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REVIEW

What can we learn from study of Alzheimer's disease in patients with Down syndrome for early-onset Alzheimer's disease in the general population?

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Abstract

The clinical and scientific study of dementia in adults with Down syndrome led to the development of the amyloid hypothesis as a fundamental concept in Alzheimer's disease pathogenesis. The journey started with the discovery of the structure and metabolic processing of β-amyloid brain deposits associated with Alzheimer's dementia in adults with Down syndrome, and then the prediction and confirmation of the amyloid precursor protein gene on chromosome 21. The processes and genes responsible for tau hyperphosphorylation contributing to toxic brain deposits were additionally identified. With increasing sophistication in genetic experimental techniques, additional mechanisms associated with excessive amyloid deposits were postulated and tested in brains of people with Down syndrome and Alzheimer's disease and in those with early-onset Alzheimer's disease. This in turn led to the proposal and testing for particular genetic defects associated with familial early-onset Alzheimer's disease. Nearly 200 genetic causes of early-onset types of Alzheimer's disease have since been identified. Only a minority of these causes are on chromosome 21, although the aetiology of excess amyloid production remains fundamental to their pathogenesis. Knowledge of the pathogenic mechanisms of Alzheimer's disease in predisposed families and in people with Down syndrome is a step closer to prevention or cure of this devastating disease.

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Introduction

Human thinking depends, ultimately, on the integrity of brain cell to brain cell communication. Any process that impairs this communication – whether it is congenital or acquired, static or degenerative, anatomic or metabolic – has devastating consequences for the health and well-being of that person. People with intellectual disabilities endure socioeconomic and health disparities as a consequence of their cognitive impairment [1]. Similarly, people with acquired cognitive impairments suffer losses in work and social status with economic and familial hardships. While the biopsychosocial barriers facing people with acquired and congenital cognitive impairments must be addressed by society, knowledge of how to prevent or cure cognitive impairment also plays a role in society's responsibility for their care.

Alzheimer's dementia is a neurodegenerative disease of the brain causing progressive cognitive impairment affecting three distinct population groups: most adults with Down syndrome aged >50 years; an early-onset group comprising people aged <60 years with specific genetic predispositions; and the largest, so-called late-onset group, a majority of the very older people. The onset of Alzheimer's dementia has profound implications for health, social and economic well-being of all the people in whom this disease develops. This applies equally for people with pre-existing intellectual disability as well as those starting with normal cognition [2,3]. Knowledge of the cause or causes of Alzheimer's disease contributes to understanding the processes of usual cognition and the cognitive changes, and potentially points research in the direction of disease prevention or cure.

In fundamental but as yet incomplete ways, studies of the cognitive skills, brains and genetics of people with Down syndrome have contributed to understanding processes not only of both normal and abnormal thinking, but also of cognitive changes and neuropathology in Alzheimer's disease development in the general

population. This is especially true for the study of this disease in the early-onset group. Moreover, studies on people with Down syndrome have provided the basis for hypotheses generation and testing of disease prevention or cure. Nevertheless, the story behind the aetiology of Alzheimer's disease is far from finished. The present review examines what is known about the causes of and processes believed to underlie Alzheimer's dementia in adults with Down syndrome, with a particular emphasis on how this research has helped in the understanding of early-onset Alzheimer's disease in the general population. As part of this process, discussions on the common clinical endpoint of brain neuropathology in Alzheimer's disease and on genotypic and phenotypic associations in Down syndrome are helpful.

Common clinical features of Alzheimer's disease

In all three at-risk groups, Alzheimer's disease is diagnosed by repeated clinical reviews over time. Patients have a history of development of multiple cognitive deficits, including memory impairment. In addition, they must have one or more of the following deficits: aphasia, apraxia, agnosia, or problems with executive functioning. The deficits must represent a significant decline in the person's previous level of functioning and interfere with social responsibilities and skills. Additionally, there is a progression of the symptoms over time. Other medical causes such as metabolic or endocrine causes, other intracerebral diseases, and mental illnesses should be considered, and have been excluded. Currently, there is no universally recommended biochemical test that confirms the diagnosis in day-to-day clinical practice.

