative of autosomal dominant sensory ataxia (Valdmanis *et al.* 2011). Interestingly, dystonia was observed in the Finnish family and also in several members of a family reported by Baker *et al.* (2014) and it could be related to the deletion of *THAP1*.

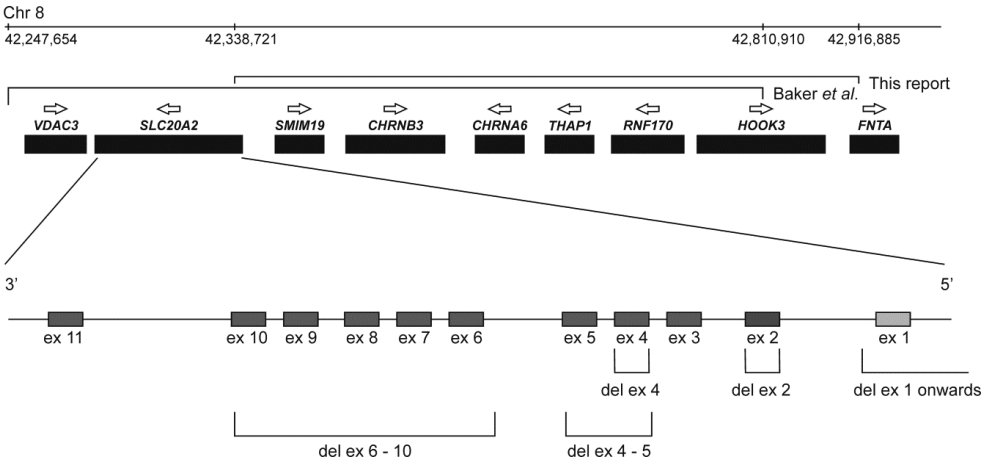

Figure 13. A schematic presentation of the deletion identified in this study compared to other deletions reported thus far (Baker *et al*. 2014, David *et al*. 2016, Grütz *et al*. 2016). Orientations of the genes are marked with arrows. Modified from Figure 1c in IV.

The results by David and coworkers (2016) show that it is possible to estimate CNVs from exome sequencing data by assessing read-depth variation across samples. We chose to assess CNVs by WGS and an SNP array. The partial *SLC20A2* deletion would not have been picked up by CNV analysis of our WES data, since the deletion only covers the noncoding exon 1 of the *SLC20A2* and this region was not captured by the exome enrichment kit used. Using SNP array alone would have allowed us to see the deletion, but the breakpoints could be more reliably identified from the WGS data.

Analysis of copy number variations is thus a crucial point in the molecular diagnostics of PFBC. In addition to exome- and genome-wide methods, CNVs can be analysed by targeted means, such as MLPA and QMPSF (quantitative multiplex PCR of short fluorescent fragments), qPCR-based copy number assays or aCGH. Targeted protocols often only include the coding regions of genes, but our results demonstrate that CNV analysis should, if possible, also assess the noncoding and regulatory regions of known causative genes. Failure to address CNVs may lead to underestimation of mutation frequency in the known genes and unnecessary searching for mutations in novel genes.

6. CONCLUSIONS AND FUTURE PROSPECTS

1. The *C9orf72* expansions are common causes of dementia in the Finnish population, especially among FTD patients with or without a family history of ALS. Screening for the *C9orf72* repeat expansions could be worthwhile in most familial dementia cases. Mutations in *APP*, *PSEN1* and *PSEN2* are rare, as are mutations in FTD-associated genes, with the exception of the *C9orf72* expansions. Exome sequencing can be used to search for rare variants, but assigning pathogenicity warrants functional studies and evidence of enrichment of variants in cases with the disease phenotype compared to unaffected controls. This often requires combining several cohorts to reach statistical significance.

2. The *SNCA* p.Ala53Glu mutation has thus far only been identified in Finnish patients with extrapyramidal symptoms. Segregation analyses and functional work support its pathogenicity, making it the fifth known pathogenic point mutation in *SNCA*. The clinical manifestations vary from patient to patient, ranging from typical early-onset PD to more MSA-like disease.

3. Patients with the *SNCA* p.Ala53Glu mutation share a common haplotype, suggesting that they originate from a common ancestor. Thus, more patients with this mutation might be found in Finland, even though our initial screening of PD patients suggests that this mutation is rare. Screening for *SNCA* is recommended particularly in severe, early-onset PD with positive family history.

4. Whole genome sequencing was required to identify the causative mutation, partial deletion of *SLC20A2*, in a Finnish PFBC family, even though the mutation affects a well-established disease gene. Our results demonstrate that analysis of copy number variation is essential when screening for mutations in known causative genes linked to PFBC. Ideally, CNV analysis should not be limited to the coding regions, as causative variants may reside outside them, in the regulatory regions.

5. Identifying the causative mutation provides a foundation upon which the follow-up studies may be built. The known functions of the mutated gene often reveal pathways that may result in neurodegeneration when disrupted. Functional studies are needed to elucidate the pathogenetic mechanisms and to find possible ways to eventually treat or even prevent the disease.

ACKNOWLEDGEMENTS

This study was carried out during the years 2012-2016 at the Department of Medical Biochemistry and Genetics, University of Turku. I wish to thank the heads of department, Professors Klaus Elenius and Johanna Schleutker for providing excellent working facilities. Professor Schleutker is also thanked for giving me time off from my duties as a geneticist at the Tyks-Sapa Department of Medical Genetics to pursue my research.

I am indebted to my three supervisors. I wish to express my sincere gratitude to Adjunct professor Minna Pöyhönen for her warm support and encouragement during these years. You have always had time for me despite your busy schedule. I am grateful to Adjunct professor Liisa Myllykangas for her efficient way of guiding me through this process. I admire your passion for science and ability to make things happen. I am thankful for Adjunct professor Marc Baumann for his friendly way of supervision and critical thinking. Thank you for having interest in my work even though the initial project metamorphosed into something quite different. Professor emeritus Hannu Kalimo and Professor Matti Viitanen are thanked for their valuable input in the final stages of this work. I admire the amount of knowledge these two gentlemen possess.

Adjunct professors Katarina Pelin and Maija Castrén are warmly thanked for their constructive comments as the reviewers of this thesis. Professor Johanna Schleutker, Adjunct professor Marja Hietala and Dr Susanna Roine are acknowledged for participating in my steering committee.

I wish to thank all my former and present co-workers in the CADASIL and familial dementias research groups: Dr Maija Siitonen, Dr Saara Tikka, Dr Maciej Lalowski, Adjunct professor Anders Paetau, Adjunct professor Auli Verkkoniemi-Ahola, Dr Liina Kuuluvainen, Professor Pentti Tienari, Dr Terhi Rantamäki-Häkkinen and Dr Hannu Laaksovirta. Auli Verkkoniemi-Ahola is warmly thanked for collecting the impressive patient cohort and letting me use it in my thesis. Dr Peter Baumann is thanked for collaboration on the Fahr's disease project. Pentti Tienari and his group are appreciated for all their help in laboratory work and data analysis. I owe big thanks to Maija for peer support and vital help on numerous occasions. The collaboration with Dr Rita Guerreiro, Dr Jose Bras and Professor John Hardy was crucial for this thesis project. Maaria and Damon Tringham are warmly thanked for language revision of my thesis.

I wish to acknowledge all my co-authors: Liisa Myllykangas, Minna Pöyhönen, Maija Siitonen, John Hardy, Jose Bras, Rita Guerreiro, Anders Paetau, Pentti J. Tienari, Auli Verkkoniemi-Ahola, Anna Raunio, Seppo Kaakkola, Jukka Lyytinen, Eino Palin, Risto Pohjolan-Pirhonen, Juha O. Rinne, Markku Päivärinta, Mika H. Martikainen, Valtteri Kaasinen, Marja Hietala, Maria Gardberg, Anna Maija Saukkonen, Johanna Eerola-Rautio, Anu Suomalainen-Wartiovaara, Jussi Mäkinen, Miko Valori, Matti Viitanen and Peter Baumann. Thank you for your help in various aspects of this project and for smooth co-operation during the drafting of the manuscripts!

I have had a great time in 'X-boksi' thanks to its former and current residents. Maija, Johanna, Pia, Maaria, Elina, Anna, Csilla, Pyttan and others are thanked for creating an

exceptionally nice atmosphere at work. I could always rely on your support and sympathy! I also wish to thank all my colleagues at the Department of Medical Genetics, Tyks-Sapa.

Thanks to all my friends for being there for me! I especially want to thank Maija P., Pirjo and Laura (The TUBI girls), Päivi and Hanna for dragging me away from work every once in a while.

I wish to express my warmest gratitude to my mother, father, sister and brother for their unwavering support. My deepest gratitude goes to my dear husband Mikko for taking care of the children and everything else during my most intensive writing periods. This thesis would not have been finished without your help. Aino and Santeri, my greatest achievements in genetics: thank you for teaching me what really matters in life.

I wish to express my gratitude to all the patients and their families for participating in these studies.

This study was financially supported by the Folkhälsan Institute of Genetics, the Päivikki and Sakari Sohlberg Foundation, the Pirkko and Veikko Mäkelä Foundation and the Finnish Cultural Foundation - Kymenlaakso Regional Fund.

Petra Pa

Turku, December 2016

ELECTRONIC RESOURCES

Alzforum mutation database (http://www.alzforum.org/mutations/)

Alzheimer disease & frontotemporal dementia mutation database (http://www.molgen.ua.ac.be/ADMutations/)

The Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/)

Exome Variant Server, NHLBI GO Exome Sequencing Project (ESP), Seattle, WA (http://evs.gs.washington.edu/EVS/)

International Classification of Diseases (http://www.who.int/classifications/icd10/)

Leiden Open Variation Database at Coppola Lab (https://coppolalab.ucla.edu/lovd/genes)

PLINK v1.07 and v1.09 (http://pngu.mgh.harvard.edu/purcell/plink/)

Sequencing Initiative Suomi project (SISu), Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland (http://sisuproject.fi), SISu v4.1, accessed 09/2016

REFERENCES

Abecasis, G. R., Altshuler, D., Auton, A., Brooks, L. D., Durbin, R. M., Gibbs, R. A., Hurles, M. E., McVean, G. A. and Consortium, G. P. (2010) 'A map of human genome variation from population-scale sequencing', *Nature*, 467(7319), 1061-73.

Adams, R. D., Vanbogaert, L. and Vandereecken, H. (1964) 'Striato-nigral degeneration', *J Neuropathol Exp Neurol*, 23, 584-608.

Adzhubei, I. A., Schmidt, S., Peshkin, L., Ramensky, V. E., Gerasimova, A., Bork, P., Kondrashov, A. S. and Sunyaev, S. R. (2010) 'A method and server for predicting damaging missense mutations', *Nat Methods*, 7(4), 248-9.

Ahmed, Z., Asi, Y. T., Sailer, A., Lees, A. J., Houlden, H., Revesz, T. and Holton, J. L. (2012) 'The neuropathology, pathophysiology and genetics of multiple system atrophy', *Neuropathol Appl Neurobiol*, 38(1), 4-24.

Al-Chalabi, A., Dürr, A., Wood, N. W., Parkinson, M. H., Camuzat, A., Hulot, J. S., Morrison, K. E., Renton, A., Sussmuth, S. D., Landwehrmeyer, B. G., Ludolph, A., Agid, Y., Brice, A., Leigh, P. N., Bensimon, G. and Group, N. G. S. (2009) 'Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy', *PLoS One*, 4(9), e7114.

Alzheimer, A. (1907) 'Über eine eigenartige Erkrankung der Hirnrinde.', *Allg Zschr Psychiatr Psych gerichtl Med.*, 64, 146-148.

Alzheimer, A. (1911) 'Über eigenartige Krankheitsfälle der späteren Alters', *Zeitschrift für die gesamte Neurologie und Psychiatrie*, (4), 356-385.

Alzheimer's Disease Collaborative Group (1995) 'The structure of the presenilin 1 (S182) gene and identification of six novel mutations in early onset AD families', *Nat Genet*, 11(2), 219-22.

Andrae, J., Gallini, R. and Betsholtz, C. (2008) 'Role of platelet-derived growth factors in physiology and medicine', *Genes Dev*, 22(10), 1276-312.

Appel-Cresswell, S., Vilarino-Guell, C., Encarnacion, M., Sherman, H., Yu, I., Shah, B., Weir, D., Thompson, C., Szu-Tu, C., Trinh, J., Aasly, J. O., Rajput, A., Rajput, A. H., Jon Stoessl, A. and Farrer, M. J. (2013) 'Alpha-synuclein p.H50Q, a novel pathogenic mutation for Parkinson's disease', *Mov Disord*, 28(6), 811-3.

Armulik, A., Genové, G., Mäe, M., Nisancioglu, M. H., Wallgard, E., Niaudet, C., He, L., Norlin, J., Lindblom, P., Strittmatter, K., Johansson, B. R. and Betsholtz, C. (2010) 'Pericytes regulate the blood-brain barrier', *Nature*, 468(7323), 557-61.

Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R. and Van Hoesen, G. W. (1991) 'The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease', *Cereb Cortex*, 1(1), 103-16.

Asi, Y. T., Simpson, J. E., Heath, P. R., Wharton, S. B., Lees, A. J., Revesz, T., Houlden, H. and Holton, J. L. (2014) 'Alpha-synuclein mRNA expression in oligodendrocytes in MSA', *Glia*, 62(6), 964-70.

Athanassiadou, A., Voutsinas, G., Psiouri, L., Leroy, E., Polymeropoulos, M. H., Ilias, A., Maniatis, G. M. and Papapetropoulos, T. (1999) 'Genetic analysis of families with Parkinson disease that carry the Ala53Thr mutation in the gene encoding alpha-synuclein', *Am J Hum Genet*, 65(2), 555-8.

Augustin, I., Betz, A., Herrmann, C., Jo, T. and Brose, N. (1999) 'Differential expression of two novel Munc13 proteins in rat brain', *Biochem J*, 337 (Pt 3), 363-71.

Autere, J. M., Hiltunen, M. J., Mannermaa, A. J., Jäkälä, P. A., Hartikainen, P. H., Majamaa, K., Alafuzoff, I. and Soininen, H. S. (2002) 'Molecular genetic analysis of the alpha-synuclein and the parkin gene in Parkinson's disease in Finland', *Eur J Neurol*, 9(5), 479-83.

Auton, A., Brooks, L. D., Durbin, R. M., Garrison, E. P., Kang, H. M., Korbel, J. O., Marchini, J. L., McCarthy, S., McVean, G. A., Abecasis, G. R. and Consortium, G. P. (2015) 'A global reference for human genetic variation', *Nature*, 526(7571), 68-74.

Baba, Y., Broderick, D. F., Uitti, R. J., Hutton, M. L. and Wszolek, Z. K. (2005) 'Heredofamilial brain calcinosis syndrome', *Mayo Clin Proc*, 80(5), 641-51.

Baborie, A., Griffiths, T. D., Jaros, E., McKeith, I. G., Burn, D. J., Richardson, A., Ferrari, R., Moreno, J., Momeni, P., Duplessis, D., Pal, P., Rollinson, S., Pickering-Brown, S., Thompson, J. C., Neary, D., Snowden, J. S., Perry, R. and Mann, D. M. (2011) 'Pathological correlates of frontotemporal lobar degeneration in the elderly', *Acta Neuropathol*, 121(3), 365-71.

Baker, M., Mackenzie, I. R., Pickering-Brown, S. M., Gass, J., Rademakers, R., Lindholm, C., Snowden, J., Adamson, J., Sadovnick, A. D., Rollinson, S., Cannon, A., Dwosh, E., Neary, D., Melquist, S., Richardson, A., Dickson, D., Berger, Z., Eriksen, J., Robinson, T., Zehr, C., Dickey, C. A., Crook, R., McGowan, E., Mann, D., Boeve, B., Feldman, H. and Hutton, M. (2006) 'Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17', *Nature*, 442(7105), 916-9.

Baker, M., Strongosky, A. J., Sanchez-Contreras, M. Y., Yang, S., Ferguson, W., Calne, D. B., Calne, S.,

Stoessl, A. J., Allanson, J. E., Broderick, D. F., Hutton, M. L., Dickson, D. W., Ross, O. A., Wszolek, Z. K. and Rademakers, R. (2014) 'SLC20A2 and THAP1 deletion in familial basal ganglia calcification with dystonia', *Neurogenetics*, 15(1), 23-30.

Bang, J., Spina, S. and Miller, B. L. (2015) 'Frontotemporal dementia', *Lancet*, 386(10004), 1672-82.

Bannwarth, S., Ait-El-Mkadem, S., Chaussenot, A., Genin, E. C., Lacas-Gervais, S., Fragaki, K., Berg-Alonso, L., Kageyama, Y., Serre, V., Moore, D. G., Verschueren, A., Rouzier, C., Le Ber, I., Augé, G., Cochaud, C., Lespinasse, F., N'Guyen, K., de Septenville, A., Brice, A., Yu-Wai-Man, P., Sesaki, H., Pouget, J. and Paquis-Flucklinger, V. (2014) 'A mitochondrial origin for frontotemporal dementia and amyotrophic lateral sclerosis through CHCHD10 involvement', *Brain*, 137(Pt 8), 2329-45.

Barrett, M. J., Hac, N. E., Yan, G., Harrison, M. B. and Wooten, G. F. (2015) 'Relationship of age of onset and family history in Parkinson disease', *Mov Disord*, 30(5), 733-5.

Bartee, E., Eyster, C. A., Viswanathan, K., Mansouri, M., Donaldson, J. G. and Früh, K. (2010) 'Membrane-Associated RING-CH proteins associate with Bap31 and target CD81 and CD44 to lysosomes', *PLoS One*, 5(12), e15132.

Bartee, E., Mansouri, M., Hovey Nerenberg, B. T., Gouveia, K. and Früh, K. (2004) 'Downregulation of major histocompatibility complex class I by human ubiquitin ligases related to viral immune evasion proteins', *J Virol*, 78(3), 1109-20.

Bedse, G., Di Domenico, F., Serviddio, G. and Cassano, T. (2015) 'Aberrant insulin signaling in Alzheimer's disease: current knowledge', *Front Neurosci*, 9, 204.

Beecham, G. W., Naj, A. C., Gilbert, J. R., Haines, J. L., Buxbaum, J. D. and Pericak-Vance, M. A. (2010) 'PCDH11X variation is not associated with late-onset Alzheimer disease susceptibility', *Psychiatr Genet*, 20(6), 321-4.

Benamer, H. T., Oertel, W. H., Patterson, J., Hadley, D. M., Pogarell, O., Höffken, H., Gerstner, A. and Grosset, D. G. (2003) 'Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations', *Mov Disord*, 18(9), 977-84.

Bendor, J. T., Logan, T. P. and Edwards, R. H. (2013) 'The function of α-synuclein', *Neuron*, 79(6), 1044-66.

Benilova, I., Gallardo, R., Ungureanu, A. A., Castillo Cano, V., Snellinx, A., Ramakers, M., Bartic, C., Rousseau, F., Schymkowitz, J. and De Strooper, B. (2014) 'The Alzheimer disease protective mutation A2T modulates kinetic and thermodynamic properties of amyloid-β (Aβ) aggregation', *J Biol Chem*, 289(45), 30977-89.

Benitez, B. A., Karch, C. M., Cai, Y., Jin, S. C., Cooper, B., Carrell, D., Bertelsen, S., Chibnik, L., Schneider, J. A., Bennett, D. A., Fagan, A. M., Holtzman, D., Morris, J. C., Goate, A. M., Cruchaga, C., Initiative, A. s. D. N. and GERAD, G. a. E. R. f. A. s. D. C. (2013) 'The PSEN1, p.E318G variant increases the risk of Alzheimer's disease in APOE-ε4 carriers', *PLoS Genet*, 9(8), e1003685.

Benke, T., Karner, E., Seppi, K., Delazer, M., Marksteiner, J. and Donnemiller, E. (2004) 'Subacute dementia and imaging correlates in a case of Fahr's disease', *J Neurol Neurosurg Psychiatry*, 75(8), 1163-5.

Bernardi, L., Frangipane, F., Smirne, N., Colao, R., Puccio, G., Curcio, S. A., Mirabelli, M., Maletta, R., Anfossi, M., Gallo, M., Geracitano, S., Conidi, M. E., Di Lorenzo, R., Clodomiro, A., Cupidi, C., Marzano, S., Comito, F., Valenti, V., Zirilli, M. A., Ghani, M., Xi, Z., Sato, C., Moreno, D., Borelli, A., Leone, R. A., St George-Hyslop, P., Rogaeva, E. and Bruni, A. C. (2012) 'Epidemiology and genetics of frontotemporal dementia: a door-to-door survey in southern Italy', *Neurobiol Aging*, 33(12), 2948.e1-2948.e10.

Beyreuther, K. and Masters, C. L. (1991) 'Amyloid precursor protein (APP) and beta A4 amyloid in the etiology of Alzheimer's disease: precursor-product relationships in the derangement of neuronal function', *Brain Pathol*, 1(4), 241-51.

Bigio, E. H., Lipton, A. M., Yen, S. H., Hutton, M. L., Baker, M., Nacharaju, P., White, C. L., Davies, P., Lin, W. and Dickson, D. W. (2001) 'Frontal lobe dementia with novel tauopathy: sporadic multiple system tauopathy with dementia', *J Neuropathol Exp Neurol*, 60(4), 328-41.

Blessed, G., Tomlinson, B. E. and Roth, M. (1968) 'The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects', *Br J Psychiatry*, 114(512), 797-811.

Blom, E. S., Viswanathan, J., Kilander, L., Helisalmi, S., Soininen, H., Lannfelt, L., Ingelsson, M., Glaser, A. and Hiltunen, M. (2008) 'Low prevalence of APP duplications in Swedish and Finnish patients with early-onset Alzheimer's disease', *Eur J Hum Genet*, 16(2), 171-5.

Bogaerts, V., Engelborghs, S., Kumar-Singh, S., Goossens, D., Pickut, B., van der Zee, J., Sleegers, K., Peeters, K., Martin, J. J., Del-Favero, J., Gasser, T., Dickson, D. W., Wszolek, Z. K., De Deyn, P. P., Theuns, J. and Van Broeckhoven, C. (2007) 'A novel locus for dementia with Lewy bodies: a clinically and genetically heterogeneous disorder', *Brain*, 130(Pt 9), 2277-91.

Bonazza, S., La Morgia, C., Martinelli, P. and Capellari, S. (2011) 'Strio-pallido-dentate calcinosis: a diagnostic approach in adult patients', *Neurol Sci*, 32(4), 537-45.

Bonifati, V., Rizzu, P., van Baren, M. J., Schaap, O., Breedveld, G. J., Krieger, E., Dekker, M. C., Squitieri, F., Ibanez, P., Joosse, M., van Dongen, J. W., Vanacore, N., van Swieten, J. C., Brice, A., Meco, G., van Duijn, C. M., Oostra, B. A. and Heutink, P. (2003) 'Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism', *Science*, 299(5604), 256-9.

Borroni, B., Bonvicini, C., Alberici, A., Buratti, E., Agosti, C., Archetti, S., Papetti, A., Stuani, C., Di Luca, M., Gennarelli, M. and Padovani, A. (2009) 'Mutation within TARDBP leads to frontotemporal dementia without motor neuron disease', *Hum Mutat*, 30(11), E974-83.

Bower, J. H., Maraganore, D. M., McDonnell, S. K. and Rocca, W. A. (1997) 'Incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota, 1976 to 1990', *Neurology*, 49(5), 1284-8.

