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Aging and Intellectual Disability: Insights from Mouse Models of Down Syndrome

Aarti Ruparelia,[1] Matthew L. Pearn,[2,3] and William C. Mobley[4]*

[1]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, WC1N 3BG, United Kingdom

[2]Department of Anaesthesiology, University of California, San Diego, La Jolla, California

[3]VA San Diego Healthcare System, 3350 La Jolla Village Drive 9125, San Diego, California

[4]Department of Neurosciences, University of California, San Diego, La Jolla, California

Down syndrome (DS) is one of many causes of intellectual disability (ID), others including but not limited to, fetal alcohol syndrome, Fragile X syndrome, Rett syndrome, Williams syndrome, hypoxia, and infection. Down syndrome is characterized by a number of neurobiological problems resulting in learning and memory deficits and early onset Alzheimer's disease. The cognitive impairment in people with DS is virtually universal but varies considerably with respect to expressivity and severity. Significant advances in medical treatment and social inclusion have increased longevity in people with DS resulting in an increased aging population, thus highlighting the significance of early onset of dementia and the importance of identifying pharmacotherapies to treat DS-associated health complications in adults. Given its prevalence and established mouse models, this review will focus on ID in the DS population; specifically, the superimposed effect of aging on the complications already manifest in DS adults and the cognitive insights gained from studies on mouse models of DS. © 2013 Wiley Periodicals, Inc. Dev Disabil Res Rev 2013;18:43–50

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INTRODUCTION

Down syndrome (DS) is a complex genetic condition resulting from an extra copy of human chromosome 21 (HSA21). It is the most common genetic cause of intellectual disability (ID) and accounts for 15% of the population with ID [Bittles et al., 2002]. Approximately 0.45% of all human conceptions are trisomic for HSA21; live births occur at a frequency of approximately 1 in 733 [Hassold et al., 1996; Bittles et al., 2007]. DS can be caused by an extra copy of the whole HSA21 or by partial trisomy of the chromosome. Complete trisomy of HSA21 accounts for 95% of the DS population, with the remaining 5% constituting mosaic or partial translocations [Dierssen et al., 2009]. While DS is characterized by moderate to severe levels of ID, individuals with a mosaic karyotype exhibit milder effects on intellectual abilities compared to the other subtypes of DS [Bittles and Glasson, 2004]. The additional copy of HSA21 results in increased expression of genes encoded on this chromosome, with different tissues displaying varied expression levels [Hattori et al., 2000; Ait Yahya-Graison et al., 2007; Prandini et al., 2007].

DS is emerging as an important topic for research and treatment development. Dramatic advances in medical treatment and social intervention over the past 60 years have increased the life expectancy of people with DS in developed countries from an average of 12 years of age in the 1940s to 60 years of age at present [Lott and Dierssen, 2010]. Moreover, even in countries with prenatal diagnosis, the incidence of DS is not diminishing; this is largely due to increasing maternal age and reduced societal stigma of having a child with DS. Over the past 25 years the number of women above 35 years of age giving birth has increased by almost 15% [Bittles and Glasson, 2004; Bittles et al., 2007; Hodapp, 2007]. This, together with increased longevity is linked to the increased prevalence of the disorder. As a consequence of life expectancy increasing 1.7 years per year among people with DS [Yang et al., 2002], there is now a larger population of adults with DS who display premature aging accompanied by a variety of age-related health problems [Glasson et al., 2002; Bittles et al., 2007]. Thus, there is a growing need to provide specialized health care management for this population to facilitate healthy adult functioning.

Identification of neuronal targets for the development of pharmacotherapies to treat DS-related phenotypes, including cognitive aspects of the disorder, has therefore become an increasingly important goal. Mouse models of DS have been

*Correspondence to: William C. Mobley, Department of Neurosciences, University of California, San Diego, 9500 Gilman Drive, CNCB Building, Room 100, La Jolla, CA. E-mail: wmobley@ucsd.edu
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pivotal in elucidating genes that contribute to DS phenotypes and in furthering our understanding of the molecular pathogenesis underlying trisomy of HSA21. In this review, we discuss aging in DS adults and the insights obtained from DS mouse models with respect to learning and memory deficits; finally, we highlight the importance of examining aging in other mouse models of ID.

