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GENOTYPE-PHENOTYPE CORRELATION AND CLINICAL FINDINGS IN 145 PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA: SINGLE CENTRE EXPERIENCE

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Background: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of adrenal steroidogenesis. CAH has 6 subgroups based on the affected enzyme. CAH due to 21-hydroxylase deficiency (21-OHD) accounts for 90-95% of the cases and is folowed by 11β-hydroxylase deficiency(11β-OHD) with a frequency between 0.2-8%. In a recent study, the frequency of classic 21-OHD in Turkish population is found out to be 1:7787 and the frequency of 11β-OHD 1:38935 .

Aim: The purpose of this study was to investigate genotype-phenotype correlation, clinical findings and long-term outcomes in patients with CAH due to11β-OHD and 21-OHD.

Subjects and Methods: The clinical records of 250 patients, followed in our clinic due to classic 21-OHD, non-classic 21-OHD and 11β-OHD were analyzed retrospectively. 145 genetically proven 21-OHD and 11β-OHD patients were included in this study. Endocrinological, clinical and molecular findings were recorded at presentation and follow-up. SPSS version 23 (Chicago, IL, USA) was used for statistical analyses.

Results: Some clinical findings of the patients are summarized in **Table 1.** Out of 145 patients diagnosed with CAH,122 had (83.6%) 21OHD, 66 salt wasting (SW),40 simple virilizing (SV),16 non-classic (NC); 23 (16.4 %) had 11β-OHD. SW 21-OHD was the most common and the earliest diagnosed CAH type. Consanguinity rate was high in all groups(47%, 45%, 25% and 69.6%, respectively). Due to severe virilization and late diagnosis, some of the XX patients were raised as male 3 (7%) in SW, 6 (21.4%) in SV, and 3 (25%) in 11-βOHD. Frequency of SGA was higher in SV and NC 21-OHD (p=0.048). While 29 different mutations were detected in 21 OHD, there were 12 different mutations in 11β-OHD. The most common mutation was IVS-2 not only in the all patients with 21-OHD, but also in the SW (34.7%)and SV(34.4%). Furthermore, the most common mutation in NC 21-OHD was p.V282L(34.4%) and p.Leu299Pro(25%) in 11-βOHD **(Figure 1).** Positive predictive value(PPV) for all 21-OHD patients was 78.4%. PPV in subgroups(according to enzyme activity) was 80.8% in group0 ('Null'=Enzyme activity:0%), 100% in groupA (1%), 62.5% in group B (1-2%), and 65.2% in group C (20-50%). There was no genotype-phenotype correlation in patients with 11-βOHD. 53.3% of patients in 21-OHD and 69.6% in 11-βOHD had reached the adult height. Mean value of the difference between the adult height and the target height for those, who have reached adult height SDS was -0.42±0.73 in SW; -0.91±1.35 in SV, - 0,14±0,94 in NC, and -0,71±1,43 in 11-βOHD. The pubertal spurt was not sufficient in classic 21-OHD **(Figure 2,3,4).** In logistic regression, the most important factor on short stature was height SDS at onset of puberty (p=0.018, B=3.058). The rate of early puberty was 24.2 % in SW, 40% in SV, 18.8% in NC 21-OHD and 56.5% in 11-βOHD(p=0.003 in all groups). Frequency of testicular adrenal rest tumour (TART) was 29.4% for SW, 33.3% for SV and 40% for 11-βOHD **(Figure 5).** While the obesity rate in all subgroups of 21-OHD(32.8% in SW,33.3% in SV, 31.2% in NC) was significantly high, it was low in the 11-βOHD (5%) (p=0.010).

