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Molecular Genetics of Neurodegenerative Dementias

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Neurodegenerative dementias are clinically heterogeneous, progressive diseases with frequently overlapping symptoms, such as cognitive impairments and behavior and movement deficits. Although a majority of cases appear to be sporadic, there is a large genetic component that has yet to be fully explained. Here, we review the recent genetic and genomic findings pertaining to Alzheimer's disease, frontotemporal dementia, Lewy body dementia, and prion dementia. In this review, we describe causal and susceptibility genes identified for these dementias and discuss recent research pertaining to the molecular function of these genes. Of particular interest, there is a large overlap in clinical phenotypes, genes, and/or aggregating protein products involved in these diseases, as well as frequent comorbid presentation, indicating that these dementias may represent a continuum of syndromes rather than individual diseases.

Neurodegenerative dementias are clinically heterogeneous, progressive diseases with frequently overlapping symptoms, such as cognitive impairments and behavior and movement deficits. This spectrum of disease includes vascular dementia (VaD), Lewy body dementia (LBD), Alzheimer's disease (AD), frontotemporal dementia (FTD), and prion dementias (Fig. 1). Recent estimates indicate that 5.9%–9.4% of people >65 years of age suffer from dementia, with approximately 44 million affected worldwide (Prince et al. 2014). Moreover, as a result of our aging population, the number of people affected with dementia is expected to double roughly every 20 years. Of these dementias, AD is by far the most frequent, comprising 50%–75% of all cases (Fig. 1) (Prince et al. 2014).

Over the last few decades, substantial progress has been made in understanding the molecular genetics of neurodegenerative dementias and identifying the pathologically aggregating proteins involved. In large part, this can be attributed to advances in sequencing techniques and bioinformatic analysis approaches. Beginning in the early 1990s with the identification of microsatellites (also known as short tandem repeats) and single nucleotide

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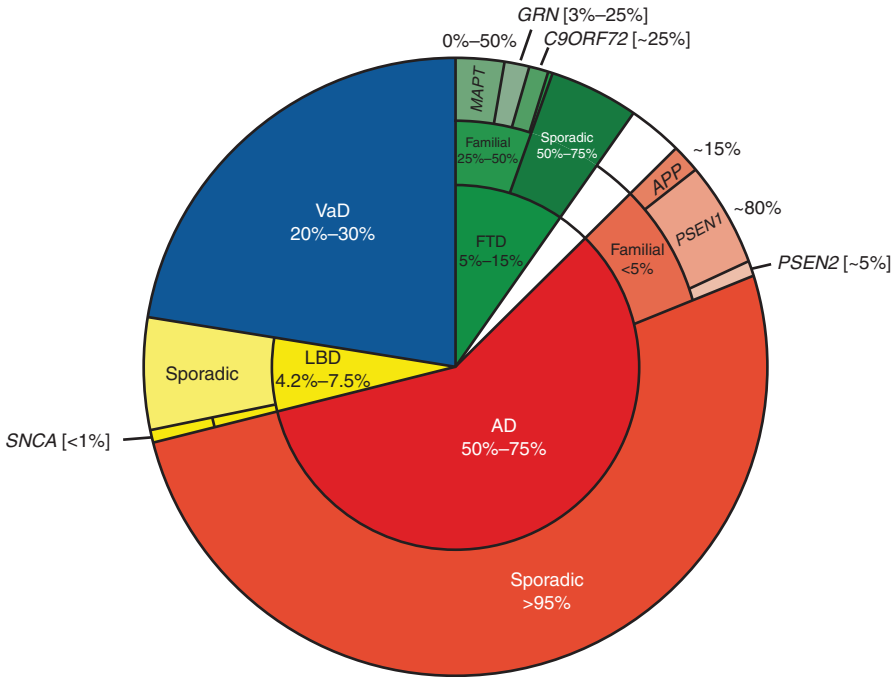

Figure 1. Frequency of specific neurodegenerative dementias. The *inner* circle shows the frequency of specific neurodegenerative dementias (indicated by different colors) as an approximate percentage of all cases of disease. The *middle* circle shows the percentage of patients that show familial or sporadic patterns of inheritance for each disease. The *outer* circle depicts the approximate percent of patients with familial inheritance patterns that harbor mutations in specific known causal genes.

polymorphisms (SNPs), researchers began to apply an approach termed linkage analysis. This technique makes use of these genomic markers to identify chromosomal regions shared by affected family members in large families with apparent dominant transmission. The assumption is that the pathogenic mutation lies within this shared chromosomal region, which carries disease risk, as it segregates with the disease in the family. Linkage analysis led to the rapid identification of a number of highly penetrant disease-causing mutations (Kerem et al. 1989; MacDonald et al. 1993; Hästbacka et al. 1994; Feder et al. 1996; Poorkaj et al. 1998; Amir et al. 1999).

However, only a small subset (~5%) of neurodegenerative dementia cases show a pattern of autosomal dominant inheritance, whereas most cases appear to be sporadic. Early on, using genetic approaches such as linkage analysis, the majority of disease genes involved in these familial, often early-onset cases were discovered. More recently, genome-wide association studies (GWAS) have been applied to identify a multitude of risk variants (mutations with low penetrance) in idiopathic dementia. This new approach was enabled by the development of comprehensive genome-wide arrays, allowing for the simultaneous evaluation of millions of SNPs in thousands of samples in a cost-effective manner. GWAS, by comparing the SNPs of millions of patients to SNPs from millions of unaffected controls, are used to identify genetic variants that are common in the population but modulate the risk of disease. Recently, GWAS and, subsequently, meta-analyses of GWAS, which pool samples from multiple studies to increase statistical power, have led to the identification of hundreds of mutations in so-called susceptibility genes, most with very

small effect sizes (odds ratios usually <2; for review, see Visscher et al. 2012). Although the effect size of these variants is not large enough to inform disease prediction, these loci may shed light on novel genes and molecular pathways dysregulated in disease. However, it is important to keep in mind that GWAS use SNPs as proxies for tagging chromosomal regions. Thus, this type of analysis can determine that a specific SNP or genomic locus is associated with disease risk, but does not necessarily mean that a particular SNP functionally contributes to disease risk or which gene in a genomic locus may be associated with the pathology.

