

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 (A β) 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 path-

ways 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, $A\beta$ deposition is a direct inducer of apoptosis [42], and early onset AD-associated mutations in the $A\beta$ 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* $\epsilon 4$ allele [46], may also be related to apoptosis through interactions with

Pathways to neurodegeneration in AD and PD

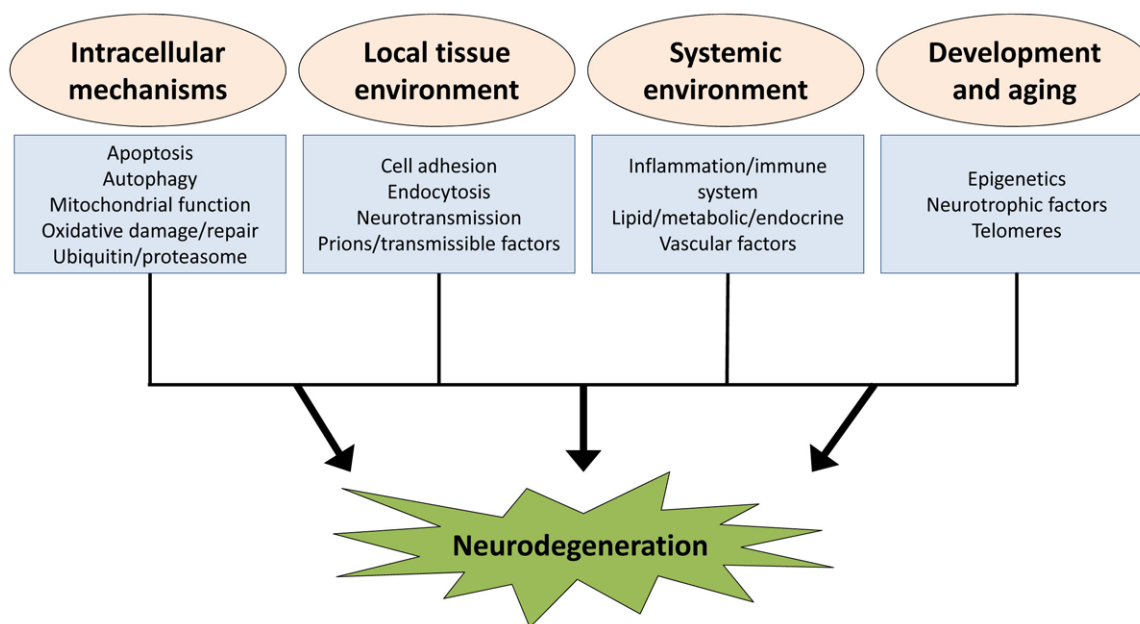


Figure 1. Conceptual model of candidate pathways contributing to neurodegeneration. Candidate pathways influencing the balance of neuronal survival and degeneration are displayed within broader functional groups based on their major site or mode of action (intracellular mechanisms, local tissue environment 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.

A β [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 A β 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 mecha-

nisms 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* ϵ 4 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 A β 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* knock-down 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 A β in AD cell culture models [111], modulate functional levels of *SYT11* (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* ϵ 4 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 A β 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- α 1) and *ITGA6* (integrin- α 6) with florbetapir positron emission tomography (PET) cerebral A β 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 A β 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 A β [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 A β and the reversal of cognitive deficits [139]. The yeast homolog of *PICALM* (phosphatidylinositol binding clathrin assembly protein) is also proposed to be an A β 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, under-expression 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 A β levels [159]. Recently, a larger study of 555 individuals discovered a genome-wide significant association of variants at the *BCHE* (butyrylcholinesterase) locus with brain A β levels [160]. Butyrylcholinesterase is enriched in senile A β plaques [161] and several additional lines of evidence point to potential mechanistic connections among *BCHE*, *APOE*, and A β [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 A β 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 Creutzfeldt-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 dis-

eases [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 A β 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-1 β (interleukin 1, beta) [189]. In animal models, IL-1 β 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 predominantly 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 ϵ 4 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 A β 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 *LRKK2* 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 A β buildup while models of A β 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* ϵ 4 allele is a well-known risk factor for dyslipidemia, athero-

sclerosis, 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 A β pathology: in mice, *SIRT1* (sirtuin 1) deacetylase activity promotes the alternative cleavage of APP by *ADAM10* (α -secretase) to decrease formation of A β [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 A β 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 A β 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*, *UCHL1*) 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 A β [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 A β pathology [312, 313]. Other genes of interest in this regulatory network include *MMP9* (matrix metalloproteinase 9) which is involved in synaptic plasticity and A β 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

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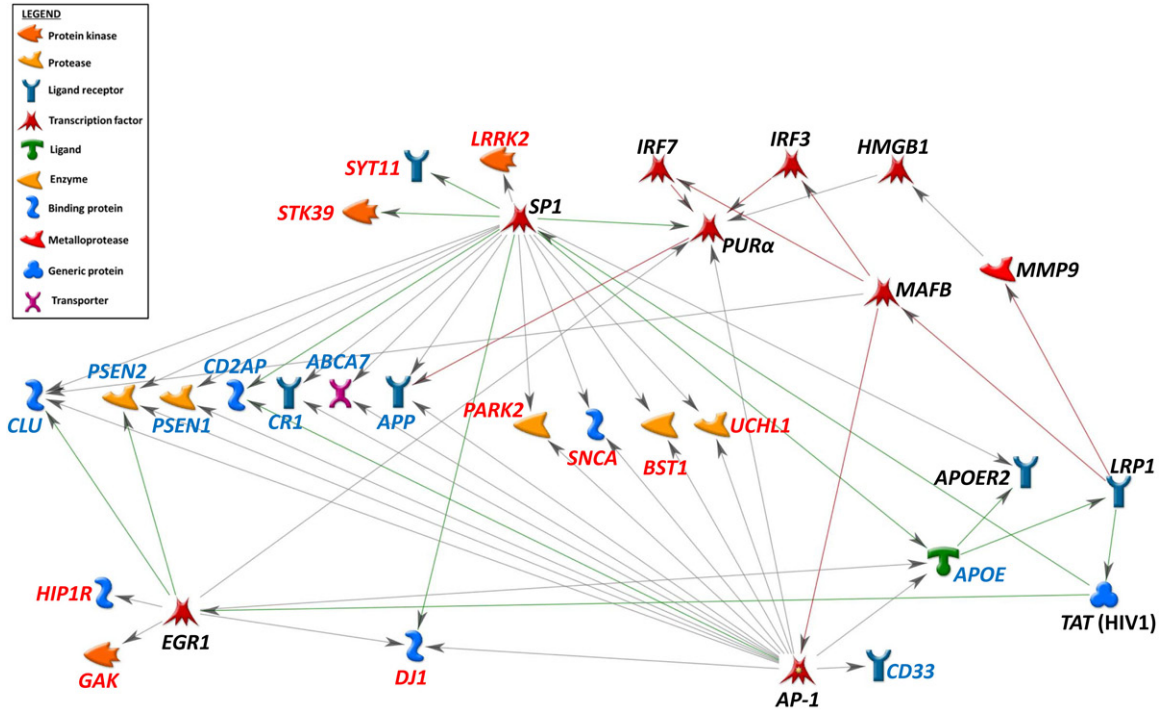


Figure 2. Regulatory network centered on the SP1 and AP-1 transcription factors is enriched with top AD and PD genes. Meta-analytic genetic association data from public databases and supplementary manual curation was used to generate a list of 13 AD genes and 15 PD genes. Network analysis was performed 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, A β 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-

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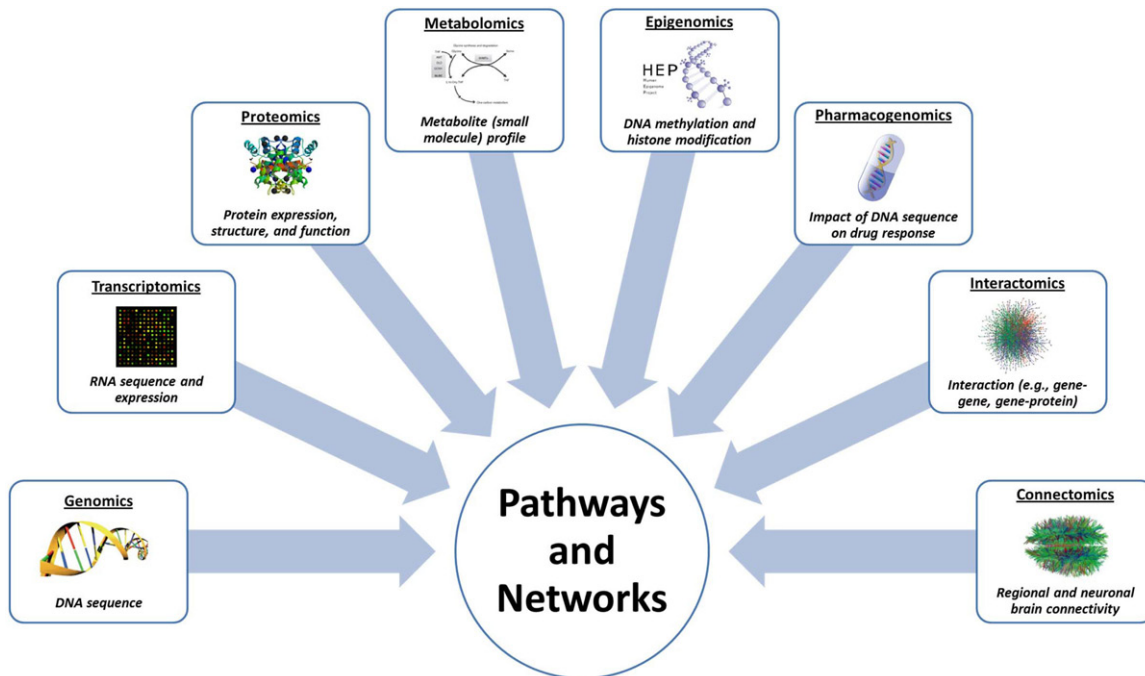


Figure 3. Biological pathways and networks: a hub for convergent omics. Numerous large scale omics approaches are being used to study complex neurodegenerative diseases and endophenotypes in human tissue and animal and other model systems. Unlike individual genes and other isolated molecules, which may 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 involv-

ing 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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References

- [1] Hardy JA and Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science* 1992; 256: 184-185.
- [2] Karran E, Mercken M and De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* 2011; 10: 698-712.
- [3] Taylor JP, Hardy J and Fischbeck KH. Toxic proteins in neurodegenerative disease. *Science* 2002; 296: 1991-1995.
- [4] Krainc D. Clearance of mutant proteins as a therapeutic target in neurodegenerative diseases. *Arch Neurol* 2010; 67: 388-392.
- [5] Rademakers R, Neumann M and Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol* 2012; 8: 423-434.
- [6] Sleegers K, Lambert JC, Bertram L, Cruts M, Amouyel P and Van Broeckhoven C. The pursuit of susceptibility genes for Alzheimer's disease: progress and prospects. *Trends Genet* 2010; 26: 84-93.
- [7] Hardy J. Genetic analysis of pathways to Parkinson disease. *Neuron* 2010; 68: 201-206.
- [8] Gandhi S and Wood NW. Genome-wide association studies: the key to unlocking neurodegeneration? *Nat Neurosci* 2010; 13: 789-794.
- [9] Bertram L and Tanzi RE. The genetic epidemiology of neurodegenerative disease. *J Clin Invest* 2005; 115: 1449-1457.
- [10] McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, Ioannidis JP and Hirschhorn JN. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet* 2008; 9: 356-369.
- [11] Chee Seng K, En Yun L, Yudi P and Kee Seng C. The pursuit of genome-wide association studies: where are we now? *J Hum Genet* 2010; 55: 195-206.
- [12] Noorbakhsh F, Overall CM and Power C. Deciphering complex mechanisms in neurodegenerative diseases: the advent of systems biology. *Trends Neurosci* 2009; 32: 88-100.
- [13] Hindorf LA, Junkins HA, Hall PN, Mehta JP and Manolio TA. A Catalog of Published Genome-Wide Association Studies. National Human Genome Research Institute, <http://www.genome.gov/gwastudies> 2011.
- [14] Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, Fiske A and Pedersen

