



## Review Article

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## ABSTRACT

This review focuses on the role of A $\beta$  in AD pathogenesis in Down syndrome and current approaches for imaging A $\beta$  in vivo. We will describe how A $\beta$  deposits with age, the posttranslational modifications that can occur, and detection in biofluids. Three unique case studies describing partial trisomy 21 cases without APP triplication, and the occurrences of low level mosaic trisomy 21 in an early onset AD patient are presented. Brain imaging for A $\beta$  includes those by positron emission tomography and ligands (Pittsburgh Compound B, Florbetapir, and FDDNP) that bind A $\beta$  have been published and are summarized here. In combination, we have learned a great deal about A $\beta$  in DS in terms of characterizing age of onset of this pathology and it is exciting to note that there is a clinical trial in DS targeting A $\beta$  that may lead to clinical benefits.

## 1. Introduction

Improved medical care for people with Down syndrome (DS) has led to a significant extension in lifespan and improved quality of life [1–3]. However, as people with DS reach their 40's and 50's, they are vulnerable to the development of Alzheimer disease (AD). Increased frequency of AD in DS may be related to two key factors: (1) aging, which is a risk factor for AD in the general population and; (2) trisomy in genes associated with AD, particularly the APP gene.

AD was first described by Alois Alzheimer in 1901 (see [4] for an excellent review). We have since learned that a key protein engaged in AD pathogenesis is beta-amyloid (A $\beta$ ). One of the current working hypotheses is that A $\beta$  is a critical initiator of AD [5,6]. Although this original hypothesis has been revised over time, due in part to the outcomes of recent clinical trials in AD targeting A $\beta$  leading to little improvement in cognition [7], it is still considered a major contributor in the disease [8]. This review discusses the more recent developments regarding the role of A $\beta$  in DS both at a molecular level and through neuroimaging as several reviews on both of these topics have been published elsewhere [9–11].

## 2. APP and chromosome 21

A $\beta$  is produced from a longer amyloid precursor protein (APP) [12,13], which is present on chromosome 21 and thus triplicated in DS

[14,15] (Fig. 1). It is interesting to note that one of the first descriptions of the biochemical properties of A $\beta$  were from samples isolated from DS brain [16,17]. In the nonamyloidogenic processing pathway, APP is first cleaved by  $\alpha$ -secretase to form sAPP $\alpha$  and subsequently cleaved by  $\gamma$ -secretase to produce p3 and AICD (APP intracellular domain). This form of APP processing prevents the production of A $\beta$ . However, in the amyloidogenic pathway, APP is first cleaved first by  $\beta$ -secretase to produce sAPP $\beta$  followed by  $\gamma$ -secretase cleavage yielding A $\beta$  and AICD. The  $\beta$ -secretase enzyme has been identified as beta-site APP cleaving enzyme or BACE1 [18] and  $\gamma$ -secretase consists of a complex that includes presenilin 1, nicastrin, PEN 2 and APH-1 [19].

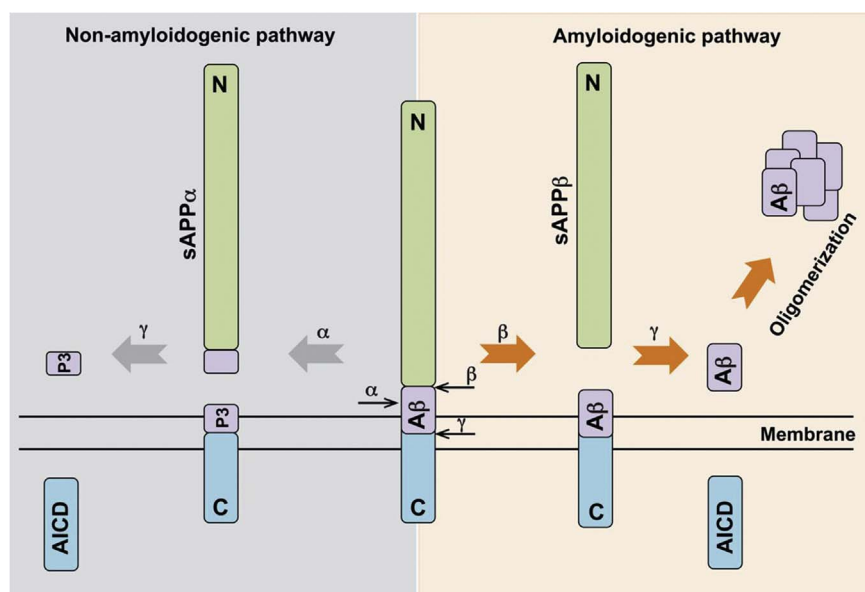
In DS, the levels of brain A $\beta$  are significantly higher when compared to controls at young ages [20] and A $\beta$  increases exponentially with age [21,22] after 40 years. Increasing age-dependent A $\beta$  in DS could be hypothesized as due to increasing APP production with age, increased  $\beta$ - or  $\gamma$ -secretase activity or reduced degradation (discussed later). In an autopsy study of 36 cases with DS,  $\alpha$ -secretase activity appears to be relatively stable except in cases over 40 years of age who show a decline [22]. In contrast, studies of  $\beta$ -secretase activity show an increase with age [22] or show modest increases in protein level [23]. Further, total APP levels do not appear to change with age despite being higher in DS overall, suggesting that APP overexpression may be the primary driver of A $\beta$  plaque accumulation [24,25].