In the past few years, with the cost of sequencing dropping and bioinformatics technology advancing, next-generation sequencing (NGS) approaches are becoming more commonly used. Rather than limiting sequencing to a gene or a small region of the chromosome, it is now possible to sequence the entire genome (whole-genome sequencing, WGS) or only the gene-coding regions, the exons (whole-exome sequencing, WES) (Ng et al. 2009). WES, as a result of focusing on only ~2% of the genome, is still considerably cheaper, and the analytical processing power, as well as the storage space required to handle the data produced, is more feasible to acquire for individual laboratories (Singleton 2011; Wang et al. 2013). Importantly, these NGS approaches allow for the direct identification of rare variants in disease, without prior linkage or GWAS. As compared to WES, WGS has the advantage of better coverage of the exome, owing in part to longer reads and more consistent read depth. Furthermore, WGS can be used to investigate regulatory variants, which are increasingly thought to play a significant role in the cause of and risk for neurodegenerative disease (Wang et al. 2013).

Despite these advances, much of the genetic contribution to the heritable liability of most sporadic forms of dementia has yet to be explained. Here, we review the recent genetic and genomic findings in studies of neurodegenerative dementias that involve abnormal protein aggregation and discuss the idea that these diseases may represent a continuum of disorders rather than individual diseases.

ALZHEIMER'S DISEASE

By far the most common form of age-related dementia, AD is clinically heterogeneous and slowly progressive, characterized by a gradual decline in memory and other cognitive functions (such as anomia, agnosia, and apraxia), depression, and apathy (www.alz.org/research/diagnostic_criteria). The brain regions most affected by neurodegeneration are the cortex, hippocampus, amygdala, basal forebrain, and brainstem (Rademakers and Rovelet-Lecrux 2009). Progressive atrophy in these regions is preceded by the accumulation of extracellular β-amyloid plaques formed by cleavage products of amyloid precursor protein (APP) and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated microtubule binding protein tau (MAPT). Plaques and tangles have been shown to interfere with calcium signaling and synaptic transmission, to induce a persistent inflammatory response, and to lead to synapse loss and ultimately neuronal degeneration. The presence of NFTs is strongly correlated with neuronal dysfunction and disease progression (for reviews of AD pathology, see Braak and Braak 1997, 1998; Serrano-Pozo et al. 2011).

AD is classified as early onset (before 65 years of age) versus late onset (after 65). Less than 10% of cases are early onset, and these usually follow an autosomal dominant inheritance pattern in which mutations in a single gene can cause the disease. Late-onset AD is much more common and far more genetically complex, possibly involving concurrent mutations in multiple genes and interactions among these susceptibility genes with each other, as well as unknown environmental factors. Although late-onset AD is largely idiopathic, there is still a significant genetic contribution to susceptibility, with twin studies predicting heritability of 60%–80% (Gatz et al. 2006).

Genes in Which Disease-Causing Mutations Have Been Identified

In early-onset AD, three different causal genes have been identified via linkage analysis (Table

1). The amyloid precursor protein gene (*APP*), located at chromosome 21q21, encodes the ubiquitously expressed transmembrane protein APP. APP is cleaved via the subsequent action of two proteases, β-secretase and γ-secretase, to release Aβ-peptides (Thinakaran and Koo 2008). Depending on the specific site of cleavage, peptides of either 40 (Aβ40) or 42 (Aβ42) amino acids are produced. Aβ42 has been shown to be more prone to aggregate into pathogenic amyloid plaques than Aβ40. More than 30 different mutations have been described in APP (www.molgen.vib-ua.be/ADMutations). Most of these mutations are heterozygous missense mutations in or near exons 16 and 17 (the site of proteolytic processing by the secretases), whole-gene duplications, rare recessive small deletions, and recessive missense mutations (reviewed in Guerreiro et al. 2012; Karch et al. 2014). These mutations most frequently result in either altered Aβ production, changes in the ratios of Aβ42 to Aβ40, and/or increased NFT formation. Interestingly, a protective variant (A676T) in *APP* has recently been identified for AD in the Icelandic population (Jonsson et al. 2012). This variant is located adjacent to the β-secretase cleavage site and has been shown to reduce β-secretase-1-mediated formation of Aβ peptides. This reduction in Aβ production is thought to modulate neurodegeneration in A676T carriers and is proposed to mediate the protective effect.

The majority of mutations causing early-onset AD are found in the presenilin 1 (*PSEN1*) gene, located at chromosome 14q24.3, and in its homolog presenilin 2 (*PSEN2*), located at chromosome 1q31. More than 180 dominant, pathogenic mutations have been identified in *PSEN1*, whereas approximately 13 dominant, pathogenic mutations have been identified in *PSEN2* (www.molgen.vib-ua.be/ADMutations). These mutations are distributed throughout the two proteins, but the mutations have a tendency to cluster in the transmembrane portions of both proteins. Interestingly, *PSEN1* and *PSEN2* encode structurally similar, integral membrane proteins that are essential components of the γ-secretase complex, which cleaves APP into Aβ peptides (Wilquet and De Strooper 2004). The finding that all three causative genes are involved in the production of Aβ peptides led to the "amyloid cascase hypothesis" (Hardy and Higgins 1992; reviewed in Karran et al. 2011). This theory states that changes in APP homeostasis or cleavage lead to aggregation of Aβ and its deposition in plaques, which is sufficient to initiate the cascade of neuropathological changes, including the aggregation of tau, and results in neuronal atrophy. Although familial, early-onset AD only accounts for a small

Table 1. Alzheimer's disease—known causal genes

Gene	Protein	Chromosome	Mutation frequency in early onset	Types of mutations reported	Known function	Pathway
APP	Amyloid precursor protein	21	15%	Missense, duplication, deletions	Neurite outgrowth, adhesion, and axonogenesis	APP processing
PSEN1	Presenilin-1	14	80%	Missense, duplication, deletions	Component of γ-secretase complex; proteolytic cleavage of membrane proteins, including APP	APP processing
PSEN2	Presenilin-2	1	5%	Missense	Component of γ-secretase complex; proteolytic cleavage of membrane proteins, including APP	APP processing

number of total AD cases, identification of these genes highlights molecular pathways involved in disease and may therefore enable identification of potential therapeutic targets in both familial and idiopathic AD.

