The Role of Amyloid Precursor Protein in Accelerated Alzheimer's Disease in Down Syndrome: A Literature Review

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Paul Feij (S4491521)

prof. U.L.M. (Ulrich L. M.) Eisel

MSc. L.M. (Lysanne) Jorna

Abstract
Down syndrome (DS) is a relatively common cause of intellectual impairment which is caused by a triplication of the 21st chromosome, leading to various health complications and the typical DS phenotype, but also often an accelerated form of Alzheimer's disease (AD). In this literature review we explore the intricate role of the amyloid precursor protein (APP) gene, which is located on the 21st chromosome and increased in expression, for the progression of AD in DS. This review shows how trisomy 21 increases production of everything in the APP processing pathways, significantly increasing risk for AD. There are more genes than APP which contribute to AD progression than APP, like DYRK1A or BACE2, but their complete roles and functions have to be studied more. To begin treating or diagnosing AD in DS with novel biomarkers discussed in this paper, which could present us with better ways to diagnose AD or treat AD from angles we haven't been able to see yet, their complete mechanisms have to be known in future research.

Introduction
Individuals with Down syndrome (DS) are affected by one of the most common causes of intellectual impairment with a prevalence of 8.27 per 10.000 people in the US (Presson et al., 2013). The syndrome is named after John Langdon Down, who initially described it in 1866 and called them Mongols under the category of idiots, which at the time was a category that described individuals with intellectual impairments, rather than now being more commonly used as an insult (Down, 1866). Due to their, often severe, intellectual disabilities, people with DS have difficulty interacting in society, as they tend to be slower and less efficient at most normal tasks in life. They require special care and need to remain healthy and on certain families this takes quite a toll, sometimes resulting in having to be admitted to specialized disability care institutions.

In 1959, it was discovered that the aetiology of DS lies on the 21st chromosome; people with DS have 3 copies of the genes on this chromosome instead of 2 which is called a trisomy. This can happen when during meiosis, gametes are formed that fail to separate the chromosome pairs and end up with one extra chromosome if fertilisation occurs. Trisomy of the 21st chromosome causes a lot of changes in interactions between the genes on this chromosome, of which the results can be seen in the phenotype of DS (Desai, 1997). In the present day, we have come a long way in research regarding DS and the people affected by it can fully be integrated into society, at least in the Western world. Almost all experienced dentists, doctors, physiotherapists and many more practitioners have encountered cases of DS a dozen times and most of the time, their protocol is quite similar to the ones of a 3-year-old child. However, it can be noticed that due to the vast amount of comorbidities that come with DS, which can range from precise conditions like cardiovascular defects, hypothyroidism, leukaemia and dementia (which will be the main scope of this paper) to more general conditions such as muscular instability, speech impairment and abnormal behaviour, obesity or sleep apnea (Desai, 1997)(Pierce et al., 2019), the combination of risk factors and the effects of DS itself causes a significant difference in life expectancy between healthy individuals and DS patients, with DS being between 43 and 55 years in 2012 (Head et al., 2012). Despite all the obstacles DS exerts, often they can live happy and fulfilling lives in caring families and have shown to experience a

good quality of life. Unfortunately, often towards the end of their lives, they experience an accelerated form of dementia also frequently observed in healthy individuals without DS: Alzheimer's disease (AD). The accelerated form of AD in DS can be attributed to the extra 21st chromosome, as this chromosome contains information about certain proteins that are believed to have important influences on the development of AD, such as Amyloid Precursor Protein (APP). APP acts as a precursor for and is heavily involved in the production of amyloid-beta (Aβ) peptides. The genetic information for the expression of APP lies on the 21st chromosome and thus it is expressed at higher rates in individuals with DS, which is thought to have a huge impact on the progression of AD. So it's clear now that dementia is a recurring issue in DS and to begin finding a solution, we must first figure out all effects of the different factors that affect this issue. In this paper we focus on APP, to find out if the effect of Trisomy 21 on APP is the main cause of accelerated AD in individuals with DS and if not, which other factors are involved?

