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Genetic architecture of common non-Alzheimer's disease dementias

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Abstract

Frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) and vascular dementia (VaD) are the most common forms of dementia after Alzheimer's disease (AD). The heterogeneity of these disorders and/or the clinical overlap with other diseases hinder the study of their genetic components. Even though Mendelian dementias are rare, the study of these forms of disease can have a significant impact in the lives of patients and families and have successfully brought to the fore many of the genes currently known to be involved in FTD and VaD, starting to give us a glimpse of the molecular mechanisms underlying these phenotypes. More recently, genome-wide association studies have also pointed to disease risk-associated loci. This has been particularly important for DLB where familial forms of disease are very rarely described. In this review we systematically describe the Mendelian and risk genes involved in these non-AD dementias in an effort to contribute to a better understanding of their genetic architecture, find differences and commonalities between different dementia phenotypes, and uncover areas that would benefit from more intense research endeavors.

1. Introduction

Alzheimer's disease (AD) is consensually known to be the major cause of dementia, comprising around 60–80% of all dementia cases (Erkkinen et al., 2018). Some rare AD cases result from specific mutations and typically present with early-onset of disease and familial structure. The vast majority, however, occurs in a sporadic form, although even that form has an estimated heritability of 58–79%, that includes the small cumulative effects of multiple variants and genes (Gatz et al., 2006). Besides AD, the major causes of dementia

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include a variety of diseases with the most prominent being dementia with Lewy bodies (DLB), frontotemporal dementia (FTD) and vascular dementia (VaD). Lewy body dementia has a prevalence of around 7.5% (Vann Jones and O'Brien, 2014), but this number can be as high as 30% (Erkkinen et al., 2018); FTD accounts for 12% of early-onset dementia cases (Rossor et al., 2010); and VaD is known to cause 13% of neuropathological cases and to contribute to at least an additional 12% of dementia cases (Knopman et al., 2003). The prevalence of each of these diseases can vary with population, age, sex and diagnostic procedures.

Even though in this review we focus on the most common causes of non-AD dementias mentioned above, other rarer forms of degenerative dementia should be briefly mentioned. These often manifest with additional clinical signs or are very rare and include, among others, corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), prion diseases, Huntington disease, spinocerebellar ataxias, mitochondrial diseases and leukodystrophies (Rossor et al., 2010).

These multiple causes of dementia are considered to be different clinical entities but, in many cases, may share pathogenic pathways and phenotypes. In fact, on an aging brain, different pathologies may occur and overlap, hampering diagnosis and the understanding of the specific biological processes underlying these disorders.

Genetics has played a critical role in our understanding of the molecular mechanisms involved in these diseases. Genetic changes lie upstream of the pathological changes, exerting effects throughout the lifetime. This is important in, at least, two dimensions: genetic signatures may be the best markers of 'pure' disorders and, given they are acting from conception, they may be the best targets for treatments and, particularly, preventing interventions. At the same time, the co-occurrence of pathologies suggests the existence of common risk factors and/or dysfunctional pathways, and this may be a result of shared genetic risk factors.

Studying the genetic similarities and contrasts between the different causes of dementia may help to build a framework of neurodegeneration pathways common to all these disorders that ultimately can contribute to more informed diagnoses, as well as the development of treatments and more directed research studies.

Here, we aim to review the current knowledge of the genetic architecture of non-AD dementias by systematically characterizing the genes and genetic loci known to be involved in the Mendelian and sporadic forms of these disorders.

2. Genetics of frontotemporal dementia

Frontotemporal dementia is heterogeneous on many levels: phenotypic, pathological and genetic. The most common clinical subtypes are behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA). Both these phenotypes overlap, in a large number of patients, with amyotrophic lateral sclerosis (ALS) and the atypical parkinsonian syndromes CBS and PSP. Being the second most common cause of early-onset degenerative dementia, about a third of FTD cases are found to be genetic. There are different genes known to cause

this disease when mutated, with the majority of cases being associated with genetic changes in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9ORF72*) (Rohrer et al., 2009). However, there are other genes known to cause FTD in a smaller number of cases and the genetic landscape is rapidly expanding.

2.1. MAPT, GRN and C9ORF72

MAPT, which encodes microtubule-associated protein tau, was the first gene to be associated with FTD. The clinical presentation can vary: 44.8% of the patients develop a behavioral variant of FTD and 3.9% some form of PPA. *MAPT* mutation carriers have also been reported to present with PSP (4.2%), Parkinson's disease (PD) (4.9%), AD (3.0%), CBS (1.8%) and rarely ALS (0.4%) phenotypes (Moore et al., 2020). *MAPT* mutations are relatively more common in the Netherlands and the US west coast (Moore et al., 2020) and, pathologically, are associated with tau deposits.

One of tau's primary functions is to bind and promote the assembly of microtubules (Caillet-Boudin et al., 2015). It has a natural alternative splicing mechanism at exon 10 that creates an equal number of isoforms containing 3 or 4 repeat segments (3R tau and 4R tau). Assembly of tau occurs at the repeats' level, so it is not surprising that many of the pathogenic mutations are located on those repeats, affecting how tau interacts with microtubules (Ghetti et al., 2015). Known disease-causing variants are missense, silent or deletions with the majority occurring in exons 9–13, as well as intronic variants. These are mostly clustered in the 5′-splice site of the intron after exon 10. The mutations identified in *MAPT* can affect protein structure or the alternative splicing of exon 10. This latter mechanism creates an imbalance of the 3R/4R ratio with a relative increase of 4R tau leading to more interactions with microtubules (Ghetti et al., 2015).

GRN encodes progranulin, a precursor protein of 593 amino acids. When cleaved, it leads to the formation of granulins. The exact role of progranulin or granulins is not yet fully understood, but it has been linked to neuronal growth, lysosomal function, inflammation and stress response (Holler et al., 2017; Petkau and Leavitt, 2014).

Around 130 *GRN* mutations in 483 families have been identified, with a high prevalence in southern Europe, especially in Italy (Moore et al., 2020). Intriguingly, *GRN* mutations have been found more in women (58.4%) than men (Moore et al., 2020). The most common disease causative mutations are nonsense, frameshift and splice site variants leading to premature stop codons that activate nonsense-mediated decay, leading to haploinsufficiency and subsequent reduced progranulin protein levels (Baker et al., 2006; Cruts et al., 2006; Cruts and Van Broeckhoven, 2008). Other pathogenic variants include genomic deletions (Rovelet-Lecrux et al., 2008) or elimination of the initiation codon for protein synthesis (Cruts et al., 2006). Some missense mutations have also been associated with disease (Kleinberger et al., 2016). Consistent with the haploinsufficiency theory, patients with heterozygous mutations have 50% less progranulin levels both in cerebrospinal fluid (CSF) and plasma (Coppola et al., 2008).

Patients carrying *GRN* mutations have also been reported to present with phenotypes resembling AD, Lewy body dementia or CBS (Moore et al., 2020) and homozygous *GRN*

mutation carriers, presenting complete loss of progranulin, develop neuronal ceroid lipofuscinosis with early onset retinal degeneration, seizures and cerebellar ataxia (Smith et al., 2012).

Pathogenic repeat expansions in *C9ORF72* are the most common genetic cause of FTD and ALS, explaining disease in 4–29% of individuals with FTD (Van Mossevelde et al., 2018). These have also been reported in patients with AD, PD, PSP, CBS, ataxia and Creutzfeldt-Jakob disease (CJD) (Balendra and Isaacs, 2018) and were reported to be the most common cause of Huntington disease phenocopies (Hensman Moss et al., 2014). Although a threshold for pathogenicity has not been clearly determined for the number of repeats, a cut-off of 30 repeats is typically used. Patients usually have expansions ranging from hundreds to thousands and most healthy individuals have less than 12 repeats (Balendra and Isaacs, 2018). The pathogenic mechanisms of *C9ORF72* mutations still need to be completely elucidated. Loss of function (possibly leading to defects in autophagy or lysosomal function), gain of protein function (characterized by toxic accumulation of dipeptide repeats) and gain of RNA function (characterized by toxic effects from the sense and antisense foci generated from the repeats) have been hypothesized as the underlying causes (Balendra and Isaacs, 2018). Epigenetic alterations in *C9ORF72* associated disease have been postulated as the cause of reduction of gene product. Hypermethylation of the CpG-island located in the promoter region of *C9ORF72* was only found in expansion carriers (Xi et al., 2013), and DNA methylation of the repeat expansion itself occurs in all carriers of alleles with > 90 repeats, while small or intermediate alleles are completely unmethylated (Xi et al., 2015). The combined analyses of epigenetic and genetic data in *C9ORF72* expansion carriers has also led to the identification of a 124.7 kb linkage disequilibrium block, tagged by rs9357140, and containing two overlapping genes (*LOC101929163* and *C6ORF10*), associated with age at onset of disease not only in *C9ORF72* expansion carriers, but also in FTD cases without expansions (Zhang et al., 2018).

2.2. Rare genetic causes of FTD

In addition to the most common mutated genes known to cause familial and a smaller proportion of sporadic FTD cases, there are several other genes that when mutated cause FTD in a much smaller number of cases. Many of these rare genetic forms fall within the spectrum of FTD-ALS with many of the genes identified so far causing one of these phenotypes or both. From these, TANK-binding kinase 1 (*TBK1*) is thought to be the one more frequently harboring FTD-causing mutations after *MAPT*, *GRN* and *C9ORF72* (Freischmidt et al., 2017; Helgason et al., 2013). TBK1 is a multifunctional kinase involved in the regulation of various cellular pathways, including immune response, inflammation, autophagy, cell proliferation, and insulin signaling. Heterozygous loss of function variants were initially shown to cause ALS and FTD (Freischmidt et al., 2015). Since then, in-frame deletions of single amino acids and missense variants have also been associated with these phenotypes, although their definite role in disease is still not known (Freischmidt et al., 2017).

Mutations in the TAR DNA binding protein 43 (TDP-43)-encoding gene, *TARDBP*, are responsible for a smaller percentage (~1%) of FTD cases (Baizabal-Carvallo and Jankovic,

2016; Caroppo et al., 2016). TDP-43 is a RNA/DNA binding protein involved in RNA-related metabolism (Prasad et al., 2019), with mutations associated with an anticipation phenomenon and reduced penetrance in most families (Caroppo et al., 2016). Reported *TARDBP* mutations causing FTD are rare and not definitely pathogenic (Hardy and Rogaeva, 2014), although recently, four patients from two kindreds were reported to carry the same mutation, increasing support for its role in "pure" FTD (Ramos et al., 2020).

Mutations in Sequestosome-1 (*SQSTM1*) were shown to segregate with FTD after the identification of p62 (the protein encoded by this gene) in neuronal and glial ubiquitin-positive inclusions in different neurodegenerative diseases (Le Ber et al., 2013). *SQSTM1* mutations were initially associated with Paget's disease. In FTD and ALS mutations are typically missense, but nonsense and deletions have also been described (Le Ber et al., 2013; van der Zee et al., 2014). In a case-control rare variant association analysis, no differences were found when taking into consideration the whole protein, but authors observed a clustering of rare variants in the ubiquitin-associated domain of p62 and argued that this domain drives the association and variants located there double the risk for FTD (van der Zee et al., 2014). Biallelic loss-of-function variants in *SQSTM1* have been shown to cause a childhood or adolescence onset, neurodegenerative disease characterized by ataxia, gait abnormalities, dysarthria, dystonia, vertical gaze palsy, and cognitive decline (Haack et al., 2016). The p62 protein participates in the degradation of ubiquitinated proteins by autophagy and is involved in cell differentiation, apoptosis and immune responses (Le Ber et al., 2013). Disease associated mutations are believed to lead to dysfunction of the degradation of proteins by affecting the binding of the p62 protein leading to disruption of selective autophagy pathways in neurodegenerative disease.

