ISSN 0006-2979, Biochemistry (Moscow), 2006, Vol. 71, No. 10, pp. 1073-1081. © Pleiades Publishing, Inc., 2006.
Published in Russian in Biokhimiya, 2006, Vol. 71, No. 10, pp. 1328-1337.

REVIEW

Glucocorticoid Resistance

Z. Orbak

Ataturk University Faculty of Medicine, Department of Pediatric Endocrinology, 25240, Erzurum, Turkey; E-mail: zerrinorbak@yahoo.com

Received February 27, 2006
Revision received June 5, 2006

Abstract—Glucocorticoids contribute fundamentally to the maintenance of basal and stress-related homeostasis in all higher organisms. The major roles of these steroids in physiology are amply matched by their remarkable contributions to pathology. Glucocorticoid resistance is a rare familial, or sporadic condition characterized by partial end-organ insensitivity to glucocorticoids. The molecular basis of glucocorticoid resistance in several families and sporadic cases has been ascribed to mutations in the human glucocorticoid receptor α (hGRα) gene, which impair the ability of the receptor to transduce the glucocorticoid signal. Glucocorticoids are crucial for life, and therefore complete glucocorticoid resistance is uncommon. The purpose of this review is to discuss the many structural and functional features of the glucocorticoid receptor and also to evaluate the main clinical and laboratory characteristics of cortisol resistance.

DOI: 10.1134/S0006297906100038

Key words: glucocorticoid, resistance, receptor

Glucocorticoids are crucial for the regulation of basal and stress-related homeostasis. These steroid hormones are necessary for maintenance of many important biologic activities, such as the homeostasis of the central nervous system, the cardiovascular system, intermediary metabolism, and the immune/inflammatory reaction. Glucocorticoids are crucial for life, and therefore complete glucocorticoid resistance is uncommon [1].

Abbreviations: ACTH) adrenocorticotropic hormone; AP-1) activating protein-1; bFGF) basic fibroblast growth factor; C/EBP) CCAAT/enhancer-binding protein; CRH) corticotropin-releasing hormone; CyP-40) cyclophilin 40; DOC) deoxycorticosterone; FKBP) FK506-binding protein; GHRH) growth hormone-releasing hormone; GR) glucocorticoid receptor; GRE) glucocorticoid-responsive element; HPA axis) hypothalamic-pituitary-adrenal axis; ICAM) intercellular adhesion molecule; IFN) interferon; IGF) insulin-like growth factor; IGF-BP-6) insulin-like growth factor-binding protein-6; iNOS) inducible NO-synthase; MMTV) murine mammary tumor virus; NGF) nerve growth factor; PEPCK) phosphoenolpyruvate-carboxykinase; POMC) proopiomelanocortin; PPAR) peroxisome proliferation activator receptor; PTHrP) parathyroid hormone-related peptide; RXR) retinoid X receptor; TCR) T-cell receptor; TNF) tumor necrosis factor; UTR) untranslated region; VIP) vasoactive intestinal peptide.

THE HUMAN GLUCOCORTICOID RECEPTOR GENE

Nuclear receptors are divided into six related subfamilies. Subfamily 3 contains the steroid receptors. Evidence suggests that subfamily 3 includes glucocorticoid, androgen, progesterone, and mineralocorticoid receptors [2]. Cortisol exerts its effects after uptake of free hormone from the circulation [3]. The actions of glucocorticoids are mediated by a ubiquitous intracellular receptor protein, the glucocorticoid receptor (GR), which functions as a hormone-activated transcription factor of glucocorticoid target genes [4]. The structure of the human glucocorticoid receptor gene was elucidated in 1991 [5]. The *GR* is ubiquitously expressed in almost all human tissue and organs [6]. The gene of the GR consists of nine exons and is located on chromosome 5 [1, 4]. Exon 1 and the first part of exon 2 contain the 5′UTR, exons 2-9 – the coding sequences, and exon 9 – the 3′UTR [5, 7]. Recently, the presence of two previously unidentified exons has been demonstrated (exon 1A and 1B) upstream from the originally defined exon 1 (which is now named exon 1C) [1]. At least three promoters regulate the activity of the glucocorticoid receptor gene, providing the opportunity for tissue-specific expression [8].

