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MOLECULAR MECHANISMS RELATING DOWN SYNDROME AS A RISK FACTOR FOR ALZHEIMER'S DISEASE: A REVIEW SYSTEMATIC

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Abstract: Down Syndrome, characterized by trisomy 21, has experienced an increase in life expectancy due to advances in health services, consequently, age-related diseases have increased in prevalence, such as Alzheimer's. The aim of this systematic review was to understand the molecular mechanisms that make Down's Syndrome a risk factor for Alzheimer's. The systematic review was carried out in accordance with the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA), using the following databases: Scientific Electronic Library Online, Pubmed and the Virtual Health Library. Eleven articles published between 2014 and 2024 were selected by applying the inclusion and exclusion criteria. The review identified that trisomy 21 makes people with Down's Syndrome more susceptible to developing early-onset Alzheimer's due to the formation of amyloid plaques and tangles neurofibrillary. In this sense, some genes have been identified in this pathogenesis, such as: APP, EST 2, DYRK 1 A, RCAN 1, SOD 1, SYNJ 1, CSTB, S100B, encoding IL-1, USP 16 and also the apoE ε4 allele. However, due to the neuropathological complexity of this relationship, further studies on the impact of this triplication of genes are essential.
Keywords: Down syndrome; Trisomy 21; Alzheimer's disease; Early Alzheimer's; Beta-amyloid peptide.

INTRODUCTION

Dementia is a Major Neurocognitive Disorder (MND) that can be caused by various pathologies of a slow, progressive, evolving and chronic nature. This disorder results in impairment of higher cortical functions, such as reasoning, judgment and language, causing significant damage to the quality of life of patients affected by the disorder. Within the TNM, Alzheimer's disease (AD) is the most common in the population and is caused by the destruction of cholinergic neurons.[1,2] AD is mainly manifested by impairments in cognition and

memory, with a clinical picture of progressive worsening with inappropriate motor behavior, psychosis, personality changes associated with neuropsychiatric symptoms such as agitation, depression and hallucinations. [3]

AD is associated with two pathophysiological pathways: extracellular beta-amyloid and TAU protein associated with intracellular microtubules. The first refers to the accumulation of beta-amyloid protein fragments outside neurons, which forms the so-called senile plaques that have a strong relationship with cell death, as they directly interfere with neuron-neuron communication at synapses. The second pathophysiological pathway associated with AD is the hyperphosphorylation of the TAU protein in neurons, which causes neurofibrillary tangles, which in turn block the transportation of nutrients into nerve cells. The two pathways of Alzheimer's disease pathogenesis come together as beta-amyloid increases and reaches a trigger point for the spread of abnormal TAU throughout the brain.[2,3] Risk factors associated with AD include advanced age, hypertension, hypotension, heart failure, stroke, coronary artery disease, history of migraine, head trauma, diabetes mellitus, obesity, smoking, sedentary lifestyle, poor diet and Down's Syndrome.[4]

Down's Syndrome has a genetic origin in the presence of an extra chromosome 21, which is an important factor in the production of beta-amyloid, given that the beta-amyloid precursor protein (APP) gene is located on chromosome 21, which is triplicated. Other associated genes such as SOD1 (superoxide dismutase type 1) and DYRK1A (dual specificity tyrosine phosphorylated kinase type 1). These similarities between DS and AD lead to a high frequency of dementia in patients with the genetic alteration quoted. Alzheimer's disease affects up to 75% of Down's Syndrome patients over the age of 60.[5,6]

Thus, due to the various technological advances in the health area, the life expectancy of the population affected by Down's Syndrome has increased sharply in recent years, calling for more research involving the association between the two pathologies, with a view to better managing AD in this specific group, considering the high incidence of the neurological syndrome in those who already suffer from the genetic syndrome.

