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Review Article

Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson's disease, and related disorders

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Abstract: The discovery of causative genetic mutations in affected family members has historically dominated our understanding of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS). Nevertheless, most cases of neurodegenerative disease are not explained by Mendelian inheritance of known genetic variants, but instead are thought to have a complex etiology with numerous genetic and environmental factors contributing to susceptibility. Although unbiased genome-wide association studies (GWAS) have identified novel associations to neurodegenerative diseases, most of these hits explain only modest fractions of disease heritability. In addition, despite the substantial overlap of clinical and pathologic features among major neurodegenerative diseases, surprisingly few GWAS-implicated variants appear to exhibit cross-disease association. These realities suggest limitations of the focus on individual genetic variants and create challenges for the development of diagnostic and therapeutic strategies, which traditionally target an isolated molecule or mechanistic step. Recently, GWAS of complex diseases and traits have focused less on individual susceptibility variants and instead have emphasized the biological pathways and networks revealed by genetic associations. This new paradigm draws on the hypothesis that fundamental disease processes may be influenced on a personalized basis by a combination of variants – some common and others rare, some protective and others deleterious – in key genes and pathways. Here, we review and synthesize the major pathways implicated in neurodegeneration, focusing on GWAS from the most prevalent neurodegenerative disorders, AD and PD. Using literature mining, we also discover a novel regulatory network that is enriched with AD- and PD-associated genes and centered on the SP1 and AP-1 (Jun/Fos) transcription factors. Overall, this pathway- and network-driven model highlights several potential shared mechanisms in AD and PD that will inform future studies of these and other neurodegenerative disorders. These insights also suggest that biomarker and treatment strategies may require simultaneous targeting of multiple components, including some specific to disease stage, in order to assess and modulate neurodegeneration. Pathways and networks will provide ideal vehicles for integrating relevant findings from GWAS and other modalities to enhance clinical translation.

Keywords: Neurodegeneration, Alzheimer's disease (AD), Parkinson's disease (PD), genome-wide association study (GWAS), single nucleotide polymorphism (SNP), pathway, network, biomarker, omics, complex disease

Introduction

Several common themes have driven prevailing notions about neurodegenerative diseases and their underlying etiology. Pathologically, a frequent characteristic of these diseases is the accumulation and aggregation of abnormal or misfolded proteins, as with amyloid-β (Aβ) in Alzheimer's disease (AD) [1, 2], α-synuclein in Parkinson's disease (PD) [3], huntingtin protein in Huntington's disease (HD) [4], and transactive response DNA-binding protein 43 (TDP-43) in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) [5]. The discovery of genetic mutations causing rare, early onset, familial forms of these diseases, as with the

APP (amyloid precursor protein) gene in AD [6] and the *SNCA* (α-synuclein) gene in PD [7], further focused attention on mechanisms directly connected to disease pathology. However, most cases of AD, PD, and other neurodegenerative diseases cannot be explained by simple Mendelian inheritance of genetic mutations in isolated disease-specific pathways. These late onset, sporadic forms of disease are thought instead to have a complex etiology, with susceptibility influenced by lifestyle and environmental factors in addition to as-yet-uncharacterized variants in numerous genes [8-12].

The development of methods for unbiased investigation of the genome initially promised to address this knowledge gap. Although analyses of neurodegenerative diseases represent a substantial fraction of the more than 1500 published genome-wide association studies (GWAS) [13], several limitations of this approach have emerged. Most GWAS-implicated common single nucleotide polymorphisms (SNPs) display modest individual effects on disease risk and together leave substantial heritability unexplained [11]. For example, although up to 60-80% of AD risk is estimated to derive from genetic factors [14], known genes including the uniquely large effect of *APOE* (apolipoprotein E) account for just half of this genetic variance [15]. In addition, while major psychiatric disorders have displayed genetic overlap through GWAS [16], similarly robust cross-disorder SNP associations have not been reported for neurodegenerative diseases, a surprising finding given their vast overlap of clinical and pathological features. As a result, there has been significant interest in the development of alternative perspectives and analytical strategies to better understand the genetic architecture underlying neurodegeneration [17, 18].

Recently, biological pathways and networks have become focal points for harnessing GWAS data [19, 20]. Numerous studies have demonstrated that genes functioning in the same pathway can collectively influence susceptibility to neurodegenerative diseases and traits, even when constituent SNPs do not individually exhibit significant association [21-28]. Pathways occupied by top GWAS "hits" can also highlight additional genes with more modest effects on disease risk but which may provide better targets for biomarker and drug development [29, 30]. Further, GWAS-implicated pathways and networks provide mechanistic hypotheses which can guide confirmatory testing in independent human study datasets, cell lines, and animal models. The ability to prioritize pathways of interest may be particularly important for approaches with high computational demand. These include whole genome sequencing (WGS) studies, which offer enhanced power to detect rare SNPs and copy number and other structural variants [31], studies of disease endophenotypes such as brain imaging [32, 33] or cerebrospinal fluid (CSF) biomarkers [34, 35], and studies of molecular interactions and epistasis [36-38], among other approaches.

We propose that pathways and networks provide an ideal framework for integrating known neurodegenerative mechanisms and nominating new targets. Here, we review the major pathways influencing neurodegeneration, focusing on shared processes implicated by GWAS of the most prevalent neurodegenerative disorders, AD and PD [39]. As part of a conceptual model (**Figure 1**), we discuss these pathways within broader, biologically driven groups representing intracellular mechanisms, influences from the local tissue environment and systemic circulation, and broader factors related to neurodevelopment and aging. We also perform network analysis of top AD- and PD-associated genes to discover additional novel functional relationships among multiple candidate genes and pathways.

Intracellular mechanisms

Apoptosis

Although definitions vary, apoptosis is generally understood as a programmed cell death process involving caspase activation, maintenance of organelle integrity, and a lack of cell swelling [40]. Aberrant regulation of apoptosis is one proposed explanation for the striking loss of hippocampal and cortical neurons in AD and midbrain dopaminergic neurons in PD [41]. In cultured neurons, Aβ deposition is a direct inducer of apoptosis [42], and early onset AD-associated mutations in the Aβ processing genes *APP*, *PSEN1* (presenilin-1), and *PSEN2* (presenilin-2) can promote apoptosis [43-45]. The largest known genetic risk factor for late-onset AD, the *APOE* ε4 allele [46], may also be related to apoptosis through interactions with

