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REVIEW

Genetics and Underlying Pathology of Dementia

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Abstract As the population steadily ages, dementia, in all its forms, remains a great societal challenge. Yet, our knowledge of their etiology remains rather limited. To this end, genetic studies can give us insight into the underlying mechanisms that lead to the development of dementia, potentially facilitating treatments in the future. In this review we cover the most recent genetic risk factors associated with the onset of the four most common dementia types today, including Alzheimer's disease (AD), Vascular Dementia (VaD), Frontotemporal Lobar Degeneration (FTLD) and Lewy Body Dementia (LBD). Moreover, we discuss the overlap in major underlying pathologies of dementia derived from their genetic associations. While all four dementia types appear to involve genes associated with tau-pathology and neuroinflammation only LBD, AD and VaD appear to involve amyloid genes while LBD and FTLD share alpha synuclein genes. Together these findings suggest that some of the dementias may exist along a spectrum and demonstrates the necessity to conduct large-scale studies pinpointing the etiology of the dementias and potential gene and environment interactions that may influence their development.

Keywords Genetics · Dementia · Alzheimer's disease · Lewy body dementia · Vascular dementia · Frontotemporal lobar degeneration

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Introduction

Worldwide the prevalence for dementia is still increasing; age-standardized prevalence for those aged >60 years varies around 5–7 % in most world regions, and the prevalence doubles about every 5 years. It is estimated that 35.6 million people were living with dementia worldwide in 2010, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (Prince et al. 2013). Although there seems to be some indication that the incidence of dementia may be decreasing in certain populations (Qiu et al. 2013), we are facing a large societal challenge.

It is known that dementia is caused by an interplay between genes, lifestyle and environmental factors (van der Flier and Scheltens 2005). Recent advances in genetic research have unveiled many potential genetic risk factors for all types of dementia. In this review we will focus on the heritability and genetic risk factors associated with the four most common types of dementia: Alzheimer's disease (AD), Vascular Dementia (VaD), Frontotemporal Lobar Degeneration (FTLD), Lewy Body dementia (LBD). Among these four types, AD is the most prevalent (34 % before age 65, and 54 % after age 65), see Table 1 for more detailed prevalence number and heritability estimates per dementia subtype (van der Flier and Scheltens 2005; Dementia Report United Kingdom 2007; Prince et al. 2013).

Gender differences in dementia prevalence clearly exist, while men suffer more from FTLD (before the age of 55), VaD (in between ages of 45 and 75), and LBD (across the age spectrum), women more often suffer from AD (Dementia Report United Kingdom 2007; Savica et al. 2013). Until recently, there was also a discrepancy in prevalence rates between developed and less developed countries, where particularly in South-East Asia VaD used to be the most prevalent dementia subtype. However due to increasing longevity and improved physical health, the prevalence of AD, with typically a later age of onset than VaD, increased in line

Table 1 Prevalence (among patients with dementia) and heritability estimates per dementia type

	Prevalence	Heritability
Alzheimer's disease	34–54 %	33 %
Vascular dementia	18–32 %	<1 %
Frontotemporal lobar degeneration	10–20 %	50 %
Lewy body dementia	4–7 %	40 %

with the aging population. Better physical health reduces cerebrovascular disease and hence the numbers with VaD. These changes also tend to shift the sex ratio towards a preponderance of female cases (Dementia Report United Kingdom 2007).

The heritability rates of the different dementia subtypes ranges from 40 to 80 % with early-onset (e.g. before the age of 65) dementia having a bigger genetic component than late-onset dementia (van der Flier and Scheltens 2005). Nevertheless, for all subtypes several genetic risk factors have already been identified and those will be covered in the next paragraphs.

Alzheimer's Disease

AD is the most common neurodegenerative disorder and it is clinically defined by a slowly progressing loss of cognitive functions, primarily memory impairment. Neuropathologically the disease is characterized by the aggregation and deposition of beta amyloid (Aβ) peptide in the form of neuritic plaques and hypophosphorylated tau protein in the form of intracellular neurofibrillary tangles.

Particularly the early-onset form of AD (EOAD) is thought to be highly heritable and to run in families, whereas the late-onset variant (LOAD) takes on a more sporadic form. However, lately several studies have been able to find many genetic risk factors for LOAD as well.

For EOAD three major genetic loci have been identified: *APP* (amyloid precursor protein) on chromosome 21q, *PSEN1* (presenilin 1) on chromosome 14q, and *PSEN2* (presenilin 2) on chromosome 1q. Within these three genes over 200 mutations have been found (see the AD&FTD mutation database: http://molgen.ua.ac.be-admutations/).

These discoveries have led to the so called amyloid hypothesis, which postulates that the abnormal production of Aβ is the initial step in triggering the pathophysiological cascade that eventually leads to AD (Glenner and Wong 1984) and that other neuropathological hallmarks of AD, such as hyperphosphorylated tau and neurofibriliary tangles, vascular damage and inflammation are consequences rather than separate causes of the disease process. Clinically and neuropathologically EOAD and LOAD are much alike (Rosenthal and Kamboh 2014). Although LOAD is much more common than EOAD; it has been estimated that 99 % of all AD cases are LOAD cases (Karch et al. 2014).

Many candidate gene studies on LOAD focused on genes that code for potential proteins that play a role in Aβ production. One of the best examples of that is the gene coding for apolipoprotein E (*APOE*), on chromosome 19q13, which was actually already discovered in linkage studies (Pericak-Vance et al. 1991). The *APOE* gene has three alleles; the ε2, ε3, and ε4 alleles. Of these the ε4 allele is associated with a 4-fold greater risk for LOAD than the ε3 allele (Genin et al. 2011). The less common ε2 allele appears to have some sort of protective effect and is associated with longevity (Olesen et al. 1997; Deelen et al. 2014). Some studies suggest that the *APOE* e4 allele does not explain all of the genetic risk for AD of this chromosomal region. Two other possible candidates that are in close proximity to *APOE* have therefore been suggested to also increase the risk for AD; *TOMM40* (encoding translocase of outer mitochondrial membrane 40 homolog;(Roses et al. 2010; Takei et al. 2009)) and *EXOC3L2* (exocyst complex component 3-like-2;(Seshadri et al. 2010)). These suggest that other biological mechanisms may be at play including mitochondrial dysfunction (Ferencz et al. 2012).

Of the hundreds of possible candidate genes that were identified based on the amyloid hypothesis only a few have consistently been shown to have a modest association with AD (odds ratios between 1.15 and 1.5 and p-value between 0.0001 and 0.01) (Karch and Goate 2014). These candidate genes include *ACE* (angiotensin-converting enzyme; (Kehoe et al. 1999)), *ADAM10* (disintegrin and metalloproteinase domain-containing protein 10; (Kim et al. 2009a)), *CHRNB2* (cholinergic receptor, nicotinic, beta2;(Cook et al. 2004)), *DAPK1* (death-associated protein kinase 1;(Y. Li et al. 2006)), *IL8* (interleukin 8;(Li et al. 2009)), *MTHFR* (methylenetetrahydropholate reductase;(Chapman et al. 1998)) and *SORL1* (sortilin-related receptor;(Rogaeva et al. 2007)).

More recently, several genome-wide studies have been conducted to find new genetic risks for AD. From all amyloid-related candidate genes only *APOE* reached significance on a genome-wide level (with p-values down to 1×10^{-160}; (Harold et al. 2009)). See Table 2 for the top genetic markers for AD that have all been identified in large genome-wide association studies (Lambert et al. 2009, 2013; Hollingworth et al. 2011; Naj et al. 2011; Seshadri et al. 2010; Harold et al. 2009). Pathway analysis has shown that many of these top genes play a role in the following possible pathophysiological mechanisms: cholesterol metabolism, immune response and endocytosis.

