Published in final edited form as:

Endocr Dev. 2013 ; 24: 67–85. doi:10.1159/000342505.

Primary Generalized Familial and Sporadic Glucocorticoid Resistance (Chrousos Syndrome) and Hypersensitivity

Evangelia Charmandari^{a,b,c}, Tomoshige Kino^c, and George P. Chrousos^{a,b,c}

^aDivision of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, University of Athens Medical School, Aghia Sophia Children's Hospital, Athens, Greece

^bDivision of Endocrinology and Metabolism, Clinical Research Center, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

^cUnit on Molecular Hormone Action, Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md., USA

Abstract

Familial or sporadic primary generalized glucocorticoid resistance or Chrousos syndrome is a rare genetic condition characterized by generalized, partial, target-tissue insensitivity to glucocorticoids and a consequent hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis. Primary generalized glucocorticoid hypersensitivity (PGGH) represents the mirror image of the former, and is characterized by generalized, partial, target-tissue hypersensitivity to glucocorticoids, and compensatory hypoactivation of the HPA axis. The molecular basis of both conditions has been ascribed to mutations in the human glucocorticoid receptor (hGR) gene, which impair the molecular mechanisms of hGR action and alter tissue sensitivity to glucocorticoids. This review summarizes the pathophysiology, molecular mechanisms and clinical aspects of Chrousos syndrome and PGGH.

In humans, glucocorticoids regulate a broad spectrum of physiologic functions essential for life, and play important roles in the maintenance of basal and stress-related homeostasis [1–4]. Glucocorticoids participate in almost every cellular, molecular and physiologic network of the organism, and play pivotal roles in critical biologic processes, such as growth, reproduction, intermediary metabolism, the immune and inflammatory reaction, as well as central nervous system and cardiovascular functions [1, 4]. In addition, glucocorticoids represent one of the most widely used therapeutic agents, 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 GR (hGR) 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. 1a). The hGR gene locus is on the long arm of chromosome 5 (q31.3) and consists of 9 exons. Alternative splicing of the hGR gene in exon 9 generates two highly homologous receptor isoforms, termed α and β . These are identical through amino acid 727, but then diverge, with hGR α having an additional 50 amino acids and hGR β having an additional 15 nonhomologous amino acids [3, 5–8] (fig. 1a). The hGR α represents the classic GR that functions as a ligand-dependent transcription factor and mediates the classic actions of glucocorticoids. The hGR β , on the other hand, does not bind glucocorticoid agonists, has intrinsic, hGR α -independent, gene-specific transcriptional activity, and exerts a dominant negative effect upon the transcriptional activity of hGR α [9, 10].

The hGR is a modular protein composed of distinct regions illustrated in figure 1b: the amino-terminal A/B region, also called immunogenic or N-terminal domain (NTD), and the C, D and E regions, which correspond to the DNA-binding domain (DBD), the hinge region and the ligand-binding domain (LBD), respectively [3, 5, 6].

Expressed hGR α is represented by a panel of 8 amino terminal translational isoforms of varying lengths. These hGR α isoforms differ at their amino-termini, cytoplasmic/ nuclear distribution and cell-specific expression, and may differentially transduce the glucocorticoid signal in target tissues. It is likely that similar differential cell-specific production and functional differences might also be present between the 8 putative hGR β 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, hGR α resides mostly in the cytoplasm of cells as part of a heterooligomeric complex, which contains chaperon heat shock proteins 90, 70 and FKBP51, as well as other proteins [7, 11]. Following ligand-induced activation, the hGR α dissociates from this multiprotein complex and translocates into the nucleus, where it binds as a homodimer to glucocorticoid response elements (GREs) in the promoter regions of target genes, and regulates their expression positively or negatively [7, 11] (fig. 2). To initiate transcription, the hGR α isoform(s) uses its transcriptional activation domains, activation function (AF)-1 and AF-2, located in the NTD and LBD, respectively, as surfaces to interact with nuclear receptor coactivators and chromatin-remodeling complexes [12–15]. The ligand-activated hGR α can also modulate gene expression independently of DNA binding, by interacting, possibly as a monomer, with other transcription factors, such as nuclear factor- κ B, activator protein-1, p53 and signal transducers and activators of transcription [7]. Following transcriptional activation or inhibition of glucocorticoid-responsive genes, hGR α dissociates from the ligand, and has a lower affinity for binding to GREs located in their regulatory areas. The unliganded hGR α remains within the nucleus for a considerable length of time, and is then exported to the cytoplasm; both within the

nucleus and within the cytoplasm, the hGR α may be recycled and/or degraded in the proteasomes [16] (fig. 2).

