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The Genetics and Mechanisms of Alzheimer's Disease in Down Syndrome

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Abstract

Down syndrome (DS), caused by trisomy 21, is the most frequent genetic cause of intellectual disability worldwide. Advances in medical care have markedly increased life expectancy, revealing a new clinical challenge: premature aging and a very high prevalence of Alzheimer's disease (AD) in adulthood. Nearly all adults with DS develop cerebral amyloid pathology by midlife, largely due to overexpression of the amyloid precursor protein gene located on chromosome 21. However, the onset and severity of dementia vary considerably, suggesting the involvement of additional genetic, cellular, and environmental modifiers.

This narrative review examines the molecular and cellular mechanisms underlying early brain aging in DS, with particular emphasis on Alzheimer-type neurodegeneration. We discuss gene dosage effects and candidate genes implicated in synaptic dysfunction, endo-lysosomal abnormalities as early cellular biomarkers, clinical and neuropsychological challenges in diagnosing dementia in individuals with DS, and recent advances linking gonadotropin-releasing hormone (GnRH) dysfunction to cognitive impairment. Experimental and preliminary clinical evidence suggests that restoration of physiological GnRH signaling may improve cognition and functional brain connectivity in adults with DS.

Understanding DS as a genetically determined form of Alzheimer's disease offers a unique opportunity to identify early biomarkers and develop preventive or disease-modifying therapies relevant not only to DS but also to sporadic neurodegenerative disorders.

Keywords: Down syndrome, Trisomy 21, Alzheimer's disease, Premature aging, Amyloid pathology, Endo-lysosomal dysfunction, GnRH, Cognitive decline

Introduction

Down syndrome, also known as trisomy 21, is the leading genetic cause of intellectual disability, affecting more than 5 million people worldwide and 500,000 in Europe. The triplication of chromosome 21, described in 1959 as the cause of Down syndrome (DS), alters the development of the central nervous system and neuronal plasticity, leading to cognitive and behavioral impairments [1]. In later life, Down syndrome significantly increases the risk of developing Alzheimer's disease. Improved care for individuals with DS has significantly increased their life expectancy and led to a notable and concomitant rise in the number of adults over 35 with DS who are at high risk of dementia [2]. Their life expectancy is currently fifty-five years. Almost 100% of adults with DS have amyloid deposits in their brains, characteristic of one of the pathologies present in Alzheimer's disease: amyloid pathology [3]. Since the gene encoding the amyloid precursor protein (APP) is located on chromosome 21, individuals with DS have higher levels of APP in their brains, responsible for their high amyloid burden and their increased risk of Alzheimer's disease, according to the amyloid cascade theory [4]. This theory posits that the initial event in the cascade leading to Alzheimer's disease is the presence of amyloid pathology. Recent amyloid imaging studies correlated with the cognitive status of individuals with Down syndrome show that some people are more resistant than others to high cerebral amyloid loads, thus suggesting the existence of genetic or environmental risk factors [5]. Individuals with DS currently face cognitive deficits from a very young age, often associated with other developmental disorders, and then with a significant risk of dementia around age fourty [6]. This review aims to better understand the early brain aging of patients with Down syndrome, and in particular Alzheimer's-type dementia.

Methodology of This Narrative Review

This article is a narrative review synthesizing current knowledge on the genetic and mechanistic links between Down syndrome and Alzheimer's disease. Literature was identified through searches in PubMed and Web of Science using combinations of the following keywords: Down syndrome, trisomy 21, Alzheimer's disease, APP, amyloid, endosome, SYNJ1, DYRK1A, GnRH, and Ts65Dn. Priority was given to peer-reviewed articles published in English, landmark studies in the field, and recent translational and clinical investigations (approximately 1990–2025). Given the narrative (non-systematic) design, article selection was guided by relevance to the mechanistic understanding of DS-associated neurodegeneration rather than predefined inclusion/exclusion criteria. Consequently, the review does not claim exhaustiveness and may reflect interpretative emphasis.

