Primary Generalized Glucocorticoid Resistance and Hypersensitivity

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Key Words
Glucocorticoid receptor · Primary generalized glucocorticoid resistance · Primary generalized glucocorticoid hypersensitivity · Glucocorticoid signal transduction

Abstract
Context: The human glucocorticoid receptor (hGR) is a ubiquitously expressed intracellular, ligand-dependent transcription factor, which mediates the action of glucocorticoids and influences physiological functions essential for life. Alterations in the molecular mechanisms of hGR action impair glucocorticoid signal transduction and alter tissue sensitivity to glucocorticoids. This review summarizes the pathophysiology, molecular mechanisms and clinical aspects of primary generalized glucocorticoid resistance (PGGR) and hypersensitivity (PGGH). Evidence Acquisition: A systematic review of the published, peer-reviewed medical literature (PubMed: 1975 through May 2011) was conducted to identify original articles and reviews on this topic. Evidence Synthesis: Evidence synthesis was relied upon the experience of a number of experts in the field, including our extensive personal experience. Conclusions: The molecular basis of PGGR and PGGH has been ascribed to mutations in the hGR gene, which alter tissue sensitivity to glucocorticoids. The stochastic nature of glucocorticoid signaling pathways in association with the variable effect that hGR.

Introduction
In humans, glucocorticoids regulate a broad spectrum of physiological functions essential for life and play an important role in the maintenance of basal and stress-related homeostasis [1–3]. Approximately 20% of the genes expressed in human leukocytes are regulated positively or negatively by glucocorticoids [4]. Glucocorticoids are involved in almost every cellular, molecular and physiological network of the organism and play a pivotal role in critical biological processes, such as growth, reproduction, intermediary metabolism, immune and inflammatory reactions, as well as central nervous system and cardiovascular functions [1, 4]. Furthermore, glucocorticoids represent one of the most widely used therapeutic compounds often employed in the treatment of inflammatory, autoimmune and lymphoproliferative disorders [1].
The Human Glucocorticoid Receptor

At the cellular level, the actions of glucocorticoids are mediated by a 94-kDa protein, the glucocorticoid receptor (GR). The human (h) GR belongs to the steroid/thyroid/retinoic acid superfamily of nuclear receptors and functions as a ligand-dependent transcription factor that regulates the expression of glucocorticoid-responsive genes positively or negatively [5–7] (fig. 1). The hGR cDNA was isolated by expression cloning in 1985 [8]. The hGR gene is one locus on the long arm of chromosome 5 (q31.3) and consists of 9 exons. Alternative splicing of the primary transcript gives rise to the two mRNA and protein isoforms, hGRα and hGRβ.

Expressed hGRα is a panel of 8 amino terminal translational isoforms of varying lengths, each of which consists of three subdomains, the N-terminal (NTD), the DNA-binding (DBD) and the ligand-binding (LBD) domain. These hGRα isoforms differ at their amino-termini and may differentially transduce the glucocorticoid signal to target tissues depending on their selective relative expression and inherent activities. It is likely that similar differential cell-specific production and functional differences might also be present between the putative hGRβ translational isoforms [5, 6]. This marked complexity in the transcription/translation of the hGR gene enables target tissues to differentially respond to circulating glucocorticoid concentrations and accounts for the highly stochastic nature of the glucocorticoid signaling pathway [11].

In the absence of ligand, hGRα resides mostly in the cytoplasm of cells as part of a hetero-oligomeric complex, which contains chaperon heat shock proteins (HSPs) 90,
70 and FKBP51, as well as other proteins [7, 11]. Upon ligand-induced activation, the hGRα dissociates from this multiprotein complex and translocates into the nucleus, where it homodimerizes and binds to glucocorticoid response elements (GREs) in the promoter region of target genes or interacts with other transcription factors (TFs), such as activator protein-1 (AP-1), nuclear factor-κB (NF-κB) and signal transducer and activator of transcription-5 (STATS), ultimately modulating the transcriptional activity of respectively GRE- or TFRE-containing genes.

