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Tau and TDP-43 proteinopathies: kindred pathologic cascades and genetic pleiotropy

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Abstract

We review the literature on Tau and TDP-43 proteinopathies in aged human brains and the relevant underlying pathogenetic cascades. Complex interacting pathways are implicated in Alzheimer's disease and related dementias (ADRD), wherein multiple proteins tend to misfold in a manner that is "reactive," but, subsequently, each proteinopathy may contribute strongly to the clinical symptoms. Tau proteinopathy exists in brains of individuals across a broad spectrum of primary underlying conditions—e.g., developmental, traumatic, and inflammatory/infectious diseases. TDP-43 proteinopathy is also expressed in a wide range of clinical disorders. Although TDP-43 proteinopathy was first described in the central nervous system of patients with amyotrophic lateral sclerosis (ALS) and in subtypes of frontotemporal dementia (FTD/FTLD), TDP-43 proteinopathy is also present in chronic traumatic encephalopathy, cognitively impaired persons in advanced age with hippocampal sclerosis, Huntington's disease, and other diseases. There is also evidence of cellular co-localization between Tau and TDP-43, suggesting common pathways or protein interactions facilitating misfolding in one protein by the other. Multiple pleiotropic gene variants can alter risk for Tau or TDP-43 pathologies, and certain gene variants (e.g., *APOE ε4, Huntingtin* triplet repeats) are associated with increases of both Tau and TDP-43 proteinopathies. Studies of genetic risk factors have provided insights into multiple nodes of the pathologic cascades involved in Tau and TDP-43 proteinopathies. Variants from a specific gene can be either a low-penetrant risk factor for a group of diseases, or alternatively, a different variant of the same gene may be a disease-driving allele that is associated with a relatively aggressive and early-onset version of a clinically and pathologically specific disease type. Overall, a complex but enlightening paradigm has emerged, wherein both Tau and TDP-43 are linked to numerous overlapping upstream influences, and both are connected with multiple downstream pathologically- and clinically-defined deleterious effects.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Introduction

A common theme that has emerged in Alzheimer's disease (AD) and related dementia (collectively termed ADRD) research is that underlying genetic and/or environmental perturbations lead to formation, aggregation, and propagation of misfolded proteins (termed a "proteinopathy") that can be deleterious through both toxic gain-of-function and also loss of normal function mechanisms [1–3]. Over the past several decades, clinical-pathologic correlation (CPC) studies, in concert with genetic studies, provided significant new insights into the roles of proteinopathies in ADRD. Modern CPC studies have established that two of the most important pathologic hallmarks associated with clinical cognitive impairment are proteinopathies associated with the microtubule-associated protein Tau, and the transactive response DNA 43 kDa binding protein (TDP-43).

Both Tau and TDP-43 proteinopathies are caused by pathologic mechanisms that occur in a wide range of disease paradigms. In the course of these diseases, common pathologic cascades are downstream of many different primary causes, while clinical symptoms are not necessarily specific to their biologic or pathologic antecedents. Whereas there is widespread appreciation that many different conditions are associated with Tau protein pathology ("the tauopathies") [4, 5], the study of TDP-43 proteinopathic conditions is a younger area of research. Interestingly, some of the paradigms associated with tauopathic disease also seem to apply to TDP-43 proteinopathies, including the tendency of specific genetic modifiers [6, 7] to apparently increase the proteinopathy that was caused by different primary upstream causes. Here, we review the relevant literature on these "misfoldingopathies", beginning with a descriptions of some of the emerging themes of pathologic cascades, then reviewing some of the pleiotropic genetic influences discovered to affect Tau and TDP-43 proteinopathies, and finally discussing a subset of the downstream effects that were discovered before the age of widespread immunohistochemistry-based neuropathologic investigations.

Pathologic cascades and synergies: protein misfolding can have multiple causes and effects

Proteinopathies can provide diagnostic histologic markers for ADRD subtypes, and also may eventually represent therapeutic targets. However, there are added levels of complexity that derive from differing upstream influences, from multi-step pathologic cascades, from overlapping downstream effects, and from biochemical interactions that may occur between the different misfolding proteins. All of these factors often occur concurrently and should be considered when studying the Tau and TDP-43 proteinopathies.

A generalizable paradigm of pathologic cascades in ADRD involving misfolding proteins (Fig. 1) can be applied more specifically in the contexts of both Tau and TDP-43 proteinopathies (Fig. 2). The red arrows in Figs 1 and 2 indicate that the presence of misfolded proteins can, by themselves, contribute via positive feedback mechanism (s) to changes in the local biochemical microenvironment, propagating further misfolding of proteins. Evidence in support of this positive-feedback hypothesis comes from multiple sources including cell culture models [8, 9] and "transmission" animal models [10–12]

where injection of misfolded proteins can lead to an auto-propagating degenerative changes in which intrinsic proteins are incorporated into a pathogenetic process by exogenous proteins.

Many questions remain regarding what, specifically, initiates Tau and TDP-43 proteinopathies. Here we focus predominantly on TDP-43 proteinopathy, as prior reviews have focused extensively on tauopathies [13–15]. Given that a majority of patients with TDP-43 proteinopathies lack strong family histories of similar illnesses (as far as we now know), it may be that exogenous factors can influence TDP-43 to form pathologic inclusions. One example of a relatively clear upstream mechanism at work is chronic traumatic encephalopathy (CTE), a progressive neurodegenerative condition in which the initiating event is recurrent brain trauma, and pathologic examination reveals both TDP-43 and Tau proteinopathies [16–19]. In one study [20], of 12 autopsied individuals with CTE, 10 had widespread TDP-43 pathology; three of these who had developed progressive motor neuron disease with weakness, atrophy, and fasciculations were found to have both Tau and TDP-43 proteinopathies. Proteins that have been found in disease-associated protein aggregates have revealed common properties—internal amino acid sequences that facilitate aggregation [21, 22]. Similar protein motifs are found in non-disease causing proteins, and their liberation and interaction with disease causing proteins allows selfpropagation and formation of cytotoxic proteins aggregations [23, 24]. In normal cells, misfolded proteins can be degraded or refolded into their homeostatic form by protein chaperones [25]. As the human brain undergoes normal aging, the chaperone proteins responsible for correct protein folding are repressed, and these changes are even more prominent in patients affected by AD, Huntington’s disease (HD), or Parkinson Disease (PD) [26], so, the lack of chaperone proteins may be contributing to these disorders.

Following or in parallel with disease initiation, specific biochemical factors, paradigms, and cellular domains have been associated with worsening (or protection from) TDP-43 proteinopathy—posttranslational modifications (phosphorylation, acetylation, proteolysis), autophagy, endosomal/lysosomal processing, mitochondrial function, nuclearcytoplasmic transport, oxidative stress, and neuroinflammation, to name a few. A comprehensive discussion of these factors is beyond the scope of this review. However, we here address several of these contributing factors.