Pathways to neurodegeneration in AD and PD

- NL. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry* 2006; 63: 168-174.
- [15] Kamboh MI, Demirci FY, Wang X, Minster RL, Carrasquillo MM, Pankratz VS, Younkin SG, Saykin AJ, Jun G, Baldwin C, Logue MW, Buros J, Farrer L, Pericak-Vance MA, Haines JL, Sweet RA, Ganguli M, Feingold E, DeKosky ST, Lopez OL and Barmada MM. Genome-wide association study of Alzheimer's disease. *Transl Psychiatry* 2012; 2: e117.
- [16] Cross-Disorder Group of the Psychiatric Genomics Consortium; Smoller JW, Craddock N, Kendler K, Lee PH, Neale BM, Nurnberger JI, Ripke S, Santangelo S, Sullivan PF. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 2013 Apr 20; 381: 1371-9.
- [17] Simon-Sanchez J and Singleton A. Genome-wide association studies in neurological disorders. *Lancet Neurol* 2008; 7: 1067-1072.
- [18] Cantor RM, Lange K and Sinsheimer JS. Prioritizing GWAS results: A review of statistical methods and recommendations for their application. *Am J Hum Genet* 2010; 86: 6-22.
- [19] Ramanan VK, Shen L, Moore JH and Saykin AJ. Pathway analysis of genomic data: concepts, methods, and prospects for future development. *Trends Genet* 2012; 28: 323-332.
- [20] Wang K, Li M and Hakonarson H. Analysing biological pathways in genome-wide association studies. *Nat Rev Genet* 2010; 11: 843-854.
- [21] Lambert JC, Grenier-Boley B, Chouraki V, Heath S, Zelenika D, Fievet N, Hannequin D, Pasquier F, Hanon O, Brice A, Epelbaum J, Berr C, Dartigues JF, Tzourio C, Campion D, Lathrop M and Amouyel P. Implication of the immune system in Alzheimer's disease: evidence from genome-wide pathway analysis. *J Alzheimers Dis* 2010; 20: 1107-1118.
- [22] Hong MG, Alexeyenko A, Lambert JC, Amouyel P and Prince JA. Genome-wide pathway analysis implicates intracellular transmembrane protein transport in Alzheimer disease. *J Hum Genet* 2010; 55: 707-709.
- [23] Ramanan VK, Kim S, Holohan K, Shen L, Nho K, Risacher SL, Foroud TM, Mukherjee S, Crane PK, Aisen PS, Petersen RC, Weiner MW, Saykin AJ; Alzheimer's Disease Neuroimaging Initiative (ADNI). Genome-wide pathway analysis of memory impairment in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort implicates gene candidates, canonical pathways, and networks. *Brain Imaging Behav* 2012; 6: 634-648.
- [24] O'Dushlaine C, Kenny E, Heron E, Donohoe G, Gill M, Morris D and Corvin A. Molecular pathways involved in neuronal cell adhesion and membrane scaffolding contribute to schizophrenia and bipolar disorder susceptibility. *Mol Psychiatry* 2011; 16: 286-292.
- [25] O'Dushlaine C, Kenny E, Heron EA, Segurado R, Gill M, Morris DW and Corvin A. The SNP ratio test: pathway analysis of genome-wide association datasets. *Bioinformatics* 2009; 25: 2762-2763.
- [26] Baranzini SE, Galwey NW, Wang J, Khankharian P, Lindberg R, Pelletier D, Wu W, Uitdehaag BM, Kappos L, Polman CH, Matthews PM, Hauser SL, Gibson RA, Oksenberg JR and Barnes MR. Pathway and network-based analysis of genome-wide association studies in multiple sclerosis. *Hum Mol Genet* 2009; 18: 2078-2090.
- [27] Sawcer S, Hellenthal G, Pirinen M, Spencer C, Patsopoulos N, Moutsianas L, Dilthey A, Su Z, Freeman C, Hunt S, Edkins S, Gray E, Booth D, Potter SC, Goris A, Band G, Oturai AB, Strange A, Saarela J, Bellenguez C, Fontaine B, Gillman M, Hemmer B, Gwilliam R, Zipp F, Jayakumar A, Martin R, Leslie S, Hawkins S, Giannoulidou E, D'Alfonso S, Blackburn H, Boneschi FM, Liddle J, Harbo HF, Perez ML, Spurkland A, Waller MJ, Mycko MP, Ricketts M, Comabella M, Hammond N, Kockum I, McCann OT, Ban M, Whitaker P, Kempainen A, Weston P, Hawkins C, Widaa S, Zajicek J, Dronov S, Robertson N, Bumpstead SJ, Barcellos LF, Ravindrarajah R, Abraham R, Alfredsson L, Ardlie K, Aubin C, Baker A, Baker K, Baranzini SE, Bergamaschi L, Bergamaschi R, Bernstein A, Berthele A, Boggild M, Bradfield JP, Brassat D, Broadley SA, Buck D, Butzkueven H, Capra R, Carroll WM, Cavalla P, Celius EG, Cepok S, Chiavacci R, Clerget-Darpoux F, Clysters K, Comi G, Cossburn M, Cournu-Rebeix I, Cox MB, Cozen W, Cree BA, Cross AH, Cusi D, Daly MJ, Davis E, de Bakker PI, Debouverie M, D'hooghe MB, Dixon K, Dobosi R, Dubois B, Ellinghaus D, Elovaaara I, Esposito F, Fontenille C, Foote S, Franke A, Galimberti D, Ghezzi A, Glessner J, Gomez R, Gout O, Graham C, Grant SF, Guerini FR, Hakonarson H, Hall P, Hamsten A, Hartung HP, Heard RN, Heath S, Hobart J, Hoshi M, Infante-Duarte C, Ingram G, Ingram W, Islam T, Jagodic M, Kabesch M, Kermode AG, Kilpatrick TJ, Kim C, Klopp N, Koivisto K, Larsson M, Lathrop M, Lechner-Scott JS, Leone MA, Leppä V, Liljedahl U, Bomfim IL, Lincoln RR, Link J, Liu J, Lorentzen AR, Lupoli S, Macciardi F, Mack T, Marriott M, Martinelli V, Mason D, McCauley JL, Mentch F, Mero IL, Mihalova T, Montalban X, Mottershead J, Myhr KM, Naldi P, Ollier W, Page A, Palotie A, Pelletier J, Piccio L, Pickersgill T, Piehl F, Pobywajlo S, Quach HL, Ramsay PP, Reunanen M, Reynolds R, Rioux JD, Rodegher M, Roesner S, Rubio JP, Rückert IM, Salvetti M, Salvi E, Santaniello A, Schaefer CA, Schreiber

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- S, Schulze C, Scott RJ, Sellebjerg F, Selmaj KW, Sexton D, Shen L, Simms-Acuna B, Skidmore S, Sleiman PM, Smestad C, Sørensen PS, Søndergaard HB, Stankovich J, Strange RC, Sulonen AM, Sundqvist E, Syvänen AC, Taddeo F, Taylor B, Blackwell JM, Tienari P, Bramon E, Tourbah A, Brown MA, Tronczynska E, Casas JP, Tubridy N, Corvin A, Vickery J, Jankowski J, Villoslada P, Markus HS, Wang K, Mathew CG, Wason J, Palmer CN, Wichmann HE, Plomin R, Willoughby E, Rautanen A, Winkelmann J, Wittig M, Trembath RC, Yaouanq J, Viswanathan AC, Zhang H, Wood NW, Zuvich R, Deloukas P, Langford C, Duncanson A, Oksenberg JR, Pericak-Vance MA, Haines JL, Olsson T, Hillert J, Ivins AJ, De Jager PL, Peltonen L, Stewart GJ, Hafler DA, Hauser SL, McVean G, Donnelly P, Compston A. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* 2011; 476: 214-219.
- [28] Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet* 2011; 43: 977-983.
- [29] Hirschhorn JN. Genomewide Association Studies — Illuminating Biologic Pathways. *N Engl J Med* 2009; 360: 1699-1701.
- [30] Penrod NM, Cowper-Sal-lari R and Moore JH. Systems genetics for drug target discovery. *Trends Pharmacol Sci* 2011; 32: 623-630.
- [31] Bras J, Guerreiro R and Hardy J. Use of next-generation sequencing and other whole-genome strategies to dissect neurological disease. *Nat Rev Neurosci* 2012; 13: 453-464.
- [32] Braskie MN, Ringman JM and Thompson PM. Neuroimaging measures as endophenotypes in Alzheimer's disease. *Int J Alzheimers Dis* 2011; 2011: 490140.
- [33] Kendler KS and Neale MC. Endophenotype: a conceptual analysis. *Mol Psychiatry* 2010; 15: 789-797.
- [34] Cruchaga C, Kauwe JS, Nowotny P, Bales K, Pickering EH, Mayo K, Bertelsen S, Hinrichs A; Alzheimer's Disease Neuroimaging Initiative; Fagan AM, Holtzman DM, Morris JC, Goate AM. Cerebrospinal fluid APOE levels: an endophenotype for genetic studies for Alzheimer's disease. *Hum Mol Genet* 2012 Oct 15; 21: 4558-71.
- [35] Jack CR Jr, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Lowe V, Kantarci K, Bernstein MA, Senjem ML, Gunter JL, Boeve BF, Trojanowski JQ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Knopman DS; Alzheimer's Disease Neuroimaging Initiative. Shapes of the Trajectories of 5 Major Biomarkers of Alzheimer Disease. *Arch Neurol* 2012; 69: 856-867.
- [36] McKinney BA and Pajewski NM. Six Degrees of Epistasis: Statistical Network Models for GWAS. *Front Genet* 2011; 2: 109.
- [37] Vidal M, Cusick ME and Barabasi AL. Interactome networks and human disease. *Cell* 2011; 144: 986-998.
- [38] Schadt EE. Molecular networks as sensors and drivers of common human diseases. *Nature* 2009; 461: 218-223.
- [39] Nussbaum RL and Ellis CE. Alzheimer's Disease and Parkinson's Disease. *N Engl J Med* 2003; 348: 1356-1364.
- [40] Bredesen DE, Rao RV and Mehlen P. Cell death in the nervous system. *Nature* 2006; 443: 796-802.
- [41] Mattson MP. Apoptosis in neurodegenerative disorders. *Nat Rev Mol Cell Biol* 2000; 1: 120-129.
- [42] Loo DT, Copani A, Pike CJ, Whittemore ER, Walencewicz AJ and Cotman CW. Apoptosis Is Induced by Beta-Amyloid in Cultured Central-Nervous-System Neurons. *Proc Natl Acad Sci U S A* 1993; 90: 7951-7955.
- [43] Wolozin B, Iwasaki K, Vito P, Ganjei JK, Lacana E, Sunderland T, Zhao B, Kusiak JW, Wasco W and D'Adamio L. Participation of presenilin 2 in apoptosis: enhanced basal activity conferred by an Alzheimer mutation. *Science* 1996; 274: 1710-1713.
- [44] Weidemann A, Paliga K, Durrwang U, Reinhard FBM, Schuckert O, Evin G and Masters CL. Proteolytic processing of the Alzheimer's disease amyloid precursor protein within its cytoplasmic domain by caspase-like proteases. *J Biol Chem* 1999; 274: 5823-5829.
- [45] Guo Q, Sebastian L, Sopher BL, Miller MW, Glazner GW, Ware CB, Martin GM and Mattson MP. Neurotrophic factors [activity-dependent neurotrophic factor (ADNF) and basic fibroblast growth factor (bFGF)] interrupt excitotoxic neurodegenerative cascades promoted by a PS1 mutation. *Proc Natl Acad Sci U S A* 1999; 96: 4125-4130.
- [46] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL and Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; 261: 921-923.
- [47] Koffie RM, Hashimoto T, Tai HC, Kay KR, Serrano-Pozo A, Joyner D, Hou S, Kopeikina KJ, Frosch MP, Lee VM, Holtzman DM, Hyman BT and Spires-Jones TL. Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-beta. *Brain* 2012; 135: 2155-2168.
- [48] Soler-Lopez M, Zanzoni A, Lluís R, Stelzl U and Aloy P. Interactome mapping suggests new

