



## Familial glucocorticoid deficiency

Familial glucocorticoid deficiency is a condition that occurs when the adrenal glands, which are hormone-producing glands located on top of each kidney, do not produce certain hormones called glucocorticoids. These hormones, which include cortisol and corticosterone, aid in immune system function, play a role in maintaining normal blood sugar levels, help trigger nerve cell signaling in the brain, and serve many other purposes in the body.

A shortage of adrenal hormones (adrenal insufficiency) causes the signs and symptoms of familial glucocorticoid deficiency. These signs and symptoms often begin in infancy or early childhood. Most affected children first develop low blood sugar (hypoglycemia). These hypoglycemic children can fail to grow and gain weight at the expected rate (failure to thrive). If left untreated, hypoglycemia can lead to seizures, learning difficulties, and other neurological problems. Hypoglycemia that is left untreated for prolonged periods can lead to neurological damage and death. Other features of familial glucocorticoid deficiency can include recurrent infections and skin coloring darker than that of other family members (hyperpigmentation).

There are multiple types of familial glucocorticoid deficiency, which are distinguished by their genetic cause.

### Frequency

The prevalence of familial glucocorticoid deficiency is unknown.

### Causes

Mutations in the *MC2R*, *MRAP*, and *NNT* genes account for the majority of cases of familial glucocorticoid deficiency; mutations in other genes, some known and some unidentified, can also cause this condition.

The *MC2R* gene provides instructions for making a protein called adrenocorticotrophic hormone (ACTH) receptor, which is found primarily in the adrenal glands. The protein produced from the *MRAP* gene transports the ACTH receptor from the interior of the cell to the cell membrane. When the ACTH receptor is embedded within the cell membrane, it is turned on (activated) by the MRAP protein. Activated ACTH receptor can then attach (bind) to ACTH, and this binding triggers the adrenal glands to produce glucocorticoids. *MC2R* gene mutations lead to the production of a receptor that cannot be transported to the cell membrane or, if it does get to the cell membrane, cannot bind to ACTH. *MRAP* gene mutations impair the transport of the ACTH receptor to the cell membrane. Without the binding of the ACTH receptor to its hormone, there is no signal to trigger the adrenal glands to produce glucocorticoids.

The *NNT* gene provides instructions for making an enzyme called nicotinamide nucleotide transhydrogenase. This enzyme is found embedded in the inner membrane of structures called mitochondria, which are the energy-producing centers of cells. This enzyme helps produce a substance called NADPH, which is involved in removing potentially toxic molecules called reactive oxygen species that can damage DNA, proteins, and cell membranes. *NNT* gene mutations impair the enzyme's ability to produce NADPH, leading to an increase in reactive oxygen species in adrenal gland tissues. Over time, these toxic molecules can impair the function of adrenal gland cells and lead to their death (apoptosis), diminishing the production of glucocorticoids.

## **Inheritance Pattern**

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.

## **Other Names for This Condition**

- ACTH resistance
- adrenal unresponsiveness to ACTH
- glucocorticoid deficiency
- hereditary unresponsiveness to adrenocorticotrophic hormone
- isolated glucocorticoid deficiency

## **Diagnosis & Management**

### Genetic Testing Information

- What is genetic testing?  
[/primer/testing/genetic-testing](#)
- Genetic Testing Registry: ACTH resistance  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4049650/>
- Genetic Testing Registry: Glucocorticoid deficiency 2  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4049714/>
- Genetic Testing Registry: Glucocorticoid deficiency 3  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1836621/>
- Genetic Testing Registry: Glucocorticoid deficiency 4 with or without mineralocorticoid deficiency  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3553587/>
- Genetic Testing Registry: Natural killer cell and glucocorticoid deficiency with DNA repair defect  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1864947/>

### Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22familial+glucocorticoid+deficiency%22+OR+%22Adrenal+Insufficiency%22>

### **Additional Information & Resources**

#### Health Information from MedlinePlus

- Encyclopedia: Adrenal Glands  
<https://medlineplus.gov/ency/article/002219.htm>
- Health Topic: Hypoglycemia  
<https://medlineplus.gov/hypoglycemia.html>

#### Genetic and Rare Diseases Information Center

- Familial glucocorticoid deficiency  
<https://rarediseases.info.nih.gov/diseases/2498/familial-glucocorticoid-deficiency>

#### Additional NIH Resources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development: Adrenal Gland Disorders  
<https://www.nichd.nih.gov/health/topics/adrenalgland/conditioninfo>
- National Endocrine and Metabolic Diseases Information Service: Adrenal Insufficiency and Addison's Disease  
<https://www.niddk.nih.gov/health-information/endocrine-diseases/adrenal-insufficiency-addisons-disease>
- National Institute of Neurological Disorders and Stroke: Seizures and Epilepsy: Hope Through Research  
<https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Epilepsies-and-Seizures-Hope-Through>

#### Educational Resources

- Australian Pituitary Foundation: Overview of the Pituitary  
<https://pituitary.asn.au/learn/overview-of-the-pituitary-foundation/>
- Hormone Health Network: Nondiabetic Hypoglycemia  
<https://www.hormone.org/diseases-and-conditions/diabetes/non-diabetic-hypoglycemia>
- Johns Hopkins Medicine: The Adrenal Glands  
<https://www.hopkinsmedicine.org/health/conditions-and-diseases/adrenal-glands>
- KidsHealth from Nemours: Adrenal Gland  
[https://kidshealth.org/en/parents/endocrine.html#kha\\_41](https://kidshealth.org/en/parents/endocrine.html#kha_41)

- MalaCards: familial glucocorticoid deficiency  
[https://www.malacards.org/card/familial\\_glucocorticoid\\_deficiency](https://www.malacards.org/card/familial_glucocorticoid_deficiency)
- Merck Manual Consumer Version: Hypoglycemia  
<https://www.merckmanuals.com/home/hormonal-and-metabolic-disorders/diabetes-mellitus-dm-and-disorders-of-blood-sugar-metabolism/hypoglycemia>
- Merck Manual Consumer Version: Overview of the Adrenal Glands  
<https://www.merckmanuals.com/home/hormonal-and-metabolic-disorders/adrenal-gland-disorders/overview-of-the-adrenal-glands>
- Orphanet: Familial glucocorticoid deficiency  
[https://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=361](https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=361)

#### Patient Support and Advocacy Resources

- Hormone Health Network: Adrenal Insufficiency  
<https://www.hormone.org/diseases-and-conditions/adrenal/adrenal-insufficiency>
- National Adrenal Diseases Foundation  
<https://www.nadf.us/>
- Resource List from the University of Kansas Medical Center: Endocrine Genetic Conditions  
<http://www.kumc.edu/gec/support/endocrin.html>
- The Hypoglycemia Support Foundation, Inc.  
<https://hypoglycemia.org/>

#### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28Adrenal+Insufficiency%5BMAJR%5D%29+AND+%28familial+glucocorticoid+deficiency%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

#### Catalog of Genes and Diseases from OMIM

- GLUCOCORTICOID DEFICIENCY 1  
<http://omim.org/entry/202200>
- GLUCOCORTICOID DEFICIENCY 2  
<http://omim.org/entry/607398>
- GLUCOCORTICOID DEFICIENCY 3  
<http://omim.org/entry/609197>

- GLUCOCORTICOID DEFICIENCY 4 WITH OR WITHOUT MINERALOCORTICOID DEFICIENCY  
<http://omim.org/entry/614736>
- IMMUNODEFICIENCY 54  
<http://omim.org/entry/609981>

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