Dementia in Down's syndrome

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Lancet Neurol 2016; 15: 622–36

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Down's syndrome is the most common genetic cause of learning difficulties, and individuals with this condition represent the largest group of people with dementia under the age of 50 years. Genetic drivers result in a high frequency of Alzheimer's pathology in these individuals, evident from neuroimaging, biomarker, and neuropathological findings, and a high incidence of cognitive decline and dementia. However, cognitive assessment is challenging, and diagnostic methods have not been fully validated for use in these patients; hence, early diagnosis remains difficult. Evidence regarding the benefits of cholinesterase inhibitors and other therapeutic options to treat or delay progressive cognitive decline or dementia is very scarce. Despite close similarities with late-onset Alzheimer's disease, individuals with Down's syndrome respond differently to treatment, and a targeted approach to drug development is thus necessary. Genetic and preclinical studies offer opportunities for treatment development, and potential therapies have been identified using these approaches.

Introduction

Down's syndrome affects 5·8 million people worldwide and is the most common genetic cause of learning difficulties.[1] The incidence of age-related cognitive decline and dementia is higher in individuals with the syndrome than in the general population, and progressive cognitive impairment develops at a far earlier age: the median age of dementia onset across all reported studies is below 60 years (table 1),[2–17] and Down's syndrome dementia is the most common form of dementia in individuals under the age of 50 years.[1] Dementia in Down's syndrome presents a major diagnostic and clinical management challenge because of the combination of learning disabilities, progressive cognitive and functional decline, and associated neuropsychiatric and behavioural symptoms. Incidence of Down's syndrome has decreased by 1% in the UK since the introduction of antenatal screening in the early 1990s, although an increase in birth rates of babies with Down's syndrome has been reported in the USA as a result of older maternal age.[18] With more people living beyond age 60 years,[19] dementia in Down's syndrome is likely to be an increasing challenge.

In the past decade, substantial progress has been made in the search for genetic risk factors for dementia in people with Down's syndrome, and in understanding the neuropathological similarities and differences between Down's syndrome dementia and Alzheimer's disease without Down's syndrome. In turn, this progress has led to opportunities in drug development, including the use of transcriptional analysis to identify treatment targets, and the emergence of potential new targets based on knowledge of neurogenesis pathways and genes such as *DYRK1A*.[20] Additionally, studies of new potential therapies are underway, such as the use of vitamin E to target oxidative stress (NCT01594346), and repurposing of existing therapies is a valuable opportunity for treatment development.

In this Review, we summarise published work on progressive dementia in people with Down's syndrome and explore potential avenues for future research. We first briefly describe the epidemiological and clinical characteristics of dementia in Down's syndrome, and then focus on the most recent developments in the neurobiology of dementia in this population, including imaging and pathophysiological changes and genetic risk factors. Additionally, we discuss existing treatment strategies and the most innovative and promising opportunities for drug development in the context of emerging knowledge from neuropathological and genetic research. A developmental approach that considers the effect on neuronal development, prodromal pathologies, and symptoms in young people with Down's syndrome is also an important area, although the focus of this Review is on the progressive cognitive impairment that is associated with Alzheimer's disease in people with Down's syndrome older than 40 years.

Epidemiology

Results from cross-sectional and longitudinal studies[2–17] show a wide range in prevalence, and substantial variability in the age of onset, of clinically significant cognitive impairment and dementia in people with Down's syndrome across all age groups (table 1). A clear age-related trend exists for emergence of impairment.[4–7,9–13,15–17] Results from eight studies[4,6,7,9,10,13,15,17] show rising prevalence from age 30 years onwards, an overall low rate of dementia in people younger than 40 years—despite lifelong intellectual impairment—and a rapid emergence of clinical symptoms from age 40 years onwards (table 1). Cognitive impairment is particularly marked in people aged 40–49 years, with a prevalence of up to 55% in this age group.[6,15] In studies examining older individuals, prevalence is even higher—up to 77% in people aged 60–69 years and 100% in people aged 70 years or older.[10]

Discrepancies between studies is likely to result from a combination of the difficulty in diagnosis, inadequate sensitivity in assessment criteria, and the use of different diagnostic methods in individual studies. Supporting the view that the diagnosis of dementia is challenging, several studies[4,6,7,9,10,13,15,17] have reported rapid progression in cognitive decline in people older than 40 years with Down's syndrome. A case series[19] reported an 11% decline in cognitive function on neuropsychological assessment

over 12 months in older people (mean age 44·5 years) with Down's syndrome, irrespective of whether they had a formal diagnosis of dementia. Results from a large randomised controlled trial (RCT)[1] in people with Down's syndrome also illustrate this complexity, with a 10% progressive annual cognitive decline in people randomised to a control group regardless of a diagnosis of clinical dementia. As a result, the measures of prevalence in published work should be interpreted with a degree of caution.

Clinical presentation and assessment

For people older than 40 years with Down's syndrome, dementia development follows a similar course to that seen in Alzheimer's disease,[6,8] with declines in recall and explicit memory[21] and in receptive language function[22] usually preceding dementia. However, when dementia emerges in younger individuals (aged 30–40 years), it often initially manifests as changes in behaviour and personality,[6,8] including onset of apathy, increasing impulsivity, and executive dysfunction.

