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Beyond Amyloid: Immune, Cerebrovascular, and Metabolic Contributions to Alzheimer Disease in People with Down Syndrome

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Summary

People with Down syndrome (DS) have increased risk of Alzheimer disease (AD) presumably conferred through genetic predispositions arising from trisomy 21. These predispositions necessarily include triplication of the amyloid precursor protein (*APP*), but also other Ch21 genes that confer risk directly or through interactions with genes on other chromosomes. We discuss evidence that multiple genes on chromosome 21 are associated with metabolic dysfunction in DS. The resulting dysregulated pathways involve the immune system, which leads to chronic inflammation, the cerebrovascular system leading to disruption of the BBB, and cellular energy metabolism promoting increased oxidative stress. In combination, these disruptions may produce a precarious biological milieu which, in the presence of accumulating amyloid, drives the pathophysiological cascade of AD in people with DS. Critically, mechanistic drivers of this dysfunction may be targetable in future clinical trials of pharmaceutical and/or lifestyle interventions.

Introduction

History

The first description of individuals with intellectual and developmental disabilities was published in 1838 by Jean-Étienne Esquirol; however, it was in 1866 that John Langdon Down identified a subcategory of people with cognitive impairments based on their phenotypic similarities, describing the clinical features of what we currently know as Down syndrome (DS). Depictions of the syndrome before 1838 are rare, but can be found in

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This review by Martini et al discusses evidence for immune, cerebrovascular, and metabolic contributions to Alzheimer's disease risk in people with Down syndrome. The authors argue that these mechanisms may interact with characteristic amyloid over expression due to trisomy 21.

historical material (Starbuck, 2011). Ancient remains found in France dating back to the 5-6th century AD are consistent with the phenotype of DS and, interestingly, suggest that individuals with DS were not stigmatized by members of the community at that time (Rivollat et al., 2014). Notably, the first hint of an association between DS and Alzheimer disease (AD) was described in 1876 by John Fraser and Arthur Mitchell (Fraser, 1876), decades before Alois Alzheimer's description of AD (Alzheimer, 1906). The evidence for this association became stronger with George Jervis reporting the presence of senile plaques in three young "mongoloid" adults (Jervis, 1948). In 1987, the description of a defective gene linked to familial AD development was mapped to chromosome 21 (Goldgaber et al., 1987; Glenner and Wong, 1984). Years before, in 1932, non-disjunction was first suggested as a cause for DS (Davenport, 1932); however, it was only in 1959 that trisomy of chromosome 21 was identified as the most common cause of DS by Drs. Léjeune, Gautier, and Turpin (Lejeune et al., 1959; Lejeune, 1959). In the following years, translocation (Carter et al., 1960; Polani et al., 1960) and mosaicism (Clarke et al., 1961; Clarke et al., 1963) were also described as forms of trisomy 21 (see Figure 1).

DS or Trisomy 21 is the most common cause of intellectual disability and prevalence in the United States is approximately 250,000 individuals (Presson et al., 2013). The United Nations estimates the prevalence of DS to be between 1 in 1,000 to 1 in 1,100 live births worldwide, but counts are not available in different parts of the world, making it harder to obtain a precise number (Nations, 2021). Meiotic nondisjunction causes the extra copy of chromosome 21 and accounts for 95% of cases. Partial trisomy (translocation) and somatic mosaicism represent 4% and less than 1% of all cases, respectively. Advances in genetic studies have continued at a rapid pace and in 1987 the characterization of a cDNA, encoding brain amyloid on chromosome 21, provided a strong explanation for the association of AD with DS (Goldgaber et al., 1987; St George-Hyslop et al., 1987). In 2000, the full sequencing of chromosome 21 was completed, and this dramatically accelerated DS research (Gardiner and Davisson, 2000; Hattori et al., 2000). Recent advances in medicine and our understanding of factors associated with the syndrome have significantly improved quality of life and extended life expectancy of people with DS, increasing from 12 in 1949 to over 60 years of age today (de Graaf et al., 2017b; Penrose, 1949). However, because increased age is the most potent known risk factor for AD, these advances have also resulted in increased prevalence of AD in people with DS (DSAD). The overexpression of the β-amyloid precursor protein gene (*APP*) on chromosome 21 leads to an enhanced production of beta-amyloid (Aβ) and is likely to be one of the main causes for increased risk of AD in this population (Doran et al., 2017; Prasher et al., 1998). People with DS show blood and cerebrospinal fluid (CSF) biomarker changes consistent with observations in both familial, autosomal dominant AD (ADAD) and sporadic, late-onset AD (LOAD). Studying AD in people with DS has the unique advantage of a distinct age-related pattern of emerging neuropathology commencing in childhood which allows us to investigate the earliest appearance of dysfunction in specific pathways that may contribute to AD pathogenesis. These changes could suggest comparisons in DSAD to the abnormal aging also observed in ADAD and LOAD. However, unlike these other clinical populations, people with DS demonstrate lifelong patterns of cognitive and neurobiological developmental differences compared to chromosomally typical individuals. Better appreciation of these unique, life-

course trajectories of elevated risk in DSAD could substantially inform specific therapies in this population, if not suggest underappreciated attributes and drivers of AD pathobiology in all at-risk populations.

Aging and Lifespan

Statistics from studies in the late 1990's suggested that after 35 years of age, mortality rates doubled every 6.4 years in people with DS as compared to every 9.6 years for people without DS (Strauss and Eyman, 1996). The mean and median age of death has significantly increased by 3.75-fold over the past 40 years (Presson et al., 2013). These statistics continue to improve with estimates from 2010 showing that 28% of people with DS are living past 40 years of age, compared to 4% in the 1950s (de Graaf et al., 2017b) More enriched lifestyles, management of co-occurring illnesses, and improvements in medical care for children and adults with DS led to this significant extension in lifespan and enhanced quality of life (Bittles et al., 2007; Glasson et al., 2002). Indeed, the number of people with DS over the age of 40 years is rapidly rising (de Graaf et al., 2017a; de Graaf et al., 2017b; 2020). Thus, in the coming decades there will be an increasing need to address age-associated health issues and, in particular, manage the development of AD in this vulnerable population.