Down Syndrome and Alzheimer's Disease: An overview

To recognise AD in DS we must define AD itself and the aspects that are important for understanding AD in DS: AD is a neurodegenerative disease that attacks the brains of (mainly) individuals of advanced age and as the most common cause of dementia, is very actual in today's society with most people having encountered a family member that is or was affected by the disease. The disease has risen in prevalence in the last century since the quality of life and life expectancy have increased, increasing the risk of dementia among the population (Dhana et al., 2022). While the symptoms of AD can vary from person to person and in between stages of AD, common symptoms include memory loss, confusion, and difficulty with daily tasks. As the disease progresses, individuals may experience personality changes, mood swings, and difficulty communicating. In DS, affected individuals may experience symptoms like this at a severely advanced age, with up to 5.7- 55% of individuals in the age group of 40-49 suffering from dementia, which greatly differs between the age of onset for typical AD patients, typically observed at 65+ years of age (Head et al., 2012) (Mendez, 2012). The symptoms are often hard to recognise because of the difficulty of testing individuals with DS for symptoms such as mood swings and difficulty communicating, which are symptoms that are already regularly observed in individuals with DS. This difficulty with diagnosing the disease provides the healthcare system with an enormous challenge and often results in late diagnosis and treatment, affecting the effectiveness of preventing and/or treating the disease in DS. Another challenge is provided by the disease to caregivers of affected individuals; DS itself is often already a big burden for these caregivers, and the extra care that is needed by AD sometimes proves too much for a caregiver to bear.

When diagnosing AD, the different stages are called Braak stages and signal the progression of the disease, which starts at the entorhinal layer and hippocampus, and eventually spreads to isocortical layers as the most progressed form of the disease (Braak & Braak, 1991). There are thought to be a multitude of factors contributing to attracting the disease, with two certain factors having the highest impact: higher amounts of β-amyloid-containing plaques outside the neuron

cells and tau-containing neurofibrillary tangles (NFTs) inside neuron cells. AD can cause a rapid decrease in cognitive function when these components are present, essentially attacking the brain's infrastructure. β-amyloid-containing plaques form through the production of a protein called β-amyloid (Aβ) from APP (Amyloid Precursor Protein). After Aβ has been produced and is present in the extracellular matrix among the neuron cells, it folds and forms Aβ oligomers, which stick to other Aβ oligomers (Röhr et al., 2020). Together with glial and neurotic debris, they form toxic β-amyloid-containing plaques. These plaques disrupt neuronal connections between synapses and form a neurotoxic extracellular environment which causes neuroinflammation, gliosis and if deposits are formed near blood vessels in the brain, angiopathy can occur which significantly increases the risk of haemorrhage (Sreekumaran et al., 2021) (Viswanathan & Greenberg, 2011). In healthy situations, tau holds the microtubules in neuron cells together, which plays an important part in the cytoskeleton. In AD pathology however, we see that these tau proteins become hyperphosphorylated and disassociate from the microtubules, becoming entangled with other hyperphosphorylated tau proteins which causes a disruption of the microtubules and accumulates inside the cell, eventually leading to cell death. The causation for the cascade of hyperphosphorylation of tau proteins has not been definitively determined, however, some studies suggest that beta-amyloid plaques influence this cascade inside the cell (Brion, 1998). In DS, due to the triplication of the 21st chromosome, there are some differences in the timing and progression of typical AD. The most notable difference is that an increase in expression of the APP gene causes a significantly advanced Aβ plaque disposition in the brain due to more production of Aβ peptides. It is also observed that there is an equally increased production of NFTs in DS, some studies suggest that this is possibly due to the increase in expression of the DYRK1A (Wegiel et al., 2011) gene or RCAN1 (Lloret et al., 2011) gene on the 21st chromosome. Next to APP, the genetic information for an enzyme utilized for the production of Aβ also lies on the triplicated chromosome: BACE2. This enzyme does not seem to be the main enzyme responsible for producing Aβ, as this is BACE1. A few studies have reviewed the amyloidogenic properties of BACE2 and have suggested that it may be involved in Aβ production (Wang et al., 2019). Apolipoprotein E4 (ApoE4) has been indicated to be a heavy influence on typical AD and this same effect is again seen in DS, but that may purely be due to the contribution of ApoE4 to AD pathology and not be an effect of DS (Tanzi, 2012). Similar to typical AD, the mentioned two factors facilitate a neurotoxic environment in the brain and cause the degradation of neuronal tissue, next to neuroinflammation mediated by the astrocytes and microglia. The main difference observed between typical AD and AD in DS pathology is a faster progression of the disease, as well as an earlier age of onset.

