CUL3-related neurodevelopmental disorder

A learning resource for individuals and their families

Purpose

- **This resource is designed for friends, family members, and caretakers of people affected with *CUL3*-related neurodevelopmental disorder (*CUL3*-NDD).**
- **The content of this presentation may help you learn more about *CUL3*-related neurodevelopmental disorder including:**

  - What the condition is
  - How someone can be affected
  - Concepts of genetics
  - Health and behavioral concerns associated with the condition
  - How the condition is different than pseudohypoaldosteronism type IIE (PHA2E)
  - Healthcare providers someone may receive care from
  - And more!

Importantly, this resource is not intended to serve as medical advice or as a substitute for care from a healthcare provider. Please consult a licensed healthcare provider about any genetic test results and health concerns.

01

The names!

Different ways you may see the disorder referred to

“CUL3”

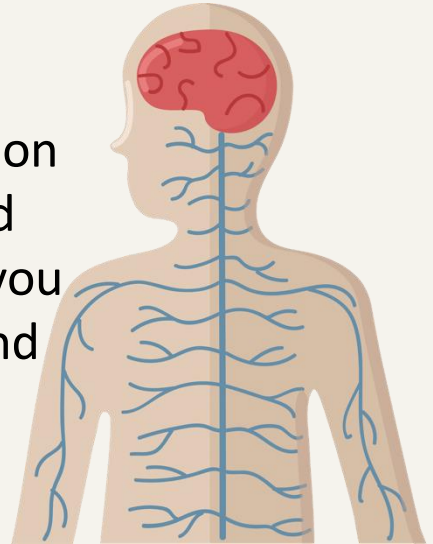
The name of the gene that is affected in this condition.

A gene is an important instruction in our body.

“Neurodevelopmental”

Refers to the nervous system and how it developed or was formed.

The nervous system is your body’s communication network. It includes the brain, spinal cord, and nerves which send messages back and forth so you can think, feel, move, and react to things around you.

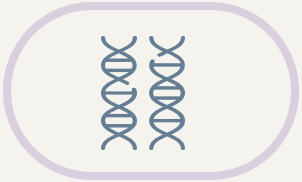


“Disorder”

When something is different or works differently than expected.

Let’s put it all together!

CUL3-related neurodevelopmental disorder (*CUL3*-NDD)



CUL3

The name of the gene affected

Neurodevelopmental

Refers to the nervous system, its parts, and how it developed

Disorder

When something works differently than expected

Other names for the condition

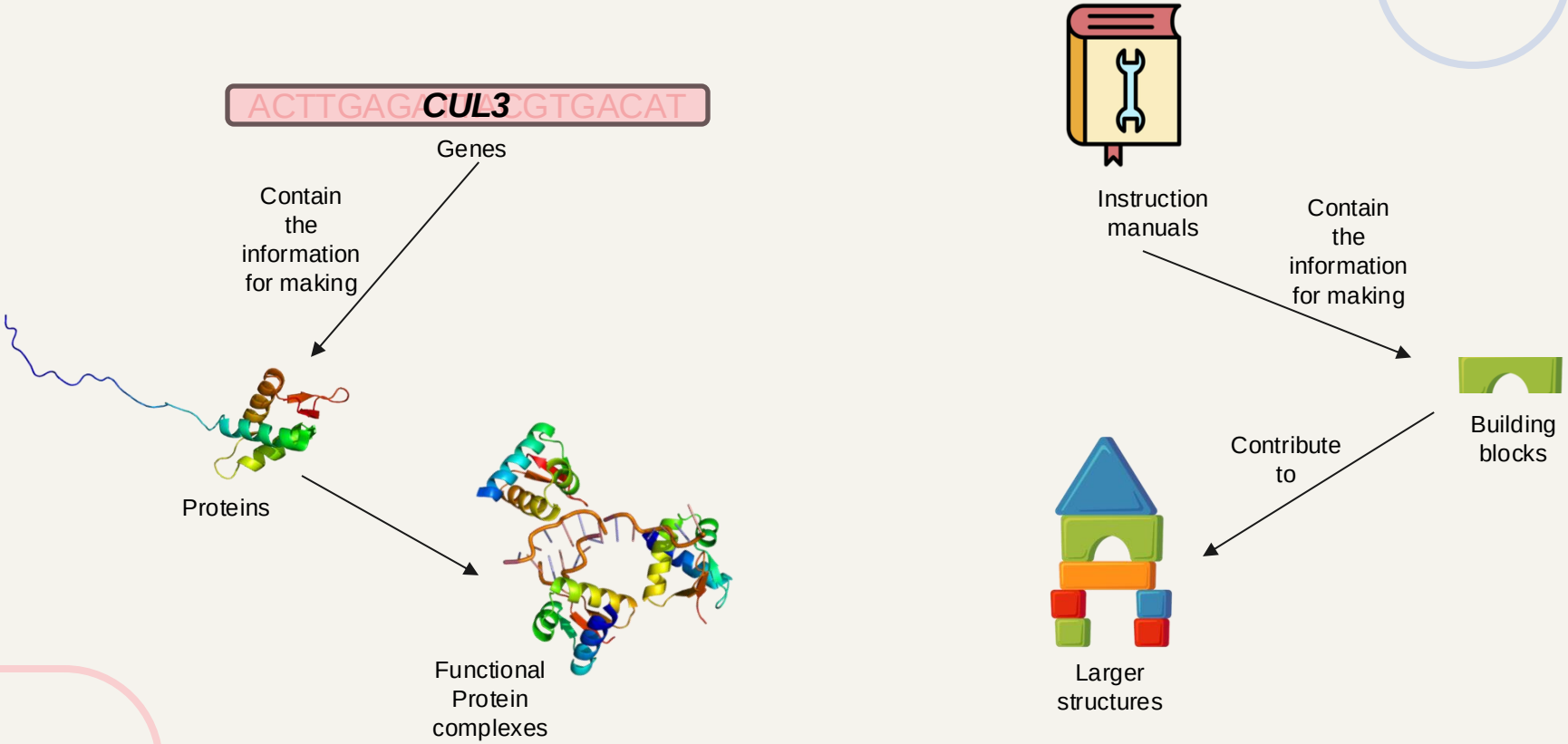
- Neurodevelopmental disorder with or without autism or seizures (NEDAUS)
- *CUL3*-related syndrome