	Participants	Study design	Assessment methods	Findings
Stancliffe et al (2012)[2]	1199 people with Down's syndrome in residential services across 25 states in the USA	Cross-sectional analysis of demographics, health status, and service use	Clinical information	Alzheimer's disease was frequently reported in people with Down's syndrome; 68% had cognitive impairment
Margallo-Lana et al (2007)[3]	92 people (63 men and 29 women) with Down's syndrome at Prudhoe Hospital, UK, in 1985; mean age 39·1 years	Longitudinal study with follow-up at 13 and 15 years after hospital admission	Prudhoe Cognitive Function Test, a 94-item schedule with five domains (orientation, recall, language, praxis, and calculation); and Adaptive Behaviour Scale Part I, an informant-based behavioural scale for people with learning disabilities to assess activities of daily living	18 (21%) of 87 participants who were dementia-free at recruitment developed cognitive impairment (median age of onset 55·5 years); 50% of people aged 60 years or older had dementia
Coppus et al (2006)[4]	506 people with Down's syndrome aged 45 years or older in the south and west Netherlands	Longitudinal study with annual follow-up for 3·3 years	ICD-10, medical history and medication review, and physical examination	Prevalence of dementia was 16·8% and roughly doubled with each 5-year increase up to age 60 years (≤49 years 8·9%, 50–54 years 17·7%, 55–59 years 32·1%, and ≥60 years 25·5%); mortality was 44·4% in people with Down's syndrome *vs* 10·7% in people without Down's syndrome
Tyrrell et al (2001)[5]	285 people with Down's syndrome, aged 35–74 years, recruited from service providers in Ireland	Cross-sectional	Modified DSM-IV criteria, Down's Syndrome Mental Status Examination, Test for Severe Impairment, and Daily Living Skills Questionnaire	Prevalence of dementia was 13·3% and was significantly higher in older age groups (30·4% in people aged 50 years or older and 41·7% in people aged 60 years or older)
Holland et al (2000)[6]	75 people with Down's syndrome, aged 30 years or older, recruited from an existing cohort	Longitudinal study with assessment at baseline and 18 months	CAMDEX and neuropsychological testing, scored against DSM-IV, ICD-10, and CAMDEX criteria	Prevalence of dementia was 38·2% at baseline; participants aged 40–49 years showed behavioural and personality changes; memory changes were more pronounced in older age groups (aged 50–59 years and 60 years or older); the largest increase in dementia was in participants aged 40–49 years
Holland et al (1998)[7]	75 people with Down's syndrome, aged 30 years or older, recruited from an existing cohort in the UK	Cross-sectional study in a population-based sample	Modified CAMDEX and neuropsychological testing, scored against DSM-IV, ICD-10, and CAMDEX criteria	Impairment increased from baseline by 3·4% in participants aged 30–39 years, 10·3% in those aged 40–49 years, and 40·0% in those aged 50–59 years
Oliver et al (1998)[8]	57 people with Down's syndrome aged 30 years or older	Prospective study with follow-up over 4 years (five visits over 50 months)	Neuropsychological test battery with domains in learning, memory, orientation, agnosia, apraxia, and aphasia	16 (28·3%) of 57 participants developed severe impairment over 4 years; severity was associated with increased age; impairment in language, memory, and orientation preceded agnosia, apraxia, and aphasia
Sekijima et al (1998)[9]	106 people with Down's syndrome aged 30 years or older in Japan	Cross-sectional	Clinical assessment	Prevalence was 0% in participants aged 30–39 years, 16% in those aged 40–49 years, and 38% in those aged 50 years or older
Visser et al (1997)[10]	307 people with Down's syndrome aged 40 years or older in institutions	Prospective study with follow-up at 5 and 10 years	Clinical assessment, EEG, cognitive function, and post-mortem analysis (where possible)	56 (18%) of 307 participants had progressive decline; mean age of dementia onset was 56 years; prevalence was 11% for the 40–49 age group, 77% for the 60–69 age group, and 100% for participants aged 70 years or older
Devenny et al (1996)[11]	90 people with Down's syndrome, aged 30 years or older, compared with people with other forms of learning difficulties	Cross-sectional	Modified versions of the IBR Evaluation of Mental Status, Selective Reminding Test, Visual Memory Test, and Wechsler Intelligence Scale for Children-Revised (block design, digit span, and coding domains)	Only minor differences in prevalence of dementia compared with groups with other forms of learning difficulties
Zigman et al (1996)[12]	People with Down's syndrome compared with people with other forms of learning difficulties	Cross-sectional	Adaptive behaviour as a measure of dementia	No significant difference in dementia prevalence in people below age 50 years; people with Down's syndrome older than 50 years were significantly more likely to develop dementia
Prasher (1995)[13]	201 people with Down's syndrome, aged 40–69 years, recruited across the West Midlands in the UK	Cross-sectional	ICD-10	Age-specific prevalence of dementia was 9·4% for participants aged 40–49 years, 36·1% for those aged 50–59 years, and 54·5% for those aged 60–69 years; dementia was associated with depression

(Table 1 continues on next page)

	Participants	Study design	Assessment methods	Findings
(Continued from previous page)				
Brugge et al (1994)[14]	People with Down's syndrome, aged 22–51 years, compared with age-matched controls	Cross-sectional	California Verbal Learning Test (short delayed savings section)	Some people with Down's syndrome had memory impairment, and some did not have memory impairment
Franceschi et al (1990)[15]	50 people with Down's syndrome living at home aged 30–52 years	Cross-sectional	Modified NINDS criteria	Prevalence of dementia was 0% in participants aged 20–29 years, 33% in those aged 30–39 years, and 55% in those aged 40–52 years; overall prevalence was 18%
Evenhuis (1990)[16]	17 people with Down's syndrome aged 49–66 (age of death)	Prospective, longitudinal study with data collected from medical notes between 1975 and 1987	Clinical observation	15 (88%) of 17 participants were diagnosed with dementia; in 14 participants without cerebrovascular or systemic vascular disease, dementia onset was early (mean age 51·3 years in people with moderate learning disabilities and 52·6 years in those with severe learning disabilities) and rapidly progressive
Lai et al (1989)[17]	96 people with Down's syndrome aged 35 years or older	Prospective, longitudinal study with one follow-up between 1980 and 1988	Functional decline in orientation, memory, verbal and motor skills, and self-care abilities	49 (51%) of 96 participants were diagnosed with dementia (mean age of onset 54·2 years); prevalence was 8% in participants aged 35–49 years, 55% in those aged 50–59 years, and 75% in those aged 60 years or older

ICD-10=International Classification of Diseases tenth revision. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders fourth edition. CAMDEX=Cambridge Examination for Mental Disorders of the Elderly. IBR=Institute of Basic Research. NINDS=US National Institute of Neurological Disorders and Stroke.

Table 1: **Published studies on the epidemiology of dementia in Down's syndrome**

Of note, some reports have described occurrence of non-Alzheimer's dementia in people with Down's syndrome, including multi-infarct dementia and dementia with Lewy bodies.[16] Age of dementia onset in Down's syndrome is clearly associated with other key medical conditions that are relevant to cognitive impairment, including hypothyroidism, depression, parkinsonism, EEG abnormalities, and late-onset epilepsy.[13,23] Attention deficit hyperactivity disorder is also frequent in people with Down's syndrome[24] and might affect the clinical presentation with early development of behavioural symptoms.

Clearly, diagnosis and assessment of dementia in people with Down's syndrome is challenging because of the cognitive deficits related to their learning disability, and no standardised assessment protocol with established validity exists at present. Studies so far have used a range of approaches, including the Cambridge Examination for Mental Disorders of the Elderly[25] and modified versions of verbal learning and memory scales, such as pattern recognition, spatial recognition, matching-to-sample tasks, delayed response, and conditional learning[21] (eg, with modified versions of the tests included in the Cambridge Neuropsychological Automated Test Battery).[26] The Down's Syndrome Attention, Memory, and Executive Function Scales (DAMES)[1] provides a method of combining different scales to reliably measure cognitive decline in people who are able to complete the assessments, and has been successfully used in clinical trials in Down's syndrome.[1] However, a substantial proportion of people are unable to complete the DAMES tests. Although this assessment provides a possible approach to measuring progressive cognitive decline, it does not provide a diagnosis per se. Tailored approaches to cognitive assessment have been developed and tested, and some have shown initial promise in validity.[27] These methods combine an informant-based approach with adapted sensory-reactive tests of learning and memory that are derived from animal models of ageing, which provide a biological rationale to underpin their use.

Although a consensus method for neuropsychological and clinical assessment is important, we believe that a fundamental shift is needed in the assessment of older people with Down's syndrome. Since the pathological changes of Alzheimer's disease and the development of progressive cognitive decline are inevitable, the exact point at which a clinical diagnosis of dementia is made is arbitrary and is generally unhelpful. For clinical care, the most important challenge is to assess changes in ongoing abilities and needs. For research, the key is to understand the relation between progressive cognitive decline and key aspects of disease biology, and to broaden treatment studies to focus on delaying decline rather than treating or preventing dementia.

