BioSCIENCE
Review Article
DOI: https://doi.org/10.55684/2025.83.S2.e00007

Can premature aging be related to Williams Syndrome?

Envelhecimento precoce pode estar relacionado com a Síndrome de Williams?

Fernanda Ritt de Souza[1], Maria Eduarda Hammerschmidt[1], Gabriela van Erven[1], Julia Daniela de Sá[1], Evelyn Mazur[1], Liya Regina Mikami[1]

ABSTRACT

Introduction: Williams syndrome (WS) is a rare, autosomal dominant genetic condition caused by a heterozygous microdeletion in 7q11.23. It presents diverse clinical manifestations, including multisystemic premature aging symptoms, such as the early development of diseases typically associated with older age. The haploinsufficiency of the ELN gene, oxidative stress triggered by the overexpression of the NCF1 gene, and mitochondrial dysfunction are identified as key factors contributing to aging-related manifestations.

Objective: To analyze the clinical and biological aspects of Williams syndrome related to premature aging, aiming to understand its causes and mechanisms of action.

Method: This study is a narrative review, including 25 articles obtained from databases such as Scielo, PubMed, ProQuest, and Google Scholar. Studies published between 1996 and 2024 in Portuguese and English were included, using the descriptors “Williams syndrome,” “aging,” “NCF1,” and “ELN.”

Result: ELN gene haploinsufficiency, high angiotensin II levels, NCF1 gene overexpression, and alterations in mitochondrial cellular respiration in individuals with Williams syndrome lead to oxidative stress and, consequently, premature aging. Individuals with the syndrome may experience hearing loss, early puberty, early-onset cataracts, and impaired cognitive development, often manifesting attention deficit disorder and anxiety.

Conclusion: Premature aging in Williams syndrome involves multisystemic manifestations associated with the ELN gene haploinsufficiency and the NCF1 gene overexpression, which promote oxidative stress and cellular dysfunction.

KEYWORDS: Williams syndrome. Aging. Elastin.

RESUMO

Introdução: A síndrome de Williams (SW) é condição genética rara, autossômica dominante causada por uma microdeleção heterozigótica em 7q11.23. Apresenta manifestações clínicas diversas, incluindo sintomas de envelhecimento precoce multissistêmicos, como o desenvolvimento precoce de doenças de idades mais avançadas. A haploinsuficiência do gene ELN, o estresse oxidativo, desencadeado pela superexpressão do gene NCF1 e disfunção mitocondrial, são apontados como responsáveis por manifestações ligadas ao envelhecimento.

Objetivo: Analisar aspectos clínicos e biológicos da síndrome de Williams relacionados ao envelhecimento precoce, buscando entender suas causas e mecanismos de ação.

Método: Trata-se de revisão narrativa, sendo utilizados 25 artigos obtidos nas bases de dados Scielo, PubMed, ProQuest e Google Acadêmico. Foram incluídos estudos publicados entre 1996 e 2024, nos idiomas português e inglês, utilizando os descritores “síndrome de Williams”, “envelhecimento”, “NCF1” e “ELN”.

Resultado: Haploinsuficiência do gene ELN, aumento da angiotensina II, superexpressão do gene NCF1 e alterações na respiração celular mitocondrial nos portadores da síndrome de Williams geram estresse oxidativo, e consequentemente, envelhecimento precoce nos afetados. Os portadores da síndrome podem apresentar perda auditiva, puberdade e catarata precoces e desenvolvimento cognitivo prejudicado, manifestando transtorno de déficit de atenção e ansiedade.

Conclusão: O envelhecimento precoce na síndrome de Williams envolve manifestações multissistêmicas associadas à haploinsuficiência do gene ELN e à superexpressão do gene NCF1, que promovem estresse oxidativo e disfunção celular.

PALAVRAS-CHAVE: Síndrome de Williams. Envelhecimento. Elastina.

Central Message

Williams-Beuren syndrome or Williams syndrome is a rare autosomal dominant, multisystemic, genetic condition caused by the heterozygous microdeletion of part of the long arm of chromosome 7, in the 7q11.23 region, involving between 21 and 28 genes. Most cases are sporadic occurring, the result of a de novo deletion. This condition has an estimated incidence of 1:7500 and 1:20000 live births, with no prevalence between sex and ethnicity or a given geographic region. This article aims to update the knowledge about the disease, emphasizing mainly the side effects on its development.