02

Genetics

Genetics basics and *CUL3* mechanics

Genes contain instructions




NPPC
TRIP12
CUL3
FAM124B
SCG2

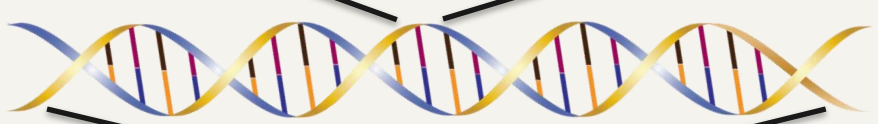
Genes

GTATGCT TAGTCAATGCTG ACTTGAG*CUL3*CGTGACAT GTCGTTAGTCAATGCTGAC ACGTGA

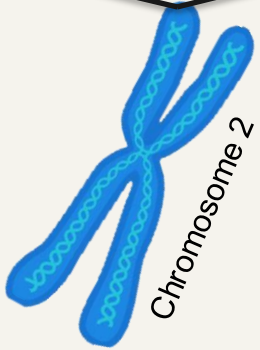
DNA

Genes

GTATGCT TAGTCAATGCTG ACTTGAGA***CUL3***CGTGACAT GTCGTTAGTCAATGCTGAC ACGTGA



DNA



Chromosomes

What does it mean when a gene does not work properly?

- A change in a gene can be like a typo or spelling error which can change the instructions that the gene contains
- If the instructions have been altered, this can affect the body's ability to make the protein that is supposed to be built from those instructions
- **A change in a gene is called a variant** (or historically referred to as a mutation)
- There are several different types of variants:
    - Missense
    - Splicing
    - Truncating
    - Nonsense
    - Frameshift
    - Loss-of-function
    - And more

Types of variants

- **Missense variant**: a genetic change that alters one part of a gene. Typically involves swapping out one letter in the DNA code for another. For example, this would be like if the word “Cat” became “Rat”.
- **Nonsense variant**: a genetic change that causes a premature stop in a gene. This causes a shortened code and therefore a shortened protein product. For example, it would be like if the word “Cat” became “Ca”.
- **Frameshift variant**: a genetic change that shifts the way a gene’s instructions are read. Usually happens when letters are added or removed which changes all instructions after the change. For example, it would be like if “The cat ran” became “The atr an”.
- **Splicing variant**: a genetic change that disrupts how a gene’s instructions are pieced together. For example, this would be like if the sentence “The cat ran fast” became “The cat faan” or “The ran fast.”
- **Deletion:** a genetic change where part or all of a gene is missing. A deletion is a type of variant that may or may not affect other nearby genes. For example, “The cat ran” might become “The ran”, or it may become “The” and delete part of an adjacent sentence.
- **Loss-of-function (LOF) variant**: a genetic change that causes the protein become non-functional or less active than normal.

