Glucocorticoid receptor and HSD11B1 gene polymorphisms influence the therapy and therapy-associated morbidities in patients with Addison’s disease

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Background: Glucocorticoids are steroid hormones responsible for a specific answer to stress. They exert their effects through the glucocorticoid receptor (GR) which is located - without ligand - in the cytoplasm in a multi-protein complex. Upon ligand binding conformation changing and translocation to the nucleus occurs. Homodimers of the GR bind to DNA through a specific DNA sequences (GR-locus-specific response element) and stimulation of transcription of the expression of target genes containing GRE may occur. The gene of the glucocorticoid receptor map to 5q31, it contains 9 exons. More than 1000 GR gene polymorphisms were identified, the majority is located in intron sections. The most commonly studied SNPs of GR are N3635, Bcl8, and A2069G. Correlations were demonstrated between these polymorphisms and decreased or increased sensitivity to glucocorticoids. Some polymorphisms may affect the dose of the glucocorticoid replacement. The local, cell-type specific glucocorticoid effect is modulated by the function of the 11-β-hydroxysteroid dehydrogenase enzymes (11βHSD) responsible for the interconversion of cortisone and cortisol. The isoform 1 (11βHSD1) is a NAD(P)H dependent bidirectional enzyme, which mainly converts inactivates cortisone to active cortisol. The isoform 2 is responsible for the opposite reaction. Individual sensitivity against glucocorticoids and activity of the 11βHSD1 enzymes are at least partly determined by genetic factors, such as polymorphisms of the HSD11B1 gene, which maps to 19q13.41 and contains 6 exons. The rs4848840 polymorphism was located in the promoter region, and rs22086634 in the 3’ exon. For both SNPs various associations with clinical and laboratory parameters have been demonstrated.

P values of statistical analysis used for evaluation of the relationship between polymorphisms and laboratory parameters and therapeutic response of patients with Addison disease

Results: The allele frequency of N3635 polymorphism was higher in patients compared to the control group (8.5% vs. 3.1%; p=0.019). The homozygous carriers of the Bcl8 had significantly higher BMI compared to the heterozygous carriers (p=0.007, power:100%), and the need the total hydrocortisone equivalent supplementation dosage was significantly lower than in heterozygous or non-carriers (p=0.015). The disease appeared earlier in the A2069G polymorphism carriers (p=0.031). The BMI of the carriers of the rs4848840 polymorphism was significantly higher compared to non-carriers (31.46 vs. 24.46 kg/m², p=0.003), and the body weight adjusted supplementation dosage was significantly lower (0.294 vs. 0.409 mg/kg/day, p=0.01, power:87.5%). The rs22086634 polymorphism showed an association with the annual change in the T-score measured at the lumbar spine. In carriers a negative tendency while in non-carriers a positive tendency was observed (−0.065 vs. 0.115, p=0.01). Annual decrease in bone mineral density, T-score and Z-score at lumbar spine were significantly lower in rs4848840 carriers comparing to the non-carriers (p=0.01, 0.005 and 0.003, power: 92.3%, 90.3%, 96.2%). The effect of the rs22086634 polymorphism on BMI and bone score is kept in case of desamethasone non-takers, but none of these associations was detected in desamethasone treated patients. Females with the age over 50 years, the rs4848840 polymorphism had a beneficial effect on the bone values while in female patients below 50- 0 years, associated with body weight and BMI

Association between rs4848840 polymorphism of the HSD11B1 gene and the BMI and body weight adjusted supplementation dosage

Conclusion: In Hungarian patients with Addison’s disease the allele frequency of N3635 polymorphism was higher than in the control group. The disease manifests earlier in carriers of A2069G polymorphism, which may refer to the predisposing role of this SNP for adrenocortical insufficiency. The Bcl8 polymorphism in homozygous form significantly affects the dose requirement of the hormone replacement therapy, the higher BMI and lower need of supplementation does may confirm the sensitizing effect of this SNP against glucocorticoids. Carriers of the rs4848840 polymorphism had favorable changes in bone density compared to the non-carriers, but this effect was not pronounced in postmenopausal women. In premenopausal women, rs22086634 polymorphism associated with body weight. In Desamethasone treated patients correlations observed in case of HSD11B1 polymorphisms were not presented, suggesting that the 11-β-hydroxysteroid dehydrogenase enzyme is involved in the metabolism of exogenous administered hydrocortisone as well.

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