Imaging and pathological changes

Imaging findings

Perhaps the most striking parallels between Alzheimer's disease and Alzheimer's disease in Down's syndrome are common neuropathologies, including the characteristic accumulation of amyloid-β (Aβ).[28] In MRI and PET studies of people with Down's syndrome, changes in hippocampal volume, glucose metabolism, and amyloid burden have been identified across a large age range. For example, in a study of individuals (aged 34–52 years) with Down's syndrome but not dementia,[29] reduced grey matter volume on structural MRI and a compensatory increase in cerebral glucose metabolism on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET imaging were reported. In another study,[30] people with Down's

syndrome dementia had increased amyloid load and reduced cerebral glucose metabolism on PET imaging, and reduced hippocampal volume on structural MRI compared with people with Down's syndrome who did not have dementia. Both studies[29,30] provide evidence of onset of neuroimaging changes before the onset of dementia. Therefore, MRI and PET imaging might enable early diagnosis of dementia and improve diagnostic accuracy (figure 1).[31,32] Neuropathological findings in people with Down's syndrome also support the imaging results, showing progression of brain changes that is similar to that in Alzheimer's disease, with involvement of the entorhinal cortex followed by the hippocampus and the parietal and prefrontal cortices.[33] Another similarity is the progressive hippocampal atrophy with enlargement of lateral ventricles and neuronal loss in the entorhinal cortex.[28,34]

However, subtle but important differences exist between Down's syndrome and late-onset Alzheimer's disease. Results from Pittsburgh compound B PET imaging show that the earliest site of Aβ accumulation in people with Down's syndrome, as in those with early-onset Alzheimer's disease, might be the striatum.[35] Initial findings from amyloid PET imaging with ^{18}F-FDDNP also suggest that compared with patients with late-onset Alzheimer's disease, people with Down's syndrome dementia have increased frontal predominance of amyloid pathology, which is consistent with clinical presentations of frontal-based symptoms.[36]

In the general population, the delay between amyloid deposition and the emergence of clinical symptoms is roughly 20 years, and a similar delay in people with Down's syndrome has been suggested.[7,37,38] In this context, according to the model developed by Jack and Holtzman[39] to illustrate the progression of Alzheimer's disease, a high proportion of people with Down's syndrome would be expected to have amyloid deposition at age 50 years but without clinically defined dementia.[35] On the basis of best available but scarce data, we propose a hypothetical model for Down's syndrome based on Jack and Holtzman's model for Alzheimer's disease (figure 2).[29,31,40–42] Systematic examination of large cohort studies will be important to refine our preliminary model.

CSF and blood biomarkers

Lumbar puncture is a challenging procedure in people with learning difficulties, but results from preliminary studies show that as people with Down's syndrome age, they have increased production of amyloid precursor protein (APP) and Aβ, and increased microglial activation.[43] Blood-based amyloid biomarkers have been more widely studied than CSF biomarkers, but are difficult to interpret in the context of the disease. However, evidence shows that the pattern of change in $A\beta_{42}$ and $A\beta_{40}$ might be predictive of conversion to dementia.[44] Concentrations of $A\beta_{40}$ and $A\beta_{42}$ are elevated in people with Down's syndrome, and those with dementia have

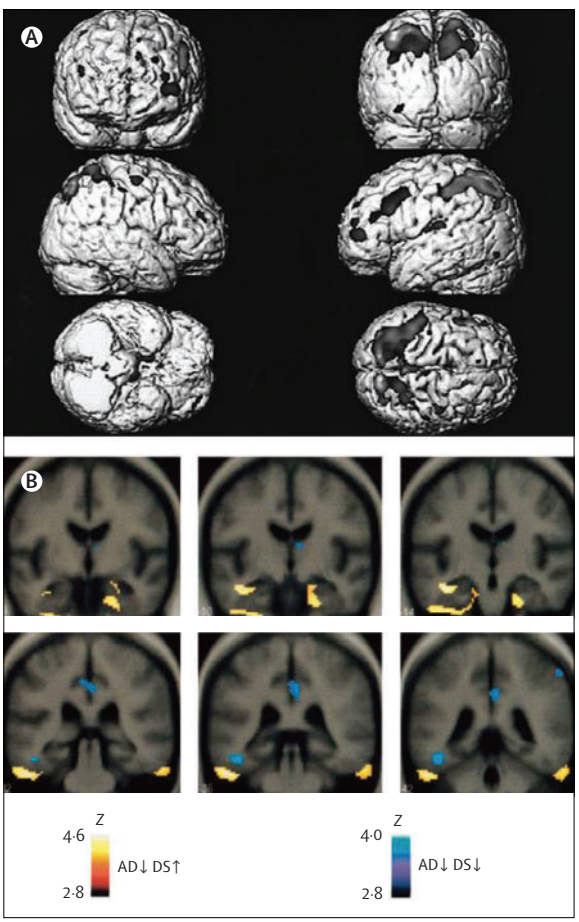

Figure 1: **Examples of MRI and ^{18}F-FDG PET findings in people with Down's syndrome**

(A) Voxel-based morphometric analysis of structural MRI scans with SPM99 in 27 adults with Down's syndrome but no dementia (15 women; mean age 4·1 years) showing age-related changes in people with Down's syndrome. The SPM(*t*) map is projected onto the normalised rendered brain surface from the MRI scan of an individual with Down's syndrome. Regional grey matter volume was decreased in the parietal cortex (bilaterally), frontal cortex with left-sided predominance, left occipital cortex, right precentral and left postcentral gyri, left transverse temporal gyrus, and right parahippocampal gyrus with increasing age. (B) SPM99 analysis of glucose metabolic rates obtained with ^{18}F-FDG PET imaging during a cognitive (attention) task in 17 people with Down's syndrome (11 men; age range 34–51 years; mean age 41·4 years [SD 5·6]) and 10 people with moderate Alzheimer's disease compared with two groups of 12 controls matched for age and sex to the patient groups.[32] None of the 17 people with Down's syndrome had dementia, as determined by the Dementia Scale for Down Syndrome and the Dementia Questionnaire for Mentally Retarded Persons. Conjunction analyses showed that compared with their control groups, people with Down's syndrome and those with Alzheimer's disease had lower glucose metabolic rates in the posterior cingulate cortex and left fusiform gyrus (blue areas), and that metabolic rates in the inferior temporal and entorhinal cortices (bilaterally) were higher for people with Down's syndrome and lower for people with Alzheimer's disease compared with their control groups (yellow areas). *Z* scores represent the magnitude of statistical differences for the conjunction analyses and are shown on six coronal MRI template slices that include a large section of the inferior temporal and entorhinal regions. Findings suggest that hypermetabolism in the inferior temporal and entorhinal cortices might represent a compensatory mechanism before onset of clinical dementia. FDG=fluorodeoxyglucose. SPM=statistical parametric mapping. Part A reproduced from Teipel and colleagues,[31] by permission of Oxford University Press. Part B reproduced from Haier and colleagues,[32] by permission of Wolter Kluwers Health.