Although all people with DS with full trisomy 21 develop AD neuropathology by the time they are 40 years of age, there is approximately a 10-year delay, on average, to when clinical features of dementia may be observed (between 53-55 years of age) (Fortea 2020; Sinai et al., 2018). Of note, a subset of people with DS, estimated to be between 10-15%, reach over 60 years of age without signs of dementia (Fortea 2020; Schupf and Sergievsky, 2002; Sinai et al., 2018). There is great interest in identifying factors that affect onset of clinical dementia because these modifiers may be targetable by either pharmacological or lifestyle interventions (Karmiloff-Smith et al., 2016). People with DS have a higher prevalence of several common conditions including hypothyroidism, high BMI/obesity, high cholesterol, sleep apnea and other sleep disturbances (Cody et al., 2020), and metabolic disorders such as diabetes, that are known to affect risk of AD and dementia in the general population (Capone et al., 2020; Capone et al., 2018; Tsou et al., 2020). Conversely, there are also protective factors that were historically underappreciated (Alić et al., 2020). For example, people with DS have low rates of hypertension and atherosclerosis (Draheim et al., 2010; Draheim et al., 2002; Murdoch et al., 1977), which are typically significant contributors to cerebrovascular dysfunction and resulting cognitive vulnerability in abnormal aging. We and others propose that multiple etiologies predispose people with DS to an elevated risk of AD that may be mediated, in part, by systemically extensive metabolic dysfunction linking immune system dyshomeostasis, inflammation, cerebrovascular pathology, and cellular metabolic deficits.

Contributions of immune system and inflammation

Immune dysregulation in people with DS is detected as early as during fetal development. Consequently, people with DS are highly susceptible to develop certain health conditions, including autoimmune diseases, hematological and autoimmune skin disorders, among others (Aversa et al., 2015; Ram and Chinen, 2011; Verstegen and Kusters, 2020). Importantly, individuals with DS are at high risk for infections, especially of the respiratory

tract (Bloemers et al., 2010a; Chan et al., 2017), usually with increased rates of hospitalization and higher mortality (Beckhaus and Castro-Rodriguez, 2018; Perez-Padilla et al., 2010). Several immune-related genes, including *ITGβ2, IFNAR1, IFNGR2, ICOSL, AIRE*, etc., are found on chromosome 21, raising potential explanation for the altered expression and function of specialized immune cells and mediators in DS (Satgé and Seidel, 2018; Wilcock and Griffin, 2013), similar to that observed with aging in the general population.

Differences in immune parameters in people with DS may affect both innate and adaptive immunity (Aiello et al., 2019; Fulop et al., 2017; Gensous et al., 2020; Goronzy and Weyand, 2019; Huggard et al., 2020). The thymus gland is a specialized organ for T cell maturation. T lymphocytes, divided into CD4+ and CD8+ cells, are key components of the adaptive immune system (Germain, 2002; Laidlaw et al., 2016). In DS, the thymus is known to be smaller, hypocellular, and has a reduced number of mature thymocytes (Murphy and Epstein, 1990; 1992), while in the periphery a reduced number of lymphocytes and Regulatory T cells (Tregs) could increase the propensity to autoimmune disorders (de Hingh et al., 2005; Marcovecchio et al., 2019). Reductions in the number of circulating CD4+ T cells, inversion of CD4+/CD8+ ratio, and impairments of other T cell subpopulations are reported in DS (Barrena et al., 1993; Cossarizza et al., 1990; Guazzarotti et al., 2009; Pellegrini et al., 2012). More recently, higher expression of markers of activation and senescence in CD8+ T cells from adults with DS were described, along with increased differentiation of CD4+ cells and overproduction of cytokines related to autoimmunity (Araya et al., 2019; Schoch et al., 2017). Upon antigen presentation, B lymphocytes proliferate, differentiate, and produce defense antibodies, while also retaining memory to rapidly react to subsequent exposure to previous stimulating antigens. Adults with DS have higher levels of differentiated B cell subsets associated with inflammation and autoimmunity (Waugh et al., 2019). In general, there are reduced numbers of circulating B cells in people with DS, particularly at young ages; although the actual levels of immunoglobulins reported between different studies is variable and may be related to differences in study cohort sizes (Carsetti et al., 2015; Cetiner et al., 2010; Dieudonne et al., 2020; Farroni et al., 2018; Verstegen et al., 2014). Altogether, overall immune dysregulation, reduction in switched memory B cells, and changes in immunoglobulins may directly affect the response of individuals with DS to vaccinations (Carsetti et al., 2015; Valentini et al., 2015) and lead to worse outcomes due to viral infections including that caused by SARS-CoV-2 (COVID-19) (De Toma and Dierssen, 2021; Espinosa, 2020; Huls et al., 2021; Illouz et al., 2021).

Recently, disturbances in iron homeostasis linked to increased cytokine expression and the hepcidin hormone were described in people with DSAD, suggesting shared mechanisms between increased susceptibility to infections and neurodegeneration (Raha, 2021). Changes in the innate immune system are consistent with the overall immune dysregulation in DS. Recent studies suggested that people with DS have lower granulocyte, myeloid dendritic cell counts (Bloemers et al., 2010b), and increased inflammatory monocytes (Waugh et al., 2019). Studies on natural killer (NK) cells are contradictory, but tend to demonstrate higher numbers of NK cells in children and adolescents with DS (Cetiner et al., 2010; Schoch et al., 2017) accompanied by hyper-reactivity to interferon-α (IFN-α) in adults (Waugh et al.,

2019), as well as inefficient and lower NK cell counts (Bloemers et al., 2010b; de Hingh et al., 2005).

Neuroinflammation is directly associated with aging and AD development and some of the mechanisms operating in people with DS involve the activation of the complement pathway, cytokine release, and glial cell alterations, among others. The inflammatory phenotype of people with DS differs from age-matched neurotypical controls and reflects an increase in pro-inflammatory gene expression (Wilcock et al., 2015). Cytokine expression across the lifespan is region specific within the brain and, with respect to some specific mediators, exacerbated before the occurrence of AD pathology (Flores-Aguilar et al., 2020; Iulita et al., 2016). Inflammatory markers measured in plasma show a striking upregulation of proinflammatory cytokines in people with DSAD compared to those without AD (Petersen et al., 2020). In the brains of people with DSAD, there is increased expression of C1q, the initial factor of the classical complement pathway, which is consistently associated with compact Aβ plaques (Head et al., 2001; Stoltzner et al., 2000). Interestingly, proteomic analysis of blood suggests an overall deficiency of complement factor in people with DS (Sullivan et al., 2017).