Amyloid Precursor Protein: Structure and Function

APP is a type 1 transmembrane protein that is expressed in neurons, as well as other peripheral tissue. APP has its origins in a multi-gene super-family from which the amyloid precursor-like proteins derive like APLP1 and APLP2 (Coulson et al., 2000). The gene for APP is encoded on the 21st chromosome, as earlier mentioned, from which it is transcribed and translated into APP. After production, it moves to the membrane of a cell and becomes a single-pass transmembrane protein by spanning across the membrane once, with a small intracellular and a large extracellular component sticking out on the sides. The transmembrane and extracellular

components have crucial cleavage points for enzymes and they determine the form of the end product. It can be sliced into different isoforms after production, with certain isoforms being found in higher concentrations in the CNS and neurons than others such as isoform APP695, which is mainly expressed in neurons (Matsui et al., 2007).
The pathway for processing the translated protein is determined by the point at which APP is cleaved and this is performed by proteases that are specialised at cutting transmembrane proteins called secretases. In the case of APP, there are 3 important secretases: alpha(α)-, beta(β)- or gamma(γ)- secretases. The two main pathways in which APP can be processed are either cleaved by an α-secretase that generates sAPPα or cleaved by a β-secretase (such as BACE1) into sAPPβ, both end products are diffused away outside the cell. After the production of sAPPα or sAPPβ, there remains a small extracellular and partly transmembrane component of APP that will be cleaved by a γ-secretase. As sAPPα or sAPPβ are different in length regarding amino acids, there is a difference in the peptides produced by the γ-secretase, these different peptides are nonamyloidogenic in the case of sAPPα and amyloidogenic in the case of sAPPβ. Aβ monomers are what result from the action of γ-secretase in the amyloidogenic pathway, with there being two forms that differ in length and ultimate risk for AD: Aβ40 and Aβ42, these two forms result from 2 slightly different sites of cleavage by the γ-secretase. In healthy individuals, there is mainly production of Aβ40 which can be safely disposed of by the body (O'Brien & Wong, 2011). The production of Aβ seems to happen intracellularly, but most harmful Aβ can be found outside the neuron cells, meaning that most probably Aβ gets secreted outside the cells (Oddo et al., 2006).

