Mutation analysis of the genes linked to early onset Alzheimer's disease and frontotemporal lobar degeneration

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Running title: Mutation analysis in early onset AD and FTLD

Abstract

A lot of efforts have been done to unravel the genetics underlying early-onset Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). However, still many familial early-onset dementia (EOD) cases show an unclear genetic background. The aim of this study was to evaluate the role of the known causative mutations and possible pathogenic variants associated with AD and FTLD in a Finnish EOD cohort. The cohort consisted of 39 patients (mean age at onset 54.8 years, range 39-65) with a positive family history of dementia or an atypical or rapidly progressive course of the disease. None of the patients carried the *C9orf72* hexanucleotide repeat expansion. Mutations and variants in *APP, PSEN1, PSEN2, MAPT, GRN, VCP, CHMP2B, FUS, TARDBP, TREM2, TMEM106B, UBQLN2, SOD1, PRNP, UBQLN1* and *BIN1* were screened by using a targeted next generation sequencing (NGS) panel. Two previously reported pathogenic mutations (*PSEN1* p.His163Arg and *MAPT* p.Arg406Trp) were identified in the cohort. Both patients had familial dementia with an atypical early onset phenotype. In addition, a heterozygous p.Arg71Trp mutation in *PSEN2* with an uncertain pathogenic nature was identified in a patient with neuropathologically confirmed AD. In conclusion, targeted investigation of the known dementia-linked genes is worthwhile in patients with onset age under 55 and a positive family history, as well as in patients with atypical features.

Key words: Alzheimer's disease, frontotemporal lobar degeneration, frontotemporal dementia, genetics, early onset, presenilin-1, mutation, missense, microtubule-associated protein tau, human.

Introduction

Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) are the two most common causes for early-onset dementia (EOD) [1]. Approximately 35-60% of the early-onset AD (EOAD) and over 40% of the FTLD patients have at least one affected first-degree relative in their family and approximately 10% of these patients present the pattern of autosomal dominant inheritance [2,3]. The patient's probability of having AD caused by a pathogenic mutation increases if the his or her family presents AD in several generations and the age at the onset is very early (under 55 years) [4]. Mutations in amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*) genes account for 5-10% of EOAD while at least 20% of the EOAD patients have been estimated to display autosomal dominant inheritance of a still unknown genetic background [2]. To date, over 50 pathogenic mutations in *APP*, over 200 mutations in *PSEN1* and over 30 mutations in *PSEN2* genes are known to cause EOAD [2]. The *C9orf72* hexanucleotide repeat expansion or *MAPT* and *GRN* mutations underlie the majority of the familial FTLD [5,6]. In Finland, the prevalence of the *C9orf72* repeat expansion is exceptionally high [7], whereas *MAPT* and *GRN* mutations associated with FTLD or *PSEN1*, *PSEN2* and *APP* mutations associated with AD have been found to be very rare [8–10].

The apolipoprotein E (*APOE4*) ε4 allele is the main genetic risk factor for both EOAD and late onset AD (LOAD)[2]. However, *APOE4* has not been indicated to elevate the risk for FTLD. Recent genome-wide association studies (GWAS) and next generation sequencing studies (NGS) have so far identified over 20 other AD risk genes and genetic loci [11]. The genetic risk factors identified for LOAD have been suggested to modulate the risk for EOAD as well [12,13]. Previous NGS studies have shown that EOD patients are more often associated with multiple rare variants or risk alleles than LOAD patients or healthy controls [12].

The aim of this study was to evaluate the genetic background of a Finnish EOD cohort by analysing genes associated with AD and FTLD using targeted next generation exome sequencing.

Patients and methods

The study population consisted of 39 patients with EOD diagnosed at two memory outpatient clinics in Finland (Oulu University and Kuopio University Hospitals). The inclusion criteria of the patients were 1) early onset of the disorder (before 65 years) and 2) at least one patient with dementia in their family or 3) atypical or rapidly progressive course of the disease. All the patients were examined and diagnosed by an experienced neurologist specialized in memory disorders. The diagnoses were made according to the current prevailing diagnostic criteria for each disease. Also re-evaluation of the diagnoses [14–17] for this study was made by experienced neurologists. In total, 29 patients were diagnosed with AD, nine with FTLD and one with progressive supranuclear paresis. Three of the FTLD patients had also motor neuron disease. In our cohort, 44% (n=17) patients had at least one first-degree relative with dementia or cognitive decline and 51% (n=20) patients had a family history of cognitive decline in at least in second-degree relatives.