Glial cells, including astrocytes and microglia, are critically involved in AD development specifically playing a role in modulating neuroinflammatory processes. S100 calcium binding protein B (S100β) is primarily found in astrocytes and promotes the healthy development of the CNS, while also exhibiting cytokine-like activities. In people with DS, the overexpression of the *S100B* gene on chromosome 21, leading to increased numbers of S100β-positive astrocytes may have negative consequences related to age-associated cognitive decline (Griffin et al., 1989). When modeled *in vitro*, DS astrocytes generate higher levels of reactive oxygen species (ROS) with reduced synaptogenic molecules (Chen et al., 2014). DS iPSC-derived astroglia can also lead to structural and functional deficits in co-cultured neurons, specifically a decreased global excitability accompanied by increased amplitudes of post-synaptic activity and density (Mizuno et al., 2018). However, the dysregulation of astrocyte functions is known to cause hyper excitability or promote the development of epilepsy through multiple different mechanisms (Verhoog et al., 2020), a prevalent comorbidity in people with DS (Altuna et al., 2021). Abnormal astrocyte function in people with DS may also be reflected in metabolic imaging studies of the aging DS brain, where significantly lowered N-acetyl-aspartate (a marker of neuron health) to myo-inositol (a marker of inflammation) ratios (NAA/MI) characterize DSAD compared to both euploid controls and cognitively stable people with DS (Lin et al., 2016; Montal et al., 2021). The hexose sugar myo-inositol becomes increasingly abundant in the brains of aging individuals with DS and may indicate elevated levels of glial neuroinflammation (Huang et al., 1999). However, it is important to consider that the gene encoding the myo-inositol transporter protein (*SLC5A3*) is on chromosome 21 and due to its triplication in DS, myo-inositol may be overexpressed for this reason (Huang et al., 1999). Expression of several other genes not found on chromosome 21 has also been implicated in the neuroinflammatory response in people with DS. For example, reactive astrocytes surrounding Aβ plaques in the hippocampus of people with DS show increased expression of *STARD1* that is involved in intracellular cholesterol trafficking (Arenas et al., 2020). Glial fibrillary acidic protein (*GFAP*), another important astrocyte protein, is stable in the plasma of people with DS until

the late 40s and increases gradually with age (Hendrix et al., 2021). Taken together, these findings suggest that glial associated neuroinflammation in DS is related, at least in part, to the triplication and overexpression of genes associated with chromosome 21 and their trans gene interactions.

Single-nuclei analyses of the neurotypical human AD brain suggest a unique microglia-related transcriptomic signature with disease (Olah et al., 2020). Although similar studies have yet to be completed in the brains of people with DS, microglial morphological phenotypes in DS and DSAD overlap with observations in AD, but also may display unique features. For example, in DSAD, there is a shift towards the presence of higher numbers of dystrophic (dying) and rod-shaped (chronically inflamed) microglial cells suggesting that microglial changes progress gradually over time as people with DS age (Flores-Aguilar et al., 2020; Martini et al., 2020). Levels of the triggering receptor expressed on myeloid cells 2 (TREM2), which are also implicated in microglial function and homeostasis, are elevated in young adults with DS (Raha-Chowdhury et al., 2018) and decline with age (Weber et al., 2020). Polymorphisms on the gene encoding TREM2 (*TREM2*) are linked to a higher risk of AD (Ulland and Colonna, 2018). In combination, there is strong evidence of significant neuroinflammation in DS, that is exacerbated with AD pathology, and present both common and distinct patterns when compared to AD in the general population. A vast body of evidence suggests an intrinsic relationship between impaired neuronal energy metabolism, inflammation, and Aβ deposition (for complete review, please see (Kapogiannis and Mattson, 2011; Yan et al., 2020)). In hippocampal neurons, hyperinsulinemia drives the upregulation of genes for inflammatory and immune pathways while downregulating insulin signaling genes. These changes result in decreased mitochondrial function and blockage of glucose utilization (Wu et al., 2008) (Blalock et al., 2010). Additionally, Aβ may also activate microglia cells and shift their metabolism to aerobic glycolysis in a transgenic mouse model (Baik et al., 2019). Age-associated changes in the immune system of people with DS occur in a relatively shorter time and at earlier ages than in the neurotypical population. These factors contribute to the unique neuroinflammatory signature in people with DS and are consistent with the notion of DS as a “segmental progeroid” condition of biologically accelerated aging. Because of their unique metabolism within the CNS and roles in driving neuroinflammation, “immunometabolic” changes involving reactive and activated glia could link immunological and biochemical perspectives in DSAD considered independently in this review (Bernier et al., 2020; Chausse et al., 2021; Muri and Kopf, 2021; Price et al., 2021). Such dysmetabolic dynamics could, however, extend distally from the CNS to also include peripheral immune cells and associated processes in AD (Gate et al., 2020; Runtsch et al., 2020; Town et al., 2005).

Neuroinflammation in people with DS may be driven in part by genetics, but also as we discuss next, may be a consequence of cerebrovascular pathology with subsequent leakage of serum proteins into the brain.

Cerebrovascular pathology in DS

Cerebral amyloid angiopathy (CAA), the progressive deposition of Aβ within the walls of leptomeningeal and cortical vessels, is a major contributor to AD pathogenesis and is found

in nearly 50% of sporadic AD cases (Jakel et al., 2021). CAA can lead to both micro- and macro- hemorrhages (Thal et al., 2003; Thal et al., 2008; Vinters, 1987). Adults with DS, especially those older than 55 years of age, consistently present with significant CAA (Belza and Urich, 1986; Head et al., 2017; Mann et al., 2018). In this population, increasing age is strongly associated with increased CAA severity (Head et al., 2017), and possible consequences include vascular dysfunction and disruptions in the blood brain barrier, among others, which can contribute to an earlier age of dementia onset.

