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Convergent pathogenic pathways in Alzheimer's and Huntington disease: Shared targets for drug development

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Abstract

Neurodegenerative diseases exemplified by Alzheimer's and Huntington disease are characterized by the progressive neuropsychiatric dysfunction and loss of specific neuronal subtypes. Even though there are differences in the exact sites of pathology and clinical profiles only partially overlap, considerable similarities in disease mechanisms and pathogenic pathways can be observed. These shared mechanisms raise the possibility of common therapeutic targets for drug development. Huntington disease with a monogenic cause and the possibility to accurately identify pre-manifest mutation carriers could be exploited as a 'model' for Alzheimer's disease to test the efficacy of therapeutic interventions targeting shared pathogenic pathways.

Introduction

The rapidly aging population in the developed world, spurred on by an increase in life expectancy, has led to increased prevalence of late onset neurodegenerative disorders and imposes an enormous financial and social burden on health care systems as well as society as a whole. In 2010, for example, 6 million people in the US were over the age of 85, and this number is projected to quadruple by 2050¹.

The clinical symptoms of neurodegenerative disorders such as Alzheimer's disease (AD) and Huntington disease (HD) are progressive and debilitating. The hallmark of HD is motor disability that features chorea, while the main symptom of AD is dementia. Nevertheless, patients with HD and AD share many clinical manifestations. These include behavioural and psychiatric disturbances (including depression and apathy) in the early stages and cognitive defects that result in forgetfulness, impaired judgement, disorientation and confusion. Cognitive deficits in patients with HD however are usually less severe than in AD; Patients also exhibit difficulty in ambulation and eating at late stages of both diseases, which ultimately lead to death^{1, 2}.

AD is genetically heterogeneous and can be caused by any one or more of several genes as well as environmental factors. Familial AD (FAD), which accounts for less than 1% of all AD cases, are caused by rare mutations in genes encoding for amyloid precursor protein (APP), presenilin (PSEN)-1 and -2^{1, 3}. Numerous genes are significantly associated with sporadic late-onset AD. The ϵ 4 allele of apolipoprotein E (APOE) is the single strongest genetic risk factor for sporadic AD⁴. APP cleavage by the β -secretase BACE1 and the γ -secretase complex, which consists of PSEN1 or PSEN2, anterior pharynx-defective-1 (APH-1), presenilin enhancer-2 (PEN-2) and nicastrin, leads to the generation of the extracellular A β peptide. This peptide fragment is prone to aggregate and form amyloid

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plaques that can be detected in post-mortem brain from AD patients^{5, 6}. In addition to amyloid plaques, neurofibrillary tangles made up of hyperphosphorylated tau aggregates, a microtubule protein, are also observed in post-mortem brain from AD patients^{5, 6}. In contrast, HD is a monogenic disorder with autosomal dominant inheritance and is caused by a CAG repeat that expands to 36 copies or more in the gene encoding the huntingtin (Htt) protein², resulting in an expansion of the polyglutamine tract. Furthermore, the length of the CAG tract is directly correlated with the disease onset, with longer expansions leading to earlier onset². β -secretase, γ -secretase and the A β peptide are well validated therapeutic targets in AD⁷, while mutant Htt (mHtt) is a promising target in HD^{8, 9}. However these targets are not shared between AD and HD and will therefore not be the focus of this review.

At a neuropathological level, the diseases are initially characterized by a specific loss of certain neuronal subtypes. In HD, it is the medium-spiny neurons (MSNs) in the striatum that undergo atrophy in early stages of the disease, while in AD, large pyramidal neurons in the CA1 zone of the hippocampus as well as neurons in the basal forebrain and the entorhinal cortex are sites of early disease¹⁰⁻¹². The process of neuronal dysfunction and death is progressive, and early changes are followed by a more wide-spread atrophy of the brain^{10, 13}. Considerable progress has been made in the elucidation of mechanisms that lead to neurodegeneration in AD and HD. There is evidence for the aberrant phosphorylation, palmitoylation and acetylation of disease-causing proteins, protein misfolding, failure to clear disease-causing proteins by the ubiquitin-proteasome system or autophagy, and changes in NMDA receptor activity at the synapse. Additional mechanisms include alterations in levels of brain-derived neurotrophic factor (BDNF) and neuronal growth factor (NGF) as well as associated receptors and trafficking pathways, and increased activity of caspase enzymes in both disorders^{5, 6, 9, 14} (Table 1).

Although no treatments are available to slow or halt neuronal degeneration and neuronal death, the analysis of disease pathways has led to the identification of common drug targets for AD and HD. These similarities have not been commonly appreciated by the HD or AD research communities, and could lead to the development of drugs that can be used for both disorders. Here we will describe the pathways and therapeutic targets and rank them with target validation (TV) scores based on a scale developed by the Cure Huntington's Disease Initiative (CHDI) (<http://www.hdresearchcrossroads.org>, Table 2, ¹⁵), which we apply to both diseases for direct comparison. Potential therapeutic targets are hereby ranked by their degree of validation from 1.0 (a gene that is linked to a disease-relevant biological mechanism) to 6.0 (therapeutic modulation of the target demonstrates efficacy in a phase 3 clinical trial) in AD and HD. Although well-studied targets will automatically rank higher in this system than understudied targets, we believe that our ranking can identify common, well-validated targets as well as knowledge gaps that warrant further studies.

For most targets, it is unknown whether their modulation will be disease-modifying or only lead to the alleviation of symptoms, and the TV score does not discriminate between these possibilities. To clarify this issue, long-term clinical studies are necessary, and we believe that these could initially be conducted in individuals carrying the mutation causing HD, since this population is well defined and alterations in the course of the disease can be determined at very early stages¹⁶. HD is the commonest purely genetic neurodegenerative disorders, while AD is the most common neurodegenerative disease overall^{1, 2}. Since many of the pathways and targets described here are also shared with other diseases such as Parkinson's disease, dementia with Lewy bodies or ataxias, HD could serve as a general model for neurodegeneration, where well-defined animal models are available for preclinical studies and endpoints for human clinical trials are well established^{16, 17}. The "Enroll-HD" study that is currently underway will provide a registry of HD mutation carriers worldwide and serve as a resource for recruiting patients to clinical trials (<http://www.enroll-hd.org>).

