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Exploring the complex nexus of Alzheimer's disease in down syndrome

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Abstract. In recent years, the life expectancy of individuals with Down Syndrome (DS) has increased significantly thanks to the advancements in healthcare and treatments, giving rise to an older population of people with DS. However, this demographic shift has brought about new concerns: as individuals with DS age, they face a higher incidence of early-onset Alzheimer's Disease (EOAD) (i.e. the development of AD before the age of 65). Research has revealed an accelerated progression of symptoms, from onset of dementia to death, in DS patients. Thus, it is essential to identify the factors (both genetic and environmental) that underlie the development of different stages of AD-DS. Concomitantly, there is a pressing need to initiate intervention trials that could slow down or prevent the rapid advancement of AD-DS. This paper underscores the growing importance of addressing AD-DS in an ageing DS population. By elucidating genetic and environmental factors, clinical features, diagnostic challenges, roles of genes in the development of AD-DS, and potential future research directions, the article aims to contribute to a deeper understanding of dementia of the Alzheimer Type (DAT) and facilitate the development of effective treatments that could improve the lives of DS individuals affected by DAT.

Keywords: Alzheimer's Disease, Down Syndrome, Amyloid Precursor Protein, Amyloid Beta, Neurofibrillary Tangles

1. Introduction

Down syndrome (DS), also referred to as Trisomy 21 (T21), is a genetic disorder due to a naturally-occurring imbalance in gene dosage which is developed when abnormal cell divisions result in nondisjunction and an extra full or partial copy of chromosome 21 (chr 21) is encoded into our genes [1]. This process has an incidence rate of one in 700 births and there are three forms of this copy: Simple Trisomy 21, Translocation Trisomy, and Mosaic Trisomy [2,3]. The one that will be discussed is Simple Trisomy 21, (T21) the most common cause of DS, which is when abnormal cell divisions during the development of the sperm or egg cell cause the individual to have three copies of chromosome 21 rather than two. This extra copy causes intellectual, developmental, and physical retardations that vary among DS individuals, as well as distinct facial features, some of which include narrow slanted eyes, flat noses, and short stature [3].

As medical treatments and technologies advance, individuals with Down syndrome now have a significantly longer life expectancy. Tsou states that in just 40 years, the average life expectancy has increased by 35 years [4]. Consequently, there has been a substantial growth in the older demographic of individuals with DS.

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Approximately 70% of DS patients will develop dementia and Hartley pointed out that the number of AD+DS will concomitantly increase with the life expectancy of DS, for there are no treatments to prevent AD [5]. Therefore, their lifespan has placed them at very huge risk for developing AD. In fact, DS currently constitutes the most extensive demographic of people impacted by EOAD, with an estimated prevalence ranging from 250,000 to 400,000 in the United States and around five million globally [5]. The growing population of middle-aged DS individuals has enabled clinical trials and experiments on AD in DS patients to be studied and documented.

Although the seriousness of AD and increasing risk for DS individuals to develop dementia has been recognized, not much awareness has been placed on this issue. The cause and cure of Alzheimer's disease is a mystery that scientists have spent years of research and trials trying to solve. A great variety of clinical trials and experiments have been done on AD patients to find the right treatment for the disease. However, there is also a need to include AD+DS patients in their study as AD+DS represents a large group of individuals globally.

This article aims to place more awareness on the seriousness of AD+DS by providing an overview of pathogenic links between AD and DS, case studies of T21's effect on the aetiology of AD+DS, clinical features of AD-DS, as well as possible future research areas.

2. Role of APP in AD

Pathological features of AD are amyloid plaques accumulation and neurofibrillary tangles (NFTs). These plaques are composed of oligomers of small peptides known as β-amyloid (Aβ). These peptides are made in a protein called β-amyloid precursor protein (APP), located on chromosome 21. Research on the aetiology of AD has shown that in cases of AD without DS, the duplication of chromosome 21 was sufficient to trigger the development of EOAD but not enough to result in the development of AD+DS [6].

Trisomy 21, the most common cause of DS, is when an extra copy of chromosome 21 is encoded. An extra copy of chromosome 21 results in the overexpression of APP as well as the increase in the formation of amyloid-beta (Aβ) oligomers and AD+DS. Although simple trisomy 21 will be discussed the most throughout the article, partial trisomy of chromosome 21 (PT21) is also important as it shows the essential role of APP in the development of AD. PT21 is when the DS individual lacks the triplication of APP, thus not having an increased chance of developing AD.