Braak, H. and Braak, E. (1987) 'Argyrophilic grains: characteristic pathology of cerebral cortex in cases of adult onset dementia without Alzheimer changes', *Neurosci Lett*, 76(1), 124-7.

Braak, H. and Braak, E. (1991) 'Neuropathological stageing of Alzheimer-related changes', *Acta Neuropathol*, 82(4), 239-59.

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H. and Del Tredici, K. (2004) 'Stages in the development of Parkinson's disease-related pathology', *Cell Tissue Res*, 318(1), 121-34.

Bradbury, S. and Eggleston, C. (1925) 'Postural hypertension. A report of three cases.', *Am Heart J*, 1, 76-83.

Bras, J., Guerreiro, R., Darwent, L., Parkkinen, L., Ansorge, O., Escott-Price, V., Hernandez, D. G., Nalls, M. A., Clark, L. N., Honig, L. S., Marder, K., Van Der Flier, W. M., Lemstra, A., Scheltens, P., Rogaeva, E., St George-Hyslop, P., Londos, E., Zetterberg, H., Ortega-Cubero, S., Pastor, P., Ferman, T. J., Graff-Radford, N. R., Ross, O. A., Barber, I., Braae, A., Brown, K., Morgan, K., Maetzler, W., Berg, D., Troakes, C., Al-Sarraj, S., Lashley, T., Compta, Y., Revesz, T., Lees, A., Cairns, N., Halliday, G. M., Mann, D., Pickering-Brown, S., Dickson, D. W., Singleton, A. and Hardy, J. (2014) 'Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies', *Hum Mol Genet*, 23(23), 6139-46.

Brown, R. G., Lacomblez, L., Landwehrmeyer, B. G., Bak, T., Uttner, I., Dubois, B., Agid, Y., Ludolph, A., Bensimon, G., Payan, C., Leigh, N. P. and Group, N. S. (2010) 'Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy', *Brain*, 133(Pt 8), 2382-93.

Brás, J., Guerreiro, R. and Hardy, J. (2015) 'SnapShot: Genetics of Parkinson's disease', *Cell*, 160(3), 570-570.e1.

Bulic, B., Ness, J., Hahn, S., Rennhack, A., Jumpertz, T. and Weggen, S. (2011) 'Chemical Biology, Molecular Mechanism and Clinical Perspective of γ-Secretase Modulators in Alzheimer's Disease', *Curr Neuropharmacol*, 9(4), 598-622.

Burrell, J. R., Kiernan, M. C., Vucic, S. and Hodges, J. R. (2011) 'Motor neuron dysfunction in frontotemporal dementia', *Brain*, 134(Pt 9), 2582-94.

Buxbaum, J. D., Liu, K. N., Luo, Y., Slack, J. L., Stocking, K. L., Peschon, J. J., Johnson, R. S., Castner, B. J., Cerretti, D. P. and Black, R. A. (1998) 'Evidence that tumor necrosis factor alpha converting enzyme is involved in regulated alpha-secretase cleavage of the Alzheimer amyloid protein precursor', *J Biol Chem*, 273(43), 27765-7.

Cacace, R., Van Cauwenberghe, C., Bettens, K., Gijselinck, I., van der Zee, J., Engelborghs, S., Vandenbulcke, M., Van Dongen, J., Bäumer, V., Dillen, L., Mattheijssens, M., Peeters, K., Cruts, M., Vandenberghe, R., De Deyn, P. P., Van Broeckhoven, C. and Sleegers, K. (2013) 'C9orf72 G4C2 repeat expansions in Alzheimer's disease and mild cognitive impairment', *Neurobiol Aging*, 34(6), 1712.e1-7.

Cairns, N. J., Bigio, E. H., Mackenzie, I. R., Neumann, M., Lee, V. M., Hatanpaa, K. J., White, C. L., Schneider, J. A., Grinberg, L. T., Halliday, G., Duyckaerts, C., Lowe, J. S., Holm, I. E., Tolnay, M., Okamoto, K., Yokoo, H., Murayama, S., Woulfe, J., Munoz, D. G., Dickson, D. W., Ince, P. G., Trojanowski, J. Q., Mann, D. M. and Degeneration, C. f. F. L. (2007) 'Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration', *Acta Neuropathol*, 114(1), 5-22.

Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., Thomas-Anterion, C., Michon, A., Martin, C., Charbonnier, F., Raux, G., Camuzat, A., Penet, C., Mesnage, V., Martinez, M., Clerget-Darpoux, F., Brice, A. and Frebourg, T. (1999) 'Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum', *Am J Hum Genet*, 65(3), 664-70.

Caporaso, G. L., Takei, K., Gandy, S. E., Matteoli, M., Mundigl, O., Greengard, P. and De Camilli, P. (1994) 'Morphologic and biochemical analysis of the intracellular trafficking of the Alzheimer beta/A4 amyloid precursor protein', *J Neurosci*, 14(5 Pt 2), 3122-38.

Carrasquillo, M. M., Zou, F., Pankratz, V. S., Wilcox, S. L., Ma, L., Walker, L. P., Younkin, S. G., Younkin, C. S., Younkin, L. H., Bisceglio, G. D., Ertekin-Taner, N., Crook, J. E., Dickson, D. W., Petersen, R. C. and Graff-Radford, N. R. (2009) 'Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease', *Nat Genet*, 41(2), 192-8.

Castellano, J. M., Kim, J., Stewart, F. R., Jiang, H., DeMattos, R. B., Patterson, B. W., Fagan, A. M., Morris, J. C., Mawuenyega, K. G., Cruchaga, C., Goate, A. M., Bales, K. R., Paul, S. M., Bateman, R. J. and Holtzman, D. M. (2011) 'Human apoE isoforms differentially regulate brain amyloid-β peptide clearance', *Sci Transl Med*, 3(89), 89ra57.

Chartier-Harlin, M. C., Kachergus, J., Roumier, C., Mouroux, V., Douay, X., Lincoln, S., Levecque, C., Larvor, L., Andrieux, J., Hulihan, M., Waucquier, N., Defebvre, L., Amouyel, P., Farrer, M. and Destée, A. (2004) 'Alpha-synuclein locus duplication as a cause of familial Parkinson's disease', *Lancet*, 364(9440), 1167-9.

Chaugule, V. K. and Walden, H. (2016) 'Specificity and disease in the ubiquitin system', *Biochem Soc Trans*, 44(1), 212-27.

Chen, Z., Cooper, B., Kalla, S., Varoqueaux, F. and Young, S. M. (2013) 'The Munc13 proteins differentially regulate readily releasable pool dynamics and calcium-dependent recovery at a central synapse', *J Neurosci*, 33(19), 8336-51.

Cheng, F., Vivacqua, G. and Yu, S. (2011) 'The role of α-synuclein in neurotransmission and synaptic plasticity', *J Chem Neuroanat*, 42(4), 242-8.

Chi, S., Jiang, T., Tan, L. and Yu, J. T. (2016) 'Distinct neurological disorders with C9orf72 mutations: genetics, pathogenesis, and therapy', *Neurosci Biobehav Rev*, 66, 127-42.

Chow, V. W., Mattson, M. P., Wong, P. C. and Gleichmann, M. (2010) 'An overview of APP processing enzymes and products', *Neuromolecular Med*, 12(1), 1-12.

Chávez-Gutiérrez, L., Bammens, L., Benilova, I., Vandersteen, A., Benurwar, M., Borgers, M., Lismont, S., Zhou, L., Van Cleynenbreugel, S., Esselmann, H., Wiltfang, J., Serneels, L., Karran, E., Gijsen, H., Schymkowitz, J., Rousseau, F., Broersen, K. and De Strooper, B. (2012) 'The mechanism of γ-Secretase dysfunction in familial Alzheimer disease', *EMBO J*, 31(10), 2261-74.

Cingolani, P., Platts, A., Wang, l. L., Coon, M., Nguyen, T., Wang, L., Land, S. J., Lu, X. and Ruden, D. M. (2012) 'A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: SNPs in the genome of Drosophila melanogaster strain w1118; iso-2; iso-3', *Fly (Austin)*, 6(2), 80-92.

Cioffi, S. M., Galimberti, D., Barocco, F., Spallazzi, M., Fenoglio, C., Serpente, M., Arcaro, M., Gardini, S., Scarpini, E. and Caffarra, P. (2016) 'Non Fluent Variant of Primary Progressive Aphasia Due to the Novel GRN g.9543delA(IVS3-2delA) Mutation', *J Alzheimers Dis*.

Clark, L. N., Kartsaklis, L. A., Wolf Gilbert, R., Dorado, B., Ross, B. M., Kisselev, S., Verbitsky, M., Mejia-Santana, H., Cote, L. J., Andrews, H., Vonsattel, J. P., Fahn, S., Mayeux, R., Honig, L. S. and Marder, K. (2009) 'Association of glucocerebrosidase mutations with dementia with lewy bodies', *Arch Neurol*, 66(5), 578-83.

Cohn-Hokke, P. E., Elting, M. W., Pijnenburg, Y. A. and van Swieten, J. C. (2012) 'Genetics of dementia: update and guidelines for the clinician', *Am J Med Genet B Neuropsychiatr Genet*, 159B(6), 628-43.

Conway, K. A., Harper, J. D. and Lansbury, P. T. (1998) 'Accelerated in vitro fibril formation by a mutant alpha-synuclein linked to early-onset Parkinson disease', *Nat Med*, 4(11), 1318-20.

Corder, E. H., Saunders, A. M., Risch, N. J., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Rimmler, J. B., Locke, P. A., Conneally, P. M. and Schmader, K. E. (1994) 'Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease', *Nat Genet*, 7(2), 180-4.

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L. and Pericak-Vance, M. A. (1993) 'Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families', *Science*, 261(5123), 921-3.

Crook, R., Verkkoniemi, A., Perez-Tur, J., Mehta, N., Baker, M., Houlden, H., Farrer, M., Hutton, M., Lincoln, S., Hardy, J., Gwinn, K., Somer, M., Paetau, A., Kalimo, H., Ylikoski, R., Pöyhönen, M., Kucera, S. and Haltia, M. (1998) 'A variant of Alzheimer's disease with spastic paraparesis and unusual plaques due to deletion of exon 9 of presenilin 1', *Nat Med*, 4(4), 452-5.

Cruchaga, C., Haller, G., Chakraverty, S., Mayo, K., Vallania, F. L., Mitra, R. D., Faber, K., Williamson, J., Bird, T., Diaz-Arrastia, R., Foroud, T. M., Boeve, B. F., Graff-Radford, N. R., St Jean, P., Lawson, M., Ehm, M. G., Mayeux, R., Goate, A. M. and Consortium, N.-L. N. F. S. (2012) 'Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families', *PLoS One*, 7(2), e31039.

Cruchaga, C., Karch, C. M., Jin, S. C., Benitez, B. A., Cai, Y., Guerreiro, R., Harari, O., Norton, J., Budde, J., Bertelsen, S., Jeng, A. T., Cooper, B., Skorupa, T., Carrell, D., Levitch, D., Hsu, S., Choi, J., Ryten, M., Hardy, J., Trabzuni, D., Weale, M. E., Ramasamy, A., Smith, C., Sassi, C., Bras, J., Gibbs, J. R., Hernandez, D. G., Lupton, M. K., Powell, J., Forabosco, P., Ridge, P. G., Corcoran, C. D.,

Tschanz, J. T., Norton, M. C., Munger, R. G., Schmutz, C., Leary, M., Demirci, F. Y., Bamne, M. N., Wang, X., Lopez, O. L., Ganguli, M., Medway, C., Turton, J., Lord, J., Braae, A., Barber, I., Brown, K., Passmore, P., Craig, D., Johnston, J., McGuinness, B., Todd, S., Heun, R., Kölsch, H., Kehoe, P. G., Hooper, N. M., Vardy, E. R., Mann, D. M., Pickering-Brown, S., Kalsheker, N., Lowe, J., Morgan, K., David Smith, A., Wilcock, G., Warden, D., Holmes, C., Pastor, P., Lorenzo-Betancor, O., Brkanac, Z., Scott, E., Topol, E., Rogaeva, E., Singleton, A. B., Kamboh, M. I., St George-Hyslop, P., Cairns, N., Morris, J. C., Kauwe, J. S., Goate, A. M., Consortium, U. B. E. and Consortium, A. s. R. U. (2014) 'Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease', *Nature*, 505(7484), 550-4.

Cruts, M., Gijselinck, I., van der Zee, J., Engelborghs, S., Wils, H., Pirici, D., Rademakers, R., Vandenberghe, R., Dermaut, B., Martin, J. J., van Duijn, C., Peeters, K., Sciot, R., Santens, P., De Pooter, T., Mattheijssens, M., Van den Broeck, M., Cuijt, I., Vennekens, K., De Deyn, P. P., Kumar-Singh, S. and Van Broeckhoven, C. (2006) 'Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21', *Nature*, 442(7105), 920-4.

Cruts, M., Theuns, J. and Van Broeckhoven, C. (2012) 'Locus-specific mutation databases for neurodegenerative brain diseases', *Hum Mutat*, 33(9), 1340-4.

Cruts, M., van Duijn, C. M., Backhovens, H., Van den Broeck, M., Wehnert, A., Serneels, S., Sherrington, R., Hutton, M., Hardy, J., St George-Hyslop, P. H., Hofman, A. and Van Broeckhoven, C. (1998) 'Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile Alzheimer disease', *Hum Mol Genet*, 7(1), 43-51.

Dai, X., Gao, Y., Xu, Z., Cui, X., Liu, J., Li, Y., Xu, H., Liu, M., Wang, Q. K. and Liu, J. Y. (2010) 'Identification of a novel genetic locus on chromosome 8p21.1-q11.23 for idiopathic basal ganglia calcification', *Am J Med Genet B Neuropsychiatr Genet*, 153B(7), 1305-10.

David, S., Ferreira, J., Quenez, O., Rovelet-Lecrux, A., Richard, A. C., Vérin, M., Jurici, S., Le Ber, I., Boland, A., Deleuze, J. F., Frebourg, T., Mendes de Oliveira, J. R., Hannequin, D., Campion, D. and Nicolas, G. (2016) 'Identification of partial SLC20A2 deletions in primary brain calcification using whole-exome sequencing', *Eur J Hum Genet*.

Davies, L., Wolska, B., Hilbich, C., Multhaup, G., Martins, R., Simms, G., Beyreuther, K. and Masters, C. L. (1988) 'A4 amyloid protein deposition and the diagnosis of Alzheimer's disease: prevalence in aged brains determined by immunocytochemistry compared with conventional neuropathologic techniques', *Neurology*, 38(11), 1688-93.

de Lau, L. M. and Breteler, M. M. (2006) 'Epidemiology of Parkinson's disease', *Lancet Neurol*, 5(6), 525-35.

de Oliveira, M. F., Steinberg, S. S. and de Oliveira, J. R. (2013) 'The challenging interpretation of genetic and neuroimaging features in basal ganglia calcification', *Gen Hosp Psychiatry*, 35(2), 210-1.

De Strooper, B., Saftig, P., Craessaerts, K., Vanderstichele, H., Guhde, G., Annaert, W., Von Figura, K. and Van Leuven, F. (1998) 'Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein', *Nature*, 391(6665), 387-90.

Dejerine, J. and Thomas, A. A. (1900) 'L'atrophie olivo-ponto-cérébelleuse', *Nouv Iconog de la Salpêtrière*, 13, 330-370.

DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., Boxer, A. L., Baker, M., Rutherford, N. J., Nicholson, A. M., Finch, N. A., Flynn, H., Adamson, J., Kouri, N., Wojtas, A., Sengdy, P., Hsiung, G. Y., Karydas, A., Seeley, W. W., Josephs, K. A., Coppola, G., Geschwind, D. H., Wszolek, Z. K., Feldman, H., Knopman, D. S., Petersen, R. C., Miller, B. L., Dickson, D. W., Boylan, K. B., Graff-Radford, N. R. and Rademakers, R. (2011) 'Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS', *Neuron*, 72(2), 245-56.

Delacour, A. (1850) 'Ossification des capillaires du cerveau', *Ann Med Psychol.* , 2, 458-461.

Devine, M. J., Ryten, M., Vodicka, P., Thomson, A. J., Burdon, T., Houlden, H., Cavaleri, F., Nagano, M., Drummond, N. J., Taanman, J. W., Schapira, A. H., Gwinn, K., Hardy, J., Lewis, P. A. and Kunath, T. (2011) 'Parkinson's disease induced pluripotent stem cells with triplication of the α-synuclein locus', *Nat Commun*, 2, 440.

Di Fonzo, A., Dekker, M. C., Montagna, P., Baruzzi, A., Yonova, E. H., Correia Guedes, L., Szczerbinska, A., Zhao, T., Dubbel-Hulsman, L. O., Wouters, C. H., de Graaff, E., Oyen, W. J., Simons, E. J., Breedveld, G. J., Oostra, B. A., Horstink, M. W. and Bonifati, V. (2009) 'FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome', *Neurology*, 72(3), 240-5.

Di Fonzo, A., Wu-Chou, Y. H., Lu, C. S., van Doeselaar, M., Simons, E. J., Rohé, C. F., Chang, H. C., Chen, R. S., Weng, Y. H., Vanacore, N., Breedveld, G. J., Oostra, B. A. and Bonifati, V. (2006) 'A common missense variant in the LRRK2 gene, Gly2385Arg, associated with Parkinson's disease risk in Taiwan', *Neurogenetics*, 7(3), 133-8.

Dickson, D. W. (1999) 'Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration', *J Neurol*, 246 Suppl 2, II6-15.

Dickson, D. W. (2001) 'Neuropathology of Pick's disease', *Neurology*, 56(11 Suppl 4), S16-20.

Dickson, D. W. (2012) 'Parkinson's disease and parkinsonism: neuropathology', *Cold Spring Harb Perspect Med*, 2(8).

Dickson, D. W., Bergeron, C., Chin, S. S., Duyckaerts, C., Horoupian, D., Ikeda, K., Jellinger, K., Lantos, P. L., Lippa, C. F., Mirra, S. S., Tabaton, M., Vonsattel, J. P., Wakabayashi, K., Litvan, I. and Health, O. o. R. D. o. t. N. I. o. (2002) 'Office of Rare Diseases neuropathologic criteria for corticobasal degeneration', *J Neuropathol Exp Neurol*, 61(11), 935-46.

Dickson, D. W., Uchikado, H., Fujishiro, H. and Tsuboi, Y. (2010) 'Evidence in favor of Braak staging of Parkinson's disease', *Mov Disord*, 25 Suppl 1, S78-82.

Duckett, S., Galle, P., Escourolle, R., Poirier, J. and Hauw, J. J. (1977) 'Presence of zinc, aluminum, magnesium in striopalledodentate (SPD) calcifications (Fahr's disease): electron probe study', *Acta Neuropathol*, 38(1), 7-10.

Duyckaerts, C., Delatour, B. and Potier, M. C. (2009) 'Classification and basic pathology of Alzheimer disease', *Acta Neuropathol*, 118(1), 5-36.

Edvardson, S., Cinnamon, Y., Ta-Shma, A., Shaag, A., Yim, Y. I., Zenvirt, S., Jalas, C., Lesage, S., Brice, A., Taraboulos, A., Kaestner, K. H., Greene, L. E. and Elpeleg, O. (2012) 'A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism', *PLoS One*, 7(5), e36458.

Elkon, H., Don, J., Melamed, E., Ziv, I., Shirvan, A. and Offen, D. (2002) 'Mutant and wild-type alpha-synuclein interact with mitochondrial cytochrome C oxidase', *J Mol Neurosci*, 18(3), 229-38.

Ellie, E., Julien, J. and Ferrer, X. (1989) 'Familial idiopathic striopallidodentate calcifications', *Neurology*, 39(3), 381-5.

Emmanouilidou, E., Stefanis, L. and Vekrellis, K. (2010) 'Cell-produced alpha-synuclein oligomers are targeted to, and impair, the 26S proteasome', *Neurobiol Aging*, 31(6), 953-68.

Esch, F. S., Keim, P. S., Beattie, E. C., Blacher, R. W., Culwell, A. R., Oltersdorf, T., McClure, D. and Ward, P. J. (1990) 'Cleavage of amyloid beta peptide during constitutive processing of its precursor', *Science*, 248(4959), 1122-4.

Fahr, T. (1930) 'Idiopathische Verkalkung der Hirngefässe', *Zbl Allg Pathol Pathol Anat.* , 50, 129-133.

Fanciulli, A. and Wenning, G. K. (2015) 'Multiple-system atrophy', *N Engl J Med*, 372(3), 249-63.

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., Myers, R. H., Pericak-Vance, M. A., Risch, N. and van Duijn, C. M. (1997) 'Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium', *JAMA*, 278(16), 1349-56.

Fauvet, B., Mbefo, M. K., Fares, M. B., Desobry, C., Michael, S., Ardah, M. T., Tsika, E., Coune, P., Prudent, M., Lion, N., Eliezer, D., Moore, D. J., Schneider, B., Aebischer, P., El-Agnaf, O. M., Masliah, E. and Lashuel, H. A. (2012) 'α-Synuclein in central nervous system and from erythrocytes, mammalian cells, and Escherichia coli exists predominantly as disordered monomer', *J Biol Chem*, 287(19), 15345-64.

Ferguson, M. C., Garland, E. M., Hedges, L., Womack-Nunley, B., Hamid, R., Phillips, J. A., Shibao, C. A., Raj, S. R., Biaggioni, I. and Robertson, D. (2014) 'SHC2 gene copy number in multiple system atrophy (MSA)', *Clin Auton Res*, 24(1), 25-30.

Fernandez, M. A., Klutkowski, J. A., Freret, T. and Wolfe, M. S. (2014) 'Alzheimer presenilin-1 mutations dramatically reduce trimming of long amyloid β-peptides (Aβ) by γ-secretase to increase 42-to-40-residue Aβ', *J Biol Chem*, 289(45), 31043-52.

Ferrari, R., Forabosco, P., Vandrovcova, J., Botía, J. A., Guelfi, S., Warren, J. D., Momeni, P., Weale, M. E., Ryten, M., Hardy, J. and (UKBEC), U. B. E. C. (2016) 'Frontotemporal dementia: insights into the biological underpinnings of disease through gene co-expression network analysis', *Mol Neurodegener*, 11, 21.

Ferrari, R., Hernandez, D. G., Nalls, M. A., Rohrer, J. D., Ramasamy, A., Kwok, J. B., Dobson-Stone, C., Brooks, W. S., Schofield, P. R., Halliday, G. M., Hodges, J. R., Piguet, O., Bartley, L., Thompson, E., Haan, E., Hernández, I., Ruiz, A., Boada, M., Borroni, B., Padovani, A., Cruchaga, C., Cairns, N. J., Benussi, L., Binetti, G., Ghidoni, R., Forloni, G., Galimberti, D., Fenoglio, C., Serpente, M., Scarpini, E., Clarimón, J., Lleó, A., Blesa, R., Waldö, M. L., Nilsson, K., Nilsson, C., Mackenzie, I. R., Hsiung, G. Y., Mann, D. M., Grafman, J., Morris, C. M., Attems, J., Griffiths, T. D., McKeith, I. G., Thomas, A. J., Pietrini, P., Huey, E. D., Wassermann, E. M., Baborie, A., Jaros, E., Tierney, M. C., Pastor, P., Razquin, C., Ortega-Cubero, S., Alonso, E., Perneczky, R., Diehl-Schmid, J., Alexopoulos, P., Kurz, A., Rainero, I., Rubino, E., Pinessi, L., Rogaeva, E., St George-Hyslop, P., Rossi, G., Tagliavini, F., Giaccone, G., Rowe, J. B., Schlachetzki, J. C., Uphill, J., Collinge, J., Mead, S., Danek, A., Van Deerlin, V. M., Grossman, M., Trojanowski, J. Q., van der Zee, J., Deschamps, W., Van Langenhove, T., Cruts, M., Van Broeckhoven, C., Cappa, S. F., Le Ber, I., Hannequin, D., Golfier, V., Vercelletto, M., Brice, A., Nacmias, B., Sorbi, S., Bagnoli, S., Piaceri, I., Nielsen, J. E., Hjermind, L. E., Riemenschneider, M., Mayhaus, M., Ibach, B.,

Gasparoni, G., Pichler, S., Gu, W., Rossor, M. N., *et al.* (2014) 'Frontotemporal dementia and its subtypes: a genome-wide association study', *Lancet Neurol*, 13(7), 686-99.

