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

Hilmi Bolat[1], Samim Özen[2], Hüseyin Onay[1], Elif Söbü[3], Ayhan Abacı[4], Hüseyin Anıl Korkmaz[5], Şule Can[6], Tahir Atik[7], Şükran Darcan[2], Ferda Özkınay[7]

[1]*Ege University Faculty of Medicine, Department of Medical Genetics, İzmir, Turkey*

[2]*Ege University Faculty of Medicine, Department of Pediatric Endocrinology, İzmir, Turkey*

[3]*Uludağ University Faculty of Medicine, Department of Pediatric Endocrinology, Bursa, Turkey*

[4]*Dokuz Eylül University Faculty of Medicine, Department of Pediatric Endocrinology, İzmir, Turkey*

[5]*Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Turkey*

[6]*Ministry of Health Tepecik Training and Research Hospital, Clinic of Pediatric Endocrinology, İzmir, Turkey*

[7]*Ege 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 classic salt-wasting; Case 6: Homozygous (I2 splice, P30L, Del8bp E3) mutations have been detected in this patient with classic salt-wasting; Case 7: Heterozygous I2 splice, I172N, ClusterE6, L307Frameshift, Q318X , V281L mutations have been detected in this patient with classic 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