The mean age at onset was 54.8 years (range 39-65) and the mean age at diagnosis was 57.6 years (range 40-67). The patients carrying the *C9orf72* repeat expansion were excluded from the study. Three patients were carriers of the *APOE4* allele and they all had *APOE* genotype E3/E4. The study was performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all the patients or their caregivers. The research protocol was approved by the ethic committees of the Northern Ostrobothnia hospital district and by the Northern Savo hospital district.

DNA was extracted from the blood samples by standard methods. DNA purification was done with Qiagen purification Kit (Qiagen, Hilden, Germany) according to the original protocol. The repeat-primed polymerase chain reaction assay (RP-PCR) was used to indicate the presence or absence of the *C9orf72* repeat expansion [18]. Targeted gene exon libraries were prepared using NimbleGen SeqCap EZ Library kit (Roche, Basel, Switzerland) with customized SeqCap EZ Neurology Panel Design (Roche, Basel, Switzerland), covering all exons and exon-intron boundaries of 258 genes associated with 87 neurological diseases and disorders (Supplementary table 1). Furthermore, 22 additional genes were included in the panel (Supplementary table 2). Samples were sequenced using Illumina MiSeq sequencer (Illumina, San Diego, USA, CA).

Based on previous genetic findings of AD and FTLD, 16 genes (*APP, PSEN1, PSEN2, MAPT, GRN, VCP, CHMP2B, FUS, TARDBP, TREM2, TMEM106B, UBQLN2, SOD1, UBQLN1, PRNP* and *BIN1)* were selected for detailed investigation from the targeted panel of 258 genes and 22 additional genes. An in-house developed analysis pipeline was used for the evaluation of raw fastq files generated by the MiSeq sequencer. The data was manually screened to find exonic single-nucleotide mutations that cause a protein change. The recognized mutations were categorized as pathogenic, non-pathogenic and possible new variants or risk variants according to the previous literature and databases [19]. The relevant findings were confirmed by Sanger sequencing with ABI3500xL Genetic Analyzer (Applied Biosystems Inc, Foster City, USA, California). Primers and reaction conditions are available upon request. Exon-intron boundaries of *APP, PSEN1, PSEN2, MAPT, GRN, VCP, CHMP2B, FUS* and *TARDBP* genes were manually screened to find splice site mutations.

Results

Two patients (5.1%) were found to harbor previously reported pathogenic mutations p.His163Arg in *PSEN1* or p.Arg406Trp in *MAPT*. In addition, a *PSEN2* p.Arg71Trp mutation with an unclear pathogenic nature [20] was detected in a neuropathologically confirmed AD patient.

We also identified non-pathogenic variants *GRN* p.Arg433Trp, *PSEN1* p.Glu318Gly, *MAPT* p.Gln230Arg and *MAPT* p.Tyr441His in our cohort. Furthermore, we detected three AD risk variants in *TREM2, UBQLN2* and *BIN1* genes. Two variants in *TMEM106B* gene which have previously been reported to be associated with mainly FTD were detected in both AD and FTLD patients (Table 1). Moreover, we found one intronic splice-site mutation in *APP* which has unknown effect on protein code (Table 1.). All the patients were heterozygous carriers of the mutations or variants. The patient carrying the *TREM2* variant had *APOE* genotype E3/E4.

Phenotypes of the patients carrying the pathogenic mutations

PSEN1 p.His163Arg (c.A488G)

A 39-year-old woman referred to a neurologist due to rapidly progressive cognitive decline. A bipolar mood disorder had been diagnosed in her early twenties. In neurological examination, the patient presented slight postural tremor in her upper limbs, clumsy movements and myoclonic jerks. In addition, tardive dyskinesia/tic-symptoms were observed around her mouth as well as vocal tics. The patient was euphoric, and she presented behavioral disinhibition. Magnetic resonance imaging (MRI) of the brain was normal. In the cerebrospinal fluid (CSF) examination, phosphorylated tau was elevated, 252 pg/ml (normal concentration under 70 pg/ml), while beta-amyloid-42 ($A\beta_{42}$) was relatively low, 582 pg/ml (normal concentration over 500 pg/ml). Neuropsychological examination revealed severe cognitive decline and the patient was diagnosed to have AD. At the age of 44 years she had an epileptic seizure and a computed

tomography (CT) of the brain was done showing severe central atrophy and Scheltens grade 2 hippocampal atrophy [21]. Slowness and central spikes, but no epileptic bursts were found in the electroencephalography. At the age of 45 years she was bedridden and unable to speak. The patient died at the age of 46 years, but no autopsy was done. Her mother and sister as well as many of the mother´s siblings had been diagnosed with psychiatric syndromes. The patient's mother had also Parkinson's disease and she had died at the age of 70 years.