AGING IN DS ADULTS

DS is characterized by clinical phenotypes that are common to all affected individuals, including craniofacial abnormalities, hypotonia, and cognitive impairment [Hassold et al., 1996; Antonarakis et al., 2004]. The universal presence by age 40 of the key neuropathological features of Alzheimer disease (AD), and the high risk of dementia by age 60 is noteworthy [Lott and Dierssen, 2010]. In addition to these invariant features are at least 80 other variable clinical phenotypes that have been reported to affect a proportion of individuals with DS, including seizures, acute megakaryoblastic leukemia, decreased incidence of some solid tumors, and atrio-ventricular septal heart defects [Johannsen et al., 1996; Hasle, 2001; Wechsler et al., 2002; Freeman et al., 2008; Smigielska-Kuzia et al., 2009]. The increased dosage of HSA21 genes and the resulting gene-dosage imbalance between HSA21 and non-HSA21 encoded genes is the proposed mechanism responsible for the phenotypes that characterize DS. The wide variation in certain phenotypes may arise from allelic differences in HSA21 genes, contribution from genes on other chromosomes, epigenetic influences, and environmental effects.

Dementia resembling AD is among the most significant age-associated concerns in DS. However, as individuals with DS age, they also become more susceptible than the general population to other age-related physical, neurological, or psychiatric conditions, including an increased incidence of seizures, thyroid dysfunction, cardiovascular disorders, hearing and vision impairments, musculoskeletal disorders, and depression. Precocious aging observed in adults with DS may be caused by alterations in early development rendering biological systems vulnerable to other health conditions by genetic influences that emerge during aging. Individuals with DS display age-related changes and senescence at an earlier age compared to those without DS, as is evident by increased biological age, early mortality, and reduced levels of DNA-repair enzymes [Bittles et al., 2007].

Language and Communication

The cognitive profiles in individuals with DS not only vary in the type of cognitive function affected but also in the severity of the impairment. Perturbed intellectual functioning in DS is characterized by anomalies in language, learning, and memory; specifically, there are impairments in morphosyntax, verbal short-term memory (STM), and explicit long-term memory (LTM) as well as difficulties in acquiring new skills [Jarrold et al., 1999; Abbeduto et al., 2007]. Difficulties with intelligible speech is particularly concerning because it is clearly associated with less societal acceptance and success. However, visuospatial STM, associative learning, and implicit memory are usually relatively preserved [Carlesimo et al., 1997; Vicari and Carlesimo, 2006; Lott and Dierssen, 2010]. Normal aging is known to affect language and memory through physiological and neuropsychological changes. In older persons, communication is disrupted due to slower psychomotor performance, less efficient respiratory support for speech, hearing and vision impairments, leading to misconstrued speech augmented by a decline in memory capacity [Rondal, 1996]. With language and memory complications already manifest in individuals with DS, one might well expect an aggravated effect of aging on communication difficulties in adults with DS. Interestingly, visual and hearing impairments are more common and appear to have an earlier age of onset among adults with DS compared to the general population [Van Buggenhout et al., 1999].

Brain Anatomy

Alterations in neural circuit structure and function almost certainly explain the cognitive deficits in DS. Post-mortem observations and MRI studies report reduced brain volume and brachycephaly. Reductions in volume are most prominent in the cerebellum, frontal lobe, and temporal lobe, including the uncus, amygdala, and hippocampus [Aylward et al., 1997; Pinter et al., 2001a,b]. The parahippocampal gyrus has been reported to be larger in people with DS [Kesslak et al., 1994]: subcortical areas including the lenticular nuclei and posterior cortical grey matter are relatively preserved [Pinter et al., 2001a,b]. Indeed, the brain structures that mature late in development, such as the hippocampus, prefrontal cortex, and the cerebellum, exhibit disproportionate impairment [Nadel, 2003]. An age-related decrease in the size of the corpus callosum has been found to correlate with cognitive performance in individuals with DS, suggesting neocortical modifications accompany allocortical changes in DS [Teipel et al., 2003]. Recently, Beacher and colleagues [2010] reported that individuals with DS, but not healthy controls, displayed age-related reductions in volume of cortical brain regions (frontal, temporal, and parietal lobes), and an associated age-related increase in volume of cerebrospinal fluid. The authors postulate that DS adults display "accelerated" aging of certain brain regions, thus predisposing them to premature age-related cognitive decline and AD.