Alterations in the molecular mechanisms of hGR α action may lead to alterations in tissue sensitivity to glucocorticoids, which may take the form of *glucocorticoid resistance* or *glucocorticoid hypersensitivity* and may be associated with significant morbidity [17–19]. In the present review, we summarize the pathophysiology and molecular mechanisms underlying Crousos syndrome and primary generalized glucocorticoid hypersensitivity (PGGH).

Chrousos Syndrome and Primary Generalized Glucocorticoid Hypersensitivity

Clinical Manifestations

Crousos syndrome is a rare familial or sporadic condition characterized by generalized, mostly partial, target-tissue insensitivity to glucocorticoids, which leads to compensatory activation of the hypothalamic-pituitary-adrenal (HPA) axis and hypersecretion of adrenocorticotrophic hormone (ACTH) in the systemic circulation [20–22]. The latter results in adrenocortical hyperplasia/hypertrophy, increased cortisol secretion as a compensation for the reduced action of glucocorticoids at the brain and pituitary negative feedback-regulated areas of the HPA axis and increased production of adrenal steroids with mineralocorticoid (cortisol, deoxycorticosterone and corticosterone) and/or androgenic activity [androstenedione, dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS)] [20–22].

The clinical manifestations of primary generalized glucocorticoid resistance (PGGR) reflect the pathophysiologic alterations described above, and primarily include those of mineralocorticoid and/or androgen excess; they are summarized in table 1 [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]. The clinical spectrum of the condition is broad, ranging from most severe to mild or even asymptomatic forms [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 -activating enzymes, such as the 11 β -hydroxysteroid dehydrogenase [25] and other genetic or epigenetic factors, such as the presence of insulin resistance and visceral obesity [21]. It has been proposed that the term Crousos syndrome is used in place of familial and sporadic PGGR [26, 27].

PGGH represents the mirror image of Crousos syndrome, and is characterized by generalized, partial, target-tissue hypersensitivity to glucocorticoids, and compensatory hypoactivation of the HPA axis. To date, there has been only one patient reported with manifestations of tissue-specific 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 Chrousos syndrome 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 Chrousos syndrome and have been reported to date are summarized in table 2. We have identified most hGR mutations associated with PGGR and have systematically investigated the molecular mechanisms through which these various natural hGR mutants affect glucocorticoid signal transduction in almost all reported cases of generalized glucocorticoid resistance. We studied: (a) the transcriptional activity of the mutant receptors; (b) the ability of the mutant receptors to exert a dominant negative effect upon the wild-type receptor; (c) the affinity of the mutant receptors for the ligand; (d) the subcellular localization of the mutant receptors and their nuclear translocation following exposure to the ligand; (e) the ability of the mutant receptors to bind to GREs, and (f) the interaction of the mutant receptors with the GR-interacting protein-1 (GRIP1) coactivator, which belongs to the p160 family of nuclear receptor coactivators and plays an important role in the hGR α -mediated transactivation of glucocorticoid-responsive genes [22, 29–40].