Targeting synaptic dysfunction in HD and AD

Excitotoxicity has been implicated in neuronal death in HD and AD. The N-methyl-D-aspartate (NMDA) subtype of glutamate receptors is thought to be a major contributor to excitotoxic cell death because of its high permeability to calcium (Ca^{2+})¹⁸. The NR2A and NR2B subunits of NMDAR differ in their sensitivities to agonists and antagonists, their channel gating properties, and in their localization. NR2A-containing receptors are generally found in the synapse, while NR2B-containing receptors are predominantly localized at extrasynaptic sites¹⁸. Enhanced activation of extrasynaptic, NR2B-containing NMDAR is common in both HD and AD.

Aberrant extrasynaptic NMDA receptor activity in HD and AD

The presence of mHtt and APP alters the subcellular distribution of NMDAR^{18, 19}. In mouse models of both diseases, deficits in trafficking mechanisms increase cell surface levels of NR2B and decrease NR2B internalization¹⁸. Increased levels of NR2B on the cell surface results in enhanced NMDAR currents in mouse models of HD and AD¹⁹. Both wild type Htt and tau, a neuronal protein that stabilizes microtubules, function in NR2B trafficking as well as the recruitment of kinases to NMDARs at the cell surface. MHtt disrupts these processes, resulting in altered tyrosine phosphorylation of NR2B and enhanced NMDAR-mediated toxicity²⁰. Similarly, A β -induced NMDAR dysfunction is mediated by Fyn, a tyrosine kinase that phosphorylates NR2B^{21, 22} and mediates its insertion into the plasma membrane²³ increasing the levels of NR2B on the cell surface. The activation of extrasynaptic NR2B-containing NMDARs also dephosphorylates and inhibits the CREB/PGC1 α signalling pathway, which makes cells expressing mHtt more susceptible to cell death²⁴ (Figure 1). Enhanced activation of extrasynaptic NMDAR further leads to excessive influx of Ca^{2+} into the cell, which results in inappropriate activation of enzymes (i.e., calpains and other Ca^{2+} -regulated enzymes) and mitochondrial dysfunction, and leads to apoptosis¹⁸.

Activation of extrasynaptic NMDARs may also underlie the cognitive impairment that is observed in patients with HD and AD. Long term potentiation (LTP), a measure of synaptic plasticity, is thought to be a mechanism underlying learning and memory. In mouse models of AD and HD, neurons derived from affected brain regions have defective LTP^{25, 26}. Furthermore, the activation of extrasynaptic NMDARs in a mouse model of AD promotes β -secretase cleavage of APP, which results in increased levels of A β that are directly correlated with the severity of the cognitive deficit²⁷. The presence of A β oligomers, early intermediates in the A β aggregation pathway, has in turn been associated with increased activation of extrasynaptic NMDARs, which could cause a feedback loop leading to synaptic dysfunction²⁸. However, the strongest evidence for the role of extrasynaptic NMDAR in cognitive impairment is the effectiveness of memantine, an NMDAR blocker (see below), in rodent models of HD and AD as well as in AD patients^{24, 29-31}.

Therapeutic approaches

Inhibition of extrasynaptic NMDARs can be achieved using memantine treatment. At a low dose (1 mg/kg = 3 mg/m² human equivalent dose (HED)), memantine blocks extrasynaptic but not synaptic NMDAR activity, whereas high doses (30 mg/kg = 90 mg/m² HED) inhibit both synaptic and extrasynaptic NMDARs (Figure 1). A low dose of memantine rescues neuropathological and behavioural phenotypes as well as electrophysiological abnormalities in models of HD. By contrast, high dose memantine worsens these symptoms^{24, 29}. Similarly, administration of a low memantine dose corrected defects in learning and memory tasks, such as performance in the Morris water maze and passive avoidance learning in a mouse model of AD³⁰.

Memantine treatment has also been tested in patients with AD and is now approved by the FDA for this indication (Namenda XR, Forest Laboratories, NDA no. 022525). In clinical trials, patients with AD who received 28 mg of memantine (extended release formulation) for 24 weeks showed significantly reduced decline in cognitive symptoms in two measures of cognitive performance compared to patients receiving placebo (FDA approval review, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022525Orig1s000MedR.pdf). Longer studies are needed to determine whether the effects of memantine are purely symptomatic or disease modifying. Nevertheless, the improvements seen in patients with AD are encouraging and NR2B receptors are currently the best validated of the shared therapeutic targets between AD and HD, with TV scores of 6 and 4, respectively (Suppl Table S1). In view of open label studies showing some potential benefit, clinical trials with memantine in HD patients might be considered.³²⁻³⁴

Non-neuronal contributions to excitotoxic pathways

Another striking similarity between AD and HD is the presence of activated microglia as markers of inflammation^{5, 14}. Microglia produce quinolinic acid (QA), a selective NMDAR agonist and a metabolite of the tryptophan degradation pathway, that elicits symptoms reminiscent of HD when injected into the striatum, and symptoms similar to AD when injected into the nucleus basalis of rodents³⁵. A recent study furthermore demonstrates that inhibiting kynurenine 3-monooxygenase, an enzyme in the pathway generating QA, can ameliorate excitotoxicity and disease phenotypes in mouse models of both AD and HD³⁵.

Modulating neurotrophic factors and receptors in HD and AD

Neurotrophic factors, including neural growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are secreted peptides that have prominent roles in neuronal development, health and function of the brain regions that are most affected in patients with AD and HD³⁶. NGF specifically binds tyrosine protein kinase A (TrkA) receptors, while BDNF recognizes TrkB receptors to activate downstream signalling pathways. In addition, both bind the p75 neurotrophin receptor (p75NTR) with lower affinity, which is associated with pro-death signalling following neuronal injury³⁶ (Figure 2). The unprocessed, precursor forms of NGF and BDNF (pro-NGF and pro-BDNF, respectively) also bind p75NTR, leading to apoptosis³⁶. Alterations in the levels of NGF and BDNF, the levels and localization of cognate receptors and changes in the pathways activated by these neurotrophins have been implicated in the pathogenesis of HD and AD (Figure 2, Suppl Table S1).

Increasing BDNF as a therapeutic approach

Reduced levels of BDNF are observed in the striatum and the hippocampus in patients suffering from HD and AD, respectively^{37, 38}. Polymorphisms in the gene encoding BDNF have been positively associated with age of onset of AD in some studies^{39, 40, 41}, although this association is controversial⁴²⁻⁴⁴. Similarly, data on an association between BDNF polymorphisms and age of onset in HD has also been conflicting^{45, 46}.