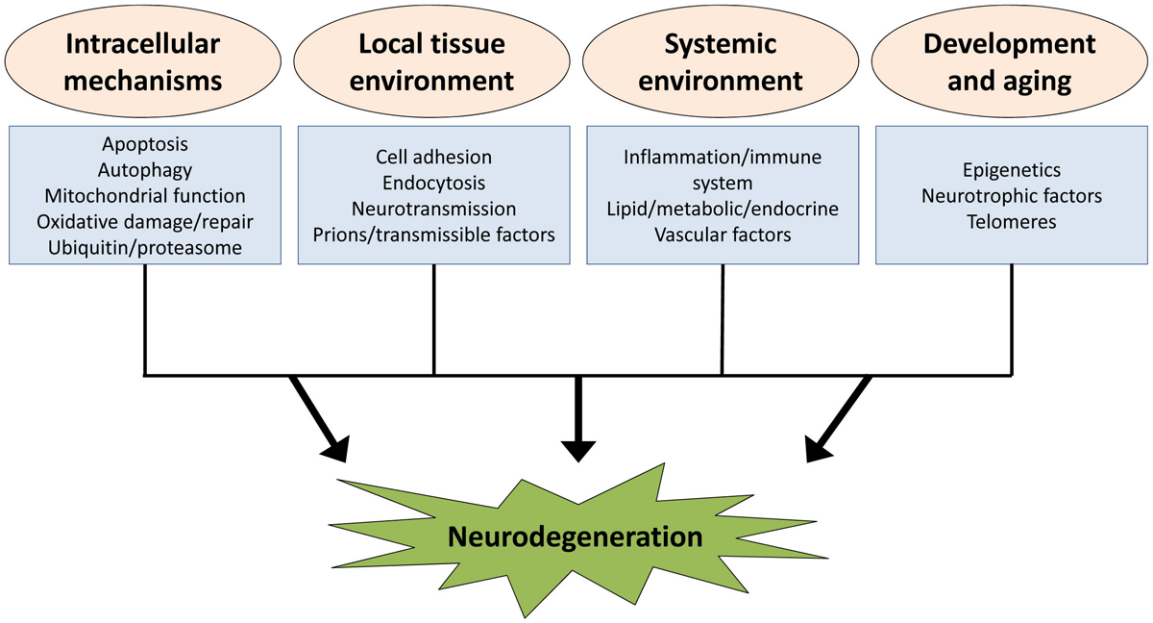

Figure 1. Conceptual model of candidate pathways contributing to neurodegeneration. Candidate pathways influencing the balance of neuronal survival and degeneration are displayed within broader functional groups based on their major site or mode of action (intracellular mechanisms, local tissue environment influences, systemic influences, and mechanisms related to neurodevelopment and aging). The pathways and overarching functional groups in this model are highly related and can have overlapping or interacting components which can collectively modulate neurodegenerative processes.

Aβ [47]. Interestingly, a recent protein interaction network analysis identified *PDCD4* (programmed cell death 4), which is up-regulated in AD brains and whose expressed protein interacts with ApoE and presenilin-2, as a potential regulator of neuronal death in AD that may bridge genetic risk factors for early- and late-onset disease [48].

Several major AD GWAS-implicated genes [49-51] also have putative roles in apoptosis. *CLU* (clusterin) is proposed to interact with BCL-2 protein family members to regulate apoptosis [52, 53], and neuroimaging studies suggest *CLU*-associated brain atrophy may be particularly evident in early stages of disease [54]. Another BCL-2 interacting gene, *HRK* (harakiri) [55], was identified in a large GWAS meta-analysis of magnetic resonance imaging (MRI) hippocampal volume, a key AD endophenotype [56]. Sequence homology and functional studies also indicate that *ABCA7* (ATP-binding cassette transporter A7) is required for efficient clearance of apoptotic cells [57]. These diverse roles suggest that AD-associated genetic variation may have pleiotropic influences on apoptotic mechanisms.

In human PD brains, molecular markers of apoptosis are abundant in the substantia nigra [58], which contains mostly dopaminergic neurons and is the primary site of atrophy and pathology in the disease [39]. The hallmark pathological feature of PD is the presence of intracellular inclusions known as Lewy bodies, which are mainly composed of insoluble aggregates of α-synuclein [3]. *SNCA* is associated with both early- and late-onset PD [7, 59] and accumulation of α-synuclein in cultured dopaminergic neurons results in apoptosis [60]. Other PD-related genes with potential roles in apoptosis include *LRRK2* (leucine-rich repeat kinase 2) [61, 62], *MAPT* (microtubule-associated protein tau) [63], and *PARK2* (parkinson protein 2, E3 ubiquitin protein ligase) [64].

Development of anti-apoptotic and other neuroprotective drugs for AD and PD is still in early stages and may ultimately require targeting of multiple genes and sub-pathways [65, 66]. Such therapies will also need to address the evolving understanding of epidemiologic and mechanistic relationships between neurodegeneration and cancer, particularly since many cancers are marked by down-regulation of

apoptosis in contrast to the up-regulation seen in neurodegeneration [67, 68]. Nevertheless, the heavy footprint of apoptotic functions among known AD and PD risk loci is encouraging for this direction of study.

Autophagy

Autophagy is a highly regulated mechanism for degradation of unnecessary or dysfunctional cellular components [4]. Controlled activation of autophagy may provide a strategy for clearance of long-lived, aggregated, or dysfunctional proteins which contribute to neurodegeneration [40]. In human brains, autophagy is transcriptionally down-regulated during normal aging but is up-regulated in AD, suggesting a possible attempted compensatory response to Aβ accumulation [69]. In mice, deletion of PD-related *LRRK2* yields impaired autophagy and augmented accumulation of α-synuclein [62]. Variants in *GBA* (glucosidase-β, acid) are also associated with PD [59, 70], and the accumulation of α-synuclein in mutant *GBA* cell lines can be reversed with administration of the autophagy inducer rapamycin [71].

An important caveat of these findings is that other potentially related outcome measures may be relevant for interpretation. For example, increased levels of apoptotic effectors such as caspase-3 have been detected after pharmacologic inhibition of autophagy in an AD mouse model [72]. Whether this represents possible cross-talk between autophagy and apoptosis to respond to cellular stress or indicates that autophagy itself is an alternate mechanism for programmed cell death remains controversial [40, 73]. Genetic analyses for epistasis (gene-gene interactions) within and between these pathways may provide alternative strategies for addressing these issues. Nevertheless, the potential for complex relationships between autophagic and other pathways involved in protein stress and response suggest that *in vivo* modulation of autophagy as a therapy for neurodegeneration may require fine-tuning to broader genetic and environmental profiles [69, 74].

Mitochondrial dysfunction

Mitochondria are primarily tasked with cellular energy production through catabolism of sugars, fats, and proteins. The underlying mechanisms for these processes are well-known to yield metabolites with the potential to promote neurodegenerative oxidative stress and DNA damage [75]. However, mitochondria also play important roles in other functions that can modulate neurodegeneration, such as apoptosis and endocytosis, and several key AD- and PD-related proteins are localized to mitochondria or the interface between mitochondria and the endoplasmic reticulum [40, 76]. The intersection of multiple pathways with mitochondrial function makes this organelle an important target for strategies to combat neurodegeneration.

In AD, the *APOE* ε4 allele is thought to cause mitochondrial dysfunction through altering the interaction capabilities of its encoded protein's lipid- and receptor-binding regions [77]. Genes involved in actin pathways, such as *CD2AP* (CD2-associated protein), may directly impact mitochondrial fission, fusion, and transport along axons due to the dynamic actin remodeling and stabilization required for these processes [78]. Impairment of mitochondrial fission, fusion, and axonal transport can promote abnormal hyperphosphorylation of MAPT (microtubule-associated protein tau), leading to the accumulation of dysfunctional mitochondria and the induction of apoptosis due to poor cellular energetics [79-81]. Components of the mitochondrial membrane are also important for normal functioning through regulation of molecular flux. For example, the AD risk genes *TOMM40* (translocase of outer mitochondrial membrane 40 homolog) and *TSPO* (translocator protein of outer membrane, 18 kDa) are essential for mitochondrial import of proteins and cholesterol, respectively [82, 83].