HUMAN *GR* mRNA

In 1985, human glucocorticoid receptor cDNAs were first cloned [9, 10]. Initially, two forms were found: hGRα and hGRβ cDNA. The hGRα and hGRβ mRNA both contain exons 1-8, but they contain different versions of exon 9 as a result of alternative splicing. The hGRα and hGRβ mRNA contain exons 9α and 9β, respectively. Also, these messengers are translated into hGRα and hGRβ. Recently, a third hGR mRNA has been shown. This transcript has a higher expression level than the other two previously discovered messengers in most tissues [1, 7]. This messenger contains exons 1-8 and the entire exon 9 containing exon 9α, the "J region", and exon 9β. It is thought that this mRNA is translated into hGRα (Fig. 1) [1, 3, 4]. hGRα is the classic GR that binds with glucocorticoids and transactivates or transrepresses glucocorticoid-responsive promoters [4]. On the other hand, hGRβ does not bind glucocorticoids [11]. Although Bamberger et al. [6] first discovered that hGRβ can act as a dominant-negative inhibitor of hGRα *in vitro* in 1995, its physiologic and pathologic roles are not well known.

Human GR protein. The hGR contains three major domains, the N-terminal or "immunogenic" domain (NTD), the central, DNA-binding domain (DBD), and C-terminal, ligand-binding domain (LBD) [4]. The NTD contains a powerful transcriptional activation region (AF1/tau1/enh2) required for maximal transcriptional enhancement [12]. The AF1 can act constitutively in the absence of the LBD, and is quite active in stimulating transcription from simple promoters containing cognate GR binding sites [13]. The flexible AF1 domain is ideally suited to provide modulated surfaces in the GR. The GR AF1 is not necessary for life [13]. The three-dimensional structure of the entire NTD or (where present) its AF1 is not known for any nuclear hormone receptor member [13]. The NTD is highly immunogenic and contains the major known sites of phosphorylation in the GR [13]. The GR is a phosphoprotein, and phosphorylation is an obvious possibility for modulating its activity [13]. It was reported that phosphorylation affects the stability of GR [14]. All seven phosphorylation sites (six Ser plus one Thr) identified in mouse GR are found in the NTD, within or near the AF1 domain [15]. Five of these are well conserved in human GRs. Individual mutations of these sites do not alter receptor activity in an MMTV-driven promoter-reporter construct, but a GR lacking all five conserved sites shows significantly decreased activity [16].

The DNA-binding domain (DBD) located centrally in the amino acid sequence of the GR is the most conserved region among the nuclear hormone receptors. GR DBD is composed of two highly conserved "zinc fingers"