Limitations

Several limitations should be acknowledged. First, as a narrative review, this work does not follow systematic review methodology and may therefore be subject to selection bias. Second, while the mechanistic links between APP overexpression and amyloid pathology are well established, other proposed contributors–such as GnRH dysregulation–are based on emerging preclinical and early clinical evidence that requires confirmation in larger, randomized controlled trials. Third, the heterogeneity of cognitive trajectories in individuals with Down syndrome suggests that additional genetic, epigenetic, and environmental modifiers remain insufficiently characterized. Finally, translational extrapolation from mouse models to human pathology must be approached with caution.

What Genes are Involved in Down Syndrome?

Human chromosome 21 (Hsa21) was fully sequenced 40 years after the discovery of DS [7]. Its sequence revealed a size of 47 Mb with the presence of 190 genes encoding known proteins and approximately 230 other sequences [8]. Tools have been developed to study the expression of all these coding and non-coding sequences in cells from individuals with Down syndrome [9]. While an overall overexpression of a factor of 1.5 was expected in three gene copies, it has been observed that approximately 60% of these genes do not show increased expression, a compensatory phenomenon occurring [10]. With less than half of the 3-copy genes exhibiting amplification equal to or greater than 1.5, it seemed more realistic to identify among these overexpressed genes those involved in phenotypes linked to trisomy 21 [11].

Research on trisomy 21 has advanced thanks to the development of mouse models. Hsa21 is orthologous to segments of mouse chromosomes 16, 17, and 10 (Mmu16, Mmu17, and Mmu10). Three-quarters of the genes on the long arm of Hsa21 (112 genes) are present on the telomeric portion of Mmu16. The telomeric segment of Hsa21 is orthologous to a portion of Mmu17 (19 genes) and Mmu10 (39 genes) [12]. The first T21 mouse model developed contained three copies of Mmu16 with a very large number of genes not orthologous to Hsa21.Then came the second model, generated serendipitously by irradiation of embryonic cells: the Ts65Dn mouse, which is currently the most widely used model [13].This model contains 65% of the genes present in humans on Hsa21 in three copies; it is relatively easy to obtain, and cognitive deficits are visible on various learning and memory tests. Subsequently, numerous models of segmental trisomy have been developed, enabling genotype/phenotype correlation studies and the definition of gene intervals whose overexpression is responsible for phenotypic traits. Similar genotype/phenotype correlation studies have been performed using cells from individuals carrying trisomy or partial monosomies of Hsa21 [12].

This is how several genes have emerged as key genes in DS and as potential therapeutic targets. One example is the DYRK1A gene (Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A), also known as the Mini brain in Drosophila, which has multiple functions, particularly in brain development and Alzheimer's disease [14]. Other genes in Hsa21 are also being studied more specifically because they are clearly involved in synaptic function: APP (Amyloid Precursor Protein), DSCAM (Down syndrome cell adhesion molecule), SIM2 (Single-Minded homolog 2), GIRK2 (Potassium Channel, Inwardly Rectifying Subfamily J), OLIG1 and OLIG2 (Oligodendrocyte Transcription Factor 1 and 2), and Synaptojanin 1 (SYNJ1) [15].

Alzheimer's Disease in Down Syndrome

More than 75 million people worldwide could have Alzheimer's disease by 2030. Individuals with Down syndrome are at the highest risk of developing Alzheimer's disease after familial cases that appear very early [16]. It may therefore be possible to find early markers of Alzheimer's disease in people with Down syndrome. A blood marker predictive of conversion to Alzheimer's-type dementia in individuals with Down syndrome has already been described [17]. Recent clinical trials for Alzheimer's disease target well-defined populations, particularly familial forms or individuals carrying the ε4 allele of the gene encoding Apolipoprotein E, a major genetic risk factor for Alzheimer's disease [18]. However, the number of these cases is small and the population of people with DS who have a relatively "pure" form of the presence of plaques and tangles in the brain are the telltale signs of Alzheimer's disease. The main component of plaques is a beta-amyloid protein (Aβ peptide) that has split off from a much larger parent protein called amyloid precursor protein

