The Princeton Journal of Interdisciplinary Research
ISSN 3069-8200

Connections between Down Syndrome and the Development of Alzheimer's Disease

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Abstract

Down syndrome (DS) results in a wide array of phenotypes due to triplication of human chromosome 21 (HSA21), including cognitive deficits, craniofacial abnormalities, increased risk of leukemia, and cardiovascular defects. DS is perhaps the most complex set of genetic anomalies that is consistently survivable, and it is the largest genetic cause of intellectual disability. HSA21 contains over 200 protein-coding genes and many non-coding elements that may alter gene expression across the genome, and dosage changes to certain genes are strongly linked with DS pathology. Importantly, individuals with DS exhibit widespread Alzheimer's Disease (AD) pathology, and triplications of HSA21 genes such as *APP*, *DYRK1A*, and *S100B* exacerbate neurodegeneration as DS individuals age. These facets have been studied using mouse models that replicate pathological patterns observed in humans with DS. Both mouse models and DS individuals show stereotypic hallmarks of AD such as the formation of Aβ plaques and tau-based neurofibrillary tangles. Here, the shared mechanisms of DS and AD are

The Princeton Journal of Interdisciplinary Research
ISSN 3069-8200

discussed, with particular emphasis on biological pathways that are important for cognition, plasticity, and neural survival, including amyloid processing, tau pathology, neuroinflammation, and oxidative stress. Analysis of these factors suggests multiple common links between DS and AD, and understanding shared mechanisms will be key for improved diagnosis and treatment in these disparate, yet linked conditions.

Keywords: HSA21, Alzheimer's Disease, mouse models, neurodegeneration, Alzheimer's biomarkers

Introduction

Down syndrome (DS) is a collection of phenotypic manifestations associated with a partial or full triplication of human chromosome 21 (HSA21; Antonarakis et al., 2004). A trisomy of HSA21 is the most commonly occurring autosomal aneuploidy that allows for survival, possibly due to HSA21 being the smallest human chromosome (Watkins et al., 1987). DS is the largest genetic cause of intellectual disability, and the number of global prevalent cases has increased from 1.26 million in 1990 to 1.58 million in 2019 (Chen et al., 2022) accounting for roughly 1 in every 700 to 1,000 live births globally (Satgé et al., 2018). The mean life expectancy for individuals with DS is lower than the general population (de Graf et al., 2017), and the increasing global prevalence of DS is due to medical advancements that have led to higher rates of childhood survival, extending life expectancies in DS individuals (Verstegen et al., 2019), with increasing integration into society. As a consequence, various phenotypes associated with longer lifespans, such as the development of Alzheimer's disease (AD) in the DS

population become magnified with age. Approximately two-thirds of people with DS by the age of 60 develop dementia (McCarron et al., 2014) and therefore understanding the mechanisms of cognitive dysfunction and dementia in DS is important for improvements to quality of life. In addition, DS provides a unique opportunity to study dementia associated with AD.

Phenotypic defects associated with DS result from impaired development due to the altered expression of HSA21 genes that exert multiple constraints on physiology, such as the reduced rate of proliferation of trisomic cells compared to euploid counterparts (Contestabile et al., 2007). People with DS exhibit various physical and mental health conditions, including cognitive deficits, early AD, short stature and fingers, hypotonia, atlantoaxial instability, small, low-set ears, epicanthic folds, flat nasal bridges, flat occiput/ brachycephaly, small mouths, and upslanting palpebral fissures, to variable extents (Antonarakis et al., 2020). Therefore, studying people with DS is important for understanding a plethora of developmental and neurological conditions.

Cognitive deficits in DS vary widely despite overall similarities in intelligence quotient (IQ) scores (Onnivello et al., 2022). Intellectual challenges associated with DS include deficits in long-term and short-term verbal memory, as well as difficulties in both verbal and nonverbal modalities of working memory. Individuals with DS who are at or under the age of 5 performed similarly to typically developing (TD) mental age-matched peers on nonverbal long-term memory (LTM) tests, such as deferred imitation tasks, with short delays of 24 hr (Roberts & Richmond, 2015), but demonstrated significant impairments in the same task with longer delays

of around 1 month (Milojevich & Lukowski, 2016). Few studies have been conducted on the short-term memory (STM) performance of children under the age of 5; adolescent tests demonstrate severely impaired verbal STM (Marcell & Weeks, 1988), yet relatively strong nonverbal STM performance when compared to other intellectual disability (ID) groups (Carney et al., 2013). Additionally, little research has been done on the working memory (WM) abilities of children with DS under the age of 5 and older adults, but adolescents have been shown to have significant impairments in the ability to process and manipulate information (Lanfranchi et al., 2009). Both nonverbal and verbal STM abilities were found to become poorer with age. Furthermore, geriatric individuals with DS performed worse than all other groups (TD and ID) on nonverbal LTM tests (Dalton et al., 1974), paving the way for questions regarding the gradual cognitive decline in individuals with DS across development.

LTM involves the encoding, storage, and retrieval of memories after a delay, STM depends on the temporary storage (often within seconds) and immediate recollection of details, and WM is similar to STM in that it relies on temporary storage, with the difference being the manipulation or processing of the stored information (Godfrey & Lee, 2018). Some examples of tests used include the California Verbal Learning Test (CVLT) for verbal LTM (Delis et al., 1987) the Rey Complex Figure Test (RCFT) for nonverbal LTM (Meyers & Meyers, 1995), and the verbal STM Digit Span test and nonverbal STM Corsi Span test, and verbal and nonverbal WM tests involving the reverse recollection of a sequence of digits or letters, or of blocks respectively. It is important to note that while studies may determine trends in DS phenotypes

with regards to memory or cognition, not all individuals with DS experience the same challenges nor to the same extent.

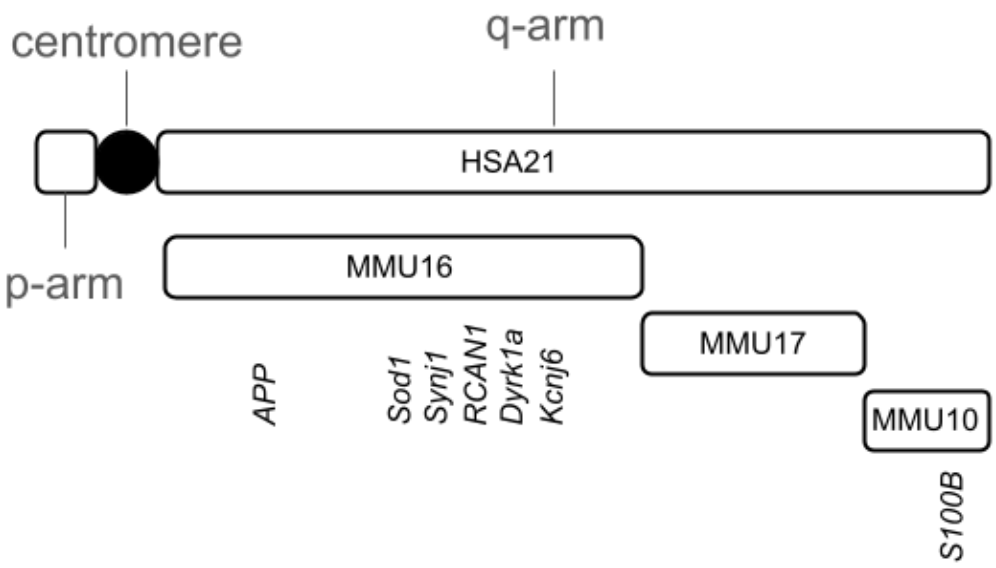
Mechanisms of Down Syndrome

According to the 'gene dosage' hypothesis, phenotypes associated with DS manifest due to the overexpression of individual genes caused by an imbalance in gene dosage (Pritchard & Kola, 1999). As such, several genes have been characterized in DS individuals and their ability to reproduce features of DS in mouse models. Several DS mouse models are particularly useful, since mouse chromosomes (MMU) 10, 16, and 17 contain syntenic regions of HSA21 gene orthologs (Herault et al., 2017) (**Figure 1**). The expression of genes associated with DS is also thought to be influenced by various other genetic components, so the manipulation of these elements in testing is highly valuable to discover nuances in the impact of genes in establishing the phenotypes of DS. As such, the availability of mouse models with varying genetic modifications is advantageous.