CHMP2B encodes the charged multivesicular body protein 2b, a subunit of the endosomal sorting complex required for transport-III, which is implicated in the final stages of cell division, egress of virus from cells, nuclear envelope reformation after mitosis and lysosomal degradation (Clayton et al., 2018; Gydesen et al., 2002). *CHMP2B* mutations can cause both FTD and ALS (Parkinson et al., 2006). Clearly pathogenic mutations lead to C-terminus truncation of the protein, causing loss of the VPS4 binding domain. The reported mutations are nonsense or affecting gene splicing (van der Zee et al., 2008). Several missense mutations have also been reported, but their pathogenicity has not yet been clearly established (Han et al., 2012).

VCP encodes the valosin-containing protein, which is a member of a superfamily of proteins that uses the energy gained from ATP hydrolysis to structurally remodel proteins. VCP is part of the ubiquitin-proteasome system and it functions in diverse cellular processes including endoplasmic reticulum-associated protein degradation, mitophagy, autophagy and DNA repair (Meyer et al., 2012). Disease-causing missense mutations were initially associated with inclusion body myopathy associated with Paget disease of bone and FTD (Watts et al., 2004). This is an adult-onset rare disorder characterized by distal muscle weakness where *VCP* pathogenic variants cause myopathy in 90% of the cases, Paget disease of bone in 50%, and FTD in 30% (Van Mossevelde et al., 2018). The phenotypes associated with *VCP* mutations have since been extended to include motor neuron disease

(Johnson et al., 2010), and, more rarely, PD, AD, and peripheral neuropathies (Van Mossevelde et al., 2018).

A minority of FTD cases result from mutations in *CHCHD10* which encodes the mitochondrial protein coiled-coil-helix-coiled-coil-helix domain containing 10 (Bannwarth et al., 2014). Other phenotypes such as myopathy, cerebellar ataxia, ALS and PD have also been associated with mutations in this gene (Perrone et al., 2017). Reported mutations are missense or nonsense (Zhou et al., 2017) and are all concentrated in exon 2 (Zhou et al., 2017). These are thought to lead to disease through a loss of function mechanism (Perrone et al., 2017). CHCHD10 is a multifunctional protein involved in the regulation of mitochondrial metabolism, synthesis of respiratory chain components, and modulation of cell apoptosis (Abramzon et al., 2020). A similar small number of cases have been associated with mutations in fused-in-sarcoma (*FUS*). In fact, evidence supporting the role of *FUS* mutations in pure FTD is conflicting (Hardy and Rogaeva, 2014; Lysikova et al., 2019). *FUS* encodes the fused in sarcoma protein, which is part of a family of DNA/RNA binding proteins. It has several roles related to RNA metabolism, as well as DNA repair and cellular proliferation (Deng et al., 2014; Ling et al., 2013). Most mutations associated with disease are missense, but insertions and deletions (some of them causing frameshift mutations) have also been reported. About half of these disease-associated mutations are located in the last exon of the gene, which encodes a nuclear localization signal. Many of the remaining mutations are located in an exon encoding for a part of the Gly-rich low-complexity (prion-like) domain, similar to the mutation distribution observed in *TARDBP* (Hardy and Rogaeva, 2014). The pathobiological mechanisms involved in disease may be due to gain of toxic function (overexpression of both the mutant and the normal protein are toxic in animal models) or loss of function (the mutant protein can bind the normal and suppress its and other proteins' function) (Ling et al., 2013).

Other genes rarely responsible for pure FTD cases that are rare causes of ALS or FTD-ALS include *UBQLN2*, *CCNF*, *OPTN*, *DCTN1, TUBA4A*, and *CYLD*. *UBQLN2* encodes ubiquilin 2, a component of the ubiquitin-proteasome system (Deng et al., 2011). The inheritance pattern is X-linked dominant, affecting equally men and women, although men have a significantly lower age at onset (Deng et al., 2011). Most patients develop ALS, but cases with FTD-ALS have been reported (Deng et al., 2011). Mutations are mostly missense but one in-frame deletion variant has also been reported (Renaud et al., 2019). Recently, *CCNF* (which encodes cyclin F) missense mutations have been shown to cause ALS and FTD (Williams et al., 2016a). The identification of mutations was performed initially in a single family, and additional variants were then identified in large international cohorts. It was also shown that expression of mutant *CCNF* in neuronal cells causes abnormal ubiquitination and accumulation of ubiquitinated proteins, including TDP-43 (Williams et al., 2016a). Mutations in *OPTN* were initially described as causing ALS (Maruyama et al., 2010), with loss-of-function as well as missense mutations being identified. Following this, pathogenic mutations in *OPTN* were also found in FTD (Pottier et al., 2015). *OPTN* encodes optineurin, a highly abundant protein, involved in several cellular processes, including the inflammatory response, autophagy, Golgi maintenance and vesicular transport (Toth and Atkin, 2018). *DCTN1* encodes the dynactin subunit p150^{Glued}. Dynactin is a motor protein involved in axonal transport, and the p150^{Glued} subunit has an important role in dynactin's

overall function. *DCTN1* mutations are associated with Perry syndrome, but have also been found to cause ALS, FTD and PSP phenotypes (Konno et al., 2017). *TUBA4A* encodes tubulin alpha 4a, a protein involved in microtubule stabilization. *TUBA4A* mutations have been found at increased frequency in ALS cases, with at least two patients also developing FTD (Smith et al., 2014). Mutations were shown to destabilize the microtubule network, emphasizing the role of the cytoskeleton in ALS. *CYLD* has been recently shown to cause FTD and ALS in one European-Australian family (Dobson-Stone et al., 2020). Only one missense mutation (p.Met719Val) has been documented so far. *CYLD* seems to be involved in inflammatory processes by regulating NF-κB, and in autophagy (Dobson-Stone et al., 2020). It has been previously shown to interact with many other genes associated with the FTD-ALS spectrum, such as *TBK1* (Friedman et al., 2008), *OPTN* (Nagabhushana et al., 2011) and *SQSTM1* (Jin et al., 2008).

In addition to the well-recognized FTD-ALS spectrum, mutations in genes known to cause AD can also be associated with FTD phenotypes. This is the case for some mutations in *PSEN1* and *PSEN2* (Dermaut et al., 2004; Marcon et al., 2009). More recently, variants in *TREM2* have been identified as a significant genetic risk factor for AD (Guerreiro et al., 2013b). The triggering receptor expressed on myeloid cells 2 is a transmembrane glycoprotein innate immune phagocytic receptor expressed on brain microglia that has a key role in regulating the immune response and phagocytic activity in the central nervous system (CNS). Homozygous or compound heterozygous *TREM2* mutations cause polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (or Nasu-Hakola disease) (Paloneva, 2002). Bi-allelic mutations in this gene have also been found in patients presenting a FTD phenotype without bone changes (Guerreiro et al., 2013a). Moreover, a recent meta-analysis of rare *TREM2* variants found that variants p.Arg47His and p.Thr96Lys confer an ~2–3-fold increase in risk for FTD (Su et al., 2018), adding to previous suggestions of a possible role of *TREM2* rare variants in this disease (Carmona et al., 2018; Cuyvers et al., 2014).

2.2.1. Other genes possibly related to FTD—In addition to *TREM2* there are some genes associated with leukodystrophies that have been linked to FTD or FTD phenotypes. *CSF1R*, encoding the colony stimulating factor 1 receptor, was originally linked to autosomal-dominant adult-onset leukoencephalopathy with axonal spheroids and pigmented glia and is highly expressed in microglia (Cuyvers et al., 2014). Some groups have identified patients harboring *CSF1R* mutations with FTD phenotypes (Kim et al., 2018; Swerdlow et al., 2009). *AARS2*, which encodes the mitochondrial alanyl-tRNA synthetase 2, has been reported to cause a leukodystrophy that sometimes has a frontal lobe-type dementia (Dallabona et al., 2014), and recently it was shown to cause FTD in a Korean cohort (Kim et al., 2018). A homozygous mutation in *TMEM106B*, a known FTD risk modifier (see next section for more details), was shown to cause a hypomyelinating leukodystrophy (Simons et al., 2017). Mutations in *PLP1* cause Pelizaeus-Merzbacher disease, a rare X-linked disorder of the CNS, characterized by a hypomyelinating leukodystrophy. It is usually present in female carriers with a mild phenotype of personality changes, gait dysfunction and dementia, resembling FTD. Brain magnetic resonance imaging (MRI) may show diffuse leukodystrophy in these cases (Nance et al., 1996). Lastly, homozygous mutations in *PSAP*

(which encodes prosaposin, a regulator of progranulin) are associated with a fatal lysosomal storage disorder, causing metachromatic leukodystrophy (Kuchar et al., 2009; Nicholson et al., 2016). This is intriguing since white matter hyperintensities (WMH) are often seen on MRI brain scans in FTD due to *GRN* mutations. Whether these changes are related to vascular pathology remains unclear (Sudre et al., 2017).

Other genes have been identified in different conditions that can be related to FTD, although no specific pathogenic mutations have so far been shown to cause FTD. These include mutations in *HNRNPA2B1* and *HNRNPA1*, which are part of the ubiquitously expressed RNA-binding proteins family and known to interact with TDP-43 (Budini et al., 2012). These were initially found as causative in multi-system proteinopathy (Kim et al., 2013a) but, so far, no pathogenic mutations have been identified in FTD (Le Ber et al., 2014; Seelen et al., 2014). In a similar manner, protein kinase CAMP-dependent type I regulatory subunit beta (*PRKAR1B*) mutations have been identified in cases of FUS-negative neuronal intermediate filament inclusion disease, an un-common neurodegenerative disorder that typically presents as early-onset FTD, associated with parkinsonism (Wong et al., 2014).

2.3. Genetic risk factors in FTD

Genome-wide association studies (GWAS) have revealed several genetic loci relevant for sporadic FTD with varying degrees of replication. In order to identify susceptibility loci specific for FTLD-TDP, Van Deerlin and colleagues performed a GWAS in 515 individuals and were able to identify a significant association with chromosome 7p21 region. This locus contains the transmembrane protein 106B (*TMEM106B*), a gene that has now been consistently replicated as an FTD risk factor and disease modifier (Pottier et al., 2018; Van Deerlin et al., 2010). It is involved in dendrite morphogenesis and maintenance by regulating lysosomal trafficking. It may act in disease by inhibiting retrograde transport of lysosomes along dendrites, and has been shown to modify disease onset in *GRN, C9ORF72* and *CHMP2B* mutation carriers, with the risk allele being associated with a decrease of 13 years in the age at onset of *GRN* mutation carriers (Cruchaga et al., 2011; Pottier et al., 2018). More recently, it was also shown to modulate disease in other conditions, such as PD (Tropea et al., 2019) and limbic-predominant age-related TDP-43 encephalopathy (LATE) (Hokkanen et al., 2020). Currently lacking replication and arising from a targeted approach, genetic variants in the myelin associated oligodendrocyte basic protein (*MOBP*) have also been suggested to be clinical modifiers in FTD, after the association of one allele with disease duration (Irwin et al., 2014).

