The genetic causes of neurodegenerative diseases

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With the application of molecular genetics, we are now beginning to understand the etiology and the early stages of pathogenesis of the major neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Pick's disease and Progressive Supranuclear Palsy. Surprisingly, these studies are showing that these diseases share pathogenic mechanisms which involve tau or synuclein aggregation. In this article, I review the progress in the molecular genetic analysis of these major neurodegenerative diseases and discuss how they are related to each other.

1. Introduction

I started to work on Alzheimer's disease in 1979, largely by accident, in Newcastle, England. Newcastle was, at that time, and still, a center of Alzheimer's disease research. It was where Blessed, Tomlinson and Roth carried out their pioneering studies in the 60s describing their discovery that Alzheimer's disease was the major cause of 'senility'. I worked in the MRC Demyelinating Unit under James Edwardson's direction and with Robert and Elaine Perry. Henry Wisniewski had been Director there until 1977 and had, for a time, combined directing the MRC Unit with directing the Staten Island group. His energy and drive was legendary and the technical staff spoke of him with awe. Stories abounded of him spending long nights, after flying from New York, working on the electron microscope. His passion, at that time, was to characterize thoroughly, the neuritic plaque and to emphasize that this was not normal ageing and to eliminate the term 'senile' plaque. Wisniewski's work brought a rigor to a field which was, of necessity, purely de-

scriptive at that time. In 1979, there were only perhaps 10 groups working on Alzheimer's disease worldwide: Wisniewski's, Terry's in the US, Kidd, the Newcastle group and Bowen and Davison in England and Gottfries and Winblad in Sweden. The field was struggling to find acceptance as worthy of study since studying normal aging was thought to be a waste of time and resources.

That political fight was won, and we now understand much about the etiology and pathogenesis of Alzheimer's disease and other neurodegenerative disease: instead of descriptive work, we now understand these prevalent and distressing diseases as processes and are able to carry out deterministic experiments to try and understand the disease processes more thoroughly. Of greatest importance is that we are now on the verge of being able to treat these diseases because of our understanding of the mechanisms of the early stages of pathogenesis. This progress has come out about largely because of the success of the application of the techniques of molecular genetics. In this chapter, I summarize this progress.

The genetic lesions underlying many of the autosomal dominant forms of Alzheimer's disease, prion diseases and Parkinson's disease and frontal temporal dementia have been discovered (see Table 1 for a summary of the pathology of these disorders). Surprisingly, it has become evident that these diseases share pathogenic pathways.

2. Alzheimer's disease

Mutations in three genes have been shown to cause autosomal dominant Alzheimer's disease: the amyloid protein precursor gene (AβPP) [10], the presenilin 1 (PS1) gene [33] and the presenilin 2 (PS2) gene [24].

2.1. Mutations in the AβPP gene

The pathogenic mutations in the AβPP gene are shown in Fig. 1 (see http://www.alzforum.org/members/

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Table 1
The pathology of human neurodegenerative disease