Risk Variants

The apolipoprotein E gene (*APOE*) was the first late-onset AD risk factor identified and, thus far, remains the risk factor carrying the greatest proportion of the population variance in liability to the disease (for review, see Ashford 2004). Located at chromosome 19q13.2, *APOE* encodes a multifunctional glycoprotein, involved in mobilization and redistribution of cholesterol (Mahley 1988). *APOE* has been shown to bind to Aβ and influence its metabolism, both in terms of clearance of soluble Aβ and Aβ aggregation (Kim et al. 2009; Castellano et al. 2011; Liu et al. 2013). There are three major alleles of *APOE* (ε2, ε3, and ε4) that result from a single amino-acid substitution between each pair of isoforms on the protein level. The presence of a single ε4 allele increases the risk for AD about threefold, whereas individuals homozygous for this allele have ∼15-fold increased risk compared to the most common genotype (ε3 homozygous) (Corder et al. 1993; Strittmatter et al. 1993). *APOE*ε4 is usually thought of as a genetic risk factor, which is defined as making only a small contribution to disease and is neither necessary nor sufficient to cause disease. However, the very high-risk estimates for *APOE*ε4 carriers have led some to assign *APOE*ε4 the status of a "moderately penetrant gene with semidominant inheritance." This status acknowledges that not all ε4 carriers develop the disease and that heterozygous ε4 carriers have intermediate risk compared with homozygous carriers (Genin et al. 2011). Interestingly, the *APOE*ε2 allele appears to be protective and has been shown to decrease the risk of AD as well as to increase longevity (Corder et al. 1994).

Numerous SNP-based GWAS, sequence-based studies, and meta-analysis have recently uncovered hundreds of additional risk factors for AD with varying levels of support (Lambert et al. 2009, 2013; Harold et al. 2009; Seshadri et al. 2010; Naj et al. 2011; Hollingworth et al. 2011; Jonsson et al. 2013; Reitz et al. 2013; Cruchaga et al. 2013; Miyashita et al. 2013; Beecham et al. 2014; Chen et al. 2015). More than 20 of these novel common risk factors are now well established (Table 2) at the stringent level of genome-wide significance (p-value $\leq 5 \times 10^{8}$) in GWAS meta-analysis and have been replicated in independent studies. Most confer much smaller risk (odds ratio of ∼0.8–1.25) than *APOE*ε4, and many of the specific pathogenic variants in or near these susceptibility genes remain to be characterized. More recently, as NGS technologies become available, a handful of low-frequency (rare) risk variants have been uncovered (Table 3), many of which have an odds ratio >2 (for review, see Lord et al. 2014). Together, these variants may be essential in suggesting additional, novel regulatory pathways contributing to disease pathogenesis, apart from Aβ metabolism and clearance. Areas of molecular dysfunction implicated by gene ontology analyses of these novel risk factors include the neural-immune system (*CLU*, *CR1*, *ABCA7*, *EPHA1*, *CD33*, *INPP5D*, *TREM2*, *HLA* complex), synaptic function (*PICALM*, *BIN1*, *EPHA1*, *CD2AP*, *MEF2C*, *PTK2B*, *AKAP9*), endocytosis (*PICALM*, *BIN1*, *EPHA1*, *CD33*, *CD2AP*, *SORL1*, *RIN3*), and lipid metabolism (*APOE*, *CLU*, *ABCA7*, *PLD3*) (for review, see Rosenthal and Kamboh 2014; Karch and Goate 2015). Many studies are actively underway to identify additional risk variants in AD, and with the rise of NGS techniques, these may soon include regulatory variants in noncoding regions, such as promoters, enhancers, and noncoding RNA.

FRONTOTEMPORAL DEMENTIA

FTD can be divided into the following three major clinical subtypes: behavioral variant (bvFTD), semantic variant primary progressive aphasia, and nonfluent variant primary progressive aphasia (Sieben et al. 2012; Bang et al. 2015). bvFTD is the most common and is associated with frontal and anterior cortex atrophy, which leads to progressive personality changes, including disinhibition, apathy, loss of sympa-

Table 2. Alzheimer's disease—known common susceptibility variants

Gene	Protein	Chromosome	Pathogenic/protective	Known function	Pathway
APOE	Apolipoprotein E	19	APOEε2, protective; APOEε4, pathogenic	Lipoprotein metabolism and homeostasis	Lipid metabolism
CR1	Complement component (3b/4b) receptor 1	1	Pathogenic	Regulates complement activation	Immune response
BIN1	Bridging integrator 1	2	Pathogenic	Regulates endocytosis; interacts with clathrin and AP2; binds to lipid membranes and induces membrane curvature	Endocytosis; synaptic function
INPP5D	Inositol polyphosphate-5-phosphatase D	2	Pathogenic	Inflammatory response; regulation of cytokine signaling	Immune response
MEF2C	Myocyte enhancer factor 2C	5	Pathogenic	Transcription enhancer involved in synaptic plasticity	Synaptic function
CD2AP	CD2-associated protein	6	Pathogenic	Scaffolding molecule that regulates the actin cytoskeleton; required for synapse formation	Endocytosis; synaptic function
HLA-DRB1/HLA-DRB5	Major histocompatibility complex class II subunits	6	Pathogenic	Member of the major histocompatibility complex	Immune response
NME8	NME/NM23 family member 8	7	Pathogenic	Ciliary functions	—
ZCWPW1	Zinc finger, CW domain with PWWP domain 1	7	Pathogenic	Contains domains identified in a number of other proteins responsible for epigenetic regulation	—
EPHA1	EPH receptor A1	7	Pathogenic	Member of tyrosine kinase receptor family involved in intercellular signaling, synapse formation and plasticity, axonal guidance	Immune response; endocytosis; synaptic function
PTK2B	Protein tyrosine kinase 2β	8	Pathogenic	Calcium-induced regulation of ion channels and activation of the map kinase signaling pathway; synaptic LTP	Synaptic signaling

Continued

Table 2. *Continued*

Gene	Protein	Chromosome	Pathogenic/ protective	Known function	Pathway
CLU	Clusterin	8	Pathogenic	Secreted, stress-activated chaperone involved in apoptosis, lipid transport, and Aβ clearance	Lipid metabolism; immune response
CELF1	CUGBP, Elav-like family member 1	11	Pathogenic	Regulates splicing, mRNA editing, and translation	—
MS4A4A, MS4A6E	Membrane spanning four domains A4A / A6E	11	Pathogenic	Little known; potentially involved in inflammatory response	Immune response
PICALM	Phosphatidylinositol-binding clathrin assembly protein	11	Pathogenic	Clathrin-mediated endocytosis; synaptic vesicle fusion to the presynaptic membrane via VAMP2 trafficking	Endocytosis; synaptic function
SORL1	Sortilin-related receptor	11	Pathogenic	Vesicle trafficking from the cell surface to the Golgi–endoplasmic reticulum	Endocytosis
FERMT2	Fermitin family member 2	14	Pathogenic	Actin assembly and cell shape	—
SLC24A/ RIN3	Ras and Rab interactor 3	14	Pathogenic	Membrane budding and trafficking	Endocytosis
ABCA7	ATP-binding cassette A7	19	Pathogenic	Intra- and extracellular transmembrane transport	Lipid metabolism; immune response
CD33	CD33 molecule	19	Pathogenic	Triggers immune cell–cell interactions via clathrin-independent endocytosis	Endocytosis; immune response
CASS4	Cas scaffolding protein family member 4	20	Pathogenic	Possibly involved in cell adhesion and cytoskeletal regulation	—

thy, and stereotyped behaviors. As the disease progresses cognitive deficits appear, but memory and visuospatial functions remain relatively spared (Riedl et al. 2014). FTD is a genetically and pathologically heterogenous disorder, typically with an earlier age of onset (between 50 and 65 years of age) and a higher incidence of familial cases than AD (Rademakers et al. 2012). Almost 50% of individuals with FTD have a positive family history, and an autosomal-dominant mode of transmission can be identified in ~10%–20% of patients (Chow et al. 1999; Seelaar et al. 2008; Rohrer et al. 2009). However, many of the causative genes identified have variable penetrance, and most result in a spectrum of phenotypes,