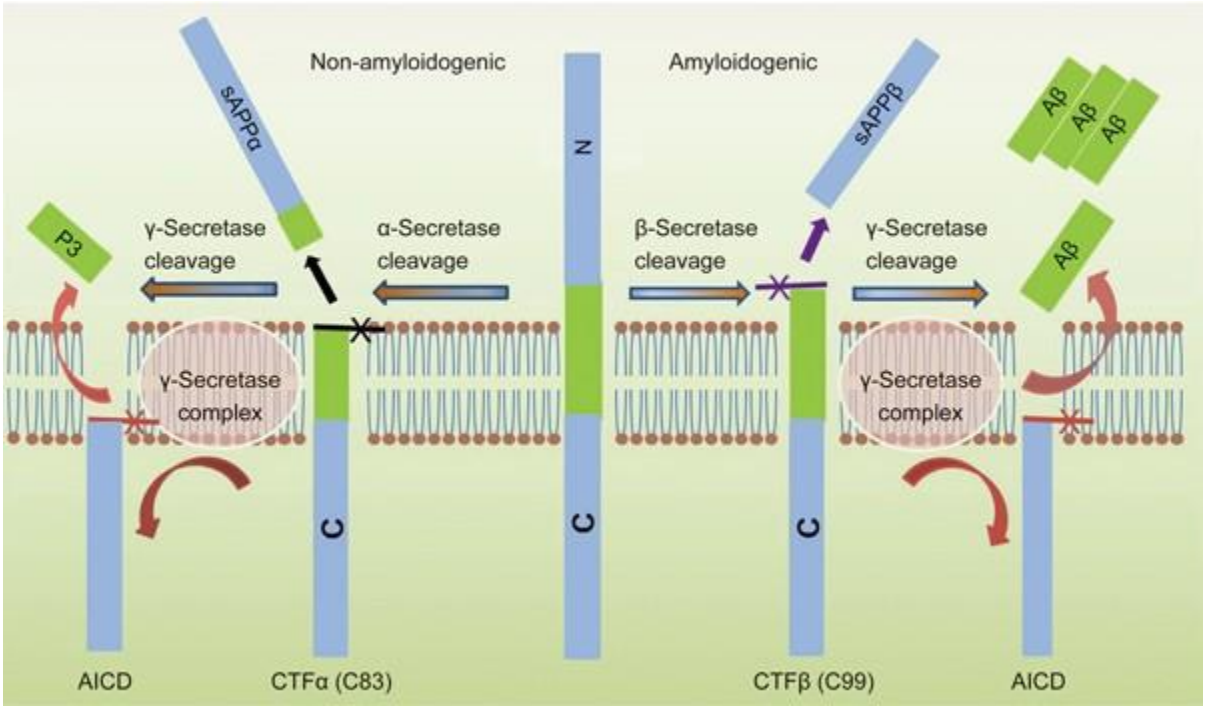

Figure 1: The non-amyloidogenic and amyloidogenic pathways of APP processing, in which α, β- or γ- secretases play important roles (Chen et al., 2017).

Since evolution hasn't resulted in the deletion of the APP gene, there must be some part in the production of APP that has a positive effect on the health of an organism. Of course, the main scope of studies on APP is aimed at the health drawbacks it's more commonly associated with, but also plenty of studies have shown that there are benefits to having APP peptides circulating in the body. A great example of this is the study done by Heber et al. (2000), wherein they created genetically modified mice with knockouts of the APP, APLP1 and APLP2 genes. Double knockouts proved to be more often lethal than compatible with life, showing the apparent importance of this gene family and its interactions. Singular knockouts of either APP or APLP1 resulted in reduced weight, which shows their importance in healthy metabolism and the knockout of APP also resulted in a multitude of other dysfunctions, of which most were related to cognitive functions (Heber et al., 2000). Dysregulation of APP expression showed that there is a synaptogenic benefit to normal APP levels (Mucke et al., 1994), as well as an increase in neuronal proliferation (Ohsawa et al., 1999) and extension (Jin et al., 1994). Most beneficial effects of APP production seem to be associated specifically with the production of sAPPα as being the 'healthy' end product and can be seen as an antagonist for sAPPβ and Aβ, which is associated with increased risk for AD. Some proof of the neuroprotective properties of sAPPα was demonstrated by Ring et al. (2007), where they expressed sAPPα in APP-deficient mice, which reversed most deficits found in APP-deficient mice like reduction in body weight and cognition impairments. The beneficial functions of sAPPα production could be due to its antagonistic properties against sAPPβ, but sAPPβ can also be neurotrophic, if at the right levels and without the byproduct of Aβ oligomers; which brings us to the neurotoxic properties of APP production (Chasseigneaux & Allinquant, 2011).