MAPT p.Arg406Trp (c.C1216T)

A 52-year-old woman presented subjective memory disturbances. In addition, her behaviour was impulsive and she had fluctuating mood changes. Neuropsychological examination revealed mild problems in concentration and her performance was slow, however at that point the neuropsychological profile was not regarded supportive for a dementing disease. At the age of 55 years, she was again referred to neurologist because of increasing memory problems. Neuropsychological examination revealed a decline in episodic memory, time orientation, visual reasoning, and perception in addition to executive dysfunction. She also suffered from depression and psychosis. In neurological examination, she had intention tremor and her speech was uninhibited but otherwise the examination was normal. Brain MRI showed moderate hippocampal atrophy bilaterally and cortical atrophy especially in the temporobasal areas. The CSF biomarkers for AD were normal. The patient was diagnosed to have frontal variant of AD. Four years after the diagnosis, the neuropsychological examination revealed severe cognitive decline, especially memory impairment, including major problems in delayed recall, working memory, learning and verbal memory in addition to executive dysfunction. The patient's mother got demented in her early fifties and her sister had been diagnosed to have AD at the age of 52 years. The patient also carried the *UBQLN2* p. Ile501Thr variant.

PSEN2 p.Arg71Trp (c.C211T)

A 55–year-old male referred to neurologist due to memory problems. Brain MRI indicated a Dandy-Walker malformation. In a follow-up, gradual cognitive decline and increasing memory problems were noticed and he was clinically diagnosed to have AD. At the age of 59 years, he indicated to have normal pressure hydrocephalus and a brain biopsy was obtained during the shunt operation. The histology of the brain biopsy showed typical neuropathological findings for AD, including considerable amount of beta-amyloid plaques but no amyloid pathology in the vessels. The accumulation of tau was detected as tangles, plaques, and cytoplasmic inclusions. There were also p62-positive cytoplasmic inclusions, tangles and fibrils, and a few TDP-43-positive cytoplasmic inclusions.

Discussion

In the present study, we have aimed at elucidating the genetic background of early-onset AD and FTLD cases. We found two previously reported pathogenic mutations in our cohort of EOD. The onset of the disease was under 55 years and both patients had a positive family history of neurodegenerative diseases. The *PSEN1* p.His163Arg mutation has been found in over 20 families worldwide so far [19]. *PSEN1* mutations have commonly been associated with very early-onset AD with atypical clinical features [22,23]. Interestingly, the location of the *PSEN1* mutation appears to lead to differences in clinical manifestations. Patients with mutations before codon 200, such as the *PSEN1* p.His163Arg mutation, usually show an early onset of the disease and more frequently display generalized seizures and myoclonus, all of which were also present in the patient of our study [24]. Interestingly, the patient also suffered from vocal tics. A few previously reported *PSEN1* p.His163Arg mutation carriers have also had

visual hallucinations and parkinsonism with rigidity and bradykinesia, but these symptoms were not observed in our patient [25]. However, the fact that the mother of the *PSEN1* p.His163Arg mutation carrier had manifested parkinsonism and psychiatric symptoms suggests that she might have been a *PSEN1* p.His163Arg mutation carrier as well.

The *MAPT* p.Arg406Trp mutation has been reported in over 60 patients so far [26]. Mutations in the *MAPT* gene are typically associated with tau pathology [26]. Despite the neuropathological findings typical for FTLD, the clinical phenotypes of the patients with the *MAPT* p.Arg406Trp mutation have suggested that they rather have AD than FTLD [26]. Especially, amnestic cognitive decline has been the most frequent first symptom in patients carrying this mutation, leading to AD diagnosis in the majority of the cases [26]. This phenotype was also present in the patient of our study. In addition to cognitive decline, the patient suffered from behavioural problems and severe psychiatric symptoms. A few *MAPT* p.Arg406Trp mutation carriers have also shown parkinsonian symptoms, but these were not detected in our patient [27]. About half of the previously reported mutation carriers have had elevated levels of tau and phosphorylated tau in the CSF. However, in our patient, the CSF AD biomarkers were normal [26]. In previous cases, the median age at onset has been 55 years, which is in line with our case [26].