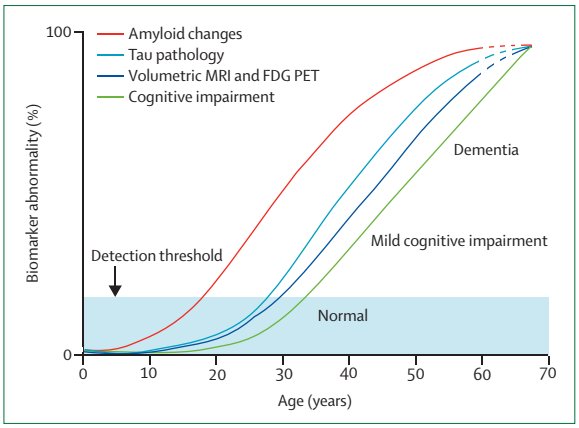

Figure 2: **Hypothetical model for development of dementia in people with Down's syndrome**
Hypothesised amyloid changes, tau pathology, and appearance of biomarkers on volumetric MRI and ^{18}F-fluorodeoxyglucose PET imaging based on published studies.[38–42] Ages are based on estimates from the few published studies. Of note, the median age of onset of Alzheimer's disease in the general population is older than 80 years.[39] FDG=fluorodeoxyglucose. Adapted from Jack and Holtzman,[39] by permission of Elsevier.

significantly higher plasma concentrations than those without dementia.[45] Furthermore, elevated levels of plasma $A\beta_{40}$ and $A\beta_{42}$ are predictive of incident dementia in the subsequent 5 years.[46] People with both Down's syndrome and dementia also show a modest but significantly increased $A\beta_{42}$:$A\beta_{40}$ ratio in the plasma (1·05 *vs* 0·98 in those with Down's syndrome but without dementia),[47] as is seen in patients with familial Alzheimer's disease. Moreover, as in Alzheimer's disease, $A\beta_{42}$ is the first species deposited in neuritic plaques, with $A\beta_{40}$ present essentially in only mature plaques.[48] Further work to explore emerging biomarkers (eg, clusterin) and to examine panels of markers might also be fruitful.[49]

Cellular changes

Intracellular accumulation of Aβ in Down's syndrome, as in Alzheimer's disease, precedes extracellular plaque accumulation.[50] The mechanistic implications of this finding are not yet clear but might be important when considering key potential treatment targets. Another hallmark of Alzheimer's disease pathology is the hyperphosphorylation of tau in neurofibrillary tangles. The density of neurofibrillary tangles triples from age 40 years to 50 years in people with Down's syndrome, mirroring the onset of dementia.[3] As in other forms of Alzheimer's disease, tangle formation correlates more closely with dementia than does amyloid deposition.[3] Additionally, smaller relative changes are seen in nuclear volume, and cell loss and atrophy are reduced compared with non-Down's syndrome Alzheimer's disease, which might suggest a differential CNS response of people with Down's syndrome to the accumulation of aggregated Aβ and tau.[3]

An interesting, but understudied, aspect of Alzheimer's disease neuropathology is dysregulation of the endocytic pathway; enlargement of early endosomes, defined by immunostaining for Rab5 and EEA1, is present before plaque and tangle formation in both Alzheimer's disease and Alzheimer's disease in Down's syndrome.[51,52] The accumulation of Aβ results from APP processing, so it is noteworthy that such processing occurs in endosomes[52] and, accordingly, $A\beta_{42}$ and the carboxy-terminal fragments of APP are present within endosomes.[53] Of the many possible effects of endocytic pathway dysfunction on pathogenesis, there is particular interest in the deficits in the retrograde transport of neurotrophin signals within endosomes, a finding for which the extent of *APP* gene activity leading to pathological change (ie, the *APP* dose), is both necessary and sufficient.[52]

Neurotransmitter changes

Results from post-mortem neurochemistry studies have showed a significant loss of choline acetyltransferase and noradrenaline in people with Down's syndrome, which is similar to the changes seen in Alzheimer's disease.[54] Results from in-vitro studies suggest additional cholinergic dysregulation in Down's syndrome mediated by choline acetyltransferase expression, which is controlled by the *DYRK1A* gene (see below).[55] However, the major focus for neurochemistry studies is GABA. At least two separate sets of factors affect GABAergic function in Down's syndrome. First, impairments in neurogenesis lead to reduced neuronal density, particularly in GABA-containing interneurons.[56] Second, results from microarray studies have shown alterations in $GABA_A$ receptor subtypes, with upregulation of the α2 subunit and downregulation of α3 and α5 subunits.[57] In post-mortem studies[58] and studies with the Ts65Dn transgenic mouse model of Down's syndrome,[59] an imbalance between excitatory and inhibitory systems has been reported, but the direction of this imbalance has not been consistent. Further work in mouse models suggests that increased inhibition in the hippocampus impairs long-term potentiation[60] and reduces synaptic plasticity,[61] but the picture in human beings is less clear. For example, imaging studies with magnetic resonance spectroscopy did not show any effect on hippocampal glutamate–glutamine concentrations or related cognitive deficit in people with Down's syndrome;[62] the potential role of glutamate as a treatment target is therefore unclear.

Concurrent pathologies

Concurrent pathologies that are seen in people with Alzheimer's disease are also present in individuals with Down's syndrome with similar frequencies, suggesting that although these pathologies might be important, they do not drive differential pathological progression in Down's syndrome. These pathologies include Lewy bodies—particularly in the amygdala—granulovacuolar degeneration, neuronal accumulation of ubiquitinated and aggregated transactive response TDP43, and cerebral amyloid angiopathy.[63–65] However, cerebral infarcts and

more extensive cerebrovascular dementia seem to be rare in Down's syndrome.

Genetic risk factors

The wide variation in age of dementia onset in individuals with Down's syndrome suggests that substantial differences exist between alleles of key genes for Alzheimer's disease on chromosome 21, or in other genes that regulate dementia risk, or both. Understanding these differences could be the key to the identification of new approaches to delay and treat Alzheimer's disease in people with Down's syndrome.

Trisomy of genes on chromosome 21

The triplication of chromosome 21 genes, some of which might be related to Alzheimer's disease risk, is thought to substantially increase risk of dementia in people with Down's syndrome, although the risk is modified by key genes on other chromosomes. Genes on chromosome 21 encode proteins with a broad range of functions, including APP processing, endosome secretion, synaptic function, neuroinflammation and the immune response, neurodevelopment and neurogenesis, oxidative stress, kinases and tau dysfunction, cellular signalling, proteases and protease inhibitors, ubiquitin–proteasome pathways, and RNA processing.[66,67]

APP processing is of particular importance, since individuals with partial trisomy of only small regions of chromosome 21 that include *APP* develop dementia.[68–70] A study of 30 people who were only partially trisomic for chromosome 21,[71] showed that the triplication of *APP* was pivotal for the accelerated development of Alzheimer's disease in Down's syndrome. Sequential cleavage of APP by the proteolytic enzymes γ-secretase and β-secretase results in the production and accumulation of Aβ.[35] An additional copy of *APP* leads not only to early-onset Alzheimer's disease but also to accompanying cerebral amyloid angiopathy.[71]

