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 adrenocorticotropic 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 adrenocorticotropic hormone
- isolated glucocorticoid deficiency

**Diagnosis & Management**

**Genetic Testing Information**

- What is genetic testing?
  /primer/testing/genetictesting
- 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%20glucocorticoid%20deficiency%22+OR+%22Adrenal%20Insufficiency%22

Other Diagnosis and Management Resources

- MedlinePlus Medical Test: Adrenocorticotropic Hormone (ACTH)
  https://medlineplus.gov/lab-tests/adrenocorticotropic-hormone-acth/

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

- Medical Test: Adrenocorticotropic Hormone (ACTH)
  https://medlineplus.gov/lab-tests/adrenocorticotropic-hormone-acth/

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

- MalaCards: 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

Patient Support and Advocacy Resources

- Hormone Health Network: Adrenal Insufficiency
  https://www.hormone.org/diseases-and-conditions/adrenal-insufficiency

- National Adrenal Diseases Foundation
  https://www.nadf.us/

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

Sources for This Summary

• Chung TT, Chan LF, Metherell LA, Clark AJ. Phenotypic characteristics of familial glucocorticoid deficiency (FGD) type 1 and 2. Clin Endocrinol (Oxf). 2010 May;72(5):589-94. doi: 10.1111/j.1365-2265.2009.03663.x. Epub 2009 Jun 24.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19558534
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2855830/

• Chung TT, Webb TR, Chan LF, Cooray SN, Metherell LA, King PJ, Chapple JP, Clark AJ. The majority of adrenocorticotropin receptor (melanocortin 2 receptor) mutations found in familial glucocorticoid deficiency type 1 lead to defective trafficking of the receptor to the cell surface. J Clin Endocrinol Metab. 2008 Dec;93(12):4948-54. doi: 10.1210/jc.2008-1744. Epub 2008 Oct 7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18840636
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2635546/

• Clark AJ, McLoughlin L, Grossman A. Familial glucocorticoid deficiency associated with point mutation in the adrenocorticotropin receptor. Lancet. 1993 Feb 20;341(8843):461-2.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/8094489

• Hughes CR, Chung TT, Habeel AM, Kelestimur F, Clark AJ, Metherell LA. Missense mutations in the melanocortin 2 receptor accessory protein that lead to late onset familial glucocorticoid deficiency type 2. J Clin Endocrinol Metab. 2010 Jul;95(7):3497-501. doi: 10.1210/jc.2009-2731. Epub 2010 Apr 28.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20427498

• Hughes CR, Guasti L, Meimaridou E, Chuang CH, Schimenti JC, King PJ, Costigan C, Clark AJ, Metherell LA. MCM4 mutation causes adrenal failure, short stature, and natural killer cell deficiency in humans. J Clin Invest. 2012 Mar;122(3):814-20. doi: 10.1172/JCI60224. Epub 2012 Feb 22.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22354170
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3287227/

• Meimaridou E, Hughes CR, Kowalczyk J, Chan LF, Clark AJ, Metherell LA. ACTH resistance: genes and mechanisms. Endocr Dev. 2013;24:57-66. doi: 10.1159/000342504. Epub 2013 Feb 1. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23392095

• Meimaridou E, Hughes CR, Kowalczyk J, Guasti L, Chapple JP, King PJ, Chan LF, Clark AJ, Metherell LA. Familial glucocorticoid deficiency: New genes and mechanisms. Mol Cell Endocrinol. 2013 May 22;371(1-2):195-200. doi: 10.1016/j.mce.2012.12.010. Epub 2012 Dec 29. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23279877

• Meimaridou E, Kowalczyk J, Guasti L, Hughes CR, Wagner F, Frommolt P, Nürnberg P, Mann NP, Banerjee R, Saka HN, Chapple JP, King PJ, Clark AJ, Metherell LA. Mutations in NNT encoding nicotinamidase nucleotide transhydrogenase cause familial glucocorticoid deficiency. Nat Genet. 2012 May 27;44(7):740-2. doi: 10.1038/ng.2299.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22634753
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3386896/
• Metherell LA, Chapple JP, Cooray S, David A, Becker C, Rüschendorf F, Naville D, Begeot M, Khoo B, Nürnberg P, Huebner A, Cheetham ME, Clark AJ. Mutations in MRAP, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2. Nat Genet. 2005 Feb;37(2):166-70. Epub 2005 Jan 16. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15654338

• Prasad R, Chan LF, Hughes CR, Kaski JP, Kowalczyk JC, Savage MO, Peters CJ, Nathwani N, Clark AJ, Storr HL, Metherell LA. Thioredoxin Reductase 2 (TXNRD2) mutation associated with familial glucocorticoid deficiency (FGD). J Clin Endocrinol Metab. 2014 Aug;99(8):E1556-63. doi: 10.1210/jc.2013-3844. Epub 2014 Mar 6. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24601690
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4207928/

Reprinted from Genetics Home Reference: 
  https://ghr.nlm.nih.gov/condition/familial-glucocorticoid-deficiency

Reviewed: February 2015
Published: May 12, 2020

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services