CUL3 gene

cullin 3

Normal Function

The *CUL3* gene provides instructions for making a protein called cullin-3. This 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. Cullin-3 is a core piece of a complex known as an E3 ubiquitin ligase. E3 ubiquitin ligases tag proteins with molecules called ubiquitin. Ubiquitin signals specialized cell structures known as proteasomes to attach (bind) to the tagged proteins and degrade them. The ubiquitin-proteasome system also regulates several critical cell activities by controlling the amounts of proteins involved in them.

E3 ubiquitin ligases that contain cullin-3 tag many proteins that perform a variety of functions, such as cell growth and division. These ligases also tag blood pressure-related proteins called WNK1 and WNK4, which are produced from the *WNK1* and *WNK4* genes. By regulating the amount of WNK1 and WNK4 available, cullin-3 plays a role in blood pressure control.

Health Conditions Related to Genetic Changes

CUL3-related neurodevelopmental disorder

CUL3 gene variants (also called mutations) can cause a condition called *CUL3*-related neurodevelopmental disorder. This condition affects neurological and physical development.

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.

Researchers suspect that each variant that causes *CUL3*-related neurodevelopmental disorder affects the tagging of specific proteins by the E3 ubiquitin ligase complex. So, each variant could interfere with the breakdown of proteins differently. This mechanism may explain the variety of signs and symptoms seen in individuals with *CUL3*-related neurodevelopmental disorder.

Pseudohypoaldosteronism type 2

Specific variants in a particular region of the *CUL3* gene can cause pseudohypoaldosteronism type 2 (PHA2), a condition characterized by high blood pressure (hypertension) and high levels of potassium in the blood (hyperkalemia). These variants lead to the production of an abnormally short cullin-3 protein that is missing a particular region.

Studies show that this change alters the function of the E3 ubiquitin ligase complex. It impairs the breakdown of the WNK4 protein, although the exact mechanism is unclear. The resulting excess of WNK4 protein disrupts normal control of blood pressure, causing hypertension and other features of PHA2. While PHA2 and *CUL3*-related neurodevelopmental disorder share a genetic cause, the features of PHA2 do not overlap with the neurological or physical problems of *CUL3*-related neurodevelopmental disorder.

It is unknown if the breakdown of WNK1 is affected by the alterations to E3 ubiquitin ligase or whether WNK1 plays a role in cases of PHA2 caused by *CUL3* gene variants.

Other Names for This Gene

- CUL-3
- cullin-3 isoform 1
- cullin-3 isoform 2
- cullin-3 isoform 3
- PHA2E

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of CUL3 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=8452[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28CUL3%5BTIAB%5D%29+OR+%28cullin+3%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- CULLIN 3; CUL3 (https://omim.org/entry/603136)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/8452)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=CUL3[gene])

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Genomic Location

The *CUL3* gene is found on chromosome 2 (https://medlineplus.gov/genetics/chromosome/2/).

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