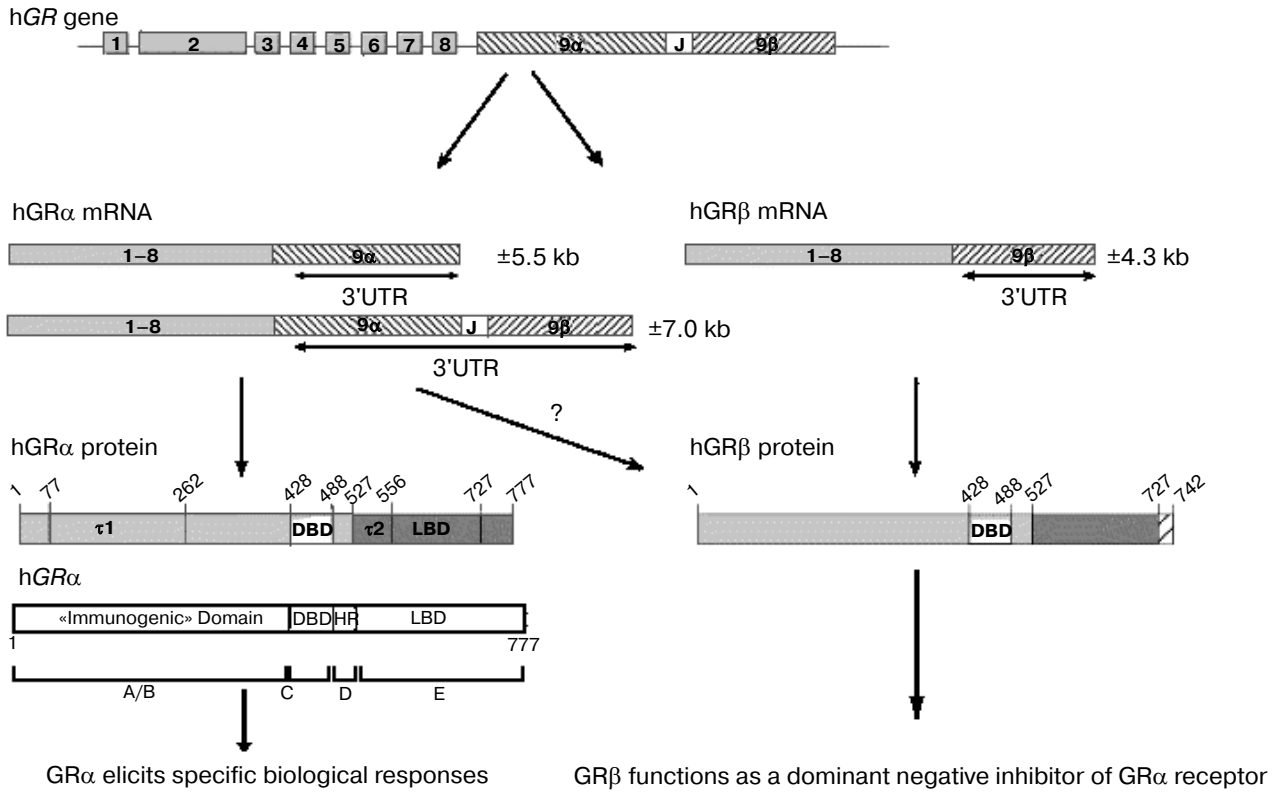

Fig. 1. Schematic structure of the human gene encoding the glucocorticoid receptor (modified from [1, 3, 4]).

(two groups of four Cys residues, each group coordinately binding a single Zn atom) though they do not form classic three-dimensional zinc finger structures as in the *Xenopus* protein and other true zinc finger proteins [13]. The resulting tertiary structure contains helices that interact specifically with DNA. The DBD contains amino acids that contact specific bases in GRE (glucocorticoid-responsive element) sequences to provide site specificity for GR–DNA binding. These amino acids are primarily located in the first zinc finger, where the "P box" comprised of three amino acids is responsible for response element discrimination. The second zinc finger region stabilizes DBD–GRE interactions, and five amino acids in the second zinc finger termed "D box" play an important role in homodimerization at the GRE [13, 17, 18]. The zinc atoms play a structural role, each capping the N-terminus of an amphipathic α-helix and supporting a peptide loop. The first stabilized helix contains the few amino acids critical for DNA sequence-specific binding in the major groove of the GRE. Two more helices are found in the second zinc finger. These bind DNA nonspecifically in the minor groove, and this contribution is important for the cooperative, high affinity binding of GR dimers at classic palindromic GREs. The central feature of the secondary structure elements within the DBD is three helical regions. Helices I and III are oriented perpendicular to each other and form the base of a hydrophobic core. These are both regular α-helices, whereas helix II is somewhat distorted [13, 17]. The DBDs also interact with certain heterologous proteins, c-Jun for example [13].

The LBD is responsible for recognition and binding of steroid hormone ligands, chaperones, and other proteins [19]. This domain consists of about 12 helices that fold overall into a globular structure consisting of three sets of helices that form the sides and top of the globule, making a central pocket, the ligand-binding site [20]. The crystal structure of the GR ligand-binding domain reveals a novel mode of receptor dimerization and coactivator recognition [13]. Molecular genetics have shown that near the C-terminus of the LBD of several of these hormone-binding receptors is a short helical amino acid sequence (usually helix-12 important for activating gene transcription) [20]. Also, the LBD contains a small but important ligand-dependent activation function (AF2) subdomain located towards its C-terminal end. The AF2 functions in a ligand-dependent manner to fold so as to complete binding surfaces for other proteins, e.g. coactivators and corepressors [13].