Classification of variants

- Most variants that are identified and help provide a genetic diagnosis to someone are considered “pathogenic” or “likely pathogenic” variants.
- **Pathogenic/likely pathogenic**: a genetic change known to or very likely to cause health concerns.
- **Variant of uncertain significance (VUS)**: A genetic change that is not completely understood yet. It might be harmless (benign), or it might cause health issues (pathogenic), but more information is needed to know for sure.
- A diagnosis is not typically provided solely on the basis of a VUS on a genetic testing report. Further testing (segregation analysis) to clarify the meaning of the variant in the context of a suspected diagnosis may be recommended.

How genes relate to *CUL3*-NDD

- *CUL3* is the name of a specific gene.
- Variants or changes in *CUL3* can cause *CUL3*-related neurodevelopmental disorder (*CUL3*-NDD).
- *CUL3*-NDD is considered an “autosomal dominant condition.”

CUL3-NDD inheritance pattern

- *CUL3*-NDD is an autosomal dominant (AD) condition.
- This means that of a person's two copies of the *CUL3* gene, only one of them has to have a variant for that person to be affected with the disorder.

- A variant in *CUL3* can be passed down or inherited from a parent. Someone who has a variant in *CUL3* or has *CUL3*-NDD has a 50% chance of passing it down to each child.
- More commonly, people with *CUL3*-NDD did not inherit their *CUL3* variant from a parent. When a genetic change is new in someone, meaning it was not passed down, it is called a de novo variant.
- It is important to ask whether the variant in *CUL3* was inherited or is new (de novo).