Elucidating the involvement of APP in the pathogenesis of AD+DS would help in understanding about the aetiology of AD and might even help us find the treatment for AD. A study of DS patients with PT21 (missing APP gene) was able to prove the essential role of APP in the aetiology of AD-DS.

Doran examined a 65-year-old patient with PT21 [6]. Prior to conducting the experiments, the patient's IQ was assessed with the Wechsler Adult Intelligence Scale (WAIS-III) and yielded a score of 69. Additionally, the VABS-II composite score indicated age-equivalent to 10.5 years old. The tests concluded that the patient functioned around the upper range of abilities compared with other DS individuals. Neuropsychological findings showed less than 3% decline over seven years, while a group of high-functioning DS adults with dementia usually has a 17-28% decline in scores per year. Therefore, the absence of dementia in the tested patient could be confirmed.

Furthermore, Plasma Aβ tests showed that the PT21 patient had normal levels of plasma Aβ40 compared with nondemented and demented DS individuals and the levels of plasma Aβ42 were lower than both [6]. The neurofibrillary degeneration observed in the PT21 patient seemed to be consistent with ageing instead of dementia, an occurrence known as Primary Age-related Tauopathy (PART), which is a normal occurrence in the ageing process.

Aβ immunocytochemistry was performed on the middle frontal gyrus of the PT21 patient, and the findings were juxtaposed with those from a patient with complete trisomy 21 who experienced dementia and passed away at the age of 43. Figure 1 shows the dramatic difference in the amount of Aβ present between the two patients.

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From the difference in testing results, the data confirmed that the DS patient lacking APP triplication was linked to the lack of dementia, low plasma Aβ42, and thus the absence of AD. These results confirm the pivotal significance of APP in the development of AD-DS.

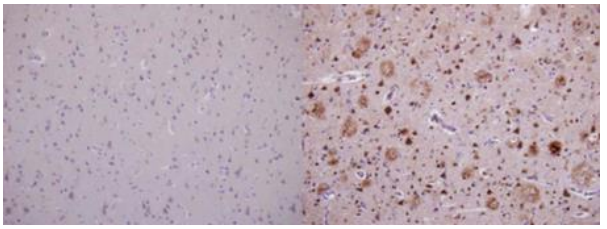

Figure 1. Aβ immunocytochemistry at 20x objective lens magnification was performed on the middle frontal gyrus; left figure displays the absence of amyloid plaques staining in the PT21 patient; right figure shows staining of a patient with full trisomy 21 and AD. Sections were counterstained with cresyl violet [6].

3. Genetic Factors and Mechanisms in AD-DS

3.1. Association Between APP Overexpression and AD+DS

An extra chromosome 21 in DS individuals results in an extra copy of the APP gene, thereby increasing the production of Aβ peptides. These peptides are a hallmark of AD, which accumulates in the brains of AD individuals. This suggests the strong connection between chromosomal imbalances and the development of AD+DS.

3.1.1. Endosomal Involvement and Gene Impact in AD-DS Associated Aβ Accumulation. APP undergoes processing within endosomes through β- and γ-secretases, suggesting the critical role of secretory and endosomal systems in Aβ generation. In the early stages of AD, the endosomes are notably enlarged. A similar enlargement process is also seen in a DS fetus even before AD pathology develops. The presence of an extra copy of the APP gene results in heightened Aβ production, causing the enlargement of endosomes and disruptions in cellular trafficking processes. These issues contribute to the progressive degeneration of neurons, as endosomal dysfunction disrupts various essential cellular processes vital for neuronal function such as local signalling, protein synthesis, and retrograde signalling. Triplications of other genes on chromosome 21 also affect the secretory-endosome system, thus affecting synaptic function, Aβ production, and trafficking. One example stated by Wiseman et al., is the gene Synaptojanin 1 (SYNJ1). Overexpression of SYNJ1 in DS individuals enlarge endosomes while reduced expression of SYNJI lowers Aβ levels and cognitive deficits [7].