Cholesterol Metabolism

There is a strong association between cholesterol and AD risk. For instance, high levels of cholesterol appear to accelerate the

Table 2 Main genetic risk factors for Alzheimer's disease

Chr	Gene	Polymorphism	Function	Major/minor allele	MAF	Ethnicity	OR (95 % CI)	*cp*-value	Reference
1	CR1	rs3818361	Intronic	C/A	0.269	Caucasian	1.174 (1.14–1.21)	4.72E-21	(Lambert et al. 2009)
2	BIN1	rs744373	5′ upstream	T/G	0.371	All	1.166 (1.13–1.20)	1.59E-26	(Seshadri et al. 2010)
2	INPP5D	rs35349669	Intronic	C/T	0.488	Caucasian	1.08 (1.05–1.11)	3.2E-8	(Lambert et al. 2013)
5	MEF2C	rs190982	Intronic	A/G	4.408	Caucasian	0.93 (0.90–0.95)	3.2E-8	(Lambert et al. 2013)
6	CD2AP	rs9349407	Intronic	G/C	0.191	All	1.117 (1.08–1.16)	2.75E-09	(Hollingworth et al. 2011; Naj et al. 2011)
7	NME8	rs2718058	Intergenic	A/G	0.373	Caucasian	0.93 (0.90–0.95)	4.8E-9	(Lambert et al. 2013)
7	ZCWPW1	rs1476679	Intronic	T/C	0.287	Caucasian	0.91 (0.89–0.94)	5.6 E-10	(Lambert et al. 2013)
8	CLU	rs11136000	Intronic	C/T	0.385	Caucasian	0.879 (0.86–0.90)	3.37E-23	(Harold et al. 2009)
11	CELF1	rs10838725	Intronic	T/C	0.316	Caucasian	1.08 (1.05–1.11)	1.1E-8	(Lambert et al. 2013)
11	MS4A4E	rs670139	Intergenic	C/T	0.400	All	1.079 (1.05–1.11)	9.51E-10	(Hollingworth et al. 2011; Naj et al. 2011)
11	MS4A6A	rs610932	3′utr	C/T	0.421	All	0.904 (0.88–0.93)	1.81E-11	(Hollingworth et al. 2011; Naj et al. 2011)
11	PICALM	rs3851179	5′ upstream	G/T	0.329	Caucasian	0.879 (0.86–0.9)	2.85E-20	(Harold et al. 2009)
14	FERMT2	rs17125944	Intronic	T/C	0.092	Caucasian	1.14 (1.09–1.19)	7.9E-9	(Lambert et al. 2013)
19	ABCA7	rs3764650	Intronic	T/G	0.199	All	1.229 (1.18–1.28)	8.17E-22	(Hollingworth et al. 2011; Naj et al. 2011)
19	APOE	rs429358	Coding	T/C	0.149	All	3.685 (3.30–4.12)	<1E-50	(Pericak-Vance et al. 1991)
19	CD33	rs3865444	5′upstream	G/A	0.238	All	0.893 (0.86–0.93)	2.04E-10	(Hollingworth et al. 2011; Naj et al. 2011)
20	CASS4	rs7274581	Intronic	T/C	0.083	Caucasian	0.88 (0.84–0.92)	2.5E-8	(Lambert et al. 2013)

formation of beta-amyloid plaques and epidemiological studies showed increased risk of AD in older individuals with dyslipidaemia (Reitz 2013).

APOE plays a central role in cholesterol metabolism; APOE protein is involved in lipid transport and is highly expressed in the central nervous system and the liver. It binds to Aβ and influences the clearance of soluble Aβ and the Aβ aggregation (Leduc et al. 2010).

The *ABCA7* (ATP-binding cassette sub-family A member 7) gene is part of the ATP binding transport family, which includes several hundreds of membrane transport proteins that utilize the energy of ATP to transport a specific group of ligands across the cell membrane. As such *ABCA7* is responsible for lipid transport. ABCA7 also participates in macrophage uptake of Aβ, and removal of ABCA7 results in increased levels of insoluble Aβ and it has been shown to mediate APP processing (Rosenthal and Kamboh 2014).

The gene *CLU* encodes for clusterin, which is also mainly involved in clearance and aggregation of Aβ (DeMattos et al. 2002, 2004). Clusterin has also been suggested to play a role regulation of brain cholesterol and lipid metabolism, and the inhibition of neuronal apoptosis/potentiation of neuroprotection (Nuutinen et al. 2009) and oxidative stress (Trougakos and Gonos 2006). Clusterin also plays a key role in protecting the immune system from the detrimental effect of Aβ aggregation, which is an activator of the complement system (Hardy et al. 2011).

Immune System

Inflammatory involvement in AD has already long been hypothesized to be one of the underlying pathophysiological mechanisms of the disease (Ridolfi et al. 2013). Inflammatory processes may be neurotoxic (Bates et al. 2009) and markers of inflammation have been shown to be associated with amyloid plaques (McGeer and McGeer 2001) Moreover, it was found that patients on NSAIDS have a lower risk to develop AD (Ridolfi et al. 2013).

The *CR1* gene codes for the complement receptor 1 (CR1) is the main receptor of the complement C3b protein and is a regulator of complement activation (RCA). As such it has numerous functions in the immune system (Khera and Das 2009). Activation of this receptor can protect against Aβ-induced neurotoxicity and may reduce the accumulation or promote the clearance of amyloid and degenerating neurons (Rogers et al. 2006).

CD33 (Siglec-3) belongs to a class of immune cell surface receptors called sialic acid-binding immunoglobulin-like lectins. CD33 triggers immune cell–cell interactions through endocytosis. It has been shown that *CD33* expression is increased in AD brains as is the number of *CD33*-positive microglia (Karch et al. 2012).

Endocytosis

Endocytosis is the process by which cells absorb molecules from outside the cell that are otherwise too large for them. Endocytosis regulates many processes, such as nutrient uptake, cell adhesion and migration, growth, neurotransmission and drug delivery. The following genes are thought to play a role in endocytosis and AD.

PICALM (Phosphatidylinositol binding clathrin assembly protein) plays a role in clathrin-mediated endocytosis, synaptic transmission, and the removal of apoptotic cells (Harel et al. 2008) . In the brain the PICALM protein is predominantly expressed in endothelial cells where it could play a role in Aβ transport into the bloodstream (Baig et al. 2010). *PICALM* may thus be involved in Aβ clearance, which is supported by the finding that individuals carrying the risk allele of the *PICALM* top SNP show lower levels of Aβ in cerebrospinal fluid (Schjeide et al. 2011).

BIN1 (Bridging integrator 1) encodes several isoforms of an adaptor protein involved in receptor mediated endocytosis (Pant et al. 2009). Additionally, it could indirectly also have an effect on Aβ production and/or the clearance of Aβ from the brain.

The neuronal sorting receptor *SORL1* (sortilin receptor 1) is involved in the trafficking of APP (Rogaeva et al. 2007) and has also been suggested to bind with lipoproteins and mediate endocytotic processes.

Taken together these confirmed AD risk genes explain about 7–8 % of the genetic variance in AD, and it has been estimated that 5.8 % can be attributed solely to the *APOE* gene. Whereas, in total it is estimated that about 33 % of the phenotypic variance in AD can be explained by genetics (Ridge et al. 2013). This suggests that besides the *APOE* gene, all other genetic risk factors identified so far have a very small effect and more importantly that there are still many risk genes to be discovered.

Vascular Dementia

Subcortical vascular dementia or cerebral small vessel disease is a common cause of disability in the elderly. A clinical diagnosis of vascular dementia (VaD) is based on a clinical representation of dementia, a history of ischemic or hemorrhagic vascular disease or hypoperfusive ischemic cerebral infarcts and a close temporal relation between the cerebrovascular disease and onset of dementia symptoms (Roman et al. 1993). Compared to AD, VaD is more often characterized by attention and concentration deficits, bradyphrenia and word finding problems. However the symptoms largely rely on the location of cerebrovascular disease and hence it is a very heterogeneous disease (Pohjasvaara et al. 2003).

A genetic basis for VaD is difficult to investigate, because of the variety in clinical presentations of the disorder. Most

patients with VaD have the sporadic form, which has a very low heritability (<1 %) (Bergem et al. 1997; Gatz et al. 2010). However there are two highly heritable forms of VaD; cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) and familial cerebral amyloid angiopathy (FCAA).

CADASIL is the most prominent inherited form of vascular dementia, which is an autosomal dominant disease that is rare with a prevalence of only 2 in 100,000. The main clinical features include migraine with aura, stroke, mood disturbances, and cognitive decline, with a mid-life (30s–60s) adult onset (Federico et al. 2005). Genetic testing is the gold standard for the diagnosis. CADASIL is caused mostly by missense mutations in the *NOTCH3* (Neurogenic locus notch homolog protein 3) gene (Federico et al. 2005). NOTCH3 is a receptor located on the wall of vascular smooth vessel cells, as such Disruption of Notch3 functioning can lead to the self-destruction (apoptosis) of these cells. Damage to vascular smooth muscle cells is thought to cause recurrent strokes and VaD (Wang et al. 2008; Schmidt et al. 2012).

FCAA is also an autosomal dominant disease that is characterized by recurrent stroke, movement impairments, and VaD with memory loss and personality changes. As for CADASIL it is a rare disorder and so far exact prevalence rates are unknown. Like other cerebrovascular disorders, FCAA usually occurs in mid-life (between ages 55 and 65) (Maia et al. 2007). Mutations in the *APP* (amyloid precursor protein), *CST3* (Cystatin 3), or *ITM2B* (Integral membrane protein 2B) genes lead to the aggregation of proteins, which form amyloid plaques in the vessel walls. The amyloid plaques damage brain cells, eventually causing cell death and impairing various parts of the brain (Federico et al. 2012).