Table 3. Alzheimer's disease—known rare susceptibility variants

Gene	Protein	Chromosome	Pathogenic/protective	Known function	Pathway
UNC5C	Unc-5 homolog C	4	T835M, pathogenic	Possible role in apoptosis in neurons	[Apoptosis]
TREM2	Triggering receptor expressed on myeloid cells 2	6	R47H/R62H, pathogenic	Regulation of phagocytosis; suppression of inflammation	Immune response
AKAP9	A-kinase anchor protein 9	7	Pathogenic	Scaffold protein attaching kinases to NMDA receptor	Synaptic function
ADAM10	A disintegrin and metalloproteinase domain-containing protein 10	15	Q170H/R181G, pathogenic	Membrane protein cleavage	APP processing
MAPT	Microtubule-binding protein tau	17	A152T, pathogenic	Assembly and stabilization of tubulin microtubules	Axonal transport; synaptic function
APOE	Apolipoprotein E	19	V236E, protective	Lipoprotein metabolism and homeostasis	Lipid metabolism
PLD3	Phospholipase D family, member 3	19	V232M, pathogenic	Hydrolysis of membrane phospholipids	Lipid metabolism
APP	Amyloid precursor protein	21	A637T, protective	Neurite outgrowth, adhesion, and axonogenesis	APP processing

extending from amyotrophic lateral sclerosis (ALS) through classic FTD variants to corticobasal syndrome and progressive supranuclear palsy (PSP) (Ng et al. 2015).

Genes in Which Disease-Causing Mutations Have Been Identified

Mutations in six genes have been implicated in FTD (Table 4). Using linkage analysis, the first causal gene for FTD to be identified was *MAPT* (coding for microtubule associated protein tau). *MAPT* is located on chromosome 17q21.1, and since its initial identification as a causal gene for FTD (Hutton et al. 1998; Poorkaj et al. 1998; Spillantini et al. 1998), >40 different pathogenic mutations (mainly missense and splicing mutations) have been described (www.molgen.vib-ua.be/FTDMutations). These mutations can account for up to 50% of familial frontotemporal lobar dementia (FTLD) cases in certain populations (Morris et al. 2001; Sieben et al. 2012). MAPT promotes the assembly and modulates the stability of tubulin microtubules. Most of the mutations identified in *MAPT* are found in exons 9–13, which code for the microtubule binding domains that mediate protein function. These mutations can alter the expression ratio of different isoforms of tau (between those containing four microtubule binding domains [4R] and those that contain only three [3R]), as well as modulate tau phosphorylation (Spillantini and Goedert 2013). This leads to abnormal accumulation of MAPT,

Table 4. Frontotemporal dementia—known causal genes

Gene	Protein	Chromosome	Mutation frequency in early onset	Types of mutations reported	Known function	Pathway
MAPT	Microtubule binding protein tau	17	0%–50%	Missense, deletions	Assembly and stabilization of tubulin microtubules	Axonal transport; synaptic function
GRN	Progranulin	17	3%–26%	Missense, deletions, insertions	Multifunctional protein suggested to be both aneurotrophic and anti-inflammatory factor	Growth factor; anti-inflammatory
C9orf72	Chromosome 9 open reading frame 72	9	25%	Hexanucleotide repeat in regulatory region	Unknown	—
VCP	Valosin-containing protein	9	<1%	Missense	Multifunctional ATPase	DNA damage response; authophagy and protein degradation
TARDBP	TAR DNA-binding protein [TDP-43]	1	<1%	Missense	Transcriptional regulator involved in RNA splicing and stability	Transcriptional regulation

which results in the formation of pathological NFTs within neurons and glia and impairs neuronal axon transport, among other cellular functions (for review, see Rademakers et al. 2004; Brandt et al. 2005; Ghetti et al. 2015). The discovery that *MAPT* mutations cause dementia runs counter to the "amyloid cascade hypothesis," which states that abnormalities in APP homeostasis are the most significant molecular event necessary to initiate the cascade of neuropathological changes that cause neurodegeneration (Hardy and Higgins 1992). The amyloid cascade hypothesis usually asserts that aggregation of tau is only a secondary event. Instead, these *MAPT* mutations show that abnormalities in tau are sufficient to induce atrophy and indicate that tau pathology may also play an important role in AD pathogenesis. Interestingly, a variant in *MAPT*, previously identified in PSP, was recently discovered in AD patients (Coppola et al. 2012), further eroding support for a dogmatic view of the "amyloid cascade hypothesis."

GRN, a disease-causing gene first identified in 2006 (Baker et al. 2006; Cruts et al. 2006), is located only 1.7 Mb away from *MAPT* on chromosome 17q21. Its proximity to *MAPT* originally made it difficult to identify through linkage mapping studies. *GRN* codes for progranulin, a cysteine-rich secreted glycoprotein, which is cleaved by enzymes such as elastase into small peptides (granulins) (Toh et al. 2011). The exact function of progranulin and granulins is still unknown in the central nervous system, but some hypothesize that these proteins have opposing cellular functions. Progranulin has been implicated in neurotrophic and anti-inflammatory pathways, as well as in modulation of Wnt signaling (Van Damme et al. 2008; Ryan et al. 2009; Laird et al. 2010; Rosen et al. 2011; for review, see Petkau and Leavitt 2014). A range of mutations, >65 of which are thought to be pathogenic, have been identified in *GRN* (Yu et al. 2010; www.molgen.vib-ua.be/FTDMutations). Mutations are found in almost all *GRN* exons (the exception being exon 13 located at the very 3′ end of the coding sequence) and include nonsense and splice-site mutations, as well as insertions and deletions leading to a frameshift in the transcript. The majority of these mutations result in the loss of function of the mutated allele, and it is now generally accepted that *GRN* mutations cause disease through haploinsufficiency (Kleinberger et al. 2013), which is supported by downregulation of progranulin in the blood of mutation carriers (Coppola et al. 2008). Aggregation of ubiquitin and TDP-43 are characteristic of all *GRN* mutation carriers (Eriksen and Mackenzie 2007).

