<https://www.ncbi.nlm.nih.gov/pubmed/18986552>

Subclasses of CFS have been associated with polymorphisms in genes that function in the HPA axis NR3C1, TPH2 and MAOA [[37](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2625353/#B37)-[39](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2625353/#B39)].

Average absolute value of severity associations for the SNPs within eight candidate genes.

| **Gene Name** | **Gene Location** | **Average Correlation (SD)** | **Count of SNPs in candidate gene** | **Most Correlated SNP** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | Name | Correlation | p-value |
| POMC | 2p24 | 0.14 (NA) | 1 | rs12473543 | 0.135 | 0.216 |
| NR3C1 | 5q34 | 0.07 (0.06) | 7 | rs258750 | 0.198 | 0.069 |

<https://www.ncbi.nlm.nih.gov/pubmed/16610957>

The top three genes containing the SNPs accounting for the highest accumulated importances were neuronal tryptophan hydroxylase (*TPH2*), catechol-*O*-methyltransferase (*COMT*) and nuclear receptor subfamily 3, group C, member 1 glucocorticoid receptor (*NR3C1*).

<https://www.ncbi.nlm.nih.gov/pubmed/19540336>

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | | | | |
| Gene | SNP[a](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn1) | Chromosome | Position (Mb)[b](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn2) | CFS vs. NF[c](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn3) | CFS-MDD/m vs. NF[d](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn4) |
| NR3C1[e](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn5) | rs2918419 | 5 | 142.641 | **0.0104** | 0.3950 |
|  | rs1866388 | 5 | 142.702 | **0.0010**[f](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub#tblfn6) | **0.0472** |
|  | rs860458 | 5 | 142.739 | **0.0104** | 0.3950 |
|  | rs852977 | 5 | 146.642 | **0.0035**[f](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub#tblfn6) | 0.1878 |
|  | rs6196 | 5 | 146.660 | **0.0208** | 0.6423 |
|  | rs6188 | 5 | 146.667 | **0.0027**[f](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub#tblfn6) | **0.0396** |
|  | rs258750 | 5 | 146.674 | **0.0035**[f](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub#tblfn6) | 0.1009 |
| COMT[g](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn7) | rs933271 | 22 | 18.311 | 0.0649 | **0.0025** |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| NR3C1[d](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn11) |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **rs852977** | 0 (230) | 0 (17,001) | 0 (2929) | **120 (9760)** | **73 (10,139)** | **0 (261)** |
|  |  |  |  |  |  |  |
| **rs6188** | 0 (171) | 7 (16,970) | 1 (3019) | **52 (2939)** | **217 (17,074)** | **0 (147)** |
| **rs258750** | **0 (242)** | **0 (16,279)** | **105 (3639)** | 0 (2769) | 14 (12,590) | 0 (4801) |

<https://www.ncbi.nlm.nih.gov/pubmed/16740143>

**Table 2.**Association of *NR3C1*polymorphisms with CFS

| **SNP ID** | **Alleles** | **NF** | **CFS** | | **ISF** | | **CFS + ISF** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Allele frequency** | **Allele frequency** | ***P*‐value**[**\*\***](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1601-183X.2006.00244.x#t2n2) | **Allele frequency** | ***P*‐value** | **Allele frequency** | ***P*‐value**[**\*\***](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1601-183X.2006.00244.x#t2n2) |
| rs1866388 | A/G | 0.57/0.43 | 0.74/0.26 | **0.0233** | 0.67/0.33 | 0.1300 | 0.71/0.29 | **0.0335** |
| rs2918419 | T/C | 0.73/0.27 | 0.88/0.12 | **0.0410** | 0.84/0.16 | 0.0744 | 0.85/0.15 | **0.0164** |
| rs860458 | G/A | 0.73/0.27 | 0.88/0.12 | **0.0375** | 0.84/0.16 | 0.0766 | 0.85/0.15 | **0.0180** |
| rs6188 | C/A | 0.57/0.43 | 0.73/0.27 | **0.0466** | 0.69/0.31 | 0.1319 | 0.70/0.30 | **0.0383** |

<https://www.ncbi.nlm.nih.gov/pubmed/16740143>

Chronic fatigue syndrome (CFS) is a significant public health problem of unknown etiology, the pathophysiology has not been elucidated, and there are no characteristic physical signs or laboratory abnormalities. Some studies have indicated an association of CFS with deregulation of immune functions and hypothalamic-pituitary-adrenal (HPA) axis activity. In this study, we examined the association of sequence variations in the glucocorticoid receptor gene (NR3C1) with CFS because NR3C1 is a major effector of the HPA axis. There were 137 study participants (40 with CFS, 55 with insufficient symptoms or fatigue, termed as ISF, and 42 non-fatigued controls) who were clinically evaluated and identified from the general population of Wichita, KS. Nine single nucleotide polymorphisms (SNPs) in NR3C1 were tested for association of polymorphisms and haplotypes with CFS. We observed an association of multiple SNPs with chronic fatigue compared to non-fatigued (NF) subjects (P < 0.05) and found similar associations with quantitative assessments of functional impairment (by the SF-36), with fatigue (by the Multidimensional Fatigue Inventory) and with symptoms (assessed by the Centers for Disease Control Symptom Inventory). Subjects homozygous for the major allele of all associated SNPs were at increased risk for CFS with odds ratios ranging from 2.61 (CI 1.05-6.45) to 3.00 (CI 1.12-8.05). Five SNPs, covering a region of approximately 80 kb, demonstrated high linkage disequilibrium (LD) in CFS, but LD gradually declined in ISF to NF subjects. Furthermore, haplotype analysis of the region in LD identified two associated haplotypes with opposite alleles: one protective and the other conferring risk of CFS. These results demonstrate NR3C1 as a potential mediator of chronic fatigue, and implicate variations in the 5' region of NR3C1 as a possible mechanism through which the alterations in HPA axis regulation and behavioural characteristics of CFS may manifest.

<https://www.ncbi.nlm.nih.gov/pubmed/16610949>

Chronic fatigue syndrome (CFS) is characterized by persistent or relapsing fatigue that is not alleviated by rest, causes substantial reduction in activities and is accompanied by a variety of symptoms. Its unknown etiology may reflect that CFS is heterogeneous. Latent class analyses of symptoms and physiological systems were used to delineate subgroups within a population-based sample of fatigued and nonfatigued subjects [1] . This study examined whether genetic differences underlie the individual subgroups of the latent class solution. Polymorphisms in 11 candidate genes related to both hypothalamic-pituitary-adrenal (HPA) axis function and mood-related neurotransmitter systems were evaluated by comparing each of the five ill classes (Class 1, n = 33; Class 3, n = 22; Class 4, n = 22; Class 5, n = 17; Class 6, n = 11) of fatigued subjects with subjects defined as well (Class 2, n = 35). Of the five classes of subjects with unexplained fatigue, three classes were distinguished by gene polymorphsims involved in either HPA axis function or neurotransmitter systems, including proopiomelanocortin (POMC), nuclear receptor subfamily 3, group C, member 1 (NR3C1), monoamine oxidase A (MAOA), monoamine oxidase B (MAOB), and tryptophan hydroxylase 2 (TPH2). These data support the hypothesis that medically unexplained chronic fatigue is heterogeneous and presents preliminary evidence of the genetic mechanisms underlying some of the putative conditions.

<https://www.ncbi.nlm.nih.gov/pubmed/16610957>

This paper asks whether the presence of chronic fatigue syndrome (CFS) can be more accurately predicted from single nucleotide polymorphism (SNP) profiles than would occur by chance.

**METHODS:**

Specifically, given SNP profiles for 43 CFS patients, together with 58 controls, we used an enumerative search to identify an ensemble of conjunctive rules that predict whether a patient has CFS.

**RESULTS:**

The accuracy of the rules reached 76.3%, with the highest accuracy rules yielding 49 true negatives, 15 false negatives, 28 true positives and nine false positives (odds ratio [OR] 8.94, p < 0.0001). Analysis of the SNPs used most frequently in the overall ensemble of rules gave rise to a list of 'most important SNPs', which was not identical to the list of 'most differentiating SNPs' that one would calculate via studying each SNP independently. The top three genes containing the SNPs accounting for the highest accumulated importances were neuronal tryptophan hydroxylase (TPH2), catechol-O-methyltransferase (COMT) and nuclear receptor subfamily 3, group C, member 1 glucocorticoid receptor (NR3C1).