Perspective

Premature aging in Williams syndrome has complex and multisystemic manifestations, involving complex biological mechanisms of genetic and biomolecular action. The causes of this premature aging are not yet widely known, but the role of haploinsufficiency of the ELN gene and overexpression of the NCF1 gene in increasing oxidative stress and consequent reduction of tissue function and cell apoptosis is highlighted. Ongoing research is essential to better understand the underlying mechanisms of the syndrome and develop interventions that can improve the prognosis and quality of life of those affected.

[1] *Evangelical Mackenzie Faculty of Parana, Curitiba, PR, Brazil.*

Conflict of interest: None | Funding: None | Received: 10/08/2025 | Accepted: 27/10/2025 | Publication date: 28/11/2025 | Correspondence: fernandaritt08@gmail.com | Associate Editor: Carmen Australia Paredes Marcondes Ribas

How to cite:
de Souza FR, Hammerschmidt ME, van Erven G, de Sá JD, Mazur E, Mikami LR. Envelhecimento precoce pode estar relacionado com a Síndrome de Williams? BioSCIENCE. 2025;83(S2):e00007

INTRODUCTION

Williams-Beuren syndrome or Williams syndrome (WS) is a rare autosomal dominant, multisystemic, genetic condition caused by the heterozygous microdeletion of part of the long arm of chromosome 7, in the 7q11.23 region, involving between 21 and 28 genes. Most cases are sporadic occurring, the result of a de novo deletion. This condition has an estimated incidence of 1:7500 and 1:20000 live births, with no prevalence between sex and ethnicity or a given geographic region.[1,2]

Although the mechanisms of action of all the genes involved are not widely known, the main clinical manifestations of those affected are linked to the haploinsufficiency of the genes ELN, GTF2I, BAZ1B, LIMK1. Because it affects several genes, the syndrome triggers clinical manifestations in almost all systems of the body. These complications vary from one affected to another and can also appear or disappear over time.[3]

The main complications occur in the endocrine, cardiac, and central nervous systems; however, there are also gastrointestinal, musculoskeletal, and other body system manifestations. Those affected usually have moderate cognitive deficit, anxiety disorders and hypersociability, which characterizes the neurological profile of the syndrome. Other commonly found features are craniofacial dysmorphology (wide forehead, periorbital fullness, large lips and wide mouth, and dental problems (microdontia and missing teeth, enamel hypoplasia, dental malocclusion), which triggers a typical facial phenotype of WS.[3-5]

Its diagnosis is usually given at birth or in early childhood by the perception of signs and/or symptoms suggestive of the condition in these 2 age groups, especially facial dysmorphism. However, there is no specific neonatal screening. Although the characteristic facial phenotype facilitates diagnosis in childhood, there are no significant studies on symptoms and complications of the syndrome in adulthood, since this information was unknown not long ago, as many affected did not reach adulthood. With the improvement in treatment and development of new drugs, the life expectancy of patients has become very similar to that of unaffected individuals.[4]

With increasing age, multisystem signs of premature aging began to be observed in patients along with early manifestations in adolescence and early adulthood with diseases characteristic of advanced ages, such as cataracts, diabetes, and emphysema. Marked cognitive decline and increased impairment of the digestive, endocrine, musculoskeletal and other systems affected by the syndrome were observed, as well as sleep regulation, possibly linked to changes in the methylation patterns of certain genes.[6]

The causes of this aging are not yet widely understood, the main ones being related to the haploinsufficiency of the ELN gene and the intensification of oxidative stress in those affected. This haploinsufficiency triggers the impairment of tissues rich in elastic fibers and consequently signs of premature aging, especially in the skin and in the cardiac and pulmonary systems. Meanwhile, the increase in oxidative stress occurs due to the increase in NOX activity, due to the increase in the compound angiotensin II and the overexpression of the NCF1 gene, which suffers an increase in its copy number due to polymorphism with pseudogenes.[7]

Studies on the symptoms of Williams syndrome in adults are scarce, being more focused on the clinical signs already apparent in children in early childhood. Thus, this study aimed to review the clinical and biological aspects of Williams syndrome related to premature aging, seeking to understand its main causes.

METHOD

This is a narrative review that used original review articles, meta-analyses and case reports in Portuguese and English, applying the following descriptors: Williams syndrome, Premature aging, Genetics and their counterparts in Portuguese. Information obtained from scientific articles from the following databases was used: Scielo, PubMed, ProQuest and Google Scholar. As inclusion criteria, articles focusing on symptoms, aging, pathophysiological cause, and diagnosis, published from 1996 to 2024, totaling 25 selected studies, were used.