METHODOLOGY

This study is a systematic review of the literature drawn up in accordance with the methodological recommendations of the PRISMA (Preferred Reporting for Systematic Reviews and Meta-Analyses) statement, in which the 4 stages for constructing a flowchart were followed (Figure 1). Using the PICO strategy, we arrived at the following research question: "What molecular mechanisms make Down's Syndrome a risk factor for the development of Alzheimer's Disease?"

The descriptors were selected from DeCS (Descriptors in Health Sciences) and their linguistic variations in Portuguese, English and Spanish were considered: Down Syndrome, Trisomy 21, Alzheimer's Disease, Early Alzheimer's and Beta Amyloid Peptide. In addition, the Boolean operator used was "and", and the databases used were Scientific Electronic Library Online (Scielo), Pubmed and Biblioteca Virtual em Saúde (BVS).

Initially, 827 articles were found and evaluated by 7 researchers using inclusion and exclusion criteria. The inclusion criteria were: papers written in Portuguese, English and Spanish, with full text available and published between 2014 and 2024, central thematic area consisting of Down's Syndrome and Alzheimer's Disease and genes involved in trisomy 21. The following exclusion criteria were then applied: duplicates, studies that did not answer the research question and incomplete studies. This resulted in the selection of 11 highly relevant articles for this study.