**CONCLUSION:**

The fact that only 28 out of several million possible SNPs predict whether a person has CFS with 76% accuracy indicates that CFS has a genetic component that may help to explain some aspects of the illness.

rs1866388

Suboptimal performance in working memory (WM) tasks and inefficient prefrontal cortex functioning are related to dysregulation of dopaminergic (DA) and hypothalamic-pituitary-adrenal systems. The aim of the present study was to investigate the joint effect of genetic polymorphisms coding for DA catabolism and glucocorticoid receptor (GR, NR3C1) on brain functioning. The study group (90 right-handed white Caucasian healthy individuals) underwent functional magnetic resonance imaging experiments to examine blood oxygenation level dependent (BOLD) response during a WM task with varying cognitive load (1-, 2- and 3-back). We have also examined skin conductance response (SCR) during the WM task and resting-state cerebral blood flow with continuous arterial spin labelling. The genetic markers of interest included Catechol-O-Methyl-Transferase (COMT) (Met(158)Val) and NR3C1 single-nucleotide polymorphisms (BclI C/G rs41423247, 9β A/G rs6198 and rs1866388 A/G). Haplotype-based analyses showed (i) a significant effect of COMT polymorphism on left anterior cingulate cortex, with greater deactivation in Met carriers than in Val/Val homozygotes; (ii) a significant effect of BclI polymorphism on right dorsolateral prefrontal cortex (DLPFC), with greater activation in G/G carriers than in C carriers and (iii) an interactive effect of BclI (G/G) and COMT (Met/Met) polymorphisms, which was associated with greater activation in right DLPFC. These effects remained significant after controlling for whole-brain resting-state blood flow. SCR amplitude was positively correlated with right DLPFC activation during WM. This study demonstrated that GR and COMT markers exert their separate, as well as interactive, effects on DLPFC function. Epistasis of COMT and BclI minor alleles is associated with higher activation, suggesting lower efficiency, of DLPFC during WM.

<https://www.ncbi.nlm.nih.gov/pubmed/17937535>

The glucocorticoid (GC) receptor (GR) gene is an important candidate gene for BMD regulation in GC-induced osteoporosis (GIO). However, no study has explored the genetic effects of the GR gene on BMD variation in the Chinese population.

#### MATERIALS AND METHODS:

Our sample consisted of 800 unrelated subjects (400 women and 400 men) with extreme age-adjusted hip BMD Z-scores selected from a population composed of 1988 normal adult Chinese Han. Four single nucleotide polymorphisms (SNPs) in the GR gene were genotyped. Both single SNP and haplotype association analyses were conducted.

#### RESULTS:

SNP rs1866388 (p(c) = 0.028) was found to be significantly associated with extreme BMD only in men. In both sexes, haplotypes involving rs1866388 and rs2918419 were found to have different frequency distributions in extremely low and high BMD groups (p(p) = 0.024, 0.001, and 0.002 in women and 0.002, 0.003, and 0.003 in men for window sizes of two, three, and four SNPs, respectively). Most shared haplotypes showed opposite effects between women and men.

#### CONCLUSIONS:

For the first time, our study suggested the possible role of the GR gene on BMD regulation and sex specificity in the association of GR with extreme BMD in the Chinese.

rs2918419

<https://www.ncbi.nlm.nih.gov/pubmed/18194492>

Clinical similarities between the metabolic syndrome and Cushing's syndrome have led to speculation of genetic association between them. The Bcl1 polymorphism in intron 2 of the glucocorticoid receptor (GR) gene has been associated with insulin resistance/hyperinsulinaemia. Our objective was to test the association of rs2918419, a T-->C single nucleotide change in intron 2 downstream of the Bcl1 locus, with components of the metabolic syndrome and its interaction with the Bcl1 locus.

#### DESIGN AND METHODS:

We genotyped a subsample of 325 White subjects (116 men) in the Newcastle Heart Project (NHP), a population-based study in north-east England. Gender-specific statistical analysis by stepwise backward multiple regression was performed to test the association of allele status with adiposity, glucose and insulin responses to oral glucose tolerance test (OGTT), fasting lipids and blood pressure.

#### RESULTS:

Minor allele frequency was 0.14 for rs2918419 and 0.39 for the Bcl1 polymorphism. rs2918419 was associated with higher fasting insulin concentration and insulin resistance in men but not in women. Contrary to earlier studies, the Bcl1 polymorphism on its own was not associated with insulin resistance/hyperinsulinaemia in either gender. Subjects carrying variant rs2918419 alleles also had variant alleles at the Bcl1 locus. In men, but not women, Bcl1 variant alleles on a background of rs2918419 wild-type alleles associated with lower fasting insulin compared to wild-type alleles at both loci or variant alleles at both loci.

#### CONCLUSIONS:

We report that rs2918419 was linked with hyperinsulinaemia and insulin resistance in men. Carrying Bcl1 variant alleles without rs2918419 was not associated with hyperinsulinaemia/insulin resistance. Previous reports of the association of Bcl1 polymorphism with obesity-related characteristics may reflect linkage disequilibrium with rs2918419.

<https://www.ncbi.nlm.nih.gov/pubmed/17937535>

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#### CONCLUSIONS:

For the first time, our study suggested the possible role of the GR gene on BMD regulation and sex specificity in the association of GR with extreme BMD in the Chinese.

rs6188

<https://www.ncbi.nlm.nih.gov/pubmed/27000245>

Various specific human glucocorticoid receptor (NR3C1) gene polymorphisms have been described in multiple sclerosis (MS) patients and correlated with disease progression, susceptibility and aggressiveness. Herein, we investigated the presence of gene alterations in the entire coding region of the NR3C1 in MS patients of variable clinical status (CIS, RRMS and SPMS) and the association(s) of these alterations with severity of disease (EDSS), response to glucocorticoid (GC) treatment and clinical improvement. Sixty Caucasian Greek MS patients were included. Sequencing the coding sequences and intron-exon boundaries of the NR3C1 did not reveal the presence of mutation(s) in any of the MS patients. Three previously described polymorphisms were detected: p.N363S (rs6195), p.N766N (rs6196) and c.1469-16G>T (rs6188). None of the identified alleles/genotypes were found to be associated with the severity of disease, response to glucocorticoids and disease subtypes. Known polymorphism, such as ER22/23EK that has been previously detected in MS patients, was not detected. There is a considerable ethnicity-related variation in the frequency of the NR3C1 polymorphisms. Although a genetic basis of the glucocorticoid sensitivity exists in healthy population, in the presence of chronic inflammation and abundance of cytokines--such in MS patients--other factors appear to play a more important role in GC sensitivity.

<https://www.ncbi.nlm.nih.gov/pubmed/24728165>

We assessed NR3C1 polymorphisms in Brazilians of Caucasian, African and Asian ancestry (n = 380). In a subgroup (n = 40), we compared the genotypes to glucocorticoid (GC) sensitivity, which was previously evaluated by plasma (PF) and salivary (SF) cortisol after dexamethasone (DEX) suppression tests, GC receptor binding affinity (K d ), and DEX-50% inhibition (IC 50 ) of concanavalin-A-stimulated mononuclear cell proliferation. p.N363S (rs6195), p.ER22/23EK (rs6189-6190), and BclI (rs41423247) allelic discrimination was performed by Real-Time PCR (Polymerase Chain Reaction). Exons 3 to 9 and exon/intron boundaries were amplified by PCR and sequenced.

#### RESULTS:

Genotypic frequencies (%) were: rs6195 (n = 380; AA:96.6/AG:3.14/GG:0.26), rs6189-6190 (n = 264; GG:99.6/GA:0.4), rs41423247 (n = 264; CC:57.9/CG:34.1/GG:8.0), rs6188 (n = 155; GG:69.6/GT:25.7/TT:4.7), rs258751 (n = 150; CC:88.0/CT:10.7/TT:1.3), rs6196 (n = 176; TT:77.2/TC:20.4/CC:2.4), rs67300719 (n = 137; CC:99.3/CT:0.7), and rs72542757 (n = 137; CC:99.3/CG:0.7). The rs67300719 and rs72542757 were found only in Asian descendants, in whom p.N363S and p.ER22/23EK were absent. The p.ER22/23EK was observed exclusively in Caucasian descendants. Hardy-Weinberg equilibrium was observed, except in the Asian for rs6188 and rs258751, and in the African for p.N363S. The K d , IC 50 , baseline and after DEX PF or SF did not differ between genotype groups. However, the mean DEX dose that suppressed PF or SF differed among the BclI genotypes (P = 0.03). DEX dose was higher in GG- (0.7 ± 0.2 mg) compared to GC- (0.47 ± 0.2 mg) and CC-carriers (0.47 ± 0.1 mg).

#### CONCLUSION:

The genotypic frequencies of NR3C1 polymorphisms in Brazilians are similar to worldwide populations. Additionally, the BclI polymorphism was associated with altered pituitary-adrenal axis GC sensitivity.

rs6196

High-altitude pulmonary edema (HAPE) is a serious acute mountain sickness that mainly occurs in non-acclimatized individuals after rapid ascent to high altitude. The precise etiology of HAPE remains unclear. This study aimed to investigate whether NR3C1 gene polymorphism is associated with the susceptibility to HAPE.

#### METHODS:

The exons of NR3C1 gene were sequenced by a ABI 3730 DNA analyzer in 133 HAPE patients and matched 135 healthy Han Chinese controls from the Yushu area in Qinghai (the altitude greater than 3500 m).