Translation of the APP gene is the first step of harmful Aβ plaque formation and APP production is thought to significantly impact the predisposition for AD due to its strong connection to Aβ accumulation, an important process in AD pathology. As earlier seen, processing of the APP protein by the secretases results in either the formation of sAPPα and a harmless byproduct or sAPPβ, Aβ40 and Aβ42, which is then normally disposed of and cleared out of the brain to prevent the pathological formation of Aβ plaques. However, an increase in the ratio of Aβ42/40 is strongly associated with neurotoxicity and is often found in neurodegenerative diseases like AD. Aβ42 is thought to be more pathogenic than Aβ40 due to its tendency to stick to more of itself and form oligomers that are the basis of Aβ plaques. These plaques then can disrupt neuronal connections, activate neuroinflammatory pathways and increase the intracellular presence of NFTs, creating a neurotoxic environment in the brain.

Amyloid Precursor Protein in Alzheimer's Disease Pathology

It's clear that APP production is prone to contributing to the pathological formation of Aβ plaques in neurodegenerative diseases, but from now on we will narrow our focus specifically on APP's role in AD. Aβ plaques are the central topic in AD, meaning that APP is crucial to the pathogenesis of the disease and has a role in AD's origin. As recently mentioned, the amyloidogenic pathway of APP processing has two end products: sAPPβ and Aβ isoforms 39-43, of which Aβ40 and Aβ42 are the most common (Sun et al., 2015). While both sAPPα and sAPPβ have not shown clear neurotoxic properties and are mostly associated with healthy neuronal plasticity, Aβ40 and Aβ42 are, as main components of Aβ plaques, strongly associated

with the progression of AD and Aβ42 has shown to have the most impact in AD pathology. APP stands as the precursor of these products and therefore is an important factor in AD pathogenesis, the extent of genetic APP expression has a huge role in predisposition for the disease, which could be seen by looking at individuals with DS.

The production of Aβ of all amino acid lengths occurs regularly throughout the life of healthy individuals, with the body being able to clear up these mostly neurotoxic proteins during a healthy life. Normally the production of the different isoforms of Aβ is in balance proportionally, but in AD we observe a significantly increased amount of Aβ42 when compared to the other isoforms, indicating that Aβ42 has an essential role in the formation of either Aβ plaques or tau hyperphosphorylation (Niemantsverdriet et al., 2017). Aβ42 is the isoform that tends to aggregate most into Aβ plaques and when increased in concentration in extracellular neuronal space, the Aβ isoforms (of which Aβ42 has the most chance to do this) have a probability to meet and stick to other Aβ isoforms and form oligomer Aβ molecules from the Aβ monomers. The Aβ oligomers then stick to other Aβ oligomers and create amyloid fibrils. The difference between oligomers and fibrils is that oligomers are still soluble, meaning that they can still roam throughout the brain, but when they assemble into amyloid fibrils they become insoluble and start the definitive creation of the neurotoxic amyloid aggregate we all know and fear: Aβ plaques (Chen et al., 2017). As the name suggests, Aβ plaques mainly consist of Aβ molecules but also of neuronal debris, which gets caught in the vastly sticky and tangled network of an Aβ plaque or due to the neurotoxic properties of plaques. Aβ plaques increase in concentration when Aβ molecules and thus APP production or cleavage are increased, causing instances of plaques on a multitude of sites in the brain which in AD typically starts in the neocortex (Thal et al., 2002).

