THE SPECTRUM OF GENETIC DEFECTS IN CONGENITAL ADRENAL HYPERPLASIA IN THE POPULATION OF CYPRUS: A retrospective analysis

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Abstract

BACKGROUND: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is worldwide the most common autosomal recessive disorder caused by defects in the CYP21A2 gene.

OBJECTIVE: The main objective of the study was to evaluate CAH in Cyprus over a 10 year period.

METHODS: All known patients were included in a population retrospective subset analysis of Cypriot patients with confirmed CAH and their clinical severity, genotype and sex were evaluated.

RESULTS: From 2007 to 2017, one hundred and twenty patients with various degrees of CAH were categorized and genotyped. Patients with the various degrees of the disorder were categorized in 4 mutation groups (null, A, B and C) based on their clinical and biochemical findings (Table 1).

Majority of patients (85.0%) belonged to the (NC)-CAH form and the disorder was more often diagnosed in females (71.7%).
The most severe classic SW form was identified in 11 neonates (9.2%). Seven (5.8%) children were also identified with the SV form and a median presentation age of 5 yrs (interquartile range (IQR) 3.2 – 6.5) (Table 2).

TABLE 1. **Null Group:** mutations with 0 enzyme residual activity **Group A:** mutations with minimal enzyme residual activity **Group B:** mutations with ~2% enzyme residual activity **Group C**: mutations with 30-60% enzyme residual activity. SW: salt-wasting; SV: simple virilising; NC: non-classical.

Group`	Genotype	No of patients	Phenotype SW	SV	NC
Null	p.Phe306insT+p.Val281Leu/ p.Phe306insT+p.Val281Leu	1	1		
	IVS2-13A/C>G/p.Gln318stop	1	1		
	DelEX1-3/DelEx1-3	2	2		
	DelEx1-3/p.Gln318stop	1	1		
A	IVS2-13A/C>G/IVS2-13A/C>G	5	4	1	
	IVS2-13A/C>G/DelEx1-3	1	1		
	Partial conv with CYP21P:-4C>T, 92C>T, 118T>C, 138A>C /DelEx1-3	1	1		
	IVS2-13A/C>G/Large del	1	1		
B	p.Ile172Asn/p.Ile172Asn	3		3	
	p.Ile172Asn/del CYP21A2	1		1	
C	p.Pro30Leu/p.Val281Leu	1		1	
	p.Pro30Leu/p.Pro30Leu	1		1	
	p.Val281Leu/p.Val281Leu	50			50
	p.Val281Leu/p.Pro453Ser	11			11
	p.Val281Leu/p.Val304Met	7			7
	p.Val281Leu/p.Gln318stop	5			5
	p.Val281Leu/p.Pro482Ser	3			3
	IVS2-13A/C>G/p.Val281Leu	7		3	4
	p.Val281Leu/p.Met283Val	1			1
	DelEX1-3/p.Val281Leu	4			4
	DelEX1-3/p.Val304Met	3			3
	p.Gln318stop/p.Pro453Ser	1			1
	p.Val304Met/ p.Gln318stop	1			1
	p.Gln318stop/p.Pro482Ser	1			1
	p.Ile172Asn/p.Val281Leu	1			1
	IVS2-13A/C>G/p.Met283Val	1			1
	p.Pro453Ser/ p.Pro453Ser	1			1
	p.Ile236Asn;p.Val237Glu;p.Met239Lys; p.Leu307frameshift/p.Val281Leu	2			2
	p.Val281Leu/30 kb del	1		1	
	p.Ile236Asn;p.Val237Glu;p.Met239Lys (Cluster E6)/p.Val281Leu	1			1
Total		120	12	11	97

TABLE 2. The type of the molecular defects with clinical and biochemical data in the patients with Classic CAH. PRA* = Plasma Renin Activity.

	Genotype	Form	Sex	Age of diagnosis	Clinical phenotype	17-OH P nmol/l basal	ACTH <60 pg/ml	Renin PRA* ng/ml/hr (02-2.8)
1	IVS2-13A/C>G/IVS2-13A/C>G	SW	F	neonate	Ambiguous genitalia - Prader 3	>75.7	1450	10.3
2	IVS2-13A/C>G/IVS2-13A/C>G	SW	F	neonate	Ambiguous genitalia - Prader 3	>75.7	1355	9.4
3	IVS2-13A/C>G/Large del	SW	F	neonate	Ambiguous genitalia - Prader 5	>75.7	103	3.1
4	IVS2-13A/C>G/p.Gln318stop	SW	F	neonate	Ambiguous genitalia	>75.7	N/A	32.3
5	p.Phe306insT+p.Val281Leu/ p.Phe306insT+p.Val281Leu	SW	F	neonate	Ambiguous genitalia - Prader 4	>75.7	>2100	12
6	IVS2-13A/C>G/IVS2-13A/C>G	SW	M	neonate	Adrenal crisis	>75.7	>2100	11.4
7	IVS2-13A/C>G/IVS2-13A/C>G	SW	M	neonate	Adrenal crisis	>75.7	> 2100	10.7
8	IVS2-13A/C>G/del Exons 1_3	SW	M	neonate	Adrenal crisis	>75.7	2352	9.8
9	del Exons 1_3/del Exons 1_3	SW	M	neonate	Adrenal crisis	>75.7	>2100	8.5
10	del Exons 1_3/del Exons 1_3	SW	M	neonate	Adrenal crisis	>75.7	>2100	10.5
11	del Exons 1_3/p.Gln318stop	SW	M	neonate	Adrenal crisis	>75.7	1680	11.3
12	p.Pro30Leu/p.Pro30Leu	SV	F	6.5 years	Exaggerated premature clitoromegaly	>75.7	76.4	0.4
13	p.Ile172Asn/p.Ile172Asn	SV	F	neonate	Ambiguous genitalia at birth	>75.7	392	8.2
14	p.Ile172Asn/del of CYP21A2	SV	M	3 years	Premature adrenarche - penile increase	>75.7	569	4.7
15	p.Ile172Asn/p.Ile172Asn	SV	M	5.0 years	Premature adrenarche - penile increase	>75.7	38	4.7
16	p.Ile172Asn/p.Ile172Asn	SV	M	3.2 years	Premature adrenarche - penile increase	>75.7	122	7.5
17	IVS2-13A/C>G/IVS2-13A/C>G	SV	M	5.5 years	GnRH independent Precocious Puberty	43.7	282	1.23
18	Partial conv with CYP21P:-4C>T, 92C>T, 118T>C, 138A>C/delEx 1_3	SV	M	6.5 years	GnRH independent Precocious Puberty	>75.7	N/A	N/A