Several candidate genes have already been identified for sporadic VaD and most of the genes play a role in lipid metabolism (*MMP1*;*MMP3*;*MMP9*;*APOE*;*PON1*;*PON2*;*VLDLR*;*SREBF2*), angiotensin (*AGT*; *ACE*) and inflammation (*IL1A*; *IL1B*; *IL6*; *TNF*;*TGFB1*) (for extensive review see (Lee and Kim 2013)). However most of these genetic findings have not been replicated and/or show only weak associations ($0.01 < p < 0.05$).

So far the strongest evidence comes from studies combining multiple genetic loci, suggesting that there is some epistasis going on. For instance, a combined genotype of the two genes *TNF β1* (tumor necrose factor receptor b1) and *AGT* (angiotensin) showed a stronger association with VaD than their individual genotypes (Kim et al. 2009b). Furthermore a strong synergistic epistasis was also suggested between the genes *FAM134B* (family with sequence similiarity 134, variant B) and *TNFRSF19* (tumor necrosis factor receptor, super family, member 19) (Kong et al. 2011).

Recently two genome-wide association studies (GWAS) on sporadic VaD have been undertaken (Schrijvers et al. 2012; Kim et al. 2013). The study with 84 patients and 200 controls from Korea did not result in any genome-wide significant hit (Kim et al. 2013), but there was a suggestive hit, that could be replicated using gene-wide analysis in the *SYK* (spleen tyrosine kinase) gene. Whereas the other study among 67 patients and 5700 controls did identify a novel locus on chromosome X near the *AR* (androgen receptor) gene. Both these findings do not seem to be related to any of the candidate pathways, such as lipid metabolism or inflammation.

Frontotemporal Lobar Degeneration

Frontotamporal lobar degeneration (FTLD) is an anatomopathological descriptive term referring to a cluster of disorders that are characterized by the atrophy of the frontal and anterior temporal lobes. Apart from the overlap in atrophy, FTLD disorders are a clinically, genetically and pathologically heterogeneous group of disorders.

FTLD is the second most common form of early-onset dementia, after AD. In approximately 75 % of the patients the onset of FTLD occurs before the age of 65 years. In the age group between 45 and 65 years, the prevalence of FTLD is estimated to be between 10 and 30 per 100,000 (*Dementia Report United Kingdom* 2007).

FTLD can manifest as two clinically distinct subtypes: a behavioral subtype and a language disturbances subtype (Karageorgiou and Miller 2014). The behavioral subtype of FTLD (bvFTLD) is characterized by severe changes in behavior and personality such as disinhibition, apathy, loss of empathy, stereotypic behavior and loss of social competence. Cognitively, executive functions are impaired, while during the early stages of the disease memory and visuospatial skills are well preserved. bvFTLD accounts for more than 50 % of the FTLD patients. The onset is typically before the age of 65, with an average onset of 58 years (Kirshner 2014).

The language subtype of FTLD is called primary progressive aphasia (PPA) and consists of a nonfluent/agrammatic variant and a semantic variant. Nonfluent/agrammatic PPA is characterized by effortful speech and grammatical errors, with relatively preserved language comprehension. While semantic PPA is characterized by impaired comprehension and conceptual knowledge with concomitant development of anomia, while speech production is spared. Each PPA subtype accounts for approximately 20–25 % of FTLD patients (Kirshner 2014).

Based on family studies it has been estimated that FTLD has a heritability of 30–50 %. Heritability varies across the different subtypes of FTLD (Rohrer et al. 2009).

In the following section we will discuss the most consistent genetic findings for FTLD. The number of mutations found in these genes and it's frequencies are described in Table 3. The majority of FTLD cases seems to be related to mutations in two genes; MAPT (the microtubule-associated protein tau;(van Swieten and Spillantini 2007)) and *PGRN*

Table 3 Main genetic risk factors FTLD

Chr	Gene	Chromosomal location	Mutation frequency	# of mutations
3	CHMP2B	3p11.2	<1 %	11
9	C9orf72	9p21.2	14–48 %	1
9	VCP	9p13.3	<1 %	20
17	GRN	17q21.32	3–26 %	148
17	MAPT	17q21.32	0–50 %	72

(progranuline;(Baker et al. 2006)). Other genes that frequently have been shown to play a role in FTLD are *CHMP2B* (charged multivesicular body protein 2B,(Skibinski et al. 2005)), *VCP* (valosin containing protein;(Weihl et al. 2008)) and *C9orf72* (Gijselinck et al. 2012) (See Table 4.).

The neuropathologic subtype that is characterized by tau-positive pathologic inclusion is caused by mutations in the *MAPT* gene. Over 70 variants of *MAPT* have been identified that lead to deletions, missense, silent and splice cite mutations (http://www.molgen.ua.ac.be-FTDmutations). These mutations lead to tau pathology due to loss of function of the microtubules or from toxic gain of function (e.g. increased aggregation properties). Tau inclusions can usually be found in neurons and glial cells of the frontal and temporal cortex and the hippocampus. The mean onset of FTLD in patients with *MAPT* mutations is around 55 years of age. Clinically most *MAPT* mutations lead to bvFTLD (Ferrari et al. 2011). Besides mutations, there are also some functional haplotypes of the *MAPT* gene, but these are mostly related to other diseases than FTLD, including Parkinson's Disease (PD), AD and amyotrophic lateral sclerosis (Ferrari et al. 2011).

The other common neuropathologic subtype of FTLD is characterized by TAR DNA-binding positive of 43 kDa (TDP-43) inclusions and has been associated with mutations in the *PGRN* gene as well as rarer mutations in other genes such as *TARDBP* (a gene coding for TDP-43) (Sieben et al. 2012). PGRN is involved in several biological processes such as cell cycle progression, cell growth regulation and inflammation. Currently over 140 variants of the *PGRN* gene have been reported in FTLD (http://www.molgen.ua.ac.be-FTDmutations). Clinically, individuals carrying *PGRN* mutations show predominantly apathy, language impairment and psychotic symptoms. The mean onset of the disease is about 60 years of age. Neuronal cell loss is usually apparent in the frontal, temporal and inferior parietal cortices of the dominant hemisphere. *PGRN* mutations are also frequently found in other neurodegenerative disorders, such as AD, PD and corticobasal syndrome (Le Ber 2013).

In FTLD with TDP-43-related pathology a genetic association has also been found with the gene *C9orf72* (chromosome 9 open reading frame 72). Clinically, most cases are bvFTLD. The mean onset of the disease is around 55 years of age and a higher number of repeat expansions is associated with earlier age of onset.

The *C9orf72* gene mainly plays a role in FTLD with motor neuron disease and FTLD with ALS (Devenney et al. 2014). The gene encodes for a protein with unknown function. Pathologically *C9orf72*-related FTLD has besides TDP-43pathology also neuronal cytoplasmic inclusions (NCI). These NCI are seen in the granular cells of the hippocampus and in patients with motor neuron disease (MND) also in the hypoglossal nuclei and motor neurons of the ventral horn of the spinal cord (van der Zee et al. 2013).

VCP (Valosin-containing protein) is involved in several cellular processes like cell cycle regulation, suppression of apoptosis, DNA damage response and protein degradation (Ferrari et al. 2011). Mutations in the *VCP* gene cause inclusion body myopathy (IBM) associated with Paget's disease of the bone (PGD) and FTLD (Weihl et al. 2008). This combination, IBMPFD, is an autosomal dominant disease. IBMFPD usually presents it-self clinically first by development of disabling weakness with a mean onset of 45 years of age, second patients have osteolytic lesions and third language and behavioral deficits become apparent, which usually happens around age 55. Neuropathologically, IBMPFD is characterized by tau-negative and ubiquitin positive inclusions.

CHMP2B (Charged multivesicular body protein 2b) plays a role in endosomal trafficking, cellular signaling and autophagy. Genetic variability in *CHMP2B* is found in a small proportion of FTLD cases. Clinically, patients usually present with bvFTLD, starting with early personality changes, aphasia characterized by a reduction in spontaneous speech, leading eventually to mutism. The average age of onset is around 58 years of age (Momeni et al. 2006). Neuropathologically, enlarged vacuoles in cortical neurons in the frontal temporal parietal and occipital cortices have been found (Urwin et al. 2010).

So far two GWA on FTLD have been published (Van Deerlin et al. 2010; Ferrari et al. 2014). In the first study by van Deerlin and colleagues, patients with TDP-43 neuropathology were investigated and a genome-wide significant hit was found for a locus near the gene *TMEM106B* (Transmembrane protein 106B) on chromosome 7p21.