Novel potential risk loci were identified in a two-stage GWAS including 3,526 FTD cases and 9,402 controls: the chromosomes 6p21.3 (*HLA* locus) and 11q14 (*RAB38/CTSC*) regions. Of these, variants in the *HLA* locus encompassing butyrophilin-like 2 (MHC class II associated) (*BTNL2*) and close to the major histocompatibility complex class II *HLA-DRA/HLA-DRB5* showed the most consistent associations when analysing the whole cohort. The *RAB38/CTSC* locus was identified as a potential novel locus for the bvFTD subtype. In this same study a suggestive signal was also observed for the *APOE/TOMM40* locus (Ferrari et al., 2014). Although with inconsistent results, *APOE* has been studied as an FTD risk factor for many years (Verpillat et al., 2002). The ε4 haplotype, the strongest

genetic risk factor for AD, has been shown in several studies to also increase the risk of FTD (Mishra et al., 2017; Su et al., 2017). It is important to highlight the possibility of these significant associations in FTD resulting from the clinical overlap consistently seen in cohorts of clinical AD and FTD cases. Interestingly, both *APOE* and *TOMM40* were identified to be associated with bvFTD when performing a gene based association analysis largely in the same cohort. The same analysis also identified *ARHGAP35* (encoding Rho GTPase-activating protein 35) and *SERPINA1* (encoding alpha-1 anti-trypsin) as modulators of risk of progressive non-fluent PPA FTD (Mishra et al., 2017). More recently a novel risk locus on chromosome 8, encompassing *GFRA2*, was identified in a genome-wide analysis. This was a replicated finding with support from *in vitro* studies that will be interesting to see replicated by other research groups in independent cohorts (Pottier et al., 2018).

Other genes also associated with FTD risk include *UNC13A* and *SORT1*. The first was initially described to modulate ALS survival, and has subsequently been associated with FTD as well (Diekstra et al., 2014; Placek et al., 2019). *UNC13A* encodes Unc-13 Homolog A, a member of a family of presynaptic proteins widespread in the nervous system and involved in the priming of presynaptic vesicles containing neurotransmitters before their release (Diekstra et al., 2014). Sortilin-1 (*SORT1*), a gene previously associated with AD risk, has also been shown to regulate progranulin levels (Carrasquillo et al., 2010). Interestingly, the C-terminus of progranulin is necessary to bind sortilin, a receptor protein that regulates intracellular protein trafficking in the Golgi (Hu et al., 2010).

Some genes known to be involved in polyQ expansion disorders have been associated with FTD. The most relevant of these findings include the identification of intermediary expansions in *ATXN2* as a risk factor for FTD and ALS (Lattante et al., 2014); and the description of a family with an intermediate length expansion of *TBP* (associated with spinocerebellar ataxia-17) presenting as FTD (Olszewska et al., 2019). Further studies clarifying the interactions between polyQ disorders and FTD are warranted, particularly since *ATXN1* intermediate-length expansions have also been associated with ALS (Lattante et al., 2018).

A rare *MAPT* variant (p.Ala152Thr) has been reported to increase the risk of developing FTD. The same variant was also associated with the risk of AD and PSP (Coppola et al., 2012). Common variants near *MAPT* (tagging the H1 haplotype, which is also associated with higher tau expression) have been associated with AD, PD, FTD, and ALS (Desikan et al., 2015; Karch et al., 2018).

Taken together, these associations add further evidence for shared pathways in neurodegenerative dementias, possibly justify, at least in part, the sometimes intermixed clinical phenotypes and pathological characteristics seen in some dementia patients.

2.4. Considerations on the genetic architecture of FTD

Neurodegenerative dementias can be considered as spectrum disorders. FTD, as an example, is a highly heterogeneous disorder, with several distinct phenotypes and different pathological changes underlying disease. It is difficult to find a common feature for all patients in the FTD spectrum. Genetics reflects this heterogeneity: there is a small number of

genes underlying Mendelian disease in a considerable number of cases and a few sporadic patients; and there is an increasing number of mutated genes leading to disease in single families or in a very small number of FTD patients (Fig. 1). However, most of these genes can be assigned to a few pathways, possibly defining an identity molecular skeleton for the disease (Ferrari et al., 2019). Pathological studies suggest aberrant protein inclusions in the cytoplasm and nucleus of neurons and glia hyperproliferation as the major pathological hallmarks of FTD (Mackenzie and Neumann, 2016). A large portion of the genes associated with FTD are involved in cellular waste disposal pathways, leading to accumulation of proteins in the cytoplasm. In parallel, glial hyperproliferation suggests an important role of immune-related processes, with several identified genes having a role in this pathway. It is also interesting to note that, although their deposition is central in FTD, *TARDBP*, *FUS* and *MAPT* do not seem to be associated with these two pathways, suggesting the existence of other dysfunctional molecular processes. *TARDBP* and *FUS* (as well as *HNRNPA2B1* and *HNRNPA1*) are involved in processes that control gene expression and RNA metabolism. The role of *MAPT* in FTD is still not fully understood, with protein aggregation or axonal transport dysfunction having been suggested as potential dysfunctional pathways. In addition to *MAPT*, other genes, namely *TUBA4A* and *DCTN1*, are also involved in axonal transport. Similarly, other pathways have been implicated in the pathogenesis of FTD, namely those sustaining neuronal development and homeostasis, synaptic dysfunction and DNA damage response (Ferrari et al., 2019). *CHCHD10* (and possibly *VCP*) may also implicate mitochondrial dysfunction in disease pathogenesis (Fang et al., 2015). Further refinement of the molecular pathways involved in FTD is needed, which may result from larger GWAS studies, similar to what has been seen in AD.

3. Genetics of dementia with Lewy bodies

Apart from the characteristic dementia, symptoms of DLB include parkinsonism, hallucinations, cognitive fluctuations, and rapid eye movement (REM) sleep behavior disorder (McKeith et al., 2017). Despite being a common disease, accounting for up to 30% of all dementia cases, the genetics of DLB remains largely understudied (Erkkinen et al., 2018). This is probably due, in part, to overlapping phenotypes with other neurodegenerative diseases, particularly PD and AD, and to a frequent coexistence of other pathologies (Robinson et al., 2018). This can lead to high rates of clinical misdiagnosis, which depending on several factors can range from 20 to 50% when comparing the accuracy of clinical diagnoses against autopsy results (Hohl et al., 2000; Rizzo et al., 2018). Evidence is growing for a strong genetic component to DLB, distinct from the genetic profile of other similar diseases. A recent study estimated the heritability of the disease to be about 60% (Guerreiro et al., 2019), and the number of studies implicating new loci is growing.

The strong overlap in phenotypic characteristics with AD and PD is also reflected in the genetics of DLB, with established risk factors *SNCA*, *GBA*, and *APOE*, also being implicated in PD (*SNCA* and *GBA*) and AD (*APOE*). Only these three genes have been consistently replicated in large scale genetic studies of DLB cases, including two recent GWAS (Guerreiro et al., 2018; Rongve et al., 2019).

3.1. Well established DLB genes

SNCA was the first gene implicated in DLB. It encodes α-synuclein, a small neuron-predominant protein, important for synaptic transmission (Benskey et al., 2016). Familial cases with dementia and parkinsonism were found to carry two point mutations, p.Ala53Thr and p.Glu46Lys (Morfis and Cordato, 2006; Singleton et al., 2003; Zarranz et al., 2004). Since this first report, a variety of mutations have been identified in *SNCA* in DLB cases (Table 1), however point mutations and copy number changes in *SNCA* are still rare overall causes of DLB. *SNCA* mutations in families lead to mixed phenotypes, and pathogenic mutations have been implicated in a variety of neurodegenerative diseases (Bougea et al., 2017; Kiely et al., 2013; Markopoulou et al., 2008; Pasanen et al., 2014), with dementia symptoms often being variable.

The *SNCA* locus has also been consistently associated with the risk of developing DLB. The profile of association is different from that observed in PD, with the most associated variants located towards the 5' end of the gene in DLB and towards the 3' end in PD (Bras et al., 2014a), suggesting a different disease mechanism between DLB and PD.

Another PD risk locus, *GBA*, has also been implicated in DLB (Gámez-Valero et al., 2016; Nalls et al., 2013; Shiner et al., 2016). *GBA* encodes glucocerebrosidase, a lysosomal enzyme thought to be responsible for increased protein aggregation and alterations in lipid levels due to lysosomal dysfunction when mutated in Lewy body disorders (Velayati et al., 2010). Mutations in *GBA* have been reported to increase the risk of dementia in PD, and have been shown to be more frequent in DLB cases than PD cases (Meeus et al., 2012). Similarly to the *SNCA* locus, the *GBA* locus has reached genome-wide significance in GWAS of DLB. The variant thought to be driving the association at this locus is the p.Glu365Lys, which is also associated with PD (Berge-Seidl et al., 2017; Blauwendraat et al., 2020). Nonetheless, a variety of other variants within the locus have reported roles in DLB (Bras et al., 2014a; Clark et al., 2009; Gámez-Valero et al., 2016; Goker-Alpan et al., 2006; Nalls et al., 2013; Nishioka et al., 2011; Shiner et al., 2016; Tsuang et al., 2012; Velayati et al., 2010) (Table 1). Some mutations such as p.Glu326Lys, decrease glucocerebrosidase activity. This change is detectable in CSF, making it a potential biomarker (Berge-Seidl et al., 2017). *GBA* has also been associated with earlier age at onset (Gámez-Valero et al., 2016; Nalls et al., 2013; Shiner et al., 2016) and worse cognitive symptoms in PD (Mata et al., 2016).

The ε4 allele of *APOE* is known to be the strongest genetic risk factor for AD. Similarly, statistically significant associations for this locus have been reported for the risk of developing DLB (Guerreiro et al., 2018). However, in DLB it has been a matter of debate if this risk arises from the ε4 allele independent stimulation of α-syn pathology (Dickson et al., 2018; Tsuang et al., 2013), or through the effects on amyloid-β and tau pathologies (similar to what happens in AD) (Irwin et al., 2017). If on one side the detection of an association of *APOE* risk in DLB brains with minimal AD-related pathology supports a dementia mechanism unrelated to amyloid pathology (Tsuang et al., 2013), on the other, the earlier age at onset of the disease as a result of AD pathology accompanying other DLB symptoms seems to support that *APOE* risk in DLB is driven by AD-related co-pathologies (Prokopenko et al., 2019). Although these are not mutually exclusive mechanisms, more

recently, two studies aiming to decipher the effect of *APOE* on α-synuclein using mouse models, reported that *APOE* ε4 increased α-synuclein phosphorylation, worsened motor and memory problems and, consequently, exacerbated neurodegeneration (Davis et al., 2020; Zhao et al., 2020). One of these studies (Davis et al., 2020) also confirmed the protective effect of *APOE* ε2 in DLB. Again, this protective effect had not been conclusively determined before, with conflicting results found in the literature (Singleton et al., 2002), but it is in line with previous results from our group (Fig. 2) (Guerreiro et al., 2015). *APOE* has also been associated with shorter survival span in DLB cases (Geiger et al., 2016; Keogh et al., 2016; Larsson et al., 2018) and has a significant potential as a therapeutic target.

