Glucocorticoid receptor gene polymorphisms in hereditary angioedema with C1-inhibitor deficiency

Zsuzsanna Zotter 1,2†, Zsolt Nagy 3,4†, Attila Patócs 4, Dorottya Csuka 1, Nóra Veszeli 1, Kinga Viktória Köhalmi 1 and Henriette Farkas 1*

Abstract

Background: Hereditary angioedema caused by C1-inhibitor deficiency (C1-INH-HAE) is a rare, autosomal dominant disorder. C1-INH-HAE is characterized by edema formation, which may occur in response to stress. The individual’s response to stress stimuli is partly genetically determined. Activation of the hypothalamic–pituitary–adrenal axis results in the release of cortisol. In turn, the secreted glucocorticoids affect the metabolism, as well as the cardiovascular and immune systems. We hypothesized that changes in serum cortisol level and polymorphisms of the glucocorticoid receptor (GR) modify the individual sensitivity to stressor stimuli of C1-INH-HAE patients.

Results: We compared the response to stress with Rahe’s Brief Stress and Coping Inventory of 43 C1-INH-HAE patients, 18 angioedema patients and 13 healthy controls. 139 C1-INH-HAE patients and 160 healthy controls were genotyped for glucocorticoid receptor polymorphisms BclI, N363S and A3669G. Serum cortisol levels were determined during attacks and during symptom-free periods in 36 C1-INH-HAE patients. The relationships between clinical, laboratory data and GR SNPs (Single Nucleotide Polymorphisms) were assessed using ANOVA. C1-INH-HAE patients have decreased coping capabilities compared to healthy controls. Cortisol levels were significantly higher during attacks than in symptom-free periods (p = 0.004). The magnitude of the elevation of cortisol levels did not show a significant correlation with any clinical or laboratory data. Among the C1-INH-HAE patients, the carriers of the A3669G allele had significantly lower cortisol levels, and increased body mass index compared with non-carriers.

Conclusions: The higher cortisol level observed during attacks may reflect the effect of a stressful situation (such as of the attack itself), on the patients’ neuroendocrine system. In A3669G carriers, the lower cortisol levels might reflect altered feedback to the hypothalamic–pituitary–adrenal axis, due to decreased sensitivity to glucocorticoids.

Keywords: Hereditary angioedema, C1-inhibitor deficiency, Trigger factor, Emotional stress, Coping, Glucocorticoid polymorphisms, Glucocorticoid sensitivity
by the frequency of edematous attacks, subjective de-
scribed attack severity and the need of on demand
C1-INH substitution.

The factors, which may trigger an attack, include infec-
tions, emotional stress, physical exertion, trauma, invasive
medical procedures, menstruation, and contraceptive use,
as well as treatment with certain medications (i.e. ACE-
inhibitors). In our recent study, we found that emotional
stress is the most common trigger factor of attacks [6].
Chronic stress as a general risk factor for the develop-
ment of several diseases; it can also modify disease ac-
tivity [7–10].

Stressor stimuli activate the hypothalamic–pituitary–
adrenal (HPA) axis, and result in the release of mineralo-
dand glucocorticoids (GCs). The sustained elevation of
glucocorticoid (GC) levels has been associated with hyper-
tension, weight gain, glucose intolerance, and hypertrigly-
ceridaemia. GCs exert their diverse actions through the
GC receptor (GR), which is ubiquitously expressed in
many tissues and cell types [11]. Differences in individ-
ual glucocorticoid sensitivity may influence stress re-
activity. Furthermore, altered glucocorticoid sensitivity
has been shown to modify the manifestations of several
diseases [12–14]. A few polymorphisms in the GR gene
are known to modify glucocorticoid sensitivity. The BclI
(rs41423247), a restriction fragment length polymorphism
(RFLP), results from an intronic region (C/G) nucleotide
substitution associated with increased glucocorticoid
sensitivity, as well as with increased abdominal obesity,
greater body mass index (BMI), decreased insulin sensi-
tivity and dyslipidaemia [15, 16]. The BclI polymorphism
has been implicated in the pathogenesis or onset of vari-
ous diseases [12–14, 17, 18]. In the central nervous sys-
tem, it has been linked to mood disorders and to the
responsiveness of the HPA axis [19, 20].