- mechanistic details underlying Alzheimer's disease. *Genome Res* 2011; 21: 364-376.
- [49] Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fievet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanche H, Dartigues JF, Tzourio C, Gut I, Van Broeckhoven C, Alperovitch A, Lathrop M and Amouyel P. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* 2009; 41: 1094-1099.
- [50] Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schurmann B, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frolich L, Hampel H, Hull M, Rujescu D, Goate AM, Kauwe JSK, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Klopp N, Wichmann HE, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ and Williams J. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* 2009; 41: 1088-1093.
- [51] Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, Abraham R, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Beaumont H, Warden D, Wilcock G, Love S, Kehoe PG, Hooper NM, Vardy ER, Hardy J, Mead S, Fox NC, Rossor M, Collinge J, Maier W, Jessen F, Ruther E, Schurmann B, Heun R, Kolsch H, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frolich L, Hampel H, Gallacher J, Hull M, Rujescu D, Giegling I, Goate AM, Kauwe JSK, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Klopp N, Wichmann HE, Pankratz VS, Sando SB, Aasly JO, Barcikowska M, Wszolek ZK, Dickson DW, Graff-Radford NR, Petersen RC, van Duijn CM, Breteler MMB, Ikram MA, DeStefano AL, Fitzpatrick AL, Lopez O, Launer LJ, Seshadri S, Berr C, Campion D, Epelbaum J, Dartigues JF, Tzourio C, Alperovitch A, Lathrop M, Feulner TM, Friedrich P, Riehle C, Krawczak M, Schreiber S, Mayhaus M, Nicolhaus S, Wagenpfeil S, Steinberg S, Stefansson H, Stefansson K, Snaedal J, Bjornsson S, Jonsson PV, Chouraki V, Genier-Boley B, Hiltunen M, Soininen H, Combarros O, Zelenika D, Delepine M, Bullido MJ, Pasquier F, Mateo I, Frank-Garcia A, Porcellini E, Hanon O, Coto E, Alvarez V, Bosco P, Siciliano G, Mancuso M, Panza F, Solfrizzi V, Nacmias B, Sorbi S, Bossu P, Piccardi P, Arosio B, Annoni G, Seripa D, Pilotto A, Scarpini E, Galimberti D, Brice A, Hannequin D, Licastro F, Jones L, Holmans PA, Jonsson T, Riemschneider M, Morgan K, Younkin SG, Owen MJ, O'Donovan M, Amouyel P and Williams J. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet* 2011 May; 43: 429-35.
- [52] Yu JT and Tan L. The Role of Clusterin in Alzheimer's Disease: Pathways, Pathogenesis, and Therapy. *Mol Neurobiol* 2012; 45: 314-326.
- [53] Youle RJ and Strasser A. The BCL-2 protein family: opposing activities that mediate cell death. *Nat Rev Mol Cell Biol* 2008; 9: 47-59.
- [54] Thambisetty M, An Y, Kinsey A, Koka D, Saleem M, Guntert A, Kraut M, Ferrucci L, Davatzikos C, Lovestone S and Resnick SM. Plasma clusterin concentration is associated with longitudinal brain atrophy in mild cognitive impairment. *Neuroimage* 2012; 59: 212-217.
- [55] Sborgi L, Barrera-Vilarmau S, Obregon P and de Alba E. Characterization of a novel interaction between Bcl-2 members Diva and Harakiri. *PLoS One* 2010; 5: e15575.
- [56] Bis JC, DeCarli C, Smith AV, van der Lijn F, Crivello F, Fornage M, Debette S, Shulman JM, Schmidt H, Srikanth V, Schuur M, Yu L, Choi SH, Sigurdsson S, Verhaaren BFJ, DeStefano AL, Lambert JC, Jack CR, Struchalin M, Stankovich J, Ibrahim-Verbaas CA, Fleischman D, Zijdenbos A, den Heijer T, Mazoyer B, Coker LH, Enzinger C, Danoy P, Amin N, Arfanakis K,

- van Buchem MA, de Bruijn RF, Beiser A, Dufouil C, Huang J, Cavalieri M, Thomson R, Nissen WJ, Chibnik LB, Gislason GK, Hofman A, Pikula A, Amouyel P, Freeman KB, Phan TG, Oostra BA, Stein JL, Medland SE, Vasquez AA, Hibar DP, Wright MJ, Franke B, Martin NG, Thompson PM, Nalls MA, Uitterlinden AG, Au R, Elbaz A, Beare RJ, van Swieten JC, Lopez OL, Harris TB, Chouraki V, Breteler MMB, De Jager PL, Becker JT, Vernooij MW, Knopman D, Fazeakas F, Wolf PA, van der Lugt A, Gudnason V, Longstreth WT, Brown MA, Bennett DA, van Duijn CM, Mosley TH, Schmidt R, Tzourio C, Launer LJ, Ikram MA and Seshadri S. Common variants at 12q14 and 12q24 are associated with hippocampal volume. *Nature Genetics* 2012; 44: 545-551.
- [57] Jehle AW, Gardai SJ, Li S, Linsel-Nitschke P, Morimoto K, Janssen WJ, Vandivier RW, Wang N, Greenberg S, Dale BM, Qin C, Henson PM and Tall AR. ATP-binding cassette transporter A7 enhances phagocytosis of apoptotic cells and associated ERK signaling in macrophages. *J Cell Biol* 2006; 174: 547-556.
- [58] Jenner P and Olanow CW. Understanding cell death in Parkinson's disease. *Ann Neurol* 1998; 44: S72-84.
- [59] International Parkinson Disease Genomics Consortium; Nalls MA, Plagnol V, Hernandez DG, Sharma M, Sheerin UM, Saad M, Simon-Sanchez J, Schulte C, Lesage S, Sveinbjornsdottir S, Stefansson K, Martinez M, Hardy J, Heutink P, Brice A, Gasser T, Singleton AB and Wood NW. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet* 2011; 377: 641-649.
- [60] Xu J, Kao SY, Lee FJ, Song W, Jin LW and Yankner BA. Dopamine-dependent neurotoxicity of alpha-synuclein: a mechanism for selective neurodegeneration in Parkinson disease. *Nat Med* 2002; 8: 600-606.
- [61] Iaccarino C, Crosio C, Vitale C, Sanna G, Carri MT and Barone P. Apoptotic mechanisms in mutant LRRK2-mediated cell death. *Hum Mol Genet* 2007; 16: 1319-1326.
- [62] Tong Y, Yamaguchi H, Giaime E, Boyle S, Kopan R, Kelleher RJ 3rd and Shen J. Loss of leucine-rich repeat kinase 2 causes impairment of protein degradation pathways, accumulation of alpha-synuclein, and apoptotic cell death in aged mice. *Proc Natl Acad Sci U S A* 2010; 107: 9879-9884.
- [63] Qureshi HY and Paudel HK. Parkinsonian neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and alpha-synuclein mutations promote Tau protein phosphorylation at Ser262 and destabilize microtubule cytoskeleton in vitro. *J Biol Chem* 2011; 286: 5055-5068.
- [64] Johnson BN, Berger AK, Cortese GP and Lavoie MJ. The ubiquitin E3 ligase parkin regulates the proapoptotic function of Bax. *Proc Natl Acad Sci U S A* 2012; 109: 6283-6288.
- [65] Sureda FX, Junyent F, Verdaguer E, Auladell C, Pelegri C, Vilaplana J, Folch J, Canudas AM, Zarate CB, Palles M and Camins A. Antiapoptotic drugs: a therapeutic strategy for the prevention of neurodegenerative diseases. *Curr Pharm Des* 2011; 17: 230-245.
- [66] Rohn TT. The role of caspases in Alzheimer's disease; potential novel therapeutic opportunities. *Apoptosis* 2010; 15: 1403-1409.
- [67] Tabares-Seisdedos R, Dumont N, Baudot A, Valderas JM, Climent J, Valencia A, Crespo-Facorro B, Vieta E, Gomez-Beneyto M, Martinez S and Rubenstein JL. No paradox, no progress: inverse cancer comorbidity in people with other complex diseases. *Lancet Oncol* 2011; 12: 604-608.
- [68] Holohan KN, Lahiri DK, Schneider BP, Foroud T and Saykin AJ. Functional microRNAs in Alzheimer's disease and cancer: differential regulation of common mechanisms and pathway. *Front Genet* 2012; 3: 323.
- [69] Lipinski MM, Zheng B, Lu T, Yan Z, Py BF, Ng A, Xavier RJ, Li C, Yankner BA, Scherzer CR and Yuan J. Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease. *Proc Natl Acad Sci U S A* 2010; 107: 14164-14169.
- [70] Sidransky E and Lopez G. The link between the GBA gene and parkinsonism. *Lancet Neurol* 2012; 11: 986-998.
- [71] Cullen V, Sardi SP, Ng J, Xu YH, Sun Y, Tomlinson JJ, Kolodziej P, Kahn I, Saftig P, Woulfe J, Rochet JC, Glicksman MA, Cheng SH, Grabowski GA, Shihabuddin LS and Schlossmacher MG. Acid β -glucosidase mutants linked to gaucher disease, parkinson disease, and lewy body dementia alter α -synuclein processing. *Ann Neurol* 2011; 69: 940-953.
- [72] Yang DS, Kumar A, Stavrides P, Peterson J, Peterhoff CM, Pawlik M, Levy E, Cataldo AM and Nixon RA. Neuronal apoptosis and autophagy cross talk in aging PS/APP mice, a model of Alzheimer's disease. *Am J Pathol* 2008; 173: 665-681.
- [73] Kroemer G and Levine B. Autophagic cell death: the story of a misnomer. *Nat Rev Mol Cell Biol* 2008; 9: 1004-1010.
- [74] Harris H and Rubinsztein DC. Control of autophagy as a therapy for neurodegenerative disease. *Nat Rev Neurol* 2012; 8: 108-117.
- [75] Atamna H and Frey WH 2nd. Mechanisms of mitochondrial dysfunction and energy deficiency

Pathways to neurodegeneration in AD and PD

- cy in Alzheimer's disease. *Mitochondrion* 2007; 7: 297-310.
- [76] De Strooper B and Scorrano L. Close encounter: mitochondria, endoplasmic reticulum and Alzheimer's disease. *EMBO J* 2012; 31: 4095-4097.
- [77] Chang S, ran Ma T, Miranda RD, Balestra ME, Mahley RW and Huang Y. Lipid- and receptor-binding regions of apolipoprotein E4 fragments act in concert to cause mitochondrial dysfunction and neurotoxicity. *Proc Natl Acad Sci U S A* 2005; 102: 18694-18699.
- [78] Bruck S, Huber TB, Ingham RJ, Kim K, Niederstrasser H, Allen PM, Pawson T, Cooper JA and Shaw AS. Identification of a novel inhibitory actin-capping protein binding motif in CD2-associated protein. *J Biol Chem* 2006; 281: 19196-19203.
- [79] DuBoff B, Gotz J and Feany MB. Tau promotes neurodegeneration via DRP1 mislocalization in vivo. *Neuron* 2012; 75: 618-632.
- [80] Iijima-Ando K, Sekiya M, Maruko-Otake A, Ohtake Y, Suzuki E, Lu B and Iijima KM. Loss of axonal mitochondria promotes tau-mediated neurodegeneration and Alzheimer's disease-related tau phosphorylation via PAR-1. *PLoS Genet* 2012; 8: e1002918.
- [81] Krstic D and Knuesel I. Deciphering the mechanism underlying late-onset Alzheimer disease. *Nat Rev Neurol* 2013; 9: 25-34.
- [82] Rupprecht R, Papadopoulos V, Rammes G, Baghai TC, Fan J, Akula N, Groyer G, Adams D and Schumacher M. Translocator protein (18 kDa) (TSPO) as a therapeutic target for neurological and psychiatric disorders. *Nat Rev Drug Discov* 2010; 9: 971-988.
- [83] Caselli RJ, Dueck AC, Huentelman MJ, Lutz MW, Saunders AM, Reiman EM and Roses AD. Longitudinal modeling of cognitive aging and the TOMM40 effect. *Alzheimers Dement* 2012; 8: 490-495.
- [84] Henchcliffe C and Beal MF. Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. *Nat Clin Pract Neurol* 2008; 4: 600-609.
- [85] Lesage S and Brice A. Role of mendelian genes in "sporadic" Parkinson's disease. *Parkinsonism Relat Disord* 2012; 18 Suppl 1: S66-70.
- [86] Palikaras K and Tavernarakis N. Mitophagy in neurodegeneration and aging. *Front Genet* 2012; 3: 297.
- [87] Liu S, Sawada T, Lee S, Yu W, Silverio G, Alapatt P, Millan I, Shen A, Saxton W, Kanao T, Takahashi R, Hattori N, Imai Y and Lu B. Parkinson's disease-associated kinase PINK1 regulates Miro protein level and axonal transport of mitochondria. *PLoS Genet* 2012; 8: e1002537.
- [88] Thomas KJ, McCoy MK, Blackinton J, Beilina A, van der Brug M, Sandebring A, Miller D, Maric D, Cedazo-Minguez A and Cookson MR. DJ-1 acts in parallel to the PINK1/parkin pathway to control mitochondrial function and autophagy. *Hum Mol Genet* 2011; 20: 40-50.
- [89] Langston JW, Ballard P, Tetrud JW and Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983; 219: 979-980.
- [90] Blesa J, Phani S, Jackson-Lewis V and Przedborski S. Classic and new animal models of Parkinson's disease. *J Biomed Biotechnol* 2012; 2012: 845618.
- [91] Jenner P. Parkinson's disease, pesticides and mitochondrial dysfunction. *Trends Neurosci* 2001; 24: 245-247.
- [92] Yan MH, Wang X and Zhu X. Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. *Free Radic Biol Med* 2013 Sep; 62: 90-101.
- [93] Lin MT and Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 2006; 443: 787-795.
- [94] Squier TC. Oxidative stress and protein aggregation during biological aging. *Exp Gerontol* 2001; 36: 1539-1550.
- [95] Kim RH, Smith PD, Aleyasin H, Hayley S, Mount MP, Pownall S, Wakeham A, You-Ten AJ, Kalia SK, Horne P, Westaway D, Lozano AM, Anisman H, Park DS and Mak TW. Hypersensitivity of DJ-1-deficient mice to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and oxidative stress. *Proc Natl Acad Sci U S A* 2005; 102: 5215-5220.
- [96] Irrcher I, Aleyasin H, Seifert EL, Hewitt SJ, Chhabra S, Phillips M, Lutz AK, Rousseaux MWC, Bevilacqua L, Jahani-Asl A, Callaghan S, MacLaurin JG, Winklhofer KF, Rizzu P, Ripstein P, Kim RH, Chen CX, Fon EA, Slack RS, Harper ME, McBride HM, Mak TW and Park DS. Loss of the Parkinson's disease-linked gene DJ-1 perturbs mitochondrial dynamics. *Hum Mol Genet* 2010 Oct 1; 19: 3734-46.
- [97] Wu ZC, Yu JT, Li Y and Tan L. Clusterin in Alzheimer's disease. *Adv Clin Chem* 2012; 56: 155-173.
- [98] Allen M, Zou F, Chai HS, Younkin CS, Miles R, Nair AA, Crook JE, Pankratz VS, Carrasquillo MM, Rowley CN, Nguyen T, Ma L, Malphrus KG, Bisceglia G, Ortolaza AI, Palusak R, Middha S, Maharjan S, Georgescu C, Schultz D, Rakhshan F, Kolbert CP, Jen J, Sando SB, Aasly JO, Barcikowska M, Uitti RJ, Wszolek ZK, Ross OA, Petersen RC, Graff-Radford NR, Dickson DW, Younkin SG and Ertekin-Taner N. Glutathione S-transferase omega genes in Alzheimer and Parkinson disease risk, age-at-diagnosis and brain gene expression: an association study with mechanistic implications. *Mol Neurodegener* 2012; 7: 13.