3.2. GWAS in DLB

Additional loci have been associated with risk of disease in the two most recent DLB GWAS studies. In one of these studies, three novel loci reached genome-wide significance, but none were replicated in all stages of the analysis. The *BCL7C/STX1B* locus on chromosome 16 and the *GABRB3* locus on chromosome 15 were replicated in a meta-analysis but were not significant in the replication stage alone. However, both these loci remained significant after excluding all non-pathologically diagnosed samples, perhaps indicating a lack of power for the association. Two more loci were suggestive of an association in the discovery stage, *SOX17* and *CNTN1*. The *SOX17* association did not improve when considering only pathological samples, however the *CNTN1* association improved and maintained a similar effect size in the replication stage, again suggesting the need for a study with improved statistical power (Guerreiro et al., 2018). Another study detected a new locus, *ZFPM1*, which showed a suggestive association, and may have a role in DLB based on a previously detected association with psychosis in AD (Zheng et al., 2015). None of the other suggestive loci in the previous GWAS were replicated.

While large scale genetic analyses are still limited in DLB, a recent paper investigated the potential role of copy number variations (CNVs) in DLB using the same cohort described by Guerreiro et al. (2018). This study detected 5 CNV regions with a significant association to DLB, 2 of which were not present in controls or publicly available databases: a deletion overlapping *LAPTM4B* and another deletion overlapping *SPG9-NME1-NME2*. The other three regions overlapped *MSR1*, *PDZD2*, and *ADGRG7/TFG*. This study also assessed the role of CNVs and genes previously identified to be associated with other neurodegenerative diseases. Five previously associated CNVs and 8 CNVs overlapping neurodegenerative associated genes were detected using this approach (Kun-Rodrigues et al., 2019).

3.3. Other variants in DLB

Given the historical unavailability of large, well-powered DLB datasets, most loci, genes and variants have been implicated in the disease through clinical case studies or using a candidate gene approach. Rare variants identified in a number of genes known to be implicated in other neurodegenerative diseases have been suggested to have a role in DLB. Many of these variants have been detailed in previous reviews (Orme et al., 2018; Outeiro et al., 2019), and are summarized in Table 1. Even though many of these variants are still lacking independent replication confirming their involvement in the disease, it is worth mentioning the potential role of some of these genes and specific variants in DLB.

Very few mutations have been shown to definitely cause DLB. A recent study identified a known pathogenic mutation in *CSF1R* (p.Ile794Thr) in a patient clinically presenting as DLB (Sharma et al., 2019). In fact, *CSF1R* has been previously associated with parkinsonian features, in addition to dementia (Sundal et al., 2013). This extends the clinical presentations known to be associated with *CSF1R* mutations but the co-occurrence of two neuropathological processes (one associating with CSF1R and the other with Lewy body pathology) cannot be excluded. Neuropathological examination of these cases would be helpful in assessing this possibility (Sharma et al., 2019).

Several new, potentially pathogenic, variants have been implicated in a very aggressive, rapidly progressive disorder, clinically similar to CJD. One patient was clinically diagnosed with DLB, but later determined to have CJD. She harbored the p.Val180Ile mutation in *PRNP* (Tomizawa et al., 2020). Another variant in this gene (p.Met232Arg) had been previously reported in a confirmed DLB case. This particular variant led to the initial diagnosis of CJD, but upon autopsy, extensive Lewy pathology in the substantia nigra and cerebral cortices, along with lack of abnormal prion aggregates, kuru plaques, and spongiform degeneration led to the diagnosis of DLB (Koide et al., 2002). Similarly, two *GBA* variants (p.Asp140His and p.Glu326Lys) were reported in one patient, and two heterozygous variants in *SORL1* (p.Asp140Asn and p.Arg1799Gln) have been identified in patients diagnosed with CJD that were later given a neuropathological diagnosis of DLB (Geut et al., 2019). In both instances, patients had a very rapid disease progression.

Other genes with potential roles in DLB are *SNCB* and *EIF4G1*: two variants (p.Val70Met and p.Pro123His) in *SNCB* were suggested to contribute to DLB (Ohtake et al., 2004), and another study implicated *EIF4G1* in two familial DLB cases (Fujioka et al., 2013).

Variants in *PLCG2* were originally associated with a protective effect in the risk of developing AD (Sims et al., 2017). More recently, a similar effect was suggested for DLB (and FTD) (van der Lee et al., 2019), although this is yet to be replicated (Orme et al., 2020).

In addition to these individual case studies, exome sequencing has been performed recently on cohorts of DLB cases. One study analyzed the exomes of 91 pathologically confirmed DLB cases for variants in previously known neurodegenerative genes. In total, likely pathogenic variants were identified in 4.4% of the cases with the identification of 18 rare heterozygous variants, 3 of which were reported as pathogenic (*CHMP2B* p.Ile29Val, *PRKN* p.Arg275Trp and p.Gly430Asp). Overall, the authors suggested that the lack of family history in most DLB cases can be associated with reduced penetrance of DLB-associated variants (Keogh et al., 2016). Additional variants in *PSEN2* (p.Asp439Ala) and *SQSTM1* (p.Ala33Val) were also reported as likely pathogenic for DLB. While *SQSTM1* had been previously detected in FTD (Fecto et al., 2011; Le Ber et al., 2013) and in a case of early onset AD (Cuyvers et al., 2015), *PSEN2* had been previously associated with DLB in another study (Meeus et al., 2012). Four other variants of unknown pathogenicity were also reported in DLB (*EIF4G1* p.Met1134Val, *SQSTM1* p.Pro27Leu, *GIGYF2* p.Ser1029Cys and p.Ser66Thr) (Keogh et al., 2016).

The largest exome analysis to date, looking at 1,118 DLB cases also focused primarily on regions previously associated with neurodegenerative disease. In this analysis a known FTD pathogenic mutation in *GRN* (p.Arg493*) was identified in one case. The authors suggest that either the case was misdiagnosed as DLB or the phenotypes were largely indistinguishable. Rare variants were also detected in other genes, such as *APP*, *CHCHD2*, *DCTN1*, *MAPT*, *NOTCH3*, *SQSTM1*, *TBK1* and *TIA1*. Given the lack of confirmed pathogenic mutations detected in genes known to be associated with other neurodegenerative diseases, the authors suggested a potential role for novel rare variation, not shared with the other diseases included in the analysis (Orme et al., 2020).

3.4. Considerations on the genetic architecture of DLB

Because Mendelian mutations have not yet been found to specifically cause DLB, this disease has been considered to be non-genetic for many years. However, DLB cases have a history of dementia and PD in the family more frequently than controls (Boot et al., 2013; Papapetropoulos et al., 2006), and siblings have 2.3 fold higher risk of developing DLB if one sibling is affected (Nervi et al., 2011). Families including DLB cases present histories of disease that include parkinsonism and other dementias, which may contribute to the small number of DLB families currently described in the literature. Another contributing factor may be the potential involvement of recessive genetic factors in a late onset disease such as DLB, leading to pedigrees with small numbers of affected relatives and to the occurrence of familial cases as apparently sporadic in the population. These factors may also contribute to the fact that the genetic architecture of DLB is currently the least understood of all common dementias with only three GWAS loci currently associated in a replicated fashion with the disease and mutations in one of these loci (*SNCA*) representing the only consistent Mendelian cause of DLB (See Fig. 3.).

4. Genetics of vascular dementia

Vascular dementia is an umbrella term referring to a group of cerebrovascular diseases that lead to cognitive impairment, being the most severe clinical manifestation of vascular cognitive impairment (Gorelick et al., 2011). Different clinical entities are covered under this umbrella term, including rare familial forms such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); and sporadic forms such as those due to cerebral small vessel disease (CSVD), large artery atherosclerosis and cardioembolic stroke. Familial forms of VaD are typically monogenic while sporadic forms can be modulated by several risk factors (Ikram et al., 2017; Sun et al., 2015).

4.1. Mendelian forms of VaD

4.1.1. CADASIL—CADASIL is a monogenic disease that is inherited in an autosomal dominant fashion, although some sporadic cases have also been described (Coto et al., 2006; Joutel et al., 2000; Stojanov et al., 2014). Characteristic symptoms include migraine with aura, recurrent subcortical strokes, gait disturbance, psychiatric disorders, and subcortical dementia due to CSVD (Chabriat et al., 1995). Genetically, CADASIL is caused by mutations in *NOTCH3* (Joutel et al., 1996). The *NOTCH* family is a highly conserved gene group that regulates cell-cell interaction, embryogenesis and tissue commitment. Notch3 is a

large type I transmembrane receptor, that regulates vasculogenesis, CNS neural stem cell maintenance and cell fate determination of CNS multipotent progenitor cells (Liu et al., 2010b; Tanigaki et al., 2001).

The vast majority of *NOTCH3* variants responsible for disease involve conserved cysteine residues, through amino acid change, deletion or splice site mutations located at the epidermal growth factor (EGF)-like repeats domain (Dichgans et al., 2001; Joutel et al., 1997, 1996; Low et al., 2007; Pavlovic et al., 2013; Salloway and Hong, 1998). Mutations in *NOTCH3* are usually heterozygous, but there are also rare descriptions of homozygous variants presenting with symptoms that can be milder, similar, or more severe than the typical phenotypes (Liem et al., 2008; Ragno et al., 2013; Soong et al., 2013; Tuominen et al., 2001; Vinciguerra et al., 2014). Whether cysteine-sparing variants can lead to CADASIL is still controversial, as many variants considered in previous studies are frequent in population databases of genome variability such as gnomAD (Bersano et al., 2012; Brass et al., 2009; Scheid et al., 2008). For a systematic review of these variants see Muiño et al. (Muiño et al., 2017). Recently, the effects of two cysteine-sparing mutations that are not present in gnomAD (p.Gly73Ala and p.Arg75Pro) and one known CADASIL mutation (p.Arg133Cys), were tested in cells and shown to follow the same trend on cell survival, suggesting that mutations not involving cysteines but located in the EGF-like repeats domain might have a role in CADASIL (Huang et al., 2020). Interestingly, loss of function mutations do not appear to cause CADASIL (Rutten et al., 2013).

4.1.2. CARASIL—CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy) is typically a recessive monogenic disease that results from mutations in *HTRA1* and usually presents with symptoms such as alopecia, spondylosis, and cognitive impairment due to CSVD (Hara et al., 2009). Mutations are generally homozygous missense, nonsense or frameshift, although some cases of compound heterozygous missense and frameshift mutations have been reported as well (Bianchi et al., 2014; Cai et al., 2015; Hara et al., 2009; Mendioroz et al., 2010; Xie and Zhang, 2018). More recently, heterozygous mutations in *HTRA1* have also been associated with disease (Verdura et al., 2015). It became apparent that there are two different phenotypes resulting from the pleiotropic effect of *HTRA1* mutation in homozygous or heterozygous state: younger onset small vessel disease (SVD) with systemic manifestations (autosomal recessive), and later age at onset with absence of the typical extra-neurological features (autosomal dominant) (Verdura et al., 2015). HTRA1 binds and inhibits proteins of the transforming growth factor-beta (TGF-β) family. TGF-β proteins normally help control many critical cell functions, including the cells' proliferation and differentiation, cell motility, and apoptosis, and TGF-β signaling is important for angiogenesis (Launay et al., 2008; Zhang et al., 2012).

4.1.3. Fabry disease—Fabry disease is a lysosomal storage disease caused by deficiency of the α-galactosidase A enzyme, which disrupts the glycosphingolipid metabolism inducing stroke and VaD through one or more distinct mechanisms: CSVD, large artery disease and/or cardioembolism. (Nance et al., 2006). It is an X-linked disease caused by mutations in *GLA* (Bernstein et al., 1989) that can be missense, nonsense,

frameshift or splice site, with the latter having major effects in splicing patterns such as exon skipping, cryptic splicing site activation, new splicing site creation, intron retention, and enhancer disruption (Auray-Blais et al., 2008; Fukuhara et al., 1990; Ishii et al., 2002; Lai et al., 2003). Although in hemizygous males the symptomatology is more severe and the disease has a higher incidence, females can also be affected particularly at later ages and with an overall lower frequency in symptoms manifestation, with the exception of cerebrovascular phenotypes which are as frequent as in males (Mehta et al., 2009). In females, the complete inactivation of the *GLA* locus and heterozygous missense variants have been described, leading the disease to have an X-linked dominant pattern of inheritance (Guffon, 2003; Whybra et al., 2001).