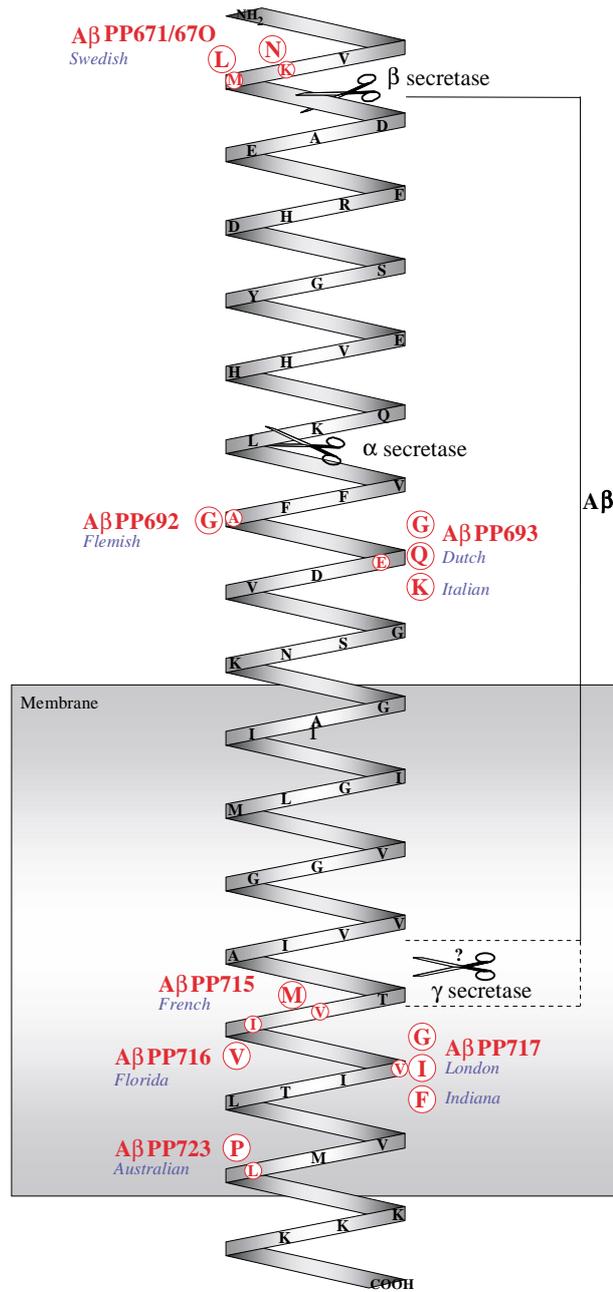|	
Alzheimer's disease	plaques (Aβ), tangles β4- and 3-repeat tau) and often, Lewy bodies (α-synuclein)
Prion disease	often PrP plaques; sometimes tangles (4- and 3-repeat tau); sometimes Lewy bodies
FTDP-17/Pick's disease	tangles (4- or both 4- and 3-repeat tau) or Pick bodies (3-repeat tau)
Parkinson's disease/Lewy body dementia	Lewy bodies
Progressive supranuclear palsy and corti-cobasal degeneration	tangles; mainly consisting of 4-repeat tau
Multiple system atuophy	oligodendroglial synuclein inclusions

Fig. 1. Amyloid β protein precursor. Pathogenic mutations in the AβPP gene in relation to the sites of cleavage of this molecule.
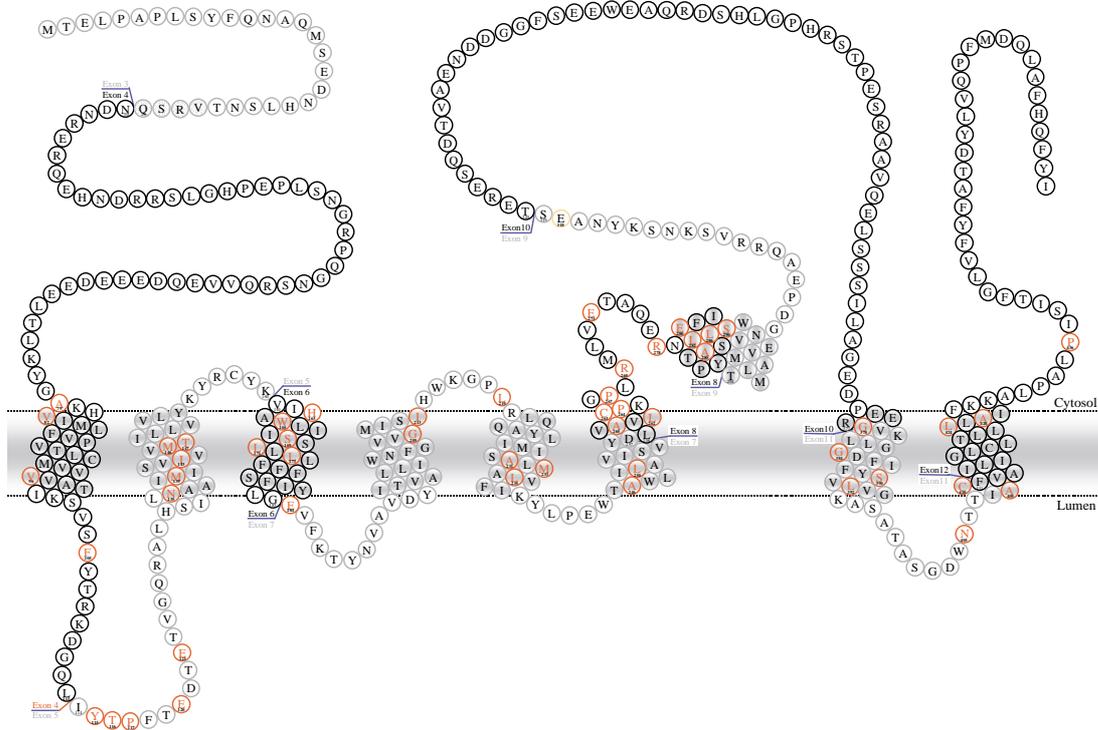
Fig. 2. Presenilin 1. Pathogenic missense mutations in the presenilin 1 protein (in red) drawn on the likely topographic representation of this molecule. Not shown are the deletion and insertion mutations.