The second GWA study reported a genome-wide significant hit on chromosome 6 near *HLA* (human leucocyte antigen) locus for three SNP's (rs9268877, rs9268856, rs1980493). The HLA genes play a role in the immune system. In total there are about 200 HLA genes that are all situated near each other on chromosome 6. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders such as viruses and bacteria. For the behavioral variant of FTLD they also found a new locus on chromosome 11 near the *RAB38 (*Ras-related protein) and *CTSC* (Cathepsin) genes. This latter locus plays a

role in lysosomal biology and is as such involved in inflammatory processes. Interestingly, these GWAS study did not find evidence for any of the previously identified candidate genes, suggesting that FTLD is a heterogenic disease that has different genetic underpinnings among families.

Lewy Body Dementia

Lewy body dementia (LBD) is one of the most common forms of dementia with a prevalence rate of 4 % in the general population (6 % for men and 3 % for women) (*Dementia Report United Kingdom* 2007). LBD encompasses Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB) (McKeith et al. 1996; Hanson and Lippa 2009). It has been estimated that 25 to 50 % of patients with LBD have symptoms of PD. The symptoms of DLB include sleep problems, hallucinations (mostly visual), deficits in executive function, attention, memory domains and visuo-spatial ability (Kehagia et al. 2010), and are accompanied within the first year by Parkinsonian motor symptoms. In PDD, cognitive deficits and/or dementia are secondary to parkinsonism with motor symptoms present for a minimum of 1 year ("1 year rule" for clinical studies) (Mollenhauer et al. 2010). If the disease is in its full-blown stage then usually no differentiation is made between the two disease entities exist, neither clinically nor neuropathologically. LBD is associated with higher rate of mortality and is considered more costly to society than AD (Oesterhus et al. 2014; Bostrom et al. 2007; Hely et al. 2008), making it imperative to find the etiology of the disease. A recent twin study did however not show a strong support for a genetic contribution to LBD (C. S. Wang et al. 2009). Yet, others have demonstrated that LBD aggregates in families and may have an autosomal inheritance pattern (Nervi et al. 2011; Bogaerts et al. 2007). A few consistent genetic markers have been identified for LBD (Table 3), and these will be discussed in the next section.

Mutations in the synuclein family have been known to play a role in PD, and recently they have received attention in LBD as well (Meeus et al. 2012; Fuchs et al. 2007). A duplication in the a-synyclein gene (*SNCA*) was recently reported in a DLB patient, but these type of mutations are rare (Meeus et al. 2012). Although duplications may be rare, association studies have found SNPs within α-, β-, and γ-synuclein genes to be associated with increased risk of DLB (Nishioka et al. 2010; Bras et al. 2014). It is not surprising that these genes may play a significant role in LBD as synucleins are one of the major components of Lewy bodies, a hallmark of the disease (George 2002; Miklya et al. 2014). Yet, their role remains to be determined, as some *SNCA* SNPs are not associated with Lewy body pathology (Wider et al. 2012), and others are associated with Lewy body pathology, but in AD (Linnertz et al. 2014).

Mutations in *glucocerebrosidase* (*GBA*), such as N370S and L444P, on the other hand are more common in LBD. Pathogenic mutations have been observed in up to 7.6 % of DLB cases (Tsuang et al. 2012; Mata et al. 2008), and found to increase the risk of DLB (Tsuang et al. 2012). Associated with the presence of cortical Lewy bodies (Clark et al. 2009) the specificity to LBD is more pronounced with *GBA,* as mutations in this gene are not related to AD type pathology (Clark et al. 2009), nor are they observed frequently in AD (Tsuang et al. 2012). Lysosomal dysfunction has been highlighted as a potential hallmark of PD. As such, *GBA* may play a prominent role as it encodes the lysosomal enzyme glucocerebrosidase (Yang et al. 2014). In conjunction with recent findings of an association between *scavenger receptor class B member 2* (*SCARB2*) and DLB lysosomal dysfunction may play a vital role in the pathogenesis of LBD. Further studies will need to confirm this association (Bras et al. 2014).

Another prominent player in LBD is the *MAPT* H1 haplotype. Suggested to regulate tau-transcription the *MAPT* gene is one of the strongest predictors of dementia in PD (Williams-Gray et al. 2013; Seto-Salvia et al. 2011). The H1 haplotype is also associated with postural instability (Williams-Gray et al. 2013) a known risk factor for PDD (Moore and Barker 2014). None of the *MAPT* haplotypes have any influence in AD or DLB (Seto-Salvia et al. 2011), suggesting that the influence is specific to PDD. The *MAPT* gene has also been found to regulate α-synuclein in the brainstem (Colom-Cadena et al. 2013), middle frontal and inferior parital cortex (Wider et al. 2012), supporting a link between *MAPT* haplotypes and synucleinopathies.

The leucine rich repeat kinase 2 (*LRRK2*) gene plays an important role in the formation of Lewy bodies (Zhu et al. 2006), yet its role in LBD remains to be elucidated. Meeus and colleagues (Meeus et al. 2012) reported an *LRKK2* (R1441C) mutation in a patient with PDD while a large case–control study was not able to show a strong association between *LRKK2* and DLB (Bras et al. 2014). Further studies should consider potential interactions with *SNCA*, as *LRKK2* was found to interact with *SNCA* in relation to Lewy body pathology (Linnertz et al. 2014).

To date only one genome-wide linkage study has been performed among patients with familial LBD. A locus on chromosome 2 q35-q36 was identified, however none of the genes in this region could explain the relation with LDB (Bogaerts et al. 2007).

Some of the genes commonly associated with AD have been implicated in LBD. Novel presenelin mutations in

Table 4 Main genetic risk factors for Lewy body dementias

Chr	Gene	Chromosomal location	#mutations
1	GBA	1q21	7
4	SNCA	4q21	25
17	MAPT	17q21.1	36

PSEN1 A79 and *PSEN2* R71W were recently observed in DLB patients (Meeus et al. 2012). These mutations could potentially lead to α-synuclein accumulation as seen in mouse models for *PSEN1* (Winslow et al. 2014). Nevertheless, these mutations can result in different clinical presentations, suggesting that differential diagnosis between AD, PDD and DLB is not feasible based on these genes (Meeus et al. 2012). *APOE*, one of the primary genetic risk factors for AD has also been associated with LBD. In a recent large case–control study with up to 788 DLB cases, *APOE* was the strongest genetic risk factor for DLB followed by *SNCA* (Bras et al. 2014). However, a recent large meta-analysis has failed to find convincing support for an *APOE* influence in PDD (Wider et al. 2012).

Overall there seem to be several prominent players when it comes to the genetic influence in LBD. Yet, it becomes evident from reviewing the literature that larger studies are warranted, as the field remains lagging behind the AD/PD field.

Summary and Conclusions

Most dementia subtypes are complex heterogenic disorders that are not caused by one sole dominant genetic mutation, but are rather the result of the interplay between environment and several genes. Moreover, the most important risk factor for all types of dementia is increasing age; with the increase of 10 years, from 65 to 75 years of age, resulting in an increased risk of dementia that's beyond of what is conveyed by any of the described genetic risk alleles.

It should be noted that many patients do not have a clear clinical presentation, because frequently patients show some overlap between several subtypes of dementia and sometimes the differential diagnosis may be rather difficult and somewhat arbitrary as seen in LBD. The most common example of this is the so-called mixed type dementia, which is a combination of Alzheimer's disease and vascular dementia. Patients usually show typical AD neuropathology accompanied by a vascular component (Lathe et al. 2014; Magaki et al. 2014). Given that vascular risk factors, such as hypertension, dyslipidemia and diabetes are risk factors for both types of dementia, also suggests that there may be some common pathophysiology (Altman and Rutledge 2010).

Figure 1 shows the overlap in the major underlying pathology of the four dementia subtypes. Overlap in genetic risks is seen in FTLD and LBD, where genetic mutations in the *MAPT* gene both play a role. Indeed tau-pathology plays a role in both disorders and there may even be some overlap in α-synuclein involvement (Kara et al. 2014). Tau-pathology is a candidate in all of the described dementia subtypes, but it should however be noted that many different forms of tau exist and that it depends on the dementia subtype which form of tau is (for extensive review please see (Tang et al. 2014; Spillantini and Goedert 2013)).