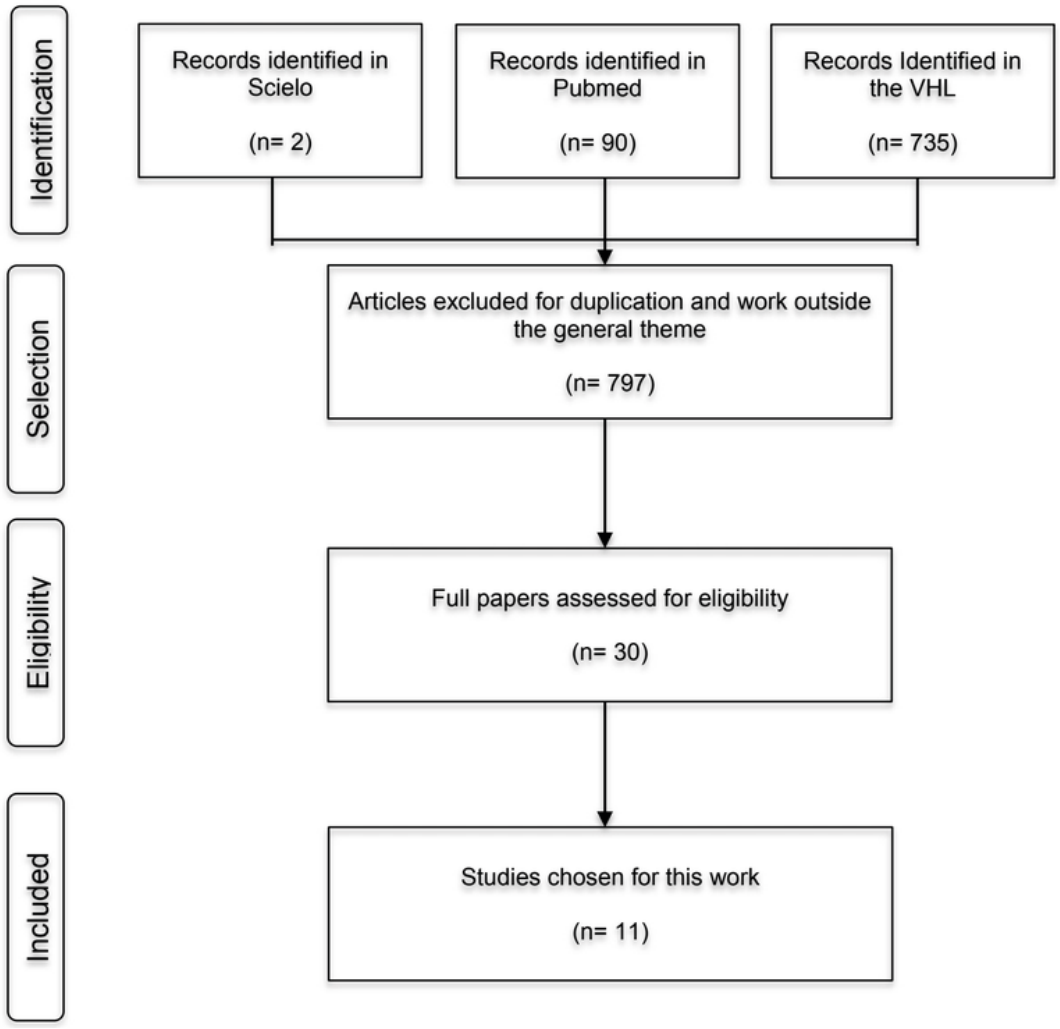

Figure 1. Flowchart of article selection

RESULTS

Author/ Year	Title	Objectives	Main Contributions
Da Silva et al.; 2022	Down Syndrome as a risk factor genetic Disease Alzheimer's: a integrative review the mechanisms molecular	Explain reasons for Syndrome Downser considered a fatorderisk for Disease Alzheimer's, through description of markers genetic involved in this relationship.	Down's Syndrome becomes a risk factor for the development of Alzheimer's disease due to the activation of genes located in the chromosome 21, in the which is triplicated in patients with syndrome form, Alzheimer's becomes becomes one of main causes of mortenesses patients. The precursor protein beta-amyloid was highlighted as main responsible for development Alzheimer's, because once too often influence on plaque formation amyloidswhich are responsible for pathogenesis Alzheimer's. In addition In addition other genes that favor this relationship, such as superoxide dismutase type 1 and tyrosine from dual specificity phosphorylated kinase type 1.
Monezi; 2023	Biomarkers amyloidogenic in the Down	Investigate markers biological disease Alzheimer's, involved in production peptideAB, in samples of blood peripheral individuals adults and seniors comsyndrome dedowne compare them with adults and typical elderly without commitment cognitive development of disease alzheimer	Disease Alzheimermore prevalent in individuals with Down syndrome if is due to the increase in gene expression protein precursor amyloid leading to peptide accumulation beta-amyloidenes brain tissue, by therefore plaque formation senile that culminate development early alzheimer's in people with syndrome this deposition triggers events cytotoxic damage the brain ecausedeath neuronal. More, it is reported that Tau protein too participate in this relationship between syndromee Early Alzheimer's, since hyperphosphorylated commitments microtubule collapse cytoskeleton Finally, demonstrated importance of investigation enzymes and products cleavage proteolytic precursor protein amyloid in the process understanding of ratio early incidence of Alzheimer's itself with Down, in that sense, the DisintegrinAnd Metallopeptidase beta-siteAPP enzyme1ea PSEN1.
Lamb; 2022	THE GENETIC DISORDER THAT CORRELATES DOWN SYNDROME WITH ALZHEIMER'S DISEASE	Clarify possible relationships genetic between Down syndrome and Alzheimer's disease	It has been shown that relationship between Down Syndrome and the Alzheimersedeve mainly the action of the beta-amyloid protein and the Tau protein. In this sense, in relation to the pathogenesis of Alzheimer's in patients with the syndrome, it was pointed out that the beta-amyloid contributes to this process forming amyloid plaques and the Tau protein corroborates this process since since it does not perform its function properly by stabilizing the the microtubules in neurons.