Pathways to neurodegeneration in AD and PD

- [99] De Jager PL, Shulman JM, Chibnik LB, Keenan BT, Raj T, Wilson RS, Yu L, Leurgans SE, Tran D, Aubin C, Anderson CD, Biffi A, Corneveaux JJ, Huentelman MJ; Alzheimer's Disease Neuroimaging Initiative; Rosand J, Daly MJ, Myers AJ, Reiman EM, Bennett DA and Evans DA. A genome-wide scan for common variants affecting the rate of age-related cognitive decline. *Neurobiol Aging* 2012; 33: 1017, e1011-1015.
- [100] Bajaj A, Driver JA and Schernhammer ES. Parkinson's disease and cancer risk: a systematic review and meta-analysis. *Cancer Causes Control* 2010; 21: 697-707.
- [101] Driver JA, Beiser A, Au R, Kregar BE, Splansky GL, Kurth T, Kiel DP, Lu KP, Seshadri S and Wolf PA. Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study. *BMJ* 2012; 344: e1442.
- [102] Devine MJ, Plun-Favreau H and Wood NW. Parkinson's disease and cancer: two wars, one front. *Nat Rev Cancer* 2011; 11: 812-823.
- [103] Tollervey JR, Wang Z, Hortobagyi T, Witten JT, Zarnack K, Kayikci M, Clark TA, Schweitzer AC, Rot G, Curk T, Zupan B, Rogelj B, Shaw CE and Ule J. Analysis of alternative splicing associated with aging and neurodegeneration in the human brain. *Genome Res* 2011; 21: 1572-1582.
- [104] Kraft C, Peter M and Hofmann K. Selective autophagy: ubiquitin-mediated recognition and beyond. *Nat Cell Biol* 2010; 12: 836-841.
- [105] Ferrari R, Hardy J and Momeni P. Frontotemporal dementia: from Mendelian genetics towards genome wide association studies. *J Mol Neurosci* 2011; 45: 500-515.
- [106] Simpson JE, Ince PG, Shaw PJ, Heath PR, Raman R, Garwood CJ, Gelsthorpe C, Baxter L, Forster G, Matthews FE, Brayne C, Wharton SB; MRC Cognitive Function and Ageing Neuropathology Study Group. Microarray analysis of the astrocyte transcriptome in the aging brain: relationship to Alzheimer's pathology and APOE genotype. *Neurobiol Aging* 2011; 32: 1795-1807.
- [107] Kopito RR and Ron D. Conformational disease. *Nat Cell Biol* 2000; 2: E207-209.
- [108] Scorrano L, Oakes SA, Opferman JT, Cheng EH, Sorcinelli MD, Pozzan T and Korsmeyer SJ. BAX and BAK regulation of endoplasmic reticulum Ca²⁺: a control point for apoptosis. *Science* 2003; 300: 135-139.
- [109] Smith DL, Pozueta J, Gong B, Arancio O and Shelanski M. Reversal of long-term dendritic spine alterations in Alzheimer disease models. *Proc Natl Acad Sci U S A* 2009; 106: 16877-16882.
- [110] Gong B, Cao Z, Zheng P, Vitolo OV, Liu S, Staniszewski A, Moolman D, Zhang H, Shelanski M and Arancio O. Ubiquitin hydrolase Uch-L1 rescues beta-amyloid-induced decreases in synaptic function and contextual memory. *Cell* 2006; 126: 775-788.
- [111] Khandelwal PJ, Herman AM, Hoe HS, Rebeck GW and Moussa CE. Parkin mediates beclin-dependent autophagic clearance of defective mitochondria and ubiquitinated Abeta in AD models. *Hum Mol Genet* 2011; 20: 2091-2102.
- [112] Huynh DP, Scoles DR, Nguyen D and Pulst SM. The autosomal recessive juvenile Parkinson disease gene product, parkin, interacts with and ubiquitinates synaptotagmin XI. *Hum Mol Genet* 2003; 12: 2587-2597.
- [113] Rana A, Rera M and Walker DW. Parkin overexpression during aging reduces proteotoxicity, alters mitochondrial dynamics, and extends lifespan. *Proc Natl Acad Sci U S A* 2013; 110: 8638-8643.
- [114] Horwitz AR. The origins of the molecular era of adhesion research. *Nat Rev Mol Cell Biol* 2012; 13: 805-811.
- [115] Blalock EM, Geddes JW, Chen KC, Porter NM, Markesbery WR and Landfield PW. Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *Proc Natl Acad Sci U S A* 2004; 101: 2173-2178.
- [116] Grunblatt E, Mandel S, Jacob-Hirsch J, Zeligson S, Amariglio N, Rechavi G, Li J, Ravid R, Roggendorf W, Riederer P and Youdim MB. Gene expression profiling of parkinsonian substantia nigra pars compacta; alterations in ubiquitin-proteasome, heat shock protein, iron and oxidative stress regulated proteins, cell adhesion/cellular matrix and vesicle trafficking genes. *J Neural Transm* 2004; 111: 1543-1573.
- [117] Miller RM, Kiser GL, Kaysser-Kranich TM, Lockner RJ, Palaniappan C and Federoff HJ. Robust dysregulation of gene expression in substantia nigra and striatum in Parkinson's disease. *Neurobiol Dis* 2006; 21: 305-313.
- [118] Xu PT, Li YJ, Qin XJ, Scherzer CR, Xu H, Schmechel DE, Hulette CM, Ervin J, Gullans SR, Haines J, Pericak-Vance MA and Gilbert JR. Differences in apolipoprotein E3/3 and E4/4 allele-specific gene expression in hippocampus in Alzheimer disease. *Neurobiol Dis* 2006; 21: 256-275.
- [119] Durakoglugil MS, Chen Y, White CL, Kavalali ET and Herz J. Reelin signaling antagonizes beta-amyloid at the synapse. *Proc Natl Acad Sci U S A* 2009; 106: 15938-15943.
- [120] Chen Y, Durakoglugil MS, Xian X and Herz J. ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing

Pathways to neurodegeneration in AD and PD

- ApoE receptor recycling. *Proc Natl Acad Sci U S A* 2010; 107: 12011-12016.
- [121] Herring A, Donath A, Steiner KM, Widera MP, Hamzehian S, Kanakis D, Kolble K, ElAli A, Hermann DM, Paulus W and Keyvani K. Reelin depletion is an early phenomenon of Alzheimer's pathology. *J Alzheimers Dis* 2012; 30: 963-979.
- [122] Kramer PL, Xu H, Woltjer RL, Westaway SK, Clark D, Erten-Lyons D, Kaye JA, Welsh-Bohmer KA, Troncoso JC, Markesbery WR, Petersen RC, Turner RS, Kukull WA, Bennett DA, Galasko D, Morris JC and Ott J. Alzheimer disease pathology in cognitively healthy elderly: a genome-wide study. *Neurobiol Aging* 2011; 32: 2113-2122.
- [123] Kopan R and Ilagan MX. Gamma-secretase: proteasome of the membrane? *Nat Rev Mol Cell Biol* 2004; 5: 499-504.
- [124] Chen KP and Dou F. Selective interaction of amyloid precursor protein with different isoforms of neural cell adhesion molecule. *J Mol Neurosci* 2012; 46: 203-209.
- [125] Wang Y, West JD, MaGee TR, McDonald BC, Risacher SL, Shen L, Ramanan VK, Kim S, O'Neill DP, Farlow MR, Ghetti B and Saykin AJ. Hippocampal subfield atrophy on 3T MRI in prodromal Alzheimer's disease and older adults with cognitive complaints. Poster Presentation, Alzheimer's Association International Conference (AAIC) in Vancouver, British Columbia, Canada, July 14-19, 2012. 2012.
- [126] Saykin AJ, Shen L, Foroud TM, Potkin SG, Swaminathan S, Kim S, Risacher SL, Nho K, Huentelman MJ, Craig DW, Thompson PM, Stein JL, Moore JH, Farrer LA, Green RC, Bertram L, Jack CR Jr, Weiner MW; Alzheimer's Disease Neuroimaging Initiative. Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans. *Alzheimers Dement* 2010; 6: 265-273.
- [127] Edwards YJ, Beecham GW, Scott WK, Khuri S, Bademci G, Tekin D, Martin ER, Jiang Z, Mash DC, French-Mullen J, Pericak-Vance MA, Tsinoremas N and Vance JM. Identifying consensus disease pathways in Parkinson's disease using an integrative systems biology approach. *PLoS One* 2011; 6: e16917.
- [128] Liu G, Jiang Y, Wang P, Feng R, Jiang N, Chen X, Song H and Chen Z. Cell adhesion molecules contribute to Alzheimer's disease: multiple pathway analyses of two genome-wide association studies. *J Neurochem* 2012; 120: 190-198.
- [129] Holmans P. Statistical methods for pathway analysis of genome-wide data for association with complex genetic traits. *Adv Genet* 2010; 72: 141-179.
- [130] Zhang M. Endocytic mechanisms and drug discovery in neurodegenerative diseases. *Front Biosci* 2008; 13: 6086-6105.
- [131] Jiang Q, Lee CY, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, Mann K, Lamb B, Willson TM, Collins JL, Richardson JC, Smith JD, Comery TA, Riddell D, Holtzman DM, Tontonoz P and Landreth GE. ApoE promotes the proteolytic degradation of Abeta. *Neuron* 2008; 58: 681-693.
- [132] Pottier C, Hannequin D, Coutant S, Rovelet-Lecrux A, Wallon D, Rousseau S, Legallic S, Paquet C, Bombois S, Pariente J, Thomas-Anterion C, Michon A, Croisile B, Etcharry-Bouyx F, Berr C, Dartigues JF, Amouyel P, Dauchel H, Boutoleau-Bretonniere C, Thauvin C, Frebourg T, Lambert JC, Campion D and Collaborators PG. High frequency of potentially pathogenic SORL1 mutations in autosomal dominant early-onset Alzheimer disease. *Mol Psychiatry* 2012; 17: 875-879.
- [133] Reitz C, Cheng R, Rogava E, Lee JH, Tokuhira S, Zou F, Bettens K, Slegers K, Tan EK, Kimura R, Shibata N, Arai H, Kamboh MI, Prince JA, Maier W, Riemenschneider M, Owen M, Harold D, Hollingworth P, Cellini E, Sorbi S, Nacmias B, Takeda M, Pericak-Vance MA, Haines JL, Younkin S, Williams J, van Broeckhoven C, Farrer LA, St George-Hyslop PH, Mayeux R; Genetic and Environmental Risk in Alzheimer Disease 1 Consortium. Meta-analysis of the association between variants in SORL1 and Alzheimer disease. *Arch Neurol* 2011; 68: 99-106.
- [134] Rogava E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, Katayama T, Baldwin CT, Cheng R, Hasegawa H, Chen F, Shibata N, Lunetta KL, Pardossi-Piquard R, Bohm C, Wakutani Y, Cupples LA, Cuenco KT, Green RC, Pinessi L, Rainero I, Sorbi S, Bruni A, Duara R, Friedland RP, Inzelberg R, Hampe W, Bujo H, Song YQ, Andersen OM, Willnow TE, Graff-Radford N, Petersen RC, Dickson D, Der SD, Fraser PE, Schmitt-Ulms G, Younkin S, Mayeux R, Farrer LA and St George-Hyslop P. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nat Genet* 2007; 39: 168-177.
- [135] Golde TE, Estus S, Younkin LH, Selkoe DJ and Younkin SG. Processing of the amyloid protein precursor to potentially amyloidogenic derivatives. *Science* 1992; 255: 728-730.
- [136] Alegre-Abarrategui J and Wade-Martins R. Parkinson disease, LRRK2 and the endocytic-autophagic pathway. *Autophagy* 2009; 5: 1208-1210.
- [137] Alegre-Abarrategui J, Christian H, Lufino MM, Mutihac R, Venda LL, Ansorge O and Wade-Martins R. LRRK2 regulates autophagic activi-