GRN mutations account for up to 26% of familial FTD cases in some populations and 1%–5% of sporadic cases. However, much variability is observed in the clinical phenotype associated with *GRN* mutations, and penetrance is incomplete (reviewed in Cruts and Van Broeckhoven 2008; Ng et al. 2015). Therefore, genetic variability—both on the wild-type *GRN* allele and in other genes—is thought to contribute to disease pathogenesis in individuals with *GRN* mutations. One such factor is variance in the transmembrane protein 106B gene (*TMEM106B*), which has been shown to associate with progranulin in endolysosomes (Lang et al. 2012). Some genetic variants in or near *TMEM106B* appear to protect *GRN* mutation carriers from FTD or delay its onset, whereas others seem to increase the risk for FTD (Finch et al. 2011; van der Zee et al. 2011; Lattante et al. 2014). Both types of variants may possibly assert their effect by modulating the levels of progranulin. Furthermore, a number of miRNAs (specifically, miR29b and miR107) may regulate *GRN* expression and thereby contribute to disease penetrance and age of onset (Jiao et al. 2010; Wang et al. 2010).

In 2011, the abnormal expansion of a GGGGCC hexanucleotide repeat in the noncoding portion (first intron) of *C9ORF72* was found to account for up to ~25% of familial FTD cases and 40% of familial ALS cases (Renton et al. 2011; DeJesus-Hernandez et al. 2011; Majounie et al. 2012a). Although *C9ORF72* codes for a protein of unknown function, structural comparison studies indicate that it is a potential DENN-type guanine nucleotide exchange factor, regulating Rab GTPases (Levine et al. 2013). Unaffected individuals carry less than 30 repeats, whereas affected mutation carriers

have been identified with an excess of 4000 repeats. Recently, Gijselinck and colleagues (2015) showed that repeat size correlates with the disease age of onset as well as methylation of CpGs in the C9orf72 promoter in a cohort of 72 Belgian patients with FTD, FTD-ALS, or ALS. Furthermore, the researchers were able to provide some evidence for genetic anticipation, as several parent–child pairs showed decreased age of onset, increased expansion size, and/or increased promoter methylation with transmission to the next generation.

A variety of pathological mechanisms by which *C9ORF72* repeat expansions result in neurodegeneration have been proposed. Haploinsufficiency, triggered by epigenetic changes to the expanded repeat region, has been suggested, and recent studies have shown reduced C9ORF72 protein levels in the frontal cortex of expanded repeat carriers (Waite et al. 2014). Furthermore, RNA foci have been identified in neurons of *C9ORF72* expansion cases (Lee et al. 2013; Haeusler et al. 2014). As in other repeat-expansion disorders (such as fragile-X syndrome), *C9ORF72* repeat-expansion transcripts may aggregate into foci, which in turn are thought to sequester RNA-binding proteins and result in major RNA-processing alterations (Wojciechowska and Krzyzosiak 2011; Cooper-Knock et al. 2015; Prudencio et al. 2015). However, no correlation between RNA focus burden and neurodegeneration has been reported for *C9ORF72* expansion carriers thus far, and, in fact, some propose that RNA foci may be neutral intermediates or possibly even neuroprotective (Tran et al. 2015), calling this proposed mode of pathogenicity into question. Furthermore, unconventional, repeat-associated, non-ATG dependent translation (RAN translation) has been shown to cause expression of a variety of dipeptide mutant proteins from the expansion (Ash et al. 2013; Mori et al. 2013). Protein-labeling studies with antibodies designed against each of the six possible dipeptides show that these dipeptides cluster into insoluble inclusions in neurons in the cortex. Most recently, in large-scale genetic screens in yeast and *Drosophila*, several groups have identified that this unconventional translation of dipeptides may lead to nucleocytoplasmic transport defects and neurodegeneration (Freibaum et al. 2015; Jovičić et al. 2015; Zhang et al. 2015; reviewed in van Blitterswijk and Rademakers 2015). Finally, there is emerging evidence that like PGRN, C9ORF72 mutation carriers have elevated prevalence of specific classes of autoimmune disorders, further implicating inflammatory mechanisms in disease pathophysiology (Miller et al. 2016). Most likely, many if not all of these mechanisms contribute to neurodegeneration in *C9ORF72* expansion carriers to some extent, possibly with synergistic effects.

Together, mutations in *MAPT*, *GRN*, and *C9ORF72* repeat expansions are the most common causes of familial and sporadic FTD and usually result in bvFTD. However, clinical presentation is considerably variable; mutations in *GRN* alone have been reported among individuals diagnosed with FTD, AD, corticobasal degeneration, and mild cognitive impairments. Furthermore, the age of onset varies widely between carriers of these causative mutations, even within families (Ng et al. 2015).

Four additional genes have been implicated in FTD. Very rare, dominant-negative mutations have been identified in charged multivesicular body protein 2B (*CHMP2B*) (Skibinski et al. 2005), which is involved in the endosomal sorting complex, required for the formation of the multivesicular body, an early precursor to the lysosome (Tanikawa et al. 2012). The discovery of mutations in *CHMP2B* further underscores the importance of membrane dynamics and autophagy in neurodegenerative disease.

TARDBP, located on chromosome 1q36, codes for TAR DNA-binding protein (TDP-43), a ribonucleoprotein functioning as a transcriptional regulator involved in RNA splicing and stability (Janssens and Van Broeckhoven 2013). TDP-43 aggregates are found in the majority of tau-negative, ubiquitin-positive inclusions in FTD (Rademakers et al. 2012). Although missense and nonsense mutations in *TARDBP* have been identified in FTD cases, these are exceedingly rare ($<1\%$) (Sieben et al. 2012). However, *TARDBP* is an important causal factor in the related motor neuron diseases without dementia—recent studies have found

mutations in TARDBP in up to ~3% of ALS patients (Kabashi et al. 2008; Rutherford et al. 2008; Sreedharan et al. 2008; Mentula et al. 2012; reviewed in Valdmanis et al. 2009).