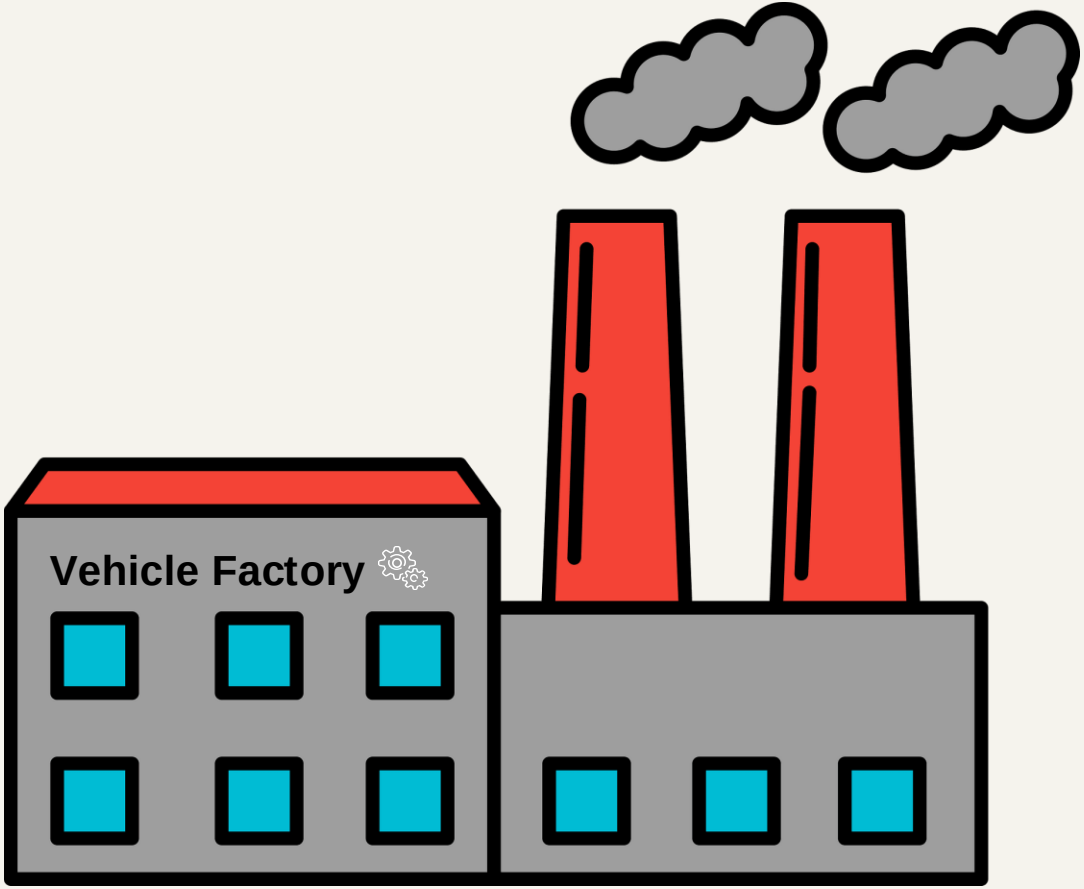
03

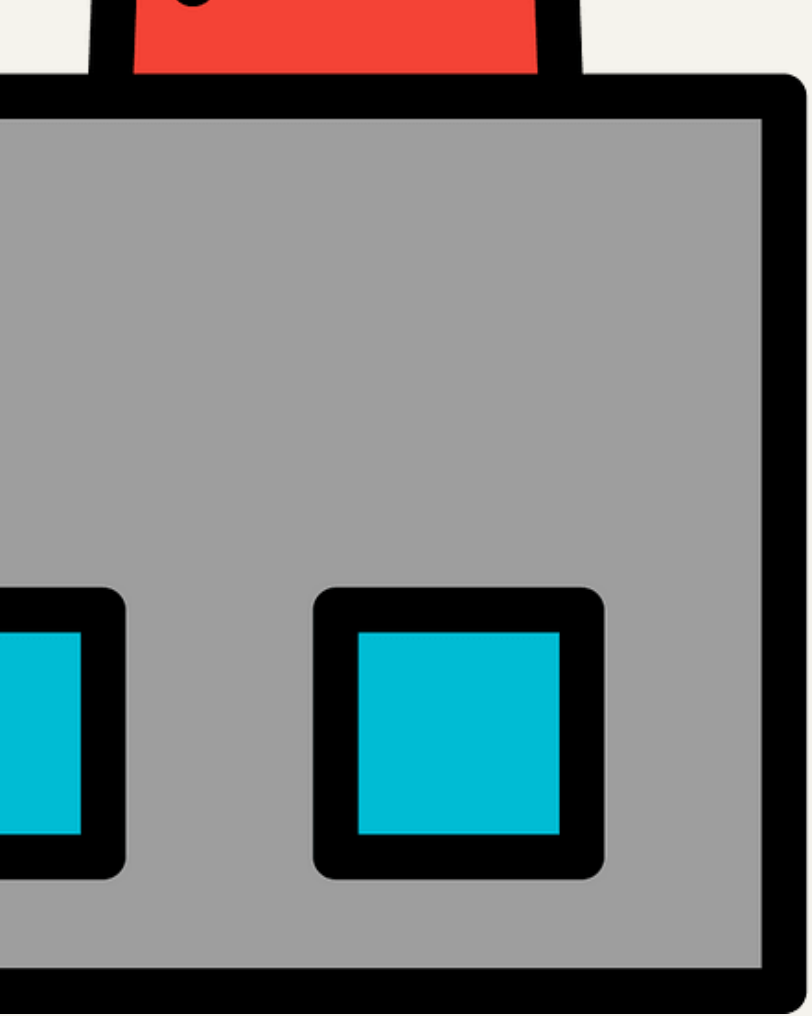
The job of *CUL3* & recap of genetics