In PD models, *SNCA* overexpression leads to the excess α-synuclein associating with the mitochondrial membrane and inducing cytochrome c release and oxidative stress [84]. Two other genes associated with both early- and late-onset PD, *PARK2* and *PINK1* (PTEN-induced putative kinase 1) [85], code for proteins that regulate axonal transport of healthy mitochondria and autophagy of old or dysfunctional mitochondria (also known as mitophagy) [86, 87]. Another cause of early-onset PD, *PARK7* (parkinson protein 7; also known as *DJ1*), appears to work in concert with *PARK2* and *PINK1* as a sensor of oxidative stress and a regulator of mitophagy [84, 88].

Interestingly, two compounds used to create experimental models of PD exert their toxic effects in mitochondria. Exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) was initially proposed as an environmental cause of PD [89]. Since this discovery, injection of MPTP has been used to generate numerous cellular and animal models for PD [90]. In the brain, the MAO-B (monoamine oxidase B) enzyme converts MPTP into MPP+ (1-methyl-4-phenylpyridinium), which interferes with complex I of the mitochondrial electron transport chain to fatally deplete ATP levels and cause neuronal death [90]. The pesticide rotenone is also used to generate PD experimental models and similarly interferes with electron transport chain function [91].

The extensive involvement of mitochondrial stressors and protectors in AD and PD also suggests that changes in mitochondrial DNA might be additional markers of disease. Increased levels of mutations in mitochondrial DNA have been identified in both diseases [92]. However, it is not yet clear whether these mutations affect specific functions or overall mitochondrial health, and it additionally remains to be discovered if specific mitochondrial DNA variants are involved in early-stage disease pathogenesis or if mutations simply provide a measure of ongoing mitochondrial disturbances.

Oxidative DNA damage and repair

Oxidative stress refers to an imbalance between levels of toxic reactive oxygen species (ROS) and the activity of mechanisms – such as the glutathione system and DNA repair pathways – to detoxify ROS to less reactive intermediates or to reverse ROS-induced cellular damage [93]. Mitochondria are the major cellular source of ROS, and therefore dysfunction of mitochondrial components is a significant contributor to oxidative stress and its downstream effects on the structures of DNA, proteins, and lipids. For example, oxidative damage to α-synuclein can change the protein's targeting sequence to affect its cellular localization and can promote its aggregation [84], and similar mechanisms initiated by oxidative stress have been proposed to affect Aβ as well as other proteins implicated in age-related and neurodegenerative changes [94]. As a result, there is significant interest in whether genetic variation that modulates oxidative stress and its responses might affect susceptibility to neurodegeneration.

The PD-associated genes *PARK2*, *PARK7*, and *PINK1* may represent one molecular axis contributing to disease risk through regulation of oxidative stress. For example, *PARK7* knockdown is known to yield hypersensitivity to oxidative stress in mouse and fly brains [95], while the administration of ROS scavengers and the overexpression of *PINK1* and *PARK2* have been shown to rescue the effects of *PARK7* loss [96]. In AD, disease-associated variants in *CLU* may inhibit the normal role of clusterin as a protective factor against oxidative stress have been proposed to inhibit the normal role of clusterin as a sensor and chaperone of ROS [97]. Variants in *GSTO2* (glutathione S-transferase omega-2), which codes for a subunit of glutathione transferase, have also been associated with decreased levels of glutathione which increase levels of ROS as well as AD susceptibility [98]. Two other genes related to oxidative stress have been identified in large studies of AD-related endophenotypes, including the associations of *MTFR1* (mitochondrial fission regulator 1) with cognitive decline [99] and *MSRB3* (methionine sulfoxide reductase B3) with hippocampal volume [56].

Oxidative stress and DNA damage repair pathways have also been proposed as points of overlap that might explain the decreased incidence of cancer in individuals with AD or PD other [67, 100-102]. It is possible that increased levels of oxidative stress which predispose to neurodegeneration may also harm precancerous cells which would otherwise proceed to unlimited replication. Other mechanisms, such as alternative splicing of genes involved in oxidative metabolism and DNA repair, may also contribute to age- and neurodegenerative disease-associated changes in the brain [103] that oppose the development of cancer. Additional study at the population and molecular levels will be needed to clarify these potential mechanisms.

Ubiquitin-proteasome system

The ubiquitin-proteasome system is responsible for targeted degradation of misfolded, aggregated, or otherwise abnormal proteins.

The first step in activating this pathway involves ubiquitin labeling of a protein to direct it to cylindrical proteasomes in the nucleus, endoplasmic reticulum, and other compartments, which recognize ubiquitin-labeled proteins and contain protease enzymes for protein degradation. In contrast to autophagy, which can also degrade proteins in addition to whole organelles, ubiquitin-mediated proteasomal degradation is thought to be highly selective [104].

For AD, PD, and other neurodegenerative diseases marked by accumulation and aggregation of specific abnormal proteins, ubiquitin-proteasome pathways represent natural candidates for modulating pathology. Ubiquitin-positive inclusions in neurons and glial cells are also frequently identified in AD, PD, HD, FTD, and other neurodegenerative disorders and may be a sequelae of dysfunction in proteasomal pathways due to variation in genes including *GRN* (progranulin) and MAPT among others [105]. Early stages of AD additionally exhibit altered expression of ubiquitin-proteasome pathway genes in astrocytes, which support neuronal function and help maintain homeostasis in the brain [106]. More broadly, ubiquitin-mediated protein degradation may be neuroprotective in modest quantities but may stimulate bulk autophagy or BCL-2-dependent apoptosis at overwhelming or chronic levels [3, 107, 108].

Interestingly, activation of PD risk genes with direct roles in ubiquitin-proteasome pathways may have beneficial effects in multiple neurodegenerative diseases. For example, *UCHL1* (ubiquitin thiolesterase) activation was suggested to reverse AD-associated changes in neuronal dendrite structure through signaling of pathways related to cognition [109, 110]. In addition, *PARK2* overexpression is proposed to promote clearance of Aβ in AD cell culture models [111], modulate functional levels of S*YT11* (synaptotagmin) and other regulators of neurotransmission [112], and increase lifespan and reduce levels of damaged proteins and mitochondria in aging fly brains [113]. These findings corroborate the potential protective effect of ubiquitin-mediated degradation in combating neurodegeneration and highlight the overlapping molecular systems involved in autophagy, mitochondrial regulation, and the ubiquitin-proteasome system.

Local tissue environment

Cell adhesion

Cell adhesion involves the binding of a cell to another cell or to an extracellular surface. In healthy brains, cell adhesion pathways are important for maintenance of synaptic contacts and blood-brain barrier integrity as well as efficient neurotransmission and intracellular signaling [114]. Altered expression of cell adhesion genes is a consistent finding in AD and PD [115-118]. In particular, *APOE* ε4 may promote neurodegeneration through sequestering targets of *RELN* (reelin), a protease which signals through *APOER2* (apolipoprotein E, receptor 2) and NMDA receptors to enhance synaptic strength and plasticity [119, 120]. Depletion of reelin levels in key AD brain regions is thought to be an early event in the disease [121]. Genetic variation in *RELN* is also associated with AD pathology in cognitively normal older individuals [122], reinforcing the potential role of cell adhesion as an early driver of neurodegenerative changes.