#### RESULTS:

DNA sequencing showed the heterozygous substitutions at codon 588 (rs6194) in exon 6 and 766 (rs6196) in exon 9 of NR3C1 gene. The genotypic distributions and allelic frequencies of NR3C1 SNP rs6194 showed significant differences in two groups (P < 0.05). The frequencies of the C allele were significantly higher in the HAPE group than in the control group (P < 0.05) with an odds ratio of 3.009 (95% CI = 1.250-7.244). There were no differences in genotypic and allelic frequencies in rs6196polymorphism between the two groups.

#### CONCLUSIONS:

NR3C1 gene rs6194 polymorphism is correlated with HAPE susceptibility. CC genotype and C allele of rs6194 polymorphism might increase the risk of HAPE in Han Chinese.

<https://www.ncbi.nlm.nih.gov/pubmed/29207898>

Sequenom MassARRAY method was used to sequence 25 SNP genotypes in 154 patients. The frequency distribution of the genotypes was compared between patients with steroid-sensitive nephrotic syndrome and those with steroid-resistant nephrotic syndrome.

#### RESULTS:

NR3C1 rs6196 G allele carriers had a decreased risk of steroid resistance compared with that of the A allele carriers. The presence of rs10052957 and rs258751 A alleles could reduce the incidence of steroid resistance compared with that with G allele. Haplotype analysis showed AAG and GGA haplotypes that contain NR3C1 rs10052957, rs258751 and rs6196 were associated with steroid resistance.

<https://www.ncbi.nlm.nih.gov/pubmed/24728165>

We assessed NR3C1 polymorphisms in Brazilians of Caucasian, African and Asian ancestry (n = 380). In a subgroup (n = 40), we compared the genotypes to glucocorticoid (GC) sensitivity, which was previously evaluated by plasma (PF) and salivary (SF) cortisol after dexamethasone (DEX) suppression tests, GC receptor binding affinity (K d ), and DEX-50% inhibition (IC 50 ) of concanavalin-A-stimulated mononuclear cell proliferation. p.N363S (rs6195), p.ER22/23EK (rs6189-6190), and BclI (rs41423247) allelic discrimination was performed by Real-Time PCR (Polymerase Chain Reaction). Exons 3 to 9 and exon/intron boundaries were amplified by PCR and sequenced.

#### RESULTS:

Genotypic frequencies (%) were: rs6195 (n = 380; AA:96.6/AG:3.14/GG:0.26), rs6189-6190 (n = 264; GG:99.6/GA:0.4), rs41423247 (n = 264; CC:57.9/CG:34.1/GG:8.0), rs6188 (n = 155; GG:69.6/GT:25.7/TT:4.7), rs258751 (n = 150; CC:88.0/CT:10.7/TT:1.3), rs6196 (n = 176; TT:77.2/TC:20.4/CC:2.4), rs67300719 (n = 137; CC:99.3/CT:0.7), and rs72542757 (n = 137; CC:99.3/CG:0.7). The rs67300719 and rs72542757 were found only in Asian descendants, in whom p.N363S and p.ER22/23EK were absent. The p.ER22/23EK was observed exclusively in Caucasian descendants. Hardy-Weinberg equilibrium was observed, except in the Asian for rs6188 and rs258751, and in the African for p.N363S. The K d , IC 50 , baseline and after DEX PF or SF did not differ between genotype groups. However, the mean DEX dose that suppressed PF or SF differed among the BclI genotypes (P = 0.03). DEX dose was higher in GG- (0.7 ± 0.2 mg) compared to GC- (0.47 ± 0.2 mg) and CC-carriers (0.47 ± 0.1 mg).

#### CONCLUSION:

The genotypic frequencies of NR3C1 polymorphisms in Brazilians are similar to worldwide populations. Additionally, the BclI polymorphism was associated with altered pituitary-adrenal axis GC sensitivity.

<https://www.ncbi.nlm.nih.gov/pubmed/21876507>

We analyzed 115 bipolar patients treated with lithium carbonate for 5-27 years. Thirty patients were identified as excellent lithium responders (ER), 58 patients as partial responders (PR), and 27 patients were non-responders. Genotypes of eight analyzed polymorphisms of GR gene (rs10052957, rs6196, rs6198, rs6191, rs258813, rs33388, rs6195, rs41423247) were established by TaqMan SNP Genotyping Assays. Statistical analysis was done with Statistica version 9.0. Linkage disequilibrium analysis was performed in Haploview v. 4.1.

#### RESULTS:

We have found significant differences in allele frequencies for BclI polymorphism between patients with different lithium response with C allele associated with excellent lithium response. For the other GR polymorphisms any significant association with different lithium response was found. We observed a strong linkage disequilibrium of five GR polymorphisms (rs6198, rs6191, rs6196, rs258813, rs33388), with TAAGA haplotype more prevalent in the group of partial- and non-responders to lithium.

#### CONCLUSION:

The GR gene variation seems to be involved in the response to lithium treatment in our group of bipolar patients.

<https://www.ncbi.nlm.nih.gov/pubmed/21633323>

 total of 296 corticosteroid-resistant, corticosteroids-dependent, and corticosteroid-responsive patients with CD were studied. Of the 12 SNPs examined, four markers, rs6196 [odds ratio (OR)=2.03; 95% confidence interval (CI): 1.03-4.0; P=0.042], rs7701443 (OR=3.43; 95% CI: 1.79-6.57; P=0.042), rs6190 (OR=4.84; 95% CI: 1.70-13.80; P=0.003), and rs860457 (OR=3.43; 95% CI: 1.79-6.57; P<0.001) were associated at the allelic level with corticosteroid resistance. Haplotype analysis of four associated markers revealed associations between two haplotypes and corticosteroid resistance (P values of 0.046 and 0.001). Three SNPs, rs10482682 (OR=1.43; 95% CI: 0.99-2.08; P=0.047), rs6196 (OR=0.55; 95% CI: 0.31-0.95; P=0.024), and rs2963155 (OR=0.64; 95% CI: 0.42-0.98; P=0.039), showed associations under an additive model, whereas rs4912911 (OR=0.37; 95% CI: 0.13-1.00; P=0.03) and rs2963156 (OR=0.32; 95% CI: 0.07-1.12; P=0.047) showed associations under a recessive model with corticosteroid dependence. Two five-marker haplotypes were associated with corticosteroid dependence (P values 0.002 and 0.004).

#### CONCLUSION:

Our results suggest that variations in the GR/NR3C1 gene are associated with corticosteroid resistance and dependency in pediatric-onset CD. Studies are required to replicate these findings and to identify the potentially relevant variants.

<https://www.ncbi.nlm.nih.gov/pubmed/21050724>

A significant effect of the rs6196 polymorphism in the NR3C1 on weight (β=-4.18; SE=2.02; p=0.018), BMI (β=-1.88; SE=0.64; p=0.004), waist (β=-5.77; SE=1.75; p=0.001) and waist/hip ratio (β=-0.03; SE=0.012; p=0.009) was found. Permutation tests confirmed the findings for BMI (p=0.037) and waist (p=0.024). Carriers of the G allele consistently displayed better parameters than patients with the wild type allele. A weak effect of rs4949184 in SDC3 on BMI was found, but this did not sustain permutation testing (β=-1.27; SE=0.58; p=0.030, p=0.270 after permutations).

#### CONCLUSION:

Variations in genes implicated in circadian regulation or its related downstream pathways may be important in the regulation of antropomorphic parameters in patients with schizophrenia during long-term treatment with SGA.

rs852977

https://www.ncbi.nlm.nih.gov/pubmed/?term=rs852977

We searched for candidate genes using RNA transcriptome network analysis of 2611 NOA-related genes that we had previously reported. We analyzed candidate genes for disease linkage with single nucleotide polymorphisms (SNP) in the genomes of 335 Japanese men with NOA and 410 healthy controls using SNP-specific real-time polymerase chain reaction TaqMan assays.

#### RESULTS:

Three candidate genes (NR3C1, YBX2, and BCL2) were identified by the transcriptome network analysis, each with three SNP. Allele frequency analysis of the nine SNP indicated a significantly higher frequency of the NR3C1 rs852977 G allele in NOA cases compared with controls (corrected P = 5.7e-15; odds ratio = 3.20; 95% confidence interval, 2.40-4.26). The other eight candidate polymorphisms showed no significant association.