The N363S (rs6195) polymorphism in exon 2 of the
GR gene, the (A/G) substitution causes an asparagine-to-
serine change, associated with enhanced glucocorticoid
sensitivity [21]. The results regarding the relationship of
autoimmune diseases and carrier status are controversial
[11]. This polymorphism has been described to modify
disease symptoms patients with congenital adrenal hyper-
plasia (CAH), and may be involved in the pathogenesis of
bilateral adrenal adenomas [22, 23]. The A3669G (GR-9ß,
rs6198) polymorphism is located in the 3’ untranslated
region of the GR gene. The (A/G) nucleotide substitu-
tion destabilizes the mRNA and causes a shift to the
stabilization of the GRß (glucocorticoid receptor beta)
splicing variant. The GRß isoform exerts a dominant,
negative activity on the GRα (glucocorticoid receptor
alpha) function, and the altered GRα/GRß ratio may lead
to relative glucocorticoid resistance [24]. The A3669G
polymorphism has been linked to a more active immune
system [11], and to the development of rheumatoid
arthritis [25]. The A3669G SNP was also attributed a role
to bipolar diseases and depressive disorders [26, 27].

In this study, we investigated whether the clinical
manifestations of C1-INH-HAE may be different in carri-
ers of the three single nucleotide polymorphisms
(SNP) of the GR gene because these SNPs have been
associated with altered GC sensitivity. We hypothesized
that they might have a role in mediating the effects of
emotional stress on edema formation in patients with
C1-INH-HAE, during attacks in the first place.

Methods

Patients

C1-INH-HAE group: All subjects had been diagnosed
and receiving regular follow-up care at the Hungarian
Angioedema Center. In each patient, we established the
diagnosis of C1-INH-HAE according to standard clinical
and laboratory criteria (positive family history, clinical
symptoms of angioedema, low functional C1-INH level,
low C4, normal C1q). During the scheduled visits, the
time of occurrence, location, and severity of the edema-
tous episodes were recorded along with the on demand
therapy (e.g. C1-INH concentrate, icatibant) administered
to relieve the attack. All these information was taken into
account to modify long-term prophylaxis as necessary.
Further, the concomitant medications taken on a regular
basis and accompanying disorders were recorded, and the
patients’ body height and weight were checked on these
occasions.

The angioedema group comprised patients with angio-
edema, a negative family history, and normal C4, C1q,
C1-INH antigen levels and functional activity.

Healthy controls: All had been referred for routine med-
cal check-up, and volunteered for the study by giving
informed consent. The healthy controls did not have
any known disease (C1-INH deficiency was excluded by
complement testing).

The study was approved by the institutional review
board of Semmelweis University of Budapest. Informed
consent was obtained from the subjects in accordance
with the Declaration of Helsinki.

Evaluation of the response to stress

The response of the subjects to stress was measured
with Rahe’s Brief Stress and Coping Inventory [28]. This
instrument is used to categorize the population tested
into four subsets, according to subjectively experienced
stress level and coping capabilities. The test was completed
by 43 patients diagnosed with C1-INH-HAE (mean age:
38.00 years, SD: 16.87 years; 22 females and 21 males), by
18 patients showing angioedematous symptoms without
C1-INH deficiency (mean age: 48.00 years, SD: 19.56 years,
15 females and 3 males), and 13 healthy controls. Statistical
analysis was performed with the Kruskal-Wallis test.
Genotyping
We genotyped 139 patients diagnosed with C1-INH-HAE (mean age 38.9 years, range: 5–84 years, 76 females and 63 males). A Hungarian control population consisting of 160 healthy individuals was used for comparison as regards the prevalence of GR SNPs. Total genomic DNA was isolated from peripheral blood with a commercially available DNA isolation kit (QiAmp DNA Blood Mini Kit (Qiagen), according to the manufacturer’s instructions. The BclI and N363S polymorphisms were detected with allele-specific polymerase chain reaction (PCR), as described previously [14, 29]. The A3669G polymorphism was measured with a pre-designed TaqMan SNP Assay (C_8951023_10) (Applied Biosystems, LifeTechnologies), by real-time PCR, according to the recommended protocol, on a 7500 Fast PCR System (Applied Biosystems, LifeTechnologies).