Table 1. Expected clinical manifestations in tissue-specific glucocorticoid resistance or hypersensitivity*

<table>
<thead>
<tr>
<th>Target tissue</th>
<th>Glucocorticoid hypersensitivity = glucocorticoid excess</th>
<th>Glucocorticoid resistance= glucocorticoid deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>insomnia, anxiety, depression, defective cognition</td>
<td>fatigue, somnolence, malaise, defective cognition</td>
</tr>
<tr>
<td>Liver</td>
<td>+ gluconeogenesis, + lipogenesis</td>
<td>hypoglycemia, resistance to diabetes mellitus</td>
</tr>
<tr>
<td>Fat</td>
<td>accumulation of visceral fat (metabolic syndrome)</td>
<td>loss of weight, resistance to weight gain</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>hypertension</td>
<td>hypotension</td>
</tr>
<tr>
<td>Bone</td>
<td>stunted growth, osteoporosis</td>
<td></td>
</tr>
<tr>
<td>Inflammation/immunity</td>
<td>immune suppression, anti-inflammation, vulnerability to certain infections and tumors</td>
<td>+ inflammation, + autoimmunity, + allergy</td>
</tr>
</tbody>
</table>

* Modified from references 21 and 27.
**Primary Generalized Glucocorticoid Resistance and Hypersensitivity**

**Clinical Manifestations**

Primary generalized glucocorticoid resistance (PGGR) is a rare, familial or sporadic condition, initially described and elucidated by Chrousos and coworkers [20–22]. PGGR is characterized by generalized, partial, target-tissue insensitivity to glucocorticoids, which leads to compensatory activation of the hypothalamic-pituitary-adrenal (HPA) axis and hypersecretion of adrenocorticotropic hormone (ACTH) in the systemic circulation. The latter results in adrenocortical hyperplasia, increased cortisol secretion as a compensation for the reduced action of glucocorticoids at target tissues, and increased production of adrenal steroids with mineralocorticoid (cortisol, deoxycorticosterone (DOC) and corticosterone) and/or androgenic activity (androstenedione, dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS)) [20–22].

The clinical manifestations of PGGR reflect the pathophysiological alterations described above and primarily include manifestations of mineralocorticoid and/or androgen excess [20–22]. Clinical manifestations of glucocorticoid deficiency might occur, but are rare and were only reported in a young child with hypoglycemic generalized tonic-clonic seizures during the course of a febrile illness [23], in a newborn baby with severe hypoglycemia, excessive fatigability with feeding, increased susceptibility to infections and concurrent growth hormone deficiency [24], and in several adult patients with chronic fatigue [20–22]. Clinical manifestations of mineralocorticoid excess include hypertension and hypokalemic alkalosis. Clinical manifestations of androgen excess include ambiguous genitalia in a karyotypic female at birth and gonadotropin-independent precocious puberty in children of either gender; acne, hirsutism and hypofertility in both sexes; male-pattern hair loss, menstrual irregularities and oligo-anovulation in females, and oligospermia in males [20–22]. The clinical spectrum of the condition is broad, ranging from most severe to mild forms, while a number of patients may be asymptomatic, displaying biochemical alterations only [20–22]. This variable clinical phenotype is due to variations in the tissue sensitivity of the glucocorticoid, mineralocorticoid and/or androgen receptor signaling pathways; variations in the activity of key hormone-inactivating or hormone-activating enzymes, such as 11β-hydroxysteroid dehydrogenase [25] and 5α-reductase [26], and other genetic or epigenetic factors, such as the presence of insulin resistance and visceral obesity [21]. In recognition of Professor George P. Chrousos’ extensive and ground-breaking research work in this field, it has been proposed that the term ‘Chrousos syndrome’ is used in place of ‘primary generalized glucocorticoid resistance’ [27].