APP splice variants have a substantial effect on age of dementia onset. APP695 is predominantly expressed in neurons, whereas APP751 and APP770 are ubiquitously expressed. A kunitz protease inhibitor domain encoded by exon 7 is present in both APP751 and APP770, but not in APP695.[72] The ratio of *APP751:APP695* mRNA is increased in the brains of people with Alzheimer's disease,[72] and is related to the density of Aβ plaques in the hippocampus and entorhinal cortex.[73] Of note, mice expressing human APP751, but not APP695, develop Alzheimer's disease-like pathology, which resembles the pathology in Down's syndrome.[74] This pathology involves not only Aβ, but also abnormal tau isoforms. Sequencing of *APP* intron 7 has led to the identification of polymorphic sites that might regulate exon 7 splicing.[75] For example, the tetranucleotide repeat $ATTT_{5–8}$ an association between the number of $ATTT_6$ alleles and age of dementia onset in 105 people with Down's syndrome.[76] Individuals with three copies of $ATTT_6$ develop dementia on average 7 years younger than those with other combinations.[76] This finding was replicated in a study of 291 older individuals with Down's syndrome,[77] confirming a substantial effect of the intron 7 polymorphism on the age of dementia onset. These findings pertaining to APP, together with the results of studies of plasma concentrations of Aβ products of APP processing,[47,48,77,78] suggest that increased *APP* dose has a defining role for Alzheimer's disease in Down's syndrome.

Other genes on chromosome 21 also modify the expression and actions of APP, and affect the age of onset of Alzheimer's disease. For example, results from a mouse model study[79] suggest that, in addition to *APP* triplication, cognitive and pathological changes are also caused by increased expression of *ETS2*, which encodes a transcription factor that activates the *APP* promoter, and *SUMO3* and *DYRK1A* have a key role in the post-translational modification of APP.[80] MicroRNA-155 has also been reported to modulate γ-secretase activity.[81] β-secretase 1 (BACE1; also known as β-site APP-cleaving enzyme 1) is a key enzyme involved in the cleavage of APP into amyloid peptides. BACE2, located on chromosome 21, is a close homologue of BACE1 but has no confirmed activity in human beings with respect to APP cleavage. In a modified genome-wide association study,[82] a significant relation was identified between variants in *BACE2* and age of dementia onset in Down's syndrome, with the rs2252576-T allele being associated with an earlier onset by 2–4 years. However, other studies have not identified a significant relation between BACE2 and age of dementia onset.[83] In an in-vitro study, BACE2 was shown to cleave APP at a site that is distinct from γ-secretase and β-secretase cleavage sites within the Aβ domain, thus preventing Aβ generation.[84] Therefore, enhancing expression of BACE2 could be protective,[84] but in mouse models such overexpression had no effect on Aβ accumulation.[85] The potential relation between *BACE2* variants and the development of dementia remains to be determined.

DYRK1A is a serine-threonine protein kinase that targets calcineurin, NFAT, CREB, SYNJ1, dynamin, and GSK3B.[86,87] Crucially, DYRK1A is involved in tau phosphorylation, and its overexpression might contribute to early onset formation of neurofibrillary tangles. DYRK1A also phosphorylates APP, which results in amyloidogenic APP cleavage that elevates $Aβ_{40}$ and $Aβ_{42}$ accumulation, leading to brain β-amyloidosis;[88] therefore, DYRK1A potentially provides a link between amyloid and tau pathologies. Transgenic mice carrying a human construct including *DYRK1A* have neuronal loss and atrophy that are rescued by correcting the *DYRK1A* gene dosage.[89] Additionally, transgenic mice overexpressing *DYRK1A* have deficits in the Morris water maze (ie, spatial memory and learning) similar to those seen in Ts65Dn mice.[90] Results from a preliminary genetic polymorphism study[20] showed a significant association

between a *DYRK1A* polymorphism and age of dementia onset in people with Down's syndrome, confirming the clinical relevance of this gene. Although the Ts65Dn transgenic mouse model of Down's syndrome replicates the triplication of key genes, complexities in regulation of gene expression are not accounted for, and preclinical studies using this model should be interpreted carefully.

See Online for appendix

Other genes on chromosome 21 affect key processes that might also be important in the development of dementia. *SOD1* triplication leads to the accumulation of reactive oxygen species such as H_2O_2, a major cause of mitochondrial dysfunction.[91] Decreased mitochondrial function was seen in skeletal muscles of individuals with Down's syndrome in an exercise task.[92] The mechanisms are not fully elucidated and probably involve other genetic functions and activity of reactive oxygen species. For example, polymorphisms in the *TFAM* gene, which encodes a key activator of mitochondrial transcription, seem to increase dementia risk across a range of neurodegenerative diseases and decrease age of dementia onset in people with Down's syndrome.[93] Increased mutations in and altered repair of mitochondrial DNA have also been reported in the brains of patients with Alzheimer's disease and those with Down's syndrome dementia.[94] Importantly, results from a study in drosophila showed a link between mitochondria and neuronal dysfunction, mediated through retrograde mitochondrial signalling, that affects nuclear signalling.[95]

Many other potential disease mechanisms are related to genes on chromosome 21. Upregulation of *USP16* and *DYRK1A* alters neurogenesis and neuronal differentiation, and genes such as *SYNJ1*, *RCAN1*, *ITSN1*, and *DSCAM* have an important role in synaptic structure and function.[86,87,96] A gene-dose effect has also been established for *S100B*, which is expressed in astrocytes, and several potential mechanisms of action of S100B involving neuroinflammation and cytoarchitecture have been suggested, but the evidence is less clear.[97] Some evidence suggests that the lipid transporter ABCG1 regulates cholesterol efflux[98] and affects Aβ generation.[99] GIRK signalling, which has diverse effects, including those on the GABA and muscarinic receptor systems, has also been suggested as an important pathway in Down's syndrome.[100]

In a meta-analysis[101] of microarray studies using the SPIED platform focusing on the top 1000 upregulated and downregulated genes from autopsy brain tissue of people with Down's syndrome, 45 upregulated genes and six downregulated genes on chromosome 21 were identified (appendix).[101] Of note, several genes were identified that have not previously been a major research focus in Down's syndrome. The most highly upregulated genes were *ADAMTS1*, which encodes a metalloproteinase and is also altered in other neurodegenerative diseases, and *TTC3*, a rare susceptibility gene for Alzheimer's disease.[101] Microarray data have also confirmed upregulation of several other key genes, including *DYRK1A*, *S100B*, *USP16*, *BACE2*, and *ABCG1*. Of note, neither *APP* nor *SOD1* were in the top 1000 upregulated or downregulated genes.[101] However, the inconsistencies between microarray data and results from other experimental studies emphasise the importance of maintaining a broad approach to identification of key pathways.

	Correlation*	Gene number	*Z* score
Alzheimer's disease[102]	0·80	141	13·02
Huntington's disease[103]	0·83	137	13·64
Parkinson's disease[104]	0·62	177	9·59

*A representative set of transcriptional profiles of Alzheimer's disease, Huntington's disease, and Parkinson's disease, compared with transcriptional profiles of Down's syndrome.