- ty and localizes to specific membrane microdomains in a novel human genomic reporter cellular model. *Hum Mol Genet* 2009; 18: 4022-4034.
- [138] Matta S, Van Kolen K, da Cunha R, van den Bogaart G, Mandemakers W, Miskiewicz K, De Bock PJ, Morais VA, Vilain S, Haddad D, Delbroek L, Swerts J, Chavez-Gutierrez L, Esposito G, Daneels G, Karran E, Holt M, Gevaert K, Moechars DW, De Strooper B and Verstreken P. LRRK2 controls an EndoA phosphorylation cycle in synaptic endocytosis. *Neuron* 2012; 75: 1008-1021.
- [139] Cramer PE, Cirrito JR, Wesson DW, Lee CYD, Karlo JC, Zinn AE, Casali BT, Restivo JL, Goebel WD, James MJ, Brunden KR, Wilson DA and Landreth GE. ApoE-Directed Therapeutics Rapidly Clear β -Amyloid and Reverse Deficits in AD Mouse Models. *Science* 2012 Mar 23; 335: 1503-6.
- [140] Treusch S, Hamamichi S, Goodman JL, Matlack KES, Chung CY, Baru V, Shulman JM, Parrado A, Bevis BJ, Valastyan JS, Han H, Lindhagen-Persson M, Reiman EM, Evans DA, Bennett DA, Olofsson A, DeJager PL, Tanzi RE, Caldwell KA, Caldwell GA and Lindquist S. Functional Links Between A β Toxicity, Endocytic Trafficking, and Alzheimer's Disease Risk Factors in Yeast. *Science* 2011 Dec 2; 334: 1241-5.
- [141] Lee DW, Zhao X, Zhang F, Eisenberg E and Greene LE. Depletion of GAK/auxilin 2 inhibits receptor-mediated endocytosis and recruitment of both clathrin and clathrin adaptors. *J Cell Sci* 2005; 118: 4311-4321.
- [142] Dumitriu A, Pacheco CD, Wilk JB, Strathearn KE, Latourelle JC, Goldwurm S, Pezzoli G, Rochet JC, Lindquist S and Myers RH. Cyclin-G-associated kinase modifies alpha-synuclein expression levels and toxicity in Parkinson's disease: results from the GenePD Study. *Hum Mol Genet* 2011; 20: 1478-1487.
- [143] Henderson DM and Conner SD. A novel AAK1 splice variant functions at multiple steps of the endocytic pathway. *Mol Biol Cell* 2007; 18: 2698-2706.
- [144] Latourelle JC, Pankratz N, Dumitriu A, Wilk JB, Goldwurm S, Pezzoli G, Mariani CB, DeStefano AL, Halter C, Gusella JF, Nichols WC, Myers RH, Foroud T; PROGENI Investigators, Coordinators and Molecular Genetic Laboratories; GenePD Investigators, Coordinators and Molecular Genetic Laboratories. Genomewide association study for onset age in Parkinson disease. *BMC Med Genet* 2009; 10: 98.
- [145] Davies P and Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* 1976; 2: 1403.
- [146] Hoehn MM and Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17: 427-442.
- [147] Edwards RH. Neural degeneration and the transport of neurotransmitters. *Ann Neurol* 1993; 34: 638-645.
- [148] Corbett A, Pickett J, Burns A, Corcoran J, Dunnett SB, Edison P, Hagan JJ, Holmes C, Jones E, Katona C, Kearns I, Kehoe P, Mudher A, Passmore A, Shepherd N, Walsh F and Ballard C. Drug repositioning for Alzheimer's disease. *Nat Rev Drug Discov* 2012; 11: 833-846.
- [149] Antonini A and Albin RL. Dopaminergic treatment and nonmotor features of Parkinson disease: The horse lives. *Neurology* 2013; 80: 784-785.
- [150] Ho A and Shen J. Presenilins in synaptic function and disease. *Trends Mol Med* 2011; 17: 617-624.
- [151] Sweatt JD. *Mechanisms of Memory*. 2nd Edition. Academic Press, 2009.
- [152] Wu K, O'Keefe D, Politis M, O'Keefe GC, Robbins TW, Bose SK, Brooks DJ, Piccini P and Barker RA. The catechol-O-methyltransferase Val(158)Met polymorphism modulates fronto-cortical dopamine turnover in early Parkinson's disease: a PET study. *Brain* 2012; 135: 2449-2457.
- [153] Serretti A and Olgiati P. Catechol-o-methyltransferase and Alzheimer's disease: a review of biological and genetic findings. *CNS Neurol Disord Drug Targets* 2012; 11: 299-305.
- [154] Spence RD and Voskuhl RR. Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration. *Front Neuroendocrinol* 2012; 33: 105-115.
- [155] Goldstein M and Lieberman A. The role of the regulatory enzymes of catecholamine synthesis in Parkinson's disease. *Neurology* 1992; 42: 8-12; discussion 41-18.
- [156] Gainetdinov RR, Fumagalli F, Jones SR and Caron MG. Dopamine transporter is required for in vivo MPTP neurotoxicity: evidence from mice lacking the transporter. *J Neurochem* 1997; 69: 1322-1325.
- [157] Baranzini SE, Srinivasan R, Khankhanian P, Okuda DT, Nelson SJ, Matthews PM, Hauser SL, Oksenberg JR and Pelletier D. Genetic variation influences glutamate concentrations in brains of patients with multiple sclerosis. *Brain* 2010; 133: 2603-2611.
- [158] Mayeux R. Clinical practice. Early Alzheimer's disease. *N Engl J Med* 2010; 362: 2194-2201.
- [159] Alkalay A, Rabinovici GD, Zimmerman G, Agarwal N, Kaufer D, Miller BL, Jagust WJ and Soreq H. Plasma acetylcholinesterase activity correlates with intracerebral beta-amyloid load. *Curr Alzheimer Res* 2013; 10: 48-56.
- [160] Ramanan VK, Risacher SL, Nho K, Kim S, Swaminathan S, Shen L, Foroud TM, Hakonarson H, Huettelman MJ, Aisen PS, Petersen RC, Green RC, Jack CR, Koeppe RA, Jagust WJ,

- Weiner MW and Saykin AJ. APOE and BCHE as modulators of cerebral amyloid deposition: a florbetapir PET genome-wide association study. *Mol Psychiatry* 2013 Feb 19; [Epub ahead of print].
- [161] Mesulam MM and Geula C. Butyrylcholinesterase reactivity differentiates the amyloid plaques of aging from those of dementia. *Ann Neurol* 1994; 36: 722-727.
- [162] Darvesh S, Hopkins DA and Geula C. Neurobiology of butyrylcholinesterase. *Nat Rev Neurosci* 2003; 4: 131-138.
- [163] Darreh-Shori T, Forsberg A, Modiri N, Andreassen N, Blennow K, Kamil C, Ahmed H, Almkvist O, Långström B and Nordberg A. Differential levels of apolipoprotein E and butyrylcholinesterase show strong association with pathological signs of Alzheimer's disease in the brain in vivo. *Neurobiol Aging* 2011 Dec; 32: 2320, e15-32.
- [164] Darvesh S, Cash MK, Reid GA, Martin E, Mitnitski A and Geula C. Butyrylcholinesterase is associated with beta-amyloid plaques in the transgenic APPSWE/PSEN1dE9 mouse model of Alzheimer disease. *J Neuropathol Exp Neurol* 2012; 71: 2-14.
- [165] Lane RM and He Y. Butyrylcholinesterase genotype and gender influence Alzheimer's disease phenotype. *Alzheimers Dement* 2013 Mar; 9: e1-73.
- [166] Sabbagh MN, Farlow MR, Relkin N and Beach TG. Do cholinergic therapies have disease-modifying effects in Alzheimer's disease? *Alzheimers Dement* 2006 Apr; 2: 118-25.
- [167] Farlow MR, Miller ML and Pejovic V. Treatment options in Alzheimer's disease: maximizing benefit, managing expectations. *Dement Geriatr Cogn Disord* 2008; 25: 408-422.
- [168] Caughey B and Baron GS. Prions and their partners in crime. *Nature* 2006; 443: 803-810.
- [169] Prusiner SB. Scrapie prions. *Annu Rev Microbiol* 1989; 43: 345-374.
- [170] Prusiner SB. Cell biology. A unifying role for prions in neurodegenerative diseases. *Science* 2012; 336: 1511-1513.
- [171] Dermaut B, Croes EA, Rademakers R, Van den Broeck M, Cruts M, Hofman A, van Duijn CM and Van Broeckhoven C. PRNP Val129 homozygosity increases risk for early-onset Alzheimer's disease. *Ann Neurol* 2003; 53: 409-412.
- [172] Riemenschneider M, Klopp N, Xiang W, Wagenpfeil S, Vollmert C, Müller U, Forstl H, Illig T, Kretschmar H and Kurz A. Prion protein codon 129 polymorphism and risk of Alzheimer disease. *Neurology* 2004; 63: 364-366.
- [173] Gossrau G, Herting B, Mockel S, Kempe A, Koch R, Reichmann H and Lampe JB. Analysis of the polymorphic prion protein gene codon 129 in idiopathic Parkinson's disease. *J Neural Transm* 2006; 113: 331-337.
- [174] Combarros O, Sanchez-Guerra M, Llorca J, Alvarez-Arcaya A, Berciano J, Pena N and Fernandez-Viadero C. Polymorphism at codon 129 of the prion protein gene is not associated with sporadic AD. *Neurology* 2000; 55: 593-595.
- [175] Jeong BH, Lee KH, Lee YJ, Kim Y, Choi EK, Kim YH, Cho YS, Carp R and Kim YS. Lack of association between PRNP 1368 polymorphism and Alzheimer's disease or vascular dementia. *BMC Med Genet* 2009; 10: 32.
- [176] Mead S, Poulter M, Uphill J, Beck J, Whitfield J, Webb TEF, Campbell T, Adamson G, Deriziotis P, Tabrizi SJ, Hummerich H, Verzilli C, Alpers MP, Whittaker JC and Collinge J. Genetic risk factors for variant Creutzfeldt-Jakob disease: a genome-wide association study. *Lancet Neurol* 2009; 8: 57-66.
- [177] Mead S, Uphill J, Beck J, Poulter M, Campbell T, Lowe J, Adamson G, Hummerich H, Klopp N, Rückert IM, Wichmann HE, Azazi D, Plagnol V, Pako WH, Whitfield J, Alpers MP, Whittaker J, Balding DJ, Zerr I, Kretschmar H and Collinge J. Genome-wide association study in multiple human prion diseases suggests genetic risk factors additional to PRNP. *Hum Mol Genet* 2012 Apr 15; 21: 1897-906.
- [178] Lukic A and Mead S. Genome wide association studies and prion disease. *Prion* 2011; 5: 154-160.
- [179] Lansbury PT and Lashuel HA. A century-old debate on protein aggregation and neurodegeneration enters the clinic. *Nature* 2006; 443: 774-779.
- [180] Swardfager W, Lanctot K, Rothenburg L, Wong A, Cappell J and Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry* 2010; 68: 930-941.
- [181] Akama KT and Van Eldik LJ. Beta-amyloid stimulation of inducible nitric-oxide synthase in astrocytes is interleukin-1beta- and tumor necrosis factor-alpha (TNFalpha)-dependent, and involves a TNFalpha receptor-associated factor- and NFkappaB-inducing kinase-dependent signaling mechanism. *J Biol Chem* 2000; 275: 7918-7924.
- [182] Blum-Degen D, Müller T, Kuhn W, Gerlach M, Przuntek H and Riederer P. Interleukin-1 beta and interleukin-6 are elevated in the cerebrospinal fluid of Alzheimer's and de novo Parkinson's disease patients. *Neurosci Lett* 1995; 202: 17-20.
- [183] Hirsch EC and Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurol* 2009; 8: 382-397.
- [184] Stewart WF, Kawas C, Corrada M and Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997; 48: 626-632.