DISCUSSION

Williams syndrome (WS) is caused by a microdeletion in 7q11.23, mainly involving the ELN gene, which encodes tropoelastin - a precursor protein of elastin, responsible for the elasticity of tissues, considered a structural protein of elastic fibers. This molecule acts on the flexibility and resistance of organs such as the skin and joints. Thus, the loss of function of this protein causes complications, especially in tissues that have a greater amount of elastic fibers, such as the cardiovascular, pulmonary, and connective fibers in regions such as bladder diverticula and hernias. Also, a peculiar characteristic of the syndrome is the development of premature aging of the carriers, resulting both from the haploinsufficiency of the ELN gene, as well as from other biological mechanisms not yet fully understood. This aging is due to phenotypic characteristics such as aging of facial features and early reduction in tissue function.[4,8]

The recruitment of older adults with WS for research has been an arduous task, due to the relatively low incidence of the condition, in addition to the low interest of family members in letting their child participate in a study whose diagnosis, prognosis and treatment have already been carried out in childhood, as they do not have good expectations about the progression of the disease. For the researchers, studies on adult patients with WS are of great interest, since they evaluate functional and aging changes associated with age, as they present characteristics that suggest premature aging in those affected by the syndrome.[9]

In the 7q11.23 region, deleted in the WS, at least 26 genes (MLXIPL, BAZ1B, STX1A, WTSF, GTF2L, FZD9, ELN, NCF1, LIMK1, ABHD11, ABHD11-AS1, BCL7B, BUD23, CLDN3, CLDN4, CLIP2, DNAJC30, EIF4H, FKBP6, FZD9, LAT2, METTL27, MIR590, MLXIPL, NSUN5 and GTF2IRD) have already been identified; however, their individual contributions to patient phenotypes are not yet completely established.[10] So far, only the deletion of the ELN gene has its effect well clarified, and the heterozygosis of the variant in ELN is necessary, but not sufficient to cause, alone, the syndrome and all the symptoms related to premature aging. Another cause already identified, although not completely understood, is the overexpression of the NCF1 gene and its role in intensifying oxidative stress.[11]

The signs of accelerated aging in patients manifest themselves in the most diverse systems of the body. Among the main ones are: cataracts, the appearance of gray hair during adolescence, reduced high-frequency sensorineural hearing, continuous weight loss, senile emphysema, and a considerable reduction in episodic memory.[6]

Other characteristics of this aging are dementia, progressive hearing loss, and skin aging, linked to the damage caused by oxidative stress.[6] There is also the development of diverticulosis in the walls of the colon, diabetes mellitus and hypertension. With advancing age, adults are also prone to joint contractures and hyperreflexia, and often become even more unstable in performing motor tasks such as going up or down stairs.[12]

Gagliardi et al.[13] In 2007, when analyzing patients between 3 and 14 years of age, they observed that symptoms related to the cerebellar system did not show significant changes between the different age groups, and mild extrapyramidal signs tended to increase with advancing age, with an increase in dystonic and involuntary movements. The study suggested the existence of mild and complex neurological dysfunctions in all cases of patients with the syndrome in different age groups.[13]

It is common knowledge that cognitive development is impaired in WS. Concomitantly, there are deficiencies in skills related to verbal comprehension, planning, problem-solving, and spatial cognition. In addition, they may have attention deficit hyperactivity disorder (ADHD), generalized anxiety, and affective disorders.[14] Even with these deficits, the average verbal intelligence quotient of patients between 20 and 30 years of age is slightly higher than the average performance intelligence quotient. However, from the age of 40, this quotient begins to deteriorate rapidly, while the average performance intelligence ratio continues to improve until approximately 50 years of age, when it also begins to decrease.[12]

Pober and Morris[15] reported in 2007 that there was a delay in the acquisition of motor landmarks and deficits in motor coordination, with muscle tone increasing with age, and older children developing progressive joint limitation and hypertonia. These authors also reported that mild to moderate high-frequency sensorineural hearing loss is present in most individuals with WS, possibly caused by cochlear dysfunction.