Bustamente et al.; 2019	disease Alzheimer's in elderly people with down syndrome: a literature review	identify the scientific knowledge produced respect Disease Alzheimer's elderlywith Down's Syndrome .	It was observed that improvements health services have led to an increase in the life expectancy of people with Down's Syndrome. In this context, a high incidence of Alzheimer's cases has been noted in this population, which has been reported to be due to a chromosome 21 triplication chromosomopathy that contributes to the deposition of amyloid protein, influencing the development of Alzheimer's in this population.
Moreira et al.; 2019	Premature aging in adultswith Down syndrome genetic, cognitive and functional aspects. and functional aspects.	Describe genetic aspects and characteristics of premature aging Down's syndrome .	The changes caused by aging in people with Down Syndrome can potentiate the effects of trisomy 21, in which there is a difference process senescence in individuals with the syndrome compared to those without, especially in relation to the higher prevalence of of manifestations of Alzheimer's in those with a syndrome. This relationship is due to the consequences of the genes located on chromosome 21, which is triplicated, in which among the gene products of this chromosome the amyloid precursor which is in increased production, consequently associated with a deficit in the cell adhesion process, in neurotoxicity and cell growth. Consequently, these processes culminate in the early formation of amyloid plaques that participate in the pathogenesisof Disease Alzheimer's.
Fonseca; 2018	Evidence of functional dysfunction, disinhibition and apathy in cognitive decline e dementia Alzheimer's peoplewith Down Syndrome	The purpose of the study is investigate factors associated with with frontal lobe functioning (executive dysfunction, disinhibition and apathy) during cognitive decline e cognitive disease Alzheimer's adultswith down syndrome	Down's syndrome is associated with early development of Alzheimer's disease, in which this process is the result of trisomy of chromosome 21 which increases the expression of proteins involved in this pathogenesis, such as Tau, the amyloid precursor. In this sense, it is reported that the twisted filaments of the Tau protein and the increased production of beta-amyloid, which leads to to development of senile plaques, culminating with the development Alzheimer's prematurely in people with Down's Syndrome. Furthermore, in this pathological process also excessive expression of the enzyme superoxide dismutase which increases oxidative stress cells propagating cell damage and neurodegeneration.