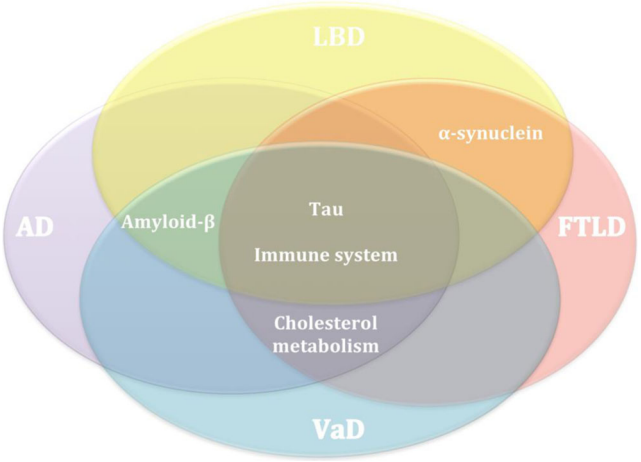

Fig. 1 Overlap in major underlying pathologies of dementia based on their genetic associations

Similarly, overlap between LBD and AD has also been suggested, as mutations in *APP*, *PSEN1* and *PSEN2* are found in both disorders. Moreover, comorbid LBD and AD is quite common (Magaki et al. 2014). It is suggested that there is some sort of spectrum between AD and PDD, with DLB in the middle of these two disorders, as both Aβ and α-synuclein play a role in DLB, while Aβ involvement in PDD is rare, as is α-synuclein in AD (Meeus et al. 2012).

As can be seen neuroinflammation is considered to play a role in all types of dementia. It is most likely not the main cause of neurodegeneration, but it could serve as a catalyst of other ongoing neurodegenerative processes (Jones et al. 2010; Ridolfi et al. 2013). Whereas cholesterol metabolism is thought to be mostly related to the onset of AD and VaD (Reitz et al. 2004), and much less to the other subtypes. Two recent studies even showed that cholesterol does not seem to play a role in onset of PDD and LBD (Gudala et al. 2013; Borroni et al. 2006).

Indeed a recent GWAS study suggests that there is some overlap in the neuropathological features of AD and related dementias (Beecham et al. 2014) The authors related AD loci with both core and comorbid neuropathological features of AD and found that core features such as neurofibrillary tangles and neuritic plaques were associated with *ABCA7, BIN1, cASS4, MEF2C* and *PICALM*, while comorbid neuropathological features such as lewy body disease and hippocampal sclerosis were associated with *SORL1* and *PTK2B* respectively. *APOE* was associated with both core and comorbid neuropathological features, including neurofibrillary tangles and neuritic plaques, lewy body disease, cerebral amyloid angiopathy (CAA), but not hippocampal sclerosis and vascular brain injury. As such, it seems that AD loci are associated not only with core neuropathological features of AD, but also comorbid neuropathological features.

In this review we focused on genetic mutations that can increase the risk for dementia, whereas it would also be of interest to examine genetic mutations that can protect an individual for the onset of dementia or that may interact beneficially with lifestyle factors. Recently, a GWA study among Icelandic people showed that a rare mutation in the *APP* gene decreases the risk for dementia and AD in particular (Jonsson et al. 2012). Also, a GWA study on longevity identified some new loci that may play a role in healthy aging (Deelen et al. 2014). These new protective genetic variations may be likely candidates to study the prevention of dementia.

Finally, because dementia is not caused by only genetics, more studies are needed that investigate epistasis and gene by environment interaction. So far some attempts have been made (Gusareva et al. 2014; Alam et al. 2014; Kong et al. 2011), but these studies require replication.

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References

Alam, R., Tripathi, M., Mansoori, N., Parveen, S., Luthra, K., Lakshmy, R., et al. (2014). Synergistic Epistasis of Paraoxonase 1 (rs662 and rs85460) and apolipoprotein E4 genes in pathogenesis of Alzheimer's disease and vascular dementia. *American Journal of Alzheimer's Disease and Other Dementias*. doi:10.1177/1533317514539541.

Altman, R., & Rutledge, J. C. (2010). The vascular contribution to Alzheimer's disease. *Clinical Science (London), 119*(10), 407–421. doi:10.1042/cs20100094.

Baig, S., Joseph, S. A., Tayler, H., Abraham, R., Owen, M. J., Williams, J., et al. (2010). Distribution and expression of picalm in Alzheimer disease. *Journal of Neuropathology and Experimental Neurology, 69*(10), 1071–1077. doi:10.1097/NEN.0b013e3181f52e01.

Baker, M., Mackenzie, I. R., Pickering-Brown, S. M., Gass, J., Rademakers, R., Lindholm, C., et al. (2006). Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature, 442*(7105), 916–919. doi:10.1038/nature05016.

Bates, K. A., Verdile, G., Li, Q. X., Ames, D., Hudson, P., Masters, C. L., et al. (2009). Clearance mechanisms of Alzheimer's amyloid-beta peptide: implications for therapeutic design and diagnostic tests. *Molecular Psychiatry, 14*(5), 469–486. doi:10.1038/mp.2008.96.

Beecham, G. W., Hamilton, K., Naj, A. C., Martin, E. R., Huentelman, M., Myers, A. J., et al. (2014). Genome-wide association meta-analysis of neuropathologic features of Alzheimer's disease and related dementias. *PLoS Genetics, 10*(9), e1004606. doi:10.1371/journal.pgen.1004606.

Bergem, A. L., Engedal, K., & Kringlen, E. (1997). The role of heredity in late-onset Alzheimer disease and vascular dementia. A twin study. *Archives of General Psychiatry, 54*(3), 264–270.

Bogaerts, V., Engelborghs, S., Kumar-Singh, S., Goossens, D., Pickut, B., van der Zee, J., et al. (2007). A novel locus for dementia with Lewy bodies: a clinically and genetically heterogeneous disorder. *Brain, 130*(Pt 9), 2277–2291. doi:10.1093/brain/awm167.

Borroni, B., Grassi, M., Costanzi, C., Archetti, S., Caimi, L., & Padovani, A. (2006). APOE genotype and cholesterol levels in lewy body dementia and Alzheimer disease: investigating genotype-phenotype effect on disease risk. *The American Journal of Geriatric Psychiatry, 14*(12), 1022–1031. doi:10.1097/01.jgp.0000225088.29353.08.

Bostrom, F., Jonsson, L., Minthon, L., & Londos, E. (2007). Patients with Lewy body dementia use more resources than those with Alzheimer's disease. *International Journal of Geriatric Psychiatry, 22*(8), 713–719. doi:10.1002/gps.1738.

Bras, J., Guerreiro, R., Darwent, L., Parkkinen, L., Ansorge, O., Escott-Price, V., et al. (2014). Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of Dementia with Lewy Bodies. *Human Molecular Genetics*. doi:10.1093/hmg/ddu334.

Chapman, J., Wang, N., Treves, T. A., Korczyn, A. D., & Bornstein, N. M. (1998). ACE, MTHFR, factor V Leiden, and APOE polymorphisms in patients with vascular and Alzheimer's dementia. *Stroke, 29*(7), 1401–1404.

Clark, L. N., Kartsaklis, L. A., Wolf Gilbert, R., Dorado, B., Ross, B. M., Kisselev, S., et al. (2009). Association of glucocerebrosidase mutations with dementia with lewy bodies. *Archives of Neurology, 66*(5), 578–583. doi:10.1001/archneurol.2009.54.

Colom-Cadena, M., Gelpi, E., Charif, S., Belbin, O., Blesa, R., Marti, M. J., et al. (2013). Confluence of alpha-synuclein, tau, and beta-amyloid pathologies in dementia with Lewy bodies. *Journal of Neuropathology and Experimental Neurology, 72*(12), 1203–1212. doi:10.1097/nen.0000000000000018.

Cook, L. J., Ho, L. W., Taylor, A. E., Brayne, C., Evans, J. G., Xuereb, J., et al. (2004). Candidate gene association studies of the alpha 4 (CHRNA4) and beta 2 (CHRNB2) neuronal nicotinic acetylcholine receptor subunit genes in Alzheimer's disease. *Neuroscience Letters, 358*(2), 142–146. doi:10.1016/j.neulet.2004.01.016.

Deelen, J., Beekman, M., Uh, H. W., Broer, L., Ayers, K. L., Tan, Q., et al. (2014). Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. *Human Molecular Genetics, 23*(16), 4420–4432. doi:10.1093/hmg/ddu139.

DeMattos, R. B., O'Dell, M. A., Parsadanian, M., Taylor, J. W., Harmony, J. A., Bales, K. R., et al. (2002). Clusterin promotes amyloid plaque formation and is critical for neuritic toxicity in a mouse model of Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America, 99*(16), 10843–10848. doi:10.1073/pnas.162228299.

DeMattos, R. B., Cirrito, J. R., Parsadanian, M., May, P. C., O'Dell, M. A., Taylor, J. W., et al. (2004). ApoE and clusterin cooperatively suppress Abeta levels and deposition: evidence that ApoE regulates extracellular Abeta metabolism in vivo. *Neuron, 41*(2), 193–202.

Dementia Report United Kingdom (2007). London.