resources/app_mutations/index.html for references). Of note is the fact that the mutations cluster around the sites of processing of the AβPP molecule and all the mutations have as an outcome that a more depositable fragment of Aβ is released [35]. Most cases with AβPP mutations have typical AD with an onset age in the late 40s to mid 50s, and with an onset age which is modulated by apolipoprotein E genotype [18]. The exceptions to this rule are E693G, the first mutation described in AβPP, which causes hereditary cerebral heamorrhage with amyloidosis-Dutch type, a disorder characterized by multiple strokes and deposition of Aβ only in blood vessels [23] and A692G [17] which is sometimes characterized by strokes and sometimes by a dementia phenotype [4].

2.2. Mutations in the PS1 gene

The pathogenic mutations in the PS1 gene are shown in Fig. 2 (see http://www.alzforum.org/members/re-sources/ps_mutations/index.html for references). Most PS1 mutations lead to typical Alzheimer's disease in a fully penetrant fashion with an onset age of 30–50: a few PS1 mutations are associated with an unusual variant of AD which is characterized by spastic paraparesis

and by the occurrence of massive congophilic angiopathy and 'cotton wool' rather than neuritic plaques [5]. The onset ages of PS1 encoded AD are typically not modulated by apolipoprotein E genotype. All the mutations tested to date alter AβPP processing such that more Aβ42 is produced [32]. Nearly all the mutations are missense mutations: the exceptions are the Δ9 mutation (an in-frame deletion of exon 9) [26] or mutations which lead to the insertion or deletion of single amino acids (see website). Thus, all mutations maintain the overall structure of the presenilin protein. The most parsimonious explanation of these genetic data is that the mutations do not lead to a simple loss of function of presenilin because this would effectively be caused by frameshift or chain termination mutations, neither of which have been found. It would seem most likely that the mutations lead to disease either by a gain of function or by a causing a complex (and greater than 50%) loss of function through, for example, a mechanism by which the mutant inactive protein displaces the active wildtype allele. In support of this latter notion are the observations that the mutant PS1 alleles fail to rescue the egl phenotype of the C elegans homologue of PS1, sel12: they are thus, loss of function alleles in this assay [22]: furthermore, a loss of function al-

Fig. 3. Presenilin 2. Pathogenic missense mutations in the presenilin 2 protein (in red) drawn on the likely topographic representation of this molecule.

lele of sel12 affects AβPP processing in the same way as pathogenic mutations [author's unpublished data]. Thus, it seems most likely that presenilin 1 mutations are loss of function mutations which lead to inactivation of the wildtype allele and lead to overall loss of function of between 50% and 99%. In agreement with this suggestion have been antisense experiments in which downregulation of presenilin 1 leads to an increase in Aβ42 production in the same way as the pathogenic mutations [30]. Complete inactivation of PS1 in mice in which the gene is knocked out leads to halting of AβPP processing at the γ-secretase point and to the build up of the C-terminal fragment of AβPP [6]. These and other data have led to the suggestion, now widely accepted, that the presenilins are γ-secretase [38].