Table 1. Clinical and laboratory findings of patients at presentation

		Group1 (Salt Wasting)	Group 2 (Simple Virilizing)	Group 3 (Non classic)	Group 4 (11 ßOHD)
Age at diagnosis (month)	*Mean±SD*	0.44±1.65	3.35±2.98	8.97±3.97	2.43±2.65
	Median (Range)	0.06 (0-5.80)	3.18 (0-10.5)	7.6 (3.09-16.9)	1.8 (0.02-11.2)
Gender*; n (%)*	**Male**	26 (39.4)	18 (45.0)	3 (18..8)	14 (60.9)
	Female	40 (60.6)	22 (55.0)	13 (81.2)	9 (39.1)
Genotype*; n (%)*	**XX**	23 (34.8)	12 (30)	3 (18.8)	11 (47.8)
	XY	43 (65.2)	28 (70)	13 (81.3)	12 (52.2)
Birthweight SDS (n=132)	*Mean±SD*	0.26±1.08	-0.27±1.39	-0.28±1.54	-0.22±1.02
	Median (Range)	0.1 (-2.4-3.1)	-0.3 (-3.2-1.9)	-0.04 (-3.7-1.7)	0.05 (-2.7-1.6)
	AGA	51 (82.3)	23 (63.9)	8 (57.2)	16 (80.0)
	SGA	3 (4.8)	9 (25.0)	3 (21.4)	3 (15.0)
	LGA	8 (12.9)	4 (11.1)	3 (21.4)	1 (5.0)
Weight SDS	*Mean±SD*	-0.98±1.36	0.41±1.42	0.54±2.16	1.43±2.18
	Median (Range)	-1.2 (-4.2-2.3)	0.4 (-3.4-2.8)	0.4 (-3.7-6.1)	2 (-3.3-4.2)
Height SDS	*Mean±SD*	-0.32±1.52	0.71±2.03	-0.02±1.38	1.77±2.40
	Median (Range)	-0.5 (-3.3-4.1)	0.5 (-3.9-5.3)	-0.06 (-2.3-3.3)	1.5 (-5.1-6.2)
BMI SDS	*Mean±SD*	-1.20±1.57	-0.07±1.31	0.50±1.83	0.62±1.65
	Median (Range)	-1.2 (-6.1-2.5)	-0.1 (-4.8-2.9)	0.7 (-2.9-4.2)	0.7 (-3.4-3.2)
	Low Weight	20 (30.8)	3 (7.5)	3 (18.8)	2 (8.7)
	Normal	35 (53.8)	30 (75)	7 (43,8)	11 (47.8)
	Overweight	3 (4.6)	3 (7.5)	2 (12,5)	5 (21.7)
	Obese	3 (4.6)	4 (10)	4 (25)	5 (21.7)
Prader stage*; n (%)* **(n=96)**	**Stage I**	0 (0)	2 (7.1)	13 (100)	0 (0)
	Stage II-III	17 (39.5)	10 (35.7)	0 (0)	6 (50)
	Stage IV-V	25 (58.1)	14 (50)	0 (0)	6 (50)
	Operated	1 (2.3)	2 (7.1)	0 (0)	0 (0)
Bone Age / Chrononlogical age	*Mean±SD*	1.52±0.88	1.84±0.51	1.25±0.20	2.41±0.67
	Median (Range)	1.2 (0.7-3.4)	1.8 (1.1-3.4)	1.3 (0.8-1.6)	2.3 (1.6-3.7)
	n	10	26	11	9
Consanguinity*; n (%)*		31 (47.0)	18 (45.0)	4 (25.0)	16 (69.6)
Target height SDS	*Mean±SD*	-0.78±0.77	-1.06±0.74	-1.29±0.70	-0.95±0.90
	Median (Range)	-0.8 (-2.9-1.1)	-1 (-2.8-0.3)	-1.4 (-2.3-0)	-1 (-2.7-0.7)
	n	62	37	14	21

BMI: body mass index, SDS: standard deviation score, TART: Testicular Adrenal Rest Tumour