Still, Bódizs at al.[16], 2014, also reported that the prevalence of GAD (generalized anxiety disorder) in the syndrome increased significantly with age.[16] The authors, when studying older adults with WS, observed that they developed age-related declines in explicit processing and, therefore, it is important to understand the cognitive processes that come with normal aging in patients. However, more research is needed to gain a clearer picture of the robustness of implicit processes, especially in people with the syndrome and in individuals with intellectual disabilities in general.

Adult memory profiles show age-associated alterations parallel to those observed in the general population. Regarding explicit memory, adults showed a marked reduction with advancing age.[16] However, it is not yet possible to determine with certainty whether the magnitude of the observed change in the performance of adults with WS is consistent with "normal" aging or with preclinical dementia. The study by Axelsson et al.[17], which analyzed the sleep of children with WS, indicated that those affected by the syndrome have sleep problems throughout their lives, but more present in infants and young children (6-12 years). Some of the complications that arise at younger ages (6-12 years) and persist into adulthood are: dispersion throughout the night, poor sleep quality, longer sleep time in stages 3 and 4, and nocturnal restlessness (evident by breathing patterns). In addition, many children, adolescents and young adults (17-35 years) with WS complain of sleepiness during the day, which persists throughout life. Adolescents in particular have nocturnal discomfort in the legs and younger children, when compared to typical children, have a higher incidence of episodes of dispersion and consequent nocturnal agitation, taking time to fall asleep. However, these symptoms are not as common in other age groups of affected individuals. A certain discrepancy in the phonological development scores of affected children compared to normal ones may also be linked to sleep quality.[17]

Advanced puberty is characterized by atypical neurodevelopmental processes in WS, since the delays in the age-dependent decrease in sleep depth are not in tune with the hormonal changes inherent to puberty. The origin of this abnormal pattern of development/aging of individuals with WS may arise from compensatory processes of increased wakefulness and decreased sleep efficiency. The possible neurocognitive consequences of this apparent developmental disharmony should be the focus of specific investigation in the near future. In summary, the list of bodily functions and anatomical signs that reflect mildly accelerated aging can be supplemented with premature sleep impairment, characterized by accelerated reductions in sleep efficiency.[16]

In individuals with WS, there is also manifestation of hypersensitivity and distress in response to selected sounds (called hyperacusis or phonophobia); in addition, the voice is typically described as hoarse and/or low, another finding presumably attributed to elastin deficiency (specifically of the vocal cords, in this case).[15]

Cherniske et al.[18] In 2004, when studying 20 patients with the syndrome, between 30 and 51 years of age, they observed that all of them had visual problems, including strabismus and cataracts. Cardiovascular abnormalities were reported in 70% of individuals, with supravalvular aortic stenosis present in approximately 93%; in addition, 60% had hypertension. In addition, 50% of individuals had elevated PTH levels, but the thyroid function of 75% of patients was considered normal; 75% of the individuals had a similar pattern of high-frequency sensorineural hearing loss; 65% had moderate to severe anxiety levels and 15% had mild or subclinical anxiety.

The causes of these multisystem signs of aging are not yet widely known, but it is known that WS leads to alterations in the regulation of the oxidation-reduction state (redox) by ELN haploinsufficiency and to the overexpression of the NCF1 gene that encodes the p47phos protein, which regulates NOX family members present in the vasculature. Changes in the redox state are capable of generating oxidative stress in the cells and tissues of those affected, so that excess free radicals, without enough antioxidants, triggers inflammation, altered cell signaling, and oxidative damage.[19]

Oxidative stress, therefore, occurs in the imbalance between the anabolism of oxidative compounds and the antioxidant defense system and when there is excessive production of reactive oxygen species. This can lead to serious consequences, such as tissue necrosis and cell apoptosis, determining a greater predisposition to cellular aging, carcinogenesis, increased development of autoimmune diseases, and less muscle mass. However, the role of oxidative stress is less well known than in other genetic diseases.[19]

Micangeli et al.[19] in 2022, reported a correlation between elastin insufficiency in WS and cardiovascular and respiratory diseases. For the cardiovascular system, the greatest impact of reactive oxygen species seems to be related to the predisposition to hypertension, since elastin is a crucial component of the vascular wall, providing retreat to elastic vessels.