Hormonal evaluation
Blood samples were collected from patients hospitalized (to the Semmelweis University, 3rd Department of Internal Medicine) for an edematous attack. During the attack-free period, morning fasting blood samples were obtained from these patients between 8:00 and 11:00 AM at the Hungarian Angioedema Center of the 3rd Department of Semmelweis University. Blood cortisol levels were measured during edematous attacks in 36 C1-INH-HAE patients. The blood samples were obtained by antecubital venipuncture. The samples were stored refrigerated (at −70 °C) until the measurement of serum cortisol levels and of C1-INH activity. Total cortisol levels in the plasma were determined by electrochemiluminescence immunoassay (Elecsys Immunoanalyser System, Roche). The functional level of the C1-inhibitor was determined with an enzyme immunoassay kit (Quidel, USA).

Statistical analysis
The allele frequencies of GR polymorphisms in C1-INH-HAE patients and in healthy controls were compared with Pearson’s χ² or Fisher’s exact test. The Hardy-Weinberg equilibrium was calculated for all polymorphisms. The associations between carrier status for polymorphisms and clinical or hormonal data were analyzed with ANOVA, and with the Kruskal-Wallis, or t-tests. We also performed statistical power analysis with a tool available online (https://www.dssresearch.com/Knowledge Center/toolkitcalculators/statisticalpowercalculators.aspx). Statistical power over 80%, and a p-value less than 0.05 were considered significant.

Results
The evaluation of response to stress
We did not find significant differences among the stress responses as measured with the Rahe’s Brief Stress and Coping Inventory tests in patients diagnosed with C1-INH-HAE, in angioedematous patients (without C1-INH deficiency), and healthy controls, using the Kruskal-Wallis one-way analysis of variance test (p = 0.1725). Reported coping capabilities differed significantly among the study populations (p = 0.0027). See Fig. 1.

Hormonal evaluation
Serum total cortisol levels were significantly (p = 0.004) different in samples obtained from the same patient during an edematous attack, or in an attack-free period (Wilcoxon matched pairs test) (Fig. 2). In particular, mean total cortisol level in the serum was 9.679 ug/dl (SD 4.68) during an attack-free period, and 14.89 ug/dl (SD 11.58) during an attack. Similarly, C1-INH activity was significantly (p < 0.0001) higher during attacks. While mean C1-INH activity was 22.88% (SD 18.98) in attack-free periods, it increased to 48.18% (SD 24.81) during attacks (Fig. 2). We did not detect a significant correlation between the changes of cortisol level and of C1-INH activity.

GR polymorphisms
There was no difference between the two populations as regards the allele frequencies of the N363S, BclI and A3669G polymorphisms (Table 1). The A3669G homozygous carrier state was significantly lower in the C1-INH-HAE group compared to healthy controls (Statistical power: 71.4%).

The association between A3669G polymorphism and cortisol levels in C1-INH-HAE patients
We grouped A3669G heterozygous and homozygous patients as A3669G carriers because of the low number of homozygous patients. Mean serum cortisol level was lower in carriers of the A3669G polymorphism compared to non-carriers (7.3 ± 3.3 vs. 10.9 ± 4.81, p = 0.0173; statistical power: 99.9%) (Fig. 3). Moreover the cortisol levels were lower during attack also in the carrier group; however, this difference did not reach significance (p = 0.0653).

In four patients, the attack was localized to the upper airway mucosa (pharynx and larynx) and caused obstruction. Such a symptom is a rather intense stressor and hence it may mask the impact of the polymorphism.

Therefore, we re-analyzed cortisol levels without the results of these patients. In A3669G carriers, lower basal cortisol levels remained significant (6.76 ± 3.14 vs. 10.96 ± 3.46, p = 0.013, statistical power: 92.9%). Meanwhile the difference between the steroid levels measured in the two groups during attacks had become significant (8.22 ± 2.64 vs. 18.34 ± 13.0394, p = 0.0148, statistical power 91.7%). Based on the previously mentioned hypothesis, patients who experienced severe attacks were also disregarded, but the difference between carrier and non-carrier groups nevertheless remained significant. Along similar
considerations, we did not take into account the attacks rated severe by the patients themselves. Notwithstanding this, we found a significant difference between the two groups (8.94 ± 2.3 vs. 16.91 ± 9.4, p = 0.0204, statistical power 85.8%) (Fig. 3).

