Table 2. Mutations of the human glucocorticoid receptor gene causing Primary Generalized Glucocorticoid Resistance

Author (Reference)	Mutation position		Molecular mechanisms	Genotype	Phenotype
	cDNA	Amino acid			
Chrousos et al[19] Hurley et al[32] Charmandari et al[39]	1922 (A→T)	641 (D→V)	Transactivation ↓ Affinity for ligand ↓ (x 3) Nuclear translocation: 22 min Abnormal interaction with GRIP1	Homozygous	Hypertension Hypokalemic alkalosis
Karl et al[33]	4 bp deletion in exon-intron 6		hGRα number: 50% of control Inactivation of the affected allele	Heterozygous	Hirsutism Male-pattern hair-loss Menstrual irregularities
Malchoff et al[34] Charmandari et al[39]	2185 (G→A)	729 (V→I)	Transactivation ↓ Affinity for ligand ↓ (x 2) Nuclear translocation: 120 min Abnormal interaction with GRIP1	Homozygous	Precocious puberty Hyperandrogenism
Karl et al[31] Kino et al[35] Charmandari et al[39]	1676 (T→A)	559 (I→N)	Transactivation ↓ Decrease in hGR binding sites Transdominance (+) Nuclear translocation: 180 Abnormal interaction with GRIP1	Heterozygous	Hypertension Oligospermia Infertility
Ruiz et al[36] Charmandari et al[41]	1430 (G→A)	477 (R→H)	Transactivation ↓ No DNA binding Nuclear translocation: 20 min	Heterozygous	Hirsutism Fatigue Hypertension
Ruiz et al.[36] Charmandari et al[41]	2035 (G→A)	679 (G→S)	Transactivation ↓ Affinity for ligand ↓ (x 2) Nuclear translocation: 30 min Abnormal interaction with GRIP1	Heterozygous	Hirsutism Fatigue Hypertension
Mendonca et al[37] Charmandari et al[39]	1712 (T→C)	571 (V→A)	Transactivation ↓ Affinity for ligand ↓ (x 6) Nuclear translocation: 25 min Abnormal interaction with GRIP1	Homozygous	Ambiguous genitalia Hypertension Hypokalemia Hyperandrogenism
Vottero et al[38] Charmandari et al[39]	2241 (T→G)	747 (I→M)	Transactivation ↓ Transdominance (+) Affinity for ligand ↓ (x 2) Nuclear translocation ↓ Abnormal interaction with GRIP1	Heterozygous	Cystic acne Hirsutism Oligo-amenorrhea
Charmandari et al[40]	2318 (T→C)	773 (L→P)	Transactivation ↓ Transdominance (+) Affinity for ligand ↓ (x 2.6) Nuclear translocation: 30 min Abnormal interaction with GRIP1	Heterozygous	Fatigue Anxiety Acne Hirsutism Hypertension
Charmandari et al[42]	2209 (T→C)	737 (F→L)	Transactivation ↓ Transdominance (+) Affinity for ligand ↓ (x 1.5) Nuclear translocation: 180 min	Heterozygous	Hypertension Hypokalemia
McMahon et al[22]	2 bp deletion at nt 2318-9	773	Transactivation ↓ Affinity for ligand: absent No suppression of IL-6	Homozygous	Hypoglycemia Fatigability with feeding Hypertension

Table 2. (continued) Mutations of the human glucocorticoid receptor gene causing Primary Generalized Glucocorticoid Resistance

Author (Reference)	Mutation position		Molecular mechanisms	Genotype	Phenotype
	cDNA	Amino acid			
Nader et al[21]	2141 (G→A)	714 (R→Q)	Transactivation ↓ Transdominance (+) Affinity for ligand ↓ (x 2) Nuclear translocation ↓ Abnormal interaction with GRIP1	Heterozygous	Hypoglycemia Hypokalemia Hypertension Mild clitoromegaly Advanced bone age Precocious pubarche
Bouligand et al[43]	1405 (C→T)	469 (R→X)	Transactivation ↓ Ligand-binding sites ↓ No DNA binding No nuclear translocation	Heterozygous	Adrenal hyperplasia Hypertension Hypokalemia
Zhu Hui-juan et al[44]	1667 (G→T)	556 (T→I)	Not studied yet	Heterozygous	Adrenal incidentaloma
Roberts et al[45]	1268 (T→C)	423 (V→A)	Transactivation ↓ Affinity for ligand: N No DNA binding Nuclear translocation: 35 min Interaction with GRIP1: N	Heterozygous	Fatigue Anxiety Hypertension
Nicolaides et al[46]	1724 (T→G)	575 (V→G)	Transactivation ↓ Transrepression Affinity for ligand ↓ (x 2) Nuclear translocation ↓ Abnormal interaction with GRIP1	Heterozygous	Melanoma Asymptomatic daughters
Nicolaides et al[47]	2177 (A→G)	726 (H→R)	Transactivation ↓ Transrepression ↓ Affinity for ligand ↓ (x 2) Nuclear translocation ↓ Abnormal interaction with GRIP1	Heterozygous	Hirsutism, Acne, Alopecia, Anxiety, Fatigue Irregular menstrual cycles