Familial Glucocorticoid Deficiency

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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.

Keywords: genetic conditions

1. Introduction

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.

2. Frequency

The prevalence of familial glucocorticoid deficiency is unknown.

3. 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.

3.1. The Genes Associated with Familial Glucocorticoid Deficiency

- MC2R
- MRAP

- NNT

4. Inheritance

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.

5. Other Names for This Condition

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

References

1. Chung TT, Chan LF, Metherell LA, Clark AJ. Phenotypic characteristics offamilial 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.
2. Chung TT, Webb TR, Chan LF, Cooray SN, Metherell LA, King PJ, Chapple JP,Clark AJ. The majority of adrenocorticotr opin receptor (melanocortin 2 receptor) mutations found in familial glucocorticoid deficiency type 1 lead to defectivetraffi cking of the receptor to the cell surface. J Clin Endocrinol Metab. 2008Dec;93(12):4948-54. doi: 10.1210/jc.2008-1744.
3. Clark AJ, McLoughlin L, Grossman A. Familial glucocorticoid deficiencyassociated with point mutation in the adrenocort icotropin receptor. Lancet. 1993 Feb 20;341(8843):461-2.
4. Hughes CR, Chung TT, Habeb AM, Kelestimur F, Clark AJ, Metherell LA. Missense mutations in the melanocortin 2 rec eptor accessory protein that lead to lateonset familial glucocorticoid deficiency type 2. J Clin Endocrinol Metab. 2010Ju l;95(7):3497-501. doi: 10.1210/jc.2009-2731.
5. 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. 2012Mar;122 (3):814-20. doi: 10.1172/JCI60224.
6. Meimaridou E, Hughes CR, Kowalczyk J, Chan LF, Clark AJ, Metherell LA. ACTHresistance: genes and mechanisms. Endocr Dev. 2013;24:57-66. doi:10.1159/000342504.
7. Meimaridou E, Hughes CR, Kowalczyk J, Guasti L, Chapple JP, King PJ, Chan LF, Clark AJ, Metherell LA. Familial gluc ocorticoid deficiency: New genes andmechanisms. Mol Cell Endocrinol. 2013 May 22;371(1-2):195-200. doi:10.1016/j. mce.2012.12.010.
8. Meimaridou E, Kowalczyk J, Guasti L, Hughes CR, Wagner F, Frommolt P, NürnbergP, Mann NP, Banerjee R, Saka H N, Chapple JP, King PJ, Clark AJ, Metherell LA.Mutations in NNT encoding nicotinamide nucleotide transhydrogenase cause familialglucocorticoid deficiency. Nat Genet. 2012 May 27;44(7):740-2. doi:10.1038/ng.2299.
9. Metherell LA, Chapple JP, Cooray S, David A, Becker C, Rüschendorf F, Naville D, Begeot M, Khoo B, Nürnberg P, Hu ebner A, Cheetham ME, Clark AJ. Mutations inMRAP, encoding a new interacting partner of the ACTH receptor, cause f amilialglucocorticoid deficiency type 2. Nat Genet. 2005 Feb;37(2):166-70.
10. Prasad R, Chan LF, Hughes CR, Kaski JP, Kowalczyk JC, Savage MO, Peters CJ,Nathwani N, Clark AJ, Storr HL, Met herell 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.