Primary generalized glucocorticoid hypersensitivity (PGGH) represents the mirror image of PGGR, and is characterized by generalized, partial, target-tissue hypersensitivity to glucocorticoids, and compensatory hypothalamic activation of the HPA axis. To date there has been only one patient reported with manifestations of tissue-specific
Table 2. Mutations of the hGR gene causing PGGR or PGGH

<table>
<thead>
<tr>
<th>Author Reference</th>
<th>Mutation position cDNA phenotype</th>
<th>amino acid</th>
<th>Molecular mechanisms</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrousos et al. [20]</td>
<td>1922 (A → T)</td>
<td>641 (D → V)</td>
<td>transactivation ↓</td>
<td>homozygous</td>
<td>hypertension</td>
</tr>
<tr>
<td>Hurley et al. [30]</td>
<td>affinity for ligand ↓ (× 3) nuclear translocation: 22 min abnormal interaction with GRIP1</td>
<td>heterozygous</td>
<td>hypokalemic alkalosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karl et al. [31]</td>
<td>4-bp deletion in exon-intron 6</td>
<td>hGRβ number: 50% of control inactivation of the affected allele</td>
<td>heterozygous</td>
<td>hirsutism male pattern hair loss menstrual irregularities</td>
<td></td>
</tr>
<tr>
<td>Malchoff et al. [32]</td>
<td>2185 (G → A)</td>
<td>729 (V → I)</td>
<td>transactivation ↓ affinity for ligand ↓ (× 2) nuclear translocation: 120 min abnormal interaction with GRIP1</td>
<td>homozygous</td>
<td>precocious puberty hyperandrogenism</td>
</tr>
<tr>
<td>Karl et al. [29]</td>
<td>1676 (T → A)</td>
<td>559 (I → N)</td>
<td>transactivation ↓</td>
<td>heterozygous</td>
<td>hypertension</td>
</tr>
<tr>
<td>Kino et al. [33]</td>
<td>decrease in hGR-binding sites transdominance (+) nuclear translocation: 180 min abnormal interaction with GRIP1</td>
<td></td>
<td>oligospermia infertility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz et al. [34]</td>
<td>1430 (G → A)</td>
<td>477 (R → H)</td>
<td>transactivation ↓</td>
<td>heterozygous</td>
<td>hirsutism</td>
</tr>
<tr>
<td>Charmandari et al. [39]</td>
<td>no DNA binding nuclear translocation: 20 min abnormal interaction with GRIP1</td>
<td></td>
<td>fatigue</td>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>Ruiz et al. [34]</td>
<td>2035 (G → A)</td>
<td>679 (G → S)</td>
<td>transactivation ↓</td>
<td>heterozygous</td>
<td>hirsutism</td>
</tr>
<tr>
<td>Charmandari et al. [39]</td>
<td>affinity for ligand ↓ (× 2) nuclear translocation: 30 min abnormal interaction with GRIP1</td>
<td></td>
<td>fatigue</td>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>Mendonca et al. [35]</td>
<td>1712 (T → C)</td>
<td>571 (V → A)</td>
<td>transactivation ↓ affinity for ligand ↓ (× 6) nuclear translocation: 25 min abnormal interaction with GRIP1</td>
<td>homozygous</td>
<td>ambiguous genitalia hypertension hypokalemia hyperandrogenism</td>
</tr>
<tr>
<td>Vottero et al. [36]</td>
<td>2241 (T → G)</td>
<td>747 (I → M)</td>
<td>transactivation ↓ transdominance (+) affinity for ligand ↓ (× 2) nuclear translocation ↓ abnormal interaction with GRIP1</td>
<td>heterozygous</td>
<td>cystic acne hirsutism oligo-amenorrhea</td>
</tr>
<tr>
<td>Charmandari et al. [38]</td>
<td>2318 (T → C)</td>
<td>773 (L → P)</td>
<td>transactivation ↓ transdominance (+) affinity for ligand ↓ (× 2.6) nuclear translocation: 30 min abnormal interaction with GRIP1</td>
<td>heterozygous</td>
<td>fatigue anxiety acne hirsutism hypertension</td>
</tr>
<tr>
<td>Charmandari et al. [40]</td>
<td>2209 (T → C)</td>
<td>737 (F → L)</td>
<td>transactivation ↓ transdominance (time-dependent) (+) affinity for ligand ↓ (× 1.5) nuclear translocation: 180 min</td>
<td>heterozygous</td>
<td>hypertension hypokalemia</td>
</tr>
<tr>
<td>Nader et al. [23]</td>
<td>2141 (G → A)</td>
<td>714 (R → Q)</td>
<td>transactivation ↓ transdominance (+) affinity for ligand ↓ (× 2) nuclear translocation ↓ abnormal interaction with GRIP1</td>
<td>heterozygous</td>
<td>hypoglycemia hypokalemia hypertension mild clitoromegaly advanced bone age precocious pubarche</td>
</tr>
<tr>
<td>McMahon et al. [24]</td>
<td>2-bp deletion at nt 2318-9</td>
<td>773</td>
<td>transactivation ↓ affinity for ligand: absent no suppression of IL-6</td>
<td>homozygous</td>
<td>hypoglycemia fatigue with feeding hypertension</td>
</tr>
</tbody>
</table>
glucocorticoid hypersensitivity caused by a novel hGR gene mutation. The patient was a 43-year-old female, who presented with a long-standing history of visceral obesity, hypercholesterolemia, hypertriglyceridemia, diabetes type 2 and hypertension [28] (table 2).