The Princeton Journal of Interdisciplinary Research
ISSN 3069-8200

Figure 1

Human chromosome 21 genes and their locations on mouse chromosomes



Prominent DS Mouse Models

The most widely utilized mouse model till date is Ts65Dn (Davisson, 1990). It contains a genomic segment that is approximately 13 Mb on MMU16 equating to roughly 55% of the orthologous genes of HSA21 triplicated (Liu et al., 2011). The advantage of Ts65Dn is that it is an aneuploidy model; however, there are severe disadvantages as this mouse model has 46 extra genes that are found on MMU17 that are irrelevant for DS (Duchon et al., 2011; Duchon et al., 2022). Additional mouse models, such as Ts1Cje and Ts1Rhr, contain triplications of shorter segments of MMU16 that are syntenic to HSA21 (Delabar et al., 1993) (Ts1Cje, contains triplications of 37% of MMU16 gene orthologs of HSA21; Olson et al., 2004). Other attempts to

model DS in mice have used transchromosomic models that introduce HSA21 into mouse cells, leading to the development of the Tc1 model. However, while these mice exhibit features associated with DS, such as impairment in learning and memory, some mouse cells do not carry the chromosome (O'Doherty et al., 2005), making the resulting mice mosaics and therefore unusable for testing. Additionally, mouse models Dp(10)1Yey/+, Dp(16)1Yey/+, and Dp(17)1Yey/+ have been developed to carry duplications of the entire syntenic regions of HSA21 on MMU10, MMU16, and MMU17 (Yu et al., 2010) using Cre/ *loxP*-mediated chromosome engineering, which allows for the production of models containing chromosomal segments specified by inserted endpoints (Yu & Bradley, 2001). Furthermore, a cross of these three mice produces a model containing triplications of all syntenic regions of HSA21 (Liu et al., 2011). However, not all mouse models containing three copies of orthologous HSA21 genes result in DS-associated phenotypic changes. The Dp1Tyb model (Lana-Elola et al., 2016), for example, does not exhibit increased endosome number or volume, raised APP (amyloid precursor protein) production, or Aβ production and associated Aβ42/ Aβ40 ratios (Cannavo et al., 2022), demonstrating the possibility that triplications in related genes may not always be sufficient to cause expected pathological changes.

Mouse models recapitulate a wide range of phenotypes associated with DS. The severity of these phenotypes depends on the mouse model and the variability is likely due to cross-species differences of modeling human disease in mice. DS mice show a range of anomalies in cognition, cardiac defects, craniofacial abnormalities, immune system regulation, and other phenotypes that are related to the human condition (Herault et al., 2017). These mice are

defective in short-term and long-term memory and learning impairments in various behavioral tasks, such as the Morris water maze, which tests mice on their ability to escape a swimming arena with the guidance of visual cues (Vorhees et al., 2006), and other tasks involving novel object recognition (NOR).

Genomic Components Associated with DS

Significant Coding Genomic Components

DYRK1A and RCAN1. Both DYRK1A (dual specificity tyrosine-phosphorylation-regulated kinase 1A) and RCAN1 are HSA21 genes, which, when overexpressed, lead to phenotypes of DS (Liu et al., 2008; Parra et al., 2018). For example, they inhibit the activity of the transcription factor NFATc (nuclear factor of activated T cells, cytoplasmic 1) (Stefos et al., 2013), which plays a significant role in the development of the vertebrate nervous system (Arron et al., 2006). Whereas DYRK1A phosphorylates NFATc to reduce its function, RCAN1 encodes for calcipressin 1 (Fuentes et al., 1995), a protein that inhibits the phosphatase functionality of calcineurin A, which generally dephosphorylates NFATc. Moreover, an increased gene dosage of RCAN1 results in impaired hippocampal LTP in DS (Xing et al., 2013).

OLIG1 and OLIG2. The overdosage of oligodendrocyte transcription factor 1 (OLIG1) and OLIG2 in the ventricular and subventricular zones of Ts65Dn mouse brains results in the increased generation of parvalbumin and somatostatin interneurons in cortical and hippocampal regions (Chakrabarti et al., 2010). As a result, mice exhibit imbalanced production of excitatory and inhibitory neurons as well as defects in the development and maintenance of synapses

(Haydar & Reeves, 2011). It has been shown that remedying the overdosage of OLIG1 and OLIG2 has worked to restore the excitatory/ inhibitory neuronal balance in Ts65Dn mice (Dierssen, 2012).

KCNJ6 and SOD1. KCNJ6 is another gene located on HSA21, and it encodes for the G protein-activated inwardly rectifying potassium channel 2 (GIRK2). A triplication of this gene in mice results in deficits in learning and memory associated with the hippocampus as well as hippocampal LTP (Cooper et al., 2012). Similarly, superoxide dismutase 1 (SOD1) is another HSA21 gene associated with DS. Interestingly, increased expression of SOD1 counteracts pathology caused by amyloid precursor protein (APP) overexpression (Carlson et al., 1997), and increased activity of the SOD1 enzyme is correlated with improved memory capabilities in DS adults (Zis et al., 2012).

Non-coding Genomic Factors

Additionally, non-coding genomic components have been found to play a role in DS pathogenesis. These include microRNAs (miRNAs) and PIWI-interacting RNAs (piRNAs). The regulation of miRNAs is essential in the appropriate transition of memories from short-term to long-term (Grinkevich, 2020). A disruption of this may therefore cause deficits in a DS individual's ability to store long-term memories. Furthermore, piRNAs play a critical role in the epigenetic expression or silencing of genes (Senti & Brennecke, 2010) which is likely to be harmed by overexpression.

The Princeton Journal of Interdisciplinary Research
ISSN 3069-8200

Impaired Excitatory-Inhibitory Balance in DS

Changes in cognition in DS are orchestrated via various cellular and molecular changes in brain cells. While some studies of DS report an increased number of interneurons (Chakrabarti et al., 2010), cells that modulate the firing of nearby neurons, and others suggest decreases (Huo et al., 2018), factors including the brain regions, types of tissue, and ages of individuals studied affect the results of these investigations. Regardless, changes in interneuron numbers contribute to aberrant neural signaling in DS (Giffin-Rao et al., 2022), likely disrupting the excitatory/ inhibitory balance and thus causing abnormalities in synaptic plasticity (Hanson et al., 2013). Ts65Dn mice have a reported decrease in the density of dendritic spines and an enlargement of spine heads (Belichenko et al., 2009). These mice also have significant long-term potentiation (LTP) impairment, specifically in the dentate gyrus (Siarey et al., 1997), a structure within the hippocampus crucial for learning and the formation of new memories. This is supposedly due to excessive inhibition caused by the dominance of inhibitory interneurons in mice (Kleschevnikov et al., 2004). Further studies of Ts65Dn mice have explored the effects of differentiation in myelination, ultimately finding that impairments in white matter function could lead to the pathology resulting from DS (Olmos-Serrano et al., 2016).