#### CONCLUSION:

The NR3C1 rs852977 polymorphism is a potential marker for genetic susceptibility to NOA in Japanese men. Further studies are necessary to clarify the association between the NR3C1 polymorphism and alterations of glucocorticoid signaling pathway leading to male infertility.

rs31192

<https://www.ncbi.nlm.nih.gov/clinvar/variation/16153/>

Pseudohermaphroditism, female, with hypokalemia, due to glucocorticoid resistance

rs31187

https://www.ncbi.nlm.nih.gov/clinvar/variation/16148/

Glucocorticoid resistance, generalized

rs31186

https://www.ncbi.nlm.nih.gov/clinvar/variation/16147/

Glucocorticoid resistance, generalized

rs31196

https://www.ncbi.nlm.nih.gov/clinvar/variation/16157/

Glucocorticoid resistance, generalized

rs31197

https://www.ncbi.nlm.nih.gov/clinvar/variation/16158/

Glucocorticoid resistance, generalized

rs31188

<https://www.ncbi.nlm.nih.gov/clinvar/variation/16149/>

Glucocorticoid resistance, cellular

rs31194

https://www.ncbi.nlm.nih.gov/clinvar/variation/16155/

Glucocorticoid resistance, generalized

rs31195

https://www.ncbi.nlm.nih.gov/clinvar/variation/16156/

Glucocorticoid resistance, generalized

rs31190

Glucocorticoid resistance, generalized

<https://www.ncbi.nlm.nih.gov/medgen/C1841972>

# Glucocorticoid resistance, generalized(GCCR)

MedGen UID:

333960

 •Concept ID:

[C1841972](https://www.ncbi.nlm.nih.gov/medgen/docs/help/#sources)

 •

Disease or Syndrome

|  |  |
| --- | --- |
| **Synonyms:** | CORTISOL RESISTANCE FROM GLUCOCORTICOID RECEPTOR DEFECT; GCCR; GCCR DEFICIENCY; GCR DEFICIENCY; GLUCOCORTICOID RECEPTOR DEFICIENCY; Glucocorticoid resistance; GRL DEFICIENCY |
| **Modes of inheritance:** | [Autosomal recessive inheritance](https://www.ncbi.nlm.nih.gov/medgen/C1841972#moi_141025) (HPO, OMIM, Orphanet)  [Autosomal dominant inheritance](https://www.ncbi.nlm.nih.gov/medgen/C1841972#moi_141047) (HPO, OMIM, Orphanet)  [not inherited](https://www.ncbi.nlm.nih.gov/medgen/C1841972#moi_832438) (Orphanet) |
|  | |
| **Gene (location):** | [NR3C1](https://www.ncbi.nlm.nih.gov/gene/2908) (5q31.3) |
| **OMIM®:** | [615962](https://omim.org/entry/615962) |
| **Orphanet:** | [ORPHA786](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=786) |

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# Definition

Generalized glucocorticoid resistance is an autosomal dominant disease characterized by increased plasma cortisol concentration and high urinary free cortisol, resistance to adrenal suppression by dexamethasone, and the absence of clinical stigmata of Cushing syndrome. The clinical expression of the disease is variable. Common features include hypoglycemia, hypertension, and metabolic alkalosis. In females, overproduction of adrenal androgens has been associated with infertility, male-pattern baldness, hirsutism, and menstrual irregularities. Other features include chronic fatigue and profound anxiety (summary by Chrousos et al., 1983; Donner et al., 2013). [from [OMIM](http://www.omim.org/)]

<https://www.orpha.net/consor/cgi-bin/ClinicalLabs_Search_Simple.php?lng=EN&LnkId=8672&Typ=Pat&fdp=y&from=rightMenu>

Molecular genetics (20)

* Targeted mutation analysis (3)
* Mutation scanning/screening and sequence analysis of selected exons (6)
* Sequence analysis: entire coding region (14)
* Deletion / Duplication analysis (1)

Cytogenetics (1)

* Detection of microdeletions/microduplications (1)

### **Technique(s)**

Sanger sequencing (11)

NGS sequencing (except WES) (7)

MLPA based techniques (1)

Array based techniques (1)



**CANADA**

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#### [Genetics and Metabolism](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=111003&Expert%20centres=Genetics-and-Metabolism&title=Genetics-and-Metabolism&search=Clinics_Search_Simple)

#### Health Sciences Centre

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#### [Clinical Genetics, Credit Valley Site, Trillium Health Partners](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=102230&Expert%20centres=Clinical-Genetics--Credit-Valley-Site--Trillium-Health-Partners&title=Clinical-Genetics--Credit-Valley-Site--Trillium-Health-Partners&search=Clinics_Search_Simple)

#### Genetics Clinic, Credit Valley Hospital

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#### [The Prenatal Diagnosis and Medical Genetics Program, Mount Sinai Hospital](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=98074&Expert%20centres=The-Prenatal-Diagnosis-and-Medical-Genetics-Program--Mount-Sinai-Hospital&title=The-Prenatal-Diagnosis-and-Medical-Genetics-Program--Mount-Sinai-Hospital&search=Clinics_Search_Simple)

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[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=98074&Expert%20centres=The-Prenatal-Diagnosis-and-Medical-Genetics-Program--Mount-Sinai-Hospital&title=The-Prenatal-Diagnosis-and-Medical-Genetics-Program--Mount-Sinai-Hospital&search=Clinics_Search_Simple)



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#### [Clinical and Metabolic Genetics Division](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=112110&Expert%20centres=Clinical-and-Metabolic-Genetics-Division&title=Clinical-and-Metabolic-Genetics-Division&search=Clinics_Search_Simple)

#### The Hospital for Sick Children and University of Toronto

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=112110&Expert%20centres=Clinical-and-Metabolic-Genetics-Division&title=Clinical-and-Metabolic-Genetics-Division&search=Clinics_Search_Simple)



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#### Centre hospitalier universitaire Sainte-Justine

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=111812&Expert%20centres=Genetique-Medicale&title=Genetique-Medicale&search=Clinics_Search_Simple)



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#### [Medical genetics pediatric clinic](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=95506&Expert%20centres=Medical-genetics-pediatric-clinic&title=Medical-genetics-pediatric-clinic&search=Clinics_Search_Simple)

#### Glen / McGill Univeristy Health Centre - Centre Universitaire de santé McGill

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=95506&Expert%20centres=Clinique-genetique-medicale-pediatrique&title=Clinique-genetique-medicale-pediatrique&search=Clinics_Search_Simple)



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#### [Medical genetics adult clinic](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=96017&Expert%20centres=Medical-genetics-adult-clinic&title=Medical-genetics-adult-clinic&search=Clinics_Search_Simple)

#### Glen / McGill Univeristy Health Centre - Centre Universitaire de santé McGill

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=96017&Expert%20centres=Clinique-genetique-medicale-pour-adultes&title=Clinique-genetique-medicale-pour-adultes&search=Clinics_Search_Simple)



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#### [Medical genetics service](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=100887&Expert%20centres=Medical-genetics-service&title=Medical-genetics-service&search=Clinics_Search_Simple)

#### CHU Sherbrooke - Hôpital Fleurimont

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#### Bristol Royal Hospital for Children

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=126703&Expert%20centres=Paediatric-Endocrinology---Diabetes-Service&title=Paediatric-Endocrinology---Diabetes-Service&search=Clinics_Search_Simple)

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#### [Rare Endocrine Disease Centre](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=123480&Expert%20centres=Rare-Endocrine-Disease-Centre&title=Rare-Endocrine-Disease-Centre&search=Clinics_Search_Simple)

#### Queen Elizabeth University Hospital Campus

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=123480&Expert%20centres=Rare-Endocrine-Disease-Centre&title=Rare-Endocrine-Disease-Centre&search=Clinics_Search_Simple)

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**UNITED KINGDOM**

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#### [Royal Hospital For Children, Disorders of Sex Development Clinic](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=115351&Expert%20centres=Royal-Hospital-For-Children--Disorders-of-Sex-Development-Clinic&title=Royal-Hospital-For-Children--Disorders-of-Sex-Development-Clinic&search=Clinics_Search_Simple)

#### Royal Hospital For Children, NHS Greater Glasgow & Clyde

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=115351&Expert%20centres=Royal-Hospital-For-Children--Disorders-of-Sex-Development-Clinic&title=Royal-Hospital-For-Children--Disorders-of-Sex-Development-Clinic&search=Clinics_Search_Simple)

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Greater London  
LONDON

#### [Disorders of Sex Development clinic](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=101493&Expert%20centres=Disorders-of-Sex-Development-clinic&title=Disorders-of-Sex-Development-clinic&search=Clinics_Search_Simple)

#### University College Hospital - Elizabeth Garrett Anderson Wing

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=101493&Expert%20centres=Disorders-of-Sex-Development-clinic&title=Disorders-of-Sex-Development-clinic&search=Clinics_Search_Simple)

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#### [Manchester Centre for Genomic Medicine](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=44313&Expert%20centres=Manchester-Centre-for-Genomic-Medicine&title=Manchester-Centre-for-Genomic-Medicine&search=Clinics_Search_Simple)

#### St Mary's Hospital

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#### [Rare Endocrine Disease Centre](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=124727&Expert%20centres=Rare-Endocrine-Disease-Centre&title=Rare-Endocrine-Disease-Centre&search=Clinics_Search_Simple)

#### Southampton General Hospital

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=124727&Expert%20centres=Rare-Endocrine-Disease-Centre&title=Rare-Endocrine-Disease-Centre&search=Clinics_Search_Simple)

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#### Birmingham Children's Hospital NHS Foundation Trust

[More information](https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN&data_id=124726&Expert%20centres=Rare-Endocrine-Disease-Centre&title=Rare-Endocrine-Disease-Centre&search=Clinics_Search_Simple)

