CUL3-related neurodevelopmental disorder

Description

CUL3-related neurodevelopmental disorder is a condition that affects neurological and physical development. Children with *CUL3*-related neurodevelopmental disorder may have intellectual disability or specific learning disorders. They may also experience delayed development of speech and motor skills, such as sitting and walking. Some individuals with this condition may have autism spectrum disorder, a developmental condition that affects communication and social skills.

Movement abnormalities can also occur in people with *CUL3*-related neurodevelopmental disorder. Affected individuals may have weak muscle tone (hypotonia) in childhood. In adulthood, they may develop involuntary muscle tensing (dystonia), rhythmic shaking (tremor), or other uncontrolled movements (spasms).

People with *CUL3*-related neurodevelopmental disorder can have distinctive facial features, including a long, triangular-shaped face; a large forehead; a large, rounded nose; small ears; deep-set eyes; or a pointed chin. Some affected individuals have a larger than normal head (macrocephaly).

Many people with *CUL3*-related neurodevelopmental disorder have hand and foot abnormalities. Hand abnormalities can include small pinky (fifth) fingers that curve inward (clinodactyly), narrow thumbs, underdevelopment of the muscle at the base of the thumb (thenar hypoplasia), or a single crease across the palm of the hand. Foot abnormalities can include high arches of the feet (pes cavus); bunions; fusion of the skin between some toes (cutaneous syndactyly); or joint deformities (contractures) in the ankles, feet, or toes. A few individuals with *CUL3*-related neurodevelopmental disorder have an abnormally curved lower back (lordosis) or a spine that curves to the side (scoliosis).

Some affected infants have a backflow of stomach acids into the esophagus (gastroesophageal reflux disease or GERD), which tends to go away after childhood. Rarely, recurrent seizures (epilepsy), congenital heart abnormalities, or genitourinary abnormalities occur in people with *CUL3*-related neurodevelopmental disorder.

Frequency

CUL3-related neurodevelopmental disorder is a rare disorder, though its exact prevalence is unknown.

Causes

CUL3-related neurodevelopmental disorder is caused by variants (also called mutations) in the *CUL3* gene. This gene provides instructions for making a protein called cullin-3. The cullin-3 protein plays a role in the ubiquitin-proteasome system, which breaks down (degrades) unwanted proteins inside cells.

The ubiquitin-proteasome system acts as the cell's quality control system by disposing of damaged, misshapen, and excess proteins. By breaking down proteins at the right time, this system regulates the timing of critical cell activities, such as cell growth and division.

The *CUL3* gene variants that cause *CUL3*-related neurodevelopmental disorder can lead to the production of nonfunctional cullin-3 proteins, and in some cases, no cullin-3 protein production at all. Without the normal amount of functioning cullin-3 proteins, the breakdown of unwanted proteins by the ubiquitin-proteasome system becomes impaired at key developmental stages. As a result, unnecessary proteins build up and interfere with the normal function of cells. Since cullin-3 is produced in nerve cells throughout the brain, it is likely that the protein's dysfunction damages nerve cells, causing many of the signs and symptoms of *CUL3*-related neurodevelopmental disorder.

Learn more about the gene associated with CUL3-related neurodevelopmental disorder

- CUL3

Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases of this condition result from new (de novo) variants in the gene that occur during the formation of reproductive cells (eggs or sperm) in an affected individual's parent or in early embryonic development. These affected individuals have no history of the disorder in their family.

Other Names for This Condition

- NEDAUS
- Neurodevelopmental disorder with or without autism or seizures

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Neurodevelopmental disorder with or without autism or seizures (https://www.ncbi.nlm.nih.gov/gtr/conditions/C5543225/)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- NEURODEVELOPMENTAL DISORDER WITH OR WITHOUT AUTISM OR SEIZURES; NEDAUS (https://omim.org/entry/619239)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=cullin-3+OR+CUL3+AND+neurodevelopmental)

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