Investigating the interplay between endosomal functions and chromosome 21's genetic triplications can help uncover the genetic imbalances that disrupt numerous cellular mechanisms that lead to protein accumulation and progressive deterioration in neurodegenerative diseases such as AD. Furthermore, a deeper understanding of endosomal dysfunction could help identify potential treatment targets such as reinstatement of cellular functions and reduction of the influence of chromosome 21 on neurodegenerative conditions.

3.1.2. Basal Forebrain Cholinergic Neurons Degeneration Mouse Models. AD-DS mouse models show that APP overexpression leads to dysfunction in endosomal system, which affects the signalling pathways of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), and ultimately contributes to the degeneration of basal forebrain cholinergic neurons (BFCNs). These neurons are essential for memory function and experience gradual degeneration in individuals with AD-DS [5]. Degeneration patterns of BFCNs can be seen in the Ts65Dn mouse models of a DS individual. Initially, the mice models process normal BFCN density, just like the early stages of DS individuals. Nevertheless, with ageing, mice models experience a gradual decline in BFCN density which corresponds to the

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decline in spatial reference and working memory. Additionally, the staining for the trkA, the high-affinity NGF receptor, decreases not only in the BFCNs of Ts65Dn mice models but also in AD+DS patients.

3.2. Association with Immune System

The role of the immune system in the development of AD-DS has been a popular field in scientific research. Mounting evidence suggests that DS individuals face a greater risk of immune system malfunction as well as an increased prevalence of autoimmune and infectious diseases. The patients also show upregulation of pro-inflammatory makers such as interleukin01, in the brain. Wiseman et al. explain that these dysregulations contribute to the development of DAT in DS individuals through alterations in the microglial activation, as the microglia have been linked to mature Aβ plaques and NFTs, which are both hallmarks of AD [7].

One example given in Wiseman's paper is the upregulation of chromosome 21 gene S100 calcium-binding protein beta (S100B) in AD and AD-DS. He states that the overexpression of S100B leads to neurodegeneration through its role in fostering Aβ accumulation, tau phosphorylation, and the creation of a neurotoxic environment by releasing external signals [7].

4. Clinical Features of AD+DS

The features of DAT in DS individuals are very much similar to the DAT in the general population as they both involve a decline in cognitive and functional abilities. However, there are still some differences that should be noted [8].

Previous studies have shown that (1) the onset of signs and symptoms of DAT occurs at an earlier age in individuals with DS compared to the general population. Furthermore, (2) the period of symptom progression from the initial onset of dementia to death is shorter in DS patients (around 3-6 years for DS individuals and 8-15 years for the general population). The third notable difference in DAT of DS patients is (3) the way initial symptoms become evident. In contrast to DAT found in the broader population where cognitive decline is first noticed, studies suggest that the initial symptoms of DAT seen in DS patients are changes in behaviour and development of difficulties in daily activities (i.e. changes in personality and irritability, loss of social interactions, daytime sleepiness, etc.) Hutchinson's paper gives a greater insight into more case studies that back up this claim. Another significant difference is (4) the connection between late-stage dementia and the heightened occurrence of late-onset epilepsy. Studies reveal that AD-DS individuals have an 84% prevalence rate for late-onset epileptic seizures, significantly higher than the 10% rate observed in the general population with DAT. Hutchinson also emphasises that the commencement of epileptic seizures might act as a predictive factor, as DS patients did not survive beyond a period of 3 years following the initiation of these seizures [8]. This helps emphasise the urgency to the research of AD-DS as the faster progression of the disease in DS patients and the higher epileptic seizure rates place the DS individuals in more danger.

5. Difficulties in the Diagnosis of AD in DS Individuals

Although the diagnosis of AD is quite obvious, such as a decline in cognition and the accumulation of amyloid plaques and NFTs, the diagnosis of DS contains multiple challenges. The assessment of activities in daily living (ADLs) used to define AD in individuals with DS cannot be used to confirm the development of dementia as the intellectual disabilities in each DS patient vary in type and severity. As a result, the cognitive assessments must be based on the individual patient's baseline.