Oxidative stress has been postulated as a triggering mechanism responsible for the formation of pathologic TDP-43 inclusions [27, 28]. Work by Iguchi et al. demonstrated that treatment of NSC34 cells and mouse primary cortical neurons with ethacrynic acid (EA) depleted their glutathione levels and causes increased oxidative stress. This caused TDP-43 phosphorylation, insolubilization, and cytoplasmic distribution [29]. The phosphorylation was reversed by N-acetylcysteine (NAC) or inhibition of CK1 and CK2, suggesting that CK1 and CK2 can mediate TDP-43 phosphorylation as a result of oxidative stress. Exploring whether other causes of oxidative stress can result in the same phenotype, the authors found that H_2O_2 also induced C-terminal phosphorylation, insolubilization, and cytoplasmic distribution of TDP-43 as observed under EA exposure [29]. Oxidative stress has been associated with various aging-related disorders [30, 31], and since some TDP-43

proteinopathies are aging-related diseases, this supports the hypothesis that oxidative stress can potentiate the pathologic TDP-43 modification.

TDP-43, when found in insoluble toxic inclusions, is known to be hyper-phosphorylated at C-terminal sites [29, 32, 33]. The best characterized phosphorylation sites on the TDP-43 protein are amino acid residues Ser409 and Ser410 [32, 34]. Additional phosphorylated residues that are associated with disease pathology are Ser379, Ser403, Ser404 [32, 35, 36], which have not been as well characterized as Ser409/410. Some studies demonstrate that phosphorylation of TDP-43 negatively affects its solubility [37–40]. There are multiple kinases that can phosphorylate TDP-43; however, the exact role for these molecules in each specific neurodegenerative disease has not been clearly established and more work is required in this area.

Another potential upstream contributing factor in TDP-43 pathology is believed to be defects in autophagy. Previous studies provided evidence that pathological forms of TDP-43 are cleared through autophagy [41–43]. For example, Wang et al. demonstrated that using an mTOR inhibitor rapamycin and three other autophagy activators (spermidine, carbamazepine, and tamoxifen) reduced the number of cytosolic TDP-43 inclusions in a FTLD-TDP mouse model [42]. Further strengthening the association between autophagy and pathological TDP-43 accumulation was work by Chang et al. [44], who, studying neurons deficient in progranulin (the polypeptide product of *GRN*), found that autophagy regulators were impaired and autophagic flux was reduced. This reduction in autophagy rendered neurons more prone to accumulate pathological TDP-43 [44]. These results suggest that, in addition to oxidative damage and phosphorylation, defects in autophagy precipitate pathologic TDP-43.

Whatever the upstream mechanisms, the accumulation of one species of misfolded protein can affect cellular processes and ultimately trigger misfolding of different proteins in the same cells [1, 3, 45–48]—a process termed “pathologic synergy” [3]. This interaction among misfolded protein species may accelerate cognitive decline in some dementing disorders [3]. Tau and TDP-43 proteinopathies appear to be have the potential for pathologic synergy. Brain conditions with Tau pathologies, including argyrophilic grain disease [49], HD [50], anti-IgLON5 tauopathy [51], corticobasal degeneration (CBD), and progressive nuclear palsy (PSP) [52–54], have been reported to also demonstrate comorbid TDP-43 pathology, often with both pathologies present in the amygdala [3]. Several studies have demonstrated co-localization of Tau and TDP-43 pathologic aggregates in the same cells [3]. For example, Higashi et al. used confocal microscopy and double-label immunostaining against TDP-43 and Tau to show that TDP-43 and Tau-positive NFT co-localize in amygdala in AD patients [55]. Smith et al., in a study of 247 subjects, found that a subset of colocalized hippocampal Tau/TDP-43 pathology was associated with advanced AD [56]. In this study, immunofluorescence experiments indicated that approximately 25% of cells with TDP-43 proteinopathy showed detectable colocalized phospho-Tau immunoreactivity [56]. Even in brains that lack appreciable AD-type amyloid plaques, there can be both Tau and TDP-43 pathologies. Note that in the representative case shown in Fig. 3, Tau and TDP-43 pathologies are demonstrated in multiple regions, including, intriguingly, near the pial

surface of the brain. We conclude that these common pathologies may occur secondarily or in parallel with each other.

It is widely accepted that tauopathies span diverse disease paradigms such as developmental/genetic diseases, viral infection, triplet repeat disorders, head trauma, myositis, and many others (Table 1). Excellent prior reviews have been written on tauopathies [13–15]. It is less well-known that pathologic promiscuity also characterizes TDP-43 proteinopathies (Table 1). For example, to the relatively well-known diseases with TDP-43 proteinopathy (ALS and FTLD), one can add Alexander disease [57], Perry syndrome [58], Cockayne syndrome [59], neurodegeneration with brain iron accumulation [60], inclusion body myositis [61], HD [50], and other conditions (Table 1). Brain diseases that have been characterized to include both Tau and TDP-43 proteinopathies are indicated by red checkmarks in Table 1. The full implications of these observations are still not well understood but some inferences can be made: (1) Both Tau and TDP-43 proteinopathies can be driven by a diverse set of upstream factors; (2) Most of the upstream factors associated with Tau and TDP-43 proteinopathies involve some sort of chronic stress or insult; (3) Both Tau and TDP-43 proteinopathies are not disease-specific, but they still may play a role in influencing—perhaps dramatically exacerbating—multiple different upstream diseasedriving mechanisms.

Genetic pleiotropy in neurodegeneration and Tau/TDP-43 proteinopathies

Genetics is (for good reasons) considered to exert upstream influences on disease phenotypes. However, genetic factors may influence diseases at different nodes of a pathologic cascade—perhaps causing protein misfolding to be worsened only after it has begun to develop. As such, there is abundant evidence of pleiotropy, wherein a given gene, or even a specific gene mutation, may be associated with more than one different phenotypes.

Pleiotropic influences have been shown to be at work in both Tau and TDP-43 proteinopathies, which should come as no surprise. Since the first genomewide association study (GWAS) was conducted, there have been over 80,000 unique single nucleotide polymorphism (SNP)-trait associations discovered and published in over 3000 manuscripts [62]. As more replicable associations were found, the magnitude of pleiotropy in human disease has been increasingly appreciated. In 2011, a study of curated results from the GWAS Catalog indicated pleiotropy in nearly 17% of genes and 4.6% of SNPs [62, 63]. Notably, the conservative criteria used in this study undoubtedly induced underestimation and the distinction between a cross-phenotype association, and, true biological pleiotropy cannot be guaranteed from these database studies [64]. In a more recent survey of GWAS results, 44% of trait-associated SNPs were found to associate with more than one phenotype [65]. The increased availability of GWAS summary statistics in concert with methodological developments for estimation of the genetic covariance shared between distinct traits—including extensions for annotationbased partitioning—has enabled accelerated progress in the investigation of genetic mechanisms shared between multiple traits [66, 67]. These exciting developments will continue to help resolve the etiologies of complex diseases that affect the aged human brain.

Before discussing pleiotropy in ADRD proteinopathies, it is important to note that there is some conceptual ambiguity in the term “pleiotropy”. The detectable crossphenotype genetic associations can be classified, and only a subset deserve the designation of true biologic pleiotropy. Hence, there are subtypes of cross-phenotype associations that could be delineated when a genetic variant or gene is correlated with more than one trait: biological pleiotropy, mediated pleiotropy and spurious pleiotropy [64]. These distinctions are important but it is notable that even when some degree of reported results are “spurious” (the study design, genotype, and/or phenotype are biasing the result), there could still be important biological commonalities between two conditions as highlighted by the genetic association; such is apparently the case for schizophrenia and bipolar disorder [64]. For an excellent discussion of this topic, please see ref. [64]. Here, we focus on four genes relevant to Tau and/or TDP-43 proteinopathies: *MAPT*, *TMEM106B*, *GRN*, and *APOE* (Table 2).