The ability to increase BDNF levels through exercise is well documented⁴⁷. Using APP/PSEN1 transgenic mice, it has been shown recently that exercise increases BDNF levels and prevents decline in spatial learning and memory through the improvement of LTP in the hippocampus⁴⁸. The beneficial effects of BDNF overexpression using genetically-modified mesenchymal stem cell transplantation, viral-mediated expression or intracranial injections of BDNF in different rodent models of HD and AD validate BDNF as a therapeutic target and led to a TV score of 4.5 and 4.0 for AD and HD, respectively (Suppl Table S1). Overexpression of BDNF protects against neurotoxicity, prevents loss of neurons, corrects

motor dysfunction, improves procedural learning and corrects synaptic plasticity⁴⁹⁻⁵¹. Increasing BDNF in a non-human primate model of AD also improved hippocampal learning and ameliorated neuronal death with no observable adverse effects⁵².

Pharmacological agents that are currently used or are undergoing testing for other clinical applications, such as lithium or the amphetamine CX929, can increase BDNF levels by increasing its expression and promoting its trafficking and improve phenotypes in animal models of HD and patients suffering from AD^{53, 54}. A Phase II clinical trial studying the effect of lithium treatment in patients with AD is currently underway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00088387) identifier: NCT00088387), and in a small cohort of patients lithium reduced the progression from mild cognitive impairment to full AD⁵⁵. In addition to increasing BDNF levels, lithium also inhibits the hyperphosphorylation of Tau mediated by GSK3 β and has additional beneficial effects in the activation of pro-survival CREB signalling and the activation of autophagy⁵⁶⁻⁵⁹ (Figure 2, and see below). Due to these multiple effects, lithium is a suboptimal tool compound to investigate specific pathways, but remains a potential therapeutic.

Trafficking defects in HD and AD: Targeting microtubule-associating proteins

Striatal MSNs rely on BDNF release from innervating cortical neurons for their normal functioning and survival, which makes axonal trafficking of BDNF from the cell body of cortical neurons to the synapse an important process⁶⁰. Defects in intracellular trafficking have been suggested as a cause for the reduced BDNF levels in the brains of patients with HD or AD^{60, 61}. Interestingly, polymorphisms in the gene encoding BDNF that are associated with an increased risk of AD and reduced age of onset of HD impair the binding of pro-BDNF to the huntingtin-associated protein-1 (HAP1), which is necessary for the intracellular trafficking of pro-BDNF^{60, 62}. These polymorphisms could therefore lead to reduced BDNF levels in both diseases (Figure 2).

Htt and Tau are predominantly found in the cytoplasm where they colocalize with microtubules and vesicular structures and associate with proteins that are involved in intracellular trafficking^{61, 63}. Wild type Htt interacts with HAP1 that associates with proteins essential for intracellular trafficking, such as kinesin and p150^{Glued} (a subunit of dynactin)^{60, 63}. Similarly, Tau, a microtubule-associated protein, regulates axonal transport by inhibiting the motor activity of kinesin and dynein (Figure 2, Suppl Table S1)^{63, 64}.

The velocity and efficiency of the transport of BDNF-containing vesicles are reduced in the presence of mHtt, PSEN1 mutations and hyperphosphorylated Tau^{60, 61}. In both neuronal cultures and post-mortem extracts of brains from patients with HD, mHtt shows increased binding to HAP1, which in turn disrupts HAP1 binding to kinesin and reduces the HAP1/p150^{Glued} interaction, thereby reducing the transport of BDNF-containing vesicles⁶⁰. Interestingly, HAP1 deficiency also affects kinesin-dependent transport of APP, which suggests a role for HAP1 in the pathogenesis of AD⁶⁵. Mutations in PSEN1 that are associated with FAD deregulate the glycogen synthase kinase-3 β (Gsk3 β), leading to hyperphosphorylation of Tau and its detachment from microtubules, which results in cytoskeletal collapse and deficits in axonal transport that contribute to the pathogenesis of AD^{61, 66, 67} (Figure 2).

Although there are currently no therapies to ameliorate trafficking deficits to increase BDNF levels, this pathway has many potential therapeutic targets, such as HAP1, kinesin, dynein/dynactin, and microtubules, which could be modified for the treatment of HD and AD.

Inhibitors of Histone deacetylases (HDACs), which are currently being used as cancer therapeutics⁶⁸, influence axonal transport through increased acetylation of α -tubulin,

enhancing its binding to kinesin^{4, 69}. The modulation of HAP1 binding to mHtt would likely be harder to achieve, since the strengthening of a protein-protein interaction is generally not considered a druggable intervention. However, microtubule (MT)-binding/stabilizing drugs, such as paclitaxel and epothilones that are also currently used as cancer therapy⁷⁰⁻⁷², could be tested in models of HD and AD to better validate therapeutic targets in axonal transport pathways (Suppl Table S1). Recently, epothilone D, a MT-binding/stabilizing agent from the epothilone natural product family, was shown to penetrate the blood-brain barrier and increase MT stability in the CNS of Tau transgenic mice⁷¹. The identification and evaluation of MT-binding/stabilizing agents is therefore a promising research area for the treatment of neurodegenerative disorders with impaired axonal transport such as HD and AD.

Increasing NGF is beneficial

A reduction in the levels of mature NGF is observed in the basal forebrain of aged animals and in rodent models of AD and patients with AD⁷³. However, the levels of NGF in human patients with HD have not been reported. Nevertheless, overexpression of NGF in both model systems of HD and AD has beneficial effects that are similar to BDNF overexpression. Rat models of AD and mouse models of HD transplanted with NGF-loaded microspheres in the forebrain show significant improvement in learning and memory tasks and better survival of cholinergic neurons^{74, 75}. Intrastriatal transplantation of genetically engineered mesenchymal stem cells expressing NGF and administration of an amplifier of NGF into transgenic mouse models of HD slow neurodegenerative processes and rescue behavioural deficits⁵⁰.

Human therapeutic trials that assess the effects of increasing NGF levels in patients with AD are underway. In a phase I clinical study, the implantation of modified fibroblasts expressing human NGF in the basal forebrain of patients with AD resulted in a decrease in the rate of cognitive decline⁷⁶. Currently, therapeutic options that are less invasive are being explored, including the intranasal delivery of recombinant NGF, which rescued behavioural and neuropathological defects in a mouse model of AD⁷⁷. NGF, like BDNF, is therefore a highly validated target for AD and HD with TV scores of 4.5 and 4.0, respectively (Suppl Table S1).

Activating Trk and reducing p75NTR signalling as a therapeutic strategy

In patients with AD and HD and animal models, there is an increase in p75NTR levels and a decrease in TrkA and TrkB levels, respectively^{73, 78}. Neurotrophin-mediated cell death that occurs through activation of p75NTR is mediated through caspase-6⁷⁹, which emerges as a therapeutic target for both AD and HD in multiple studies (Suppl Table S1, see below).