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 hGR α I559N, hGR α F737L, hGR α I747M and hGR α L773P 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 mutant receptors that demonstrated normal affinity for the ligand were the hGR α R477H and hGR α V423A, in which the mutations were located in the DBD [39, and unpublished data]. Most pathologic mutant receptors were observed primarily in the cytoplasm of cells in the absence of ligand, except for the hGR α V729I and hGR α F737L receptors, which were localized both in the cytoplasm and the nucleus of cells. Exposure to dexamethasone induced a slow translocation of the mutant receptors into the nucleus, which ranged from 20 to 180 min compared with the wild-type hGR α , which required only 12 min for complete translocation [29–40]. All mutant receptors in which the mutations were located in the LBD preserved their ability to bind to DNA and displayed an abnormal interaction with the GRIP1 coactivator in vitro [29–40]. The mutant receptors that failed to bind to DNA or reduced the ability of the receptor to bind to DNA but displayed a normal interaction with the GRIP1 coactivator were the hGR α R477H and hGR α V423A, respectively, in which the mutation was localized in the DBD of the receptor, thus preserving the structure and function of both NTD and LBD and ensuring normal interaction with this coactivator [39, and unpublished data]. Since the binding of these receptors to DNA is followed by the attraction of GRIP1 coactivator to the transcriptional complex formed with GR on DNA, the normal interaction of hGR α R477H and hGR α V423A with GRIP1 would contribute minimally to the transcriptional activity induced by these receptors [39].

In the patient with the symptomatology suggestive of PGGH, 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 hGR α , the hGR α D401H 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 hGR α D401H 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).

The impact of the mutation on the structure of the LBD of the hGR α has been examined only for hGR α R714Q. Structural changes of the mutant receptors may underlie the functional defects observed in the above-indicated functional assay systems, such as those for affinity to the ligand (ligand-binding pocket) and interaction with the GRIP1 LXXLL coactivator motif (AF2 transactivation surface). Previously reported crystallographic analyses on the hGR α LBD revealed that it consists of 12 α -helices and 4 β -sheets, which fold into a three-layer structure [42]. In the 3-D crystallographic structural model of the wild-type hGR α LBD bound to dexamethasone, arginine (R) 714 is located in the C-terminal portion of the helix 10, and a large positively charged side chain of this amino acid protrudes into a space created by helices 7, 8, 9 and 10, where this residue forms a salt bridge with glutamic acid (E) 662 located in helix 8 [23] (fig. 4a). In hGR α R714Q LBD, the arginine (R) residue is replaced by glutamine (Q), which has a smaller, uncharged side chain; thus, the mutation breaks the salt bridge with E662, and instead forms a stable new salt bridge with arginine (R) 704 of helix 9 (fig. 4b). This change in electrostatic bonding displaces helix 10 from its former salt bridge constraint, leading to further conformational changes in the ligand-binding pocket (fig. 4c, d). The mutation also destabilizes the AF-2 surface and obstructs optimal binding of the LXXLL coactivator motif to this transactivation domain (fig. 4e, f). Since the arginine (R) residue at amino acid position 714 in the hGR α is preserved in the GRs of different species and in the other human nuclear receptors [23], R714 appears to play an important role in the formation of the 3-D structure of many of the nuclear receptors, including the GR.

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 [43–45].

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 nucleotide replacement in codon 22 is silent, not resulting in an amino acid change [GAG to GAA, both coding for glutamic acid (E)], but the second replacement in codon 23 (AGG to AAG) results in arginine (R) to lysine (K) substitution [45, 46]. The ER22/23EK polymorphism results in a small reduction of the transcriptional activation of glucocorticoid-responsive genes compared with the wild-type receptor, but it does not influence transcriptional repression [46]. 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 in carriers compared with non-carriers [47], and results in a phenotype that is characterized by a more favorable metabolic profile, leading to longevity. Carriers of the ER22/23EK polymorphism display relative glucocorticoid resistance, lower fasting insulin concentrations and improved insulin sensitivity, lower total and LDL cholesterol concentrations and lower C-reactive protein concentrations [45, 48]. In line with this favorable metabolic profile, the ER22/23EK polymorphism demonstrates significantly higher incidence in the oldest half of the population. At young age, a sexually dimorphic pattern in body composition has been documented in this polymorphism [49]. Finally, at an older age, carriers of the ER22/23EK polymorphism have lower risk of dementia and fewer white matter lesions in the brain compared to non-carriers [45]. The molecular mechanisms through which the ER22/23EK polymorphism produces the above effects are likely to involve a higher expression of the hGR α -A (94-kDa) isoform at the expense of the hGR α -B (91-kDa) one. Given that the latter isoform has greater transactivational activity, the shift in hGR α -A to hGR α -B expression ratio leads to an overall decrease in transcriptional activity [50] (fig. 5).