Alzheimer's Disease

AD is a neurological condition characterized by cognitive impairments (often amnestic) that may be familial (related to genetic mutations) or sporadic (influenced by both genetic and environmental factors) and is often acquired in midlife and late-life, with the exception of early-

onset AD. Decline in cognition is observed during these periods, but the buildup of molecules associated with AD pathology often begins one to two decades earlier (Jagust & Landau, 2021). Essentially, mild cognitive impairment (MCI), defined as the initial stage of cognitive decline in one or more facets to a degree that does not pose significant challenges to the individual (Peterson, 2004), is often the first symptom of general cognitive decline associated with AD. AD is also the most common cause of dementia, which is defined as cognitive impairment to an extent to which an individual faces extreme challenges in daily life. Furthermore, the prevalence of dementia (including cases not related with AD) was roughly 51.6 million in 2019 and is projected to increase to 152.8 million by 2050 (Li et al., 2022), making the investigation of factors that contribute to the onset and progression of AD a strategic healthcare priority.

Existing Therapeutics

Several pharmacological therapies have been tested for counteracting the progression of symptoms associated with AD. Three cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, have been approved in the USA and Europe for dementia, and they have shown capabilities of delaying dementia progression by over 6 months (Fink et al., 2018; Mohs et al., 2001). However, these drugs come with limited efficacy and side effects, including nausea, vomiting, and loss of appetite. Memantine, an NMDA receptor antagonist, is yet another drug approved in the USA. Although memantine, cholinesterases, and a handful of additional drugs do provide some benefit in slowing dementia progression, they do not have noteworthy impacts on

relieving existing AD pathology (Knopman et al., 2021). Therefore, finding new cures for AD is of utmost importance.

Developing novel therapeutics requires mechanistic understanding of disease biology to target efficacious pathways. Several theories have been proposed to underlie the mechanisms most closely linked with cognitive defects observed in individuals with AD and dementia. These include neurodegeneration via Aβ accumulation and tau aggregation, neuroinflammation, disruptions in autophagy, cortical network dysfunctions, and synaptic loss. These theories focus on varying mechanisms, yet all complement the idea that disruptions in neural functionality and connectivity are a main driver of neurodegeneration and related observable declines in intellectual capabilities in AD.

AD Pathology

Amyloid and Tau

Two of the hallmarks of AD are the buildup of plaques consisting of amyloid-β (Aβ) peptides as well as tau-containing neurofibrillary tangles (NFTs) in the brain (Knopman et al., 2021). Aβ, specifically $A\beta_{42}$, is highly relevant for AD pathology. Aβ is derived from APP following processing by β- and γ-secretases (Holtzman et al., 2011; Thinakaran & Koo, 2008) (**Figure 2**). It is produced in higher quantities with increased synaptic activity (Cirrito et al., 2005) and released outside cells as monomers (Holtzman et al., 2011). However, Aβ may form oligomers, increasing its likelihood to have toxic effects when interfering with various proteins, such as metabotropic glutamate receptor 5 (mGluR5) and N-methyl-D-aspartate (NMDA)

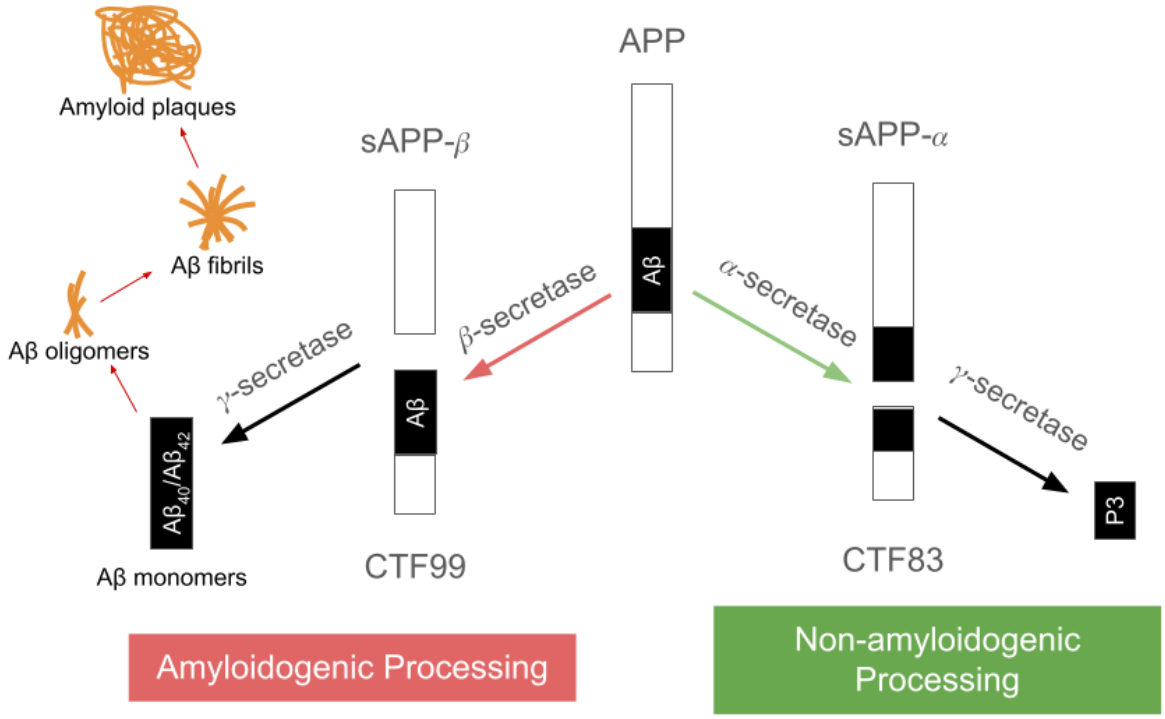
receptors, both of which modulate excitatory glutamatergic signaling (Spires-Jones & Hyman, 2014; Benarroch, 2018), or result in neurodegeneration via additional pathways.

Tau is a protein that stabilizes microtubules, which provide structural integrity to neurons. It exists in six isoforms based on the number of binding domains present (either 3 or 4), and the balance of the ratio of 3R and 4R tau species is critical to the maintenance of cognitive function (Goedert & Jakes, 2005). However, hyperphosphorylation severely impairs its ability to perform its function (Lindwall et al., 1984) by altering its conformations. As a result, microtubules become unstable and NFTs form, ultimately leading to neuronal death (LaPointe et al., 2009). Tauopathy in the medial temporal lobe is associated with cognitive decline in AD (Braak & Braak, 1991); interestingly, tau aggregations do not migrate to cortical areas in other lobes in the absence of Aβ (Jack et al., 2019; Ossenkoppele et al., 2016). Post-transcriptional modifications to tau may impact its patterns of uptake by glia and neurons as well as its tendency to aggregate.

The Princeton Journal of Interdisciplinary Research
ISSN 3069-8200

Figure 2

APP processing by α- and β-secretases



Neuroinflammation and Autophagy

Emerging evidence suggests the involvement of inflammatory pathways in AD involving microglia. Microglia are the brain's resident immune cells that prevent infection and cellular damage. The membrane permeabilization of microglial lysosomes is most directly linked to AD-associated neuroinflammation, which is a significant driver of AD-related declines in cognition. Lysosomal permeabilization events trigger the release of cathepsin B, which indirectly facilitates the release of interleukin (IL)-1β that causes neuroinflammation (Sarlus & Heneka, 2017; Lowry

& Klegeris, 2018). IL-1β is also linked with worsened rates of neurodegeneration in AD patients (Nakanishi, 2020).

Processes that remove damaged cellular components are important for healthy brain function. Autophagy is the process by which waste is removed and recycled within a cellular environment and is often activated as a result of nutrient or energy deficiencies. Common targets for autophagy include damaged or deteriorating organelles and protein aggregations (Levine & Kroemer, 2019); therefore, properly regulated autophagy can be neuroprotective in AD pathology (Moreira et al., 2010; Nixon, 2020). However, it is also possible that waste builds up in lysosomes, clogging neuronal waste management and ultimately exacerbating neurodegeneration.