Interestingly, individuals with DS have a low prevalence of systemic vascular risk factors (e.g. hypertension) and low risk for intracerebral hemorrhage, despite the high prevalence of obesity and sleep apnea (which can cause vascular disease), suggesting that genes on chromosome 21 and other factors may be protective (Buss et al., 2016; Morrison et al., 1996; Rodrigues et al., 2011). Some of the comorbidities associated with cerebrovascular disease or protection in DS include atherosclerosis and Moyamoya disease, hypertension/hypotension, dyslipidemia, obesity and sleep apnea, among others that will be discussed shortly (for complete reviews see (Carmona-Iragui et al., 2019; Wilcock et al., 2016). Cerebrovascular pathology in the brains of people with DS may also drive neuroinflammation. In work by Wilcock and colleagues, levels of pro-inflammatory factors including CHI3L3, IL-1Ra, CD86 and TGF-β were significantly elevated (Wilcock et al., 2015). These mediators are typically associated with the formation of immune complexes (Edwards et al., 2006; Sudduth et al., 2013) and suggest that the vascular leakage results in extravasation of serum proteins into the brain causing microglial activation which, in turn, may be linked to metabolic stress. The neurovascular unit – the union of endothelial cells, pericytes, astrocytes, neurons, and vascular smooth muscle cells – require ongoing metabolic adaptations to accommodate the brain's blood flow and metabolic supplies. With ongoing aging processes, both neurovascular coupling or unit and blood brain barrier may become progressively perturbed, directly affecting cerebrovascular health. These and other perturbations could contribute to an earlier age of dementia onset in the DS population, and similar lines of inquiry could be very productive for better understanding DSAD-associated pathobiology broadly and beyond amyloidosis itself. Importantly, substantial cortical amyloidosis and bioenergetics may both exist subject to metabolically dyshomeostatic constraints in emerging AD (Agrawal et al., 2020; Wilkins and Swerdlow, 2017).

"Type III Diabetes" and lipid metabolism in DS and AD

AD has recently been described as "Type III diabetes" and this moniker serves to highlight the importance of metabolic contributions to its histopathological, molecular, and biochemical dyshomeostases (de la Monte, 2014; 2019; de la Monte et al., 2019; Kandimalla et al., 2017; Stanley et al., 2016). Along with dysregulated glucose metabolism itself, recent studies also demonstrate abnormal insulin signaling early in the development of DSAD (Tramutola et al., 2020). This accompanies an early-onset, disproportionately elevated occurrence of type 1 diabetes in people with DS (Aitken et al., 2013; Gillespie et al., 2006; Mortimer and Gillespie, 2020). Interestingly, type 2 diabetes in people with DS appears to be lower than in the general population (Esbensen, 2010; Jørgensen et al., 2019) despite sometimes substantial, sedentary dysmetabolic and lifestyle risk in aging (Agiovlasitis et al., 2020; Pape et al., 2021).

One early feature of diabetes is insulin resistance (IR), broadly studied in muscle and other tissues. Recent studies have shown that IR in the brain of neurotypical individuals matched on diabetes status was associated with AD neuropathology and cognitive function (Arvanitakis et al., 2020). Given that diabetes may cause vascular complications in many organs, it is not surprising that brain infarcts may be associated with diabetes and IR, and that IR in the periphery is related to cerebrovascular disease (Lee et al., 2016). Recently, an association of IR with cerebrovascular disease was reported in postmortem neurotypical human brains, a finding that links brain metabolism and function (Arvanitakis et al., 2021). Furthermore, in AD patients, CAA-related microbleeds are found along with gray matter atrophy and glucose hypometabolism, in positive correlation with cognitive function (Samuraki et al., 2015). In DS, brain IR develops early, in association with mitochondrial defects and loss of synaptic proteins, all of which may promote the development of AD (Barone, 2022; Tramutola et al., 2020), but more evidence for involvement in cerebrovascular disease is still needed.

Most strikingly, dysmetabolic risk factors including elevated triglycerides, total cholesterol, and central adiposity occur more frequently in people with DS despite lower rates of cardiovascular pathologies such as atherosclerosis and hypertension (Draheim et al., 2010; Wiseman et al., 2015; Zigman et al., 2007). This disconnect of metabolic and vascular features in people with DS contrasts with the typical concordance of dysmetabolic and vascular risk observed in the neurotypical population, where these factors in the absence of AD neuropathology can contribute to cognitive decline. Infarcts and vascular dementia, are relatively rare in DSAD compared to LOAD (Wiseman et al., 2015).

Cerebral glucose metabolism – a measure of metabolic dysfunction

Cerebral glucose metabolism can provide important insights into AD-related brain metabolic dysfunction in people with DS. Numerous studies have reported higher levels of glucose metabolism measured by FDG-PET in younger non-demented adults with DS (Azari et al., 1994; Cutler, 1986; Haier et al., 2003; Lengyel et al., 2006; Matthews et al., 2016; Schwartz et al., 1983) compared to similarly aged neurotypical adults (Schapiro et al., 1992). Most of these studies show increased glucose metabolism in prefrontal, sensorimotor, and inferior temporal/entorhinal cortices, in addition to the thalamus. Haier and colleagues (2008) also show that increased glucose metabolism is linked to decreased gray matter volume in the temporal cortex (parahippocampus/hippocampus), suggesting that hypermetabolism non-demented adults with DS may be an early compensatory response to neuronal loss (Haier et al., 2008). However, as evidence of cognitive decline or dementia emerges, FDG-PET studies consistently indicate a loss of glucose metabolism, particularly in posterior brain regions including posterior cingulate cortex, hippocampus, parietal, and temporal cortex (Azari et al., 1994; Cutler, 1986; Head et al., 2018; Lao et al., 2018; Matthews et al., 2016; Neale et al., 2018; Rafii et al., 2017; Rafii et al., 2015; Sabbagh et al., 2015; Schapiro et al., 1992; Schwartz et al., 1983; Zammit et al., 2020).

Many studies have now shown a link between brain regions where glucose metabolism declines with age and the emergence of AD pathology. Specifically, reduced glucose metabolism in older adults with DS and dementia is associated with decreased cortical

volumes (Matthews et al., 2016), increased amyloid PET binding (Lao et al., 2018; Matthews et al., 2016) and increased tau PET binding (Rafii et al., 2017). An exception to negative correlations between amyloid accumulation (amyloid PET) and metabolism (FDG-PET) is in the putamen, which is affected early during aging in DS where higher amyloid binding is linked to higher glucose metabolism (Zammit et al., 2020). This finding corresponds with recent amyloid PET studies in people with DS suggesting that striatal subcortical regions disproportionately accumulate early amyloid as in ADAD, but unlike LOAD (Cohen et al., 2018). Recent work by Fortea and colleagues (2021) further suggests that the presence of the *APOE*4 allele, one of the strongest risk factors for AD, shifts brain glucose hypometabolism to younger ages in people with DS (Bejanin et al., 2021).