Specific mutations in *MAPT* produce different pathologic features and correspondingly different clinical symptoms. The *MAPT* gene codes for the Tau protein. Alternative splicing of *MAPT* is able to generate six Tau isoforms ranging from 352 to 441 amino acids in adult human brain [68]. Direct associations between *MAPT* mutation and neurodegenerative diseases were established when dominantly inherited forms of frontotemporal dementia and parkinsonism (FTDP) were linked to chromosome 17q21–22 (FTDP-17) [69–71]. There are now dozens of known pathogenic mutations identified in *MAPT* [72]. The *MAPT* mutations exert different effects—the mutations in exons 9–12 typically impair the function of Tau microtubulebinding repeats, whereas other mutations affect alternative splicing of *Tau* pre-mRNA [73].

Underscoring the pleiotropic effects of *MAPT* gene variants, two haplotypes of *MAPT* exist and they are associated with a variety of different ADRD phenotypes. The haplotypes themselves are characterized by a 900-kilobase inversion (H1) or noninversion (H2) polymorphism [74]. Prior to discovery of H1 haplotype in *MAPT*, it was demonstrated that TG repeats (A0/A0 genotype, which is present in > 50% of Caucasians [75, 76]) in exon 9 were linked with increased risk of development of PSP [77]. Further work demonstrated that the H1 allele is also associated with increased risk of developing other tauopathies including FTLD-Tau, AD, and primary age-related tauopathy (PART) (see refs [78–81]). Perhaps surprisingly, Pastor et al. genotyped 152 PD and 52 AD patients and demonstrated that the tau A0/A0 allelic frequency was increased in PD (not considered a tauopathy) as well as AD [82]. Other groups confirmed that the H1 polymorphism was associated with PD risk [79, 83]. Collectively, these studies indicate that single nucleotide mutations, nucleotide duplications, and inversions in *MAPT* produce pleiotropic phenotypes, linking one gene to numerous downstream diseases. More specifically, *MAPT* demonstrates that a particular gene can harbor rare, high-penetrance, diseasedriving mutations that cause one set of diseases (PSP, CBD, argyrophilic grain disease, or globular glial tauopathy), or, alternatively, a separate variant in the same gene can contain relatively common, low-penetrance alleles (*MAPT* haplotypes) that are associated with altered risk for separate complex diseases (AD, PD, and PART). We recognize that it is debatable how one fits these observations into the concept of pleiotropy, however, we emphasize that these diseases differ importantly in terms of clinical and pathological features, and the genetic associations provide important clues of pathogenetic overlap.

As is the case for *MAPT*/Tau in neurodegenerative disease, evidence has emerged of genetic modifiers in TDP-43 proteinopathies [6, 7]. TDP-43 is the polypeptide product of the *TARDBP* gene, which is mutated in some cases of amyotrophic lateral sclerosis (ALS) [84, 85]. However, the far greater number of "sporadic" TDP-43 proteinopathy cases remain largely unexplained. In an attempt to find genetic risk factors for FTLD-TDP, Van Deerlin at al. studied patients with FTLD-TDP pathology and conducted a GWAS [86]. This led to the discovery of SNPs on chromosome 7p21.3 that were associated with FTLD-TDP risk. Nine SNPs in the original Van Deerlin study were found to span the transmembrane protein 106B (*TMEM106B*) gene locus. Of these gene variants, only one SNP (rs3173615) is located within the coding region of *TMEM106B* and results in a threonine to serine substitution at amino acid 185 (T185S). The missense variant affecting codon 185 is only two amino acids downstream from a critical site of N-glycosylation, residue 183 that is part of the N-X-T/S glycosylation consensus sequence [87]. The T185 isoform of TMEM106B produces ~2-fold increase in TMEM106B protein levels compared to the S185 isoform [88].

TMEM106B gene variants now have been associated with risk for numerous TDP-43 proteinopathies [86, 89–96]. However, the function of TMEM106B protein in the context of brain physiology has only partly been explored. TMEM106B is a 274 amino acid single pass, type-II transmembrane protein that localizes to cellular lysosomes [87]. It contains a highly glycosylated luminal domain and this posttranslational modification is required to transport TMEM106B from the endoplasmic reticulum to late endosomes and lysosomes. Interestingly when vacuolar H+-ATPases are inhibited, the levels of TMEM106B and GRN/progranulin (see below) significantly increase, suggesting a link between these two proteins [87]. Further, it has been demonstrated that TMEM106B has a role in regulation of lysosome synthesis, size, trafficking, and localization [87, 97–100]. Schwenk et al. [100] found that TMEM106B knockdown in primary neurons alters neuronal trafficking and blunts dendritic arborization, increasing retrograde transport of lysosomes in dendrites. This supports the finding by Stagi et al. [99] that demonstrated TMEM106B knockdown resulted in distribution of lysosomes in cell soma. Collectively, these studies provide strong evidence that TMEM106B participates in lysosomal function, and suggest that alterations in lysosomal cell physiology can be linked to neurodegeneration. Beyond FTDP-TDP, *TMEM106B* variants have been associated with hippocampal sclerosis (HS) pathology [92] (see below) and, in a recent study by Cherry and colleagues, *TMEM106B* allele rs3173615 SNP was linked to alteration of the CTE phenotype [101].

In addition to *TMEM106B*, another gene implicated in TDP-43 proteinopathy was granulin (*GRN*), as first became clear when germline mutations in *GRN* were discovered to cause FTLD-TDP [102–104]. Further, a common SNP, rs5848 (~40% of most human populations harbor one copy of this allele), located in the 3′-untranslated region (UTR) of *GRN*, was demonstrated to be associated with a ~3-fold increased risk of developing FTLD-TDP among individuals homozygous for the T-allele of rs5848 compared to C-allele [105]. Rademakers and colleagues demonstrated that the expression of *GRN* is partly regulated by a microRNA (miR-659) that binds to the mRNA's 3′-UTR [105]. Moreover, *GRN* rs5848 allele is also associated with HS pathology and TDP-43 proteinopathy in non-FTLD aged persons [106–108]. Recent work suggests that the impact of *GRN* on multiple different neurodegenerative conditions may be more extensive than was previously thought [109].

Additional discussion of the genetic factors involved in TDP-43 proteinopathy in aged individuals is provided below.

As with *MAPT*, *TMEM106B*, and *GRN*, the *APOE* locus can influence more than one disease, again suggesting shared pathophysiology among neurodegenerative diseases. The *APOE* ε4 allele, which is strongly associated with deposition of Aβ peptide and AD pathogenesis [110, 111], has also been associated with Lewy body disease [112, 113], TDP-43 proteinopathy [112, 114], and HS pathology [115]. We note that there is an entirely different list of genes (e.g., *Huntingtin, NPC1*) in which mutations can lead to both Tau and TDP-43 pathologies [116–118]. Collectively, these results underscore that—reflecting differing upstream causes and downstream pathologies—individual gene changes can exert pleiotropic effects that influence misfolded proteins and help drive resulting degenerative brain changes. The mechanistic influences of each individual gene change are still being debated although the importance of genetics is beyond doubt.