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#### Leeds Children's Hospital

<https://www.orpha.net/consor/cgi-bin/Clinics_Search_Simple.php?Clinics_Clinics_Search_ActivitiesList_Sort=null&lng=EN&LnkId=8672&Typ=Pat&CnsGen=n>

<https://www.omim.org/entry/615962>

**#** 615962

### **GLUCOCORTICOID RESISTANCE, GENERALIZED; GCCR**

Alternative titles; symbols

#### GLUCOCORTICOID RECEPTOR DEFICIENCY GCCR DEFICIENCY GCR DEFICIENCY GRL DEFICIENCY CORTISOL RESISTANCE FROM GLUCOCORTICOID RECEPTOR DEFECT

#### ****Phenotype-Gene Relationships****

| **Location** | **Phenotype** | **Phenotype MIM number** | **Inheritance** | **Phenotype mapping key** | **Gene/Locus** | **Gene/Locus MIM number** |
| --- | --- | --- | --- | --- | --- | --- |
| [5q31.3](https://www.omim.org/geneMap/5/557?start=-3&limit=10&highlight=557) | Glucocorticoid resistance | [615962](https://www.omim.org/entry/615962) | AD | 3 | NR3C1 | [138040](https://www.omim.org/entry/138040) |

[Clinical Synopsis](https://www.omim.org/clinicalSynopsis/615962)Toggle Dropdown

#### ▼ ****TEXT****

A number sign (#) is used with this entry because generalized glucocorticoid resistance (GCCR) is caused by heterozygous mutation in the glucocorticoid receptor gene (NR3C1, GCCR; [138040](https://www.omim.org/entry/138040)) on chromosome 5q31.

#### ▼ ****Description****

Generalized glucocorticoid resistance is an autosomal dominant disease characterized by increased plasma cortisol concentration and high urinary free cortisol, resistance to adrenal suppression by dexamethasone, and the absence of clinical stigmata of Cushing syndrome. The clinical expression of the disease is variable. Common features include hypoglycemia, hypertension, and metabolic alkalosis. In females, overproduction of adrenal androgens has been associated with infertility, male-pattern baldness, hirsutism, and menstrual irregularities. Other features include chronic fatigue and profound anxiety (summary by [Chrousos et al., 1983](https://www.omim.org/entry/615962" \l "6" \o "); [Donner et al., 2013](https://www.omim.org/entry/615962#7)).

#### ▼ ****Clinical Features****

[Vingerhoeds et al. (1976)](https://www.omim.org/entry/615962#16) reported a case of cortisol resistance. High levels of cortisol (without stigmata of Cushing syndrome), resistance of the hypothalamic-pituitary-adrenal axis to dexamethasone, and an affinity defect of the glucocorticoid receptor characterized the disorder. [Chrousos et al. (1982)](https://www.omim.org/entry/615962" \l "5" \o ") restudied the family reported by [Vingerhoeds et al. (1976)](https://www.omim.org/entry/615962" \l "16" \o "). A man who was presumably homozygous had mineralocorticoid excess resulting in hypertension, hypokalemia, and metabolic alkalosis. One of his brothers, who had severe hypertension and died of a cerebrovascular accident at age 54, may also have been homozygous. Another brother and his son were apparently heterozygous; they showed slightly elevated 24-hour mean plasma cortisol levels and increased urinary free cortisol. [Lipsett et al. (1986)](https://www.omim.org/entry/615962#14)provided further follow-up on the 4-generation family originally reported by [Vingerhoeds et al. (1976)](https://www.omim.org/entry/615962" \l "16" \o "). Autosomal dominant inheritance of glucocorticoid resistance was clearly demonstrated. [Lipsett et al. (1986)](https://www.omim.org/entry/615962#14) believed that a mutation in the glucocorticoid receptor was responsible, although other explanations could be invoked. The single homozygote in the family was the proband; the other persons with elevated plasma cortisol levels and increased urinary free cortisol represented heterozygotes. The parents of the proband descended from families with consanguinity that occurred before the 16th century. The 2 parental families had lived in close proximity for many generations. This cortisol resistance is probably the rarest cause of treatable hypertension yet described.

Affected mother and son with primary cortisol resistance and a reduction in glucocorticoid receptors were reported by [Iida et al. (1985)](https://www.omim.org/entry/615962#10).

[Bronnegard et al. (1986)](https://www.omim.org/entry/615962#2) described a woman with receptor-mediated resistance to cortisol as indicated by elevated 24-hour mean plasma cortisol levels and increased free urinary cortisol. Plasma ACTH concentrations were normal but she was resistant to adrenal suppression by dexamethasone. No stigmata of Cushing syndrome were present. The patient had symptoms of pronounced fatigue. Menopause had occurred at age 43. The patient's only child, a son, aged 29 years, had periods of inexplicable fatigue that had made him stay home from school and work. Because of the extreme fatigue that led to the mother's working only half-time, Addison's disease was suspected, but rather than hypocortisolism, elevation of urinary cortisol values was found. [Bronnegard et al. (1986)](https://www.omim.org/entry/615962" \l "2" \o ")found that the end-organ insensitivity to cortisol was not due to decreased concentration or ligand affinity of the receptor. The woman and her son instead showed an increased thermolability of the cortisol receptor, a phenomenon also observed with the androgen receptor in patients with the testicular feminization syndrome ([300068](https://www.omim.org/entry/300068)).

[Lamberts et al. (1986)](https://www.omim.org/entry/615962#12) described cortisol resistance in a 26-year-old woman with hirsutism, mild virilization, and menstrual difficulties. They thought that the abnormality was autosomal dominant because her father and 2 brothers had increased plasma cortisol concentrations that did not suppress normally in response to dexamethasone. No hypertension or hypokalemic alkalosis was present. The proband had male-pattern scalp baldness.

[Nawata et al. (1987)](https://www.omim.org/entry/615962#15) studied a 27-year-old woman with glucocorticoid resistance. She was initially thought to have Cushing disease, based on high plasma ACTH and serum cortisol levels, increased urinary cortisol secretion, resistance to adrenal suppression with dexamethasone, and bilateral adrenal hyperplasia by computed tomography and scintigraphy; however, she had no clinical signs or symptoms of Cushing syndrome. Laboratory studies indicated that the patient's glucocorticoid resistance was due to a decrease in the affinity of the receptor for glucocorticoids and a decrease in the binding of the GCCR complex to DNA.

[Charmandari et al. (2008)](https://www.omim.org/entry/615962#3) reviewed the clinical aspects, molecular mechanisms, and implications of primary generalized glucocorticoid resistance. They noted that the clinical spectrum is broad, ranging from asymptomatic to severe cases of hyperandrogenism, fatigue, and/or mineralocorticoid excess. Mutations in the GCCR gene resulting in the disorder impair glucocorticoid signal transduction and reduce tissue sensitivity to glucocorticoids. A consequent increase in the activity of the hypothalamic-pituitary-adrenal axis compensates for the reduced sensitivity of peripheral tissues to glucocorticoids at the expense of ACTH hypersecretion-related pathology. The study of functional defects of GCCR mutants highlighted the importance of integrated cellular and molecular signaling mechanisms for maintaining homeostasis and preserving normal physiology.

#### ▼ ****Molecular Genetics****

In affected members of the kindred originally reported by [Vingerhoeds et al. (1976)](https://www.omim.org/entry/615962" \l "16" \o ") with generalized glucocorticoid deficiency, [Hurley et al. (1991)](https://www.omim.org/entry/615962#9) identified a heterozygous missense mutation in the GCR gene (D641V; [138040.0001](https://www.omim.org/entry/138040#0001)).

In all 3 affected members of a Dutch kindred with glucocorticoid resistance, [Karl et al. (1993)](https://www.omim.org/entry/615962#11) identified heterozygosity for a 4-bp deletion in the GCR gene ([138040.0002](https://www.omim.org/entry/138040#0002)).

[Bray and Cotton (2003)](https://www.omim.org/entry/615962#1) stated that a total of 15 missense, 3 nonsense, 3 frameshift, 1 splice site, and 2 alternatively spliced mutations had been reported in the NR3C1 gene to be associated with glucocorticoid resistance. Sixteen polymorphisms in the gene had also been reported.

#### ▼ ****Heterogeneity****

[Huizenga et al. (2000)](https://www.omim.org/entry/615962#8) described 5 patients with biochemical and clinical cortisol resistance. They found alterations in receptor number or ligand affinity and/or the ability of dexamethasone to inhibit mitogen-induced cell proliferation. To investigate the molecular defects leading to the clinical and biochemical pictures in these patients, they screened the GCCR gene using PCR-SSCP sequence analysis. No GCCR gene alterations were found in these patients. The authors concluded that alterations somewhere in the cascade of events starting with ligand binding to the GCCR protein, and finally resulting in the regulation of the expression of glucocorticoid-responsive genes, or postreceptor defects or interactions with other nuclear factors, form the pathophysiologic basis of cortisol resistance in these patients.