LOPES, Bruno Sousa et al; 2014	Down's syndrome and the process of aging: a systematic review.	Identify update the main knowledge on elderly individuals with DS, describing key topics for o understanding the peculiarities of the ageing process in this population.	The article discusses the relationship between Down Syndrome (DS) and Alzheimer's Disease (AD), highlighting the formation of senile plaques beta-amyloid in the brains of individuals with DS. Studies show an early association between AD and the DS population, supporting the amyloid cascade theory due to the localization of the protein forerunner chromosome 21. Imaging evaluations revealed an increase in of beta-amyloid in people with DS. A prospective study indicated cognitive in individuals with DSD, suggesting possible premature aging e development of AD. In addition, elderly people with DS and AD may have other pathologies, as senile myoclonic epilepsy Genton's senile myoclonic epilepsy, which appears after cognitive decline established in AD.
TORRES QUINTANA, Rocíoetal; 2014.	Cognitive impairment and Alzheimer's disease con Down's Syndrome .	Association Syndrome Downà dementia, especially of the Alzheimer's, through its pathophysiological processes.	Sickness Alzheimer's is associated with a three essential pathophysiological events that contribute to the loss of neuronal synapses : a) the extracellular deposition of β-amyloid fibrils, which result in degeneration of nerve endings; b) intraneuronal neurofibrils composed of hyperphosphorylated Tau protein; and c) the accumulation of of β-amyloid at the edges of the vessels, causing vascular amyloidosis. The more recent research has focused on on search for associations between genetic determinants, biological markers e the reduction of specific cognitive domains, with the aim of preventing o development of this disease or to create innovative therapeutic strategies, especially in the early stages, such as mild cognitive impairment.
ForteaJ, et al.; 2021.	Alzheimer's disease associated withDown syndrome: a geneticformof dementia.	Summarized which indicate that sickness Alzheimer's main problem doctor and cause death in peoplewith syndrome Down. Discuss like history naturalea presentation clinic disease Alzheimer's associated with syndrome Downsizing similar to disease Alzheimer's autosomal dominant. finally, explain how peoplewith syndrome Down could bebetter population to carry out tests deprevention disease Alzheimer's.	Research studies clinicandanalysis longitudinal consistently indicate that lifetime probability dementia individuals with Down syndrome exceeds 90%. occurrence of dementia common before 40 years, butua incidence prevalence increase significantly after this age, reaching 88-100% in people with Down with more than 65 years old. the universality of neuropathology Alzheimer's disease in adults with Down Syndrome at 40 years old age. However amyloid angiopathy cerebralapresenta a more pronounced in comparisonwith sporadic Alzheimer's disease. Furthermore, Down Syndrome presents an intrinsic immune dysregulation, associated with in maturation of T cells, in the function of B cells and in a state pro-oxidative. Notably, four of the six interferon receptors are encoded in the chromosome 21, contributing to the onset of a chronic inflammatory state. Finally, future studies evaluating the relationship between inflammatory biomarkers and Alzheimer's disease will help in discovery of disease benefit the general population as well as those with trisomy 21.
ForteaJ, et al.; 2020	Clinical and biomarker changes of Alzheimer's disease in adults withDown syndrome: a cross-sectional study.	Characterize the order and the timing of changes in disease biomarkers biomarkers Alzheimer's a population of adults with Down syndrome.	Between February 2013 and June 2019 (Barcelona) and between June 2009 and December 2014 (Cambridge), they were examined 388 participants with Down syndrome, of whom 257 (66%) were asymptomatic, 48 (12%) had prodromal Alzheimer's disease83 (21%) had dementia due to Alzheimer's disease. Additionally, 242 controls were included euploid controls. Changes were observed in biomarkers, such as the values of Aβ 1-42/1-40 in cerebrospinal fluid and neurofilament in plasma, already in the third decade of life in individuals with Down syndrome. PET uptake amyloid was altered in the decade, while changes in in 18F-fluorodeoxyglucose PET and p-tau in cerebrospinal fluid occurred later, in the fourth decade. Prodromal Alzheimer's disease was diagnosed on average at 50.2 years of age, and dementia due to Alzheimer's disease at 53.7 years. The symptomatic prevalence of disease increased with age, reaching 90-100% in the seventh decade of life in individuals with Down syndrome.
Iulita MF et al.; 2022.	Association of Alzheimer Disease WithLife Expectancy in People With Down Syndrome.	Evaluate whether the variability at the beginning of the symptoms of disease Alzheimer's in syndrome Downé similar to autosomal dominant Alzheimer's disease and evaluate its association with mortality.	The research highlights an early link between AD and the DS population, supporting the amyloid cascade theory due to the localization of the protein forerunner chromosome 21. Images show an increase in beta-amyloid levels in people with DS. A retrospective study points to cognitive impairment in individuals with DS, suggesting possible premature aging e development of AD. In addition, elderly people with DS and AD can manifest other pathologies, such as Genton's senile myoclonic epilepsy, appearing after cognitive decline in AD.