Holland et al. identified four factors that limit the applicability of diagnostic criteria for AD in the general populace when applied to individuals with intellectual disabilities. The factors include intellectual distortion (i.e. in situations where individuals with DS face challenges in expressing their issues, emotions, and symptoms), psycho-social masking (i.e. limited social skills and life experiences that lead to 'bland' and 'naive' clinical presentations), cognitive disintegration (i.e. emotional stress that could cause abnormal performance during clinical assessments), and baseline exaggeration (i.e. worsening of existing cognitive deficits and behavioural issues, thus complication the determination of the exact onset of DAT.) They also point out that people with DS initially live in a lifestyle that is very

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easy and less demanding than the general population, which makes it harder to determine behaviour deficits and cognition declines.

Another difficulty in diagnosing DAT in DS individuals is common diseases that may involve similar symptoms as DAT such as sensory impairments and fatigue. One example is Hypothyroidism, a common problem that occurs in 30% of DS individuals. The symptoms include lethargy, disorientation, functional decline, and other various symptoms that resemble DAT. Due to the similarities, these symptoms are frequently misdiagnosed as DAT [8]. A case study of a 38-year-old woman with DS was presented in Hutchinson's article. She was assessed for DAT due to her 6-month history of gradual deterioration in functional abilities, alongside issues such as urinary incontinence, lethargy, and reduction in emotional responsiveness. Although DAT was suspected, the individual returned to her normal state after 4 months of therapy for hypothyroidism [8].

The use of neuropsychological tests as diagnostic is also a notable difficulty in the diagnosis of DAT in DS patients. This is because the neuropsychological tests are designed for the general population, thus the tests assume a baseline cognitive function level based on those that don't have disabilities. DS patients wouldn't be able to use these tests because each patient has various baselines and they often end up performing near the lowest achievable scores on the tests due to their learning disabilities, rendering it impossible to track the cognitive decline over time.

It is also important to note that the progression of DAT in DS individuals is faster than in the general population. Thus, the technology for diagnosis of the disease plays an essential role as it is important that the disease is diagnosed in the earlier stages of the disease so the individual can receive therapeutic procedures that could help them cope with dementia and lead to a better quality of life as early as possible.

6. Future Approaches

The lifespan of DS patients has risen significantly, from only 9 years to 60 years in 90 years of research, less than a century [9]. However, this longer lifespan has brought about an elevated susceptibility to AD-like symptoms. The pathology and possible treatments of AD alone is still a mystery, making the research for possible cures of DAT in DS individuals an exceptionally challenging task. Furthermore, medications proven to be successful in alleviating AD symptoms in the general population, such as cholinesterase inhibitors and Memantine, have not demonstrated such positive outcomes in demented DS individuals.

6.1. APP Gene Dosage and the Reduce in Aβ

Since the overexpression of the APP gene is the major reason why the risk of DAT is so high in DS individuals, one approach to enhancing the outcomes of AD-DS patients is to explore treatments that reduce the production of Aβ such as BACE inhibition or Aβ immunisation [7]. A study utilised a vaccine called DS-01 developed through liposome technology to target mouse Aβ, aiming to assess its potential to disrupt Aβ self-tolerance, enhance cognitive levels, and safeguard BFCNs from atrophy while avoiding negative effects such as brain inflammation and haemorrhage [9].

Ts65Dn mice are mice models specially used for the study of DS. These mice possess an additional segment of mouse chromosome 16, mirroring the structure and characteristic human chromosome 21 (i.e contains the gene for APP). As a result of the extra chromosome 16, the levels of APP gene products such as Aβ42 and Aβ40 are higher in Ts65Dn mice than in normal mice. Ts65Dn mice do not develop neuronal abnormalities seen in AD such as NFTs, observations do show structural and functional changes in the synapses. Furthermore, the mice experience cognitive decline early at 3 months old and neuron dysfunction and degeneration are consistent with their ageing process. This shows that the extra dosage of APP in the Ts65Dn mice causes the degeneration of brain cells such as the BFCNs leading to shrinkage and loss. Thus, Ts65Dn mice have been used as an essential model in the investigation of the development of DAT in DS individuals.

The vaccine used contained the Aβ 1-15 peptide within liposomes with adjuvant monophosphoryl lipid A (MPLA). Ts65Dn mice received the vaccine 5 months after birth and were officially tested and

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studied when at 8 months of age. The study mainly consisted of determining the condition of BFCNs and measuring the levels of APP in the brain of the Ts65Dn mice compared to normal mice.