A protein homologous to BACE 1, BACE2, can also cleave APP at the  $\beta$ -secretase site [26]. BACE-2 is also located on chromosome 21 and

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**Fig. 1. The proteolytic processing of APP.** APP can be cleaved by  $\alpha$ -,  $\beta$ - and  $\gamma$ -secretases; the cleavage sites of these proteases are indicated in the full-length APP shown in the center of the figure. APP can undergo amyloidogenic (right) or non-amyloidogenic (left) processing. In the amyloidogenic pathway, cleavage by  $\beta$ -secretase results in the formation of soluble APP $\beta$  (sAPP $\beta$ ) and  $\beta$ APP-CTF. The subsequent action of  $\gamma$ -secretase on  $\beta$ APP-CTF releases A $\beta$  from the amyloid precursor protein intracellular domain (AICD). In the non-amyloidogenic pathway, cleavage by  $\alpha$ -secretase prevents the formation of A $\beta$ ;  $\alpha$ -secretase cleaves within the A $\beta$  sequence, giving rise to sAPP $\alpha$  and the membrane-tethered  $\alpha$ APP-CT, which in turn is cleaved by  $\gamma$ -secretase resulting in release of the P3 peptide and AICD.

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may potentially contribute to increased A $\beta$  production in DS. In DS fetal tissue, BACE-2 RNA levels are significantly higher relative to controls [27]. In addition, in cultured fibroblasts from adults with DS, BACE-2 mRNA (i.e. protein expression) was 2.6 fold higher than normal controls. In 13 individuals with DS ranging in age from 27 weeks to 37 years, frontal cortex BACE-2 immunoreactivity was observed only in neurons of adults with DS and AD. BACE-2 immunoreactivity was not observed in younger individuals [28]. However, several studies comparing DS brain to similarly aged control brains do not find higher levels of BACE2 protein overall [24,29]. Similarly, no differences in DS as compared to controls was observed for BACE2 in the intracellular compartment [27]. It is therefore possible that despite increased RNA for BACE2 in DS, there may be posttranscriptional regulatory mechanisms that lead to normal levels of BACE 2 or that increase the degradation of this enzyme [25]. Thus, APP overexpression and production of A $\beta$  may be the primary driver of accumulation with age in DS [24,25].

### 3. Soluble A $\beta$ and oligomers in DS

Once A $\beta$  is cleaved from APP it appears in soluble forms that can be detected either within neurons or in the extracellular space. Higher levels of soluble A $\beta$  are observed in DS fetal tissue relative to tissue from controls [20]. A $\beta$  can assemble into oligomers, protofibrils and A $\beta$ -derived diffusible ligands (ADDLs) [30,31] (Fig. 2). Importantly, A $\beta$  oligomers cause neuronal dysfunction prior to overt neuron loss [32]. Both biochemical and immunohistochemical experiments reveal significant amounts of oligomeric A $\beta$  in the AD brain [33–35].