Including an analogy for *CUL3*'s function in the body

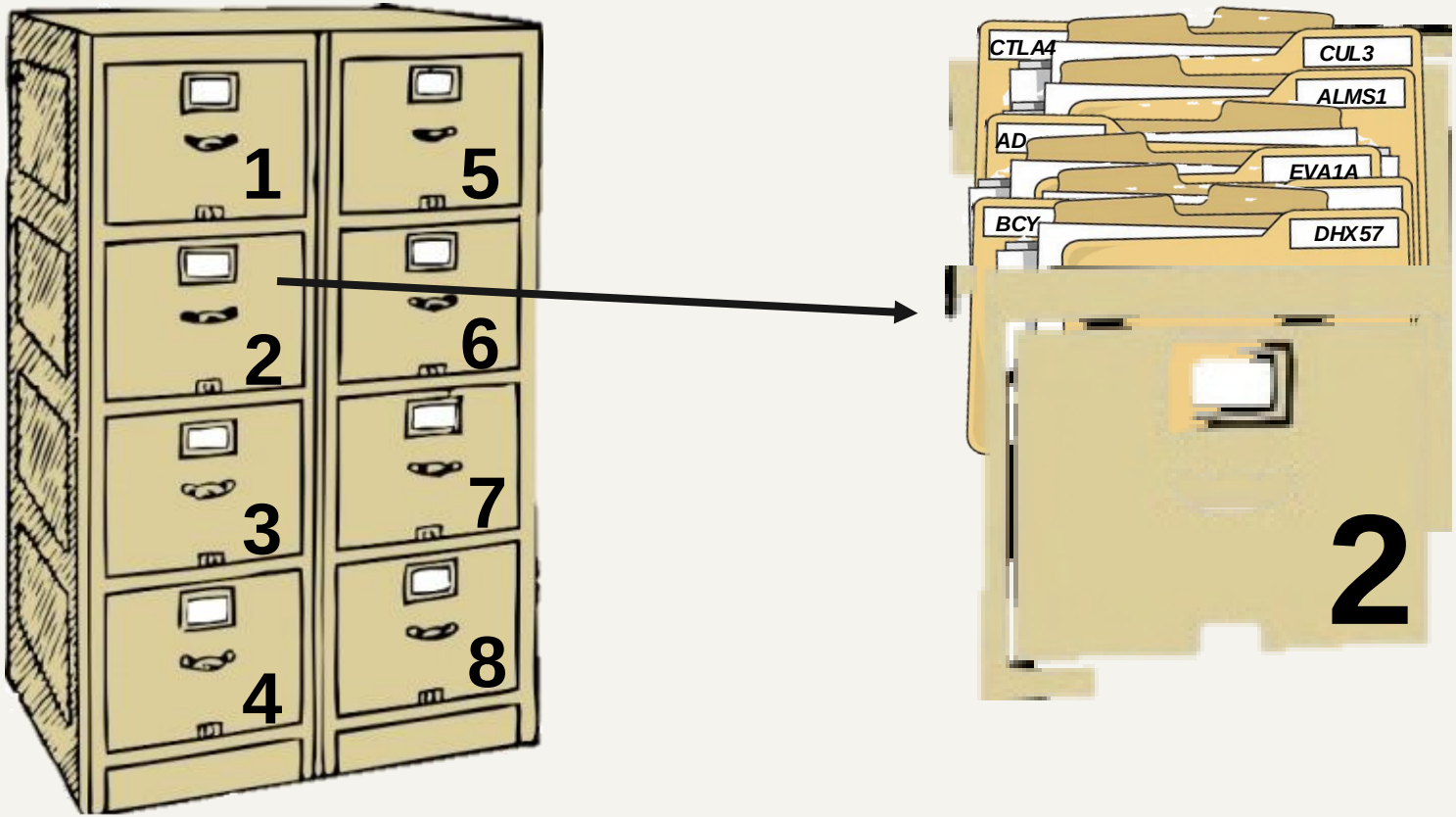
Why is *CUL3* important?