6.1.1. Vaccine-Induced Reduction of Aβ Levels in Immunised Ts65Dn Mice. Immunised Ts65Dn mice led to a slight decrease in Aβ levels in comparison to non-vaccinated Ts65Dn mice and their Aβ levels were on par with those of diploid (2N) mice (i.e. containing two complete sets of chromosomes) (Fig 2) [9]. This can be seen in Figures 2 A and B, where initially, the untreated Ts65Dn mice exhibited elevated levels of Aβ42 and Aβ40 in comparison to the 2N vehicle-treated mice. However, it can be observed that the Aβ concentration in the immunised Ts65Dn mice did not exhibit a noteworthy difference compared to the vaccinated 2N mice [9].

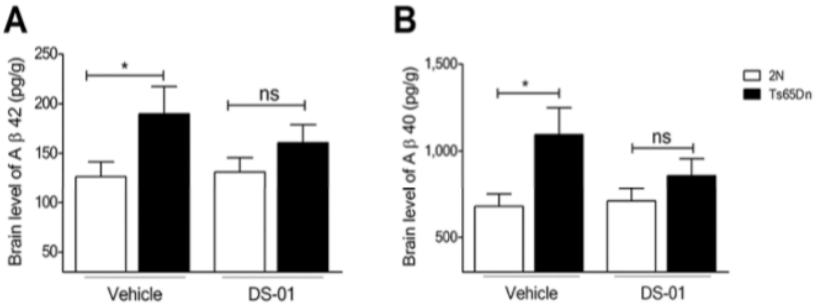

Figure 2. Immunisation with DS-01 led to decrease in levels of Aβ42 and Aβ40 in the Ts65Dn brain. (A) Aβ42 and (B) Aβ40 levels in brain samples of 2N and Ts65Dn mice [9].

6.1.2. Effects of DS-01 Vaccine on Cholinergic Neuron Atrophy: Medial Septum Analysis. To witness the influence of the vaccine on neurodegeneration, analysis of cholinergic neurons in the medial septum took place. This observation took place by using a staining method for a specific enzyme called choline acetyltransferase (ChAT). The results showed that there was approximately a 10% increase in the size of ChAT-positive (ChAT+) cell bodies in immunised mice compared to those treated with a placebo. The size of cell bodies in the DS mice model after treatment was similar to that in normal 2N mice treated with DS-01 (Fig 3). Thus, it can be concluded that the DS-01 vaccine reduced the atrophy of cholinergic neurons.

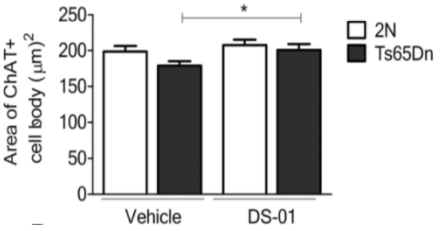

Figure 3. DS-01 vaccination halted degeneration of cholinergic neurons. Notable increase in size of ChAT+ cell body region of Ts65Dn immunised mice compared to Ts65Dn mice treated with a vehicle [9].

6.1.3. Positive Cognitive Effects of DS-01 Vaccine Immunisation Revealed in Object Recognition and Fear Conditioning Testing. Numerous trials were conducted to assess the impact of the vaccine on cognitive function. These experiments took place a fortnight after the final vaccination, and they included assessments of locomotor activity, object recognition, and fear conditioning, conducted in the specified sequence. Two tests resulted in positive results after immunisation by the DS-01 vaccine. The first one was recognition memory, which was conducted through the object recognition test. The results concluded that initially, the DS-model mice had a discrimination index (DI) 11% lower than 2N mice. Nonetheless, following immunisation, Ts65Dn mice exhibited a notable rise in DI, underscoring the

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potential of DS-01 to enhance cognitive function (Fig 4). The 2N mice also showed an improvement in cognition however, the increase was much smaller than in the Ts65Dn mice. The fear conditioning test, assessing alterations in contextual memory following DS-01 immunisation, also yielded positive outcomes. In comparison to the control subjects, the Ts65Dn mice treated with the vehicle displayed reduced freezing behaviour, indicating an inability to recognize negative valence context. In contrast, immunised Ts65Dn mice showed a 90% increase in freezing, reaching a level similar to that of 2N mice. This reduction in the contextual fear memory deficiency in Ts65Dn was observed as a result of the DS-01 immunisation.