We also detected a *PSEN2* p.Arg71Trp mutation, the pathogenicity of which is unclear [20]. This mutation has been found both in late-onset AD (LOAD) and EOAD patients [28–31]. However, the facts that it did not appear to segregate with AD in the families of the carriers, nor did it affect the Aβ42/Aβ40 ratio in an in vitro assay, and it was also found in healthy controls suggest that it is likely a benign mutation [10,20,28]. Interestingly though, the brain biopsy of the patient in our study revealed AD-type neuropathology. There is also a previous report of severe AD-type neuropathological findings of one *PSEN2* p.Arg71Trp mutation carrier, who had an early onset, but very slowly progressive AD [31]. Patients carrying the

PSEN2 mutations have usually an onset of the disease around 60 years and the disease duration may be even 20 years further suggesting that this mutation associates with slow disease progression [24]. Allele frequency of the *PSEN2* p.Arg71Trp in the Finnish population is low (0.0195 %, Table 1). However, since it has been found also in Finnish healthy controls, it has been suggested that alone this mutation is not likely sufficient to cause AD [10]. Nevertheless, *PSEN2* p.Arg71Trp mutation might be a risk factor for AD or possibly even pathogenic with a slowly progressive course of the disease regarding that the frequency of the mutation has been reported to be higher in LOAD patients than in the general population [32] and it is possible that some of the healthy controls in the previous studies that were found to carry the *PSEN2* p.Arg71Trp mutation might have developed AD later.

We also identified *GRN* p.Arg433Trp, *PSEN1* p.Glu318Gly, *MAPT* p.Gln230Arg, and *MAPT* p.Tyr441His variants that have been suggested to be benign in previous studies [19]. *PSEN1* p.Glu318Gly might be a risk factor for familial AD, but the results so far are controversial [33].

Furthermore, we identified three variants, which have previously been described as possible risk variants for AD or FTLD and one variant with possible risk-reducing effect (Table 1). The carrier of the *TREM2* p.Arg62His variant had also *APOE* genotype E3/E4. *TREM2* p.Arg62His has been reported as a possible risk factor for LOAD (OR 0.8-2.3) [34] and it has also been found in a few EOAD cases [12]. The interaction of the *APOE4* allele and *TREM2* has been suggested to accelerate the development of neurodegeneration [35]. The effects of the other identified possible risk variants have been less significant [36–39]. The frequencies of these polymorphisms in our cohort did not differ from the population frequencies reported in the ExAC database. In any case, our cohort was too small to make any conclusions regarding the involvement of these variants in influencing the risk for dementia.

The key role of the *C9orf72* repeat expansion has been well demonstrated in FTLD and its prevalence is high in Finland [5–7]. In this study we focused on to search for other pathogenic

mutations and risk factors for AD and FTLD in the cohort of EOD patients of still unknown genetic background after exclusion of the *C9orf72* repeat expansion. The strength of this study is that our cohort is clinically very well-characterized, and the patients have been thoroughly examined by experienced neurologists specialized in memory disorders, increasing the validity of our results.

In conclusion, we identified two pathogenic mutations in *PSEN1* and *MAPT* genes in a Finnish EOD cohort. Both identified cases had a very early onset of the disease and a positive family history of dementia or psychiatric diseases. Even though autosomal dominant mutations are rare causes of dementia, our study suggests that it is worthwhile to screen for them in EOD patients, who show an onset age under 55 years and a positive family history.

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Conflict of Interest/Disclosure Statement

The authors have no conflict of interest to report.

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Table 1. Identified variants in the genes associated with the risk of EOD.