Early Onset Alzheimer's Disease

DS is characterized by a high incidence of early onset AD; the prevalence of dementia increases with age above 45 years, with the majority of people with DS developing dementia by the age of 65 [Coppus et al., 2006]. However, the histopathological hallmark features of AD, extracellular β-amyloid (Aβ) deposits and the accumulation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau, are already manifest in all individuals with DS by the age of 40 [Holtzman et al., 1996; Cataldo et al., 2008]. Early onset of dementia in people with DS could be linked to the dysfunction of the frontal lobe and the hippocampus, which are the regions where Aβ first accumulates during the early stages of AD [Cataldo et al., 2004]. Consistent with frontal lobe degeneration, the earliest reported changes occurring in older adults commonly include personality and behavioral differences [Holland et al., 2000]. The amyloid precursor protein (APP), from which Aβ is produced, is encoded on HSA21 and triplication of *APP* is the proposed mechanism through which individuals with trisomy 21 succumb to early onset AD [Rovelet-Lecrux et al., 2006; Sleegers et al., 2006]. Evidence in favor of this hypothesis comes from rare families with early onset AD who have small internal duplications of HSA21 that include APP, and tends to be present with cerebral amyloid angiopathy

[Cabrejo et al., 2006; Rovelet-Lecrux et al., 2006; Sleegers et al., 2006].

The temporal discrepancy between the presence of full-blown pathology and onset of dementia is evidence that these phenotypes are not tightly linked. Speculations as to the meaning of the discrepancy include the participation of genetic and environmental factors that more powerfully influence cognition than the established neuropathological markers of AD [Stanton and Coetzee, 2004]. Whatever the cause(s) for the temporal discrepancy, in our view, with increasing age comes a significant and progressive increase in the likelihood of dementia.

Mortality

Despite the prolific increase in life expectancy of adults with DS over the past 60 years [Yang et al., 2002], life expectancy in DS is still lower than that of other ID populations and the general population [Glasson et al., 2002]. Age-related dementia or other health problems likely contribute to earlier mortality. Unlike in other ID populations, males with DS have a comparative survival advantage over females with DS with an increased life expectancy of approximately 3.3 years more than females [Glasson et al., 2003]. This gender-specific bias could be ascribed to an increase in prevalence of congenital heart defects in females with DS, leading to reduced life expectancy [Morris et al., 1992]. Another putative explanation is that women with DS experience menopause at an average age of 46 years old, which is approximately 2 years earlier than other women with ID and 4–6 years earlier than the general population [Seltzer et al., 2001]. Early onset of menopause and the accompanying drop in estrogen levels is a risk factor for premature mortality caused by heart disease, stroke, breast cancer, and dementia in the general population and in females with DS [Harlow and Ephross, 1995]. The apolipoprotein E (APOE) genotype has been also related to survival in the general population and in DS; the presence of the APOE ε2 allele is associated with longevity and preserved cognitive functioning, whereas the presence of the APOE ε4 allele is associated with increased risk for dementia and early mortality [Prasher et al., 1997; Zigman et al., 2005].

MOUSE MODELS OF DS

An important goal of DS research is to correlate the effects of triplicated HSA21 encoded gene(s) to clinical aspects of the syndrome, to decipher the cellular, and molecular mechanisms responsible for abnormal phenotypes, to identify and validate potential therapeutic targets, and to encourage the development of effective treatments for these defects. Analyses of DS patients with partial trisomy 21, resulting from translocations or duplications of segments of HSA21, have provided crucial insight into mapping genes to various phenotypes [Korbel et al., 2009; Lyle et al., 2009]. However, this approach is limited by the small number of DS patients who have partial trisomy and substantial variation of clinical phenotypes. Mouse models of DS recapitulate many neuroanatomical, neurobiological, and behavioral phenotypes of DS and have thus been instrumental in furthering our understanding of the clinical manifestation of DS and in unraveling the pathogenic mechanisms by which these phenotypes arise. Little is known about aging in people with ID and even less is known about aging in mouse models of ID. However, as mouse models of DS recapitulate several DS phenotypes, it is possible to utilize mouse models of DS to examine aging in this subtype of ID.

The approach through which mouse models have been strategically exploited is by first, defining a quantitative phenotype that can be assessed. The second step involves identifying mouse models which contain a large segment of genes associated with the phenotype and then embarking on a persistent pursuit to identify smaller segments; eventually identifying key candidate genes. A thorough study would then entail examining the smallest segment minus the gene of interest to assess whether the phenotype disappears (a proof of necessity) and also assessing whether the phenotype can be recapitulated in mice that are trisomic for this same gene (a test of sufficiency). In practice, this has been done for only a few phenotypes, but with good success in those cases [Salehi et al., 2006; Hill et al., 2009; Chakrabarti et al., 2010]. The most important pitfalls include: (1) the need for more than one gene or segment to demonstrate the change—the approach can still be successful but more effort is needed; (2) the difficulty of knowing that the transgenic mouse recapitulates faithfully the expression of the endogenous gene; and (3) the possible difficulty moving to mechanism of disease and therapeutic target once the gene has been shown to be necessary and sufficient.