(APP) [19]. The tangles are found inside nerve cells, and the accumulation of Aβ peptide may cause them to grow outside the cells. These tangles and the beta-amyloid protein work together to make the cell diseased and eventually die [20]. The disease, which begins in certain parts of the brain, tends to spread, which explains the impairment of various functions as it progresses. Researchers have discovered a link between amyloid protein production and chromosome 21. Alzheimer's disease, without vascular disease, could be the subject of targeted clinical studies. Because individuals with Down syndrome have an extra chromosome 21, they are more prone to an overproduction of APP [21]. As noted above, having more APP can lead to increased production of β-amyloid protein, so these individuals do indeed develop the plaques and tangles characteristic of Alzheimer's disease. However, they will not exhibit all the symptoms of the disease. Other factors are believed to contribute to its development, such as a family history of Alzheimer's, premature aging, environmental factors, and the role of unknown genes [22]. The prevalence rate of the disease in adults with DS varies with age [23]. Approximately 25% of those over 35 years of age report symptoms associated with Alzheimer's disease, while the overall incidence of Alzheimer's in the Down syndrome population is estimated to be three to five times higher than in the general population. Finally, the risk of developing plagues and tangles characteristic of the disease increases with age, both for individuals with and without Down syndrome [24].

How Can a Neurodegenerative Disease Be Detected in A Person with Down Syndrome?

Subtle memory/executive deficits can appear from 35 years of age; prodromal Alzheimer's disease appears with a mean age of presentation of 50.8 years while dementia presents with a mean age of onset of 53.8 years of age [25]. The diagnosis is based on a progressive cognitive decline compared to the previous level of functioning, detected by family or caregivers.

Cognitive symptoms

Decline in recent memory (difficulty remembering recent events or usual routines); Disorientation (time, places, people); increasing difficulties with language and comprehension; reduced attention span and inhibitory control; progressive loss of independence in daily activities [26].

Behavioral and psychological symptoms

Apathy, social withdrawal, irritability, increased anxiety, sleep disturbances, possibly new seizures, which are frequent in this context [27].

As with any diagnosis of suspected cognitive impairment, it is crucial to first rule out other possible illnesses or explanations. Some of the changes could be caused by depression, thyroid problems [28], trauma or abuse, sensory issues, or some other event. The difficulty in diagnosing individuals with Down syndrome stems from the fact that many of the tools used to diagnose the general population are not necessarily suitable for assessing these individuals. These tools do not consider the intellectual abilities and needs of people with Down syndrome and may misrepresent the situation [29]. The individual physician should administer tests specifically designed for people with Down syndrome.

Here are some of these tests:

- *Dementia Rating Scale for Down Syndrome (DSDS) [30]*
- *Test for Severe Impairment (TSI) [31]*
- *Down Syndrome Mental State Examination (DSMSE) [32]*
- *Dementia Questionnaire for People with Learning Disabilities (DLD) [33]*

Regardless of the assessment tool used, it remains important for the person's family members and healthcare providers to document any changes in behavior, habits, and mood. These observations will help the physician assess the person and make a diagnosis. The person should also be asked to describe the changes they are experiencing. These accounts and family observations, combined with the medical examination, will facilitate the diagnostic process. It is important to note that none of these tests can conclusively determine whether a person with Down syndrome has Alzheimer's disease or a related dementia. But added to the comments and observations of caregivers, they nevertheless constitute the basis on which a probable diagnosis can be based [34].

Dysfunctions of the Endo-Lysosomal System in Alzheimer's Disease and Down Syndrome

It was demonstrated using immunohistochemistry that certain pyramidal neurons in the prefrontal cortex of postmortem brains from patients with Alzheimer's disease and individuals with Down syndrome contained abnormally sized endosomes, which they termed "enlarged endosomes" [35]. The experiments were performed with antibodies against specific proteins of early endosomes (Rab5, a small G protein, and EEA1 for Early Endosome Antigen 1). This subcellular compartment serves to internalize membrane proteins or extracellular molecules, which then travel to compartments where they are degraded, recycled to the membrane, or secreted as exosomes. The endosomal compartment is particularly important in Alzheimer's disease because it is in this compartment that APP is cleaved by β- and γ-secretases. Indeed, enlarged endosomes contain Aβ. In DS, from gestation until adulthood the number of neurons containing enlarged endosomes increases. Interestingly,