Neurotrophin signalling through Trk receptors activates pro-survival pathways, such as the PI3K/Akt signalling pathway. However, reduced signalling through Trk receptors results in increased Gsk3 β activity, which has been implicated in the prevention of LTP, induction of microglia-mediated inflammation and promotion of neuronal death in models of AD and HD^{57, 80}. In AD, increased Gsk3 β signalling also increases Tau phosphorylation and amyloid production, while in HD, increased Gsk3 β activity enhances the toxicity of mHtt^{57, 80}.

Reduced NGF signalling also results in the increased production and intracellular aggregation of A β peptides, mediated through increased transcription of APP and increased processing of APP by β - and γ -secretases⁸¹. The pathogenic effects of altered Trk and p75NTR signalling in HD are not well-characterised (Suppl Table S1).

Glucocorticoids (GCs) have protective effects in the CNS and this protection is dependent on an increase in Trk receptor activity⁸². Such treatments may be beneficial in HD and AD,

but this remains to be shown in the relevant disease models, which is reflected by currently low target validation scores for Trk receptors (Figure 2, Suppl Table S1).

Targeting apoptotic pathways in HD and AD

The caspase proteases are best known for their roles in apoptotic cell death, where they are activated in a signalling cascade involving either extrinsic signals mediated through death receptors or intrinsic pathways initiated by DNA or mitochondrial damage⁸³. Both pathways culminate in the activation of one or more members of the so called executioner caspase subfamily (caspases-3, -7 and -6), which cleave cytoskeletal proteins as well as pro-survival and antiapoptotic factors and thereby commit the cell to death⁸³. However, in addition to this classical role, caspases are also involved in non-apoptotic processes⁸⁴. In the brain in particular, activation of the ‘executioner’ caspases has been observed in events associated with learning and memory such as synaptic plasticity and LTP, as well as the developmental pruning of axons⁸⁵⁻⁸⁸. These findings challenge the view of caspases as the final executioners of cell death and suggest that the role of these enzymes in neurodegeneration might be more upstream in signalling pathways, where they could mediate early neuronal dysfunction.

Preventing caspase-6 cleavage is beneficial in AD and HD

Caspase-6 is activated in brain tissue from pre-symptomatic individuals carrying the HD mutation and in individuals with only mild cognitive impairment that could progress into AD, supporting the idea of caspase activation as an early event in the pathogenesis of neurodegenerative disease^{89, 90}. These findings are paralleled by results that show the aberrant cleavage of caspase-6 substrates in brain tissue from patients suffering from HD or AD⁹⁰⁻⁹². Interestingly, the disease-causing proteins mHtt, Tau and APP are substrates for caspase-6, and the abrogation of mHtt or APP cleavage in mouse models is protective and leads to a dramatic improvement of the disease phenotype^{93, 94}.

Therapeutic approaches

While the findings discussed above make caspase-6 an interesting and well-validated target in the apoptotic pathway for both diseases (Suppl Table S2), it may not easily be tractable by small molecule inhibitors. The inhibition of ‘executioner’ caspases by compounds such as IDN-6556 (Pfizer), compound 34 (Sunesis) or M867 (Merck-Frosst) may also have some liabilities including the concern of carcinogenic side-effects^{95, 96}. An alternative would be to inhibit activators of caspase-6. However the exact mechanism underlying aberrant caspase activation is not understood in either AD or HD. Activation could occur through the activation of ‘initiator’ caspases such as caspase-9 via death or neurotrophic receptors (DR6, p75NTR, TrkB or TrkA). As described above, alterations in these receptors occur in HD and AD, and neuronal death mediated through p75NTR in a seizure model is dependent on the downstream activation of caspase-6⁷⁹ (Figure 3).

The intrinsic apoptotic pathway is another well-described paradigm for caspase activation and it can be triggered by ER stress, protein misfolding (see below), DNA and mitochondrial damage or oxidative stress⁸³. mHtt and A β may directly alter mitochondrial function in HD and AD. Htt can be found at the mitochondrial membrane⁹⁷ and in the presence of mHtt oligomers, expression levels of mitochondrial fusion and fission proteins are altered. These changes in expression levels may be responsible for decreased mitochondrial function by causing structural abnormalities in and defective trafficking of mitochondria in HD⁹⁷. In AD, mitochondria, especially synaptic mitochondria, show age-dependent A β accumulation^{98, 99}, which enhances the permeability of the mitochondrial permeability transition pore and causes the generation of reactive oxygen species⁹⁹. Clinical

trials of antioxidants that might ameliorate oxidative stress, DNA and mitochondrial damage, have not yielded conclusive results in patients with either AD or HD^{100, 101}. However a better understanding of endogenous antioxidant levels in patients before and after treatment might help to stratify potential responders from non-responders¹⁰⁰.

Caspases can also be activated by disturbances of developmental and synaptic plasticity signals such as axonal pruning or LTP^{85-88, 102}. In these non-apoptotic paradigms, caspase activation is usually contained in a well-defined subcellular compartment such as the synapse, and the active executioner caspases are kept under tight control by endogenous inhibitor proteins or through degradation by the proteasome^{88, 103}. This insures that the activation of enzymes such as caspase-3, which are usually highly efficient in amplifying the cell death cascade, remains locally contained and does not trigger the demise of the whole cell. Under pathological conditions, toxic proteins or fragments thereof (such as mHtt, A β) can cause proteasomal dysfunction, which might lead to an impaired degradation and thus accumulation of active caspase-6 and -3¹⁰³. The resulting increase in caspase activity could then lead to an amplification of the apoptotic cascade and commit the cell to death, even though the initial caspase activating signal was meant to only trigger non-apoptotic functions.

Further studies are needed to better understand apoptotic pathways in AD and HD and to better validate therapeutic targets that are further upstream in the signalling cascade.

Targeting posttranslational modifications of disease-causing proteins

Although the proteolytic cleavage of mHtt and APP can be considered a relevant posttranslational modification (PTM) in the pathogenesis of both disorders, additional, reversible PTMs of mHtt, A β and Tau have been described extensively^{6, 9, 104} and lead to considerable overlap in potential therapeutic strategies that will be discussed below.