HSA21 is syntenic to three regions of the mouse genome, with many genes highly conserved between mouse and man [Hattori et al., 2000]. The majority of the HSA21 homologous genes are present on mouse chromosome 16 (Mmu16), but two smaller gene rich regions have conserved synteny with Mmu17 and Mmu10 (Fig. 1). The majority of DS mouse models are segmentally trisomic for large regions of Mmu16. The Ts65Dn mouse, first described in 1995, is the most widely studied and well established model; it carries a reciprocal translocation that is trisomic for approximately 104 genes (~56%) on Mmu16 that have homologues on HSA21 [Reeves et al., 1995]. It recapitulates several neuroanatomical and behavioral alterations in people with DS including learning and memory deficits. The Ts1Cje mouse model contains approximately 81 of the genes trisomic in the Ts65Dn mouse model, a segment that extends from *Sod1* to *Mx1* [Sago et al., 1998]. Another segmentally trisomic model is the Ts1Rhr mouse model, which contains only 33 trisomic Mmu16 genes that have conserved synteny with genes in the human DS critical region (DSCR); a region originally thought to be sufficient in causing most DS phenotypes [Olson et al., 2007]. Both Ts1Cje and Ts1Rhr models demonstrate DS-associated learning and memory deficits, however generally to a lesser extent and severity than the deficits presented in the Ts65Dn model [Das and Reeves, 2011]. The Ts1Yey mouse was recently developed using chromosome engineering to carry a duplication spanning the entire Mmu16 region that is conserved with Hsa21 [Yu et al., 2010b]. The Ts1Yey model exhibits cognitive deficits in behavioral tasks similar to Ts65Dn mice and heart defects similar to those seen in individuals with DS.

Segmentally trisomic mouse models for Mmu17 include the Ts1Yah model, which is trisomic for 12 genes found on the HSA21 sub-telomeric region [Pereira et al., 2009], and the Ts3Yey model, which spans the complete HSA21 conserved synteny region on Mmu17 [Yu et al., 2010b]. The Ts2Yey mouse model is segmentally trisomic for the entire HSA21 conserved syntenic region on Mmu10 [Yu et al., 2010b]. Though still under evaluation, all these recently developed models show some DS-associated cognitive impairment. A new mouse model, Ts1Yey;Ts2Yey;Ts3Yey, has been