In DS frontal cortex, the amount of soluble A $\beta$ 40 and A $\beta$ 42 is higher in DS relative to controls [36,37]. Interestingly, phosphate buffered saline (PBS) extracted soluble A $\beta$ 40 in the frontal cortex increases in an exponential function with age in DS, particularly after age 40 years [21]. However, soluble A $\beta$ 42 declines with increasing age but with a parallel increase in insoluble A $\beta$ 42 suggesting sequestration into plaques [21]. PBS soluble A $\beta$ 40/42 was also not different between DS and control cases in a study by Miners et al. [23]. Water soluble A $\beta$  also appears to include modifications to N-terminal glutamates [38].

Oligomeric A $\beta$  also accumulates exponentially after the age of 40 years [21]. Further, increasing amounts of oligomeric A $\beta$  in DS frontal cortex is associated with lower synaptophysin protein levels, suggesting impaired synaptic function [39]. Soluble and insoluble A $\beta$  fibrils are also present in higher levels in aged DS cases with AD neuropathology compared to similarly aged control cases [40]. Thus, oligomeric A $\beta$  may

play a critical role in causing neuron dysfunction during both development and aging in DS. Indeed, a recent study in the Ts65Dn mouse using environmental enrichment, led to reduced hippocampal oligomers and improved cognition [41].

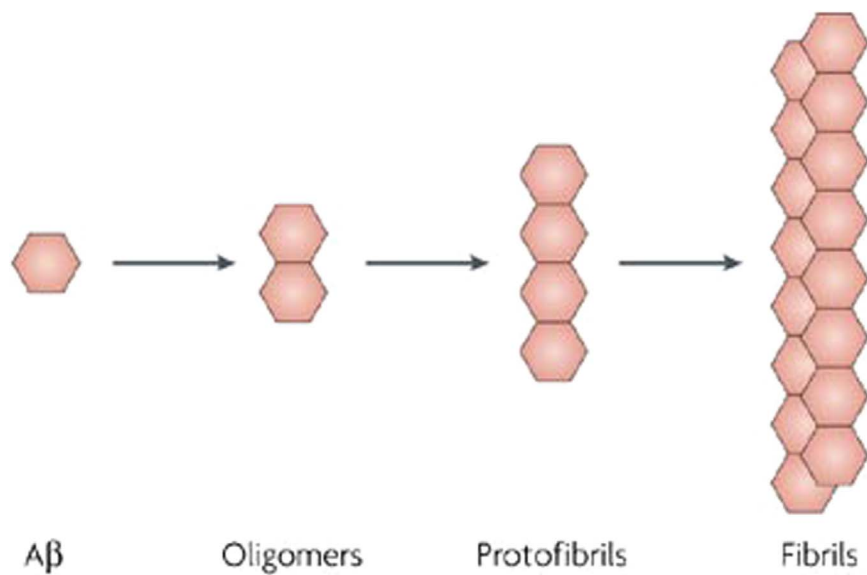
### 4. Intracellular A $\beta$ in DS

Although a large amount of A $\beta$  exists in a soluble form, insoluble deposits also begin to progressively form over time. However, the subcellular location for these events is less well understood [42], particularly in DS, which has been discussed in a previous review and is updated here [10]. Gyure et al. report intracellular A $\beta$ 1-40 but not A $\beta$ 1-42 [43]. In contrast, other studies report intracellular A $\beta$ 1-42 but not A $\beta$ 1-40 [44,45], which in one study was clearly distinguished from intracellular APP immunoreactivity [44]. A report by Hirayama et al. found neither A $\beta$ 1-40 nor A $\beta$ 1-42 but observed intracellular A $\beta$ 1-43 [46]. Each length of A $\beta$  has different properties. A $\beta$ 1-40 is more rapidly degraded within lysosomes than the longer, more toxic A $\beta$ 1-42/43 [47,48]. The reasons for observations of different length A $\beta$  species in intracellular deposits in each of these studies may therefore be due in part to technical differences.

A common observation in the majority of the studies of intracellular A $\beta$  in DS is the early age of onset; both infants and children with DS accumulate intracellular A $\beta$ . In addition, intracellular A $\beta$  is consistently observed prior to the accumulation of extracellular A $\beta$  deposits [44], which parallels reports in transgenic mouse models of AD [49,50]. These findings suggest that prior to extracellular A $\beta$  deposition there is an accumulation of intracellular A $\beta$  within neurons in DS at a much earlier age than in the general population. Thus, intracellular A $\beta$  accumulation may be important in the developmental course of DS and occurs prior to and contributes to age-associated extracellular A $\beta$  deposition. The accumulation of neuronal A $\beta$  may be associated with caspase cleavage products leading to increased apoptosis [51], which in turn may partially account for observed brain atrophy and neuronal loss. Intracellular A $\beta$  is localized to endosomes, intracellular organelles responsible for degrading and turning over proteins within cells [52,53]. Interestingly, partially reducing BACE1 in the Ts2 mouse model of DS leads to a reduction in endosomal abnormalities [54] typically observed in the DS brain [53].