#### ▼ ****Pathogenesis****

Generalized glucocorticoid resistance is caused by impaired cortisol signaling. This defect results in compensatory activation of the hypothalamic-pituitary adrenal axis, which leads to increased secretion of hypothalamic corticotropin-releasing hormone (CRH) and elevated secretion of the circulating ACTH from the pituitary gland. The excess ACTH secretion, in turn, results in increased secretion of cortisol, the adrenal mineralocorticoids deoxycorticosterone and corticosterone, and adrenal steroids with androgenic activity (summary by [Donner et al., 2013](https://www.omim.org/entry/615962#7)).

# glucocorticoid resistance.

<https://www.ncbi.nlm.nih.gov/pubmed/22728894>

Glucocorticoids (GCs) are the most potent anti-inflammatory agents known. A major factor limiting their clinical use is the wide variation in responsiveness to therapy. The high doses of GC required for less responsive patients means a high risk of developing very serious side effects. Variation in sensitivity between individuals can be due to a number of factors. Congenital, generalized GC resistance is very rare, and is due to mutations in the glucocorticoid receptor (GR) gene, the receptor that mediates the cellular effects of GC. A more common problem is acquired GC resistance. This localized, disease-associated GC resistance is a serious therapeutic concern and limits therapeutic response in patients with chronic inflammatory disease. It is now believed that localized resistance can be attributed to changes in the cellular microenvironment, as a consequence of chronic inflammation. Multiple factors have been identified, including alterations in both GR-dependent and -independent signaling downstream of cytokine action, oxidative stress, hypoxia and serum derived factors. The underlying mechanisms are now being elucidated, and are discussed here. Attempts to augment tissue GC sensitivity are predicted to permit safe and effective use of low-dose GC therapy in inflammatory disease.

https://www.ncbi.nlm.nih.gov/pubmed/8239231

Glucocorticoid resistance results from the partial, albeit apparently generalized, inability of glucocorticoids to exert their effects on target tissues. The condition is associated with compensatory increases in circulating pituitary corticotropin and cortisol, with the former causing excess secretion of both adrenal androgens and adrenal steroid biosynthesis intermediates with salt-retaining activity. The manifestations of glucocorticoid resistance vary from chronic fatigue (perhaps a result of glucocorticoid deficiency in the central nervous system) to various degrees of hypertension with or without hypokalemic alkalosis or hyperandrogenism, or both, caused by increased cortisol and other salt-retaining steroids and adrenal androgens, respectively. In women, hyperandrogenism can result in acne, hirsutism, menstrual irregularities, oligoanovulation, and infertility; in men, it may lead to infertility and in children, to precocious puberty. Different molecular defects, such as point mutations or a microdeletion of the highly conserved glucocorticoid receptor gene, alter the functional characteristics or concentrations of the intracellular receptor and appear to cause glucocorticoid resistance. The extreme variability in the clinical manifestations of glucocorticoid resistance and its mimicry of many common diseases can be explained by the overall degree of glucocorticoid resistance, differing sensitivity of target tissues to mineralocorticoids or androgens or both, and perhaps different biochemical defects of the glucocorticoid receptor, with selective resistance of certain glucocorticoid responses in specific tissues. The various different symptoms of classic glucocorticoid resistance and the theoretical potential of this condition to appear surreptitiously emphasize the importance of the glucocorticoid receptor in the pathogenesis of human disease.

<https://www.ncbi.nlm.nih.gov/pubmed/17161335>

<https://www.ncbi.nlm.nih.gov/pubmed/27643454>

Glucocorticoids are involved in several responses triggered by a variety of environmental and physiological stimuli. These hormones have a wide-range of regulatory effects in organisms. Synthetic glucocorticoids are extensively used to suppress allergic, inflammatory, and immune disorders. Although glucocorticoids are highly effective for therapeutic purposes, some patients chronically treated with glucocorticoids can develop reduced glucocorticoid sensitivity or even resistance, increasing patient vulnerability to exaggerated inflammatory responses. Glucocorticoid resistance can occur in several chronic diseases, including asthma, major depression, and cardiovascular conditions. In this review, we discuss the complexity of the glucocorticoid receptor and the potential role of glucocorticoid resistance in the development of chronic diseases.

<https://www.ncbi.nlm.nih.gov/pubmed/19482216>

Glucocorticoid resistance or insensitivity is a major barrier to the treatment of several common inflammatory diseases-including chronic obstructive pulmonary disease and acute respiratory distress syndrome; it is also an issue for some patients with asthma, rheumatoid arthritis, and inflammatory bowel disease. Several molecular mechanisms of glucocorticoid resistance have now been identified, including activation of mitogen-activated protein (MAP) kinase pathways by certain cytokines, excessive activation of the transcription factor activator protein 1, reduced histone deacetylase-2 (HDAC2) expression, raised macrophage migration inhibitory factor, and increased P-glycoprotein-mediated drug efflux. Patients with glucocorticoid resistance can be treated with alternative broad-spectrum anti-inflammatory treatments, such as calcineurin inhibitors and other immunomodulators, or novel anti-inflammatory treatments, such as inhibitors of phosphodiesterase 4 or nuclear factor kappaB, although these drugs are all likely to have major side-effects. An alternative treatment strategy is to reverse glucocorticoid resistance by blocking its underlying mechanisms. Some examples of this approach are inhibition of p38 MAP kinase, use of vitamin D to restore interleukin-10 response, activation of HDAC2 expression by use of theophylline, antioxidants, or phosphoinositide-3-kinase-delta inhibitors, and inhibition of macrophage migration inhibitory factor and P-glycoprotein.

<https://www.ncbi.nlm.nih.gov/pubmed/20188830>

Glucocorticoids are the most effective anti-inflammatory therapy for many chronic inflammatory and immune diseases, such as asthma, but are relatively ineffective in other diseases such as chronic obstructive pulmonary disease (COPD). Glucocorticoids suppress inflammation by several mechanisms. Glucocorticoids suppress the multiple inflammatory genes that are activated in chronic inflammatory diseases, such as asthma, by reversing histone acetylation of activated inflammatory genes through binding of liganded glucocorticoid receptors (GR) to coactivator molecules and recruitment of histone deacetylase-2 (HDAC2) to the activated transcription complex. At higher concentrations of glucocorticoids GR homodimers interact with DNA recognition sites to activate transcription through increased histone acetylation of anti-inflammatory genes and transcription of several genes linked to glucocorticoid side effects. Decreased glucocorticoid responsiveness is found in patients with severe asthma and asthmatics who smoke, as well as in all patients with COPD and cystic fibrosis. Several molecular mechanisms of glucocorticoid resistance have now been identified. HDAC2 is markedly reduced in activity and expression as a result of oxidative/nitrative stress so that inflammation becomes resistant to the anti-inflammatory actions of glucocorticoids. Dissociated glucocorticoids have been developed to reduce side effects but so far it has been difficult to dissociate anti-inflammatory effects from adverse effects. In patients with glucocorticoid resistance alternative anti-inflammatory treatments are being investigated as well as drugs that may reverse the molecular mechanism of glucocorticoid resistance.

<http://www.uniprot.org/uniprot/P04150>

**Glucocorticoid receptor**

Receptor for glucocorticoids (GC) (PubMed:[27120390](http://www.uniprot.org/citations/27120390)). Has a dual mode of action: as a transcription factor that binds to glucocorticoid response elements (GRE), both for nuclear and mitochondrial DNA, and as a modulator of other transcription factors. Affects inflammatory responses, cellular proliferation and differentiation in target tissues. Involved in chromatin remodeling (PubMed:[9590696](http://www.uniprot.org/citations/9590696)). Plays a role in rapid mRNA degradation by binding to the 5' UTR of target mRNAs and interacting with PNRC2 in a ligand-dependent manner which recruits the RNA helicase UPF1 and the mRNA-decapping enzyme DCP1A, leading to RNA decay (PubMed:[25775514](http://www.uniprot.org/citations/25775514)). Could act as a coactivator for STAT5-dependent transcription upon growth hormone (GH) stimulation and could reveal an essential role of hepatic GR in the control of body growth (By similarity).By similarity3 Publications

Isoform Alpha: Has transcriptional activation and repression activity (PubMed:[15866175](http://www.uniprot.org/citations/15866175), PubMed:[19248771](http://www.uniprot.org/citations/19248771), PubMed:[20484466](http://www.uniprot.org/citations/20484466), PubMed:[23820903](http://www.uniprot.org/citations/23820903), PubMed:[11435610](http://www.uniprot.org/citations/11435610), PubMed:[15769988](http://www.uniprot.org/citations/15769988), PubMed:[17635946](http://www.uniprot.org/citations/17635946), PubMed:[19141540](http://www.uniprot.org/citations/19141540), PubMed:[21664385](http://www.uniprot.org/citations/21664385)). Mediates glucocorticoid-induced apoptosis (PubMed:[23303127](http://www.uniprot.org/citations/23303127)). Promotes accurate chromosome segregation during mitosis (PubMed:[25847991](http://www.uniprot.org/citations/25847991)). May act as a tumor suppressor (PubMed:[25847991](http://www.uniprot.org/citations/25847991)). May play a negative role in adipogenesis through the regulation of lipolytic and antilipogenic gene expression (By similarity).By similarity11 Publications