Downstream effects: insights and controversies in an evolving research field

The field of ADRD research is characterized by both a rapid pace of discovery and also areas of controversy, some of which directly pertain to current ideas on Tau and TDP-43 proteinopathies. Although each novel scientific discovery builds on the prior corpus of knowledge, the resulting new paradigms can be challenging to reconcile with prior assumptions and hypotheses. One contributing factor that generates both insights and confusion is the constantly changing methods used for making pathologic observations—notably, the immunohistochemical detection of proteinopathies. Here we highlight several important perceptions that have affected the field of ADRD research: first, since AD itself (Tau tangles and amyloid plaques) was discovered relatively early as a driver of cognitive impairment in the elderly, this also led to an assumption that most or all of non-vascular dementia was secondary to AD; and, second, relatively nonspecific neuropathologic features including synapse loss and HS pathology were attributed to specific causes, and therefore considered to define specific diseases. New data contradict these assumptions.

The neuropathologic hallmarks of AD (AD neuropathologic changes, or ADNC) were discovered at the beginning of the 20th century using silver-based histologic stains [119]. Since then, the strong correlative impact of Tau tangles on cognition has been firmly established [4, 5, 13]. However, many CPC studies have revealed that the neuropathologic substrate(s) of amnestic cognitive impairment are not usually “pure” ADNC [2, 93, 120–122], and there is now ample evidence of common non-ADNC pathways to dementia [123, 124]. The reasons that this is important are several: (1) there are multiple common, clinically impactful diseases that affect aged persons’ brains and which need to be addressed in clinical and research contexts; (2) different proteinopathic changes (e.g., Tau, TDP-43, and α-synuclein proteinopathies) often co-occur in the same brain; (3) Tau and TDP-43 proteinopathies are both evidently the result of pathologic cascades that provide possible overlap in therapeutic targets for conditions that have different upstream causes. Some of the hypothesized pathogenetic mechanisms are described above; it is important to note the

downstream effects were discovered during an era when the underlying mechanistic explanations were much less well understood.

We note two phenomena—synapse loss and HS pathology—that have been associated with dementia, and which relate to our central foci of Tau and TDP-43 proteinopathies. Synapse loss was considered for a time to be a relatively specific feature of AD, but this has been shown to be an incorrect hypothesis, for the simple reason that synapse loss characterizes numerous different neurodegenerative conditions. Multiple studies have reported ADassociated changes in specific synaptic proteins in different areas of the brain, and, these changes include both presynaptic (synaptophysin, synaptobrevin) and postsynaptic proteins (PSD-95, drebrin) [125]. The overall picture from these studies is that the loss of synapses and/or synaptic proteins is widespread in AD [125]. However, synapse loss is a nonspecific proxy for multiple diseases, a good indicator for neurodegeneration without specifically indicating AD or indeed any underlying ADRD subtype [125]. Recent CPC studies helped explain why there is an imperfect correlation between AD-type pathology per se (plaques and tangles) and cognitive status [124]. Thus, particularly in the aged brain where coexisting/mixed pathologies are common, *non-specific* markers of neurodegeneration (synapse loss, or neuronal loss) have stronger correlations with cognitive status than specific markers related to any one disease entity.

Another nonspecific histopathologic hallmark that has been associated with dementia, and that is directly related to TDP-43 proteinopathy, is HS pathology. This ill-defined pathologic endpoint has been associated with various underlying disease categories including epilepsy, hypoxia/ anoxia, infectious diseases, and various neurodegenerative conditions [52, 126–128]. The term HS is applied in clinical radiology, usually in relation to seizure disorders, and ~90% of PubMed hits for the search term “hippocampal sclerosis” are papers related to seizure disorders. From the neuropathologic standpoint, there is no specific terminology or classification system to characterize HS pathology in older individuals. In 1993, Dickson et al. [129] identified 13 elderly subjects with documented antemortem dementia and HS pathology, yet who lacked substantial ADNC. Larger case series of persons with HS and dementia were subsequently reported [130–134]. Following the 2006 discovery of TDP-43 in subjects with rare diseases (ALS and FTLD) [135], TDP-43 proteinopathy was also discovered to be a common pathologic features of brains of elderly persons lacking ALS or FTLD, including in individuals with comorbid HS pathology [136, 137]. These persons tended to be diagnosed clinically as AD [107, 138]. For the brain disease of which HS pathology was the initially discovered histopathologic indicator, it is now clear that TDP-43 proteinopathy is a more sensitive and specific feature than HS itself [48, 139–143]. A hypothetical pathologic cascade that may underlie the age-related TDP-43 proteinopathy is shown in Fig. 4, integrating findings from multiple prior studies [48, 92, 94, 144–148]. This proposed sequence illustrates how the upstream influences (*ABCC9* gene variant and arteriolosclerosis) may occupy different pathogenetic nodes in comparison to the misfolding of TDP-43 that may be affected more directly by the genetic modifiers— *TMEM106B* and *GRN* genotypes. It is hoped that the various causes of the common TDP-43 proteinopathy/ies of aging will be better characterized in future studies.

Summary

The aged brain is an extremely complex milieu and the pathologies of old age are correspondingly challenging to understand for researchers and clinicians alike. Neurodegenerative diseases evolve in a multi-step and multi-factorial manner, yet coherent paradigms are emerging (Fig. 5). Both Tau and TDP-43 proteinopathies are linked to multiple upstream influences, and both are connected with numerous deleterious downstream endpoints. Gene variants can be either disease-specific, or, they appear to be able to exert influence on the misfolding pathology itself rather than the upstream cause. Therefore, the gene variants may be associated with pleiotropic effects in multiple disease conditions. We conclude that the intriguing similarities between the pathogenetic cascades involved in Tau and TDP-43 proteinopathies may—when considered together—shed light on both, and help to guide researchers toward much-needed diagnostic and therapeutic strategies.