Ferreira, J. B., Pimentel, L., Keasey, M. P., Lemos, R. R., Santos, L. M., Oliveira, M. F., Santos, S., Jensen, N., Teixeira, K., Pedersen, L., Rocha, C. R., Dias da Silva, M. R. and Oliveira, J. R. (2014) 'First report of a de novo mutation at SLC20A2 in a patient with brain calcification', *J Mol Neurosci*, 54(4), 748-51.

Freischmidt, A., Wieland, T., Richter, B., Ruf, W., Schaeffer, V., Müller, K., Marroquin, N., Nordin, F., Hübers, A., Weydt, P., Pinto, S., Press, R., Millecamps, S., Molko, N., Bernard, E., Desnuelle, C., Soriani, M. H., Dorst, J., Graf, E., Nordström, U., Feiler, M. S., Putz, S., Boeckers, T. M., Meyer, T., Winkler, A. S., Winkelman, J., de Carvalho, M., Thal, D. R., Otto, M., Brännström, T., Volk, A. E., Kursula, P., Danzer, K. M., Lichtner, P., Dikic, I., Meitinger, T., Ludolph, A. C., Strom, T. M., Andersen, P. M. and Weishaupt, J. H. (2015) 'Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia', *Nat Neurosci*, 18(5), 631-6.

Fuchs, J., Nilsson, C., Kachergus, J., Munz, M., Larsson, E. M., Schüle, B., Langston, J. W., Middleton, F. A., Ross, O. A., Hulihan, M., Gasser, T. and Farrer, M. J. (2007) 'Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication', *Neurology*, 68(12), 916-22.

Fuchs, T., Gavarini, S., Saunders-Pullman, R., Raymond, D., Ehrlich, M. E., Bressman, S. B. and Ozelius, L. J. (2009) 'Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia', *Nat Genet*, 41(3), 286-8.

Fujishiro, H., Ferman, T. J., Boeve, B. F., Smith, G. E., Graff-Radford, N. R., Uitti, R. J., Wszolek, Z. K., Knopman, D. S., Petersen, R. C., Parisi, J. E. and Dickson, D. W. (2008) 'Validation of the neuropathologic criteria of the third consortium for dementia with Lewy bodies for prospectively diagnosed cases', *J Neuropathol Exp Neurol*, 67(7), 649-56.

Furukawa, K., Sopher, B. L., Rydel, R. E., Begley, J. G., Pham, D. G., Martin, G. M., Fox, M. and Mattson, M. P. (1996) 'Increased activity-regulating and neuroprotective efficacy of alpha-secretase-derived secreted amyloid precursor protein conferred by a C-terminal heparin-binding domain', *J Neurochem*, 67(5), 1882-96.

Gans, A. (1925) ' De Ziekten van Pick en van Alzheimer', *Nederlands tijdschrift voor geneeskunde*, (68), 1953.

Garre-Olmo, J., Genís Batlle, D., del Mar Fernández, M., Marquez Daniel, F., de Eugenio Huélamo, R., Casadevall, T., Turbau Recio, J., Turon Estrada, A., López-Pousa, S. and Group), R. o. D. o. G. S. G. R. S. (2010) 'Incidence and subtypes of early-onset dementia in a geographically defined general population', *Neurology*, 75(14), 1249-55.

Gatz, M., Reynolds, C. A., Fratiglioni, L., Johansson, B., Mortimer, J. A., Berg, S., Fiske, A. and Pedersen, N. L. (2006) 'Role of genes and environments for explaining Alzheimer disease', *Arch Gen Psychiatry*, 63(2), 168-74.

Gellera, C., Tiloca, C., Del Bo, R., Corrado, L., Pensato, V., Agostini, J., Cereda, C., Ratti, A., Castellotti, B., Corti, S., Bagarotti, A., Cagnin, A., Milani, P., Gabelli, C., Riboldi, G., Mazzini, L., Sorarù, G., D'Alfonso, S., Taroni, F., Comi, G. P., Ticozzi, N., Silani, V. and Consortium, S. (2013) 'Ubiquilin 2 mutations in Italian patients with amyotrophic lateral sclerosis and frontotemporal dementia', *J Neurol Neurosurg Psychiatry*, 84(2), 183-7.

Geschwind, D. H., Loginov, M. and Stern, J. M. (1999) 'Identification of a locus on chromosome 14q for idiopathic basal ganglia calcification (Fahr disease)', *Am J Hum Genet*, 65(3), 764-72.

Ghosh, D., Sahay, S., Ranjan, P., Salot, S., Mohite, G. M., Singh, P. K., Dwivedi, S., Carvalho, E., Banerjee, R., Kumar, A. and Maji, S. K. (2014) 'The newly discovered Parkinson's disease associated Finnish mutation (A53E) attenuates α-synuclein aggregation and membrane binding', *Biochemistry*, 53(41), 6419-21.

Gibb, W. R. and Lees, A. J. (1988) 'A comparison of clinical and pathological features of young- and old-onset Parkinson's disease', *Neurology*, 38(9), 1402-6.

Gijselinck, I., Van Mossevelde, S., van der Zee, J., Sieben, A., Philtjens, S., Heeman, B., Engelborghs, S., Vandenbulcke, M., De Baets, G., Bäumer, V., Cuijt, I., Van den Broeck, M., Peeters, K., Mattheijssens, M., Rousseau, F., Vandenberghe, R., De Jonghe, P., Cras, P., De Deyn, P. P., Martin, J. J., Cruts, M., Van Broeckhoven, C. and Consortium, B. (2015) 'Loss of TBK1 is a frequent cause of frontotemporal dementia in a Belgian cohort', *Neurology*, 85(24), 2116-25.

Gilberti, N., Turla, M., Alberici, A., Bertasi, V., Civelli, P., Archetti, S., Padovani, A. and Borroni, B. (2012) 'Prevalence of frontotemporal lobar degeneration in an isolated population: the Vallecamonica study', *Neurol Sci*, 33(4), 899-904.

Gilman, S. (2005) 'Functional imaging with positron emission tomography in multiple system atrophy', *J Neural Transm (Vienna)*, 112(12), 1647-55.

Gilman, S., Low, P. A., Quinn, N., Albanese, A., Ben-Shlomo, Y., Fowler, C. J., Kaufmann, H., Klockgether, T., Lang, A. E., Lantos, P. L., Litvan, I., Mathias, C. J., Oliver, E., Robertson, D., Schatz, I. and Wenning, G. K. (1999) 'Consensus statement on the diagnosis of multiple system atrophy', *J Neurol Sci*, 163(1), 94-8.

Gilman, S., Wenning, G. K., Low, P. A., Brooks, D. J., Mathias, C. J., Trojanowski, J. Q., Wood, N. W., Colosimo, C., Dürr, A., Fowler, C. J., Kaufmann, H., Klockgether, T., Lees, A., Poewe, W., Quinn, N., Revesz, T., Robertson, D., Sandroni, P., Seppi, K. and Vidailhet, M. (2008) 'Second consensus statement on the diagnosis of multiple system atrophy', *Neurology*, 71(9), 670-6.

Giovannini, D., Touhami, J., Charnet, P., Sitbon, M. and Battini, J. L. (2013) 'Inorganic phosphate export by the retrovirus receptor XPR1 in metazoans', *Cell Rep*, 3(6), 1866-73.

Glenner, G. G. and Wong, C. W. (1984) 'Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein', *Biochem Biophys Res Commun*, 122(3), 1131-5.

Goate, A., Chartier-Harlin, M. C., Mullan, M., Brown, J., Crawford, F., Fidani, L., Giuffra, L., Haynes, A., Irving, N. and James, L. (1991) 'Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease', *Nature*, 349(6311), 704-6.

Goedert, M. (2015) 'Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein', *Science*, 349(6248), 1255555.

Goedert, M., Masuda-Suzukake, M. and Falcon, B. (2016) 'Like prions: the propagation of aggregated tau and α-synuclein in neurodegeneration', *Brain*.

Goldman, J. S., Farmer, J. M., Wood, E. M., Johnson, J. K., Boxer, A., Neuhaus, J., Lomen-Hoerth, C., Wilhelmsen, K. C., Lee, V. M., Grossman, M. and Miller, B. L. (2005) 'Comparison of family histories in FTLD subtypes and related tauopathies', *Neurology*, 65(11), 1817-9.

Goodwin, S., McPherson, J. D. and McCombie, W. R. (2016) 'Coming of age: ten years of next-generation sequencing technologies', *Nat Rev Genet*, 17(6), 333-51.

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., Ogar, J. M., Rohrer, J. D., Black, S., Boeve, B. F., Manes, F., Dronkers, N. F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B. L., Knopman, D. S., Hodges, J. R., Mesulam, M. M. and Grossman, M. (2011) 'Classification of primary progressive aphasia and its variants', *Neurology*, 76(11), 1006-14.

Graham, J. G. and Oppenheimer, D. R. (1969) 'Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy', *J Neurol Neurosurg Psychiatry*, 32(1), 28-34.

Griciuc, A., Serrano-Pozo, A., Parrado, A. R., Lesinski, A. N., Asselin, C. N., Mullin, K., Hooli, B., Choi, S. H., Hyman, B. T. and Tanzi, R. E. (2013) 'Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta', *Neuron*, 78(4), 631-43.

Grundke-Iqbal, I., Iqbal, K., Quinlan, M., Tung, Y. C., Zaidi, M. S. and Wisniewski, H. M. (1986a) 'Microtubule-associated protein tau. A component of Alzheimer paired helical filaments', *J Biol Chem*, 261(13), 6084-9.

Grundke-Iqbal, I., Iqbal, K., Tung, Y. C., Quinlan, M., Wisniewski, H. M. and Binder, L. I. (1986b) 'Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology', *Proc Natl Acad Sci U S A*, 83(13), 4913-7.

Grütz, K., Volpato, C. B., Domingo, A., Alvarez-Fischer, D., Gebert, U., Schifferle, G., Buffone, E., Wszolek, Z. K., Rademakers, R., Ferbert, A., Hicks, A. A., Klein, C., Pramstaller, P. P. and Westenberger, A. (2016) 'Primary familial brain calcification in the 'IBGC2' kindred: All linkage roads lead to SLC20A2', *Mov Disord*.

Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaeva, E., Majounie, E., Cruchaga, C., Sassi, C., Kauwe, J. S., Younkin, S., Hazrati, L., Collinge, J., Pocock, J., Lashley, T., Williams, J., Lambert, J. C., Amouyel, P., Goate, A., Rademakers, R., Morgan, K., Powell, J., St George-Hyslop, P., Singleton, A., Hardy, J. and Group, A. G. A. (2013) 'TREM2 variants in Alzheimer's disease', *N Engl J Med*, 368(2), 117-27.

Guglielmotto, M., Aragno, M., Autelli, R., Giliberto, L., Novo, E., Colombatto, S., Danni, O., Parola, M., Smith, M. A., Perry, G., Tamagno, E. and Tabaton, M. (2009) 'The up-regulation of BACE1 mediated by hypoxia and ischemic injury: role of oxidative stress and HIF1alpha', *J Neurochem*, 108(4), 1045-56.

Guo, J. L., Covell, D. J., Daniels, J. P., Iba, M., Stieber, A., Zhang, B., Riddle, D. M., Kwong, L. K., Xu, Y., Trojanowski, J. Q. and Lee, V. M. (2013) 'Distinct α-synuclein strains differentially promote tau inclusions in neurons', *Cell*, 154(1), 103-17.

Gustafson, L. (1987) 'Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis', *Arch Gerontol Geriatr*, 6(3), 209-23.

Guyant-Marechal, I., Berger, E., Laquerrière, A., Rovelet-Lecrux, A., Viennet, G., Frebourg, T., Rumbach, L., Campion, D. and Hannequin, D. (2008) 'Intrafamilial diversity of phenotype associated with app duplication', *Neurology*, 71(23), 1925-6.

Haeusler, A. R., Donnelly, C. J. and Rothstein, J. D. (2016) 'The expanding biology of the C9orf72 nucleotide repeat expansion in neurodegenerative disease', *Nat Rev Neurosci*, 17(6), 383-95.

Hara, K., Momose, Y., Tokiguchi, S., Shimohata, M., Terajima, K., Onodera, O., Kakita, A., Yamada, M., Takahashi, H., Hirasawa, M., Mizuno, Y., Ogata, K., Goto, J., Kanazawa, I., Nishizawa, M. and Tsuji, S.

(2007) 'Multiplex families with multiple system atrophy', *Arch Neurol*, 64(4), 545-51.

Hardy, J. and Allsop, D. (1991) 'Amyloid deposition as the central event in the aetiology of Alzheimer's disease', *Trends Pharmacol Sci*, 12(10), 383-8.

Hardy, J., Crook, R., Prihar, G., Roberts, G., Raghavan, R. and Perry, R. (1994) 'Senile dementia of the Lewy body type has an apolipoprotein E epsilon 4 allele frequency intermediate between controls and Alzheimer's disease', *Neurosci Lett*, 182(1), 1-2.

Hardy, J. and Singleton, A. (2009) 'Genomewide association studies and human disease', *N Engl J Med*, 360(17), 1759-68.

Hardy, J. A. and Higgins, G. A. (1992) 'Alzheimer's disease: the amyloid cascade hypothesis', *Science*, 256(5054), 184-5.

Harms, M., Benitez, B. A., Cairns, N., Cooper, B., Cooper, P., Mayo, K., Carrell, D., Faber, K., Williamson, J., Bird, T., Diaz-Arrastia, R., Foroud, T. M., Boeve, B. F., Graff-Radford, N. R., Mayeux, R., Chakraverty, S., Goate, A. M., Cruchaga, C. and Consortium, N.-L. N. F. S. (2013) 'C9orf72 hexanucleotide repeat expansions in clinical Alzheimer disease', *JAMA Neurol*, 70(6), 736-41.

Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M. L., Pahwa, J. S., Moskvina, V., Dowzell, K., Williams, A., Jones, N., Thomas, C., Stretton, A., Morgan, A. R., Lovestone, S., Powell, J., Proitsi, P., Lupton, M. K., Brayne, C., Rubinsztein, D. C., Gill, M., Lawlor, B., Lynch, A., Morgan, K., Brown, K. S., Passmore, P. A., Craig, D., McGuinness, B., Todd, S., Holmes, C., Mann, D., Smith, A. D., Love, S., Kehoe, P. G., Hardy, J., Mead, S., Fox, N., Rossor, M., Collinge, J., Maier, W., Jessen, F., Schürmann, B., Heun, R., van den Bussche, H., Heuser, I., Kornhuber, J., Wiltfang, J., Dichgans, M., Frölich, L., Hampel, H., Hüll, M., Rujescu, D., Goate, A. M., Kauwe, J. S., Cruchaga, C., Nowotny, P., Morris, J. C., Mayo, K., Sleegers, K., Bettens, K., Engelborghs, S., De Deyn, P. P., Van Broeckhoven, C., Livingston, G., Bass, N. J., Gurling, H., McQuillin, A., Gwilliam, R., Deloukas, P., Al-Chalabi, A., Shaw, C. E., Tsolaki, M., Singleton, A. B., Guerreiro, R., Mühleisen, T. W., Nöthen, M. M., Moebus, S., Jöckel, K. H., Klopp, N., Wichmann, H. E., Carrasquillo, M. M., Pankratz, V. S., Younkin, S. G., Holmans, P. A., O'Donovan, M., Owen, M. J. and Williams, J. (2009) 'Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease', *Nat Genet*, 41(10), 1088-93.

Hass, M. R. and Yankner, B. A. (2005) 'A {gamma}-secretase-independent mechanism of signal transduction by the amyloid precursor protein', *J Biol Chem*, 280(44), 36895-904.

Hellström, M., Gerhardt, H., Kalén, M., Li, X., Eriksson, U., Wolburg, H. and Betsholtz, C. (2001) 'Lack of pericytes leads to endothelial hyperplasia and abnormal vascular morphogenesis', *J Cell Biol*, 153(3), 543-53.

Hiltunen, M., Helisalmi, S., Mannermaa, A., Alafuzoff, I., Koivisto, A. M., Lehtovirta, M., Pirskanen, M., Sulkava, R., Verkkoniemi, A. and Soininen, H. (2000) 'Identification of a novel 4.6-kb genomic deletion in presenilin-1 gene which results in exclusion of exon 9 in a Finnish early onset Alzheimer's disease family: an Alu core sequence-stimulated recombination?', *Eur J Hum Genet*, 8(4), 259-66.

Hippius, H. and Neundörfer, G. (2003) 'The discovery of Alzheimer's disease', *Dialogues Clin Neurosci*, 5(1), 101-8.

Hogan, D. B., Fiest, K. M., Roberts, J. I., Maxwell, C. J., Dykeman, J., Pringsheim, T., Steeves, T., Smith, E. E., Pearson, D. and Jetté, N. (2016) 'The Prevalence and Incidence of Dementia with Lewy Bodies: a Systematic Review', *Can J Neurol Sci*, 43 Suppl 1, S83-95.

Holland, P. M., Abramson, R. D., Watson, R. and Gelfand, D. H. (1991) 'Detection of specific polymerase chain reaction product by utilizing the 5'----3' exonuclease activity of Thermus aquaticus DNA polymerase', *Proc Natl Acad Sci U S A*, 88(16), 7276-80.

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J. C., Carrasquillo, M. M., Abraham, R., Hamshere, M. L., Pahwa, J. S., Moskvina, V., Dowzell, K., Jones, N., Stretton, A., Thomas, C., Richards, A., Ivanov, D., Widdowson, C., Chapman, J., Lovestone, S., Powell, J., Proitsi, P., Lupton, M. K., Brayne, C., Rubinsztein, D. C., Gill, M., Lawlor, B., Lynch, A., Brown, K. S., Passmore, P. A., Craig, D., McGuinness, B., Todd, S., Holmes, C., Mann, D., Smith, A. D., Beaumont, H., Warden, D., Wilcock, G., Love, S., Kehoe, P. G., Hooper, N. M., Vardy, E. R., Hardy, J., Mead, S., Fox, N. C., Rossor, M., Collinge, J., Maier, W., Jessen, F., Rüther, E., Schürmann, B., Heun, R., Kölsch, H., van den Bussche, H., Heuser, I., Kornhuber, J., Wiltfang, J., Dichgans, M., Frölich, L., Hampel, H., Gallacher, J., Hüll, M., Rujescu, D., Giegling, I., Goate, A. M., Kauwe, J. S., Cruchaga, C., Nowotny, P., Morris, J. C., Mayo, K., Sleegers, K., Bettens, K., Engelborghs, S., De Deyn, P. P., Van Broeckhoven, C., Livingston, G., Bass, N. J., Gurling, H., McQuillin, A., Gwilliam, R., Deloukas, P., Al-Chalabi, A., Shaw, C. E., Tsolaki, M., Singleton, A. B., Guerreiro, R., Mühleisen, T. W., Nöthen, M. M., Moebus, S., Jöckel, K. H., Klopp, N., Wichmann, H. E., Pankratz, V. S., Sando, S. B., Aasly, J. O., Barcikowska, M., Wszolek, Z. K., Dickson, D. W., Graff-Radford, N. R., Petersen, R. C*., et al.* (2011) 'Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease', *Nat Genet*, 43(5), 429-35.

Hsu, S. C., Sears, R. L., Lemos, R. R., Quintáns, B., Huang, A., Spiteri, E., Nevarez, L., Mamah, C., Zatz, M., Pierce, K. D., Fullerton, J. M., Adair, J. C., Berner, J. E., Bower, M., Brodaty, H., Carmona, O., Dobricić, V., Fogel, B. L., García-Estevez, D., Goldman, J., Goudreau, J. L., Hopfer, S., Janković, M., Jaumà, S., Jen, J. C., Kirdlarp, S., Klepper, J., Kostić, V., Lang, A. E., Linglart, A., Maisenbacher, M. K., Manyam, B. V., Mazzoni, P., Miedzybrodzka, Z., Mitarnun, W., Mitchell, P. B., Mueller, J., Novaković, I., Paucar, M., Paulson, H., Simpson, S. A., Svenningsson, P., Tuite, P., Vitek, J., Wetchaphanphesat, S., Williams, C., Yang, M., Schofield, P. R., de Oliveira, J. R., Sobrido, M. J., Geschwind, D. H. and Coppola, G. (2013) 'Mutations in SLC20A2 are a major cause of familial idiopathic basal ganglia calcification', *Neurogenetics*, 14(1), 11-22.

Hu, M. T., White, S. J., Chaudhuri, K. R., Morris, R. G., Bydder, G. M. and Brooks, D. J. (2001) 'Correlating rates of cerebral atrophy in Parkinson's disease with measures of cognitive decline', *J Neural Transm (Vienna)*, 108(5), 571-80.

Hughes, A. J., Daniel, S. E., Kilford, L. and Lees, A. J. (1992) 'Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases', *J Neurol Neurosurg Psychiatry*, 55(3), 181-4.

Hung, A. Y., Koo, E. H., Haass, C. and Selkoe, D. J. (1992) 'Increased expression of beta-amyloid precursor protein during neuronal differentiation is not accompanied by secretory cleavage', *Proc Natl Acad Sci U S A*, 89(20), 9439-43.

Hussain, I., Powell, D. J., Howlett, D. R., Chapman, G. A., Gilmour, L., Murdock, P. R., Tew, D. G., Meek, T. D., Chapman, C., Schneider, K., Ratcliffe, S. J., Tattersall, D., Testa, T. T., Southan, C., Ryan, D. M., Simmons, D. L., Walsh, F. S., Dingwall, C. and Christie, G. (2000) 'ASP1 (BACE2) cleaves the amyloid precursor protein at the beta-secretase site', *Mol Cell Neurosci*, 16(5), 609-19.

Hutton, M., Lendon, C. L., Rizzu, P., Baker, M., Froelich, S., Houlden, H., Pickering-Brown, S., Chakraverty, S., Isaacs, A., Grover, A., Hackett, J., Adamson, J., Lincoln, S., Dickson, D., Davies, P., Petersen, R. C., Stevens, M., de Graaff, E., Wauters, E., van Baren, J., Hillebrand, M., Joosse, M., Kwon, J. M., Nowotny, P., Che, L. K., Norton, J., Morris, J. C., Reed, L. A., Trojanowski, J., Basun, H., Lannfelt, L., Neystat, M., Fahn, S., Dark, F., Tannenberg, T., Dodd, P. R., Hayward, N., Kwok, J. B., Schofield, P. R., Andreadis, A., Snowden, J., Craufurd, D., Neary, D., Owen, F., Oostra, B. A., Hardy, J., Goate, A., van Swieten, J., Mann, D., Lynch, T. and Heutink, P. (1998) 'Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17', *Nature*, 393(6686), 702-5.