### 5. A $\beta$ plaques

There is a well established literature that A $\beta$  accumulates within



**Fig. 2. Oligomer pathway.** Amyloid- (A) can exist in multiple assembly states—monomers, oligomers, protofibrils and fibrils—and it is the ability of this peptide to form fibrils and other intermediate states that impart the unique pathophysiological characteristics that define Alzheimer's disease pathology. Fibril formation is a complex, nucleation-dependent process. The mechanism driving this process, particularly in the elderly brain, is not yet known, but it appears to be closely related to protein misfolding. In its monomeric state, A does not appear to be neurotoxic. By contrast, oligomeric and protofibrillar species are considered potent blockers of long-term potentiation, a form of synaptic plasticity.

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plaques in DS in an age dependent process [10]. Cerebral A $\beta$  deposition occurs decades earlier in DS compared to AD and control brains [14]. The deposition of extracellular A $\beta$  in diffuse plaques is consistent after the age of 30 years [55], although widespread diffuse A $\beta$ 42 plaques have also been observed in brain sections from young DS individuals under 20 years of age [10,56–58]. However, it is important to note that the early A $\beta$  deposits reported by Lemere and colleagues were from individuals who were institutionalized [56] suggesting a possible environmental impact or severity of intellectual disability in DS on A $\beta$  accumulation. It is also apparent that diffuse plaques precede neuritic plaques with age in the cortex.

In DS, A $\beta$ 42 diffuse plaques precede fibrillar senile plaques containing dystrophic neurites and the formation of neurofibrillary tangles, and A $\beta$ 42 plaques are more prevalent than A $\beta$ 40 plaques at all ages [56,59]. Diffuse A $\beta$ 42 is also deposited in DS cerebellum and striatum in the third decade of life, but fibrillar plaques are rarely observed in these brain areas in the older DS brain [60], suggesting regional effects on plaque maturation. Overall, senile plaques progress in the same brain regions and cortical layers as in AD, however, plaque density is higher in DS brain [61].

Between the ages of 30 and 40 years, neuropathology accumulates until it reaches levels sufficient for a diagnosis of AD in DS by age 40 years [62]. In fact, there is an exponential rise in A $\beta$  plaques, and specifically insoluble (formic acid extracted) A $\beta$  measured biochemically after the age of 40 years [21,22], suggesting an acceleration phase to clinical and neuropathological disease development. Identifying factors engaged during this rapid AD pathogenesis phase in DS may provide novel targets for intervention. For example, the presence of an Apo E  $\epsilon$ 4 allele doubles the cerebral amyloid plaque burden and shortens life span in DS [63].

## 6. Post-translationally modified A $\beta$

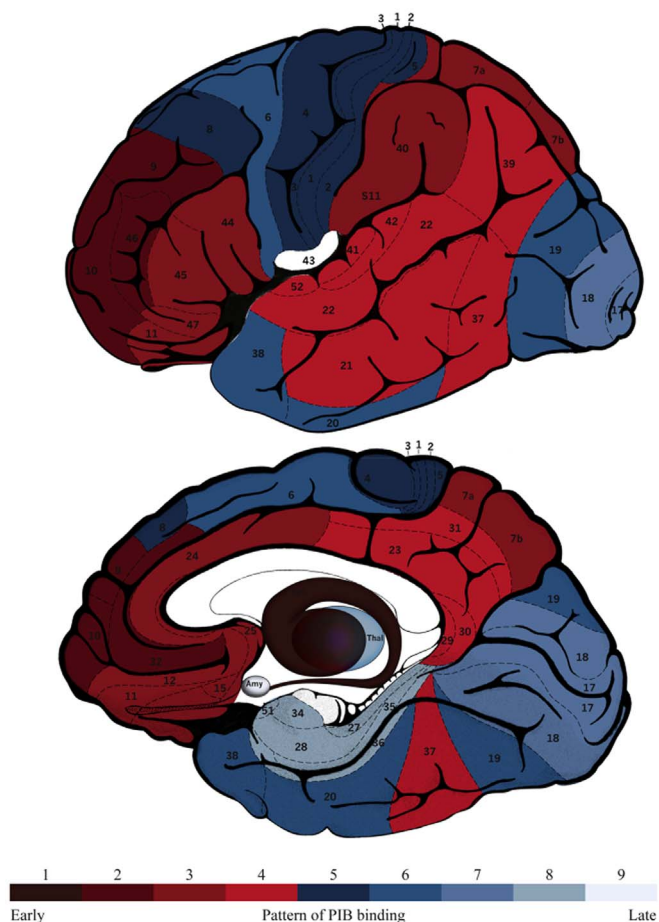
A characteristic of A $\beta$  is that there are several amino acids that are vulnerable to posttranslational modifications and identifying these species provides a measure of biologically “older” deposits (reviewed in [9,10]). With age, extracellular A $\beta$  with the N-terminus starting at Asp1 in DS is post-translationally modified by isomerization [64], racemization [65] and oxidation [66]. Oxidized A $\beta$  may reflect abnormalities