Neural Network Connectivity

Recently, the role of neural network activity in the pathology of AD is becoming more prominent. Analyzing the activity of cortical networks and pathology associated with these may provide insights regarding patterns of Aβ deposition and NFT development. For instance, brain regions that are important for cognition, such as the entorhinal cortex, are functionally connected with association areas of the temporal, frontal, and parietal neocortex (Braak & Braak, 1991; Delacourte et al., 1999), and a dysfunction of these networks is present in symptomatic AD. Furthermore, the default mode network (DMN) is a highly active collection of brain areas that continues to function even whilst the individual is not engaging with their environment. Aβ deposition shows repeating patterns between individuals in these networks that work in concert

(Buckner et al., 2009), leading to the conclusion that synaptic activity is positively correlated with the rate at which Aβ builds up. On the other hand, the accumulation and spread of tau is based upon the patterns of function in cortical networks (Jones et al., 2017), with regions associated with existing tauopathy at higher risk of aggregate formation (Franzmeier et al., 2020; Sintini et al., 2021). The development of Aβ and tau aggregates in these networks and neighboring regions leads to a cascading loss of homeostasis that is central to neurodegeneration in AD (Jones et al., 2017).

Synapse Loss

Synapse loss is a key contributing factor to cognitive decline in AD (Terry et al., 1991). This is characterized by the loss of both presynaptic and postsynaptic sites as a result of extensive Aβ plaques in the extracellular space (Spires-Jones & Hyman, 2014; Spires et al., 2005), tau accumulation in the sites themselves (Zhou et al., 2017), and/ or immune overactivation involving excessive synaptic pruning and complement proteins (Brucato et al., 2020). Tauopathy may also alter synaptic homeostasis in a way that induces abnormalities in the activation patterns of neocortical pyramidal neurons, disrupting excitatory signaling in the AD brain (Menkes-Caspi et al., 2015). Interestingly, aberrant synaptic pruning by microglia and other components has been associated with early-onset AD (Wilton et al., 2019). C1q, which is a complement protein that prunes synapses by tagging them for removal by microglia, is observed at higher levels in DS individuals (Head et al., 2001), suggesting that excessive synaptic pruning may be a key factor in drastic synapse loss in AD.

The Princeton Journal of Interdisciplinary Research
ISSN 3069-8200

Mitochondrial Dysfunction

Mitochondrial dysfunction is a tremendous contributor to the age-related cognitive decline associated with AD. The brain requires the most energy of all organs in the human body. Since mitochondria are the sites of aerobic cellular respiration, their preservation is critical to the maintenance of typical cognitive performance. Regular mitochondrial function leads to the production and release of reactive oxygen species (ROS), which may have harmful impacts on other cellular components. Mitochondrial Aβ deposition impairs its ability to remove these natural byproducts (Petersen et al., 2008), causing significant oxidative stress. Deficits in energy impair synaptic function and disrupt critical cognitive processes such as memory formation that have high energy demands (Calkins & Reddy, 2011). This may underlie the short-term memory loss observed in individuals with AD or other amnestic diseases, since they are unable to meet the energy requirements necessary to transfer temporary memories to long-term storage. In addition, clearance of phosphocreatine (PCr), a compound that acts as an energy buffer during rapid cellular respiration, from the muscles is significantly associated with Aβ deposition, especially in the striatum (Beresford-Webb et al., 2025).

AD Mouse Models

As with DS, several mouse models exist that attempt to recapitulate the mechanisms of AD in a living organism. Unfortunately, mouse Aβ does not form aggregates like human Aβ due to a difference in 3 amino acids in the primary structures (Lv et al., 2013). Thus, mice used to model human patterns of Aβ aggregation and deposition contain point mutations, which are

insertions, deletions, or changes to specific nucleotides in their genetic sequences. A few examples of mutations to the APP gene that are used to induce human-like Aβ aggregation include the Swedish mutations (Mullen et al., 1992) as well as the *APP* Indiana (Murrell et al., 1991) and Iberian (Guerreiro et al., 2010) mutations. Along with mutating the *APP* gene in mice, transgenic models carrying human *APP* can be used to model patterns of human Aβ distribution. For example, the J20 (Mucke et al., 2000) model is transgenic, but also contains the Swedish and Indiana mutations. This model has significant Aβ accumulation between 5-7 months and plaque formation by 8-10 months of age in the hippocampus and neocortex. The J20 transgene disrupts the expression of *Zbtb20* (Tosh et al., 2018), which normally facilitates hippocampal development (Mitchelmore et al., 2002). Another model, 5XFAD (Oakley et al., 2006), has 3 *APP* mutations that are AD-causal and two in *PSEN1*. This model exhibits Aβ deposition at even 2 months of age, and is one of the only amyloid-based models to also display neuronal loss associated with patterns of plaque formation (Oakley et al., 2006).

Neuron loss associated with AD pathology is another important component that is measured in mice. Basal forebrain cholinergic neurons (BFCNs) produce acetylcholine, serving as the primary cholinergic provider for the cerebral cortex, hippocampus, and amygdala (Geula et al., 2021). Neuroinflammation, along with a loss of BFCNs and norepinephrine, which is strongly involved in the development of neuronal circuits (Saboory et al., 2020), is seen in Ts65Dn (Holtzman et al., 1996) and Dp(16)1Yey models (Lana-Elola et al., 2021). Dp(16)1Yey mice contain another gene, *USP25*, which is linked with significantly worsened AD-DS-like neuroinflammation in this model but not 5XFAD (Zheng et al., 2022). On the other hand,

Ts65Dn mice exhibit neuroinflammation with increasing age, likely due to increased levels of proinflammatory cytokines such as IL-1β (Farrell et al., 2022; Rueda et al., 2018). Mouse models for AD and DS display similar pathologies, including neuroinflammation and loss of cholinergic neurons, suggesting common pathways between the two conditions. An assessment of the nature of Aβ pathology in DS models is hindered by the differences in the primary structure of APP as discussed previously. Therefore, approaches that humanize APP in DS models will be important for shedding more light into the amyloidogenesis pathway in DS.

Ongoing research seeks to pinpoint factors contributing to the onset and progression of this disease, ranging from molecular anomalies to cortical network dysfunction. Although theories regarding the importance of amyloid and tau in AD have emerged at the forefront of this investigation, growing studies document the criticality of synaptic and neuronal failure, immune dysfunctions, and several other potential contributors to AD development. DS offers a unique opportunity to characterize the impact of genetic factors in the pathology of AD, given the high incidence of dementia within the DS population.

Common Pathways in AD and DS

Individuals carrying segments of HSA21 in three copies, known as partial trisomies, show DS phenotypes. Similarly, a triplication of all or some of the HSA21 genes generally leads to the formation of amyloid plaques and NFTs, hallmark signs of AD, in the DS brain by the age of 40 (Wiseman et al., 2015). Due to these pathological developments, the lifetime risk of dementia is drastically increased in DS individuals (McCarron et al., 2017; Fortea et al., 2020),

and dementia is the leading cause of death among the aging DS population (Hithersay et al., 2019). While speculations can be made as to which mechanisms contribute to AD pathology, there are currently no known factors that have been proven to cause AD. Roughly 85-90% of early-onset AD cannot be explained by mutations in *APP*, *PSEN1*, and *PSEN2*, which are all strongly linked with the disease (Ayodele et al., 2021). Virtually all individuals who have mutations in these genes develop AD during their lifetime (Tanzi et al., 1996), so they are considered to have exceptionally high penetrance. Moreover, almost everyone with a full trisomy of HSA21 exhibits associated phenotypes; therefore, this trisomy is considered to have a high penetrance as well. Therefore, DS provides a unique and consistent means to study the mechanisms of AD that contribute to the development of the disease over a long time span. Additionally, the wide variability in the extent to which individuals within this group exhibit this pathology allows researchers to analyze the genetic and/ or environmental factors that may be protective against cognitive decline and other AD symptoms.