4.1.4. Cerebral amyloid angiopathy—Cerebral amyloid angiopathy (CAA) is caused by the preferential and progressive deposition of amyloid-β in the walls of small arterioles and capillaries of the leptomeninges and cerebral cortex leading to lobar intracerebral haemorrhage, superficial siderosis and VaD symptoms (Levy et al., 1990). Missense mutations in *APP* (the first gene where mutations were shown to cause AD) and a deletion of two base pairs in a highly conserved region of the 3' UTR of the gene, have been shown to cause CAA (Levy et al., 1990; Nicolas et al., 2016). Variants in *PSEN1* and *PSEN2* have also been described to cause CAA in AD patients (Dermaut et al., 2001; Mann et al., 2001; Nochlin et al., 1998). Du et al. proposed that *SORL1*, another gene related to AD, causes CAA-related inflammation. However, that finding, based on the identification of p.Lys1634Met, occurred in an *APOE* ε4 homozygous patient and the variant had an appreciable frequency in East Asia, where the patient originated from (Du et al., 2019). Other genes have also been shown to cause rare forms of CAA: stop-loss variants in *ITM2B* cause familial British and Danish dementias (Vidal et al., 1999, 2000); a missense mutation in *CST3* causes the Icelandic type of CAA (Ghiso et al., 1986); mutations in *TTR* cause different forms of amyloidosis, including the transthyretin-type CAA (Petersen et al., 1997; Uchida et al., 1993); nonsense mutations in *PRNP* are associated with *PRNP*-related CAA (Ghetti et al., 1996; Revesz et al., 2009); and missense mutations in *GSN* lead to gelsolin amyloid angiopathy (de la Chapelle et al., 1992; Ghiso et al., 1990).

4.1.5. Other types of Mendelian VaD—It is worth briefly mentioning other genes that have also been associated with familial CSVD. These include *COL4A1* and *COL4A2* where heterozygous missense variants have been shown to cause CSVD with subcortical intracerebral hemorrhages and ischemic lacunar infarcts (Shah et al., 2010; Verbeek et al., 2012). Mutations in *COL4A1* 3'UTR disrupt a miR-29 binding site with subsequent upregulation of COL4A1, causing pontine autosomal dominant microangiopathy with leukoencephalopathy (PADMAL) (Verdura et al., 2016) and multi-infarct dementia of Swedish type (Siitonen et al., 2017).

CARASAL (cathepsin A–related arteriopathy with strokes and leukoencephalopathy) is a recently described hereditary adult-onset CSVD in which the clinical picture seems to be dominated by therapy-resistant hypertension, ischemic and hemorrhagic strokes and late cognitive deterioration. It is an autosomal dominant disease caused by genetic variants in *CTSA*, encoding cathepsin A which functions include the degradation of endothelin-1.

Whether this peptide, a potent vasoconstrictor, plays a role in the pathogenesis of the disease is still unclear (Bugiani et al., 2016).

Heterozygous frameshift variants in *TREX1* cause retinal vasculopathy with cerebral leukodystrophy (Richards et al., 2007). Bi-allelic missense variants in *ADA2* cause an autoinflammatory disease presenting in child- or early-adulthood and manifesting with small vessel vasculitis resulting in ischemic and/or hemorrhagic strokes, or Sneddon syndrome (Bras et al., 2014b; Zhou et al., 2014).

Stroke mechanisms in autosomal dominant *FOXC1* mutations include CSVD and large artery disease (mainly aneurysms of intracranial segment of internal carotid artery) (Søndergaard et al., 2017).

Other Mendelian conditions that may manifest with ischemic stroke and can lead to vascular cognitive impairment are represented in Table 2.

4.2. Sporadic forms of VaD

The majority of genetic studies in sporadic VaD have, so far, used a candidate gene approach. These case-control association studies typically focused on genes either known to be associated with other relevant diseases (such as AD, peripheral or cerebrovascular diseases), or known to be involved in molecular processes important for VaD (e.g.: inflammation or lipid metabolism) (Chapman et al., 1998; Endo et al., 2019). This approach, as it is the case in many other complex diseases, has not identified consistent, replicated associations between variants of interest and VaD. Examples of genes frequently studied in association with VaD but for which results are still inconclusive include: *ACE*, *AGTR1*, *APOA1*, *CLU*, *F5*, *PSEN1*, *SERPINE1*, *SERPINA3*, and *UNC5C* (Chapman et al., 1998; Kim et al., 2006a; Montañola et al., 2016; Nordestgaard et al., 2018; Skrobot et al., 2016; Sun et al., 2015; Wilson and Turnbough Jr, 1990; Yang et al., 2017; Zuliani et al., 2001). *VEGFA* is another candidate gene commonly mentioned as a risk factor for VaD. Its function probably relates to atherosclerosis whereas its expression appears to increase after damage caused by VaD to promote angiogenesis and recovery from neurological damage (Howell et al., 2005; Kim et al., 2006b; Park et al., 2018).

GWAS have also been used to study sporadic VaD but to a much smaller extent when compared with AD, for example, with only three GWAS currently reported in the literature specifically for VaD. Additionally, these studies were largely underpowered (the Dutch GWAS based on the Rotterdam Study included 67 patients, for example) and failed at the replication stage (Kim et al., 2013b; Schrijvers et al., 2012; Woo and Lee, 2012). Therefore, until independent replication is achieved, current GWAS hits for VaD should be treated with caution and perceived as not replicated.

In an attempt to overcome the small size of the individual cohorts in VaD association studies, several meta-analyses have been performed. Sun et al. focused on 69 studies comprising a total of 4,462 cases and 11,583 controls. The authors reported different levels of associations, particularly for *APOE*, *MTHFR*, *PON1*, *TGFB1* and *TNF* (Sun et al., 2015). A similar study suggested an association for *APOE* and *MTHFR*, but not for *PON1* (Skrobot

et al., 2016), highlighting the contradictory nature of many of these reports (Alam et al., 2014; Bednarska-Makaruk et al., 2013; Dantoine et al., 2002; Liu et al., 2010a). On the other hand, there is growing evidence for the risk of VaD being modulated by variants in genes related to inflammation, although so far these associations have not reached genome-wide significance. Nonetheless, quantitative association studies have found *TGFB1*, *TNF*, *IL1B*, and *IL6* serum or CSF levels to be different between VaD and controls (Kim and Lee, 2006; Peila et al., 2007; Pola et al., 2002; Yasutake, 2006; Yucesoy et al., 2006; Zuliani et al., 2007).

4.2.1. VaD GWAS based on associated diseases and endophenotypes—

Additional lines of research have focused on the study of genes and GWAS results identified in related clinical entities, or in intermediate phenotypes. Endophenotypes are usually quantitative and part of disease causal pathway(s). This puts endophenotypes closer to genes when compared to clinical phenotypes, allowing for a greater power in gene discovery studies (Jian and Fornage, 2018). It should be noted that sample selection for association studies based on endophenotypes can be a source of bias if different underlying conditions are related to the endophenotype being tested. This can make interpretation of association signals specific to endophenotypes that show no correlation to association signals related to clinical diagnoses very challenging (Dick et al., 2006). Nonetheless, the use of endophenotypes to understand the genetic basis of several complex diseases has been successful. VaD endophenotypes have been tested for association using GWAS and GWAS meta-analyses approaches, including stroke (Malik et al., 2018; Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, the Stroke Genetics Network (SiGN), and the International Stroke Genetics Consortium (ISGC), 2016; Williams et al., 2016b), ischemic stroke (Malik et al., 2016; NINDS Stroke Genetics Network (SiGN), International Stroke Genetics Consortium (ISGC), 2016), intracerebral hemorrhage (Woo et al., 2014), WMHs burden (Fornage et al., 2011; Opherk et al., 2014; Traylor et al., 2016, 2019), and migraine phenotypes (Freilinger et al., 2012; Gormley et al., 2016). In 2016 a two-stage GWAS including 16,851 stroke cases and 32,473 controls replicated previous findings either in stroke or in subtypes of stroke for the associations of *ALDH2*, *HDAC9*, *PITX2* and *ZFHX3* and risk of disease (NINDS Stroke Genetics Network (SiGN), International Stroke Genetics Consortium (ISGC), 2016). Two years later, a larger GWAS was performed in a cohort of approximately 70,000 stroke patients and 455,000 controls, and identified genome-wide significant associations at 32 loci. Three of these loci overlapped known Mendelian genes (*HTRA1*, *COL4A1* and *COL4A2*), while others confirmed previous findings for *ABO*, *FOXF2, MMP12, PMF1/SEMA4A*, *SH2B3, TSPAN2* and *ZCCHC14* (Malik et al., 2018).

In a recent meta-analysis including 60,000 individuals with migraine and 300,000 controls, 44 independent risk variants mapping to 38 loci were identified as genome-wide significant. Several previously reported loci were replicated, including *HTRA1*, *PRDM16*, *TSPAN2/NGF*, *MEF2D*, *TRPM8/HJURP*, *TGFBR2*, *PHACTR1*, *FHL5/UFL1*, *SUGCT*, *ASTN2*, and *LRP1/STAT6/SDR9C7* (Gormley et al., 2016). Two studies focused on WMHs burden in stroke patients replicated the associations with *COL4A2*, *TRIM65*, *TRIM47*, *EFEMP1* and *PMF1* as well as a novel association for *PLEKHG1* (Traylor et al., 2016, 2019). WMHs

burden has also been specifically studied in CADASIL patients. Although not reaching genome-wide significance, the results suggested that several variants in addition to *NOTCH3* have a role in WMHs in CADASIL (Opherk et al., 2014).

A GWAS study subdivided AD patients by their co-morbid features such as CAA and vascular brain injury (VBI), but none of their hits for both these features were genome-wide significant, with the exception of *APOE* in CAA. Variants in other loci were close to significance in association with CAA, including *HDAC9*, *MCC* and *NCALD*, and with VBI, *AGBL3*, *CIP2A*, *CFAP58*, *PCSK5* and *SEZ6L* (Beecham et al., 2014). More recently, a meta-analysis of association studies focusing on AD endophenotypes reported *CNTNAP2* as a risk factor for the vascular burden in AD, although this result was not genome-wide significant (Moreno-Grau et al., 2019).

4.2.2. APOE in VaD—Over the years *APOE* has been one of the main targets of genetic studies in VaD. Conflicting results can be found in the literature for the effect of *APOE* on VaD as some studies showed ε2 and ε4 were risk alleles through different mechanisms (one promoting hemorrhages and the other promoting amyloid-β accumulation), others showed that only one of the two alleles conferred risk, and others that *APOE* had no effect on risk of VaD (Engelborghs et al., 2003; Frank et al., 2002; McCarron and Nicoll, 2000; Nicoll et al., 1996; Nicoll and McCarron, 2001; Rannikmäe et al., 2014; Yamada et al., 1996). Several reasons have been suggested to underlie these conflicting results, including the study of small sample sizes, diverse populations (*APOE* haplotypes are known to have very significant differences in the risk of AD across populations) or the study of VaD as a homogeneous clinical entity. Related to the latter, grouping VaD types with different etiologies might be masking the ε2 effect on hemorrhages, since this effect has been consistently shown for sporadic CAA (Charidimou et al., 2019; McCarron and Nicoll, 1998; Nicoll et al., 1997). Thal et al. have actually proposed to separate CAA in two types: type 1 with a high *APOE* ε4 frequency and type 2 with a high frequency of ε2, and they saw that both types have the same disease severity when compared to controls (Thal et al., 2002). When endophenotypes, such as stroke subtypes, are taken into account to assess allelic risk, the same pattern is observed, where ε2 promotes hemorrhages and ε4 promotes amyloid-β accumulation (Sudlow et al., 2006). Some have suggested that the ε4 allele is only associated with an earlier onset of disease and not with disease severity both in CAA and stroke (Greenberg et al., 1996; Lagging et al., 2019).

