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

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Mutation position</th>
<th>cDNA</th>
<th>Amino acid</th>
<th>Molecular mechanisms</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
</table>
| Chrousos et al\(^{19}\) | 1922 (A→T) | 1922 | 641 (D→V) | Transactivation ↓  
Affinity for ligand ↓ (x 3)  
Nuclear translocation: 22 min  
Abnormal interaction with GRIP1 | Homozygous | Hypertension  
Hypokalemic alkalosis |
| Hurley et al\(^{12}\) | | | | | | |
| Charmandari et al\(^{39}\) | 4 bp deletion in exon-intron 6 | | | | | |
| Karl et al\(^{33}\) | 1676 (T→A) | 559 | 559 (I→N) | Transactivation ↓  
Affinity for ligand ↓ (x 2)  
Nuclear translocation: 120 min  
Abnormal interaction with GRIP1 | Heterozygous | Hypertension  
Male-pattern hair-loss  
Menstrual irregularities |
| Malchoff et al\(^{34}\) | 2185 (G→A) | 729 | 729 (V→I) | Transactivation ↓  
Affinity for ligand ↓ (x 2)  
Nuclear translocation: 120 min  
Abnormal interaction with GRIP1 | Homozygous | Precocious puberty  
Hyperandrogenism |
| Charmandari et al\(^{39}\) | 1430 (G→A) | 477 | 477 (R→H) | Transactivation ↓  
No DNA binding  
Nuclear translocation: 20 min | Heterozygous | Hirsutism  
Fatigue  
Hypertension |
| Ruiz et al\(^{36}\) | 2035 (G→A) | 679 | 679 (G→S) | Transactivation ↓  
Affinity for ligand ↓ (x 2)  
Nuclear translocation: 30 min  
Abnormal interaction with GRIP1 | Heterozygous | Hirsutism  
Fatigue  
Hypertension |
| Mendonca et al\(^{37}\) | 1712 (T→C) | 571 | 571 (V→A) | Transactivation ↓  
Affinity for ligand ↓ (x 6)  
Nuclear translocation: 25 min  
Abnormal interaction with GRIP1 | Homozygous | Ambiguous genitalia  
Hypertension  
Hypokalemia  
Hyperandrogenism |
| Charmandari et al\(^{39}\) | | | | | | |
| Vottero et al\(^{38}\) | 2241 (T→G) | 747 | 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 | 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 | 737 (F→L) | Transactivation ↓  
Transdominance (+)  
Affinity for ligand ↓ (x 1.5)  
Nuclear translocation: 180 min | Heterozygous | Hypertension  
Hypokalemia |
| McMahon et al\(^{32}\) | 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

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| Nader et al21        | 2141   | 714 (R→Q) | Transactivation ↓                                       | Heterozygous| Hypoglycemia
|                      |        |            | Transdominance (+)                                      |            | Hypokalemia
|                      |        |            | Affinity for ligand ↓ (x 2)                             |            | Hypertension
|                      |        |            | Nuclear translocation ↓                                 |            | Mild clitoromegaly
|                      |        |            | Abnormal interaction with GRIP1                         |            | Advanced bone age
|                      |        |            | Affinity for ligand ↓ (x 2)                             |            | Precocious puberty
|                      |        |            | No DNA binding                                          |            |
|                      |        |            | No nuclear translocation                                |            |
| Bouligand et al43    | 1405   | 469 (R→X) | Transactivation ↓                                       | Heterozygous| Adrenal hyperplasia
|                      |        |            | Ligand-binding sites ↓                                  |            | Hypertension
|                      |        |            | No DNA binding                                          |            | Hypokalemia
|                      |        |            | No nuclear translocation                                |            |
| Zhu Hui-juan et al44 | 1667   | 556 (T→I) | Not studied yet                                         | Heterozygous| Adrenal incidentaloma
| Roberts et al45      | 1268   | 423 (V→A) | Transactivation ↓                                       | Heterozygous| Fatigue
|                      |        |            | Affinity for ligand: N                                  |            | Anxiety
|                      |        |            | No DNA binding                                          |            | Hypertension
|                      |        |            | Nuclear translocation: 35 min                            |            |
| Nicolaides et al46   | 1724   | 575 (V→G) | Transactivation ↓                                       | Heterozygous| Melanoma
|                      |        |            | Transrepression ↓                                       |            | Asymptomatic daughters
|                      |        |            | Affinity for ligand ↓ (x 2)                             |            |
| Nicolaides et al47   | 2177   | 726 (H→R) | Transactivation ↓                                       | Heterozygous| Hirsutism, Acne
|                      |        |            | Transrepression ↓                                       |            | Alopecia, Anxiety
|                      |        |            | Affinity for ligand ↓ (x 2)                             |            | Fatigue
|                      |        |            | Nuclear translocation ↓                                 |            | Irregular menstrual cycles

The hGRαV423A displayed reduced transcriptional activity, had a significant reduction in its ability to bind to DNA sequences within the promoter regions of glucocorticoid-target genes, and required a longer time to translocate into the nucleus following exposure to dexamethasone, compared with the wild-type receptor (Figure 4A and 4B). Structural biology studies highlighted the critical role of the hydrophobic valine at this position within the first zinc finger of the DBD of the receptor. The hydrophobic nature of valine at amino acid position 423 protects the four zinc-binding cysteines (C421, C424, C438, and C441) from the destructive diffusion of water molecules. The substitution of valine by alanine results in water diffusion into the ion-binding region of the mutant receptor and causes reduced binding of the mutant receptor hGRαV423A to GREs.45

The second mutation in the NR3C1 gene was identified in a 70-year-old man and his two daughters, who had increased urinary free cortisol excretion and showed resistance of the HPA axis to dexamethasone suppression without any symptoms or signs suggestive of Cushing syndrome.46 Sequencing of the NR3C1 gene revealed a substitution of valine (V) by glycine (G) at amino acid 575 in the LBD of the receptor. Compared with the wild-type receptor, the hGRαV575G had 50% lower affinity for dexamethasone, displayed reduced transactivation of glucocorticoid-responsive genes, had a 2.5-fold delay in nuclear translocation, and interacted with the GRIP1 coactivator mostly through its AF-1