Kinases and phosphatases

Both mHtt and APP are phosphorylated at multiple sites, and phosphorylation at certain amino acids (S421 for mHtt, T668 for APP) reduces the amount of caspase cleavage at adjacent sites as well as the toxicity that is associated with this process^{105, 106}. mHtt is phosphorylated at S421 by Akt, and its dephosphorylation depends on the phosphatases PP1/PP2A^{107, 108}, whereas APP is phosphorylated by Cdk5 and Gsk3 β in neurons¹⁰⁴ (Suppl Table S3). Gsk3 β is also the major kinase phosphorylating Tau in AD, which leads to the formation of insoluble Tau aggregates (Tau tangles) and subsequent disruption of the microtubule system⁶⁷. The phosphatases that are responsible for the dephosphorylation of APP or Tau are unknown.

Therapeutic strategies

Inhibition of Gsk3 using lithium is protective in models of AD, which has been partly attributed to a decrease of Tau hyperphosphorylation and improved BDNF trafficking (see above) as well as a reduction in APP cleavage and A β accumulation, since the GSK3 α isoform has been implicated in processing of APP by γ -secretase^{67, 109}. Lithium treatment has also shown benefits in mouse models of HD^{57, 110}, and levels of GSK3 β are increased prior to symptom onset in an HD model¹¹¹. The treatment of primary neurons derived from these mice with GSK3 β inhibitors reduces neuronal death¹¹¹ (Suppl Table S3).

Sodium valproate, which is widely used as a mood stabilizer and antiepileptic drug, has also shown promising neuroprotective effects in several models of AD¹¹². It inhibits GSK3 β , but has additional effects by acting as a transcriptional modulator through the inhibition of HDACs, and by reducing excitotoxicity^{110, 113}. While valproate might not be suited for the

management of agitation in dementia¹¹⁴, longer-term studies are necessary to be able to judge its neuroprotective effects.

PP1/PP2A phosphatase inhibition is a possible strategy to boost phosphorylation of mHtt in HD and reduce its toxicity¹⁰⁸. As illustrated by the low TV score for phosphatases (Suppl Table S3), further validation studies are needed before phosphatase inhibition can be pursued as a therapeutic option. Of note, the identity of the PP1/PP2A regulatory subunits mediating Htt dephosphorylation remains unknown, although their inhibition might be more successful than the development of active site inhibitors, since the active phosphatase subunits are very promiscuous in terms of substrate specificity¹¹⁵. Upregulation of Akt activity on the other hand could be achieved through the modulation of the upstream IGF-1 and PI3K signalling pathway¹⁰⁷. This pathway also emerges as a target in the upregulation of autophagy in both AD and HD.

Palmitoylation: Palmitoyl transferases and Thioesterases as targets in AD and HD

Palmitoylation¹¹⁶⁻¹¹⁹, a PTM that attaches a single palmitate moiety to a cysteine residue, is important in synaptic transmission and neuronal plasticity¹²⁰. In AD, palmitoylation of BACE1 reduces the shedding of the ectodomain of the protease, which in turn reduces the generation of A β ¹¹⁹. In HD, the Htt protein itself is palmitoylated by the palmitoyl transferases HIP14 and HIP14L¹¹⁷, and acts as a cofactor for the palmitoylation of other HIP14 substrates¹²¹. The interaction of mHtt with HIP14 is reduced in a mouse model of HD¹¹⁸. The resulting decrease in the palmitoylation of multiple synaptic substrates could lead to the phenotype observed in HD¹²² (Suppl Table S3). Furthermore, the ablation of HIP14 leads to a phenotype similar to HD in a mouse model¹²³.

An increase of palmitoyl transferase activity or the inhibition of thioesterases could therefore be beneficial by reducing A β generation in AD as well as normalizing the aberrant palmitoylation of numerous synaptic substrates in HD. However, the lack of information on the palmitoyl transferase(s) involved in BACE1 palmitoylation and on the thioesterases depalmitoylating Htt or BACE1 warrants further studies before targeted therapies to correct palmitoylation defects can be developed.

Aberrant protein acetylation and HDACs in HD and AD

In both AD and HD, transcriptional dysregulation that is linked to altered histone acetylation as well as defective axonal transport due to a lack of tubulin acetylation^{69, 124}. These defects could account for a variety of the disease phenotypes associated with AD and HD, such as the altered expression and transport of neurotrophic factors¹²⁵, and might therefore be upstream events in the pathogenic pathways of both disorders.

As a therapeutic strategy to increase acetylation, the inhibition of HDACs by compounds such as phenyl butyrate, trichostatin A or Suberoylanilide hydroxamic acid (SAHA) is protective in cellular and animal models of both AD and HD^{69, 126, 127} (Suppl Table S3). HDAC inhibitors such as SAHA (Vorinostat, Merck) or valproic acid are currently undergoing Phase II/III clinical trials for different types of cancer, which together with the high degree of target validation for HDACs makes them good candidates for clinical trials in neurodegenerative disease.

Protein aggregation and clearance mechanisms in AD and HD

Protein aggregation is a prime neuropathological hallmark of AD and HD that has been recognized for many decades. In HD, this involves the deposition of intracellular (and intranuclear) aggregates of mHtt, whereas in AD, there is accumulation of extracellular A β plaques and intracellular Tau tangles¹²⁸. The accumulation of misfolded proteins that have

amyloid characteristics (a tertiary structure that is rich in β -sheets and can be visualized by staining with dyes such as Congo red and Thioflavin S) is thought to result from improper folding of the mutant proteins as well as insufficient clearance mechanisms¹²⁹. Endogenous chaperones, in particular the heat-shock proteins, prevent misfolding and aggregation of mHtt, Tau and A β ¹³⁰, and their overexpression is protective against neurotoxic insults such as excitotoxicity¹³¹ (Suppl Table S4).

Targeting protein misfolding directly and/or through chaperones

Large screening campaigns have led to the identification of a variety of compounds that directly interfere with A β , mHtt and Tau protein misfolding and aggregation in cell-free systems, as well as compounds that modulate the activity of heat-shock proteins and other chaperones¹³²⁻¹³⁸ (Figure 4). However, for both classes of compounds, the translation of therapeutic efficacy into mouse models has been difficult. Geldanamycin, a compound that is highly efficient in the upregulation of chaperone proteins and can thus reduce amyloid formation in cell culture, has the drawback of substantial toxicity and low blood-brain-barrier (BBB) penetration. Another example is (-) epigallocatechin gallate, a compound that provides benefits to patients suffering from systemic amyloidoses by reducing the amount of aggregated protein in tissues such as the heart¹³⁹. It stabilizes a non-toxic form with low β -sheet content of both mHtt and A β ^{134, 135}, and although some studies report beneficial effects in animal models of AD¹⁴⁰, delivery to the central nervous system is difficult¹⁴¹. Lack of translation of the effects seen in cell culture into mouse models has also been attributed to the high drug-to-amyloid protein ratios that need to be achieved to directly influence aggregation.