An important limitation in scientific endeavour is the difficulty of clinical assessment of dementia in individuals with Down syndrome compared with the general population. Tests used to confirm dementia in the general population are not reliable or valid in populations with congenital intellectual disability. Cognitive assessment batteries and diagnostic criteria in populations with congenital intellectual disability are required to detect dementia in the early stages and to improve studies of risk factors [4]

Alzheimer's disease starts to affect most adults with Down syndrome at about the age of 50 years (for reviews see [5,6]). In the early-onset group, the dementia can start as early as in one's 40s [7]. Collectively, the early-onset general population group accounts for about 1% of all cases of Alzheimer's disease.

Common neuropathology in Alzheimer's disease

The three at-risk groups for Alzheimer disease also share common endpoint neuropathologic changes in the medial temporal lobe structures and cortical areas of the brain. The mechanisms leading to these changes,

however, appear to differ significantly between the groups. In other words, the cumulative brain lesions currently considered characteristic of Alzheimer's disease should be considered as endpoints, rather than as defining aetiology of the disease [8].

The endpoint lesions consist of neuritic plaques, extracellular deposits of fibrillar β-amyloid surrounded by degenerating neuronal processes and terminals, intraneural neurofibrillary tangles primarily composed of abnormally phosphorylated tau protein, vascular β-amyloidosis associated with fibrillar amyloid deposition within the vascular wall, inflammation, and oxidative damage. It is important to highlight that two processes, excess β-amyloid deposition and tau hyperphosphylation, contribute to these endpoint changes. These processes are toxic, presumably because they interfere with cell-to-cell communication via energy failure and with other possible mechanisms leading to neurotransmitter failure, synaptic and neuronal loss, deterioration of neuronal networks, and brain atrophy [9].

In populations of people with Down syndrome who develop dementia and in those with early-onset Alzheimer's dementia, the characteristic brain lesions are hypothesised to develop because of various mechanisms leading to the overproduction of toxic changes and deposits, whereas in the older groups with Alzheimer's disease there is predominance for failure of clearance mechanisms. Among the group of overproduction Alzheimer's diseases there are multiple contributory pathways to amyloid deposition and tau hyperphosphorylation, and similarly there are, in turn, many mechanisms for the failure to clear group. The paradigm of overproduction versus impaired clearance of particular amyloid peptides and tau hyperphosphorylation comprises the basis of the so-called amyloid hypothesis of Alzheimer's disease.

Early history of amyloid homology in Alzheimer's disease and Down syndrome

It was the study of Alzheimer's disease in individuals with Down syndrome that predominantly led to the development of the amyloid hypothesis. It is nevertheless difficult to define the single precise paper in which the idea that Alzheimer's disease in Down syndrome was first linked with amyloid and then later a familial early-onset type of dementia. Rather, it was probably a series of published observations, experiments, and discoveries enabled by increased molecular and genomic technologies that led to the discovery of this association.

Zigman and colleagues' historical review [5] cites a reference from 1876 [10] as the first account of presenile dementia in an individual with Down syndrome. Forty years later, in 1907, the first report of dementia (later renamed Alzheimer's disease) in a woman with probable

early-onset Alzheimer's disease was reported by Alzheimer [11]. Zigman and colleagues' review [5] also cites references as early as the 1920s, 1940s and 1970s [12-14] describing what later became known to be characteristic brain neuropathologic changes of Alzheimer disease among individuals with Down syndrome. Trisomy 21 was discovered in 1959 as the genetic cause of Down syndrome [15], and in 2000 the full genome was elucidated [16].

The study of Alzheimer's disease in individuals with Down syndrome really accelerated in the 1980s. Around this time, for a variety of social reasons, disability issues became prominent across a whole range of disciplines including science. People with intellectual disabilities were increasingly more visible as they moved from institutional to supported community group homes. With the general improvement in living and social conditions of people with intellectual disabilities, their life expectancy improved and suddenly their ageing issues were considerations for economists, disability advocates, and health professionals [17]. For example, by the late 1980s the lifespan of people with Down syndrome increased from 9 years at the middle of the last century to at least middle age and older [18,19]. Interest and research into Down syndrome increased, and was adequately funded and facilitated by the establishment of dedicated brain banks of deceased individuals with Down syndrome (for example see [5]) and the development of mouse models of trisomy 21 [20]. This turn of events coincided with a revolution in scientific genomic studies and technological skills.