in redox homeostasis observed in DS [67] and also possibly suggests amelioration through upregulation of vitagenes [68]. An N-terminally truncated form of A $\beta$  is generated by degradation of the first 2 amino acids followed by cyclization of the newly formed N-terminus by glutaminyl cyclase, resulting in degradation-resistant, highly toxic aggregates of pyroglutamate-3 A $\beta$  that deposit into plaques and blood vessel walls in AD and DS brain [56,69–71]. Pyroglutamate-11 A $\beta$ , a minor species, is also detected in some plaque cores and vascular amyloid in DS brain [72,73]. Unmodified A $\beta$ 1-40/42 is also elevated in DS brain, possibly due to the overexpression of BACE 2, a gene encoded on chromosome 21 [73]. In addition, the APP P3 peptide, starting at the non-amyloidogenic  $\alpha$ -secretase site (A $\beta$ 17leu), can be observed readily in DS brain extracts [74] and cerebellar plaques [75]. These modifications may reflect mechanisms of A $\beta$  production and could potentially serve as possible chronobiological age markers for individual deposits and AD progression.

## 7. Cerebrovascular A $\beta$ pathology in DS

The contribution of cerebrovascular disease (CVD) to AD is increasingly being recognized as a critical comorbidity that accelerates the age of onset of dementia and also leads to a faster progression of the disease [76]. Further, estimates of a mixed etiology of AD that includes CVD range from 5.7% to 45% of autopsy cases from the general population [77]. CVD can serve as a “second hit” necessary for clinical signs of dementia, particularly when significant A $\beta$  is present in the brain [78]. DS represents a unique opportunity to study the cerebrovascular features of aging and AD in the context of limited systemic vascular risk factors (reviewed in [79]) including absence of atheroma and hypertension.

Cerebral amyloid angiopathy (CAA) is the deposition of amyloid in the walls of medium- and small-size leptomeningeal and cortical arteries, arterioles and, less frequently, capillaries and veins. CAA can lead to micro and macro hemorrhages [80]. CAA is consistently observed in older individuals with DS (> 55 yrs – [81–83] although study sizes include relatively small cohorts. CAA contains post-translationally modified A $\beta$  [71] as described in plaques. There are few reports of CAA in DS being associated with hemorrhages [83–87] in some but not all case reports [81,82]. Brain A $\beta$ 40 (typically associated with CAA) rises



**Fig. 3. PiB binding in DS.** A schematic brain map of numbered Brodmann areas and subcortical regions of interest colored according to the PiB staging model, where shade 1 denotes the area affected first (i.e. the striatum) and shade 9 the area affected latest (the amygdala). Abbreviations: thal, thalamus; amy, amygdala; PiB, Pittsburgh compound-B. Reproduced from Annus et al. (Creative Commons Attribution License (CC BY) [107].

exponentially with age in DS [21]. The functional consequences of CAA remains an area rich for further study as adults with DS represent a unique cohort to study the consequences of CVD co-morbidities in the absence of several cardiovascular risk factors. There are currently no systematic reports of CVD as a function of aging or cognition in DS. In terms of designing future clinical trials, characterizing the age of onset and extent of CVD in adults with DS will be critical given that CVD is mediated to large extent by lifestyle factors that are amenable to intervention such as individuals with hypertension, high cholesterol, obesity or type II diabetes (reviewed in: [88]).