The presence of enough Aβ plaques in the brain creates a highly neurotoxic environment which is characteristic of AD and mediated by different factors that interact closely with each other. These different factors contributing to the neurotoxic environment are still largely undefined but some of these factors include but are not limited to loss of dendritic spines, synapses, increased neuroinflammation, increased NFT formation and even neuronal cell death, which all can be observed in AD. Dendritic spines and synapses seem to be affected by amyloid plaques because they interfere with the synaptic processes and signalling pathways such as long-term potentiation, which is an essential process in memory formation, something that is impaired in AD. With the presence of plaques, there often is also an increase in neuroinflammation due to the chronic activation of microglia in the brain, which produce pro-inflammatory cytokines and activate the immune system which essentially attacks the neuronal tissue by creating this toxic environment (Tanokashira et al., 2017). NFTs are believed to have an important role in AD pathology as they reside intracellularly, which logically has a huge impact on the health of neuronal cell bodies. As earlier explained, tau has an important part in the pathological process of NFT production and seems to be influenced by its hyperphosphorylation by Aβ and vice versa. Neither one nor the other is a direct causation for each other, rather interactions that mutually reinforce the production. Aβ promotes the activation of tau phosphatases and kinases which causes tau hyperphosphorylation and thus increases chances of NFTs, while NFTs more indirectly promote Aβ formation by causing death of neurons themselves, which activates a

cascade of inflammatory responses and increases oxidative stress (Bloom, 2014). Neuronal cell death isn‘t solely caused by NFTs, but NFTs mainly attack the cell body of a neuron, while the extracellular neurotoxic environment created by Aβ mainly attacks the dendrites, spines, synapses and axons of a neuron.

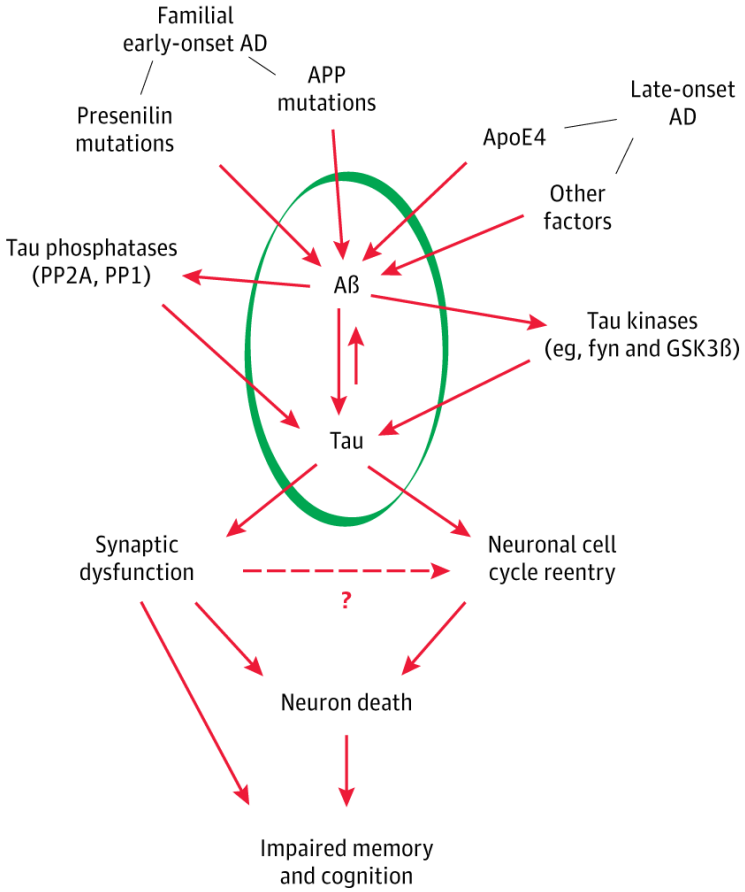

Figure 1: Interactions between Aβ and tau, influencing the pathological progression of AD (Bloom, 2014).