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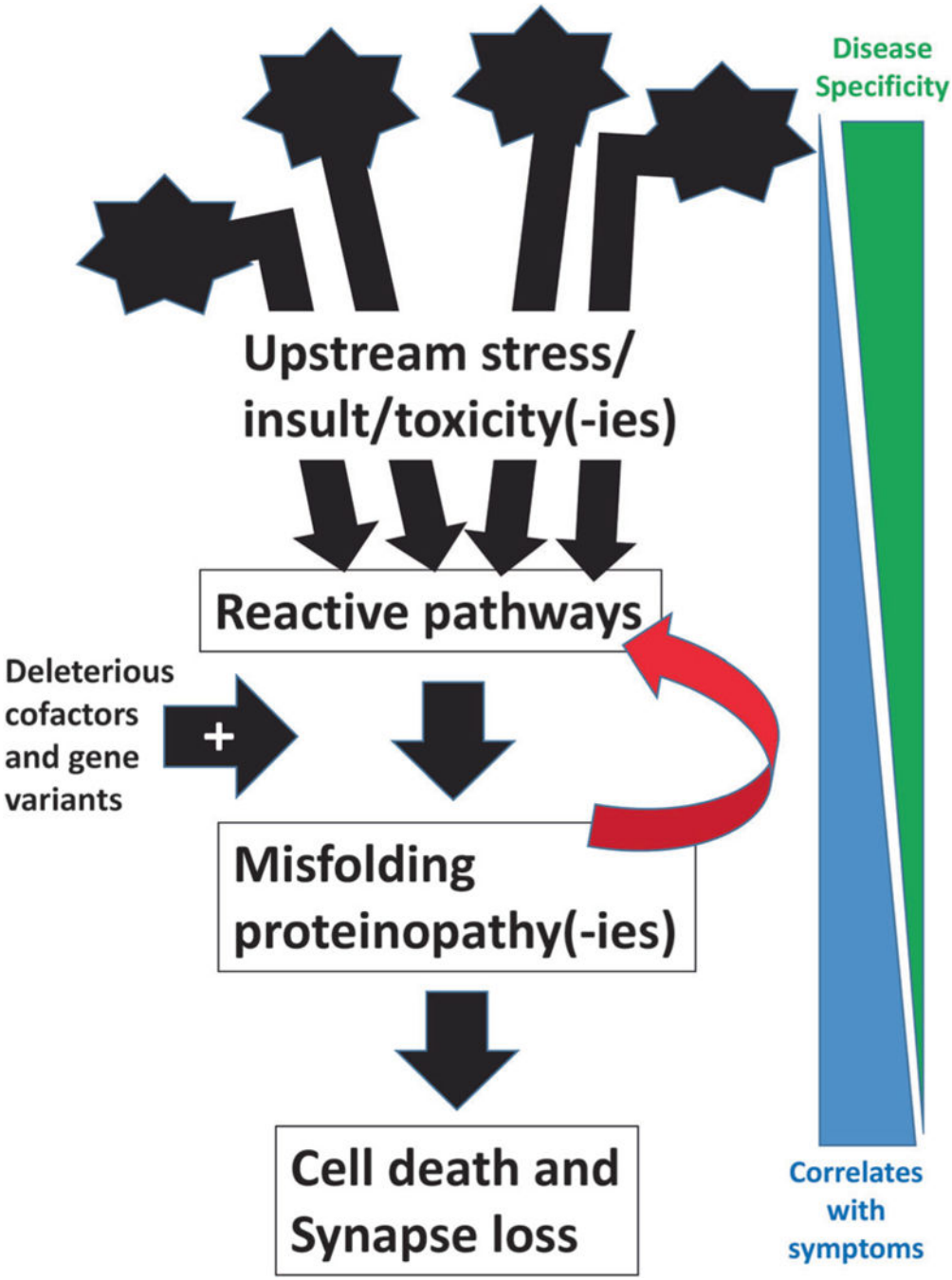

Fig. 1.

Schematic cartoon depicts a paradigm for the mechanisms underlying neurodegenerative conditions of aging. Multiple different upstream genetic and/or environmental factors have the potential to constitute a trigger for reactive changes in the brain. The reactive mechanisms and pathways may be compensatory or beneficial in some contexts. However, those same pathways may also contribute to one or multiple different proteins misfolding. The tendency to generate misfolding proteins appears to be augmented among individuals with specific genetic risk factors. Importantly, a salient feature of misfolding proteins that

are impactful, in a clinical and biologic sense, is that they appear to have a propensity to create or promote a micro-environmental shift toward biochemical pathways that augment their own misfolding. This deleterious feedback mechanism (signified by the red arrow) may promote an auto-propagating cycle, greatly amplifying the impact of the primary disease mechanism(s). The net effects of the upstream trigger, reactive pathways, and misfolding proteinopathies, are cell death and synapse elimination that can culminate in clinical manifestations. Note that on the right of the figure is indicated an inverse relationship between the factors that are disease-specific (related to upstream mechanisms) and the downstream pathologic phenomena, such as synapse loss, that correlate best with antemortem clinical symptoms

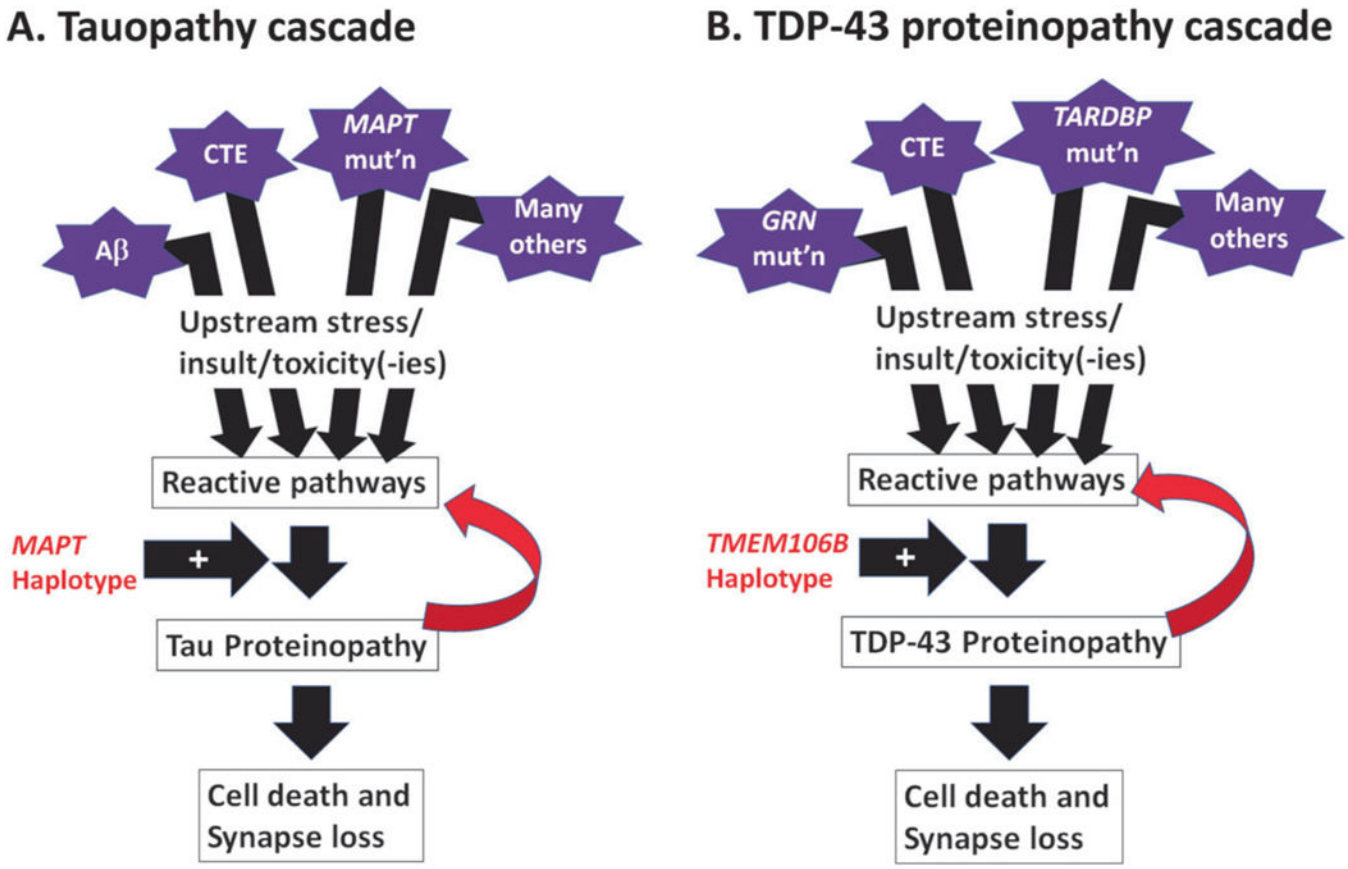

Fig. 2.

