(FC-08)

Hyperinsulinemic Hypoglycemia Due to Homozygous C.706 C>T (P. R236X) Mutation in 3 Siblings: Presentation with Resistant Epilepsy

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Hyperinsulinemic hypoglycemia (HH) is the most common cause of severe resistant hypoglycemia in newborn, infancy, and childhood period. Diazoxide is the mainstay of medical therapy in HH. In about half of patients, HH is diazoxide-unresponsive. Mutations in *HADH* gene cause diazoxide-responsive and protein-sensitive HH. Although *HADH* mutations can present with severe neonatal hypoglycemia, they usually present at infancy and childhood period with relatively mild hypoglycemia. A 17-year-old male patient with the diagnosis of core triatriatum was admitted to our pediatric cardiology department for cardiac catheterization. He had epilepsy and neuro-developmental delay and was on triple-antiepileptic therapy. During his hospitalization period, one of his sisters developed generalized tonic-clonic seizure. Blood glucose level measured was 32 mg/dL with a simultaneous insulin level of 28.8 mIU/mL and C-peptide of 2.8 ng/mL. Urine ketone test was negative. Further evaluation of our patient revealed hypoglycemia with serum insulin level of 22.2 mIU/mL and C-peptide of 2.4 ng/mL. A diagnosis of HH was considered. Parents were second cousins. Another female patient also suffered from epileptic seizures-like episodes. Two sisters had died at 3-month-old and 1-year-old. Molecular genetics analysis revealed homozygous nonsense, c.706C > T(p.R236X) mutation in exon-6 of *HADH* gene. Parents were heterozygous. Diazoxide therapy was commenced for the siblings with homozygous mutation. The frequency of epileptic seizures in patient on antiepileptic therapy was decreased, while other siblings remained free of seizure during follow-up. We had planned to perform a protein loading test. In conclusion, since HH due to *HADH* gene mutations can present during childhood period, it should be kept in mind in the differential diagnosis of resistant epilepsy, particularly in consanguineous pedigrees.

(FC-09)

Investigation of *LDLR* Gene Mutations in Turkish Patients with Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is characterized by severely elevated LDL cholesterol (LDL-C) levels that lead to an increased risk for cardiovascular disease. An estimated 70%-95% of FH results from a heterozygous pathogenic variant in one of three genes *(APOB, LDLR, PCSK9)*. Many people have mutations in the *LDLR (low-density lipoprotein receptor)* gene that encodes the LDL receptor protein, which normally removes LDL from the circulation. The aim of our study was to examine the genetic background of Turkish patients suspected of FH.

In this study, we characterize the spectrum of mutations causing FH in 40 Turkish probands suspected to have FH. Next-generation sequencing was performed in all subjects for *LDLR* gene.

A total of 25 mutations in the *LDLR* gene were detected in 40 subjects. For the patients who did not have a mutation in *LDLR* gene, sequencing analysis for APOB and PCSK9 has been performed.

FH diagnosis was achieved with a high success rate by using a combination of clinical criteria and targeted next-generation sequencing.

(FC-10)

A Novel *THRA* Gene Mutation in Patient with Thyroid Hormone Resistance

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Thyroid receptor alpha (THRA) gene mutation causes thyroid hormone resistance syndrome characterized by near normal thyroid function tests and tissue-specific hypothyroidism.

Case: A 4-year-old male patient was admitted with short stature, motor-mental retardation, and constipation. Motor-mental retardation has been assessed at the age of one year and no etiologic cause was found. In past medical history, he was born at 38 weeks gestational age with a birth weight of 2900 g. His motor-mental milestones were delayed. He had transient

hypogammaglobulinemia. Mother and father were first-degree relatives. In his physical examination, height, weight, and head circumference were 17.4 kg (SDS: -0.12), 96.4 cm (SDS: -2.47), and 54.5 cm (SDS: 2.08), respectively. Pubertal stage was A1P1, testes were 2 + 2 mL palpable. He had edema in the eyelids, face was coarse, and umbilical hernia was found. In the lab exam, Hb was 10.4 g/dL, MCV 88.5 fL, RDW 14.7%, electrolytes, liver and kidney function tests were normal, CK and CK-MB were 396 IU/L (41-277) and 55.3 U/L (0-24), respectively. fT_3 was 5.04 pg/mL (2.3-4.2), fT_4 0.93 ng/dL (0.89-1.76), and TSH was 3.89 µIU/mL (0.35-5.5); bone age was 2 years. Craniography revealed thickness of the scalp. Phenotypically hypothyroid findings and at moderate elevation of fT_3 levels, normochrome normocytic anemia and elevation of CK and CK-MB levels were consistent with primary thyroid hormone resistance. In the mutation analysis, a novel *de novo* p.G291S heterozygous mutation in the *THRA* gene was detected. Na-L thyroxin replacement therapy was initiated.

THRA gene mutation should be considered in patients who are clinically hypothyroid with increased/moderately increased fT_3, decreased/normal fT_4, normal TSH levels, and increased muscle enzymes.

(FC-11)

Analysis of THRB Gene in Turkish Patients and Definition of Three Novel Pathogenic Variants

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We aimed to investigate possible new pathogenic variations in Turkish population by determining thyroid hormone receptor-beta *(THRβ)* variations in patients clinically diagnosed as having thyroid hormone resistance.

The results of eighty-two patients [F: 56 (mean age: 30.6), M: 26 (mean age: 31.1) who have been directed to our center between 08.05.2012-28.11.2016 were included in this study. The gene region of interest was amplified by PCR using the deep intronic primers covering exons 7, 8, 9, and 10 of the *THRβ* gene (ENT00000356447.8 transcript) and the nucleotide sequences were determined by the Sanger Sequence method. ProSeq and BioEdit softwares were used to compare patient and reference genomic nucleotide sequences.

Any variation was found in 18.3% of the patients, whereas 29.3% had single nucleotide polymorphisms. 18.3% of patients were determined to have NM_001252634.1:c.735C > T (p.Phe245 =) variation that has been reported as benign SNP (rs3752874) in ClinVar database but reported as modifier variant (CM099823) for thyroid hormone resistance in Human Gene Mutation Database. In 28% of patients, pathogenic variations reported in ClinVar, HGMD, and COSMIC databases were determined. Three novel variations [NM_000461.4: c.701C > A, (p.Ala234Asp), c.737T > A (Leu246Gln), c.1024A > G (p.Lys342Glu)], which were not reported in ClinVar, HGMD, and COSMIC databases before, have been determined in five patients and *in silico* analysis with Mutation Taster, Polyphen tools scored these variants as pathogenic.

This is the first study in Turkish population investigating *THRβ* gene variations in patients clinically diagnosed as having thyroid hormone resistance. In addition, three novel pathogenic variants have been reported in this study.

(FC-12)

Muscular Type Lipodystrophy Diagnosed with Neonatal Findings: Berardinelli-Seip Congenital Lipodystrophy Type 4 and Comparison Between the Types

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Berardinelli-Seip congenital generalized lipodystrophy (BSCL) is characterized by absence of functional adipocytes, thus, lipid is stored in other tissues, including muscle and liver. Classic findings are reduced adipose tissue, muscle hypertrophy, enlarged hands and feet, enlarged external genitalia, hypertriglyceridemia, insulin resistance, hepatomegaly, hypertrophic cardiomyopathy (HCMP), and arrhythmia. Four types have been described. Type 1 (AGPAT2 mutation) and type2 (*BSCL2* mutation) have