Gene	**chr**	**Reference sequence**	**exon**	**Coding**	**Protein change**	**rs code**	**Number of carriers**	**Phenotype**	**Allele frequency in ExAC database** [40] **European Finnish**	**Allelle frequency in SiSu database** [41]	**Allele frequency in this dataset**
GRN	chr17	NM_002087	exon11	c.C1297T	p.Arg433Trp	rs63750412	4	AD n=2 FTLD n=2 FTLD+MND n=1	0.0366	0.0380747	0.05128
PSEN1	chr14	NM_000021	exon9	c.A953G	p.Glu318Gly	rs17125721	5	AD n=2 FTLD n=2 FTLD+MND n=1	0.0358	0.0331107	0.06410
MAPT	chr17	NM_001123066 NM_016835	exon6	c.A689G	p.Gln230Arg	rs63750072	3	AD n=1 FTLD n=1 PSP n=1	0.03024	0.0266384	0.03846
MAPT	chr17	NM_001123066 NM_016835	exon8	c.T1321C	p.Tyr441His	rs2258689	22	AD n=17 FTLD n=3 FTLD+MND n=1	0.2895	0.27733	0.29487
PSEN2	chr1	NM_000447 NM_01248	exon5	c.C211T	p.Arg71Trp	rs140501902	1	AD n=1	0.0195	0.018678	0.012821
TREM2	chr6	NM_001271821 NM_018965	exon2	c. G185A	p.Arg62His	rs143332484	1	AD n=1	0.007893	0.00750611	0.012821
BIN1	chr2	NM_139351	exon12	c. A1073G	p.Lys358Arg	rs138047593	2	AD n=2	0.01604	0.0137882	0.02564

UBQLN2	chrX	NM_013444	exon1	c. T1502C	p.Ile501Thr	rs756917208	1	AD n=1	no data	0.00220775	0.012821
TMEM106B	chr7	NM_001134232	exon 4	c. G401A	p.Ser134Asn	rs147889591	3	AD n=2 FTLD+MND n=1	0.01482	0.015885	0.038462
TMEM106B	chr7	NM_001134232	exon5	c. C554G	p.Thr185Ser	rs3173615	19	AD n=15 FTLD n=4	0.3293	0.319523	0.245359
APP	chr21	NM_000484.3	splice site, intron	c. T663-7T	NA	rs183084252	1	AD n=1	0.01164	0.00947097	0.012821

ExAC=The Exome Aggregation Consortium, SiSu=The Sequencing Initiative Suomi, AD=Alzheimer's disease, FTLD=frontotemporal lobar degeneration, MND=motor neuron disease, PSP=progressive supranuclear paresis

Supplementary table 1. The genes included in the targeted Neurology panel of 258 genes

AARS	alanyl-tRNA synthetase
ABCD1	"ATP-binding cassette, sub-family D (ALD), member 1"
ADCK3	aarF domain containing kinase 3
AFG3L2	AFG3 ATPase family gene 3-like 2 (S. cerevisiae)
AHI1	Abelson helper integration site 1
ALS2	amyotrophic lateral sclerosis 2 (juvenile)
AMN	amnionless homolog (mouse)
ANG	"angiogenin, ribonuclease, RNase A family, 5"
APOE	apolipoprotein E
APP	amyloid beta (A4) precursor protein
AR	androgen receptor
ARL13B	ADP-ribosylation factor-like 13B
ARSA	arylsulfatase A
ARSB	arylsulfatase B
ARX	aristaless related homeobox
ASPA	aspartoacylase
ASPM	"asp (abnormal spindle) homolog, microcephaly associated (Drosophila)"
ATL1	atlastin GTPase 1
ATM	ataxia telangiectasia mutated
ATP1A3	"ATPase, Na+/K+ transporting, alpha 3 polypeptide"
ATP6AP2	"ATPase, H+ transporting, lysosomal accessory protein 2"
ATP7A	"ATPase, Cu++ transporting, alpha polypeptide"
ATP7B	"ATPase, Cu++ transporting, beta polypeptide"
ATP13A2	ATPase type 13A2