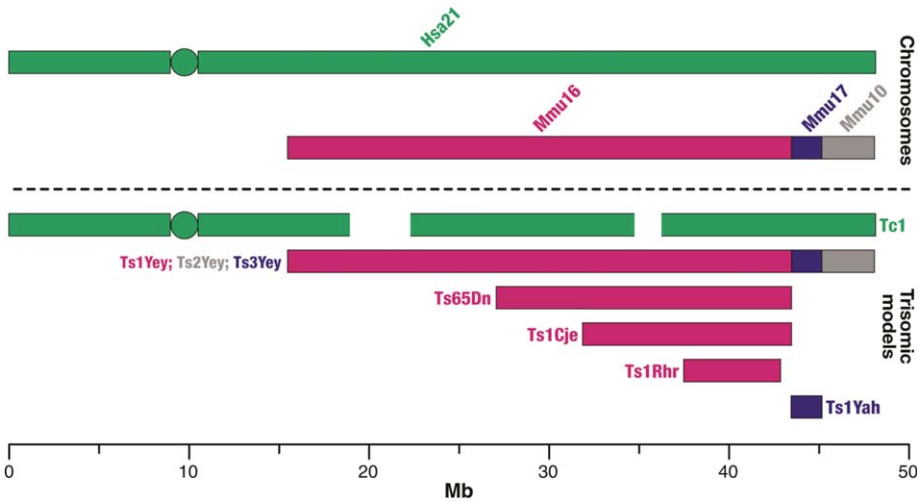

Figure 1 Mouse models of Down syndrome. HSA21 is syntenic with three regions on the mouse genome: mouse chromosomes 16 (Mmu16), 17 (Mmu17) and 10 (Mmu10). The Tc1 mouse model carries a freely segregating copy of HSA21 and is trisomic for 80% of HSA21 genes [O'Doherty et al., 2005]. The Ts1Yey;Ts2Yey;Ts3Yey mouse model is trisomic for all mouse orthologs of HSA21 genes [Yu et al., 2010b) and was developed by breeding Ts1Yey, Ts2Yey, and Ts3Yey segmentally trisomic models [Yu et al., 2010a]. The Ts65Dn mouse model is the most commonly used DS mouse model and is segmentally trisomic for approximately 104 genes on Mmu16 [Reeves et al., 1995]. Other segmentally trisomic models for Mmu16 include Ts1Cje, which contains approximately 81 of the trisomic genes on the Ts65Dn mouse model [Sago et al., 1998], and Ts1Rhr, which encodes 33 genes that have conserved synteny with genes in the human "Down syndrome critical region" [Olson et al., 2004]. The Ts1Yah mouse model is segmentally trisomic for Mmu17 and contains 12 genes found on the HSA21 sub-telomeric region [Pereira et al., 2009]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

developed by breeding Ts1Yey, Ts2Yey, and Ts3Yey models such that the resulting mouse model is trisomic for all mouse orthologs of HSA21 genes [Yu et al., 2010a]. This new model is a complete trisomic model of DS and recapitulates most of the DS-associated phenotypes displayed in the Ts65Dn mouse.

Using a very different approach, Fisher, Tybulewicz and colleagues developed the Tc1 mouse; a transchromosomic model that carries a freely segregating, almost complete copy of HSA21 in addition to the normal complement of the mouse chromosomes [O'Doherty et al., 2005]. This mouse model is trisomic for approximately 80% of HSA21 genes; however, it is mosaic for HSA21-carrying cells such that not all cells contain the human chromosome. The model also demonstrates mild cognitive deficits in learning and memory, electrophysiological abnormalities, and other DS-associated deficits.

AGING IN MOUSE MODELS OF DS

Behavioral Tests

Individuals with DS display cognitive deficits throughout development and age-related cognitive decline and dementia [Bittles et al., 2007]. Mouse models of DS also recapitulate DS-associated cognitive deficits and therefore should be assessed over longer time-points to examine the effects of aging on behavior and cognitive decline. Behavioral tests are routinely conducted on mouse models to assess learning and memory deficits. Ideally the tests chosen can be linked to the function of one or more brain regions. However a limitation of behavioral tests is that most tasks depend on the functioning of multiple brain regions, thus making it difficult to dissociate the relative contribution of one brain region over another in a particular task. A thorough review was recently published detailing the performance of mouse models of DS on various behavioral tasks [Das and Reeves, 2011]. The Morris water maze (MWM) navigation task is widely used to assess spatial learning and memory and relies heavily on the hippocampus as well as the entorhinal cortex, striatum, fimbria and fornix [Reeves et al., 1995]. Ts65Dn mice have demonstrated impaired performance on the cued and hidden platform variations of this task, therefore evidencing hippocampal-dependent learning deficits [Reeves et al., 1995; Sago et al., 2000]. Ts1Cje mice exhibit similar learning deficits in the hidden platform task [Sago et al., 1998], as do the triple trisomy mice (Ts1Yey; Ts2Yey;Ts3Yey) and Ts1Yey mice [Yu et al., 2010a,b]. However, Ts1Rhr, Ts2Yey, or Ts3Yey mice show no deficits in either version of this task [Olson et al., 2007; Yu et al., 2010a), suggesting that trisomic human genes with orthologs on Mmu16, but not on the DSCR of Mmu16, Mmu17, or Mmu10, are necessary for this learning deficit [Fig. 1]. Interestingly, despite Ts1Yah mice displaying cognitive deficits in working and short-term memory, an enhancement in hippocampal-dependent spatial learning was demonstrated by showing that trisomic mice performed better than littermate controls in the hidden platform MWM [Pereira et al., 2009]. The transchromosomic Tc1 mouse retained intact spatial recognition memory but had impaired spatial working memory in various versions of the MWM [Morice et al., 2008].