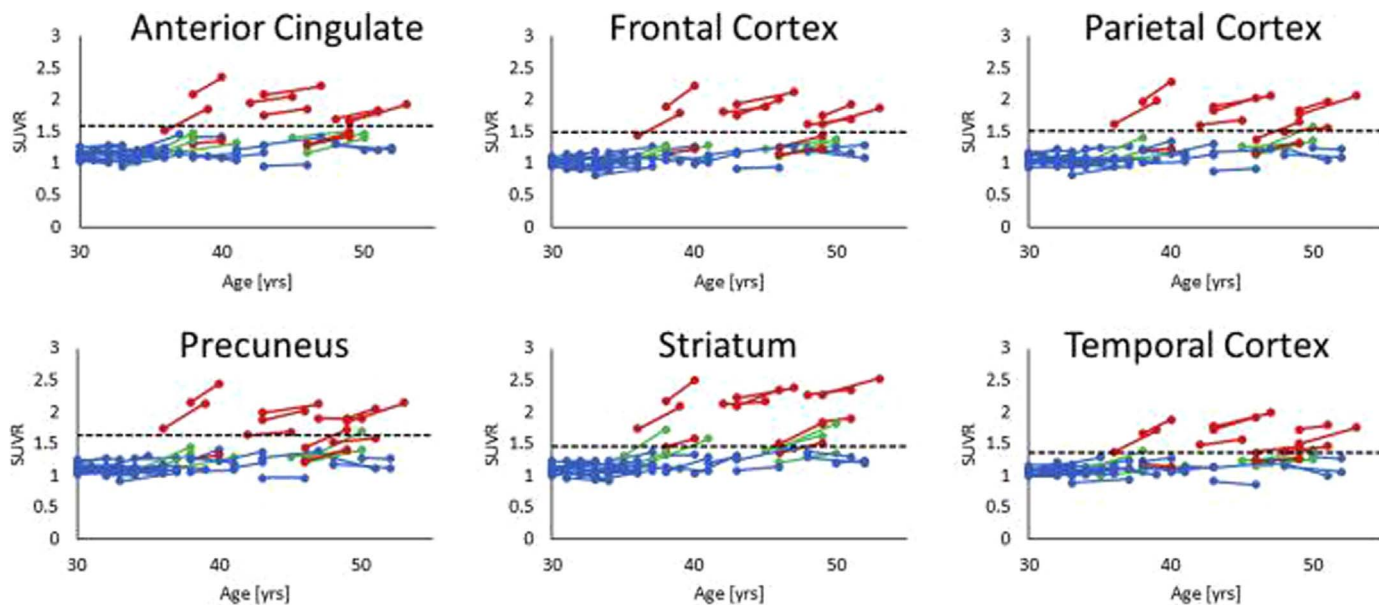
**8. Enzymes involved with Aβ degradation and clearance in the brain and DS**

Several enzymes in the brain are involved with the degradation and clearance of Aβ. These Aβ clearing enzymes include insulin degrading enzyme (IDE), neprilysin, and tissue plasminogen activator [89–91]. In DS, two components leading to increased production of Aβ are present in triplicate and include APP and BACE2. However, despite life-long overexpression of these two proteins, full blown AD neuropathology is not consistently observed until after age 40 years. Thus, Aβ may be cleared or degraded in the DS brain by the activity of these Aβ degrading enzymes.