Critically, disordered glucose metabolism observed in DSAD (Haier et al., 2003; Zammit et al., 2020) could reflect more than simply neurodegeneration alone, in contrast with some prevailing, common interpretations of glucose hypometabolism in sporadic AD (Jack et al., 2018; Jagust, 2018). This possibility remains to be examined in detail in DSAD; however, accumulating evidence suggests this to be the case in sporadic, euploid LOAD. Specifically, AD-associated changes in cortical glucose metabolism impact primate-specific (if not human-specific) neocortical metabolism via aerobic glycolysis and associated biosynthesis (Bauernfeind and Babbitt, 2014; Bauernfeind et al., 2014; Goyal et al., 2020; Terada et al., 2020; Terada et al., 2021; Vlassenko et al., 2018; Vlassenko et al., 2010). These AD-associated changes are also dynamically hypo- and hyper-metabolic in the sequence of advancing cognitive decline (Ashraf et al., 2015; Corriveau-Lecavalier et al., 2019; Dickerson et al., 2005), spare (if not favor) ketone body fuel metabolism (Castellano et al., 2019; Castellano et al., 2015; Croteau et al., 2018; Cunnane et al., 2020), and exist in white matter tracts apart from neuronal cell bodies ultimately subject to degeneration (Roy et al., 2020).

Recent imaging studies targeting the synaptic density/ neurodegenerative marker synaptic vesicle glycoprotein 2A (SV2A) most directly suggest that glucose hypometabolism in LOAD does not directly correspond to neurodegeneration. In one study, the neocortex, but not medial temporal lobes, demonstrated glucose metabolic deficits in excess of those accounted for by neurodegeneration alone (Chen et al., 2021). Further studies should address if similar interregional neurometabolic dissociations can be observed in emerging DSAD, especially as they relate to complex patterns of dynamic change and homoeostasis, rather than dysmetabolism associated with frank cortical atrophy itself. Importantly, this could include or be mediated by diffusible signaling molecules such as insulin.

How does trisomy 21 contribute to metabolic dysfunction in DSAD beyond the role of *APP*?

Genetic overexpression of the *APP* gene explains the substantial cortical amyloidosis observed in aging adults with DS. *APP* overexpression may also precipitate downstream proteopathies (i.e. neuritic Aβ plaques, neurofibrillary tangles), neurodegeneration, and cognitive deficits in these adults as they age (Doran et al., 2017; Head et al., 2012; Lott and Head, 2005; Teller et al., 1996). Supporting the importance of *APP* gene dosage in DSAD, two case studies have reported cognitive sparing in aging adults with DS who

possessed otherwise euploid copy number for *APP* (Doran et al., 2017; Prasher et al., 1998). Interestingly, recent findings challenge whether overabundant APP production alone is sufficient or necessary to initiate and drive cognitive decline in DSAD (Ovchinnikov et al., 2018; Wiseman et al., 2018) based upon work in mouse models of DS and induced pluripotent stem cell (iPSC) derived from DS participants. Evidence for successful cognitive aging, hereby considered as a lack of decline in cognitive or functional capacities indicative of dementia, in humans with DS is limited, but one case with complete, non-mosaic trisomy 21 has been described based on cognitive monitoring, without biomarker assessment (Krinsky-McHale et al., 2008). Thus, although there is strong evidence that *APP* overexpression in aging people with DS drives AD, it will be important to consider additional mechanisms and genes (Table 1).

Of the approximately 284 protein coding, predicted, and pseudo-genes on chromosome 21 (Gardiner and Davisson, 2000; Hattori et al., 2000), several are directly and indirectly involved in metabolic processes. Within the Down Syndrome Critical Region (DSCR), these include the holocarboxylase synthetase (*HLCS*) gene involved in the activating conjugation of biotin to carboxylase enzymes which metabolize lipids, proteins, and carbohydrates. This region of chromosome 21 also encodes the gene phosphatidylinositol glycan anchor biosynthesis class P (*PIGP*), which participates in inositol-phospholipid anchor formation where its dysfunction has been linked to several blood disorders. Additionally, the gene encoding the enzyme cystathionine beta-synthase (*CBS*) localizes to this same genomic region of chromosome 21 and participates in homocysteine, transulfuration, and folate biochemical pathways (Iacobazzi et al., 2014). Other genes present on chromosome 21 outside the DSCR encode components of glucose metabolism (phosphofructokinase liver type, *PFKL*; FAM3 metabolism regulating signaling molecule B, *FAM3B*) and lipid metabolism (lipase 1, *LIPI*; 1-acylglycerol-3-phosphate O-acyltransferase 3, *AGPAT3*) in addition to redox-associated genes (superoxide dismutase, *SOD1*; glutathione peroxidase pseudogene 2, *GPX1P2*). Of particular interest, *PFKL* regulates the second of three enzymatically rate-limiting steps of glycolysis by catalyzing the phosphorylation of fructose-6-phosphate to fructose-1,6-bisphosphate. This liver-expressed isoenzyme of phosphofructokinase is also active in the brain. In DS, *PFKL* is overexpressed in a manner consistent with the anticipated 3:2 trisomic gene dosage ratio and has been associated with glucose dysmetabolism in AD broadly (Bigl et al., 1996; Elson et al., 1992; Elson et al., 1994; Sims et al., 1987).

Overproduction of phosphofructokinase resulting from triplication of *PFKL* may also explain the faster brain glucose metabolic rate seen in younger individuals with DS (Lengyel et al., 2006), but the reasons for glucose *hypo*metabolism in older adults with DS described previously and especially those with LOAD remains unclear. These similarities in brain glucose dysmetabolism suggest a possible common final pathway despite and perhaps as a function of dissociable genetic contributions across predisposing etiologies in AD. Future investigations in this population might consider mechanistically how the development of cognitive decline in AD represents both the incidence of “progressive proteopathies with many metabolic spectators,” yet also a “progressive metabolic disorder with associated proteopathies” in aging. In this capacity, *APP* triplication could directly or indirectly

modulate several interesting and metabolically relevant genes on chromosome 21 possibly important in AD pathogenesis.

