Glucocorticoid receptor polymorphisms do not affect the therapy efficiency in adult, Hungarian patients with 21-hydroxylase deficiency

Klára Koncz[1,2], Abigél Farkas[1], Marton Doleschall[3], Nikolette Szucs[1], Miklos Toth[1], Peter Igaz[1], Karoly Racz[1], Attila Patocs[1,2]

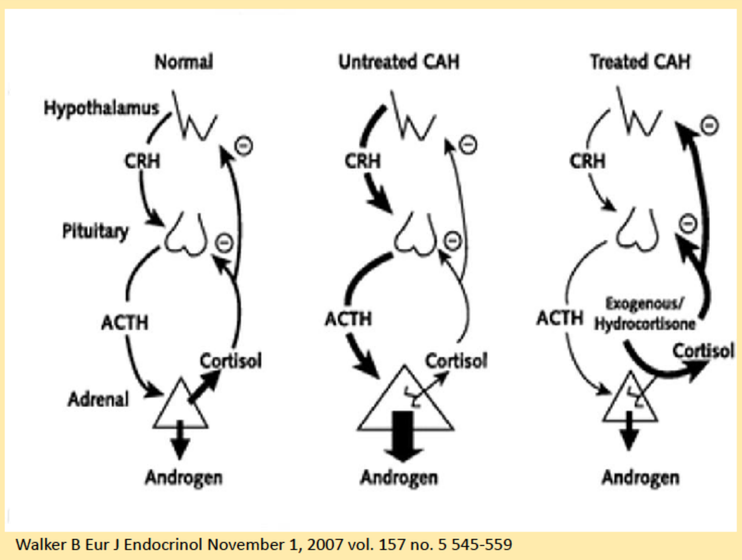
[1] 2nd Department of Medicine, Semmelweis University, Budapest, Hungary

[2] "Lendület" Hereditary Endocrine Tumors Research Group, Hungarian Academy of Sciences – Semmelweis University, Budapest, Hungary

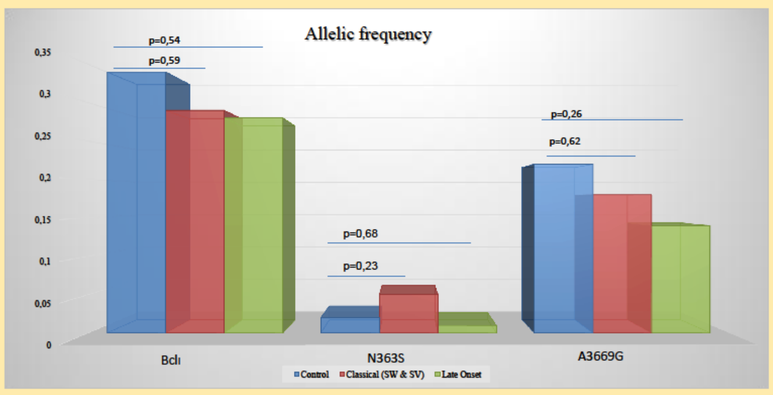
[3] Molecular Medicine Research Group, Hungarian Academy of Sciences – Semmelweis University, Budapest, Hungary

Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive inherited disorder caused by 21-hydroxylase deficiency in 95% of all cases. Two main clinical subtypes: the classical (manifested after birth or in early newborn period) and the late onset (LO) phenotype (manifested commonly during puberty) can be distinguished. The lifelong glucocorticoid (GC) supplementation is essential in therapy of these patients. Response and need for GC therapy is individual and partly genetically determined.