The most frequent mutation was found to be p.Val281Leu (60.0%) followed by IVS2-13A/C>G (8.8%), DelEx1-3 (5.8%), p.Val304Met (4.6%) and p.Gln318stop (4.2%). A series of other less frequent mutations including rare deletions were also identified (Figure 1).

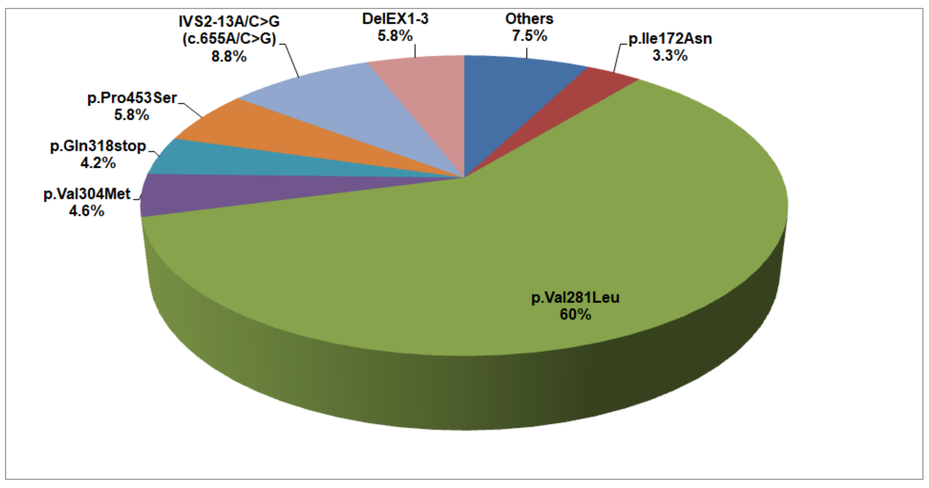
With an estimated population of 701,000 Greek Cypriots (Cyprus statistical service 2016) the prevalence of CAH is estimated to be around 1.7/10000 people.

Based on a recent study the true carrier frequency of *CYP21A2* was reported to be 1:10 (Phedonos *et al.* 2013). Therefore, the identified CAH patients of the present study in the Greek Cypriot population make the 6.9% of the ones estimated (approximately 1,750) to exist in the Greek-Cypriot population.

TABLE 3. Estimate of the prevalence in the Greek-Cypriot population of 11 rare *CYP21A2* mutations identified in 45 patients.

	Number of patients with disease: Tested, (n Positive for mutation, %)	Point estimate of mutation prevalence in patients with disease (95% exact CI)	Number of individuals without disease: Tested (n Positive for mutation, %)	Point estimate of mutation prevalence in the Greek-Cypriot population (95% exact CI)
p.Pro30Leu	45 (2, 4.4)	4.4 (1.0, 15.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
p.Phe306insT+p.Val281Leu	45 (1, 2.2)	2.2 (0.0, 12.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
p.Ile172Asn	45 (5, 11.1)	11.1 (4.0, 24.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
DelEX1-3	45 (13, 28.9)	28.9 (16.0, 44.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
IVS2-13A/C>G (c.655A/C>G)	45 (17, 37.8)	37.8 (24.0, 53.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
Partial conv with CYP21P:-4C>T, 92C>T, 118T>C, 138A>C	45 (1, 2.22)	2.2 (0.0, 12.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
del CYP21A2	45 (1, 2.22)	2.2 (0.0, 12.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
Large del	45 (1, 2.22)	2.2 (0.0, 12.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
p.Ile236Asn;p.Val237Glu;p.Met239Lys; p.Leu307frameshift	45 (2, 4.44)	4.4 (1.0, 15.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
p.Ile236Asn;p.Val237Glu;p.Met239Lys (Cluster E6)	45 (1, 2.22)	2.2 (0.0, 12.0)	300 (0, 0.0)	0.0 (0.0, 1.22)
30 kb del	45 (1, 2.22)	2.2 (0.0, 12.0)	300 (0, 0.0)	0.0 (0.0, 1.22)

FIGURE 1. Pie-chart showing the percentage of mutations across the 120 CAH patients



CONCLUSION

The compiled data of the present work from a coherent population such as the Greek-Cypriot could be valuable for the antenatal diagnosis, management and genetic counselling of the existing and prospect families with CAH.

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