Chromosome 21 also encodes several genes which may contribute to insulin dyshomeostasis observed in both LOAD and DSAD, specifically as these relate to the elevated risk of type 1 diabetes in DS. This may occur through their effect of indirectly increasing the genetic penetrance of human leukocyte antigen (HLA) risk haplotypes associated with type 1 diabetes overall (Aitken et al., 2013; Gillespie et al., 2006; Labudova et al., 1999; Mortimer and Gillespie, 2020). Specifically, the chromosome 21 gene Down Syndrome Critical Region Gene 1 (*DSCR1, RCAN1*), when overexpressed in rodent models, has been associated with pancreatic β-cell mitochondrial dysfunction, decreased ATP synthesis, and blunted glucose-stimulated insulin secretion like that seen in people with DS, who also demonstrate increased levels of *DSCR1*-mediated oxidative stress (Helguera et al., 2013; Peiris et al., 2016). It remains to be seen if these same risk genes or gene × gene interactions moderate cognitive trajectories in aging individuals with DS. This includes the consideration of insulin dyshomeostasis specifically as a driver of AD and DSAD.

Bioenergetic dyshomeostasis: cause or consequence of DS and AD?

Because DS itself is rarely heritable, it might be possible that those parental and sporadically heritable genetic factors leading to the birth of a person with DS might also relate to AD outcomes in parents (particularly mothers), but possibly more distant family relations. There is some support for this notion of joint overrepresentation of DS and LOAD within these families (Petronis, 1999) but see also: (Berr et al., 1989). Thus, the genetic architecture and associated systems biology underlying the shared risk of DS and AD remains incompletely considered across LOAD and DSAD and potentially dissociable from trisomy 21 gene dosage effects themselves. Aneuploidy itself almost certainly contributes directly to the cognitive decline in DS through the copy number expansion of genes such as *APP*. Overexpression of chromosome 21 genes consequent to trisomy and resulting in age-associated neurodegeneration may thus represent a second, *de novo* genomic insult following from or possibly recapitulating early developmental vulnerabilities to DS within gametes and fertilized, reproductive tissues undergoing active mitosis. Another compelling line of evidence linking DS and maternal biology shows there is an increased risk of AD in mothers of DS adults, particularly those who completed such pregnancies prior to age 35 (Kline et al., 2000; Schupf et al., 1994; Schupf et al., 2001). This represents a four to five-fold elevated risk of AD neurodegeneration specifically compared to mothers of neurotypical children, but not fathers (Schupf et al., 2001). Advancing maternal age has also been linked to impaired cognitive aging in women and their chromosomally typical offspring (Mosconi et al., 2017; Mosconi et al., 2007; Mosconi et al., 2012; Rahman et al., 2020; Scheyer et al., 2018).

One possible mechanism linking risk of AD in mothers and their children with DS could be mitochondrial dysfunction associated with abnormal aging. There is a rich literature indicating mitochondrial and reactive oxygen species (ROS) dyshomeostasis in DS and DSAD (Busciglio and Yankner, 1995; Coskun and Busciglio, 2012; Lott, 2012; Pagano and Castello, 2012; Perluigi and Butterfield, 2012), which implicates metabolic and bioenergetic

processes as drivers of emerging cognitive vulnerability (Cunnane et al., 2020; Zilberter and Zilberter, 2017). Consistent with complex, sporadic heritability, these metabolic and bioenergetic processes demonstrate potential maternal imprinting effects (Mosconi et al., 2010; Mosconi et al., 2011; Schupf et al., 1994; Schupf et al., 2001). Schon and colleagues suggest the bioenergetically demanding process of typical euploid chromosomal segregation within developing oocytes may itself depend upon the integrity of mitochondria and mitochondrial genomes within these reproductive cells (Schon et al., 2000). This is consistent with the hypothesis that subsequently emerging AD may mechanistically recapitulate heritable, early developmental risk predisposing toward DS. These same mechanisms have been considered by Mosconi and colleagues in AD, where maternal, but not paternal, family history of AD predisposes individuals toward a diversity of dementia-associated biological risk (Mosconi et al., 2010; Mosconi et al., 2007; Mosconi et al., 2011; Mosconi et al., 2012). Critically, these processes in AD progression are frequently associated with mitochondrial and bioenergetic dysmetabolism within an abnormally aging brain-peripheral metabolic axis spanning multiple scales of systems biology (Astarita et al., 2010; Astarita and Piomelli, 2011; Bassendine et al., 2020; Camandola and Mattson, 2017; Demetrius and Driver, 2013; Folch et al., 2019; Ghosh et al., 2018; Kim and Mook-Jung, 2019; Morris et al., 2019; Neth and Craft, 2017; Peng et al., 2020; Qi et al., 2019; Raz and Daugherty, 2018; Wang et al., 2017). This metabolic axis may jointly mediate A) critical embryological events in DS development and B) sporadic genetic risk for abnormal aging relevant to LOAD or DSAD.

A similar pattern of complex heritable liability may exist in the overlap between DS, AD, and metabolic syndrome. Specifically, diabetic mothers may be at higher risk of giving birth to infants with DS (Narchi and Kulaylat, 1997) (although see Martinez-Frias and colleagues: (Martínez-Frías et al., 2002)). Consistent with mitochondrial and bioenergetic heritable risk in DS and DSAD, intergenerational findings may also suggest that dysmetabolism could initially follow from elevated sporadically heritable risk dissociable from, but predisposing toward trisomy 21 during early embryonic development. Were this the case, mothers, and particularly young mothers of children with DS might demonstrate biological differences compared to parents of euploid children. Furthermore, these differences might anticipate and resemble changes observed in the evolution of LOAD and DSAD.