FUS is located at chromosome 16q11 and codes for fused in sarcoma (*FUS*), which has been shown to co-localize with ubiquitin-immunoreactive inclusions in FTD patients (Rademakers et al. 2012). However, whereas mutations in *FUS* have been identified in both familial and sporadic ALS, none have been associated with FTD. When located in the nucleus, FUS is thought to be involved in regulating transcription and pre-mRNA splicing, whereas cytoplasmic FUS is implicated in mRNA transport and local protein synthesis at the synapse (Colombrita et al. 2012). The discovery of mutations in *FUS* and *TARDBP*, as well as the suggestion that *C9ORF72* repeat expansions may lead to RNA-processing alterations, highlights the importance of RNA metabolism in both FTD and ALS.

VCP, located at chromosome 9q13, codes for valosin-containing protein, a highly abundant, multifunctional ATPase involved in a variety of cellular pathways (Yamanaka et al. 2012). Deficiency in VCP in neurons leads to mitochondrial uncoupling and significant reduction of cellular ATP production (Bartolome et al. 2013). Mutations in *VCP* cause a pleiotropic degenerative disorder called multisystem proteinopathy, which can manifest clinically as a variety of neurodegenerative diseases including classical ALS, FTD, inclusion body myopathy, Paget's disease of bone, or as a combination of these disorders (Watts et al. 2004).

Common, non-Mendelian risk variants for FTLD remain to be explored for the most part. As described previously, variants in *TMEM106B* are thought to modulate levels of granulin secretion and may therefore influence *GRN*-mutation-carrier pathological phenotype (Lattante et al. 2014). Furthermore, Ferrari and colleagues (2014) recently identified two new FTD-associated risk variants in a GWAS with more than 3500 cases and more than 9400 controls (Ferrari et al. 2014). First, the HLA locus at 6p21.3, coding for key molecular components of the immune system, showed significant genome-wide association. Second, in a separate association analysis for each of the different subtypes of FTD, the *RAB38/CTSC* locus, involved in lysosomal processing (Bultema et al. 2012), was significantly associated with bvFTD cases specifically.

With the discovery of the hexanucleotide repeat expansion in *C9ORF72*, and mutations in *TARDBP* and *VCP*, which result in FTD, ALS, and concomitant FTD-ALS, it has become clear that cases of FTD-ALS are not the result of simple coincidence, but most likely represent a continuum of disease between classical FTD and motor neuron disease (Ng et al. 2015). This is further supported by the clustering of neurodegenerative diseases in relatives of patients with ALS (Al-Chalabi et al. 2012). As has been recently described, up to 50% of ALS cases show some functional loss in frontal lobe tests, whereas in ~15% of cases, frontal lobe functional loss was enough to justify diagnosis of FTD. Similarly, ~40% of FTD cases show measurable motor dysfunction, whereas up to 15% of FTD cases are eventually diagnosed with concomitant ALS (for review, see Callister and Pickering-Brown 2014; Ng et al. 2015). From the progress that has been made in our understanding of the molecular genetics of FTD and ALS over the last decade, it is evident that these diseases form part of a spectrum, with the same genes often implicated in both.

How mutations in the same genes and/or aggregation of their protein products cause these divergent phenotypes is a key question that we now have the genetic tools to answer. Using next-generation sequencing approaches, we can identify rare variants that contribute to a slew of what were previously thought of as separate dementias and motor neuron diseases. One example is the *MAPT* A152T variant, which was originally found in a patient with PSP but has been recently shown to be associated with FTD, AD, and LBD, as well as other atypical tauopathies (Coppola et al. 2012; Kara et al. 2012; Labbé et al. 2015). In the future, careful application of such techniques will be useful in mapping the genetic and molecular commonalities and differences of diseases on this spectrum.

LEWY BODY DEMENTIA

LBD is a complex neurodegenerative disease characterized by progressive cognitive decline, motor symptoms, visual hallucination, and fluctuating levels of attention and alertness (Molano 2013). It is considered to be a common cause of neurodegenerative dementia, with a prevalence of up to 7.5% (Vann Jones and O'Brien 2014). Being a member of the family of synucleinopathies, which also includes Parkinson's disease (PD), a key feature of LBD pathology is interneuronal α-synuclein aggregation into Lewy bodies. However, most LBD-affected brains also show comorbid AD pathology in the form of β-amyloid plaques and NFTs (Colom-Cadena et al. 2013).

Although a number of families have been identified in which a mixed phenotype of dementia and parkinsonism is inherited in a Mendelian manner (Meeus et al. 2012), most LBD is late onset and sporadic, with twin studies not lending much support for a major genetic etiology (Wang et al. 2009). Linkage analysis in a large Belgian family with prominent dementia and parkinsonism showed significant genetic linkage to a novel locus on the long arm of chromosome 2. However, extensive sequence analysis of five candidate genes within this 2q35-q36 region did not reveal a single nucleotide or structural chromosomal variant (gene dosage) mutation that cosegregated with LBD (Bogaerts et al. 2007).

In cohorts of unrelated and largely sporadic LBD patients, molecular genetic investigations have revealed mutations in genes that have previously been implicated both with Parkinson's disease (*SNCA*) (Yamaguchi et al. 2005) and with AD (*APP* and *PSEN1*) (Ishikawa et al. 2005; Guyant-Marechal et al. 2008), indicating that these disorders may be members of the same disease continuum. The most strongly implicated LBD-causative gene is *SNCA*, in which a number of rare mutations have been identified associated with LBD. *SNCA*, located at chromosome 4q21, codes for α-synuclein, a protein thought to be involved in neurotransmitter release and vesicle turnover at presynaptic terminals (Bendor et al. 2013). Of note, different mutations in *SNCA* appear to be loosely correlated with different clinical presentations (Bonifati 2008). Although duplications are more often associated with classic PD (Ibáñez et al. 2004; Chartier-Harlin et al. 2004), triplications result in PD with dementia and LBD (Singleton et al. 2003; Fuchs et al. 2007). Furthermore, the missense mutation A30P is rarely associated with dementia. Instead, patients with this mutation present with typical PD (Krüger et al. 2001). In contrast, the missense mutations E46K and A53T, which have been shown to promote α-synuclein polymerization into amyloid in vitro, are associated with a mixed presentation of PD, PD with dementia, and LBD (Zarranz et al. 2004; Yamaguchi et al. 2005). Although mutations in β-synuclein have not been associated with PD, two missense mutations (V70M and P123H) were identified in one LBD patient each (Ohtake et al. 2004). Further genetic studies are needed to verify pathogenicity.

Carriers of mutations in genes usually associated with AD, including *APP*, *PSEN1*, and *PSEN2*, often show Lewy body pathology as well. Increased expression of APP and point mutations near the β-secretase cleavage sites (V717I) can result in Lewy body formation (Meeus et al. 2012). However, the process by which these mutations cause Lewy body pathology in some patients but not others is still unresolved.