Impacts of HSA21 Triplication on Transcription

While a triplication of the genes located on HSA21 may lead to their overexpression, the transcription of these genes may be regulated by components that lie both inside and outside the triplicated chromosome. Furthermore, proteins encoded by genes on HSA21 may have regulatory functions that impact the genes of other human chromosomes, since at least 324 genes have dosage effects across the genome, with most of these located outside HSA21 (Vilardell et al., 2011). On the other hand, HSA21 genes likely impact transcription across the genome,

leading to the aberrant functioning of associated genetic products. For example, *APOE* (discussed later) is a gene associated with AD that is not on HSA21, but its expression may be altered nonetheless. In addition, the triplication of an entire chromosome may disrupt epigenetic patterns (Tolmacheva et al., 2020), further contributing to abnormal genomic expression. Epigenetics refers to histone modification pathways that affect genome-wide expression without altering the DNA sequence itself (Zhang et al., 2020). Histone proteins in chromatin can be acetylated or methylated at CpG sites, which are nucleotide sequences where a cytosine is directly followed by guanosine (Jang et al., 2017), to unbind or bind DNA, facilitating or preventing transcription of a given region (Zhang et al., 2020). If patterns in these mechanisms are disrupted, the resulting phenotypes may be vastly different from that which were intended by one's genetics. Importantly, epigenetic mechanisms are heavily influenced by factors such as one's environment or intracellular signaling cascades. Indeed, epigenetic studies of fetal DS brains exhibit substantial differences in DNA hyper- and hypomethylation compared to TD fetuses (Hajj et al., 2016). Furthermore, analyses of blood and brain tissue show that these fetuses exhibit accelerated epigenetic aging by an average of 6.6 years (Horvath et al., 2015) in correspondence with the epigenetic clock (Horvath, 2013). Since epigenetics impacts gene expression on such a wide scale, drugs specifically targeting these mechanisms, such as DNA methylation inhibitors or histone deacetylases (HDACs) are significant targets for therapeutics in DS (Gupta et al., 2020). In addition, clustered regularly interspaced palindromic repeats (CRISPR)-associated protein 9 (Cas9)-based techniques have prospects for future genome editing, allowing for direct corrections of the epigenomes of DS individuals (Liu et al., 2019).

However, since there are vast epigenetic differences between individuals, these treatments will require extensive characterization of personalized epigenetics in order to mitigate some of the associated risks.

Common Genes Associated with DS-AD Pathology

Due to the vast array of complications that result from a chromosomal triplication, as well as several ethical concerns regarding human testing, mouse models have been an indispensable resource in studies linking DS with AD. Different lines of mouse models have been engineered to exhibit a select few characteristics of DS rather than all, allowing researchers to fully analyze the pathology and cognitive changes that result from isolated genomic alterations over the course of the mice's lifespans. The overdosage of several genes in DS leads to the development of AD pathology (**Table 1**), and understanding the roles of these components is critical in establishing a connection between their functioning in each case.

Table 1

Selected genes involved in AD pathology

Name of gene	Chromosome Location	Regular function	Role in DS/AD pathology
APP	21q21.3	Neuronal development	Aberrant cleavage overproduces Aβ, which forms

		synapse formation; synaptic plasticity; neuroprotection	fibrils and plaques that disrupt neuronal function
DYRK1A	21q22.13	Cell cycle regulation; transcription regulation; synaptic function; learning and memory	Premature neuronal maturation, enhances amyloidogenic processing of APP, tau hyperphosphorylation, disrupts balance of tau species
RCAN1	21q22.12	Negatively regulates calcineurin-NFAT signaling (important for myelination); aids neuronal development; immune regulation	Overinhibits calcineurin pathway, leading to inadequate myelination, weakened T-cell activation
SOD-1	21q22.11	Protects cells from oxidative stress by detoxifying ROS	Accumulating byproducts of ROS detoxification generate more radicals
S100B	21q22.3	Calcium signaling in astrocytes, promotes neuron growth	Promotes neuroinflammation, influences APP-processing pathway to produce more Aβ,

			drives tau phosphorylation
SYNJ1	21q22.11	Regulates recycling of synaptic vesicles	Enlargement of endosomes and transport deficits; synaptic impairment
APOE	19q13.32	Lipid transport; supports neuronal plasticity and synapse repair	ε4 allele is the strongest genetic risk for late-onset AD; promotes tau pathology and neuroinflammation
PSEN1	14q24.2	Encodes catalytic cores for γ-secretases	Large risk factor for familial early-onset AD when mutated; altered APP processing, more Aβ42
PSEN2	1q42.13	Encodes catalytic cores for γ-secretases; supports lysosomal function	Mutations cause risks for rare familial AD; lysosomal degradation and exacerbated Aβ buildup
PICALM	11q14	Drives clathrin-mediated endocytosis	Alters APP transport, worsens endosomal enlargement and Aβ clearance

CSTB	21q22.3	Inhibits cathepsin proteins, prevents excessive proteolysis	Promotes Aβ accumulation, increased vulnerability to neuroinflammation and impaired lysosomal function

HSA21 Genes

APP. Importantly, HSA21 contains the APP gene, which encodes for a transmembrane protein involved in neuronal growth, synapse formation, signaling, and potentially neuroprotection (Coronel et al., 2018). However, its triplication in DS may lead to the overexpression of APP, resulting in excess production of Aβ among other APP-derived molecules such as βCTF. Although rare, individuals may exhibit a duplication of only the APP gene (a familial form of AD known as Dup-APP) (Hooli et al., 2012). Interestingly, these people develop early-onset AD at extremely high rates despite this duplication being the only genetic abnormality. In contrast, individuals that contain a triplication of all or most HSA21 genes with the exception of APP have far lower rates of lifetime dementia onset than those with a full trisomy (Prasher et al., 1998). Trends seen in these populations highlight the significance of APP in the onset and progression of AD in general.

DYRK1A. DYRK1A is another HSA21 gene strongly linked to DS phenotypes and AD development. It is involved in neuronal development, cognition, and motor function (Toiber et al., 2010; Altafaj et al., 2001; Ahn et al., 2006), but a triplication of this gene heavily contributes

to defects in these mechanisms, contributing to AD-like pathology in DS brains. Since the gene promotes cell cycle termination, overdosage of DYRK1A is associated with premature neuronal maturation; its inhibition has been shown to prevent maturation in Ts65Dn mice (Mazur-Kolecka et al., 2012). Furthermore, transgenic DYRK1A mice and mice which only overexpress DYRK1A exhibit substantial deficits in learning and memory (Altafaj et al., 2001; Ahn et al., 2006), highlighting this gene's importance in the context of neurodegeneration associated with DS. Moreover, DYRK1A phosphorylates APP and enhances the amyloidogenic processing of APP, drastically increasing the levels of phosphoAPP and harmful Aβ variants in the brains of DS individuals (Ryoo et al., 2008), leading to the development of the amyloid cascade hypothesis (Hardy & Higgins, 1992) and heightening APP-associated pathology found in DS and AD. Additionally, DYRK1A phosphorylates the protein tau, and this in turn paves the way for further phosphorylation of tau by glycogen synthase kinase 3β (GSK3β). Triplications of these genes lead to the hyperphosphorylation of tau, which can facilitate pathological changes in conformation that are observed in AD. However, DYRK1A also affects tau expression by activating alternative splicing factors of the tau-coding gene *MAPT* (Antonarakis et al., 2020), ultimately disrupting the balance of 3R and 4R tau species. The concentration of these proteins in Ts65Dn mice is negatively correlated with their learning and memory abilities (Chakrabarti et al., 2010).