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., Dickson, D. W., Duyckaerts, C., Frosch, M. P., Masliah, E., Mirra, S. S., Nelson, P. T., Schneider, J. A., Thal, D. R., Thies, B., Trojanowski, J. Q., Vinters, H. V. and Montine, T. J. (2012) 'National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease', *Alzheimers Dement*, 8(1), 1-13.

International HapMap Consortium (2005) 'A haplotype map of the human genome', *Nature*, 437(7063), 1299-320.

International Human Genome Sequencing Consortium (2004) 'Finishing the euchromatic sequence of the human genome', *Nature*, 431(7011), 931-45.

Itagaki, S., McGeer, P. L., Akiyama, H., Zhu, S. and Selkoe, D. (1989) 'Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease', *J Neuroimmunol*, 24(3), 173-82.

Itoh, K., Kasai, T., Tsuji, Y., Saito, K., Mizuta, I., Harada, Y., Sudoh, S., Mizuno, T., Nakagawa, M. and Fushiki, S. (2014) 'Definite familial multiple system atrophy with unknown genetics', *Neuropathology*, 34(3), 309-13.

Jakes, R., Spillantini, M. G. and Goedert, M. (1994) 'Identification of two distinct synucleins from human brain', *FEBS Lett*, 345(1), 27-32.

Jankovic, J. (2008) 'Parkinson's disease: clinical features and diagnosis', *J Neurol Neurosurg Psychiatry*, 79(4), 368-76.

Jarmolowicz, A. I., Chen, H. Y. and Panegyres, P. K. (2015) 'The patterns of inheritance in early-onset dementia: Alzheimer's disease and frontotemporal dementia', *Am J Alzheimers Dis Other Demen*, 30(3), 299-306.

Jellinger, K., Danielczyk, W., Fischer, P. and Gabriel, E. (1990) 'Clinicopathological analysis of dementia disorders in the elderly', *J Neurol Sci*, 95(3), 239-58.

Jellinger, K. A. (1991) 'Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway', *Mol Chem Neuropathol*, 14(3), 153-97.

Jellinger, K. A. (2003) 'Alpha-synuclein pathology in Parkinson's and Alzheimer's disease brain: incidence and topographic distribution--a pilot study', *Acta Neuropathol*, 106(3), 191-201.

Jellinger, K. A. and Lantos, P. L. (2010) 'Papp-Lantos inclusions and the pathogenesis of multiple system atrophy: an update', *Acta Neuropathol*, 119(6), 657-67.

Jensen, N., Autzen, J. K. and Pedersen, L. (2016) 'Slc20a2 is critical for maintaining a physiologic inorganic phosphate level in cerebrospinal fluid', *Neurogenetics*, 17(2), 125-30.

Jensen, N., Schrøder, H. D., Hejbøl, E. K., Füchtbauer, E. M., de Oliveira, J. R. and Pedersen, L. (2013) 'Loss of function of Slc20a2 associated with familial

idiopathic Basal Ganglia calcification in humans causes brain calcifications in mice', *J Mol Neurosci*, 51(3), 994-9.

Jensen, P. H., Nielsen, M. S., Jakes, R., Dotti, C. G. and Goedert, M. (1998) 'Binding of alpha-synuclein to brain vesicles is abolished by familial Parkinson's disease mutation', *J Biol Chem*, 273(41), 26292-4.

Jiao, B., Liu, X., Zhou, L., Wang, M. H., Zhou, Y., Xiao, T., Zhang, W., Sun, R., Waye, M. M., Tang, B. and Shen, L. (2015) 'Polygenic Analysis of Late-Onset Alzheimer's Disease from Mainland China', *PLoS One*, 10(12), e0144898.

Jicha, G. A., Parisi, J. E., Dickson, D. W., Johnson, K., Cha, R., Ivnik, R. J., Tangalos, E. G., Boeve, B. F., Knopman, D. S., Braak, H. and Petersen, R. C. (2006) 'Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia', *Arch Neurol*, 63(5), 674-81.

Johnson, J. K., Diehl, J., Mendez, M. F., Neuhaus, J., Shapira, J. S., Forman, M., Chute, D. J., Roberson, E. D., Pace-Savitsky, C., Neumann, M., Chow, T. W., Rosen, H. J., Forstl, H., Kurz, A. and Miller, B. L. (2005) 'Frontotemporal lobar degeneration: demographic characteristics of 353 patients', *Arch Neurol*, 62(6), 925-30.

Jonsson, T., Atwal, J. K., Steinberg, S., Snaedal, J., Jonsson, P. V., Bjornsson, S., Stefansson, H., Sulem, P., Gudbjartsson, D., Maloney, J., Hoyte, K., Gustafson, A., Liu, Y., Lu, Y., Bhangale, T., Graham, R. R., Huttenlocher, J., Bjornsdottir, G., Andreassen, O. A., Jönsson, E. G., Palotie, A., Behrens, T. W., Magnusson, O. T., Kong, A., Thorsteinsdottir, U., Watts, R. J. and Stefansson, K. (2012) 'A mutation in APP protects against Alzheimer's disease and age-related cognitive decline', *Nature*, 488(7409), 96-9.

Jonsson, T., Stefansson, H., Steinberg, S., Jonsdottir, I., Jonsson, P. V., Snaedal, J., Bjornsson, S., Huttenlocher, J., Levey, A. I., Lah, J. J., Rujescu, D., Hampel, H., Giegling, I., Andreassen, O. A., Engedal, K., Ulstein, I., Djurovic, S., Ibrahim-Verbaas, C., Hofman, A., Ikram, M. A., van Duijn, C. M., Thorsteinsdottir, U., Kong, A. and Stefansson, K. (2013) 'Variant of TREM2 associated with the risk of Alzheimer's disease', *N Engl J Med*, 368(2), 107-16.

Josephs, K. A., Hodges, J. R., Snowden, J. S., Mackenzie, I. R., Neumann, M., Mann, D. M. and Dickson, D. W. (2011) 'Neuropathological background of phenotypical variability in frontotemporal dementia', *Acta Neuropathol*, 122(2), 137-53.

Junn, E. and Mouradian, M. M. (2002) 'Human alpha-synuclein over-expression increases intracellular reactive oxygen species levels and susceptibility to dopamine', *Neurosci Lett*, 320(3), 146-50.

Kaivorinne, A. L., Krüger, J., Kuivaniemi, K., Tuominen, H., Moilanen, V., Majamaa, K. and Remes, A. M. (2008) 'Role of MAPT mutations and haplotype in frontotemporal lobar degeneration in Northern Finland', *BMC Neurol*, 8, 48.

Kamal, A., Stokin, G. B., Yang, Z., Xia, C. H. and Goldstein, L. S. (2000) 'Axonal transport of amyloid precursor protein is mediated by direct binding to the kinesin light chain subunit of kinesin-I', *Neuron*, 28(2), 449-59.

Kanatsu, K., Morohashi, Y., Suzuki, M., Kuroda, H., Watanabe, T., Tomita, T. and Iwatsubo, T. (2014) 'Decreased CALM expression reduces Aβ42 to total Aβ ratio through clathrin-mediated endocytosis of γ-secretase', *Nat Commun*, 5, 3386.

Kara, E., Lewis, P. A., Ling, H., Proukakis, C., Houlden, H. and Hardy, J. (2013) 'α-Synuclein mutations cluster around a putative protein loop', *Neurosci Lett*, 546, 67-70.

Katzman, R. (1976) 'Editorial: The prevalence and malignancy of Alzheimer disease. A major killer', *Arch Neurol*, 33(4), 217-8.

Kavanaugh, M. P., Miller, D. G., Zhang, W., Law, W., Kozak, S. L., Kabat, D. and Miller, A. D. (1994) 'Cell-surface receptors for gibbon ape leukemia virus and amphotropic murine retrovirus are inducible sodium-dependent phosphate symporters', *Proc Natl Acad Sci U S A*, 91(15), 7071-5.

Keasey, M. P., Lemos, R. R., Hagg, T. and Oliveira, J. R. (2016) 'Vitamin-D receptor agonist calcitriol reduces calcification in vitro through selective upregulation of SLC20A2 but not SLC20A1 or XPR1', *Sci Rep*, 6, 25802.

Keller, A., Westenberger, A., Sobrido, M. J., García-Murias, M., Domingo, A., Sears, R. L., Lemos, R. R., Ordoñez-Ugalde, A., Nicolas, G., da Cunha, J. E., Rushing, E. J., Hugelshofer, M., Wurnig, M. C., Kaech, A., Reimann, R., Lohmann, K., Dobričić, V., Carracedo, A., Petrović, I., Miyasaki, J. M., Abakumova, I., Mäe, M. A., Raschperger, E., Zatz, M., Zschiedrich, K., Klepper, J., Spiteri, E., Prieto, J. M., Navas, I., Preuss, M., Dering, C., Janković, M., Paucar, M., Svenningsson, P., Saliminejad, K., Khorshid, H. R., Novaković, I., Aguzzi, A., Boss, A., Le Ber, I., Defer, G., Hannequin, D., Kostić, V. S., Campion, D., Geschwind, D. H., Coppola, G., Betsholtz, C., Klein, C. and Oliveira, J. R. (2013) 'Mutations in the gene encoding PDGF-B cause brain calcifications in humans and mice', *Nat Genet*, 45(9), 1077-82.

Kero, M., Paetau, A., Polvikoski, T., Tanskanen, M., Sulkava, R., Jansson, L., Myllykangas, L. and Tienari, P. J. (2013) 'Amyloid precursor protein (APP) A673T mutation in the elderly Finnish population', *Neurobiol Aging*, 34(5), 1518.e1-3.

Kiely, A. P., Asi, Y. T., Kara, E., Limousin, P., Ling, H., Lewis, P., Proukakis, C., Quinn, N., Lees, A. J.,

Hardy, J., Revesz, T., Houlden, H. and Holton, J. L. (2013) 'α-Synucleinopathy associated with G51D SNCA mutation: a link between Parkinson's disease and multiple system atrophy?', *Acta Neuropathol*, 125(5), 753-69.

Kiely, A. P., Ling, H., Asi, Y. T., Kara, E., Proukakis, C., Schapira, A. H., Morris, H. R., Roberts, H. C., Lubbe, S., Limousin, P., Lewis, P. A., Lees, A. J., Quinn, N., Hardy, J., Love, S., Revesz, T., Houlden, H. and Holton, J. L. (2015) 'Distinct clinical and neuropathological features of G51D SNCA mutation cases compared with SNCA duplication and H50Q mutation', *Mol Neurodegener*, 10, 41.

Kim, M., Suh, J., Romano, D., Truong, M. H., Mullin, K., Hooli, B., Norton, D., Tesco, G., Elliott, K., Wagner, S. L., Moir, R. D., Becker, K. D. and Tanzi, R. E. (2009) 'Potential late-onset Alzheimer's disease-associated mutations in the ADAM10 gene attenuate {alpha}-secretase activity', *Hum Mol Genet*, 18(20), 3987-96.

Kim, W. S., Li, H., Ruberu, K., Chan, S., Elliott, D. A., Low, J. K., Cheng, D., Karl, T. and Garner, B. (2013) 'Deletion of Abca7 increases cerebral amyloid-β accumulation in the J20 mouse model of Alzheimer's disease', *J Neurosci*, 33(10), 4387-94.

Kim, W. S., Weickert, C. S. and Garner, B. (2008) 'Role of ATP-binding cassette transporters in brain lipid transport and neurological disease', *J Neurochem*, 104(5), 1145-66.

Kimberly, W. T., LaVoie, M. J., Ostaszewski, B. L., Ye, W., Wolfe, M. S. and Selkoe, D. J. (2003) 'Gamma-secretase is a membrane protein complex comprised of presenilin, nicastrin, Aph-1, and Pen-2', *Proc Natl Acad Sci U S A*, 100(11), 6382-7.

Kimura, T., Miura, T., Aoki, K., Saito, S., Hondo, H., Konno, T., Uchiyama, A., Ikeuchi, T., Takahashi, H. and Kakita, A. (2015) 'Familial idiopathic basal ganglia calcification: Histopathologic features of an autopsied patient with an SLC20A2 mutation', *Neuropathology*.

Kircher, M., Witten, D. M., Jain, P., O'Roak, B. J., Cooper, G. M. and Shendure, J. (2014) 'A general framework for estimating the relative pathogenicity of human genetic variants', *Nat Genet*, 46(3), 310-5.

Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y. and Shimizu, N. (1998) 'Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism', *Nature*, 392(6676), 605-8.

Klambauer, G., Schwarzbauer, K., Mayr, A., Clevert, D. A., Mitterecker, A., Bodenhofer, U. and Hochreiter, S. (2012) 'cn.MOPS: mixture of Poissons for discovering copy number variations in next-generation sequencing data with a low false discovery rate', *Nucleic Acids Res*, 40(9), e69.

Klein, C. and Vieregge, P. (1998) 'Fahr's disease--far from a disease', *Mov Disord*, 13(3), 620-1.

Knopman, D. S. and Roberts, R. O. (2011) 'Estimating the number of persons with frontotemporal lobar degeneration in the US population', *J Mol Neurosci*, 45(3), 330-5.

Knowles, R. B., Wyart, C., Buldyrev, S. V., Cruz, L., Urbanc, B., Hasselmo, M. E., Stanley, H. E. and Hyman, B. T. (1999) 'Plaque-induced neurite abnormalities: implications for disruption of neural networks in Alzheimer's disease', *Proc Natl Acad Sci U S A*, 96(9), 5274-9.

Kobari, M., Nogawa, S., Sugimoto, Y. and Fukuuchi, Y. (1997) 'Familial idiopathic brain calcification with autosomal dominant inheritance', *Neurology*, 48(3), 645-9.

Kobayashi, S., Yamadori, I., Miki, H. and Ohmori, M. (1987) 'Idiopathic nonarteriosclerotic cerebral calcification (Fahr's disease): an electron microscopic study', *Acta Neuropathol*, 73(1), 62-6.

Kohli, M. A., John-Williams, K., Rajbhandary, R., Naj, A., Whitehead, P., Hamilton, K., Carney, R. M., Wright, C., Crocco, E., Gwirtzman, H. E., Lang, R., Beecham, G., Martin, E. R., Gilbert, J., Benatar, M., Small, G. W., Mash, D., Byrd, G., Haines, J. L., Pericak-Vance, M. A. and Züchner, S. (2013) 'Repeat expansions in the C9ORF72 gene contribute to Alzheimer's disease in Caucasians', *Neurobiol Aging*, 34(5), 1519.e5-12.

Koike, H., Tomioka, S., Sorimachi, H., Saido, T. C., Maruyama, K., Okuyama, A., Fujisawa-Sehara, A., Ohno, S., Suzuki, K. and Ishiura, S. (1999) 'Membrane-anchored metalloprotease MDC9 has an alpha-secretase activity responsible for processing the amyloid precursor protein', *Biochem J*, 343 Pt 2, 371-5.

Kong, A., Frigge, M. L., Masson, G., Besenbacher, S., Sulem, P., Magnusson, G., Gudjonsson, S. A., Sigurdsson, A., Jonasdottir, A., Wong, W. S., Sigurdsson, G., Walters, G. B., Steinberg, S., Helgason, H., Thorleifsson, G., Gudbjartsson, D. F., Helgason, A., Magnusson, O. T., Thorsteinsdottir, U. and Stefansson, K. (2012) 'Rate of de novo mutations and the importance of father's age to disease risk', *Nature*, 488(7412), 471-5.

Kosaka, K. (1994) 'Diffuse neurofibrillary tangles with calcification: a new presenile dementia', *J Neurol Neurosurg Psychiatry*, 57(5), 594-6.

Kosaka, K., Yoshimura, M., Ikeda, K. and Budka, H. (1984) 'Diffuse type of Lewy body disease: progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree--a new disease?', *Clin Neuropathol*, 3(5), 185-92.

Kovacs, G. G. (2016) 'Molecular Pathological Classification of Neurodegenerative Diseases: Turning towards Precision Medicine', *Int J Mol Sci*, 17(2).

Kozik, M. and Kulczycki, J. (1978) 'Laser-spectrographic analysis of the cation content in Fahr's syndrome', *Arch Psychiatr Nervenkr (1970)*, 225(2), 135-42.

Kraepelin, E. (1910) Psychiatrie. 8th ed. Vol I: Allgemeine Psychiatrie; Vol II: KlinischePsychiatrie, Leipzig, Germany: Barth.

Krebs, C. E., Karkheiran, S., Powell, J. C., Cao, M., Makarov, V., Darvish, H., Di Paolo, G., Walker, R. H., Shahidi, G. A., Buxbaum, J. D., De Camilli, P., Yue, Z. and Paisán-Ruiz, C. (2013) 'The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive Parkinsonism with generalized seizures', *Hum Mutat*, 34(9), 1200-7.

Krüger, J., Kaivorinne, A. L., Udd, B., Majamaa, K. and Remes, A. M. (2009) 'Low prevalence of progranulin mutations in Finnish patients with frontotemporal lobar degeneration', *Eur J Neurol*, 16(1), 27-30.

Krüger, J., Moilanen, V., Majamaa, K. and Remes, A. M. (2012) 'Molecular genetic analysis of the APP, PSEN1, and PSEN2 genes in Finnish patients with early-onset Alzheimer disease and frontotemporal lobar degeneration', *Alzheimer Dis Assoc Disord*, 26(3), 272-6.

Krüger, R., Kuhn, W., Müller, T., Woitalla, D., Graeber, M., Kösel, S., Przuntek, H., Epplen, J. T., Schöls, L. and Riess, O. (1998) 'Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease', *Nat Genet*, 18(2), 106-8.

Kuhn, P. H., Wang, H., Dislich, B., Colombo, A., Zeitschel, U., Ellwart, J. W., Kremmer, E., Rossner, S. and Lichtenthaler, S. F. (2010) 'ADAM10 is the physiologically relevant, constitutive alpha-secretase of the amyloid precursor protein in primary neurons', *EMBO J*, 29(17), 3020-32.

Kumar, P., Henikoff, S. and Ng, P. C. (2009) 'Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm', *Nat Protoc*, 4(7), 1073-81.

Kuopio, A. M., Marttila, R. J., Helenius, H. and Rinne, U. K. (1999) 'Changing epidemiology of Parkinson's disease in southwestern Finland', *Neurology*, 52(2), 302-8.

Kurochkin, I. V. and Goto, S. (1994) 'Alzheimer's beta-amyloid peptide specifically interacts with and is degraded by insulin degrading enzyme', *FEBS Lett*, 345(1), 33-7.

Kuuluvainen, L., Pöyhönen, M., Pasanen, P., Siitonen, M., Rummukainen, J., Tienari, P. J., Paetau, A. and Myllykangas, L. (2016) 'A Novel Loss-of-Function GRN Mutation p.(Tyr229*): Clinical and Neuropathological Features', *J Alzheimers Dis*.

Kwiatkowski, T. J., Bosco, D. A., Leclerc, A. L., Tamrazian, E., Vanderburg, C. R., Russ, C., Davis, A., Gilchrist, J., Kasarskis, E. J., Munsat, T., Valdmanis, P., Rouleau, G. A., Hosler, B. A., Cortelli, P., de Jong, P. J., Yoshinaga, Y., Haines, J. L., Pericak-Vance, M. A., Yan, J., Ticozzi, N., Siddique, T., McKenna-Yasek, D., Sapp, P. C., Horvitz, H. R., Landers, J. E. and Brown, R. H. (2009) 'Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis', *Science*, 323(5918), 1205-8.

Kämäläinen, A., Herukka, S. K., Hartikainen, P., Helisalmi, S., Moilanen, V., Knuuttila, A., Jansson, L., Tienari, P. J. and Remes, A. M. (2015) 'Cerebrospinal fluid biomarkers for Alzheimer's disease in patients with frontotemporal lobar degeneration and amyotrophic lateral sclerosis with the C9ORF72 repeat expansion', *Dement Geriatr Cogn Disord*, 39(5-6), 287-93.

LaFerla, F. M., Green, K. N. and Oddo, S. (2007) 'Intracellular amyloid-beta in Alzheimer's disease', *Nat Rev Neurosci*, 8(7), 499-509.

Lambert, J. C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., Combarros, O., Zelenika, D., Bullido, M. J., Tavernier, B., Letenneur, L., Bettens, K., Berr, C., Pasquier, F., Fiévet, N., Barberger-Gateau, P., Engelborghs, S., De Deyn, P., Mateo, I., Franck, A., Helisalmi, S., Porcellini, E., Hanon, O., de Pancorbo, M. M., Lendon, C., Dufouil, C., Jaillard, C., Leveillard, T., Alvarez, V., Bosco, P., Mancuso, M., Panza, F., Nacmias, B., Bossù, P., Piccardi, P., Annoni, G., Seripa, D., Galimberti, D., Hannequin, D., Licastro, F., Soininen, H., Ritchie, K., Blanché, H., Dartigues, J. F., Tzourio, C., Gut, I., Van Broeckhoven, C., Alpérovitch, A., Lathrop, M., Amouyel, P. and Investigators, E. A. s. D. I. (2009) 'Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease', *Nat Genet*, 41(10), 1094-9.

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., DeStafano, A. L., Bis, J. C., Beecham, G. W., Grenier-Boley, B., Russo, G., Thorton-Wells, T. A., Jones, N., Smith, A. V., Chouraki, V., Thomas, C., Ikram, M. A., Zelenika, D., Vardarajan, B. N., Kamatani, Y., Lin, C. F., Gerrish, A., Schmidt, H., Kunkle, B., Dunstan, M. L., Ruiz, A., Bihoreau, M. T., Choi, S. H., Reitz, C., Pasquier, F., Cruchaga, C., Craig, D., Amin, N., Berr, C., Lopez, O. L., De Jager, P. L., Deramecourt, V., Johnston, J. A., Evans, D., Lovestone, S., Letenneur, L., Morón, F. J., Rubinsztein, D. C., Eiriksdottir, G., Sleegers, K., Goate, A. M., Fiévet, N., Huentelman, M. W., Gill, M., Brown, K., Kamboh, M. I., Keller, L., Barberger-Gateau, P., McGuiness, B., Larson, E. B., Green, R., Myers, A. J., Dufouil, C., Todd, S., Wallon, D., Love, S., Rogaeva, E., Gallacher, J., St George-Hyslop, P., Clarimon, J., Lleo, A., Bayer, A., Tsuang, D. W., Yu, L., Tsolaki, M., Bossù, P., Spalletta, G., Proitsi, P., Collinge, J., Sorbi, S., Sanchez-Garcia, F., Fox, N. C., Hardy, J., Deniz Naranjo, M. C., Bosco, P., Clarke, R., Brayne, C., Galimberti, D., Mancuso, M., Matthews, F., Moebus, S., Mecocci, P., Del Zompo,

M., Maier, W., Hampel, H., Pilotto, A., Bullido, M., Panza, F., Caffarra, P., Nacmias, B., Gilbert, J. R., Mayhaus, M., Lannefelt, L., Hakonarson, H., Pichler, S*., et al.* (2013) 'Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease', *Nat Genet*, 45(12), 1452-8.

Larsen, T. A., Dunn, H. G., Jan, J. E. and Calne, D. B. (1985) 'Dystonia and calcification of the basal ganglia', *Neurology*, 35(4), 533-7.