The change from baseline of the cortisol levels measured during edematous attacks was smaller in the A3669G carrier group compared with non-carriers, but this difference did not reach significance (1.00 ± 3.04 vs. 6.85 ± 14.40, p = 0.057).

We also found that A3669G carriers had significantly higher BMI values, whereas hypertension was more common in the group of BclI homozygous carriers, compared with non-carriers (Table 2). We did not find any association between the investigated polymorphisms and any other clinical variable (the initial onset of attacks, the frequency of edematous episodes, C1-INH consumption). There were no gender-specific associations between carrier status and hormonal levels.

Discussion
In this study, we showed that stress response is intact in patients with C1-INH-HAE, although the reported coping capabilities differed significantly among the subsets of the study population. The lifelong management of any chronic and/or life-threatening disease requires considerable mental strength [30]. This might have contributed to the C1-INH-HAE-patients’ propensity for depression. The latter we have investigated in a previous study, the findings of which are in agreement with those published by Fouche et al. [31].

During stress, activation of the HPA axis results in the elevation of stress hormone levels: the serum concentrations of cortisol and of catecholamines reflect the activation of HPA axis. In our patient population, basal cortisol level was lower in C1-INH-HAE patients carrying the A3669G polymorphism. This SNP increases the stability of the splicing variant GRβ [24], which inhibits the function of GRα. Our results are consistent with
those reported by van Schoor et al., who found reduced serum fasting cortisol levels in female carriers of the A3669G polymorphism, compared with homozygous carriers of the wild type [17]. In stressful situations, the elevation of the cortisol levels of C1-INH-HAE patients during an edematous attack might result from the activation of HPA axis. This offers a possible, alternative explanation for the increase of white blood cell count during attacks described previously by our study group [32], which previously has been attributed to haemoconcentration. Remarkably, during non-severe attacks, carriers of the A3669G polymorphism had lower cortisol levels, and exhibited a smaller elevation of serum cortisol level than non-carriers. This suggests blunted responsiveness of the HPA axis – in agreement with the findings by Kumsta et al. These authors reported higher awakening

| Table 1 Minor allele frequency and carrier state for GR polymorphisms in C1-INH-HAE patients and in healthy controls |
|---|
| Polymorphism | C1-INH- HAE | Healthy control group | $p$ value |
|---|---|---|---|
| N363S | | | |
| Minor allele frequency | 0.05 | 0.031 | 0.78 |
| Heterozygous carriers (+/−) | 13 (9.3%) | 10 (6.3%) | 0.77 |
| Homozygous carriers (+/+ | - | - | - |
| Non-carriers | 126 (90.7%) (96.7%) (90.7%) | 150 (93.7%) | 0.77 |
| BclI | | | |
| Minor allele frequency | 0.36 | 0.35 | 0.87 |
| Heterozygous carriers (+/−) | 53 (38.1%) | 82 (51.3%) | 0.08 |
| Homozygous carriers (+/+ | 24 (17.3%) | 16 (10%) | 0.24 |
| Non-carriers | 62 (44.6%) | 62 (38.7%) | 0.72 |
| A3669G | | | |
| Minor allele frequency | 0.15 | 0.22 | 0.11 |
| Heterozygous carriers (+/−) | 39 (28.1%) | 48 (30%) | 0.99 |
| Homozygous carriers (+/+ | 2 (1.4%) | 12 (7.5%) | 0.04 |
| Non-carriers | 98 (70.5%) | 100 (62.5%) | 0.42 |

Minor allele frequency and carrier state for GR polymorphisms in C1-INH-HAE patients and in healthy controls. The $p$ value was adjusted with Bonferroni correction. Statistically significant values are marked by bold typeset.
ACTH and salivary cortisol levels after dexamethasone administration in male A3669G carriers [33]. Remarkably, they also found that healthy male carriers of the A3669G minor allele showed the highest ACTH and cortisol levels in response to social stress; however this observation was not confirmed by a subsequent study in adolescents [33, 34]. These somewhat controversial results on the association between polymorphisms and cortisol levels under stress may be related to the differences in the study populations and stressors. Nevertheless, there is strong evidence that polymorphisms in the GR gene may modify the responsiveness of the HPA, along with individual stress responses [19]. Together, these data confirm that the A3669G carrier state is associated with relative glucocorticoid resistance during activation of the HPA axis. In C1-INH-HAE patients, edematous attacks are a chronic source of stress, permanently elevated populations.