The tests conducted two weeks after the DS-01 vaccine injection revealed positive effects on cognition in Ts65Dn mice: particularly in object recognition where cognitive function improved notably, and in the fear conditioning test where contextual memory defects were significantly reduced after immunisation.

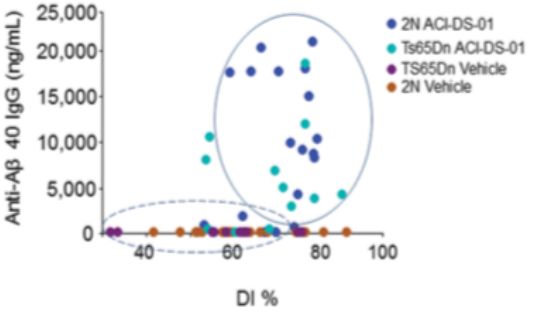

Figure 4. Recognition memory evaluation following DS-01 immunisation.

Figure 4 shows a Positive correlation between the amount of anti-Aβ40 IgG and the immunisation vaccine (with a correlation coefficient 0.4, p=0.002). Top performers with the highest DI% are 2N mice and the lowest DI% belongs to the untreated Ts65Dn mice. Vaccinated mice (both 2N and Ts65Dn) show a spread of data above a DI of 70% (solid circle) while most untreated mice have lower DI values (dashed circle) [9].

6.1.4. No Inflammations and Hemorrhage Depicted in DS-01 Vaccine Safety Evaluation in Mouse Models: Health Parameters and Immunological Markers. In order to assure the safety of the vaccine, the impact of DS-01 immunisation on mouth health was assessed through weight measurements. Although the body weights of DS-model mice were notably lower than general mice, they were unaffected by the vaccination. Brain weights and general health parameters (i.e. appearance, dietary habits, and fluid intake) showed no changes after immunisation. Astroglia activation and CD45 (lymphocyte common antigen) were evaluated to examine glial fibrillary acidic protein (GFAP) and microglial activation (Fig 5A). The results showed no noteworthy differences between the 2N and DS mice model, regardless of whether they were treated with the vehicle or DS-01, in both cortex and hippocampus regions (Fig 5B). The vaccine had no noteworthy impact on IFN or TNF levels in plasma and no significant changes in II-6 levels.

Various staining techniques, including Perls Prussian blue (PPB) staining, immunostaining with an anti-CD4 (clusters of differentiation 4) antibody, and hematoxylin and eosin (H&E) staining, were applied to cortical sections of mice from different experimental groups (Fig 5C). Results showed no positive staining, providing evidence that there was no presence of lymphocytic infiltration or microhemorrhage in the DS-01 immunised mice. Thus, one can deduce from the findings that the vaccination, DS-01, is safe in a mouse model of DS as it showed no evident changes in brain weight, injury, or inflammatory markers.

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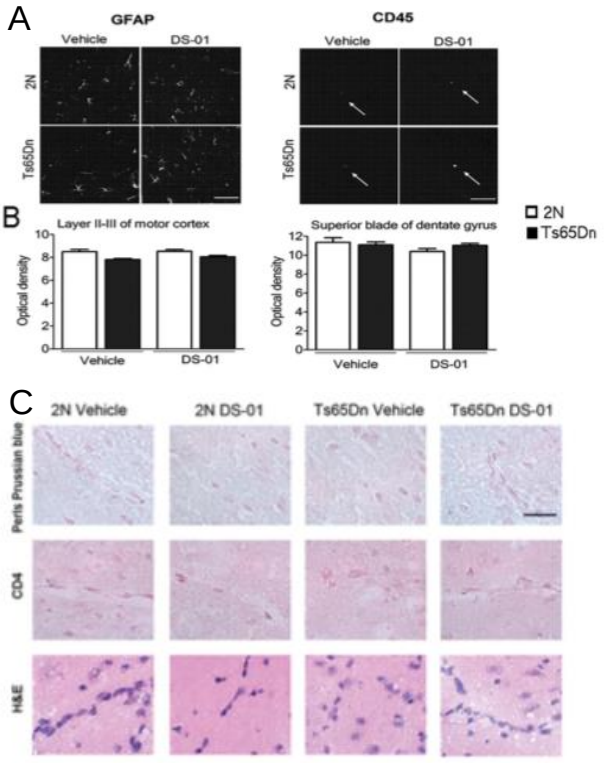