A major limitation to the development of aggregation inhibitors is the fact that the protein misfolding and aggregation pathway is incompletely understood. While early studies focused on preventing the formation of large amyloid aggregates, it is now clear that misfolding events occurring early in the amyloidogenic process lead to the generation of monomers or small oligomers that can mediate neurotoxicity and degradation^{142, 143}. Due to difficulties in detecting these smaller toxic assemblies, the exact mechanism of action for many aggregation inhibitors such as the benzothiazoles, C2-8 or triazines remains unknown, and while they prevent the formation of large A β plaques and mHtt aggregates^{132, 133, 136}, they might not interfere with initial misfolding steps and thus not have a significant impact on pathogenesis (Figure 4).

Proof for the therapeutic benefits of inhibitors of protein aggregation in mammalian models of AD and HD is therefore necessary to increase the TV score (Suppl Table S4), and such studies would also answer the question whether the prevention of protein aggregation alone is sufficient to slow down the pathogenesis in AD and HD.

Increasing the clearance of misfolded proteins: The ubiquitin-proteasome system as a target

Intracellular aggregates of both mHtt and Tau contain high levels of ubiquitin, which led to the hypothesis that proteasomal degradation of ubiquitinated proteins could be impaired in HD and AD, and might lead to the accumulation of amyloid aggregates^{144, 145}. There is conflicting evidence for an impairment of the ubiquitin-proteasome system (UPS) in HD and AD. A recent time-lapse study of single neurons that expressed mHtt showed that the UPS is impaired before the formation of visible aggregates. However UPS function normalizes at later time points in the presence of aggregates¹⁴⁶. Recent studies further show that the UPS has an important function in the degradation of signalling molecules at the synapse, and contributes to synaptic plasticity¹⁴⁷. Since synaptic dysfunction occurs early in the pathogenesis of neurodegenerative disease, it is possible that localized UPS impairment

plays an important role, even if overall UPS function at other subcellular localizations remains intact¹⁴⁸.

Although the UPS is a popular target in cancer, where its activity is reduced by compounds such as bortezomib (Velcade, Millenium Pharmaceuticals)¹⁴⁹, upregulation of proteasomal degradation by a small molecule has only recently been reported¹⁵⁰. It will be interesting to follow the further development of such compounds and monitor their effects in models of HD and AD, as they are valuable tools for the further validation of the UPS as a therapeutic target.

Lysosomal proteases as therapeutic targets in AD and HD

In addition to the UPS, macroautophagy is an important pathway for the elimination of toxic or misfolded proteins. Protein degradation in the autophagic pathway takes place upon fusion of the autophagosome with lysosomes, and these vesicles are known sites of pathology in AD and HD (Figure 5). A β can be generated from APP in autophagic vesicles through cleavage by γ -secretase, and these vesicles accumulate in dystrophic neurites in AD patients and mouse models¹⁵¹. PSEN1 is not only an essential part of the γ -secretase complex in lysosomes, but also necessary to maintain an acidic pH in these vesicles, which in turn is required to guarantee the degradation of protein cargo¹⁵². PSEN1 mutations that are linked to FAD impair this function, leading to the accumulation of vesicles that contain A β ¹⁵².

Proteases of the cathepsin family finally break down cargo proteins after fusion of the autophagosome with the lysosome (Figure 5). The genetic deletion of an endogenous inhibitor of cathepsins, cystatin B, ameliorates the memory deficits and A β aggregate load in a mouse model of AD¹⁵³, which indicates that lysosomal proteases are able to clear disease-causing proteins in AD and that their upregulation should be beneficial (Suppl Table S4). In HD, it was proposed that the expression of mHtt impairs vesicular transport from the Golgi to the lysosomes and thus leads to a reduction in lysosomal cathepsins¹⁵⁴ (Figure 5), which would result in inefficient autophagy in HD. Cystatin B knockdown in models of HD and studies with cathepsin inhibitors in animal models for both AD and HD could help to further confirm and validate these therapeutic targets.

Targeting the PI3 kinase and beclin pathway

The Beclin1/PI3 kinase type III (PI3K) complex influences autophagy through the modulation of autophagosome formation, maturation and degradation¹⁵⁵ (Figure 5). In a mouse model of AD, loss of Beclin1 leads to the accumulation of A β plaques and lysosomes as well as neuronal loss¹⁵⁵. A reduction of levels of Beclin1 leads to the accumulation of mHtt and reduced the viability of animals in a mouse model of HD¹⁵⁶. The autophagic response initiated by the exposure of cultured cells to A β is mediated by PI3K¹⁵⁷, and a similar induction of autophagy through PI3K occurs in cell culture models of HD¹⁵⁸. On the other hand, blocking autophagy through the pharmacological inhibition of PI3K by 3-methyladenine increases the levels of mHtt and reduces viability¹⁵⁹.

Preservation or upregulation of the function of PI3K and Beclin1, which normally declines with aging¹⁵⁶, is therefore a promising strategy to increase the degradation of mHtt and A β (Suppl Table S4), although pharmacological agents to achieve this effect are currently not available. Beclin1 gene transfer has been used successfully to activate autophagy in a mouse model of Parkinson's disease, and similar strategies could be tested in models for AD and HD¹⁶⁰.

Targeting mTOR to modulate autophagy in AD and HD

mTOR, the mammalian target of rapamycin, negatively regulates autophagy through the phosphorylation of its target proteins ULK1 and Atg13¹⁶¹, which prevents the formation of autophagosomes¹⁶¹ (Figure 5). The mTOR inhibitors rapamycin (sirolimus) and its analogs everolimus and temsirolimus increase the autophagic clearance of mHtt and A β , which was associated with decreased toxicity in cellular models and rescue of different disease phenotypes in animal models of AD and HD^{162, 163} (Suppl Table S4). Everolimus (Afinitor, Novartis), temsirolimus (Torisel, Wyeth Pharmaceuticals) and sirolimus (Rapamune, Wyeth Pharmaceuticals) are FDA-approved drugs for the prevention of organ transplant rejection as well as for the treatment of different forms of cancer, and pre-clinical trials have been conducted for a number of autoimmune and infectious diseases (reviewed in¹⁶⁴). However, haematological side-effects are common and often lead to the termination of treatment¹⁶⁴, which makes the long-term use of these drugs for HD or AD unlikely.