Pathways to neurodegeneration in AD and PD

- [185] Wahner AD, Bronstein JM, Bordelon YM and Ritz B. Nonsteroidal anti-inflammatory drugs may protect against Parkinson disease. *Neurology* 2007; 69: 1836-1842.
- [186] Prinz M, Priller J, Sisodia SS and Ransohoff RM. Heterogeneity of CNS myeloid cells and their roles in neurodegeneration. *Nat Neurosci* 2011; 14: 1227-1235.
- [187] Lucin KM and Wyss-Coray T. Immune activation in brain aging and neurodegeneration: too much or too little? *Neuron* 2009; 64: 110-122.
- [188] Lee EJ, Woo MS, Moon PG, Baek MC, Choi IY, Kim WK, Junn E and Kim HS. α -Synuclein Activates Microglia by Inducing the Expressions of Matrix Metalloproteinases and the Subsequent Activation of Protease-Activated Receptor-1. *J Immunol* 2010 Jul 1; 185: 615-23.
- [189] Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, Fitzgerald KA, Latz E, Moore KJ and Golenbock DT. The NALP3 inflammasome is involved in the innate immune response to amyloid- β . *Nat Immunol* 2008; 9: 857-865.
- [190] Kitazawa M, Cheng D, Tsukamoto MR, Koike MA, Wes PD, Vasilevko V, Cribbs DH and LaFerla FM. Blocking IL-1 Signaling Rescues Cognition, Attenuates Tau Pathology, and Restores Neuronal β -Catenin Pathway Function in an Alzheimer's Disease Model. *J Immunol* 2011 Dec 15; 187: 6539-49.
- [191] Pott Godoy MC, Tarelli R, Ferrari CC, Sarchi MI and Pitossi FJ. Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease. *Brain* 2008; 131: 1880-1894.
- [192] Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, Griep A, Axt D, Remus A, Tzeng TC, Gelpi E, Halle A, Korte M, Latz E and Golenbock DT. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* 2013; 493: 674-678.
- [193] White GE and Greaves DR. Fractalkine: a survivor's guide: chemokines as antiapoptotic mediators. *Arterioscler Thromb Vasc Biol* 2012; 32: 589-594.
- [194] Cardona AE, Pioro EP, Sasse ME, Kostenko V, Cardona SM, Dijkstra IM, Huang D, Kidd G, Dombrowski S, Dutta R, Lee JC, Cook DN, Jung S, Lira SA, Littman DR and Ransohoff RM. Control of microglial neurotoxicity by the fractalkine receptor. *Nat Neurosci* 2006; 9: 917-924.
- [195] Bamberg ME, Harris ME, McDonald DR, Husemann J and Landreth GE. A cell surface receptor complex for fibrillar beta-amyloid mediates microglial activation. *J Neurosci* 2003; 23: 2665-2674.
- [196] El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C and Luster AD. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. *Nat Med* 2007; 13: 432-438.
- [197] Heneka MT, Nadrigny F, Regen T, Martinez-Hernandez A, Dumitrescu-Ozimek L, Terwel D, Jardanhazi-Kurutz D, Walter J, Kirchhoff F, Hanisch UK and Kummer MP. Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. *Proc Natl Acad Sci U S A* 2010; 107: 6058-6063.
- [198] Ramos EM, Lin MT, Larson EB, Maezawa I, Tseng LH, Edwards KL, Schellenberg GD, Hansen JA, Kukull WA and Jin LW. Tumor necrosis factor alpha and interleukin 10 promoter region polymorphisms and risk of late-onset Alzheimer disease. *Arch Neurol* 2006; 63: 1165-1169.
- [199] Wahner AD, Sinsheimer JS, Bronstein JM and Ritz B. Inflammatory cytokine gene polymorphisms and increased risk of Parkinson disease. *Arch Neurol* 2007; 64: 836-840.
- [200] Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Hazrati L, Collinge J, Pockock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J; Alzheimer Genetic Analysis Group. TREM2 variants in Alzheimer's disease. *N Engl J Med* 2013; 368: 117-127.
- [201] Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, Bjornsson S, Huttenlocher J, Levey AI, Lah JJ, Rujescu D, Hampel H, Giegling I, Andreassen OA, Engedal K, Ulstein I, Djurovic S, Ibrahim-Verbaas C, Hofman A, Ikram MA, van Duijn CM, Thorsteinsdottir U, Kong A and Stefansson K. Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med* 2013; 368: 107-116.
- [202] Hamerman JA, Jarjoura JR, Humphrey MB, Nakamura MC, Seaman WE and Lanier LL. Cutting edge: inhibition of TLR and FcR responses in macrophages by triggering receptor expressed on myeloid cells (TREM)-2 and DAP12. *J Immunol* 2006; 177: 2051-2055.
- [203] Turnbull IR, Gilfillan S, Cella M, Aoshi T, Miller M, Piccio L, Hernandez M and Colonna M. Cutting edge: TREM-2 attenuates macrophage activation. *J Immunol* 2006; 177: 3520-3524.
- [204] Zhang B, Gaiteri C, Bodea LG, Wang Z, McElwee J, Podtelezchnikov AA, Zhang C, Xie T, Tran L, Dobrin R, Fluder E, Clurman B, Melquist S, Narayanan M, Suver C, Shah H, Mahajan M, Gillis T, Mysore J, MacDonald ME, Lamb JR, Bennett DA, Molony C, Stone DJ, Gudnason V, Myers AJ, Schadt EE, Neumann H, Zhu J and Emilsson V. Integrated systems approach iden-

Pathways to neurodegeneration in AD and PD

- tifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell* 2013; 153: 707-720.
- [205] Moehle MS, Webber PJ, Tse T, Sukar N, Standaert DG, DeSilva TM, Cowell RM and West AB. LRRK2 inhibition attenuates microglial inflammatory responses. *J Neurosci* 2012; 32: 1602-1611.
- [206] Kim B, Yang MS, Choi D, Kim JH, Kim HS, Seol W, Choi S, Jou I, Kim EY and Joe EH. Impaired inflammatory responses in murine Lrrk2-knockdown brain microglia. *PLoS One* 2012; 7: e34693.
- [207] Gardet A, Benita Y, Li C, Sands BE, Ballester I, Stevens C, Korzenik JR, Rioux JD, Daly MJ, Xavier RJ and Podolsky DK. LRRK2 Is Involved in the IFN- γ Response and Host Response to Pathogens. *J Immunol* 2010; 185: 5577-5585.
- [208] Jun G, Naj AC, Beecham GW, Wang LS, Buros J, Gallins PJ, Buxbaum JD, Ertekin-Taner N, Fallin MD, Friedland R, Inzelberg R, Kramer P, Rogaeva E, St George-Hyslop P, Arnold SE, Baldwin CT, Barber R, Beach T, Bigio EH, Bird TD, Boxer A, Burke JR, Cairns N, Carroll SL, Chui HC, Clark DG, Cotman CW, Cummings JL, DeCarli C, Diaz-Arrastia R, Dick M, Dickson DW, Ellis WG, Fallon KB, Farlow MR, Ferris S, Frosch MP, Galasko DR, Gearing M, Geschwind DH, Ghetti B, Gilman S, Giordani B, Glass J, Graff-Radford NR, Green RC, Growdon JH, Hamilton RL, Harrell LE, Head E, Honig LS, Hulette CM, Hyman BT, Jicha GA, Jin LW, Johnson N, Karlawish J, Karydas A, Kaye JA, Kim R, Koo EH, Kowall NW, Lah JJ, Levey AI, Lieberman A, Lopez OL, Mack WJ, Markesbery W, Marson DC, Martiniuk F, Masliah E, McKee AC, Mesulam M, Miller JW, Miller BL, Miller CA, Parisi JE, Perl DP, Peskind E, Petersen RC, Poon W, Quinn JF, Raskind M, Reisberg B, Ringman JM, Roberson ED, Rosenberg RN, Sano M, Schneider JA, Schneider LS, Seeley W, Shelanski ML, Smith CD, Spina S, Stern RA, Tanzi RE, Trojanowski JQ, Troncoso JC, Van Deerlin VM, Vinters HV, Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Woltjer RL, Younkin SG, Cantwell LB, Dombroski BA, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Lunetta KL, Martin ER, Montine TJ, Goate AM, Blacker D, Tsuang DW, Beekly D, Cupples LA, Hakonarson H, Kukull W, Foroud TM, Haines J, Mayeux R, Farrer LA, Pericak-Vance MA, Schellenberg GD; Alzheimer's Disease Genetics Consortium. Meta-analysis Confirms CR1, CLU, and PICALM as Alzheimer Disease Risk Loci and Reveals Interactions With APOE Genotypes. *Arch Neurol* 2010; 67: 1473-1484.
- [209] Chibnik LB, Shulman JM, Leurgans SE, Schneider JA, Wilson RS, Tran D, Aubin C, Buchman AS, Heward CB, Myers AJ, Hardy JA, Huentelman MJ, Corneveaux JJ, Reiman EM, Evans DA, Bennett DA and De Jager PL. CR1 is associated with amyloid plaque burden and age-related cognitive decline. *Ann Neurol* 2011; 69: 560-569.
- [210] Wijsman EM, Pankratz ND, Choi Y, Rothstein JH, Faber KM, Cheng R, Lee JH, Bird TD, Bennett DA, Diaz-Arrastia R, Goate AM, Farlow M, Ghetti B, Sweet RA, Foroud TM, Mayeux R; NIA-LOAD/NCRAD Family Study Group. Genome-Wide Association of Familial Late-Onset Alzheimer's Disease Replicates BIN1 and CLU and Nominates CUGBP2 in Interaction with APOE. *PLoS Genet* 2011; 7: e1001308.
- [211] Barral S, Bird T, Goate A, Farlow MR, Diaz-Arrastia R, Bennett DA, Graff-Radford N, Boeve BF, Sweet RA, Stern Y, Wilson RS, Foroud T, Ott J, Mayeux R; National Institute on Aging Late-Onset Alzheimer's Disease Genetics Study. Genotype patterns at PICALM, CR1, BIN1, CLU, and APOE genes are associated with episodic memory. *Neurology* 2012; 78: 1464-1471.
- [212] Keenan BT, Shulman JM, Chibnik LB, Raj T, Tran D, Sabuncu MR; Alzheimer's Disease Neuroimaging Initiative; Allen AN, Corneveaux JJ, Hardy JA, Huentelman MJ, Lemere CA, Myers AJ, Nicholson-Weller A, Reiman EM, Evans DA, Bennett DA, De Jager PL. A coding variant in CR1 interacts with APOE-epsilon4 to influence cognitive decline. *Hum Mol Genet* 2012; 21: 2377-2388.
- [213] Stephan AH, Barres BA and Stevens B. The complement system: an unexpected role in synaptic pruning during development and disease. *Annu Rev Neurosci* 2012; 35: 369-389.
- [214] Evans MC, Couch Y, Sibson N and Turner MR. Inflammation and neurovascular changes in amyotrophic lateral sclerosis. *Mol Cell Neurosci* 2013; 53: 34-41.
- [215] Yin F, Banerjee R, Thomas B, Zhou P, Qian L, Jia T, Ma X, Ma Y, Iadecola C, Beal MF, Nathan C and Ding A. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. *J Exp Med* 2010; 207: 117-128.
- [216] Jones KA and Thomsen C. The role of the innate immune system in psychiatric disorders. *Mol Cell Neurosci* 2013; 53: 52-62.
- [217] Vom Berg J, Prokop S, Miller KR, Obst J, Kalin RE, Lopategui-Cabezas I, Wegner A, Mair F, Schipke CG, Peters O, Winter Y, Becher B and Heppner FL. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. *Nat Med* 2012; 18: 1812-1819.
- [218] Gao HM, Liu B, Zhang W and Hong JS. Novel anti-inflammatory therapy for Parkinson's disease. *Trends Pharmacol Sci* 2003; 24: 395-401.