Peripheral lymphocytes from young mothers of DS infants contain several markers of genome instability and premature aging, including a higher frequency of micronuclei, telomere attrition, and global changes in DNA methylation patterns (Albizua et al., 2015; Božović et al., 2015; Migliore et al., 2006). Deficits in maternal folate metabolism and its epigenetic regulation have been similarly reported in this population relative to control mothers (Coppedè, 2016; Coppedè et al., 2016). All of these biological systems which are implicated in the pathophysiological evolution of LOAD, ADAD, and DSAD represent metabolically intensive, anabolic processes maintained at substantially catabolic, bioenergetic cost in vulnerably aging adults (López-Otín et al., 2016; Mattson and Arumugam, 2018; Nitsch et al., 1992; Rijpma et al., 2017; Saez-Atienzar and Masliah, 2020; Vlassenko and Raichle, 2015; Wurtman, 2011; 2014; Wurtman et al., 1985; Zhang and Raichle, 2010). Critically, these dyshomeostatic processes might pathologically self-

organize to a point of irreparable failure which is incompatible with successful cognitive aging in people with DS and leads to clinical and neuropathological AD.

Conclusions

Although Jerome Lejeune is best known for helping to establish the trisomic basis of DS, his later work focused on DS and DSAD cognition in metabolic terms (Lejeune, 1990; Lejeune et al., 1990). This perspective remains understudied in DSAD, but is seeing application now in recent perspectives in LOAD (Goyal et al., 2020; Pettegrew et al., 1988; Rijpma et al., 2018; Vlassenko et al., 2018). Metabolic deficits are a prevalent feature of the AD pathobiological process, including those changes specifically accompanying DSAD (Gross et al., 2019; Mapstone et al., 2020; Pecze et al., 2020; Pecze and Szabo, 2021). Importantly, these findings not only suggest read outs of emerging metabolic dysfunction, but might also advance specific therapeutic strategies to normalize and support vulnerable metabolic pathways in DS aging (Fortier et al., 2021; Soininen et al., 2021; Wurtman, 2011). Lejeune's observations on metabolic dysfunction in DSAD parallel a longstanding literature investigating metabolic therapeutics in AD (Cunnane et al., 2011; Cunnane et al., 2020; Jennings et al., 2020; Nitsch et al., 1992; Rijpma et al., 2017; Wurtman, 2011).

The recent development of advanced metabolomics technologies has prompted the reconciliation of molecular and metabolic perspectives on multifactorial diseases of abnormal aging including AD and DSAD (McKnight, 2010). This accords with recently proposed translational policy and funding initiatives to advance the study and treatment of biologically complex, refractory human diseases through data-intensive technologies including -omics methods (Collins et al., 2021). Omics-scale measurement approaches including metabolomics have allowed researchers to explicitly pursue metabolic hypotheses of the kind suggested by Lejeune and others in DS and LOAD. These metabolic considerations have, however, only been recently considered in their specific contributions to the pathogenesis and dynamic course of DSAD.

More broadly in abnormal aging, the catabolic functions of metabolism could often belie the anabolically vital biosynthetic and signaling roles often served by these same biomolecules in support of prolonged cognitive resilience. Critically, all such metabolic programs may become limited as a function of DS, advancing AD, or their combination in pathological aging. This presents a particular challenge because the extent, scale, duration, and scope of these changes in the DSAD pathobiological process remain unclear. The current limits on this knowledge, however, also suggest many opportunities to identify novel therapeutic targets and biomarkers in LOAD and DSAD specifically.

Amyloid-attenuating pharmaceutical therapies have recently been approved by the FDA; however, their efficacy to robustly halt, reverse, or stabilize emerging cognitive deficits in prodromal LOAD remains to be clarified in coming years (Nisticò and Borg, 2021). This only encourages the pursuit of Lejeune's assertion in DS that: "[…] victory over the neural disturbances resulting from the genetic overdose of trisomy 21 would very likely also lead to a cure or to a prevention of Alzheimer [*sic*] dementia" (Lejeune, 1990). For DS and other dissociable, AD-risk-imposing etiologies, these dynamics of biologically and metabolically

"futile cycles" could accompany, if not drive dementia progression in which "compensations for failure" precipitate biologically non-random "failures of compensation."

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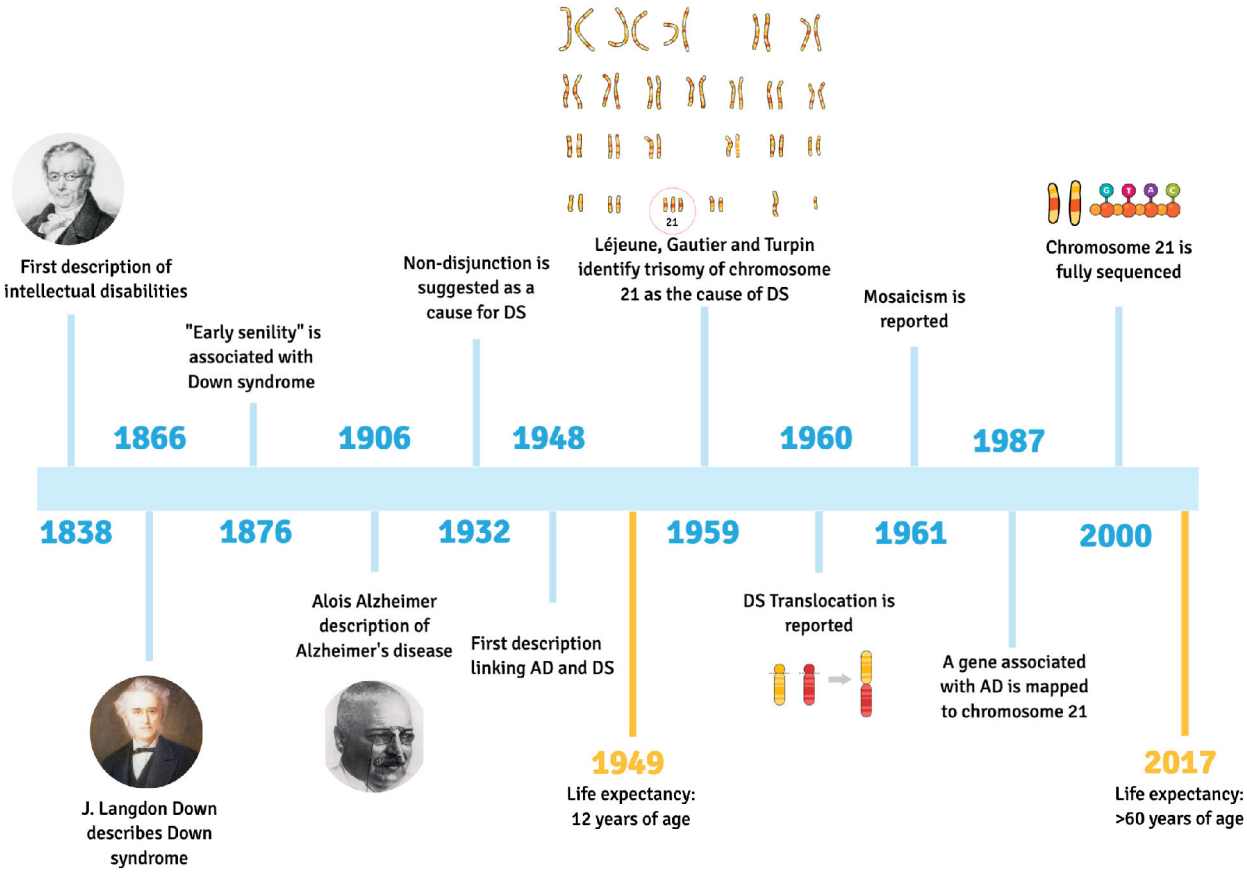