Isoform Beta: Acts as a dominant negative inhibitor of isoform [Alpha](http://www.uniprot.org/uniprot/P04150#P04150) (PubMed:[7769088](http://www.uniprot.org/citations/7769088), PubMed:[8621628](http://www.uniprot.org/citations/8621628), PubMed:[20484466](http://www.uniprot.org/citations/20484466)). Has intrinsic transcriptional activity independent of isoform [Alpha](http://www.uniprot.org/uniprot/P04150" \l "P04150)when both isoforms are coexpressed (PubMed:[19248771](http://www.uniprot.org/citations/19248771), PubMed:[26711253](http://www.uniprot.org/citations/26711253)). Loses this transcription modulator function on its own (PubMed:[20484466](http://www.uniprot.org/citations/20484466)). Has no hormone-binding activity (PubMed:[8621628](http://www.uniprot.org/citations/8621628)). May play a role in controlling glucose metabolism by maintaining insulin sensitivity (By similarity). Reduces hepatic gluconeogenesis through down-regulation of PEPCK in an isoform Alpha-dependent manner (PubMed:[26711253](http://www.uniprot.org/citations/26711253)). Directly regulates STAT1 expression in isoform Alpha-independent manner (PubMed:[26711253](http://www.uniprot.org/citations/26711253)).By similarity5 Publications

Isoform Alpha-2: Has lower transcriptional activation activity than isoform [Alpha](http://www.uniprot.org/uniprot/P04150#P04150). Exerts a dominant negative effect on isoform [Alpha](http://www.uniprot.org/uniprot/P04150#P04150) trans-repression mechanism (PubMed:[20484466](http://www.uniprot.org/citations/20484466)).

Isoform GR-P: Increases activity of isoform [Alpha](http://www.uniprot.org/uniprot/P04150#P04150).1 Publication

Isoform Alpha-B: More effective than isoform [Alpha](http://www.uniprot.org/uniprot/P04150#P04150) in transcriptional activation, but not repression activity.2 Publications

Isoform 10: Has transcriptional activation activity.1 Publication

Isoform Alpha-C1: Has transcriptional activation activity.1 Publication

Isoform Alpha-C2: Has transcriptional activation activity.1 Publication

Isoform Alpha-C3: Has highest transcriptional activation activity of all isoforms created by alternative initiation (PubMed:[15866175](http://www.uniprot.org/citations/15866175), PubMed:[23820903](http://www.uniprot.org/citations/23820903)). Has transcriptional repression activity (PubMed:[23303127](http://www.uniprot.org/citations/23303127)). Mediates glucocorticoid-induced apoptosis (PubMed:[23303127](http://www.uniprot.org/citations/23303127), PubMed:[23820903](http://www.uniprot.org/citations/23820903)).3 Publications

Isoform Alpha-D1: Has transcriptional activation activity.1 Publication

Isoform Alpha-D2: Has transcriptional activation activity.1 Publication

Isoform Alpha-D3: Has lowest transcriptional activation activity of all isoforms created by alternative initiation (PubMed:[15866175](http://www.uniprot.org/citations/15866175), PubMed:[23820903](http://www.uniprot.org/citations/23820903)). Has transcriptional repression activity (PubMed:[23303127](http://www.uniprot.org/citations/23303127)).3 Publications

#### Miscellaneous

Isoform Beta: High constitutive expression by neutrophils may provide a mechanism by which these cells escape glucocorticoid-induced cell death and up-regulation by proinflammatory cytokines such as IL8 further enhances their survival in the presence of glucocorticoids during inflammation.1 Publication

Can up- or down-modulate aggregation and nuclear localization of expanded polyglutamine polypeptides derived from AR and HD through specific regulation of gene expression. Aggregation and nuclear localization of expanded polyglutamine proteins are regulated cellular processes that can be modulated by this receptor, a well-characterized transcriptional regulator.

* [core promoter binding](https://www.ebi.ac.uk/QuickGO/term/GO:0001047) Source: CAFA
* [DNA binding transcription factor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0003700) Source: UniProtKB
* [glucocorticoid-activated RNA polymerase II transcription factor binding transcription factor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0038051) Source: UniProtKB
* [glucocorticoid receptor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0004883) Source: ProtInc
* [Hsp90 protein binding](https://www.ebi.ac.uk/QuickGO/term/GO:0051879) Source: UniProtKB
* [protein kinase binding](https://www.ebi.ac.uk/QuickGO/term/GO:0019901) Source: ARUK-UCL
* [RNA binding](https://www.ebi.ac.uk/QuickGO/term/GO:0003723) Source: UniProtKB-KW
* [RNA polymerase II proximal promoter sequence-specific DNA binding](https://www.ebi.ac.uk/QuickGO/term/GO:0000978) Source: NTNU\_SB
* [RNA polymerase II transcription factor activity, sequence-specific DNA binding](https://www.ebi.ac.uk/QuickGO/term/GO:0000981) Source: NTNU\_SB
* [steroid binding](https://www.ebi.ac.uk/QuickGO/term/GO:0005496) Source: UniProtKB
* [steroid hormone binding](https://www.ebi.ac.uk/QuickGO/term/GO:1990239) Source: UniProtKB
* [SUMO binding](https://www.ebi.ac.uk/QuickGO/term/GO:0032183) Source: CAFA
* [transcriptional activator activity, RNA polymerase II proximal promoter sequence-specific DNA binding](https://www.ebi.ac.uk/QuickGO/term/GO:0001077) Source: UniProtKB
* [zinc ion binding](https://www.ebi.ac.uk/QuickGO/term/GO:0008270) Source: InterPro

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=P04150)

#### GO - Biological processi

* [apoptotic process](https://www.ebi.ac.uk/QuickGO/term/GO:0006915) Source: UniProtKB-KW
* [cell cycle](https://www.ebi.ac.uk/QuickGO/term/GO:0007049) Source: UniProtKB-KW
* [cell division](https://www.ebi.ac.uk/QuickGO/term/GO:0051301) Source: UniProtKB-KW
* [cellular response to dexamethasone stimulus](https://www.ebi.ac.uk/QuickGO/term/GO:0071549) Source: CAFA
* [cellular response to glucocorticoid stimulus](https://www.ebi.ac.uk/QuickGO/term/GO:0071385) Source: UniProtKB
* [cellular response to steroid hormone stimulus](https://www.ebi.ac.uk/QuickGO/term/GO:0071383) Source: UniProtKB
* [cellular response to transforming growth factor beta stimulus](https://www.ebi.ac.uk/QuickGO/term/GO:0071560) Source: CAFA
* [chromatin organization](https://www.ebi.ac.uk/QuickGO/term/GO:0006325) Source: UniProtKB-KW
* [chromosome segregation](https://www.ebi.ac.uk/QuickGO/term/GO:0007059) Source: UniProtKB-KW
* [negative regulation of transcription by RNA polymerase II](https://www.ebi.ac.uk/QuickGO/term/GO:0000122) Source: CAFA
* [positive regulation of transcription by RNA polymerase II](https://www.ebi.ac.uk/QuickGO/term/GO:0045944) Source: UniProtKB
* [regulation of transcription, DNA-templated](https://www.ebi.ac.uk/QuickGO/term/GO:0006355) Source: UniProtKB
* [signal transduction](https://www.ebi.ac.uk/QuickGO/term/GO:0007165) Source: ProtInc
* [transcription, DNA-templated](https://www.ebi.ac.uk/QuickGO/term/GO:0006351) Source: CAFA
* [transcription by RNA polymerase II](https://www.ebi.ac.uk/QuickGO/term/GO:0006366) Source: ProtInc
* [transcription initiation from RNA polymerase II promoter](https://www.ebi.ac.uk/QuickGO/term/GO:0006367) Source: Reactome

###### [**Glucocorticoid resistance, generalized (GCCR)**](http://www.uniprot.org/diseases/DI-04226)**14 Publications**

The disease is caused by mutations affecting the gene represented in this entry.

Disease descriptionAn autosomal dominant disease characterized by increased plasma cortisol concentration and high urinary free cortisol, resistance to adrenal suppression by dexamethasone, and the absence of Cushing syndrome typical signs. Clinical features include hypoglycemia, hypertension, metabolic alkalosis, chronic fatigue and profound anxiety.