Table 2: **Correlation between transcriptional profiles of Down's syndrome and other neurodegenerative diseases[101]**

Additional risk genes

The meta-analysis of microarray studies using the SPIED platform[101] confirmed the high degree of correlation between the gene expression profiles of Down's syndrome and Alzheimer's disease as expected, but also other neurodegenerative diseases such as Huntington's disease and Parkinson's disease (table 2), which might create additional research opportunities such as mitochondrial treatment targets, which are emerging from research into Parkinson's disease. Further analysis highlighted oxidative phosphorylation and WNT signalling as pathways of particular interest,[101] suggesting the importance of non-chromosome 21 genes that might contribute to the development of dementia in people with Down's syndrome.

The ε4 allele of the *APOE* gene, which is located on chromosome 19, is the most significant genetic risk factor for late-onset Alzheimer's disease, with carriers having a relative risk of 3–10 times that of non-carriers.[105] The *APOE* ε4 allele is known to be associated with increased amyloid burden and cholinergic dysfunction,[106] and is probably the most studied genetic risk factor in people with Down's syndrome, with most studies showing that presence of the *APOE* ε4 allele increases Alzheimer's disease risk.[107,108] Aβ deposition is also increased in *APOE* ε4 carriers with Down's syndrome.[109]

Tau exists as six splice isoforms depending on the inclusion of amino-terminal exons 2 and 3, and the exon 10 microtubule-binding domain.[110] Mutations in the gene encoding Tau (*MAPT*) can affect splicing and microtubule binding efficiency. The relation between the tau haplotype and late-onset Alzheimer's disease is unclear,[111] but tau haplotype seems to be more important as a dementia risk factor in people with Down's syndrome. In a study examining the potential effect of the tau haplotype in 172 people with Down's syndrome, H1/H2 heterozygotes were significantly more likely to develop dementia before age 45 years—3 years younger on average—than people with Down's syndrome with other genotypes.[112]

The relation between other candidate risk genes for Alzheimer's disease—including *TOMM40, PICALM,* and *SORL*—and the age of dementia onset was examined in a small modified genome-wide association study of 67 people with Down's syndrome (mean age 46·6 years).[113] *TOMM40* is located on a region of chromosome 19 that is in linkage disequilibrium with *APOE* and is associated with the age of onset in late-onset Alzheimer's disease (AlzGene odds ratio 0·6 for the rs8106922 G allele; allele frequency of 40% in controls and 30% in cases).[114] The median age of onset of dementia in people with Down's syndrome homozygous for the A (risk) allele was 5 years lower than in those homozygous for the G allele.

PICALM is present in endosomes that are enlarged in early Alzheimer's disease.[51] Results from genome-wide association studies have suggested that single-nucleotide polymorphisms (SNPs) in *PICALM* are a small but significant risk factor for late-onset Alzheimer's disease.[115] In the modified genome-wide association study in Down's syndrome,[113] an association between age of onset and variation in the *PICALM* region of chromosome 11 was confirmed. Three SNPS, rs2888903, rs7941541, and rs10751134, were associated with an earlier age of onset.

SORL1, a member of the VPS10 domain-containing receptor gene family, reduces the interaction between APP and β-secretase.[116] A study in 208 people with Down's syndrome,[117] 53 of whom had dementia, examined seven SNPs of *SORL1,* and a significant association was identified between two SNPs (rs536360 and rs556349) and dementia. Results from a subsequent study in 187 people with Down's syndrome[118] suggested a significant association between the *SORL1* SNP rs3824968 and the presence of Alzheimer's disease. This study[118] has more substantial caveats than the previous study,[117] since 43 SNPs were examined in 28 genes without correction for multiple testing, and the group with dementia was 17 years older than the one without. Nevertheless, the two studies together are important in highlighting the likely relevance of *SORL1* in the emergence of dementia in people with Down's syndrome. Evidence for the role of some non-chromosome 21 genes in risk for Alzheimer's disease is largely based on isolated genome-wide association studies or candidate gene studies, and the findings therefore need to be validated with replication in independent samples.

Treatment

Existing treatments for Alzheimer's disease

The UK National Institute for Health and Care Excellence recommends treatment with cholinesterase inhibitors and the NMDA receptor antagonist memantine for people with moderate to severe Alzheimer's disease and their use is also approved in the context of learning disability. The US guidelines for treatment of people with learning disabilities are more nuanced and recommend decisions based on individual patient assessments.[119,120] Although evidence from preclinical models suggests that targeting the glutamatergic system by blocking NMDA receptors might be a viable treatment approach in this patient group, the clinical evidence to support guidance on use of memantine is less encouraging. The large MEADOWS RCT in 173 people with Down's syndrome (>40 years; mean 51 years) with or without dementia[1] confirmed tolerability of memantine but reported no significant advantages over placebo in preventing cognitive decline. These results highlight the risk in assuming that effective therapies for people with Alzheimer's disease will also be beneficial in older people with Down's syndrome and emphasise the challenge of translating findings from preclinical models to patients.

Clear evidence shows cholinergic deficits in older people with Down's syndrome,[54] and other mechanisms might also augment the effect of cholinergic deficits, highlighting the potential of cholinesterase inhibitors as a candidate treatment. Among these inhibitors, donepezil has the strongest evidence—the results of a systematic review showed that it is reasonably well tolerated but has inconsistent benefits on any measures of cognition or function in people with Down's syndrome.[121] Differences in donepezil dose, cohort characteristics, and outcome measures complicate the interpretation of this conflicting evidence.[121] Few studies have been completed with the other cholinesterase inhibitors. Two case note audit series[122,123] provide anecdotal evidence of benefit with rivastigmine, and results from a study[124] of a transgenic mouse model of Down's syndrome support further investigation of galantamine, but no RCTs or other studies have been done. Although identification of other new therapies might seem exciting, cholinesterase inhibitors are a good candidate, and robust and adequately powered RCTs are urgently needed to clarify their role in treatment of dementia and cognitive dysfunction in individuals with Down's syndrome.

New treatments

Several new treatments have been proposed for dementia in Down's syndrome. In this section, we discuss potential candidate therapies emerging from genetic studies and neuropathological or neurochemical studies. Although APP, Aβ, and tau phosphorylation remain central to pathogenesis, several key elements, including the substantial increase in oxidative stress and reduced neurogenesis, might provide more specific treatment opportunities.

Anti-amyloid treatments

In view of the substantial overproduction of Aβ and the central importance of the genetic effects of *APP* in the genesis of dementia in people with Down's syndrome, the potential use of anti-amyloid therapies developed for the treatment of Alzheimer's disease is an interesting area for development. Concerns regarding vasculogenic oedema and the potential risks of haemorrhage

associated with amyloid angiopathy, which is prominent in people with Down's syndrome, have delayed development of immunotherapies in older people with this condition, although a pilot RCT of crenezumab is being planned.[125] In a mouse model of Down's syndrome, the γ-secretase inhibitor N-[N-(3,5-difluophenacetyl-L-alanyl)]-S-phenylglycine t-butyl ester (DAPT) lowered amyloid serum concentrations and conferred marginal improvements on the Morris water maze task,[126] although results from a further preclinical study[52] showed that γ-secretase inhibitors lead to marked and deleterious changes in BDNF trafficking and signalling, and might detrimentally affect endosomal pathology.