Performance in the novel object recognition test (NORT), requiring a mouse to discriminate between a new object and familiar objects, is linked with the functions of the perirhinal, insular, medial prefrontal cortices, and the hippocampus. Ts65Dn mice display impaired performance in this task [Fernandez et al., 2007]. Ts1Rhr mice also showed deficits on this test [Belichenko et al., 2009], suggesting that the contribution of the 33 trisomic genes present

Table 1. Cognitive Insights Gained from Mouse Models of DS

Mouse Model	Behavioral Tests	Brain Anatomy	Neurodegeneration and AD
Ts65Dn	Impaired performance in MWM [Reeves et al., 1995); Impaired performance in NORT [Fernandez et al., 2007].	Altered brain shape and reduced cerebellar volume [Aldridge et al., 2007]; Reduced density of cerebellar granule cells [Contestabile et al., 2009].	BFCN neurodegeneration [Granholm et al., 2000]; Enlarged early endosomes [Cataldo et al., 2003]; Severely impaired NGF retrograde axonal transport [Salehi et al., 2006]; Degeneration of locus coeruleus neurons [Salehi et al., 2009].
Ts1Cje	Impaired performance in MWM [Sago et al., 1998]; No deficits in NORT [Belichenko et al., 2007].	Smaller brains, hypoplasia of cerebellum and enlarged ventricles [Ishihara et al., 2009]; Reduced density of cerebellar granule cells [Moldrich et al., 2009]; Elevated neuronal apoptosis [Micali et al., 2010].	No BFCN neurodegeneration [Sago et al., 1998]; No enlargement of early endosomes [Cataldo et al., 2003]; Moderately impaired NGF retrograde axonal transport [Salehi et al., 2006]; Hyperphosphorylation of tau [Shukkur et al., 2006].
Ts1Rhr	No deficits in MWM [Olson et al., 2007]; Impaired performance in NORT [Belichenko et al., 2009].	Altered brain shape but normal cerebellum volume [Olson et al., 2007].	Not available.
Tc1	Impaired spatial working memory in MWM [Morice et al., 2008]; Short-term impairments in NORT [Morice et al., 2008].	Reduced density of cerebellar granule cells [O'Doherty et al., 2005].	Not available.
Ts1Yey; Ts2Yey; Ts3Yey	Impaired performance in MWM [Yu et al., 2010b].	Not available.	Not available.
Ts1Yey	Impaired performance in MWM [Yu et al., 2010a].	Not available.	Not available.
Ts2Yey	No deficits in MWM [Yu et al., 2010b].	Not available.	Not available.
Ts3Yey	No deficits in MWM [Yu et al., 2010b].	Not available.	Not available.
Ts1Yah	Enhanced performance in MWM [Pereira et al., 2009].; Impaired performance in NORT [Pereira et al., 2009].	Not available.	Not available.

Abbreviations: Aβ, β-amyloid; AD, Alzheimer disease; APOE, apolipoprotein E; APP, amyloid precursor protein; BFCN, basal forebrain cholinergic neuron; DS, Down syndrome; DSCR, Down syndrome critical region; DYRK1A, dual-specificity tyrosine-(Y)-phophorylation-regulated kinase 1A; FMR-1, fragile X mental retardation; FMRP, fragile X mental retardation protein; FXS, Fragile X syndrome; HSA21, human chromosome 21; ID, intellectual disability; ITSN1, intersectin 1; LTM, long-term memory; MeCP2, methyl-CpG-binding protein 2; Mmu10, mouse chromosome 16; Mmu16, mouse chromosome 16; Mmu17, mouse chromosome 17; MWM, Morris water maze; NFT, neurofibrillary tangle; NGF, nerve growth factor; NORT, novel object recognition test; RCAN1, regulator of calcineurin 1; RS, Rett syndrome; STM, short-term memory; SYNJ1, synaptojanin 1.

on Mmu16 in the Ts1Rhr model are crucial for this phenotype. However, the Ts1Cje model displayed normal performance in the NORT despite the presence of all the genes in Ts1Rhr mice [Fernandez and Garner, 2007]. The Ts1Yah model, which is trisomic for 12 HSA21 syntenic genes on Mmu17, also produced deficits in this task [Pereira et al., 2009], suggesting a complex interplay between Mmu16 and Mmu17 genes. The Tc1 mouse demonstrated short-term deficits in the NORT but no long-term deficits [Table 1; Morice et al., 2008].