Figure 5. Assessments of inflammatory indicators after vaccination. (A) Confocal images displaying GFAP (left) and CD45 immunoreactivity (right) in 2N and Ts65Dn mice treated with either the vehicle or DS-01. Arrows indicate individual CD45-positive microglial cells. Images from cortex (scale bars=100μm). (B) Density of substances exhibiting GFAP immunoreactive in the layers II-III of the motor cortex (left) and the superior blade of dentate gyrus (right). Error bars, standard error of the mean (SEM). (C) Use of Perls Prussian blue, immunostaining with anti-CD4 antibody, and H&E staining on cortical sections did not show positive staining in all groups. Evidence that there is no indication of lymphocytic infiltration and microhemorrhage. Number of mice used: 2N-vehicle/Ts65Dn-vehicle/2N-DS-01/Ts65Dn-DS-01 = 3/5/5/5 [9].

6.1.5. Discussion of Results. Around two decades ago, the first clinical trial of anti-Aβ42 immune treatment took place. The AD patient showed promising results as the cognitive decline was slowed down. However, 6% of the treated, immunised patients developed meningoencephalitis due to Aβ42-specific CD4+T-cell infiltration in the brain [9]. Since then, researchers have tried to improve the Aβ vaccines by reducing the side effects.

The findings demonstrated the safety and efficacy of the DS-01 in a mouse model of DS. The assessments of the vaccinated Ts65Dn demonstrated consistent trends in the reduction of Aβ42 and Aβ40 levels, the ability to prevent cholinergic neuron atrophy and improvements in hippocampal-dependent memory function. Overall, the findings conclude that targeting Aβ through immunisation is a possible strategy for treating DAT in DS individuals and that a vaccine similar to DS-01 would likely be safe for DS individuals.

6.2. Genetic Mechanisms Underlying AD-DS: A Schematic Overview

The occurrence of DAT in individuals with Down syndrome (DS) is attributed to the presence of an additional set of chromosome 21 genes. In order to find a cure for AD-DS, it is essential to understand genes and mechanisms that may play a role in its development. Once there is a profound understanding of each gene's association in the progression of DAT in individuals with DS, deeper insights could be uncovered, thereby increasing the likelihood of discovering a suitable cure for AD in DS patients [7].

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The genes involved in AD-DS could be sorted into two large categories: non-chromosome 21 genes and chromosome 21 genes (i.e. genes that were triplicated in DS individuals) (Fig 6).

Although the triplication of chromosome 21 is the primary driver of DAT development in DS individuals, several genes outside of chromosome 21 could also exert an influence on AD-DS pathogenesis. One example would be apolipoprotein E (APOE) which could alter AD-DS by modulating cholesterol metabolism and other related pathways. Studies indicate that individuals carrying the APOE ε4 allele face increased susceptibility to AD, whereas those progressing the ε2 allele exhibit a reduced risk of AD development [10]. The reduce in amount of ε2 allele in AD-DS individuals when compared to DS controls of the same age without dementia suggests that ε2 allele may play a protective role in preventing dementia in DS while the decreased prevalence of ApoE ε4 in older DS individuals compared to the general population suggests that the ε4 allele may have a detrimental influence on AD-DS patients. Phosphatidylinositol-binding clathrin assembly protein (PICALM) and sortilin-related receptor 1 (SORL1) could affect demented DS individuals through the endocytosis system and the processing of APP, while the microtubule-associated protein tau (MAPT) contributes to the formation of NFTs.

Furthermore, numerous chromosome 21 genes play a pivotal role in the development of AD-DS. For instance, the transcription factor ETS Proto-Oncogene 2 (ETS2) is believed to drive the overexpression of APP by activating the promoter of APP. Additionally, Cystatin B (CSTB), DOPEY2, and SYNJ1 could impact synaptic function while MicroRNA 155 (mir-155) could affect inflammation. Ubiquitin Specific Peptidase 16 (USP16) and Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A (DYRK1A) play a massive role in neurodevelopment.