Devenney, E., Hornberger, M., Irish, M., Mioshi, E., Burrell, J., Tan, R., et al. (2014). Frontotemporal dementia associated with the C9ORF72 mutation: a unique clinical profile. *JAMA Neurology, 71*(3), 331–339. doi:10.1001/jamaneurol.2013.6002.

Federico, A., Bianchi, S., & Dotti, M. T. (2005). The spectrum of mutations for CADASIL diagnosis. *Neurological Science, 26*(2), 117–124. doi:10.1007/s10072-005-0444-3.

Federico, A., Di Donato, I., Bianchi, S., Di Palma, C., Taglia, I., & Dotti, M. T. (2012). Hereditary cerebral small vessel diseases: a review. *Journal of Neurological Sciences, 322*(1–2), 25–30. doi:10.1016/j.jns.2012.07.041.

Ferencz, B., Karlsson, S., & Kalpouzos, G. (2012). Promising genetic biomarkers of preclinical Alzheimer's disease: the influence of

APOE and TOMM40 on brain integrity. *International Journal of Alzheimer's Disease, 2012*, 421452. doi:10.1155/2012/421452.

Ferrari, R., Hardy, J., & Momeni, P. (2011). Frontotemporal dementia: from Mendelian genetics towards genome wide association studies. *Journal of Molecular Neuroscience, 45*(3), 500–515. doi:10.1007/s12031-011-9635-y.

Ferrari, R., Hernandez, D. G., Nalls, M. A., Rohrer, J. D., Ramasamy, A., Kwok, J. B., et al. (2014). Frontotemporal dementia and its subtypes: a genome-wide association study. *Lancet Neurology, 13*(7), 686–699. doi:10.1016/s1474-4422(14)70065-1.

Fuchs, J., Nilsson, C., Kachergus, J., Munz, M., Larsson, E. M., Schule, B., et al. (2007). Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. *Neurology, 68*(12), 916–922. doi:10.1212/01.wnl.0000254458.17630.c5.

Gatz, M., Reynolds, C. A., Finkel, D., Pedersen, N. L., & Walters, E. (2010). Dementia in Swedish twins: predicting incident cases. *Behavior Genetics, 40*(6), 768–775. doi:10.1007/s10519-010-9407-4.

Genin, E., Hannequin, D., Wallon, D., Sleegers, K., Hiltunen, M., Combarros, O., et al. (2011). APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Molecular Psychiatry, 16*(9), 903–907. doi:10.1038/mp.2011.52.

George, J. M. (2002). The synucleins. *Genome Biology*, *3*(1). REVIEWS3002.

Gijselinck, I., Van Langenhove, T., van der Zee, J., Sleegers, K., Philtjens, S., Kleinberger, G., et al. (2012). A C9orf72 promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. *Lancet Neurology, 11*(1), 54–65. doi:10.1016/s1474-4422(11)70261-7.

Glenner, G. G., & Wong, C. W. (1984). Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical and Biophysical Research Communications, 120*(3), 885–890.

Gudala, K., Bansal, D., & Muthyala, H. (2013). Role of serum cholesterol in Parkinson's disease: a meta-analysis of evidence. *Journal of Parkinsons Disease, 3*(3), 363–370. doi:10.3233/jpd-130196.

Gusareva, E. S., Carrasquillo, M. M., Bellenguez, C., Cuyvers, E., Colon, S., Graff-Radford, N. R., et al. (2014). Genome-wide association interaction analysis for Alzheimer's disease. *Neurobiology of Aging*. doi:10.1016/j.neurobiolaging.2014.05.014.

Hanson, J. C., & Lippa, C. F. (2009). Lewy body dementia. *International Review of Neurobiology, 84*, 215–228. doi:10.1016/s0074-7742(09)00411-5.

Hardy, J., Guerreiro, R., & Lovestone, S. (2011). Clusterin as an Alzheimer biomarker. *Archives of Neurology, 68*(11), 1459–1460. doi:10.1001/archneurol.2011.1000.

Harel, A., Wu, F., Mattson, M. P., Morris, C. M., & Yao, P. J. (2008). Evidence for CALM in directing VAMP2 trafficking. *Traffic, 9*(3), 417–429. doi:10.1111/j.1600-0854.2007.00694.x.

Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M. L., et al. (2009). Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nature Genetics, 41*(10), 1088–1093. doi:10.1038/ng.440.

Hely, M. A., Reid, W. G., Adena, M. A., Halliday, G. M., & Morris, J. G. (2008). The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Movement Disorders, 23*(6), 837–844. doi:10.1002/mds.21956.

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J. C., Carrasquillo, M. M., et al. (2011). Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nature Genetics, 43*(5), 429–435. doi:10.1038/ng.803.

Jones, L., Holmans, P. A., Hamshere, M. L., Harold, D., Moskvina, V., Ivanov, D., et al. (2010). Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. *PLoS One, 5*(11), e13950. doi:10.1371/journal.pone.0013950.

Jonsson, T., Atwal, J. K., Steinberg, S., Snaedal, J., Jonsson, P. V., Bjornsson, S., et al. (2012). A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature, 488*(7409), 96–99. doi:10.1038/nature11283.

Kara, E., Kiely, A. P., Proukakis, C., Giffin, N., Love, S., Hehir, J., et al. (2014). 6.4 Mb duplication of the alpha-Synuclein Locus causing frontotemporal dementia and Parkinsonism: phenotype-genotype correlations. *JAMA Neurology*. doi:10.1001/jamaneurol.2014.994.

Karageorgiou, E., & Miller, B. L. (2014). Frontotemporal lobar degeneration: a clinical approach. *Seminars in Neurology, 34*(2), 189–201. doi:10.1055/s-0034-1381735.

Karch, C. M., & Goate, A. M. (2014). Alzheimer's disease risk genes and mechanisms of disease pathogenesis. *Biological Psychiatry*. doi:10.1016/j.biopsych.2014.05.006.

Karch, C. M., Jeng, A. T., Nowotny, P., Cady, J., Cruchaga, C., & Goate, A. M. (2012). Expression of novel Alzheimer's disease risk genes in control and Alzheimer's disease brains. *PLoS One, 7*(11), e50976. doi:10.1371/journal.pone.0050976.

Karch, C. M., Cruchaga, C., & Goate, A. M. (2014). Alzheimer's disease genetics: from the bench to the clinic. *Neuron, 83*(1), 11–26. doi:10.1016/j.neuron.2014.05.041.

Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2010). Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurology, 9*(12), 1200–1213. doi:10.1016/s1474-4422(10)70212-x.

Kehoe, P. G., Russ, C., McIlory, S., Williams, H., Holmans, P., Holmes, C., et al. (1999). Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. *Nature Genetics, 21*(1), 71–72. doi:10.1038/5009.

Khera, R., & Das, N. (2009). Complement receptor 1: disease associations and therapeutic implications. *Molecular Immunology, 46*(5), 761–772. doi:10.1016/j.molimm.2008.09.026.

Kim, M., Suh, J., Romano, D., Truong, M. H., Mullin, K., Hooli, B., et al. (2009a). Potential late-onset Alzheimer's disease-associated mutations in the ADAM10 gene attenuate {alpha}-secretase activity. *Human Molecular Genetics, 18*(20), 3987–3996. doi:10.1093/hmg/ddp323.

Kim, Y., Park, J., & Lee, C. (2009b). Multilocus genotypic association with vascular dementia by multifactor dimensionality reduction and entropy-based estimation. *Psychiatric Genetics, 19*(5), 253–258. doi:10.1097/YPG.0b013e32832ceebd.

Kim, Y., Kong, M., & Lee, C. (2013). Association of intronic sequence variant in the gene encoding spleen tyrosine kinase with susceptibility to vascular dementia. *World Journal of Biological Psychiatry, 14*(3), 220–226. doi:10.3109/15622975.2011.559272.

Kirshner, H. S. (2014). Frontotemporal dementia and primary progressive aphasia, a review. *Neuropsychiatric Disease and Treatment, 10*, 1045–1055. doi:10.2147/ndt.s38821.

Kong, M., Kim, Y., & Lee, C. (2011). A strong synergistic epistasis between FAM134B and TNFRSF19 on the susceptibility to vascular dementia. *Psychiatric Genetics, 21*(1), 37–41. doi:10.1097/YPG.0b013e3283413496.

Lambert, J. C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., et al. (2009). Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nature Genetics, 41*(10), 1094–1099. doi:10.1038/ng.439.

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., et al. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics, 45*(12), 1452–1458. doi:10.1038/ng.2802.

Lathe, R., Sapronova, A., & Kotelevtsev, Y. (2014). Atherosclerosis and Alzheimer - diseases with a common cause? Inflammation,

oxysterols, vasculature. *BMC Geriatrics, 14*, 36. doi:10.1186/1471-2318-14-36.