In the early 1980s, the senile plaques in brains of people with dementia and in brains of people with Down syndrome were sequenced and identified as identical β-amyloid by Glenner and Wong [21] and by Masters and colleagues [22]. Assuming that the β-amyloid protein was a human gene product, Glenner and Wong postulated that the genetic defect of Alzheimer's disease was thus localised on chromosome 21 [21]. Interestingly, about 10 years earlier, the amyloid deposition noted in cerebral vessels in a patient with Down syndrome was assumed to be 'merely an incidental aspect of the disorder' [23].

In the late 1980s, using brain tissue from normal aged individuals, one with Alzheimer's disease and one with Down syndrome, Robakis and colleagues found that the β-amyloid identified by Glenner and Masters was cleaved post-translationally from a larger precursor, the so-called amyloid precursor protein (APP) [24,25] – a finding supported by Tanzi and colleagues [26] and Kang and colleagues [27]. In 1987, Kang and colleagues [27] and Goldgaber and colleagues [28] discovered that the APP protein from which the β-amyloid found in the plaques, tangles and blood vessel deposits in Alzheimer's disease and Down syndrome derived was a product of a gene

mapped to chromosome 21. The *APP* gene structure was identified formally in 1990 by Yoshikai and colleagues [29]. The *APP* gene was found to contain 19 exons and spanned more than 170 kb. The gene had several isoforms generated by alternative splicing of exons, and these encoded different β-amyloid proteins, each with differing pathological significance. In 1990 the *APP* gene was isolated to the long arm of chromosome 21 (see review by Price and colleagues [30]), as postulated by Glenner and Wong [21]. This position was refined by Jenkins and colleagues, who found that the *APP* gene is located within the region 21q11.2-q21.05 of chromosome 21 [31].

Individuals with Down syndrome due to trisomy 21 would therefore have three copies of the *APP* gene with a presumed increase of gene product, and hence an increased risk for toxic β-amyloid deposition. Later studies confirmed a 55% increase in the *APP* gene product [32]. Although the concept of a critical region on chromosome 21 has largely been discounted, it is interesting to note that the *APP* gene was later found to lie outside this region [33]. Normal individuals also have APP, but there is a maintained homeostasis of production and clearance of β-amyloid.

Gene dosage as a cause of early-onset Alzheimer's disease

Given the gene dosage theory of Alzheimer's disease in adults with Down syndrome, the earliest search for a cause for known cases of early-onset Alzheimer's disease therefore started with chromosome 21. Using genetic linkage techniques available in 1987, St George-Hyslop and colleagues found evidence that a genetic cause of a familial early-onset Alzheimer's disease gene was located on chromosome 21, but were disappointed later that year when, in another 40 familial cases, no duplication of chromosome 21 genes were found in familial or sporadic Alzheimer's disease [26].

Nearly 10 years later, however, mutant *APP* genes and isolated trisomy *APP* genes were confirmed and identified as a cause of early-onset Alzheimer's disease, although only in a small number of familial cases of direct trisomy *APP* [34].

There was an understandable appeal of simplicity for two earlier hypotheses that the phenotypic features of Down syndrome were due to a simple gene dosage effect (that is, 1.5 times normal) of genes and only of those genes within a certain so-called critical region on the long arm of chromosome 21. Both of these hypotheses appear to be incorrect based on information gleaned from mouse models of Down syndrome and also from later genomic and phenotypic correlations of individuals with Down syndrome. Some genes are produced 1.5 times more than usual, but others are reduced [20,35,36]. The phenotypic features in trisomy 21 Down syndrome

definitely vary in prevalence and expression. Although intellectual disability and neonatal hypotonia are present in close to 100% of individuals with Down syndrome, the expression of these features varies widely. The variability in phenotype is due to allelic heterogeneity for chromosome 21, epistatic interactions of chromosome 21 genes with genes on other chromosomes or chromosome 21, imprinting effects of gene expression associated with the parental origin of the third chromosome 21, and environmental effects including stochastic and other prenatal and postnatal events [33]. For those individuals with partial trisomy there are additional possibilities for phenotypic variability due to the partial aneuploidy interfering with the expression of genes nearby. Such apposition and the consequent potential change in the expression may generate phenotypic variability unrelated to the genes in the aneupleudy region. Many studies (for example [33,37]) now provide evidence against a critical region as any specific part of chromosome 21 being both necessary and sufficient for Down syndrome.