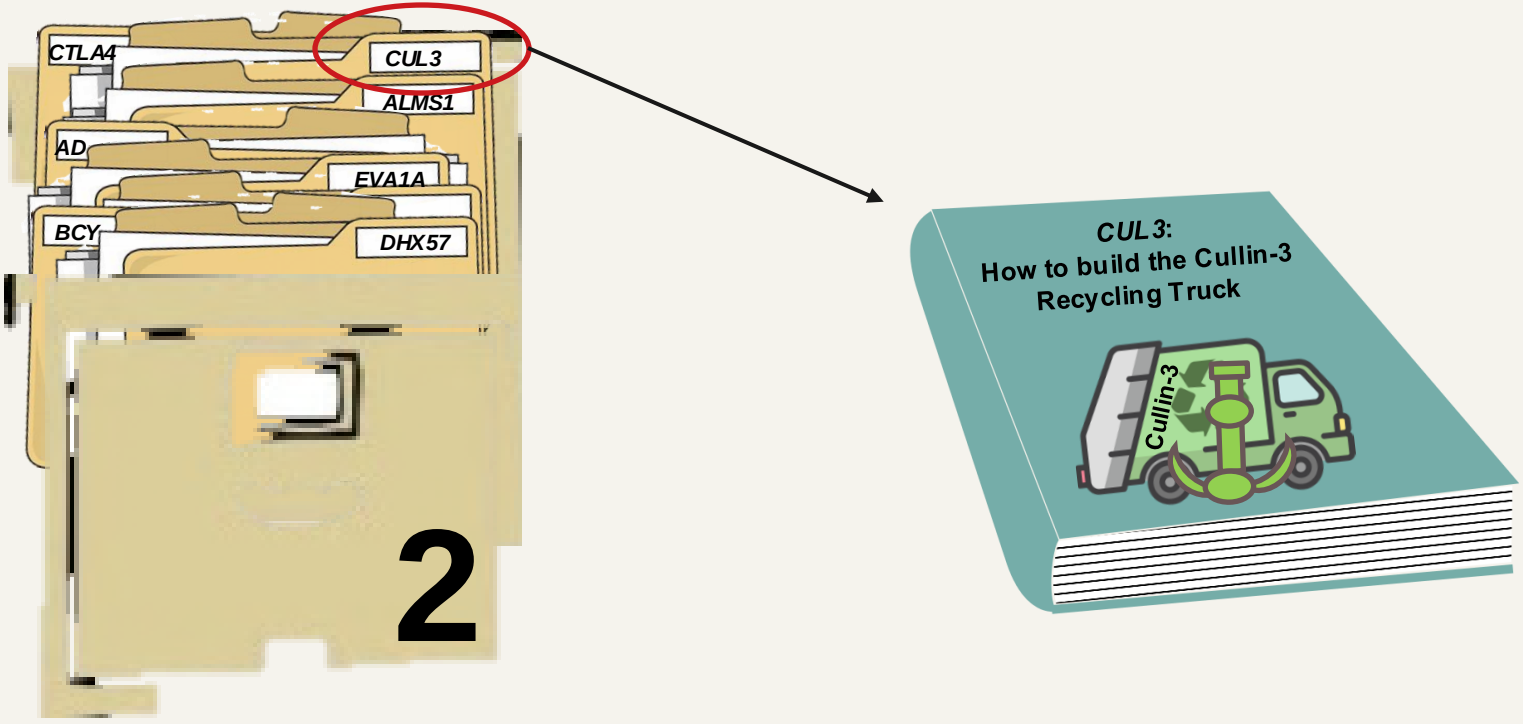
- *CUL3* makes a protein called cullin-3. The job of cullin-3 is to help get rid of other unneeded proteins in the cell.
- If there is a variant in *CUL3*, the protein cullin-3 may not be made correctly or not made at all.
- If cullin-3 is not working correctly, unneeded proteins can build up in the cell during development and interfere with important processes in the nervous system.
- Interfering with some of these critical developmental processes in the nervous system likely cause many of the signs and symptoms of *CUL3*-NDD.
- The symptoms each person with *CUL3*-NDD has are not the same because different variants affect protein function differently and cause unique health issues in each person.