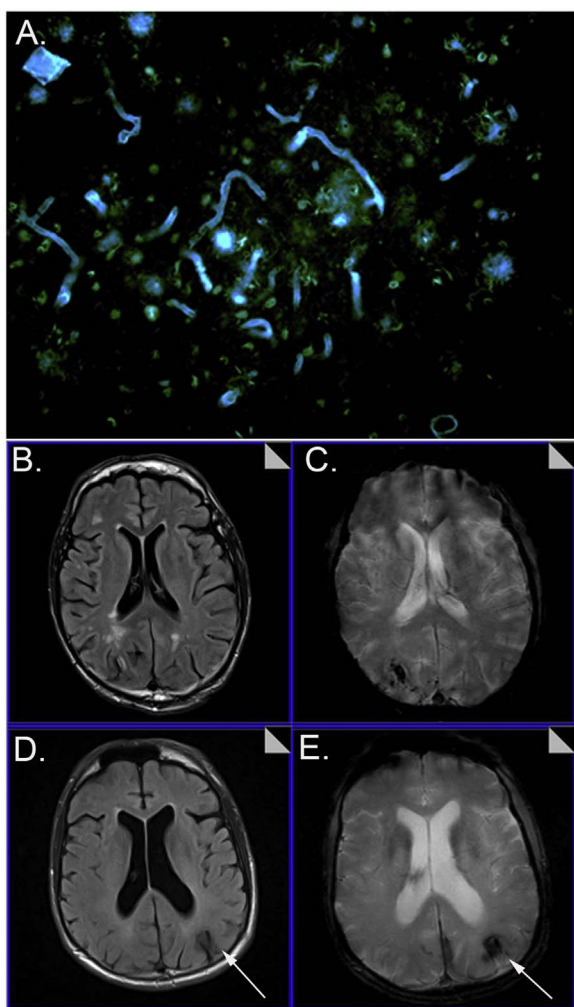
Neprilysin protein concentration is increased in DS and correlates with levels of insoluble Aβ [23]. Further, the overexpression of DRK1a in DS [92] reduces neprilysin activity in DS fibroblasts [93]. Normalization of reduced neprilysin protein levels in the Ts65Dn mouse model of DS by environmental enrichment is associated with improved cognition [41]. Considering the therapeutic potential of enhancing Aβ degradation and clearance, this represents a major gap in our knowledge in the study of development and aging in DS. Studies of age-dependent changes in IDE or tissue plasminogen activator were not found suggesting this is an area requiring further study in DS.

**9. Case studies supporting the role of APP and Aβ in AD pathogenesis in DS**

The most common cause of DS is trisomy 21 accounting for 95% of all individuals with DS. However, two other causes include partial



**Fig. 4. Longitudinal plots of mean PiB SUVR against age** with the PiB positivity thresholds in each ROI shown as the dotted line. Each line represents a nondemented adult with DS. The PiB(–) group (N = 35) is shown in blue, the PiB(0) group (N = 6) is shown in green, and the PiB(+) group (N = 11) is shown in red. Abbreviations: PiB, Pittsburgh compound B; ROI, region of interest; SUVR, standard uptake value ratio. Reproduced from Lao et al. (open access article CC BY-NC-ND) [119].



**Fig. 5.** PiB binding to CAA and vascular pathology in DS. (A) 6-CN-PiB (blue) binds to CAA and to plaques (green thioflavin S staining) in the brain of a 41 year old female with DS and AD. CVD in two DS volunteers in the University of Kentucky aging study, 57 and 59 year old males imaged with T2\* (B and D) and FLAIR (C and E) sequences showing that microbleeds are present in older people with DS and may be due to CAA (arrows distinguish edema and hemisiderin positive microbleeds (arrows)).

trisomy 21 (4% of people) and mosaicism (1% of people). There are few case studies of unique individuals with DS who are mosaic or have partial trisomy and thus, have varying degrees of APP overexpression. In 1998, Prasher and colleagues described a 78 year old female with DS who did not develop dementia and who did not show autopsy evidence of AD. Molecular mapping studies determined that this person was disomic for APP and SOD1 but trisomic for S100 $\beta$  [94]. Recently, Doran and colleagues describe a second partial trisomy case, a male who lived to 72 years of age without dementia [95]. This person was negative for Pittsburgh Compound B (PiB) amyloid imaging and at autopsy, showed little A $\beta$  (sporadic plaques) and a Braak stage III. Genetic mapping of this partial trisomy case indicated that APP was present in duplicate but S100 $\beta$  and SOD1 were triplicated. Thus, studies of people with partial trisomy 21 strongly suggest that the presence of APP is critically involved with the development of AD.

Another fascinating case report by Ringman and colleagues describes a 55 year old man with a mild intellectual delay but early onset dementia [96]. Standard karyotyping showed that he was 10% mosaic for chromosome 21. There have been three similar previous reports of people with mosaicism with varying degrees of a DS phenotype but all developed early onset dementia (41–52 years) [97–99]. Older people with DS also show evidence of an acquired low level mosaicism

suggesting a loss of chromosome 21, the functional consequences of this observation are as yet unknown [100]. Mosaic DS case studies suggest that even a small increase in genetic APP load and possibly A $\beta$  is sufficient to drive early onset dementia in DS.