Pathways to neurodegeneration in AD and PD

- [219] Tan ZS and Seshadri S. Inflammation in the Alzheimer's disease cascade: culprit or innocent bystander? *Alzheimers Res Ther* 2010; 2: 6.
- [220] Martins LJ, Hone E, Foster JK, Sunram-Lea SI, Gnjec A, Fuller SJ, Nolan D, Gandy SE and Martins RN. Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. *Mol Psychiatry* 2006; 11: 721-736.
- [221] Sparks DL. Alzheimer disease: statins in the treatment of Alzheimer disease. *Nat Rev Neurol* 2011; 7: 662-663.
- [222] Gao X, Simon KC, Schwarzschild MA and Ascherio A. Prospective study of statin use and risk of Parkinson disease. *Arch Neurol* 2012; 69: 380-384.
- [223] Karasinska JM and Hayden MR. Cholesterol metabolism in Huntington disease. *Nat Rev Neurol* 2011; 7: 561-572.
- [224] Anchisi L, Dessi S, Pani A and Mandas A. Cholesterol homeostasis: a key to prevent or slow down neurodegeneration. *Front Physiol* 2012; 3: 486.
- [225] Han X, Rozen S, Boyle SH, Hellegers C, Cheng H, Burke JR, Welsh-Bohmer KA, Doraiswamy PM and Kaddurah-Daouk R. Metabolomics in early Alzheimer's disease: identification of altered plasma sphingolipidome using shotgun lipidomics. *PLoS One* 2011; 6: e21643.
- [226] Wood PL. Lipidomics of Alzheimer's disease: current status. *Alzheimers Res Ther* 2012; 4: 5.
- [227] Holtzman DM, Herz J and Bu G. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. *Cold Spring Harb Perspect Med* 2012; 2: a006312.
- [228] Calero M, Tokuda T, Rostagno A, Kumar A, Zlokovik B, Frangione B and Ghiso J. Functional and structural properties of lipid-associated apolipoprotein J (clusterin). *Biochem J* 1999; 344: 375-383.
- [229] Kim WS, Weickert CS and Garner B. Role of ATP-binding cassette transporters in brain lipid transport and neurological disease. *J Neurochem* 2008; 104: 1145-1166.
- [230] Socia SJ and Fitzgerald ML. The ABCA7 transporter, brain lipids and Alzheimer's disease. *Clinical Lipidology* 2013; 8: 97-108.
- [231] Biskup S, Moore DJ, Celsi F, Higashi S, West AB, Andrabi SA, Kurkinen K, Yu SW, Savitt JM, Waldvogel HJ, Faull RL, Emson PC, Torp R, Otersen OP, Dawson TM and Dawson VL. Localization of LRRK2 to membranous and vesicular structures in mammalian brain. *Ann Neurol* 2006; 60: 557-569.
- [232] Kim KY, Stevens MV, Akter MH, Rusk SE, Huang RJ, Cohen A, Noguchi A, Springer D, Bocharov AV, Eggerman TL, Suen DF, Youle RJ, Amar M, Remaley AT and Sack MN. Parkin is a lipid-responsive regulator of fat uptake in mice and mutant human cells. *J Clin Invest* 2011; 121: 3701-3712.
- [233] Hatano T, Kubo S, Imai S, Maeda M, Ishikawa K, Mizuno Y and Hattori N. Leucine-rich repeat kinase 2 associates with lipid rafts. *Hum Mol Genet* 2007; 16: 678-690.
- [234] Chan RB, Oliveira TG, Cortes EP, Honig LS, Duff KE, Small SA, Wenk MR, Shui G and Di Paolo G. Comparative lipidomic analysis of mouse and human brain with Alzheimer disease. *J Biol Chem* 2012; 287: 2678-2688.
- [235] Cheng D, Jenner AM, Shui G, Cheong WF, Mitchell TW, Nealon JR, Kim WS, McCann H, Wenk MR, Halliday GM and Garner B. Lipid pathway alterations in Parkinson's disease primary visual cortex. *PLoS One* 2011; 6: e17299.
- [236] Ho PP, Kanter JL, Johnson AM, Srinagesh HK, Chang EJ, Purdy TM, van Haren K, Wikoff WR, Kind T, Khademi M, Matloff LY, Narayana S, Hur EM, Lindstrom TM, He Z, Fiehn O, Olsson T, Han X, Han MH, Steinman L and Robinson WH. Identification of Naturally Occurring Fatty Acids of the Myelin Sheath That Resolve Neuroinflammation. *Sci Transl Med* 2012; 4: 137ra173.
- [237] Willey JZ and Elkind MS. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the treatment of central nervous system diseases. *Arch Neurol* 2010; 67: 1062-1067.
- [238] Kroner Z. The relationship between Alzheimer's disease and diabetes: type 3 diabetes? *Altern Med Rev* 2009; 14: 373-379.
- [239] Liu Y, Liu F, Grundke-Iqbal I, Iqbal K and Gong CX. Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. *J Pathol* 2011; 225: 54-62.
- [240] Vignini A, Giulietti A, Nanetti L, Raffaelli F, Giusti L, Mazzanti L and Provinciali L. Alzheimer's disease And Diabetes: New Insights and Unifying Therapies. *Curr Diabetes Rev* 2013 May; 9: 218-27.
- [241] de la Monte SM. Contributions of brain insulin resistance and deficiency in amyloid-related neurodegeneration in Alzheimer's disease. *Drugs* 2012; 72: 49-66.
- [242] Chen DY, Stern SA, Garcia-Osta A, Saunier-Rebori B, Pollonini G, Bambah-Mukku D, Blitzer RD and Alberini CM. A critical role for IGF-II in memory consolidation and enhancement. *Nature* 2011; 469: 491-497.
- [243] Lue LF, Andrade C, Sabbagh M and Walker D. Is There Inflammatory Synergy in Type II Diabetes Mellitus and Alzheimer's Disease? *Int J Alzheimers Dis* 2012; 2012: 918680.
- [244] Iwasaki T, Yoneda M, Nakajima A and Terauchi Y. Serum Butyrylcholinesterase is Strongly Associated with Adiposity, the Serum Lipid Profile

- and Insulin Resistance. *Intern Med* 2007; 46: 1633-9.
- [245] Meigs JB, Manning AK, Fox CS, Florez JC, Liu C, Cupples LA and Dupuis J. Genome-wide association with diabetes-related traits in the Framingham Heart Study. *BMC Med Genet* 2007; 8 Suppl 1: S16.
- [246] Gao C, Holscher C, Liu Y and Li L. GSK3: a key target for the development of novel treatments for type 2 diabetes mellitus and Alzheimer disease. *Rev Neurosci* 2012; 23: 1-11.
- [247] Akinyemi R, Mukaetova-Ladinska E, Attems J, Attems J, Ihara M and Kalaria RN. Vascular Risk Factors and Neurodegeneration in Ageing related Dementias: Alzheimer's Disease and Vascular Dementia. *Curr Alzheimer Res* 2013 Jul; 10: 642-53.
- [248] McCarron MO, DeLong D and Alberts MJ. APOE genotype as a risk factor for ischemic cerebrovascular disease: a meta-analysis. *Neurology* 1999; 53: 1308-1311.
- [249] Desai BS, Monahan AJ, Carvey PM and Hendey B. Blood-brain barrier pathology in Alzheimer's and Parkinson's disease: implications for drug therapy. *Cell Transplant* 2007; 16: 285-299.
- [250] Chen X, Ghribi O and Geiger JD. Caffeine protects against disruptions of the blood-brain barrier in animal models of Alzheimer's and Parkinson's diseases. *J Alzheimers Dis* 2010; 20 Suppl 1: S127-141.
- [251] Bartels AL. Blood-brain barrier P-glycoprotein function in neurodegenerative disease. *Curr Pharm Des* 2011; 17: 2771-2777.
- [252] Silver M, Janousova E, Hua X, Thompson PM and Montana G. Identification of gene pathways implicated in Alzheimer's disease using longitudinal imaging phenotypes with sparse regression. *Neuroimage* 2012; 63: 1681-1694.
- [253] Biffi A, Shulman JM, Jagiella JM, Cortellini L, Ayres AM, Schwab K, Brown DL, Silliman SL, Selim M, Worrall BB, Meschia JF, Slowik A, De Jager PL, Greenberg SM, Schneider JA, Bennett DA and Rosand J. Genetic variation at CR1 increases risk of cerebral amyloid angiopathy. *Neurology* 2012; 78: 334-341.
- [254] Mihci E, Ozkaynak SS, Sallakci N, Kizilay F and Yavuzer U. VEGF polymorphisms and serum VEGF levels in Parkinson's disease. *Neurosci Lett* 2011; 494: 1-5.
- [255] He D, Lu W, Chang K, Liu Y, Zhang J and Zeng Z. Vascular endothelial growth factor polymorphisms and risk of Alzheimer's disease: a meta-analysis. *Gene* 2013; 518: 296-302.
- [256] Topiwala A and Ebmeier KP. Vascular changes and brain plasticity: a new approach to neurodegenerative diseases. *Am J Neurodegener Dis* 2012; 1: 152-159.
- [257] Alvarez JI, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, Sabbagh M, Wosik K, Bourbonniere L, Bernard M, van Horssen J, de Vries HE, Charron F and Prat A. The Hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. *Science* 2011; 334: 1727-1731.
- [258] Schrijvers EM, Schurmann B, Koudstaal PJ, van den Bussche H, Van Duijn CM, Hentschel F, Heun R, Hofman A, Jessen F, Kolsch H, Kornhuber J, Peters O, Rivadeneira F, Ruther E, Uitterlinden AG, Riedel-Heller S, Dichgans M, Wiltfang J, Maier W, Breteler MM and Ikram MA. Genome-wide association study of vascular dementia. *Stroke* 2012; 43: 315-319.
- [259] Chuang DM, Leng Y, Marinova Z, Kim HJ and Chiu CT. Multiple roles of HDAC inhibition in neurodegenerative conditions. *Trends Neurosci* 2009; 32: 591-601.
- [260] Egger G, Liang G, Aparicio A and Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. *Nature* 2004; 429: 457-463.
- [261] Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suner D, Cigudosa JC, Urioste M, Benitez J, Boix-Chornet M, Sanchez-Aguilera A, Ling C, Carlsson E, Poulsen P, Vaag A, Stephan Z, Spector TD, Wu YZ, Plass C and Esteller M. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci U S A* 2005; 102: 10604-10609.
- [262] Kontopoulos E, Parvin JD and Feany MB. Alpha-synuclein acts in the nucleus to inhibit histone acetylation and promote neurotoxicity. *Hum Mol Genet* 2006; 15: 3012-3023.
- [263] Outeiro TF, Kontopoulos E, Altmann SM, Kufareva I, Strathearn KE, Amore AM, Volk CB, Maxwell MM, Rochet JC, McLean PJ, Young AB, Abagyan R, Feany MB, Hyman BT and Kazantsev AG. Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. *Science* 2007; 317: 516-519.
- [264] Graff J, Rei D, Guan JS, Wang WY, Seo J, Hennig KM, Nieland TJ, Fass DM, Kao PF, Kahn M, Su SC, Samiei A, Joseph N, Haggarty SJ, Delalle I and Tsai LH. An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature* 2012; 483: 222-226.
- [265] Donmez G, Wang D, Cohen DE and Guarente L. SIRT1 suppresses beta-amyloid production by activating the alpha-secretase gene ADAM10. *Cell* 2010; 142: 320-332.
- [266] Beck J, Poulter M, Hensman D, Rohrer JD, Mahoney CJ, Adamson G, Campbell T, Uphill J, Borg A, Fratta P, Orrell RW, Malaspina A, Rowe J, Brown J, Hodges J, Sidle K, Polke JM, Houlden H, Schott JM, Fox NC, Rossor MN, Tabrizi SJ, Isaacs AM, Hardy J, Warren JD, Collinge J and Mead S. Large C9orf72 hexanucleotide

Pathways to neurodegeneration in AD and PD

- repeat expansions are seen in multiple neurodegenerative syndromes and are more frequent than expected in the UK population. *Am J Hum Genet* 2013; 92: 345-353.
- [267] Mori K, Weng SM, Arzberger T, May S, Rentzsch K, Kremmer E, Schmid B, Kretzschmar HA, Cruts M, Van Broeckhoven C, Haass C and Edbauer D. The C9orf72 GGGGCC repeat is translated into aggregating dipeptide-repeat proteins in FTL/ALS. *Science* 2013; 339: 1335-1338.
- [268] Taylor JP. Neuroscience. RNA that gets RAN in neurodegeneration. *Science* 2013; 339: 1282-1283.
- [269] Rao JS, Keleshian VL, Klein S and Rapoport SI. Epigenetic modifications in frontal cortex from Alzheimer's disease and bipolar disorder patients. *Transl Psychiatry* 2012; 2: e132.
- [270] Chowdhury PD, Che DL and Cui B. Neurotrophin signaling via long-distance axonal transport. *Annu Rev Phys Chem* 2012; 63: 571-594.
- [271] Schindowski K, Belarbi K and Buee L. Neurotrophic factors in Alzheimer's disease: role of axonal transport. *Genes Brain Behav* 2008; 7 Suppl 1: 43-56.
- [272] Kauwe JS, Wang J, Mayo K, Morris JC, Fagan AM, Holtzman DM and Goate AM. Alzheimer's disease risk variants show association with cerebrospinal fluid amyloid beta. *Neurogenetics* 2009; 10: 13-17.
- [273] Karamohamed S, Latourelle JC, Racette BA, Perlmutter JS, Wooten GF, Lew M, Klein C, Shill H, Golbe LI, Mark MH, Guttman M, Nicholson G, Wilk JB, Saint-Hilaire M, DeStefano AL, Prakash R, Tobin S, Williamson J, Suchowersky O, Labell N, Growdon BN, Singer C, Watts R, Goldwurm S, Pezzoli G, Baker KB, Giroux ML, Pramstaller PP, Burn DJ, Chinnery P, Sherman S, Vieregge P, Litvan I, Gusella JF, Myers RH and Parsian A. BDNF genetic variants are associated with onset age of familial Parkinson disease: GenePD Study. *Neurology* 2005; 65: 1823-1825.
- [274] Voineskos AN, Lerch JP, Felsky D, Shaikh S, Rajji TK, Miranda D, Lobaugh NJ, Mulsant BH, Pollock BG and Kennedy JL. The brain-derived neurotrophic factor Val66Met polymorphism and prediction of neural risk for Alzheimer disease. *Arch Gen Psychiatry* 2011; 68: 198-206.
- [275] Chen DY, Bambah-Mukku D, Pollonini G and Alberini CM. Glucocorticoid receptors recruit the CaMKII alpha-BDNF-CREB pathways to mediate memory consolidation. *Nature Neuroscience* 2012; 15: 1707-14.
- [276] Choi JM, Hong JH, Chae MJ, Ngyuen PH, Kang HS, Ma HI and Kim YJ. Analysis of mutations and the association between polymorphisms in the cerebral dopamine neurotrophic factor (CDNF) gene and Parkinson disease. *Neurosci Lett* 2011; 493: 97-101.
- [277] Lin LF, Doherty DH, Lile JD, Bektesh S and Collins F. GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science* 1993; 260: 1130-1132.
- [278] Gash DM, Zhang Z, Ovadia A, Cass WA, Yi A, Simmerman L, Russell D, Martin D, Lapchak PA, Collins F, Hoffer BJ and Gerhardt GA. Functional recovery in parkinsonian monkeys treated with GDNF. *Nature* 1996; 380: 252-255.
- [279] Patani N, Jiang WG and Mokbel K. Brain-derived neurotrophic factor expression predicts adverse pathological & clinical outcomes in human breast cancer. *Cancer Cell Int* 2011; 11: 23.
- [280] Cao L and Doring MJ. What is the brain-cancer connection? *Annu Rev Neurosci* 2012; 35: 331-345.
- [281] Calado RT and Young NS. Telomere diseases. *N Engl J Med* 2009; 361: 2353-2365.
- [282] Hadley EC, Lakatta EG, Morrison-Bogorad M, Warner HR and Hodes RJ. The future of aging therapies. *Cell* 2005; 120: 557-567.
- [283] Honig LS, Kang MS, Schupf N, Lee JH and Mayeux R. Association of shorter leukocyte telomere repeat length with dementia and mortality. *Arch Neurol* 2012; 69: 1332-1339.
- [284] Rolyan H, Scheffold A, Heinrich A, Begus-Nahrmann Y, Langkopf BH, Holter SM, Vogt-Weisenhorn DM, Liss B, Wurst W, Lie DC, Thal DR, Biber K and Rudolph KL. Telomere shortening reduces Alzheimer's disease amyloid pathology in mice. *Brain* 2011; 134: 2044-2056.
- [285] Wang H, Chen H, Gao X, McGrath M, Deer D, De Vivo I, Schwarzschild MA and Ascherio A. Telomere length and risk of Parkinson's disease. *Mov Disord* 2008; 23: 302-305.
- [286] Eerola J, Kananen L, Manninen K, Hellstrom O, Tienari PJ and Hovatta I. No evidence for shorter leukocyte telomere length in Parkinson's disease patients. *J Gerontol A Biol Sci Med Sci* 2010; 65: 1181-1184.
- [287] Hudson G, Faini D, Stutt A, Eccles M, Robinson L, Burn DJ and Chinnery PF. No evidence of substantia nigra telomere shortening in Parkinson's disease. *Neurobiol Aging* 2011; 32: 2107, e2103-2105.
- [288] Njajou OT, Blackburn EH, Pawlikowska L, Mangino M, Damcott CM, Kwok PY, Spector TD, Newman AB, Harris TB, Cummings SR, Cawthon RM, Shuldiner AR, Valdes AM and Hsueh WC. A common variant in the telomerase RNA component is associated with short telomere length. *PLoS One* 2010; 5: e13048.
- [289] Shen Q, Zhang Z, Yu L, Cao L, Zhou D, Kan M, Li B, Zhang D, He L and Liu Y. Common variants near TERC are associated with leukocyte