Le Ber, I., Camuzat, A., Guerreiro, R., Bouya-Ahmed, K., Bras, J., Nicolas, G., Gabelle, A., Didic, M., De Septenville, A., Millecamps, S., Lenglet, T., Latouche, M., Kabashi, E., Campion, D., Hannequin, D., Hardy, J., Brice, A. and FTD/FTD-ALS, F. C. a. G. R. N. o. (2013) 'SQSTM1 mutations in French patients with frontotemporal dementia or frontotemporal dementia with amyotrophic lateral sclerosis', *JAMA Neurol*, 70(11), 1403-10.

Le Ber, I., De Septenville, A., Millecamps, S., Camuzat, A., Caroppo, P., Couratier, P., Blanc, F., Lacomblez, L., Sellal, F., Fleury, M. C., Meininger, V., Cazeneuve, C., Clot, F., Flabeau, O., LeGuern, E., Brice, A. and FTLD/FTLD-ALS, F. C. a. G. R. N. o. (2015) 'TBK1 mutation frequencies in French frontotemporal dementia and amyotrophic lateral sclerosis cohorts', *Neurobiol Aging*, 36(11), 3116.e5-8.

Le Ber, I., Guedj, E., Gabelle, A., Verpillat, P., Volteau, M., Thomas-Anterion, C., Decousus, M., Hannequin, D., Véra, P., Lacomblez, L., Camuzat, A., Didic, M., Puel, M., Lotterie, J. A., Golfier, V., Bernard, A. M., Vercelletto, M., Magne, C., Sellal, F., Namer, I., Michel, B. F., Pasquier, J., Salachas, F., Bochet, J., Brice, A., Habert, M. O., Dubois, B. and FTD/FTD-MND, F. r. n. o. (2006) 'Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia', *Brain*, 129(Pt 11), 3051-65.

Legati, A., Giovannini, D., Nicolas, G., López-Sánchez, U., Quintáns, B., Oliveira, J. R., Sears, R. L., Ramos, E. M., Spiteri, E., Sobrido, M. J., Carracedo, Á., Castro-Fernández, C., Cubizolle, S., Fogel, B. L., Goizet, C., Jen, J. C., Kirdlarp, S., Lang, A. E., Miedzybrodzka, Z., Mitarnun, W., Paucar, M., Paulson, H., Pariente, J., Richard, A. C., Salins, N. S., Simpson, S. A., Striano, P., Svenningsson, P., Tison, F., Unni, V. K., Vanakker, O., Wessels, M. W., Wetchaphanphesat, S., Yang, M., Boller, F., Campion, D., Hannequin, D., Sitbon, M., Geschwind, D. H., Battini, J. L. and Coppola, G. (2015) 'Mutations in XPR1 cause primary familial brain calcification associated with altered phosphate export', *Nat Genet*, 47(6), 579-81.

Lek, M., Karczewski, K. J., Minikel, E. V., Samocha, K. E., Banks, E., Fennell, T., O'Donnell-Luria, A. H., Ware, J. S., Hill, A. J., Cummings, B. B., Tukiainen, T., Birnbaum, D. P., Kosmicki, J. A., Duncan, L. E., Estrada, K., Zhao, F., Zou, J., Pierce-Hoffman, E., Berghout, J., Cooper, D. N., Deflaux, N., DePristo, M., Do, R., Flannick, J., Fromer, M., Gauthier, L., Goldstein, J., Gupta, N., Howrigan, D., Kiezun, A., Kurki, M. I., Moonshine, A. L., Natarajan, P., Orozco, L., Peloso, G. M., Poplin, R., Rivas, M. A., Ruano-Rubio, V., Rose, S. A., Ruderfer, D. M., Shakir, K., Stenson, P. D., Stevens, C., Thomas, B. P., Tiao, G., Tusie-Luna, M. T., Weisburd, B., Won, H. H., Yu, D., Altshuler, D. M., Ardissino, D., Boehnke, M., Danesh, J., Donnelly, S., Elosua, R., Florez, J. C., Gabriel, S. B., Getz, G., Glatt, S. J., Hultman, C. M., Kathiresan, S., Laakso, M., McCarroll, S., McCarthy, M. I., McGovern, D., McPherson, R., Neale, B. M., Palotie, A., Purcell, S. M., Saleheen, D., Scharf, J. M., Sklar, P., Sullivan, P. F., Tuomilehto, J., Tsuang, M. T., Watkins, H. C., Wilson, J. G., Daly, M. J., MacArthur, D. G. and Consortium, E. A. (2016) 'Analysis of protein-coding genetic variation in 60,706 humans', *Nature*, 536(7616), 285-91.

Lelieveld, S. H., Spielmann, M., Mundlos, S., Veltman, J. A. and Gilissen, C. (2015) 'Comparison of Exome and Genome Sequencing Technologies for the Complete Capture of Protein-Coding Regions', *Hum Mutat*, 36(8), 815-22.

Lemos, R. R., Ramos, E. M., Legati, A., Nicolas, G., Jenkinson, E. M., Livingston, J. H., Crow, Y. J., Campion, D., Coppola, G. and Oliveira, J. R. (2015) 'Update and Mutational Analysis of SLC20A2: A Major Cause of Primary Familial Brain Calcification', *Hum Mutat*, 36(5), 489-95.

Lescai, F., Pirazzini, C., D'Agostino, G., Santoro, A., Ghidoni, R., Benussi, L., Galimberti, D., Federica, E., Marchegiani, F., Cardelli, M., Olivieri, F., Nacmias, B., Sorbi, S., Bagnoli, S., Tagliavini, F., Albani, D., Martinelli Boneschi, F., Binetti, G., Forloni, G., Quadri, P., Scarpini, E. and Franceschi, C. (2010) 'Failure to replicate an association of rs5984894 SNP in the PCDH11X gene in a collection of 1,222 Alzheimer's disease affected patients', *J Alzheimers Dis*, 21(2), 385-8.

Levy-Lahad, E., Wasco, W., Poorkaj, P., Romano, D. M., Oshima, J., Pettingell, W. H., Yu, C. E., Jondro, P. D., Schmidt, S. D. and Wang, K. (1995) 'Candidate gene for the chromosome 1 familial Alzheimer's disease locus', *Science*, 269(5226), 973-7.

Lewy, F. (1912) 'Paralysis agitans. I. Pathologische Anatomie. ' in Lewandowsky, M. A., G., ed., *Handbuch der Neurologie Vol. 3*.

Lindahl, P., Johansson, B. R., Levéen, P. and Betsholtz, C. (1997) 'Pericyte loss and microaneurysm formation in PDGF-B-deficient mice', *Science*, 277(5323), 242-5.

Lippa, C. F., Duda, J. E., Grossman, M., Hurtig, H. I., Aarsland, D., Boeve, B. F., Brooks, D. J., Dickson, D. W., Dubois, B., Emre, M., Fahn, S., Farmer, J. M., Galasko, D., Galvin, J. E., Goetz, C. G., Growdon, J.

H., Gwinn-Hardy, K. A., Hardy, J., Heutink, P., Iwatsubo, T., Kosaka, K., Lee, V. M., Leverenz, J. B., Masliah, E., McKeith, I. G., Nussbaum, R. L., Olanow, C. W., Ravina, B. M., Singleton, A. B., Tanner, C. M., Trojanowski, J. Q., Wszolek, Z. K. and Group, D. P. W. (2007) 'DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers', *Neurology*, 68(11), 812-9.

Logue, M. W., Schu, M., Vardarajan, B. N., Farrell, J., Bennett, D. A., Buxbaum, J. D., Byrd, G. S., Ertekin-Taner, N., Evans, D., Foroud, T., Goate, A., Graff-Radford, N. R., Kamboh, M. I., Kukull, W. A., Manly, J. J. and Consortium, A. D. G. (2014) 'Two rare AKAP9 variants are associated with Alzheimer's disease in African Americans', *Alzheimers Dement*, 10(6), 609-618.e11.

Lui, H., Zhang, J., Makinson, S. R., Cahill, M. K., Kelley, K. W., Huang, H. Y., Shang, Y., Oldham, M. C., Martens, L. H., Gao, F., Coppola, G., Sloan, S. A., Hsieh, C. L., Kim, C. C., Bigio, E. H., Weintraub, S., Mesulam, M. M., Rademakers, R., Mackenzie, I. R., Seeley, W. W., Karydas, A., Miller, B. L., Borroni, B., Ghidoni, R., Farese, R. V., Paz, J. T., Barres, B. A. and Huang, E. J. (2016) 'Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation', *Cell*, 165(4), 921-35.

Luk, K. C., Kehm, V., Carroll, J., Zhang, B., O'Brien, P., Trojanowski, J. Q. and Lee, V. M. (2012) 'Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice', *Science*, 338(6109), 949-53.

Luukkainen, L., Bloigu, R., Moilanen, V. and Remes, A. M. (2015) 'Epidemiology of Frontotemporal Lobar Degeneration in Northern Finland', *Dement Geriatr Cogn Dis Extra*, 5(3), 435-41.

MacArthur, D. G., Manolio, T. A., Dimmock, D. P., Rehm, H. L., Shendure, J., Abecasis, G. R., Adams, D. R., Altman, R. B., Antonarakis, S. E., Ashley, E. A., Barrett, J. C., Biesecker, L. G., Conrad, D. F., Cooper, G. M., Cox, N. J., Daly, M. J., Gerstein, M. B., Goldstein, D. B., Hirschhorn, J. N., Leal, S. M., Pennacchio, L. A., Stamatoyannopoulos, J. A., Sunyaev, S. R., Valle, D., Voight, B. F., Winckler, W. and Gunter, C. (2014) 'Guidelines for investigating causality of sequence variants in human disease', *Nature*, 508(7497), 469-76.

MacDonald, J. R., Ziman, R., Yuen, R. K., Feuk, L. and Scherer, S. W. (2014) 'The Database of Genomic Variants: a curated collection of structural variation in the human genome', *Nucleic Acids Res*, 42(Database issue), D986-92.

Mackenzie, I. R., Baborie, A., Pickering-Brown, S., Du Plessis, D., Jaros, E., Perry, R. H., Neary, D., Snowden, J. S. and Mann, D. M. (2006) 'Heterogeneity of ubiquitin pathology in frontotemporal lobar degeneration: classification and relation to clinical phenotype', *Acta Neuropathol*, 112(5), 539-49.

Mackenzie, I. R., Foti, D., Woulfe, J. and Hurwitz, T. A. (2008) 'Atypical frontotemporal lobar degeneration with ubiquitin-positive, TDP-43-negative neuronal inclusions', *Brain*, 131(Pt 5), 1282-93.

Mackenzie, I. R., Munoz, D. G., Kusaka, H., Yokota, O., Ishihara, K., Roeber, S., Kretzschmar, H. A., Cairns, N. J. and Neumann, M. (2011a) 'Distinct pathological subtypes of FTLD-FUS', *Acta Neuropathol*, 121(2), 207-18.

Mackenzie, I. R., Neumann, M., Baborie, A., Sampathu, D. M., Du Plessis, D., Jaros, E., Perry, R. H., Trojanowski, J. Q., Mann, D. M. and Lee, V. M. (2011b) 'A harmonized classification system for FTLD-TDP pathology', *Acta Neuropathol*, 122(1), 111-3.

Mackenzie, I. R., Neumann, M., Bigio, E. H., Cairns, N. J., Alafuzoff, I., Kril, J., Kovacs, G. G., Ghetti, B., Halliday, G., Holm, I. E., Ince, P. G., Kamphorst, W., Revesz, T., Rozemuller, A. J., Kumar-Singh, S., Akiyama, H., Baborie, A., Spina, S., Dickson, D. W., Trojanowski, J. Q. and Mann, D. M. (2010) 'Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update', *Acta Neuropathol*, 119(1), 1-4.

Majounie, E., Abramzon, Y., Renton, A. E., Perry, R., Bassett, S. S., Pletnikova, O., Troncoso, J. C., Hardy, J., Singleton, A. B. and Traynor, B. J. (2012a) 'Repeat expansion in C9ORF72 in Alzheimer's disease', *N Engl J Med*, 366(3), 283-4.

Majounie, E., Renton, A. E., Mok, K., Dopper, E. G., Waite, A., Rollinson, S., Chiò, A., Restagno, G., Nicolaou, N., Simon-Sanchez, J., van Swieten, J. C., Abramzon, Y., Johnson, J. O., Sendtner, M., Pamphlett, R., Orrell, R. W., Mead, S., Sidle, K. C., Houlden, H., Rohrer, J. D., Morrison, K. E., Pall, H., Talbot, K., Ansorge, O., Hernandez, D. G., Arepalli, S., Sabatelli, M., Mora, G., Corbo, M., Giannini, F., Calvo, A., Englund, E., Borghero, G., Floris, G. L., Remes, A. M., Laaksovirta, H., McCluskey, L., Trojanowski, J. Q., Van Deerlin, V. M., Schellenberg, G. D., Nalls, M. A., Drory, V. E., Lu, C. S., Yeh, T. H., Ishiura, H., Takahashi, Y., Tsuji, S., Le Ber, I., Brice, A., Drepper, C., Williams, N., Kirby, J., Shaw, P., Hardy, J., Tienari, P. J., Heutink, P., Morris, H. R., Pickering-Brown, S., Traynor, B. J., Consortium, C.-A. F., FTLD/FTLD/ALS, F. r. n. o. and Consortium, I. (2012b) 'Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study', *Lancet Neurol*, 11(4), 323-30.

Maloney, J. A., Bainbridge, T., Gustafson, A., Zhang, S., Kyauk, R., Steiner, P., van der Brug, M., Liu, Y., Ernst, J. A., Watts, R. J. and Atwal, J. K. (2014) 'Molecular mechanisms of Alzheimer disease

protection by the A673T allele of amyloid precursor protein', *J Biol Chem*, 289(45), 30990-1000.

Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., McCarthy, M. I., Ramos, E. M., Cardon, L. R., Chakravarti, A., Cho, J. H., Guttmacher, A. E., Kong, A., Kruglyak, L., Mardis, E., Rotimi, C. N., Slatkin, M., Valle, D., Whittemore, A. S., Boehnke, M., Clark, A. G., Eichler, E. E., Gibson, G., Haines, J. L., Mackay, T. F., McCarroll, S. A. and Visscher, P. M. (2009) 'Finding the missing heritability of complex diseases', *Nature*, 461(7265), 747-53.

Manyam, B. V. (2005) 'What is and what is not 'Fahr's disease'', *Parkinsonism Relat Disord*, 11(2), 73-80.

Manyam, B. V., Bhatt, M. H., Moore, W. D., Devleschoward, A. B., Anderson, D. R. and Calne, D. B. (1992) 'Bilateral striopallidodentate calcinosis: cerebrospinal fluid, imaging, and electrophysiological studies', *Ann Neurol*, 31(4), 379-84.

Manyam, B. V., Walters, A. S., Keller, I. A. and Ghobrial, M. (2001a) 'Parkinsonism associated with autosomal dominant bilateral striopallidodentate calcinosis', *Parkinsonism Relat Disord*, 7(4), 289-295.

Manyam, B. V., Walters, A. S. and Narla, K. R. (2001b) 'Bilateral striopallidodentate calcinosis: clinical characteristics of patients seen in a registry', *Mov Disord*, 16(2), 258-64.

Maraganore, D. M., de Andrade, M., Elbaz, A., Farrer, M. J., Ioannidis, J. P., Krüger, R., Rocca, W. A., Schneider, N. K., Lesnick, T. G., Lincoln, S. J., Hulihan, M. M., Aasly, J. O., Ashizawa, T., Chartier-Harlin, M. C., Checkoway, H., Ferrarese, C., Hadjigeorgiou, G., Hattori, N., Kawakami, H., Lambert, J. C., Lynch, T., Mellick, G. D., Papapetropoulos, S., Parsian, A., Quattrone, A., Riess, O., Tan, E. K., Van Broeckhoven, C. and Consortium, G. E. o. P. s. D. G.-P. (2006) 'Collaborative analysis of alpha-synuclein gene promoter variability and Parkinson disease', *JAMA*, 296(6), 661-70.

Maroteaux, L., Campanelli, J. T. and Scheller, R. H. (1988) 'Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminal', *J Neurosci*, 8(8), 2804-15.

Martikainen, M. H., Päivärinta, M., Hietala, M. and Kaasinen, V. (2015) 'Clinical and imaging findings in Parkinson disease associated with the A53E *SNCA* mutation', *Neurology Genetics*, 1, e27.

Martikainen, P., Pikkarainen, M., Pöntynen, K., Hiltunen, M., Lehtovirta, M., Tuisku, S., Soininen, H. and Alafuzoff, I. (2010) 'Brain pathology in three subjects from the same pedigree with presenilin-1 (PSEN1) P264L mutation', *Neuropathol Appl Neurobiol*, 36(1), 41-54.

Mattila, P. M., Röyttä, M., Torikka, H., Dickson, D. W. and Rinne, J. O. (1998) 'Cortical Lewy bodies and Alzheimer-type changes in patients with Parkinson's disease', *Acta Neuropathol*, 95(6), 576-82.

May, P. C. and Finch, C. E. (1992) 'Sulfated glycoprotein 2: new relationships of this multifunctional protein to neurodegeneration', *Trends Neurosci*, 15(10), 391-6.

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., Santini, V. E., Lee, H. S., Kubilus, C. A. and Stern, R. A. (2009) 'Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury', *J Neuropathol Exp Neurol*, 68(7), 709-35.

McKeith, I., Mintzer, J., Aarsland, D., Burn, D., Chiu, H., Cohen-Mansfield, J., Dickson, D., Dubois, B., Duda, J. E., Feldman, H., Gauthier, S., Halliday, G., Lawlor, B., Lippa, C., Lopez, O. L., Carlos Machado, J., O'Brien, J., Playfer, J., Reid, W. and DLB, I. P. A. E. M. o. (2004) 'Dementia with Lewy bodies', *Lancet Neurol*, 3(1), 19-28.

McKeith, I. G., Dickson, D. W., Lowe, J., Emre, M., O'Brien, J. T., Feldman, H., Cummings, J., Duda, J. E., Lippa, C., Perry, E. K., Aarsland, D., Arai, H., Ballard, C. G., Boeve, B., Burn, D. J., Costa, D., Del Ser, T., Dubois, B., Galasko, D., Gauthier, S., Goetz, C. G., Gomez-Tortosa, E., Halliday, G., Hansen, L. A., Hardy, J., Iwatsubo, T., Kalaria, R. N., Kaufer, D., Kenny, R. A., Korczyn, A., Kosaka, K., Lee, V. M., Lees, A., Litvan, I., Londos, E., Lopez, O. L., Minoshima, S., Mizuno, Y., Molina, J. A., Mukaetova-Ladinska, E. B., Pasquier, F., Perry, R. H., Schulz, J. B., Trojanowski, J. Q., Yamada, M. and DLB, C. o. (2005) 'Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium', *Neurology*, 65(12), 1863-72.

McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., Salmon, D. P., Lowe, J., Mirra, S. S., Byrne, E. J., Lennox, G., Quinn, N. P., Edwardson, J. A., Ince, P. G., Bergeron, C., Burns, A., Miller, B. L., Lovestone, S., Collerton, D., Jansen, E. N., Ballard, C., de Vos, R. A., Wilcock, G. K., Jellinger, K. A. and Perry, R. H. (1996) 'Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop', *Neurology*, 47(5), 1113-24.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E. M. (1984) 'Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease', *Neurology*, 34(7), 939-44.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R.

C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S. and Phelps, C. H. (2011) 'The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease', *Alzheimers Dement*, 7(3), 263-9.

McKinnon, C. and Tabrizi, S. J. (2014) 'The ubiquitin-proteasome system in neurodegeneration', *Antioxid Redox Signal*, 21(17), 2302-21.

Meeus, B., Verstraeten, A., Crosiers, D., Engelborghs, S., Van den Broeck, M., Mattheijssens, M., Peeters, K., Corsmit, E., Elinck, E., Pickut, B., Vandenberghe, R., Cras, P., De Deyn, P. P., Van Broeckhoven, C. and Theuns, J. (2012) 'DLB and PDD: a role for mutations in dementia and Parkinson disease genes?', *Neurobiol Aging*, 33(3), 629.e5-629.e18.

Mercy, L., Hodges, J. R., Dawson, K., Barker, R. A. and Brayne, C. (2008) 'Incidence of early-onset dementias in Cambridgeshire, United Kingdom', *Neurology*, 71(19), 1496-9.

Miar, A., Alvarez, V., Corao, A. I., Alonso, B., Díaz, M., Menéndez, M., Martínez, C., Calatayud, M., Morís, G. and Coto, E. (2011) 'Lack of association between protocadherin 11-X/Y (PCDH11X and PCDH11Y) polymorphisms and late onset Alzheimer's disease', *Brain Res*, 1383, 252-6.

Miklossy, J., Mackenzie, I. R., Dorovini-Zis, K., Calne, D. B., Wszolek, Z. K., Klegeris, A. and McGeer, P. L. (2005) 'Severe vascular disturbance in a case of familial brain calcinosis', *Acta Neuropathol*, 109(6), 643-53.

Miller, J. A., Woltjer, R. L., Goodenbour, J. M., Horvath, S. and Geschwind, D. H. (2013) 'Genes and pathways underlying regional and cell type changes in Alzheimer's disease', *Genome Med*, 5(5), 48.

Minikel, E. V., Vallabh, S. M., Lek, M., Estrada, K., Samocha, K. E., Sathirapongsasuti, J. F., McLean, C. Y., Tung, J. Y., Yu, L. P., Gambetti, P., Blevins, J., Zhang, S., Cohen, Y., Chen, W., Yamada, M., Hamaguchi, T., Sanjo, N., Mizusawa, H., Nakamura, Y., Kitamoto, T., Collins, S. J., Boyd, A., Will, R. G., Knight, R., Ponto, C., Zerr, I., Kraus, T. F., Eigenbrod, S., Giese, A., Calero, M., de Pedro-Cuesta, J., Haïk, S., Laplanche, J. L., Bouaziz-Amar, E., Brandel, J. P., Capellari, S., Parchi, P., Poleggi, A., Ladogana, A., O'Donnell-Luria, A. H., Karczewski, K. J., Marshall, J. L., Boehnke, M., Laakso, M., Mohlke, K. L., Kähler, A., Chambert, K., McCarroll, S., Sullivan, P. F., Hultman, C. M., Purcell, S. M., Sklar, P., van der Lee, S. J., Rozemuller, A., Jansen, C., Hofman, A., Kraaij, R., van Rooij, J. G., Ikram, M. A., Uitterlinden, A. G., van Duijn, C. M., Daly, M. J., MacArthur, D. G. and (ExAC), E. A. C. (2016) 'Quantifying prion disease penetrance using large population control cohorts', *Sci Transl Med*, 8(322), 322ra9.

Moreira, P. I., Duarte, A. I., Santos, M. S., Rego, A. C. and Oliveira, C. R. (2009) 'An integrative view of the role of oxidative stress, mitochondria and insulin in Alzheimer's disease', *J Alzheimers Dis*, 16(4), 741-61.

Morfis, L. and Cordato, D. J. (2006) 'Dementia with Lewy bodies in an elderly Greek male due to alpha-synuclein gene mutation', *J Clin Neurosci*, 13(9), 942-4.

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., Mellits, E. D. and Clark, C. (1989) 'The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease', *Neurology*, 39(9), 1159-65.

Moya, K. L., Benowitz, L. I., Schneider, G. E. and Allinquant, B. (1994) 'The amyloid precursor protein is developmentally regulated and correlated with synaptogenesis', *Dev Biol*, 161(2), 597-603.