Le Ber, I. (2013). Genetics of frontotemporal lobar degeneration: an update and diagnosis algorithm. *Revue Neurologique (Paris), 169*(10), 811–819. doi:10.1016/j.neurol.2013.07.014.

Leduc, V., Jasmin-Belanger, S., & Poirier, J. (2010). APOE and cholesterol homeostasis in Alzheimer's disease. *Trends in Molecular Medicine, 16*(10), 469–477. doi:10.1016/j.molmed.2010.07.008.

Lee, C., & Kim, Y. (2013). Complex genetic susceptibility to vascular dementia and an evidence for its underlying genetic factors associated with memory and associative learning. *Gene, 516*(1), 152–157. doi:10.1016/j.gene.2012.12.032.

Li, Y., Grupe, A., Rowland, C., Nowotny, P., Kauwe, J. S., Smemo, S., et al. (2006). DAPK1 variants are associated with Alzheimer's disease and allele-specific expression. *Human Molecular Genetics, 15*(17), 2560–2568. doi:10.1093/hmg/ddl178.

Li, K., Liu, S., Yao, S., Wang, B., Dai, D., & Yao, L. (2009). Interaction between interleukin-8 and methylenetetrahydrofolate reductase genes modulates Alzheimer's disease risk. *Dementia and Geriatric Cognitive Disorders, 27*(3), 286–291. doi:10.1159/000204766.

Linnertz, C., Lutz, M. W., Ervin, J. F., Allen, J., Miller, N. R., Welsh-Bohmer, K. A., et al. (2014). The genetic contributions of SNCA and LRRK2 genes to Lewy body pathology in Alzheimer's disease. *Human Molecular Genetics*. doi:10.1093/hmg/ddu196.

Magaki, S., Yong, W. H., Khanlou, N., Tung, S., & Vinters, H. V. (2014). Comorbidity in dementia: update of an ongoing autopsy study. *Journal of the American Geriatrics Society*. doi:10.1111/jgs.12977.

Maia, L. F., Mackenzie, I. R., & Feldman, H. H. (2007). Clinical phenotypes of cerebral amyloid angiopathy. *Journal of Neurological Sciences, 257*(1–2), 23–30. doi:10.1016/j.jns.2007.01.054.

Mata, I. F., Samii, A., Schneer, S. H., Roberts, J. W., Griffith, A., Leis, B. C., et al. (2008). Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. *Archives of Neurology, 65*(3), 379–382. doi:10.1001/archneurol.2007.68.

McGeer, E. G., & McGeer, P. L. (2001). Innate immunity in Alzheimer's disease: a model for local inflammatory reactions. *Molecular Interventions, 1*(1), 22–29.

McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., et al. (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), 1113–1124.

Meeus, B., Theuns, J., & Van Broeckhoven, C. (2012). The genetics of dementia with Lewy bodies: what are we missing? *Archives of Neurology, 69*(9), 1113–1118. doi:10.1001/archneurol.2011.3678.

Miklya, I., Pencz, N., Hafenscher, F., & Goltl, P. (2014). The role of alpha-synuclein in Parkinson's disease. *Neuropsychopharmacologia Hungarica, 16*(2), 77–84.

Mollenhauer, B., Forstl, H., Deuschl, G., Storch, A., Oertel, W., & Trenkwalder, C. (2010). Lewy body and Parkinsonian dementia: common, but often misdiagnosed conditions. *Deutsches Ärzteblatt International, 107*(39), 684–691. doi:10.3238/arztebl.2010.0684.

Momeni, P., Rogaeva, E., Van Deerlin, V., Yuan, W., Grafman, J., Tierney, M., et al. (2006). Genetic variability in CHMP2B and frontotemporal dementia. *Neurodegenerative Diseases, 3*(3), 129–133. doi:10.1159/000094771.

Moore, S. F., & Barker, R. A. (2014). Predictors of Parkinson's disease dementia: towards targeted therapies for a heterogeneous disease. *Parkinsonism & Related Disorders, 20*(Suppl 1), S104–S107. doi:10.1016/s1353-8020(13)70026-9.

Naj, A. C., Jun, G., Beecham, G. W., Wang, L. S., Vardarajan, B. N., Buros, J., et al. (2011). Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nature Genetics, 43*(5), 436–441. doi:10.1038/ng.801.

Nervi, A., Reitz, C., Tang, M. X., Santana, V., Piriz, A., Reyes, D., et al. (2011). Familial aggregation of dementia with Lewy bodies. *Archives of Neurology, 68*(1), 90–93. doi:10.1001/archneurol.2010.319.

Nishioka, K., Wider, C., Vilarino-Guell, C., Soto-Ortolaza, A. I., Lincoln, S. J., Kachergus, J. M., et al. (2010). Association of alpha-, beta-, and gamma-Synuclein with diffuse lewy body disease. *Archives of Neurology, 67*(8), 970–975. doi:10.1001/archneurol.2010.177.

Nuutinen, T., Suuronen, T., Kauppinen, A., & Salminen, A. (2009). Clusterin: a forgotten player in Alzheimer's disease. *Brain Research Reviews, 61*(2), 89–104. doi:10.1016/j.brainresrev.2009.05.007.

Oesterhus, R., Soennesyn, H., Rongve, A., Ballard, C., Aarsland, D., & Vossius, C. (2014). Long-term mortality in a cohort of home-dwelling elderly with mild Alzheimer's disease and Lewy body dementia. *Dementia and Geriatric Cognitive Disorders, 38*(3–4), 161–169. doi:10.1159/000358051.

Olesen, O. F., Mikkelsen, J. D., Gerdes, C., & Jensen, P. H. (1997). Isoform-specific binding of human apolipoprotein E to the non-amyloid beta component of Alzheimer's disease amyloid. *Brain Research. Molecular Brain Research, 44*(1), 105–112.

Pant, S., Sharma, M., Patel, K., Caplan, S., Carr, C. M., & Grant, B. D. (2009). AMPH-1/Amphiphysin/Bin1 functions with RME-1/Ehd1 in endocytic recycling. *Nature Cell Biology, 11*(12), 1399–1410. doi:10.1038/ncb1986.

Pericak-Vance, M. A., Bebout, J. L., Gaskell, P. C., Jr., Yamaoka, L. H., Hung, W. Y., Alberts, M. J., et al. (1991). Linkage studies in familial Alzheimer disease: evidence for chromosome 19 linkage. *American Journal of Human Genetics, 48*(6), 1034–1050.

Pohjasvaara, T., Mantyla, R., Ylikoski, R., Kaste, M., & Erkinjuntti, T. (2003). Clinical features of MRI-defined subcortical vascular disease. *Alzheimer Disease & Associated Disorders, 17*(4), 236–242.

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's & Dementia, 9*(1), 63–75. doi:10.1016/j.jalz.2012.11.007. e62.

Qiu, C., von Strauss, E., Backman, L., Winblad, B., & Fratiglioni, L. (2013). Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. *Neurology, 80*(20), 1888–1894. doi:10.1212/WNL.0b013e318292a2f9.

Reitz, C. (2013). Dyslipidemia and the risk of Alzheimer's disease. *Current Atherosclerosis Reports, 15*(3), 307. doi:10.1007/s11883-012-0307-3.

Reitz, C., Tang, M. X., Luchsinger, J., & Mayeux, R. (2004). Relation of plasma lipids to Alzheimer disease and vascular dementia. *Archives of Neurology, 61*(5), 705–714. doi:10.1001/archneur.61.5.705.

Ridge, P. G., Mukherjee, S., Crane, P. K., & Kauwe, J. S. (2013). Alzheimer's disease: analyzing the missing heritability. *PLoS One, 8*(11), e79771. doi:10.1371/journal.pone.0079771.

Ridolfi, E., Barone, C., Scarpini, E., & Galimberti, D. (2013). The role of the innate immune system in Alzheimer's disease and frontotemporal lobar degeneration: an eye on microglia. *Clinical and Developmental Immunology, 2013*, 939786. doi:10.1155/2013/939786.

Rogaeva, E., Meng, Y., Lee, J. H., Gu, Y., Kawarai, T., Zou, F., et al. (2007). The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nature Genetics, 39*(2), 168–177. doi:10.1038/ng1943.

Rogers, J., Li, R., Mastroeni, D., Grover, A., Leonard, B., Ahern, G., et al. (2006). Peripheral clearance of amyloid beta peptide by complement C3-dependent adherence to erythrocytes. *Neurobiology of Aging, 27*(12), 1733–1739. doi:10.1016/j.neurobiolaging.2005.09.043.