ATXN1	ataxin 1
ATXN2	ataxin 2
ATXN3	ataxin 3
ATXN7	ataxin 7
ATXN8OS	ATXN8 opposite strand (non-protein coding)
ATXN10	ataxin 10
BCS1L	BCS1-like (S. cerevisiae)
BIN1	bridging integrator 1
CACNA1A	"calcium channel, voltage-dependent, P/Q type, alpha 1A subunit"
CC2D2A	coiled-coil and C2 domain containing 2A
CCT5	"chaperonin containing TCP1, subunit 5 (epsilon)"
CDK5RAP2	CDK5 regulatory subunit associated protein 2
CDKL5	cyclin-dependent kinase-like 5
CENPJ	centromere protein J
CEP152	centrosomal protein 152kDa
CEP290	centrosomal protein 290kDa
CLCN1	"chloride channel, voltage-sensitive 1"
CLN3	"ceroid-lipofuscinosis, neuronal 3"
CLN5	"ceroid-lipofuscinosis, neuronal 5"
CLN6	"ceroid-lipofuscinosis, neuronal 6, late infantile, variant"
CLN8	"ceroid-lipofuscinosis, neuronal 8 (epilepsy, progressive with mental retardation)"
COX10	"COX10 homolog, cytochrome c oxidase assembly protein, heme A: farnesyltransferase (yeast)"
CTSD	cathepsin D
CYP7B1	"cytochrome P450, family 7, subfamily B, polypeptide 1"
DLD	dihydrolipoamide dehydrogenase

DNAJC5	"DnaJ (Hsp40) homolog, subfamily C, member 5"
DNM2	dynamin 2
DRG1	developmentally regulated GTP binding protein 1
DYNC1H1	"dynein, cytoplasmic 1, heavy chain 1"
EBP	emopamil binding protein (sterol isomerase)
EGR2	early growth response 2
ELN	elastin
EMX2	empty spiracles homeobox 2
EPM2A	"epilepsy, progressive myoclonus type 2A, Lafora disease (laforin)"
ERMAP	erythroblast membrane-associated protein (Scianna blood group)
ETHE1	ethylmalonic encephalopathy 1
FAH	fumarylacetoacetate hydrolase (fumarylacetoacetase)
FGD4	"FYVE, RhoGEF and PH domain containing 4"
FGF14	fibroblast growth factor 14
FGFR1	fibroblast growth factor receptor 1
FGFR2	fibroblast growth factor receptor 2
FGFR3	fibroblast growth factor receptor 3
FIG4	"FIG4 homolog, SAC1 lipid phosphatase domain containing (S. cerevisiae)"
FLG	filaggrin
FMN1	formin 1
FOXH1	forkhead box H1
FOXP2	forkhead box P2
FUS	fused in sarcoma
FXN	frataxin

FXYD6	FXYD domain containing ion transport regulator 6
GALC	galactosylceramidase
GALNS	galactosamine (N-acetyl)-6-sulfate sulfatase
GARS	glycyl-tRNA synthetase
GAST	gastrin
GBA	"glucosidase, beta, acid"
GDAP1	ganglioside induced differentiation associated protein 1
GDF6	growth differentiation factor 6
GFAP	glial fibrillary acidic protein
GJB1	"gap junction protein, beta 1, 32kDa"
GJC2	"gap junction protein, gamma 2, 47kDa"
GLA	"galactosidase, alpha"
GLB1	"galactosidase, beta 1"
GLI2	GLI family zinc finger 2
GNE	glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase
GNS	glucosamine (N-acetyl)-6-sulfatase
GPR56	G protein-coupled receptor 56
GSS	glutathione synthetase
GUSB	"glucuronidase, beta"
HESX1	HESX homeobox 1
HEXB	hexosaminidase B (beta polypeptide)
HGSNAT	heparan-alpha-glucosaminide N-acetyltransferase
HLA-B	"major histocompatibility complex, class I, B"
HPCA	hippocalcin
HPRT1	hypoxanthine phosphoribosyltransferase 1
HSPB1	heat shock 27kDa protein 1
HSPB8	heat shock 22kDa protein 8

HSPD1	heat shock 60kDa protein 1 (chaperonin)
HTRA2	HtrA serine peptidase 2
HTT	huntingtin
HYAL1	hyaluronoglucosaminidase 1
HYLS1	hydrolethalus syndrome 1
IDS	iduronate 2-sulfatase
IDUA	"iduronidase, alpha-L-"
IFRD1	interferon-related developmental regulator 1
IKBKAP	"inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein"
IKBKG	"inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma"
INPP5E	"inositol polyphosphate-5-phosphatase, 72 kDa"
ITPR1	"inositol 1,4,5-trisphosphate receptor, type 1"
KCNC3	"potassium voltage-gated channel, Shaw-related subfamily, member 3"
KIAA0196	KIAA0196
KIF1B	kinesin family member 1B
KIF5A	kinesin family member 5A
KIF7	kinesin family member 7
LITAF	lipopolysaccharide-induced TNF factor
LMNA	lamin A/C
LMNB1	lamin B1
LRRK2	leucine-rich repeat kinase 2
LRSAM1	leucine rich repeat and sterile alpha motif containing 1
MCPH1	microcephalin 1
MED25	mediator complex subunit 25
MFN2	mitofusin 2