## 10. A $\beta$ neuroimaging

There have been several reviews describing structural and functional neuroimaging outcomes in people with DS [11,101]. For this review, we will focus on A $\beta$  neuroimaging. *In vivo* ligands have been developed that selectively bind to A $\beta$  and can be used in conjunction with positron emission tomography (PET) to visualize A $\beta$  plaques in people antemortem [102–105]. Pittsburgh Compound B (PiB) [106], the first of these A $\beta$  ligands, has now been used in a large number of clinical studies in patients with AD and can detect A $\beta$  load early in the disease [103].

In DS, PiB PET imaging studies indicate that binding is age-dependent [107–111] (Fig. 3). In people with DS who are cognitively impaired, there is a positive correlation with the extent of PiB binding [107,110]. Interestingly, the striatum is the earliest site of PiB binding in DS, typically observed after 35 years of age [107–109]. This finding is similar to reports of patients with presenilin-1 mutations [112–114]. With age, more brain regions, primarily cortical, show *in vivo* A $\beta$  binding [107].

Similar results have been reported for other A $\beta$  ligands including Florbetapir [115–117] and 2-(1-[118]ethylidene) malonitrile ([18F]FDDNP) [118]. FDDNP also binds to tau and it is not possible to distinguish A $\beta$  plaques from neurofibrillary tangles. It is interesting to note, however, that florbetapir and FDDNP do not show early striatal binding as reported for PiB, suggesting that either the various ligands have different affinity for different types of A $\beta$  or that PiB binding may also indicate additional neuropathologies.

A recent report of 3 years of longitudinal study of PiB binding in nondemented people with DS showed that 85% of PiB negative subjects remained negative while 15% converted to being PiB positive [119]. Those who converted to being PiB positive tended to show a 3.7% increase in binding per year (Fig. 4).

## 11. PiB in DS – autopsy studies

*In vivo* imaging using PiB suggests that cortical binding is age dependent. In autopsy cases with sporadic AD, <sup>3</sup>H-PiB and 6-CN-PiB binding *in vitro* has been described [112,120–123]. In these studies, PiB binds to A $\beta$ 40 and A $\beta$ 42 positive plaques as well as vascular A $\beta$ . Further, PiB binding was more robust in compact or cored plaques and less so with diffuse plaques. PiB binding also correlates with insoluble A $\beta$  measures and with plaque loads. In one case that was PET imaged in life with PiB and then came to autopsy, there was a significant overlap in the regional distribution of the *in vivo* plaque binding and *in vitro* PiB binding [122].

A recent study described PiB binding *in vitro* in DS brain [124]. Biochemical measures of PiB binding *in vitro* using <sup>3</sup>H-PiB was significantly associated with increasing age. After age 40 years in DS, <sup>3</sup>H-PiB binding rose dramatically along with increasing individual variability. <sup>3</sup>H-PiB binding correlated with the amount of A $\beta$ 42. Frontal cortex neuritic and cored plaques in DS brain along with extensive cerebral amyloid angiopathy (CAA) were positive for 6-CN-PiB. Thus, cortical PiB binding *in vivo* as shown by PET imaging reflects plaques and CAA in DS brain (Fig. 5).

## 12. Summary

People with DS show age-dependent accumulations of A $\beta$  in plaques and in CAA similar to that observed in sporadic AD. However, the age of onset of A $\beta$  appears to be at least a decade if not more, earlier than that reported for the general population. The age-dependency of A $\beta$

accumulation provides unique opportunities for targeted clinical trials in people with DS to slow or prevent AD as prophylactic windows can be identified based on plasma, neuroimaging, and clinical markers of AD processes. However, there are still several gaps remaining in our understanding of A $\beta$  accumulation in DS including a lack of information regarding Braak amyloid staging and severity of dementia as well as the need to learn more about PiB binding in striatum (along with functional consequences). Autopsy studies in people with DS are challenging and the amount of tissue available for research from clinically characterized and prospectively followed people is very limited. New ligands that bind to tau pathology are currently being examined in DS cohorts and will provide novel and exciting information as to the staging of A $\beta$  vs tau with age and links to cognition.

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