An additional pathway for the induction of autophagy has been described, that is independent of mTOR and mediated through the inhibition of Inositol monophosphatase (IMPase) and the subsequent reduction in Inositol or inositol-3-phosphate (IP₃) levels¹⁶⁵. Therapeutically, this inhibition can be achieved through the treatment with lithium or valproate and is beneficial in *Drosophila* and Zebrafish models of HD¹⁶⁵ (Figure 5). Lithium has additional effects on neurotrophic factors and tau phosphorylation, and while an initial short-term trial in AD patients did not result in altered levels of phospho-Tau¹⁶⁶, a potential disease-modifying effect has been shown recently in a more long-term study⁵⁵. Another recently described pharmacophore is the so-called small molecule enhancers of rapamycin (SMER) series of compounds that induce neuronal autophagy independent of mTOR¹⁶⁷. SMERs induce autophagy in mammalian cells independently or downstream of mTOR and were protective in a *Drosophila* model for HD¹⁶⁸.

In summary, the autophagic pathway contains a number of well validated targets with TV scores of 3 or higher that are involved in the pathogenesis of AD and HD. While the inhibition of mTOR has been studied in great detail, the application of currently available compounds is hampered by severe side-effects. If no alternatives can be developed, other avenues such as the stabilization of Beclin1 could be pursued to increase the autophagic clearance of disease-causing proteins in AD and HD.

Moving towards clinical trials- the power of predictive testing

Clinical trials in AD have often been criticized for only including patients in late stages of the disease, where substantial neurodegeneration has already occurred, or for including patients that suffer from forms of dementia other than AD¹⁶⁹. The development of biomarkers to reliably diagnose AD in early disease stages and monitor disease progression has made significant progress, and CSF levels of total Tau, phosphorylated Tau and A β yield reasonable sensitivity (95%) and specificity (83%)¹⁷⁰. However, CSF studies still show considerable variability and the accurate identification of patients with early stage AD is difficult¹⁷¹.

The monogenic cause for HD, however, makes it possible to determine the effect of therapeutic interventions on the onset of symptoms in patients that do not yet show significant neuronal loss. A more homogeneous disease phenotype, clinical endpoints and longitudinal markers of disease progression that are currently being established allow for the assessment of disease-modifying effects of therapeutics in a timeframe of 1-2 years¹⁶ in HD. Effective compounds could then be prioritized for clinical trials in AD patients, whereas drugs that do not show effects in HD patients could be ranked lower in priority. However, the challenge for clinical trials in AD remains in the development of reliable biomarkers that

correlate with early stages of the disease. Currently, interventions are being tested in patients with mild cognitive impairment and their progression to clinically manifest AD is being monitored⁵⁵. Therapeutics that have been beneficial in clinical trials of patients with HD and for which early proof of concept for the modulation of pathways perturbed in both disorders has thus been shown, could similarly be assessed.

Despite the numerous common therapeutic targets identified for AD and HD, the question remains why the phenotype of AD and HD is largely different, with different brain areas affected, different sets of proteins misfolded and accumulated as well as a different clinical appearance. The most obvious explanation is the difference in underlying genetic mutations: HD is defined by the expression of mHtt protein, whereas AD is largely of unknown etiology or in rare cases caused by mutations in APP, PSEN1 or PSEN2. Differences in expression patterns as well as alterations in protein-protein interactions of these critical proteins could account for the susceptibility of distinct neuronal subpopulations, which are in turn correlated with the major clinical symptoms of chorea in HD or dementia in AD. While mHtt, APP, PSEN1 and PSEN2 are therapeutic targets in their own right, their dysfunction triggers similar pathogenic pathways that are shared between AD and HD and that comprise promising therapeutic targets. The modulation of these targets will likely be possible with the same therapeutic strategy for both diseases, and also similar side-effects from these interventions would be expected for both patient populations.

Overall, the convergence of pathways that are shared between AD and HD should encourage greater interaction between scientists working in each of these diseases as lessons from one may have significance for the other.

Supplementary Material

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Figure 1. Therapeutic targets in synaptic dysfunction pathway

NMDAR receptor signalling can be triggered by glutamate released from the presynaptic neuron or through the NMDAR agonist quinolinic acid (QA), a product of tryptophan metabolic pathways in microglia. While glutamate signalling through synaptic NMDARs promotes neuronal survival, QA leads to excessive NMDAR activation and synaptic dysfunction. The levels of QA generation can be altered through inhibition of kynurenine 3-monooxygenase, an enzyme in the tryptophan metabolic pathway. An imbalance in synaptic and extrasynaptic NMDARs is seen in both HD and AD. Htt and Tau are both involved in regulating the trafficking of NR2B to the extrasynaptic membrane. NR2B-containing NMDARs are hyperphosphorylated as mHtt and Tau increase recruitment of kinases to

NR2B-containing NMDARs. An increase in both the levels and phosphorylation of NR2B-containing NMDARs leads to an increased extrasynaptic NMDA current that triggers cell death through multiple pathways. Two major pathways leading to cell death in HD and AD are represented: 1) inhibition of CREB phosphorylation that inhibits pro-survival pathways and 2) increases in Ca^{2+} influx, leading to mitochondrial dysfunction. Therapeutic targets are highlighted in red; Drugs are highlighted in green.

Figure 2. Therapeutic targets in the neurotrophin pathway

BDNF and NGF levels are reduced in both HD and AD. Presynaptically, Htt, APP and Tau influence trafficking mechanisms via interaction with HAP1, kinesin and dynein/dynactin, influencing their binding to microtubules. Pro-BDNF and pro-NGF are processed by unknown proteases to generate mature BDNF and NGF. Furthermore, TrkA and TrkB receptor levels are decreased in AD and HD, respectively. Signalling through Trk receptors is reduced, thereby increasing Gsk3 β activity and enhancing cell death pathways. Increased p75NTR levels and signalling mediated by pro-BDNF and pro-NGF also triggers cell death. Therapeutics examined to date include: Epothilone D, BDNF, NGF, glucocorticoids and Lithium. Therapeutic targets are highlighted in red; Drugs are highlighted in green.

Figure 3. Therapeutic targets in the apoptotic pathway

The aberrant activation of caspase-6 that is seen in animal models and patients of both HD and AD could be mediated through multiple pathways: 1) Excitotoxicity, as described above, leads to an excessive influx of Ca^{2+} , which can depolarize mitochondria and lead to caspase activation. 2) Aberrant signalling through trophic receptors or death receptors as outlined can result a release of cytochrome c and Smac/Diablo from mitochondria, which activate caspase-9 and inhibit Bcl-2 as well as IAP proteins. These events lead to a subsequent activation of caspase-6 by both blocking of inhibitory pathways as well as direct activation through caspase-9. 3) Caspase-6 and -3 could furthermore be activated through the intrinsic pathway, since evidence for DNA and mitochondrial damage, ER stress and

protein misfolding as well as oxidative stress is found in AD and HD patients and animal models. Degradation of caspase-6 through the proteasome reduces its activity. Therapeutic targets are highlighted in red.