MFSD8	major facilitator superfamily domain containing 8
MPZ	myelin protein zero
MSX2	msh homeobox 2
MTM1	myotubularin 1
MTMR2	myotubularin related protein 2
MYH2	"myosin, heavy chain 2, skeletal muscle, adult"
NAGA	"N-acetylgalactosaminidase, alpha-"
NAGLU	"N-acetylglucosaminidase, alpha"
NAT6	N-acetyltransferase 6 (GCN5-related)
NBN	nibrin
NDE1	nudE nuclear distribution E homolog 1 (A. nidulans)
NDRG1	N-myc downstream regulated 1
NDUFA1	"NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa"
NDUFAF2	"NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 2"
NDUFS1	"NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase)"
NDUFS4	"NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa (NADH-coenzyme Q reductase)"
NDUFS7	"NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme Q reductase)"
NDUFS8	"NADH dehydrogenase (ubiquinone) Fe-S protein 8, 23kDa (NADH-coenzyme Q reductase)"
NDUFV1	"NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa"
NEFL	"neurofilament, light polypeptide"
NF1	neurofibromin 1

NF2	neurofibromin 2 (merlin)
NHLRC1	NHL repeat containing 1
NIPA1	non imprinted in Prader-Willi/Angelman syndrome 1
NLGN3	neuroligin 3
NLGN4X	"neuroligin 4, X-linked"
NODAL	nodal homolog (mouse)
NPC1	"Niemann-Pick disease, type C1"
NPC2	"Niemann-Pick disease, type C2"
NPHP1	nephronophthisis 1 (juvenile)
NR4A2	"nuclear receptor subfamily 4, group A, member 2"
NSD1	nuclear receptor binding SET domain protein 1
OFD1	oral-facial-digital syndrome 1
OPTN	optineurin
PARK2	"parkinson protein 2, E3 ubiquitin protein ligase (parkin)"
PARK7	parkinson protein 7
PDHA1	pyruvate dehydrogenase (lipoamide) alpha 1
PDYN	prodynorphin
PEX7	peroxisomal biogenesis factor 7
PHYH	phytanoyl-CoA 2-hydroxylase
PINK1	PTEN induced putative kinase 1
PMEL	premelanosome protein
PMPCA	peptidase (mitochondrial processing) alpha
PNPLA6	patatin-like phospholipase domain containing 6
POLG	"polymerase (DNA directed), gamma"
PPP2R2B	"protein phosphatase 2, regulatory subunit B, beta"
PPT1	palmitoyl-protein thioesterase 1
PQBP1	polyglutamine binding protein 1

PRKCG	"protein kinase C, gamma"
PRKRA	"protein kinase, interferon-inducible double stranded RNA dependent activator"
PRNP	prion protein
PRODH	proline dehydrogenase (oxidase) 1
PRODH2	proline dehydrogenase (oxidase) 2
PRPS1	phosphoribosyl pyrophosphate synthetase 1
PRX	periaxin
PSAP	prosaposin
PSEN1	presenilin 1
PSEN2	presenilin 2 (Alzheimer disease 4)
PTCH1	patched 1
RAB7A	"RAB7A, member RAS oncogene family"
RAX	retina and anterior neural fold homeobox
REEP1	receptor accessory protein 1
RELN	reelin
RPGRIP1L	RPGRIP1-like
RPS6KA3	"ribosomal protein S6 kinase, 90kDa, polypeptide 3"
SBF2	SET binding factor 2
SCO1	SCO cytochrome oxidase deficient homolog 1 (yeast)
SCO2	SCO cytochrome oxidase deficient homolog 2 (yeast)
SDHA	"succinate dehydrogenase complex, subunit A, flavoprotein (Fp)"
9-Sep	septin 9
SETX	senataxin
SGCE	"sarcoglycan, epsilon"
SGSH	N-sulfoglucosamine sulfohydrolase
SH3TC2	SH3 domain and tetratricopeptide repeats 2