As far as Alzheimer's disease is concerned, however, the overexpression of APP from the extra normal *APP* gene in chromosome 21 is alleged to be a fundamental cause of Alzheimer's disease in adults with Down syndrome. This is consistent with knowledge of the metabolism and cleavage processes that occur in APP in Alzheimer disease pathology; the increased APP produced by the triplicate gene results in increased substrate for toxic amyloid deposits. The hypothesis for trisomy *APP* predisposing to Alzheimer's disease pathology in individuals with Down syndrome was further supported by a case report from Prasher and colleagues [38]. They reported the case of a 78-year-old woman with Down syndrome with partial trisomy without Alzheimer's disease on neuropsychological, magnetic resonance imaging, and neuropathic assessments. The gene sequence for *APP* was present only in two copies of chromosome 21. At autopsy, the neuronal density for tau was normal, there were no excessive amyloid plaques, and amyloid angiopathy was not found.

The role of secretases in increased β-amyloid deposition

The means of APP metabolism and pathogenic mechanisms of the products of APP are summarised in several reviews and are relevant when considering factors that lead to excess toxic deposits of the APP products. APP undergoes post-translational proteolytic processing by α-secretase, β-secretase or γ-secretase, which appear to confer differing toxicity to the β-amyloids produced [9,39,40]. Factors affecting these secretase activities impact on the type and amount of β-amyloid produced and are a potential cause for overproduction of toxic deposits. The α-secretase generates shorter-chain soluble

amyloid protein, amyloid β40, which until recently was thought possibly not as toxic. The other two secretases, β-secretase and subsequent γ-secretase, generate longer APP components, amyloid β42 and amyloid β43, with definite amyloidogenic (toxic) features. Both the longer and shorter types of β-amyloid are increased in the brains of people with Down syndrome, but the longer β-amyloid deposits seem more common in people with Down syndrome and dementia compared with those without dementia [41]. The gene locations for the β-secretase amyloid cleaving enzymes (BACE-1 and BACE-2) have been identified: BACE-1 is on chromosome 14 and BACE-2 is on chromosome 21 [42].

It was noted that that the vast majority of the familial early-onset Alzheimer disease mutations conferred a similar biochemical phenotype: an increased ratio of cerebral amyloid β ending at position 42 as opposed to position 40. Among early-onset Alzheimer's disease patients, this led to a search for mutations in the secretases, especially those which were responsible for the cleavage of longer β-amyloid proteins [43]. Proteases with proposed α-secretase function, one of which is mapped to a gene on the long arm of chromosome 21, has not been associated with Alzheimer's disease. In contrast, cleavage at the β-secretase site is mediated by BACE-1 from the *BACE-1* gene on chromosome 11q23, and a mutation of this gene has been implicated in familial early-onset Alzheimer's disease. The *BACE-2* gene is located on chromosome 21 [42], but no cases of familial early-onset Alzheimer's disease have been found with this mutation alone. There are at least five γ-secretase-related genes. Of these, mutations of the *PSEN1*, *PSEN2* and *NCSTN* genes appear to be implicated in the early-onset familial disease [43].

The location of the amyloid-β synthesis may also play a role in plaque burden. APP is known to be cleaved within the cytoplasmic tail by caspases [44], especially if the brain suffers from an ischaemic or acute excitotoxic event. Caspases play a dual role in the proteolytic processing of APP with the resulting propensity for amyloid-β peptide formation and apoptotic death of neurons in Alzheimer's disease. This feature may be speculated to be an added factor contributing to the severity of plaque burden in both Down syndrome and early-onset Alzheimer's dementia.

Other mechanisms may indirectly or directly impact on the various secretase expressions, which in turn alters the APP cleavage and toxic potential. Baek and colleagues demonstrated that IL-1β may impact on the presenilin-dependent (that is, γ-secretase-dependent) cleavage of APP in individuals with Alzheimer's disease [45]. Interestingly, increased IL-1 expression has been found in brains of individuals with Down syndrome and Alzheimer's disease [46]. IL-1, in addition to possibly

impacting on cleavage secretases of APP, also promotes gliosis, which itself contributes to impaired brain cell to brain cell communication. The gene encoding IL-1 is not on chromosome 21, however, and whether the increased IL-1 in Down syndrome and Alzheimer's disease is a cause of or an effect of neuronal damage is not known. Cathepesin B provides a major contribution to the β-secretase activity [47]; interestingly, this protein is elevated in Down syndrome cells [48].

