Genotype and phenotype in congenital adrenal hyperplasia

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Abstract

Genotype and phenotype of congenital adrenal hyperplasia (CAH)

<Pathophysiology>

- More than 90% of CAH is caused by 21-hydroxylase deficiency
- Based on the severity of the clinical manifestations, 21-hydroxylase deficiency is classified into classic form (further classified into salt-wasting and simple virilizing type) and nonclassic form

<Genotype of CAH>

- 21-hydroxylase genes, CYP21A2 and CYP21A1P

-mutations are due to structural similarity between two genes

-Intergenic recombination (95%) or spontaneous mutation (5%)

<Genotype and phenotype of CAH>

Mutations in the CYP21A2 gene->varying degrees of loss of 21-hydroxylase activity->different severity

- Complete inactivation of 21-hydroxylase activity -> salt-wasting phenotype
- Enzyme activity 0-2% -> simple virilizing phenotype
- Enzyme activity 10-75% -> nonclassic phenotype

But..

- There are only small number of studies investigating genotype-phenotype relationship, and most of them involve small number of patients
- Most of the studies did not investigate the long term complications such as short stature, obesity

Objective

In children with congenital adrenal hyperplasia, we investigated
- distribution of gene mutations
- the correlation between genotype and phenotype, including long-term complications

Materials & Methods

Inclusion

- **Retrospectively recruited from Jul 2009 to Jul 2019 in PUNCH**
- **Patients (age ≤16 yrs.) diagnosed as 21-hydroxylase deficiency**
- **21-hydroxylase deficiency confirmed by genetic testing**

Exclusion

- Follow up loss
- Other endocrine disorders such as type1 DM, thyroid disease
- Other diseases that can affect growth such as chromosomal abnormality
- Other diseases that require steroid use

Baseline clinical and laboratory profiles	Monitoring parameters
Initial presentation	Height, weight, BMI (kg/m^2)
Genetic testing	Tanner stage, bone age
Chromosome study	
Height, weight, BMI (kg/m^2)	17-OHP
Tanner stage, bone age	Renin
	Electrolyte
17-OHP	
Renin	US of Pelvis & kidney
Electrolyte	
	Glucocorticoid dose
US of Pelvis & kidney	Florinef dose
Glucocorticoid dose	
Florinef dose	

Results

Table 1. Clinical and laboratory findings

Variable	N (%)
No. of patients	**33**
Male	**16 (48.5)**
Age at diagnosis (months)	**11.1±48.3**
Current age (yr)	**8.5±6.4**
Initial presentation	
Ambiguous genitalia	13 (39.4)
Skin pigmentation	5 (15.2)
Initial 17-OHP (ng/mL)	**167.7±125.5**
Initial hyponatremia(<130 mmol/L)	**11(36.7)**
Genitalia surgery	**7(21.2)**
***Overweight/obese(BMI>85 percentile)**	**15(55.6)**
***Short stature /GH use**	**11(40.7)**
Hydrocortisone dose(mg/m^2)	**14.1±5.6**
Currently taking florinef	**28(84.8)**
Precocious puberty	**5()**

*Among patients >2 years of age (N=27)

Table 2. Allelic frequency of CYP21A2 mutation

Mutation	N(total 65 alleles)
c.293-13A/C>G	22
Large deletion/conversion	7
c.1066C>T	2
c.518T>A	10
8-bp deletion	1
complete deletion	6
c.92C>T	1
1450_1451insC	1
1451_1452delinsC	2
1451_1452delGGinsC	1
955C>T	2
188 A>T	1
c.874G>A	1
c.1069C>T	1
c.1069C>T+c.955C>T	1
c.515T>A+c.920_921ins(T)	1
exon6 mutation cluster	2
c.[1066C>T]+[Fusion]	1
C.332del(p.G111fs)	1
c.923dup(T)+c.955C>T	1

Table 3. Characteristics of high risk genotype patients

Sex	Phenotype	Genotype
Male	Salt wasting	Complete deletion/complete deletion
Male	Salt wasting	c.[1066C>T]+[Fusion](p.[Arg356Trp]+[Fusion])
Female	Salt wasting	exon 6 cluster/exon 6 cluster
Female	Salt wasting	complete deletion/complete deletion
Male	Salt wasting	c.1069C>T/c.1069C>T+c.955C>T
Male	Salt wasting	complete deletion/complete deletion

Table 4. Clinical features and complications

Complication	High risk genotype (N=6)	Non high risk genotype (N=27)	*P*
Salt wasting phenotype	6 (100.0%)	23(85.2%)	1.000
Genitalia surgery	1 (16.7%)	6 (22.2%)	1.000
Glucocorticoid dose (mg/kg)	16.2 ± 8.1	13.6 ± 5.0	0.313
Short stature/GH use	3 (50.0%)	8 (29.6%)	0.375
Overweight/obesity	1 (25.0%)	14 (60.9.%)	0.294

Conclusion

Total 33 children

- **Boy / girl = 16/17 pts**
- **Median age = 7.7 yrs**
- **High risk genotype = 6 pts**

•High proportion of the CAH pts had complications such as short stature(40.7%),overweight/obesity(55.6%)
•No significant differences in complications were observed between high-risk and non-high risk genotype