Walker B Eur J Endocrinol November 1, 2007 vol. 157 no. 5 545-559

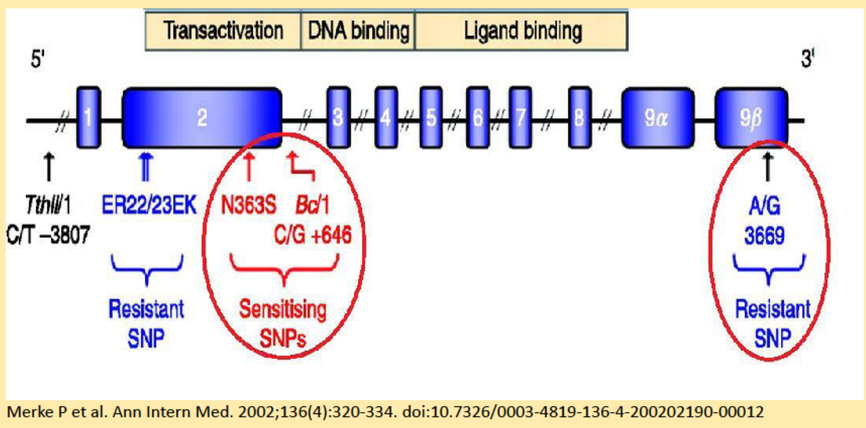


Parameters (n=93)		Classical CAH (n=54)				Late Onset CAH (n=39)		
		BclI	N363S	A3669G	CN of CYP21A2 (1 vs. 2)	BclI	A3669G	CN of CYP21A2 (1 vs. 2)
		P values of the statistical analysis (significancy level p≤0,05)						
Hormone levels	17-OHP (ng/dL)	0,232	0,250	0,706	0,594	0,918	0,52	0,967
	ACTH (pg/mL)	0,241	0,873	0,943	0,889	0,998	0,902	0,594
	Androstendion (ng/dL)	0,802	0,796	0,954	0,856	0,568	0,595	0,136
	DHEA (ng/dL)	0,956	0,195	0,676	0,199	0,546	0,976	0,017
	DHEAS (µg/dL)	0,758	0,681	0,434	0,175	0,014	0,636	0,829
	Cortisol (µg/dL)	0,459	0,871	0,422	0,887	0,685	0,209	0,452
	Aldosteron (ng/dL)	0,745	0,757	0,273	0,293	0,858	0,133	0,391
	Testosteron (ng/dL)	0,323	0,935	0,171	0,799	0,415	0,175	0,278
	Renin aktivitás (ng/mL/óra)	0,537	0,501	0,919	0,999	0,772	0,498	0,117
Therapy	Hydrocortison-ekvivalent/mg	0,503	0,672	0,454	**0,028***	0,786	0,246	**0,024***
	Hydrocortisonekvivalent-dose/weight	0,642	0,660	0,382	**0,02***	0,917	0,591	**0,03***
Radiology	CT morphology of the adrenal glands	0,291	0,546	0,402	0,063	0,803	-	0,054
Antropometry	BMI	0,817	0,864	0,942	0,894	0,440	0,335	0,531

Objective

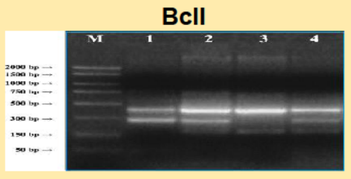
- Our aim was to study the effect of three well-known polymorphisms (SNPs) (BclI, N363S, A3669G) of the GR gene on therapy, clinical and laboratory parameters in adult Hungarian patients with 21-hydroxylase deficiency.
- To examine whether the copy number (CN) of the CYP21A2 gene influences the therapy in our patients.

SNPs of the GC receptor

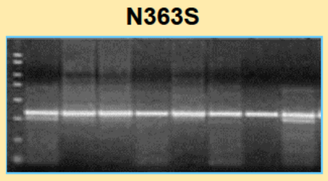


Merke P et al. Ann Intern Med. 2002;136(4):320-334. doi:10.7326/0003-4819-136-4-200202190-00012

BclI



N363S



Results

Allelic frequency of the GR polymorphisms did not differ from those observed in control population and did not associate with clinical, laboratory parameters or dosage of the GC supplementation. The copy number of the CYP21A2 in both groups of patients significantly negatively correlated with GC therapy **(p=0,03)**.

