Wiedemann-Rautenstrauch Syndrome

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1. Introduction

Wiedemann-Rautenstrauch syndrome is a type of progeria, which is a group of genetic conditions characterized by the dramatic, rapid appearance of aging earlier in life than expected. Signs and symptoms of Wiedemann-Rautenstrauch syndrome begin before birth. Affected individuals do not grow and gain weight at the expected rate before and after birth. People with this condition have distinctive facial features that give the appearance of old age. They often have a large head, a triangular face with a prominent forehead and pointed chin, a small mouth with a thin upper lip, low-set ears, and abnormal lower eyelids. In most affected individuals, the middle of the face looks as though it has been drawn inward (midface retraction). On the head, hair is sparse and the veins stand out. Also contributing to the appearance of aging is a lack of fatty tissue under the skin (lipodystrophy), particularly in the face, arms, and legs. In addition, the skin is thin and translucent. Some affected individuals develop joint abnormalities called contractures that can limit movement.

In people with Wiedemann-Rautenstrauch syndrome, the spaces (fontanelles) between the skull bones (that are noticeable as "soft spots" on the heads of infants) are larger than normal. The fontanelles normally close in early childhood, but they may remain open throughout life in people with this condition. Many affected infants are born with teeth (natal teeth), which fall out a few weeks after birth; however, some or all of their permanent (adult) teeth may never develop (hypodontia).

In some individuals with Wiedemann-Rautenstrauch syndrome, movement problems, such as difficulty with coordination and balance (ataxia) or involuntary rhythmic shaking (tremor), appear in childhood and worsen over time.

The life expectancy in Wiedemann-Rautenstrauch syndrome is variable. While some affected individuals do not survive past infancy, others live into young adulthood.

2. Frequency

Wiedemann-Rautenstrauch syndrome is a rare disorder. Its prevalence is unknown.

3. Causes

Wiedemann-Rautenstrauch syndrome is caused by mutations in a gene called *POLR3A*. This gene provides instructions for making the largest piece (subunit) of an enzyme called RNA polymerase III. This enzyme is involved in the production (synthesis) of ribonucleic acid (RNA), a chemical cousin of DNA. RNA polymerase III helps synthesize several forms of RNA, including those that assemble protein building blocks (amino acids) into working proteins. This process is essential for the normal functioning and survival of cells in tissues throughout the body.

The *POLR3A* gene mutations that cause Wiedemann-Rautenstrauch syndrome lead to production of abnormal subunit proteins. The abnormal subunits may prevent assembly of the RNA polymerase III enzyme or result in an RNA polymerase III with impaired ability to synthesize RNA. Reduced function of the RNA polymerase III molecule likely affects development and function of many parts of the body, but how the *POLR3A* gene mutations result in the specific signs and symptoms of Wiedemann-Rautenstrauch syndrome is unknown.

3.1 The gene associated with Wiedemann-Rautenstrauch syndrome

- POLR3A

4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- congenital pseudohydrocephalic progeroid syndrome
- neonatal progeroid syndrome
- neonatal pseudo-hydrocephalic progeroid syndrome
- neonatal pseudohydrocephalic progeroid syndrome

References

1. Jay AM, Conway RL, Thiffault I, Saunders C, Farrow E, Adams J, Toriello HV.Neonatal progeriod syndrome associated with biallelic truncating variants inPOLR3A. Am J Med Genet A. 2016 Dec;170(12):3343-3346. doi: 10.1002/ajmg.a.37960.
2. Lessel D, Ozel AB, Campbell SE, Saadi A, Arlt MF, McSweeney KM, Plaiasu V,Szakszon K, Szőllős A, Rusu C, Rojas AJ, Lopez-Valdez J, Thiele H, Nürnberg P,Nickerson DA, Bamshad MJ, Li JZ, Kubisch C, Glover TW, Gordon LB. Analyses ofLMNA-negative juvenile progeroid cases confirms biallelic POLR3A mutations inWiedemann-Rautenstrauch-like syndrome and expands the phenotypic spectrum ofPYCR1 mutations. Hum Genet. 2018 Dec;137(11-12):921-939. doi:10.1007/s00439-018-1957-1.
3. Paolacci S, Bertola D, Franco J, Mohammed S, Tartaglia M, Wollnik B, Hennekam RC. Wiedemann-Rautenstrauch syndrome: A phenotype analysis. Am J Med Genet A.2017 Jul;173(7):1763-1772. doi: 10.1002/ajmg.a.38246.
4. Paolacci S, Li Y, Agolini E, Bellacchio E, Arboleda-Bustos CE, Carrero D,Bertola D, Al-Gazali L, Alders M, Altmüller J, Arboleda G, Beleggia F, Bruselles A, Ciolfi A, Gillessen-Kaesbach G, Krieg T, Mohammed S, Müller C, Novelli A,Ortega J, Sandoval A, Velasco G, Yigit G, Arboleda H, Lopez-Otin C, Wollnik B,Tartaglia M, Hennekam RC. Specific combinations of biallelic POLR3A variantscause Wiedemann-Rautenstrauch syndrome. J Med Genet. 2018 Dec;55(12):837-846. doi: 10.1136/jmedgenet-2018-105528.
5. Wambach JA, Wegner DJ, Patni N, Kircher M, Willing MC, Baldridge D, Xing C,Agarwal AK, Vergano SAS, Patel C, Grange DK, Kenney A, Najaf T, Nickerson DA,Bamshad MJ, Cole FS, Garg A. Bi-allelic POLR3A Loss-of-Function Variants CauseAutosomal-Recessive Wiedemann-Rautenstrauch Syndrome. Am J Hum Genet. 2018 Dec6;103(6):968-975. doi: 10.1016/j.ajhg.2018.10.010.