Multiple-System Atrophy Research Collaboration (2013) 'Mutations in COQ2 in familial and sporadic multiple-system atrophy', *N Engl J Med*, 369(3), 233-44.

Munoz, D. G., Neumann, M., Kusaka, H., Yokota, O., Ishihara, K., Terada, S., Kuroda, S. and Mackenzie, I. R. (2009) 'FUS pathology in basophilic inclusion body disease', *Acta Neuropathol*, 118(5), 617-27.

Murray, M. E., DeJesus-Hernandez, M., Rutherford, N. J., Baker, M., Duara, R., Graff-Radford, N. R., Wszolek, Z. K., Ferman, T. J., Josephs, K. A., Boylan, K. B., Rademakers, R. and Dickson, D. W. (2011) 'Clinical and neuropathologic heterogeneity of c9FTD/ALS associated with hexanucleotide repeat expansion in C9ORF72', *Acta Neuropathol*, 122(6), 673-90.

Naj, A. C., Jun, G., Beecham, G. W., Wang, L. S., Vardarajan, B. N., Buros, J., Gallins, P. J., Buxbaum, J. D., Jarvik, G. P., Crane, P. K., Larson, E. B., Bird, T. D., Boeve, B. F., Graff-Radford, N. R., De Jager, P. L., Evans, D., Schneider, J. A., Carrasquillo, M. M., Ertekin-Taner, N., Younkin, S. G., Cruchaga, C., Kauwe, J. S., Nowotny, P., Kramer, P., Hardy, J., Huentelman, M. J., Myers, A. J., Barmada, M. M., Demirci, F. Y., Baldwin, C. T., Green, R. C., Rogaeva, E., St George-Hyslop, P., Arnold, S. E., Barber, R., Beach, T., Bigio, E. H., Bowen, J. D., Boxer, A., Burke, J. R., Cairns, N. J., Carlson, C. S., Carney, R. M., Carroll, S. L., Chui, H. C., Clark, D. G., Corneveaux, J., Cotman, C. W., Cummings, J. L., DeCarli, C., DeKosky, S. T., Diaz-Arrastia, R., Dick, M., Dickson, D. W., Ellis, W. G., Faber, K. M., Fallon, K. B., Farlow, M. R., Ferris, S., Frosch, M. P., Galasko, D. R., Ganguli, M., Gearing, M., Geschwind, D. H., Ghetti, B., Gilbert, J. R., Gilman, S., Giordani, B., Glass, J. D., Growdon, J. H.,

Hamilton, R. L., Harrell, L. E., Head, E., Honig, L. S., Hulette, C. M., Hyman, B. T., Jicha, G. A., Jin, L. W., Johnson, N., Karlawish, J., Karydas, A., Kaye, J. A., Kim, R., Koo, E. H., Kowall, N. W., Lah, J. J., Levey, A. I., Lieberman, A. P., Lopez, O. L., Mack, W. J., Marson, D. C., Martiniuk, F., Mash, D. C., Masliah, E., McCormick, W. C., McCurry, S. M., McDavid, A. N., McKee, A. C., Mesulam, M., Miller, B. L*., et al.* (2011) 'Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease', *Nat Genet*, 43(5), 436-41.

Nalls, M. A., Pankratz, N., Lill, C. M., Do, C. B., Hernandez, D. G., Saad, M., DeStefano, A. L., Kara, E., Bras, J., Sharma, M., Schulte, C., Keller, M. F., Arepalli, S., Letson, C., Edsall, C., Stefansson, H., Liu, X., Pliner, H., Lee, J. H., Cheng, R., Ikram, M. A., Ioannidis, J. P., Hadjigeorgiou, G. M., Bis, J. C., Martinez, M., Perlmutter, J. S., Goate, A., Marder, K., Fiske, B., Sutherland, M., Xiromerisiou, G., Myers, R. H., Clark, L. N., Stefansson, K., Hardy, J. A., Heutink, P., Chen, H., Wood, N. W., Houlden, H., Payami, H., Brice, A., Scott, W. K., Gasser, T., Bertram, L., Eriksson, N., Foroud, T., Singleton, A. B., (IPDGC), I. P. s. D. G. C., (PROGENI), P. s. S. G. P. P. s. R. T. O. G. I., 23andMe, GenePD, (NGRC), N. R. C., (HIHG), H. I. o. H. G., Investigator, A. J. D., (CHARGE), C. f. H. a. A. R. i. G. E., (NABEC), N. A. B. E. C., (UKBEC), U. K. B. E. C., Consortium, G. P. s. D. and Group, A. G. A. (2014) 'Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease', *Nat Genet*, 46(9), 989-93.

Nalls, M. A., Plagnol, V., Hernandez, D. G., Sharma, M., Sheerin, U. M., Saad, M., Simón-Sánchez, J., Schulte, C., Lesage, S., Sveinbjörnsdóttir, S., Stefánsson, K., Martinez, M., Hardy, J., Heutink, P., Brice, A., Gasser, T., Singleton, A. B., Wood, N. W. and Consortium, I. P. D. G. (2011) 'Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies', *Lancet*, 377(9766), 641-9.

Neary, D., Snowden, J. S., Northen, B. and Goulding, P. (1988) 'Dementia of frontal lobe type', *J Neurol Neurosurg Psychiatry*, 51(3), 353-61.

Nervi, A., Reitz, C., Tang, M. X., Santana, V., Piriz, A., Reyes, D., Lantigua, R., Medrano, M., Jiménez-Velázquez, I. Z., Lee, J. H. and Mayeux, R. (2011) 'Familial aggregation of dementia with Lewy bodies', *Arch Neurol*, 68(1), 90-3.

Neumann, M., Rademakers, R., Roeber, S., Baker, M., Kretzschmar, H. A. and Mackenzie, I. R. (2009a) 'A new subtype of frontotemporal lobar degeneration with FUS pathology', *Brain*, 132(Pt 11), 2922-31.

Neumann, M., Roeber, S., Kretzschmar, H. A., Rademakers, R., Baker, M. and Mackenzie, I. R. (2009b) 'Abundant FUS-immunoreactive pathology in neuronal intermediate filament inclusion disease', *Acta Neuropathol*, 118(5), 605-16.

Nicolas, G., Jacquin, A., Thauvin-Robinet, C., Rovelet-Lecrux, A., Rouaud, O., Pottier, C., Aubriot-Lorton, M. H., Rousseau, S., Wallon, D., Duvillard, C., Béjot, Y., Frébourg, T., Giroud, M., Campion, D. and Hannequin, D. (2014a) 'A de novo nonsense PDGFB mutation causing idiopathic basal ganglia calcification with laryngeal dystonia', *Eur J Hum Genet*, 22(10), 1236-8.

Nicolas, G., Pottier, C., Charbonnier, C., Guyant-Maréchal, L., Le Ber, I., Pariente, J., Labauge, P., Ayrignac, X., Defebvre, L., Maltête, D., Martinaud, O., Lefaucheur, R., Guillin, O., Wallon, D., Chaumette, B., Rondepierre, P., Derache, N., Fromager, G., Schaeffer, S., Krystkowiak, P., Verny, C., Jurici, S., Sauvée, M., Vérin, M., Lebouvier, T., Rouaud, O., Thauvin-Robinet, C., Rousseau, S., Rovelet-Lecrux, A., Frebourg, T., Campion, D., Hannequin, D. and group, F. I. s. (2013a) 'Phenotypic spectrum of probable and genetically-confirmed idiopathic basal ganglia calcification', *Brain*, 136(Pt 11), 3395-407.

Nicolas, G., Pottier, C., Maltête, D., Coutant, S., Rovelet-Lecrux, A., Legallic, S., Rousseau, S., Vaschalde, Y., Guyant-Maréchal, L., Augustin, J., Martinaud, O., Defebvre, L., Krystkowiak, P., Pariente, J., Clanet, M., Labauge, P., Ayrignac, X., Lefaucheur, R., Le Ber, I., Frébourg, T., Hannequin, D. and Campion, D. (2013b) 'Mutation of the PDGFRB gene as a cause of idiopathic basal ganglia calcification', *Neurology*, 80(2), 181-7.

Nicolas, G., Rovelet-Lecrux, A., Pottier, C., Martinaud, O., Wallon, D., Vernier, L., Landemore, G., Chapon, F., Prieto-Morin, C., Tournier-Lasserve, E., Frébourg, T., Campion, D. and Hannequin, D. (2014b) 'PDGFB partial deletion: a new, rare mechanism causing brain calcification with leukoencephalopathy', *J Mol Neurosci*, 53(2), 171-5.

Nilsberth, C., Westlind-Danielsson, A., Eckman, C. B., Condron, M. M., Axelman, K., Forsell, C., Stenh, C., Luthman, J., Teplow, D. B., Younkin, S. G., Näslund, J. and Lannfelt, L. (2001) 'The 'Arctic' APP mutation (E693G) causes Alzheimer's disease by enhanced Abeta protofibril formation', *Nat Neurosci*, 4(9), 887-93.

Nordstedt, C., Caporaso, G. L., Thyberg, J., Gandy, S. E. and Greengard, P. (1993) 'Identification of the Alzheimer beta/A4 amyloid precursor protein in clathrin-coated vesicles purified from PC12 cells', *J Biol Chem*, 268(1), 608-12.

O'Sullivan, S. S., Massey, L. A., Williams, D. R., Silveira-Moriyama, L., Kempster, P. A., Holton, J. L., Revesz, T. and Lees, A. J. (2008) 'Clinical outcomes of progressive supranuclear palsy and multiple system atrophy', *Brain*, 131(Pt 5), 1362-72.

Okazaki, H., Lipkin, L. E. and Aronson, S. M. (1961) 'Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion', *J Neuropathol Exp Neurol*, 20, 237-44.

Okochi, M., Tagami, S., Yanagida, K., Takami, M., Kodama, T. S., Mori, K., Nakayama, T., Ihara, Y. and Takeda, M. (2013) 'γ-secretase modulators and presenilin 1 mutants act differently on presenilin/γ-secretase function to cleave Aβ42 and Aβ43', *Cell Rep*, 3(1), 42-51.

Olah, Z., Lehel, C., Anderson, W. B., Eiden, M. V. and Wilson, C. A. (1994) 'The cellular receptor for gibbon ape leukemia virus is a novel high affinity sodium-dependent phosphate transporter', *J Biol Chem*, 269(41), 25426-31.

Onari, K. and Spatz, H. (1926) 'Anatomische Beiträge zur Lehre von der Pickschen umschriebenen Grosshirnrinden-Atrophie (Picksche Krankheit)', *Z. ges. Neurol. Psychiat.* , 101, 470.

Ozawa, T., Paviour, D., Quinn, N. P., Josephs, K. A., Sangha, H., Kilford, L., Healy, D. G., Wood, N. W., Lees, A. J., Holton, J. L. and Revesz, T. (2004) 'The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations', *Brain*, 127(Pt 12), 2657-71.

Paisan-Ruiz, C., Bhatia, K. P., Li, A., Hernandez, D., Davis, M., Wood, N. W., Hardy, J., Houlden, H., Singleton, A. and Schneider, S. A. (2009) 'Characterization of PLA2G6 as a locus for dystonia-parkinsonism', *Ann Neurol*, 65(1), 19-23.

Paisán-Ruíz, C., Jain, S., Evans, E. W., Gilks, W. P., Simón, J., van der Brug, M., López de Munain, A., Aparicio, S., Gil, A. M., Khan, N., Johnson, J., Martinez, J. R., Nicholl, D., Carrera, I. M., Pena, A. S., de Silva, R., Lees, A., Martí-Massó, J. F., Pérez-Tur, J., Wood, N. W. and Singleton, A. B. (2004) 'Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease', *Neuron*, 44(4), 595-600.

Pankratz, N., Wilk, J. B., Latourelle, J. C., DeStefano, A. L., Halter, C., Pugh, E. W., Doheny, K. F., Gusella, J. F., Nichols, W. C., Foroud, T., Myers, R. H. and PSG-PROGENI and GenePD Investigators, C. o. a. M. G. L. (2009) 'Genomewide association study for susceptibility genes contributing to familial Parkinson disease', *Hum Genet*, 124(6), 593-605.

Papp, M. I., Kahn, J. E. and Lantos, P. L. (1989) 'Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome)', *J Neurol Sci*, 94(1-3), 79-100.

Papp, M. I. and Lantos, P. L. (1994) 'The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology', *Brain*, 117 (Pt 2), 235-43.

Parkinson, J. (1817) *An essay on the shaking palsy*, London: Sherwood, Neely, and Jones.

Parkkinen, L., Soininen, H. and Alafuzoff, I. (2003) 'Regional distribution of alpha-synuclein pathology in unimpaired aging and Alzheimer disease', *J Neuropathol Exp Neurol*, 62(4), 363-7.

Peelaerts, W. and Baekelandt, V. (2016a) 'α-Synuclein strains and the variable pathologies of synucleinopathies', *J Neurochem*.

Peelaerts, W. and Baekelandt, V. (2016b) 'α-synuclein folds: the cards are on the table', *Nat Struct Mol Biol*, 23(5), 359-60.

Peelaerts, W., Bousset, L., Van der Perren, A., Moskalyuk, A., Pulizzi, R., Giugliano, M., Van den Haute, C., Melki, R. and Baekelandt, V. (2015) 'α-Synuclein strains cause distinct synucleinopathies after local and systemic administration', *Nature*, 522(7556), 340-4.

Peuralinna, T., Myllykangas, L., Oinas, M., Nalls, M. A., Keage, H. A., Isoviita, V. M., Valori, M., Polvikoski, T., Paetau, A., Sulkava, R., Ince, P. G., Zaccai, J., Brayne, C., Traynor, B. J., Hardy, J., Singleton, A. B. and Tienari, P. J. (2015) 'Genome-wide association study of neocortical Lewy-related pathology', *Ann Clin Transl Neurol*, 2(9), 920-31.

Pick, A. (1892) 'Über die Beziehungen der senilen Hirnatrophie zur Aphasie', *Prager Medicinische Wochenschrift*, 17(16), 165-167.

Pieri, L., Madiona, K., Bousset, L. and Melki, R. (2012) 'Fibrillar α-synuclein and huntingtin exon 1 assemblies are toxic to the cells', *Biophys J*, 102(12), 2894-905.

Polymeropoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E. S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W. G., Lazzarini, A. M., Duvoisin, R. C., Di Iorio, G., Golbe, L. I. and Nussbaum, R. L. (1997) 'Mutation in the alpha-synuclein gene identified in families with Parkinson's disease', *Science*, 276(5321), 2045-7.

Pottier, C., Bieniek, K. F., Finch, N., van de Vorst, M., Baker, M., Perkersen, R., Brown, P., Ravenscroft, T., van Blitterswijk, M., Nicholson, A. M., DeTure, M., Knopman, D. S., Josephs, K. A., Parisi, J. E., Petersen, R. C., Boylan, K. B., Boeve, B. F., Graff-Radford, N. R., Veltman, J. A., Gilissen, C., Murray, M. E., Dickson, D. W. and Rademakers, R. (2015) 'Whole-genome sequencing reveals important role for TBK1 and OPTN mutations in frontotemporal lobar degeneration without motor neuron disease', *Acta Neuropathol*, 130(1), 77-92.

Prihar, G., Verkkoniem, A., Perez-Tur, J., Crook, R., Lincoln, S., Houlden, H., Somer, M., Paetau, A.,

Kalimo, H., Grover, A., Myllykangas, L., Hutton, M., Hardy, J. and Haltia, M. (1999) 'Alzheimer disease PS-1 exon 9 deletion defined', *Nat Med*, 5(10), 1090.

Prince, M. J., Wimo, A., Guerchet, M. M., Ali, G. C., Wu, Y.-T. and Prina, M. (2015) *World Alzheimer Report 2015: The Global Impact of Dementia. An analysis of prevalence, incidence, cost and trends* [Commissioned report], Alzheimer's Disease International.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., Maller, J., Sklar, P., de Bakker, P. I., Daly, M. J. and Sham, P. C. (2007) 'PLINK: a tool set for whole-genome association and population-based linkage analyses', *Am J Hum Genet*, 81(3), 559-75.

Puschmann, A., Ross, O. A., Vilariño-Güell, C., Lincoln, S. J., Kachergus, J. M., Cobb, S. A., Lindquist, S. G., Nielsen, J. E., Wszolek, Z. K., Farrer, M., Widner, H., van Westen, D., Hägerström, D., Markopoulou, K., Chase, B. A., Nilsson, K., Reimer, J. and Nilsson, C. (2009) 'A Swedish family with de novo alpha-synuclein A53T mutation: evidence for early cortical dysfunction', *Parkinsonism Relat Disord*, 15(9), 627-32.

Qi-Takahara, Y., Morishima-Kawashima, M., Tanimura, Y., Dolios, G., Hirotani, N., Horikoshi, Y., Kametani, F., Maeda, M., Saido, T. C., Wang, R. and Ihara, Y. (2005) 'Longer forms of amyloid beta protein: implications for the mechanism of intramembrane cleavage by gamma-secretase', *J Neurosci*, 25(2), 436-45.

Quadri, M., Fang, M., Picillo, M., Olgiati, S., Breedveld, G. J., Graafland, J., Wu, B., Xu, F., Erro, R., Amboni, M., Pappatà, S., Quarantelli, M., Annesi, G., Quattrone, A., Chien, H. F., Barbosa, E. R., Oostra, B. A., Barone, P., Wang, J., Bonifati, V. and Network, I. P. G. (2013) 'Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset Parkinsonism', *Hum Mutat*, 34(9), 1208-15.

Rahkonen, T., Eloniemi-Sulkava, U., Rissanen, S., Vatanen, A., Viramo, P. and Sulkava, R. (2003) 'Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older', *J Neurol Neurosurg Psychiatry*, 74(6), 720-4.

Ramirez, A., Heimbach, A., Gründemann, J., Stiller, B., Hampshire, D., Cid, L. P., Goebel, I., Mubaidin, A. F., Wriekat, A. L., Roeper, J., Al-Din, A., Hillmer, A. M., Karsak, M., Liss, B., Woods, C. G., Behrens, M. I. and Kubisch, C. (2006) 'Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase', *Nat Genet*, 38(10), 1184-91.

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., van Swieten, J. C., Seelaar, H., Dopper, E. G., Onyike, C. U., Hillis, A. E., Josephs, K. A., Boeve, B. F., Kertesz, A., Seeley, W. W., Rankin, K. P., Johnson, J. K., Gorno-Tempini, M. L., Rosen, H., Prioleau-Latham, C. E., Lee, A., Kipps, C. M., Lillo, P., Piguet, O., Rohrer, J. D., Rossor, M. N., Warren, J. D., Fox, N. C., Galasko, D., Salmon, D. P., Black, S. E., Mesulam, M., Weintraub, S., Dickerson, B. C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T. W., Manes, F., Grafman, J., Cappa, S. F., Freedman, M., Grossman, M. and Miller, B. L. (2011) 'Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia', *Brain*, 134(Pt 9), 2456-77.

Ratnavalli, E., Brayne, C., Dawson, K. and Hodges, J. R. (2002) 'The prevalence of frontotemporal dementia', *Neurology*, 58(11), 1615-21.

Renton, A. E., Majounie, E., Waite, A., Simón-Sánchez, J., Rollinson, S., Gibbs, J. R., Schymick, J. C., Laaksovirta, H., van Swieten, J. C., Myllykangas, L., Kalimo, H., Paetau, A., Abramzon, Y., Remes, A. M., Kaganovich, A., Scholz, S. W., Duckworth, J., Ding, J., Harmer, D. W., Hernandez, D. G., Johnson, J. O., Mok, K., Ryten, M., Trabzuni, D., Guerreiro, R. J., Orrell, R. W., Neal, J., Murray, A., Pearson, J., Jansen, I. E., Sondervan, D., Seelaar, H., Blake, D., Young, K., Halliwell, N., Callister, J. B., Toulson, G., Richardson, A., Gerhard, A., Snowden, J., Mann, D., Neary, D., Nalls, M. A., Peuralinna, T., Jansson, L., Isoviita, V. M., Kaivorinne, A. L., Hölttä-Vuori, M., Ikonen, E., Sulkava, R., Benatar, M., Wuu, J., Chiò, A., Restagno, G., Borghero, G., Sabatelli, M., Heckerman, D., Rogaeva, E., Zinman, L., Rothstein, J. D., Sendtner, M., Drepper, C., Eichler, E. E., Alkan, C., Abdullaev, Z., Pack, S. D., Dutra, A., Pak, E., Hardy, J., Singleton, A., Williams, N. M., Heutink, P., Pickering-Brown, S., Morris, H. R., Tienari, P. J., Traynor, B. J. and Consortium, I. (2011) 'A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD', *Neuron*, 72(2), 257-68.

Reva, B., Antipin, Y. and Sander, C. (2011) 'Predicting the functional impact of protein mutations: application to cancer genomics', *Nucleic Acids Res*, 39(17), e118.

Reyes, J. F., Rey, N. L., Bousset, L., Melki, R., Brundin, P. and Angot, E. (2014) 'Alpha-synuclein transfers from neurons to oligodendrocytes', *Glia*, 62(3), 387-98.

Roeber, S., Mackenzie, I. R., Kretzschmar, H. A. and Neumann, M. (2008) 'TDP-43-negative FTLD-U is a significant new clinico-pathological subtype of FTLD', *Acta Neuropathol*, 116(2), 147-57.

Rogaev, E. I., Sherrington, R., Rogaeva, E. A., Levesque, G., Ikeda, M., Liang, Y., Chi, H., Lin, C., Holman, K. and Tsuda, T. (1995) 'Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene', *Nature*, 376(6543), 775-8.

Rogaeva, E., Meng, Y., Lee, J. H., Gu, Y., Kawarai, T., Zou, F., Katayama, T., Baldwin, C. T., Cheng, R., Hasegawa, H., Chen, F., Shibata, N., Lunetta, K. L., Pardossi-Piquard, R., Bohm, C., Wakutani, Y., Cupples, L. A., Cuenco, K. T., Green, R. C., Pinessi, L., Rainero, I., Sorbi, S., Bruni, A., Duara, R., Friedland, R. P., Inzelberg, R., Hampe, W., Bujo, H., Song, Y. Q., Andersen, O. M., Willnow, T. E., Graff-Radford, N., Petersen, R. C., Dickson, D., Der, S. D., Fraser, P. E., Schmitt-Ulms, G., Younkin, S., Mayeux, R., Farrer, L. A. and St George-Hyslop, P. (2007) 'The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease', *Nat Genet*, 39(2), 168-77.

Roheim, P. S., Carey, M., Forte, T. and Vega, G. L. (1979) 'Apolipoproteins in human cerebrospinal fluid', *Proc Natl Acad Sci U S A*, 76(9), 4646-9.

Rohrer, J. D., Guerreiro, R., Vandrovcova, J., Uphill, J., Reiman, D., Beck, J., Isaacs, A. M., Authier, A., Ferrari, R., Fox, N. C., Mackenzie, I. R., Warren, J. D., de Silva, R., Holton, J., Revesz, T., Hardy, J., Mead, S. and Rossor, M. N. (2009) 'The heritability and genetics of frontotemporal lobar degeneration', *Neurology*, 73(18), 1451-6.

Rosen, H. J., Gorno-Tempini, M. L., Goldman, W. P., Perry, R. J., Schuff, N., Weiner, M., Feiwell, R., Kramer, J. H. and Miller, B. L. (2002) 'Patterns of brain atrophy in frontotemporal dementia and semantic dementia', *Neurology*, 58(2), 198-208.