In WS, haploinsufficiency of the ELN gene occurs, so that a single copy of the gene cannot meet the body's need for tropoelastin. Thus, the production of elastic fibers is impaired. These allow distension to tissues that suffer repeated deformities, such as blood vessels, skin and lungs, for example. Elastin is the main component of elastic fibers; In this way, syndromes that impact the production of elastin directly affect the function of these fibers. This alteration is widely linked to heart problems, skin aging, and lung problems, since elastin is responsible for maintaining the elasticity and resistance of these tissues.[20]

Patients with WS have vascular characteristics similar to patients with supravalvular aortic stenosis (ASE), but have other phenotypes due to deletion of other genes. Patients with SW/SVAS mutations deposit less total elastin, but elastic fibers usually appear normal but less organized. 21 Regarding vascular alterations, a study carried out by Brengle et al.[22] in 2023 with mice, showed changes in the vascular structure related to haploinsufficiency of the ELN gene. There was an increase in the number of smooth muscle cells, vascular stiffness and consequent increase in blood pressure.

Hypertension is more prevalent in individuals with the syndrome compared to unaffected individuals, and its etiology is multifactorial, possibly due to elastin haploinsufficiency. Also, presumably, due to the haploinsufficiency of the ELN gene, about 50% of affected adults have chronic constipation, which generates a greater probability of developing diverticulosis before old age (about 60 years).[15] The authors also showed that elastin insufficiency leads to increased stiffness of the great arteries. Thus, the mice achieved maximum dilation at lower pressures than those that had the 2 elastin genes. The study shows that pressure changes occurred due to the elastin gene independently of increased plasma renin levels and activation of the renin-angiotensin system, despite elevated renin levels contributing to systolic and diastolic hypertension.[22]

Also, in relation to elastin deficiency, Gagliardi et al.[13] in 2007, reported accelerated aging in facial and somatic features in the patients studied, in addition to altered glucose tolerance and decreased bone mineral density, and this deficiency of elastic fibers triggers the loss of skin elasticity and the early formation of wrinkles.

In the respiratory system, individuals with WS with haploinsufficient ELN may be more predisposed to the early development of pulmonary emphysema, since elastin is a key component of elastic fibers in the lung.[6]

The NCF1 gene is also present in the deleted region in the WS. However, there is a change in its number of copies in those affected, which can have from 1 to 4 copies of this gene. This occurs because next to the deleted region, there are regions with low number of gene copies, including NCF1 and 2 of its pseudogenes - NCF1B and NCF1C - which differ from this by the absence of 2 base pairs at the beginning of exon 2. Thus, polymorphism can occur in which there is a conversion of the gene with its pseudogenes, triggering overexpression of the NCF1 gene. This genomic instability is attributed to the location of the gene and its pseudogenes and favors chromosomal rearrangements.[23,24]

NCF1 is responsible for the production of the protein p47phox, which regulates the activation of NADPH (enzyme complex involved in the creation of reactive oxygen species). Thus, while the heterozygosity of this gene leads to the reduction of this process by the significant decrease of the encoded protein, an increase in the number of copies of NCF1 is linked to the intensification of oxidative stress due to the greater production of ROS. The increase in the number of copies of the NCF1 gene generates an increase in the individual's NOX activity and an increase in the expression of p47phox, generating overexpression of this gene.[7,23]

In addition, elastin haploinsufficiency triggers vascular stiffness and fragmentation of elastic fibers, favoring an increase in blood pressure. analysis by Kozel et al.[23] in 2015 with 103 patients with WS verified, by comparing the speed of the pulse wave in the vessels in common individuals (with diabetes, hypertension and those using anti-hypertension medications) and in individuals affected by the syndrome, an increase in vascular stiffness in those affected. Pulse wave velocity was higher in those who had 2 or more copies of the NCF1 gene when compared to those who had only 1 copy. In this way, it was possible to identify that 1 single copy of this gene confers protection against hypertension, while 2 or more favored the development of the condition. In other words, a reduced number of the NCF1 gene confers not only lower oxidative stress, but also protection against a higher risk of hypertension in WS.[23,25]

Vascular stiffness and narrowing of the vessels predispose to the elevation of angiotensin II, which acts to regulate blood pressure. The stiffness of the vessels usually occurs with aging and is greater in diabetics and hypertensives; however, in WS it is more favored and intense due to the haploinsufficiency of the gene.[23,25]

The haploinsufficiency of elastin triggers increased stiffness of the blood vessel wall, also increasing blood pressure. This triggers increased angiotensin II and NADPH activation. Oxidative stress and the response of cells to angiotensin II depends on the copy number of the NCF1 gene.[6,7,23]