Role of Amyloid Precursor Protein in Down Syndrome-associated Alzheimer’s Disease

As we know, due to the presence of an extra 21st chromosome in DS there are a lot of induced differences between healthy individuals and DS patients. APP is one of the many genes that are encoded on the chromosome and is believed to have profound effects on the progression of typical AD and an extremer version of this effect can be found in DS, as they seem to progress at a higher rate through the disease. The about 1.5 times increased APP expression in DS causes a chronically increased production of APP and its processing, producing more of the end products mentioned earlier like sAPPα, sAPPβ, Aβ40 and Aβ42 (Sawa et al., 2021). This means that both the amyloidogenic and non-amyloidogenic pathways of APP processing are increased and are not all detrimental. Individuals with DS aren’t affected by this increase in APP expression for the largest part of their life, but their risk for acquiring AD is significantly increased and the disease is often observed at the end of their lives. More production of especially Aβ causes a chronic increase of extracellular Aβ concentrations, which heavily

promotes the development of new Aβ plaques in the brain. The increase in side-products of APP processing may also be beneficial, as some of the products like sAPPα have been indicated to show possible interactions regarding neuroprotection. The activity of α, β- or γ-secretases also has to be increased with more substrates for them to turn over into products. A trisomy on the 21st chromosome doesn't only mean an increase in APP expression, but also that of other genes, such as Beta-site APP Cleaving Enzyme 2 (BACE2). BACE2 is an enzyme that has a very similar structure to BACE1 and their functions have been shown to significantly overlap, with them both functioning as β-secretases. Notably, the increase of epigenetic expression of BACE2 isn't reflected in the concentration of BACE2 proteins in the body, indicating that somehow, for instance, posttranscriptional regulatory mechanisms either inhibit an increase in translation or influence protein turnover by accelerating the degradation rate. Some studies have also indicated that BACE2 may have anti-amyloidogenic properties as overexpression of BACE2 showed a decrease in Aβ production, as well as cleaving APP on another site which avoids the production of Aβ (Webb & Murphy, 2012). This more likely indicates that BACE2 has a protective role in AD, but in DS the activity of amyloidogenic APP processing is likely too high for BACE2 to save a patient from AD.

It can be speculated that because of the profound difference we see in AD in DS, APP is the most important protein in the development of AD. This can be because we see an increase in AD progression with an increase in APP genes and expression. However, the 21st chromosome is home to many genes, which all are most probably deeply interconnected with proteins encoded in the whole genome, causing a plethora of various complications in DS, of which most likely a large part influences AD. In a study done by Wiseman et al. (2018) in a tc1 mouse model, meaning that this mouse essentially has a trisomy of the human 21st chromosome but without the gene encoding for APP, they saw that several proteins influenced the biology of Aβ. One of these proteins is SUMO3, which attaches itself to proteins and may modulate functions of proteins essential in APP processing. DYRK1A is another one, which can phosphorylate APP and thereby change its structure, stability and therefore potential for Aβ formation. In the study of Branca et al. (2017), they even proved that inhibiting DYRK1a's actions reduced Aβ plaque load in AD model mice. CSTB is also found on the 21st chromosome and is an inhibitor of lysosomal cathepsins (proteases) and reducing activity of this protein has also shown anti-amyloidogenic properties.

Alternative Factors contributing to Alzheimer's in Down Syndrome

Up until now, we have mainly looked at only one of the two most important contributing factors of AD, namely Aβ production. But what about the production of hyperphosphorylated tau and eventually NFTs in DS? As earlier shown in a study from Bloom (2014), increased Aβ causes an increase in the enzymes that cause hyperphosphorylation of tau and NFTs steadily form as more plaques are also formed. This would mean that in the case of DS, we would also see a steady increase of NFTs with more Aβ, as in DS the production of Aβ is already higher. This is also reflected in present studies on tau pathology in DS, showing a higher amount of seeding and pathological tau processes in DS (Granholm & Hamlett, 2024). Oxidative stress is also often a factor in the progression of AD as it seems to contribute to the formation of Aβ plaques and NFTs, which is no different in DS. SOD1 seems to have an important role in regulating