Several groups have identified an aberrant form of ubiquitin B in addition to APP and in neurofibrillary tangles, neuritic plaques, and neuropil threads in the cerebral cortex of patients with Down syndrome and patients with Alzheimer's disease [49-51]. Ubiquitin B is encoded on chromosome 9 and has been implicated in familial forms of Alzheimer's disease. Ubiquitin B appears to contribute to tau hyperphosphorylation.

There is some evidence that accumulating mitochondrial DNA mutations in aging adults with Down syndrome and Alzheimer's dementia contribute to worsening dementia via the impact on increasing β-secretase activity and the accumulation of β-amyloid [52]. The impact of the genetic or acquired mitochondrial DNA mutations may be fundamentally more relevant for older-age sporadic Alzheimer's disease. Conceivably, however, such mutations could also influence the clinical performance of those individuals with early-onset Alzheimer's disease.

Tau in Down syndrome and Alzheimer's disease

A second necessary neuropathology of Alzheimer's disease involves pathology in the neuronal cytoskeleton (for a review see [39]). Tau is a normal axonal protein that binds to microtubules. Tau phosphorylation is regulated by the balance between multiple protein kinases and phosphatases, and in normal circumstances this process promotes assembly and stabilises micro-tubules. When tau is hyperphosphorylated, neurons exhibit fibrillary accumulations in the cytoplasm including neurofibrillary pathology in cell bodies and proximal dendrites. Ultrastructurally, fibrillary inclusions represent intracellular accumulations of straight filaments and paired helical filaments, both of which are composed of hyperphosphorylated isoforms of tau, a low-molecular-weight microtubule-associated protein. Because hyper-phosphorylated tau species bind poorly to microtubules and alter microtubular stability, their biochemical modification could affect cytoskeletal constituents, intracellular transport, cellular geometry, and/or neuronal viability. Oxidative damage and protein glycosylation involving cytoskeleton components may also play a role. Eventually neurofibrillary tangle-bearing cells die, by mechanisms that involve apoptotic pathways.

An interesting feature, not yet completely explained, is the presence of β-amyloid and diffuse nonfibrillar, amorphous plaques in young people with Down syndrome who do not have any evidence of dementia. It is only when these plaques undergo degeneration with the appearance of neurofibrillary tangles in older people with Down syndrome that the development of clinical dementia occurs. What triggers the neurodegeneration is still topical (for review see [5]). Tau hyperphosphorylation is known to be the mechanism for the development of the fibrillary tangles, however, and thus is a necessary contribution to the development of dementia. Some compelling evidence using Down syndrome mouse and human models suggests that individuals with Down syndrome produce an excess of certain protein kinases that directly and indirectly hyperphosphorylate tau [53,54]. The minibrain gene mutation dual-specificity tyrosine phosphorylation-regulated kinase 1A (*DYRK1A*), mapped to chromosome 21q22.2, may explain the change. Neurofibrillary tangles have been found to be immunoreactive with antibodies detecting *DYRK1A*. A higher prevalence of mini-kinase neurofibrillary tangles in the brains of people with Down syndrome and people with early-onset Alzheimer's disease suggest that the overexpression of the *DYRK1A* gene in trisomy 21 may be the factor modifying the onset and progression of neurofibrillary degeneration in Down syndrome [32,53,54].

Other factors affecting tau phosphorylation have been considered as potential contributory mechanisms for early-onset Alzheimer's disease in Down syndrome. Genetic variants of the ubiquitin 1 gene, *UBQLN1*, on chromosome 9q22 appear to increase the risk of Alzheimer's disease possible via its mechanism on *PSEN1* and *PSEN2*, but the gene is also considered a possible contributor to neurofibrillary degeneration, a process attributed to tau hyperphosphorylation. Aberrant forms of ubiquitin along with the β-amyloid proteins have been found in the brains of individuals with Down syndrome and Alzheimer's disease, but not in individuals with Down syndrome without Alzheimer's disease [50,51]. There is some suggestive evidence of a familial risk of Alzheimer's disease in individuals with *UBQLN1* variants, although this evidence was not strong for familial early-onset cases [49]. Interestingly, no general population familial early-onset forms associated with minibrain kinase abnormalities have been identified.