RCAN1. RCAN1, another gene present on HSA21, activates GSK3, leading to tau phosphorylation (Ermak et al., 2006). RCAN1 also regulates calcineurin-NFAT signaling, which promotes oligodendrocyte maturation and axonal growth (Nguyen & Giovanni, 2008). An

overexpression of RCAN1 leads to excessive inhibition of this signaling pathway, resulting in inadequate myelination and neural development. Furthermore, the pattern of NFT distribution is similar in DS and AD, transitioning from the entorhinal cortex to the hippocampus and finally the neocortex (Hof et al., 1995). Studies of the roles that these genes and abnormal tau content play in the development of AD-like pathology in DS may provide greater understanding of the functions of these components in AD in the general population.

DOPEY2, CSTB, and SYNJ1. HSA21 also contains genes vital for endosomal functioning, such as *DOPEY2*, chromosome 21 gene cystatin B (*CSTB*), and synaptojanin 1 (*SYNJ1*). Autophagy and other clearance mechanisms are critical to neuronal homeostasis and cellular functioning, so it is understandable that aberrant dosages of genes associated with endosome and lysosome function have been linked to MCI and forms of AD (Swaminathan et al., 2012a, Swaminathan et al., 2012b). A reduction in *CSTB* dosage has been shown to have neuroprotective effects against Aβ deposition and cognitive decline (Yang et al., 2011), so a triplication in this gene likely has an opposite result (Wu et al., 2021). Furthermore, triplications of *APP* and *SYNJ1* have been linked to endosomal enlargement (Salehi et al., 2006; Cossec et al., 2012; Torroja et al., 1999). This is significant because the enlargement of neuronal endosomes lead to axonal defects that largely contribute to neuronal dysfunction (Salehi et al., 2006).

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Non-HSA21 Genes

Although DS is a triplication of HSA21 alone, substantial alterations in genome-wide expression occur (Olmos-Serrano et al., 2016). Therefore, genes that are not on HSA21 can also play a role in the development of AD-related impairments in DS.

NPTX2, RPH3A, and BDNF. Three genes notably associated with synaptic dysfunction are downregulated in the developmental DS brain: neuronal pentraxin 2 (*NPTX2*), rabphilin 3A (*RPH3A*), and brain-derived neurotrophic factor (*BDNF*) (Mathys et al., 2023). *NPTX2* (on chromosome 7) codes for a neuronal pentraxin, which aids the growth and strengthening of synapses (Xu et al., 2003), *RPH3A* (on chromosome 12) codes for Rab3A, a GTPase that drives the joining of presynaptic membranes and vesicles (Tan et al., 2014), and *BDNF* (on chromosome 11) codes for a neurotrophin, promoting the development and survival of neurons (Zuccato et al., 2001). Synaptic function across the developing DS brain is likely perturbed by the downregulation of these genes. On the other hand, the adult DS brain displays further aberrant regulation in processes associated with neurodegeneration, such as vesicle transport, immune activation, and oxidative stress (Lockstone et al., 2007). The overexpression of these and other genes across the genome compounds dysfunctional synaptic development to exacerbate cognitive decline in aging DS individuals.

APOE. APOE is a gene located on chromosome 19 that regularly facilitates endosomal regulation and the transport of amyloid fibrils (Flowers & Rebeck, 2020). There are three alleles of this gene (ε2, ε3, and ε4), and the ε4 allele being the greatest genetic risk factor for late-onset

AD (Antonarakis et al., 2020). The presence of this allele has been linked with earlier cognitive decline and mortality in AD, and while APOE is not located on HSA21, the ε4 allele exacerbates risks of dementia in DS individuals (Rohn et al., 2014). Here, it is important to bear in mind that genome-wide transcriptional changes resulting from the triplication of some or all of HSA21 may affect the impact APOE has on individuals with DS.

PICALM. Phosphatidylinositol binding clathrin assembly protein gene (PICALM) is located on chromosome 11 and its expression is strongly linked with the age at which DS-AD develops (Jones et al., 2013). This gene is critical in the modulation of clathrin-mediated endocytosis (Willy et al., 2021), which is involved in internalization of cargo and proteins into the cell. This process is significant for Aβ clearance and the regulation of other mechanisms that worsen amyloid burden and exacerbate the progression of DS-AD (Zhao et al., 2015) by removing substances from the extracellular space and targeting them for intracellular degradation.

PSEN1 and PSEN2. PSEN1 and PSEN2, located on chromosomes 14 and 1, respectively, encode for presenilins that are the catalytic cores of γ-secretase complexes (Xiao et al., 2021). Catalytic cores are fundamental structures within enzymes that contain the amino acids necessary for the catalytic function of proteins. γ-secretases are critical for the processing of APP, so disturbances in their function as a result of aberrant PSEN1 or PSEN2 expression are linked with heightened generation of Aβ. In addition, variants of these genes are connected with autosomal dominant forms of AD (Sherrington et al., 1995). Due to the crucial importance of γ-

secretase activity levels in the modulation of APP processing, some γ-secretase inhibitors have been developed as a prospective treatment for AD progression (Hur, 2022). These approaches are confounded by variances in the levels of γ-secretases within individuals, making the implementation of these treatments challenging.

Pathophysiology and Non-Genomic Factors Related to AD-DS

Neuroinflammation

Neuroinflammation is also significantly more present in DS individuals due to the fact that four of six interferon receptors are coded by HSA21 (Sullivan et al., 2017). Interferons are proteins that trigger antiviral, inflammatory, and adaptive immune responses in response to pathogens (González-Navajas et al., 2012). An overexpression of these pro-inflammatory cytokines leads to a chronic state of neuroinflammation in DS individuals (Ahmed et al., 2021). Astrocytes express the HSA21 gene S100 calcium-binding beta (*S100B)*, the expression of which is increased in AD and AD-DS, and its protein (S100β) likely exacerbates neurodegeneration by increasing rates of Aβ plaque formation (Mori et al., 2010) and tau phosphorylation (Esposito et al., 2008). Furthermore, S100β was detected along with IL-1β at higher concentrations in cases of neuroinflammation (Griffin et al., 1989). Additionally, inflammatory cytokines such as tumor necrosis factor, IL-10, and IL-6 have been observed at higher levels in DS individuals than in the euploid population (Rodrigues et al., 2014), and the presence of these same molecules is furthered in DS with dementia (Iulita et al., 2016). Analyzing the behaviors of these cytokines may yield insights into their effects on facilitating cognitive decline through neuroinflammation

in DS, potentially suggesting mechanisms of neurodegeneration that can be applied to the progression of AD in the general population.

Oxidative Stress

Free radicals are elements that contain unpaired electrons, and they are prone to disrupting the structures or functions of macromolecules (proteins, lipids, carbohydrates, or nucleic acids). In addition, superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH) are all examples of ROS. Oxidative stress occurs when cells struggle to manage ROS levels, and this can lead to faster aging (as seen in DS individuals; Franceschi et al., 2019), and higher rates of neuronal apoptosis (Loh et al., 2006), which contributes to neurodegeneration. SOD-1 is a cytosolic enzyme encoded by an HSA21 gene that plays a role in relieving oxidative stress by converting superoxide (O_2^-) radicals into H_2O_2 or O_2 (**Figure 3**). After this, H_2O_2 is converted to H_2O and O_2 and removed from the cell (Zigman & Lott, 2007). However, an imbalance in this process can result in the formation of hydroxyl (OH), which may damage cellular components (Badwey et al., 1980). In DS individuals, SOD-1 is likely overexpressed due to the triplication of its gene. This directly perturbs the superoxide removal pathway, and has been shown to lead to increased brain lipid peroxidation in DS individuals (Capone et al., 2002) and also transgenic mice carrying human SOD-1 (Yarom et al., 1987).