### Table 2 Clinical and metabolic parameters of C1-INH-HAE patients in relation to the investigated GR polymorphisms

| GR Polymorphism | Non-carriers | Carriers | Heterozygous Carriers | Homozygous Carriers |
|-----------------|-------------|---------|----------------------|---------------------|
| N363S           | n = 94      | n = 12  | n = 51               | n = 39              |
|                 | (5f + 40 m) | (5f + 7 m) | (20f + 19 m)         | (8f + 8 m)          |
| Age (mean ± SD) | 39.88 ± 18.04 | 32.54 ± 11.88 | 35.02 ± 17.84       | 42.33 ± 15.99      |
| Onset of the initial attack (age) (mean ± SD) | 12.23 ± 9.51 | 8.08 ± 5.68 | 11.71 ± 11.34 | 11.18 ± 6.58 |
| Number of attacks /year (mean ± SD) | 8.4 ± 11.2 | 119 ± 13.3 | 10.2 ± 13.6 | 7.4 ± 9.9 |
| Average C1-INH consumption (amp/year) (mean ± SD) | 1.6 ± 3.5 | 2.4 ± 3.9 | 1.8 ± 4.0 | 1.6 ± 3.1 |
| BMI (kg/m²) (mean ± SD) | 24.99 ± 5.55 | 27.29 ± 5.39 | 24.17 ± 5.56 | 25.99 ± 5.21 |
| Prevalence of hypertension (%) | 18 | 8.33 | 7.80* | 17.95 |
| Prevalence of diabetes (%) | 5.3 | 0% | 3.9 | 5.13 |

Clinical and metabolic parameters of C1-INH-HAE patients in relation to the investigated GR polymorphisms. Results are mean ± SD. Statistically significant values are marked by bold typeset. *p < 0.0001 statistical power 98.2%, **p = 0.0126, statistical power 84.6%.

**Abbreviations:** f female, m male.
glucocorticoid levels due to the chronic activation of the HPA axis may lead to the development stress-related disorders, e.g. dysfunction of the immune system, hypertension, diabetes and adverse cardiovascular events. Hypothetically alterations of HPA axis responsivity may influence these unfavourable outcomes of chronic stress, however the impact of GR polymorphisms on stress response needs further examinations, including the measurement of ACTH and prospective follow up of patients.

Stress responsiveness, and activation of the HPA axis are known to differ between the sexes [35]. Furthermore, Kumsta et al. found gender-specific differences in the modulation of the responsiveness of the HPA axis by GR polymorphisms [33]. However, we could not observe sex-specific associations in our study.

We found that the allelic frequencies of the investigated three polymorphisms in the GR gene (BclI, N363S, A3669G) did not differ significantly between C1-INH-HAE patients and healthy controls. Although the A3669G homozygous carrier state was significantly lower in C1-INH-HAE patients, the low statistical power rather indicate this finding a bias.

We could not detect any relationship between the investigated GR polymorphisms and the severity of edematous attacks (as regards attack frequency, and C1-INH consumption) in C1-INH-HAE patients. Furthermore, the during-attack elevation of C1-INH functional levels did not exhibit any correlation with cortisol levels. These data suggest that glucocorticoids are not involved in the mechanism of edema formation due to C1-INH deficiency.

Glucocorticoids play an important role in the regulation of metabolism. Polymorphisms in the GR gene have been previously linked with various clinical parameters [11]. In our C1-INH-HAE patients, the prevalence of hypertension was higher in carriers of the polymorphic BclI allele. BclI polymorphism has been implied with an increased response to glucocorticoids. Our results are in accord with earlier observations regarding the unfavourable effect of BclI polymorphisms on blood pressure in different patient populations [36–38]. Interestingly, carriers of the A3669G allele had increased BMI. This is rather intriguing, as lower serum cortisol levels are expected to protect the carriers against weight gain. This finding suggests a poor correlation among blood cortisol levels and metabolic parameters.