Independently of the molecular mechanism involved in disease, the current burden of proof clearly indicates a significant role of *APOE* genetic variability in the risk of developing VaD, which has been corroborated by different meta-analyses (Skrobot et al., 2016; Sun et al., 2015).

4.3. Considerations on the genetic architecture of VaD

VaD is often considered a different condition when compared with the other dementias described here. It is regarded more as a sporadic, ‘environment-associated’, and non-degenerative type, mostly linked to traditional vascular risk factors. It encompasses a range of distinct diseases which have an end result of cognitive impairment. The heterogeneity of

the group makes it difficult to investigate underlying causes, although some genes are starting to be consistently replicated across studies. Interestingly, GWAS identified some loci containing the same genes that had been previously associated with disease using candidate gene approaches. In addition, some forms of VaD genetic disorders imply that continuous degenerative mechanisms underlie at least some forms of the disease. The involvement of *APOE* and inflammation-associated genes in the genetic architecture of VaD suggests that immune dysfunction is contributing to the condition, as seen in neurodegenerative disorders. The involvement of *ADA2*, *TGFB1*, *TNF*, *IL1B* and *IL6* adds further support to this. Consistent with the association of the disease with vessel dysfunction, many of the genes known to have a role in VaD are related with vessel development or functioning (*NOTCH3*, *HTRA1*, *COL4A1*, *COL4A2*, *FOXC1*, *VEGFA*, *AGT*, *FVL*). However, for some other genes their functional role in the disease is currently not clear and may implicate additional mechanisms of disease (*TREX1*, *GLA*, *MTHFR*). Together, this evidence suggests a continuous dysfunction at the vascular and immune levels, challenging the notion of a more static or stepwise disorder (Fig. 4).

5. Discussion

Even though Mendelian forms of dementia are rare, family history is a frequent occurrence in dementia and sporadic cases are now known to have a significant genetic component. Given that dementia is a common disorder, it is important to fully understand the genetic architecture of this group of diseases (Loy et al., 2014).

In a familial setting the identification of genetic causal factors is essential for risk estimation. Even in the absence of effective therapies to prevent or delay dementias, knowing an individual's genetic risk gives the opportunity for genetic counseling, informed preparation of life affairs (including reproductive options), and may contribute to achieve a more accurate in-life diagnosis (Cohn-Hokke et al., 2012).

Genetic information also has an important role in sporadic disease. It can be used to establish polygenic risk scores and can critically inform the selection of cohorts for enrollment in clinical trials as well as in the evaluation of the response to treatment (Berkowitz et al., 2018). Genetic studies of both familial and sporadic disease have been essential to understand the molecular mechanisms of disease and to the development of successful drugs (Nelson et al., 2015).

In order to use genetics in an effective way in these different scenarios it is important to have a complete knowledge and understanding of all genetic factors involved in each dementia. One important aspect to consider in this context is the many overlaps occurring across dementias.

5.1. Overlaps between dementias

Correlations between pathological and clinical aspects of dementias have never been perfect. As genetic changes are upstream of both pathology and clinical features, genetic knowledge has established important foundations on which to build our understanding of these diseases. Hence, disease classification is increasingly being based on underlying genetic defects or

focusing on disease-specific molecular pathways (Iourov et al., 2019). This happens, however, not without challenges. The genetic overlap between different forms of dementia (and other diseases) has been increasingly apparent with the application of modern genetic technologies to the study of familial and sporadic dementias (Guerreiro et al., 2014). Not only the same genes can be associated with clinically and pathologically different diseases, but the proteins abnormally aggregating in these diseases can also be the same.

A common overlap occurs between AD and other dementias, having the potential to significantly complicate the clinical differential diagnosis of dementias. Several studies have examined the accuracy of clinical diagnoses of AD based on autopsy results (considered the “gold standard”). One of these studies used data collected as part of the National Alzheimer’s Coordinating Center Uniform Data Set between 2005 and 2010 to identify 88 participants misdiagnosed with AD and 438 participants accurately diagnosed with AD (Lim et al., 1999). Sensitivity and specificity of clinical diagnoses of AD were found to range between 70–87% and 44–71%, respectively (Beach et al., 2012) In general, between 12% and 23% of clinically diagnosed AD cases do not have sufficient pathology at autopsy to account for the presence of dementia. The most common misdiagnoses occurs with other forms of progressive dementias such as FTD, DLB and VaD (Gaugler et al., 2013) with Lewy body disease and cerebrovascular injury being the most common AD mimics (Shim et al., 2013). Misdiagnoses can have direct and significant impacts in patients and families. These can lead to wrong/unnecessary treatments and to poor clinical management. A number of medications have been identified as potentially unnecessary for patients with FTD (Kerchner et al., 2011) and DLB (Baskys, 2004), whereas patients with cerebrovascular disease will typically benefit from treatments with statins, antiplatelet agents and anticoagulants. Misdiagnoses can also have an impact on the selection of subjects for genetic studies and clinical trials.

It is worth mentioning that the different degrees of diagnostic accuracy may be dependent of factors such as 1) the cohort being studied (differences have been seen between community and clinical-based case series), 2) the diagnostic criteria used (more recent diagnostic criteria have a tendency to perform better as these are typically developed to address shortcomings of sensitivity and/or specificity of previous criteria), 3) the use of imaging or biomarker tests, and 4) the levels of expertise of the diagnosticians (even among experts, the diagnostic accuracy of clinical AD was found to be variable (Sabbagh et al., 2017)).

While there is a significant amount of evidence suggesting that cerebrovascular and AD pathologies exert an additive, synergistic effect on cognitive impairment, less is known about the impact of cerebrovascular disease in DLB and FTD. Autopsy studies revealed a frequency of 20–34% of cerebrovascular disease (CVD) in DLB (which is not significantly different from controls) (Jellinger, 2003) and that more advanced Lewy body pathology is less likely to show severe CVD, suggesting that cognitive impairment in DLB is independent of vascular disease (Ghebremedhin et al., 2010). In FTD, data on CVD is contradictory with some studies finding a role for SVD in FTD progression (Thal et al., 2015) and others not confirming this (Toledo et al., 2013). Diverging frequencies of CVD in FTD have also been found, ranging from 5% in FTD-tau to 17% in FTD-TDP (Toledo et al., 2013).

Mixed pathologies are common in the brains of elderly individuals and their prevalence and severity increases with advancing age (Jellinger and Attems, 2010). In fact, these are so common that Visanji and colleagues recently proposed the term “concomitant pathology” instead of “co-pathology” to reflect the important contributions of each aberrantly deposited protein in the neurodegenerative process (Visanji et al., 2019).

Genetic pleiotropy (where one genetic locus contributes variance to different phenotypes) is also a common feature of dementias and neurodegenerative diseases in general. The contribution of pleiotropy can be appreciated across the different forms of genetic burden of disease. This has been evident from several GWAS finding common risk loci between different neurodegenerative diseases (Ferrari et al., 2017; Yokoyama et al., 2016), but also from low frequency and very rare variants. Many of these have been mentioned in the genetics of FTD, DLB and VaD sections.

5.2. APOE as a pleiotropic gene

One gene that has been mentioned multiple times across the different dementias discussed here is *APOE*. Common risk alleles with strong effects are mainly associated with AD risk, but associations have also been found for the risk of development of DLB (Guerreiro et al., 2018) and, potentially, FTD (Ferrari et al., 2017) and for the age at onset in *C9ORF72* repeat expansion carriers (van Blitterswijk et al., 2014). In addition to its role in different dementias, *APOE* has also been implicated in other diseases. It is one of the two loci most consistently associated with longevity (Shadyab and LaCroix, 2015). Its associations with cardiovascular diseases are also well replicated. *APOE* ε4 carriers have a 30% higher risk of ischemic stroke (Wei et al., 2017) and *APOE* genotypes are significantly associated with the risk of developing coronary artery disease and myocardial infarction (Wang et al., 2015; Xu et al., 2016). The risk conferred by *APOE* for the development of these diseases is undeniably linked to the strong correlation between *APOE* genotypes and the plasma levels of high- and low-density lipoprotein cholesterol, as well as triglycerides. However, this strong correlation makes it difficult to fully dissect if the risk is always mediated by changes in cholesterol levels or a proportion of risk can be independent of these changes (Corsetti et al., 2012; Rasmussen et al., 2016).

APOE is a truly pleomorphic gene: the recent analysis of the structure of genetic pleiotropy in the UK biobank hospital data has shown that 96.9% of the associated variants analysed affect more than one diagnostic term. The top 3 most pleomorphic variants identified in this study included a variant in the *APOE* locus (rs4420638) (Cortes et al., 2020). Making use of these data to analyse the two SNPs involved in the *APOE* ε2 ε3 ε4 haplotypes (rs429358 and rs7412) we can easily see evidence for association with increased or decreased risk of many different phenotypes in the UK Biobank (Fig. 5). These analyses capture the known impact of these variants by finding the strong associations with AD and cardiovascular disease, and suggest potential interactions with unexpected diseases, such as the protective effect seen for diseases of the digestive system conferred by rs429358. Given the relatively small number of UK Biobank participants with other dementias, currently this dataset does not have enough resolution to assess the effect of *APOE* in specific dementias like FTD or

DLB. It is however a dataset that clearly allows the depiction of the broad and complex range of effects in different phenotypes.

6. Conclusion

On one hand the sharing of genes, proteins and molecular pathways between dementias and diseases in general can complicate the diagnosis not only by leading to similar clinical phenotypes and neuropathological features, but also by creating a challenging framework for the development of specific biomarkers. On the other hand, the identification of common genetic and molecular factors between dementias can help us understand these diseases and can lead to the possibility of using these common points as targets for the development of drugs that ultimately will have an effect on more than one dementia.

Notwithstanding the fact that very significant advances have been made in the last decade in the identification of disease associated variants, the genetic architecture of non-AD dementias is still far from being complete. Future studies attempting to identify the missing pieces of these architectures should apply next generation genomic technologies to the study of families and statistically well powered cohorts of deeply phenotyped cases and controls. Given the extension of genetic, pathological and clinical overlaps of neurodegenerative dementias, a potential alternative avenue of research is to investigate in a given phenotype the relevance of genes and genetic factors known to be involved in a different disease. The application of next generation genomic technologies can facilitate this approach by testing full genomes instead of candidate genes or genetic regions. In addition to ever increasing numbers of samples studied by GWAS, approaches based on endophenotypes and on the integration of functional data can have very positive results (Moreno-Grau et al., 2019).

In summary, replication of recently identified genetic regions and implication of more novel loci will be essential to better characterize the genetic architectures of these diseases. Advancing our understanding of the genetic factors driving concomitant proteinopathies is crucial for the development of disease-modifying interventions. These may be unique to each clinical entity, or, as suggested by the many overlaps and connecting points between the dementias described here, may be based on shared common therapeutic targets, raising the possibility of the development of single therapies providing disease modifying benefits that are horizontal to dementias or even neurodegenerative diseases.