Several studies propose relationships between the Aβ and cell adhesion pathways, including the cleavage of the key synaptic adhesion molecule N-cadherin by presenilin-1 and -2 [123] as well as the interaction of NCAM140 (neuronal cell adhesion molecule 140) with APP to regulate neuronal outgrowth [124]. Recent GWAS of imaging endophenotypes have also identified suggestive associations of cell adhesion genes, including *ITGA1* (integrin-α1) and *ITGA6* (integrin-α6) with florbetapir positron emission tomography (PET) cerebral Aβ burden [125] and *CDH8* (cadherin 8, type 2) with hippocampal volume [126].

In addition, pathway analyses have discovered collective effects on risk among cell adhesion genes in AD and PD. An innovative study integrating PD case-control GWAS and genome-wide expression data for nearly 3500 individuals found enrichment of association for numerous adhesion pathways, including four of the top five results (axon guidance, focal adhesion, cell adhesion molecules, adherens junction) [127]. In AD, cell adhesion pathways have also displayed enrichment of association using case-control GWAS [128] and quantitative trait GWAS of episodic memory impairment [23]. Although cell adhesion genes and pathways are

often large and therefore carry risks of false positive associations [19, 129], the similarity of findings across these three methodologically diverse studies is striking and provides further support of the hypothesis that adhesion mechanisms can contribute to neurodegeneration.

Endocytosis

The process known as endocytosis, where extracellular molecules are engulfed into membrane-bound vesicles for internalization, is important for gathering nutrients, facilitating molecular interactions and protein degradation in a protected environment, and recycling ligands and receptors [130]. Several AD- and PD-associated genes have central roles in endocytic pathways. For example, *APOE* is required for microglia to degrade Aβ following endocytosis, and *APOE* allelic variation affects the efficiency of this degradation in animal models [131]. *SORL1* (sortilin 1), whose associations to AD were recently confirmed using exome sequencing [132] and GWAS meta-analysis [133], directs APP to endocytic pathways for recycling and is crucial in preventing the sorting of APP to alternative pathways which generate Aβ [134, 135]. In PD, *LRRK2* similarly regulates the recycling and/or degradation of α-synuclein [136, 137] and is a key influence on the endocytic formation of synaptic vesicles containing neurotransmitters [138].

Promising strategies for therapeutic targeting of endocytic pathways in AD have recently emerged. In an AD mouse model, the retinoid acid receptor (RXR) agonist bexarotene was found to transcriptionally induce *APOE* to enhance clearance of Aβ and the reversal of cognitive deficits [139]. The yeast homolog of *PICALM* (phosphatidylinositol binding clathrin assembly protein) is also proposed to be an Aβ toxicity modifier [140]. Thus far, these new findings and their therapeutic implications have not yet been replicated or validated in other systems.

Targeting of endocytic pathways may also be a viable approach to combat PD. The PD-associated gene *GAK* (cyclin G associated kinase) [59] is a key mediator of endocytic vesicle trafficking by regulating interactions with adaptor proteins and later driving disassembly of the vesicle clathrin coat [141]. In cell culture, underexpression of *GAK* through knockdown or PD-related mutations accentuates α-synuclein load and toxicity [142]. The closely related gene *AAK1* (AP-2 associated kinase 1) [143] has also been associated through GWAS with age of PD onset [144]. The prevalence of disease risk genes and potential drug targets in endocytic pathways is likely to spur continued interest in the coming years.

Neurotransmission

Neurotransmitters are endogenous substances used to relay signals across a synapse. Although overshadowed in recent years by proteinopathy-related theories, initial hypotheses about AD and PD focused on disease-associated neurotransmitter deficits. The selective loss of brain acetylcholine-signaling neurons understood to be crucial for learning and memory drove the hypothesis that AD manifested from a cholinergic deficit [145]. Similarly, the loss of dopaminergic neurons from the substantia nigra understood to be important for motor functioning led to the hypothesis that dysfunction of dopaminergic neurotransmission was a primary cause of PD [146, 147]. As a result, modulation of cholinergic or dopaminergic neurotransmission forms the basis of several symptomatic therapies for AD and PD [148, 149].

Genetic and molecular studies support a role for neurotransmitter mechanisms in neurodegenerative disease. Pathways related to calcium signaling, which are important for presynaptic neurotransmitter release and postsynaptic signal transduction involving cyclic AMP (cAMP), protein kinase A (PKA), and cAMP response element binding protein (CREB), have displayed association to AD and PD [23, 127, 128, 150, 151]. The gene *COMT* (catechol-O-methyltransferase) encodes an enzyme that degrades dopamine and other catecholamine neurotransmitters, and *COMT* variants have been associated with dopamine levels in early PD [152] and may contribute to cognitive and psychiatric deficits in AD through interactions with estrogen [153, 154]. Further, in addition to its effects on mitochondria, MPP+ gains entry to cells via the dopamine transporter and inhibits synthesis of dopamine and other catecholamines [155, 156]. Variation in multiple genes also contributes to elevated glutamate levels in multiple sclerosis (MS), which is classically marked by demyelination and neuroinflammation [157].

Cholinesterase inhibitors, which attempt to increase active levels of acetylcholine in the synaptic cleft by inhibiting the enzymes that degrade acetylcholine, are a first line symptomatic therapy for AD [158]. An initial imaging study in humans identified a correlation between plasma activity of acetylcholinesterase and brain Aβ levels [159]. Recently, a larger study of 555 individuals discovered a genome-wide significant association of variants at the *BCHE* (butyrylcholinesterase) locus with brain Aβ levels [160]. Butyrylcholinesterase is enriched in senile Aβ plaques [161] and several additional lines of evidence point to potential mechanistic connections among *BCHE*, *APOE*, and Aβ [162-165]. Further, some have suggested that cholinesterase inhibitors which preferentially target butyrylcholinesterase may have disease-modifying effects in AD [166, 167]. Future work to understand the genetic relationships between the cholinergic and Aβ pathways and their impact on response to drug treatments will be important to improve risk stratification and therapeutic targeting.

Prions and transmissible factors

Prion protein is a membrane-associated, protease-sensitive glycoprotein that is typically enriched in lipid rafts consisting of tightly packed signaling and trafficking molecules [168]. As with other misfolded proteins, misfolded prion protein is normally susceptible to proteasome-mediated and other forms of protein degradation. However, accumulation of misfolded prion protein through inhibition of protein degradation pathways has been proposed to lead to the formation of protease-resistant, aggregated, infectious (i.e., transmissible) particles which can be released to neighboring cells and promote misfolded protein states in those cells [169]. This mechanism is thought to underlie the development of fatal degenerative transmissible spongiform encephalopathies such as Creutzfeld-Jakob disease (CJD), and more controversially has been proposed as a unifying factor promoting neurodegeneration across multiple neurodegenerative diseases including AD, PD, and ALS [170].