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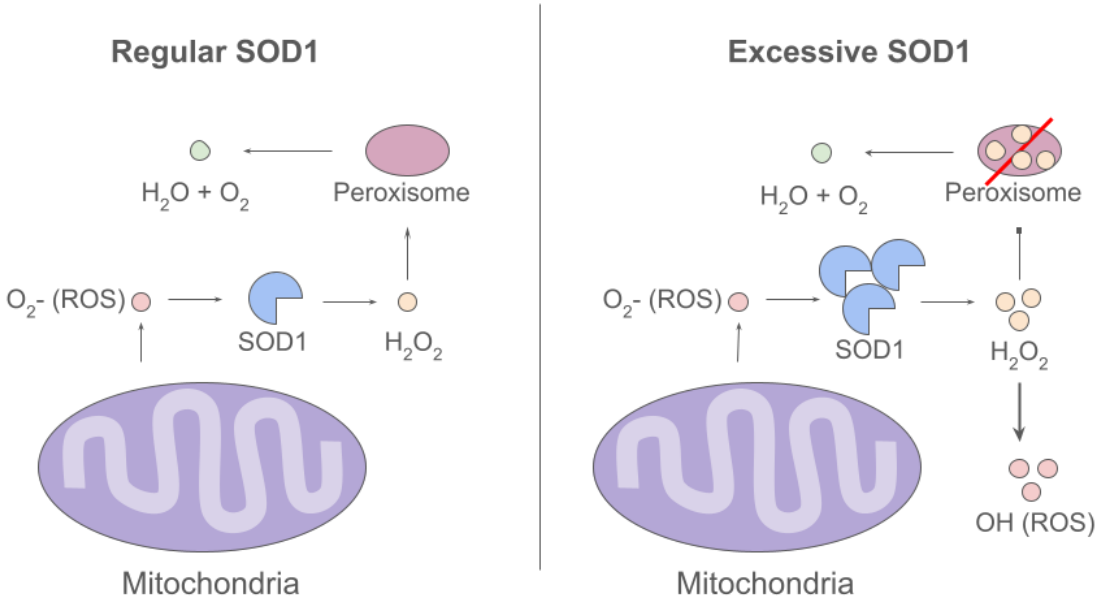
ISSN 3069-8200

Figure 3

ROS clearance with normal and excessive SOD1 expression



Cerebrovascular Pathology

Cerebrovascular pathology, or complications surrounding interactions between the brain and bloodstream, also poses a significant risk to DS individuals, for it has been documented to lower the expected age of onset of dementia and expedite its progression (Snyder et al., 2015; Jellinger, 2013). Cerebral amyloid angiopathy (CAA) is the buildup of amyloid in smaller blood vessels in individuals with DS and/ or AD, which leads to haemorrhages of varying severities that are more commonly occurring in DS (Head et al., 2017). In addition, DS individuals are

approximately 1.21 times more likely to develop CAA than people with AD, and they are 4.6 times more prone to this progression than those in the general population (Head et al., 2017). However, cardiovascular issues such as atherosclerosis and hypertension are found extremely rarely in DS individuals (Murdoch et al., 1977). Therefore, the DS population presents a unique opportunity to examine the effects of CAA on cognition and overall neurological function without risks of associated complications.

Estrogen

The steroid hormone estrogen has also been shown to have neuroprotective qualities (Yaffe et al., 2000). Declines in estrogen levels have been linked to a progression of AD, especially in women after menopause. In DS women, menopause occurs far earlier than average (Schupf et al., 2007), drastically increasing the likelihood of these individuals experiencing cognitive decline and developing dementia.

AD-DS Proteomics

Along with Aβ40, Aβ42, and tau, all of which are linked with cognitive impairments (Schworer et al., 2024), proteomic findings elucidate the significance of the upregulation of other AD-related proteins encoded by *APP*, *MAPT*, *GFAP*, and *NEFL*. In total, AD and DS share around 1483 upregulated proteins and 1214 downregulated proteins (Bai et al., 2021). Of these, only 15 and 4, respectively, are encoded by HSA21, demonstrating the criticality of non-HSA21 genes in the developments exhibited by these conditions (Bai et al., 2021). While HSA21 genes are triplicated in DS, certain proteins are found in reduced levels. For example, intersectin 1

(*ITSN1*) is a gene involved in the formation and recycling of clathrin-coated vesicles, but there is a reduction in its generation in DS. Overall, AD and DS exhibit many of the same proteins with similar changes in their respective levels; however, it is important to note that discrepancies in results of proteomic studies may occur as a result of differences in methodologies.

Biomarkers

Biomarkers are measurable signs, commonly molecules, found in blood, bodily fluid, or tissues, that indicate the development of a disease or condition (Ahmad et al., 2023). Identifying dementia and other AD-associated progressions through observations or cognitive exams is more difficult in DS individuals than in the general population due to the varying levels of pre-existing intellectual disability displayed by each person in this group. Therefore, biomarkers serve as an indispensable means to recognize further disease pathology through the analysis of biological indicators in the nervous systems of people with DS and/ or AD. They are especially useful in diseases that occur over long periods of time because they pave the way for a greater understanding of when, throughout the individual's lifespan, causative factors may arise. For example, biomarkers of AD begin to accumulate ten to twenty years before cognitive decline can be observed (Jagust & Landau, 2021). The ability to identify consistently-occurring mechanisms allows for diagnosis that is more grounded in these biological processes rather than general observations of individuals. There is yet to be an established causative factor that always leads to the onset of AD, but the analysis of biomarkers is a significant step toward such future discoveries. Similarly, the identification of specific molecules strongly associated with disease

progression will enable the production of therapeutic strategies targeting these pathways. There are two types of biomarkers that are predominantly characterized in the AD population: imaging and non-imaging.

Imaging Biomarkers

MRI Scans

Neuroimaging enables diagnosis of AD within the brain and allows for the monitoring of disease progression. Among these techniques, various modalities of magnetic resonance imaging (MRI) scans capture observable differences in brain volumes and allow researchers to make associations between patterns of atrophy and disease progression (Neale et al., 2017; Annus et al,. 2017). Structural MRI tracks brain atrophy as a whole, and has been useful in determining patterns of regional atrophy in AD, such as consistent neuronal loss in most AD hippocampi and parietal and temporal isocortices (Knopman et al., 2016). Structural MRI also helps detect microbleeds, which are caused by CAA. Conversely, functional MRI (fMRI) highlights the activity of networks within the brain, potentially exposing regions that are active in aging brains (Neale et al., 2017). fMRI is unique in that it provides results with immense spatial and temporal resolution, while being a non-invasive technique that is generally less expensive than other types of imaging. Due to these qualities, this form of neuroimaging can be used repeatedly to investigate network integrity or lack thereof. However, fMRI scans measure blood oxygenation as a sign of neuronal signaling rather than the firing itself, so most benefits of this technique lie in the analysis of large-scale networks rather than the functioning of specific components

(Glover, 2011). MRI techniques lack specificity for AD, so it is difficult to draw conclusions or produce diagnoses solely through these scans. Rather, MRI scans display structural and functional degradation that can be interpreted to link back to the onset and progression of AD, requiring longitudinal studies.