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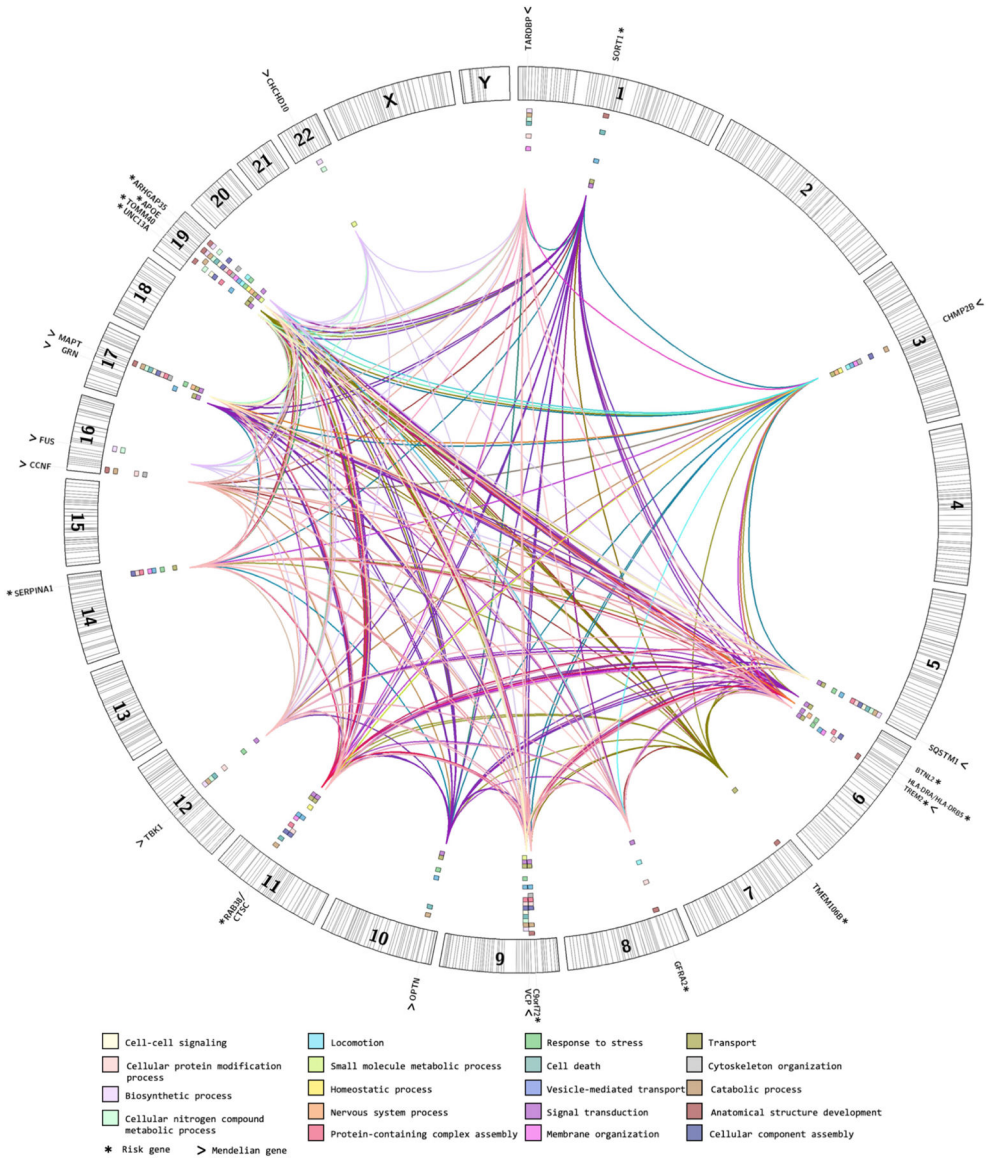

Fig. 1.

Genetic architecture of FTD.

Circos plot of Mendelian and risk genes with confirmed roles in FTD. The links between genes and the colored outer layer correspond to biological processes annotated from Gene Ontology terms as obtained from GOSlim (https://go.princeton.edu/cgi-bin/GOTermMapper) which prioritizes annotations based on a previously curated subset of GO terms. The terms shown here annotate genes in all three dementias to better highlight the functional differences between these diseases. Here we can see genes in FTD are well dispersed throughout the genome and have roles in a wide range of functions, with many of these genes having annotations in a variety of biological processes.

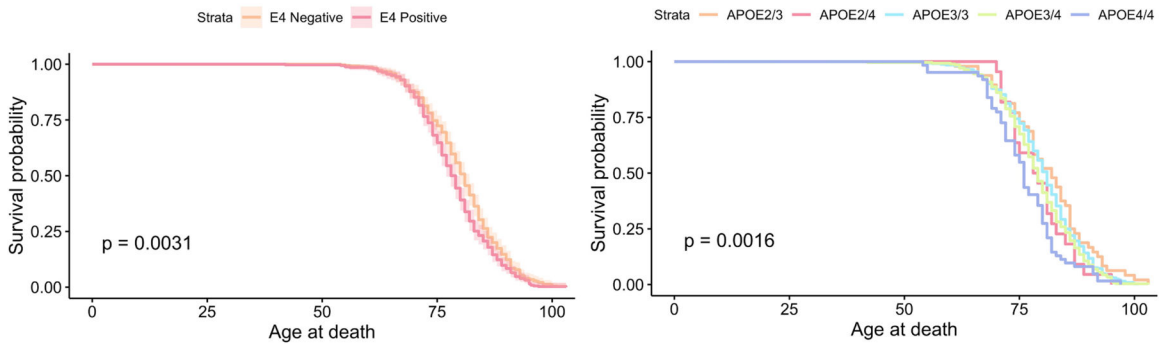

Fig. 2.

Survival analyses of age at death by means of Kaplan–Meier curves for *APOE* in an international cohort of 679 DLB cases.

On the left, the effect on age at death of the presence/absence of the *APOE* ε4 allele is shown. The analysis showed a significant difference in the ages at death between carriers and non-carriers of the *APOE* ε4 risk allele. On the right panel the effect on age at death of the different *APOE* haplotypes was found to be significantly different groups.

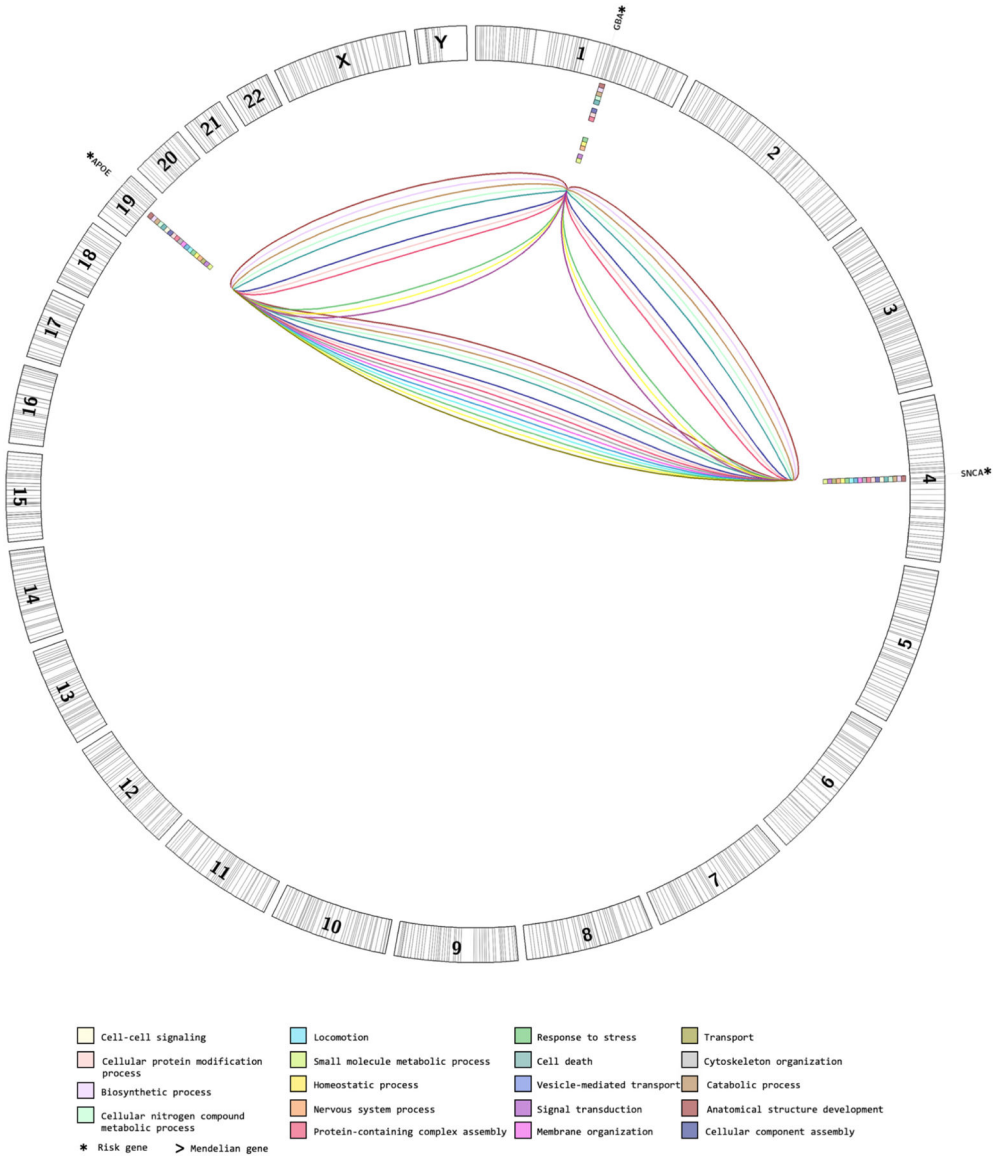

Fig. 3.

Genetic architecture of DLB.

Circos plot of genes with established roles in DLB. As in the FTD circos plot, links and colored outer layer represent GOSlim biological processes which are shared by all three dementias. While the number of genes with conclusive roles in DLB are much fewer than other dementias, these genes are involved in a wide variety of biological functions.