Brain Anatomy

Similar to the reduction in cerebellum volume observed in humans with DS [Pinter et al., 2001b], morphometric analyses have revealed that Ts65Dn mice display altered brain shape and a reduced cerebellar volume [Aldridge et al., 2007]. The Ts1Cje model recapitulates a DS-associated brain phenotype including a smaller brain, hypoplasia of the cerebellum and enlarged ventricles [Ishihara et al., 2010]. Ts1Rhr mice only show altered brain shape, suggesting that the triplication of genes encoded on the DSCR is not sufficient to recapitulate reduced cerebellar volume (Table 1). It also raises the possibility that the trisomic region in common for the Ts65Dn and Ts1Cje models contains the genes whose dose increase causes these neurodevelopmental phenotypes [Olson et al., 2007]. It has been established that individuals with DS have differing brain anatomy compared to controls and portray age-related reductions and "accelerated" aging in certain brain regions [Beacher et al., 2010]. Conducting age-related studies on brain anatomy in DS mouse models would be informative to further understand the independent process of precocious aging in this disorder.

Neurodegeneration and AD

Neurodegenerative phenotypes that are seen in people with DS are recapitulated to some extent in mouse models of DS. Unlike in DS and AD, Ts65Dn mice do not produce Aβ plaque deposits or hyperphosphorylation of tau [Holtzman et al., 1996], but they do show the loss of basal forebrain cholinergic neurons (BFCNs) at approximately 12 months of age, which is correlated with cognitive decline in these mice [Granholm et al., 2000; Hunter et al., 2003]. This subset of neurons is selectively vulnerable to neurodegeneration in DS and AD and may contribute to the dementia that is prevalent in both conditions [Holtzman et al., 1996]. BFCN neurodegeneration does not occur in Ts1Cje mice (Table 1), suggesting that the contribution of one or more of the approximately 23 extra trisomic genes in the Ts65Dn mouse model is necessary for neurodegeneration [Sago et al., 1998].

Endosomal alterations have been shown to develop in neurons of brain regions that are most severely affected in AD and DS, including the hippocampus, neocortex, and the basal forebrain. In

human pyramidal neurons in lamina III of the prefrontal cortex, early endosomes were up to 32-fold larger in volume compared to controls [Cataldo et al., 1997]. Enlarged early endosomes and aberrations in the endocytic pathway have been observed in DS brain as early as 2 months of age, in DS fibroblasts and in the Ts65Dn mouse [Cataldo et al., 2003; Salehi et al., 2006; Cataldo et al., 2008; Jiang et al., 2010].

Endocytic enlargements are also linked to *App* gene-dose. Ts1Cje mice, which lack the trisomic segment containing the *App* gene, do not show enlarged early endosomes [Cataldo et al., 2003]. Moreover, reducing App gene dose to normal in the Ts65Dn mouse eliminated the increase in endosomal size [Salehi et al., 2006]. Morphological and functional perturbations in the endocytic pathway in DS and AD may be the process through which neurodegeneration develops in several brain regions including BFCNs.

Retrograde axonal transport of nerve growth factor (NGF) is linked to the survival and function of BFCNs [Cooper et al., 2001]. Retrograde transport of NGF was found to be severely reduced in Ts65Dn mice relative to controls and was six-fold lower than that in Ts1Cje mice [Salehi et al., 2006]. Interestingly, retrograde transport was restored to approximately that of Ts1Cje mice in Ts65Dn mice that harbored only two copies of *App* [Salehi et al., 2006], which had the effect of bringing down App expression to disomic levels. In follow-on studies, it was demonstrated that reduced transport of NGF was also seen in a mouse harboring a transgene encoding wild type human *APP* and in one carrying a transgene for human mutant *APP*; this provided evidence that increased *App* gene dose is both necessary and sufficient for abnormal axonal transport of NGF. Significantly, normalizing App protein levels in the Ts65Dn mouse prevented the loss of BFCNs [Salehi et al., 2006]. Cholinergic axon terminals in Ts65Dn mice were reported to display enlarged early endosomes that contained markers for both NGF and APP, suggesting that disrupted NGF retrograde axonal transport is largely a result of *App* overexpression, causing the enlargement of early endosomes and consequently, neurodegeneration [Salehi et al., 2006]. In more recent studies, gene dose for *App* was also linked to degeneration of neurons of the locus coeruleus whose loss predates that for BFCNs [Salehi et al., 2009]. As suggested above, the analysis is now at a point whereby the mechanism through which *App* gene dose acts can be further deciphered to elucidate the functional role of this gene in causing neurodegeneration.

Age-dependent alterations in APP metabolite levels and NGF levels have also been found in the Ts65Dn mouse model. In proportion to the *App* gene-dosage imbalance, at the age of 10 months APP brain levels were increased in Ts65Dn mice, however no such difference was apparent at 4 months of age [Choi et al., 2009]. A significant age-related decline in NGF levels is also present in the Ts65Dn basal forebrain by 6–8 months of age, accompanied with a reduction in the hippocampus by the age of 13–16 months [Hunter et al., 2003].