this phenotype is present before the appearance of amyloid deposits and is also found in familial cases of Alzheimer's disease with mutations in the APP-encoding gene, but not in cases with mutations in presenilin 1 and 2, components of the γ-secretase complex [36]. Furthermore, endothelial cells contain enlarged endosomes, as do fibroblasts in individuals with Down syndrome. A genotype/phenotype correlation study on eight lymphoblastoid cell lines from individuals with partial Down syndrome identified the Hsa21 gene, SYNJ1, whose overexpression was responsible for the presence of enlarged endosomes [37]. This gene, synaptojanine I, is a phosphatase that dephosphorylates phosphatidylinositol 4,5-bisphosphate and is also an adaptor protein for clathrin coat nucleation in DS. In the context of DS and Alzheimer's disease, endosomes are altered in cells of the central nervous system. In the context of DS, endosomes are also altered in the periphery, giving them potential as a predictive biomarker for the progression of the disease [38]. Endosomes from lymphocytes of Alzheimer's patients were analyzed at different stages of the disease (mild cognitive impairment [MCI] and dementia) using immunocytochemistry. Analysis of 23 controls, 25 Alzheimer's patients with MCI, and 23 Alzheimer's patients with dementia showed that the percentage of abnormally large endosomes is higher in Alzheimer's patients than in controls, with a gradual effect between prodromal and demented individuals [39]. Furthermore, the mean endosome volume is correlated with the retention of the PIB compound, which assesses amyloid burden in the brains of individuals using PET (Positron Emission Tomography) imaging. Finally, it was demonstrated that fibroblasts from 6 patients with sporadic Alzheimer's disease contain abnormally large endosomes compared to fibroblasts from 5 controls. The presence of enlarged endosomes in blood cells could therefore be an early cellular biomarker of Alzheimer's disease and Down syndrome.

Trisomy 21, Gonadotropin-Releasing Hormone (GnRH) and Cognition

Individuals with trisomy 21 have various conditions [40], including learning disabilities that worsen at puberty, impaired axonal myelination of neurons in adulthood, and cognitive decline due to the early onset of Alzheimer's disease, but also impaired sense of smell beginning before puberty, as well as subfertility in women and infertility in most men [41]. Today, there is no treatment for the cognitive and olfactory deficits of people with trisomy 21. In the case of an early defect in the development of the peripheral olfactory nervous system, infertility or subfertility associated with the congenital absence of smell (anosmia) is the consequence of a deficiency or absence of gonadotropin-releasing hormone (GnRH)1, due to an interruption of the embryonic migration, from the nasal region to the brain, of the neurons producing this hormone (olfactogenital syndrome) [42].

The advent of new neuroanatomical approaches, including the ability to make tissues transparent, and the use of light-sheet fluorescence microscopy [6] have shown that hypothalamic neurons synthesizing GnRH project their axons not only to the median eminence, where neurosecretion of the hormone takes place, but also to other brain regions, including the hippocampus and cerebral cortex, which are involved in cognitive functions [43]. The question is whether the cognitive deficits observed in trisomy 21 are correlated with the maturation of the neuronal system producing GnRH, what alterations in this system, if any, occurred in an animal model of this trisomy, and whether these alterations could be corrected by treatment in adulthood [44].