Reactive Oxygen Species (ROS) in healthy situations and normally acts as an antioxidant, reducing the amount of ROS and thus oxidative stress in the body. The gene for SOD1 lies on the 21st chromosome and is thus increased in concentration in DS, creating an imbalance ratio of SOD1 to other antioxidants which results in an accumulation of hydrogen peroxide, a ROS. Higher oxidative stress could interestingly enough also be due to the overproduction of Aβ and its side products, which have been shown to increase ROS presence (Perluigi & Butterfield, 2012), or because people with DS have less antioxidant capacity to take care of the ROS (Revilla & Martínez-Cué, 2020). Neuroinflammation regularly stands central in the diagnosis of AD, proving that it's an important indicator of the disease and in DS, there often is an increase in the amount of neuroinflammation found. This can be due to the proven activation of microglia by Aβ plaques, but there already seems to be a difference in both microglia and astrocytes in DS, with the microglia being decreased over age and number of astrocytes changing during certain phases of life (García & Flores-Aguilar, 2022). There also is a genetic basis for increased neuroinflammation in DS, ⅔ of the interferon receptors are encoded on the 21st chromosome and are again increased in expression. Binding to these interferon receptors can induce antiviral immune responses and are thus important in the increased activation of the immune system in the brain in DS (Chung et al., 2021). Even the relative dysfunction of the mitochondria in DS has been linked to AD, which is involved in the oxidative stress found in individuals with DS (Pagano & Castello, 2012).

Clinical Implications and Therapeutic Strategies

After doing this deep dive into the possible mechanisms and different genes that influence AD in DS we ponder if there must come a different strategy regarding diagnosing and treating DS patients with AD. Currently, the diagnosis of AD in DS has proven quite difficult, as there is a wide variety of cognitive levels of functioning amongst the DS population and there's not a certain protocol that has to be followed all over the world when diagnosing AD in DS. It's hard to establish a baseline of cognitive functioning when some of them can do tests, while others are incapable of understanding the tests (Nieuwenhuis-Mark, 2009). Making it even more difficult, there seem to be individuals with DS that never acquire AD, because they have a partial trisomy, in this case coincidentally excluding APP on the third copy of the chromosome (Dekker, 2017). Diagnosis and treatment are both subject to a lot of change in the future as a lot of research is being done in the field of both AD and DS in AD, which uncovers more and more biomarkers which could be targeted for diagnosis and treatment. Currently, as soon as dementia is diagnosed in individuals with DS, they receive the same standard treatment as typical dementia patients, such as cholinesterase inhibitors. However, the implementation of these novel biomarkers for AD diagnosis in DS is still an unfinished form and has to go through several clinical trials before they can be relied on.

Conclusion

To conclude, in this literature review we explored the different roles and mechanisms of APP in both AD and DS, showing us that APP seems indeed to have the main role in accelerated AD in DS and all enzymes or substrates that are associated with APP processing influence the severity of Aβ plaque formation in the brain, which stands central to the progression of AD. Overexpression of APP due to trisomy 21 causes an increase in risk for AD and also increases

the activity of all that is involved in the amyloidogenic, but also non-amyloidogenic, pathways which causes more Aβ production, plaque formation and indirectly also more formation of NFTs. Triplication of the 21st chromosome also seems to influence the risk for AD in the absence of a triplicated APP gene, meaning that other genes like BACE2 or DYRK1a also contribute to the risk for AD. Knowing this, it's also really important to acknowledge the other factors that contribute to AD in DS like the baseline of oxidative stress, neuroinflammation and mitochondrial dysfunction being different in DS than in typical persons. Emerging therapeutic strategies that target APP processing could be promising, but we face difficult challenges in implementing these strategies because of their novelty and the fact that there's such a high variability in cognitive functioning in the DS population. Future research should focus on more precisely targeting the biomarkers mentioned, figuring out how their mechanisms work and exactly what their roles are in the production of Aβ.

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