Genotype-Phenotype Correlation of Congenital Adrenal Hyperplasia Cases Having Complex (Multiple) Mutation Detected in CYP21A2 Gene

Hilmi Bolat1, Samim Özen2, Hüseyin Onay1, Elif Söbü3, Ayhan Abacı4, Hüseyin Anıl Korkmaz5, Şule Can6, Tahir Attik7, Şükran Darcan2, Ferda Özkınay7

1Ege University Faculty of Medicine, Department of Medical Genetics, İzmir, Turkey
2Ege University Faculty of Medicine, Department of Pediatric Endocrinology, İzmir, Turkey
3Uludağ University Faculty of Medicine, Department of Pediatric Endocrinology, Bursa, Turkey
4Dokuz Eylül University Faculty of Medicine, Department of Pediatric Endocrinology, İzmir, Turkey
5Dr. Behçet Uz Children’s Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Turkey
6Ministry of Health Tepecik Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Turkey
7Ege University Faculty of Medicine, Department of Pediatric Genetics, İzmir, Turkey

Introduction: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorder and is characterized by impaired cortisol synthesis. The most common form is 21-hydroxylase deficiency which is responsible for 95% of cases. More than 100 patients with CYP21A2 mutation have been described so far in the literature. Some patients have more than two different CYP21A2 mutations in both alleles.

Aim: In this study, evaluation of genotype-phenotype relationships in patients with more than two complex (multiple) mutations in the CYP21A2 gene was aimed.

Methods: Genotypes and phenotypic findings of 8 patients who have received a diagnosis of CAH based on clinical and endocrine testing and have complex mutations were compared. The reverse dot-blot method which shows the most common CYP21A2 mutations was used to investigate mutations in patients and parents.

Results: Cases 1-2-3: Homozygous (I2 splice, P30L, Del8bp E3) mutations have been detected in patients with classic salt-wasting; Case 4: Homozygous (I2 splice, P30L, Del8bp E3) mutations have been detected in this patient with simple virilizing; Case 5: Homozygous (I2 splice, P30L, Del8bp E3, V281L) mutations have been detected in this patient with classical salt-wasting; Case 6: Homozygous (I2 splice, P30L, Del8bp E3) mutations have been detected in this patient with classical salt-wasting; Case 7: Heterozygous I2 splice, I172N, ClusterE6, L307Frameshift, Q318X , V281L mutations have been detected in this patient with classical salt-wasting; Case 8: Heterozygous (I2 splice, P30L, Del8bp E3, V281L) mutations have been detected in this patient with clinical symptoms compatible with non-CAH.

Conclusion: Clinical course of patients with heterozygous multiple mutations is aggravating as number of mutations in allele increases. This case series has shown that patients with homozygous 12 splice mutation are associated with serious clinical condition as it is known also in the literature.

Key words: Complex mutation, CYP21A2 gene, congenital adrenal hyperplasia