Schematic cartoons depict the overlapping elements of the pathological cascades that are seen in Tau (a) and TDP-43 (b) proteinopathies. Multiple factors can contribute to Tau or TDP-43 proteinopathies, or both (see Table 1). For Tau and TDP-43 proteins, reactive pathways—perhaps related to oxidative stress, phosphorylation, autophagy, proteolysis, inflammation, and/or other biochemical changes—appear to have an influence on the proteins' structural properties, making the polypeptides more likely to misfold and to generate both toxicity and loss of normal function. Whereas the *MAPT* haplotype appears to be an important genetic risk factor in multiple different Tau proteinopathies, the *TMEM106B* haplotype (signaled by the rs1990662 risk variant) is associated with increased risk for multiple TDP-43 proteinopathies. Both Tau and TDP-43 proteinopathies also appear to be "transmissible" in animal models (see ref. [10]), meaning that their presence in the brain can—even without another "upstream factor"—potentiate additional "downstream" proteinopathy, contributing to cell death and synapse loss

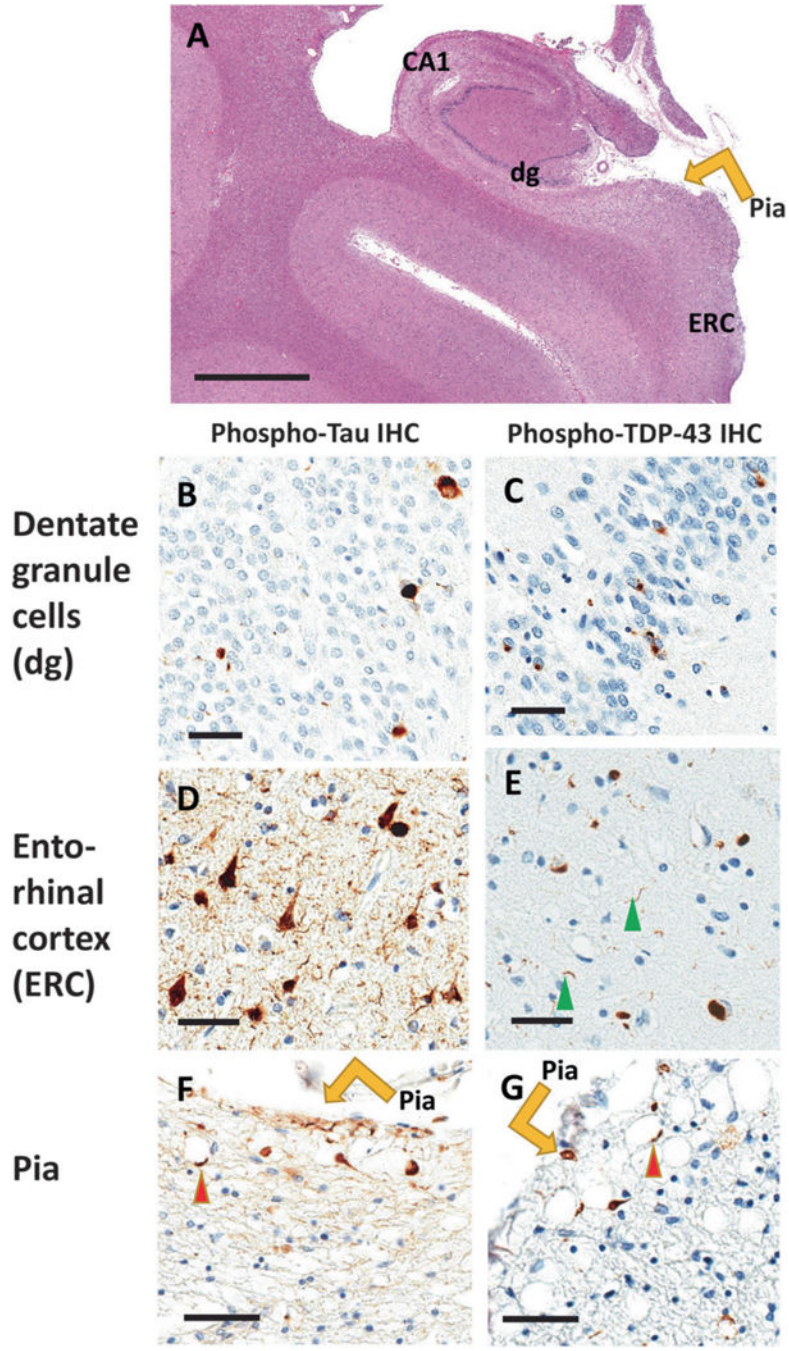

Fig. 3.

Comorbid Tau and TDP-43 pathologies are relatively common pathologic phenomena. Here are shown photomicrographs depicting stained sections from the brain of a 102-year-old woman who died with a history of dementia. Autopsy showed minimal Alzheimer's disease-type changes (no neuritic Aβ plaques and Braak NFT stage II). Portions of the brain were stained using hematoxylin and eosin (H&E; **a**), and near-adjacent sections were stained for phospho-Tau immunohistochemistry (IHC; **b**, **d**, **f**), and phospho-TDP-43 IHC (**c**, **e**, **g**). The hippocampus is shown in the coronal plane (**a**) with anatomic regions labeled. Panels **b** and

c show dentate granule (dg) cells, **d** and **e** show entorhinal cortex (ERC), and **f** and **g** demonstrate IHC staining near the pia lining (orange arrows). Sections are counterstained using hematoxylin (blue nuclei) and IHC reaction product is brown. Note that both Tau and TDP-43 proteinopathy are seen in dentate granule cells, entorhinal cortex, and within twiglike processes around corpora amylacea (red arrowheads) near the pia layer at the surface of the medial temporal lobes. Scale bars = 4 mm (**a**), 70 μm (**b**–**e**), and 100 μm (**f**, **g**)