MECHANISM OF GLUCOCORTICOID RECEPTOR ACTION

The GR in its unliganded but ligand-friendly state is located primarily in the cytoplasm, as part of heterooligomeric complexes containing heat shock proteins (hsp) 90, 70, and 50, and, possibly, other proteins as well [21]. This complex has been studied extensively and best estimates indicate that it consists of several proteins including hsp90, hsp70, immunophilins, FKBPs, CyP-40, and P23 [13]. A key part of the complex is the receptor–hsp90 interaction, which seems to keep the ligand-binding pocket of the receptor in its optimal, high-affinity configuration [13]. In the absence of ligand, hGRα forms a large heteromeric complex with several proteins. A central role in this complex is played by hsp90, which associates with the LBD of the receptor [22]. After binding to its agonist ligand, the GR undergoes conformational changes, dissociates from the heat shock proteins, homodimerizes, and translocates into the nucleus through the nuclear pore via an active process [4]. After translocation to the nucleus, gene transcription is stimulated or repressed following binding of dimerized GR–ligand complexes to specific nucleotide sequences in the promoter regions of target genes [3]. The concepts of what defines these sites have changed significantly in recent years. Once in the nucleus, the "activated" GR interacts at the regulatory regions of its primary targets to either enhance (upregulate, induce) or repress (downregulate, de-induce) transcription. This sequence of events is termed primary regulation [13]. Genes that are under primary regulation show changes in transcriptional output in a few hours [23].

The ligand-activated GR directly interacts with DNA sequences named the glucocorticoid-responsive elements (GREs) in the promoter regions of target genes [4]. Several amino acids in the DBD interact with the DNA. The DBD consists of two protein loops, which are coordinated by zinc ion, forming two zinc fingers [18]. This stabilizes the RNA polymerase II complex, facilitating gene transcription [3]. Optimal transactivation of target genes requires the presence of two domains in hGRα: τ-1 and τ-2 [24]. Hormone binding is required for the activity of τ-2 [1]. The steroid receptor may be simply "tethered" indirectly to the DNA or may also make secondary DNA contacts as well. Tethering sites were discovered in genes down-regulated by addition of steroids to cells [13]. More recent data however has shown that upregulation is also possible at receptor-tethering sites, depending on the particular DNA binding site involved for the heterologous transcription factor and/or the factor interaction with receptor [25].

Naturally occurring GR mutations and GR mutants generated *in vitro* have highlighted critical regions of the receptor responsible for binding and transactivation [21, 26], but numerous other factors are also required (coactivators, corepressors [27]) that may confer tissue specificity of response. The interactions between GR and two particular transcription factors are important in mediating the anti-inflammatory effects of glucocorticoids and explain the effect of glucocorticoids on genes that do not

contain obvious glucocorticoid response elements in their promoter regions. Activator protein-1 (AP-1) comprises Fos and Jun subunits and is a pro-inflammatory transcription factor induced by a series of cytokines and phorbol ester. The GR–ligand complex can bind to c-jun and prevent interaction with the AP-1 site to repress AP-1 and GR transactivation functions [3, 28]. Similarly, functional antagonism exists between the GR and nuclear factor κB (NF-κB). NF-κB is a ubiquitously expressed transcription factor that activates a series of genes involved in

Table 1. Some of the genes regulated by glucocorticoids or glucocorticoid receptors (modified from [3, 28])

Site of action	Induced genes	Repressed genes
Immune system	NF-κB inhibitor haptoglobin TCRξ p21, p27, p57 lipocortin	interleukins TNF-α IFN-γ E-selectin ICAM-1 cyclooxygenase 2 iNOS
Metabolism	PPAR-γ tyrosine aminotransferase glutamine synthase glycogen synthase PEPCK ob/leptin γ-fibrinogen cholesterol 7α-hydroxylase cytochrome P450 C/EBP/β	tryptophan hydroxylase metalloprotease
Bone	androgen receptor calcitonin receptor alkaline phosphatase IGF-BP-6	osteocalcin collagenase
Channels and transporters	epithelial sodium channel (EnaC) α, β, γ serum- and glucocorticoid-induced kinase (SGK)	
Endocrine system	aquaporin 1 bFGF VIP endothelin RXR GHRH receptor natriuretic peptide receptors androgen receptor IGF-binding protein calcitonin receptor	glucocorticoid receptor PRL (prolactin) POMC (ACTH, β-endorphin, β-lipotropin) CRH PTHrP vasopressin osteocalcin
Growth and development	surfactant proteins A, B, C	fibronectin α-fetoprotein NGF erythropoietin G1 cyclins cyclin-dependent kinases

lymphocyte development, inflammatory response, host defense, and apoptosis [28]. In keeping with the diverse array of actions of cortisol, many hundreds of glucocorticoid-responsive genes have been identified (Table 1) [3, 28].