So far, genetic association tests of this hypothesis have been mixed, with some studies identifying moderate associations of *PRNP* (prion protein) variants with neurodegenerative diseases [171-173] and other studies not finding associations [174, 175]. Recent GWAS of CJD have also implicated other genes, suggesting that larger pathways related to protein conformational states and prions may be active in neurodegeneration [176-178]. More broadly, a better understanding of the forces contributing to protein conformation and susceptibility to aggregation and transmissibility would be a crucial for unlocking novel diagnostic and therapeutic approaches for neurodegenerative diseases [179]. Genetic variation affecting several related pathways, including translational machinery, endoplasmic reticulum function, chaperone-mediated folding assistance and transportation, and secondary, tertiary, and quaternary protein structural interactions, might represent plausible candidates for association testing to clarify these mechanisms.

Systemic environment

Inflammation and immune dysfunction

Published literature on AD and PD includes robust evidence of disturbances in inflammation and immune pathways. Increased levels of pro-inflammatory cytokines are common findings in blood, cerebrospinal fluid (CSF), and post-mortem brain tissue in both diseases [180-183], and non-steroidal anti-inflammatory drugs have been proposed to have protective effects [184, 185]. Active debate has endured on whether inflammation and immune dysregulation are contributors to neurodegeneration or are instead secondary to ongoing cell death. In particular, a fundamental question remains outstanding in neurodegenerative disorders: is inflammation deleterious, protective, or disease stage-dependent?

Studies of microglia, the resident immune system macrophages in the brain and CSF, provide some clues for resolving these issues. Post-mortem tissue analyses as well as newer *in vivo* PET imaging methods have identified an abundance of activated microglia in AD and PD brains [186]. Both Aβ and α-synuclein are known to activate microglia, stimulating the release of inflammatory cytokines and activation of inflammation-mediating enzymes such as matrix metalloproteinases (MMPs) [186-188]. Activated microglia also express *NLRP3* (nucleotide-binding domain and leucine-rich repeat family, pyrin domain containing 3), a

component of larger structures known as inflammasomes which promote several inflammatory processes including the maturation of IL-1β (interleukin 1, beta) [189]. In animal models, IL-1β exacerbates AD and PD progression [190, 191], and the protective effect of *NLRP3* knockout in AD mice likely reflects these underlying mechanisms [192].

Nevertheless, the role of microglia and their secreted products may not be unidirectional. For example, activated microglia are also unique among central nervous system cells in expressing *CX3CR1* (chemokine receptor 1), a receptor for the cell survival promoting chemokine known as fractalkine [193]. In PD and ALS mouse models, *CX3CR1* knockout resulted in more extensive neuronal loss [194], suggesting that augmentation of signaling through this microglial product may be required for therapy. In addition, microglia may have divergent roles across the course of neurodegenerative diseases. Whereas activation of microglia to stimulate phagocytosis of aggregated disease-related proteins may be protective during early disease stages [195, 196], chronic activation of microglia may enhance production of different cytokines which impair phagocytosis and other cell survival-related processes [197].

Genetic associations in inflammation- and immune-related pathways may have similar implications. Variants in *IL1B* (interleukin 1, beta) and *TNFA* (tumor necrosis factor, alpha) have been associated with AD and PD and may contribute to altered cytokine levels and inflammatory signaling [198, 199]. Meanwhile, AD-associated variants in *CLU* [97] and *TREM2* (triggering receptor expressed on myeloid cells 2) [200-203] may impair the normal anti-inflammatory functions of these genes. *TREM2* is predominately expressed on microglia, and recent expression analyses of post-mortem AD human and mouse brain tissue identified perturbations of networks regulated by the *TREM2* ligand *TYROBP* (protein tyrosine kinase binding protein) and enriched with genes functioning in phagocytosis [204], highlighting the potential importance of microglia and their expressed products in modulating neurodegenerative processes.

Other genes appear to bridge inflammation and innate immune responses. For example, the PD- and Crohn's disease-associated gene *LRRK2* both mediates microglial-induced inflammation [205, 206] and is a target of IFN-γ (interferon gamma), suggesting an additional role in the immune response to pathogens [207]. Similarly, the AD-associated gene *CR1* (complement component receptor 1) [49, 208-212] encodes a receptor which may regulate both inflammatory processes as well as classical complement pathways of innate immunity to eliminate synaptic connections [213]. The common involvement of inflammation and immune mechanisms is not limited to AD and PD and appears to extend to ALS [214], MS [27], FTD [215], and psychiatric disorders [216].

These findings suggest that fulfilling the promise of therapies targeting these pathways in neurodegenerative disease might be quite complex [183, 217-219]. Appropriate modulation of inflammatory and immune mechanisms may require combinatorial regulation of multiple factors, with some being activated and others deactivated depending on disease stage and an individual's genetic profile.

Lipid, metabolic, and endocrine factors

Recent epidemiological and molecular studies are converging to support the hypothesis that loss of lipid homeostasis can prominently contribute to neurodegeneration. Findings that atherosclerosis and other cardiovascular diseases are impacted by APOE ε4 and can increase the risk of AD [220] are complemented by studies suggesting that statin use to lower circulating cholesterol may modestly reduce the risk of AD and PD [221, 222]. Importantly, neuronal membranes contain substantial amounts of cholesterol and other lipids, and disturbances in lipid pathways have been frequently proposed to impact synaptic signaling and neuronal plasticity and degeneration [223-226].

As the major lipoprotein of the brain, ApoE transports key lipids and associated proteins to cells for uptake via receptor-mediated endocytosis [220]. The degree of lipidation in ApoE is an important factor in maintaining lipid homeostasis and in mediating interactions with Aβ which can promote its endocytic clearance, and *APOE* allelic variants may affect both processes [227]. Strikingly, two other AD GWAS-implicated genes have primary roles in lipid homeostasis: *CLU* represents the second major

lipoprotein of the brain (also known as apolipoprotein J) [6, 228] and *ABCA7* codes for a microglia-enriched trans-membrane cholesterol and phospholipid transporter [229, 230]. Among PD-related genes, both *PARK2* and *LRRK2* code for proteins which regulate cellular uptake of lipid-rich structures [231-233].

Recently, lipidomics analyses of the complete profile of lipids and their metabolites in tissue samples have provided initial unbiased views of lipid pathway disturbances in AD and PD [225, 234, 235]. In PD, this approach identified changes in lipid metabolism in human primary visual cortex, a region that does not exhibit significant Lewy body pathology but may be important for visual symptoms in PD [235]. These large-scale findings reinforce the concept that lipid pathways are highly complex and include numerous components with the potential for local and remote impacts on inflammation, oxidative stress, vascular, and other pathways. As a result, drugs targeting lipid pathways, including supplementary administration of endogenous compounds [236], would be expected to have pleiotropic effects in the context of neurodegenerative disease which may require modulation based on the functional status of other pathways in an individual [237].