**Molecular Mechanisms**

**hGR Mutations**

The molecular basis of PGGR has been ascribed primarily to mutations in the hGR gene, which impair the molecular mechanisms of hGR action and decrease tissue sensitivity to glucocorticoids (table 2; fig. 3) [23, 24, 29–41]. The molecular defects that have been elucidated in cases with PGGR and have been reported to date are summarized in table 2. Compared with the wild-type receptor, all mutant receptors demonstrated variable reduction in their ability to transactivate glucocorticoid-responsive genes in response to dexamethasone [29–40]. The mutant receptors hGRαI559N, hGRαF737L, hGRαL747M and hGRαL773P exerted a dominant negative effect upon the wild-type receptor, which might have contributed to manifestation of the disease at the heterozygote state [29, 33, 35, 37, 40]. All mutant receptors in which the mutations were located in the LBD of the receptor showed a variable reduction in their affinity for the ligand [29–40]. The only mutant receptor that failed to bind to DNA but displayed a normal interaction with the GRIP1 coactivator was the hGRαR477H, in which the mutation was located at the C-terminal zinc finger of the DBD [39].

In the patient with the symptomatology suggestive of PGGR, we identified a novel, heterozygous guanine to cytosine (G → C) substitution at nucleotide position 1201 in exon 2 of the hGR gene, resulting in aspartic acid (D) to histidine (H) substitution at amino acid position 401 in the NTD of the receptor. Functional studies showed that compared with the wild-type hGRα, the hGRαD401H demonstrated a 2.4-fold increase in its ability to transactivate the glucocorticoid-responsive genes and exerted a dominant positive effect upon the wild-type receptor at low concentrations. The mutant receptor hGRαD401H had similar affinity for the ligand and time to nuclear translocation, it preserved its ability to bind to GREs, and displayed a normal interaction with the GRIP1 coactivator [28] (table 2).

**hGR Polymorphisms**

Further to the hGR gene mutations, interindividual variations in tissue sensitivity to glucocorticoids have been described within the normal population and have been partly attributed to polymorphisms in the hGR gene. Several polymorphisms of the hGR gene have been reported to date [42–44].

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**Table 2 (continued)**

<table>
<thead>
<tr>
<th>Author [Reference]</th>
<th>Mutation position</th>
<th>Molecular mechanisms</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu et al. [41]</td>
<td>1667 (G → T)</td>
<td>not studied yet</td>
<td>heterozygous</td>
<td>adrenal incidentaloma</td>
</tr>
<tr>
<td>Charmandari et al. [28]</td>
<td>1201 (G → C)</td>
<td>transactivation † transdominance (+) affinity for ligand: N nuclear translocation: N interaction with GRIP1: N</td>
<td>heterozygous</td>
<td>visceral obesity hypercholesterolemia hypertriglyceridemia hypertension diabetes type 2</td>
</tr>
</tbody>
</table>