Figure 4. Therapeutic targets in the protein misfolding pathway

The disease proteins mHtt, Tau and A β undergo misfolding and aggregation, which is a multi-step process involving misfolded monomers, oligomers and large aggregate structures. Endogenous chaperone proteins of the Hsp family can inhibit aggregation and are likely able to interfere at different steps. Hsp's can be transcriptionally upregulated through Heat shock factor 1 (Hsf-1), which in turn is activated by compounds such as Celastrol or Geldanamycin that are known to reduce protein aggregation and toxicity in cell culture and *Drosophila* models of AD and HD. Chemical compounds that directly interfere with the aggregation cascade are often identified as inhibitors of aggregate formation, and with the exception of EGCG it is unknown for most compounds at which step they interfere. Therapeutic targets are highlighted in red; Drugs are highlighted in green.

Figure 5. Therapeutic targets in the autophagy pathway

Upregulation of autophagy is an efficient way to clear disease proteins in AD and HD, and therapeutic interventions have been tested against a variety of different targets. The balance between inhibition of autophagy by Akt and activation by AMPK has been shifted through treatment with resveratrol analogs, which increase AMPK activity. Inhibition of GSK3 β through Lithium prevents excessive Tau phosphorylation and allows pro-survival CREB signalling (see above), autophagy is increased through inhibition of the IMPase pathway. Inhibition of mTOR with rapamycin and analog compounds lifts the block on autophagosome formation and is beneficial in both AD and HD mouse models. An mTOR independent pathway activating autophagy can be triggered by treatment with Valproate and

is mediated a decrease in Inositol and IP₃ levels. The Beclin 1-PI3K type III complex promotes autophagosome formation and loss or inhibition of either protein is detrimental in mouse and cell culture models of AD and HD. Autophagosomes not only engulf aggregates of disease proteins present in the cytoplasm but are also capable of generating A β through γ -secretase cleavage. Upon fusion with the lysosome, the autophagosome becomes acidic and lysosomal proteases such as the cathepsins degrade the disease proteins. Deletion of the endogenous cathepsin inhibitor cystatin B is beneficial in an AD mouse model. Furthermore mHtt interferes with lysosome function by impairing vesicle transport from the Golgi, resulting in a decrease of proteases in the lysosome. PSEN1 deletion or mutations interfere with the acidification of the lysosome, thus reducing the activity of lysosomal proteases and rendering autophagic protein degradation less efficient.

Table 1
Similarities in pathogenic pathways for AD and HD

Pathway	Alteration	References
Synaptic dysfunction	Increased extrasynaptic NR2B-containing NMDARs	18, 19
	Increased phosphorylation of NMDARs	20, 22
	Affected neurons have defective LTP	25, 26
	Increased Ca ²⁺ influx	18
	Defects in mitochondrial trafficking	18
	Mitochondrial fragmentation & dysfunction	
	Alterations in microglial tryptophan metabolism, leading to increased release of neurotoxic metabolites	5, 14, 35
Neurotrophic factor related abnormalities	Reduced BDNF levels	39, 40
	Increasing BDNF & NGF levels is beneficial in disease models	51-54
	Increased p75 ^{NTR} levels and signalling	75, 172
	Decreased Trk receptor levels and signalling	75, 172
	Increased Gsk3 β activity	66, 173
	Altered ERK activity	174
	Reduced velocity and efficiency of axonal transport of BDNF	65, 66
Apoptotic pathways	Increased caspase-6 activity	89, 90
	Caspase-6 cleavage of disease proteins	89-92
	Preventing caspase cleavage of disease proteins is beneficial in mouse models	93, 94
Posttranslational modifications	Palmitoylation of disease proteins is linked to aggregate formation	118, 119
	Phosphorylation of disease proteins reduces their cleavage by caspases	105, 106
	HDAC inhibition is beneficial in disease models	69, 126, 127
Protein aggregation and clearance mechanisms	Misfolding and aggregation of disease proteins	128
	UPS impairment	144, 145
	Impaired autophagy	161
	Upregulation of autophagy is beneficial in disease models	153, 155, 156, 158, 162, 163, 165, 167, 168
	Increased expression of Beclin 1 is beneficial in disease models	

Table 2
Target validation (TV) scoring

TV score	Description
1.0	A gene that is conceivably linked to a disease-relevant biological mechanism
2.0	A gene that is associated with the disease and binds to a disease protein OR has an altered expression pattern in the disease OR has an altered cellular distribution in the disease
2.5	A gene that shows an altered pathway or functional activity in the disease
3.0	A gene that shows a causal relationship with the disease when manipulated genetically or pharmacologically in an in vitro or non-rodent lower organismal model of the disease
3.5	A gene that when genetically manipulated, modifies the disease phenotype in a rodent model of the disease or shows disease-like effects in a normal rodent, OR is identified as a genetic modifier of the disease phenotype in humans by a linkage/association study
4.0	A therapeutically relevant drug or genetic intervention, that is highly specific for this gene target, improves the disease phenotype in a rodent model of the disease
4.5	Manipulation of this gene target improves the disease phenotype in a larger, non-rodent mammalian model of the disease
5.0	A drug or gene therapy known to modulate this gene target demonstrates positive outcome in a Phase 2 clinical trial efficacy in a Phase 3 clinical trial
6.0	A drug or gene therapy known to modulate this gene target demonstrates efficacy in a Phase 3 clinical trial

Table 3
Comparison of TV scores for top targets in AD and HD

Target	TV score (AD)	TV score (HD)
NR2B	6.0	4.0
BDNF	4.5	4.0
NGF	4.5	4.0
HDACs	4.0	4.0
Kynurenine 3-Monooxygenase	4.0	4.0
HAP1	2.5	3.5
Caspase-6	3.5	3.5
Caspase-9	3.5	2.5
Bcl-2	3.5	3.5
GSK3 β	3.5	3.0
Hsps	3.5	3.5
Cystatin B	3.5	not characterized
Cathepsins	3.5	2.0
Beclin 1	3.5	3.0
mTOR	3.5	3.5
IAPs	2.0	3.0
HIP14	not characterized	3.0
misfolded proteins	3.0	3.0
PI3 kinase type III	2.0	3.0