Recently, mutations in glucocerebrosidase (*GBA*) have been identified as potential risk variants for both PD and LBD. Goker-Alpan and colleagues found a higher incidence of heterozygous *GBA* variant carriers among patients with LBD than healthy controls (Goker-Alpan et al. 2006). This study was expanded on by Tsuang and colleagues, who screened the entire coding sequence of *GBA* in 79 pure LBD cases and almost 400 controls to show that LBD patients had an increased odds ratio of 7.6 (Tsuang et al. 2012). Interestingly, GBA is an important enzyme involved in lysosomal storage, which has been recently implicated in α-synuclein processing and homeostasis (Cullen et al. 2011). A second main risk factor for LBD is *APOE*ε4. Investigations of clinically confirmed LBD cohorts show that *APOE*ε4 is overrepresented in LBD cases compared with controls,

and individuals with ε4 alleles have a threefold increased risk for LBD, which is similar to the increased risk associated with *APOE*ε4 for AD (Tsuang et al. 2013). As most LBD-affected brains show comorbid AD pathology in the form of β-amyloid plaques, and *APOE*ε4 is thought to modulate Aβ homeostasis and clearance, it is not altogether surprising that *APOE*ε4 is also a prominent risk factor for LBD. However, these genes explain only a minority of cases, and identification of novel risk loci, including possible pathogenic regulatory variants, remains an important goal.

PRION DISEASES

Human prion diseases, a rare group of neurodegenerative disorders, are characterized by progressive cognitive decline (most commonly presenting as memory impairment and executive and/or language dysfunction), parkinsonism, and behavioral symptoms (Takada and Geschwind 2013). Prion diseases can be classified into three groups: sporadic (most common), genetic, and acquired (Brown and Mastrianni 2010). In all three forms, neurodegeneration is caused by the propagation of conformational remodeling of properly folded, cellular prion-related protein (PrP^C; predominantly α-helical) into the aberrant, aggregating PrP^{Sc} (β-sheet enriched, in which the superscript "Sc" refers to "scrapie"). Importantly, it is the exposure of PrP^C to PrP^{Sc} that induces its pathogenic conformational change. PrP^{Sc} can aggregate to form oligomers and subsequent intra- and extracellular depositions of amyloid fibrils. PrP^C is a membrane-bound protein that is most likely involved in synapse formation during neuronal development. Whether loss of function of PrP^C, either via conformational change or oligomerization, leads to neuronal impairment and cell death or whether PrP^{Sc} oligomers are neurotoxic is unclear.

PrP is encoded by the prion-related protein gene (*PRNP*) located at chromosome 20q13. Genetic prion disease is caused by dominantly inherited mutations in *PRNP*, which are found in ∼10% of all cases (Takada and Geschwind 2013). Interestingly, not all of these genetic prion disease cases have a positive family history of prion disease. This may be caused by a number of factors, including misdiagnosis of family members, late onset of disease symptoms, rare occurrence of de novo mutations in *PRNP*, and incomplete penetrance of some of the disease-causing mutations in *PRNP* (Kovács et al. 2005). More than 30 pathogenic mutations in *PRNP* have been identified, including missense mutations, insertions (specifically an octapeptide-repeat insertion), and deletions, though some of these mutations are very rare, and occurrence is restricted to specific geographic regions (Mastrianni 2010). Penetrance is high for most *PRNP* mutations but is strongly age-dependent, with disease onset usually between 40 and 60 years of age. Although specific clinical features are often associated with specific *PRNP* mutations, a single *PRNP* mutation can be associated with variable phenotypes even within a family (Kovács et al. 2005).

Polymorphisms in *PRNP* are also the most common risk factors identified in sporadic prion disease to date. Specifically, individuals who are heterozygous for *PRNP* codon 129 (which can code for either methionine or valine) have reduced risk for developing both sporadic and acquired prion disease, whereas homozygous individuals (either MM or VV) are overrepresented in prion disease affected populations (Parchi et al. 1999). Homozygosity at this codon can decrease the age of onset in genetic prion disease cases, and whether methionine or valine is present in the mutant PrP protein can influence clinical presentation (Mead et al. 2009a). Furthermore, two protective variants in *PRNP* have been described. The E219K variant has been reported in roughly 6% of the Japanese population but is absent in prion disease cases (Shibuya et al. 1998), whereas the G127V polymorphism has been identified to reduce the risk of developing kuru, a prion disease transmitted by cannibalism (Mead et al. 2009b). Although variants in genes other than *PRNP* are likely to contribute to disease risk, the low incidence of prion disease makes statistically significant identification of these risk factors of modest effect via SNP-based GWAS exceedingly difficult.