SHH	sonic hedgehog
SIX3	SIX homeobox 3
SLC2A1	"solute carrier family 2 (facilitated glucose transporter), member 1"
SLC6A4	"solute carrier family 6 (neurotransmitter transporter, serotonin), member 4"
SLC12A6	"solute carrier family 12 (potassium/chloride transporters), member 6"
SLC33A1	"solute carrier family 33 (acetyl-CoA transporter), member 1"
SLITRK1	"SLIT and NTRK-like family, member 1"
SMAD1	SMAD family member 1
SMN1	"survival of motor neuron 1, telomeric"
SMN2	"survival of motor neuron 2, centromeric"
SNCA	"synuclein, alpha (non A4 component of amyloid precursor)"
SNCAIP	"synuclein, alpha interacting protein"
SNRPN	small nuclear ribonucleoprotein polypeptide N
SOD1	"superoxide dismutase 1, soluble"
SP110	SP110 nuclear body protein
SPAST	spastin
SPG7	spastic paraplegia 7 (pure and complicated autosomal recessive)
SPG11	spastic paraplegia 11 (autosomal recessive)
SPG20	spastic paraplegia 20 (Troyer syndrome)
SPG21	"spastic paraplegia 21 (autosomal recessive, Mast syndrome)"
SPRED1	"sprouty-related, EVH1 domain containing 1"
SPTBN2	"spectrin, beta, non-erythrocytic 2"
STIL	SCL/TAL1 interrupting locus
STXBP1	syntaxin binding protein 1
SURF1	surfeit 1

SYNE1	"spectrin repeat containing, nuclear envelope 1"
TAAR6	trace amine associated receptor 6
TARDBP	TAR DNA binding protein
TBP	TATA box binding protein
TCTN1	tectonic family member 1
TCTN2	tectonic family member 2
TDP1	tyrosyl-DNA phosphodiesterase 1
TGFB1	"transforming growth factor, beta 1"
TGIF1	TGFB-induced factor homeobox 1
THAP1	"THAP domain containing, apoptosis associated protein 1"
TIMM8A	translocase of inner mitochondrial membrane 8 homolog A (yeast)
TMEM67	transmembrane protein 67
TMEM216	transmembrane protein 216
TOR1A	"torsin family 1, member A (torsin A)"
TPP1	tripeptidyl peptidase I
TRPV4	"transient receptor potential cation channel, subfamily V, member 4"
TSC1	tuberous sclerosis 1
TSC2	tuberous sclerosis 2
TTBK2	tau tubulin kinase 2
TTPA	tocopherol (alpha) transfer protein
TUBA1A	"tubulin, alpha 1a"
TWIST1	twist homolog 1 (Drosophila)
UBE3A	ubiquitin protein ligase E3A
UCHL1	ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)
VANGL1	"vang-like 1 (van gogh, Drosophila)"
VAPB	VAMP (vesicle-associated membrane protein)-associated protein B and C

VCP	valosin containing protein
WDR62	WD repeat domain 62
ZFYVE26	"zinc finger, FYVE domain containing 26"
ZFYVE27	"zinc finger, FYVE domain containing 27"
ZIC2	Zic family member 2

Supplementary table 2. The additional genes included in the analyse

Chromosome	**Start position**
APP, chr21	27252861-27543138
PSEN1, chr14	73603525-73690399
PSEN2, chr1	227058273-227083804
MAPT, chr17	762281-895830
GRN, chr17	42422491-42430470
VCP, chr9	35057373-35071974
CHMP2B, chr3	87276413-87304698
FUS, chr16	31191431-31194671
TARDBP, chr1	11072679-11085549
TREM2, chr6	41126246-41130922
TMEM106B, chr7	12250848-12276890
SNCA, chr4	90743397-90758348
PARK2, chr6	161768590-163148834
PARK7, chr1	8021714-8045342
LRRK2, chr12	40689229-40763086
PINK1, chr1	20972001-20978004
CSF1R, chr5	149456467-149466170
PRNP, chr20	4679867-4680628
UBQLN2, chrX	56590060-56592380
Profilin1, chr17	4848947-4851825
SOD1, chr21	33031935-33041243
UBQLN1, chr9	86274878-86323168