The development of specific therapies targeting the toxic effects of the *APOE* ε4 allele has been an increased focus in Alzheimer's disease research,[127] and given that the strongest evidence for the role of non-chromosome 21 genetic factors in dementia in people with Down's syndrome is for the *APOE* ε4 allele, such therapies might also have potential use for prevention or treatment of dementia in this patient group. The toxic effects of the *APOE* ε4 allele are diverse but might include an increased amyloid burden, and substantial evidence from genome-wide association studies and numerous candidate gene studies[112,113,117,118] suggests accelerated onset of dementia in people with Down's syndrome who carry the *APOE* ε4 allele. Of interest, some evidence suggests that cognitive benefits of exercise might be greater in individuals carrying the *APOE* ε4 allele,[128] but this finding has not been specifically examined in people with Down's syndrome.

Antioxidants

The triplication of *SOD1* in people with Down's syndrome—and the resultant upregulation in established mechanisms of neurotoxicity, including increased production of reactive oxygen species[91]—highlights the potential use of antioxidant treatment strategies in this patient group. High-dose vitamin E (alpha-tocopherol; 1000–2000 international units [IU] per day), an antioxidant and neuroprotectant, has shown some clinical trial evidence of benefit in Alzheimer's disease,[129] although potential safety concerns include coagulation-related issues. In Ts65Dn mice, vitamin E improved spatial working memory and reduced cholinergic neurodegeneration in the basal forebrain.[130] Results from a subsequent study[131] suggested that perinatal treatment improved subsequent performance on the Morris water maze task. Both studies also showed that vitamin E treatment reduced markers of oxidative stress in the brain. In a 24-month RCT of antioxidant supplementation including vitamin E (900 IU alpha-tocopherol, 200 mg ascorbic acid, and 600 mg alpha-lipoic acid) in 53 people with Down's syndrome,[132] mean plasma levels of alpha-tocopherol were increased by two times, but no benefits in cognition or function were seen. Although the results were disappointing, this trial was powered as a feasibility study only and does not discount the possibility of benefit. A multicentre RCT of vitamin E (NCT01594346) is underway to assess 36-month outcomes with a detailed neuropsychological battery in more than 300 people aged 50 years or older with Down's syndrome (table 3). However, antioxidant therapy might require a complex approach that involves reduction of reactive oxygen species generation or upregulation of the mitochondrial and intracellular antioxidant defence network, or both.

The evidence for the role of *SOD1* triplication in Down's syndrome[91] suggests that novel compounds developed for the treatment of amyotrophic lateral sclerosis, in which SOD1 is pathogenically implicated, might be beneficial in people with Down's syndrome dementia. Studies in *SOD1* transgenic mice have shown potential benefit of the antibiotic minocycline and COX2 inhibitors,[133] and new drugs such as arimoclomol and pyrimethamine are in clinical trials in patients with amyotrophic lateral sclerosis who carry *SOD1* mutations (NCT00047723 and NCT01083667). Minocycline has potentially valuable properties (eg, anti-inflammatory effects) and has been shown to enhance cognitive function and reduce cholinergic loss in Ts65Dn mice.[134] Other mediators of mitochondrial function, such as TFAM,[93] might also be potential treatment targets.

Tau phosphorylation inhibitors

The strong association between neurofibrillary tangle burden and the development of dementia in people with Down's syndrome,[3] the altered age of dementia onset in individuals with different tau haplotypes,[112] and the potential role of DYRK1A in mechanisms underlying dementia in this patient group[20] suggest that treatment strategies targeting tau, particularly tau phosphorylation and DYRK1A, might be useful.

Several studies in overexpression mouse models, including Ts65Dn mice, show that compounds acting on the DYRK1A pathway, such as epigallocatechin and harmine, improve synaptic plasticity and behavioural performance.[135] Epigallocatechin, an extract from green tea, is particularly interesting as it could be easily taken forward into a clinical trial because it is safe, inexpensive, and readily available. The potential value of epigallocatechin, in combination with environmental enrichment, has been shown in a study in Ts65Dn mice,[136] and findings from a pilot study[137] have also suggested that epigallocatechin significantly improves cognition in younger adults (aged 14–29 years) with Down's syndrome, further supporting epigallocatechin as a candidate therapy. Several other DYRK1A inhibitors, such as leucettine, have also been highlighted.[138]

Therapy to promote neurogenesis

On the basis of our increasing understanding of the biology of dementia in Down's syndrome and emerging knowledge from genetic factors that might affect age of

	Trial type	Intervention	Eligibility criteria	Primary outcomes	Secondary outcomes	Trial status	Sponsor
Nicotinic treatment of age-related cognitive decline in Down's syndrome (NCT01778946)	4-week open-label study (n=15)	Nicotine patch, 14 mg for people with mild cognitive impairment and 7 mg for those without	People with Down's syndrome aged 25 years or older, with or without cognitive impairment	Safety	Cognitive function and performance (memory, learning, and attention); specific measures not described	Ongoing	Vanderbilt University, Nashville, TN, USA
Multicentre trial of vitamin E in ageing people with Down's syndrome (NCT01594346)	36-month randomised, double-blind, placebo-controlled phase 3 trial (n=349)	Alpha-tocopherol (vitamin E), 1000 international units twice per day	People with Down's syndrome aged 50 years or older	Brief Praxis Test	Safety, other cognitive outcomes, and global clinical outcome	Completed, but results not yet published	New York State Institute for Basic Research, Staten Island, NY, USA
Lithium carbonate in Down's Syndrome (DownsLit; EudraCT number 2008-008342-20)	8-week randomised, single-blind, placebo-controlled phase 2 trial (n=34)	Lithium carbonate, 250 mg daily	People with Down's syndrome aged 18 years or older	Brain myo-inositol concentration on MRS	Effect on other MRS and blood biomarkers	Completed; results being analysed	King's College London, London, UK
Prevention of cognitive decline in adults with Down's syndrome (TOP-COG study; EudraCT number 2011-001564-21)	12-month randomised, double-blind, placebo-controlled trial (n=70)	Simvastatin, 40 mg daily	People with Down's syndrome aged 50 years or older	Feasibility	Safety, to inform outcomes for a larger trial	Ongoing	National Health Service Greater Glasgow and Clyde, UK
RO5186582 in adults and adolescents with Down's syndrome (CLEMATIS; EudraCT number 2013-001263-23)	26-week randomised, double-blind, placebo-controlled phase 2 trial (n=180)	$GABA_A$ α5 receptor negative allosteric modulator (RO5186582/F07), 20–120 mg daily	People with Down's syndrome aged 12–30 years	Composite outcome based on function and cognition	Safety and efficacy on specific cognitive domains; assessment instruments not described	Ongoing	Hoffmann-La Roche
Treatment with fluoxetine and of cognitive and physical training (EudraCT number 2011-001556-11)	6-month randomised, single-blind phase 2 trial without placebo (n=40)	Fluoxetine, 20 mg daily; environmental enrichment (not specifically described)	People with Down's syndrome older than 30 years	Cognition, function, and EEG and MRI outcomes; specific parameters not described	Quality of life	Completed, but results not yet published	IRCCS Fondazione Stella Maris

MRS=magnetic resonance spectroscopy.