Further downstream in exon 2, a polymorphism was identified that changes codon 363 from AAT to AGT (rs 6195), resulting in a serine (N) for asparagine (S) substitution. The N363S polymorphism is associated with higher sensitivity to glucocorticoids in vivo, resulting in an increase in the transcriptional activation of glucocorticoid-responsive genes compared with the wild-type receptor, although it does not influence transcriptional repression [46]. The N363S polymorphism is associated with higher sensitivity to glucocorticoids in vivo, increased insulin response to exogenous dexamethasone administration [45, 51], higher body mass index, higher waist-to-hip ratio, a tendency toward lower bone mineral density in trabecular bone, elevated cholesterol and triglyceride concentrations, and higher incidence of coronary artery disease independent of weight [45, 51–57] (fig. 5).

A frequent *BclI* restriction fragment length polymorphism (rs 41423247) is also associated with increased sensitivity to glucocorticoids, hypertension, visceral adiposity [45, 58, 59] and increased insulin concentrations in obese women [60]. 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 tendency towards lower lean body mass, which is likely to arise as a result of the increased sensitivity to glucocorticoids [61] (fig. 5).

The *TthIII* variant (rs10052957) is a restriction site length polymorphism in the promoter region of the hGR gene, which is not functional by itself [45]. However, the ER22/23EK variant was invariably linked to the *TthIII* polymorphism. Therefore, associations with glucocorticoid resistance and healthier metabolic profile observed in the *TthIII* 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 9 β has also been described [62]. This polymorphism does not change the amino acid sequence, but increases the stability of hGR β mRNA and hGR β protein expression, leading to greater inhibition of hGR α -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 [62]. Furthermore, this polymorphism selectively affects the transrepressive activity of the GR and is associated with an increased inflammatory state, rheumatoid arthritis and cardiovascular disease [63–68].

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 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. 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 (h) urinary free cortisol (UFC) excretion on 2 or 3 consecutive days is central to the diagnosis, given that patients with Crousos syndrome demonstrate increased 24-hour UFC excretion in the absence of clinical manifestations suggestive of hypercortisolism. In patients with Crousos syndrome, the rise in serum cortisol and androgen concentrations, as well as in the 24-hour UFC excretion varies considerably depending on the severity of impairment of glucocorticoid signal transduction. In most severe cases, serum cortisol and 24-hour UFC concentrations may be, respectively, up to 7-fold higher and 50-fold higher than the upper limit of normal range. Plasma ACTH concentrations may be normal or high in Crousos syndrome 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 Crousos syndrome. Increasing doses of dexamethasone 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.

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, 29–40]. In Crousos syndrome, the thymidine incorporation assays reveal resistance to dexamethasone-induced suppression of phytohemagglutinin-stimulated thymidine incorporation, while the dexamethasonebinding 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 Crousos syndrome [27, 29–40].

Management

In Crousos syndrome, 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), which activate the mutant and/or wild-type hGR α , 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 in the pituitary gland and an adrenocortical adenoma in the adrenal glands [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 GR is a ubiquitously expressed intracellular, ligand-dependent transcription factor, which mediates the action of glucocorticoids and influences physiologic 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, such as the behavioral and physiologic responses to stress, the immune and inflammatory reaction, the process of sleep, as well as basic functions, such as growth and reproduction. 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.

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Fig. 1.

a Schematic representation of the structure of the hGR gene. Alternative splicing of the primary transcript gives rise to the two mRNA and protein isoforms, hGRα and hGRβ. **b** Functional domains of the hGRα. The functional domains and subdomains are indicated beneath the linearized protein structures. NL = Nuclear localization.

Fig. 2.