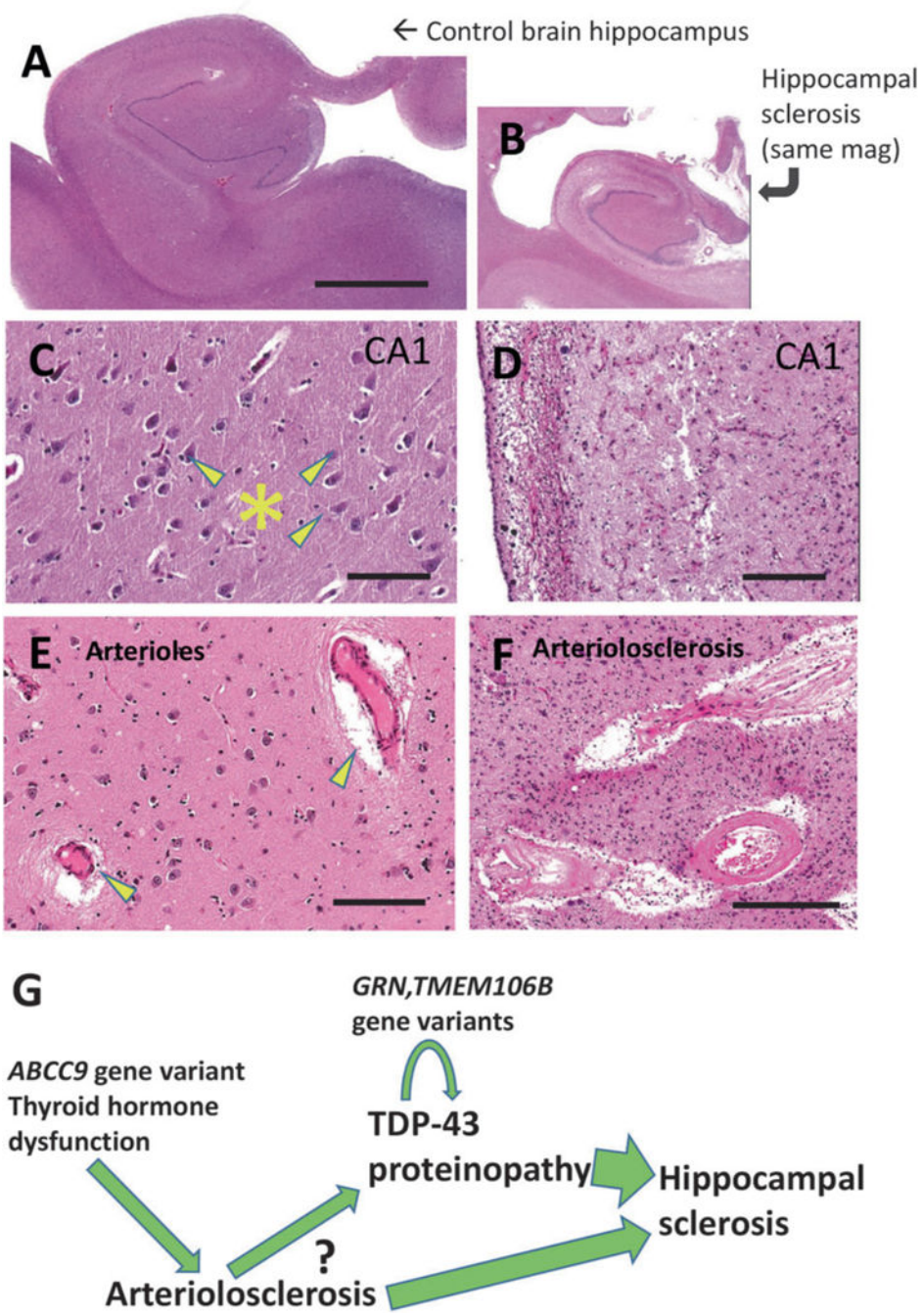

Fig. 4.

TDP-43 proteinopathy with hippocampal sclerosis (HS) pathology and arteriolosclerosis pathology provide the basis for a hypothetical pathologic cascade in aged human brains. Shown are aged control brain (**a**, **c**, **e**) and HS brain (**b**, **d**, **f**) for comparison's sake, stained using H&E. This HS brain is the same one that is depicted in Fig. 3. Note that the photomicrographs in (**a**) and (**b**) are at the same magnification, indicating the amount of atrophy in the hippocampus shown in (**b**). Portions of the hippocampal CA1 sector are shown for comparison in panels **c**, **d**. Note that the control brain has large pyramidal neurons

(arrowheads) and dense, intact eosinophilic neuropil (*). By contrast, the CA1 sector in the brain with HS pathology shows astrocytosis, dropout of neurons, and neuropil that is looser and rarefied. Brain arterioles that have histopathologic features within normal limits in aged brains (arrowheads in panel **e**) can be contrasted with arteriolosclerosis pathology (**f**) where the arteriolar walls are thickened and dysmorphic with eosinophilic material in the vessel wall that may impair cerebral blood flow. A hypothetical sequence, influenced by various factors, is shown (**g**) that incorporates findings from multiple prior studies [48, 92, 94, 144–148]. Upstream genetic risk factors may contribute to brain arteriolosclerosis in a manner that induces chronic stress in the brain, potentiating TDP-43 proteinopathy that also is influenced by additional genetic risk factors (e.g., *TMEM106B*, *GRN*). The question-mark conveys that the detailed mechanisms are as yet mostly unknown. The combination of 'upstream' stresses and TDP-43 proteinopathy may contribute to the cell loss and gliosis that manifests as HS pathology and contributes to the dementia syndrome. Scale bars = 6 mm (**a**, **b**), 120 μm (**c**, **d**), and 200 μm (**f**, **g**)