On the other hand, a reduced number of copies of NCF1 is related to a lower risk of hypertension and lower oxidative stress, even with vascular stiffness caused by elastin deficiency. Thus, cell damage is decreased, but it still exists and, also, triggers the characteristics of premature aging, even if more slowly and controlled. Increased oxidative stress generates cell damage, apoptosis, and loss of cellular function, causing multisystem premature aging symptoms.[7,23]

Mitochondrial dysfunction is also observed, which also contributes to the increase in oxidative damage. Due to the haploinsufficiency of the ELN gene, the fibroblasts of affected individuals show changes in the capacity for basal respiration, so that there is a decrease in ATP production and an increase in the production of reactive oxygen species. This dysfunction may have its origin in the deletion of the DNAJC30 gene, also present in the critical deleted region and is mainly involved with lung damage, disturbances of cellular homeostasis and mitophagy associated with chronic lung disease and activation of cell necrosis and apoptosis pathways.[20]

Mitochondrial dysfunction may also be related to problems in brain development. Characteristics of the mitochondria of the patients show that the integrity of oxidative phosphorylation supercomplexes and ATP-synthase dimers are decreased in WS.[20]

CONCLUSION

Premature aging in Williams syndrome has complex and multisystemic manifestations, involving complex biological mechanisms of genetic and biomolecular action. The causes of this premature aging are not yet widely known, but the role of gene haploinsufficiency is highlighted ELN and gene overexpression NCF1 in the increase of oxidative stress and consequent reduction of tissue function and cell apoptosis. Ongoing research is essential to better understand the underlying mechanisms of the syndrome and develop interventions that can improve the prognosis and quality of life of those affected.

Authors' contributions

Fernanda Ritt de Souza: Conceptualization
Maria Eduarda Hammerschmidt: Formal analysis
Gabriela van Erven: Investigation
Liya Regina Mikami: Methodology
Julia Daniela de Sá: Project administration
Evelyn Mazur Writing: (original draft)
Liya Regina Mikami: Writing (proofreading and editing)

REFERENCES

1. Rech A, Rinaldi IC, Marega T. Restorative treatment in patient with Williams Syndrome: case report. Revista Gaúcha de Odontologia. 2022;70:e20220026. https://doi.org/10.1590/1981-86372022002620200155
2. Michele Moreira Nunes. Avaliação do funcionamento cognitivo de pacientes com Síndrome de Williams-Beuren. 2011
3. Stanley TL, Leong AL, Pober BR. Growth, Body Composition, and Endocrine Issues in Williams Syndrome. Current Opinion in Endocrinology, Diabetes & Obesity. 2021;28(1):64-74. https://doi.org/10.1097/med.0000000000000588.
4. Kozel BA, Barak B, Kim CA, Mervis CB, Osborne LR, Porter M, et al. Williams Syndrome. Nature Reviews Disease Primers. 2021;7(1):42. https://doi.org/10.1038/s41572-021-00276-z.
5. Morris CA, Braddock SR, Council on Genetics. Health Care Supervision for Children With Williams Syndrome. Pediatrics. 2020;145(2):e20193761. https://doi.org/10.1542/peds.2019-3761
6. Ferrari M, Stagi S. Oxidative Stress in Down and Williams-Beuren Syndromes: An Overview. Molecules. 2021;26(11):3139. https://doi.org/10.3390/molecules26113139
7. Del Campo M, Antonell A, Magano LF, Muñoz FJ, Flores R, Bayés M, et al. Hemizygosity at the NCF1 Gene in Patients with Williams-Beuren Syndrome Decreases Their Risk of Hypertension. The American Journal of Human Genetics. 2006;78(4):533–42. https://doi.org/10.1086/501073
8. ELN gene: MedlinePlus Genetics. medlineplus.gov. Available from: https://medlineplus.gov/genetics/gene/eln/
9. Krinsky-McHale SJ, Kittler P, Brown WT, Jenkins EC, Devenny DA. Repetition Priming in Adults With Williams Syndrome: Age-Related Dissociation Between Implicit and Explicit Memory. American Journal on Mental Retardation. 2005;110(6):482-96. https://doi.org/10.1352/0895-8017(2005)110[482:rpiaww]2.0.co;2
10. MedlinePlus. Williams syndrome: MedlinePlus Genetics. medlineplus.gov. 2022. Available from: https://medlineplus.gov/genetics/condition/williams-syndrome/
11. Topázio BA. Estudo genético e clínico da Síndrome de Williams-Beuren em pacientes do nordeste brasileiro. Ibict.br. 2016. Available from: https://bdtd.ibict.br/vufind/Record/UFBA-2_15ea9b3c1b1eb962577bbb676f7d7ae7
12. Sauna-aho O, Bjelogrlic-Laakso N, Sirén A, Kangasmäki V, Arvio M. Cognition in adults with Williams syndrome—A 20-year follow-up study. Molecular Genetics & Genomic Medicine. 2019;7(6):e695. https://doi.org/10.1002/mgg3.695
13. Gagliardi C, Martelli S, Burt MD, Borgatti R. Evolution of Neurologic Features in Williams Syndrome. Pediatric Neurology. 2007;36(5):301–6. https://doi.org/10.1016/j.pediatrneurol.2007.01.001
14. Elison S, Stinton C, Howlin P. Health and social outcomes in adults with