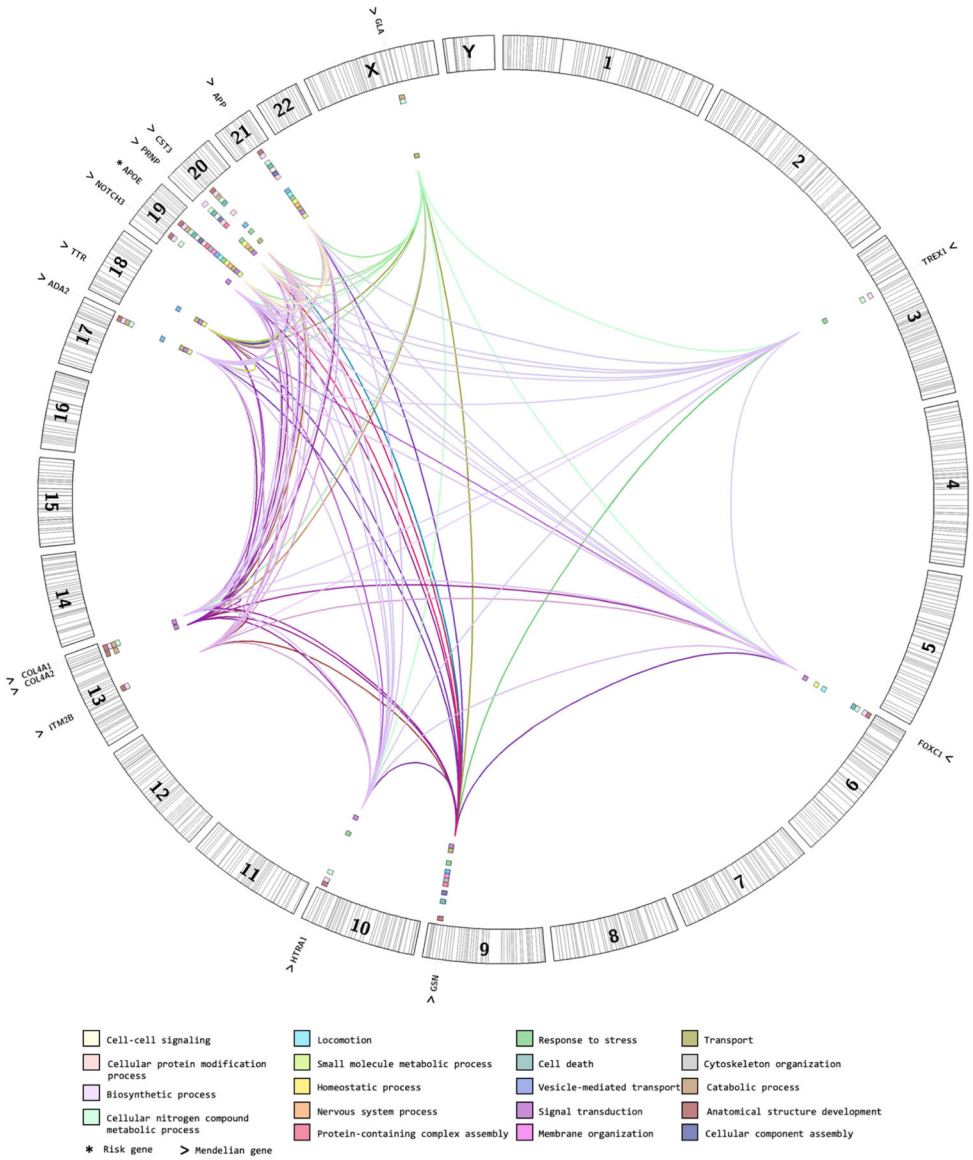

Fig. 4.

Genetic architecture of VaD.

Circos plot of established VaD genes. Links and colored outer layer were obtained from biological process Gene Ontology annotations shared by all three dementias as described in Fig. 1. Given the burden of proof for genetic risk associations with the different genes studied in VaD we only considered *APOE* to be represented here. All other genes are Mendelian causes of hereditary vasculopathies which typically cause arteriopathy and microvascular disease leading to vascular cognitive impairment and dementia.

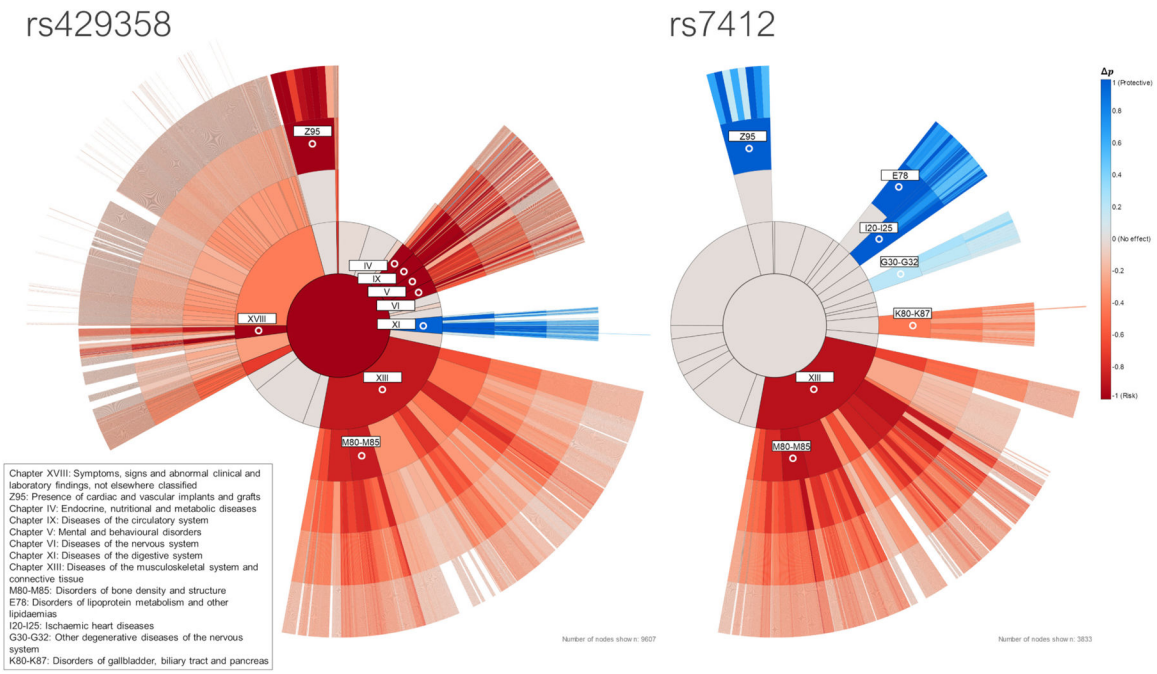

Fig. 5.

Posterior decoding of genetic effect direction and strength of evidence for the rs429358 (*APOE* ε4) and rs7412 (*APOE* ε2) variants in *APOE*.

In this figure the International Classification of Diseases, tenth revision (ICD-10) is depicted as a radial tree where the first orbit represents the 22 ICD-10 chapters, followed by an orbit representing blocks of categories, and then by 2 consecutive orbits representing the ICD-10 categories including the observed annotation codes. This TreeWAS (https://treewas.org) refers to a Bayesian approach for mapping genetic risk across disease classification codes within a hierarchical ontology (Cortes et al., 2017). Each genetic variant in the TreeWAS Database was analysed to infer its association with a given diagnostic term. These terms are structured hierarchically, where a given term (ICD-10 clinical code) is nested within a broader disease/disorder category. Here, this tree structure is displayed with the “top node” or “root” as a circle in the middle and nested terms subtend from the root or their parent terms outwards. Each node is colored according to its dominant effect; protective (blue), risk (red), or no effect (gray) posterior probability, computed as $\Delta p = p(protective) - p(risk)$. The analyses represented here relate to hospitalization episode statistics provided by the UK Biobank as a source of phenotypic data and is derived from linkage with the hospital episode statistics registry (UK Biobank data fields 41142 and 41078).

Table 1

Genes and variants linked to DLB.

Gene	Reference	Proposed reported type of effect in disease	Replicated	Variants
SNCA	Guerreiro et al. (2018)	GWAS risk and Mendelian	Yes	p.Ala53Thr, p.Glu46Lys, rs7681440
GBA	Nalls et al. (2013)	GWAS risk	Yes	p.Asp448His, p.Asn409Ser, p.Glu365Lys, p.Arg296Gln, p.Arg87Gln, rs35749011, p.Glu326Lys, p.Asp140His
APOE	Tsuang et al. (2013)	GWAS risk	Yes	p.Arg176Cys, p.Cys130Arg, rs429358
CHMP2B	Keogh et al. (2016)	Dominant Mendelian	No	p.Ile29Val
PRKN	Keogh et al. (2016)	Recessive Mendelian	No	p.Arg275Trp, p.Gly430Asp
EIF4G1	Keogh et al. (2016)	Dominant Mendelian	No	p.Met1134Val, p.Gly686Cys, p.Ala502Val
PRNP	Koide et al. (2002)	Sporadic case, incomplete penetrance	No	p.Met232Arg
SORL1	Geut et al. (2019)	Dominant Mendelian	No	p.Asp140Asn, p.Arg1799Gln
CSF1R	Sharma et al. (2019)	Dominant Mendelian	No	p.Ile794Thr
PSEN2	Keogh et al. (2016)	Dominant Mendelian	No	p.Asp439Ala
SQSTM1	Keogh et al. (2016)	Dominant Mendelian	No	p.Ala33Val, p.Pro27Leu, p.Met404Val
GIGYF2	Keogh et al. (2016)	Dominant Mendelian	No	p.Ser1029Cys, p.Ser66Thr
APP	Orme et al. (2020)	Rare, potentially pathogenic	No	p.Val717Ile, p.Glu599Lys, p.Glu674Lys
CHCHD2	Orme et al. (2020)	Rare, potentially pathogenic	No	p.Gly4Arg
DCTN1	Orme et al. (2020)	Rare, potentially pathogenic	No	p.Ile780Thr
GRN	Orme et al. (2020)	Nonsense: rare, potentially pathogenic (pathogenic in FTD) Missense: rare, potentially pathogenic	No	p.Arg493*, p.Ala276Val
MAPT	Orme et al. (2020)	Rare, potentially pathogenic	No	p.Gly86Ser
NOTCH3	Orme et al. (2020)	Rare, potentially pathogenic	No	p.Arg578Cys, p.Arg578His, p.Arg607His
TBK1	Orme et al. (2020)	Rare, potentially pathogenic	No	p.Arg384Trp, p.Arg384Gln
TIA1	Orme et al. (2020)	Rare, potentially pathogenic	No	p.Pro362Leu
CNTN1	Guerreiro et al. (2018)	Suggestive GWAS risk	No	rs7314908
GABRB3	Guerreiro et al. (2018)	Suggestive GWAS risk	No	rs1426210
BCL7C/STX1B	Guerreiro et al. (2018)	Suggestive GWAS risk	No	rs897984
ASH1L	Rongve et al. (2019)	GWAS risk	No	rs12734374
SCARB2	Bras et al. (2014a)	Suggestive GWAS risk	No	rs6812193
ZFPM1	Rongve et al. (2019)	Suggestive GWAS risk	No	rs12926163
PSEN1	Geiger et al. (2016)	Sporadic, incomplete penetrance, present in estimated 10% of cohort, likely risk	No	p.Glu318Gly, p.Gly206Ala

Gene	Reference	Proposed reported type of effect in disease	Replicated	Variants
SNCB	Ohtake et al. (2004)	Dominant with incomplete penetrance or risk	No	p.Val70Met, p.Pro123His

Table 2

Mendelian conditions that may manifest with ischemic stroke and can lead to vascular cognitive impairment.

Mendelian condition	Gene	Inheritance pattern	Features	Reference
Marfan's syndrome	*FBN1*	Autosomal dominant	Inherited in an autosomal dominant pattern. The stroke mechanisms implicated are large arterial dissection or cardioembolism.	(Maski et al., 2011)
Vascular Ehlers-Danlos syndrome	*COL3A1*	Autosomal dominant	Usually causes stroke by arterial dissection	(Superti-Furga et al., 1988)
Pseudoxanthoma elasticum	*ABCC6*	Autosomal recessive	Patients may develop small as well as large artery disease	(Chassaing et al., 2005)
Homocystinuria	*CBS*	Autosomal recessive	Small and large artery disease, cardioembolism or arterial dissection have been implicated in stroke and vascular cognitive dysfunction	(Kelly et al., 2003)
Sickle-cell disease	*HBB*	Autosomal recessive	Progressive stenosis or occlusion of large/medium size intracranial arteries	(Armstrong et al., 1996)

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