Ross, O. A., Braithwaite, A. T., Skipper, L. M., Kachergus, J., Hulihan, M. M., Middleton, F. A., Nishioka, K., Fuchs, J., Gasser, T., Maraganore, D. M., Adler, C. H., Larvor, L., Chartier-Harlin, M. C., Nilsson, C., Langston, J. W., Gwinn, K., Hattori, N. and Farrer, M. J. (2008a) 'Genomic investigation of alpha-synuclein multiplication and parkinsonism', *Ann Neurol*, 63(6), 743-50.

Ross, O. A., Toft, M., Whittle, A. J., Johnson, J. L., Papapetropoulos, S., Mash, D. C., Litvan, I., Gordon, M. F., Wszolek, Z. K., Farrer, M. J. and Dickson, D. W. (2006) 'Lrrk2 and Lewy body disease', *Ann Neurol*, 59(2), 388-93.

Ross, O. A., Wu, Y. R., Lee, M. C., Funayama, M., Chen, M. L., Soto, A. I., Mata, I. F., Lee-Chen, G. J., Chen, C. M., Tang, M., Zhao, Y., Hattori, N., Farrer, M. J., Tan, E. K. and Wu, R. M. (2008b) 'Analysis of Lrrk2 R1628P as a risk factor for Parkinson's disease', *Ann Neurol*, 64(1), 88-92.

Rosso, S. M., Donker Kaat, L., Baks, T., Joosse, M., de Koning, I., Pijnenburg, Y., de Jong, D., Dooijes, D., Kamphorst, W., Ravid, R., Niermeijer, M. F., Verheij, F., Kremer, H. P., Scheltens, P., van Duijn, C. M., Heutink, P. and van Swieten, J. C. (2003) 'Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study', *Brain*, 126(Pt 9), 2016-22.

Rovelet-Lecrux, A., Frebourg, T., Tuominen, H., Majamaa, K., Campion, D. and Remes, A. M. (2007) 'APP locus duplication in a Finnish family with dementia and intracerebral haemorrhage', *J Neurol Neurosurg Psychiatry*, 78(10), 1158-9.

Rovelet-Lecrux, A., Hannequin, D., Raux, G., Le Meur, N., Laquerrière, A., Vital, A., Dumanchin, C., Feuillette, S., Brice, A., Vercelletto, M., Dubas, F., Frebourg, T. and Campion, D. (2006) 'APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy', *Nat Genet*, 38(1), 24-6.

Rutherford, N. J. and Giasson, B. I. (2015) 'The A53E α-synuclein pathological mutation demonstrates reduced aggregation propensity in vitro and in cell culture', *Neurosci Lett*, 597, 43-8.

Rutherford, N. J., Moore, B. D., Golde, T. E. and Giasson, B. I. (2014) 'Divergent effects of the H50Q and G51D SNCA mutations on the aggregation of α-synuclein', *J Neurochem*, 131(6), 859-67.

Ryan, B. J., Hoek, S., Fon, E. A. and Wade-Martins, R. (2015) 'Mitochondrial dysfunction and mitophagy in Parkinson's: from familial to sporadic disease', *Trends Biochem Sci*, 40(4), 200-10.

Sailer, A., Scholz, S. W., Nalls, M. A., Schulte, C., Federoff, M., Price, T. R., Lees, A., Ross, O. A., Dickson, D. W., Mok, K., Mencacci, N. E., Schottlaender, L., Chelban, V., Ling, H., O'Sullivan, S. S., Wood, N. W., Traynor, B. J., Ferrucci, L., Federoff, H. J., Mhyre, T. R., Morris, H. R., Deuschl, G., Quinn, N., Widner, H., Albanese, A., Infante, J., Bhatia, K. P., Poewe, W., Oertel, W., Höglinger, G. U., Wüllner, U., Goldwurm, S., Pellecchia, M. T., Ferreira, J., Tolosa, E., Bloem, B. R., Rascol, O., Meissner, W. G., Hardy, J. A., Revesz, T., Holton, J. L., Gasser, T., Wenning, G. K., Singleton, A. B., Houlden, H. and Group, E. M. S. A. S. G. a. t. U. M. S. A. S. (2016) 'A genome-wide association study in multiple system atrophy', *Neurology*.

Saint-Aubert, L., Sagot, C., Wallon, D., Hannequin, D., Payoux, P., Nemmi, F., Bezy, C., Chauveau, N., Campion, D., Puel, M., Chollet, F. and Pariente, J. (2014) 'A case of logopenic primary progressive aphasia with C9ORF72 expansion and cortical florbetapir binding', *J Alzheimers Dis*, 42(2), 413-20.

Sampathu, D. M., Neumann, M., Kwong, L. K., Chou, T. T., Micsenyi, M., Truax, A., Bruce, J., Grossman, M., Trojanowski, J. Q. and Lee, V. M. (2006) 'Pathological heterogeneity of frontotemporal lobar degeneration with ubiquitin-positive inclusions delineated by ubiquitin immunohistochemistry and novel monoclonal antibodies', *Am J Pathol*, 169(4), 1343-52.

Sanchez-Contreras, M., Baker, M. C., Finch, N. A., Nicholson, A., Wojtas, A., Wszolek, Z. K., Ross, O. A., Dickson, D. W. and Rademakers, R. (2014) 'Genetic screening and functional characterization

of PDGFRB mutations associated with basal ganglia calcification of unknown etiology', *Hum Mutat*, 35(8), 964-71.

Sanger, F. and Coulson, A. R. (1975) 'A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase', *J Mol Biol*, 94(3), 441-8.

Sasaki, H., Emi, M., Iijima, H., Ito, N., Sato, H., Yabe, I., Kato, T., Utsumi, J. and Matsubara, K. (2011) 'Copy number loss of (src homology 2 domain containing)-transforming protein 2 (SHC2) gene: discordant loss in monozygotic twins and frequent loss in patients with multiple system atrophy', *Mol Brain*, 4, 24.

Satake, W., Nakabayashi, Y., Mizuta, I., Hirota, Y., Ito, C., Kubo, M., Kawaguchi, T., Tsunoda, T., Watanabe, M., Takeda, A., Tomiyama, H., Nakashima, K., Hasegawa, K., Obata, F., Yoshikawa, T., Kawakami, H., Sakoda, S., Yamamoto, M., Hattori, N., Murata, M., Nakamura, Y. and Toda, T. (2009) 'Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease', *Nat Genet*, 41(12), 1303-7.

Scheuner, D., Eckman, C., Jensen, M., Song, X., Citron, M., Suzuki, N., Bird, T. D., Hardy, J., Hutton, M., Kukull, W., Larson, E., Levy-Lahad, E., Viitanen, M., Peskind, E., Poorkaj, P., Schellenberg, G., Tanzi, R., Wasco, W., Lannfelt, L., Selkoe, D. and Younkin, S. (1996) 'Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease', *Nat Med*, 2(8), 864-70.

Schmechel, D. E., Saunders, A. M., Strittmatter, W. J., Crain, B. J., Hulette, C. M., Joo, S. H., Pericak-Vance, M. A., Goldgaber, D. and Roses, A. D. (1993) 'Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease', *Proc Natl Acad Sci U S A*, 90(20), 9649-53.

Scholz, S. W., Houlden, H., Schulte, C., Sharma, M., Li, A., Berg, D., Melchers, A., Paudel, R., Gibbs, J. R., Simon-Sanchez, J., Paisan-Ruiz, C., Bras, J., Ding, J., Chen, H., Traynor, B. J., Arepalli, S., Zonozi, R. R., Revesz, T., Holton, J., Wood, N., Lees, A., Oertel, W., Wüllner, U., Goldwurm, S., Pellecchia, M. T., Illig, T., Riess, O., Fernandez, H. H., Rodriguez, R. L., Okun, M. S., Poewe, W., Wenning, G. K., Hardy, J. A., Singleton, A. B., Del Sorbo, F., Schneider, S., Bhatia, K. P. and Gasser, T. (2009) 'SNCA variants are associated with increased risk for multiple system atrophy', *Ann Neurol*, 65(5), 610-4.

Schottlaender, L. V., Houlden, H. and Collaboration, M.-S. A. M. B. B. (2014) 'Mutant COQ2 in multiple-system atrophy', *N Engl J Med*, 371(1), 81.

Schrag, A., Ben-Shlomo, Y. and Quinn, N. P. (1999) 'Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study', *Lancet*, 354(9192), 1771-5.

Schwarz, J. M., Cooper, D. N., Schuelke, M. and Seelow, D. (2014) 'MutationTaster2: mutation prediction for the deep-sequencing age', *Nat Methods*, 11(4), 361-2.

Selkoe, D. J. (1991) 'The molecular pathology of Alzheimer's disease', *Neuron*, 6(4), 487-98.

Seppi, K., Schocke, M. F., Wenning, G. K. and Poewe, W. (2005) 'How to diagnose MSA early: the role of magnetic resonance imaging', *J Neural Transm (Vienna)*, 112(12), 1625-34.

Seshadri, S., Fitzpatrick, A. L., Ikram, M. A., DeStefano, A. L., Gudnason, V., Boada, M., Bis, J. C., Smith, A. V., Carassquillo, M. M., Lambert, J. C., Harold, D., Schrijvers, E. M., Ramirez-Lorca, R., Debette, S., Longstreth, W. T., Janssens, A. C., Pankratz, V. S., Dartigues, J. F., Hollingworth, P., Aspelund, T., Hernandez, I., Beiser, A., Kuller, L. H., Koudstaal, P. J., Dickson, D. W., Tzourio, C., Abraham, R., Antunez, C., Du, Y., Rotter, J. I., Aulchenko, Y. S., Harris, T. B., Petersen, R. C., Berr, C., Owen, M. J., Lopez-Arrieta, J., Varadarajan, B. N., Becker, J. T., Rivadeneira, F., Nalls, M. A., Graff-Radford, N. R., Campion, D., Auerbach, S., Rice, K., Hofman, A., Jonsson, P. V., Schmidt, H., Lathrop, M., Mosley, T. H., Au, R., Psaty, B. M., Uitterlinden, A. G., Farrer, L. A., Lumley, T., Ruiz, A., Williams, J., Amouyel, P., Younkin, S. G., Wolf, P. A., Launer, L. J., Lopez, O. L., van Duijn, C. M., Breteler, M. M., Consortium, C., Consortium, G. and Consortium, E. (2010) 'Genome-wide analysis of genetic loci associated with Alzheimer disease', *JAMA*, 303(18), 1832-40.

Shakibai, S. V., Johnson, J. P. and Bourgeois, J. A. (2005) 'Paranoid delusions and cognitive impairment suggesting Fahr's disease', *Psychosomatics*, 46(6), 569-72.

Sharma, M., Wenning, G., Krüger, R. and (EMSA-SG), E. M.-S. A. S. G. (2014) 'Mutant COQ2 in multiple-system atrophy', *N Engl J Med*, 371(1), 80-1.

Sherrington, R., Rogaev, E. I., Liang, Y., Rogaeva, E. A., Levesque, G., Ikeda, M., Chi, H., Lin, C., Li, G., Holman, K., Tsuda, T., Mar, L., Foncin, J. F., Bruni, A. C., Montesi, M. P., Sorbi, S., Rainero, I., Pinessi, L., Nee, L., Chumakov, I., Pollen, D., Brookes, A., Sanseau, P., Polinsky, R. J., Wasco, W., Da Silva, H. A., Haines, J. L., Perkicak-Vance, M. A., Tanzi, R. E., Roses, A. D., Fraser, P. E., Rommens, J. M. and St George-Hyslop, P. H. (1995) 'Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease', *Nature*, 375(6534), 754-60.

Sherry, S. T., Ward, M. H., Kholodov, M., Baker, J., Phan, L., Smigielski, E. M. and Sirotkin, K. (2001) 'dbSNP: the NCBI database of genetic variation', *Nucleic Acids Res*, 29(1), 308-11.

Shi, Z., Liu, S., Xiang, L., Wang, Y., Liu, M., Han, T., Zhou, Y., Wang, J., Cai, L., Gao, S. and Ji, Y. (2016)

'Frontotemporal dementia-related gene mutations in clinical dementia patients from a Chinese population', *J Hum Genet*.

Shirahama, M., Akiyoshi, J., Ishitobi, Y., Tanaka, Y., Tsuru, J., Matsushita, H., Hanada, H. and Kodama, K. (2010) 'A young woman with visual hallucinations, delusions of persecution and a history of performing arson with possible three-generation Fahr disease', *Acta Psychiatr Scand*, 121(1), 75-7.

Shy, G. M. and Drager, G. A. (1960) 'A neurological syndrome associated with orthostatic hypotension: a clinical-pathologic study', *Arch Neurol*, 2, 511-27.

Sieben, A., Van Langenhove, T., Engelborghs, S., Martin, J. J., Boon, P., Cras, P., De Deyn, P. P., Santens, P., Van Broeckhoven, C. and Cruts, M. (2012) 'The genetics and neuropathology of frontotemporal lobar degeneration', *Acta Neuropathol*, 124(3), 353-72.

Simoni, M., Pantoni, L., Pracucci, G., Palmertz, B., Guo, X., Gustafson, D. and Skoog, I. (2008) 'Prevalence of CT-detected cerebral abnormalities in an elderly Swedish population sample', *Acta Neurol Scand*, 118(4), 260-7.

Simón-Sánchez, J., Schulte, C., Bras, J. M., Sharma, M., Gibbs, J. R., Berg, D., Paisan-Ruiz, C., Lichtner, P., Scholz, S. W., Hernandez, D. G., Krüger, R., Federoff, M., Klein, C., Goate, A., Perlmutter, J., Bonin, M., Nalls, M. A., Illig, T., Gieger, C., Houlden, H., Steffens, M., Okun, M. S., Racette, B. A., Cookson, M. R., Foote, K. D., Fernandez, H. H., Traynor, B. J., Schreiber, S., Arepalli, S., Zonozi, R., Gwinn, K., van der Brug, M., Lopez, G., Chanock, S. J., Schatzkin, A., Park, Y., Hollenbeck, A., Gao, J., Huang, X., Wood, N. W., Lorenz, D., Deuschl, G., Chen, H., Riess, O., Hardy, J. A., Singleton, A. B. and Gasser, T. (2009) 'Genome-wide association study reveals genetic risk underlying Parkinson's disease', *Nat Genet*, 41(12), 1308-12.

Singleton, A. B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., Hulihan, M., Peuralinna, T., Dutra, A., Nussbaum, R., Lincoln, S., Crawley, A., Hanson, M., Maraganore, D., Adler, C., Cookson, M. R., Muenter, M., Baptista, M., Miller, D., Blancato, J., Hardy, J. and Gwinn-Hardy, K. (2003) 'alpha-Synuclein locus triplication causes Parkinson's disease', *Science*, 302(5646), 841.

Sinha, S., Anderson, J. P., Barbour, R., Basi, G. S., Caccavello, R., Davis, D., Doan, M., Dovey, H. F., Frigon, N., Hong, J., Jacobson-Croak, K., Jewett, N., Keim, P., Knops, J., Lieberburg, I., Power, M., Tan, H., Tatsuno, G., Tung, J., Schenk, D., Seubert, P., Suomensaari, S. M., Wang, S., Walker, D., Zhao, J., McConlogue, L. and John, V. (1999) 'Purification and cloning of amyloid precursor protein beta-secretase from human brain', *Nature*, 402(6761), 537-40.

Sisodia, S. S. (1992) 'Beta-amyloid precursor protein cleavage by a membrane-bound protease', *Proc Natl Acad Sci U S A*, 89(13), 6075-9.

Skibinski, G., Parkinson, N. J., Brown, J. M., Chakrabarti, L., Lloyd, S. L., Hummerich, H., Nielsen, J. E., Hodges, J. R., Spillantini, M. G., Thusgaard, T., Brandner, S., Brun, A., Rossor, M. N., Gade, A., Johannsen, P., Sørensen, S. A., Gydesen, S., Fisher, E. M. and Collinge, J. (2005) 'Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia', *Nat Genet*, 37(8), 806-8.

Skoglund, L., Viitanen, M., Kalimo, H., Lannfelt, L., Jönhagen, M. E., Ingelsson, M., Glaser, A. and Herva, R. (2008) 'The tau S305S mutation causes frontotemporal dementia with parkinsonism', *Eur J Neurol*, 15(2), 156-61.

Smeyers-Verbeke, J., Michotte, Y., Pelsmaeckers, J., Lowenthal, A., Massart, D. L., Dekegel, D. and Karcher, D. (1975) 'The chemical composition of idiopathic nonarteriosclerotic cerebral calcifications', *Neurology*, 25(1), 48-57.

Soba, P., Eggert, S., Wagner, K., Zentgraf, H., Siehl, K., Kreger, S., Löwer, A., Langer, A., Merdes, G., Paro, R., Masters, C. L., Müller, U., Kins, S. and Beyreuther, K. (2005) 'Homo- and heterodimerization of APP family members promotes intercellular adhesion', *EMBO J*, 24(20), 3624-34.

Sobrido, M. J., Coppola, G., Oliveira, J., Hopfer, S. and Geschwind, D. H. (2014) 'Primary Familial Brain Calcification' in Pagon RA, A. M., Ardinger HH, et al., editors., ed., *GeneReviews® [Internet]*, Seattle (WA): University of Washington, Seattle.

Solans, A., Estivill, X. and de La Luna, S. (2000) 'A new aspartyl protease on 21q22.3, BACE2, is highly similar to Alzheimer's amyloid precursor protein beta-secretase', *Cytogenet Cell Genet*, 89(3-4), 177-84.

Soma, H., Yabe, I., Takei, A., Fujiki, N., Yanagihara, T. and Sasaki, H. (2006) 'Heredity in multiple system atrophy', *J Neurol Sci*, 240(1-2), 107-10.

Song, Y. J., Lundvig, D. M., Huang, Y., Gai, W. P., Blumbergs, P. C., Højrup, P., Otzen, D., Halliday, G. M. and Jensen, P. H. (2007) 'p25alpha relocalizes in oligodendroglia from myelin to cytoplasmic inclusions in multiple system atrophy', *Am J Pathol*, 171(4), 1291-303.

Spillantini, M. G., Crowther, R. A., Jakes, R., Cairns, N. J., Lantos, P. L. and Goedert, M. (1998) 'Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies', *Neurosci Lett*, 251(3), 205-8.

Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R. and Goedert, M. (1997)

'Alpha-synuclein in Lewy bodies', *Nature*, 388(6645), 839-40.

Stefanis, L. (2012) 'α-Synuclein in Parkinson's disease', *Cold Spring Harb Perspect Med*, 2(2), a009399.

Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G. S. and Roses, A. D. (1993) 'Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease', *Proc Natl Acad Sci U S A*, 90(5), 1977-81.

Sulem, P., Helgason, H., Oddson, A., Stefansson, H., Gudjonsson, S. A., Zink, F., Hjartarson, E., Sigurdsson, G. T., Jonasdottir, A., Sigurdsson, A., Magnusson, O. T., Kong, A., Helgason, A., Holm, H., Thorsteinsdottir, U., Masson, G., Gudbjartsson, D. F. and Stefansson, K. (2015) 'Identification of a large set of rare complete human knockouts', *Nat Genet*, 47(5), 448-52.

Sun, X., He, G., Qing, H., Zhou, W., Dobie, F., Cai, F., Staufenbiel, M., Huang, L. E. and Song, W. (2006) 'Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression', *Proc Natl Acad Sci U S A*, 103(49), 18727-32.

Sveinbjornsdottir, S. (2016) 'The clinical symptoms of Parkinson's disease', *J Neurochem*.

Synofzik, M., Born, C., Rominger, A., Lummel, N., Schöls, L., Biskup, S., Schüle, C., Grasshoff, U., Klopstock, T. and Adamczyk, C. (2014) 'Targeted high-throughput sequencing identifies a TARDBP mutation as a cause of early-onset FTD without motor neuron disease', *Neurobiol Aging*, 35(5), 1212.e1-5.

Tacik, P., DeTure, M., Hinkle, K. M., Lin, W. L., Sanchez-Contreras, M., Carlomagno, Y., Pedraza, O., Rademakers, R., Ross, O. A., Wszolek, Z. K. and Dickson, D. W. (2015a) 'A Novel Tau Mutation in Exon 12, p.Q336H, Causes Hereditary Pick Disease', *J Neuropathol Exp Neurol*, 74(11), 1042-52.

Tacik, P., DeTure, M., Lin, W. L., Sanchez Contreras, M., Wojtas, A., Hinkle, K. M., Fujioka, S., Baker, M. C., Walton, R. L., Carlomagno, Y., Brown, P. H., Strongosky, A. J., Kouri, N., Murray, M. E., Petrucelli, L., Josephs, K. A., Rademakers, R., Ross, O. A., Wszolek, Z. K. and Dickson, D. W. (2015b) 'A novel tau mutation, p.K317N, causes globular glial tauopathy', *Acta Neuropathol*, 130(2), 199-214.

Tacik, P., DeTure, M. A., Yari, C., Lin, W. L., Murray, M. E., Baker, M. C., Josephs, K. A., Boeve, B. F., Wszolek, Z. K., Graff-Radford, N. R., Parisi, J. E., Petrucelli, L., Rademakers, R., Isaacson, R. S., Heilman, K. M., Petersen, R. C., Dickson, D. W. and Kouri, N. (2016) 'FTDP-17 with pick body-like inclusions associated with a novel tau mutation, p.E372G', *Brain Pathol*.

Taghdiri, F., Sato, C., Ghani, M., Moreno, D., Rogaeva, E. and Tartaglia, M. C. (2016) 'Novel GRN Mutations in Patients with Corticobasal Syndrome', *Sci Rep*, 6, 22913.

Takami, M., Nagashima, Y., Sano, Y., Ishihara, S., Morishima-Kawashima, M., Funamoto, S. and Ihara, Y. (2009) 'gamma-Secretase: successive tripeptide and tetrapeptide release from the transmembrane domain of beta-carboxyl terminal fragment', *J Neurosci*, 29(41), 13042-52.

Tallquist, M. D., French, W. J. and Soriano, P. (2003) 'Additive effects of PDGF receptor beta signaling pathways in vascular smooth muscle cell development', *PLoS Biol*, 1(2), E52.

Tang, M., Gu, X., Wei, J., Jiao, B., Zhou, L., Zhou, Y., Weng, L., Yan, X., Tang, B., Xu, J. and Shen, L. (2016) 'Analyses MAPT, GRN, and C9orf72 mutations in Chinese patients with frontotemporal dementia', *Neurobiol Aging*.

Tayebi, N., Walker, J., Stubblefield, B., Orvisky, E., LaMarca, M. E., Wong, K., Rosenbaum, H., Schiffmann, R., Bembi, B. and Sidransky, E. (2003) 'Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism?', *Mol Genet Metab*, 79(2), 104-9.

The Lund and Manchester groups (1994) 'Consensus statament: Clinical and neuropathological criteria for

frontotemporal dementia', Journal of Neurology, Neurosurgery, and Psychiatry, 57, 416-418.

Theillet, F. X., Binolfi, A., Bekei, B., Martorana, A., Rose, H. M., Stuiver, M., Verzini, S., Lorenz, D., van Rossum, M., Goldfarb, D. and Selenko, P. (2016) 'Structural disorder of monomeric α-synuclein persists in mammalian cells', *Nature*, 530(7588), 45-50.

Ticozzi, N., Silani, V., LeClerc, A. L., Keagle, P., Gellera, C., Ratti, A., Taroni, F., Kwiatkowski, T. J., McKenna-Yasek, D. M., Sapp, P. C., Brown, R. H. and Landers, J. E. (2009) 'Analysis of FUS gene mutation in familial amyotrophic lateral sclerosis within an Italian cohort', *Neurology*, 73(15), 1180-5.