Nucleocytoplasmic shuttling of the GR. Upon binding to the ligand, the activated hGR α dissociates from heat shock proteins (HSPs) and translocates into the nucleus, where it homodimerizes and binds to GREs in the promoter region of target genes or interacts with other transcription factors (TFs), such as activator protein-1, nuclear factor- κ B and signal transducer and activator of transcription-5, ultimately modulating the transcriptional activity of respectively GRE- or TFRE-containing genes.

Fig. 3.
Location of the known mutations of the hGR gene causing Chrousos syndrome.

Fig. 4. Arginine (R) to glutamine (Q) replacement at amino acid 714 of the hGR α alters 3-D structure of its LBD. **a, b** Arginine (R) to glutamine (Q) replacement at amino acid 714 of the hGR α causes formation of a new salt bridge between arginine (R) at 704 and aspartic acid (D) at 662. **a** In the wild-type hGR α LBD, R714 is tightly bound to D662 through an electrostatic salt bridge. **b** Substitution of arginine by glutamine in the hGR α R714Q LBD results in a rearrangement of the side chains, forming a new salt bridge between R704 and D662, while displacing Q714. This relaxes some constraint on helix 10 and results in

structural changes throughout the LBD. **c, d** hGR α R714Q LBD has altered ligand-binding pocket. The ligand-binding pocket of the wild-type hGR α (**c**) and hGR α R714Q (**d**) are shown. Arginine to glutamine replacement at amino acid 714 causes alteration in the ligand-binding pocket in hGR α R714Q LBD. The greatest change observed between the wild-type hGR α LBD and hGR α R714Q LBD is in the rotameric state of Y735. **e, f** hGR α R714Q LBD has the destabilized AF-2 surface that blocks optimal binding of the LXXLL coactivator motif. The thickness and color of the C α trace of the wild-type hGR α LBD (**e**) and hGR α R714Q LBD (**f**) indicate the areas of least (thin and blue) to most (thick and red) motion over the course of the simulation. As expected, the termini of the LBD and the bound peptide move the most. **f** There is significant motion at the mutation site (asterisk) in the mutant LBD, but not in the wildtype LBD, suggesting that the mutation causes destabilization in this structural area. The bound LXXLL peptide is, thus, more labile in the mutant LBD structure, as seen by the thickness of its C α trace.

Fig. 5. Schematic representation of the hGR gene polymorphisms located in the aminoterminal domain of the receptor and a summary of their clinical associations. CRP = C-reactive protein.

Table 1**Clinical manifestations and diagnostic evaluation of generalized glucocorticoid resistance***Clinical presentation*

Apparently normal glucocorticoid function

Asymptomatic

Chronic fatigue (glucocorticoid deficiency?)

Mineralocorticoid excess

Hypertension

Hypokalemic alkalosis

Androgen excess

Children: ambiguous genitalia at birth¹, premature adrenarche, precocious puberty

Females: acne, hirsutism, male-pattern hair loss, menstrual irregularities, oligoanovulation, infertility

Males: acne, hirsutism, oligospermia, adrenal rests in the testes, infertility

Increased HPA axis activity (CRH/ACTH hypersecretion)

Anxiety

Adrenal rests

Diagnostic evaluation

Absence of clinical features of Cushing syndrome

Normal or elevated plasma ACTH concentrations

Elevated plasma cortisol concentrations

Increased 24-hour UFC excretion

Normal circadian and stress-induced pattern of cortisol and ACTH secretion

Resistance of the HPA axis to dexamethasone suppression

Thymidine incorporation assays: increased resistance to dexamethasone-induced suppression of phytohemagglutinin-stimulated thymidine incorporation compared to control subjects

Dexamethasone-binding assays: decreased affinity of the GR for the ligand compared to control subjects

Molecular studies: mutations/deletions of the GR

Modified from Charmandari et al. [22].

¹This is the only case of ambiguous genitalia documented in a child with 46,XX karyotype who also harbored a heterozygous mutation of the 21-hydroxylase gene.

