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CYP21A2 gene mutations, its nature and frequency in a paediatric portuguese cohort with congenital adrenal hyperplasia

Rosmaninho-Salgado J.¹; Serra Caetano J.²; Gomes S.³; Pereira-Caetano I.³;Cardoso R.²; Dinis I.²; Ramos L.¹; Ramos F.¹; Carvalho A.L.^{1,4}; Garabal A.¹; Sá J.¹; Maia S.^{1,4}; Sousa S.B.^{1,4}; Saraiva J.M.^{1,5}; Gonçalves J.³; Mirante A.²

¹Medical Genetics Unit, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; ²Pediatric Endocrinology Unit, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; ³Human Genetics Department - National Institute of Health Dr Ricardo Jorge, Lisbon, Portugal; ⁴University Clinic of Genetics, Faculty of Medicine, University of Coimbra, Portugal; ⁵University Clinic of Pediatrics, Faculty of Medicine, University of Coimbra, Portugal

Introduction: The most common cause of congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency (21-OHD) caused by alterations in CYP21A2 gene. The clinical phenotypes of this autosomal recessive disease are classified as classic (saltwasting and simple virilizing) and non-classic forms of CAH. The severity of the disease is directly related with the impairment of the 21-OH enzymatic activity. Genetic testing can confirm the disease and is crucial for familial studies and genetic counseling. **Aim:** The aim of this work was to perform the clinical and molecular characterization of the patients observed at the Hospital Pediátrico de Coimbra (Portugal) with the clinical suspicion of CAH.

Methods: Retrospective analysis of patient medical records of all cases observed in our hospital with suspicion of CAH and detailed literature comparison. CYP21A2 molecular analysis had been performed in 81 unrelated Portuguese patients (51 female, 30 males) with clinical and endocrine laboratorial findings suggestive of CAH, using mini-sequencing, restriction enzyme digestion, Sanger sequencing or/and multiplex ligation-dependent probe amplification (MLPA). **Results:** CYP21A2 variants were identified in 74/81 (91%) of the patients. Homozygosity for CYP21A2 was found in 39.2% (29/74) of the patients while 55.4% (41/74) were compound heterozygous and, in 5.4% of the cases (4/74), only one pathogenic variant was identified. The most frequent alterations were p.Val281Leu, g.655A/C>G (splicing variant) and p.Ile172Asn, that account for more than 50% of the alleles of this patient's cohort. All variants were already described except a novel missense variant identified in a salt-wasting patient, g.1173T>C(p.Trp201Arg). The rare variant p.Gly424Ser which was detected in one patient had been previously associated with a possible founder effect in Brazil and the splicing variant g.391G>A, only described in the Portuguese population.

Conclusion: Our study provides a detailed clinical and molecular characterization of a large cohort of CAH Portuguese patients. The overall concordance between the clinical phenotype and the inferred phenotype (based on genotype) was 90%.