Williams syndrome: Findings from cross-sectional and longitudinal cohorts. Research in Developmental Disabilities. 2010;31(2):587–99. https://doi.org/10.1016/j.ridd.2009.12.013

15. Pober BR, Morris CA. Diagnosis and management of medical problems in adults with Williams–Beuren syndrome. American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 2007;145C(3):280–90. https://doi.org/10.1002/ajmg.c.30139

16. Bódizs R, Gombos F, Gerván P, Szőcs K, Réthelyi JM, Kovács I. Aging and sleep in Williams syndrome: Accelerated sleep deterioration and decelerated slow wave sleep decrement. Research in Developmental Disabilities. 2014;35(12):3226–35. https://doi.org/10.1016/j.ridd.2014.07.056

17. Axelsson EL, Hill CM, Sadeh A, Dimitriou D. Sleep problems and language development in toddlers with Williams syndrome. Research in Developmental Disabilities. 2013;34(11):3988–96. https://doi.org/10.1016/j.ridd.2013.08.018

18. Cherniske EM, Carpenter TO, Klaiman C, Young E, Bregman J, Insogna K, et al. Multisystem study of 20 older adults with Williams syndrome. American Journal of Medical Genetics. 2004;131A(3):255–64. https://doi.org/10.1002/ajmg.a.30400

19. Micangeli G, Menghi M, Profeta G, Tarani F, Mariani A, Petrella C, et al. The Impact of Oxidative Stress on Pediatrics Syndromes. Antioxidants. 2022;11(10):1983–3. https://doi.org/10.3390/antiox11101983

20. Shek N, Choy AM, Lang CC, Miller BE, Tal-Singer R, Bolton CE, et al. Accelerated elastin degradation by age-disease interaction: a common feature in age-related diseases. NPJ Aging. 2024;10(1):1–4. https://doi.org/10.1038/s41514-024-00143-7

21. Duque Lasio ML, Kozel BA. Elastin-driven genetic diseases. Matrix Biology. 2018;71-72:144–60. https://doi.org/10.1016/j.matbio.2018.02.021

22. Brengle BM, Lin M, Roth RA, Jones KD, Wagenseil JE, Mecham RP, et al. A new mouse model of elastin haploinsufficiency highlights the importance of elastin to vascular development and blood pressure regulation. Matrix Biology. 2023;117:1–14. https://doi.org/10.1016/j.matbio.2023.02.003

23. Kozel BA, Danback JR, Waxler JL, Knutsen RH, de las Fuentes L, Reusz GS, et al. Williams Syndrome Predisposes to Vascular Stiffness Modified by Antihypertensive Use and Copy Number Changes in NCF1. Hypertension. 2014;63(1):74–9. https://doi.org/10.1161/hypertensionaha.113.02087

24. Raimondi F, Siow KM, Wrona D, Fuster-García C, Pastukhov O, Schmitz M, et al. Gene editing of NCF1 loci is associated with homologous recombination and chromosomal rearrangements. Communications Biology. 2024;7(1):1291. https://doi.org/10.1038/s42003-024-06959-z

25. Pezet M, Jacob MP, Escoubet B, Gheduzzi D, Tillet E, Perret P, et al. Elastin Haploinsufficiency Induces Alternative Aging Processes in the Aorta. Rejuvenation research. 2008;11(1):97–112. https://doi.org/10.1089/rej.2007.0587