Conclusions
In summary, the examined polymorphisms of the GR gene are most likely not involved in the pathomechanism of C1-INH HAE. Minor allele carriers of the A3669G polymorphism have lower cortisol levels both in attack free periods, and during attacks. Possibly, this reflects a relative resistance against glucocorticoids on the level of the HPA axis. In contrast with this observation, we could not find any association between carrier state and disease severity in HAE patients. Further hormonal evaluations are necessary to clarify the impact of GR polymorphisms on the responsiveness of the HPA axis in C1-INH-HAE patients.
References

1. Farkas H. Current pharmacotherapy of bradykinin-mediated angioedema. Expert Opin Pharmacother. 2013;14(5):571–86.
2. Kaplan AP, Joseph K. Pathogenic mechanisms of bradykinin mediated diseases: dysregulation of an innate inflammatory pathway. Adv Immunol. 2014;121:1–86.
3. Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol. 2004;114(3 Suppl):S51–S531.
4. Bork K, Meng G, Staabach P, Harst J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med. 2006;119(3):267–74.
5. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy. 2016; doi:10.1111/all.13001.
6. Zotter Z, Csuka D, Szabo E, Czaller I, Nebenfuhrer Z, Temesszentandrasi G, et al. The influence of trigger factors on hereditary angioedema due to C1-inhibitor deficiency. Orphanet J Rare Dis. 2014;9(1):44.
7. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA. 2007;298(14):1685–7.
8. Mawdsley JE, Rampton DS. The role of psychological stress in inflammatory bowel disease. Neuroimmunomodulation. 2006;13(5–6):327–36.
9. Morell Dubois S, Carpenter O, Cottencin O, Queyrel V, Hachulla E, Hatron PY, et al. Stressful life events and periphraxis. Dermatology. 2008;216(2):104–8.
10. Peralta-Ramírez MI, Jiménez-Alonso J, Godoy-García JF, Perez-Garcia M. The effects of daily stress and stressful life events on the clinical symptomatology of patients with lupus erythematosus. Psychosom Med. 2004;66(5):788–94.
11. Manenschijn L, van den Akker EL, Lamberts SW, van Rossum EF. Clinical features associated with glucocorticoid receptor polymorphisms. An overview. Ann N Y Acad Sci. 2009;1179:79–98.
12. Bertalan R, Patocs A, Nagy B, Derzsy Z, Gullai N, Szappanos A, et al. Overrepresentation of the BclI polymorphism of the glucocorticoid receptor gene in pregnant women with HELLP syndrome. Clin Chim Acta. 2009;405(1–2):148–52.
13. Boyle B, Koranyi K, Patocs A, Liko I, Szappanos A, Bertalan R, et al. Polymorphisms of the glucocorticoid receptor gene in Graves ophthalmopathy. Br J Ophthalmol. 2008;92(1):131–4.
14. Szappanos P, Patocs A, Toke J, Boyle B, Sereg M, Majnik J, et al. BclI polymorphism of the glucocorticoid receptor gene is associated with decreased bone mineral density in patients with endogenous hypercortisolism. Clin Endocrinol (Oxf). 2009;71(5):636–43.
15. Geelen CC, van Greevenbroek MM, van Rossum EF, Schaper NC, Nijpels GT, Hart LM, et al. BclI glucocorticoid receptor polymorphism is associated with greater body fatness: the Hoorn and CODAM studies. J Clin Endocrinol Metab. 2013;98(3):E595–9.
16. Giordano R, Marzotti S, Berardelli R, Karamouzis I, Brizzetti A, D’Angelo V, et al. BCL1I polymorphism of the glucocorticoid receptor gene is associated with increased obesity, impaired glucose metabolism and dyslipidaemia in patients with Addison’s disease. Clin Endocrinol (Oxf). 2012;77(6):863–70.
17. van Schoor NM, Dennison E, Lips P, Utterlinde AG, Cooper C. Serum fasting cortisol in relation to bone, and the role of genetic variations in the glucocorticoid receptor. Clin Endocrinol (Oxf). 2007;67(6):871–8.