The evidence was classified according to the Agency for Healthcare Research and Quality (aHrQ) categorization in order to ensure success. And the data collected was categorized for analysis into: 1) Year, 2) Database, 3) Definition of Down Syndrome, 4) Definition of Alzheimer's Disease, 5) Genes related to early Alzheimer's, 6) Effects of trisomy 21 on the expression of genes related to Alzheimer's, 6) Language of the publication.

DISCUSSION

Down's Syndrome (DS) consists of a trisomy of chromosome 21, and is the main genetic cause of intellectual disability, in which its clinical picture is characterized by delayed intellectual and motor development, face typical and the presence of malformations, which may be congenital, cardiac and/or systemic.[7]

DS affects 5.8 million people worldwide. Improvements in health care for this population have increased their life expectancy in recent years,[8] consequently, age-related diseases have become more frequent.[9] In this sense, people with DS experience premature aging and the alterations resulting from this process can potentiate the effects of the trisomy, such as the development of Alzheimer's disease (AD).[7]

In Alzheimer's disease, there is a loss of neuronal activity which leads to dementia symptoms such as loss of short-term memory, which progresses to loss of other cognitive abilities.[10] In this context, early onset AD is mainly related to the presence of Down's Syndrome, since trisomy 21 leads to overexpression of the beta-amyloid precursor protein, which is the genetic basis of this association,[8] and also causes other homeostasis alterations such as a reduction in neurogenesis and the induction of apoptosis.[10]

The molecular mechanisms related to the development of AD prematurely in people with DS include beta-amyloid deposition, which leads to the formation of senile plaques, and the formation of neurofibrillary tangles resulting from the twisting of Tau protein filaments, which results in the neuropathological characteristics of Alzheimer's disease.[11]

Chromosome 21 trisomy leads to overexpression of the beta-amyloid protein, corroborating its greater deposition and the development of the amyloid cascade that leads to the formation of senile plaques, the center of Alzheimer's pathophysiology. Furthermore, this deposition is age-related, but in people with Down's Syndrome it occurs earlier, and it begins in the striatum and progresses to the prefrontal and anterior cingulate cortex, eventually spreading to other regions of the brain, leading to cognitive decline in the prodromal phase of AD.[11]

In the physiology of the neurological system, the amyloid precursor protein (APP), a fundamental transmembrane in neuronal function, follows two pathways after being translated: amyloidogenic and non-amyloidogenic. In this context, in the non-amyloidogenic pathway this protein is cleaved into fragments that have a neuroprotective effect. However, when this protein passes through the amyloidogenic pathway, it is initially cleaved by beta-secretase, resulting in a beta-amyloid fragment, after which gamma-secretase completes this process by releasing the amyloid peptide. In this sense, in people with DS there may be an imbalance in this quantity of enzymes, resulting in a reduction in alpha-secretases and an increase in beta-secretases, corroborating a greater production of the amyloid peptide, thus contributing to a pathological accumulation of amyloid plaques early on, even in childhood and adolescence, and the development of Alzheimer's disease.[5]

The deposition of amyloid peptide triggers immune defense mechanisms, causing inflammation and also leads to the formation of neuritic plaques that destroy neuronal connections and interrupt the synapse, con-

sequently, it leads to the degeneration of neurons, tissue loss and a reduction in brain mass. Thus, amyloid peptide is one of the most important pathophysiological markers of AD in people with DS. However, it is worth highlighting the importance of the gene responsible for coding ETS proto-oncogenesis transcription 2 (EST 2), which activates the APP promoter, generating its excessive expression and corroborating the formation of amyloid plaques.[5]

Furthermore, the pathogenesis of the amyloid cascade triggers secondary mechanisms that accelerate this process, consisting of activation of the inflammatory response, oxidative stress, favoring apoptosis, alteration of membrane-related homeostasis, impairment of neurotrophic action and neurochemical alterations.[10]

Furthermore, brain atrophy has been reported in patients with concomitant DS and AD when compared to patients without the syndrome but with Alzheimer's, as a consequence of the early beta-amyloid deposition that causes cognitive decline in AD. However, some people with both clinical conditions may be resistant to atrophy.[11]

Subsequent to these APP protein events, there is a hyperphosphorylation of the Tau protein which alters the stability of the microtubules, resulting in a collapse of the cytoskeleton of the neurons (Monezi). The genes encoding DYRK 1A and the regulator of calcineurin 1 (RCAN 1) are involved in this process. In this context, DYRK 1 acts by deregulating the phosphorylation of splicing factors, leading to hyperphosphorylation of the Tau protein, leading to the development of neurofibrillary tangles that trigger the early onset of AD in people with DS. On the other hand, in trisomy 21, RCAN 1 expression is increased, causing damage to synaptic functions, increased oxidative stress and stimulating the formation of neurofibrillary tangles. In addition, it inhibits the signaling pathways monitored by the nuclear factor of activated T cells, which is important for controlling the expression of RCAN 1 itself, consequently stimulating the amyloid cascade.[5]