* Modified from references 20–22.
The first polymorphism, ER22/23EK, consists of two linked, single-nucleotide mutations in codons 22 and 23 in exon 2 of the hGR gene (rs 6189 and rs 6190). The first mutation in codon 22 is silent, not resulting in an amino acid change (GAG to GAA, both coding for glutamic acid (E)), but the second mutation in codon 23 (AGG to AAG) results in arginine (R) to lysine (K) substitution [44, 45]. The ER22/23EK polymorphism results in a significant reduction of the transcriptional activation of glucocorticoid-responsive genes compared with the wild-type receptor, but it does not influence transcriptional repression [45]. This polymorphism reduces sensitivity to glucocorticoids, as evidenced by the higher serum cortisol concentrations and the smaller decrease in cortisol concentrations following dexamethasone suppression testing [46]. The ER22/23EK polymorphism results in arginine (R) to lysine (K) substitution in exon 2 of the hGR gene (rs 6189 and rs 6190). The first polymorphism produces the above effects are likely to involve a higher expression of the hGRα-A (94 kDa) isoform at the expense of the hGRα-B (91 kDa) isoform. Given that the latter isoform has greater transrepressional activity, the shift in hGRα-A to hGRα-B expression ratio leads to an overall decrease in transcriptional activity [49] (fig. 4).

Further downstream in exon 2, a polymorphism was identified that changes codon 363 from AAT to AGT (rs 6198), resulting in a serine (N) for asparagine (S) substitution. The molecular mechanisms through which the N363S polymorphism results in glucocorticoid-resistant genes compared with the wild-type receptor, although it does not influence transcriptional repression [45]. The N363S polymorphism is associated with higher sensitivity to glucocorticoids in vivo, increased insulin response to exogenous dexamethasone administration [44, 50], higher BMI [44, 50–53], higher waist-to-hip ratio [54], and a tendency toward lower bone mineral density in trabecular bone [50, 51]. The N363S variant is also associated with elevated cholesterol and triglyceride concentrations and higher incidence of coronary artery disease independent of weight [51, 55] (fig. 4). The molecular mechanism through which the N363S polymorphism exerts its effects is unknown. It has been postulated that this polymorphism contributes a new serine residue for phosphorylation, whereby protein interactions with transcription co-factors might be altered.

A frequent BclI restriction fragment length polymorphism (rs 41423247) is also associated with increased sensitivity to glucocorticoids, hypertension, visceral adiposity [44, 56, 57] and increased insulin concentrations in obese women [58]. The exact mutation of this polymorphic site was identified as a C → G substitution in intron 2. In the elderly, the G allele of the BclI polymorphism is associated with a lower BMI and a tendency towards lower lean body mass, which is likely to arise as a result of the increased sensitivity to glucocorticoids [59] (fig. 4).

The ThlIII variant (rs10052957) is a restriction site length polymorphism in the promoter region of the hGR gene, which is not functional by itself [44]. However, the ER22/23EK variant was found to be invariably linked to the ThlIII polymorphism. Therefore, associations with glucocorticoid resistance and healthier metabolic profile observed in the ThlIII carriers are likely to arise as a result of the ER22/23EK polymorphism.

Finally, a single nucleotide polymorphism that replaces A with G at the nucleoside 3669 (A3669G) (rs 6198) located in the 3’ end of exon 9β has also been described [60]. This polymorphism does not change the amino acid sequence but increases the stability of hGRβ mRNA and hGRβ protein expression, leading to greater inhibition of hGRα-induced transcriptional activity and glucocorticoid resistance. The presence of the A3669G allele is associated with reduced central obesity and a more favorable lipid profile in affected subjects [60]. Furthermore, this polymorphism selectively affects the transrepressive activity of the glucocorticoid receptor and is associated with an increased inflammatory state, rheumatoid arthritis and cardiovascular disease [61–66].
Clinical Evaluation

The first step in evaluating a patient with suspected alterations in tissue sensitivity to glucocorticoids is to obtain a complete personal and family history, with particular attention to evidence suggesting alterations in the activity of the HPA axis. In addition, any evidence suggesting possible CNS dysfunction, such as headaches, visual impairment or seizures, should be noted. In female subjects, the regularity of menstrual cycles should be documented. In children and adolescents, growth and sexual maturation should be evaluated carefully. The physical examination should include an assessment for signs of hyperandrogenism, virilization and glucocorticoid excess, as well as a complete neurologic examination. Arterial blood pressure should be recorded and preferably monitored over a 24-hour period.