Ting, S. K., Chong, M. S., Kandiah, N., Hameed, S., Tan, L., Au, W. L., Prakash, K. M., Pavanni, R., Lee, T. S., Foo, J. N., Bei, J. X., Yu, X. Q., Liu, J. J., Zhao, Y., Lee, W. L. and Tan, E. K. (2013) 'Absence of A673T amyloid-β precursor protein variant in Alzheimer's disease and other neurological diseases', *Neurobiol Aging*, 34(10), 2441.e7-8.

Tsuang, D., Leverenz, J. B., Lopez, O. L., Hamilton, R. L., Bennett, D. A., Schneider, J. A., Buchman, A. S., Larson, E. B., Crane, P. K., Kaye, J. A., Kramer, P., Woltjer, R., Kukull, W., Nelson, P. T., Jicha, G. A., Neltner, J. H., Galasko, D., Masliah, E., Trojanowski, J. Q., Schellenberg, G. D., Yearout, D., Huston, H., Fritts-Penniman, A., Mata, I. F., Wan, J. Y., Edwards, K. L., Montine, T. J. and Zabetian, C. P.

(2012) 'GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology', *Neurology*, 79(19), 1944-50.

Ulmer, T. S., Bax, A., Cole, N. B. and Nussbaum, R. L. (2005) 'Structure and dynamics of micelle-bound human alpha-synuclein', *J Biol Chem*, 280(10), 9595-603.

Ulrich, J. D., Finn, M. B., Wang, Y., Shen, A., Mahan, T. E., Jiang, H., Stewart, F. R., Piccio, L., Colonna, M. and Holtzman, D. M. (2014) 'Altered microglial response to Aβ plaques in APPPS1-21 mice heterozygous for TREM2', *Mol Neurodegener*, 9, 20.

Vaarmann, A., Kovac, S., Holmström, K. M., Gandhi, S. and Abramov, A. Y. (2013) 'Dopamine protects neurons against glutamate-induced excitotoxicity', *Cell Death Dis*, 4, e455.

Valdmanis, P. N., Dupré, N., Lachance, M., Stochmanski, S. J., Belzil, V. V., Dion, P. A., Thiffault, I., Brais, B., Weston, L., Saint-Amant, L., Samuels, M. E. and Rouleau, G. A. (2011) 'A mutation in the RNF170 gene causes autosomal dominant sensory ataxia', *Brain*, 134(Pt 2), 602-7.

Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M., Harvey, K., Gispert, S., Ali, Z., Del Turco, D., Bentivoglio, A. R., Healy, D. G., Albanese, A., Nussbaum, R., González-Maldonado, R., Deller, T., Salvi, S., Cortelli, P., Gilks, W. P., Latchman, D. S., Harvey, R. J., Dallapiccola, B., Auburger, G. and Wood, N. W. (2004) 'Hereditary early-onset Parkinson's disease caused by mutations in PINK1', *Science*, 304(5674), 1158-60.

Van Deerlin, V. M., Sleiman, P. M., Martinez-Lage, M., Chen-Plotkin, A., Wang, L. S., Graff-Radford, N. R., Dickson, D. W., Rademakers, R., Boeve, B. F., Grossman, M., Arnold, S. E., Mann, D. M., Pickering-Brown, S. M., Seelaar, H., Heutink, P., van Swieten, J. C., Murrell, J. R., Ghetti, B., Spina, S., Grafman, J., Hodges, J., Spillantini, M. G., Gilman, S., Lieberman, A. P., Kaye, J. A., Woltjer, R. L., Bigio, E. H., Mesulam, M., Al-Sarraj, S., Troakes, C., Rosenberg, R. N., White, C. L., Ferrer, I., Lladó, A., Neumann, M., Kretzschmar, H. A., Hulette, C. M., Welsh-Bohmer, K. A., Miller, B. L., Alzualde, A., Lopez de Munain, A., McKee, A. C., Gearing, M., Levey, A. I., Lah, J. J., Hardy, J., Rohrer, J. D., Lashley, T., Mackenzie, I. R., Feldman, H. H., Hamilton, R. L., Dekosky, S. T., van der Zee, J., Kumar-Singh, S., Van Broeckhoven, C., Mayeux, R., Vonsattel, J. P., Troncoso, J. C., Kril, J. J., Kwok, J. B., Halliday, G. M., Bird, T. D., Ince, P. G., Shaw, P. J., Cairns, N. J., Morris, J. C., McLean, C. A., DeCarli, C., Ellis, W. G., Freeman, S. H., Frosch, M. P., Growdon, J. H., Perl, D. P., Sano, M., Bennett, D. A., Schneider, J. A., Beach, T. G., Reiman, E. M., Woodruff, B. K., Cummings, J., Vinters, H. V., Miller, C. A., Chui, H. C., Alafuzoff, I., Hartikainen, P., Seilhean, D., Galasko, D., Masliah, E., Cotman, C. W., Tuñón, M. T., Martínez, M. C., Munoz, D. G., Carroll, S. L., Marson, D., Riederer, P. F., Bogdanovic, N., Schellenberg, G. D., Hakonarson, H., Trojanowski, J. Q. and Lee, V. M. (2010) 'Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions', *Nat Genet*, 42(3), 234-9.

Van Langenhove, T., van der Zee, J., Sleegers, K., Engelborghs, S., Vandenberghe, R., Gijselinck, I., Van den Broeck, M., Mattheijssens, M., Peeters, K., De Deyn, P. P., Cruts, M. and Van Broeckhoven, C. (2010) 'Genetic contribution of FUS to frontotemporal lobar degeneration', *Neurology*, 74(5), 366-71.

Vassar, R., Bennett, B. D., Babu-Khan, S., Kahn, S., Mendiaz, E. A., Denis, P., Teplow, D. B., Ross, S., Amarante, P., Loeloff, R., Luo, Y., Fisher, S., Fuller, J., Edenson, S., Lile, J., Jarosinski, M. A., Biere, A. L., Curran, E., Burgess, T., Louis, J. C., Collins, F., Treanor, J., Rogers, G. and Citron, M. (1999) 'Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE', *Science*, 286(5440), 735-41.

Verkkoniemi, A., Somer, M., Rinne, J. O., Myllykangas, L., Crook, R., Hardy, J., Viitanen, M., Kalimo, H. and Haltia, M. (2000) 'Variant Alzheimer's disease with spastic paraparesis: clinical characterization', *Neurology*, 54(5), 1103-9.

Vilariño-Güell, C., Wider, C., Ross, O. A., Dachsel, J. C., Kachergus, J. M., Lincoln, S. J., Soto-Ortolaza, A. I., Cobb, S. A., Wilhoite, G. J., Bacon, J. A., Behrouz, B., Melrose, H. L., Hentati, E., Puschmann, A., Evans, D. M., Conibear, E., Wasserman, W. W., Aasly, J. O., Burkhard, P. R., Djaldetti, R., Ghika, J., Hentati, F., Krygowska-Wajs, A., Lynch, T., Melamed, E., Rajput, A., Rajput, A. H., Solida, A., Wu, R. M., Uitti, R. J., Wszolek, Z. K., Vingerhoets, F. and Farrer, M. J. (2011) 'VPS35 mutations in Parkinson disease', *Am J Hum Genet*, 89(1), 162-7.

Viramo, P. and Sulkava, R. (2015) 'Muistisairauksien epidemiologia' in Erkinjuntti, T., Remes, A., Rinne, J. and Soininen, H., eds., *Muistisairaudet*, Helsinki: Kustannus Oy Duodecim.

Volles, M. J. and Lansbury, P. T. (2002) 'Vesicle permeabilization by protofibrillar alpha-synuclein is sensitive to Parkinson's disease-linked mutations and occurs by a pore-like mechanism', *Biochemistry*, 41(14), 4595-602.

Volles, M. J., Lee, S. J., Rochet, J. C., Shtilerman, M. D., Ding, T. T., Kessler, J. C. and Lansbury, P. T. (2001) 'Vesicle permeabilization by protofibrillar alpha-synuclein: implications for the pathogenesis and treatment of Parkinson's disease', *Biochemistry*, 40(26), 7812-9.

Volpato, C. B., De Grandi, A., Buffone, E., Facheris, M., Gebert, U., Schifferle, G., Schönhuber, R., Hicks, A. and Pramstaller, P. P. (2009) '2q37 as a susceptibility locus for idiopathic basal ganglia

calcification (IBGC) in a large South Tyrolean family', *J Mol Neurosci*, 39(3), 346-53.

Wakabayashi, K., Yoshimoto, M., Tsuji, S. and Takahashi, H. (1998) 'Alpha-synuclein immunoreactivity in glial cytoplasmic inclusions in multiple system atrophy', *Neurosci Lett*, 249(2-3), 180-2.

Wallingford, M. C., Chia, J., Leaf, E. M., Borgeia, S., Chavkin, N. W., Sawangmake, C., Marro, K., Cox, T. C., Speer, M. Y. and Giachelli, C. M. (2016) 'SLC20A2 deficiency in mice leads to elevated phosphate levels in cerbrospinal fluid and glymphatic pathway-associated arteriolar calcification, and recapitulates human idiopathic basal ganglia calcification', *Brain Pathol*.

Wallon, D., Rovelet-Lecrux, A., Deramecourt, V., Pariente, J., Auriacombe, S., Le Ber, I., Schraen, S., Pasquier, F., Campion, D. and Hannequin, D. (2012) 'Definite behavioral variant of frontotemporal dementia with C9ORF72 expansions despite positive Alzheimer's disease cerebrospinal fluid biomarkers', *J Alzheimers Dis*, 32(1), 19-22.

Wang, C., Li, Y., Shi, L., Ren, J., Patti, M., Wang, T., de Oliveira, J. R., Sobrido, M. J., Quintáns, B., Baquero, M., Cui, X., Zhang, X. Y., Wang, L., Xu, H., Wang, J., Yao, J., Dai, X., Liu, J., Zhang, L., Ma, H., Gao, Y., Ma, X., Feng, S., Liu, M., Wang, Q. K., Forster, I. C., Zhang, X. and Liu, J. Y. (2012) 'Mutations in SLC20A2 link familial idiopathic basal ganglia calcification with phosphate homeostasis', *Nat Genet*, 44(3), 254-6.

Wang, K., Li, M. and Hakonarson, H. (2010) 'ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data', *Nucleic Acids Res*, 38(16), e164.

Wang, L. S., Naj, A. C., Graham, R. R., Crane, P. K., Kunkle, B. W., Cruchaga, C., Murcia, J. D., Cannon-Albright, L., Baldwin, C. T., Zetterberg, H., Blennow, K., Kukull, W. A., Faber, K. M., Schupf, N., Norton, M. C., Tschanz, J. T., Munger, R. G., Corcoran, C. D., Rogaeva, E., Lin, C. F., Dombroski, B. A., Cantwell, L. B., Partch, A., Valladares, O., Hakonarson, H., St George-Hyslop, P., Green, R. C., Goate, A. M., Foroud, T. M., Carney, R. M., Larson, E. B., Behrens, T. W., Kauwe, J. S., Haines, J. L., Farrer, L. A., Pericak-Vance, M. A., Mayeux, R., Schellenberg, G. D., Albert, M. S., Albin, R. L., Apostolova, L. G., Arnold, S. E., Barber, R., Barmada, M., Barnes, L. L., Beach, T. G., Becker, J. T., Beecham, G. W., Beekly, D., Bennett, D. A., Bigio, E. H., Bird, T. D., Blacker, D., Boeve, B. F., Bowen, J. D., Boxer, A., Burke, J. R., Buxbaum, J. D., Cairns, N. J., Cao, C., Carlson, C. S., Carroll, S. L., Chui, H. C., Clark, D. G., Cribbs, D. H., Crocco, E. A., DeCarli, C., DeKosky, S. T., Demirci, F. Y., Dick, M., Dickson, D. W., Duara, R., Ertekin-Taner, N., Fallon, K. B., Farlow, M. R., Ferris, S., Frosch, M. P., Galasko, D. R., Ganguli, M., Gearing, M., Geschwind, D. H., Ghetti, B., Gilbert, J. R., Glass, J. D., Graff-Radford, N. R., Growdon, J. H., Hamilton, R. L., Hamilton-Nelson, K. L., Harrell, L. E., Head, E., Honig, L. S., Hulette, C. M., Hyman, B. T., Jarvik, G. P., Jicha, G. A., Jin, L. W., Jun, G., Kamboh, M. I., Karydas, A., Kaye, J. A.*, et al.* (2015) 'Rarity of the Alzheimer disease-protective APP A673T variant in the United States', *JAMA Neurol*, 72(2), 209-16.

Watts, G. D., Wymer, J., Kovach, M. J., Mehta, S. G., Mumm, S., Darvish, D., Pestronk, A., Whyte, M. P. and Kimonis, V. E. (2004) 'Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein', *Nat Genet*, 36(4), 377-81.

Watts, J. C., Giles, K., Oehler, A., Middleton, L., Dexter, D. T., Gentleman, S. M., DeArmond, S. J. and Prusiner, S. B. (2013) 'Transmission of multiple system atrophy prions to transgenic mice', *Proc Natl Acad Sci U S A*, 110(48), 19555-60.

Westenberger, A. and Klein, C. (2014) 'The genetics of primary familial brain calcifications', *Curr Neurol Neurosci Rep*, 14(10), 490.

Wetzel-Smith, M. K., Hunkapiller, J., Bhangale, T. R., Srinivasan, K., Maloney, J. A., Atwal, J. K., Sa, S. M., Yaylaoglu, M. B., Foreman, O., Ortmann, W., Rathore, N., Hansen, D. V., Tessier-Lavigne, M., Mayeux, R., Pericak-Vance, M., Haines, J., Farrer, L. A., Schellenberg, G. D., Goate, A., Behrens, T. W., Cruchaga, C., Watts, R. J., Graham, R. R. and Consortium, A. s. D. G. (2014) 'A rare mutation in UNC5C predisposes to late-onset Alzheimer's disease and increases neuronal cell death', *Nat Med*, 20(12), 1452-7.

Wider, C., Dickson, D. W., Schweitzer, K. J., Broderick, D. F. and Wszolek, Z. K. (2009) 'Familial idiopathic basal ganglia calcification: a challenging clinical-pathological correlation', *J Neurol*, 256(5), 839-42.

Wilhelmsen, K. C., Lynch, T., Pavlou, E., Higgins, M. and Nygaard, T. G. (1994) 'Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22', *Am J Hum Genet*, 55(6), 1159-65.

Williams, K. L., Topp, S., Yang, S., Smith, B., Fifita, J. A., Warraich, S. T., Zhang, K. Y., Farrawell, N., Vance, C., Hu, X., Chesi, A., Leblond, C. S., Lee, A., Rayner, S. L., Sundaramoorthy, V., Dobson-Stone, C., Molloy, M. P., van Blitterswijk, M., Dickson, D. W., Petersen, R. C., Graff-Radford, N. R., Boeve, B. F., Murray, M. E., Pottier, C., Don, E., Winnick, C., McCann, E. P., Hogan, A., Daoud, H., Levert, A., Dion, P. A., Mitsui, J., Ishiura, H., Takahashi, Y., Goto, J., Kost, J., Gellera, C., Gkazi, A. S., Miller, J., Stockton, J., Brooks, W. S., Boundy, K., Polak, M., Muñoz-Blanco, J. L., Esteban-Pérez, J., Rábano, A., Hardiman, O., Morrison, K. E., Ticozzi, N., Silani, V., de Belleroche, J., Glass, J. D., Kwok, J. B., Guillemin, G. J., Chung, R. S., Tsuji, S., Brown, R. H., García-

Redondo, A., Rademakers, R., Landers, J. E., Gitler, A. D., Rouleau, G. A., Cole, N. J., Yerbury, J. J., Atkin, J. D., Shaw, C. E., Nicholson, G. A. and Blair, I. P. (2016) 'CCNF mutations in amyotrophic lateral sclerosis and frontotemporal dementia', *Nat Commun*, 7, 11253.

Wingo, T. S., Lah, J. J., Levey, A. I. and Cutler, D. J. (2012) 'Autosomal recessive causes likely in early-onset Alzheimer disease', *Arch Neurol*, 69(1), 59-64.

Winner, B., Jappelli, R., Maji, S. K., Desplats, P. A., Boyer, L., Aigner, S., Hetzer, C., Loher, T., Vilar, M., Campioni, S., Tzitzilonis, C., Soragni, A., Jessberger, S., Mira, H., Consiglio, A., Pham, E., Masliah, E., Gage, F. H. and Riek, R. (2011) 'In vivo demonstration that alpha-synuclein oligomers are toxic', *Proc Natl Acad Sci U S A*, 108(10), 4194-9.

Wirdefeldt, K., Adami, H. O., Cole, P., Trichopoulos, D. and Mandel, J. (2011) 'Epidemiology and etiology of Parkinson's disease: a review of the evidence', *Eur J Epidemiol*, 26 Suppl 1, S1-58.

Wolfe, M. S., Xia, W., Ostaszewski, B. L., Diehl, T. S., Kimberly, W. T. and Selkoe, D. J. (1999) 'Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity', *Nature*, 398(6727), 513-7.

Woollacott, I. O. and Rohrer, J. D. (2016) 'The clinical spectrum of sporadic and familial forms of frontotemporal dementia', *J Neurochem*.

Wszolek, Z. K., Baba, Y., Mackenzie, I. R., Uitti, R. J., Strongosky, A. J., Broderick, D. F., Baker, M. C., Melquist, S., Hutton, M. L., Tsuboi, Y., Allanson, J. E., Carr, J., Kumar, A., Calne, S. M., Miklossy, J., McGeer, P. L., Calne, D. B. and Stoessl, A. J. (2006) 'Autosomal dominant dystonia-plus with cerebral calcifications', *Neurology*, 67(4), 620-5.

Wu, Z. C., Yu, J. T., Wang, N. D., Yu, N. N., Zhang, Q., Chen, W., Zhang, W., Zhu, Q. X. and Tan, L. (2010) 'Lack of association between PCDH11X genetic variation and late-onset Alzheimer's disease in a Han Chinese population', *Brain Res*, 1357, 152-6.

Wüllner, U., Schmitt, I., Kammal, M., Kretzschmar, H. A. and Neumann, M. (2009) 'Definite multiple system atrophy in a German family', *J Neurol Neurosurg Psychiatry*, 80(4), 449-50.

Yamada, M., Asano, T., Okamoto, K., Hayashi, Y., Kanematsu, M., Hoshi, H., Akaiwa, Y., Shimohata, T., Nishizawa, M., Inuzuka, T. and Hozumi, I. (2013) 'High frequency of calcification in basal ganglia on brain computed tomography images in Japanese older adults', *Geriatr Gerontol Int*, 13(3), 706-10.

Yamada, M., Tanaka, M., Takagi, M., Kobayashi, S., Taguchi, Y., Takashima, S., Tanaka, K., Touge, T., Hatsuta, H., Murayama, S., Hayashi, Y., Kaneko, M., Ishiura, H., Mitsui, J., Atsuta, N., Sobue, G., Shimozawa, N., Inuzuka, T., Tsuji, S. and Hozumi, I. (2014) 'Evaluation of SLC20A2 mutations that cause idiopathic basal ganglia calcification in Japan', *Neurology*, 82(8), 705-12.

Yan, R., Bienkowski, M. J., Shuck, M. E., Miao, H., Tory, M. C., Pauley, A. M., Brashier, J. R., Stratman, N. C., Mathews, W. R., Buhl, A. E., Carter, D. B., Tomasselli, A. G., Parodi, L. A., Heinrikson, R. L. and Gurney, M. E. (1999) 'Membrane-anchored aspartyl protease with Alzheimer's disease beta-secretase activity', *Nature*, 402(6761), 533-7.

Yang, C. B., Kiser, P. J., Zheng, Y. T., Varoqueaux, F. and Mower, G. D. (2007) 'Bidirectional regulation of Munc13-3 protein expression by age and dark rearing during the critical period in mouse visual cortex', *Neuroscience*, 150(3), 603-8.

Yang, C. B., Zheng, Y. T., Li, G. Y. and Mower, G. D. (2002) 'Identification of Munc13-3 as a candidate gene for critical-period neuroplasticity in visual cortex', *J Neurosci*, 22(19), 8614-8.

Ylikotila, P., Tiirikka, T., Moilanen, J. S., Kääriäinen, H., Marttila, R. and Majamaa, K. (2015) 'Epidemiology of early-onset Parkinson's disease in Finland', *Parkinsonism Relat Disord*, 21(8), 938-42.

Yonetani, M., Nonaka, T., Masuda, M., Inukai, Y., Oikawa, T., Hisanaga, S. and Hasegawa, M. (2009) 'Conversion of wild-type alpha-synuclein into mutant-type fibrils and its propagation in the presence of A30P mutant', *J Biol Chem*, 284(12), 7940-50.

Zarranz, J. J., Alegre, J., Gómez-Esteban, J. C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atarés, B., Llorens, V., Gomez Tortosa, E., del Ser, T., Muñoz, D. G. and de Yebenes, J. G. (2004) 'The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia', *Ann Neurol*, 55(2), 164-73.

Zhang, Y., Guo, X. and Wu, A. (2013) 'Association between a novel mutation in SLC20A2 and familial idiopathic basal ganglia calcification', *PLoS One*, 8(2), e57060.

Zhao, Z., Sagare, A. P., Ma, Q., Halliday, M. R., Kong, P., Kisler, K., Winkler, E. A., Ramanathan, A., Kanekiyo, T., Bu, G., Owens, N. C., Rege, S. V., Si, G., Ahuja, A., Zhu, D., Miller, C. A., Schneider, J. A., Maeda, M., Maeda, T., Sugawara, T., Ichida, J. K. and Zlokovic, B. V. (2015) 'Central role for PICALM in amyloid-β blood-brain barrier transcytosis and clearance', *Nat Neurosci*, 18(7), 978-87.

Zheng, X., Liu, D., Roychaudhuri, R., Teplow, D. B. and Bowers, M. T. (2015) 'Amyloid β-Protein Assembly: Differential Effects of the Protective A2T Mutation and Recessive A2V Familial Alzheimer's Disease Mutation', *ACS Chem Neurosci*, 6(10), 1732-40.

Zimprich, A., Benet-Pagès, A., Struhal, W., Graf, E., Eck, S. H., Offman, M. N., Haubenberger, D., Spielberger, S., Schulte, E. C., Lichtner, P., Rossle, S. C., Klopp, N., Wolf, E., Seppi, K., Pirker, W., Presslauer, S., Mollenhauer, B., Katzenschlager, R.,

Foki, T., Hotzy, C., Reinthaler, E., Harutyunyan, A., Kralovics, R., Peters, A., Zimprich, F., Brücke, T., Poewe, W., Auff, E., Trenkwalder, C., Rost, B., Ransmayr, G., Winkelmann, J., Meitinger, T. and Strom, T. M. (2011) 'A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease', *Am J Hum Genet*, 89(1), 168-75.

Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S., Kachergus, J., Hulihan, M., Uitti, R. J., Calne, D. B., Stoessl, A. J., Pfeiffer, R. F., Patenge, N., Carbajal, I. C., Vieregge, P., Asmus, F., Müller-Myhsok, B., Dickson, D. W., Meitinger, T., Strom, T. M., Wszolek, Z. K. and Gasser, T. (2004) 'Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology', *Neuron*, 44(4), 601-7.