18. Fleury I, Primeau M, Doreau A, Costea I, Mohgrabi A, Sinnett D, et al. Polymorphisms in genes involved in the corticosterone response and the outcome of childhood acute lymphoblastic leukemia. Am J Pharmacogenomics. 2004;4(5):331–41.
19. Derijck RH, Derijk RH, Rahe RH, Haffmans J, Bloem M, et al. Functional polymorphism of the glucocorticoid receptor gene associated with mania and hypomania in bipolar disorder. Bipolar Disord. 2009;11(1):95–101.
20. Derijk RH, Derijk RH, Rahe RH, Haffmans J, Bloem M, et al. Functional polymorphism of the glucocorticoid receptor gene associated with mania and hypomania in bipolar disorder. Bipolar Disord. 2009;11(1):95–101.
21. Huizenga NA, Koper JW, De Lange P, Pols HA, Stolk RP, Burger H, et al. Detection of the Bcl I polymorphism of the glucocorticoid receptor gene by single-tube allele-specific polymerase chain reaction. J Steroid Biochem Mol Biol. 2006;100(4–5):161–6.
22. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med. 1999;48(11):1507–15.
23. Kobus R, Farkas H, Varga I, Toth M, et al. Detection of the Bcl I polymorphism of the glucocorticoid receptor gene by single-tube allele-specific polymerase chain reaction. J Steroid Biochem Mol Biol. 2006;100(4–5):161–6.
24. Derijk RH, Tolles RL. The Brief Stress and Coping Inventory: A Useful Stress Management Instrument. International Journal of Stress Management. Int J Stress Manag. 2002;9(2):61–70.
25. Derijk RH, Tolles RL. The Brief Stress and Coping Inventory: A Useful Stress Management Instrument. International Journal of Stress Management. Int J Stress Manag. 2002;9(2):61–70.
26. Derijk RH, Tolles RL. The Brief Stress and Coping Inventory: A Useful Stress Management Instrument. International Journal of Stress Management. Int J Stress Manag. 2002;9(2):61–70.
27. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. J Allergy Clin Immunol. 2004;114(3 Suppl):S51–S531.
28. Derijk RH, Schaaf MJ, Turner G, Datson NA, Vreugdenhil E, Cidlowski J, et al. A human glucocorticoid receptor gene variant that increases the stability of the glucocorticoid receptor beta isoform mRNA is associated with rheumatoid arthritis. J Rheumatol. 2001;28(11):2983–8.
29. van Oosten MJ, Dolhain RJ, Koper JW, van Rossum EF, Emonts M, Han KH, et al. Polymorphisms in the glucocorticoid receptor gene that modulate glucocorticoid sensitivity are associated with rheumatoid arthritis. Arthritis Res Ther. 2010;12(4):R159.
30. Fleury I, Primeau M, Doreau A, Costea I, Mohgrabi A, Sinnett D, et al. Polymorphisms in genes involved in the corticosterone response and the outcome of childhood acute lymphoblastic leukemia. Am J Pharmacogenomics. 2004;4(5):331–41.
31. Derijk RH, Schaaf MJ, Turner G, Datson NA, Vreugdenhil E, Cidlowski J, et al. A human glucocorticoid receptor gene variant that increases the stability of the glucocorticoid receptor beta isoform mRNA is associated with rheumatoid arthritis. J Rheumatol. 2001;28(11):2983–8.
32. van Oosten MJ, Dolhain RJ, Koper JW, van Rossum EF, Emonts M, Han KH, et al. Polymorphisms in the glucocorticoid receptor gene that modulate glucocorticoid sensitivity are associated with rheumatoid arthritis. Arthritis Res Ther. 2010;12(4):R159.
33. Spijker AT, van Rossum EF, Hoencamp E, Derijk RH, Haffmans J, Bloem M, et al. Functional polymorphism of the glucocorticoid receptor gene associates with mania and hypomania in bipolar disorder. Bipolar Disord. 2009;11(1):95–101.
34. Derijk RH, Schaaf MJ, Turner G, Datson NA, Vreugdenhil E, Cidlowski J, et al. A human glucocorticoid receptor gene variant that increases the stability of the glucocorticoid receptor beta isoform mRNA is associated with rheumatoid arthritis. J Rheumatol. 2001;28(11):2983–8.