CHANGES IN TISSUE SENSITIVITY TO GLUCOCORTICOIDS

Since glucocorticoids have a broad array of life-sustaining functions and play an important role in therapeutic interventions, changes in tissue sensitivity to glucocorticoids may be associated with and influence the course of many pathologic states (Table 2) [4, 29]. These changes may be glucocorticoid resistance or hypersensitivity, and may be a generalized or tissue specific. Primary generalized glucocorticoid resistance has been described as a rare familial or sporadic syndrome mostly due to inactivating mutations of the GR gene. On the other hand, several autoimmune/inflammatory states, such as rheumatoid arthritis, osteoarthritis, Crohn's disease, and asthma, are often associated with resistance of the inflamed tissues to glucocorticoids [11]. In addition, septic shock and respiratory distress syndrome have been associated with systemic glucocorticoid resistance [30].

Familial/sporadic glucocorticoid resistance syndrome. Glucocorticoid resistance is a rare familial or sporadic condition characterized by partial end-organ insensitivity to glucocorticoids. Familial/sporadic glucocorticoid resistance syndrome was first described in 1976 as a glucocorticoid receptor-mediated disorder characterized by hypercortisolism without Cushingoid features [31]. The molecular basis of glucocorticoid resistance in several families and sporadic cases has been ascribed to mutations in the human glucocorticoid receptor-α (hGRα) gene. Until now, cortisol resistance mutation has been discovered in a small number of families. The propositus of the original kindred was a homozygote for a single non-conservative point mutation, replacing aspartic acid with valine at amino acid 641 in GR LBD. This mutation reduced binding affinity for dexamethasone by three-fold and caused concomitant loss of transactivation activity [32]. The propositus of the second family had a 4-base deletion at the 3′-boundary of exon 6 in one GR allele (δ4). This resulted in complete ablation of one of the GR alleles in affected members of the family [33]. The propositus of the third kindred had a single homozygotic point mutation at amino acid 729 (valine to isoleucine) of the LBD. This mutation reduced both affinity and transactivation activity of the GR [34]. There was a *de novo*, heterozygotic GR mutation at amino acid 559 (isoleucine to asparagine) of the LBD in a sporadic case, presenting with infertility and hypertension at age 33. This mutant GR bound no ligand. The mutation was present in all of the patient's cultured lymphoblasts and fibroblasts as well as in 50% of his sperm [35, 36]. A fifth case had glucocorticoid resistance and a heterozygotic GR mutation in the LBD (amino acid 747, replacing isoleucine with methionine). The mutant receptor had mildly reduced affinity for dexamethasone and markedly decreased transactivation activity [37, 38]. The sixth and seventh sporadic cases were also due to heterozygous mutations, replacing arginine to histidine at amino acid 477 and glycine to serine at amino acid 679, respectively [39]. The former is located in the second zinc finger in the DBD. This mutant receptor has no transactivation activity due to impaired binding to GREs. The latter mutation is found in the LBD. This mutation caused reduction of ligand-binding affinity with reduction of the transactivation activity. The propositus of the eighth familial case had a homozygotic point mutation replacing valine by alanine at amino acid 571 of the LBD [40]. The mutant receptor had six-fold reduction in its binding affinity to dexamethasone and 10-50-fold less transactivation activity than the wild type receptor. Interestingly, this baby born with ambiguous genitalia also suffered from 21-hydroxylase deficiency, suggesting that this congenital disease exacerbated the hyperandrogenism and virilization potential of the glucocorticoid resistance syndrome [40]. Charmandari et al. [41] identified a new case of generalized glucocorticoid resistance in a young woman who presented with a long-standing history of fatigue, anxiety, hyperandrogenism, and hypertension. The disease was caused by a novel, heterozygous mutation (T > C) at nucleotide position 2318 (exon 9) of the hGRα gene, which resulted in substitution of leucine by proline at amino acid position 773 in the ligand-binding domain in receptor [41]. Location of the known mutations of the glucocorticoid receptor is shown in Table 3 and Fig. 2. GR mutations are inactivating mutations and glucocorticoid resistance is often an autosomal dominant

Table 2. Pathologic states associated with changes in tissue sensitivity to glucocorticoids [4, 29]

Resistance
– familial/sporadic glucocorticoid resistance syndrome
– rheumatoid arthritis
– osteoarthritis
– systemic lupus erythematosus
– Crohn's disease
– ulcerative colitis
– septic shock/respiratory distress syndrome
– bronchial asthma
Hypersensitivity
– visceral-type obesity-related hypertension and insulin resistance
– acquired immunodeficiency syndrome (human immunodeficiency virus type-1 infection)