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| DrugBanki | [DB00240](https://www.drugbank.ca/drugs/DB00240) Alclometasone [DB00288](https://www.drugbank.ca/drugs/DB00288) Amcinonide [DB00394](https://www.drugbank.ca/drugs/DB00394) Beclomethasone dipropionate [DB00443](https://www.drugbank.ca/drugs/DB00443) Betamethasone [DB01222](https://www.drugbank.ca/drugs/DB01222) Budesonide [DB01410](https://www.drugbank.ca/drugs/DB01410) Ciclesonide [DB01013](https://www.drugbank.ca/drugs/DB01013) Clobetasol propionate [DB13158](https://www.drugbank.ca/drugs/DB13158) Clobetasone [DB00838](https://www.drugbank.ca/drugs/DB00838) Clocortolone [DB01380](https://www.drugbank.ca/drugs/DB01380) Cortisone acetate [DB01260](https://www.drugbank.ca/drugs/DB01260) Desonide [DB00547](https://www.drugbank.ca/drugs/DB00547) Desoximetasone [DB01234](https://www.drugbank.ca/drugs/DB01234) Dexamethasone [DB00223](https://www.drugbank.ca/drugs/DB00223) Diflorasone [DB06781](https://www.drugbank.ca/drugs/DB06781) Difluprednate [DB00687](https://www.drugbank.ca/drugs/DB00687) Fludrocortisone [DB00663](https://www.drugbank.ca/drugs/DB00663) Flumethasone [DB00180](https://www.drugbank.ca/drugs/DB00180) Flunisolide [DB00591](https://www.drugbank.ca/drugs/DB00591) Fluocinolone Acetonide [DB01047](https://www.drugbank.ca/drugs/DB01047) Fluocinonide [DB00324](https://www.drugbank.ca/drugs/DB00324) Fluorometholone [DB01185](https://www.drugbank.ca/drugs/DB01185) Fluoxymesterone [DB00846](https://www.drugbank.ca/drugs/DB00846) Flurandrenolide [DB08906](https://www.drugbank.ca/drugs/DB08906) Fluticasone furoate [DB00588](https://www.drugbank.ca/drugs/DB00588) Fluticasone Propionate [DB00769](https://www.drugbank.ca/drugs/DB00769) Hydrocortamate [DB00741](https://www.drugbank.ca/drugs/DB00741) Hydrocortisone [DB00873](https://www.drugbank.ca/drugs/DB00873) Loteprednol [DB00253](https://www.drugbank.ca/drugs/DB00253) Medrysone [DB00351](https://www.drugbank.ca/drugs/DB00351) Megestrol acetate [DB00959](https://www.drugbank.ca/drugs/DB00959) Methylprednisolone [DB00834](https://www.drugbank.ca/drugs/DB00834) Mifepristone [DB00764](https://www.drugbank.ca/drugs/DB00764) Mometasone [DB05423](https://www.drugbank.ca/drugs/DB05423) ORG-34517 [DB01384](https://www.drugbank.ca/drugs/DB01384) Paramethasone [DB01130](https://www.drugbank.ca/drugs/DB01130) Prednicarbate [DB00860](https://www.drugbank.ca/drugs/DB00860) Prednisolone [DB00635](https://www.drugbank.ca/drugs/DB00635) Prednisone [DB00896](https://www.drugbank.ca/drugs/DB00896) Rimexolone [DB00421](https://www.drugbank.ca/drugs/DB00421) Spironolactone [DB00620](https://www.drugbank.ca/drugs/DB00620) Triamcinolone [DB08867](https://www.drugbank.ca/drugs/DB08867) Ulipristal [DB00596](https://www.drugbank.ca/drugs/DB00596) Ulobetasol |

https://medlineplus.gov/hypoglycemia.html

Hypoglycemia means low blood glucose, or [blood sugar](https://medlineplus.gov/bloodsugar.html). Your body needs glucose to have enough energy. After you eat, your blood absorbs glucose. If you eat more sugar than your body needs, your muscles, and liver store the extra. When your blood sugar begins to fall, a hormone tells your liver to release glucose.

In most people, this raises blood sugar. If it doesn't, you have hypoglycemia, and your blood sugar can be dangerously low. Signs include

* Hunger
* Shakiness
* Dizziness
* Confusion
* Difficulty speaking
* Feeling anxious or weak

In people with diabetes, hypoglycemia is often a side effect of [diabetes medicines](https://medlineplus.gov/diabetesmedicines.html). Eating or drinking something with [carbohydrates](https://medlineplus.gov/carbohydrates.html) can help. If it happens often, your health care provider may need to change your treatment plan.

You can also have low blood sugar without having diabetes. Causes include certain medicines or diseases, hormone or enzyme deficiencies, and tumors. Laboratory tests can help find the cause. The kind of treatment depends on why you have low blood sugar.

If you begin to feel one or more hypoglycemia symptoms, [check your blood glucose](https://www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes). If your blood glucose level is below your target or less than 70, eat or drink 15 grams of carbohydrates right away. Examples include

* four [glucose tablets](https://www.niddk.nih.gov/Dictionary/G/glucose-tablets) or one tube of [glucose gel](https://www.niddk.nih.gov/Dictionary/G/glucose-gel)
* 1/2 cup (4 ounces) of fruit juice—not low-calorie or reduced sugar\*
* 1/2 can (4 to 6 ounces) of soda—not low-calorie or reduced sugar
* 1 tablespoon of sugar, honey, or corn syrup
* 2 tablespoons of raisins

https://medlineplus.gov/highbloodpressure.html

High blood pressure usually has no symptoms, but it can cause serious problems such as [stroke](https://medlineplus.gov/stroke.html), [heart failure](https://medlineplus.gov/heartfailure.html), [heart attack](https://medlineplus.gov/heartattack.html) and [kidney failure](https://medlineplus.gov/kidneyfailure.html).

You can control high blood pressure through [healthy lifestyle habits](https://medlineplus.gov/howtopreventhighbloodpressure.html) such as exercise and the [DASH diet](https://medlineplus.gov/dasheatingplan.html) and taking [medicines](https://medlineplus.gov/bloodpressuremedicines.html), if needed.

<https://nccih.nih.gov/health/anxiety>

Although there are many forms of treatment, several approaches have proven to be effective in addressing anxiety disorders and depression. You can read more about the different approaches here:

* [Therapy](https://adaa.org/finding-help/treatment/therapy)
* [Learn More About Cognitive-Behavior Therapy (CBT)](https://www.adaa.org/finding-help/treatment/therapy)
* [Medication](https://adaa.org/finding-help/treatment/medication)
* [Residential Treatment](https://www.adaa.org/living-with-anxiety/treatment/qa-what-is-residential-treatment)
* [Complementary and Alternative Treatment](https://adaa.org/finding-help/treatment/complementary-alternative-treatment)
* [Transcranial Magnetic Stimulation (TMS)](http://www.adaa.org/finding-help/transcranial-magnetic-stimulation)

<https://medlineplus.gov/ency/article/001183.htm>

# Alkalosis

Metabolic alkalosis is caused by too much bicarbonate in the blood. It can also occur due to certain kidney diseases.

Symptoms of alkalosis can include any of the following:

* [Confusion](https://medlineplus.gov/ency/article/003205.htm) (can progress to stupor or coma)
* Hand tremor
* Lightheadedness
* Muscle twitching
* Nausea, vomiting
* Numbness or tingling in the face, hands, or feet
* Prolonged [muscle spasms](https://medlineplus.gov/ency/article/003193.htm) (tetany)

## Exams and Tests

The doctor will perform a physical exam and ask about your symptoms.

Laboratory tests that may be ordered include:

* [Arterial blood gas analysis](https://medlineplus.gov/ency/article/003855.htm)
* Electrolytes test, such as [basic metabolic panel](https://medlineplus.gov/ency/article/003462.htm) to confirm alkalosis and show whether it is respiratory or metabolic alkalosis.

Other tests may be needed to determine the cause of the alkalosis. These may include:

* [Urinalysis](https://medlineplus.gov/ency/article/003579.htm)
* [Urine pH](https://medlineplus.gov/ency/article/003583.htm)

## Treatment

To treat alkalosis, your health care provider needs to first find the underlying cause.

For alkalosis caused by hyperventilation, breathing into a paper bag allows you to keep more carbon dioxide in your body, which improves the alkalosis. If your oxygen level is low, you may receive oxygen.

Medicines may be needed to correct chemical loss (such as chloride and potassium). Your provider will monitor your [vital signs](https://medlineplus.gov/ency/article/002341.htm)(temperature, pulse, rate of breathing, blood pressure).

<https://www.ncbi.nlm.nih.gov/gene/2908>

This gene encodes glucocorticoid receptor, which can function both as a transcription factor that binds to glucocorticoid response elements in the promoters of glucocorticoid responsive genes to activate their transcription, and as a regulator of other transcription factors. This receptor is typically found in the cytoplasm, but upon ligand binding, is transported into the nucleus. It is involved in inflammatory responses, cellular proliferation, and differentiation in target tissues. Mutations in this gene are associated with generalized glucocorticoid resistance. Alternative splicing of this gene results in transcript variants encoding either the same or different isoforms. Additional isoforms resulting from the use of alternate in-frame translation initiation sites have also been described, and shown to be functional, displaying diverse cytoplasm-to-nucleus trafficking patterns and distinct transcriptional activities