Endocrinologic Evaluation

The concentrations of plasma ACTH, plasma renin activity (recumbent and upright) and aldosterone, as well as those of serum cortisol, testosterone, androstenedione, DHEA, DHEAS, total cholesterol, HDL, LDL, triglycerides, and fasting glucose and insulin should be recorded in the morning. Determination of the 24-hour urinary free cortisol (UFC) excretion on 2 or 3 consecutive days is central to the diagnosis, given that patients with PGGR demonstrate increased 24 h UFC excretion in the absence of clinical manifestations suggestive of hypercortisolism. In patients with PGGR, the rise in serum cortisol and androgen concentrations, as well as in the 24 h UFC excretion varies considerably depending on the severity of impairment of glucocorticoid signal transduction. In most severe cases, serum cortisol and 24 h UFC concentrations may be, respectively, up to 7- and 50-fold higher than the upper
limit of normal range. Plasma ACTH concentrations may be normal or high in PGGR and normal or low in PGGH.

The responsiveness of the HPA axis to exogenous glucocorticoids should also be tested with dexamethasone in patients suspected to have PGGR. Increasing doses of dexamethasone (0.3, 0.6, 1.0, 1.5, 2.0, 2.5 and 3.0 mg) should be given orally at midnight every other day, and a serum sample should be drawn at 08.00 h the following morning for determination of serum cortisol and dexamethasone concentrations. The concurrent measurement of serum dexamethasone concentrations is suggested in order to exclude the possibility of nonadherence to treatment, increased metabolic clearance or decreased absorption of this medication. Affected subjects demonstrate resistance of the HPA axis to dexamethasone suppression, which varies depending on the severity of the condition. The dose of dexamethasone required to suppress serum cortisol concentrations by 50% may be up to 7.5-fold higher than that required to achieve the same degree of HPA axis suppression in normal subjects.

### Molecular Studies

Thymidine incorporation assays and dexamethasone-binding assays on peripheral blood mononuclear cells in association with sequencing of the hGR gene are necessary to confirm the diagnosis [28–40]. In PGGR, the thymidine incorporation assays reveal resistance to dexamethasone-induced suppression of phytohemagglutinin-stimulated thymidine incorporation, while the dexamethasone-binding assays often show decreased affinity of the hGR receptor for the ligand compared to control subjects [22, 27]. The opposite is true for patients with PGGH. Sequencing of the coding region of the hGR gene, including the intron/exon junctions, will reveal mutations or deletions in most but not all cases with PGGR [27, 29–40]. Once a structural defect is determined, it is suggested that functional characterization of the mutant receptor should be undertaken in order to determine the molecular mechanisms through which the mutant hGR impairs glucocorticoid signal transduction.

### Management

In PGGR, the aim of treatment is to suppress the excess secretion of ACTH, thereby suppressing the increased production of adrenal steroids with mineralocorticoid and androgenic activity. Treatment involves administration of high doses of mineralocorticoid-sparing synthetic glucocorticoids, such as dexamethasone (1–3 mg given once daily at night), which activate the mutant and/or wild-type hGRα, and suppress the endogenous secretion of ACTH in affected subjects [20–22]. It is important to achieve adequate suppression of the HPA axis to prevent the development of an ACTH-secreting adenoma [29]. Long-term dexamethasone treatment should be carefully titrated according to the clinical manifestations and biochemical profile of the affected subjects [20–22]. In PGGH, treatment aims to address the manifestations of glucocorticoid hypersensitivity, such as dyslipidemia, diabetes type 2 and hypertension [28].

### Conclusions

The glucocorticoid receptor is a ubiquitously expressed intracellular, ligand-dependent transcription factor, which mediates the action of glucocorticoids and influences physiological functions essential for life. The stochastic nature of glucocorticoid signaling pathways in association with the variable effect that hGR gene mutations/polymorphisms might have on glucocorticoid signal transduction, indicates that alterations in hGR action may have important implications for many critical biological processes. In clinical practice, the effects of glucocorticoid treatment may vary considerably between patients and may be partly attributed to mutations or polymorphisms in the hGR gene. Therefore, when the presence of these hGR gene variants is known, the dose of glucocorticoids should be adjusted accordingly to ensure optimal therapy and minimal adverse effects.

### Disclosure Statement

The author has nothing to disclose.

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