Pathways to neurodegeneration in AD and PD

- telomere length in the Chinese Han population. *Eur J Hum Genet* 2011; 19: 721-723.
- [290] Kim S, Parks CG, Xu Z, Carswell G, DeRoo LA, Sandler DP and Taylor JA. Association between genetic variants in DNA and histone methylation and telomere length. *PLoS One* 2012; 7: e40504.
- [291] Deelen J, Uh HW, Monajemi R, van Heemst D, Thijssen PE, Bohringer S, van den Akker EB, de Craen AJ, Rivadeneira F, Uitterlinden AG, Westendorp RG, Goeman JJ, Slagboom PE, Houwing-Duistermaat JJ and Beekman M. Gene set analysis of GWAS data for human longevity highlights the relevance of the insulin/IGF-1 signaling and telomere maintenance pathways. *Age (Dordr)* 2013; 35: 235-249.
- [292] Fossel M. Telomerase and the aging cell: implications for human health. *JAMA* 1998; 279: 1732-1735.
- [293] Bertram L, McQueen MB, Mullin K, Blacker D and Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet* 2007; 39: 17-23.
- [294] Lill CM, Roehr JT, McQueen MB, Kavvoura FK, Bagade S, Schjeide BM, Schjeide LM, Meissner E, Zauft U, Allen NC, Liu T, Schilling M, Anderson KJ, Beecham G, Berg D, Biernacka JM, Brice A, DeStefano AL, Do CB, Eriksson N, Factor SA, Farrer MJ, Foroud T, Gasser T, Hamza T, Hardy JA, Heutink P, Hill-Burns EM, Klein C, Latourelle JC, Maraganore DM, Martin ER, Martinez M, Myers RH, Nalls MA, Pankratz N, Payami H, Satake W, Scott WK, Sharma M, Singleton AB, Stefansson K, Toda T, Tung JY, Vance J, Wood NW, Zabetian CP; 23andMe Genetic Epidemiology of Parkinson's Disease Consortium; International Parkinson's Disease Genomics Consortium; Parkinson's Disease GWAS Consortium; Wellcome Trust Case Control Consortium 2); Young P, Tanzi RE, Khoury MJ, Zipp F, Lehrach H, Ioannidis JP, Bertram L. Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database. *PLoS Genet* 2012; 8: e1002548.
- [295] Maloney B, Ge YW, Petersen RC, Hardy J, Rogers JT, Perez-Tur J and Lahiri DK. Functional characterization of three single-nucleotide polymorphisms present in the human APOE promoter sequence: Differential effects in neuronal cells and on DNA-protein interactions. *Am J Med Genet B Neuropsychiatr Genet* 2010; 153B: 185-201.
- [296] Citron BA, Dennis JS, Zeitlin RS and Echeverria V. Transcription factor Sp1 dysregulation in Alzheimer's disease. *J Neurosci Res* 2008; 86: 2499-2504.
- [297] Chu J, Zhuo JM and Pratico D. Transcriptional regulation of beta-secretase-1 by 12/15-lipoxygenase results in enhanced amyloidogenesis and cognitive impairments. *Ann Neurol* 2012; 71: 57-67.
- [298] Santpere G, Nieto M, Puig B and Ferrer I. Abnormal Sp1 transcription factor expression in Alzheimer disease and tauopathies. *Neurosci Lett* 2006; 397: 30-34.
- [299] Karin M, Liu Z and Zandi E. AP-1 function and regulation. *Curr Opin Cell Biol* 1997; 9: 240-246.
- [300] Calon F, Grondin R, Morissette M, Goulet M, Blanchet PJ, Di Paolo T and Bedard PJ. Molecular basis of levodopa-induced dyskinesias. *Ann Neurol* 2000; 47: S70-78.
- [301] Andersson M, Konradi C and Cenci MA. cAMP response element-binding protein is required for dopamine-dependent gene expression in the intact but not the dopamine-denervated striatum. *J Neurosci* 2001; 21: 9930-9943.
- [302] Jegga AG, Schneider L, Ouyang X and Zhang J. Systems biology of the autophagy-lysosomal pathway. *Autophagy* 2011; 7: 477-489.
- [303] Fahrig T, Gerlach I and Horvath E. A synthetic derivative of the natural product rocaglaol is a potent inhibitor of cytokine-mediated signaling and shows neuroprotective activity in vitro and in animal models of Parkinson's disease and traumatic brain injury. *Mol Pharmacol* 2005; 67: 1544-1555.
- [304] Perez-Cadahia B, Drobic B and Davie JR. Activation and function of immediate-early genes in the nervous system. *Biochem Cell Biol* 2011; 89: 61-73.
- [305] Gomez Ravetti M, Rosso OA, Berretta R and Moscato P. Uncovering molecular biomarkers that correlate cognitive decline with the changes of hippocampus' gene expression profiles in Alzheimer's disease. *PLoS One* 2010; 5: e10153.
- [306] Lu Y, Li T, Qureshi HY, Han D and Paudel HK. Early growth response 1 (Egr-1) regulates phosphorylation of microtubule-associated protein tau in mammalian brain. *J Biol Chem* 2011; 286: 20569-20581.
- [307] Lindersson EK, Hojrup P, Gai WP, Locker D, Martin D and Jensen PH. alpha-Synuclein filaments bind the transcriptional regulator HMGB-1. *Neuroreport* 2004; 15: 2735-2739.
- [308] Takata K, Kitamura Y, Kakimura J, Shibagaki K, Tsuchiya D, Taniguchi T, Smith MA, Perry G and Shimohama S. Role of high mobility group protein-1 (HMG1) in amyloid-beta homeostasis. *Biochem Biophys Res Commun* 2003; 301: 699-703.
- [309] Takata K, Takada T, Ito A, Asai M, Tawa M, Saito Y, Ashihara E, Tomimoto H, Kitamura Y and Shimohama S. Microglial Amyloid-beta1-40

- Phagocytosis Dysfunction Is Caused by High-Mobility Group Box Protein-1: Implications for the Pathological Progression of Alzheimer's Disease. *Int J Alzheimers Dis* 2012; 2012: 685739.
- [310] Scaffidi P, Misteli T and Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature* 2002; 418: 191-195.
- [311] Gao HM, Zhou H, Zhang F, Wilson BC, Kam W and Hong JS. HMGB1 acts on microglia Mac1 to mediate chronic neuroinflammation that drives progressive neurodegeneration. *J Neurosci* 2011; 31: 1081-1092.
- [312] Clifford DB, Fagan AM, Holtzman DM, Morris JC, Teshome M, Shah AR and Kauwe JS. CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. *Neurology* 2009; 73: 1982-1987.
- [313] Giunta B, Hou H, Zhu Y, Rrapo E, Tian J, Takashi M, Commins D, Singer E, He J, Fernandez F and Tan J. HIV-1 Tat contributes to Alzheimer's disease-like pathology in PSAPP mice. *Int J Clin Exp Pathol* 2009; 2: 433-443.
- [314] Hickman SE, Allison EK and El Khoury J. Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *J Neurosci* 2008; 28: 8354-8360.
- [315] Tarassishin L, Loudig O, Bauman A, Shafit-Zagardo B, Suh HS and Lee SC. Interferon regulatory factor 3 inhibits astrocyte inflammatory gene expression through suppression of the proinflammatory miR-155 and miR-155*. *Glia* 2011; 59: 1911-1922.
- [316] Chakrabarty P, Ceballos-Diaz C, Lin WL, Beccard A, Jansen-West K, McFarland NR, Janus C, Dickson D, Das P and Golde TE. Interferon-gamma induces progressive nigrostriatal degeneration and basal ganglia calcification. *Nat Neurosci* 2011; 14: 694-696.
- [317] Soares HD, Potter WZ, Pickering E, Kuhn M, Immermann FW, Shera DM, Ferm M, Dean RA, Simon AJ, Swenson F, Siuciak JA, Kaplow J, Thambisetty M, Zagouras P, Koroshetz WJ, Wan HI, Trojanowski JQ, Shaw LM; Biomarkers Consortium Alzheimer's Disease Plasma Proteomics Project. Plasma biomarkers associated with the apolipoprotein E genotype and Alzheimer disease. *Arch Neurol* 2012; 69: 1310-1317.
- [318] Barcia C, Ros CM, Annese V, Gomez A, Ros-Bernal F, Aguado-Yera D, Martinez-Pagan ME, de Pablos V, Fernandez-Villalba E and Herrero MT. IFN-gamma signaling, with the synergistic contribution of TNF-alpha, mediates cell specific microglial and astroglial activation in experimental models of Parkinson's disease. *Cell Death Dis* 2011; 2: e142.
- [319] Jaeger S and Pietrzik CU. Functional role of lipoprotein receptors in Alzheimer's disease. *Curr Alzheimer Res* 2008; 5: 15-25.
- [320] Waldron E, Heilig C, Schweitzer A, Nadella N, Jaeger S, Martin AM, Weggen S, Brix K and Pietrzik CU. LRP1 modulates APP trafficking along early compartments of the secretory pathway. *Neurobiol Dis* 2008; 31: 188-197.
- [321] Liu Q, Trotter J, Zhang J, Peters MM, Cheng H, Bao J, Han X, Weeber EJ and Bu G. Neuronal LRP1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration. *J Neurosci* 2010; 30: 17068-17078.
- [322] Sloan CD, Shen L, West JD, Wishart HA, Flashman LA, Rabin LA, Santulli RB, Guerin SJ, Rhodes CH, Tsongalis GJ, McAllister TW, Ahles TA, Lee SL, Moore JH and Saykin AJ. Genetic pathway-based hierarchical clustering analysis of older adults with cognitive complaints and amnesic mild cognitive impairment using clinical and neuroimaging phenotypes. *Am J Med Genet B Neuropsychiatr Genet* 2010; 153B: 1060-1069.
- [323] Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorf LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmanacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TF, McCarroll SA and Visscher PM. Finding the missing heritability of complex diseases. *Nature* 2009; 461: 747-753.
- [324] Zuk O, Hechter E, Sunyaev SR and Lander ES. The mystery of missing heritability: Genetic interactions create phantom heritability. *Proc Natl Acad Sci U S A* 2012; 109: 1193-1198.
- [325] Peregrin-Alvarez JM, Sanford C and Parkinson J. The conservation and evolutionary modularity of metabolism. *Genome Biol* 2009; 10: R63.
- [326] Ayalew M, Le-Niculescu H, Levey DF, Jain N, Changala B, Patel SD, Winiger E, Breier A, Shekhar A, Amdur R, Koller D, Nurnberger JI, Corvin A, Geyer M, Tsuang MT, Salomon D, Schork NJ, Fanous AH, O'Donovan MC and Niculescu AB. Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. *Mol Psychiatry* 2012; 17: 887-905.
- [327] Zhong H, Yang X, Kaplan LM, Molony C and Schadt EE. Integrating pathway analysis and genetics of gene expression for genome-wide association studies. *Am J Hum Genet* 2010; 86: 581-591.
- [328] Ala-Korpela M, Kangas AJ and Inouye M. Genome-wide association studies and systems biology: together at last. *Trends Genet* 2011; 27: 493-498.