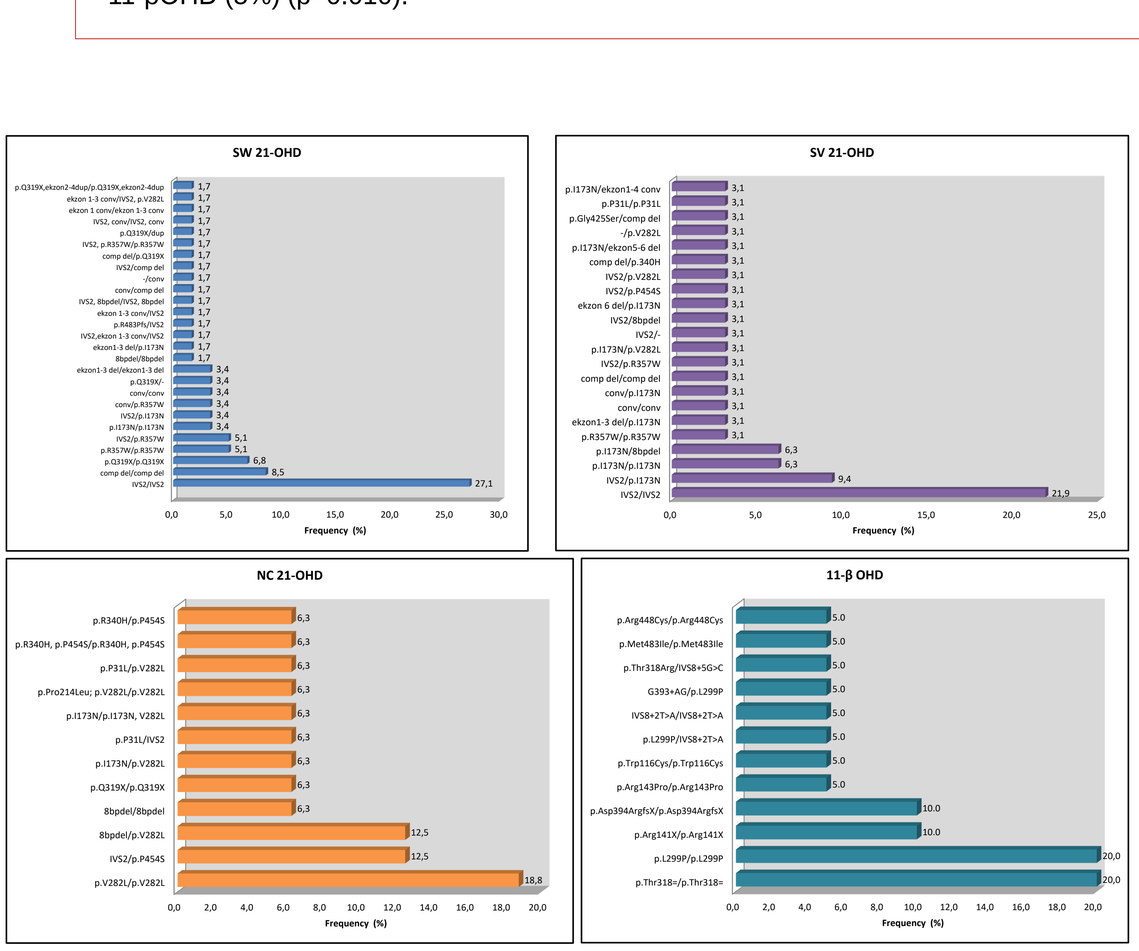


Figure 1. Molecular findings in the patients with CAH

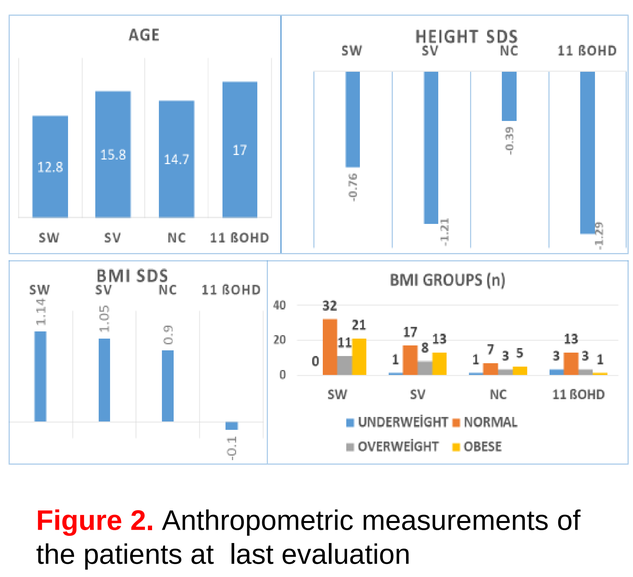


Figure 2. Anthropometric measurements of the patients at last evaluation

	SW (n:63)	SV (n:38)	NC (n:16)	11 ßOHD (n:22)
Patients reached adult height(n)	30 (47.6)	25 (65.8)	10 (62.5)	16 (72.7)
Patients didn't reached adult height(n)	33 (52.4)	13 (34.2)	6 (37.5)	6 (27.3)