2.3. Mutations in the PS2 gene

The pathogenic mutations in the PS2 gene are shown in Fig. 3 (see http://www.alzforum.org/members/resources/ps_mutations/index.html for references). Pathogenic PS2 mutations appear to have a very variable onset age, and in an individual family, the same mu-

tation can lead to disease onsets as disparate as ∼ 40 and ∼ 80. The reason for this variability is not clear, although apolipoprotein E genotype does not appear to be a major determinant. Only three pathogenic PS2 mutations have been found, although there plausibly could be many others yet to be found, in individuals who have not been sequenced because they appear as 'sporadic' cases, or because they constitute a tiny percentage of late onset cases. Complete inactivation of the PS2 gene in PS2 knockout mice does not appear to have a large effect on AβPP processing, suggesting that its role in AβPP processing can be substituted for by PS1 [34].

2.4. The effects of pathogenic mutations

All of the mutations in AβPP and in PS1 and PS2 which have been tested have been shown to affect AβPP processing such that more Aβ42 is produced [14]: these data are the intellectual underpinning of the amyloid cascade hypothesis (see Fig. 4).
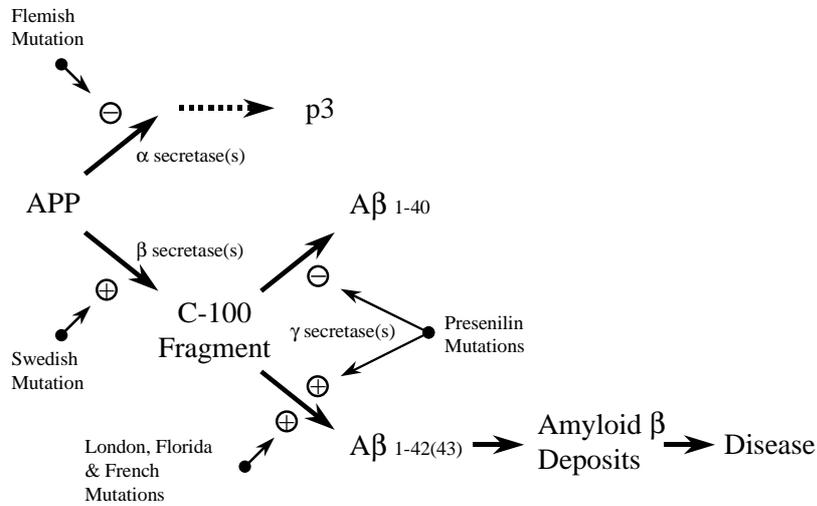
Fig. 4. The amyloid cascade hypothesis. Amyloid cascade hypothesis (adapted from [34]) showing the sites of the effects of the different pathogenic mutations shown in Figs 1–3.
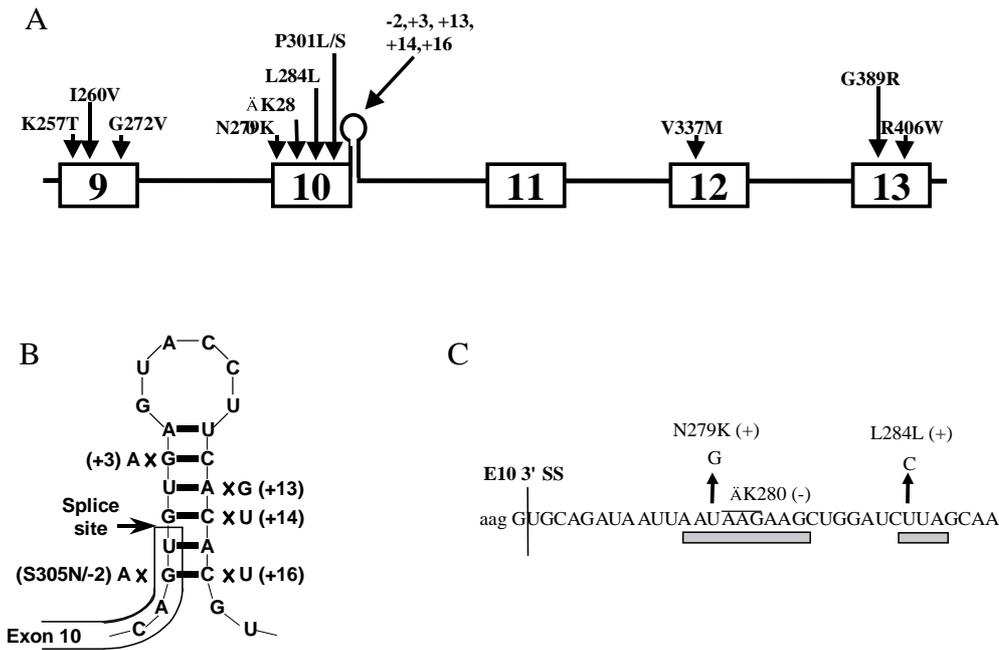
Fig. 5. Mutations in the tau gene, both in the open reading frame (A) and showing the positions which affect splicing alone at the stem loop structure (B) or affect both splicing and the open reading frame (C).