A multitude of genes contribute to the development of DAT in people with DS. Thus, understanding the role of each gene constitutes an area for future study as it is pivotal in advancing our understanding of AD-DS and exploring potential cures for this disease.

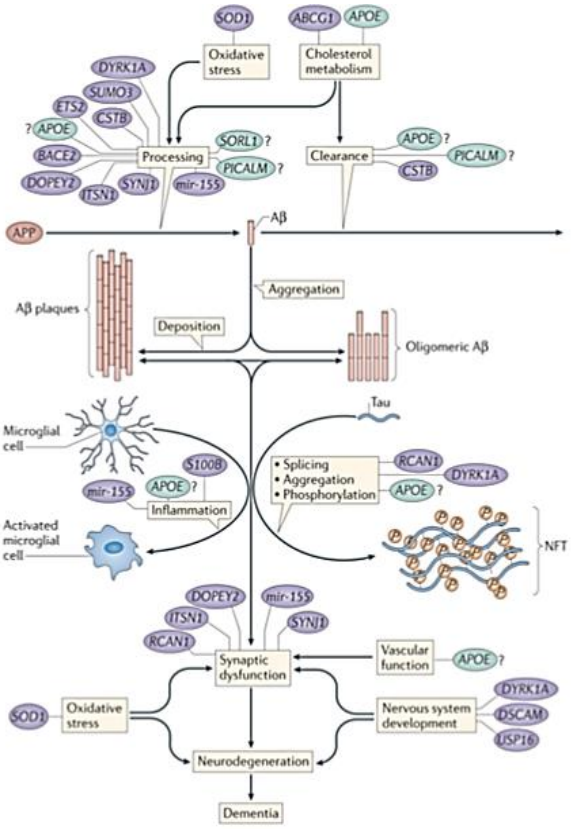

Figure 6. Schematic overview of crucial mechanisms in AD-DS and their associated genes [7]. Genes and gene products related to chromosome 21 are depicted in purple; non-chromosome 21 genes and gene products are depicted in green.

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6.3. Neuropsychological Tests Improvements

As mentioned in section 5, the neuropsychological test is a huge obstacle in the diagnosis of AD in DS individuals because the baseline cognitive function level is based on the general population. The baseline for DS individuals varies, thus resulting in inaccurate neuropsychological test results.

The creation of a neuropsychological test for DS individuals could be an approach that could not only help diagnose the disease at an early stage so the patient can receive treatment as early as possible but also allow those stages of AD-DS to be recorded, examined, and studied to gain a deeper understanding about the progression of AD in DS individuals.

Hutchinson pointed out several requirements to a neuropsychological test specialized for DS individuals [8]. Firstly, an optimal neuropsychological test should involve (1) conducting the test early in the DS individual's life to gain a baseline of the patient's cognitive and functional abilities. Furthermore, (2) subsequent evaluations should occur periodically through their ageing to track any abnormalities or changes in the individual levels of functioning based on their initial baseline as various research mentioned that initial cognitive declines in AD+DS individuals are extremely hard to notice and only become obvious when the disease reaches the later stages.

7. Conclusion

This review has provided an extensive overview of AD-DS, delving into various critical aspects of this complex disease, illuminating the pivotal role played by APP in AD, investigating genetic factors and mechanisms associated with AD-DS, pointing out the differences between features of AD in the general population and AD in DS individuals, and analysis of various future research directions. This paper highlighted several factors and genes that could influence AD-DS and examined the clinical features of the development of AD-like dementia in people with DS. Emphasis was drawn to the difficulties in the diagnosis of DAT in DS and the urgent need for improvement in diagnostic tools and methods was pointed out. Differences between features of AD in the general population and AD in DS individuals defined in the article shed light on the danger of demented DS individuals compared to AD in the general population. Most importantly, this paper highlights the paramount importance of increasing awareness of the high incidence for the rate of AD in DS and the fast-paced progression of dementia from light symptoms to death, especially as there is a notable increase in the population of ageing DS individuals. In conclusion, it is important to overemphasize the critical need for ongoing research about the pathogenic and clinical features of AD in DS and the necessity to advance diagnostic methods and treatments of AD-DS in order to enhance the life of those grappling with the rapid progression of the disease and degeneration of neurons.

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