Also in this pathological process, there is the SOD 1 gene, also located on chromosome 21 in triplicate, in which its increased expression leads to a oxidative stress due to the non-conversion of H O_{22} into O_2 resulting from this deregulation. Furthermore, this gene is also responsible for inflammation, activation of factors that induce apoptosis and stimulation of cellular aging of neurons, consequently providing neurodegeneration, as well as making the environment more susceptible to toxicity, thus contributing to the premature development of dementia.[5]

However, it is worth highlighting the role of the synaptojanin 1 (SYNJ 1) and cystatin (CSTB) genes, also affected by the trisomy, in the relationship between Down's Syndrome and Alzheimer's. The former contributes to this process by influencing the pathway responsible for the production and accumulation of beta-amyloid peptide in the pathogenesis of AD. The former contributes to this process by influencing the pathway responsible for the production and accumulation of beta-amyloid peptide in the pathogenesis of AD, since it has been reported that there is a relationship between its lower expression and a decrease in beta-amyloid peptide. The second is included in this the process of neuronal degeneration, when in excess, by causing an imbalance in lysosomal proteolysis which consequently influences the formation of amyloid plaques and the early development of Alzheimer's.[5]

Another important event in the prematurity of Alzheimer's in individuals with DS is neuroinflammation, which is mainly related to the calcium-binding protein B gene (S100B), affected by the trisomy, which acts by encoding the cytokine S100B which, in excess, causes a significant growth in amyloid neuro-

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nal processes, induces the synthesis and translation of APP mRNA, regulates the expression of the neuroinflammatory cytokine IL-1 gene, thus favoring the neuropathology of AD. In this sense, IL-1 in excess, in the case of Down Syndrome patients, causes the evolution of amyloid plaques by inducing the production of the APP protein, reduces synaptophysin, synthesizes and activates the enzyme acetylcholinesterase which degrades acetylcholine (an essential neurotransmitter for learning and memory) and stimulates MARK-p38, which is essential in the hyperphosphorylation of the Tau protein and in the appearance of neurofibrillary tangles related to AD.[5]

It should be noted that among the genes triplicated in DS that influence early AD, the ubiquinite-specific peptidase 16 gene (UDP 16) contributes by increasing cellular senescence. However, the presence of at least one allele of Apolipoprotein ε4 influences, albeit indirectly, the increase in endosomes and the rise in beta-amyloid peptide.[5]

CONCLUSION

Down's Syndrome is a genetically determined form of Alzheimer's Disease, since its existence increases the risk of developing dementia, evident in the increase in its prevalence with advancing age.

Improved health services have contributed to an increase in the life expectancy of people with Down's Syndrome, which has led to an increase in the number of cases of age-related illnesses, such as Alzheimer's Disease. In this sense, due to chromosomal pathology, the presence of this syndrome becomes a risk factor for the early development of Alzheimer's, since it increases the expression of genes present on chromosome 21, consequently, its effects act mainly on the deposition of the beta-amyloid peptide that forms senile plaques and on the formation of neurofibrillary tangles that act on neuronal deterioration and death, resulting in AD.

This relationship is due to the genes located on chromosome 21 that undergo an increase in expression and have been shown to be involved in the pathogenesis of AD, such as APP, EST 2, DYRK 1 A, RCAN 1, SOD 1, SYNJ 1, CSTB, S100B, IL-1, USP 16 and also the apoE ε4 allele, which indirectly contributes to neurodegeneration. Therefore, these genes are important molecular mechanisms for understanding early dementia in DS, since they direct future interventionist measures to delay, prevent and treat Alzheimer's in this population. Given the neuropathological complexity of this relationship, it is essential to expand further studies on the impacts of gene triplication, especially given the increase in life expectancy and mortality caused by complications of dementia, in order to target Alzheimer's care for these individuals.

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