Figure 1. Down syndrome research and life expectancy.

Timeline of events from the first description of intellectual disabilities, in 1838, to the complete sequencing of Chromosome 21 in the year 2000. Life expectancy improved from 12 years of age in 1949, to more than 60 years of age in 2017. Created with MindtheGraph.com.

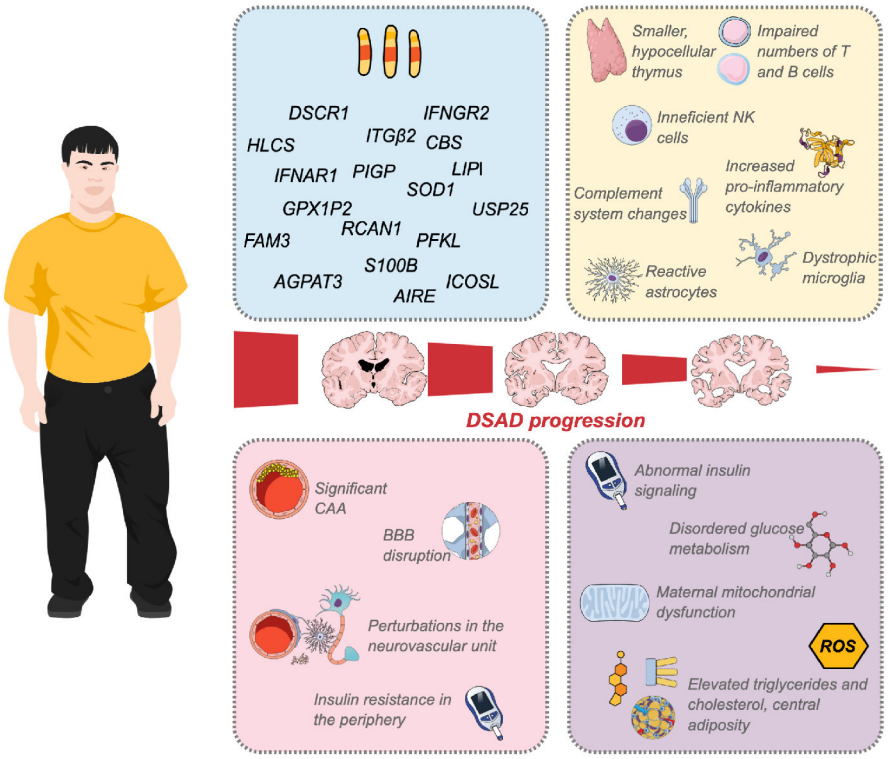

Figure 2. Systems and mechanisms altered in Down syndrome leading to DSAD.

Immune- and metabolism-related genes encoded on Chromosome 21 may lead to and potentially explain the altered expression and function of cells and mediators in DS. Disturbances in innate and adaptive immunity and inflammatory response may include a smaller and hypocellular thymus gland; impaired numbers of T and B lymphocytes, increasing the propensity to autoimmune disorders; changes in the function and counts of NK cells; overexpression of inflammatory cytokines; increased C1q in the brain and deficiency of complement factors in blood; and, ultimately, changes in the phenotypes of essential cells like microglia and astrocytes. In the vascular system, CAA is a critical component of AD pathogenesis, and frequently found in aged people with DS. Its consequences may include disruptions in the BBB and neurovascular unit. In the periphery, insulin resistance can also contribute to cerebrovascular disease. Dysregulated insulin signaling and glucose metabolism are observed early in the development of DSAD. Additionally, maternal mitochondrial dysfunction, ROS dyshomeostasis, and dysmetabolic risk factors represented by elevated triglycerides, cholesterol, and adiposity, may promote the development of AD in DS. Created with MindtheGraph.com.

Table 1.

Selected Human Chromosome 21 Genes with Metabolic Ontologies

***Gene Name* (*HGNC* ID)**	**Cytoband Coordinates**	**DSCR* Locus?**	**Metabolic Gene Ontologies**
holocarboxylase synthetase (***HLCS***)	21q22.13	Yes	biotin metabolism lipid, protein, and carbohydrate carboxylation
phosphatidylinositol glycan anchor biosynthesis class P (***PIGP***)	21q22.13	Yes	lipid metabolism
cystathionine beta-synthase (***CBS***)	21q22.3	Yes	homocysteine, transulfuration, and folate metabolism
phosphofructokinase liver type (***PFKL***)	21q22.3	No	glucose metabolism
FAM3 metabolism regulating signaling molecule B (***FAM3B***)	21q22.3	No	glucose metabolism
Lipase I (***LIPI***)	21q11.2	No	lipid metabolism
1-acylglycerol-3-phosphate O-acyltransferase 3 (***AGPAT3***)	21q22.3	No	lipid metabolism
superoxide dismutase (***SOD1***)	21q22.11	No	redox metabolism
glutathione peroxidase pseudogene 2 (***GPX1P2***)	21q21.3	No	redox metabolism
regulator of calcineurin 1 (**RCAN1**)	21q22.12	No	insulin homeostasis

*DSCR Down Syndrome Critical Region on Chromosome 21.