2.5. The occurrence of Lewy bodies in Alzheimer's disease

The occurrence of Lewy bodies in AD is well established [13]. Of particular note is the frequent occurrence of Lewy bodies in cases of AD with AβPP and PS mutations [21,25]. These data suggest that Lewy bodies, like tangles, can be a secondary consequence of Aβ42 production.

3. Tangles and Lewy bodies in prion diseases

The genetics of prion diseases is outside the scope of this review: (see [29] and http://www.mad-cow.org/).

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                              1
                41
Mouse α-synuclein  MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAGKTKEGVLYVG
Human α-synuclein  MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAGKTKEGVLYVG
Mutations                                          P
Human β-synuclein  MDVFMKGLSMAKEGVVAAAEKTKQGVTEAAEKTKEGVLYVG
Human γ-synuclein  MDVFKKGFSIAKEGVVGAVEKTKQGVTEAAEKTKEGVMYVG
Human synorectin   MDVFKKGFSIAKEGVVGAVEKTKQGVTEAAEKTKEGVMYVG


                42
                101
SKTKEGVVHGVTTVAETTKEQVTNVGGAVVTGVTAVAQKTVEGAGNIAAATGFVKKDQMG
SKTKEGVVHGVATVAEKTKEQVTNVGGAVVTGVTAVAQKTVEGAGSIAAATGFVKKDQLG
                 T
SKTREGVVQGVASVAEKTKEQASHLGGAVFSGAGNIAAATGLVKREEFPTDLKPEEVAQE
AKTKENVVQSVTSVAEKTKEQANAVSEAVVSSVNTVATKTVEEAENIAVTSGVVRKEDLR
AKTKEGVVQSVTSVAEKTKEQANAVSEAVVSSVNTVATKTVEEVENIAVTSGVVHKEALK


                102                  127    134   140
KGEEGYPQEGILEDMPVDPGSEAYEMPSEEGYQDYEPEA
KNEEGAPQEGILEDMPVDPDNEAYEMPSEEGYQDYEPEA

AAEEPLIEPLMEPEGESYEDPPQEEYQEYEPEA
PSAPQQEGVASKEKEEVAEEAQSGGD
QPVPSQEDEAAKAEEQVAEETKSGGD
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Fig. 6. Synuclein sequences and mutations. The sequences of the human synucleins and of mouse α-synuclein: note that the better characterized human mutations (A53T) changes the human sequence to the rodent sequence at that residue.

However, of note is that several families with prion mutations, most notably the Indiana kindred, have neurofibrillary tangles identical to those found in Alzheimer's disease [9]. In addition the Indiana kindred has Lewy bodies [B. Ghetti, personal Communication]. Thus, both tau and α-synuclein pathology can be downstream events to prion disease.

4. Frontal-temporal dementia

A large proportion of cases of frontal-temporal dementia are caused by mutations in the tau gene [19,28]. The pathogenic tau gene mutations are shown in Fig. 5 (see http://www.alzforum.org/members/research/tau/tau_references.html). The tau mutations so far described all either affect the ratios of 3-repeat to 4-repeat tau by affecting the alternate splicing of exon 10 [12] or they occur in microtubule binding domains where they would be predicted to affect the microtubule binding of the tau protein. These data indicate that tau pathology can be caused as a direct consequence of mutations in tau [11] and show that this tau pathology can lead directly to neuronal loss and dementia [15].

5. Progressive supranuclear palsy (PSP) and Corticobasal degeneration (CBD)

Extensive tau sequencing has revealed that there are two ancestral tau haplotypes in the caucasian population [1]. The H1 (70%) haplotype shows a robust association with the occurrence of both PSP and CBD: thus, the tau gene is a risk factor locus for both these diseases ([1,2], H. Houlden, personal communication).