Among metabolic disorders, a particularly interesting relationship is apparent between diabetes and AD. The presence of type 2 diabetes doubles the risk of AD [238] and metabolic dysregulation, including loss of insulin signaling through the PI3 kinase and AKT, occurs in the brain in early AD [239]. In addition, models of insulin resistance or deficiency result in cerebral Aβ buildup while models of Aβ toxicity lead to decreased insulin signaling [240]. As a result, diabetes and AD may share several drug targets, including insulin and IGF (insulin-like growth factor) stimulation [241, 242], inflammation [243], *BCHE* [160, 244, 245], and *GSK3* (glycogen synthase kinase 3) [246].

Vascular changes

Vascular pathology, including increases in vessel wall stiffness, changes in endothelial cell adhesion and metabolism, and dysfunction of the blood-brain barrier, can promote neurodegeneration through yielding chronic, low perfusion [247]. Presence of the *APOE* ε4 allele is a well-known risk factor for dyslipidemia, atherosclerosis, and coronary heart disease [100, 248], suggesting that part of the impact of *APOE* on AD may be mediated through vascular mechanisms. Pathological changes to the blood-brain barrier have also been identified in AD and PD through histological and molecular analyses and may explain the proposed modest protective effect of caffeine intake in these diseases [249-251].

Vascular smooth muscle pathways have displayed genetic associations with AD imaging phenotypes [252], and the AD-associated gene *CR1* was also found to increase the risk of cerebral amyloid angiopathy, a leading cause of intracerebral hemorrhage in older individuals [253]. Although other vascular-related genes such as *VEGF* (vascular endothelial growth factor) have displayed mostly mixed results in association tests for AD and PD [254, 255], additional studies will be important to determine the effects of *in situ* genetic risk factors on vascular functioning and brain plasticity [256], relationships of vascular pathways to other mechanisms of neurodegeneration [257], and the impact of lifestyle measures such as healthy diet and exercise on disease onset and progression. Comparisons of genetic and environmental risk factors for AD and PD with those impacting vascular dementia will also illuminate common and discordant features of their underlying pathophysiology [258].

Neurodevelopment and biological aging

Epigenetic changes

Epigenetic factors provide mechanisms for genetic control that do not involve modifications to an individual's DNA sequence [259]. These heritable changes, including RNA-associated silencing and methylation or acetylation of DNA or histones, can dynamically respond to environmental stimuli [260] and also appear to increase in frequency with aging [261]. Several AD- and PD-related genes are regulators or targets of epigenetic mechanisms. For example, nuclear α-synuclein accumulation inhibits histone acetylation and promotes apoptosis in cell culture [262]. While PD-related *SNCA* mutations potentiate this effect, inhibition of *SIRT2* (sirtuin 2) deacetylase activity may reverse *SNCA*-induced toxicity [263]. Similarly, inhibition of *HDAC2* (histone deacetylase 2) facilitates expression of genes

related to learning and memory and reverses AD symptoms in mice [264]. Epigenetic pathways may also impact Aβ pathology: in mice, *SIRT1* (sirtuin 1) deacetylase activity promotes the alternative cleavage of APP by *ADAM10* (α-secretase) to decrease formation of Aβ [265]. In addition, nucleotide repeat expansions in *C9orf72* (chromosome 9 open reading frame 72), which are a major cause of familial FTD, ALS, and related neurodegenerative disorders [266], may exert their pathologic effects via mechanisms related to RNA-mediated silencing or unconventional translation [267, 268].

Human epigenome-wide studies have not yet been reported for AD or PD. In analyses of candidate genes related to neuroinflammation and synaptic functioning, changes in methylation of CpG islands in the promoters of *BDNF* (brain-derived neurotrophic factor), *COX2* (cyclooxygenase-2), *CREB* (cyclic AMP response element binding protein), and *NFKB* (nuclear factor kappa B) were identified in human post-mortem AD frontal cortex [269]. Epigenome-wide studies might discover novel loci contributing to AD and PD and would be particularly informative for early stages of the disease spectrum, where targeted therapies would likely be most effective, and to capture dynamic changes in epigenetic markers longitudinally.

Neurotrophic factors

Neurotrophic factors (neurotrophins) are secreted growth factors that promote the development, functioning, and survival of neurons through regulation of gene transcription. Neurotrophins typically affect transcription through binding receptors at neuron terminals to stimulate second messenger signaling cascades or to promote their internalization and direct transport along the axon to the nucleus [270]. Diminished signaling and axonal transport of BDNF and NGF (nerve growth factor) have been identified in post-mortem AD brain tissue [271], and variants in *BDNF* have been associated with CSF Aβ levels in AD [272], age of onset in familial PD [273], and age-related changes in brain structure and cognitive function in individuals without frank disease [274], suggesting a primary role for neurotrophin signaling in susceptibility to neurodegeneration.

Novel treatment approaches for augmenting neurotrophin signaling appear promising for enhancing neuronal survival and functioning to combat degenerative changes. For example, exogenous administration of BDNF was observed to rescue stress hormone-induced AD-like memory impairment in rats through activation of several memory-related signaling pathways [275]. In addition, SNPs in the dopaminergic neurotrophin gene *CDNF* (cerebral dopamine neurotrophic factor) have been associated with PD risk [276], and the highly related gene *GDNF* (glial cell derived neurotrophic factor) is also being explored as a potential therapeutic target for PD [277, 278]. It should be noted that neurotrophins can be expressed in non-neuronal tissue and may have roles in promoting or inhibiting cancer at those sites [279, 280] which will require further evaluation in the context of potential neurotrophin-related treatment strategies for neurodegenerative disease.

Telomeres

Telomeres are DNA sequences at the ends of chromosomes that provide protection against the loss of more proximal genetic material during DNA replication in mitosis [281]. In germline and some somatic cells, the enzyme telomerase is responsible for maintaining telomere length and structure. However, most adult somatic cells do not express telomerase and as a result gradually lose telomere length and structure with each cycle of mitosis. While reactivation of telomerase contributes to many types of cancer by maintaining a limitless proliferative ability for tumor cells, excessively short telomere length in aging cells is proposed to signal for senescence and apoptosis [281, 282].

Although shortened telomere length in peripheral white blood cells has been associated with dementia and mortality in older adults, even after adjusting for *APOE* genotype [283], the relationship between telomere length in neurons and neurodegeneration is not yet clear. In one study, neuronal telomere shortening induced microglial proliferation (microgliosis) in aging mice but reduced microgliosis and Aβ pathology while improving memory and learning in AD mice [284]. Changes in telomere length have not been widely observed in peripheral white blood cells or in the brain in PD or ALS but will likely receive continued scrutiny [285-287]. In particular, several genetic influ-

ences on telomere length have been identified which may provide novel candidates for study in relation to neurodegenerative disease. Variants in *TERC* (telomerase RNA component), which codes for a component of telomerase, have been associated with telomere length in several human study samples [288, 289], as have genes related to DNA and histone methylation [290]. In addition, telomere pathways have exhibited enrichment of genetic association to human longevity in a large cohort study [291]. These preliminary findings suggest that neurodegenerative diseases may be amenable to therapies targeting mechanisms of cellular and biological aging more broadly [282, 292].

Network analysis of top AD- and PD-associated genes

To complement the pathway-driven approach, we performed network analysis to identify additional functional relationships between top AD- and PD-associated genes. While pathways are defined by overarching goals and the mechanistic steps involved, networks can display other types of relationships which may cut across multiple pathways or may indicate novel pathways which have not yet been characterized [19].