PET Scans

On the other hand, positron emission tomography (PET) scans provide high-resolution imaging of the buildup of neuritic plaque and other proteins in the brain (Johnson et al., 2012). While these scans do expose individuals to radiation, limiting the potential for repeated use, they are capable of imaging specific pathology, such as accumulation of amyloid and tau and neuroinflammation. Aβ PET images the deposition of fibrillar amyloid plaques, and fluorodeoxyglucose (FDG)-PET measures glucose uptake and metabolism within the brain (Jack et al., 2010). Moreover, Pittsburgh compound B (PiB) (Klunk et al., 2004) is a significant ligand in a plethora of ongoing studies of Aβ deposition, as it can detect early sites of Aβ aggregation (Klunk et al., 2004), and PiB-PET tracks the deposition of Aβ with a focus on patterns of accumulation. Conducting PET scans for tau has shown similar binding characteristics in individuals who have AD with and without DS (Petersen et al., 2022). Tau buildup is also strongly intertwined with amyloid burden, neurodegeneration, and cognitive decline (Medeiros et al., 2010). The use of various modalities of PET scanning aids in the formation of associations between these factors, leading to a greater understanding of where mechanisms overlap and influence one another.

The Princeton Journal of Interdisciplinary Research
ISSN 3069-8200

Non-Imaging Biomarkers

Cerebrospinal Fluid Biomarkers

Non-imaging biomarkers are far more accessible than other techniques, and provide valuable insights into disease progression and mechanisms. Cerebrospinal fluid (CSF) biomarkers have been implemented to measure the concentrations of Aβ and tau in AD, particularly the ratio of β-amyloid 42 and 40 as well as 181-phosphorylated tau and t-tau. CSF Aβ42 is reduced in individuals with symptomatic AD and people who will develop symptoms of AD in the future. Furthermore, Aβ42 levels vary within each person, so studies with a normalization of these have higher diagnostic accuracy than Aβ42 on its own (Hansson et al., 2007). Both p-tau181 and t-tau are present in high concentrations in the CSF of individuals exhibiting AD-linked MCI and dementia (Mattsson et al., 2009), and their levels are tightly intertwined in AD (Skillback et al., 2015), a distinction from other neurodegenerative diseases. In addition, neurofilament light (NfL) is part of the cytoskeleton in axons, and it serves as a biomarker that can be studied from the CSF to examine neurodegeneration through axonal damage (Teunissen & Khalil, 2012). The concentrations of NfL in CSF are inversely correlated with cognitive function, since NfL levels rise with disease progression (Lee et al., 2022). By contrast, in DS, Aβ42 levels are heightened during childhood and decrease during aging. Interestingly, CSF Aβ42 concentration is inversely correlated with CSF tau levels, which continuously increase with age. Despite these findings, only a handful of CSF studies have been conducted on individuals with DS (Dekker et al., 2017). CSF biomarkers for AD are obtained

through lumbar puncture (LP), which is the insertion of a needle into the lumbar subarachnoid space of the lower back (Shaw et al., 2023). However, people with DS experience orthopedic anomalies at much higher rates than TD individuals. For example, roughly 4.8% of children with DS develop scoliosis, an abnormal spinal curve (Foley & Killeen, 2019), and 32.7% of adults exhibit lumbar spondylolisthesis, a shift in vertebra that often results in the distortion of the spinal canal (Hansdorfer et al., 2013). As a result of these conditions, LP procedures carry increased risk of causing traumatic tap, where blood is collected instead of CSF. Due to challenges in CSF extraction from DS individuals, there has been increasing emphasis on blood-based biomarkers as a more practical and accessible class of non-imaging biomarkers for detecting particles linked to AD in this population.

Plasma Biomarkers

Neurofilament Light. NfL is the only biomarker that is found in similar levels in both CSF and plasma, and is currently the most widely characterized plasma biomarker associated with AD and DS (Abu-Rumeileh et al., 2023). As in CSF, NfL concentrations in plasma indicate cognitive decline in non-DS individuals. In DS, plasma NfL levels can provide a distinction between DS and DS-AD (Fortea et al., 2018), providing tremendous diagnostic potential. Moreover, levels of NfL in plasma are correlated with other signs of AD progression, such as amyloid accumulation, abnormalities in neuronal glucose metabolism, and cognitive impairment (Rafii et al., 2019).

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ISSN 3069-8200

Phosphorylated-Tau and Amyloid. Plasma phosphorylated-tau assays have also been developed, and as in CSF, plasma concentrations in p-tau181 have strong potential for AD diagnosis (Lleo et al., 2021). In contrast, Aβ42 and Aβ40 levels in plasma have not proven useful for diagnostics due to a plethora of factors influencing the concentrations of these molecules outside the brain.

Exosomes. In addition, exosomes isolated from plasma samples contain AD-associated molecules in higher concentrations in DS than in non-DS individuals (Hamlett et al., 2017). Exosomes are vesicles released from cells, carrying proteins, nucleic acids, lipids, and other molecules. They have the potential to serve as a biomarker as they may contain waste products associated with disease pathology (Hamlett et al., 2019). This is especially significant as exosomes play a role in Aβ and p-tau clearance (Lewczuk et al., 2018).

Future Directions

Although there are multiple types of AD (including early-onset, late-onset, familial, and AD-like pathology seen in DS) with subtle molecular and genetic differences between them, these subtypes ultimately share many similarities in mechanisms and general patterns of pathogenesis. Thus, findings involving individuals exhibiting one subtype could be used to understand the pathogenesis mechanisms of other subtypes. With improvements in health care, the life expectancy of people with DS will likely continue to rise, increasing the prevalence of AD in this population due to the connection between these conditions. As studies are conducted in the DS population, findings regarding AD mechanisms may provide valuable insights

involving disease progression and potential therapeutic targets for neurodegenerative conditions in the general population. These studies will benefit from large-scale -omics analyses across different AD subtypes longitudinally over lifespan. While there are several limitations to the collection and interpretation of -omics data, genome-wide association studies have already revealed multiple factors that are implicated in the pathology of AD. However, results derived from large-scale studies should be validated for individual subtypes to assess validity of mechanisms.

In DS, an overdosage of the *APP* gene alone is largely sufficient to cause AD-associated pathology. Therefore, therapies aimed at modulating APP processing (specifically by β-secretase) may prove beneficial in reducing amyloid burden. Treatments targeting DYRK1A could also alleviate multiple pathways of disease progression, since it is involved in several aspects of AD pathogenesis, and a normalization of the gene dosage in DS mice has rescued several impairments. Although genetic analyses are at the forefront of AD-DS studies, several non-coding genetic elements that are not fully understood are at play in this pathology. Additionally, while various drugs have been proposed to correct epigenetic abnormalities in DS, target APP processing, and slow the onset of dementia, there exist far too many risks and considerations to take into account for each individual for the treatment to be safe, effective, and widespread. The production of new mouse models, such as TcMAC21 (Kazuki et al., 2020), which provides a triplication of nearly all HSA-syntenic genes in an aneuploidy model, will allow for more extensive characterization of the effects of gene overdosage on pathological development and the complex interplay between various genes with increased expression.

The Princeton Journal of Interdisciplinary Research
ISSN 3069-8200

Conclusions

Individuals with DS exhibit a uniquely elevated risk of developing AD during their lifespan, and this is largely driven by the triplication of HSA21 and all of its genetic components as well as the resulting overexpression of genes such as APP. Studies of both humans and mouse models with overexpressed HSA21 highlight a subsequent increase in pathological signs including Aβ, tau, neuroinflammation, synapse loss, ROS, and cognitive decline, which are also observed in AD. Due to the significant prevalence of AD development in the DS population, this group provides a natural and reliable glance into the early mechanisms of AD onset. As such, several biomarkers that aid in the diagnosis of disease progression have been identified, with applications providing sooner support for the DS population and a greater understanding of AD mechanisms in the general population.

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