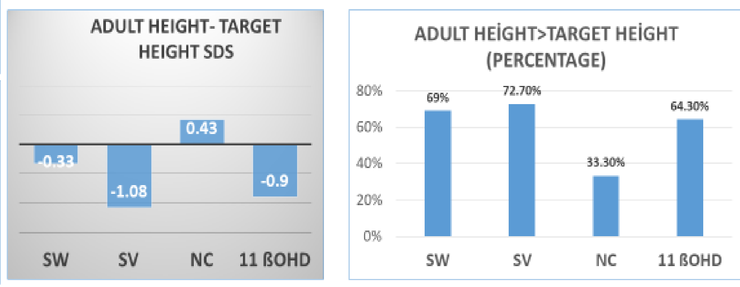


Figure 3. Growth of the patients with CAH

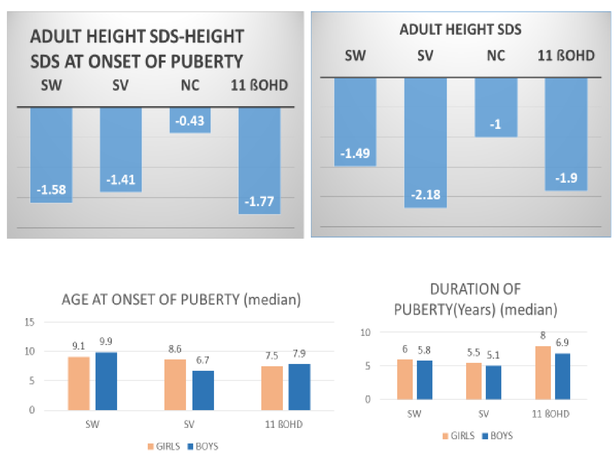
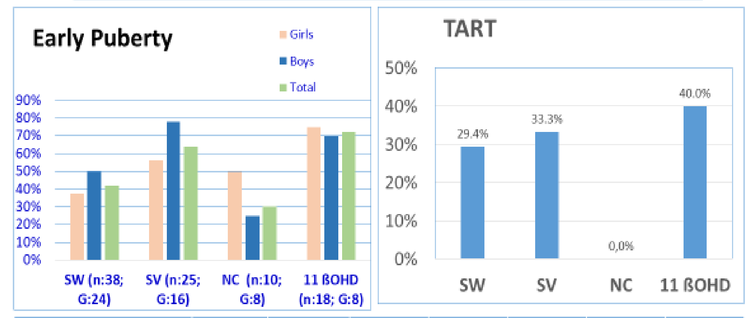


Figure 4. Pubertal development of the patients with CAH



LAST EVALUATION	Group1-Group2 P	Group1-Group3 P	Group1-Group4 P	Group2-Group3 P	Group2-Group4 P	Group3-Group4 P	ALL groups P
TART	1.000	1.000	0.683	1.000	1.000	1.000	0.933
Early puberty	0.014*	0.128	0.005**	0.182	0.761	0.056	0.003**

Figure 5. Early Puberty and TART in the patients with CAH

Conclusion

- ❑ In Turkey, where there is a high rate of consanguinty, the frequency of 11-βOHD is also high.
- ❑The rate of mutation diversity for both 21-OHD and 11-βOHD was very high.
- ❑The positive predictive value of genotype-phenotype correlation in 21-OHD was good.
- ❑The pubertal spurt was not sufficient in classical 21-OHD.
- ❑While the rate of obesity development was high in 21-OHD, the prevalence of TART and early puberty were higher in 11-βOHD.
- ❑Detection of the frequency of mutations may be important for early diagnosis, prenatal diagnosis and treatment, and establishing a screening strategy.

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