A phenotype of Ts65Dn mice, in which regions analogous to human chromosome 21, located on mouse chromosome 16, are present in three copies. This mouse model of trisomy 21 has been found to exhibit not only infertility in males and subfertility in females, similar to that found in men and women with trisomy 21, but also olfactory and cognitive impairments that appear progressively with age [45]. These neurological symptoms, not directly related to reproductive function, were instead associated with a progressive decrease in GnRH immunohistofluorescence staining in the cell bodies of the hypothalamic neurons that synthesize it and in their neurite processes, particularly those projecting out of the hypothalamus. The decrease in GnRH production results in changes in the levels and mode of release of luteinizing hormone (LH)2 in the blood. It is important to note that in Ts65Dn mice, the decreased expression of GnRH (several of which are encoded in the trisomal region) and transcription factors such as ZEB1 (zinc finger E-box-binding homeobox 1), which acts as a "switch controlling the expression of the GnRH1 gene and the maturation of GnRH-producing neurons in the hypothalamus," begins in infancy or "mini-puberty." Indeed, it was observed that the elements of this switch were dysregulated in the hypothalamus of Ts65Dn mice as early as the mini-pubertal period, well before the onset of cognitive or olfactory deficits [46]. Furthermore, this altered expression of microRNAs, particularly those of the miR-200 family, and of transcription factors controlling Gnrh1 expression (increased repressors such as ZEB1, or decreased activators such as OTX2) in the hypothalamus appears to lead to altered expression of several other target genes, some of which are involved in axon myelination and synaptic transmission of nerve impulses, not only in the hypothalamus itself, but also and especially in the hippocampus, as well as altered nerve conduction in the hippocampus. A targeted overexpression experiment of miR-200b in the hypothalamus of Ts65Dn mice corrected both the altered gene expression and the abnormal nerve conduction in the hippocampus, as well as the olfactory and cognitive deficits in these mice. Surprisingly, even though this experimental overexpression of miR-200b was performed in adult mice, that is, long after the physiological maturation of

the Gnrh1 gene promoter, which occurs in the first weeks of life at the time of Mini puberty [47], it enabled the reactivation of transcription of this gene in adulthood, thus increasing the number of neurons expressing it in the hypothalamus. It also increased the proportion of neurons expressing Otx2 in the hypothalamus, particularly in neurons synthesizing GnRH. Otx2 is a gene also known to control the opening and closing of other critical periods in brain maturation [48]. To verify that these improvements in olfaction, cognition, and hippocampal neuronal activity, all involving brain structures distant from the miR-200b overexpression site, were due to the restoration of GnRH1 expression in hypothalamic neurons, and were confirmed by transplanting hypothalamic neurons from wild-type mice into adult Ts65Dn mice, as well as by chemo genetic and pharmacological interventions to induce these mice to produce GnRH at a physiological level and rate (pulsatile hormone secretion) [49]. A pilot clinical study conducted in adult men with Down syndrome found that a six-month treatment with a pulsatile GnRH pump [50] improved both intellectual performance and the resting functional connectivity of certain neural circuits known to be altered by this trisomy, which were visualized by fMRI (functional magnetic resonance imaging). This treatment notably reduced the resting functional connectivity of the neural circuit linking the hippocampus and the amygdala, known to be exacerbated in individuals with Down syndrome and to be involved in anxiety phenomena [51], while it increased resting functional connectivity in large regions of the cerebral cortex including circuits linking visual and sensorimotor areas, which are known to be less active in individuals with Down syndrome [52], reaching levels close to those observed in the general population. In conclusion, the control and maintenance of GnRH production by hypothalamic neurons appear to play a critical role in brain development and maturation and in the development of cognitive functions. While it is necessary to await the results of the multicenter, randomized, double-blind, placebo-controlled clinical trial involving patients with Down syndrome before drawing definitive conclusions, the treatment of individuals with Down syndrome using pulsatile GnRH administration appears promising for improving the cognitive deficits associated with this condition. Could this treatment also be considered for certain age-related cognitive disorders, for example, to mobilize cognitive reserve in neurodegenerative diseases such as Alzheimer's or Parkinson's?

Conclusion

Over the past decades, increased life expectancy in individuals with Down syndrome has led to a marked rise in age-related comorbidities, particularly Alzheimer's disease. The triplication of chromosome 21, especially the overexpression of genes such as APP, plays a central role in early amyloid accumulation and neurodegeneration. Additional mechanisms, including endo-lysosomal dysfunction, synaptic alterations, and dysregulation of GnRH signaling–further contribute to cognitive decline.

Although nearly all adults with Down syndrome develop amyloid pathology, clinical expression varies, suggesting the influence of modifying genetic and environmental factors. Advances in biomarker research and experimental therapies, including pulsatile GnRH administration, offer promising avenues for early detection and intervention. Continued translational and clinical research is essential to develop targeted strategies that may benefit not only individuals with Down syndrome but also broader populations affected by Alzheimer's disease.

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