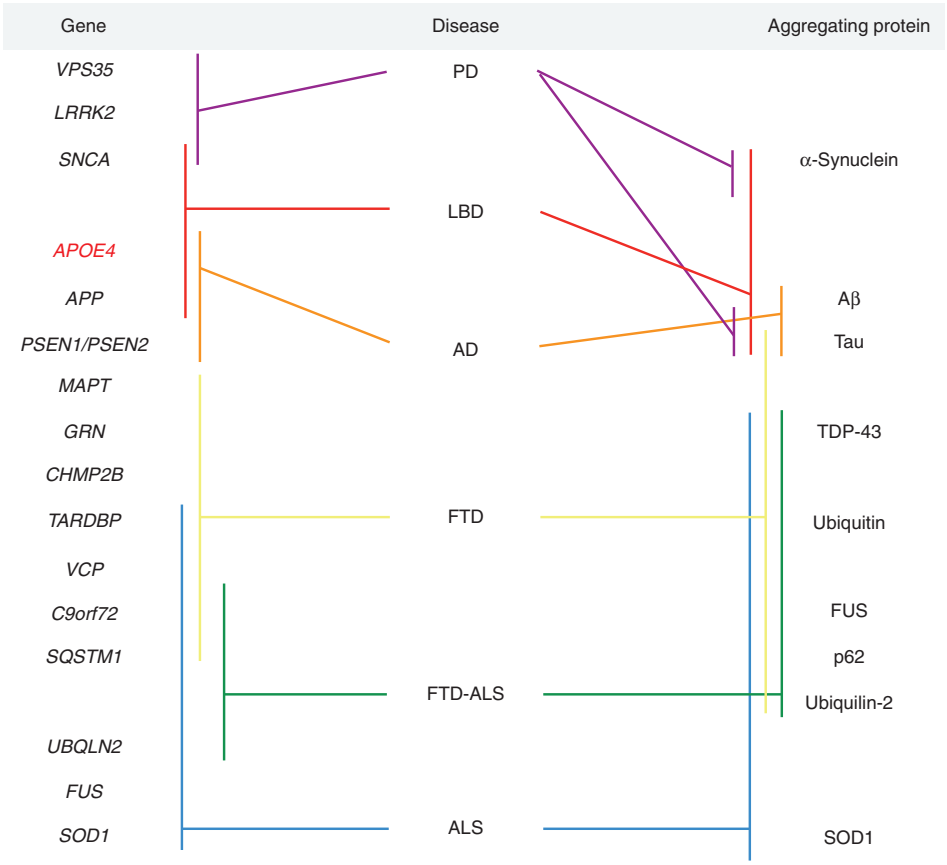

Figure 2. Neurodegenerative dementias as a spectrum disorder. Genes (*left*) and their pathologically aggregating protein products (*right*) and the neurodegenerative disorders (*center*) in which they have been implicated are shown.

DISCUSSION

Independent Diseases or Spectrum Disorder?

A number of the same genes and their pathologically aggregating protein products are involved in several clinically and pathologically distinct neurodegenerative disorders (Fig. 2). Mutations in *SNCA* and aggregation of its protein product α-synuclein are characteristic of both PD and LBD, whereas *APP* mutations and pathological aggregations of the resulting amyloid protein cleavage product Aβ are found in both LBD and AD. Although mutations in *MAPT* are commonly associated only with FTD, aggregation of hyperphosphorylated tau into NFTs is common to LBD, AD, and FTD. More recently, it has become clear that the hexanucleotide repeat expansion in *C9ORF72* and mutations in *TARDBP* and *VCP* are common to FTD, ALS, and concomitant FTD-ALS (Callister and Pickering-Brown 2014).

Furthermore, a number of rare cases have been described in which a gene previously thought to be associated with only one specific form of dementia was found to be mutated in patients whose clinical phenotype and neuropathology matched a different neurodegenerative disorder. Examples of such cases include, but are not limited to, the discovery of *MAPT* mutations (R406T, A406W, and A152T) in AD (Rademakers et al. 2003; Coppola et al. 2012; Wojtas et al, 2012); *PSEN1* G183V and M146V missense mutations in Pick's disease (Dermaut et al. 2004) and FTD with amyloid plaques,

NFTs, and Pick's bodies (Riudavets et al. 2013), respectively; and a number of patients with *C9ORF72* repeat expansions that presented with AD, PD, and LBD (Majounie et al. 2012b; Wojtas et al. 2012; Kohli et al. 2013; Robinson et al. 2014; for review, see Liu et al. 2014). Moreover, mutations in *GRN* have been identified in both AD and PD cases (Brouwers et al. 2007, 2008; Wojtas et al. 2012), and there is mounting evidence that *GRN* may act as a susceptibility gene for AD (Sheng et al. 2014).

As the clinical phenotype of these disorders is often highly variable, it is possible that some of these cases are examples of an initial misdiagnosis of the inherent condition. However, the overlap in clinical phenotype of these diseases and frequent comorbid presentation, along with the phenotypic variability associated with genetic variants described above, speaks to the fact that these neurodegenerative dementias may be better considered as part of a disease spectrum, ranging from PD to LBD, AD, FTD, and, on the far end, to ALS, than distinct disorders. Although neurodegeneration is typically targeted to distinct brain regions, which in turn affects clinical phenotypes, the underlying genetic variants, molecular pathology, and general cellular pathways involved in disease progression may show remarkable overlap throughout this disease continuum.

Prion-Like Behavior of Aggregation-Prone Pathogenic Proteins Underlying Neurodegenerative Dementias

It has been proposed recently that a common pathogenic mechanism, the prion-like behavior of aggregation-prone protein species, may underlie most neurodegenerative diseases (Prusiner 2012, 2013; Peggion et al. 2014). "Prion-like" refers to the capacity of an abnormally folded peptide or protein to induce the same abnormal conformation in a regularly folded protein of the same kind, thereby initiating a self-amplifying cascade. It is postulated that aging—and with it impairment of misfolded protein clearance mechanisms—is necessary as a pathogenic event. Only when misfolded prion-like proteins reach a certain threshold does self-propagation, which leads to neuronal dysfunction, occur. Some evidence that such abnormal conformational changes occur in proteins associated with neurodegenerative diseases and result in atrophy of affected tissue has been provided for Aβ (Stöhr et al. 2014; Watts et al. 2014; reviewed in Prusiner 2013), tau (Frost et al. 2009; Guo and Lee 2011; Holmes et al. 2014; Sanders et al. 2014), α-synuclein (Prusiner et al. 2015; reviewed in Oueslati et al. 2014), SOD-1 (Grad et al. 2015), and TDP-43 (Smethurst et al. 2015), but these findings are mainly restricted to mouse models thus far (for review, see Peggion et al. 2014).

However, this hypothesis is attractive, as it would explain the sporadic nature and late onset of most neurodegenerative diseases as well as the progressive spread of atrophy to different areas of the brain. Furthermore, different conformations of aggregating protein could act as different "strains" of the same disease, explaining different cellular pathology and clinical symptoms seen in diseases with the same underlying mutation or aggregating protein. Lastly, some disease-causing mutations and risk variants may exert their pathogenic effect by modulating specifically the "prion-like" properties of aggregation-prone proteins.

These findings suggest that it may be helpful to consider neurodegenerative dementias as a spectrum disorder with shared pathogenic mechanisms.

CONCLUSION

Over the last decade, a multitude of disease variants implicated in neurodegenerative dementias has been identified using linkage-based analysis, SNP-mediated GWAS techniques, and, more recently, next-generation sequencing approaches. Genetic screening for a number of these disease-causing mutations and risk variants is now commonly available. This not only will improve patient care but also may enable the identification of case and control cohorts for drug trials that aim to test the efficacy of new treatments before onset of widespread neuronal atrophy and associated clinical phenotypes. Furthermore, the function of proteins

encoded by disease-causing and susceptibility genes and the molecular pathways these act as part of will inform and direct future investigations of the underlying cellular pathology. Forty-four million people currently suffer from neurodegenerative dementias, and the associated health-care costs for AD in the United States in 2013 alone exceeded $200 billion (alz.org), underscoring the severe need to develop currently lacking treatment options. Hopefully, in the future, a multidisciplinary approach that combines genetic, transcriptomic, proteomic, and epigenetic information will provide a more complete picture of underlying disease mechanisms and point the way toward improved therapeutic options.

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