Other risk factors for Alzheimer's disease in Down syndrome and possible treatments

Increased age, oestrogen deficiency, reduced cerebral reserve, hypercholesterolaemia, and the presence of multiple medical problems are raised as potential risk factors for the development of Alzheimer's dementia in people with Down syndrome (see [5]). There have been no conclusive studies linking these risk factors to familial

early-onset Alzheimer's disease. The implication of apoprotein Eε allele status (on chromosome 19) appears primarily more relevant to older-age sporadic-onset Alzheimer's disease. Nevertheless, the apoprotein $E\varepsilon_2$ variant may be confer a delay in onset or severity of Alzheimer's disease in adults with Down syndrome [55].

The amyloid hypothesis and its appealing simplicity in the framework of overproduction versus reduced clearance, and the identification of some of the genes responsible for these processes, opens the door for genetic or downstream intervention to prevent the onset of the disease. However, no treatments used in adults with Down syndrome and dementia have yet been shown to prevent or ameliorate the onset of Alzheimer's disease. Only a minority of people with familial early-onset disease have *APP* gene mutations, but models of the processes involved in the discovery of treatments for Alzheimer's disease in people with Down syndrome, such as the amyloid hypothesis, will probably be of benefit in the search for treatments for people with familial early-onset Alzheimer's disease.

Conclusion

The study of Alzheimer's disease in individuals with Down syndrome has assisted in the understanding of early-onset Alzheimer's disease in many ways, but not enough to provide a basis for successful treatment or prevention of dementia. First, there was the recognition of the homology of the damaging amyloid protein in the brains of individuals with Down syndrome and Alzheimer's disease and of that in those with early-onset Alzheimer's disease. The protein was further shown to derive from cleavage from an APP. Then there was the postulation that the gene encoding APP was situated on chromosome 21, which was later proved. Although few adults with early-onset Alzheimer's disease necessarily had mutations or isolated trisomy of the *APP* gene, features and processes that somehow impaired the metabolism of APP and would result in its excessive production were sought and discovered. A second component of the Alzheimer disease neuropathology, the neurofibrillary tangles from tau hyperphosphorylation, has been hypothesised in adults with Down syndrome to be at least partly due to another gene on chromosome 21 – *DYRK1A*, a gene that encodes a protein kinase enzyme which promotes tau hyperphosphorylation.

As a result of these studies, the hypothesis that Alzheimer's disease was fundamentally due to an imbalance of production and clearance of toxic forms of amyloid and tau proteins was made. The simultaneous development of gene technology and using the amyloid hypothesis led to the discovery of many mutations in other genes causing early-onset Alzheimer's disease. For people with Down syndrome and Alzheimer's disease

and for those with early-onset Alzheimer's disease, a common problem is the overproduction of the toxic deposits. To date, the majority of genetic defects in familial early-onset Alzheimer's disease result in mechanisms leading to overproduction of the amyloid protein rather than mechanisms causing tau hyperphosphorylation. In addition to identification of a range of causal genetic defects, an astounding variety of mechanisms of actions causing overproduction and direct toxicity or downstream damage has now been identified.

Along the way, much has been learned about normal versus congenitally impaired cognitive processes and a vast array of neurodegenerative causes and processes. Generic processes underlying brain neurodegeneration and the roles of apoptotic pathways and factors that trigger such cascades, inflammation, and immunity have been important byproducts of this study and search for similarity. Identification of the mini-kinases has been particularly useful in the consideration of developmental intellectual disability. So far, however, the studies have not translated into significant preventive or curative clinical strategies, despite the proposal of seemingly plausible treatments. The story has not yet finished.

This article is part of a review series on *Early-Onset Dementia*. Other articles in the series can be found online at http://alzres.com/series/earlyonsetdementia

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Abbreviations
APP, amyloid precursor protein; BACE, β-secretase amyloid cleaving enzyme; IL, interleukin.

Competing interests
The authors declare that they have no competing interests.

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