Due to the numerous pathways implicated in AD and PD and the pleiotropic effects of many key disease-associated genes, we hypothesized that regulatory relationships among these genes might impact multiple pathways. To explore this hypothesis, we performed transcription factor network analysis using the MetaCore software (GeneGo, Inc.). This approach incorporates knowledge from published literature to relate an input list of genes to known transcription factors and proximal targets such as ligand-receptor interactions. As input, we used the top 10 genes from the AlzGene (*APOE*, *BIN1*, *CLU*, *ABCA7*, *CR1*, *PICALM*, *MS4A6A*, *CD33*, *MS4A4E*, *CD2AP*) [293] and PDGene (*MAPT*, *SNCA*, *GBA*, *LRRK2*, *PM20D1*, *GAK*, *MCCC1*, *STK39*, *BST1*, *GPNMB*) [294] databases in addition to a small number of genes (*APP*, *PSEN1*, *PSEN2*, *DJ1*, *HIP1R*, *PARK2*, *SYT11*, *UCHL*) implicated in both Mendelian and sporadic forms of AD or PD.

A network was identified which displays relationships among 31 factors, including 19 of the 28 input genes (**Figure 2**). The probability of the software algorithm generating a network with this level of interconnectedness by random selection of input genes was exceedingly small ($p = 1.14 \times 10^{-54}$). Strikingly, numerous genes in the network exhibit co-regulation by the SP1 (specificity protein 1) and AP-1 (activating protein 1) transcription factors. SP1 has been previously noted to regulate the expression of multiple AD-related genes [23, 295]. Elevated levels of SP1 have been identified in AD human brains and mouse models [296, 297] and may be induced by inflammation and oxidative stress [296, 298]. The AP-1 transcription factor is composed of heterodimers of several proteins, including those encoded by the *FOS* and *JUN* proto-oncogenes [299]. AP-1 is an important regulator of dopaminergic signaling pathways [300, 301] as well as numerous genes related to autophagy and lysosomal function [302]. Interestingly, animal models indicate that inhibition of SP1 may be neuroprotective in AD [297] and inhibition of AP-1 may be neuroprotective in PD [303]. The connections among SP1, AP-1, and AD- and PD-associated genes suggest that coordinate modulation of these transcription factors may be a viable strategy for combating neurodegeneration.

This transcriptional network also includes several additional genes of interest which were not in the initial input list. For example, *EGR1* (early growth response 1) encodes a zinc-finger transcription factor that is important for synaptic plasticity [304] and cognitive performance [305] and whose up-regulation in AD brains may promote phosphorylation of tau [306]. The transcription factor encoded by *HMGB1* (high-mobility group protein 1) can also directly bind aggregated α-synuclein [307], regulate phagocytosis of Aβ [308, 309], and promote inflammation when secreted by activated microglia or necrotic neurons [310, 311]. Interactions between HIV-1 *TAT* (transactivator of transcription) and genes involved in AD and PD may be involved in HIV-associated cognitive impairment and Aβ pathology [312, 313]. Other genes of interest in this regulatory network include *MMP9* (matrix metalloproteinase 9) which is involved in synaptic plasticity and Aβ degradation [314], *IRF3* and *IRF7* (interferon regulatory factors 3 and 7) which regulate interferon-mediated inflammation and immune responses [315-318], and *LRP1* (low density lipoprotein receptor-related protein 1) which may affect

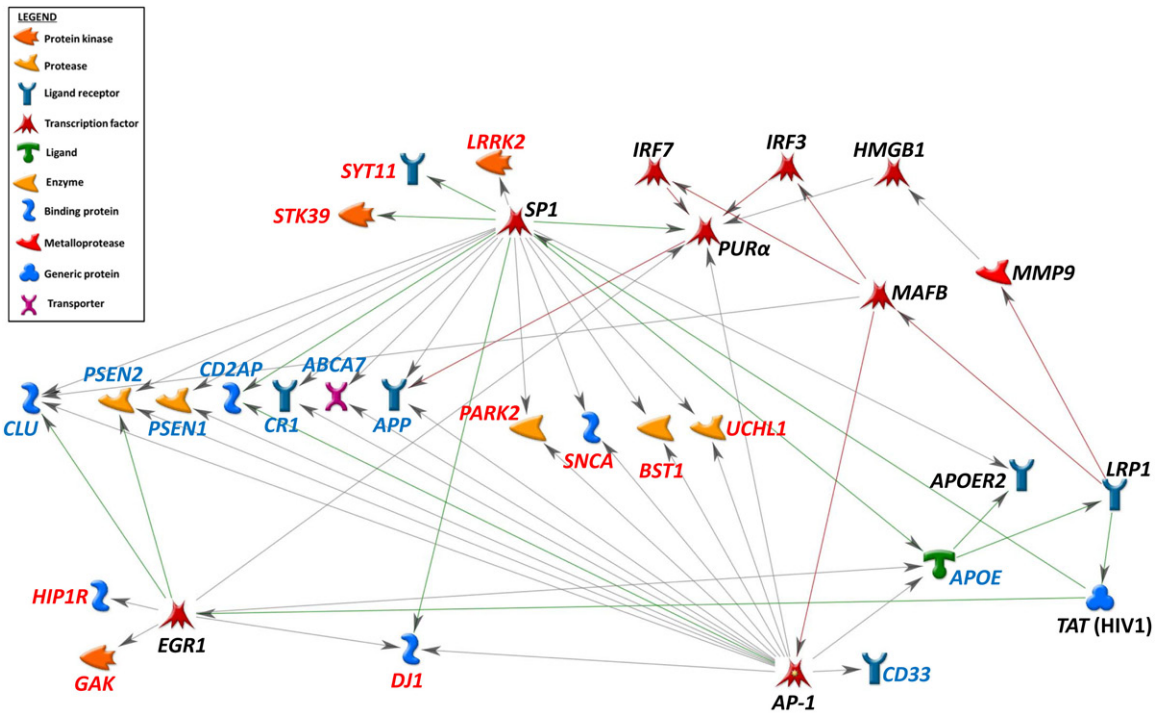

Figure 2. Regulatory network centered on the SP1 and AP-1 transcription factors is enriched with top AD and PD genes. Meta-analytic genetic association data from public databases and supplementary manual curation was used to generate a list of 13 AD genes and 15 PD genes. Network analysis was performed using MetaCore (GeneGo, Inc.) to relate these input genes to known transcription factors and proximal targets based on published findings. A highly interconnected network including 9 AD genes (labeled in blue), 10 PD genes (labeled in red), and 13 additional genes (labeled in black) was identified. Many of the input AD and PD genes exhibit co-regulation by the SP1 and AP-1 transcription factors. Other genes of interest were also related to input AD and PD genes and represent a variety of candidate pathways in neurodegeneration.

several neurodegeneration pathways including lipid metabolism, Aβ endocytosis, and inflammation [319-322].