Rohrer, J. D., Guerreiro, R., Vandrovcova, J., Uphill, J., Reiman, D., Beck, J., et al. (2009). The heritability and genetics of frontotemporal lobar degeneration. *Neurology, 73*(18), 1451–1456. doi:10.1212/WNL.0b013e3181bf997a.

Roman, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., et al. (1993). Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology, 43*(2), 250–260.

Rosenthal, S. L., & Kamboh, M. I. (2014). Late-onset Alzheimer's disease genes and the potentially implicated pathways. *Current Genetics Medicine Reports, 2*, 85–101. doi:10.1007/s40142-014-0034-x.

Roses, A. D., Lutz, M. W., Amrine-Madsen, H., Saunders, A. M., Crenshaw, D. G., Sundseth, S. S., et al. (2010). A TOMM40 variable-length polymorphism predicts the age of late-onset Alzheimer's disease. *The Pharmacogenomics Journal, 10*(5), 375–384. doi:10.1038/tpj.2009.69.

Savica, R., Grossardt, B. R., Bower, J. H., Boeve, B. F., Ahlskog, J. E., & Rocca, W. A. (2013). Incidence of dementia with Lewy bodies and Parkinson disease dementia. *JAMA Neurology, 70*(11), 1396–1402. doi:10.1001/jamaneurol.2013.3579.

Schjeide, B. M., Schnack, C., Lambert, J. C., Lill, C. M., Kirchheiner, J., Tumani, H., et al. (2011). The role of clusterin, complement receptor 1, and phosphatidylinositol binding clathrin assembly protein in Alzheimer disease risk and cerebrospinal fluid biomarker levels. *Archives of General Psychiatry, 68*(2), 207–213. doi:10.1001/archgenpsychiatry.2010.196.

Schmidt, H., Freudenberger, P., Seiler, S., & Schmidt, R. (2012). Genetics of subcortical vascular dementia. *Experimental Gerontology, 47*(11), 873–877. doi:10.1016/j.exger.2012.06.003.

Schrijvers, E. M., Schurmann, B., Koudstaal, P. J., van den Bussche, H., Van Duijn, C. M., Hentschel, F., et al. (2012). Genome-wide association study of vascular dementia. *Stroke, 43*(2), 315–319. doi:10.1161/strokeaha.111.628768.

Seshadri, S., Fitzpatrick, A. L., Ikram, M. A., DeStefano, A. L., Gudnason, V., Boada, M., et al. (2010). Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA, 303*(18), 1832–1840. doi:10.1001/jama.2010.574.

Seto-Salvia, N., Clarimon, J., Pagonabarraga, J., Pascual-Sedano, B., Campolongo, A., Combarros, O., et al. (2011). Dementia risk in Parkinson disease: disentangling the role of MAPT haplotypes. *Archives of Neurology, 68*(3), 359–364. doi:10.1001/archneurol.2011.17.

Sieben, A., Van Langenhove, T., Engelborghs, S., Martin, J. J., Boon, P., Cras, P., et al. (2012). The genetics and neuropathology of frontotemporal lobar degeneration. *Acta Neuropathologica, 124*(3), 353–372. doi:10.1007/s00401-012-1029-x.

Skibinski, G., Parkinson, N. J., Brown, J. M., Chakrabarti, L., Lloyd, S. L., Hummerich, H., et al. (2005). Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nature Genetics, 37*(8), 806–808. doi:10.1038/ng1609.

Spillantini, M. G., & Goedert, M. (2013). Tau pathology and neurodegeneration. *Lancet Neurology, 12*(6), 609–622. doi:10.1016/s1474-4422(13)70090-5.

Takei, N., Miyashita, A., Tsukie, T., Arai, H., Asada, T., Imagawa, M., et al. (2009). Genetic association study on in and around the APOE in late-onset Alzheimer disease in Japanese. *Genomics, 93*(5), 441–448. doi:10.1016/j.ygeno.2009.01.003.

Tang, W., Huang, Q., Yao, Y. Y., Wang, Y., Wu, Y. L., & Wang, Z. Y. (2014). Does CSF p-tau help to discriminate Alzheimer's disease from other dementias and mild cognitive impairment? A meta-analysis of the literature. *Journal of Neural Transmission*. doi:10.1007/s00702-014-1226-y.

Trougakos, I. P., & Gonos, E. S. (2006). Regulation of clusterin/apolipoprotein J, a functional homologue to the small heat shock proteins, by oxidative stress in ageing and age-related diseases. *Free Radical Research, 40*(12), 1324–1334. doi:10.1080/10715760600902310.

Tsuang, D., Leverenz, J. B., Lopez, O. L., Hamilton, R. L., Bennett, D. A., Schneider, J. A., et al. (2012). GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology. *Neurology, 79*(19), 1944–1950. doi:10.1212/WNL.0b013e3182735e9a.

Urwin, H., Authier, A., Nielsen, J. E., Metcalf, D., Powell, C., Froud, K., et al. (2010). Disruption of endocytic trafficking in frontotemporal dementia with CHMP2B mutations. *Human Molecular Genetics, 19*(11), 2228–2238. doi:10.1093/hmg/ddq100.

Van Deerlin, V. M., Sleiman, P. M., Martinez-Lage, M., Chen-Plotkin, A., Wang, L. S., Graff-Radford, N. R., et al. (2010). Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions. *Nature Genetics, 42*(3), 234–239. doi:10.1038/ng.536.

van der Flier, W. M., & Scheltens, P. (2005). Epidemiology and risk factors of dementia. *Journal of Neurology, Neurosurgery, and Psychiatry, 76*(Suppl 5), v2–v7. doi:10.1136/jnnp.2005.082867.

van der Zee, J., Gijselinck, I., Dillen, L., Van Langenhove, T., Theuns, J., Engelborghs, S., et al. (2013). A pan-European study of the C9orf72 repeat associated with FTLD: geographic prevalence, genomic instability, and intermediate repeats. *Human Mutation, 34*(2), 363–373. doi:10.1002/humu.22244.

van Swieten, J., & Spillantini, M. G. (2007). Hereditary frontotemporal dementia caused by Tau gene mutations. *Brain Pathology, 17*(1), 63–73. doi:10.1111/j.1750-3639.2007.00052.x.

Wang, T., Baron, M., & Trump, D. (2008). An overview of Notch3 function in vascular smooth muscle cells. *Progress in Biophysics and Molecular Biology, 96*(1–3), 499–509. doi:10.1016/j.pbiomolbio.2007.07.006.

Wang, C. S., Burke, J. R., Steffens, D. C., Hulette, C. M., Breitner, J. C., & Plassman, B. L. (2009). Twin pairs discordant for neuropathologically confirmed Lewy body dementia. *Journal of Neurology, Neurosurgery, and Psychiatry, 80*(5), 562–565. doi:10.1136/jnnp.2008.151654.

Weihl, C. C., Temiz, P., Miller, S. E., Watts, G., Smith, C., Forman, M., et al. (2008). TDP-43 accumulation in inclusion body myopathy muscle suggests a common pathogenic mechanism with frontotemporal dementia. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*(10), 1186–1189. doi:10.1136/jnnp.2007.131334.

Wider, C., Ross, O. A., Nishioka, K., Heckman, M. G., Vilarino-Guell, C., Jasinska-Myga, B., et al. (2012). An evaluation of the impact of MAPT, SNCA and APOE on the burden of Alzheimer's and Lewy body pathology. *Journal of Neurology, Neurosurgery, and Psychiatry, 83*(4), 424–429. doi:10.1136/jnnp-2011-301413.

Williams-Gray, C. H., Mason, S. L., Evans, J. R., Foltynie, T., Brayne, C., Robbins, T. W., et al. (2013). The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *Journal of Neurology, Neurosurgery, and Psychiatry, 84*(11), 1258–1264. doi:10.1136/jnnp-2013-305277.

Winslow, A. R., Moussaud, S., Zhu, L., Post, K. L., Dickson, D. W., Berezovska, O., et al. (2014). Convergence of pathology in dementia with Lewy bodies and Alzheimer's disease: a role for the novel interaction of alpha-synuclein and presenilin 1 in disease. *Brain, 137*(Pt 7), 1958–1970. doi:10.1093/brain/awu119.

Yang, C., Swallows, C. L., Zhang, C., Lu, J., Xiao, H., Brady, R. O., et al. (2014). Celastrol increases glucocerebrosidase activity in Gaucher disease by modulating molecular chaperones. *Proceedings of the National Academy of Sciences of the United States of America, 111*(1), 249–254. doi:10.1073/pnas.1321341111.

Zhu, X., Babar, A., Siedlak, S. L., Yang, Q., Ito, G., Iwatsubo, T., et al. (2006). LRRK2 in Parkinson's disease and dementia with Lewy bodies. *Molecular Neurodegeneration, 1*, 17. doi:10.1186/1750-1326-1-17.