6. Parkinson's disease and lewy body dementia

Two mutations in the synuclein gene have been described which cause familial Lewy body disease, A53T and A30P [20,27] (see Fig. 6): the former has been described in many families of Graeco-Italian ancestry: typically, the age of onset of parkinsonism in these families is 40–60 but it is very variable and can include a dementia phenotype. The latter mutation has been described only in a single small family with parkinsonism. The mutations both cause synuclein to aggregate in model systems [3]. There are at least two, and probably more, genetic loci which lead to Lewy body disease, one on chromosome 2p and one on chromosome 4p [7,8].
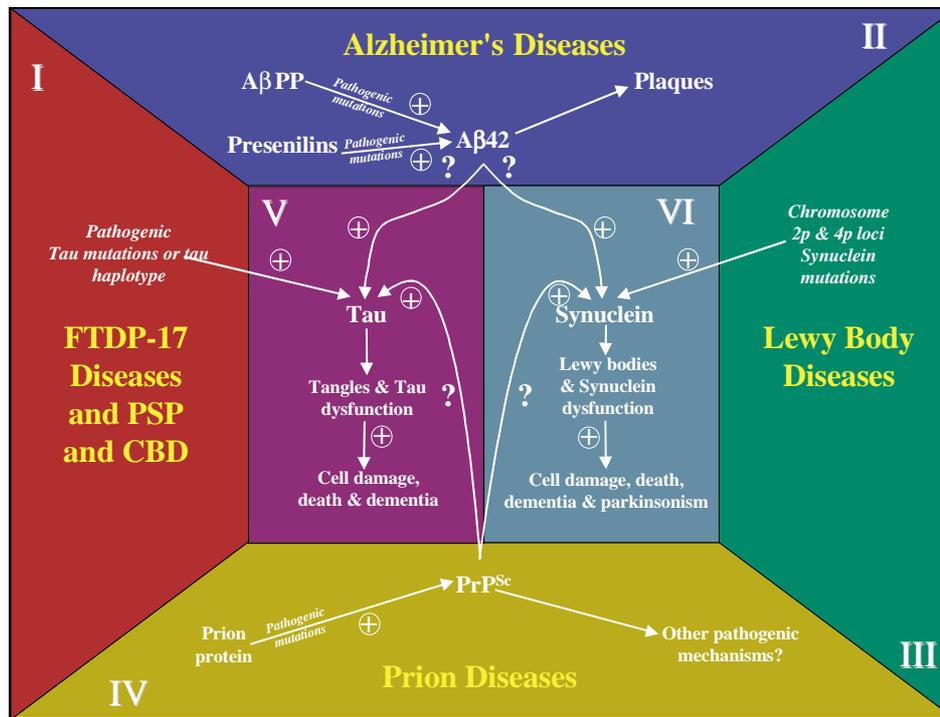
Fig. 7. Summary diagram linking all the tau and synucleinopathies is one broad framework of pathogenesis: note that (for example) this scheme is concordant both with the amyloid cascade hypothesis and with the notion that Alzheimer's disease is a tauopathy (adapted from [36]). Typical Alzheimer's disease is shown in boxes I, II and V: with Lewy bodies, VI etc. Worster Drought syndrome (British dementia) and Danish Dementia could also be fitted into this scheme as tauopathies [36,37] in the same way as prion diseases. It would be of interest in these disorders to look for Lewy bodies as they have not yet been described.

7. The pathogenic relationships between the different tau and synucleinopathies

A possible scheme illustrating plausible hierarchical relationships between the different pathologies is illustrated in Fig. 7. In this scheme, there are two broad pathways to cell death, one leading through tau and tangles and the other through synuclein and Lewy bodies. These pathways can either be triggered directly through mutations in their cognate genes, or either of them can be triggered (as alternatives to each other) by Aβ or by pathological prion protein [16]. Prediction of this hypothesis for Alzheimer's disease, which is an extension of the amyloid cascade hypothesis, are that reducing depositable Aβ should improve the clinical phenotype of Alzheimer's disease and that the amyloid and tau pathologies should interact. Both of these predictions are now being subject to test in transgenic animal models of disease ([31], M. Hutton and D. Morgan, personal communication).

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