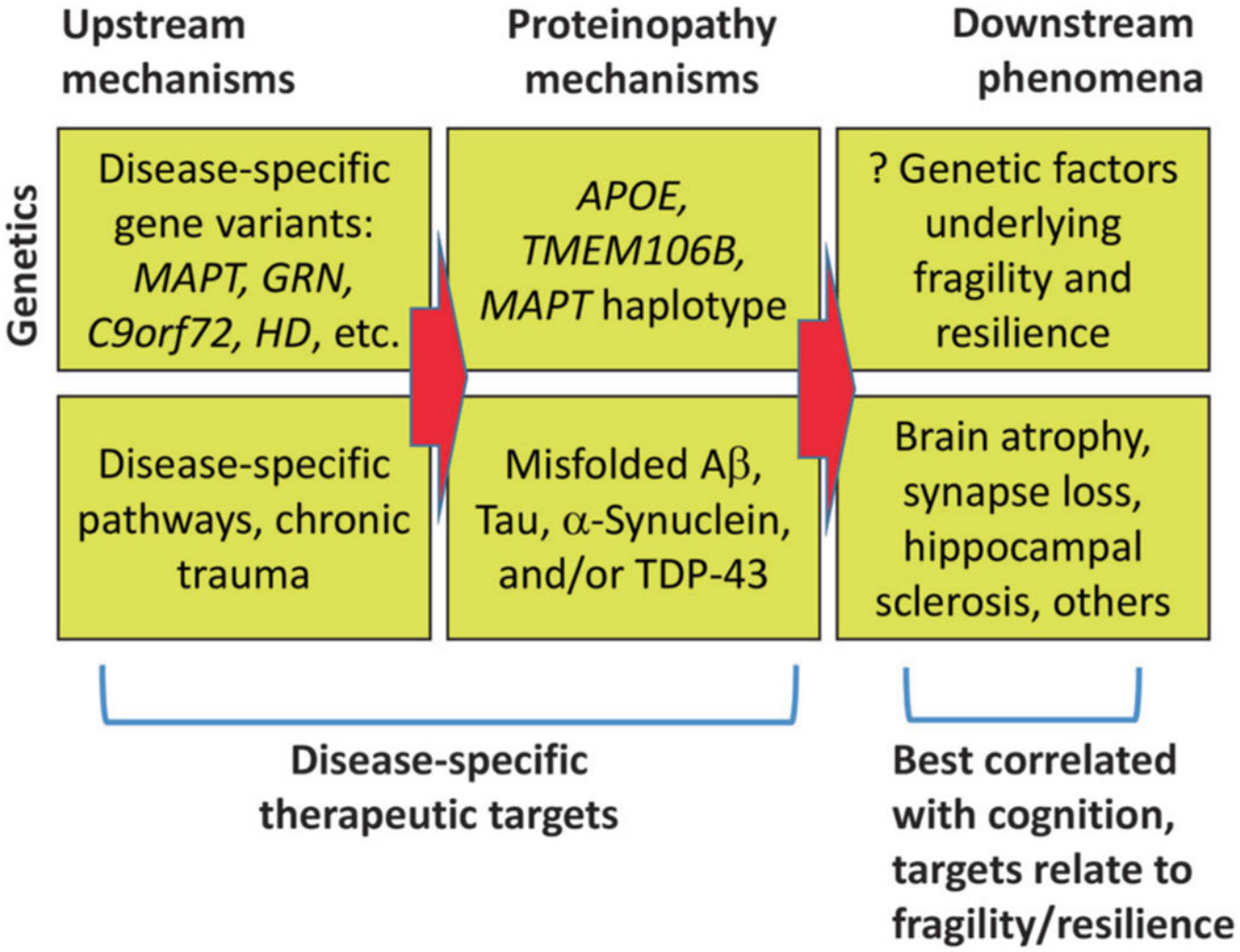

Fig. 5.

Schematic depiction of the genetic (top) and non-genetic (bottom) factors that are contributory to the complex, multi-stage pathologic cascades of neurodegenerative diseases. Different genetic factors may either contribute to “primary” condition-specific aspects of disease progression, or may induce pleiotropic effects that can influence (protect from, or exacerbate) misfolded proteins in multiple diseases, resulting in phenotypes that overlap in both clinical and pathological contexts. The aspects that may be most amenable to disease-specific therapeutic strategies are “upstream” influences, whereas the “downstream” pathologic manifestations correlate best with clinical symptoms

Table 1

A selection of Tau and/or TDP-43 proteinopathies

	Disease	Primarily genetic (Yes/No/ Subset)	There are *known* "secondary " genetic risk factors	A *known* tau-opathy?	Tau pathology a constant disease feature?	A *known* TDP-43 protein-opathy?	TDP-43 pathology a constant feature?	Selected reference(s)
✓	Late-onset AD	+/–	Y	Y	Y	Y	N	[149–151]
	FTLD-Tau (CBD, PSP, others)	N	Y	Y	Y	N	N	[78, 152, 153]
	GSS	Y	N	Y	Y	?	?	[154]
✓	Huntington's disease	Y	N	Y	N	Y	N	[50, 116]
	Argyrophilic grain disease	S	N	Y	Y	N	N	[155, 156]
✓	NBIA type 1	S	N	Y	?	Y	?	[60, 157]
	GGT	S	N	Y	Y	N	N	[158, 159]
	PART	N	Y	Y	Y	N	N	[81, 160]
	ARTAG	N	N	Y	Y	N	N	[161]
	FTLD-TDP	N	Y	N	N	Y	Y	[86, 162, 163]
	Amyotrophic lateral sclerosis	N	Y	N	N	Y	Y	[89, 135]
✓	PEP	N	N	Y	Y	Y	"Most"	[164, 165]
	SSPE	N	N	Y	N	N	N	[166]
✓	Anti-IgLON5 syndrome	N	N	Y	Y	Y	?	[51, 167]
✓	Down syndrome, early-onset AD	Y	?	Y	Y	Y	N	[149, 168]
	Myotonic dystrophy	Y	N	Y	Y	N	N	[169]
✓	Lipofuscinosis	Y	N	Y	N	Y	Y	[170, 171]
	Niemann-Pick disease, type C	Y	N	Y	Y	Y	?	[118, 172]
	Alexander disease	Y	N	N	N	Y	N	[57]
✓	Perry Syndrome	Y	N	Y	N	Y	Y	[58, 173]
	Cockayne Syndrome	Y	N	N	N	Y	Y	[59]
	Ganglioglioma/gangliocytoma	N/A	N/A	Y	Y	?	?	[174]
	Pilocytic astrocytoma	N/A	N/A	?	?	Y	N	[175]
	Lead encephalopathy	N	N	Y	?	N	N	[176]
✓	CTE	N	Y	Y	Y	Y	N	[18, 101]
	Traumatic brain injury (acute)	N	N	Y	Y	+/–	N	[177–179]
✓	Inclusion body myositis	S	N	Y	Y	Y	Y	[61, 180]

Both a Tauopathy and a TDP-43 proteinopathy? ✓

AD=Alzheimer's disease; FTLD=frontotemporal lobar degeneration; CBD=Corticobasal degeneration; PSP=Progressive supranuclear palsy; GSS=Gerstmann Straussler Scheinker; NBIA=Neurodegeneration with brain iron accumulation ; GGT=Globular glial tauopathies; PART=primary age-related tauopathy; ARTAG=Age-related tau astrogliopathy; PEP=Post-encephalitic parkinsonism; SSPE=Subacute sclerosis panencaphalitis; PKAN=Pantothenate kinase-associated neurodegeneration; CTE=chronic traumatic encephalopathy

Primary neurodegenerative
Inflammatory/infectious
Developmental/genetic
Neoplasia
Toxic/traumatic
Myopathy

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Table 2

Pleiotropy in neurodegenerative conditions: select genes

Gene	# Unique traits with GWAS hits[a]	# Total SNP-trait GWAS associations[a]	Associated conditions related to neurologic/ neurodegenerative diseases	Selected reference (s)
MAPT	26	69	FTLD-Tau (including CBD, PSP, others)	[78, 162, 181]
			Alzheimer's disease	[78, 79]
			Parkinson's disease	[78, 182, 183]
			Primary age-related tauopathy	[81]
			Globular glial tauopathy	[159, 184]
TMEM106B	9	18	FTLD-TDP and ALS	[86, 89]
			TDP-43/hippocampal sclerosis	[92, 108, 185]
			Chronic traumatic encephalopathy	[101]
			Healthy brain aging	[186, 187]
GRN	5	3	FTLD-TDP	[103, 104, 188, 189]
			TDP-43/hippocampal sclerosis	[93, 94, 106]
			Neuronal ceroid lipofuscinosis[b]	[171, 190, 191]
APOE	77	271	Alzheimer's disease	[111, 192, 193]
			TDP-43/hippocampal sclerosis	[112, 114, 115]
			Lewy body disease	[193–195]
ABCC9	2	2	TDP-43/hippocampal sclerosis	[94, 108, 196]
			Cantu syndrome	[144, 197]

[a]Association counts were based on the database from the NHGRI-EBI GWAS Catalog [62]: https://www.ebi.ac.uk/gwas/ as of 26 November 2018 and filtered to include only results with $p < 5e^{-8}$

[b]Due to homozygous *GRN* mutations