It should be noted that this analysis is not comprehensive or unbiased. Complementary strategies, including the use of alternative criteria for selection or statistical weighting of input genes as well as other schema for defining network connections, might highlight different relationships. Nevertheless, this regulatory network generates hypotheses for further investigation and reflects, at the transcriptional level, many of the same pathways implicated by genetic studies of AD and PD. More broadly, a better understanding of altered transcriptional regulation patterns through whole genome expression arrays and whole transcriptome sequencing (RNA-seq) would augment GWAS findings in neurodegenerative disease and would provide functional information to connect genetic associations with their biochemical outcomes.

Conclusions and future prospects

Through a detailed review of GWAS, we identified numerous pathways common to AD and PD which nominate promising new targets for further study as well as biomarker and drug development. These findings build on established notions of complex disease etiology, with multiple processes presumed to influence neurodegeneration and clinical outcomes in AD, PD, and related disorders. They also advance the understanding of mechanisms likely to be crucial in maintaining brain structure and function during normal aging, in contrast to changes seen in AD and PD. These insights suggest that collaborative efforts to leverage genetic and biomarker data in AD, PD, and related disorders would likely provide major stimuli for developing unified treatment approaches to combat neurodegeneration.

For neurodegenerative and other complex diseases, accounting for the substantial heritabil-

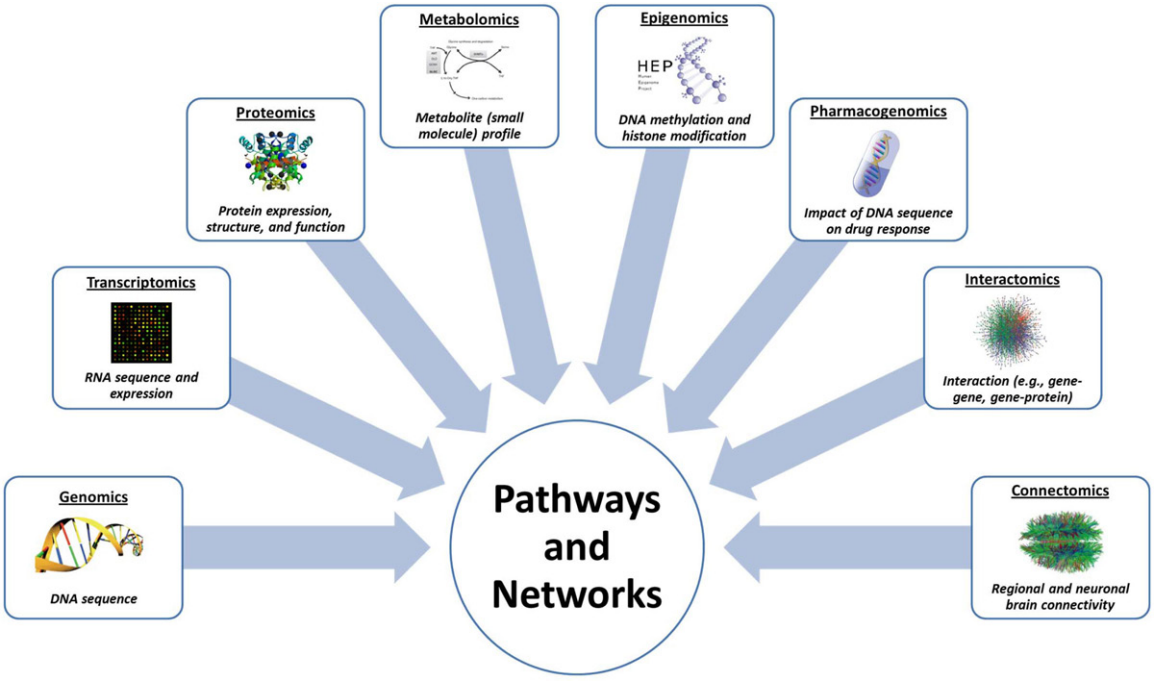

Figure 3. Biological pathways and networks: a hub for convergent omics. Numerous large scale omics approaches are being used to study complex neurodegenerative diseases and endophenotypes in human tissue and animal and other model systems. Unlike individual genes and other isolated molecules, which may not be present in all model systems and may have differential sensitivity for detection with various study designs, pathways and networks are well-conserved and can be evaluated for convergence across diverse methodological approaches. Integration of findings to identify pathways and networks with consistent relationships to disease is likely to enhance the development of diagnostic biomarkers and treatment and prevention strategies.

ity that is not explained by individual GWAS-implicated variants is an ongoing challenge [11, 323]. The pathways and networks identified here provide several routes for addressing this limitation. For example, pathway analysis of GWAS data relies on high quality pathway definitions, and for some biological realms, expert and updated manual curation of pathways can be superior to public databases and enhance statistical power for these analyses [19, 20]. Pathways implicated by common SNPs from GWAS also provide a knowledge-driven framework for targeting initial studies with WGS data, which is better suited for detection of rare SNPs and copy number and other structural variants but is computationally demanding to store and analyze [31]. Finally, interactions among known variants and lifestyle, environmental, and epigenetic factors may impact susceptibility [324], and pathways and networks understood to be involved in pathogenesis may be more likely to contain these interactions [36, 38].

Diagnosis and treatment strategies for neurodegenerative diseases may also need to evolve to reflect a complex genetic architecture involving multiple pathways. One possibility is that a combination of clinical biomarkers – such as genotype, blood and CSF analyte, brain imaging, cognitive assessment, and medical history data – might be required in order to detect the effects of multiple pathways. Since the functions of many disease pathways may be disease stage-specific, high blood levels of a particular cytokine might have different implications for risk stratification depending on genotype, brain structure, and other measures. Similarly, therapeutic and preventative strategies for neurodegenerative disease may benefit from drug combinations based on the cocktail approaches used for HIV infection and some cancers. It is possible that efficacy, and therefore the choice of particular drugs to include in the cocktail, may depend on an individual's profile of biomarkers and key genetic variants – some of which may be protective and others deleterious – in targeted pathways. The development of advanced statistical models for analysis of large, multimodal datasets will help to explore these potentially new paradigms that may facilitate a personalized medicine for neurodegenerative diseases.

More broadly, pathways and networks can serve as vehicles for integrating findings from diverse studies of neurodegeneration. There are many active strategies for large scale omics analysis of neurodegenerative disease (**Figure 3**), and findings that converge across these multiple study designs can provide confirmatory evidence that is crucial for efficient clinical translation. Isolated genes and molecules can be challenging to evaluate for convergence since they may not be represented in all data modalities or experimental model systems. In contrast, pathways and networks can incorporate data from multiple biological levels (e.g., genes, transcripts, proteins, and metabolites, among others) and may be more likely to be evolutionarily conserved [325]. For example, recent pathway-based studies integrating GWAS and gene expression data have demonstrated enhanced power, reproducibility, and connections of top findings to hypothesized disease processes [127, 326, 327]. The utility of these studies will increase as present limitations of pathway-based approaches are addressed, including how to incorporate associations from intergenic regions and from genes without known functions. A pathway-based framework also emphasizes that the discovery of a strongly associated genetic variant represents a foundation to study functionally related genes, since other components in the pathway may yield better targets for biomarker and drug development [29, 30, 328]. These advantages will be vital in harnessing the wealth of existing data on neurodegenerative disease to develop an integrated understanding of its mechanisms and formulate optimal clinical guidelines.

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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