Table 3: **Ongoing clinical trials related to cognition in people with Down's syndrome**

dementia onset, several potential treatments that are in development for other neurodegenerative diseases might also be beneficial for people with Down's syndrome. The antidepressant fluoxetine is a candidate treatment with a range of potential beneficial effects, including enhanced neurogenesis and a postulated mechanism related to activity within GIRK channels.[139] A trial of fluoxetine is in progress in adults with Down's syndrome older than 30 years (EuDract 2011-001556-11), although increased seizure risk is a concern (table 3).[140] Many other compounds—such as retinoids, cannabinoids, and some newer antidepressants—might enhance neurogenesis to a greater extent than does fluoxetine.[141]

The potential benefits of stem cell implantation are increasingly thought to be mediated mainly through trophic effects and enhanced neurogenesis rather than by direct replacement of lost cells with neurons derived from implanted stem cells.[142] Results from studies in other neurodegenerative[141] and cerebrovascular diseases[143] suggest that stem cell implantation could enhance synaptic function in Down's syndrome.

GABA inhibitors

Building on findings in mouse models that have linked excess GABA-mediated inhibition to impairments of memory and learning, inhibition of GABA has been shown to reverse impairment in long-term potentiation in Ts65Dn mice.[144] GABA antagonists have the propensity to increase anxiety and seizures, but no increase in seizures was reported in this study. A $GABA_A$-benzodiazepine receptor inverse agonist targeting the α5-subtype, a potentially safer alternative to GABA antagonists, has also led to cognitive benefits with improved memory and learning on the Morris water maze and novel object recognition tests in this mouse model.[145] Results are pending from an initial clinical trial with a 38-day treatment period of the α5 inverse agonist RG1662 in 35 people with Down's syndrome (Roche trials database number BP25543).

Additional potential treatments

Several other classes of compound have emerged as potential candidates on the basis of preclinical work but have not yet been investigated in clinical studies. Building on the identification of noradrenergic deficits in older people with Down's syndrome, results from preliminary studies in mice have highlighted potential benefits of β1-adrenergic receptor antagonists.[146] In a study in transgenic mice with Down's syndrome,[147] treatment of young mice with sonic hedgehog pathway agonists normalised the size of key brain structures, such as the cerebellum, which were underdeveloped. Other compounds being assessed in preliminary clinical trials include statins (EudraCT 2011-001564-21), nicotine (NCT01778946), and lithium carbonate

For the **Down Syndrome Lithium Trial** see http://www.hra.nhs.uk/news/research-summaries/down-syndrome-lithium-trial-downslit-v1-1/

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 1969, and Jan 21, 2016, with the search terms "Down OR Downs OR Down's", "syndrome", "dementia", "cognitive", and "Alzheimer OR Alzheimer's". Additional search terms were used for specific sections of the Review: "prevalence", "incidence", "epidemiology", "frequency", "diagnosis", "assessment", "identification", "neuroimaging", "biomarker", "pathology", "neuropathology", "genetic", "gene", "genotype", "GWAS", "transgenic", "treatment", "therapy", "trial", and "RCT". Only studies written in English were included from the main search, but key papers published in other languages identified from the additional searches were included as appropriate. Study selection was achieved through author consensus, with a focus on clinical trials and systematic reviews.

(EudraCT 2008-008342-20). Several safety studies have been undertaken with other commercial compounds in development, including ELN005 (NCT01791725) and R05186582. Many other compounds have also been highlighted as potential treatments, including trophic factors[148] and anti-inflammatory compounds.[97]

Transcriptional profiling can be used to identify potential therapies, and has already been used successfully in cancer research.[149] In particular, this approach can help to repurpose drugs on the basis of an anti-correlation between the respective transcription profile and the profile generated by compounds of interest. The Broad Institute Connectivity Map (CMap) database of transcriptional profiles associated with 1300 drugs provides an opportunity to identify candidate treatments and pathways. Although this project is still in preliminary stages, several candidates, such as adrenergic compounds, are emerging. These candidates have independently been shown to affect Aβ-induced toxicity in vitro[150] and might also have relevance for concurrent attention deficit hyperactivity disorder.[24] Ginkgo extracts, several anti-inflammatory compounds, antibiotics, and anticonvulsants have also emerged as potential candidates.[151]

For the **Broad Institute Connectivity Map** see https://www.broadinstitute.org/cmap/

Of note, many studies have shown only weak correlations between transcriptional signatures from mouse models and patient tissues (table 2).[102–104] This finding is a fundamental concern with transcriptional profiling, and should be taken into account when considering potential treatments identified in mouse models. Further preclinical studies are needed to understand potential mechanisms of action and to determine whether transcriptional profiling can contribute additional treatment candidates.

Preventive measures

Evidence from epidemiological studies, cohort studies, and some RCTs highlights the potential benefits on cognitive function of management of cardiovascular risk factors and lifestyle factors, such as maintaining a healthy weight and diet, and regular physical exercise in people in mid-life and later life (aged 40–70 years).[152] These factors are also likely to be important in people with Down's syndrome and will be an interesting focus for further research.

Conclusions

In this Review, we have focused on new findings in the genetic and neuropathological manifestations of Down's syndrome, and examined how this knowledge might be applied to the development and design of treatments. We are in an encouraging, but preliminary, position in this regard. A large RCT of vitamin E is still in progress, but other clinical trials are preliminary. Results from studies in mouse models of Down's syndrome suggest that some targets of Alzheimer's disease might be of particular interest for use in people with Down's syndrome, and interest in therapeutics targeting DYRK1A and neurogenesis is increasing, but the value of transgenic mice as a translational model is still uncertain. The development of therapeutics for other diseases with overlapping pathways, such as amyotrophic lateral sclerosis, might provide additional opportunities. The most rational next step in Down's syndrome treatment research would be to assess existing therapies for Alzheimer's disease, while the preliminary evidence around other novel therapeutics is tested more robustly.

Contributors

CB did the literature review, wrote the treatment section, and contributed to editing and writing of the full Review. WM wrote the neuropathology section and reviewed all sections. JH wrote the genetics section and reviewed all sections. GW contributed to the genetics and treatment sections. AC did the literature review for the epidemiology, diagnosis, and assessment sections, and contributed to the writing of the full Review and the creation of figures.

Declaration of interests

CB reports grants and personal fees from Lundbeck and Acadia, and personal fees from Roche, Orion, GSK, Otsuka, Heptares, and Lilly outside the submitted work. WM has patents awarded or pending for potential treatments for Down's syndrome with AC Immune, University of California, San Diego, CA, USA, and Stanford University, CA, USA. All other authors declare no competing interests.

Acknowledgments

AC and CB thank the UK National Institute for Health Research Biomedical Research Centre and Dementia Biomedical Research Unit at South London and Maudsley National Health Service Foundation Trust and the Institute of Psychiatry, King's College London, for their support. WM has been supported by grants from the US National Institutes of Health, LuMind Research Down Syndrome Foundation, and Cure Alzheimer's Fund.

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