It is important to note that HSA21 genes other than *APP* may also contribute to aberrant endocytic pathway function and signaling and in abnormal synaptic morphology. These include *ITSN1 (intersectin1)*, *SYNJ1* (*synptojanin1*) and *RCAN1* (*regulator of calcineurin 1*) [Chang and Min, 2009]. An early neurohistopathological feature of AD and DS is the formation of NFTs composed of hyperphosphorylated microtubule-associated protein Tau [Ball and Nuttall, 1980]. The Ts1Cje mouse does not produce NFTs but is the only DS mouse model that exhibits hyperphosphorylation of Tau, prevalent by the age of 3 months old [Shukkur et al., 2006]. *DYRK1A (dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A)*, an HSA21 encoded kinase, phosphorylates Tau at a key priming site and is suggested to facilitate Tau hyperphosphorylation, when overexpressed, contributing to the development of AD in people with DS [Ryoo et al., 2007].

AGING IN OTHER MOUSE MODELS OF ID

As in DS, individuals with other subtypes of ID such as Fragile X syndrome (FXS), Rett syndrome (RS) and Williams syndrome, are also experiencing increased life expectancies as a result of advanced medical care and technology and greater social and health enrichment, despite co-morbid health problems [Lotan et al., 2010; Utari et al., 2010; Brown et al., 2011]. Thus, there is a growing population of aging adults with ID that have age-related health needs that need to be recognized and addressed. Surprisingly little is known about aging and adult functioning in these other subtypes of ID. In FXS, the abnormal expansion of CCG repeat (above 200 repeats) in the 5′-UTR of the fragile X mental retardation (*FMR-1*) gene leads to the silencing of the gene and the loss of encoded fragile X mental retardation protein (FMRP) [Utari et al., 2010]. Based on the few studies that have examined aging in an *Fmr-1* knock-out mouse model, it has been discovered that FMRP levels decrease as a function of age, and the expression of *Fmr-1* transcript declines in male mice in an age-dependent manner. However, *Fmr-1* mRNA greatly increases in old aged female mice [Singh et al., 2007; Singh and Prasad, 2008]. These age-dependent alterations may be related to cognitive decline in old age. In another study using the same mouse model, FMRP deficiency was found to induce age-dependent impairments in long-term synaptic plasticity in a specific brain region [Larson et al., 2005]. Another cause of ID is RS, which is characterized by mutations in the methyl-CpG-binding protein 2 (*MeCP2*) gene. Using an adult onset mouse model of RS, such that *Mecp2* expression is deleted only when the animals are fully mature, it was discovered that several RS-associated features could be recapitulated after adult deletion of *Mecp2* [McGraw et al., 2011]. This finding suggests that MeCP2 expression provides limited protection against the disease during early development and may not be dependent on epigenetic instructions programmed early in life.

CONCLUSION

The population of individuals with intellectual disability is increasing and aging, presenting a need for specialized health care management that caters to improving their quality of life, health, and general well-being [Brown et al., 2011]. DS leads to the overexpression of over 300 HSA21 genes resulting in an intricate network of aberrant genetic and molecular processes [Sturgeon and Gardiner, 2011]. Consequently, complications arise when attempting to dissociate the pathogenic mechanisms underlying DS and identifying the contribution of individual genes and neurobiological pathways that characterize the plethora of clinical phenotypes seen in DS. This is further complicated by the variation in the extent and severity of the phenotypes displayed amidst those with DS. However, recent human and mouse studies have deepened our knowledge about what was once thought to be an

impossible condition to understand. Collectively, studies of mouse models have contributed to several discoveries of the molecular mechanisms underlying learning and memory deficits in DS and have formed the basis from which neuronal targets are currently being tested in clinical trials [for a review on this topic, refer to Ruparelia et al., 2012]. The insights gained from mouse models of DS, and their contribution to our understanding of the DS field has been unequivocal. However, relatively little evidence is available about the compounded effect of aging on adult functioning in DS and very little evidence is available for other ID populations. Better models for understanding aging in DS may include the development of crossing mouse strains of DS and AD then evaluating their pathology and age-related behavioral phenotypes. The development and study of mouse models that explore the aggravated effects of aging in ID will be informative in furthering our understanding of how to effectively manage an aging population. ■

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