Table 3. Pathologic mutations in the glucocorticoid receptor gene [4]

References	Position of mutations		Biochemical phenotype	Genotype/transmission
	cDNA	amino acid		
Hurley et al. [32]	2054A > T	D641V	affinity ↓ transactivation ↓	homozygote/autosomal recessive
Karl et al. [33]	Δ4 at the 3′-boundary of exon and intron 6		GR number ↓ inactivation of the affected allele	heterozygote/autosomal dominant
Malchoff et al. [34]	2317G > A	V729I	affinity ↓ transactivation ↓	homozygote/autosomal recessive
Karl et al. [35] Kino et al. [36]	1808T > A	I559N	GR number ↓ transactivation ↓ dominant negative activity	heterozygote/sporadic
Vottero et al. [37]	2373T > G	I747M	affinity ↓ transactivation ↓↓ dominant negative activity	heterozygote/autosomal dominant
Ruiz et al. [39]	1430G > A 2035G > A	R477H G679S	transactivation (–) сродство ↓ transactivation ↓	heterozygote/sporadic heterozygote/sporadic
Mendonca et al. [40]	1844C > T	V571A	affinity ↓ transactivation ↓↓	homozygote/autosomal recessive
Charmandari et al. [41]	2318T > C	L773P	affinity ↓ transactivation ↓	heterozygote

familial disease [2]. Glucocorticoid resistance is not always hormone specific. New et al. [42] described two sisters with multiple, partial steroid resistance, whose pathological manifestations were those originally associated with isolated generalized partial glucocorticoid resistance.

In case of generalized glucocorticoid resistance, patients present with increased cortisol concentrations compared with the normal population [43]. The negative glucocorticoid feedback on both corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) secretion is reduced as a consequence of diminished sensitivity to glucocorticoid. As a result, the hypothalamic-pituitary-adrenal (HPA) axis is set at a higher level. CRH and ACTH secretion increase, resulting in higher serum cortisol concentrations. So, the organism tries to achieve a balance between cortisol requirement and cortisol secretion. The increased cortisol levels appear to compensate adequately for the reduced sensitivity. However, patients with glucocorticoid resistance do not show signs or symptoms of cortisol excess, because they simply need these increased serum cortisol concentrations. The sensitivity to glucocorticoids is diminished at the hypothalamic and the pituitary level, but also at the peripheral target tissue level. Therefore, symptoms seen in patients with glucocorticoid resistance are not due to glucocorticoid excess. These symptoms are secondary to the activation of the HPA axis, which result in an increased production of ACTH, resulting in the stimulation of mineralocorticoid and androgen secretion [43, 44]. So in patients suffering from glucocorticoid resistance, the increased ACTH secretion leads to a secondary adrenal overproduction of hormones with mineralocorticoid activity, such as deoxycorticosterone, and with androgen activity such as androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate [43].

In all cases, the resistance appeared partial: none of the affected subjects completely lacked glucocorticoid activity [31, 45, 46]. The clinical spectrum of the condition ranges from completely asymptomatic to signs of severe hyperandrogenism and/or mineralocorticoid excess (hypokalemia, hypertension, fatigue, metabolic alkalosis) [2, 44, 45, 47-49]. Variable clinical phenotype