Table 2

Mutations of the hGR gene causing PGGR or hypersensitivity

Reference	Mutation position		Molecular mechanisms	Genotype	Phenotype
	cDNA	amino acid			
Chrousos et al. [20]	1922 (A→T)	641 (D→V)	transactivation ↓	homozygous	hypertension
Hurley et al. [30]			affinity for ligand ↓ (×3)		hypokalemic alkalosis
			nuclear translocation: 22 min		
			abnormal interaction with GRIP1		
Karl et al. [31]	4-bp deletion in exon-intron 6		hGRα number: 50% of control	heterozygous	hirsutism
			inactivation of the affected allele		male pattern hair-loss menstrual irregularities
Malchoff et al. [32]	2185 (G→A)	729 (V→I)	transactivation ↓	homozygous	precocious puberty
			affinity for ligand ↓ (×2)		hyperandrogenism
			nuclear translocation: 120 min		
			abnormal interaction with GRIP1		
Karl et al. [29]	1676 (T→A)	559 (I→N)	transactivation ↓	heterozygous	hypertension
Kino et al. [33]			decrease in hGR-binding sites		oligospermia
			transdominance (+)		infertility
			nuclear translocation: 180		
			abnormal interaction with GRIP1		
Ruiz et al. [34]	1430 (G→A)	477 (R→H)	transactivation ↓	heterozygous	hirsutism
Charmandari et al. [39]			no DNA binding		fatigue
			nuclear translocation: 20 min		hypertension
Ruiz et al. [34]	2035 (G→A)	679 (G→S)	transactivation ↓	heterozygous	hirsutism
Charmandari et al. [39]			affinity for ligand ↓ (×2)		fatigue
			nuclear translocation: 30 min		hypertension
			abnormal interaction with GRIP1		
Mendonca et al. [35]	1712 (T→C)	571 (V→A)	transactivation ↓	homozygous	ambiguous genitalia
			affinity for ligand ↓ (×6)		hypertension
			nuclear translocation: 25 min		hypokalemia

Reference	Mutation position		Molecular mechanisms	Genotype	Phenotype
	cDNA	amino acid			
Vottero et al. [36]	2241 (T→G)	747 (I→M)	abnormal interaction with GRIP1		hyperandrogenism
			transactivation ↓	heterozygous	cystic acne
			transdominance (+)		hirsutism
			affinity for ligand ↓ (×2)		oligoamenorrhea
			nuclear translocation ↓		
Charmandari et al. [38]	2318 (T→C)	773 (L→P)	abnormal interaction with GRIP1		
			transactivation ↓	heterozygous	fatigue
			transdominance (+)		anxiety
			affinity for ligand ↓ (×2.6)		acne
			nuclear translocation: 30 min		hirsutism
Charmandari et al. [40]	2209 (T→C)	737 (F→L)	abnormal interaction with GRIP1		hypertension
			transactivation ↓	heterozygous	hypertension
			transdominance (time-dependent) (+)		hypokalemia
			affinity for ligand ↓ (×1.5)		
			nuclear translocation: 180 min		
Nader et al. [23]	2141 (G→A)	714 (R→Q)	transactivation ↓	heterozygous	hypoglycemia
			transdominance (+)		hypokalemia
			affinity for ligand ↓ (×2)		hypertension
			nuclear translocation ↓		mild clitoromegaly
			abnormal interaction with GRIP1		advanced bone age
McMahon et al. [24]	2-bp deletion at nt 2318-9	773			precocious pubarche
			transactivation ↓	homozygous	hypoglycemia
			affinity for ligand: absent		fatigability with feeding
Zhu et al. [41]	1667 (G→T)	556 (T→I)	no suppression of IL-6		hypertension
			not studied yet	heterozygous	adrenal incidentaloma
Charmandari et al. [28]	1201 (G→C)	401 (D→H)	transactivation ↑	heterozygous	visceral obesity
			transdominance (+)		hypercholesterolemia
			affinity for ligand: N		hypertriglyceridemia

Reference	Mutation position	Molecular mechanisms	Genotype	Phenotype
	cDNA			
		nuclear translocation: N		hypertension
		interaction with GRIP1: N		diabetes type 2

Modified from Chrousos et al. [20, 21] and Charmandari et al. [22].