Vehicle Factory



DNA


1
5
2
6
3
7
4
8
CTLA4
CUL3
ALMS1
AD
EVA1A
BCY
DHX57
2


CTLA4
CUL3
ALMS1
AD
EVA1A
BCY
DHX57
2
CUL3:
How to build the Cullin-3
Recycling Truck
Cullin-3

Typically functioning *CUL3*

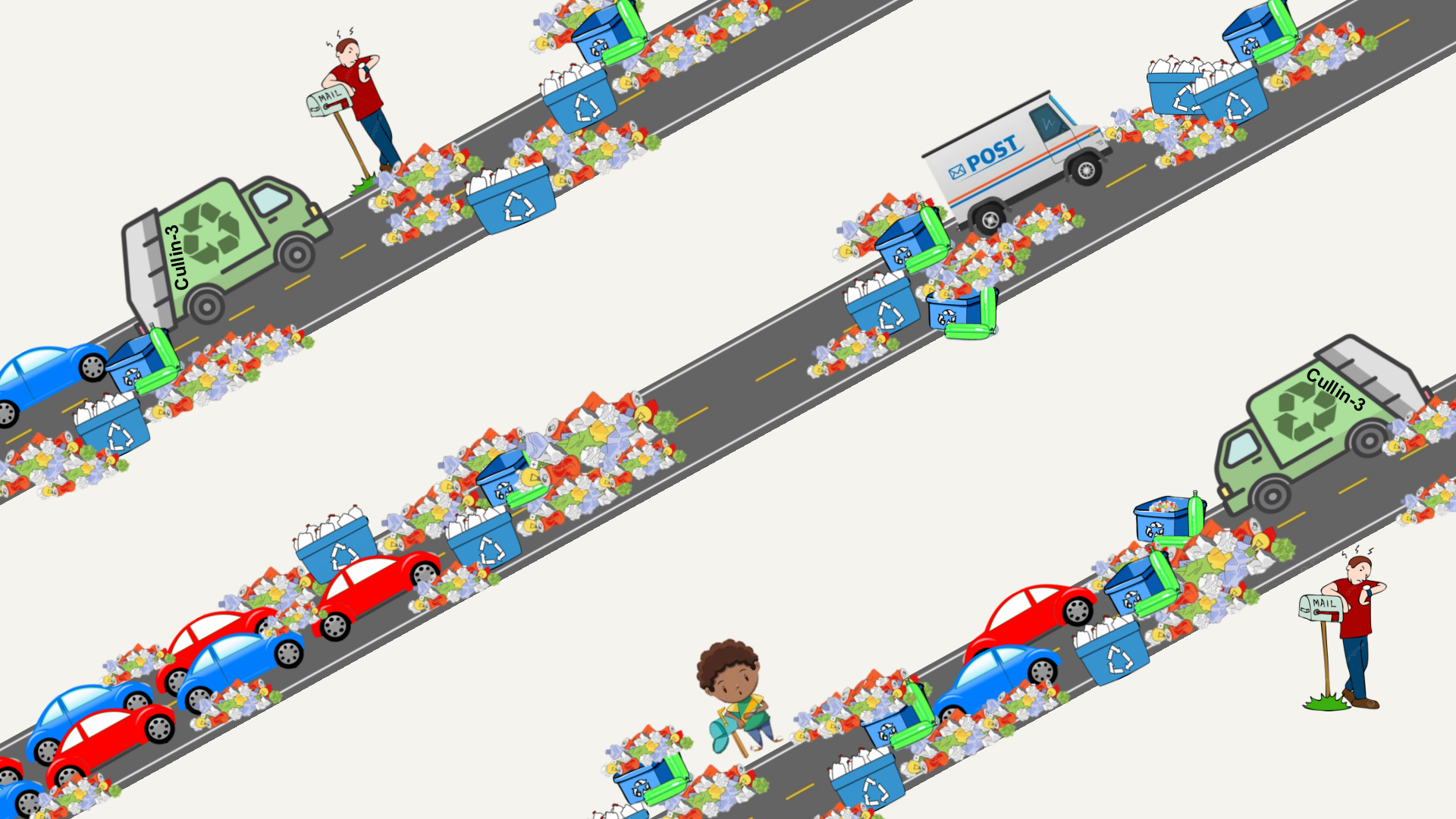
+

=

Variant in *CUL3*

+

=


MAIL
Cullin-3
POST
Cullin-3
MAIL

04

Features of *CUL3*-NDD

Health and behavioral concerns discussed in plain language

Common features of *CUL3*-NDD

*Note: CUL3-related neurodevelopmental disorder is considered to be a non-progressive and non-fatal condition

Neurodevelopmental concerns or differences

- **Global developmental delay (GDD):** A general term used when a child takes longer than expected to reach milestones or develop skills in two or more areas of development.
- **Intellectual disability (ID):** A term used when a person has more difficulty learning, thinking, or solving problems compared to others the same age.
- **Speech and language delay:** A term used when a child takes longer than expected to start talking, understand words, or use language to communicate.

Common features of *CUL3*-NDD

*Note: CUL3-related neurodevelopmental disorder is considered to be a non-progressive and non-fatal condition

Behavioral differences and neurodiversity

- **Autism Spectrum Disorder (ASD)**: A term used when a person thinks, learns, and experiences the world in a unique way. It can include challenges with social situations, communication, or behavior, but it is also a part of natural brain diversity.
- **Attention-Deficit/Hyperactivity Disorder (ADHD)**: When a person has difficulty with focus, staying organized, or controlling their impulses and behavior.
- **Anxiety and mood regulation:** Anxiety is when a person feels worry, fear, or nervousness that may interfere with daily life. They may find it difficult to focus or feel calm even when an apparently dangerous or distressing situation is not apparent. Mood regulation challenges can result in feelings of extreme sadness, irritability, or anger. These shifts can happen quickly and can be difficult to manage in everyday situations.

Common features of *CUL3*-NDD

*Note: CUL3-related neurodevelopmental disorder is considered to be a non-progressive and non-fatal condition

Physical findings

- **Hypotonia**: A term used when a person has low muscle tone, meaning their muscles feel softer or less firm than usual. It can make it harder to control movements or maintain posture.
    - Notably, hypotonia and muscle weakness are NOT the same thing.

Feeding and growth concerns

- **Feeding difficulties**: When a person has trouble eating or drinking, which can include problems with sucking, chewing, or swallowing.
- **Intrauterine growth restriction (IUGR)**: When a baby grows slower than expected during pregnancy, leading to a smaller size at birth.
- **Growth faltering**: When a child is not gaining weight or growing as expected for their age.

Less common features of *CUL3*-NDD

Neurological concerns

- **Seizures:** When there is sudden changes in brain activity that can cause uncontrolled movements, staring spells, or a loss of awareness.
- **Brain imaging differences:** Differences in the way the brain was formed may be detected when someone recieves imaging to look at their brain.

Cardiac differences

- **Septal defects (ASD/VSD):** When the wall that separates chambers of the heart is not formed correctly. This can affect how blood flows through the heart and body.
    - Other heart differences are possible in *CUL3*-NDD, but septal defects are most common.

Less common features of *CUL3*-NDD

Other medical concerns

- **GERD/GI concerns:** GERD (gastroesophageal reflux disease) is when stomach acid flows back into the esophagus and causes discomfort. Other concerns with the digestive system can include constipation and diarrhea.
- **Hand/foot differences:** Variations in the size or shape of fingers and toes. The shape of someone's hands or feet may also differ, and these variations may or may not affect movement or the use of the hands or feet.
- **Skeletal differences:** Differences in the bones that make up the spine or backbone. These differences are usually atypical curvature of the spine (scoliosis).

Does every person have the same symptoms?