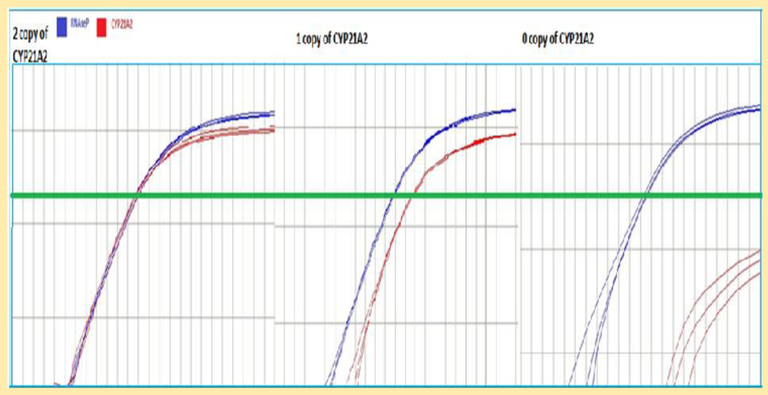
Discussion

The GR polymorphisms-related sensitivity against glucocorticoids is not a major factor in determination of the dose of glucocorticoid supplementation in Hungarian, adult patients with CAH. The CYP21A2 copy number measurement is a rapid, cheap and sensitive method for prediction the GC need in patients with 21-hydroxylase deficiency.

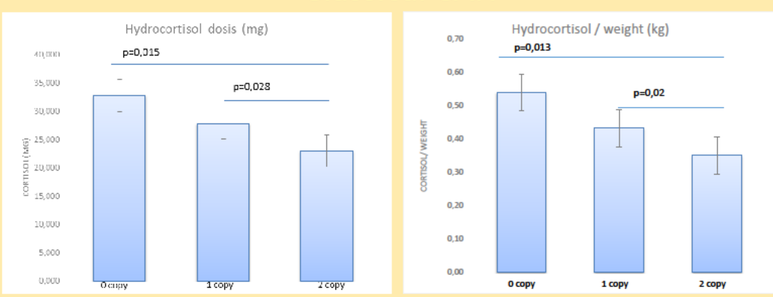
Patients and Methods

The diagnosis of 21-hydroxylase deficiency was based on clinical, laboratory and molecular genetic tests including the identification of the most common *CYP21A2* gene mutations and determination of the allelic copy number (CN) of the *CYP21A2* gene.

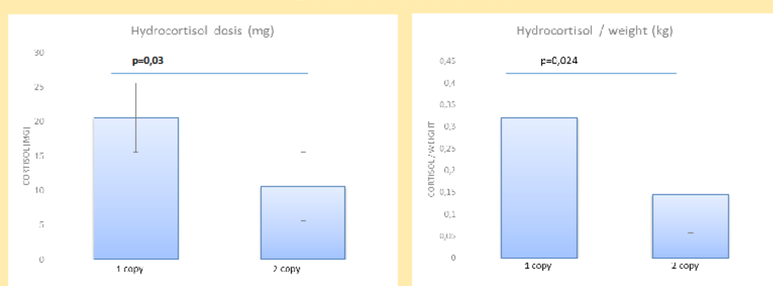
In 93 patients (54 classical: 34 salt wasting + 20 simple virilising and 39 late-onset, age: 28,8 13,7 years) with 21-hydroxylase deficiency the BclI and N363S polymorphisms were measured using allele-specific PCR, the A3669G polymorphism and the CN variations were detected by real-time qPCR. Allele frequencies of GR polymorphisms were compared to a Hungarian, control population (n=160). Association between GR SNPs and clinical, hormone laboratory and GC supplementation dosage was studied. For statistical analysis were used ANOVA, Student t test, Fisher's exact test and Chi-square test.



Classical CAH



Late onset CAH



The authors acknowledge the financial support from Hungarian Research Found (OTKA PD100648) and from National Development Agency (KTIA_AIK-2-2012-0010)