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 one of the most common autosomal recessive disorders 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 CYP21A2 patients with confirmed CAH and their clinical severity, genotype and sex were evaluated.

RESULTS: From 2007 to 2017, one hundred and twenty two patients with various degrees of CAH were categorized and genotyped. Patients with 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 SW form and a median presentation age of 5 yrs (interquartile range (IQR) 3.2 – 6.5) (Table 2).

The most frequent mutation was found to be p.Val218Ileu (60.0%) followed by IVS-13 A/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 2015) 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 (Phedonas 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 1. Mutations involvement in congenital adrenal hyperplasia (CAH). p.Phe306insT+p.Val281Leu (60.0%) followed by IVS-13 A/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).

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

TABLE 3. Estimate of the prevalence in the Greek-Cypriot population of 11 rare CYP21A2 mutations identified in 45 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 prospective families with CAH.

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