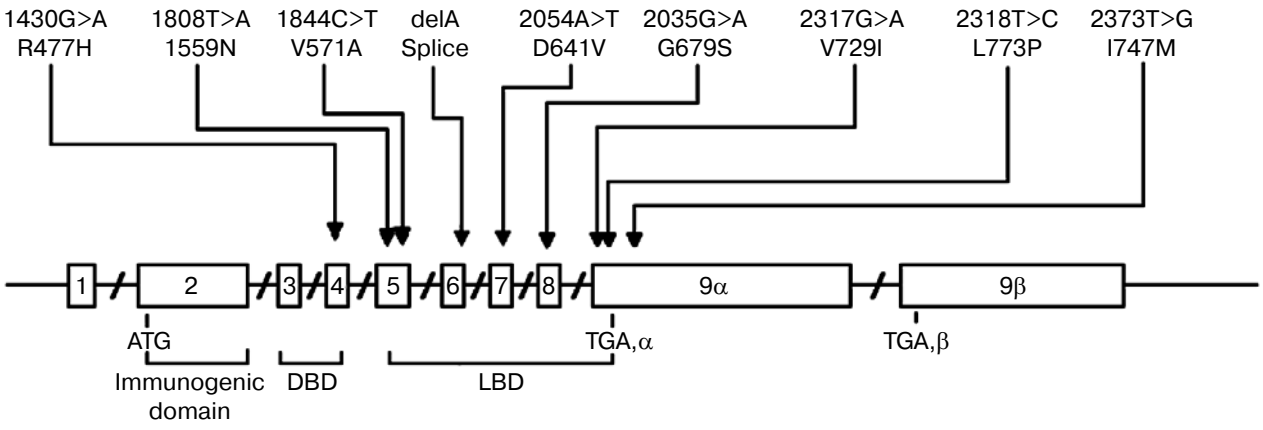

Fig. 2. Location of the known mutations of the glucocorticoid receptor (modified from [4]).

might be explained by different functional defects upon the glucocorticoid signal transduction pathway and the autosomal recessive or dominant transmission of the disorder [47]. Many of the patients present with hypertension, with or without hypokalemic alkalosis, as a result of elevated concentrations of cortisol and other salt-retaining steroids [50]. The clinical features of glucocorticoid resistance in females include hirsutism, acne, male pattern baldness, oligomenorrhea, oligoanovulation, irregular menses, and infertility [2]. Mendonca et al. [40] described a new phenotype, female pseudohermaphroditism and severe hypokalemia, caused by a homozygous inactivating mutation of the GR gene. This phenotype indicates that pre- and postnatal virilization can occur in females with the glucocorticoid resistance syndrome [40]. Boys may also present with isosexual precocity [51].

In recent decades, there has been an increasing interest in the role of endogenous glucocorticoids such as cortisol in the pathogenesis of metabolic syndrome. Studies in humans have suggested a positive association between obesity, hypertension, and insulin resistance, with alleles at the glucocorticoid receptor (GR) gene. Although several other mutations in the GR gene have been postulated as being relevant to the progression to type 2 diabetes and cardiovascular diseases, conflicting results makes it difficult to determine exactly what effect these GR variations have on metabolic syndrome incidence and progression [52]. Charmandari et al. [47] suggested that each of the hGRα mutations imparts different functional defects upon the glucocorticoid signal transduction pathway, which explains the autosomal recessive or dominant transmission of the disorder, but might only explain in part its variable clinical phenotype.

It is known that steroid hormone administration causes behavior changes. For this possibility, Feng et al. [53] investigated and found no association with puerperal psychosis or schizophrenia in five missense variants in the amino-terminal domain of the glucocorticoid receptor.

The main laboratory characteristics of cortisol resistance are markedly increased plasma concentrations of cortisol and ACTH, as well as elevated excretion of urinary free cortisol and total 17-hydroxycorticosteroids. ACTH levels are elevated and lead to increased adrenal production of androgens and DOC (deoxycorticosterone) [3]. In addition, these patients are resistant to suppression of cortisol with low-dose dexamethasone but respond to high doses [3]. Such laboratory findings are typical of patients with Cushing's disease, yet subjects with cortisol resistance do not present with any of the symptoms of this disorder. A useful clinical discriminatory test to differentiate this condition from Cushing's syndrome is to measure bone mineral density; this is preserved in patients with glucocorticoid resistance or even increased in female patients because of the androgen excess [3]. In addition, the circadian rhythm of ACTH and cortisol is intact (albeit at a high level) in patients with glucocorticoid resistance [44, 54].

The level of adrenal steroids including cortisol level is decreased with dexamethasone administration [39, 45]. Treatment with a dose of dexamethasone adequate to suppress ACTH (usually 3 mg/day) results in a fall in adrenal androgens and often returns plasma potassium and blood pressure to normal levels [3]. In the literature low dose dexamethasone therapy (1-1.5 mg/day) successful in female patients with acne and hirsutism has been documented [44].

In conclusion, glucocorticoid resistance is a rare familial or sporadic condition characterized by partial end-organ insensitivity to glucocorticoids. The clinical spectrum of the condition ranges from completely asymptomatic to severe hyperandrogenism and/or mineralocorticoid excess. The molecular basis of glucocorticoid resistance in several families and sporadic cases has been ascribed to mutations in the human glucocorticoid receptor-α (hGRα) gene, which impair the ability of the receptor to transduce the glucocorticoid signal.

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