- It's important to know that *CUL3*-NDD affects every person differently. It's unlikely that two people will have the exact same health concerns present in an identical way.
- Several factors, including the specific *CUL3* variant someone has, can influence the types of differences and what health concerns they have.
- Also, the previously listed health and behavioral differences are not all the potential concerns someone with *CUL3*-NDD may have.
- We may discover more features or health concerns related to the disorder over time.
- It's important to work with a healthcare provider(s) to identify an affected person's unique concerns and needs.

05

CUL3-NDD vs Pseudohypoaldosteronism Type IIE

Differentiating the two conditions

Pseudohypoaldosteronism type IIE (PHA2E)

- Caused by variants in *CUL3*
- ***Importantly* these are NOT the same variants that cause *CUL3*-related neurodevelopmental disorder.**
    - Variants that affect specific sections of *CUL3* (intron 8, exon 9, and intron 9) cause PHA2E.
    - These same variants are not thought to be related to *CUL3*-NDD
- PHA2E is a condition that affects the body's ability to maintain the right balance of sodium and potassium in the body.

Pseudohypoaldosteronism type IIE (PHA2E)

- **Pseudo:** Prefix means “false” or “not real”. Implies that the condition mimics the effects of a hormone or substance, but is not actually caused by a lack of that hormone.
- **Hypo:** Means “low”
- **Aldosteronism:** Related to aldosterone which is a hormone that helps regulate sodium and potassium levels in the body.
- **Type IIE**: The classification of the condition.

Pseudohypoaldosteronism type IIE (PHA2E)

- PHA2E is a condition that causes mineral imbalances in the body and can cause high blood pressure.
- Can be treated with medication and diet modifications.
- *CUL3*-related neurodevelopmental disorder is NOT the same as PHA2E, even though they are both caused by variants in *CUL3*.
- Symptoms of PHA2E and *CUL3*-NDD are not known to overlap.

06

Providers and specialists

Healthcare providers someone with CUL3-NDD might see

Providers and specialists

- **Geneticist:** A doctor with special training in genetic conditions. They may help give a diagnosis and may follow patients after their initial diagnosis over the course of their life.
- **Neurogeneticist:** A doctor very similar to a geneticist who has specialized training in identifying and managing neurogenetic conditions.
- **Genetic counselor:** May be seen to discuss genetic conditions like *CUL3*-related neurodevelopmental disorder and to help facilitate genetic testing and discuss what results of testing mean for an affected person and their relatives.
- **Neurologist:** A doctor that may help manage neurological symptoms like possible seizures.
- **Dietician:** Help with ensuring proper growth and development through monitoring and adjusting a person's diet.
- **Feeding therapist:** Helps people who have difficulties eating. They may help identify interventions to help someone eat better or work with them to eat more effectively.

Providers and specialists

- **Gastroenterologist:** Helps with digestive issues like reflux, trouble eating, and constipation.
- **Physical therapist (PT):** Help support motor and sensory development and build muscle tone.
- **Occupational therapist (OT):** Helps people build skills and independence related to everyday tasks and may help build fine motor skills.
- **Speech-language pathologist (SLP):** Support language development and assist in addressing possible feeding difficulties.
- **Cardiologist:** May help address differences in the shape or function of the heart that can be associated with the condition.
- **Nephrologist:** Doctor with special training about the kidneys. May help address medication or treatment for people who have pseudohypoaldosteronism type IIE (PHA2E).
- **Social Worker:** Help people navigate challenges in their life. They can connect families to support services, resources, and advocacy to improve quality of life.

There are a lot of different specialists that someone with a genetic condition like *CUL3*-related neurodevelopmental disorder might need to see.

The previous is list is not exhaustive, and it may not be representative of all types of providers available in all locations.

However, it is incredibly important to keep up with the recommended specialists and therapies for someone with *CUL3*-NDD to make sure they are becoming and maintaining their best self!

Questions to ask healthcare providers

Here are some questions that might be helpful to consider when discussing genetic test results with a provider:

1. What does this result mean for my child's health?
2. Is this genetic change inherited or new?
3. What medical conditions might this genetic change be linked to?
4. Does any additional genetic testing need to be done?
5. Are there other children or family members that should consider testing?
6. What steps should we take next?

Thank you for viewing this resource

References

https://medlineplus.gov/genetics/condition/cul3-related-neurodevelopmental-disorder/
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://medlineplus.gov/download/genetics/condition/cul3-related-neurodevelopmental-disorder.pdf
https://www.simonssearchlight.org/research/what-we-study/cul3/
https://pubmed.ncbi.nlm.nih.gov/39501558/
https://pubmed.ncbi.nlm.nih.gov/36710200/
https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2023.1215110/full
https://pubmed.ncbi.nlm.nih.gov/39301775/
Google Images